Chiral separation by terminal chirality triggered P-helical quinoline oligoamide foldamer

Hiroki Noguchi[1,2,3] · Makoto Takafuji[1] · Victor Maurizot[2,3] · Ivan Huc[**2,3] · Hirotaka Ihara[*1,4]

[1]Department of Applied Chemistry and Biochemistry, Kumamoto University, 2-39-1 Chuoku, Kurokami, Kumamoto 860-8555, Japan

[2]University of Bordeaux, CBMN (UMR 5248), Institut Européen de Chimie Biologie, 2rue Escarpit 33600 Pessac, France

[3] CNRS, CBMN (UMR 5248), 2 rue Escarpit 33600 Pessac, France

[4] Kumamoto Institute for Photo-electro Organics (PHOENICS), 3-11-38 Higashimachi, Kumamoto, Japan

[*]Corresponding author. Tel: +81-96-342-3661 Fax: +81-96-342-3662

[**]Corresponding author. Tel: +33-540-002-219 Fax: +33-540-002-215

E-mail address:
ihara@kumamoto-u.ac.jp (H. Ihara),
i.huc@iecb.u-bordeaux.fr (I. Huc)

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1. Synthetic Schemes

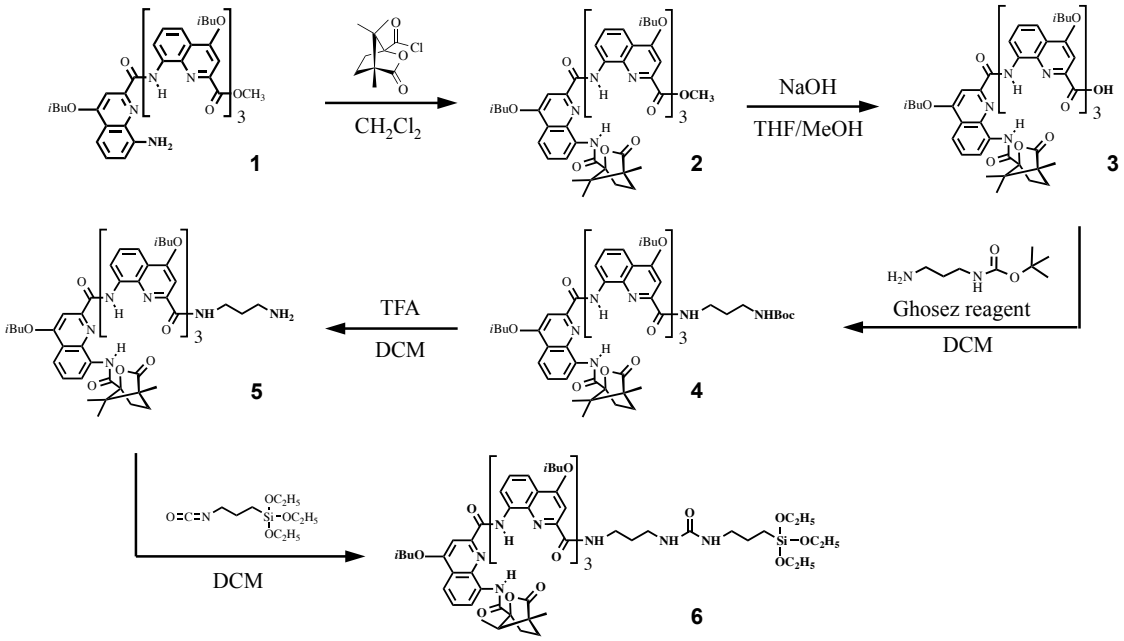

Fig. S1 Synthetic scheme of P-helical tetrameric quinoline oligo amide with silane coupling agent.

2. Synthetic Methods

Synthesis of **2**

Compound **1** was synthesized according to previous report. To an ice cold mixture of **1** (2.00 g, 2.00 mmol) and *N,N*-diisopropylethylamine (DIPEA) (0.70 mL, 4.00 mmol) in dry DCM (40 mL) was added a solution of (1S)-(-)- camphanyl chloride (0.43 mg, 2.00 mmol) in dry $CHCl_3$ (1 mL) dropwise under an argon atmosphere. After 10 min, the ice bath was removed and the reaction mixture was stirred at room temperature overnight. Solvents were removed under reduced pressure and the residue was dissolved in MeOH to yield compound **2** as a yellow precipitate (2.29 g, 97 %).

1H NMR (300 MHz, CDCl3): δ 12.39 (s, 1H), 11.80 (s, 1H), 11.73 (s, 1H), 9.86 (s, 1H), 8.96 (d, J = 7.55 Hz, 1H), 8.47 (d, J = 6.42 Hz, 1H), 7.95-7.94 (m, 1H), 7.92-7.90 (m, 2H), 7.89-7.88 (dd, J = 1.13, 6.04 Hz, 1H), 7.84-7.82 (dd, J = 1.13, 5.29 Hz, 1H), 7.62-6.79 (m, 2H), 7.56 (d, J = 3.02 Hz, 1H) 7.34 (s, 1H), 7.21-7.14 (m, 2H), 6.72 (s, 1H), 6.61 (s, 1H), 4.39-4.32 (m, 1H), 4.13-4.08 (m, 3H), 3.85 (s, 1H), 3.83 (s, 1H), 3.80 (d, J = 1.89 Hz, 1H), 3.78 (d, J = 1.51 Hz, 1H), 3.45 (s, 3H), 2.47-2.21 (m, 5H), 2.14-2.06 (m, 1H), 1.76-1.67 (m, 1H), 1.60-1.56 (m, 1H), 1.24-1.12 (m, 27H), 0.81-0.78 (m, 1H), 0.73 (s, 3H), 0.71 (s, 3H), 0.31 (s, 3H). 13C NMR (75 MHz, CDCl3) δ 176.8, 166.3, 166.2, 163.7, 163.1, 162.9, 162.8, 151.4, 147.5, 140.0, 138.8, 134.7, 133.6, 127.9, 127.3, 122.3, 118.7, 118.2, 117.1, 116.6, 101.3, 99.4, 92.2, 77.5, 77.2, 77.1, 76.6, 75.4, 75.1, 55.1, 54.3, 52.7, 30.2, 29.0, 28.3, 28.2, 19.3, 19.2, 16.7, 16.6, 9.72. HRMS: (ESI) m/z calculated for [C67H67N8O12]+ 1181.36; found 1181.56

Synthesis of 3

Compound **2** 1.50 g (1.27 mmol) was dissolved in 240 mL THF and MeOH mixture (7/1=v/v). NaOH 0.15 g (3.81 mmol) aqueous solution (20 mL) added slowly in Compound 2 solution and the mixture was stirred for 2 h at room temperature. 5wt% citric acid solution was carefully added to acidify to pH 5, then, reaction solvent was evaporated by rotary evaporator and DCM was added. Mixture was transferred to separation funnel and organic layer was removed. The aqueous layer was extracted a further two times with DCM and the combined organic layers washed twice H_2O, once with brine, dried over $MgSO_4$ and evaporated under reduced pressure to yield compound as white solid. (1.42 g, 94 %).

1H NMR (300 MHz, CDCl3): δ 12.26 (s, 1H), 11.75 (s, 1H), 11.27 (s, 1H), 9.87 (s, 1H), 8.98 (d, J = 7.55 Hz, 1H), 8.58 (d, J = 6.42 Hz, 1H), 8.01 (d, J = 1.13 Hz, 1H), 7.98 (d, J = 1.51 Hz, 1H), 7.93-7.83 (m, 5H), 7.70 (s, 1H), 7.61 (dd, J = 7.93, 23.79 Hz, 2H), 7.29 (s, 1H), 7.20-7.25 (t, 1H), 6.75 (s, 1H), 6.70 (s, 1H), 5.23 (s, 1H), 4.31-4.29 (m, 1H), 4.25-4.20 (m, 1H), 4.16-4.06 (m, 2H), 3.87-3.83(m, 4H), 3.70-3.65 (m, 1H), 2.44-2.25 (m, 5H), 2.09 (s, 4H), 1.79-1.75 (m, 1H), 1.70-1.65 (m, 1H), 1.23-1.12 (m, 37H), 0.81-0.78 (m, 1H), 0.73 (s, 3H), 0.71 (s, 3H), 0.31 (s, 3H). 13C NMR (75 MHz, CDCl3) δ 176.5, 164.7, 164.0, 163.8, 163.4, 163.0, 162.3, 160.9, 160.6, 151.6, 150.4, 148.3, 144.5, 138.0, 137.9, 137.4, 137.4, 134.2, 133.1, 132.9, 132.4, 127.5, 126.4, 126.2, 122.3, 122.0, 121.8, 117.9, 116.9, 116.8, 116.6, 116.4, 116.3, 115.7, 99.5, 99.4, 98.6, 97.9,

91.8, 78.2, 77.4, 77.2, 77.0, 76.6, 76.4, 75.4, 75.4, 75.1, 54.7, 54.2, 30.3, 29.7, 29.1, 28.7, 28.2, 28.2, 28.1, 28.0, 24.8, 19.4, 19.4, 19.3, 19.2, 16.2, 16.1, 9.6. HRMS: (ESI) m/z calculated for [C66H70N8O12]+ 1167.51; found 1167.53

Synthesis of N-Boc-1,3-propanediamine

Di-*tert*-butyl dicarbonate (1.36 g, 6.26 mmol) was dissolved in dry $CHCl_3$ and added dropwise over 2 h period to 1,3-diaminepropane (2.61 mL, 31.3 mmol) was dissolved in 120 mL dry $CHCl_3$ and stirred on ice bath. The reaction mixture was stirred over night at room temperature and filtered. The filtrate was concentrated under vacuum and the resulting oil dissolved in EtOAc (400 mL) was washed with saturated brine (150 mL), dried ($MgSO_4$) and concentrated under vacuum to afford pure mono-Boprotected diamine (4.5 g, 83 %).

1H NMR (300 MHz, CDCl3): δ 5.23 (s, 1H), 4.87 (s, broad, 1H), 3.62-3.56 (m, 2H), 2.65 (t, 1H), 1.59 (m, 2H), 1.37 (s, 9H).

Synthesis of 4

To an ice cold compound **3** (1.5 g, 1.29 mmol) solution in dry DCM (130 mL), 5 eq. oxalyl chloride was added divide into several times and stirred for 10 min, and stirred 2 h at room temperature. DCM and excess oxalyl chloride was evaporated under reduced pressure and obtained white solid was dissolved in small amount of DCM under N_2 gas. The prepared solution was added to the 2 eq. of mono-Boc-protected diamine and 5 eq. of DIPEA mixture in dry DCM (50 mL) divided in the several times on ice bath and then stirred 10 min. The mixture was stirred overnight at room temperature and extracted with distilled water, saturated $NaHCO_3$ solution, 0.1 M HCl, and brine. The organic layer was dried over the MgSO4, and solvent was evaporated by using rotary evaporator. The residue was purified reprecipitation in MeOH to give **4**. (1.3 g, 57.9 %).

1H NMR (300 MHz, CDCl3): δ 12.46 (s, 1H), 11.65 (s, 1H), 11.54 (s, 1H), 9.84 (s, 1H), 8.91 (d, J = 7.55 Hz, 1H), 8.45 (d, J = 7.55 Hz, 1H), 7.93-7.83 (m, 6H), 7.63-7.53 (m, 3H), 7.37 (s, 1H), 7.20-7.19 (t, 1H), 6.74 (s, 1H), 6.68 (s, 1H), 4.86 (s, broad, 1H), 4.38-4.33 (m, 1H), 4.21-4.10 (m, 3H), 3.87-3.83 (m, 4H), 3.39-3.25 (m, 1H), 2.98-2.81 (s, broad, 1H), 2.74-2.61 (s, broad, 1H), 2.50-2.20 (m, 5H), 2.08 (s, broad, 1H), 1.79-1.75 (m, 1H), 1.58-1.54 (m, 1H), 1.23-1.12 (m, 40H), 0.81-0.78 (m, 1H), 0.73 (s,

3H), 0.71 (s, 3H), 0.31 (s, 3H). 13C NMR (75 MHz, CDCl3) 176.6, 164.9, 164.3, 163.7, 163.4, 162.9, 162.8, 161.2, 160.7, 151.0, 150.7, 149.2, 148.6, 138.4, 138.3, 138.2, 137.6, 134.4, 133.3, 133.3, 132.7, 127.7, 126.7, 126.5, 122.5, 122.4, 122.2, 121.9, 117.2, 117.1, 116.9, 116.8, 116.7, 99.9, 98.8, 98.5, 98.4, 92.0, 77.5, 77.2, 76.9, 75.7, 75.6, 75.4, 75.2, 54.9, 54.4, 39.6, 37.7, 32.0 29.9, 29.4, 28.9, 28.4, 28.4, 19.7, 19.6, 19.6, 19.5, 19.5, 16.4, 9.8. HRMS: (ESI) m/z calculated for [C74H86N10O13]+ 1323.64; found 1323.65

Synthesis of 5

Boc deprotection of **4** was perfomed at room temperature with 20 % v/v solution of TFA in DCM for 2 h. $NaHCO_3$ was used for cleavage. The organic layer was evaporated by rotary evaporator to yield **5** (1.21 g, 97.2 %).

1H NMR (300 MHz, CDCl3): δ 12.36 (s, 1H), 11.62 (s, 1H), 11.47 (s, 1H), 9.81 (s, 1H), 8.94 (d, J = 7.55 Hz, 1H), 8.48 (d, J = 7.93 Hz, 1H), 8.30 (s, broad, 2H) 7.95-7.81 (m, 7H), 7.64-7.54 (m, 3H), 7.51-7.45 (m, 1H), 7.36 (s, 1H), 7.20-7.15 (t, 1H), 6.75 (s, 1H), 6.65 (s, 1H), 4.34-4.31 (m, 1H), 4.26-4.24 (m, 1H), 4.17-4.08 (m, 2H), 3.85 (d, J = 6.23 Hz, 4H), 2.47-2.22 (m, 5H), 2.03 (s, broad, 2H), 1.76-1.66 (m, 1H), 1.33 (t, J = 9.44 Hz, 1H), 1.23-1.12 (m, 24H), 0.73 (s, 3H), 0.70 (s, 3H), 0.31 (s, 3H). 13C NMR (75 MHz, CDCl3) δ 176.4,164.8, 164.2, 163.5, 163.2, 162.7, 162.6, 161.1, 160.5, 150.8, 150.5, 149.1, 148.4, 138.2, 138.1, 138.1, 137.4, 134.2, 133.2, 133.1, 132.5, 127.6, 126.5, 126.3, 122.3, 122.2, 122.0, 121.7, 117.0, 116.9, 116.7, 116.6, 116.5, 115.9, 99.8, 98.6, 98.3, 98.2, 91.9, 77.3, 77.0, 76.7, 75.5, 75.4, 75.2, 75.0, 54.8, 54.2, 39.5, 37.5, 31.8, 29.7, 29.2, 28.8, 28.3, 28.2, 19.5, 19.4, 19.4, 19.3, 19.3, 16.2, 9.6. HRMS: (ESI) m/z calculated for [C69H78N10O11]+ 1223.58; found 1223.58

Synthesis of 6 and immobilization onto silica surface

To the solution of **5** (1 g, 4.5 mM) in DCM (150 mL), 0.98 eq of 3-(triethoxysilyl)-propyl isocyanate (0.16 mL, 0.67 mmol) was added and stirred 3 hours under N_2 atmosphere. Then, mixture was concentrated less than 10 mL by rotary evaporator. The concentrated mixture was added to the silica particle (5 μm, 150 Å, 330 m^2g^{-1}) suspended toluene 15 mL solution. The mixture stirred at reflux for 24 h to immobilize compound **5** onto silica surface.

3. ^{1}H-NMR, ^{13}C-NMR and MS spectra

Compound 2

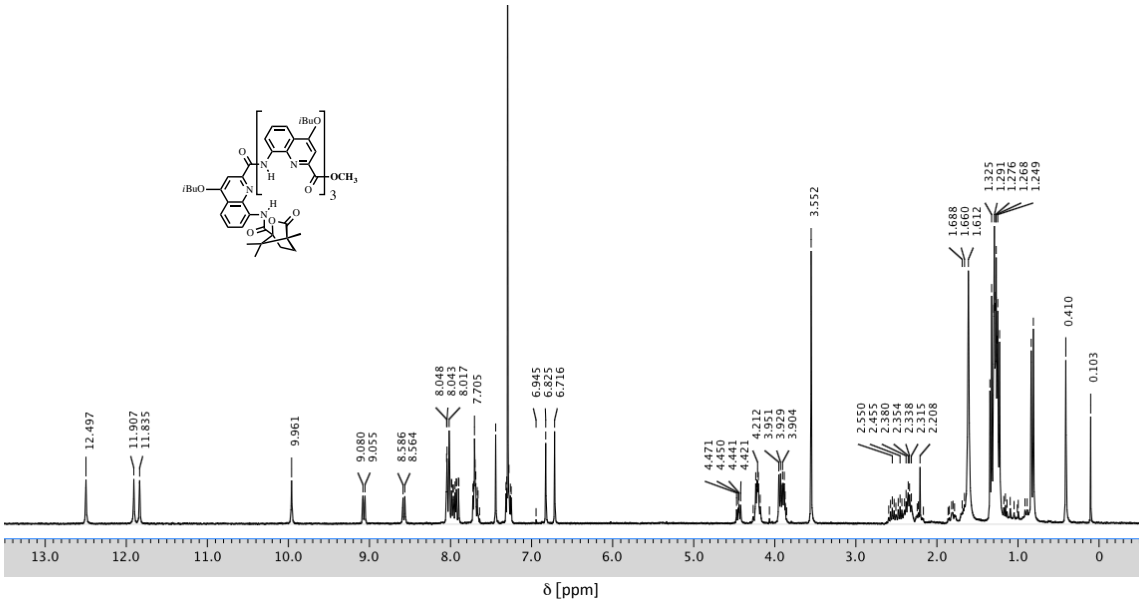

Fig. S2 ^{1}H-NMR spectrum of compound **2**

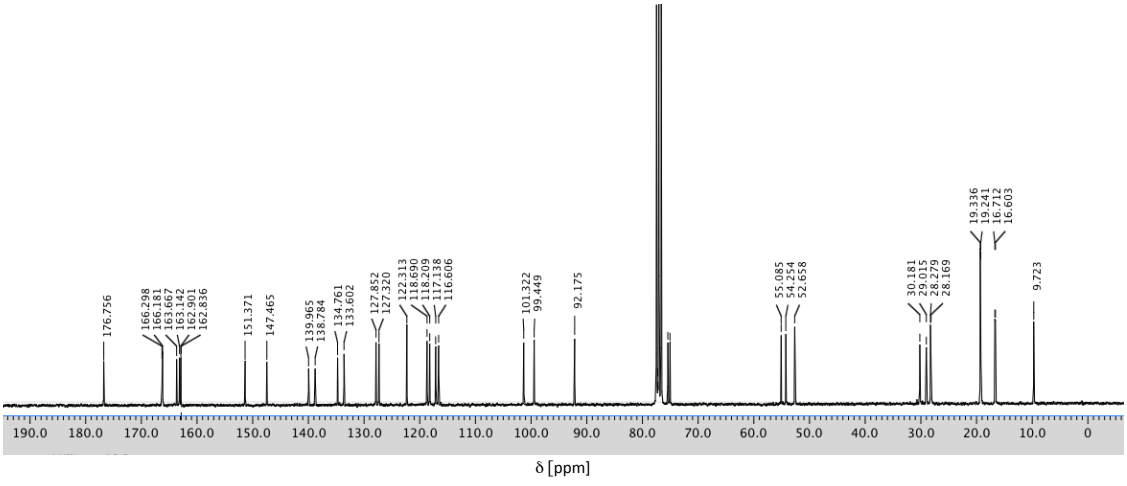

Fig. S3 ^{13}C-NMR spectrum of compound **2**

Compound **3**

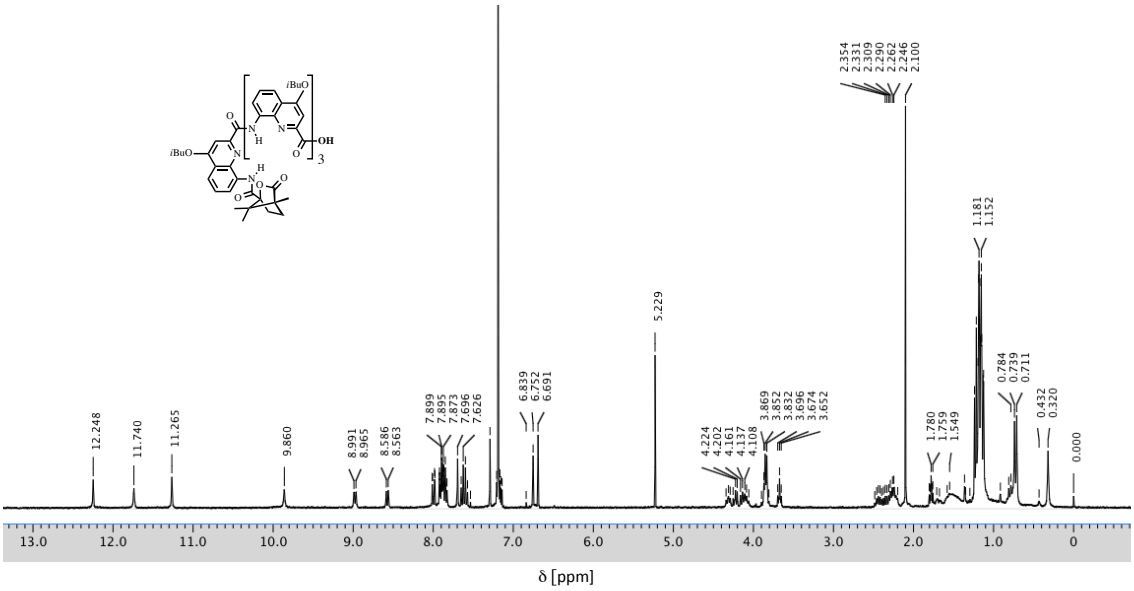

Fig. S4 ^{1}H-NMR spectrum of compound **3**

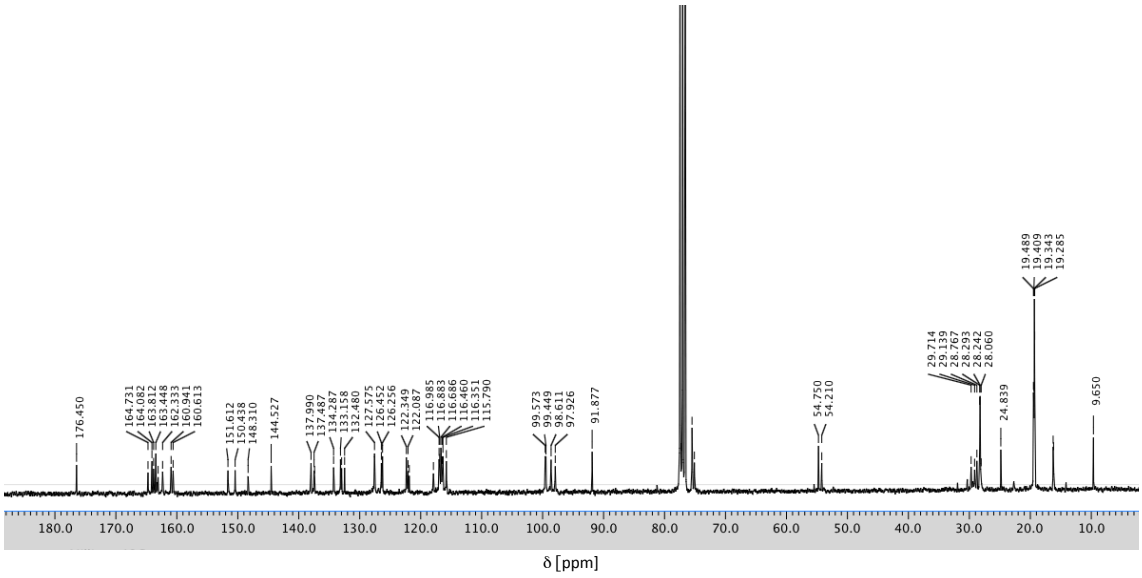

Fig. S5 ^{13}C-NMR spectrum of compound **3**

Compound 4

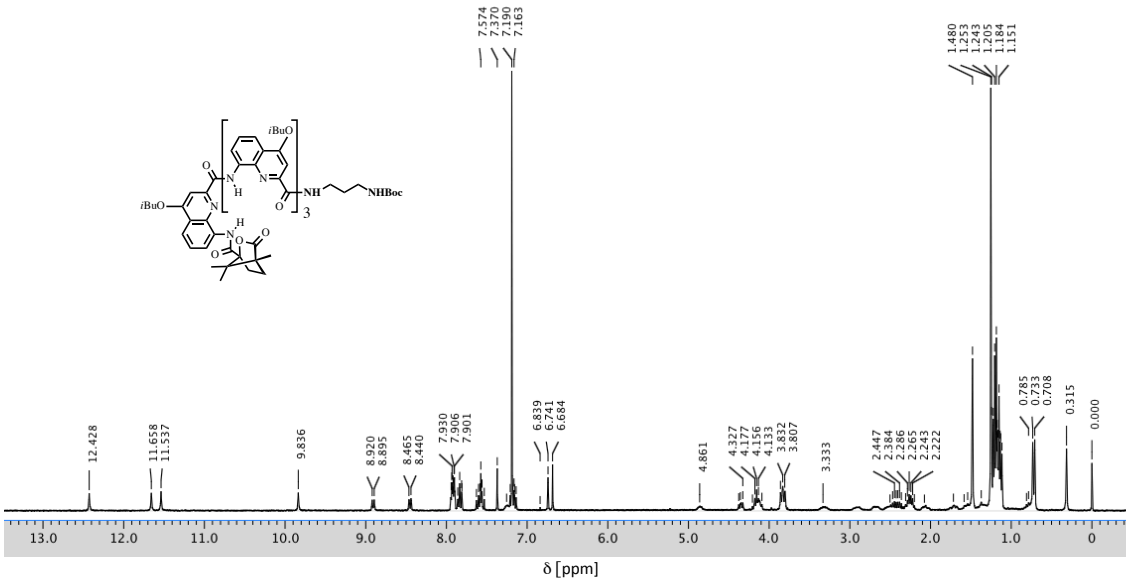

Fig. S6 ^{1}H-NMR spectrum of compound **4**

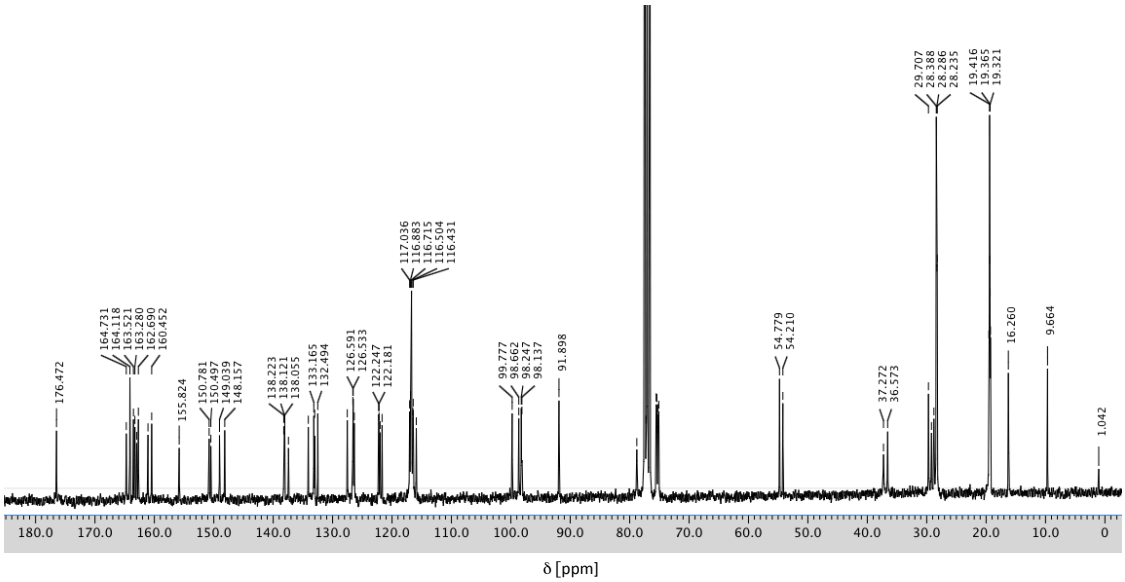

Fig. S7 ^{13}C-NMR spectrum of compound **4**

Compound 5

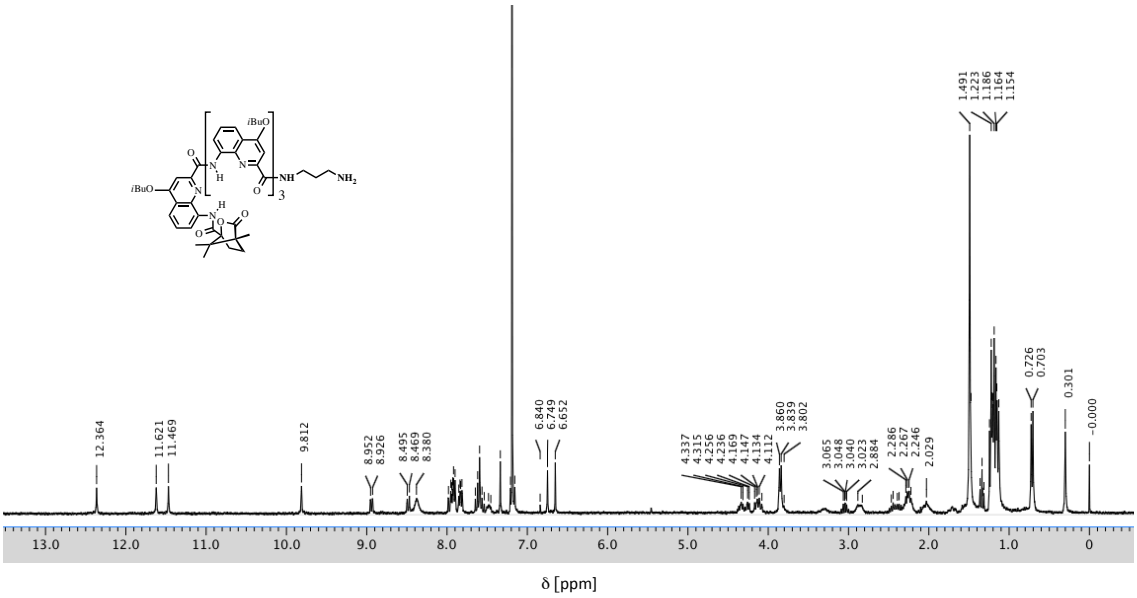

Fig. S8 ^{1}H-NMR spectrum of compound **5**

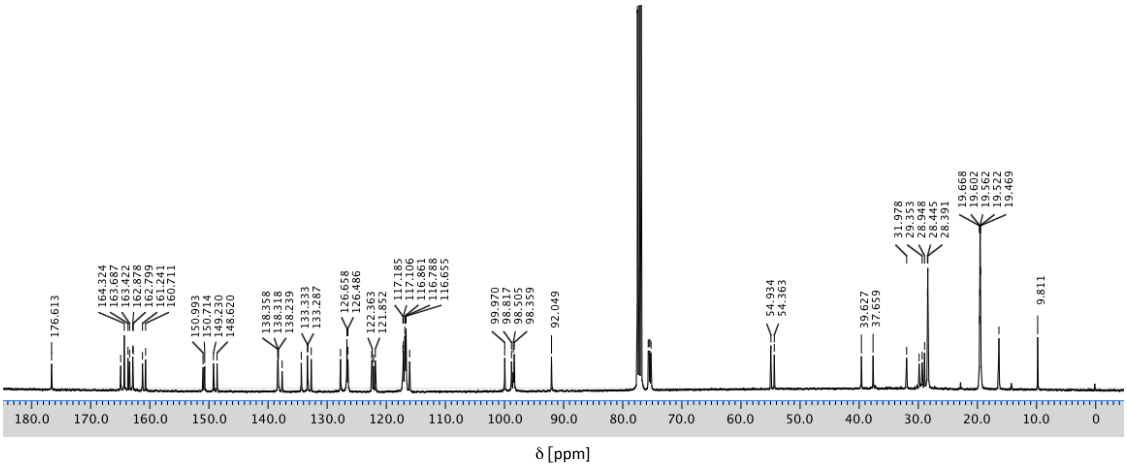

Fig. S9 ^{13}C-NMR spectrum of compound **5**

Compound 6

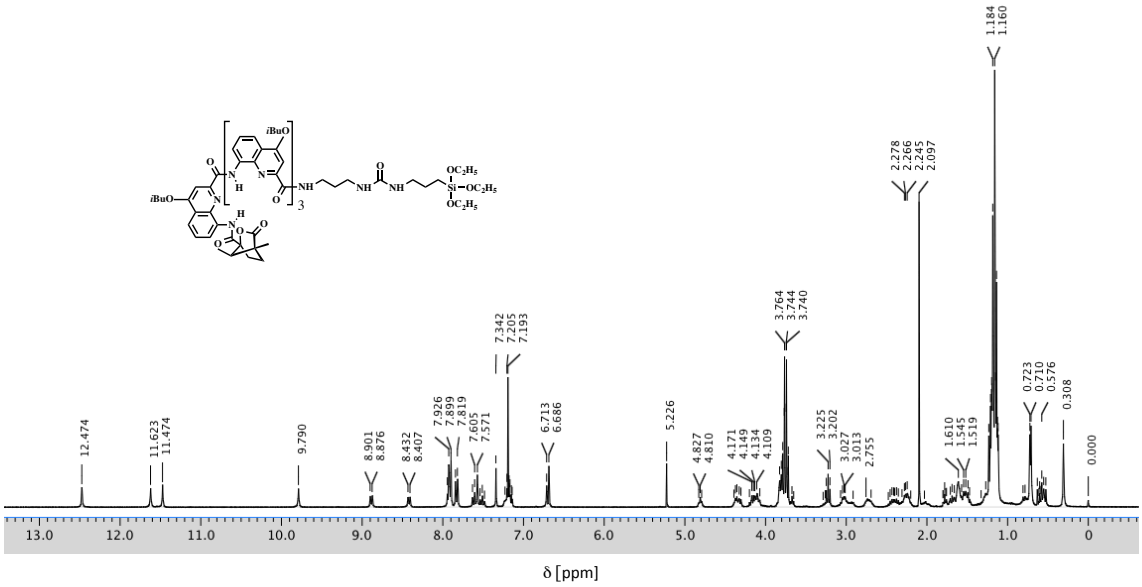

Fig. S10 ^{1}H-NMR spectrum of compound **6**

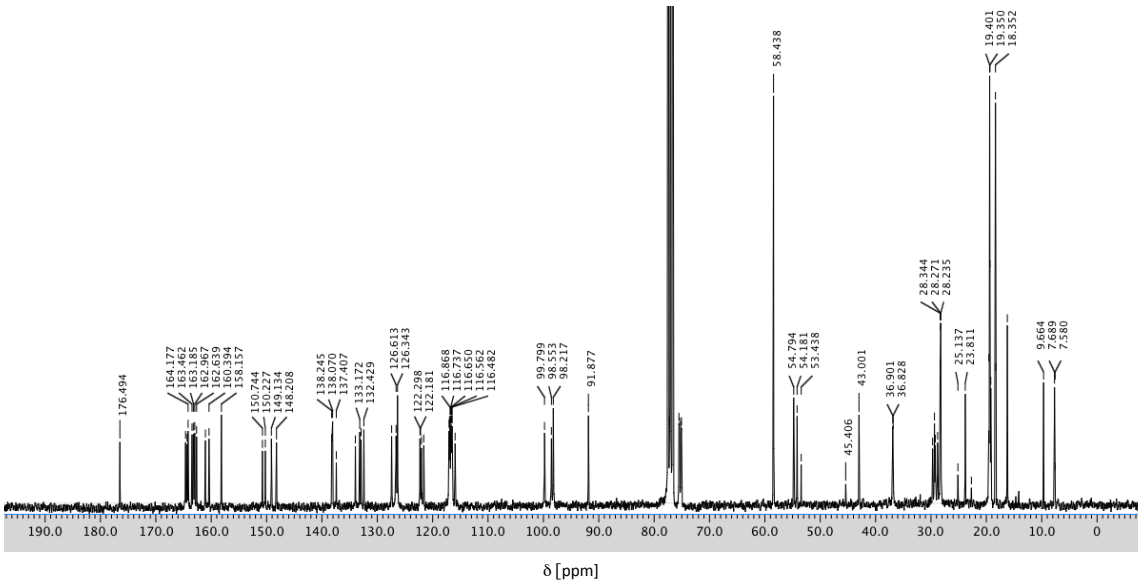

Fig. S11 ^{13}C-NMR spectrum of compound **6**

4. CD and UV-vis spectra

4-1 Chirality Investigation

The chirality inducing and preservation of quinoline oligoamides (**2**-**5**) in the synthetic process were confirmed by CD spectra. For measuring each spectrum, the quartz cells of 2 mm optical path length were used. Scans were measured at room temperature, over a wavelength range of 250-450 nm, with a response time of 0.5 s and a scanning speed of 100 nm min^{-1}. All quinoline oligoamides were dissolved in $CHCl_3$ (0.01 mM). Through the synthesis process, no CD intensity reduction was observed.

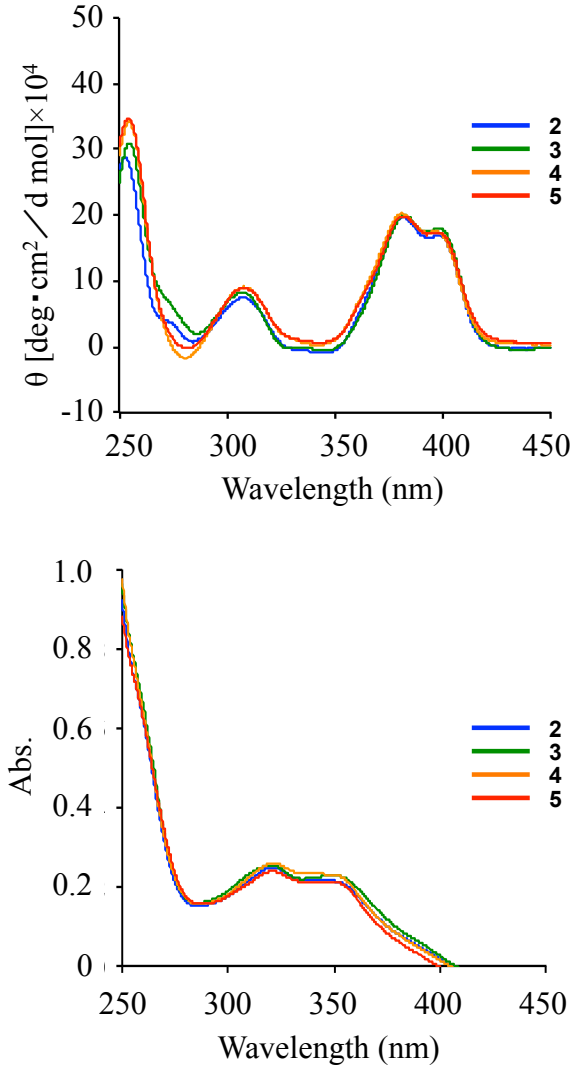

Fig. S12 CD (top) and UV-vis (bottom) spectra of compound **2**-**5**

4-2 Stability of P-helical structure of Cmp-Q_4

The thermal stability of Cmp-Q_4 (**2**) in $CHCl_3$ and DMSO at various temperatures was investigated by CD spectra. CD spectra were measured at 10 to 50 °C in $CHCl_3$ and 20 to 100 °C in DMSO. By increasing the temperature, CD intensity was slightly decreased (The reduction rate was 91% from 10 °C to 50 °C in $CHCl_3$ and 81% from 20 °C to 100 °C in DMSO at 380 nm). And this changes is reversible. This result suggests that the intramolecular interaction for consisting P-helical structure was lowered by increasing temperature, however the P-helical structure was retained and no helical inversion occurred.

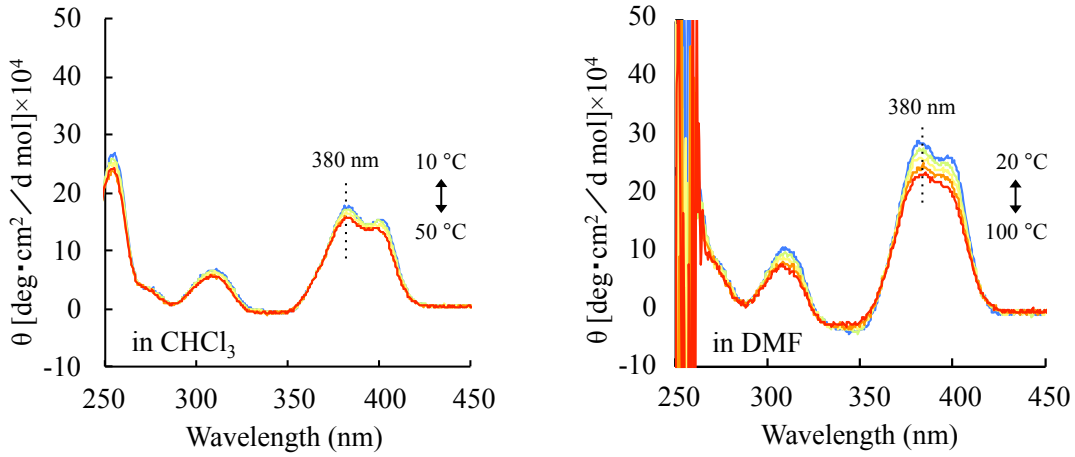

Fig. S13 Temperature dependency of CD spectrum of Cmp-Q_4 in $CHCl_3$ and DMSO.

5. van't Hoff plot

All thermal parameter were obtained from each van't Hoff plot (Fig. S14- S16).

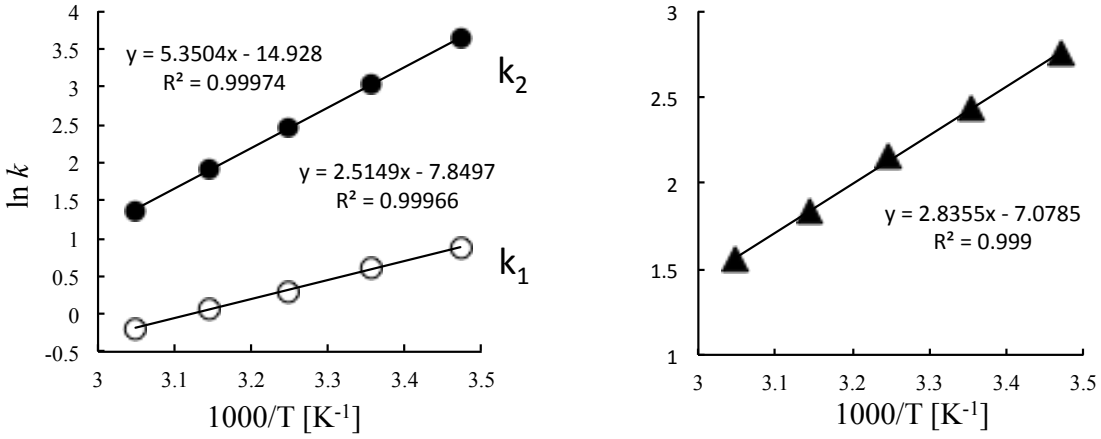

Fig. S14 van't Hoff plot of Q_8^{iBu}

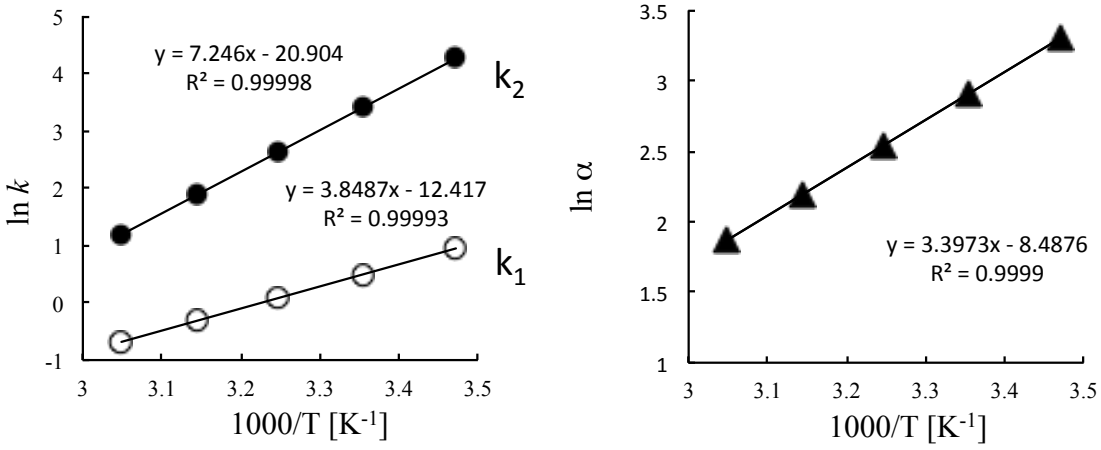

Fig. S15 van't Hoff plot of Q_8^{Tg}

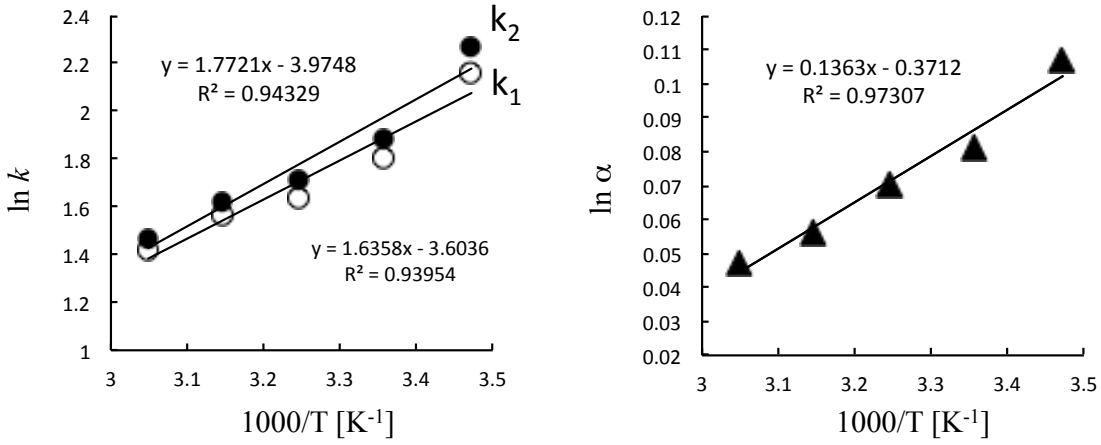

Fig. S16 van't Hoff plot of Troger's base