Synthesis and properties of macrocyclic 1,1’-biarenol derivatives prepared by the tandem Claisen rearrangement

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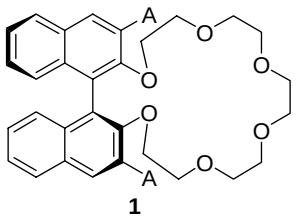
Abstract—Crown ether-type macrocycles consisting of an enantiopure biarenol derivative and an oligoethylene glycol were synthesized by the lewis acid-mediated tandem Claisen rearrangement. This is the first example of the successful application of the tandem Claisen rearrangement to the synthesis of enantiopure macrocyclic biarenol derivatives. The enantiopure macrocyclic biarenols were found to form 1:1 complexes with amino acid salts and to discriminate their chirality.

Enantiopure 1,1'-bi-2-naphthol and its derivatives provide highly stable C_2 symmetric environment and have been widely used as the components of chiral host compounds[1-5] and chiral catalysts.[6-10] Since the early 1970s, extensive studies on the application of enantiopure binaphthol-based crown ethers as hosts for chiral recognition have been conducted by Cram and his co-workers. One example of these enantiopure crown ethers is the binaphthol-containing crown ether **1**, which has been found to form host-guest complexes with amino acid salts and to discriminate their chirality.[11-13] The driving force for the complexation of the crown ether **1** with amino acid salts is mainly hydrogen bonding between the lone pairs of the oxygen atoms of the crown ether and the ammonium cation of the amino acid salts. The steric repulsion or dispersive energy between the crown ether and each enantiomer of the amino acid salts determines the stability of the diastereomeric host-guest complexes.



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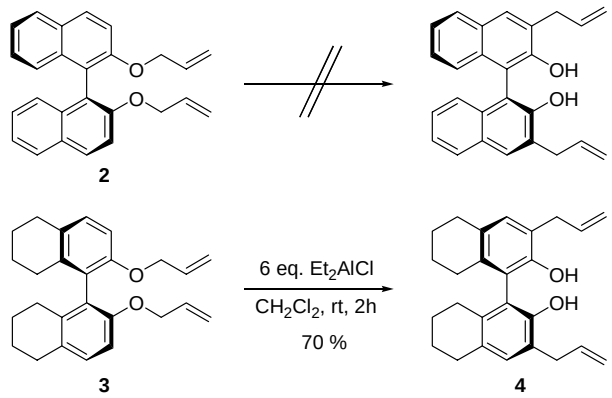
Although the crown ether **1** is synthesized from enantiopure 1,1’-bi-2-naphthol, its phenolic hydroxy groups, which would be able to play as hydrogen donors in host-guest complexations, are transformed into ether linkages in the construction of the macrocyclic ring, inevitably resulting in no phenolic hydroxy group in the host molecule. This means that in order to utilize the phenolic hydroxy groups of an enantiopure binaphthol derivative as functional groups in a binaphthol-contained crown ether, some bond



Scheme 1.

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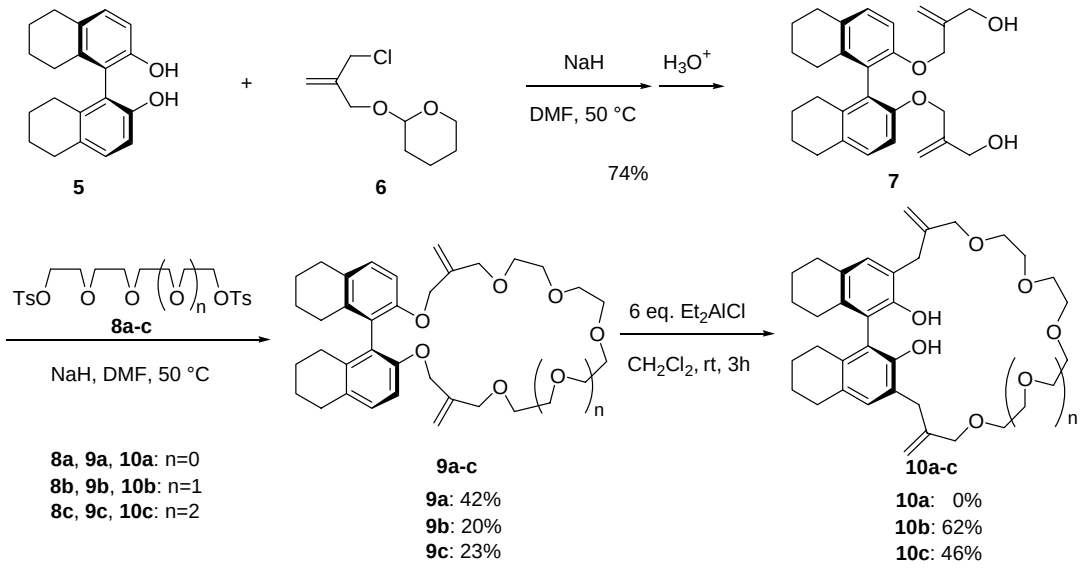
Keywords: Tandem Claisen rearrangement; 1,1’-bi-2-naphthol; Chiral recognition; Host-guest complex; Amino acid salt.

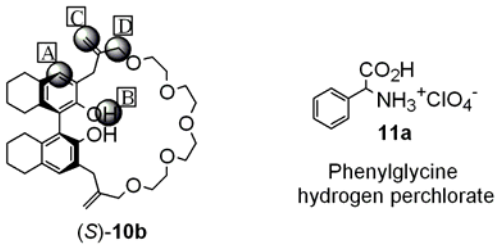


Scheme 2.

formation on the aromatic ring should be applied. However, such a C-C bond formation often requires toxic and/or flammable reagents, longer reaction time, and/or drastic reaction conditions leading to the racemization of the binaphthol derivative.

On the other hand, our group has found that the tandem Claisen rearrangement reaction is useful for the preparation of achiral arenol-containing macrocyclic host molecules, which could bind guest molecules by using the hydrogen bonding of the aromatic hydroxy groups.[14,15] In this paper, we describe the synthesis of enantiopure arenol-containing crown ether-type compounds by the simple tandem Claisen rearrangement and their properties as host molecules.

(*S*)-1,1'-Bi-2-naphthol was considered to be one of simple candidates for the construction of enantiopure arenol-containing crown ether-type compounds. Then, the tandem Claisen rearrangement of the enantiopure binaphthol diallyl ether (*S*)-**2** was at first tried as a model reaction. However, the corresponding rearranged product could not be obtained at all by thermal nor Lewis acid-mediated rearrangement (Scheme 1). Although the reason why the reaction did not take place is not clear at present, we considered that the expanded conjugated system over the naphthalene ring would be concerned. On the basis of this consideration, we next tried the tandem Claisen rearrangement of the enantiopure biphenol diallyl ether (*S*)-**3** under Lewis acidic conditions. Among Lewis acids we examined, diethylaluminum chloride was found to be the most effective; the reaction proceeded very smoothly in the presence of an excess amount of diethylaluminum chloride to give the corresponding product **4** in 70% yield. On the basis of the successful result, we next tried the tandem Claisen rearrangement of three kinds of the macrocyclic bis(allylic ether)s (*S*)-**9**, of which the ring sizes are different from each other.



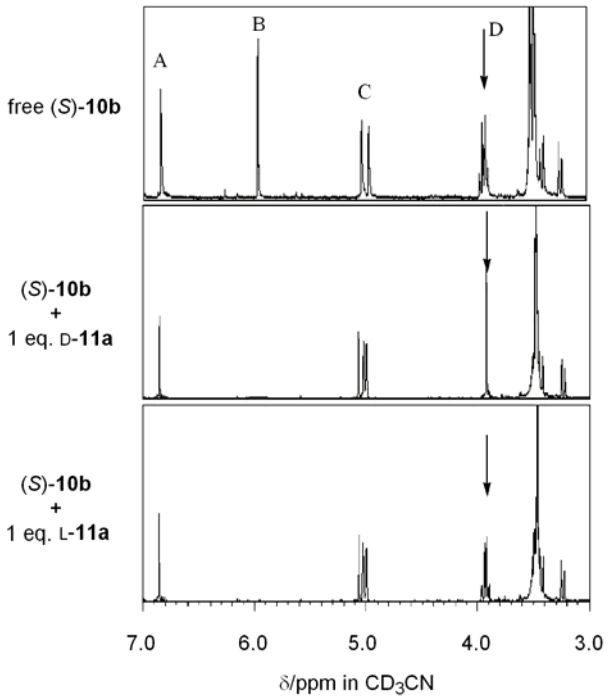


Figure 1. NMR spectral change of (*S*)-**10b** upon addition of L-**11a** or D-**11a**. [(*S*)-**10b**]=1×10^{-2} M, 25 °C.

Table 1. Association constants of the complexes of (*S*)-**10b**,**c** with **11**

entry	guest	(*S*)-**10b**			(*S*)-**10c**		
		K/M^{-1}		K_D/K_L	K/M^{-1}		K_D/K_L
		D-form	L-form		D-form	L-form	
1	Phenylglycine hydrogen perchlorate **11a**	62.3	46.2	1.4	313	185	1.7
2	Alanine hydrogen perchlorate **11b**	71.1	39.6	1.8	337	193	1.8
3	Valine hydrogen perchlorate **11c**	32.0	17.6	1.8	96.5	43.5	2.2

Associaton constants were determined by NMR spectrum titration using the non-linear regression method. [(*S*)-**10b**,**c**] = 1×10^{-2} M, solvent: CD_3CN, 25 °C.

The precursors (*S*)-**9** were synthesized from the biphenol (*S*)-**5**[16] through three steps (Scheme 2): The reaction of (*S*)-**5** with the *O*-tetrahydropyranylated 2-(hydroxymethyl)allyl chloride **6**,[17] followed by hydrolysis, gave the bis(allyl ether) (*S*)-**7**.[18] Then, (*S*)-**7** was allowed to react with the oligoethylene glycol ditosylates **8a-c** under high dilution conditions to give the precursors (*S*)-**9a-c**.[19] The MS analysis of the product, isolated from each reaction mixture, revealed that the product was a condensate of one mole of (*S*)-**7** and one mole of **8**. The tandem Claisen rearrangements of (*S*)-**9a-c** were carried out in the presence of diethylaluminum chloride. In the case of the rearrangement of (*S*)-**9a** with the smallest ring, the desired product (*S*)-**10a** was not obtained at all, although (*S*)-**9a** was completely consumed (TLC monitoring), suggesting that the product (*S*)-**10a** was unstable due to the strain of the ring. In contrast, the rearrangements of (*S*)-**9b**,**c** proceeded very smoothly at room temperature in the presence of 6 equivalents of diethylaluminum chloride to give the macrocyclic biphenol (*S*)-**10b**,**c**[20] in good yields.

Since (*S*)-**10b**,**c** contain both hydrogen-donating groups (the phenolic hydroxy groups) and hydrogen-accepting groups (the ether oxygens), molecules with plural functional groups such as amino acid salts were considered to be suitable as guests for the complexation with (*S*)-**10b**,**c**. Then, the guest binding and chiral recognition abilities of (*S*)-**10b** were at first examined by using amino acid salts as guests (Figure 1). Upon addition of either L- and D-phenylglycine hydrogen perchlorate (L- and D-**11a**), the ^{1}H-NMR signal of the phenolic hydroxy protons was completely disappeared. This phenomenon strongly indicates that the phenolic hydroxy protons at first interacted with the amino acid salt in any case. On the other hand, there observed no significant change in the ^{1}H-NMR spectrum of (*S*)-**10b** with L-**11a**, whereas the signals of the allylic methylene protons of free (*S*)-**10b** (D in Figure 1), split in four lines, coalesced into a sharp singlet upon addition of D-**11a**. The coalescence of the signal would arise from the interaction of the amino acid salt with the macrocyclic polyether ring in (*S*)-**10b**. On the basis of the observations of the spectral changes, ^{1}H-NMR titrations were next carried out for the complexation of (*S*)-**10b**,**c** with **11a**, alanine hydrogen perchlorate (**11b**), and valine hydrogen perchlorate (**11c**). The changes in the chemical shifts of the aromatic proton (A in Figure 1) were monitored for the complexes of (*S*)-**10b**,**c** with **11** and plotted (the plots for **10b**,**c**/**11a** were shown in Figure 2). The curve-fittings of the titrations by the non-linear regression method showed that the ratios of (*S*)-**10b**,**c** to **11** were 1:1. Moreover, the association constants were calculated on the basis of the curve-fittings (Table 1). As shown in Table 1, (*S*)-**10b**,**c** could recognize the chirality of **11** and bind the D-forms commonly stronger than the L-forms ($K_D>K_L$). The enlargement of the ring size from a 25-membered ring ((*S*)-**10b**) to a 28-membered ring ((*S*)-**10c**) resulted in the increase of the association constants by several times with a slight improvement of the selectivity, indicating that the 25-membered ring of (*S*)-**10b** is a little small for the inclusion of the guests.

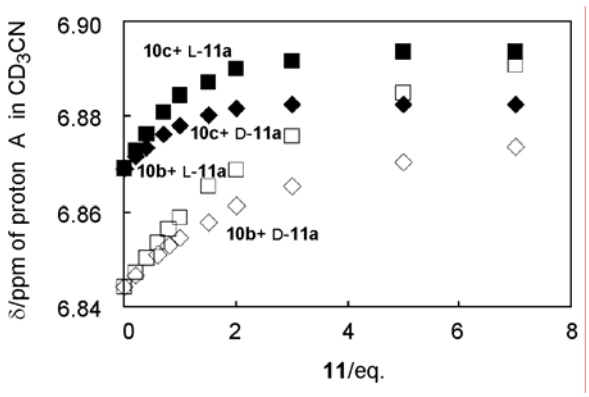


Figure 2. Plots of the chemical shifts of (*S*)-**10b,c** against the amount of L-**11a** or D-**11a**. [(*S*)-**10b**,**c**]=1×10^{-2} M, 25 °C.

In order to understand the chiral recognition phenomena of (*S*)-**10b**,**c**, a theoretical caluculation was carried out for (*S*)-**10b**. Geometry optimization was performed at B3LYP/3-21g* level of theory.[21] The optimized structure is shown in Figure 3. The aromatic ring of the biphenyl moiety in (*S*)-**10b** is parallel to the plane of the oligo(oxyethylene) moiety in contrast with the fact that the binaphthyl moiety in **1** is perpendicular to the plane of the oligo(oxyethylene) moiety.[11] Therefore, the biphenyl moiety of (*S*)-**10b** could not bring so effective steric effect that the moderate K_D/K_L was resulted in. However, it is noteworthy that (*S*)-**10b**,**c** is

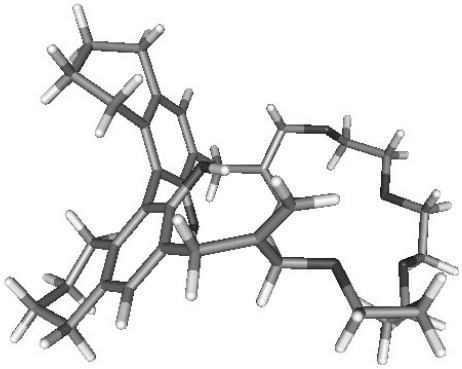


Figure 3. Structure of (*S*)-**10b** optimized with B3LYP/3-21g*.

D-selective while (*S*)-**1** is L-selective[11] even though the absolute configurations of (*S*)-**1** and (*S*)-**10b**,**c** are the same as each other.

The present study suggests that the chiral recognition ability of (*S*)-**10b**,**c** arises from the strong hydrogen bonding of the phenolic hydroxy groups with guests, indicating that the phenolic hydroxy group(s) in a macrocyclic biarenols is one of promising functional groups in host-guest interaction phenomena. The study on the synthesis and binding properties of macrocyclic polyether containing two biarenol moieties is under investigation.s

References and notes

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18. ^{1}H NMR data for **7**: (500 MHz, $CDCl_3$) δ 1.64-1.74 (8H, m), 1.81 (2H, s), 2.14-2.31 (4H, m), 2.75-2.79 (4H, m), 3.89 (4H, dd, *J*=6.0, 10.6 Hz), 4.48 (4H, dd, *J*=11.7, 21.4 Hz), 5.02 (2H, d, *J*=1.2 Hz), 5.06 (2H, d, *J*=1.0 Hz), 6.78 (2H, d, *J*=8.4 Hz), 7.06 (2H, d, *J*=8.4 Hz).
19. **9a**: LRMS (FAB) 548 (M^+); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.64-1.72 (8H, m), 2.13-2.37 (4H, m), 2.74-2.76 (4H, m), 3.37-3.46 (4H, m), 3.56-3.62 (8H, m), 3.84 (4H, dd, *J*=12.7, 59.0 Hz), 4.42 (4H, d, *J*=3.4 Hz), 4.96 (2H, d, *J*=1.4 Hz), 5.03 (2H, d, *J*=1.4 Hz), 6.75 (2H, d, *J*=8.4 Hz), 7.00 (2H, d, *J*=8.4 Hz). **9b**: LRMS (FAB) 592 (M^+); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63-1.72 (8H, m), 2.10-2.24 (4H, m), 2.74-2.76 (4H, m), 3.37-3.44 (4H, m), 3.59-3.64 (12H, m), 3.82 (4H, dd, *J*=12.6, 46.3 Hz), 4.41 (4H, dd, *J*=6.2, 11.3 Hz), 4.95 (2H, d, *J*=1.5 Hz), 5.05 (2H, d, *J*=1.3 Hz), 6.74 (2H, d, *J*=8.4 Hz), 7.00 (2H, d, *J*=8.4 Hz). **9c**: LRMS (FAB) 636 (M^+); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.61-1.74 (8H, m), 2.11-2.34 (4H, m), 2.74-2.76 (4H, m), 3.42-3.47 (4H, m), 3.56-3.66 (16H, m), 3.84 (4H, dd, *J*=13.2, 59.9 Hz), 4.40 (4H, dd, *J*=13.2, 23.6 Hz), 4.96 (2H, d, *J*=1.1 Hz), 5.05 (2H, d, *J*=1.1 Hz), 6.74 (2H, d, *J*=8.3 Hz), 7.00 (2H, d, *J*=8.3 Hz).
20. **10b**: LRMS (FAB) 592 (M^+); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65-1.78 (8H, m), 2.16-2.23 (4H, m), 2.70-2.73 (4H, m), 3.41 (4H, dd, *J*=15.3, 25.2 Hz), 3.57-3.59 (16H, m), 3.99 (4H, dd, J=7.1, 4,5 Hz), 4.99 (2H, s), 5.05 (2H, s), 5.64 (2H, s), 6.87 (2H, s). **10c**: LRMS (FAB) 636 (M^+); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.63-1.74 (8H, m), 2.12-2.26 (4H, m), 2.70-2.72 (4H, m), 3.41 (4H, dd, *J*=15.4, 48.9 Hz), 3.53-3.65 (20H, m), 3.99 (4H, s), 4.95 (2H, s), 5.04 (2H, s), 5.63 (2H, s), 6.87 (2H, s).
21. The calculation was performed using Gaussian 98 program package (Revision A.9) Gaussian, Inc.: Pittsburgh, PA, see http://www.gaussian.com/citation.htm.