Chiral Ligands Containing Heteroatoms; 12.[1] Synthesis of Optically Active 2-Amino-2-(2'-pyridyl)-1-alkanols from β-Hydroxy-α-amino Acids

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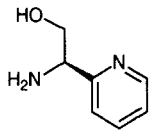
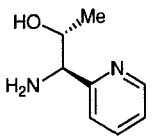
The synthesis of a new class of optically active ligands such as the title compounds is presented. All the multistep procedures adopted start by the conversion of L-serine and L-threonine into the proper 2,2-dimethyloxazolidines, followed by transformation of the corresponding nitriles to pyridines. The reaction sequence occurs without loss of enantiomeric purity and with overall satisfactory yield.

Recently the synthesis of a series of optically active 1-(2'-pyridyl)alkylamines from α-amino acids has been described.[2] These compounds show high efficiency in the asymmetric alkylation of aldehydes with dialkylzinc reagents.[3] As part of our studies in this field,[3,4] we have focused our attention on the preparation of trifunctionalized compounds such as (*R*)-2-amino-2-(2'-pyridyl)ethanol **(1a)** and (1*R*,2*R*)-1-amino-1-(2'-pyridyl)propan-2-ol **(1b)**. These new β-amino alcohols may be used in stereoselective reactions[5] and may constitute useful intermediates for the synthesis of C_2-symmetric bis(oxazolines), containing the pyridine moiety.[6]



1a

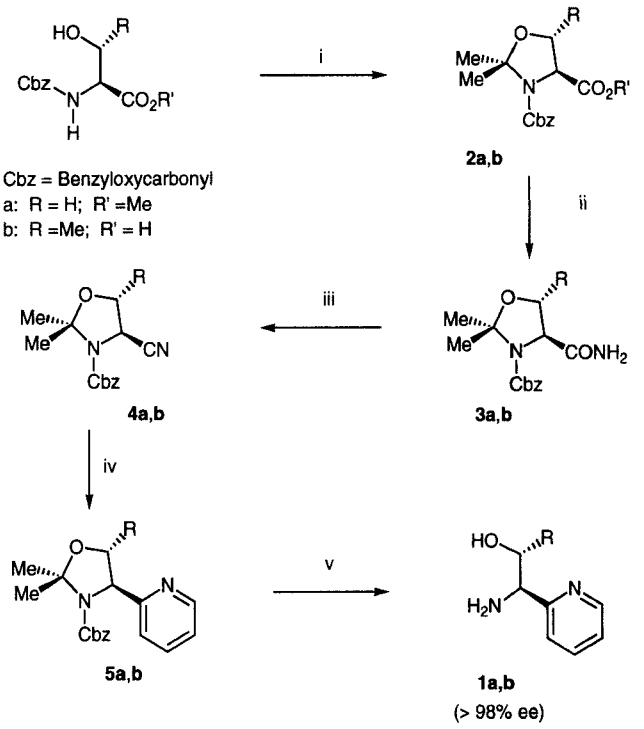


1b

Our synthetic strategy involves the simultaneous protection of hydroxy and amino groups of the starting L-serine and L-threonine. From literature reports, 2-amino-1-alkanols may be efficiently converted into oxazolines and oxazolidines.[5,7]

Although oxazolines seemed to be more convenient for our purpose, several attempts to obtain the pyridine derivatives in high enantiomeric purity failed. In fact, enantiomerically pure (*S*)-4-methoxycarbonyl-2-phenyl-2-oxazoline racemized during the conversion into the corresponding amide.[8] Thus, the preparation of title compounds **1a** and **1b** was accomplished in satisfactory yield by the multistep synthetic sequence depicted in the Scheme, that engages the 2,2-dimethyl-1,3-oxazolidine derivative instead.[9]

For the preparation of **1a**, the protection of hydroxy and amino functions was accomplished through acid catalyzed condensation of (*S*)-*N*-benzyloxycarbonylserine methyl ester[10] with 2,2-dimethoxypropane to give (4*S*)-*N*-benzyloxycarbonyl-4-methoxycarbonyl-2,2-dimethyl-1,3-oxazolidine **(2a)** (85%). Compound **2a** was converted into (4*S*)-*N*-benzyloxycarbonyl-4-carbamoyl-2,2-dimethyl-1,3-oxazolidine **(3a)** (70%) by treatment with ammonia in anhydrous methanol during 6 days. Subsequent reaction with *p*-TsCl in pyridine furnished (4*R*)-*N*-benzyloxycarbonyl-4-cyano-2,2-dimethyl-1,3-oxazolidine **(4a)** (70%) which was cocyclotrimerized with acetylene using (η-cyclopentadienyl) (η-1,5-cyclooctadienyl)cobalt [CpCo(COD)][11] as catalyst, affording (4*R*)-*N*-benzyloxycarbonyl-2,2-dimethyl-4-(2'-pyridyl)-1,3-oxazolidine **(5a)** (160°C, 14 bar, 6 days, 54% yield).



i. $Me_2C(OMe)_2$, BF_3 x Et_2O, 24 h, 85%; ii. for a: NH_3/MeOH, 3 days, r.t. 70%; for b: $ClCO_2Et$, THF, TEA, -20 °C, 30 min, NH_3 (g), -20 °C to r.t., 20 h, 70%; iii. *p*-TsCl, pyridine, 80 °C, 1 h, 70-88%; iv. 3% (CPD) Co (COD), toluene, acetylene, 12-14 bar, 160 °C, 3-6 days, 40-54%; v. HCl 4N, 24 h,100 °C, 75-80%.

Scheme

The critical role of temperature in the cocyclotrimerization step is noteworthy. In fact, up to 150°C no appreciable reaction was observed, while at 160°C the reaction took place, though with moderate convertion owing to the degradation of the catalyst. By increasing the amount of catalyst no improvement both in conversion and yield was observed.

The synthesis of pyridine **5b** was also accomplished according to the same procedure (Scheme) with a modification due to the very low yield in the conversion of the ester, (4*S*,5*R*)-*N*-benzyloxycarbonyl-4-methoxycarbonyl-2,2-dimethyl-5-methyl-1,3-oxazolidine into (4*S*,5*R*)-*N*-benzyloxycarbonyl-4-carbamoyl-2,2-dimethyl-5-methyl-1,3-oxazolidine **(3b)**. Thus, (1*S*,2*R*)-*N*-benzyloxycarbonylthreonine was directly treated with 2,2-dimethoxy-

propane affording (4*S*,5*R*)-*N*-benzyloxycarbonyl-2,2-dimethyl-5-methyl-1,3-oxazolidine-4-carboxylic acid **(2b)** (85%). Sequential treatment of the latter with ethyl chloroformate and ammonia gas furnished **3b** (70%). (4*R*,5*R*)-*N*-Benzyloxycarbonyl-4-cyano-2,2-dimethyl-5-methyl-1,3-oxazolidine **4b** (88%) and (4*R*,5*R*)-*N*-benzyloxycarbonyl-2,2-dimethyl-4-(2′-pyridyl)-5-methyl-1,3-oxazolidine **5b** (40%) were obtained analogously as described for compound **4a** and **5a**.

Finally, compounds **5a** and **5b** were hydrolyzed with 4 N hydrochloric acid affording **1a** (75%) and **1b** (80%) respectively. The enantiomeric (for **1a**) and diastereoisomeric (for **1b**) purities were determined by means of the reaction product with (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(+)-MPTACl]. For **1a** and **1b** the ^{19}F NMR analysis of the "Mosher amide" show that they exist in a 99:1 mixture of diastereoisomers, corresponding to a 98% ee, the same as the starting L-amino acids.

The diastereoisomeric purity of **1b** was further confirmed through the analysis of its ^1H NMR spectrum in which no signals due to a second diastereoisomer were detected. The ^1H NMR spectrum of the Mosher amide of compound **1a** in the presence of Eu(hfc)$_3$ confirms the ee value above mentioned.

It should be noted that on the basis of ^1H NMR and ^{13}C NMR data, all the amido compounds **2–5** here discussed exist, in solution and at room temperature, as a mixture of conformational isomers arising from restricted rotation about the amide bond. Under these conditions the C-2 methylene protons and benzylic protons of the benzyloxycarbonyl group are anisochronous in both isomers, and show different chemical shifts and coupling constants.[12]

In conclusion, the data reported suggest that the optically active 2-amino-2-(2′-pyridyl)-1-alkanols **1a, b** can be conveniently obtained from the suitable β-hydroxy-α-amino acids with complete retention of the configuration of the chiral centres.

Boiling points are uncorrected. Melting points were measured on a Kofler apparatus and are uncorrected. Elemental analyses were obtained at the Dipartimento di Chimica of the Università di Sassari with a Perkin–Elmer 2400 analyzer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter in a 1 dm tube. ^1H NMR (300 MHz), ^{13}C NMR (75.4 MHz), and ^{19}F NMR (282 MHz) spectra were obtained with a Varian VXR 300 spectrometer. The cocyclotrimerization reactions were carried out in a Parr 4560 (type 316 stainless steel) apparatus with 4842 controller. All known compounds used in this research were prepared according to the literature procedures or purchased from standard chemical suppliers and purified to match the reported physical and spectral data. The chiral compounds L-serine, L-threonine and (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid were purchased from Fluka or Aldrich. For new compounds satisfactory microanalyses were obtained: C ± 0.3, H ± 0.27, N ± 0.3.

(4*S*)-*N*-Benzyloxycarbonyl-4-methoxycarbonyl-2,2-dimethyl-1,3-oxazolidine (2a):

A solution of *N*-benzyloxycarbonylserine methyl ester (17.92 g, 70 mmol) in 2,2-dimethoxypropane (35 mL) was placed in a 250 mL two-necked flask and stirred at r.t. in the presence of $BF_3 \cdot OEt_2$ (0.3 mL) as catalyst under an Ar atmosphere, while monitoring by TLC (eluent: CH_2Cl_2). After 24 h the mixture was concentrated at reduced pressure, diluted with Et_2O, washed with a sat. solution of $NaHCO_3$ (3 × 100 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (silica gel, petroleum ether bp 40–70 °C/EtOAc, 8:2) to afford pure **2a**; yield: 17.3 g (85%); oil; $[\alpha]_D^{27}$ −55.9 (*c* = 2.7, MeOH).

^1H NMR ($CDCl_3$, mixture of 2 isomers in 33:64 ratio): δ = 1.50–1.75 (m, 12H, 2 isom.), 3.65 (s, 3H, maj. isom., OCH_3), 3.80 (s, 3H, min. isom., OCH_3), 4.05–4.20 (m, 4H, 2 isom.), 4.49 (dd, 1H, *J* = 12.2, 4.0 Hz, maj. isom.), 4.56 (dd, 1H, *J* = 12.2, 4.0 Hz, min. isom.), 5.05 (d, 1H, 1/2 AB system, *J* = 14.0 Hz, maj. isom.), 5.17 (d, 1H 1/2 AB system, *J* = 14.0 Hz, maj. isom.), 5.19 (d, 1, 1/2 AB system, *J* = 9.8 Hz, min. isom.), 5.23 (d, 1H, 1/2 AB system, *J* = 9.8 Hz, min. isom.), 7.25–7.40 (m, 10H, C_6H_5).

^{13}C NMR ($CDCl_3$, maj. isom.): δ = 24.10, 24.92, 52.38, 58.84, 66.15, 66.56, 95.50, 127.73, 128.16, 128.40, 136.20, 151.90, 171.50.

^{13}C NMR ($CDCl_3$, min. isom., all aromatic carbons omitted): δ: 25.15, 26.02, 52.55, 59.53, 66.76, 67.56, 95.00.

(4*S*,5*R*)-*N*-Benzyloxycarbonyl-2,2-dimethyl-5-methyl-1,3-oxazolidine-4-carboxylic Acid (2b):

A solution of *N*-benzyloxycarbonylthreonine[13] (2.68 g, 10.6 mmol), 2,2-dimethoxypropane (10 mL) and a few drops of $BF_3 \cdot OEt_2$ was stirred at r.t. with monitoring by TLC (eluent: CH_2Cl_2). After 24 h the resulting solution was concentrated at reduced pressure, treated with sat. $NaHCO_3$ solution and extracted with EtOAc. The organic phase was discarded and the aqueous solution was made acidic (10% HCl) until pH 1. Extraction with EtOAc (3 × 100 mL) gave pure **2b**; yield: 2.65 g (85%); oil; $[\alpha]_D^{27}$ −51.8 (*c* = 1.0, $CHCl_3$).

^1H NMR ($CDCl_3$, mixture of 2 isomers in 2:1 ratio): δ = 1.42 (d, 6H, *J* = 7.0 Hz, CH_3 at C-5, 2 isom.), 1.55, (s, 3H, CH_3 at C-2, min. isom.), 1.57 (s, 3H, CH_3 at C-2, min. isom.), 1.58 (s, 3H, CH_3 at C-2, maj. isom.), 1.67 (s, 3H, CH_3 at C-2, maj. isom.), 4.00 (d, 1H, *J* = 7.0 Hz, H-4, maj. isom.) 4.19 (d, 1H, *J* = 7.0 Hz, H-4, min. isom.), 4.15–4.30 (m, 2H, H-5, 2 isom.), 5.04 (d, 1H, 1/2 AB system, *J* = 12.3 Hz, $PhC\underline{H}_2$, maj. isom.), 5.08 (d, 1H, 1/2 AB system, *J* = 12.3 Hz, $PhC\underline{H}_2$, maj. isom.), 5.12 (d, 1H, 1/2 AB system, *J* = 12.3 Hz, $PhC\underline{H}_2$, min. isom.), 5.19 (d, 1H, 1/2 AB system, *J* = 12.3 Hz, $PhC\underline{H}_2$, min. isom.), 7.20–7.40 (m, 10H, C_6H_5, 2 isom.), 9.80 (br s, 1H, OH, exchangeable with D_2O).

^{13}C NMR ($CDCl_3$, maj. isom.): δ = 19.07, 23.86, 26.45, 65.40, 66.98, 74.22, 95.77, 127.70, 127.95, 128.40, 135.89, 151.65, 175.79.

^{13}C NMR ($CDCl_3$, min. isom., an aromatic carbon omitted): δ = 18.92, 24.87, 27.59, 66.07, 67.75, 73.69, 95.10, 128.20, 128.52, 135.75, 152.84, 174.98.

(4*S*)-*N*-Benzyloxycarbonyl-4-carbamoyl-2,2-dimethyl-1,3-oxazolidine (3a):

A solution of **2a** (18.9 g, 64.5 mmol) and MeOH (200 mL) was stirred at 0 °C and saturated with NH_3 gas. After 6 d the mixture was concentrated and the solid residue was recrystallized from a 1:1 mixture of acetone/hexane affording pure **3a**; yield: 12.5 g (70%) mp 117–119 °C; $[\alpha]_D^{27}$ −35.7 (*c* = 1.9, MeOH).

^1H NMR ($CDCl_3$): δ = 1.50 (br s, 3H), 1.70 (br s, 3H), 4.17 (br s, 2H), 4.40 (br s, 1H), 5.18 (br s, 2H), 6.00–6.60 (very broad signal, 2H, NH_2), 7.30 (br s, 5H, C_6H_5).

^{13}C NMR ($CDCl_3$): δ = 22.73, 26.59, 60.11, 65.20, 67.15, 95.50, 127.91, 128.25, 128.60, 135.80, 152.50, 173.60.

(4*S*,5*R*)-*N*-Benzyloxycarbonyl-4-carbamoyl-2,2-dimethyl-5-methyl-1,3-oxazolidine (3b):

To a cooled (−20 °C) solution of **2b** (35.6 g, 121 mmol) in anhydr. THF (250 mL) was added Et_3N (16.94 mL, 121 mmol) during 20 min. After 10 min ethyl chloroformate (11.37 mL, 121 mmol) was added at the same temperature during 10 min and stirred for an additional 20 min. The resulting mixture was saturated with NH_3 gas and kept at r.t. overnight. The mixture was concentrated at reduced pressure (20 Torr), the residue diluted with H_2O (100 mL) and extracted with EtOAc (4 × 50 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated affording pure **3b**; yield: 24.9 g (70%); oil; $[\alpha]_D^{25}$ −30.2 (*c* = 1.2, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 50 °C): δ = 1.40 (d, 3 H, J = 5.7 Hz), 1.58 (br s, 6 H), 3.83 (br s, 1 H), 4.23 (br s, 1 H), 5.04 (d, 1 H, 1/2 AB system, J = 12.6 Hz, PhC$\underline{H}_2$), 5.10 (d, 1 H, 1/2 AB system, J = 12.6 Hz, PhC$\underline{H}_2$), 5.80 (br s, 1 H, NH), 6.05 (br s, 1 H, NH), 7.12–7.44 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 50 °C): δ = 18.86, 25.21, 27.15, 61.01, 67.14, 74.32, 95.25, 128.03, 128.19, 128.51, 135.82, 153.36, 172.15.

(4*R*)-*N*-Benzyloxycarbonyl-4-cyano-2,2-dimethyl-1,3-oxazolidine (4a) and (4*R*,5*R*)-*N*-Benzyloxycarbonyl-4-cyano-2,2-dimethyl-5-methyl-1,3-oxazolidine (4b); General Procedure:

A solution of either **3a** or **3b** (36 mmol), *p*-TsCl (10.29 g, 54 mmol) and pyridine (70 mL) was purged with Ar and stirred at 80 °C for 1 h. The crude mixture was concentrated at reduced pressure and diluted with EtOAc (200 mL). The organic phase was washed with 2N HCl (3 × 50 mL), with H_2O (3 × 50 mL), $NaHCO_3$ (3 × 50 mL of a saturated solution), dried (Na_2SO_4), concentrated and purified by flash chromatography (CH_2Cl_2/hexane, 1:1).

4a: yield: 70 %; mp 70–72 °C (Et_2O/hexane); $[\alpha]_D^{25}$ −90.7 (c = 1.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$, mixture of 2 isomers in 1:2.5 ratio): δ = 1.45 (s, 3 H, min. isom.), 1.55 (s, 3 H, maj. isom.), 1.62 (s, 3 H, min. isom.), 1.70 (s, 3 H, maj. isom.), 4.09 (dd, 2 H, 1/2 AB system, J = 9.6, 5.7 Hz, 2 isom.), 4.24 (d, 2 H, 1/2 AB system, J = 9.6 Hz, 2 isom.), 4.64 (d, 1 H, J = 5.7 Hz, maj. isom.), 4.70 (d, 1 H, J = 5.7 Hz, min. isom.), 5.20 (m, 4 H, 2 isom.), 7.35–7.60 (m, 10 H, C_6H_5).

^{13}C NMR ($CDCl_3$, maj. isom.): δ = 23.68, 25.55, 46.93, 65.96, 66.38, 95.77, 117.62, 127.97, 128.30, 128.54, 135.47, 150.90.

^{13}C NMR ($CDCl_3$, min. isom., an aromatic carbon omitted): δ = 24.76, 26.55, 47.83, 67.63, 68.17, 95.17, 117.43, 128.16, 128.42, 135.25, 152.14.

IR (KBr): ν = 2900, 2220, 1700, 1400 cm^{-1}.

4b: yield: 88 %; oil; $[\alpha]_D^{25}$ −75.1 (c = 1.3, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 50 °C): δ = 1.42 (d, 3 H, J = 19.8 Hz, CH_3 at C-5), 1.58 (s, 3 H, CH_3 at C-2), 1.66 (s, 3 H, CH_3 at C-2), 4.10–4.20 (m, 1 H, H-4), 4.47 (qd, 1 H, J_1 = J_2 = 6.0 Hz, H-5), 5.18 (br s, 2 H, PhC$\underline{H}_2$), 7.25–7.50 (m, 5 H, C_6H_5).

^{13}C NMR ($CDCl_3$, 50 °C): δ = 18.20, 23.35, 26.35, 52.23, 60.14, 67.64, 74.40, 96.12, 116.77, 128.08, 128.40, 135.27, 150.97.

IR (KBr disk): ν = 2890, 2215, 1700, 1378 cm^{-1}.

(4*R*)-*N*-Benzyloxycarbonyl-2,2-dimethyl-4-(2′-pyridyl)-1,3-oxazolidine (5a), (4*R*,5*R*)-*N*-Benzyloxycarbonyl-2,2-dimethyl-5-methyl-4-(2′-pyridyl)-1,3-oxazolidine (5b); General Procedure:

CpCo(COD) (100 mg, 0.43 mmol) was placed in a stainless steel autoclave, purged with Ar, sealed and the gas removed by vacuum pump (0.1 Torr). A solution of either **4a** or **4b** (14.0 mmol) in toluene (100 mL) was added by suction. The reaction vessel was pressurized with acetylene (12–14 Bar), and stirred at 160 °C for the times indicated below. After cooling at r.t., the mixture was filtered, and extracted with 10 % aq HCl (50 mL). The aqueous phase was separated from toluene solution, washed with EtOAc (3 × 50 mL), then made alkaline (NaOH). Extraction with EtOAc (3 × 50 mL), drying (Na_2SO_4), and removal of the solvent at reduced pressure gave the product which was purified by flash chromatography (eluent: EtOAc). Unreacted starting material was recovered without loss of ee, by concentration of the toluene solution and subsequent purification of the residue by chromatography through a short silica gel column.

5a: time: 6 d; yield: 54 %; oil; $[\alpha]_D^{25}$ −97.8 (c = 1.9, $CHCl_3$).

^{1}H NMR ($CDCl_3$, mixture of 2 isomers in a 3:1 ratio): δ = 1.58 (s, 3 H, min. isom., CH_3), 1.64 (s, 3 H, maj. isom., CH_3), 1.73 (s, 3 H, min. isom., CH_3), 1.81 (s, 3 H, maj. isom. CH_3), 4.08–4.22 (m, 2 H, 2 isom.), 4.32–4.42 (m, 2 H, 2 isom.), 4.95 (d, 2 H, 1/2 of AB system, J = 12.0 Hz, PhC$\underline{H}_2$, 2 isom.), 6.93 (d, 2 H, 1/2 of AB system, J = 12.0 Hz, PhC$\underline{H}_2$, 2 isom.), 5.06–5.25 (m, 2 H, 2 isom.), 5.06–7.02 (m, 2 H, Py, 2 isom.), 7.12–7.30 (m, 2 H, Py, 2 isom.), 7.34–7.42 (m, 2 H, Py, 2 isom.), 7.54–7.68 (m, 10 H, C_6H_5, 2 isom.), 8.52–8.60 (m, 2 H, Py, 2 isom.).

^{13}C NMR ($CDCl_3$, 50 °C): δ = 23.40, 25.81, 62.17, 67.39, 66.68, 95.28, 119.98, 122.13, 127.42, 127.67, 128.13, 128.50, 136.49, 149.15, 152.46, 160.66.

IR (neat): ν = 3500, 3061, 3030, 2983, 2936, 2883, 1704, 1591, 1566, 1465, 1433, 1403, 1378, 1349, 1287, 1255, 1210, 1151, 1093, 849, 767, 750, 698, 626 cm^{-1}.

5b: time: 3 d; yield: 40 %; oil; $[\alpha]_D^{25}$ −63.4 (c = 1.9, $CHCl_3$).

^{1}H NMR ($CDCl_3$, mixture of 2 isomers in 1:1 ratio): δ = 1.34 (d, 3 H, J = 6.0 Hz, CH_3, 1 isom.), 1.35 (d, 3 H, J = 6.0 Hz, CH_3, 1 isom.), 1.76 (b, 12 H, 2 isom., CH_3), 4.02–4.24 (m, 2 H, 2 isom.), 4.40–4.54 (m, 2 H, 2 isom.), 4.68–5.20 (m, 4 H, 2 isom.), 6.66–6.82 (m, 2 H, Py, 2 isom.), 7.04–7.42 (m, 12 H, C_6H_5, Py, 2 isom.), 7.44–7.70 (m, 2 H, Py, 2 isom.), 8.42–8.62 (m, 2 H, Py, 2 isom.).

^{13}C NMR ($CDCl_3$, 50 °C): δ = 17.52, 24.93, 26.55, 66.37, 69.56, 77.79, 95.02, 120.64, 122.25, 127.63, 128.06, 128.45, 135.88, 136.48, 149.26, 152.28, 159.21.

IR (neat): ν = 3369, 2932, 1704, 1589, 1469, 1435, 1405, 1377, 1347, 1255, 1212, 1135, 1118, 767, 749, 697, 661 cm^{-1}.

(*R*)-2-Amino-2-(2′-pyridyl)ethanol (1a) and (1*R*,2*R*)-1-Amino-1-(2′-pyridyl)propan-2-ol (1b); General Procedure:

A solution of either **5a** or **5b** (6.4 mmol) and 4N HCl (6 mL) was heated while stirring at 100 °C for 24 h. After cooling at 0 °C, the mixture was made cautiously alkaline with 5 % NaOH solution and then saturated with NaCl. The mixture was extracted with EtOAc (5 × 40 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The oily residue was distilled at reduced pressure.

1a: yield: 75 %; bp 125 °C/0.05 Torr; $[\alpha]_D^{27}$ −10.4 (c = 2.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 2.82 (s, 3 H, NH_2, OH, exchangeable with D_2O), 3.68 (dd, 1 H, 1/2 AB system, J = 10.8, 6.4 Hz), 3.78 (dd, 1 H, 1/2 AB system, J = 10.8, 4.8 Hz), 4.01 (dd, 1 H, 1/2 AB system, J = 6.4, 4.8 Hz), 7.15 (ddd, 1 H, J = 7.5, 5.6, 1.1 Hz, Py), 7.29 (d, 1 H, J = 7.9 Hz, Py), 7.63 (td, 1 H, J = 7.7, 1.8 Hz, Py), 8.48 (d of multiplets, 1 H, J = 5.6 Hz, Py).

^{13}C NMR ($CDCl_3$): δ = 57.28, 67.15, 121.65, 122.34, 136.82, 148.93, 162.09.

IR (neat): ν = 3276, 2917, 2861, 2500, 1590, 1566, 1471, 1433, 1296, 889, 782, 750, 620 cm^{-1}.

1b: yield: 80 %; bp 120 °C/0.05 Torr; $[\alpha]_D^{25}$ +5.6 (c = 1.6, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 1.08 (d, 3 H, J = 6.0 Hz, CH_3 at C-5), 2.70 (br s, 3 H, NH_2, OH, exchangeable with D_2O), 3.58 (d, 1 H, J = 5.6 Hz, H-4), 3.87 (dd, 1 H, J = 6.0, 5.6 Hz, H-5), 7.12–7.22 (m, 2 H, Py), 7.62 (td, 1 H, J = 7.8, 1.8 Hz, Py), 8.49 (d, 1 H, J = 4.8 Hz, Py).

^{13}C NMR ($CDCl_3$): δ = 19.24, 61.94, 70.16, 122.33 (2C), 136.63, 149.08, 162.65.

IR (neat): ν = 3350, 3280, 3190, 2975, 2960, 1590, 1567, 1471, 1433, 1369, 1299, 1115, 783, 752, 620 cm^{-1}.

2-Amino-*N*-(α-methoxy-α-trifluoromethylphenylacetyl)-2-(2′-pyridyl)ethanol; Typical Procedure:

A sample of **1a** (0.124 g, 0.9 mmol) and freshly distilled (+)-MPTACl (0.196 g, 0.77 mmol) were mixed with CCl_4 (1 mL) and dry pyridine (1 mL) at 0 °C and then allowed to stand for 48 h at r.t. H_2O (20 mL) was added and the mixture was extracted with Et_2O (60 mL). The ethereal phase was washed successively with sat. Na_2CO_3 solution (3 × 20 mL), H_2O (5 × 30 mL) and dried (Na_2SO_4). After removal of the solvent at reduced pressure, the residual 2-amino-*N*-(α-methoxy-α-trifluoromethylphenylacetyl)-2-(2′-pyridyl)ethanol was analyzed by ^{19}F and ^{1}H NMR spectra; yield: 0.259 g (95 %).

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