

Reversal of the Stereochemical Course of the Addition of Phenylmagnesium Bromide to *N*-Benzylimines Derived from *R*-Glyceraldehyde Depending on the *O*-Protecting Group and its Application to the Synthesis of both Enantiomers of Phenylglycine

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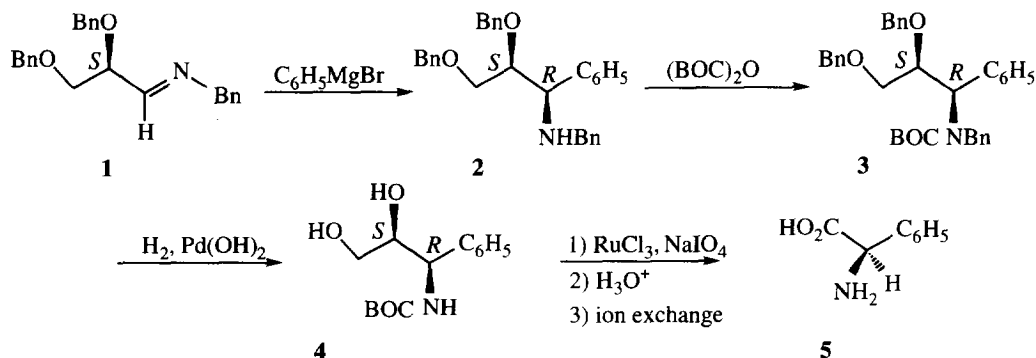
Abstract: The *N*-Benzyl imines derived from 2,3-di-*O*-benzyl-*D*-glyceraldehyde and 2,3-di-*O*-isopropylidene-*D*-glyceraldehyde reacted with phenylmagnesium bromide to afford fully protected aminodiols with total diastereoselectivity. The stereochemical course of the addition reaction depends on the nature of the *O*-protecting group. These compounds can be easily transformed to enantiomerically pure (*R*) and (*S*) α -phenylglycine. © 1997, Elsevier Science Ltd. All rights reserved.

The importance of enantiomerically pure α -amino acids makes the development of new and efficient general approaches to their synthesis a significant and active area of research.¹

In a previous study² on the synthesis of α -hydroxy- β -amino acids using *D*-glyceraldehyde as the chiral source we have shown that the aminodiol obtained by stereoselective addition of methylmagnesium bromide to the *N*-benzyl imine derived from 2,3-di-*O*-benzyl-*D*-glyceraldehyde can easily be converted into (*R*)-alanine. In the previous study the transformation was only performed in order to unambiguously establish the absolute stereochemistry of the chiral aminodiol.

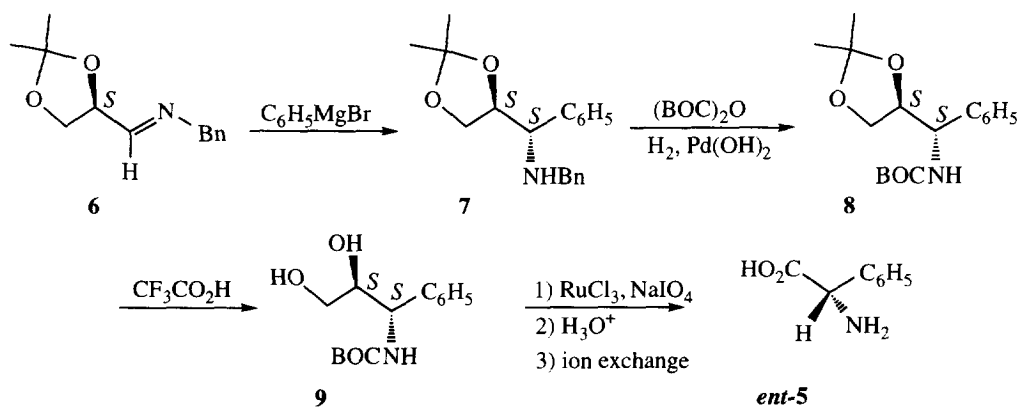
However, the enormous potential of this synthetic methodology has led us to apply it to the synthesis of (*R*)-phenylglycine, a compound which belongs to an interesting and important kind of non-proteinogenic amino acids, the arylglycines. Arylglycines are constituents of glycopeptide antibiotics³ which inhibit bacterial cell biosynthesis,⁴ and norcardicins and other β -lactam antibiotics.⁵ Arylglycines are difficult to synthesise in optically pure form as they can easily undergo racemisation under basic conditions. Despite this problem, several methodologies have been developed that allow their asymmetric synthesis and these are collected in a recent review by Williams.⁶

Our strategy for the synthesis of enantiomerically pure α -phenylglycine employs inexpensive and readily available starting materials and is outlined in scheme 1. Imine **1** is prepared from 2,3-di-*O*-benzyl-*D*-glyceraldehyde and benzylimine in the presence of anhydrous magnesium sulphate and is subsequently reacted with phenylmagnesium bromide in diethyl ether. This reaction affords the corresponding addition compound **2** in 78 % yield as a single diastereoisomer, as confirmed by NMR spectroscopy. This result is in contrast with that observed by Jäger *et al.*,⁷ who found only a moderate stereoselectivity on addition of Grignard reagents to *N*-benzylimines derived from 2-*O*-benzylglyceraldehyde under similar conditions.



Scheme 1

Conversion of compound **2** into the corresponding diastereomerically pure *N*-Boc derivative **3** was achieved using di-*tert*-butyldicarbonate in dioxane in the presence of diisopropylethylamine in 82 % yield. Compound **3** underwent hydrogenolysis in the presence of palladium hydroxide to afford the *tert*-butoxycarbonylaminodiol **4** in nearly quantitative yield as a single diastereoisomer. In the final step, oxidative cleavage of the 1,2-diol moiety was performed by treatment with excess sodium periodate in the presence of ruthenium trichloride according to the procedure described by Pericas *et al.*⁸ Subsequent acid hydrolysis yielded enantiomerically pure (*R*)-phenylglycine whose specific rotation value $\{[\alpha]^{25}_{\text{D}} = -155$ (c, 1 in 1N HCl), lit⁹ $[\alpha]^{25}_{\text{D}} = -157$ (c, 1 in 1N HCl)} confirmed the stereochemical course and high stereoselectivity obtained in the organometallic addition reaction.



Scheme 2

As an alternative, we also studied the use of the *N*-benzyl imine derived from 2,3-diisopropylidene-*D*-glyceraldehyde **6** as the starting material (Scheme 2). Treatment of compound **6** with phenylmagnesium bromide in diethyl ether afforded the corresponding addition compound **7** in 69 % yield and also gave only a single diastereoisomer. Hydrogenolysis of compound **7** in the presence of di-*tert*-butyldicarbonate using palladium hydroxide as the catalyst gave the *N*-Boc derivative **8**, whose acid hydrolysis yielded the *N*-Boc amino diol **9**. ¹H NMR spectroscopy revealed that compound **9** differs from **4**, the *N*-Boc amino diol obtained in Scheme 1. The $[\alpha]_{\text{D}}$ value measured for compound **9** $\{[\alpha]^{25}_{\text{D}} = +52.0$ (c, 1 in chloroform)} is opposite to that described

by Pericas *et al.*⁸ for the (2*R*,3*R*) diastereoisomer $\{[\alpha]^{25}_{\text{D}} = -52.7$ (c, 1 in chloroform) $\}$. This indicates a reversal in the stereochemical course of the reaction leading to the synthesis of the (2*S*,3*S*) diastereoisomer. Finally, oxidative cleavage of the diol followed by acid hydrolysis yielded (*S*)-phenylglycine $\{[\alpha]^{25}_{\text{D}} = +152$ (c, 1 in 1*N* HCl) $\}$ which clearly confirms the reversal in the stereochemical course of the phenylmagnesium bromide addition reaction depending on the nature of the *O*-protecting group.

A phenomenon related to that described above was reported some years ago by Macdonald *et al.*¹⁰ They observed the formation of either *syn* or *anti* products in the nucleophilic addition of organometallic reagents to α,β -dialkoxy carbonyl compounds which was dependent on the nature of the *O*-protecting group. These authors suggested that the stereochemical course of the reaction depends on competitive reactions *via* α -chelate controlled, β -chelate controlled or non-chelate controlled additions. Recently, Jäger *et al.*⁷ have also observed a reversal in the stereochemical course of Grignard additions to *N*-(1-phenylethyl) imines derived from 2-*O*-benzylglyceraldehyde controlled by the chirality of the chiral amine. They explain this observation in terms of the π -face accessibility of competing α -chelate and β -chelate structures. On the basis of the above precedents we propose the following possible chelated structures **A-D** as intermediates in the phenylmagnesium bromide addition to imines **1** and **6**.

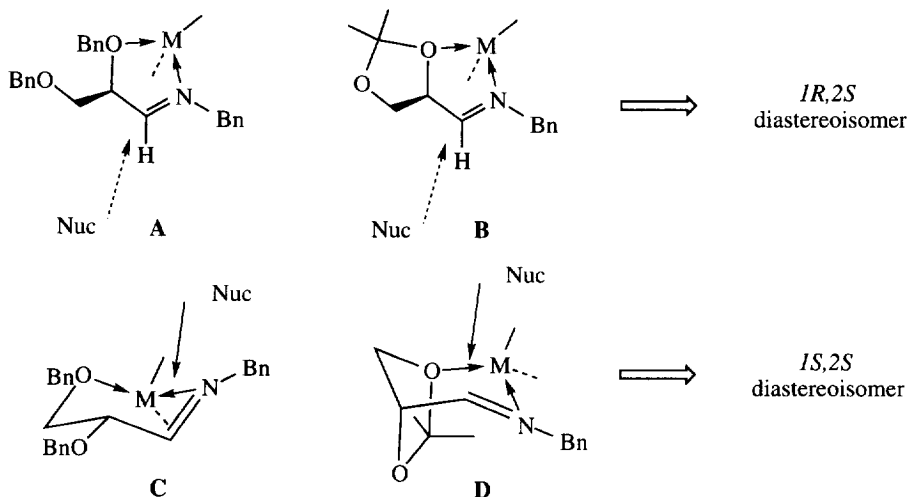


Figure 1

The reaction of **1** with phenylmagnesium bromide *via* the α -chelate **A** without competition of β -chelate controlled addition would account for the total stereoselectivity of the reaction, whereas in the case of imine **6**, the addition reaction has to occur exclusively through the β -chelated intermediate **D**, as confirmed by the isolation of the (1*S*,2*S*) diastereoisomer with total diastereoselectivity.

In conclusion, this paper describes a simple methodology which allows the synthesis of both enantiomers phenylglycine starting from commercially available *D*-mannitol.

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EXPERIMENTAL

Apparatus: Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1600 FT IR infrared spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Unity-300 or a Bruker ARX-300 spectrometer in deuteriochloroform or deuterated water using the residual solvent signal as the internal standard; chemical shifts (δ) are given in parts per million and the coupling constants (J) in Hertz. The ^1H NMR and ^{13}C NMR spectra of *N*-Boc protected compounds were not conclusive at room temperature due to the presence of a dynamic equilibrium between rotamers caused by the restricted rotation of the nitrogen-carbon bond of the amide group. In order to overcome this problem NMR spectra of these compounds were run at 55 °C. Elemental analyses were performed with a Perkin-Elmer 2400 analyser. Optical rotations were measured on a Perkin-Elmer 241-C polarimeter at 25 °C.

Chemicals: All reactions were carried out under argon with magnetic stirring. Solvents were dried prior to use. All reagents were purchased from The Aldrich Chemical Co. and used as received. TLC was performed on precoated silica-gel plates which were visualised using UV light and anisaldehyde/sulphuric acid/ethanol (2/1/100). Flash column chromatography was performed using silica-gel (Kieselgel 60).

(1*R*,2*S*)-*N*-Benzyl-2,3-dibenzyloxy-1-phenyl-1-propylamine 2. A solution of chiral imine **1**² (1.8 g, 5 mmol) in diethyl ether (20 ml) was added dropwise over 30 min to a stirred solution of phenylmagnesium bromide 0.5M solution in diethyl ether (25 ml, 12.5 mmol) at 0 °C under argon. After being stirred for 15 h at room temperature, the reaction mixture was poured into saturated aqueous NH_4Cl (30 ml), the organic layer separated and the aqueous layer extracted with ether (2 x 30 ml). The combined organic layer was dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography (ethyl acetate:hexane 1:4) afforded 1.7 g (78 %) of (1*R*,2*S*)-*N*-benzyl-2,3-dibenzyloxy-1-phenyl-1-propylamine **2** as a colourless oil. $[\alpha]_D^{25} = -43.1$ (c, 1 in chloroform); IR (Nujol) 3334, 1603 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 2.5 (brs, 1H), 3.30 (dd, 1H, $J = 10.5$, $J = 4.8$), 3.45 (d, 1H, $J = 13.2$), 3.52 (dd, 1H, $J = 10.5$, $J = 3.3$), 3.58 (d, 1H, $J = 13.2$), 3.69-3.75 (m, 1H), 3.91 (d, 1H, $J = 7.8$), 4.39 (s, 2H), 4.51 (d, 1H, $J = 11.7$), 4.72 (d, 1H, $J = 11.7$), 7.20-7.41 (m, 20H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 51.1, 63.4, 69.8, 73.0, 73.3, 83.0, 126.7, 127.5, 127.5, 127.6, 127.7, 127.9, 128.1, 128.2, 128.3, 128.3, 128.4, 128.5, 138.2, 138.4, 140.6, 140.7; Anal. Calcd. for $\text{C}_{30}\text{H}_{31}\text{NO}_2$: C, 82.35; H, 7.14; N, 3.20. Found: C, 82.18; H, 7.07; N, 3.51.

(1*R*,2*S*)-*N*-Benzyl-*N*-tert-butoxycarbonyl-2,3-dibenzyloxy-1-phenyl-1-propylamine 3. Di-*tert*-butyl dicarbonate (1.9 g, 8.7 mmol) was added to a stirred solution of (1*R*,2*S*)-*N*-benzyl-2,3-dibenzyloxy-1-phenyl-1-propylamine **2** (1.6 g, 3.75 mmol) and diisopropylethylamine (52 mg, 0.4 mmol) in dioxane (10 ml). After being stirred at 50 °C for 20 h the reaction mixture was treated with ether (50 ml), washed with 1M aqueous KHSO_4 (10 ml), dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo* to afford a crude product which was purified by flash chromatography (ethyl acetate:hexane 1:9) to give 1.65 g (82 %) of (1*R*,2*S*)-*N*-benzyl-*N*-tert-butoxycarbonyl-2,3-dibenzyloxy-1-phenyl-1-propylamine **3** as a colourless oil. $[\alpha]_D^{25} = -24.2$ (c, 1 in chloroform); IR (Nujol) 1691 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 1.34 (s, 9H), 3.45 (dd, 1H, $J = 10.7$, $J = 5.0$), 3.61 (dd, 1H, $J = 10.7$, $J = 2.7$), 4.32-4.50 (m, 4H), 4.52-4.60 (m, 1H), 4.55 (d, 1H, $J = 11.5$), 4.80 (d, 1H, $J = 11.5$), 5.17 (d, 1H, $J = 9.0$), 6.96-7.40 (m, 20H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 28.4, 50.5, 62.1, 71.3, 72.4, 73.5, 78.6, 79.9, 126.3, 127.3, 127.5, 127.7, 127.8, 128.2, 128.3, 129.1, 138.5, 139.0, 139.1, 139.7, 156.3; Anal. Calcd. for $\text{C}_{35}\text{H}_{39}\text{NO}_4$: C, 78.18; H, 7.31; N, 2.61. Found: C, 78.98; H, 7.18; N, 2.40.

(2S,3R)-3-*tert*-Butoxycarbonylamino-3-phenyl-1,2-propanediol 4. A solution of (1*R*,2*S*)-*N*-benzyl-*N*-*tert*-butoxycarbonyl-2,3-dibenzyloxy-1-phenyl-1-propylamine **3** (1.35 g, 2.5 mmol) in methanol (15 ml) was hydrogenated with 20% wt Pd(OH)₂ (400 mg) as catalyst at room temperature and atmospheric pressure for 3 days. When the reaction was complete the catalyst was removed by filtration and the filtrate evaporated to dryness. The resulting crude material was purified by flash chromatography (ethyl acetate:hexane 1:1) to afford 625 mg (94 % yield) of (2*S*,3*R*)-3-*tert*-butoxycarbonylamino-3-phenyl-1,2-propanediol **4** as a white solid. M. p. = 99 °C; $[\alpha]^{25}_{\text{D}} = -19.2$ (c, 1 in chloroform); IR (Nujol) 3377, 1681 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 1.40 (s, 9H), 2.85 (brs, 2H), 3.46-3.63 (m, 2H), 3.89 (dd, 1H, J = 10.8, J = 5.1), 4.73 (dd, 1H, J = 7.8, J = 4.2), 5.37 (bd, 1H, J = 7.8), 7.20-7.40 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz): δ 28.3, 56.4, 63.9, 75.1, 80.2, 126.8, 127.6, 128.6, 140.1, 156.6; Anal. Calcd. for C₁₄H₂₁NO₄: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.09; H, 7.91; N, 5.12.

(*R*)-Phenylglycine 5. Small portions of NaIO₄ (856 mg, 4 mmol) were added to a stirred solution of (2*S*,3*R*)-3-*tert*-butoxycarbonylamino-3-phenyl-1,2-propanediol **4** (267 mg, 1 mmol) in a mixture of acetonitrile-carbon tetrachloride-water (2:2:3) (20 ml). On completion of the addition the mixture was vigorously stirred for 5 min and was treated with RuCl₃·H₂O (10 mg, 0.044 mmol). The mixture was stirred for a further 2 h. Dichloromethane (25 ml) was added, and the mixture was extracted with 1M NaHCO₃. The aqueous solution was washed with ether, carefully acidified with saturated KHSO₄ and extracted with ether (3 x 30 ml). The combined organic extracts were dried over anhydrous MgSO₄, filtered and concentrated *in vacuo*. The resulting crude (*R*)-*N*-*tert*-butoxycarbonylphenylglycine was dissolved in THF (5 ml) and hydrolysed by stirring with 3N hydrochloric acid (10 ml) for 2 h at room temperature. The reaction mixture was washed with ether and evaporated *in vacuo* to give the crude amino acid hydrochloride which was purified by ion exchange chromatography (Dowex 50 x 8) to afford 113 mg (75 %) of (*R*)-phenylglycine **5** as a white solid. M.p. > 300 °C; $[\alpha]^{25}_{\text{D}} = -155$ (c, 1 in 1N HCl), lit⁹ $[\alpha]^{25}_{\text{D}} = -157$ (c, 1 in 1N HCl); ¹H NMR (D₂O, 300 MHz): δ 4.80 (s, 1H), 7.31-7.40 (m, 5H); ¹³C NMR (D₂O, 75 MHz): δ 58.5, 127.9, 129.4, 129.5, 134.2, 173.4.

(2*S*,3*S*)-3-Benzylamino-1,2-di-*O*-isopropyliden-3-phenyl-1,2-propanediol 7. A solution of chiral imine **6** (1.1 g, 5 mmol) in diethyl ether (20 ml) was added dropwise over a period of 30 min to a stirred solution of phenylmagnesium bromide 0.5M solution in diethyl ether (25 ml, 12.5 mmol) at 0 °C under argon. After being stirred for 15 h at room temperature, the reaction mixture was poured into saturated aqueous NH₄Cl (30 ml), the organic layer separated and the aqueous layer extracted with ether (2 x 30 ml). The combined organic layer was dried over anhydrous MgSO₄, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography (ethyl acetate:hexane 1:3) afforded 1 g (69 %) of (2*S*,3*S*)-3-benzylamino-1,2-di-*O*-isopropyliden-3-phenyl-1,2-propanediol **7** as a colourless oil. $[\alpha]^{25}_{\text{D}} = +41.7$ (c, 1 in chloroform); IR (Nujol) 3327 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 1.32 (s, 3H), 1.39 (s, 3H), 2.00 (brs, 1H), 3.54 (d, 1H, J = 13.2), 3.73 (d, 1H, J = 13.2), 3.76 (dd, 1H, J = 8.1, J = 6.3), 3.95 (d, 1H, J = 4.5 Hz), 4.06 (dd, 1H, J = 8.1, J = 8.1), 4.25-4.31 (m, 1H), 7.25-7.40 (m, 10H); ¹³C NMR (CDCl₃, 75 MHz): δ 25.3, 26.5, 51.2, 62.9, 65.3, 79.5, 109.2, 126.9, 127.6, 127.9, 128.1, 128.4, 128.6, 139.7, 140.5; Anal. Calcd. for C₁₉H₂₃NO₂: C, 76.74; H, 7.79; N, 4.71. Found: C, 76.94; H, 7.86; N, 4.87.

(2*S*,3*S*)-3-*tert*-Butoxycarbonylamino-1,2-di-*O*-isopropyliden-3-phenyl-1,2-propanediol 8. A solution of (2*S*,3*S*)-3-benzylamino-1,2-di-*O*-isopropyliden-3-phenyl-1,2-propanediol **7** (890 mg, 3 mmol) and di-*tert*-butyl dicarbonate (1.9 g, 9 mmol) in absolute ethanol (10 ml) was added to a stirred suspension of 20% wt Pd(OH)₂ (300 mg) in absolute ethanol (10 ml) and the mixture was hydrogenated with H₂ at atmospheric pressure by shaking at room temperature for 12 h. After completion the reaction mixture was filtered and concentrated *in vacuo* to afford a crude product which was purified by flash chromatography (ethyl acetate) to provide 820 mg (89 %) of (2*S*,3*S*)-3-*tert*-butoxycarbonylamino-1,2-di-*O*-isopropyliden-3-phenyl-1,2-

propanediol **8** as a white solid. M.p. = 115 °C; $[\alpha]^{25}_D = +24.2$ (c, 1 in chloroform); IR (Nujol) 3377, 1694 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 1.30 (s, 3H), 1.32 (s, 3H), 1.39 (s, 9H), 3.72 (dd, 1H, $J = 8.7$, $J = 6.3$), 3.93 (dd, 1H, $J = 8.7$, $J = 6.5$), 4.30-4.40 (m, 1H), 4.75 (dd, 1H, $J = 8.2$, $J = 5.5$), 5.07 (dd, 1H, $J = 8.2$), 7.25-7.34 (m, 5H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 25.3, 26.3, 28.4, 56.9, 66.1, 78.1, 79.8, 109.9, 127.5, 127.6, 128.4, 139.1, 155.4; Anal. Calcd. for $\text{C}_{17}\text{H}_{25}\text{NO}_4$: C, 66.43; H, 8.20; N, 4.55. Found: C, 66.68; H, 8.03; N, 4.75.

(2S,3S)-3-tert-Butoxycarbonylamino-3-phenyl-1,2-propanediol 9. A solution of (2S,3S)-3-tert-butoxycarbonylamino-1,2-di-*O*-isopropyliden-3-phenyl-1,2-propanediol **8** (770 mg, 2.5 mmol) in methanol-water (3:1) (10 ml) was treated with trifluoroacetic acid (0.1 ml) and stirred at room temperature for 15 h. When the reaction was complete the solvent was removed *in vacuo* and the residue was diluted with water and extracted with dichloromethane. The organic layer was dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo* and the crude residue purified by flash chromatography (ether) to afford 600 mg (90 %) of (2S,3S)-3-tert-butoxycarbonylamino-3-phenyl-1,2-propanediol **9** as a white solid. M.p. = 118 °C; $[\alpha]^{25}_D = +52.0$ (c, 1 in chloroform); IR (Nujol) 3377, 1681 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 1.40 (s, 9H), 2.51 (brs, 2H), 3.54-3.70 (m, 2H), 3.82-3.88 (m, 1H), 4.70 (dd, 1H, $J = 7.3$, $J = 7.3$), 5.50 (bs, 1H), 7.25-7.40 (m, 5H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 28.0, 57.0, 63.0, 73.9, 80.1, 127.3, 127.7, 128.6, 138.9, 156.0; Anal. Calcd. for $\text{C}_{14}\text{H}_{21}\text{NO}_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.08; H, 7.87; N, 5.11.

(S)-Phenylglycine ent-5. (2S,3S)-3-tert-Butoxycarbonylamino-3-phenyl-1,2-propanediol **9** (267 mg, 1 mmol) was treated as described for compound **9** to afford 120 mg (80 % yield) of (S)-phenylglycine *ent-5* as a white solid. M.p. > 300 °C; $[\alpha]^{25}_D = +152$ (c, 1 in 1N HCl); lit. for its enantiomer⁹ $[\alpha]^{25}_D = -155$ (c, 1 in 1N HCl); ^1H NMR (D_2O , 300 MHz): δ 4.53 (s, 1H), 7.31-7.40 (m, 5H); ^{13}C NMR (D_2O , 75 MHz): δ 58.5, 127.9, 129.4, 129.5, 134.2, 173.4.

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