Enantioselective Synthesis of 2,3-Diamino Acids by the Bislactim Ether Method

Wolfgang Hartwig, Joachim Mittendorf *
Bayer AG, Chemisches Wissenschaftliches Labor Pharma, Postfach 101 709, D-5600 Wuppertal 1, Germany

Dedicated to Professor Karl-Heinz Büchel on the occasion of his 60th birthday

A method is described for the asymmetric synthesis of both enantiomers of 2-alkyl-substituted 2,3-diaminopropionic acids with different protecting groups using the Schöllkopf–Hartwig bislactim ether method, starting from 2-alkyl-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazines.

As building blocks for peptide drugs we needed optical pure 2-alkyl-substituted (2R)- and (2S)-2,3-diamino acids with different protecting groups which can be selectively removed, allowing the incorporation into peptide chains via either the 2- or the 3-amino function. We describe here a method for the asymmetric synthesis of 2-alkyl-2,3-diaminopropionic acids starting from the commercially available bislactim ethers of cyclo-(L- or D-Val-Ala) and cyclo-(L- or D-Val-Gly). 1,2 The bislactim ethers 1 (or ent-1; 2-alkyl-2,5-dihydro-5-isopropyl-3,6-dimethoxypyrazines) 3 are lithiated with butyllithium to give the lithioazaenolates 2, which react with dibromomethane to yield the bromomethyl compounds 3 with a high diastereomeric excess (de) (3a: de > 95%, 3b: de 93%, 3c: de 84%). 3,4 After column chromatography the bislactim ethers 3 are obtained in satisfactory chemical yield (62–79%) and with a de of > 95% (only one diastereomer is detectable in the 1H-NMR spectrum and by HPLC).

Under the influence of strongly basic nucleophiles, e.g., potassium hydroxide, the bromomethyl bislactim ethers 3 undergo ring expansion to 1,4-diazepines. 5 However, nucleophilic substitution of bromide is accomplished with less basic sodium azide in dimethyl sulfoxide at 80°C in almost quantitative yield. The resulting azides 4 are reduced with triphenylphosphine/water 6 to the corresponding amines which are converted without isolation to the benzoylcarbonyl(Z) derivatives 5.

Hydrolysis of bislactim ether 5a, with two equivalents of 0.1 N hydrochloric acid at r.t. and treatment of the intermediate diamino ester with di-tert-butyl dicarbonate (BocO) and triethylamine affords the 2-N-Boc-3-N-Z,2,3-diamino ester 6 in 53% yield starting from 5a. Diamino ester 6 represents a versatile intermediate for syntheses of peptide drugs. The amino protecting groups can be selectively removed allowing the incorporation of the resulting 2,3-diamino acid derivatives into peptide chains either via the 2- or the 3-amino function. Palladium-catalyzed hydrogenolytical removal of the Z-protecting group of 6, for example, affords the 2,3-diamino propanoic ester 7 in 87% yield. Acidic hydrolysis of 7 and treatment with propene oxide and ethanol yields the 2,3-diaminopropanoic acid monohydrochloride 8 in 75% yield.

All diamino isobutyrlic acid derivatives 6–8 were shown to have the 2R-configuration with an enantiomeric excess (e.e.) > 95% 7 (the (2S)-diamino acid derivatives ent-6–8 are analogously obtained from ent-1a). The configuration of compounds 6–8 has already been established in bislactim ether 3a. Racemization in one of the following steps can be excluded.

Not surprisingly in the reaction of bromomethyl bislactim ether 3c with sodium azide in dimethyl sulfoxide at
80 °C an intramolecular 1,3-dipolar cycloaddition of the intermediate azide 4e to the thermolabile dihydrotriazole 9 takes place. Under the reaction conditions used, 9 is converted to dihydropyrrole 10 by ring opening, [1,2]-hydrogen shift, and simultaneous loss of nitrogen. Spiro bislactim ether 10 could offer an access to optical active, substituted 3-aminoimidazole-3-carboxylic acids of potential pharmacological interest. On hydrolysis of 10 with 0.1 N hydrochloric acid 3-carbamoyl pyrrole 11 is obtained in 68 % yield.

Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 281 infrared spectrophotometer. Optical rotations were determined using a Perkin-Elmer 241 MC polarimeter. 1H-NMR spectra were recorded on Bruker WM 250 and AM 300 spectrometers in either CDCl3, DMSO-d6, or D2O solution. Microanalyses were obtained using a Perkin-Elmer 240 element analyzer. Mass spectra were obtained on the following mass spectrometers: Electron ionization (EI) on a Kratos MS 80; desorption chemical ionization (DCI) on a Finnigan MAT 311 A. High resolution mass spectra (HRMS) were recorded on a Finnigan MAT 90 under FAB conditions. All reactions were performed under a positive atmosphere of argon. Reactions were monitored by analytical TLC using 5 x 10 cm plates: silica gel 60 F-254, layer thickness 0.25 mm (E. Merck). Silica gel columns for chromatography utilized silica gel 60 (230–400 mesh ASTM; E. Merck) and a slightly positive pressure of air. Commercial “anhydrous” solvents were distilled shortly before use from an appropriate drying agent. Bislactim ethers 1b, e are obtained according to Ref. 1. Bromomethyl compound 3a is obtained according to Ref. 3.

(2S,5R,5S)-2-Alkyl-2-bromomethyl-2,5-dihydro-5-isopropyl-3,6-dimethoxyazines (3):

To a stirred solution of the bislactim ether 1 (14.0 mmol; 3.85 g 1b, 3.14 g 1e) in THF (25 mL) at −70 °C, a 1.8 M solution (8.3 mL, 15.0 mmol) of BuLi in hexane is added by syringe and stirring is continued for 15 min. Then, a precooled solution of CH2Br2 (26.1 g, 0.15 mol) in THF (15 mL) is added and stirring is continued for 30 min at −70 °C. The cooling bath is removed, the solvent evaporated in vacuo, and the residue dissolved in Et2O (30–40 mL). The ether solution is washed with water (30–40 mL), the water layer is extracted with Et2O (3 x 20 mL), and the combined ether solution is dried (MgSO4). The solvent is evaporated in vacuo and the residual crude product purified by low-pressure chromatography on silica gel using toluene as eluent (3b: Rf = 0.33; 3c: Rf = 0.38).

2-Benzyl derivative 3b: yield: 3.19 g (62%), mp 61 °C (E + OH); [α]D20 + 42.0° (c = 1.05, CHCl3);
Colorless oil.
C21H13BrN2O2 (367.3).
MS (DEI): m/z = 368 (M + H).
IR (film): ν = 1700 cm⁻¹ (C=N).
1H-NMR (CDCl3): δ = 0.17, 0.85 (2S, 3H each, J = 7 Hz, CH(CH3)2), 1.96 (dsp, 1H, J = 3 and 7 Hz, CH(CH3)2), 2.86, 3.27 (AB signal, 2H, JAB = 12 Hz, CH2Ph), 3.51, 3.90 (AB signal, 2H, JAB = 9 Hz, CH2Br), 3.72, 3.74 (2S, 3H each, OCH3), 3.82 (d, 1H, J = 3 Hz, 5-H), 7.02–7.39 (m, 5 H arom).
2-Allyl derivative 3c: yield: 3.06 g (69%); [α]D20 + 3.0° (c = 0.86, CHCl3); colorless oil.
C21H13BrN2O2 (3172).
MS (DEI): m/z = 318 (M + H).
IR (film): ν = 1700 cm⁻¹ (C=N).
1H-NMR (CDCl3): δ = 0.65, 1.09 (d, 3H each, J = 7 Hz, CH(CH3)2), 2.23 (dsp, 1H, J = 3 and 7 Hz, CH(CH3)2), 2.42, 2.60 (AB of ABX, 2H, JAB = 12 Hz, JAX = JBX = 7 Hz, CH2CH=CH2), 3.44, 3.74 (AB signal, 2H, JAB = 9 Hz, CH2Br), 3.69, 3.70 (2S, 3H each, OCH3), 3.99 (d, 1H, J = 3 Hz, 5-H), 4.95–5.10 (m, 1H, CH = CH2), 5.56–5.74 (m, 2H, CH = CH2).

2-Methyl derivative 4a: yield 1.99 g (98%), colorless oil.
C11H14N2O2 (253.3).
MS (DEI): m/z = 254 (M + H).
IR (film): ν = 2150 (N=), 1700 cm⁻¹ (C=N).
1H-NMR (CDCl3): δ = 0.70, 1.09 (2S, 3H each, CH(CH3)2), 1.28 (s, 3H, 2-CH3), 2.28 (dsp, 1H, J = 3 and 7 Hz, CH(CH3)2), 3.28, 3.42 (AB signal, 2H, JAB = 10 Hz, CH2N), 3.68 (s, 6H, OCH3), 4.06 (d, 1H, J = 3 Hz, 5-H).
2-Benzyl derivative 4b: yield 2.58 g (98%) colorless oil.
C21H13N2O2 (329.4).
MS (DEI): m/z = 330 (M + H).
IR (film): ν = 2190 (N=), 1690 cm⁻¹ (C=N).
1H-NMR (CDCl3): δ = 0.09, 0.87 (2 d, 3H each, J = 7 Hz, CH(CH3)2), 1.89 (dsp, 1H, J = 3 and 7 Hz, CH(CH3)2), 2.82, 3.15 (AB signal, 2H, JAB = 12 Hz, CH2Ph), 3.38, 3.53 (AB signal, 2H, JAB = 10 Hz, CH2Br), 3.72 (s, 6H, OCH3), 3.85 (d, 1H, J = 3 Hz, 5-H), 7.03–7.21 (m, 5 H arom).

(2S,5R,5S)-2-Alkyl-2-(benzoxycarbonylamino)methyl-2,5-dihydro-5-isopropyl-3,6-dimethoxyazines (5):

To a stirred solution of azidobromomethylbislactim ethers 4 (7.00 mmol; 1.77 g 4a, 2.31 g 4b) in THF (40 mL) is added Ph2P (2.20 g, 8.40 mmol) and water (0.19 g, 10.50 mmol) and stirring at r.t. is continued for 24 h. The solvent is removed in vacuo, the residue is stirred in Et2O/petroleum ether (1:1, 40 mL), triphenylphosphine oxide is filtered off, and the solvent is evaporated in vacuo. The same procedure is repeated a second time. The residue then is dissolved in CH2Cl2 (35 mL) and N,N-disopropylethylamine (2.71 g, 21.0 mmol) and benzyl carbonochloridite (1.19 g, 7.00 mmol) is added. The resulting solution is stirred for 3 h at r.t., washed with water (20 mL; 0.5 N HCl (20 mL), sat. aq. NaHCO3 (20 mL) and dried (MgSO4). The solvent is evaporated in vacuo, and the residual crude product is purified by chromatography on silica gel using Et2O/petroleum ether (1:1) as eluent (5a: Rf = 042; 5b: Rf = 0.49).

2-Methyl derivative 5a: yield 2.18 g (86%); [α]D20 = + 13.2° (c = 1.12, CHCl3); colorless oil.
C26H19N2O2 calc. C 63.2 H 7.5 N 11.6
found 63.5 7.6 11.7
HRMS (MAB): m/z calc. for C26H19N2O2 (M + H): 362.208; found: 362.208.

2-Benzyl derivative 5b: yield 1.84 g (60%); mp 70 °C (hexane); [α]D20 = + 39.2° (c = 0.90, CHCl3).
C27H21N2O4 calc. C 68.7 H 7.1 N 9.6
(437.5) found 68.7 7.0 9.7

1H-NMR (CDCl3): δ = 0.18, 0.70 (2 d, J = 7 Hz, 6 H, CH(CH3)2), 1.82 (dsp, J = 3 and 7 Hz, 1H, CH(CH3)2), 2.82, 3.24 (AB, JAB = 12 Hz, 2H, CH2Ph), 3.38, 3.70 (AB of ABX, JAB = 20 Hz, JAX =
Methyl (2R)-3-Benzoylcarboxyramin-2-(tert-butyloxy carbonylamino)-2-methylpropanoate (6):
A suspension of compound 5a (1.81g, 5.00 mmol) in 0.1 N HCl (100 mL, 10.0 mmol) and acetonitrile (10 mL) is stirred at r.t. for 3 d. The acetonitrile is evaporated in vacuo, the solution is extracted with EtO\(_2\) (25 mL) to remove unreacted 5a and is then evaporated to dryness. The residue is dissolved in the minimum amount of water (ca. 5 mL), ether (40 mL) is added, and conc. aq ammonia is added with shaking to adjust the mixture to pH 8–10. The ether layer is separated and the aqueous layer extracted with EtO\(_2\) (3 × 10 mL). The combined ether solution is dried (MgSO\(_4\)), the solvent is evaporated in vacuo, and t-Val-OCH\(_3\) is distilled off in a Kugelrohr at 70°C/1 mbar. The residue is dissolved in CH\(_2\)Cl\(_2\) (25 mL), EtN (1 g, 10.0 mmol) and then di-tert-butyl dicarbonate (1.64 g, 7.50 mmol) are added, the solution is stirred for 12 h at r.t., washed with water (2 × 20 mL), and dried (MgSO\(_4\)). The solvent is evaporated in vacuo, and the residual crude product is purified by chromatography on silica gel using toluene/EtOAc (3:1) as eluent (R\(_f\) = 0.40); yield 0.97 g (53%) colorless oil; [α]\(^{20}\) + 1.51° (c = 1.06, CHCl\(_3\)). C\(_{16}\)H\(_{22}\)N\(_2\)O\(_4\) (364.6). HRMS: m/z calc. for C\(_{16}\)H\(_{22}\)N\(_2\)O\(_4\) (M + H\(^+\)) 367.187; found: 367.187.

1H-NMR (CDCl\(_3\)): δ = 1.93 (s, 9 H, C(CH\(_3\))\(_3\)), 1.48 (s, 3 H, CH\(_3\)), 1.60–2.80 (m, 2 H, CH\(_2\)-N), 3.73 (s, 3 H, OCH\(_3\)), 5.08 (s, 2 H, OCH\(_2\)), 7.52–7.88 (m, 2 H, NH), 7.12–7.48 (m, 5 H, arom.).

Methyl (2R)-3-Amino-2-tert-butyloxy carbonylamino-2-methylpropionate (7):
Compound 6 (0.73 g, 2.00 mmol) is dissolved in EtO\(_2\) (25 mL). Pd/C (10%, 40 mg) is added, the mixture is hydrogenated with H\(_2\) (3 bar) at 25°C for 4 h, and filtered through Celite. The solvent is evaporated to give 7 as a colorless oil; yield 0.40 g (87%); [α]\(^{20}\) + 13.9° (c = 1.0, EtOH).

C\(_{15}\)H\(_{20}\)N\(_2\)O\(_4\) (232.3). MS (FAB): m/z = 233 (M + H).

1H-NMR (CDCl\(_3\)): δ = 1.39 (s, 2 H, NH\(_2\)), 1.45 (s, 9 H, C(CH\(_3\))\(_3\)), 1.51 (s, 3 H, CH\(_3\)), 0.20, 3.12 (AB, J\(_{AB}\) = 12 Hz, 2 H, CH\(_2\)), 3.77 (s, 3 H, OCH\(_3\)), 5.60 (br s, 1 H, NH).

(2R)-2,3-Diamino-2-methylpropanoic acid Monohydroloride (8):
A solution of compound 7 (0.30 g, 1.29 mmol) in 3 N HCl (8 mL) is heated for reth 3 h. The solution is evaporated in vacuo and the residue is dried at 60°C/1 mbar. The resulting dihydrochloride is dissolved in EtOH (5 mL) and propene oxide (1 mL) is added. The solution is heated to reflux for 3 h, cooled and pure monohydroloride \(8\) is filtered off; yield 0.15 g (75%); mp 281–284°C (dec.); [α]\(^{20}\) + 3.5° (c = 0.7, H\(_2\)O).

C\(_{6}\)H\(_{12}\)N\(_2\)O\(_3\)·HCl. calc. C 31.1 H 6.5 N 18.1 (118.1 + 36.5) found 31.1 6.6 17.8

HRMS (FAB): m/z calc. for C\(_{6}\)H\(_{11}\)N\(_2\)O\(_2\) (M + H\(^+\)) 119.082; found: 119.082.

IR (KBr): ν = 3487, 3387 (NH), 1727 cm\(^{-1}\) (C=O).

1H-NMR (H\(_2\)O): δ = 1.60 (s, 3 H, CH\(_3\)), 3.31, 3.43 (AB signal, 2 H, J\(_{AB}\) = 14 Hz, CH\(_2\)).

(5R,8S)-8-Isopropy-7,10-dimethoxy-3-methyl-2,6,9-triazaspiro-[4.5]decan-2-6,9-triene (10):
To a stirred suspension of bromomethylbislactim ether 3c (10.0 g, 31.5 mmol) in DMSO (80 mL) is added NaN\(_3\) (8.20, 126 mmol) and stirring is continued for 48 h at 80°C. The solution is mixed with Et\(_2\)O (240 mL) and shaken with water (150 mL), the water layer is extracted with Et\(_2\)O (× 200 mL), and the combined organic phase is washed with water (100 mL) and dried (MgSO\(_4\)). The solvent is evaporated in vacuo and the residual crude product is purified by chromatography using Et\(_2\)O/acetonitrile/conc. aq NH\(_3\) (10:1:0.1) as eluent (R\(_f\) = 0.39); yield 4.01 g (51%); [α]\(^{20}\) + 57.2° (c = 0.71, MeOH); colorless oil.

C\(_{16}\)H\(_{14}\)N\(_2\)O (c = 61.1 H 8.4 N 16.7 (251.3) found 61.8 8.3 16.6

MS (DEI): m/z = 252 (M + H).

IR (film): ν = 1690, 1660 (C=O).

1H-NMR (CDCl\(_3\)): δ = 0.68, 1.07 (2 d, J = 7 Hz, 6 H, CH\(_2\)(CH\(_3\))\(_3\)), 2.06 (s, 3 H, CH\(_3\)), 2.24 (d, J = 3 and 7 Hz, 1 H, CH\(_2\)(CH\(_3\))\(_3\)), 2.52, 3.00 (AB, J\(_{AB}\) = 17 Hz, 2 H, CH\(_3\)), 3.62, 3.69 (2 s, 3 H each, OCH\(_3\)), 3.79, 4.22 (AB, J\(_{AB}\) = 14 Hz, 2 H, CHN), 3.98 (d, J = 3 Hz, 1 H, H-5).

(5S)-N-(2-Methyl-proplyl-3-carboxyl)-valeryl Methyl Ester (11):
A solution of 10 (1.00 g, 3.58 mmol) in 0.25 N HCl (43.0 mL, 10.74 mmol) is stirred at r.t. for 6 h. The solution is concentrated in vacuo to a volume of 10 mL, Et\(_2\)O (20 mL) is added, and conc. aq ammonia is added with shaking to adjust the mixture to pH 5–10. The ether layer is separated and the aqueous layer is extracted with EtO\(_2\) (3 × 10 mL). The combined ether solution is dried (MgSO\(_4\)), the solvent is evaporated in vacuo and the residual crude product is purified by chromatography using Et\(_2\)O/acetonitrile/conc. aq NH\(_3\) (10:1:0.1) as eluent (R\(_f\) = 0.31); yield 0.58 g (68%), mp 65°C (Et\(_2\)O); [α]\(^{20}\) -12.1° (c = 0.98, MeOH).

C\(_{14}\)H\(_{14}\)N\(_2\)O\(_3\) (238.28). MS (DEI): m/z = 239 (M + H).

IR (film): ν = 3200 (NH), 1735, 1725 cm\(^{-1}\) (C=O).

1H-NMR (CDCl\(_3\)): δ = 0.96, 1.00 (2 d, 3 H each, J = 7 Hz, CH\(_2\)(CH\(_3\))\(_3\)), 2.20 (d, 1 H, J = 6 and 7 Hz, CH\(_2\)(CH\(_3\))\(_3\)), 2.27 (s, 3 H, CH\(_3\)), 3.77 (s, 3 H, OCH\(_3\)), 4.74 (dd, 1 H, J = 7 and 8 Hz, 2-H), 6.65 (dd, 1 H, J = 1 and 2 Hz, 3-H\(_{\text{Ar}}\)), 6.27 (d, 1 H, J = 8 Hz, NH-5), 7.20 (dd, 1 H, 1 J = 2 and 2 Hz, 5'-H\(_{\text{Ar}}\)). 9.25 (br s, 1 H, H\(_{\text{Ar}}\)).