Synthesis of chiral polyazamacrocycles of variable ring size†

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Synthesis and structure elucidation of optically active tri-, tetra-, and penta-azamacrocycles having 4-methoxyphenyl pendants are described. Regioselective ring opening of a nosylaziridine with secondary benzyl amines was repeatedly performed to afford the cyclization precursors. Intramolecular N-alkylation of N-(ω-haloalkyl) nosylamide provided tri-, tetra-, and penta-azamacrocycles. On the basis of our study of the tetra-azamacrocycle previously elucidated by X-ray single-crystal analysis and in solution by NMR analysis, we conclude that the tri-azamacrocycle does not mainly have a vase-type conformation because of the steric hindrance of the 4-methoxyphenyl groups but the penta-azamacrocycle has a vase-type conformation in $CDCl_3$ and in CD_2Cl_2. The vase-type conformation of the penta-azamacrocycle is, however, not as much stable as that observed in the tetra-azamacrocycle because conformational flexibility of the penta-azamacrocycle was observed in deuterated benzene.

Introduction

Polyazamacrocycle–metal complexes have been studied as MRI contrast agents in medicinal chemistry and as fluorescence probes in chemical biology.[1,2] We envisaged that chiral polyazamacrocyclic compounds with properly positioned substituents have a vase-type conformation in which functional groups are oriented toward the same face of the macrocyclic ring,[3] and thus would be useful as novel sensors with a molecular recognition site.

A C-nitrobenzyl cyclen derivative has been synthesized and the nitro group used as a linker in the synthesis of a bifunctional chelator.[4] More complexed C-substituted polyazamacrocyclic compounds have also been studied.[5] We recently reported the efficient synthesis of tetra-azamacrocyclic molecule **1**, in which four N-benzyl groups and four C-methoxybenzyl groups with (*S*)-stereochemistry are on a cyclic skeleton as pendant arms.[6] Interestingly, all methoxybenzyl groups on the tetra-azamacrocycle are oriented toward the same face by CH–π interactions of the alkoxyphenyl rings to give a vase-type conformation, as elucidated in the solid state by X-ray single-crystal analysis and in solution by NMR analysis on the basis of computational studies. For the synthesis of **1**, we utilized regioselective ring opening of N-nosylaziridine with secondary amines and efficient macrocyclization of N-(ω-iodoalkyl) nosylamide. In this article, we report the details of the ring-opening reaction of C-substituted aziridines with secondary amines and its application to the synthesis of tri- and penta-azamacrocycles, **2** and **3**, having 4-methoxybenzyl pendants (Fig. 1).

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† Electronic supplementary information (ESI) available: Experimental procedure and spectral data for **4** and **6**, ^1H and ^{13}C NMR spectra of **1–3**, **4a–4f**, **6a–6f**, and **8–18**, COSY spectrum of **10**, COSY, HMQC, and HMBC spectra of **1**, and HMQC spectrum of **3**. See DOI: 10.1039/c001228a

Results and discussion

Ring opening of N-substituted aziridines with secondary benzylamine

Aziridine derivatives **4** and secondary benzylamine **5** were readily prepared from L-tyrosine in optically pure form.[6] The ring-opening reaction of **4** of various benzylamines can be adopted for preparing

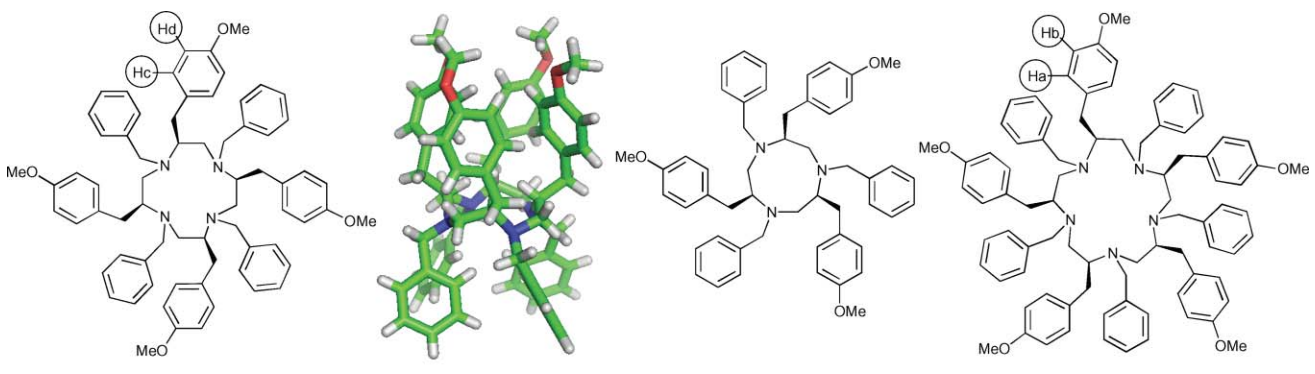
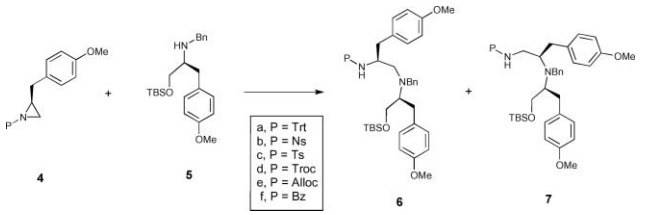


Fig. 1 Polyazamacrocycles **1–3** having methoxybenzyl pendants.

Table 1 Investigation of regioselective ring opening of N-substituted aziridines **4** with secondary benzylamine **5**[a]



4 5 6 7

Entry	4	P	Lewis acid	Solvent	Yield of 6 [b]%	Yield of 7 [b]%
1	**4a**	Trt	$Sc(OTf)_3$	CH_3CN	31	13
2	**4a**	Trt	$Sm(OTf)_3$	CH_3CN	27	14
3	**4a**	Trt	$Y(OTf)_3$	CH_3CN	33	12
4	**4a**	Trt	$La(OTf)_3$	CH_3CN	25	6
5	**4a**	Trt	$Yb(OTf)_3$	CH_3CN	43	5
6	**4b**	Ns	$Yb(OTf)_3$	CH_3CN	81	<1
7	**4c**	Ts	$Yb(OTf)_3$	CH_3CN	51	<1
8	**4d**	Troc	$Yb(OTf)_3$	CH_3CN	48	<1
9	**4e**	Alloc	$Yb(OTf)_3$	CH_3CN	41	<1
10	**4f**	Bz	$Yb(OTf)_3$	CH_3CN	8	<1
11[d]	**4b**	Ns	$Yb(OTf)_3$	CH_3CN–HMPA[c]	98	<1
12[e]	**4b**	Ns	$Yb(OTf)_3$	C_2H_5CN	78	<1
13[e]	**4b**	Ns	$Yb(OTf)_3$	DMF	67	<1
14[d]	**4b**	Ns	$Yb(OTf)_3$	DMSO	64	<1
15	**4b**	Ns	$Yb(OTf)_3$	THF	28	<1

[a] Reaction of **4** (1.5 equiv.) and **5** (1.0 equiv.) was performed in the presence of Lewis acid (0.2 equiv.) at 60 °C. [b] Isolated yield. [c] CH_3CN:HMPA = 9 : 1. [d] Reaction was performed at 100 °C. [e] Reaction was performed at 80 °C.

cyclization precursors composed of different numbers of 2-amino-1-(4-methoxyphenylmethyl)ethylamino moieties. Hansen and Burg reported that cyclen was synthesized by a cyclic tetramer of N-benzylaziridine.[7] Tsuboyama *et al.* reported that optically active N-benzyl-C-ethylaziridine in the presence of $BF_3{\cdot}OEt_2$ reacts to afford a cyclic tetramer in 30% yield.[8] For the synthesis of **1–3**, it is necessary to perform regioselective ring opening of C-substituted aziridine **4**. We initially investigated the reaction of sterically hindered N-trityl-(4-methoxybenzyl)aziridine **4a** and secondary benzylamine **5** (Table 1). We considered that the trityl group would be effective for highly regioselective ring opening and avoiding over-reaction with aziridine **4a**. Although the reaction proceeded in the presence of lanthanide triflates, $Sc(OTf)_3$, $Sm(OTf)_3$, $Y(OTf)_3$, and $La(OTf)_3$, the desired product **6** was obtained in only moderate yield with low regioselectivity (Table 1, entries 1–4). Interestingly, no significant steric effect was observed in the reaction. The structures of **6** and **7** were determined by analysis of COSY, HMQC, and HMBC spectra. Use of $Yb(OTf)_3$, however, resulted in the formation of **6** in 48% yield with 90% regioselectivity (entry 5). As Yamamoto *et al.* reported,[9] $Yb(OTf)_3$ is an effective Lewis acid for regioselective ring opening of C-substituted aziridines with dibenzylamine. It is noteworthy that metal species of lanthanide triflates affect the regioselectivity of the ring-opening reaction of C-substituted aziridines.

Next, we investigated the effects of various N-substituents in (4-methoxybenzyl)aziridines **4b–4f** in place of N-trityl (N-Trt) aziridine **4a** (entries 6–10). All reactions proceeded regioselectively to yield **6** without evidence of **7**, as determined by HPLC analysis. In particular, *o*-nitrobenzenesulfonyl (nosyl)[10] aziridine **4b** produced **6b** (81%). For N-2,2,2-trichloroethoxycarbonyl (N-Troc) **4d**, N-allyloxycarbonyl (N-Alloc) **4e**, and N-Bz aziridine **4f**, the desired products **6d–6f** were produced in moderate to low yields (8–48%) because of the decomposition of the aziridines under the reaction conditions (entries 8–10). It should be noted that in the previous reports, ring opening of N-tosyl- and N-nosyl-C-substituted aziridines proceeded regioselectively with the less-hindered amine under mild conditions.[5b,5c,11]

Finally, we investigated the effects of solvents (CH_3CN, CH_3CN–HMPA, C_2H_5CN, DMF, DMSO and THF) and reaction temperature (entries 11–15). Addition of HMPA in acetonitrile promoted the reaction significantly (entry 11). Regioselective ring opening of N-nosylaziridine **4b** with secondary benzylamine **5** proceeded in acetonitrile–HMPA (9 : 1) at 100 °C in the presence of 20 mol% $Yb(OTf)_3$ to afford **6b** in 98% isolated yield with complete regioselectivity.

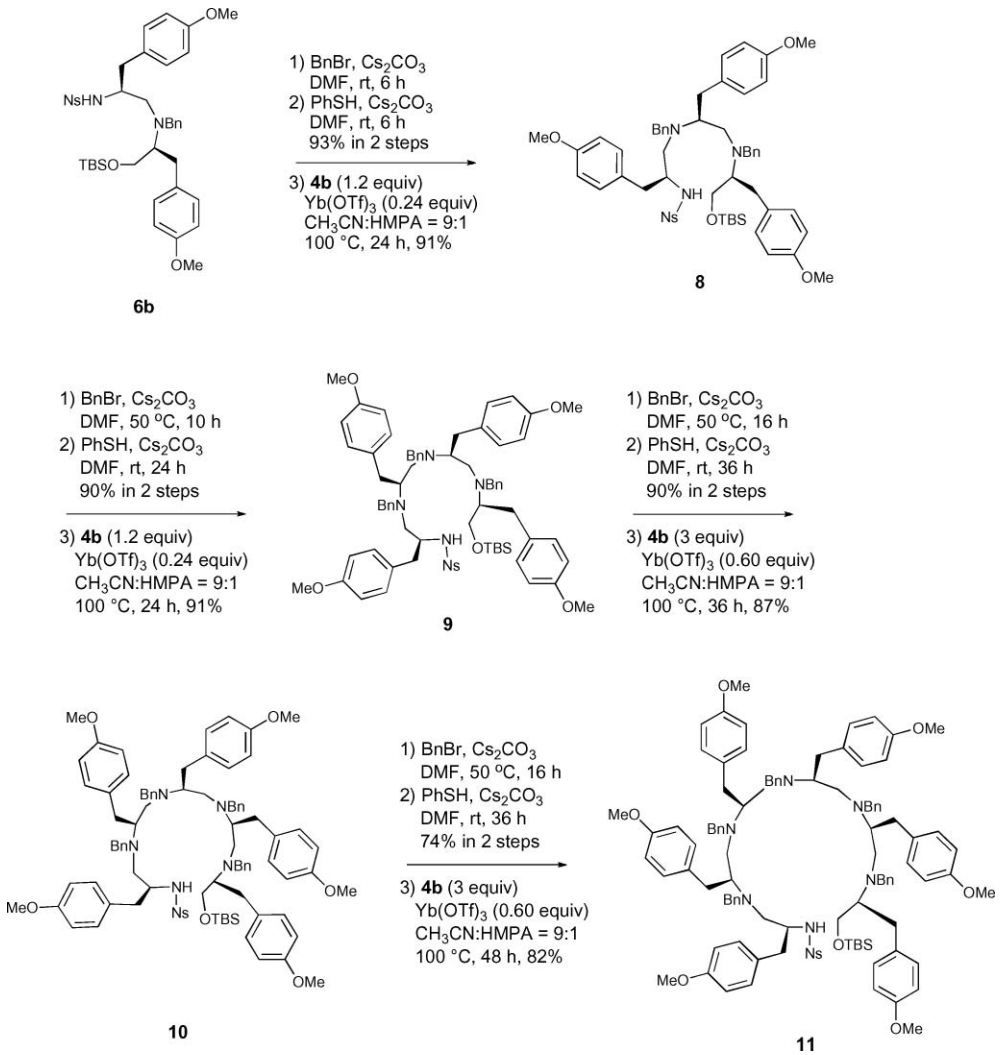
Repeated ring-opening reactions using N-nosylaziridine for the preparation of the polyamines

The coupling reaction was applicable to the synthesis of the cyclization precursors (Scheme 1). Elongation of a 2-amino-1-(4-methoxyphenylmethyl)ethylamino moiety involves the following steps: 1) N-Benzylation of the resulting nosylamides with BnBr–Cs_2CO_3; 2) Removal of the nosyl group with thiophenol–Cs_2CO_3; 3) Regioselective ring opening of the resulting secondary benzylamine with N-nosylaziridine **4b**. First, benzylation of the resulting nosylamide **6b**, followed by deprotection of the nosyl group, afforded the secondary benzylamine in 93% yield in two steps. Regioselective ring opening of **4b** (1.2 equiv.) with the resulting secondary benzylamine (1.0 equiv.) in acetonitrile–HMPA (9 : 1) at 100 °C in the presence of 20 mol% $Yb(OTf)_3$ afforded **8** in 91% isolated yield as a single regioisomer.

Encouraged by this result, we investigated the scope and generality of the sequential reaction. By the same process, repeated elongation of the 2-amino-1-(4-methoxyphenylmethyl)ethylamino moiety yielded tetra-, penta-, and hexa-azacompounds **9–11**. In fact, regioselective ring opening of the different-length of secondary benzylamines with N-nosylaziridine **4b** converted them to the corresponding nosylamides in good yields (82–91%) with complete regioselectivity, even though 3.0 equiv of **4b** was necessary in the synthesis of **10** and **11**. Thus, our sequential reaction process rapidly provides different-length nosylamides and is practical because it was carried out in a 10 g scale.

Synthesis of the poly-azamacrocycles

To investigate the application of macrocyclization using nosylamides to the construction of tri-, tetra-, penta-, and hexa-azamacrocycles, we removed the TBS groups in **8–11** by treatment with TBAF to produce the corresponding alcohols **12–15** in 72–95% yields (Scheme 2). We then investigated the synthesis of tri-azamacrocycle **16** by halogenation of alcohol **12**, followed by intramolecular N-alkylation using the nosylamide.[12,13] For iodination of **12**, we used I_2–PPh_3 in CH_3CN at 0 °C. Addition of bases played a crucial role in this reaction; the use of 5.0 equiv. of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in DIEA–CH_3CN was found to be optimal. The resulting iodo compound was immediately subjected to macrocyclization to avoid



Scheme 1 Repeated ring-opening reactions using N-nosylaziridine **4b**.

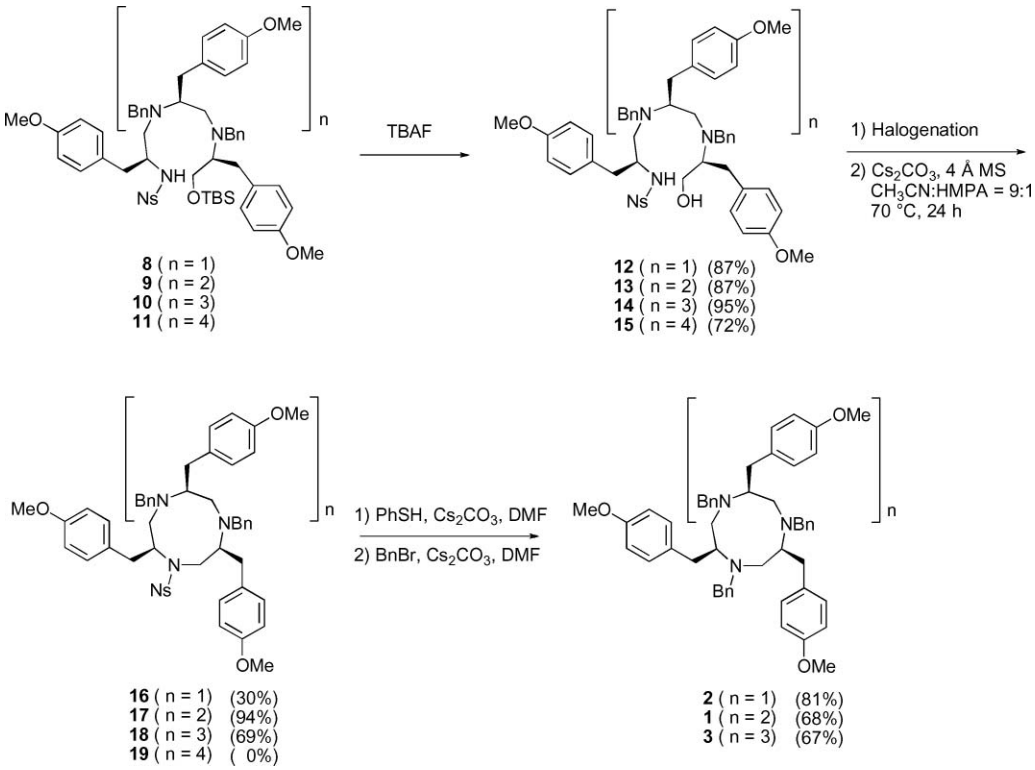
decomposition during purification by silica gel column chromatography. Macrocyclization proceeded at 70 °C with Cs_2CO_3 as a base in the presence of molecular sieves (4 Å) in CH_3CN–HMPA (9 : 1) under high dilution conditions (1 mM)[6] to provide the desired 9-membered **16** (30%) accompanied by its cyclic dimer (28%) in two steps.[14] Although a template effect based on the size of metal ions, *i.e.*, K^+ and Na^+, was expected, macrocyclization did not proceed smoothly with either K_2CO_3 or Na_2CO_3.

Next, we attempted the synthesis of tetra-, penta-, and hexa-azamacrocycles **17–19**. In contrast to the low yield of **16**, iodination of **13**, followed by macrocyclization under the above mentioned optimal conditions proceeded effectively to provide the desired 12-membered **17** in a remarkable 94% overall yield.[6] In contrast, iodination of **14** and **15** failed to yield the 15-membered **18** and 18-membered **19**, probably because the alcohols **14** and **15** become too hindered as the number of the 2-amino-1-(4-methoxyphenylmethyl)ethylamino moieties increases. After optimization of reaction conditions, we found that phosphorus reagents size and reaction temperature play a crucial role. Treatment of alcohol **14** with CBr_4–PMe_3–DTBMP in DIEA–CH_3CN at 65 °C afforded the corresponding bromide, which immediately underwent macrocyclization under the above conditions to produce the 15-membered **18** (69%). However, neither iodination nor bromination of alcohol **15** proceeded sufficiently in spite of our best efforts.

Tri-, tetra-, and penta-azamacrocycles **16–18** were converted to the corresponding N-polybenzylpolyazamacrocycles. Removal of the nosyl group in **16–18** with thiophenol–Cs_2CO_3 followed by N-benzylation of the resulting secondary amine with BnBr–Cs_2CO_3 produced tri-azamacrocycle **2** (81%), tetra-azamacrocycle **1** (68%), and penta-azamacrocycle **3** (67%), respectively.

Conformational analysis of the poly-azamacrocycles

Next, we investigated the three-dimensional structures of tri-azamacrocycle **2** and penta-azamacrocycle **3**. ^1H and ^{13}C NMR spectra of **3** exhibited simple signals corresponding to the single unit of 2-(benzylamino)-1-(4-methoxyphenyl)propyl, *i.e.*, 13 carbon signals, as we previously reported for tetra-azamacrocycle **1**.[6] In contrast, the NMR spectrum of **2** exhibited unsymmetrical conformation in the NMR time scale. The 4-methoxyphenyl groups in **2** are probably too hindered to be oriented toward the



Scheme 2 Synthesis of tri-, tetra-, and penta-azamacrocycles **2**, **1**, and **3**.

Table 2 ^{1}H NMR analysis of **3** *vs.* **1**

Compound	Proton	$CDCl_3$ [a] (Δ^b) (ppm)	CD_2Cl_2 [a] (Δ^b) (ppm)	Benzene-d_6 [a] (Δ^b) (ppm)
3	Ha	6.82 (–0.33)	6.81 (–0.31)	7.07 (0.08)
	Hb	6.79 (–0.08)	6.78 (–0.05)	6.99 (0.18)
1	Hc	6.57 (–0.58)	6.62 (–0.50)	6.53 (–0.46)
	Hd	6.80 (–0.07)	6.79 (–0.04)	6.97 (0.16)

[a] ^{1}H NMR was measured at 25 °C. [b] Differences in chemical shifts between those of Ha and Hb in **3** and Hc and Hd in **1** and those of the corresponding H–3 and H–2 in 4-methylanisole measured in the respective solvents (see Fig. 1)

same face because **2** has a 9-membered ring, which is much smaller than the 12- and 15-membered rings of **1** and **3**.[5d]

For the penta-azamacrocycle **3**, ^{1}H NMR analysis using $CDCl_3$ and CD_2Cl_2 exhibited high-field shifts for Ha (–0.33 ppm in $CDCl_3$, –0.31 ppm in CD_2Cl_2) and small high-field shifts for Hb (–0.08 ppm in $CDCl_3$, –0.05 ppm in CD_2Cl_2; Table 2 & Fig. 1). This tendency toward a large high-field shift for Ha and a small high-field shift for Hb is in good accordance with the results observed for Hc and Hd in **1** as previously reported.[6] Therefore, we conclude that the vase-type conformation is dominant in **3** as well as in **1** in these solvents. In contrast, no noticeable high-field shifts were observed in deuterated benzene for Ha (+0.08 ppm [low-field shift]) and for Hb (+0.18 ppm [low-field shift]), suggesting that the vase-type conformation of **3** is not as stable as that of **1** in solution. It is conceivable that benzene stabilizes the open-type conformation of the 4-methoxybenzyl wings in solution by stacking with the benzene rings more strongly in benzene than in $CDCl_3$ and CD_2Cl_2.

Conclusion

In summary, we have demonstrated the efficient synthesis and elucidated the structures of tri-, tetra-, and penta-azamacrocycles **2**, **1**, and **3**. Regioselective ring opening of a nosylaziridine with secondary benzylamines was repeatedly performed to prepare the cyclization precursors, which underwent intramolecular N-alkylation using the nosylamides to produce **2**, **1**, and **3**. On the basis of the three-dimensional structure of **1** elucidated by single-crystal X-ray analysis and NMR analysis in solution, we conclude that **2** does not, but **3** does, dominantly have a vase-type conformation in $CDCl_3$ and CD_2Cl_2. The vase-type conformation of **3** is, however, not as stable as that of **1** because of the conformational flexibility of **3** observed in deuterated benzene. Polyazamacrocycles **1–3** can contribute to the development of novel sensors for use in the fields of materials and medicinal chemistry, and further study is underway in our laboratory.

Experimental section

General procedures

NMR spectra were recorded on a JEOL Model ECP-400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) instrument in the indicated solvent. Chemical shifts are reported in units parts per million (ppm) relative to the signal for internal tetramethylsilane (0 ppm for ^{1}H) for solutions in $CDCl_3$. ^{1}H NMR spectral data are

reported as follows: chloroform (δ 7.26), methanol (δ 3.30), dichloromethane (δ 5.30) and benzene (δ 7.16). ^{13}C NMR spectral data are reported as follows: chloroform (δ 77.1) and methanol (δ 49.0). Multiplicities are reported by the following abbreviations: s; singlet, d; doublet, t; triplet, q; quartet, m; multiplet, br.; broad, *J*; coupling constants in Hertz. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrophotometer. Only the strongest and/or structurally important absorption is reported as the IR data given in cm^{-1}. Optical rotations were measured with a JASCO P-1020 polarimeter. All reactions were monitored by thin-layer chromatography carried out on 0.2 mm E. Merck silica gel plates (60F-254) with UV light, visualized by *p*-anisaldehyde solution, ceric sulfate or 10% ethanolic phosphomolybdic acid. Merck silica gel 60 (0.063–0.200 mm) was used for column chromatography. ESI-TOF Mass spectra were measured with Waters LCT Premier™ XE. HRMS (ESI-TOF) was calibrated with leucine enkephalin (SIGMA) as an external standard.

General procedure for ring opening of nosylaziridine 4b with N-benzylamines

To a stirred solution of N-benzylamine (1.0 equiv.) in dry acetonitrile (4.5 mL mmol^{-1}) and HMPA (0.5 mL mmol^{-1}) was added N-(2-nitrobenzenesulfonyl)-2-(4-methoxybenzyl)aziridine (**4b**) (1.05–3.00 equiv.) and ytterbium(III) trifluoromethanesulfonate (0.21–0.60 equiv.) at 0 °C. After being stirred at 100 °C, the mixture was quenched with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with H_2O and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to afford nosylamide as a yellow oil.

General procedure for N-benzylation of nosylamides

To a stirred solution of the nosylamide in DMF was added caesium carbonate and benzyl bromide at 0 °C. After being stirred at room temperature, the mixture was quenched with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with H_2O and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to afford N-benzylnosylamide as a yellow oil.

General procedure for removal of the nosyl group

To a stirred solution of N-benzylnosylamide in DMF was added caesium carbonate and thiophenol at 0 °C. After being stirred at room temperature, the mixture was quenched with saturated aqueous sodium thiosulfate and saturated aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with H_2O and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to afford N-benzylamine as a colorless oil.

(2*S*,5*S*,8*S*,11*S*,14*S*)-3,6,9,12-Tetrabenzyl-1-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,8,11,14-pentakis(4-methoxybenzyl)-13-(2-nitrobenzenesulfonyl)-1,4,7,10,13-pentaazapentadecane (10). Yield 87%; $[\alpha]_D^{30}$ +12.4 (*c* 1.02 in $CHCl_3$); IR ν (neat, cm^{-1}) 3361, 3027, 2835, 1612, 1540, 1512, 1247, 1037, 837, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, 1H, J = 7.3 Hz, aromatic), 7.45 (d, 1H, J = 8.3 Hz, aromatic), 7.35 (d, 1H, J = 7.3 Hz, aromatic), 7.35–7.03 (m, 21H, aromatic), 6.87 (d, 2H, J = 8.8 Hz, aromatic), 6.71 (d, 2H, J = 8.8 Hz, aromatic), 6.69–6.61 (m, 12H, aromatic), 6.17 (d, 2H, J = 8.8 Hz, aromatic), 6.12 (d, 2H, J = 8.8 Hz, aromatic), 5.06 (d, 1H, J = 5.4 Hz, NH), 3.94–3.56 (m, 6H), 3.92 (d, 1H, J = 14.2 Hz), 3.90 (d, 1H, J = 13.2 Hz), 3.76 (s, 3H, OMe), 3.74 (s, 6H, OMe × 2), 3.65 (s, 3H, OMe), 3.61 (s, 3H, OMe), 3.61 (d, 1H, J = 13.2 Hz), 3.41 (d, 1H, J = 14.2 Hz), 3.12 (d, 1H, J = 11.2 Hz), 2.95–2.56 (m, 16H), 2.52 (dd, 1H, J = 2.4, 14.2 Hz), 2.41–2.29 (m, 4H), 2.23–2.14 (m, 2H), 1.00 (s, 9H, *t*-Bu), 0.14 (s, 3H, Me), 0.14 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 157.6 × 2, 157.5 × 2, 146.5, 140.9, 140.5, 140.3, 133.5, 133.3, 132.6, 132.5, 132.3, 130.4, 130.2 × 2, 130.1 × 2, 129.5, 129.1, 129.0, 128.9, 128.8, 128.6, 128.2, 128.1, 128.0, 126.8, 126.7, 126.5, 126.4, 125.4, 113.6, 113.3 × 3, 113.0, 63.1, 62.7, 62.5, 62.0, 60.8, 57.2, 56.4, 55.7, 55.1 × 2, 54.9, 50.5, 37.4, 36.3, 35.6, 34.4, 26.0, 18.2,–5.4,–5.5; HRMS (ESI–TOF) calcd for $[C_{90}H_{109}N_6O_{10}SiS + H]^+$ 1493.7690, found 1493.7722.

(2*S*,5*S*,8*S*,11*S*,14*S*,17*S*)-3,6,9,12,15-Pentabenzyl-1-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,8,11,14,17-hexakis(4-methoxybenzyl)-16-(2-nitrobenzenesulfonyl)-1,4,7,10,13,16-hexaazaoctadecane (11). Yield 82%; $[\alpha]_D^{26}$ +5.07 (*c* 1.48 in $CHCl_3$); IR ν (neat, cm^{-1}) 3061, 3028, 2934, 2835, 1612, 1513, 1247, 1176, 1110, 1037, 837, 755, 738, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, 1H, J = 8.3 Hz, aromatic), 7.43 (dd, 1H, J = 7.3, 7.8 Hz, aromatic), 7.35–6.93 (m, 25H, aromatic), 6.84 (d, 2H, J = 8.3 Hz, aromatic), 6.69 (d, 2H, J = 8.8 Hz, aromatic), 6.63–6.51 (m, 18H, aromatic), 6.14 (d, 2H, J = 8.8 Hz, aromatic), 6.08 (d, 2H, J = 8.8 Hz, aromatic), 5.01 (d, 1H, J = 5.4 Hz, NH), 3.90–3.51 (m, 9H), 3.74 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.70 (s, 3H, OMe), 3.63 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.55 (d, 1H, J = 15.1 Hz), 3.53 (d, 1H, J = 14.2 Hz), 3.34 (d, 1H, J = 14.2 Hz), 3.11 (d, 1H, J = 2.0, 12.7 Hz), 2.91–2.07 (m, 25H), 2.47 (dd, 1H, J = 2.4, 14.7 Hz), 1.50 (dd, 1H, J = 11.2, 14.2 Hz), 0.99 (s, 9H, *t*-Bu), 0.12 (s, 3H, Me), 0.10 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 157.5 × 2, 157.4 × 3, 146.4, 140.9, 140.8, 140.5, 140.4, 133.8, 133.5, 133.4, 133.3, 132.5, 132.2, 130.4, 130.2 × 3, 130.1 × 2, 129.5, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.1 × 2, 128.0, 126.8, 126.7, 126.6, 126.4, 125.4, 113.3 × 3, 113.2, 112.9, 63.1, 62.7, 62.2 × 2, 62.1, 60.7 × 2, 57.1, 56.4, 55.6, 55.2, 55.1 × 2, 54.9, 54.8, 54.6, 50.5, 43.2, 37.4, 36.3, 35.5, 34.3, 26.1, 18.2,–5.3,–5.4; HRMS (ESI–TOF) calcd for $[C_{107}H_{127}N_7O_{11}SSi + H]^+$ 1746.9162, found 1746.9142.

General procedure for deprotection of the TBS group

To a stirred solution of the nosylamide in THF was added tetrabutylammonium fluoride at 0 °C. After being stirred at 0 °C, the mixture was quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate. The extract was washed with H_2O, saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel to afford the cyclization precursor as a yellow oil.

(2*S*,5*S*,8*S*)-3,6-Dibenzyl-2,5,8-tris(4-methoxybenzyl)-9-(2-nitrobenzenesulfonyl)-3,6,9-triaza-1-nonanol (12). Yield 87%; $[\alpha]_D^{30}$ +65.7 (*c* 1.05 in $CHCl_3$); IR ν (neat, cm^{-1}) 3027, 2936, 2837, 1612,

1539, 1513, 1248, 1167, 1036, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 1H, J = 7.8 Hz, aromatic), 7.57 (d, 1H, J = 7.8 Hz, aromatic), 7.50 (dd, 1H, J = 7.8 Hz, aromatic), 7.46 (dd, 1H, J = 7.8 Hz, aromatic), 7.28–7.09 (m, 10H, aromatic), 6.96 (d, 2H, J = 8.8 Hz, aromatic), 6.89 (d, 2H, J = 8.8 Hz, aromatic), 6.79 (d, 2H, J = 8.8 Hz, aromatic), 6.76 (d, 2H, J = 8.8 Hz, aromatic), 6.61 (d, 2H, J = 8.8 Hz, aromatic), 6.36 (d, 2H, J = 8.8 Hz, aromatic), 3.77 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.65 (s, 3H, OMe), 3.61 (d, 1H, J = 13.7 Hz), 3.54 (d, 1H, J = 13.7 Hz), 3.51 (d, 1H, J = 13.7 Hz), 3.49–3.40 (m, 2H), 3.35 (d, 1H, J = 13.7 Hz), 3.08–3.00 (m, 3H), 2.96 (dd, 1H, J = 6.4, 13.2 Hz), 2.88 (dd, 1H, J = 5.8, 13.6 Hz), 2.78 (dd, 1H, J = 5.4, 13.7 Hz), 2.73 (dd, 1H, J = 4.9, 13.7 Hz), 2.63 (dd, 1H, J = 3.9, 14.2 Hz), 2.55 (dd, 1H, J = 7.8, 13.6 Hz), 2.47 (dd, 1H, J = 8.3, 13.7 Hz), 2.39 (dd, 1H, J = 4.4, 13.2 Hz), 2.36 (dd, 1H, J = 9.3, 13.7 Hz), 2.12 (dd, 1H, J = 9.8, 14.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9 × 2, 157.7, 146.8, 139.5, 139.2, 134.4, 132.4 × 2, 132.2, 131.2, 130.3, 130.1, 130.0, 129.9, 129.4, 129.3, 129.2, 128.4, 128.3, 127.1 × 2, 125.1, 113.8 × 2, 113.2, 62.2, 62.1, 60.7, 56.3, 56.1, 55.2, 55.1, 54.9, 54.8, 54.4, 49.7, 38.1, 33.8, 31.4; HRMS (ESI–TOF) calcd for $[C_{50}H_{57}N_4O_8S + H]^+$ 873.3892, found 873.3879.

(2*S*,5*S*,8*S*,11*S*,14*S*)-1,4,7,10-Tetrabenzyl-2,5,8,11,14-pentakis(4-methoxybenzyl)-13-(2-nitrobenzenesulfonyl)-1,4,7,10,13-pentaazapentadecane (14). Yield 95%; $[\alpha]_D^{30}$ +25.0 (*c* 0.98 in $CHCl_3$); IR ν (neat, cm^{-1}) 3361, 2936, 2835, 1612, 1539, 1512, 1247, 1036, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, 1H, J = 7.8 Hz, aromatic), 7.47 (dd, 1H, J = 7.8 Hz, aromatic), 7.45 (d, 1H, J = 7.8 Hz, aromatic), 7.36–7.06 (m, 21H, aromatic), 6.90 (d, 2H, J = 8.8 Hz, aromatic), 6.78 (d, 2H, J = 8.8 Hz, aromatic), 6.76 (d, 2H, J = 8.8 Hz, aromatic), 6.76–6.74 (m, 4H, aromatic), 6.68 (d, 2H, J = 8.8 Hz, aromatic), 6.66–6.59 (m, 4H, aromatic), 6.23–6.15 (m, 4H, aromatic), 5.14 (d, 1H, J = 4.9 Hz, NH), 3.84–3.42 (m, 7H), 3.82 (d, 1H, J = 13.2 Hz), 3.78 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.66 (s, 3H, OMe), 3.62 (s, 3H, OMe), 3.41 (d, 1H, J = 12.2 Hz), 3.38 (d, 1H, J = 13.2 Hz), 3.15 (dd, 1H, J = 6.4, 13.7 Hz), 3.06–2.19 (m, 21H), 2.61 (dd, 1H, J = 4.9, 13.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9 × 2, 157.6, 157.5 × 2, 146.5, 141.2, 140.5, 140.2, 139.5, 133.9, 133.5, 133.2, 132.6, 132.3 × 2, 131.1, 130.4, 130.3, 130.1, 129.9, 129.6, 129.4, 129.2, 128.9, 128.8, 128.6, 128.5, 128.3, 128.2, 128.1, 127.4, 126.8, 126.7, 126.4, 125.4, 113.8 × 2, 113.4, 113.3, 113.0, 63.7, 62.8, 62.4, 62.1, 61.0, 57.0, 56.4, 55.9, 55.5, 55.2, 55.1, 54.9, 54.6 × 2, 51.2, 50.9, 50.8, 50.7, 37.5, 37.2, 36.0, 35.3, 31.1; HRMS (ESI–TOF) calcd for $[C_{84}H_{95}N_6O_{10}S + H]^+$ 1379.6825, found 1379.6881.

(2*S*,5*S*,8*S*,11*S*,14*S*,17*S*)-3,6,9,12,15-Pentabenzyl-1-[(1,1-dimethylethyl)dimethylsilyloxy]-2,5,8,11,14,17-hexakis(4-methoxybenzyl)-16-(2-nitrobenzenesulfonyl)-1,4,7,10,13,16-hexaazaoctadecane (15). Yield 72%; $[\alpha]_D^{24}$ +21.2 (*c* 2.40 in $CHCl_3$); IR ν (neat, cm^{-1}) 2936, 2835, 1612, 1539, 1512, 1454, 1247, 1177, 1036, 738, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, 1H, J = 7.8 Hz, aromatic), 7.43 (d, 1H, J = 7.3 Hz, aromatic), 7.39 (d, 1H, J = 7.8 Hz, aromatic), 7.32–7.07 (m, 24H, aromatic), 6.96 (d, 2H, J = 6.8 Hz, aromatic), 6.85 (d, 2H, J = 8.3 Hz, aromatic), 6.86–6.72 (m, 6H, aromatic), 6.65–6.58 (m, 10H, aromatic), 6.53 (d, 2H, J = 8.3 Hz, aromatic), 6.16 (d, 2H, J = 8.8 Hz, aromatic), 6.12 (d, 2H, J = 8.8 Hz, aromatic), 5.07 (d, 1H, J = 5.4 Hz, NH), 3.86–3.34 (m, 13H), 3.74 (s, 6H, OMe × 2), 3.71 (s, 6H, OMe × 2), 3.63 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.13 (dd, 1H, J = 6.4, 13.7 Hz), 3.02–2.11 (m, 25H), 1.61–1.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9 × 2, 157.5 × 2, 157.4, 146.4, 140.9, 140.7, 140.4, 140.3, 139.6, 133.8, 133.5, 133.3, 133.2, 132.5, 132.3, 131.0, 130.3, 130.2 × 2, 130.0, 129.8, 129.5, 129.4, 129.1, 128.9, 128.7, 128.5 × 2, 128.3, 128.2, 128.1, 128.0, 127.2, 126.7, 126.5, 126.3, 125.4, 113.8, 113.7, 113.4, 113.3, 113.2, 112.9, 63.7, 62.5, 62.4, 61.9, 60.9, 56.9, 56.3, 56.0, 55.1, 55.0, 54.8, 54.6, 51.2, 51.0, 50.8, 37.4, 37.1, 35.8, 35.5, 35.4, 31.1; HRMS (ESI–TOF) calcd for $[C_{101}H_{114}N_7O_{11}S + H]^+$ 1632.8297, found 1632.8297.

(2*S*,5*S*,8*S*)-4,7-Dibenzyl-2,5,8-tris(4-methoxybenzyl)-1-(2-nitrobenzenesulfonyl)-1,4,7-triaza-cyclononane (16). To a stirred solution of (2*S*,5*S*,8*S*)-3,6-dibenzyl-2,5,8-tris-(4-methoxybenzyl)-9-(2-nitrobenzenesulfonyl)-3,6,9-triaza-1-nonanol (**12**) (373 mg, 428 μmol) in acetonitrile (17 mL) was added DIEA (8.6 mL), 2,6-di-*tert*-butyl-4-methylpyridine (439 mg, 2.14 mmol), iodine (1.09 g, 4.28 mmol) and PPh_3 (561 mg, 2.14 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the mixture was quenched with saturated aqueous sodium thiosulfate and saturated aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with H_2O and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a stirred suspension of caesium carbonate (1.39 g, 4.28 mmol) and activated 4 Å molecular sieves (1.0 g) in dry acetonitrile (107 mL) and HMPA (13 mL) was slowly added the residue in dry acetonitrile (21 mL) at 70 °C over 10 h. After being stirred at the same temperature for 24 h, the mixture was filtered and concentrated *in vacuo*. The residue was diluted with H_2O, and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on amine silica gel, eluting with 10% ethyl acetate in hexane to afford (2*S*,5*S*,8*S*)-1,4-dibenzyl-2,5,8-tris(4-methoxybenzyl)-7-(2-nitrobenzenesulfonyl)-1,4,7-triazacyclononane (**16**) (109 mg, 128 μmol, 2 steps 30%) as a yellow oil: $[\alpha]_D^{26}$ +100.2 (*c* 1.10 in $CHCl_3$); IR ν (neat, cm^{-1}) 3027, 2934, 2836, 1609, 1540, 1512, 1249, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, 1H, J = 7.8 Hz, aromatic), 7.63 (d, 1H, J = 7.8 Hz, aromatic), 7.56 (dd, 1H, J = 7.8 Hz, aromatic), 7.49 (dd, 1H, J = 7.8 Hz, aromatic), 7.30–7.21 (m, 10H, aromatic), 7.23 (d, 2H, J = 8.8 Hz, aromatic), 6.89 (d, 2H, J = 8.8 Hz, aromatic), 6.87 (d, 2H, J = 8.8 Hz, aromatic), 6.84 (d, 2H, J = 8.8 Hz, aromatic), 6.65 (d, 2H, J = 8.8 Hz, aromatic), 6.48 (d, 2H, J = 8.8 Hz, aromatic), 6.15–6.08 (m, 1H), 3.80 (s, 3H, OMe), 3.70 (s, 6H, OMe × 2), 3.88–3.56 (m, 6H), 3.35 (dd, 1H, J = 4.9, 14.6 Hz), 3.16 (dd, 1H, J = 5.9, 14.6 Hz), 3.11–3.07 (m, 1H), 2.83 (dd, 2H, J = 5.4, 13.2 Hz), 2.64 (dd, 1H, J = 6.3, 13.2 Hz), 2.55 (dd, 1H, J = 6.3, 14.2 Hz), 2.56–2.49 (m, 1H), 2.38 (dd, 1H, J = 5.8, 12.7 Hz), 2.40–2.35 (m, 2H), 2.14 (dd, 1H, J = 6.4, 13.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 157.8, 157.7, 147.3, 139.1, 138.0, 135.1, 132.6, 132.4, 132.3, 132.1, 130.3, 129.9, 129.8, 129.7, 129.6, 128.3, 128.0, 127.4, 127.2, 126.9, 124.7, 124.0, 113.9, 113.6, 113.4, 58.4, 57.8, 56.1, 55.3, 55.1, 55.0, 54.7, 53.4, 52.1, 38.9, 33.4, 29.7, 23.4, 20.2; HRMS (ESI–TOF) calcd for $[C_{50}H_{55}N_4O_7S + H]^+$ 855.3786, found 855.3769.

(2*S*,5*S*,8*S*,11*S*,14*S*)-1,4,7,10-Tetrabenzyl-2,5,8,11,14-pentakis(4-methoxybenzyl)-13-(2-nitrobenzenesulfonyl)-1,4,7,10,13-pentaazacyclopentadecane (18). In a sealed tube, to a suspension

of (2*S*,5*S*,8*S*,11*S*,14*S*)-1,4,7,10-tetrabenzyl-2,5,8,11,14-pentakis(4-methoxybenzyl)-13-(2-nitrobenzenesulfonyl)-1,4,7,10,13-pentaazapentadecane (**14**) (315 mg, 228 μmol) in acetonitrile (9.1 mL) was added DIEA (4.5 mL), 2,6-di-*tert*-butyl-4-methylpyridine (234 mg, 1.14 mmol), tetrabromomethane (1.52 g, 4.57 mmol) and PMe_3 (0.40 mL, 4.57 mmol) at 0 °C. After being stirred at reflux for 6 h, the mixture was quenched with saturated aqueous sodium thiosulfate and saturated aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with H_2O and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a stirred suspension of caesium carbonate (1.46 g, 4.56 mmol) and activated 4 Å molecular sieves (3.0 g) in dry acetonitrile (57 mL) and HMPA (5.7 mL) was slowly added the residue in dry acetonitrile (11 mL) at 70 °C over 10 h. After being stirred at the same temperature for 24 h, the mixture was filtered, and concentrated *in vacuo*. The residue was diluted with H_2O, and extracted with ethyl acetate. The extract was washed with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on amine silica gel, eluting with 15% ethyl acetate in hexane to afford (2*S*,5*S*,8*S*,11*S*,14*S*)-1,4,7,10-tetrabenzyl-2,5,8,11,14-pentakis(4-methoxybenzyl)-13-(2-nitrobenzenesulfonyl)-1,4,7,10,13-pentaazacyclopentadecane (**18**) (214 mg, 157 μmol, 2 steps 69%) as a yellow oil: $[\alpha]_D^{28}$ +64.7 (*c* 0.99 in $CHCl_3$); IR ν (neat, cm^{-1}) 2933, 2835, 1725, 1612, 1543, 1513, 1248, 1036, 755; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–6.56 (m, 40H, aromatic), 6.18–6.13 (m, 4H, aromatic), 4.25–3.40 (m, 8H), 3.85 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.66 (s, 6H, OMe × 2), 3.47 (s, 3H, OMe), 3.30–1.70 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 157.6 × 2, 157.5, 157.2, 139.9, 133.3, 133.2, 132.9, 132.5, 132.3, 131.3, 130.9, 130.6, 130.4, 130.1, 130.0, 129.7, 129.6, 129.3, 129.0, 128.7, 128.4, 128.3, 128.2, 128.0, 127.8, 127.3, 126.8, 126.6, 126.4, 124.5, 114.0, 113.8, 113.6, 113.2, 113.0, 63.9, 60.2, 55.9, 55.4, 55.2, 55.1, 55.0, 52.4, 44.4, 35.9, 34.6, 34.2, 33.6, 29.7; HRMS (ESI–TOF) calcd for $[C_{84}H_{93}N_6O_9S + H]^+$ 1361.6719, found 1361.6752.

(2*S*,5*S*,8*S*)-1,4,7-Tribenzyl-2,5,8-tris(4-methoxybenzyl)-1,4,7-triazacyclononane (2). To a stirred solution of (2*S*,5*S*,8*S*)-1,4-dibenzyl-2,5,8-tris(4-methoxybenzyl)-7-(2-nitrobenzenesulfonyl)-1,4,7-triazacyclononane (**16**) (109 mg, 128 μmol) in DMF (6.4 mL) was added caesium carbonate (417 mg, 1.28 mmol) and thiophenol (66 μL, 640 μmol) at 0 °C. After being stirred at room temperature for 12 h, the mixture was quenched with saturated aqueous sodium thiosulfate and saturated aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with H_2O and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on amine silica gel, eluting with 50% ethyl acetate in hexane to afford (2*S*,5*S*,8*S*)-1,4-dibenzyl-2,5,8-tris(4-methoxybenzyl)-1,4,7-triazacyclononane (76.5 mg, 114 μmol, 89%) as a colorless oil.

To a stirred solution of (2*S*,5*S*,8*S*)-1,4-dibenzyl-2,5,8-tris(4-methoxybenzyl)-1,4,7-triazacyclononane (85.7 mg, 128 μmol) in DMF (6.4 mL) was added caesium carbonate (417 mg, 1.28 mmol), benzyl bromide (64 μL, 640 μmol) and a catalytic amount of TBAI at 0 °C. After being stirred at reflux for 12 h, the mixture was quenched with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with H_2O and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on amine silica gel, eluting with 30% ethyl acetate in hexane to afford (2*S*,5*S*,8*S*)-1,4,7-tribenzyl-2,5,8-tris(4-methoxybenzyl)-1,4,7-triazacyclononane (**2**) (88.5 mg, 116 μmol, 91%) as a yellow oil: $[\alpha]_D^{28}$ −5.3 (*c* 0.99 in $CHCl_3$); IR ν (neat, cm^{-1}) 3062, 2934, 2835, 1747, 1512, 1455, 1248, 1035, 743, 699; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–6.96 (m, 15H, aromatic), 7.29 (d, 2H, J = 8.8 Hz, aromatic), 6.85 (d, 1H, J = 8.8 Hz, aromatic), 6.82 (d, 1H, J = 8.8 Hz, aromatic), 6.69 (d, 2H, J = 8.8 Hz, aromatic), 6.67 (d, 2H, J = 8.8 Hz, aromatic), 6.48 (d, 2H, J = 8.8 Hz), 6.41 (d, 1H, J = 15.6 Hz, aromatic), 6.13–6.06 (m, 2H), 3.81 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.67 (d, 1H, J = 14.2 Hz), 3.58 (d, 1H, J = 14.2 Hz), 3.56 (d, 2H, J = 14.2 Hz), 3.39 (d, 2H, J = 14.2 Hz), 3.19 (dd, 1H, J = 5.9, 14.2 Hz), 3.13 (dd, 1H, J = 7.3, 14.2 Hz), 3.00–2.87 (m, 2H), 2.85 (dd, 1H, J = 4.4, 14.2 Hz), 2.80 (dd, 1H, J = 4.9, 12.7 Hz), 2.61–2.54 (m, 2H), 2.49 (dd, 1H, J = 5.8, 14.2 Hz), 2.47 (dd, 1H, J = 7.8, 12.7 Hz), 2.33 (dd, 1H, J = 9.8, 12.2 Hz), 2.16 (dd, 1H, J = 10.2, 13.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 157.6, 140.8, 140.2, 139.6, 133.4, 133.3, 132.1, 130.6, 130.0 × 2, 129.1, 128.9, 128.3, 128.2, 128.0, 127.4, 126.9, 126.5, 126.4, 125.2, 114.0, 113.6, 113.0, 61.1, 59.1, 58.2, 56.8, 55.3 × 2, 55.1, 55.0, 53.8, 53.1 × 2, 50.5, 36.9, 35.0, 29.7; HRMS (ESI–TOF) calcd for $[C_{51}H_{58}N_3O_3 + H]^+$ 760.4473, found 760.4484.

(2*S*,5*S*,8*S*,11*S*,14*S*)-1,4,7,10,13-Pentabenzyl-2,5,8,11,14-pentakis(4-methoxybenzyl)-1,4,7,10,13-pentaazacyclopentadecane (3). To a stirred solution of (2*S*,5*S*,8*S*,11*S*,14*S*)-1,4,7,10-tetrabenzyl-2,5,8,11,14-pentakis(4-methoxybenzyl)-13-(2-nitrobenzenesulfonyl)-1,4,7,10,13-pentaazacyclopentadecane (**18**) (352 mg, 259 μmol) in DMF (13 mL) was added caesium carbonate (843 mg, 2.59 mmol) and thiophenol (0.27 mL, 2.6 mmol) at 0 °C. After being stirred at room temperature for 12 h, the mixture was quenched with saturated aqueous sodium thiosulfate and saturated aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with H_2O and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on amine silica gel, eluting with 50% ethyl acetate in hexane to afford (2*S*,5*S*,8*S*,11*S*,14*S*)-1,4,7,10-tetrabenzyl-2,5,8,11,14-pentakis-(4-methoxybenzyl)-1,4,7,10,13-pentaazacyclopentadecane (247 mg, 210 μmol, 81%) as a yellow oil.

To a stirred solution of (2*S*,5*S*,8*S*,11*S*,14*S*)-1,4,7,10-tetrabenzyl-2,5,8,11,14-pentakis-(4-methoxybenzyl)-1,4,7,10,13-pentaazacyclopentadecane (151 mg, 128 μmol) in DMF (6.4 mL) was added caesium carbonate (417 mg, 1.28 mmol), benzyl bromide (64 μL, 0.64 mmol) and catalytic amount of TBAI at 0 °C. After being stirred at reflux for 12 h, the mixture was quenched with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate. The extract was washed with H_2O and brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on amine silica gel, eluting with 30% ethyl acetate in hexane to afford (2*S*,5*S*,8*S*,11*S*,14*S*)-1,4,7,10,13-petrabenzyl-2,5,8,11,14-pentakis-(4-methoxybenzyl)-1,4,7,10,13-pentaazacyclopentadecane (**3**) (134 mg, 106 μmol, 83%) as a yellow

oil: $[\alpha]_D^{28}$ –42.7 (*c* 1.02 in $CHCl_3$); IR ν (neat, cm^{-1}) 3412, 2953, 1612, 1513, 1456, 1251, 1180, 1034, 755; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.06 (m, 25H, aromatic), 6.82 (d, 10H, $J = 8.8$ Hz, aromatic), 6.78 (d, 10H, $J = 8.8$ Hz, aromatic), 3.68 (s, 15H, OMe × 5), 3.66 (d, 5H, $J = 14.2$ Hz, Bn), 3.06–3.00 (m, 10H), 2.97 (d, 5H, $J = 14.2$ Hz, Bn), 2.38–2.30 (m, 5H), 2.25–2.16 (m, 5H), 1.78–1.66 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 140.1, 133.6, 130.5, 129.0, 127.9, 126.7, 113.3, 65.3, 58.0, 55.2, 52.1, 34.1; HRMS (ESI–TOF) calcd for $[C_{85}H_{96}N_5O_5 + H]^+$ 1266.7406, found 1266.7465.

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