

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

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Dedication ((optional))

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**Abstract:** A biphenyl derivative in which two benzene rings are strapped with two chains is prepared. The synthesized product shows molecular asymmetry, which was confirmed by HPLC analysis with chiral column and named as winding vine-shaped biphenyl. The synthesis of such vine shaped molecule was performed by ring-closing metathesis or alternatively by annulation with nosylated ethylenediamine. The structure of the obtained product was confirmed by X-ray crystallographic analysis. The absolute configuration of the molecular asymmetry was assigned after leading to the corresponding camphor sulfonamide through denosylation and re-amidation process.

## 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.<sup>[1,2]</sup> Chirality switching also is a class of an attractive issue in organic chemistry.<sup>[3-5]</sup> 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. configuration. configuration. property

except the absolute configuration.<sup>[6-10]</sup> 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*.<sup>[11]</sup> The first preparation was shown with bis(benzo)imidazole<sup>[12]</sup> and several related hetero<sup>[13-15]</sup> and non-heteroaromatic<sup>[16]</sup> vine-shaped molecules have also been synthesized. We have also shown that the annulation reactions with nosylated diamine (nosyl: 2-nitro-benzenesulfonyl)<sup>[17,18]</sup> with benzylic halide also furnishes another class of vine-shaped molecules and thus obtained compounds also showed molecular asymmetry.<sup>[19]</sup> 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<sup>[20]</sup> and DFT calculation<sup>[21]</sup> 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.<sup>[22,23]</sup> 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 vine-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

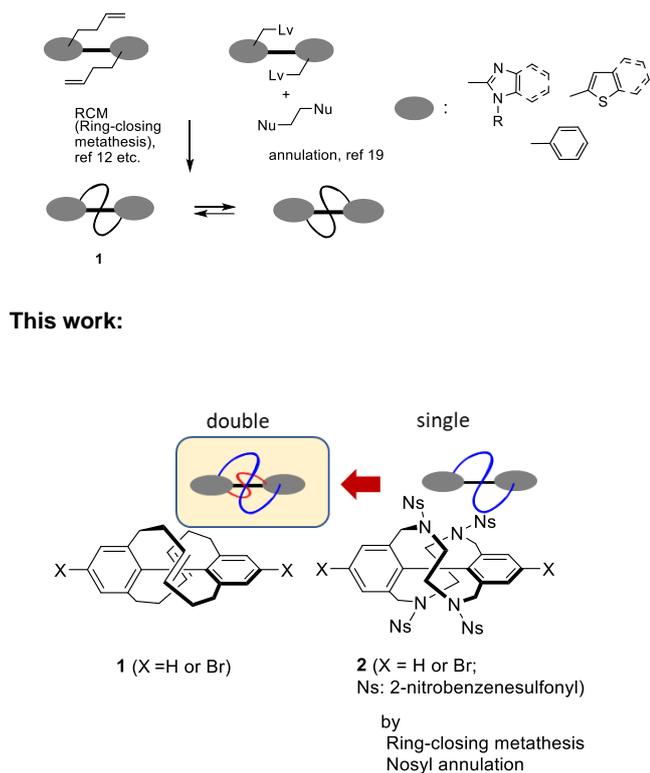
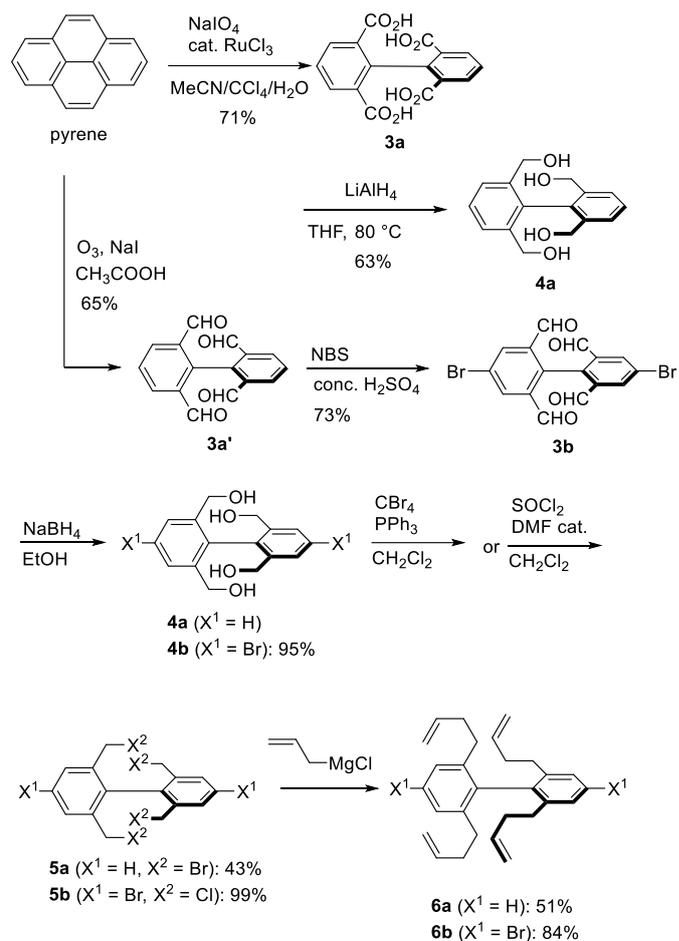


Figure 1. Double winding vine-shaped biphenyl with molecular asymmetry

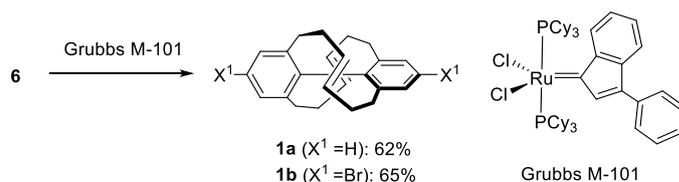
## Results and Discussion

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  $\text{NaIO}_4$  in the presence of a catalytic amount of  $\text{RuCl}_3$  afforded the biphenyl tetracarboxylic acid **3a** in 71% yield by following the literature procedure.<sup>[24]</sup> Reduction of **3a** was carried out with  $\text{LiAlH}_4$  to afford tetraol **4a** in 63% yield in a similar manner to that for the preparation of single vine-shaped biphenyl.<sup>[16]</sup> Tetraol **4b** bearing bromine on the benzene ring was alternatively synthesized by reductive ozonolysis to afford tetraldehyde **3a'** (65% yield)<sup>[25]</sup> followed by bromination with NBS to afford **3b** in 73% yield. Reduction of **3b** was carried out with  $\text{NaBH}_4$  as a reducing agent to afford brominated tetraol **4b** in 95% yield.<sup>[26]</sup> Tetraol **4a** was transformed into bromide **5a** and **4b** was treated with  $\text{SOCl}_2$  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**

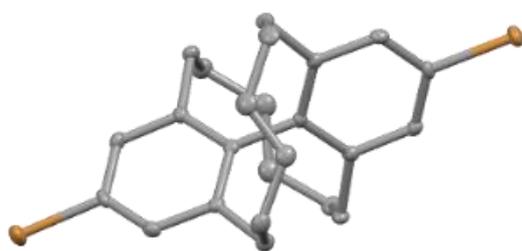
We first examined the ring-closing metathesis with ruthenium catalyst.<sup>[27]</sup> When the reaction of **6a** was carried out with ruthenium complex Grubbs M101 as a catalyst,<sup>[6,26]</sup> smooth RCM reaction proceeded at room temperature. The cyclized product **1a** was obtained in 62% yield 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 an intramolecular manner. (Scheme 2)



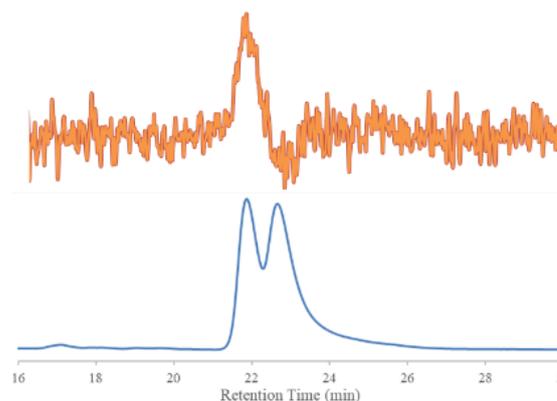
Scheme 2. Ring-closing metathesis of **6** bearing 3-alkenyl groups

Although attempted X-ray crystal structure analysis of **1a** has been unsuccessful so far, it was found that the recrystallization 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.<sup>[11]</sup> 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°).<sup>[16]</sup> 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 <sup>1</sup>H NMR spectrum of **1b** indicated a signal at  $\delta = 4.22$  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<sub>2</sub> 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)



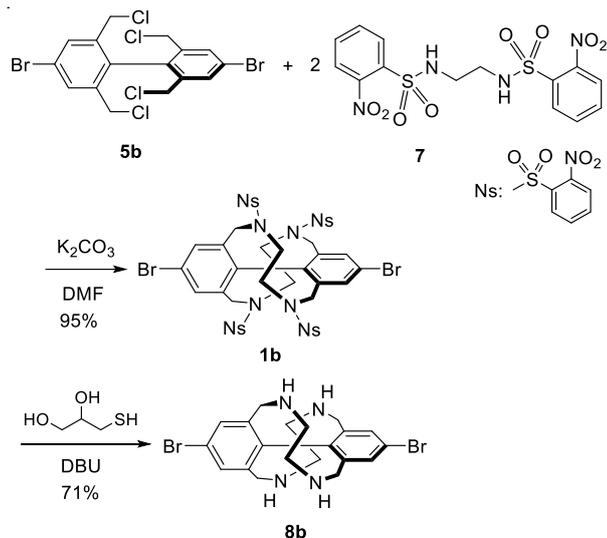
(b)



**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<sup>-1</sup>) detected by UV (lower) and CD (upper) detectors

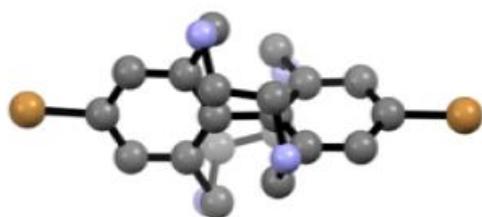
We next envisaged preparation of double winding vine-shaped biphenyl by the nosyl annulation of tetrahalomethyl biphenyl **5** with nosylated ethylenediamine.<sup>[19]</sup> The reaction of **5b** with twice molar amounts of diamine **7** proceeded smoothly in the presence of potassium carbonate as a 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 ( $\pm$ )-**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**.

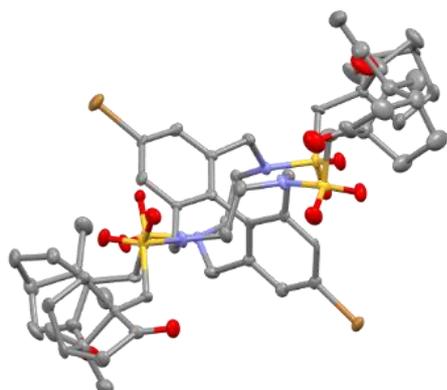


**Scheme 3.** Nosyl annulation of **5b** and desonylation

(a)



(b)

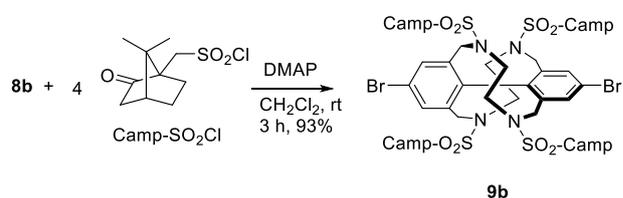


**Figure 3.** (a) HPLC profile of **8b** by chiral column with UV (blue) and CD (g-factor, red) detectors. (b) X-ray crystal structure of ( $\pm$ )-**8b** as a 4HCl salt. Hydrogen, chloride ion and oxygen (water) were omitted for clarity. CCDC: 2291769 (ref 29)

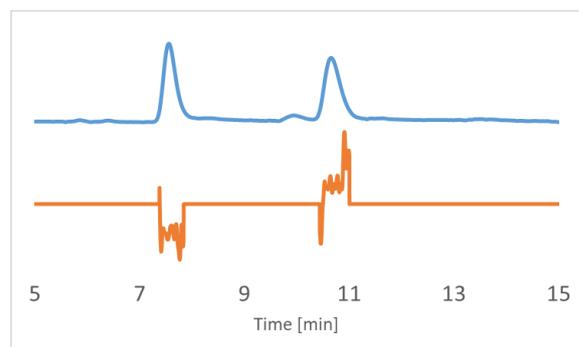
The obtained tetramine **8b** was then subjected to the reaction of chiral (+)-camphor sulfonyl chloride at room temperature for 3 h in dichloromethane to afford the corresponding sulfonate as a pair of the 1:1 diastereomer. (Figure 4a) The  $^1\text{H}$  NMR spectrum showed a pair of singlet signal 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 desulfonated analog **8b** indicated a sharp angle.

(a)



(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  $\Delta H$  values of **1b** and **2b** are calculated as  $2.44 \times 10^6$  kJmol<sup>-1</sup> and  $1.60 \times 10^7$  kJmol<sup>-1</sup>, respectively, the calculation of the estimated energy of the transition state, assuming the dihedral angle between biphenyl to be 0°,<sup>[21]</sup> 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 tetra-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.<sup>[28]</sup>

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**Keywords:** biphenyl • molecular asymmetry • winding vine • ring-closing metathesis • nosyl annulation

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- [28] Deposition numbers 2291758 (for **1b**), 2291769 (for **8b**), and 2291778 (for **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](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto: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.

