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Synthesis and racemization studies of winding vine-shaped biphenyl derivatives

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Dedicated to Professor Christian Bruneau

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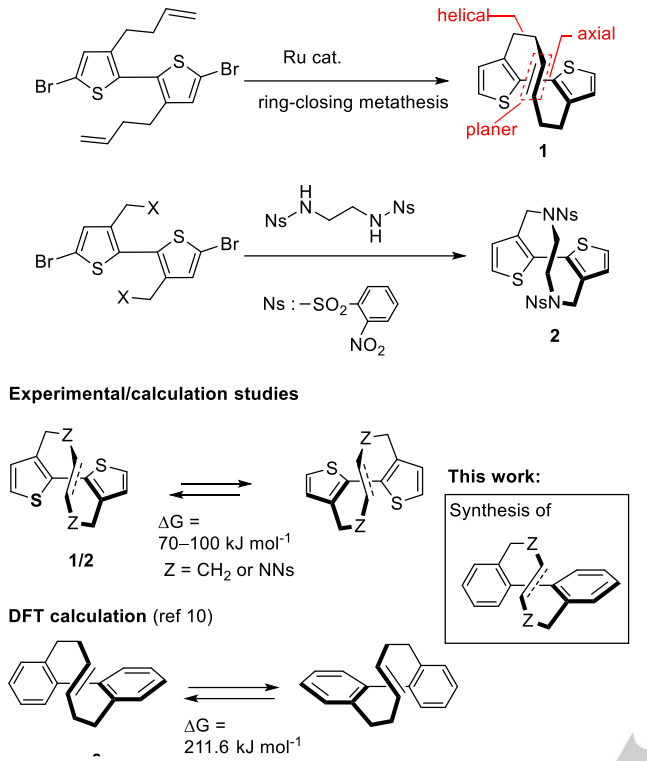
Abstract: Winding vine-shaped biphenyl derivatives were synthesized through the annulation reaction of nosylated (2-nitrobenzenesulfonyl) ethylenediamine and the *E*-selective ring-closing metathesis reaction. The structure of the cyclized products were confirmed by measurements of ^{1}H and ^{13}C NMR spectra and single crystal X-ray analyses. The obtained cyclic product was revealed to exhibit molecular asymmetry, which was confirmed by HPLC analyses on chiral stationary phase. Compared with our previous results on the related bithiophene derivatives, the obtained vine-shaped biphenyls were shown to hardly racemize under ambient conditions and experimental studies on racemization behaviors suggested energy barriers of 134 kJmol^{-1} to 211 kJmol^{-1}. These results reasonably agreed with those of the calculated values based on DFT.

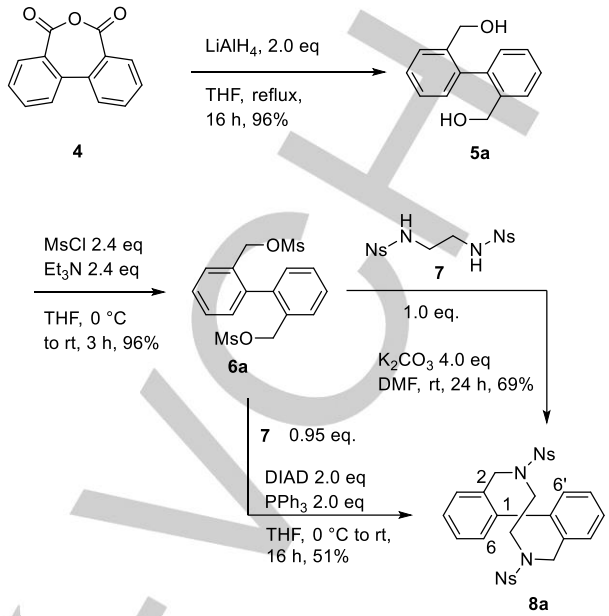
Introduction

Synthetic studies for the finding of a new class of chiral molecules have attracted a major concern in organic chemistry because of a wide range of utilization of chiral compounds towards auxiliaries in enantioselective organic reactions, asymmetric catalysis for enantiodifferentiation, chiral recognition, liquid crystal engineering, etc.[1] As shown in Scheme 1, we have previously shown that several heterobiayls bearing substituents with terminal alkenes undergo ring-closing metathesis[2] leading to the cyclized product **1**, where the obtained carbon-carbon double bond showed *E*-stereochemistry.[3,4] We named such a compound of the (hetero)biaryl structure, each of which aromatic ring was connected by a certain number of alkylene chain, as winding vine-shaped molecule.[5] It was also revealed that the obtained product exhibited molecular asymmetry, in which axial, helical, and planar chiralities were involved in the molecule and their inversion of the chirality took place in a synchronized manner. Separation of the enantiomer with HPLC on chiral stationary phase,[3,6] resolution with the preparative column,[3] and enantioselective metathesis[7,8] have been successful to afford the enantiomerically pure/enriched compounds. It was also shown to undergo an additional protocol to afford winding vine-shaped molecules employing annulative nucleophilic substitution with nosyl (2-nitrobenzenesulfonyl) diamines to give vine-shaped biaryl **2**.[9] We have also studied the racemization behaviors of the obtained compounds of molecular asymmetry. The vine-shaped product composed of five-membered bithiophene by ring-closing metathesis was shown to slowly racemize at room temperature while the related nosyl derivative **2** resulted to hardly observe enantiomers by the attempted separation by HPLC on chiral stationary phase probably because of the rapid racemization since the vine part is composed of the single bond allowing diverse conformational rotation.

We have preliminarily studied the DFT calculation on the racemization behavior[10] of thus cyclized heterobiaryls **2** and found that the isomerization barrier of **2** was much lower because of the ease of the free rotation of the carbon-carbon single bond. It was also shown to be calculated that the energy barrier of the related derivative **1** bearing C–C double bond was slightly higher but **1** still slowly racemized experimentally even at room temperature.[6] Although the related non-heteroaromatic analogs **3** composed of the benzene ring was suggested to racemize with a higher energy barrier by DFT calculation,[10] the actual synthesis of such biphenyl **3** has not been successful to date. Accordingly, we envisaged to synthesize the vine-shaped biphenyl derivatives and to study their racemization behaviors. We herein report the first synthesis and the racemization study of novel winding vine-shaped biphenyls prepared by nosyl annulation and ring-closing metathesis reactions and that remarkably higher racemization barriers were indeed observed experimentally.



Scheme 1. Synthesis of winding vine-shaped (hetero)biaryls and the suggested molecular asymmetries



Scheme 2. Nosyl annulation of biphenyl

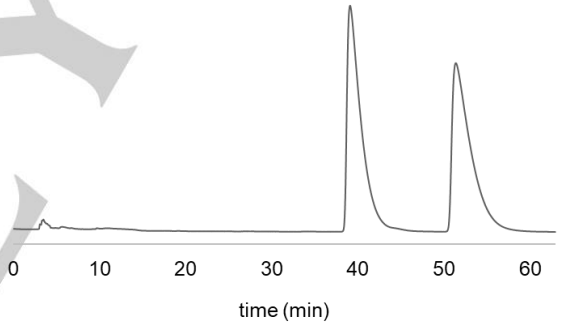


Figure 1. HPLC profile of **8a** on chiral stationary phase

Results and Discussion

Synthesis of the winding-vine biphenyl was carried out with nosyl annulation protocol as outlined in Scheme 2. Reduction of 2,2'-biphenyl dicarboxylic anhydride (**4**) with $LiAlH_4$ afforded the corresponding diol **5a** in a quantitative yield.[11,12] The obtained **5a** was transformed into dimesylate **6a** with methanesulfonyl chloride in 96% yield. Treatment of **6a** with dinosylated ethylenediamine **7** resulted to furnish the vine-shaped **8a** in 69% yield. It was also shown that the reaction of diol **5a** through the Mitsunobu reaction with diisopropyl azo dicarboxylate (DIAD) and PPh_3 proceeded to afford the annulation reaction yielding **8a** in 51% yield.[13,14] The obtained **8a** was subjected to HPLC analysis on chiral stationary phase DAICEL Chiralpak IF to observe clear baseline separation of the two enantiomers as shown in Figure 1. In contrast that attempted HPLC analysis of bithiophene derivative obtained by a similar nosyl annulation has been unsuccessful, the clear separation of biphenyl derivative **8a** suggests higher isomerization barrier. Indeed the DFT calculation showed 125.9 kJmol^{-1}, which was ca. 54 kJmol^{-1} higher than that of bithiophene **2**. The result suggests steric repulsion of the hydrogen atoms of 6, 6'-positions at the biphenyl moiety that has not been observed in the five-membered analog **2**[9] plays a key role to exhibit a high enantiomerization barrier. As a result, **8a** allows to show molecular asymmetry by HPLC analysis despite that all the bonds in the vine moiety are composed of the freely rotatable single bond.

Figure 2 shows the result of X-ray structure analysis of **8a** and its aniline derivative **8a'**, which was obtained by the reduction of **8a** under hydrogen in the presence of Pd/C.[15,16] The structure of **8a** (Figure 2(a)) shows the formation of the winding vine-shaped conformation. The dihedral angle of biphenyl was found to be 76.4°. The angle was similar to that of the bithiophene derivative **2** (76.9°).[6] The C–C bond of the ethylenediamine moiety (C7–C8) was revealed to be intersected with the C–C bond between two benzene rings of biphenyl (C15–C16) with the torsion angle of 61.9°. By contrast, the aniline derivative **8a'** was found to show almost parallel conformation of the C–C bond of the two phenyl rings of biphenyl (C13–C14) and the C–C bond of the diamine moiety (C21–C22) with the torsion angle of 7.8°, as shown in Figure 2 (b). The benzene ring of sulfonamide was accordingly located to be close to an aromatic ring of biphenyl. The dihedral angle of aniline **8a'** was 85.0°, which was found larger than that of **8a** suggesting the parallel conformation enhances the torsion of the biphenyl moiety.

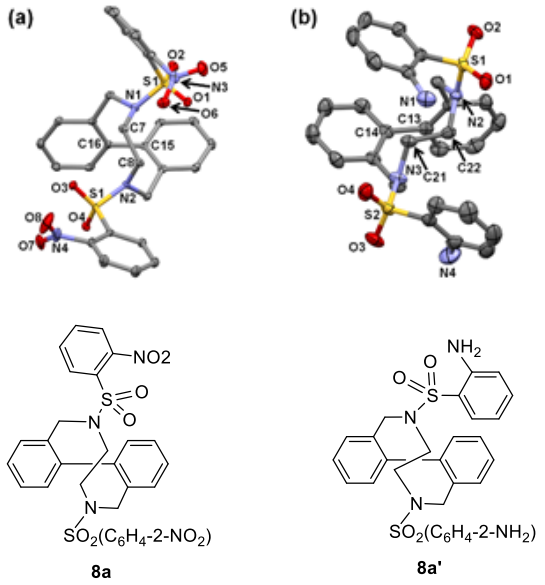


Figure 2. X-ray crystal structure of (a) **8a** and (b) reduction product **8a'**. ORTEP drawn with 50% probability. Hydrogen atoms are omitted for clarity.

We next studied synthesis of several winding vine-shaped biphenyls bearing various substituents. Diol bearing bromo groups at the 4,4'-positions was prepared[11] and subjected to the Mitsunobu reaction with ethylenediamine **7** in a similar manner. The reaction was found to proceed to afford the cyclized product **8b** in 61% yield. Attempted preparation of mesylate **6b** resulted in giving accompanying formation of the 7-membered ether as a byproduct.[17] Preparation of related bromide **6b'** was thus carried out by the reaction with CBr_4/PPh_3[18] and the obtained **6b'** was subjected to the reaction with diamine **7** to afford **8b** in 96% yield. Biphenyl bearing tertiary butyl group at the 4,4'-positions **5c** was prepared by the literature procedure from commercially available 4-*t*-butyl-salicylaldehyde by the formation of triflate/palladium-catalyzed dimerization/reduction of the aldehyde moiety leading to diol **5c**.[19] The Mitsunobu reaction **5c** with diamine **7** afforded **8c** in 35% yield and **8c** was also obtained by the cyclization of mesylate **6c** with **7** in 87% yield. These results were summarized in Table 1. Because of the improved solubility of the vine-shaped biphenyl derivative **8c** bearing tertiary butyl group to organic solvents, separation of (±)-**8c** with preparative HPLC on chiral stationary phase (DAICEL Chiralpak IF, 20 mm id x 25 cm) was performed. Elution of the racemic **8c** with (hexane:*i*-PrOH =5:1) resulted in separation as shown in Figure 3. The former elution appeared at the retention time of t_R=33.5 min showing detection of a (+)-CD value at 254 nm, by contrast, the latter one at t_R=4.7 min with a negative CD value.

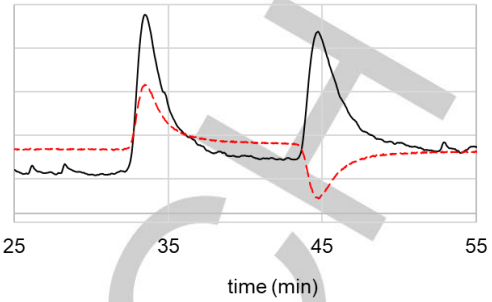
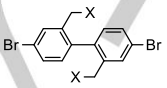
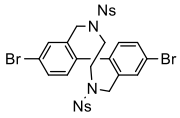
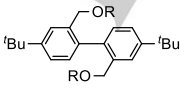
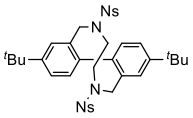


Figure 3. HPLC profile of (±)-**8c** on chiral stationary phase detected by UV (solid) and CD at 254 nm (red dotted)

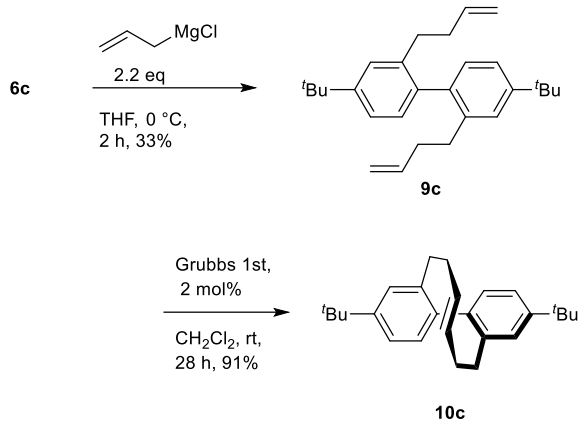
Table 1. The annulation reaction of biphenyl derivatives with nosylated ethylenediamine **7**

Annulation precursor	Method[a]	Product	% Yield
 **5b** (X = OH)	A		61
6b' (X = Br)	B	**8b**	96
 **5c** (R = H)	A		35
6c (R =SO_2CH_3)	B	**8c**	87

[a] Annulation method A: [b] The reaction was carried out with diol **5** and nosylated diamine **7** (0.95 eq) with diisopropyl azodicarboxylate (DIAD, 2.0 eq) and triphenylphosphine (2.0 eq) in THF. Annulation method B: The reaction was carried out with dimesylate or bromide, diamine **7** (1.0 eq), and potassium carbonate (4.0 eq) in DMF.

We next studied the preparation of the vine-shaped biphenyl, in which the vine moiety is composed of hydrocarbon, by ring-closing metathesis. Preparation of the metathesis precursor was carried out as shown in Scheme 3 by the reaction of **6c** with allyl Grignard reagent to give **9c**. The ring-closing metathesis was performed catalyzed by Grubbs' 1st generation catalyst[2,3] in dichloromethane to give the vine-shaped cyclized product **10c** in 91% yield. The reaction proceeded selectively, which was suggested by ^{1}H and/or ^{13}C NMR analyses, to result in giving a predominant formation of a single stereoisomer. The X-ray analysis of obtained **10c** showed the vine-shaped structure and that *E*-stereochemistry of the formed carbon–carbon double bond (C13-C14 = 1.32 Å) was confirmed.[20] The structure suggests that **10c** shows molecular asymmetry. Dihedral angle of two phenyl rings of **10c** showed 66.6°, which was found to be smaller than that of **8a** bearing the nosyl group (Figure 4a). The obtained biphenyl was subjected to the HPLC analysis on chiral stationary phase to observe separation of the enantiomers. The HPLC profile was shown in Figure 4b, in which clear separation of each enantiomer was observed at t_R=77.3 min with a negative CD and

85.1 min with positive, respectively, employing DAICEL Chiralpak IF (hexane as an eluent). We thus examined the separation of vine-shaped biphenyl derivatives (±)-**10c** with a preparative HPLC on chiral stationary phase to afford the enantiomers.



Scheme 3. Preparation of the vine-shaped biphenyl **10c**, whose vine moiety is composed of hydrocarbon by ring-closing metathesis

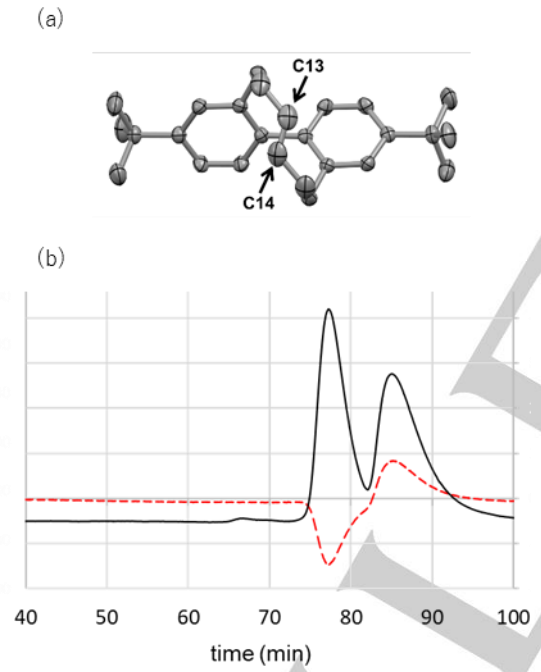


Figure 4. (a) X-ray crystal structure of **10c**. ORTEP drawn with 50% probability. Hydrogen atoms are omitted for clarity. (b) HPLC profile of **10c** on chiral stationary phase detected by UV (solid) and CD at 254 nm (red dotted)

Employing enantiomerically-enriched vine-shaped biphenyls **8c** and **10c** racemization studies of such biphenyl derivatives were performed. Enantiomerically enriched **8c** thus separated as enantiomeric ratio of 13:87 was found to be hardly racemized in a solution of chlorobenzene at 100 °C after 24 h. Racemization of **8c** slowly took place as shown in Figure 5 by heating the solution at 131 °C and the enantiomeric ratio was decreased to 38:62 (24% ee) after heating for 4 h. The energy barrier of racemization was experimentally calculated as 134 kJmol^{-1}, which well corresponded to the calculated one by DFT (126.34 kJmol^{-1}). By contrast, biphenyl **10c** cyclized by the ring-closing metathesis was found to hardly racemize under similar conditions to that of **8c** at 131 °C even after 14 h, which results reasonably agreed with the calculation study suggesting the energy barrier for the isomerization of **10c** as 211.6 kJmol^{-1} by DFT.[10] The remarkably high racemization barrier of **10c** toward **8c** is ascribed to the difficulty of free rotation of the carbon-carbon double bond in the vine moiety, while that of **8c** is composed of freely rotating single bonds.[21] The structural difference of the benzene ring from thiophene (**8c/10c** vs. **1/2**) is the presence of the C-H bond at the 6,6'-positions of biphenyl, which significantly inhibit the rotation of the C-C bond between phenyl rings to result in a higher racemization barrier compared with less sterically congested five-membered thiophene bearing no substituent on the sulfur atom.

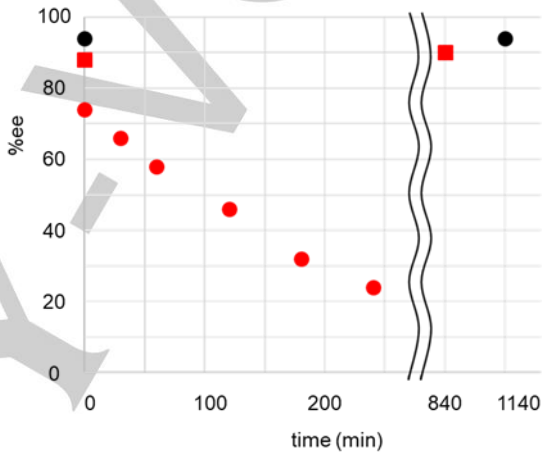


Figure 5. Racemization of **8c** at 100 °C (■ red); at 131 °C (● red), and **10c** at 131 °C (●)

Conclusion

In summary, we have shown synthesis and characterization of winding vine-shaped non-heterocyclic biaryl composed of biphenyl structure. Both molecules bearing nosylated-nitrogen and olefinic hydrocarbon in the vine moiety were prepared successfully. The formation of cyclic structures were confirmed by X-ray structure analyses and separation of enantiomers was confirmed by HPLC analyses on chiral stationary phase to show molecular asymmetry. Studies on racemization behaviors were also performed to reveal that the molecule composed of biphenyl hardly racemized. We have shown the first example to observe the separation of the product of nosyl annulation **8**, which vine part is composed of all of carbon-carbon and carbon-heteroatom single bonds. In addition, biphenyl **10c** showed highest racemization barrier higher than 200 kJmol^{-1} in the winding vine-shaped molecules that we have synthesized to date. These results clearly contrast with those of bithiophene as well as bisimidazole derivatives, which racemized much easier than biphenyls.

Experimental Section

General. Analytical thin layer chromatography (TLC) was performed on Merck 60 F 254 aluminum sheets precoated with a 0.25 mm thickness of silica gel. Melting points (mp) were measured on a Yanaco MP J3 and are uncorrected. Infrared (IR) spectra were recorded on a Bruker Alpha with an ATR attachment (Ge) and are reported in wavenumbers (cm^{-1}). ^1H NMR (400 MHz) and $^{13}C\{^1H\}$ NMR (100 MHz) spectra were measured on a JEOL ECZ400 spectrometer. Chemical shifts for ^1H NMR are parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 ppm, tetramethylsilane: δ 0 ppm, CHD_2SOCD_3: δ 2.50 ppm, CHD_2OD: δ 3.31 ppm) and coupling constants are in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Chemical shifts for $^{13}C\{^1H\}$ NMR are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm, DMSO-d_6: δ 39.52 ppm). High resolution mass spectra (HRMS) were performed on a JEOL JMS T100LP AccuTOF LC Plus (ESI) with a JEOL MS 5414DART attachment. Analytical high performance liquid chromatography (HPLC) was carried out with JASCO LC 2000 Plus on chiral stationary phase Daicel Chiralpak IF (0.46 cm I.D. x 25 cm, flow rate: 0.5–1.0 mL/min) using UV and CD (CD-4095) detectors. Single-crystal X-ray crystallography was performed using a Bruker APEX DUO Dual Wavelength System for **8a** and a Bruker Single-Crystal D8 Venture diffractometer for **8a'** and **10c**. Preparative HPLC was performed with JASCO PU-4086 with Daicel Chiralpak IF (2.0 cm I.D. x 25 cm, flow rate: 1–10 mL/min).

Materials. Preparation of 2,2'-(bishydroxymethyl)biphenyl (**5a**) and 4,4'-dibromo-2,2'-(bishydroxymethyl)biphenyl (**5b**) were performed in a manner as reported[11] with commercially available biphenyl-2,2'-dicarboxylic acid or the related acid anhydride. Preparation of 4,4'-di-tert-butyl-2,2'-diformylbiphenyl was performed by the literature procedure[19] from commercially available 4-*t*-butyl-2-formylphenol. Nosylated ethylenediamine was prepared by the procedure as we reported previously.[9] Other chemicals were purchased and used as received without further purification.

2,2'-(Bis(methanesulfonyloxy)methyl)biphenyl (6a): To a solution of **5a** (0.63 g, 3.0 mmol) and triethylamine (1 mL) in THF (12 mL) was added methanesulfonyl chloride(0.51 mL , 6.6 mmol) at 0 °C. After stirring for 24 h at room temperature, the reaction was quenched with aqueous HCl (1.0 M) to result in phase separation. The organic phase was washed with water, aqueous $NaHCO_3$ and brine. The combined organic extracts were dried over anhydrous sodium sulfate, and concentrated under reduced pressure to leave crude **6a** as a colorless oil, which was used for the next reaction without further purification.

(*N*,*N*'-Bis(2-nitrobenzenesulfonyl)-9,10,11,12,13,14-tetrahydro-dibenzo[f,h][1,4]diazecine (8a)[15]: To a 100 mL round-bottomed flask equipped with a teflon-coated magnetic stirring bar were added dimesylate **6a** (430 mg, 1.47 mmol), *N*,*N*-bis(2-nitrobenzenesulfonyl)-1,2-ethylenediamine (**7**, 623 mg, 1.45 mmol), K_2CO_3 (828 mg, 6.0 mmol) and DMF (8 mL) at room temperature. After stirring for 24 h, the reaction was quenched with aqueous HCl (1.0 M) to form a precipitate, which was filtered and the residue was washed with water and diethyl ether. The remaining solid was dried under reduced pressure to give **8a** as a colorless solid (616 mg, 69%). HPLC analysis of **8a** with DAICEL Chiralpak IF t_R = 39.1 min; 51.4 min (hexane:CH_2Cl_2= 2:1). Mp 291-292 ℃; IR (ATR) 2930, 2923, 2854, 1540, 1375, 1365, 1346, 1329, 1162, 913, 851, 767, 756, 740, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.92–7.95 (m, 2H), 7.66–7.71 (m, 4H), 7.60–7.64 (m, 4H), 7.36–7.46 (m, 4H), 7.18 (dd, *J* = 7.3, 1.8 Hz, 2H), 4.69 (d, *J*=14.6 Hz, 2H), 4.18 (d, *J*= 14.6 Hz, 2H), 3.13–3.27 (m, 2H), 2.78–2.96 (m, 2H); $^{13}C\{^1H\}$ NMR: (DMSO-d_6) δ 147.8, 140.4, 134.7, 133.6, 132.7, 130.7, 130.5, 129.9, 129.8, 128.5, 124.4x2, 50.9, 47.2, 39.5; HRMS (ESI+) *m/z* calcd for $C_{28}H_{24}N_4NaO_8S_2$, 631.0933 $[M+Na]^+$; found, 631.0944.

The Mitsunobu reaction of diol 5a with nosylated ethylenediamine 7: To a solution of **5a** (107 mg, 0.5 mmol), *N*,*N*-bis(2-nitrobenzenesulfonyl)-1,2-ethylenediamine (**7**, 200 mg, 0.47 mmol), and triphenylphosphine (262 mg, 1.0 mmol) in THF (5 mL) was added diisopropyl azodicarboxylate as a 1.9 M toluene solution (0.53 mL, 1.0 mmol) at 0 °C. After stirring for 16 h at room temperature, the reaction mixture was poured into water to form a precipitate, which was filtered off. The residue was washed with water followed by diethyl ether and the remaining solvent was removed under reduced pressure to afford **8a** as a colorless solid (156 mg, 51%). Spectroscopic data of the obtained **8a** was identical with those of the annulation product from mesylate **6a**.

Reduction of the nitro group of 8a by hydrogenation catalyzed in the presence of Pd/C leading to 8a'[16]: To a solution of **8a** (610 mg, 1.0 mmol) in 20 mL of dichloromethane was added 10% (w/w) Pd/C (53 mg) and the reaction mixture was stirred at room temperature for 24 h under hydrogen at an ambient atmosphere. The mixture was filtered off through a Celite pad and the filtrate was concentrated under reduced pressure to leave a crude solid, which was purified by column chromatography on silica gel to give **8a'** (580 mg, 95% yield) as a colorless solid. Mp 205-207 °C; IR (ATR) 3460, 3367, 3012, 2986, 2973, 1620, 1483, 1453, 1329, 1311, 1244, 1143, 1094, 1032, 916, 806 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.54 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.32-7.40 (m, 6H), 7.30 (d, *J* = 6.0 Hz, 2H), 7.11 (dd, *J* = 6.0, 2.3 Hz, 2H), 6.72 (ddd, *J* = 7.2, 6.9, 0.9 Hz, 2H), 6.69 (dd, *J* = 8.2, 0.9 Hz, 2H), 4.92 (s, 4H), 4.34 (d, *J* = 13.7 Hz, 2H), 4.08 (d, *J* = 13.7 Hz, 2H), 3.17-3.21 (m, 2H), 2.79-2.89 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 145.7, 141.3, 134.3, 134.1, 130.9, 130.04, 129.99, 128.7, 128.2, 120.7, 117.9, 117.6, 48.8, 44.0; HRMS (DART+) *m/z* calcd for $C_{28}H_{29}N_4O_4S_2$, 549.1630 $[M+H]^+$; found, 549.1657.

4,4'-Dibromo-2,2'-(bisbromomethyl)biphenyl (6b')[18]: To a solution of biphenyl **5b** (1.12 g, 3.0 mmol) in CH_2Cl_2 (7.5 mL) was added triphenylphosphine (2.05 g, 7.8 mmol) at room temperature. After the mixture was cooled to 0 °C, addition of carbon tetrabromide (2.59 g, 7.8 mmol) dissolved in CH_2Cl_2 (7.5 mL) followed and stirring was continued for further 4 h. Removal of the solvent under reduced pressure left a crude material, which was purified by column chromatography on silica gel using hexane/diethyl ether = 10:1 as an eluent to afford 1.28 g of **6b'** (96%). ^1H NMR ($CDCl_3$): δ 7.69 (d, *J* = 1.6 Hz, 2H), 7.51 (dd, *J* = 8.2, 1.8 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 4.24 (d, *J* = 10.1 Hz, 2H), 4.09 (d, *J* = 10.1 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 138.1, 137.2, 133.74, 133.71, 131.7, 122.8, 30.5.

4,4'-Di-*tert*-butyl-2,2'-(bishydroxymethyl)biphenyl (5c): To a solution of 4,4'-di-*tert*-butyl-2,2'-diformylbiphenyl (3.23 g, 10 mmol) and in methanol (50 mL) was added $NaBH_4$ (0.40 g, 11 mmol) at room temperature. After stirring for 1 h at room temperature, the resulting mixture was poured into water and the organic product was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to leave **5c** (3.2 g, 9.8 mmol, 98%) as a colorless solid. Mp 166-167 °C. IR (ATR) 3345, 2961, 2903, 2869, 1487, 1462, 1406, 1395, 1363, 1264, 1193, 1119, 833 cm^{-1};^1H NMR ($CDCl_3$): δ 7.49 (d, *J* = 1.8 Hz, 2H), 7.36 (dd, *J* = 8.2, 1.8 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 4.43 (d, *J* = 11.4 Hz, 2H), 4.35 (d, *J*= 11.4 Hz, 2H), 2.46-2.50 (br, 2H), 1.37 (s, 18H); $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 149.4, 139.2, 135.5, 129.0, 123.8, 123.2, 61.0, 34.4, 31.34 HRMS (ESI+) *m/z* calcd. for $C_{22}H_{30}NaO_2$, 349.2144 $[M+Na]^+$; found, 349.2096.

(*N*,*N*'-Bis(2-nitrobenzenesulfonyl)-9,10,11,12,13,14-tetrahydro-2,7-dibromo-dibenzo[f,h][1,4]diazecine (8b): The reaction was carried out in a similar manner to the preparation of **8a**. IR (ATR) 3098, 2943, 1543, 1470, 1371, 1164, 1125, 1090, 1060, 1004, 916, 852, 820 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.95 (ddd, *J* =6.0, 1.8, 1.4 Hz, 2H), 7.76 (d, *J* = 1.8 Hz, 2H), 7.73-7.70 (m, 4H), 7.64 (ddd, *J* =6.0, 1.8, 1.8 Hz, 2H), 7.53 (dd, *J* = 8.2, 1.8 Hz, 2H), 7.03 (d, *J* = 8.2 Hz, 2H), 4.62 (d, *J* = 14.2 Hz, 2H), 4.12 (d, *J* = 14.2 Hz, 2H), 3.24 (br, 2H), 2.91 (br, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.1, 138.5, 136.4, 134.1, 134.0, 132.4, 132.1, 131.9, 131.6, 131.0, 124.5, 123.3, 50.0, 46.6; HRMS (ESI+) *m/z* calcd. for $C_{28}H_{22}{}^{79}Br^{81}BrN_4NaO_8S_2$, 788.9123 $[M+Na]^+$; found, 788.9146.

(*N*,*N*'-Bis(2-nitrobenzenesulfonyl)-9,10,11,12,13,14-tetrahydro-2,7-di-*tert*-butyl-dibenzo[f,h][1,4]diazecine (8c): The reaction was carried out in a similar manner to the preparation of **8a**.Mp. 117-118 ℃. IR (ATR) 2964, 1544, 1365, 1164, 1125, 1061, 1037, 910, 852, 777 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.98 (ddd, *J* = 5.5, 2.0, 1.8 Hz, 2H), 7.73-7.66 (m, 4H), 7.66-7.62 (m, 2H), 7.47 (d, *J* = 1.4 Hz, 2H), 7.38 (dd, *J* = 8.0, 1.8 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 4.62 (d, *J* = 14.2 Hz, 2H), 4.18 (d, *J* = 14.2 Hz, 2H), 3.05 (s, 4H), 1.30 (s, 18H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 152.1, 148.1, 138.2, 133.8, 133.5, 132.9, 132.0, 130.9, 130.1, 127.8, 125.5, 124.4, 49.5, 45.0, 34.7, 31.3; HRMS (ESI+) *m/z* calcd. for $C_{36}H_{40}N_4NaO_8S_2$, 743.2185 $[M+Na]^+$; found, 743.2178.

Separation of (±)-8c with preparative HPLC on chiral stationary phase (DAICEL Chiralpak IF (2.0 cm I.D. x 25 cm**):** The vine-shaped biphenyl (±)-**8c** (0.5 mg) was dissolved in 1.0 mL of the eluent (hexane/2-PrOH=10:1) and subjected to the separation with HPLC on chiral stationary phase (DAICEL Chiralpak IF (2.0 cm I.D. x 25 cm, flow rate: 10 mL/min) t_R = 33.5 min: >99 %ee; t_R = 44.7 min: 74% ee.

4,4'-Di-*tert*-butyl-2,2'-(bis(3-buten-1-yl))biphenyl (9c): To a solution of mesylate **6c** (480 mg, 1.0 mmol) in THF (2 mL) was added a solution of allylmagnesium chloride (2.2 mmol) in THF (1.1 mL) at 0 °C. After stirring for 5 h at 0 °C, the reaction was quenched with aqueous NH_4Cl and the organic product was extracted with diethyl ether. The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to leave a crude oil. Purification by column chromatography (hexane/dichloromethane = 4:1) afforded **9c** as a colorless oil. IR (ATR) 2964, 2925, 2861, 2349, 1640, 1487, 1457, 1363, 1263, 911 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.27 (d, *J* = 1.8 Hz, 2H), 7.21 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.04 (d, *J* = 7.8 Hz, 2H), 5.70 (ddt, *J* = 16.9, 10.5, 6.4 Hz, 2H), 4.88 (dd, *J* = 16.9, 1.8 Hz, 2H), 4.86 (dd, *J* = 10.1, 1.8 Hz, 2H), 2.50-2.36 (m, 4H), 2.23-2.11 (m, 4H), 1.36 (s, 18H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 149.8, 139.2, 138.7, 138.1, 129.9, 125.9, 122.4, 114.7, 35.2, 34.6, 33.2, 31.6; HRMS (DART+) *m/z* calcd. for $C_{28}H_{38}$, 374.2974 $[M]^+$; found, 374.2985.

9,10,13,14-Tetrahydro-2,7-di-*tert*-butyl-(11*E*)-dibenzo[a,c]cyclodecene (10c)[20]: To a solution of **9c** (125 mg, 0.33 mmol) in 13 mL of dichloromethane was added Grubbs 1st generation catalyst[5] (5.6 mg, 6.6 μmol) and stirring was continued at room temperature for 28 h. The solvent was removed under reduced pressure to leave a crude solid. Purification by chromatography on silica gel using hexane as an eluent to afford **10c** as a colorless solid. (106 mg, 91%)**.** Mp 130-131 °C; IR (ATR) 2960, 2930, 2865, 1487, 1447, 1362, 1283, 1257, 1194, 1121, 965, 827 cm^{-1}; ^1H NMR (CD_3OD): δ 7.30 (d, *J* = 2.3 Hz, 2H), 7.22 (dd, *J* = 8.2, 2.3 Hz, 2H), 6.87 (d, *J* = 8.2 Hz, 2H), 4.27 (dd, *J* = 4.1, 3.7 Hz, 2H), 2.68 (td, *J* = 12.4, 2.7 Hz, 2H), 2.60 (dt, *J* = 12.4, 3.7 Hz, 2H), 2.25-2.29 (m, 2H), 1.67-1.73 (m, 2H), 1.36 (s, 18H); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 149.9, 140.6, 139.3, 130.0, 128.4, 128.0, 122.1, 35.6, 34.6, 33.2, 31.6; HRMS (DART+) *m/z* calcd. for $C_{26}H_{35}$, 347.2739 $[M+H]^+$; found, 347.2753.

Separation of (±)-10c with preparative HPLC on chiral stationary phase (DAICEL Chiralpak IF (2.0 cm I.D. x 25 cm**):** The vine-shaped biphenyl (±)-**10c** (0.5 mg) was dissolved in a 1.0 mL of the eluent (hexane) and subjected to the separation by HPLC on chiral stationary phase (DAICEL Chiralpak IF (2.0 cm I.D. x 25 cm, flow rate: 1.0 mL/min) t_R = 77.3 min: >99% ee; t_R = 85.1 min: 94% ee.

Studies on the racemization behavior of the winding vine-shaped biphenyl: In a screw-capped test tube equipped with a magnetic stirring bar **8c** (1.2 mg) was dissolved in 1.2 mL of chlorobenzene and the resulting solution was heated in an oil bath. Aliquot of the solution was taken and subjected to HPLC analysis on chiral stationary phase. Analysis of **10c** was also carried out in the above manner.

Single-crystal X-ray crystallographic data: CCDC Number 2074149-2074151 contain crystallographic data for this paper. The data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.[15,16,20]

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Keywords: Winding vine-shaped biphenyl • molecular asymmetry •nosyl annulation• metathesis • Density functional calculations

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[20] CCDC Number 2074151 (**10c**)
[21] Calculation of racemization barrier of the hydrogenated derivative of **11c** revealed decrease the energy of ca. 90 $kJmol^{-1}$ lower (120.9 $kJmol^{-1}$). See also Supporting Information

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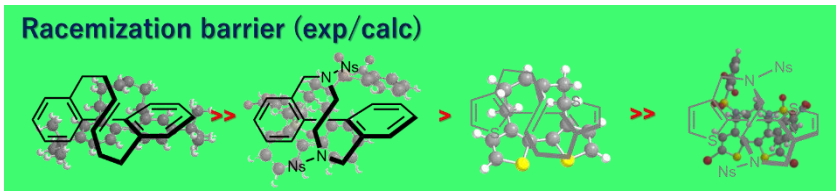

Winding vine-shaped biphenyls are synthesized. The molecule formed by ring-closing metathesis was found hardly racemized (ΔG = >200 kJmol^{-1}) even a harsh condition under refluxing chlorobenzene and the one by nosyl annulation also showed higher racemization barrier (ca. 130 kJmol^{-1}) compared with the related bithiophene derivatives, which we prepared previously (ca. 70-100 kJmol^{-1}).

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