Efficient Synthesis of New Macrocycles with Planar Chirality

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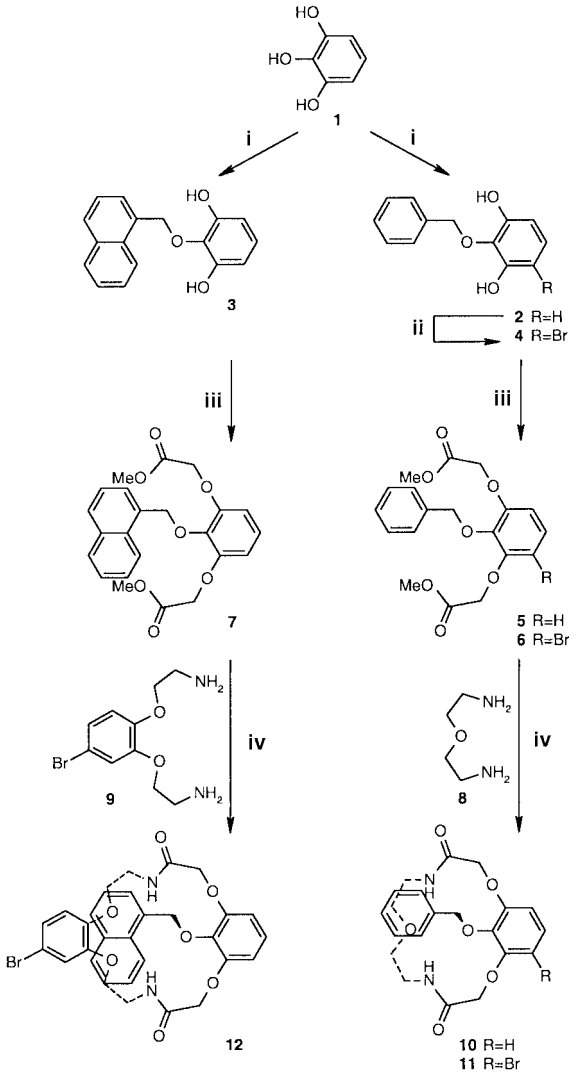
Abstract: Two new macrocycles possessing planar chirality were efficiently synthesized and resolved into enantiomers employing HPLC. CD spectra of **11** and **12** confirm their enantiomeric relationship and chiral stability.

Key words: amides, macrocycles, synthesis, supramolecular chemistry, enantiomeric resolution

The element of planar chirality plays an important role in many modern ligand systems.[1,2] The majority of planar chiral ligands are based on ferrocene[3] derivatives or arene-transition metal complexes.[4] There are, however, relatively few examples in the literature on the use of planar chiral cyclophane-based ligands in catalytic asymmetric processes,[5] despite the fact that the parent 1,12-dioxa[12]paracyclophane (the first chiral 'ansa' compound) was first synthesized and resolved into enantiomers in the 1940s.[6,7]

In our communication we present the synthesis of two macrocycles with planar chirality based on chiral systems similar to those of metacyclophanes.[8] There are some advantages of our approach compared to [2.2]metacyclophanes. Macrocyclic amides can interact with cations via ethereal oxygen atoms or with anions via amide groups.[9] In our compounds, as an intraannular group, we introduced an additional ethereal group which could play an important role in the interactions with cations and in increasing the preparation yield. For the preparation of compounds **11** and **12**, as well as their analogs, we planned to apply the double-amidation reaction, developed recently in our laboratory.[10] In this reaction, dimethyl α,ω-dicarboxylates react with primary α,ω-diamines in the presence of MeO^- under ambient conditions (MeOH as solvent, r.t., several hours, reagent concentration of 0.1 mol dm^{-3}) to afford macrocyclic diamides in good to excellent yields. Thus, the initial stage of the synthesis is the preparation of appropriate dimethyl dicarboxylates and α,ω-diamines.[11] O-Alkylation of pyrogallol **1** with BnBr or $NaphCH_2Cl$ afforded the corresponding compounds **2**[12] and **3** in 33% and 20% yields, respectively. Subsequently, the benzyl derivative **2** was reacted with NBS to give compound **4**. The 1,3-dihydroxy derivatives **2–4** were subjected to reaction with methyl bromoacetate to give the corresponding dimethyl dicarboxylates **5–7**, respectively. Compound **5** was then examined in a model reaction with diamino ether **8**, affording macrocyclic compound **10**[13] in good (60%) isolated yield (Scheme 1). Analogous compounds lacking such an intraannular group were synthesized in 16% yield.[14] This clearly proved our assumption that an intraannular ethereal group significantly increases the yield of macrocyclization.

Further examination of molecular models of **11** shows that the macro-ring and the benzyl group are located in differ-



Scheme 1 Reagents and conditions: i) NaH, $PhCH_2Br$ or $NaphCH_2Cl$, DMF; ii) NBS, SiO_2, CCl_4; iii) methyl bromoacetate, K_2CO_3, 2-butanone; iv) Na, MeOH, r.t.

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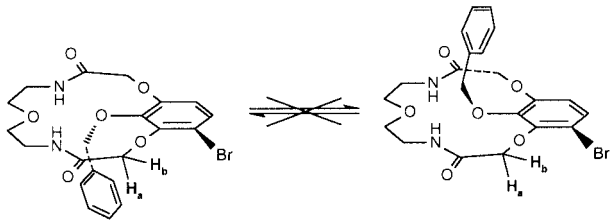
ent faces of the aromatic plane because the macro-ring is too small to accommodate the intraannular group (Scheme 2). If we introduce an asymmetric group in such a macrocyclic compound, the right and left sides will be different, and the substance will show chiral properties.



Scheme 2 Molecular model of **11**

In order to verify this assumption, we carried out a temperature-dependent ^{1}H NMR experiment of **10**, which showed AB-type splitting for the isolated methylene group. Even at 373 K, the benzyl group cannot pass through the macro-ring plane. In order to introduce an element of planar chirality, we carried out an analogous reaction of dimethyl dicarboxylates **6** with diamino ether **8** which gave the desired compounds **11**[15] in good yield (72%). The size of the macrocyclic cavity plays an important role in intermolecular interactions, especially in cation binding. To synthesize a macrocyclic compound possessing a larger macro-ring, we reacted dimethyl dicarboxylate **7** with diamino ether **9**.[16] In the case of compound **12**, the yield was not as satisfactory as it was for macrocyclic diamides **10** and **11**. This is probably due to the steric hindrance of the naphthyl group. Racemic compounds **11** and **12**[17] were successfully resolved into enantiomers by analytical HPLC on chiral stationary phase (Chiralcel OD-H®).[18] The separation factors α were found to be 1.10 and 1.13, respectively, and high enough to allow a semi-preparative resolution. The pure enantiomers of compounds **11** and **12** were subjected to CD experiments[19] (Figure 1 and Table 1).

It is noteworthy that the MeCN solutions of (–)**11**, (+)**11**, (–)**12**, and (+)**12** retained their enantiomeric purity for at least three months at room temperature and even extended

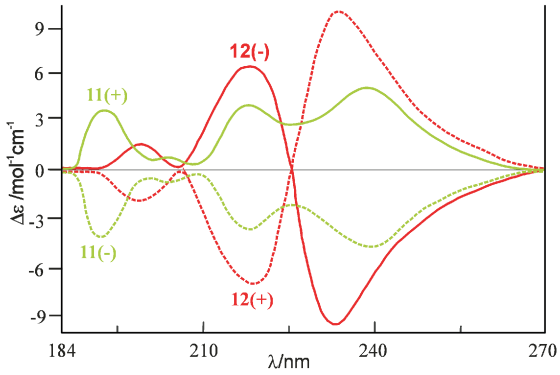


Figure 1 CD spectra of the enantiomers **11** and **12** in MeCN

Table 1 CD Data for **11** and **12**

Compounds	CD spectral data ($\lambda_{ext.}$)
(+)11	192.5 (Δε +3.8), 218.0 (Δε +4.2), 238.5 (Δε +5.3)
(-)11	192.5 (Δε –4.1), 218.0 (Δε –3.6), 238.5 (Δε –4.7)
(+)12	200.5 (Δε –1.9), 220.0 (Δε –6.9), 234.5 (Δε +10.2)
(-)12	199.5 (Δε +1.5), 219.0 (Δε +6.5), 234.5 (Δε –9.4)

boiling of solutions in MeCN for 20 hours caused no racemization.

In summary, we have demonstrated that *O*-benzyl or *O*-methylenenaphthyl substituted macrocyclic diamides can be synthesized in excellent yields and resolved into enantiomers. These products are stable towards racemization. Such compounds, possessing planar chirality, could serve as chiral ligands for the inclusion complexes, especially for cationic guests.

Acknowledgment

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(11) **General Procedure for Synthesis of Macrocyclic Compounds 10–12**: To a mixture of appropriate ester (5 mmol) and appropriate amine (5 mmol) in anhyd MeOH (60 mL) was added solution of MeONa (12.5 mmol) in anhyd MeOH (50 mL). The mixture was left at r.t. for several hours (monitored by TLC). The solvent was evaporated and the residue was purified by column chromatography.

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(13) **19-Benzyloxy-2,8,14-trioxa-5,11-diaza-bicyclo[13.3.1]nonadeca-1 (18),15 (19),16-triene-4,12-dione (10)**. Purified by column chromatography (silica gel, EtOAc) to give **10** (60%) as a white solid; mp 183.9–184.5 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.82–7.76 (m, 2 H, NHCO), 7.60 (d, *J* = 7.0 Hz, 2 H), 7.48 (t, *J* = 7.0 Hz, 2 H), 7.43–7.39 (m, 1 H), 7.16 (dd, J_1 = 1.9 Hz, J_2 = 7.3 Hz, 1 H), 7.09 (d, *J* = 7.8 Hz, 2 H), 5.04 (s, 2 H, CH_2Ph), 4.76 (d_{AB}, *J* = 16.5 Hz, 2 H, CH_2CO), 4.69 (d_{AB}, *J* = 16.5 Hz, 2 H, CH_2CO), 3.52–3.43 (m, 2 H), 3.12–3.05 (m, 4 H), 2.87–2.82 (m, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 167.9, 152.7, 139.4, 136.1, 128.8, 128.7, 128.6, 128.5, 125.9, 125.7, 113.4, 113.2, 76.7, 71.3, 68.4, 38.6. HR–ESI (MeOH): *m/z* [M + Na]$^+$ calcd for $C_{21}H_{24}N_2O_6$Na: 423.1532; found: 423.1542. Anal. Calcd for $C_{21}H_{24}N_2O_6$: C, 63.00; H, 6.00; N, 7.00. Found: C, 63.10; H, 6.01; N, 7.06.

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(15) **19-Benzyloxy-18-bromo-2,8,14-trioxa-5,11-diaza-bicyclo[13.3.1]nonadeca-1 (18),15 (19),16-triene-4,12-dione (11)**. Purified by column chromatography (silica gel, EtOAc) to give **11** (1720 mg, 72%) as a white solid; mp 172.6–173.6 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.59–8.53 (br d, 1 H, NHCO), 7.99–7.93 (br d, 1 H, NHCO), 7.58–7.54 (m, 2 H), 7.46–7.41 (m, 3 H), 7.37 (d, *J* = 9 Hz, 1 H), 6.81 (d, *J* = 9 Hz, 1 H), 5.06 (d_{AB}, *J* = 9.5 Hz, CH_2Ph, 1 H), 4.99 (d_{AB}, *J* = 9.5, CH_2Ph, 1 H), 4.89 (d_{A1B1}, *J* = 16.5, CH_2CO, 1 H), 4.82 (d_{A2B2}, *J* = 16.1 Hz, CH_2CO, 1 H), 4.63 (d_{A1B1}, *J* = 16.5 Hz, CH_2CO, 1 H), 4.52 (d_{A2B2}, *J* = 16.1 Hz, CH_2CO), 3.80–3.71 (m, 2 H), 3.19–3.10 (m, 3 H), 3.04–2.99 (m, 1 H), 2.96–2.88 (m, 1 H), 2.64–2.57 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.5, 168.1, 153.0, 151.3, 142.5, 134.9, 130.2, 129.8, 129.3, 128.8, 115.5, 109.1, 78.5, 73.8, 72.5, 69.3, 69.1, 38.9, 38.8. HR–ESI (MeOH): *m/z* [M + Na]$^+$ calcd for $C_{21}H_{23}N_2O_6{}^{79}$BrNa: 501.0632; found: 501.0646. Anal. Calcd for $C_{21}H_{23}N_2O_6$Br: C, 52.62; H, 4.84; N, 5.84; Br, 16.67. Found: C, 52.49; H, 4.93; N, 5.63; Br, 16.52.

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(17) **11-Bromo-26-(1-naphthylmethoxy)-2,8,15,21-tetraoxa-5,18-diaza-tricyclo[20.3.1.0*9,14*]hexacosa-1 (25),9 (14),10,12,22 (26),23-hexaene-4,19-dione (12)**. Purified by column chromatography (silica gel, EtOAc) to give **12** (465 mg, 15%) as white solid; mp 166.5–167.8 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.30–8.26 (m, 1 H), 7.98–7.93 (m, 2 H, NHCO), 7.85–7.80 (m, 1 H), 7.74–7.67 (m, 2 H), 7.52–7.47 (m, 2 H), 7.35–7.30 (m, 1 H), 7.13 (t, 1 H, *J* = 8.4), 6.89 (dd, 1 H, J_1 = 8.6 Hz, J_2 = 2.2 Hz), 6.79–6.74 (m, 2 H), 6.55 (d, 1 H, *J* = 2.2 Hz), 6.36 (d, 1 H, *J* = 8.6 Hz), 5.47 (s, 2 H, CH_2Naph), 4.79 (dd_{AB}, J_1 = 8.2 Hz, J_2 = 15.6 Hz, 2 H, CH_2CO), 4.58 (d_{AB}, *J* = 15.6 Hz, 2 H, CH_2CO), 3.90–3.80 (m, 2 H), 3.71–3.65 (m, 1 H), 3.62–3.52 (m, 3 H), 3.38–3.30 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.7, 168.6, 153.4, 153.3, 148.3, 146.8, 139.3, 133.5, 132.0, 131.5, 129.5, 128.9, 127.1, 126.4, 125.8, 125.7, 125.1, 123.4, 123.2, 115.4, 112.9, 112.7, 111.2, 111.0, 74.2, 70.9, 70.7, 67.3, 67.2, 38.6, 38.5. HR–ESI (MeOH): *m/z* [M + Na]$^+$ calcd for $C_{31}H_{29}N_2O_7{}^{79}$BrNa: 643.1050, found: 643.1039. Anal. Calcd for $C_{31}H_{29}N_2O_7$Br: C, 59.91; H, 4.70; N, 4.51; Br, 12.86. Found: C, 60.01; H, 4.84; N, 4.38; Br, 12.74.

(18) HPLC analyses for **11** and **12**. Column: Chiralcel OD-H®, length 250 mm; i.d. 4.6 mm. For **11**: *i*-PrOH–hexane, 3:1; flow rate 0.7 mL/min.; λ = 254 nm. For **12**: *i*-PrOH–hexane, 1:1; flow rate 1.1 mL/min.; λ = 254 nm. Enantiomeric purities obtained: **(+)11**: 93% ee, $[\alpha]_D{}^{26}$ = +61.8 (*c* = 0.56, $CHCl_3$); **(–)11**: 88% ee, $[\alpha]_D{}^{26}$ –59.3 (*c* = 0.55, $CHCl_3$); **(+)12**: 99% ee, $[\alpha]_D{}^{26}$ = +18.9 (*c* = 0.37, $CHCl_3$); **(–)12**: 94% ee, $[\alpha]_D{}^{26}$ –17.9 (*c* = 0.37, $CHCl_3$).

(19) CD experiments were measured in MeCN in a 0.1 cm cell at 24 °C.