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GENERAL SYNTHESIS OF ENANTIOMERICALLY PURE β-AMINO ACIDS

Peter Gmeiner

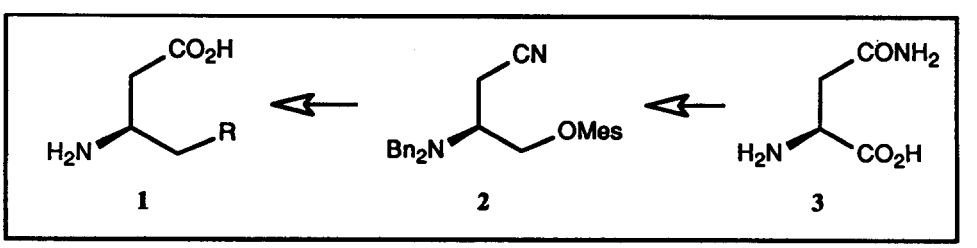
Institut für Pharmazie und Lebensmittelchemie der Ludwig-Maximilians-Universität, Sophienstraße 10, 8000 München 2, BRD

Summary: An efficient method for the synthesis of chiral β-amino acids starting from (S)-asparagine is shown. The key intermediate is an activated β-homoserine equivalent, which can be reacted with organocuprates to yield β-N,N-dibenzylamino nitrile derivatives. After deprotection the β-amino acids are obtained enantiomerically pure in high overall yield.

In recent years EPC syntheses of the biologically important class of α-amino acids have attracted considerable attention.[1] The isomeric β-amino acids are valuable intermediates in the field of β-lactam synthesis[2] and effective tools for peptide modifications.[3] Some representatives occur naturally.[4] However the preparation of chiral β-amino acids is known to be tricky and derivatives, being not homologous to the natural α-amino acids are scarcely assessable enantiomerically pure.[5] As a consequence, the development of new methods, providing an expedient approach to β-amino acids continues an active area of investigation. Very recent advances featured a synthesis of optically pure 3-aminobutanoic acid, obtained from methyl crotonate and (S)-phenethylamine using HPLC separation of the diastereomeric intermediates.[6] An asymmetric synthesis of α,α-dimethyl derivatives was also reported.[7]

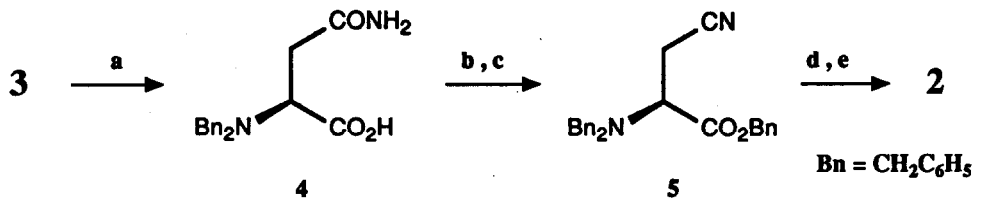
In this communication we present a general synthetic methodology for the preparation of β-amino acids **1** starting from L-asparagine **3** via the activated β-homoserine equivalent **2** (Scheme 1). The key intermediate **2**, which is derived efficiently from **1** by standard methods, can be readily reacted with organocuprates to yield **1** after deprotection.

SCHEME 1



Previously we demonstrated, that asparagine is a valuable educt for the synthesis of chiral aminotetrahydroindolizidines.[8] For this project asparagine was selected as a suitable educt because a) the molecule bears the chiral β-amino acid unit already, b)it is cheap and c) the compound is available optically pure in both configurations. For amine protection the dibenzyl group was chosen. It was supposed to be stable towards hydride reduction and it should prevent from ß-elimination during the organocuprate displacement reaction, which we anticipated to be problematic when using carbamate or amide protection. After introduction of the dibenzyl group to yield **4** [8] the carboxylic acid was esterified with benzylbromide / triethylamine, followed by dehydration of the amide function with tosylchloride / pyridine to afford **5** (α_D^{23} -91°, c=1.05, $CHCl_3$). The dehydration was an important step, because the nitrile allowed selective reduction of the α-ester group and and it was stable towards nucleophilic or electrophilic ring closure side reactions at the same time. The reduction of **5** to the primary alcohol with $LiAlH_4$ in THF at dry ice temperature proceeded chemoselectively and almost quantitatively.[9] Subsequent treatment with mesylchloride / triethylamine afforded the β-homoserine derivative **2** (α_D^{23} +5.5°, c=1.03, $CHCl_3$) in 61 % overall yield from L-asparagine **1** (Scheme 2).

SCHEME 2



a: PhCHO, $NaCNBH_3$, H_2O (83%)[8]; b: BnBr, Et_3N, THF, 2 h, reflux (85%); c) TosCl, Pyridine, CH_2Cl_2, 16 h, RT (92%); d) $LiAlH_4$, THF, 6 h, -78° (94%); e: MesCl, Et_3N, THF, 1 h, RT (97%).

To demonstrate the versatility of our method, we proposed to synthesize (R)-β-aminopropanoic acid (**1a**)[10] (**1a** was identified in hot water extracts of the Murchison meteorite),[11] (R)-β-aminooctanoic acid (**1b**) and (R)-4-phenyl-3-amino butanoic acid [12] as an aromatic representative.

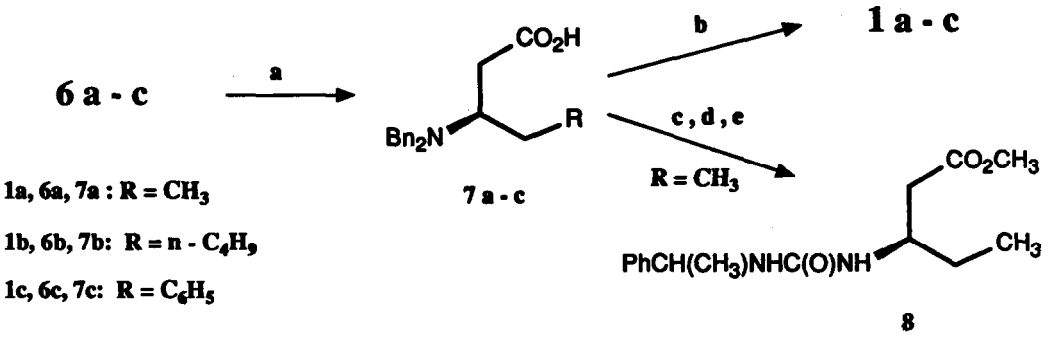
SCHEME 3

6a R = CH_3 (65 %)
6b R = n - C_4H_9 (72 %)
6c R = C_6H_5 (48 %)

2 was reacted with Me_2CuLi, Bu_2CuLi and Ph_2CuLi to yield the β-N,N-dibenzylamino nitrile derivatives **6a** (α_D^{23} +42°, c=1.05, $CHCl_3$), **6b** (α_D^{23} +19°, c=1.0, $CHCl_3$) and **6c** (α_D^{23} +25°, c=1.05, $CHCl_3$) respectively (Scheme 3). The reactions had to be carried out in diethylether. Changing the solvent to tetrahydrofuran resulted in a dramatic decrease in the yield of the displacement reactions.

Acidic hydrolysis of the nitriles **6a-c** [13] afforded the (R)-N,N-dibenzyl-β-amino acids **7a-c** [14], which could be deprotected readily by catalytic hydrogenolysis to yield the target compounds **1a-c** (Scheme 4).

SCHEME 4



a: $HCl_{conc.}$, 3 h, reflux, (90 %); b: $Pd(OH)_2/C$-H_2, MeOH, 3 h, RT (90-95 %); c: MeOH/ HCl, 3 h, RT (76 %); d: $Pd(OH)_2/C$-H_2, PrOH, 3 h, RT (94 %); e: (R)-1-phenylethylisocyanate, THF, 1h, 0°.

The optical integrity of the method was established by esterifying **7a** followed by hydrogenolysis and subsequent derivatizing with optically pure (R)-1-phenylethylisocyanate to yield **8**. Examination of the ^{1}H-NMR spectra (400 MHz), calibrated by appropriate doping experiments, revealed the synthetic material to be isomerically pure (de > 99 %).

General Procedure:

To a stirred suspension of 1.14 g (6 mmol) CuI in Et_2O (20 ml) was added 9.6 mmol of the organolithium reagent at -60°. After 30 min 300 mg (1.08 mmol) of **2** was added and the reaction mixture was allowed to warm to -20° during 2 h. It was then quenched with aqueous NH_4Cl, the org. layer was dried, evaporated and purified by flash chromatography (petrolether-EtOAc 9:1) to yield pure **6**.

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13. **7a**: α_D^{23} -29° (c=1.03, $CHCl_3$); **7b**: α_D^{23} -37° (c=1.03, $CHCl_3$); **7c**: α_D^{23} -23° (c=1.07,$CHCl_3$).
14. **1a**: α_D^{23} -37° (c=0.7, H_2O); **1b**: α_D^{23} -22° (c=0.5, H_2O); **1c**: α_D^{23} -8.5° (c=0.2, H_2O).

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