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

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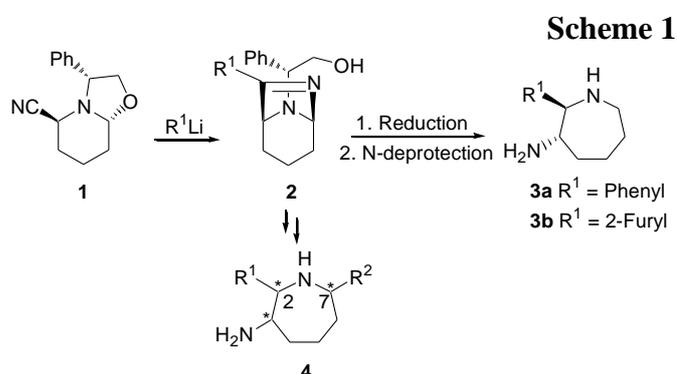
Abstract: A simple and versatile method for the enantio- and diastereoselective synthesis of mono- or disubstituted 3-aminoazepanes is described. The key step involves a highly regio- and diastereoselective tandem ring-enlargement/alkylation or reduction process. This novel synthetic route provides enantiomerically 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 considering 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 non-rigid Gadolinium (III) complexes.² Various CNS receptor ligands³ and antitumor chiral *cis*-platin analogues⁴ 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).

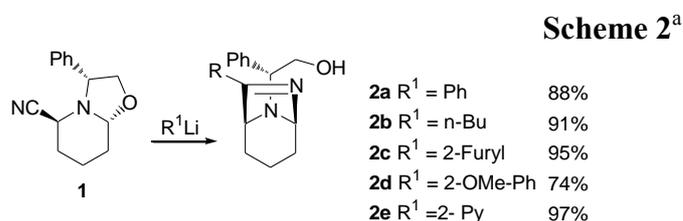


We report in this article our full investigations in this field, as well as the generalization of this original ring-enlargement reaction for the diastereo- and enantioselective preparation of 2,7-disubstituted 3-aminoazepanes **4**.

Results and Discussion

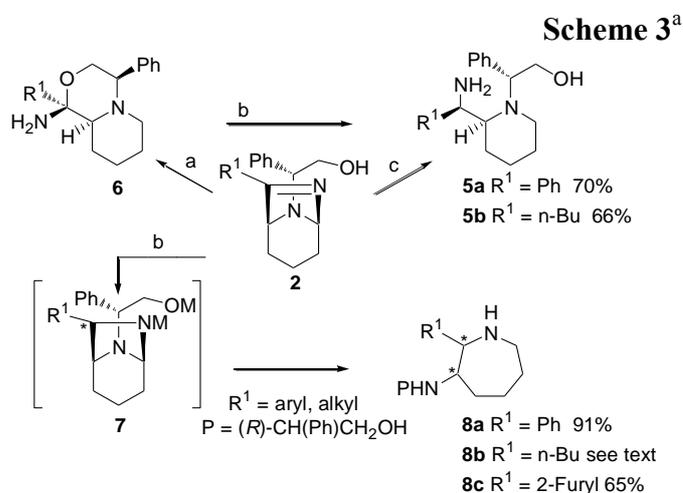
Synthesis of 2-substituted 3-aminoazepanes.

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).



^a Reagents and conditions : R¹ = Ph, n-Bu, 2-Py : R¹Li, Et₂O, - 78 °C ; R¹ = 2-OMe-Ph, 2-Furyl: R¹Li, TMEDA, THF, - 78 °C.

These stable compounds are key intermediates for the ring enlargement strategy. Under protic conditions, reaction of butyl or phenyl derivatives **2a,b** with NaBH₄ or NaBH₃CN have been reported to give piperidines **5** or morpholines **6** respectively in a high diastereoselective manner (Scheme 3).⁸

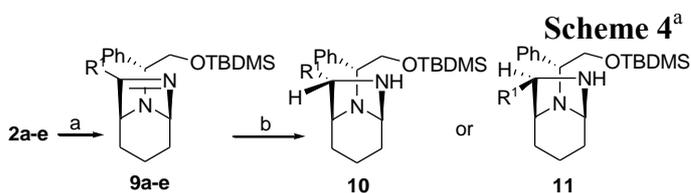


^a Reagents and conditions : (a) NaBH₃CN, H⁺, THF, MeOH; (b) LAH, Et₂O; (c) NaBH₄, MeOH.

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, 3h; **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 6-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 prepared and protected as O-silylated compounds **10a-e** in 70-90% yield (Scheme 4).



^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

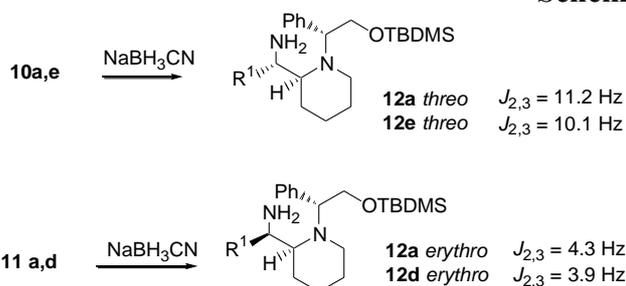
^a Major diastereomer. ^b Yield of diastereomerically pure compound.

Selective imine reductions proved to be particularly troublesome and highly dependent on their substitution patterns. Our first attempts to reduce **9a** using LAH under

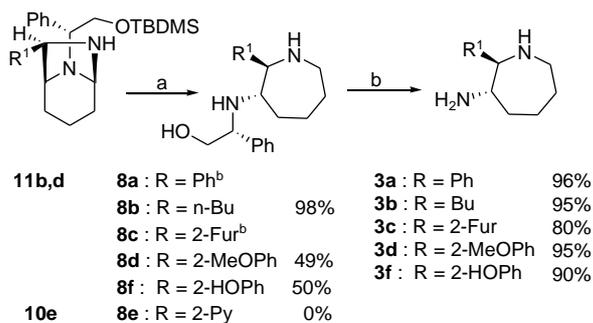
various experimental conditions led to either irreproducible results or the known desilylated azepane derivative **8a**. More encouraging results were obtained using dissolving-metal conditions.⁹ Treatment of **9a** with lithium in liquid ammonia afforded, in a first experiment, a mixture of amins **10a** 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 ¹H and the ¹³C 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 NaBH₃CN 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 amins **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 amins **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, ¹H and ¹³C NMR spectra revealed characteristic signals of bridged bicyclic structures as 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* ($J = 3.9\text{-}4.3$ Hz) or *threo* ($J = 10.1\text{-}11.2$ Hz) O-silylated aminoalkyl piperidines **12** after acidic NaBH₃CN aminal reduction of analytical samples (Scheme 5).

Scheme 5



Since bicyclic amins 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 amination **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

Scheme 6^a

^a Reagents and conditions : (a) LAH, $i\text{Pr}_2\text{O}$ or Et_2O , reflux; (b) H_2 , Pd/C, MeOH-HCl for **8a,b,d,f** or H_5IO_6 (2.6 eq), MeNH_2 , H_2O , MeOH, then MeOH-HCl for **8c**.

^b From **2a,c** via one step reduction (Scheme 3).

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 6-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 an hydride. However, the use a of Lewis acidic nucleophile should lead to the same reactive species from bicyclic amins **10** or **11** and enable further functionalizations of the azepane at the C-7 position. Although the reactivity of such amins is unknown, the related reaction of nucleophilic reagents, especially organomagnesium compounds, with oxazolidines is well documented.¹¹

Scheme 7

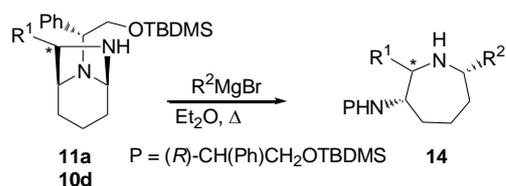


Table 2. Diastereoselective access to polysubstituted azepanes 14

product	R ¹	R ²	Yield (%) ^a	d.e. (%) ^b
14a	Ph (2 <i>R</i>)	Me	57	>95
14b	Ph (2 <i>R</i>)	<i>i</i> -Bu	84	>95
14c	Ph (2 <i>R</i>)	Bn	95	>95
14d	2-Py (2 <i>R</i>)	Me	69	>95
14e	2-Py (2 <i>R</i>)	<i>i</i> -Bu	70	>95
14f	2-Py (2 <i>R</i>)	Bn	65	>95

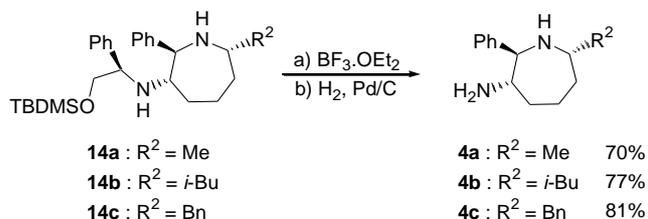
^a Yield of diastereomerically pure compound.

^b Determined by ¹H NMR of the crude reaction mixture.

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 ^1H 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.

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 amins **11b,d**, the ring-enlargement occurred without any O-desilylation. Final compounds **4a,b,c** could be obtained after desilylation and hydrogenolysis.

Scheme 8



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 ^1H and ^{13}C NMR spectra.

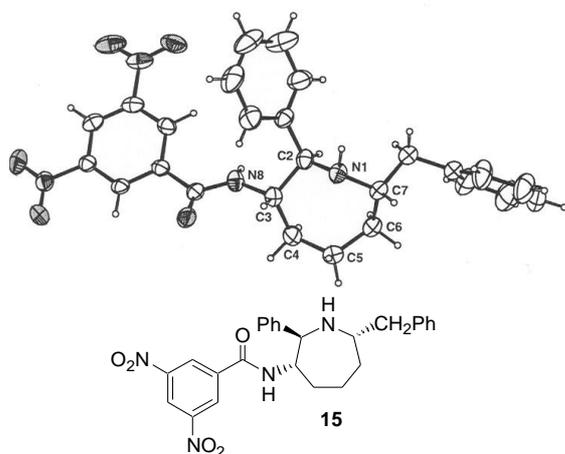


Figure 1 : X-ray structure of derivative 15.

The same ring-enlargement reactions were then performed starting from pyridyl aminal **10e**, in order to study the 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 n.O.e experiments on its desilylated derivative, and attributed to the other compounds by comparisons of their ^1H 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).

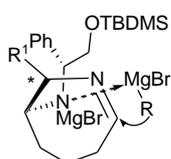


Figure 2 : Origin of the relative configuration of disubstituted aminoazepanes.

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 amins 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. ^1H 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 $i\text{Pr}_2\text{O}$) 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.^{6,7,8}

(1S, 5S) 2-[7-(2-Methoxyphenyl)-6,8-diazabicyclo[3.2.1]oct-6-en-8-yl]-(2R)-phenylethanol 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-phenyloxazolo-piperidine (**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 x), and the combined organic layers were dried (MgSO_4). The solvent was evaporated to give an oily residue. The

residue was purified by chromatography (CH₂Cl₂/MeOH 95/5) to provide imine **2d** (yellow oil, 2.18 g, 74%). [α]_D = + 46 (*c* 1.4, CH₂Cl₂); IR (neat) 3326, 2940, 1656, 1599 cm⁻¹; MS *m/z* 337 (MH⁺); ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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.

(1S, 5S) 2-(7-Furan-2-yl-6,8-diazabicyclo[3.2.1]oct-6-en-8-yl)-(2R)-phenyl-ethanol 2c (yellow oil, 2.47 g, 95%). [α]_D = -11 (*c* 1.1, CH₂Cl₂); IR (neat) 3320, 2947, 1622 cm⁻¹; MS *m/z* 297 (MH⁺); ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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.

(1S, 5S) 2R-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 Et₂O (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 Et₂O (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 NH₄Cl, extracted with CH₂Cl₂ (2 x), and the combined organic layers were dried (MgSO₄). The residue was purified by chromatography (CH₂Cl₂/MeOH 95/5) to provide **2c** (amorphous yellow solid, 2.61 g, 97%). [α]_D = - 44 (*c* 1.1, CH₂Cl₂); IR (neat) 3330, 2945, 2871, 1609, 1586 cm⁻¹; MS *m/z* 308 (MH⁺); ¹H NMR (CDCl₃) 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 , extracted with CH_2Cl_2 (2 x), and the combined organic layers were dried (MgSO_4). 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%).

(1S, 5S) 8-[2-(*tert*-Butyl-dimethyl-silanyloxy)-(1*R*)-phenyl-ethyl]-7-phenyl-6,8-diazabicyclo[3.2.1]oct-6-ene 9a. Oil, $[\alpha]_{\text{D}} = +10$ (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.

(1S, 5S)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%). $[\alpha]_{\text{D}} = -18$ (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%). $[\alpha]_{\text{D}} = +72$ (*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%). $[\alpha]_{\text{D}} = -1$ (*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 amina 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*-butanol (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, the organic layers were dried over MgSO₄ and concentrated to give a mixture of diastereomers (**11a/10a**, 81/19). The residue was purified by chromatography (AcOEt/MeCN/NH₄OH, 246/3/1) to provide the major compound **11a** as a yellow oil (321 mg, 64%).

(1S, 5S) 8-[2-(tert-Butyl-dimethyl-silanyloxy)-(1R)-phenyl-ethyl]-7R-phenyl-6,8-diaza bicyclo [3.2.1]octane 11a. Oil. $[\alpha]_D = -5$ (*c* 1.0, CH₂Cl₂); IR (neat) 3427, 2928, 2855, 1493 cm⁻¹; MS *m/z* 423 (MH⁺); ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 amina **11b,d**.

The preparation of amina **11d** is representative. To a solution of imine **9d** (500 mg, 1.11 mmol) in Et₂O (25 mL) under argon was carefully added LiAlH₄ (329 mg, 8.67 mmol). The reaction mixture was stirred 3 h at room temperature then treated successively with aqueous NaOH (1N, 658 μ L) and H₂O (987 μ L). After filtration through celite, the organic phase was concentrated *in vacuo*. The residue was purified by flash chromatography (AcOEt/MeCN/NH₄OH, 237/12/1) to provide **11d** as a colorless oil (371 mg, 74%).

(1S, 5S) 8-[2-(tert-Butyl-dimethyl-silanyloxy)-(1R)-phenyl-ethyl]-7R-(2-methoxy phenyl)-6,8-diaza-bicyclo[3.2.1]octane 11d. Oil. $[\alpha]_D = +12$ (*c* 0.8, CH₂Cl₂); IR (neat) 3320, 2952, 2926, 1492 cm⁻¹; MS *m/z* 453 (MH⁺); ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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.

(1S, 5S) 7R-Butyl-8-[2-(tert-butyl-dimethyl-silanyloxy)-(1R)-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 amina 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%).

(1S, 5S) 8-[2-(tert-Butyl-dimethyl-silanyloxy)-(1R)-phenyl-ethyl]-(7R)-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 amina **11d** (1.32 g, 2.93 mmol) in Et_2O (50 mL) under argon. The reaction mixture was stirred for 24 h at reflux, then allowed to cool and treated at room temperature

successively with aqueous NaOH (1N, 2.64 mL) and H₂O (3.96 mL). After filtration through celite and washing the residue several times with Et₂O, the organic layer was concentrated *in vacuo*. The residue was purified by flash chromatography (AcOEt/MeCN/NH₄OH, 237:12:1) to provide **8d** as a colorless oil (488 mg, 49%).

(2R)-[(2R)-(2-Methoxy-phenyl)-azepan-3S-ylamino]-2-phenyl-ethanol 8d. Oil. $[\alpha]_D = -62$ (*c* 1.4, CH₂Cl₂); IR (neat) 3407, 2928, 1600 cm⁻¹; MS *m/z* 341 (MH⁺); ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₂₁H₂₉N₂O₂ (MH⁺) : 341.2229, found : 341.2231.

2-[(2R)-Butyl-azepan-(3S)-ylamino]-(2R)-phenyl-ethanol 8b was prepared from compound **11b** according to the previous procedure, although Et₂O was replaced by *i*-Pr₂O. 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 (CDCl₃) 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); ¹³C NMR (CDCl₃) 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.

(2R)-[(3S)-(2-Hydroxy-(1R)-phenyl-ethylamino)-azepan-2-yl]-phenol 8f was prepared from compound **11d** according to previous procedure, although Et₂O was replaced by *i*-Pr₂O. The residue was purified by flash chromatography (AcOEt/MeCN/NH₄OH, 237:12:1) to provide compound **8f** as a colorless oil (478 mg, 50%). $[\alpha]_D = -17$ (*c* 1.1, CH₂Cl₂); IR (neat) 3301, 2928, 1732 cm⁻¹; MS *m/z* 327 (MH⁺); ¹H NMR (CDCl₃) 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 2N HCl solution. Aqueous layers were made basic (NaOH 6N) 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%).

(2R)-(2-Methoxyphenyl)-azepan-(3S)-ylamine 3d. Oil. $[\alpha]_{\text{D}} = -42$ (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 $\text{C}_{13}\text{H}_{21}\text{N}_2\text{O}$ (MH^+) 221.1654, found 221.1654.

(2R)-Butyl-azepan-(3S)-ylamine 3b 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). $[\alpha]_{\text{D}} = +3$ (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 $\text{C}_{10}\text{H}_{23}\text{N}_2$ (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, CH₂Cl₂); IR (neat): 3352, 2929, 1588 cm⁻¹; MS *m/z* 207 (MH⁺); ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₁₂H₁₉N₂O (MH⁺) 207.1497, found 207.1499.

General Procedure for the preparation of trisubstituted azepanes 14a-c.

The preparation of diamine **14 a** is representative. An ethereal solution of methyl magnesium bromide (3 M/Et₂O, 2.71 mL, 8.12 mmol) was added at room temperature to a solution of amina **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 NH₄Cl, extracted with CH₂Cl₂ (2 x), and the combined organic layers were dried (MgSO₄). The residue was purified by flash chromatography (AcOEt/MeCN/NH₄OH, 237/12/1) to afford **14a** as a yellow oil (577 mg, 57%).

[2-(*tert*-Butyl-dimethyl-silyloxy)-(1*R*)-phenyl-ethyl]-(7*R*-methyl-(2*R*)-phenyl-azepan-(3*S*)-yl)-amine 14a. Oil. $[\alpha]_D = -16$ (*c* 0.6, CH₂Cl₂); IR (neat) 3362, 2927 cm⁻¹; MS *m/z* 439 (MH⁺); ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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-silyloxy)-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, CH₂Cl₂); IR (neat) 3356, 2928, 1600 cm⁻¹; MS *m/z* 481 (MH⁺); ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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.

[(7S)-Benzyl-(2R)-phenyl-azepan-(3S)-yl]-[2-(tert-butyl-dimethyl-silanyloxy)-(1R)-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)-(1R)-phenyl-ethyl]-[7R-methyl-2-pyridin-(2R)-yl-azepan-(3S)-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)-(1R)-phenyl-ethyl]-[7S-isobutyl-2-pyridin-(2R)-yl-azepan-(3S)-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

(CDCl₃) 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, CH₂Cl₂); IR (neat) 3390, 3028, 2952 cm⁻¹; MS *m/z* 516 (MH⁺); ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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. BF₃.Et₂O (809 μ L, 6.6 mmol) was added to a solution of azepane **14a** (577 mg, 1.3 mmol) in CHCl₃ (15 mL) under argon. The reaction mixture was stirred 15 h at reflux, allowed to cool and treated with an aqueous saturated NaHCO₃ solution. The organic layer were separated, dried on MgSO₄ and the solvent was evaporated. The crude product was then submitted to hydrogenolysis in methanol (15 mL) under H₂ 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 (6N NaOH) and then extracted with AcOEt. The organic layer was dried (Na₂SO₄) 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, CH₂Cl₂); IR (neat) 3363, 2924, 1644, 1600 cm⁻¹; MS *m/z* 205 (MH⁺); ¹H NMR (CDCl₃) 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 $\text{C}_{13}\text{H}_{21}\text{N}_2$ 205.1705, found 205.1707.

(7S)-Isobutyl-(2R)-phenyl-azepan-(3S)-ylamine 4b (77% yield, Oil). $[\alpha]_{\text{D}} = -20$ (c 0.9, CHCl_3); IR (neat) 3367, 2951, 1666, 1602 cm^{-1} ; MS m/z 247 (MH^+); ^1H 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 $\text{C}_{16}\text{H}_{27}\text{N}_2$ 247.2174, found 247.2174.

(7S)-Benzyl-(2R)-phenyl-azepan-(3S)-ylamine 4c (81%, oil). $[\alpha]_{\text{D}} = +67$ (c 1.0, CHCl_3); IR (neat) 3359, 3025, 2926, 1673, 1601 cm^{-1} ; MS m/z 281 (MH^+); ^1H 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 $\text{C}_{19}\text{H}_{25}\text{N}_2$ 281.2018, found 281.2015.

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

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