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REGIO- AND STEREOSELECTIVE RING-OPENING REACTION OF CHIRAL AZIRIDINES: A FACILE SYNTHESIS OF CHIRAL β-AMINO ALCOHOLS

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Abstract – The reaction of chiral 2-alkylsubstituted aziridines (**1a-d**) with acetic acid afforded β-amino alcohols with an (*S*)-chiral center at the β position (with respect to oxygen). In contrast, a reaction of the same chiral aziridines with acetyl chloride followed by treatment with water gave β-amino alcohols that have an (*S*)-chiral center at the α position. In addition, the reaction of the same chiral aziridines with benzyl bromide followed by treatment with 2% sulfuric acid gave the β-amino alcohols with an (*R*)-chiral center at the α position. Thus, we could control the regioselectivity and stereoselectivity of the ring-opening reaction of chiral aziridines (**1a-d**).

INTRODUCTION

Chiral aziridine derivatives are of interest not only for theoretical reasons but also because of the high reactivity that arises from the release of strain energy inherent in a small ring. In fact, the regio- and stereocontrolled ring-opening reaction of chiral aziridine using a reagents such as electrophiles, nucleophiles, acids, and reducing agents, allows easy access to versatile synthetic intermediates for the synthesis of biologically active *N*-containing compounds.[1,2] In particular, there are many reports on the ring-opening reaction of the chiral aziridine with oxygen nucleophiles,[3] which gives the β-amino alcohol unit included in many biologically active natural products and important pharmaceuticals.

The cleavage of the *C*(3)-*N* bond in aziridine-2-methanols by acetic acid treatment results in high regioselectivity.[4] The regioselective cleavage of the *C*(2)-*N* bond can also be achieved with 2-acylaziridines by using acid chloride and water,[5] producing β-amino alcohols with substituents at different positions. A second group reported that cleavage of 3-subsutituted *N*-ethoxycarbonyl aziridine-2-carboxylate could be controlled by using different metallic halides to synthesize different α-amino and β-amino acids.[6]

We also recently reported a simple synthetic method for the synthesis of chiral 2-substituted aziridines.[7] The reaction pathway consists of the diastereoselective addition of dimethylsulfonium methylide to the chiral imines derived from (*R*)-*O*-methylphenylglycinol and various aldehydes, producing high stereo-selectivity. This finding indicated the possibility for reacting chiral 2-substituted aziridines to produce chiral β-amino alcohols. Herein, we report a regio- and stereoselective synthetic method for chiral β-amino alcohols with multiple substituents.

RESULTS AND DISCUSSION

Initial reactions were performed on the chiral 2-alkylsubstituted aziridines, which were easily obtained from our methodology, and acetic acid according to a modification of Lee's procedure.[4] The reaction proceeds smoothly at the reflux temperature of toluene by treating substrates **1a-d** with 2 equivalents of acetic acid to yield the ring opening products (**2a-d**) in 82-93% yields, which have an (*S*)-chiral center at the β position because of the *C*(3)-*N* bond cleavage of the aziridine ring. The reactions showed excellent regioselectivity, except for reaction **1a**, which has a sterically small substituent.

From these observations we believe that the reaction follows the same mechanism Lee proposed for the ring-opening reaction of aziridine-2-methanol with acetic acid.[4] This reaction proceeds through the formation of an intermediate aziridinium salt with protonation by acetic acid, which undergoes a regioselective ring-opening reaction by AcO^- at the less hindered *C*(3) position (Scheme 1).

Scheme 1

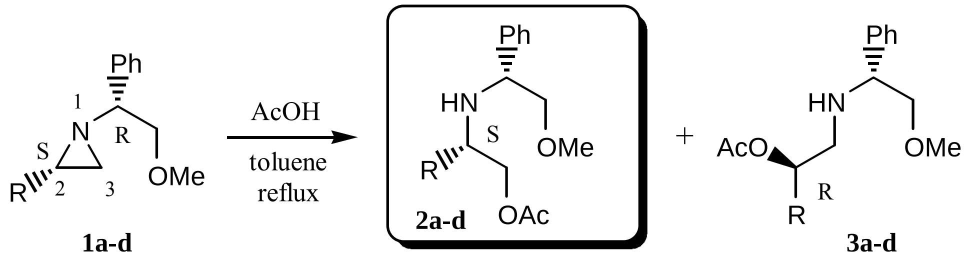


Table 1. Reaction of Aziridines with Acetic Acid

	R	Yield of **2**[a)]	ratio (**2** : **3**)[b)]
a	Me	**82** %	**89 : 11**
b	Et	**93** %	**97 : 3**
c	Pr	**83** %	**95 : 5**
d	*i*-Pr	**90** %	**99 : 1**

a) Isolated yield. b) Estimated from the ^{1}H-NMR (270MHz) spectrum.

Next, we tried a ring-opening reaction with acetyl chloride. The 2-substituted chiral aziridines (**1a-d**) were reacted with acetyl chloride in THF at 0 °C, followed by treatment with excess water, to produce β-amino alcohols having an (*S*)-chiral center at the α position due to *C*(2)-*N* bond cleavage of the aziridine ring in 72-86% yields. The regioselectivity of this reaction was excellent, except for the reaction for **1d**, which possessed a sterically bulky substituent. The stereoselectivity of the ring-opening products (**4a-d**) was extremely high, since no diastereomer signals for **4a-d** were detected in the ^{1}H-NMR spectrum.

In this reaction, the *S* configuration of *C*(2) of the starting aziridine was completely retained in **4a-d**, with its position denoted by the α position of the β-amino alcohols (**4a-d**). The high regio- and stereocontrol of this reaction probably proceeds through the formation an *N*-acylaziridinium salt resulting from the reaction of acid chloride. Subsequently, this *N*-acylaziridinium salt undergoes a ring-opening reaction by an anti-attack of chloride at the *C*(2) position. Next, the initial product of *N*-acyl-β-chloroamine is readily reacted by the internal oxygen nucleophile by replacement of the chloride to make the oxazoline derivative. Finally, by adding water, the oxazoline derivative was hydrolyzed to yield β-amino alcohols (**4a-d**) as a final product in Scheme 2. *N*-Acylaziridine shows a ring expansion like other compounds in this class, as discussed by Hori el al. and by Lee et al. [5,8]

Scheme 2

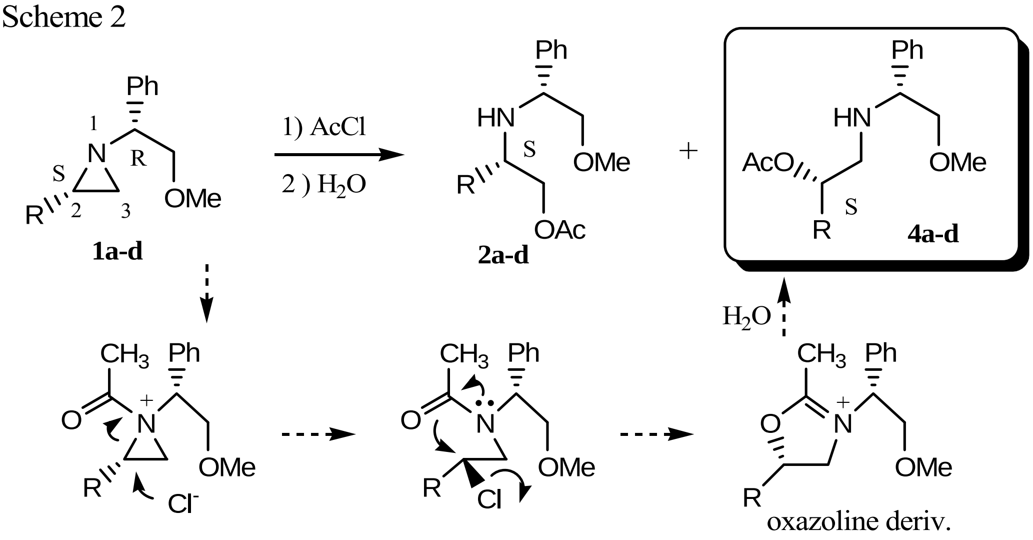


Table 2. Reaction of Aziridines with Acetyl Chloride

	R	Yield of **4**[a)]	ratio (**2** : **4**)[b)]
a	Me	**86** %	**2 : 98**
b	Et	**82** %	**4 : 96**
c	Pr	**72** %	**4 : 96**
d	*i*-Pr	**72** %	**13 : 87**

a) Isolated yield. b) Estimated from the ^{1}H-NMR (270MHz) spectrum.

The reaction of the same chiral aziridines (**1a-d**) with benzyl bromide afforded the β-bromoamines (**5a-d**) by *C*(2)-*N* bond cleavage of the aziridine ring. Next, hydroxylation of the β-bromoamines (**5a-d**) with 2% sulfuric acid at 90 °C for 4 h gave the β-amino alcohols (**6a-d**) with (*R*)-chiral centers at the α position in good yields. However, an equivalent of benzyl bromide and reaction solvent concentration influenced chemical yield and stereoselectivity. The optimum condition for ring opening with benzyl bromide is using it at a 10-fold excess, with a 40-fold excess of acetone versus the aziridine. When reacting the chiral aziridines (**1a-d**) under these conditions, **5a-d** was obtained as a single diastereomer with a yield of 90% or more (Scheme 3). The stereochemistry of β-bromoamines (**5a-d**) was estimated by X-ray analysis of **5d'**, which was produced by the ring-opening reaction of **1d** with 4-bromobenzyl bromide (Figure 1).[9]

The first step seems to have proceeded through the formation of an aziridinium intermediate by *N*-benzylation, which underwent a regiospecific ring opening reaction through anti-attack of bromide at the *C*(2) position.[10] Further, the addition of water at the *C*(2) position could be explained by neighboring group participation of the nitrogen atom, resulting in a highly activated aziridinium salt that underwent water attack to give the *C*(2) addition products.

Scheme 3

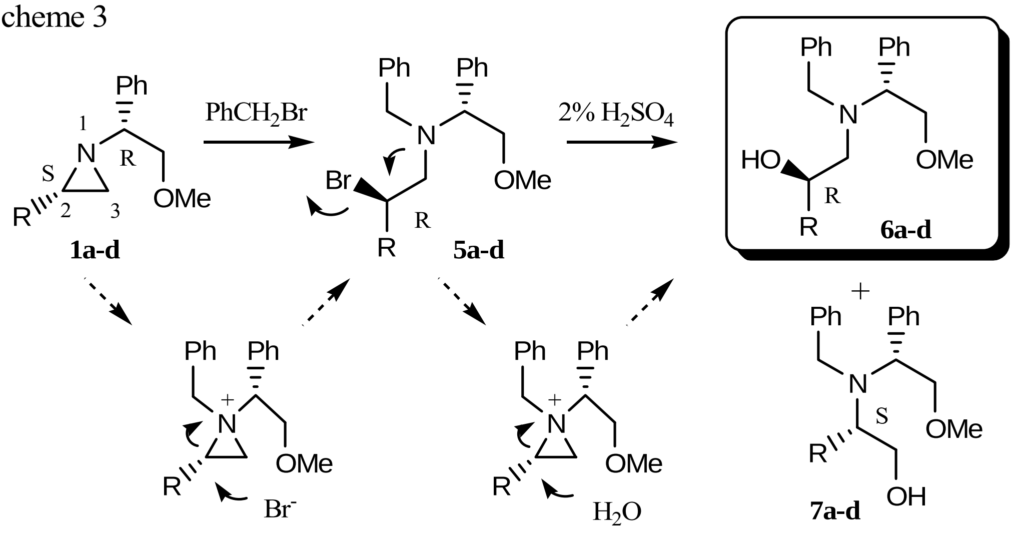


Table 3. Reaction of Aziridines with Benzyl bromide

	R	Yield of **5**[a)]	Yield of **6**[a)]	ratio (**6** : **7**)[b)]
a	Me	**90** %	**65** %	> **99 : 0**
b	Et	**93** %	**59** %	**95 : 5**
c	Pr	**92** %	**57** %	**96 : 4**
d	*i*-Pr	**92** %	**73** %	**99 : 1**

a) Isolated yield. b) Estimated from the ^{1}H-NMR (270MHz) spectrum.

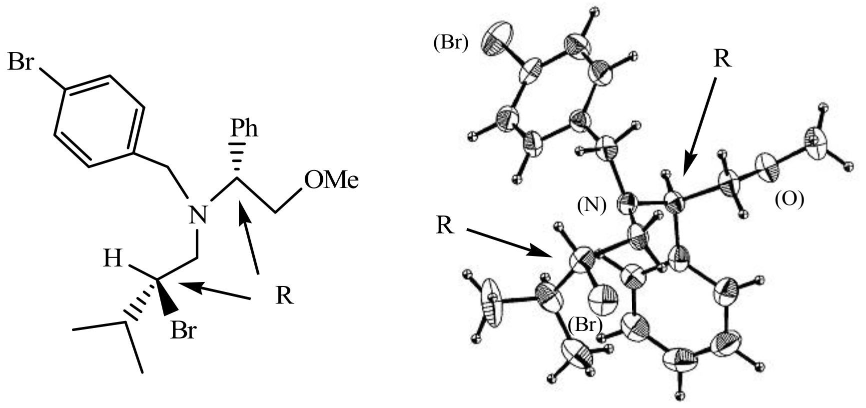
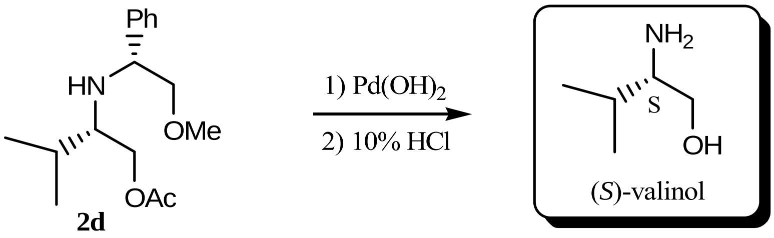


Figure 1. ORTEP view of compound (**5d'**).

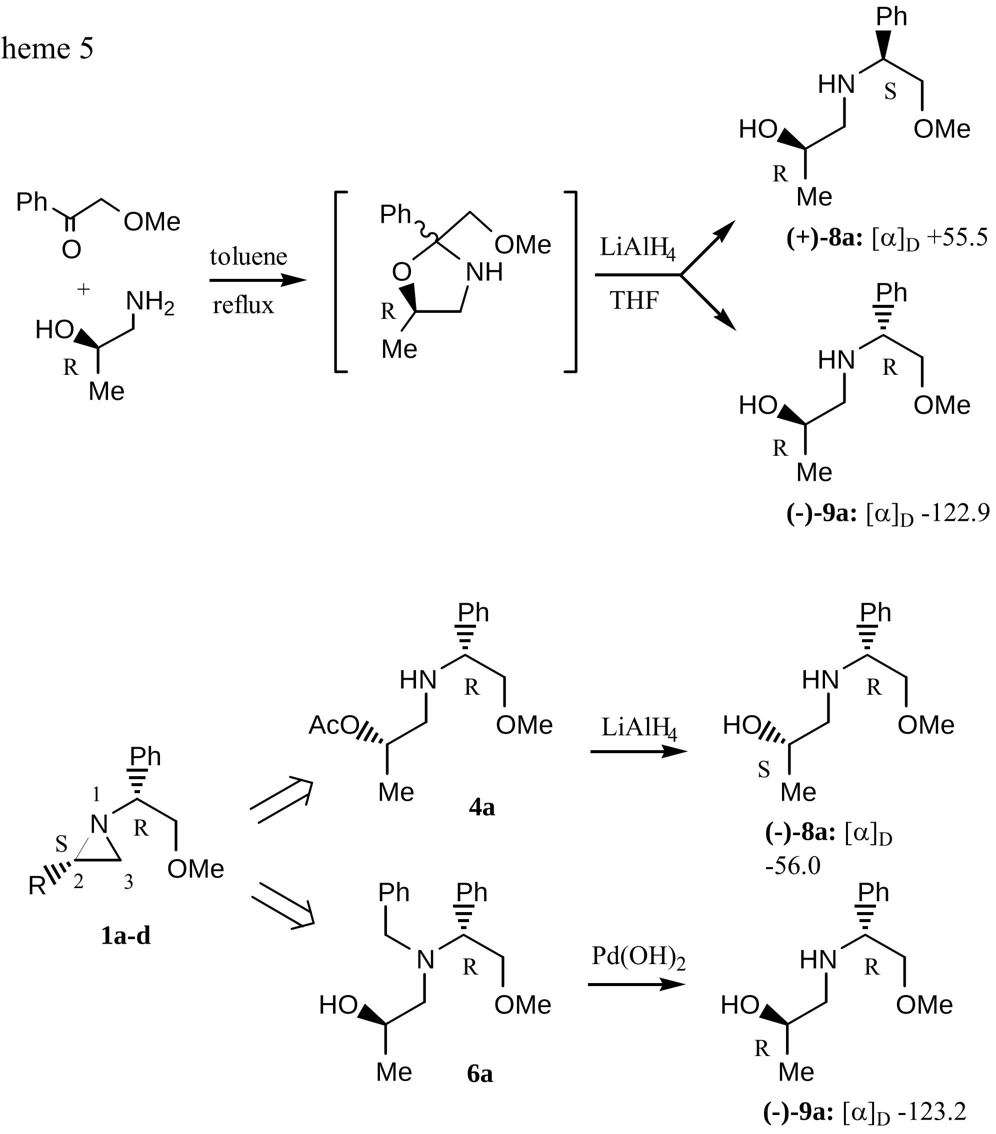
Confirmation of the absolute stereochemistry of ring opening products (**2a-d**, **4a-d** and **6a-d**) was estimated (Scheme 4 and 5). In the case of ring opening products (**2a-d**), hydrogenolysis of **2d** with $Pd(OH)_2/H_2$ and subsequent hydrolysis with 10% HCl afforded valinol, and its spectrum and optical rotation date were consistent with commercially available (*S*)-valinol. Therefore, the absolute configuration of **2a-d** that had been obtained from the reaction of the chiral aziridine and the acetic acid was the (*S*,*R*) form (Scheme 4).

Scheme 4



On the other hand, the absolute configuration of the chiral center formed by a new ring opening product (**4a-d** and **6a-d**) was estimated by comparing **8a** or **9a** obtained from another synthetic route (Scheme 5). Namely, condensation of 2-methoxyacetophenone with (*R*)-1-amino-2-propanol in toluene gave a sensitive oxazolidine, which was reduced by LAH to give the separable chiral β-amino alcohol [(+)-**8a** and (-)-**9a**]. Meanwhile, reduction by LAH of the ring-opening product (**4a**) afforded a β-amino alcohol [(-)-**8a**] with the same NMR data of (+)-**8a** of another synthetic route, but with opposite specific rotation. Moreover, the removal of the benzyl group of the ring-opening product (**6a**) by catalytic hydrogenation gave the β-amino alcohol [(-)-**9a**] with the same NMR data and specific rotation of (-)-**9a** of another synthetic route. These experimental results show that the compound (-)-**8a** has (2*S*,1'*R*) stereochemistry, and compound (-)-**9a** has (2*R*,1'*R*) stereochemistry. Therefore, the absolute configuration of **4a-d** obtained from the reaction of the acetyl chloride was the (2*S*,1'*R*) form, and **6a-d** that had been obtained from the reaction of the benzyl bromide was estimated to be the (2*R*,1'*R*) form.

Scheme 5



In conclusion, we developed an efficient and practical method for preparing chiral β-amino alcohols from regio- and stereocontrolled ring-opening reactions of chiral aziridine. Moreover, this synthesis method can synthesize various chiral β-amino alcohols by selecting ring-opening reagents while using a single chiral aziridine as a raw material. We believe that the present reaction will be useful for constructing biologically important compounds. Further study in this area is under investigation in our laboratory.

EXPERIMENTAL

General: Melting points were measured with a Yanagimoto Micro melting point apparatus without collection. IR spectra were recorded on a JASCO FT/IR-200, and major absorption is listed in cm^{-1}. ^{1}H and ^{13}C NMR spectra were obtained on a JEOL GSX 270 instrument, and chemical sifts are reported in ppm on the δ-scale from internal Me_4Si. MS spectra were measured with a JEOL JMS 600 spectrometer by using the chemical ionization(CI) with isobutene and the electron impact(EI) methods. Elemental analyses were performed on a Perkin-Elmer 240-B instrument. Optical rotation were taken with a JASCO-DIP-1000 polarimeter at rt. Column chromatography was performed on silica gel (45−75μm, Wakogel C-300). The reaction solvents were prepared as the following. THF was distilled over potassium metal. Dichloromethane was distilled over phosphorus pentoxide.

General procedure for the ring-opening reaction of aziridine with acetic acid.

A mixture of aziridine (3.0 mmol) and acetic acid (6.0 mmol) in toluene (15 mL) was stirred at reflux temperature for 4 h. After cooling, the reaction mixture was quenched with saturated aqueous Na_2CO_3 (10 mL). The organic layer was separated, and aqueous layer was extracted with Et_2O (10 mL x 2). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated to give the crude product, which was purified by silica gel flash chromatography with hexane/EtOAc (1 : 1) to afford pure product (**2a-d**) as a viscous oil.

(1*S*, 1'*R*)-*N*-(2'-Methoxy-1'-phenylethyl)-1-acetoxymethylethylamine (2a).

$[\alpha]_D$ -70.43 (*c* 1.10, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.6Hz, 3H), 1.91 (brs, 1H), 2.07 (s, 3H), 2.76-2.86 (m, 1H), 3.33-3.44 (m, 2H), 3.35 (s, 3H), 3.94 (dd, *J* = 4.8, 11.0Hz, 1H), 4.04 (dd, *J* = 4.6, 8.2Hz, 1H), 4.09 (dd, *J* = 4.8, 11.0Hz, 1H), 7.22-7.40 (m, 5H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 170.79, 141.01, 128.21, 127.38, 127.25, 77.63, 66.62, 59.64, 58.43, 48.96, 20.61, 19.13. IR (film): 3339, 2980, 2930, 2895, 2822, 1740, 1460, 1375, 1230, 1118 cm^{-1}. MS *m/z*: CI, 252 (M^++1). *Anal.* Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.82; H, 8.40; N, 5.54.

Minor component: (2*R*, 1'*R*)-*N*-(2'-Methoxy-1'-phenylethyl)-2-acetoxypropylamine (3a).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.4Hz, 3H), 2.03 (brs, 1H), 2.06 (s, 3H), 2.55 (dd, *J* = 6.9, 12.9Hz, 1H), 2.63 (dd, *J* = 4.0, 12.9Hz, 1H), 3.32-3.44 (m, 2H), 3.36 (s, 3H), 3.90 (dd, *J* = 4.2, 8.8Hz, 1H), 4.97-5.08 (m, 1H), 7.24-7.39 (m, 5H).

(1*S*, 1'*R*)-*N*-(2'-Methoxy-1'-phenylethyl)-1-acetoxymethylpropylamine (2b).

$[\alpha]_D$ -92.86 (*c* 1.07, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.3Hz, 3H), 1.35-1.47 (m, 2H), 1.91 (brs, 1H), 2.07 (s, 3H), 2.46-2.54 (m, 1H), 3.34-3.41 (m, 2H), 3.35 (s, 3H), 3.96 (dd, *J* = 4.0, 11.2Hz, 1H), 4.04 (dd, *J* = 5.5, 7.3Hz, 1H), 4.09 (dd, *J* = 4.6, 11.2Hz, 1H), 7.23-7.40 (m, 5H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 170.94, 140.86, 128.18, 127.58, 127.30, 77.77, 64.49, 59.16, 58.42, 54.24, 25.96, 20.74, 10.44. IR (film): 3340, 2960, 2930, 2880, 2821, 1740, 1465, 1380, 1230, 1118 cm^{-1}. MS *m/z*: CI, 266 (M^++1). *Anal.* Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.83; H, 8.72; N, 5.31.

Minor component: (2*R*, 1'*R*)-*N*-(2'-Methoxy-1'-phenylethyl)-2-acetoxybutylamine (3b).

^{1}H NMR (270 MHz, CDCl$_3$): δ = 0.81 (t, *J* = 7.4Hz, 3H), 1.57 (quintet, *J* = 7.4Hz, 2H), 1.99 (brs, 1H), 2.08 (s, 3H), 2.55 (dd, *J* = 9.9, 13.0Hz, 1H), 2.65 (dd, *J* = 3.6, 13.0Hz, 1H), 3.32-3.43 (m, 2H), 3.35 (s, 3H), 3.49 (dd, *J* = 4.2, 8.8Hz, 1H), 4.86-4.95 (m, 1H), 7.22-7.39 (m, 5H).

(1*S*, 1'*R*)-*N*-(2'-Methoxy-1'-phenylethyl)-1-acetoxymethylbutylamine (2c).

[α]$_D$ -83.29 (*c* 1.15, CHCl$_3$). ^{1}H NMR (270 MHz, CDCl$_3$): δ = 0.81 (t, *J* = 7.0Hz, 3H), 1.20-1.49 (m, 4H), 1.95 (brs, 1H), 2.07 (s, 3H), 2.54-2.62 (m, 1H), 3.37 (s, 3H), 3.37-3.41 (m, 2H), 3.94 (dd, *J* = 3.9, 11.3Hz, 1H), 4.08 (t, *J* = 6.4Hz, 1H), 4.09 (dd, *J* = 4.5, 11.3Hz, 1H), 7.22-7.40 (m, 5H). ^{13}C NMR (67.8 MHz, CDCl$_3$): δ = 170.41, 140.71, 127.95, 127.40, 127.07, 77.63, 64.64, 58.89, 58.10, 52.18, 35.32, 20.40, 18.80, 13.71. IR (film): 3339, 2960, 2931, 2875, 2821, 1740, 1454, 1380, 1235, 1120 cm^{-1}. MS *m/z*: CI, 280 (M$^+$+1). *Anal.* Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.70; H, 9.04; N, 5.03.

Minor component: (2*R*, 1'*R*)-*N*-(2'-Methoxy-1'-phenylethyl)-2-acetoxypentylamine (3c).

^{1}H NMR (270 MHz, CDCl$_3$): δ = 0.87 (t, *J* = 7.4Hz, 3H), 1.18-1.29 (m, 2H), 1.43-1.57 (m, 2H), 2.07 (s, 3H), 2.09 (brs, 1H), 2.56 (dd, *J* = 6.8, 13.0Hz, 1H), 2.64 (dd, *J* = 3.8, 13.0Hz, 1H), 3.32-3.43 (m, 2H), 3.35 (s, 3H), 3.90 (dd, *J* = 4.3, 8.7Hz, 1H), 4.95-5.03 (m, 1H), 7.23-7.39 (m, 5H).

(1*S*, 1'*R*)-*N*-(2'-Methoxy-1'-phenylethyl)-1-acetoxymethyl-2-methylpropylamine (2d).

[α]$_D$ -95.47 (*c* 1.09, CHCl$_3$). ^{1}H NMR (270 MHz, CDCl$_3$): δ = 0.89 (d, *J* = 6.8Hz, 3H), 0.92 (d, *J* = 6.8Hz, 3H), 1.60-1.82 (m, 1H), 1.86 (brs, 1H), 2.06 (s, 3H), 2.29-3.34 (m, 1H), 3.35 (s, 3H), 3.37-3.43 (m, 2H), 4.04 (dd, *J* = 4.1, 11.5Hz, 1H), 4.07 (t, *J* = 7.6Hz, 1H), 4.23 (dd, *J* = 4.7, 11.5Hz, 1H), 7.22-7.40 (m, 5H). ^{13}C NMR (67.8 MHz, CDCl$_3$): δ = 170.90, 140.87, 128.09, 127.79, 127.27, 77.84, 63.07, 59.38, 58.37, 57.81, 30.12, 20.77, 19.28, 18.51. IR (film): 3340, 2960, 2930, 2890, 2821, 1740, 1458, 1380, 1228, 1107 cm^{-1}. MS *m/z*: CI, 280 (M$^+$+1). *Anal.* Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.74; H, 8.91; N, 5.04.

Minor component: (2*R*, 1'*R*)-*N*-(2'-Methoxy-1'-phenylethyl)-2-acetoxy-3-methylbutylamine (3d).

^{1}H NMR (270 MHz, CDCl$_3$): δ = 0.79 (d, *J* = 6.8Hz, 3H), 0.84 (d, *J* = 6.8Hz, 3H), 1.86-1.97 (m, 1H), 1.95 (brs, 1H), 2.10 (s, 3H), 2.58 (dd, *J* = 7.0, 13.2Hz, 1H), 2.63 (dd, *J* = 3.6, 13.2Hz, 1H), 3.31-3.41 (m, 2H), 3.33 (s, 3H), 3.88 (dd, *J* = 4.3, 8.7Hz, 1H), 4.70-4.84 (m, 1H), 7.22-7.38 (m, 5H).

General procedure for the ring-opening reaction of aziridine with acetyl chloride/H_2O.

To the stirred solution of aziridine (3.0 mmol) in anhydrous THF (20 mL) at 0°C under nitrogen atmosphere, acetyl chloride (4.5 mmol) was added dropwise. After the reaction mixture was stirred for 1 h at 0°C, H_2O (5 mL) was then added and stirred for 20 min at room temperature. The reaction mixture was made basic with saturated aqueous Na_2CO_3 (25 mL). The aqueous layer was extracted with Et_2O (15 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated to give the crude product, which was purified by silica gel flash chromatography with hexane/EtOAc (1 : 1) to afford pure product (**4a-d**) as a viscous oil.

(2*S*, 1'*R*)-*N*-(2'-Methoxy-1'-phenylethyl)-2-acetoxypropylamine (4a).

$[\alpha]_D$ -56.67 (*c* 1.09, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 6.3Hz, 3H), 2.04 (s, 3H), 2.10 (brs, 1H), 2.46 (dd, *J* = 4.6, 12.2Hz, 1H), 2.65 (dd, *J* = 7.7, 12.2Hz, 1H), 3.33-3.45 (m, 2H), 3.37 (s, 3H), 3.87 (dd, *J* = 4.1, 9.1Hz, 1H), 4.89-4.96 (m, 1H), 7.24-7.39 (m, 5H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 170.15, 140.28, 128.03, 127.26, 127.20, 77.49, 70.82, 62.48, 58.37, 51.70, 20.92, 17.74. IR (film): 3340, 2980, 2931, 2890, 2821, 1740, 1478, 1371, 1240, 1109 cm^{-1}. MS *m/z*: CI, 252 (M^++1). *Anal.* Calcd for $C_{14}H_{21}NO_3HCl$: C, 58.43; H, 7.70; N, 4.86. Found: C, 58.21; H, 7.74; N, 4.99. HCl salt: colorless crystal, mp 100°C (Et_2O).

(2*S*, 1'*R*)-*N*-(2'-Methoxy-1'-phenylethyl)-2-acetoxybutylamine (4b).

$[\alpha]_D$ -71.02 (*c* 0.98, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.5Hz, 3H), 1.49-1.67 (m, 2H), 2.02 (brs, 1H), 2.05 (s, 3H), 2.52 (dd, *J* = 4.9, 12.3Hz, 1H), 2.63 (dd, *J* = 7.0, 12.3Hz, 1H), 3.32-3.44 (m, 2H), 3.36 (s, 3H), 3.86 (dd, *J* = 4.2, 9.0Hz, 1H), 4.83-4.88 (m, 1H), 7.25-7.39 (m, 5H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 170.71, 140.50, 128.27, 127.46. 127.38, 77.68, 75.43, 62.77, 58.64, 49.88, 25.04, 21.16, 9.34. IR (film): 3340, 2970, 2935, 2880, 2821, 1740, 1458, 1371, 1240, 1110 cm^{-1}. MS *m/z*: CI, 266 (M^++1). *Anal.* Calcd for $C_{15}H_{23}NO_3HCl$: C, 59.69; H, 8.01; N, 4.64 Found: C, 59.47; H, 8.01; N, 4.59. HCl salt: colorless crystal, mp 105°C (Et_2O).

(2*S*, 1'*R*)-*N*-(2'-Methoxy-1'-phenylethyl)-2-acetoxypentylamine (4c).

$[\alpha]_D$ -62.99 (*c* 1.17, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.3Hz, 3H), 1.22-1.35 (m, 2H), 1.48-1.57 (m, 2H), 2.00 (brs, 1H), 2.05 (s, 3H), 2.52 (dd, *J* = 4.8, 12.4Hz, 1H), 2.63 (dd, *J* = 7.0, 12.4Hz, 1H), 3.34-3.45 (m, 2H), 3.37 (s, 3H), 3.86 (dd, *J* = 4.3, 8.9Hz, 1H), 4.88-4.97 (m, 1H), 7.23-7.39 (m, 5H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 170.02, 140.27, 127.93, 127.14, 127.03, 77.37, 73.68, 62.46, 58.19, 50.10, 33.99, 20.61, 18.02, 13.48. IR (film): 3340, 2960, 2931, 2871, 2821, 1740, 1459, 1378, 1240, 1110 cm^{-1}. MS *m/z*: CI, 280 (M^++1). *Anal.* Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.60; H, 9.08; N, 5.04.

(2*S*, 1'*R*)-*N*-(2'-Methoxy-1'-phenylethyl)-2-acetoxy-3-methylbutylamine (4d).

$[\alpha]_D$ -62.02 (*c* 1.22, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$): δ = 0.82 (d, *J* = 6.8Hz, 3H), 0.86 (d, *J* = 6.8Hz, 3H), 1.75 (brs, 1H), 1.83-1.99 (m, 1H), 2.07 (s, 3H), 2.56 (dd, *J* = 4.8, 12.4Hz, 1H), 2.61 (dd, *J* = 6.9, 12.4Hz, 1H), 3.32-3.44 (m, 2H), 3.36 (s, 3H), 3.84 (dd, *J* = 4.2, 9.0Hz, 1H), 4.77-4.83 (m, 1H), 7.22-7.39 (m, 5H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 170.42, 140.36, 128.03, 127.24, 127.14, 78.13, 77.47, 62.68, 58.35, 47.84, 29.45, 20.67, 18.29, 17.04. IR (film): 3340, 2961, 2930, 2880, 2822, 1738, 1453, 1372, 1240, 1110 cm^{-1}. MS *m/z*: CI, 280 (M^++1). *Anal.* Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.64; H, 8.95; N, 5.08.

General procedure for the ring-opening reaction of aziridine with benzyl bromide.

A mixture of aziridine (1.5 mmol) and benzyl bromide (15.0 mmol) in acetone (4.5 mL) was heated for 12 h at 60°C under nitrogen atmosphere. After cooling, the reaction mixture was evaporated to give the crude product, which was purified by silica gel flash chromatography with hexane/EtOAc (16 : 1) to afford pure product (**5a-d**) as a viscous oil.

(2*R*, 1'*R*)-*N*-Benzyl-*N*-(2'-methoxy-1'-phenylethyl)-2-bromopropylamine (5a).

$[\alpha]_D$ -45.9 (*c* 1.05, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.48 (d, *J* = 6.6Hz, 3H), 2.70 (dd, *J* = 7.5, 13.9Hz, 1H), 3.11 (dd, *J* = 6.4, 13.9Hz, 1H), 3.36 (s, 3H), 3.63 (d, *J* = 14.0Hz, 1H), 3.78 (d, *J* = 14.0Hz, 1H), 3.83-3.93 (m, 3H), 4.02 (t, *J* = 6.5Hz, 1H), 7.26-7.37 (m, 10H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 139.54, 138.76, 128.67, 128.38, 128.12, 128.01, 127.17, 126.97, 72.21, 62.86, 60.13, 58.71, 56.11, 49.17, 23.46. IR(film): 3028, 2980, 2920, 2878, 1600, 1497, 1453, 1375, 1200, 1120 cm^{-1}. MS *m*/*z*: EI, 361(M$^+$). HRMS: *m/z* calcd for $C_{19}H_{24}BrNO$ 361.1041, Found 361.1025.

(2*R*, 1'*R*)-*N*-Benzyl-*N*-(2'-methoxy-1'-phenylethyl)-2-bromobutylamine (5b).

$[\alpha]_D$ -47.2 (*c* 1.14, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.3Hz, 3H), 1.38-1.52 (m, 1H), 1.82-1.94 (m, 1H), 2.80 (dd, *J* = 7.5, 14.0Hz, 1H), 3.10 (dd, *J* = 6.6, 14.0Hz, 1H), 3.35 (s, 3H), 3.62 (d, *J* = 14.0Hz, 1H), 3.73-3.94 (m, 4H), 4.02 (t, *J* = 6.3Hz, 1H), 7.24-7.37(m, 10H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 139.30, 138.41, 128.57, 128.29, 128.00, 127.90, 127.09, 126.87, 71.97, 62.89, 58.56, 58.35, 57.93, 55.95, 28.64, 11.47. IR(film): 3027, 2970, 2925, 2878, 1600, 1497, 1452, 1378, 1198, 1120 cm^{-1}. MS *m*/*z*: EI, 375(M$^+$). HRMS: *m/z* calcd for $C_{20}H_{26}BrNO$ 375.1197, Found 375.1191.

(2*R*, 1'*R*)-*N*-Benzyl-*N*-(2'-methoxy-1'-phenylethyl)-2-bromopentylamine (5c).

$[\alpha]_D$ -34.0 (*c* 1.12, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.78 (t, *J* = 7.3Hz, 3H), 1.20-1.51 (m, 2H), 1.68-1.81 (m, 2H), 2.79 (dd, *J* = 7.1, 14.1Hz, 1H), 3.10 (dd, *J* = 6.8, 14.1Hz, 1H), 3.35 (s, 3H), 3.62 (d, *J* = 14.0Hz, 1H), 3.73-3.94 (m, 4H), 4.02 (dd, *J* = 5.9, 7.1Hz, 1H), 7.26-7.35 (m, 10H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 139.50, 138.62, 128.59, 128.29, 128.00, 127.89, 127.05, 126.85, 72.08, 62.98, 58.94, 58.58, 56.06, 55.94, 37.65, 20.07, 13.09. IR(film): 3026, 2960, 2930, 2873, 1600, 1497, 1453, 1372, 1195, 1118 cm^{-1}. MS *m*/*z*: EI, 389(M$^+$). HRMS: *m/z* calcd for $C_{21}H_{28}BrNO$ 389.1354, Found 389.1349.

(2*R*, 1'*R*)-*N*-Benzyl-*N*-(2'-methoxy-1'-phenylethyl)-2-bromo-3-methylbutylamine (5d).

$[\alpha]_D$ -53.9 (*c* 1.01, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.54 (d, *J* = 6.7Hz, 3H), 0.86 (d, *J* = 6.7Hz, 3H), 1.84-1.90 (m, 1H), 2.84 (dd, *J* = 7.6, 14.1Hz, 1H), 3.08 (dd, *J* = 6.6, 14.1Hz, 1H), 3.36 (s, 3H), 3.64 (d, *J* = 13.8Hz, 1H), 3.76 (d, *J* = 13.8Hz, 1H), 3.82-4.00 (m, 3H), 4.02 (dd, *J* = 5.7, 7.3Hz, 1H), 7.24-7.37 (m, 10H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 139.83, 139.11, 128.85, 128.53, 128.24, 128.13, 127.24, 127.06, 71.97, 64.78, 62.78, 58.87, 56.69, 56.12, 30.29, 21.53, 16.45. IR (film): 3028, 2962, 2927, 2875, 1600, 1497, 1457, 1363, 1195, 1120 cm^{-1}. MS *m*/*z*: EI, 389(M$^+$). HRMS: *m/z* calcd for $C_{21}H_{28}BrNO$ 389.1354, Found 389.1335.

(2*R*, 1'*R*)-*N*-(4-Bromobenzyl)-*N*-(2'-methoxy-1'-phenylethyl)-2-bromo-3-methylbutylamine (5d').

Compound (**5d'**) was obtained from **1d** using the 4-bromobenzyl bromide instead of benzyl bromide by the same procedure used for **5d**. Yield: 70%, colorless crystal, mp 47°C (hexane). [α]$_D$ -55.6 (*c* 1.00, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.59 (d, *J* = 6.6Hz, 3H), 0.89 (d, *J* = 6.6Hz, 3H), 1.94 (quintet, *J* = 6.6Hz, 1H), 2.81 (dd, *J* = 7.1, 14.1Hz, 1H), 3.07 (dd, *J* = 7.0, 14.1Hz, 1H), 3.35 (s, 3H), 3.59 (d, *J* = 14.2Hz, 1H), 3.72 (d, *J* = 14.2Hz, 1H), 3.77-4.01 (m, 4H), 7.23-7.46 (m, 9H). MS *m*/*z*: EI, 469(M^+). HRMS(CI): *m/z* calcd for $C_{21}H_{28}Br_2NO$ 470.0518, Found 470.0529.

General procedure for the reaction of β-bromoamines (5a-d) with 2% H_2SO_4.

The stirred solution of **5a-d** (1.0 mmol) in 2% aqueous H_2SO_4 (20 mL) was heated for 4 h at 90°C. After cooling the reaction mixture was made basic with saturated aqueous Na_2CO_3, and extracted with CH_2Cl_2 (20 mL x 3). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated to give the crude product, which was purified by silica gel flash chromatography with hexane/EtOAc (5 : 1) to afford pure product (**6a-d**) as a viscous oil.

(2*R*, 1'*R*)-1-[*N*-Benzyl-*N*-(2'-methoxy-1'-phenylethyl)amino]propan-2-ol (6a).

[α]$_D$ -114.0 (*c* 0.90, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.10 (d, *J* = 6.3Hz, 3H), 2.31 (dd, *J* = 2.5, 13.2Hz, 1H), 2.67 (dd, *J* = 10.4, 13.2Hz, 1H), 3.34 (s, 3H), 3.42 (d, *J* = 14.1Hz, 1H), 3.48 (dd, *J* = 4.9, 9.9Hz, 1H), 3.75-3.83 (m, 1H), 3.80 (d, *J* = 14.1Hz, 1H), 3.90 (t, *J* = 9.9Hz, 1H), 4.03 (dd, *J* = 4.9, 9.9Hz, 1H), 4.20 (brs, 1H), 7.16-7.37 (m, 10H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 139.36, 136.72, 128.71, 128.56, 128.42, 128.33, 127.67, 127.10, 72.39, 63.63, 61.15, 58.59, 57.15, 55.64, 19.70. IR(film): 3448, 3027, 2962, 2928, 2880, 1600, 1497, 1452, 1372, 1198, 1119, 1092 cm^{-1}. MS *m*/*z*: CI, 300(M^++1). *Anal.* Cacld for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.03; H, 8.52; N, 4.76.

(2*R*, 1'*R*)-1-[*N*-Benzyl-*N*-(2'-methoxy-1'-phenylethyl)amino]butan-2-ol (6b).

[α]$_D$ -111.0 (*c* 1.00, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.4Hz, 3H), 1.30-1.52 (m, 2H), 2.34 (dd, *J* = 2.4, 13.1Hz, 1H), 2.69 (dd, *J* = 10.3, 13.1Hz, 1H), 3.33 (s, 3H), 3.40 (d, *J* = 14.2Hz, 1H), 3.47 (dd, *J* = 4.9, 10.0Hz, 1H), 3.52-3.63 (m, 1H), 3.90 (t, *J* = 10.0Hz, 1H), 4.03 (dd, *J* = 4.9, 10.0Hz, 1H), 4.22 (brs, 1H), 7.23-7.40 (m. 10H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 139.33, 136.63, 128.74, 128.58, 128.40, 128.33, 127.67, 127.08, 72.33, 68.92, 60.98, 58.58, 55.46, 55.23, 27.41, 10.11. IR(film): 3440, 3028, 2960, 2928, 2880, 1600, 1497, 1452, 1372, 1198, 1120, 1093 cm^{-1}. MS *m*/*z*: CI, 314(M^++1). *Anal.* Cacld for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.52; H, 8.81; N, 4.44.

Minor component: (2*S*, 1'*R*)-2-[*N*-Benzyl-*N*-(2'-methoxy-1'-phenylethyl)amino]butan-1-ol (7b).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.4Hz, 3H), 1.25-1.37 (m, 1H), 1.57-1.66 (m, 1H), 2.80-2.93 (m, 1H), 3.13 (t, *J* = 10.3Hz, 1H), 3.36 (s, 3H), 3.64-3.90 (m, 5H), 4.22 (dd, *J* = 5.7, 8.0Hz, 1H), 7.10-7.46 (m, 10H).

(2*R*, 1'*R*)-1-[*N*-Benzyl-*N*-(2'-methoxy-1'-phenylethyl)amino]pentan-2-ol (6c).

$[\alpha]_D$ -101.5 (*c* 1.02, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.3Hz, 3H), 1.21-1.53 (m, 4H), 2.32 (dd, *J* = 2.4, 13.1Hz, 1H), 2.68 (dd, *J* = 10.4, 13.1Hz, 1H), 3.33 (s, 3H), 3.41 (d, *J* = 14.1Hz, 1H), 3.47 (dd, *J* = 4.9, 9.9Hz, 1H), 3.63 (m, 1H), 3.80 (d, *J* = 14.1Hz, 1H), 3.90 (t, *J* = 9.9Hz, 1H), 4.03 (dd, *J* = 4.9, 9.9Hz, 1H), 4.21 (brs, 1H), 7.23-7.39 (m, 10H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 139.33, 136.66, 128.76, 128.61, 128.43, 128.35, 127.69, 127.11, 72.37, 67.29, 61.06, 58.61, 55.68, 55.53, 36.78, 19.00, 14.22. IR(film): 3452, 3028, 2960, 2928, 2874, 1600, 1497, 1452, 1373, 1198, 1120, 1095 cm^{-1}. MS *m*/*z*: CI, 328 (M^++1). *Anal.* Cacld for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.95; H, 9.04; N, 4.30.

Minor component: (2*S*, 1'*R*)-2-[*N*-Benzyl-*N*-(2'-methoxy-1'-phenylethyl)amino]pentan-1-ol (7c).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.3Hz, 3H), 1.24-1.34 (m, 4H), 2.84-3.02 (m, 1H), 3.13 (t, *J* = 10.1Hz, 1H), 3.36 (s, 3H), 3.69 (dd, *J* = 5.8, 9.7Hz, 1H), 3.73 (d, *J* = 14.0Hz, 1H), 3.84 (d, *J* = 14.0Hz, 1H), 3.81-3.89 (m, 2H), 4.11 (dd, *J* = 5.8, 8.1Hz, 1H), 7.21-7.46 (m, 10H).

(2*R*, 1'*R*)-1-[*N*-Benzyl-*N*-(2'-methoxy-1'-phenylethyl)amino]-3-methylbutan-2-ol (6d).

$[\alpha]_D$ -124.8 (*c* 0.90, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.8Hz, 3H), 0.97 (d, *J* = 6.8Hz, 3H), 1.57-1.67 (m, 1H), 2.37 (dd, *J* = 2.5, 13.0Hz, 1H), 2.61 (dd, *J* = 10.4, 13.0Hz, 1H), 3.33 (s, 3H), 3.33-3.43 (m, 1H), 3.38 (d, *J* = 14.1Hz, 1H), 3.47 (dd, *J* = 5.0, 10.0Hz, 1H,), 3.82 (d, *J* = 14.1Hz, 1H), 3.90 (t, *J* = 10.0Hz, 1H), 4.03 (dd, *J* = 5.0, 10.0Hz, 1H), 4.27 (brs, 1H), 7.26-7.41 (m, 10H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 139.20, 136.50, 128.76, 128.58, 128.36, 128.30, 127.65, 127.05, 72.26, 72.03, 60.89, 58.54, 55.24, 52.82, 32.01, 18.47, 18.36. IR (film): 3448, 3028, 2960, 2927, 2878, 1600, 1497, 1452, 1371, 1198, 1120, 1095 cm^{-1}. MS *m*/*z*: CI, 328 (M^++1). *Anal.* Calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.82; H, 9.03; N, 4.31.

Minor component: (2*S*, 1'*R*)-2-[*N*-Benzyl-*N*-(2'-methoxy-1'-phenylethyl)amino]-3-methylbutan-1-ol (7d).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.8Hz, 3H), 0.86 (d, *J* = 6.8Hz, 3H), 1.74-1.87 (m, 1H), 2.68-2.73 (m, 1H), 3.21 (t, *J* = 9.9Hz, 1H), 3.31 (s, 3H), 3.45 (m, 1H), 3.54 (dd, *J* = 5.4, 8.7Hz, 1H), 3.77 (t, *J* = 8.7Hz, 1H) 3.84 (d, *J* = 14.7Hz, 1H), 3.96 (d, *J* = 14.7Hz, 1H), 4.14 (dd, *J* = 5.4, 8.7Hz, 1H), 7.22-7.42 (m, 10H).

The another synthetic route of (+)-8a and (-)-9a.

A mixture of 2-methoxyacetophenone (1.0 g, 6.65 mmol) and (*R*)-1-amino-2-propanol (0.5 g, 6.65 mmol) in toluene (50 mL) was refluxed for 1.5 h using a Dean-Stark trap. After cooling, the reaction mixture was concentrated to give the residue, which was dissolved in THF (10 mL). The above THF solution was added dropwise to a suspension of lithium aluminum hydride (0.26 g, 6.85 mmol) in dry THF (40 mL) at rt over a 10 min period. After stirred for 1 h, the excess hydride was decomposed by the slow addition of water and mixture was filtered through a Celite. Evaporation of the filtrate gave a colorless oil, which was purified by silica gel flash chromatography with hexane/EtOAc (1 : 3) to afford pure product [**(+)-8a** and **(-)-9a]**.

(2*R*,1'*S*)-(2'-Methoxy-1'-phenylethyl)amino-2-propanol[(+)-8a].

Yield: 33 %, colorless oil. $[\alpha]_D$ +55.5 (*c* 1.08, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 1.80$ (d, *J* = 6.3Hz, 3H), 2.41 (brs, 2H), 2.42 (dd, *J* = 8.5, 12.2Hz, 1H,), 2.54 (dd, *J* = 3.5, 12.2Hz, 1H), 3.37 (s, 3H), 3.43-3.48 (m, 2H), 3.55-3.67 (m, 1H), 3.86 (dd, *J* = 5.4, 7.4Hz, 1H), 7.23-7.37 (m, 5H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 140.89, 128.43, 127.52, 127.42, 77.46, 66.49, 63.29, 58.79, 55.26, 20.77. IR (film): 3317, 3060, 2970, 2923, 2882, 1600, 1448, 1380, 1232, 1198, 1109 cm^{-1}. MS *m*/*z*: CI, 210 (M^++1). *Anal.* Cacld for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.92; H, 9.20; N, 6.59.

(2*R*,1'*R*)-(2'-Methoxy-1'-phenylethyl)amino-2-propanol[(-)-9a].

Yield: 38 %, colorless crystal, mp 68°C (hexane-Et_2O). $[\alpha]_D$ -122.9 (*c* 1.12, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 1.07$ (d, *J* = 6.3Hz, 3H), 2.22 (dd, *J* = 9.8, 11.8Hz, 1H), 2.45 (brs, 2H), 2.62 (dd, *J* = 2.7, 11.8Hz, 1H), 3.38 (s, 3H), 3.43-3.49 (m, 2H), 3.73-3.84 (m, 1H), 3.92 (dd, *J* = 4.0, 9.1Hz, 1H), 7.26-7.34 (m, 5H). ^{13}C NMR (67.8 MHz, $CDCl_3$): δ = 140.23, 128.44, 127.51, 127.45, 77.64, 66.06, 62.11, 58.77, 54.35, 20.08. IR(KBr): 3430, 3062, 2970, 2930, 2892, 1600, 1453, 1379, 1218, 1197, 1108 cm^{-1}. MS *m*/*z*: CI, 210 (M^++1). *Anal.* Cacld for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.92; H, 9.28; N, 6.62.

Reduction of ring-opening product (4a) by LAH.

To a stirred suspension of $LiAlH_4$ (76.0 mg, 2.0 mmol) in THF (5 mL) was added ring-opening product (**4a**) (0.5 g, 2.0 mmol) in THF (5 mL) at rt. The reaction mixture was stirred for 6 h after which the excess of hydride was decomposed by the slow addition of water and the mixture was filtered through a little Celite. Evaporation of the filtrate gave a colorless oil, which was purified by silica gel flash chromatography with hexane/EtOAc (1 : 1) to afford pure product [**(-)-8a**].

Yield: 70 %, colorless oil. $[\alpha]_D$ -56.0 (*c* 1.14, $CHCl_3$). The spectral data are identical with above-mentioned authentic sample [**(+)-8a**].

Hydrogenation of ring-opening product (6a) by $Pd(OH)_2/H_2$.

A solution of ring-opening product (**6a**) (0.45 g, 1.5 mmol) in methanol (20 mL) and 20% palladium hydroxide on carbon (10 mg) under H_2 for 6 h at rt. The reaction mixture was then filtered through a little Celite and the filtrate was evaporated under reduced pressure to give a residue, which was purified by silica gel flash chromatography with hexane/EtOAc (1 : 1) to afford pure product [**(-)-9a**].

Yield: 65 %, colorless oil. $[\alpha]_D$ -123.2 (*c* 1.00, $CHCl_3$). The spectral data are identical with above-mentioned authentic sample [**(-)-9a**].

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9. X-Ray Crystal structure determinations: A colorless prismatic crystal of $C_{21}H_{27}NOBr_2$ having an

approximate dimension of 0.4 x 0.4 x 0.4 mm grown from hexane was used for the data collection of a Rigaku AFC7R diffractometer with graphic monochromated Cu-Kα radiation (r = 1.54178 Å) and rotating anode generator. Crystal data of **5d'**: M = 469.26; orthorhombic, space group $P2_12_12_1$ (#19), Z = 4 with a = 10.979(2) Å, b = 19.261(4) Å, c = 10.289(1) Å, V = 2175.8(6) Å^3, and D_{cale} = 1.432g/cm^3. All calculations were performed using the teXsan program. The structure was solved by direct methods and expanded using Fourier techniques. The final R- and R_W-factors after full-matrix least-squares refinement were 0.043 and 0.040, respectively, based on 1475 observed reflections (I>3.00σ(I)).

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