Asymmetric Synthesis. 39.[1] Synthesis of 2-(1-Aminoalkyl)piperidines *via* 2-Cyano-6-phenyl Oxazolopiperidine

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The asymmetric synthesis of a series of 2-(1-aminoalkyl) piperidines using (−)-2-cyano-6-phenyloxazolopiperidine **1** is described. $LiAlH_4$ reduction of **1** followed by hydrogenolysis led to the diamine **3**. The same strategy applied to C-2-methylated compound **7** afforded [(2*S*)-2-methylpiperidin-2-yl]methanamine (**9**). Addition of lithium derivatives to the cyano group of **1** resulted in the formation of an intermediate imino bicyclic system (**11a**−**c**) which could be diastereoselectively reduced to substituted diamino alcohols **13a**−**c**. The addition of an excess of PhLi to **1** in the presence of LiBr furnished disubstituted amine **19**, the precursor of diphenyl-[(2*S*)-piperidin-2-yl]methanamine (**22**).

Introduction

An ever growing interest in 1,2-diamine compounds exists since this system is an integral feature in many compounds of pharmaceutical value and in chiral ligands for asymmetric synthesis.[2] Among this family 2-(aminomethyl)pyrrolidine and -piperidine derivatives are of particular interest.[3,4] These compounds are generally prepared in optically pure form from the corresponding amino acids[5] or amino esters;[3a] neither of these methods allows the diastereoselective preparation of derivatives substituted on the carbons bearing the amine functions. Furthermore, the preparation of (aminomethyl)piperidine derivatives requires not easily available enantiomerically pure pipecolic acid as a starting material, in contrast with proline which is available in its enantiomeric forms.[6]

In a continuation of our studies on 2-cyano-6-phenyloxazolopiperidine **1**,[7] , we were interested in the reactivity of nucleophiles toward the cyano group. Our first results showed that the reaction of organolithium or cuprate derivatives with **1** gave an imine which was reduced to a primary amine with a remarkable stereoselectivity.[8] This reactivity has been used for the preparation of spiropiperidines related to histionicotoxin.[9,10] We also observed that the aminonitrile function of alkylated derivatives of **1** could be reduced without elimination to give intermediate imines which can in turn be reduced to 1,2-diamines or react with electrophiles.[9]

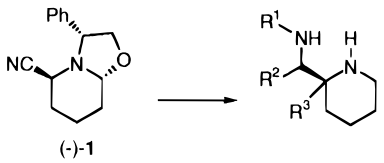

Figure 1.

We decided to investigate these reactivities in order to prepare unsubstituted and substituted aminomethyl piperidine derivatives (Figure 1).

Results and Discussion

Synthesis of (−)-[(2*S*)-piperidin-2-yl]methanamine (3). It was felt that synthon **1** was a good candidate for a short asymmetric synthesis of 2-(aminomethyl)piperidine, provided that the cyano group could be reduced cleanly without competitive elimination. It is known that α-aminonitriles can be reduced with $LiAlH_4$ either to diamines by reduction of the cyano group or into monoamines by a decyanation process. The results depend greatly on the substitution pattern.[11] Generally, monosubstituted α-aminonitriles yield diamines. Recently an example of reduction of 2-cyanopiperidine leading to a diamine has been published.[12]

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(4) For recent examples of use of 2-(aminomethyl)pyrrolidine and -piperidine derivatives in asymmetric synthesis, see: (a) Froelich, O.; Bonin, M.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron: Asymmetry* **1993**, *4*, 2335. (b) Kobayashi, S.; Hayashi, T. *J. Org. Chem.* **1995**, *60*, 1098. (c) Asami, M.; Usui, K.; Higuchi, S.; Inoue, S. *Chem. Lett.* **1994**, 297.

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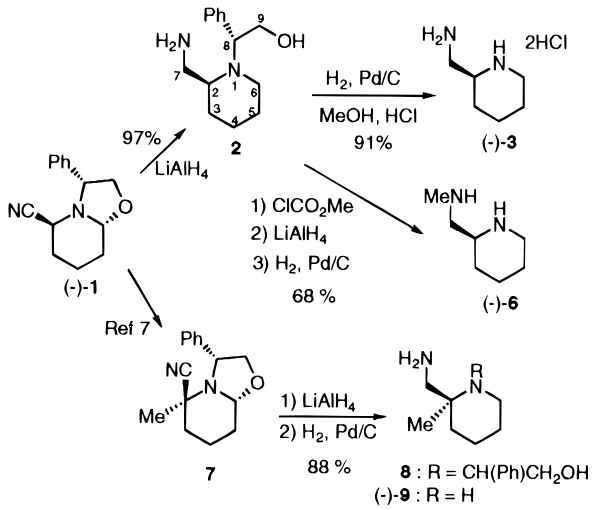
Scheme 1



2-Cyano-6-phenyloxazolopiperidine (**1**) was easily prepared from (*R*)-(−)-phenylglycinol and glutaraldehyde in the presence of KCN.[7] When (−)-**1** was treated with $LiAlH_4$ in Et_2O at rt, diamino alcohol **2** (Scheme 1) was obtained in 97% yield. As observed by Hoornaert,[12] the aminomethyl chain adopted a mixed axial−equatorial position ($\Sigma J_{2,3} = 11.5$ Hz)[13] ascribed to a strong gauche interaction between aminomethyl group and the *N*-(phenylethanol) substituent. Hydrogenolysis of the chiral appendage led easily to the 1,2-diamine **3** in 91% yield isolated as its dihydrochloride salt. Examination of the ^1H NMR spectrum indicated that an equatorial position was adopted by the aminomethyl chain ($\Sigma J_{2,3} > 14$ Hz).

To demonstrate the versatility of our strategy for preparing chiral ligands used in asymmetric synthesis, we decided to study the selective N-alkylation of the primary amine. For this purpose, diamino alcohol **2** was treated with methyl chloroformate followed by reduction of the resulting carbamate **4** with $LiAlH_4$ then hydrogenolysis of *N*-methyl intermediate **5**. Under these conditions *N*-methyl diamine **6** was obtained as an optically pure compound in 66% overall yield from synthon **1**.

Synthesis of [(2*S*)-2-methylpiperidin-2-yl]methanamine (9). In order to prepare C-2-substituted derivatives of (aminomethyl)piperidine, we first examined the reduction of C-2-methylated compound **7** obtained as a pure isomer by a deprotonation−alkylation sequence from synthon **1**.[7] At rt in Et_2O, compound **7** was quantitatively reduced to diamino alcohol **8**. Reduction of the nitrile function was confirmed by the appearance of an AB spin system (δ 2.87) in the ^1H NMR spectrum assigned to H-7 protons. This result was unexpected as it is known that disubstituted aminonitriles are generally reduced to monoamines by elimination of the cyano group, especially when the cyano group and nitrogen lone pair are in an antiperiplanar disposition.[14] In the 2-cyano-6-phenyloxazolopiperidine series, it is known[15] that the cyano group adopts an axial position antiperiplanar to the nitrogen lone pair (Figure 2). It is likely that the

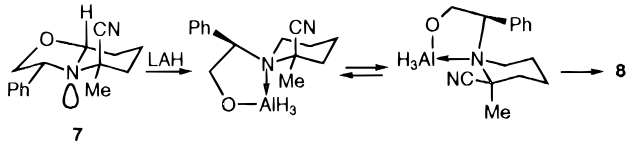
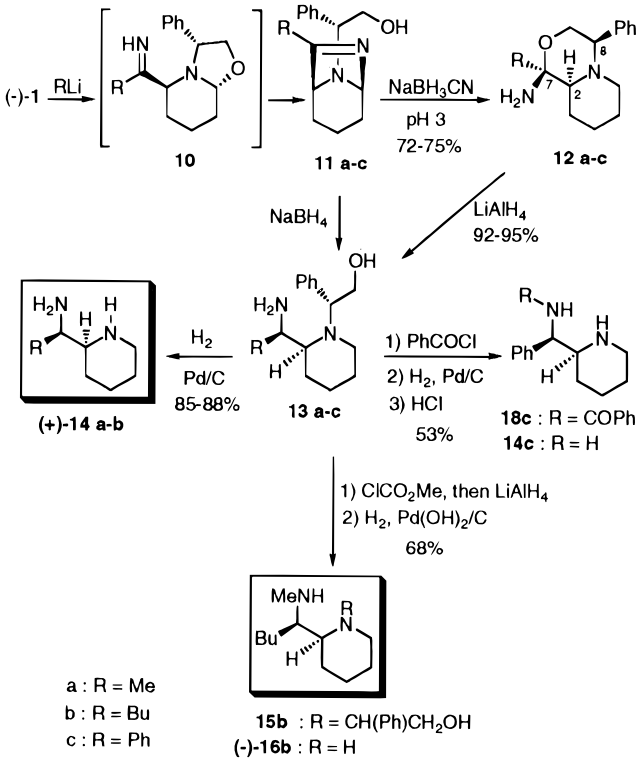


Figure 2.

Scheme 2



oxazolidine function is reduced, leading first to a five-membered chelating intermediate via the participation of the ring nitrogen. As a consequence, elimination of the nitrile cannot be assisted by the N-lone pair electron and an alternative mechanism; i.e reduction to the amino function prevails. Hydrogenolysis of **8** under standard conditions furnished C-2-methylated (aminomethyl)piperidine **9** in 90% yield.

Synthesis of (1-piperidin-2-yl)alkylamines 14a,b and 16b and (*R*)-phenyl[(2*S*)-piperidin-2-yl]methanamine (14c). The next target was the preparation of diamines substituted on the side chain (Scheme 2). A reinvestigation of the reaction of organolithium derivatives (MeLi, BuLi, or PhLi) with **1** indicated that the expected imines **10** were isolated in the cyclized form **11**[16] as indicated by spectral analyses. All attempts to purify crude **11a** led to decomposition products. A structural study was conducted on compound **11b**. In MS (EI), the base peak was observed at m/z 255 (M − 31, M − CH_2-OH), indicating a product with a phenylethanol opened chain substituent on the nitrogen. In the ^1H NMR two narrow triplets were observed at δ 3.34 ($J = 4.1$ Hz) and 5.2 ppm ($J = 2.5$ Hz); they were attributed to bridgehead H-2 and H-6, respectively, by $^1H-^{13}C$ COSY and are indicative of diaxial substituents at C-2 and C-6. The formation of these imines can be easily explained by the attack of an intermediate imine salt on the potential iminium ion at C-6.

(12) Compernolle, F.; Saleh, M. A.; Toppet, S.; Hoornaert, G. *J. Org. Chem.* **1991**, *56*, 5192.

(13) In order to make easier comparison of NMR data, the products are described with the numbering indicated for **2** in Scheme 1.

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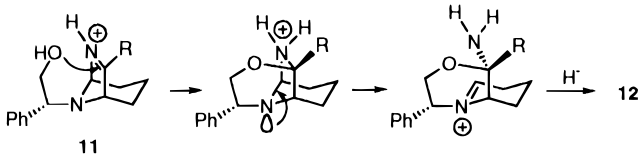
(16) The imino-oxazolidine structure was first proposed: Delgado, A.; Mauleon, D. *Synth. Commun.* **1988**, *18*, 823. We reported the same type of structure in our first communication (ref 8).

Scheme 3



Complete reduction of **11b** with $NaBH_4$ in CH_3OH occurred with a remarkable stereoselectivity, giving the amino alcohol **13b**. However, in the case of **11a** and **11c** the reaction was not diastereoselective. The problem was circumvented using a two-step route: (i) $NaBH_3CN$ reduction of **11a**−**c** at pH 3 affording **12a**−**c** (ii) $LiAlH_4$ reduction of **12a**−**c** leading stereoselectively to compounds **13a**−**c**. Morpholines **12** were obtained as single isomers for R = Bu (**12b**) and R = Ph (**12c**) and as a 9/1 mixture of two isomers at C-7 for R = Me (**12a**). For **12b**, **12c**, and the major isomer of **12a**, an axial position for H-2 and H-8 was indicated by similar chemical shifts and coupling constant values in their ^1H NMR spectra. A NOE experiment conducted on **12a** (major) indicated a *cis* relationship for H-2, H-8, and the C-7 methyl group. Thus it was possible to assign the (2*S*,7*S*,8*R*) absolute configuration for compound **12a** (major) and consequently the same for compounds **12b** and **12c**.

This configuration is explained by a preferential intramolecular attack of the primary alcohol of **11** on the accessible *si* face of the protonated imine, followed by the reduction of the aminal function of the intermediate, which could not be isolated (Scheme 3).

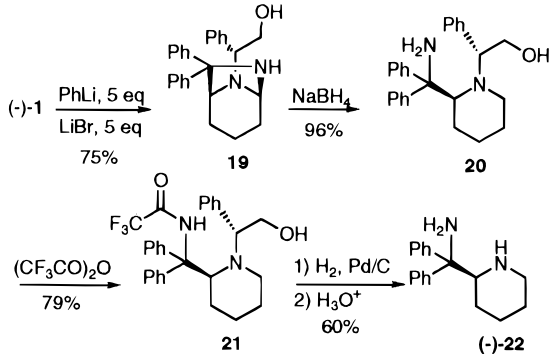
Stereoselective opening of the amino ether function of **12a**−**c** with $LiAlH_4$ afforded exclusively 1,2-diamines **13a**−**c**. The H-2, H-7 coupling constant values indicated an *erythro* stereochemistry.[17] This configuration has been previously confirmed by the preparation of a rigid intermediate derived from diamine **14b**.[8] It is interesting to notice that the major products of the direct reduction of **11b** with $NaBH_4$ furnished compounds **13b** with the same configuration. This result indicates that reduction of morpholines **12** occurred *via* a retention mechanism as proposed for ketals[18] and oxazolidines.[19] Reduction with $LiAlH_4$ of the mixture of epimeric methylated derivatives **12a** furnished exclusively *erythro* compound **13a**. This observation could indicate a mechanism involving a transient iminium form with an intramolecular delivery of hydride. However, it might be possible that the major diastereomer of **12a** is reduced much faster than the minor diastereomer.

Finally 1,2-diamines **14a** and **14b** were obtained by hydrogenolysis of the chiral appendage, in 59 and 50% overall yields, respectively, from **1**.

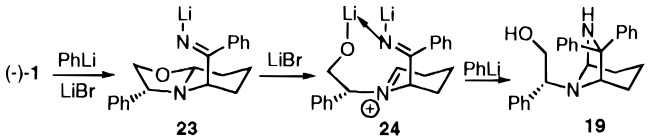
The synthesis of diamine **14c** containing a benzylamine function necessitated protection of **13c** as a benzamide **17c** before hydrogenolysis of the chiral phenylethanol moiety to give **18c**. Acid hydrolysis of the amide function of **18c** led finally to **14c**.

Compounds **13** represent useful intermediates allowing selective N-methylation *via* a two-step process involving an intermediate carbamate which was directly reduced ($LiAlH_4$) to compound **15b**. Hydrogenolysis of the chiral appendage afforded *N*-methyl diamine **16b**. Thus chemoselective substitution can be envisaged on each amino group.

Scheme 4



Scheme 5



Synthesis of diphenyl[(2*S*)-piperidin-2-yl]methanamine (22). When compound **1** was treated with an excess of PhLi, concomitant formation of **11c** and diphenyl aminal **19** was observed (Scheme 4). Selective formation of **19** (75% yield) could be obtained using 5 equiv of PhLi and LiBr. This product was characterized by the absence of the imine absorption in the IR spectra. In the ^{13}C NMR spectra a quaternary carbon was observed (δ 72.8 ppm), and in the ^1H NMR spectra, H-2 and H-6 appeared as broad singlets (δ 4.10 and 4.35). The mechanism of the reaction probably involves initial formation of imine salt **23** (Scheme 5), followed by association of LiBr, acting as a Lewis acid, allowing opening of the oxazolidine ring. Addition of PhLi on the intermediate iminium ion **24** gives the observed diphenyl aminal product **19**. This hypothesis is supported by the non-reactivity of the unactivated monophenyl derivative **11c** toward PhLi, even in the presence of LiBr. All attempts to introduce two different substituents during this reaction failed.

Generally the reaction of nitriles with organometallic species (RLi, RMgX), gives the corresponding imines.[20] Recently, Ciganek[21] reported a double addition of alkylcerium dichlorides to nitriles to give tertiary carbinamines, while Wemple[22] described the first example of double addition with the retention of chiral integrity of the asymmetric center α to the nitrile. However, to the best of our knowledge, this reaction has never been applied to α-aminonitrile in order to prepare 1,1-disubstituted 1,2-diamines.

$NaBH_4$ reduction of aminal **19** afforded diamino alcohol **20**. An examination of the ^1H NMR spectrum of **20** indicated that the piperidine ring of this compound adopts a boat conformation ($J_{2,3\ ax} = J_{2,3\ eq} = 7.5$ Hz) which may be attributed to a strong gauche interaction between the C-2 substituent and the N-1 benzyl chain. Elimination of the chiral appendage of **20** required prior protection of the primary amine as a trifluoroacetamide **21**, followed by hydrogenolysis and then deprotection by acid treatment leading to **22** (34% yield from **1**).

Conclusion

We have achieved the enantiospecific synthesis of a series of piperidines bearing a 2-aminomethyl group which can be substituted at N and/or C atoms.

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(19) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084.

(20) Schaeffer, F. C. in *Chemistry of the Cyano Group*; Rappoport, Z., Ed.; Interscience: New York, 1971; p 239.

(21) Ciganek, E. *J. Org. Chem.* **1992**, *57*, 4521.

(22) Fedij, V.; Lenoir III, E. A.; Suto, M. J.; Zeller, J. R.; Wemple, J. *Tetrahedron: Asymmetry* **1994**, *5*, 1131.

These diamines constitute precursors for the elaboration of more sophisticated biologically interesting compounds. Furthermore the selective functionalization of the side chain allows the modulation of the catalytic properties of this series of chiral ligands.

Experimental Section

Infrared spectra were recorded as solution in $CHCl_3$. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were recorded in $CDCl_3$ or CD_3OD solution; chemical shifts were measured as ppm downfield of internal tetramethylsilane. Mass spectral data were recorded either in the electron-impact (EI) or chemical-ionization (CI) mode. Analytical TLC was performed on glass plates coated with silica gel 60 F_{254} (Merck). Optical rotations of $CHCl_3$ or MeOH solutions were measured at 20 ± 3 °C. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone immediately prior to use. All reactions were performed under an atmosphere of dry N_2.

(2*R*)-2-[(2*S*)-2-(Aminomethyl)piperidin-1-yl]-2-phenylethanol (2). To a stirred suspension of $LiAlH_4$ (0.5 g, 13.14 mmol) in Et_2O (25 mL) at −10 °C under N_2 atmosphere was slowly added a solution of 2-cyanopiperidine **1** (1 g, 4.38 mmol) in Et_2O (5 mL). After 2 h at rt the mixture was treated with 0.5 mL of H_2O, 0.5 mL of 15% aqueous NaOH, and 1.5 mL of H_2O. The white precipitate was filtered and washed several times with Et_2O. After removal of the solvent under reduced pressure, the compound **2** was isolated pure as a pale yellow oil in 97% yield (1.0 g, 4.25 mmol): $[\alpha]_D$ −70 (*c* 0.87, $CHCl_3$); MS (EI) *m*/*z* (rel intensity) 234 (M^+, 1), 204 (80), 121 (10), 84 (80); ^1H NMR ($CDCl_3$) δ 1.0−1.65 (m, 6 H), 1.80 (ddd, *J* = 11.6, 11.0, 2.8 Hz), 2.46 (m), 2.82 (dd, *J* = 13.5, 2.8 Hz), 2.90 (dt, *J* = 11.6, 3.2 Hz), 3.30 (dd, *J* = 13.5, 5.0 Hz), 3.63 (dd, *J* = 10.5, 4.8 Hz), 4.02 (t, *J* = 10.5 Hz), 4.27 (dd, *J* = 10.5, 4.8 Hz), 7.12−7.35 (m, 5 H); ^{13}C NMR δ 23.1, 25.2, 28.8, 42.7, 44.7, 57.6, 60.4, 61.5, 126.7, 127.5, 128.2, 136.5; dihydrochloride (recryst MeOH/ Et_2O). Anal. Calcd for $C_{14}H_{24}N_2OCl_2$: C, 54.72; H, 7.87; N, 9.12. Found: C, 54.41; H, 7.64; N, 8.80.

[(2*S*)-Piperidin-2-yl]methanamine (3). To a solution of amino alcohol **2** (0.9 g, 3.85 mmol) and 10% palladium on charcoal (150 mg) in MeOH (8 mL) was added 4 mL of MeOH−2 N HCl. The mixture was hydrogenated with stirring for 6 h. After filtration on Celite with MeOH, the solvent was removed under reduced pressure. The residue was washed several times with Et_2O to eliminate 2-phenylethanol. Crystallization of the dihydrochloride salt in MeOH/Et_2O gave **3** as white crystals in 91% yield (655 mg, 3.51 mmol): mp 240−242 °C; $[\alpha]_D$ −5.7 (*c* 0.42, MeOH); MS (CI) 115 (M + 1, 100), 84 (20); ^1H NMR (D_2O) δ 1.65, 1.95, 2.15 (3m, 6 H), 3.10 (td), 3.28 (dd, *J* = 13.6, 7.0 Hz), 3.40 (dd, *J* = 13.6, 5.8 Hz), 3.55 (m, 2H); ^{13}C NMR (D_2O) δ 23.3, 23.8, 28.4, 43.5, 47.6, 56.2. Anal. Calcd for $C_6H_{16}N_2Cl_2$: C, 38.51; H, 8.61; N, 14.97. Found: C, 38.48; H, 8.71; N, 14.78.

(2*R*)-2-[(2*S*)-2-[(Methylamino)methyl]piperidin-1-yl]-2-phenylethanol (5). A solution of amino alcohol **2** (1.15 g, 4.91 mmol) and methyl chloroformate (417 μL, 5.40 mmol) in $CHCl_3$ (15 mL) and 15% aqueous NaOH solution (3 mL) was stirred for 3 h at rt. The resulting mixture was washed with saturated aqueous NH_4Cl and extracted with $CHCl_3$. The combined organic layers were washed with water, dried over $MgSO_4$, and then evaporated to furnish the corresponding carbamate **4** as an oil which was dissolved in Et_2O (25 mL) and added to a stirred suspension of $LiAlH_4$ (0.38 g, 10 mmol) in anhydrous Et_2O (20 mL) at 0 °C. After stirring for 3 h at rt, the mixture was treated with H_2O (0.38 mL), 15% NaOH (0.38 mL), and then H_2O (1.14 mL). The resulting precipitate was filtered off and washed with Et_2O. After removal of the solvent under reduced pressure, methyl amine **5** was isolated as a colorless oil in 76% (0.914 g, 3.68 mmol): $[\alpha]_D$ +15 (*c* 1.2, $CHCl_3$); IR 3415, 2936, 1686, 1543, 1109 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 249 (MH^+, 100), 218 (12), 204 (20), 141 (8), 121 (10), 105 (25), 91 (35), 84 (95). ^1H NMR ($CDCl_3$) δ 1.1−1.7 (m, 6H), 1.82 (ddd, *J* = 11.8, 10.5, 3.0 Hz), 2.47 (s), 2.62 (m), 2.71 (dd, *J* = 12.3, 3.5 Hz), 2.81 (dt, *J* = 11.8, 4.0 Hz), 3.00 (dd, *J* = 12.3, 4.8 Hz), 3.62 (dd, *J* = 10.3, 4.4 Hz), 3.95 (t, *J* = 10.3 Hz), 4.22 (dd, *J* = 10.3, 4.4 Hz), 7.1−7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.8, 25.9, 30.9, 37.0, 45.2, 54.3, 57.2, 61.0, 62.1, 127.4, 128.1, 128.7, 137.5; HRMS calcd for $C_{15}H_{25}N_2O$ (MH^+) 249.1966, found 249.1963.

[(2*S*)-Piperidin-2-yl]-*N*-methylmethanamine (6). Hydrogenolysis of a solution of diamino alcohol **5** (0.85 g, 3.42 mmol) in MeOH (20 mL) in the presence of palladium on charcoal (0.15 g) afforded after filtration and evaporation of the solvent 0.84 g of an oily residue. 2-Phenylethanol was eliminated by trituration of the residue with Et_2O. Diamine **6** was obtained as an oil (0.394 g, 3.08 mmol) in 90% yield: $[\alpha]_D$ −12 (*c* 0.8, MeOH); IR 3425, 2933, 1647, 1450 cm^{-1}; MS (CI) 129 (M + 1), 98, 84; ^1H NMR ($CDCl_3$) δ 1.1−1.8 (m, 6H), 2.4 (s), 2.5−2.7 (m, 4 H), 3.10 (br d, *J* = 11.9 Hz); ^{13}C NMR δ 24.6, 26.4, 30.7, 36.7, 46.7, 56.2, 57.8. Anal. Calcd for $C_7N_2H_{16}$: C, 65.57; H, 12.58; N, 21.84. Found: C, 65.40; H, 12.67, N, 21.74.

(2*R*)-2-[(2*S*)-2-(Aminomethyl)-2-methylpiperidin-1-yl]-2-phenylethanol (8). To a suspension of $LiAlH_4$ (1.0 g, 26.2 mmol) in ether (50 mL) was added a solution of compound **7**[7] (1.0 g, 4.15 mmol) in ether. After stirring of the mixture for 3h, H_2O (0.5 mL) was carefully added, followed by NaOH (10%) (0.5 mL) and then water (1.5 mL). After filtration, concentration of the organic phases gave a solid which was crystallized from methanol (1.01 g, 98%): mp 252 °C; $[\alpha]_D$ +166 (*c* 1.0, MeOH); IR 3394, 2946, 1405, 1027 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 249 (MH^+, 10), 218 (50), 121 (25), 98 (100); ^1H NMR δ 0.70 (s), 1.05−1.80 (m, 6H), 2.48 (td, *J* = 11.2, 3.0 Hz), 2.72 (br s OH), 2.87 (AB system, 2 H), 2.95 (dt, *J* = 11.2, 3.6 Hz), 3.45 (dd, *J* = 10.6, 4.7 Hz), 3.85 (t, *J* = 10.6 Hz), 4.27 (dd, *J* = 10.6, 4.7 Hz), 7.1−7.4 (m, 5 H); ^{13}C NMR δ 18.7, 20.7, 27.1, 36.8, 40.8, 49.6, 57.2, 61.1, 62.1, 127.3, 129.3, 139.6. Anal. Calcd for $C_{15}H_{24}N_2O$: C, 72.54; H, 9.74; N, 11.28. Found C, 72.83, H, 9.86, N, 10.99.

[(2*S*)-2-Methylpiperidin-2-yl]methanamine (9). Hydrogenolysis of 180 mg of **8** in the manner described in the preparation of **3** afforded **9** as hygroscopic crystals in 90% yield: $[\alpha]_D$ −4.5 (*c* 1.0, MeOH); IR 3421, 2923 cm^{-1}; MS (CI) 129 (MH^+), 112, 102, 98; ^1H NMR (CD_3OD) δ 1.65 (s), 1.8−2.0 (m, 6H), 3.34 (br t, *J* = 5.9 Hz, 2H), 3.48 (br s, 2H); ^{13}C NMR (CD_3OD) δ 18.6, 19.7, 22.6, 32.3, 41.2, 46.0, 57.1.

(2*R*)-2-[(1*S*,5*S*)-7-Methyl-6,8-diazabicyclo[3.2.1]oct-6-en-8-yl]-2-phenylethanol (11b). A solution of **1** (2 g, 8.77 mmol) in freshly distilled Et_2O (30 mL) was cooled to −10 °C under a N_2 atmosphere. After addition of n-BuLi (6.4 mL, 9.6 mmol), the resulting solution was stirred for 2 h at rt and then quenched with saturated aqueous NH_4Cl. The general workup procedure gave an orange oil which was purified by flash chromatography (SiO_2, cyclohexane/AcOEt 1:1) to give *n*-butylimine **11b** (yellow oil, 2.1 g, 7.39 mmol, 85% yield): $[\alpha]_D$ −57 (*c* 1.5, $CHCl_3$); IR 3400, 1650, 1510 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 286 (M^+, 10), 255 (100), 203 (80); ^1H NMR ($CDCl_3$) δ 0.90 (t, *J* = 7 Hz), 1.2−1.9, 2.0, 2.3 (m, 12 H), 3.34 (t, *J* = 4.1 Hz), 3.42 (dd, *J* = 5.5, 4.1 Hz), 3.75 (dd, *J* = 11.0, 4.1 Hz), 3.82 (dd, *J* = 11.0, 5.5 Hz), 5.2 (t, *J* = 2.5 Hz), 7.2−7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.8, 16.8, 22.7, 24.4, 25.3, 27.8, 30.6, 64.5, 66.1, 67.0, 85.6, 127.7, 128.4, 128.5, 140.5, 177.3.

(2*R*)-2-Phenyl-2-[(1*S*,5*S*)-7-phenyl-6,8-diazabicyclo[3.2.1]-oct-6-en-8-yl]ethanol (11c). A solution of **1** (2 g, 8.77 mmol) in freshly distilled Et_2O (40 mL) was cooled to −78 °C. After addition of PhLi (5 mL, 10 mmol), the resulting solution was stirred for 1.5 h at rt and then quenched with saturated aqueous NH_4Cl. The general workup procedure gave an oily residue which was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH 95:5) to give imine **11c** as a yellow oil in 93% yield, (2.5 g, 8.15 mmol): $[\alpha]_D$ −43 (*c* 2.0, $CHCl_3$); IR 3350, 3027, 1640, 1520, 1428 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 306 (M^+, 14), 275 (100), 203 (45); ^1H NMR ($CDCl_3$) δ 1.1−1.9 (m, 6 H), 3.45 (dd, *J* = 5.3, 4.7 Hz), 3.81 (dd, *J* = 11.2, 4.7 Hz), 3.88 (dd, *J* = 11.2, 5.3 Hz), 3.95 (t, *J* = 2.9 Hz), 5.50 (t, *J* = 2.4 Hz), 7.3−7.6 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 16.8, 25.0, 25.2, 64.8, 65.7, 66.2, 86.2, 127.6, 127.9, 128.4, 128.5, 128.6, 131.0, 131.9, 140.4, 171.9; HRMS calcd for $C_{20}H_{22}N_2O$ 306.1732, found 306.1725.

(1*S*,4*R*,9a*S*)-1-Methyl-4-phenyloctahydropyrido[2,1-*c*]-[1,4]oxazin-1-amine (12a). A solution of **1** (2 g, 8.77 mmol) in freshly distilled Et_2O (30 mL) was cooled to −10 °C. After addition of MeLi (6 mL, 9.60 mmol), the yellow solution was

stirred for 2 h at rt and then quenched with saturated aqueous NH_4Cl. The general workup procedure gave an orange oil which decomposed rapidly at room temperature. Direct solubilization with MeOH and THF (20 mL of each) gave a yellow solution which was acidified with 1 N aqueous HCl (pH 3). After addition of $NaBH_3CN$ (580 mg, 9.23 mmol), the mixture was maintained at pH 3, refluxed for 1.5 h, and then neutralized at pH 7 with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried on $MgSO_4$, concentrated, and purified by flash chromatography on silica gel (hexane/diethyl ether 1:1) to give a mixture of two epimeric compounds in 74% yield and in a 90/10 ratio. An analytical sample of **12a** was obtained by preparative TLC: $[\alpha]_D$ −108 (*c* 0.46, $CHCl_3$); MS (EI) *m*/*z* (rel intensity) 246 (1), 245 (16), 231 (42), 212 (37), 187 (100), 186 (86), 104 (89); ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.4−1.8 (m, 7H), 2.1 (s, 2H, NH_2), 2.18 (dd, *J* = 10.8, 2.5 Hz), 2.72 (dt, *J* = 11.6, 3.6 Hz), 3.20 (dd, *J* = 11.0, 4.0 Hz), 3.48 (dd, *J* = 12.1, 4.0 Hz), 3.68 (dd, *J* = 12.1, 11.0 Hz), 7.2−7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 24.5, 25.5, 27.7, 26.4, 53.5, 65.3, 68.5, 69.1, 84.5, 127.5, 127.9, 128.5, 140.0. Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 72.97; H, 8.94, N, 11.18.

(1*S*,4*R*,9a*S*)-1-Butyl-4-phenyloctahydropyrido[2,1-*c*]-[1,4]oxazin-1-amine (12b). A solution of *n*-butylimine **11b** (2 g, 6.99 mmol) in MeOH/THF (25 mL of each) was acidified with 1 N aq HCl (pH 3). After addition of $NaBH_3CN$ (0.48 g, 7.69 mmol), the reaction mixture was maintained at pH 3, refluxed for 1.5 h, and then neutralized at pH 7 with saturated aq $NaHCO_3$ and extracted three times with CH_2Cl_2. The organic layers were dried over $MgSO_4$, concentrated, and purified by flash chromatography on silica gel (cyclohexane/AcOEt 3:1) to give the butylmorpholine **12b** in 72% yield (1.4 g, 4.86 mmol) as a pale yellow oil: $[\alpha]_D$ −97 (*c* 1.2, $CHCl_3$); IR 3400, 3020, 2938, 1480, 1224 cm^{-1}; MS (EI) *m*/*z* 288 (M^+, 1), 272 (3), 231 (5), 187 (100); ^{1}H NMR ($CDCl_3$) δ 0.92 (t, *J* = 7 Hz), 1.2−1.8 (m, 13 H), 2.10 (br s, NH_2), 2.20 (dd, *J* = 11, 2.1 Hz), 2.70 (dt, *J* = 11.5, 2.5 Hz), 3.18 (dd, *J* = 11.1, 4.0 Hz), 3.46 (dd, *J* = 12, 4.0 Hz), 3.75 (dd, *J* = 12, 11.1 Hz), 7.2−7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 23.3, 24.5, 24.7, 25.5, 27.3, 39.0, 53.6, 65.3, 67.2, 69.2, 85.6, 127.5, 127.9, 128.5, 140.2. Anal. Calcd for $C_{18}H_{28}N_2O$: C, 74.95; H, 9.78; N, 9.71. Found: C, 75.01; H, 9.89; N, 9.76.

(1*S*,4*R*,9a*S*)-1,4-Diphenyloctahydropyrido[2,1-*c*][1,4]-oxazin-1-amine (12c). Following the same procedure as for product **12a**, phenylimine **11c** (2 g, 6.53 mmol) was reduced with $NaBH_3CN$ (0.45 g, 7.18 mmol) in 1.5 h at reflux under acidic conditions (MeOH/THF 1:1, 50 mL; 1 N HCl, pH 3). Identical workup and flash chromatography purification (SiO_2, hexane/ether 1:1) gave a white solid (**12c**) in 75% yield (1.5 g, 4.89 mmol): mp 155 °C (ether/heptane); $[\alpha]_D$ −50 (*c* 0.92, $CHCl_3$); IR 3400, 3090, 2950, 1510 cm^{-1}; MS (CI) 309 (M + 1, 100), 292 (35); ^{1}H NMR ($CDCl_3$) δ 1.0−1.8 (m, 7 H), 2.45 (dd, *J* = 11.0 and 2.4 Hz), 2.55 (br s, NH_2) 2.78 (br d, *J* = 11.2 Hz), 3.40 (dd, *J* = 11.2, 4.1 Hz), 3.68 (dd, *J* = 12.1, 4.1 Hz), 3.98 (dd, *J* = 12.1, 11.2 Hz), 7.3, 7.8 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 24.6, 25.6, 26.9, 53.8, 65.6, 69.6, 69.8, 87.9, 127.3−128.7, 140.1, 143.6. Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84; N, 9.08. Found: C, 77.55; H, 7.78; N, 8.88.

(2*R*)-2-[(2*S*)-2-[(1*R*)-1-Aminoethyl]piperidin-1-yl]-2-phenylethanol (13a). To a stirred suspension of $LiAlH_4$ (0.25 g, 6.57 mmol) in anhydrous Et_2O (25 mL) at −5 °C was added slowly a solution of methyl morpholine **12a** as a mixture of isomers (1.4 g, 5.69 mmol) in ether (5 mL). After 1.5 h at rt, the mixture was treated with H_2O (0.25 mL), 15% aqueous NaOH (0.25 mL), and H_2O (0.75 mL). The resulting white precipitate was filtered and washed several times with Et_2O. After removal of the solvent under reduced pressure, compound **13a** was isolated pure as a pale yellow oil in 95% yield (1.34 g, 5.4 mmol): $[\alpha]_D$ −68 (*c* 2.3, $CHCl_3$); IR 3010, 2890, 1600 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 248 (M^+, 2), 204 (100); (CI) 249, ^{1}H NMR ($CDCl_3$) δ 1.1 (d, *J* = 6.6 Hz), 1.2−1.6 (m, 6 H), 1.7 (td, *J* = 11.5, 2.5 Hz), 2.25 (dt, *J* = 10.8, 2.8 Hz), 2.6−2.7 (br s, NH_2, OH), 2.92 (br d, *J* = 11.5 Hz), 3.65 (dd, *J* = 10.5, 4.8 Hz), 3.85 (qd, *J* = 6.6, 2.8 Hz), 4.08 (t, *J* = 10.5 Hz), 4.45 (dd, *J* = 10.5, 4.8 Hz), 7.1−7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.5, 23.3, 24.0, 26.0, 44.6, 45.9, 59.7, 60.4, 61.9, 127.3, 128.0, 128.8, 136.1; HRMS calcd for $C_{15}H_{24}N_2O$ 249.1966, found 249.1964.

(2*R*)-2-[(2*S*)-2-[(1*R*)-1-Aminopentyl]piperidin-1-yl]-2-phenylethanol (13b). Aminoalcohol **13b** (1.21 g, 4.15 mmol) was prepared from butylmorpholine **12b** (1.3 g, 4.51 mmol) in 92% yield as described for **13a** to give pale yellow crystals: mp 212−214 °C (Et_2O/hexane); $[\alpha]_D$ −80 (*c* 1.0, $CHCl_3$); IR 3400, 1510 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 290 (M^+, 20), 204 (100); ^{1}H NMR ($CDCl_3$) δ 0.95 (t, *J* = 7 Hz), 1.3−1.6 (m, 12 H), 1.8 (br t, *J* = 11.2 Hz), 2.35 (br d, *J* = 10.7 Hz), 2.75 (br s, NH_2, OH), 2.98 (br d, *J* = 11.2 Hz), 3.62 (m, 2 H), 4.10 (t, *J* = 10.4 Hz), 4.48 (dd, *J* = 10.4, 4.5 Hz), 7.1−7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.9, 23.8, 24.2, 26.2, 29.2, 34.7, 46.2, 49.5, 59.8, 60.5, 60.9, 127.4, 128.0, 128.9, 136.4; HRMS calcd for $C_{18}H_{31}N_2O$ 291.2434, found 291.2434.

(2*R*)-2-[(2*S*)-2-[(*R*)-(1-Aminophenyl)methyl]piperidin-1-yl]-2-phenylethanol (13c). Aminoalcohol **13c** (1.27 g, 4.12 mmol) was prepared from phenylmorpholine **12c** (1.35 g, 4.38 mmol) in 94% yield as described for **13a** to yield an oil: $[\alpha]_D$ −40 (*c* 1.0, $CHCl_3$); IR 3015, 2895, 1550, 1520 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 310 (M^+, 15), 279 (100), 204 (100); ^{1}H NMR ($CDCl_3$) δ 0.8−1.9 (m, 7 H), 2.68 (dt, *J* = 10.7, 3.8 Hz), 3.0 (dt, 11.5, 2.5 Hz), 3.65 (dd, *J* = 10.8, 4.4 Hz), 3.9 (br s, NH_2, OH), 4.10 (dd, *J* = 10.8, 10.4), 4.5 (dd, *J* = 10.4, 4.4 Hz), 5.00 (d, *J* = 3.8 Hz), 7.1−7.5 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 23.6, 23.9, 25.6, 45.7, 53.8, 60.8, 61.8, 62.4, 126.7, 127.2, 127.9, 128.4, 128.5, 129.0, 136.5; HRMS calcd for $C_{20}H_{26}N_2O$ 310.2044, found 310.2042.

(1*R*)-1-[(2*S*)-Piperidin-2-yl]ethanamine (14a). A solution of amino alcohol **13a** (0.95 g, 3.83 mmol) and 10% palladium on charcoal (0.15 g) in MeOH (10 mL) was acidified with 4 mL of MeOH/2 N HCl. The reaction mixture was stirred for 5 h under an H_2 atmosphere and then filtered over a Celite bed with MeOH and concentrated. After trituration with Et_2O, the resulting precipitate was washed several times (Et_2O, 20 mL) to eliminate 2-phenylethanol. Recrystallization in MeOH/Et_2O led to white crystals of diamine **14a** as a dihydrochloride salt (0.677 g, 3.37 mmol) in 88% yield: $[\alpha]_D$ +43 (*c* 0.56, MeOH); MS (CI) 201 (M + 1, 100), 112 (10), 84 (25); ^{1}H NMR (CD_3OD) δ 1.55 (d, *J* = 6.9 Hz), 1.7−2.2 (m, 6 H), 3.20 (td, *J* = 12.8, 3.8 Hz), 3.52 (ddd, *J* = 11.8, 5.1, 3.1), 3.60 (dt, *J* = 12.8, 1.6 Hz), 3.73 (qd, *J* = 6.9, 5.1 Hz); ^{13}C NMR (CD_3OD) δ 15.7, 22.8, 25.6, 25.6, 46.8, 50.6, 60.0. Anal. Calcd for $C_7H_{18}N_2Cl_2$: C, 41.79; H, 9.02; N, 13.92. Found: C, 42.04; H, 8.72; N, 13.85.

(1*R*)-1-[(2*S*)-Piperidin-2-yl]pentan-1-amine (14b). A solution of amino alcohol **13b** (0.9 g, 3.10 mmol) and palladium hydroxide (20% on charcoal, 0.15 g) in MeOH (10 mL) was stirred for 6 h under an H_2 atmosphere and then filtered over Celite and concentrated under vacuo. The oily residue was purified by chromatography on alumina. The first elution with CH_2Cl_2/MeOH 98:2 gave the 2-phenylethanol byproduct, then CH_2Cl_2/MeOH/NH_4OH 85:10:5 led to butylamine **14b** (0.44 g, 2.63 mmol) as a pale yellow oil (85% yield): $[\alpha]_D$ +6.3 (*c* 1.56, $CHCl_3$); IR 3288, 2930, 1590 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 170 (M^+, 100), 84 (35); ^{1}H NMR ($CDCl_3$) δ 0.90 (t), 1.2−1.6 (m, 12 H), 2.40 (ddd, *J* = 11.1, 4.0, 2.3 Hz), 2.62 (m), 2.65 (td, *J* = 11.9, 2.9 Hz), 3.10 (br d, *J* = 11.9 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.8, 24.8, 26.4, 26.7, 28.9, 33.4, 47.4, 55.7, 61.7. Anal. Calcd for $C_{10}H_{22}N_2$: C, 70.52; H, 13.02; N, 16.45. Found: C, 70.37; H, 13.17; N, 16.35.

(2*R*)-2-[(2*S*)-2-[(1*R*)-1-(*N*-Methylamino)pentyl]piperidin-1-yl]-2-phenylethanol (15b). A solution of amino alcohol **13b** (1.4 g, 4.82 mmol) in $CHCl_3$ (40 mL) was heated for 2 h under reflux with methyl chloroformate (0.41 mL, 5.31 mmol). The resulting mixture was quenched with saturated aqueous NH_4Cl and extracted following a general workup procedure to give a pale yellow oil which was dissolved in Et_2O (10 mL) and added to a stirred suspension of $LiAlH_4$ (0.16 g, 4.2 mmol) in anhydrous Et_2O (30 mL) at −5 °C. After 3 h at rt, the mixture was treated with H_2O (0.16 mL), 15% aqueous NaOH (0.16 mL), and H_2O (0.48 mL). The resulting white precipitate was filtered and washed several times with Et_2O. After removal of the solvent under reduced pressure, methyl amine **15b** was isolated as a colorless oil in 78% yield (1.14 g, 3.76 mmol): $[\alpha]_D$ −105 (*c* 1.0, $CHCl_3$); IR 3250, 2930, 1450 cm^{-1};

MS (EI) *m/z* (rel intensity) 304 (M^+, 12), 274 (10), 204 (100); ^{1}H NMR ($CDCl_3$) δ 0.95 (t), 1.35−1.7 (m, 13 H), 2.45 (dt, J = 11.1, 2.7 Hz), 2.50 (s), 2.97 (br d, J = 11.6 Hz), 3.14 (m), 3.62 (dd, J = 10.4, 4.9 Hz), 4.05 (dd, J = 10.9, 10.4 Hz), 4.28 (dd, J = 10.9, 4.9 Hz), 7.2, 7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 23.2, 24.5, 24.8, 26.2, 28.6, 30.4, 35.0, 46.3, 58.6, 59.2, 59.7, 60.4, 127.5, 128.0, 128.9, 136.1; HRMS calcd for $C_{19}H_{32}N_2O$ 304.2512, found 304.2515.

(1*R*)-*N*-Methyl-1-[(2*S*)-piperidin-2-yl]pentan-1-amine (16b). A solution of diamino alcohol **15b** (0.5 g, 1.65 mmol) and 20% palladium hydroxide on charcoal (80 mg) in MeOH (10 mL) was stirred for 3 h under a hydrogen atmosphere and then filtered over a Celite pad and concentrated under vacuo. The oily residue was purified by flash chromatography (SiO_2). First elution gave the 2-phenylethanol byproduct (CH_2Cl_2/MeOH, 95:5), then other solvent mixture (CH_2Cl_2/MeOH, 90:10) led to the title compound **16b** (0.26 g, 1.43 mmol) as a colorless oil in 87% yield: $[\alpha]_D$ −12 (*c* 1.0, $CHCl_3$); IR 3420, 2950, 2700, 1592, 1467 cm^{-1}; MS (EI) *m/z* (rel intensity) 185 (M + 1, 18), 151 (10), 137 (15), 123 (15); ^{1}H NMR ($CDCl_3$) δ 0.85 (t), 1.20−2.0 (m, 12 H), 2.60 (s), 2.90 (td, J = 12.4, 4.0 Hz), 3.12 (dt, J = 12.0, 2.0 Hz), 3.20 (m), 3.45 (brd, J = 12.4 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.6, 22.6, 22.7, 22.9, 28.4, 28.4, 33.7, 45.4, 58.0, 61.3; HRMS calcd for $C_{11}H_{24}N_2$ 184.1938, found 184.1929.

***N*-[(*R*)-[(2*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]piperidin-2-yl]phenylmethyl]benzamide (17c).** To a solution of amino alcohol **13c** (1.24 g, 4 mmol) in CH_2Cl_2 (60 mL) was added diluted aqueous NaOH (15%, 4 mL) and benzoyl chloride (0.62 g, 4.4 mmol). The reaction mixture was stirred for 2.5 h at rt and then diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic layers were concentrated and purified by chromatography (Al_2O_3, CH_2Cl_2/MeOH 99:1) to give compound **17c** as a yellow oil (1.37 g, 3.32 mmol, 83% yield): $[\alpha]_D$ −38.4 (*c* 1.0, $CHCl_3$); IR 3332, 2931, 1637 cm^{-1}; MS (EI) *m/z* (rel intensity) 414 (M^+, 15), 383 (100), 309 (25), 293 (15); ^{1}H NMR ($CDCl_3$) δ 0.9−1.8 (m, 6 H), 2.11 (td, J = 11.4, 2.8 Hz), 2.75 (ddd, J = 8.6, 5.2, 4.8 Hz), 3.08 (dt, J = 11.4, 3.6 Hz), 3.52 (dd, J = 10.8, 5.3 Hz), 3.97 (dd, J = 10.8, 10.1 Hz), 4.40 (dd, J = 10.1, 5.3 Hz), 6.08 (dd, J = 7.1, 5.2 Hz), 6.82 (d, J = 7.1 Hz), 7.3−7.9 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 23.5, 25.4, 25.6, 45.1, 52.7, 60.5, 61.7, 62.2, 126.2−131.6, 135.6, 135.9, 140.2, 167.7; HRMS calcd for $C_{26}H_{27}N_2O$ (M − CH_2OH) 383.2122, found 383.2116.

***N*-[(*R*)-Phenyl[(2*S*)-piperidin-2-yl]methyl]benzamide (18c).** A solution of amino alcohol **17c** (1.2 g, 2.91 mmol) and activated 10% palladium on charcoal (180 mg) in MeOH (10 mL) was stirred for 3 h under an H_2 atmosphere and then filtered over Celite and concentrated. 2-Phenylethanol was eliminated by trituration of the oily residue with Et_2O. Pure compound **18c** was thus obtained in 81% yield as a colorless viscous oil (0.69 g, 2.35 mmol): $[\alpha]_D$ +14 (*c* 1, $CHCl_3$); IR 3340, 2940, 1638 cm^{-1}; MS (EI) *m/z* (rel intensity) 295 (M + 1, 10), 174 (50), 122 (50), 105 (100); ^{1}H NMR ($CDCl_3$) δ 0.9−1.9 (m, 6 H), 2.51 (td, J = 13.0, 2.4 Hz), 2.84 (ddd, J = 10.7, 6.1, 1.8), 2.97 (br d, J = 13.0 Hz), 5.0 (dd, J = 7.8, 6.1 Hz), 7.1−7.9 (m, 10 H), 7.62 (d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 24.6, 26.8, 30.1, 47.0, 57.8, 60.4, 126.5−131.3, 134.6, 139.2, 166.6; HRMS calcd for $C_{19}H_{22}N_2O$ 294.1732, found 294.1748.

(*R*)-Phenyl[(2*S*)-piperidin-2-yl]methanamine (14c). A solution of benzamide **18c** (0.6 g, 2.04 mmol) in 6 N HCl (12 mL) was heated for 24 h under reflux and then diluted at rt and washed three times with Et_2O to eliminate benzoic acid. The aqueous layers were concentrated up to 5 mL, basified with NaOH (30%, pH 7), and extracted with CH_2Cl_2. The general workup procedure gave **14c** as a pale yellow oil in 79% yield (0.3 g, 1.61 mmol): $[\alpha]_D$ +0.7 (*c* 1, MeOH); MS (EI) *m/z* (rel intensity) 191 (M + 1, 15), 172 (10), 153 (25), 106 (25), 84 (100); IR 3600, 2900, 1600, 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.3−1.9 (m, 6 H), 2.62 (td, J = 12.1, 3.1 Hz), 2.80 (ddd, J = 10.9, 6.7, 2.2 Hz), 3.05 (dt, J = 12.1, 2.0 Hz), 3.9 (d, J = 6.7 Hz), 7.3 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 24.4, 25.7, 28.0, 46.9, 60.4, 62.8, 127.2, 127.4, 128.5, 149.1; HRMS calcd for $C_{12}H_{19}N_2$ (M + 1) 191.1548; found 191.1559.

(2*R*)-2-[(1*S*,5*R*)-7,7-Diphenyl-6,8-diazabicyclo[3.2.1]oct-8-yl]-2-phenylethanol (19). A solution of **1** (0.3 g, 1.31 mmol) and LiBr (0.592 g, 6.81 mmol) in freshly distilled Et_2O (20 mL) was stirred for 10 min at rt and then cooled to −20 °C before addition of phenyl lithium (3.4 mL, 6.8 mmol). The solution was slowly warmed to rt over 1.5 h and then quenched with saturated aq NH_4Cl. The combined organic layers were washed with H_2O, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (SiO_2, CH_2Cl_2/MeOH 98:2) led to compound **19** (0.380 g, 0.98 mmol) as a viscous oil in 75% yield: $[\alpha]_D$ −142 (*c* 1.7, MeOH); IR 3455, 3248, 2944, 2831, 1443, 1423 cm^{-1}; MS (EI) *m/z* (rel intensity) 384 (M^+, 8), 367 (5), 353 (11), 307 (6), 289 (6), 265 (100); ^{1}H NMR ($CDCl_3$) δ 1.4−2.1 (m, 6 H), 3.80, 3.95 (2 m, 3 H), 4.10 (br s); 4.35 (br s), 7.2−7.6 (15 H); ^{13}C NMR ($CDCl_3$) δ 15.6, 20.4, 25.6, 60.1, 62.0, 65.5, 71.8, 72.8, 125.7−128−4, 140.3, 140.9, 154.2. Anal. Calcd for $C_{26}H_{28}N_2O$: C, 80.21; H, 7.34; N, 7.29. Found: C, 80.21; H, 7.34; N, 7.03.

(2*R*)-2-[(2*S*)-2-(Aminodiphenylmethyl)piperidin-1-yl]-2-phenylethanol. (20). A methanolic solution (15 mL) of **19** (0.3 g, 0.78 mmol) and $NaBH_4$ (61 mg, 1.6 mmol) was stirred for 2.5 h at rt and then quenched with saturated aq NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated to yield 96% of pure amino alcohol **20** (0.291 g, 0.75 mmol) as an oil: $[\alpha]_D$ −101 (*c* 1.4, MeOH); IR 3521, 3196, 2366, 2333, 1428 cm^{-1}; MS (EI) *m/z* (rel intensity) 386 (M^+, 17), 355 (3), 265 (17), 204 (100); ^{1}H NMR ($CDCl_3$) δ 0.65−1.15 (4 H), 1.6 (m), 1.80 (m), 2.0 (ddd, J = 14.4, 9.6, 7.2 Hz), 2.53 (ddd, J = 14.4, 4.3, 3.3 Hz), 3.72 (dd, J = 15.6, 8.2 Hz), 4.0 (m, 2 H), 4.22 (t, J = 7.5 Hz), 7.2−7.5 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 19.7, 21.0, 23.7, 40.7, 63.5, 63.7, 66.8, 71.1, 126.0−129.0, 141.4, 144.1, 147.7; HRMS calcd for $C_{26}H_{30}N_2O$ 386.2356, found: 386.2355.

***N*-[[(2*S*)-1-[(1*R*)-2-Hydroxy-1-phenylethyl]piperidin-2-yl]diphenylmethyl]-2,2,2-trifluoroacetamide (21).** A solution of amino alcohol **20** (1 g, 2.59 mmol) in CH_2Cl_2 (30 mL) was stirred for 4 h at 20 °C with trifluoroacetic anhydride (0.43 mL, 3.10 mmol) and triethylamine (0.73 mL, 5.18 mmol) and then quenched with saturated aq NH_4Cl. The general workup procedure gave an oily residue which was purified by flash chromatography (SiO_2, CH_2Cl_2). Pure compound **21** was isolated in 79% yield as a colorless oil (0.99 g, 2.04 mmol): $[\alpha]_D$ −18.4 (*c* 1, $CHCl_3$); IR 3420, 3250, 3100, 1750 cm^{-1}; MS (EI) *m/z* (rel intensity) 483 (M + 1, 25), 345 (20), 297 (30), 204 (100); ^{1}H NMR ($CDCl_3$) δ 1.2−1.7 (m, 7 H), 2.11 (br d, J = 14.7 Hz), 3.87, 4.21 (2 br d, J = 12.0 Hz), 4.10 (dd, J = 4.0, 3.8 Hz), 4.42 (dd, J = 6.7, 6.0 Hz), 7.1−7.5, 7.6 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 18.3, 19.1, 21.3, 42.1, 60.8, 64.2, 67.6, 68.0, 127.4−129.8, 141.0, 141.2.

Diphenyl[(2*S*)-piperidin-2-yl]methanamine (22). A solution of trifluoroacetamide **21** (0.85 g, 1.76 mmol) in MeOH (12 mL) was acidified with concentrated HCl (4 mL) and stirred for 1 h under hydrogene atmosphere with 10% activated palladium on charcoal (100 mg). After filtration over Celite, the mixture was heated directly under reflux in diluted aqueous HCl (6 N, 20 mL) for 12 h. 2-Phenylethanol and trifluoroacetic acid byproducts were extracted of the crude mixture with CH_2Cl_2. Aqueous layer was concentrated under vacuo (up to 5 mL), then neutralized (pH 7) and extracted following the usual work-up procedure. Pure diphenylamine **22** was then isolated as a colorless oil in 60% yield (0.28 g, 1.05 mmol): $[\alpha]_D$ −28.6 (*c* 0.5, $CHCl_3$); IR 3317, 3057, 2932, 2852, 1596 cm^{-1}; MS (EI) *m/z* (rel intensity) 267 (M + 1, 20), 250 (25), 182 (26), 165 (12), 104 (54), 85 (67), 84 (100); ^{1}H NMR ($CDCl_3$) δ 1.20−1.80 (m, 6 H), 1.95 (br s, NH, NH_2), 2.68 (td, J = 11.5, 2.7 Hz), 3.05 (br d, J = 11.5 Hz), 3.49 (dd, J = 10.5, 2.0 Hz), 7.35, 7.5 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 25.4, 26.8, 27.1, 47.8, 63.5, 63.8, 126.8−129.2, 146.0, 146.8; HRMS calcd for $C_{18}H_{23}N_2$ 267.1860, found 267.1854.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **5**, **9**, **11c**, **13a−c**, **14c**, **15b**, **16b**, **18c**, and **20−22** (26 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

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