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Communication

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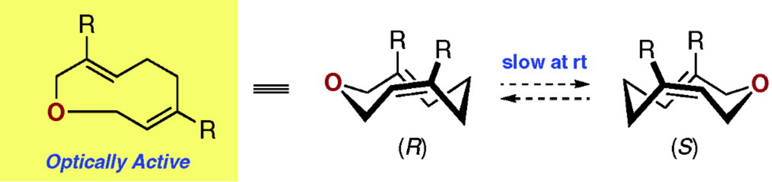

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Planar Chiral Cyclic Ether: Asymmetric Resolution and Chirality Transformation

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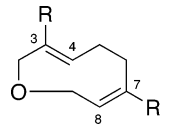
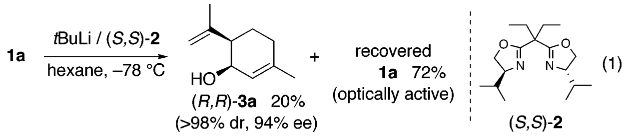
Nearly a half-century ago, Blomquist predicted that *trans*-cycloalkene should have inherent chirality.[1] Since then, medium-sized cycloalkenes with stable planar chirality have aroused much theoretical and synthetic interest.[2,3] On the other hand, their ether congener with sole planar chirality has not appeared so far, to the best of our knowledge.[4] Here, we wish to report the discovery of the remarkably stable planar chirality in a simple cyclic ether **1** and its utility for asymmetric synthesis. The details of the finding of this unique stereochemical phenomenon are as follows.



1a: R=Me
1b: R=H

Recently, we have found that a chiral bis(oxazoline) **2** acts as an efficient chiral coordinating agent for asymmetric carbanion reactions, such as [1,2]-, [2,3]-Wittig rearrangements, and S_E2 reaction of benzyllithium.[5] To demonstrate the efficiency and generality of our protocol, we further examined the enantioselective transannular [2,3]-Wittig rearrangement of nine-membered diallylic ether **1a**, which has been previously investigated by Marshall and Lebreton.[6] The reaction of ether **1a** with a *t*BuLi/(*S*,*S*)-**2** complex (3 equiv) in hexane at −78 °C afforded the desired [2,3]-rearrangement product (*R*,*R*)-**3a** in high enantiopurity (94% ee). However, the chemical yield of **3a** was surprisingly low, and a substantial amount of **1a** was recovered (eq 1).[7−9]



We then suspected the possibility that ether **1a** may have inherent chirality. In fact, we found that recovered ether **1a** is optically active {$[\alpha]_D^{25} = -25.3$ ($c = 2.6$, $CHCl_3$)} and *its optical rotation value is not changed at* room temperature for a week, at least.[10] Fortunately, we were able to obtain a baseline separation of enantiomers of **1a** on chiral HPLC analysis, whereby the enantiopurity of recovered (−)-**1a** was determined as 26% ee. These results clearly indicate that ether **1a** has remarkably stable planar chirality at ambient temperature.[11] An nOe experiment of ether **1a** irradiating at the methyl group on C3 showed 3% enhancement in the signal of the vinyl proton at C8. This result along with the molecular modeling suggests that the C3−C4 and C7−C8 olefinic moieties of **1a** form stereogenic planes in the most stable conformation (Figure 1).[12,13] On the basis of these observations, it was concluded that a kinetic resolution of *rac*-**1a** proceeded in this particular reaction. As Marshall reported, the rearrangement should proceed via inversion of the configuration at the carbanion center,[6] thus (*R*,*R*)-**3a** must be formed from the *R*-enantiomer and, therefore, the unreacted substrate **1a** should be *S*-enriched (eq 2).

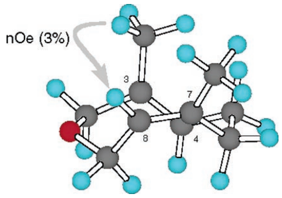
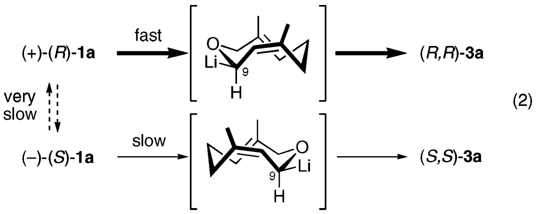
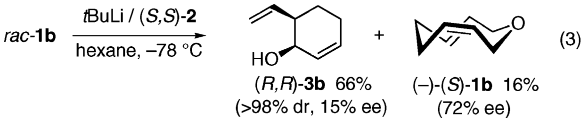


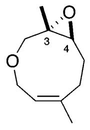
Figure 1. Optimized structure of **1a** and nOe experiment.



Furthermore, we found that unsubstituted analogue **1b** (R = H) also has stable planar chirality at room temperature, as revealed by the chiral HPLC analysis. Indeed, a similar asymmetric rearrangement of **1b** was found to give (*R*,*R*)-**3b** (15% ee) together with (−)-(*S*)-**1b** in 72% ee (eq 3).[8,14] Thus, the methyl substitution is not an essential factor responsible for the planar chirality of ether **1**.



To develop the potential synthetic utility of these cyclic ethers, we next examined a number of derivatizations using *rac*-**1a**. The epoxidation of *rac*-**1a** with *m*-CPBA (1.1 equiv) provides C3−C4 epoxide *rac*-**4** as a major product, along with C7−C8 epoxide *rac*-**5** and diepoxide *rac*-**6** in 65, 12, and 8%.[16] More significant selectivity was observed in the reaction with dimethyldioxylane (1.1 equiv), where *rac*-**4** was obtained as the sole product in 91% yield.



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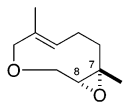

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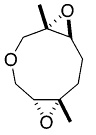

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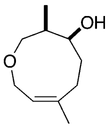

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Moreover, the hydroboration of *rac*-**1a** with 9-BBN provides only C3−C4 reacted product, alcohol *rac*-**7** in 91% yield. The thus observed high reactivity of C3−C4 olefin compared with that of C7−C8 is explainable by means of its distortion; the C3−C4 bond is twisted by ca. 32°, while the C7−C8 bond is almost flat (ca. 2°) in the most stable conformation (Figure 1).

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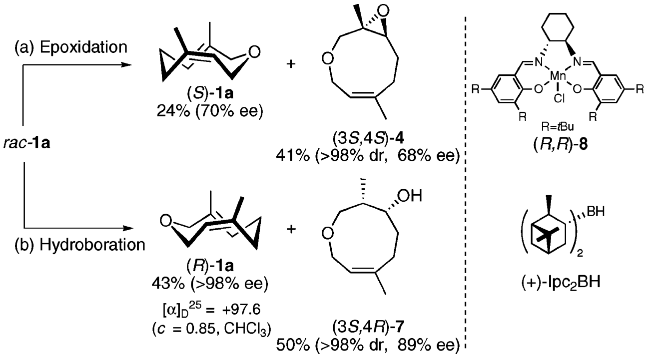
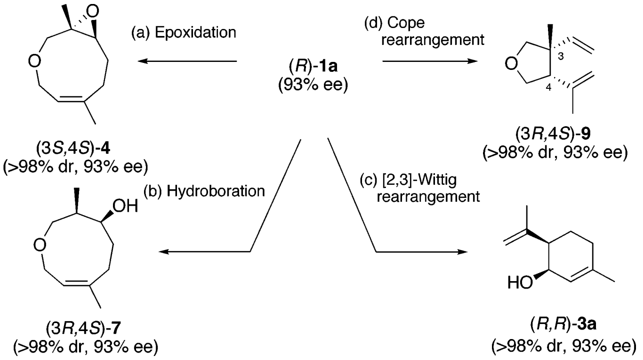
Scheme 1. Asymmetric Resolution of *rac*-**1a**[a]



[a] Reagents and conditions: (a) (*R*,*R*)-**8** (5 mol %), *m*-CPBA (2.0 equiv), NMO, CH_2Cl_2, −78 °C; (b) (+)-Ipc_2BH (1.2 equiv), THF, −50 to −10 °C; then NaO_2H.

Scheme 2. Chirality Transmission of (*R*)-**1a**[a]



[a] Reagents and conditions: (a) dimethyldioxirane, acetone-CH_2Cl_2, 0 °C, 91%; (b) 9-BBN, THF, reflux, then NaO_2H, 68%; (c) *t*BuLi, TMEDA, hexane, −78 °C to rt, 78%; (d) $PdCl_2(PhCN)_2$ (cat.), CH_2Cl_2, rt, 82%.

With these promising results in hand, next we examined the kinetic resolution of *rac*-**1a** with asymmetric epoxidation and hydroboration. The epoxidation with chiral (salen)Mn(III) complex **8**[17] afforded enantioenriched (*S*)-**1a** (70% ee) in 24% yield along with an epoxide (3*S*,4*S*)-**4** (68% ee, 41% yield) (Scheme 1).[15] Moreover, asymmetric hydroboration using (+)-Ipc_2BH (1.2 equiv)[18] in THF afforded the almost enantiopure (*R*)-**1a** (>98% ee) in 43% yield along with an alcohol (3*S*,4*R*)-**7** (89% ee) in 50% yield.

Enantioenriched **1a** thus obtained is valuable as a novel type of chiral building block. As shown in Scheme 2, (*R*)-**1a** (93% ee) can transform to enantioenriched central chiral compounds using *achiral reagents*. The epoxidation with dimethyldioxirane and the hydroboration with 9-BBN provide epoxide (3*S*,4*S*)-**4** (93% ee) and alcohol (3*R*,4*S*)-**7** (93% ee), respectively. Furthermore, transannular reactions, such as the [2,3]-Wittig rearrangement and Pd(II)-catalyzed Cope rearrangement,[19] also proceed in a stereospecific manner, which provide alcohol (*R*,*R*)-**3a** (93% ee) and cyclic ether (3*R*,4*S*)-**9** (93% ee), respectively. These reactions are rare examples of planar chirality to central chirality transmission.

In summary, we have described a discovery of the first example of a purely planar chiral cyclic ether and its chirality transformation. These new classes of planar chiral heterocyclic compounds are potentially useful as a novel type of chiral building block, chiral ligand, and a key component of chiral reagents. Further work is in progress to expand the planar chirality concept to other heterocyclic molecules.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Ether **1a** was prepared from neryl acetate in four steps by a slight modification of the procedure described by Marshall (ref 6); see the Supporting Information.

(8) The enantiopurities were determined by chiral HPLC analysis (for **1a**, **1b**, **4**, and **9**) or ^1H NMR analysis of MTPA ester (for **3a**, **3b**, and **7**).

(9) The absolute stereochemistry of (*R*,*R*)-**3a** was assigned by the optical rotation of isopiperitenone, which was derived by oxidation with MnO_2. See: Anglea, T. A.; Pinder, A. R. *Tetrahedron* **1987**, *43*, 5537−5543.

(10) It is worth noting that Marshall and Lebreton recognized the possibility of chirality of **1a**, but measured no optical activity in the recovered material (10% yield) upon chiral base-promoted [2,3]-Wittig rearrangement.

(11) Only a trace amount of racemization (<1%) was detected by chiral HPLC analysis, when it was maintained at 25 °C in hexane for 2 weeks.

(12) Conformational analysis of ether **1a** was carried out with the MacroModel 8.0 package and PC Spartan Pro 1.0.5. Conformational search was performed with the Mixed MCMM/LowMode method (5000 structures) using the MM2* force field. Further geometry optimization and the potential energy calculation of the most stable conformers were performed by PM3 calculation using Spartan.

(13) To determine the configurational stability of **1a**, we carried out variable temperature ^1H NMR analyses. Significantly, no appreciable change in peak shape and width was observed up to 110 °C, while at around 80 °C, **1a** began to undergo the Cope rearrangement.

(14) The absolute stereochemistry of (*R*,*R*)-**3b** was determined by the modified Mosher’s method. See: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(15) The absolute stereochemistry of **4**, **7**, and **9** was deduced from the configuration of **1a** and the steric course of the reactions.

(16) The structure of **6** was determined by X-ray crystallography; see the Supporting Information. It is worth noting that the nine-membered carbon framework of the X-ray crystal structure of diepoxide **6** is found to be superimposable to the framework of the calculated conformation of ether **1a**. It shows the validity of the proposed conformation of **1a**.

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