A Practical Ex-Chiral-Pool Synthesis of β-Proline and Homo-β-Proline

Christoph Thomas, Florian Orecher, Peter Gmeiner*
Institut für Pharmazie und Lebensmittelchemie der Friedrich-Alexander-Universität Erlangen-Nürnberg, Schuhstraße 19, D-91052 Erlangen, Germany
Fax +49(9131)852585; E-mail: gmeiner@pharmazie.uni-erlangen.de
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Dedicated to Prof. Dr. H.-D. Stachel on the occasion of his 70th birthday

Abstract: Starting from aspartic acid an efficient synthesis of enantiomerically pure β-proline and homo-β-proline is described. The key step of the synthesis includes formation of the 1,4-bis-electrophile 6, followed by rearrangement via the aziridinium intermediate 7 and ring closure to give the pyrrolidinium salt 9a which can serve as a common precursor for both target compounds.

Key words: β-proline, homo-β-proline, aziridinium intermediate, aspartic acid, rearrangement

β-Amino acids attract particular interest for the construction of bioactive compounds including β-lactams, peptidomimetics, and anti-tumor agents (e.g. taxol). It has been shown that pyrrolidine-3-carboxylic acid (β-proline) is a potent agonist at the strychnine-sensitive glycine receptor, serves as a building block for the preparation of novel inhibitors of bacterial DNA gyrase and forms the central moiety of a conformationally restricted, highly potent fibrinogen receptor antagonist. In addition, β-proline and pyrrolidine-3-acetic acid (homo-β-proline) both can serve as a conformationally restricted γ-amino acid and bind to the γ-amino butyric acid (GABA) transport system in the brain. On the other hand, it has been demonstrated that β-peptides (peptides derived from β-amino acids), as well as cyclo-β-peptides, adopt remarkably compact and well-ordered conformations. Since proline plays a special role in directing the secondary structure of peptides the investigation of β-proline containing β-peptides should be an interesting field.

We have recently developed methodology for regioselective transformations of (S)-aspartic acid (Asp) yielding the enantiomerically pure 1,2- and 1,3-amino alcohols 2 and 3, respectively (Scheme 1). Depending on the order of activation and O-protection of the butanediol 1 and subsequent displacement reactions of the intermediates the target molecules could be synthesized selectively. Due to aziridinium intermediates, the route to the 1,3-amino alcohols included a twofold migration of the dibenzylamino group. Furthermore, we found that regioselective functionalization of a 1,4-bis-electrophile, obtained from the diol 1 and an excess of methanesulfonyl chloride (MesCl), is possible when the activating anchimeric participation of the dibenzylamino group overrides the protecting steric effect. Employing this strategy a general synthesis of open chain β-amino acids 4 could be elaborated. Furthermore, it was observed that the bis-electrophilic intermediate shows the tendency to form a pyrrolidinium salt through migration of the dibenzylamino group giving access to β-proline derivatives 5.

As an extension to these studies we herein report an application of these reactions for the chirospecific preparation of both enantiomers of β-proline and homo-β-proline in detail.

For the preparation of the key intermediate 1 a two-step procedure which we have described earlier was applied under slightly modified reaction conditions. Thus, perbenzylolation of aspartic acid and subsequent reduction by LiAlH₄ afforded the diol 1 in 84% overall yield (Scheme 2).

Our synthetic route included the activation of both alcohol functions of 1 which should be followed by rearrangement of the dibenzylamino group and cyclization. After careful hydrogenolysis the pyrrolidine 10a was planned to serve as a common precursor for (S)-β-proline (12b) and (R)-homo-β-proline (15e). Depending on the configuration of aspartic acid the method should give access to the target molecules in both enantiomeric forms.

In practice, treatment of the diol 1 with an excess of MesCl and Et₃N gave the dimesylate 6 which could be characterized in solution by immediately performed 1H NMR spectroscopy. In order to obtain the projected pyr-
1. K₂CO₃, BnBr, H₂O, 100°C, 3h  
Asp  
2. LiAlH₄, THF, -10°C - r.t., 15h  
97%

Et₃N, MesCl, THF, -25°C, 1.5h  
B~N(OMes)x(-NBn₂)SbX= CI  
H₂, Pd(OH₂)₂C, EtOH, 20 min  
99% from 1

Scheme 2

rolidinium salt 9a in high yield it was important to purify 6 by low-temperature flash chromatography. Subsequent rearrangement and cyclization afforded 9a via the intermediates 7 and 8a in quantitative yield. If the temperature was raised before or during the separation the chlorides 8b and 9b were formed by byproducts. Furthermore, the highly polar pyrrolidinium salt 9a was built before or during the chromatographic step resulting in an obstruction of the column. Employing Pearlman’s catalyst a selective hydrogenolytic monodebenzylation of 9a or 9b could be performed to give 10a (in 99% yield, based on 1) or 10b, respectively.

The preparation of β-proline is outlined in Scheme 3. Displacement reaction of the mesylate 10a in the presence of NaCN/But₄NCN resulted in the formation of the nitrile 11 in 93% yield. Subsequent acidic hydrolysis gave N-benzyl-β-proline 12a as the hydrochloride salt. For the isolation of the free amino acid transformation of the hydrochloride by ion-exchange chromatography (Amberlite IRA 400) or addition of 1 equivalent of Ba(OH)₂ followed by chromatography on Amberlite XAD 2 could be applied. Removal of the benzyl group was accomplished under hydrogenolytic conditions [H₂, Pd(OH)₂/C, MeOH] to give the pure β-proline 12b. The β-proline ester 13a was prepared directly from crude hydrochloride 12a by treatment with SOCl₂/MeOH at -60°C and subsequent warming to room temperature. Benzyl protection by cyclodehydration resulted in the formation of the β-amino ester 13b. The enantiomeric integrity of the synthesis was established by derivatization of 13b. Thus, coupling of the amino ester 13b with (S)-1-phenylethyl isocyanate gave the urea 13c. Subsequent ¹³C NMR studies, including doping experiments with the diastereomer obtained by reaction of 13b with (R)-1-phenylethyl isocyanate, proved the synthetic material to be isomerically pure.

For the preparation of the (R)-homo-β-proline derivatives the mesylate 10a was reacted with diethyl malonate in the presence of CsF (which promotes S_N2 reactions of mesylates) to afford the diester 14a in 58% yield (Scheme 4). Mild acidic hydrolysis of 14a gave 14b which could be characterized by ¹H NMR spectroscopy. Subsequent decarboxylation was accomplished to afford the crude amino acid 15b as the hydrochloride salt. For purification of 15b the most effective way was esterification, followed by flash chromatography, mild hydrolysis, and chromatography on Amberlite XAD 2. Hydrogenolytic debenzylation of 15b yielded (R)-homo-β-proline 15c. Optical purity studies were performed by the coupling of 15b with (S)-alanine methyl ester. The isomeric purity of the resulting dipeptide 16 was >95%, as determined by ¹H NMR studies, including doping experiments with the diastereomer obtained by reaction of 15b with (R)-alanine methyl ester.

Diethylmalonate, CsF

Diethylmalonate, CsF  
DMSO, 80°C, 12h  
58%  
10a  
HClaq, 45°C, 24h  
14a  
93%  
11

Scheme 3

Under the conditions described above (R)-β-proline (ent-12b) and (S)-homo-β-proline (ent-15c) were synthesized from (R)-aspartic acid.
THF was distilled from Na, MeOH from Mg, EtOH from Ca, and EtOAc from P₂O₅ in all cases immediately before use. All liquid reagents were purified by distillation. Unless otherwise noted reactions were performed under dry argon. Evaporations of product solutions were done in vacuo with a rotary evaporator. Flash chromatography was carried out with 230–400 mesh silica gel (Merck Kieselgel 60). Mps: Büchi melting point apparatus. IR: Perkin–Elmer 1420 spectrophotometer. MS: Hewlett Packard 5989A. NMR: Bruker AM-400, Jeol JNM-GX 400 at 400 MHz, Bruker AM-360 at 360 MHz. Bruker AC-200 at 200 MHz, unless otherwise noted spectra were measured as CDC₁₇ solutions. Elemental analyses: Heraeus CHN Rapid, Vario EL instruments. Optical rotations: Perkin–Elmer 241, Zeiss 83204 polarimeters. Light petroleum used had a bp of 40–60°C.

(2S)-2-(Dibenzyloxymethyl)buteno-1,4-diol (1): To a solution of (S)-aspartic acid (50.0 g, 376 mmol) and KH₂PO₄ (300 g, 2.14 mol) in water (400 mL) at 100°C was added slowly over 1 h benzy1 bromide (300 mL, 2.52 mol). After refluxing for 2 h, the mixture was concentrated and the residue was purified by flash chromatography (light petroleum/EtOAc 1:1 to 1:4) to give 1 (89.88 g, 97%). Analytical data were in agreement with those previously reported.¹⁻³

A solution of (S)-N,N-dibenzyloxymethyl aspartic acid dibenzyl ester (160.1 g, 306 mmol) in THF (120 mL) was slowly added to a stirred suspension of LiAlH₄ (20.1 mL, 145 mmol) in THF (0.096 mL, 0.69 mmol) at 0°C. After stirring for 1.5 h the mixture was cooled to 0°C and then sat. NaHC0₃ (60°CI40:60:1) was added. After stirring for an additional 1 h at 0°C and 1°C for 1 h at r.t. Then sat. NaHC0₃ was added slowly until the color of the suspension changed from light grey to white, followed by addition of Et₂O (100 mL). The mixture was filtered and the residue washed with Et₂O (2 x 250 mL). The organic layer was evaporated (60°C/10⁻³ mbar) and the residue was purified by flash chromatography (light petroleum/EtOAc 1:1 to 1:4) to give 1 (89.88 g, 97%). Analytical data were in agreement with those previously reported.¹⁻³

Ent-1 was prepared under the same reaction conditions starting from (R)-aspartic acid.

(2S)-2-(Dibenzyloxymethyl)-1,4-bis(mesyloxy)butane (6): MesCl (0.045 mL, 0.58 mmol) was added to a solution of 1 (0.0664 g, 0.23 mmol) in THF-d₆ (1.5 mL) and Et₃N (0.096 mL, 0.69 mmol) at −20°C. After stirring for 20 min the mixture was filtered and NMR spectroscopy (¹H NMR, H–H COSY) was immediately performed at −20°C.

¹H NMR (400 MHz): δ = 1.81–1.86 (m, 1H, H3, 2.89–2.93 (m, 1H, H2), 3.07–3.19 (m, 1H, H2), 3.10 (s, 3H, CH₃), 3.63 (d, J = 13.4 Hz, 2H, NCH₂Ph), 3.83 (d, J = 13.4 Hz, 2H, NCH₂Ph), 4.19–4.27 (m, 1H, H4), 4.32–4.36 (m, 1H, H4), 4.34 (dd, J = 10.4, 5.2 Hz, 1H, H1), 4.46 (dd, J = 10.4, 6.0 Hz, 1H, H1), 7.08–7.30 (m, 10H, H-arom).

(3R)-1-Benzyl-3-mesyloxypropyridoxine (10a): Using ent-1 (10.00 g, 35.0 mmol) as starting material, ent-9b was prepared as previously described for 9a, except that activation was done at −3°C and the mixture was stirred for an additional 1 h at −3°C. The crude mixture of products (9a and 9b) was debenzylated as described for 10a. Flash chromatographic purification gave ent-10b (0.0652 g, 1.0%) besides ent-10a (1.4029 g, 15%).

Analytical data were in agreement with those previously reported.¹⁻³

(3S)-1-Benzyl-3-chloropyridoxine (10b): A stirred suspension of ent-1 (1.24 g, 4.86 mmol), NaCN (1.38 g, 28.1 mmol) and tetrabutylammonium cyanide (1.28 g, 4.76 mmol) in DMSO (5 mL) was heated (60–65°C) for 60 h. Then, sat. NaHC0₃ (4 mL) and water (10 mL) were added. After extraction with Et₂O (4 x 10 mL) the organic layer was dried (MgSO₄), evaporated, and the residue was purified by flash chromatography (light petroleum/EtOAc 1:100:1) to give 11 (0.842 g, 93%) as a colorless oil.
Methyl (35)-Pyrrolidine-3-carboxylate (13b):
A solution of 13a (0.259 g, 1.18 mmol) in MeOH (5 mL) was hydrogenated (16 h, 1013 mbar H2) at r.t., using 20% Pd(OH)2/C (0.032 g) as a catalyst. The mixture was filtered (Celite) and evaporated to give pure 13b (0.1114 g, 75%) as a colorless, volatile oil; [α]D 23 +7.2 (c = 1.0, CHCl3).

1H NMR (400 MHz): δ = 1.92–2.09 (m, 2H, H4), 2.26 (s, 1H, NH), 2.84–3.00 (m, 2H), 3.05–3.16 (m, 3H), 3.69 (s, 3H, OCH3).
IR (NaCl): ν = 3056, 1732, 1634, 1204, 1172 cm⁻¹.
CI-MS: m/z = 130 (M + 1).

C12H14N2O2: calcd: C 75.88 H 7.58 N 18.62; found: C 75.79 H 7.44 N 18.58.

Determination of the Enantiomeric Purity of 13b:
(5)-1-Phenylpyrrolidin-3-ylmalonate (14a):
A stirred suspension of 10a (5.60 g, 21.9 mmol), CsF (10.0 g, 65.8 mmol) and diethyl malonate (10.0 mmol, 65.8 mmol) in DMSO (15 mL) was heated to 80°C for 12 h. Then water (75 mL) was added and the solution was washed with sat. NaHCO3. The solution was extracted with Et2O (4 x 85 mL), the organic layer was dried (MgSO4), evaporated, and the residue was purified by flash chromatography (light petroleum/EtOAc 7:3 to 1) to give 14a (4.05 g, 58%) as a colorless oil.

Methyl (35)-Pyrrolidine-3-carboxylate (13a):
A solution of 11 (1.684 g, 9.041 mmol) in 37% HCl (15 mL) was refluxed for 0.5 h, lyophilized and dissolved in MeOH (20 mL). The stirred mixture was cooled to -50°C, and SOCl2 (0.73 mmol, 9.99 mL) was added. After addition of HCl (3 x 60 mL) the organic layer was dried (MgSO4), evaporated, and the residue was purified by flash chromatography (CH2Cl2/MeOH 1:30 to 95:5) to give 13a (1.950 g, 99%) as a colorless oil.

(35)-1-Benzylpyrrolidine-3-carboxylic Acid (12a):
A solution of 11 (1.445 g, 7.76 mmol) in 37% HCl (15 mL) was diluted for 0.5 h, lyophilized and resuspended in water. After second lyophilization sat. Ba(OH)2 (30.0 mL) was added. The mixture was filtered (Celite), and the filtrate lyophilized. The residue was purified by column chromatography (XAD 2, H2O/MeOH 1:0 to 1:1) to give 12a (1.391 g, 87%) as an amorphous powder; mp 102–104°C.

Ent-12a was prepared under the same reaction conditions starting from ent-11.

12a: [α]D 23 +18.6 (c = 3.0, CHCl3); ent-12a: [α]D 23 -17.9 (c = 1.0, CHCl3).

Determination of the Enantiomeric Purity of 13b:
(5)-1-Phenylpyrrolidin-3-ylmalonate (14a):
A stirred suspension of 10a (5.60 g, 21.9 mmol), CsF (10.0 g, 65.8 mmol) and diethyl malonate (10.0 mmol, 65.8 mmol) in DMSO (15 mL) was heated to 80°C for 12 h. Then water (75 mL) was added and the solution was washed with sat. NaHCO3. The solution was extracted with Et2O (4 x 85 mL), the organic layer was dried (MgSO4), evaporated, and the residue was purified by flash chromatography (light petroleum/EtOAc 7:3 to 1) to give 14a (4.05 g, 58%) as a colorless oil.

Ent-14a was prepared under the same reaction conditions starting from ent-10a.

14a: [α]D 23 +3.8 (c = 10, CHCl3); ent-14a: [α]D 23 -1.8 (c = 5.0, CHCl3).

Methyl (3R)-2-(1-Benzylpyrrolidin-3-yl)malonate (15a):
A stirred mixture of 13a (0.527 g, 1.65 mmol) in 4 M HCl (0.20 M) was heated to 45°C for 24 h. Subsequent lyophilization of the mixture gave crude 14b, which was directly used for the next step. Thus, 14b was dissolved in water (2 mL) and the water was distilled off over 6 h at 110°C. The residue was again dissolved in water (2 mL), the previous procedure repeated (12 h, 110°C) and the residue dried (r.t./103 mbar) to give crude 15b as the hydrochloride salt. Crude 15b was dissolved in EtOH (4 mL), cooled to -60°C and SOCl2 (0.189 mL, 2.56 mmol) was added. Then, the mixture was stirred at -60°C for 2 h and evaporated. The residue was dissolved in water (8 mL) and the solution was washed with Et2O (2 x 8 mL). Then the aqueous
layer was adjusted to pH = 11 with K₂CO₃, extracted with CHCl₃ (4 x 4 mL) and the organic layer was dried (MgSO₄). The residue was evaporated and purified by flash chromatography (light petroleum/EtOAc/Et₂NMe 50:15:1 to 7:3:0) to give Ent-1Sa (0.341 g, 84%) as a colorless oil.

Ent-1Sa was prepared under the same reaction conditions starting from less oil.

2.12 (dd, J = 7.5 Hz, 1H, H₂), 2.32 (d, J = 7.2 Hz, 2H, CH₂COO), 2.45 (ddd, J = 8.7, 9.1, 6.1 Hz, 1H, H₃), 2.46-2.57 (m, 2H, H₅, H₆), 2.74 (dd, J = 9.3, 7.5 Hz, 1H, H₂), 3.51 (d, J = 12.6 Hz, 1H, NCH₂Ph), 3.04 (ddd, J = 16.2, 7.5 Hz, 1H, H₂), 3.51 (d, J = 12.6 Hz, 1H, NCH₂Ph), 4.04 (q, J = 7.1 Hz, 2H, OCH₂CH₂), 7.14-7.26 (m, 5H, H-arom).

IR (NaCl): ν = 3090, 3070, 3030, 2960, 2930, 2880, 2795, 1735, 1605, 1545, 1495, 1480, 1455, 745, 700 cm⁻¹.

CI-MS: m/z = 247 (M⁺).

HRMS: m/z C₁₅H₂₁NO₂: calcd: 247.1572, found: 247.1568.

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Determinant of the Enantiomeric Purity of 15b:
A stirred solution of 15b (0.0472 g, 0.215 mmol) and N-methylmorpholine (NMM) (0.0237 mL, 0.215 mmol) in THF (3 mL) was cooled to −15°C and isobutyl chloroformate (0.029 mL, 0.23 mmol) was added. After 1 min, a solution of (S)-alanine hydrochloride (0.033 g, 0.24 mmol) and NMM (0.026 mL, 0.24 mmol) in DMF (1 mL) was added. After 5 min the mixture was warmed to 5°C, stirred for 2 h, filtered and evaporated (r.t./10⁻³ mbar). The residue was dissolved in anhyd EtOAc, filtered (Celite) and evaporated to give the dipeptide 16 (0.0246 g, 38%). Coupling was also carried out with (R)-alanine hydrochloride to give the appropriate (2'R)-diastereomer.

Diagnostic signals: ¹H NMR (400 MHz): 16. δ = 3.73; (2'R)-diastereomer: δ = 3.72.

(1) For examples, see:


(4) For reviews on the synthesis of nonracemic β-amino acids, see:


(b) Hintermann, T.; Seebach, D. Synlett 1997, 437.

(c) Gmeiner, P.; Kärtner, A. Synthesis 1995, 83.