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Dynamic Chirality of (*E*)-5-Cyclononen-1-one and its Enolate

Katsuhiko Tomooka,*[,†] Takayuki Ezawa,[‡] Hiroko Inoue,[§] Kazuhiro Uehara,[†] and Kazunobu Igawa[†]

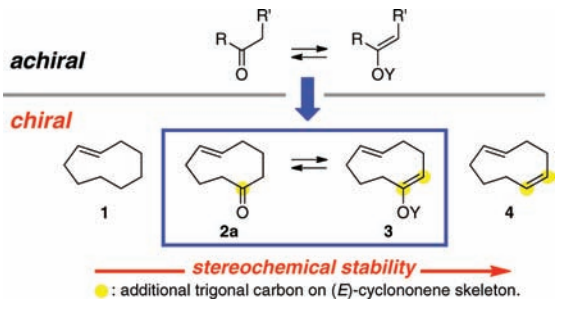
[†]Institute for Materials Chemistry and Engineering, Kyushu University, Kasuga, Fukuoka 816-8580, Japan
[‡]Department of Applied Chemistry, Tokyo Institute of Technology, Meguro-ku, Tokyo 152-8552, Japan
[§]Department of Molecular and Material Sciences, Kyushu University, Kasuga, Fukuoka 816-8580, Japan

Supporting Information

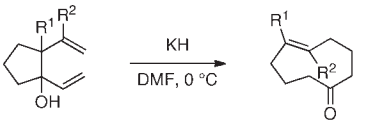
ABSTRACT: It has been found that (*E*)-5-cyclononen-1-one (**2a**) exhibits marginal planar chirality owing to an insufficient topological constraint, whereas the enolates **3** derived from **2a** show robust planar chirality. Enantioenriched enolates are easily prepared by enzymatic hydrolysis, and they show an ability to serve as chiral nucleophiles.

Ketone is one of the most fundamental and important motifs in organic chemistry.[1] While the trigonal planar structure function of ketonic functionalities allows their widespread use as prochiral structural motifs in asymmetric synthesis, little attention has been paid to their use as stereogenic elements. In this situation, introduction of inherent chirality to ketones is a challenging issue, and it would open a new field of molecular chirality. To this end, we anticipated that a ketone incorporated in a reasonably strained *trans*-cycloalkene skeleton may show a unique dynamic chirality without the presence of any stereogenic carbon (Scheme 1). It is well-known that certain medium-sized *trans*-cycloalkenes have planar chirality and their stereochemical stabilities are highly dependent on the ring size.[2] For example, (*E*)-cyclooctene has a remarkably stable planar chirality, whereas its one-carbon homologue (*E*)-cyclononene (**1**) has only marginal chirality.[3,4] On the other hand, the presence of additional trigonal carbon in the ring also may affect the stereochemical stability owing to the decrease of the conformational flexibility. For example, it was estimated by calculation that (1*E*,5*Z*)-cyclonona-1,5-diene (**4**), having two additional trigonal carbons on the (*E*)-cyclononene skeleton, shows more stable chirality than that of **1**.[5,6] On the basis of this structure and stereochemical stability relationship, we expected ketone **2a** having the (*E*)-cyclononene skeleton with one additional trigonal carbon to be a chiral molecule and assumed its stereochemical stability to lie in between those of **1** and **4**.[7] More importantly, conversion of ketone **2a** to enolate **3** should increase the stereochemical stability to a level similar to that of **4**, owing to the introduction of an additional trigonal carbon. Thus, these molecular designs will allow unique control and modification of stereochemical stability by a simple keto−enol transformation.[8−10] Herein, we describe a detailed stereochemical analysis of thus designed ketone and its enolate in addition to their asymmetric synthesis and transformations.

Scheme 1. Design of Dynamic Chiral Ketone 2a and its Enolate 3



Ketone **2a** along with its substituted analogues **2b**−**d** were readily synthesized by a ring-enlarging anionic oxy-Cope rearrangement of **5** in good yields (eq 1).[11]



(1)

5a: R^1 = H, R^2 = H
5b: R^1 = H, R^2 = Me
5c: R^1 = CH_2OH, R^2 = H
5d: R^1 = Me, R^2 = Me

2a: R^1 = H, R^2 = H (86%)
2b: R^1 = H, R^2 = Me (59%)
2c: R^1 = CH_2OH, R^2 = H (65%)
2d: R^1 = Me, R^2 = Me (77%)

The existence of isolable enantiomers of **2a** was revealed by a HPLC analysis using a chilled chiral stationary column equipped with a CD spectropolarimeter. As shown in Scheme 2, both enantiomers of **2a** were successfully separated on an analytical as well as a semipreparative scale.[12]

The half-lives of the optical activity for **2a** in hexane at −5, 0, 5, and 10 °C are 22.1, 10.7, 5.1, and 2.4 h, respectively. The activation parameters for the racemization of **2a** are calculated from an Eyring plot by the analysis of the rate constants of racemization as $\Delta H^{\ddagger}$= 21.7 kcal mol^{-1} and $\Delta S^{\ddagger}$ = −1.96 cal mol^{-1} K^{-1}.[13] This result clearly demonstrates that ketone **2a** has dynamic chirality at ambient temperature and its stereochemical stability is higher than that of **1** ($\Delta H^{\ddagger}$ = 19.4 kcal mol^{-1}),[4] as we expected. The absolute stereochemistry of enantiomers of **2a** was determined by formation of a Pt-complex derivative as shown in Scheme 2.[14,15] Reaction of *rac*-**2a** with $PtCl_2$(2,4,6-trimethylpyridine)(CH_2=CH_2) provided *rac*-**6** in 92% yield, and its separation by chiral HPLC afforded both

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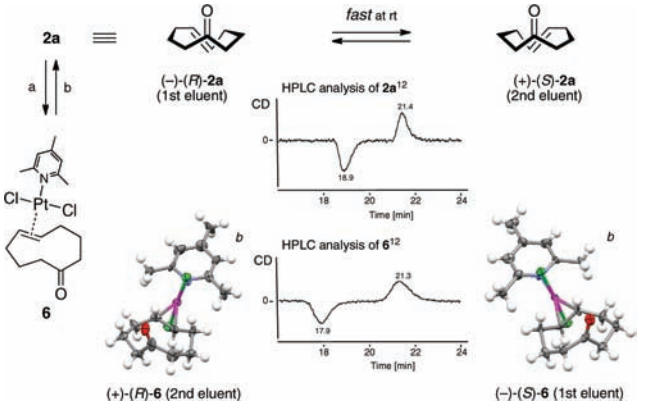
Scheme 2. Stereochemical Behavior and Determination of Absolute Stereochemistry of Ketone 2a[a]



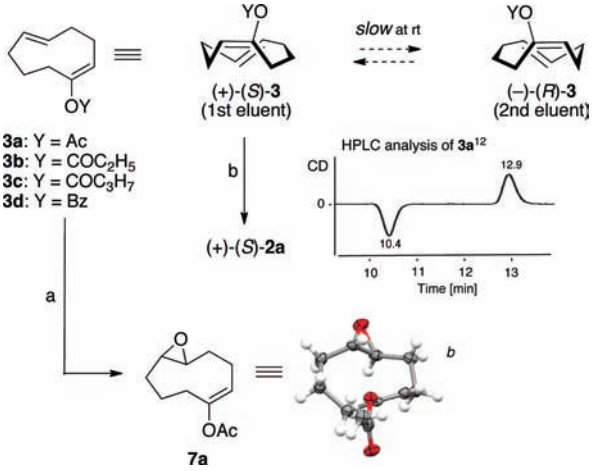
[a] Reagents and conditions: (a) $PtCl_2$(2,4,6-trimethylpyridine)(CH_2=CH_2), CH_2Cl_2, rt, 92%; (b) PPh_3, CH_2Cl_2, −30 °C. [b]ORTEP drawing of **6** (60% probability ellipsoids).

enantiomers of **6** in enantiopure crystalline form.[12] X-ray diffraction revealed the stereochemistry of the (−)-isomer of **6** to be (*S*) and that of the (+)-isomer of **6** to be (*R*).[16] Treatment of (*S*)-**6** with PPh_3 at −30 °C provided **2a** as an enantioenriched form, and its CD spectrum was identical to that of (+)-**2a**; therefore, we unequivocally determined that (+)-**2a** has an (*S*)-configuration. Furthermore, we found that substituted analogues **2b**−**d** also possess planar chirality at ambient temperature, as revealed by chiral HPLC analysis.[12] Monosubstituted **2b** and **2c** are stereochemically less stable than **2a** ($t_{1/2}$ = 4.1 and 1.6 h, respectively, at 0 °C in hexane).[13] In contrast, introduction of dimethyl substituents in the olefin moiety dramatically increased the stereochemical stability; enantiopurity of **2d** remained unchanged at 40 °C for at least 200 h.[17] These results demonstrate that it is possible to produce chiral ketones having a variable stereochemical stability by introducing the appropriate substituent on the olefin.

With the dynamic chiral ketone in hand, we next turned our attention to changing stereochemical behavior via a keto−enol transformation. Enol acetate **3a** was prepared from ketone **2a**, as a sole (*E*)-isomer in 67% yield by a reaction with KH in DME and subsequent acetylation. The configuration of **3a** was determined by X-ray analysis of its epoxide **7a** (Scheme 3).[16]

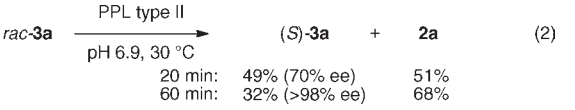
Using similar chiral HPLC separation and a measurement of the half-lives of the optical activity mentioned above, we found that **3a** has robust chirality ($t_{1/2}$ = 134 h, at 25 °C in hexane) ($\Delta H^{\ddagger}$ = 24.5 kcal mol^{-1}, $\Delta S^{\ddagger}$ = −4.20 cal mol^{-1} K^{-1}).[12,18] The difference in the half-lives of the optical activity between **3a** and **2a**, which was estimated by a calculation, indicates that a simple keto−enol transformation increases the stereochemical stability by *more than 520 times* at 0 °C. A transformation from **3a** to **2a** with retention of optical activity was achieved by a low-temperature treatment with an alkyl lithium reagent such as MeLi or *n*-BuLi followed by protonation. By applying this procedure, the absolute stereochemistry of (+)-**3a** was determined as (*S*) by comparison of the specific rotation and CD spectrum after conversion to ketone **2a**. We also prepared **3b**−**d** bearing different ester groups. Stereochemical analysis shows that the difference in ester moiety (Y) does not significantly influence the stereochemical stability ($t_{1/2}$ = 114 h for **3b**, 130 h for **3c**, 122 h for **3d** at 25 °C in hexane).[12,19,20]

Scheme 3. Stereochemical Behavior and Determination of Absolute Stereochemistry of Enolate 3[a]



[a] Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C, 53%; (b) *n*-BuLi, THF, −78 °C. [b]ORTEP drawing of **7a** (60% probability ellipsoids).

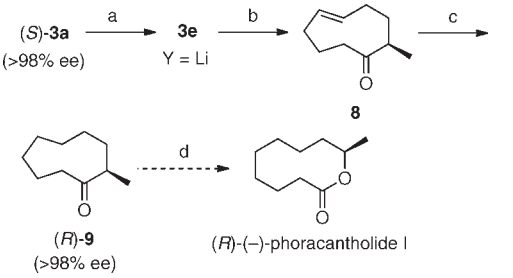
It is noteworthy that the ester moiety of **3** permits hydrolysis which provides an opportunity for kinetic resolution of enantiomers of **3** by enzyme-mediated asymmetric hydrolysis.[21] For instance, a reaction of *rac*-**3a** with porcine pancreatic lipase (PPL) type II provides (*S*)-**3a** with 70% ee and >98% ee in 49% and 32% yields, respectively (eq 2).[22] Thus, a large-scale preparation of enantioenriched **3** via this simple technique can be accomplished.



(2)

The molecular modeling shows that the enolate plane of **3** is approximately perpendicular to the plane of the ring; thus, the intermolecular reaction is expected to occur only from the outer peripheral face. Therefore, the planar chirality of enolate **3** can be transformed to central chirality in a stereospecific manner. Indeed, a reaction of lithium-enolate **3e** derived from (*S*)-**3a** (>98% ee) with methyl iodine and subsequent hydrogenation provided chiral ketone (*R*)-**9** (>98% ee) which is known as a key intermediate in an asymmetric synthesis of (*R*)-(−)-phoracantholide I, a component of the defensive secretion of the eucalypt longicorn beetle (Scheme 4).[23−26]

Scheme 4. Transformation of Planar Chirality of 3 to Central Chirality[a]



[a] Reagents and conditions: (a) MeLi, THF, −78 °C; (b) MeI, THF, −78 → 0 °C, 88% (2 steps); (c) H_2, 10% Pd−C, AcOEt, rt, 97%; (d) *m*-CPBA; see ref.[25,26]

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In summary, we have shown that newly designed cyclic ketone exhibits marginal planar chirality owing to an insufficient topological constraint. This chiral ketone can be converted to the corresponding enolate derivatives that possess robust planar chirality. In other words, the stereochemical behavior of a medium-sized cycloalkene can be drastically changed by introduction of a ketone moiety as well as by a keto−enol transformation. This phenomenon should be applied to a wide range of molecules to develop novel dynamic chiral chemistry.

■ ASSOCIATED CONTENT

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

■ AUTHOR INFORMATION

Corresponding Author
ktomooka@cm.kyushu-u.ac.jp

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(2) For reviews, see (a) Marshall, J. A. *Acc. Chem. Res.* **1980**, *13*, 213–218. (b) Nakazaki, M.; Yamamoto, K.; Naemura, K. *Top. Curr. Chem.* **1984**, *125*, 1–25. (c) Schlögl, K. *Top. Curr. Chem.* **1984**, *125*, 27–62.(d) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 1172−1175.

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(5) The activation parameters for the racemization of **4** was estimated as $\Delta H^{\ddagger}$ = 25.9 kcal mol^{-1} by Hoppe's group; see Deiters, A.; Mück-Lichtenfeld, C.; Fröhlich, R.; Hoppe, D. *Chem.—Eur. J.* **2002**, *8*, 1833–1842.

(6) We have reported that heterocycle congeners of **4** have stable planar chirality at ambient temperature; see (a) Tomooka, K.; Komine, N.; Fujiki, D.; Nakai, T.; Yanagitsuru, S. *J. Am. Chem. Soc.* **2005**, *127*, 12182–12183. (b) Tomooka, K.; Suzuki, M.; Shimada, M.; Yanagitsuru, S.; Uehara, K. *Org. Lett.* **2006**, *8*, 963–965. (c) Uehara, K.; Tomooka, K. *Chem. Lett.* **2009**, *38*, 1028–1029.

(7) Ketone **2a** has been reported by two groups already; however, its stereochemical behavior has not yet been reported. (a) Lange, G. T.; Hall, T.-W. *J. Org. Chem.* **1974**, *39*, 3819–3822. (b) Kato, T.; Kondo, H.; Nishino, M.; Tanaka, M.; Hata, G.; Miyake, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2958–2961.

(8) Owing to the symmetric structure of **2a**, only one regioisomer of **3** is present.

(9) It is known that the length of the C=C bond of enol ether is nearly identical to that of simple alkene; see Samdal, S.; Seip, H. M. *J. Mol. Struct.* **1975**, *28*, 193–203. Therefore, it can be anticipated that the rigidity of the ring conformation, and hence the stereochemical stability of **3**, would be at a level similar to that of **4**

(10) The generation and synthetic application of dynamic chiral enolate from α-chiral ketone has been reported by Fuji and Kawabata's group; see (a) Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694–9696. (b) Fuji, K.; Kawabata, T. *Chem.—Eur. J.* **1998**, *4*, 373–376 and references cited therein.

(11) Kato and coworkers originally synthesized **2a** in 60% yield by a thermal oxy-Cope rearrangement of **5a**; see ref 7b. A similar transformation by anionic oxy-Cope rearrangement provides a rather high yield of **2a** (86%). For a review of a ring-enlarging oxy-Cope rearrangement, see Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609–626.

(12) Analytical HPLC and GC: CHIRALPAK AS-H (4.6 mm × 250 mm) for **2a**, **2b**, **2d**; CHIRALPAK AD-H (4.6 mm × 250 mm) for **3a**−**d**; CHIRALCEL OD-H (4.6 mm × 250 mm) for **2c**, **6**; SUPELCO γ-DEX 225 (0.25 mm × 30 m) for **9**; see Supporting Information for details.

(13) We estimated the racemization energy by DFT calculation [B3LYP/6-311G(d,p)] as $\Delta E^{\ddagger}$ = 22.2, 20.7, and 26.7 kcal mol^{-1} for **2a**, **2b**, and **3a**, respectively; see Supporting Information for details.

(14) Determination of the absolute stereochemistry of **2a** itself was difficult, owing to its stereochemical instability at ambient temperature and noncrystallinity.

(15) Recently, we have synthesized a $PtCl_2$(2,4,6-trimethylpyridine) complex of planar chiral nitrogencycles. Tomooka, K.; Shimada, M.; Uehara, K.; Ito, M. *Organometallics* **2010**, *29*, 6632–6635.

(16) The structures of **6** and **7a** were determined by X-ray crystallography; see Supporting Information.

(17) Stereochemical stabilizing effect of dimethyl substituent in (*E*)-cyclodecene system has been reported; see Marshall, J. A.; Konicek, T. R.; Flynn, K. E. *J. Am. Chem. Soc.* **1980**, *102*, 3287–3288.

(18) By comparison of activation parameters for the racemization, a stereochemical stability of **3a** lies between those of compounds **1** and **4** (ref 5).

(19) (*E*,*E*)-Stereochemistry of **3d** was determined by X-ray diffraction of $PtCl_2$(2,4,6-trimethylpyridine) complex derivative; see Supporting Information for details.

(20) Silyl enol ether congener of **3** has been synthesized; see Kende, A. S.; Nelson, C. E. M.; Fuchs, S. *Tetrahedron Lett.* **2005**, *46*, 8149–8152. However, its stereochemical behavior has not been reported.

(21) Enzyme-mediated asymmetric hydrolysis of prochiral or α-chiral enolates has been reported; see (a) Matsumoto, K.; Ohta, H. *Chem. Lett.* **1989**, 1109–1112. (b) Matsumoto, K.; Tsutsumi, S.; Ihori, T.; Ohta, H. *J. Am. Chem. Soc.* **1990**, *112*, 9614–9619.

(22) We measured the conversion yields by HPLC analysis. The enantiopurity of ketone **2a** was not determined due to its rapid racemization. We also performed a 100-mg-scale reaction and isolated an enantioenriched **3a** in 32% yield with >96% ee; see Supporting Information for details.

(23) We have observed a rapid epimerization of **8** in terms of planar chirality at ambient temperature.

(24) This result also shows that interconversion of enolates **3** (Y = Ac → Li) under these conditions proceeds without loss of enantiopurity.

(25) *rac*-**8** and *rac*-**9** have been synthesized and ulitized as a precursor of rac-phoracantholide I by Baldwin's group; see Baldwin, J. E.; Adlington, R. M.; Singh, R. *Tetrahedron* **1992**, *48*, 3385–3412.

(26) (*R*)-**9** has been synthesized and ulitized as a precursor of (*R*)-(−)-phoracantholide I by Enders's group; see Enders, D.; Plant, A.; Drechsel, K.; Prokopenko, O. F. *Liebigs Ann.* **1995**, 1127–1128.