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An efficient synthesis of chiral terminal 1,2-diamines using an enantiomerically pure [1-(1′*R*)-methylbenzyl]aziridine-2-yl]methanol

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The authors dedicate this article to Professor Peter Beak on the occasion of his 70th birthday

Abstract—Enantiomerically pure terminal 1,2-diamines, which can serve as precursors for the synthesis of many biologically important compounds, were synthesized efficiently from a commercially available chiral [1-(1′*R*)-methylbenzyl]aziridine-2-yl]methanol. Various enantiomerically pure 2-vinylaziridines were prepared by Wittig reactions from aziridine-2-carboxaldehyde and the corresponding phosphonium salts. The C(2)–N bond of the vinyl substituted aziridine ring was regioselectively cleaved by azidotrimethylsilane ($TMSN_3$). The azido group and the double bond were reduced successively to give the target compounds in high yields.

1. Introduction

Compounds incorporating the terminal chiral 1,2-diamine functionality attract attentions from a variety of scientific areas. Previous research shows that some terminal 1,2-diamines and their derivatives have biological activities. For example, 1,2-diaminoplatinum complexes are considered as antitumor agents, biotins[1] have been used as protein immobilization agent in biosensor, and emeriamines[2] are used as inhibitors in fatty acid oxidation. These compounds also play important roles in organic synthesis and they are used as intermediates in the synthesis of heterocycles[3] or nitrogen containing macrocycles,[4] chiral ligands, and auxiliaries in catalytic asymmetric transformations.[5]

Although there has been a variety of applications, only a few preparative methods are available for the chiral terminal 1,2-diamines: from chiral alcohols,[6] alkylimines,[7] simple heterocycles,[8–10] 2-(sufonyloxy)nitriles,[11] nitrones,[12] aziridinium ion,[13] and ephedrine or pseudoephedrine.[14,15] However, each of the above methods has limited scope due to the lack of stereoselectivity and availability of enantiomerically pure starting materials. In addition, we need to consider different factors to establish generalized procedure for each application.[16] The requirement of more efficient preparative pathways to enantiomerically pure terminal 1,2-diamines prompted us to develop a simple and highly efficient new synthetic route.

In this report we described an efficient preparative route to enantiomerically pure terminal 1,2-diamines from commercially available enantiomerically pure 2-hydroxymethylaziridines.

2. Results and discussion

We previously reported the preparation and the application of enantiomerically pure aziridine-2-carboxaldehydes from commercially available aziridine-2-carboxylates.[17] Starting from the aldehydes (2*R*)-**1a–g**, a variety of 2-alkenyl aziridines (2*S*)-**2a–g** were prepared efficiently as a cis/trans mixture by Wittig reaction with the corresponding phosphonium salts in high yields. We also prepared the diastereomeric 2-alkenyl aziridines (2*R*)-**2h–l** using the same reaction conditions from (2*S*)-**1h–l** (Table 1; Scheme 1).

The aziridine ring C(2)–N bond is regioselectively cleaved by treating the 2-alkenyl aziridines ((2*S*)-**2a–g** and (2*R*)-**2h–l**) with 3 equiv of $TMSN_3$ in CH_2Cl_2 to provide 1-amino-2-azido-3-alkenes. Based on our previous results,

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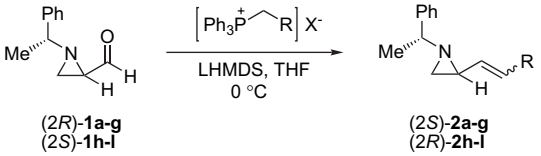
Table 1. Preparation of (2*S*)- and (2*R*)-2-alkenyl aziridines ((2*S*)-**2a–g** and (2*R*)-**2h–l**) from enantiomerically pure (2*R*)- and (2*S*)-aziridine-2-carboxaldehydes ((2*R*)-**1a–g** and (2*S*)-**1h–l**)

Entry	R	Yield (%)
2a	Phenyl	91
2b	2-Cl-Phenyl	94
2c	4-Biphenyl	89
2d	Propyl	92
2e	Nonyl	89
2f	1-Naphthyl	86
2g	Penta-F-phenyl	95
2h	Phenyl	89
2i	1-Naphthyl	87
2j	4-Cl-Phenyl	89
2k	Propyl	96
2l	Benzyl	90



Scheme 1.

the regiochemistry of Lewis acid or protic acid catalyzed nucleophilic ring opening reaction of *N*-α-methylbenzyl-2-alkyl aziridine is determined by steric requirement of the aziridine ring carbon and the ring opening reaction takes place at the less sterically hindered C-3.[18] However, in case of acyl or vinyl substituted aziridine, the ring opening reaction takes place at C-2 due to the assistance of the activating effect of the substituent (Fig. 1).

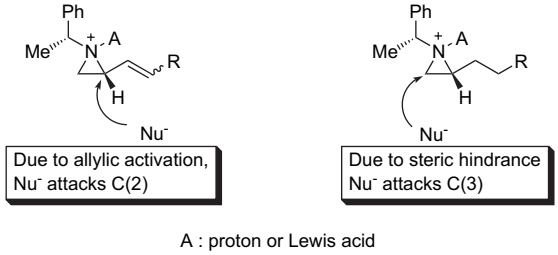
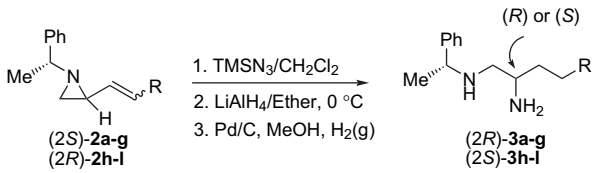


Figure 1. Regiochemistry in aziridine ring opening reactions.

The treatment of 1-amino-2-azido-3-alkenes with LAH in diethyl ether at 0 °C provided the corresponding 1,2-diamino-3-alkenes in high yields. It was unnecessary to separate the cis/trans mixture of the 1,2-diamino-3-alkenes since the double bond was saturated by catalytic hydrogenation in the presence of 20 wt % of Pd/C catalyst. The catalytic hydrogenation in MeOH was completed in 1 h at room temperature to provide the corresponding chiral terminal 1,2-diamines ((2*R*)-**3a–g** and (2*S*)-**3h–l**) and the results are summarized in Scheme 2. Therefore, the present



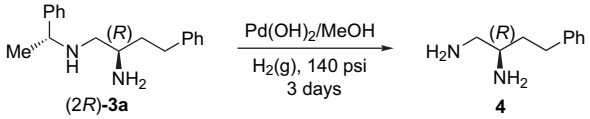
Scheme 2.

transformations show that the absolute configuration at C-2 of the final terminal 1,2-diamines is originated from that of C-2 position of the chiral aziridines and results are summarized in Table 2. The benzyl group on the nitrogen was successfully removed by catalytic hydrogenation in the presence of 20 wt % $Pd(OH)_2$ at 140 psi of H_2(g) to give the terminal 1,2-diamine **4** in high yields (Scheme 3).

Table 2. Preparation of (2*R*)- and (2*S*)-1,2-diaminoalkanes ((2*R*)-**3a–g** and (2*S*)-**3h–l**) from (2*S*)- and (2*R*)-2-alkenyl aziridines ((2*S*)-**2a–g** and (2*R*)-**2h–l**)

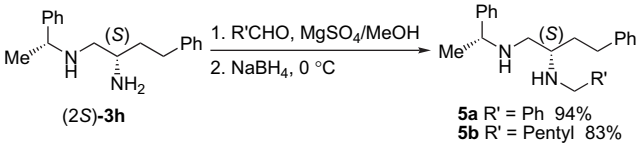
Entry	R	Yield (%)[a]
2a	Phenyl	80
2b	2-Cl-Phenyl	85
2c	4-Biphenyl	83
2d	Propyl	86
2e	Nonyl	80
2f	1-Naphthyl	79[b]
2g	Penta-F-phenyl	75[b]
2h	Phenyl	77
2i	1-Naphthyl	81
2j	4-Cl-Phenyl	80
2k	Propyl	78
2l	Benzyl	81

[a] Isolated yields.
[b] 2HCl salts.

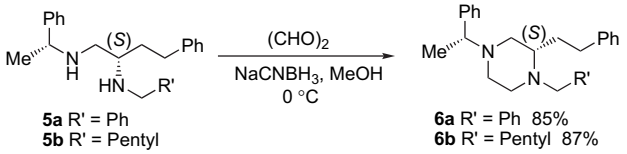


Scheme 3.

We have also applied the enantiomerically pure terminal 1,2-diamines for the preparation of orthogonally protected 2-substituted piperazine. The importance of substituted piperazines can be found in a wide variety of pharmacologically active compounds.[19–23] The reaction of terminal 1,2-diamine (2*S*)-**3h** with RCHO and $MgSO_4$ at room temperature generated the corresponding imine, which was then reduced with $NaBH_4$ at 0 °C to provide the 1-(1′*R*)-phenethyl-2-(*S*)-alkylamino-1,2-diamine **5** in high yields (Scheme 4). Reductive cyclization of **5** with 40% aqueous glyoxal solution in the presence of $NaCNBH_3$ as the reducing agent in MeOH at 0 °C proceeded smoothly and the desired 2-substituted-1,4-piperazine **6** was isolated in high yields (Scheme 5).



Scheme 4.



Scheme 5.

In summary, an operationally simple and high yielding four-step synthesis of 1-(*N*)-protected chiral terminal 1,2-diamine compounds has been developed from commercially available enantiomerically pure aziridine-2-methanols. The process includes regioselective ring opening of 2-vinyl substituted aziridines by azidotrimethylsilane followed by the sequential reduction of the azido group and the double bond. We also developed an efficient new synthetic route for the preparation of enantiomerically pure orthogonally protected 2-substituted-1,4-piperazines using N′-alkylation and intramolecular reductive cyclization.

3. Experimental

3.1. General methods

All reactions were carried out using standard Schlenk technique in an N_2 atmosphere. Solvents were dried by standard methods and distilled under N_2. Flash chromatography was performed with 230–400 mesh silica gel. Melting points were determined on a capillary melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Gemini 300 and 500 MHz spectrometers. NMR spectra were recorded in parts per million (δ) relative to the peak for tetramethylsilane (δ=0.00) as an internal standard unless stated otherwise and are reported as follows: chemical shift, multiplicity (br=broad, s=singlet, t=triplet, q=quartet, m=multiplet), coupling constant, and integration. Elemental analyses were performed by an elemental analyzer. Optical rotations were obtained on a digital polarimeter. Data are reported as follows: $[\alpha]_D^{24}$ (concentration (g/1000 mL), solvent). Solvents and liquid reagents were transferred using hypodermic syringes. All other reagents and solvents used were reagent grade. All glassware was dried in an oven at 150 °C prior to use. Small- and medium-scale purifications were performed using flash chromatography.

3.1.1. Preparation of the 4-phenyl-*N*-[(*R*)-(+)-α-methylbenzyl]butane-1,2(*R*)-diamine ((2*R*)-3a). To a solution of 1,2-diamino-3-alkene (120 mg, 0.43 mmol)[18a] in 1.42 mL of MeOH was added Pd/C (24 mg, 20 wt %). The reaction mixture was stirred at room temperature with 1 atm of H_2(g) for 1 h and then the catalyst was filtered and concentrated in vacuo. Purification by silica gel flash chromatography (CH_2Cl_2/MeOH 50:50) provided 109 mg (90%) of the product (2*R*)-**3a** as a yellow oil. $[\alpha]_D^{24}$ +123.5 (*c* 3.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.16 (m, 10H), 3.73 (q, *J*=6.6 Hz, 1H), 2.81 (m, 1H), 2.68 (m, 1H), 2.55 (m, 2H), 2.19 (dd, *J*=11.5, 8.6 Hz, 1H), 1.66 (m, 1H), 1.53 (m, 1H), 1.34 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 146.2, 142.4, 128.7, 128.6, 128.5, 127.1, 126.8, 126.0, 59.0, 54.9, 51.3, 38.2, 32.8, 24.6; Anal. Calcd for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44. Found: C, 80.47; H, 9.12; N, 10.45.

Compound (2*R*)-**3b**: liquid, $[\alpha]_D^{24}$ +27.3 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.05 (m, 9H), 3.71 (q, *J*=6.5 Hz, 1H), 2.76–2.45 (m, 4H), 2.31 (td, *J*=8.4, 3.0 Hz, 1H), 1.69 (m, 1H), 1.55 (m, 1H), 1.34 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 146.2, 140.8, 129.9, 128.7, 128.6, 127.1, 126.8, 126.0, 59.0, 55.0, 51.2, 38.1, 32.1, 24.6; Anal. Calcd for $C_{18}H_{23}ClN_2$: C, 71.39; H, 7.66; N, 9.25. Found: C, 71.44; H, 7.75; N, 9.11.

Compound (2*R*)-**3c**: liquid, $[\alpha]_D^{24}$ +59.5 (*c* 2.7, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.19 (m, 14H), 3.62 (q, *J*=6.5 Hz, 1H), 2.71–2.50 (m, 3H), 2.31 (dd, *J*=9.8, 5.9 Hz, 1H), 2.13 (m, 1H), 1.52 (m, 1H), 1.35 (m, 1H), 1.29 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 146.0, 141.9, 139.7, 130.2, 129.4, 129.3, 128.5, 128.3, 127.6, 127.0, 126.9, 126.7, 125.9, 58.8, 54.4, 51.1, 38.0, 29.7, 24.5; Anal. Calcd for $C_{24}H_{28}N_2$: C, 83.68; H, 8.19; N, 8.13. Found: C, 83.61; H, 8.06; N, 8.22.

Compound (2*R*)-**3d**: liquid, $[\alpha]_D^{24}$ +127.1 (*c* 3.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.23 (m, 5H), 3.74 (q, *J*=6.5 Hz, 1H), 2.74 (m, 1H), 2.51 (qd, *J*=11.6, 3.4 Hz, 1H), 2.21 (qd, *J*=11.4, 2.9 Hz, 1H), 1.35 (d, *J*=6.5 Hz, 3H), 1.31–1.24 (m, 8H), 0.86 (t, *J*=6.3 Hz, 3H); ^{13}C NMR (755 MHz, $CDCl_3$) 146.2, 128.6, 127.1, 126.8, 126.9, 58.9, 54.8, 51.7, 36.5, 32.2, 26.0, 24.7, 22.8, 14.2; Anal. Calcd for $C_{15}H_{26}N_2$: C, 76.87; H, 11.18; N, 11.95. Found: C, 76.80; H, 11.10; N, 12.05.

Compound (2*R*)-**3e**: liquid, $[\alpha]_D^{24}$ −69.2 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.19 (m, 5H), 3.72 (q, *J*=6.5 Hz, 1H), 2.72 (m, 1H), 2.50 (qd, *J*=11.6, 3.5 Hz, 1H), 2.20 (qd, *J*=11.6, 2.5 Hz, 1H), 1.35 (d, *J*=6.5 Hz, 3H), 1.29–1.23 (m, 20H), 0.88 (t, *J*=6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 146.2, 128.6, 127.0, 126.7, 58.9, 58.4, 55.0, 51.6, 36.7, 32.1, 29.9, 29.8, 29.7, 29.6, 29.5, 26.3, 24.6, 22.9, 14.4; Anal. Calcd for $C_{21}H_{38}N_2$: C, 79.18; H, 12.02; N, 8.79. Found: C, 79.22; H, 12.32; N, 8.65.

Compound (2*R*)-**3h**: liquid, $[\alpha]_D^{24}$ +109.8 (*c* 1.3, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.19 (m, 10H), 3.72 (q, *J*=6.5 Hz, 1H), 2.78–2.47 (m, 4H), 2.30 (qd, *J*=11.6, 8.4 Hz, 1H), 1.74–1.46 (m, 1H), 1.34 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 146.3, 142.4, 128.7, 128.6, 128.5, 127.1, 126.8, 126.0, 59.0, 55.0, 51.3, 38.2, 32.8, 24.6; Anal. Calcd for $C_{18}H_{24}N_2$: C, 80.55; H, 9.01; N, 10.44. Found: C, 80.60; H, 9.13; N, 10.41.

Compound (2*R*)-**3i**: liquid, $[\alpha]_D^{24}$ +64.6 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.13 (m, 12H), 3.70 (q, *J*=6.5 Hz, 1H), 2.90–2.69 (m, 3H), 2.56 (qd, *J*=11.6, 3.5 Hz, 1H), 2.31 (qd, *J*=11.6, 8.4 Hz, 1H), 1.84–1.56 (m, 2H), 1.34 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 145.8, 139.8, 133.8, 132.1, 128.6, 128.1, 127.7, 127.5, 127.4, 127.0, 126.7, 126.4, 126.0, 125.3, 58.3, 54.2, 51.0, 37.9, 32.8, 24.7; HRMS (EI) calcd for $C_{22}H_{26}N_2$: 318.2096, found: 318.2099.

Compound (2*R*)-**3j**: liquid, $[\alpha]_D^{24}$ +53.0 (*c* 1.9, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.05 (m, 9H), 3.73 (q, *J*=6.5 Hz, 1H), 2.80 (m, 1H), 2.76–2.49 (m, 3H), 2.20 (qd, *J*=8.7, 3.7 Hz, 1H), 1.76–1.43 (m, 2H), 1.34 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 145.9, 140.8, 129.9, 128.7, 128.6, 127.2, 126.8, 126.0, 58.4, 54.3, 51.0, 38.0, 32.1, 24.8; Anal. Calcd for $C_{18}H_{23}ClN_2$: C, 71.39; H, 7.66; N, 9.25. Found: C, 71.46; H, 7.65; N, 9.14.

Compound (2*R*)-**3k**: liquid, $[\alpha]_D^{24}$ +387.0 (*c* 5.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.22 (m, 5H), 3.74

(q, J=6.5 Hz, 1H), 2.74 (m, 1H), 2.54 (dd, J=11.6, 3.4 Hz, 1H), 2.14 (dd, J=11.4, 8.8 Hz, 1H), 1.35 (d, J=6.5 Hz, 3H), 1.25–1.06 (m, 8H), 0.87 (t, J=5.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 145.8, 128.6, 127.0, 126.8, 58.5, 54.7, 51.6, 36.7, 32.2, 26.1, 24.9, 22.8, 14.3; Anal. Calcd for $C_{15}H_{26}N_2$: C, 76.87; H, 11.18; N, 11.95. Found: C, 76.90; H, 11.16; N, 12.01.

Compound (2*R*)-**3l**: liquid, $[\alpha]_D^{24}$ +54.5 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.22 (m, 10H), 3.72 (q, J=6.6 Hz, 1H), 2.78 (m, 1H), 2.59–2.42 (m, 3H), 2.14 (dd, J=11.6, 8.7 Hz, 1H), 1.72–1.40 (m, 2H), 1.33 (d, J= 6.6 Hz, 3H), 1.29–1.17 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 146.0, 142.6, 128.7, 128.6, 128.5, 127.1, 126.8, 126.0, 58.5, 54.4, 51.5, 36.2, 29.4, 28.3, 24.9; Anal. Calcd for $C_{15}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.92; H, 9.51; N, 10.11.

3.1.2. Preparation of the 2HCl salt of 4-naphthyl-*N*-[(*R*)-(+)-α-methylbenzyl]butane-1,2(*R*)-diamine ((2*R*)-3f*). To a solution of 4-naphthyl-*N*-[(*R*)-(+)-α-methylbenzyl]-butane-1,2(*R*)-diamine (2*R*)-**3f** (90 mg, 0.28 mmol) in 1.40 mL of THF under nitrogen atmosphere was added concd HCl at room temperature. The mixture was stirred for 2 h at room temperature. After evaporation, Et_2O was added and the product was filtered and recrystallized from Et_2O to give 102 mg (92%) of (2*R*)-**3f*** as a white solid; mp 294–295 °C; $[\alpha]_D^{24}$ +14.8 (*c* 1.5, DMSO); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88–7.82 (m, 3H), 7.71 (s, 1H), 7.64 (d, J=6.6 Hz, 1H), 7.51–7.38 (m, 6H), 4.41 (q, J=6.3 Hz, 1H), 3.59 (m, 1H), 3.37 (m, 1H), 3.02 (d, J=12.1 Hz, 1H), 2.80 (t, J=7.8 Hz, 1H), 2.01 (m, 1H), 1.64 (d, J=6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 138.1, 137.2, 133.1, 131.7, 129.0, 128.9, 127.9, 127.8, 127.5, 127.3, 127.2, 126.2, 126.1, 125.4, 58.3, 48.1, 47.0, 32.2, 30.6, 19.2; Anal. Calcd for $C_{22}H_{23}Cl_2N_2$: C, 67.51; H, 7.21; N, 7.16. Found: C, 67.54; H, 7.24; N, 7.08.

Compound (2*R*)-**3g***: mp 264–265 °C; $[\alpha]_D^{24}$ +28.8 (*c* 1.8, DMSO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72–7.43 (m, 5H), 4.59 (q, J=6.6 Hz, 1H), 3.74 (m, 1H), 3.52–3.41 (m, 2H), 3.21 (d, J=4.3 Hz, 1H), 2.94 (t, J=8.1 Hz, 1H), 2.16–2.04 (m, 2H), 1.89 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 137.3, 131.1, 131.0, 130.7, 130.6, 129.2, 129.1, 127.8, 61.5, 50.3, 48.1, 32.7, 31.5, 19.2; Anal. Calcd for $C_{18}H_{21}F_5Cl_2N_2$: C, 50.13; H, 4.91; N, 6.50. Found: C, 50.20; H, 5.02; N, 6.37.

3.1.3. Preparation of the 4-phenyl-butane-1,2(*R*)-diamine (4). To a solution of 4-phenyl-*N*-[1(*R*)-(+)-α-methylbenzyl]butane-1,2(*R*)-diamine (2*R*)-**3a** (80 mg, 0.30 mmol) in 1.49 mL of MeOH under H_2(g) was added $Pd(OH)_2$ at room temperature. The mixture was stirred for 70 h under 120 psi of H_2(g) at room temperature, then the catalyst was filtered and washed with MeOH. The solvent was evaporated to give the product as yellow oil which was purified by silica gel flash chromatography with 50% CH_2Cl_2/MeOH to give 46 mg (93%) of **4**; $[\alpha]_D^{24}$ −4.2 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.16 (m, 5H), 2.81–2.61 (m, 4H), 2.49 (dd, J=12.2, 7.4 Hz, 1H), 1.74 (m, 1H), 1.59 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 142.4, 128.7, 128.6, 126.1, 53.5, 49.0, 37.7, 32.8; Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.13; H, 9.82; N, 17.06. Found: C, 73.22; H, 9.96; N, 16.98.

3.1.4. Preparation of the 2-*N*-benzyl-4-phenyl-*N*-(1(*R*)-(+)-α-methylbenzyl)butane-1,2(*S*)-diamine (5a). To a solution of 4-phenyl-*N*-[1(*R*)-α-methylbenzyl]butane-1,2(*S*)-diamine **3h** (100 mg, 0.37 mmol) in 1.86 mL of MeOH under nitrogen atmosphere was added benzaldehyde (0.08 mL, 0.75 mmol) at room temperature. To the mixture was added $MgSO_4$ (90 mg, 0.75 mmol) and stirred for 6 h. To the mixture was slowly added $NaBH_4$ (21 mg, 0.56 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C. The reaction was quenched with water at room temperature. The aqueous layer was extracted with CH_2Cl_2. The combined extract was dried over $MgSO_4$, and the solvent was evaporated to give the crude product, which was purified by silica gel flash chromatography with 30% EtOAc/hexane to give 125 mg (94%) of the product **5a** as a colorless oil; $[\alpha]_D^{24}$ +14.5 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.10 (m, 15H), 3.70 (q, J=13.1 Hz, 2H), 3.61 (q, J=6.5 Hz, 1H), 2.69–2.45 (m, 4H), 2.34 (dd, J=11.4, 7.4 Hz, 1H), 1.84–1.60 (m, 2H), 1.32 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 146.0, 142.6, 141.1, 128.7, 128.6, 128.5, 128.4, 128.3, 127.0, 126.9, 126.8, 125.9, 58.2, 56.2, 51.0, 50.4, 34.6, 32.4, 24.9; HRMS (EI) calcd for $C_{25}H_{30}N_2$: 358.2409, found: 358.2414.

Compound **5b**: liquid, $[\alpha]_D^{24}$ +6.9 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.12 (m, 10H), 3.72 (q, J= 6.5 Hz, 1H), 2.63–2.45 (m, 6H), 2.31 (dd, J=12.4, 8.5 Hz, 1H), 1.79–1.10 (m, 13H), 0.89 (t, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 146.3, 142.8, 128.7, 128.6, 128.5, 127.0, 126.9, 125.9, 58.6, 57.5, 50.8, 47.1, 34.8, 32.7, 32.1, 30.8, 27.4, 24.9, 22.9, 14.3; Anal. Calcd for $C_{24}H_{36}N_2$: C, 81.76; H, 10.29; N, 7.95. Found: C, 81.90; H, 10.21; N, 8.05.

3.1.5. Preparation of the 1-*N*-benzyl-2(*R*)-phenethyl-*N*-(4(*R*)-(+)-α-methylbenzyl)piperazine (6a). To a solution of 2-*N*-benzyl-4-phenyl-*N*-(1(*R*)-(+)-α-methylbenzyl)-butane-1,2(*S*)-diamine **5a** (120 mg, 0.33 mmol) in MeOH (0.01 M, 33.5 mL) under nitrogen atmosphere was added glyoxal (0.05 mL, 0.47 mmol) and $NaCNBH_3$ (43.0 mg, 0.67 mmol) at 0 °C. The mixture was stirred for 14 h. The reaction was quenched with water at room temperature. The solvent was evaporated and washed with $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The combined extract was dried over $MgSO_4$, and the solvent was evaporated to give the crude product, which was purified by silica gel flash chromatography with 30% EtOAc/hexane to give 110 mg (85%) of the product **6a** as a yellow oil; $[\alpha]_D^{24}$ +14.5 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.05 (m, 15H), 3.94 (d, J=13.3 Hz, 1H), 3.32 (q, J=6.6 Hz, 1H), 3.26 (d, J=13.2 Hz, 1H), 2.74–2.59 (m, 3H), 2.52–2.43 (m, 3H), 2.39–2.23 (m, 3H), 2.03–1.87 (m, 2H), 1.35 (q, J=6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 144.4, 142.8, 139.2, 129.1, 128.6, 128.5, 128.4, 128.3, 127.8, 127.0, 126.9, 125.9, 65.2, 59.4, 58.0, 54.8, 51.1, 50.4, 34.7, 32.3, 20.2; Anal. Calcd for $C_{27}H_{32}N_2$: C, 84.33; H, 8.39; N, 7.28. Found: C, 84.29; H, 8.24; N, 7.32.

Compound **6b**: liquid, $[\alpha]_D^{24}$ +39.6 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.14 (m, 10H), 3.32 (q, J=6.5 Hz, 1H), 2.80–2.20 (m, 12H), 1.84 (d, J=6.8 Hz, 1H), 1.36 (d, J=6.6 Hz, 3H), 1.31–1.19 (m, 8H), 0.87 (q, J=6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 144.6, 142.9,

128.6, 128.5, 128.4, 127.9, 127.1, 126.0, 65.2, 64.9, 59.0, 54.9, 53.8, 50.7, 32.7, 32.1, 27.6, 26.4, 22.9, 20.3, 15.3, 14.3; Anal. Calcd for $C_{26}H_{38}N_2$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.29; H, 9.97; N, 7.34.

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