*Tetrahedron: Asymmetry* Vol. 3, No. 6, pp. 769-774, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

# Stereoselective Synthesis of ß-Hydroxy-α-Amino Acids from Chiral Cyanohydrins.

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(*Received* 30 *April* 1992)

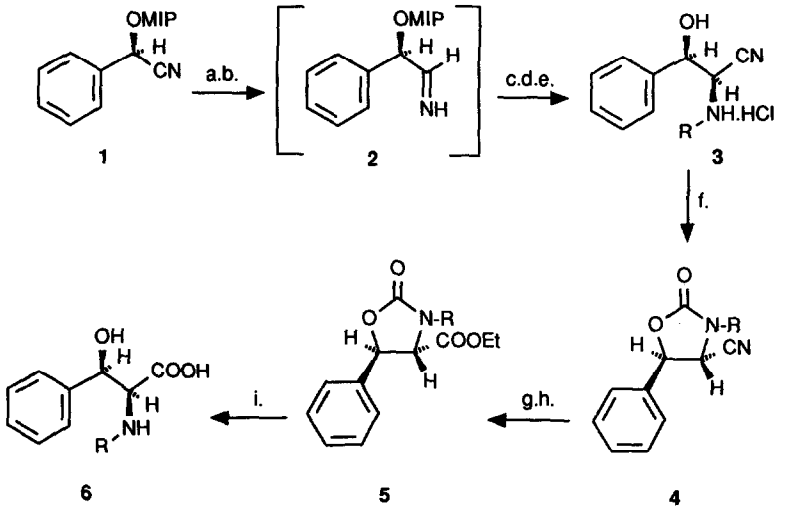
***Abstract:*** An efficient one-pot reduction-transimination-hydrocyanation synthesis of ß-hydroxy-α-cyanoamines **3** from optically active O-protected mandelonitrile (**1**) is described. These ß-hydroxy-α-cyanoamines were easily converted into optically active (2*S*,3*R*) ß-hydroxy-α-amino acids **6**.

ß-Hydroxy-α-amino acids are an important class of compounds. They occur in nature both as free amino acids (e.g. serine) and as essential structural components of more complex molecules, as, for example, ß-hydroxyphenylalanine derivatives in vancomycin[1] and bouvardin[2], and MeBmt in cyclosporine[3]. Additionally, they are valuable precursors for the synthesis of ß-lactams[4]. Because of their biological and pharmaceutical interest a variety of approaches toward the stereoselective preparation of these compounds has been developed, including enzymatic resolution[5], enzymatic synthesis[6], aldol condensation[7], Sharpless epoxidation[8] and synthesis *via* oxazolidinone intermediates[9].

In a recent paper[10], we reported a convenient one-pot synthesis of enantiopure N-alkyl ß-ethanolamines from O-protected (*R*)-cyanohydrins[10,11]. The reaction sequence involved di*iso*-butylaluminium hydride (DIBAL) reduction of the nitrile functionality to a primary imine. Transimination with a primary amine afforded the more stable secondary imine, which was reduced by sodium borohydride to yield the desired N-alkyl ß-ethanolamines. We would now like to report a one-pot reduction-transimination-hydrocyanation reaction sequence leading to ß-hydroxy-α-cyanoamines, which are excellent precursors for the synthesis of ß-hydroxy-α-amino acids.

2-Methoxy-*iso*-propyl (MIP) protected (*R*)-cyanohydrin **1** was reduced by DIBAL at low temperature (-70°C). Quenching with ammonium bromide ($NH_4Br$) in methanol afforded the free primary imine **2**. Transimination with methylamine or benzylamine to introduce the N-alkyl group, followed by hydrocyanation of the secondary imine with *in situ* prepared hydrocyanic acid (HCN), yielded MIP protected N-alkyl ß-hydroxy-α-cyanoamines. These were easily deprotected and converted

into the HCl salts of the free ß-hydroxy-α-cyanoamines **3** by addition of 1N HCl. In the case of **3a** the diastereoselectivity of this one-pot reduction-transimination-hydrocyanation sequence was found to be 88:12 in favour of the *threo* (2*R*,3*R*) over the *erythro* (2*S*,3*R*) compound[12] (ratio determined by $^1$H NMR), while in the case of **3b**, carrying the larger N-benzyl substituent, the *threo* diastereoisomer was formed exclusively.




**3a,4a,5a,6a**: R = $CH_3$
**3b,4b,5b,6b**: R = $CH_2Ph$

**a**: DIBAL; **b**: $NH_4Br$/MeOH; **c**: $RNH_2$; **d**: HCN; **e**: HCl; **f**: $(im)_2CO/Et_3N$; **g**: $K_2CO_3$/EtOH; **h**: 1N HCl; **i**: 2N KOH.

Scheme 1: N-alkyl ß-hydroxy-α-amino acids from O-MIP mandelonitrile.

The ß-hydroxy-α-cyanoamines **3** were converted into the oxazolidinone derivatives **4** in an overnight reaction with 1,1'-carbonyldiimidazole ($(im)_2CO$). The coupling constants of the obtained products supported the assigned *threo* (= trans) configuration[13] of the major product. Addition of potassium carbonate ($K_2CO_3$) to a solution of **4** in ethanol is known to result in abstraction of the proton α to CN to form a didehydroimine. Ethanol adds stereoselectively to this didehydroimine to yield the oxazolidinone ethyl carboximidate in the thermodynamically favoured trans configuration[9]. Hydrolysis of the carboximidates with 1N HCl yielded the trans configurated amino acid derivatives **5**. Saponification of the ester and oxazolidinone moiety with 2N KOH at 80°C afforded, after Sephadex LH-20 column chromatography, the (2*S*,3*R*) N-alkyl ß-hydroxy-α-amino acids **6**. The enantiomeric excess was determined (after conversion to the methyl ester with diazomethane) in the case of **6a** by HPLC analysis using a Chiralcel OD column and was found to be over 97%. The overall yields for the total reaction sequence (**1** → **6**, scheme 1) were 89% (**6a**) and 69% (**6b**), respectively.

## EXPERIMENTAL.

**(2*R*,3*R*)-(-)-3-Hydroxy-2-methylamino-3-phenylpropionitrile.HCl (3a).**

To a cooled solution (-70°C) of 1.02 g (5 mmol) of **1**[10] (e.e. > 99%) in dry ether (40 mL) was added 12.5 mL of a 1M DIBAL solution (12.5 mmol) in hexanes. After stirring at -70°C for 3 h 1.25 g (12.5 mmol) $NH_4Br$ in methanol (20 mL) was added. The cooling bath was removed and 3 mL of an 8M $CH_3NH_2$ solution (24 mmol) in ethanol was added. Stirring was continued for 45 min (-70°C → room temperature). The mixture was cooled in an ice bath and a solution of 0.75 g NaCN (15 mmol) and 1.5 g $NH_4Br$ (15 mmol) in 30 mL of methanol (**CAUTION:** HCN formation) was added in 15 min. Stirring was continued for 1 h at room temperature and then ether (100 mL) and 1N NaOH (50 mL) were added. The water layer was extracted with ether (2x 50 mL) and the combined organic layers were washed with saturated brine (4x 10 mL), dried ($MgSO_4$) and evaporated. The resulting oil was dissolved in ethanol (25 mL, 96%) and 5 mL of a 1N HCl solution (5 mmol) was added. The solvent was evaporated and the solid was dried by azeotropic removal of water *in vacuo* twice with toluene. Yield: 1.03 g (98%) of **3a**.

$^1$H NMR (200 MHz, 2% DCl in $D_2O$): δ 2.75 (88%) and 2.77 (12%) (*s*, 3H, $NCH_3$); 4.73 (*d*, 1H, CH(CN), J = 8.2 Hz); 5.07 (*d*, 1H, CH(Ph), J = 8.2 Hz); 7.3 (5H, arom).

$^{13}$C NMR (50 MHz): δ 32.4; 55.7; 71.0; 113.3; 127.3-136.5.

**3a** was crystallized from *iso*-propanol for optical rotation and melting point measurements.

$[\alpha]_D^{20}$ -70 (c = 1, 0.1N HCl). m.p. 162°C (dec.).

**(2*R*,3*R*)-(-)-2-Benzylamino-3-hydroxy-3-phenylpropionitrile.HCl (3b).**

Prepared in the same manner as described for **3a**, using benzylamine in the transimination reaction.

Yield: 83% of **3b**. $[\alpha]_D^{20}$ -67 (c = 1, 0.1N HCl). m.p. 224°C (dec.).

$^1$H NMR (200 MHz, 2% DCl in $D_2O$): δ 4.28 and 4.42 (*d*, 1H, $NCH_2$, J = -13.4 Hz); 4.64 (*d*, 1H, CH(CN), J = 8.2 Hz); 5.10 (*d*, 1H, CH(Ph), J = 8.2 Hz); 7.3 (10H, arom).

$^{13}$C NMR (50 MHz): δ 52.4; 55.4; 73.0; 114.7; 128.9-138.8.

**(4*R*,5*R*)-(+)-4-Carbonitrile-3-methyl-5-phenyloxazolidin-2-one (4a).**

To a suspension of 0.21 g (1 mmol) of **3a** in $CH_2Cl_2$ (7 mL) was added 0.10 g (1 mmol) triethylamine. Subsequently 0.32 g (2 mmol) $(im)_2CO$ was added and stirring was continued overnight at room temperature. Water (10 mL) and $CH_2Cl_2$ (25 mL) were added and the water layer was extracted with $CH_2Cl_2$ (10 mL). The combined organic layers were washed with 0.1N HCl (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Yield: 0.21 g (quant.) of **4a**.

$^1$H NMR (200 MHz, $CDCl_3$): δ 3.05 (90%) and 3.07 (10%) (*s*, 3H, $NCH_3$); 4.37 (*d*, 1H, CH(CN), J = 5.7 Hz); 5.63 (*d*, 1H, CH(Ph), J = 5.7 Hz); 7.4 (5H, arom).

$^{13}$C NMR (50 MHz): δ 29.8; 55.5; 76.5; 114.8; 125.0-135.2; 155.6.

**4a** was crystallized from ether/PE (40-60°C) for optical rotation and melting point measurements. $[\alpha]_D^{20}$ +68 (c = 1, $CHCl_3$). m.p. 84-85°C.

**(4*R*,5*R*)-(+)-3-Benzyl-4-carbonitrile-5-phenyloxazolidin-2-one (4b).**

Prepared in the same manner as described for **4a**, using **3b** as the starting material.

Yield: 96% of **4b**. $[\alpha]_D^{20}$ +79 (c = 1, $CHCl_3$). m.p. 95-96°C.

$^1$H NMR (200 MHz, $CDCl_3$): δ 4.10 (*d*, 1H, CH(CN), J = 6.2 Hz); 4.21 and 5.04 (*d*, 1H, $NCH_2$, J = -14.9 Hz); 5.62 (*d*, 1H, CH(Ph), J = 6.2 Hz); 7.3 (10H, arom).

$^{13}$C NMR (50 MHz): δ 47.2; 52.9; 76.9; 114.7; 125.2-135.3; 155.5.

**Ethyl (4*S*,5*R*)-(+)-4-carboxylate-3-methyl-5-phenyloxazolidin-2-one (5a).**

To a solution of 0.40 g (2 mmol) of **4a** in ethanol (10 mL, 96%) was added 0.70 g (5 mmol) $K_2CO_3$ and stirring was continued for 6 h. After removal of $K_2CO_3$ by filtration, the solution was treated with 1N HCl (3 mL). After 30 min, a saturated $NaHCO_3$ solution (10 mL) was added and the mixture was taken up in $CH_2Cl_2$ (100 mL) and water (100 mL). The water layer was extracted with $CH_2Cl_2$ (50 mL). The combined organic layers were washed with water (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave a slightly yellow solid. Yield: 0.48 g (97%) of **5a**.

$^1$H NMR (200 MHz, $CDCl_3$): δ 1.36 (*t*, 3H, $CH_3$); 2.98 (*s*, 3H, $NCH_3$); 4.12 (*d*, 1H, CH(COOEt), J = 5.1 Hz); 4.34 (*m*, 2H, $CH_2CH_3$); 5.46 (*d*, 1H, CH(Ph), J = 5.1 Hz); 7.4 (5H, arom).

$^{13}$C NMR (50 MHz): δ 13.8; 30.2; 62.0; 66.3; 76.3; 124.9-137.8; 168.7.

**5a** was crystallized from ether/PE (40-60°C) for optical rotation and melting point measurements. $[\alpha]_D^{20}$ +26 (c = 1, $CHCl_3$). m.p. 74-75°C.

**Ethyl (4*S*,5*R*)-(+)-3-benzyl-4-carboxylate-5-phenyloxazolidin-2-one (5b).**

Prepared in the same manner as described for **5a**, using **4b** as the starting material.

Yield: 96% of **5b**. $[\alpha]_D^{20}$ +64 (c = 1, $CHCl_3$).

$^1$H NMR (200 MHz, $CDCl_3$): δ 1.30 (*t*, 3H, $CH_3$); 3.93 (*d*, 1H, CH(COOEt), J = 5.1 Hz); 4.24 (*m*, 2H, $CH_2CH_3$); 4.28 and 4.79 (*d*, 1H, $NCH_2$, J = -14.9 Hz); 5.48 (*d*, 1H, CH(Ph), J = 5.1 Hz); 7.3 (10H, arom).

$^{13}$C NMR (50 MHz): δ 14.0; 47.3; 62.2; 63.5; 76.8; 125.2-137.9; 169.0.

**(2*S*,3*R*)-(-)-3-Hydroxy-2-methylamino-3-phenylpropionic acid, L-(-)-N-methyl-3-phenylserine (6a).**

A suspension of 0.30 g (1.2 mmol) of **5a** in 2N KOH (6 mL) was stirred at 80°C for 3 h, then cooled to room temperature and adjusted to pH 5 by addition of 6N HCl. The solvent was evaporated and the residue was diluted with methanol (20 mL) and filtered. The filtrate was chromatographed over 100 g of Sephadex LH-20 and the ninhydrin positive fractions were concentrated *in vacuo*. Yield: 0.22 g (94%) of **6a**. The resulting white solid was crystallized from *iso*-propanol/water for analytical data.

$[\alpha]_D^{20}$ -30 (c = 0.5, 1N HCl). E.e. > 97% (after conversion to the methyl ester with diazomethane, HPLC Chiralcel OD column, eluent = hexane : *iso*-propanol = 95 : 5). m.p. 201-203°C (dec.).
$^1$H NMR (200 MHz, 2% DCl in $D_2O$): δ 2.65 (*s*, 3H, $NCH_3$); 3.77 (*d*, 1H, CH(COOH), J = 7.2 Hz); 5.04 (*d*, 1H, CH(Ph), J = 7.2 Hz); 7.4 (5H, arom).
$^{13}$C NMR (50 MHz): δ 33.2; 70.5; 72.6; 126.9-129.4.
IR (KBr): ν 3150-3600 (broad); 1590 $cm^{-1}$.
LRMS: 272 (M+H); 196 (M+H); 133; 105; 89; 77.

**(2*S*,3*R*)-(-)-2-Benzylamino-3-hydroxy-3-phenylpropionic acid, (L)-N-benzyl-3-phenylserine (6b).**
Prepared in the same manner as described for **6a**, using **5b** as the starting material.
A quantitative yield of **6b** was obtained. $[\alpha]_D^{20}$ -23 (c = 0.5, 1N HCl). m.p. 208-209°C (dec.).
$^1$H NMR (200 MHz, 2% DCl in $D_2O$): δ 4.03 (*d*, 1H, CH(COOH), J = 5.7 Hz); 4.16 and 4.91 (*d*, 1H, $NCH_2$, J = -3.1 Hz); 5.14 (*d*, 1H, CH(Ph), J = 5.7 Hz); 7.4 (10H, arom).
$^{13}$C NMR (50 MHz): δ 51.3; 62.2; 73.4; 126.9-130.2.
IR (KBr): ν 3100-3600 (broad); 1595 $cm^{-1}$.
LRMS: 272 (M+H); 226; 210; 136; 120; 108; 106.

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12. In analogy with the stereochemical outcome of the reduction of secondary imines with $NaBH_4$ it is assumed that attack of cyanide ion is governed in the same manner by stereochemical factors as attack of hydride (Brussee, J.; Van der Gen, A. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 25-26.). The diastereomeric ratio in favour of the *threo* products can be improved by hydrocyanation of the secondary imine at lower temperatures.
13. Observed vicinal coupling constants: **4a**: J = 5.7 Hz; **4b**: J = 6.2 Hz.
Literature[6b,9]: cis oxazolidinone: J = 8-9 Hz; trans oxazolidinone: J = 5-6 Hz.