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Pd(0)−Catalyzed Amination in the Synthesis of Planar−Chiral Macrobicyclic Compounds Comprising 1,5−Disubstituted Anthraquinone Moiety

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Planar-chiral N- and O-containing macrocycles were obtained via enantioselective Pd(0)-catalyzed amination of 1,5-dichloroanthraquinone and converted into corresponding di(bromobenzyl) substituted derivatives. The latter compounds were introduced in the Pd(0)-catalyzed macrocyclization reactions with several linear oxadiamines and certain pairs of reagents gave macrobicyclic compounds with a central planar-chiral structural fragment.

Keywords: Macrocycles, Pd catalysis, chirality, polyamines, amination.

Pd(0)−Катализируемое аминирование в синтезе планарно−хиральных макробициклических соединений, содержащих фрагмент 1,5−дихлорантрахинонона

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Планарно-хиральные N- и O-содержащие макроцилы получены энантиоселективным Pd(0)-катализируемым аминированием 1,5-дихлорантрахинона и превращены далее в соответствующие ди(бромбензил) производные. Данные соединения были введены в Pd(0)-катализируемую макроциклизацию с несколькими линейными оксадиаминами, и некоторые пары реагентов привели к образованию макробициклических соединений, содержащих центральный планарно-хиральный структурный фрагмент.

Ключевые слова: Макроциклы, Pd катализ, хиральность, полиамины, аминирование.

Introduction

Macrocyclic compounds containing endocyclic chiral fragments are of substantial interest due to their ability for selective binding of optical isomers of small organic molecules thus acting as molecular chemosensors. Also they are useful as chiral ligands for the preparation of the complexes with metals, especially with those active in transition metal catalysis, in order to ensure enantioselective version of the catalytic processes. From the early days of the macrocycles era, a number of such compounds which contain one or several identical chiral elements in the structure of the macrocycle are known. In 1984 the first micro-review on the chiral macrocycles was published,[1] and in 1991 an unprecedented review on the hundreds of the macrocycles synthesized to that date also contained several macrocycles with various elements of chirality.[2] During last two decades many macrocyclic compounds differing by the nature of chiral fragments, cavity size and heteroatoms present in their structure were reported. They include the compounds which are based on chiral diamines and Schiff bases,[3-5] contain amino acid fragments,[6] in other molecules macrocycles are cyclocondensed with chiral skeletons,[7] usually such molecules comprise oxygen and nitrogen donor atoms, and also phosphorus-containing chiral macrocycles have been described.[8-10] Planar-chiral macrocycles are still quite rare.[11-13] Until last time macrocycles with BINOL *C2*-chiral moiety have been of constant interest.[14] Almost all these reactions were accomplished using non-catalytic methods, and a rare exception is the synthesis of several planar-chiral macrocycles using metathesis reaction at the macrocyclization step.[15]

Several years ago we have proposed a direct route to planar-chiral macrocycles using Pd(0)-catalyzed macrocyclization in the presence of chiral phosphine ligands,[16] and further the possibility to synthesize planar-chiral macrobicycles comprising cyclam central moiety was also shown.[17] In this connection the present research is aimed at the synthesis of macrobicycles based on the central planar-chiral macrocycle formed around 1,5-disubstituted anthraquinone. Such compounds may be of interest not only due to their chirality but also due to their properties as chromophores and possibility to form chiral complexes with metal cations.

Experimental

NMR spectra were registered using Bruker Avance 400 spectrometer in $CDCl_3$ at 298K, MALDI-OF spectra were obtained with Bruker Autoflex II spectrometer using 1,8,9-trihydroxyanthracene as matrix and PEGs as internal standards. HPLC for the determination of enantiomeric excess was performed with Bischoff liquid chromatograph using OJ-H and OD-H Chiralcel columns or Chiralpak AD columns and hexane/*i*-PrOH 7:3 v/v or hexane/*i*-PrOH/Et_3N 70:30:0.2 v/v eluents (1 ml/min, 219 nm and 254 nm UV detectors). X-Ray study was carried out on STOE STADI VARI PILATUS-100K single crystal diffractometer (focusing mirrors, rotation method, 3493 frames, detector distance=60 mm) using microfocus Cu GeniX 3D radiation source. Structure was solved by direct methods and refined by full-matrix Least Squares procedure using SHELX program complex. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre, and assigned to the following deposition number: CCDC 949468. Preparative column chromatography was performed using silica gel 40–60 mesh purchased from Fluka. 1,5-Dichloroanthraquinone (**1**), dioxadiamines **2a**,**e**, trioxadiamines **2b**,**c**, tetraoxadiamine **2d**, *rac*-BINAP, DavePhos and Josiphos SL-J002-2 and SL-J009-2 ligands, cesium carbonate, potassium carbonate, were purchased from Aldrich and used without further purification, $Pd(dba)_2$ was synthesized according to the method described,[18] 1-(bromomethyl)-3-iodobenzene and 1-(bromomethyl)-4-iodobenzene were obtained from commercially available *m*-iodotoluene by a standard bromination with NBS in CCl_4. 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.

*Typical procedure for the synthesis of macrocycles **3a-d**.* A flask equipped with a condenser and magnetic stirrer was charged with 1,5-dichloroanthraquinone (0.2–3 mmol, 55–831 mg), $Pd(dba)_2$ (8 or 16 mol %) and *rac*-BINAP (9 or 18 mol%) or Josiphos SL-J002-2, Josiphos SL-J002-9 (9 or 18 mol%). Then absolute dioxane (10–150 ml) and cesium carbonate (0.8–12 mmol, 261–3192 mg, 4 equiv.) were added and the reaction mixture was refluxed for 30–40 h. After cooling the reaction mixture down to room temperature the precipitate was filtered off, washed with CH_2Cl_2, combined organic phases were evaporated *in vacuo*, and the solid residue was chromatographed on silica gel using a sequence of eluents: CH_2Cl_2, CH_2Cl_2/MeOH (500:1 – 50:1). Corresponding experimental details with yields and spectra are described below only for racemic macrocycles as enantiomerically enriched mixtures were isolated with the same eluents and possess essentially the same spectra. Their yields, type of chiral catalyst, their loadings and enantiomeric excess are given in Table 1.

*1,5-(Epiminopropanooxybutanooxypropanoimino)anthracene-9,10-dione (**3a-r**).* Obtained from 1,5-dichloroanthraquinone (**1**) (0.5 mmol, 139 mg) and dioxadiamine **2a** (0.5 mmol, 102 mg) in the presence of $Pd(dba)_2$ (8 mol%, 23 mg), *rac*-BINAP (9 mol%, 28 mg) and Cs_2CO_3 (2 mmol, 672 mg) in 25 ml absolute dioxane. Eluent: CH_2Cl_2/MeOH (200:1). Yield 93 mg (45 %). NMR data are consistent with those described in literature.[16,19]

*5,5'-(3,3'-(Butane-1,4-diylbis(oxy))bis(propane-3,1-diyl)) bis(azanediyl)bis(1-chloroanthracene-9,10-dione) (**4a**).* Obtained as the second product in the synthesis of compound **3a** from 1,5-dichloroanthraquinone (**1**) (3 mmol, 831 mg) and dioxadiamine **2a** (3 mmol, 612 mg) in the presence of $Pd(dba)_2$ (8 mol%, 138 mg), *rac*-BINAP (9 mol%, 168 mg) and Cs_2CO_3 (12 mmol, 4.032 g) in 150 ml absolute dioxane. Eluent: CH_2Cl_2/MeOH (500:1). Yield 122 mg (12 %). Deep-red solid. (MALDI-TOF) found: 685.1945. $C_{38}H_{35}Cl_2N_2O_6$ requires 685.1872 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.68 – 1.72 (4H, m), 1.96 (4H, quintet, ^3J=6.4 Hz), 3.39 (4H, q, ^3J=6.1 Hz), 3.45-3.49 (4H, m), 3.55 (4H, t, ^3J=5.8 Hz), 6.99 (2H, dd, ^3J=7.7 Hz, ^4J=2.0 Hz), 7.44 – 7.52 (4H, m), 7.58 (2H, ^3J=7.3 Hz), 7.65 (2H, dd, ^3J=8.0 Hz, ^4J=1.1 Hz), 8.21 (2H, dd, ^3J=7.7 Hz, ^4J=1.4 Hz), 9.60 (2H, br.s).

*1,5-(Epiminoethanooxyethanooxyethanooxyethanoimino) anthracene-9,10-dione (**3b-r**)*. Obtained from 1,5-dichloroanthraquinone (**1**) (0.25 mmol, 69 mg) and trioxadiamine **2b** (0.25 mmol, 48 mg) in the presence of $Pd(dba)_2$ (16 mol%, 23 mg), *rac*-BINAP (18 mol%, 28 mg) and Cs_2CO_3 (1 mmol, 336 mg) in 12 ml absolute dioxane. Eluent: CH_2Cl_2/MeOH (200:1). Yield 27 mg (31 %). Deep-red crystalline powder, m.p. 235–237 °C. (MALDI-TOF) found: 397.1737. $C_{22}H_{25}N_2O_5$ requires 397.1764 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.47 (2H, ddd, ^2J=13.5 Hz, ^3J=8.1 Hz, ^3J=5.6 Hz), 2.78 (2H, ddd, ^2J=13.5 Hz, ^3J=9.2 Hz, ^3J=5.7 Hz), 2.98 (2H, ddd, ^2J=14.4 Hz, ^3J=9.1 Hz, ^3J=5.7 Hz), 3.04 (2H, ^2J=14.4 Hz, ^3J=9.1 Hz, ^3J=5.4 Hz), 3.27–3.34 (4H, m), 3.60-3.66 (2H, m), 3.71 – 3.80 (2H, m), 7.23 (2H, d, ^3J=8.2 Hz), 7.49 (2H, t, ^3J=8.0 Hz), 7.65 (2H, dd, ^3J=7.3 Hz, ^4J=0.9 Hz), 8.82 (2H, dd, ^3J=10.2 Hz, ^3J=2.5 Hz). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 45.1 (2C), 69.9 (2C), 70.2 (2C), 71.0 (2C), 116.7 (2C), 118.1 (2C), 122.6 (2C), 133.8 (2C), 135.8 (2C), 153.9 (2C), 185.6 (2C).

*5,5'-(2,2'-(2,2'-Oxybis(ethane-2,1-diyl)bis(oxy)) bis(ethane-2,1-diyl))bis(azanediyl)bis(1-chloroanthracene-9,10-dione) (**4b**)*. Obtained as the second product in the synthesis of compound **3b** from 1,5-dichloroanthraquinone (**1**) (2 mmol, 554 mg) and trioxadiamine **2b** (2 mmol, 384 mg) in the presence of $Pd(dba)_2$ (16 mol%, 184 mg), *rac*-BINAP (18 mol%, 224 mg) and Cs_2CO_3 (8 mmol, 2.688 g) in 100 ml absolute dioxane. Eluent: CH_2Cl_2/MeOH (200:1). Yield 31 mg (5 %). Deep-red solid. (MALDI-TOF) found: 673.1562. $C_{36}H_{31}Cl_2N_2O_7$ requires 673.1508 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 3.47 (4H, q, $^3J_{obs}$=5.0 Hz), 3.71 – 3.76 (8H, m), 3.79 (4H, t, ^3J=5.6 Hz), 6.92-6.96 (2H. m), 7.43 – 7.48 (4H, m), 7.54 (2H, t, ^3J=7.8 Hz), 7.63 (2H, dd, ^3J=7.8 Hz, ^4J=1.3 Hz), 8.19 (2H, dd, ^3J=7.8 Hz, ^4J=1.3 Hz), 9.65 (2H, br.s). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 42.7 (2C), 69.5 (2C), 70.8 (4C), 112.4 (2C), 116.0 (2C), 117.1 (2C), 126.1 (2C), 126.6 (2C), 129.2 (2C), 133.2 (2C), 134.4 (2C), 135.5 (2C), 136.3 (2C), 137.5 (2C), 151.2 (2C), 182.3 (2C), 183.1 (2C).

*1,5-(Epiminopropanooxyethanooxyethanooxypropanoimino) anthracene-9,10-dione (**3c-r**)*. Obtained from 1,5-dichloroanthraquinone (**1**) (0.5 mmol, 139 mg) and trioxadiamine **2c** (0.5 mmol, 110 mg) in the presence of $Pd(dba)_2$ (16 mol%, 46 mg), *rac*-BINAP (18 mol%, 56 mg) and Cs_2CO_3 (2 mmol, 672 mg) in 25 ml absolute dioxane. Eluent: CH_2Cl_2/MeOH (100:1). Yield 80 mg (38 %). NMR data are consistent with those described in literature.[16,19]

*1,5-(Epiminoethanooxyethanooxyethanooxyethanooxyethanoimino)anthracene-9,10-dione (**3d-r**)*. Obtained from 1,5-dichloroanthraquinone (**1**) (0.2 mmol, 55 mg) and tetraoxadiamine **2d** (0.2 mmol, 47 mg) in the presence of $Pd(dba)_2$ (16 mol%, 18 mg), *rac*-BINAP (18 mol%, 22 mg) and Cs_2CO_3 (0.8 mmol, 269 mg) in 10 ml absolute dioxane. Eluent: CH_2Cl_2/MeOH (200:1). Yield 32 mg (36 %). Deep-red crystalline powder, m.p. 105–107 °C. (MALDI-TOF) found: 441.2054. $C_{24}H_{29}N_2O_6$ requires 441.2026 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.79–2.84 (4H, m), 3.05 (2H, ddd, ^2J=10.9 Hz, ^3J=6.1 Hz, ^3J =3.9 Hz), 3.25 (2H, ddd, ^2J=10.9, ^3J=5.4, ^3J=4.3), 3.30-3.36 (2H, m), 3.37 – 3.48 (6H, m), 3.68 – 3.73 (2H, m), 3.81 – 3.90 (2H, m), 7.16 (2H, d, ^3J=8.5 Hz), 7.49 (2H, t, $^3J_{obs}$=7.8 Hz), 7.59 (2H, dd, ^3J=7.3 Hz, ^4J=1.0 Hz), 9.63 (2H, d, ^3J=7.1 Hz). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 44.3 (2C), 69.6 (2C), 70.1 (2C), 70.3 (2C), 71.1 (2C), 115.8 (2C), 120.6 (2C), 134.6 (2C), 150.7 (2C), 185.2 (2C).

*5,5'-(3,6,9,12-Tetraoxatetradecane-1,14-diylbis(azanediyl)) bis(1-chloroanthracene-9,10-dione) (**4d**)*. Obtained as the second product in the synthesis of compound **3d**. Eluent: CH_2Cl_2/MeOH (200:1). Yield 19 mg (26 %). Deep-red crystalline powder, m.p. 128–130 °C. (MALDI-TOF) found: 717.1839. $C_{38}H_{35}Cl_2N_2O_8$ requires 717.1771 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 3.49 (4H, q, ^3J=5.5 Hz), 3.70–3.73 (12H, m), 3.78 (4H, t, ^3J=5.5 Hz), 6.97–7.01 (2H, m), 7.47–7.51 (4H, m), 7.57 (2H, t, ^3J=7.8 Hz), 7.65 (2H, dd, ^3J=8.0 Hz, ^4J=1.4 Hz), 8.22 (2H, dd, ^3J=7.7 Hz, ^4J=1.4 Hz), 9.68 (2H, br. t, $^3J_{obs}$=4.7 Hz). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 42.7 (2C), 69.4 (2C), 70.6 (2C), 70.7 (4C), 112.3 (2C), 115.9 (2C), 117.1 (2C), 126.1 (2C), 126.5 (2C), 129.1 (2C), 133.2 (2C), 134.4 (2C), 135.5 (2C), 136.2 (2C), 137.4 (2C), 151.1 (2C), 182.2 (2C), 183.0 (2C).

*5,5'-(14,14'-(9,10-Dioxo-9,10-dihydroanthracene-1,5-diyl)bis(azanediyl)bis(3,6,9,12-tetraoxatetradecane-14,1-diyl)) bis(azanediyl)bis(1-chloroanthracene-9,10-dione) (**5d**)*. Obtained as the third product in the synthesis of compound **3d**. Eluent: CH_2Cl_2/MeOH (75:1). Yield 23 mg (30 %). Deep-red crystalline powder, m.p. 103 – 105 °C. (MALDI-TOF) found: 1157.35. $C_{62}H_{63}Cl_2N_4O_{14}$ requires 1157.37 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 3.43 – 3.48 (8H, m), 3.69 – 3.75 (24H, m), 3.76 (8H, t, ^3J=5.5 Hz), 6.86 (2H, d, ^3J=7.8 Hz), 6.93 – 6.98 (2H, m), 7.40 (2H, t, ^3J=7.8 Hz), 7.43 (2H, d, ^3J=7.3 Hz), 7.46 – 7.49 (4H, m), 7.50 (2H, t, ^3J=7.8 Hz), 7.64 (2H, dd, ^3J=8.0 Hz, ^4J=0.9 Hz), 8.21 (2H, dd, ^3J=7.7 Hz, ^4J=0.9 Hz), 9.65 (2H, br.t, $^3J_{obs}$=5.1 Hz), 9.71 (2H, br.t, $^3J_{obs}$=4.9 Hz). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 42.7 (2C), 42.8 (2C), 69.4 (2C), 69.5 (2C), 70.7 (4C), 70.8 (8C), 112.4 (2C), 115.1 (2C), 116.0 (2C), 116.4 (2C), 117.2 (2C), 118.3 (2C), 126.2 (2C), 126.8 (2C), 133.3 (2C), 133.4 (2C), 134.2 (2C), 135.0 (2C), 135.5 (2C), 136.1 (2C), 136.3 (2C), 137.5 (2C), 151.1 (2C), 151.3 (2C), 182.4 (2C), 183.1 (2C), 185.1 (2C).

*Typical procedure for the synthesis of N,N'-di(iodobenzyl) substituted macrocycles **6a-c** and **7a-c***. A flask equipped with a condenser and magnetic stirrer was charged with racemic macrocycles **3a-c** (0.2–2 mmol), 1-(bromomethyl)-3-iodobenzene or 1-(bromomethyl)-4-iodobenzene (0.4–4 mmol), potassium carbonate (0.8–8 mmol) and dry MeCN (1–6 ml) and the reaction mixture was refluxed for 24 h. After cooling the reaction mixture down to room temperature the precipitate was filtered off, washed with CH_2Cl_2, combined organic phases were evaporated *in vacuo*, and the solid residue was chromatographed on silica gel using a sequence of eluents: CH_2Cl_2, CH_2Cl_2/MeOH (500:1 – 50:1).

*Macrocycle **6a***. Obtained from 1-(bromomethyl)-4-iodobenzene (0.5 mmol, 149 mg) and macrocycle **3a-r** (0.25 mmol, 102 mg) in the presence of K_2CO_3 (1 mmol, 138 mg) in 1.5 ml dry acetonitrile. Eluent: CH_2Cl_2/MeOH (200:1).Yield 138 mg (66 %). Deep-red crystalline powder, m.p. 125–127 °C (MALDI-TOF) found: 841.0936. $C_{38}H_{39}I_2N_2O_4$ requires 841.0999 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 0.99–1.12 (4H, m), 1.66-1.73 (4H, m), 2.60–2.67 (2H, m), 2.98 – 3.03 (2H, m), 3.06–3.12 (2H, m), 3.25 – 3.33 (6H, m), 4.37 (2H, d, ^2J=15.4 Hz), 4.68 (2H, d, ^2J=15.4 Hz), 7.10 (2H, d, ^3J=8.5 Hz), 7.26 (4H, d, $^3J_{obs}$=8.0 Hz), 7.41 (2H, t, $^3J_{obs}$=7.9 Hz), 7.61 (4H, d, $^3J_{obs}$=8.0 Hz), 7.77 (2H, d, ^3J=7.5 Hz). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 27.1 (2C), 27.7 (2C), 52.4 (2C), 52.6 (2C), 66.4 (2C), 70.5 (2C), 92.4 (2C), 118.2 (2C), 122.2 (2C), 122.9 (2C), 129.8 (4C), 133.1 (2C), 137.3 (2C), 137.5 (4C), 137.8 (2C), 151.6 (2C), 182.1 (2C).

*Macrocycle **6b***. Obtained from 1-(bromomethyl)-4-iodobenzene (0.24 mmol, 72 mg) and macrocycle **3b-r** (0.12 mmol, 48 mg) in the presence of K_2CO_3 (0.5 mmol, 92 mg) in 1 ml dry acetonitrile. Eluent: CH_2Cl_2/MeOH (200:1).Yield 74 mg (74 %). Deep-red crystalline powder, m.p. 97–99 °C (MALDI-TOF) found: 829.0577. $C_{36}H_{35}I_2N_2O_5$ requires 829.0635 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.83 (2H, ddd, ^2J=13.9 Hz, ^3J=7.8 Hz, ^3J=5.2 Hz), 3.05–3.11 (4H, m), 3.12–3.19 (2H, m), 3.20–3.27 (4H, m), 3.53 (2H, td, ^3J=10.7 Hz, ^3J=3.8 Hz), 3.67–3.75 (2H, m), 4.42 (2H, d, ^2J=15.5 Hz), 4.73 (2H, d, ^2J=15.5 Hz), 7.21 (2H, d, ^3J=8.5 Hz), 7.24 (4H, d,^{3} J_{obs}=8.2 Hz), 7.48 (2H, t, $^3J_{obs}$=7.9 Hz), 7.66 (4H, d, $^3J_{obs}$=8.2 Hz), 7.78 (2H, d, ^3J=7.1 Hz). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 52.5 (2C), 56.4 (2C), 68.6 (2C), 69.9 (2C), 70.4 (2C), 92.5 (2C), 118.8 (2C), 123.4 (2C), 125.1 (2C), 129.7 (4C), 133.3 (2C), 137.2 (2C), 137.7 (4C), 137.8 (2C), 150.2 (2C), 183.6 (2C).

*Macrocycle **6c***. Obtained from 1-(bromomethyl)-4-iodobenzene (0.9 mmol, 271 mg) and macrocycle **3c-r** (0.46 mmol, 193 mg) in the presence of K_2CO_3 (1.8 mmol, 248 mg) in 3 ml dry acetonitrile. Eluent: CH_2Cl_2/MeOH (200:1). Yield 204 mg (54 %). Deep-red solid. (MALDI-TOF) found: 857.0882. $C_{38}H_{39}I_2N_2O_5$ requires 857.0948 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.62 – 1.69 (2H, m), 1.71–1.77 (2H, m), 2.80 – 2.85 (2H, m), 3.09 – 3.20 (8H, m), 3.25 – 3.35 (6H, m), 4.38 (2H, d, ^2J=15.4 Hz), 4.69 (2H, d, ^2J=15.4 Hz), 7.14 (2H, d, ^3J=8.3 Hz), 7.22 (4H, d, $^3J_{obs}$=8.0 Hz), 7.43 (2H, d, $^3J_{obs}$=7.8 Hz), 7.61 (4H, d, $^3J_{obs}$=8.0 Hz), 7.75 (2H, d, ^3J=7.5 Hz). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 27.7 (2C), 51.5 (2C), 53.3 (2C), 67.2 (2C), 70.8 (4C), 92.5 (2C), 118.4 (2C), 122.0 (2C), 123.5 (2C), 129.8 (4C), 133.2 (2C), 137.3 (2C), 137.5 (4C), 137.8 (2C), 151.4 (2C), 182.3 (2C).

*Macrocycle **7a***. Obtained from 1-(bromomethyl)-3-iodobenzene (2.02 mmol, 601 mg) and macrocycle **3a-r** (1.01 mmol, 414 mg) in the presence of K_2CO_3 (4.05 mmol, 559 mg) in 6 ml of dry acetonitrile. Eluent: CH_2Cl_2/MeOH (100:1). Yield 541 mg (64 %). Deep-red solid. (MALDI-TOF) found: 841.1057. $C_{38}H_{39}I_2N_2O_4$ requires 841.0999 $[M+H]^+$. ^1H NMR ($CDCl_3$, 298 K) δ_H ppm: 0.98–1.11 (4H, m), 1.66–1.73 (4H, m), 2.61–2.65 (2H, m), 2.99–3.04 (2H, m), 3.06 – 3.12 (2H, m), 3.27 – 3.35 (6H, m), 4.38 (2H, d, ^2J=15.5 Hz), 4.68 (2H, d, ^2J=15.5 Hz), 7.02 (2H, t, ^3J=7.8 Hz), 7.11

(2H, d, ^3J=8.3 Hz), 7.42 (2H, t, ^3J=7.9 Hz), 7.51-7.56 (4H, m), 7.79 (2H, d, ^3J=7.7 Hz), 7.80 (2H, br.s). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 27.1 (2C), 27.6 (2C), 52.4 (4C), 66.3 (2C), 70.4 (2C), 94.3 (2C), 118.3 (2C), 122.2 (2C), 122.9 (2C), 127.1 (2C), 130.4 (2C), 133.1 (2C), 136.1 (2C), 136.4 (2C), 137.8 (2C), 140.1 (2C), 151.4 (2C), 182.1 (2C).

Macrocycle ***7b***. Obtained from 1-(bromomethyl)-3-iodobenzene (0.24 mmol, 72 mg) and macrocycle **3b-r** (0.12 mmol, 48 mg) in the presence of K_2CO_3 (0.5 mmol, 92 mg) in 1 ml dry acetonitrile. Eluent: CH_2Cl_2/MeOH (200:1). Yield 72 mg (72 %). Deep-red solid. (MALDI-TOF) found: 829.0589. $C_{36}H_{35}I_2N_2O_5$ requires 829.0635 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 2.84 (2H, ddd, ^2J=13.0 Hz, ^3J=6.8 Hz, ^3J =4.9 Hz), 3.06–3.12 (4H, m), 3.13 – 3.30 (6H, m), 3.52 (2H, ddd, ^2J=10.7 Hz, ^3J=7.5 Hz, ^3J=3.7 Hz), 3.67 – 3.75 (2H, m), 4.44 (2H, d, ^2J=15.7 Hz), 4.73 (2H, d, ^2J=15.7 Hz), 7.08 (2H, t, ^3J=7.8 Hz), 7.22 (2H, d, ^3J=8.2 Hz), 7.41–7.45 (4H, m), 7.58 (2H, d, ^3J=7.8 Hz), 7.79–7.81 (4H, m). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 52.4 (2C), 56.5 (2C), 68.6 (2C), 69.9 (2C), 70.4 (2C), 94.5 (2C), 119.0 (2C), 123.6 (2C), 125.3 (2C), 127.0 (2C), 130.5 (2C), 133.3 (2C), 136.3 (2C), 136.5 (2C), 137.2 (2C), 140.7 (2C), 150.1 (2C), 183.7 (2C).

Macrocycle ***7c***. Obtained from 1-(bromomethyl)-3-iodobenzene (1.44 mmol, 428 mg) and macrocycle **3c-r** (0.72 mmol, 305 mg) in the presence of K_2CO_3 (2.88 mmol, 397 mg) in 3.5 ml dry acetonitrile. Eluent: CH_2Cl_2/MeOH (200:1). Yield 438 mg (71 %). Deep-red crystalline powder, m.p. 97–98 °C. (MALDI-TOF) found: 857.1023. $C_{38}H_{39}I_2N_2O_5$ requires 857.0948 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.63 – 1.80 (4H, m), 2.82–2.87 (2H, m), 3.10 – 3.21 (8H, m), 3.27 – 3.37 (6H, m), 4.40 (2H, d, ^2J=15.5 Hz), 4.71 (2H, d, ^2J=15.5 Hz), 7.03 (2H, t, ^3J=7.8 Hz), 7.16 (2H, d, ^3J=8.2 Hz), 7.45 (2H, t, ^2J=8.0 Hz), 7.50 (2H, d, ^2J=7.7 Hz), 7.54 (2H, d, ^2J=7.8 Hz), 7.77 – 7.79 (4H, m). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 27.7 (2C), 51.5 (2C), 53.2 (2C), 67.2 (2C), 70.8 (4C), 94.4 (2C), 118.6 (2C), 122.2 (2C), 123.7 (2C), 127.1 (2C), 130.4 (2C), 133.2 (2C), 136.2 (2C), 136.6 (2C), 137.9 (2C), 140.2 (2C), 151.4 (2C), 182.4 (2C).

Typical procedure for the synthesis of macrobicycles ***8-12***. A flask equipped with a condenser and magnetic stirrer was charged with *N,N'*-di(iodobenzyl) derivative **7a-c** (0.1–0.3 mmol), $Pd(dba)_2$ (16 mol%) and DavePhos (18 mol%). Then absolute dioxane (2.5-8 ml) and cesium carbonate (0.4–1.2 mmol, 4 equiv.) were added and the reaction mixture was refluxed for 30–40 h. After cooling the reaction mixture down to room temperature the precipitate was filtered off, washed with CH_2Cl_2, combined organic phases were evaporated *in vacuo*, and the solid residue was chromatographed on silica gel using a sequence of eluents: CH_2Cl_2, CH_2Cl_2/MeOH (200:1 – 3:1).

Macrobicycle ***8***. Obtained from compound **7a** (0.308 mmol, 259 mg) and trioxadiamine **2b** (0.308 mmol, 59 mg) in the presence of $Pd(dba)_2$ (16 mol%, 28 mg), DavePhos (18 mol%, 22 mg) and Cs_2CO_3 (1.232 mmol, 401 mg) in 8 ml absolute dioxane. Eluent: CH_2Cl_2/MeOH (50:1).Yield 12 mg (3 %). Deep-red solid. (MALDI-TOF) found: 777.4150. $C_{46}H_{57}N_4O_7$ requires 777.4227 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.69–1.77 (4H, m), 1.79 – 1.86 (4H, m), 2.60 – 2.66 (2H, m), 3.02 – 3.40 (26H, m), 4.46 (2H, d, ^2J=16.2 Hz), 4.68 (2H, d, ^2J=16.2 Hz), 6.39 (2H, dd, ^3J=7.8 Hz, ^4J=1.8 Hz), 6.62 (2H, d, ^3J=7.3 Hz), 6.91 (2H, br.s), 7.02 (2H, d, ^3J=8.5 Hz), 7.07 (2H, t, ^3J=7.8 Hz), 7.33 (2H, t, ^3J=8.0 Hz), 7.69 (2H, d, ^3J=7.5 Hz), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 27.2 (2C), 28.8 (2C), 41.8 (2C), 52.8 (2C), 53.2 (2C), 66.5 (2C), 69.7 (2C), 70.2 (2C), 70.5 (2C), 70.6 (2C), 111.5 (2C), 112.0 (2C), 116.0 (2C), 117.6 (2C), 122.9 (2C), 127.1 (2C), 128.7 (2C), 132.8 (2C), 137.8 (2C), 138.6 (2C), 149.1 (2C), 151.5 (2C), 182.2 (2C).

Macrobicycle ***9***. Obtained from compound **7a** (0.241 mmol, 180 mg) and trioxadiamine **2c** (0.241 mmol, 47 mg) in the presence of $Pd(dba)_2$ (16 mol%, 20 mg), DavePhos (18 mol%, 15 mg) and Cs_2CO_3 (0.8 mmol, 260 mg) in 5 ml absolute dioxane. Eluent: CH_2Cl_2/MeOH (50:1). Yield 9 mg (5 %). Deep-red solid. (MALDI-TOF) found: 805.4592. $C_{48}H_{61}N_4O_7$ requires 805.4540 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.60 – 1.84 (12H, m), 2.60 – 2.66 (2H, m), 3.01 – 3.14 (6H, m), 3.20 – 3.58 (20H, m), 4.41 (2H, d, ^2J=15.7 Hz), 4.68 (2H, d, ^2J=15.7 Hz), 6.40 (2H, dd, ^3J=7.7 Hz, ^4J=1.8 Hz), 6.60 (2H, d, ^3J=7.5 Hz), 6.93 (2H, br.s), 7.07 (2H, t, ^2J=7.6 Hz), 7.09 (2H, d, ^2J=8.2 Hz), 7.37 (2H, t, ^2J=8.0 Hz), 7.72 (2H, d, ^2J=7.6 Hz), two NH protons were not assigned.

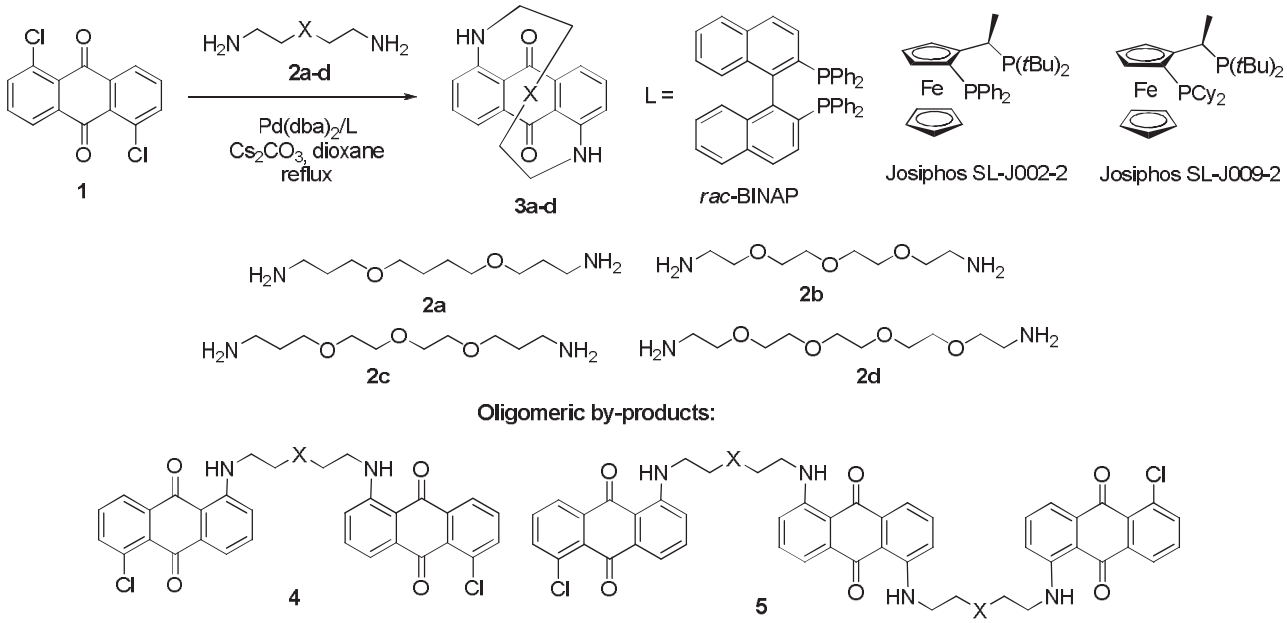
Macrobicycle ***10***. Obtained from compound **7c** (0.1 mmol, 79 mg) and dioxadiamine **2e** (0.1 mmol, 15 mg) in the presence of $Pd(dba)_2$ (16 mol%, 9 mg), DavePhos (18 mol%, 7 mg) and Cs_2CO_3 (0.4 mmol, 131 mg) in 2.5 ml absolute dioxane. Eluent: CH_2Cl_2/MeOH (50:1). Yield 21 mg (29 %). Deep-red crystalline powder, m.p. 121 – 122 °C (MALDI-TOF) found: 749.3987. $C_{44}H_{53}N_4O_7$ requires 749.3914 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.78–1.85 (2H, m), 1.86 – 1.95 (2H, m), 2.75–2.80 (2H, m), 3.00 – 3.28 (22H, m), 3.38 – 3.43 (4H, m), 4.47 (2H, d, ^2J=16.2 Hz), 4.73 (2H, d, ^2J=16.2 Hz), 6.36 (2H, dd, ^3J=8.0 Hz, ^4J=1.5 Hz), 6.61 (2H, d, ^3J=7.5 Hz), 6.83 (2H, br.s), 7.01–7.07 (4H, m), 7.32 (2H, t, ^3J=8.0 Hz), 7.68 (2H, d, ^3J=7.3 Hz), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 28.9 (2C), 43.3 (2C), 53.0 (2C), 53.8 (2C), 67.2 (2C), 68.7 (2C), 69.9 (2C), 71.1 (2C), 71.2 (2C), 111.4 (2C), 112.8 (2C), 116.6 (2C), 117.8 (2C), 123.8 (2C), 127.9 (2C), 128.7 (2C), 132.7 (2C), 137.8 (2C), 138.8 (2C), 148.5 (2C), 150.8 (2C), 182.4 (2C).

Macrobicycle ***11***. Obtained from compound **7c** (0.1 mmol, 79 mg) and dioxadiamine **2a** (0.1 mmol, 21 mg) in the presence of $Pd(dba)_2$ (16 mol%, 9 mg), DavePhos (18 mol%, 7 mg) and Cs_2CO_3 (0.4 mmol, 131 mg) in 2.5 ml absolute dioxane. Eluent: CH_2Cl_2/MeOH (50:1).Yield 19 mg (24 %). Deep-red crystalline powder, m.p. 123-124 °C (MALDI-TOF) found: 805.4453. $C_{48}H_{61}N_4O_7$ requires 805.4540 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.62-1.90 (12H, m), 2.82–2.88 (2H, m), 3.05–3.24 (14H, m), 3.28 (4H, t, ^3J=6.0 Hz), 3.32–3.46 (8H, m), 4.41 (2H, d, ^2J=15.5 Hz), 4.71 (2H, d, ^2J=15.5 Hz), 6.42 (2H, dd, ^3J=7.9 Hz, ^4J=1.5 Hz), 6.59 (2H, d, ^3J=7.3 Hz), 6.90 (2H, br.s), 7.08 (2H, t, ^3J=7.8 Hz), 7.15 (2H, d, ^3J=8.4 Hz), 7.41 (2H, t, ^3J=7.9 Hz), 7.71 (2H, d, ^3J=7.4 Hz), two NH protons were not assigned. ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 26.1 (2C), 28.1 (2C), 28.8 (2C), 42.1 (2C), 51.9 (2C), 53.4 (2C), 67.3 (2C), 69.6 (2C), 70.5 (2C), 70.8 (4C), 112.0 (2C), 112.7 (2C), 116.9 (2C), 117.8 (2C), 123.4 (2C), 128.9 (2C), 133.0 (2C), 137.9 (2C), 138.6 (2C), 148.6 (2C), 151.6 (2C), 182.5 (2C), two quaternary carbon atoms were not assigned.

Macrobicycle **12**. Obtained from compound **7c** (0.1 mmol, 79 mg) and trioxadiamine **2c** (0.1 mmol, 22 mg) in the presence of $Pd(dba)_2$ (16 mol%, 9 mg), DavePhos (18 mol%, 7 mg) and Cs_2CO_3 (0.4 mmol, 131 mg) in 2.5 ml absolute dioxane. Eluent: CH_2Cl_2/MeOH (50:1).Yield 26 mg (32 %). Deep-red crystalline powder, m.p. 116–118 °C (MALDI-TOF) found: 821.4436. $C_{48}H_{61}N_4O_8$ requires 821.4489 $[M+H]^+$. ^{1}H NMR ($CDCl_3$, 298 K) δ_H ppm: 1.68-1.92 (8H, m), 2.80–2.85 (2H, m), 3.07 – 3.22 (10H, m), 3.24–3.44 (16H, m), 4.39 (2H, d, ^2J=15.5 Hz), 4.70 (2H, d, ^2J=15.5 Hz), 6.40 (2H, dd, ^3J=7.8 Hz, ^4J=1.5 Hz), 6.59 (2H, d, ^3J=7.3 Hz), 6.87 (2H, br.s), 7.06 (2H, t, ^3J=7.7 Hz), 7.14 (2H, d, ^3J=8.6 Hz), 7.39 (2H, t, ^3J=7.9 Hz), 7.70 (2H, d, ^3J=7.3 Hz). ^{13}C NMR ($CDCl_3$, 298 K) δ_C ppm: 28.2 (2C), 28.8 (2C), 41.8 (2C), 52.2 (2C), 53.5 (2C), 67.3 (2C), 69.7 (2C), 70.2 (2C), 70.5 (4C), 111.5 (2C), 112.1 (2C), 116.2 (2C), 117.8 (2C), 123.5 (2C), 127.5 (2C), 128.8 (2C), 132.9 (2C), 138.0 (2C), 138.6 (2C), 149.1 (2C), 151.5 (2C), 182.5 (2C).

Results and Discussion

At the first step we synthesized 4 planar-chiral macrocycles **3a-d** by the reaction of 1,5-dichloroanthraquinone (**1**) with dioxadiamine **2a** and trioxadiamines **2b-d** differing by the chain length (13–16 atoms) and the number of oxygen



Scheme 1.

Table 1. Synthesis of macrocyclic compounds **3a-d**.

Entry	Amine	Ligand	[Pd]/L, mol%	Product[a)]	Yield, %[b)]	Enantiomeric excess, %
1	**2a**	*rac*-BINAP	8/9	**3a-r**	45	
2[c)]	**2a**	Josiphos SL-J002-2	8/9	**3a-ee**	31	60
3[d)]	**2b**	*rac*-BINAP	16/18	**3b-r**	31	
4	**2b**	Josiphos SL-J002-2	16/18	**3b-ee**	25	55
5	**2b**	Josiphos SL-J009-2	16/18	**3b-ee**	12	30
6	**2c**	*rac*-BINAP	16/18	**3c-r**	38	
7	**2c**	*rac*-BINAP	8/9	**3c-r**	36	
8	**2c**	Josiphos SL-J002-2	8/9	**3c-ee**	18	66
9	**2c**	Josiphos SL-J002-2	16/18	**3c-ee**	27	58
10	**2d**	*rac*-BINAP	16/18	**3d-r** **4d** **5d**	36 26 30	
11	**2d**	Josiphos SL-J002-2	16/18	**3d-ee**	13	34

[a)] "r" after the macrocycle's number denotes "racemic", "ee" denotes "enantiomerically enriched";
[b)] After column chromatography;
[c)] In the scaled-up reaction with 3 mmol of **1** and **2a** compound **4a** was isolated in 12% yield;
[d)] In the scaled-up reaction with 2 mmol of **1** and **2b** compound **4b** was isolated in 5% yield.

atoms. The macrocyclization was catalyzed by $Pd(dba)_2$/*rac*-BINAP to form racemic mixtures of the macrocycles **3** or by $Pd(dba)_2$/Josiphos SL-J002-2 which was found out by us previously to be the best for ensuring the enantiomeric induction in such processes.[16] The reactions were run in boiling dioxane in the presence of Cs_2CO_3 as base for 30–40 h using 0.02 M concentration of the reagents (Scheme 1). Usually the reactions were first run with 0.2–0.25 mmol of starting compounds and in the case of success they were scaled up to 2–3 mmol of the starting reagents. The results of the experiments are summarized in Table 1.

It is clearly seen that the outcome of the macrocyclization processes in the majority of cases do not differ much for oxadiamines under investigation. The chemical yields of compounds **3a-r – 3d-r** ranged from 31 to 45 % when using *rac*-BINAP ligand (entries 1, 3, 6, 7, 10) what is a good result for a such type of the catalytic processes, with oxadiamines **2a,c** the possibility of the application of 8 mol% catalytic system instead of 16 mol% was demonstrated (entries 1, 7). The macrocyclization with oxadiamine **2a** in the presence of Josiphos SL-J002-2 ligand (8/9 mol% catalytic system) was quite successful as it produced the macrocycle **3a-ee** also in

a good yield and with 60 % enantiomeric excess (entry 2). In the scaled-up reaction with 3 mmol of **1** and **2a** a linear diaryl derivative **4a** was isolated in 12 % yield. The macrocyclization with trioxadiamine **2b** was carried out using 16/18 mol% of the catalytic systems $Pd(dba)_2$/*rac*-BINAP or $Pd(dba)_2$/Josiphos SL-J002-2, the first system provided 31 % yield of the target compound **3b-ee** (entry 3) while with the second one the yield was slightly smaller and enantiomeric excess reached 55 % (entry 4). Again, scaling up the synthesis allowed the isolation of a linear diaryl derivative **4b**. It is noteworthy that the application of another chiral ligand with more electron-rich substituents at the phosphorus atom, namely Josiphos SL-J009-2, provided both poorer chemical and optical yields of the macrocycle (entry 5). Note that the macrocyclization with trioxadiamine **2c** in the presence of $Pd(dba)_2$/Josiphos SL-J002-2 (8/9 mol%) gave smaller yield of the product (18 %) but provided higher enantioselectivity (66 %) compared to the result with 16/18 mol% of the same catalytic system (entries 8, 9). The reaction with the longest tetraoxadiamine **2d** was quite successful with *rac*-BINAP as a ligand (entry 10) and not only the target macrocycle **3d-r** but also linear oligomers **4d** and **5d** were isolated, but the result with chiral ligand was more modest and enantioselectivity reached only 34 % (entry 11). Our new results notably surpass those reported in the ref.[19] where the yields of the macrocycles **3a**,**c** were 30 and 28 %, respectively, in the presence of the same catalytic systems.

In the case of the macrocycles **3a-ee**, **3c-ee** it is possible to isolate individual isomers by crystallization and in the case of compound **3b-ee**, on contrary, crystallization gave pure racemate and the mother liquor was enriched with the major isomer. The same was true for the macrocycle **3d-ee** possessing the longest tetraoxadiamine chain.

In ^{1}H NMR spectra of the macrocycles **3a-d** protons in all CH_2 groups are inequivalent what leads to complex multiplets, moreover, the protons of all methylene groups except CH_2N are shifted more or less upfield due to their

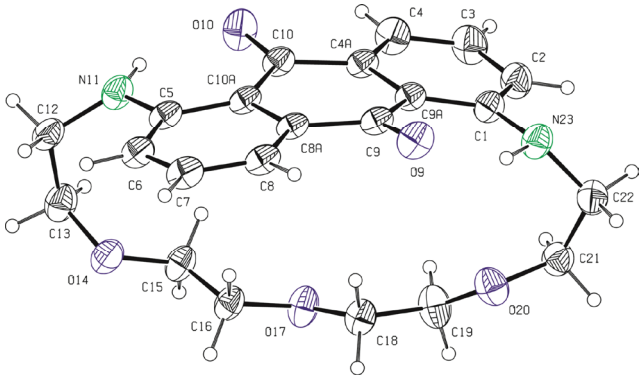
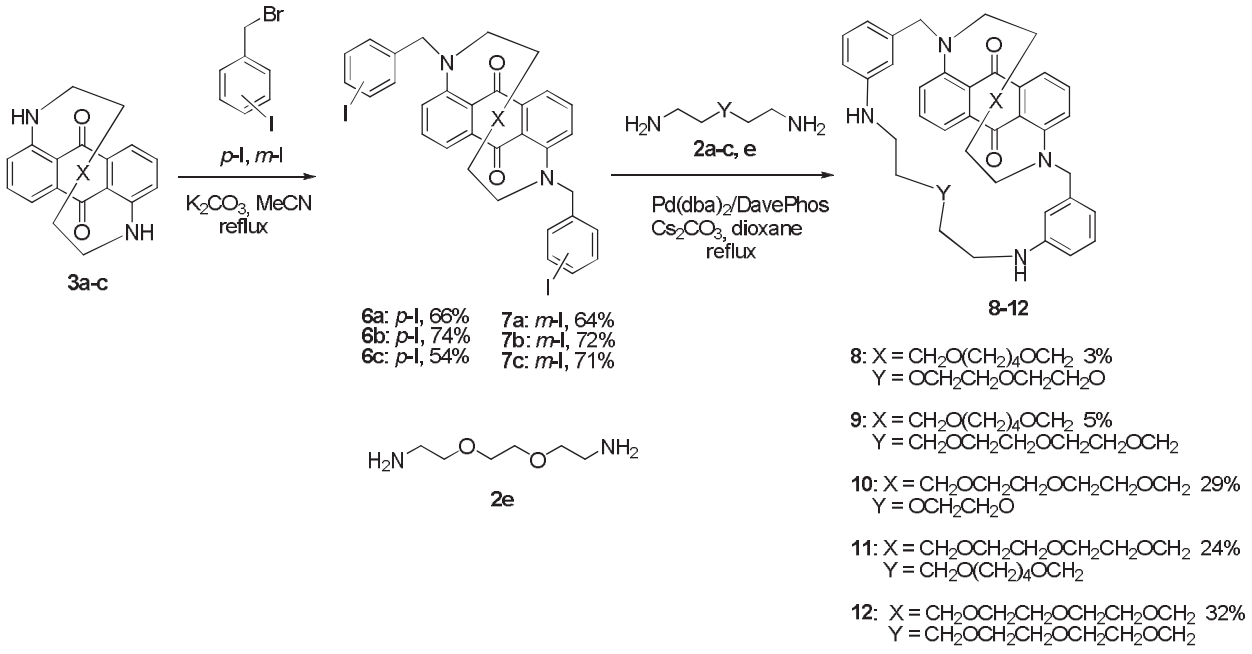


Figure 1. Molecular structure of the macrocycle **3b**.

position above the aromatic rings. On contrary, carbon atoms have usual chemical shifts. We carried out the X-Ray analysis of the compound **3b** (racemate), the molecular structure is given in Figure 1. This compound crystallizes as deep-red prisms in a triclinic symmetry space group, each cell containing two opposite enantiomers.

At the next step we modified the macrocycles **3a-r**–**3c-r** with two iodobenzyl substituents in view of the further macrocyclization of these compounds. The reactions were conducted using 2 equiv. of *para*- and *meta*-iodobenzyl bromides in boiling MeCN with K_2CO_3 as a base, the target derivatives **6a-c** and **7a-c** were obtained after chromatographic purification in 54–74 % and 64–72 % yields, respectively (Scheme 2). Macrocycles substituted with iodobenzyl groups were synthesized in order to favor their Pd(0)-catalyzed amination in the presence of a weak base, Cs_2CO_3, because anthraquinone moiety does not tolerate stronger sodium *tert*-butoxide and iodine is more active than bromine in the catalytic amination reactions.

Catalytic transformation of compounds **6** and **7** into macrobicyclic compounds with oxadiamines **2a-c** and



Scheme 2.

2e was carried out using the catalytic system $Pd(dba)_2$/DavePhos, this electron-donor phosphine ligand is known to provide amination with weak bases better than *rac*-BINAP.[20] It was found that only some pairs of the reagents gave target compounds: bis(4-iodobenzyl) derivatives **6a-c** did not provide corresponding products of macrocyclization at all but rather produced only linear oligomers and the products of the catalytic reduction of C-I bonds and debenzylation in the starting reagents **6a-c**. These compounds were not isolated in pure state but were analyzed as fractioned mixtures by ^{1}H NMR and mass spectrometry. Better results were obtained with bis(3-iodobenzyl) derivatives: compound **7a** gave the target macrobicycle **8** with trioxadiamine **2b**, though in a very low yield (3 %), the yield of the macrobicycle **9** in the reaction with another trioxadiamine **2c** was also small (5 %). The rest in both reaction mixtures was composed of the reduction products and oligomers. However, the compound **7c** was much more active and gave macrobicycles **10**–**12** with oxadiamines **2a**,**c**,**e** in yields 24–32 % which are quite good for the macrocyclization reactions especially with such a weak base as Cs_2CO_3. Unfortunately, derivative **7b** did not afford macrobicycles but rather produced linear oligomers and the products of reduction. We suppose that such difference in the reactivity of bis(iodobenzyl) substituted macrocycles may be due to different orientation of the iodine atoms caused by the difference in the geometry of the substituents around nitrogen atoms. The analysis of the molecular structures of the macrocycles **3a-c** demonstrates that the oxadiamine chains of various length cause different cycle strain resulting in the arrangement of the substituents at the nitrogen atoms which is probably translated to mutual orientation of two iodine atoms which favors or disfavors intramolecular cyclization. ^{1}H NMR spectra of compounds **6**, **7** and **8**–**12** are characterized by the inequivalence of CH_2 protons in benzyl substituents (spacers). The protons in methylene groups of the second chain in macrobicycles **8**–**12** are also inequivalent, thus aliphatic protons in these compounds present a complex set of multiplets.

Conclusions

To sum up, we synthesized several nitrogen- and oxygen-containing macrocycles based on 1,5-disubstituted anthraquinone in yields up to 45 % with enantioselective excess up to 66 %, and using these molecules as a platform we obtained the first representatives of the macrobicycles containing planar-chiral central fragment by means of Pd(0)-catalyzed amination, and demonstrated the dramatic dependence of the result of the macrocyclization on the structures of starting bis(iodobenzyl) derivatives and oxadiamines. The investigations of the binding properties of synthesized macrobicycles are underway now.

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