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SYNTHESIS AND STEREOCHEMICAL ANALYSIS OF DYNAMIC PLANAR CHIRAL NINE-MEMBERED DIALLYLIC AMIDE: SIGNIFICANT SUBSTITUENT EFFECT ON STEREOCHEMICAL STABILITY

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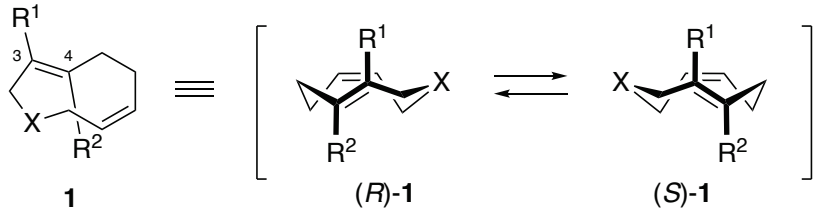
Abstract – C4-Methyl substituted nine-membered diallylic cyclic amide **1ac** was synthesized. HPLC analysis using a chiral stationary phase revealed the presence of isolable enantiomers, whose absolute stereochemistry were determined by X-ray analysis. Studies on the stereochemical stability of **1ac** showed that its chirality is more labile than that of the non-substituted congener **1aa** and C3-methyl substituted congener **1ab**.

Recently, we found that a series of nine-membered diallylic heterocycles **1** displayed appreciable planar chirality arising from the topological constraints in the ring system.[1] The stereochemical stability of **1** was strongly dependent on the heteroatom X (NY, O, SO_n) embedded in the ring and the substituent R on the alkene moiety.



Dedicated to Prof. Dr. Tohru Fukuyama on the occasion of his 70th birthday

As a part of our stereochemical studies on **1**, we revealed that the introduction of a substituent at the C3 position increases the stereochemical stability; the half-lives of the optical activity of the nonsubstituted tosyl-amide **1aa** and C3-methyl substituted congener **1ab** at 25 °C in *n*-hexane are 352 h and 2,114 h, respectively.[1c] To systematically analyze substituent effects on the stereochemical stability of planar chiral heterocycles, we synthesized C4-methyl substituted congener **1ac** and found that its chirality is significantly less stable than that of **1aa** and **1ab** (Figure 1).

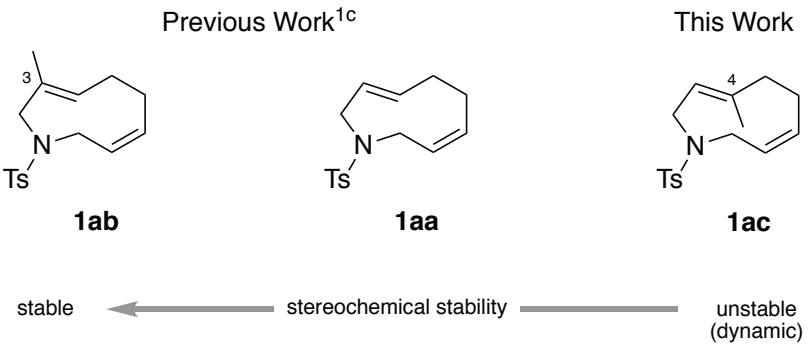
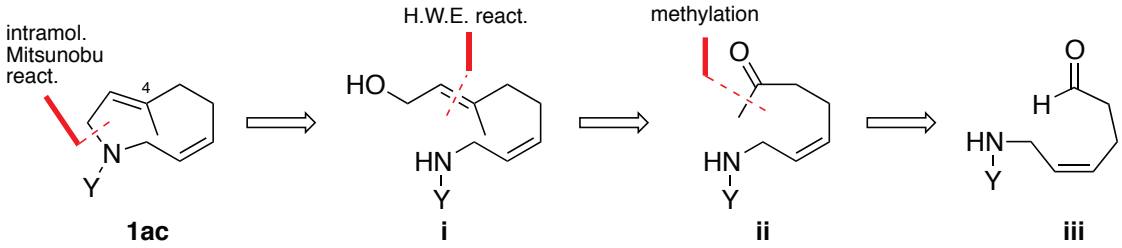


Figure 1. Stereochemical stability of planar chirality of **1a**

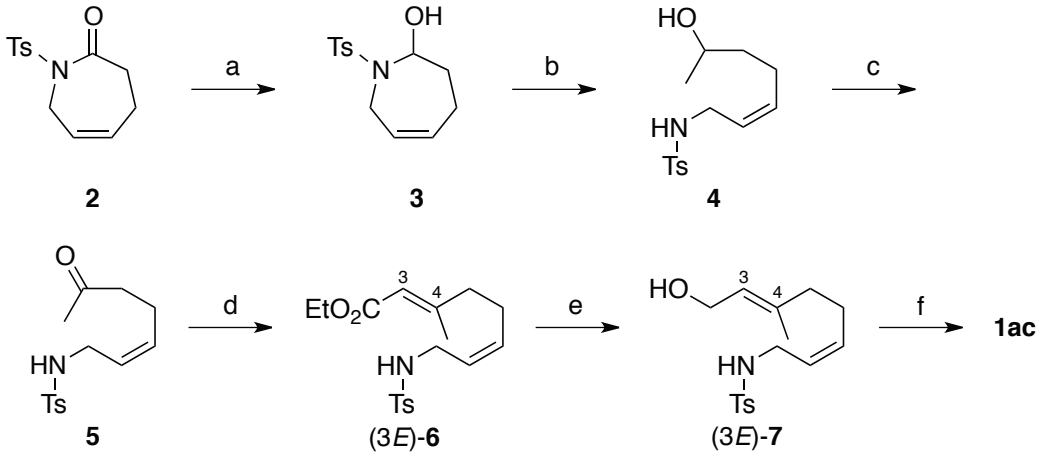
Scheme 1 illustrates the retrosynthetic analysis of **1ac** (Y = Ts). We planned to construct the strained nine-membered skeleton of **1ac** in the final step via C–N bond formation by the intramolecular Mitsunobu reaction of aminoalcohol **i**,[2,3] which can be prepared by the Horner–Wadsworth–Emmons (H.W.E.) reaction of methylketone **ii**, derived from aldehyde **iii** through methylation and oxidation.



Scheme 1. Retrosynthetic analysis of **1ac**

The synthesis of **1ac** was started from our previously reported ε-lactam **2** (Scheme 2).[1c] DIBAL reduction of **2** gave hemiaminal **3**, a tautomer of aldehyde **iii** (Y = Ts).[4] The reaction of **3** with excess methyllithium afforded secondary alcohol **4** in 78% yield (two steps from **2**). Oxidation of **4** with PDC (89% yield), followed by the H.W.E. reaction, provided ester **6** with moderate *E*-selectivity (78% yield, 3*E*/3*Z* = 64:36). After the separation of (3*E*)-**6** and (3*Z*)-**6** by silica gel column chromatography, reduction of (3*E*)-**6** using DIBAL provided aminoalcohol (3*E*)-**7** [≡ **i** (Y = Ts)] in 88% yield. Then,

(3*E*)-**7** was subjected to the intramolecular Mitsunobu reaction; treatment of (3*E*)-**7** with DEAD and PPh_3 in THF under high-dilution conditions (0.01 M) afforded the desired cyclic amide **1ac** in 72% yield.[5,6]



Scheme 2. Reagents and conditions: (a) DIBAL, CH_2Cl_2, –78 °C; (b) MeLi, THF–Et_2O, –78 °C, 78% (2 steps); (c) PDC, CH_2Cl_2, rt, 89%; (d) $EtOCOCH_2PO(O$*i*$-Pr)_2$, *n*-BuLi, DME, 0→85 °C, 78%, 3*E*/3*Z* = 64:36; (e) DIBAL, CH_2Cl_2, –78→0 °C, 88%; (f) DEAD, PPh_3, THF, 0 °C, 72%

The ^{1}H NMR spectrum of **1ac** in $CDCl_3$ at ambient temperature showed signals attributed to four sets of nonequivalent geminal methylene protons, suggesting that **1ac** showed planar chirality in solution on the NMR time scale. The presence of isolable enantiomers of **1ac** was revealed by HPLC analysis using a chiral stationary phase.

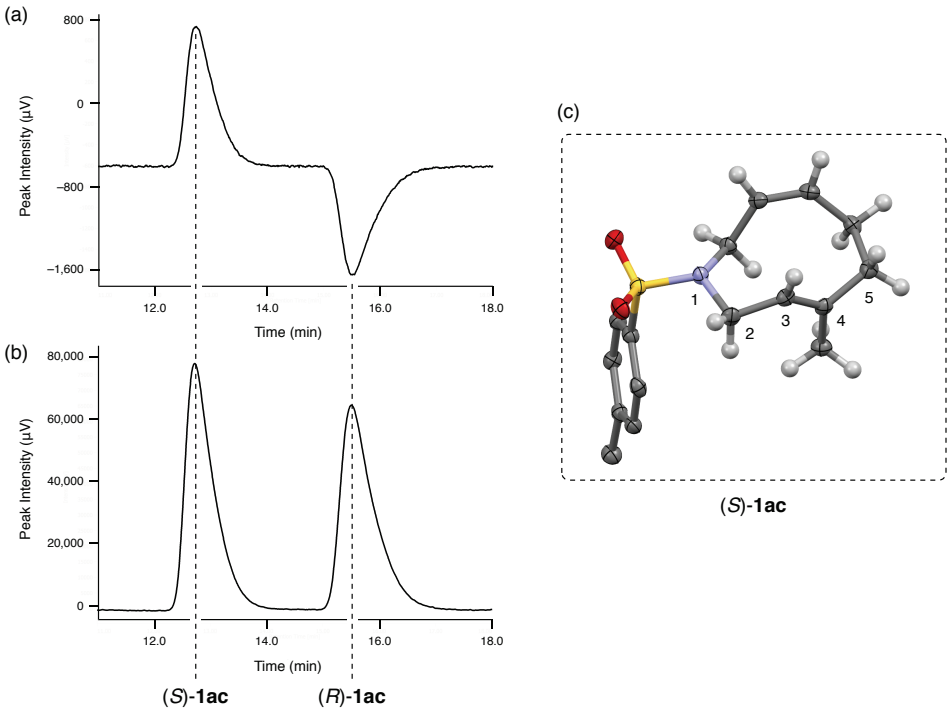


Figure 2. HPLC and X-ray analysis of **1ac**: (a) chromatogram with a CD detector; (b) chromatogram with a UV detector; and (c) ORTEP drawing of (*S*)-**1ac** (ellipsoid set at 50% of probability level)

As shown in Figure 2, both enantiomers of **1ac** were successfully separated by analytical and semipreparative-scale HPLC using a CHIRALPAK AS–H column at ambient temperature; the CD signs of the first and second eluates were + and –, respectively, at 240 nm.[7] Further, the first eluate afforded a crystal suitable for X-ray analysis upon recrystallization at –35 °C, and the absolute stereochemistry of (+)-**1ac** was established as *S*.[8] The rate constants for racemization in *n*-hexane were obtained by HPLC measurements of enantiopurity at proper time intervals.[7] The plot of ln *a* [$a = |S - R| / (S + R)$] versus time furnished a straight line, affording the first-order rate constant *k*. The half-lives of the optical activity of **1ac** at 15, 20, 25, 30, and 35 °C were 31.6, 15.3, 8.19, 3.98, and 2.14 h, respectively [Figure 3(a)]. The activation parameters for the racemization of **1ac** were obtained from the Eyring plot of the rate constants [$\ln(k'\cdot T^{-1}$; $k' = k/2$) versus T^{-1}], as $\Delta H^{\ddagger}$= 23.2 kcal mol^{-1} and $\Delta S^{\ddagger}$= –3.32 cal mol^{-1} K^{-1} [Figure 3(b)]. This kinetic study revealed that the planar chirality of **1ac** is more dynamic than that of the previously reported **1aa** and **1ab** [$\Delta G^{\ddagger}_{(298\ \mathrm{K})}$ for **1aa**, **1ab**, and **1ac** is 26.4, 27.5, and 24.2 kcal mol^{-1}, respectively.].[1c]

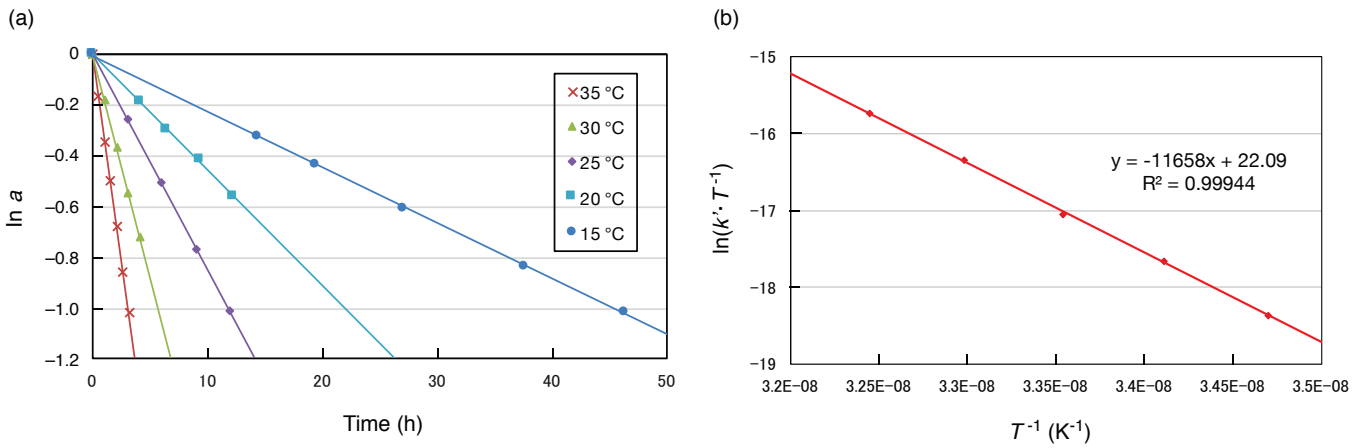


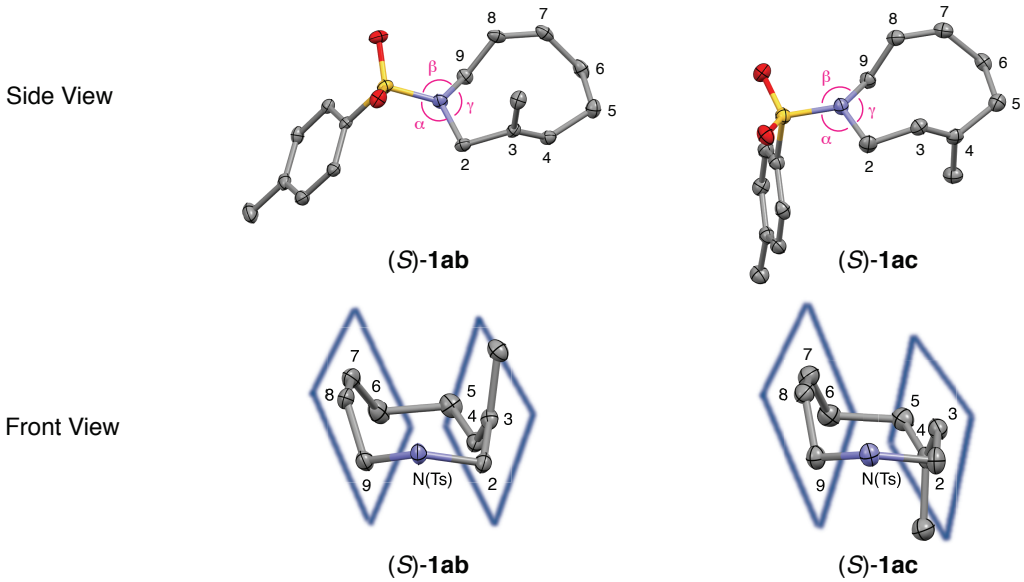
Figure 3. (a) Kinetic measurements for the racemization of **1ac**; and (b) Eyring plot for the racemization of **1ac**

The X-ray crystallographic analyses of **1ab**[9] and **1ac** show their structural differences in the solid state [Figure 4(a)]. The sum of the bond angles of the nitrogen atom (α, β, γ) is 359.0° for **1ab** and 352.3° for **1ac**, which suggests the nitrogen atom of **1ab** has stronger sp^2 characteristics than that of **1ac** [Figure 4(a), 1)]. The *E*-alkene moieties of **1ab** and **1ac** are significantly twisted (dihedral angle ∠C2C3C4C5, **1ab**: 150.8°; **1ac**: 154.5°), and the deviation of the dihedral angle from 180° is 29.2° and 25.5°, respectively, which suggests that the *E*-alkene of **1ab** has a larger strain than that of **1ac** [Figure 4(a), 2)]. On the other hand, the *Z*-alkene moieties of **1ab** and **1ac** are almost flat (dihedral angle ∠C6C7C8C9, **1ab**: 0.9°; **1ac**: 3.1°) [Figure 4(a), 3)]. The relative configuration of the *E*, *Z*-alkene moieties is determined based on the dihedral angle of the C2C3C4-plane and C7C8C9-plane (**1ab**: 42.5°; **1ac**: 29.6°), and that of the

C3C4C5-plane and C6C7C8-plane (**1ab**: 31.6°; **1ac**: 25.8°). This means that the *E*, *Z*-alkene moieties of **1ac** are in near-parallel arrangement than that of **1ab** [Figure 4(a), 4), 5)].

To understand the significant difference between the stereochemical stabilities of **1ab** and **1ac**, it is essential to compare the transition states for racemization.[10] The energy barrier for the transition state depends on the ease of flipping of the *E*-alkene moiety [Figure 4(b)].[1c] In the case of **1ab**, *E*-alkene flips to the direction that allows for the C4-hydrogen to pass through the ring for the racemization, because the C3-methyl cannot pass through the ring. In the case of **1ac**, the *E*-alkene flips in the opposite direction that allows for the C3-hydrogen pass through the ring. Such differences in the flipping mode may be responsible for the significant difference in stereochemical stability.

(a)

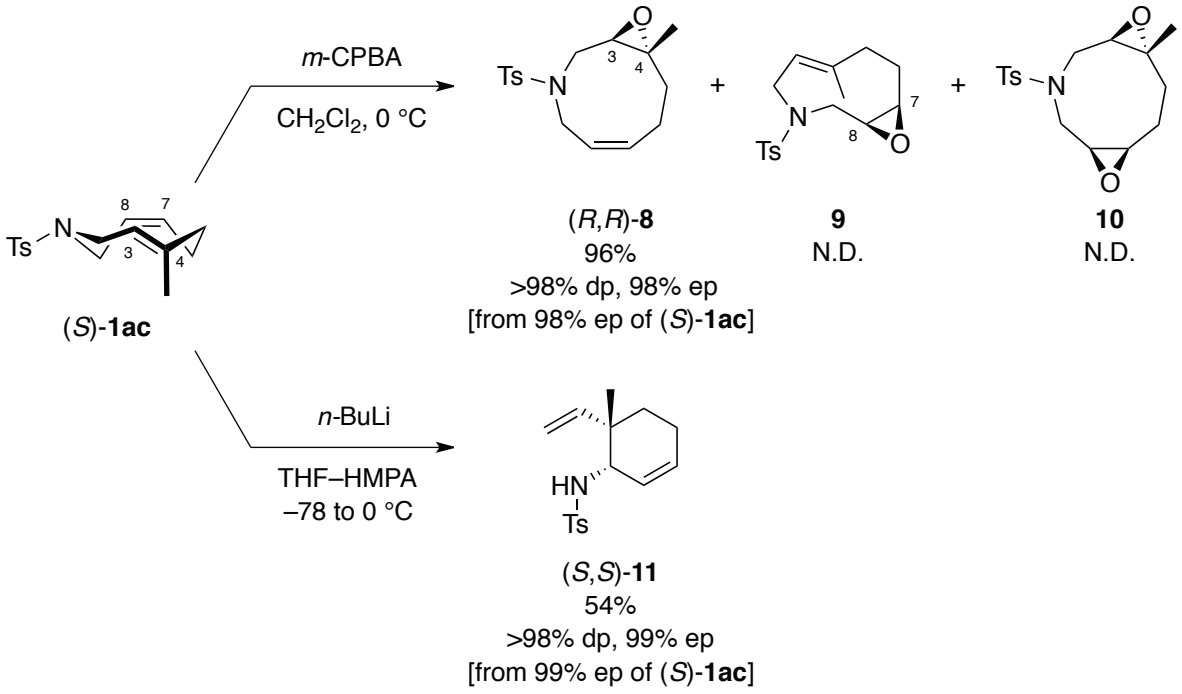


	(*S*)-**1ab**	(*S*)-**1ac**
1) sum of α, β, γ	359.0°	352.3°
2) dihedral angle of *E*-alkene moiety: ∠C2C3C4C5 (deviation of the dihedral angle from 180°)	150.8° (29.2°)	154.5° (25.5°)
3) dihedral angle of *Z*-alkene moiety: ∠C6C7C8C9	0.9°	3.1°
4) ∠plane(C2C3C4)–(C7C8C9)	42.5°	29.6°
5) ∠plane(C3C4C5)–(C6C7C8)	31.6°	25.8°

(b)

Figure 4. (a) ORTEP drawing of (*S*)-**1ab** (ellipsoid set at 25% of probability level) and (*S*)-**1ac** (ellipsoid set at 50% probability level); and (b) Direction of *E*-alkene flipping for the racemization of **1ab** and **1ac**

Although the enantioenriched **1ac** obtained by HPLC separation racemizes slowly at ambient temperature, it is easy to handle without significant racemization at low temperature. The reaction of (*S*)-**1ac** (98% ep[11]) with *m*-CPBA at 0 °C provided C3–C4 epoxide (*R*,*R*)-**8**[12,13] (96%, >98% dp, 98% ep) without loss of enantiopurity, while epoxide **9** and diepoxide **10** were not detected (N.D.).[1a,1b,14] The high group selectivity between the *E*-alkene and *Z*-alkene moieties can be explained by the difference in distortion: the *E*-bond is twisted by ca. 26°, while the *Z*-bond is almost flat (twisted by only ca. 3°), as mentioned above.[15] Furthermore, the reaction of (*S*)-**1ac** (99% ep) with *n*-BuLi in THF–HMPA at –78 to 0 °C afforded the transannular aza-[2,3]-Wittig rearrangement product (*S*,*S*)-**11**[16] (54%, >98% dp, 99% ep) in a stereospecific manner (Scheme 3).[1a,1c,1d,17]



Scheme 3. Transformation of (*S*)-**1ac**

In summary, we have synthesized C4-methyl substituted nine-membered diallylic amide **1ac** and investigated its stereochemical behavior. Compound **1ac** has isolable enantiomers at ambient temperature, and its stereochemical stability is more labile than that of the non-substituted congener **1aa**, and C3-methyl substituted congener **1ab**. Moreover, the absolute stereochemistry of the enantiomers of **1ac** was determined by X-ray analysis. The planar chirality of **1ac** was converted into central chirality of carbon in a stereospecific fashion. Further detailed studies on the racemization mechanism and synthetic applications of **1a** derivatives are in progress.

ACKNOWLEDGEMENTS

This research was supported by JSPS KAKENHI Grants JP16H04113 and JP18H04419 in Middle Molecular Strategy, and the Cooperative Research Program "NJRC Mater. & Dev.". We thank T. Nishi (Kyushu University) for assistance with the HRMS measurements.

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4. A trace amount of aldehyde tautomer was observed by ^{1}H NMR analysis (<5%).
5. **1ac**: colorless crystals; IR (crystal using a diffuse reflector) cm^{-1}: 2936, 1598, 1494, 1339, 1160, 1097, 1030, 943, 889, 816; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.69 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.70 (dddd, *J* = 11.4, 11.1, 4.5, 1.2 Hz, 1H), 5.44-5.35 (m, 1H), 5.19 (dd, *J* = 11.4, 4.2 Hz, 1H), 4.13 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.82 (dd, *J* = 13.8, 4.5 Hz, 1H), 3.49 (dd, *J* = 11.4, 10.8 Hz, 1H), 2.58 (dd, *J* = 13.8, 11.4 Hz, 1H), 2.44 (s, 3H), 2.19-2.11 (m, 2H), 1.89-1.77 (m, 1H), 1.72-1.63 (m, 1H), 1.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 143.0, 139.9, 136.1, 133.0, 129.6, 127.9, 127.1, 122.9, 47.3, 44.0, 36.8, 25.7, 21.7, 17.1; Mp (racemate): 82.1–83.3 °C; HRMS (EI, positive): calcd for $C_{16}H_{21}NO_2S$ $[M]^+$ 291.1293, found 291.1293.
6. The Mitsunobu reaction of a mixture of aminoalcohol (3*E*)-**7** and (3*Z*)-**7** (70:30) afforded a mixture of cyclic amide (3*E*)-**1ac** and (3*Z*)-**1ac** (71:29), and these isomers are difficult to separate by standard silica gel column chromatography. Thus, the separation of the *E*/*Z* isomers of **6** or **7** before the Mitsunobu reaction is reasonable.
7. Analytical-scale HPLC [column: CHIRALPAK AS-H (4.6 × 250 mm), eluent: hexane/*i*-PrOH = 1:1, flow rate: 0.5 mL/min, detection: UV 240 nm, temperature: 25 °C]: t_1 = 12.7 min [(*S*)-isomer], t_2 = 15.5 min [(*R*)-isomer] or [column: CHIRALPAK AD-H (4.6 × 250 mm), eluent: hexane/*i*-PrOH = 1:1, flow rate: 0.5 mL/min, detection: UV 254 nm, temperature: 0 °C]: t_1 = 15.8 min [(*R*)-isomer], t_2 = 23.6 min [(*S*)-isomer]; semipreparative-scale HPLC [column: CHIRALPAK AS-H (20 × 250 mm), eluent: hexane/EtOH = 9:1, flow rate: 8.0 mL/min, detection: UV 254 nm, temperature: rt]: t_1 = 24.6

min [(*S*)-isomer], t_2 = 31.9 min [(*R*)-isomer].

8. Deposition number for compound (*S*)-**1ac** is CCDC 1871154. Selected crystallographic data: orthorhombic, $P2_12_12_1$ (No. 19), a = 9.6912(4) Å, b = 12.077(5) Å, c = 12.746(5) Å, V = 1492(11) Å^3, Z = 4, R_1 = 0.0367, wR_2 = 0.0917, Flack parameter = 0.047(11). Free copies of the data can be obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html.
9. Deposition number for compound (*S*)-**1ab** is CCDC 1871155. Selected crystallographic data: orthorhombic, $P2_12_12_1$ (No. 19), a = 11.067(6) Å, b = 11.275(6) Å, c = 12.311(7) Å, V = 1536(14) Å^3, Z = 4, R_1 = 0.0467, wR_2 = 0.1092, Flack parameter = 0.055(9).
10. DFT calculation for the racemization mechanism of **1ab** and **1ac** are in progress.
11. The mole fractions of major enantiomer and major diastereomer are described here as the enantiomeric purity (ep) and diastereomeric purity (dp), respectively.
12. (*R*,*R*)-**8**: colorless crystals; IR (crystal using a diffuse reflector) cm^{-1}: 2942, 1597, 1340, 1228, 903, 814; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.69 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 5.73 (ddd, J = 11.4, 11.1, 4.5 Hz, 1H), 5.62-5.52 (m, 1H), 4.13 (dd, J = 11.4, 3.0 Hz, 1H), 4.06 (dd, J = 14.4, 4.5 Hz, 1H), 3.31 (dd, J = 10.8, 3.0 Hz, 1H), 3.20 (dd, J = 14.4, 11.4 Hz, 1H), 2.59 (dd, J = 11.4, 10.8 Hz, 1H), 2.43 (s, 3H), 2.27-2.01 (m, 3H), 1.26 (s, 3H), 1.02-0.93 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 143.5, 135.7, 130.7, 129.8, 128.8, 127.1, 59.4, 59.0, 46.3, 44.4, 34.0, 22.5, 21.5, 17.4; HPLC analysis [column: CHIRALPAK AS-H (4.6 × 250 mm), eluent: hexane/*i*-PrOH = 1:1, flow rate: 0.5 mL/min, detection: UV 254 nm, temperature: 25 °C]: t_1 = 24.3 min [(*R*,*R*)-isomer], t_2 = 31.4 min [(*S*,*S*)-isomer]; $[\alpha]_D^{27}$ –54.9 (*c* 0.72, $CHCl_3$, 98% ep); Mp (98% ep): 135.0–138.1 °C; HRMS (EI, positive): calcd for $C_{16}H_{21}NO_3S$ $[M]^+$ 307.1242, found 307.1242.
13. The absolute stereochemistry of **8** was determined by X-ray diffraction analysis. Deposition number for compound (*R*,*R*)-**8** is CCDC 1871349. Selected crystallographic data: orthorhombic, $P2_12_12_1$ (No. 19), a = 6.8107(13) Å, b = 10.919(2) Å, c = 20.896(4) Å, V = 1554(5) Å^3, Z = 4, R_1 = 0.0403, wR_2 = 0.0937, Flack parameter = –0.09(6).
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15. Basic study on the relationship between alkene strain and reactivity of epoxidation has been reported, see: K. J. Shea and J.-S. Kim, *J. Am. Chem. Soc.*, 1992, **114**, 3044.
16. (*S*,*S*)-**11**: a colorless oil; IR (neat) cm^{-1}: 3283, 2924, 1599, 1330, 1160, 815; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.74 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 5.88 (dd, J = 17.4, 10.8 Hz, 1H), 5.69-5.63 (m, 1H), 5.24-5.19 (m, 1H), 5.16 (d, J = 10.8 Hz, 1H), 5.12 (d, J = 17.4 Hz, 1H), 4.35 (d, J = 9.3 H, 1H), 3.65-3.60 (m, 1H), 2.44 (s, 3H), 2.15-1.94 (m, 2H), 1.66-1.53 (m, 2H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 143.3, 140.1, 138.5, 129.8, 129.3, 127.9, 127.2, 116.2, 57.7, 39.1, 33.7, 23.8, 22.5, 21.7; HPLC analysis [column: CHIRALPAK AS-H (4.6 × 250 mm), eluent:

hexane/*i*-PrOH = 4:1, flow rate: 0.5 mL/min, detection: UV 254 nm, temperature: 8 °C]: t_1 = 27.3 min [(*S*,*S*)-isomer], t_2 = 32.7 min [(*R*,*R*)-isomer]; $[\alpha]_D^{27}$ +67.4 (*c* 0.67, $CHCl_3$, 99% ep); HRMS (EI, positive): calcd for $C_{16}H_{21}NO_2S$ $[M]^+$ 291.1293, found 291.1293.

17. The absolute stereochemistry of **11** was speculated from the steric course of the rearrangement.