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Chiral Ligands Containing Heteroatoms:13.[1] Optically Active 4-(2'-Pyridyl)-1,3-oxazolidines: an Improved Synthesis of 2-(2'-Pyridyl)-2-aminoalcohols

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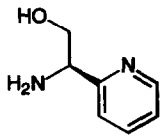
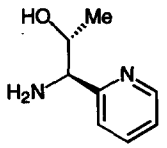
Abstract: An improved synthesis of 2-(2'-pyridyl)-2-aminoalcohols **1a** and **1b**, in enantiomerically pure form *via* 1,3-oxazolidine derivatives is presented. Some efficient and selective methods for both the cleavage of the oxazolidine ring and the removal of the *N*-Boc protecting group are also reported.

Optically active amino alcohols are of relevance as tools in asymmetric processes.[2,3,4] Very recently we have reported the preparation of (*R*)-2-amino-2-(2'-pyridyl)ethan-1-ol (**1a**) and (1*R*,2*R*)-1-amino-1-(2'-pyridyl)propan-2-ol (**1b**) starting from natural L-serine and L-threonine by means of a multistep reaction sequence, in *ca.* 25 % overall yield.[1]



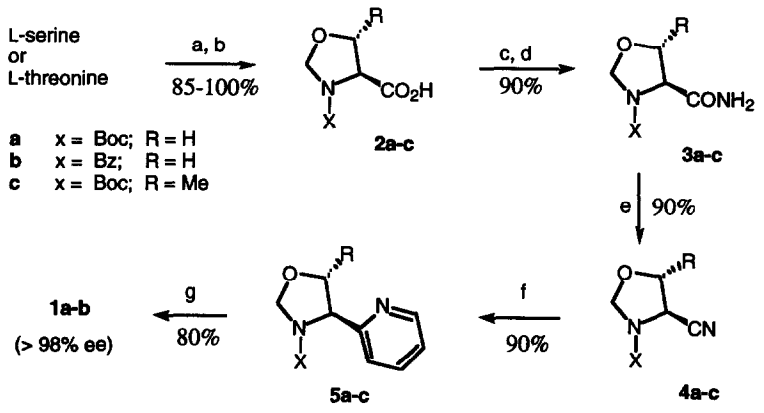
1a



1b

In the context of a project designed to use these compounds in asymmetric reactions, such as the alkylation of aldehydes with dialkylzinc reagents,[3] the reduction of ketones to alcohols with boranes[4] and for the preparation of bis oxazoline derivatives with C_2 axial symmetry,[5] we required an efficient route to prepare multigram quantities of both **1a** and **1b**. In this paper we wish to describe a very simple preparation of *N*-*t*-butoxycarbonyl- or *N*-benzoyl- protected 4-(2'-pyridyl)-1,3-oxazolidines **5a-c** as versatile precursors of **1a** and **1b**. Efficient procedures for the selective removal of the *N*-protecting groups are also reported.

Compounds **1a-b** were achieved through a five step reaction sequence (Scheme 1) with 60% overall yield without loss of enantiomeric excess. (*S*)-*N*-Benzoyl-1,3-oxazolidine-4-carboxylic acid (**2b**) was obtained as previously described for the D enantiomer.[6] Through a simple modification, (*S*)-*N*-*t*-butoxycarbonyl-1,3-oxazolidine-4-carboxylic acid (**2a**) and (4*S*,5*R*)-*N*-*t*-butoxycarbonyl-5-methyl-1,3-oxazolidine-4-carboxylic acid (**2c**) were obtained by reaction of L-serine or L-threonine with formaldehyde (aq 37%, NaOH 2N), followed by trapping with Boc_2O up to 250 mmol scale, in a facile one pot reaction (Scheme 1).



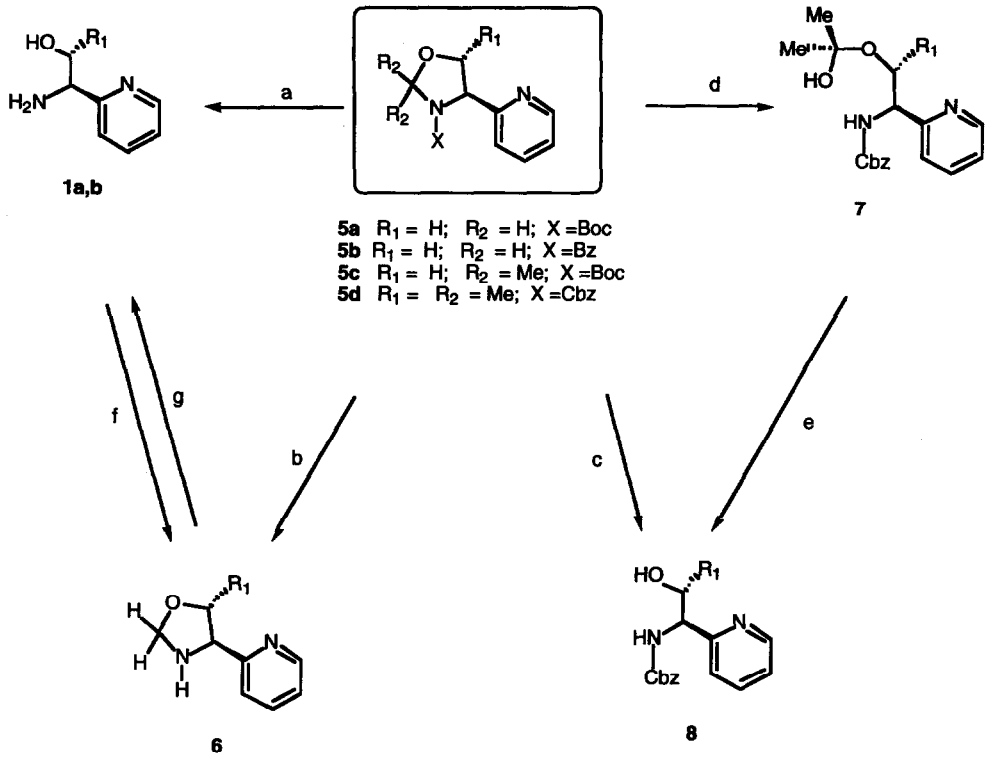
Scheme 1

a. HCHO, NaOH 2 N, 2 °C, 24 h; b. pH 8, Acetone, $(Boc)_2O$ or BzCl, 2°C to r.t., 1 h; c. $ClCO_2Et$, THF, TEA, -20°C, 30 min; d. NH_3 g, -30°C to r.t., 20 h; e. *p*-TsCl, pyridine, 80 °C, 1 h; f. 3% Cp Co (COD), toluene, acetylene, 14 bar, 120 °C, 2 h; g. HCl 6-12N, 24 h, 100 °C.

Compounds **2a-c** were reacted with ethyl chloroformate and ammonia gas affording (4*S*)-*N*-*t*-butoxycarbonyl-4-carbamoyl-1,3-oxazolidine **3a** (90%), (4*S*)-*N*-benzoyl-4-carbamoyl-1,3-oxazolidine **3b** (90%), and (4*S*,5*R*)-*N*-*t*-butoxycarbonyl-4-carbamoyl-5-methyl-1,3-oxazolidine **3c** (90%). Carbamoyl compounds **3a-c** were treated under standard conditions[1] with *p*-TsCl in pyridine (1 hr, 80 °C) leading to (4*R*)-*N*-*t*-butoxycarbonyl-4-nitrile-1,3-oxazolidine **4a** (90%), (4*R*)-*N*-benzoyl-4-nitrile-1,3-oxazolidine **4b** (90%) and (4*R*,5*R*)-*N*-*t*-butoxycarbonyl-4-nitrile-5-methyl-1,3-oxazolidine **4c** (90%). Compounds **4a-c** were converted quantitatively into the pyridyl derivatives (4*R*)-*N*-*t*-butoxycarbonyl-4-(2'-pyridyl)-1,3-oxazolidine **5a**, (4*R*)-*N*-benzoyl-4-(2'-pyridyl)-1,3-oxazolidine **5b** and (4*R*,5*R*)-*N*-*t*-butoxycarbonyl-4-(2'-pyridyl)-5-methyl-1,3-oxazolidine **5c** by a cobalt catalyzed co-cyclotrimerization with acetylene.[7]

We have reported that during the conversion of (4*R*)-*N*-benzyloxycarbonyl-2,2-dimethyl-4-nitrile-1,3-oxazolidine into the corresponding pyridyl derivative by co-cyclotrimerization with acetylene, the temperature played a very critical role.[1] In fact the reaction had to be carried out at 160 °C for a long time and with moderate conversion. When **4a-c** were involved, the reaction required mildest conditions (120 °C, 2 hr for **4a,b**; 10 hr for **4c**), confirming the role of steric hindrance of substituents at C2 and at nitrogen atom. The acidic hydrolysis of **5a,b** or **5c** furnished **1a** or **1b** respectively in good yield (60% overall yield starting from the corresponding α-aminoacid).

During the course of our researches it appeared interesting to remove selectively the *N*-protecting groups while retaining the 1,3-oxazolidine ring, in order to obtain an interesting class of ligands such as (4*R*)-4-(2'-pyridyl)-1,3 oxazolidine (**6**). Note that compounds like **5a-c** are peculiar owing to the acid lability of the oxazolidine ring. To the best of our knowledge, only a few examples are reported of the selective removal of the *N*-Boc protecting group in the presence of other acid sensitive functions.[8] Therefore we have deblocked the oxazolidine derivatives **5a-d** under various experimental conditions leading to different products (Scheme 2).



Scheme 2

a. HCl 6N, 24 h, 100 °C, 80 %; b. R_2 = H, X =Boc, CF_3COOH, CH_2Cl_2 , 20 min, r.t.,100 % or 10% aq H_2SO_4 : Dioxane 1:1 ratio, 24 h, r.t. 85%; c. R_2 = Me, X = Cbz, MeOH/HCl $_{gas}$, 24 h, reflux, 100%; d. R_2 = Me, X = Cbz, MeOH/HCl $_{gas}$, 24 h, r.t., 100%; e. MeOH/HCl $_{gas}$, 24 h, reflux, 100%; f. HCHO 37%, NH_4Cl, 24 h, r.t. 80%; g. aq HCl/MeOH, r.t. 24 h, 100%.

Compound **5c** reacted with trifluoroacetic acid in dichloromethane at room temperature affording **6** in quantitative yield. This reaction was shown to be clean only on 0.01 mmol scale: using greater quantities of substrate, significant concentration of **1b** was also detected. The same results were obtained using dry 4.5 N HCl in MeOH, the ratio of products **6** and **1b** being strongly influenced both from traces of water and from HCl normality. These problems were overcome by treating **5c** with 10% aqueous H_2SO_4 and dioxane (1:1 ratio; r.t.; 24 hr): the reaction, scaled up to 3 g (11.4 mmol), affords **6** (85%).

Surprisingly, (4*R*,5*R*)-*N*-benzyloxycarbonyl-2,2-dimethyl-4-(2'-pyridyl)-5-methyl-1,3-oxazolidine (**5d**)[1] underwent reaction with 4.5 N HCl in MeOH to give (1*R*,2*R*)-1-(*N*-benzyloxycarbonyl)amino-1-(2'-pyridyl)propan-2-(1'-hydroxy-1'-methyl)ethylether (**7**) at room temperature, or alternatively (1*R*,2*R*)-1-(*N*-benzyloxycarbonyl)amino-1-(2'-pyridyl)propan-2-ol (**8**) at reflux temperature, in each case in quantitative yield. It is noteworthy that retention of the *N*-protecting group should allow direct modification of the hydroxylic function of the substrate.

From a synthetic point of view the results presented here underline the advantage offered by little differences in the stability of widely used protecting groups toward acid reagents. All the processes involved occurred without racemization. Each compound **5-8** was in fact converted into **1a,b** whose optical rotation - e.e. relationship is known.[1]

More extensive studies in the preparation and application of new chiral auxiliaries from α-amino-β-hydroxy acids are in progress.

Acknowledgments.

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EXPERIMENTAL

Boiling points are uncorrected. Melting points were measured on a Kofler apparatus and are uncorrected. Microanalytical determinations were performed on a Perkin Elmer 2400 analyser. Optical rotations were measured with a Perkin Elmer 241 polarimeter in a 1 dm tube. ^{1}H NMR (300 MHz), ^{13}C NMR (75.4 MHz) spectra were obtained with a Varian VXR 300 spectrometer. The co-cyclotrimerization reactions were carried out into 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 were purchased from Fluka Chemie AG or Aldrich Company. For new compounds satisfactory microanalyses were obtained: C ± 0.3, H ± 0.27, N ± 0.3.

(*R*)-2-amino-2-(2'-pyridyl)-ethan-1-ol (1a) and (1*R*,2*R*)-1-(2'-pyridyl)-1-amino-propan-2-ol (1b). General procedure:

A solution of **5a-d** (40 mmol) and 6 *N* HCl (50 mL) (12 *N* HCl for **5b**) was heated at 100 °C for 24 hr. After cooling at 0 °C the crude was made cautiously alkaline with 5% sodium hydroxide and then saturated with NaCl. The mixture was extracted with AcOEt (5 x 60 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The oily residue was distilled at reduced pressure. Compounds **1a** (80 % yield) and **1b** (80 % yield) were recognized by comparison with an authentic sample.[1]

(4*S*)-*N*-*t*-butoxycarbonyl-1,3-oxazolidine-4-carboxylic acid (2a), (4*S*)-*N*-benzoyl-1,3-oxazolidine-4-carboxylic acid (2b) and (4*S*,5*R*)-*N*-*t*-butoxycarbonyl-5-methyl-1,3-oxazolidine-4-carboxylic acid (2c):

A solution of L-serine (26.27 g, 250 mmol) and 37% formaldehyde (250 mmol) in 2*N* NaOH (125 mL) was stirred at 2 °C for 24 hr. A solution of an equimolar amount of either benzoyl chloride (35.04 g) or di-*tert*-butyl dicarbonate (54.5 g) in acetone (100 mL) was added dropwise at this temperature. During the benzoylation the pH was adjusted above 7 with solid $NaHCO_3$. After 1 hr water was added and the mixture extracted with AcOEt (3 x 100 mL). The combined organic phases were discarded and the aqueous solution was made acidic until pH 1 (10% HCl). Extraction with diethyl ether (3 x 100 mL) affords, after concentration of the solvent, pure **2a,b**. Compound **2c** was prepared following the described procedure starting from L-

threonine.

2a: 100% yield; oil. $[\alpha]_D^{25}$ = -81.8 (c = 2.6, $CHCl_3$) ^1H NMR ($CDCl_3$) δ (ppm): 1.50 (s, 9 H, *t*-Bu), 4.20 (bs, 2 H), 4.45 (bs, 1 H), 4.85-5.00 (m, 2 H), 7.80-8.10 (b signal, 1 H, OH, exchangeable with D_2O). ^{13}C NMR ($CDCl_3$) δ (ppm): 28.18, 56.75, 70.47, 79.37, 82.01, 153.5, 173.94. IR (neat) ν: 3445, 2977, 2884, 1704, 1418, 1368, 1171, 1143, 861, 806, 768 cm^{-1}.

2b: 85% yield; mp.144-6 °C (CH_2Cl_2-light petrol); $[\alpha]_D^{25}$ = -138.6 (c = 2.0, MeOH). ^1H NMR ($CDCl_3$) δ (ppm): 4.10-30 (m, 1 H), 4.38 (bs, 1 H), 4.80-5.30 (m, 3 H), 7.30-7.70 (series of m, 5 H, Ph), 10.00 (s, 1 H, OH, exchangeble with D_2O). ^{13}C NMR ($CDCl_3$) δ (ppm): 56.88, 69.46, 80.89, 127.18, 128,58, 130.00, 131.45, 169.50, 172.58.

2c: 95% yield; $[\alpha]_D^{25}$ = -101.1 (c = 2.2, $CHCl_3$). ^1H NMR ($CDCl_3$, mixture of isomers) δ (ppm): 1.40-1.55 (m, 12 H), 3.85-3.90 (m, 1 H), 4.25 (bs, 1 H), 4.75-4.85 (m, 1 H), 5.10-5.20 (m, 1 H), 8.6 (bs, 1 H, OH, exchangeable with D_2O). ^{13}C NMR ($CDCl_3$, mixture of isomers) δ (ppm): 18.38, 28.16, 63.09, 63.74, 78.34, 78.77, 79.29, 81.38, 81.88, 152.17, 153.37, 173.82, 175.12. IR (neat) ν: 3473, 2977, 2933, 1705, 1686, 1412, 1368, 1231, 1174, 1150, 883, 865, 768 cm^{-1}.

(4*S*)-*N*-*t*-butoxycarbonyl-4-carbamoyl-1,3-oxazolidine (3a), (4*S*)-*N*-benzoyl-4-carbamoyl-1,3-oxazolidine (3b), (4*S*,5*R*)-*N*-*t*-butoxycarbonyl-4-carbamoyl-5-methyl-1,3-oxazolidine (3c):

A solution of **2a**, **2b** or **2c** (121 mmol) in dry THF (250 mL) was cooled to -20 °C and Et_3N (16.94 mL; 121mmol) was added during 20 min and kept stirring for an additional 10 min.; at the same temperature ethylchloroformate (11.37 mL, 121 mmol) was slowly dropped in and after 20 min the resulting mixture, previously cooled at -30 °C, was saturated with ammonia gas and warmed to room temperature while stirring, for 20 hr. The reaction mixture was concentrated at reduced pressure (20 Torr) and the residue was diluted with water (100 mL) and extracted with AcOEt (4 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated.

3a: 90% yield, oil; $[\alpha]_D^{27}$ = -83.7 (c = 3.3, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.41 (s, 9 H, *t*-Bu), 4.08 (bs, 1 H), 4.28 (bs, 2 H), 4.73 (bs, 1 H), 4.90 (bs, 1 H), 5.63 (bs, 1 H, NH), 6.70 (bs, 1 H, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 28.32, 58.07, 69.79, 79.56, 81.77, 153.34, 173.45. IR (neat) ν: 3408, 2975, 2933, 1683, 1398, 1367, 1255, 1168, 863, 769 cm^{-1}.

3b: 90% yield, oil; $[\alpha]_D^{27}$ = -296.5 (c = 1.7, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 4.20-4.45 (m, 2 H), 4.78-5.10 (m, 3 H), 5.70-5.90 (bs, 1 H, NH), 6.85, 7.10 (bs, 1 H, NH), 7.35-7.60 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$) δ (ppm): 56.70, 68.43, 81.17, 89.70, 127.37, 128.68, 131.63, 134.52, 170.56, 171.17. IR (neat) ν: 3393, 3057, 3010, 2977, 2880, 2866, 1683, 1634, 11446, 1404, 1308, 1228, 1193, 871, 790, 721 cm^{-1}.

3c: 90% yield, oil; $[\alpha]_D^{27}$ = -98.9 (c = 2.2, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.37-1.49 (m, 12 H), 3.79 (m, 1 H, H5), 4.10-4.30 (m, 1 H), 3.65 (d, *J* = 6.3 Hz, 1 H, H4), 5.00-5.20 (m, 1 H), 6.20-6.60 (broad signal, 2 H, NH_2). ^{13}C NMR ($CDCl_3$) δ (ppm): 18.55, 28.16, 64.65, 78.78 (2 C), 81.71, 153.87, 172.54. IR (neat) ν: 3333, 3159, 2973, 2933, 1698, 1670, 1625, 1404, 1367, 1257, 1231, 1154 cm^{-1}.

(4*R*)-*N*-*t*-butoxycarbonyl-4-nitrile-1,3-oxazolidine (4a), (4*R*)-*N*-benzoyl-4-nitrile-1,3-oxazolidine (4b), and (4*R*,5*R*)-*N*-*t*-butoxycarbonyl-4-nitrile-5-methyl-1,3-oxazolidine (4c). General procedure:

A solution of **3a-c** (36 mmol), *p*-TsCl (10.29 g, 54 mmol) and pyridine (54 mL) was purged with argon and stirred at 80°C for 1 hr. The crude was concentrated at reduced pressure, diluted with AcOEt (200 mL) and the organic phase was cooled with an ice bath, and sequentially washed with 2*N* HCl (3 x 50 mL), H_20 (3 x 50 mL), $NaHCO_3$ (3 x 50 mL of a saturated solution), dried (Na_2SO_4), concentrated and purified by flash chromatography (CH_2Cl_2-*n*-hexane 1/1):

4a: 90% yield. oil; $[\alpha]_D^{25}$ = -121.5 (c = 1.6, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.50 (s, 9 H, *t*-Bu), 4.15-4.30 (m, 2 H), 4.50-70 (broad signal, 1 H), 4.80-5.00 (broad signal, 2 H). ^{13}C NMR ($CDCl_3$) δ (ppm): 28.15, 45.54, 70.87, 76.59, 82.50, 117.06, 151.15. IR (neat) ν: 2976, 2933, 2882, 2245, 1720, 1395, 1259, 1215, 1165, 896, 855, 768 cm^{-1}.

4b: 90% yield. oil; $[\alpha]_D^{25}$ = -197.9 (c = 2.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 4.05-4.18 (m, 1 H), 4.20-4.45 (series of m, 2 H), 5.10 (bs, 2 H), 7.40-7.70 (series of m, 5 H, Ph). ^{13}C NMR ($CDCl_3$) δ (ppm): 45.03, 69.83, 80.79, 116.75, 127.51, 128.72, 131.95, 133.70, 169.00. IR (neat) ν: 3058, 2979, 2883, 2246, 1741, 1651, 1600, 1446, 1386, 1203, 1159, 786, 721, 700, 669 cm^{-1}.

4c: 90% yield. oil; $[\alpha]_D^{25}$ = -129.9 (c = 2.3, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.38-1.58 (m, 12 H), 3.90-4.15 (m, 1 H), 4.35 (quintet, *J* = 6.0 Hz, 1 H, H5), 4.71 (d, *J* = 6.0 Hz, 1 H, H4), 5.00-5.20 (m, 1 H). ^{13}C NMR ($CDCl_3$) δ (ppm): 17.20, 28.09, 51.64, 78.76, 79.36, 82.38, 116.49, 151.93. IR (neat) ν: 2977, 2936, 2878, 2248, 1707, 1393, 1368, 1256, 1174, 1150, 874, 769 cm^{-1}.

(4*R*)-*N*-*t*-butoxycarbonyl-4-(2'-pyridyl)-1,3-oxazolidine (5a), (4*R*)-*N*-benzoyl-4-(2'-pyridyl)-1,3-oxazolidine (5b), (4*R*,5*R*)-*N*-*t*-butoxycarbonyl-4-(2'-pyridyl)-5-methyl-1,3-oxazolidine (5c). General Procedure:

CpCo(COD) (200 mg, 0.86 mmol) in a stainless steel autoclave was purged with argon, sealed and the gas removed by *vacuum* pump (0.1 Torr). A solution of **4a-c** (80 mmol) in toluene (100 mL) was added by suction. The reaction vessel was pressurized with acetylene (14 Bar), and stirred at temperatures for the times indicated. After cooling at room temperature the reaction mixture was filtered, and extracted with 10% aq HCl (50 mL). The aqueous phase was washed with AcOEt (3 x 50 mL) and then made alkaline (NaOH). Extraction with AcOEt (3 x 50 mL), drying (Na_2SO_4), and removal of the solvent at reduced pressure gave the product which was purified by flash chromatography (eluant AcOEt) giving the pure pyridine derivative.

5a: 2 hr, 120 °C, 90% yield; oil; $[\alpha]_D^{30}$ = -86.3 (c = 1.6, $CHCl_3$). ^1H NMR ($CDCl_3$, mixture of isomers) δ (ppm): 1.10-1.60 (series of bs, 9 H, *t*-Bu), 3.60-3.80 (m, 1 H), 4.05-4.25 (bs, 1 H), 4.30-4.50 (bs, 1 H), 4.95-5.30 (bs, 2 H), 7.10-7.40 (m, 2 H, Py), 7.60-7.85 (m, 1 H, Py), 8.50-8.60 (m, 1 H, Py). ^{13}C NMR ($CDCl_3$) δ (ppm): 28.19, 60.74, 73.30, 79.89, 120.28, 122.33, 136.65, 149, 27, 152.96, 160.06. IR (neat) ν: 3053, 2974, 2932, 2869, 1699, 1590, 1472, 1433, 1395, 1366, 1168, 770, 750, 718, 665 cm^{-1}.

5b: 2 hr, 120 °C, 90% yield; oil; $[\alpha]_D^{25}$ = -145.4 (c = 3.3, $CHCl_3$). ^1H NMR ($CDCl_3$, mixture of isomers) δ (ppm): 4.00-4.55 (m, 2 H), 4.90-5.60 (m, 3 H), 6.98-7.70 (m, 8 H, Ph and Py), 8.35-8.70 (bs, 1 H, Py).

^{13}C NMR ($CDCl_3$, temp. 50 °C) δ (ppm): 59.26, 72.30, 81.40, 121.67, 122.44, 127.25, 128.23, 128.60, 130.97, 135.37, 136.57, 149.43, 158.28. IR (neat) ν: 3445, 3057, 3001, 2938, 2873, 1731, 1702, 1634, 1590, 1575, 1470, 1444, 1434, 1398, 1284, 1244, 1181, 1156, 1076, 844, 788, 750, 721, 700, 664 cm^{-1}.

5c: 10 hr, 120 °C, 90% yield; oil; $[\alpha]_D^{25}$ = -97.1 (c = 1.9, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.00-1.55 (m, 12 H), 4.13 (bs, 1 H), 4.30-4.46 (m, 1 H), 4.96 (bs, 1 H), 5.18-5.38 (m, 1 H), 7.17 (t, *J* = 6.3 Hz, 1 H, Py), 7.26 (d, *J* = 7.2 Hz, 1 H, Py),7.65 (t, *J* = 6.3 Hz, 1 H, Py), 8.54 (d, *J* = 4.5 Hz, 1 H, Py). ^{13}C NMR ($CDCl_3$) δ (ppm): 17.46, 27.99, 67.74, 79.23, 80.36, 82.54, 120.69, 122.37, 136.57, 149.27, 159.70. IR (neat) ν: 2973, 2929, 2868, 1698, 1472, 1433, 1393, 1365, 1173, 867, 769, 749 cm^{-1}.

(4*R*)-4-(2'-pyridyl)-1,3 oxazolidine (6):

Compound **6** was prepared in three different ways as follows:

Mode A: a solution of **5c** (3g, 11.4 mmol), dioxane (60 mL) and 10% aq H_2SO_4 (60 mL) was stirred at r.t. for 24 hr. The reaction mixture was treated with powdered $NaHCO_3$ up to pH 9 then extracted with AcOEt (5 x 40 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. Chromatography on alumina (mixture of light petrol-dichloromethane in 8:2 ratio as eluant) afforded pure **6** (85% yield) as a pale yellow oil and unreacted **5c**.

Mode B: **5c** (0.01 mmol) was reacted with trifluoroacetic acid (50 eq) in dichloromethane (1 mL) at r.t. for 20 min affording **6** in quantitative yield.

Mode C: a solution of **1b** (0.1 g, 0.66mmol), 37% aq formaldehyde (0.13 mL), and NH_4Cl (0.034 g, 0.66 mmol) was stirred at r.t. for 18 hr. Ethanol (0.128 mL) and pyridine (0.2 mL) were then added and the mixture was allowed to stand for 1 hr, diluted with H_2O (3 mL) and extracted with AcOEt (3 x 20 mL). The combined organic phases were washed several times with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure affording **6** in 80% yield.

6: oil; $[\alpha]_D^{25}$ = - 201.7 (c = 2.1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.40 (d, 3 H, *J* = 9.00 Hz, Me at C5), 3.55-3.61 (m, 1 H), 3.80-3.90 (m, 1 H), 4.56 (d, 1 H, 1/2 AB system, *J* = 6.0 Hz), 4.80 (d, 1 H, 1/2 AB system, *J* = 6.0 Hz), 7.08-7.14 (m, 1 H, Py), 7.42 (d, 1 H, *J* = 6.3 Hz, Py), 7.56 (td, 1 H, *J* = 6.3, 1.0 Hz, Py), 8.45-8.52 (m, 1 H, Py). ^{13}C NMR ($CDCl_3$) δ (ppm): 18.96, 73.51, 80.91, 85.55, 120.74, 122.21, 136.64, 149.12, 160.44. IR (neat) ν: 3428, 3051, 2970, 2857, 1675, 1588, 1466, 1431, 1379, 1195, 1089, 863, 845, 768, 750 cm^{-1}.

(1*R*,2*R*)-1-(*N*-benzyloxycarbonyl)amino-1-(2'-pyridyl)propan-2-ol (8):

A solution of **5d** (1 g, 3.2 mmol) and dry 4.5 M HCl in MeOH (2 mL, 9.6 mmol) was stirred ar r.t. for 24 hr. The reaction mixture was concentrated under reduced pressure and the residue was diluted with dichloromethane and washed with 10 % aq NaOH. The organic phase was dried and concentrated affording **7**: (100% yield). ^1H NMR ($CDCl_3$, mixture of isomers in 3:2 ratio) δ (ppm):1.50 (d, 6 H, *J* = 7.0 Hz, Me, 2 isomers), 1.60-1.85 (series of singlets, 12 H, Me at C2, 2 isomers), 4.55 (d, 1 H, 1/2 AB system, *J* = 10.7 Hz, Ph$\underline{CH_2}$, min isomer), 4.70 (d, 1 H, 1/2 AB system, *J* = 10.7 Hz, Ph$\underline{CH_2}$, min isomer), 5.05 (d, 1 H, 1/2 AB system, *J* = 10.7 Hz, Ph$\underline{CH_2}$, maj isomer), 5.15 (d, 1 H, 1/2 AB system, *J* = 10.7 Hz, Ph$\underline{CH_2}$, maj isomer), 5.20-5.40 (m, 2 H, 2 isomers), 6.85-7.10, 7.16-7.95, 8.00-8.20, 8.30-8.60, 8.70-8.85 (series of

m, 18 H, Ar). A solution of **7** (3.2 mmol) and dry 4.5 M HCl in MeOH (2 mL, 9.6 mmol) was stirred at reflux temperature for 24 hr. The reaction mixture, after work-up as described above for **7**, furnished a solid which was recrystallized from dichloromethane-diethyl ether affording **8** as colorless needles in almost quantitative yield.

8: m.p. 89-90 °C; $[\alpha]_D^{25}$ = -45.2 (c = 1.4, $CHCl_3$). ^1H NMR ($CDCl_3$) δ (ppm): 1.25 (d, 3 H, *J* = 6.6 Hz, Me), 4.31 (qd, 1 H, *J* = 8.7, 6.3 Hz, H5), 4.50-4.60 (broad signal, 1 H, exchangeable with D_2O, OH), 4.66 (d, 1 H, *J* = 8.7 Hz, H4), 5.04 (d, 1 H, 1/2 AB system, *J* = 12.3 Hz, Ph$\underline{CH_2}$), 5.13 (d, 1 H, 1/2 AB system, *J* = 12.3 Hz, Ph$\underline{CH_2}$), 5.91 (bs, 1 H, NH), 7.20-7.38 (m, 7 H, Py and Ph), 7.68 (t, 1 H, *J* = 6.3 Hz, Py), 8.46-8.50 (m, 1 H, Py). ^{13}C NMR ($CDCl_3$) δ (ppm): 19.34, 58.48, 66.85, 68.98, 122.93, 123.31, 127.93, 128.01, 128.46, 136.35, 137.30, 148.75, 156.62, 160.18. IR (KBr disk) ν: 3343, 3062, 2971, 1686, 1527, 1292, 1264, 1229, 782, 764, 747, 695, 669 cm^{-1}.

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