Macrobicycles based on cyclen and cyclam containing 1,3-disubstituted adamantane moieties

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Dedicated to Prof. Keith Smith on the occasion of his 65th anniversary

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Abstract
Bis(bromobenzyl)derivatives of cyclen and cyclam obtained according to previously described procedures were introduced in a palladium-catalyzed reaction with 1,3-bis(aminomethyl)adamantane and 1,3-bis(2-aminoethyl)adamantane to produce macrobicycles in moderate yields. The formation of tricyclic cyclodimers was observed in many cases. Tetrabenzyl derivatives of cyclen and cyclam were synthesized from the corresponding dibenzyl derivatives and reacted with 1,3-bis(2-aminoethyl)adamantane to give macrobicyclic products in similar yields.

Keywords: Amination, macrocycles, Pd catalysis, adamantane

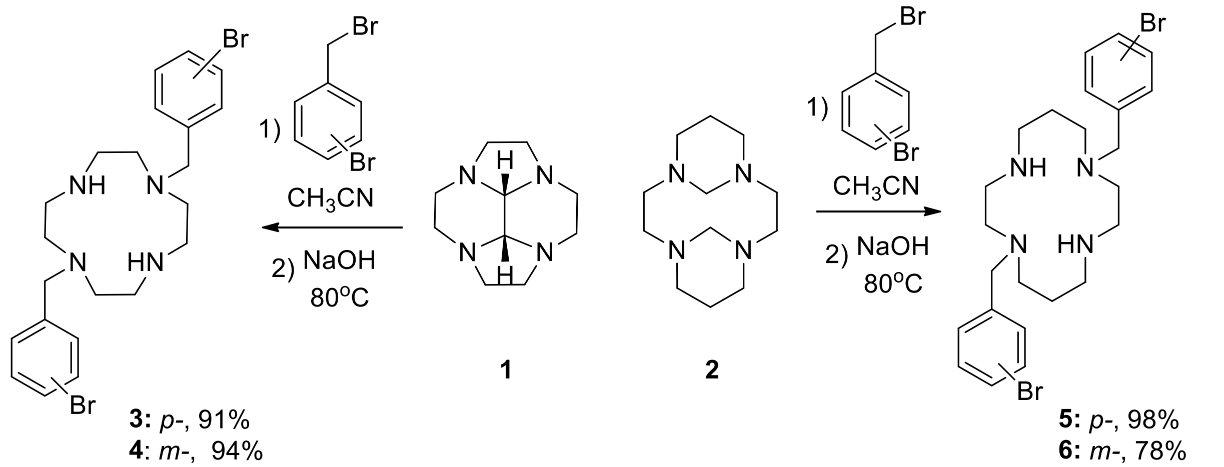
Introduction

Macropolycyclic compounds containing cyclen (1, 4, 7, 10-tetraazacyclododecane) and cyclam (1, 4, 8, 11-tetraazacyclotetradecane) moieties have been known for the last decades and can be classified in different classes of topology: macrobicyclic and macrotricyclic cryptands, macropolycycles of cylindrical shape, macropolycycles incorporating other macrocyclic structures. The simplest bicyclic compounds based on tetraazamacrocycles are various so-called cross-bridged cyclens and cyclams.[1-3] Usually these compounds do not contain many donor atoms like nitrogen, oxygen or sulfur in the second cycle,[4-8] however, macrobicycles with several donor atoms have been described.[9] Macrotricyclic compounds mainly posses two macrocycles *cis*-fused with the central tetraazamacrocycle.[10-12] The most interesting macrotricycles are actually cryptands of cylindrical shape and they often contain two cyclen or cyclam fragments arranged in a face-to-face manner *via* two symmetrical aromatic spacers.[13-15] Additional macrocycles can be used as linkers to furnish macropentacyclic structures.[16] Porphyrin systems were successfully incorporated into heteropolycyclic systems with cyclen and cyclam.[17-20] All these complicated molecules were synthesized with a view to studying their coordinating properties.

A special interest is evoked by the polyazamacrobicycles containing a bulky lipophilic adamanatane backbone that may improve their solubility in non-polar organic solvents and significantly change the geometry of the macrocyclic cavity. Also, such macrocycles can be viewed as potentially physiologically active compounds, like other adamantane-containing amines and diamines. For example, 1,3-bis(2-aminoethyl)adamantane together with its analogue, 1,3-bis(aminomethyl)adamantane, as well as their dihydrochlorides were tested as antiviral agents.[21] While the first was found to be active against the poultry plague,[22] the latter was patented as an anti-viral agent for home animals.[23,24] Cyclic Schiff bases were synthesized using 1,3-bis(2-aminoethyl)adamantane for biological activity studies.[25] The *N*,*N'*-dipyridyl derivative of this amine was synthesized by us earlier[26] and showed nootropic effect in mice. Having acquired a good experience in the synthesis of polyazamacrocycles *via* Pd-catalyzed amination reactions,[27-30] we decided to investigate the applicability of this approach to previously unknown adamantane-containing macrobicycles derived from cyclen and cyclam.

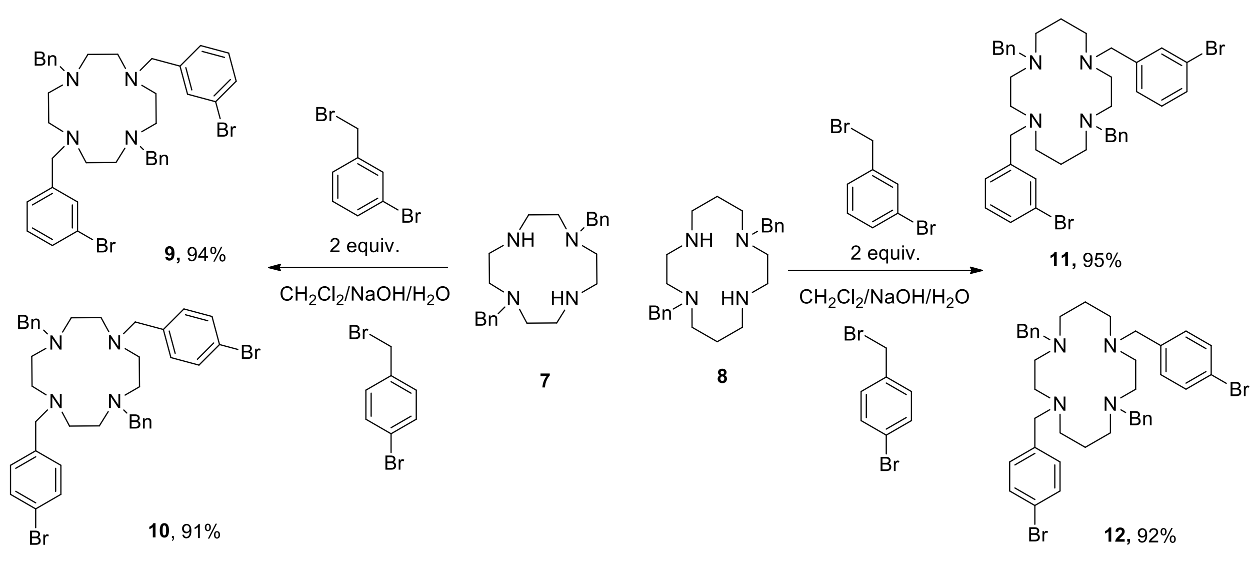
Results and Discussion

Bis(bromobenzyl) derivatives of cyclens **3**, **4** and cyclams **5**, **6** were obtained in high yields according to previously described two-step synthetic procedures[30,31] starting from *cis*-glyoxal-cyclen **1** and formaldehyde-cyclam **2** (Scheme 1). The first step of this process is quaternization of two nitrogen atoms in *trans*-positions, and the second one is the basic hydrolysis of iminium salts with the cleavage of two C-N bonds of CN_2 fragments which leads to the formation of free amino groups.



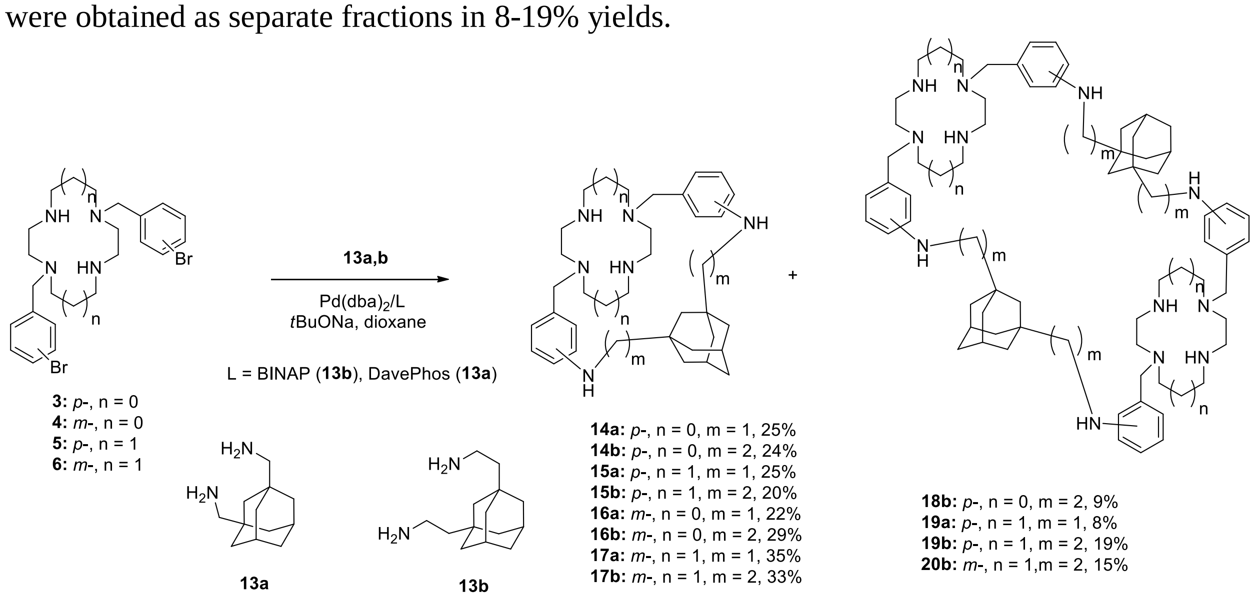
Scheme 1

In our recent communication[31] we showed that the presence of two additional substituents in the tetraazamacrocyclyc fragment can dramatically change the macrocyclization path leading to preferable formation of macrotricyclic cryptands rather than to macrobicycles. For this reason we also synthesized tetrabenzyl derivatives of cyclens **9**, **10** and cyclams **11**, **12** in order to check their reactivity with adamantane-containing diamines. Dibenzyl substituted cyclen and cyclams **7**, **8** were introduced in the reactions with two equivalents of 3- and 4-bromobenzyl bromides in a two-phase CH_2Cl_2/H_2O 1:1 system containing excess of NaOH at room temperature. As a result, the desired tetrabenzyl derivatives **9-12** were obtained in excellent yields 91-95% (Scheme 2). It is to be noted that running the same reactions under standard conditions (CH_3CN/K_2CO_3) or benzylation of compounds **3-6** with benzyl bromide were unsuccessful.



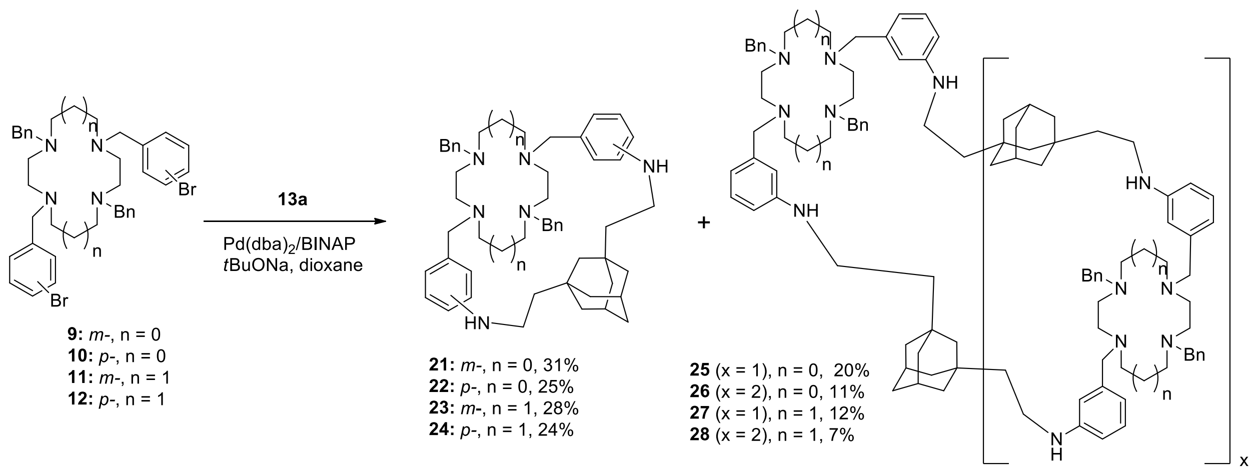
Scheme 2

The synthesis of macrobicycles **14-17** was carried out by the reaction of Pd-catalyzed amination of bis(bromobenzyl) derivatives **3-6** with equimolar amounts of 1,3-bis(aminomethyl)adamantane **13a** or 1,3-bis(2-aminoethyl)adamantane **13b** (Scheme 3). The reaction with diamine **13b** was catalyzed by the standard system Pd(dba)$_2$/BINAP (BINAP 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene) which was found by us to be most appropriate for the synthesis of polyazamacrocycles.[29] However, diamine **13a** required the application of a donor ligand DavePhos (2-dimethylamino-2'-dicyclohexylphosphinobiphenyl) due to sterical hindrances in this diamine. All reactions were run in boiling dioxane at concentration c 0.02 M, *t*BuONa was used as a base. The reactions ran to completion in 24 h. The reaction mixtures were analyzed by ^{1}H NMR and then subjected to column chromatography on silica gel. The yields of isolated compounds **14-17** ranged from 20 to 35%, the best results were provided by the reactions of 1,8-bis(3-bromobenzyl)cyclam (**6**) with both diamines **13a,b** (33 and 35%). The reaction of 1,7-bis(3-bromobenzyl)cyclen (**4**) with diamine **13b** also gave quite good yield for the macrocyclization reactions (29%). The results suggest that cyclen and cyclam derivatives with *m*-bromobenzyl substituent are more suitable for the macrocyclization with adamantanediamines **13a,b** with a rigid and bulky central fragment. In all reactions the formation of cyclic and linear oligomers was verified by NMR and MALDI mass spectra, but the isolation of these compounds in pure state by column chromatography was successful only in several cases. Cyclic dimers **18-20**, which are actually macrotricyclic cryptands of cylindrical shape, were obtained as separate fractions in 8-19% yields.



Scheme 3

Tetrabenzyl substituted derivatives of cyclen and cyclam **9-12** were reacted with diamine **13b** using the same reaction conditions, and the compounds were isolated by the column chromatography (Scheme 4).



Scheme 4

Target macrobicycles **21-24** were obtained in 24-31% yields which are almost the same as those of macrobicycles **14-17**. It shows that the introduction of two additional benzyl derivatives in the tetraazamacrocycles did not affect their reactivity in the catalytic macrocyclization reaction. In two reactions we isolated cyclic dimers **25** (x=1) and **27** (x=1) and even cyclic trimers **26** (x=2) and **28** (x=2) in yields up to 20%. The ^{1}H and ^{13}C spectra of the compound **23** recorded at 298K could not be easily interpreted because the signals of several rotational conformers were observed simultaneously. At 363K in DMSO-d_6 signals of the conformers in the ^{1}H NMR spectrum coalesced while the signals in the ^{13}C NMR spectrum were still too broad.

Conclusions

As a result of the experiments described above, a simple and sufficiently efficient synthetic approach to macrobicyclic cryptands containing cyclen or cyclam moieties and adamantane fragment was elaborated. The possibility to change the size and geometry of the macrocyclic cavity by using isomeric bromobenzyl derivatives of tetraazamacrocycles and diamines with various chain length was demonstrated. Valuable macrotricyclic cryptands of cylindrical shape were obtained as second products in some reactions. Similar reactivity of dibenzyl and tetrabenzyl substituted tetraazamacrocycles in the catalytic macrocyclization reactions was shown; this effect substantially broadens the scope of these reactions for further construction of macropolycyclic compounds of sophisticated architecture. Macropolycycles incorporating lipophilic and geometrically constrained adamantane moieties are thought to be useful for coordination studies with heavy and toxic metals, possessing high coordination numbers, in organic media like alcohols or acetone.

Experimental Section

General. All chemicals were purchased from the Aldrich and Acros companies and used without further purification. *Cis*-glyoxal-cyclen (**1**), formaldehyde-cyclam (**2**), 1,7-dibenzylcyclen (**7**) and 1,8-dibenzylcyclam (**8**) were supported by CheMatech Co. 1,3-Bis(aminomethyl)adamantane (**13a**) and 1,3-bis(2-aminoethyl)adamantane (**13b**) were synthesized according to a described procedure.[26] Pd(dba)$_2$ was synthesized according to a known method.[32] Commercial 1,4-dioxane was distilled over NaOH and sodium under argon, dichloromethane and methanol were freshly distilled prior to use. Column chromatography was carried out using silica gel (40-60 mkm) purchased from Fluka. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker Avance 400 spectrometer at 400 and 100.6 MHz respectively. Chemical shift values δ are given in ppm and coupling constants *J* in Hz. MALDI-TOF mass spectra of positive ions were recorded with Bruker Ultraflex spectrometer using 1,8,9-trihydroxyanthracene as matrix and PEGs as internal standards. Synthetic procedures and spectral data for compounds **3**, **5** are given in reference 31 and for compounds **4**, **6** in reference 30.

Standard method for the synthesis of tetrabenzyl substituted tetraazamacrocycles 9-12. A 50 mL flask equipped with a magnetic stirrer was charged with a solution of 1,7-dibenzylcyclen (**7**) or 1,8-dibenzylcyclam (**8**) (1 mmol in 10 mL CH_2Cl_2), a water solution of NaOH (160 mg (4 mmol) in 10 mL H_2O) was added in one portion, and a solution of *m*- or *p*-bromobenzyl bromide (500 mg (2 mmol) in 10 mL CH_2Cl_2) was added dropwise to a stirred two-phase mixture during 1 h. The reaction mixture was stirred for 48 h, organic phase was separated, dried over anhydrous sodium sulfate and solvent was evaporated *in vacuo* to produce a pure product.

1,7-Dibenzyl-4,10-bis-(3-bromobenzyl)-1,4,7,10-tetraazacyclododecane (9) was synthesized from 352 mg (1 mmol) of compound **7**, 500 mg (2 mmol) of *m*-bromobenzyl bromide in the presence of 160 mg (4 mmol) of NaOH in a two-phase system CH_2Cl_2 (20 mL)/H_2O (10 mL). White crystalline powder, mp 121-123 °C. Yield 647 mg (94%). ^{1}H NMR δ 2.67 (br.s, 16H), 3.37 (s, 4H), 3.44 (s, 4H), 7.10 (t, ^3J 7.7 Hz, 2H), 7.20 (t, ^3J 7.2 Hz, 2H), 7.23-7.32 (м, 10H), 7.34 (d, ^3J 8.4 Hz, 2H), 7.52 (br.s, 2H). ^{13}C NMR δ 52.9 (8C), 59.3 (2C), 60.1 (2C), 122.2 (2C), 126.6 (2C), 127.5 (2C), 128.1 (4C), 128.9 (4C), 129.6 (4C), 131.8 (2C), 139.8 (2C), 142.6 (2C). MALDI-TOF *m/z*: calcd. for $C_{36}H_{43}Br_2N_4$ 689.1854 $[M+H]^+$. $[M+H]^+$, found 689.1822.

1,7-Dibenzyl-4,10-bis-(4-bromobenzyl)-1,4,7,10-tetraazacyclododecane (10) was synthesized from 352 mg (1 mmol) of compound **7**, 500 mg (2 mmol) of *p*-bromobenzyl bromide in the presence of 160 mg (4 mmol) of NaOH in a two-phase system CH_2Cl_2 (20 mL)/H_2O (10 mL). White crystalline powder, mp 135-136 °C. Yield 626 mg (91%). ^{1}H NMR δ 2.65 (br.s, 16H), 3.34 (s, 4H), 3.41 (s, 4H), 7.19 (d, ^3J 7.7 Hz, 4H), 7.21-7.32 (m, 10H), 7.34 (d ^3J 8.2 Hz, 4H). ^{13}C NMR δ 53.0 (8C), 59.3 (2C), 60.1 (2C), 120.2 (2C), 126.7 (2C), 128.0 (4C), 128.9 (4C), 130.6 (4C), 131.1 (4C), 139.1 (2C), 139.8 (2C). MALDI-TOF *m/z*: calcd. for $C_{36}H_{43}Br_2N_4$. 689.1854 $[M+H]^+$, found 689.1898.

1,8-Dibenzyl-4,11-bis-(3-bromobenzyl)-1,4,8,11-tetraazacyclotetradecane (11) was synthesized from 380 mg (1 mmol) of compound **8**, 500 mg (2 mmol) of *m*-bromobenzyl bromide in the presence of 160 mg (4 mmol) of NaOH in a two-phase system CH_2Cl_2 (20 mL)/H_2O (10 mL). White crystalline powder, mp 129-131 °C. Yield 680 mg (95%). ^{1}H NMR δ 1.80 (quintet, ^3J 6.6 Hz, 4H), 2.53 (t, ^3J 6.6 Hz, 4H), 2.56 (t, ^3J 7.1 Hz, 4H), 2.60-2.64 (m, 4H), 2.65-2.69 (m, 4H), 3.38 (s, 4H), 3.49 (s, 4H), 7.15 (t, ^3J 7.8 Hz, 2H), 7.22-7.33 (m, 12H), 7.38 (d, ^3J 8.0 Hz, 2H), 7.61 (br.s, 2H). ^{13}C NMR δ 24.3 (2C), 50.2 (2C), 50.6 (2C), 51.2 (2C), 51.6 (2C), 58.1 (2C), 59.3 (2C), 122.2 (2C), 126.6 (2C), 127.3 (2C), 128.0 (4C), 128.8 (4C), 129.5 (2C), 129.6 (2C), 131.9 (2C), 139.8 (2C), 142.8 (2C). MALDI-TOF *m/z*: calcd. for $C_{38}H_{47}Br_2N_4$ 717.2167 $[M+H]^+$, found 717.2120.

1,8-Dibenzyl-4,11-bis-(4-bromobenzyl)-1,4,8,11-tetraazacyclotetradecane (12) was synthesized from 380 mg (1 mmol) of compound **8**, 500 mg (2 mmol) of *p*-bromobenzyl bromide in the presence of 160 mg (4 mmol) of NaOH in a two-phase system CH_2Cl_2 (20 mL)/H_2O (10 mL). White crystalline powder, mp 139-141 °C. Yield 659 mg (92%). ^{1}H NMR δ 1.78 (quintet, ^3J 6.6 Hz, 4H), 2.54 (t, ^3J 6.6 Hz, 4H), 2.55 (t, ^3J 6.7 Hz, 4H), 2.63 (br.s, 8H), 3.39 (s, 4H), 3.48 (s, 4H), 7.19 (d, ^3J 8.2 Hz, 4H), 7.25-7.36 (m, 10H), 7.41 (d, ^3J 8.2 Hz, 4H). ^{13}C NMR δ 23.9 (2C), 50.3 (2C), 50.4 (2C), 51.2 (2C), 51.4 (2C), 58.5 (2C), 59.3 (2C), 120.2 (2C), 128.0 (4C), 128.8 (4C), 130.4 (4C), 131.0 (4C), 132.1 (2C), 139.8 (2C), 142.7 (2C). MALDI-TOF *m/z*: calcd. for $C_{38}H_{47}Br_2N_4$ 717.2167 $[M+H]^+$, found 717.2113.

Standard method for the synthesis of macrobicycles comprising a 1,3-disubstituted adamantane fragment. A two-necked 50 mL flask equipped with a magnetic stirrer and reflux condenser was charged with 1,7-bis(bromobenzyl)cyclen or 1,8-bis(bromobenzyl)cyclam (0.2 mmol), $Pd(dba)_2$ (16 mol%), BINAP or DavePhos (18 mol%), absolute 1,4- dioxane (10 mL). The mixture was stirred for 2-3 min, then corresponding diamine **13a,b** (0.2 mmol) and sodium *tert*-butoxide (58 mg, 0.6 mmol) were added. The reaction mixture was refluxed for 24-30 h, cooled down to ambient temperature, filtered and solid residue was washed with CH_2Cl_2. Combined organic fractions were evaporated *in vacuo* and the residue was chromatographed on silica gel using a sequence of eluents: CH_2Cl_2, CH_2Cl_2/MeOH 25:1 – 3:1, CH_2Cl_2/MeOH/NH_3(aq) 100:20:1 – 10:4:1.

1,7,17,23,26,31-Hexaazaheptacyclo[21.5.5.2^{3,6}.2^{18,21}.1^{9,13}.1^{9,15}.1^{11,15}]tetraconta-3,5,18,20,34,-39-hexaene (14a) was synthesized from 102 mg (0.20 mmol) of compound **3**, 39 mg (0.20 mmol) of diamine **13a** in the presence of $Pd(dba)_2$ (16 mol%, 18 mg), DavePhos (18 mol%, 14 mg). Eluent: CH_2Cl_2/MeOH 10:1-5:1. Beige crystalline powder, mp 198-200 °C. Yield 27 mg (25%). ^{1}H NMR δ 1.25-1.31 (m, 4H), 1.54-1.61 (м, 4H), 1.63-1.67 (м, 4H), 2.09 (br.s, 2H), 2.75 (br.s, 16H), 2.85 (s, 4H), 3.64 (s, 4H), 6.61 (d, ^3J 8.3 Hz, 4H), 7.07 (d, ^3J 8.3 Hz, 4H), four NH protons were not assigned. ^{13}C NMR δ 28.4 (2C), 35.8 (1C), 37.1 (2C), 39.7 (4C), 45.6 (1C), 47.1 (4C), 51.0 (4C), 58.2 (2C), 61.7 (2C), 113.4 (4C), 128.6 (2C), 129.3 (4C), 149.7 (2C). MALDI-TOF *m/z*: calcd. for $C_{34}H_{51}N_6$ 543.4175 $[M+H]^+$, found 543.4150.

1,7,19,25,28,33-Hexaazaheptacyclo[23.5.5.2^{3,6}.2^{20,23}.1^{10,14}.1^{10,16}.1^{12,16}]dotetraconta-3,5,20,22,-36,41-hexaene (14b) was synthesized from 102 mg (0.20 mmol) of compound **3**, 44 mg (0.20

mmol) of diamine **13b** in the presence of Pd(dba)$_2$ (16 mol%, 18 mg), BINAP (18 mol%, 22 mg). Eluent: CH_2Cl_2:MeOH 5:1-3:1, CH_2Cl_2/MeOH/NH_3(aq) 100:20:1. Beige crystalline powder, mp 169-171 °C. Yield 28 mg (24%). ^{1}H NMR δ 1.35-1.44 (m, 8H), 1.46-1.52 (m, 4H), 1.63-1.67 м (4H), 2.02 (br.s, 2H), 2.66-2.84 (m, 16H), 3.20 (t, ^3J 7.1 Hz, 4H), 3.58 (s, 4H), 6.60 (d, ^3J 8.1 Hz, 4H), 7.14 (d, ^3J 8.1 Hz, 4H), four NH protons were not assigned. ^{13}C NMR δ 28.9 (2C), 32.8 (2C), 36.7 (1C), 38.5 (2C), 42.5 (4C), 42.7 (2C), 45.3 (1C), 47.6 (4C), 51.6 (4C), 62.2 (2C), 112.7 (4C), 127.6 (2C), 129.9 (4C), 147.5 (2C). MALDI-TOF *m/z*: calcd. for $C_{36}H_{55}N_6$ 571.4488 [M+H]$^+$, found 571.4437.

1,7,19,25,28,31,37,49,55,58,63,75-Dodecaazatridecacyclo[53,5.5.5^{25,31}.2^{3,6}.2^{20,23}.2^{33,36}.2^{50,53}.-1^{10,14}.1^{10,16}.1^{12,16}.1^{40,44}.1^{40,46}.1^{42,46}]tetraoctaconta-3,5,20,22,33,35,50,52,66,71,78,83-dodecaene (18b) was obtained as the second product in the synthesis of macrobicycle **14b**. Eluent: CH_2Cl_2/ MeOH/ NH_3(aq) 100:20:2. Yellowish glass. Yield 10 mg (9%). ^{1}H NMR δ 1.30-1.55 (m, 24H), 1.56-1.62 (m, 8H), 2.01 (br.s, 4H), 2.51-2.65 (m, 32H), 3.05-3.11 (m, 8H), 3.49 (s, 8H), 6.56 (d, ^3J 8.3 Hz, 8H), 7.12 (d, ^3J 8.3 Hz, 8H), eight NH protons were not assigned. ^{13}C NMR δ 28.9 (4C), 32.7 (4C), 36.4 (2C), 38.6 (4C), 41.9 (8C), 43.7 (4C), 45.3 (10C), 51.7 (8C), 59.9 (4C), 112.5 (8C), 127.7 (4C), 130.0 (8C), 147.6 (4C). MALDI-TOF *m/z*: calcd. for $C_{72}H_{109}N_{12}$ 1141.8898 [M+H]$^+$, found 1141.8987.

1,7,17,23,26,32-Hexaazaheptacyclo[21.6.6.2^{3,6}.2^{18,21}.1^{9,13}.1^{9,15}.1^{11,15}]dotetraconta-3,5,18,20,-36,41-hexaene (15a) was synthesized from 108 mg (0.20 mmol) of compound **5**, 39 mg (0.20 mmol) of diamine **13a** in the presence of Pd(dba)$_2$ (16 mol%, 18 mg), DavePhos (18 mol%, 14 mg). Eluent: CH_2Cl_2/MeOH/NH_3(aq) 100:20:3. Yellowish glass. Yield 29 mg (25%). ^{1}H NMR δ 1.30-1.46 (m, 8H), 1.56-1.63 (m, 4H), 1.79 (br.s, 4H), 2.06 (br.s, 2H), 2.39-2.97 (m, 20H), 3.38 (br.s, 4H), 3.77 (t, ^3J 6.6 Hz, 2H), 6.45 (d, ^3J 8.0 Hz, 4H), 7.08 (d, ^3J 8.0 Hz, 4H), two NH protons were not assigned. ^{13}C NMR δ 26.1 (2C), 28.4 (2C), 36.3 (1C), 37.1 (2C), 39.6 (4C), 46.0 (1C), 48.5 (2C), 49.4 (2C), 53.7 (2C), 54.1 (2C), 55.3 (2C), 60.1 (2C), 112.2 (4C), 126.7 (2C), 129.5 (4C), 148.3 (2C). MALDI-TOF *m/z*: calcd. for $C_{36}H_{55}N_6$ 571.4488 [M+H]$^+$, found 571.4523.

1,7,17,23,26,30,36,46,52,55,61,74-Dodecaazatridecacyclo[50.6.6.6^{23,30}.2^{3,6}.2^{18,21}.2^{32,35}.2^{47,50}.-1^{9,13}.1^{9,15}.1^{11,15}.1^{38,42}.1^{38,44}.1^{40,44}]tetraoctaconta-3,5,18,20,32,34,47,49,65,70,78,83-dodecaene (19a) was obtained as the second product in the synthesis of macrobicycle **15a**. Eluent: CH_2Cl_2/MeOH/NH_3(aq) 100:4:1. Yellowish glass. Yield 9 mg (8%). ^{1}H NMR δ 1.30-1.46 (m, 16H), 1.56-1.63 (m, 8H), 1.79 (br.s, 8H), 2.06 (br.s, 4H), 2.40-2.80 (m, 40H), 3.56 (br.s, 8H), 6.51 (d, ^3J 7.7 Hz, 8H), 7.04 (d, ^3J 7.7 Hz, 8H), eight NH protons were not assigned. MALDI-TOF *m/z*: calcd. for $C_{72}H_{109}N_{12}$ 1141.8898 [M+H]$^+$, found 1141.8716.

1,7,19,25,28,34-Hexaazaheptacyclo[23.6.6.2^{3,6}.2^{20,23}.1^{10,14}.1^{10,16}.1^{12,16}]tetratetraconta-3,5,20,-22,38,43-hexaene (15b) was synthesized from 108 mg (0.20 mmol) of compound **5**, 44 mg (0.20 mmol) of diamine **13b** in the presence of Pd(dba)$_2$ (16 mol%, 18 mg), BINAP (18 mol%, 22 mg). Eluent: CH_2Cl_2/MeOH/NH_3(aq) 100:20:2. Beige crystalline powder, mp 132-134 ºC. Yield 25 mg (20%). ^{1}H NMR δ 1.32-1.41 (м, 8H), 1.46-1.52 (м, 6H), 1.61 (br.s, 2H), 1.70 (br.s, 4H), 2.00 (br.s, 2H), 2.42-2.56 (m, 8H), 2.61-2.70 (m, 8H), 3.11 (q, ^3J 5.6 Hz, 4H), 3.35 (br.s, 4H), 3.42 (br.s, 2H), 6.50 (d, ^3J 8.2 Hz, 4H), 7.14 (d, ^3J 8.2 Hz, 4H), two NH protons were not assigned. ^{13}C NMR δ 26.2 (2C), 29.0 (2C), 32.8 (2C), 36.7 (1C), 38.9 (2C), 42.6 (4C), 43.1 (2C), 45.3 (1C), 48.9 (2C), 49.3 (2C), 53.5 (2C), 54.4 (2C), 59.7 (2C), 112.7 (4C), 127.7 (2C), 130.2 (4C), 147.3 (2C). MALDI-TOF *m/z*: calcd. for $C_{38}H_{59}N_6$ 599.4801 [M+H]$^+$, found 599.4835.

1,7,19,25,28,32,38,50,56,59,65,78-Dodecaazatridecacyclo[54.6.6.6^{25,32}.2^{3,6}.2^{20,23}.2^{34,37}.2^{51,54}.-1^{10,14}.1^{10,16}.1^{12,16}.1^{41,45}.1^{41,47}.1^{43,47}]octaoctaconta-3,5,20,22,34,36,51,53,69,74,82,87-dodecaene (19b) was obtained as the second product in the synthesis of macrobicycle **15b**. Eluent: CH_2Cl_2/MeOH/NH_3(aq) 100:20:3. Yellowish glass. Yield 23 mg (19%). ^{1}H NMR δ 1.20-1.61 (m, 32H), 1.79 (br.s, 8H), 1.99 (br.s, 4H), 2.46 (br.s, 8H), 2.52 (br.s, 8H), 2.62-2.72 (m, 16H), 3.04 (br.s, 8H), 3.41 (br.s, 8H), 6.50 (d, ^3J 7.0 Hz, 8H), 7.07 (d, ^3J 7.0 Hz, 8H), eight NH protons were not assigned. ^{13}C NMR δ 25.8 (4C), 28.9 (4C), 32.6 (4C), 36.4 (2C), 38.7 (4C), 41.9 (8C), 43.7 (4C), 45.5 (2C), 47.7 (4C), 47.8 (4C), 53.6 (8C), 57.1 (4C), 112.3 (8C), 128.1 (4C), 130.7 (8C), 147.5 (4C). MALDI-TOF *m/z*: calcd. for $C_{76}H_{117}N_{12}$ 1197.9524 [M+H]$^+$, found 1197.9410.

1,8,18,25,28,33-Hexaazaheptacyclo[23.5.5.1^{3,7}.1^{10,14}.1^{10,16}.1^{12,16}.1^{19,23}]tetraconta-3(40),4,6,-19(36),20,22-hexaene (16a) was synthesized from 102 mg (0.20 mmol) of compound **4**, 39 mg (0.20 mmol) of diamine **13a** in the presence of Pd(dba)$_2$ (16 mol%, 18 mg), DavePhos (18 mol%, 14 mg). Eluent: CH_2Cl_2/MeOH 10:1. Beige glass. Yield 24 mg (22%). ^{1}H NMR δ 1.41-1.47 (m, 4H), 1.59-1.68 (m, 8H), 2.09 (br.s, 2H), 2.71-2.81 (m, 16H), 2.85 (s, 4H), 3.56 (s, 4H), 6.36 (d, ^3J 7.2 Hz, 2H), 6.41 (d, ^3J 7.9 Hz, 2H), 7.00 (t, ^3J 7.6 Hz, 2H), 7.18 (br.s, 2H), four NH protons were not assigned. ^{13}C NMR δ 28.6 (2C), 34.5 (2C), 37.0 (1C), 40.3 (4C), 42.2 (1C), 48.7 (4C), 51.1 (4C), 55.5 (2C), 61.9 (2C), 109.8 (2C), 114.6 (2C), 116.9 (2C), 128.8 (2C), 139.3 (2C), 149.9 (2C). MALDI-TOF *m/z*: calcd. for $C_{34}H_{51}N_6$ 543.4175 [M+H]$^+$, found 543.4112.

1,8,20,27,30,35-Hexaazaheptacyclo[25.5.5.1^{3,7}.1^{11,15}.1^{11,17}.1^{13,17}.1^{21,25}]dotetraconta-3(42),4,6,-21(38),22,24-hexaene (16b) was synthesized from 102 mg (0.20 mmol) of compound **4**, 44 mg (0.20 mmol) of diamine **13b**, in the presence of Pd(dba)$_2$ (16 mol%, 18 mg), BINAP (18 mol%, 22 mg). Eluent: CH_2Cl_2/MeOH 3:1. Beige glass. Yield 33 mg (29%). ^{1}H NMR δ 1.29-1.36 (m, 4H), 1.40 (t, ^3J 6.6 Hz, 4H), 1.46-1.52 (m, 4H), 1.54 (br.s, 2H), 1.60 (br.s, 2H), 1.99 (br.s, 2H), 2.67 (br.s, 16H), 3.13 (t, ^3J 6.6 Hz, 4H), 3.58 (s, 4H), 3.75 (br.s, 2H), 6.45-6.51 (m, 4H), 6.64 (br.s, 2H), 7.06 (t, ^3J 7.7 Hz, 2H), two NH protons were not assigned. ^{13}C NMR δ 28.9 (2C), 32.9 (2C), 36.8 (1C), 38.7 (2C), 42.5 (4C), 43.0 (2C), 45.4 (1C), 46.0 (4C), 51.7 (4C), 60.7 (2C), 112.0 (2C), 112.8 (2C), 118.1 (2C), 129.0 (2C), 139.8 (2C), 148.8 (2C). MALDI-TOF *m/z*: calcd. for $C_{36}H_{55}N_6$ 571.4488 [M+H]$^+$, found 571.4467.

1,8,18,25,28,34-Hexaazaheptacyclo[23.6.6.1^{3,7}.1^{10,14}.1^{10,16}.1^{12,16}.1^{19,23}]dotetraconta-3(42),4,6,-19(38),20,22-hexaene (17a) was synthesized from 108 mg (0.20 mmol) of compound **6**, 39 mg (0.20 mmol) of diamine **13a** in the presence of Pd(dba)$_2$ (16 mol%, 18 mg), DavePhos (18 mol%, 14 mg). Eluent: CH_2Cl_2/MeOH 5:1-3:1. Beige glass. Yield 40 mg (35%). ^{1}H NMR δ 1.33-1.39 (m, 8H), 1.58-1.67 (m, 4H), 1.81 (br.s, 4H), 2.07 (br.s, 2H), 2.30-3.30 (m, 16H), 2.80 (s, 4H), 3.37 (s, 4H), 6.35-6.42 (m, 4H), 6.99 (t, ^3J 7.6 Hz, 2H), 7.13 (br.s, 2H), four NH protons were not assigned. ^{13}C NMR δ 22.9 (2C), 28.6 (2C), 35.2 (2C), 37.1 (1C), 40.2 (4C), 43.0 (1C), 46.5 (2C), 47.5 (br., 2C), 50.9 (br., 2C, $\Delta\nu_{1/2}$ 10 Hz), 52.3 (br., 2C, $\Delta\nu_{1/2}$ 20 Hz), 55.7 (br., 2C), 59.0

(br., 2C, $\Delta\nu_{1/2}$ 15 Hz), 110.4 (br., 2C, $\Delta\nu_{1/2}$ 17 Hz), 114.2 (2C), 116.8 (2C), 129.1 (2C), 137.9 (br., 2C, $\Delta\nu_{1/2}$ 20 Hz), 150.2 (2C). MALDI-TOF *m/z*: calcd. for $C_{36}H_{55}N_6$ 571.4488 $[M+H]^+$, found 571.4537.

1,8,20,27,30,36-Hexaazaheptacyclo[25.6.6.1^{3,7}.1^{11,15}.1^{11,17}.1^{13,17}.1^{21,25}]tetratetraconta-3(44),4,-6,21(40),22,24-hexaene (17b) was synthesized from 108 mg (0.20 mmol) of compound **6**, 44 mg (0.20 mmol) of diamine **13b** in the presence of Pd(dba)$_2$ (16 mol%, 18 mg), BINAP (18 mol%, 22 mg). Eluent: CH_2Cl_2/MeOH 3:1, CH_2Cl_2/MeOH/NH_3(aq) 100:20:1-100:20:2. Beige crystalline powder, mp 155-157 ºC. Yield 40 mg (33%). ^{1}H NMR δ 1.35-1.51 (m, 14H), 1.60 (br.s, 2H), 1.72 (br.s, 4H), 2.01 (br.s, 2H), 2.48-2.76 (m, 16H), 3.07-3.13 (m, 4H), 3.40 (s, 4H), 3.52 (br.s, 2H), 6.44 (d, ^3J 8.0 Hz, 2H), 6.51 (d, ^3J 7.5 Hz, 2H), 6.62 (br.s, 2H), 7.04 (t, ^3J 7.7 Hz, 2H), two NH protons were not assigned. ^{13}C NMR δ 26.1 (2C), 28.9 (2C), 32.7 (2C), 36.6 (1C), 39.0 (2C), 42.4 (4C), 43.5 (2C), 46.0 (1C), 48.4 (2C), 49.0 (2C), 51.4 (2C), 54.4 (2C), 58.3 (2C), 112.4 (2C), 113.4 (2C), 118.6 (2C), 128.7 (2C), 139.4 (2C), 148.6 (2C). MALDI-TOF *m/z*: calcd. for $C_{38}H_{59}N_6$ 599.4801 $[M+H]^+$, found 599.4768.

1,8,20,27,30,34,41,53,60,63,69,80-Dodecaazatridecacyclo[58.6.6.6^{27,34}.1^{3,7}.1^{11,15}.1^{11,17}.1^{13,17}.1^{21,25}.1^{36,40}.1^{44,48}.1^{44,50}.1^{46,50}.1^{54,58}]-octaoctaconta-3(88),4,6,21(84),22,24,36,(77),37,39,54(73),55,57-dodecaene (20b) was obtained as the second product in the synthesis of macrobicycle **17b**. Eluent: CH_2Cl_2/MeOH/NH_3(aq) 100:20:3. Yellowish glass. Yield 18 mg (15%). ^{1}H NMR δ 1.19-1.52 (m, 28H), 1.56 (br.s, 4H), 1.79 (br.s, 8H), 1.99 (br.s, 4H), 2.45-2.74 (m, 32H), 3.03 (br.s, 8H), 3.43 (br.s, 8H), 6.43 (d, ^3J 7.2 Hz, 4H), 6.48 (br.s, 4H), 6.63 (d, ^3J 7.3 Hz, 4H), 7.07 (t, ^3J 7.2 Hz, 4H), eight NH protons were not assigned. ^{13}C NMR δ 25.8 (4C), 28.9 (4C), 32.6 (4C), 36.5 (2C), 38.5 (4C), 41.9 (8C), 43.7 (4C), 47.7 (4C), 47.8 (4C), 51.4 (4C), 53.9 (4C), 58.1 (4C), 111.0 (8C), 118.5 (4C), 128.9 (4C), 138.4 (4C), 148.4 (4C), two carbon atoms of the adamantane fragment were not assigned. MALDI-TOF *m/z*: calcd. for $C_{76}H_{117}N_{12}$ 1197.9524 $[M+H]^+$, found 1197.9660.

30,35-Dibenzyl-1,8,20,27,30,35-hexaazaheptacyclo[25.5.5.1^{3,7}.1^{11,15}.1^{11,17}.1^{13,17}.1^{21,25}]dotetra-conta-3(42),4,6,21(38),22,24-hexaene (21) was synthesized from 138 mg (0.20 mmol) of compound **9**, 44 mg (0.20 mmol) of diamine **13b** in the presence of Pd(dba)$_2$ (16 mol%, 18 mg), BINAP (18 mol%, 22 mg). Eluent CH_2Cl_2/MeOH 10:1. Pale-beige crystalline compound, mp 153-155 ºC. Yield 46 mg (31%). ^{1}H NMR δ 1.16-1.26 (m, 8H), 1.29 (t, ^3J 7.0 Hz, 4H), 1.40 (br.s, 2H), 1.53 (s, 2H), 1.87 (s, 2H), 2.82 (br.s, 8H), 2.90-3.00 (m, 4H), 3.03 (t, ^3J 6.7 Hz, 4H), 3.06-3.15 (m, 4H), 3.40 (s, 4H), 3.81 (s, 4H), 6.37 (br.s, 2H), 6.46 (d, ^3J 8.8 Hz, 2H), 6.48 (d, ^3J 7.7 Hz, 2H), 7.06 (d, ^3J 7.3 Hz, 4H), 7.07 (t, ^3J 7.8 Hz, 2H), 7.23-7.29 (m, 6H), two NH protons were not assigned; ^{13}C NMR δ 28.6 (2C), 32.6 (2C), 36.4 (1C), 38.4 (2C), 42.2 (4C), 43.3 (2C), 45.0 (1C), 49.0 (4C), 51.3 (4C), 57.0 (2C), 60.8 (2C), 112.7 (2C), 113.3 (2C), 119.3 (2C), 128.4 (2C), 128.6 (4C), 129.2 (2C), 130.5 (4C), 133.3 (2C), 137.4 (2C), 148.9 (2C). HRMS MALDI-TOF *m/z*: calcd. for $C_{50}H_{67}N_6$ 751.5427 $[M+H]^+$, found 751.5454.

30,62,67,77-Tetrabenzyl-1,8,20,27,30,33,40,52,59,62,67,77-dodecaazatridecacyclo-[57.5.5.-5^{27,33}.1^{3,7}.1^{11,15}.1^{11,17}.1^{13,17}.1^{21,25}.1^{35,39}.1^{43,47}.1^{43,49}.1^{45,49}.1^{53,57}]tetraoctaconta-3(84),4,6,21(80),-

22,24,35(74),36,38,53(70),54,56-dodecaene (25, x=1) was obtained as the second product in the synthesis of compound **21**. Eluent: CH_2Cl_2/MeOH/NH_3(aq) 100:20:3. Yellowish glass. Yield 30 mg (20%). ^{1}H NMR δ 1.23-1.57 (m, 28H), 1.60 (br.s, 4H), 2.04 (br.s, 4H), 2.71 (br.s, 32H), 3.05 (br.s, 8H), 3.39 (s, 8H), 3.48 (s, 8H), 6.45 (br.d, $^3J_{obs}$ 7.1 Hz, 4H), 6.62 (br.s, 4H), 6.68 (br.d, $^3J_{obs}$ 7.1 Hz, 4H), 7.06 (t, ^3J 7.6 Hz, 4H), 7.17-7.30 (m, 12H), 7.36-7.44 (m, 8H), four NH protons were not assigned; ^{13}C NMR δ 28.9 (4C), 32.6 (4C), 36.4 (2C), 38.6 (4C), 41.9 (8C), 43.7 (4C), 47.9 (2C), 52.7 (8C), 52.8 (8C), 59.9 (4C), 60.3 (4C), 110.6 (4C), 113.5 (4C), 117.9 (4C), 126.5 (4C), 128.0 (8C), 128.8 (4C), 128.9 (8C), 140.1 (4C), 141.0 (4C), 148.4 (4C); MS MALDI-TOF *m/z*: calcd. for $C_{100}H_{133}N_{12}$ 1502.08 [M+H]$^+$, found 1502.05.

Cyclic trimer 26, x=2 was obtained as the third product in the synthesis of compound **21**. Eluent: CH_2Cl_2/MeOH/NH_3(aq) 100:20:3. Yellowish glass. Yield 16 mg (11%). ^{1}H NMR δ 1.23-1.57 (m, 42H), 1.60 (br.s, 6H), 2.04 (br.s, 6H), 2.71 (br.s, 48H), 3.05 (br.s, 12H), 3.39 (s, 12H), 3.48 (s, 12H), 6.45 (br.d, $^3J_{obs}$ 7.1 Hz, 6H), 6.62 (br.d, $^3J_{obs}$ 7.1 Hz, 6H), 6.74 (br.s, 6H), 7.05 (t, ^3J 7.3 Hz, 6H), 7.17-7.30 (m, 18H), 7.36-7.44 (m, 12H), six NH protons were not assigned; ^{13}C NMR δ 28.9 (6C), 32.6 (6C), 36.4 (3C), 38.6 (6C), 41.9 (12C), 43.7 (6C), 47.7 (3C), 52.5 (12C), 52.9 (12C), 59.9 (6C), 60.3 (6C), 110.8 (6C), 113.3 (6C), 117.7 (6C), 126.5 (6C), 128.0 (12C), 128.8 (6C), 128.9 (12C), 140.1 (6C), 141.0 (6C), 148.5 (6C); MS MALDI-TOF *m/z*: calcd. for $C_{150}H_{199}N_{18}$ 2252.61 [M+H]$^+$; found 2252.35.

28,33-Dibenzyl-1,7,19,25,28,33-hexaazaheptacyclo-[23.5.5.2^{3,6}.2^{20,23}.1^{10,14}.1^{10,16}.1^{12,16}]do-tetraconta-3,5,20,22,36,41-hexaene (22) was synthesized from 138 mg (0.20 mmol) of compound **10**, 44 mg (0.20 mmol) of diamine **13b** in the presence of Pd(dba)$_2$ (16 mol%, 18 mg), BINAP (18 mol%, 22 mg). Eluent: CH_2Cl_2/MeOH 10:1. Pale-beige crystalline compound, mp 178-180 ºC. Yield 38 mg (25%). ^{1}H NMR δ 1.32-1.48 (m, 12H), 1.61 (s, 2H), 1.72 (s, 2H), 1.99 (br.s, 2H), 2.65-2.80 (m, 8H), 3.06 (br.s, 8H), 3.20-3.28 (m, 8H), 3.48 (s, 4H), 4.26 (br.s, 2H), 6.69 (d, ^3J 8.1 Hz, 4H), 6.82 (br.s, 4H), 7.15-7.24 (m, 10H); HRMS MALDI-TOF *m/z*: calcd. for $C_{50}H_{67}N_6$ 751.5427 [M+H]$^+$, found 751.5376.

30,36-Dibenzyl-1,8,20,27,30,36-hexaazaheptacyclo[25.6.6.1^{3,7}.1^{11,15}.1^{11,17}.1^{13,17}.1^{21,25}]tetra-tetraconta-3(44),4,6,21(40),22,24-hexaene (23) was synthesized from 144 mg (0.20 mmol) of compound **11**, 44 mg (0.20 mmol) of diamine **13b** in the presence of Pd(dba)$_2$ (16 mol%, 18 mg), BINAP (18 mol%, 22 mg). Eluent: CH_2Cl_2/MeOH 10:1. Pale-beige crystalline compound, mp 178-180 ºC. Yield 44 mg (28%). In the ^{1}H and ^{13}C NMR spectra at 298 K signals of several rotational conformers are observed. ^{1}H NMR (DMSO-d_6, 363 K) δ 1.20-1.85 (m, 20H), 2.00 (br.s, 2H), 2.25-2.90 (m, 16H), 3.09 (br.s, 4H), 3.51 (br.s, 4H), 3.54 (br.s, 4H), 4.68 br.s + 5.14 br.s (2H), 6.28-6.74 (m, 6H), 6.96 (br.s, 2H), 7.25 (br.s., 10H), two NH protons were not assigned; ^{13}C NMR ($CDCl_3$, 298 K) δ 22.2 + 25.5 br.s (2C, $CH_2\underline{C}H_2CH_2$), 28.9 (2C, $\underline{C}$H(Ad)), 32.5 + 32.6 + 32.7 (2C, C(Ad)), 36.4 + 36.6 + 36.8 (1C, $\underline{C}H_2$(Ad)), 38.3 + 38.5 (2C, Ad-$C\underline{H}_2$), 41.9 + 42.0 + 42.6 + 43.0 + 43.3 + 43.6 + 44.5 (6C, $\underline{C}H_2$(Ad), $\underline{C}H_2$NH), 48.5 + 48.8 (1C, $\underline{C}H_2$(Ad)), 51.3 + 51.5 + 54.0 (8C, $\underline{C}H_2$N(cyclam)), 57.7 + 58.1 br.s + 59.0 br.s + 59.7 br.s (4C, N$\underline{C}H_2$Ph), 111.2 br.s (2C, $\underline{C}$H(Ar)), 116.3 br.s (2C, $\underline{C}$H(Ar)), 117.7 + 117.8 (2C, $\underline{C}$H(Ar)), 126.8-129.8 (m, 12C, $\underline{C}$H(Ar)), 135.2 br.s + 136.3 (2C, $\underline{C}$(Ar).), 148.5 br.s + 149.7 (2C, $\underline{C}$(Ar)), two quaternary carbon atoms were not assigned; HRMS MALDI-TOF *m/z*: calcd. for $C_{52}H_{71}N_6$ 779.5740 $[M+H]^+$, found 779.5789.

30,63,69,80-Tetrabenzyl-1,8,20,27,30,34,41,53,60,63,69,80-dodecaazatridecacyclo-[58.6.6.-$6^{27,34}.1^{3,7}.1^{11,15}.1^{11,17}.1^{13,17}.1^{21,25}.1^{36,40}.1^{44,48}.1^{44,50}.1^{46,50}.1^{54,58}$]-octaoctaconta-3(88),4,6,21(84),-22,24,36,(77),37,39,54(73),55,57-dodecaene (27, x=1) was obtained as the second product in the sysnthesis of compound **23**. Eluent: CH_2Cl_2/MeOH 3:1. Yellowish glass. Yield 20 mg (12%). ^{1}H NMR δ 1.27 (s, 4H), 1.30-1.55 (m, 24H), 1.58 (s, 4H), 1.81 (br.s, 8H), 2.01 (br.s, 4H), 2.52 (br.s, 8H), 2.65 (br.s, 24H), 3.03 (br.s, 8H), 3.41 (s, 8H), 3.46 (s, 8H), 4.27 (br.s, 4H), 6.44 (br.d, $^3J_{obs}$ 6.8 Hz, 4H), 6.53 (br.d, $^3J_{obs}$ 7.5 Hz, 4H), 6.60 (br.s, 4H), 7.04 (t, ^3J 7.5 Hz, 4H), 7.18-7.30 (m, 20H), four NH protons were not assigned; ^{13}C NMR δ 23.9 (4C), 28.9 (4C), 32.7 (4C), 36.4 (2C), 38.5 (4C), 41.9 (8C), 43.6 (4C), 49.9 (2C), 50.2 (4C), 51.4 (12C), 58.9 (4C), 59.1 (4C), 111.1 (4C), 113.9 (4C), 117.9 (4C), 127.0 (4C), 128.2 (8C), 128.9 (4C), 129.2 (8C), 148.6 (4C), eight quaternary carbon atoms were not assigned; MS MALDI-TOF *m/z*: calcd. for $C_{104}H_{141}N_{12}$ 1558.14 $[M+H]^+$, found 1558.18.

Cyclic trimer 28, **x=2** was observed as the third compound in the synthesis of compound **23**. Eluent: CH_2Cl_2/MeOH/NH_3(aq) 100:20:3. Yellowish glass. Yield 11 mg (7%). ^{1}H NMR δ 1.27 (s, 6H), 1.30-1.55 (m, 36H), 1.58 (s, 6H), 1.81 (br.s, 12H), 2.01 (br.s, 6H), 2.52 (br.s, 12H), 2.65 (br.s, 36H), 3.03 (br.s, 12H), 3.41 (s, 12H), 3.46 (s, 12H), 4.27 (br.s, 6H), 6.44 (br.d, $^3J_{obs}$ 6.8 Hz, 6H), 6.60 (br.d, 6H), 6.69 (br.s, 6H), 7.03 (t, ^3J 7.3 Hz, 6H), 7.17-7.30 (m, 30H), six NH protons were not assigned; ^{13}C NMR δ 23.9 (6C), 28.9 (6C), 32.7 (6C), 36.4 (3C), 38.5 (6C), 41.9 (12C), 43.6 (6C), 49.9 (3C), 50.2 (6C), 51.4 (18C), 58.9 (6C), 59.1 (6C), 110.9 (6C), 113.8 (6C), 117.9 (6C), 127.1 (6C), 128.2 (12C), 128.9 (6C), 129.2 (12C), 142.3 (6C), 148.7 (6C), six quaternary carbon atoms were not assigned; MS MALDI-TOF *m/z*: calcd. for $C_{156}H_{211}N_{18}$ 2336.71 $[M+H]^+$, found 2336.55.

28,34-Dibenzyl-1,7,19,25,28,34-hexaazaheptacyclo-[23.6.6.$2^{3,6}.2^{20,23}.1^{10,14}.1^{10,16}.1^{12,16}$]-tetra-tetraconta-3,5,20,22,38,43-hexaene (24) was synthesized from 144 mg (0.20 mmol) of compound **12**, 44 mg (0.20 mmol) of diamine **13b** in the presence of $Pd(dba)_2$ (16 mol%, 18 mg), BINAP (18 mol%, 22 mg). Eluent: CH_2Cl_2/MeOH 10:1. Pale-beige crystalline compound, mp 152-154 ºC. Yield 38 mg (24%). ^{1}H NMR δ 1.30-1.49 (m, 10H), 1.50-1.55 (m, 2H), 1.61 (br.s, 4H), 1.79 (br.s, 2H), 2.00 (br.s, 4H), 2.42-2.80 (m, 12H), 2.93 (br.s, 4H), 3.12-3.19 (m, 4H), 3.42-3.57 (m, 8H), 6.55 (d, ^3J 7.7 Hz, 4H), 7.11 (d, ^3J 7.7 Hz, 4H), 7.19-7.29 (m, 10H), two NH protons were not assigned; ^{13}C NMR δ 24.6 (br., 2C, $\Delta\nu_{1/2}$ 30 Hz), 28.8 (2C), 32.8 (2C), 36.6 (1C), 38.7 (2C), 42.1 (2C), 42.8 (4C), 45.2 (1C), 51.1 (br., 2C, $\Delta\nu_{1/2}$ 50 Hz), 51.7 (br., 4C, $\Delta\nu_{1/2}$ 35 Hz), 52.1 (br., 2C, $\Delta\nu_{1/2}$ 30 Hz), 58.3 (br., 2C, $\Delta\nu_{1/2}$ 20 Hz), 58.9 (br., 2C, $\Delta\nu_{1/2}$ 30 Hz), 112.4 (4C), 127.7 (2C), 128.4 (4C), 129.9 (4C), 130.9 (4C), 135.5 (br., 2C, $\Delta\nu_{1/2}$ 50 Hz), 147.9 (2C), two quaternary carbon atoms were not assigned; HRMS MALDI-TOF *m/z*: calcd. for $C_{52}H_{71}N_6$ 779.5740 $[M+H]^+$, found 779.5790.

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