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

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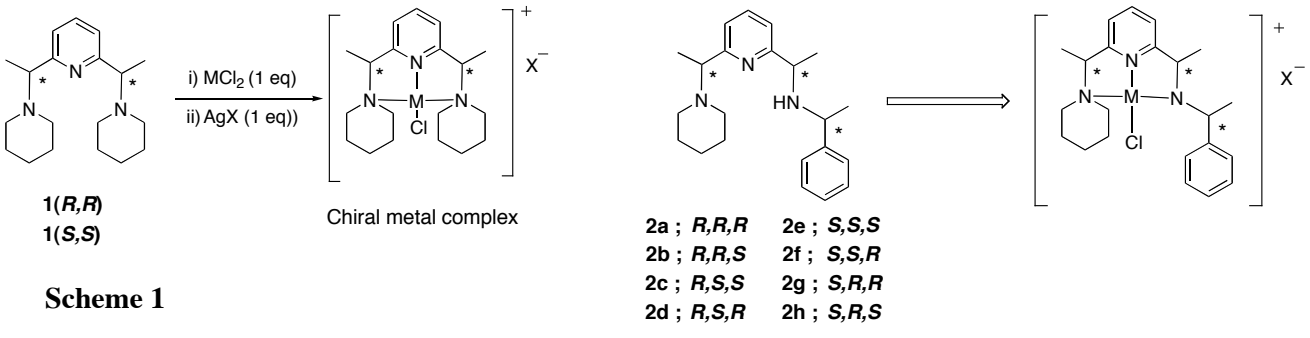
Abstract – All eight stereoisomers of the title pyridines were synthesized. Stereospecific substitution reactions of 1-(2-pyridinyl)ethanol unit with piperidine and optically pure (*R*)- and (*S*)-1-phenethylamines were performed via tosylates or mesylates.

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*)-phenylethylamine 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 diastereisomers (**2a-h**)



1(*R,R*)
1(*S,S*)

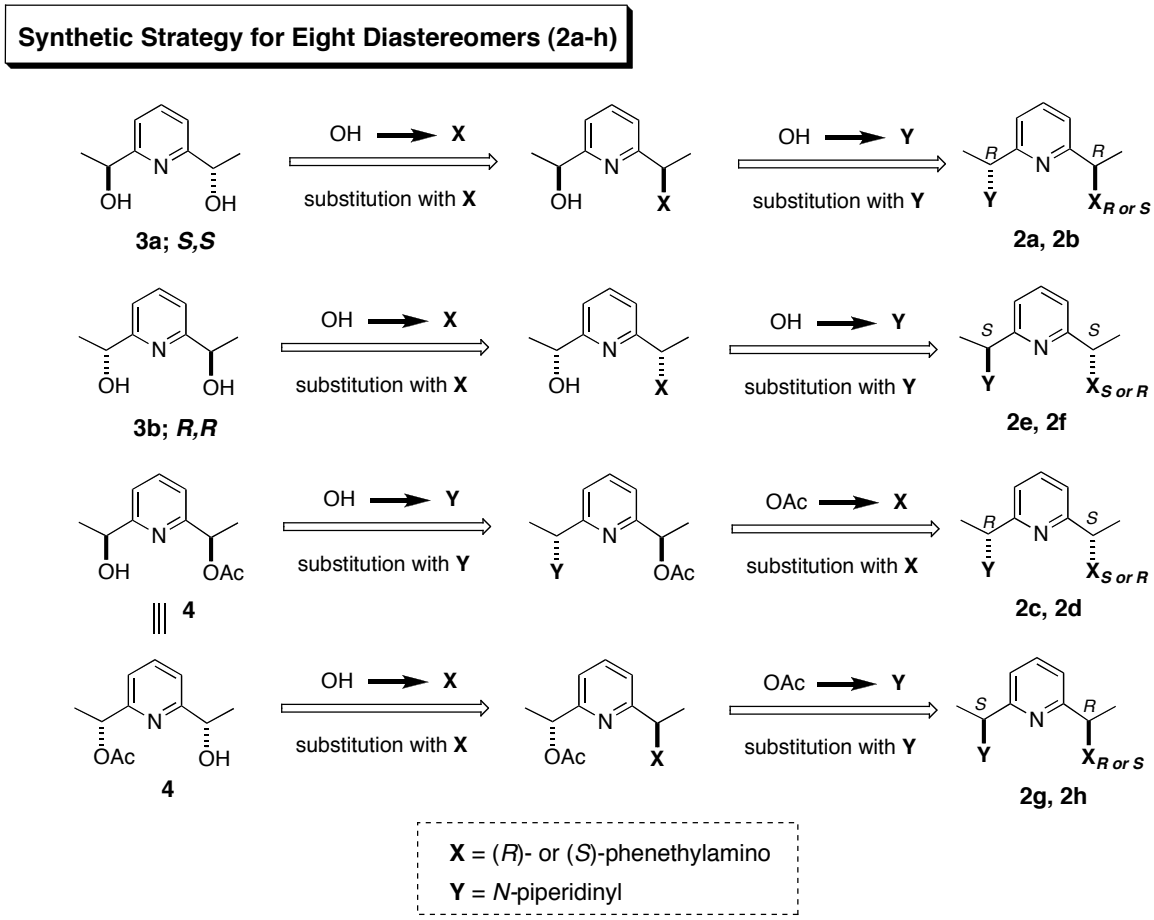
Chiral metal complex

2a ; *R,R,R* **2e ; *S,S,S***
2b ; *R,R,S* **2f ; *S,S,R***
2c ; *R,S,S* **2g ; *S,R,R***
2d ; *R,S,R* **2h ; *S,R,S***

Scheme 1

This paper is dedicated to Prof. Yoshito Kishi on the occasion of his 70th birthday.

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.

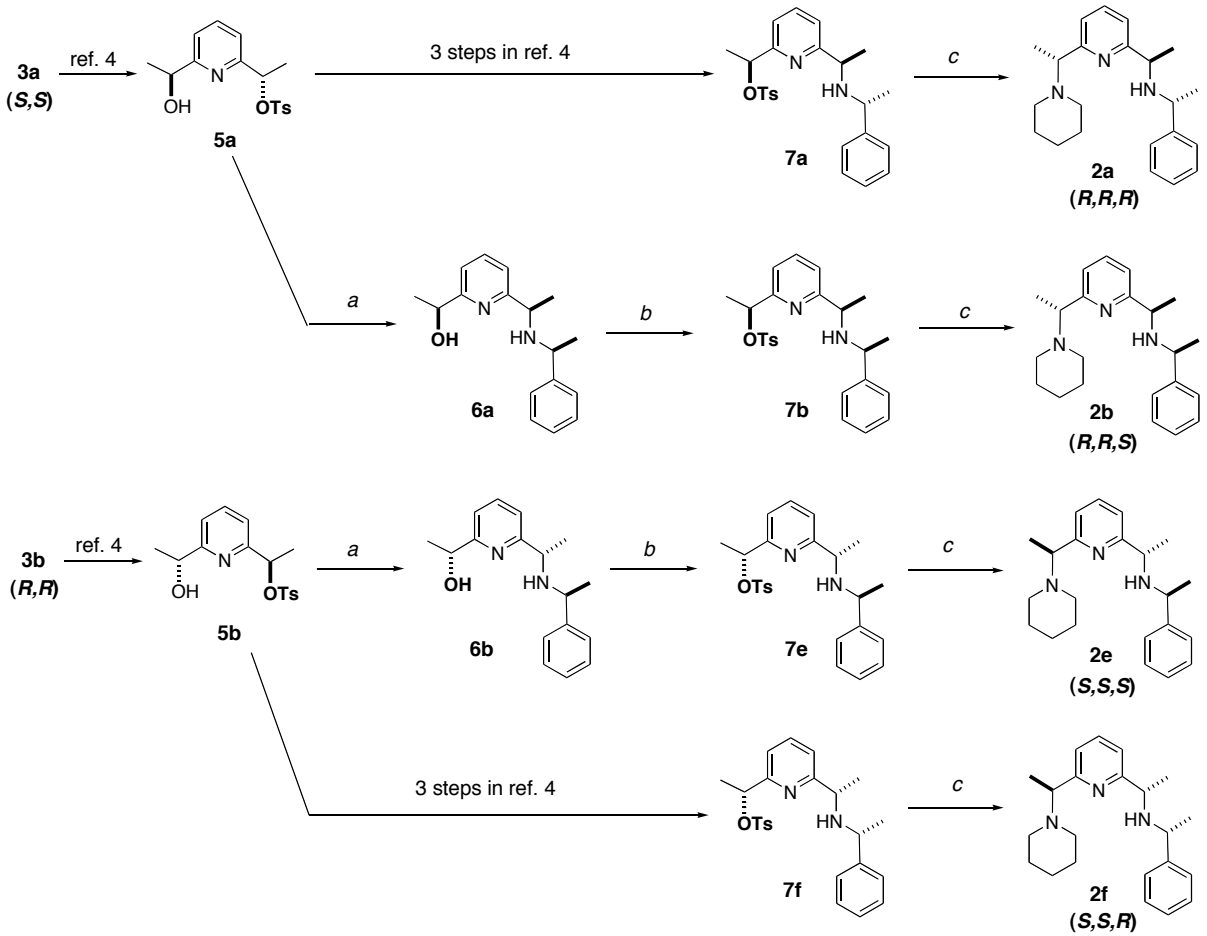


Scheme 2

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]

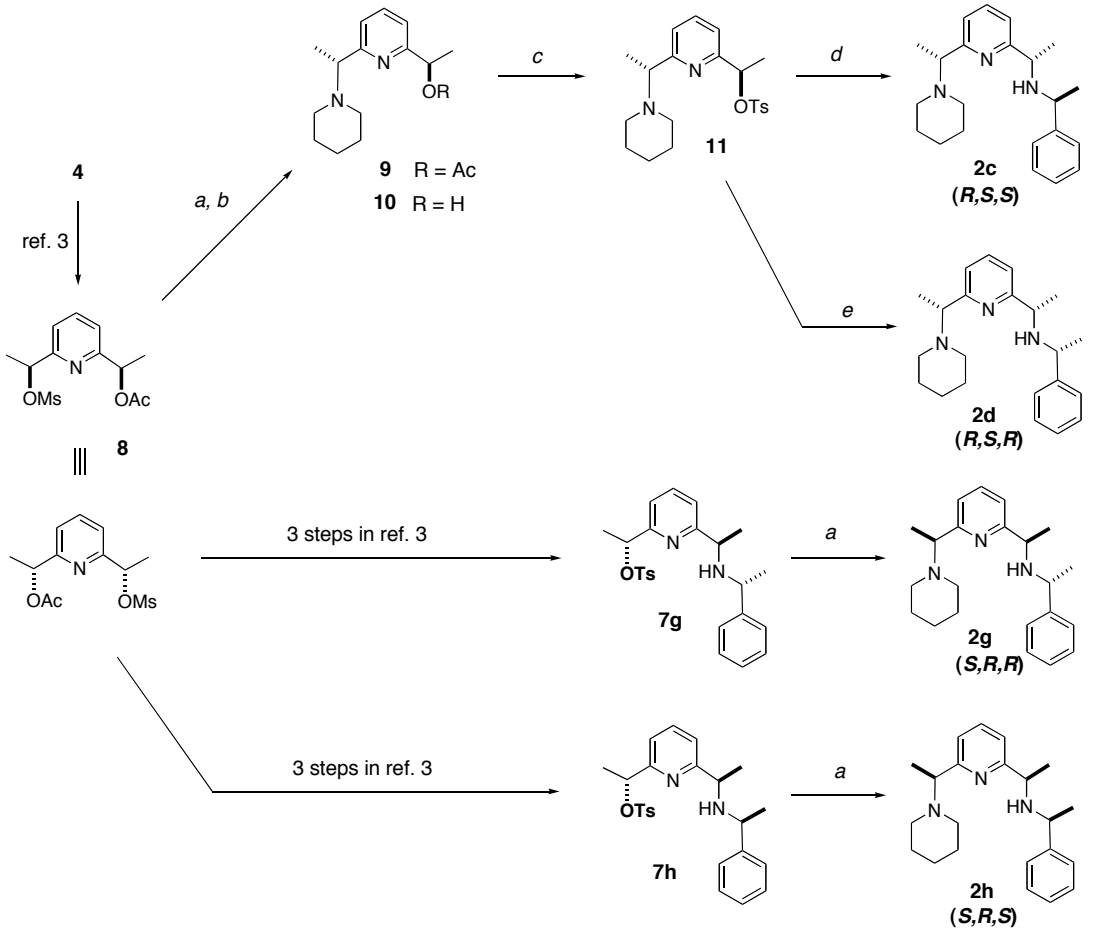
Compound **5a** was obtained by mono tosylation of **3a**[4] and used for the synthesis of **2a** and **2b**. Treatment of **5a** with (*S*)-phenylethylamine in MeCN in the presence of diisopropylethylamine at 60 °C for 9 h gave **6a** in 85% yield. No other diastereoisomer was found in the product. Tosylation of **6a** was conducted in CH_2Cl_2 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, $^{iso}Pr_2NEt$, MeCN, 60 °C. *b,* TsCl, Et_3N, DMAP, CH_2Cl_2, 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 K_2CO_3 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,* K_2CO_3, MeOH, rt. *c,* TsCl, Et_3N, DMAP, CH_2Cl_2, rt. *d,* (*S*)-phenylethylamine, $^{iso}Pr_2NEt$, MeCN, 60 °C. *e*, (*R*)-phenylethylamine, $^{iso}Pr_2NEt$, 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

^{1}H 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 $60F_{245}$ 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. *Rf* = 0.16 (EtOAc). $[\alpha]_D^{27}$ +22 (*c* 0.21, $CHCl_3$). ^{1}H 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 (M^++H). CI-MS *m/z*: 271.1818 (Calcd for $C_{25}H_{32}N_3$: 271.1810).

(1'*R*,1"*S*)-2-(1'-Hydroxyethyl)-6-{1"-[(*S*)-1-phenylethyl]aminoethyl}pyridine (6b). Colorless oil, 85% yield. *Rf* = 0.16 (EtOAc). $[\alpha]_D^{26}$ -152 (*c* 0.05, $CHCl_3$). ^{1}H 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 (M^++H). CI-MS *m/z*: 271.1808 (Calcd for $C_{25}H_{32}N_3$: 271.1810).

(1'*S*,1"*R*)-2-{1'-[(*S*)-1-Phenylethyl]aminoethyl}-6-[1"-(*N*-piperidinyl)ethyl]pyridine (2c). Colorless oil, 27% yield. *Rf* = 0.39 (MeOH). $[\alpha]_D^{27}$ -89 (*c* 0.2, $CHCl_3$). ^{1}H 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 (M^++H). FAB-MS *m/z*: 338.2592 (Calcd for $C_{22}H_{32}N_3$: 338.2596).

(1'*S*,1"*R*)-2-(1'-[(*R*)-1-Phenylethyl]aminoethyl)-6-[1"-(*N*-piperidinyl)ethyl]pyridine (2d). Colorless oil, 50% yield. *Rf* = 0.29 (MeOH). $[\alpha]_D^{25}$ -25 (*c* 0.5, $CHCl_3$). ^{1}H 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 (M^++H). FAB-MS *m/z*: 338.2592 (Calcd for $C_{22}H_{32}N_3$: 338.2596).

Hydrolysis of acetate 9; (1*R*,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. *Rf* = 0.30 (MeOH). $[\alpha]_D^{22}$ +36 (*c* 0.1, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (1H, t, *J* = 7.7 Hz), 7.30 (1H, d, *J* = 7.7 Hz), 77.10 (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 (M^++H). CI-MS *m/z*: 235.1809 (Calcd for $C_{14}H_{23}N_2O$: 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 clumn 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. *Rf* = 0.52 (EtOAc). $[\alpha]_D^{27}$ -13 (*c* 0.08, $CHCl_3$). ^{1}H 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 (M^++H). CI-MS *m/z*: 425.1897 (Calcd for $C_{25}H_{32}N_3$: 425.1899).

(1'*S*,1"*R*)-2-{1'-[(*S*)-1-Phenylethyl]aminoethyl}-6-(1"-*p*-toluenesulfoxyethyl)pyridine (7e). Colorless oil, 77% yield. *Rf* = 0.65 (EtOAc). $[\alpha]_D^{27}$ -66 (*c* 0.13, $CHCl_3$). ^{1}H 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 (M^++H). CI-MS *m/z*: 425.1908 (Calcd for $C_{25}H_{32}N_3$: 425.1899).

(1*R*,1'*R*)-2-(1-*p*-Toluenesulfoxyethyl)-6-[1'-(*N*-piperidinyl)ethyl]pyridine (11). Colorless oil, 61% yield. *Rf* = 0.48 (MeOH). $[\alpha]_D^{26}$ +61 (*c* 0.48, $CHCl_3$). ^{1}H 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 (M^++H). CI-MS *m/z*: 389.1908 (Calcd for $C_{21}H_{29}N_2O_3S$: 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**.

(1*R*,1'*R*)-2-(1-Acetoxyethyl)-6-[1'-(*N*-piperidinyl)ethyl]pyridine (9). Colorless oil, 80% yield. *Rf* = 0.60 (50% MeOH in $CHCl_3$). $[\alpha]_D^{27}$ +88 (*c* 0.55, $CHCl_3$). ^{1}H 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 (M^++H). CI-MS *m*/*z*: 277.1917 (Calcd for $C_{16}H_{25}N_2O_2$: 277.1916).

(1'*R*,1"*R*)-2-{1'-[(*R*)-1-Phenylethyl]aminoethyl}-6-[1"-(*N*-piperidinyl)ethyl]pyridine (2a). Colorless oil, 95% yield. *Rf* = 0.12 (MeOH). $[\alpha]_D^{24}$ +132 (*c* 0.2, $CHCl_3$). ^{1}H 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 (M^++H). FAB-MS *m*/*z*: 338.2601 (Calcd for $C_{22}H_{32}N_3$: 338.2596).

(1'*R*,1"*R*)-2-{1'-[(*S*)-1-Phenylethyl]aminoethyl}-6-[1"-(*N*-piperidinyl)ethyl]pyridine (2b). Colorless oil, 71% yield. *Rf* = 0.43 (EtOAc). $[\alpha]_D^{26}$ +60 (*c* 0.10, $CHCl_3$). ^{1}H 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 (M^++H). FAB-MS *m*/*z*: 338.2593 (Calcd for $C_{22}H_{32}N_3$: 338.2596).

(1'*S*,1"*S*)-2-{1'-[(*S*)-1-Phenylethyl]aminoethyl}-6-[1"-(*N*-piperidinyl)ethyl]pyridine (2e). Colorless oil, 92% yield. *Rf* = 0.42 (EtOAc). $[\alpha]_D^{27}$ -170 (*c* 0.12, $CHCl_3$). ^{1}H 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 (M^++H). FAB-MS *m*/*z*: 338.2592 (Calcd for $C_{22}H_{32}N_3$: 338.2596).

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

oil, 96% yield. *Rf* = 0.43 (5% Et_3N in EtOAc). $[\alpha]_D^{25}$ -61 (*c* 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{22}H_{32}N_3$: 338.2596).

(1'*R*,1"*S*)-2-{1'-[(*R*)-1-Phenylethyl]aminoethyl}-6-[1"-(*N*-piperidinyl)ethyl]pyridine (2g). Colorless oil, 72% yield. *Rf* = 0.39 (MeOH). $[\alpha]_D^{24}$ +98 (*c* 0.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{22}H_{32}N_3$: 338.2596).

(1'*R*,1"*S*)-2-{1'-[(*S*)-1-Phenylethyl]aminoethyl}-6-[1"-(*N*-piperidinyl)ethyl]pyridine (2h). Colorless oil, 81% yield. *Rf* = 0.36 (5% Et_3N in AcOEt). $[\alpha]_D^{23}$ +25 (*c* 0.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) 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). ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{22}H_{32}N_3$: 338.2596).

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