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Practical Asymmetric Synthesis of 1,2-Diamines in the 3-Aminoazepane Series

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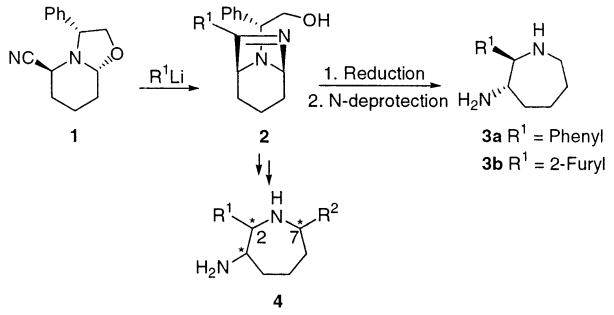
A simple and versatile method for the enantio- and diastereoselective synthesis of mono- or disubstituted 3-aminoazepanes is described. The key step involves a highly regio- and diastereoselective tandem ring-enlargement/alkylation or reduction process. This novel synthetic route provides enantiomerically pure constrained diamines interesting as scaffolds for medicinal chemistry.

Introduction

Vicinal diamines and their derivatives have been shown to play key roles in medicinal chemistry, coordination chemistry, and asymmetric catalysis.[1] Among this family, constrained diamine systems continue to attract synthetic interest due to their wide potential as medicinal agents. Novel polyamino derivatives recently reported as potential contrast enhancement agents in MRI have displayed considerable improvement of in vivo stability and biodistribution relative to nonrigid gadolinium(III) complexes.[2] Various CNS receptor ligands[3] and antitumor chiral *cis*-platin analogues[4] have been developed in the 3-aminoazepane series. Although various synthetic pathways have been devised for the preparation of functionalized azepanes,[5] a straightforward access to enantiopure polysubstituted 3-aminoazepanes, as general scaffolds for the elaboration of bioactive compounds, would be desirable.

In previous preliminary synthetic studies, we reported the asymmetric synthesis of optically pure *trans*-2-phenyl- and 2-furyl-3-aminoazepanes **3a,c** from 2-cyano-6-oxazolopiperidine **1**.[6] The key step involved a one-pot reduction and ring-enlargement process of intermediates **2** occurring in a totally regio- and diastereoselective manner (Scheme 1).

SCHEME 1



We report in this article our full investigations in this field, as well as the generalization of this original ring-enlargement reaction for the diastereo- and enantioselective preparation of 2,7-disubstituted 3-aminoazepanes **4**.

Results and Discussion

Synthesis of 2-Substituted 3-Aminoazepanes. Multigram quantities of bicyclic imines **2** can be prepared in one step from 2-cyano 6-oxazolopiperidine **1**[7] in yields ranging from 74% to 97% (Scheme 2).

These stable compounds are key intermediates for the ring-enlargement strategy. Under protic conditions, reac-

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(3) (a) Matecka, D.; Rothman, R. B.; Radesca, L.; De Costa, B. R.; Dersch, C. M.; Partilla, J. S.; Pert, A.; Glowa, J. R.; Wojnicki, H. E.; Rice, K. C. *J. Med. Chem.* **1996**, *39*, 4704. (b) Hirokawa, Y.; Morie, T.; Yamazaki, H.; Yoshida, N.; Kato, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 619. (c) Zhao, S.; Freeman, J. P.; Bacon, C. L.; Fox, G. B.; O'Driscoll, E.; Foley, A. G.; Kelly, J.; Farrell, U.; Regan, C.; Mizsak, S. A.; Szmuszkovicz, J. *Bioorg. Med. Chem.* **1999**, *7*, 1647.
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(5) (a) Meyers, A. I.; Downing, S. V.; Weiser, M. J. *J. Org. Chem.* **2001**, *66*, 1413. (b) Chong, H.-S.; Ganguly, B.; Broker, G. A.; Rogers, R. D.; Brechbiel, M. W. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2080 and references therein. (c) Kantorowski, E. J.; Kurth, M. J. *Tetrahedron* **2000**, *56*, 4317. (d) Evans, A. P.; Robinson, J. E. *Org. Lett.* **1999**, *1*, 1929.
(6) Cutri, S.; Bonin, M.; Micouin, L.; Froelich, O.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **2000**, *41*, 1179.
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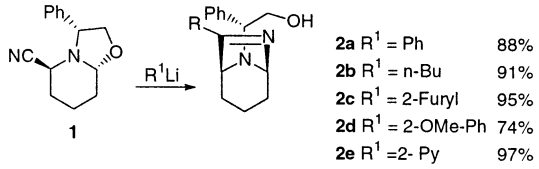
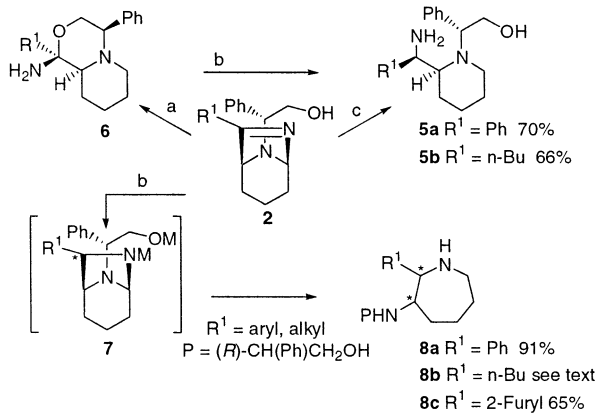
SCHEME 2[a]



[a] Reagents and conditions: R^1 = Ph, ^{n}Bu, 2-Py/R^1Li, Et_2O, −78 °C; R^1 = 2-OMe-Ph, 2-furyl/R^1Li, TMEDA, THF, −78 °C.

SCHEME 3[a]



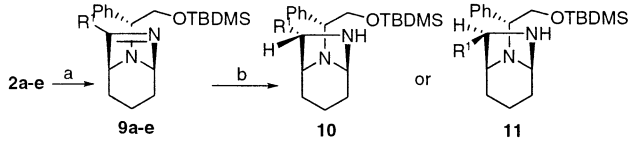
[a] Reagents and conditions: (a) $NaBH_3CN$, H^+, THF, MeOH; (b) LAH, Et_2O; (c) $NaBH_4$, MeOH.

tion of butyl or phenyl derivatives **2a,b** with $NaBH_4$ or $NaBH_3CN$ have been reported to give piperidines **5** or morpholines **6**, respectively, in a high diastereoselective manner (Scheme 3).[8]

Treatment of the same imines with LAH led to a completely different 1,2-diamine system. No trace of six-membered ring derivatives could be observed starting from aromatic conjugated imines **2a,c**. However, in the butyl series an inseparable mixture of compounds **8b** and **5b** was obtained. The best conditions were found by adding LAH carefully to an ether solution of the imine (20 °C, 3 h; **8b**/**5b** = 9/1). The different issues of reductions can be explained by chemoselective nitrogen activation. On the one hand, activation of the secondary aminal nitrogen under protic conditions leads to a six-membered ring; on the other hand, activation of the piperidine nitrogen under Lewis acidic conditions leads to the ring enlargement. The lack of selectivity observed in the aliphatic series probably relies on the formation of a transient morpholine **6b**, known to be reduced into piperidine systems by LAH. This morpholine was indeed isolated when LAH reduction of **2b** was performed at low temperature (−78 °C).

Since the ring enlargement proceeds by a two-step reduction, isolation of the transient aminal should allow selective functionalization at the C-7 azepane position by a nucleophilic opening with a suitable organometallic nucleophile instead of a hydride. Before selective reductions trials, the alcohol function was first protected in order to avoid the formation of morpholine-type intermediates. Various aryl and alkyl imines **2a**−**e** were thus

SCHEME 4[a]



[a] Reagents and conditions: (a) NaH, TBDMSCl, 94% (R = Ph), 86% (R = ^{n}Bu), 81% (R= 2-OMe-Ph), 95% (R = 2-Py); (b) see Table 1.

TABLE 1. Diastereoselective Access to Aminals 10 or 11

product[a]	R^1	conditions	**10**:**11**	yield (%)[b]
11a	Ph	Li/NH_3	19:81	64
11b	^{n}Bu	LAH	<5:95	65
11d	2-MeOPh	LAH	<5:95	74
10e	2-Py	H_2, Pd/C	98:2	68

[a] Major diastereomer. [b] Yield of diastereomerically pure compound.

prepared and protected as O-silylated compounds **10a**−**e** in 70−90% yield (Scheme 4).

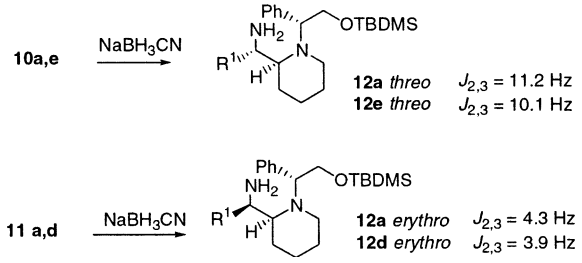
Selective imine reductions proved to be particularly troublesome and highly dependent on their substitution patterns. Our first attempts to reduce **9a** using LAH under various experimental conditions led to either irreproducible results or the known desilylated azepane derivative **8a**. More encouraging results were obtained using dissolving-metal conditions.[9] Treatment of **9a** with lithium in liquid ammonia afforded, in a first experiment, a mixture of aminals **10a** and **11a** in a 1/1 ratio. Careful optimization of the reprotonation conditions improved this ratio significantly in favor of the **11a** isomer, leading to pure material in 64% yield (Table 1). The presence of a bicyclic aminal could be ascertained by typical NMR chemical shifts (a doublet at 4.58 ppm and a peak at 60.5 ppm observed, respectively, in the ^{1}H and the ^{13}C NMR spectra were attributed to the C-7 reduced position, two broad deshielded proton signals consistent with the searched bicyclic aminal system). Absolute configuration of the newly created asymmetric center was determined unambiguously by chemical transformation of **11a** into O-silylated piperidine derivative **12a** by acidic $NaBH_3$-CN reduction.[7] In the 2-methoxyphenyl series, simple LAH reduction afforded the corresponding aminal **11d** with reasonable yield and high diastereoselectivity, without over-reduction into the corresponding azepane. Both methods failed when applied to the pyridinyl imine **9e** reduction. LAH reduction led only to desilylation or degradation material, whereas lithium or sodium in liquid ammonia gave an inseparable mixture of aminals **10e** and **11e** (60:40 ratio, 95% yield). Pd-catalyzed hydrogenation in various solvents was therefore investigated. The hydrogenation of the imine in ethyl acetate afforded the corresponding aminals **10e** and **11e** as an equimolar mixture, whereas in methanol, the major derivative **10e** could be isolated in a diastereomerically pure form. Finally, **11b** could be obtained as a single diastereomer after LAH reduction.

In each case, ^{1}H and ^{13}C NMR spectra revealed characteristic signals of bridged bicyclic structures as

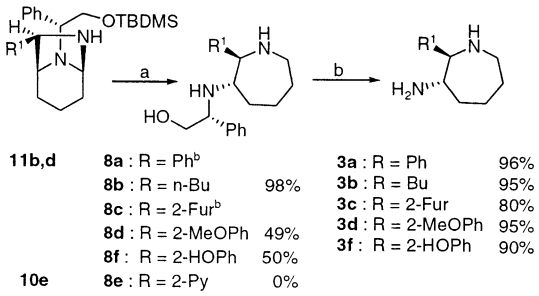
(8) Froelich, O.; Desos, P.; Bonin, M.; Quirion, J.-C.; Husson, H.-P. *J. Org. Chem.* **1996**, *61*, 6700.

(9) Corey, E. J.; Imwinkelried, R.; Pikul S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493.

SCHEME 5



SCHEME 6[a]



[a] Reagents and conditions: (a) LAH, $^{i}Pr_2O$ or Et_2O, reflux; (b) H_2, Pd/C, MeOH−HCl for **8a,b,d,f** or H_5IO_6 (2.6 equiv), $MeNH_2$, H_2O, MeOH, then MeOH−HCl for **8c**. [b]From **2a,c** via one-step reduction (Scheme 3).

shown above. However, the relative configuration of the newly created stereogenic center (C-7) could not be determined directly from the NMR data. This was achieved by correlation with the corresponding *erythro* (J = 3.9−4.3 Hz) or *threo* (J = 10.1−11.2 Hz) O-silylated aminoalkyl piperidines **12** after acidic $NaBH_3CN$ aminal reduction of analytical samples (Scheme 5).

Since bicyclic aminals are believed to be intermediates in the one-step ring enlargement process, their reduction with LAH should lead to the known azepanes **8**. This was indeed the case, although this transformation required harsher reaction conditions than with the direct imine reduction. LAH treatment of aminal **11d** in refluxing diisopropyl ether afforded in a diastereoselective manner the desilylated and demethylated azepane **8f** with the desired azepane cyclic core **8d** as a minor side product (**8d**/**8f** = 25/75).[10]Using milder conditions (refluxing in diethyl ether), the desired product **8d** was obtained as the major product (**8d**/**8f** = 80/20). Unfortunately, presence of a pyridine ring seemed to inhibit the ring-enlargement process. Finally, unprotected 2-substituted 3-amino azepanes were obtained in good yield after hydrogenolysis or oxidative cleavage. Interestingly, using this two-step process, diamine **8b** could be obtained in good yield and total diastereoselectivity, without any six-membered ring contaminants. Once again, the *trans* relative configuration of such azepanes could be ascertain by the typical H-2/H-3 coupling constant of 9 Hz.

Synthesis of 2,7-Disubstituted 3-Aminoazepanes. During the ring-enlargement process, a transient seven-membered imine was reduced by a hydride. However, the use of a Lewis acidic nucleophile should lead to the same reactive species from bicyclic aminals **10** or **11** and enable further functionalizations of the azepane at the C-7 position. Although the reactivity of such aminals is unknown, the related reaction of nucleophilic reagents, especially organomagnesium compounds, with oxazolidines is well-documented.[11] Initial experiments were performed on phenylaminal **11a**, using methylmagnesium bromide as a nucleophile and a Lewis acid (Table 2). The best results were obtained via refluxing **11a** in ether with an excess of organomagnesium reagent (3.5 equiv), leading to compound **14a** in 57% yield as a single diastereomer. The formation of a ring-enlarged derivative could be ascertained by typical NMR data: ^{13}C NMR spectrum displayed the three CH peaks at 49.5, 62.2, 62.8 ppm and one methyl signal at 23.4 ppm as expected from the alkylation process. The ^{1}H NMR spectrum showed a multiplet at 2.90 ppm for the C-7 proton and a doublet at δ 3.82 ppm for the C-2 proton.

SCHEME 7

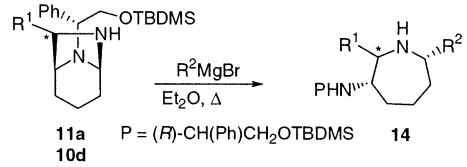


TABLE 2. Diastereoselective Access to Polysubstituted Azepanes 14

product	R^1	R^2	yield (%)[a]	de (%)[b]
14a	Ph (2*R*)	Me	57	>95
14b	Ph (2*R*)	^{i}Bu	84	>95
14c	Ph (2*R*)	Bn	95	>95
14d	2-Py (2*R*)	Me	69	>95
14e	2-Py (2*R*)	^{i}Bu	70	>95
14f	2-Py (2*R*)	Bn	65	>95

[a] Yield of diastereomerically pure compound. [b] Determined by ^{1}H NMR of the crude reaction mixture.

The use of *iso*-butyl as well as benzyl Grignards as nucleophiles afforded exclusively ring-enlarged derivatives **14b,c** in diastereomerically pure form. Interestingly, no reduction product arising from an hydride transfer with the branched organomagnesium reagent could be detected. Unlike the LAH reduction of aminals **11b,d**, the ring enlargement occurred without any O-desilylation. Final compounds **4a,b,c** could be obtained after desilylation and hydrogenolysis. Following standard procedure, benzylazepane **4c** was finally converted to crystalline benzamide **15**, and its relative configuration was determined by X-ray crystallography analysis. The 3,7-*cis* configuration could be attributed to derivatives **4a,b** by comparisons of their ^{1}H and ^{13}C NMR spectra.

The same ring-enlargement reactions were then performed starting from pyridyl aminal **10e**, to study the

(10) Such reductive demethylation has been previously described on *ortho*-substituted methoxyphenols: Kimura, K.; Tanaka, M.; Iketani S.-I.; Shono, T. *J. Org. Chem.* **1987**, *52*, 836.

(11) (a) For a general review on aminals preparation, see: Pawlenko, S.; Lang-Fugmann, S. In *Houben-Weyl Methoden der Organische Chemie*; Hageman, H., Klaman, D., Eds.; Georg Thieme Verlag: Stuttgart, 1992, E14a/3. Aminals as chiral auxiliary: (b) Alexakis, A.; Mangeney, P.; Nelsen, N.; Tranchier, J. P.; Gosmini, R.; Raussou, S. *Pure Appl. Chem.* **1996**, *68*, 531. (c) Jung, M. E.; Huang, A. *Org. Lett.* **2000**, *2*, 2659. Nucleophilic opening of oxazolidines: (d) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (e) Enders, D.; Reinhold: U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. (f) Steinig, A. G.; Spero, D. M. *Org. Prep. Proc. Int.* **2000**, *32*, 205.

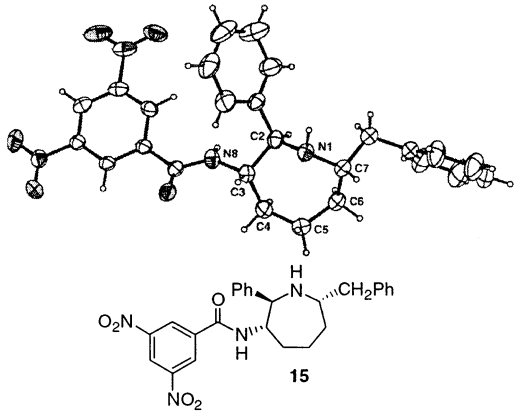


FIGURE 1. X-ray structure of derivative **15**.

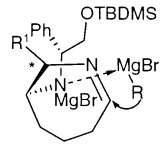
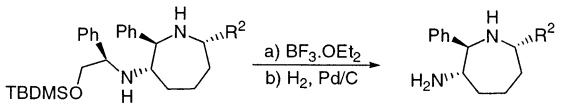


FIGURE 2. Origin of the relative configuration of disubstituted aminoazepanes.

SCHEME 8



14a : R^2 = Me	**4a** : R^2 = Me 70%
14b : R^2 = *i*-Bu	**4b** : R^2 = *i*-Bu 77%
14c : R^2 = Bn	**4c** : R^2 = Bn 81%

influence of each stereogenic center on the stereochemical outcome of this reaction. Compounds **14d,e,f** were obtained in good yields as single diastereomers. Once again, a 3,7-*cis* configuration could be established for compound **14f** by NOE experiments on its desilylated derivative and attributed to the other compounds by comparisons of their ^{1}H and ^{13}C NMR spectra.

Alkylations are therefore totally diastereoselective. Surprisingly, the stereochemical outcome is independent of the C-2 stereogenic center configuration, unlike previous examples in the piperidine series.[12] The 3,7-*cis* configuration could be explained by a mechanism involving an intramolecular delivery of nucleophile in an early transition state (Figure 2).

In summary, we have developed a simple and versatile method for the rapid elaboration of 2-mono- or 2,7-disubstituted 3-aminoazepanes. We have shown that bicyclic aminals are powerful synthetic intermediates in allowing a tandem ring-enlargement/alkylation process in a highly regio- and diastereoselective manner. This novel synthetic route leads to various enantiomerically constrained diamines interesting as scaffolds for medicinal chemistry. Application of this method to the preparation of biologically active compounds is currently underway in our laboratory.

Experimental Section

General Methods. ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 MHz) were recorded in $CDCl_3$ or CD_3OD solution. IR spectra were recorded as thin film unless otherwise stated. Mass spectral data were recorded in chemical-ionization (CI) mode. Tetrahydrofuran (THF) and ether (Et_2O or $^iPr_2O$) were distilled from sodium/benzophenone immediately prior to use; CH_2Cl_2, TMEDA, Et_3N, MeOH, $CHCl_3$ were distilled from CaH_2. Compounds **1**, **2a**, **2b**, **3a**, **3c** were prepared according to previously reported procedures.[6−8]

(1*S*,5*S*)-2-[7-(2-Methoxyphenyl)-6,8-diazabicyclo[3.2.1]-oct-6-en-8-yl]-(2*R*)-phenyl-ethanol 2d. Anisole (4.28 mL, 39.5 mmol) was added to a cold (0 °C) mixture of *n*-butyllithium (1.6 M in hexanes, 16.4 mL, 26 mmol) and TMEDA (3.96 mL, 26.3 mmol) in THF (20 mL) under an atmosphere of Ar. The reaction mixture was maintained at 20 °C for 45 min and then cooled to −78 °C. A solution of 2-cyano-6-phenyloxazolopiperidine (**1**) (2.0 g, 8.8 mmol) in THF (20 mL) was added, and the reaction mixture was allowed to warm to room temperature and maintained overnight. The reaction mixture was cautiously diluted with a saturated, aqueous solution of NH_4Cl, extracted with CH_2Cl_2 (2 ×), and the combined organic layers were dried ($MgSO_4$). The solvent was evaporated to give an oily residue. The residue was purified by chromatography (CH_2Cl_2/MeOH 95/5) to provide imine **2d** (yellow oil, 2.18 g, 74%). $[\alpha]_D = +46$ (*c* 1.4, CH_2Cl_2); IR (neat) 3326, 2940, 1656, 1599 cm^{-1}; MS *m*/*z* 337 (MH^+); ^{1}H NMR ($CDCl_3$) δ 1.20−1.80 (m, 6H), 3.52 (t, J = 4.8 Hz, 1H), 3.53 (s, 3H), 3.77 (dd, J = 11.1, 4.3 Hz, 1H), 3.87 (dd, J = 11.1, 5.2 Hz, 1H), 4.22 (t, J = 2.9 Hz, 1H), 5.45 (t, J = 2.6 Hz, 1H), 6.83 (d, J = 7.4 Hz, 1H), 6.94 (td, J = 7.7, 0.9 Hz, 1H), 7.21−7.33 (m, 5H), 7.37 (td, J = 7.7, 1.7 Hz, 1H), 7.79 (dd, J = 7.7, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.0, 24.4, 26.0, 55.0, 65.1, 65.9, 68.0, 84.3, 111.2, 120.7, 121.6, 127.4, 128.3, 128.5, 130.6, 132.1, 141.1, 158.6, 172.2.

(1*S*,5*S*)-2-(7-Furan-2-yl-6,8-diazabicyclo[3.2.1]oct-6-en-8-yl)-(2*R*)-phenyl-ethanol 2c. Yellow oil, 2.47 g, 95%; $[\alpha]_D$ = −11 (*c* 1.1, CH_2Cl_2); IR (neat) 3320, 2947, 1622 cm^{-1}; MS *m*/*z* 297 (MH^+); ^{1}H NMR ($CDCl_3$) δ 1.20−1.85 (m, 6H), 3.47 (t, J = 4.7 Hz, 1H), 3.78 (dd, J = 11.1, 4.2 Hz, 1H), 3.85 (t, J = 2.9 Hz, 1H), 3.92 (dd, J = 11.1, 5.2 Hz, 1H), 5.50 (t, J = 2.9 Hz, 1H), 6.46 (dd, J = 3.4, 1.5 Hz, 1H), 6.67 (d, J = 3.4 Hz, 1H), 7.25−7.35 (m, 5H), 7.51 (t, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.7, 25.3, 25.4, 64.6, 65.8, 66.3, 86.2, 111.9, 114.4, 127.8, 128.4, 128.6, 140.2, 145.4, 162.4.

(1*S*,5*S*)-2*R*-Phenyl-2-(7-pyridin-2-yl-6,8-diazabicyclo-[3.2.1]oct-6-en-8-yl)-ethanol 2e. ^{n}BuLi (21.9 mL, 1.6 M in hexanes, 35.1 mmol) was added to a stirred solution of 2-bromopyridine (4.48 mL, 46.8 mmol) in anhydrous Et_2O (30 mL) at −70 °C under argon. After 30 min a solution of 2-cyano-6-phenyl-oxazolopiperidine **1** (2 g, 8.77 mmol) in Et_2O (10 mL) was added. The mixture was stirred at −70 °C for 5 h. The reaction mixture was cautiously diluted with a saturated, aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (2 ×), and the combined organic layers were dried ($MgSO_4$). The residue was purified by chromatography (CH_2Cl_2/MeOH 95/5) to provide **2c** (amorphous yellow solid, 2.61 g, 97%). $[\alpha]_D$ = −44 (*c* 1.1, CH_2Cl_2); IR (neat) 3330, 2945, 2871, 1609, 1586 cm^{-1}; MS *m*/*z* 308 (MH^+); ^{1}H NMR ($CDCl_3$) δ 1.13−1.92 (m, 6H), 3.57 (t, J = 5.4 Hz, 1H), 3.85 (d, J = 5.4 Hz, 1H), 4.38 (t, J = 2.9 Hz, 1H), 5.49 (t, J = 2.5 Hz, 1H), 7.13−7.24 (m, 5H), 7.29 (ddd, J = 7.7, 4.8, 1.5 Hz, 1H), 7.68 (td, J = 7.7, 1.5 Hz, 1H), 7.96 (br. d, J = 7.7 Hz, 1H), 8.53 (br. d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.0, 24.7, 25.1, 64.0, 65.1, 66.4, 87.2, 122.1, 124.9, 127.6, 128.2, 128.4, 136.3, 139.8, 149.2, 151.3, 173.2.

General Procedure for the Preparation of O-Silylated Imines 9. The preparation of imine **9a** is representative. NaH (60% suspension in mineral oil, 614 mg, 15.4 mmol) was added at 0 °C under argon to a stirred solution of imine **2a** (2.36 g, 7.71 mmol) in THF (94 mL). After 30 min at room temperature, *tert*-butyldimethylsilyl chloride (2.33 g, 15.4 mmol) was added. The resulting mixture was stirred for an additional 16 h at 20 °C. The reaction mixture was cautiously diluted with a saturated, aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (2 ×), and the combined organic layers were dried ($MgSO_4$).

(12) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289.

The residue was purified by flash chromatography (cyclohexane/AcOEt 1/1, then 2/8, then AcOEt) to provide **9a** as a yellow oil (3.04 g, 94%).

(1*S*,5*S*)-8-[2-(*tert*-Butyl-dimethyl-silanyloxy)-(1*R*)-phenyl-ethyl]-7-phenyl-6,8-diazabicyclo[3.2.1]oct-6-ene 9a. Oil, $[\alpha]_D = +10$ (*c* 0.9, CH_2Cl_2); IR (neat) 2951, 2858, 1605 cm^{-1}; MS *m*/*z* 421 (MH^+); ^1H NMR ($CDCl_3$) δ −0.22 (s, 3H), −0.17 (s, 3H), 0.71 (s, 9H), 1.11−1.78 (m, 6H), 3.32 (t, $J = 5.6$ Hz, 1H), 3.63 (dd, $J = 10.3$, 5.6 Hz, 1H), 3.82 (t, $J = 2.9$ Hz, 1H), 3.88 (dd, $J = 10.3$, 5.6 Hz, 1H), 5.54 (t, $J = 2.7$ Hz, 1H), 7.14−7.37 (m, 8H), 7.61 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −1.5, −0.5, 16.9, 24.8, 18.2, 25.9, 66.5, 68.0, 86.0, 127.4, 128.0, 128.4, 128.7, 130.9, 132.5, 142.8, 150.2, 171.8.

(1*S*,5*S*)7-Butyl-8-[2-(*tert*-butyl-dimethyl-silanyloxy)-(1*R*)-phenyl-ethyl]-6,8-diazabicyclo [3.2.1]oct-6-ene 9b. Yellow oil, 2.65 g, 86%; $[\alpha]_D = -18$ (*c* 1.8, CH_2Cl_2); IR (neat) 2954, 2856, 1636 cm^{-1}; MS *m*/*z* 401 (MH^+); ^1H NMR ($CDCl_3$) δ −0.26 (s, 3H), 0.20, (s, 3H), 0.70 (s, 9H), 0.83 (t, $J = 7.3$ Hz, 1H), 1.10−1.80 (m, 10H), 2.13 (m, 1H), 2.27 (m, 1H), 3.24 (m, 2H), 3.57 (dd, $J = 10.2$, 6.0 Hz, 1H), 3.84 (dd, $J = 10.2$, 5.4 Hz, 1H), 5.27 (br. s, 1H), 7.02−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.3, 14.1, 18.3, 18.5, 23.0, 24.4, 25.2, 26.1, 28.4, 31.2, 66.8, 68.2, 68.5, 85.4, 127.5, 128.5, 128.8, 128.9, 142.1, 177.2.

(1*S*,5*S*)-8-[2-(*tert*-Butyl-dimethyl-silanyloxy)-(1*R*)-phenyl-ethyl]-7-(2-methoxy-phenyl)-6,8-diazabicyclo[3.2.1]oct-6-ene 9d. Yellow oil, 2.81 g, 81%; $[\alpha]_D = +72$ (*c* 1.0, CH_2Cl_2); IR (neat) 2951, 2855, 1600 cm^{-1}; MS *m*/*z* 451 (MH^+); ^1H NMR ($CDCl_3$) δ −0.17 (s, 3H), −0.10 (s, 3H), 0.77 (s, 9H), 1.20−1.90 (m, 6H), 3.47 (t, $J = 5.6$ Hz, 1H), 3.53 (s, 3H), 3.68 (dd, $J = 10.2$, 5.8 Hz, 1H), 3.94 (dd, $J = 10.2$, 5.4 Hz, 1H), 4.13 (t, $J = 3.5$ Hz, 1H), 5.56 (t, $J = 2.6$ Hz, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 6.96 (td, $J = 7.5$, 0.9 Hz, 1H), 7.16−7.37 (m, 5H), 7.86 (dd, $J = 7.7$, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −1.5, 17.0, 18.3, 24.3, 25.9, 54.9, 66.4, 68.3, 68.8, 84.5, 111.3, 120.7, 122.4, 127.0, 128.0, 128.8, 130.4, 131.8, 142.4, 158.8, 171.9.

(1*S*,5*S*)-8-[2-(*tert*-Butyl-dimethyl-silanyloxy)-1*R*-phenyl-ethyl]-7-pyridin-2-yl-6,8-diazabicyclo[3.2.1]oct-6-ene 9e. Yellow oil, 3.08 g, 95%; $[\alpha]_D = -1$ (*c* 1.4, CH_2Cl_2); IR (neat) 2950, 2927, 2855, 1607 cm^{-1}; MS *m*/*z* 422 (MH^+); ^1H NMR ($CDCl_3$) δ −0.19 (s, 3H), −0.16 (s, 3H), 0.75 (s, 9H), 1.06−1.85 (m, 6H), 3.37 (t, $J = 5.6$ Hz, 1H), 3.64 (dd, $J = 10.3$, 5.6 Hz, 1H), 3.90 (dd, $J = 10.3$, 5.6 Hz, 1H), 4.13 (t, $J = 2.9$ Hz, 1H), 5.67 (t, $J = 2.5$ Hz, 1H), 7.12−7.26 (m, 6H), 7.88 (td, $J = 7.8$, 1.7 Hz, 1H), 8.10 (d, $J = 7.8$ Hz, 1H), 8.48 (dt, $J = 4.8$, 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −1.5, 17.0, 18.2, 24.4, 24.6, 25.9, 66.4, 66.9, 68.1, 86.3, 122.3, 124.9, 127.2, 128.3, 128.5, 136.4, 140.6, 149.4, 152.0, 173.3.

Preparation of Aminal 11a. NH_3 (3.5 mL) was condensed at −78 °C under argon onto a stirred solution of **9a** (500 mg, 1.19 mmol) in THF (2.5 mL). After addition of small pieces of lithium (25 mg, 3.56 mmol), stirring was continued for 3 h. A solution of anhydrous *tert*-butyl alcohol (527 mg, 7.13 mmol) in THF (10 mL) was then added dropwise at −40 °C. The reaction mixture was allowed to warm gradually to ambient temperature with stirring for the slow evaporation of NH_3. After addition of solid NH_4Cl (763 mg, 14.3 mmol), the reaction mixture was filtered through a Celite bed, and the organic layers were dried over $MgSO_4$ and concentrated to give a mixture of diastereomers (**11a**/**10a**, 81/19). The residue was purified by chromatography (AcOEt/MeCN/NH_4OH, 246/3/1) to provide the major compound **11a** as a yellow oil (321 mg, 64%).

(1*S*,5*S*)-8-[2-(*tert*-Butyl-dimethyl-silanyloxy)-(1*R*)-phenyl-ethyl]-(7*R*)-phenyl-6,8-diazabicyclo[3.2.1]octane 11a. Oil; $[\alpha]_D = -5$ (*c* 1.0, CH_2Cl_2); IR (neat) 3427, 2928, 2855, 1493 cm^{-1}; MS *m*/*z* 423 (MH^+); ^1H NMR ($CDCl_3$) δ −0.20 (s, 3H), −0.16 (s, 3H), 0.72 (s, 9H), 0.98−1.79 (m, 6H), 2.53 (br. s, 1H), 3.19 (br. s, 1H), 3.59 (m, 2H), 3.88 (dd, $J = 11.7$, 7.6 Hz, 1H), 4.58 (d, $J = 5.8$ Hz, 1H), 4.74 (br. s, 1H), 7.0−7.34 (m, 10H); ^{13}C NMR ($CDCl_3$) δ −1.4, −1.5, 16.4, 18.3, 26.0, 26.8, 33.5, 60.7, 62.0, 65.9, 69.2, 74.7, 125.8, 127.1, 127.5, 127.8, 128.4, 128.6, 141.6, 142.1.

Preparation of Aminal 11b,d. The preparation of aminal **11d** is representative. To a solution of imine **9d** (500 mg, 1.11 mmol) in Et_2O (25 mL) under argon was carefully added $LiAlH_4$ (329 mg, 8.67 mmol). The reaction mixture was stirred 3 h at room temperature and then treated successively with aqueous NaOH (1 N, 658 mL) and H_2O (987 μL). After filtration through Celite, the organic phase was concentrated in vacuo. The residue was purified by flash chromatography (AcOEt/MeCN/NH_4OH, 237/12/1) to provide **11d** as a colorless oil (371 mg, 74%).

(1*S*,5*S*)-8-[2-(*tert*-Butyl-dimethyl-silanyloxy)-(1*R*)-phenyl-ethyl]-(7*R*)-(2-methoxy phenyl)-6,8-diazabicyclo[3.2.1]-octane 11d. Oil; $[\alpha]_D = +12$ (*c* 0.8, CH_2Cl_2); IR (neat) 3320, 2952, 2926, 1492 cm^{-1}; MS *m*/*z* 453 (MH^+); ^1H NMR ($CDCl_3$) δ −0.17 (s, 3H), −0.12 (s, 3H), 0.74 (s, 9H), 0.80−1.78 (m, 6H), 2.43 (s, 1H), 3.43 (br. s, 3H), 3.36−3.47 (m, 1H), 3.60−3.73 (m, 2H), 3.93 (br. s, 1H), 4.58 (d, $J = 4.1$ Hz, 1H), 4.67 (br. s, 1H), 6.63 (d, $J = 7.3$ Hz, 1H), 6.86 (t, $J = 7.3$ Hz, 1H), 7.08 (td, $J = 7.6$, 1.4 Hz, 1H), 7.17−7.38 (m, 5H), 7.97 (d, $J = 7.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −1.4, −1.5, 16.3, 18.3, 25.9, 29.8, 33.4, 54.9, 57.8, 60.3, 66.6, 69.1, 74.3, 109.5, 120.0, 127.0, 127.3, 128.1, 128.5, 128.8, 130.2, 141.7, 156.6.

(1*S*,5*S*)-7*R*-Butyl-8-[2-(*tert*-butyl-dimethyl-silanyloxy)-(1*R*)-phenyl-ethyl]-6,8-diazabicyclo[3.2.1]octane 11b. Colorless oil, 290 mg, 65%; $[\alpha]_D = +6$ (*c* 1.0, CH_2Cl_2); IR (neat) 2954, 2929, 2857, 1463 cm^{-1}; MS *m*/*z* 403 (MH^+); ^1H NMR ($CDCl_3$) δ -0.22 (s, 3H), −0.17 (s, 3H), 0.72 (s, 9H), 0.81 (t, $J = 7.1$ Hz, 1H), 0.96−1.91 (m, 12H), 2.76 (br. s, 1H), 2.80 (br. s, 1H), 3.22 (dt, $J = 8.7$, 5.3 Hz, 1H), 3.55 (m, 2H), 3.82 (dd, $J = 12.2$, 7.7 Hz, 1H), 4.56 (br. s, 1H), 7.11−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −1.6, −1.5, 14.1, 17.3, 18.2, 23.0, 25.9, 26.1, 30.4, 31.0, 32.4, 58.0, 59.6, 65.9, 69.0, 73.8, 127.2, 128.2, 128.5, 141.7.

Preparation of Aminal 10e. A solution of **9e** (929 mg, 2.20 mmol) in dry methanol (36 mL) containing palladium catalyst (10% Pd/C, 186 mg) was stirred at room temperature under hydrogen atmosphere. After 48 h, catalyst was removed by filtration through Celite, and the solvent removed in vacuo. The residue was purified by flash chromatography (AcOEt/MeCN/NH_4OH, 237/12/1) to provide **10e** as a pale yellow amorphous solid (633 mg, 68%).

(1*S*,5*S*)-8-[2-(*tert*-Butyl-dimethyl-silanyloxy)-(1*R*)-phenyl-ethyl]-(7*R*)-pyridin-2-yl-6,8-diazabicyclo[3.2.1]-octane 10e. Amorphous; $[\alpha]_D = -31$ (*c* 1.4, CH_2Cl_2); IR (neat) 3299, 2929, 2857, 1592 cm^{-1}; MS *m*/*z* 424 (MH^+); ^1H NMR ($CDCl_3$) δ −0.15 (s, 3H), −0.13 (s, 3H), 0.78 (s, 9H), 1.51−1.94 (m, 7H), 3.21 (br. s, 1H), 3.38 (t, $J = 5.5$ Hz, 1H), 3.44 (dd, $J = 10.2$, 5.2 Hz, 1H), 3.80 (dd, $J = 10.2$, 5.7 Hz, 1H), 4.15 (br. s, 1H), 4.98 (br. s, 1H), 6.61 (d, $J = 6.8$ Hz, 1H), 6.92−7.06 (m, 4H), 7.10 (dd, $J = 7.5$, 4.9, 1H), 7.46 (td, $J = 7.5$, 1.8 Hz, 1H), 8.51 (d, $J = 4.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −1.5, −1.4, 17.7, 18.1, 25.8, 31.9, 33.0, 65.1, 65.2, 66.2, 69.2, 76.0, 121.4, 121.8, 126.7, 127.7, 128.2, 136.0, 141.5, 147.8, 162.3.

General Procedure for the Preparation of Diamines 8b, 8d, 8f. The preparation of diamine **8d** is representative. $LiAlH_4$ (445 mg, 11.7 mmol) was carefully added at room temperature to a solution of aminal **11d** (1.32 g, 2.93 mmol) in Et_2O (50 mL) under argon. The reaction mixture was stirred for 24 h at reflux, allowed to cool, and treated at room temperature successively with aqueous NaOH (1 N, 2.64 mL) and H_2O (3.96 mL). After filtration through Celite, the residue was washed several times with Et_2O, and the organic layer was concentrated in vacuo. The residue was purified by flash chromatography (AcOEt/MeCN/NH_4OH, 237:12:1) to provide **8d** as a colorless oil (488 mg, 49%).

(2*R*)-[(2*R*)-(2-Methoxy-phenyl)-azepan-3*S*-ylamino]-2-phenyl-ethanol 8d. Oil; $[\alpha]_D = -62$ (*c* 1.4, CH_2Cl_2); IR (neat) 3407, 2928, 1600 cm^{-1}; MS *m*/*z* 341 (MH^+); ^1H NMR ($CDCl_3$) δ 1.42−1.92 (m, 9H), 2.79 (m, 1H), 2.95 (m, 1H), 3.15 (m, 1H), 3.33 (dd, $J = 11.6$, 4.2 Hz, 1H), 3.84 (d, $J = 7.6$ Hz, 1H), 3.86 (s, 3H), 6.91 (d, $J = 7.8$ Hz, 1H), 6.98 (td, $J = 7.8$−1.4 Hz, 1H), 7.08−7.30 (m, 6H), 7.34 (dd, $J = 7.5$, 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.9, 31.0, 34.5, 49.8, 55.5, 63.2, 63.6, 66.0,

110.9, 121.1, 127.0, 127.3, 128.1, 128.3, 128.5, 133.6, 142.5, 156.7; HRMS calcd for $C_{21}H_{29}N_2O_2$ (MH^+) 341.2229, found 341.2231.

2-[(2*R*)-Butyl-azepan-(3*S*)-ylamino]-(2*R*)-phenyl-ethanol 8b. The compound was prepared from compound **11b** according to the previous procedure, although Et_2O was replaced by $^iPr_2O$. Pure **8b** was obtained without any purification, as a colorless oil (833 mg, 98%). $[\alpha]_D = -17$ (*c* 1.0, MeOH); IR (neat) 3425, 1636 cm^{-1}; MS *m*/*z* 291 (MH^+); ^1H NMR ($CDCl_3$) δ 0.84 (t, $J = 6.4$ Hz, 3H), 1.12−1.63 (m, 12H), 2.14 (br. s, 3H), 2.34 (m, 1H), 2.47 (m, 1H), 2.54 (m, 1H), 2.97 (dt, $J = 13.2$, 4.0 Hz, 1H), 3.40 (dd, $J = 10.6$, 7.6 Hz, 1H), 3.58 (dd, $J = 10.6$, 4.7 Hz, 1H), 3.70 (dd, $J = 7.6$, 4.8 Hz, 1H), 7.05−7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.5, 22.1, 23.2, 29.4, 32.0, 32.3, 34.4, 49.0, 62.2, 63.3, 66.6, 127.4, 127.8, 128.9, 142.8.

(2*R*)-[(3*S*)-(2-Hydroxy-(1*R*)-phenyl-ethylamino)-azepan-2-yl]-phenol 8f. The compound was prepared from compound **11d** according to previous procedure, although Et_2O was replaced by $^iPr_2O$. The residue was purified by flash chromatography (AcOEt/MeCN/NH_4OH, 237:12:1) to provide compound **8f** as a colorless oil (478 mg, 50%). $[\alpha]_D = -17$ (*c* 1.1, CH_2Cl_2); IR (neat) 3301, 2928, 1732 cm^{-1}; MS *m*/*z* 327 (MH^+); ^1H NMR ($CDCl_3$) δ 1.50−1.92 (m, 9H), 2.78 (m, 1H), 2.94 (m, 1H), 3.12 (dt, $J = 13.7$, 4.3 Hz, 1H), 3.33 (dd, $J = 10.5$, 6.7 Hz, 1H), 3.41−3.52 (m, 2H), 3.72 (d, $J = 7.9$ Hz, 1H), 6.85 (td, $J = 7.8$, 1.2 Hz, 1H), 6.92 (dd, $J = 7.8$, 1.1 Hz, 1H), 7.11−7.35 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 21.9, 31.0, 34.6, 49.8, 55.5, 63.2, 63.6, 66.0, 110.9, 121.1, 127.0, 127.3, 128.0, 128.2, 128.5, 133.7, 142.6, 156.8.

General Procedure for the Synthesis of 2,3-Diamines 3a,b,d,f. The preparation of diamine **3d** is representative. Stirring under hydrogen atmosphere of compound **8d** (645 mg, 1.90 mmol) in methanol (30 mL) in the presence of aqueous HCl (pH 2) and 10% Pd/C (129 mg) for 48 h at room temperature afforded a compound, which after filtration and concentration, was dissolved in ether and extracted three times with an aqueous 2 N HCl solution. Aqueous layers were made basic (NaOH 6 N) and then extracted with AcOEt. The organic layer were dried (Na_2SO_4) and concentrated to provide **3d** as a colorless oil (397 mg, 95%).

(2*R*)-(2-Methoxyphenyl)-azepan-(3*S*)-ylamine 3d. Oil; $[\alpha]_D = -42$ (*c* 1.1, CH_2Cl_2); IR (neat) 3355, 2928, 1640 cm^{-1}; MS *m*/*z* 221 (MH^+); ^1H NMR ($CDCl_3$) δ 1.42−2.08 (m, 8H), 2.86 (m, 2H), 3.14 (m, 1H), 3.72 (d, $J = 9.4$ Hz, 1H), 3.83 (s, 3H), 6.88 (d, $J = 7.5$ Hz, 1H), 6.95 (td, $J = 7.5$, 1.4 Hz, 1H), 7.22 (td, $J = 7.5$, 1.5 Hz, 1H), 7.34 (dd, $J = 7.5$, 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0, 30.1, 36.3, 49.1, 55.5, 58.0, 66.1, 110.8, 121.1, 127.9, 128.9, 132.5, 156.9; HRMS calcd for $C_{13}H_{21}N_2O$ (MH^+) 221.1654, found 221.1654.

(2*R*)-Butyl-azepan-(3*S*)-ylamine 3b. The compound was prepared from compound **8b** (663 mg, 95%). It proved to be air-sensitive and was characterized in its bis hydrochloride form (prepared after standing in an HCl atmosphere for 0.5 h). $[\alpha]_D = +3$ (*c* 1.0, MeOH); IR (neat) 3418 cm^{-1}; MS (base) *m*/*z* 171 (MH^+); ^1H NMR (D_2O, hydrochloride) δ 0.72 (t, $J = 6.9$ Hz, 3H), 1.03−2.00 (m, 15H), 3.08 (m 1H), 3.24 (m, 1H), 3.35 (dt, $J = 11.9$, 3.8 Hz, 1H), 3.48 (dt, $J = 11.9$, 4.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.5, 22.3, 22.7, 26.3, 27.4, 31.4, 31.8, 47.9, 54.0, 61.8; HRMS calcd for $C_{10}H_{23}N_2$ (MH^+) 171.1861, found 170.1863.

2-[(3*S*)-Amino-azepan-(2*R*)-yl]-phenol 3f. Oil, 272 mg, 90%; $[\alpha]_D = -85$ (*c* 1.0, CH_2Cl_2); IR (neat): 3352, 2929, 1588 cm^{-1}; MS *m*/*z* 207 (MH^+); ^1H NMR ($CDCl_3$) δ 1.60−1.90 (m, 6H), 2.80 (td, $J = 13.4$, 3.4 Hz, 1H), 3.03−3.19 (m, 2H), 3.50 (d, $J = 8.7$ Hz, 1H), 3.60 (br. s, 2H), 6.81 (td, $J = 7.8$, 1.1 Hz, 1H), 6.87 (dd, $J = 8.8$, 1.0 Hz, 1H), 7.07−7.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 22.2, 28.4, 34.5, 47.6, 56.5, 71.5, 117.5, 119.2, 128.1, 128.8, 156.4; HRMS calcd for $C_{12}H_{19}N_2O$ (MH^+) 207.1497, found 207.1499.

General Procedure for the Preparation of Trisubstituted Azepanes 14a−c. The preparation of diamine **14a** is representative. An ethereal solution of methylmagnesium bromide (3 M/Et_2O, 2.71 mL, 8.12 mmol) was added at room temperature to a solution of aminal **11a** (976 mg, 2.31 mmol) in ether (40 mL) under argon. The reaction mixture was stirred for 3 h at reflux. The reaction mixture was cautiously diluted with a saturated, aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (2 ×), and the combined organic layers were dried ($MgSO_4$). The residue was purified by flash chromatography (AcOEt/MeCN/NH_4OH, 237/12/1) to afford **14a** as a yellow oil (577 mg, 57%).

[2-(*tert*-Butyl-dimethyl-silanyloxy)-(1*R*)-phenyl-ethyl]-(7*R*)-methyl-(2*R*)-phenyl-azepan-(3*S*)-yl)-amine 14a. Oil; $[\alpha]_D = -16$ (*c* 0.6, CH_2Cl_2); IR (neat) 3362, 2927 cm^{-1}; MS *m*/*z* 439 (MH^+); ^1H NMR ($CDCl_3$) δ −0.21 (s, 6H), 0.70 (s, 9H), 0.97 (d, $J = 6.4$ Hz, 3H), 1.10−1.85 (m, 8H), 2.90 (m, 1H), 3.01 (m, 1H), 3.23−3.38 (m, 3H), 3.82 (d, $J = 8.6$ Hz, 1H), 7.10−7.35 (m, 10H); ^{13}C NMR ($CDCl_3$) δ −1.4, 18.4, 23.3, 23.4, 26.0, 36.6, 37.6, 49.5, 62.2, 62.8, 63.6, 68.0, 127.0, 127.1, 127.5, 127.8, 128.1, 128.8, 142.8, 145.1.

[2-(*tert*-Butyl-dimethyl-silanyloxy)-(1*R*)-phenyl-ethyl]-(7*S*)-isobutyl-(2*R*)-phenyl-azepan-(3*S*)-yl)-amine 14b. Oil, 931 mg, 84%; $[\alpha]_D = -16$ (*c* 0.8, CH_2Cl_2); IR (neat) 3356, 2928, 1600 cm^{-1}; MS *m*/*z* 481 (MH^+); ^1H NMR ($CDCl_3$) δ −0.12 (s, 6H), 0.72 (d, $J = 6.2$ Hz, 6H), 0.80 (s, 9H), 1.00−1.90 (m, 9H), 2.89 (m, 1H), 3.0 (td, $J = 8.7$, 3.6 Hz, 1H), 3.30−3.46 (m, 3H), 3.75 (d, $J = 8.7$ Hz, 1H), 7.18−7.40 (m, 10H); ^{13}C NMR ($CDCl_3$) δ −1.5, 18.4, 22.3, 23.2, 23.5, 24.6, 26.0, 36.3, 36.6, 46.4, 51.7, 62.4, 63.0, 63.7, 68.0, 127.0, 127.2, 127.7, 127.8, 128.1, 128.7, 142.8, 144.8.

[(7*S*)-Benzyl-(2*R*)-phenyl-azepan-(3*S*)-yl]-[2-(*tert*-butyl-dimethyl-silanyloxy)-(1*R*)-phenyl-ethyl]-amine 14c. Oil, 1.13 g, 95%; $[\alpha]_D = +15$ (*c* 1.1, CH_2Cl_2); IR (neat) 3415, 2926 cm^{-1}; MS *m*/*z* 515 (MH^+); ^1H NMR ($CDCl_3$) δ −0.20 (s, 6H), 0.75 (s, 9H), 1.20−1.90 (m, 8H), 2.53 (dd, $J = 13.3$, 8.2 Hz, 1H), 2.62 (dd, $J = 13.3$, 5.6 Hz, 1H), 2.90 (m, 1H), 3.03 (m, 1H), 3.27 (dd, $J = 13.1$, 7.5 Hz, 1H), 3.38 (dd, $J = 13.1$, 7.5 Hz, 1H), 3.76 (d, $J = 8.5$ Hz, 1H), 6.87−7.40 (m, 15H); ^{13}C NMR ($CDCl_3$) δ −1.4, 18.4, 23.2, 26.0, 35.5, 36.9, 43.4, 56.3, 62.7, 62.8, 63.5, 68.0, 127.0, 127.1, 127.6, 127.8, 128.1, 128.3, 128.7, 129.3, 139.5, 142.8, 144.2.

[2-(*tert*-Butyl-dimethyl-silanyloxy)-(1*R*)-phenyl-ethyl]-((7*R*)-methyl-2-pyridin-(2*R*)-yl-azepan-(3*S*)-yl)-amine 14d. Oil, 739 mg, 69%; $[\alpha]_D = -15$ (*c* 0.8, CH_2Cl_2); IR (neat) 3424, 2929, cm^{-1}; MS *m*/*z* 440 (MH^+); ^1H NMR ($CDCl_3$) δ -0.15 (s, 3H), −0.13 (s, 3H), 0.80 (s, 9H), 1.10−1.50 (m, 6H), 1.30 (d, $J = 6.7$ Hz, 3H), 2.05 (br. s, 2H), 2.75 (m, 2H), 3.54 (m, 1H), 3.54 (d, $J = 5.0$ Hz, 1H), 3.67 (dd, $J = 7.6$, 4.3 Hz, 1H), 3.78 (dd, $J = 13.5$, 7.6 Hz, 1H), 7.01 (dd, $J = 6.6$, 5.0 Hz, 1H), 7.10−7.33 (m, 6H), 7.51 (td, $J = 8.2$, 1.7 Hz, 1H), 8.42 (br.d, $J = 5.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −1.3, 18.7, 20.1, 23.5, 26.1, 30.3, 30.7, 58.7, 58.9, 59.7, 64.9, 68.9, 121.2, 121.8, 127.2, 127.9, 128.2, 128.4, 136.4, 142.7, 149.1, 167.8.

[2-(*tert*-Butyl-dimethyl-silanyloxy)-(1*R*)-phenyl-ethyl]-((7*S*)-isobutyl-2-pyridin-(2*R*)-yl-azepan-(3*S*)-yl)-amine 14e. Oil, 822 mg, 70%; $[\alpha]_D = -12$ (*c* 0.8, CH_2Cl_2); IR (neat) 3412, 2928, 1468, 1434 cm^{-1}; MS *m*/*z* 482 (MH^+); ^1H NMR ($CDCl_3$) δ −0.15 (s, 3H), −0.13 (s, 3H), 0.75 (s, 9H), 0.82 (m, 7H), 0.90−1.60 (m, 6H), 1.51 (t, $J = 6.5$ Hz, 2H), 2.17 (br. s, 2H), 2.73 (m, 2H), 3.55 (m, 1H), 3.55 (d, $J = 5.8$ Hz, 1H), 3.67 (m, 2H), 6.99 (ddd, $J = 7.5$, 4.5, 1.3 Hz, 1H), 7.10−7.30 (m, 6H), 7.49 (td, $J = 7.5$, 1.3 Hz, 1H), 8.41 (d, $J = 4.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 1.3, 18.5, 20.0, 23.0, 25.0, 26.1, 30.4, 30.6, 47.2, 59.6, 59.7, 62.6, 64.0, 68.8, 121.7, 122.0, 127.2, 127.9, 128.1, 136.1, 142.6, 149.0, 166.3.

[(7*S*)-Benzyl-2-pyridin-(2*R*)-yl-azepan-(3*S*)-yl]-[2-(*tert*-butyl-dimethyl-silanyloxy)-(1*R*)-phenyl-ethyl]-amine 14f. Oil, 817 mg, 65%; $[\alpha]_D = -11$ (*c* 1.1, CH_2Cl_2); IR (neat) 3390, 3028, 2952 cm^{-1}; MS *m*/*z* 516 (MH^+); ^1H NMR ($CDCl_3$) δ −0.20 (s, 3H), −0.15 (s, 3H), 0.75 (s, 9H), 1.00−1.40 (m, 8H), 2.60 (m, 2H), 2.79 (dd, $J = 13.6$, 8.6 Hz, 1H), 2.99 (dd, $J = 13.6$, 5.7 Hz, 1H), 3.24 (dd, $J = 6.6$, 4.5 Hz, 1H), 3.30 (m, 2H), 3.89 (dd, $J = 8.6$, 5.7 Hz, 1H), 6.97 (ddd, $J = 7.6$, 4.8, 1.5 Hz, 1H), 7.04−7.27 (m, 11H), 7.44 (td, $J = 7.6$, 1.5 Hz, 1H), 8.34 (ddd,

J = 4.8, 1.7, 0.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ − 1.2, 18.4, 20.0, 26.0, 30.2, 30.5, 44.1, 59.3, 59.6, 63.7, 65.6, 68.4, 121.1, 121.9, 126.3, 127.0, 127.5, 127.9, 128.0, 128.4, 128.5, 129.5, 136.3, 139.0, 142.7, 148.8, 164.9.

General Procedure for the Preparation of Trisubstituted Azepanes 4a−c. The preparation of diamine **4a** is representative. $BF_3.Et_2O$ (809 μL, 6.6 mmol) was added to a solution of azepane **14a** (577 mg, 1.3 mmol) in $CHCl_3$ (15 mL) under argon. The reaction mixture was stirred 15 h at reflux, allowed to cool, and treated with an aqueous saturated $NaHCO_3$ solution. The organic layer were separated and dried on $MgSO_4$, and the solvent was evaporated. The crude product was then submitted to hydrogenolysis in methanol (15 mL) under H_2 atmosphere in the presence of HCl (pH 2) and 10% Pd/C (76 mg) for 48 h, to afford a compound, which after filtration and concentration, was dissolved in ether and extracted three times with aqueous HCl solution. Aqueous layers were made basic (6 N NaOH) and then extracted with AcOEt. The organic layer was dried (Na_2SO_4) and concentrated to give **4a** as a colorless oil (224 mg, 70%).

(7*R*)-Methyl-(2*R*)-phenyl-azepan-(3*S*)-ylamine 4a. Oil; $[\alpha]_D$ = −18 (*c* 0.8, CH_2Cl_2); IR (neat) 3363, 2924, 1644, 1600 cm^{-1}; MS *m*/*z* 205 (MH^+); ^{1}H NMR ($CDCl_3$) δ 1.08 (d, J = 6.3 Hz, 3H), 1.17−2.15 (m, 9H), 3.05−3.10 (m, 2H), 3.55 (d, J = 9.5 Hz, 1H), 7.17−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.5, 37.2, 39.2, 50.6, 58.0, 63.5, 127.3, 129.0, 145.1; HRMS (CI, MH^+) calcd for $C_{13}H_{21}N_2$ 205.1705, found 205.1707.

(7*S*)-Isobutyl-(2*R*)-phenyl-azepan-(3*S*)-ylamine 4b. Oil, 77%; $[\alpha]_D$ = −20 (*c* 0.9, $CHCl_3$); IR (neat) 3367, 2951, 1666, 1602 cm^{-1}; MS *m*/*z* 247 (MH^+); ^{1}H NMR ($CDCl_3$) δ 0.78 (d, J = 6.3 Hz, 3H), 0.82 (d, J = 6.3 Hz, 3H), 1.12−1.80 (m, 10H), 1.95 (m, 1H), 2.12 (m, 1H), 2.99 (m, 1H), 3.10 (td, J = 9.5, 4.4 Hz, 1H), 3.49 (d, J = 9.5 Hz, 1H), 7.20−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.3, 23.0, 23.1, 24.7, 35.6, 39.3, 46.1, 52.7, 57.8, 63.1, 127.3, 128.9, 144.7; HRMS (CI, MH^+) calcd for $C_{16}H_{27}N_2$ 247.2174, found 247.2174.

(7*S*)-Benzyl-(2*R*)-phenyl-azepan-(3*S*)-ylamine 4c. Oil, 81%; $[\alpha]_D$ = +67 (*c* 1.0, $CHCl_3$); IR (neat) 3359, 3025, 2926, 1673, 1601 cm^{-1}; MS *m*/*z* 281 (MH^+); ^{1}H NMR ($CDCl_3$) δ 1.17−2.17 (m, 9H), 2.63 (dd, J = 13.6, 8.3 Hz, 1H), 2.70 (dd, J = 13.6, 6.0 Hz, 1H), 3.06 (td, J = 9.5, 4.5 Hz, 1H), 3.18 (m, 1H), 3.59 (d, J = 9.5 Hz, 1H), 6.91−7.38 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 23.0, 35.2, 39.5, 43.3, 57.5, 58.3, 63.1, 126.0, 127.4, 128.3, 128.6, 128.9, 129.3, 139.6, 144.3; HRMS (CI, MH^+) calcd for $C_{19}H_{25}N_2$ 281.2018, found 281.2015.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds. X-ray structure determination and crystal data for compound **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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