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Synthesis and characterization of 1,8-naphthalimide with [6]helicene skeleton†

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A 1,8-naphthalimide with [6]helicene derivative scaffold has been designed and synthesized. The (*P*)- and (*M*)-enantiomers of the [6]helicene derivative were resolved by HPLC on a chiral column. The single crystal of the [6]helicene derivative exhibits an intermolecular interactions of the 1,8-naphthalimide units.

Naturally occurring chiral helical architectures such as DNA duplex and α-helix in peptides play critical roles in biological functions. Helical molecules are also significant in materials science and chemical processes as they are widely applied in numerous fields such as enantioselective catalysis,[1] chiral recognition[2] and self-assembly,[3] nonlinear optics,[4] and molecular switches.[5] In recent years, chiral π-conjugated molecules have attracted attention in the field of organic electronic materials because of their specific electronic properties.[6]

1,8-Naphthalimide derivatives have been used as supramolecular moieties in model compounds for photoinduced electron transfer in photophysical studies,[7] and for fluorescent probes in the medical and biological fields.[8] In addition, such *N*-substituted derivatives have also been used as ligands in asymmetric reactions.[9] Although some 1,8-naphthalimide derivatives with chiral *N*-substituents have been designed and synthesized,[10] 1,8-naphthalimide derivatives based on helical geometry have not been reported except for twisted perylene bisimide.[11] We became particularly interested in the chiroptical properties of 1,8-naphthalimide with a chiral helicene skeleton because helicenes with well-defined helicoidal polyaromatic structures are known to be photo-stable. [*n*]Helicene derivatives are helicoidally shaped benzologues of phenanthrene comprising ortho-fused aromatic and/or hetero-aromatic rings,[12] which exhibit unique structural features and have a wide range of potential applications in chiral materials and asymmetric synthesis.[13] One important challenge with regard to further expanding the potential of helicenes is to develop new frameworks with functionality that may lead to a new class of materials with useful electronic properties.

Herein, we describe the synthesis of 1,8-naphthalimide with [6]helicene skeleton by photochemical cyclization.

Retrosynthetic analysis of a 1,8-naphthalimide-based helicene molecule is shown in Fig. 1. We envisioned that the [6]helicene derivative could be constructed from the mono(arylvinyl)arene and bis(arylvinyl)arene *via* oxidative photocyclization. The single- and double-oxidative photocyclization processes have indeed proved to be very convenient for the preparation of helicene derivatives, starting from readily accessible mono- and bis(arylvinyl)arene intermediates.[14]

The synthesis of mono(arylvinyl)arene **2** is depicted in Scheme 1 (top). Compound **6** was synthesized starting from naphthalic anhydride **4** by regioselective bromination and subsequent amidation. L-Proline catalyzed the coupling reaction of **6** with CuCN using Wang's protocol, providing the nitrile-substituted derivative **7** in 82% yield,[15] and the nitrile group was converted to the corresponding aldehyde **8** with RANEY® Ni. The aldehyde **8** was subsequently reacted with phosphonate **9** to furnish **2**.

The synthesis of bis(arylvinyl)arene **3** was performed as shown in Scheme 1 (bottom). The vinyl moiety of **10** was installed by Stille coupling using tributyl(vinyl)tin. The

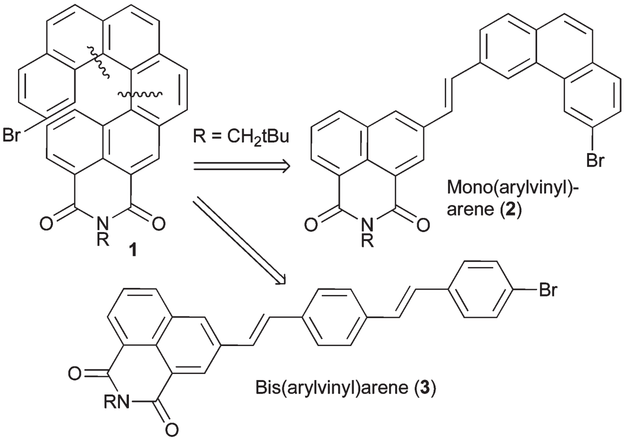

Fig. 1 Retrosynthetic approach to 1,8-naphthalimide with [6]helicene skeleton.

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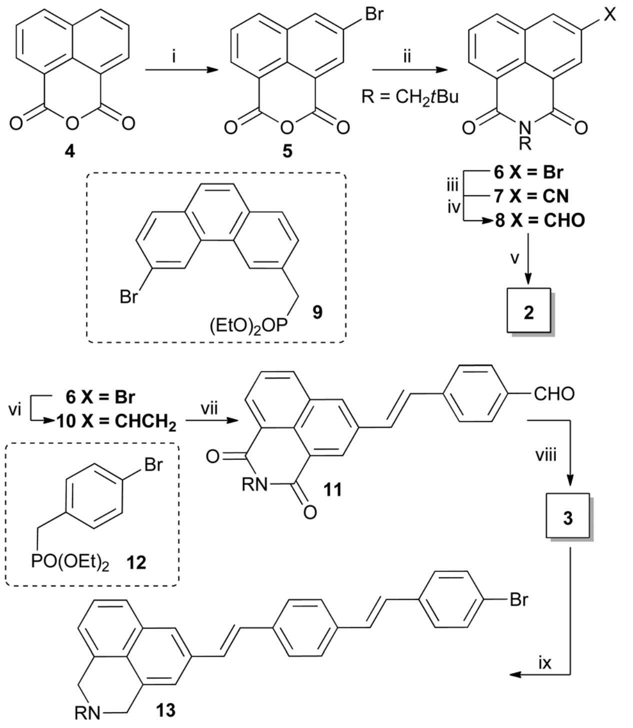
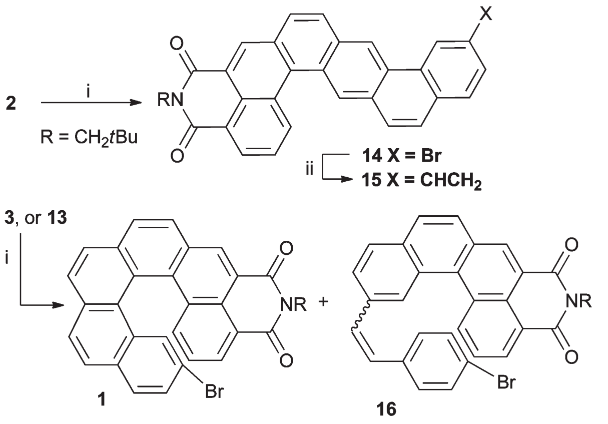


Scheme 1 Synthesis of mono(arylvinyl)arene **2** and bis(arylvinyl) arene **3**. *Reagents and conditions*: i, Br_2, Ag_2SO_4, H_2SO_4, 65 °C (93%); ii, neopentylamine, dioxane, 100 °C (quant.); iii, CuCN, L-proline, DMF, 160 °C (82%); iv, RANEY® Ni, HCO_2H, reflux (29%); v, **9**, NaH, THF, 0 °C–r.t. (98%); vi, tributyl(vinyl)tin, $Pd_2(dba)_3$, $P(tBu)_3$, toluene, 80 °C (73%); vii, 4-bromobenzaldehyde, $Pd(OAc)_2$, PPh_3, AcONa, DMF, 120 °C (96%); viii, **12**, NaH, THF, 0–30 °C (79%); ix, $LiAlH_4$, $AlCl_3$, THF, 0 °C–r.t. (76%).



Scheme 2 *Reagents and conditions*: i, *hν*, I_2, toluene, r.t.; ii, tributyl (vinyl)tin, $Pd_2(dba)_3$, $P(tBu)_3$, toluene, 80 °C (86%).

Table 1 Oxidative photochemical reaction of **3** and **13**

Substrate	Device	Conc. (mM)	Reaction time (h)	Yield (%) of **1**	Yield (%) of **16**
3	Batch[a]	1	72	4	27
13	Batch[a]	1	72	16	Trace
13	Batch[a]	0.25	72	19	Trace
13	Microreactor[b]	0.25	0.17[c]	55	Trace

[a] Black lights (20 W × 7 pieces, total 140 W) with a peak wavelength of 350 nm. [b] UV LEDs (250 mW × 6 pieces, total 1.5 W) with a peak wavelength of 365 nm. [c] Residence time is given, which was calculated according to the equation, *t* (h) × flow rate (μL h^{-1}) = volume of microchannel (μL).

Mizoroki–Heck cross-coupling reaction of vinyl-substituted **10** with a 4-bromobenzaldehyde afforded the mono(arylvinyl)arene derivative **11** in 96% yield after purification by column chromatography. The Horner–Wadsworth–Emmons (HWE) reaction of compound **11** with phosphonate **12** gave **3** in 79% yield.

To complete the synthesis of [6]helicene **1**, **2** and **3** were then photocyclized in the presence of a stoichiometric amount of iodine as an oxidizing agent and an excess amount of THF as a hydrogen iodide scavenger.[14d] Oxidative photocyclization of **2** in toluene on the scale of 1.5 mM did not give the desired **1**, but the corresponding 1,8-naphthalimide with dibenzo[*a*,*k*]tetraphene derivative **14** as a sole product was obtained in 91% yield (Scheme 2). Structures of compound **14** and its vinyl derivative **15** were determined on the basis of COSY, NOESY, HSQC, and HMBC correlations (see Fig. S1 in ESI†).

Oxidative photocyclization of **3** on the scale of 1.0 mM afforded **1** and mono(arylvinyl)arene derivative **16** (Scheme 2, Table 1). This result shows strong evidence that the double photocyclization of **3** leading to **1** proceeds *via* intermediate **16** rather than intermediate **2**. In the case of oxidative photocyclization using a reduced bis(arylvinyl)arene **13**, compound **1** was obtained in a better yield than that of **3** (Schemes 1 and 2). The reaction yield of **1** was slightly improved by decreasing the reaction concentration of the substrate from the scale of 1 mM to 0.25 mM. In addition, the use of a microflow system resulted in a dramatic improvement of the yield of **1** (55%, Table 1).

We proposed that the species responsible for the oxidation of the benzylic position to yield the 1,8-naphthalimide was the iodine radical, generated from I_2 and/or HI under light irradiation (see Fig. S5 in ESI†). Subsequently, the produced radical species is reacted with molecular oxygen, followed by dehydration to afford the ketone.[16] Since the rate constants for H-atom abstraction by radical species should be related to the bond dissociation enthalpy (BDE) of the relevant C–H bond, we calculated the C–H BDE by a density functional theory (DFT)-based approach with the B3LYP functional. As a result, it was shown that the BDE at the benzylic carbon with neighboring N-atom is lower than that of other model compounds (see Table S1 in ESI†).

The structure of **1** was confirmed by single-crystal X-ray analysis (Fig. 2). The interplanar angle between the terminal rings of **1** in a solid state was 45.7°. Furthermore, inspection of the crystal structure of **1** revealed that the packing is mainly governed by antiparallel π–π stacking interactions between naphthalimide chromophores of opposite helicity (Fig. 2).[17]

The absorption of UV/vis spectra of the racemic mixtures **1** in $CHCl_3$ is shown in Fig. 3 (top).

The separation of the enantiomers was accomplished *via* HPLC on a chiral column (Daicel Chiralpak IA, 4.6 mm × 250 mm) using a UV light detector at 254 nm. The chromatogram showed successful separation of the enantiomers (see Fig. S4 in ESI†). The absolute stereochemistry of (*P*)-(+)- and (*M*)-(−)-**1** was determined by their optical rotation ($[a]_D$ = +2294 (*c* = 5.0

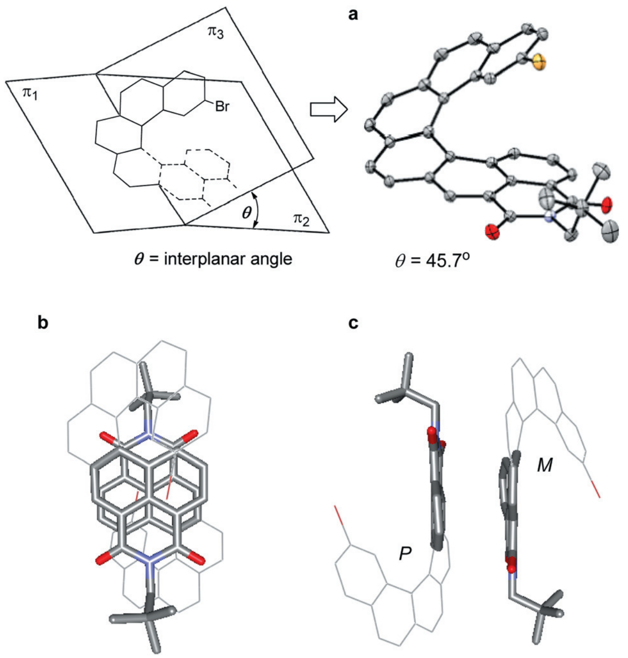


Fig. 2 X-ray structure of compound **1**. (a) The ellipsoid drawn at 50% probability level, H atoms and THF solvents omitted for clarity. Views of the 1,8-naphthalimide π–π stack of **1** perpendicular (b) and parallel (c) to the arene plane.

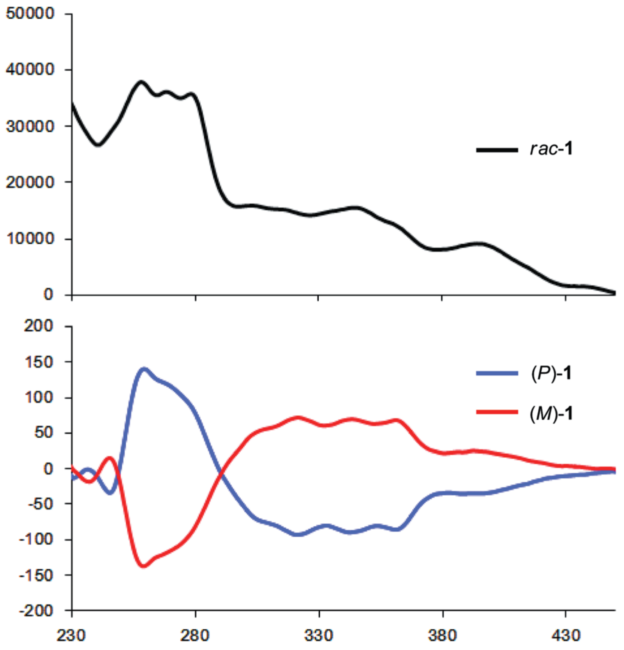


Fig. 3 UV/vis spectra (top, *rac*-[6]helicene **1**) and CD spectra (bottom) of (*P*)-**1** (solid blue line) and (*M*)-**1** (solid red line) enantiomers in dilute $CHCl_3$ solution.

$\times 10^{-3}$, 20 °C, $CHCl_3$), $[\alpha]_D = -2379$ ($c = 4.4 \times 10^{-3}$, 20 °C, $CHCl_3$)).[18]

The CD spectra obtained for the enantiomers of (*P*)-**1** (blue trace) and (*M*)-**1** (red trace) showed a mirror image relationship, as depicted in Fig. 3 (bottom). In the region of 290–450 nm of the CD spectra, a broad monosignated peak with a maximum at 342 nm can be seen, which properly correlates with the absorption maximum at 342 nm (Fig. 3, top).

In conclusion, we demonstrated the first synthesis of novel optical active 1,8-naphthalimide with [6]helicene derivative **1** from the oxidative photocyclization of a bis(arylvinyl)arene. The oxidative photocyclization of **13** involves concomitant oxidation at the benzylic position. Further functionalization at the reactive bromine site of **1** is currently underway in our group.

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Notes and references

1 For the case of DNA, see: (*a*) A. J. Boersma, R. P. Megens, B. L. Feringa and G. Roelfes, *Chem. Soc. Rev.*, 2010, **39**, 2083; (*b*) S. Juliá, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annuziata and H. Molinari, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1317; For the case of synthetic chiral compounds, see:(*c*) T. Ooi and K. Maruoka, *Angew. Chem., Int. Ed.*, 2007, **46**, 4222; (*d*) S. D. Dreher, T. J. Katz, K.-C. Lam and A. L. Rheingold, *J. Org. Chem.*, 2000, **65**, 815.

2 T. W. Bell and N. M. Hext, *Chem. Soc. Rev.*, 2004, **33**, 589.

3 (*a*) C. Maeda, T. Kamada, N. Aratani and A. Osuka, *Coord. Chem. Rev.*, 2007, **251**, 2743; (*b*) D. K. Smith, *Chem. Soc. Rev.*, 2009, **38**, 684.

4 L. M. Haupert and G. J. Simpson, *Annu. Rev. Phys. Chem.*, 2009, **60**, 345.

5 B. L. Feringa, R. A. van Delden, N. Koumura and E. M. Geertsma, *Chem. Rev.*, 2000, **100**, 1789.

6 (*a*) A. Rajca and M. Miyasaka, *Angew. Chem., Int. Ed.*, 2003, **42**, 2448; (*b*) C. Nuckolls, R. F. Shao, W. G. Jang, N. A. Clark, D. M. Walba and T. Katz, *Chem. Mater.*, 2002, **14**, 773; (*c*) H. Osuga and K. Tanaka, *J. Synth. Org. Chem. Jpn.*, 2002, **60**, 593.

7 A. Prasanna da Silva, H. Q. Nimal Gunaratne, J. L. Habib-Jiwan, C. P. McCoy, T. E. Rice and J.-P. Soumillion, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1728.

8 K. K. Dubey, R. K. Singh and K. Misra, *Indian J. Chem.*, 1995, **B34**, 876.

9 P. Müller and A. Ghanem, *Org. Lett.*, 2004, **6**, 4347.

10 (*a*) J. Gawroński, M. Kwit and K. Gawrońska, *Org. Lett.*, 2002, **4**, 4185; (*b*) Q. Yang, P. Yang, X. Qian and L. Tong, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 6210.

11 (*a*) Z. Xie and F. Würthner, *Org. Lett.*, 2010, **12**, 3204; (*b*) C. L. Eversloh, Z. Liu, B. Müller, M. Stangl, C. Li and K. Müllen, *Org. Lett.*, 2011, **13**, 5525.

12 Y. Shen and C.-F. Chen, *Chem. Rev.*, 2011, DOI: 10.1021/cr200087r.

13 (*a*) D. Nakano and M. Yamaguchi, *Tetrahedron Lett.*, 2003, **44**, 4969; (*b*) T. Kawasaki, K. Suzuki, E. Licandro, A. Bossi, S. Maiorana and K. Soai, *Tetrahedron: Asymmetry*, 2006, **17**, 2050; (*c*) J. Chen, B. Captain and N. Takenaka, *Org. Lett.*, 2011, **13**, 1654; (*d*) M. R. Crittall, H. S. Rzepa and D. R. Carbery, *Org. Lett.*, 2011, **13**, 1250.

14 For selected syntheses of helicene compounds using an electrocyclization/oxidation sequence see: (*a*) F. B. Mallory and C. W. Mallory, *Org. React.*, 1984, **30**, 1, and references therein (*b*) P. Kovacic and M. B. Jons, *Chem. Rev.*, 1987, **87**, 357; (*c*) C. Stammel, R. Fröhlich, C. Wolff, H. Wenck, A. d. Meijere and J. Mattay, *Eur. J. Org. Chem.*, 1999, **7**, 1709; (*d*) H. R. Talele, M. J. Gohil and A. V. Bedekar, *Bull. Chem. Soc. Jpn.*, 2009, **82**, 1182; (*e*) M. S. M. Pearson and D. R. Carbery, *J. Org. Chem.*, 2009, **74**, 5320.

15 D. Wang, L. Kuang, Z. Li and K. Ding, *Synlett*, 2008, 69.

16 S. Hirashima, T. Nobuta, N. Tada, T. Miura and A. Itoh, *Org. Lett.*, 2010, **12**, 3645.

17 (*a*) D. L. Reger, J. D. Elgin, R. F. Semeniuc, P. J. Pellechia and M. D. Smith, *Chem. Commun.*, 2005, 4068; (*b*) D. L. Reger, J. D. Elgin, M. D. Smith and B. K. Simpson, *Polyhedron*, 2009, **28**, 1469.

18 Positive and negative signs of $[\alpha]_D$ are usually found for (*P*)- and (*M*)-[*n*] helicenes, respectively. See: (*a*) K. P. Meurer and F. Vögtle, *Top. Curr. Chem.*, 1985, **127**, 1; (*b*) W. H. Laarhoven and W. J. C. Prinsen, *Top. Curr. Chem.*, 1984, **125**, 63.