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SYNTHESIS AND STEREOCHEMICAL ANALYSIS OF PLANAR CHIRAL NINE-MEMBERED AZA-ORTHOCYCLOPHYNE

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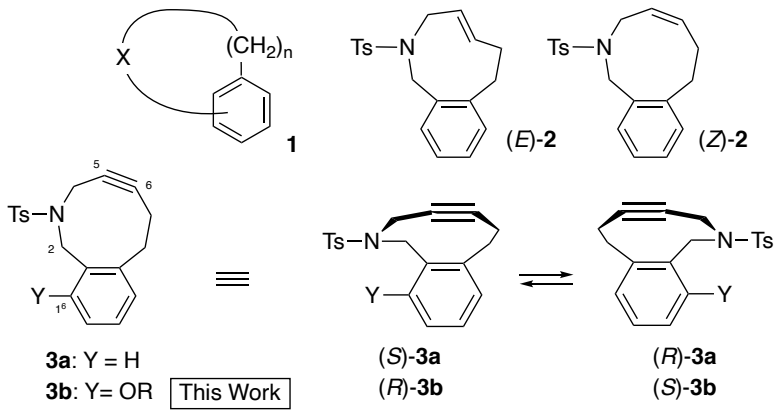
Abstract – Aza-orthocyclophyne **3b** with an oxy-substituent on the 1^6 position of the benzene ring was synthesized, and it was revealed that the stereochemical stability of **3b** is consistent with the order of 1,3-steric repulsion between the C2 methylene protons and the oxy-substituent.

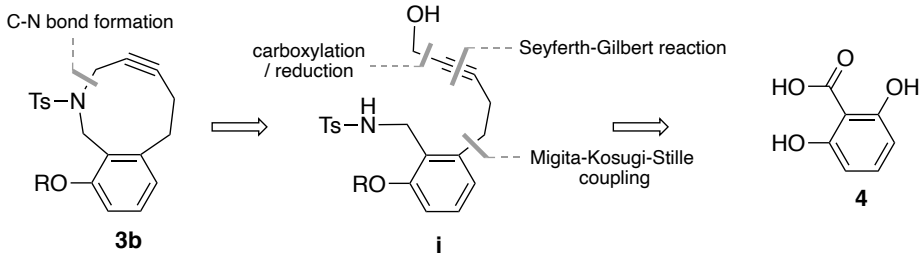
Cyclophanes with heteroatom-embedded ansa chains, namely, heterocyclophane **1**, have attracted considerable interest because of their unusual chemical and conformational properties caused by the deformation and strain of the molecule.[1] Among heterocyclophanes, the *ortho*-isomer has received less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



Dedicated to Professor Somsak Ruchirawat on 80th Birthday

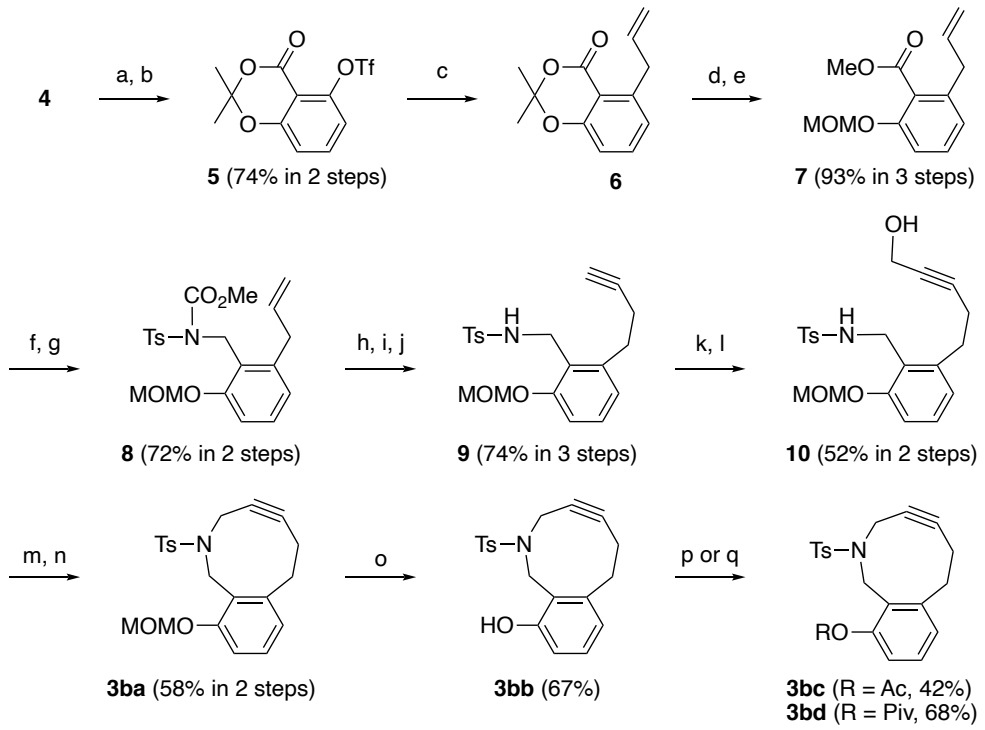
of the stable planar chirality of (*E*)-**2** is the presence of the (*E*)-alkene. Indeed, the diastereomer (*Z*)-**2** has no detectable planar chirality.[4] Furthermore, we did not observe the presence of isolable enantiomers of nine-membered aza-orthocyclophyne **3a**,[5] an alkyne analogue of **2**; 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-orthocyclophyne; cyclophyne **3b** with oxy-substituent (OR) on the 1^6 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 $Pd(PPh_3)_4$ afforded **6**. Alcoholysis followed by MOMCl treatment of **6** afforded **7** in 93% yield (three steps from **5**). Reduction of the ester moiety using $LiAlH_4$, followed by the Mitsunobu reaction with $TsNHCO_2Me$, 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_2CO_3 in DMF to afford the desired **3ba** in 58% yield (two steps). Derivatives of **3ba** with different oxy functionalities at the 1^6 position, **3bb** (R = H), **3bc** (R = Ac), and **3bd** (R = Piv) were prepared through the conversion of the MOM-ether moiety of **3ba**.[6]



Scheme 2. Reagents and conditions: (a) acetone, $SOCl_2$, cat. DMAP, $(MeOCH_2)_2$, 0 °C to rt; (b) Tf_2O, pyridine, CH_2Cl_2, 0 °C; (c) allyltributyltin, cat. $Pd(PPh_3)_4$, LiCl, THF, 65 °C; (d) K_2CO_3, MeOH, rt; (e) MOMCl, Hünig base, CH_2Cl_2, 0 °C to rt; (f) $LiAlH_4$. Et_2O, 0 °C; (g) $TsNHCO_2Me$, PPh_3, bis(2-methoxyethyl) azodicarboxylate, THF, 0 °C to rt; (h) BH_3·THF then 38% aq. H_2O_2, 3 M aq. NaOH, THF, 0 °C to rt; (i) Dess-Martin periodinane, CH_2Cl_2, 0 °C; (j) dimethyl (1-diazo-2-oxopropyl)phosphonate, K_2CO_3, MeOH, 0 °C; (k) *n*-BuLi then $ClCO_2Me$, THF, –78 °C; (l) DIBAL, CH_2Cl_2, –78 °C; (m) MsCl, NEt_3, CH_2Cl_2, 0 °C; (n) K_2CO_3, DMF, 0 °C to rt; (o) TMSCl, MeCN/CH_2Cl_2, rt; (p) Ac_2O, NEt_3, cat. DMAP, CH_2Cl_2, 0 °C; (q) PivCl, NEt_3, cat. DMAP, CH_2Cl_2, 0 °C.

The ^{1}H NMR spectrum of **3ba** in $CDCl_3$ 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**.

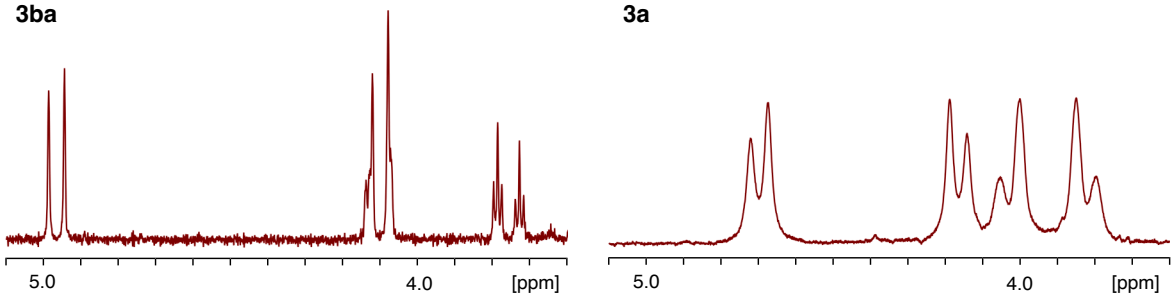


Figure 1. ^{1}H NMR spectra (300 MHz in $CDCl_3$ at ambient temperature) of **3ba** and **3a**

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 °C, only broad peaks and coalesced plateau-shaped peaks were observed, as shown in Figure 2.[7] 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 °C. Moreover, both enantiomers of **3bd** were partially separated at 10 °C, and baseline separation and measurement of CD signs were accomplished at –20 °C. These results are the first direct observation of the existence of enantiomers of nine-membered aza-orthocyclophyne and suggest that the trend of stereochemical stability would be **3bb** < **3ba** < **3bc** < **3bd**.[8]

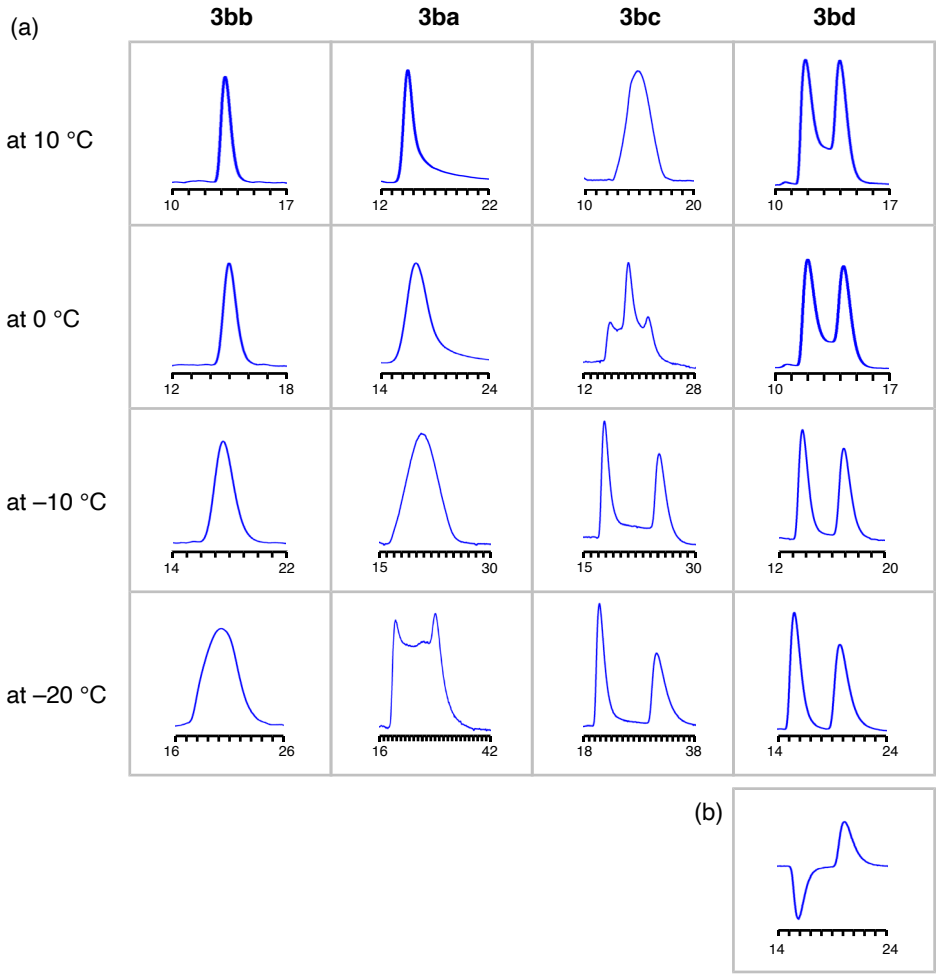


Figure 2. HPLC analysis using a CHIRALPAK IB (a) UV chart of **3ba-3bd** at 10 to –20 °C; (b) CD chart of **3bd** at –20 °C.

Furthermore, **3bd** afforded suitable single crystals to elucidate its detailed structure in the solid state through X-ray crystallographic analysis (Figure 3).[9] 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° and 162°, 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° and 164°, respectively.

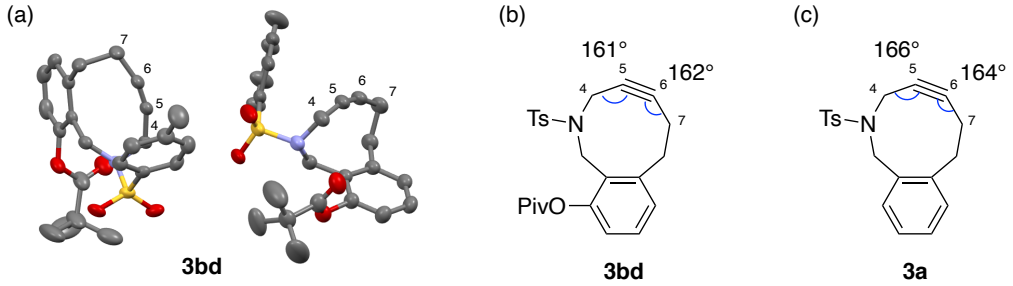


Figure 3. Structure of **3**; (a) X-ray analysis of **3bd** (Hydrogen atoms are omitted for clarity. Ellipsoid set at 50% of probability level.); (b) bond angles of **3bd**; (c) bond angles of **3a**.

The former primitive density functional theory calculations revealed that the transition state for the racemization of **3** involves flipping of the benzene ring.[10] 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 1^6 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).

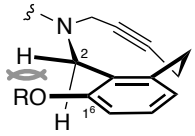


Figure 4. 1,3-Steric repulsion between the C2 methylene protons and the OR on the 1^6 position of benzene ring.

In conclusion, we described the synthesis of a novel nine-membered aza-orthocyclophyne **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[11] and synthetic applications are in progress.

SUPPORTING INFORMATION

Supplementary (synthesis of all compounds, ^{1}H, ^{13}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.

ACKNOWLEDGEMENTS

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6. All new compounds were fully characterized by ^{1}H, ^{13}C NMR, IR, and HRMS analysis: see, Supporting Information for details.
7. Analytical conditions; column: CHIRALPAK IB (0.46 cm × 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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9. Deposition number for compound **3bd** is CCDC 2156588. Selected crystallographic data: triclinic, *P*–1, a = 11.50586(17) Å, b = 12.5371(2) Å, c = 17.1225(2) Å, α = 83.5826(14)°, β = 79.8978(12)°, γ = 69.6621(16)°, V = 2276.59(7) Å^3, Z = 2, R_1 = 0.0623, wR_2 = 0.1725.: see, Supporting Information for details.
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