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Synthesis of Trismacrocyclic and Macrotricyclic Compounds Possessing Structural Fragments of Aza– and Diazacrown Ethers, Cyclen and Cyclam *via* Pd–Catalyzed Amination Reactions

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Dedicated to Academician of Russian Academy of Sciences Oleg N. Chupakhin on the occasion of his 80th Anniversary

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Synthesis of trismacrocyclic compounds with a central tetraazamacrocyclic moiety and two aza-crown ether fragments was carried out using the Pd-catalyzed amination of trans-bis(bromobenzyl) substituted cyclen and cyclam with 3 equiv. of azacrown ethers. The yields were shown to be dependent on the nature of the starting tetraazamacrocycles and reached 45 % in the best case. Formation of the cylindrically-shaped cryptands was achieved by reacting equimolar amounts of trans-bis(bromobenzyl) substituted cyclen or cyclam and diazacrown ethers. The yields of the target cryptands reached 30 % and a clear dependence of the result of the reaction on the reciprocal position of two bromine atoms and two nitrogen atoms in the reactants was observed.

Keywords: Macrocycles, amination, Pd catalysis.

Синтез трисмакроциклических и макротрициклических соединений, содержащих фрагменты аза– и диазакраун–эфиров, циклена и циклама, с помощью реакций Pd–катализируемого аминирования

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Синтез трисмакроциклических соединений с центральным тетраазамакроциклическим и двумя фрагментами азакраун-эфиров осуществлен с помощью Pd-катализируемого аминирования транс-бис(бромбензил)замещенных циклена и циклама 3 экв. азакраун-эфиров. Показано, что выходы продуктов зависят от природы исходных соединений и в лучшем случае достигают 45 %. Образование криптандов цилиндрической формы происходит при реакции эквимольных количеств транс-бис(бромбензил)замещенных циклена и циклама и диазакраун-эфиров. Выходы целевых криптандов достигают 30 %, при этом наблюдается четкая зависимость выходов целевых соединений от взаимного расположения атомов брома и аминогрупп в исходных соединениях.

Ключевые слова: Макроциклы, аминирование, Pd катализ.

Introduction

Macropolycycles of cylindrical topology based on tetraazamacrocycles are valuable compounds for supramolecular chemistry due to their ability to form binuclear complexes with metal cations. The fixed distance between the two cations induces cations interactions leading to unique electronic properties.[1,2] Two of us previously described several convenient methods for the synthesis of macrotricycles possessing two cyclen (1,4,7,10-tetraazacyclododecane) or cyclam (1,4,8,11-tetraazacyclotetradecane) moieties linked *via* two xylylene bridges. These 3-step approaches utilize either N^1,N^8-ditosyl-N^4-Boc-cyclam[3] or *N*-Boc-substituted dioxocyclen and dioxocyclam.[4] So-called bisaminal strategy exploits protected glyoxal-cyclen and glyoxal-cyclam and the synthetic scheme also comprises three steps with a reduction reaction at the last step,[5] this method was used for the synthesis of macrotricycles with two cross-bridged cyclen fragments.[6] On the basis of these cryptands, mono- and bimetallic homonuclear and heteronuclear complexes were obtained with Cu(II) and Ni(II) cations.[7-10] 1,8-Ditosylcyclam, 1,8-diBoccyclam and 2,9-dioxocyclam were applied for the synthesis of macrotricycles and macrotetracycles comprising cyclam and porphyrin moieties,[11-13] while more sophisticated macropolycles possessing tetraazamacrocycles were obtained using functionalized porphyrins.[14,15] Homo- and heterobinuclear metal complexes with Cu(II), Fe(III) and Co(III) were synthesized on the basis of macrotetracycle and studied as cytochrome oxidase model.[12] All reported approaches to cyclen- and cyclam-containing cryptands utilize only non-catalytic pathways with protected tetraazamacrocycles. During our previous investigations we demonstrated the possibility to synthesize macrobicyclic cryptands on the basis of cyclen and cyclam using Pd(0)-catalyzed amination of their *trans*-bis(bromobenzyl) and *trans*-bis(halopyridinylmethyl) derivatives.[16-19] In this work we decided to elaborate a simple and general one-pot approach to trismacrocyclic compounds using the Pd(0)-mediated reactions of *trans*-bis(bromobenzyl) substituted cyclen and cyclam with azacrown ethers and to macrotricyclic cylindrical cryptands using catalytic amination of the same substrates with diazacrown ethers.

Experimental

NMR spectra were registered using Bruker Avance 400 spectrometer, MALDI-TOF spectra were obtained with Bruker Ultraflex spectrometer using 1,8,9-trihydroxyanthracene as matrix and PEGs as internal standards. 1-Aza-15-crown-5 (**5**), 1-aza-18-crown-6 (**6**), 1,4,10-trioxa-7,13-diazacyclopentadecane (**15**), 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**16**), 2-(dicyclohexylphosphino)-2'-(dimethylamino)-1,1'-biphenyl (DavePhos ligand), sodium *tert*-butoxide were purchased from Aldrich and Acros and used without further purification. 1,7-bis(3-bromobenzyl) cyclen (**1**), 1,7-bis(4-bromobenzyl) cyclen (**2**), 1,8-bis(3-bromobenzyl) cyclam (**3**), 1,8-bis(4-bromobenzyl) cyclam (**4**) were obtained from cyclen or cyclam according to reported procedures,[16,17] Cyclen and cyclam were provided by CheMatech Co. $Pd(dba)_2$ was synthesized according to the method described.[20] Dioxane was distilled over NaOH followed by the distillation over sodium under argon, dichloromethane and methanol were used freshly distilled.

*Typical procedure for the synthesis of trismacrocycles **7-14**.*

A two-neck flask equipped with a condenser and magnetic stirrer, flushed with dry argon, was charged with *trans*-bis(bromobenzyl) derivative of cyclen or cyclam **1-4** (0.2 mmol), $Pd(dba)_2$ (18 mg, 0.032 mmol, 16 mol%) and DavePhos (14 mg, 0.036 mmol, 18 mol%), abs. dioxane (2 mL), the mixture was stirred for 2-3 min, then corresponding azacrown ether **5** or **6** (0.6 mmol) and *t*-BuONa (58 mg, 0.6 mmol) were added, and the reaction mixture was refluxed for 24-30 h. After cooling it down to ambient temperature the reaction mixture was diluted with CH_2Cl_2, the residue was filtered off, washed with dichloromethane, combined organic solvents were evaporated *in vacuo*, the residue was dissolved in CH_2Cl_2 (5 mL), washed with distilled water (3×10 mL), organic layer was dried over molecular sieves 4 Å and evaporated *in vacuo*, 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_3aq (100:20:1-10:4:1).

*13,13'-[1,4,7,10-Tetraazacyclododecane-1,7-diylbis-(methylene-3,1-phenylene)]bis-1,4,7,10-tetraoxa-13-azacyclopentadecane (**7**).* Obtained from compound **1** (102 mg, 0.2 mmol) and azacrown ether **5** (131 mg, 0.6 mmol). Eluent CH_2Cl_2/MeOH 10:1. Yield 48 mg (31 %), yellowish glassy compound. (MALDI-TOF) found: 787.5419. $C_{42}H_{71}N_6O_8$ requires 787.5333 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.65-2.72 (8H, m), 2.73-2.77 (8H, m), 3.50 (8H, t, ^3J = 5.9 Hz), 3.54-3.63 (28H, m), 3.66 (8H, t, ^3J = 5.9 Hz), 6.46 (2H, br.s), 6.48 (2H, d, ^3J = 8.4 Hz), 6.64 (2H, d, ^3J = 7.2 Hz), 7.11 (2H, t, ^3J =7.8 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 47.2 (4C), 51.3 (4C), 52.1 (4C), 61.8 (2C), 68.2 (4C), 69.7 (4C), 69.8 (4C), 70.9 (4C), 111.0 (2C), 111.8 (2C), 115.8 (2C), 129.1 (2C), 139.6 (2C), 147.4 (2C).

*13,13'-[1,4,8,11-Tetraazacyclotetradecane-1,8-diylbis-(methylene-3,1-phenylene)]bis-1,4,7,10-tetraoxa-13-azacyclopentadecane (**8**).* Obtained from compound **3** (108 mg, 0.2 mmol) and azacrown ether **5** (131 mg, 0.6 mmol). Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:3. Yield 34 mg (21 %), yellowish glassy compound. (MALDI-TOF) found: 815.5693. $C_{44}H_{75}N_6O_8$ requires 815.5646 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.80 (4H, br.s), 2.50 (4H, br.s), 2.57 (4H, br.s), 2.67 (4H, br.s), 2.72 (4H, br.s), 3.55 (8H, t, ^3J = 5.5 Hz), 3.58-3.66 (28H, m), 3.71 (8H, t, ^3J = 5.5 Hz), 6.49 (2H, d, ^3J = 8.0 Hz), 6.50 (2H, br.s), 6.63 (2H, d, ^3J =7.1 Hz), 7.10 (2H, t, ^3J = 7.5 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 25.8 (2C, br., $\Delta\nu_{1/2}$ = 10 Hz), 47.7 (2C), 49.4 (2C, br., $\Delta\nu_{1/2}$ = 20 Hz), 50.7 (2C), 52.4 (4C), 53.8 (2C, br., $\Delta\nu_{1/2}$ = 20 Hz), 58.2 (2C), 68.5 (4C), 70.1 (8C), 71.2 (4C), 109.9 (2C), 112.6 (2C), 117.0 (2C), 129.0 (2C), 138.3 (2C), 147.3 (2C).

*16,16'-[1,4,7,10-Tetraazacyclododecane-1,7-diylbis-(methylene-3,1-phenylene)]bis-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (**9**).* Obtained from compound **1** (102 mg, 0.2 mmol) and azacrown ether **6** (158 mg, 0.6 mmol). Eluent CH_2Cl_2/MeOH 10:1. Yield 54 mg (31 %), yellowish glassy compound. (MALDI-TOF) found: 875.5791. $C_{46}H_{79}N_6O_{10}$ requires 875.5858 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.60-2.67 (8H, m), 2.68-2.73 (8H, m), 3.47-3.55 (44H, m), 3.57 (8H, t, ^3J = 6.0 Hz), 6.43-6.50 (4H, m), 6.61 (2H, d, ^3J = 7.0 Hz), 7.07 (2H, t, ^3J = 7.7 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 46.9 (4C), 50.8 (4C), 51.1 (4C), 61.5 (2C), 68.3 (4C), 70.1 (4C), 70.2 (12C, br.), 110.3 (2C), 112.2 (2C), 116.1 (2C), 128.9 (2C), 139.3 (2C), 147.6 (2C).

*16,16'-[1,4,8,11-Tetraazacyclotetradecane-1,8-diylbis-(methylene-3,1-phenylene)]bis-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (**10**).* Obtained from compound **3** (108 mg, 0.2 mmol) and azacrown ether **6** (158 mg, 0.6 mmol). Eluent CH_2Cl_2/MeOH/NH_3aq 100:35:6. Yield 58 mg (32 %), yellowish glassy compound. (MALDI-TOF) found: 903.6026. $C_{48}H_{83}N_6O_{10}$ requires 903.6171 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.81 (4H, br.s), 2.50 (4H, t, ^3J = 4.9 Hz), 2.59 (4H, br.s), 2.67-2.75 (8H, m), 3.54-3.69 (52H, m), 6.49-6.54 (4H, m), 6.62 (2H, d, ^3J = 7.3 Hz), 7.09 (2H, t, ^3J = 8.0 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 25.2 (2C), 47.5 (2C), 48.9 (2C, br., $\Delta\nu_{1/2}$ = 12 Hz), 50.8

(2C), 51.0 (4C), 52.6 (2C, br., $\Delta\nu_{1/2}$ = 15 Hz), 58.8 (2C), 68.7 (4C), 70.5 (4C), 70.6 (8C), 70.7 (4C), 110.3 (2C), 113.0 (2C), 117.0 (2C), 129.1 (2C), 138.4 (2C), 147.8 (2C).

*13,13'-[1,4,7,10-Tetraazacyclododecane-1,7-diylbis-(methylene-4,1-phenylene)]bis-1,4,7,10-tetraoxa-13-azacyclopentadecane (**11**).* Obtained from compound **2** (102 mg, 0.2 mmol) and azacrown ether **5** (131 mg, 0.6 mmol). Eluent CH_2Cl_2/MeOH 10:1. Yield 66 mg (42 %), yellowish glassy compound. (MALDI-TOF) found: 787.5397. $C_{42}H_{71}N_6O_8$ requires 787.5333 $[M+H]^+$. ^1H NMR δ_H ($CDCl_3$, 298 K) 2.71 (8H, br.s), 2.75 (8H, br.s), 3.53-3.68 (36H, m), 3.72 (8H, t, ^3J = 5.1 Hz), 6.61 (4H, d, ^3J = 7.8 Hz), 7.13 (4H, d, ^3J = 7.8 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 47.4 (4C), 51.3 (4C), 52.5 (4C), 60.8 (2C), 68.5 (4C), 69.9 (4C), 70.1 (4C), 71.2 (4C), 111.2 (4C), 125.6 (2C), 130.1 (4C), 147.0 (2C).

*13,13'-[1,4,8,11-Tetraazacyclotetradecane-1,8-diylbis-(methylene-4,1-phenylene)]bis-1,4,7,10-tetraoxa-13-azacyclopentadecane (**12**).* Obtained from compound **4** (108 mg, 0.2 mmol) and azacrown ether **5** (131 mg, 0.6 mmol). Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:2. Yield 18 mg (11 %), yellowish glassy compound. (MALDI-TOF) found: 815.5602. $C_{44}H_{75}N_6O_8$ requires 815.5646 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.79 (4H, br.s), 2.46 (4H, t, ^3J = 4.7 Hz), 2.53 (4H, br.s), 2.62-2.72 (8H, m), 3.51 (8H, t, ^3J = 5.9 Hz), 3.53-3.64 (28H, m), 3.66 (8H, t, ^3J = 5.9 Hz), 6.54 (4H, d, ^3J = 8.5 Hz), 7.07 (4H, d, ^3J = 8.5 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 25.6 (2C), 47.6 (2C), 50.0 (2C, br., $\Delta\nu_{1/2}$ = 30 Hz), 51.2 (2C, br., $\Delta\nu_{1/2}$ = 10 Hz), 52.4 (4C), 53.3 (2C, br., $\Delta\nu_{1/2}$ = 20 Hz), 56.8 (2C), 68.5 (4C), 70.0 (8C), 71.2 (4C), 110.9 (4C), 123.9 (2C), 130.7 (4C), 146.5 (2C).

*16,16'-[1,4,7,10-Tetraazacyclododecane-1,7-diylbis-(methylene-4,1-phenylene)]bis-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (**13**).* Obtained from compound **2** (102 mg, 0.2 mmol) and azacrown ether **6** (158 mg, 0.6 mmol). Eluent CH_2Cl_2/MeOH 3:1. Yield 79 mg (45 %), yellowish glassy compound. (MALDI-TOF) found: 875.5784. $C_{46}H_{79}N_6O_{10}$ requires 875.5858 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.76 (16H, br.s), 3.53-3.66 (52H, m), 6.61 (4H, d ^3J = 8.1 Hz), 7.11 (4H, d, ^3J = 8.1 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 46.9 (4C), 50.9 (4C), 51.2 (4C), 60.3 (2C), 68.6 (4C), 70.4 (4C), 70.5 (8C), 70.6 (4C), 111.6 (4C), 125.2 (2C), 130.1 (4C), 147.3 (2C).

*16,16'-[1,4,8,11-Tetraazacyclotetradecane-1,8-diylbis-(methylene-4,1-phenylene)]bis-1,4,7,10,13-pentaoxa-16-azacyclooctadecane (**14**).* Obtained from compound **4** (108 mg, 0.2 mmol) and azacrown ether **6** (158 mg, 0.6 mmol). Eluent CH_2Cl_2/MeOH/NH_3aq 100:35:6. Yield 27 mg (15 %), yellowish glassy compound. (MALDI-TOF) found: 903.6253. $C_{48}H_{83}N_6O_{10}$ requires 903.6171 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.80 (4H, br.s), 2.46 (4H, t, ^3J = 4.9 Hz), 2.53 (4H, br.s), 2.63-2.72 (8H, m), 3.51-3.58 (16H, m), 3.59-3.66 (36H, m), 6.57 (4H, d, ^3J = 8.7 Hz), 7.08 (4H, d, ^3J = 8.7 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 25.6 (2C, br., $\Delta\nu_{1/2}$ = 15 Hz), 47.7 (2C), 50.0 (2C, br., $\Delta\nu_{1/2}$ = 30 Hz), 51.2 (6C), 53.3 (2C, br., $\Delta\nu_{1/2}$ = 50 Hz), 56.9 (2C), 68.7 (4C), 70.6 (4C), 70.7 (4C), 70.8 (8C), 111.2 (4C), 124.1 (2C), 130.8 (4C), 146.9 (2C).

*Typical procedure for the synthesis of cryptands **17, 18, 20-23**.*

A two-neck flask equipped with a condenser and magnetic stirrer, flushed with dry argon, was charged with *trans*-bis(bromobenzyl) derivative of cyclen or cyclam **1-4** (0.15 mmol), $Pd(dba)_2$ (14 mg, 0.024 mmol, 16 mol%) and DavePhos (10.5 mg, 0.027 mmol, 18 mol%), abs. dioxane (8 mL), the mixture was stirred for 2-3 min, then corresponding diazacrown ether **15** or **16** (0.15 mmol) and *t*-BuONa (44 mg, 0.45 mmol) were added, and the reaction mixture was refluxed for 24-30 h. After cooling it down to ambient temperature the reaction mixture was diluted with CH_2Cl_2, the residue was filtered off, washed with dichloromethane, combined organic solvents were evaporated *in vacuo*, the residue was dissolved in CH_2Cl_2 (5 mL), washed with distilled water (3×10 mL), organic layer was dried over molecular sieves 4 Å and evaporated *in vacuo*, and the residue was chromatographed on silica gel using a sequence of eluents: CH_2Cl_2, CH_2Cl_2/MeOH (25:1–3:1), CH_2Cl_2/MeOH/NH_3aq (100:20:1–10:4:1).

*23,26,31-Trioxa-1,8,11,14,21,37-hexaazapentacyclo[19.7.5.5^{8,14}.1^{2,6}.1^{16,20}]tetraconta-2(40),3,5,16(34),17,19-hexaene (**17**).* Obtained from compound **1** (77 mg, 0.15 mmol) and diazacrown ether **15** (33 mg, 0.15 mmol). Eluent CH_2Cl_2/MeOH 10:1. Yield 9 mg (10 %), yellow glassy compound. (MALDI-TOF) found: 567.3979. $C_{32}H_{51}N_6O_3$ requires 567.4023 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.64-2.93 (16H, m), 3.44-3.52 (8H, m), 3.60 (8H, br.s), 3.62 (4H, br.s), 3.88 (4H, t, ^3J = 5.3 Hz), 6.48 (4H, br.s), 7.06 (2H, t, ^3J = 8.0 Hz), 7.15 (2H, s), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 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).

*7,7'-[1,4,7,10-Tetraazacyclododecane-1,7-diylbis-(methylene-3,1-phenylene)]bis-1,4,10-trioxa-7,13-diazacyclopentadecane (**19**).* Obtained as the main product in the synthesis of cryptands **17**. Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:3. Yield 13 mg (22 %), yellow glassy compound. (MALDI-TOF) found: 785.58. $C_{42}H_{73}N_8O_6$ requires 785.57 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.65 (16H, br.s), 2.77 (4H, t, ^3J = 5.9 Hz), 2.78 (4H, t, ^3J = 5.2 Hz), 3.52-3.67 (32H, m), 3.74 (4H, t, ^3J = 6.8 Hz), 6.52 (2H, s), 6.56 (2H, d, ^3J = 7.6 Hz), 6.71 (2H, d, ^3J = 7.5 Hz), 7.18 (2H, t, ^3J = 7.7 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 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).

*22,25,30-Trioxa-1,7,10,13,19,37-hexaazapentacyclo[17.8.5.5^{7,13}.2^{2,5}.2^{15,18}]hentetraconta-2,4,15,17,33,40-hexaene (**18**).* Obtained from compound **2** (77 mg, 0.15 mmol) and diazacrown ether **15** (33 mg, 0.15 mmol). Eluent CH_2Cl_2/MeOH 10:1. Yield 19 mg (22 %), yellow glassy compound. (MALDI-TOF) found: 567.3988. $C_{32}H_{51}N_6O_3$ requires 567.4023 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.48 (4H, br.s), 2.60-2.82 (8H, m), 2.99-3.11 (4H, m), 3.16-3.26 (4H, m), 3.49 (4H, br.s), 3.59 (4H, br.s), 3.66-3.91 (12H, m), 6.97 (4H, br.s), 7.25 (4H, br.s), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 47.6 (4C), 50.6 (2C), 53.4 (2C), 58.8 (2C), 61.4 (2C), 66.9 (2C), 68.9 (2C), 70.3 (2C), 117.8 (4C), 131.5 (4C), four quaternary carbon atoms were not assigned.

*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 (**20**)*. Obtained from compound **1** (77 mg, 0.15 mmol) and diazacrown ether **16** (39 mg, 0.15 mmol). Eluent CH_2Cl_2/MeOH 3:1. Yield 27 mg (30 %), yellow glassy compound. (MALDI-TOF) found: 611.4261. $C_{34}H_{55}N_6O_4$ requires 611.4285 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.77-2.81 (8H, m), 2.83-2.85 (8H, m), 3.54-3.61 (24H, m), 3.65 (4H, s), 6.52 (2H, d, ^3J = 7.3 Hz), 6.57 (2H, dd, ^3J = 8.3 Hz, ^4J = 1.5 Hz), 6.77 (2H, br.s), 7.07 (2H, t, ^3J = 7.7 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 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).

*7,7'-[1,4,7,10-Tetraazacyclododecane-1,7-diylbis-(methylene-3,1-phenylene)]bis-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**24**)*. Obtained as the second compound in the synthesis of cryptand **20**. Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:3. Yield 19 mg (29 %), yellow glassy compound. (MALDI-TOF) found: 873.6095. $C_{46}H_{81}N_8O_8$ requires 873.6177 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.64 (16H, br.s), 2.78 (8H, t, ^3J = 4.4 Hz), 3.55-3.63 (36H, m), 3.65 (8H, t, ^3J = 4.9 Hz), 6.51 (2H, s), 6.55 (2H, d, ^3J = 8.1 Hz), 6.69 (2H, d, ^3J = 7.5 Hz), 7.18 (2H, t, ^3J = 7.8 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 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).

*22,25,30,33-Tetraoxa-1,7,10,13,19,40-hexaazapentacyclo[17.8.8.5^{7,13}.2^{2,5}.2^{15,18}]tetratetraconta-2,4,15,17,36,43-hexaene (**21**).* Obtained from compound **2** (77 mg, 0.15 mmol) and diazacrown

ether **16** (39 mg, 0.15 mmol). Eluent CH_2Cl_2/MeOH 10:1. Yield 24 mg (27 %), yellow glassy compound. (MALDI-TOF) found: 611.4230. $C_{34}H_{55}N_6O_4$ requires 611.4285 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.69-2.71 (12H, m), 2.88 (4H, br.s), 3.28-3.37 (4H, m), 3.46-3.53 (4H, m), 3.55-3.69 (20H, m), 6.73 (4H, d, ^3J = 7.8 Hz), 7.16 (4H, d, ^3J = 7.8 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 47.1 (4C), 50.9 (4C), 52.9 (4C), 61.4 (2C), 68.7 (4C), 71.2 (4C), 115.1 (4C, br., $\Delta\nu_{1/2}$ = 25 Hz), 125.0 (2C), 129.2 (4C), 148.0 (2C).

23,26,31,34-Tetraoxa-1,7,10,14,20,41-hexaazapentacyclo[18.8.8.6^{7,14}.2^{2,5}.2^{16,19}]hexatetraconta-2,4,16,18,37,45-hexaene ***(23)***. Obtained from compound **4** (81 mg, 0.15 mmol) and diazacrown ether **16** (39 mg, 0.15 mmol). Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:3. Yield 12 mg (12 %), yellow glassy compound. (MALDI-TOF) found: 639.4562. $C_{36}H_{59}N_6O_4$ requires 639.4598 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.80 (4H, br.s), 2.42-2.48 (4H, m), 2.53 (4H, br.s), 2.69 (4H, br.s), 2.76 (4H, t, ^3J = 4.2 Hz), 3.49-3.65 (28H, m), 6.48 (4H, d, ^3J = 8.5 Hz), 7.04 (4H, d, ^3J = 8.5 Hz), NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 25.6 (2C), 48.3 (2C), 49.9 (2C), 50.5 (4C), 51.1 (2C), 53.3 (2C), 58.9 (2C), 68.7 (4C), 70.5 (4C), 112.5 (4C), 124.0 (2C), 129.7 (4C), 146.9 (2C).

Results and Discussion

Initially we synthesized *trans*-bis(bromobenzyl) substituted cyclen and cyclam **1-4** in high yields *via* previously described two-step procedure from protected tetraazamacrocycles (Figure 1).[16,17]

These compounds were reacted with three equivalents of azacrown ethers **5** and **6** (Scheme 1). The reactions were run in absolute dioxane and catalyzed with $Pd(dba)_2$/DavePhos system in the presence of sodium *tert*-butoxide. The use of DavePhos ligand instead of more convenient BINAP was due to the necessity of the azacrown ethers secondary amino

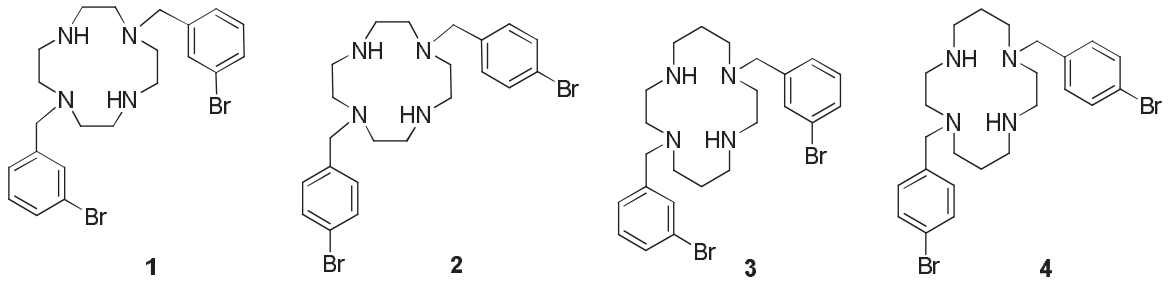
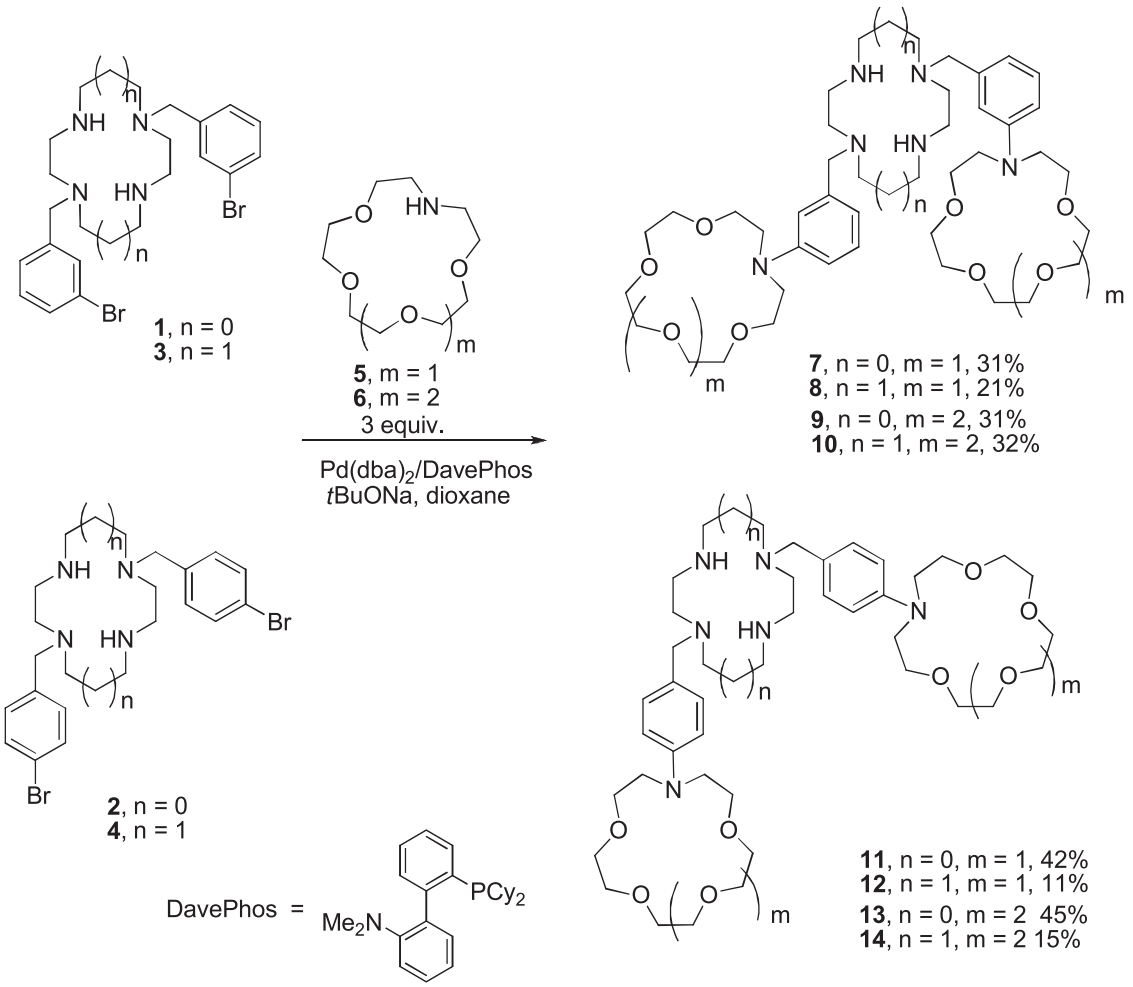
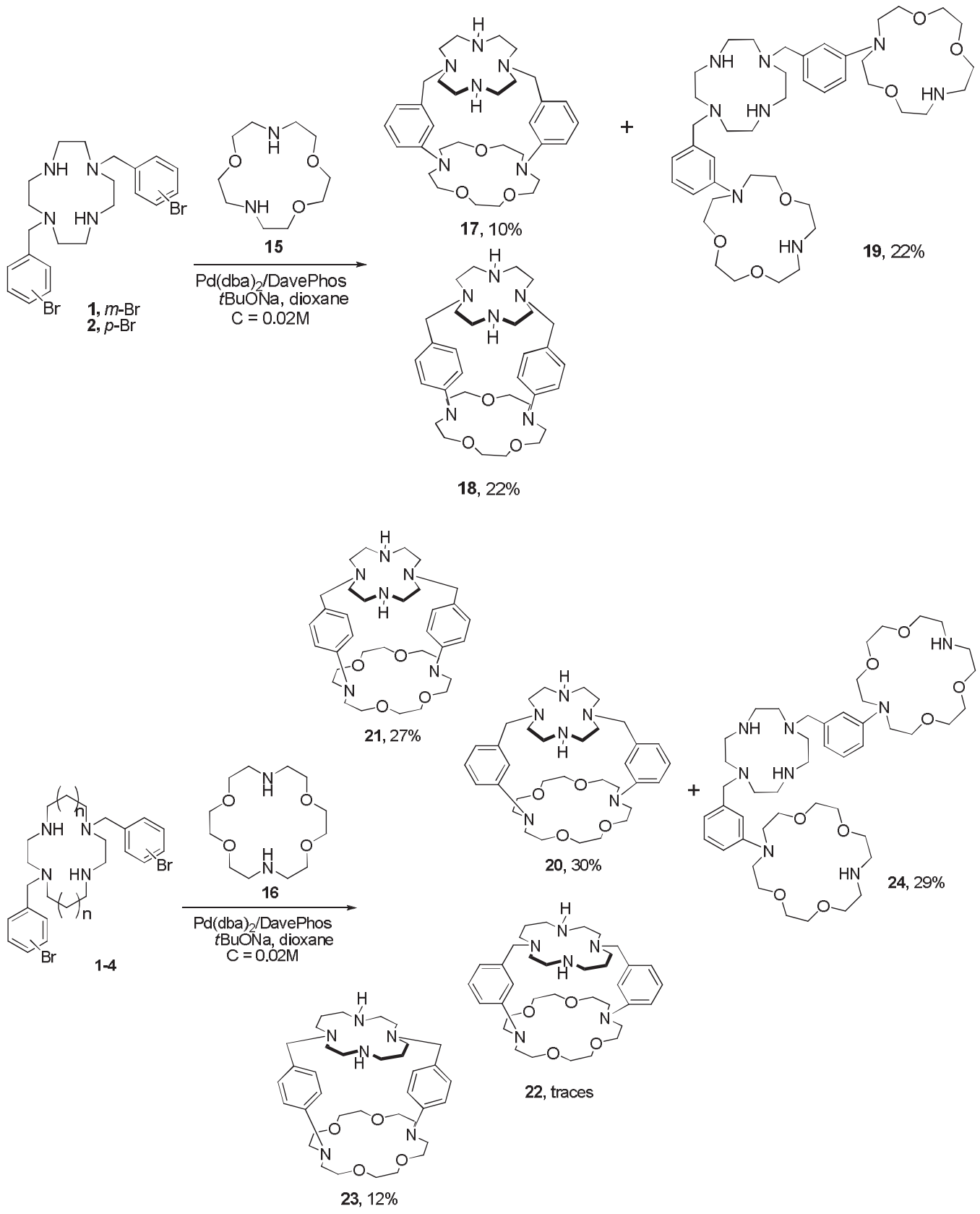


Figure 1. *Trans*-bis(bromobenzyl) substituted tetraazamacrocycles.



Scheme 1.


1, m-Br
2, p-Br
15
Pd(dba)2/DavePhos
tBuONa, dioxane
C = 0.02M
17, 10%
19, 22%
18, 22%
21, 27%
20, 30%
24, 29%
1-4
16
22, traces
23, 12%

Scheme 2.

groups arylation which is more difficult and demands more electron-rich phosphine ligands.

Trismacrocycles **7-14** were isolated as individual compounds by column chromatography on silica gel. In the majority of cases the yields of the target trismacrocyclic compounds were higher when cyclen derivatives **1** or **3** were reacted (31-45 %), while cyclam derivatives **2** and **4** provided 11-32 % yields. This may be due to a stronger coordination of Pd(0) by cyclam which removes it from the catalytic cycle. In our previous studies similar lower reactivity of cyclam derivatives was noted.[17,18] Almost in all reactions we observed the formation of bismacrocyclic by-products comprising one cyclen or cyclam and one azacrown moiety. Their formation was due to the catalytic reduction of one C-Br bond which is a typical by-process especially in the case of secondary amines arylation. However, these bismacrocycles were not isolated in individual state but rather as mixtures with the target trismacrocyclic compounds and were analyzed by NMR and MALDI-TOF spectra. A characteristic feature of ^{13}C NMR spectra of cyclam-based compounds **8**, **10**, **12**, **14** is a notable broadening (up to 50 Hz) of the signals of some aliphatic carbons which is due to hindered conformational changes in cyclam.

A one-pot synthesis of cylindrically shaped macrotricyclic cryptands employed the reactions of equimolar amounts of tetraazamacrocycles **1-4** and diazacrown ethers **15**, **16** (Scheme 2). They were also catalyzed with $Pd(dba)_2$/DavePhos system but lower concentrations of starting compounds (C = 0.02 M) were applied to promote cyclization and limit formation of oligomers. Cyclen derivatives **1** and **2** afforded target cryptands **17**, **18**, **20** and **21** in 10-30 % yields, while only in one case the reaction of cyclam derivative (compound **4** with diazacrown ether **16**) was successful. In two reactions we managed to isolate trismacrocyclic by-products **19** and **24** which were formed due to a competition between macrocyclization and oligomerization processes. The difference in the yields of macrotricycles can be explained by strong geometric demands for the reciprocal position of two bromine atoms and two nitrogen atoms in the reactants.

Conclusions

To sum up, we elaborated a straightforward approach to trismacrocyclic and macrotricyclic compounds possessing cyclen or cyclam central fragment and azacrown or diazacrown moieties using Pd(0)-mediated amination of *trans*-bis(bromobenzyl) derivatives of tetraazamacrocycles. The yields of trismacrocycles reached 45 % while macrotricyclic cryptands were obtained in yields up to 30 %. Cyclen derivatives were shown to be more reactive affording better yields of the target polymacrocyclic compounds. As novel cylindrically shaped cryptands possess two secondary amino groups, they can be easily modified with two identical fluorophores and further tested as fluorescent chemosensors or molecular probes for metal cations.

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