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Synthesis and Stereochemical Behavior of (*E*)-Cyclononene Derivatives

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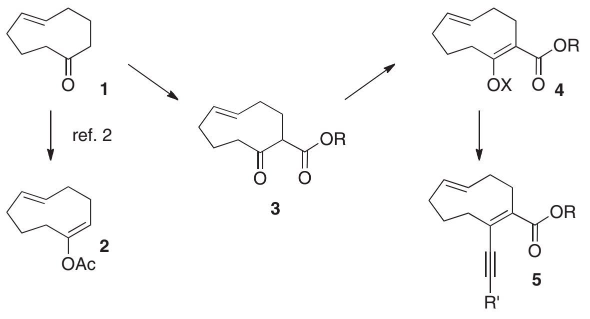
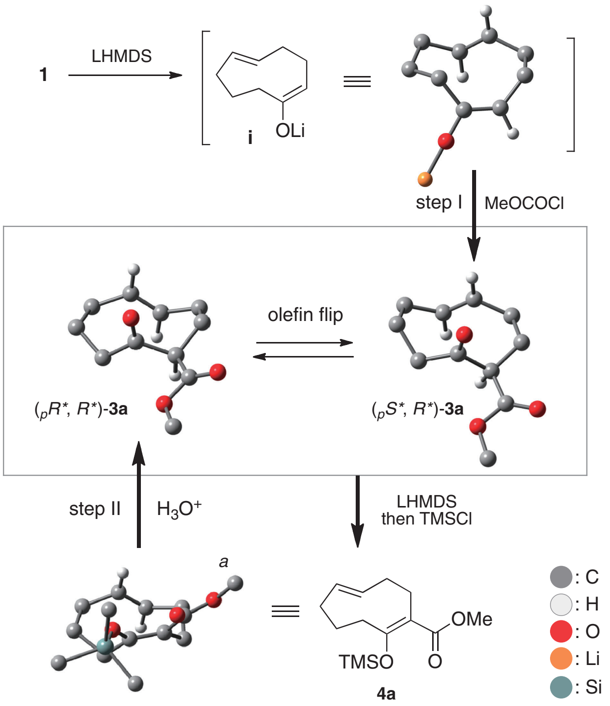
A versatile synthetic approach to planar chiral molecules from (*E*)-5-cyclononen-1-one (**1**) has been developed; these molecules have multifunctionalities with (*E*)-cyclononene skeleton. The newly synthesized keto-ester **3** having central chirality shows labile planar chirality. In contrast, enol derivative **4** and enyne **5** show robust planar chirality.

The planar chirality of medium-sized *trans*-cycloalkenes is an attractive and potentially useful stereochemical property with respect to chiral technology.[1] However, apart from a double bond, medium-sized *trans*-cycloalkenes do not possess other functional groups, which could lead to their further synthetic elaboration. Therefore, the synthetic application of this class of chiral compounds is very limited. Quite recently, we found a novel class of planar chiral, medium-sized compounds containing a synthetically valuable ketone moiety such as (*E*)-5-cyclononen-1-one (**1**).[2,3] This compound exhibits dynamic planar chirality at ambient temperature, and its stereochemical stability is higher than that of (*E*)-cyclononene.[4] Furthermore, we found that ketone **1** could be converted to the corresponding enol acetate **2**, whose planar chirality is more robust than that of **1** (Scheme 1).[2] Owing to the brilliant reactivity of the ketone functionality of **1**, a variety of derivatives having an (*E*)-cyclononene skeleton can be prepared by the transformation of **1**; it is expected that the resulting derivatives will exhibit unique chirality. As a part of studies along these lines, we examined the synthesis of keto-ester **3** having central- and planar chiralities along with a versatile reactivity. Furthermore, we transformed **3** into compounds **4** and **5** having sole planar chirality. Herein, we describe the details of their synthesis and their stereochemical behavior.



Scheme 1. Transformation of ketone **1** via keto-ester **3**.

First, we synthesized keto-ester **3a** (R = Me) from ketone **1** in 88% yield by a reaction with LHMDS in THF–toluene and subsequent acylation with methyl chloroformate.[5,6] It is interesting to note that the ^{1}H NMR analysis of **3a** shows a single set of signals (set-A) immediately after it is synthesized; however, by maintaining **3a** at ambient temperature, another set of signals (set-B) appeared and the ratio reached approximately 1:1 after 2.5 h (Scheme 2). The thus obtained **3a** can be transformed to TMS enol ether **4a** (X = TMS, R = Me) by a reaction with LHMDS in THF and subsequent silylation (65% yield). Furthermore, we also found that acidic hydrolysis of **4a** yields **3a**, which shows only set-B signals, immediately after it is synthesized. These observations along with the molecular modeling of enolate intermediates **i** and **4a** strongly suggest that the acylation of enolate **i** (step I) and the protonation of **4a** (step II) proceed from the outer side of the ring in a stereospecific manner to yield ($_pS^*$,R^*)-**3a** or ($_pR^*$,R^*)-**3a**, respectively.[7] However, the planar chirality of **3a** is labile at ambient temperature, hence the resulting **3a** will contain a 1:1 mixture of diastereomer. DFT calculations confirm that the two epimers of **3a** show almost the same stereochemical stability; the relative Gibbs free energy at 298 K [ΔG(298 K)] is within 0.2 kcal mol^{-1} between ($_pS^*$,R^*)-**3a** and ($_pR^*$,R^*)-**3a**.



^{a} To simplify the explanation, **i** and **4a** were shown by opposite enantiomer each other of planar chirality.

Scheme 2. Synthesis and stereochemical behavior of **3a** and **4a**.

Next, we focused on the stereochemical behavior of enol derivative **4** having no central chirality. We synthesized not only **4a** but also enol tosylate **4b** (X = Ts, R = Me) and enol triflate **4c** (X = Tf, R = Me) from **3a** in good yields (Scheme 3).[8] The

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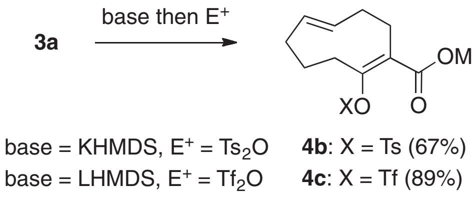
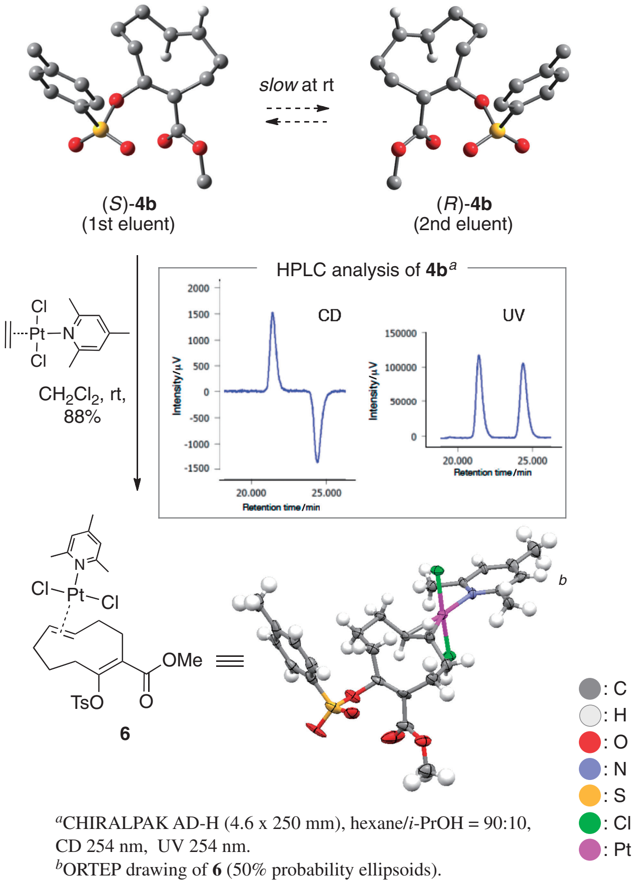


Scheme 3. Synthesis of **4b** and **4c**.

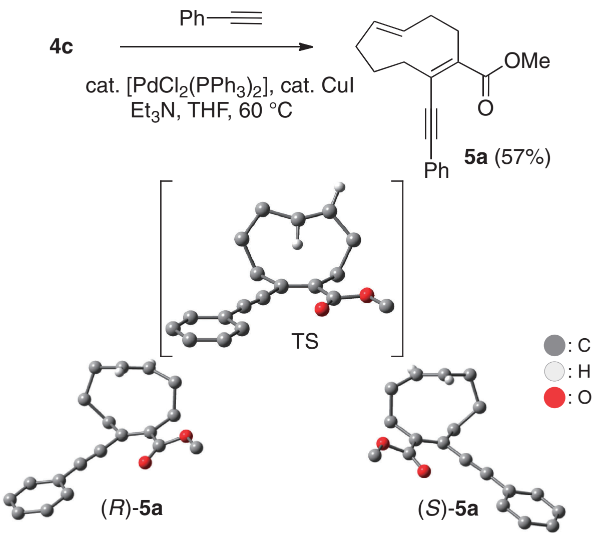


[a] CHIRALPAK AD-H (4.6 x 250 mm), hexane/*i*-PrOH = 90:10, CD 254 nm, UV 254 nm.
[b] ORTEP drawing of **6** (50% probability ellipsoids).

Scheme 4. Stereochemical behavior and determination of absolute stereochemistry of **4b**.

existence of isolable enantiomers of **4b** and **4c** was revealed by an HPLC analysis using a chiral stationary column equipped with a CD spectropolarimeter.[9]

For instance, as shown in Scheme 4, both enantiomers of **4b** were successfully separated on an analytical as well as on a semipreparative scale using an AD-H column. The absolute stereochemistry of the enantiomers of **4b** was determined by an X-ray analysis of a Pt-complex derivative **6**.[10,11] The half-lives of the optical activity of **4b** in hexane at 25, 30, 35, and 40 °C are 330, 168, 86.8, and 47.3 h, respectively. The activation parameter for the racemization of **4b** was calculated from an Eyring plot by analyzing the rate constants of racemization as $\Delta G^{\ddagger}(298\,\mathrm{K}) = 26.4\,\mathrm{kcal\,mol^{-1}}$. This result clearly shows that enol tosylate **4b** has dynamic planar chirality at ambient temperature.[12] We estimated the racemization energy of **4b** by DFT calculations as $\Delta G^{\ddagger}(298\,\mathrm{K}) = 27.7\,\mathrm{kcal\,mol^{-1}}$, which is roughly consistent with the observed result.[13]



Scheme 5. Synthesis and stereochemical analysis of **5a**.

Finally, we examined further transformation of **4c** by the Sonogashira coupling. The reaction of **4c** with phenylacetylene in the presence of cat. $[PdCl_2(PPh_3)_2]$, cat. CuI, and Et_3N afforded enyne **5a** in 57% yield (Scheme 5). The resulting **5a** also shows dynamic planar chirality at ambient temperature; the half-lives of the optical activity of **5a** in hexane at 25, 30, 35, and 40 °C are 114, 57.3, 24.6, and 12.7 h, respectively. The activation parameter for the racemization of **5a** was calculated as $\Delta G^{\ddagger}(298\,\mathrm{K}) = 25.8\,\mathrm{kcal\,mol^{-1}}$. We performed the conformational analysis of **5a** by DFT calculations and found the most stable conformers and transition state $[\Delta G^{\ddagger}(298\,\mathrm{K}) = 26.5\,\mathrm{kcal\,mol^{-1}}]$ for the racemization as shown in Scheme 5. The newly synthesized enol derivatives **4a**–**4c** and enyne **5a** can serve as multifunctionalized chiral building blocks for a variety of planar chiral molecules.

In summary, we described a versatile synthetic approach to planar chiral molecules from (*E*)-5-cyclononen-1-one (**1**). The newly synthesized keto-ester **3** having central chirality shows labile planar chirality. In contrast, enol derivative **4** and enyne **5** show robust planar chirality. Further detailed studies on the relationship between the structure and the stereochemical stability of medium-sized cycloalkenes and their synthetic application are in progress.

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References and Note

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3 Ketone **1** was prepared by a slightly modified procedure of the one described by: T. Kato, H. Kondo, M. Nishino, M. Tanaka, G. Hata, A. Miyake, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2958.

4 Stereochemical study on (*E*)-cyclononene has been reported, see: ref. 1c.

5 All new compounds were fully characterized by IR, ^{1}H-, ^{13}C NMR and HRMS analysis: see, Supporting Information for details.[14]

6 Alkylation reaction of keto-ester **3** has been reported, see: H. Inoue, K. Igawa, K. Tomooka, *Eng. Sci. Rep., Kyushu Univ.* **2010**, *32*, 19.

7 All DFT calculations were performed with Gaussian 03 program at the B3LYP/6-311G(d,p) level of theory.

8 A similar reaction using other base provides **4** in rather low yield; **4b** in 25% yield with LHMDS, **4c** in 50% yield with KHMDS.

9 HPLC analysis of **4a**, **4c**, and **5a**: CHIRALPAK AD-H (4.6 × 250 mm), CD 254 or 292 nm, UV 254 or 292 nm: see, Supporting Information for details.[14]

10 Determination of the absolute stereochemistry of **4b** itself was difficult owing to its noncrystallinity.

11 Recently, we have synthesized a $PtCl_2$(2,4,6-trimethylpyridine) complex of planar chiral molecules. K. Tomooka, M. Shimada, K. Uehara, M. Ito, *Organometallics* **2010**, *29*, 6632, and ref. 2.

12 The magnitude of its stereochemical stability is approximately same with that of (1*E*,5*Z*)-cyclonona-1,5-diene [$\Delta G^{\ddagger}(298\,\mathrm{K}) = 26.5\,\mathrm{kcal\,mol^{-1}}$]; see: A. Deiters, C. Mück-Lichtenfeld, R. Fröhlich, D. Hoppe, *Chem.—Eur. J.* **2002**, *8*, 1833.

13 All transition structures were characterized by analytical frequency calculations: see, Supporting Information for details.[14]

14 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.