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Pd-catalyzed amination in the synthesis of cyclen-based macrotricycles

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ABSTRACT

Three approaches to three types of cyclen-based macrotricycles have been elaborated starting from *trans*-bis(3-bromobenzyl)cyclen. The macrotricycles were synthesized via Pd-catalyzed amination. The first approach employed consecutive macrocyclization and benzylation steps giving a cage-like tricycle. In the second, cyclen amino groups were Boc-protected prior to formation of the second and the third rings. In the third method, macrotricycles were synthesized according to a one-step procedure using diaza-crown ethers.

Macropolycyclic compounds attract interest from researchers due to their suitability as frameworks for many receptor sites.[1] Diazacrown ethers were the first to be employed in the construction of macrobicyclic and macrotricyclic compounds.[2] The simplest molecules comprise several isolated diazacrown ethers,[3] and more complex species possess cryptand-like structures. Polymacrocyclic compounds may be of different geometry owing to various modes of attaching several macrocycles. Spherical macrobicyclic cryptates of the polyether series were introduced by Lehn,[4] and cage-type macrobicycles were thoroughly studied by Italian chemists.[5] Also, spherical and cylindrical macrotricycles were developed,[6] with the latter being arranged in a coplanar manner. Various methods were developed for the introduction of arene moieties to the framework of sophisticated macropolycyclic compounds which serve as sensing units. In the majority of these compounds the arene unit is linked to the nitrogen atoms of the macrocycle via methylene goups,[7] but in some compounds the arene moiety is attached through a direct C(sp^2)–N bond.[8] The synthesis of chiral macrobicycles, for example, those containing diazacrown and binaphthol has been described.[9] A number of macropolycycles derived from cyclam and cyclen were reported,[10] a mutual feature of these compounds being the attachment of two tetraazamacrocycles via xylyl linkers. Detailed information on various types of macropolycyclic ligands can be found in reviews.[11]

We were the first to employ Pd-catalyzed amination in the synthesis of cryptand-like macrobicycles containing cyclen moieties; macrotricyclic cyclodimers were formed in the majority of cases as by-products.[12] In this Letter, we describe approaches to three structurally different types of macrotricycle each of which possesses a cyclen unit and which differs in the mode of attaching oxadiamine linkers to the tetraazamacrocyclic backbone.

The first approach (Scheme 1) started from *trans*-bis(3-bromobenzyl)cyclen (**2**), which was synthesized via a previously described two-step procedure from cyclen **1**.[12] On reacting **2** with trioxadiamine **3** under Pd-catalyzed amination conditions [$Pd(dba)_2$/BINAP, 8 mol %, *t*BuONa, 1,4-dioxane, c = 0.02 M], macrobicycle **4** was obtained in a 28% yield. Next, this compound was treated with *m*-bromobenzyl bromide to give cyclen derivative **5**. The yield in this reaction was moderate due to substantial alkylation of the alkylaryl amino groups in the bicycle, thus tri- and tetrabenzylated products as well as isomeric dibenzyl derivatives competed with the formation of the target compound **5**.[13] To suppress polybenzylation it was necessary to use 1.7 equiv of bromobenzyl bromide. However, the second macrocyclization step was successful and was conducted using the same trioxadiamine **3** and catalyst, and led to a 33% yield of the desired macrotricycle **6**, in which two trioxadiamine units are attached on opposite sides of the cyclen via benzyl spacers, forming a spherical cryptand.

The alternative to this method of attaching the third macrocycle is via preliminary protection of two secondary amino groups on the dibenzyl cyclen **2** with Boc substituents (Scheme 2). The reaction was run in CH_2Cl_2 using 2.5 equiv of Boc_2O and gave the

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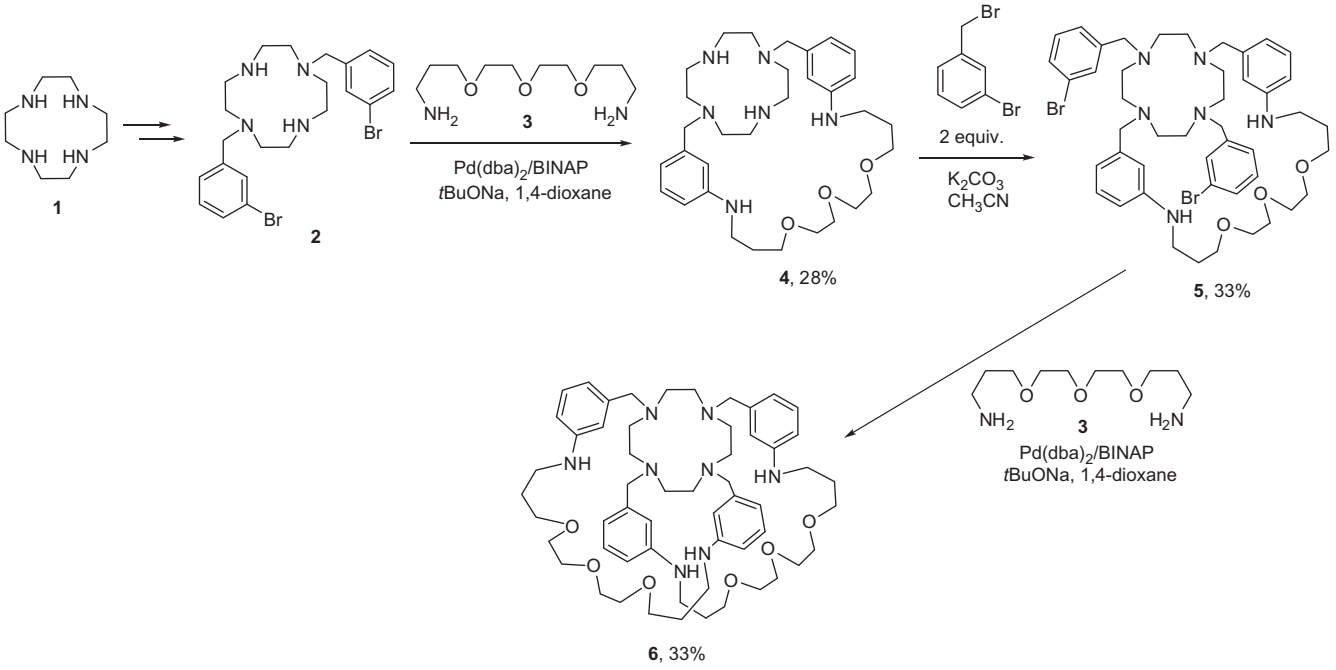
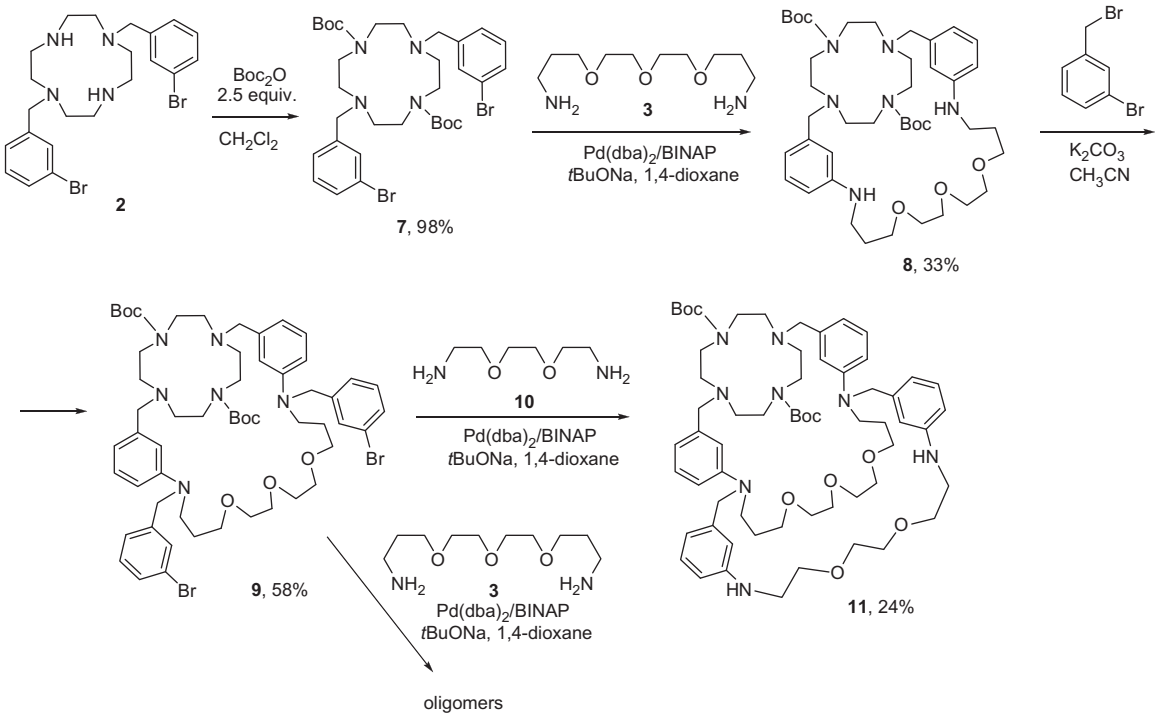


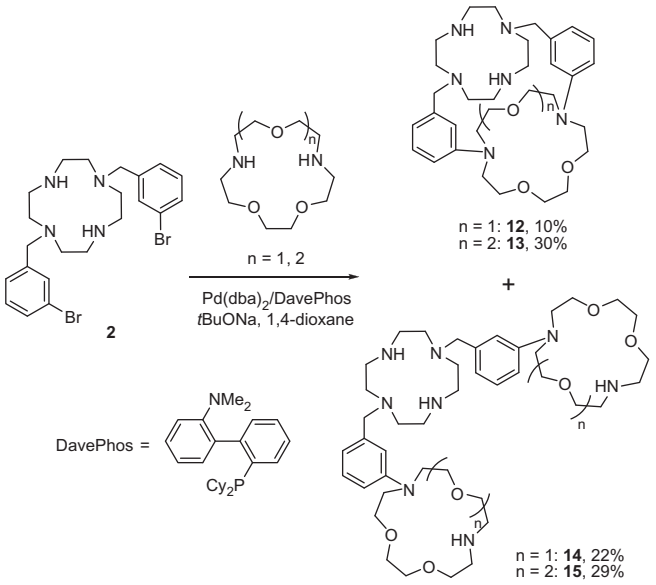
Scheme 1. Synthesis of macrotricycle **6**.



Scheme 2. Synthesis of macrotricycle **11**.

bis-protected cyclen derivative **7** in quantitative yield. This was employed in the Pd-catalyzed amination reaction with trioxadiamine **3** to afford macrobicycle **8** which was isolated in a 33% yield after column chromatography on silica gel. Compound **8** was reacted with 2 equiv of *m*-bromobenzyl bromide to give bis(bromobenzyl) derivative **9** in a 58% yield. The formation of this compound was not quantitative due to easy quaternization of the tertiary amino groups with the very reactive bromobenzyl bromide. In the last step we carried out the reaction with a second molecule of trioxadiamine **3**, however, in this case the target macrotricycle was not formed, and only the formation of cyclooligomers was observed. Changing trioxadiamine **3** for dioxadiamine **10** with a shorter chain resulted in a 24% yield of the macrotricyclic compound **11**. We assume that in this reaction the length of the diamine is crucial for successful ring-closure of the third macrocycle.

The third approach to macrotricycles based on cyclen is much simpler than the two described above. The reaction of *trans*-bis(3-bromobenzyl)cyclen (**2**) with 1 equiv of diaza-15-crown-5



Scheme 3. Synthesis of cylindrical cryptands **12**, **13** and trimacrocycles **14** and **15**.

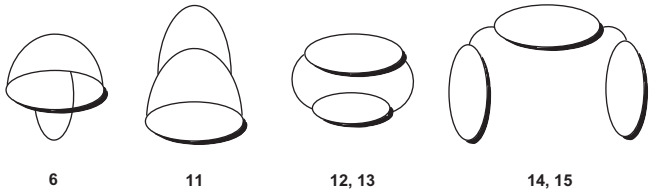


Figure 1. Structural types of macrotricycles **6** and **11**–**13** and trimacrocycles **14** and **15**.

or diaza-18-crown-6 led directly to the corresponding cylindrical cryptands **12** and **13** (Scheme 3). These reactions were catalyzed with $Pd(dba)_2$/DavePhos catalyst because BINAP was found to be much less active in the arylation of secondary amino groups in aza-crown ethers. The target compounds were obtained in 10% and 30% yields, respectively. Such pronounced differences in the yields can be explained by the different distances between the two reacting nitrogen atoms of the diazacrown ethers. In both reactions bis(diazacrown) derivatives **14** and **15** were isolated in comparable yields (22% and 29%); these molecules are also of interest as they contain isolated macrocycles with different binding properties.

In conclusion, we have elaborated approaches to three structural types of macrotricycles organized around the cyclen moiety. The shapes of the synthesized macropolycycles **6** and **11–15** can be outlined schematically as shown in Figure 1. Further work on the synthesis of macrotricycles of these types bearing isomeric aromatic spacers and various oxadiamine linkers, which will alter the sizes of certain cavities, is underway.

Acknowledgments

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13. All reactions were run under dry argon using MeCN distilled over CaH_2 and 1,4-dioxane distilled over Na. After completion of the reactions (^{1}H NMR) the mixture was evaporated in vacuo and chromatographed on silica gel using a sequence of eluents: CH_2Cl_2, CH_2Cl_2–MeOH 50:1–3:1, CH_2Cl_2/MeOH/NH_3(aq) 100:20:1–10:4:1. For the synthesis of macrobicycle **4** see Ref. 12.
32,37-Bis(3-bromobenzyl)-12,15,18-trioxa-1,8,22,29,32,37-hexaazatetracyclo[27.5.5.1^{3,7}.1^{23,27}]hentetraconta-3(41),4,6,23(40),24,26-hexaene (**5**) was synthesized from macrobicycle **4** (130 mg, 0.23 mmol) and 3-bromobenzyl bromide (115 mg, 0.46 mmol) in MeCN (5 mL) in the presence of K_2CO_3 (95 mg, 0.69 mmol) at room temperature (reaction time 48 h). Eluent CH_2Cl_2–MeOH–NH_3(aq) 100:20:1. Yield 69 mg (33%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.85 (quin, J = 6.1 Hz, 4H), 2.64–2.74 (m, 16H), 3.19 (q, J = 5.8 Hz, 4H), 3.38 (s, 4H), 3.41 (s, 4H), 3.57 (t, J = 6.0 Hz, 4H), 3.59–3.62 (m, 4H), 3.65–3.70 (m, 4H), 3.96 (t, J = 5.4 Hz, 2H), 6.48 (d, J = 8.0 Hz, 2H), 6.60 (d, J = 7.3 Hz, 2H), 6.74 (s, 2H), 7.06 (t, J = 7.6 Hz, 2H), 7.11 (t, J = 7.8 Hz, 2H), 7.31 (d, J = 7.7 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.52 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 29.1 (2C), 41.6 (2C), 52.5 (4C), 53.0 (4C), 59.2 (2C), 60.5 (2C), 69.6 (2C), 70.2 (2C), 70.6 (2C), 110.8 (2C), 113.2 (2C), 117.6 (2C), 122.1 (2C), 127.5 (2C), 128.7 (2C), 129.7 (4C), 131.7 (2C), 141.0 (2C), 142.6 (2C), 148.6 (2C); MALDI-TOF m/z 905.3271 [M+H]$^+$; calcd for $C_{46}H_{63}Br_2N_6O_3$: 905.3328.
12,15,18,43,46,49-Hexaoxa-1,8,22,29,32,39,53,60-octaazaheptacyclo[30.30.2.2^{29,60}.1^{3,7}.1^{23,27}.1^{34,38}.1^{54,58}]heptaconta-3(70),4,6,23(69),24,26,34(68),35,37,54(67),55,57-dodecaene (**6**) was synthesized from compound **5** (130 mg, 0.14 mmol) and trioxadiamine **3** (31 mg, 0.14 mmol), in the presence of $Pd(dba)_2$ (6.5 mg), BINAP (8 mg), tBuONa (40 mg, 0.42 mmol), in boiling absolute 1,4-dioxane (6 mL, reflux time 24 h). Eluent CH_2Cl_2–MeOH 3:1. Yield 45 mg (33%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.73 (quin, J = 6.2 Hz, 8H), 2.72–2.87 (m, 16H), 3.07 (t, J = 6.8 Hz, 8H), 3.38–3.48 (m, 16H), 3.50–3.55 (m, 16H), 5.27 (br s, 4H), 6.39 (d, J = 7.7 Hz, 4H), 6.51 (s, 4H), 6.53 (d, J = 8.3 Hz, 4H), 7.01 (t, J = 7.5 Hz, 4H); ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 28.8 (4C), 40.1 (4C), 50.0 (br s, 8C), 58.9 (4C), 68.1 (4C), 69.2 (4C), 69.5 (4C), 112.0 (4C), 113.0 (4C), 117.2 (4C), 128.3 (4C), 135.7 (4C), 148.8 (4C); MALDI-TOF m/z 965.84 [M+H]$^+$; calcd for $C_{56}H_{85}N_8O_6$: 965.66.
Di-*tert*-butyl 4,10-bis(3-bromobenzyl)-1,4,7,10-tetraazacyclo-dodecane-1,7-dicarboxylate (**7**) was synthesized from compound **2** (510 mg, 1 mmol) and Boc_2O (545 mg, 2.5 mmol), in CH_2Cl_2 (1.5 mL), at room temperature. The reaction was complete in 24 h. Yield 694 mg (98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 18H), 2.61 (br s, 8H), 3.29 (br s, 4H), 3.40 (br s, 4H), 3.52 (s, 4H), 7.12 (br t, J_{obs} = 6.3 Hz, 2H), 7.17 (br s, 2H), 7.31 (br d, J_{obs} = 6.5 Hz, 2H), 7.44 (br s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 28.2 (6C), 45.9 (4C), 54.7 (4C), 59.1 (2C), 79.5 (2C), 122.2 (2C), 127.7 (2C), 129.6 (2C), 130.0 (2C), 132.2 (2C), 141.5 (2C), 155.6 (2C); MALDI-TOF m/z 709.1920 [M+H]$^+$; calcd for $C_{32}H_{47}Br_2N_4O_4$: 709.1964.
Di-*tert*-butyl 12,15,18-trioxa-1,8,22,29,32,37-hexaazatetra-cyclo[27.5.5.1^{3,7}.1^{23,27}]hentetraconta-3(41),4,6,23(40),24,26-hexaene-32,37-dicarboxylate (**8**) was synthesized from compound **7** (734 mg, 1.03 mmol), trioxadiamine **3** (220 mg, 1 mmol), in the presence of $Pd(dba)_2$ (92 mg), BINAP (112 mg), tBuONa (290 mg, 3.02 mmol), in boiling absolute 1,4-dioxane (50 mL, reflux time 24 h). Eluent CH_2Cl_2–MeOH 25:1. Yield 294 mg (33%). ^{1}H NMR (400 MHz, $CDCl_3$, 328 K): δ 1.35 (s, 18H), 1.84 (quin, J = 5.5 Hz, 4H), 2.78 (br s, 8H), 3.23 (t, J = 6.0 Hz, 4H), 3.36 (br s, 8H), 3.54 (br s, 4H), 3.55–3.60 (m, 8H), 3.65–3.68 (m,

4H), 6.46 (br d, J_{obs} = 7.5 Hz, 2H), 6.56 (br d, J_{obs} = 6.6 Hz, 2 H), 6.65 (br s, 2H), 7.04 (br t, J_{obs} = 7.3 Hz, 2H) (NH protons were not assigned); ^{13}C NMR (100.6 MHz, $CDCl_3$, 328 K): δ 28.5 (6C), 29.6 (2C), 41.9 (2C), 47.4 (4C), 54.4 (4C), 60.6 (2C), 69.8 (2C), 70.4 (2C), 70.8 (2C), 79.5 (2C), 111.8 (2C), 113.6 (2C), 118.3 (2C), 128.9 (2C), 140.0 (2C), 148.9 (2C), 156.1 (2C);); ESI-TOF *m*/*z* 769.5212 $[M+H]^+$; calcd for $C_{42}H_{69}N_6O_7$: 769.5228.

Di-*tert*-butyl 8,22-bis(3-bromobenzyl)-12,15,18-trioxa-1,8,22,29,32,37-hexaazatetracyclo[27.5.5.$1^{3,7}$.$1^{23,27}$]-hentetraconta-3(41),4,6,23(40),24,26-hexaene-32,37-dicarboxylate (**9**) was synthesized from compound **8** (315 mg, 0.4 mmol), 3-bromobenzyl bromide (200 mg, 0.8 mmol), in MeCN (8 mL) in the presence of K_2CO_3 (138 mg, 1 mmol) at room temperature (reaction time 48 h). Eluent CH_2Cl_2–MeOH 25:1. Yield 255 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 18H), 1.88 (quin, *J* = 6.1 Hz, 4H), 2.70 (br s, 8H), 3.31 (br s, 8H), 3.45–3.59 (m, 16H), 3.65–3.69 (m, 4H), 4.48 (s, 4H), 6.50 (br d, J_{obs} = 6.2 Hz, 2H), 6.61 (d, *J* = 7.2 Hz, 2H), 6.73 (br s, 2H), 7.06 (t, *J* = 7.9 Hz, 2H), 7.11 (br s, 2H), 7.12 (t, *J* = 7.6 Hz, 2H), 7.33 (br d, J_{obs} = 7.1 Hz, 2H), 7.34 (br s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$, 328 K): δ 27.8 (2C), 28.5 (6C), 46.9 (4C), 48.2 (2C), 54.3 (2C), 54.5 (4C), 60.6 (2C), 68.8 (2C), 70.5 (2C), 70.9 (2C), 79.5 (2C), 111.9 (2C), 113.6 (2C), 118.3 (2C), 122.8 (2C), 125.4 (2C), 129.8 (2C), 129.9 (2C), 130.1 (4C), 139.9 (2C), 142.1 (2C), 148.7 (2C), 155.9 (2C); ESI-TOF *m*/*z* 1105.4373 $[M+H]^+$; calcd for $C_{56}H_{79}N_6O_7$: 1105.4377.

Di-*tert*-butyl 12,15,18,52,55,58-hexaoxa-1,8,22,29,36,39,42,65-octaazaheptacyclo-[27.19.13.$5^{36,42}$.$1^{3,7}$.$1^{23,27}$.$1^{30,34}$.$1^{44,48}$]heptaconta-3(70),4,6,23(69),24,26,30(68),31,33,44(62),45,47-dodecaene-39,65-dicarboxylate (**11**) was synthesized from compound **9** (126 mg, 0.114 mmol), dioxadiamine **10** (17 mg, 0.115 mmol) in the presence of $Pd(dba)_2$ (10.5 mg), BINAP (13 mg), *t*BuONa (33 mg, 0.34 mmol), in boiling absolute 1,4-dioxane (6 mL, reflux time 24 h). Eluent CH_2Cl_2–MeOH 10:1. Yield 30 mg (24%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 18H), 1.86 (br s, 4H), 2.60–2.95 (m, 8H), 3.17 (br s, 4H), 3.30–3.70 (m, 40H), 4.41 (s, 2H), 4.43 (s, 2H), 6.44 (br s, 4H), 6.50–6.61 (m, 6H), 6.72 (br s, 2H), 7.05 (br s, 4H) (NH protons were not assigned); ^{13}C NMR (100.6 MHz, $CDCl_3$, 328 K): δ 27.9 (2C), 28.5 (6C), 43.8 (2C), 47.0 (4C), 48.0 (2C), 54.5 (4C), 54.7 (2C), 60.9 (2C), 68.9 (2C), 69.9 (2C), 70.5 (4C), 70.9 (2C), 110.8 (2C), 112.2 (4C), 113.7 (2C), 116.1 (2C), 117.8 (2C), 128.9 (2C), 129.4 (2C), 139.0 (2C), 140.5 (2C), 148.8 (2C), 149.3 (2C), 156.1 (2C) (two quaternary carbon atoms of Boc groups were not assigned); MALDI-TOF *m*/*z* 1093.7032 $[M+H]^+$; calcd for $C_{62}H_{93}N_8O_9$: 1093.7066.

24,27,32-Trioxa-1,8,11,14,21,38-hexaazapentacyclo-[19.8.5.$5^{8,14}$.$1^{2,6}$.$1^{16,20}$] hentetraconta-2(41),3,5,16(35),17,19-hexaene (**12**) was synthesized from compound **2** (77 mg, 0.15 mmol), diaza-15-crown-5 (33 mg, 0.15 mmol), in the presence of $Pd(dba)_2$ (14 mg), DavePhos (11 mg), *t*BuONa (44 mg, 0.46 mmol), in boiling absolute 1,4-dioxane (8 mL, reflux time 24 h). Eluent CH_2Cl_2–MeOH 3:1. Yield 9 mg (10%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.64–2.93 (m, 16H), 3.44–3.52 (m, 8H), 3.60 (br s, 8H), 3.62 (m, 4H), 3.88 (t, *J* = 5.3 Hz, 4H), 6.48 (br s, 4H), 7.06 (t, *J* = 8.0 Hz, 2H), 7.15 (s, 2H) (NH protons were not assigned); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 49.4 (4C), 52.0 (6C), 54.3 (2C), 63.0 (2C), 69.6 (2C), 70.2 (2C), 70.4 (2C), 110.4 (2C), 114.0 (2C), 117.8 (2C), 128.6 (2C), 139.9 (2C), 149.2 (2C); MALDI-TOF *m*/*z* 567.3959 $[M+H]^+$; calcd for $C_{32}H_{51}N_6O_3$: 567.4023.

7,7′-[1,4,7,10-Tetraazacyclododecane-1,7-diylbis(methylene-3,1-phenylene)] bis-1,4,10-trioxa-7,13-diazacyclopentadecane (**14**) was obtained as the main product in the synthesis of compound **12**. Eluent CH_2Cl_2–MeOH–NH_3(aq) 100:20:3. Yield 13 mg (22%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.65 (br s, 16H), 2.77 (t, *J* = 5.9 Hz, 4H), 2.78 (t, *J* = 5.2 Hz, 4H), 3.52–3.67 (m, 32H), 3.74 (t, *J* = 6.8 Hz, 4H), 6.52 (s, 2H), 6.56 (d, *J* = 7.6 Hz, 2H), 6.71 (d, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 7.7 Hz, 2H) (NH protons were not assigned); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 45.8 (4C), 48.5 (2C), 48.7 (2C), 51.6 (4C), 52.5 (2C), 52.9 (2C), 60.7 (2C), 68.9 (4C), 69.4 (2C), 70.0 (2C), 70.2 (2C), 71.0 (2C), 110.5 (2C), 112.7 (2C), 116.9 (2C), 129.3 (2C), 139.6 (2C), 147.9 (2C); MALDI-TOF *m*/*z* 785.58 $[M+H]^+$; calcd for $C_{42}H_{73}N_8O_6$: 785.57.

24,27,32,35-Tetraoxa-1,8,11,14,21,41-hexaazapentacyclo-[19.8.8.$5^{8,14}$.$1^{2,6}$.$1^{16,20}$]tetratetraconta-2(44),3,5,16(38),17,19-hexaene (**13**) was synthesized from compound **2** (77 mg, 0.15 mmol), diaza-18-crown-6 (39 mg, 0.15 mmol), in the presence of $Pd(dba)_2$ (14 mg), DavePhos (11 mg), *t*BuONa (44 mg, 0.46 mmol), in boiling absolute 1,4-dioxane (8 mL, reflux time 24 h). Eluent CH_2Cl_2-MeOH 3:1. Yield 27 mg (30%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.77–2.81 (m, 8H), 2.83–2.85 (m, 8H), 3.54–3.61 (m, 24H), 3.65 (s, 4H), 6.52 (d, *J* = 7.3 Hz, 2H), 6.57 (dd, *J* = 8.3 Hz, *J* = 1.5 Hz, 2H), 6.77 (br s, 2H), 7.07 (t, *J* = 7.7 Hz, 2H) (NH protons were not assigned); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 48.1 (4C), 51.0 (4C), 51.6 (4C), 62.3 (2C), 68.8 (4C), 70.8 (4C), 112.1 (2C), 113.5 (2C), 117.7 (2C), 129.1 (2C), 139.6 (2C), 148.3 (2C); MALDI-TOF *m*/*z* 611.4261 $[M+H]^+$; calcd for $C_{34}H_{55}N_6O_4$: 611.4285.

7,7′-[1,4,7,10-Tetraazacyclododecane-1,7-diylbis(methylene-3,1-phenylene)] bis-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**15**) was obtained as the second product in the synthesis of compound **13**. Eluent CH_2Cl_2–MeOH–NH_3(aq) 100:20:3. Yield 19 mg (29%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.64 (br s, 16H), 2.78 (t, *J* = 4.4 Hz, 8H), 3.55–3.63 (m, 36H), 3.65 (t, *J* = 4.9 Hz, 8H), 6.51 (s, 2H), 6.55 (d, *J* = 8.1 Hz, 2H), 6.69 (d, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 7.8 Hz, 2H) (NH protons were not assigned); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 45.8 (4C), 49.2 (4C), 50.5 (4C), 51.6 (4C), 60.6 (2C), 68.7 (4C), 70.4 (8C), 70.5 (4C), 110.2 (2C), 112.5 (2C), 116.6 (2C), 129.3 (2C), 139.7 (2C), 147.9 (2C); MALDI-TOF *m*/*z* 873.6090 $[M+H]^+$; calcd for $C_{46}H_{81}N_8O_8$: 873.6177.