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Novel synthesis of macrocycles with 1,1′-binaphthalene-2,2′-diol using intramolecular oxidative coupling

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Abstract—A new series of BINOL-based macrocycles with two phenolic protons have been synthesized via oxidative coupling reaction using CuCl(OH)–TMEDA.

Macrocycles containing hydrogen bonding sites have attracted much attention due to their complexing ability toward ions or molecules.[1] 1,1′-Binaphthol (BINOL)-based macrocycles possess an excellent ability of chiral recognition, which has been applied to chiral stationary phases for HPLC.[2] It has been expected that macrocycles with a 1,1′-binaphthalene-2,2′-diol moiety have superior chiral recognition ability compared with the established BINOL-based chiral macrocycles, because their two phenolic protons can interact with chiral molecules by hydrogen bonding. Cram and co-workers synthesized macrocycles having a 1,1′-binaphthalene-2,2′-diol unit from 1,1′-binaphthalene-2,2′-diol derivative and oligothioethers.[3] Kellogg and co-worker synthesized their analogues of α,ω-bis(hydroxynaphthyl)oligoethers by intramolecular oxidative coupling using $FeCl_3$, $K_3Fe(CN)_6$ and $Cu(II)(RNH_2)_4$ as oxidants, although the starting materials were recovered.[4] In our laboratory, various macrocyclic compounds with plural phenolic protons have been synthesized via tandem Claisen rearrangement. These macrocycles recognized ions or molecules effectively.[5] Macrocycles with a chiral 1,1′-bi-4,5,6,7-tetrahydroxynaphthalene-2,2′-diol have been synthesized from macrocyclic bis(allylic ether)s by Lewis acid-mediated tandem Claisen rearrangement.[6] However, the synthesis of macrocycles with 1,1′-binaphthalene-2,2′-diol-based macrocycles has been limited in this synthetic strategy, because of difficulty in optimizing tandem Claisen rearrangement using precursor macrocycles. We report here the novel synthesis of macrocycles bearing the 1,1′-binaphthalene-2,2′-diol unit, **1** and **2**, by intramolecular oxidative coupling reaction of α,ω-bis(hydroxynaphthyl)oligoethers using CuCl(OH)–TMEDA as oxidant.[7]

Schemes 1 and 2 show synthesis of the target 1,1′-binaphthalene-2,2′-diol-based macrocycles bearing phenolic protons **1a–c** and **2a–c**. Catechol was reacted with 2-(2-chloroethoxy)ethanol, 2-(2-(2-chloroethoxy)-ethoxy)ethanol, and 2-(2-(2-(2-ethoxy)ethoxy)ethoxy)-ethanol monotosylate in the presence of NaOH to give diols **3a–c** in good yields (50–70%), respectively. Ditosylates **4a–c** and **7a–c** were obtained by reaction of *p*-toluenesulfonylchloride with **3a–c** and oligoethyleneglycols ($n = 1, 2, 3$), respectively, in excellent yields (82–96%). Ditosylates **4a–c** and **7a–c** were converted to the corresponding diiodides **5a–c** and **8a–c** with excess NaI in acetone, respectively (81–93%).[8]

Chain compounds **6a–c** and **9a–c** were obtained by etherification between the polyether diiodides **5a–c**, **8a–c** and 2,3-dihydroxynaphthalene derivative **10** in 60–70% yield, followed by deprotection of THP. Mono-THP-protected 2,3-dihydroxynaphthalene **10** was prepared from 2,3-dihydroxynaphthalene in two steps as previously reported.[9] The target macrocycles **1a–c** and **2a–c** were then obtained as racemic mixtures by oxidative coupling reaction under high dilution (1.0 mmol/100 ml) using CuCl(OH)–TMEDA in acceptable yield (18–32%), and their cyclic oligomers (dimer,

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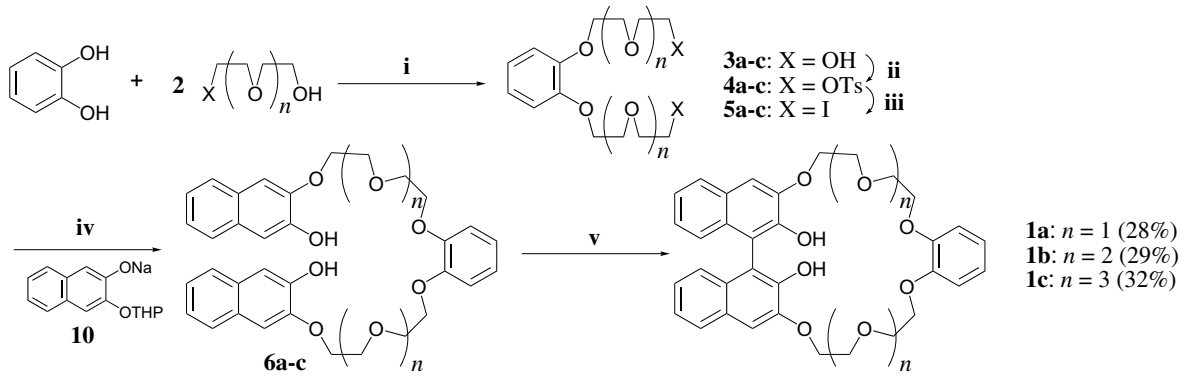
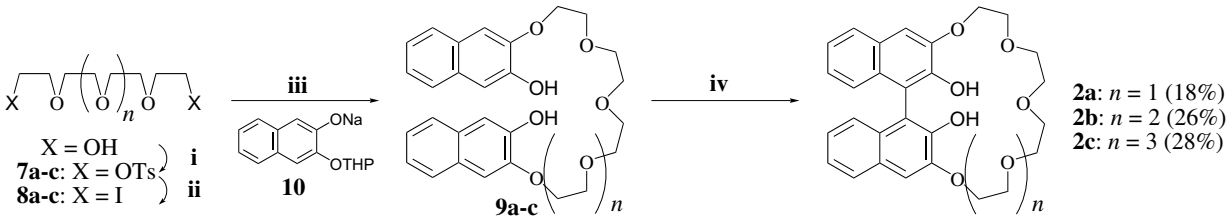


Scheme 1. Reagents and conditions: (i) NaOH, *n*-BuOH, reflux, 2 d; (ii) TsCl, NaOH, THF–H_2O (1:1), 0 °C, 4 h; (iii) NaI, acetone, reflux, 8 h; (iv) *n*-BuOH, reflux, 12 h, then *p*-TsOH, MeOH, reflux, 8 h; (v) air, CuCl(OH)–TMEDA, rt.



Scheme 2. Reagents and conditions: (i) TsCl, NaOH, THF–H_2O (1:1), 0 °C, 4 h; (ii) NaI, acetone, reflux, 8 h; (iii) *n*-BuOH, reflux, 12 h, then *p*-TsOH, MeOH, reflux, 8 h; (iv) air, CuCl(OH)–TMEDA, rt.

trimer, and tetramer) were also detected by TOF-MS.[10,11] When $FeCl_3$ was used as an oxidative coupling reagent, the starting materials were recovered, which is consistent with the report by Kellogg et al.[4]

Figure 1 represents HPLC profiles of 22-membered macrocycles **1a** and **2b**. Stereoisomers of 22-membered **1a** and 28-membered **1b** macrocycles were separated completely using a chiral HPLC column (DAICEL CHIRALPAK IA); eluent, chloroform:*n*-hexane:ethanol = 55:45:1). The (*S*)-isomer eluted earlier than the (*R*)-isomer in each case, assigned by using the exciton chirality method (Fig. 2).[12] In contrast, the enantiomer of macrocycle **2b** that has the same ring size as **1a** could not be separated by using the above chiral column, indicating that the chiral recognition ability of the macrocycles is drastically changed by introduction of the benzene unit on the polyether ring. Interestingly, neither macrocycles without the benzene unit **2** nor larger macrocycles **1c** (34-membered) have been separated under any conditions due to flexibility of the ring moiety. Macrocycles **1** and **2** could not exhibit chiral recognition ability for any amino acids, sugar derivatives, and amino alcohols.

Single crystals of macrocycles **1a**, **1b**, and **2b** were readily obtained from several solvents such as acetonitrile, ethyl acetate, and a mixture of ethyl acetate–toluene (1:1), respectively. In each case, the single crystal consisted of a racemic mixture. One water molecule was included in the center position of the cyclic polyether moiety, and was fixed triply by hydrogen bondings with

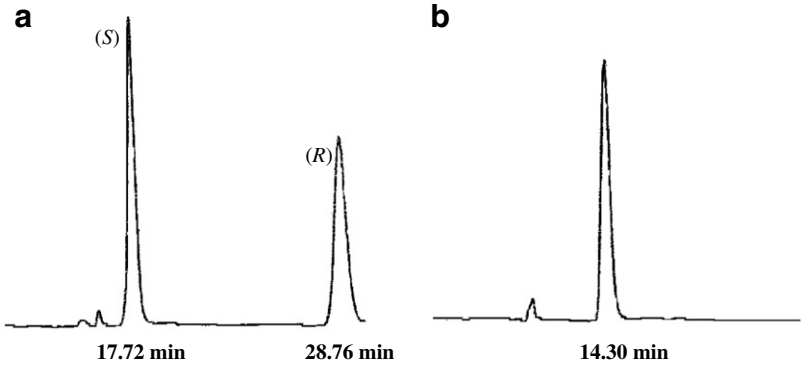


Figure 1. HPLC profiles of 25-membered macrocycles **1a** (a) and **2b** (b). HPLC conditions: column, DAICEL CHIRALPAK IA; eluent, chloroform:*n*-hexane:ethanol = 55:45:1; flow rate, 0.3 ml/min.

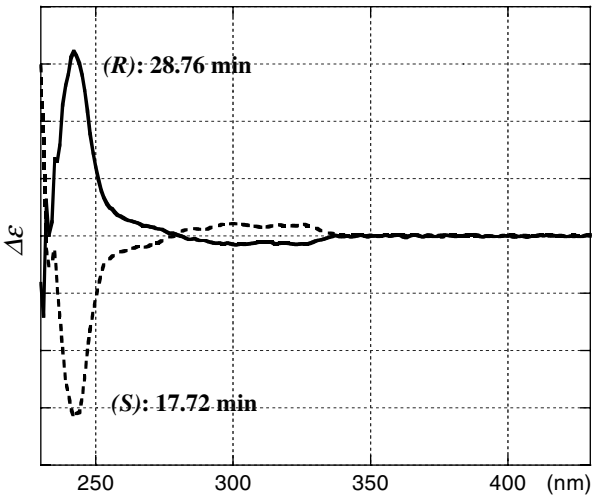


Figure 2. CD spectra of (*R*)-**1a** and (*S*)-**1a**.

the macrocycles (O10–H–O16, O7–H–O16, and O11–H–O16 in Fig. 3: dotted lines). The cavity of macrocycles **1** and **2** was reduced by intramolecular hydrogen bonding (C65–H–O4 in Fig. 3: wavy line).[13] These resemble the crystal structures of macrocycles with a 1,1′-binaphthalene-2,2′-diol unit reported by Cram and coworkers.[3]

In summary, we have developed a novel synthesis of macrocycles with a 1,1′-binaphthalene-2,2′-diol unit by using intramolecular oxidative coupling reaction. These macrocycles will also be converted to novel asymmetric catalysts or chiral supramolecules. We are now exploring the chiral recognition ability of macrocycles **1** and **2** as well as the synthesis of novel chiral supramolecules such as rotaxanes and catenanes.[14]

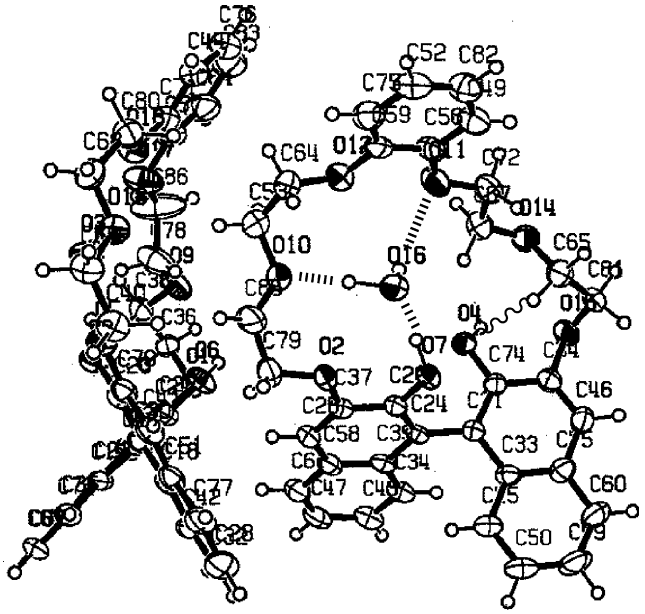


Figure 3. ORTEP diagram of macrocycle **1a** with crystallographic numbering system.

Acknowledgments

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10. Typical procedure of macrocycle **1a**: A solution of **6a** (1.75 g, 3.07 mmol) and CuCl(OH)–TMEDA (68.5 mg, 0.30 mmol) in $CHCl_3$ (500 ml) was stirred for one day at room temperature under air. The reaction mixture was washed with water (× 3) and brine (× 1). The organic phase was dried with anhydrous Na_2SO_4 and evaporated to dryness on a rotary evaporator. After evaporation, macrocycle **1a** was purified by column chromatography (silica gel) using $CHCl_3$/EtOH (93:7) as eluent. It was then crystallized from acetonitrile (0.494 g, 28%) as white plates.
11. Selected spectra data for **6a**: colorless paste; ^{1}H NMR ($CDCl_3$): δ 8.51 (s, 2H), 7.60 (m, 4H), 7.28–7.20 (m, 6H), 7.04 (s, 2H), 6.91–6.64 (m, 4H), 4.30 (m, 4H), 4.18 (m, 4H), 4.11 (m, 4H), and 4.04 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 148.1, 147.2, 146.7, 130.0, 128.7, 126.4, 124.1, 123.4, 121.3, 112.8, 110.0, 107.0, 69.4, 69.3, 67.8, and 67.8; MS (MALDI-TOF) *m*/*z* 571 ($M+H^+$). Anal. Calcd for $C_{34}H_{34}O_8$: C, 71.56; H, 6.01. Found: C, 71.18; H, 6.23. Compound **1a**: white crystals: mp = 146–148 °C; ^{1}H NMR ($CDCl_3$): δ 7.71 (d, 2H), 7.43 (br s, 2H, O*H*), 7.41 (s, 2H), 7.28 (m, 2H), 7.15 (m, 4H), 6.87 (m, 4H), 4.50–4.37 (m, 4H), 4.20–4.10 (m, 4H), and 4.02–3.73 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 147.9, 146.1, 146.0, 130.4, 128.7,

126.9, 125.1, 124.8, 123.5, 121.3, 116.1, 113.0, 111.8, 70.2, 68.9, 66.9, and 66.9; MS (MALDI-TOF) *m*/*z* 569 ($M+H^+$). Anal. Calcd for $C_{34}H_{32}O_8 \cdot H_2O$: C, 69.61; H, 5.84. Found: C, 69.08; H, 5.75. Compound **9b**: colorless paste; ^1H NMR ($CDCl_3$) 7.63–7.58 (m, 4H), 7.30–7.23 (m, 4H), 7.22 (s, 2H), 7.08 (s, 2H), 6.65 (br s, 2H, O*H*), 4.29–4.25 (m, 4H), 3.96–3.92 (m, 4H), 3.76–3.67 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 146.9, 146.1, 130.1, 128.7, 126.4, 126.2, 124.2, 123.5, 110.7, 107.9, 70.5, 70.3, 69.3, 69.2, 68.2; MS (MALDI-TOF) *m*/*z* 523 ($M+H^+$). Anal. Calcd for $C_{30}H_{34}O_8$: C, 68.95; H, 6.56. Found: C, 69.19; H, 6.66. Compound **2b**: colorless crystals; mp = 198–199 °C, ^1H NMR ($CDCl_3$) δ 7.73 (d, 2H), 7.39 (br s, 2H, O*H*), 7.38 (s, 2H), 7.30–7.25 (m, 2H), 7.12 (m, 4H), 4.43 (m, 4H), 3.92–3.56 (m, 16H); ^{13}C NMR ($CDCl_3$) δ 146.5, 145.6, 130.2, 128.6, 126.8, 125.0, 124.6, 123.4, 116.2, 111.2, 70.4, 70.2, 69.9, 69.8, 68.8; MS (MALDI-TOF) 520 (M^+). Anal. Calcd for $C_{30}H_{32}O_8 \cdot H_2O$: C, 65.80; H, 6.44. Found: C, 66.04; H, 6.41.

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