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. The stereochemical stability of 1 was strongly dependent on the heteroatom X (NY, O, SOn) 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 $1_{aa}$ and C3-methyl substituted congener $1_{ab}$ at 25 °C in n-hexane are 352 h and 2,114 h, respectively. To systematically analyze substituent effects on the stereochemical stability of planar chiral heterocycles, we synthesized C4-methyl substituted congener $1_{ac}$ and found that its chirality is significantly less stable than that of $1_{aa}$ and $1_{ab}$ (Figure 1).

![Figure 1. Stereochemical stability of planar chirality of 1a](image)

Scheme 1 illustrates the retrosynthetic analysis of $1_{ac} (Y = Ts)$. We planned to construct the strained nine-membered skeleton of $1_{ac}$ 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](image)

The synthesis of $1_{ac}$ 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 methyl lithium 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, $3E/3Z = 64:36$). After the separation of $(3E)$-6 and $(3Z)$-6 by silica gel column chromatography, reduction of $(3E)$-6 using DIBAL provided aminoalcohol $(3E)$-7 $[\equiv i (Y = Ts)]$ in 88% yield. Then,
(3E)-7 was subjected to the intramolecular Mitsunobu reaction; treatment of (3E)-7 with DEAD and PPh₃ in THF under high-dilution conditions (0.01 M) afforded the desired cyclic amide 1ac in 72% yield.⁵,⁶

![Chemical structure](image)

Scheme 2. Reagents and conditions: (a) DIBAL, CH₂Cl₂, –78 °C; (b) MeLi, THF–Et₂O, –78 °C, 78% (2 steps); (c) PDC, CH₂Cl₂, rt, 89%; (d) EtOCOCH₂PO(Oi-Pr)₂, n-BuLi, DME, 0→85 °C, 78%, 3E/3Z = 64:36; (e) DIBAL, CH₂Cl₂, –78→0 °C, 88%; (f) DEAD, PPh₃, THF, 0 °C, 72%

The ¹H NMR spectrum of 1ac in CDCl₃ 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.

![HPLC and X-ray analysis](image)

**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. 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. The rate constants for racemization in n-hexane were obtained by HPLC measurements of enantiopurity at proper time intervals. 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 [\(\Delta G^\ddagger(298 \text{K})\) for 1aa, 1ab, and 1ac is 26.4, 27.5, and 24.2 kcal mol$^{-1}$, respectively.]

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 (\(\alpha, \beta, \gamma\)) 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 \(\angle C2C3C4C5, 1ab: 150.8°; 1ac: 154.5°\)), 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 \(\angle C6C7C8C9, 1ab: 0.9°; 1ac: 3.1°\)) [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. The energy barrier for the transition state depends on the ease of flipping of the E-alkene moiety [Figure 4(b)]. 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.

![Figure 4](image_url)

**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.
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REFERENCES AND NOTES


4. A trace amount of aldehyde tautomer was observed by 1H 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; 1H NMR (CDCl₃, 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); 13C NMR (CDCl₃, 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 C₁₆H₂₁NO₂S [M⁺] 291.1293, found 291.1293.

6. The Mitsunobu reaction of a mixture of aminoalcohol (3E)-7 and (3Z)-7 (70:30) afforded a mixture of cyclic amide (3E)-**1ac** and (3Z)-**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 x 250 mm), eluent: hexane/i-PrOH = 1:1, flow rate: 0.5 mL/min, detection: UV 240 nm, temperature: 25 °C]: t₁ = 12.7 min [(S)-isomer], t₂ = 15.5 min [(R)-isomer] or [column: CHIRALPAK AD-H (4.6 x 250 mm), eluent: hexane/i-PrOH = 1:1, flow rate: 0.5 mL/min, detection: UV 254 nm, temperature: 0 °C]: t₁ = 15.8 min [(R)-isomer], t₂ = 23.6 min [(S)-isomer]; semipreparative-scale HPLC [column: CHIRALPAK AS-H (20 x 250 mm), eluent: hexane/EtOH = 9:1, flow rate: 8.0 mL/min, detection: UV 254 nm, temperature: rt]: t₁ = 24.6
8. Deposition number for compound (S)-1ac is CCDC 1871154. Selected crystallographic data: orthorhombic, \(P2_12_12_1\) (No. 19), \(a = 9.6912(4) \text{ Å}, b = 12.077(5) \text{ Å}, c = 12.746(5) \text{ Å}, V = 1492(11) \text{ Å}^3,\) \(Z = 4, R_1 = 0.0367, wR_2 = 0.0917,\) 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), \(a = 11.067(6) \text{ Å}, b = 11.275(6) \text{ Å}, c = 12.311(7) \text{ Å}, V = 1536(14) \text{ Å}^3,\) \(Z = 4, R_1 = 0.0467, wR_2 = 0.1092,\) 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) \(\delta\): 7.69 (d, \(J = 8.1 \text{ Hz}, 2\)H), 7.32 (d, \(J = 8.1 \text{ Hz}, 2\)H), 5.73 (ddd, \(J = 11.4, 11.1, 4.5 \text{ Hz}, 1\)H), 5.62-5.52 (m, 1H), 4.13 (ddd, \(J = 11.4, 3.0 \text{ Hz}, 1\)H), 4.06 (ddd, \(J = 14.4, 4.5 \text{ Hz}, 1\)H), 3.31 (dd, \(J = 10.8, 3.0 \text{ Hz}, 1\)H), 3.20 (dd, \(J = 14.4, 11.4 \text{ Hz}, 1\)H), 2.59 (dd, \(J = 11.4, 10.8 \text{ Hz}, 1\)H), 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) \(\delta\): 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 \text{ min} [(R,R)-isomer], t_2 = 31.4 \text{ 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\(_3\)S [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), \(a = 6.8107(13) \text{ Å}, b = 10.919(2) \text{ Å}, c = 20.896(4) \text{ Å}, V = 1554(5) \text{ Å}^3,\) \(Z = 4, R_1 = 0.0403, wR_2 = 0.0937,\) Flack parameter = -0.09(6).


16. \((S,S)-11\): a colorless oil; IR (neat) cm\(^{-1}\): 3283, 2924, 1599, 1330, 1160, 815; \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\): 7.74 (d, \(J = 8.4 \text{ Hz}, 2\)H), 7.29 (d, \(J = 8.4 \text{ Hz}, 2\)H), 5.88 (dd, \(J = 17.4, 10.8 \text{ Hz}, 1\)H), 5.69-5.63 (m, 1H), 5.24-5.19 (m, 1H), 5.16 (d, \(J = 10.8 \text{ Hz}, 1\)H), 5.12 (d, \(J = 17.4 \text{ Hz}, 1\)H), 4.35 (d, \(J = 9.3 \text{ Hz}, 1\)H), 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) \(\delta\): 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$_2$S [M]$^+$ 291.1293, found 291.1293.

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