Synthesis of (*S*)-*N*-Boc-3-Amino-2-Arylpropanol from Optically Active β-Amino Esters

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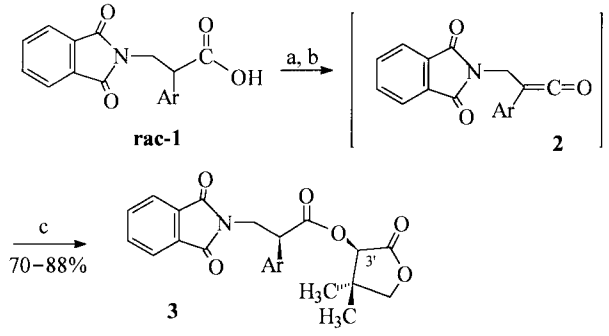
Abstract: The reduction of various (α*S*,3'*R*)-pantolactonyl-2-aryl-3-phthalimidopropanoates **3** followed by an acidic treatment and direct N-Boc protection afforded the corresponding (*S*)-*N*-Boc-3-amino-2-arylpropanols **4** in good yield and without loss of the optical purity.

Keys words: 1,3-amino alcohols, reduction, β-amino esters

Synthesis of optically active amino alcohols is of great importance in synthetic organic chemistry since they are a well established source of ligands in asymmetric synthesis including the enantioselective borane reduction of prochiral ketones,[1] enantioselective addition of dialkylzinc,[2] or asymmetric hydrogen transfer from alcohols to ketones.[3] 1,2-Amino alcohols have received much attention because they are generally readily accessible in enantiomerically pure form from natural precursors.[4] On the other hand, the synthesis and use of chiral 1,3-amino alcohols[5] are rather rare although these compounds frequently possess interesting pharmacological properties.[6] This prompted us to synthesize new 1,3-aminoalcohols from the recently obtained optically pure β-amino esters.

We have recently reported[7] the asymmetric synthesis of (*S*)-β[2]-homoarylglycines through the stereoselective addition of the (*R*)-pantolactone chiral alcohol to *N*-phthalyl-2-aminomethyl-2-aryl ketenes **2** (Scheme 1).

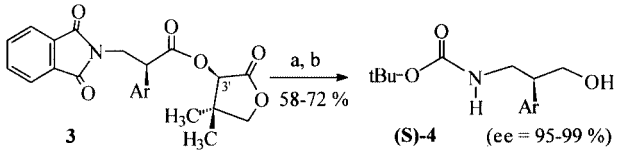


Scheme 1 Reagents and conditions: a) $(COCl)_2$, 30 °C, 12 h; b) NR_3, THF, r.t.; c) (*R*)-pantolactone, r.t. or 0 °C, THF

The ketenes **2** were obtained in situ by dehydrochlorination of the corresponding acyl chloride resulting from *rac*-**1** after treatment at room temperature with oxalyl chloride. The corresponding (α*S*,3'*R*)-*N*-phthalyl pantolactonyl esters **3**[8] were obtained both in high chemical yield and with high diastereoisomeric excess (de = 86–94%). Although the reaction was not totally diastereoselective, the optically pure (α*S*,3'*R*)-esters **3** could be easily isolated by recrystallization.[7]

It was shown[9] that the phthalimido protecting group of amino acids could be removed under mild conditions using successively sodium borohydride and glacial acetic acid. Furthermore, lithium aluminium hydride has been used for the reductive removal of pantolactonyl esters to give the corresponding alcohols.[10]

Therefore, we envisaged the possible simultaneous reduction of the phthalimido group and the pantolactonyl ester of the optically pure compounds **3a**–**e** to produce directly the corresponding chiral 1,3-amino alcohols **4a**–**e** (Scheme 2).



Scheme 2 Reagents and conditions: a) $NaBH_4$, 2-PrOH–H_2O (6:1), 12 h; HOAc (pH 5), 80 °C, 6 h; b) BOC_2O, CH_2Cl_2, 12 h

The best results were obtained when an excess of sodium borohydride (5 equivalents) was used, at room temperature for 12 hours, followed by an acidic treatment (pH 5) at 80 °C for 6 hours. The amino group of the corresponding chiral 1,3-amino alcohol was then directly converted into its N-Boc derivative using the conventional method. The (*S*)-*N*-Boc-3-amino-2-arylpropanol **4a**–**e** were obtained in good yield and without loss of the stereochemical integrity (Table).

The enantiomeric purity of **4a**–**e** was controlled by HPLC after removal of the Boc group of an aliquot and derivatization with Marfey's reagent[11] (FDAA = 1-fluoro 2,4-dinitrophenyl 5-(*S*)-alanine amide).

Mps were determined with a Büchi apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer, model 241

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Table (*S*)-*N*-Boc-3-amino-2-arylpropanol **4a**–**e** Obtained

(*S*)-**4**	Ar	Yield	ee (%)
a	phenyl	62	98
b	*p*-methoxyphenyl	72	99
c	*p*-fluorophenyl	67	99
d	*o*,*p*-dimethoxyphenyl	65	96
e	α-naphthyl	58	95

polarimeter. NMR spectra were recorded with a Bruker DRX 400 spectrometer. Data are reported as follows: chemical shifts (δ) are in ppm with respect to TMS, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (*J*) in Hz. HPLC analyses were performed with a water 510 instrument with variable detector; column I: chiracel OD, 25 cm × 4 mm, flow: 1 mL/min, eluent: hexane–2-PrOH, 95:5; column II: nucleosil C_{18}, 5μ, 25 cm × 4.6 mm, flow: 1 mL/min, H_2O–CH_3CN–0.1% TFA: gradient A: 10% to 60% CH_3CN/30 min followed by 60% CH_3CN/10 min; gradient B: 10% to 50%/40 min followed by 50% CH_3CN/10 min; gradient C: 10% to 40%/60 min followed by 40% CH_3CN/10 min.

The ESI mass spectra were recorded with a platform II quadrupole mass spectrometer (Micromass, Manchester, UK) fitted with an electrospray source and the voltages were set at 3.5 kV for the capillary and 30 V for the cone.

(*S*)-*N*-Boc-3-amino-2-arylpropanol (4a–e): General Procedure

To a stirred solution of (α*S*,3'*R*)-*N*-phthalyl pantolactonyl ester **3** (1.5 mmol) in 2-PrOH–H_2O (6:1, 19 mL) was added slowly $NaBH_4$ (5 equiv, 7.5 mmol). After stirring for 12 h at r.t., TLC indicated complete consumption of the starting material. Glacial HOAc was added dropwise to adjust the pH to 5 and the mixture was heated to 80 °C for 6 h. The reaction mixture was dried by repeated co-evaporation with MeOH and toluene and finally dried in vacuo over phosphorus pentoxide. To the solution of this deprotected aminoalcohol in CH_2Cl_2 (15 mL) was added di-*tert*-butyldicarbonate (1.2 equiv). After stirring for 12 h at r.t., salts were removed by filtration and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography to yield **4**.

(*S*)-*N*-Boc-3-amino-2-phenylpropanol [(*S*)-**4a**]
Prepared from (α*S*,3'*R*)-**3a** (610 mg, 1.5 mmol). Obtained as a colourless solid after flash chromatography (CH_2Cl_2–EtOAc, 9:1), R_f = 0.3.

Yield: 233 mg (0.93 mmol, 62%); mp 70 °C.

$[\alpha]_D^{20}$ +17 (*c* 1.0, CH_2Cl_2)

HPLC (column I): t_R = 18.1 min.

^{1}H NMR ($CDCl_3$): δ = 1.37 [s, 9H, (C*H*$_3$)$_3$C], 2.84 (m, 1H, C*H*-C_6H_5), 3.42 (t, 2H, $J_1 = J_2$ = 6.3 Hz, C*H*$_2$-N), 3.73 (d, 2H, *J* = 6.3 Hz, C*H*$_2$-O), 4.66 (br, 1H, N*H*Boc), 7.17 (m, 3H, Ar-H), 7.25 (m, 2H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 28.77 [(*C*H$_3$)$_3$C], 42.62 (*C*H$_2$-N), 48.77 (*C*H), 63.85 (*C*H$_2$-O), 80.34 [(CH$_3$)$_3$*C*], 127.48 (Ar-*C*H), 128.44 (Ar-*C*H), 129.32 (Ar-*C*H), 140.99 (Ar-*C*), 157.53 (N-*C*O-O).

ESI-MS: *m/z* (%) = 195.9 (100), 252.0 (50) [M + H$^+$], 503.1 (12).

Anal. Calcd for $C_{14}H_{21}NO_3$ (251.32): C, 66.91; H, 8.42; N, 5.57. Found: C, 66.72; H, 8.52; N, 5.41.

(*S*)-*N*-Boc-3-amino-2-(4-methoxyphenyl)propanol [(*S*)-**4b**]
Prepared from (α*S*,3'*R*)-**3b** (655 mg, 1.5 mmol). Obtained as a colourless solid after chromatography (EtOAc–Hexane, 1:1), R_f = 0.40.

Yield: 310 mg (1.1 mmol, 72%); mp 86.5 °C.

$[\alpha]_D^{20}$ +20 (*c* = 1.0, CH_2Cl_2)

HPLC (column I): t_R = 20.3 min.

^{1}H NMR ($CDCl_3$): δ = 1.48 [s, 9H, (C*H*$_3$)$_3$C], 2.91 (m, 1H, C*H*-$C_6H_4OCH_3$), 3.48 (t, 2H, $J_1 = J_2$ = 6.3 Hz, C*H*$_2$-N), 3.80 (d, 2H, *J* = 6.3 Hz, C*H*$_2$-O), 3.83 (s, 3H, OC*H*$_3$), 4.73 (br, 1H, N*H*Boc), 6.91 (d, 2H, *J* = 8.6 Hz, Ar-H), 7.19 (d, 2H, *J* = 8.6 Hz, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 28.77 [(*C*H$_3$)$_3$C], 42.74 (*C*H$_2$-N), 47.92 (*C*H-$C_6H_4OCH_3$), 55.69 (O*C*H$_3$), 64.00 (*C*H$_2$-O), 80.30 [(CH$_3$)$_3$*C*], 114.58 (Ar-*C*H), 129.39 (Ar-*C*H), 132.91 (Ar-*C*H), 157.50 (N-*C*O-O) 159.05 (Ar-*C*-OCH$_3$).

ESI-MS: *m/z* (%) = 226.0 (70), 282.2 (100) [M + H$^+$], 563.2 (18).

Anal. Calcd for $C_{15}H_{23}NO_4$ (281.35): C, 64.03; H, 8.24; N, 4.98. Found: C, 64.10; H, 8.28; N, 5.04.

(*S*)-*N*-Boc-3-amino-2-(4-fluorophenyl)propanol [(*S*)-**4c**]

Prepared from (α*S*,3'*R*)-**3c** (637 mg, 1.5 mmol). Obtained as a colourless solid after chromatography (EtOAc–Hexane, 1:1), R_f = 0.46.

Yield: 269 mg (1.0 mmol, 67%); mp 78 °C.

$[\alpha]_D^{20}$ +18 (*c* 1.0, CH_2Cl_2)

HPLC (column I) : t_R = 13.5 min.

^{1}H NMR ($CDCl_3$): δ = 1.48 [s, 9H, (C*H*$_3$)$_3$C], 2.92 (m, 1H, C*H*-C_6H_4F), 3.47 (m, 2H, C*H*$_2$-N), 3.82 (m, 2H, C*H*$_2$-O), 4.77 (br, 1H, N*H*Boc), 7.04 (t, 2H, $J_1 = J_2$ = 8.7 Hz, Ar-H), 7.19 (q, 2H, J_1 = 8.7 Hz, J_2 = 3 Hz, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 28.75 [(*C*H$_3$)$_3$C], 42.63 (*C*H$_2$-N), 48.03 (*C*H-C_6H_4F), 63.73 (*C*H$_2$-O), 80.48 [(CH$_3$)$_3$*C*], 115.81 (Ar-*C*H), 116.02 (Ar-*C*H), 129.90 (Ar-*C*H), 136.79 (Ar-*C*), 157.56 (N-*C*O-O), 162.30 (d, *J* = 220 Hz, Ar-CF).

ESI-MS: *m/z* (%) = 213.9 (90), 270.2 (100) [M + H$^+$].

Anal. Calcd for $C_{14}H_{20}FNO_3$ (269.31): C, 62.44; H, 7.49; N, 5.20. Found: C, 62.79; H, 7.54; N, 5.31.

(*S*)-*N*-Boc-3-amino-2-(3,4-dimethoxyphenyl)propanol [(*S*)-**4d**]
Prepared from (α*S*,3'*R*)-**3d** (700 mg, 1.5 mmol). Obtained as a colourless solid after chromatography (EtOAc–Hexane, 1:1), R_f = 0.32.

Yield: 305 mg (0.97 mmol, 65%); mp 87.5 °C.

$[\alpha]_D^{20}$ +16 (*c* 1.0, CH_2Cl_2)

HPLC (column I): t_R = 18.6 min.

^{1}H NMR ($CDCl_3$): δ = 1.48 [s, 9H, (C*H*$_3$)$_3$C], 2.89 [m, 1H, C*H*-$C_6H_3(OCH_3)_2$], 3.48 (m, 2H, C*H*$_2$-N), 3.81 (d, 2H, *J* = 5.6 Hz, C*H*$_2$-O), 3.89 (s, 3H, OC*H*$_3$), 3.91 (s, 3H, OC*H*$_3$), 4.75 (br, 1H, N*H*Boc), 6.79 (d, 1H, *J* = 8.0 Hz, Ar-H), 6.80 (s, 1H, Ar-H), 6.86 (d, 1H, *J* = 8.0 Hz, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 28.78 [(*C*H$_3$)$_3$C], 42.73 (*C*H$_2$-N), 48.35 [*C*H-$C_6H_3(OCH_3)_2$], 56.30 (O*C*H$_3$), 64.09 (*C*H$_2$-O), 80.29 [(CH$_3$)$_3$*C*], 111.80 (Ar-*C*H), 120.27 (Ar-*C*H), 133.44 (Ar-*C*), 148.50 (Ar-*C*OCH$_3$), 149.50 (Ar-*C*OCH$_3$), 157.44 (N-*C*O-O).

ESI-MS: *m/z* (%) = 256.0 (80), 312.1 (100) [M + H$^+$], 623.4 (38).

Anal. Calcd for $C_{16}H_{25}NO_5$ (311.37): C, 61.72; H, 8.09; N, 4.50. Found: C, 61.33; H, 8.02; N, 4.48.

(*S*)-*N*-Boc-3-amino-2-(α-naphthyl)propanol [(*S*)-**4e**]

Prepared from (α*S*,3′*R*)-**3e** (685 mg, 1.5 mmol). Obtained as a colourless solid after flash chromatography (EtOAc–Hexane, 1:1), $R_f = 0.25$

Yield: 262 mg (0.87 mmol, 58%); mp 90 °C.

$[\alpha]_D^{20}$ +26 (*c* 1.0, CH_2Cl_2)

HPLC (column I): $t_R = 26.2$ min.

^{1}H NMR ($CDCl_3$): δ = 1.37 [s, 9H, (C*H*$_3$)$_3$C], 3.50 (m, 2H, C*H*$_2$-N), 3.77 (m, 1H, C*H*-naphthyl), 3.89 (m, 2H, C*H*$_2$-O), 4.67 (br, 1H, N*H*-Boc), 7.31 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.41 (m, 3H, Ar-H), 7.68 (d, 1H, *J* = 8.6 Hz, Ar-H), 7.79 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.98 (d, 1H, *J* = 8.6 Hz, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 28.78 [(*C*H$_3$)$_3$C], 42.19 (*C*H$_2$-N), 42.56 (*C*H-naphthyl), 63.54 (*C*H$_2$-O), 80.40 [(CH$_3$)$_3$*C*], 123.18 (Ar-*C*H), 124.41 (Ar-*C*H), 125.83 (Ar-*C*H), 126.08 (Ar-*C*H), 126.75 (Ar-*C*H), 127.90 (Ar-*C*H), 129.53 (Ar-*C*H), 132.15 (Ar-*C*), 134.50 (Ar-*C*), 136.75 (Ar-*C*), 157.70 (N-*C*O-O).

ESI-MS: *m/z* (%) = 246.4 (100), 302.2 (70) [M + H$^+$], 603.8 (10).

Anal. Calcd for $C_{18}H_{23}NO_3$ (301.38): C, 71.73; H, 7.69; N, 4.65. Found: C, 71.58; H, 7.82; N, 4.76.

FDAA Derivatives; General Procedure

(*S*)-*N*-Boc-3-amino-2-arylpropanol **4** (10 μmol) was deprotected with TFA in CH_2Cl_2 (30:70) after standing for 30 min at r.t. The solution was then concentrated under reduce pressure and the residue was dissolved in 400 μL of 1% acetone solution of 1-fluoro-2,4-dinitrophenyl-5-(*S*)-alanine amide (FDAA) (4 mg, 15 μmol) and $NaHCO_3$ (1 M, 80 μL). The reaction mixture was heated at 40 °C for 1 h with frequent stirring. After cooling to r.t., HCl (1 N, 80 μL) was added and the combined solvents were evaporated under reduced pressure. The resulting residue was dried in vacuo over phosphorus pentoxide and analysed by HPLC. The optical purity was deduced by comparison with the data of the racemic mixture.

To obtain racemic samples of **4** and then prepared racemic FDAA derivatives, racemic *N*-phthalyl pantolactonyl esters **3** were reduced as previously described.

HPLC (column II): (*S*)-**4a**: $t_R = 30.5$ min, (*R*)-**4a**: $t_R = 30.8$ min (gradient A), (*S*)-**4b**: $t_R = 41.8$ min, (*R*)-**4b**: $t_R = 42.3$ min (gradient B), (*S*)-**4c**: $t_R = 31.1$ min, (*R*)-**4c**: $t_R = 31.4$ min (gradient A), (*S*)-**4d**: $t_R = 58.7$ min, (*R*)-**4d**: $t_R = 58.9$ min (gradient C), (*S*)-**4e**: $t_R = 34.1$ min, (*R*)-**4e**: $t_R = 34.3$ min (gradient A).

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