Double winding vine-shaped biphenyl with molecular asymmetry. Synthesis, structure, and properties

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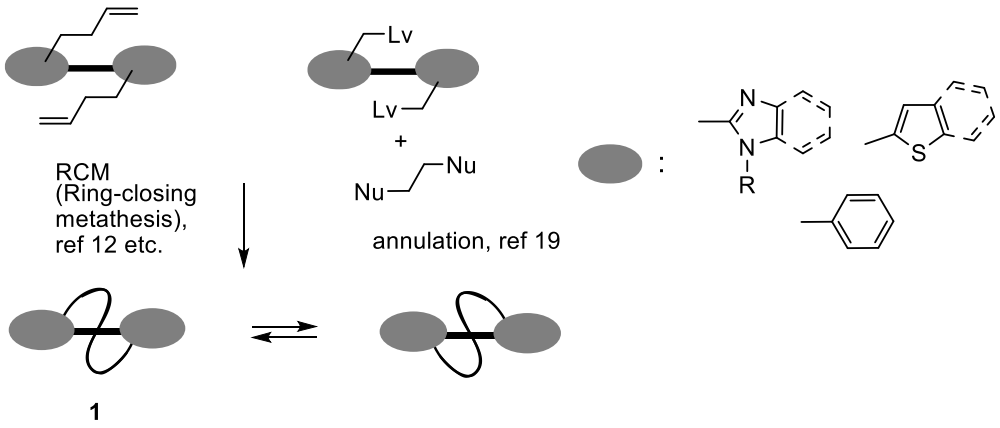
Introduction

Organic molecules involving molecular asymmetry, which shows chirality without possessing carbogenic chiral center, are of considerable interest directed to a wide range of applications for asymmetric catalysis, chirality recognition, etc., as well as a novel class of chirality based on molecular structural interest.[1,2] Chirality switching also is a class of an attractive issue in organic chemistry.[3–5] Such switching at the asymmetric carbon in a chiral molecule must take place through the disconnection/connection pathway of the chemical bond. In a sharp contrast, chirality based on molecular asymmetry is switchable only by a conformational change without the cleavage and regeneration of the chemical bond. Accordingly, chirality switching employing organic compounds involving molecular asymmetry can be translated into digital information without changing its chemical property except the absolute configuration.[6–10] We have reported that the ring-closing metathesis (RCM) of (hetero)biaryl bearing a terminal alkenyl substituent at each aromatic ring undergoes a cyclization reaction and the thus formed product indicates molecular asymmetry. We have been studying the thus obtained cyclized product, which we call such a kind of chirality as the *winding vine-shaped molecular asymmetry*.[11] The first preparation was shown with bis(benzo)imidazole[12] and several related hetero[13–15] and non-heteroaromatic[16] vine-shaped molecules have also been synthesized. We have also shown that the annulation reactions with nosylated diamine (nosyl: 2-nitro-benzenesulonyl)[17,18] with benzylic halide also furnishes another class of vine-shaped molecules and thus obtained compounds also showed molecular asymmetry.[19] The isomerization behaviors of the obtained molecular asymmetry are our major concern and among those we have revealed that biphenyl derivatives indicates a high racemization energy barrier by experimental[20] and DFT calculation[21] studies. Our

interest has thus turned to develop a novel class of winding vine-shaped biphenyl derivatives showing molecular asymmetry and it is intriguing to synthesize biphenyl with each of benzene ring is annulated by two vine-like functionalities.[22,23] Such a molecule would allow formation of the hardly racemizable chirality due to the further-enhanced difficulties on the twisting of the doubly strapped axial chirality. We herein disclose that such double winding wine-shaped biphenyl derivatives **1** and **2** can be synthesized by ring-closing metathesis and nosyl annulation reactions.

■ Winding vine-shaped (hetero)biaryls with molecular asymmetry



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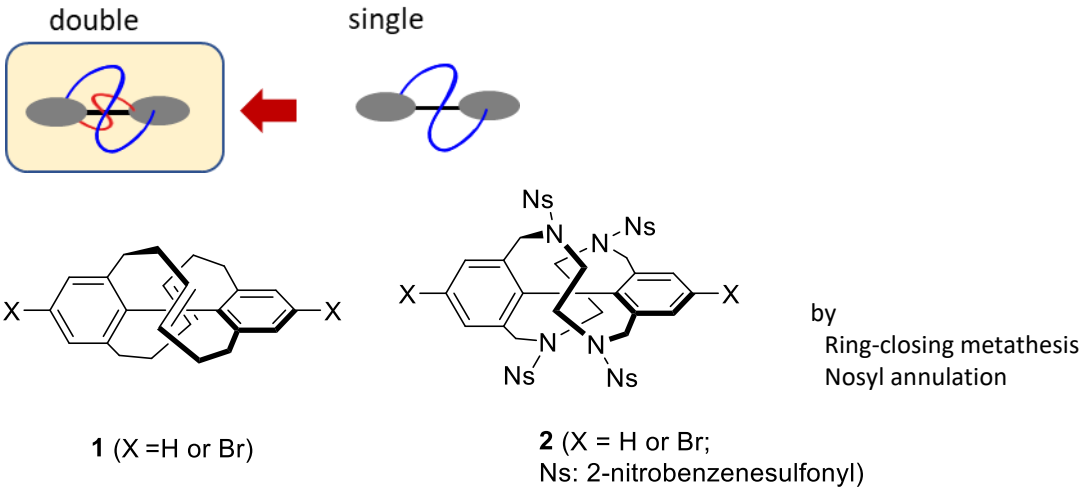
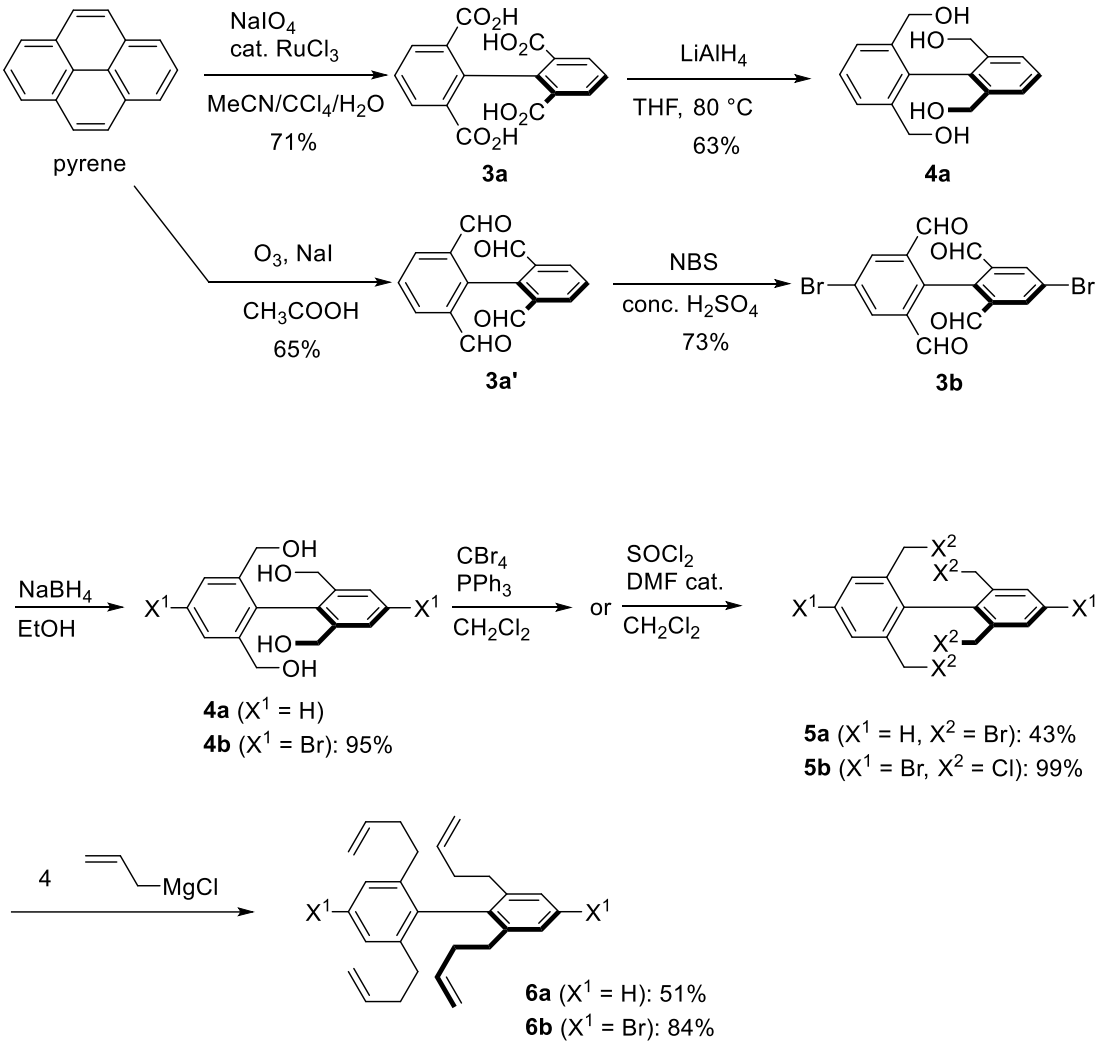


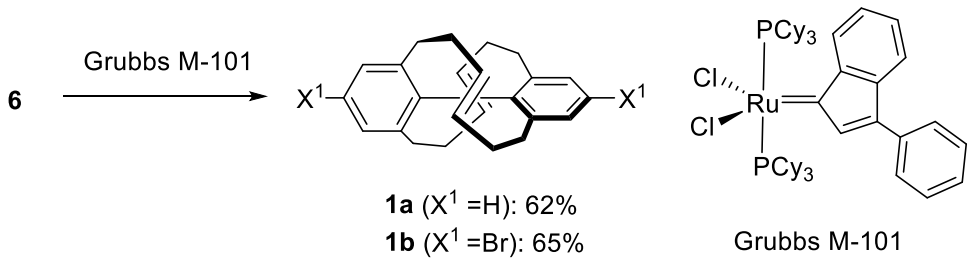
Figure 1. Double winding vine-shaped biphenyl with molecular asymmetry

Synthesis of double winding vine-shaped biphenyl was carried out using pyrene as a starting material as summarized in Scheme 1. Treatment of pyrene with $NaIO_4$ in the presence of a catalytic amount of $RuCl_3$ afforded the biphenyl tetracarboxylic acid **3a** in 71% yield by following the literature procedure.[24] Reduction of **3a** was carried out with $LiAlH_4$ to afford tetraol **4a** in 63% yield in a similar manner to that for the preparation of single vine-shaped biphenyl.[16] Tetraol **4b** bearing bromine on the benzene ring was alternatively synthesized by reductive ozonolysis to afford tetraldehyde **3a'** (65% yield)[25] followed by bromination with NBS to afford **3b** in 73% yield. Reduction of **3b** was carried out with $NaBH_4$ as a reducing agent to afford brominated tetraol **4b** in 95% yield.[26] Tetraol **4a** was transformed into bromide **5a** and **4b** was treated with $SOCl_2$ leading to chloromethylated biphenyl **5b**. The obtained tetra-halomethylated biphenyls **5** was subjected to the reaction with allyl Grignard reagent to afford the metathesis precursor **6** in excellent yields. (51% for **6a** and 84% for **6b**)



Scheme 1. Preparation of cyclization precursor of double winding vine-shaped biphenyl derivatives **6**

We first examined the ring-closing metathesis with ruthenium catalyst.[27] When the reaction of **6a** was carried out with ruthenium complex Grubbs M101 as a catalyst,[6,28] smooth RCM reaction proceeded at room temperature. The cyclized product **1a** was obtained in 62% yield after stirring for 24 h. The reaction of brominated biphenyl **6b** was also found to proceed in a similar manner to yield **1b** in 65% yield. The measurement of HRMS of obtained **1a** and **1b** showed *m*/*z* (M+H) of 315.2122 and 471.0325, respectively, suggesting that the metathesis reaction took place in a intramolecular manner. (Scheme 2)



Scheme 2. Ring-closing metathesis of **6** bearing 3-alkenyl groups

Although attempted X-ray crystal structure analysis of **1a** has been unsuccessful so far, it was found that the recrystalization of related **1b** bearing a bromo group on each of the benzene ring of biphenyl afforded a single crystal for the X-ray analysis by recrystallization. The X-ray crystal structure of **1b** shows that RCM reaction took place at the terminal alkenyl group between opposite benzene rings of biphenyl to form two straps on the biphenyl moiety. (Figure 2a) The racemate of **1b** was revealed to be consisted of two sets of enantiopairs in a unit cell similar to the cases of our previous single vine-shaped (het)biaryls.[11] Stereochemistry of the carbon–carbon double bond was found to be the *E*-form stereoselectively. The dihedral angle of the C–C bond of biphenyl showed 70.2°, which was slightly larger than that of the single vine-shaped biphenyl (66.6°).[16] Because of the strain by the dual linkage at the 2,2' and 6,6'-positions of biphenyl, two benzene rings of **1b** was slightly portioned, accordingly. The ^{1}H NMR spectrum of **1b** indicated a signal at δ = 4.22 ppm, which was assigned as vinylic proton, which shifted to lower frequency than that of the usual one (> 5 ppm), This would be due to the deshielded effect of the benzene rings of the biphenyl moiety. In contrast that benzylic and allylic CH_2 protons of the metathesis precursor **6a** and **6b** appeared at the mostly same chemical shift (ca. 2 ppm), those signals appeared as four separate ones. The finding also supported that the ring formation took place to observe magnetically non-equivalent methylene signals.

HPLC analysis of **1b** with a chiral column (DAICEL Chiralpak IF) showed two peaks with the retention time of 21.9 min and 22.7 min by UV detector whereas clear baseline separation was not observed (hexane as an eluent). The profile with CD detector indicated that the former peak as positive and the latter slightly negative. The result suggests separation of the racemic mixture of **1b** to each enantiomer as shown in Figure 2b.

(a) (b)

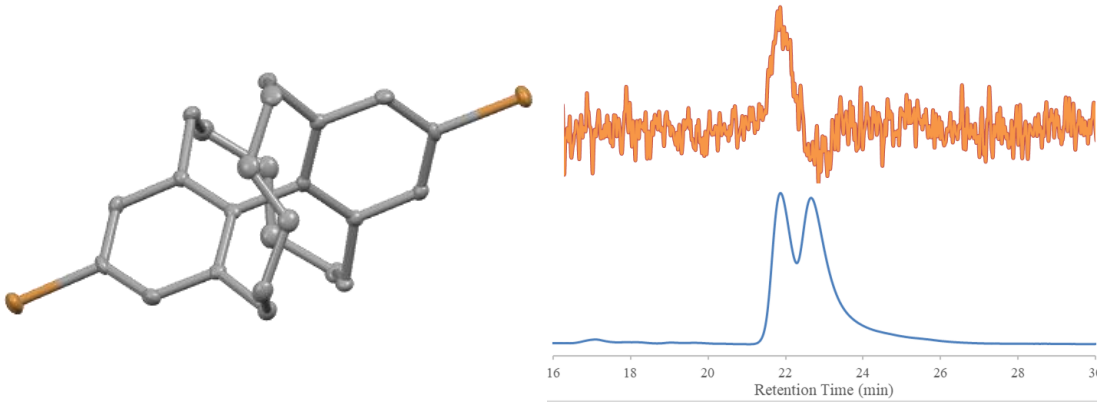
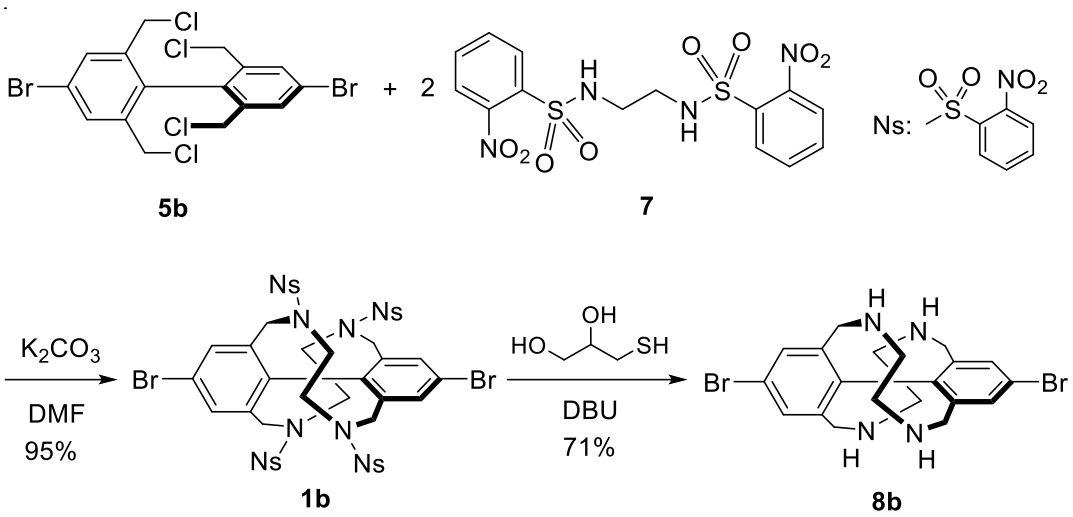


Figure 2. (a) X-ray crystal structure of dibromobiphenyl **1b** (protons were omitted for clarity). CCDC: 2291758: See ref 29. (b) HPLC profile of winding vine-shaped biphenyl **1b** by DAICEL Chiralpak IF as a chiral column using hexane as an eluent (flow rate 0.5 min^{-1}) detected by UV (lower) and CD (upper) detectors

We next envisaged preparation of double winding vine-shaped biphenyl by the nosyl annulation of tetrahalomethyl biphenyl **5** with nosylated ethylenediamine.[19] The reaction of **5b** with twice molar amounts of diamine **7** proceeded smoothly in the presence of potassium carbonate as a base in DMF at room temperature for 24 h to afford the cyclized product **1b** in excellent yield as shown in Scheme 3.

The removal of four nosyl groups of **1b** was carried out by the treatment of thioglycerol in the presence of DBU as a base to afford the denosylated product **8b** in 71% yield. HPLC analyses of **8b** with a chiral column showed clear separation of the enantiomer (retention time: t_R = 7.6 min and 10.7 min/eluent: hexane:ethanol=6:4) as shown in Figure 3a. The HPLC profile by CD detector also indicated separated peaks, where the former eluate showed negative and the latter one as positive, suggesting the separation of each enantiomer. X-ray crystal structure analysis of **8b** was also successful after the conversion to the corresponding HCl salt. (Figure 3b) The measurement showed formation of two sets of enantiopair of (±)-**8b** in a unit cell. The dihedral angle between benzene rings of biphenyl was shown to be 85–89°. The dihedral angle of **8b** was found to be larger than that of RCM-derived **1b**.



Scheme 3. Nosyl annulation of **5b** and denosylation.

(a) (b)

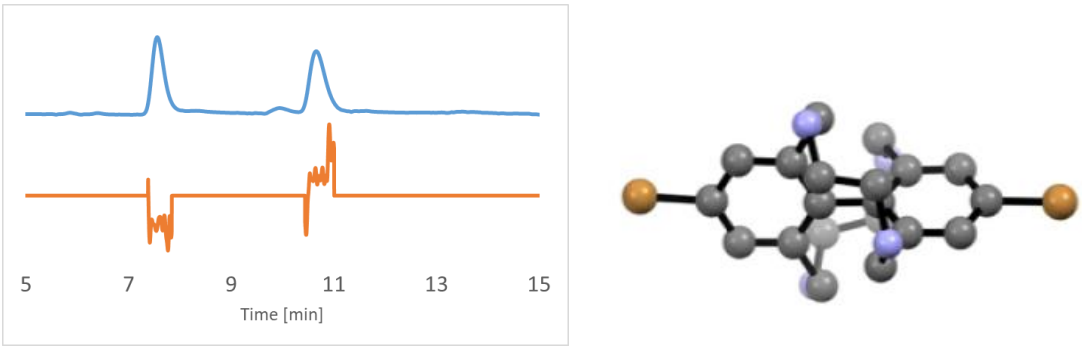


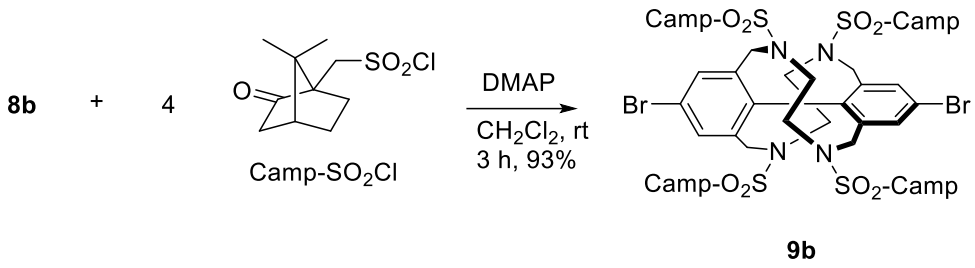
Figure 3. (a) HPLC profile of **8b** by chiral column with UV (blue) and CD (g-factor, red) detectors. (b) X-ray crystal structure of (±)-**8b** as a 4HCl salt. Hydrogen, chloride ion and oxygen (water) were omitted for clarity. CCDC: 2291769 (ref 29)

The obtained tetramine **8b** was then subjected to the reaction of chiral (+)-camphor sulfonyl chloride at room temperature for 3 h in dichloromethane to afford the corresponding sulfonate as a pair of the 1:1 diastereomer. (Figure 4a) The ^{1}H NMR spectrum showed a pair of singlet signal assigned as aromatic proton along with two pairs of doublets at 3.7–4.5 ppm characterized as benzylic protons that were adjacent to nitrogen. (See Supporting Information) TLC analysis of **9b** also showed the separation of diastereomer, which R_f indicated 0.21 and 0.18 in the use of chloroform as an eluent. The

chromatographic separation of the mixture on silica gel was also found to be successful to isolate 29% of the former eluate accompanied by 25% of the latter one using chloroform as an eluent.

The X-ray crystal structure analysis of thus separated **9b** (latter eluate) showed that the absolute configuration of the vine-shaped moiety was assigned as left-handed. This is the first example of the successful chromatographic separation without using a chiral column as a diastereomeric mixture. Accordingly, the absolute configuration of the winding vine-shaped biaryl derivative has been confirmed for the first time. The dihedral angle of the C–C bond of biphenyl in camphor sulfonamide **9b** showed as 78–81°, which was slightly smaller than that of tetramine hydrochloride **8b**·4HCl (85–89°). As a result, the crossing angle of the C–C bond between diamine in **9b** toward the C–C bond of biphenyl was obtuse. In contrast, the desulfonylated analog **8b** indicated a sharp angle.

(a)



9b

(b)

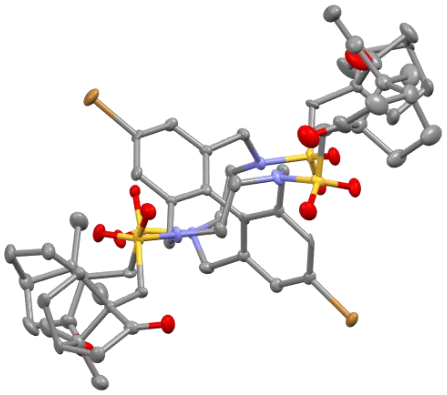


Figure 4. (a) Transformation of **8b** to diastereomeric camphor sulfonamide **9b** (b) X-ray crystal structure of the **9b** (latter eluate) by the separation of column chromatography (hydrogen atoms were omitted for clarity). CCDC: 2291778 (ref 29)

Because of difficulties of preparative separation of enantiomers of **1** and **2**, experimental racemization studies have not been achieved so far. The DFT calculation studies to

estimate the racemization barrier was attempted, accordingly. Although ΔH values of **1b** and **2b** are calculated as 2.44 x 10^6 kJmol^{-1} and 1.60 x 10^7 kJmol^{-1}, respectively, the calculation of the estimated energy of the transition state, assuming the dihedral angle between biphenyl to be 0°,[21] did not converge. The result strongly suggests that the energy of the transition state is considerably high and thus the racemization of the double winding vine biphenyl **1** and **2** would hardly take place.

In conclusion, we have shown that double winding vine-shaped biphenyl was synthesized by the double ring-closing metathesis of biphenyl derivative bearing 3-buten-1-yl substituents at the 2,2',6,6'-positions of biphenyl **6**. The ring-closing reaction was shown to take place smoothly with a ruthenium catalyst Grubbs M-101. The structure of the ring-closed product **1** was confirmed by X-ray crystal structure analysis and the separation of enantiomer was confirmed by HPLC analysis with chiral column. The related vine-shaped biphenyl **2** was shown to proceed also with annulation refraction of tetera-halomethylated biphenyl **5** and nosylated ethylenediamine **7**. The absolute configuration of the vine-shaped product was confirmed by the transformation to the corresponding diastereomeric camphor sulfonamide and the silica gel column chromatography and the X-ray analysis of thus separated **9b** revealed that the latter eluate showed the left-handed structure. The obtained product is potentially applicable as a chiral constituent for a variety of supramolecular composite as well as chiral catalysis for asymmetric reactions and further efforts on the double vine-shaped molecules are in progress.

Experimental

General. Unless otherwise specified all the reactions were carried out under a nitrogen or argon atmosphere with standard Schlenk technique. 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}). ^{1}H (400 MHz) and $^{13}C\{^{1}H\}$ NMR (100 MHz) spectra were measured on a JEOL ECZ400 spectrometer. Chemical shifts for ^{1}H NMR are parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 ppm, DMSO-d_6: δ 2.50 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 $^{13}C\{^{1}H\}$ 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, benzene-d_6: δ 128.06 ppm). High resolution mass spectra (HRMS) were performed on a JEOL JMS T100LP AccuTOF LC Plus (ESI) with a JEOL MS 5414DART attachment. Silica gel flash column chromatography was performed with Wakogel® 60N (63–212 μm, Fujifilm Wako Pure Chemical Industries, Ltd.) or high-efficiency irregular silica (25–40 μm, Santai Science Inc.). HPLC analyses with a chiral column were carried out with JASCO LC-2000 Plus with chiral column Daicel Chiralpak IF or IC (0.46 cm I.D. × 25 cm, flow rate: 0.5–1.0 mL/min) using UV (254 nm) detector. DFT calculation was performed by Spartan ver. 16. Single crystal X-ray analysis was performed using Rigaku VariMaXSaturnCCD724/α with MEXT Joint Usage/Joint Center at Ehime University and Bruker Single-Crystal D8 Venture diffractometer at Department of Chemical Engineering, National Tsing Hua University.

Material. Pyrene was purchased and employed for ozonolysis without further purification. Grubbs M101 catalyst Dichloro(3-phenyl-1H-inden-1-ylidene)bis(tricyclohexylphosphine)ruthenium(II)[28] was purchased from TCI Co. Ltd. and stored at room temperature under nitrogen. Preparation of biphenyl tetracarboxylic acid **3a** and tetraol **4a** was carried out by ozonolysis of pyrene and following reduction with $LiAlH_4$ in a manner as described in the literature.[25] Biphenyl derivatives bearing bromine at the 4,4'-positions **3b** and **4b** were synthesized in a manner as shown in the literature.[27] Dichloromethane and THF were purchased from Fuji Film Wako Pure Chemicals Co. Ltd. as an anhydrous grade.

4,4'-Dibromo-2,2',6,6'-Tetrahydroxymethyl-biphenyl (4b): To a 100 mL round-bottomed flask were added **3b** (1.34 g, 3.2 mmol) and ethanol (19 mL). $NaBH_4$ was added to the mixture and stirring was continued for 2 h at room temperature. The reaction mixture was poured into a mixture of water and diethyl ether to result in phase separation. The aqueous phase was extracted with with diethyl ether. The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford 1.30 g of **4b** as a colorless solid (95%). The spectroscopic properties of obtained **4b** was identical with the authentic sample.[26] ^{1}H NMR (DMSO-d_6) δ 7.60 (s, 4H), 3.35 (br, 8H); ^{13}C NMR (DMSO-d_6) δ 142.29, 130.64, 127.96, 121.81, 60.08; HRMS (ESI+) Calcd for $C_{16}H_{16}O_4{}^{79}Br^{81}BrNa$ [M+Na]+: 454.9293; found: *m/z* 454.9309; IR (ATR) 3301, 2928, 1579, 1460, 1435, 1240, 1067, 1028, 879, 869, cm^{-1}.

2,2',6,6'-Tetrakis(bromomethyl)-1,1'-biphenyl (5a): To a 100 mL round-bottomed flask equipped with a teflon-coated magnetic stirring bar were added **4a** (863 mg, 3.2 mmol), carbon tetrabromide (5.34 g, 16 mmol), triphenyl phosphine (4.22 g, 16 mmol) and THF (38 mL) at room temperature. After stirring for 21 h, the mixture was filtered off and the residue was washed with *n*-hexane and dichloromethane, and the filtrate was concentrated under reduced pressure to leave a crude oil. Purification by column chromatography on silica gel using dichloromethane as an eluent to afforded **5a'** as a colorless solid (713 mg, 43%). The product was identical with the authentic sample.[25] ^{1}H NMR ($CDCl_3$) δ 7.40–7.61 (m, 6H), 4.23 (s, 8H).

4,4'-Dibromo-2,2',6,6'-tetrachloromethyl-biphenyl (5b): To a 200 mL round-bottomed flask were added **4b** (1.23 g, 2.9 mmol), dichloromethane (7.8 mL), and a drop of DMF. Thionyl chloride (11.5 mL) was added dropwise to the resulting mixture, stirred at room temperature for 4 h. The solvent was removed under reduced pressure to leave 1.42g of **5b** as a colorless solid. (99%) Mp 123.3 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (s, 4H), 4.20 (s, 8H) ; ^{13}C{^{1}H} NMR ($CDCl_3$) δ 138.67, 134.12, 133.34, 124.01, 43.66; IR (ATR) 2953, 2924, 2854, 1580, 1447, 1377, 1265, 1243, 1116, 1004, 986, 905, 874, 832, 783, 722, 684, 614 cm^{-1}. HRMS (ESI+) Calcd for $C_{16}H_{13}O_4{}^{81}Br_2{}^{35}Cl_4$ [M+H]+: 506.8097; found: *m/z* 506.8106.

2,2',6,6'-(Tetrakis(3-buten-1-yl))-biphenyl (6a): To a solution of **5a'** (156 mg, 0.3 mmol) in THF (0.8 mL) was added a solution of allylmagnesium chloride (1.5 mmol) in THF (0.75 mL) at 0 °C under an argon atmosphere. After stirring for 4 h at room temperature, 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, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to leave a crude oil. Purification by column chromatography on silica gel using hexane as an eluent to afforded **3** as a colorless oil (57 mg, 51%). ^{1}H NMR ($CDCl_3$) δ 7.28 (t, J =7.6 Hz, 2H), 7.19 (d, J = 7.6 Hz, 4H), 5.66–5.76 (m, 4H), 4.85–4.95 (m, 8H), 2.17–2.32 (m, 16H); ^{13}C{^{1}H} NMR (benzene-d_6): δ 139.72, 138.88, 138.50, 126.53, 115.01, 77.66, 34.21, 33.11; IR (ATR) 2964, 2925, 2861, 2349, 1640, 1487, 1457, 1363, 1263, 911 cm^{-1}. HRMS (DART+) *m/z* calcd for $C_{28}H_{35}$, 371.2739 $[M+H]^+$; found, 371.2729.

4,4'-Dibromo-2,2',6,6'-tetrakis(3-buten-1-yl)-biphenyl (6b): To a solution of **5b** (2.68 g, 5.3 mmol) in THF (30 mL) was added a solution of allylmagnesium chloride (26 mL as a 1 M THF solution, 26 mmol) in THF (30 mL) at 0 °C under an argon atmosphere. After stirring for 4 h at room temperature, the reaction mixture was poured into aqueous NH_4Cl to result in phase separation. The aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with water, dried over anhydrous sodium sulfate. Concentration of the solvent under reduced pressure to leave a crude oil, which was purified by column chromatography on silica gel using dichloromethane as an eluent to afforded **6b** as a colorless solid (2.4 g, 84%).^{1}H NMR ($CDCl_3$) δ 7.34 (s, 4H), 5.63–5.74 (m, 4H), 4.91–4.96 (m, 8H), 2.17–2.24 (m, 16H), ^{13}C NMR ($CDCl_3$) δ 141.85, 137.61, 136.43, 129.33, 121.85, 115.50, 33.54, 32.37; IR (ATR) 3076, 2977, 2926, 2861, 1641, 1573, 1436, 1415, 999, 914 cm^{-1}. HRMS (DART+) *m/z* calcd for $C_{28}H_{33}{}^{79}Br^{81}Br$, 529.0929 $[M+H]^+$; found, 529.0924.

Ring-closing metathesis of 6 with Grubbs M101 as a catalyst: To a solution of **6a** (57 mg, 0.153 mmol) in 5 mL of dichloromethane was added Grubbs catalyst M101 (2 mg, 0.15 μmol) and stirring was continued at room temperature for 24 h. The solvent was removed under reduced pressure to leave a crude solid. Purification by column chromatography on silica gel using hexane as an eluent to afford **1a** as a colorless solid. (30 mg, 62%).

4,5,8,9,13,14,17,18-Octahydrodibenzo[hi,qr]decalene (1a): ^{1}H NMR ($CDCl_3$) δ 7.26 (t, J = 7.2 Hz, 2H), 7.10 (d, J = 7.2 Hz, 4H), 4.25–4.35 m, 4H), 2.50–2.71 (m, 4H), 2.20 (d, J = 12.4 Hz, 4H), 2.04 (t, J = 12.4 Hz, 4H), 1.69–1.86 (m, 4H); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 142.48, 139.81, 129.03, 128.07, 127.32, 35.22, 34.70; IR (ATR) 2960, 2930, 2865, 1487, 1447, 1362, 1283, 1257, 1194, 1121, 965, 827 cm^{-1}. HRMS (DART+) Calcd for $C_{24}H_{27}$ [M+H]+: 315.2113; found: *m/z* 315.2122.

Synthesis of **1b** was also carried out in the above manner with **6b** (30 mg, 0.06 mmol) in 2.5 mL of dichloromethane was added Grubbs catalyst M101 (0.5 mg, 0.06 μmol). (18 mg, 65%)

2,11-Dibromo-4,5,8,9,13,14,17,18-octahydrodibenzo[hi,qr]decalene (1b): ^{1}H NMR (DMSO-d_6) δ 7.38 (s, 4H), 4.22 (t, J = 3.7 Hz, 4H), 2.65-2.67 (m, 4H), 2.14–2.23 (m, 4H), 1.83 (t, J = 12.0 Hz, 4H), 1.63-1.75 (m, 4H); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 142.28, 140.39, 131.89, 128.07, 121.14, 53.46, 34.86, 34.60; IR (ATR) 2922, 2857, 1740, 1446, 1216, 966, 794, 748 cm^{-1}. HRMS (DART+) calcd for $C_{24}H_{25}{}^{79}Br_2$ [M+H]+: 471.0323; found: *m/z* 471.0325.

Annulation of 5b with nosylated ethylenediamine 7: To a 100 mL round-bottomed flask were added **5b** (1.49 g, 2.9 mmol), *N*,*N*'-1,2-ethanediylbis[2-nitrobenzenesulfonamide] (**7**) (5.88 g, 2.54 mmol), K_2CO_3 (3.24 g, 23.5 mmol), DMF (22 mL). The mixture was stirred at room temperature for 24 h. Addition of H_2O to the resulting mixture formed a precipitate, which was filtered off to afford a 3.36 g of **2b** as a colorless solid. (95%)

5,8,14, 17-Tetrakis(2-nitrobenzenesulfonyl)-2,11-Dibromo-4,5,6,7,8,9,13,14,15,16,17,18-dodecahydro[2,5]benzodiazecino[9,8,7-ghi][2,5]benzodiazecine-5,8,14,17-tetramine (2b): Mp >250 °C (decomp); ^{1}H NMR (DMSO-d_6) δ 7.80–8.04 (m, 16H), 7.67 (s, 4H), 4.22-4.32 (m, 8H), 3.01-3.172 (m, 8H); ^{13}C{^{1}H} NMR (DMSO-d_6) δ 148.09, 137.04, 135.91, 134.76, 134.04, 132.68, 130.14, 129.48, 124.41, 121.85, 52.32, 48.93; IR (ATR), 3333, 1543, 1440, 1362, 1348, 1168, 1126, 909, 851, 745, cm^{-1}. HRMS (ESI+) calcd for $C_{44}H_{36}O_{16}N_8S_4{}^{79}Br^{81}BrNa$ [M+Na]+: 1242.9376; found: *m/z* 1242.9323.

Synthesis of **2a** was carried out in a similar manner using 107 mg of **5a** (0.2 mmol), 180 mg of **7** (0.4 mmol). (53% yield)

5,8,14, 17-Tetrakis(2-nitrobenzenesulfonyl)-4,5,6,7,8,9,13,14,15,16,17,18-dodecahydro[2,5]benzodiazecino[9,8,7-ghi][2,5]benzodiazecine-5,8,14,17-tetramine (2a): ^{1}H NMR (DMSO-d_6) δ 7.82-7.97 (m, 16H), 7.45 (s, 6H), 4.38 (d, J = 14.0 Hz, 4H), 4.10 (d, J = 14.0 Hz, 4H), 2.95–3.03 (m, 8H), ^{13}C{^{1}H} NMR (DMSO-d_6) δ 147.91, 137.77, 134.76, 134.29, 132.66, 131.38, 130.39, 129.64, 129.35, 124.38, 51.65, 47.18. IR (ATR) 1540, 1375, 1365, 1346, 1329, 1162, 913, 851, 767, 756, 740, 698 cm^{-1}. HRMS (ESI+) calcd for $C_{44}H_{38}N_8NaO_{16}S_4$, 1085.1186 $[M+Na]^+$; found: *m/z* 1085.1185.

The removal of the nosyl group of 2b: To a 200 mL round-bottomed flask were added **2b** (4.26 g, 3.5 mmol) and DMF (17.5 mL). To the solution were added 1,8-diazabicyclo[5.4.0]-7-undecene (2.61 mL, 17.5 mmol) and α-thioglycerol (1.51 mL, 17.5 mmol) and the mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and conc. HCl was added to form a precipitetes. The residue was washed with ethanol and acetone. The obtained solid was dissolved in water and the addition of aqueous NaOH until neutralized formed a precipitate to afford 1.19 g of **8b**. (71% yield)

2,11-Dibromo-4,5,6,7,8,9,13,14,15,16,17,18-dodecahydro[2,5]benzodiazecino[9,8,7-ghi][2,5]benzodiazecine-5,8,14,17-tetramine (8b): ^{1}H NMR ($CDCl_3$) δ 7.46 (s, 4H), 3.58 (d, J = 6.4 Hz, 4H), 3.43 (d, J = 6.4 Hz, 4H), 2.35–2.46 (m, 8H), 2.17 (s, 4H); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 142.90, 137.04, 132.14, 123.13, 50.65, 47.24; HRMS (ESI+) Calcd for $C_{20}H_{25}{}^{79}Br^{81}BrN_4$ [M+H]+: 481.0426; found: *m/z* 481.0420; IR (ATR) 3250, 2931, 2851, 2349, 1574, 1439, 1233, 1118, 867, 731 cm^{-1}.

Transformation of **8b** to a diastereomeric mixture of sulfonamide with (+)-camphorsulfonyl chloride: To a screw-capped test tube equipped with a magnetic stirring bar were added **8b** (198 mg, 0.4 mmol), 4-dimethylaminopyridine (205 mg, 1.6 mmol), (+)-camphorsulfonyl chloride (404 mg, 1.6 mmol) and dichloromethane (8 mL). After stirring at room temperature for 4 h, the resulting mixture was poured into H_2O and the organic product was extracted three times with dichloromethane. The solution was dried over anhydrous sodium sulfate and concentrated under reduced pressure to leave **9b** as a pale yellow solid (501 mg, 93%). Separation of 241 mg of **9b** by column chromatography on silica gel using chloroform as an eluent isolated 79.1 mg of the first eluate (R_f = 0.21) and 61.2 mg of the second eluate (R_f = 0.18).

Fraction 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 4H), 4.38 (d, J = 14.4 Hz, 4H), 3.86 (d, J = 14.4 Hz, 4H), 3.32 (d, J = 6.8 Hz, 4H), 3.11 (d, J = 14.0 Hz, 4H), 2.84 (d, J = 6.4 Hz, 4H), 2.72 (d, J = 14.4 Hz, 4H), 2.32-2.44 (m, 8H), 1.98–2.11 (m, 8H), 1.91 (d, J = 14.0 Hz, 4H), 1.62-1.69 (m, 4H), 1.39-1.45 (m, 4H), 1.07 (s, 12H), 0.88 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 215.19, 137.96, 135.80, 134.70, 123.78, 58.22, 51.87, 50.13, 47.92, 47.06, 42.87, 42.65, 27.02, 25.46, 19.91, 19.86.

Fraction 2: ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 4H), 4.24 (d, J = 14.4 Hz, 4H), 3.99 (d, J = 14.4 Hz, 43H), 3.30 (d, J = 6.8 Hz, 4H), 3.24 (d, J = 14.4 Hz, 4H), 2.86 (d, J = 6.8 Hz, 4H), 2.66 (d, J = 14.4 Hz, 4H), 2.29-2.45 (m, 8H), 1.96–2.13 (m, 8H), 1.91 (d, J = 14.0 Hz, 4H), 1.54-1.61 (m, 4H), 1.35-1.45 (m, 4H), 1.08 (s, 12H), 0.87 (s, 12H); ^{13}C{^{1}H} NMR ($CDCl_3$) δ 215.52, 137.75, 135.82, 134.54, 123.20, 58.37, 52.16, 50.23, 48.24, 46.66,

42.98, 42.63, 27.00, 25.55, 19.99, 19.89; IR (ATR) 2959, 1745, 1454, 1416, 1393, 1339, 1284, 1147, 1106, 1051, 1003, 909, 849, 829, 791, 730, 648, cm^{-1}.

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References

(1) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.

(2) Eliel, E. L.; Wilson, S. H.; Doyle, M. P. *Basic Organic Stereochemistry,*; Wiley: New York, 2001.

(3) Hardwick, T.; Ahmed, N. Memory of Chirality as a Prominent Pathway for the Synthesis of Natural Products through Chiral Intermediates. *ChemistryOpen* **2018**, *7*, 484–487, DOI: 10.1002/open.201800061.

(4) Fujii, S.; Ziatdinov, M.; Higashibayashi, S.; Sakurai, H.; Kiguchi, M. Bowl Inversion and Electronic Switching of Buckybowls on Gold. *J. Am. Chem. Soc.* **2016**, *138*, 12142–12149, DOI: 10.1021/jacs.6b04741.

(5) Yashima, E.; Maeda, K.; Okamoto, Y. Memory of Macromolecular Helicity Assisted by Interaction with Achiral Small Molecules. *Nature* **1999**, *399*, 449–451, DOI: 10.1038/20900.

(6) Hosokawa, K.; Tabuchi, K.; Nakanishi, Y.; Okano, K.; Horie, M.; Mori, A. Studies on the Stereochemical Behaviors of a Winding Vine-Shaped Molecular Wire of a Bithiophene Dimer with Molecular Asymmetry. *Mol. Syst. Des. Eng.* **2023**, DOI: 10.1039/D3ME00106G.

(7) Yashima, E.; Ousaka, N.; Taura, D.; Shimomura, K.; Ikai, T.; Maeda, K. Supramolecular Helical Systems: Helical Assemblies of Small Molecules, Foldamers, and Polymers with Chiral Amplification and Their Functions. *Chem. Rev.* **2016**, *116*, 13752–13990, DOI: 10.1021/acs.chemrev.6b00354.

(8) Ye, X.; Wang, Z.; Zhang, J.; Wan, X. Noncovalently Functionalized Commodity Polymers as Tailor-Made Additives for Stereoselective Crystallization. *Angew. Chem. Int. Ed.* **2021**, *60*, 20243–20248, DOI: 10.1002/anie.202106603.

(9) Ye, X.; Li, B.; Wang, Z.; Li, J.; Zhang, J.; Wan, X. Tuning Organic Crystal Chirality by the Molar Masses of Tailored Polymeric Additives. *Nat. Commun.* **2021**, *12*, 6841, DOI: 10.1038/s41467-021-27236-1.

(10) Zuo, Y.; Liu, X.; Fu, E.; Zhang, S. A Pair of Interconverting Cages Formed from Achiral Precursors Spontaneously Resolve into Homochiral Conformers. *Angew. Chem. Int. Ed.* **2023**, *62*, in press. DOI: 10.1002/anie.202217225.

(11) Mori, A. Structure- and Functionality-Based Molecular Design of Azoles and Thiophenes. *Bull. Chem. Soc. Jpn.* **2020**, *93*, 1200–1212, DOI: 10.1246/bcsj.20200169.

(12) Nishio, S.; Somete, T.; Sugie, A.; Kobayashi, T.; Yaita, T.; Mori, A. Axially Chiral Macrocyclic E -Alkene Bearing Bisazole Component Formed by

Sequential C–H Homocoupling and Ring-Closing Metathesis. *Org. Lett.* **2012**, *14*, 2476–2479, DOI: 10.1021/ol300755y.

(13) Okayama, Y.; Tsuji, S.; Toyomori, Y.; Mori, A.; Arae, S.; Wu, W.-Y.; Takahashi, T.; Ogasawara, M. Enantioselective Synthesis of Macrocyclic Heterobiaryl Derivatives of Molecular Asymmetry by Molybdenum-Catalyzed Asymmetric Ring-Closing Metathesis. *Angew. Chem. Int. Ed.* **2015**, *54*, 4927–4931, DOI: 10.1002/anie.201500459.

(14) Toyomori, Y.; Tsuji, S.; Mitsuda, S.; Okayama, Y.; Ashida, S.; Mori, A.; Kobayashi, T.; Miyazaki, Y.; Yaita, T.; Arae, S.; Takahashi, T.; Ogasawara, M. Bithiophene with Winding Vine-Shaped Molecular Asymmetry. Preparation, Structural Characterization, and Enantioselective Synthesis. *Bull. Chem. Soc. Jpn.* **2016**, *89*, 1480–1486, DOI: 10.1246/bcsj.20160265.

(15) Maruhashi, K.; Okayama, Y.; Inoue, R.; Ashida, S.; Toyomori, Y.; Okano, K.; Mori, A. Chirality Recognition of Winding Vine-Shaped Heterobiaryls with Molecular Asymmetry. Kinetic and Dynamic Kinetic Resolution by Shi's Asymmetric Epoxidation. *Sci. Rep.* **2018**, *8*, 1704, DOI: 10.1038/s41598-018-19878-x.

(16) Hayashi, M.; Cheng, J.; Hosokawa, K.; Hatta, T.; Wang, C.; Horie, M.; Okano, K.; Mori, A. Synthesis and Racemization Studies of Winding Vine-Shaped Biphenyl Derivatives. *Eur. J. Org. Chem.* **2021**, *2021*, 3465–3471, DOI: 10.1002/ejoc.202100488.

(17) Kan, T.; Fukuyama, T. Ns Strategies: A Highly Versatile Synthetic Method for Amines. *Chem. Commun.* **2004**, No. 4, 353, DOI: 10.1039/b311203a.

(18) Kan, T.; Kobayashi, H.; Fukuyama, T. Efficient Synthesis of Medium-Sized Cyclic Amines by Means of 2-Nitrobenzenesulfonamide. *Synlett* **2002**, 697–699, DOI: 10.1055/s-2002-25369.

(19) Ashida, S.; Tanaka, N.; Ito, Y.; Matsuoka, M.; Hashimoto, T.; Okano, K.; Miyazaki, Y.; Kobayashi, T.; Yaita, T.; Mori, A. Nosyl (2-Nitrobenzenesulfonyl) Annulation Strategy toward Winding Vine-Shaped Bithiophenes. *J. Org. Chem.* **2018**, *83*, 14797–14801, DOI: 10.1021/acs.joc.8b02382.

(20) Okayama, Y.; Maruhashi, K.; Tsuji, S.; Mori, A. Studies on Diastereoselective Functionalization, Optical Resolution, and Racemization Behaviors of Macrocyclic Bisimidazole of Winding-Vine-Shaped Molecular Asymmetry. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 1331–1337, DOI: 10.1246/bcsj.20150164.

(21) Mori, A.; Ashida, S.; Ito, Y.; Cheng, J.; Suzuki, T.; Okano, K.; Hashimoto, T. Computational Studies on the Racemization Barriers of Winding Vine-Shaped

Heterobiaryls with Molecular Asymmetry. *Heterocycles* **2019**, *99*, 294–300, DOI: 10.3987/COM-18-S(F)23.

(22) Watson, J. D.; Crick, F. H. C. Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid. *Nature* **1953**, *171*, 737–738, DOI: 10.1038/171737a0.

(23) Kato, K.; Takaba, K.; Maki-Yonekura, S.; Mitoma, N.; Nakanishi, Y.; Nishihara, T.; Hatakeyama, T.; Kawada, T.; Hijikata, Y.; Pirillo, J.; Scott, L. T.; Yonekura, K.; Segawa, Y.; Itami, K. Double-Helix Supramolecular Nanofibers Assembled from Negatively Curved Nanographenes. *J. Am. Chem. Soc.* **2021**, *143*, 5465–5469, DOI: 10.1021/jacs.1c00863.

(24) Liu, Q.; Wen, K.; Zhang, Z.; Wu, Z.; Zhang, Y. J.; Zhang, W. Pd(II)-Catalyzed Asymmetric Wacker-Type Cyclization for the Preparation of 2-Vinylchroman Derivatives with Biphenyl Tetraoxazoline Ligands. *Tetrahedron* **2012**, *68*, 5209–5215, DOI: 10.1016/j.tet.2012.03.077.

(25) Yu, S.; Zhang, X. X. X.; Yan, Y.; Cai, C.; Dai, L.; Zhang, X. X. X. Synthesis and Application of Tetraphosphane Ligands in Rhodium-Catalyzed Hydroformylation of Terminal Olefins: High Regioselectivity at High Temperature. *Chem. Eur. J.* **2010**, *16*, 4938–4943, DOI: 10.1002/chem.200903109.

(26) Bösch, C. D.; Langenegger, S. M.; Häner, R. Light-Harvesting Nanotubes Formed by Supramolecular Assembly of Aromatic Oligophosphates. *Angew. Chem. Int. Ed.* **2016**, *55*, 9961–9964, DOI: 10.1002/anie.201604508.

(27) Vougioukalakis, G. C.; Grubbs, R. H. Ruthenium-Based Heterocyclic Carbene-Coordinated Olefin Metathesis Catalysts. *Chem. Rev.* **2010**, *110*, 1746–1787, DOI: 10.1021/cr9002424.

(28) Clavier, H.; Urbina-Blanco, C. A.; Nolan, S. P. Indenylidene Ruthenium Complex Bearing a Sterically Demanding NHC Ligand: An Efficient Catalyst for Olefin Metathesis at Room Temperature. *Organometallics* **2009**, *28*, 2848–2854, DOI: 10.1021/om900071t.

(29) CCDC 2291758 (**1b**), 2291769 (**8b**), and 2291778 (**9b**) contain the supplementary crystallographic data for this paper. These 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; fax: + 44 1223 336033.