A pillar[5]arene-calix[4]pyrrole enantioselective receptor for mandelate anion recognition

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1. Materials and methods

All chemicals and solvents were used as supplied without further purification. Dicarboxylic acid functionalized pillar[5]arene was synthesized according to literature procedures. ^{1}H NMR and ^{13}C NMR spectra at 400 and 100 MHz were performed on a Bruker AMX-400 spectrometer at room temperature. High resolution mass data were recorded in waters-MALDI-TOF-MS. Circular dichroism spectra were acquired using J-1500 CD spectrometer by a quartz cuvette of 1 cm path length. Chiral HPLC for separation of PC used the following conditions: a chiral chromatographic column CHIRALPAK IA (250 mm × 4.6 mm, 5 μm) connected in series, the flow rate 1 mL/min, the injection volume for PC racemic mixtures 20 μL, column temperature 30 °C, and the mobile phase gradient: 0 min -85% hexane + 15% THF, 60 min 50% hexane + 50% THF (v/v). The column was conditioned 30 min before each analysis to achieve good reproducibility. The UV detector was operating at 295 nm. For better resolution of PC mixtures, the ratio of hexane towards THF was selected to be 85/15 (v/v). Then, the final separation and purification of PC enantiomers was performed by preparative HPLC packed with a column CHIRALPAK IA (250 mm × 20 mm, 5 μm) under similar conditions. The flow rate was 4 mL/min, the injection volume was 5 mL, and the eluent was the mixture of hexane/THF (85/15, v/v).

2. Synthetic procedure

2.1 Dicarboxylic Pillar[5]arene. Ethyl bromoacetate (4.10 g, 24.0 mmol) and K_2CO_3 (6.62 g, 48.0 mmol) were added into a solution of dihydroxylated pillar[5]arene[S1] (2.50 g, 3.00 mmol) in CH_3CN (50 mL). The mixture was heated at reflux for 20 h under N_2. The cooled solution was filtered and washed with CH_3Cl, and the filtrate was evaporated. The residue was crystallized in CH_3OH/CH_3Cl to obtain dietherificated pillar[5]arene (2.71 g, 90%). Then, a solution of dietherificated pillar[5]arene (2.01 g, 2.00 mmol) in CH_3CH_2OH (100 mL) was treated with 40% NaOH (100 mL) at reflux for 12 h. The mixture was concentrated, diluted with H_2O (25 mL), and acidified with HCl (1 mol/L). The resulting precipitant was collected and dried under vacuum to give dicarboxylic pillar[5]arene (1.73 g, 91%) as a white solid. HRMS (ESI) calcd for [$C_{55}H_{66}O_{14}$] 950.4453, found 950.4476.

2.2 Hydroxylmethyl calix[4]pyrrole. To a mixture of pyrrole (9.4 mL, 135 mmol), hydroxyacetone (2.50 g, 33.8 mmol) and acetone (7.5 mL, 101 mmol) in CH_3OH (150 mL) was added slowly methanesulphonic acid (2.20 mL, 33.8 mmol) at 0°C. after stirring for 2 h at 25 °C, the precipitant was collected and purified by column chromatography over silica gel (eluent: ethyl acetate/hexane = 1/3) to give hydroxylmethyl calix[4]pyrrole (1.2 g, 8%) as a white solid. HRMS (ESI) calcd for [$C_{28}H_{36}N_4O_1Na^+$] 467.2781, found 467.2772.

2.3 PC Compound. Dicarboxylic acid functionalized pillar[5]arene (285 mg, 0.30 mmol), hydroxylmethyl calix[4]pyrrole (400 mg, 0.90 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide Hydrochloride (EDCI) (230

mg, 1.20 mmol) and 4-dimethylaminopyridine (DMAP) (264 mg, 2.13 mmol) were dissolved in dry dichloromethane (10 mL) under an atmosphere of N_2. The reaction mixture was stirred at 0 °C for 30 min and then allowed to room temperature for 12h. After completion of the reaction, the mixture was washed first with 0.1 N HCl (10mL), followed by an aqueous solution saturated with NaCl (10 mL), and finally water (10 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under pressure. Column chromatography (silica gel, petroleum ether/dichloromethane/ethyl acetate: 10/10/1) afforded PC in the form of a light yellow solid (271 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (s, 2H, 2NH), 7.09 (s, 2H, 2NH), 7.03(s, 4H, 4NH), 6.86 (s, 2H, $2CH_{Ar}$), 6.70-6.74 (m, 8H, $8CH_{Ar}$), 5.89-5.92 (m, 16H, $16CH_{Pyrrol}$), 4.39-4.48 (q, J = 10.8 Hz, 8H, $4CH_2$), 3.66-3.85 (m, 30H, $15CH_2$), 1.49-1.54 (s, 42H, $14CH_3$), 1.25-1.32 (s, 24H, $8CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 150.0, 149.9, 149.8, 149.7, 149.6, 139.1, 139.1, 138.6, 138.3, 133.3, 133.2, 129.3, 128.6, 128.5, 128.5, 127.8, 115.5, 115.4, 115.1, 115.0, 104.5, 104.3, 103.3, 103.0, 103.0, 102.9, 102.8, 70.3, 66.2, 63.9, 63.8, 63.8, 63.7, 60.4, 39.5, 35.2, 35.2, 29.3, 29.3, 29.2, 29.0, 21.1, 15.2, 15.1, 15.1, 15.1, 14.2. MALDI-TOF-HRMS: *m/z* calcd for $C_{111}H_{134}N_8O_{14}$M, 1803.0020, found 1803.0985.

3. NMR and MS spectra

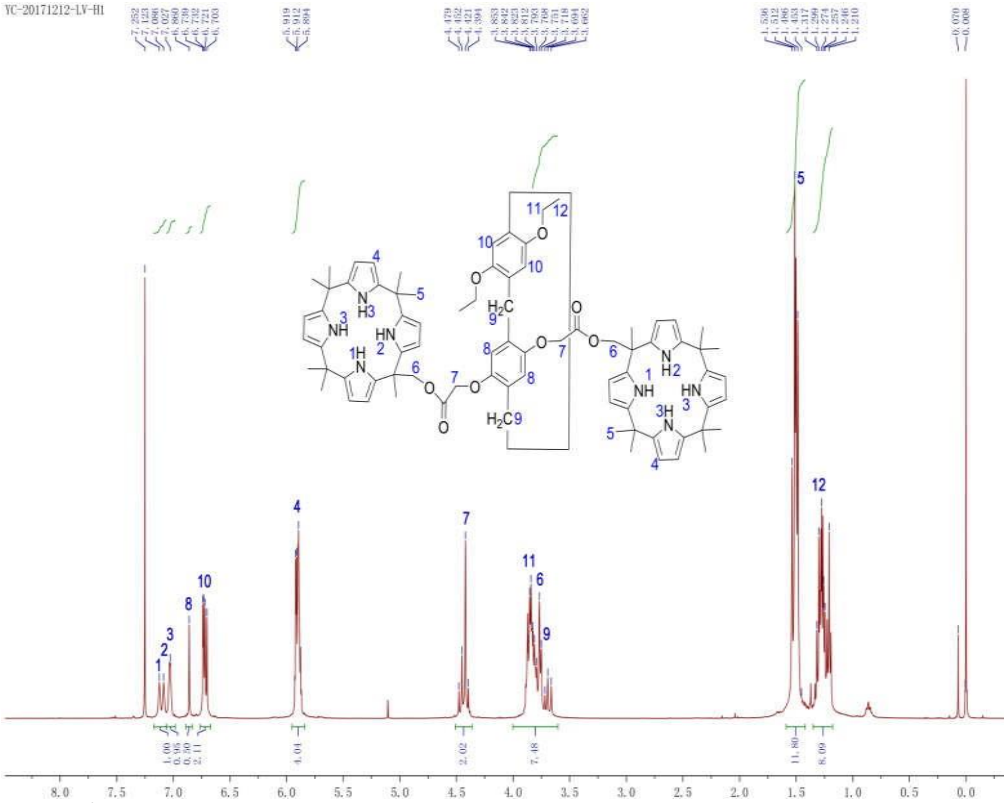

Figure S1. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, room temperature) of compound **PC**.

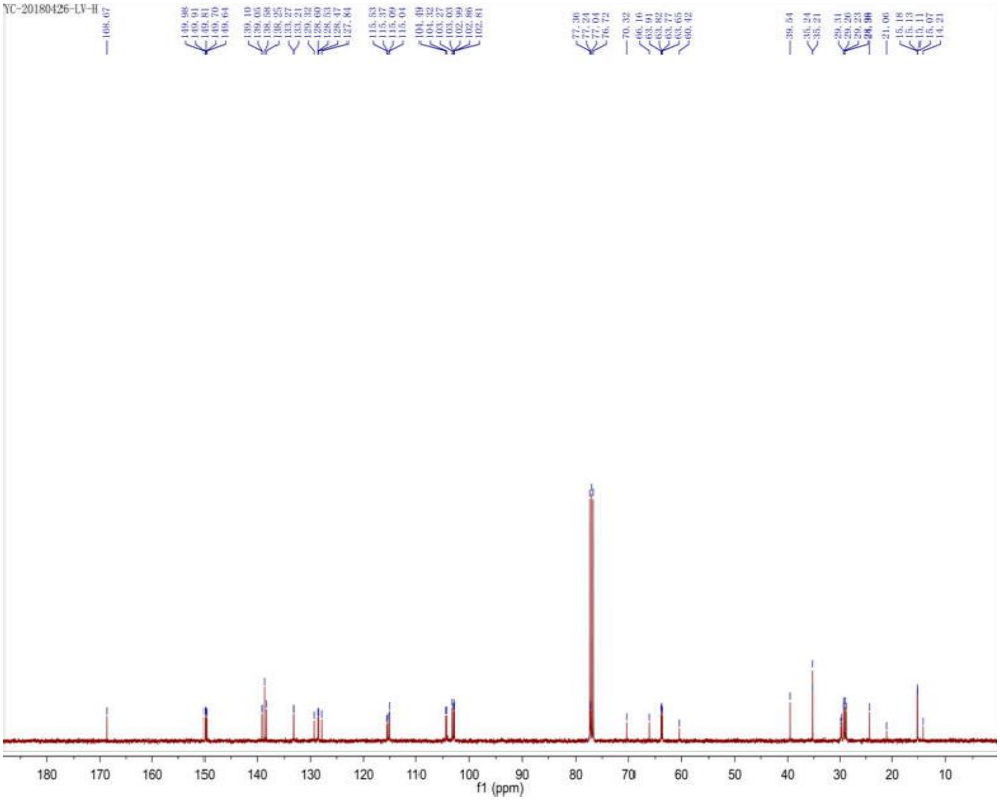

Figure S2. ^{13}C NMR spectrum (100 MHz, $CDCl_3$, room temperature) of compound **PC**.

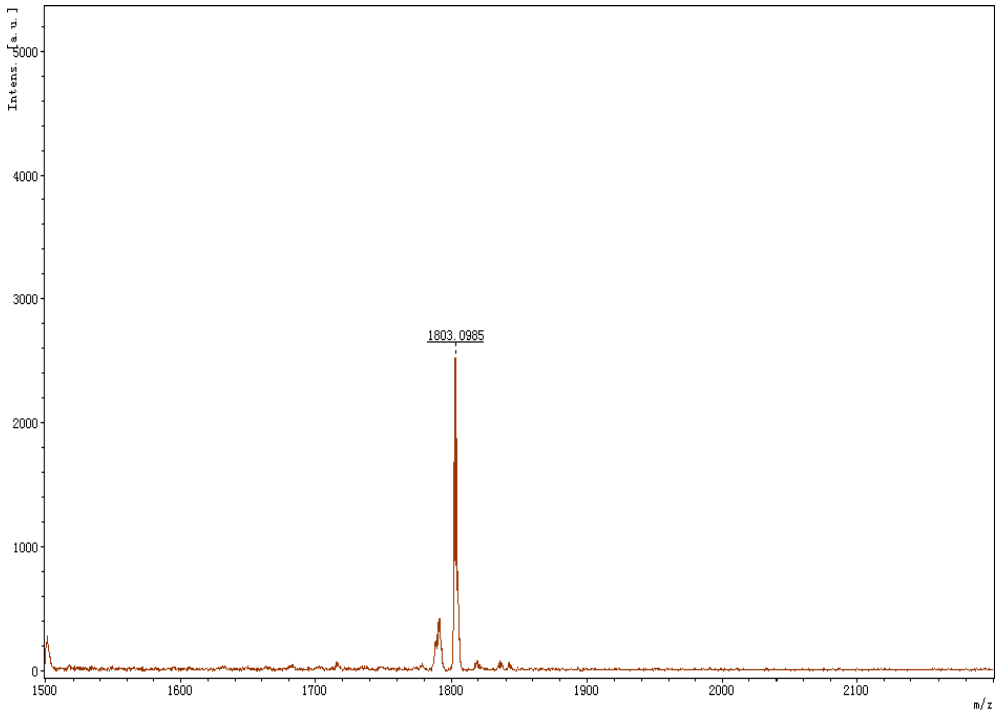

Figure S3. MALDI-TOF-HRMS spectrum of compound **PC**.

4. ITC measurements

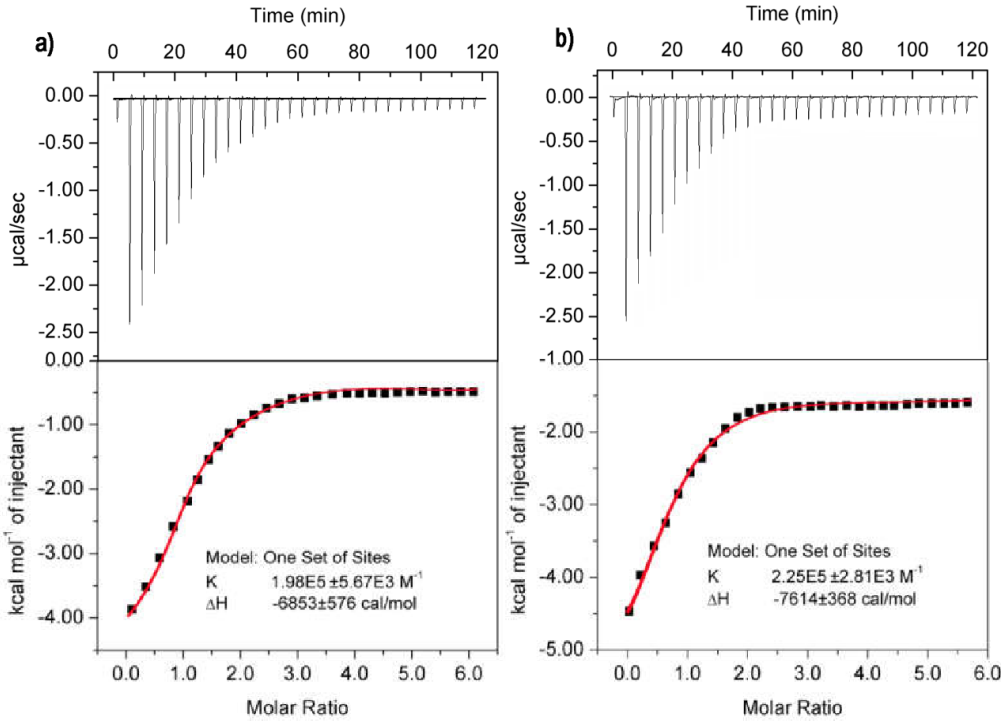

Figure S4. ITC titration profile of 2.5 mM **PC** with 0.1 mM *S*-MA (a) and 0.1 mM *R*-MA (b) in DMSO at 25 ^{o}C.

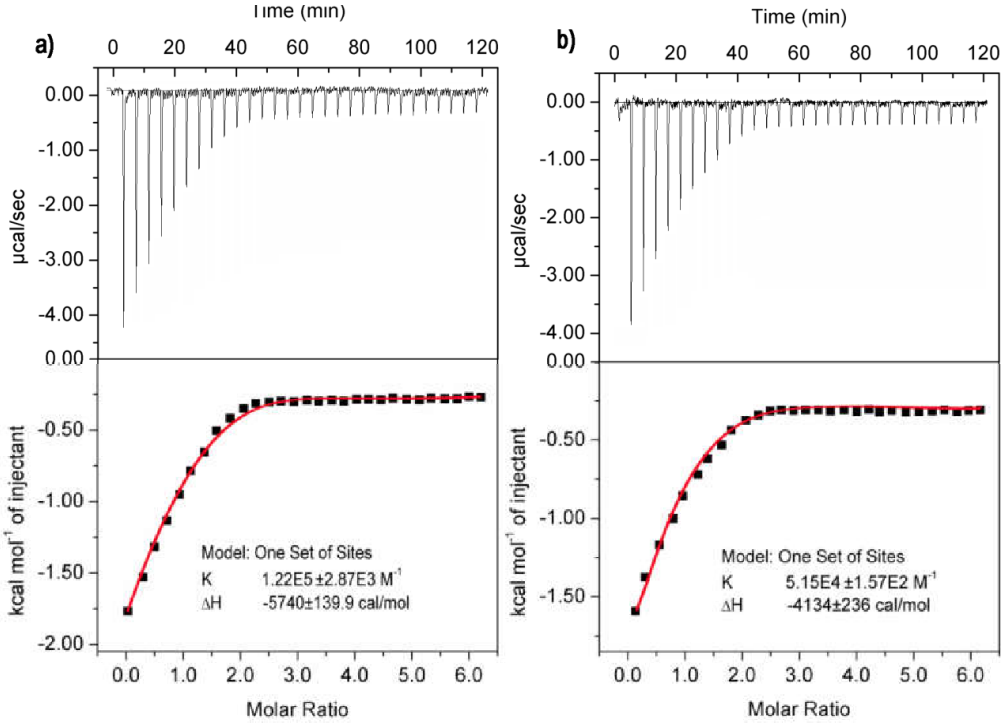

Figure S5. ITC titration profile of 2.5 mM **PC**-f1 with 0.1 mM *S*-MA (a) and 0.1 mM *R*-MA (b) in DMSO at 25 ^{o}C.

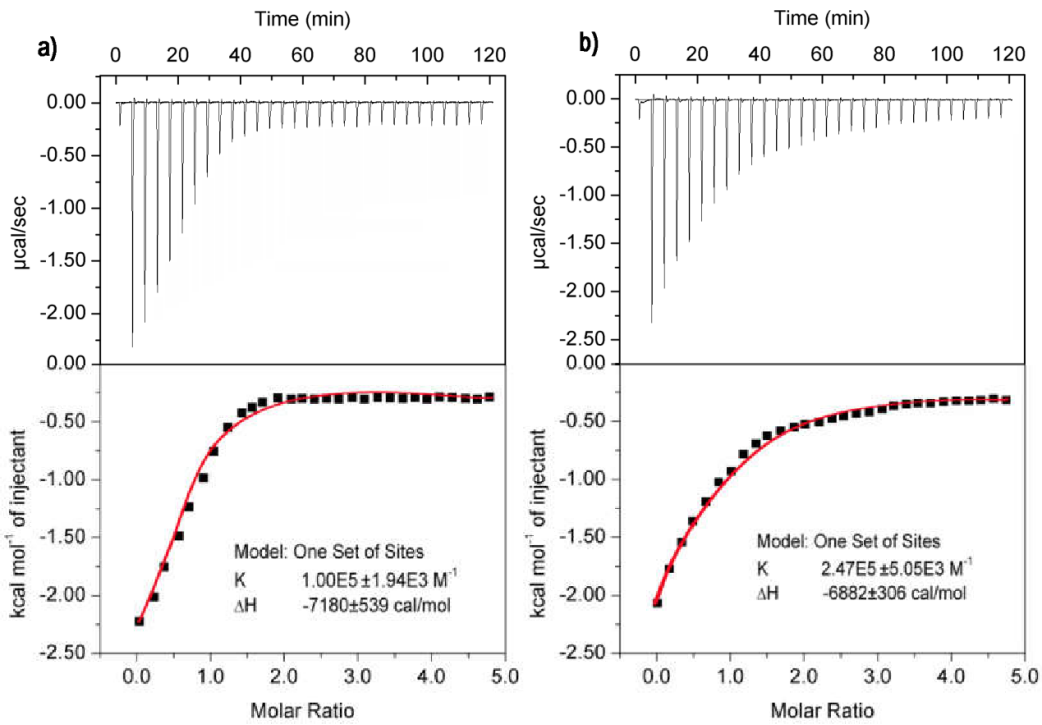

Figure S6. ITC titration profile of 2.5 mM **PC**-f2 with 0.1 mM *S*-MA (a) and 0.1 mM *R*-MA (b) in DMSO at 25 ^{o}C.

Reference:

S1. Han, C. Zhang, Z. Yu, G. Huang, F. *Chem. Commun.* 2012, **48**, 9876-9878.