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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, mediumsized 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.



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,



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

the unreacted substrate 1a should be S-enriched (eq 2).



Furthermore, we found that unsubstituted analogue **1b** ($\mathbf{R} = \mathbf{H}$) 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.



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).

Scheme 1. Asymmetric Resolution of rac-1a^a



^{*a*} Reagents and conditions: (a) (R,R)-8 (5 mol %), *m*-CPBA (2.0 equiv), NMO, CH₂Cl₂, -78 °C; (b) (+)-Ipc₂BH (1.2 equiv), THF, -50 to -10 °C; then NaO₂H.

Scheme 2. Chirality Transmission of (R)-1a^a



^{*a*} Reagents and conditions: (a) dimethyldioxirane, acetone-CH₂Cl₂, 0 °C, 91%; (b) 9-BBN, THF, reflux, then NaO₂H, 68%; (c) *t*BuLi, TMEDA, hexane, -78 °C to rt, 78%; (d) PdCl₂(PhCN)₂ (cat.), CH₂Cl₂, 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 (+)-Ipc₂BH (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 MnO₂. 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
- (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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