Advance Publication Cover Page



## Synthesis and Stereochemical Properties of Chiral Hetero[7]helicenes Structured by a Benzodiheterole Ring Core

Sachie Arae, Takaaki Mori, Takahiro Kawatsu, Daiki Ueda, Yusuke Shigeta, Nobutsugu Hamamoto, Hitoshi Fujimoto, Michinori Sumimoto, Tatsushi Imahori, Kazunobu Igawa, Katsuhiko Tomooka, Tharmalingam Punniyamurthy, and Ryo Irie\*

> Advance Publication on the web June 3, 2017 doi:10.1246/cl.170410

© 2017 The Chemical Society of Japan

Advance Publication is a service for online publication of manuscripts prior to releasing fully edited, printed versions. Entire manuscripts and a portion of the graphical abstract can be released on the web as soon as the submission is accepted. Note that the Chemical Society of Japan bears no responsibility for issues resulting from the use of information taken from unedited, Advance Publication manuscripts.

## Synthesis and Stereochemical Properties of Chiral Hetero[7]helicenes Structured by a Benzodiheterole Ring Core

Sachie Arae,<sup>1</sup> Takaaki Mori,<sup>1</sup> Takahiro Kawatsu,<sup>1</sup> Daiki Ueda,<sup>1</sup> Yusuke Shigeta,<sup>1</sup> Nobutsugu Hamamoto,<sup>1</sup> Hitoshi Fujimoto,<sup>1</sup>

Michinori Sumimoto,<sup>2</sup> Tatsushi Imahori,<sup>3</sup> Kazunobu Igawa,<sup>4</sup> Katsuhiko Tomooka,<sup>4</sup> Tharmalingam Punniyamurthy,<sup>5</sup> and Ryo Irie<sup>\*1</sup>

<sup>1</sup>Department of Chemistry, Faculty of Advanced Science and Technology, Kumamoto University,

2-39-1 Kurokami, Chuo-ku, Kumamoto 860-8555, Japan

<sup>2</sup>Graduate School of Science and Technology for Innovation, Yamaguchi University, Ube, Yamaguchi 755-8611, Japan

<sup>3</sup>Department of Industrial Chemistry, Faculty of Engineering, Tokyo University of Science,

1-3 Kagurazaka, Shinjyuku-ku, Tokyo 162-8601, Japan

<sup>4</sup>Institute for Materials Chemistry and Engineering, Kyushu University, Kasuga, Fukuoka 816-8580, Japan

<sup>5</sup>Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781039, India

(E-mail: irie@kumamoto-u.ac.jp)

A new hetero[7]helicene  $\mathbf{1}_{NN}$  structured by a diazabenzodiheterole (pyrroloindole) ring core was successfully synthesized by catalytic domino cyclodehydrogenation with Pd(OAc)<sub>2</sub> and O<sub>2</sub> as the key step. Significantly,  $\mathbf{1}_{NN}$  was stereochemically stable at room temperature and could be subjected to optical resolution by chiral HPLC. Furthermore, kinetic analysis of  $\mathbf{1}_{NN}$  and DFT calculations on its variants revealed that the stereochemical stability of the benzodiheterole-based helicenes was highly dependent on not only the heteroaromatic ring component but also the *N*substituent of the pyrrole ring unit.

Phenanthrene is one of the basic aromatic hydrocarbons composed of an angularly fused three-benzene ring unit (Figure 1a). Fusing additional rings of benzene into the *c* and *g* sides of this carbocycle leads to  $\pi$ -extended helical architectures known as carbo-helicenes or simply helicenes. Since the discovery of the elegant chiral helical form and chiroptical properties of carbo[6]helicene by Newman and coworkers,<sup>1</sup> much effort has been devoted to the synthesis of helicene derivatives and the evaluation of their structural characteristics and physical properties.<sup>2</sup> In this context, introduction of a heteroaromatic ring to the helical framework has gained increasing attention for modulating the electronic states of helicenes.<sup>2a</sup> Hence, we have been interested in the structural motif of **A** based on benzodiheteroles, heterocyclic congeners of phenanthrene (Figure 1b).<sup>3</sup>

Heteroles such as furan, pyrrole, and thiophene are typical electron-rich heteroarenes. They have been used to constitute extended  $\pi$ -conjugated systems with a characteristic

(a) phenanthrene as a core structure of helicenes



**Figure 1**. (a) Phenanthrene and its angularly fused  $\pi$ -extended systems (helicenes), (b) benzodiheteroles and its heterohelicene-derivatives

low oxidation potential, thereby creating useful organic functional materials such as those exhibiting hole-transport properties.<sup>4</sup> Thus, heterole-containing helicenes should also be attractive as chiral functional molecules.<sup>2a</sup> In particular, our primary concern has been the benzodiheterole-based helicenes **A**, the two heterole rings of which may introduce some more unique physical properties through electronic interactions of the heteroatoms at the para position on the central benzene ring.<sup>5</sup> However, there still remain issues concerning the development of catalytic and practical syntheses of chiral non-racemic variants of **A**.<sup>6</sup>

In order to overcome the synthetic issue described above, we recently introduced a new concept of domino cyclodehydrogenation (non-classical Bergman-Masamune reaction)<sup>7</sup> of ethenylene-linked diynes with suitable heteronucleophilic units at the alkyne termini to construct benzodiheterole frameworks (Scheme 1a).<sup>8-10</sup> This strategy was suitable for the synthesis of dioxa-benzodiheteroles (benzodifurans) in heterohelicenes from *o*-phenylene-linked diynes with nucleophilic phenol groups by the action of a palladium catalyst and molecular oxygen (Scheme 1b, previous work).<sup>8</sup> In this work, we have designed a new



Scheme 1. Our cyclodehydrogenation strategy for the synthesis of benzodiheterole-based helicenes

synthetic route to hetero[7]helicene  $\mathbf{1}_{NN}$  with a diazabenzodiheterole (pyrroloindole) unit based on the Pdcatalyzed cyclodehydrogenation (Scheme 1b, this work).<sup>11,12</sup>

Since we had demonstrated that the related dioxaundergoes benzodiheterole-based [7]helicene 200 racemization in solution at room temperature,<sup>8a</sup> it was a crucial point to evaluate the stereochemical behavior of its aza-variants prior to their synthetic study. It has been claimed that pyrrole constitutes stereochemically more stable heterohelicenes than furan.<sup>3c,12c</sup> Accordingly, we performed DFT calculations on energy barriers to the racemization of  $2_{NO}(H)$  and  $2_{NN}(H)$ , which substituted one or two pyrrole rings for the furan rings of  $2_{00}$  (Figure 2).<sup>13</sup> The order of stereochemical stability was indeed indicated to be  $2_{00}$  <  $2_{NO}(H) < 2_{NN}(H)$ , the substitution of furan by pyrrole leading to about 2 kcal/mol increase in the racemization barrier. These preliminary results encouraged us to pursue the synthesis of  $1_{NN}$ , a synthetically more accessible analogue of  $2_{NN}$ (H).<sup>14</sup>



**Figure 2.** DFT calculations at a B3LYP/6-311G(d,p) level on the racemization barriers ( $\Delta G^{\dagger}_{298K}$ , shown in parentheses) of the hetero[7]helicenes 2<sub>00</sub>, 2<sub>N0</sub>(H), and 2<sub>NN</sub>(H) with a dioxa-, aza-oxa, and diaza-benzodiheterole unit, respectively

We synthesized *o*-phenylenediynes  $3_{NN}^{15}$  and examined its cyclodehydrogenation for the production of  $1_{NN}$  (Scheme 2). Consequently, the reaction produced  $1_{NN}$  in 47% yield under almost the same reaction conditions as those for the synthesis of  $2_{00}^{8a}$ : Pd(OAc)<sub>2</sub> (10 mol%) and molecular oxygen (1 atm) in DMSO in the presence of aq. NaOH (1 M, 4 eq.) and MS 4A at 50 °C. Without the base additive, the yield of  $1_{NN}$  significantly decreased, as in the synthesis of  $2_{00}^{16}$ .



Scheme 2. Pd-catalyzed cyclodehydrogenation to synthesize 1<sub>NN</sub>

We next attempted to evaluate the stereochemical stability of  $\mathbf{1}_{NN}$ . Chiral HPLC analysis of  $\mathbf{1}_{NN}$  at room temperature resulted in complete peak separation of enantiomers.<sup>17</sup> This indicates that  $\mathbf{1}_{NN}$  has sufficient stereochemical stability for optical resolution, as predicted by the DFT calculation on its model  $\mathbf{2}_{NN}$ (H). Indeed, enantiomerically pure  $\mathbf{1}_{NN}$  was obtained by the chiral HPLC separation of *rac*- $\mathbf{1}_{NN}$ . Further experiments were performed to measure its rate of racemization at 120-150 °C (Figure 3). The

following kinetic analysis based on Eyring's theory revealed the unexpectedly high activation free energy to racemization of  $\mathbf{1}_{NN}$ :  $\Delta G_{298K}^{\ddagger}$  31.7 kcal/mol.  $\mathbf{1}_{NN}$  was found to be stereochemically much more stable than  $\mathbf{2}_{NN}(\mathbf{H})$ .



**Figure 3**. Eyring plot for the racemization of  $\mathbf{1}_{NN}$ ;  $\ln(k/T)$  vs.  $T^{-1}/10^{-3} \cdot \mathrm{K}^{-1}$ , where *k* stands for rate constant with a unit of s<sup>-1</sup>

In order to evaluate the effects of the substituents on the high racemization barrier of  $1_{NN}$ , we performed DFT calculations on  $2_{NN}(Ts)$ , which was structurally the same as that of  $\mathbf{1}_{NN}$ , except for the absence of any substituents on the benzene rings (Figure 4). The result indicates that  $2_{NN}(Ts)$ also has a high-energy barrier to racemization (34.9 kcal/mol) like  $1_{NN}$ , considerably exceeding that of the related NH-free  $2_{NN}(H)$  (26.5 kcal/mol). Thus, the *N*-Ts group of the pyrrole ring in  $\mathbf{1}_{NN}$  is crucial for stereochemical stabilization, its contribution to the increase in the racemization barrier being estimated to about 4 kcal/mol per group.<sup>18</sup> The same calculation was also applied to  $2_{NN}(t-Bu)$  with a bulky N-tbutyl group for comparison, and its racemization barrier (27.4 kcal/mol) was found to be close to that of  $2_{NN}(H)$ .<sup>13</sup> This indicates that the N-Ts group should affect the racemization process of  $1_{NN}$  electronically, rather than sterically. To the best of our knowledge, this is the first proof for the significant effect of the N-substituent on the stereochemical stability of heterohelicenes.



Figure 4. Evaluation of the N-substituent effect on the racemization barriers of benzodipyrrole-based [7]helicenes  $2_{NN}(R)$  by DFT calculations at a B3LYP/6-311G(d,p) level

In summary, the new chiral hetero[7]helicene  $\mathbf{1}_{NN}$  based a diaza-benzodiheterole ring core was successfully on synthesized by palladium-catalyzed domino cyclodehydrogenation of o-phenylene-linked diyne  $\mathbf{3}_{NN}$  as the key step. Subsequent enantiomeric separation by chiral HPLC afforded  $\mathbf{1}_{NN}$  in an optically pure form. Kinetic analysis of  $\mathbf{1}_{NN}$ and DFT calculations on its variants revealed that the stereochemical stability of the benzodiheterole-based helicenes was highly dependent on not only the heteroaromatic ring component but also on the N-substituent of the pyrrole ring unit.

This work was financially supported by a Grant-in-Aid for Scientific Research (C) (No. 24550059) and pursued under the Cooperative Research Program "CORE Lab" of Network Joint Research Center for Materials and Devices: Dynamic Alliance for Open Innovation Bridging Human, Environment and Materials.

Supporting Information is available on http://dx.doi.org/10.1246/cl.\*\*\*\*\*.

## **References and Notes**

- a) M. S. Newman, W. B. Lutz, D. Lednicer, J. Am. Chem. Soc. 1955, 77, 3420. b) M. S. Newman, D. Lednicer, J. Am. Chem. Soc. 1956, 78, 4765.
- For recent reviews, see: a) Y. Shen, C.-F. Chen, *Chem. Rev.* 2012, *112*, 1463. b) M. Gingras, *Chem. Soc. Rev.* 2013, *42*, 968. c) M. Gingras, G. Félix, R. Peresutti, *Chem. Soc. Rev.* 2013, *42*, 1007. d) M. Gingras, *Chem. Soc. Rev.* 2013, *42*, 1051.
- 3 A number of chiral non-racemic A-type dithia-helicenes have been reported so far. See: a) H. Wynberg, M. B. Groen, J. Am. Chem. Soc. 1968, 90, 5339. b) M. B. Groen, H. Wynberg, J. Am. Chem. Soc. 1971, 93, 2968. c) M. B. Groen, H. Schadenberg, H. Wynberg, J. Org. Chem. 1971, 36, 2797. d) K. Tanaka, H. Osuga, H. Suzuki, H. Kishida, Tetrahedron Lett. 1992, 33, 4599. e) K. Tanaka, H. Osuga, H. Suzuki, Tetrahedron: Asymmetry 1993, 4, 1843. f) K. Tanaka, H. Osuga, K. Koyama, H. Suzuki, K. Imai, Y. Yoshida, Enantiomer 1997, 2, 193. g) K. Tanaka, H. Suzuki, H. Osuga, J. Org. Chem. 1997, 62, 4465. h) K. Tanaka, T. Kume, T. Takimoto, Y. Kitahara, H. Suzuki, H. Osuga, Y. Kawai, Chem. Lett. 1997, 26, 501. i) K. E. S. Phillips, T. J. Katz, S. Jockusch, A. J. Lovinger, N. J. Turro, J. Am. Chem. Soc. 2001, 123, 11899. j) Y. Kitahara, K. Tanaka, Chem. Commun. 2002, 932. k) P. Aillard, A. Voituriez, D. Dova, S. Cauteruccio, E. Licandro, A. Marinetti, Chem. Eur. J. 2014, 20, 12373. 1) J. Doulcet, G. R. Stephenson, Chem. Eur. J. 2015, 21, 18677. m) J. Doulcet, G. R. Stephenson, Chem. Eur. J. 2015, 21, 13431. n) P. Aillard, D. Dova, V. Magné, P. Retailleau, S. Cauteruccio, E. Licandro, A. Voituriez, A. Marinetti, Chem. Commun. 2016, 52, 10984.
- 4 For some recent reviews, see: a) I. F. Perepichka, D. F. Perepichka, *Handbook of Thiophene-Based Materials*, John Wiley & Sons, Ltd, 2009. b) Grigalevicius, *Synth. Met.* 2006, 156, 1. c) H. Tsuji, E. Nakamura, *Acc. Chem. Res.* 2017, 50, 396. c) G. Sathiyan, E. K. T. Sivakumar, R. Ganesamoorthy, R. Thangamuthu, P. Sakthivel, *Tetrahedron Lett.* 2016, 57, 243.
- 5 The related carbazole-containing diaza-[5]helicenes have recently been synthesized to reveal their characteristic photoelectronic properties. See: a) T. Suzuki, Y. Tokimizu, Y. Sakano, R. Katoono, K. Fujiwara, S. Naoe, N. Fujii, H. Ohno, *Chem. Lett.* 2013, 42, 1001. b) T. Suzuki, Y. Sakano, Y. Tokimizu, Y. Miura, R. Katoono, K. Fujiwara, N. Yoshioka, N. Fujii, H. Ohno, *Chem. Asian J.* 2014, 9, 1841.
- 6 For diastereoselective synthesis, see refs. 3d-g.
- a) N. Darby, C. U. Kim, J. A. Salaün, K. W. Shelton, S. Takada, S. Masamune, J. Chem. Soc. D, 1971, 1516. b) R. R. Jones, R. G. Bergman, J. Am. Chem. Soc. 1972, 94, 660. c) R. G. Bergman, Acc. Chem. Res. 1973, 6, 25.
- 8 a) R. Irie, A. Tanoue, S. Urakawa, T. Imahori, K. Igawa, T. Matsumoto, K. Tomooka, S. Kikuta, T. Uchida, T. Katsuki, *Chem. Lett.* 2011, 40, 1343. b) M. Furusawa, T. Imahori, K. Igawa, K. Tomooka, R. Irie, *Chem. Lett.* 2013, 42, 1134.
- 9 For non-classical and non-redox type Bergman-Masamune reactions associated with addition of a nucleophile, see: a) M.-J. Wu, C.-Y. Lee, C.-F. Lin, Angew. Chem., Int. Ed. 2002, 41, 4077. b) A. Odedra, C.-J. Wu, T. B. Pratap, C.-W. Huang, Y.-F. Ran, R.-S. Liu, J. Am. Chem. Soc. 2005, 127, 3406. c) B. P. Taduri, Y.-F. Ran, C.-W. Huang, R.-S. Liu, Org. Lett. 2006, 8, 883. d) B. P. Taduri, A. Odedra, C.-Y. Lung, R.-S. Liu, Synthesis, 2007, 2050. e) A. Das, H.-K. Chang, C.-H. Yang, R.-S. Liu, Org. Lett. 2008, 10, 4061. f) K. Hirano, Y. Inaba, T. Watanabe, S. Oishi, N. Fujii, H. Ohno, Adv. Synth. Catal. 2010, 352, 368. g) K. Miki, H. Kuge, R. Umeda, M. Sonoda, Y. Tobe, Synth. Commun. 2011, 41, 1077. h) K. Hirano, Y. Inaba, N. Takahashi, M. Shimano, S. Oishi, N. Fujii,

H. Ohno, J. Org. Chem. 2011, 76, 1212. i) R. Liedtke, M. Harhausen, R. Fröhlich, G. Kehr, G. Erker, Org. Lett. 2012, 14, 1448. j) P. M. Byers, J. I. Rashid, R. K. Mohamed, I. V. Alabugin, Org. Lett. 2012, 14, 6032. k) G. Ferrara, T. Jin, K. Oniwa, J. Zhao, A. M. Asiri, Y. Yamamoto, Tetrahedron Lett. 2012, 53, 914. 1) A. S. K. Hashmi, I. Braun, M. Rudolph, F. Rominger, Organometallics, 2012, 31, 644. m) S. Naoe, Y. Suzuki, K. Hirano, Y. Inaba, S. Oishi, N. Fujii, H. Ohno, J. Org. Chem. 2012, 77, 4907. n) M. M. Hansmann, M. Rudolph, F. Rominger, A. S. K. Hashmi, Angew. Chem., Int. Ed. 2013, 52, 2593. o) J. Storch, M. Bernard, J. Sýkora, J. Karban, J. Čermák, Eur. J. Org. Chem. 2013, 2013, 260. p) Y. Wang, A. Yepremyan, S. Ghorai, R. Todd, D. H. Aue, L. Zhang, Angew. Chem., Int. Ed. 2013, 52, 7795. q) K. Nakamura, S. Furumi, M. Takeuchi, T. Shibuya, K. Tanaka, J. Am. Chem. Soc. **2014**, *136*, 5555. r) M. Sivaraman, P. T. Perumal, *Org. Biomol. Chem.* **2014**, *12*, 1318. s) R. Liedtke, F. Tenberge, C. G. Daniliuc, G. Kehr, G. Erker, J. Org. Chem. 2015, 80, 2240. t) S. Nayak, N. Ghosh, B. Prabagar, A. K. Sahoo, Org. Lett. 2015, 17, 5662. u) P. Nöesel, V. Müller, S. Mader, S. Moghimi, M. Rudolph, I. Braun, F. Rominger, A. S. K. Hashmi, Adv. Synth. Catal. 2015, 357, 500. v) J. Schädlich, M. Wieteck, M. Rudolph, M. H. Larsen, A. S. K. Hashmi, Tetrahedron 2015, 71, 5858. w) M. Tanaka, Y. Shibata, K. Nakamura, K. Teraoka, H. Uekusa, K. Nakazono, T. Takata, K. Tanaka, Chem. Eur. J. 2016, 22, 9537. x) S. Tšupova, M. M. Hansmann, M. Rudolph, F. Rominger, A. S. K. Hashmi, Chem. Eur. J. 2016, 22, 16286.

- 10 For non-classical Bergman-Masamune reactions associated with halogenation, see: a) W.-R. Chang, Y.-H. Lo, C.-Y. Lee, M.-J. Wu, Adv. Synth. Catal. 2008, 350, 1248. b) C.-C. Chen, L.-Y. Chin, S.-C. Yang, M.-J. Wu, Org. Lett. 2010, 12, 5652. c) C.-C. Chen, S.-C. Yang, M.-J. Wu, J. Org. Chem. 2011, 76, 10269. d) G. Ferrara, T. Jin, M. Akhtaruzzaman, A. Islam, L. Han, H. Jiang, Y. Yamamoto, Tetrahedron Lett. 2012, 53, 1946. e) C.-C. Chen, C.-M. Chen, M.-J. Wu, J. Org. Chem. 2014, 79, 4704.
- For helicene synthesis based on Bergman-Masamune reactions, see: a) S. Roy, A. Anoop, K. Biradha, A. Basak, *Angew. Chem., Int. Ed.* 2011, 50, 8316. b) S. Roy, A. Basak, *Tetrahedron*, 2013, 69, 2184. See also refs 90, 9q, and 9w.
- 12 For synthetic studies on pyrrole- and/or furan-containing chiral heterohelicenes, see: a) I. Pischel, S. Grimme, S. Kotila, M. Nieger, F. Vögtle, Tetrahedron: Asymmetry, 1996, 7, 109. b) S. D. Dreher, D. J. Weix, T. J. Katz, J. Org. Chem. 1999, 64, 3671. c) K. Nakano, Y. Hidehira, K. Takahashi, T. Hiyama, K. Nozaki, Angew. Chem., Int. Ed. 2005, 44, 7136. d) M. Salim, A. Akutsu, T. Kimura, M. Minabe, M. Karikomi, Tetrahedron Lett. 2011, 52, 4518. e) K. Goto, R. Yamaguchi, S. Hiroto, H. Ueno, T. Kawai, H. Shinokubo, Angew. Chem., Int. Ed. 2012, 51, 10333. f) H. Kelgtermans, L. Dobrzańska, L. V. Meervelt, W. Dehaen, Org. Lett. 2012, 14, 1500. g) L. Kötzner, M. J. Webber, A. Martinez, C. De Fusco, B. List, Angew. Chem., Int. Ed. 2014, 53, 5202. h) M. S. Sundar, A. V. Bedekar, Org. Lett. 2015, 17, 5808. i) T. Matsuno, Y. Koyama, S. Hiroto, J. Kumar, T. Kawai, H. Shinokubo, Chem. Commun. 2015, 51, 4607. j) M. Sako, Y. Takeuchi, T. Tsujihara, J. Kodera, T. Kawano, S. Takizawa, H. Sasai, J. Am. Chem. Soc. 2016, 138, 11481
- 13 For details of calculations, see the Supporting Information.
- 14 We also synthesized the racemic aza-oxa-variant  $\mathbf{1}_{NO}$ , which was structurally comparable to  $\mathbf{1}_{NN}$  but had a furan and an *N*-Ts-pyrrole ring such as  $\mathbf{2}_{NO}$ , in the similar manner, although its enantiomeric separation by chiral HPLC has so far been unsuccessful. For further details of  $\mathbf{1}_{NO}$ , see the Supporting Information.
- 15 For the synthesis of  $\mathbf{3}_{NN}$ , see the Supporting Information.
- 16 In the absence of the base additive and under otherwise the identical conditions,  $1_{NO}$  and  $1_{NN}$  were obtained in lower yields. See the Table S1 in the Supporting Information.
- 17 For the HPLC conditions, see the Supporting Information.
- 18 To gain an experimental evidence about the *N*-Ts group effect on the stereochemical stability of  $\mathbf{1}_{NN}$ , we attempted to prepare the NH-free derivative of  $\mathbf{1}_{NN}$  for its stereochemical analysis. After various attempts, detosylation of  $\mathbf{1}_{NN}$  was performed by treatment with KOH to provide the desired product. However, it was difficult to isolate for further experiments due to its high air-sensitivity. We are currently revisiting the synthesis, isolation, analysis of the NHfree derivative of  $\mathbf{1}_{NN}$  under a strictly inert atmosphere.