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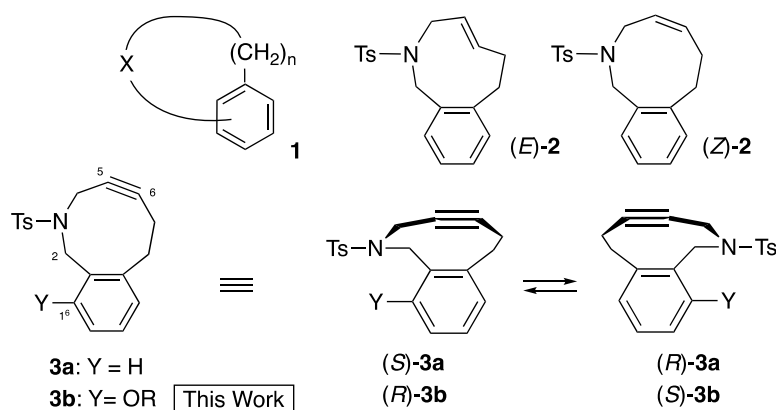
## SYNTHESIS AND STEREOCHEMICAL ANALYSIS OF PLANAR CHIRAL NINE-MEMBERED AZA-ORTHO CYCLOPHYNE

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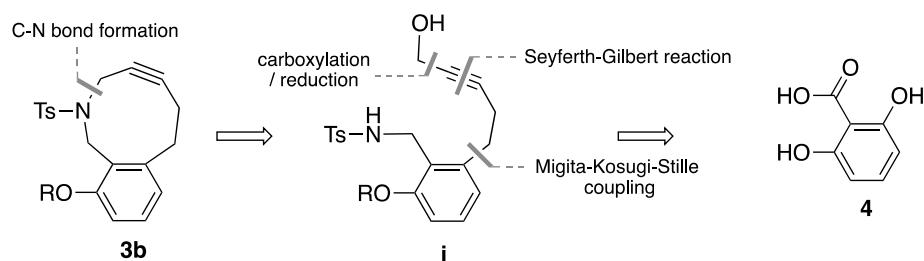
**Abstract** – Aza-orthocyclophane **3b** with an oxy-substituent on the 1<sup>6</sup> position of the benzene ring was synthesized, and it was revealed that the stereochemical stability of **3b** is consistent with the order of 1,3-steric repulsion between the C2 methylene protons and the oxy-substituent.

Cyclophanes with heteroatom-embedded ansa chains, namely, heterocyclophane **1**, have attracted considerable interest because of their unusual chemical and conformational properties caused by the deformation and strain of the molecule.<sup>1</sup> Among heterocyclophanes, the *ortho*-isomer has received less attention than the *meta*- and *para*-isomers owing to its relatively simple topology and lack of planar chirality in general.<sup>2</sup> As an exceptional example of planar chiral orthoheterocyclophane, we found that a nine-membered (*E*)-aza-orthocyclophane (*E*)-**2**, that is orthocyclophane with an ansa chain containing a nitrogen functionality along with the (*E*)-alkene, has isolable enantiomers at ambient temperature.<sup>3</sup> The key factor



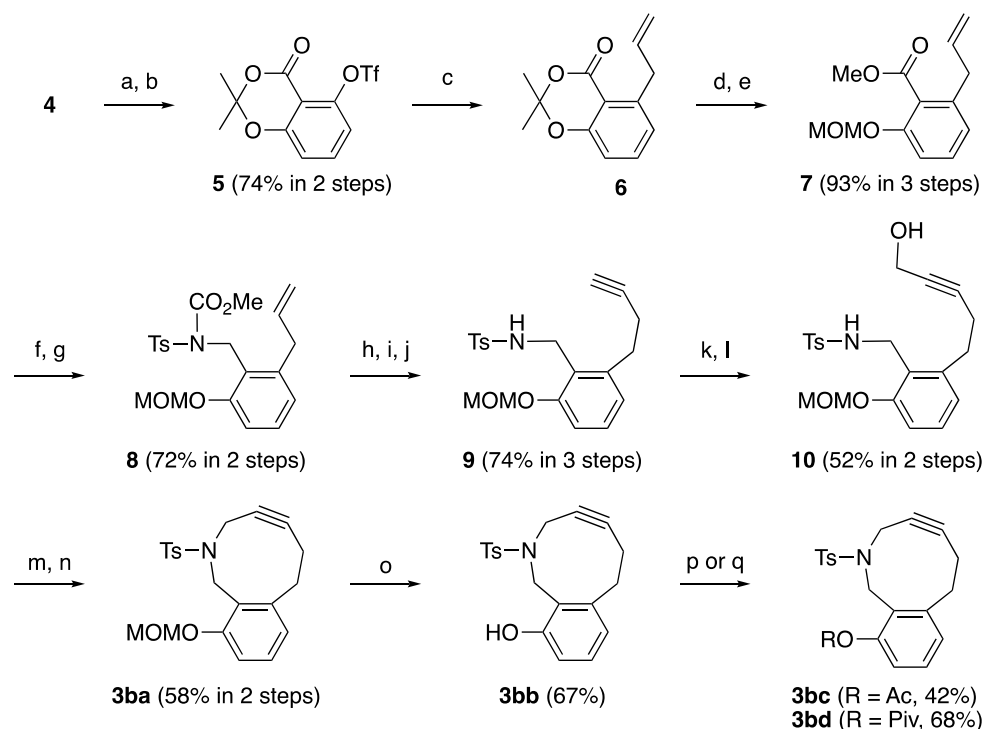
of the stable planar chirality of (*E*)-**2** is the presence of the (*E*)-alkene. Indeed, the diastereomer (*Z*)-**2** has no detectable planar chirality.<sup>4</sup> Furthermore, we did not observe the presence of isolable enantiomers of nine-membered aza-orthocyclophynes **3a**,<sup>5</sup> an alkyne analogue of **2**; its chirality would be very labile, unlike that of (*E*)-**2**. In our continuous study on this field of chemistry, quite recently, we have found the significant substituent effect on the stability of planar chirality of the aza-orthocyclophynes; cyclophynes **3b** with oxy-substituent (OR) on the 1<sup>6</sup> position of the benzene ring has more stable planar chirality than **3a**. Herein, we wish to report the detailed synthesis and stereochemical analysis of **3b**.

We planned to construct the strained nine-membered skeleton of **3b** via intramolecular C–N bond formation of **i**, as shown in Scheme 1. Key intermediate **i** can be prepared from 2,6-dihydroxybenzoic acid (**4**) through stepwise construction of the pentynyl alcohol moiety via i) Migita–Kosugi–Stille coupling, ii) Seyferth–Gilbert reaction, and iii) carboxylation followed by reduction.



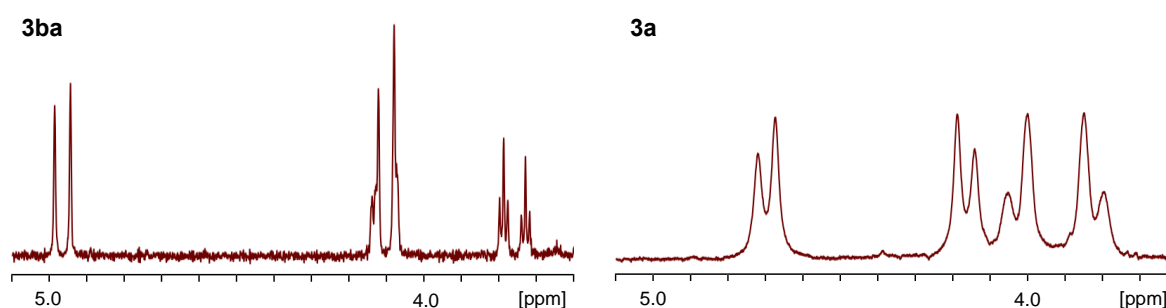
**Scheme 1.** Retrosynthetic analysis of **3b**

At the outset, we synthesized **3b** as shown in Scheme 2. The protection of the carboxylic acid and hydroxyl groups of **4** by acetonide formation, followed by trifluoromethanesulfonylation of the hydroxyl group, afforded **5** in 74% yield (two steps). The Migita–Kosugi–Stille coupling of **5** and allyltributyltin catalyzed by Pd(PPh<sub>3</sub>)<sub>4</sub> afforded **6**. Alcoholysis followed by MOMCl treatment of **6** afforded **7** in 93% yield (three steps from **5**). Reduction of the ester moiety using LiAlH<sub>4</sub>, followed by the Mitsunobu reaction with TsNHCO<sub>2</sub>Me, afforded **8** in 72% yield (two steps). Hydroboration of the alkene moiety of **8**, followed by oxidation of the resulting alcohol into aldehyde, and the reaction with Ohira–Bestmann reagent afforded alkyne **9** in 74% yield (three steps from **8**). Hydroxymethylation of the terminal alkyne of **9** was performed using a carboxylation and reduction sequence in 52% yield over two steps. The resulting alcohol **10** was converted into a methanesulfonyloxy derivative, and cyclization was performed through treatment with K<sub>2</sub>CO<sub>3</sub> in DMF to afford the desired **3ba** in 58% yield (two steps). Derivatives of **3ba** with different oxy-functionalities at the 1<sup>6</sup> position, **3bb** (R = H), **3bc** (R = Ac), and **3bd** (R = Piv) were prepared through the conversion of the MOM-ether moiety of **3ba**.<sup>6</sup>



**Scheme 2.** Reagents and conditions: (a) acetone,  $\text{SOCl}_2$ , cat. DMAP,  $(\text{MeOCH}_2)_2$ ,  $0^\circ\text{C}$  to rt; (b)  $\text{Tf}_2\text{O}$ , pyridine,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ; (c) allyltributyltin, cat.  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{LiCl}$ , THF,  $65^\circ\text{C}$ ; (d)  $\text{K}_2\text{CO}_3$ , MeOH, rt; (e) MOMCl, Hünig base,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$  to rt; (f)  $\text{LiAlH}_4$ ,  $\text{Et}_2\text{O}$ ,  $0^\circ\text{C}$ ; (g)  $\text{TsNHCO}_2\text{Me}$ ,  $\text{PPh}_3$ , bis(2-methoxyethyl) azodicarboxylate, THF,  $0^\circ\text{C}$  to rt; (h)  $\text{BH}_3 \cdot \text{THF}$  then 38% aq.  $\text{H}_2\text{O}_2$ , 3 M aq. NaOH, THF,  $0^\circ\text{C}$  to rt; (i) Dess-Martin periodinane,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ; (j) dimethyl (1-diazo-2-oxopropyl)phosphonate,  $\text{K}_2\text{CO}_3$ , MeOH,  $0^\circ\text{C}$ ; (k) *n*-BuLi then  $\text{ClCO}_2\text{Me}$ , THF,  $-78^\circ\text{C}$ ; (l) DIBAL,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ ; (m) MsCl,  $\text{NEt}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ; (n)  $\text{K}_2\text{CO}_3$ , DMF,  $0^\circ\text{C}$  to rt; (o)  $\text{TMSCl}$ , MeCN/ $\text{CH}_2\text{Cl}_2$ , rt; (p)  $\text{Ac}_2\text{O}$ ,  $\text{NEt}_3$ , cat. DMAP,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ ; (q) PivCl,  $\text{NEt}_3$ , cat. DMAP,  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ .

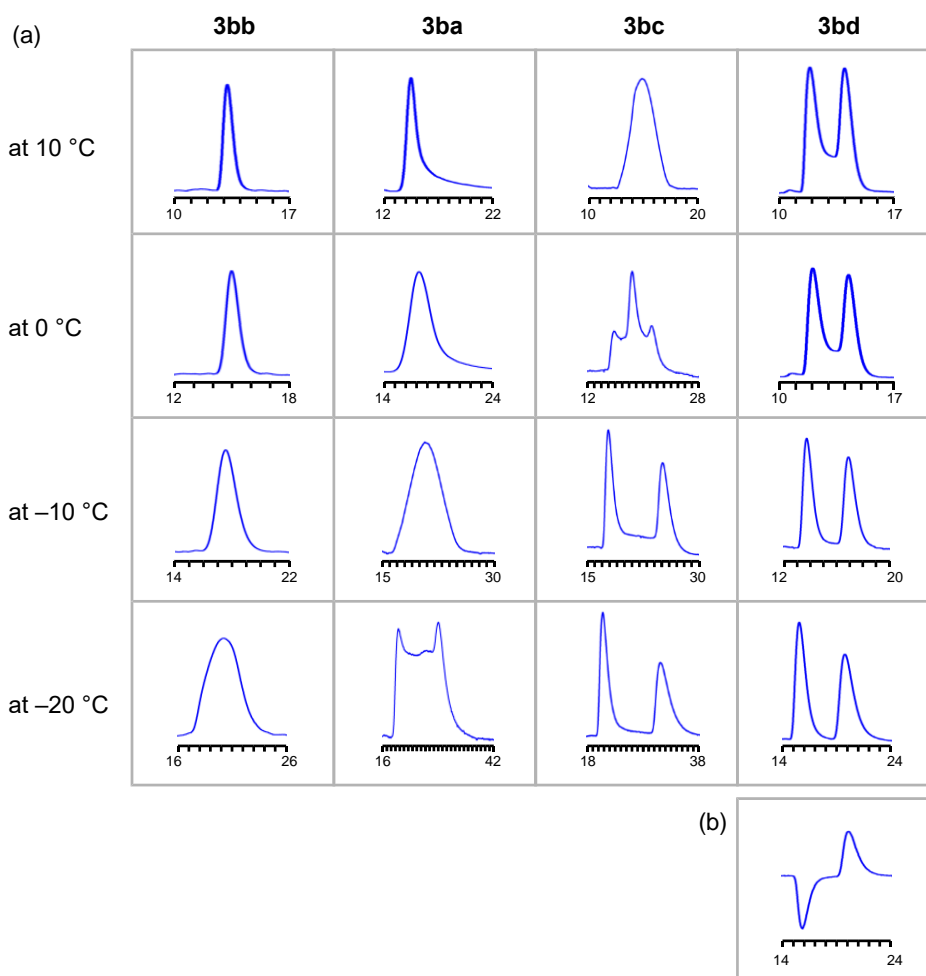
The  $^1\text{H}$  NMR spectrum of **3ba** in  $\text{CDCl}_3$  at ambient temperature exhibited two sets of sharp signals of non-equivalent geminal methylene protons, which is in sharp contrast to a similar analysis of **3a** exhibiting broad signals (Figure 1). This result suggests that the planar chirality of **3ba** is more stable than that of **3a**.



**Figure 1.**  $^1\text{H}$  NMR spectra (300 MHz in  $\text{CDCl}_3$  at ambient temperature) of **3ba** and **3a**

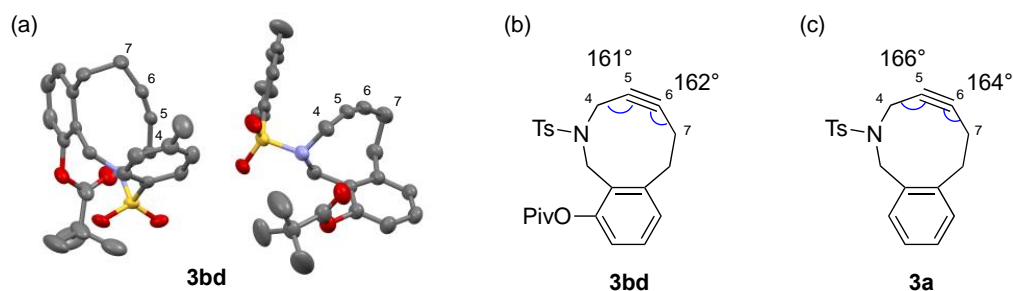
However, our attempts to separate the enantiomers of **3bb** and **3ba** through HPLC analysis using a chiral stationary phase failed; even with cooling of the column at  $-20^\circ\text{C}$ , only broad peaks and coalesced plateau-shaped peaks were observed, as shown in Figure 2.<sup>7</sup> In contrast, similar attempts of **3bc** and **3bd** exhibited

excellent results; the existence of isolable enantiomers was revealed through the HPLC analysis. As shown in Figure 2, both enantiomers of **3bc** were successfully separated at  $-20\text{ }^{\circ}\text{C}$ . Moreover, both enantiomers of **3bd** were partially separated at  $10\text{ }^{\circ}\text{C}$ , and baseline separation and measurement of CD signs were accomplished at  $-20\text{ }^{\circ}\text{C}$ . These results are the first direct observation of the existence of enantiomers of nine-membered aza-orthocyclophynes and suggest that the trend of stereochemical stability would be **3bb** < **3ba** < **3bc** < **3bd**.<sup>8</sup>



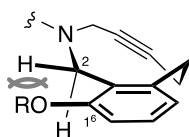
**Figure 2.** HPLC analysis using a CHIRALPAK IB (a) UV chart of **3ba-3bd** at 10 to  $-20\text{ }^{\circ}\text{C}$ ; (b) CD chart of **3bd** at  $-20\text{ }^{\circ}\text{C}$ .

Furthermore, **3bd** afforded suitable single crystals to elucidate its detailed structure in the solid state through X-ray crystallographic analysis (Figure 3).<sup>9</sup> The analysis reveals the packing of two similar conformers of **3bd**; the alkyne-containing ansa chains are located outside the plane of the benzene ring. Therefore, **3bd** possesses planar chirality in the solid state. The average bond angles of C4–C5–C6 and C5–C6–C7 are  $161^{\circ}$  and  $162^{\circ}$ , respectively. It means that the alkyne moiety of **3bd** is more bent than that of the previously synthesized **3a**: the C4–C5–C6 and C5–C6–C7 bond angles of **3a** are  $166^{\circ}$  and  $164^{\circ}$ , respectively.



**Figure 3.** Structure of **3**; (a) X-ray analysis of **3bd** (Hydrogen atoms are omitted for clarity. Ellipsoid set at 50% of probability level.); (b) bond angles of **3bd**; (c) bond angles of **3a**.

The former primitive density functional theory calculations revealed that the transition state for the racemization of **3** involves flipping of the benzene ring.<sup>10</sup> The energy barrier for the racemization of **3b** should be higher than that of **3a** because of the substantial 1,3-steric repulsion between the C2 methylene protons and the OR on the 1<sup>6</sup> position of the benzene ring, as shown in Figure 4. As above mentioned, the trend of stereochemical stability of **3b** (**3bb** < **3ba** < **3bc** < **3bd**) was consistent with the order of 1,3-steric repulsion (OH < OMOM < OAc < OPiv).



**Figure 4.** 1,3-Steric repulsion between the C2 methylene protons and the OR on the 1<sup>6</sup> position of benzene ring.

In conclusion, we described the synthesis of a novel nine-membered aza-orthocyclophynane **3b** and revealed the presence of isolable enantiomers thereof. Further detailed studies on the relationship between the structures and stereochemical stability of aza-orthocyclophynes, and the preparation of their enantioenriched form by DYASIN<sup>11</sup> and synthetic applications are in progress.

## SUPPORTING INFORMATION

Supplementary (synthesis of all compounds, <sup>1</sup>H, <sup>13</sup>C NMR, IR, and HRMS, etc.) data associated with this article can be found, in the online version, at URL: <https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27626/105/1>.

## ACKNOWLEDGEMENTS

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7. Analytical conditions; column: CHIRALPAK IB (0.46 cm  $\times$  25 cm), eluent: hexane/IPA = 30:70, flow rate: 0.5 mL/min, detection: UV and CD (270 nm): see, Supporting Information for details.
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