Stereoselective and regioselective synthesis of azepane and azepine derivatives *via* piperidine ring expansion

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Diastereomerically pure azepane derivatives **5**, **13** were prepared by piperidine ring expansion with exclusive stereoselectivity and regioselectivity and in excellent yield. The structure and stereochemistry of **5** were confirmed *via* X-ray crystallographic analysis. The ring expansion strategy was applied to the construction of an azepine backbone **22** of a potential biologically active compound. The regiochemistry and stereochemistry of the piperidine ring expansion process were investigated by semiempirical molecular orbital calculations.

Introduction

Natural and synthetic compounds containing a chiral azepine ring display a range of potential or proven biological activities including gastroprokinetic action and protein kinase C inhibitory effect.[1] Numerous reports on synthetic approaches towards these compounds have been published.[2] However, their synthesis still remains a challenge due to the difficulty in constructing an asymmetric, seven-membered azepine backbone.

Recently, we reported the synthesis of an azepane-backboned chelating agent as a potential gadolinium contrast agent in magnetic resonance imaging (MRI), which displays a comparable relaxivity to commercially used MR contrast agents and excellent *in vitro* stability.[3] As reported therein, the synthesis of this chelating agent was based on a piperidine ring expansion, which leads to an azepane-backboned diazide with exclusive regioselectivity and diastereoselectivity. The possibility that the piperidine ring expansion might be a useful methodology for the construction of stereochemically pure azepine backbones in biologically active compounds prompted us to further investigate this rearrangement using either mono- or di-substituted piperidine substrates. Herein, we report the synthesis of a series of azepane and azepine derivatives *via* piperidine ring expansion. The stereo- and regio-selectivity observed during ring expansion have been investigated using computational methods.

Results and discussion

Previously, we reported that reaction of dichloride **1** with NaN_3 in DMSO provided the ring-expanded diazide **5** rather than the desired diazide **3** (Scheme 1). Interestingly, the ring-expanded diazide **5** was obtained only as a diastereomerically pure *cis*-isomer and in 92% yield. The structure of diazide **5** was solved *via* ^{1}H and ^{13}C NMR, and HRMS as reported previously.[3] Ultimately, the viscous diazide **5** was converted to bis-sulfonamide **6**[3] to confirm the structure and stereochemistry *via* X-ray analysis. The synthesis and X-ray crystal structure[4] of the derivative **6** are shown in Scheme 2. The X-ray crystal structure of **6** proves the stereochemistry of absolute configuration in *cis*-**5**. The seven-membered azepane ring in **6** is found to be planar with the ring atoms within 0.43 Å from the plane. The torsion angles between the azepane ring and the *cis* substituents are C2–C3–N3–S2 (133.3°) and C6–C1–C7–N1 (67.9°). It seems likely that ring expansion leading to diazide **5** proceeds *via* an aziridinium intermediate, which further undergoes regiospecific nucleophilic attack of azide anion at the methine carbon (Scheme 1).[5] As shown in Scheme 1, two possible diastereomeric ring-expanded products can be formed when the nucleophilic attack is on the stereogenic methine carbon in the intermediate **2**. Interestingly, the reaction provided only *cis*-**5**. The obtained exclusive diastereoselectivity and the absolute configuration in **5** suggest that the nucleophilic attack of the azide ion at the methine carbon proceeds with a backside S_N2 mechanism.

Considering that the protecting groups of the piperidine amine might influence the formation of the aziridinium ion, we planned to prepare compounds **10** and **11**[3] whose nitrogens were protected with more electron-withdrawing groups, *i.e.*, either benzyloxycarbonyl (CBz) or tosyl (Ts). The synthesis of compounds **10** and **11** is shown in Scheme 3. *N*-Benzyloxycarbonyl protected diol **8** was prepared by reduction of **7** by following the previously reported procedure.[6] Diol **8** was reacted with TsCl to afford *N*-CBz protected ditosylate **10** in 68% yield. Compounds **10** and **11** were each reacted with NaN_3 under the same reaction conditions used for the preparation of **5**. The results of the substitution reactions are summarized in Table 1. Interestingly, even when the piperidine amine was protected with a CBz group, the reaction again provided the ring-expanded diazide **13** in high yield (90%). The ^{1}H and ^{13}C NMR spectra of crude **13** taken after work-up display only signals corresponding to the rearranged diazide **13**, confirming the absence of the symmetric piperidine diazide. As expected, the substitution reaction when the piperidine amine was protected with a tosyl group did not afford any rearranged diazide contrary to **1** or **10** protected by a benzyl group or a CBz group.[3]

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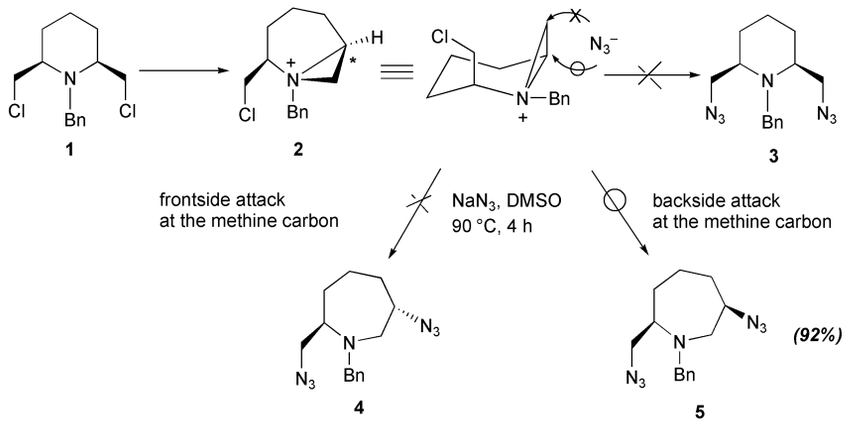
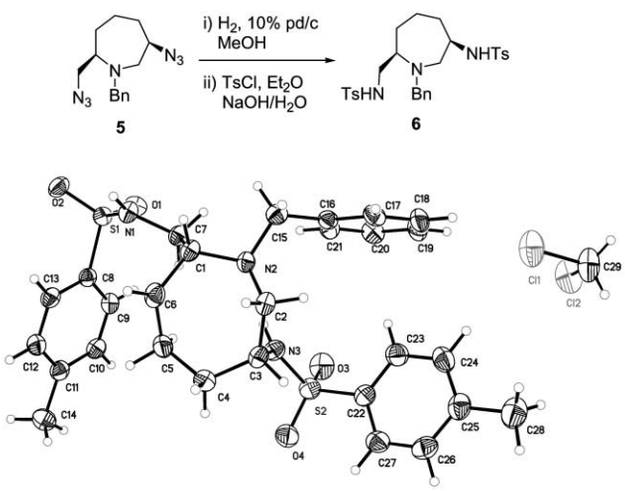
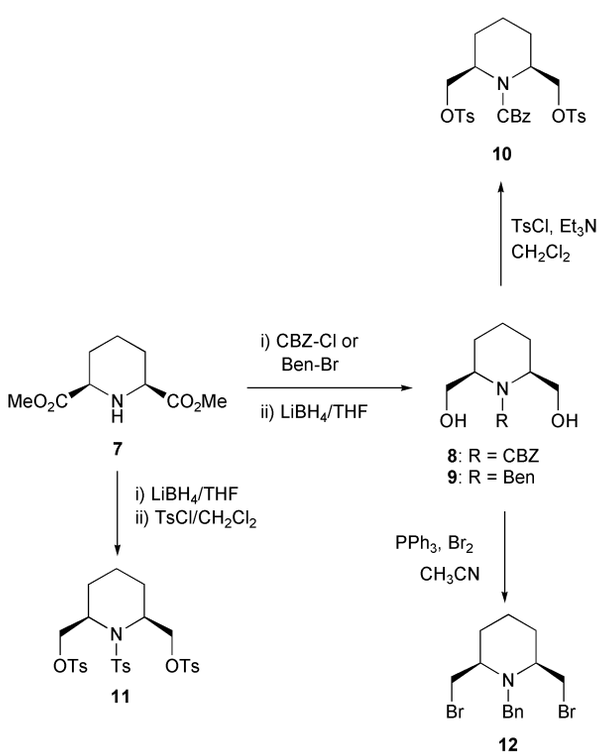


Scheme 1



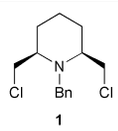
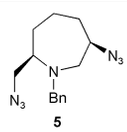
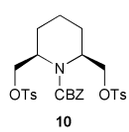
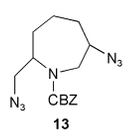
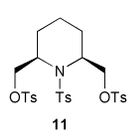
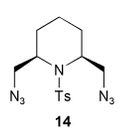
Scheme 2 Synthesis and X-ray crystal structure of **6**.

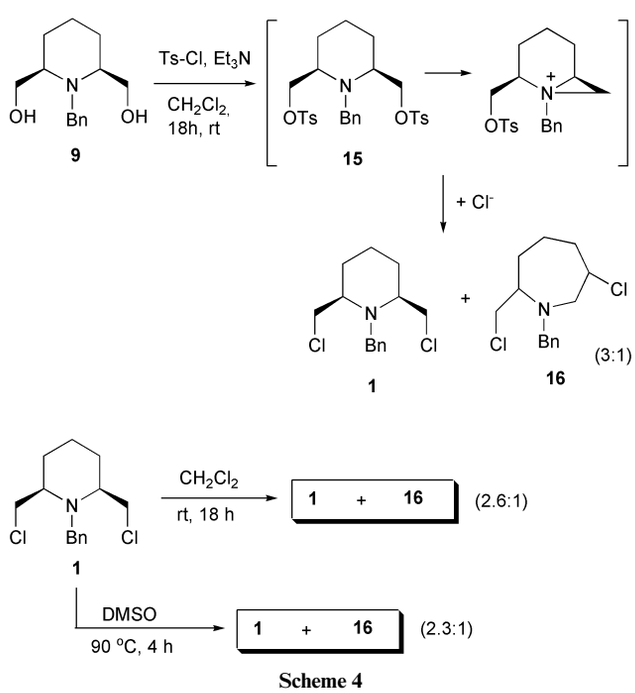


Scheme 3

For a better understanding of the influence of *N*-protecting groups on the aziridinium intermediate formation, we were interesting in performing electronic calculations. For this

Table 1 Reactions with NaN_3 in DMSO at 90 °C

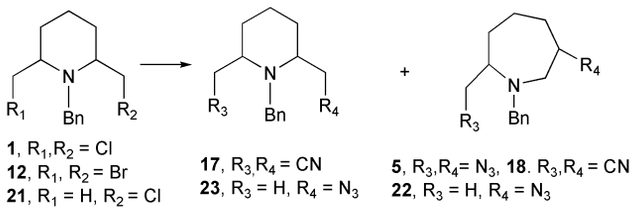
Starting material	Product	Yield (%)
		92
		90
		87



Scheme 4

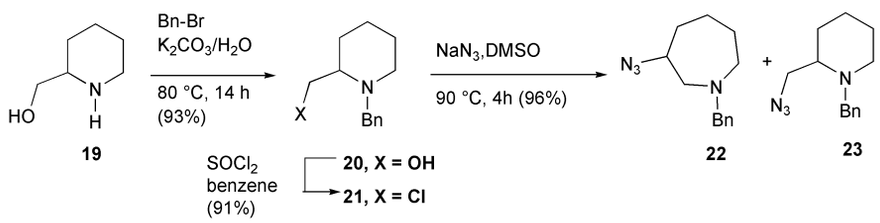
purpose, the experimental results obtained from ditosylate **15** having the same leaving groups as **10** and **11** were required. As a typical synthetic method for tosylation, diol **9** was reacted with TsCl in the presence of Et_3N for 18 h (Scheme 4). However, this attempted reaction failed to provide ditosylate **15**. Instead, both piperidine dichloride (**1**) and rearranged dichloride (**16**) were

Table 2 Substitution reactions of **1**, **12**, or **21** under various conditions



Entry	Starting material	Nucleophile	Solvent	Temp./°C	Time/h	Product (yield)
1	**1**	NaN_3	DMSO	90	4	**5** (92%)
2	**1**	NaN_3	DMSO	90	0.5	**5** (88%)
3	**1**	NaN_3	CH_3CN	Reflux	0.5	**5** (90%)
4	**1**	NaCN	DMSO	90	4	**17**, **18** (88%) [a]
5	**12**	NaN_3	DMSO	90	4	**5** (94%)
6	**12**	NaN_3	CH_3CN	Reflux	0.5	**5** (91%)
7	**21**	NaN_3	DMSO	90	4	**22**, **23** (96%) [b]

[a] Yield as a mixture of **17** and **18** in a ratio of 1 : 1 determined by ^{13}C NMR. [b] Yield as a mixture of **22** and **23** in a ratio of 1.6 : 1 determined by ^{13}C NMR.



Scheme 5

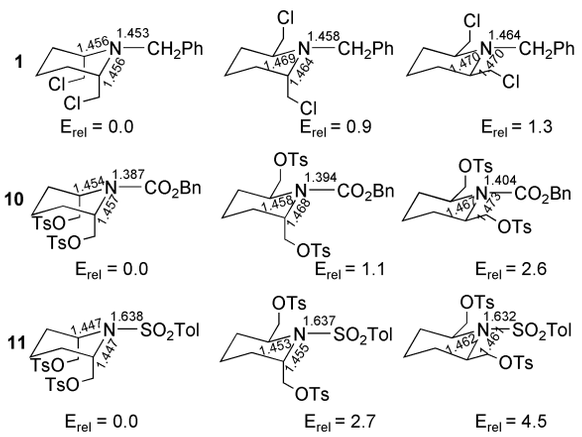
obtained as an inseparable mixture in a 3 : 1 ratio as determined by ^{13}C NMR. Mass spectra, ^1H, and ^{13}C NMR spectra of **1** obtained from the reaction were the same as that of authentic **1**.[3] The structure of the ring-expanded dichloride **16** obtained as an inseparable mixture along with **1** was confirmed *via* mass spectra, ^1H, and ^{13}C NMR spectra. The ^1H and ^{13}C NMR spectra taken after work-up did not contain any signals corresponding to either the target ditosylate **15** or starting material **9**. At this point, the mechanism of the reaction is not clear. However, **15** formed by reaction of **9** with TsCl appears to proceed to the aziridinium intermediate, which then undergoes nucleophilic attack by the chloride displaced from TsCl. In an attempt to demonstrate that the chloride can act as a nucleophile, the same substrate dichloride **1** in CH_2Cl_2 was stirred at room temperature for 18 h in the absence of TsCl and triethylamine. ^{13}C NMR spectra taken after evaporation of the solvent display both **1** and **16** at a ratio of 2.6 : 1. Dichloride **1** also was stirred in DMSO at 90 °C, the same conditions used for preparation of **5**. This time, the ratio of **1** : **16** was 2.3 : 1 as determined by NMR analysis (Scheme 4).

As shown in Table 2, it seems likely that neither solvent (CH_3CN or DMSO) nor reaction time (4 h or 0.5 h) had a significant influence on stereoselectivity and regioselectivity in the course of the ring expansion leading to diazide **5**. As another substrate, dibromide **12** was prepared by bromination of diol **9** in 68% yield (Scheme 3) and was reacted with NaN_3 under the same conditions used for preparation of **5**. The results in Table 2 show that the presence of bromide as a leaving group made little difference to the exclusive formation of **5**. However, when dichloride **1** was reacted with sodium cyanide using the same conditions as for the preparation of **5**, the dinitriles **17**, **18** were obtained as a mixture of rearranged and desired products in a 1 : 1 ratio as determined by ^{13}C NMR. The formation of the normal substitution product **17** seems likely attributable to the use of cyanide, a stronger nucleophile than azide successfully competing with the rearrangement pathway.

In an effort to demonstrate the utility of this regioselective and stereoselective ring expansion toward synthesis of chiral azepine rings, synthesis of 3-azido-1-benzylhexahydro-1*H*-azepine **22**, a common backbone of several potential biologically active compounds[1c,d] was attempted (Scheme 5). A commercially available starting material, piperidine-2-methanol **19**, was reacted with benzyl bromide in the presence of K_2CO_3 to provide *N*-benzyl-2-hydroxymethylpiperidine **20**,[7] which was further reacted with $SOCl_2$. The latter reaction provided 2-chloromethylpiperidine **21**[8] in 91% yield. However, reaction of **21** with NaN_3 provided both **22** and **23** in 96% yield as a 1.6 : 1 mixture based on ^{13}C NMR analysis. This result was somewhat surprising in the light of this being the same reaction conditions employed for the preparation of diazide **5**. In fact, Morie and co-workers synthesized the isomers **22** and **23**, as an inseparable mixture, which were characterized after being converted to the respective acetylamino derivatives of the isomers through several steps.[9] Contrary to this report, however, we were in fact successful in separating the isomers **22** and **23** chromatographically and fully characterized the isomers *via* ^1H, ^{13}C NMR, mass spectra, and CH analysis (see Experimental section). In the NMR spectrum of azepine **22**, an overlapping AB spin system corresponding to the benzylic protons was observed. The ^1H NMR spectrum of **23** contains a pair of doublets (δ 3.32 and 4.01) corresponding to the benzylic protons. Although the formation yield of **22** was somewhat decreased as compared to that of the disubstituted azepanes, this result demonstrates that this piperidine ring expansion strategy might be extended to the synthesis of a variety of enantiomerically pure azepine backbones in biologically active compounds such as (−)-balanol, a potent protein kinase C inhibitor.

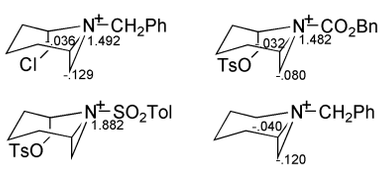
A noteworthy aspect was that the reactions of **1** and **10** with NaN_3 gave a rearranged product whereas **11** led to the unrearranged desired product (Table 1). At this juncture, we decided to examine these reactions qualitatively using computational methods. Semi-empirical molecular orbital calculations were performed employing the AM1 method and geometries were

completely optimized at the AM1 level of theory. The geometries have been fully characterized using vibrational analysis.[10] First, we examined the possible conformations of **1**, **10**, and **11**. Di-axial, axial–equatorial and the di-equatorial chair conformations of **1**, **10**, and **11** have been calculated at the AM1 level (Scheme 6). The calculated results suggest that the di-axial



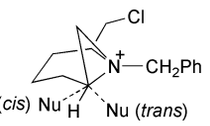
Scheme 6 Relative energies of conformations for **1**, **10**, and **11**.

conformations are the most stable in all the cases and that the di-equatorial conformers are found to be the least stable (Scheme 6). Such results suggest that the formation of an aziridinium ion intermediate would be favorable as the di-axial and axial–equatorial conformations are in the proper orientation for intramolecular S_N2 type attack from the nitrogen lone-pair. Furthermore, the aziridinium ion intermediates for the corresponding **1**, **10**, and **11** were calculated at the AM1 level (Scheme 7). The aziridinium ion formed from **11** appears



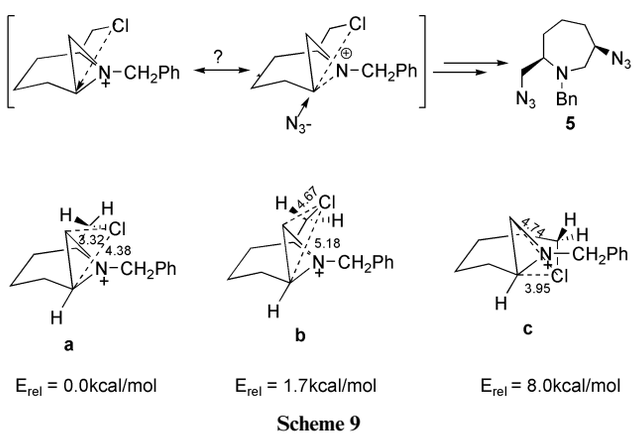
Scheme 7 Charge analysis of aziridinium cations corresponding to **1**, **10**, and **11**.

to possess a lengthened and perhaps weakened N–S bond. The calculated N–S bonds for di-axial, axial–equatorial, di-equatorial conformations are 1.638, 1.637, 1.632 Å, respectively (Scheme 6), while the calculated N–S bond in the aziridinium ion is 1.882 Å. This could be attributed to the strain induced by the formation of the aziridinium ion fused with the cyclohexane ring, which results in the dissociation of the N–S bond. Lengthening of the relevant bonds is also observed in the case of **1** and **10**, but these changes are within the limits of normal N–C bond lengths (Scheme 7). Additionally, *ab initio* calculations also have been performed on model systems of **1** and **11** to examine whether such a phenomenon is not an artifact of the AM1 calculations. Interestingly, the lengthening of the N–S bond has been observed at the HF/3-21G* level of theory consistent with our AM1 calculated results. These results indicate that formation of the aziridinium ion is unlikely in the case of **11**. The regioselective attack of azide as a nucleophile at the methine carbon of the aziridinium ion can be qualitatively explained *via* charge analysis. AM1 calculated natural charges for the aziridinium ions corresponding to **1** and **10** clearly indicate that the methine carbon is the more electrophilic site for nucleophilic attack Therefore, the favored attack to the methine carbon leads to the exclusive formation of the ring expanded products **1** and **10**. The exclusive formation of a diastereomerically rearranged *cis*-isomer is another important issue to be addressed. Therefore, we examined the geometry of the aziridinium ion intermediate of compound **1** as obtained from the most stable diaxial conformations. It is noteworthy that the formation of aziridinium ion induces strain in the parent cyclohexane ring, perturbing the ring conformation and causing the substituents to be in a pseudo-axial and equatorial arrangement. The backside attack of the nucleophile at the methine carbon in the aziridinium ion leads to formation of the *cis*-isomer. In order to obtain a *trans*-isomer, the nucleophile has to make a frontside attack at the methine carbon, which is not a favorable situation for S_N2-type reactions (Scheme 8).



Scheme 8 Optimized geometry of aziridinium cation **2**

In the case of the aziridinium cation corresponding to mono-substituted piperidine **21**, the calculated charges predict preferential formation of ring expanded **22** (Scheme 7). However, both ring expanded azepine **22** and piperidine **23** were experimentally obtained (Scheme 5). Contrary to the exclusive formation of rearranged products from disubstituted **1** and **10**, the formation of both rearranged and unrearranged products from mono-substituted piperidine derivative **21** prompted us to examine the possibility of anchimeric assistance of the neighboring chloride in azepine ring formation. In the case of the di-substituted derivatives, such participation is possible whereas it is not possible with the mono-substituted derivative. The formation of aziridinium ion intermediates from di-axial and axial–equatorial conformations of **1** has been considered here and the AM1 calculated energies are shown in Scheme 9. The



Scheme 9

calculated relative energies show that aziridinium ion intermediate **a** is the most stable geometry originating from **1** on a di-axial conformation. Considering the geometries of aziridinium ions, neighboring group assistance appears to be only possible in **a**, where the chloride is at a closer distance to the primary carbonium ion (3.32 Å). However, the methine carbon is at the furthest distance from chloride in **a** (4.38 Å). In the case of aziridinium ion intermediate **c** obtained from **1** on the axial–equatorial conformation, the distance between the methine carbon of the aziridinium ion and the chloride is 3.95 Å, at which anchimeric assistance of chloride to the formation of rearranged product is possible. However, the intermediate **c** is energetically unfavorable compared **a** and **b** (Scheme 9). It appears from the AM1 calculated energies and distances that anchimeric assistance does not play a significant role in the formation of ring expanded product. Alternatively, the exclusive formation of rearranged products in the case of di-substituted derivatives **1** and **10** can be argued on the possible increase in interactions between a chloromethyl group and the nitrogen lone-pair leading to an increased formation of aziridinium ion concentration compared to mono-substituted derivatives.

Conclusion

The *N*-benzyl or *N*-benzyloxycarbonyl protected azepane derivatives **5**, **13** were prepared by exclusive stereoselective and regioselective piperidine ring expansion in excellent yield. The influence of *N*-protecting groups, leaving groups, and nucleophiles on the formation of ring-expanded products was investigated in a preliminary form. We have demonstrated the potential of this ring expansion reaction as a useful route for the construction of enantiomerically pure azepine backbones of a variety of biologically active compounds *via* synthesis of an azepine ring **22**. The experimental results of the ring expansion reactions were supported by semi-empirical molecular orbital calculations.

Experimental

General

^{1}H, ^{13}C, and APT NMR spectra were obtained using a Varian Gemini 300 instrument. Chemical shifts are reported in δ ppm, and coupling constants J are in Hz. Elemental analyses were performed at Galbraith Laboratories, GA. Fast atom bombardment mass spectra (FAB-MS) were obtained on an Extrel 4000 in the positive ion detection mode.

N-Benzyloxycarbonyl-*cis*-2,6-bis(*p*-tolylsulfonyloxymethyl)-piperidine (10)

To a solution of **8**[6] (850 mg, 3.0 mmol) and Et_3N (1.3 mL, 9.1 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added dropwise a solution of TsCl (1.73 g, 9.1 mmol) in CH_2Cl_2 (3 mL) . The resulting solution was allowed to reach room temperature and stirred for 18 h. The resulting mixture was diluted with CH_2Cl_2 (30 mL) and washed with H_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel eluting with 25% EtOAc–hexane. Pure **10** was thereby obtained as a colorless viscous oil (1.2 g, 68%); δ_H (200 MHz: $CDCl_3$; Me_3Si) 1.25–1.86 (6 H, m, 3-H, 4-H, and 5-H), 2.48 (6 H, s, ArCH_3), 3.90–4.08 (2 H, m, 2-H and 6-H), 4.42–4.56 (4 H, m, CH_2OTS), 5.15 (2 H, s, OCH_2Ph), 7.32–7.45 (9 H, m, Ph), 7.83 (4 H, d, J 9.4, ArH); δ_C (200 MHz: $CDCl_3$; Me_3Si) 13.9 (t, 4-C), 21.3 (q, Me), 24.0 (t, 3-C and 5-C), 48.0 (d, 2-C and 6-C), 67.3 (t, CH_2OSO_2Ar), 69.1 (t, CH_2Ph), 127.5, 127.6, 127.8, 128.2, 129.7 (each d, 5 × Ar–CH), 132.2, 135.8, 144.8 (each s, 3 × Ar–C), 155.2 (C=O). This material was observed to be unstable; accordingly, it was used immediately as obtained in the next step.

N-Benzyl-*cis*-2,6-bis(bromomethyl)piperidine (12)

To a solution of triphenylphosphine (524 mg, 2 mmol) in dry CH_3CN (25 mL) cooled to 0 °C and under nitrogen was added bromine (0.27 mL, 5.26 mmol) dropwise. After stirring of the mixture for 0.5 h at 0 °C, a solution of **9**[3] (620 mg, 2.63 mmol) in CH_3CN (5 mL) was added dropwise and the resulting mixture was stirred for 7 days at room temperature. The solvents were evaporated and the residue was dissolved in $CHCl_3$ (30 mL). The organic phase was washed successively with saturated $NaHCO_3$ solution (30 mL) and brine (30 mL), dried, filtered, and evaporated. The residue was purified *via* column chromatography on silica gel eluting with 10% EtOAc–hexane. Pure **12** was thereby obtained as a colorless viscous oil (290 mg, 51%). The crude product was used directly in the next step. δ_H (200 MHz: $CDCl_3$; Me_3Si) 1.23–1.80 (6 H, m, 3-H, 4-H, and 5-H), 2.75–2.88 (2 H, m, 2-H and 6-H), 3.04–3.33 (4 H, m, CH_2Br), 3.74 (2 H, s, CH_2Ph), 7.13–7.28 (5 H, m, Ph); δ_C (200 MHz: $CDCl_3$; Me_3Si) 17.0 (t, 4-C), 26.3 (t, 3-C and 5-C), 34.1 (t, CH_2Br), 55.7 (t, CH_2Ph), 59.8 (d, 2-C), 126.8, 127.6, 127.8 (each d, 3 × Ar–CH), 139.8 (s, Ar–C); HRMS (Positive ion FAB) Found: M^+, 361.9942. $C_{14}H_{19}NBr_2$ requires M, 361.9937.

General procedure of NaN_3 reactions in DMSO

A mixture of either **1**,[3] **10**, **11**,[3] **12**, or **21** (5 mmol) and NaN_3 (15 mmol) in DMSO (20 mL) was heated to 90 °C for 0.5 h or 4 h. The resulting mixture was poured into ice–water and extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with H_2O (3 × 30 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated in *vacuo*.

cis-6-Azido-2-azidomethyl-1-benzylazepane (5)

A mixture of **12** (273 mg, 1 mmol) and NaN_3 (195 mg, 3 mmol) in DMSO (5 mL) was heated to 90 °C for 4 h. After work-up, pure **5** was obtained in 94% yield. The ^{1}H and ^{13}C NMR spectra of **5** are essentially identical to data reported previously.[3]

cis-6-Azido-2-azidomethyl-1-benzyloxycarbonylazepane (13)

A mixture of **10** (1.37 g, 5 mmol) and NaN_3 (15 mmol) in DMSO (20 mL) was heated to 90 °C for 4 h. After work-up, the residue was purified *via* column chromatography on basic alumina eluting with 10% EtOAc–hexane. Pure **13** was thereby obtained as a colorless viscous oil (1.40 g, 90%): δ_H (200 MHz: $CDCl_3$; Me_3Si) 1.20–2.03 (6 H, m, 3-H, 4-H and 5-H), 3.20–3.32 (1 H, m, 2-H), 3.49–3.63 (1 H, m, 6-H), 3.93 (1 H, m, CH_2N_3), 3.98–4.13 (2 H, m, 7-H), 4.36 (3 H, m, CH_2N_3 and CH_2Ph), 7.28–7.45 (5 H, m, Ph); δ_C (200 MHz: $CDCl_3$; Me_3Si) 22.7 (t, 4-C), 28.6 (t, 3-C), 29.1 (t, 5-C), 51.6 (t, CH_2N_3), 54.7 (t, 7-C), 55.4 (d, 2-C), 57.1 (d, 6-C), 67.6 (t, CH_2Ph), 128.3, 128.4, 128.6 (each d, 3 × Ar-CH), 135.5 (s, Ar-C), 156.9 (C=O). *m*/*z* (positive ion FAB) 330 (M^+), 197(M^+ − 135).

3-Azido-1-benzylhexahydro-1*H*-azepine (22) and *N*-benzyl-2-azidomethylpiperidine (23)

A mixture of **21** (2 g, 8.94 mmol) and NaN_3 (1.74 g, 26.8 mmol) in DMSO (20 mL) was heated to 90 °C for 4 h. The mixture of **22** and **23** (1.98 g, 96%) after work-up was separated *via* column chromatography on silica gel eluting with pentane to 5% EtOAc in hexanes to afford **22** (1.06 g, 52%). δ_H (200 MHz: $CDCl_3$; Me_3Si) 1.30–1.80–2.19 (6 H, m, 4-H, 5-H, and 6-H), 2.61–2.91 (4 H, m, 2-H and 7-H), 3.46–3.54 (1 H, m, 3-H), 3.68 (2 H, dd, J 15 and 15, CH2Ph), 6.90–7.10 (5 H, m, Ph); δ_C (200 MHz: $CDCl_3$; Me_3Si) 22.1 (t, 5-C), 29.0 (t, 6-C), 32.9 (t, 4-C), 55.9 (t, 7-C), 59.0 (t, 2-C), 61.3 (d, 3-C), 63.1 (t, CH_2Ph), 126.9, 128.2, 128.6 (each d, 3 × Ar-CH), 139.7 (s, Ar-C). Found: C, 68.00; H, 8.16. Calc. for $C_{13}H_{18}N_4$: C, 67.80; H, 7.88%. Continued elution with 8% EtOAc in hexanes provided **23** (605 mg, 29%). δ_H (200 MHz: $CDCl_3$; Me_3Si) 1.26–1.76 (6 H, m, 3-H, 4-H, and 5-H), 2.01–2.12 (1 H, m, 6-H), 2.46–2.52 (1 H, m, 2-H), 2.73–2.80 (1 H, m, 6-H), 3.32 (1 H, d, J 16, CH_2Ph), 3.45–3.50 (2 H, m, CH_2N_3), 4.01 (1 H, d, J 16, CH_2Ph), 7.22–7.35 (5 H, m, Ph); δ_C (200 MHz: $CDCl_3$; Me_3Si) 23.1 (t, 4-C), 24.9 (t, 3-C), 29.3 (t, 5-C), 51.4 (t, 6-C), 53.0 (t, CH_2N_3), 58.5 (t, CH_2Ph), 60.2 (d, 2-C), 126.8, 128.2, 128.7 (each d, 3 × Ar-CH), 139.0 (s, Ar-C). Found: C, 67.71; H, 8.08. Calc. for $C_{13}H_{18}N_4$: C, 67.80; H, 7.88%. Chromatographic elution also provided fractions containing a mixture of **22** and **23** (120 mg, 6%). Structures of **22** and **23** also are confirmed by HPLC retention time data reported previously.[9]

Reactions of 1 or 12 with NaN_3 in CH_3CN

A mixture of either **1** or **12** (5 mmol) and NaN_3 (15 mmol) in CH_3CN (20 mL) was heated to reflux for 0.5 h. The solvent was evaporated to dryness and dissolved in CH_2Cl_2 and washed with water. The organic phase was separated, dried ($MgSO_4$), and filtered. The filtrate was concentrated in *vacuo*. Pure **5** (>90% yield) was obtained from starting materials **1** or **12**. The ^{1}H NMR, ^{13}C NMR spectra of **5** are essentially identical to data reported previously.[3]

A mixture of *N*-benzyl-*cis*-2,6-bis(chloromethyl)piperidine (1) and 6-chloro-2-chloromethyl-1-benzylazepane (16)

Method 1. To a solution of **9** (850 mg, 3.0 mmol) and Et_3N (1.3 mL, 9.1 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added dropwise a solution of TsCl (1.73 g, 9.1 mmol) in CH_2Cl_2 (3 mL). The resulting solution was allowed to the room temperature and stirred for 18 h. The resulting mixture was diluted with CH_2Cl_2 (30 mL) and washed with H_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel eluting with 10% EtOAc–hexane to afford **1** and **16** (310 mg, 38%) as an inseparable mixture in a 3 : 1 ratio. ^{1}H and ^{13}C NMR signals corresponding to **1** are essentially identical to that of authentic **1**. Compound **16**: δ_H (200 MHz, obtained as a mixture of **16** with **1**, $CDCl_3$; Me_3Si) 1.40–2.40 (6 H, m, 3-H, 4-H, and 5-H), 2.81–4.06 (8 H, m, 2-H, 6-H, 7-H, CH_2Cl, and CH_2Ph), 7.22–7.45 (5 H, m, Ph); δ_C (200 MHz: $CDCl_3$; Me_3Si) 23.0 (t, 4-C), 31.6 (t, 3-C), 40.0 (t, 5-C), 46.8 (t, CH_2Cl), 55.1 (t, 7-C), 57.7 (d, 6-C), 59.2 (t, CH_2Ph), 62.3 (d, 2-C), 127.19, 128.3, 128.7 (each d, 3 × Ar-CH), 139.4 (Ar-C).;*m*/*z* (positive ion FAB) 272 (M^+).

Method 2. Dichloride **1** (100 mg, 0.37 mmol) was dissolved in DMSO (5 mL) and the resulting solution was heated to 90 °C for 4 h. The resulting mixture was poured into ice–water and extracted with Et_2O (2 × 30 mL). The combined organic layers was washed with H_2O (3 × 10 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated in *vacuo*. Both **1** and **16** were thereby obtained as a mixture in quantitative yield. The ^{1}H NMR, ^{13}C NMR spectra of **1** and **16** obtained as a mixture are essentially identical to data obtained in Method 1.

Method 3. Dichloride **1** (100 mg, 0.38 mmol) was dissolved in CH_2Cl_2 (5 mL) and the resulting solution was stirred at room temperature for 18 h. Evaporation of solvent provided both **1** and **16** as a mixture in quantitative yield. The ^{1}H NMR, ^{13}C NMR spectra of **1** and **16** obtained as a mixture are essentially identical to data obtained from Method 1.

A mixture of 2,6-bis(cyanomethyl)piperidine (17) and 6-cyano-2-cyanomethyl-1-benzylazepane (18)

A mixture of **1** (150 mg, 0.55 mmol) and NaCN (81 mg, 1.65 mmol) in DMSO (2 mL) was heated to 90 °C for 4 h. The resulting mixture was poured into ice–water and extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with H_2O (3 × 30 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated in *vacuo*. The residue was purified *via* column chromatography on basic alumina eluting with 10% EtOAc–hexane. A fraction containing the mixture of **17** and **18** was obtained (368 mg, 88%). The **17** : **18** ratio (1 : 1) was determined by ^{1}H NMR: δ_H (200 MHz, obtained as a mixture of **17** with **18**, $CDCl_3$; Me_3Si) 1.10–1.73 (m, 4 H), 1.87–2.61 (m, 8 H), 2.70–3.23 (m, 3 H), 3.80–3.96 (m, 2 H), 7.18–7.45 (10 H, m, Ph); δ_C (200 MHz: $CDCl_3$; Me_3Si) 21.2 (t), 21.9 (t), 23.4 (t), 24.0 (t), 30.0 (d), 30.2 (t), 33.0 (t), 33.6 (t), 49.2 (t), 56.9 (t), 58.6 (d), 58.7 (t), 59.0 (d), 117.8 and 118.4 (2 × CN), 126.4, 126.8, 127.1, 127.6, 128.4, and 128.6 (each d, 6 × Ar–CH), 138.0, 139.4 (each s, 2 × Ar–C); *m*/*z* (Positive ion FAB) 253 (M^+).

***N*-Benzyl-2-hydroxymethylpiperidine (20).[7]**

To a solution of **19** (2.3 g, 20 mmol) in ethanol (40 mL) and water (6 mL) was added benzyl bromide (3.58 g, 20 mmol) and potassium carbonate (8.28 g, 60 mmol). The resulting mixture was stirred at 80 °C for 12 h. Solvent was removed from the reaction mixture and the residue was dissolved in EtOAc and washed with H_2O (3 × 30 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on silica gel eluting with 50% EtOAc–hexane. Pure **20** was thereby obtained as a colorless viscous oil (3.8 g, 93%). δ_H (200 MHz: $CDCl_3$; Me_3Si) 1.33–1.71 (6 H, m, 3-H, 4-H, and 5-H), 2.10–2.19 (1 H, m, 6-H), 2.43–2.47 (1 H, m, 6-H), 2.70 (1 H, br s, OH), 2.73–2.89 (1 H, m, 2-H), 3.31 (1 H, d, *J* 10, CH_2OH), 3.52 (1 H, dd, *J* 5 and 4, CH_2Ph), 3.84 (1 H, dd, *J* 5 and 4, CH_2Ph), 4.05 (2 H, d, *J* 10, CH_2OH), 7.23–7.35 (m, 5 H); δ_C (200 MHz: $CDCl_3$; Me_3Si) 23.9 (t, 4-C), 25.6 (t, 5-C), 27.9 (t, 3-C), 45.9 (t, CH_2Ph), 57.7 (d, 2-C), 65.2 (t, CH_2OH), 126.7, 128.0, 128.6 (each d, 3 × Ar–CH), 138.8 (s, Ar–C). Found: C, 75.83; H, 9.59. Calc. for $C_{13}H_{19}NO$: C, 76.06; H, 9.33%.

***N*-Benzyl-2-chloromethylpiperidine (21).[8]**

A solution of **20** (2.8 g, 13.6 mmol) in dry benzene (30 mL) was saturated with HCl (g) at 0 °C. After addition of thionyl chloride (5 mL), the mixture was heated at 60 °C for 3 h. The cooled reaction mixture was concentrated and neutralized with 5% Na_2CO_3 solution. The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$) and filtered, and the filtrate was concentrated in *vacuo* to afford crude **21** (2.76 g, 91%). δ_H (200 MHz: $CDCl_3$; Me_3Si) 1.33–1.79 (6 H, 3-H, 4-H, and 5-H), 2.15–2.25 (1 H, m, 6-H), 2.64–2.82 (2 H, m, 2-H and 6-H), 3.40 (1 H, d, *J* 7, CH_2Ph), 3.68 (2 H, d, *J* 10, CH_2Cl), 4.04 (1 H, d, *J* 7, CH_2Ph), 7.26–7.39 (5 H, m, Ph); δ_C (200 MHz: $CDCl_3$; Me_3Si) 22.7 (t, 4-C), 25.1 (t, 5-C), 28.9 (t, 3-C), 45.6 (t, CH_2Cl), 51.1 (t, 6-C), 58.2 (t, CH_2Ph), 61.4 (d, 2-C), 126.9, 128.2, 128.9 (each d, 3 × Ar–CH), 139.5 (s, Ar–C). The ^{1}H NMR, ^{13}C NMR spectra of **21** as an acidic salt are essentially identical to data reported previously.[8]

X-Ray crystal structure determination of compound 6

Crystals for structure and stereochemistry determination were obtained by recrystallization of **6** from CH_2Cl_2–hexanes. $C_{29}H_{37}Cl_2N_3O_4S_2$, M = 626.64, triclinic, a = 10.245(8), b = 10.338(8), c = 15.970(12) Å, α = 79.037(13), β = 88.444(13), γ = 65.605(11)°, U = 1509.7(19) Å,^{3} T = 173(2) K, space group $P\bar{1}$, Z = 2, μ(Mo-Kα) = 0.393 mm^{-1}, 6844 reflections collected, independent/observed reflections 4307 (R_{int} = 0.0198), R_1 = 0.0412, wR_2 = 0.1096 [$I > 2\sigma(I)$].

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