Notizen / Notes

Efficient EPC Synthesis of β-Aminobutanoic Acid

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A practical approach to enantiomerically pure (*R*)-3-aminobutanoic acid (**6**) from L-asparagine (**1**) is presented. The key step of the synthesis is the chemoselective reduction of the β-homoserine derivative **2**.

Chiral β-amino acids have attracted recent interest, which is due to their natural occurrence[1] as well as their value for β-lactam syntheses[2] and peptide backbone modifications[1]. However, the synthesis of enantiomerically pure β-amino acids is known to be difficult[3]. In our previous publications we have presented an efficient method for the preparation of enantiomerically pure β-amino acids of type **3**[4,5]. A key step of the synthesis is the reaction of the chiral building block **2** with lower-order organo cuprates. The β-homoserine derivative **2** can be readily derived from L-asparagine (**1**) in 59% overall yield with complete retention of the chiral center. As a complement to our recent studies we now report on the preparation of the naturally occurring (*R*)-3-aminobutanoic acid **6**[6,7] as the simplest chiral β-amino acid.

To obtain **6**, we again started from the *N,N*-dibenzyl-protected β-homoserine derivative **2**, which we tried to reduce chemoselectively by cleavage of the C–O bond. In fact, treatment of **2** with $LiBH_4$ in THF affords the amino nitrile **4**. Acidic hydrolysis of **4** yields the *N,N*-dibenzyl-protected β-amino acid **5**, which can be debenzylated by catalytic hydrogenolysis [$Pd(OH_2)$/C] to give the target compound **6** in 35% yield from **2**. Starting from D-asparagine, the *S*-configurated enantiomer may be prepared by use of the identical protocol. Alternatively, we envisaged to synthesize **6** via the dibenzyl-protected β-homoserine methyl ester **7**, which we derived from L-asparagine (**1**) following a reaction sequence which we have newly elaborated[5]. Since **7** is unstable due to lactonization under basic or acidic conditions, we planned to convert **7** into the thiocarbonyl imidazolide **8**, which should be reduced by radically induced deoxygenation[8]. However, treatment of **7** with thiocarbonyldiimidazole and subsequent reaction with Bu_3SnH in toluene at different temperatures did not afford **9**, although the intermediate **8** was proved spectroscopically[9].

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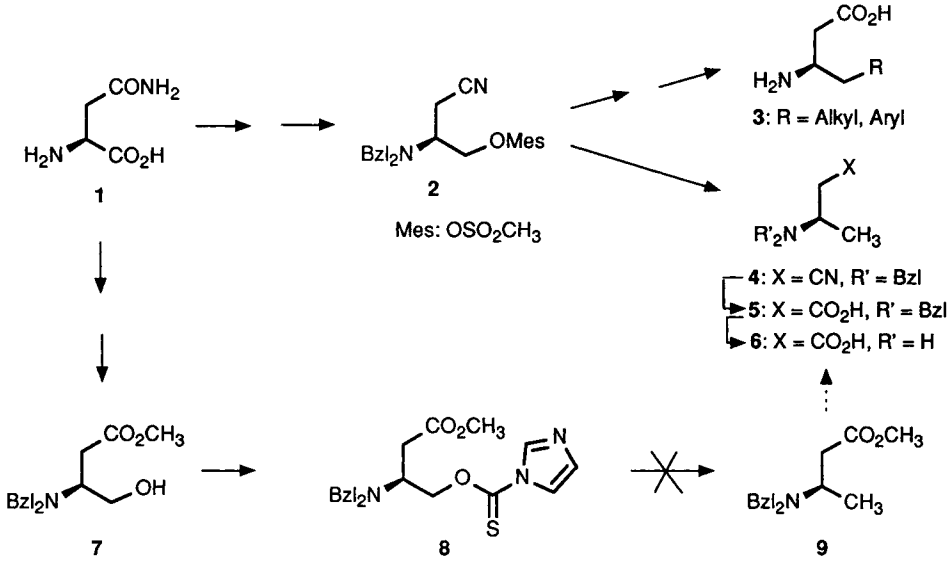
Experimental

Tetrahydrofuran (THF) was distilled from $LiAlH_4$ immediately before use. All liquid reagents were also purified by distillation. Unless otherwise noted, reactions were conducted under dry nitrogen. Evaporations of final product solutions were performed in vacuo with a rotatory evaporator. – Flash chromatography:



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230–400 mesh silica gel. – Melting points: Büchi melting point apparatus, values are uncorrected. – IR spectra: Perkin-Elmer 881. – Mass spectra: Varian CH7 instrument. – NMR spectra: Jeol 400 JNM-GX, 400 MHz, tetramethylsilane was used as an internal standard. – Elemental analyses: Heraeus CHN Rapid.

(R)-3-(Dibenzylamino)butanenitrile (**4**): To a mixture of **2** (528 mg, 2 mmol) in THF (30 ml) was added $LiBH_4$ (1 ml, 2 M in THF) at room temp. The reaction mixture was stirred at 50°C for 90 min, then MeOH (1 ml) and saturated aqueous $NaCO_3$ was added. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (petroleum ether/EtOAc, 4:1) to give 295 mg (52%) of **4** as a colorless solid, m.p. 29–30°C. – $[\alpha]_D^{23} = -3$ ($c = 1.0$ in $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3030, 2930, 2245, 1605 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.19 (d, J = 6.5 Hz, 3H, 4-H_3), 2.35 (dd, J = 16.9, 6.6 Hz, 1H, 2-H_a), 2.54 (dd, J = 16.9, 8.0 Hz, 1H, 2-H_b), 3.19–3.28 (m, 1H, 3-H), 3.52 (d, J = 13.9 Hz, 2H, NCH_2Ph), 3.67 (d, J = 13.9 Hz, 2H, NCH_2Ph), 7.24–7.42, m, 10H, Ar).

$C_{18}H_{20}N_2$ (264.4) Calcd. C 81.77 H 7.63 N 10.60
Found C 81.67 H 7.93 N 10.39
Mol. mass 264 (MS)

(R)-3-(Dibenzylamino)butanoic Acid (**5**): A solution of **4** (265 mg, 1 mmol) in concentrated aqueous HCl (15 ml) was stirred at 80°C for 3 h. Then the mixture was concentrated, basified with 2 N aqueous NaOH and extracted with Et_2O. The aqueous layer was adjusted to pH 6 by addition of 10% aqueous citric acid, then extracted with Et_2O and the organic layer dried ($MgSO_4$) and evaporated to dryness to give 260 mg (91%) of pure **5** as a colorless solid; m.p. 25–28°C; $[\alpha]_D^{23} = -40$ ($c = 2.0$ in $CHCl_3$). – IR (NaCl): $\tilde{\nu}$ = 3300–2500, 3030, 2980, 1715, 1605 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.19 (t, J = 6.5 Hz, 3H, 4-H_3), 2.35 (dd, J = 17.6, 3.7 Hz, 1H, 2-H_a), 2.61 (dd, J = 17.6, 12.5 Hz, 1H, 2-H_b), 3.31–3.40 (m, 1H, 3-H), 3.44 (d, J = 13.2 Hz, 2H, NCH_2Ph), 4.03 (d, J = 13.2 Hz, 2H, NCH_2Ph), 7.26–7.42 (m, 10H, Ar).

$C_{18}H_{21}NO_2$ (283.4) Calcd. C 76.29 H 7.47 N 4.94
Found C 76.00 H 7.71 N 4.69
Mol. mass 283 (MS)

(R)-3-Aminobutanoic acid (**6**): A mixture of **5** (280 mg, 1 mmol) and 20% $Pd(OH)_2/C$ (140 mg) in MeOH (10 ml) was stirred in a flask connected to a balloon filled with hydrogen for 3 h at room temp. The mixture was filtered through Celite and the filtrate was evaporated to give 97 mg (94%) of pure **6** as a colorless solid; m.p. 216–218°C (ref.[7]: m.p. 218–219°C); $[\alpha]_D^{23} = -39$ ($c = 0.4$ in H_2O) (ref.[7]: $[\alpha]_D = -39.5$ ($c = 0.56$ in H_2O)). – ^1H NMR (CD_3OD): δ = 1.30 (t, J = 6.6 Hz, 3H, 4-H_3), 2.32 (dd, J = 16.8, 8.8 Hz, 1H, 2-H_a), 2.47 (dd, J = 16.8, 4.4 Hz, 1H, 2-H_b), 3.42–3.51 (m, 1H, 3-H).

$C_4H_9NO_2$ (93.1) Mol. mass 93 (MS)

CAS Registry Numbers

2: 131270-10-5 / **4**: 132540-66-0 / **5**: 132540-67-1 / **6**: 3775-73-3 / **6** (enant.): 3775-72-2 / **7**: 132540-68-2 / **8**: 132540-69-3 / D-asparagine: 2058-58-4

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[9] **8**: IR (NaCl): 3030, 3000, 1740, 1620 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 2.47 (dd, J = 14.5, 8.0 Hz, 1H, 2-H_a), 2.82 (dd, J = 14.5, 5.8 Hz, 1H, 2-H_b), 3.62 (d, J = 13.7 Hz, 2H, NCH_2Ph), 3.73 (d, J = 13.7 Hz, 2H, NCH_2Ph), 3.70–3.77 (m, 1H, 3-H), 4.64 (dd, J = 11.7, 5.3 Hz, 1H, 4-H_a), 4.84 (dd, J = 11.7, 7.3 Hz, 1H, 4-H_b), 7.04 (dd, J = 1.6, 0.8 Hz, 1H, NC*H*CHN), 7.22–7.32 (m, 1H, Ar), 7.56–7.57 (m, 1H, NCHC*H*N), 8.27 (s, 1H, NCHN).

[3/91]