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SYNTHESIS OF AXIALLY CHIRAL BINAPHTHOTHIOPHENE δ-AMINO ACID DERIVATIVES BEARING CHALCOGEN BONDS

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This paper is dedicated to the celebration of Professor Kaoru Fuji on his 80th birthday.

Abstract – Axially chiral binaphthothiophene amino acid was synthesized as a stable artificial δ-amino acid. *N*- and *C*-protected derivatives of this unnatural amino acid were also prepared and applied for derivatization to the dipeptide. The crystal structure of the dipeptide revealed that the carbonyl groups of both the amide and the ester moieties were fixed with naphthothiophene rings in coplanar geometry via intramolecular chalcogen bonds.

Unnatural amino acids have played significant roles as key building blocks for bioactive compounds in the production of small-molecule drugs[1] and artificial peptides in peptide mimetics.[2-4] In catalytic asymmetric synthesis, asymmetric unnatural amino acids possessing central chirality have also been employed as chiral organocatalysts.[5-8] Unnatural amino acids bearing axial chirality have unique structural features, as their chiral environments are different from that of amino acids with central chirality. Although unnatural amino acids have been well developed, the synthesis and application of axially chiral amino acids have not yet been fully exploited.[9,10] Therefore, the development of axially chiral amino acids possessing novel structural features would have a significant impact in the field of medicinal chemistry, peptide mimetics, and catalytic asymmetric synthesis.

We have synthesized axially chiral binaphthyl δ-amino acid (*S*)-**1** and its *N*-protected derivatives bearing aniline-type amines as well as carboxy groups at 2,2'-positions (Figure 1a).[11-14] Furthermore, the *N*-protected derivative of (*S*)-**1** was found to be applicable as a chiral building block for artificial peptides,[11] and a chiral ligand for dirhodium(II) carboxylate catalyst.[13] The structure of **1** was characterized by its axial chirality, which leads the amino and the carboxy groups to locate in perpendicular geometry. Unfortunately, however, the stability of **1** itself was greatly affected by spontaneous lactamization to **2**, and therefore **1** was not stable enough for storage.

On the other hand, we have also reported the synthesis of axially chiral binaphthothiophene dicarboxylic acid (*S*)-**3**, which has the distinct feature of sulfur atoms incorporated into its fused tricyclic π-systems (Figure 1b).[15] The crystal structure of **3** revealed that the carboxy groups were aligned in coplanar geometry with the naphthothiophene rings due to conformational lock via intramolecular chalcogen bonds (S•••O interactions).[16-21]

From both of these studies of axially chiral compounds, we envisaged that binaphthothiophene δ-amino acid (*S*)-**4**, and its derivatives may have characteristic structures due to their axial chirality as well as intramolecular chalcogen bonds (Figure 1b). Herein, we describe the synthesis of (*S*)-**4** and its *C*- and *N*-protected derivatives from (*S*)-**3**, stability of (*S*)-**4**, as well as the structural features of artificial dipeptide composed of **4**.

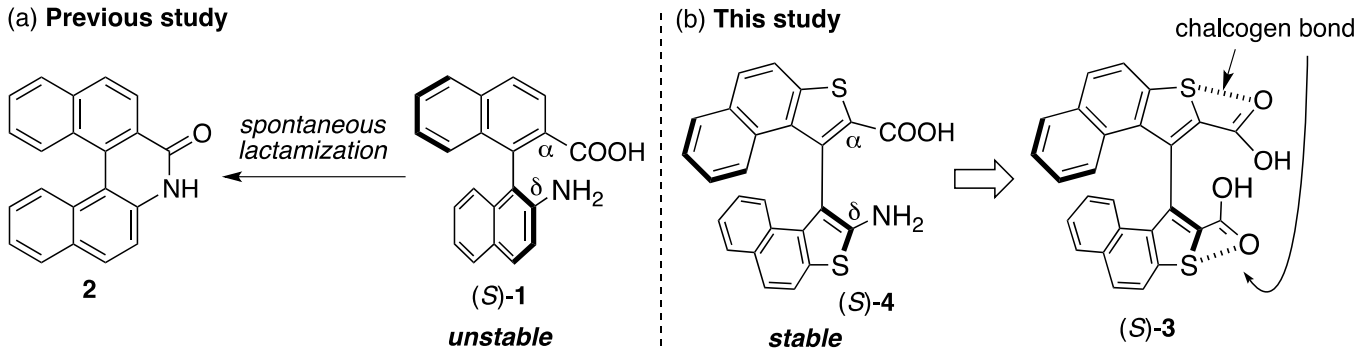
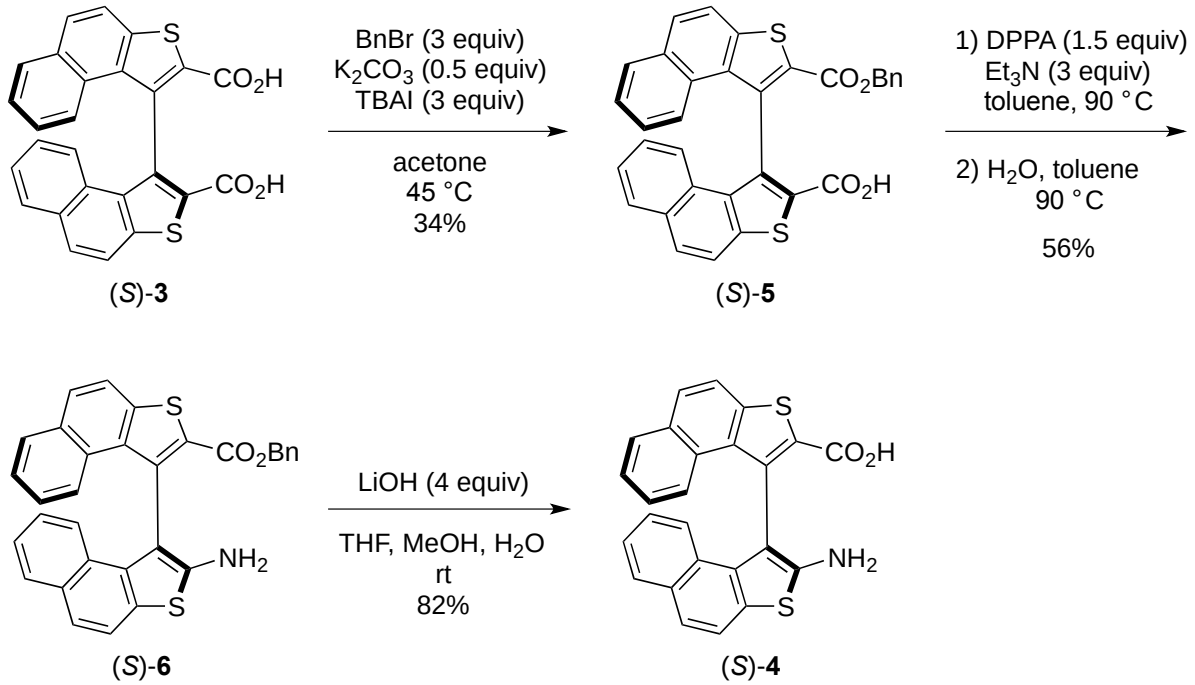


Figure 1. (a) Spontaneous lactamization of (*S*)-**1**. (b) Structure of axially chiral binaphthothiophene δ-amino acid (*S*)-**4** and dicarboxylic acid (*S*)-**3**.

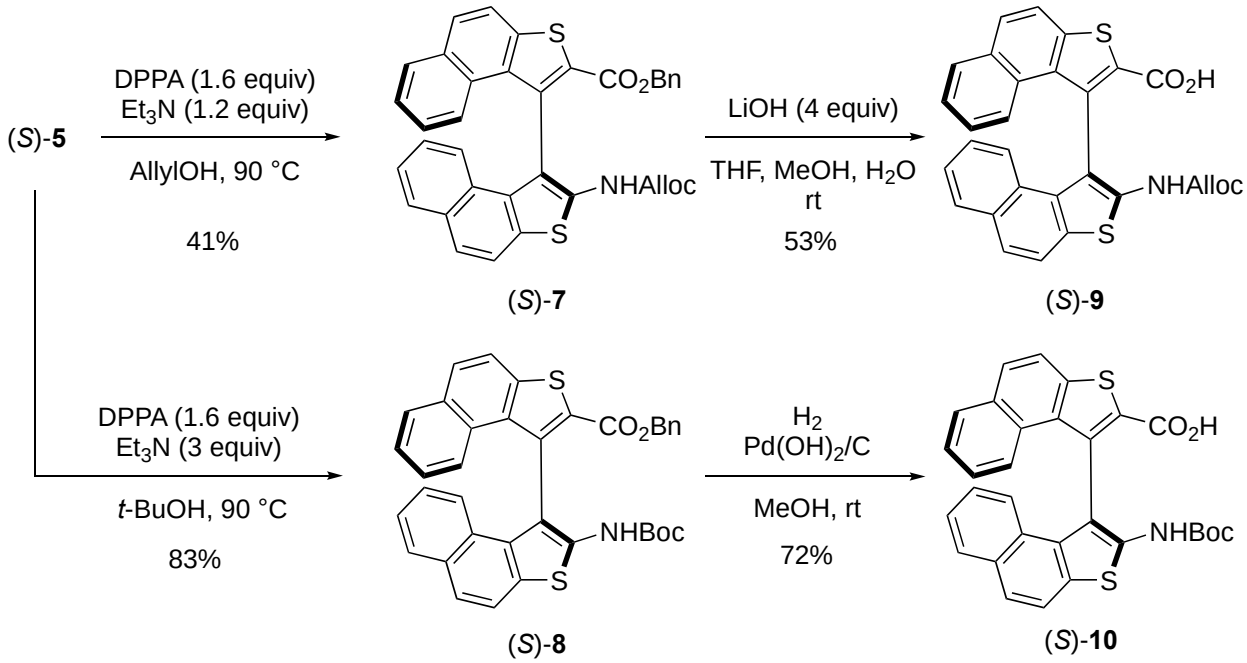
We began the synthesis of (*S*)-**4** and its *C*-protected derivative (*S*)-**6** from *O*-benzylation of (*S*)-**3** (Scheme 1). This monobenzylation was carried out under previously developed conditions for the selective monoesterification of biphenyl as well as binaphthyl dicarboxylic acids.[12] In this case however, the yield obtained was not sufficient (34%) to yield (*S*)-**5**. Curtius rearrangement of (*S*)-**5** in the presence of diphenylphosphoryl azide (DPPA), and subsequent hydrolysis of the isocyanate intermediate with water yielded amino acid benzyl ester (*S*)-**6**. HPLC analysis with chiral stationary phase indicated that

racemization did not occur during Curtius rearrangement. Indeed, (*S*)-**6** was found to be stable without racemization even after heating at 100 °C for 12 h in toluene.



Scheme 1. Synthesis of (*S*)-**4**

Next, hydrolytic cleavage of the benzyl group of (*S*)-**6** yielded axially chiral amino acid (*S*)-**4** in a yield of 82%. In sharp contrast to the case of (*S*)-**1**, gratifyingly, (*S*)-**4** was found to be stable and storable in a refrigerator for at least a month without forming the corresponding lactam.[11]

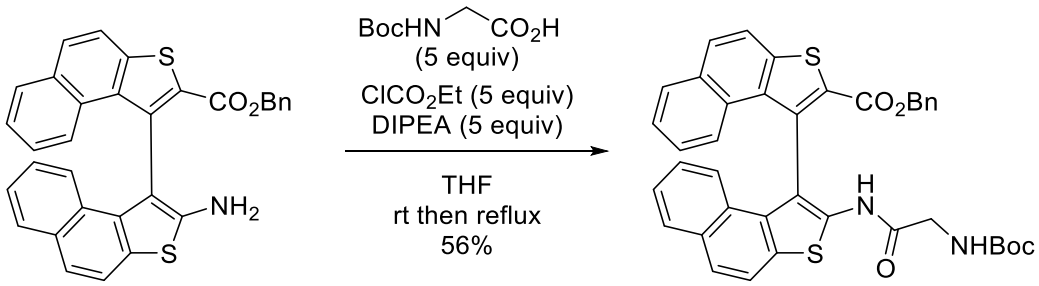


Scheme 2. Transformation to *N*-protected axially chiral binaphthothiophene amino acids

One of the reasons why binaphthothiophene amino acid **4** is more tolerant than **1** toward lactamization may be due to the repulsion between the distal aromatic rings of naphthothiophene moieties during the lactam ring formation. Another reason might be the greater distance in **4** between the carboxy and amino groups caused by the presence of five-membered rings. Intramolecular chalcogen bonding might also contribute to the remoteness of π* orbital of the carbonyl group and lone pair of the amine due to the conformational lock of the carboxy group.

Next, we investigated the synthesis of *N*-protected binaphthothiophene amino acids, which could be useful as chiral building blocks for artificial peptides (Scheme 2). Curtius rearrangement of (*S*)-**5** and subsequent treatment of allyl alcohol or *tert*-butyl alcohol yielded (*S*)-**7** and (*S*)-**8** without racemization in 41% and 83% yields, respectively. The ester groups of (*S*)-**7** and (*S*)-**8** were successively cleaved to give *N*-Alloc and *N*-Boc binaphthothiophene amino acids (*S*)-**9** and (*S*)-**10**, respectively.

As a preliminary application of the protected binaphthothiophene amino acid, *C*-protected analog **6** was used as a chiral building block (Scheme 3). Condensation of racemic **6** with *N*-Boc glycine by mixed anhydride method yielded dipeptide **11**.



6 **11**

Scheme 3. Synthesis of dipeptide **11**

X-Ray analysis revealed that **11** exhibited some characteristic properties of a binaphthothiophene peptide. As shown in Figure 2, the two naphthothiophene rings were twisted in a nearly perpendicular geometry around the chiral axis with dihedral angles of 95.8(3)° (*ϕa,b-c,d*), which create the perpendicular arrangement of the carboxy and aniline-type amino groups. The most remarkable structural features of **11** are short contacts between the sulfurs in the naphthothiophene rings and the oxygens of the carbonyl groups of the ester moiety (1,4-type S•••O´ short contact: 2.913(2) Å) and the amide moiety (1,5-type S´•••O´´ short contact: 2.688(3) Å) (Figure 2a).[15] The distances of both contacts are shorter than the sum of the van der Waals radii of sulfur and oxygen atoms (3.32 Å). This indicated formation of chalcogen bonds in an intramolecular fashion.

These chalcogen bonds were found to work as a conformational lock around the C–C bonds tethering the carboxy group as well as the amide group to the naphthothiophene rings. This is typically shown by the

coplanar geometries of the ester and amide groups toward the π-faces of the naphthothiophene rings without any remarkable twist (ϕS-C-C´-O´ = 6.3(3)° and ϕS´-C´´-N-C´´´ = –5.2(3)°). These coplanar arrangements are secured through three bonds (C´´-N, N-C´´´, and C´´´-C´´´´) towards the *N*-terminus and two bonds (C-C´ and C´-O) towards the *C*-terminus from naphthothiophene moieties, due to the conformational lock (Figures 2a and 2b). These conformational constraints due to chalcogen bonds allow the axially chiral binaphthothiophene amino acid **4** to be a promising chiral building block for structurally defined artificial peptides.

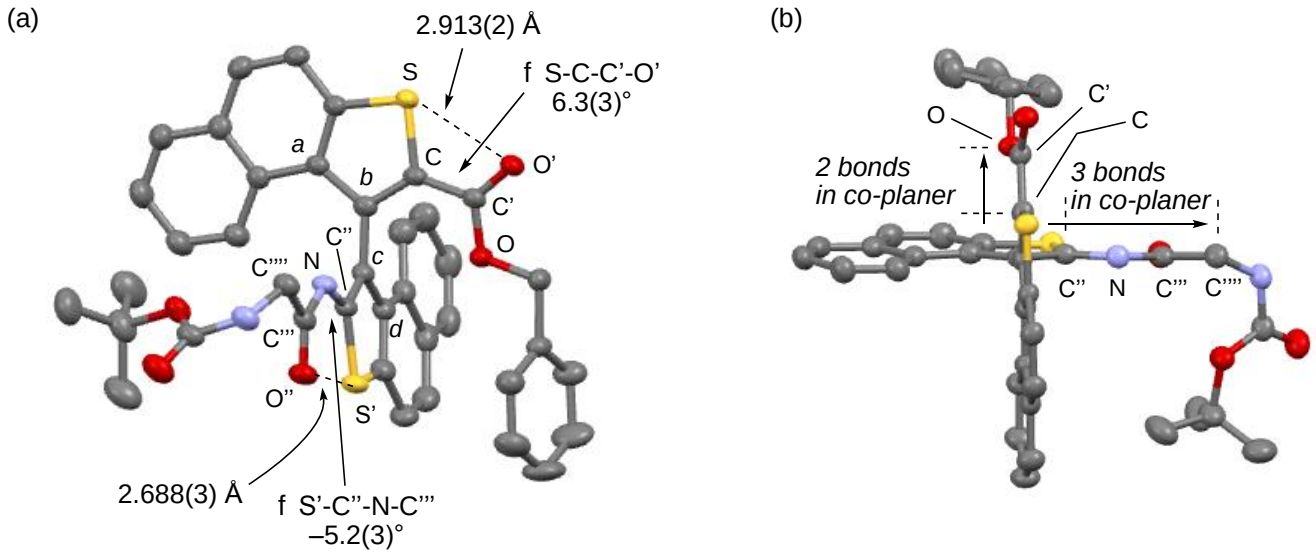


Figure 2. (a) Side view and (b) top view of the crystal structure of racemic **11** (60% probability)

In conclusion, the preparation of axially chiral binaphthothiophene δ-amino acid (*S*)-**4** and its derivative **11** as stable, axially chiral δ-amino acids, was achieved. The carboxy group and the amide group in dipeptide **11** were almost coplanar with the naphthothiophene rings due to sulfur and oxygen interacting through chalcogen bonds. These novel, axially chiral amino acids and peptides with unique structural features would be useful as chiral building blocks, ligands, as well as organocatalysts. Applications of these molecules is currently under investigation.

EXPERIMENTAL

General Methods

NMR spectra were obtained with a Bruker Ascend 500 spectrometer, a JEOL JNM-ECS-400 spectrometer, and a JEOL JNM-ECA-600 spectrometer, with chemical shifts in ppm. ^{1}H NMR in $CDCl_3$: $CHCl_3$ was used as an internal standard, indicating 7.26; tetramethylsilane as an internal standard, indicating 0; and ^{13}C NMR in $CDCl_3$: $CDCl_3$ as an internal standard, indicating 77.1. Spin-spin coupling constants are in Hz. IR spectra were recorded with a JASCO FT-IR4200 spectrometer or a JASCO

FT-IR4600 spectrometer. HRMS was recorded with a Bruker Daltonics impactHD-KC or Shimazu LSMS-IT-TOF. Specific rotation was measured with a JASCO P-2200 Polarimeter. 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

(*S*)-2'-[(Benzyloxy)carbonyl]-(1,1'-binaphtho[2,1-*b*]thiophene)-2-carboxylic acid ((*S*)-**5**):

To a mixture of (*S*)-**3**[15] (2.20 g, 4.84 mmol), K_2CO_3 (334 mg, 2.42 mmol), and TBAI (5.36 g, 14.5 mmol) in acetone (50 mL) was added benzyl bromide (1.72 mL, 14.5 mmol) at rt. After being stirred for 12 h at 45 °C, the reaction was quenched with sat. aq. NH_4Cl, and extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, *n*-hexane/AcOEt = 5/1 to 1/1) to give (*S*)-**5** (890 mg, 34%).

Yellow prisms (*n*-hexane–AcOEt); Mp 110–112 ºC; $[\alpha]_D^{20}$ –86.6 (c 0.6, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.93 (1H, d, *J* = 12.4 Hz), 4.95 (1H, d, *J* = 12.4 Hz), 6.82–6.86 (2H, m), 6.96 (1H, ddd, *J* = 1.4, 6.9, 8.5 Hz), 7.03 (1H, ddd, *J* = 1.4, 6.9, 8.5 Hz), 7.10–7.14 (2H, m), 7.15–7.18 (1H, m), 7.18–7.22 (1H, m), 7.23–7.29 (2H, m), 7.33 (1H, ddd, *J* = 1.1, 6.9, 8.0 Hz), 7.81–7.89 (5H, m), 7.97 (1H, d, *J* = 8.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 67.2, 120.8, 122.5, 122.6, 125.7, 125.8, 127.4, 127.5, 127.9, 128.0 (2C), 128.1, 128.4 (2C), 129.1, 129.2, 129.15, 129.18, 129.3, 129.6, 130.58, 130.63, 131.96, 131.98, 133.6, 133.7, 135.0, 139.4, 141.0, 141.5, 141.6, 162.3, 167.4; IR (KBr) cm^{-1}: 3059, 2602, 1681, 1481, 1434, 1316, 1271, 1227, 907, 733; HRMS (ESI) calcd for $C_{33}H_{20}NaO_4S_2$ $[M+Na]^+$ 567.0695, found 567.0693.

(*S*)-Benzyl 2'-amino-(1,1'-binaphtho[2,1-*b*]thiophene)-2-carboxylate ((*S*)-**6**):

To a solution of (*S*)-**5** (100 mg, 0.184 mmol) and Et_3N (76.0 μL, 0.551 mmol) in toluene (20 mL) was added DPPA (59.2 μL, 0.275 mmol) at rt under Ar atmosphere. After being stirred for 1 h at 90 °C, water (0.331 mL, 18.4 mmol) was added. The reaction mixture was stirred for 15 h at 90 °C. The reaction was quenched with sat. aq. NH_4Cl, and extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, *n*-hexane/AcOEt = 4/1) to give (*S*)-**6** (53.0 mg, 56%). Optical purity of (*S*)-**6** (>99% ee) was confirmed by HPLC analysis with a chiral stationary phase (HPLC conditions: COSMOSIL CHIRAL5B (0.46 × 25 cm), *n*-hexane/*i*-PrOH = 80/20, 1.0 mL/min, 320 nm, t_R = 6.7 min (*S*), 8.9 min (*R*)).

Yellow amorphous; $[\alpha]_D^{20}$ –28.6 (c 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (2H, s), 5.03 (2H, s), 6.86–6.97 (3H, m), 7.12–7.30 (6H, m), 7.39 (1H, ddd, *J* = 1.1, 7.0, 8.1 Hz), 7.61 (1H, d, *J* = 8.6 Hz), 7.74 (1H, d, *J* = 8.7 Hz), 7.80 (1H, d, *J* = 8.0 Hz), 7.84–7.93 (3H, m), 7.97 (1H, d, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.2, 111.8, 120.6, 120.7, 122.6, 122.8, 122.9, 124.6, 125.7, 126.0, 127.8, 127.9 (2C), 128.0, 128.4 (2C), 128.6, 128.7, 129.0, 129.5, 131.1, 131.4, 132.0, 132.3, 133.8, 134.1, 135.2, 138.5, 141.3, 146.8, 162.4 (One carbon signal was further overlapped.); IR (Neat) cm^{-1}: 3351, 3055, 1686, 1492, 1406, 1219, 1065, 906, 802, 732; HRMS (ESI) calcd for $C_{32}H_{21}NNaO_2S_2$ $[M+Na]^+$ 538.0906, found 538.0913.

(*S*)-2'-Amino-(1,1'-binaphtho[2,1-*b*]thiophene)-2-carboxylic acid ((*S*)-**4**):

To a solution of (*S*)-**6** (20.0 mg, 38.8 μmol) in THF/MeOH/H_2O (2/1/1, 4.0 mL) was added LiOH•H_2O (6.5 mg, 0.16 mmol) at rt. After being stirred for 12 h at rt, the reaction was quenched with 2 *N* aq. HCl, and extracted with AcOEt. The organic layer was washed with brine, and dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a residue. The residue was purified by preparative TLC (SiO_2, *n*-hexane: AcOEt = 1:2) to yield (*S*)-**4** (13.6 mg, 82%).

Yellow amorphous; $[\alpha]_D^{22}$ –25.4 (c 0.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (1H, t, *J* = 7.8 Hz), 7.03–7.15 (3H, m), 7.30 (1H, ddd, *J* = 1.2, 7.0, 8.0 Hz), 7.53 (1H, d, *J* = 8.7 Hz), 7.65–7.75 (3H, m), 7.79 (1H, dd, *J* = 1.3, 8.1 Hz), 7.82–7.90 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 110.8, 120.4, 120.7, 122.4, 122.6, 123.1, 124.7, 125.8, 126.0, 127.8, 128.59, 128.63, 128.8, 128.9, 129.7, 130.7, 131.0, 131.9, 132.2, 133.6, 133.7, 139.0, 141.7, 147.2, 165.3. IR (Neat) cm^{-1}: 3443, 3341, 2961, 1657, 1258, 797, 750. HRMS (ESI) calcd for $C_{25}H_{15}NNaO_2S_2$ $[M+Na]^+$ 448.0436, found 448.0434.

(*S*)-Benzyl 2'-{[(allyloxy)carbonyl]amino}-(1,1'-binaphtho[2,1-*b*]thiophene)-2-carboxylate ((*S*)-**7**):

To a solution of (*S*)-**5** (20 mg, 0.18 mmol) and Et_3N (31 μL, 0.22 mmol) in allyl alcohol (4.0 mL) was added DPPA (59 μL, 0.28 mmol) at rt under Ar atmosphere. After being stirred for 12 h at 90 °C, the reaction was quenched with sat. aq. NH_4Cl, and extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a residue. The residue was purified by preparative TLC (SiO_2, *n*-hexane/AcOEt = 3/1) to give (*S*)-**7** (9.1 mg, 41%). Optical purity of (*S*)-**7** (>99% ee) was confirmed by HPLC analysis with a chiral stationary phase (HPLC conditions: Chiralpak AD-H (0.46 × 25 cm), *n*-hexane/*i*-PrOH = 80/20, 0.5 mL/min, 254 nm, t_R = 31.9 min (*R*), 36.2 min (*S*)).

Yellow prisms (*n*-hexane–AcOEt); Mp 83–84 °C; $[\alpha]_D^{20}$ –58.0 (c 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50–4.65 (2H, m), 4.95–5.05 (2H, m), 5.15–5.35 (2H, m), 5.73–5.93 (1H, m), 6.82 (1H, br s), 6.88 (2H, d, *J* = 7.2 Hz), 6.96 (1H, ddd, *J* = 1.4, 6.9, 8.5 Hz), 7.07–7.19 (4H, m), 7.19–7.25 (1H, m),

7.25–7.31 (1H, m), 7.38 (1H, ddd, *J* = 1.2, 7.0, 8.1 Hz), 7.61 (1H, d, *J* = 8.6 Hz), 7.72 (1H, d, *J* = 8.7 Hz), 7.82–7.91 (3H, m), 7.93 (1H, d, *J* = 8.8 Hz), 7.98 (1H, d, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.1, 67.4, 115.1, 119.6, 120.6, 120.7, 122.4, 122.7, 124.5, 124.9, 126.2, 128.0 (2C), 128.2, 128.4 (2C), 128.9, 129.1, 129.2, 129.8, 130.8, 131.4, 131.7, 131.8, 132.0, 132.1, 132.2, 133.5, 134.9, 136.5, 136.9, 141.5, 152.7, 162.1 (Two carbon signals were further overlapped.); IR (KBr) cm^{-1}: 3405, 3279, 3058, 1722, 1577, 1543, 1499, 1209, 1065, 908, 733; HRMS (ESI) calcd for $C_{36}H_{25}NNaO_4S_2$ $[M+Na]^+$ 622.1117, found 622.1116.

(*S*)-Benzyl 2'-[(*tert*-butoxycarbonyl)amino]-(1,1'-binaphtho[2,1-*b*]thiophene)-2-carboxylate ((*S*)-**8**):

To a solution of (*S*)-**5** (100 mg, 0.18 mmol) in *t*-BuOH (10 mL) were added DPPA (59 μL, 0.28 mmol) and Et_3N (77 μL, 0.55 mmol) at rt under Ar atmosphere. After being stirred for 12 h at 90 °C, the reaction was quenched with sat. aq. NH_4Cl, and extracted with AcOEt. The organic layer was washed with water and brine, and dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a residue. The residue was purified by preparative TLC (SiO_2, *n*-hexane: AcOEt = 3:1) to afford (*S*)-**8** (93 mg, 83%). Optical purity of (*S*)-**8** (>99% ee) was confirmed by HPLC analysis with a chiral stationary phase (HPLC conditions: Chiralpak AD-H (0.46 × 25 cm), *n*-hexane/*i*-PrOH = 80/20, 1.0 mL/min, 254 nm, t_R = 8.0 min (*S*), 10.3 min (*R*)).

Yellowish green amorphous; $[\alpha]_D^{21}$ –3.2 (c 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (9H, s), 4.95 (1H, d, *J* = 12.2 Hz), 5.00 (1H, d, *J* = 12.2 Hz), 6.57 (1H, br s), 6.86 (2H, d, *J* = 7.5 Hz), 6.92 (1H, ddd, *J* = 1.3, 6.8, 8.4 Hz), 7.09–7.15 (4H, m), 7.17–7.22 (1H, m), 7.23–7.27 (1H, m), 7.37 (1H, ddd, *J* = 1.2, 7.0, 8.0 Hz), 7.63 (1H, d, *J* = 8.6 Hz), 7.68 (1H, d, *J* = 8.7 Hz), 7.82 (1H, d, *J* = 7.9 Hz), 7.85 (1H, d, *J* = 8.7 Hz), 7.87 (1H, d, *J* = 7.9 Hz), 7.93 (1H, d, *J* = 8.8 Hz), 7.99 (1H, d, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2 (3C), 67.3, 82.3, 113.9, 120.5, 120.6, 122.55, 122.63, 124.0, 124.6, 125.9, 126.1, 127.9 (2C), 128.0, 128.1, 128.4 (2C), 128.7, 128.9, 129.1, 129.7, 130.8, 131.3, 131.85, 131.92, 132.1, 133.6, 134.8, 137.0, 137.1, 141.4, 152.0, 162.2 (One carbon signal was further overlapped.); IR (KBr) cm^{-1}: 1721, 1689, 1541, 1496, 1263, 1156, 1066, 804, 757; HRMS (ESI) calcd for $C_{37}H_{29}NNaO_4S_2$ $[M+Na]^+$ 638.1430, found 638.1465.

(*S*)-2'-{[(Allyloxy)carbonyl]amino}-(1,1'-binaphtho[2,1-*b*]thiophene)-2-carboxylic acid ((*S*)-**9**):

To a solution of (*S*)-**7** (71 mg, 0.12 mmol) in THF/MeOH/H_2O (2/1/1, 4.0 mL) was added LiOH•H_2O (20 mg, 0.47 mmol) at rt. After being stirred for 3 h at rt, the reaction was quenched with 2 *N* aq. HCl, and extracted with AcOEt. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a residue. The residue was purified by preparative TLC (SiO_2, *n*-hexane: AcOEt = 1:2) to yield (*S*)-**9** (31 mg, 53%).

Yellow amorphous; $[\alpha]_D^{21}$ –62.5 (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (2H, s), 5.10–5.27 (2H, m), 5.72–5.85 (1H, m), 6.81 (1H, br s), 6.89 (1H, t, *J* = 7.7 Hz), 7.04 (1H, d, *J* = 8.5 Hz), 7.08 (1H, t, *J* = 7.8 Hz), 7.21 (1H, t, *J* = 7.5 Hz), 7.36 (1H, t, *J* = 7.5 Hz), 7.51 (1H, d, *J* = 8.6 Hz), 7.70 (1H, d, *J* = 8.7 Hz), 7.79 (1H, d, *J* = 8.1 Hz), 7.85 (1H, d, *J* = 8.0 Hz), 7.87–7.99 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.0, 114.7, 119.5, 120.5, 120.6, 122.4, 122.5, 124.5, 124.8, 126.2, 128.0, 128.8, 129.0, 130.1, 130.7, 131.2, 131.6, 131.9, 132.0, 132.2, 133.5, 136.5, 138.2, 142.0, 152.7, 166.1 (Three carbon signals were further overlapped.); IR (KBr) cm^{-1}: 3282, 2925, 1703, 1680, 1577, 1543, 1501, 1259, 1063, 802; HRMS (ESI) calcd for $C_{29}H_{19}NNaO_4S_2$ $[M+Na]^+$ 532.0648, found 532.0645.

(*S*)-2'-[(*tert*-Butoxycarbonyl)amino]-(1,1'-binaphtho[2,1-*b*]thiophene)-2-carboxylic acid ((*S*)-**10**):

To a solution of (*S*)-**8** (108 mg, 0.176 mmol) in MeOH (5.0 mL) was added Pd/C (11 mg) at rt. After being stirred under H_2 atmosphere for 12 h at rt, the reaction mixture was filtered, and the filtrate was concentrated *in vacuo* to give (*S*)-**10** (70 mg, 72%).

Yellow amorphous; $[\alpha]_D^{21}$ –5.8 (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (9H, s), 6.66 (1H, br s), 6.89 (1H, ddd, *J* = 1.3, 6.8, 8.4 Hz), 7.04 (1H, d, *J* = 8.5 Hz), 7.11 (1H, t, *J* = 7.8 Hz), 7.21 (1H, ddd, *J* = 1.2, 6.9, 8.1 Hz), 7.37 (1H, t, *J* = 7.5 Hz), 7.57 (1H, d, *J* = 8.6 Hz), 7.70 (1H, d, *J* = 8.7 Hz), 7.80 (1H, d, *J* = 8.0 Hz), 7.85 (1H, d, *J* = 8.0 Hz), 7.88–7.97 (3H, m), 9.89 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1 (3C), 82.4, 113.3, 120.46, 120.52, 122.4, 122.5, 124.1, 124.6, 126.0, 126.1, 128.1, 128.7, 128.9, 130.0, 130.3, 130.7, 131.1, 131.8, 132.0, 133.6, 136.9, 138.7, 142.0, 152.0, 167.0 (Two carbon signals were further overlapped.); IR (KBr) cm^{-1}: 3412, 2979, 1682, 1572, 1542, 1497, 1432, 1247, 1156, 803, 756; HRMS (ESI) calcd for $C_{30}H_{23}NNaO_4S_2$ $[M+Na]^+$ 548.0961, found 548.0980.

Benzyl 2'-{2-[(*tert*-butoxycarbonyl)amino]acetamido}-(1,1'-binaphtho[2,1-*b*]thiophene-2-carboxylate (**11**):

To a solution of *N*-Boc glycine (335 mg, 1.9 mmol) and DIPEA (0.32 mL, 1.8 mmol) in THF (10 mL) was added a solution of ethyl chloroformate (0.18 mL, 1.9 mmol) in THF (0.1 mL) at 0 ºC. After being stirred for 30 min at the same temperature, racemic **6** (197 mg, 0.382 mmol) in THF (10 mL) was added dropwise and stirred for 12 h at rt, then refluxed for 4 h. The reaction was quenched with sat. aq. NH_4Cl and extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, *n*-hexane/AcOEt = 5/1) to give **11** (144 mg, 56%).

Colorless prisms (CH_2Cl_2–*n*-hexane); Mp 222–224 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (9H, s), 3.57–3.69 (2H, m), 4.69 (1H, br s), 4.93 (1H, d, *J* = 12.2 Hz), 5.03 (1H, d, *J* = 12.2 Hz), 6.86–6.97 (3H, m), 7.02–7.08 (1H, m), 7.10–7.18 (3H, m), 7.18–7.23 (1H, m), 7.23–7.30 (1H, m), 7.31–7.38 (1H, m), 7.49

(1H, d, J = 8.7 Hz), 7.72 (1H, d, J = 8.7 Hz), 7.81–7.93 (4H, m), 7.97 (1H, d, J = 8.7 Hz), 8.62 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ28.1 (3C), 41.1, 67.4, 80.7, 116.4. 120.6, 120.7, 122.5, 122.8, 124.8, 124.9, 126.1, 126.2, 128.0, 128.2 (2C), 128.5 (2C), 128.9, 129.0, 129.3, 129.7, 130.8, 131.7, 132.0, 132.1, 132.8, 133.6, 135.0, 135.4, 136.9, 141.5, 156.1, 162.1, 166.6 (Two carbon signals were further overlapped.); IR (KBr) cm^{-1}: 3363, 3299, 1720, 1694, 1574, 1502, 1261, 1066, 802; HRMS (ESI) calcd for $C_{39}H_{33}N_2O_5S_2$ $[M+Na]^+$ 695.1645, found 695.1648.

Crystallographic data for the single crystal of **11** obtained by recrystallization from CH_2Cl_2 and *n*-hexane: $C_{39}H_{32}N_2O_5S_2$, M = 672.78, 0.18 × 0.08 × 0.05 mm^3, Triclinic, *P*-1 (#2), a = 11.0505(2), b = 12.2836(3), c = 14.4309(3) Å, α = 67.8460(10)°, β = 69.471(2)°, γ = 79.494(2)°, V = 1696.19(7) Å^3, Z = 2, ρ_{calcd} = 1.317 gcm^{-3}, T = 103(2) K, 33138 reflections measured, 6943 unique. The final R_1 and wR were 0.0623 and 0.1658 (all data). These data have been deposited with the Cambridge Crystallographic Data Center as CCDC 1914808.

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