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STEREO DIFFERENTIATED SYNTHESIS OF OPTICALLY PURE 2-[1-(1-PHENYLETHYLAMINO)ETHYL]-6-[1-(*N*-PIPERIDINYL)ETHYL]-PYRIDINES

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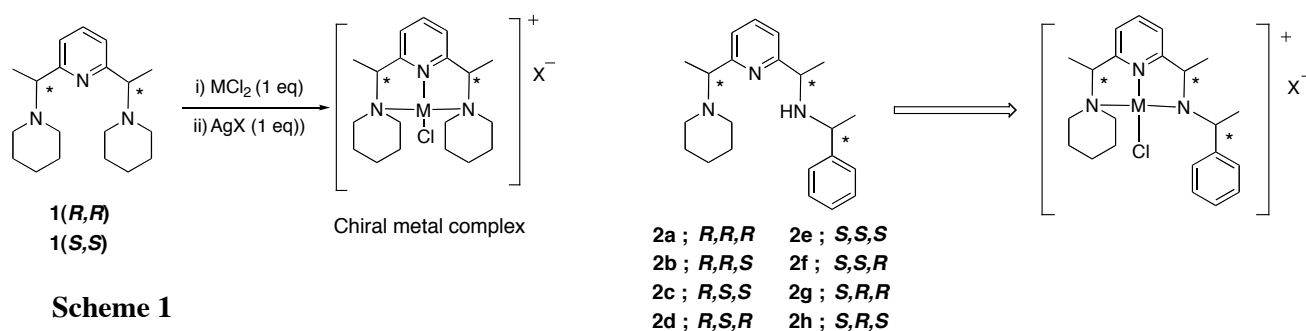
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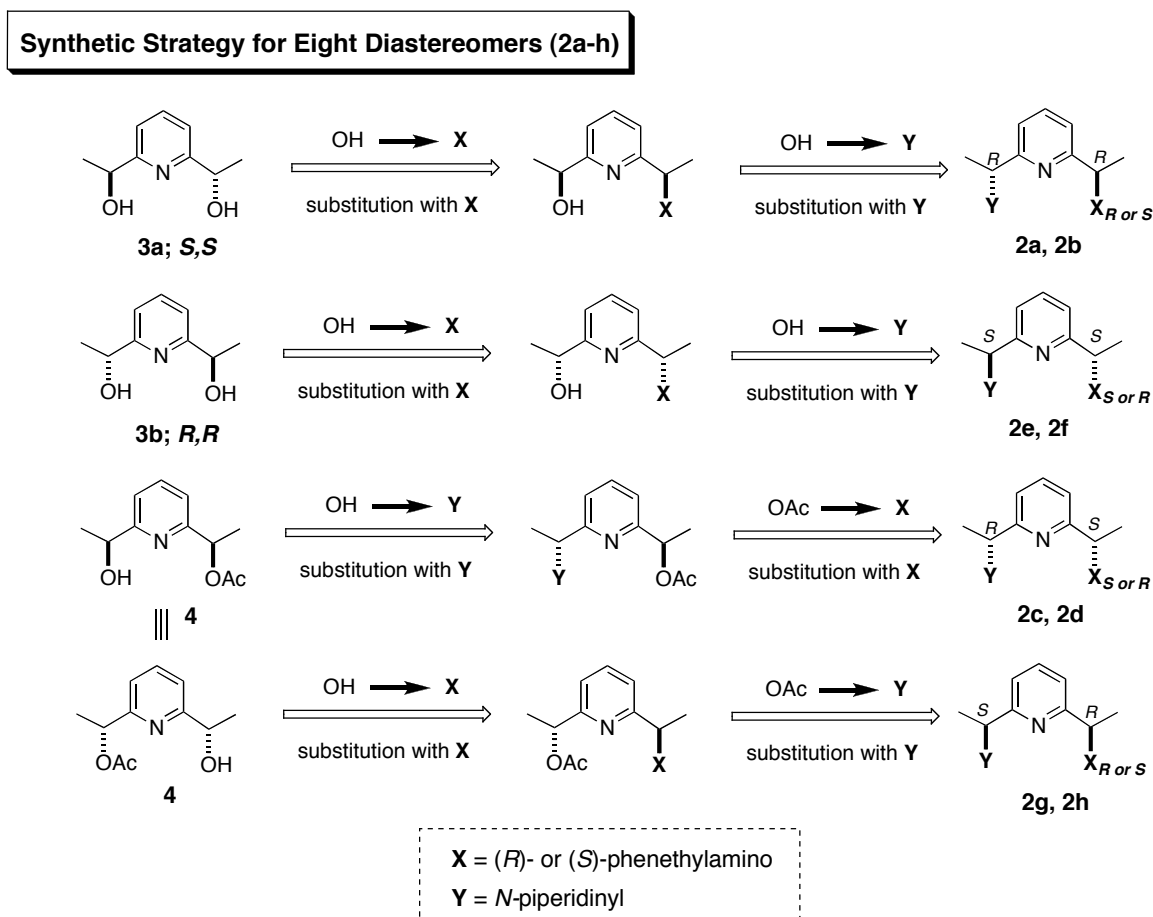
Abstract – All eight stereoisomers of the title pyridines were synthesized. Stereospecific substitution reactions of 1-(2-pyridinyl)ethanol unit with piperidine and optically pure (*R*)- and (*S*)-1-phenethylamines were performed via tosylates or mesylates.

INTRODUCTION

Synthesis of chiral ligand is an important subject in coordination chemistry and organometallic chemistry.¹ Pincer-type ligands including *N,N,N*-pincer ligands having a pyridine ring in the center of the ligand have been investigated.² In the preceding paper, we have reported the synthesis of chiral non-racemic 2,6-bis[1-(*N*-piperidinyl)ethyl]pyridines and the crystal structures of their metal complexes.^{3,4} In an extension of the synthesis of these chiral triamine ligands having a pyridine unit in the molecule,⁴ new chiral non-racemic triamine ligands (**2**) were designed by replacing one of the two piperidines with (*R*)- or (*S*)-phenethylamine in (*R,R*)-**1** or (*S,S*)-**1**, as shown in Scheme 1. These new triamine ligands (**2**) may form optically active metal triamine-complexes that may exhibit more interesting structures. Since these molecules possess three chiral centers, eight diastereoisomers (**2a-h**)



including four pairs of enantiomers are available. In this paper, we report stereo differentiated synthesis of these stereoisomers selectively by stereospecific substitution of 1-(2-pyridinyl)ethyl sulfonates. The synthetic strategy is shown in Scheme 2.

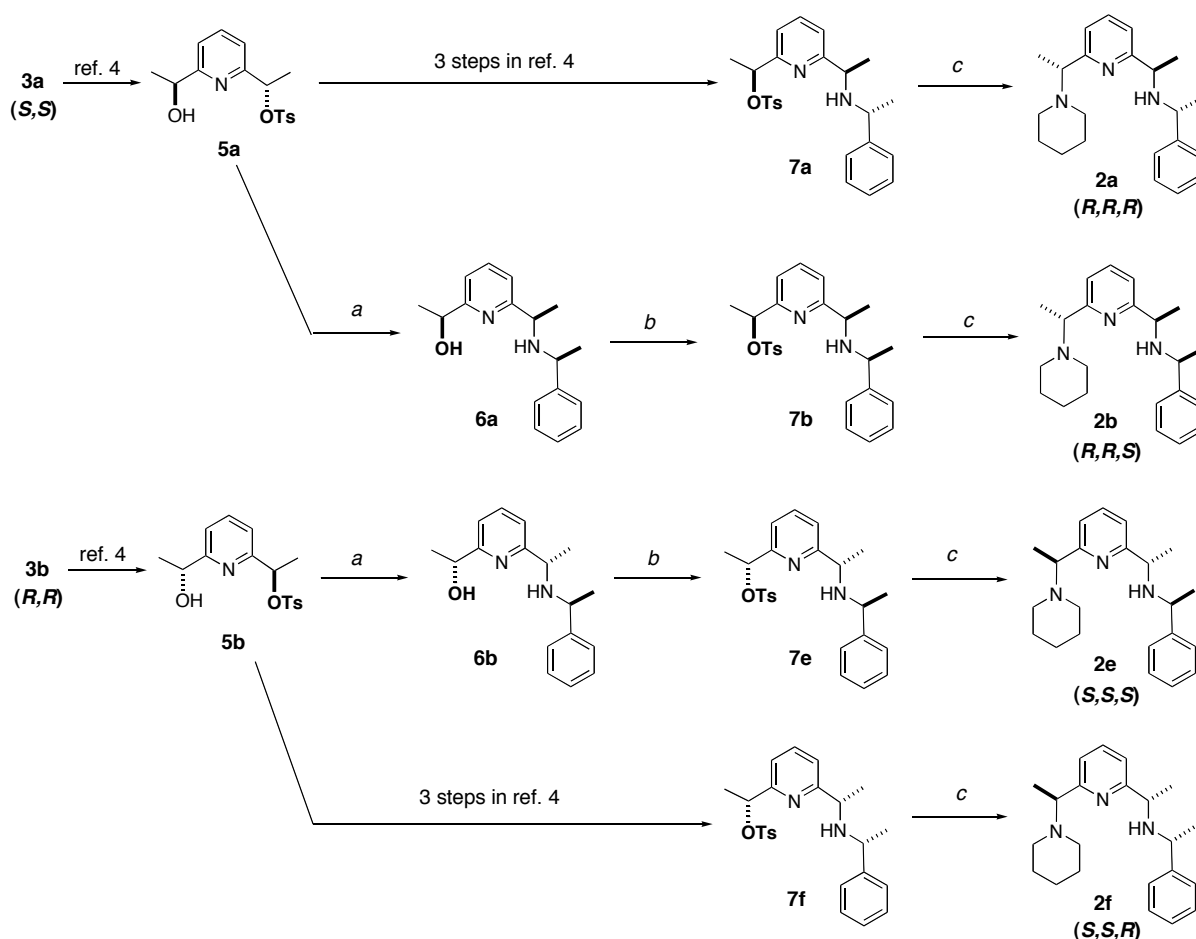


Scheme 2

RESULTS AND DISCUSSION

Our synthetic strategy for **2a-2h** is based on stereospecific substitution of chiral secondary alcohol with piperidine and (*R*)- and (*S*)-phenylethylamines.⁵ Stepwise introduction of these amines to (*S,S*)-secondary alcohols of **3a** will give **2a** and **2b**. By the same manner, **3b** having (*R,R*)-secondary alcohols will give their enantiomers **2e** and **2f**. Chiral non-racemic 2-(1-acetoxyethyl)-6-(1-hydroxyethyl)pyridine (**4**) will be a starting material for the synthesis of their isomers (**2c**, **2d**, **2g** and **2h**). First, the hydroxy group is replaced with piperidine and then the acetoxy group is replaced with (*S*)- and (*R*)-phenylethylamines to give **2c** and **2d**, respectively. On the other hand, the replacement of the hydroxy group first with (*R*)- and (*S*)-phenylethylamines and then that with piperidine will provide **2g** and **2h**, respectively. The starting chiral non-racemic pyridine-2,6-diethanols and acetate (**3a**, **3b**, and **4**) were obtained by lipase-catalyzed kinetic acetylation reaction reported previously.⁴

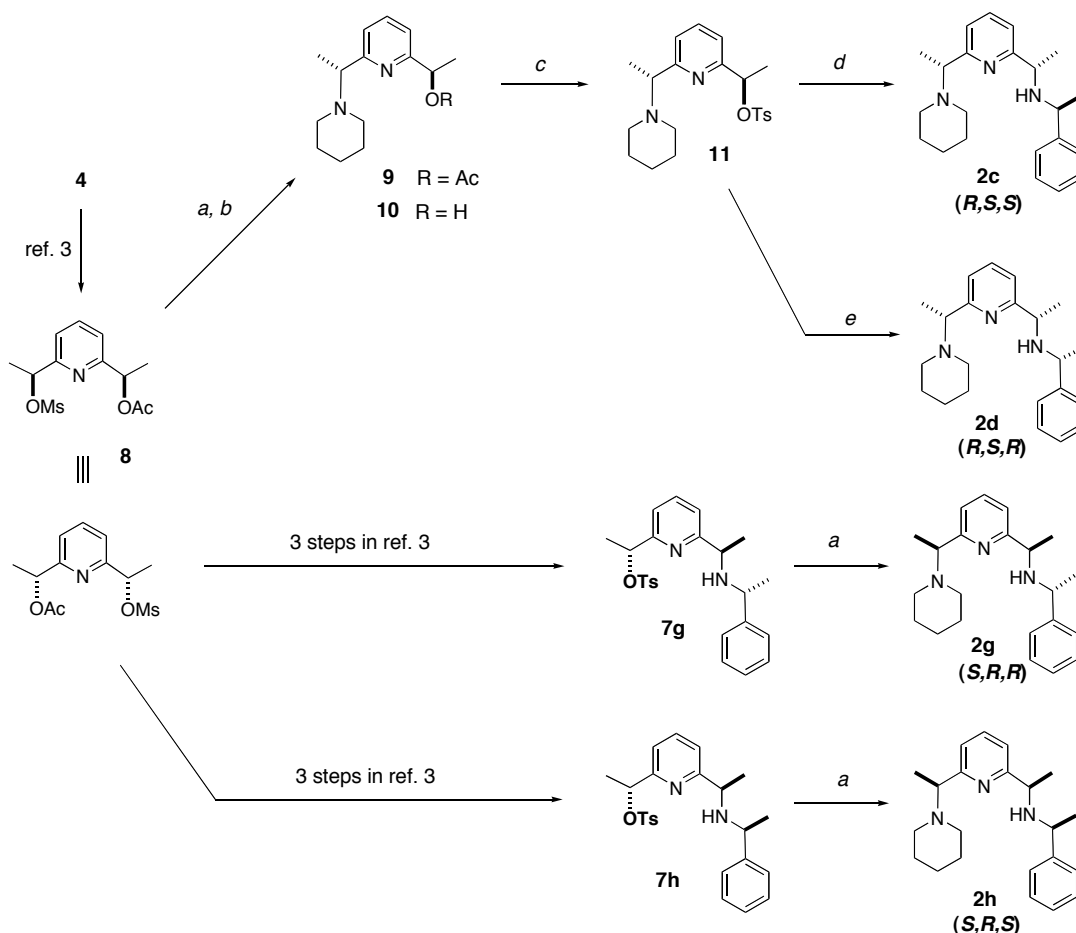
Compound **5a** was obtained by mono tosylation of **3a**⁴ and used for the synthesis of **2a** and **2b**. Treatment of **5a** with (*S*)-phenylethylamine in MeCN in the presence of diisopropylethylamine at 60 °C for 9 h gave **6a** in 85% yield. No other diastereoisomer was found in the product. Tosylation of **6a** was conducted in CH₂Cl₂ with *p*-toluenesulfonyl chloride under standard conditions to give **7b** in 80% yield. Tosylates **7a**⁴ and **7b** were subjected to a substitution reaction with piperidine. They were heated with an excess of piperidine in MeCN for 1 h to give **2a** and **2b** in 95% and 71% yields, respectively. On the other hand, their enantiomers **2e** and **2f** were synthesized by the same method from **5b**. Compound **2e** was obtained in 60% yield from **5b** in three steps, while compound **2f** was yielded from **7f**⁴ in 96% yield. They are shown in Scheme 3.



Scheme 3. Reagents and conditions; a, (*S*)-phenylethylamine, *iso*Pr₂NEt, MeCN, 60 °C. b, TsCl, Et₃N, DMAP, CH₂Cl₂, rt. c, piperidine, MeCN, 60 °C.

The syntheses of **2c**, **2d**, **2g** and **2h** were started from mesylate (**8**) derived from **4**.⁴ Substitution of the mesylate with piperidine gave **9** in 80% yield. Methanolysis of **9** by treating with K₂CO₃ followed by tosylation with *p*-toluenesulfonyl chloride gave **11** in 57% yield in two steps. Somehow, the subsequent substitution of the tosylate with chiral phenethylamine proceeded poorly. Although considerable amount

of starting materials were recovered, **2c** and **2d** were obtained with (*S*)- and (*R*)-phenethylamines in only 27% and 50% yields, respectively. When the corresponding mesylate was used instead of the tosylate, the reaction became messy. Syntheses of **2g** and **2h** were also accomplished by the reaction of **7g** with (*R*)-phenethylamine in 72% yield and by that of **7h** with (*S*)-phenethylamine in 81% yield, respectively.



Scheme 4. Reagents and conditions; a, piperidine, MeCN, 60 °C. b, K₂CO₃, MeOH, rt. c, TsCl, Et₃N, DMAP, CH₂Cl₂, rt. d, (*S*)-phenylethylamine, *iso*Pr₂NEt, MeCN, 60 °C. e, (*R*)-phenylethylamine, *iso*Pr₂NEt, MeCN, 60 °C.

In summary, three chiral non-racemic pyridine-2,6-bisethanols (**3**) and (**4**) have been successfully converted to eight enantiomerically pure chiral non-racemic pyridines (**2a-2h**) with high yields and excellent stereoselectivities. These compounds will be useful as tridentate ligands for the synthesis of new optically active metal-ligand complexes.

EXPERIMENTAL

^1H NMR and ^{13}C NMR spectra were recorded on JEOL JNM-AL-300 (300 MHz and 75 MHz) spectrometer in CDCl_3 with tetramethylsilane internal standard or CDCl_3 . MS spectra were obtained on JMS-GC mate and JMS-SX 102A QQ instruments. IR spectra were recorded on JASCO FT/IR-410 instrument. Thin layer chromatography (TLC) was performed with Merck 60F₂₄₅ precoated silica gel plates. Column chromatography was carried out using Merck silica gel 60 (70-230 mesh) for gravity column.

General procedure for the substitution reaction of tosylate with (*R*)- or (*S*)-phenethylamine; 5a to 6a, 5b to 6b, 11 to 2c and 2d. To a mixture of tosylate **5a**, **5b** or **11** (1.2 mmol) and diisopropylethylamine (6 mmol) in MeCN (4 mL) was added (*R*)- or (*S*)-phenylethylamine (3 eq, 3.6 mmol) in MeCN (1 mL) at rt. The mixture was heated at 60 °C for 7-9 h. Aq. NaHCO_3 was added to the mixture and it was extracted with CHCl_3 . The extract was washed with water and brine, and dried over MgSO_4 . The residue was purified by column chromatography on silica gel eluted with 80% EtOAc containing hexane or by GPC to give **6a**, **6b**, **2c** or **2d**.

(1'*S*,1''*R*)-2-(1'-Hydroxyethyl)-6-{1''-[(*S*)-1-phenylethyl]aminoethyl}pyridine (6a). Colorless oil, 85% yield. $R_f = 0.16$ (EtOAc). $[\alpha]_D^{27} +22$ (c 0.21, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 7.57 (1H, t, $J = 7.7$ Hz), 7.25-7.15 (5H, m), 7.09 (1H, d, $J = 7.7$ Hz), 7.06 (1H, d, $J = 7.7$ Hz), 4.83 (1H, q, $J = 6.4$ Hz), 3.87 (1H, q, $J = 6.6$ Hz), 3.75 (1H, q, $J = 6.6$ Hz), 1.46 (3H, d, $J = 6.6$ Hz), 1.37 (3H, d, $J = 6.6$ Hz), 1.36 (3H, d, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 162.8, 162.1, 145.6, 137.2, 128.4 (2C), 126.9, 126.6 (2C), 119.7, 117.7, 68.4, 56.0, 55.4, 24.2, 23.4, 21.8. IR (neat) cm^{-1} : 3323 (O-H, N-H). MS (CI) m/z : 271 ($\text{M}^+ + \text{H}$). CI-MS m/z : 271.1818 (Calcd for $\text{C}_{25}\text{H}_{32}\text{N}_3$: 271.1810).

(1'*R*,1''*S*)-2-(1'-Hydroxyethyl)-6-{1''-[(*S*)-1-phenylethyl]aminoethyl}pyridine (6b). Colorless oil, 85% yield. $R_f = 0.16$ (EtOAc). $[\alpha]_D^{26} -152$ (c 0.05, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 7.57 (1H, t, $J = 7.7$ Hz), 7.25-7.15 (5H, m), 7.09 (1H, d, $J = 7.7$ Hz), 7.06 (1H, d, $J = 7.7$ Hz), 4.83 (1H, q, $J = 6.6$ Hz), 3.87 (1H, q, $J = 6.6$ Hz), 3.75 (1H, q, $J = 6.6$ Hz), 1.46 (3H, d, $J = 6.6$ Hz), 1.37 (3H, d, $J = 6.6$ Hz), 1.36 (3H, d, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 162.8, 162.1, 145.6, 137.2, 128.4 (2C), 126.9, 126.6 (2C), 119.7, 117.7, 68.4, 56.0, 55.4, 24.2, 23.4, 21.8. IR (neat) cm^{-1} : 3323 (O-H, N-H). MS (CI) m/z : 271 ($\text{M}^+ + \text{H}$). CI-MS m/z : 271.1808 (Calcd for $\text{C}_{25}\text{H}_{32}\text{N}_3$: 271.1810).

(1'*S*,1''*R*)-2-{1'-[(*S*)-1-Phenylethyl]aminoethyl}-6-[1''-(*N*-piperidinyl)ethyl]pyridine (2c). Colorless oil, 27% yield. $R_f = 0.39$ (MeOH). $[\alpha]_D^{27} -89$ (c 0.2, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 7.54 (1H, t, $J = 7.5$ Hz), 7.33-7.21 (5H, m), 7.20 (1H, d, $J = 7.5$ Hz), 6.90 (1H, d, $J = 7.5$ Hz), 3.66 (1H, t, $J = 6.8$ Hz),

3.56 (1H, q, $J = 6.6$ Hz), 3.42 (1H, q, $J = 6.6$ Hz), 2.56-2.40 (4H, m), 2.27 (1H, brs), 1.59 (4H, quint, $J = 5.3$ Hz), 1.44-1.35 (2H, m), 1.43 (3H, d, $J = 6.8$ Hz), 1.28 (3H, d, $J = 6.6$ Hz), 1.26 (3H, d, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 163.6 (2C), 145.7, 136.2, 128.3 (2C), 126.9 (2C), 126.8, 120.4, 119.8, 66.2, 56.2, 55.7, 51.3 (2C), 26.2 (2C), 25.1, 24.6, 23.7, 17.6. IR (neat) cm^{-1} : 3420 (N-H). MS (FAB) m/z : 338 ($\text{M}^+\text{+H}$). FAB-MS m/z : 338.2592 (Calcd for $\text{C}_{22}\text{H}_{32}\text{N}_3$: 338.2596).

(1'S,1'R)-2-(1'-[(R)-1-Phenylethyl]aminoethyl)-6-[1''-(N-piperidinyl)ethyl]pyridine (2d). Colorless oil, 50% yield. $R_f = 0.29$ (MeOH). $[\alpha]_{\text{D}}^{25} -25$ (c 0.5, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 7.51 (1H, t, $J = 7.7$ Hz), 7.26-7.16 (6H, m), 7.03 (1H, d, $J = 7.7$ Hz), 3.84 (1H, q, $J = 6.6$ Hz), 3.73 (1H, q, $J = 6.6$ Hz), 3.63 (1H, q, $J = 6.6$ Hz), 2.50-2.35 (4H, m), 1.57-1.53 (4H, m), 1.40-1.35 (11H, m). ^{13}C NMR (75 MHz, CDCl_3) δ 163.1, 145.9, 136.3, 128.8 (2C), 126.7, 127.6 (2C), 120.0, 119.0, 66.3, 55.9, 55.2, 51.3 (2C), 26.1 (2C), 24.5, 23.3, 22.0, 17.6. IR (neat) cm^{-1} : 3315 (N-H). MS (FAB) m/z : 338 ($\text{M}^+\text{+H}$). FAB-MS m/z : 338.2592 (Calcd for $\text{C}_{22}\text{H}_{32}\text{N}_3$: 338.2596).

Hydrolysis of acetate 9; (1R,1'R)-2-(1-Hydroxyethyl)-6-[1'-(N-piperidinyl)ethyl]pyridine (10). A solution of **9** (390 mg, 1.4 mmol) in MeOH (8 mL) was added K_2CO_3 (970 mg, 7 mmol). It was stirred for 5 min at rt and diluted with water. The mixture was extracted with CHCl_3 and chloroform layer was washed with water and brine, dried over MgSO_4 , and condensed. The residual oil was purified by silica gel column chromatography eluted with MeOH to give **10** (310 mg) in 94% yield. Colorless oil. $R_f = 0.30$ (MeOH). $[\alpha]_{\text{D}}^{22} +36$ (c 0.1, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 7.64 (1H, t, $J = 7.7$ Hz), 7.30 (1H, d, $J = 7.7$ Hz), 7.10 (1H, d, $J = 7.7$ Hz), 4.86 (1H, q, $J = 6.6$ Hz), 3.66 (1H, q, $J = 6.8$ Hz), 2.51-2.35 (4H, m), 1.57 (4H, quint, $J = 5.6$ Hz), 1.49 (3H, d, $J = 6.6$ Hz), 1.41 (3H, d, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 161.6, 161.5, 136.9, 120.4, 117.6, 68.2, 66.0, 51.2 (2C), 26.2 (2C), 24.5, 24.2, 17.3. IR (neat) cm^{-1} : 3389 (O-H). MS (CI) m/z : 235 ($\text{M}^+\text{+H}$). CI-MS m/z : 235.1809 (Calcd for $\text{C}_{14}\text{H}_{23}\text{N}_2\text{O}$: 235.1810).

Tosylation reactions: 6a to 7b, 6b to 7e and 10 to 11. To a mixture of alcohol (0.74 mmol), Et_3N (0.74 mmol), DMAP (0.44 mmol) in CH_2Cl_2 (5 mL) was added TsCl (0.89 mmol) at rt. After stirring for 3.5-6 h, aq. NaHCO_3 was added and the mixture was extracted with CHCl_3 . The extract was washed with sat. NaHCO_3 and dried over Na_2SO_4 . Solvent was removed and the residue was purified by column chromatography eluted with EtOAc or 5% MeOH in CHCl_3 .

(1'R,1'S)-2-{1'-[(S)-1-Phenylethyl]aminoethyl}-6-(1''-p-toluenesulfoxyethyl)pyridine (7b). Colorless oil, 80% yield. $R_f = 0.52$ (EtOAc). $[\alpha]_{\text{D}}^{27} -13$ (c 0.08, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 7.73 (2H, t, $J = 8.4$ Hz), 7.51 (1H, t, $J = 7.7$ Hz), 7.27-7.16 (8H, m), 7.05 (1H, d, $J = 7.7$ Hz), 5.60 (1H, q, $J = 6.6$ Hz),

3.80 (1H, q, $J = 6.6$ Hz), 3.69 (1H, q, $J = 6.6$ Hz), 2.39 (3H, s), 2.02 (1H, brs), 1.60 (3H, d, $J = 6.6$ Hz), 1.36 (3H, d, $J = 6.6$ Hz), 1.30 (3H, d, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 163.8, 157.8, 145.7, 144.4, 137.0, 134.1, 129.6 (2C), 128.3 (2C), 127.8 (2C), 126.8, 126.6 (2C), 120.5, 118.4, 81.0, 55.9, 55.2, 23.2, 22.0, 21.7, 21.6. IR (neat) cm^{-1} : 3319 (N-H), 1365, 1177 (S=O). MS (CI) m/z : 425 ($\text{M}^+\text{+H}$). CI-MS m/z : 425.1897 (Calcd for $\text{C}_{25}\text{H}_{32}\text{N}_3$: 425.1899).

(1'S,1'R)-2-{1'-[(S)-1-Phenylethyl]aminoethyl}-6-(1''-p-toluenesulfoxyethyl)pyridine (7e). Colorless oil, 77% yield. $R_f = 0.65$ (EtOAc). $[\alpha]_{\text{D}}^{27} -66$ (c 0.13, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 7.76 (2H, t, $J = 8.4$ Hz), 7.54 (1H, t, $J = 7.7$ Hz), 7.33-7.20 (8H, m), 6.96 (1H, q, $J = 7.7$ Hz), 5.66 (1H, q, $J = 6.6$ Hz), 3.53 (1H, q, $J = 6.6$ Hz), 3.34 (1H, q, $J = 6.6$ Hz), 2.40 (3H, s), 1.62 (3H, d, $J = 6.6$ Hz), 1.24 (3H, d, $J = 6.6$ Hz), 1.21 (3H, d, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 163.2, 158.2, 145.6, 144.5, 136.9, 134.0, 129.6 (2C), 128.3 (2C), 127.8 (2C), 126.8 (3C), 121.0, 118.3, 80.9, 56.0, 55.7, 25.0, 23.5, 21.7, 21.6. IR (neat) cm^{-1} : 3332 (N-H), 1365, 1176 (S=O). MS (CI) m/z : 425 ($\text{M}^+\text{+H}$). CI-MS m/z : 425.1908 (Calcd for $\text{C}_{25}\text{H}_{32}\text{N}_3$: 425.1899).

(1R,1'R)-2-(1-p-Toluenesulfoxyethyl)-6-[1'-(N-piperidinyl)ethyl]pyridine (11). Colorless oil, 61% yield. $R_f = 0.48$ (MeOH). $[\alpha]_{\text{D}}^{26} +61$ (c 0.48, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 7.72 (2H, d, $J = 8.1$ Hz), 7.55 (1H, t, $J = 7.7$ Hz), 7.27 (1H, d, $J = 7.7$ Hz), 7.22 (2H, d, $J = 8.1$ Hz), 7.17 (1H, d, $J = 7.7$ Hz), 5.61 (1H, q, $J = 6.6$ Hz), 3.50 (1H, q, $J = 6.8$ Hz), 2.48-2.27 (4H, m), 2.38 (2H, s), 1.59 (3H, d, $J = 6.6$ Hz), 1.56-1.39 (6H, m), 1.31 (3H, d, $J = 6.86$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 157.5 (2C), 144.4, 136.8, 134.1, 129.5 (2C), 127.8 (2C), 121.2, 118.3, 66.3, 51.4 (2C), 26.1 (2C), 24.5, 21.9, 21.5, 17.6. IR (neat) cm^{-1} : 1365, 1177 (S=O). MS (CI) m/z : 389 ($\text{M}^+\text{+H}$). CI-MS m/z : 389.1908 (Calcd for $\text{C}_{21}\text{H}_{29}\text{N}_2\text{O}_3\text{S}$: 389.1899).

Replacement of mesylate or tosylate with piperidine; 8 to 9, 7a to 2a, 7b to 2b, 7e to 2e, 7f to 2f, 7g to 2g, and 7h to 2h. To a mixture of tosylate (0.5 mmol) in MeCN (4 mL) was dropped piperidine (5 mmol) and the mixture was heated at 60 °C for 0.5-1 h. The mixture was quenched with sat. NaHCO_3 and extracted with CHCl_3 for 3 times. The combined extracts were washed with water and brine, dried over MgSO_4 and condensed. The oily residue was purified by column chromatography on silica gel eluted with EtOAc for the compound **9**. A solvent of EtOAc then 50% Et_3N in EtOAc was used as an eluent for the purification of compounds **2**.

(1R,1'R)-2-(1-Acetoxyethyl)-6-[1'-(N-piperidinyl)ethyl]pyridine (9). Colorless oil, 80% yield. $R_f = 0.60$ (50% MeOH in CHCl_3). $[\alpha]_{\text{D}}^{27} +88$ (c 0.55, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 7.60 (1H, t, $J =$

7.7 Hz), 7.28 (1H, d, $J = 7.7$ Hz), 7.15 (1H, d, $J = 7.7$ Hz), 5.88 (1H, q, $J = 6.6$ Hz), 3.64 (1H, q, $J = 6.6$ Hz), 2.54-2.36 (4H, m), 2.10 (3H, s), 1.59-1.53 (4H, m), 1.55 (3H, d, $J = 6.6$ Hz), 1.44-1.37 (2H, m), 1.39 (3H, d, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 170.2, 159.5 (2C), 136.9, 121.1, 118.2, 73.2, 66.3, 51.2 (2C), 25.7 (2C), 21.2, 20.8, 17.6. IR (neat) cm^{-1} : 1739, 1238 (C=O). MS (CI) m/z : 277 ($\text{M}^+\text{+H}$). CI-MS m/z : 277.1917 (Calcd for $\text{C}_{16}\text{H}_{25}\text{N}_2\text{O}_2$: 277.1916).

(1'R,1''R)-2-{1'-[(R)-1-Phenylethyl]aminoethyl}-6-[1''-(N-piperidiny)ethyl]pyridine (2a). Colorless oil, 95% yield. $R_f = 0.12$ (MeOH). $[\alpha]_{\text{D}}^{24} +132$ (c 0.2, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 7.55 (1H, t, $J = 7.7$ Hz), 7.33-7.23 (5H, m), 7.20 (1H, d, $J = 7.7$ Hz), 6.92 (1H, d, $J = 7.7$ Hz), 3.70 (1H, q, $J = 6.8$ Hz), 3.56 (1H, q, $J = 6.6$ Hz), 3.43 (1H, q, $J = 6.6$ Hz), 2.60-2.40 (4H, m), 2.19 (1H, brs), 1.61-1.55 (4H, m), 1.47-1.38 (2H, m), 1.44 (3H, d, $J = 6.6$ Hz), 1.27 (6H, d, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 163.6 (2C), 145.6, 136.4, 128.3 (2C), 126.9 (2C), 126.8, 120.4, 120.0, 66.2, 56.2, 55.7, 51.2 (2C), 25.9, 25.1, 24.4 (2C), 23.7, 17.5. IR (neat) cm^{-1} : 3316 (N-H). MS (FAB) m/z : 338 ($\text{M}^+\text{+H}$). FAB-MS m/z : 338.2601 (Calcd for $\text{C}_{22}\text{H}_{32}\text{N}_3$: 338.2596).

(1'R,1''R)-2-{1'-[(S)-1-Phenylethyl]aminoethyl}-6-[1''-(N-piperidiny)ethyl]pyridine (2b). Colorless oil, 71% yield. $R_f = 0.43$ (EtOAc). $[\alpha]_{\text{D}}^{26} +60$ (c 0.10, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 7.49 (1H, t, $J = 7.7$ Hz), 7.24-7.19 (5H, m), 7.16 (1H, d, $J = 7.7$ Hz), 7.00 (1H, d, $J = 7.7$ Hz), 3.82 (1H, q, $J = 6.6$ Hz), 3.70 (1H, q, $J = 6.6$ Hz), 3.58 (1H, q, $J = 6.6$ Hz), 2.49-2.32 (4H, m), 1.53-1.49 (4H, m), 1.37-1.32 (2H, m), 1.36 (3H, d, $J = 6.6$ Hz), 1.35 (3H, d, $J = 6.6$ Hz), 1.34 (3H, d, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 163.1, 162.5, 145.9, 136.3, 128.2 (2C), 126.7 (2C), 126.6, 119.9, 119.0, 66.4, 55.9, 51.4 (2C), 26.3 (2C), 24.6, 23.2, 22.1, 17.8. IR (neat) cm^{-1} : 3304 (N-H). MS (FAB) m/z : 338 ($\text{M}^+\text{+H}$). FAB-MS m/z : 338.2593 (Calcd for $\text{C}_{22}\text{H}_{32}\text{N}_3$: 338.2596).

(1'S,1''S)-2-{1'-[(S)-1-Phenylethyl]aminoethyl}-6-[1''-(N-piperidiny)ethyl]pyridine (2e). Colorless oil, 92% yield. $R_f = 0.42$ (EtOAc). $[\alpha]_{\text{D}}^{27} -170$ (c 0.12, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ 7.51 (1H, t, $J = 7.7$ Hz), 7.30-7.17 (5H, m), 7.17 (1H, d, $J = 7.7$ Hz), 6.88 (1H, d, $J = 7.7$ Hz), 3.63 (1H, q, $J = 6.6$ Hz), 3.53 (1H, q, $J = 6.6$ Hz), 3.40 (1H, q, $J = 6.6$ Hz), 2.50-2.35 (4H, m), 1.54-1.50 (4H, m), 1.40-1.36 (2H, m), 1.40 (3H, d, $J = 6.6$ Hz), 1.24 (3H, d, $J = 6.6$ Hz), 1.23 (3H, d, $J = 6.6$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 163.4, 162.6, 145.8, 136.1, 128.3 (2C), 126.9 (2C), 126.7, 120.0, 119.7, 66.3, 56.2, 55.7, 51.3 (2C), 26.3 (2C), 25.1, 24.7, 23.7, 17.6. IR (neat) cm^{-1} : 3319 (N-H). MS (FAB) m/z : 338 ($\text{M}^+\text{+H}$). FAB-MS m/z : 338.2592 (Calcd for $\text{C}_{22}\text{H}_{32}\text{N}_3$: 338.2596).

(1'S,1''S)-2-{1'-[(R)-1-Phenylethyl]aminoethyl}-6-[1''-(N-piperidiny)ethyl]pyridine (2f). Colorless

oil, 96% yield. $R_f = 0.43$ (5% Et₃N in EtOAc). $[\alpha]_D^{25} -61$ (c 0.2, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.53 (1H, t, $J = 7.7$ Hz), 7.27-7.18 (6H, m), 7.03 (1H, d, $J = 7.7$ Hz), 3.85 (1H, d, $J = 7.7$ Hz), 3.72 (1H, q, $J = 6.6$ Hz), 3.63 (1H, q, $J = 6.6$ Hz), 2.48-2.41 (4H, m), 1.57 (4H, m), 1.41-1.36 (11H, m). ¹³C NMR (75 MHz, CDCl₃) δ 163.1 (2C), 145.9, 136.3, 128.3 (2C), 126.7, 126.7 (2C), 120.0, 119.1, 66.4, 55.9, 55.2, 51.2 (2C), 26.2 (2C), 24.5, 23.2, 22.1, 17.8. IR (neat) cm⁻¹: 3304 (N-H). MS (FAB) m/z : 338 (M⁺+H). FAB-MS m/z : 338.2600 (Calcd for C₂₂H₃₂N₃: 338.2596).

(1'*R*,1''*S*)-2-{1'-[(*R*)-1-Phenylethyl]aminoethyl}-6-[1''-(*N*-piperidinyl)ethyl]pyridine (2g). Colorless oil, 72% yield. $R_f = 0.39$ (MeOH). $[\alpha]_D^{24} +98$ (c 0.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.53 (1H, t, $J = 7.5$ Hz), 7.33-7.18 (6H, m), 6.90 (1H, d, $J = 7.5$ Hz), 3.64 (1H, t, $J = 6.8$ Hz), 3.55 (1H, q, $J = 6.8$ Hz), 3.42 (1H, q, $J = 6.6$ Hz), 2.51-2.41 (4H, m), 2.06 (1H, brs), 1.58 (4H, quint, $J = 5.6$ Hz), 1.44-1.41 (2H, m), 1.42 (3H, d, $J = 6.8$ Hz), 1.27 (3H, d, $J = 6.8$ Hz), 1.26 (3H, d, $J = 6.6$ Hz). ¹³C NMR (75 MHz, CDCl₃) δ 163.6 (2C), 145.7, 136.2, 128.3 (2C), 126.9 (2C), 126.8, 120.3, 119.8, 66.3, 56.2, 55.7, 51.3, 26.2, 25.1, 24.6, 23.7, 17.6. IR (neat) cm⁻¹: 3316 (N-H). MS (FAB) m/z : 338 (M⁺+H). FAB-MS m/z : 338.2600 (Calcd for C₂₂H₃₂N₃: 338.2596).

(1'*R*,1''*S*)-2-{1'-[(*S*)-1-Phenylethyl]aminoethyl}-6-[1''-(*N*-piperidinyl)ethyl]pyridine (2h). Colorless oil, 81% yield. $R_f = 0.36$ (5% Et₃N in AcOEt). $[\alpha]_D^{23} +25$ (c 0.1, CHCl₃). ¹H NMR (300 MHz, CDCl₃) δ 7.49 (1H, t, $J = 7.7$ Hz), 7.24-7.16 (6H, m), 7.00 (1H, d, $J = 7.7$ Hz), 3.82 (1H, q, $J = 6.6$ Hz), 3.70 (1H, q, $J = 6.6$ Hz), 3.65 (1H, q, $J = 6.6$ Hz), 2.50-2.35 (4H, m), 1.54-1.50 (4H, m), 1.37-1.33 (11H, m). ¹³C NMR (75 MHz, CDCl₃) δ 163.1, 146.0, 136.3, 128.2 (2C), 126.7, 127.6 (2C), 120.0, 119.0, 66.4, 55.9, 55.2, 51.3 (2C), 26.3 (2C), 24.6, 23.4, 22.1, 17.6. IR (neat) cm⁻¹: 3314 (N-H). MS (FAB) m/z : 338 (M⁺+H). FAB-MS m/z : 338.2592 (Calcd for C₂₂H₃₂N₃: 338.2596).

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