Макрогетероциклы
http://macroheterocycles.isuct.ru

DOI: 10.6060/mhc140502a

Pd–Catalyzed Amination for the Synthesis of Macropolycycles Comprising Cyclen, Cyclam and Naphthalene Moieties

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Dedicated to Corresponding member of Russian Academy of Sciences Prof. Oscar Koifman on the occasion of his 70th Anniversary

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Pd-catalyzed amination reactions were employed for the synthesis of macrobicyclic compounds possessing cyclen or cyclam moieties, naphthylmethyl spacers and polyamine linkers. The results of the macrocyclization reactions involving 1,7-bis(4-bromonaphthyl-1-methyl)cyclen and 1,8-bis(4-bromonaphthyl-1-methyl)cyclam were shown to be dependent on the nature of starting tetraazamacrocycles and polyamines, the better yields being observed in the case of cyclen derivatives. Valuable macrotricyclic compounds were obtained as the second products in the reactions of 1,7-bis(4-bromonaphthyl-1-methyl)cyclen with the majority of polyamines.

Keywords: Pd-Catalized amination, macropolycycles, cyclen, cyclam.

Pd–Катализируемое аминирование в синтезе макрополициклических соединений с фрагментами циклена, циклама и нафталина

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Посвящается Член-корреспонденту РАН профессору Оскару Иосифовичу Койфману по случаю его 70-летнего юбилея

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Реакции Pd-катализируемого аминирования использованы для синтеза макробициклических соединений, содержащих фрагменты циклена или циклама, нафтилметильные спейсеры и полиаминовые линкеры. Показано, что результат реакции макроциклизации с участием 1,7-бис(4-бромнафтил-1-метил)циклена и 1,8-бис(4-бромнафтил-1-метил)циклама зависят от природы исходных тетраазамакроциклов и полиаминов, лучшие выходы наблюдались для производных циклена. Ценные макротрициклические соединения получены в качестве вторых продуктов реакций 1,7-бис(4-бромнафтил-1-метил)циклена с большинством полиаминов.

Ключевые слова: Pd-Катализируемое аминирование, макрополициклические соединения, циклен, циклам.

Introduction

The first macrocycles incorporating naphthalene moieties were described in 1930s,[1] and since that time dozens of works appeared in which various macrocyclic compounds bearing this endocyclic fragment were described. Macrocycles containing 2,3-disubstituted naphthalene fragment have been investigated for alkali metals, ammonium and alkylammonium salts coordination,[2-7] as well as macrocycles possessing two naphthalene and two polyoxa fragments.[8,9] Macrocycles with polyoxa chains were obtained on the basis of 1,5-1,7- and 1,8-disubstituted naphthalene and their complexing properties towards alkali metals were studied.[5-10] Several works deal with polyoxamacrocycles organized around 2,2'- and 3,3'-disubstituted 1,1'-binaphthalenes,[6,7] among these compounds there are sophisticated macrotricyclic cryptands bearing two 1,10-diaza-18-crown-6 fragments.[11] Spherands with 2,2'-dioxy-1,1'-binaphthalenes and 2,7-disubstituted 1,8-dihydroxynaphtahlene moieties constitute another class of macrocycles,[10,12] the latter compound was tested in the coordination studies with Mg(II), Fe(II), Co(II), Ni(II) and Zn(II) cations. Various nitrogen-containing macrocycles with naphthalene moieties were reported, among them are cyclic Schiff bases,[13] diamides and diimides,[14,15] lactams;[16] naphthalene fragments were also condensed with tetraazamacrocycles.[17] Naphthalene fragments were combined with calixarenes,[18] catenanes,[19] and porphyrins.[20] Besides coordination with alkali cations, naphthalene-containing macrocycles were used for the formation of anion receptors and molecular rotors.[21,22]

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-Bromo-4-methylnaphthalene, di- and polyamines **7a-j**, 2-(dicyclohexylphosphino)-2'-(dimethylamino)-1,1'-biphenyl (DavePhos ligand), sodium *tert*-butoxide were purchased from Aldrich and Acros and used without further purification. *Cis*-glyoxal-cyclen **1** and bis-formaldehyde-cyclam **2** were provided by CheMatech Co. 1-Bromo-4-(bromomethyl)naphthalene was synthesized in 90 % yield from 1-bromo-4-methylnaphthalene according to a standard procedure using bromination with Br_2 in CCl_4. $Pd(dba)_2$ was synthesized according to a known method.[23] Dioxane was distilled over NaOH followed by the distillation over sodium under argon, acetonitrile was distilled over CaH_2, dichloromethane and methanol were used freshly distilled.

*2a,6a-Bis[(4-bromo-1-naphthyl)methyl]decahydro-4a,8a-dioxa-2a,6a-diazoniacyclopenta-[fg]acenaphtene dibromide (**3**)*. A flask equipped with a reflux condenser and magnetic stirrer was charged with *cis*-glyoxal-cyclen **1** (1.00 g, 5.1 mmol), 1-bromo-4-(bromomethyl)naphthalene (3.06 g, 10.2 mmol) and 17 mL of acetonitrile. The mixture was heated at 50-60 °C for 80 h, the white precipitate formed was filtered off, washed with cold acetonitrile (2×15 mL) and dried *in vacuo* at 100 °C. Yield 3.58 g (88 %). ^{1}H NMR (DMSO-d_6, 298 K) δ_H ppm: 2.91-2.99 (2H, m), 3.57 (2H, t, J = 11.7 Hz), 3.64-3.83 (6H, m), 3.93 (2H, td, J = 11.1 Hz, ^3J = 4.5 Hz), 5.57 (2H, s), 5.62 (2H, s), 7.81-7.86 (2H, m), 7.86-7.91 (2H, m), 7.97 (2H, d, ^3J = 7.8 Hz), 8.11 (2H, d, ^3J = 7.7 Hz), 8.32 (2H, d, ^3J = 8.2 Hz), 8.69 (2H, d, ^3J = 8.1 Hz) (6 protons in 3.30-3.40 ppm region are overlapped by the signal of H_2O of the solvent). ^{13}C NMR (DMSO-d_6, 298 K) δ_c ppm: 42.5 (2C), 46.1 (2C), 55.9 (2C), 56.3 (2C), 59.6 (2C), 76.0 (2C), 123.9 (2C), 124.7 (2C), 126.1 (2C), 127.8 (2C), 128.5 (2C), 128.8 (2C) 129.9 (2C), 131.7 (2C), 134.0 (2C), 134.3 (2C).

*N^1,N^7-di((4-bromonaphth-1-yl)methyl)cyclen (**5**)*. A flask equipped with a reflux condenser and magnetic stirrer was charged with disalt **3** (3.58 g, 4.45 mmol), KOH (8.1 g, 0.145 mol) and 50 mL of water. The mixture was stirred at 80-90 °C for 72 h, cooled down to ambient temperature, extracted with CH_2Cl_2 (3×50 mL). The organic phase was dried over Na_2SO_4, the solvent was evaporated *in vacuo*, and the product was obtained as a beige crystalline powder. Yield 2.68 g (99 %), m.p. 133-135 °C. (MALDI-TOF) found: 609.1274. $C_{30}H_{35}Br_2O_4$ requires 609.1228 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 292 (14000). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.59-2.67 (16H, m), 3.96 (4H, s), 7.22 (2H, d, ^3J = 7.6 Hz), 7.43 (2H, t, $^3J_{obs}$ = 7.6 Hz), 7.55 (2H, t, $^3J_{obs}$ = 7.7 Hz), 7.61 (2H, d, ^3J = 7.6 Hz), 8.10 (2H, d, ^3J = 8.5 Hz), 8.28 (2H, d, ^3J = 8.4 Hz) (two NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 45.7 (4C), 52.3 (4C), 58.1 (2C), 122.5 (2C), 123.8 (2C), 126.8 (2C), 126.9 (2C), 127.6 (2C), 127.9 (2C), 129.4 (2C), 132.0 (2C), 133.4 (2C) 134.5 (2C).

*1,8-Bis[(4-bromo-1-naphthyl)methyl]-4,11-diaza-1,8-diazoniatricyclo[9.3.1.1^{4,8}]hexadecane dibromide (**4**)*. A flask equipped with a magnetic stirrer was charged with bis-formaldehyde-cyclam **2** (2.5 g, 11.2 mmol), 1-bromo-4-(bromomethyl)naphthalene (6.9 g, 23 mmol) and 75 mL of acetonitrile. The reaction mixture was stirred at room temperature for 24 h, the white precipitate formed was filtered off, washed with cold acetonitrile (3×50 mL) and dried *in vacuo* at 100 °C. Yield 7.05 g (76 %). The compound is almost insoluble in common solvents like D_2O, CD_3OD and DMSO-d_6, thus NMR spectra were not recorded and the compound was used directly in the second step.

*N^1,N^7-di((4-bromonaphth-1yl)methyl)cyclam (**6**)*. A flask equipped with a reflux condenser and magnetic stirrer was charged with disalt **4** (7.05 g, 8.56 mmol), NaOH (14 g, 0.35 mmol) and 100 mL of water. The mixture was stirred at 90 °C for 48 h, cooled down to ambient temperature, extracted with CH_2Cl_2 (3×50 mL). The organic phase was dried over Na_2SO_4, the solvent was evaporated *in vacuo*, and the product was obtained as a yellowish crystalline powder. Yield 3.32 g (61 %), m.p. 137-139 °C. (MALDI-TOF) found: 637.1517. $C_{32}H_{39}Br_2N_4$ requires 637.1541 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 292 nm (13000). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.77 (4H, quintet, ^3J = 5.4 Hz), 2.53 (4H, t, ^3J = 5.4 Hz), 2.57 (4H, t, ^3J = 5.7 Hz), 2.61-2.66 (4H, m), 2.68-2.72 (4H, m), 3.91 (4H, s), 7.27 (2H, d, ^3J = 7.8 Hz), 7.53-7.61 (6H, m), 8.21-8.25 (2H, m), 8.36-8.40 (2H, m) (two NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 26.3 (2C), 47.8 (2C), 48.5 (2C), 52.7 (2C), 53.7 (2C), 57.0 (2C), 122.4 (2C), 124.6 (2C), 126.6 (2C), 127.0 (2C), 127.5 (2C), 127.8 (2C), 129.2 (2C), 132.0 (2C), 133.4 (2C), 134.7 (2C).

*Typical procedure for the synthesis of macrobicycles **8, 9***. A two-neck flask equipped with a reflux condenser and magnetic stirrer, flushed with dry argon, was charged with compound **5** or **6** (0.5 mmol), $Pd(dba)_2$ (44 mg, 16 mol%), DavePhos ligand (32 mg, 16 mol%), absolute dioxane (25 mL), the mixture was stirred for 2-3 min, then appropriate polyamine 7 (0.5 mmol) was added followed by *t*-BuONa (144 mg, 1.5 mmol). The reaction mixture was stirred at reflux for 24 h, cooled down to ambient temperature, the solvent was filtered and the residue washed with CH_2Cl_2 (3×5 mL), combined organic fractions were evaporated *in vacuo* and the oily residue 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_3aq (100:20:1-10:4:1).

*Macrobicycle **8a**.* Obtained from compound **5** (304 mg, 0.5 mmol) and diamine **7a** (37 mg, 0.5 mmol). Eluent CH_2Cl_2/MeOH 3:1. Yield 54 mg (20 %), light-beige crystalline powder, m.p. 183-185 °C. (MALDI-TOF) found: 523.3506. $C_{33}H_{43}N_6$ requires 523.3549 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 340 (8300). ^{1}H NMR

($CDCl_3$, 298 K) δ_H ppm: 2.04 (2H, quintet, ^3J = 6.8 Hz), 2.35-2.44 (4H, m), 2.68-2.76 (4H, m), 2.76-2.85 (4H, m), 2.90-2.97 (4H, m), 3.59 (4H, t, ^3J = 6.8 Hz), 3.98 (4H, s), 4.83 (2H, br.s), 6.49 (2H, d, ^3J = 7.8 Hz), 6.97 (2H, d, ^3J = 7.8 Hz), 7.42 (2H, t, $^3J_{obs}$ = 7.6 Hz), 7.50 (2H, t, $^3J_{obs}$ = 7.6 Hz), 7.83 (2H, d, ^3J = 8.4 Hz), 8.04 (2H, d ^3J = 8.4 Hz) (two NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 27.2 (1C), 41.1 (2C), 47.1 (4C), 51.8 (4C), 57.7 (2C), 105.0 (2C), 120.5 (2C), 123.4 (2C), 123.5 (2C), 123.8 (2C), 124.4 (2C), 125.9 (2C), 128.2 (2C), 133.1 (2C), 142.1 (2C).

*Cyclodimer **10a***. Obtained as the second product in the synthesis of macrobicycle **8a**. Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:1. Yield 44 mg (17 %), beige glassy compound. (MALDI-TOF) found: 1045.56. $C_{66}H_{85}N_{12}$ requires 1045.70 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.96 (4H, quintet, ^3J = 6.7 Hz), 2.51-2.70 (32H, m), 3.51 (8H, br.s), 3.88 (8H, s), 4.64 (4H, br.s), 6.44 (4H, d, ^3J = 8.0 Hz), 6.97 (4H, d, ^3J = 8.0 Hz), 7.35 (4H, t, $^3J_{obs}$ = 7.9 Hz), 7.47 (4H, t, $^3J_{obs}$ = 7.6 Hz), 7.77 (4H, d, ^3J = 8.7 Hz), 8.04 (4H, d, ^3J = 8.7 Hz) (four NH protons were not assigned).

*Macrobicycle **8b.*** Obtained from compound **5** (304 mg, 0.5 mmol) and diamine **7b** (44 mg, 0.5 mmol). Eluent CH_2Cl_2/MeOH 3:1. Yield 19 mg (7 %), beige crystalline powder, m.p. 163-165 °C. (MALDI-TOF) found: 537.3741. $C_{34}H_{45}N_6$ requires 537.3706 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 340 (8300). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.95 (4H, br.s), 2.21 (4H, br.s), 2.69-2.81 (12H, m), 3.39 (4H, br.s), 3.98 (4H, s), 4.83 (2H, br.s), 6.49 (2H, d, ^3J = 7.8 Hz), 6.97 (2H, d, ^3J = 7.8 Hz), 7.42 (2H, t, $^3J_{obs}$ = 7.6 Hz), 7.50 (2H, t, $^3J_{obs}$ = 7.6 Hz), 7.83 (2H, d, ^3J = 8.4 Hz), 8.04 (2H, d, ^3J = 8.4 Hz) (two NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 24.6 (2C), 41.8 (2C), 47.1 (4C), 52.5 (4C), 58.7 (2C), 103.4 (2C), 120.7 (2C), 122.8 (2C), 123.5 (2C), 124.2 (2C), 124.5 (2C), 125.8 (2C), 128.6 (2C), 133.0 (2C), 142.9 (2C).

*Macrobicycle **8c.*** Obtained from compound **5** (304 mg, 0.5 mmol) and diamine **7c** (86 mg, 0.5 mmol). Eluent CH_2Cl_2/MeOH 3:1. Yield 53 mg (17 %), yellowish crystalline powder, m.p. 152-154 °C. (MALDI-TOF) found: 621.4618. $C_{40}H_{57}N_6$ requires 621.4645 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 340 (11000). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.40-1.48 (8H, m), 1.57 (4H, quintet, ^3J = 6.2 Hz), 1.80 (4H, quintet, ^3J = 6.8 Hz), 2.55 (8H, br.s), 2.82 (8H, t, ^3J = 5.1 Hz), 3.24 (4H, t, ^3J = 6.5 Hz), 4.03 (4H, s), 6.32 (2H, d, ^3J = 7.8 Hz), 7.17 (2H, d, ^3J = 7.8 Hz), 7.42-7.47 (2H, m), 7.46-7.51 (2H, m), 7.81 (2H, d, ^3J = 8.5 Hz), 8.14 (2H, d, ^3J = 8.5 Hz) (NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 26.8 (2C), 28.0 (2C), 28.2 (2C), 28.6 (2C), 43.8 (2C), 47.0 (4C), 52.6 (4C), 59.1 (2C), 103.8 (2C), 120.2 (2C), 122.8 (2C), 123.6 (2C), 124.3 (2C), 124.4 (2C), 125.9 (2C), 128.3 (2C), 132.9 (2C), 143.3 (2C).

*Macrobicycle **8d.*** Obtained from compound **5** (304 mg, 0.5 mmol) and triamine **7d** (65 mg, 0.5 mmol). Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:1. Yield 52 mg (18 %), yellowish crystalline powder, m.p. 158-160 °C. (MALDI-TOF) found: 580.4087. $C_{36}H_{50}N_7$ requires 580.4128 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 339 (13000). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.96 (4H, quintet, ^3J = 5.0 Hz), 2.40 (4H, br.s), 2.66 (12H, br.s), 2.91 (4H, t, ^3J = 5.0 Hz), 3.21 (4H, t, ^3J = 6.4 Hz), 3.89 (4H, s), 5.82 (2H, d, ^3J = 7.8 Hz), 6.94 (2H, d, ^3J = 7.8 Hz), 7.38 (2H, t, $^3J_{obs}$ = 7.5 Hz), 7.49 (2H, t, $^3J_{obs}$ = 7.6 Hz), 7.88 (2H, d, ^3J = 8.5 Hz), 8.10 (2H, d, ^3J = 8.5 Hz) (NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 28.6 (2C), 44.6 (2C), 46.4 (4C), 49.3 (2C), 52.7 (4C), 58.9 (2C), 104.0 (2C), 120.9 (2C), 122.7 (2C), 123.7 (2C), 123.9 (2C), 124.2 (2C), 125.7 (2C), 129.1 (2C), 132.7 (2C), 143.6 (2C).

*Cyclodimer **10d.*** Obtained as the second product in the synthesis of macrobicycle **8d.** Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:2. Yield 55 mg (19 %), beige glassy compound. (MALDI-TOF) found: 1159.67. $C_{72}H_{99}N_{14}$ requires 1159.82 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.98 (8H, br.s), 2.51-2.69 (32H, m), 2.87 (8H, br.s), 3.34 (8H, br.s), 3.91 (8H, br.s), 6.43 (4H, d, ^3J = 7.7 Hz), 7.23 (4H, d, ^3J = 7.7 Hz), 7.29-7.46 (8H, m), 7.84 (4H, br.s), 8.09 (4H, br.s) (NH protons were not assigned).

*Macrobicycle **8e.*** Obtained from compound **5** (304 mg, 0.5 mmol) and tetraamine **7e** (80 mg, 0.5 mmol). Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:2. Yield 28 mg (9 %), yellowish glassy compound. (MALDI-TOF) found: 609.4367. $C_{37}H_{53}N_8$ requires 609.4393 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 339 (10000). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.82 (2H, br.s), 2.47 (4H, br.s), 2.68-2.95 (20H, m), 3.17 (4H, br.s), 3.92 (4H, s), 5.81 (2H, d, ^3J = 7.7 Hz), 6.97 (2H, d, ^3J = 7.7 Hz), 7.39-7.44 (2H, m), 7.50-7.55 (2H, m), 7.92 (2H, d, ^3J = 8.2 Hz), 8.08 (2H, d, ^3J = 8.2 Hz) (NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 31.8 (1C), 41.7 (2C), 43.9 (2C), 47.3 (4C), 51.8 (4C), 53.5 (2C), 58.7 (2C), 104.4 (2C), 120.8 (2C), 122.9 (2C), 123.4 (2C), 123.8 (2C), 124.4 (2C), 126.0 (2C), 129.2 (2C), 133.0 (2C), 143.3 (2C).

*Cyclodimer **10e.*** Obtained as the second product in the synthesis of macrobicycle **8e.** Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:2. Yield 37 mg (12 %), yellowish glassy compound. (MALDI-TOF) found: 1217.91. $C_{74}H_{105}N_{16}$ requires 1217.87 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 339 (20000). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.75 (4H, quintet, ^3J = 5.6 Hz), 2.45-2.71 (32H, m), 2.87 (8H, t, ^3J = 5.5 Hz), 3.02 (8H, t, ^3J = 5.8 Hz), 3.24 (8H, t, ^3J = 5.4 Hz), 3.90 (8H, s), 4.76 (4H, br.s), 6.03 (4H, d, ^3J = 7.8 Hz), 7.05 (4H, d, ^3J = 7.8 Hz), 7.40 (4H, t, $^3J_{obs}$ = 7.5 Hz), 7.48 (4H, t, $^3J_{obs}$ = 7.8 Hz), 7.89 (4H, d, ^3J = 8.0 Hz), 8.12 (4H, d, ^3J = 8.4 Hz) (four NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 28.9 (2C), 43.8 (4C), 45.9 (8C), 48.8 (4C), 49.4 (4C), 53.2 (8C), 59.3 (4C), 104.6 (4C), 120.6 (4C), 123.5 (4C), 123.9 (4C), 124.1 (4C), 124.4 (4C), 125.8 (4C), 128.4 (4C), 132.8 (4C), 143.1 (4C).

*Macrobicycle **8f.*** Obtained from compound **5** (304 mg, 0.5 mmol) and tetraamine **7f** (87 mg, 0.5 mmol). Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:1. Yield 40 mg (13 %), beige glassy compound. (MALDI-TOF) found: 622.4504. $C_{38}H_{55}N_8$ requires 623.4550 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 340 (10000). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm:1.95 (4H, quintet, ^3J = 5.6 Hz), 2.45-2.80 (16H, m), 2.85 (4H, t, ^3J = 5.2 Hz), 3.04 (4H, s), 3.34 (4H, t, ^3J = 6.3 Hz), 3.95 (4H, s), 6.24 (2H, d, ^3J = 7.8 Hz), 7.15 (2H, d, ^3J = 7.8 Hz), 7.49 (2H, t, $^3J_{obs}$ = 7.8 Hz), 7.56 (2H, t, $^3J_{obs}$ = 8.1 Hz), 7.95 (2H, d, ^3J = 8.5 Hz), 8.14 (2H, d, ^3J = 8.9 Hz) (NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 28.7 (2C), 44.3 (2C), 46.2 (4C), 49.4 (2C), 50.1 (2C), 52.1 (4C), 59.6 (2C), 103.5 (2C), 120.8 (2C), 122.4 (2C), 123.7 (2C), 124.0 (2C), 124.3 (2C), 125.7 (2C), 128.1 (2C), 133.1 (2C), 143.7 (2C).

*Cyclodimer **10f.*** Obtained as the second product in the synthesis of macrobicycle **8f.** Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:1. Yield 19 mg (6 %), yellowish glassy compound. (MALDI-TOF) found: 1245.74. $C_{76}H_{109}N_{16}$ requires 1245.90 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 340 (20000). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.93 (8H, quintet, ^3J = 5.6 Hz), 2.45-2.75 (32H, m), 2.88 (8H, s), 2.91 (8H, t, ^3J = 5.6 Hz), 3.32 (8H, t, ^3J = 6.3 Hz), 3.91 (8H, s), 6.29 (4H, d, ^3J = 7.8 Hz), 7.19 (4H, d, ^3J = 7.8 Hz), 7.35-7.44 (8H, m), 7.86 (4H, d, ^3J = 7.9 Hz), 8.11 (4H, d, ^3J = 9.1 Hz) (NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 27.1 (4C), 44.3 (4C), 46.3 (8C), 50.3 (4C), 51.9 (4C), 52.7 (8C), 59.5 (4C), 103.6 (4C), 121.1 (4C), 123.8 (4C), 124.0 (4C), 124.1 (4C), 124.3 (4C), 125.8 (4C), 128.7 (4C), 132.8 (4C), 144.1 (4C).

*Macrobicycle **8g.*** Obtained from compound **5** (304 mg, 0.5 mmol) and tetraamine **7g** (94 mg, 0.5 mmol). Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:2. Yield 55 mg (17 %), beige glassy compound. (MALDI-TOF) found: 637.4753. $C_{39}H_{57}N_8$ requires 637.4706 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 340 (12000). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.84 (4H, quintet, ^3J = 6.8 Hz), 1.96 (2H, quintet, ^{3}J = 6.5 Hz), 2.45-2.90 (20H, m), 2.94 (4H, t, ^3J = 6.5 Hz), 3.32 (4H, t, ^3J = 6.2 Hz), 3.92 (4H, s), 6.09 (2H, d, ^3J = 7.8 Hz), 7.06 (2H, d, ^3J = 7.8 Hz), 7.39-7.46 (4H, m), 7.88 (2H, d, ^3J = 8.3 Hz), 8.13 (2H, d, ^3J = 7.9 Hz) (NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 25.1 (1C), 30.4 (2C), 44.6 (2C), 46.2 (4C), 53.1 (4C), 55.4 (2C), 57.6 (2C), 59.8 (2C), 104.0 (2C), 121.5 (2C), 123.4 (2C), 123.8 (2C), 124.1 (2C), 124.2 (2C), 126.0 (2C), 128.6 (2C), 133.1 (2C), 143.9 (2C).

Cyclodimer ***10g*****.** Obtained as the second product in the synthesis of macrobicycle **8g**. Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:2. Yield 12 mg (4 %), yellowish glassy compound. (MALDI-TOF) found: 1273.81. $C_{78}H_{113}N_{16}$ requires 1273.93 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 339 (23000). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.84 (4H, quintet, ^3J = 6.8 Hz), 1.91 (8H, quintet, ^3J = 5.9 Hz), 2.45-2.72 (32H, m), 2.77 (8H, t, ^3J = 6.8 Hz), 2.87 (8H, t, ^3J = 5.7 Hz), 3.32 (8H, t, ^3J = 6.2 Hz), 3.89 (8H, s), 6.34 (4H, d, ^3J = 7.8 Hz), 7.20 (4H, d, ^3J = 7.8 Hz), 7.30 (4H, t, $^3J_{obs}$ = 7.6 Hz), 7.37 (4H, t, $^3J_{obs}$ = 8.0 Hz), 7.88 (4H, d, ^3J = 8.3 Hz), 8.10 (4H, d, ^3J = 8.1 Hz) (NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 25.3 (2C), 28.6 (4C), 43.9 (4C), 45.9 (8C), 48.8 (4C), 49.1 (4C), 52.9 (8C), 59.6 (4C), 103.3 (4C), 120.9 (4C), 122.5 (4C), 123.8 (4C), 124.0 (4C), 124.1 (4C), 125.8 (4C), 128.2 (4C), 132.9 (4C), 143.8 (4C).

Macrobicycle ***8h*****.** Obtained from compound **5** (304 mg, 0.5 mmol) and dioxadiamine **7h** (74 mg, 0.5 mmol). Eluent CH_2Cl_2/MeOH 3:1. Yield 32 mg (11 %), beige crystalline powder. (MALDI-TOF) found: 597.3867. $C_{36}H_{49}N_6O_2$ requires 597.3917 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 337 (12000). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.53 (8H, br.s), 2.69 (8H, br.s), 3.34 (4H, t, ^3J = 5.9 Hz), 3.75 (4H, s), 3.86 (4H, t, ^3J = 6.0 Hz), 3.94 (4H, s), 4.66 (2H, br.s), 6.05 (2H, d, ^3J = 7.8 Hz), 7.00 (2H, d, ^3J = 7.8 Hz), 7.39-7.44 (2H, m), 7.48-7.53 (2H, m), 7.91 (2H, d, ^3J = 8.2 Hz), 8.13 (2H, d, ^3J = 8.4 Hz) (two NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 43.9 (2C), 46.6 (4C), 52.9 (4C), 59.3 (2C), 69.3 (2C), 70.4 (2C), 104.7 (2C), 120.8 (2C), 123.8 (2C), 124.1 (4C), 124.5 (2C), 125.9 (2C), 128.6 (2C), 132.8 (2C), 143.0 (2C).

Cyclodimer ***10h*****.** Obtained as the second product in the synthesis of macrobicycle **8h.** Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:1-100:20:2. Yield 18 mg (6 %), yellowish glassy compound. (MALDI-TOF) found: 1193.59. $C_{72}H_{97}N_{12}O_4$ requires 1193.78 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 336 (23000). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.50-2.65 (32H, m), 3.41 (8H, t, ^3J = 5.5 Hz), 3.73 (8H, s), 3.85 (8H, t, ^3J = 5.5 Hz), 3.92 (8H, s), 4.86 (4H, br.s), 6.40 (4H, d, ^3J = 7.8 Hz), 7.20 (4H, d, ^3J = 7.8 Hz), 7.31 (4H, t, $^3J_{obs}$ = 7.9 Hz), 7.34-7.39 (4H, m), 7.83 (4H, d, ^3J = 8.3 Hz), 8.06 (4H, d, ^3J = 8.0 Hz) (four NH protons were not assigned).

Macrobicycle ***8i.*** Obtained from compound **5** (304 mg, 0.5 mmol) and dioxadiamine **7i** (102 mg, 0.5 mmol). Eluent CH_2Cl_2/MeOH 3:1. Yield 87 mg (26 %), beige crystalline powder, m.p. 143-145 °C. (MALDI-TOF) found: 653.4507. $C_{40}H_{57}N_6O_2$ requires 653.4543 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 340 (10000). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.82-1.86 (4H, m), 2.06 (4H, quintet, ^3J = 5.9 Hz), 2.55 (8H, br.s), 2.67 (8H, br.s), 3.39 (4H, t, ^3J = 6.5 Hz), 3.53-3.57 (4H, m), 3.70 (4H, t, ^3J = 5.2 Hz), 3.90 (4H, s), 5.09 (2H, br.s), 6.43 (2H, d, ^3J = 7.8 Hz), 7.20 (2H, d, ^3J = 7.8 Hz), 7.38-7.43 (2H, m), 7.43-7.48 (2H, m), 7.85 (2H, d, ^3J = 8.0 Hz), 8.11 (2H, d, ^3J = 8.0 Hz) (two NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 27.1 (2C), 29.0 (2C), 43.3 (2C), 48.3 (4C), 52.2 (4C), 60.0 (2C), 70.8 (2C), 71.5 (2C), 102.7 (2C), 120.7 (2C), 122.0 (2C), 123.5 (2C), 124.2 (2C), 124.3 (2C), 126.0 (2C), 128.6 (2C), 132.8 (2C), 143.8 (2C).

Cyclodimer ***10i*****.** Obtained as the second product in the synthesis of macrobicycle **8i**. Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:1. Yield 53 mg (16 %), beige glassy compound. (MALDI-TOF) found: 1305.66. $C_{80}H_{113}N_{12}O_4$ requires 1305.90 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.73-1.77 (8H, m), 2.01 (8H, quintet, ^3J = 5.6 Hz), 2.52-2.70 (32H, m), 3.30 (8H, br.s), 3.45-3.50 (8H, m), 3.61 (8H, t, ^3J = 5.4 Hz), 3.88 (8H, s), 5.12 (4H, br.s), 6.41 (4H, d, ^3J = 7.8 Hz), 7.22 (4H, d, ^3J = 7.8 Hz), 7.34-7.39 (8H, m), 7.89 (4H, d, ^3J = 9.0 Hz), 8.06 (4H, d, ^3J = 8.9 Hz) (four NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 26.6 (4C), 28.9 (4C), 43.0 (4C), 45.9 (8C), 52.2 (8C), 58.5 (4C), 70.7 (4C), 71.1 (4C), 103.2 (4C), 120.6 (4C), 122.2 (4C), 123.8 (4C), 124.1 (4C), 124.3 (4C), 125.8 (4C), 128.7 (4C), 133.0 (4C), 143.7 (4C).

Macrobicycle ***8j***. Obtained from compound **5** (304 mg, 0.5 mmol) and trioxadiamine **7j** (110 mg, 0.5 mmol). Eluent CH_2Cl_2/MeOH 3:1. Yield 78 mg (23 %), beige glassy compound. (MALDI-TOF) found: 669.4468. $C_{40}H_{57}N_6O_3$ requires 669.4492 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 340 (12000). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.05 (4H, quintet, ^3J = 5.8 Hz), 2.56 (8H, br.s), 2.66 (8H, br.s), 3.37 (4H, t, ^3J = 6.2 Hz), 3.67-3.70 (4H, m), 3.71 (4H, t, ^3J = 5.3 Hz), 3.75-3.78 (4H, m), 3.90 (4H, s), 5.03 (2H, br.s), 6.33 (2H, d, ^3J = 7.8 Hz), 7.18 (2H, d, ^3J = 7.8 Hz), 7.35-7.40 (2H, m), 7.41-7.46 (2H, m,), 7.88 (2H, d, ^3J = 8.3 Hz), 8.11 (2H, d, ^3J = 8.2 Hz) (two NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 28.9 (2C), 42.9 (2C), 46.2 (4C), 52.7 (4C), 59.2 (2C), 70.4 (2C), 70.7 (4C), 103.6 (2C), 120.7 (2C), 122.6 (2C), 123.7 (2C), 124.0 (2C), 124.2 (2C), 125.8 (2C), 128.3 (2C), 132.8 (2C), 143.5 (2C).

Cyclodimer ***10j***. Obtained as the second product in the synthesis of macrobicycle **8j**. Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:1. Yield 19 mg (6 %), yellowish glassy compound. (MALDI-TOF) found: 1337.71. $C_{80}H_{113}N_{12}O_6$ requires 1337.89 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 340 (23000). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.98 (8H, quintet, ^3J = 5.7 Hz), 2.48-2.70 (32H, m), 3.32 (8H, t, ^3J = 5.4 Hz), 3.56-3.61 (8H, m), 3.62 (8H, t, ^3J = 5.4 Hz), 3.66-3.70 (8H, m), 3.88 (8H, s), 5.07 (4H, br.s), 6.41 (4H, d, ^3J = 7.7 Hz), 7.22 (4H, d, ^3J = 7.7 Hz), 7.32-7.41 (8H, m), 7.81 (4H, d, ^3J = 7.7 Hz), 8.07 (4H, d, ^3J = 8.5 Hz) (four NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 28.8 (4C), 42.6 (4C), 45.9 (8C), 52.2 (8C), 58.5 (4C), 70.4 (4C), 70.6 (4C), 70.8 (4C), 103.3 (4C), 120.7 (4C), 122.3 (4C), 123.8 (4C), 124.1 (4C), 124.2 (4C), 125.8 (4C), 128.7 (4C), 133.1 (4C), 143.6 (4C).

Macrobicycle ***9a***. Obtained from compound **6** (318 mg, 0.5 mmol) and diamine **7a** (37 mg, 0.5 mmol). Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:2. Yield 7 mg (2.5 %), beige crystalline powder, m.p. 192-194 °C. (MALDI-TOF) found: 551.3820. $C_{35}H_{47}N_6$ requires 551.3862 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 336 (6300). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.00 (2H, br.s), 2.10 (2H, quintet, ^3J = 5.9 Hz), 2.29-2.81 (18H, m), 3.50 (4H, br.s), 3.87 (4H, s), 4.87 (2H, br.s), 6.34 (2H, d, ^3J = 7.8 Hz), 6.81 (2H, d, ^3J = 7.8 Hz), 7.16-7.21 (2H, m), 7.39-7.44 (2H, m), 7.60 (2H, d, ^3J = 8.4 Hz), 7.93 (2H, d, ^3J = 8.7 Hz) (two NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 25.5 (2C), 28.3 (1C), 43.0 (2C), 43.8 (2C), 49.1 (2C), 53.3 (2C), 54.2 (2C), 57.8 (2C), 104.6 (2C), 120.4 (2C), 123.4 (2C), 123.6 (2C), 123.7 (2C), 124.1 (2C), 125.4 (2C), 127.7 (2C), 133.9 (2C), 142.7 (2C).

Macrobicycle ***9b***. Obtained from compound **6** (318 mg, 0.5 mmol) and diamine **7b** (44 mg, 0.5 mmol). Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:3. Yield 11 mg (4 %), beige crystalline powder, m.p. 148-150 °C. (MALDI-TOF) found: 565.3981. $C_{36}H_{49}N_6$ requires 565.4019 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 340 (8300). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.74 (4H, br.s), 1.99 (4H, br.s), 2.40-2.75 (16H, m), 3.39 (4H, br.s), 3.98 (4H, br.s), 4.45 (2H, br.s), 6.11 (2H, d, ^3J = 7.8 Hz), 6.33 (2H, d, ^3J = 7.8 Hz), 7.26-7.31 (2H, m,), 7.47-7.52 (2H, m), 7.68 (2H, d, ^3J = 8.6 Hz), 8.18 (2H, d, ^3J = 8.2 Hz) (two NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 23.8 (2C), 26.3 (2C), 41.8 (2C), 43.9 (2C), 48.5 (2C), 50.4 (2C), 55.4 (2C), 58.2 (2C), 104.2 (2C), 120.6 (2C), 122.9 (2C), 123.7 (2C), 124.1 (2C), 124.5 (2C), 125.6 (2C), 129.6 (2C), 133.2 (2C), 142.1 (2C).

Macrobicycle ***9c***. Obtained from compound **6** (318 mg, 0.5 mmol) and diamine **7c** (86 mg, 0.5 mmol). Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:2. Yield 33 mg (10 %), beige glassy compound. (MALDI-TOF) found: 649.4920. $C_{42}H_{61}N_6$ requires 649.4958 $[M+H]^+$. UV (CH_2Cl_2) λ_{max} nm (ε): 340 (12000). ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.16-1.38 (12H, m), 1.64 (4H, quintet, ^3J = 6.8 Hz), 1.77 (4H, br.s), 2.49-2.67 (16H, m), 3.20 (4H, q, ^3J = 5.0 Hz), 3.92 (4H, s), 4.33 (2H, br.s), 6.50 (2H, d, ^3J = 7.7 Hz), 7.29-7.36 (6H, m), 7.74-7.77 (2H, m), 8.03-8.07 (2H, m) (two NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 25.9 (2C), 26.3 (2C), 28.0 (2C), 28.2 (2C), 29.4 (2C), 43.6 (2C), 44.2 (2C), 48.8 (2C), 53.0 (2C), 53.4 (2C), 56.0 (2C), 103.8 (2C), 120.3 (2C), 122.4 (2C), 123.6 (2C), 124.1 (2C), 124.2 (2C), 125.7 (2C), 128.6 (2C), 133.1 (2C), 142.9 (2C).

Macrobicycle ***9d***. Obtained from compound **6** (214 mg, 0.34 mmol) and triamine **7d** (45 mg, 0.34 mmol). Eluent CH_2Cl_2/MeOH 3:1. Yield 15 mg (7 %), beige glassy compound. (MALDI-TOF) found: 608.4473. $C_{38}H_{54}N_7$ requires 608.4441 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.95-2.06 (8H, m), 2.40-2.75 (16H, m), 2.97 (4H, t, ^3J = 5.8 Hz), 3.31 (4H, t, ^3J = 6.3 Hz), 3.97 (4H, s), 5.98 (2H, d, ^3J = 7.9 Hz), 6.85 (2H, d, ^3J = 7.9 Hz), 7.31-7.51 (4H, m), 7.85 (2H, d, ^3J = 8.5 Hz), 8.16 (2H, d, ^3J = 8.2 Hz) (NH protons were not assigned).

Macrobicycle ***9h***. Obtained from compound **6** (214 mg, 0.34 mmol) and dioxadiamine **7h** (50 mg, 0.34 mmol). Eluent CH_2Cl_2/MeOH 3:1. Yield 10 mg (5 %), yellow glassy compound. UV (CH_2Cl_2) λ_{max} nm (ε): 339 (11000). (MALDI-TOF) found: 625.4208. $C_{38}H_{53}N_6O_2$ requires 625.4230 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm:1.87 (4H, br.s), 2.49 (4H, br.s), 2.65 (4H, t, ^3J = 5.6 Hz), 2.69 (4H, t, ^3J = 5.1 Hz), 2.75 (4H, br.s), 3.32 (4H, t, ^3J = 5.7 Hz), 3.73 (4H, s), 3.81 (4H, t, ^3J = 5.7 Hz), 3.83 (4H, br.s), 6.09 (2H, d, ^3J = 7.8 Hz), 6.97 (2H, d, ^3J = 7.8 Hz), 7.36-7.41 (2H, m), 7.44-7.49 (2H, m), 7.81 (2H, d, ^3J = 8.3 Hz), 8.02 (2H, d, ^3J = 8.5 Hz) (NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 24.9 (2C), 43.8 (2C), 48.5 (2C), 49.7 (2C), 52.1 (2C), 54.3 (2C), 57.9 (2C), 69.1 (2C), 70.4 (2C), 104.5 (2C), 121.0 (2C), 122.7 (2C), 123.3 (2C), 123.8 (2C), 124.7 (2C), 126.0 (2C), 128.3 (2C), 132.7 (2C), 143.2 (2C).

Macrobicycle ***9i***. Obtained from compound **6** (214 mg, 0.34 mmol) and dioxadiamine **7i** (69 mg, 0.34 mmol). Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:2. Yield 23 mg (10 %), yellow glassy compound. UV (CH_2Cl_2) λ_{max} nm (ε): 340 (11000). (MALDI-TOF) found: 681.4881. $C_{42}H_{61}N_6O_2$ requires 681.4856 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.74 (4H, br.s), 1.83 (4H, br.s), 1.96 (4H, br.s), 2.45-2.50 (4H, m), 2.57-2.62 (4H, m), 2.65-2.72 (8H, m), 3.11 (4H, br.s), 3.48 (4H, br.s), 3.58 (4H, t, ^3J = 5.0 Hz), 3.81 (4H, s), 5.22 (2H, br.s), 6.21 (2H, d, ^3J = 7.8 Hz), 7.13 (2H, d, ^3J = 7.4 Hz), 7.16-7.21 (2H, m), 7.23-7.28 (2H, m), 7.73 (2H, d, ^3J = 8.3 Hz), 7.87 (2H, d, ^3J = 8.5 Hz) (two NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 25.1 (2C), 27.0 (2C), 28.7 (2C), 43.4 (2C), 48.3 (2C), 49.6 (2C), 52.2 (2C), 54.4 (2C), 57.9 (2C), 71.1 (2C), 71.4 (2C), 102.6 (2C), 120.9 (2C), 121.9 (2C), 123.5 (2C), 123.7 (2C), 123.9 (2C), 125.6 (2C), 128.3 (2C), 132.5 (2C), 143.5 (2C).

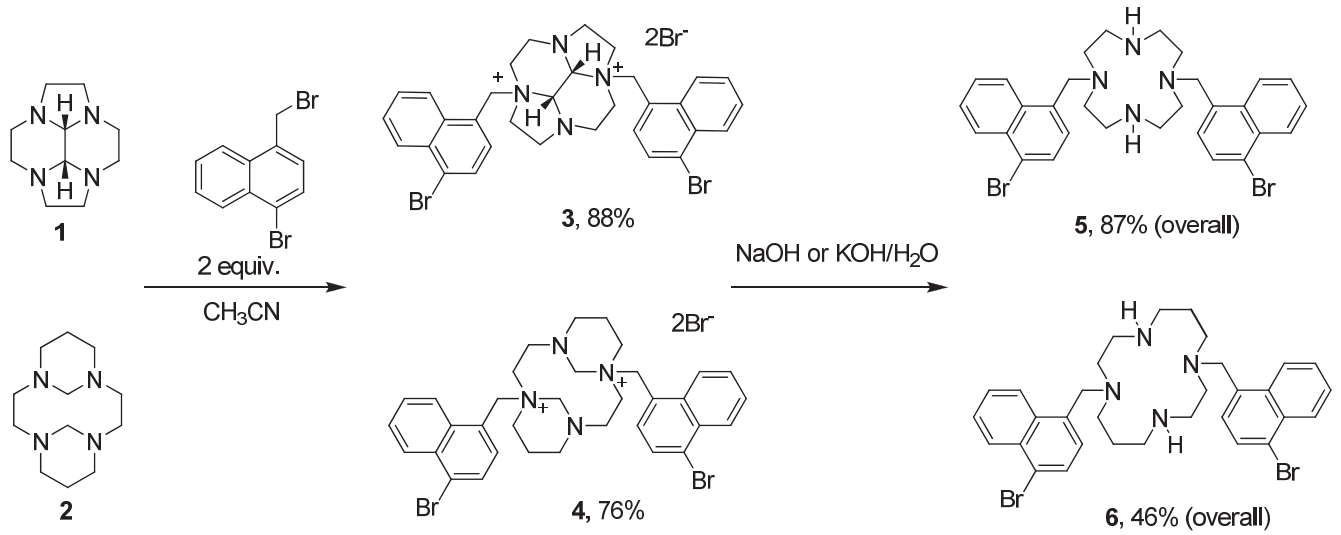
Macrobicycle ***9j***. Obtained from compound **6** (318 mg, 0.5 mmol) and trioxadiamine **7i** (110 mg, 0.5 mmol). Eluent CH_2Cl_2/MeOH/NH_3aq 100:20:3. Yield 45 mg (13 %), yellow glassy compound. UV (CH_2Cl_2) λ_{max} nm (ε): 340 (11000). (MALDI-TOF) found: 697.4841. $C_{42}H_{61}N_6O_3$ requires 697.4805 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.82 (4H, quintet, ^3J = 5.8 Hz), 1.98 (4H, br.s), 2.50-2.60 (4H, m), 2.65-2.75 (4H, m), 2.90 (8H, br.s), 3.48-3.53 (12H, m), 3.60-3.64 (4H, m), 3.85 (4H, s), 4.89 (2H, br.s), 6.01 (2H, d, ^3J = 7.7 Hz), 7.12 (2H, d, ^3J = 7.8 Hz), 7.26-7.31 (4H, m), 7.72-7.75 (2H, m), 7.93-7.96 (2H, m) (two NH protons were not assigned). ^{13}C NMR ($CDCl_3$, 298 K) δ_c ppm: 26.0 (2C), 28.5 (2C), 43.0 (2C), 48.4 (2C), 49.9 (2C), 54.0 (2C), 55.0 (2C), 56.3 (2C), 70.3 (2C), 70.4 (2C), 71.3 (2C), 103.0 (2C), 120.9 (2C), 121.7 (2C), 123.5 (2C), 123.7 (2C), 124.1 (2C), 125.3 (2C), 127.5 (2C), 132.7 (2C), 142.9 (2C).

Results and Discussion

In our previous investigations we successfully synthesized macrobicycles based on cyclen and cyclam central moieties containing benzyl[24-26] and pyridinylmethyl spacers.[27] The yields of the corresponding cryptands were shown to be dependent on the nature of the tetraazamacrocyclic fragment and the spacer used, the better results being obtained for cyclen derivatives, especially those with benzyl spacers. We have also shown the possibility to synthesize macrobicycles based on cyclam possessing two naphthylmethyl substituents on the nitrogen atoms of the cryptand.[28] In this communication we report the synthesis of macrobicyclic derivatives of cyclen and cyclam with naphthylmethyl spacers which can be viewed as a valuable and simple chromophore and fluorophore group useful for the creation of macrocyclic chemosensors for metal cations.

For this purpose we synthesized 1-bromo-4-(bromomethyl)naphthalene in 90 % yield from commercially available 1-bromo-4-methylnaphthalene by its bromination with NBS in CCl_4. Protected tetraazamacrocycles, *cis*-glyoxal-cyclen **1** and bis-formaldehyde-cyclam **2**, were dialkylated in MeCN using this bromide to give disalts **3** and **4** in 88 and 76 % yields respectively, and after a standard deprotection step (heating with NaOH in water) *trans*-bis(4-bromonaphth-1-ylmethyl) substituted cyclen and cyclam **5** and **6** were obtained in overall 87 and 46 % yields (Scheme 1).

Compounds **5** and **6** were introduced in the Pd-catalyzed amination reactions with a series of di- and polyamines **7a-j** (Scheme 2). Starting compounds were taken in equimolar



Scheme 1.

amounts, the macrocyclization was catalyzed with $Pd(dba)_2$/DavePhos catalytic system (DavePhos = 2-(dimethylamino)-2'-(dicyclohexylphosphino)biphenyl) because initial experiments unexpectedly demonstrated low efficiency of a standard BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthalene) ligand. It was surprising because 1- and 2-bromonaphthalenes are known to be very active substrates in Pd-catalyzed amination reactions.[29-31] This fact may be explained by the presence of the tetraazamacrocyclic fragment which competes with the phosphine ligand in the coordination of Pd(0) partially removing it from the catalytic cycle.

Target compounds **8** and **9** were obtained after column chromatography on silica gel, in order to isolate them from mixtures with macrotricyclic cyclodimers which were formed in comparable amounts. The use of the minimal amount of silica gel helped to obtain pure target cryptands. Cyclen-containing macrobicycles **8** were obtained in moderate yields, while the yields of cyclam-containing cryptands **9** were always low (Table 1). Higher yields of the cyclen derivatives compared to cyclam derivatives were observed by us earlier in the majority of cases where macrobicycles were synthesized.[27] The cryptands yields do not notably depend on the chain length of polyamines but rather on the number of nitrogen atoms, it was noted that $NHCH_2CH_2NH$ and OCH_2CH_2O fragments present in polyamine structure diminish the yields (Table 1, entries 5, 6, 8). It may be explained by a better coordination of Pd(0) by these fragments which form stable chelates and hinder amination reaction. It is interesting to note that in some cases the decrease in the catalyst loading from 16 to 8 mol% together with the increase in the reagents concentration from 0.02 to 0.04 M and application of 1.5 equiv. of polyamine led to better yields of the target macrobicycles **8** (entries 9, 12). The formation of cyclic dimers and higher mass oligomers was noted in all reactions, however, macrotricycles **10** were isolated only in the case of cyclen derivatives and in some cases their yields were even higher than those of target cryptands **8** (entries 4, 5, 11). Cyclic oligomers of higher masses have been never isolated as individual compounds, but in some cases corresponding signals were observed in MALDI-TOF spectra of mixtures.

Conclusions

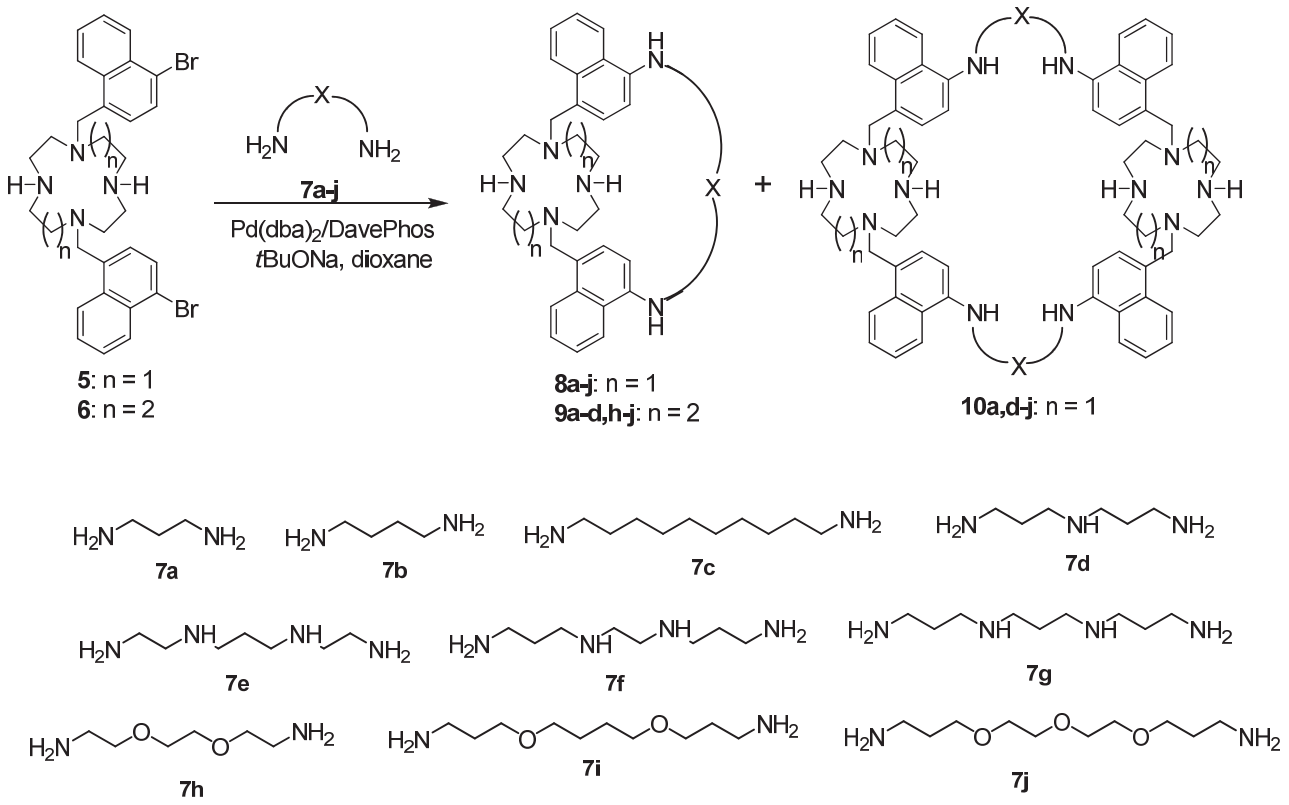
As a result, we elaborated cryptands containing tetraazamacrocycle, two naphthylmethyl and polyamine moieties using Pd-catalyzed macrocyclization of easily avaialable *trans-N,N'*-bis(naphthylmethyl) derivatives of cyclen and cyclam. The yields of the target macrobicycles were shown to be dependent on the nature of starting compounds, better yields being observed in the case of cyclen derivatives. Interesting macrotricyclic compounds were obtained as the second products in the reactions of the cyclen derivative with polyamines.

Acknowledgements. This work was carried out in the frame of the International Associated French-Russian Laboratory of Macrocycle Systems and Related Materials (LAMREM) of RAS and CNRS and financially supported by the RFBR grants 12-03-93107, 13-03-00813 and 13-03-90453. Generous provision of cyclen and cyclam derivatives by CheMatech Co is acknowledged.

Table 1. Synthesis of cryptands **8** and **9** ($Pd(dba)_2$/DavePhos, 16/16 mol%, C = 0.02 M).

Entry	Tetraazamacrocycle derivative	Polyamine **7**	Yields of macrobicycles	Yields of cyclodimers
1	**5**	$NH_2(CH_2)_3NH_2$ **7a**	**8a**, 20%	**10a**, 17%
2	**5**	$NH_2(CH_2)_4NH_2$ **7b**	**8b**, 7%	
3	**5**	$NH_2(CH_2)_{10}NH_2$ **7c**	**8c**, 17%	
4	**5**	$NH_2(CH_2)_3NH(CH_2)_3NH_2$ **7d**	**8d**, 18%	**10d**, 19%
5	**5**	$NH_2(CH_2)_2NH(CH_2)_3NH(CH_2)_2NH_2$ **7e**	**8e**, 9%	**10e**, 12%
6	**5**	$NH_2(CH_2)_3NH(CH_2)_2NH(CH_2)_3NH_2$ **7f**	**8f**, 13%	**10f**, 6%
7	**5**	$NH_2(CH_2)_3NH(CH_2)_3NH(CH_2)_3NH_2$ **7g**	**8g**, 17%	**10g**, 4%
8	**5**	$NH_2(CH_2)_2O(CH_2)_2O(CH_2)_2NH_2$ **7h**	**8h**, 11%	**10h**, 6%[a]
9	**5**	$NH_2(CH_2)_2O(CH_2)_2O(CH_2)_2NH_2$ **7h**[b]	**8h**, 29%	
10	**5**	$NH_2(CH_2)_3O(CH_2)_4O(CH_2)_3NH_2$ **7i**	**8i**, 13%	**10i**, 8%
11	**5**	$NH_2(CH_2)_3[O(CH_2)_2]_2O(CH_2)_3NH_2$ **7j**	**8j**, 10%	**10j**, 13%
12	**5**	$NH_2(CH_2)_3[O(CH_2)_2]_2O(CH_2)_3NH_2$ **7j**[b]	**8j**, 28%	
13	**6**	$NH_2(CH_2)_3NH_2$ **7a**	**9a**, 2.5%	
14	**6**	$NH_2(CH_2)_4NH_2$ **7b**	**9b**, 4%	
15	**6**	$NH_2(CH_2)_{10}NH_2$ **7c**	**9c**, 10%	
16	**6**	$NH_2(CH_2)_3NH(CH_2)_3NH_2$ **7d**	**9d**, 7%	
17	**6**	$NH_2(CH_2)_2O(CH_2)_2O(CH_2)_2NH_2$ **7h**	**9h**, 5%	
18	**6**	$NH_2(CH_2)_3O(CH_2)_4O(CH_2)_3NH_2$ **7i**	**9i**, 10%	
19	**6**	$NH_2(CH_2)_3[O(CH_2)_2]_2O(CH_2)_3NH_2$ **7j**	**9j**, 13%	

[a] Cyclodimer **10h** was obtained in a mixture with macrobicycle **8h**.
[b] The reaction was run using 8/9 mol% $Pd(dba)_2$/DavePhos, C = 0.04 M, and polyamine:**5** mole ratio 1.5:1.



Scheme 2.

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Received 12.05.2014
Accepted 27.05.2014