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Synthesis of chiral [5]helicenes using aromatic oxy-Cope rearrangement as a key step

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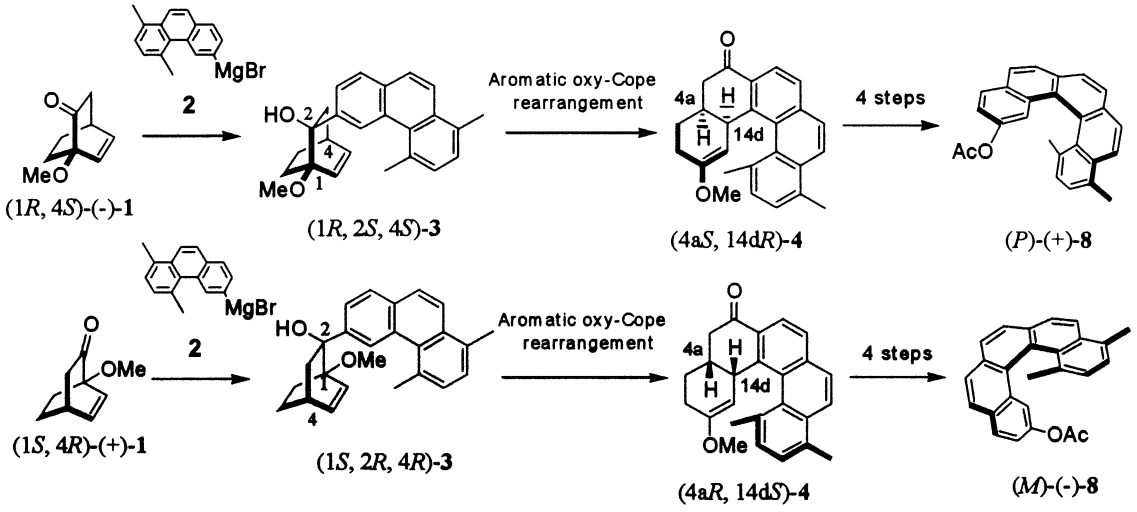
Abstract—Both enantiomers of (*P*)-(+)-2- and (*M*)-(−)-2-acetoxy-11,14-dimethyl[5]helicenes **8** were synthesized by asymmetric aromatic oxy-Cope rearrangement of the corresponding chiral bridged bicyclic compounds, which were obtained by enzymatic resolution. The absolute configurations of **8** were assigned by their circular dichroism spectra.

Helicenes contain twisted nonplanar π-electron systems, the correlation between the helical structures and the optical properties of which is of interest. Especially, chiral helicenes exhibit large specific rotation and a nonlinear optical property.[1] The application of these compounds to various kinds of photonic devices has therefore been expected.

The chiral helicenes are generally obtained by the optical resolution of their racemate using a resolving agent,[2] chiral HPLC,[3] and a biocatalyst.[4] To our knowledge, only several enantioselective approaches have been reported so far.[5]

In the previous letter, we reported the synthesis of 2-acetoxy[5]helicene and 2-acetoxy-11,14-dimethyl[5]-helicene by sequential double aromatic oxy-Cope rearrangement.[6] This strategy would be applicable to the synthesis of various helical compounds. We report herein a novel synthetic strategy for chiral



Scheme 1. Aromatic oxy-Cope rearrangements of bicyclo[2.2.2]octane derivatives **3**.

Keywords: bicyclic compounds; aromatic oxy-Cope rearrangement; chiral [5]helicenes.

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helicenes based on an asymmetric aromatic oxy-Cope rearrangement (Scheme 1).

The starting chiral bicyclo[2.2.2]ketone (1*R*,4*S*)-(−)-**1** (>98% ee) was obtained from racemic **1** by the enzymatic resolution method, which has already been established by us.[7] The reaction of (1*R*,4*S*)-(−)-**1** with 5,8-dimethylphenanthrenylmagnesium bromide gave (1*R*,2*S*,4*S*)-**3** as a major product in 60% yield. Aromatic oxy-Cope rearrangement of (1*R*,2*S*,4*S*)-**3** using 3 equiv. of potassium bis(trimethylsilyl)amide [KHMDS] and 1.5 equiv. of 18-crown-6 in THF at 0°C afforded a fused-ring compound (4a*S*,14d*R*)-**4** in 47% yield.

Reduction of the ketone **4** with $NaBH_4$ gave the corresponding alcohol (4a*S*,14d*R*)-**5**, which on hydrolysis and dehydration was converted into (4a*S*,14d*R*)-**6**. Enolacetylation of the resulting ketone **6**, followed by dehydrogenation with DDQ afforded 2-acetoxy-11,14-dimethyl[5]helicene (*P*)-(+)-**8** in 24% overall yield[8] from compound **4**. The enantiomeric excess of (*P*)-(+)-**8** was determined to be >98% ee by HPLC analysis using a chiral column.[9]

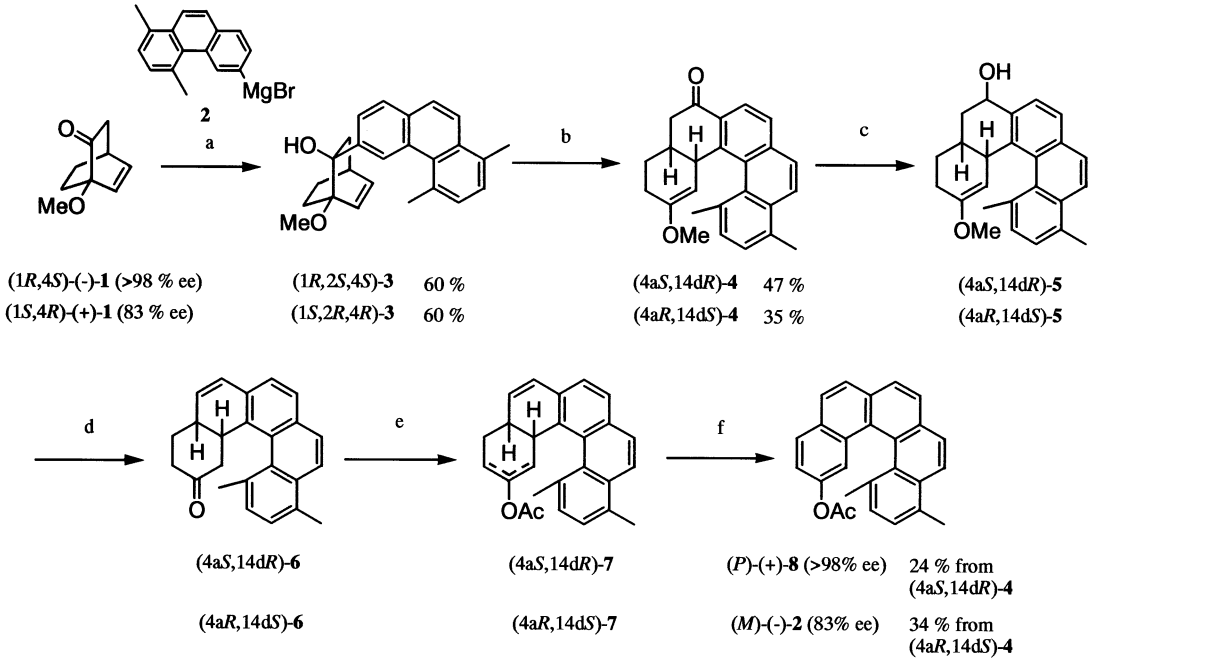
Thus, the chirality of **3** was completely transferred into the helical chirality of **8** during the above transformation. According to the same procedure, its enantiomer, (*M*)-(−)-**8**, was also synthesized from (1*S*,4*R*)-(+)-**1** (Scheme 2). At the first synthesis for (*M*)-(+)-**8**, a small decline of enantiomer excess of (*M*)-(+)-**8** was observed ((+)-**6** (93% ee) gave (+)-**8** (80% ee)). When (+)-**6**, (+)-**7**, and (+)-**8** were refluxed in benzene for several hours, no decline of ee was observed (Table 1).[10] Thus, the racemization occurred during the reactions. When oxidation by DDQ from (+)-**7** to (+)-**8** was conducted in benzene at rt instead of under reflux conditions, the racemization was successfully suppressed.

In contrast to the thermal instability of (*M*)-(−)-pentahelicene,[11] (*M*)-(−)-**8** was sufficiently stable to thermal racemization under heating in octane at 120°C for 24 h. The specific rotations of (*P*)-(+)-**8** (>98% ee) and (*M*)-(−)-**8** (83% ee) were found to be $[\alpha]_D^{25}$ +1243 (*c* 0.0149, $CHCl_3$) and $[\alpha]_D^{25}$ −1005 (*c* 0.0157, $CHCl_3$), respectively. Their absolute configurations were then determined by CD spectra. The CD spectrum of (*P*)-(+)-**8** recorded a distinct positive maximum at 319 nm and a negative maximum at 270 nm, as depicted in Figure 1. The CD spectral characteristic is in good agreement with those of known (*P*)-helicenes,[12] so the absolute configuration of (−)- and (+)-helicenes **8** must be *M* (left-handed helix) and *P* (right-handed helix), respectively.

X-Ray analysis of the [5]helicene **8** was performed on a single crystal, obtained from racemic **8**. As shown in Figure 2, the ORTEP drawing of **8** reveals that the dihedral angles (C1–C22–C21–C20), (C22–C21–C20–C19), and (C21–C20–C19–C18) are 31.2°, 29.6°, and 9.7°, respectively. The deformation of the dihedral angles of the interior side in **8** is mainly attributed to steric repulsion between the methyl group (C23)

Table 1. Thermal stability of chiral intermediates

Entry	Subs. (% ee)	Conditions	% ee
1	(+)-**6** (93)	Benzene, reflux, 4 h	93
2	(+)-**7** (>98)	Benzene, reflux, 14 h	>98
3	(+)-**8** (80)	Benzene, reflux, 8 h	80
4	(+)-**8** (80)	Octane, 120°C, 24 h	80



Scheme 2. Synthesis of 2-acetoxy-11,14-dimethyl[5]helicenes (*P*)-(+)-**8** and (*M*)-(−)-**8**. *Reagents and conditions*: (a) **2**, THF, 0°C–reflux; (b) KHMDS, 18-crown-6, THF, 0°C; (c) $NaBH_4$, EtOH, rt; (d) *p*-TsOH, benzene, rt; (e) LHMDS, Ac_2O, THF, −78°C; (f) DDQ, benzene, rt.

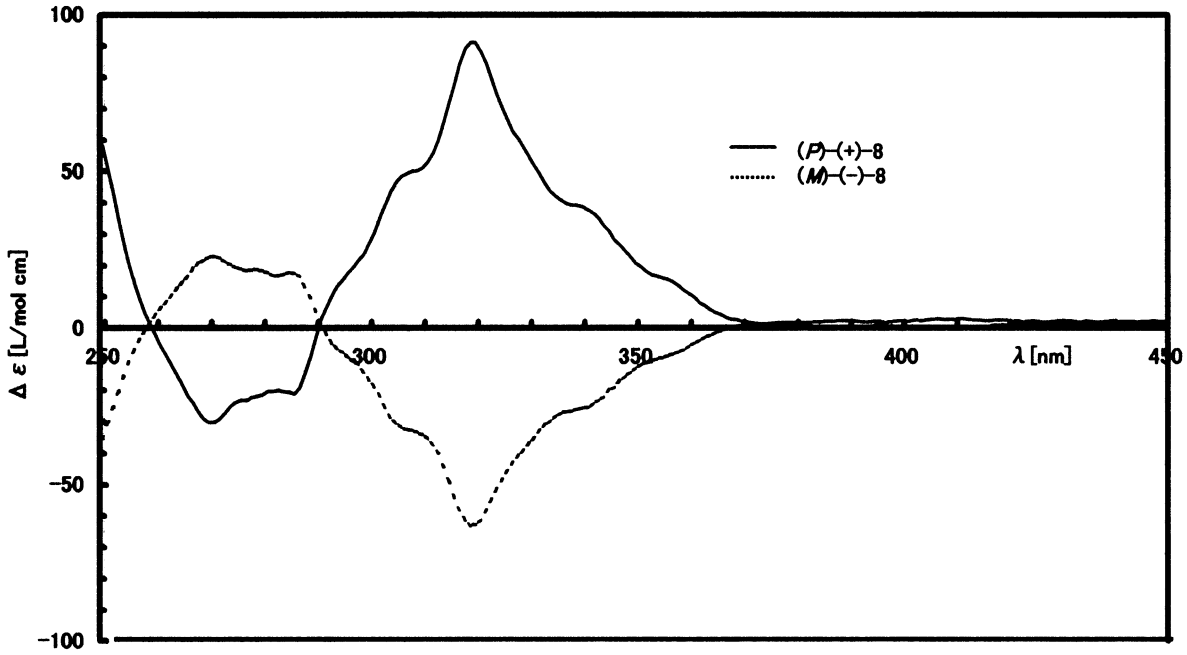


Figure 1. CD spectra of (*P*)-(+)-**8** and (*M*)-(−)-**8** in $CHCl_3$.

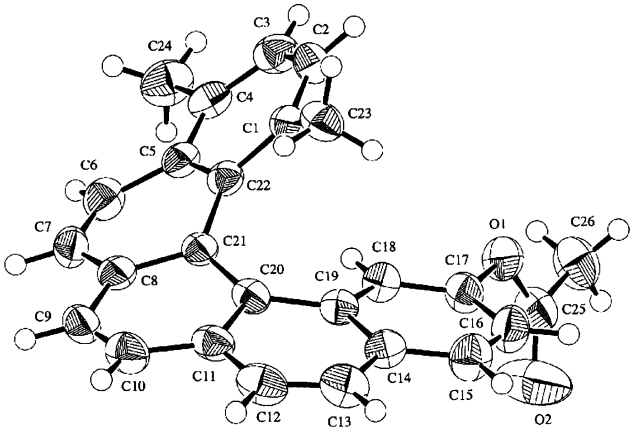
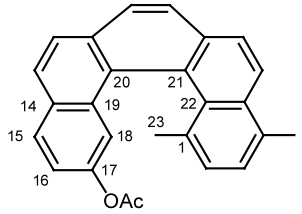
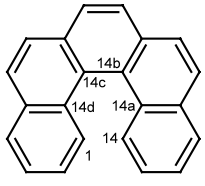


Figure 2. ORTEP drawing of (±)-**8**.



8

(C1-C22-C21-C20)	31.2°
(C22-C21-C20-C19)	29.6°
(C21-C20-C19-C18)	9.7°



pentahelicene

(C14-C14a-C14b-C14c)	33.5°
(C14a-C14b-C14c-C14d)	8.1°
(C14b-C14c-C14d-C1)	36.5°

Figure 3. Dihedral angles of **8** and pentahelicene.

and the benzene ring (C14–C15–C16–C17–C18–C19), in comparison with those of pentahelicene (see Fig. 3) (C14b–C14c–C14d–C1: 36.5°; C14a–C14b–C14c–C14d: 8.1°; C14–C14a–C14b–C14c: 33.5°).[13]

In summary, we have developed a practical method for the synthesis of chiral [5]helicenes using the aromatic oxy-Cope rearrangement strategy. The carbonyl groups of the intermediates **4** and **6** can be easily converted to other functional groups, so that these compounds are useful for further synthetic studies of chiral helical compounds possessing a variety of functionalities.

Acknowledgements

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8. (*P*)-(+)-2-Acetoxy-11,14-dimethyl[5]helicene (**8**) (>98% ee): mp = 138–140°C; IR (KBr) 1758, 1216, 1166 and 845 cm^{-1}; $[\alpha]_D^{25}$ +1243 ($CHCl_3$); CD ($CHCl_3$) $\lambda_{max(nm)}$ ($\Delta\varepsilon$) 408 (−1), 357 (sh, 13), 339 (sh, 37), 319 (88), 306 (sh, 46), 270 (−30); UV–vis ($CHCl_3$) $\lambda_{max(nm)}$ ($\log\varepsilon$) 354 (4.0), 314 (4.5), 288 (4.4), 275(4.5); ^1H NMR (300 MHz, $CDCl_3$) $\delta = 8.07$ (1H, d, $J = 8.7$ Hz), 7.90 (1H, d, $J = 9.0$ Hz), 7.88–7.85 (4H, m), 7.79 (1H, d, $J = 8.7$ Hz), 7.50 (1H, d, $J = 2.4$ Hz), 7.37 (1H, d, $J = 7.2$ Hz), 7.18 (1H, dd, $J = 2.4$ and 8.7 Hz), 7.10 (1H, d, $J = 6.9$ Hz), 2.81 (3H, s), 2.15 (3H, s), 1.58 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta =$ 169.78, 148.10, 133.60, 132.63, 132.38, 131.97, 131.04, 130.96, 130.48, 129.55, 129.06, 128.51, 128.17, 127.44, 126.91, 126.59, 126.54, 126.12, 125.14, 123.74, 120.74, 117.29, 23.01, 20.97, 19.84; EI-MS (70 eV) m/z (%) 364 (M^+, 100), 321 ($[M-C_2H_3O]^+$, 29), 307 ($[M-C_2H_2O_2]^+$, 92): (*M*)-(−)-2-Acetoxy-11,12-dimethyl[5]helicene (**8**) (83% ee): $[\alpha]_D^{25}$ −1005 ($CHCl_3$); CD ($CHCl_3$) $\lambda_{max(nm)}$ ($\Delta\varepsilon$) 411 (3), 359 (sh, −6), 341 (sh, −25), 319 (−63), 306 (sh, −31), 271 (22).
9. Analytical conditions are as follows. (Daicel chiralcel OC), n-C_6H_{14}/2-propanol = 99/1, monitored at 254 nm, flow rate 1.0 ml/min, and Rs = 1.14.
10. Determination of % ee of (+)-**7** was performed on (+)-**6** which was obtained by hydrolysis of (+)-**7**.
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