Iodine-Mediated Cyclization of (4*R*,5*R*)-4,5-Diamino-*N*,*N*′-bis[(1*S*)-1-phenylethyl]-1,7-octadiene – A Stereoselective Route to 2,5-Diazabicyclo[2.2.1]heptanes

Claudio Fiorelli,[a] Carla Marchioro,[b] Gianluca Martelli,[a] Magda Monari,[a] and Diego Savoia*[a]

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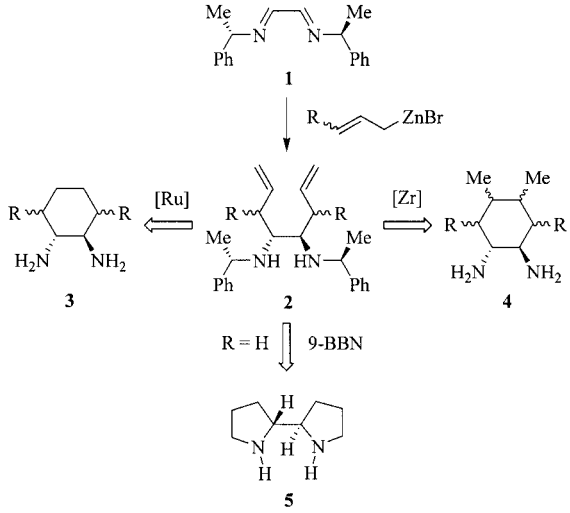
Treatment of (4*R*,5*R*)-4,5-diamino-*N*,*N*′-bis[(1*S*)-1-phenylethyl]-1,7-octadiene with 2 equiv. of iodine in CH_2Cl_2/aq. $NaHCO_3$ gave a mixture of two quaternary ammonium salts in 70:30 ratio and almost quantitative yield. The structure of the prevalent salt was determined by X-ray analysis, which showed a bridged diazatricyclic skeleton, derived from two iodoamination steps, both involving the 5-*exo* cyclization of two 5-aminoalkene moieties, and an intramolecular substitution involving the amine and iodide functions. The minor salt is an isomer of the prevalent one, formed by a pathway involving the stereospecific isomerization of the diastereomeric (iodomethyl)pyrrolidine produced in the first step to an iodopiperidine via an aziridinium intermediate. Treatment of both products with different reagents, including *i*PrMgCl, *n*BuLi, $Bu_3SnH{\cdot}Et_3B$, $Cr(OAc)_2$ and $Na_2S_2O_4$, invariably gave the bridged piperazine (1*S*,3*R*,4*S*)-3-allyl-2,5-bis[(1*S*)-1-phenylethyl]-2,5-diazabicyclo[2.2.1]heptane by a retro reaction, and hydrogenolysis of the *N*-substituents and concomitant hydrogenation of the C=C bond were then achieved in the presence of Pd/C.

Introduction

Enantiomerically pure compounds containing the 4,5-diamino-1,7-octadiene moiety (e.g., **2**), available through the highly stereoselective addition of allylic organozinc reagents to the chiral glyoxal diimine **1** or its enantiomer,[1] are valuable intermediates for the preparation of novel, more highly functionalized 1,2-diamines by identical transformation of both alkene functions. As an example, 1,2-diamino-4-cyclohexane derivatives **3** (R = H, Et) are available through ring-closing metathesis reactions of the corresponding precursors **2** (R = H, vinyl) catalysed by the Grubbs (benzylidene)-ruthenium complex,[2] followed by hydrogenation/hydrogenolysis of the intermediate substituted diaminocyclohexenes. On the other hand, 1,2-diamino-4,5-dimethylcyclohexanes **4** (R = H, Et, Ph) have been prepared through preliminary zirconium-promoted or -catalysed reductive cyclization reactions of the substituted diamino-dienes **2**[3] (R = H, vinyl, Ph). Moreover, 2,2′-bipyrrolidine (**5**) was prepared by Alexakis through hydroboration of the two alkene functions[4] (Scheme 1).



Scheme 1.

We envisioned that **2**, featuring both 4- and 5-aminoalkene moieties, might be usefully employed to prepare aza-heterocycles by electrophile-promoted intramolecular aminations of the C=C bonds.[5] In principle, different nitrogen heterocycles can be formed by competitive pathways, but 5-*exo* cyclization of the two 5-aminoalkene moieties would be expected to be the preferred pathway, over the 4-*exo* and 6-*endo* cyclizations of the 4- and 5-aminoalkene moieties, respectively, according to Baldwin's rules for ring closure.[6]

[a] Dipartimento di Chimica "G. Ciamician", Università di Bologna,
via Selmi 2, 40126 Bologna, Italy
[b] GlaxoSmithKline S.p.A., Medicines Research Centre,
via A. Fleming 4, 37135 Verona, Italy
Fax: +39-051-2099456
E-mail: diego.savoia@unibo.it
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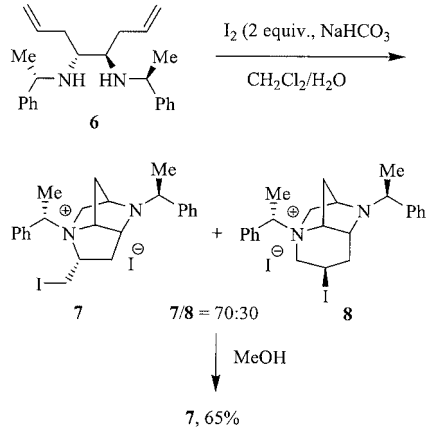
Results and Discussion

In analogy with the reported procedures for the cyclization of unsaturated primary, secondary and tertiary amines, which involve treatment with iodine or *N*-iodosuccinimide,[7] we treated the prototypical diamino-diene **6** with 2 equiv. of iodine in the biphasic dichloromethane/aqueous sodium hydrogencarbonate system (Scheme 2). A mixture of two polar products was observed by TLC, but these partially decomposed during the GC-MS analysis. Moreover, concentration of the organic solution at reduced pressure resulted in the isolation of a dark and viscous residue unless the bath temperature was kept below 30 °C. If this precaution was taken, an off-white solid was obtained in almost quantitative yield. ^{1}H NMR analysis of the crude product showed it to be mainly composed of two compounds in a 70:30 ratio, and chromatography on a silica gel column then allowed their partial separation. Later, we observed that the major product **7** would precipitate as a white powder if the crude reaction product was dissolved in methanol and could be separated by filtration. A further crop could then be collected from the filtered solution. After concentration of the mother liquor, the other, more polar compound could be isolated almost pure in low yield by column chromatography.



Scheme 2.

The 1D and 2D NMR spectra of the separated compounds gave interesting indications. Most importantly, an surprising difference in the chemical shifts of the methine protons in the two *N*-substituents was observed in the ^{1}H NMR spectra of the two compounds: in the first case, in fact, the methine hydrogen was detected as a signal at δ = 6.12 ppm, suggesting that the methine group was bound to a positively charged, quaternary nitrogen atom (also confirmed for both compounds by means of ^{1}H-^{15}N HNMQC NMR experiments). Moreover, the presence of only one iodine-bearing carbon atom was observed in each compound. Elemental and MS analyses (*m*/*z* = 473) gave identical results for both, strongly suggesting that they were isomers. At first, crystallisation of the main compound in different solvents proved unsuccessful. By chance, though, small crystals were observed after a few months in a residue resulting from one such attempt, although the original solvent is unknown, and these were suitable for X-ray diffraction studies. X-ray analysis (Figure 1) showed the structure of the ammonium iodide **7**, with the fused diazatricyclic skeleton and a *C*-iodomethyl substituent as well as the *N*-substituents. On the other hand, the minor product was the isomeric salt **8**, the structure of which, as well as the configuration of the iodo-substituted carbon atom, were determined by NMR studies. COSY, HSQC, and CIGAR-HMBC experiments were in agreement with the proposed structure. The ROESY data on this compound, also compared with those of compound **7**, indicated the reported stereochemistry. Trace amounts of another unidentified compound were detected in the ^{1}H NMR spectrum of a chromatographic fraction mainly containing **8**.

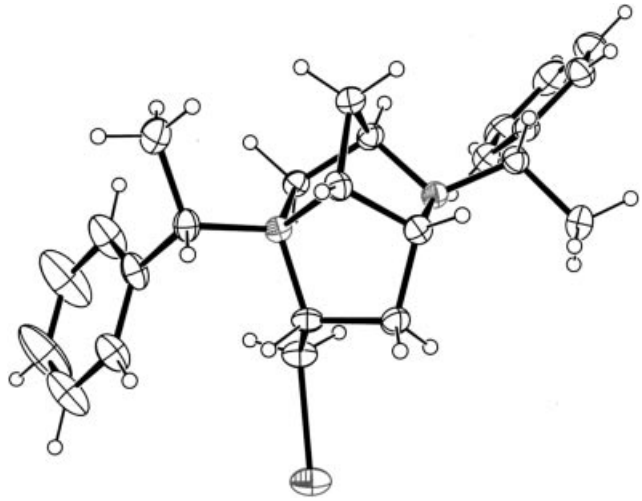
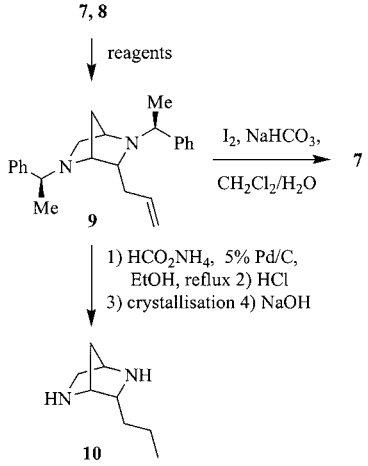


Figure 1. ORTEP drawing of the cation of compound **7**.

We treated both salts with organometallic reagents to achieve the reversal of the last iodoamination step through iodine/metal exchange and subsequent β-cleavage of the intermediate organometallic reagent. As a matter of fact, on use of isopropylmagnesium chloride at –30 °C, the lowest temperature allowing dissolution of **7** in tetrahydrofuran, we obtained compound **9**, featuring the 2,5-diazabicyclo[2.2.1]heptane ring, in high yield (Scheme 3 and Table 1).

The bridged bicyclic structure of the new product **9** was confirmed by ^{1}H NMR investigation. The same product resulted from a crude mixture of **7** and **8** on treatment with *n*-butyllithium and lithium aluminium hydride (Table 1). On the other hand, the reaction with magnesium turnings, activated with a catalytic amount of iodine in THF, was sluggish. Hydrogenolysis of the benzylic *N*-substituents in **9**, with concomitant hydrogenation of the C=C bond, was easily accomplished by treatment with ammonium formate and 5% palladium on carbon at reflux in ethanol. In this way the bridged piperazine **10** was obtained in a pure state through its dihydrochloride, which was crystallised from methanol and then treated with base (Scheme 3).

In an attempt to avoid the β-cleavage of the β-iodo-ammonium function and to preserve the tricyclic skeleton, we



Scheme 3.

Table 1. Conversion of compounds **7** and **8** into the bridged pyridazine **9**.

Substrate	Reagents (mol-equiv.)	Conditions	Yield (%)[a]
7	*i*PrMgCl (2.2)	THF, 0 °C, 1 h[b]	90, 68[c]
7	*n*BuLi (2.2)	THF, 0 °C, 1 h	97, 80[c]
7, **8**[d]	*n*BuLi (2.5)	THF, 0 °C, 1 h	97
7, **8**[e]	$LiAlH_4$ (1)	THF, 0 °C, 1 h	82
7	Zn (3)	THF, AcOH	95
7, **8**[e]	Bu_3SnH (2.5), Et_3B (2.5)	THF, –30 °C, 3 h	80[f]
7	$Cr(OAc)_2$ (5), *t*BuSH (5)	THF, 25 °C	71[f]
7	$Na_2S_2O_4$ (4)[g]	MeOH–H_2O/DMF	69

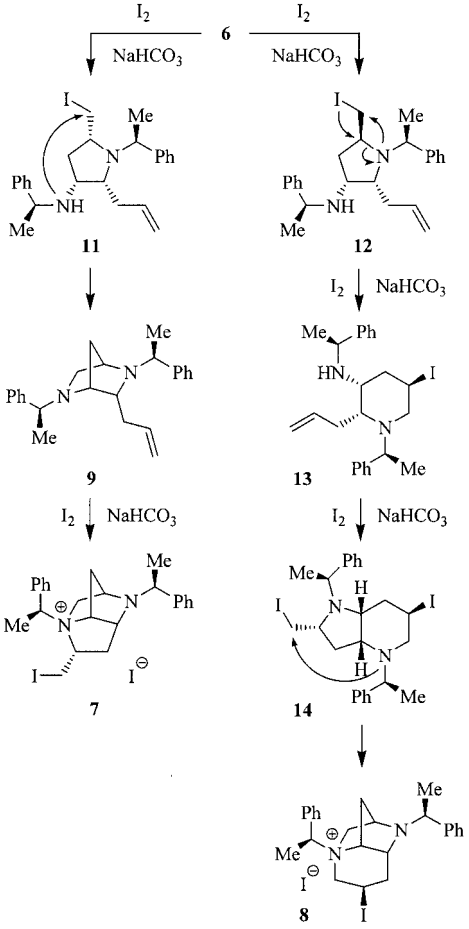
[a] Yield of crude product, >95% pure by ^1H NMR analysis. [b] The same result was obtained at –30 °C. [c] After crystallisation (MeOH) of the crude product. [d] Ratio **7**/**8** = 35:65. [e] Ratio **7**/**8** = 65:35. [f] After chromatography (SiO_2) of the crude product. [g] In the presence of $NaHCO_3$ (10 equiv.).

investigated the reductive deiodination of **7** by methods not involving the formation of an organometallic reagent from the iodide,[8] such as by treatment with zinc in tetrahydrofuran/acetic acid[9] and lithium aluminium hydride. However, partial or almost complete conversion to **9** was again observed in all cases (Table 1). In particular, the result of the latter reaction is in contrast with the successful reduction of β-bromo-amines by the same hydride, where no competing elimination was observed.[7b–7e] Even more surprisingly, we observed the complete conversion of **7**/**8** to **9** on treatment with tributyltin hydride and triethylborane[10] (2.5 equiv. each) in tetrahydrofuran at –30 °C, a procedure that proceeds by a radical pathway[11] and had been successfully employed for reductive deiodination of a β-iodoamine.[7f] Similarly, treatment of **7** with chromium(II) acetate/*tert*-butyl hydrosulfide in tetrahydrofuran[12] and with sodium dithionite in methanol/water/dimethylformamide[13] followed the same pathway, with slightly less efficiency. Moreover, hydrogenation of **7** in the presence of common palladium catalysts under different experimental conditions gave complex mixtures of products, in some cases containing **9** with low yields (GC-MS and NMR analyses), but the results were not reproducible and in no case did the desired reductive deiodination occur to a significant extent. These results are in contrast with the results of the palladium-mediated hydrogenolysis of both *N*-benzyl and C–I bonds of a (β-iodoalkyl)amine.[7h]

These reactions imply the fragmentation of the β-ammonium radical derived from the salts **7**/**8**. To the best of our knowledge, fragmentation of an ammonium salt through the unambiguous generation of a β-carbon radical has not been reported in the literature.[14] A plausible pathway for this process is the formation of an alkene and an aminium radical $[R_3N]^{\cdot+}$, which should then be reduced to the corresponding amine by one-electron transfer or to a metal amide by reaction with a low-valent metal salt, or converted to an ammonium ion $[R_3NX]^+$ by trapping of a radical $X^{\cdot}$ (hydrogen atom or a stannyl radical) from the reaction medium. In our case the cleavage is presumably favoured by the removal of the steric hindrance present in the compounds **7**/**8**.

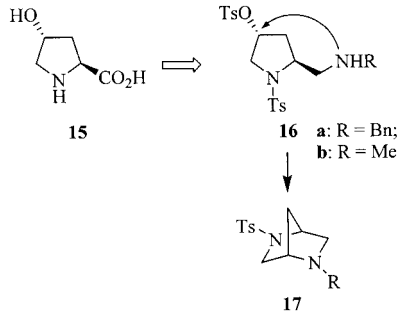
In order to assess the effect of different experimental conditions on the reaction outcome and especially to gain information on the reaction pathway/intermediates, further experiments were carried out on the diamino-diene **6**. Repetition of the reaction with 2 equiv. of iodine and stirring for a longer time (a further 12 h), or heating of the reaction mixture at reflux temperature for 3 h did not change the composition of the crude reaction mixture. Similarly, the same outcome was observed when the reaction was performed with 2 equiv. of iodine in diethyl ether for 3 h, with subsequent addition of aqueous sodium hydrogencarbonate to the still coloured solution. Moreover, treatment of the diamino-diene **6** with only 1 equiv. of iodine gave a mixture of the starting material and products **7**/**8**, rather than any intermediate. Finally, we treated the allyl-substituted bridged piperazine **9** with 1 equiv. of iodine and obtained the ammonium iodide **7** as the only product (Scheme 3).

In the light of these and previous results, we suggest that products **7** and **8** are formed from the diamino-diene **6** by the pathways described in Scheme 4. The cyclization of one 5-aminoalkene moiety could give the (iodomethyl)pyrrolidines **11** and **12** through the corresponding diastereomeric iodonium ions or iodine–alkene complexes. It is apparent that **11** should be prone to undergo cyclization to give the bridged piperazine **9** by intramolecular substitution of the primary iodide by the secondary amine. Then, a second iodoamination step from **9** could afford the ammonium ion **7**. On the other hand, **12** could undergo a stereospecific rearrangement to give the iodopiperidine **13**. Such ring expansions of 2-(halomethyl)- and 2-(hydroxymethyl)pyrrolidines, occurring through aziridinium intermediates, have been described in the literature.[7j,15] This could be followed by a second iodoamination step involving the residual 5-aminoalkene moiety, thus affording the fused pyrrolidinopiperidine **14**. The ammonium salt **8** could then be formed from **14** by intramolecular substitution. The intramolecular substitution steps (i.e., **6** to **11** and **14** to **8**) could also occur via aziridinium ions.



Scheme 4.

It is worth mentioning that the bridged piperazines **9** and **10** each have the 2,5-diazabicyclo[2.2.1]heptane skeleton of known *N*,*N*′-disubstituted derivatives, such as **17** (Scheme 5). This moiety has been incorporated in a variety of medicinal agents[16] to achieve enhanced microbiological activity, due to the increased rigidity with respect to the simple piperazine ring. Compounds **17** and analogues with different *N*-substituents, as well as their enantiomers, have been prepared from (*S*)- and (*R*)-4-hydroxyproline (e.g., **15**) through the intermediates **16**, which undergo cyclization by intramolecular S_N2 reaction at 80–110 °C (Scheme 5); *exo*- and *endo*-6-methyl-substituted derivatives have also been prepared by an analogous but longer sequence,[16f] whilst 6- and/or 7-methyl-substituted derivatives have been similarly prepared from *trans*-3,4-epoxyproline ethyl ester.[16g] A series of azabicyclo[2.2.1]-hydantoins has also been prepared in an enantiospecific way.[16h] It should be noted that our route is relatively short and requires milder reaction conditions for the cyclization step, taking advantage of the increased reactivity and interchanged positions of the iodide and amino functions in the intermediates **11**, **13** and **14** (Scheme 4), relative to **16** (Scheme 5). Another reported route to *C*-substituted derivatives of the bridged piperazine skeleton involves the poorly selective or inefficient metallation (*s*BuLi/TMEDA, THF, –78 °C) of *N*-Boc-*N*′-methyl-2,5-diazabicyclo[2.2.1]heptane, followed by the addition of an electrophile (aromatic ketone, diphenyl disulfide) and Boc hydrolysis.[17,18]



Scheme 5.

Conclusion

The described iodine-mediated cyclization of the 4,5-diamino-1,7-diene **6** allows the unprecedented differentiation of the two termini (C=C bonds) in a two-directional chain transformation of dienes.[16] It is possible to envisage potential applications of bridged piperazines such as **10** and its *N*-substituted derivatives in asymmetric reactions, such as their use as bases or ligands,[17] since their rigidities should reduce the variability of the inherent transition states. It is likely that other cyclization procedures should have potential for the construction of fused diazaheterocycles, with the same 2,6-diazabicyclo[3.3.0]octane skeleton as in the intermediate **13** (Scheme 4), provided that suitable intermediates unable to undergo a further intramolecular substitution step are formed. This should be the case for aminomercuration and hydroamination reactions. Finally, the iodine-mediated cyclization can be applied to chain-substituted 4,5-diamino-1,7-octadienes (e.g., **2**) and 4,5-diaminoalkenes, allowing the synthesis of differently substituted/functionalized bridged piperazines.

Experimental Section

General: Melting points are uncorrected. Solvents were distilled from the appropriate drying agent under Ar before use: THF (sodium benzophenone ketyl, then $LiAlH_4$), CH_2Cl_2 (P_2O_5). Optical rotations were measured with a digital polarimeter in a 1-dm cell and $[\alpha]_D$ values are given in 10^{-1} deg·cm^3·g^{-1}. ^{1}H NMR spectra were recorded with Varian Inova and Gemini instruments for samples in $CDCl_3$, which was stored over Mg. ^{1}H chemical shifts are reported in ppm relative to $CHCl_3$: δ_H = 7.27 ppm, *J* values are given in Hz (assignments: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br s = broad singlet, br m = broad multiplet, dd = doublet of doublets and dt = doublet of triplets). Assignments were assisted by several 2D experiments for structural and stereochemical determinations. Infrared spectra were recorded with a Nicolet FT-210 spectrometer and IR assignments are reported in wavenumbers [cm^{-1}]. MS spectra were taken at an ionising voltage of 70 eV with a Hewlett–Packard 5970 or 5890 spectrometer with GLC injection. Accurate masses were determined with an Micromass QTOF2 spectrometer operated in ES$^+$ ioniza-

tion mode. Molecular weights were determined with an Agilent Technologies MS 1100 instrument. Chromatographic separations were performed on columns of SiO_2 (Merck, 230–400 mesh) at medium pressure. The following materials were purchased from Aldrich: *n*BuLi (2.5 M in hexanes), *i*PrMgCl (2 M in THF), Et_3B (1 M in THF), $LiAlH_4$, Zn, Bu_3SnH, $Cr(OAc)_2$, $Na_2S_2O_4$.

Iodine-Mediated Cyclization of the Diamino-diene 6: A solution of I_2 (2.55 g, 10 mmol) in CH_2Cl_2 (50 mL) was slowly added to a magnetically stirred mixture of the diamino-diene **6** (1.74 g, 5 mmol), dissolved in CH_2Cl_2 (15 mL) and satd. aq. $NaHCO_3$ (30 mL). After stirring had been continued for 3 h, decoloration was observed. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The collected organic layers were dried with $CaCl_2$ and concentrated at reduced pressure at a temperature <30 °C. The solid pale-brownish residue consisted mainly of the two products in a 30:70 ratio (by ^{1}H NMR analysis). However, on dissolving the crude reaction product in MeOH (5 mL) at room temperature and then scratching the walls of the flask with a spatula, a white precipitate of **7a** was formed, and was then filtered off, washed with methanol and dried at reduced pressure: 1.60 g (53%). A further quantity of **7a** precipitated from the mother liquor, and was collected, representing a total yield of 1.96 g (65%). Chromatography of the mother liquor, containing **7a** and **7b** in a 2:1 ratio, on a silica gel column with elution with an EtOAc/MeOH mixture (4:1) gave pure fractions of compound **7b**, which were collected and concentrated to leave a white solid: 0.122 g (4%).

Ammonium Salt 7: M.p. 165–167 °C (dec). $[\alpha]_D^{25}$ = +21.4 (*c* = 0.69, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, see Figure 2 for atom numbering): δ = 1.29 (d, *J* = 6.8 Hz, 3 H, H-11), 1.78 (d, *J* = 6.5 Hz, 3 H, H-13), 2.03 (dd, *J* = 3.7, 9.8 Hz, 1 H, H-9), 2.18 (d, *J* = 12.4 Hz, 1 H, H-4), 2. 42 (m, 2 H, H-4, H-14), 3.07 (m, 1 H, H-9), 3.17 (dd, *J* = 10.7, 7.4 Hz, 1 H, H-14), 3.31 (d, *J* = 11.3 Hz, 1 H, H-6), 3.42 (br. s, 1 H, H-5), 3.53 (br. s, 1 H, H-2), 3.60 (q, *J* = 6.8 Hz, 1 H, H-10), 3.86 (dd, *J* = 11.3, 1.9 Hz, 1 H), 4.98 (m, 1 H, H-8), 5.28 (br. s, 1 H, H-3), 6.12 (q, *J* = 6.9 Hz, 1 H, H-12), 7.20 (d, 2 H, Ph), 7.27 (t, 1 H, Ph), 7.32 (t, 2 H, Ph), 7.47–7.51 (m, 3 H, Ph), 7.62 (d, 2 H, Ph) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ = 3.0, 17.3, 22.1, 33.9, 38.3, 56.2, 61.0, 62.7, 64.7, 72.0, 76.8, 81.5, 126.8, 126.8, 127.9, 129.0, 129.0, 129.2, 129.2, 129.9, 129.9, 131.0, 134.1, 143.7 ppm. IR (Nujol): $\tilde{\nu}_{max}$ = 3400, 1597 cm^{-1}. ES MS: *m*/*z* = 473 [$C_{24}H_{30}IN_2^+$]. $C_{24}H_{30}I_2N_2$ (600.32): C 48.02, H 5.04, N 4.67; found C 48.18, H 5.08, N 4.60.

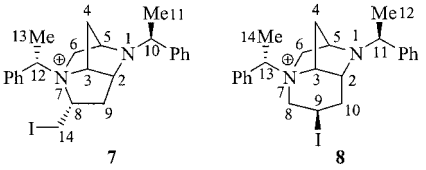


Figure 2. Atom numbering of compounds **7** and **8** for assignment of NMR absorptions.

Ammonium Salt 8: M.p. 139–141 °C (dec). $[\alpha]_D^{25}$ = +3.2 (*c* = 0.30, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, see Figure 2 for atom numbering): δ = 1.26 (d, *J* = 6.5 Hz, 3 H, H-12), 1.78 (d, *J* = 7.5 Hz, 3 H, H-14), 1.86 (t, *J* = 12.9 Hz, 1 H, H-10), 2.09 (m, 1 H, H-4), 2.47 (d, *J* = 12.9 Hz, 1 H, H-10), 3.11 (br. s, 1 H, H-2), 3.33 (d, *J* = 12.4 Hz, 1 H, H-4), 3.38 (t, *J* = 12.6 Hz, 1 H, H-8), 3.54–3.65 (m, 4 H, H-3, H-5, H-6, H-11), 4.09 (m, 1 H, H-8), 4.46 (br. d, *J* = 11.3 Hz, 1 H, H-6), 4.84 (m, 1 H, H-9), 5.89 (q, *J* = 7.5 Hz, 1 H, H-13), 7.23–7.29 (m, 3 H, Ph), 7.32 (t, 2 H, Ph), 7.49–7.57 (m, 5 H, Ph) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ = 10.0, 14.7, 22.2, 33.7, 38.9, 57.2, 60.1, 61.8, 63.4, 68.6, 70.1, 73.7, 126.9, 126.9, 127.9, 129.0, 129.0, 129.7, 129.7, 130.8, 130.8, 131.2, 132.0, 143.6 ppm. IR (Nujol): $\tilde{\nu}_{max}$ = 3422, 1620, 1279, 1230, 1038, 706 cm^{-1}. ES MS: *m*/*z* = 473 [$C_{24}H_{30}IN_2^+$]. $C_{24}H_{30}I_2N_2$ (600.32): C 48.02, H 5.04, N 4.67; found C 48.21, H 5.10, N 4.58.

Preparation of (1*R*,3*R*,4*R*)-2,5-Bis[(1*S*)-1-phenylethyl)]-3-(2-propenyl)-2,5-diazabicyclo[2.2.1]heptane (9)

Treatment of 7 with Isopropylmagnesium Chloride: *i*PrMgCl (2 M in THF, 3.3 mL, 6.6 mmol) was added over 5 min at 0 °C under Ar with stirring to a solution of **7** (1.80 g, 3 mmol) in dry THF (30 mL). After 1 h, the mixture was quenched with satd. aq. $NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (3×20 mL). The collected organic layers were dried with anhydrous $CaCl_2$ and concentrated to leave **9** as an off-white solid (1.02 g, 2.95 mmol, 98%), which was crystallised from MeOH: white needles, 0.71 g (2.05 mmol, 68%); m.p. 71–72 °C. $[\alpha]_D^{25}$ = –101.4 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (500 MHz, 25 °C): δ = 1.21 (d, *J* = 6.5 Hz, 6 H, 2×CH_3), 1.35 (br m, 2 H), 2.20 (br m, 1 H), 2.28 (dd, *J* = 3.10 and 9.48 Hz, 1 H), 2.32 (dt, *J* = 5.34 and 10.30 Hz, 1 H), 2.81 (d, *J* = 9.25 Hz, 1 H), 2.87–2.97 (m, 2 H), 2.99 (m, 1 H), 3.30 (q, *J* = 6.5 Hz, 1 H), 3.35 (q, *J* = 6.5 Hz, 1 H), 4.93 and 4.81 (m + m, 2 H), 5.45 (m, 1 H), 7.16–7.35 (m, 10 H, Ph) ppm. ^{13}C NMR (200 MHz, $CDCl_3$, 25 °C): δ = 22.5, 23.6, 28.7, 36.5, 59.9, 61.4, 64.5, 64.8, 69.5, 114.9, 126.5, 126.8, 128.1, 137.3, 140.1, 147.1 ppm. IR (Nujol): $\tilde{\nu}_{max}$ = 1635, 1598, 1299, 1213, 1103, 1095, 913, 770, 700 cm^{-1}. GC/EI-MS: *m*/*z* (%) = 105 (100), 241 (29), 68 (28), 137 (25), 305 (24), 173 (17), 80 (15), 172 (12), 346 (2) [M]$^+$. $C_{24}H_{30}N_2$ (346.24): C 83.19, H 8.73, N 8.08; found C 83.28, H 8.78; N, 8.02.

Treatment of 7 with *n*-Butyllithium: The reaction was performed as in the experiment described above but with *n*BuLi (2.5 M in hexanes, 2.4 mL, 6 mmol) to give crude **9** (1.01 g, 97%). Crystallisation from MeOH gave pure **9**: 0.83 g (80%). Treatment of a **7/8** mixture (35:65 ratio) with *n*BuLi (2.5 equiv.) gave crude **9** in 97% yield.

Treatment of 7 with Zinc/Acetic Acid: Zinc powder (0.59 g, 9 mmol) was flamed under a stream of argon, and was then cooled and covered with dry THF (10 mL). Glacial AcOH (5 mL) was added, followed by **7** (1.80 g, 3 mmol), and the mixture was magnetically stirred for 3 h, after which NaOH (40%) was carefully added until pH = 11. The mixture was extracted with CH_2Cl_2 (3×20 mL) and the collected organic layers were washed with brine (10 mL), dried with $CaCl_2$ and concentrated to leave crude **9** as an off-white solid: 0.99 g, (95%).

Treatment of 7 with Lithium Aluminium Hydride: $LiAlH_4$ (0.126 g, 3 mmol) was added at 0 °C under Ar to a stirred solution of **7** (1.80 g, 3 mmol) in THF (25 mL). After 1 h, the mixture was quenched with satd. aq. $NaHCO_3$ (10 mL) and stirred for a further 1 h. The organic phase was extracted with CH_2Cl_2 (3×20 mL), and the collected organic layers were washed with brine (10 mL), dried with $CaCl_2$ and concentrated to leave **9** as an off-white solid: 0.85 g (82%).

Treatment of 7 with Tributyltin Hydride/Triethylborane/Oxygen: Oxygen was bubbled at –30 °C for 2 min through a mixture of **7** (1.20 g, 2 mmol), Bu_3SnH (1.73 g, 6 mmol) and Et_3B (1 M in THF, 4.2 mL, 4.2 mmol) in THF (30 mL). The mixture was stirred for 3 h and then quenched with satd. aq. $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The collected organic layers were washed with brine (20 mL), dried with $CaCl_2$ and concentrated to leave a crude oil, which was chromatographed on a silica gel column, with elution with cyclohexane/EtOAc (10:1), to give **9** as an off-white solid: 0.55 g (80%).

Treatment of 7 with Chromium(II) Acetate/*tert*-Butyl Hydrosulfide: *t*BuSH (1.80 g, 20 mmol) and freshly prepared $Cr(OAc)_2$ (1.11 g,

10 mmol) were added in that order under Ar to a solution of **7** (1.20 g, 2 mmol) in THF (30 mL) . The mixture was magnetically stirred for 15 h, and then quenched with water (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The collected organic layers were washed with brine (10 mL), dried with $CaCl_2$ and concentrated to leave a crude oil, which was chromatographed on a silica gel column, with elution with cyclohexane/EtOAc (10:1), to give **9** as an off-white solid: 0.49 g (71%).

Treatment of 7 with Sodium Dithionite: Compound **7** (0.98 g, 2 mmol), $NaHCO_3$ (1.68 g, 20 mmol) and $Na_2S_2O_4$ (1.54 g, 8 mmol) were added sequentially to a mixture of solvents [DMF (8 mL), water (8 mL) and MeOH (12 mL)], and the mixture was magnetically stirred overnight. The mixture was diluted with CH_2Cl_2 (100 mL) and washed with brine (3 × 50 mL), dried with $CaCl_2$ and then concentrated to leave **9** as an off-white powder: 0.48 g (69%).

Preparation of (1*R*,3*R*,4*R*)-3-Propyl-2,5-diazabicyclo[2.2.1]heptane (10): A mixture of **9** (1.04 g, 3 mmol), NH_4HCO_2 (1.80 g, 27 mmol) and Pd/C (5%, 0.45 g) in EtOH (40 mL) was heated at reflux temperature for 2 h and then cooled, and the solid was filtered off. HCl (37%, 0.5 mL, 6.5 mmol) was added to the solution, which was then concentrated at reduced pressure. Toluene (10 mL) and EtOH (10 mL) were added to the residue and the solution was concentrated. The operation was repeated to leave the salt **10·2HCl** as an off-white solid (0.62 g), which was crystallised from a toluene/EtOH mixture (4:1): 0.48 g (76%); m.p. 289–291 °C (dec.). $[\alpha]_D^{25}$ = –28.7 (*c* = 0.6, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, [D_6]-DMSO): δ = 0.88 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.34 (m, 2 H, $CH_2CH_2CH_3$), 1.76 (m, 2 H, $CH_2CH_2CH_3$), 2.04 (m, 2 H, $CHCH_2CH$), 3.54 (m, 2 H, NCH_2), 3.62 (m, 1 H, $CHCH_2CH_2$), 4.34 (s, 2 H, $CHCH_2CH$), 9.0–11.0 (br m, 2 × NH_2^+) ppm. The free base **10** was obtained from the salt (400 mg, 1.88 mmol) by treatment with aq. NaOH (20%, 2 mL) and extraction with CH_2Cl_2 (10 × 3 mL), drying of the collected organic layers with $CaCl_2$ and concentration: brownish oil, 0.164 g (62%). $[\alpha]_D^{25}$ –45.2 (c, 0.6, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 0.94 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.20–1.60 (m, 4 H, $CH_2CH_2CH_3$), 1.76 (m, 2 H, $CHCH_2CH$), 1.82 (br. s, 2 H, NH), 2.70 (d, *J* = 9.8 Hz, 1 H, NCH_2), 2.97 (dd, J_1 = 2.2, J_2 = 9.8 Hz, 1 H, NCH_2), 3.12 (dt, J_1 = 1.4, J_2 = 6.8 Hz, 1 H, $CHCH_2CH_2$), 3.37 and 3.52 (2 s, 2 H, $CHCH_2CH$) ppm. ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ_C = 14.0, 20.1, 34.2, 38.6, 53.9, 56.7, 57.7, 62.3 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3443, 3264, 1261, 1169, 1116, 1063, 957, 751 cm^{-1}. GC/EI-MS: *m*/*z* (%) = 68 (100), 69 (56), 98 (44), 140 $[M]^+$ (22), 82 (19), 56 (11), 111 (10), 125 $[M - CH_3]^+$ (3). HR-MS: calcd. for $C_8H_{17}N_2$ $[M + H]^+$ *m*/*z* = 141.1392, found 141.1392.

X-ray Crystallographic Study of 7: The diffraction experiments for **7** were carried out at room temperature with a Bruker AXS SMART 2000 CCD based diffractometer with use of graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). Intensity data were measured over full diffraction spheres with use of 0.3° wide ω-scans, crystal-to-detector distance 5.0 cm. The software SMART[19a] 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[19a] software and an empirical absorption correction was applied with SADABS.[19b] The structure was solved by direct methods (SIR, 97)[19c] and subsequent Fourier syntheses, and refined by full-matrix least-squares calculations on F^2 (SHELXTL)[20] 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 idealised 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. The absolute configuration was determined [Flack parameter 0.01(2)]. CCDC-271177 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.

Supporting Information (see footnote on the first page of this article): X-ray crystallographic study of compound **7** and complete list of crystallographic parameters, bond lengths and angles, together with a labelled drawing of **7**. ^{1}H, ROESY and ^{13}C NMR spectra of compounds **7** and **8**.

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