Remarkable Enantioselective α-Amination in 1-Phenyl-2-(*N*-alkylamino)-1-propanol

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ABSTRACT (1*R*,2*R*)-1-Phenyl-1-alkyl/arylamino-2-(*N*-alkylamino)propane hydrochloride salts have been synthesized with high degree of enantiomeric purity from (1*S*,2*R*)-(+)-1-phenyl-2-(*N*-alkylamino)-1-propanol through the corresponding chloro derivatives. This reaction sequence involves three inversions with overall inversion of configuration at C-1. *Chirality 24:262–270, 2012.*

KEY WORDS: asymmetric 1,2-chloroamines; asymmetric 1,2-diamines; aziridinium chloride; SN_2 mechanism; 1-amino-2-*N*-tosylpropanes

INTRODUCTION

α-Amination reactions constitute an important class of regiospecific and stereospecific substitution reactions as a result of their impact in commercial applications. The products of α-amination such as diamines, triamines and their derivatives have important applications such as chelating agents in radiopharmaceuticals,[1,2] precursors of aza-macrocycles[3] and heterocycles in medicinal chemistry.[4] They also play a vital role as chiral auxiliaries in a variety of asymmetric transformations involving chiral phosphonamides,[5] Lewis acids,[6] metal enolates,[7] dienophiles,[8] and transition metal reagents.[9,10]

The methods available for preparing vicinal diamines are rather limited, particularly when other sensitive functionalities are present elsewhere in the molecule. Olefins react with azide anions oxidatively to form vicinal diazides[11,12] which on reduction afford diamines. But this method requires careful selection of reductants to avoid possible explosion. Iodoisocyanation of olefins followed by hydrolysis results in the formation of aziridine which can be opened up with ammonia to give vicinal diamines[13] stereospecifically. Cycloaddition of chlorosulphonylisocyanate to olefins followed by Curtius rearrangement and hydrolysis of the resulting cyclic urea gives vicinal diamines.[14] Reductive amination of α-aminoketones, Michael addition of urethanes of dehydroalanine derivatives, reduction of α-aminonitriles and α-aminoamides[15] lead to vicinal diamines. Diamines are also prepared from dienes through a Diels Alder adduct of sulphone bisimides[15] and also from 1,3-diamino-2-propanols.[1]

A highly stereoselective and regioselective synthetic route to a series of chiral diamines and triamines for use as ligands in organocopper conjugate addition reactions has been developed with ephedrine and pseudoephedrine as starting aminoalcohols by Dieter et al.[16] Synthesis of stereospecific-substituted 1-pyrrolidinyl-2-benzylaminoethane has been achieved starting from 1,2-diphenylethene.[17]

Chiral salicyl-1,2-diamines[18] show great promise as anticancer molecules. These compounds have been shown to induce inhibition of the growth of cancer cells. These vicinal diamines display pharmaceutical potency in the treatment of human breast cancer. Enantiomerically enriched 1,2-diamines are powerful drug intermediates in the asymmetric synthesis[19] of Tamiflu which is a very important anti-influenza drug containing a chiral 1,2-diamino functionality.

Chiral 1-phenyl-1-methylamino-2-(1-pyrrolidinyl)propane is synthesized[20] from the corresponding 1-phenyl-2-amino-1-propanol through the intermediacy of mesyloxy derivative. Considering the enormous utility of the chiral 1,2-diamines, the syntheses of several stereospecific and regiospecific 1,2-diamines are undertaken in this work from (1*S*,2*R*)-norephedrine through the corresponding chloro derivatives.

EXPERIMENTAL

General Remarks

All reactions were carried out under nitrogen atmosphere unless otherwise noted. Solvents are dried according to established procedures. Reactions were monitored by thin layer chromatography (TLC). Optical rotations were recorded on a Jasco DIP-370 digital polarimeter. Melting points were measured on Scientific Melting Point Apparatus and were uncorrected. The chromatographic purity and enantiomeric excess (ee) values were determined by using high performance liquid chromatography (HPLC), Shimadzu LC-10AT_{VP} and SPD-M10A_{VP}. Infrared (IR) spectra were recorded on a FTIR spectrometer Shimadzu IR Prestige 21. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on Brucker Avance 300 MHz spectrometer, and ^{13}C NMR spectra were recorded on Brucker Avance 75 MHz using trimethylsilane as internal standard and hexadeuterated dimethyl suphoxide (DMSO-d_6) or deuterochloroform ($CDCl_3$) unless otherwise noted. Data are presented as follows: chemical shift, integration, multiplicity (br s = broad singlet, s = singlet, d = doublet, t= triplet, q = quartet, and m = multiplet). Mass spectra (MS) was measured using Agilent Liquid Chromatograpy - Mass Spectra (LCMS) using chemical ionisation (CI) or Electro Spray Ionisation (ESI) as specified.

Typical procedure for the synthesis of 1-phenyl-2-(1-piperidinyl/pyrrolidinyl)-1-propanol hydrochloride. To a solution of 0.66 mol of 1-phenyl-2-amino-1-propanol hydrochloride in 150 ml of water, 50% sodium hydroxide was added to attain a pH of 12–13. The liberated nore-

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phedrine base was extracted in dichloromethane. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to yield an oily residue that was dissolved in 400 ml of toluene. To this solution, 0.8 mol of 1,5-dibromopentane/1,4-dibromobutane and 1.0 mol of sodium carbonate were added, and the resulting suspension was heated to reflux for 12 h. The progress of the reaction was monitored by TLC. After cooling to room temperature, the solids were removed by filtration. The toluene filtrate was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure to yield an oil. The oily product was dissolved in 300 ml of acetone and acidified to pH 2–3 by bubbling HCl gas. The precipitated product was removed by filtration and was washed with acetone to obtain white crystalline 1-phenyl-2-(1-piperidinyl/1-pyrrolidinyl)-1-propanol hydrochloride.

Typical procedure for N-tosylation of (1S,2R)-(+)-1-phenyl-2-amino-1-propanol. About 0.662 mol of (1*S*,2*R*)-(+)-1-phenyl-2-amino-1-propanol was taken in a round bottom flask and 500 ml of tetrahydrofuran was added and the mixture was stirred under nitrogen atmosphere. Triethylamine (0.79 mol) was added and cooled to 10°C. Tosylchloride (0.795 mol) dissolved in 150 ml of tetrahydrofuran was added slowly over 30–40 min by maintaining the temperature at 10–15°C. The reaction mixture was stirred overnight at 15–20°C. The reaction was monitored for the completion by TLC. Then 150 ml of water and 300 ml of chloroform were added and the product was extracted into chloroform layer. Chloroform layer was separated. Chloroform layer was dried over anhydrous sodium sulfate, filtered, and concentrated to yield an oily residue.

The oily residue was dissolved in 50 ml of chloroform and 240 ml of *n*-hexane. White crystals formed were filtered, and the crystals were washed with 60 ml of *n*-hexane.

Typical procedure for chlorination of 1-phenyl-2-(N-alkyl/tosylamino)-1-propanol hydrochloride. To a suspension of 0.45 mol of 1-phenyl-2-(*N*-alkyl)-1-propanol hydrochloride or 1-phenyl-2-(*N*-tosyl)-1-propanol, 600 ml of chloroform and 3 ml of dimethylformamide heated to 45°C and 0.68 mol of thionyl chloride were added slowly over a period of 2 h by maintaining the temperature at 45 to 50°C. The reaction was monitored by TLC. Chloroform was evaporated under reduced pressure yielding a white solid that was triturated with acetone or hexane, filtered, and washed with acetone/hexane to obtain white crystalline chloro derivative.

Typical procedure for the synthesis of 1-phenyl-1-alkyl/arylamino-2-(N-alkyl/tosylamino)propane hydrochloride. 1-Phenyl-1-chloro-2-(*N*-alkylamino)propane hydrochloride or 1-phenyl-1-chloro-2-(tosyl amino)propane (0.02 mol) was dissolved in 50 ml of dichloromethane/acetonitrile and cooled to 5°C. Alkyl/arylamine, 0.08 mol in 10 ml of dichloromethane, was added slowly to the mixture over a period of 2 h. The resulting solution was stirred overnight at room temperature. The progress of the reaction was followed by TLC. The reaction mixture was washed with water followed by brine. The organic layer was separated, and the solvent was removed under reduced pressure. The oily residue was dissolved in 2-propanol and acidified with HCl in 2-propanol to obtain 1-phenyl-1-alkyl/arylamino-2-(*N*-alkyl/tosylamino)propane hydrochloride. The product was filtered and recrystallized from 2-propanol. The crude samples in the case of all the diamines prepared contained only achiral impurities.

Typical procedure for Walden inversion. To (1*S*,2*R*)-1-phenyl-2-amino-1-propanol hydrochloride (5 g, 0.0232 mol), 12.0 ml of acetic anhydride was added and heated to 120–130°C for 1 h. The reaction mass was concentrated under reduced pressure to yield an oil. To the oily residue, 20 ml of 10% hydrochloric acid was added and heated to reflux for 3 h. The reaction mass was concentrated under reduced pressure to give an oily residue that was triturated with acetone to obtain a white precipitate. The precipitated product was filtered and washed with acetone to obtain (1*R*,2*R*)-1-phenyl-2-amino-1-propanol hydrochlorides.

Reaction of (1R,2R)-1-chloro-1-phenyl-2-(1-piperidinyl)-1-propanol hydrochloride with H_2O. (1*R*,2*R*)-1-Chloro-1-phenyl-2-(1-piperidinyl)-1-propanol hydrochloride, 0.021 mol, was dissolved in 15 ml of H_2O. The solution was stirred at room temperature for 12 h. The progress of the reaction was monitored by TLC. The reaction mass was evaporated under reduced pressure to remove excess of water, when a white solid was obtained. The solid was triturated with acetone, filtered, and dried.

Characterization of the Products

(1R,2R)-(+)-1-Phenyl-1-methylamino-2-(1-piperidinyl)propane hydrochloride 1. Compound 1 (3.13 g, 64%); $[\alpha]_D^{25}$ = +8.7 (*c*= 1.0, CH_3OH); mp (2-propanol) 250–254°C. The ee was determined by CSP HPLC to be 100% (Chiral AGP, 95% 0.01 M ammonium acetate pH 4.5 using acetic acid, 5% 2-propanol, 0.5 ml/min); t_R (1*R*,2*R*) = 3.6 min (100%); IR (KBr, cm^{-1}): 3428, 3005, 2943, 2662, 1576, 1464, 1379, 1171, 704; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 1.21 (d, *J* = 6.4 H_z, 3H, CH−C*H*$_3$), 1.32–2.24 (6H, m, N−CH$_2$−C*H*$_2$−C*H*$_2$−C*H*$_2$),* 2.45 (s, 3H,CH−NH−C*H*$_3$), 2.80–3.82, (m, 4H,C*H*$_2$−N−C*H*$_2$), 4.59 (m,1H,C*H*−CH$_3$), 5.28 (d, *J* = 6.5 H_z, 1H, C*H*−C$_6$H$_5$), 7.47–7.92 (m, 5H, H aromatic), 10.56 (br s, CH−N$^+$H$_2$−CH$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 11.5, 21.5, 22.6, 31.0, 48.1, 53.4, 62.1, 63.8, 78.5, 129.4, 129.6, 129.9, 130.8; MS (CI, CH_3OH) *m/z* (rel. intens.) 233 (M+H$^+$, 100), 202 (31), 112 (16); Anal. Calcd for $C_{15}H_{24}N_2$·HCl†: C, 67.16; H, 9.33; N, 10.45. Found: C, 66.93; H, 9.40; N, 10.43.

(1R,2R)-(+)-1-Phenyl-1-ethylamino-2-(1-piperidinyl)propane hydrochloride 2. Compound 2 (2.83 g, 55%); $[\alpha]_D^{25}$ = +2.2 (*c* = 1.0, CH_3OH); mp (2-propanol) 220–226°C. The ee was determined by CSP HPLC to be 100% (Chiral AGP, 95% 0.01 M ammonium acetate pH 4.5 using acetic acid, 5% 2-propanol, 0.5 ml/min); t_R (1*R*,2*R*) = 3.8 min (100 %); IR (KBr, cm^{-1}): 3474, 3406, 3022, 2945, 2667, 1649, 1575, 1458, 1369, 1096, 710; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.08 (d, *J* = 6.6 H_z, 3H, CH−C*H*$_3$), 1.43 (t, *J* = 6.5 H_z, 3H, CH$_2$−C*H*$_3$), 1.95–2.70 (m, 6H, N−CH$_2$−C*H*$_2$−C*H*$_2$−C*H*$_2$), 2.73, (q, *J* = 6.4 H_z, 2H, −C*H*$_2$−CH$_3$), 2.75–3.15 (m, 4H,C*H*$_2$−N−C*H*$_2$), 4.79 (m, 1H, C*H*−CH$_3$), 5.00 (d, *J* = 6.4 H_z, 1H, C*H*−C$_6$H$_5$), 7.30–7.50 (m, 5H, H aromatic), 10.96 (br s, 2H, CH−N$^+$H$_2$−CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 11.2, 12.0, 21.8, 22.8, 42.0, 48.5, 54.4, 61.5, 64.2, 77.7, 129.7, 130.2, 130.9; MS (CI, CH_3OH) *m/z* (rel. intens.) 247 (M+H$^+$, 100), 202 (27), 112 (12); Anal. Calcd for $C_{16}H_{26}N_2$·HCl: C, 68.09; H, 9.57; N, 9.93. Found: C, 67.97; H, 9.63; N, 9.93.

(1R,2R)-(+)-1-Phenyl-1-(N,N-diethylamino)-2-(1-piperidinyl)propane dihydrochloride 3. Compound 3 (3.85 g, 68%); $[\alpha]_D^{25}$ = +12.0 (*c* = 1.0, CH_3OH); mp (2-propanol) 188–191°C. The ee was determined by CSP HPLC to be 100% (Chiral AGP, 95% 0.01 M ammonium acetate pH 4.5 using acetic acid, 5% 2-propanol, 0.5 ml/min); t_R (1*R*,2*R*) = 2.4 min (100%); IR (KBr, cm^{-1}): 3545, 3462, 2953, 2872, 2660, 1636, 1541, 1458, 1391, 1305, 1130, 1070, 714; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.27 (t, *J* = 6.5 H_z, 3H, N−CH$_2$−C*H*$_3$), 1.60 (t, *J* = 6.5 H_z, 3H, N−CH$_2$−C*H*$_3$), 1.83 (d, *J* = 6.4 H_z, 3H, CH−C*H*$_3$), 1.90–2.21 (m, 6H, N−CH$_2$−C*H*$_2$−C*H*$_2$−C*H*$_2$), 2.35 (m, 2H,CH$_2$−N−C*H*$_2$), 2.78 (m, 2H, C*H*$_2$−N−CH$_2$), 3.13 (m, 2H, N−C*H*$_2$−CH$_3$), 3.60 (m, 2H, N−C*H*$_2$−CH$_3$), 4.07 (q, *J* = 6.6 H_z, 1H, C*H*−CH$_3$), 6.32 (d, *J* = 6.4 H_z, 1H, C$_6$H$_5$−C*H*), 7.52–8.13 (m, 5H, H aromatic), 11.94 (br s, 1H, CH$_3$−CH$_2$−N$^+$H), 12.08 (br s, 1H, CH$_2$−N$^+$H−CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 7.9, 8.7, 10.2, 21.9, 22.3, 23.2, 44.8, 48.7, 56.2, 61.4, 65.2, 77.2, 129.7, 129.9, 130.1, 131.1; MS (ESI) *m/z* (rel. intens.) 275 (M+H$^+$, 100); Anal. Calcd for $C_{18}H_{30}N_2$·2HCl: C, 62.25; H, 9.22; N, 8.07. Found: C, 62.39; H, 9.18; N, 8.03.

(1R,2R)-(–)-1-Phenyl-1-(propan-2-yl-amino)-2-(1-piperidinyl)propane dihydrochloride 4. Compound 4 (4.30 g, 80%); $[\alpha]_D^{25}$ = − 7.0 (*c* = 1.0, CH_3OH); mp (2-propanol) 232–236°C. The ee was determined by CSP HPLC to be 100% (Chiral AGP, 95% 0.01 M ammonium acetate pH

*The protons and carbons of the piperidinyl/pyrrolidinyl rings and the *N*,*N*-dialkyl groups at C-1 appear to be experiencing magnetic anisotropy being in the vicinity of chiral environment.

†The number of HCl molecules associated with each diamine is ascertained by nonaqueous titrimetry and confirmed by proton NMR spectroscopy.

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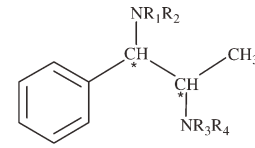
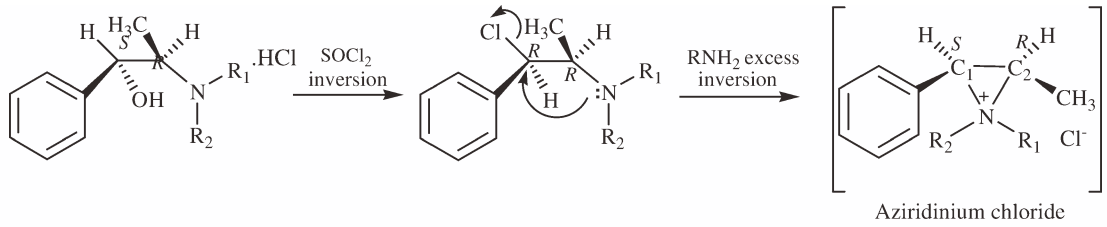
TABLE 1. Physical properties and HPLC retention times of 1-phenyl-1-alkyl/arylamino-2-(*N*-alkylamino)propane hydrochlorides (compounds 1–14)



							Chemical purity by HPLC using RP C18 column (%)			Enantiomeric excess (%) (using chiral column)		
							1*R*,2*R* isomer			1*R*,2*R* isomer		
Compound No.	R_1	R_2	R_3	R_4	Melting point (°C)	Yield (%)	$[\alpha]_D^{25}$	RT	Content	Content of 1*S*,2*R* isomer (diastereomer)	RT	ee	1*S*,2*S* isomer
1	H	Methyl	1-Piperidinyl		250–254	64	+8.7	3.82	99.9	11.28 (RT) Nil	8.08	100	Nil
2	H	Ethyl	1-Piperidinyl		220–226	55	+2.2	4.85	98.6	Nil	6.01	100	Nil
3	C_2H_5	Ethyl	1-Piperidinyl		188–191	68	+12.0	3.7	98.8	43.92 (RT) Nil	12.14	100	8.2 (RT) Nil
4	H	2-Propyl	1-Piperidinyl		232–236	80	−7.0	5.36	98.6	Nil	10.28	100	Nil
5	H	l-Butyl	1-Piperidinyl		244–248	90	−7.0	8.77	99.8	Nil	4.52	100	6.31 (RT) Nil
6	H	1,1-Dimethyl ethyl	1-Piperidinyl		184–186	67	+2.4	5.06	99.4	Nil	5.26	100	Nil
7	H	Phenyl	1-Piperidinyl		236–238	83	−101.5	40.52	98.3	10.30 (RT) Nil	10.0	100	5.25 (RT) Nil
8	H	(*S*)-1′-Phenylethyl	1-Piperidinyl		218–220	76	−40.7	12.25	98.0	Nil	13.15	100	10.43 (RT) Nil
9	H	(*R*)-1′-Phenylethyl	1-Piperidinyl		222–226	58	+4.7	9.79	99.7	Nil	5.17	100	Nil
10	H	Cyclohexyl	1-Pyrrolidinyl		144–147	75	−13.0	6.77	99.0	Nil	5.27	100	6.56 (RT) Nil
11	H	2-Propyl	1-Pyrrolidinyl		247–250	72	−11.0	11.4	97.0	Nil	6.68	100	7.21 (RT) Nil
12	H	1,1-Dimethyl ethyl	1-Pyrrolidinyl		190–192	55	−30.0	8.28	98.0	Nil	5.12	100	5.58 (RT) Nil
13	H	1-Butyl	CH_3	C_2H_5	215–218	62	−4.9	5.82	99.9	Nil	7.85	100	10.25 (RT) Nil
14	H	2-Fluoro phenyl	CH_3	C_2H_5	205–210	70	−141.1	6.97	99.29	Nil	3.85	100	6.3 (RT) Nil



Scheme 1. Formation of aziridinium chloride.

4.5 using acetic acid, 5% 2-propanol, 0.5 ml/min); t_R (1*R*,2*R*) = 14.6 min (100%); IR (KBr, cm^{-1}): 3522, 3462, 2978, 2870, 2671, 1566, 1456, 1443, 1400, 1304, 1128, 1084, 710; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.02 (d, J = 6.5 H_z, 3H, CH−CH_3), 1.31 (d, J = 6.5 H_z, 3H, CH_3−CH−CH_3), 1.56 (d, J = 6.4 H_z, 3H, CH_3−CH−CH_3), 1.95–2.63 (m, 6H, N−CH_2−CH_2−CH_2−CH_2), 2.84 (m, 1H,CH_3−CH−CH_3), 3.01 (m, 2H, CH_2−N−CH_2), 3.76 (m, 2H, CH_2−N−CH_2), 4.79 (m, 1H, CH−CH_3), 5.15 (d, J = 6.5 H_z, 1H, C_6H_5−CH), 7.47–8.30 (m, 5H, H aromatic), 10.56 (br s, 1H, CH_2−$\overset{+}{N}H$−CH_2), 11.14 (d, 2H, CH−$\overset{+}{N}H_2$−CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 12.4, 17.2, 20.3, 21.9, 22.3, 23.0, 48.2, 49.7, 54.7, 59.6, 64.3, 129.5, 129.8, 130.2, 130.8; MS (CI, CH_3OH) *m/z* (rel. intens.) 261 (M+H^+, 100), 202 (72), 112 (55), 56(25); Anal. Calcd for $C_{17}H_{28}N_2$·2HCl: C, 61.44; H, 9.04; N, 8.43. Found: C, 61.55; H, 9.22; N, 8.34.

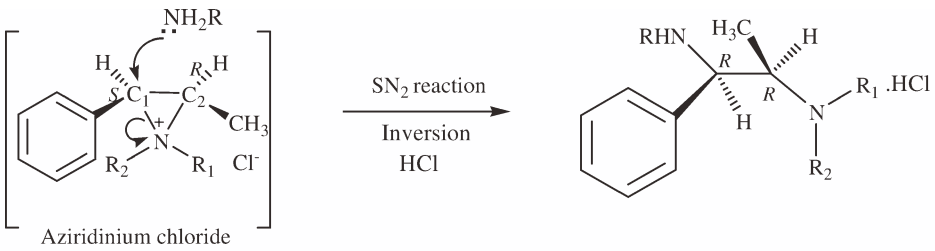
(1R,2R)-(–)-1-Phenyl-1-(1-butylamino)-2-(1-piperidinyl)propane dihydrochloride 5. Compound 5 (5.10 g, 90%); $[\alpha]_D^{25}$ = −7.0 (*c* = 1.0, CH_3OH); mp (2-propanol) 240–244°C. The ee was determined by CSP HPLC to be 100% (Chiral AGP, 95% 0.01 M ammonium acetate pH 4.5 using acetic acid, 5% 2-propanol, 0.5 ml/min); t_R (1*R*,2*R*) = 10.5 min (100%); IR (KBr, cm^{-1}): 3482, 3038, 2936, 2879, 2691, 1574, 1497, 1460, 1400, 1379, 1112, 1087, 700; ^1H NMR (300 MHz, DMSO-d_6) δ_H 0.78 (t, J = 6.6 H_z, 3H, CH_2−CH_3), 0.94 (d, J = 6.4 H_z, 3H, CH−CH_3), 1.23 (m, 2H, −CH_2−CH_3), 1.41–1.67 (2H, m, −CH_2−CH_2−CH_3), 1.69–2.16 (m, 6H, N−CH_2−CH_2−CH_2−CH_2), 2.19–2.38 (m, 2H, CH_2−N−CH_2), 2.70–3.00 (m, 2H, CH_2−N−CH_2), 3.50 (t, J = 6.7 H_z, 2H, C_6H_5−CH−NH−CH_2), 4.40 (m, 1H, CH−CH_3), 5.12 (d, J = 6.5 H_z, 1H, C_6H_5−CH), 7.49–7.74 (m, 5H, H aromatic), 10.44 (br s, 2H, CH−$\overset{+}{N}H_2$−CH_2), 10.62 (br s, 1H, CH_2−$\overset{+}{N}H$−CH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 11.4, 13.3, 19.2, 21.0, 21.8, 22.4, 27.0, 45.4, 46.9, 52.8, 60.3, 63.0, 129.1, 129.3, 129.6, 131.7; MS (CI, CH_3OH) *m/z* (rel. intens.): 275 (M+H^+, 100), 202 (43), 112 (37), 56(15); Anal. Calcd for $C_{18}H_{30}N_2$·2HCl: C, 62.43; H, 9.25; N, 8.09. Found: C, 62.52; H, 9.14; N, 7.91

(1R,2R)-(+)-1-Phenyl-1-(1,1-dimethylethylamino)-2-(1-piperidinyl) propane dihydrochloride 6. Compound 6 (3.80 g, 67.0%); $[\alpha]_D^{25}$ = + 2.5 (*c* = 1.0, H_2O); mp (2-propanol) 184–186°C. The ee was determined by CSP HPLC to be 100% (Chiral AGP, 95% 0.01 M ammonium acetate pH 4.5 using acetic acid, 5% 2-propanol, 0.5 ml/min); t_R (1*R*,2*R*) = 7.2 min (100%); IR (KBr, cm^{-1}): 3482, 3377, 3017, 2882, 2650, 1576, 1504, 1458, 1375, 1188, 714; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.37 (s, 9H, t-bu protons), 1.48 (d, J = 6.6 H_z, 3H, CH−CH_3), 1.71–2.61 (m, 6H, N−CH_2−CH_2−CH_2−CH_2), 2.96–3.26 (m, 4H, CH_2−N−CH_2), 4.94 (m, 1H, CH−CH_3), 5.62 (d, J = 6.5 H_z, 1H, C_6H_5−CH), 7.31–8.30 (m, 5H, H aromatic), 9.47 (br s, 1H, CH_2−$\overset{+}{N}H$−CH_2), 10.29–11.60 (br s, 2H, C_6H_5CH−$\overset{+}{N}H_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 10.7, 21.9, 22.4, 23.1, 27.4, 48.6, 55.0, 58.5, 62.0, 64.0, 129.5, 130.3, 130.7, 132.0; MS (CI, CH_3OH) m/z (rel. intens.) 275 (M+H^+, 100), 202 (91), 112 (82), 56 (32); Anal. Calcd for $C_{18}H_{30}N_2$·2HCl: C, 62.43; H, 9.25; N, 8.09. Found: C, 62.36; H, 9.18; N, 7.95.

(1R,2R)-(–)-1-Phenyl-1-phenylamino-2-(1-piperidinyl)propane hydrochloride 7. Compound 7 (5.0 g, 83%); $[\alpha]_D^{25}$ = −99.0 (*c* = 1.0, CH_3OH); mp (2-propanol) 236–239°C. The ee was determined by CSP HPLC to be 100% (Chiralcel OD-R, 62% of 0.1% perchloric acid, pH 5.0 using sodium hydroxide, 38% acetonitrile, 0.5 ml/min); t_R (1*R*,2*R*) = 22.8 min (100%); IR (KBr, cm^{-1}): 3406, 3252, 3017, 2947, 2675, 1601, 1560, 1456, 1258, 708; ^1H NMR (400 MHz, CF_3COOH) δ_H 1.36 (d, J = 6.7 H_z, 3H, CH−CH_3), 1.54–2.37 (m, 6H, N−CH_2−CH_2−CH_2−CH_2), 3.05–3.75 (m, 4H, CH_2−N−CH_2), 4.70 (m, 1H, CH−CH_3), 5.20 (d, J = 6.6 H_z, 1H, C_6H_5−CH), 7.25–7.47 (m, 10H, H aromatic), 9.06 (br s, 2H, C_6H_5−CH−$\overset{+}{N}H_2$); ^{13}C NMR (100 MHz, CF_3COOH) δ_C 12.7, 22.5, 24.0, 24.6, 50.0, 57.1, 66.2, 70.2, 111.6, 114.5, 117.3, 120.1, 124.6, 129.8, 131.7, 133.4; MS (CI, CH_3OH) *m/z* (rel. intens.) 295 (M+H^+, 100), 202 (33), 112 (36); Anal. Calcd for $C_{20}H_{26}N_2$·HCl: C, 72.62; H, 8.17; N, 8.47. Found: C, 72.60; H, 8.23; N, 8.36.

(1R,2R)-(–)-1-Phenyl-1-(1-(S)-phenylethylamino)-2-(1-piperidinyl) propane dihydrochloride 8. Compound 8 (5.0 g, 76%); $[\alpha]_D^{25}$ = −40.4 (*c* = 1.0, CH_3OH); mp (2-propanol) 218–220°C. The ee was determined by CSP HPLC to be 100% (Chiralcel OD-R, 80% of 0.1 M KH_2PO_4 using orthophosphoric acid, 20% acetonitrile, 0.5 ml/min); t_R (1*R,*2*R,* 1′*S*) = 37.5 min (100%); IR (KBr, cm^{-1}): 3445, 3026, 2880, 2662, 1570, 1499, 1458, 1240, 1200, 704; ^1H NMR (400 MHz, $CDCl_3$) δ_H 0.94 (d, 3H, C_6H_5−CH−CH_3), 1.82 (d, J = 6.5 H_z, 3H, CH−CH−CH_3), 1.89–2.61 (m, 6H, N−CH_2−CH_2−CH_2−CH_2), 2.98–3.87 (m, 4H, CH_2−N−CH_2), 3.95 (q, J = 6.4 H_z, 1H, C_6H_5−CH−CH_3), 4.05 (m, 1H, CH−CH−CH_3), 5.07 (d, J = 6.6 H_z, 1H, C_6H_5−CH−CH), 7.28–7.45 (m, 10H, H aromatic), 11.12 (br s, 2H, C_6H_5−CH−$\overset{+}{N}H_2$), 11.29 (br s, 1H, CH_2−$\overset{+}{N}H$−CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 12.6, 21.3, 21.7, 22.1, 22.7, 47.4, 54.3, 58.4, 60.4, 63.9, 127.3, 128.3, 129.0, 129.3, 130.1, 130.4, 132.3, 135.2; MS (CI, CH_3OH) *m/z* (rel. intens.) 323 (M+H^+, 100), 202 (18), 112 (27), 56(5); Anal. Calcd for $C_{22}H_{30}N_2$·2HCl: C, 67.00; H, 8.12; N, 7.11. Found: C, 67.33; H, 7.97; N, 7.32.

(1R,2R)-(+)-1-Phenyl-1-(1-(R)-phenylethylamino)-2-(1-piperidinyl)propane dihydrochloride 9. Compound 9 (3.80 g, 58%); $[\alpha]_D^{25}$ = + 4.7 (*c* = 1.0, CH_3OH); mp (2-propanol) 222–226°C. The ee was determined by CSP HPLC to be 100% (Chiralcel OD-R, 80% of 0.1 M KH_2PO_4



Scheme 2. Formation of the diamine.

(1*S*,2*R*)-Aminoalcohol —Inversion→ (1*R*,2*R*)-Aminochloride —Inversion→ (1*S*,2*R*)-Aziridinium chloride —Inversion→ (1*R*,2*R*)-Diamine

Scheme 3. Stereochemical pathway from aminoalcohol to diamine.

pH 2.0 using orthophosphoric acid, 20% acetonitrile, 0.5 ml/min); t_R (1*R*,2*R,* 1′*R*) = 49.8 min (100%); IR (KBr, cm^{-1}): 3534, 3445, 3026, 2881, 2666, 1580, 1497, 1456, 1306, 1208, 706; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.96 (d, *J* = 6.7 H_z, 3H, $C_6H_5-CH-CH_3$), 1.68 (d, *J* = 6.8 H_z, 3H, $CH-CH-CH_3$), 1.91–2.75 (m, 6H, $N-CH_2-CH_2-CH_2-CH_2$), 3.00–3.93 (m, 4H, CH_2-N-CH_2), 3.94 (q, *J* = 6.4 H_z, 1H, $CH-CH-CH_3$), 4.89 (q, *J* = 6.4 H_z, 1H, $C_6H_5-CH-CH_3$), 5.36 (d, *J* = 6.6 H_z, 1H, $C_6H_5-\overset{+}{C}H-CH$), 7.28–7.53 (m, 10H, H aromatic), 10.54 (br s, 1H, $CH_2-\overset{+}{N}H-CH_2$), 11.44 (br s, 2H, $C_6H_5-CH-\overset{+}{N}H_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 12.2 17.8, 22.0, 22.6, 23.0, 47.9, 54.5, 57.9, 61.2, 63.9, 128.3, 128.8, 129.0, 129.7, 130.0, 131.3, 133.7, 136.7; MS (CI, CH_3OH) *m/z* (rel. intens.) 323 ($M+H^+$, 100), 202 (46), 112 (30), 56(11); Anal. Calcd. for $C_{22}H_{30}N_2.2HCl$: C, 67.00; H, 8.12; N, 7.11. Found: C, 67.29; H, 8.13; N, 7.27.

(1R,2R)-(−)-(1-phenyl-1-cyclohexylamino-2-(1-pyrrolidinyl)propane dihydrochloride 10. Compound 10 (10.6 g, 75.0%); $[\alpha]_D^{25}$ = −13.0 (*c* = 5.0, H_2O); mp 144–147°C. The ee was determined by CSP HPLC to be 100% (chiralpak AD-H, 99% *n*-hexane,1% 2-propanol, 0.1% diethylamine, 2.0 ml/min,210 nm); t_R = 5.27 min (100%); IR (KBr, cm^{-1}): 3429, 2986, 2940, 2673, 2434, 1572, 1501, 1352, 775, 714; ^1H NMR (200 MHz, D_2O): δ_H 1.26–1.91 (m,17 H, $N-CH_2-CH_2-CH_2-CH_2$, $CH-(CH_2)_5$, $C_6H_5-CH-CH-CH_3$), 3.09–3.34 (m, 5H, CH_2-N-CH_2, $CH-(CH_2)_5$), 4.12 (m, 1H, $C_6H_5-CH-CH-CH_3$), 4.70 (d, *J* = 6.5 H_z, 1H, $C_6H_5-CH-CH-CH_3$), 7.56 (s, 5H, H aromatic); ^{13}C NMR (50 MHz, D_2O): δ_C 8.8, 21.0, 22.4, 26.4, 27.9, 48.6, 55.5, 57.2, 59.3, 126.0–129.4; MS (ESI) *m/z* (rel. intens.): 287 ($M+H^+$, 100); Anal. Calcd for $C_{19}H_{30}N_2{\cdot}2HCl$: C, 63.50; H, 8.98; N, 7.79. Found: C, 63.64; H, 8.65; N, 7.57.

(1R,2R)-(-)-1-phenyl-1-(propan-2yl amino)-2-(1-pyrrolidinyl)propane dihydrochloride 11. Compound 11 (9.2 g, 72.0%); $[\alpha]_D^{25}$ = −11.0 (*c* = 5.0, H_2O); mp 247–250°C. The ee was determined by CSP HPLC to be 100% (chiralpak AD-H, 99% *n*-hexane,1% 2-propanol, 0.1% diethylamine, 2.0 ml/min, 210nm); t_R = 6.67 min (100%); IR (KBr, cm^{-1}): 3456, 2980, 2941, 2668, 2479, 1566, 1458, 1396, 781, 718; ^1H NMR (200 MHz, D_2O): δ_H 1.14–1.21 (m, 6H, $CH_3-CH-CH_3$), 1.47 (d, *J* = 6.6 H_z, 3H $C_6H_5-CH-CH-CH_3$), 1.88 (m, 4H, $N-CH_2-CH_2-CH_2-CH_2$), 3.25 (m, 5H, $N-CH_2-CH_2-CH_2-CH_2$, $CH_3-CH-CH_3$), 3.96 (m, 1H, $C_6H_5-CH-CH-CH_3$), 4.71 (d, *J* = 6.5 H_z, 1H, $C_6H_5-CH-CH-CH_3$), 7.49 (s, 5H, H aromatic); ^{13}C NMR (50 MHz, D_2O): δ_C 11.5, 18.7, 19.8, 23.5, 51.5, 54.1, 60.3, 61.9, 128.4–132.1; MS (ESI) *m/z* (rel. intens.): 247 ($M+H^+$, 100); Anal. Calcd for $C_{16}H_{26}N_2{\cdot}2HCl$: C, 60.18; H, 8.84; N, 8.77. Found: C, 60.36; H, 9.03; N, 8.52.

(1R,2R)-(−)-1-phenyl-1-(1,1-dimethylethylamino)-2-(1-pyrrolidinyl)propane oxalate 12. Compound 12 (7.3 g, 55.0%); $[\alpha]_D^{25}$ = −30.0 (*c* = 1.0, 1 N HCl); mp 190–192°C. The ee was determined by CSP HPLC to be 100% (chiralpak AD-H, 99% *n*-hexane, 1% 2-propanol, 0.1% diethylamine, 2.0 ml/min, 210 nm); t_R = 5.13 min (100%); IR (KBr, cm^{-1}): 3429, 3042, 2914, 2681, 2486, 1721, 1601, 1589, 1489, 1460, 1402, 1383, 1312, 1196, 746, 708; ^1H NMR (200 MHz, $CDCl_3$): δ_H 0.76 (d, *J* = 6.6 H_z, 3H, $C_6H_5-CH-CH-CH_3$), 1.12 (s, 9H, $-C(CH_3)_3$, 1.84–1.92 (m, 4H, $N-CH_2-CH_2-CH_2-CH_2$), 2.76–2.95, (m, 4H, $N-CH_2-CH_2-CH_2-CH_2$), 3.51 (m, 1H, $C_6H_5-CH-CH-CH_3$), 3.70 (d, *J* = 6.5 H_z, 1H, $C_6H_5-CH-CH-CH_3$), 7.26–7.5 (m, 5H, H aromatic), 8.72 (br s, 3H, $CH_2-\overset{+}{N}H-CH_2$, $C_6H_5-CH-\overset{+}{N}H_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 9.7, 24.5, 29.1, 48.5, 56.3, 59.9, 63.3, 129.1–137.8, 164.0; MS (ESI) *m/z* (rel. intens.): 261 ($M+H^+$,100); Anal. Calcd for $C_{17}H_{28}N_2{\cdot}C_2H_2O_4$: C, 65.12; H, 8.63; N, 7.99. Found: C, 64.91; H, 8.48; N, 8.13.

(1R,2R)-(+)-1-Phenyl-1-(1-butylamino)-2-(N-ethyl-N-methylamino)propane dihydrochloride 13. Compound 13 (5.2 g, 62%); $[\alpha]_D^{25}$ = −4.9 (*c* = 1.0, CH_3OH); mp 215–218°C. The ee was determined by CSP HPLC to be 100% (chiralpak AD-H, 99% *n*-hexane,1% 2-propanol, 0.1% diethylamine, 1.0 ml/min,210 nm); t_R = 6.49 min (100%); IR (KBr, cm^{-1}): 3496, 3036, 2932, 2664, 1570, 1470, 1381, 702; ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.81 (t, *J* = 6.5 Hz, 3H, $CH_2-CH_2-CH_3$), 1.07 (d, *J* = 6.3 Hz, 3H, $N-CH-CH_3$), 1.25 (m, 2H, $CH_3-CH_2-CH_2$), 1.63 (t, *J* = 6.6 Hz, 3H, $N-CH_2-CH_3$), 1.86 (m, 2H, $NH-CH_2-CH_2$), 2.62 (t, *J* = 6.5 Hz, 2H, $NH-CH_2$), 2.90 (s, 3H, $N-CH_3$), 3.35 (q, *J* = 6.5 Hz, 2H, $N-CH_2-CH_3$), 3.66 (m, 1H, $N-CH-CH_3$), 4.82 (d, *J* = 6.5 Hz, 1H, $C_6H_5-CH-NH$) 7.45–7.91 (m, 5H, H aromatic), 10.27 (br s, 1H, $\overset{+}{N}H-CH_3$), 11.19 (br s, 2H, $CH-\overset{+}{N}H_2-CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 10.4, 11.7, 13.4, 19.9, 27.8, 34.9, 46.6, 52.8,61.9, 62.7, 129.4, 130.0, 130.4, 130.6; MS (ESI) *m/z* (rel. intens.): 249 ($M+H^+$, 100); Anal. Calcd for $C_{16}H_{28}N_2{\cdot}2HCl$: C, 59.81; H, 9.41; N, 8.72. Found: C, 59.77; H, 9.38; N, 8.69.

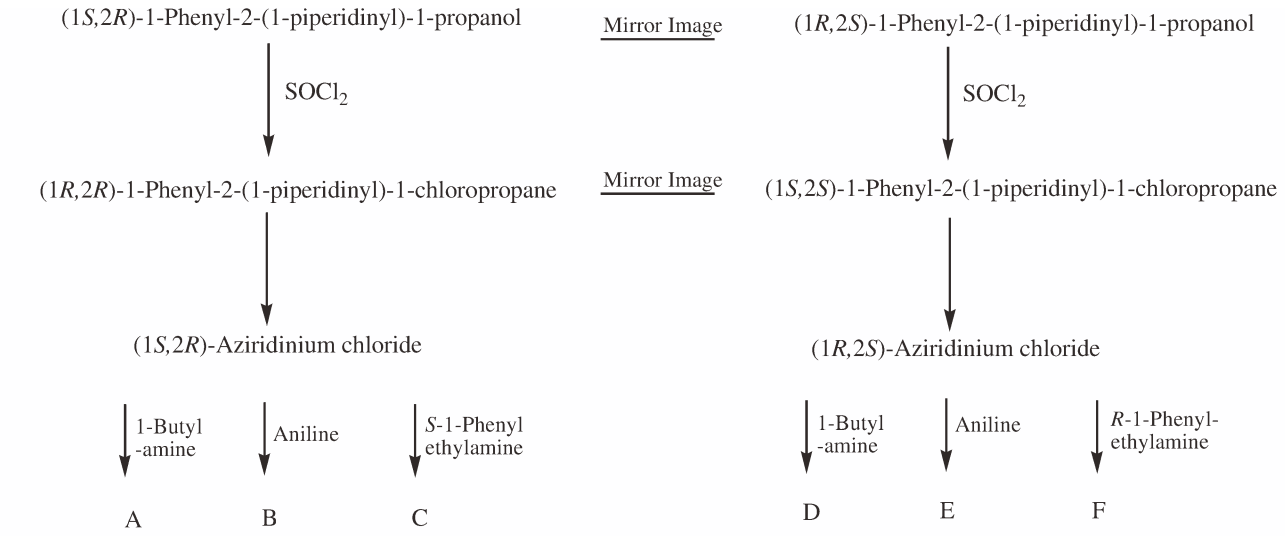
(1R,2R)-(+)-1-Phenyl-1-(2-fluorophenylamino)-2-(N-ethyl-N-methylamino)propane hydrochloride 14. Compound 14 (5.8 g, 70%); $[\alpha]_D^{25}$ = −141.1 (*c* = 1.0, CH_3OH); mp 205–210°C. The ee was determined by CSP HPLC to be 100% (chiralpak AD-H, 99% *n*-hexane, 1% 2-propanol, 0.1% diethylamine, 1.0 ml/min, 210 nm); t_R = 14.14 min (100%); IR (KBr, cm^{-1}): 3264, 3032, 2992, 2635, 1618, 1456, 1329, 748, 712; ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.21 (d, *J* = 6.8 Hz, 3H, $N-CH-CH_3$), 1.52 (t, *J* = 6.4 Hz, 3H, $N-CH_2-CH_3$), 2.91 (s, 3H, $N-CH_3$), 3.13 (q, *J* = 6.4 Hz, 2H, $N-CH_2-CH_3$), 3.46 (m, 1H, CH_3-CH-N), 4.21 (d, *J* = 6.4 Hz, 1H, $C_6H_5-CH-NH$), 6.71 (m, 5H, C_6H_5), 7.40 (m, 4H, C_6H_4F), 9.98 (br s, 1H, $C_6H_5-CH-NH$), 10.47 (br s, 1H, $\overset{+}{N}H-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 9.7–64.3 (six signals due to nonaromatic carbons), 115.0–154.5 (10 signals due to aromatic carbons (both ^1H and ^{13}C NMR spectra contain signals due to short and long range H—F and C—F coupling); MS (ESI) *m/z* (rel. intens.): 287($M+H^+$, 100); Anal. Calcd for $C_{18}H_{23}N_2{\cdot}HCl$: C, 66.96; H, 7.49; N, 8.68. Found: C, 66.93; H, 7.45; N, 8.66.

(1S,2R)-(+)-1-Phenyl-1-phenylamino-2-(tosylamino)propane 15. Compound 15 (2.8 g, 56%); $[\alpha]_D^{25}$ = +9.5 (*c* = 1.0, CH_3OH); mp 161–163°C. The ee was determined by CSP HPLC to be 100% (chiralpak AD-H, 99% *n*-hexane, 1% 2-propanol, 0.1% diethylamine,1.0 ml/min, 210 nm); t_R = 5.10 min (100%); IR (KBr, cm^{-1}): 3416, 3223, 3049, 2982, 1603, 1516, 1332, 1321, 1143, 815, 700; ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.88 (d,

TABLE 2. Retention time, specific rotation, and enantiomeric purities (in parentheses) of (1*R*,2*R*), (1*S*,2*S*), and (1*RS*,2*SR*) isomers of 1-phenyl-1-alkyl/arylamino-2-(1-piperidinyl)propane hydrochlorides

		(1*R*,2*R*) isomer	(1*S*,2*S*) isomer	(1*SR*,2*RS*) isomer	
Compound	1-Amino group	RT, $[\alpha]_D^{25}$, enantiomeric purity (%)	RT, $[\alpha]_D^{25}$, enantiomeric purity (%)	RT, $[\alpha]_D^{25}$, enantioneric purity (%)	
5	1-Butyl	11.60, −7.00, (100)	13.18, +6.64, (100)	11.93, 0, (49)	13.03, 0, (51)
7	Phenyl	20.30, −101.50, (100)	22.77, +98.50, (100)	20.54, 0, (48)	23.37, 0, (52)
		(1*R*,2*R*,1′*S*,) isomer	(1*S*,2*S*,1′*R*) isomer	(1*SR*,2*RS*,1′*SR*) isomer[a]	
8	(*S*)-1′-Phenylethyl	37.96, −40.70, (100)	–		
9	(*R*)-1′-Phenylethyl	_	49.80, +37.70, (100)	38.20, 0, (48)	48.0, 0, (52)

[a]Prepared from the (*S*/*R*)-phenyethylamine.



A= (1*R*,2*R*)-1-Phenyl-1-(1-butylamino)-2-(1-piperidinyl)propanedihydrochloride — Mirror Image — D= (1*S*,2*S*)-1-Phenyl-1-(1-butylamino)-2-(1-piperidinyl)propane dihydrochloride

B= (1*R*,2*R*)-1-Phenyl-1-phenylamino-2-(1-piperidinyl)propane hydrochloride — Mirror Image — E= (1*S*,2*S*)-1-Phenyl-1-phenylamino-2-(1-piperidinyl)propane hydrochloride

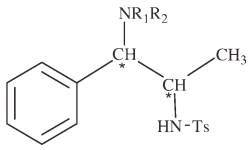
C= (1*R*,2*R*)-1-Phenyl-1-(1'-(*S*)-phenyl ethylamino)-2-(1-piperidinyl)-propane dihydrochloride — Mirror Image — F= (1*S*,2*S*)-1-Phenyl-1-(1'-(*R*)-phenyl ethylamino)-2-(1-piperidinyl)propane dihydrochloride

Scheme 4. Stereochemical pathway for the enantiomeric diamines.

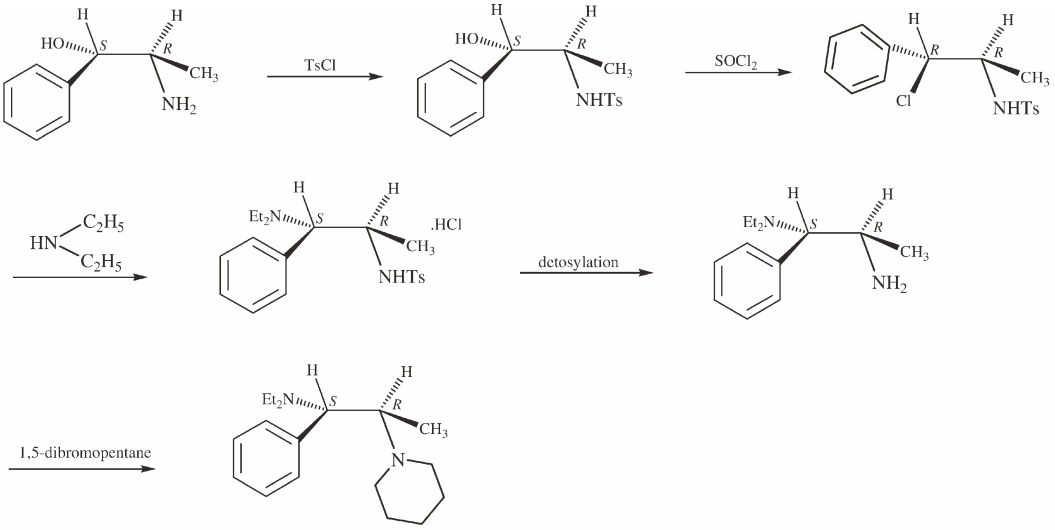
J = 6.4 Hz, 3H, NH−CH−C*H*$_3$), 2.44 (s, 3H, C_6H_4−C*H*$_3$), 3.76–3.87 (m, 1H, CH−C*H*−CH_3), 4.26–4.33, (m, 2H, N*H*−CH−CH−N*H*), 4.73 (d, *J* = 6.4 Hz, 1H, C*H*−CH−CH_3), 6.76–7.79 (m, 14H, H aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 18.0, 21.5, 53.4, 60.7, 113.4, 117.4, 127.0, 127.6,127.7, 128.5, 128.9, 129.9, 137.6, 138.2, 143.7, 146.4; MS (ESI) *m/z* (rel. intens.): 381 ($M+H^+$, 100), High Resolution Mass Spectra- Electro Spray Ionisation (HRMS-ESI) (*m/z*): calcd for $C_{22}H_{25}N_2O_2S$ (M+H): 381.1637; found 381.1637, 0.0 ppm.

(1S,2R)-(−)-1-Phenyl-1-(4-fluorophenylamino)-2-(tosylamino)-propane 16. Compound 16 (3.4 g, 68%); $[\alpha]_D^{25}$ = −5.1 (*c* = 1.0, CH_3OH); mp 160–162°C. The ee was determined by CSP HPLC to be 100%

TABLE 3. Physical properties and HPLC retention times of 1-phenyl-1-alkyl/arylamino-2-(*N*-tosylamino)propane (compounds 15–18)



						Chemical purity by HPLC using RP C18 column (%)			Enantiomeric excess (%) using chiral column			
						1*S*,2*R* isomer			1*S*,2*R* isomer		1*R*,2*S* isomer	
Compound No.	R_1	R_2	Melting point (°C)	Yield (%)	$[\alpha]_D^{25}$	RT	Content	Content of 1*R*,2*R* isomer (diastereomer)	RT	ee	RT	Content
15	Aniline	H	161–163	56	+9.5	28.3	98.37	8.2 (RT) Nil	3.05	100	7.17	Nil
16	4-Fluoro aniline	H	160–162	68	−5.05	29.12	100	Nil	6.23	100	13.95	Nil
17	Benzyl-amine	H	124–128	57	−38.9	29.45	98.6	Nil	3.96	100	4.62	Nil
18	*N*,*N*-Diethyl	H	131–135	62	+32.0	31.35	99.31	20.00 (RT) Nil	4.12	100	6.73	Nil



Scheme 5. Formation of the diamines through *N*-tosylation.

(chiralpak AD-H, 99% *n*-hexane, 1% 2-propanol, 0.1% diethylamine, 1.0 ml/min, 210 nm); t_R = 14.10 min (100%); IR (KBr, cm^{-1}): 3412,3227, 3030, 2982, 1597,1518, 1332, 1321, 1144, 816, 700; ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.86 (d, J = 6.4 H_z, 3H, CH−C*H*$_3$), 2.43 (s, 3H, C_6H_4−C*H*$_3$), 3.75–3.86 (m, 1H,CH−C*H*−CH_3), 4.22–4.40, (m, 2H, N*H*−CH−CH−N*H*), 4.68 (d, J = 6.5 H_z 1H,C*H*−CH−CH_3), 6.27–7.78 (m, 13H, H aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 17.8, 21.5, 53.5, 61.3, 114.1–157.2 (12 aromatic); MS (ESI) m/z (rel. intens.): 399 ($M+H^+$, 100), HRMS-ESI (*m/z*): calcd for $C_{22}H_{24}N_2O_2SF$ (M+H): 399.1543; found 399.1537, 1.5 ppm.

(1S,2R)-(-)-1-Phenyl-1-(1-benzylamino)-2-(tosylamino)propane 17. Compound 17 (3.5 g, 57%); $[\alpha]_D^{25}$ = −39.9 (c = 1.0, CH_3OH); mp 124–128°C. The ee was determined by CSP HPLC to be 100% (chiralpak AD-H, 99% *n*-hexane, 1% 2-propanol, 0.1% diethylamine,1.0 ml/min,210 nm); t_R = 5.95 min (100%); IR (KBr, cm^{-1}): 3331, 3231, 3059, 2938, 1597, 1491, 1331, 1308, 818, 700; ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.88 (d, J = 6.5 H_z, 3H,CH−C*H*$_3$), 2.40 (s,3H,C_6H_4−C*H*$_3$), 3.36 (m, 1H, CH_3−C*H*−NH), 3.44–3.52, (m, 2H, NH−C*H*$_2$−C_6H_5), 3.65 (s, 1H, SO_2−N*H*), 5.05 (d, J = 6.6 H_z 1H, C_6H_5−C*H*−CH), 7.08–7.67 (m, 14H, H aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 16.6, 21.5, 51.0, 53.4, 64.6, 127.1–143.2 (12 aromatic); MS (ESI) *m/z* (rel. intens.): 395 ($M+H^+$, 100), HRMS-ESI (*m/z*): calcd for $C_{23}H_{27}N_2O_2S$ (M+H): 395.1793; found 395.1805, 3.0 ppm.

(1S,2R)-(-)-1-Phenyl-1-(N,N-diethylamino)-2-(tosylamino) propane 18. Compound 18 (2.29 g, 65%); $[\alpha]_D^{25}$ = −32.0 (c = 1.0, CH_3OH); mp 131–135°C. The ee was determined by CSP HPLC to be 100% (chiralpak AD-H, 99% *n*-hexane,1% 2-propanol, 0.1% diethylamine,1.0 ml/min,210 nm); t_R = 5.11 min (100%); IR (KBr, cm^{-1}): 3240, 3059, 2974, 1597, 1493, 1331, 1169, 826, 704; ^1H NMR (300 MHz, $CDCl_3$): δ_H 0.89 (t, J = 6.7 H_z, 6H, N−(CH_2−C*H*$_3$)$_2$), 1.00 (d, J = 6.4 H_z, 3H, CH−C*H*$_3$), 2.20 (m, 2H, N−C*H*$_2$−CH_3), 2.43 (m, 5H, N−C*H*$_2$−CH_3, C_6H_5−C*H*$_3$), 3.38 (d, J = 6.5 H_z, 1H, C_6H_5−C*H*−N), 3.68 (m, 1H, CH_3−C*H*−CH), 5.09 (br s, 1H, N*H*−SO_2), 7.07–7.67 (m, 9H, H aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 11.6, 19.4, 21.5, 42.2, 49.5, 68.8, 127.2–143.1 (eight aromatic); MS (ESI) *m/z* (rel. intens.): 361 ($M+H^+$, 100); Anal. Calcd for $C_{20}H_{28}N_2O_2S$: C, 66.63; H, 7.83; N, 7.77; S, 8.89. Found: C, 66.68; H, 7.86; N, 7.72; S, 8.91.

RESULTS AND DISCUSSION

(1*S*,2*R*)-(+)-1-Phenyl-2-(1-piperidinyl)-1-propanol and (1*S*,2*R*)-(+)-1-phenyl-2-(1-pyrrolidinyl)-1-propanol are prepared from (1*S*,2*R*)-(+)-1-phenyl-2-amino-1-propanol[‡] and the corresponding dibromoalkanes in the presence of sodium carbonate. The hydroxyl function in the aminoalcohols is converted as a chloro derivative using thionyl chloride. The 1-chloro compounds are used for the preparation of the diamines using various alkyl/aryl amines.

The diamines have been isolated as hydrochlorides with high ee and their physical properties along with the details of the HPLC retention times are reported in Table 1. It can be noticed that many 1,2-diamines of varying nature are prepared to show the generality of this method.

The chlorination of a chiral alcohol with thionyl chloride proceeds through an inversion of configuration[21,22] in the presence of an amino function. The alkyl/aryl amination reaction of the chloro compound at C-1 is performed in the less-polar solvent, dichloromethane, and hence is expected to go through a SN_2 reaction mechanism inducing another inversion. It can be seen that an overall retention of configuration at C-1 would have taken place during the reactions from the alcohol to alkyl/aryl amino compounds.

STEREOCHEMICAL ASPECTS

It is known that α-chloroamines readily form aziridinium chlorides[16,17,20] through an intramolecular substitution reaction. This reaction takes place through an inversion of configuration at C-1 (Scheme 1). The reaction of the amine nitrogen to displace the chlorine at C-1 during the formation of the 1,2-diamine, infact, takes place through the aziridinium chloride.

The incoming amine nitrogen can, in principle, attack at C-1 or C-2 in the aziridinium chloride. But it is reported[23] that the nucleophile attacks the benzylic carbon in the aziridinium intermediate during the reaction of phenols with aminoindanols. Hence the approach of the nitrogen of the amine will be preferably toward more electrophilic benzylic carbon (C-1) (Scheme 2) during the reactions leading to 1,2-diamines in this work.

It can be observed that there are three inversions during the reactions starting from aminoalcohols to the diamines (Scheme 3) giving rise to overall inversion of configuration.

The 1,2-diamines are also prepared from (1*R*,2*S*)-(+)-1-phenyl-2-(1-piperidinyl)-1-propanol and from the corresponding racemic aminoalcohol using *n*-butylamine, aniline, and

[‡]The (1*S*,2*R*)- and (1*R*,2*S*)-1-phenyl-2-amino-1-propanols were obtained from Malladi Drugs & Pharmaceuticals Ltd., Chennai.

TABLE 4. Specific rotation, retention times, and melting points of 1-phenyl-1-diethylamino-2-(1-piperidinyl)propane dihydrochloride

Configuration of the amino alcohol	Synthetic route	Configuration of the diamine	Overall stereochemistry	$[\alpha]_D^{25}$	Melting point (°C)	Retention time
1*S*,2*R*	Aziridinium chloride	1*R*,2*R* (compound 3)	Inversion	+12.0	188–191	3.69
1*S*,2*R*	N-detosylation	1*S*,2*R* (compound 19)	Retention	+32.0	131–135	43.92
1*S*,2*R*	Walden inversion	1*S*,2*R* and 1*R*,2*R*	Partial racemization	+18.0	148–154	3.72 (29) and 43.56 (69)

(*R*)-1-phenylethylamine through the chloro derivative. The retention times in the HPLC analysis, specific rotations, and the enantiomeric purities of the products are given in Table 2. It can be noticed that the 1,2-diamines prepared from (1*S*,2*R*)-aminoalcohol are mirror images of the 1,2-diamines obtained from (1*R*,2*S*)-aminoalcohol (Scheme 4 and Table 2). These observations strongly support the absolute configuration assigned to C-1 of the 1,2-diamine.

(1*S*,2*R*)-(+)-1-Phenyl-2-amino-1-propanol is tosylated to obtain the *N*-tosyl derivative. This compound is chlorinated at C-1 followed by amination (compounds 15–18; Table 3). It is expected in the *N*-tosylated chloro compound the lone pair of electrons on the nitrogen gets delocalized to oxygen and not available for the formation of the aziridinium intermediate. Hence the amino derivative should form with overall retention of configuration at C-1 (Scheme 5). When the diamine (compound 18) is detosylated and the piperidinyl ring is constructed on NH_2 function, the compound obtained is (1*S*,2*R*)-(+)-1-phenyl-1-diethylamino-2-(1-piperidinyl)propane (compound 19) which is a diastereomer of compound 3. It can be observed from Table 4 that the specific rotations, melting points, and the HPLC retention times of compounds 3 and 19 are different.

Furthermore, the (1*S*,2*R*)-1-phenyl-2-amino-1-propanol hydrochloride is subjected to Walden inversion[§] at C-1 and the piperidinyl ring is built at C-2 with 1,5-dibromopentane. The diamine is prepared from (1*R*,2*R*)-1-phenyl-2-(1-piperidinyl)-1-propanol hydrochloride with diethylamine through the chloro derivative. But it is known[22] that (1*R*,2*R*)- and (1*S*,2*S*)-1-phenyl-2-methylamino-1-propanol hydrochlorides give the 1-chloro derivatives on treatment with $SOCl_2$ with inversion and retention with partial racemization at C-1. Hence the diamine prepared from the 1-chloro compound shows partial racemization with inversion of configuration at C-1 as shown by the retention times of the diamine products (Table 4). These observations support the absolute configuration assigned to C-1 in the diaminated product (compounds 1–14).

TABLE 5. Specific rotation, chemical purity (HPLC), retention time, and configuration of the products of the reaction of (1*R*,2*R*)-1-phenyl-2-(1-piperidinyl)-1-chloropropane hydrochloride (PPCP·HCl) with H_2O

Reaction	$[\alpha]_D^{25}$	Chemical purity (%) (HPLC)	Retention time	Configuration of the product
PPCP·HCl and H_2O	−22.0	51, 48	3.22, 6.00	1*S*,2*R*, 1*R*,2*R*
PPCP·HCl, triethylamine and H_2O	−54.5	99	6.10	1*R*,2*R*
Walden inversion[a]	−52.4	100	6.05	1*R*,2*R*

[a]Product of Walden inversion of (1*S*,2*R*)-1-phenyl-2-(1-piperidinyl)-1-propanol.

To establish the occurrence of SN_2 mechanism in the reaction of the aziridinium chloride intermediate with the alkyl/arylamine during the formation of the 1,2-diamine, (1*R*,2*R*)-1-phenyl-2-(1-piperidinyl)-1-chloropropane hydrochloride[¶] is treated with triethyl amine to release the base facilitating the formation of aziridinium chloride before heating with water overnight with stirring. The alcohol thus obtained shows the specific rotation ($[\alpha]_D^{25}$) as −54.5 which agrees with the value of −52.4 for the (1*R*,2*R*)-1-phenyl-2-(1-piperdinyl)-1-propanol (Table 5). This observation confirms the absolute configuration at C-1 to be "R" in the alcohol, formed through the aziridinium chloride, which is in agreement with the proposed inversion of configuration at C-1 during the amination of the aziridinium chloride intermediate.

Furthermore, (1*R*,2*R*)-1-phenyl-2-(1-piperdinyl)-1-chloropropane hydrochloride is heated at 40 °C overnight with water to obtain the 1-alcohol back. In this experiment, the formation of the aziridinium salt is prevented. The HPLC analysis of the 1-alcohol as the hydrochloride shows the presence of two diastereomeric alcohols which must be (1*S*,2*R*)-alcohol (48%) with inversion at C-1 and (1*R*,2*R*)-alcohol (51%) with retention at C-1.

This observation indicates the occurrence of racemization at C-1 during the reaction of H_2O with the 1-chloro compound as hydrochloride proceeding through SN_1 mechanism in the aqueous medium.

CONCLUSION

(1*R*,2*R*)-1-Phenyl-1-alkyl/arylamino-2-(N-alkyl)propane hydrochlorides have been prepared from (1*S*,2*R*)-(+)-1-phenyl-2-(N-alkyl)-1-propanol hydrochloride through the chloro derivative. When the base is liberated from the hydrochloride salt of the chloro derivative, aziridinium chloride intermediate is formed which reacts with the alkyl/aryl amine at the benzylic carbon with inversion of configuration. The 1,2-diamines are formed with overall inversion of configuration at C-1. But in the case of (1*S*,2*R*)-(+)-1-phenyl-2-N-tosyl-1-propanol, the aziridinium intermediate is not formed and the diamine is formed with overall retention of configuration at C-1. In all these cases, the chiral purity obtained is remarkably enantioselective.

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[§]The (1*R*,2*R*)-1-phenyl-2-amino-1-propanol was prepared from the (1*S*,2*R*)-isomer through a process involving Walden inversion at C-1.

[¶]The chloro derivative was obtained from (1*S*,2*R*)-1-phenyl-2-(1-piperdinyl)-1-propanol on treatment with thionyl chloride.

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