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New Approaches to the Asymmetric Synthesis of α-Methylphenylalanine

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Abstract: A strategy of highly selective alkylation of chiral 2-cyanoesters followed by the corresponding degradation process allows a divergent asymmetric synthesis of *(R)* and *(S)* -α-methylphenylalanine.

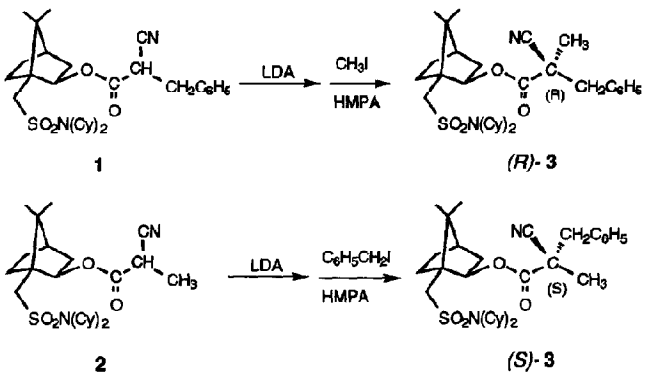
Non-proteinogenic, unnatural α-amino acids have attracted the attention of numerous researchers due to the widespread use of such compounds in physical and life science. Many synthetic methodologies have already been developed to obtain a wide range of optically active α-amino acids.[1]

In recent years the synthesis of α-substituted-α-amino acids has attracted particular attention,[2] especially the α-methyl series, and the increasing interest in the study of this type of compound is caused by their apparent importance as enzyme inhibitors[3] and as conformational modifiers of physiologically active peptides.[4] α-Methylphenylalanine has been incorporated into two classes of sweeteners as a substitute for L-phenylalanine and the α-methylphenylalanine analogue of aspartame was found to possess the same sweetness as aspartame and superior stability.[5]

Bearing this in mind, we carried out the chiral synthesis of α-methylphenylalanine extending our previously described methodology[6] based on the diastereoselective alkylation of *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanoesters and the corresponding degradation process.

Diastereoselective methylation of *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 3-phenyl-2-cyanopropanoate **1** was performed by the generation of the enolate with lithium diisopropylamide for one hour in dry THF at -78°C, followed by the addition of methyl iodide in the presence of hexamethylphosphoramide (HMPA) to yield *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-2-methyl-3-phenylpropanoate *(R)* -**3** as a mixture of diastereoisomers (d.r. = 80/20) in 96% yield. The minor diastereoisomer was eliminated by selective crystallization in hexane as it was the less soluble compound. Alternatively, diastereoselective benzylation of *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-

cyanopropanoate **2** was carried out by the generation of the enolate with lithium diisopropylamide for one hour in dry THF at -78°C followed by the addition of benzyl iodide in the presence of hexamethylphosphoramide (HMPA) to yield *(2S)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-2-methyl-3-phenylpropanoate *(S)* **-3**. Compound *(S)* **-3** was also obtained as a mixture of diastereoisomers (d.r. = 91/9) in 96% yield from which the major diastereoisomer was isolated in diastereoisomerically pure form by selective crystallization in hexane (Scheme 1).



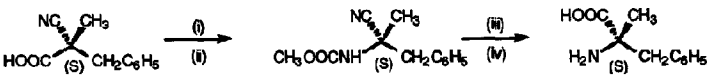
SCHEME 1

The diastereoisomeric ratio of the products was determined in the crude reaction spectra by integration of the ^1H NMR (300 MHz) absorptions of the benzylic protons, as each diastereoisomer gave separate signals. The absolute configuration at C_2 was assigned in accordance with that of the corresponding 2-cyano-2-methyl-3-phenylpropanoic acid and the final α-methylphenylalanine.

The stereochemical results are consistent with the model proposed for the alkylation of the enolate generated by 1,4-addition of hydride to E *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanocinnamate.[7]

Diastereoisomerically pure *(2S)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-2-methyl-3-phenylpropanoate *(S)* **-3** was hydrolysed with 10% potassium hydroxide in methanol to the corresponding *(2S)*-2-cyano-2-methyl-3-phenylpropanoic acid *(S)* **-4**, which was subjected to the corresponding degradation process.

Curtius-type rearrangement afforded *(2S)*-2-methoxycarbonylamino-2-methyl-3-phenylpropanonitrile *(S)* **-5**. The cyanourethane *(S)* **-5**, obtained in 87% yield was deprotected with concomitant hydrolysis of the cyano group by treatment with 20% hydrochloric acid to afford *(S)*-α-methylphenylalanine hydrochloride from which enantiomerically pure *(S)*-α-methylphenylalanine was obtained in 93% overall yield for the two steps (Scheme 2)

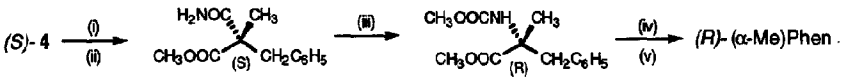


(S)-**4** *(S)*-**5** *(S)*-(α-Me)Phen

(i)PCl_5, NaN_3 (ii) MeOH, Δ, (iii) HCl, (iv) propylene oxide, EtOH, Δ

SCHEME 2

On the other hand, Hoffman-type rearrangement of *(2S)*-methyl 2-carbamoyl-2-methyl-3-phenylpropanoate *(S)*-**6** afforded *(2R)*-methyl 2-methoxycarbonylamino-2-methyl-3-phenylpropanoate *(R)*-**7**. The urethane *(R)*-**7**, obtained in 77% overall yield from *(S)*-**4** was deprotected by treatment with 20% hydrochloric acid to afford *(R)*-α-methylphenylalanine hydrochloride from which enantiomerically pure *(R)*-α-methylphenylalanine was obtained in 89% overall yield for the two steps. (Scheme 3)



(S)-**5** *(R)*-**7**

(i) NaOH, H_2O_2, (ii) CH_2N_2, (iii) $Hg(AcO)_2$, NBS, MeOH, (iv) HCl, (v) propylene oxide, EtOH, Δ

SCHEME 3

To sum up, both enantiomers of α-methylphenylalanine were synthesized with useful overall yields and excellent diastereoselectivities. Various different and complementary routes were studied and we can conclude that the absolute configuration at the stereogenic centre can easily be directed in either direction by interchanging the carbonyl compound used in the synthesis of the starting material and the alkylating agent, as well as subjecting the alkylated compound to Curtius or Hoffman type rearrangement. Naturally we can also obtain either of the enantiomers by using *(1S,2R,4R)*-10-dicyclohexylsulfamoylisoborneol or its antipode as previously described for *(R)*- and *(S)*-2-methylbutanoic acid.[6]

Acknowledgement: This work was supported by the Dirección General de Investigación Científica y Técnica, project number PB91-0696.

EXPERIMENTAL

Apparatus: ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Unity-300 spectrometer in $CDCl_3$, DMSO-d_6 or D_2O , using the solvent signal as internal standard, chemical shifts are expressed in ppm. IR spectra were recorded on a Perkin-Elmer 1600 FTIR infrared spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241-C polarimeter at 25°C. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. Mass spectra (MS) were determined on a high-resolution VG-Autospec spectrometer.

Chemicals: All the reactions were carried out under Ar with magnetic stirring. Solvents were dried prior to use. Lithium diisopropylamide (LDA) was generated in situ from diisopropylamine and butyl lithium. Hexamethylphosphoramide was purchased from Aldrich Chemical Co. *(2RS)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 3-phenyl-2-cyanopropanoate **1** was prepared following the method described in the literature.[8] TLC was performed on Merck precoated silica-gel plates which were visualised using UV light and anisaldehyde/sulphuric acid/ethanol (2/1/100). Flash column chromatography was performed using 230-400 mesh (Merck) silica-gel.

(2RS)-(1S,2R,4R)-10-Dicyclohexylsulfamoylisobornyl 2-cyanopropanoate **2.**

2-Cyanopropanoyl chloride (1.386 g, 12 mmol) was added by means of a syringe to a stirred mixture of silver cyanide (1.206 g, 9 mmol) and *(1S,2R,4R)*-10-dicyclohexylsulfamoylisoborneol (2.382 g, 6 mmol) in toluene (60 ml) under argon and the mixture was heated at 80 °C for 4 h. The reaction mixture was then filtered, washed successively with a 10% aqueous sodium hydrogen carbonate solution and water, dried with magnesium sulphate and concentrated in vacuo. Purification of the residue by flash chromatography on a silica-gel column (eluent ether/hexane 1/3) afforded 2.523 g (88% yield) of *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate **2** as a mixture of diastereoisomers (d.r. 50/50)

Spectral data of the mixture: IR 2244, 1747, cm^{-1}; HRMS (FAB): m/z = 476.2869 (M^+ calc for $C_{26}H_{42}N_2O_4S$ 478.2865); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (s, 3H), 1.03 (s, 3H), 1.55 and 1.61 (d, 3H, J = 7.5 Hz), 1.00-2.00 (m, 27H), 2.59 and 2.62 (d, 1H, J = 13.5 Hz), 3.30 and 3.34 (d, 1H, J = 13.5 Hz), 3.14-3.30 (m, 2H), 3.49 (m, 1H, J = 7.5 Hz), 4.94-5.04 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.92 and 15.34, 19.84 and 19.88, 20.24, 25.14 and 25.19, 26.21 and 26.31, 26.37 and 26.41, 26.91 and 26.94, 30.55 and 30.73, 31.17 and 31.76, 32.24 and 32.49, 33.00 and 33.25, 39.05 and 39.07, 44.40 and 44.42, 49.27, 49.81 and 49.86, 53.77 and 53.95, 57.45 and 57.53, 80.29 and 80.62, 117.48 and 117.64, 165.08.

(2R)-(1S,2R,4R)-10-Dicyclohexylsulfamoylisobornyl 2-cyano-2-methyl-3-phenylpropanoate *(R)* **-3.**

To a dry THF solution (100 ml) of lithium diisopropylamine, generated in situ from diisopropylamine (480 mg, 4.8 mmol) and butyl lithium (4.4 mmol), under argon at -78° C was added a solution of *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 3-phenyl-2-cyanopropanoate **1** (2.21 g, 4 mmol) in dry THF (20 ml). After 1 h a solution of methyl iodide (5.68 g, 40 mmol) and HMPA (1.08 g, 6 mmol) in dry THF (20 ml) was added by syringe. The reaction

mixture was allowed to warm to room temperature and stirring was continued for 1 day. The mixture was then quenched with a saturated aqueous NH_4Cl solution (20 ml). Ether extraction, washing with water, drying on $MgSO_4$ and concentration in vacuo yielded a mixture of diastereoisomers of *(R)* **-3** as a crude oil in 93% yield. Purification of the crude product by flash chromatography and recrystallization afforded diastereoisomerically pure *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-2-methyl-3-phenylpropanoate *(R)* **-3.**

Mp 123 °C; $[\alpha]_D$ = - 62.8 (c = 1.56 in $CHCl_3$); IR 2243, 1748, cm^{-1}; HRMS (FAB): m/z = 568.3392 (M^+ calc for $C_{33}H_{48}N_2O_4S$ 568.3334); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (s, 3H), 1.08 (s, 3H), 1,43 (s, 3H), 1.00-2.20 (m, 27H), 2.66 (d, 1H, J = 13.5 Hz), 3.09 (d, 1H, J = 13.8 Hz), 3.22-3.36 (m, 2H), 3.37 (d, 1H, 13.8 Hz), 3.44 (d, 1H, J = 13.5 Hz), 5.06 (dd, 1H, J = 7.8 Hz, J = 3.3 Hz), 7.26-7.32 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.0, 20.3, 21.9, 25.1, 26.2, 26.4, 26.9, 30.8, 32.1, 33.3, 39.3, 42.1, 44.0, 44.3, 49.3, 49.8, 53.9, 57.4, 80.5, 119.9, 127.6, 128.4, 130.3, 134.0, 167.9.

(2S)-(1S,2R,4R)-10-Dicyclohexylsulfamoylisobornyl 2-cyano-2-methyl-3-phenylpropanoate *(S)* **-3.**

To a dry THF solution (100 ml) of lithium diisopropylamine, generated in situ from diisopropylamine (480 mg, 4.8 mmol) and butyl lithium (4.4 mmol), under argon at -78° C was added a solution of *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate **2** (1.91 g, 4 mmol) in dry THF (20 ml). After 1 h a solution of benzyl iodide (8.72 g, 40 mmol) and HMPA (1.08 g, 6 mmol) in dry THF (20 ml) was added by syringe. The reaction mixture was allowed to warm to room temperature and stirring was continued for 1 day. The mixture was then quenched with a saturated aqueous NH_4Cl solution (20 ml). Ether extraction, washing with water, drying on $MgSO_4$ and concentration in vacuo yielded a mixture of diastereoisomers of *(S)* **-3** as a crude oil in 93% yield. Purification of the crude product by flash chromatography and recrystallization afforded diastereoisomerically pure *(2S)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-2-methyl-3-phenylpropanoate *(S)* **-3.**

Mp 220 °C; $[\alpha]_D$ = - 51.4 (c = 1 in $CHCl_3$); IR 2240, 1743, cm^{-1}; HRMS (FAB): m/z = 568.3387 (M^+ calc for $C_{33}H_{48}N_2O_4S$ 568.3334); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.51 (s, 3H), 0.74 (s, 3H), 1.74 (s, 3H), 1.00-1.80 (m, 27H), 2.48 (d, 1H, J = 13.2 Hz), 2.98 (d, 1H, J = 13.2 Hz), 3.15 (d, 1H, J = 13.2 Hz), 3.20-3.34 (m, 2H), 3.29 (d, 1H, J = 13.2 Hz), 4.87 (dd, 1H, J = 7.8 Hz, J = 3.0 Hz), 7.26-7.32 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.3, 20.2, 23.8, 25.2, 26.2, 26.4, 26.9, 30.7, 32.1, 33.4, 38.5, 44.3, 44.5, 45.8, 49.1, 49.7, 53.7, 57.4, 80.0, 120.3, 127.8, 128.4, 130.0, 134.4, 167.6.

(2S)-2-Cyano-2-methyl-3-phenylpropanoic acid *(S)* **-4**

To a solution of KOH 10% in methanol (20 ml) was added *(2S)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-2-methyl-3-phenylpropanoate *(S)* **-3** (2.272 g, 4 mmol) and the reaction mixture was refluxed for 5 h. The resulting solution was cooled and the solvent evaporated. The residue was diluted in water (15 ml) and washed with ether. The aqueous layer was then acidified and extracted with ether. The organic layer was dried on $MgSO_4$ and concentration in vacuo yielded *(2S)*-2-cyano-2-methyl-3-phenylpropanoic acid *(S)* **-4** as a white solid in 93% yield.

Mp 84 °C (Lit [9] 88 °C); $[\alpha]_D$ = 27.2 (c = 2, in $CHCl_3$) [Lit.[9] $[\alpha]_D$ = 27.4 (c = 2.556 in $CHCl_3$)]; IR 2262, 1747, cm^{-1}; HRMS (FAB): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.64 (s, 3H), 3.06 (d, 1H, J = 13.5 Hz), 3.26 (d, 1H, J = 13.5 Hz), 7.26-7.34 (m, 5H), 10.25 (brs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.8, 43.2, 118.9, 128.0, 128.7, 130.0, 133.6, 174.1.

(2S)-2-Methoxycarbonylamino-2-methyl-3-phenylpropanonitrile *(S)* -5

Phosphorus pentachloride (625 mg, 3 mmol) was added to a solution of *(2S)*-2-cyano-2-methyl-3-phenylpropanoic acid *(S)* -4 (567 mg, 3 mmol) in dry ether (20 ml) and the reaction mixture was stirred at room temperature for 1 h. The ether and most of the phosphorus oxychloride was removed at reduced pressure. The oily residue was dissolved in toluene (20 ml) and the solvent and the residual phosphorus oxychloride distiled under *vacuo*. This operation was repeated to ensure complete removal of the phosporus oxychloride. The acid chloride was then cooled to room temperature and dissolved in dry acetone (6 ml). Then a solution of sodium azide (292 mg, 4.5 mmol) in water (2 ml) was added and stirring was continued for 1 h. Concentration in vacuo yielded a white solid which was extracted with toluene. The organic layer was dried on $MgSO_4$ and after filtration dry methanol (10 ml) was added. The solution was stirred at 80 °C for 2 h and the toluene was removed under reduced pressure. Purification of the residue by flash chromatography (eluent hexane/ether 1:2) afforded 569 mg of *(2S)*-2-methoxycarbonylamino-2-methyl-3-phenylpropanonitrile *(S)* -5 as a white solid (87% yield).

Mp 81 °C ; $[\alpha]_D$ = - 46.1 (c = 2 in $CHCl_3$) ; IR 3283, 2234, 1690, cm^{-1}; HRMS (EI): m/z = 218.1058 (M^+ calc for $C_{12}H_{14}N_2O_2$ 218.2056); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.60 (s, 3H), 3.14 (d, J = 1H, 15 Hz), 3.24 (d, 1H, J = 15 Hz), 3.69 (s, 3H), 4.88 (brs, 1H), 7.22-7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.2, 44.4, 51.0, 52.5, 120.2, 128.0, 128.7, 130.5, 133.2, 154.9.

(S)-α-Methylphenylalanine

(2S)-2-Methoxycarbonylamino-2-methyl-3-phenylpropanonitrile *(S)* -5 (436 mg, 2 mmol) was hydrolysed by refluxing for 2 h with 20% aqueous hydrochloric acid (30 ml). After filtration and extraction with ether the solution was evaporated under *vacuo*. The residue was dissolved in water and evaporated under reduced pressure to expel the excess hydrochloric acid. Then ethanol (6 ml) and propylene oxide (2 ml) were added and the mixture was refluxed for 30 min. After removal of the ethanol the white residue was dissolved in distiled water and eluted through a C18 reverse-phase sep-pak cartridge. Removal of water afforded 369 mg of *(S)*-α-methylphenylalanine (94% yield).

Mp >300 °C ; $[\alpha]_D$ = - 21.5 (c = 1 in H_2O) [Lit.[10] $[\alpha]_D$ = - 22 (c = 1 in H_2O)]; IR 3550-2500, 1654 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 1.41 (s, 3H), 2.83 (d, 1H, J = 14.5 Hz), 3.16 (d, 1H, J = 14.5 Hz), 7.10-7.26 (m, 5H). ^{13}C NMR (D_2O, 75 MHz) δ 22.7, 43.0, 62.5, 128.2, 129.3, 130.3, 134.5, 176.5.

(2S)-Methyl 2-carbamoyl-2-methyl-3-phenylpropanoate *(S)* -6

(2S)-2-Cyano-2-methyl-3-phenylpropanoic acid *(S)* -4 (567 mg, 3 mmol) was dissolved in 1N aqueous solution of sodium hydroxide (3.5 ml). To this stirred solution were added successively 30% hydrogen peroxide (10 ml) and 10% aqueous solution of sodium hydroxide (5 ml) and stirring was continued for another 12 h. The resulting mixture was acidified and extracted with ether. The organic layer was dried on $MgSO_4$ and after filtration diazomethane was added. The

solvent was removed under reduced pressure and the resulting product purified by flash chromatography (eluent ether) to afford 525 mg of *(2S)*-methyl 2-carbamoyl-2-methyl-3-phenylpropanoate *(S)* **-6** as a white solid (79% yield).

Mp 112 °C ; $[\alpha]_D$ = - 8.8 (c = 2 in $CHCl_3$) ; IR 3405, 1722, 1667, cm^{-1}; HRMS (EI): m/z = 221.1047 (M^+ calc for $C_{12}H_{15}NO_3$ 221.1051); ^1H NMR (DMSO-d_6, 300 MHz) δ 1.15 (s, 3H), 3.06 (d, J = 1H, 13.5 Hz), 3.11 (d, 1H, J = 13.5 Hz), 3.61 (s, 3H), 7.06-7.36 (m, 7H) 9.17 (brs, 1H). ^{13}C NMR (DMSO-d_6,, 75 MHz) δ 19.5, 40.7, 51.9, 54.6, 126.5, 128.0, 130.0, 136.8, 176.5, 172.8.

(2R)-Methyl 2-methoxycarbonylamino-2-methyl-3-phenylpropanoate *(R)* **-7**

To a solution of *(2S)*-methyl 2-carbamoyl-2-methyl-3-phenylpropanoate *(S)* **-6** (442 mg, 2 mmol) and $Hg(OAc)_2$ (765 mg, 2.4 mmol) in dry DMF (10 ml), dry methanol (1.92 g, 60 mmol) and a solution of NBS (463 mg, 2.6 mmol) in dry DMF (3 ml) were added at room temperature. The reaction was stirred for 12 h at room temperature and the resulting mixture was evaporated under vacuo. The solid residue was extracted with ether washed successively with water, 5% hydrochloric acid and saturated aqueous $NaHCO_3$ solution, the organic layer dried on $MgSO_4$, the solvent removed under reduced pressure and the resulting product purified by flash chromatography (eluent ether) to afford 491 mg of *(2R)*-methyl 2-methoxycarbonylamino-2-methyl-3-phenylpropanoate *(R)* **-7** (98% yield).

Mp oil ; $[\alpha]_D$ = - 24.5 (c = 2 in $CHCl_3$) ; IR 3351, 1726 cm^{-1}; HRMS (EI): m/z = 192.1023 (M^+-$COOCH_3$ calc for $C_{11}H_{14}NO_2$ 192.1024); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.60 (s, 3H), 3.15 (d, J = 1H, 13.5 Hz), 3.37 (d, 1H, J = 13.5 Hz), 3.66 (s, 3H), 3.73 (s, 3H), 5.36 (brs, 1H), 7.00-7.08 (m, 2H), 7.20-7.30 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.5, 41.9, 51.9, 52.6, 60.6, 126.9, 128.3, 129.8, 136.0, 155.3, 174.1.

(R)-α-Methylphenylalanine

(2R)-Methyl 2-methoxycarbonylamino-2-methyl-3-phenylpropanoate *(R)* **-7** (502 mg, 2 mmol) was hydrolysed by refluxing for 2 h with 20% aqueous hydrochloric acid (30 ml). After filtration and extraction with ether the solution was evaporated under *vacuo*. The residue was dissolved in water and evaporated under reduced pressure to expel the excess hydrochloric acid. Then ethanol (6 ml) and propylene oxide (2 ml) were added and the mixture was refluxed for 30 min. After removal of the ethanol the white residue was dissolved in distilled water and eluted through a C18 reverse-phase sep-pak cartridge. Removal of water afforded 369 mg of *(R)*-α-methylphenylalanine (94% yield).

Mp >300 °C ; $[\alpha]_D$ = 21 (c = 1 in H_2O) ; IR 3550-2500, 1654, cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 1.41 (s, 3H), 2.83 (d, 1H, J = 14.5 Hz), 3.16 (d, 1H, J = 14.5 Hz), 7.10-7.26 (m, 5H). ^{13}C NMR (D_2O, 75 MHz) δ 22.7, 43.0, 62.5, 128.2, 129.3, 130.3, 134.5, 176.5.

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