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A novel synthesis of chiral rotaxanes *via* covalent bond formation†

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Chiral rotaxanes composed of the asymmetric crownophane incorporating two hydroxy groups as a rotor moiety and the asymmetric axis were effectively synthesized *via* covalent bond formation, *i.e.* tandem Claisen rearrangement, esterification, and aminolysis.

Much attention has been paid to supramolecular systems such as rotaxanes and catenanes from a view point of the construction of molecular machines.[1] In particular, it should be noted that mechanically bonded molecules like rotaxanes, catenanes, and pretzel-shaped molecules consisting of the asymmetric rotor and the asymmetric axis can have a chirality even if both the rotor and the axis are achiral themselves (Fig. 1). Topologically knotted molecules also have a chirality based on the left- and right-helical structures. Several synthetic methods for the preparation of those chiral supramolecular systems have been reported so far. For example, Sauvage and co-workers successfully synthesized chiral rotaxanes, catenanes, and knots by using the metal (Cu^{I} and Fe^{II}) template technique.[2] Vögtle and co-workers developed the method utilizing the hydrogen bond formation between the rotor and the axis molecules, and synthesized cycloenantiomeric rotaxanes as well as topologically chiral catenanes and pretzelanes.[3] Surprisingly, those corresponding racemic compounds could be separated into each enantiomer by high performance liquid chromatography (HPLC) equipped with a chiral column although the highly conformational flexibility of those topological molecules leads hardly to discriminate between the enantiomers in general.

Recently, we proposed a new synthetic strategy to make achiral rotaxanes including the process of covalent bond formation.[4] This method through short and simple step processes gave the achiral rotaxanes in good yield compared to the method *via* covalent bond formation pioneered by Schill and Zollenkopf.[5] In this work, we tried to establish a novel synthetic methodology of chiral rotaxanes *via* covalent bond formation, *i.e.* tandem Claisen rearrangement, esterification, and aminolysis. Furthermore, the enantiomeric separation of those racemates was investigated by HPLC equipped with a chiral column and circular dichloism (CD) spectrophotometry.

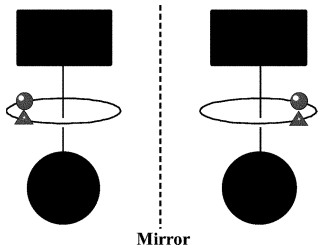
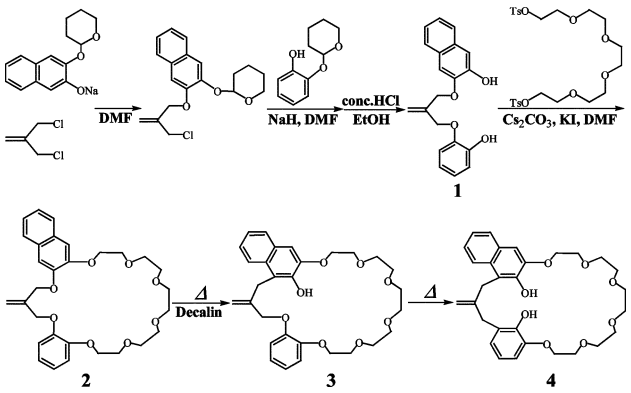


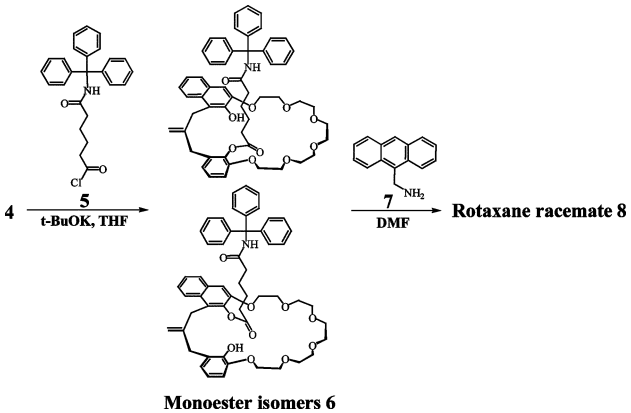
Fig. 1 Chiral rotaxane composed of the asymmetric rotor and the asymmetric axis.

Scheme 1 shows the synthesis of the asymmetric crownophane as a rotor moiety. Macrocyclic polyether compound **2** was obtained by the reaction between the aromatic compound **1**, containing the isobutenyl group synthesized through a three-step process, and pentaethylene glycol ditosylate in the presence of base under high dilution conditions (yield 52%). We have already found that various macrocyclic isobutenyl bis(aryl ether) derivatives are easily converted into compounds having two phenolic hydroxy groups *via* tandem Claisen rearrangement.[6] In the thermal reaction of the macrocyclic compound **2** carried out in decalin at 160 °C for 3 h, however, the obtained product was a macrocyclic compound **3** having only one hydroxy group (yield 71%). A second thermal reaction at 195 °C for 6 h without solvent was performed under vacuum conditions, and crownophane **4** having two hydroxy groups was obtained in good isolated yield (81%). The crownophane **4** is an asymmetrical structure having both benzene and naphthalene rings. The resulting two hydroxy groups in the rotor molecule are available for the introduction of the axis into the rotor as detailed below.

Scheme 2 indicates the synthetic route of rotaxane racemates via covalent bond formation. Monoesterification of the crownophane **4**



Scheme 1 Synthesis of the asymmetric rotor.



Scheme 2 Synthesis of rotaxane racemate *via* monoesterification and aminolysis.

† Electronic supplementary information (ESI) available: synthesis of rotaxanes **9** and **10**, and ^{1}H NMR, IR and ESI-MS spectral data for crownophane **4**, monoesters **6**, **12**, diester **11**, and rotaxanes **8**, **9**, **10**. See http://www.rsc.org/suppdata/cc/b3/b314744d/

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with an acid chloride **5** (1.0 equiv.) having a bulky group as a stopper was performed in THF at room temperature (yield 35%). The obtained monoesters **6** were used in the next reaction without isomeric separation. Aminolysis of the monoesters **6** with an amine compound **7** having a different bulky group was carried out in a small amount of DMF at room temperature, and the asymmetric axis was threaded into the rotor. The rotaxane racemate **8** was synthesized in good yield (46%) by a new strategy including the process of covalent bond formation. Rotaxane racemates **9** and **10**, as shown in Fig. 2, were synthesized *via* diesterification and aminolysis (the synthetic scheme is shown in the ESI†). That is, intramolecular diesterification of the crownophane **4** with adipoyl chloride in a similar way as previously reported follwed by the two aminolysis with different amines gave rotaxane racemates **9** and **10**. By these methods descrived above, we can introduce an axis having a variety of structures into our rotaxane system.

The enantiomeric separation of the synthesized racemates was investigated using HPLC equipped with a Chiralcel OC as a chiral column.[7] Fig. 3 shows a typical chromatogram of the enantiomeric separation of rotaxane **8**. Two peaks on the chromatogram indicate a clear separation with $a = 1.46$. CD spectra of each eluted fraction were measured in $CHCl_3$ (Fig. 4). Two circular dichrograms show a completely symmetric shape having the opposite Cotton effects in the aromatic region of each other. On the other hand, racemic compounds of rotaxane **9** and **10** could not be separated by using the same equipment and conditions. These results suggest that the structure (end group and chain length) of the axis might be an important factor affecting the separation of the chiral rotaxanes.

In conclusion, a novel synthetic method of chiral rotaxanes composed of the asymmetric rotor and the asymmetric axis *via* covalent bond formation has been developed. The corresponding racemate was completely separated into each enantiomer by HPLC equipped with a chiral column.

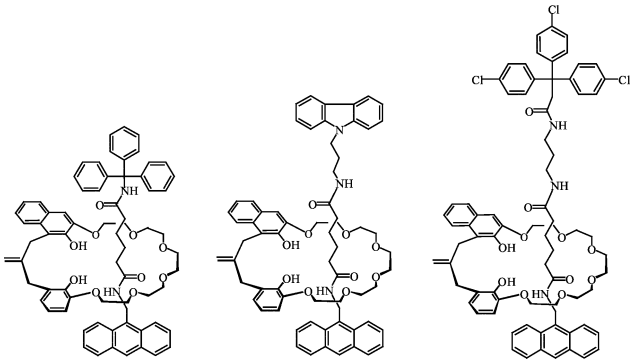

Fig. 2 Synthesized rotaxane racemates **8**, **9**, and **10**.

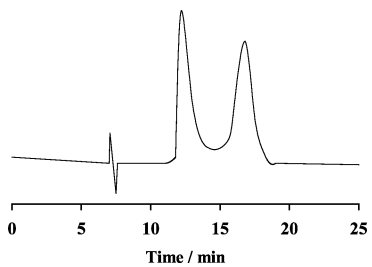

Fig. 3 Chromatogram for the enantiomeric separation of rotaxane **8**. Column: Chiralcel OC (0.46 cm i.d. × 25 cm); mobile phase: hexane:EtOH = 40:60; flow rate = 0.7 ml min^{-1}; detection (UV): 260 nm.

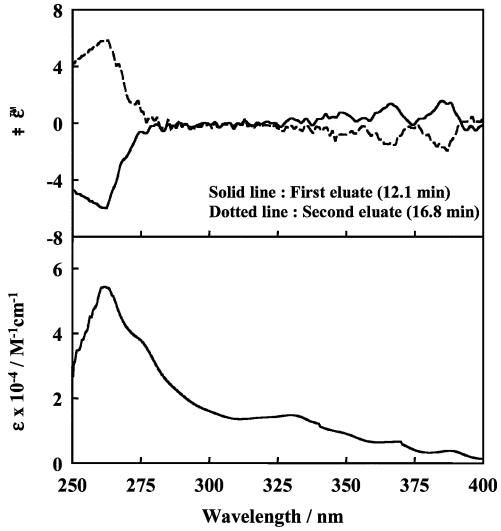

Fig. 4 CD (upper) and absorption (lower) spectrum of rotaxane **8** in $CHCl_3$.

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7 Equipment: column, Chiralcel OC (Daicel Chemical Industries) (cellulose trisphenylcarbamate); detector and pump, Liquid chromatograph PLC-5D (EYELA).