SYNTHESIS OF MACROCYCLES COMPRISING 2,7-DIAMINO-NAPHTHALENE MOIETY VIA PALLADIUM-CATALYZED AMINATION REACTION

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Abstract – An original synthetic approach to bismacroyclic ligands bearing naphthalene moiety was developed. First, the macrocycles comprising 2,7-diaminonaphthalene fragment were reacted with 2,7-dibromonaphthalene, 4,4’-dibromobiphenyl or bromobenzyl bromide affording corresponding N,N’-bis(bromoaryl) or N,N’-bis(bromobenzyl) substituted macrocycles. Pd-catalyzed macrocyclization of these compounds with a wide range of di- and polyamines led to a series of new macrobicyclic ligands. The yields of the macrobicycles are strongly dependent on the nature of starting compounds, reaching 35% in some cases.

INTRODUCTION

Different fields of coordination chemistry find practical applications in modern technology such as development of chemosensors for environment control, chemotherapeutic or diagnostic agents, treatment
of nuclear waste. Thus there is a great demand for the design and synthesis of efficient complexing agents, first of all, able of binding selectively different metal cations. Macrocycles comprising several donor atoms are an important class of compounds possessing valuable coordination properties, and complex architectures have been developed on their basis to finely fit the needs for selective cation binding. Ligand properties could be tuned not only by varying the number and nature of donor groups but also by introducing different non-coordinating structural motifs. Condensed aromatic moieties are of major interest in ligand design for chemosensoring and sequestration of toxic and radioactive metal ions. The first macrocyclic compounds involving the naphthalene moiety were described in the literature over 70 years ago. This emissive hydrophobic aromatic system is drawing considerable attention and dozen of works appeared dealing with the synthesis and investigation of azacrown ethers derivatives functionalized by exocyclic naphthalene substituents and macrocycles of different geometry based on naphthalene, which are of the main interest for us. A number of polyoxamacrocycles containing 2,3-, 1,5- and 1,8-disubstituted naphthalene were investigated in binding alkali metals using NMR titration technique; macrocycles with larger cavities with two 2,3-disubstituted naphthalene moieties were synthesized, other substituents were introduced in positions 1 and 4 to modify their coordination properties. A number of works is dedicated to coordination properties of the macrocycles based on 1,1'-binaphthalene fragment including interesting spherands. All these monomacrocyclic compounds coordinate alkali metal cations, ammonia and simplest alkylammonium cations, as do more sophisticated polyoxa bismacrocycles, macrobicycle, and macrotricycle. Azamacrocycles involving naphthalene and Schiff bases, diamides, diimides, lactames were prepared. Naphthalene system can be linked to tetraazamacrocycles or incorporated into calixarene and catenane structures, attached to porphyrins. These compounds are of interest for supramolecular chemistry and could be used e.g. as organic anions receptors or molecular rotors. Recently, we have developed an efficient synthesis of polyoxa and polyaza macrocycles of type A involving 2,7-diaminonaphthalene moiety. These macrocycles could be used as starting compounds for the synthesis of more sophisticated bismacroyclic ligands. For example, N-functionalization of aromatic amino groups providing dibromides B followed by Pd-catalyzed cyclization reaction could be a rational way to new cryptands C (Scheme 1). In this work the influence of structural parameters of intermediate compounds on the synthesis of macrobicycles C was investigated. The described results clearly demonstrated the interest and limitation of this synthetic approach.
RESULTS AND DISCUSSION

The synthetic approach illustrated on Scheme 1 is based on selective transformations, thus the structure of dihalogenides \( B \) is a key factor for successful preparation of target macrobicycles. Indeed, the selective substitution of one halogen atom by a macrocyclic diamine \( A \) is important for the first step. In the second step, the macrocyclization involving substitution of the second resting halogen atoms by another diamine should proceed smoothly. Pd-Catalyzed amination reaction could provide the desirable selectivity for both transformations according to our earlier investigations.\(^{25-27}\) Moreover, the difference in the reactivity of alkyl and aryl halogenides could be used to perform a selective first step. Bearing this in mind we have prepared two series of \( N,N' \)-disubstituted macrocyclic compounds using model dioxa- and trioxadiazamacrocycles \( 1 \) and \( 4 \) (Scheme 2, 3). The first series of macrocycles was prepared using selective Pd-catalyzed arylation of the macrocycle \( 1 \) with aromatic dibromides\(^{25}\) such as 2,7-dibromonaphthalene, and 4,4’-dibromobiphenyl (Scheme 2). These arylation agents were chosen due to the fact that two bromine atoms are located in different aromatic rings what would make the cyclization step easier.

![Scheme 1](image)

![Scheme 2](image)
A careful choice of the ligand was needed for the successful catalytic reaction of the sterically hindered macrocycle 1 with the dihalides 2, 3. Moreover, to obtain the target products in good yields, an excess of the dihalides was employed to prevent undesirable oligomerization reactions. While the reaction of 1 with 4 equiv. of 2,7-dibromonaphthalene proceeded equally smoothly with BINAP and Xantphos, the reaction with 4,4’-dibromobiphenyl worked only with BINAP. After optimization of the reaction conditions we obtained two N,N’-bis(bromoaryl) substituted macrocycles 2 and 3 in 35 and 44% yields, respectively. An attempt to employ 3,3’-dibromobiphenyl for N,N’-difunctionalization of the macrocycle 1 was unsuccessful as this reaction afforded only a monoarylated compound and oligomers according to the \(^1\)H NMR and MALDI-TOF analysis of the reaction mixture.

The second series of N,N’-bis(bromobenzyl) derivatives 5-7 was obtained starting from the macrocycle 4 and isomeric bromobenzyl bromides in the presence of K\(_2\)CO\(_3\) as a base (Scheme 3).

![Scheme 3](image)

Next, we investigated the macrocyclization reaction using various di- and polyamines 8a-l and the halogen-substituted macrocycles 2, 3, 5-7 in the presence of Pd catalyst according to our procedure for selective N,N’-diarylation of linear polyamines.\(^26,27\) All our attempts to obtain macrobicycles from dibromoaryl derivatives 2, 3 using the most long-chain trioxadiamine 8g were unsuccessful though a full conversion of starting compounds was observed. Probably, the distance between the two bromine atoms in these rigid structures is too long to provide the desirable macrocyclization.

In contrast, the macrocyclization reaction proceeds easily when dibromide 5 reacted with di- and polyamines 8 including diazacrown ethers 8h,i and adamantanediamines 8j-l (Scheme 4, Table 1).
The reactions were conducted using equimolar amounts of the reagents in boiling dioxane (C = 0.02 M) with tBuONa as a base. In the majority of experiments we applied Pd(dba)$_2$/BINAP (8/9 mol\%) catalytic system. However, Pd(dba)$_2$/DavePhos (16/18 mol\%) was used to carry out macrocyclization with 1,3-bis(aminomethyl)adamantane 8j and diazacrown ethers 8h,i in accordance with our previous investigations of the arylation of adamantanediamines.$^{28-30}$

As shown in Table 1, a wide range of linear di- and polyamines afforded the target macrobicycles 9a-l in quite good yields which attained 33-35\% in some cases (entries 6, 7). The $^1$H NMR and MALDI-TOF analysis of the reaction mixtures indicated that a complete conversion of starting dibromides 5-7 was achieved in all investigated reactions but side products (macrotricylic cyclodimers 11 and other oligomers) were obtained along with the target compounds. The macrobicycles 9a-l were isolated by column chromatography and were characterized using conventional methods, $^1$H, $^{13}$C NMR spectroscopy, MALDI-TOF and HRMS mass-spectrometry.

It is to be noted that the $^1$H NMR spectra are useful for structural characterization of macrobicycles 9a,b,f,h-l bearing a short or conformationally rigid spacer linking benzyl moieties. The chemical shifts of diastereotopic PhCH$_2$N protons are significantly different from one another due to hindered rotation, thus these protons are easily distinguishable from the corresponding signals of the side products. Moreover, some proton resonances of the short spacers are upfield shifted, probably due to their location in the cone-shape shielding zone of the naphthalene ring. The most pronounced upfield shifts are observed for the adamantane-containing macrobicycles.
Table 1. The synthesis of macrobicyclic compounds 9a-l from \(N,N'\)-bis(3-bromobenzyl) substituted macrocycle 5.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Polyamine</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>Polyamine</th>
<th>Product</th>
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<td>8(^b)</td>
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<td>16</td>
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<td>20</td>
<td>9(^b)</td>
<td><img src="image11.png" alt="Image" /></td>
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<tr>
<td>4</td>
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<td><img src="image14.png" alt="Image" /></td>
<td>14</td>
<td>10(^b)</td>
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<td>23</td>
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\(^a\) Pd(dba)\(_2\)/BINAP (8/9 mol%), equimolar amounts of the reagents in boiling dioxane (C = 0.02 M);  
\(^b\) Pd(dba)\(_2\)/DavePhos (16/18 mol%).
Table 2. The synthesis of macrobicyclic compounds 10a,f,g,k from \(N,N'-\text{bis}(2\text{-bromobenzyl})\) substituted macrocycle 5.a)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Polyamine</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>Polyamine</th>
<th>Product</th>
<th>Yield (%)</th>
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<tr>
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<td>10a</td>
<td>19</td>
<td>4b)</td>
<td>(8i)</td>
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<td>46</td>
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<tr>
<td>2</td>
<td>(8f)</td>
<td>10f</td>
<td>18</td>
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<td>(8j)</td>
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<tr>
<td>3</td>
<td>(8g)</td>
<td>10g</td>
<td>27</td>
<td>5</td>
<td>(8k)</td>
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<td>7</td>
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</table>

a) Pd(dba)\(_2\)/BINAP (8/9 mol%), equimolar amounts of the reagents in boiling dioxane (C = 0.02 M); b) Pd(dba)\(_2\)/DavePhos (16/18 mol%).

The results presented in Table 1 indicated that there is no clear dependence of the macrobicycles yields on the chain length of polyamines what implies that the two \(m\)-bromobenzyl substituents are easily adjusted to structural parameters of polyamines by rotation of these groups. This conformation flexibility of dibromide 5 allows the successful macrocyclization reaction for rigid adamantane-containing diamines \(8j-l\) (entries 10-12). It is important to note that diazacrown ethers with secondary amino groups are also suitable reagents with the studied reaction and afford original macrotricyclic ligands \(9h,i\) (entries 8, 9).

Surprisingly, an attempt to prepare macrobicycles using bis(4-bromobenzyl) derivative 6 was unsuccessful even when a long-chain trioxadiamine \(8g\) was used for macrocyclization. According to NMR and MALDI-TOF analysis, the target macrobicycle was observed in the crude reaction mixtures but only in small amounts. However, all our attempts to isolate these compounds in pure form by column chromatography failed.
On the other hand, ortho-isomer 7 turned to be suitable for the macrocyclization (Scheme 4) and we managed to obtain macrobicycles 10 using different diamines (Table 2). The reactions of this isomer with linear polyamines 8a,f,g led to corresponding macrobicycles 10a,f,g in 18-27% yields (entries 1-3). The most sterically demanding macrocyclization between dibromide 7 and diazacrown ether 8i gave only compound 13 resulting from the reduction of both bromine atoms (entry 4) while the macrocyclization with another rigid amine, i.e. adamantandediamine 8k, resulted in a low yield of the bicyclic compound (entry 5). Thus, the cyclization reaction of this dibromide with diamines is significantly restricted by the nature of the diamine spacer.

To conclude, we have developed an interesting synthetic approach to sophisticated macrobicyclic ligands via Pd-catalyzed macrocyclization reaction. The structure of \( N,N' \)-difunctionalized intermediate B is the key parameter and should be carefully optimized. In favourable cases, the desirable macrobicycles could be obtained in good yields. The cavity size and the donor atoms of these macrobicyclic ligands can be varied according to the nature of starting compounds. Interesting macrotetrayclic ligands combining diazacrown and more rigid oxamacrocyclic moieties could also be prepared using this approach.

**EXPERIMENTAL**

All chemicals were purchased from Aldrich and Acros companies and used without further purification. 4,4’-Dibromobiphenyl, polyamines 8a-i, BINAP, DavePhos were purchased from Aldrich Co and used without purification. 2,7-Dibromonaphthalene was synthesized following a known method. Adamantane-containing diamines 8j,l were provided by Professor G.M. Butov from the Volzhskii Polytechnical Institute, and diamine 8k was provided by Professor B.S. Orlinson from the Volgograd State Technical University. Pd(dba)\(_2\) was synthesized according to a procedure described. Macrocycles 1 and 4 were synthesized using a procedure described earlier. Commercial dioxane was distilled over NaOH and sodium under argon, acetonitrile was distilled over P₂O₅, dichloromethane and methanol were 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 registered in CDCl₃ using Bruker Avance 400 spectrometer at 400 and 100.6 MHz respectively. Chemical shift values \( \delta \) are given in ppm and coupling constants \( J \) in Hz. MALDI-TOF spectra were recorded with Bruker Ultraflex and Bruker Autoflex II spectrometers using 1,8,9-trihydroxyanthracene as matrix and PEGs as internal standards. ESI-TOF spectra were registered using Bruker microQ-TOF spectrometer.

**Typical procedure for the Pd-catalyzed amination reactions.**

A two-neck flask (25 mL) flushed with dry argon, equipped with a magnetic stirrer and condenser was charged with aryl halide, Pd(dba)\(_2\) (8-16 mol%), BINAP or Xantphos (9-18 mol%), and absolute dioxane.
The mixture was stirred for 2 min, then appropriate polyamine 8 was added followed by sodium tert-butoxide. The reaction mixture was refluxed for 6-30 h, after cooling to room temperature the residue was filtered off, dioxane evaporated in vacuo, and the residue was analyzed by NMR spectroscopy. Column chromatography was carried out using a sequence of eluents: petroleum ether-CH$_2$Cl$_2$ 10:1-1:4, CH$_2$Cl$_2$ in the case of compounds 2 and 3 and CH$_2$Cl$_2$, CH$_2$Cl$_2$ CH$_2$Cl$_2$-MeOH 200:1 – 3:1, CH$_2$Cl$_2$-MeOH-NH$_3$aq 100:20:1 – 10:4:1 in the case of compounds 13-17.

2,15-Bis-(7-bromonaphth-2-yl)-6,11-dioxa-2,15-diazatricyclo[14.5.3.0$^{19,23}$]tetracosa-1(21),16(24),17,19,22-pentaene (2) was synthesized according to two procedures: a) from macrocycle 1 (82 mg, 0.25 mmol), 2,7-dibromonaphthalene (286 mg, 1 mmol) in the presence of Pd(dba)$_2$ (12 mg, 8 mol%), Xantphos (13 mg, 9 mol%), sodium tert-butoxide (72 mg, 0.75 mmol) in 2.5 mL dioxane, reflux time 20 h; b) from the same amounts of starting compounds in the presence of Pd(dba)$_2$ (23 mg, 16 mol%), BINAP (28 mg, 18 mol%). Reaction mixtures were combined and chromatographed on silica gel. Eluent petroleum ether – CH$_2$Cl$_2$ 1:4, yellow solid. Yield 130 mg (35%). $^1$H NMR (CDCl$_3$): $\delta$ 1.91 (bs, 4H), 2.03 (quintet, $^3$$J$ = 5.0 Hz, 4H), 3.55 (t, $^3$$J$ = 5.3 Hz, 4H), 3.56 (bs, 4H), 4.22 (t, $^3$$J$ = 6.6 Hz, 4H), 7.04 (dd, $^3$$J$ = 8.5 Hz, $^4$$J$ = 1.8 Hz, 2H), 7.33-7.36 (m, 4H), 7.41 (dd, $^3$$J$ = 8.7 Hz, $^4$$J$ = 1.8 Hz, 2H), 7.49 (d, $^3$$J$ = 8.8 Hz, 2H), 7.60 (d, $^3$$J$ = 8.6 Hz, 2H), 7.68 (d, $^3$$J$ = 8.6 Hz, 2H), 7.72 (s, 2H), 7.85 (s, 2H). $^{13}$C NMR (CDCl$_3$): $\delta$ 27.2 (2CH$_2$), 27.4 (2CH$_2$), 49.2 (2CH$_2$), 67.1 (2CH$_2$), 70.7 (2CH$_2$), 115.0 (2CH), 115.8 (2CH), 120.2 (2CH), 120.4 (2C), 123.6 (2CH), 125.1 (1C), 127.1 (2CH), 127.6 (2C), 127.8 (2CH), 128.6 (4CH), 129.1 (2CH), 135.7 (2C), 136.6 (1C), 145.1 (2C), 146.9 (2C). HRMS (MALDI-TOF) m/z calcd for C$_{40}$H$_{39}$Br$_2$N$_2$O$_2$ [M+H]$^+$ 737.1378, found 737.1324.

2,15-Bis-(7-bromonaphth-2-yl)-6,11-dioxa-2,15-diazatricyclo[14.5.3.0$^{19,23}$]tetracosa-1(21),16(24),17,19,22-pentaene (2) was synthesized according to two procedures: a) from macrocycle 1 (115 mg, 0.35 mmol), 4,4´-dibromobiphenyl (437 mg, 1.4 mmol) in the presence of Pd(dba)$_2$ (32 mg, 16 mol%), BINAP (39 mg, 18 mol%), sodium tert-butoxide (100 mg, 1.05 mmol) in 3.5 mL dioxane, reflux time 20 h. Eluent petroleum ether – CH$_2$Cl$_2$ 1:4 and CH$_2$Cl$_2$ – MeOH, 200:1, beige crystalline powder, m.p. 108-110°C. Yield 126 mg (44%). $^1$H NMR (CDCl$_3$): $\delta$ 1.89 (bs, 4H), 2.00 (quintet, $^3$$J$ = 5.0 Hz, 4H), 3.52-3.57 (m, 8H), 4.14 (t, $^3$$J$ = 6.6 Hz, 4H), 7.05 (dd, $^3$$J$ = 8.7 Hz, $^4$$J$ = 1.8 Hz, 2H), 7.20 (m, AA’MM’-biph, 4H), 7.46 (m, AA’MM’-biph, 4H), 7.48 (d, $^3$$J$ = 8.0 Hz, 2H), 7.50 (m, AA’MM’-biph, 4H), 7.55 (m, AA’MM’-biph, 4H), 7.62 (bs, 2H). $^{13}$C NMR (CDCl$_3$): $\delta$ 27.2 (2CH$_2$), 27.5 (2CH$_2$), 49.0 (2CH$_2$), 67.2 (2CH$_2$), 70.7 (2CH$_2$), 113.8 (2CH), 119.7 (2CH), 120.2 (1C), 120.7 (2C), 122.5 (4CH), 127.5 (4CH), 127.7 (2CH), 128.1 (4CH), 131.8 (4CH), 132.9 (2C), 136.7 (1C), 139.6 (2C), 146.4 (2C), 146.9 (2C). HRMS (MALDI-TOF) m/z calcd for C$_{44}$H$_{39}$Br$_2$N$_2$O$_2$ [M+H]$^+$ 789.1691, found 789.1735.
2,16-Bis(3-bromobenzyl)-6,9,12-trioxa-2,16-diazatricyclo[15.5.3.0^{20,24}]pentacosa-1(22),17(25),18,20,23-pentaene (5) was synthesized from the macrocycle 4 (500 mg, 1.35 mmol), m-bromobenzyl bromide (675 mg, 2.7 mmol), in the presence of K₂CO₃ (785 mg, 5.7 mmol) in 15 mL MeCN and 2 mL CH₂Cl₂, by stirring for 48 h at rt. The reaction mixture was diluted with 50 mL CH₂Cl₂, the residue was filtered off, the organic solvents were evaporated in vacuo, and the target compound 5 was obtained as a pale-yellow glassy solid. Yield 910 mg (98.5%). ¹H NMR (CDCl₃): δ 1.98 (quintet, 3 J = 5.5 Hz, 4H), 3.56 (t, 3 J = 5.1 Hz, 4H), 3.64–3.70 (m, 8Н), 3.87–3.91 (m, 4Н), 4.60 (s, 4Н), 6.59 (dd, 3 J = 9.0 Hz, 4 J = 2.1 Hz, 2H), 7.10 (d, 4 J = 2.1 Hz, 2H), 7.13–7.21 (m, 4Н), 7.36 (d, 3 J = 6.6 Hz, 2H), 7.38–7.42 (m, 4Н). ¹³C NMR (CDCl₃): δ 26.7 (2СН₂), 48.3 (2СН₂), 53.3 (2СН₂), 68.5 (2СН₂), 71.0 (2СН₂), 71.4 (2СН₂), 103.8 (2СН), 111.6 (2СН), 119.9 (1С), 122.7 (2С), 125.1 (2С), 128.5 (2С), 129.4 (2С), 130.1 (2С), 136.8 (1С), 142.2 (2С), 146.6 (2С). HRMS (MALDI-TOF) m/z calcd for C₃₄H₃₉N₂Br₂O₃ [M+H]+ 681.1327, found 681.1322.

2,16-Bis(4-bromobenzyl)-6,9,12-trioxa-2,16-diazatricyclo[15.5.3.0^{20,24}]pentacosa-1(22),17(25),18,20,23-pentaene (6) was synthesized from the macrocycle 4 (317 mg, 0.92 mmol), p-bromobenzyl bromide (504 mg, 2 mmol), in the presence of K₂CO₃ (550 mg, 4 mmol) in 10 mL MeCN and 1 mL CH₂Cl₂, by stirring for 48 h at rt. The reaction mixture was diluted with 40 mL CH₂Cl₂, the residue was filtered off, the organic solvents were evaporated in vacuo, and the target compound 6 was obtained as a pale-yellow glassy solid. Yield 560 mg (90%). ¹H NMR (CDCl₃): δ 1.96 (quintet, 3 J = 4.5 Hz, 4H), 3.55 (t, 3 J = 5.0 Hz, 4H), 3.61–3.68 (m, 8Н), 3.85–3.89 (m, 4Н), 4.56 (s, 4Н), 6.58 (dd, 3 J = 8.8 Hz, 4 J = 2.3 Hz, 2H), 7.08 (d, 4 J = 2.3 Hz, 2H), 7.11 (m, AA’MM’-Ph, 4Н), 7.37 (d, 3 J = 8.8 Hz, 2H), 7.39 (m, AA’MM’-Ph, 3 J = 8.2 Hz, 4Н). ¹³C NMR (CDCl₃): δ 26.7 (2СH₂), Δν₁/₂ = 20 Hz), 48.0 (2СH₂, Δν₁/₂ = 20 Hz), 52.8 (2СH₂ Δν₁/₂ = 20 Hz), 68.2 (2СH₂, Δν₁/₂ = 15 Hz), 70.5 (2СH₂, Δν₁/₂ = 15 Hz), 71.0 (2СH₂), 103.5 (2СH, Δν₁/₂ = 15 Hz), 111.2 (2СH, Δν₁/₂ = 20 Hz), 119.6 (1С), 120.1 (2С, Δν₁/₂ = 15 Hz), 127.9 (4СH, Δν₁/₂ = 15 Hz), 128.1 (2С, Δν₁/₂ = 15 Hz), 131.2 (4СH), 136.6 (1С, Δν₁/₂ = 15 Hz), 138.2 (2С, Δν₁/₂ = 20 Hz), 146.2 (2С, Δν₁/₂ = 15 Hz). HRMS (MALDI-TOF) m/z calcd for C₃₄H₃₉N₂Br₂O₃ [M+H]+ 681.1327, found 681.1356.

2,16-Bis(2-bromobenzyl)-6,9,12-trioxa-2,16-diazatricyclo[15.5.3.0^{20,24}]pentacosa-1(22),17(25),18,20,23-pentaene (7) was synthesized from the macrocycle 4 (140 mg, 0.38 mmol), o-bromobenzyl bromide (207 mg, 0.84 mmol), in the presence of K₂CO₃ (254 mg, 1.8 mmol) in 5 mL MeCN and 1 mL CH₂Cl₂, by stirring for 48 h at rt. The reaction mixture was diluted with 40 mL CH₂Cl₂, the residue was filtered off, the organic solvents were evaporated in vacuo, and the target compound 7 was obtained as a pale-yellow glassy solid. Yield 245 mg (95%). ¹H NMR (CDCl₃): δ 2.08–2.15 (m, 4Н), 3.66 (t, 3 J = 5.0 Hz, 4Н),
3.75–3.82 (m, 8H), 3.97–4.01 (m, 4H), 4.70 (s, 2H), 6.55 (d, $^3J = 8.8$ Hz, 2H), 7.15–7.20 (m, 2H), 7.22–7.26 (m, 6H), 7.44 (d, $^3J = 8.8$ Hz, 2H), 7.65 (s, 4H), 7.70 (2CH$_3$), 7.85 (2CH$_3$), 7.90 (2CH$_3$), 7.94 (d, $^3J = 7.7$ Hz, 2H). $^{13}$C NMR (CDCl$_3$): δ 26.9 (2CH$_2$), 48.4 (2CH$_2$), 48.4 (2CH$_2$), 68.5 (2CH$_2$), 70.9 (2CH$_2$), 71.4 (2CH$_2$), 103.2 (2CH), 111.2 (2CH), 119.7 (1C), 122.6 (2C), 127.4 (2CH), 128.0 (2CH), 128.2 (2CH), 128.4 (2CH), 132.6 (2CH), 136.8 (1C), 137.6 (2C), 146.4 (2C). HRMS (MALDI-TOF) m/z calcld for C$_{34}$H$_{39}$N$_2$Br$_2$O$_3$ [M+H]$^+$ 681.1327, found 681.1302.

**Macrobicycle 9a** was synthesized from compound 5 (136 mg, 0.2 mmol), triamine 8a (26 mg, 0.2 mmol) in the presence of Pd(dba)$_2$ (9 mg, 8 mol%), BINAP (11 mg, 9 mol%), sodium tert-butoxide (58 mg, 0.6 mmol) in 10 mL dioxane. Reflux time 24 h. Eluent CH$_2$Cl$_2$-MeOH 5:1, pale-yellow glassy compound. Yield 32 mg (25%). $^1$H NMR (CDCl$_3$): δ 1.93 (bs, 4H), 2.02 (bs, 4H), 2.83–2.89 (m, 4H), 3.04–3.12 (m, 8H), 3.49–3.90 (m, 16H), 4.34 (d, $^2J = 18.0$ Hz, 2H), 4.68 (bs, 2H), 4.80 (d, $^2J = 18.0$ Hz, 2H), 6.17 (bs, 2H), 6.24 (d, $^3J = 8.3$ Hz, 2H), 6.43 (d, $^3J = 8.8$ Hz, 2H), 6.54 (d, $^3J = 7.5$ Hz, 2H), 7.01–7.07 (m, 4H), 7.18 (d, $^3J = 9.0$ Hz, 2H), NH proton of dialkylamino group was not assigned. $^{13}$C NMR (CDCl$_3$): δ 25.9 (2CH$_2$), 27.4 (2CH$_2$), 40.7 (2CH$_2$), 45.9 (2CH$_2$), 49.7 (2CH$_2$), 53.7 (2CH$_2$), 68.7 (2CH$_2$), 70.9 (2CH$_2$), 71.1 (2CH$_2$), 103.1 (2CH), 108.3 (2CH), 111.8 (2CH), 112.3 (2CH), 114.4 (2CH), 119.1 (1C), 127.8 (2CH), 129.4 (2CH), 137.0 (1C), 140.2 (2C), 146.3 (2C), 147.9 (2C). HRMS (MALDI-TOF) m/z calcld for C$_{40}$H$_{54}$N$_5$O$_3$ [M+H]$^+$ 652.4227, found 652.4208.

**Macrobicycle 9b** was synthesized from compound 5 (136 mg, 0.2 mmol), tetraamine 8b (29 mg, 0.2 mmol) in the presence of Pd(dba)$_2$ (9 mg, 8 mol%), BINAP (11 mg, 9 mol%), sodium tert-butoxide (58 mg, 0.6 mmol) in 10 mL dioxane. Reflux time 24 h. Eluent CH$_2$Cl$_2$-MeOH 3:1, pale-yellow glassy compound. Yield 27 mg (20%). $^1$H NMR (CDCl$_3$): δ 1.93 (bs, 2H), 2.04 (bs, 2H), 2.19 (bs, 2H), 2.45 (bs, 4H), 3.15 (bs, 4H), 3.51 (t, $^3J = 7.4$ Hz, 4H), 3.54–3.70 (m, 8H), 3.81–3.89 (m, 4H), 4.32 (d, $^2J = 17.6$ Hz, 2H), 4.50 (bs, 2H), 4.85 (d, $^2J = 17.6$ Hz, 2H), 6.31 (bs, 2H), 6.41 (d, $^3J = 7.8$ Hz, 2H), 6.54 (d, $^3J = 8.6$ Hz, 2H), 6.60 (d, $^3J = 7.6$ Hz, 2H), 7.03 (bs, 2H), 7.07 (t, $^3J = 7.8$ Hz, 2H), 7.21 (d, $^3J = 8.8$ Hz, 2H), two NH protons of dialkylamino groups were not assigned. $^{13}$C NMR (CDCl$_3$): δ 27.4 (2CH$_2$), 41.2 (2CH$_2$), 45.8 (2CH$_2$), 46.6 (2CH$_2$), 49.3 (2CH$_2$), 53.4 (2CH$_2$), 68.7 (2CH$_2$), 70.9 (2CH$_2$), 71.2 (2CH$_2$), 103.8 (2CH), 109.3 (2CH), 111.8 (2CH), 112.5 (2CH), 115.7 (2CH), 119.2 (1C), 127.8 (2CH), 129.5 (2CH), 137.1 (1C), 140.4 (2C), 146.5 (2C), 147.4 (2C). HRMS (MALDI-TOF) m/z calcld for C$_{40}$H$_{55}$N$_6$O$_3$ [M+H]$^+$ 667.4335, found 667.4320.

**Macrobicycle 9c** was synthesized from compound 5 (136 mg, 0.2 mmol), tetraamine 8c (32 mg, 0.2 mmol) in the presence of Pd(dba)$_2$ (9 mg, 8 mol%), BINAP (11 mg, 9 mol%), sodium tert-butoxide (58 mg, 0.6 mmol) in 10 mL dioxane. Reflux time 24 h. Eluent CH$_2$Cl$_2$-MeOH-NH$_3$aq 100:20:1, pale-yellow
glassy compound. Yield 27 mg (20%). $^1$H NMR (CDCl$_3$): δ 1.49 (bs, 2H), 1.97 (bs, 4H), 2.46 (t, $^3J = 7.0$ Hz, 4H), 2.64 (bs, 4H), 3.05 (t, $^3J = 5.2$ Hz, 4H), 3.40–3.72 (m, 12H), 3.86 (s, 4H), 4.03 (bs, 2H), 4.33 (bs, 2H), 4.88 (bs, 2H), 6.36 (bs, 2H), 6.40 (dd, $^3J = 7.8$ Hz, $^4J = 1.9$ Hz, 2H), 6.58 (d, $^3J = 7.7$ Hz, 2H), 6.82 (dd, $^3J = 9.1$ Hz, $^4J = 2.4$ Hz, 2H), 7.07 (d, $^3J = 2.4$ Hz, 2H), 7.14 (t, $^3J = 7.7$ Hz, 2H), 7.34 (d, $^3J = 8.8$ Hz, 2H), two NH protons of dialkylamino groups were not assigned. $^{13}$C NMR (CDCl$_3$): δ 27.4 (2CH$_2$), 30.3 (1CH$_2$), 43.1 (2CH$_2$), 47.7 (2CH$_2$), 48.3 (2CH$_2$), 49.0 (2CH$_2$), 53.1 (2CH$_2$), 68.8 (2CH$_2$), 70.9 (2CH$_2$), 71.3 (2CH$_2$), 103.0 (2CH), 109.8 (2CH), 111.3 (2CH), 111.5 (2CH), 115.4 (2CH), 119.5 (1C), 128.2 (2CH), 129.4 (2CH), 140.3 (1C), 142.6 (2C), 146.6 (2C), 148.6 (2C). HRMS (MALDI-TOF) m/z calcd for C$_{41}$H$_{77}$N$_6$O$_3$ [M+H]$^+$ 681.4492, found 681.4464.

Macrobicycle 9d was synthesized from compound 5 (136 mg, 0.2 mmol), tetraamine 8d (35 mg, 0.2 mmol) in the presence of Pd(dba)$_2$ (9 mg, 8 mol%), BINAP (11 mg, 9 mol%), sodium tert-butoxide (58 mg, 0.6 mmol) in 10 mL dioxane. Reflux time 24 h. Eluent CH$_2$Cl$_2$-MeOH-NH$_3$aq 100:20:1, pale-yellow glassy compound. Yield 20 mg (14%). $^1$H NMR (CDCl$_3$): δ 1.59 (quintet, $^3J = 6.4$ Hz, 4H), 1.95–2.01 (m, 4H), 2.44 (s, 4H), 2.47 (t, $^3J = 6.8$ Hz, 4H), 3.03 (t, $^3J = 6.4$ Hz, 4H), 3.55 (t, $^3J = 4.9$ Hz, 4H), 3.62–3.69 (m, 8H), 3.84–3.88 (m, 4H), 4.59 c (4H), 6.38–6.42 (m, 4H), 6.57 (d, $^3J = 7.6$ Hz, 2H), 6.64 (dd, $^3J = 9.0$ Hz, $^4J = 2.3$ Hz, 2H), 7.05 (d, $^3J = 2.3$ Hz, 2H), 7.13 (t, $^3J = 8.0$ Hz, 2H), 7.35 (d, $^3J = 9.0$ Hz, 2H), NH protons were not assigned. $^{13}$C NMR (CDCl$_3$): δ 27.1 (2CH$_2$), 28.9 (2CH$_2$), 42.6 (2CH$_2$), 47.9 (2CH$_2$), 48.6 (2CH$_2$), 48.7 (2CH$_2$), 53.1 (2CH$_2$), 68.8 (2CH$_2$), 70.9 (2CH$_2$), 71.3 (2CH$_2$), 102.8 (2CH), 110.3 (2CH), 110.9 (2CH), 111.3 (2CH), 115.2 (2CH), 119.5 (1C), 128.2 (2CH), 129.3 (2CH), 137.2 (1C), 140.4 (2C), 146.8 (2C), 148.6 (2C). HRMS (MALDI-TOF) m/z calcd for C$_{40}$H$_{79}$N$_6$O$_3$ [M+H]$^+$ 695.4648, found 695.4673.

Macrobicycle 9e was synthesized from compound 5 (225 mg, 0.33 mmol), tetraamine 8e (62 mg, 0.33 mmol) in the presence of Pd(dba)$_2$ (15 mg, 8 mol%), BINAP (17 mg, 9 mol%), sodium tert-butoxide (96 mg, 1 mmol) in 17 mL dioxane. Reflux time 24 h. Eluent CH$_2$Cl$_2$-MeOH-NH$_3$aq 100:20:2-100:20:3, pale-yellow glassy compound. Yield 43 mg (19%). $^1$H NMR (CDCl$_3$): δ 1.54 (quintet, $^3J = 6.2$ Hz, 2H), 1.61 (quintet, $^3J = 6.6$ Hz, 4H), 1.95–2.02 (m, 4H), 2.51–2.58 (m, 8H), 3.03 (t, $^3J = 6.3$ Hz, 4H), 3.55 (t, $^3J = 4.9$ Hz, 4H), 3.63–3.69 (m, 8H), 3.84–3.88 (m, 4H), 4.58 (s, 4H), 6.37 (bs, 2H), 6.40 (d, $^3J = 8.1$ Hz, 2H), 6.58 (d, $^3J = 7.6$ Hz, 2H), 6.62 (dd, $^3J = 9.0$ Hz, $^4J = 2.1$ Hz, 2H), 7.04 (d, $^4J = 2.1$ Hz, 2H), 7.14 (t, $^3J = 7.7$ Hz, 2H), 7.33 (d, $^3J = 9.0$ Hz, 2H), NH protons were not assigned. $^{13}$C NMR (CDCl$_3$): δ 27.0 (2CH$_2$), 29.3 (3CH$_2$), 42.3 (2CH$_2$), 47.7 (2CH$_2$), 48.3 (2CH$_2$), 48.7 (2CH$_2$), 53.3 (2CH$_2$), 68.8 (2CH$_2$), 70.9 (2CH$_2$), 71.3 (2CH$_2$), 102.9 (2CH), 110.2 (2CH), 110.9 (2CH), 111.4 (2CH), 115.3 (2CH), 119.4 (1C), 128.2 (2CH), 129.3 (2CH), 137.1 (1C), 140.4 (2C), 146.8 (2C), 148.8 (2C). HRMS (MALDI-TOF) m/z
calcd for C_{43}H_{61}N_{6}O_{3} [M+H]^+ 709.9829, found 709.9790.

**Macrobicycle 9f** was synthesized from compound 5 (119 mg, 0.18 mmol), dioxadiamine 8f (26 mg, 0.18 mmol) in the presence of Pd(dba)_{2} (8 mg, 0.18 mol%), BINAP (10 mg, 9 mol%), sodium tert-butoxide (50 mg, 0.54 mmol) in 5 mL dioxane. Reflux time 24 h. Eluent CH_{2}Cl_{2}-MeOH 50:1, pale-yellow glassy compound. Yield 48 mg (33%). \(^1\)H NMR (CDCl_{3}): \(\delta\) 1.87–1.98 (m, 2H), 2.01–2.11 (m, 2H), 3.08–3.14 (m, 8H), 3.27–3.40 (m, 4H), 3.37–3.43 (m, 4H), 3.47–3.53 (m, 4H), 3.57–3.74 (m, 4H), 4.31 (d, \(\text{J} = 17.5\) Hz, 2H), 4.93 (d, \(\text{J} = 17.5\) Hz, 2H), 6.36 (bs, 2H), 6.43 (d, \(\text{J} = 7.8\) Hz, 2H), 6.56–6.64 (m, 4H), 7.04 (bs, 2H). 13C NMR (CDCl_{3}): \(\delta\) 27.5 (2CH_{2}), 43.2 (2CH_{2}), 48.9 (2CH_{2}), 68.6 (2CH_{2}), 69.2 (2CH_{2}), 70.3 (2CH_{2}), 71.0 (2CH_{2}), 71.4 (2CH_{2}), 103.3 (2CH), 111.4 (2CH), 111.6 (2CH), 115.8 (2CH), 119.6 (1C), 128.1 (2CH), 129.2 (2CH), 137.3 (1C), 140.4 (2C), 146.5 (2C), 148.2 (2C). HRMS (MALDI-TOF) m/z calcd for C_{40}H_{53}N_{4}O_{5} [M+H]^+ 669.4016, found 669.4085.

**Macrobicycle 9g** was synthesized from compound 5 (68 mg, 0.10 mmol), trioxadiamine 8g (22 mg, 0.10 mmol) in the presence of Pd(dba)_{2} (4.5 mg, 8 mol%), BINAP (5.5 mg, 9 mol%), sodium tert-butoxide (28 mg, 0.30 mmol) in 5 mL dioxane. Reflux time 24 h. Eluent CH_{2}Cl_{2}-MeOH 50:1, pale-yellow glassy compound. Yield 30 mg (35%). \(^1\)H NMR (CDCl_{3}): \(\delta\) 1.94–2.01 (m, 8H), 3.12 (t, \(\text{J} = 6.1\) Hz, 4H), 3.24 (bs, 4H), 3.30–3.33 (m, 4H), 3.38 (t, \(\text{J} = 5.6\) Hz, 4H), 3.54 (t, \(\text{J} = 4.9\) Hz, 4H), 3.60–3.70 (m, 8H), 3.84–3.88 (m, 4H), 4.57 (s, 4H), 6.41–6.49 (m, 4H), 6.59 (d, \(\text{J} = 7.6\) Hz, 2H), 6.64 (d, \(\text{J} = 8.0\) Hz, 2H), 7.02 (bs, 2H), 7.15 (t, \(\text{J} = 7.7\) Hz, 2H), 7.35 (d, \(\text{J} = 8.6\) Hz, 2H), NH protons were not assigned. 13C NMR (CDCl_{3}): \(\delta\) 26.9 (2CH_{2}), 28.6 (2CH_{2}), 42.4 (2CH_{2}), 48.4 (2CH_{2}), 53.4 (2CH_{2}), 68.7 (2CH_{2}), 69.9 (2CH_{2}), 70.2 (2CH_{2}), 70.3 (2CH_{2}), 71.0 (2CH_{2}), 71.4 (2CH_{2}) 103.2 (2CH), 110.3 (2CH), 111.4 (2CH), 111.6 (2CH), 115.5 (2CH), 119.7 (1C), 128.3 (2CH), 129.4 (2CH), 137.2 (1C), 140.5 (2C), 147.0 (2C), 148.7 (2C). HRMS (MALDI-TOF) m/z calcd for C_{44}H_{61}N_{4}O_{6} [M+H]^+ 741.4591, found 741.4622.

**Macrotricycle 9h** was synthesized from compound 5 (225 mg, 0.33 mmol), diazacrown ether 8h (72 mg, 0.33 mmol) in the presence of Pd(dba)_{2} (30 mg, 16 mol%), DavePhos (23 mg, 18 mol%), sodium tert-butoxide (96 mg, 1 mmol) in 13 mL dioxane. Reflux time 24 h. Eluent CH_{2}Cl_{2}-MeOH 100:1, pale-yellow glassy compound. Yield 38 mg (16%). \(^1\)H NMR (CDCl_{3}): \(\delta\) 2.01 (quintet, \(\text{J} = 6.0\) Hz, 4H), 2.46–2.60 (m, 4H), 3.02 (ddd, \(\text{J} = 13.8\) Hz, \(\text{J} = 6.5\) Hz, \(\text{J} = 4.2\) Hz, 2H), 3.29–3.36 (m, 2H), 3.41–3.48 (m, 2H), 3.49–3.62 (m, 16H), 3.64–3.70 (m, 4H), 3.84 (dt, \(\text{J} = 14.8\) Hz, \(\text{J} = 7.5\) Hz, 2H), 3.91 (t, \(\text{J} = 4.2\) Hz, 4H), 4.32 (d, \(\text{J} = 17.5\) Hz, 2H), 5.01 (d, \(\text{J} = 17.5\) Hz, 2H), 6.27 (bs, 2H), 6.36 (d, \(\text{J} = 8.3\) Hz, 2H), 6.55 (d, \(\text{J} = 7.5\) Hz, 2H), 6.58 (d, \(\text{J} = 9.1\) Hz, 2H), 7.08 (bs, 2H), 7.13 (t, \(\text{J} = 7.8\) Hz, 2H), 7.29 (d, \(\text{J} = 9.0\) Hz, 2H). \(^1\)C
Macrocyclone 9i was synthesized from compound 5 (225 mg, 0.33 mmol), diazacrown ether 8i (86 mg, 0.33 mmol) in the presence of Pd(dba)_2 (30 mg, 16 mol%), DavePhos (23 mg, 18 mol%), sodium tert-butoxide (96 mg, 1 mmol) in 13 mL dioxane. Reflux time 24 h. Eluent CH_2Cl_2-MeOH 50:1, pale-yellow glassy compound. Yield 27 mg (10%). ^1H NMR (CDCl_3): δ 1.85–1.98 (m, 4H), 3.25–3.55 (m, 24H), 3.56–3.70 (m, 8H), 3.81–3.91 (m, 8H), 4.29 (d, J = 17.1 Hz, 2H), 5.01 (d, J = 17.1 Hz, 2H), 6.37 (bs, 2H), 6.42 (d, J = 8.4 Hz, 2H), 6.54 (d, J = 7.3 Hz, 2H), 6.73 (d, J = 8.9 Hz, 2H), 7.05 (bs, 2H), 7.12 (t, J = 7.8 Hz, 2H), 7.33 (d, J = 9.0 Hz, 2H). ^13C NMR (CDCl_3): δ 27.9 (2CH_2), 49.0 (2CH_2), 50.1 (4CH_2), 54.3 (2CH_2), 68.7 (2CH_2), 69.0 (4CH_2) 70.5 (4CH_2), 70.9 (2CH_2), 71.3 (2CH_2), 105.2 (2CH), 110.2 (2CH), 110.9 (2CH), 112.9 (2CH), 114.5 (2CH), 120.1 (1C), 128.1 (2CH), 129.0 (2CH), 137.0 (1C), 140.0 (2C), 146.9 (2C), 148.5 (2C). HRMS (ESI-TOF) m/z calcd for C_{46}H_{59}N_4O_6 [M+H]^+ 739.4434, found 739.4429.

Macrocyclone 9j was synthesized from compound 5 (225 mg, 0.33 mmol), diame 8j (63 mg, 0.33 mmol) in the presence of Pd(dba)_2 (30 mg, 16 mol%), DavePhos (23 mg, 18 mol%), sodium tert-butoxide (96 mg, 1 mmol) in 13 mL dioxane. Reflux time 24 h. Eluent CH_2Cl_2-MeOH 100:1, pale-yellow glassy compound. Yield 41 mg (17%). ^1H NMR (CDCl_3): δ −0.42 (d, J = 12.0 Hz, 1H), 0.13 (d, J = 2.0 Hz, 1H), 0.54 (d, J = 11.6 Hz, 1H), 0.63 (d, J = 11.5 Hz, 1H), 0.90–0.95 (m, 4H), 1.21 ym. (s, 2H), 1.56 (d, J = 11.6 Hz, 2H), 1.89 (bs, 2H), 1.92–2.00 (m, 4H), 2.41 (d, J = 14.7 Hz, 2H), 2.73 (d, J = 14.7 Hz, 2H), 3.52–3.83 (m, 10H), 3.86–3.93 (m, 4H), 3.98 (ddd, J = 11.3 Hz, J = 6.6 Hz, J = 2.7 Hz), 4.30 (d, J = 18.1 Hz, 2H), 5.05 (d, J = 18.1 Hz, 2H), 6.31 (bs, 2H), 6.32 (d, J = 7.0 Hz, 2H), 6.49 (d, J = 7.5 Hz, 2H), 6.58 (dd, J = 9.1 Hz, J = 2.1 Hz, 2H), 7.05 (t, J = 8.0, 2H), 7.11 (d, J = 2.1 Hz, 2H), 7.26 (d, J = 9.1 Hz, 2H), NH protons were not assigned. ^13C NMR (CDCl_3): δ 28.1 (2CH_2, 1CH), 28.4 (1CH), 35.0 (2C), 36.0 (1CH_2), 38.7 (2CH_2), 39.4 (2CH_2), 44.7 (1CH_2), 49.4 (2CH_2), 52.4 (2CH_2), 55.0 (2CH_2), 68.6 (2CH_2), 71.2 (2CH_2), 71.6 (2CH_2), 102.6 (2CH), 108.0 (2CH), 111.1 (2CH), 111.5 (2CH), 113.7 (2CH), 119.3 (1C), 128.2 (2CH), 129.0 (2CH), 137.5 (1C), 140.2 (2C), 146.4 (2C), 149.3 (2C). HRMS (ESI-TOF) m/z calcd for C_{46}H_{59}N_4O_7 [M+H]^+ 783.4696, found 783.4691.

Macrocyclone 9k was synthesized from compound 5 (136 mg, 0.2 mmol), diame 8k (45 mg, 0.2 mmol) in the presence of Pd(dba)_2 (9 mg, 8 mol%), BINAP (11 mg, 9 mol%), sodium tert-butoxide (58 mg, 0.6
mmol) in 10 mL dioxane. Reflux time 24 h. Eluent CH$_2$Cl$_2$-MeOH 200:1, pale-yellow glassy compound. Yield 30 mg (20%). $^1$H NMR (CDCl$_3$): δ 0.13 (d, $J$ = 12.2 Hz, 1H), 0.53 (d, $J$ = 12.2 Hz, 1H), 0.74 (d, $J$ = 11.6 Hz, 2H), 0.80 (dd, $^3$J = 12.8 Hz, $^3$J = 6.3 Hz, 2H), 0.90 (td, $^3$J = 12.9 Hz, $^3$J = 3.3 Hz, 2H), 1.10 (d, $^3$J = 11.9 Hz, 2H), 1.47 (d, $^3$J = 12.0 Hz, 2H), 1.51 (s, 2H), 1.56 (d, $^3$J = 12.0 Hz, 2H), 1.92 (bs, 3H), 2.05 (bs, 1H), 2.13–2.23 (m, 2H), 2.93 (td, $^3$J = 12.8 Hz, $^3$J = 6.1 Hz, 2H), 3.08 (td, $^3$J = 14.3 Hz, $^3$J = 3.2 Hz, 2H), 3.50–3.60 (m, 4H), 3.62–3.71 (m, 4H), 3.75–3.80 (m, 2H), 3.84–3.97 (m, 6H), 4.44 (d, $^3$J = 17.8 Hz, 2H), 4.72 (d, $^3$J = 17.8 Hz, 2H), 6.37 (d, $^3$J = 8.0 Hz, 2H), 6.41–6.46 (m, 4H), 6.66 (d, $^3$J = 7.5 Hz, 2H), 7.03 (d, $^4$J = 1.9 Hz, 2H), 7.10 (t, $^3$J = 7.7 Hz, 2H), 7.28 (d, $^3$J = 9.0 Hz, 2H), NH protons were not assigned. $^{13}$C NMR (CDCl$_3$): δ 27.3 (2CH$_2$), 28.7 (2CH), 28.8 (2CH), 32.2 (2C), 36.4 (1CH), 38.0 (2CH$_2$), 39.9 (2CH$_2$), 40.1 (2CH$_2$), 42.2 (2CH$_2$), 49.4 (2CH$_2$), 51.6 (1CH$_2$), 53.7 (2CH$_2$), 68.7 (2CH$_2$), 71.6 (2CH$_2$), 103.2 (2CH), 106.8 (2CH), 111.6 (2CH$_2$), 112.6 (2CH), 113.8 (2CH), 119.7 (1C), 128.0 (2CH), 129.2 (2CH), 136.8 (1C), 140.7 (2C), 146.5 (2C), 148.4 (2C). HRMS (ESI-TOF) m/z calcd for C$_{48}$H$_{63}$N$_4$O$_3$ [M+H]$^+$ 743.4900, found 743.4864.

**Cyclic dimer 11k** was obtained as the second product in the synthesis of the macrobicycle 9k. Eluent CH$_2$Cl$_2$-MeOH 100:1, pale-yellow glassy compound. Yield 12 mg (8%). $^1$H NMR (CDCl$_3$): δ 1.18–1.62 (m, 32H), 1.90–2.02 (m, 12H), 2.93–2.97 (m, 8H), 3.53 (t, $^3$J = 4.6 Hz, 8H), 3.60–3.67 (m, 16H), 3.83–3.88 (m, 8H), 4.52 (s, 8H), 6.39–6.43 (m, 8H), 6.56 (d, $^3$J = 7.2 Hz, 4H), 6.62 (dd, $^3$J = 8.7 Hz, $^4$J = 2.0 Hz, 4H), 7.03 (bs, 4H), 7.09 (t, $^3$J = 7.6 Hz, 4H), 7.32 (d, $^3$J = 9.0 Hz, 4H), NH protons were not assigned. $^{13}$C NMR (CDCl$_3$): δ 26.8 (4CH$_2$), 28.8 (4CH), 32.4 (4C), 36.4 (2CH$_2$), 38.4 (4CH$_2$), 41.8 (8CH$_2$), 43.5 (4CH$_2$), 47.6 (2CH$_2$), 48.4 (4CH$_2$), 53.7 (4CH$_2$), 68.7 (4CH$_2$), 71.0 (4CH$_2$), 71.4 (4CH$_2$), 103.3 (4CH), 110.2 (4CH), 111.2 (4CH), 111.7 (4CH), 115.0 (4CH), 119.7 (2C), 128.3 (4CH), 129.3 (4CH), 137.0 (2C), 140.7 (4C), 147.0 (4C), 148.7 (4C). MS (MALDI-TOF) m/z calcd for C$_{98}$H$_{125}$N$_8$O$_6$ [M+H]$^+$ 1485.97, found 1486.92.

**Macrobicycle 9l** was synthesized from compound 5 (225 mg, 0.33 mmol), diamine 8l (87 mg, 0.33 mmol) in the presence of Pd(dba)$_2$ (15 mg, 8 mol%), BINAP (17 mg, 9 mol%), sodium tert-butoxide (96 mg, 1 mmol) in 17 mL dioxane. Reflux time 24 h. Eluent CH$_2$Cl$_2$-MeOH 200:1, pale-yellow glassy compound. Yield 60 mg (23%). $^1$H NMR (CDCl$_3$): δ 1.34–1.38 (m, 2H), 1.45–1.80 (m, 12H), 1.86–2.05 (m, 4H), 2.15 (bs, 2H), 2.96–3.00 (m, 2H), 3.42–3.75 (m, 12H), 3.82–3.87 (m, 4H), 4.56 (s, 2H), 4.59 (s, 2H), 4.64 (bs, 1H), 5.66 (bs, 1H), 6.45 (d, $^3$J = 8.0 Hz, 1H), 6.57–6.65 (m, 3H), 6.70 (m, AA’MM’, 2H), 6.78–6.82 (m, 2H), 6.99 (bs, 1H), 7.03 (bs, 1H), 7.09–7.16 (m, 4H), 7.21–7.25 (m, 2H), 7.42 (m, AA’MM’, 2H). $^{13}$C NMR (CDCl$_3$): δ 26.5 (1CH$_2$), 27.7 (1CH$_2$), 29.2 (2CH$_2$), 32.8 (1C), 36.1 (1CH$_2$), 38.1 (1CH$_2$), 41.8 (bs, 2CH$_2$), 42.6 ym. (2CH$_2$), 43.2 (1CH$_2$), 47.5 (1CH$_2$), 48.3 (1C), 48.5 (1CH$_2$), 48.8
(1CH₂), 53.4 (1CH₂), 54.0 (1CH₂), 68.6 (1CH₂), 68.8 (1CH₂) 71.0 (2CH₂), 71.1 (1CH₂), 71.5 (1CH₂), 103.1 (1CH), 103.3 (1CH), 108.3 (1CH), 111.2 (1CH), 111.4 (1CH), 113.3 (1CH), 113.4 (1CH), 115.1 (1CH), 116.0 (1CH), 117.4 (2CH), 118.1 (1CH), 119.8 (1C), 125.2 (2CH), 128.1 (1CH), 128.5 (1CH), 128.9 (1CH), 129.5 (1CH), 139.9 (1C), 140.4 (1C), 141.6 (1C), 143.2 (1C), 143.8 (1C), 146.4 (1), 147.1 (1C), 148.8 (1C), one quaternary carbon atom was not assigned. HRMS (MALDI-TOF) m/z calcd for C₅₂H₆₃N₄O₃ [M+H]+ 791.4900, found 791.4950.

Macrobicycle 10a was synthesized from compound 7 (112 mg, 0.16 mmol), triamine 8a (21 mg, 0.16 mmol) in the presence of Pd(dba)₂ (7.5 mg, 8 mol%), BINAP (9 mg, 9 mol%), sodium tert-butoxide (48 mg, 0.5 mmol) in 8 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH 10:1, pale-yellow glassy compound. Yield 20 mg (19%). ¹H NMR (CDCl₃): δ 1.31–1.37 (m, 4 Н), 1.71–1.78 (m, 4 Н), 2.69–2.75 (m, 4 Н), 3.30 (ddd, 2 J = 14.7 Hz, 3 J = 10.2 Hz, 3 J = 5.1 Hz, 2H), 3.34–3.58 (m, 14 Н), 3.66–3.70 (m, 4 Н), 4.06 (d, 3 J = 14.7 Hz, 2H), 5.02 (d, 2 J = 14.7 Hz, 2H), 6.53 (d, 3 J = 8.0 Hz, 2H), 6.67 (t, 3 J = 7.3 Hz, 2H), 7.03 (d, 4 J = 2.0 Hz, 2H), 7.11 (d, 3 J = 7.3 Hz, 2H), 7.14–7.21 (m, 4 Н), 7.61 (d, 3 J = 9.0 Hz, 2H), NH protons were not assigned. ¹³C NMR (CDCl₃): δ 25.8 (2 СН₂), 30.0 (2 СН₂), 42.0 (2 СН₂), 45.2 (2 СН₂), 48.6 (2Ч₂), 51.4 (2Ч₂), 68.9 (2Ч₂), 70.7 (2Ч₂), 71.0 (2Ч₂), 106.1 (2Ч), 110.2 (2Ч), 111.4 (2Ч), 116.4 (2Ч), 120.4 (1C), 123.0 (2C), 127.4 (2Ч), 128.6 (2Ч), 128.8 (2Ч), 130.3 (2Ч), 137.5 (1C), 146.1 (2C). HRMS (MALDI-TOF) m/z calcd for C₄₀H₅₄N₅O₃ [M+H]+ 652.4226, found 652.4260.

Macrobicycle 10f was synthesized from compound 7 (133 mg, 0.19 mmol), dioxadiamine 8f (28 mg, 0.19 mmol) in the presence of Pd(dba)₂ (9 mg, 8 mol%), BINAP (11 mg, 9 mol%), sodium tert-butoxide (55 mg, 0.57 mmol) in 10 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH 100:1, pale-yellow glassy compound. Yield 24 mg (18%). ¹H NMR (CDCl₃): δ 1.67–1.74 (m, 4 Н), 2.79 (dt, 3 J = 10.4 Hz, 3 J = 5.7 Hz, 2H), 3.00 (dd, 3 J = 10.4 Hz, 3 J = 5.7 Hz, 2H), 3.05–3.23 (m, 8 Н), 3.32–3.51 (m, 8 Н), 3.55–3.68 (m, 4 Н), 3.71 (t, 3 J = 4.4 Hz, 4H), 4.09 (d, 2 J = 13.8 Hz, 2H), 4.89 (bs, 2H), 4.93 (d, 2 J = 13.8 Hz, 2H), 6.57 (d, 3 J = 8.0 Hz, 2H), 6.69 (t, 3 J = 7.3 Hz, 2H), 7.11–7.18 (m, 6 Н), 7.20 (t, 3 J = 7.8 Hz, 2H), 7.60 (d, 3 J = 8.7 Hz, 2H). ¹³C NMR (CDCl₃): δ 25.8 (2CH₂), 30.0 (2CH₂), 42.0 (2CH₂), 45.2 (2CH₂), 48.6 (2CH₂), 51.4 (2CH₂), 68.9 (2CH₂), 70.7 (2CH₂), 71.0 (2CH₂), 106.1 (2CH), 110.2 (2CH), 111.4 (2CH), 116.4 (2CH), 120.4 (1C), 123.0 (2C), 127.4 (2CH), 128.6 (2CH), 128.8 (2CH), 130.3 (2CH), 137.5 (1C), 146.1 (2C). HRMS (MALDI-TOF) m/z calcd for C₄₀H₅₃N₄O₅ [M+H]+ 669.4016, found 669.4042.

Macrobicycle 10g was synthesized from compound 7 (112 mg, 0.16 mmol), trioxadiamine 8g (35 mg, 0.16 mmol) in the presence of Pd(dba)₂ (7.5 mg, 8 mol%), BINAP (9 mg, 9 mol%), sodium tert-butoxide
(48 mg, 0.5 mmol) in 8 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH 100:1, pale-yellow glassy compound. Yield 33 mg (27%). ¹H NMR (CDCl₃): δ 1.76 (quintet, ³J = 6.1 Hz, 4H), 1.78–1.83 (m, 4H), 3.08–3.17 (m, 12H), 3.29 (t, ³J = 6.4 Hz, 4H), 3.39–3.46 (m, 8H), 3.54–3.58 (m, 4H), 3.74–3.78 (m, 4H), 4.47 (s, 4H), 4.81 (bs, 2H), 6.82 (d, ³J = 8.1 Hz, 2H), 6.88 (t, ³J = 7.3 Hz, 2H), 7.11–7.17 (m, 6H), 7.21 (t, ³J = 7.7 Hz, 2H), 7.57 (d, ³J = 8.7 Hz, 2H). ¹³C NMR (CDCl₃): δ 25.2 (2CH₂), 28.6 (2CH₂), 40.6 (2CH₂), 45.3 (2CH₂), 52.9 (2CH₂), 68.8 (2CH₂), 69.3 (2CH₂), 69.8 (2CH₂), 70.0 (2CH₂), 70.7 (2CH₂), 71.1 (2CH₂), 107.4 (2CH), 109.8 (2CH), 113.2 (2CH), 116.3 (2CH), 121.4 (1C), 122.0 (2C), 128.5 (2CH), 128.7 (2CH), 129.7 (2CH), 136.9 (1C), 147.0 (2C), 147.7 (2C). HRMS (MALDI-TOF) m/z calcd for C₄₄H₆₁N₄O₆ [M+H]+ 741.4653, found 741.4653.

2,16-Bis(bromobenzyl)-6,9,12-trioxa-2,16-diazatricyclo[15.5.3.0²⁰,₂⁴]pentacosa-1(22),17(25),18,20,23-pentaene (13) was obtained instead of the cyclization product from compound 7 (133 mg, 0.19 mmol), diazacrown ether 8i (49 mg, 0.19 mmol) in the presence of Pd(dba)₂ (17.5 mg, 16 mol%), BINAP (13.5 mg, 18 mol%), sodium tert-butoxide (55 mg, 0.57 mmol) in 10 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH 200:1, pale-yellow glassy compound. Yield 46 mg (46%). ¹H NMR (CDCl₃): δ 1.95–2.02 (m, 4H), 3.56 (t, ³J = 5.1 Hz, 4H), 3.65–3.70 (m, 8H), 3.88–3.92 (m, 4H), 4.64 (s, 4H), 6.65 (dd, ³J = 8.8 Hz, ⁴J = 2.1 Hz, 2H), 7.09 (d, ⁴J = 2.1 Hz, 2H), 7.21–7.32 (m, 10H), 7.38 (d, ³J = 9.0Hz, 2H). ¹³C NMR (CDCl₃): δ 26.8 (2CH₂), 48.3 (2CH₂), 53.7 (2CH₂), 68.7 (2CH₂), 71.0 (2CH₂), 71.5 (2CH₂), 103.6 (2CH), 111.7 (2CH), 119.7 (1C), 126.5 (4CH), 126.7 (2CH), 128.4 (2CH), 128.5 (4CH), 137.0 (1C), 139.5 (2C), 147.0 (2C). HRMS (MALDI-TOF) m/z calcd for C₃₄H₄₁N₂O₃ [M+H]+ 525.3117, found 525.3078.

Macrobicycle 10k was synthesized from compound 7 (133 mg, 0.19 mmol), diamine 8k (42 mg, 0.19 mmol) in the presence of Pd(dba)₂ (9 mg, 8 mol%), BINAP (11 mg, 9 mol%), sodium tert-butoxide (55 mg, 0.57 mmol) in 10 mL dioxane. Reflux time 24 h. Eluent CH₂Cl₂-MeOH 200:1, pale-yellow glassy compound. Yield 10 mg (7%). ¹H NMR (CDCl₃): δ 0.32 (d, ³J = 12.0 Hz, 1H), 0.50 (d, ³J = 12.0 Hz, 1H), 0.56 (d, ³J = 11.3 Hz, 2H), 0.86–1.99 (m, 18H), 2.86–2.94 (m, 4H), 3.29–3.59 (m, 12H), 3.64–3.68 (m, 4H), 4.11 (d, ³J = 14.3 Hz, 2H), 4.99 (d, ³J = 14.3 Hz, 2H), 6.54 (d, ³J = 8.0 Hz, 2H), 6.66 (t, ³J = 7.3 Hz, 2H), 6.99 (bs, 2H), 7.13 (t, ³J = 7.1 Hz, 2H), 7.19 (d, ³J = 7.7 Hz, 2H), 7.21 (d, ³J = 7.6 Hz, 2H), 7.62 (d, ³J = 9.0 Hz, 2H), NH protons were not assigned. ¹³C NMR (CDCl₃): δ 25.7 (2CH₂), 28.9 (2CH), 32.7 (2C), 35.8 (1CH₂), 38.1 (2CH₂), 39.4 (2CH₂), 41.3 (2CH₂), 43.1 (2CH₂), 44.7 (2CH₂), 48.3 (1CH₂), 51.4 (2CH₂), 68.6 (2CH₂), 70.6 (2CH₂), 71.1 (2CH₂), 106.9 (2CH), 110.1 (2CH), 112.0 (2CH), 115.9 (2CH), 120.9 (1C), 122.6 (2C), 128.5 (2CH), 128.7 (2CH), 130.4 (2CH), 137.6 (1C), 146.4 (2C), 148.1 (2C). HRMS (MALDI-TOF) m/z calcd for C₄₈H₆₃N₄O₃ [M+H]+ 743.4900, found 743.4947.
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