Novel Synthetic Approach to Nine-Membered Diallylic Amides: Stereochemical Behavior and Utility as Chiral Building Block

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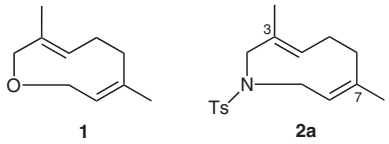
Abstract: An efficient approach to nine-membered diallylic cyclic amides having a variety of substituents has been developed. The synthesized amides have stable planar chirality at ambient temperature. The transformation of the enantiomerically enriched amides provides optically active compounds containing stereogenic centers in a stereospecific fashion. As a demonstration of the synthetic utility of the amides, we have synthesized (+)-γ-lycorane using such an optically active amide as a chiral building block.

Key words: atropisomerism, amides, asymmetric synthesis, alkaloids, planar chirality

The planar chirality of medium-sized cycloalkenes such as (*E*)-cyclooctene and (*E*)-cyclononene is an attractive and potentially useful stereochemical phenomenon.[1] However, the synthetic application of this class of chiral compounds is highly limited mainly due to the lack of functional groups other than a double bond, which would lead to their further synthetic elaboration.[2] Recently, we have synthesized novel chiral heterocycles including ether **1** and amide **2a** with solely planar chirality (Figure 1).[3] Their chirality has been proved to be fairly stable at ambient temperature and is readily transferred to a variety of central chiralities in a stereospecific fashion.

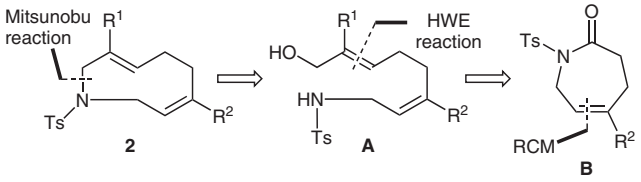


1 **2a**

Figure 1

These variable stereochemical properties clearly show the synthetic potential of planar chiral heterocycles as useful chiral building blocks or key components of chiral reagents. However, the structural essence of their planar chirality has not been elucidated fully, especially in terms of the influence of substituents in the ring, and further studies on the physical properties of their analogues are necessary to address this issue. Our previous synthetic approach to **1** and **2a** starts from neryl acetate; hence, the approach lacks the flexibility in the preparation of their congeners with specific substituents other than a methyl substituent at C3 and at C7.[3b] Here, we report a new approach to nine-membered cyclic amides with planar chirality, having a variety of substituents at the C3 or C7 position. In addition, we demonstrate the synthetic utility of the newly synthesized planar chiral cyclic amide as a building block in the synthesis of alkaloid.

As shown in Scheme 1, our retrosynthetic analysis of the cyclic amide **2** involves (i) an intramolecular Mitsunobu reaction of the amide alcohol **A** for the construction of the nine-membered skeleton, (ii) a Horner–Wadsworth–Emmons (HWE) reaction, and (iii) a ring-closing metathesis (RCM) for the stereoselective construction of the *E*- and *Z*-alkene moieties. Thus, the seven-membered lactam **B** would be a reasonable intermediate of this synthesis.



Scheme 1 Retrosynthetic analysis of amide **2**

For the preparation of **B**, the acyclic amides **4a** and **4b** were initially prepared from *N*-allyl tosylamide and the easily available carboxylic acids **3a** or **3b**, respectively (Scheme 2). The ring-closing metathesis of the amides **4a** and **4b** provided **5a** and **5b** (≡**B**) in excellent yield, respectively.[3] Their partial reduction using DIBAL-H provided hemiaminals **6a** and **6b**,[5] which serve as synthetic equivalents of amide aldehydes in the subsequent Horner–Wadsworth–Emmons reaction with **7a–c**, providing the *E*-esters **8b–d** in good yield with high stereoselectivities (**8b**: 3*E*/3*Z* = 88:12, **8c**, **8d**: 3*E*/3*Z* = >95:<5). The reduction of **8b–d** using DIBAL-H provided **9b–d**, precursors for the final cyclization. The intramolecular Mitsunobu reaction of **9b–d** was carried out under high-dilution conditions (0.01 M) with diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD) and Ph_3P, providing the desired cyclic amides **2b–d** in good yields (77–90%).[6,7] It should be noted that only a negligible amount of dimerized product (<1%) was formed in these cyclization reactions. The HPLC analysis using a chiral stationary column shows that all the newly synthesized amides **2b–d** have a fairly stable planar chirality at ambient tem-

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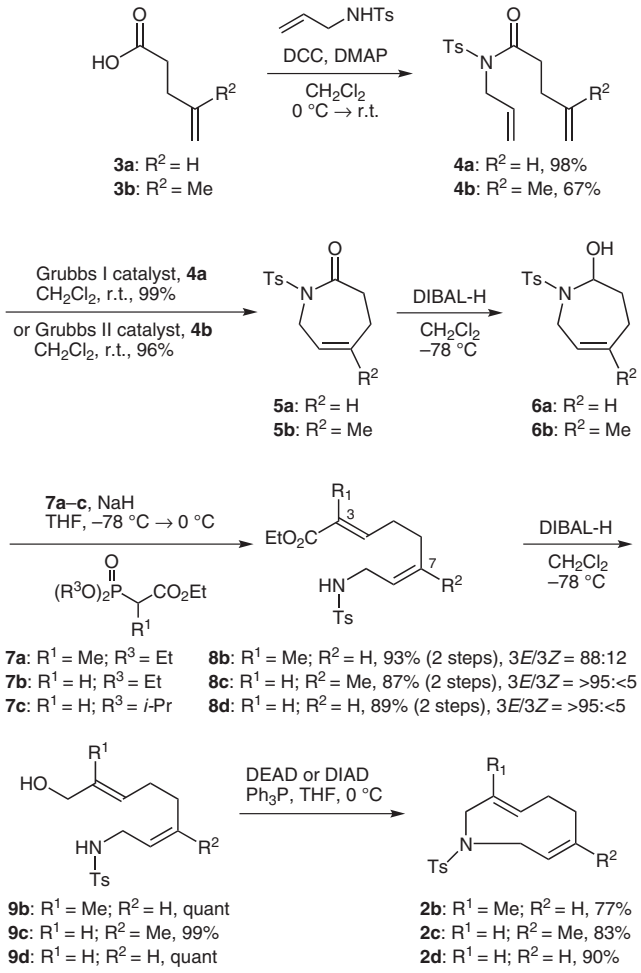
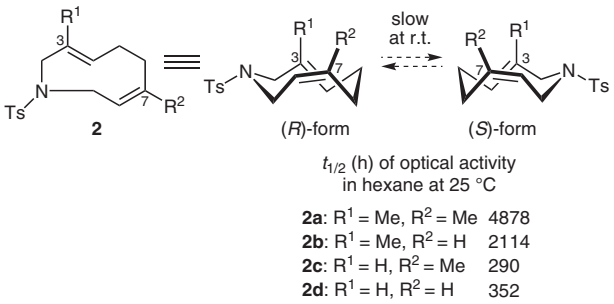
perature.[8] Furthermore, both the enantiomers of **2b–d** can be separated successfully by semipreparative HPLC.[8–10] Time-dependent measurements of their optical purities in hexane indicate that their stereochemical stability is highly dependent on the substituents R^1 and R^2. The half-lives of the optical activity for **2b**, **2c**, and **2d** in hexane at 25 °C are 2114, 290, and 352 hours, respectively (Equation 1).



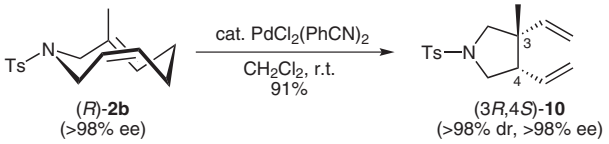
Scheme 2 Synthesis of amides **2b–d**



Equation 1

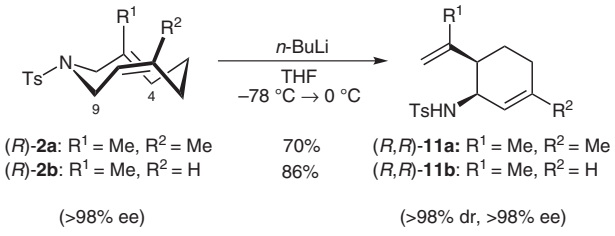
A comparison of these results with the previously reported stereochemical stability of **2a** ($t_{1/2}$ = 4878 h at 25 °C)[3b] clearly shows that (a) the methyl substituent on the ring is not essential for the planar chirality of amides, and (b) the methyl substituent at the C3 position significantly increases the stereochemical stability of the amide, while the substituent at the C7 position has less impact on the stereochemical stability. These observations may suggest that the flipping of the C3–C4 olefin moiety is a rate-determining step of racemization.[11] The activation parameters for the racemization of **2b** and **2d** are calculated from an Eyring plot by the analysis of the rate constants of racemization as ΔH = 27.0 kcal mol^{-1}, ΔS = –1.68 cal mol^{-1} K^{-1} and ΔH = 26.3 kcal mol^{-1}, ΔS = –0.36 cal mol^{-1} K^{-1}, respectively.

It is noteworthy that all the cyclic amides can thus be obtained easily in optically pure form by a separation of enantiomers, and that their planar chirality can be transferred to the central chirality without the loss of stereopurity.[12] For instance, the Pd(II)-catalyzed Cope rearrangement of enantioenriched (*R*)-**2b** (>98% ee) provided (3*R*,4*S*)-**10** having a quaternary chiral center as a single diastereomer in 91% yield (>98% dr, >98% ee; Equation 2).[13,14]



Equation 2

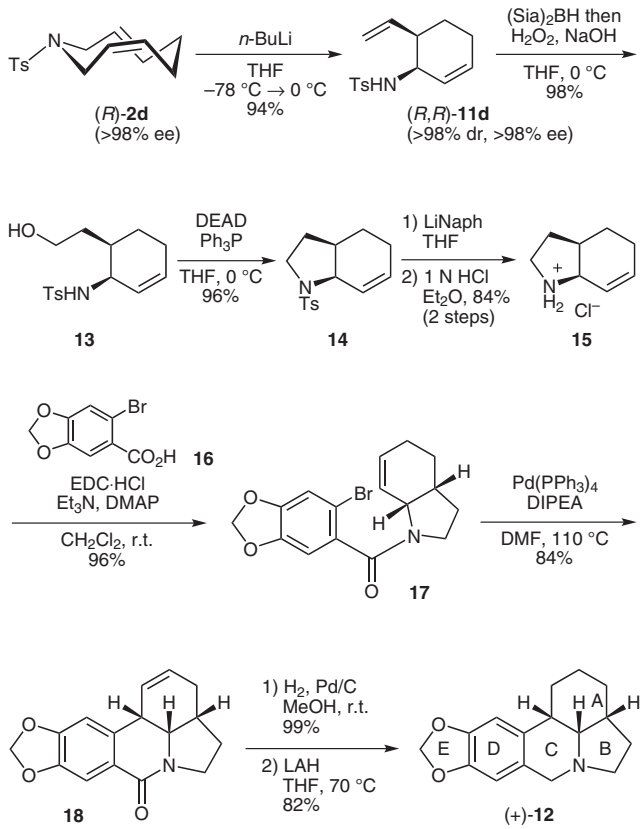
Moreover, we have found that the carbanion rearrangement of this class of cyclic amides proceeds in a stereospecific fashion. The reaction of the enantioenriched **2a** and **2b** (>98% ee) with *n*-BuLi in THF at –78 °C afforded transannular aza-[2,3]-Wittig rearrangement products **11a** and **11b** (>98% dr, >98% ee), respectively, in good yield (Equation 3). The high reactivity of the rearrangement would be attributable to the strain release of the nine-membered strain as well as the fact that in the ground state the C4 and C9 positions possibly face each other with a short distance between them.[15,16]



Equation 3

This transformation of planar to central chirality clearly shows that enantioenriched cyclic amides **2** could serve as a synthetic precursor for a variety of chiral nitrogen-containing compounds with central chirality. To realize this concept, we carried out the asymmetric synthesis of (+)-γ-lycorane (**12**), representative of the lycorine class of Amaryllidaceae alkaloids (Scheme 3).[17,18] This compound has a *cis* configuration on the A ring, identical to that in the

aza-[2,3]-Wittig rearrangement product of **2**. Our synthesis started from the aza-[2,3]-Wittig rearrangement of enantiopure (*R*)-**2d** (>98% ee) under the above-mentioned conditions, which provided (*R*,*R*)-**11d** as a single stereoisomer in excellent yield. The group-selective hydroboration of monosubstituted alkene of **11d** using disiamylborane, followed by an intramolecular Mitsunobu reaction of the resulting amide alcohol **13** provided the bicycloamide **14**. The reductive detosylation of **14** using lithium naphthalenide (LiNaph), followed by the treatment with a solution of hydrochloric acid in diethyl ether afforded the crystalline salt of **15**. The benzodioxole moiety (D and E rings) of lycorane was introduced by coupling carboxylic acid **16** to **15**. Compound **16** was separately prepared from the commercially available piperonyl alcohol in three steps.



Scheme 3 Asymmetric synthesis of (+)-γ-lycorane (**12**)

The C ring was constructed by an intramolecular Mizoroki–Heck reaction of **17** using $Pd(PPh_3)_4$ and Hünig's base.[19] Finally, the asymmetric synthesis of (+)-**12** was accomplished by the reduction of the remaining alkene in the A ring and of the carbonyl moiety in the C ring by H_2/Pd on carbon and $LiAlH_4$, respectively. Thus, the asymmetric synthesis of (+)-lycorane was achieved from planar chiral amide (*R*)-**2d** in eight steps, with an overall yield of 49%. (–)-Lycorane can be synthesized from (*S*)-**2d** using the same strategy.

In summary, we have described an efficient synthetic approach to planar chiral cyclic amides and their stereochemical behavior. The synthetic utility of the synthesized cyclic amide has been demonstrated by the asymmetric synthesis of a chiral alkaloid. Further detailed mechanistic studies of the planar chirality of such heterocycles and synthetic application of this unique dynamic chirality are in progress.

Acknowledgment

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References and Notes

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

(2) For recent studies on planar chiral medium-sized rings, see: (a) Sudau, A.; Münch, W.; Nubbemeyer, U. *J. Org. Chem.* **2000**, *65*, 1710. (b) Nubbemeyer, U. *Eur. J. Org. Chem.* **2001**, 1801; and references cited therein. (c) Deiters, A.; Mück-Lichtenfeld, C.; Fröhlich, R.; Hoppe, D. *Chem. Eur. J.* **2002**, *8*, 1833. (d) Gauvreau, D.; Barriault, L. *J. Org. Chem.* **2005**, *70*, 1382. (e) Larionov, O. V.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 2954.

(3) (a) Tomooka, K.; Komine, N.; Fujiki, D.; Nakai, T.; Yanagitsuru, S. *J. Am. Chem. Soc.* **2005**, *127*, 12182. (b) Tomooka, K.; Suzuki, M.; Shimada, M.; Yanagitsuru, S.; Uehara, K. *Org. Lett.* **2006**, *8*, 963.

(4) For ring-closing-metathesis-based seven-membered lactam synthesis, see: (a) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856. (b) Vo-Thanh, G.; Boucard, V.; Sauriat-Dorizon, H.; Guibé, F. *Synlett* **2001**, 37.

(5) The ^{1}H NMR analysis of **6a** and **6b** revealed a trace amount of the aldehyde tautomer was contained (<5%).

(6) **General Procedure of the Synthesis of Amide 2 from 9**
To a solution of Ph_3P (96.2 mg, 0.368 mmol) in anhydrous THF (10 mL) at 0 °C was added DEAD (0.166 mL of 40 wt% in toluene, 0.366 mmol) and **9b** (42.4 mg, 0.137 mmol) dissolved in anhydrous THF (4 mL). The resulting mixture was stirred at that temperature for 4 h, concentrated in vacuo, and the residue was purified by silica gel chromatography (hexane–EtOAc, 10:1 to 5:1) to afford 30.7 mg (77%) of **2b** as a white solid and a trace amount of dimerized product (<1%, analyzed by ^{1}H NMR).

(7) All new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy.
Data for Selected Compounds
Compound **2b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 5.47 (ddd, *J* = 11.4, 10.8, 4.2 Hz, 1 H), 5.43–5.34 (m, 1 H), 5.24 (dd, *J* = 11.4, 4.5 Hz, 1 H), 4.26 (d, *J* = 9.9 Hz, 1 H), 3.89 (dd, *J* = 14.1, 4.2 Hz, 1 H), 3.05 (dd, *J* = 14.1, 10.8 Hz, 1 H), 3.00 (d, *J* = 9.9 Hz, 1 H), 2.44 (s, 3 H), 2.22–2.06 (m, 2 H), 1.99–1.70 (m, 2 H), 1.55 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.0, 136.3, 134.2 (2 C), 132.2, 131.1, 129.7, 127.1, 59.0, 44.3, 27.0, 26.5, 21.7, 17.3. IR (reflection): 2934, 1597, 1452, 1324, 1158, 1095, 1023, 960, 869, 821, 767, 714, 658, 596 cm^{-1}. Mp 123 °C. For *R*-isomer (>98% ee): $[\alpha]_D^{27}$ –65.3

(*c* 0.80, $CHCl_3$); for *S*-isomer (>98% ee): $[\alpha]_D^{27}$ +67.7 (*c* 0.88, $CHCl_3$). Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.95; H, 7.26; N, 4.81; S, 11.00. Found: C, 65.55; H, 7.24; N, 4.70; S, 11.52.

Compound **2c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.1 Hz, 2 H), 7.30 (d, *J* = 8.1 Hz, 2 H), 5.47–5.24 (m, 3 H), 4.40 (dd, *J* = 10.2, 3.9 Hz, 1 H), 3.82 (dd, *J* = 14.2, 4.2 Hz, 1 H), 3.00 (dd, *J* = 10.2, 9.9 Hz, 1 H), 2.80 (dd, *J* = 14.2, 11.9 Hz, 1 H), 2.43 (s, 3 H), 2.33–2.28 (m, 1 H), 2.03–1.96 (m, 1 H), 1.91–1.83 (m, 1 H), 1.69 (s, 3 H), 1.67–1.52 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.0, 138.1, 135.9, 132.8, 129.6, 128.4, 127.1, 126.1, 53.2, 45.0, 32.1, 29.4, 25.3, 21.6. IR (neat): 2934, 1319, 1149, 983, 893, 815, 734, 655, 597, 547 cm^{-1}. For *R*-isomer (>98% ee): $[\alpha]_D^{28}$ –88.8 (*c* 1.23, $CHCl_3$); for *S*-isomer (>98% ee): $[\alpha]_D^{29}$ +88.5 (*c* 1.60, $CHCl_3$). Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.95; H, 7.26; N, 4.81. Found: C, 65.92; H, 7.26; N, 4.68.

Compound **2d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.1 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 5.63 (dddd, *J* = 11.4, 11.1, 4.8, 1.2 Hz, 1 H), 5.40–5.24 (m, 3 H), 4.41 (dd, *J* = 9.9, 3.3 Hz, 1 H), 3.83 (dd, *J* = 14.1, 4.2 Hz, 1 H), 3.00 (dd, *J* = 9.9, 9.9 Hz, 1 H), 2.84 (dd, *J* = 14.1, 11.7 Hz, 1 H), 2.43 (s, 3 H), 2.37–2.30 (m, 1 H), 2.26–2.17 (m, 1 H), 1.77–1.65 (m, 1 H), 1.58–1.45 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.1, 136.9, 135.8, 131.7, 129.7, 128.8, 127.1, 126.1, 53.4, 44.0, 30.2, 26.6, 21.7. IR (reflection): 3016, 2934, 2869, 1920, 1806, 1661, 1596, 1459, 1347, 988 cm^{-1}. For *R*-isomer (>98% ee): $[\alpha]_D^{25}$ –114.2 (*c* 1.21, $CHCl_3$); for *S*-isomer (>98% ee): $[\alpha]_D^{26}$ +118.9 (*c* 1.97, $CHCl_3$). Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05; S, 11.56. Found: C, 65.22; H, 7.07; N, 4.92; S, 11.25.

Compound (3*S*,4*R*)-**10**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.1 Hz, 2 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 5.53 (dd, *J* = 17.4, 10.8 Hz, 1 H), 5.43 (ddd, *J* = 17.1, 10.5, 8.4 Hz, 1 H), 5.04 (dd, *J* = 10.5, 1.5 Hz, 1 H), 4.98 (dd, *J* = 17.1, 1.5 Hz, 1 H), 4.98 (d, *J* = 10.8 Hz, 1 H), 4.88 (d, *J* = 17.4 Hz, 1 H), 3.50 (dd, *J* = 9.9, 7.5 Hz, 1 H), 3.44 (d, *J* = 9.6 Hz, 1 H), 3.16 (dd, *J* = 9.9, 9.9 Hz, 1 H), 3.01 (d, *J* = 9.6 Hz, 1 H), 2.44 (s, 3 H), 2.33–2.24 (m, 1 H), 1.02 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.3, 139.1, 134.1, 133.8, 129.6, 127.3, 118.2, 114.2, 58.2, 53.3, 51.0, 47.0, 21.8, 21.7. IR (neat): 2965, 1346, 1155, 1094, 1052, 922, 813, 711, 663, 587 cm^{-1}. $[\alpha]_D^{19}$ –6.5 (*c* 1.03, $CHCl_3$).

Compound (*R*,*R*)-**11d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.1 Hz, 2 H), 7.29 (d, *J* = 8.1 Hz, 2 H), 5.83–5.69 (m, 2 H), 5.36–5.32 (m, 1 H), 5.07 (dd, *J* = 9.0, 0.9 Hz, 1 H), 5.00 (dd, *J* = 17.1, 0.6 Hz, 1 H), 4.54 (d, *J* = 9.6 Hz, 1 H), 3.92–3.84 (m, 1 H), 2.42 (s, 3 H), 2.37–2.29 (m, 1 H), 2.12–1.88 (m, 2 H), 1.77–1.67 (m, 1 H), 1.58–1.47 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.3, 138.4, 137.2, 130.2, 129.7, 127.3, 127.2, 117.6, 51.5, 41.8, 24.8, 22.8, 21.6. IR (neat): 3278, 2925, 1433, 1331, 1160, 1084, 915, 814, 709, 660 cm^{-1}. $[\alpha]_D^{25}$ –86.1 (*c* 1.27, $CHCl_3$).

Compound **13**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.1 Hz, 2 H), 7.29 (d, *J* = 8.1 Hz, 2 H), 5.65 (ddd, *J* = 9.6, 3.6, 3.3 Hz, 1 H), 5.12 (ddd, *J* = 9.6, 4.5, 2.1 Hz, 1 H), 4.95–4.85 (m, 1 H), 3.79–3.62 (m, 3 H), 2.42 (s, 3 H), 2.04–1.75 (m, 5 H), 1.63–1.42 (m, 2 H), 1.36–1.23 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.2, 138.3, 130.9, 129.6, 126.9, 126.4, 60.9, 51.1, 34.9, 34.2, 24.8, 24.2, 21.6. IR (neat): 3274, 2928, 1598, 1432, 1327, 1159, 1094, 1021, 915, 815, 663 cm^{-1}. $[\alpha]_D^{26}$ –153.5 (*c* 1.10, $CHCl_3$).

Compound **14**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.1 Hz, 2 H), 7.28 (d, *J* = 8.1 Hz, 2 H), 5.83–5.70 (m, 2 H), 3.96 (d, *J* = 6.9 Hz, 1 H), 3.45 (ddd, *J* = 14.1, 7.5, 4.5 Hz, 1 H), 3.17 (ddd, *J* = 9.9, 8.4, 7.5 Hz, 1 H), 2.40 (s, 3 H), 2.03–1.89 (m, 3 H), 1.80–1.49 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.1, 134.8, 129.5, 128.2, 127.5, 127.3, 57.5, 47.3, 36.5, 27.8, 22.9, 21.6, 20.9. IR (neat): 2924, 1598, 1450, 1343, 1161, 1092, 848, 817, 659, 593 cm^{-1}. $[\alpha]_D^{25}$ –98.6 (*c* 1.31, $CHCl_3$).

Compound **17**; 60:40 rotamer ratio (# denotes major, * denotes minor rotamer signals): ^{1}H NMR (300 MHz, $CDCl_3$): d = 6.96* (s, 1 H), 6.95# (s, 1 H), 6.76* (s, 1 H), 6.71# (s, 1 H), 6.04# (d, *J* = 10.2 Hz, 1 H), 5.99–5.96* (m, 1 H), 5.96 (s, 2 H), 5.80–5.73# (m, 1 H), 5.68–5.63* (m, 1 H), 5.23* (d, *J* = 9.9 Hz, 1 H), 4.62# (dd, *J* = 4.8, 2.1 Hz, 1 H), 4.04–3.98* (m, 1 H), 3.64# (dd, *J* = 9.0, 6.0 Hz, 1 H), 3.32–3.13 (m, 1 H), 2.54–2.37 (m, 1 H), 2.14–1.58 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1*, 167.0#, 148.6*, 148.5#, 147.4#, 147.3*, 132.6#, 132.4*, 129.0, 128.0, 125.8*, 125.0#, 112.7#, 109.8*, 108.0*, 107.3#, 102.1*, 102.0#, 57.0*, 55.3#, 47.0#, 44.8*, 36.6*, 35.6#, 27.6#, 25.3*, 22.7#, 22.1*, 21.0#, 20.2*. IR (neat): 2922, 1631, 1482, 1440, 1374, 1239, 1109, 1035, 932, 863, 732, 617 cm^{-1}. $[\alpha]_D^{25}$ –146.4 (*c* 0.86, $CHCl_3$).

Compound **18**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52 (s, 1 H), 6.69 (s, 1 H), 5.99 (d, *J* = 1.2 Hz, 1 H), 5.98 (d, *J* = 1.2 Hz, 1 H), 5.70–5.63 (m, 1 H), 5.36 (dd, *J* = 9.9, 2.4 Hz, 1 H), 4.02 (dd, *J* = 5.7, 4.8 Hz, 1 H), 3.69 (d, *J* = 9.6 Hz, 1 H), 3.67 (d, *J* = 9.6 Hz, 1 H), 3.62–3.56 (m, 1 H), 2.53–2.44 (m, 1 H), 2.29–2.18 (m, 1 H), 2.07–1.70 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.8, 150.5, 146.9, 135.6, 125.9, 125.3, 123.0, 107.6, 107.4, 101.6, 56.6, 42.4, 37.1, 34.2, 30.0, 25.2. IR (neat): 2885, 1645, 1609, 1465, 1387, 1349, 1269, 1244, 1036, 933, 770, 703 cm^{-1}. $[\alpha]_D^{24}$ –111.4 (*c* 0.38, $CHCl_3$).

Compound **12**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.61 (s, 1 H), 6.49 (s, 1 H), 5.89 (d, *J* = 1.2 Hz, 1 H), 5.88 (d, *J* = 1.2 Hz, 1 H), 4.02 (d, *J* = 14.1 Hz, 1 H), 3.37 (ddd, *J* = 9.3, 9.0, 3.6 Hz, 1 H), 3.22 (d, *J* = 14.1 Hz, 1 H), 2.75 (ddd, *J* = 11.7, 4.5, 4.5 Hz, 1 H), 2.39 (dd, *J* = 4.8, 4.5 Hz, 1 H), 2.25–2.11 (m, 2 H), 2.08–1.97 (m, 1 H), 1.80–1.60 (m, 3 H), 1.55–1.30 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.0, 145.6, 133.1, 127.3, 108.4, 106.3, 100.7, 63.0, 57.2, 53.9, 39.6, 37.5, 31.9, 30.6, 29.5, 25.4. IR (neat): 2925, 1505, 1483, 1376, 1318, 1230, 1138, 1040, 938, 867 cm^{-1}. $[\alpha]_D^{25}$ +15.0 (*c* 0.44, EtOH) {lit.[17] $[\alpha]_D^{20}$ +17.1 (*c* 0.25, EtOH)}. MS (ESI^+): *m/z* = 258 $[M + H]^+$.

(8) Analytical and semipreparative-scale HPLC were carried out with a chiral stationary column [CHIRALCEL OD-H (4.6 × 250 mm or 20 × 250 mm)] equipped with a UV detector and a CD spectropolarimeter.

(9) The absolute configurations of **2b** and **2c** were speculated on the basis of the similarity of the CD spectra of **2a** and **2d**.

(10) Enantioenriched **2** can be prepared via the fractional crystallization of its ammonium salt with chiral carboxylic acid, see ref. 3b.

(11) The detailed transition-state analysis of racemization by ab initio calculation is in progress.

(12) The enantiopurity of **2a**–**d** remains unchanged in the solid state(crystal) at –30 °C for at least one year.

(13) Pd(II)-catalyzed Cope rearrangement, see: Overman, L. E.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1982**, *104*, 7225.

(14) The absolute stereochemistry of **10** was deduced from the configuration of **2b** and the steric course of the reactions.

(15) In general, the aza-Wittig rearrangement is considerably slower than the corresponding oxa-Wittig rearrangement. To enhance the reactivity of the aza-Wittig rearrangement, several contrivances have been developed. For reviews, see: (a) Vogel, C. *Synthesis* **1997**, 497. (b) Tomooka, K. In *The Chemistry of Organolithium Compounds*, Vol. 2; Rappoport, Z.; Marek, I., Eds.; John Wiley and Sons: Chichester, **2004**, 749–828.

(16) The X-ray crystal structure analysis shows that the distance between C4 and C9 of **2a** is 3.8 Å (Figure 2). The present rearrangement should proceed via a deprotonation of the C9 equatorial proton and an inversion of the configuration at the carbanion chiral center. It has been reported that [2,3]-Wittig rearrangement proceeds with inversion of configuration at the migrating terminus, see: (a) Verner, E. J.; Cohen, T. *J. Am. Chem. Soc.* **1992**, *114*, 375. (b) Tomooka, K.; Igarashi, T.; Watanabe, M.; Nakai, T. *Tetrahedron Lett.* **1992**, *33*, 5795.

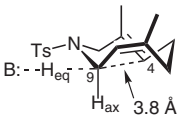

Figure 2

(17) (+)-γ-Lycorane was obtained by Kotera in his degradation studies of lycorine, see: Kotera, K. *Tetrahedron* **1961**, *12*, 248.

(18) Six different asymmetric syntheses of γ-lycorane(**12**) have been reported thus far, see: (a) Yoshizaki, H.; Satoh, H.; Sato, Y.; Nukui, S.; Shibasaki, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 2016. (b) Ikeda, M.; Ohtani, S.; Sato, T.; Ishibashi, H. *Synthesis* **1998**, 1803. (c) Banwell, M. G.; Harvey, J. E.; Hockless, D. C. R. *J. Org. Chem.* **2000**, *65*, 4241. (d) Dong, L.; Xu, Y.-J.; Cun, L.-F.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2005**, *7*, 4285. (e) Fujioka, H.; Murai, K.; Ohba, Y.; Hirose, H.; Kita, Y. *Chem. Commun.* **2006**, 832. (f) Chapsal, B. D.; Ojima, I. *Org. Lett.* **2006**, *8*, 1395.

(19) Mori and co-workers constructed the C ring of γ-lycorane by a Pd-catalyzed Mizoroki–Heck reaction, see ref. 18a.