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Stereoselective synthesis of substituted 2,5-diazabicyclo[2.2.1]-heptanes by iodine-mediated cyclization of optically pure compounds containing the 4,5-diamino-1,7-octadiene and 1,2-diamino-4-alkene moieties

Giuseppe Alvaro,[a] Romano Di Fabio,[a] Andrea Gualandi,[b] Claudio Fiorelli,[b] Magda Monari,[b] Diego Savoia[b,*] and Luca Zoli[b]

[a]*Psychiatry Centre of Excellence for Drug Discovery, GlaxoSmithKline S.p.A., via Fleming 4, 37135 Verona, Italy*
[b]*Dipartimento di Chimica 'G. Ciamician', Università di Bologna, via Selmi 2, 40126 Bologna, Italy*

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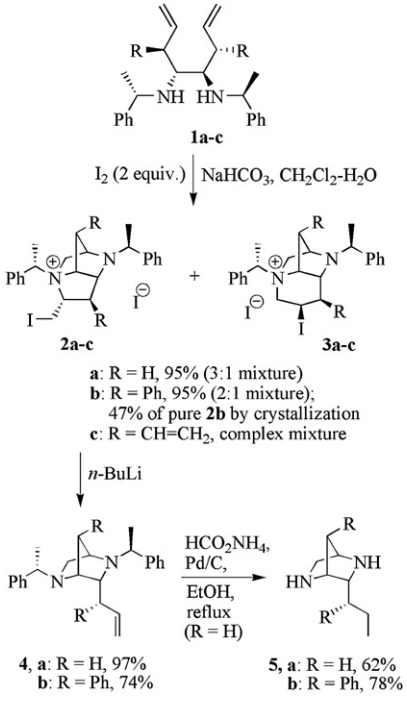
Abstract—3,7-*endo*-Disubstituted 2,5-diazabicyclo[2.2.1]heptanes were obtained by iodo-cyclization of *N*,*N*′-di[(*S*)-1-phenylethyl]-(*E*,*E*)-4,5-diamino-1,8-diphenyl-1,7-octadiene and substituted *N*,*N*′-di[(*S*)-1-phenylethyl]-1,2-diamino-4-alkenes. Removal of only one *N*-substituent of the bridged piperazines was achieved by reduction with ammonium formate and Pd/C. Unexpected cleavage of the skeleton of vinyl-substituted bridged piperazines was observed using hydrogen, leading to substituted 3-aminopyrrolidines.

1. Introduction

In a recent report[1] we described the asymmetric synthesis of the bridged piperazine **5a** by a route in which the key step is the iodine-mediated cyclization of the optically pure C_2-symmetric 4,5-diaminodiene **1a** in the biphasic system dichloromethane/aqueous sodium hydrogencarbonate (Scheme 1). A mixture of two tricyclic ammonium salts, **2a** and **3a**, was obtained in which the main product **2a** was formed by a sequence of three consecutive cyclization steps, analogously to the pathway described in Scheme 3 (see later). The product **2a** was formed by an alkene iodo-amination step from the bridged piperazine **4a**, which could not be isolated or obtained by treatment of **1a** with only 1 equiv of iodine. We wish to point out that the salts **2** and **3** are presumably formed through divergent pathways, already differing in the preliminary formation of the iodonium ion by poor diastereoface differentiation of the prochiral alkene function. However, the lack of selectivity has no influence on the subsequent preparation of the bridged piperazine. As a matter of fact, treatment of the salts **2a** and **3a**, separately or as a mixture, with organometallic reagents or radical reaction initiators gave back the bridged piperazine **4a** by β-cleavage of the intermediate organometallic reagent or carbon radical. Finally, hydrogenolysis of the benzylic *N*-substituents and concomitant hydrogenation of the C═C bond was achieved



Scheme 1.

Keywords: Alkenes; Cyclization; 1,2-Diamines; Iodine; Nitrogen heterocycles; Piperazines.
* Corresponding author. Tel.: +39 051 2099571; fax: +39 051 2099456; e-mail: diego.savoia@unibo.it

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by treatment with ammonium formate and palladium on carbon in refluxing ethanol to give the *n*-propyl-substituted bridged piperazine **5a**.

We decided to further explore the potential of this new approach to this bicyclic skeleton, especially investigating the role of chain-substituents at the C3,C6 and C1,C8 positions in the starting 4,5-diamino-1,7-octadiene, since steric effects in the former case and electronic effects in the latter case might affect the feasibility and the regioselectivity of the cyclization step(s). Moreover, we reasoned that the iodination reaction applied to the 1,2-diamino-4-alkenes, which can undergo only one iodine-mediated cyclization, would lead directly to the same bicyclic skeleton.

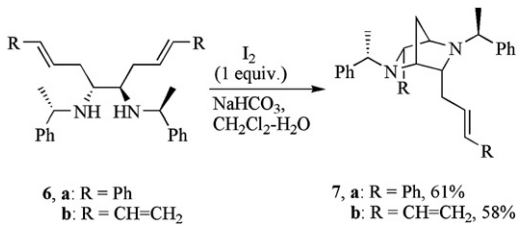
We were also stimulated by the paucity of useful methods for the asymmetric synthesis of bridged piperazines, which are potentially useful for the preparation of more complex, pharmacologically active molecules. As a matter of fact, the 2,5-diazabicyclo[2.2.1]heptane skeleton has been incorporated in a variety of medicinal agents in order to enhance the microbiological activity, due to the increased rigidity with respect to the simple piperazine ring. A few enantiomerically pure compounds of this type, with different *N*- and *C*-substituents, have been prepared from (*S*)- and (*R*)-proline derivatives, by a long sequence of steps including an intramolecular S_N2 reaction at high temperature.[2] *C*-Substituted bridged piperazines were also prepared by a poorly (enantio)selective metalation of *N*-methyl-*N*′-Boc-2,5-diazabicyclo[2.2.1]heptane, followed by the addition of an electrophile.[3]

2. Results and discussion

The reaction of the branched allylbenzene-substituted diaminodiene **1b**[4] with iodine (2 equiv) followed the same reaction pathways previously observed with the prototypical compound **1a**, rapidly leading to a ca. 2:1 mixture of the tricyclic ammonium salts **2b** and **3b**. This was deduced from the ^{1}H NMR spectrum of the crude reaction product, which was very complex, although presenting similarity to that of the **2a/3a** mixture. Also in this case, repeating the reaction with 1 equiv of iodine led to incomplete formation of the same products, and the presumed intermediate **4b** was not observed. The products **2b** and **3b** were not separated; instead the crude mixture was submitted to treatment with *n*-BuLi in tetrahydrofuran at 0 °C to give the substituted bridged piperazine **4b**, which was preferentially obtained in 74% yield (Scheme 1).

Unfortunately, the reaction of the branched pentadienyl-substituted diamine **1c**[4] with 2 equiv of iodine under the same reaction conditions was incomplete and led to a complex mixture of products, which were not separated by column chromatography. Modifying the experimental conditions we did not obtain better results, so this reaction was abandoned.

Then we examined the behaviour of the linear allylbenzene- and pentadienyl-substituted diamines **6a** and **6b**, respectively, in the typical reaction conditions (Scheme 2), supposing that the conjugated alkene moieties would affect the regioselectivity of the first iodo-cyclization step, at least in part inducing the nucleophilic nitrogen to attack at the benzylic (allylic) carbon of the intermediate iodonium ion. Surprisingly, only 1 equiv of iodine was readily consumed by the phenyl-substituted diaminodiene **6a** and a single product was observed by TLC analysis. Moreover, the addition of a second equivalent of iodine did not modify the composition of the reaction mixture, with no other product being observed after several hours. The product was isolated in 61% yield by crystallization of the crude product from methanol. The structure of **7a**, featuring the same skeleton of the compounds **4**, was determined by accurate two-dimensional ^{1}H NMR (COSY) and ^{13}C NMR (APT) analyses and also by an X-ray diffraction analysis (Fig. 1). Similarly, treatment of compound **6b** with 1 equiv of iodine gave the corresponding bridged piperazine **7b** in 58% yield after chromatographic purification (Scheme 2).



Scheme 2.

Mechanistic considerations are appropriate at this point. The same pathway is apparently followed in the formation of the intermediates **4a**,**b** and the products **7a**,**b**, as is shown in Scheme 3 for the formation of **7a**. A 5-*exo* iodo-cyclization step takes place to give the substituted pyrrolidine **10** via the transition state **8**. This is followed by a rapid intramolecular substitution by attack of the secondary amine on the highly reactive (benzylic) iodide to yield the bridged piperazine **7a**. Reasoning on the possible electronic effects of the R substituents in compounds **6**, especially when R=Ph in **6a**, we thought that the 5-*endo* iodo-cyclization of the 4-amino-1-alkene moiety might be operative, as described for *N*-protected homoallylic amines.[5] Particularly, the 5-*endo*

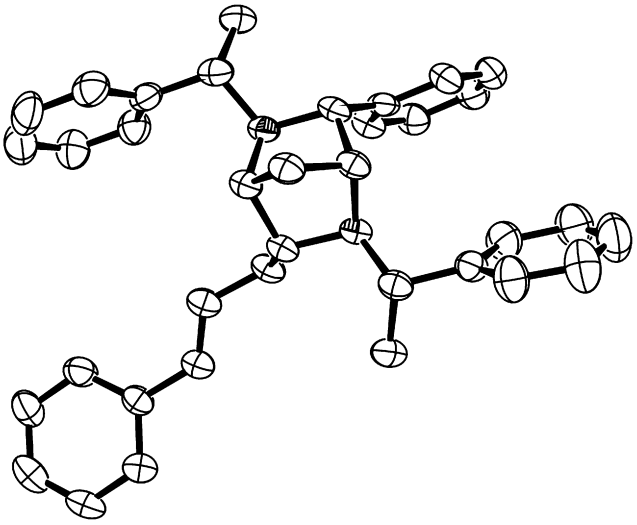
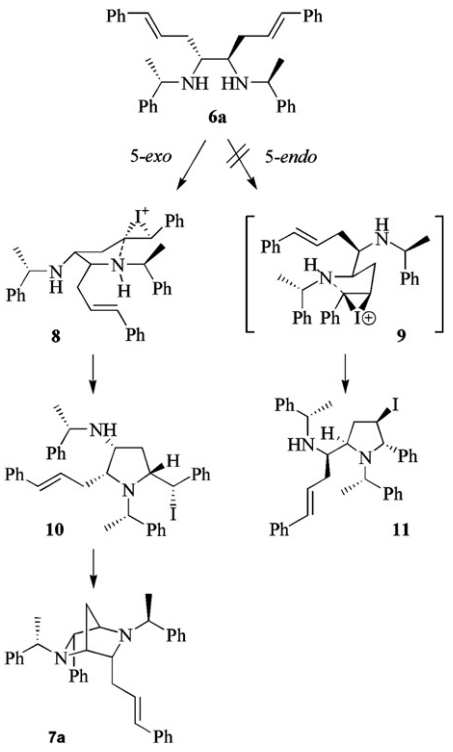


Figure 1. ORTEP drawing of compound **7a**.

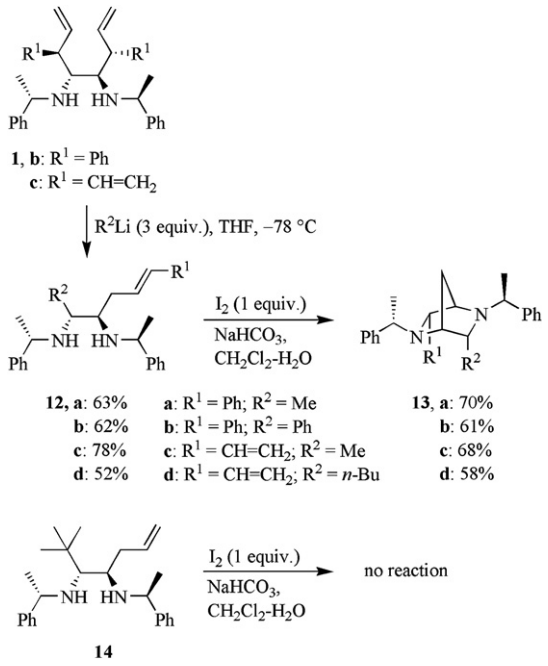
iodo-cyclization of 1,4-diphenyl-3-buten-1-yl tosylamide afforded the 2,5-*trans*-diphenyl-*N*-tosylpyrrolidine in basic conditions.[5b] However, the pyrrolidine **11**, which would have been formed by the alternative 5-*endo* cyclization of the 4-amino-1-alkene moiety, was not observed in the reaction mixture. Moreover, **11** could not undergo further cyclization because of the cis-relationship of the iodine and aminoalkyl ring substituents.



Scheme 3.

It is surprising that the bridged piperazines **7a**,**b**, in contrast to **4a**,**b**, do not undergo a subsequent iodo-cyclization to give the corresponding tricyclic ammonium salts. Apparently, the substituent at the alkene terminus inhibits the second iodo-cyclization step, perhaps by steric effects, so allowing the 3,6-*cis*-disubstituted bridged piperazines to be obtained directly in one step.

It is easy to recognize that the synthesis of bridged piperazines can be accomplished by iodination of 1,2-diamino-1-alkenes, owing to the presence of only one alkene function. Hence, we decided to prepare a few compounds having such a structure. Despite the fact that a number of methods can be applied for the preparation of unsymmetrical 1,2-disubstituted 1,2-diamines,[6] we found it convenient to apply our recently described procedure[7] that exploits the same diamines **1b**,**c** used in this work as intermediates. Addition of 3 equiv of commercially available organolithium reagents to the branched 1,2-disubstituted-1,2-diamines **1b**,**c** in THF at −78 °C afforded the desired compounds **12a–d** with satisfactory to good yields after chromatographic separation of minor amounts of by-products and minor diastereomers (Scheme 4). As expected, the reactions of **12** with iodine afforded the bridged piperazines **13** with 58–70% yields.



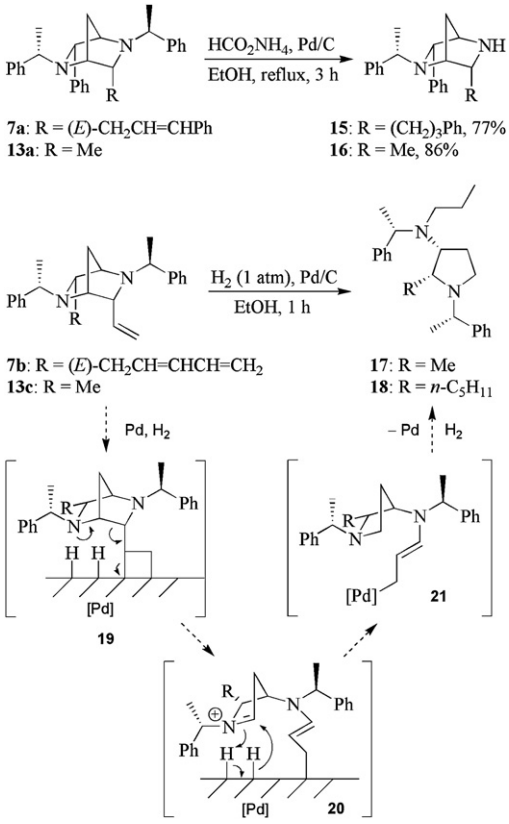
Scheme 4.

We also prepared the known diamine **14** by the procedure described by Roland and Mangeney,[8] involving the sequential addition of *tert*-butylmagnesium chloride and allylmagnesium chloride to the glyoxal diimine. However, no reaction occurred upon addition of iodine to **14**, probably because the bulky *tert*-butyl substituent impedes the attack of the vicinal amine function on the iodonium ion, and the 5-*endo* cyclization mode of the other amine function is unfavourable.

Finally, we wished to assess the possibility to remove the *N*-substituents from the bridged piperazines so far prepared. With this aim, we employed the hydrogenolysis protocol using ammonium formate and Pd/C in ethanol at reflux temperature previously used to convert the bridged piperazine **4a** to the *N*,*N*′-unsubstituted one **5a**. Treatment of the 3,7-disubstituted compound **4b** led to the corresponding product **5b**, which was isolated in 78% yield, together with small amounts (ca. 8% yield) of a partially debenzylated compound. On the other hand, the piperazines **7a** and **13a**, featuring *endo* substituents at C2 and C5, in the same experimental conditions were converted to the piperazines **15** and **16** (77 and 86% isolated yields, respectively), which maintained one *N*-substituent. The position of the *N*-substituent in both compounds was determined by NOE experiments. Prolonged reaction times gave a mixture of products, probably derived from cleavage of the other *N*-substituent and/or the ring benzylic C–N bond.

Treatment of the bridged piperazines **13c** and **7b**, bearing a vinylic *endo* ring substituent, with ammonium formate in the presence of Pd/C in ethanol or methanol at reflux did not give the analogous products, but the starting materials were recovered almost quantitatively after several hours. Instead, hydrogenation (1 atm of hydrogen) of **13c** and **7b** in the presence of Pd/C in ethanol or methanol gave, unexpectedly, the 3-aminopyrrolidine derivatives **17** and **18**

(Scheme 5). Although unambiguous X-ray structure determination was not achieved, only the depicted structures were consistent with their ^{1}H and ^{13}C NMR spectra, in particular with the DEPT experiments, which showed the presence of four/eight methylene and four methine carbons in the molecules. A tentative explanation for this unprecedented reaction is the concerted or stepwise mechanism described in Scheme 5, where the cleavage of the ring C–C bond after alkene complexation at the palladium surface is induced by the electron-donating effect of nitrogen, so forming a pyrrolidinium ion which is then reduced to the pyrrolidine **21**, perhaps by the hydrogen adsorbed on the palladium surface as depicted in structure **20**. This step is followed by reductive elimination and C=C bond hydrogenation steps leading to the pyrrolidines **17** and **18**.



Scheme 5.

3. Conclusions

The influence of the substitution pattern in the iodine-mediated cyclization of C_2-symmetrical 4,5-diamino-1,7-octadienes has been determined. The presence of substituents at C3 and C6 did not modify the reaction pathway, and tricyclic ammonium salts were formed as previously obtained with the 3,6-unsubstituted compound. On the other hand, substituents at C1 and C8 allowed direct formation of the corresponding bridged piperazines; similar bridged piperazines are assumed to be non-isolable intermediates in the formation of the ammonium salts. Similarly, bridged piperazines were obtained by iodination of 1,2-diamino-4-alkenes, i.e., 1,2-diamines bearing only one allylic substituent. These reactions allow a more convenient approach to ring-substituted 2,5-diazabicycloheptanes from the properly substituted 1,2-diamines, which can be prepared by allylmetalation of chiral glyoxal diimines[9] or by other reported methodologies.[6] Removal of the *N*-(1-phenylethyl) substituents of the *C*,*C*-disubstituted bridged piperazines by hydrogenolysis is often difficult, e.g., for compound bearing *endo* substituents at C3 and C6 only one *N*-substituent could be selectively cleaved. Moreover, in the case of alkenyl-substituted bridged piperazines an unexpected C–C ring cleavage was observed leading to 3-aminopyrrolidine derivatives. The capability of the chiral diamines so far prepared to act as bases, organo-catalysts or ligands of metal species in enantioselective processes[3] is currently under investigation in our laboratory. It is also expected that the iodination protocol can be applied to analogous diaminoalkenes and diaminoalkadienes bearing different, more readily removable *N*-substituents (chiral auxiliaries).

4. Experimental section

4.1. General

Melting points are uncorrected. Optical rotations were measured on a digital polarimeter in a 1-dm cell and $[\alpha]_D$-values are given in 10^{-1} deg cm^3 g^{-1}. NMR spectra were recorded on Varian Inova and Gemini instruments for samples in $CDCl_3$, which was stored over Mg. ^{1}H chemical shifts are reported in parts per million relative to $CHCl_3$ δ_H 7.27), *J*-values are given in hertz and in the assignments s=singlet, d=doublet, t=triplet, q=quartet, quint=quintet, m=multiplet, br s=broad singlet, br m=broad multiplet, dd=doublet of doublets and dt=doublet of triplets. Assignments were assisted with several 2D experiments for structural and stereochemical determinations. Infrared spectra were recorded on a Nicolet FT-210 spectrometer and IR assignments are reported in wavenumbers (cm^{-1}). MS spectra were taken at an ionizing voltage of 70 eV on a Agilent Technologies 5975 spectrometer with GLC injection. Molecular weight was determined on an Agilent Technologies MS 1100 instrument. Chromatographic separations were performed on columns of SiO_2 (Merck, 230–400 mesh) at medium pressure. All the organic and inorganic reagents and anhydrous solvents were purchased from Aldrich.

4.2. Iodine-mediated cyclization of the diaminodiene 1b. Preparation of tricyclic ammonium salts 2b, 3b

A solution of I_2 (1.02 g, 5 mmol) in CH_2Cl_2 (30 mL) was slowly added to a magnetically stirred solution of the diaminodiene **1b** (1.00 g, 2 mmol) dissolved in CH_2Cl_2 (10 mL) and satd aq $NaHCO_3$ (20 mL). After stirring was continued for 0.5 h, decolouration was observed. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×15 mL). The collected organic layers were dried over $CaCl_2$ and evaporated at reduced pressure at a temperature <30 °C. The solid pale brownish residue was mainly composed of the two salts **2b** and **3b** in 90% yield and ca. 2:1 ratio, as determined by ^{1}H NMR analysis, which were not separated by TLC analysis. The crude mixture was then used for the preparation of the bridged piperazine **4b**.

4.3. Preparation of the bridged piperazine 4b from the ammonium salts 2b, 3b

To the mixture of salts **2b**, **3b** (0.65 g, 0.86 mmol) dissolved in THF (10 mL) and cooled to 0 °C was slowly added a solution of *n*-BuLi (2.5 M in hexanes, 3.44 mL, 8.6 mmol). After stirring for 1 h, the mixture was quenched with satd aq $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The collected organic layers were dried over anhydrous $CaCl_2$ and concentrated to leave an oily residue, which was subjected to column chromatography (SiO_2) eluting with a 5:1 cyclohexane/EtOAc mixture to give **4b** as a white solid.

4.3.1. (1*R*,3*R*,4*R*,7*R*)-2,5-Di[(*S*)-1-phenylethyl)]-7-phenyl-3-[(*R*)-1-phenylprop-2-en-1-yl]-2,5-diazabicyclo[2.2.1]heptane (4b). Yield 0.32 g (74%), R_f 0.5 (7:3 cyclohexane/EtOAc), mp=85.9–86.6 °C. $[\alpha]_D^{25}$ +41.7 (*c* 1.06, $CHCl_3$). IR (KBr): ν_{max} 2958, 2928, 1948, 1875, 1801, 1451, 759. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.29 (d, *J*=6.2, 3H, CHC*H*$_3$), 1.34 (d, *J*=7.3, 3H, CHC*H*$_3$), 2.63 (dd, J^1=8.4, J^2=2.4, 1H, NC*H*), 3.04 (q, *J*=6.2, 1H, NC*H*Ph), 3.26 (d, *J*=8.0, 1H, PhC*H*CHCH$_2$N), 3.32 (s, 1H, C*H*CH$_2$N), 3.55 (s, 2H, C*H*$_2$N), 3.55 (q, *J*=7.3, 1H, NC*H*Ph), 3.62 (s, 1H, PhCHCHCHN), 4.30 (q, *J*=6.7, 1H, PhC*H*CH=CH$_2$), 4.97 (dd, J^1=1.5, J^2=17.1, 1H, CH=C*H*$_2$), 5.09 (dd, J^1=1.5, J^2=10.0, 1H, CH=C*H*$_2$), 6.50 (ddd, J^1=8.0, J^2=10.0, J^3=17.1, 1H, CHC*H*=CH$_2$), 6.90 (m, 5H, Ph), 7.00 (m, 5H, Ph), 7.20 (m, 5H, Ph), 7.50 (m, 5H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.2, 48.7, 60.31, 62.5, 63.8, 64.3, 65.4, 115.0, 125.6, 140.0, 140.3, 143.8, 144.5, 148.5. GC–MS (EI) *m*/*z*: 207 (100), 105 (86), 172 (36), 394 (30), 144 (23), 189 (22), 281 (21), 232 (16), 337 (16). Anal. Calcd for $C_{36}H_{38}N_2$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.99; H, 7.70; N, 5.60.

4.4. Synthesis of 1,2-diamines 12a–d from C_2-symmetric 1,2-diamines 1b,c: general procedure

A solution of the diamine **1** (5 mmol) in anhydrous THF (30 mL) was cooled to −78 °C and *n*-BuLi (2.5 M, 15 mmol, 6 mL) was added over 15 min while magnetically stirring. The mixture was further stirred for 1.5 h, during which the temperature was raised to −60 °C, and then quenched by slow addition of de-aerated H_2O (30 mL). The organic phase was extracted with Et_2O (3×30 mL), the collected ethereal layers were washed with brine and dried over Na_2SO_4, then concentrated at reduced pressure. The residue was subjected to column chromatography on SiO_2 eluting with cyclohexane/EtOAc mixture. The compounds **12b**[6b] and **12d**[6a] have been previously described.

4.4.1. (5*E*)-(2*R*,3*R*)-2,3-Di-[(*S*)-1-phenylethylamino]-6-phenyl-5-hexene (12a). Yellowish oil; 63%, R_f 0.3 (1:1 cyclohexane/EtOAc). $[\alpha]_D^{25}$ −120.3 (*c* 1.7, $CHCl_3$). IR (neat): ν_{max} 3059, 1945, 1873, 1805, 1109. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, *J*=6.2, 3H, CHC*H*$_3$), 1.35 (d, *J*=6.2, 3H, CHC*H*$_3$), 1.37 (d, *J*=5.2, 3H, CHC*H*$_3$), 1.70 (br s, 2H, N*H*), 2.14 (m, 2H, NCHC*H*$_2$), 2.20 (m, 1H, NC*H*), 2.30 (m, 1H, NC*H*CH$_3$), 3.72 (q, *J*=6.2, 1H, C*H*CH$_3$), 4.81 (q, *J*=6.2, 1H, C*H*CH$_3$), 5.82 (m, 1H, C*H*=CH), 6.05 (d, J_{trans}=15.8, 1H, CH=C*H*), 7.18–7.32 (m, 15H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.9, 25.2, 25.3, 33.9, 52.1, 55.3, 55.7, 59.6, 125.9, 126.8, 126.8, 126.9, 127.0, 127.7, 128.3, 128.4, 131.8, 137.6, 145.9. GC–MS (EI) *m*/*z*: 105 (100), 250 (44), 281 (22), 148 (19). Anal. Calcd for $C_{28}H_{34}N_2$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.12; H, 8.62; N, 7.05.

4.4.2. (5*E*)-(2*R*,3*R*)-2,3-Di-[(*S*)-1-phenylethylamino]-5,7-octadiene (12c). Yellowish oil; 78%, R_f 0.2 (8:2 cyclohexane/EtOAc). $[\alpha]_D^{25}$ −104.9 (*c* 1.2, $CHCl_3$). IR (neat): ν_{max} 3407, 3323, 3083, 3062, 3025, 2960, 2924, 1492, 1451, 1369, 1273, 1110, 1006, 762, 701. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, *J*=6.3, 3H, NCHC*H*$_3$), 1.05 (d, *J*=6.3, 3H, NCHC*H*$_3$), 1.33 (d, *J*=6.5, 6H, CHC*H*$_3$), 1.38 (d, *J*=6.5, 6H, CHC*H*$_3$), 1.56 (br s, 2H, N*H*), 2.14–2.44 (m, 4H, NC*H*NC*H*CH$_2$), 3.87 (q, *J*=6.2, 1H, NC*H*Ph), 3.88 (q, *J*=6.2, 1H, NC*H*Ph), 4.99 (dd, J^1=1.8, J^2=10.3, 1H, CH=C*H*$_2$), 5.08 (dd, J^1=1.8, J^2=17.2, 1H, CH=C*H*$_2$), 5.47 (m, 1H, CH$_2$C*H*=CH), 5.89 (dd, J^1=10.4, J^2=15.2, 1H, CH=C*H*CH), 6.25 (ddd, J^1=10.3, J^2=17.2, J^3=19.8, 1H, CHC*H*=CH$_2$), 7.25–7.45 (m, 10H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): 17.0, 25.2, 25.4, 33.4, 52.0, 55.1, 55.5, 59.4, 114.9, 126.6, 126.7, 126.9, 127.0, 128.2, 131.9, 133.0, 137.0, 146.0, 146.1. GC–MS (EI) *m*/*z*: 105 (100), 200 (61), 148 (3), 96 (31), 79 (20), 281 (20), 177 (4), 348 (2). Anal. Calcd for $C_{24}H_{32}N_2$: C, 82.71; H, 9.25; N, 8.04. Found: C, 82.57; H, 9.23; N, 8.06.

4.5. Iodine-mediated cyclization of the diaminodienes 6a,b and diaminoalkenes 12a–d. Preparation of bridged piperazines 7a,b and 13a–d

The same procedure previously described for the iodine-mediated cyclization of compound **1b** was followed, but using a 1:1 molar ratio **6**/I_2 or **12**/I_2.

4.5.1. (1*R*,3*R*,4*R*,6*R*)-2,5-Di[(*S*)-1-phenylethyl)]-3-phenyl-6-[(*E*)-3-phenyl-2-propen-1-yl)]-2,5-diazabicyclo[2.2.1]heptane (7a). White solid; 61%, R_f 0.7 (9:1 cyclohexane/EtOAc), mp 59–61 °C. $[\alpha]_D^{20}$ −11 (*c* 0.75, $CHCl_3$). IR (Nujol): ν_{max} 2925, 2850, 1492, 1450, 1100, 968, 749, 701. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (d, *J*=6.5, 3H, CHC*H*$_3$), 1.20 (d, *J*=6.7, 3H, CHC*H*$_3$), 1.64 (dd, J^1=9.8, J^2=1.6, 1H, NCHC*H*$_2$CHN), 1.81 (dd, J^1=9.8, J^2=1.6, 1H, NCHC*H*$_2$CHN), 2.37 (dt, J^1=10.3, J^2=2.5, 1H, CHC*H*$_2$CH=CH), 2.52 (td, J^1=10.3, J^2=2.5, 1H, CHC*H*$_2$CH=CH), 3.19 (s, 1H, NC*H*CHCH$_2$), 3.27 (s, 1H, NC*H*CHPh), 3.38 (q, *J*=6.5, 1H, NC*H*CH$_3$), 3.46 (m, 1H, NC*H*CH$_2$CH=CH), 3.62 (q, *J*=6.7, 1H, NC*H*CH$_3$), 3.81 (d, *J*=2.5, 1H, NC*H*(Ph)CHN), 5.80 (ddd, J^1=15.8, J^2=10.3, J^3=2.5, 1H, C*H*=CHPh), 6.38 (d, J^1=15.8, 1H, CH=C*H*Ph), 6.69–7.53 (m, 20H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.9, 23.5, 31.8, 34.1, 62.8, 64.6, 65.2, 67.1, 70.4, 73.6, 125.8, 129.2, 130.0, 137.8, 143.0, 146.4. MS *m*/*z*: 499.2 $[M+H]^+$. Anal. Calcd for $C_{36}H_{38}N_2$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.86; H, 7.69; N, 5.61.

4.5.2. (1*R*,3*R*,4*R*,6*R*)-2,5-Di[(*S*)-1-phenylethyl)]-3-ethenyl-6-[(*E*)-2,4-pentadien-1-yl)-2,5-diazabicyclo[2.2.1]heptane (7b). Clear oil; 58%, R_f 0.8 (9:1 cyclohexane/EtOAc). $[\alpha]_D^{20}$ −49.8 (*c* 0.60, $CHCl_3$). IR (neat): ν_{max} 3024, 2971, 2010, 1960, 1903, 1451, 1301, 1101, 1003, 910, 766, 700. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (d, J^1=6.6, 3H, CHC*H*$_3$), 1.35 (d, J^1=6.6, 3H, CHC*H*$_3$), 1.55 (br s, 2H, NCHC*H*$_2$CHN), 2.36 (dt, J^1=9.6, J^2=2.5, 1H, C*H*$_2$CH=

CH), 2.54 (dt, J^1=10.3, J^2=2.5, 1H, CH_2CH=CH), 3.08 (br s, 1H, NCHCH$_2$CH), 3.12 (br s, 1H, NCHCH$_2$CH), 3.14 (m, 1H, NCHCH=CH$_2$), 3.26 (m, 1H, NCHCH$_2$CH=CH), 3.50 (q, J=6.2, 1H, NCHPh), 3.59 (q, J=6.3, 1H, NCHPh), 5.02 (dd, J^1=1.8, J^2=10.2, 1H, CH=CH_2), 5.16 (dd, J^1=1.8, J^2=15.9, 1H, CH=CH_2), 5.20 (dd, J^1=6.7, J^2=10.2, 2H, CH=CH_2), 5.39 (ddd, J^1=6.3, J^2=8.0, J^3=15.1, 1H, CH=CH$_2$), 6.18 (m, 2H, CH=CH–CH=CH$_2$), 6.44 (m, 1H, CH=CH–CH=CH$_2$), 7.26–7.46 (m, 10H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.5, 24.4, 31.3, 34.5, 63.1, 65.1, 65.3, 66.9, 70.3, 72.6, 114.8, 115.1, 127.2, 127.4, 128.9, 132.3, 135.2, 142.7, 145.5, 146.8. GC–MS (EI) m/z: 105 (100), 331 (52), 293 (26), 189 (14), 332 (14), 398 (4). Anal. Calcd for $C_{28}H_{34}N_2$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.70; H, 8.62; N, 7.01.

4.5.3. (1*R*,3*R*,4*R*,6*R*)-2,5-Di[(*S*)-1-phenylethyl)]-3-methyl-6-phenyl-2,5-diazabicyclo[2.2.1]heptane (13a). Yellowish oil; 70%, R_f 0.7 (2:1 cyclohexane/EtOAc). $[\alpha]_D^{20}$ −65.0 (c 0.7, $CHCl_3$). IR (neat): ν_{max} 2924, 2852, 1731, 1450, 1372, 1096, 802, 765, 700. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.08 (d, J=6.4, 3H, NCHCH_3), 1.16 (d, J=6.4, 3H, NCHCH_3), 1.44 (d, J=6.1, 3H, NCHCH_3), 1.74 (dd, J^1=9.5, J^2=14.1, 2H, CHCH_2CH), 2.69 (dq, J^1=2.8, J^2=6.1, 1H, NCHCH$_3$), 3.06 (s, 1H, CH$_3$CHCH), 3.18 (s, 1H, PhCHCH), 3.37 (q, J=6.6, 1H, NCHPh), 3.61 (q, J=6.6, 1H, NCHPh), 3.79 (d, J=2.6, 1H, NCHPh), 6.72–7.54 (m, 15H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.0, 24.1, 31.5, 63.9, 64.2, 64.8, 65.4, 64.1, 73.3, 125.6, 126.2, 126.6, 127.0, 128.2, 142.7, 146.4. GC–MS (EI) m/z: 105 (100), 291 (94), 82 (35), 187 (22). Anal. Calcd for $C_{28}H_{32}N_2$: C, 84.80; H, 8.13; N, 7.06. Found: C, 85.06; H, 8.15; N, 7.05.

4.5.4. (1*R*,3*R*,4*R*,6*R*)-2,5-Di[(*S*)-1-phenylethyl)]-3,6-diphenyl-2,5-diazabicyclo[2.2.1]heptane (13b). Yellowish oil; 61%, R_f 0.4 (9:1 cyclohexane/EtOAc). $[\alpha]_D^{20}$ −25.9 (c 0.4, $CHCl_3$). IR (neat): ν_{max} 2927, 1954, 1900, 1840, 1496, 1450, 1262, 1089, 739, 704. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 (d, J=6.7, 6H, CHCH_3), 1.81 (d, J=1.1, 2H, CHCH_2), 3.41 (q, J=6.7, 2H, NCHCH$_3$), 3.45 (s, 2H, CHCH$_2$), 3.77 (s, 2H, NCHPh), 6.84–7.12 (m, 10H, Ph), 7.27 (m, 5H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.6, 32.1, 65.2, 67.7, 73.2, 76.4, 126.0, 129.2, 126.9, 127.6, 128.2, 129.3, 142.3, 146.3. GC–MS (EI) m/z: 247 (100), 207 (92), 105 (90), 77 (31), 281 (24), 352 (21). Anal. Calcd for $C_{33}H_{34}N_2$: C, 86.42; H, 7.47; N, 6.11. Found: C, 86.63; H, 7.49; N, 6.09.

4.5.5. (1*R*,3*R*,4*R*,6*R*)-2,5-Di[(*S*)-1-phenylethyl)]-3-methyl-6-ethenyl-2,5-diazabicyclo[2.2.1]heptane (13c). Yellowish oil; 68%, R_f 0.8 (4:1 cyclohexane/EtOAc). $[\alpha]_D^{20}$ −49.0 (c 0.6, $CHCl_3$). IR (neat): ν_{max} 2921, 2868, 1956, 1879, 1801, 1736, 1674, 1446, 1360, 1204, 694. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (d, J=6.5, 3H, NCHCH_3), 1.23 (d, J=5.8, 3H, NCHCH_3), 1.26 (d, J=6.1, 3H, NCHCH_3), 1.43 (q, J=9.5, 2H, CHCH_2CH), 2.56 (dq, J^1=5.8, J^2=2.5, 1H, NCHCH$_3$), 2.84 (s, 1H, NCHCH), 2.92 (s, 1H, NCHCH), 2.95 (s, 1H, NCHCH), 3.35 (q, J=6.5, 1H, NCHPh), 3.47 (q, J=6.1, 1H, NCHPh), 5.06 (m, 2H, CH=CH_2), 6.30 (ddd, J^1=6.3, J^2=10.1, J^3=17.3, 1H, CH=CH$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.6, 23.5, 23.8, 30.9, 43.3, 64.2, 64.6, 64.7, 65.4, 66.9, 71.0, 97.1, 113.9, 126.4, 126.5, 128.1, 142.1, 147.2, 164.1. GC–MS (EI) m/z: 105 (100), 241 (31), 82 (31), 137 (24), 199 (21). Anal. Calcd for $C_{24}H_{30}N_2$: C, 83.19; H, 8.73; N, 8.08. Found: C, 83.35; H, 8.74; N, 8.06.

4.5.6. (1*R*,3*R*,4*R*,6*R*)-2,5-Di[(*S*)-1-phenylethyl)]-3-(*n*-butyl)-6-ethenyl-2,5-diazabicyclo[2.2.1]heptane (13d). Yellowish oil; 58%, R_f 0.7 (3:1 cyclohexane/EtOAc). $[\alpha]_D^{20}$ −94.8 (c 0.47, $CHCl_3$). IR (neat): ν_{max} 2941, 2868, 2582, 1952, 1875, 1813, 1446, 1102, 910, 702. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76 (m, 2H, CH_2CH$_2$), 0.86 (t, J=7.4, 3H, CH$_2$CH_3), 1.19 (d, J=6.6, 3H, NCHPh), 1.21 (d, J=6.6, 3H, NCHPh), 1.32 (m, 4H, CH_2CH_2), 2.32 (m, 2H, NCHCH_2CH), 2.93 (s, 1H, NCH), 2.97 (s, 3H, NCHCH=CH$_2$ and NCH), 3.36 (q, J=6.6, 1H, NCHPh), 3.46 (q, J=6.4, 1H, NCHPh), 5.03 (m, 2H, CH=CH_2), 6.35 (m, 1H, CH=CH$_2$), 7.26 (m, 10H, Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4, 23.2, 23.3, 23.8, 27.0, 29.2, 30.4, 30.6, 62.5, 66.6, 70.0, 71.9, 113.9, 126.5, 126.8, 127.5, 127.7, 128.1, 128.2, 142.3, 146.9, 147.1. Anal. Calcd for $C_{27}H_{36}N_2$: C, 83.45; H, 9.34; N, 7.21. Found: C, 83.65; H, 9.37; N, 7.20.

4.6. X-ray crystallographic study of 7a

The diffraction experiments for **7a** were carried out at room temperature with a Bruker SMART Apex II CCD area detector diffractometer with use of graphite-monochromated Mo Kα radiation (λ=0.71073 Å). Intensity data were measured over full diffraction spheres with use of 0.3° wide ω-scans. The software SMART[10a] was used for collection of frames of data, indexing of reflections and determination of lattice parameters. The collected frames were then processed for integration by SAINT[10a] software and an empirical absorption correction was applied with SADABS.[10b] The structure was solved by direct methods (SIR, 97)[10c] and subsequent Fourier syntheses, and refined by full-matrix least-squares calculations on F^2 (SHELXTL)[11] with attribution of anisotropic thermal parameters to the non-hydrogen atoms. The aromatic, methyl and methylene hydrogen atoms were placed in calculated positions and refined with idealized geometry [C(sp^2)–H=0.93 Å, C(sp^3)–H=0.97 Å] whereas the other H atoms were located in the Fourier map and refined isotropically.

CCDC-637923 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.7. Hydrogenolysis of the bridged piperazines 4b, 7a and 13a. Preparation of the compounds 5b, 15 and 16

Typical procedure: A mixture of **4b** (0.230 g, 0.46 mmol), ammonium formate (0.261 g, 4.14 mmol) and 5% Pd/C (0.070 g) in EtOH (20 mL) was stirred at reflux for 3 h, then cooled, and the solid was filtered off. The solution was concentrated at reduced pressure and the oily residue was subjected to chromatography on a SiO_2 column eluting with EtOAc/MeOH/30% NH_4OH (9:1:0.1) mixture to give the compound **5b** (0.105 g, 78%) as a yellowish oil.

4.7.1. (1*R*,3*R*,4*R*,7*R*)-7-Phenyl-3-[(*R*)-1-phenylpropyl]-2,5-diazabicyclo[2.2.1]heptane (5b). Yellowish oil; 78%, R_f 0.2 (9:1:0.1 EtOAc/MeOH/30% NH_4OH). $[\alpha]_D^{20}$ −68.7

(c 1.7, $CHCl_3$). IR (neat): ν_{max} 3332, 3082, 3058, 3025, 2962, 2927, 2872, 1601, 1493, 1452, 1404, 1061, 732. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.63 (t, J=7.2, 3H, CH_2CH_3), 1.46 (m, 1H, CH_2CH_3), 1.65 (m, 1H, CH_2CH_3), 1.94 (br s, 2H, NH), 2.62 (dt, J^1=3.4 J^2=10.6, 1H, PhCHCH$_2$), 2.99 (d, J=10.6, 1H, NCH$_2$), 3.10 (dd, J^1=3.4 J^2=10.7, 1H, NCHCHCHPh), 3.32 (dd, J^1=3.1 J^2=10.6, 1H, NCH-CH$_2$N), 3.41 (s, 1H, PhCHCHCH$_2$), 3.67 (s, 1H, CH$_2$N), 3.82 (s, 1H, NCHCHCHPh), 7.16 (m, 3H, Ph), 7.22 (m, 3H, Ph), 7.41 (m, 4H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.5, 26.4, 50.0, 54.1, 55.1, 58.2, 60.8, 64.1, 126.2, 126.5, 127.6, 128.4, 128.5, 128.6, 137.4, 143.0. GC–MS (EI) m/z: 119 (100), 173 (38), 91 (35), 144 (34), 292 (26). Anal. Calcd for $C_{20}H_{24}N_2$: C, 82.15; H, 8.27; N, 9.58. Found: C, 82.45; H, 8.29; N, 8.25.

4.7.2. (1*R*,3*R*,4*R*,6*R*)-2-[(*S*)-1-Phenylethyl)]-3-phenyl-6-(3-phenylprop-1-yl)-2,5-diazabicyclo[2.2.1]heptane (15). Yellowish oil; 77%, R_f 0.3 (9:1 EtOAc/MeOH). $[\alpha]_D^{20}$ −63.8 (c 1.8, $CHCl_3$). IR (neat): ν_{max} 3330, 3085, 3052, 3024, 2965, 2921, 2875, 1600, 1492, 1410, 1068, 735. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (d, J=6.6, 3H, CH$_3$CHN), 1.37 (m, 2H, PhCH$_2$CH$_2$), 1.62 (m, 2H, NCHCH$_2$CH$_2$), 1.87 (d, J=9.6, 1H, CHCH$_2$CH), 2.01 (d, J=9.6, 1H, CHCH$_2$CH), 2.60 (dd, J^1=7.3, J^2=13.6, 1H, PhCH$_2$), 2.69 (dd, J^1=7.5, J^2=13.6, 1H, PhCH$_2$), 2.96 (ddd, J^1=1.8, J^2=5.9, J^3=7.7, 1H, NCHCH$_2$CH$_2$), 3.17 (s, 1H, NCHCHCH$_2$), 3.64 (s, 1H, PhCHCH), 3.66 (q, J=6.6, 1H, PhCHCH$_3$), 4.18 (s, 1H, PhCHN), 7.20 (m, 1H, Ph), 7.26–7.42 (m, 12H, Ph), 7.62 (d, J=7.4, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.6, 28.6, 28.8, 35.7, 36.0, 62.1, 63.2, 64.0, 64.5, 74.0, 125.7, 126.8, 127.1, 127.5, 128.1, 128.2, 128.3, 128.4, 128.5, 140.9, 142.4, 146.0. GC–MS (EI) m/z: 291 (100), 105 (51), 91 (33), 145 (24), 250 (21), 186 (15), 396 (6). Anal. Calcd for $C_{28}H_{32}N_2$: C, 84.80; H, 8.13; N, 7.06. Found: C, 84.62; H, 8.15; N, 7.04.

4.7.3. (1*R*,3*R*,4*R*,6*R*)-2-[(*S*)-1-Phenylethyl)]-6-methyl-3-phenyl-2,5-diazabicyclo[2.2.1]heptane (16). Yellowish oil; 86%, R_f 0.1 (9:1:0.1 EtOAc/MeOH/30% NH_4OH). $[\alpha]_D^{20}$ −63.8 (c 0.9, $CHCl_3$). IR (neat): ν_{max} 3332, 3085, 3022, 2962, 2924, 2872, 1494, 1415, 1063, 730. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (d, J=6.7, 3H, NCHCH$_3$), 1.30 (d, J=6.6, 3H, NHCHCH$_3$), 1.91 (dd, J^1=1.6, 9.9, 1H, CH$_2$), 2.00 (dd, J^1=1.6, J^2=9.9, 1H, CH$_2$), 3.08 (s, 1H, NCHCHCH$_3$), 3.16 (dq, J^1=1.9, 6.7, 1H, NHCHCH$_3$), 3.49 (br s, 1H, NH), 3.67 (q, J=6.6, 1H, PhCHCH$_3$), 3.70 (s, 1H, PhCHCHN), 4.19 (PhCHN), 7.29 (m, 4H, Ph), 7.42 (m, 4H, Ph), 7.68 (d, J=7.7, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.7, 22.9, 35.8, 58.8, 63.5, 63.6, 64.5, 73.5, 126.7, 126.9, 127.0, 127.3, 128.1, 128.3, 128.4, 140.5, 146.0. GC–MS (EI) m/z: 187 (100), 105 (82), 82 (46), 144 (32), 91 (28), 250 (19), 292 (12). Anal. Calcd for $C_{20}H_{24}N_2$: C, 82.15; H, 8.27; N, 9.58. Found: C, 82.34; H, 8.29; N, 9.56.

4.8. Hydrogenation of the bridged piperazines 7b and 13c. Preparation of the compounds 17 and 18

Typical procedure: A mixture of **7b** (0.166 g, 0.5 mmol) and 5% Pd/C (0.100 g) in MeOH (5 mL) was stirred under hydrogen (1 atm) for 1 h, then the solid was filtered off and the solution was concentrated at reduced pressure. The oily residue was subjected to column chromatography on a SiO_2 column eluting with cyclohexane/EtOAc (95:5) mixture to give the compound **17** as a whitish oil.

4.8.1. (2*R*,3*R*)-2-Methyl-1-[(*S*)-1-phenylethyl]-3-{*N*-[(*S*)-1-phenylethyl]propylamino}pyrrolidine (17). Yield 0.150 g (86%), R_f 0.4 (1:1 cyclohexane/EtOAc). $[\alpha]_D^{20}$ −59.4 (c 1.0, $CHCl_3$). IR (neat): ν_{max} 3062, 3025, 2957, 2925, 2855, 1492, 1451, 1369, 1110, 761, 700. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J=7.1, 3H, CH$_3$CH$_2$CH$_2$N), 0.92 (d, J^1=6.2, 3H, NCHCH$_3$), 1.04 (m, 2H), 1.22 (m, 5H), 1.33 (d, J^1=6.6, 3H, PhCHN), 1.35 (d, J^1=6.6, 3H, PhCHN), 1.49 (m, 1H,), 2.04 (ddd, J^1=5.1, J^2=5.9, J^3=5.9, 1H, NCHCHCH$_3$), 2.23 (quint, J=6.2, 1H, NCHCH$_3$), 3.82 (q, J=6.6, 1H, PhCHN), 3.84 (q, J=6.6, 1H, PhCHN), 7.27 (m, 2H, Ph), 7.34 (m, 8H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 16.8, 22.6, 25.2, 25.4, 30.3, 32.3, 52.0, 55.0, 55.6, 59.6, 126.7, 126.8, 127.0, 128.2, 146.1, 146.2. GC–MS (EI) m/z: 204 (100), 105 (100), 101 (94), 148 (35), 79 (20), 132 (5), 188 (2), 281 (2). Anal. Calcd for $C_{24}H_{34}N_2$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.40; H, 9.81; N, 7.97.

4.8.2. (2*R*,3*R*)-2-Pentyl-1-[(*S*)-1-phenylethyl]-3-{*N*-[(*S*)-1-phenylethyl]propylamino}pyrrolidine (18). White oil; 82%, R_f 0.5 (1:1 cyclohexane/EtOAc). $[\alpha]_D^{20}$ −56.7 (c 1.1, $CHCl_3$). IR (neat): ν_{max} 3321, 3062, 3026, 2956, 2925, 2854, 1492, 1452, 1369, 1262, 1106, 1027, 762, 700. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 (m, 2H), 0.84 (t, J=7.1, 6H, CH$_3$CH$_2$CH$_2$), 0.87 (m, 3H), 0.91 (m, 2H), 1.08 (m, 5H), 1.10 (m, 4H), 1.38 (d, J^1=6.6, 6H, PhCHN), 2.01 (m, 2H, NCHCHN), 3.82 (q, J=6.6, 2H, PhCHN), 7.26 (m, 2H, Ph), 7.32 (m, 8H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.5, 22.7, 24.7, 25.1, 29.3, 29.7, 30.2, 31.0, 55.7, 55.9, 126.9, 127.1, 127.5, 128.2, 128.7, 145.6. GC–MS (EI) m/z: 204 (100), 105 (85), 101 (46), 79 (6), 337 (6). Anal. Calcd for $C_{28}H_{42}N_2$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.95; H, 10.44; N, 6.88.

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Supplementary data

X-ray crystallographic study of compound **7a** and complete list of crystallographic parameters, bond lengths and angles, together with a labelled ORTEP drawing of **7a**. ^{1}H NMR and COSY of compounds **4b**, **5b**, **7b**, **13a**, **15** and **16**; ^{1}H and ^{13}C NMR, DEPT, HMQC, HMBC and HETCOR spectra of compound **17**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.09.035.

References and notes

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