

Synthesis of macrocyclic 1,1'-biarenol derivatives by the tandem Claisen rearrangement and their binding properties

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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.

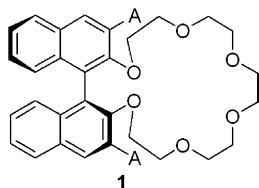
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Enantiopure 1,1'-bi-2-naphthol and its derivatives provide highly stable C_2 symmetric environment and have been widely used as the components of chiral host compounds^{1–5} and chiral catalysts.^{6–10} Since the early 1970s, extensive studies on the application of enantiopure binaphthol-based crown ethers as hosts for chiral recognition have been conducted by Cram and 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 deter-

mines the stability of the diastereomeric host–guest complexes.

Although the crown ether **1** is synthesized from enantiopure 1,1'-bi-2-naphthol, its phenolic hydroxy groups, which would be a useful functional group 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. From the view of effective application of phenolic hydroxy groups as interaction sites, several binaphthol-containing crown ethers with free phenolic hydroxy groups have been synthesized,¹⁴ and their properties as a chiral catalyst¹⁵ and chiral host compounds^{16–18} have been examined. In the preparation of these compounds, however, some bond 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.^{19,20} 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.



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

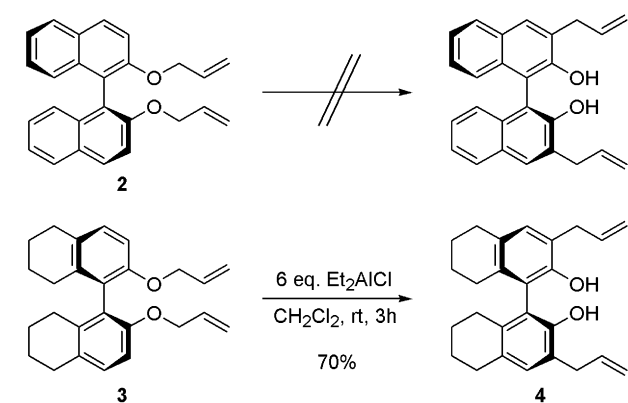
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(*S*)-1,1'-Bi-2-naphthol was considered to be one of simple candidates for the construction of enantiopure arene-containing crown ether-type compounds. Then, the tandem Claisen rearrangement of the enantiopure binaphthol diallyl ether (*S*)-**2** was 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

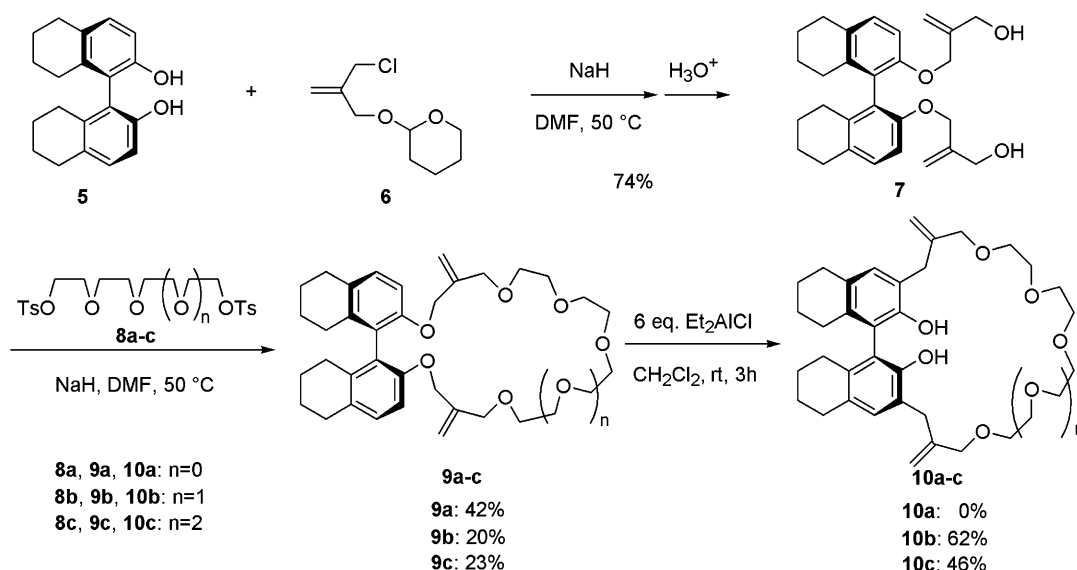
macrocyclic bis(allylic ether)s (*S*)-**9**, of which the ring sizes are different from each other.

The precursors (*S*)-**9** were synthesized from the biphenol (*S*)-**5**²¹ through three steps (Scheme 2): The reaction of (*S*)-**5** with the *O*-tetrahydropyranylated 2-(hydroxymethyl)allyl chloride **6**,²² followed by hydrolysis, gave the bis(allyl ether) (*S*)-**7**.²³ 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**.²⁴ The MS analysis of the product, isolated from each reaction mixture, revealed that the product was a condensate of one molecule of (*S*)-**7** and one molecule 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). In contrast, the rearrangements of (*S*)-**9b** and **c** proceeded very smoothly at room temperature in the presence of an excess amount of diethylaluminum chloride to give the macrocyclic biphenol (*S*)-**10b** and **c**²⁵ in good yields.

Since (*S*)-**10b** and **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** and **c**. Then, the guest binding and chiral recognition abilities of (*S*)-**10b** were at first examined by using amino acid salts as guests (Fig. 1). Upon addition of either *L*- and *D*-phenylglycine hydrogen perchlorate (*L*- and *D*-**11a**), the ¹H NMR signal of the phenolic hydroxy protons 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 ¹H NMR spectrum of (*S*)-**10b** with



Scheme 1.



Scheme 2.

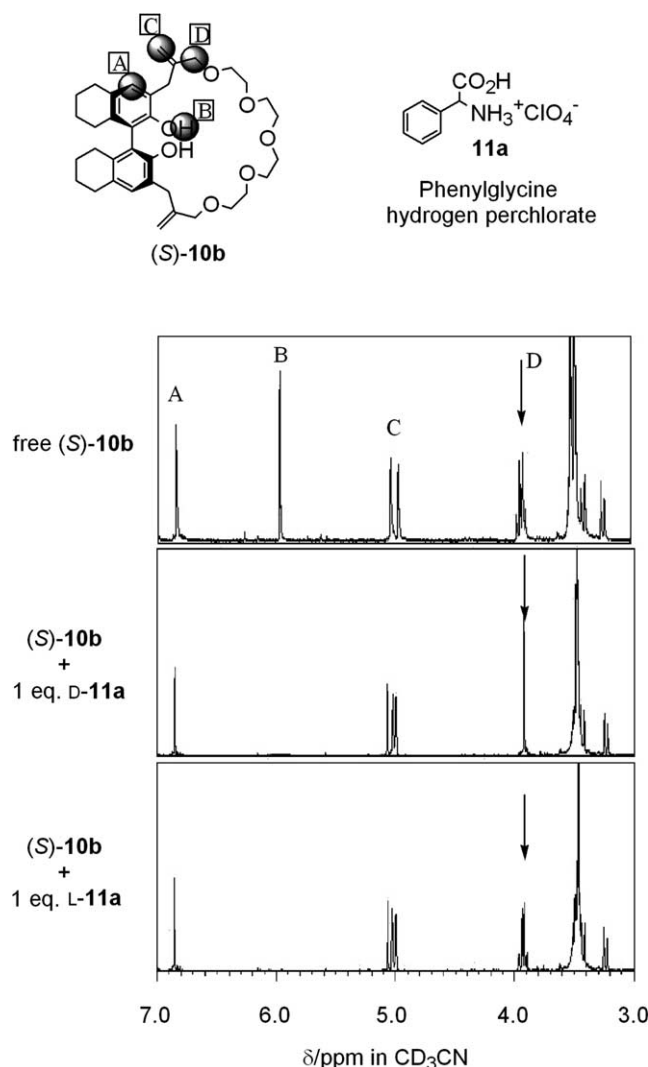


Figure 1. NMR spectral change of (*S*)-**10b** upon addition of L-**11a** or D-**11a**. [(*S*)-**10b**] = 1×10^{-2} M, 25 °C.

L-**11a**, whereas the signals of the allylic methylene protons of free (*S*)-**10b** (D in Fig. 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 result of the spectral change, ^1H NMR titrations were next carried out for the complexation of (*S*)-**10b** and **c** with **11a**, alanine hydrogen perchlorate (**11b**), and valine hydrogen

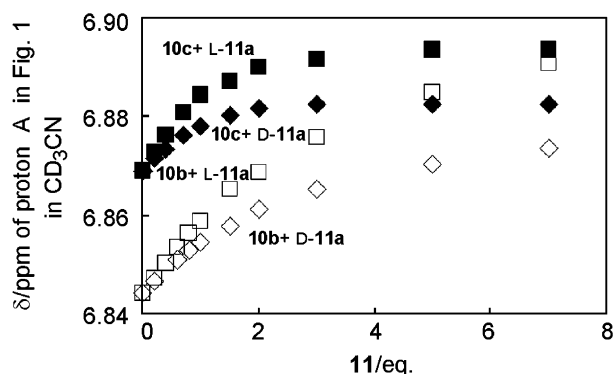


Figure 2. Change in the chemical shifts of the aromatic proton (A in Fig. 1) of (*S*)-**10b** and **c** against the amount of L-**11** or D-**11**. [(*S*)-**10b** and **c**] = 1×10^{-2} M, 25 °C.

perchlorate (**11c**). The changes in the chemical shifts of the aromatic proton (A in Fig. 1) were monitored for the complexes of (*S*)-**10b** and **c** with **11** and plotted in Figure 2. The curve-fittings of the titrations by the non-linear regression method showed that the (*S*)-**10b** and **c**/**11** ratios 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** and **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.

In order to understand the chiral recognition phenomena of (*S*)-**10b** and **c**, a theoretical calculation was carried out for (*S*)-**10b**. Geometry optimization was performed at B3LYP/3-21g* level of theory.²⁶ 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, which is 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 an effective steric effect, eventually leading to the moderate K_D/K_L . Although the participation of the phenolic hydroxy groups in binding the guests is not clear at present, it is noteworthy that (*S*)-**10b** and

Table 1. Association constants of (*S*)-**10b** and **c** with amino acid salts

Entry	Guest	(<i>S</i>)- 10b			(<i>S</i>)- 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	62.3	46.2	1.4	313	185	1.7
2	Alanine hydrogen perchlorate	71.1	39.6	1.8	337	193	1.8
3	Valine hydrogen perchlorate	32.0	17.6	1.8	96.5	43.5	2.2

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

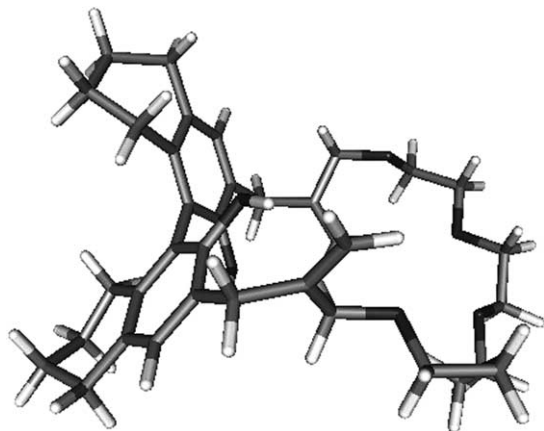


Figure 3. Structure of (S)-10b optimized with B3LYP/3-21g*.

c is D-selective while (S)-1 is L-selective¹¹ even though the absolute configurations of (S)-1 and (S)-10b and c are the same.

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23. ¹H NMR data for compound **7**: (500 MHz, CDCl₃) 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).
24. Compound **9a**: LRMS (FAB) 548 (M⁺); ¹H NMR (500 MHz, CDCl₃) 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). Compound **9b**: LRMS (FAB) 592 (M⁺); ¹H NMR (500 MHz, CDCl₃) 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). Compound **9c**: LRMS (FAB) 636 (M⁺); ¹H NMR (600 MHz, CDCl₃) 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).
25. Compound **10b**: LRMS (FAB) 592 (M⁺); ¹H NMR (500 MHz, CDCl₃) 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). Compound **10c**: LRMS (FAB) 636 (M⁺); ¹H NMR (600 MHz, CDCl₃) 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).
26. The calculation was performed using Gaussian 98 program package (Revision A.9) Gaussian, Inc.: Pittsburgh, PA, see <http://www.gaussian.com/citation.htm>.