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Synthesis and Stereochemical Behavior of a New Chiral Oxa[7]heterohelicene

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A new chiral oxa[7]heterohelicene **1b** was synthesized by catalytic aerobic-oxidative tandem cyclization of the *o*-phenylene-linked bis(2-naphthol) derivative **3** with palladium acetate in dimethyl sulfoxide. Optical resolution of **1b** was possible on chiral HPLC, but it was found stereochemically rather unstable at ambient temperature. Kinetic analysis and DFT calculation for the dynamics of racemization of **1b** were also disclosed.

Because of their unique helical structures and chirality, helicenes are fascinating targets in organic synthesis.[1] Since the pioneering work by Newman et al. on the preparation of [6]helicene in an optically pure form,[2] synthetic studies on chiral helicenes have been accelerated.[3] Besides typical carbohelicenes composed of an all-carbon ring framework, heterohelicenes incorporating one or more heteroaromatic units in the skeleton have also gained increasing attention.[1a–1d,4] Stereochemically defined thiophene-containing helical ring systems are prime examples.[5] In contrast to this, the furan-alternatives have been rarely focused on.[6,7] That would be partially because oxa-heterohelicenes are supposed to be stereochemically less stable resulting from small overlapping at the helix termini.[6c,6d,8] Moreover, it seems to pose another issue that synthetic methods to embed furan into a helicene framework have not been well elaborated. These points have inspired us to devise a novel synthetic approach to chiral furan-containing heterohelicenes. To begin with, we were intrigued by the fact that the thia[7]heterohelicene **2a**[6c,6d,8] holds a robust helicity, though the oxa[7]-heterohelicene **1a** is unknown (Figure 1). Thus, we launched studies on the synthesis of **1b**, an analog of **1a**, to gain some insight into the molecular design on optically active furan-containing oxa-heterohelicenes as reliable chiral platforms.

o-Alkynylphenols are known to undergo palladium(II)-catalyzed annulation to give 3-benzofuranylpalladium(II) intermediates, which serve for further C–C coupling reactions in a tandem fashion.[9] Thus, we envisioned that the phenylenediyne-linked bis(2-naphthol) **3** would be submitted to the serial C–O and C–C bond formation under Wacker-type oxidation conditions, leading to **1b** (Scheme 1). The precursor **3** should be accessible by assembling 2-naphthol, *o*-phenylene, and acetylene segments through conventional Sonogashira coupling reactions. Herein we report on the synthesis of a new oxa-heterohelicene **1b** and the evaluation of its stereochemical stability.

The target oxa-heterohelicene **1b** was synthesized as shown in Scheme 2. Regioselective iodination of 2-naphthol at C1 position[10] and the subsequent acetylation of the hydroxy group gave **4**. The iodinated compound **4** underwent the Sonogashira coupling reaction with trimethylsilylacetylene followed by the desilylation with tetrabutylammonium fluoride to obtain **5**. The alkyne **5** was subjected to the double Sonogashira coupling with *o*-diiodobenzene to give **6**. Although deacetylation of **6** under the conventional conditions with K_2CO_3 in methanol triggered undesired nonoxidative cyclization into a naphthofuran derivative (see the Supporting Information[24]),[9e,11] the desired **3** was obtained by the treatment of **6** with aqueous hydrazine in acetonitrile.[12] Finally, aerobic-oxidative tandem cyclization worked on **3** under catalysis with $Pd(OAc)_2$ in DMSO[13] at room temperature to provide **1b** in good yield.

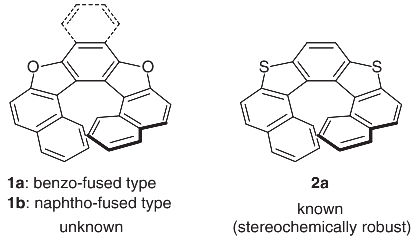
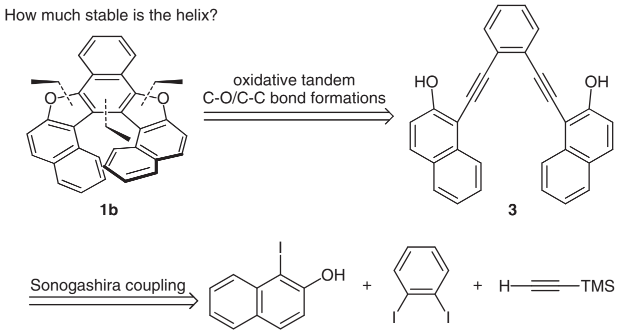
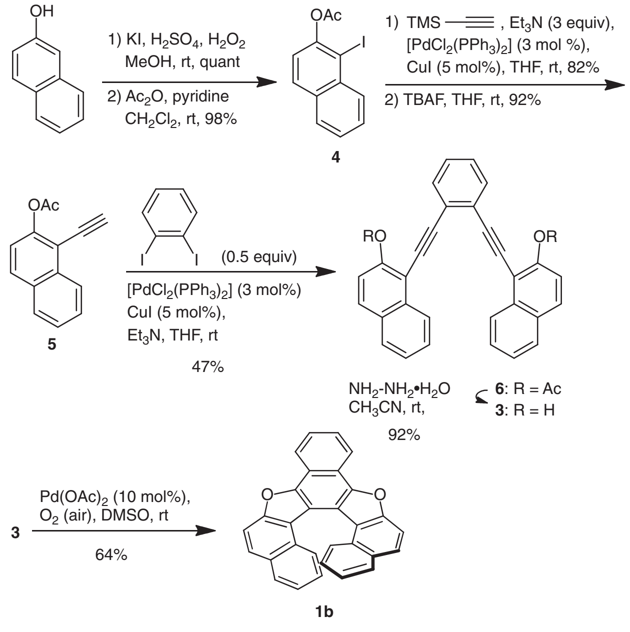


Figure 1. Oxa- and thia[7]heterohelicenes of interest.



Scheme 1. Synthetic strategy for **1b**.

The molecular structure of **1b** was determined by X-ray crystallography to prove the helicity induced in solid state (Figure 2).[14] Moreover, the ^1H NMR spectrum of **1b** in $CDCl_3$ indicates a significant upfield shift (7.10 ppm) of an aromatic proton located in the mutually overlapping naphthalene rings as compared to the corresponding chemical shift (in a range of 7.46–7.61 ppm) for planar naphtho[2,1-*b*]furan.[15] This also supports a helical form of **1b** in solution. However, we noted



Scheme 2. Synthesis of **1b**.

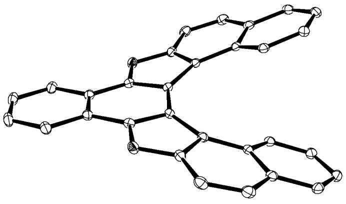


Figure 2. An ORTEP diagram for the X-ray structure of **1b** with 30% ellipsoids. Hydrogen atoms have been omitted for clarity.

that **1b** was not as overcrowded at the helical ends as structurally defined analogous thia-heterohelicenes.[16,17]

We next performed optical resolution of **1b** by chiral HPLC to obtain one enantiomer in ca. 70% ee.[18,19] However, the enantioenriched **1b** thus obtained was proven to racemize at room temperature. Thus, we turned to kinetic analysis on the racemization and measured variation of the enantiomeric excess of **1b** with time at different temperatures (0, 10, 20, and 25 °C).[18] Plot of ln(% ee) vs. time showed a good linear relationship at each temperature (Figure 3a), permitting to calculate the rate constant for racemization: k (s^{-1}) = 5.83×10^{-6} (0 °C), 2.31×10^{-5} (10 °C), 9.39×10^{-5} (20 °C), and 1.78×10^{-4} (25 °C).[20] From the Arrhenius plot with these kinetic data (Figure 3b), we determined the activation energy for racemization of **1b** to be 22.2 kcal mol^{-1}.

We also evaluated the dynamics of racemization of **1b** by DFT calculation (Figure 4a).[21] The transition state structure $\mathbf{TS_O}$ was found to be 22.5 kcal mol^{-1} higher in energy than the global minimum structure $\mathbf{GM_O}$ in good agreement with the above-mentioned kinetic analysis. Interestingly, much higher activation energy (35.4 kcal mol^{-1}) ensued by the same calculation for the thiophene-based analog **2b** (Figure 4b), which was consistent with the stereochemical stability of **2a**[6c,6d] and its derivatives.[16,22] The deeper winding structure of **2b** originates from a

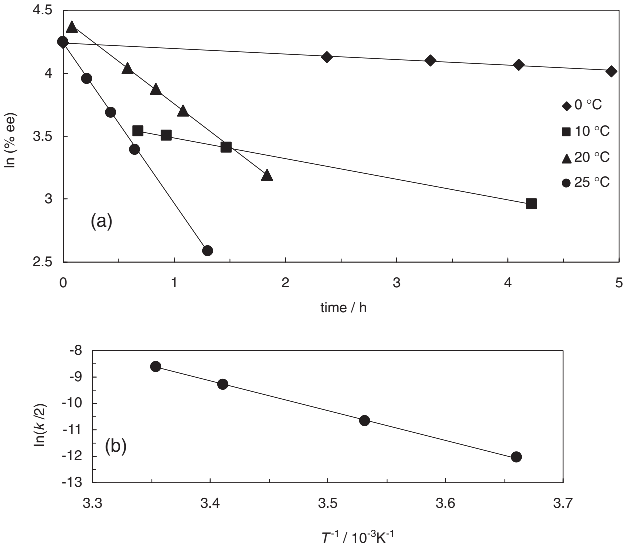


Figure 3. Kinetic plots for the racemization of **1b**: (a) ln(% ee of **1b**) vs. time/h, (b) Arrhenius plot; ln(k/2) vs. $T^{-1}/10^{-3}\,\mathrm{K}^{-1}$, where k stands for rate constant with a unit of s^{-1}.

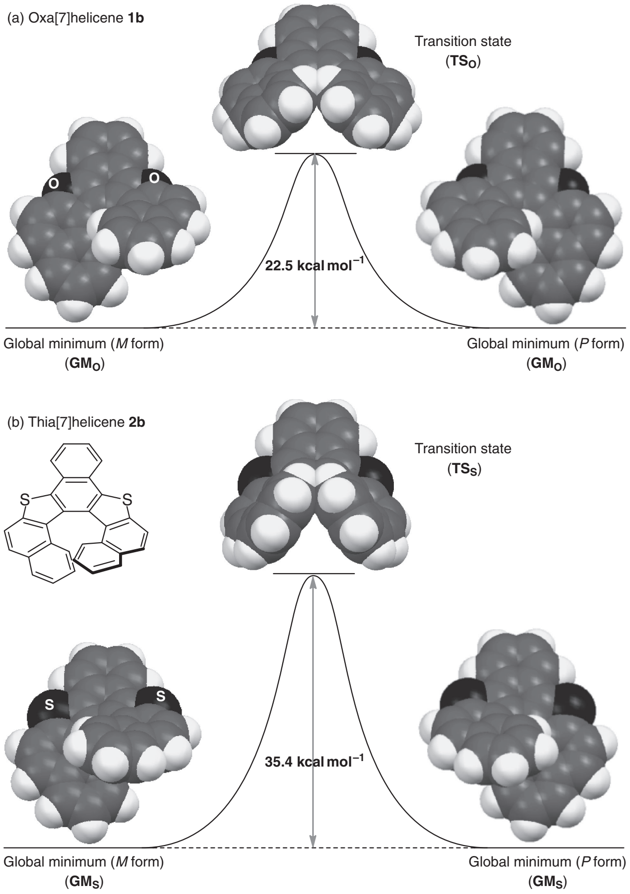


Figure 4. DFT calculation on the helical ring inversion: (a) for the oxa[7]helicene **1b** and (b) for the thia[7]helicene **2b**.

small inner angle of ∠C–S–C (ca. 91°) as well as an elongated C–S bond in the thiophene ring units (ca. 1.75 Å). In contrast, the corresponding ∠C–O–C angle (ca. 105°) is significantly larger and the C–O bond (ca. 1.37 Å) is much shorter for the furan ring moieties in **1b**, leading to the observed small overcrowding at the helix termini and less stereochemical stability.[8,23]

In summary, we constructed a unique oxa-heterohelicene **1b** by assembling 2-naphthol, *o*-phenylene, and acetylene segments through serial Sonogashira-coupling and palladium(II)-catalyzed aerobic oxidative tandem cyclization as key steps. The dynamics of racemization of **1b** was also investigated by the kinetic analysis and DFT calculation. Based on the present study, design and asymmetric synthesis of stereochemically robust furan-containing heterohelicenes are underway in our laboratory.

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