Макрогетероциклы
http://macroheterocycles.isuct.ru

DOI: 10.6060/mhc121214a

Synthesis of Macropolycycles Comprising Diazacrown and Adamantane Moieties *via* Pd–Catalyzed Amination Reaction

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N,N'-bis(bromobenzyl) substituted diazacrown ethers were obtained in the reactions of corresponding free diazacrowns with two equivalents of bromobenzyl bromides in high yields. These compounds were introduced in the Pd-catalyzed amination reaction with 1,3-bis(aminomethyl) and 1,3-bis(2-aminoethyl)adamantanes to give macrobicyclic products. The yields were shown to be dependent on the nature of starting diazacrown derivatives and diamines. N,N'-bis(3-bromobenzyl) substituted diazacrown ethers provided better yields of the target macrobicycles than N,N'-bis(4-bromobenzyl) derivatives. In the latter case substantial amounts of cyclic oligomers were formed and isolated.

Keywords: Diazacrown ethers, macropolycycles, palladium-catalyzed amination, adamantane.

Синтез макрополициклов с фрагментами диазакраунa и адамантана с помощью реакции Pd–катализируемого аминирования

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N,N'-бис(бромбензил)замещенные диазакраун-эфиры были получены с высокими выходами по реакции соответствующих диазакраун-эфиров с двумя эквивалентами бромбензилбромидов. Данные соединения были введены в реакции палладий-катализируемого аминирования с 1,3-бис(аминометил)- и 1,3-бис(2-аминоэтил)-адамантанами с образованием макробициклических продуктов. Показано, что выходы зависят от природы производных диазакраун-эфиров и диаминов. N,N'-Бис(3-бромбензил)замещенные диазакраун-эфиры обеспечили более высокие выходы целевых макробициклов, чем N,N'-бис(4-бромбензил) замещенные изомеры. При использовании последних образовались значительные количества циклических олигомеров.

Ключевые слова: Диазакраун-эфиры, макрополициклы, палладий-катализируемое аминирование, адамантан.

Introduction

During last three decades various synthetic approaches were elaborated for the synthesis of polymacrocyclic compounds comprising two or more crown and azacrwon ether moieties. In particular, bis(azacrown) ethers with isolated macrocycles linked *via* aliphatic bridges were described,[1] as well as the molecules with spiro-conjugated macrocycles,[2] and with condensed macro rings possessing saturated and unsaturated cyclic spacers.[3] The majority of known bis(azacrown) ethers possess two macrocyclic units which are symmetrically arranged around the aromatic,[4,5] matallocene,[6] porphyrin,[7] or calixarene[8] spacer. A special attention has been paid to the macrobicycles of the cryptand type derived from azacrown ethers: known are di- and triazapolyoxacryptands,[9,10] benzocryptands containing fragments of 1,2-, 1,3-, and 1,4-disubstituted benzene,[11,12] 2,6-disubstituted pyridine,[13] described are the compounds in which two diazacrown ethers are combined in macrotricyclic systems *via* aliphatic[14] or benzyl[15] linkers. Reported are so-called cross-bridged tetracyclic compounds containing diazacrown ethers.[16] Convenient and versatile synthetic approaches to bi- and polycyclic compounds of this type, to cryptands and supercryptands, were elaborated in 1990s by Krakowiak and coauthors using simple nucleophilic substitution reactions.[17-19]

A special interest is evoked by the polyazamacrobicycles containing a bulky lipophilic adamanatane backbone which 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.[20] While the first was found to be active against the poultry plague,[21] the latter was patented as an anti-viral agent for home animals.[22,23] Cyclic Schiff bases were synthesized using 1,3-bis(2-aminoethyl)adamantane for biological activity studies.[24] *N,N′*-dipyridyl derivative of this amine was synthesized by us earlier[25] and showed nootropic effect in mice. Having acquired a good experience in the synthesis of macropolycycles *via* Pd-catalyzed amination reactions,[26,27] as well as in the arylation of adamantane-containing amines[28,29] and diamines,[30-32] we decided to investigate the applicability of this approach to previously unknown adamantane-containing macrobicycles derived from diazacrown ethers.

Experimental

NMR spectra were registered using Bruker Avance 400 spectrometer, MALDI-TOF spectra were obtained on Bruker Autoflex II spectrometer using 1,8,9-trihydroxyanthracene as matrix and PEGs as internal standards. 3- and 4-bromobenzyl bromide, 1,7-diaza-15-crown-5 and 1,10-diaza-18-crown-6, BINAP and DavePhos ligands, sodium *tert*-butoxide were purchased from Aldrich and Acros and used without further purification, $Pd(dba)_2$ was synthesized according to the method described.[33] 1,3-Bis(aminomethyl)-adamantane and 1,3-bis(2-aminoethyl)adamantane were obtained according to a method described earlier.[25] Dioxane was distilled over NaOH followed by the distillation over sodium under argon, acetonitrile, dichloromethane and methanol were used freshly distilled.

Typical procedure for the synthesis of N,N'-bis(bromobenzyl) derivatives of diazacrown ethers ***3-6***.

A one-neck flask equipped with a condenser and magnetic stirrer was charged with diazacrown ether **1** or **2** (1-4.5 mmol), 3- or 4-bromobenzyl bromide (2-9 mmol), acetonitrile (3-15 ml), sodium or potassium carbonate (8-36 mmol), and the reaction mixture was refluxed for 15 h. The solvent was filtered, residue washed with CH_2Cl_2 (5-15 ml), combined organic fractions were evaporated *in vacuo*. Solid or viscous residue was dissolved in CH_2Cl_2 and washed with water (3×5-10 ml), organic layer was separated, aqueous layer was washed with CH_2Cl_2 (3×10-20 ml), and combined organic fractions were dried over molecular sieves 4 Å. The solvent was evaporated *in vacuo*, and resulting compounds 3-6 were obtained as crystalline or glassy compounds.

*7,13-Bis(3-bromobenzyl)-1,4,10-trioxa-7,13-diazacyclopentadecane (**3**)*. Obtained from diazacrown ether **1** (4.5 mmol, 1 g). Yield 2.226 g (89 %), yellowish glassy compound. (MALDI-TOF) found: 555.0821. $C_{24}H_{33}Br_2N_2O_3$ requires 555.0858 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.57 (4H, t, ^3J = 5.1 Hz, CH_2N), 2.80 (4H, t, ^3J = 5.9 Hz, CH_2N), 3.60 (8H, t, ^3J = 5.3 Hz, CH_2O), 3.62 (4H, s, CH_2O), 3.63 (4H, s, $ArCH_2N$), 7.14 (2H, t, ^3J = 7.8 Hz, H5-Ar), 7.26 (2H, d, ^3J = 7.7 Hz, H6-Ar), 7.34 (2H, d, ^3J = 7.8 Hz, H4-Ar), 7.55 (2H, br.s, H2-Ar). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 54.2 (2C, CH_2N), 54.3 (2C, CH_2N), 59.9 (2C, $ArCH_2N$), 69.4 (2C, CH_2O), 70.3 (2C, CH_2O), 70.6 (2C, CH_2O), 122.4 (2C, C3-Ar), 127.2 (2C, CH-Ar), 129.7 (2C, CH-Ar), 129.9 (2C, CH-Ar), 131.6 (2C, CH-Ar), 142.3 (2C, C1-Ar).

*7,16-Bis(3-bromobenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**4**)*. Obtained from diazacrown ether **2** (1.5 mmol, 393 mg). Yield 816 mg (91 %), yellowish crystalline powder, m.p. 79-81 °C. (MALDI-TOF) found: 599.1087. $C_{26}H_{37}Br_2N_2O_4$ requires 599.1120 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.79 (8H, t, ^3J = 4.8 Hz, CH_2N), 3.58-3.66 (20H, m, CH_2O, $ArCH_2N$), 7.13 (2H, t, ^3J = 7.6 Hz, H5-Ar), 7.24 (2H, d, ^3J = 7.2 Hz, H4-Ar or H6-Ar), 7.33 (2H, d, ^3J = 8.0 Hz, H6-Ar or H4-Ar), 7.50 (2H, br.s, H2-Ar). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 53.8 (4C, CH_2N), 59.3 (2C, $ArCH_2N$), 69.9 (4C, CH_2O), 70.6 (4C, CH_2O), 122.3 (2C, C3-Ar), 127.2 (2C, CH-Ar), 129.7 (2C, CH-Ar), 129.9 (2C, CH-Ar), 131.5 (2C, CH-Ar), 142.4 (2C, C1-Ar).

*7,13-Bis(4-bromobenzyl)-1,4,10-trioxa-7,13-diazacyclopentadecane (**5**)*. Obtained from diazacrown ether **1** (2.3 mmol, 0.5 g). Yield 1.211 g (95 %), yellowish glassy compound. (MALDI-TOF) found: 555.0873. $C_{24}H_{33}Br_2N_2O_3$ requires 555.0858 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.72 (4H, t, ^3J = 5.1 Hz, CH_2N), 2.77 (4H, t, ^3J = 5.9, CH_2N), 3.55-3.62 (16H, m, CH_2O, $ArCH_2N$), 7.22 (4H, d, ^3J = 8.2 Hz, H2-Ar, H2'-Ar), 7.39 (4H, d, ^3J = 8.2 Hz, H3-Ar, H3'-Ar). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 54.2 (2C, CH_2N), 54.3 (2C, CH_2N), 59.9 (2C, $ArCH_2N$), 69.4 (2C, CH_2O), 70.3 (2C, CH_2O), 70.6 (2C, CH_2O), 120.5 (2C, C4-Ar), 130.4 (4C, C2-Ar, C2'-Ar), 131.2 (4C, C3-Ar, C3'-Ar), 138.8 (2C, C1-Ar).

*7,16-Bis(4-bromobenzyl)-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**6**)*. Obtained from diazacrown ether **2** (2 mmol, 0.5 g). Yield 568 mg (95 %), yellowish crystalline powder, m.p. 96-98 °C. (MALDI-TOF) found: 599.1161. $C_{26}H_{37}Br_2N_2O_4$ requires 599.1120 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.77 (8H, br.s, CH_2N), 3.55-3.62 (20H, m, CH_2O, $ArCH_2N$), 7.20 (4H, d, ^3J = 8.0 Hz, H2-Ar, H2'-Ar), 7.39 (4H, d, ^3J = 8 Hz, H3-Ar, H3'-Ar). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 53.7 (4C, CH_2N), 59.2 (2C, $ArCH_2N$), 69.9 (4C, CH_2O), 70.6 (4C, CH_2O), 120.5 (2C, C4-Ar), 130.4 (4C, CH-Ar), 131.2 (4C, CH-Ar), 138.7 (2C, C1-Ar).

Typical procedure for the synthesis of macropolycycles ***8-16***.

A two-neck flask (25 ml) equipped with a condenser and magnetic stirrer, flushed with argon, was charged with corresponding derivative of diazacrown ether 3-6 (0.25 mmol), $Pd(dba)_2$ (12-24

mg, 8-16 mol%), diphosphine ligand BINAP or DavePhos (9-18 mol%), and absolute dioxane (12 ml). The mixture was stirred for several min, then appropriate diamine **7a**,**b** (0.25 mmol) and ^{t}BuONa (72 mg, 0.75 mmol) were added, and the reaction mixture was refluxed for 24-30 h. After the reaction was complete, the mixture was cooled, filtered, the residue was washed with CH_2Cl_2, the combined organic solvents were evaporated *in vacuo*, the residue was dissolved in CH_2Cl_2 (5 ml), washed with water (3×10 ml), aqueous phase was washed with CH_2Cl_2 (3×15 ml). Combined organic phases were dried over molecular sieves 4 Å, the solvent evaporated *in vacuo*, and the residue 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.

*28,31,36-Trioxa-1,8,18,25-tetraazaheptacyclo[23.8.5.1^{3,7}.1^{10,14}.1^{10,16}.1^{12,16}.1^{19,23}]-tritetraconta-3(43),4,6,19(39),20,22-hexaene (**8a**)*. Obtained from compound **3** (139 mg, 0.25 mmol), diamine **7a** (49 mg, 0.25 mmol) in the presence of Pd(dba)$_2$ (23 mg, 16 mol%) and DavePhos (18 mg, 18 mol%). Eluent CH_2Cl_2-MeOH 10:1 – 5:1. Yield 50 mg (34 %), yellow glassy compound. (MALDI-TOF) found: 589.4072. $C_{36}H_{53}N_4O_3$ requires 589.4117 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.38-1.57 (8H, m, H-Ad), 1.62-1.68 (4H, m, H-Ad), 2.08 (2H, br.s, H2-Ad), 2.78 (4H, s, CH_2NH), 2.84 (8H, br.s, CH_2N), 3.55-3.65 (12H, m, CH_2O, $ArCH_2N$), 3.65 (4H, t, ^3J = 5.5 Hz, CH_2O), 6.41 (2H, d, ^3J = 7.6 Hz, H4-Ar or H6-Ar), 6.43 (2H, d, ^3J = 7.1 Hz, H6-Ar or H4-Ar), 6.97 (2H, br.s, H2-Ar), 7.01 (2H, t, ^3J = 7.5 Hz, H5-Ar), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 28.5 (2C, CH-Ad), 35.4 (2C, C-Ad), 36.8 (1C, CH_2-Ad), 40.4 (4C, CH_2-Ad), 42.3 (1C, CH_2-Ad), 53.3 (2C, CH_2NAr), 55.2 (2C, CH_2N), 55.5 (2C, CH_2N), 60.1 (2C, $ArCH_2N$), 68.8 (2C, CH_2O), 69.2 (2C, CH_2O), 69.9 (2C, CH_2O), 110.9 (2C, CH-Ar), 112.7 (2C, CH-Ar), 116.6 (2C, CH-Ar), 128.7 (2C, C5-Ar), 140.5 (2C, C1-Ar), 149.5 (2C, C3-Ar).

*28,31,61,64,69,79-Hexaoxa-1,8,18,25,34,41,51,58-octaazatridecacyclo-[56.8.5.5^{25,34}.1^{3,7}.1^{10,14}.1^{10,16}.1^{12,16}.1^{19,23}.1^{36,40}.1^{43,47}.1^{43,49}.1^{45,49}.1^{52,56}]hexaoctaconta-3(86),4,6,19(82),20,22,36(76),37,39,52(72),53,55-dodecaene (**9a**)*. Obtained as the second product in the synthesis of 8a. Eluent CH_2Cl_2-MeOH-NH_3(aq) 100:20:1. Yield 24 mg (16 %), yellow glassy compound. (MALDI-TOF) found: 1177.8243. $C_{72}H_{105}N_8O_6$ requires 1177.8157 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.34-1.68 (24H, m, H-Ad), 2.09 (4H, br.s, H2-Ad), 2.71-2.85 (24H, m, CH_2N), 3.50-3.70 (32H, m, CH_2O, $ArCH_2N$), 6.46 (4H, d, ^3J = 8.0 Hz, H4-Ar or H6-Ar), 6.59 (4H, br.d, $^3J_{obs}$ = 6.4 Hz, H6-Ar or H4-Ar), 6.69 (4H, br.s, H2-Ar), 7.04 (4H, t, ^3J = 7.6 Hz, H5-Ar), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 28.4 (4C, CH-Ad), 34.5 (4C, C-Ad), 36.4 (2C, CH_2-Ad), 40.2 (8C, CH_2-Ad), 43.7 (2C, CH_2-Ad), 54.1 (8C, CH_2N), 56.0 (4C, CH_2NAr), 60.6 (4C, $ArCH_2N$), 69.5 (4C, CH_2O), 70.3 (4C, CH_2O), 70.4 (4C, CH_2O), 110.6 (4C, CH-Ar), 113.4 (4C, CH-Ar), 117.3 (4C, CH-Ar), 128.8 (4C, C5-Ar), 140.6 (4C, C1-Ar), 149.1 (4C, C3-Ar).

*30,33,38-Trioxa-1,8,20,27-tetraazaheptacyclo[25.8.5.1^{3,7}.1^{11,15}.1^{11,17}.1^{13,17}.1^{21,25}]-pentatetraconta-3(45),4,6,21(41),22,24-hexaene (**8b**)*. Obtained from compound **3** (139 mg, 0.25 mmol), diamine **7b** (56 mg, 0.25 mmol) in the presence of Pd(dba)$_2$ (12 mg, 8 mol%) and BINAP (14 mg, 9 mol%). Eluent CH_2Cl_2-MeOH 5:1 – 3:1. Yield 74 mg (48 %), yellow glassy compound. (MALDI-TOF) found: 617.4483. $C_{38}H_{57}N_4O_3$ requires 617.4430 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.35 (2H, br.s, H-Ad), 1.40-1.44 (4H, m, $AdCH_2$), 1.54 (8H, br.s, H-Ad), 1.64 (2H, br.s, H-Ad), 2.07 (2H, br.s, H2-Ad), 2.76 (4H, t, ^3J = 5.2 Hz, CH_2N), 2.82 (4H, t, ^3J = 5.2 Hz, CH_2N), 3.13-3.17 (4H, m, CH_2NAr), 3.53 (4H, t, ^3J = 5.5 Hz, CH_2O), 3.57 (4H, s, CH_2O or $ArCH_2N$), 3.64 (4H, t, ^3J = 5.2 Hz, CH_2O), 3.65 (4H, s, CH_2NAr or CH_2O), 6.43 (2H, d, ^3J = 7.6 Hz, H4-Ar or H6-Ar), 6.48 (2H, d, ^3J = 7.1 Hz, H6-Ar or H4-Ar), 6.82 (2H, br.s, H2-Ar), 7.00 (2H, t, ^3J = 7.6 Hz, H5-Ar), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 29.0 (2C, CH-Ad), 32.8 (2C, C-Ad), 36.6 (1C, CH_2-Ad), 38.5 (2C, $AdCH_2$), 42.0 (4C, CH_2-Ad), 43.3 (2C, CH_2NAr), 47.7 (1C, CH_2-Ad), 54.1 (2C, CH_2N), 55.4 (2C, CH_2N), 61.1 (2C, $ArCH_2N$), 70.4 (2C, CH_2O), 70.7 (4C, CH_2O), 111.3 (2C, C6-Ar), 113.3 (2C, C4-Ar), 117.5 (2C, C2-Ar), 128.6 (2C, C5-Ar), 141.2 (2C, C1-Ar), 148.5 (2C, C3-Ar).

*28,31,36,39-Tetraoxa-1,8,18,25-tetraazaheptacyclo[23.8.8.1^{3,7}.1^{10,14}.1^{12,16}.1^{19,23}]hexatetraconta-3(46),4,6,19(22),20,22-hexaene (**10a**)*. Obtained from compound **4** (150 mg, 0.25 mmol), diamine **7a** (49 mg, 0.25 mmol) in the presence of Pd(dba)$_2$ (23 mg, 16 mol%) and DavePhos (18 mg, 18 mol%). Eluent CH_2Cl_2-MeOH 10:1 – CH_2Cl_2-MeOH-NH_3(aq) 100:20:2. Yield 46 mg (29 %), yellow glassy compound. (MALDI-TOF) found: 633.4325. $C_{38}H_{57}N_4O_4$ requires 633.4380 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.33-1.67 (12H, m, H-Ad), 2.09 (2H, br.s, H-Ad), 2.76 (8H, br.s, CH_2N), 2.86 (4H, s, CH_2NAr), 3.55-3.68 (20H, m, CH_2O, $ArCH_2N$), 6.43 (4H, d, ^3J = 7.3 Hz, H4-Ar, H6-Ar), 6.92 (2H, br.s, H2-Ar), 7.01 (2H, t, ^3J = 7.6 Hz, H5-Ar), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 28.5 (2C, CH-Ad), 35.4 (2C, C-Ad), 36.7 (1C, CH_2-Ad), 40.3 (4C, CH_2-Ad), 43.2 (1C, CH_2-Ad), 54.6 (4C, CH_2N), 55.9 (2C, CH_2NAr), 60.2 (2C, $ArCH_2N$), 70.1 (4C, CH_2O), 70.7 (4C, CH_2O), 111.2 (2C, CH-Ar), 112.4 (2C, CH-Ar), 116.8 (2C, CH-Ar), 128.7 (2C, C5-Ar), 139.2 (2C, C1-Ar), 149.5 (2C, C3-Ar).

*30,33,38,41-Tetraoxa-1,8,20,27-tetraazaheptacyclo[25.8.8.1^{3,7}.1^{11,15}.1^{11,17}.1^{13,17}.1^{21,25}]-octatetraconta-3(48),4,6,21(44),22,24-hexaene (**10b**)*. Obtained from compound **4** (150 mg, 0.25 mmol), diamine **7b** (56 mg, 0.25 mmol) in the presence of Pd(dba)$_2$ (12 mg, 8 mol%) and BINAP (14 mg, 9 mol%). Eluent CH_2Cl_2-MeOH 5:1 – CH_2Cl_2-MeOH-NH_3(aq) 100:20:1. Yield 89 mg (54 %), yellow glassy compound. (MALDI-TOF) found: 661.4720. $C_{40}H_{61}N_4O_4$ requires 661.4693 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.39 (2H, br.s, H-Ad), 1.40-1.44 (4H, m, $AdCH_2$), 1.51 (8H, br.s, H-Ad), 1.63 (2H, br.s, H-Ad), 2.05 (2H, br.s, H2-Ad), 2.81 (8H, br.s, CH_2N), 3.12-3.16 (4H, m, CH_2NAr), 3.58-3.63 (20H, m, CH_2O, $ArCH_2N$), 6.44 (2H, dd, ^3J = 8.0 Hz, ^4J = 1.8 Hz, H6-Ar), 6.54 (2H, br.d, $^3J_{obs}$ = 6.7 Hz, H4-Ar), 6.75 (2H, br.s, H2-Ar), 7.03 (2H, t, ^3J = 7.7 Hz, H5-Ar), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 29.0 (2C, CH-Ad), 32.8 (2C, C-Ad), 36.6 (1C, CH_2-Ad), 38.6 (2C, $AdCH_2$), 42.2 (4C, CH_2-Ad), 43.6 (2C, CH_2NAr), 47.0 (1C, CH_2-Ad), 54.2 (4C, CH_2N), 60.3 (2C, $ArCH_2N$), 70.0 (4C, CH_2O), 70.7 (4C, CH_2O), 112.0 (2C, C4-Ar or C6-Ar), 112,6 (2C, C6-Ar or C4-Ar), 117.5 (2C, C2-Ar), 128.7 (2C, C5-Ar), 141.0 (2C, C1-Ar), 148.5 (2C, C3-Ar).

*26,29,34-Trioxa-1,8,16,23-tetraazaheptacyclo[23.8.5.1^{3,7}.1^{9,13}.1^{9,15}.1^{11,15}.1^{17,21}]hentetraconta-3(41),4,6,17(37),18,20-hexaene (**11a**)*. Obtained from compound **5** (139 mg, 0.25 mmol), diamine **7a** (49 mg, 0.25 mmol) in the presence of Pd(dba)$_2$ (23 mg, 16 mol%) and DavePhos (18 mg, 18 mol%). Eluent CH_2Cl_2-MeOH-NH_3(aq) 100:20:3. Yield 18 mg (12 %), yellow glassy compound. (MALDI-TOF) found: 589.4135. $C_{36}H_{53}N_4O_3$ requires 589.4117 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.39-1.66 (12H, m, H-Ad), 2.10 (2H, br.s, H2-Ad), 2.70-2.82 (8H, m, CH_2N), 2.84 (4H, s, CH_2NAr), 3.50 (4H, s, CH_2O or $ArCH_2N$), 3.55-3.63 (8H, m, CH_2O or CH_2O, $ArCH_2N$), 3.69 (4H, t, ^3J = 5.1 Hz, CH_2O), 6.48 (4H, d, ^3J = 8.5 Hz, H3-Ar, H3'-Ar), 7.14 (4H, d, ^3J = 8.5 Hz, H2-Ar, H2'-Ar), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 28.5 (2C, CH-Ad), 35.8 (2C, C-Ad), 37.2 (1C, CH_2-Ad), 39.9 (4C, CH_2-Ad), 44.3 (1C, CH_2-Ad), 54.5 (2C, CH_2N), 55.6 (2C, CH_2N), 56.4 (2C, CH_2NAr), 60.1 (2C, $ArCH_2N$), 69.6 (2C, CH_2O), 70.2 (2C, CH_2O), 70.7 (2C, CH_2O), 112.1 (4C, C3-Ar, C3'-Ar), 128.8 (2C, C1-Ar), 130.1 (4C, C2-Ar, C2'-Ar), 148.6 (2C, C4-Ar).

*28,31,61,64,69,79-Hexaoxa-1,8,18,25,34,41,51,58-octatridecacyclo [56.8.5.5^{25,34}.1^{3,7}.1^{10,14}.1^{10,16}.1^{12,16}.1^{19,23}.1^{36,40}.1^{43,47}.1^{43,49}.1^{45,49}.1^{52,56}]hexaconta-3(86),4,6,19(82),20,22,36(76),37,39,52(72),53,55-dodecaene (**12a**)*. Obtained as the second product in the synthesis of compound **11a**. Eluent CH_2Cl_2-MeOH-NH_3(aq) 100:20:3. Yield 18 mg (12 %). Additionally a mixture of **12a** with a cyclic trimer **13a** was obtained. Eluent CH_2Cl_2-MeOH-NH_3(aq) 100:20:3. Yield 15 mg (10 %). Cyclodimer **12a**: (MALDI-TOF) found: 1177.8090. $C_{72}H_{105}N_8O_6$ requires 1177.8157 $[M+H]^+$. ^{1}H

NMR ($CDCl_3$, 298 K) δ_H ppm: 1.39-1.66 (24H, m, H-Ad), 2.10 (4H, br.s, H2-Ad), 2.70-2.83 (24H, m, CH_2N, CH_2NAr), 3.54 (8H, s, CH_2O or $ArCH_2N$), 3.55-3.63 (24H, m, CH_2O, $ArCH_2N$), 6.54 (8H, d, ^3J = 8.3 Hz, H3-Ar, H3'-Ar), 7.09 (8H, d, ^3J = 8.3 Hz, H2-Ar, H2'-Ar), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 28.5 (4C, CH-Ad), 34.5 (4C, C-Ad), 36.6 (2C, CH_2-Ad), 40.2 (8C, CH_2-Ad), 43.0 (2C, CH_2-Ad), 53.8 (4C, CH_2N), 54.1 (4C, CH_2N), 60.1 (4C, $ArCH_2N$), 69.4 (4C, CH_2O), 70.5 (4C, CH_2O), 70.6 (4C, CH_2O), 112.3 (8C, C3-Ar, C3'-Ar), 128.1 (4C, C1-Ar), 130.1 (8C, C2-Ar, C2'-Ar), 148.1 (4C, C4-Ar). Cyclotrimer **13a**: (MALDI-TOF) found: 1766.25. $C_{108}H_{157}N_{12}O_9$ requires 1766.2196 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.39-1.63 (36H, m, H-Ad), 2.10 (6H, br.s, H2-Ad), 2.72 (12H, d, ^3J = 4.6 Hz, CH_2N), 2.78 (12H, br.s, CH_2N), 2.81 (8H, s, CH_2NAr), 3.51-3.62 (48H, m, CH_2O, $ArCH_2N$), 6.54 (12H, d, ^3J = 8.0 Hz, H3-Ar, H3'-Ar), 7.08 (12H, d, ^3J = 8.0 Hz, H2-Ar, H2'-Ar), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 28.5 (6C, CH-Ad), 34.5 (6C, C-Ad), 36.6 (3C, CH_2-Ad), 40.2 (12C, CH_2-Ad), 43.0 (3C, CH_2-Ad), 53.7 (12C, CH_2N), 56.2 (6C, CH_2NAr), 60.0 (6C, $ArCH_2N$), 69.4 (6C, CH_2O), 70.5 (6C, CH_2O), 70.6 (6C, CH_2O), 112.4 (12C, C3-Ar, C3'-Ar), 128.1 (6C, C1-Ar), 130.0 (12C, C2-Ar, C2'-Ar), 148.1 (6C, C4-Ar).

*30,33,38-Trioxa-1,8,20,27-tetraazaheptacyclo[25.8.5.1^{3,7}.1^{11,15}.1^{11,17}.1^{21,25}]pentatetraconta-3(45),4,6,21(41),22,24-hexaene **(11b)***. Obtained from compound **5** (139 mg, 0.25 mmol), diamine **7b** (56 mg, 0.25 mmol) in the presence of $Pd(dba)_2$ (12 mg, 8 mol%) and BINAP (14 mg, 9 mol%). Eluent CH_2Cl_2-MeOH 5:1 – CH_2Cl_2-MeOH-NH_3(aq) 100:20:1. Yield 54 mg (35 %), yellow glassy compound. (MALDI-TOF) found: 617.4467. $C_{38}H_{57}N_4O_3$ requires 617.4430 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.35-1.41 (4H, m, H-Ad), 1.43 (4H, t, ^3J = 7.3 Hz, $AdCH_2$), 1.50-1.59 (6H, m, H-Ad), 1.62-1.68 (2H, m, H-Ad), 2.03 (2H, br.s, H2-Ad), 2.64 (4H, t, ^3J = 5.1 Hz, CH_2N), 2.71 (4H, t, ^3J = 5.6 Hz, CH_2N), 3.16 (4H, t, ^3J = 7.3 Hz, CH_2NAr), 3.51 (4H, s, CH_2O or $ArCH_2N$), 3.58 (4H, t, ^3J = 5.1 Hz, CH_2O), 3.61 (4H, s, $ArCH_2N$ or CH_2O), 3.71 (4H, t, ^3J = 5.6 Hz, CH_2O), 6.54 (4H, d, ^3J = 8.3 Hz, H3-Ar, H3'-Ar), 7.23 (4H, d, ^3J = 8.3 Hz, H2-Ar, H2'-Ar), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 29.0 (2C, CH-Ad), 32.9 (2C, C-Ad), 36.8 (1C, CH_2-Ad), 39.8 (2C, $AdCH_2$), 42.6 (4C, CH_2-Ad), 43.0 (2C, CH_2NAr), 45.1 (1C, CH_2Ad), 55.0 (2C, CH_2N), 55.7 (2C, CH_2N), 60.2 (2C, $ArCH_2N$), 69.9 (2C, CH_2O), 70.3 (2C, CH_2O), 70.8 (2C, CH_2O), 112.5 (4C, C3-Ar, C3'-Ar), 128.6 (2C, C1-Ar), 129.7 (4C, C2-Ar, C2'Ar), 147.2 (2C, C4-Ar).

*29,32,64,72,82-Hexaoxa-1,8,19,26,35,42,54,61-octaazatriheptacyclo-[59.8.8.5.5^{25,35}.1^{3,7}.1^{10,14}.1^{10,16}1^{12,16}.1^{20,24}.1^{37,41}.1^{45,49}.1^{45,51}.1^{47,51}.1^{55,59}.]nonaoctaconta-3(89),4,6,20(85),21,23,37(79),38,40,55(75),56,58-dodecaene **(12b)***. Obtained as the second product in the synthesis of compound **11b**. Eluent CH_2Cl_2-MeOH-NH_3(aq) 100:20:2. Yield 15 mg (10 %), yellow glassy compound. (MALDI-TOF) found: 1233.8832. $C_{76}H_{113}N_8O_6$ requires 1233.8783 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.32-1.67 (32H, m, H-Ad, $AdCH_2$), 2.05 (4H, br.s, H2-Ad), 2.73 (8H, t, ^3J = 4.0 Hz, CH_2N), 2.79 (8H, t, ^3J = 5.8 Hz, CH_2N), 3.09 (8H, t, ^3J = 7.0 Гц, CH_2NAr), 3.51-3.64 (32H, m, CH_2O, $ArCH_2N$), 6.52 (8H, d, ^3J = 8.3 Hz, H3-Ar, H3'-Ar), 7.10 (8H, d, ^3J = 8.3 Hz, H2, H2'-Ar), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 29.0 (4C, CH-Ad), 32.7 (4C, C-Ad), 36.5 (2C, CH_2-Ad), 38.8 (4C, $AdCH_2$), 42.0 (8C, CH_2-Ad), 43.8 (4C, CH_2NAr), 47.9 (2C, CH_2-Ad), 53.8 (4C, CH_2N), 53.9 (4C, CH_2N), 60.1 (4C, $ArCH_2N$), 69.5 (4C, CH_2O), 70.6 (8C, CH_2O), 112.5 (8C, C3-Ar, C3'-Ar), 127.8 (4C, C1-Ar), 130.0 (8C, C2-Ar, C2'-Ar), 147.5 (4C, C4-Ar).

*Cyclotrimer **13b***. Obtained as the third product in the synthesis of compound **11b**. Eluent CH_2Cl_2-MeOH-NH_3(aq) 100:20:2. Yield 15 mg (10 %), yellow glassy compound. (MALDI-TOF) found: 1850.26. $C_{114}H_{169}N_{12}O_9$ requires 1850.3135 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.32 (6H, br.s, H-Ad), 1.39-1.43 (12H, m, $AdCH_2$), 1.43-1.67 (30H, m, H-Ad), 2.04 (6H, br.s, H2-Ad), 2.73 (12H, t, ^3J = 4.9 Hz, CH_2N), 2.78 (12H, t, ^3J = 5.6 Hz, CH_2N), 3.07-3.10 (12H, m, CH_2NAr), 3.52-3.64 (48H, m, CH_2O, $ArCH_2N$), 6.52 (12H, d, ^3J = 8.1 Hz, H3-Ar, H3'-Ar), 7.10 (12H, d, ^3J = 8.1 Hz, H2-Ar, H2'-Ar), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 29.0 (6C, CH-Ad), 32.7 (6C, C-Ad), 36.5 (3C, CH_2-Ad), 38.8 (6C, $AdCH_2$), 42.0 (12C, CH_2-Ad), 43.8 (6C, CH_2NAr), 47,9 (3C, CH_2-Ad), 53.7 (12C, CH_2N), 60.1 (6C, $ArCH_2N$), 69.5 (6C, CH_2O), 70.5 (6C, CH_2O), 70.6 (6C, CH_2O), 112.5 (12C, C3-Ar, C3'-Ar), 127.8 (6C, C1-Ar), 130.1 (12C, C2-Ar, C2'-Ar), 147.5 (6C, C4-Ar).

*28,31,36,39-Tetraoxa-1,8,18,25-tetraazaheptacyclo[23.8.8.1^{3,7}.1^{10,14}.1^{10,16}.1^{12,16}.1^{19,23}-hexatetraconta-3(46),4,6,19(42),20,22-hexaene **(14a)***. Obtained from compound **6** (150 mg, 0.25 mmol), diamine **7a** (49 mg, 0.25 mmol) in the presence of $Pd(dba)_2$ (23 mg, 16 mol%) and DavePhos (18 mg, 18 mol%). Eluent CH_2Cl_2-MeOH-NH_3(aq) 100:20:3. Yield 22 mg (14 %), yellow glassy compound. (MALDI-TOF) found: 633.4410. $C_{38}H_{57}N_4O_4$ requires 633.4380 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.34 (4H, d, ^3J = 10.9 Hz, H-Ad), 1.41 (2H, s, H-Ad), 1.57 (4H, d, ^3J = 11.7 Hz, H-Ad), 1.66 (2H, br.s, H-Ad), 2.09 (2H, br.s, H-Ad), 2.75 (8H, t, ^3J = 5.4 Hz, CH_2N), 2.82 (4H, s, CH_2NAr), 3.60 (12H, s, CH_2O, $ArCH_2N$), 3.62 (8H, t, ^3J = 5.6 Hz, CH_2O), 6.48 (4H, d, ^3J = 8.5 Hz, H3-Ar, H3'-Ar), 7.10 (4H, d, ^3J = 8.5 Hz, H2-Ar, H2'-Ar), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 28.5 (2C, CH-Ad), 35.7 (2C, C-Ad), 37.1 (1C, CH_2-Ad), 40.1 (4C, CH_2-Ad), 44.0 (1C, CH_2-Ad), 54.3 (4C, CH_2N), 56.3 (2C, CH_2NAr), 59.3 (2C, $ArCH_2N$), 70.1 (4C, CH_2O), 70.9 (4C, CH_2O), 112.6 (4C, C3-Ar, C3'-Ar), 128.2 (2C, C1-Ar), 129.8 (4C, C2-Ar, C2'-Ar), 148.5 (2C, C4-Ar).

*Cyclodimer **15a***. Obtained as the second product in the synthesis of compound **14a**. Eluent CH_2Cl_2-MeOH-NH_3(aq) 100:20:3. Yield 30 mg (19 %). Additionally a mixture of **15a** with a cyclic trimer **16a** was obtained. Eluent CH_2Cl_2-MeOH-NH_3(aq) 100:20:3. Yield 40 mg (25 %). Cyclodimer **15a**: (MALDI-TOF) found: 1265.89. $C_{76}H_{113}N_8O_8$ requires 1265.87 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.37-1.64 (24H, m, H-Ad), 2.09 (4H, br.s, H2-Ad), 2.77 (16H, t, ^3J = 5.8 Hz, CH_2N), 2.81 (8H, s, CH_2NAr), 3.54 (8H, s, $ArCH_2N$), 3.57-3.62 (32H, m, CH_2O), 6.54 (8H, d, ^3J = 8.5 Hz, H3-Ar, H3'-Ar), 7.07 (8H, d, ^3J = 8.5 Hz, H2-Ar, H2'-Ar), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 28.5 (4C, CH-Ad), 34.5 (4C, C-Ad), 36.6 (2C, CH_2-Ad), 40.4 (8C, CH_2-Ad), 43.8 (2C, CH_2-Ar), 53.4 (8C, CH_2N), 56.2 (4C, CH_2NAr), 59.4 (4C, $ArCH_2N$), 70.0 (8C, CH_2O), 70.6 (8C, CH_2O), 112.3 (8C, C3-Ar, C3'-Ar), 128.1 (4C, C1-Ar), 130.0 (8C, C2-Ar, C2'-Ar), 148.1 (4C, C2-Ar, C2'-Ar). Cyclotrimer **16a**: (MALDI-TOF) found: 1898.23. $C_{114}H_{169}N_{12}O_{12}$ requires 1898.30 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.39-1.64 (36H, m, H-Ad), 2.10 (6H, br.s, H2-Ad), 2.77 (24H, t, ^3J = 5.6 Hz, CH_2N), 2.81 (12H, s, CH_2NAr), 3.54 (12H, s, $ArCH_2N$), 3.56-3.62 (48H, m, CH_2O), 6.54 (12H, d, ^3J = 8.3 Hz, H3-Ar, H3'-Ar), 7.07 (12H, d, ^3J = 8.3 Hz, H2-Ar, H2'-Ar), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 28.4 (6C, CH-Ad), 34.5 (6C, C-Ad), 36.6 (3C, CH_2-Ad), 40.2 (12C, CH_2-Ad), 43.7 (3C, CH_2-Ad), 53.4 (12C, CH_2N), 56.1 (6C, CH_2NAr), 59.3 (6C, $ArCH_2N$), 69.9 (12C, CH_2O), 70.6 (12C, CH_2O), 112.3 (12C, C3-Ar, C3'-Ar), 128.1 (6C, C1-Ar), 130.0 (12C, C2-Ar, C2'-Ar), 148.1 (6C, C4-Ar).

*30,33,38,41-Tetraoxa-1,8,20,27-tetraazaheptacyclo[25.8.8.1^{3,7}.1^{11,15}.1^{11,17}.1^{13,17}.1^{21,25}]octatetraconta-3(48),4,6,21(44),22,24-hexaene **(14b)***. Obtained from compound 6 (150 mg, 0.25 mmol), diamine 7b (56 mg, 0.25 mmol) in the presence of $Pd(dba)_2$ (12 mg, 8 mol%) and BINAP (14 mg, 9 mol%). Eluent CH_2Cl_2- CH_2Cl_2-MeOH-NH_3(aq) 100:20:3. Yield 26 mg (16 %), yellow glassy compound. (MALDI-TOF) found: 661.4671. $C_{40}H_{61}N_4O_4$ requires 661.4693 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.36-1.40 (4H, m, H-Ad), 1.42 (4H, t, ^3J = 7.2 Hz, $AdCH_2$), 1.49-1.55 (6H, m, H-Ad), 1.63 (2H, br.s, H-Ad), 2.03 (2H, br.s, H-Ad), 2.71 (8H, t, ^3J = 4.9 Hz, CH_2N), 3.14 (4H, t, ^3J = 7.2 Hz, CH_2NAr), 3.56 (4H, s, $ArCH_2N$), 3.61 (8H, t, ^3J = 5.4 Hz, CH_2O), 3.63 (8H, s, CH_2O), 6.53 (4H, d, ^3J = 8.1 Hz, H3-Ar, H3'-Ar), 7.17 (4H, d, ^3J = 8.1 Hz,

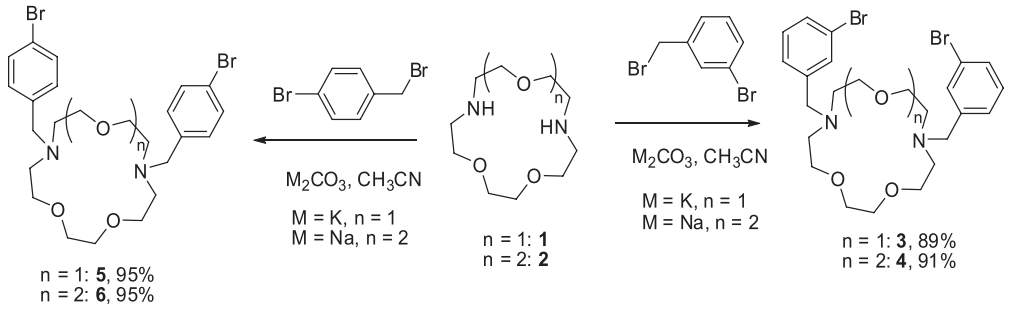
H2-Ar, H2'-Ar), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 29.0 (2C, CH-Ad), 32.8 (2C, C-Ad), 36.7 (1C, CH_2-Ad), 39.0 (2C, $AdCH_2$), 42.6 (4C, CH_2-Ad), 43.1 (2C, CH_2NAr), 45.2 (1C, CH_2-Ad), 54.5 (4C, CH_2N), 59.6 (2C, $ArCH_2N$), 69.9 (4C, CH_2O), 70.8 (4C, CH_2O), 112.6 (4C, C3-Ar, C3'-Ar), 128.0 (2C, C1-Ar), 129.8 (4C, C2-Ar, C2'-Ar), 147.4 (2C, C4-Ar).

Cyclodimer ***15b***. Obtained as the second product in the synthesis of compound **14b**. Eluent CH_2Cl_2-MeOH-NH_3(aq) 100:25:5. Yield 26 mg (16 %). Additionally a mixture of **15b** with a cyclic trimer **16b** was obtained. Eluent CH_2Cl_2-MeOH-NH_3(aq) 100:25:5. Yield 37 mg (22 %). Cyclodimer **15b**: (MALDI-TOF) found: 1321.91. $C_{80}H_{121}N_8O_8$ requires 1321.93 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.32 (4H, br.s, H-Ar), 1.39-1.43 (8H, m, $AdCH_2$), 1.43-1.63 (20H, m, H-Ad), 2.03 (4H, br.s, H2-Ad), 2.78 (16H, t ^3J = 5.6 Hz, CH_2N), 3.07-3.10 (8H, m, CH_2NAr), 3.55 (8H, s, $ArCH_2N$), 3.57-3.63 (32H, m, CH_2O), 6.52 (8H, d, ^3J = 8.1 Hz, H3-Ar, H3'-Ar), 7.09 (8H, d, ^3J = 8.1 Hz, H2-Ar, H2'-Ar), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 28.9 (4C, CH-Ad), 32.7 (4C, C-Ad), 36.4 (2C, CH_2-Ad), 38.8 (4C, $AdCH_2$), 42.0 (8C, CH_2-Ad), 43.8 (4C, CH_2NAr), 47.9 (2C, CH_2-Ad), 53.4 (8C, CH_2N), 59.4 (4C, $ArCH_2N$), 70.0 (8C, CH_2O), 70.7 (8C, CH_2O), 112.5 (8C, C3-Ar, C3'-Ar), 128.0 (4C, C1-Ar), 130.0 (8C, C2-Ar, C2'-Ar), 147.5 (4C, C4-Ar). Cyclotrimer **16b**. (MALDI-TOF) found: 1982.34. $C_{120}H_{181}N_{12}O_{12}$ requires 1982.39 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.31 (6H, br.s, H-Ar), 1.39-1.42 (12H, m, $AdCH_2$), 1.43-1.61 (30H, m, H-Ad), 2.04 (6H, br.s, H2-Ad), 2.78 (24H, t, ^3J = 5.4 Hz, CH_2N), 3.06-3.10 (12H, m, CH_2NAr), 3.55 (12H, s, $ArCH_2N$), 3.57-3.63 (48H, m, CH_2O), 6.52 (12H, d, ^3J = 8.3 Hz, H3-Ar, H3'-Ar), 7.09 (12H, d, ^3J = 8.3 Hz, H2-Ar, H2'-Ar), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 28.9 (6C, CH-Ad), 32.7 (6C, C-Ad), 36.4 (3C, CH_2-Ad), 38.7 (6C, $AdCH_2$), 41.9 (12C, CH_2-Ad), 43.7 (6C, CH_2NAr), 47.9 (3C, CH_2-Ad), 53.4 (12C, CH_2N), 59.4 (6C, $ArCH_2N$), 69.9 (12C, CH_2O), 70.6 (12C, CH_2O), 112.4 (12C, C3-Ar, C3'-Ar), 127.6 (6C, C1-Ar), 130.0 (12C, C2-Ar, C2'-Ar), 147.5 (6C, C4-Ar).

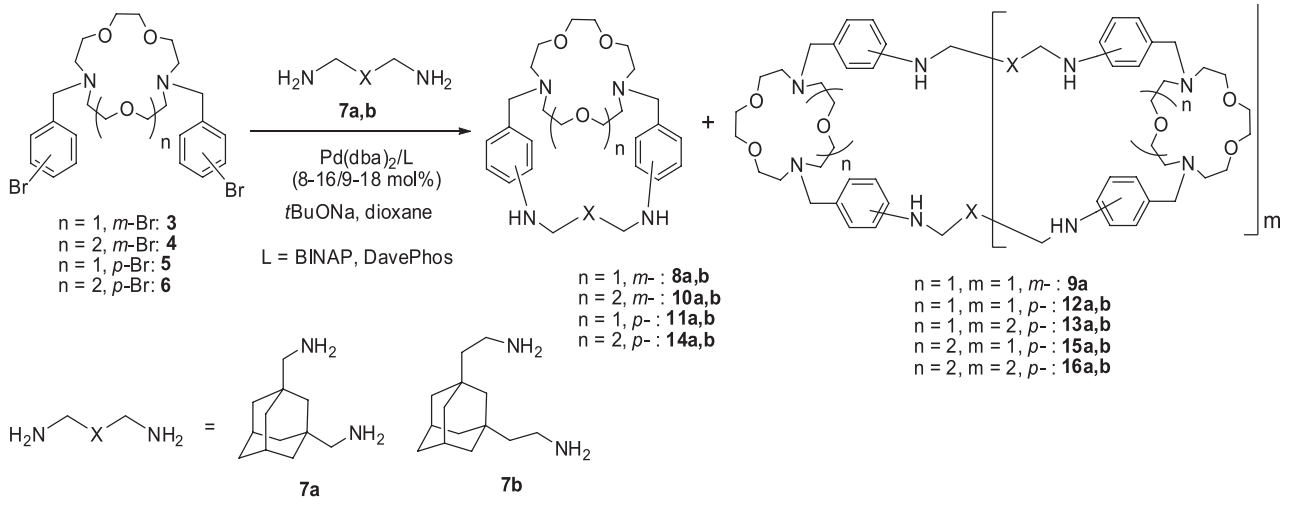
Results and Discussion

To synthesize macrobicyclic compounds comprising diazacrown units, first we synthesized *N,N'*-bis(bromobenzyl) derivatives of diazacrwon ethers **3-6** (Scheme 1). The reactions were carried out using exactly two equivalents of bromobenzyl bromides, in boiling acetonitrile, K_2CO_3 was used as base in the case of a smaller macrocycle **1** whereas Na_2CO_3 was employed in the reaction with a larger diazacrown ether **2** in order to minimize the coordination of the cation. However, the work-up of the reaction mixtures included a meticulous washing of the resulting compounds **3-6** with water to avoid coordinated salts. As a result, the target compounds were obtained in high yields 89-95 %.

Diazacrown derivatives **3-6** were introduced in the palladium-catalyzed reactions with adamantane-containing diamines **7a**,**b** (Scheme 2). We employed $Pd(dba)_2$/BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthalene) (8 mol%) catalytic system for the reactions with 1,3-bis(2-aminoethyl)-adamantane **7b**, while the cyclization with 1,3-bis(aminomethyl)adamantane **7a** was catalyzed in the presence of $Pd(dba)_2$/DavePhos (2-dicyclohexylphosphino-2'-dimethylaminobiphenyl) (16 mol%). The choice of the catalytic



Scheme 1.



Scheme 2.

Table 1.

Entry	Diazacrown ether derivative	Diamine	Ligand	$Pd(dba)_2$/L, mol%	Product, yield, %	By-product, yield, %
1	**3**	**7a**	DavePhos	16/18	**8a**, 34	**9a**, 16
2	**3**	**7b**	BINAP	8/9	**8b**, 48	
3	**4**	**7a**	DavePhos	16/18	**10a**, 29	
4	**4**	**7b**	BINAP	8/9	**10b**, 54	
5	**5**	**7a**	DavePhos	16/18	**11a**, 12	**12a**, 12[a)]
6	**5**	**7b**	BINAP	8/9	**11b**, 35	**12b**, 10[b)]
7	**6**	**7a**	DavePhos	16/18	**14a**, 14	**15a**, 19[c)]
8	**6**	**7b**	BINAP	8/9	**14b**, 16	**15b**, 16[d)]
9	**6**	**7b**	BINAP	16/18	**14b**, 15	**15b**, 19

[a)] Additionally a mixture of **12a** and **13a** was isolated (10 %).
[b)] Cyclotrimer **13b** was isolated (10 %).
[c)] Additionally a mixture of **15a** and **16a** was isolated (25 %).
[d)] Additionally a mixture of **15b** and **16b** was isolated (22 %).

system was based on our previous research of the Pd-catalyzed arylation of these diamines with dihalobenzenes. [32] The results of the cyclization reactions are presented in Table 1.

The yields of the target macrobicycles were dramatically dependent on the nature of starting diazacrown derivatives and diamines. For the majority of cases, the reactions with the diamine **7b** gave better results than with the diamine **7a**, the best yields being 48 and 54 % (entries 2, 4). Probably it was due to the fact that amino groups in the diamine **7a** are more sterically hindered by a closer adamantane core. Also the diamine **7a** is more rigid compared to the diamine **7b**, thus the geometric demands for a successful cyclization with this diamine are stricter. Derivatives of the 3-bromobenzyl substituted diazacrown ethers **3** and **4** provided higher yields of the macrobicycles **8** and **10** (entries 1-4) if compared with 4-bromobenzyl substituted diazacrowns **5** and **6** (entries 5-8). This fact might be also explained by a better adjustment of two bromine atoms to the nitrogen atoms of diamines in the diazacrown ethers with *meta*-bromobenzyl substituents. On the other hand, we did not observe a pronounced dependence of the reaction result on the size of the diazacrown moiety, thus the different ability of the starting compounds **3-6** to coordinate sodium cation was not important. As the yield of the macrobicycle **14b** was low (16 %, entry 8), we tried the application of the twofold amount of the catalyst (entry 9) but obtained almost the same result. It means that 8 mol% of the $Pd(dba)_2$/BINAP system is quite sufficient for the reaction with the diamine **7b** while **7a** demands greater catalyst loading.

In many cases we obtained not only the target macro-bicyclic compounds but also macrotricyclic cyclodimers and even macrotetracyclic cyclotrimers. These compounds were formed primarily with *para*-bromobenzyl derivatives **5** and **6** and their yields were comparable with those of macrobicycles (entries 5, 7, 8). This fact can be also explained by the higher sterical demands of bis(4-bromobenzyl) substituted diazacrown ethers which hindered the intramolecular di-amination and decreased the yields of macrobicycles **11**, **14** simultaneously boosting the formation of cyclic oligomers.

Conclusions

To sum up, we elaborated a convenient synthesis of the macrobicycles containing diazacrown ether and adamantane moieties using the Pd-catalzyed amination reaction, demonstrated the dependence of the macrobicycles yields on the nature of starting compounds. The reactions with 1,3-bis(2-amonoethyl)adamantane were catalyzed with $Pd(dba)_2$/BINAP whereas 1,3-bis(aminomethyl) adamantane needed the application of $Pd(dba)_2$/DavePhos catalytic system. *N,N'*-bis(3-bromobenzyl) substituted diazacrown ethers were shown to provide better yields of the target macrobicycles (up to 54 %), whereas the reactions with their 4-bromo-benzyl-containing isomers gave reasonable amounts of cyclic oligomers, *i.e.* macrotricycles and macrotetracycles.

Acknowledgements. This work was carried out in the frame of the International Associated French-Russian Laboratory of Macrocycle Systems and Related Materials (LAMREM) of the Centre National de la Recherche Scientifique (CNRS). It was financially supported by CNRS, RFBR grants 12-03-93107, 10-03-01108, 12-03-00796, and by the Russian Academy of Sciences program P-8 "Development of the methods for the synthesis of new chemicals and creation of new materials".

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Received 13.12.2012
Accepted 10.02.2013