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CONCISE SYNTHESIS OF AN AMIDE-FUNCTIONALIZED [7]HELICENE-LIKE MOLECULE VIA INTRAMOLECULAR AMIDATION

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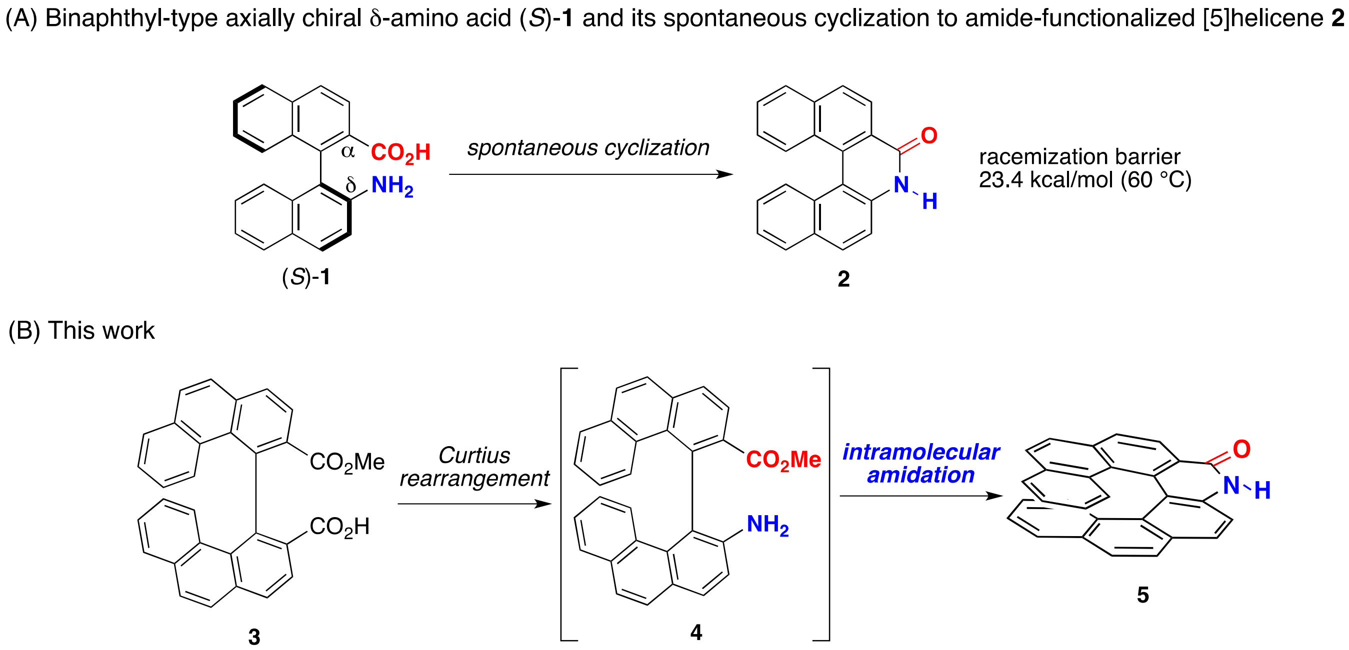
This paper is dedicated to Professor Yasuyuki Kita on the occasion of his 77th birthday.

Abstract – A concise synthesis of an amide-functionalized [7]helicene-like molecule was achieved via the intramolecular amidation of an *in-situ*-generated biaryl δ-amino acid derivative. An X-ray analysis of racemic mixture of this helicene-like molecule revealed a helically twisted π-system and that the (*M*)- and (*P*)-isomers associate pairwise via hydrogen-bonding interactions, which results in a one-dimensional columnar packing in the crystal structure.

Helicenes are unique chiral polycyclic aromatic compounds that possess a helically twisted conjugated π-system. Due to this unique helical structure, helicenes exhibit noteworthy chiroptical properties such as prominent optical rotation and circularly polarized luminescence,[1] as well as unique chemical behavior.[2] Heterohelicenes and heterohelicene-like molecules, which bear hetero-functional groups as a constituent moiety in the helical backbone, have attracted particular attention due to potential applications as chiral elements in organic materials,[3] chiral catalysts,[4] and bioactive compounds.[5] On account of the growing demand of these helical molecules, concise synthetic methods to yield functionalized helicenes have become highly desirable.

To achieve the cyclization to sterically hindered helical structure in these hetero-functionalized molecules, a photo-induced cyclization of the corresponding styrene derivative, originally applied in carbohelicene synthesis, has been adapted.[1,6] However, this method is not readily applicable to gram-scale syntheses because such reactions often require high-dilution conditions and special apparatuses for the photo-irradiation. Transition-metal catalyzed reactions represent another promising way for cyclization to heterohelicenes and heterohelicene-like molecules.[1,6] In particular, catalytic asymmetric syntheses mediated by a chiral transition-metal catalyst are an effective way to prepare optically active these hetero-functionalized molecules.[6e,7] That said, a method that does not employ transition-metal catalysts would be simpler, as well as more cost-effective and beneficial for the cyclization especially in the scaled-up preparation of heterohelicenes and heterohelicene-like molecules. Therefore, simple cyclization conditions that do not use photocyclization or a transition-metal catalyst are required.

We have conducted a synthetic investigation of axially chiral biaryl δ-amino acids that possess aniline-type amino and carboxyl groups at the C-2 and C-2’ positions.[8] In the course of this research we discovered the spontaneous cyclization of binaphthyl-type molecule (*S*)-**1** to give amide-functionalized [5]helicene-like molecule **2**.[8a] During this process, the amide group was incorporated into the fused cyclic system as a constituent moiety (Scheme 1A). Furthermore, the properties of **2**, e.g. its twisted aromatic system, were also revealed. However, its racemization barrier (23.4 kcal/mol at 60 °C) is too low to allow to exist in a configurationally stable form at ambient temperature.

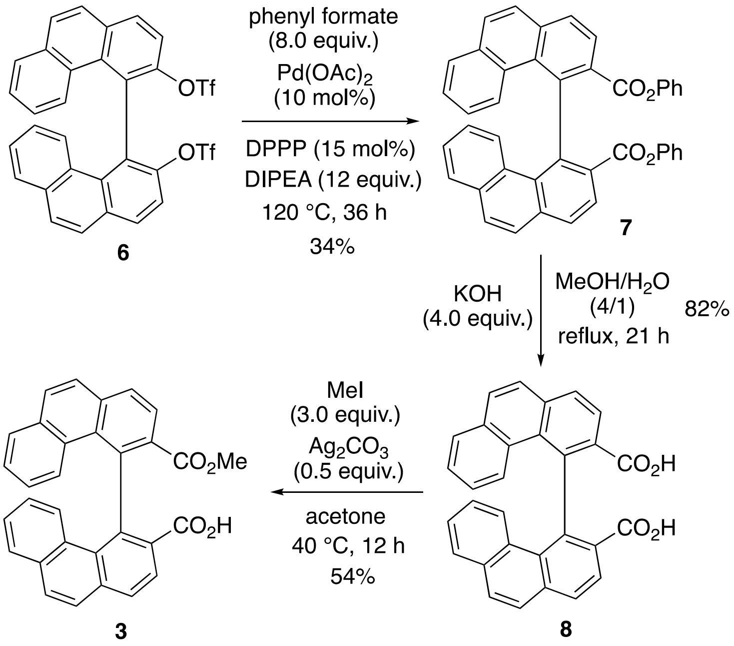

(A) Binaphthyl-type axially chiral δ-amino acid (*S*)-**1** and its spontaneous cyclization to amide-functionalized [5]helicene **2**

(B) This work

Scheme 1. Intramolecular amidations that furnish amide-functionalized helicene-like molecules

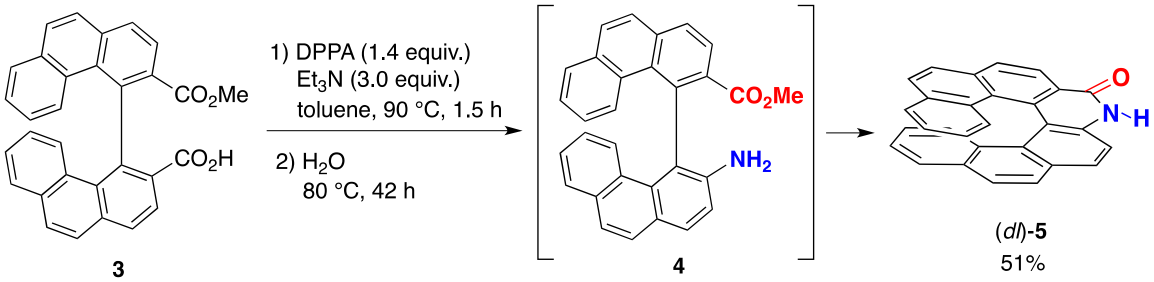
We envisioned that such amide-functionalized molecules could become promising chiral functionalized heterohelicene-like molecules if their racemization barrier was increased sufficiently. Furthermore, the intramolecular amidation reaction related to the spontaneous cyclization of **1** to **2** could be employed as a convenient and powerful method to prepare these molecules without the use of photo-irradiation or transition-metal catalysts. To the best of our knowledge, there is no precedent for employing an intramolecular amidation for a cyclization reaction that yields a heterohelicene-like molecule except for our example.[8a] Therefore, we intended to prepare amide-functionalized [7]helicene-like molecule **5**, with the expectation that it would exhibit stable helical chirality, via the intramolecular amidation of *in*-*situ*-generated biaryl δ-amino acid **4** prepared from the Curtius rearrangement of the corresponding monomethyl ester **3** (Scheme 1B). Herein, we report the synthesis of **5** via an intramolecular amidation, together with its crystal structure.[9]

Initially, we prepared monomethyl ester **3** from the racemic triflate **6**[10] of biphenanthrene diol (Scheme 2). Carbonylation of **6** with phenyl formate in the presence of a Pd catalyst afforded the corresponding diphenyl ester **7**.[11] Hydrolysis of the ester groups furnished dicarboxylic acid **8**, and a subsequent selective monomethyl esterification with a combination of MeI and Ag_2CO_3 generated **3**.[8b]



Scheme 2. Preparation of monomethyl ester **3**

With desired **3** successfully synthesized, we moved to the cyclization of **5** via the *in situ* generation of the corresponding δ-amino acid derivative **4** under Curtius rearrangement conditions (Scheme 3). Treatment of **3** with diphenylphosphoryl azide (DPPA; 1.4 equiv.) and Et_3N (3.0 equiv.) in toluene at 90 °C completed the Curtius rearrangement. Subsequently, H_2O was added to hydrolyze the isocyanate intermediate, and further heating furnished racemic **5** in 51% yield. The key intramolecular amidation was expected to occur via intermediary δ-amino acid **4**.[12]



Scheme 3. Transformation of **3** to the amide-functionalized helicene-like molecule **5**

An X-ray diffraction analysis of the racemic mixture of **5** revealed a typical helicene structure with a twisted π-system (ϕa,b–c,d: 23(1)° for the (*P*)-enantiomer and ϕa’,b’–c’,d’: –28(1)° for the (*M*)-enantiomer) and an amide group as a constituent moiety of the molecular framework (Figure 1A).[13]

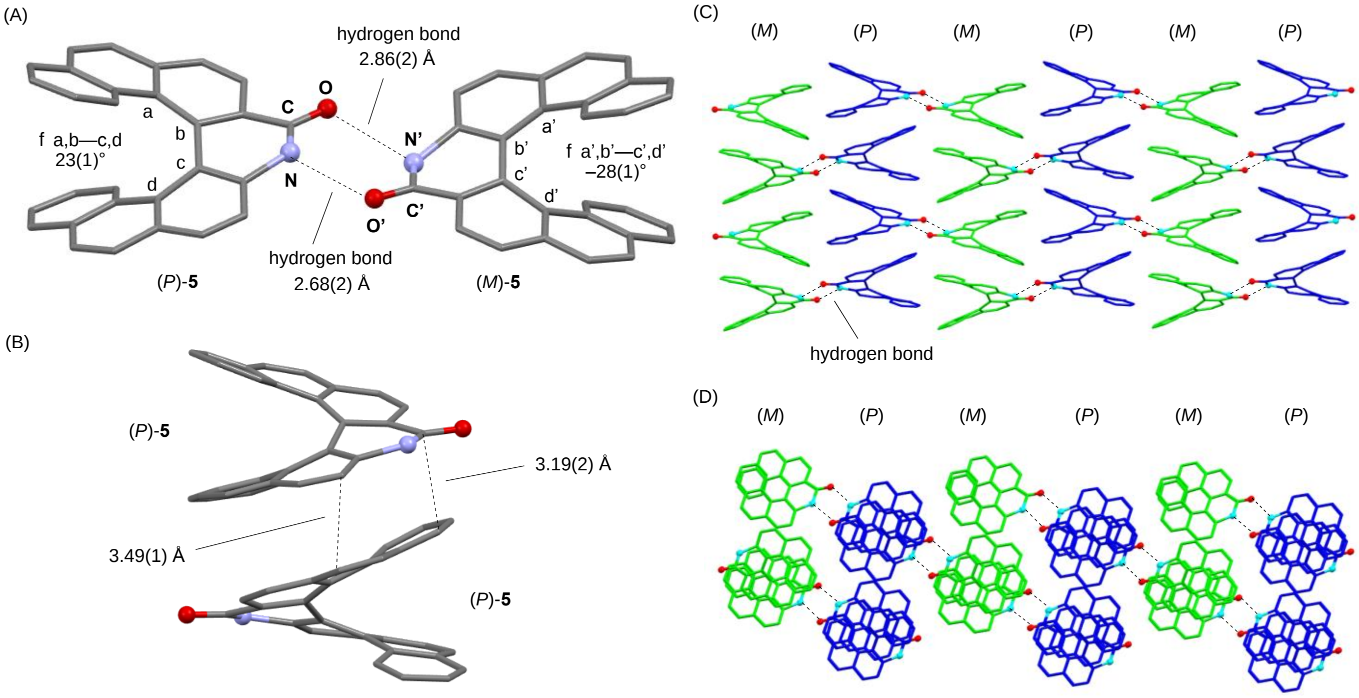


Figure 1. Crystal structure of racemic **5**. Hydrogen atoms are omitted for clarity. (A) Association of (*P*)-**5** and (*M*)-**5** via hydrogen-bonding interactions. (B) π-π Stacking interactions in a homochiral column of (*P*)- **5** (C) Columnar packing viewed along the a-axis of the crystal lattice (D) Columnar packing viewed along the b-axis of the crystal lattice.

Furthermore, it is worth noting that the amide group functions as a molecular recognition moiety that manifests in pairwise association between the (*P*)- and (*M*)-enantiomers via hydrogen-bonding interactions (O···N’ = 2.86(2) Å; O’···N = 2.68(2) Å).

This observation can be considered as a typical feature of amide-functionalized helicenes.[14] This paired complex furthermore forms alternatingly aligned *M*, *P*, *M*, *P* columnar packs (Figures 1C and 1D), in which each column is created by the π-π stacking of a homochiral enantiomer (Figures 1B). This π-π stacking interaction is typically supported by short contacts between the π-faces of (*P*)-**5** (e.g., 3.19(2) Å and 3.49(1) Å) as shown in Figures 1B. Each homochiral column is connected by hydrogen-bonding interactions (Figures 1C and 1D). It should be noted here that columnar aggregates of helical molecules have been recognized as key molecular arrangements for providing unique optical properties.[3a,15,16] The columnar packing of **5** would thus represent an attractive starting point for potential applications in chiral organic materials.

Finally, to evaluate the stability of the helical chirality of **5**, an estimation of the racemization barrier was undertaken using density functional theory (DFT) calculations at the wB97xd/6-311+G(d,p)//B3LYP/6-31G(d,p) level of theory.[17] The results of these calculations showed that 41.4 kcal/mol is required for the racemization to proceed via the C_s-symmetric transition state structure, in which the terminal rings bend to the same sides (Figure 2).[18] This theoretical result confirmed that the helical chirality of **5** is very stable under ambient conditions.

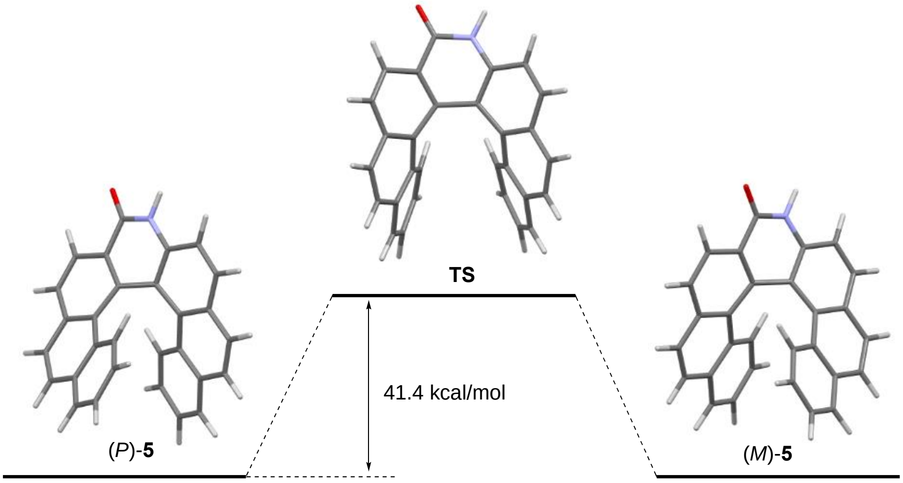


Figure 2. DFT calculations for the racemization of **5**

In conclusion, we have prepared an amide-functionalized [7]helicene-like molecule via an intramolecular amidation. This transformation provides a simple but useful cyclization method for the synthesis of heterohelicene-like molecules. An amide functional group modified at the periphery of the molecular framework was found to be pivotal for the molecular recognition via hydrogen-bonding interactions in the crystal. Further synthetic studies to prepare optically active forms and investigations into the chiroptical properties of these heterohelicene-like molecules are currently in progress in our laboratories.

EXPERIMENTAL

General Methods

NMR spectra were obtained with a JEOL JNM-ECS-400 spectrometer with chemical shifts in ppm (^{1}H NMR in $CDCl_3$: $CHCl_3$ as internal standards, indicating 7.26, tetramethylsilane as internal standards, indicating 0, ^{13}C NMR in $CDCl_3$: $CDCl_3$ as internal standards, indicating 77.0. ^{1}H NMR in acetone-d_6: acetone as internal standards, indicating 2.04, ^{13}C NMR in acetone-d_6: acetone-d_6 as internal standards, indicating 206.5. ^{1}H NMR in DMSO-d_6: DMSO as internal standards, indicating 2.49, ^{13}C NMR in DMSO-d_6: DMSO-d_6 as internal standards, indicating 39.7.). Spin-spin coupling constants are in Hz. IR spectra were recorded with a JASCO FT-IR4200 spectrometer. HRMS was recorded with a Bruker Daltonics impact HD-KC or a JEOL MStation JMS-700 spectrometer. Silica gel column chromatography was carried out by using Silica gel 60 N (spherical, neutral, 63~210 μm, Kanto Chemical Co., Inc.). TLC analysis and PTLC were performed on commercial glass plates bearing a 0.25 mm layer and a 0.5 mm layer of Merck Kiesel–gel 60 F254, respectively. All chemicals and reagents were commercially purchased and used without further purification.

Synthetic Procedures

(*dl*)-Diphenyl 4,4'-biphenanthryl-3,3'-dicarboxylate (**7**):

(*dl*)-Triflate **6**[10] (552 mg, 0.85 mmol. 1.0 equiv.), $Pd(OAc)_2$ (19 mg, 0.085 mmol, 10 mol%) and DPPP (53 mg, 0.128 mmol, 15 mol%) were added to a screw-capped 30 mL reaction tube containing a magnetic stirring bar. The tube was evacuated and backfilled with Argon three times. Phenyl formate (762 μL, 6.79 mmol, 8.0 equiv.) and DIPEA (1.8 mL, 10.2 mmol, 12 equiv.) were added to the tube under a flow of Argon and the tube was equipped with a screw cap. The reaction mixture was heated to 120 °C in an oil bath and stirred for 36 h. The reaction mixture was cooled to rt and diluted with CH_2Cl_2, washed with water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The resulting residue was purified by column chromatography (SiO_2, Hexane : AcOEt = 5 : 1) to afford **7** (170 mg, 34%).

Colorless prisms (*n*-hexane–AcOEt); Mp 229–230 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (2H, d, J = 8.2 Hz), 8.12 (2H, d, J = 8.2 Hz), 7.90–7.80 (6H, m), 7.66 (2H, d, J = 8.7 Hz), 7.37 (2H, t, J = 7.1 Hz), 7.20–6.91 (8H, m), 6.40–6.37 (4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.4, 150.4, 140.6, 136.0, 133.7, 130.8, 130.2, 130.1, 129.9, 129.4, 129.0, 128.9, 127.6, 127.2, 126.8, 126.6, 126.3, 125.4, 121.1; IR (neat) 3057, 1750, 1725, 1587, 1495, 1260, 1189, 1161, 1120, 1049, 1024, 921, 841, 746 cm^{-1}.; HRMS (ESI) *m/z* calcd for $C_{42}H_{26}O_4$ (M+Na)$^+$ 617.1723, found. 617.1721.

(*dl*)-4,4'-Biphenanthryl-3,3'-dicarboxylic acid (**8**):

To a solution of **7** (170 mg, 0.29 mmol, 1.0 equiv.) dissolved in MeOH (20 mL) was added the solution of KOH (651 mg, 11.6 mmol, 40 equiv.) in water (5.0 mL). The resulting mixture was allowed to stir for 48 h under reflux conditions. The resulting mixture was concentrated under reduced pressure to remove solvent, giving crude residue. Then the residue was dissolved in water (50 mL). The aqueous phase was washed by Et_2O (10 mL), and then the aqueous phase was acidified by 6.0 M aq. HCl until the pH turn to be 1~2. The resulting suspension was extracted by AcOEt (15 mL) for three times. The combined organic layer was washed with H_2O, brine, and dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give **8** (108 mg, 82%).

Colorless prisms (AcOEt); Mp 264–265 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.11 (2H, d, *J* = 8.2 Hz), 7.99 (2H, d, *J* = 8.2 Hz), 7.85 (2H, d, *J* = 9.2 Hz), 7.74 (2H, d, *J* = 8.7 Hz), 7.67 (2H, d, *J* = 7.8 Hz), 7.20–7.10 (4H, m), 6.65 (2H, q, *J* = 8.2 Hz); ^{13}C NMR (100 MHz, acetone-d_6) δ 169.3, 142.0, 136.8, 134.8, 132.4, 132.2, 131.0, 130.6, 130.3, 130.0, 128.6, 128.4, 127.6, 127.3, 126.8; IR (KBr) 3050, 1696, 1592, 1556, 1517, 1419, 1375, 1317, 1269, 1227, 1201, 1170, 1068, 1008, 888, 867, 849, 745 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{18}O_4$ (M)$^+$ 442.1205, found. 442.1208.

(*dl*)-3'-(Methoxycarbonyl)-4,4'-biphenanthrene-3-carboxylic acid (**3**):

To a solution of **8** (108 mg, 0.24 mmol, 1.0 equiv.), and Ag_2CO_3 (33 mg, 0.12 mmol, 0.5 equiv.) in acetone (5.0 mL) was added MeI (45 µL, 0.72 mmol, 3.0 equiv.) at rt. After stirring at 40 °C for 12 h, the reaction was diluted by water (20 mL) and quenched with 1.0 M aq. HCl (5.0 mL), and extracted with AcOEt (10 mL) for three times. The combined organic layer was washed with H_2O, brine, and dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The resulted residue was purified by column chromatography (SiO_2, Hexane : AcOEt : AcOH = 100 : 100 : 1) to afford **3** (60 mg, 54%). Colorless prisms (AcOEt); Mp 265–266 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12–8.01 (3H, m), 7.91 (1H, d, *J* = 8.2 Hz), 7.87–7.77 (6H, m), 7.51 (1H, d, *J* = 8.7 Hz), 7.43 (1H, d, *J* = 8.7 Hz), 7.36–7.32 (2H, m), 6.90–6.83 (2H, m), 3.19 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 169.4, 140.4, 139.7, 135.9, 135.7, 133.7, 133.6, 130.9, 130.6, 130.2, 130.1, 130.0, 129.7, 129.5, 129.4, 129.0, 128.9, 127.4, 127.12, 127.09, 126.8, 126.7, 126.59, 126.56, 126.54, 126.34, 126.29, 52.1 (Two carbon signals were overlapped.); IR ($CHCl_3$) 3426, 1691, 1542, 1383, 1266, 1058, 745 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{31}H_{20}O_4$ (M)$^+$ 456.1362, found 456.1362.

Amide-functionalized [7]helicene-like molecule (**5**):

To a solution of **3** (25 mg, 55 µmol, 1.0 equiv.) in toluene (2.0 mL) were added DPPA (17 µL, 77 µmol, 1.4 equiv.) and Et_3N (13 µL, 0.17 mmol, 3.0 equiv.) at 0 °C under argon atmosphere. Then, the mixture was stirred for 1.5 h at 90 °C. After cooling to rt, the mixture was treated with H_2O (1.0 mL) and then the resulted solution was stirred at 80 °C for 42 h. Then the reaction was extracted with AcOEt (5.0 mL) for three times. The combined organic layer was dried over Na_2SO_4, filtered, and evaporated *in vacuo* to give the crude product. The crude product was washed with *n*-hexane-$CHCl_3$ (1 : 6) to afford **5** (11 mg, 51%). Yellow prisms (*n*-hexane-AcOEt); Mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (1H, s), 8.43 (1H, d, J = 8.2 Hz), 8.13 (1H, d, J = 8.2 Hz), 8.07 (1H, d, J = 8.7 Hz), 7.88 (1H, d, J = 8.7 Hz), 7.76–7.69 (3H, mH), 7.49 (1H, d, J = 8.7 Hz), 7.42 (1H, d, J = 7.3 Hz), 7.36 (1H, d, J = 7.8 Hz), 7.05 (1H, d, J = 8.7 Hz), 6.99–6.92 (2H, m), 6.84 (1H, d, J = 8.2 Hz), 6.40–6.30 (2H, m); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.9, 136.8, 134.6, 132.5, 132.3, 132.0, 131.1, 129.8, 129.5, 129.1, 128.8, 128.7, 128.3, 127.5, 127.44, 127.39, 126.7, 126.4, 126.3, 126.25, 126.19, 125.9, 124.2, 124.10, 124.06, 123.4, 116.8, 111.9 (One carbon signal was overlapped.); IR ($CHCl_3$) 3049, 2872, 1657, 1603, 794, 719 cm^{-1}; HRMS (FAB) *m/z* calcd for $C_{29}H_{18}NO$ $(M+H)^+$ 396.1373, found 396.1388.

Crystallographic data for the single crystal of racemic **5** obtained by recrystallization from toluene and *n*-hexane: $C_{29}H_{17}NO$, M = 395.43, monoclinic, $P2_1$, a = 9.0465(2), b = 11.3071(3), c = 19.1900(5) Å, α = 90°, β = 95.411(2)°, γ = 90°, V = 1954.19(8) Å^3, Z = 4, ρ_{calcd} = 1.317 gcm^{-3}, T = 103 K, 22156 reflections measured, 7194 unique. The final R_1 and wR were 0.0587 and 0.1787 (all data). These data have been deposited with the Cambridge Crystallographic Data Center as CCDC 2031916.

Intermediary δ-amino acid **4** was isolated in 1.5 h after Curtius rearrangement and H_2O addition. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (1H, d, J = 8.7 Hz), 8.17–8.00 (1H, m), 7.97–7.81 (5H, m), 7.78–7.69 (2H, m), 7.67–7.62 (1H, m), 7.57–7.52 (1H, m), 7.45 (1H, t, J = 7.6 Hz), 7.30–7.26 (1H, m), 7.10–6.99 (2H, m), 6.86–6.79 (1H, m), 3.41 (2H, s), 3.00 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 143.2, 137.3, 135.6, 134.0, 133.4, 133.2, 131.2, 130.7, 130.5, 130.4, 129.9, 129.5, 129.3, 128.9, 128.4, 127.5, 127.4, 127.2, 127.1, 126.6, 125.9, 125.5, 125.2, 124.3, 121.2, 117.2, 51.8 (Two carbon signals were overlapped.); IR (KBr) 3470, 2960, 2853, 1730, 1603, 1157, 1129, 842, 798, 746 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{21}N_1O_2$ $(M+H)^+$ 428.1645, found. 428.1633.

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12. Intermediary δ-amino acid **4** was detected after Curtius rearrangement and H_2O addition. See, the experimental section.
13. The crystal structure of (*dl*)-**5** is disordered over two positions; only one of the disordered structures is shown in Figure 1. For the full disordered structures, see the Supporting Information. The X-ray data for (*dl*)-**5** has been deposited at the Cambridge Crystallographic Data Center under reference number CCDC 2031916.
14. There is only one precedent for amide-functionalized [7]helicene, which also shows association behavior via hydrogen-bonding interactions through the amide group, which resides on the periphery of the molecular framework. For details, see: ref. 9a.
15. a) T. Verbiest, S. V. Elshocht, M. Kauranen, L. Hellemans, J. Snauwaert, C. Nuckolls, T. J. Katz, and A. Persoons, *Science*, 1998, **282**, 913; b) B. Busson, M. Kauranen, C. Nuckolls, T. J. Katz, and A. Persoons, *Phys. Rev. Lett.*, 2000, **84**, 79; c) T. Verbiest, S. V. Elshocht, A. Persoons, C. Nuckolls, K. E. Phillips, and T. J. Katz, *Langmuir*, 2001, **17**, 4685.
16. For examples of columnar organization of helicenes and heterohelicenes, see: a) M. A. Shcherbina, X.-B. Zeng, T. Tadjiev, G. Ungar, S. H. Eichhorn, K. E. S. Phillips, and T. J. Katz, *Angew. Chem. Int. Ed.*, 2009, **48**, 7837; b) K. Usui, K. Yamamoto, Y. Ueno, K. Igawa, R. Hagihara, T. Masuda, A. Ojida, S. Karasawa, K. Tomooka, G. Hirai, and H. Suemune, *Chem. Eur. J.*, 2018, **24**, 14617; c) T. Hirao, Y. Ono, N. Kawata, and T. Haino, *Org. Lett.*, 2020, **22**, 5294. See also, ref. 7e and ref. 10.
17. For computational details, see the Supporting Information.
18. Following reference discussed about *C*s-symmetric transition state for racemization, see, R. H. Janke, G. Haufe, E.-U. Würthwein, and J. H. Borkent, *J. Am. Chem. Soc.*, 1996, **118**, 6031.