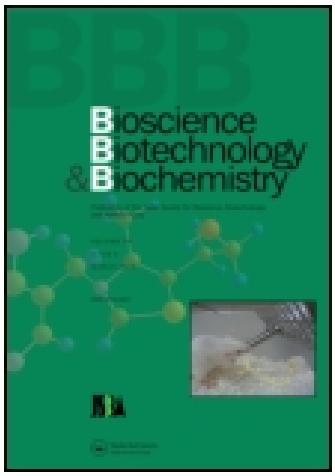

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A Facile Synthesis of (R)-3-Amino-4-phenylbutyric Acid from L-Aspartic Acid

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Note

A Facile Synthesis of (*R*)-3-Amino-4-phenylbutyric Acid from L-Aspartic Acid†

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A practical synthesis of (*R*)-3-amino-4-phenylbutyric acid 1, based on Friedel-Crafts acylation with the α-aminocarboxyl group of L-aspartic acid retaining its original α-carbon chirality, is described.

Key words: β-amino acid; L-aspartic acid; 4-phenyl-3-aminobutyric acid; Friedel–Crafts acylation; α-aminoketone

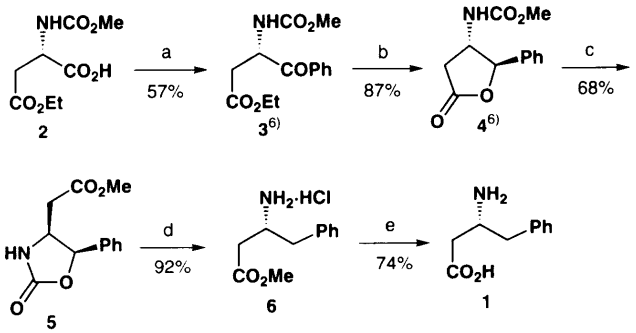
β-Amino acids have recently attracted strong attention on as useful building blocks for the synthesis of biologically active compounds such as peptides, β-lactams and anticancer agents.[1] (*R*)-3-Amino-4-phenylbutyric acid **1** is recognized as one of the most representative β-amino acids and has been utilized, for instance, as a component of antihypertensive angiotensin II analogs.[2] Earlier studies on the synthesis of **1** relied upon the homologation of phenylalanine by the Arndt–Eistert method.[2] Recent approaches[3] based on the stereospecific transformation of aspartic acid are especially of preparative value,[4] since aspartic acid inherently bears the β-amino acid fragment in its molecule and both enantiomers are readily available.[5] We have recently reported a versatile synthesis of γ-aryl-β-amino acids from L-homoserine lactone with aryllithiums used as an arylating reagent (M. Seki and K. Matsumoto, manuscript submitted to *Tetrahedron Lett.*). However, for the synthesis of (*R*)-3-amino-4-phenylbutyric acid **1** carrying an unsubstituted phenyl group, a method based on the Friedel–Crafts reaction, using benzene as a nucleophile, is considered to be more practical. We now report a short-step and high-yielding synthesis of (*R*)-3-amino-4-phenylbutyric acid **1** from L-aspartic acid.

The required phenylation of the α-aminocarboxyl group of an L-aspartic acid derivative was achieved by the use of our previously reported procedure (Scheme 1).[6] Thus, optically pure α-amino phenyl ketone **3** was synthesized by Friedel–Crafts acylation of benzene with the acid chloride derived from *N*-methoxycarbonyl-L-aspartatic acid β-ethyl ester **2**. The reduction of **3**, with dimethylphenylsilane used as a reductant, furnished *trans*-β-amino-γ-butyrolactone **4** stereoselectively.[6] Ring opening of the lactone **4** and subsequent cyclization to 2-oxazolidone acetate **5** were readily effected by treating **4** with sodium methoxide in methanol. This transformation made it easier to remove the protective group of the amino function of **4**. The relative configuration of **5** was confirmed by NOE experiments with ^{1}H-NMR spectroscopy: enhancement (14.6%) of the *C*-4 hydrogen signal was observed when the benzylic (*C*-5) hydrogen was irradiated. Simple hydrogenolysis of **5** with palladium on carbon as a catalyst afforded methyl (*R*)-3-amino-4-phenylbutyrate **6** in a high yield. β-Amino acid **1** was readily obtained by acid hydrolysis of **6** and a subsequent treatment with propylene oxide. The optical purity of product **6** was confirmed by converting into its α-methylbenzylureas (**7** and **8**) and comparing their ^{1}H-NMR spectra at 200 MHz (Scheme 2). The methyl group of the ester function of urea **8** derived from D,L-α-methylbenzylamine showed two singlets at 3.64 ppm and 3.61 ppm, while L-α-methylbenzylurea **7** showed just one singlet at 3.61 ppm assigned to the methyl signal. This clearly revealed that β-amino ester **6** was essentially enantiomerically pure (*e.e.* >95%). β-Amino acid **1** had an optical rotation of −8.6° (*c*, 0.86, H_2O) in good accordance with the reported value [$[\alpha]_D^{25}$ −8.5° (*c*, 0.20, H_2O)].[3a]

Experimental

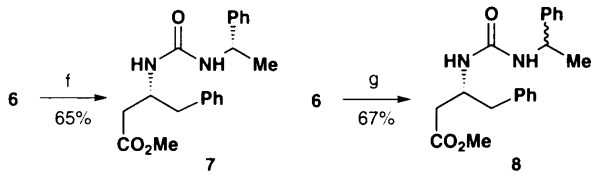
Melting point (mp) values were obtained by using Yamato melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 1640 infrared spectrophotometer and are reported as λ_{max} (cm^{-1}) values. ^{1}H-NMR data were recorded with a Bruker AC-200 (200 MHz) spectrometer and are reported as δ values. Mass spectra were taken with a Hitachi M-2000A spectrometer at an ionizing potential of 70eV. Microanalyses were performed with a Perkin-Elmer 2400 Series II CHNS/O analyzer, and flash chromatography was accomplihsed by using Kieselgel 60 (230–400 mesh, E. Merck).

(4S,5R)-4-Methoxycarbonylmethyl-5-phenyl-2-oxazolidone (**5**). To a solution of aminolactone **4**[6] (2.35 g, 10 mmol) in MeOH (10 ml) was added NaOMe (28% in MeOH; 1.93 g, 10 mmol) at 25 C, and the mixture was stirred at 25 C for 6 h. The mixture was evaporated *in vacuo*, and the



a: i) PCl_5, Et_2O; ii) $AlCl_3$, benzene. b: $PhMe_2SiH$, TFA. c: NaOMe, MeOH. d: H_2/Pd C, MeOH. e: i) 6N HCl; ii) propylene oxide, EtOH, H_2O.

Scheme 1.



f: i) L-α-methylbenzylamine, triphosgene, Et_3N; ii) **6**, Et_3N. g: i) DL-α-methylbenzylamine, triphosgene, Et_3N; ii) **6**, Et_3N.

Scheme 2.

† Synthesis of Amino Acids and Related Compounds. Part 45. For Part 44, see M. Seki and K. Matsumoto, *Synthesis*, in press.

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residue was dissolved in AcOEt, washed with water, dried over anhydrous $MgSO_4$ and evaporated. The residue was crystallized from AcOEt and hexane to afford 1.6 g (68.1%) of **5** as colorless crystals, mp 115–116 °C. IR (KBr) *v*: 1745, 1726, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.26–7.45 (m, 5H, Ph), 6.54 (s, 1H, NH), 5.77 (d, J = 8.1 Hz, 1H, C5-H), 4.43–4.55 (m, 1H, C4-H), 3.58 (s, 3H), 1.96–2.28 (m, methylene). ^{13}C-NMR ($CDCl_3$) δ: 171.2, 153.8, 134.4 (3s); 128.9, 128.8, 126.14 (3d); 79.6, 53.1 (2d); 51.9 (q); 36.6 (t). $[\alpha]_D^{25}$ −71.7 (*c* 0.95, MeOH). MS *m/z*: 235 (M^+). *Anal.* Found: C, 61.14; H, 5.78; N, 5.86%. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95%.

Methyl (R)-3-amino-4-phenylbutyrate hydrochloride (**6**). A mixture of **5** (4 g, 17 mmol), conc. HCl (2.8 ml) and 10% Pd–C (50% wet; 1.6 g) in MeOH was stirred under 1 atm of hydrogen for 4 h. The mixture was then filtered, and the filtrate was evaporated *in vacuo*. The resulting crystals were collected by adding acetone and Et_2O to afford 3.60 g (92.2%) of **6** as colorless crystals, mp 133–134 °C. IR (KBr) *v*: 2898, 1726, 1703 cm^{-1}. NMR (DMSO-d_6) δ: 8.51 (br. s, 3H, NH_3), 7.23–7.38 (m, 5H, phenyl), 3.60–3.80 (m, 1H, methine), 3.53 (s, 3H, Me), 3.10–3.20 and 2.54–2.90 (m, 4H, benzyl + methylene). ^{13}C-NMR (DMSO-d_6) δ: 170.0, 136.0 (2s); 129.4, 128.5, 126.9 (3d); 51.6 (q); 48.9 (d); 37.9, 35.8 (2t). SIMS *m/z*: 194 ($M^+ - HCl + 1$). $[\alpha]_D^{25}$ −9.2° (*c*, 1.5, MeOH). *Anal.* Found: C, 57.17; H, 7.09; N, 6.22%. Calcd. for $C_{11}H_{15}NO_2 \cdot HCl$: C, 57.52; H, 7.02; N, 6.10%.

General procedure for preparing the α-methylbenzylureas (**7** and **8**).

L-α-*Methylbenzylurea* (**7**): To a solution of triphosgene (64.5 mg, 0.218 mmol) in CH_2Cl_2 (1 ml) were added L-α-methylbenzylamine (52.7 mg, 0.435 mmol) and Et_3N in CH_2Cl_2 (1 ml) at −60 °C. The mixture was warmed to 25 °C and evaporated. To the residue were added CH_2Cl_2 (1 ml), **6** (100 mg, 0.435 mmol) and Et_3N (0.15 ml, 1.09 mmol), and the mixture was stirred at 25 °C for 30 min. The mixture was washed with water, dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica-gel column chromatography (hexane AcOEt = 3 : 1) to afford 96 mg (64.8%) of **7** as a colorless syrupy oil. IR (Nujol) *v*: 3328, 1739, 1629 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.12–7.37 (m, 10H, Ph), 4.90 (d, J = 8.8 Hz, 1H, NH), 4.71–4.76 (m, 2H, benzyl + NH), 4.19–4.36 (m, 1H, methine), 3.61 [s, 3H, Me (ester)], 2.72–2.95 (m, 2H, benzyl), 2.29–2.50 (m, 2H, methylene), 1.41 (d, J = 6.2 Hz, 3H, Me). SIMS *m/z*: 341 ($M^+ + 1$).

DL-α-*Methylbenzylurea* (**8**): This was obtained as a colorelss syrupy oil in a yield of 67.4%. IR (Nujol) *v*: 3330, 1737, 1632 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.01–7.38 (m, 10H, Ph), 4.76–5.00 (m, 1H, NH), 4.55–4.76 (m, 2H, benzyl + NH), 4.18–4.40 (m, 1H, methine), 3.64 and 3.61 [s, 3H, Me (ester)], 2.62–2.95 (m, 2H, benzyl), 2.30–2.55 (m, 2H, methylene), 1.33–1.44 (m, 3H, Me). SIMS *m/z*: 341 ($M^+ + 1$).

(*R*)-*3-Amino-4-phenylbutyric acid* (**1**). A mixture of **6** (200 mg, 0.87 mmol) and conc. HCl (1.5 ml) in water (1.5 ml) was refluxed for 4 h and then evaporated *in vacuo*. To the residue were added propylene oxide (1 ml), EtOH (2 ml) and water (0.6 ml), and the mixture was refluxed for 1 h. The mixture was evaporated *in vacuo*, and the resulting crystals were collected by adding acetone to afford 115 mg (74.0%) of **1** as colorless crystals, mp 222–225 °C (dec.). IR (Nujol) *v*: 2680, 1650 cm^{-1}. NMR (D_2O) δ: 7.31–7.49 (m, 5H, Ph), 3.69–3.83 (m, 1H, methine), 2.88–3.09 (m, 2H, benzyl), 2.38–2.63 (m, 2H, methylene). ^{13}C-NMR (D_2O) δ: 180.6, 138.5 (2s); 132.3, 131.9, 130.3, 53.5 (4d); 41.0, 40.9 (2t). SIMS *m/z*: 180 ($M^+ + 1$). $[\alpha]_D^{25}$ −8.6° (*c*, 0.72, H_2O) [lit. $[\alpha]_D^{25}$ −8.5° (*c*, 0.2, H_2O)[3a)]]. *Anal.* Found: C, 66.66; H, 7.28; N, 8.00%. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82%.

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