Design and efficient synthesis of a pillar[5]arene-based [1]rotaxane

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Electronic Supplementary Information (15 pages)

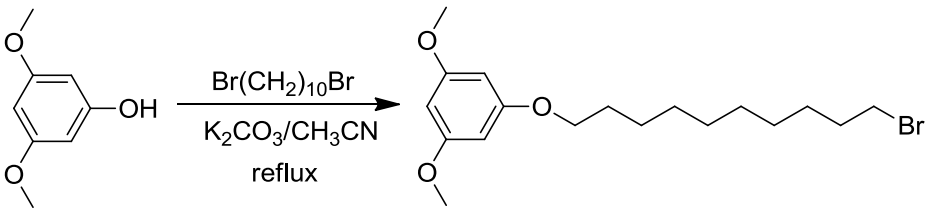
1. Materials and methods

3,5-Dimethoxyphenol, 1,10-dibromodecane, 1,4-dimethoxybenzene, boron trifluoride diethyl etherate, paraformaldehyde, 4-(*N*, *N*-dimethylamino)pyridine (DMAP) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) were reagent grade and used as received. Ethyl-4-methoxy phenoxy acetate[S1] was synthesized according to literature procedures. Solvents were employed as purchased or dried according to procedures described in the literature.

NMR spectra were collected on a Bruker AVANCE DMX-500 spectrometer or a Varian Unity INOVA-400 spectrometer with TMS as the internal standard. Low-resolution electrospray ionization (LRESI) mass spectra were obtained on a Bruker Esquire 3000 plus mass spectrometer (Bruker-Franzen Analytik GmbH Bremen, Germany) equipped with an ESI interface and an ion trap analyzer. High-resolution electrospray ionization (HRESI) mass spectra were obtained on a Bruker 7-Tesla FT-ICR mass spectrometer equipped with an electrospray source (Billerica, MA, USA). The melting points were collected on a SHPSIC WRS-2 automatic melting point apparatus. The energy-minimized structure of **4** was calculated using the GAUSSIAN 03 software, based on the arithmetic method B3LYP/6-31G(D) (Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.;Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision D.01; Gaussian, Inc.: Wallingford, CT, 2005).

2. *Characterizations of compounds*

*2.1. Compound **1***



1

A mixture of 3,5-dimethoxyphenol (3.08 g, 20.0 mmol), and potassium carbonate (5.53 g, 40.0 mmol) in CH_3CN (250 mL) was stirred at room temperature under nitrogen atmosphere for 30 minutes. Then 1,10-dibromodecane (24.0 g, 80.0 mmol) in CH_3CN (50 mL) was added slowly and the solution was heated at reflux overnight. After filtration, the solvent was removed and the residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate, 10:1) to give **1** as a white solid. (4.62 g, 62%). M.p. 46.3–48.1 °C. ^{1}H NMR (400 MHz, chloroform-*d*, room temperature) δ (ppm): 6.08 (s, 3H), 3.91 (t, J = 6.0 Hz, 2H), 3.76 (s, 6H), 3.41 (t, J = 6.0 Hz, 2H), 1.89–1.82 (m, 2H), 1.79–1.72 (m, 2H), 1.47–1.39 (m, 4H), 1.36–1.25 (m, 8H). ^{13}C NMR (100 MHz, chloroform-*d*, room temperature) δ (ppm): 161.5, 161.1, 93.4, 92.8, 68.0, 55.3, 34.0, 32.8, 29.4, 29.3, 29.2, 28.7, 28.2, 26.0. LRESIMS: *m*/*z* 374.8 $[M + H]^+$ (100%). HRESIMS: *m*/*z* calcd for $[M]^+$ $C_{18}H_{29Br}O_3^+$, 372.1300; found 372.1303; error 0.8 ppm.

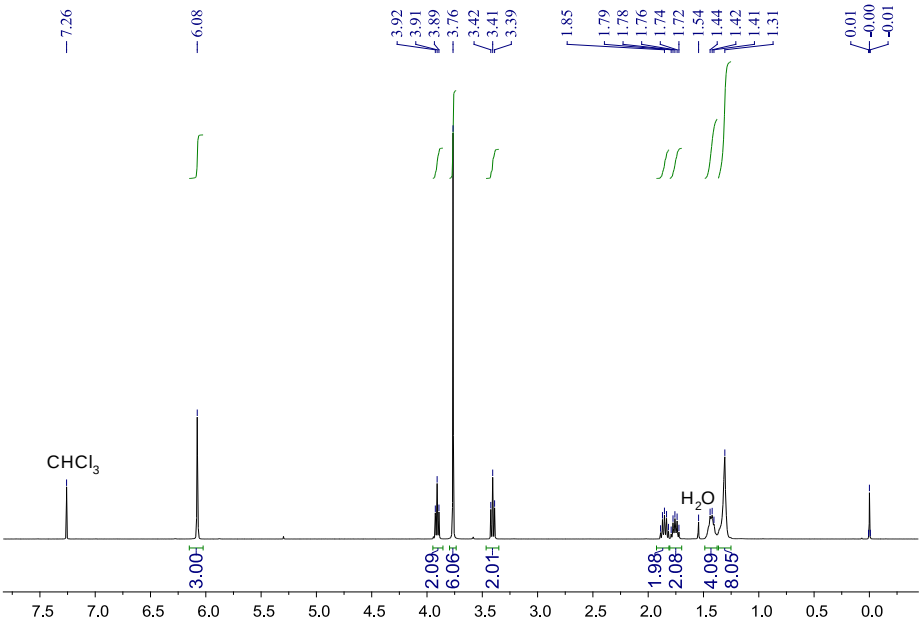


Figure S1. ^{1}H NMR spectrum (400 MHz, chloroform-*d*, room temperature) of **1**.

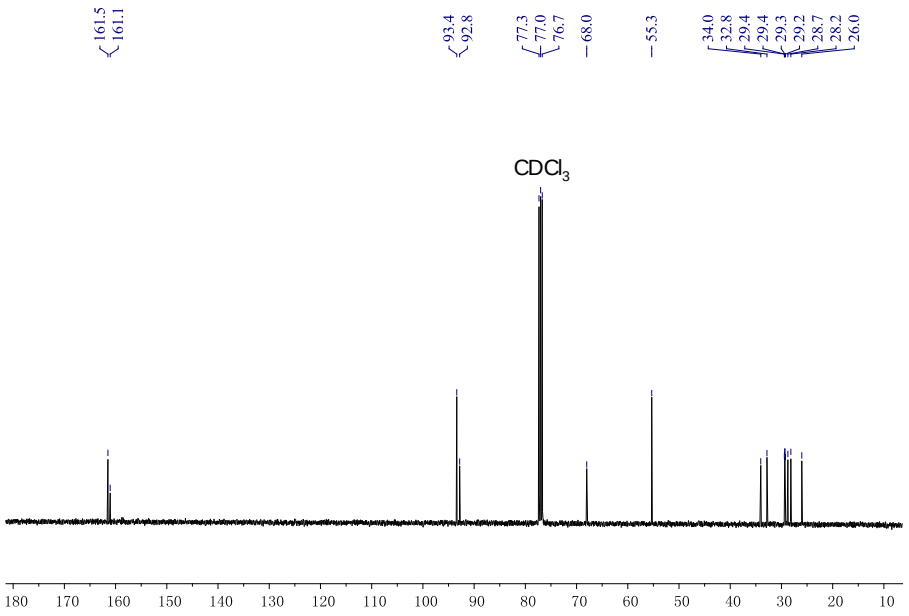


Figure S2. ^{13}C NMR spectrum (100 MHz, chloroform-*d*, room temperature) of **1**.

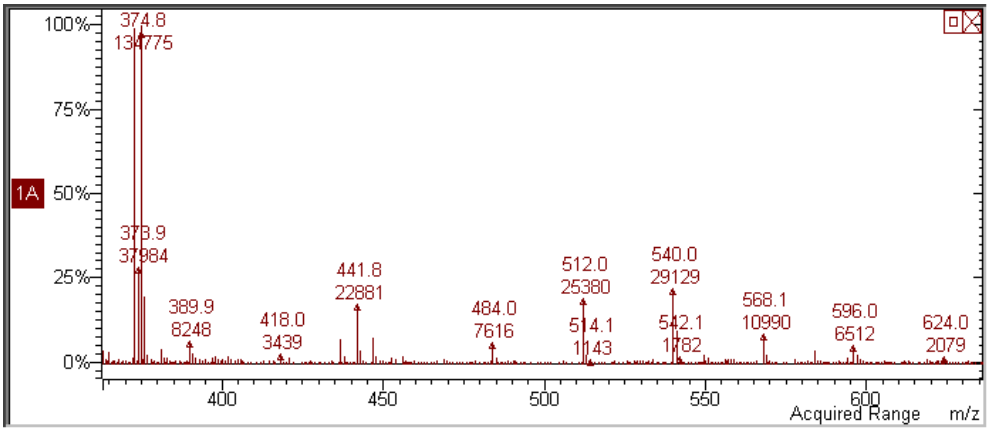
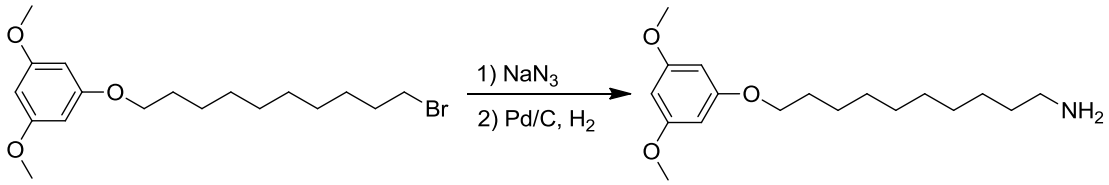


Figure S3. Electrospray ionization mass spectrum of **1**. Assignment of main peak: *m*/*z* 374.8 $[M + H]^+$ (100%).

*2.2. Compound **2***



1 **2**

A solution of **1** (3.70 g, 9.91 mmol) and sodium azide (3.25 g, 50.0 mmol) in acetone/H_2O (3:1 *v*/*v*, 100 mL) was heated at reflux for 24h under nitrogen atmosphere and then gradually cooled to room temperature. The organic solvent was evaporated carefully under vacuum. The residue was extracted by $CHCl_2$ (20 mL × 3) and the combined organic layer was dry over anhydrous Na_2SO_4 then concentrated by rotary evaporation to give the yellow oil. All the yellow oil was dried and placed in a 150 mL round-bottomed flask, Pd/C (300 mg) and $CH_3OH/CDCl_3$ (1:1 *v*/*v*, 80 mL) was added. The flask was evacuated and hydrogen was introduced. Then the solution was heated at reflux for 24h. After filtration, the solvent was evaporated to afford the crude product, which was purified by column chromatography (SiO_2, CH_2Cl_2/CH_3OH, 10:1) to give **2** (2.79 g, 91%) as a white solid. M.p. 83.4–84.5 °C. ^{1}H NMR spectrum (400 MHz, chloroform-*d*, room temperature) δ (ppm): 6.07 (s, 3H), 3.90 (t, J = 6.0 Hz, 2H), 3.76 (s, 6H), 2.97 (t, J = 6.0 Hz, 2H), 1.79–1.71 (m, 4H), 1.44–1.36 (m, 4H), 1.33–1.25 (m, 8H). ^{13}C NMR (100 MHz, chloroform-*d*, room temperature) δ (ppm):

161.5, 161.0, 93.4, 92.8, 68.0, 55.3, 40.0, 29.5, 29.4, 29.2, 29.0, 27.7, 26.5, 26.1. LRESIMS: *m*/*z* 309.9 $[M + H]^+$ (100%). HRESIMS: *m*/*z* calcd for $[M + Na]^+$ $C_{18}H_{31}NO_3Na$, 332.2202; found 332.2212; error 3 ppm.

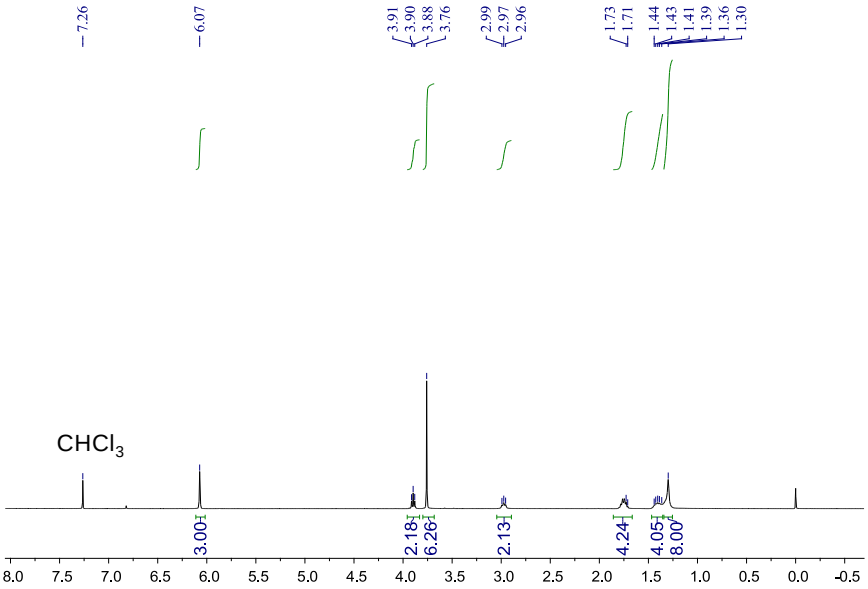


Figure S4. ^{1}H NMR spectrum (400 MHz, chloroform-*d*, room temperature) of **2**.

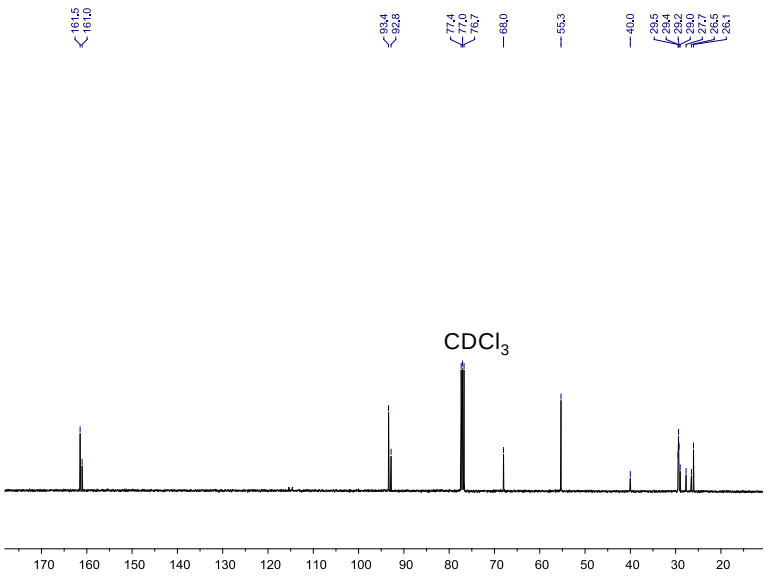


Figure S5. ^{13}C NMR spectrum (100 MHz, chloroform-*d*, room temperature) of **2**.

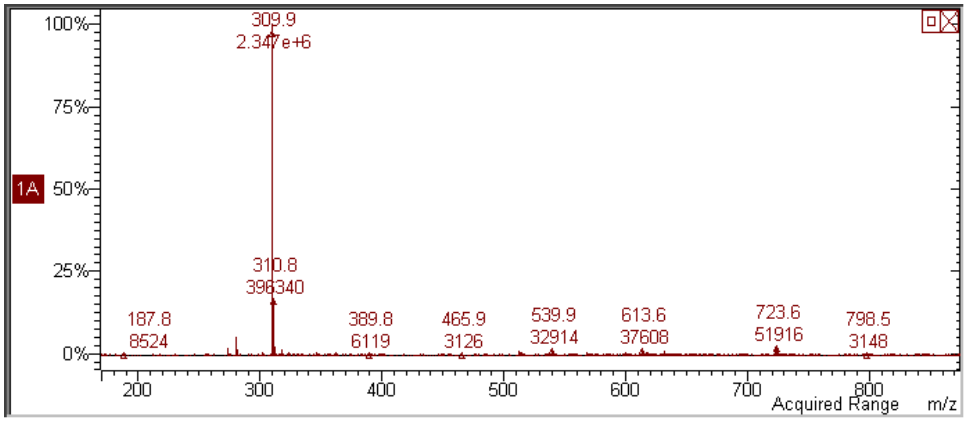
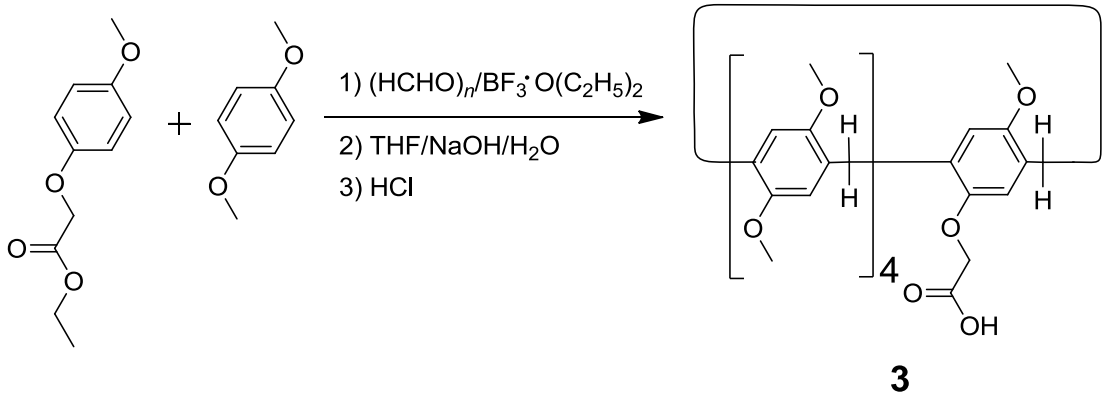


Figure S6. Electrospray ionization mass spectrum of **2**. Assignment of main peaks: *m/z* 309.9 $[M + H]^+$ (100%).

*2.3. Compound **3***



3

A mixture of 1,4-dimethoxybenzene (12.4 g, 90.0 mmol), ethyl-4-methoxy phenoxy acetate (2.10 g, 10.0 mmol), and paraformaldehyde (3.10 g, 100 mmol) in dry 1,2-dichloroethane (800 mL) was stirred at room temperature for 30 min. After the addition of $BF_3{\cdot}O(C_2H_5)_2$ (12.5 mL, 100 mmol), the mixture was stirred for 4 hours. After filtration, the solvent was removed in vacuo. Then the resultant residue was dissolved in CH_2Cl_2 (100 mL) and washed with water (100 mL × 3). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford the yellow solid, which was used without further purification. A solution of the yellow solid and 20% aqueous NaOH (20.0 mL) in THF (100 mL) was stirred at 65 °C for 4 hours. After cooling, the solution was treated with 30 mL of 4 M HCl (aqueous). The mixture was concentrated, the residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate, 10:1 to 5:1) to give **3** (1.50 g, 19%) as a white solid. M.p.

103.6–104.3 °C. ^{1}H NMR (400 MHz, chloroform-*d*, room temperature) δ (ppm): 6.76–6.59 (m, 10H), 4.27 (s, 2H), 3.80–3.76 (m, 10H), 3.64–3.54 (m, 27H), 1.80 (br, 1H). ^{13}C NMR (100 MHz, chloroform-*d*, room temperature) 150.9，128.4, 128.3, 114.1, 113.8, 56.0, 55.9, 55.8. δ (ppm): LRESIMS: *m*/*z* 793.4 $[M - H]^-$ (100%). HRESIMS: *m*/*z* calcd for $[M - H]^-$ $C_{46}H_{49}O_{12}^+$, 793.3230; found 793.3225; error –0.6 ppm.

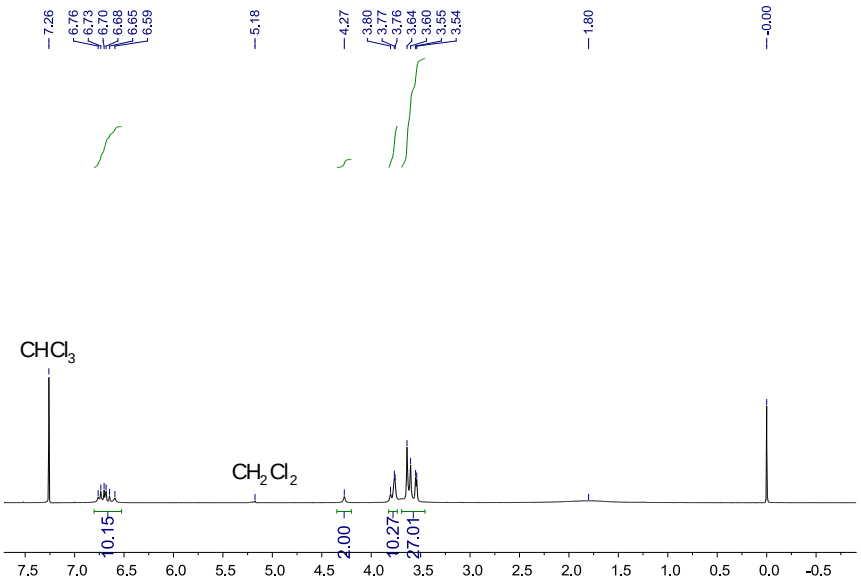


Figure S7. ^{1}H NMR spectrum (400 MHz, chloroform-*d*, room temperature) of **3**.

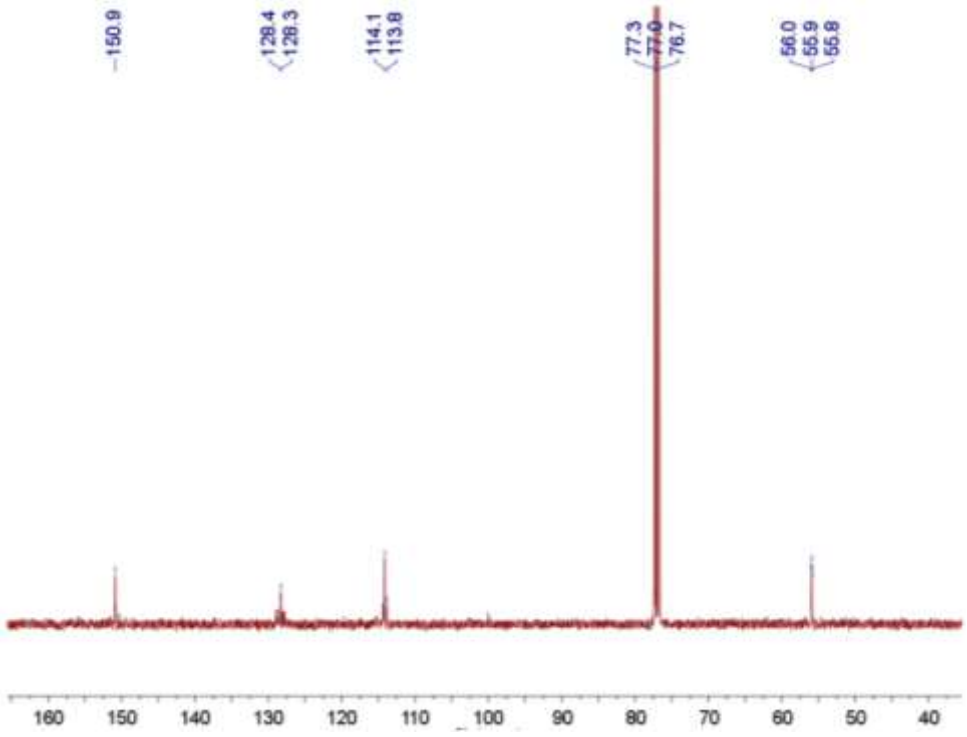


Figure S8. ^{13}C NMR spectrum (100 MHz, chloroform-*d*, room temperature) of **3**.

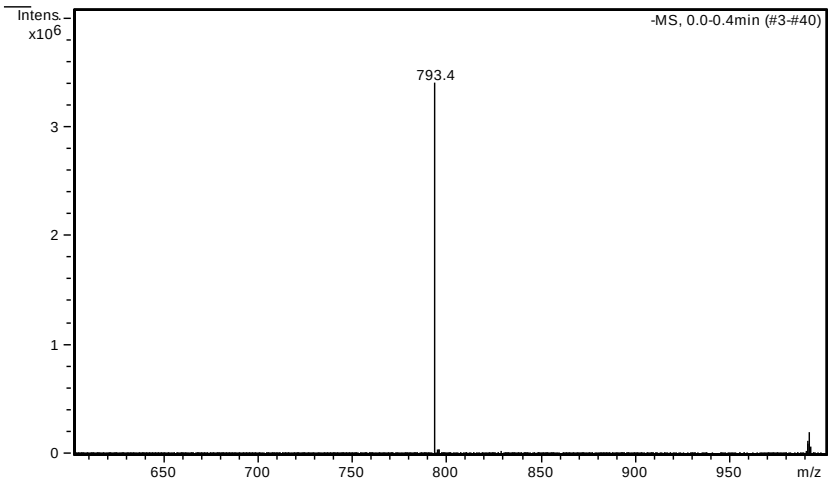
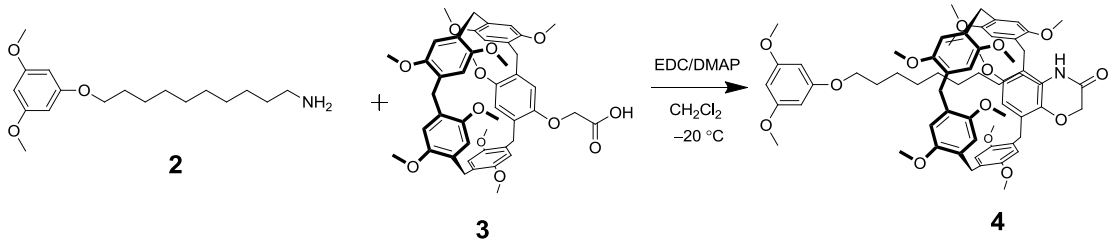


Figure S9. Electrospray ionization mass spectrum of **3**. Assignment of main peaks: *m*/*z* 793.4 $[M - H]^-$ (100%).

*2.4. Compound **4***



2 **3** **4**

A solution of **2** (0.585 g, 1.89 mmol), **3** (1.50 g, 1.89 mmol), EDC (0.725 g, 3.78 mmol) and DMAP (catalytic amount) in dry dichloromethane (50 mL) was stirred at −20 °C for 24h. The solvent was removed in vacuo. The residue was purified by column chromatography (SiO_2, CH_2Cl_2/CH_3OH, 10:1) to give **4** (1.50 g, 73%) as a white solid. M.p. 188.9–190.4 °C. ^{1}H NMR (400 MHz, chloroform-*d*, room temperature) δ (ppm): 6.93–6.83 (m, 9H), 6.70 (s, 1H), 6.12 (s, 3H), 4.57 (s, 2H), 3.96 (t, J = 6.0 Hz, 2H), 3.80–3.72 (m, 37H), 2.46 (br, 1H), 1.84–1.77 (m, 2H), 1.62 (s, 6H), 1.50–1.42 (m, 2H), 1.25–1.17 (m, 4H), 0.79 (br, 2H), –0.08 (br, 2H), –1.38 (br, 4H), –2.36 (br, 2H). ^{13}C NMR (100 MHz, chloroform-*d*, room temperature) δ (ppm): 167.3, 161.1, 161.0, 150.9, 150.4, 150.3, 150.2, 150.1, 147.1, 129.3, 129.1 128.3, 128.0, 127.9, 127.8, 127.1, 126.9, 114.0, 113.8, 113.6, 113.5, 113.3, 112.8, 112.4, 93.4, 92.7, 67.9, 55.7, 55.4, 55.3, 55.2, 38.0, 30.7, 30.5, 30.3, 29.5, 29.3, 28.9, 28.7, 28.2, 26.8. LRESIMS: *m*/*z* 1108.3 $[M + Na]^+$ (100%). HRESIMS: *m*/*z* calcd for $[M + Na]^+$ $C_{64}H_{79}NNa\ O_{14}^+$, 1108.5398; found 1108.5393; error −5 ppm.

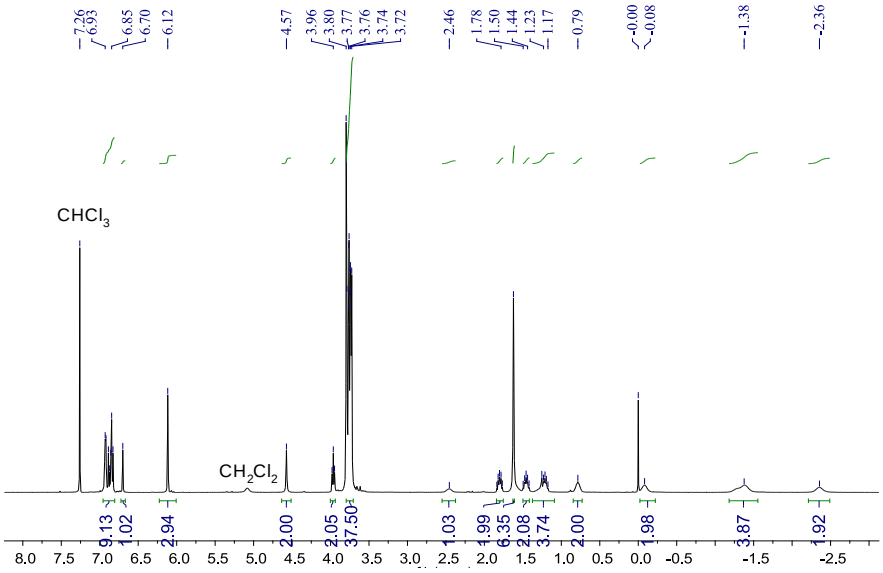


Figure S10. ^{1}H NMR spectrum (400 MHz, chloroform-*d*, room temperature) of **4**.

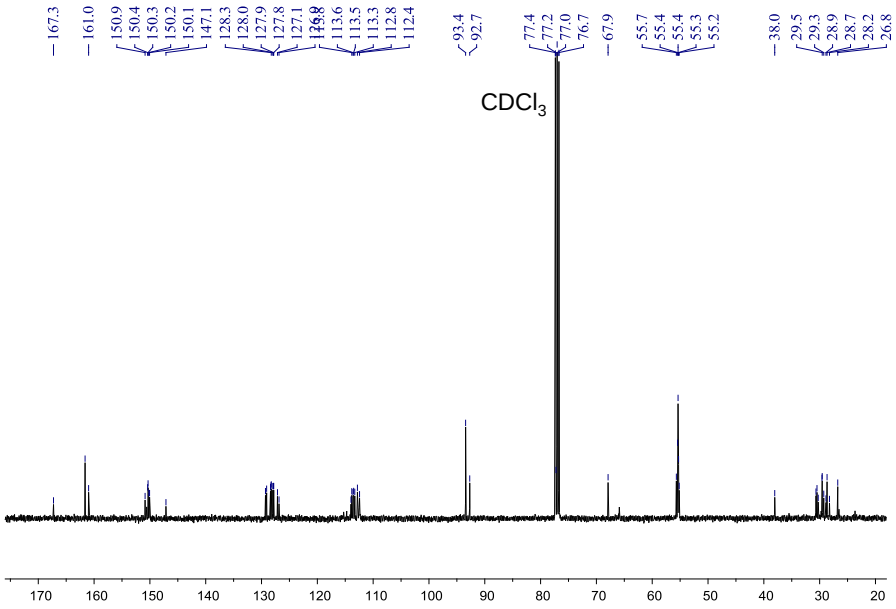


Figure S11. ^{13}C NMR spectrum (100 MHz, chloroform-*d*, room temperature) of **4**.

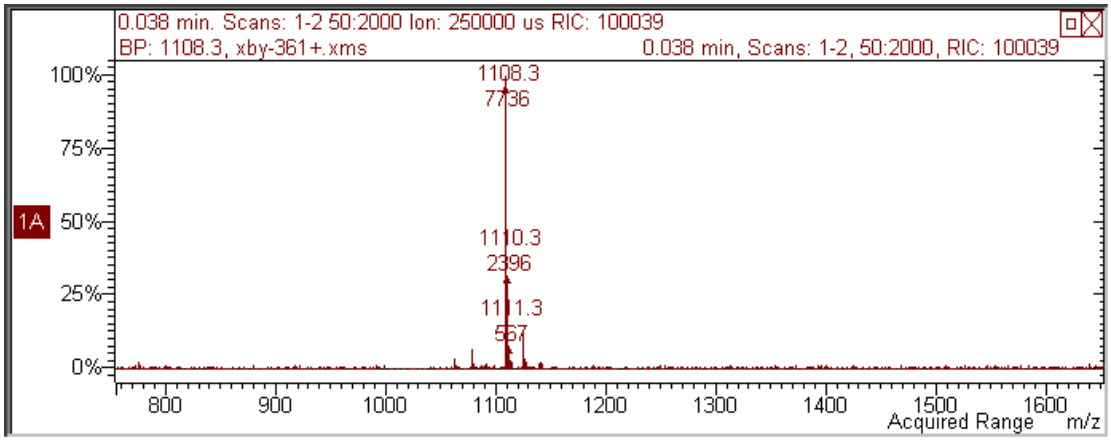


Figure S12. Electrospray ionization mass spectrum of **4**. Assignment of main peak: *m*/*z* 1108.3 $[M + Na]^+$ (100%).

*3. Electrospray ionization mass spectrum of a mixture of **3** and **2***

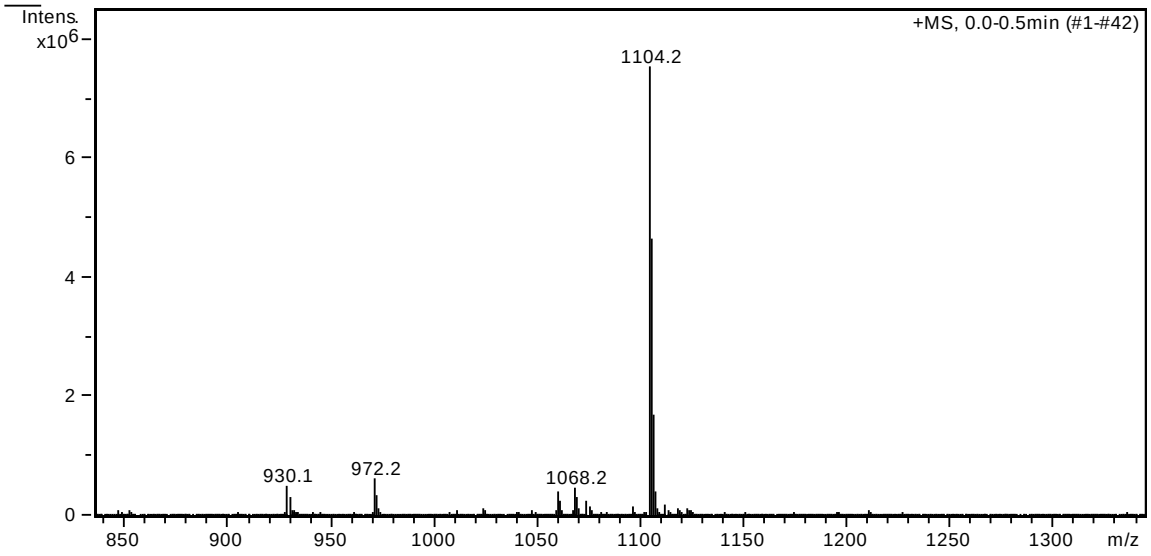


Figure S13. Electrospray ionization mass spectrum of a mixture of **3** and **2**. Assignment of main peak: *m*/*z* 1104.2 $[M + H_3O]^+$ (100%), corresponding to 1:1 complex.

*4. Partial 2D COSY spectrum of a chloroform-d solution of **4***

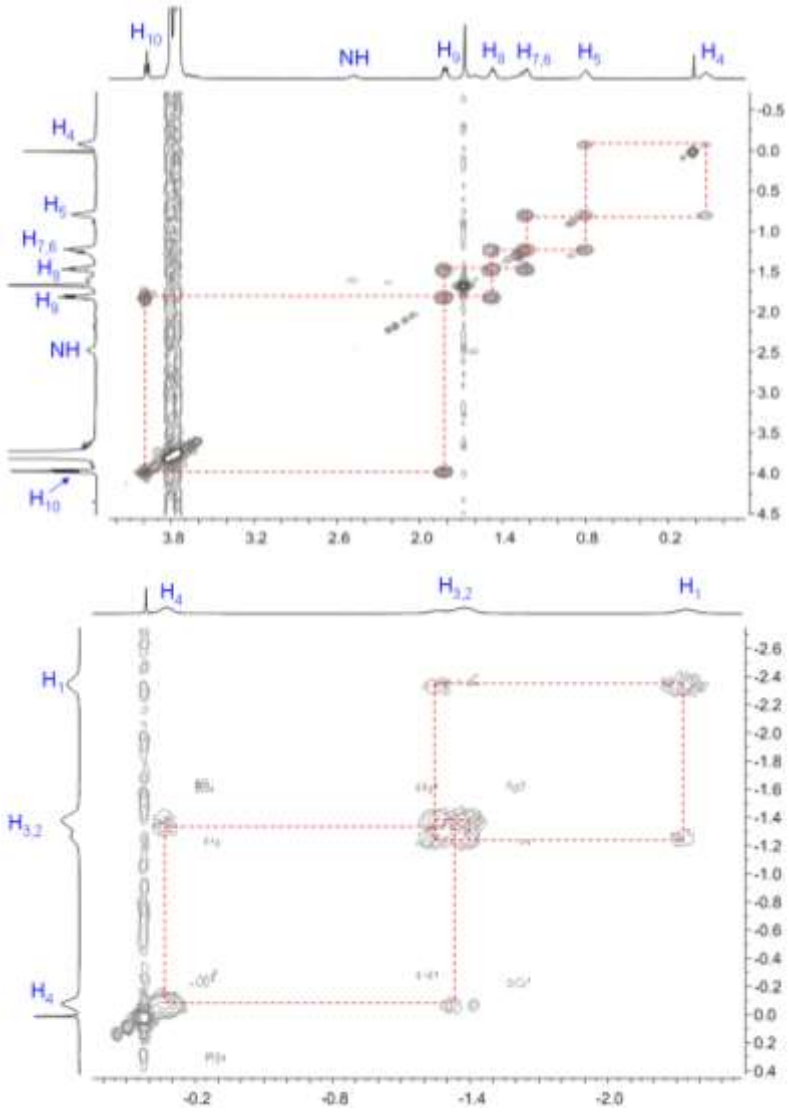


Figure S14. Partial 2D COSY spectrum of a chloroform-*d* solution of **4**.

5. *Association constant determination for the complexation between* ***3*** *and* ***2***

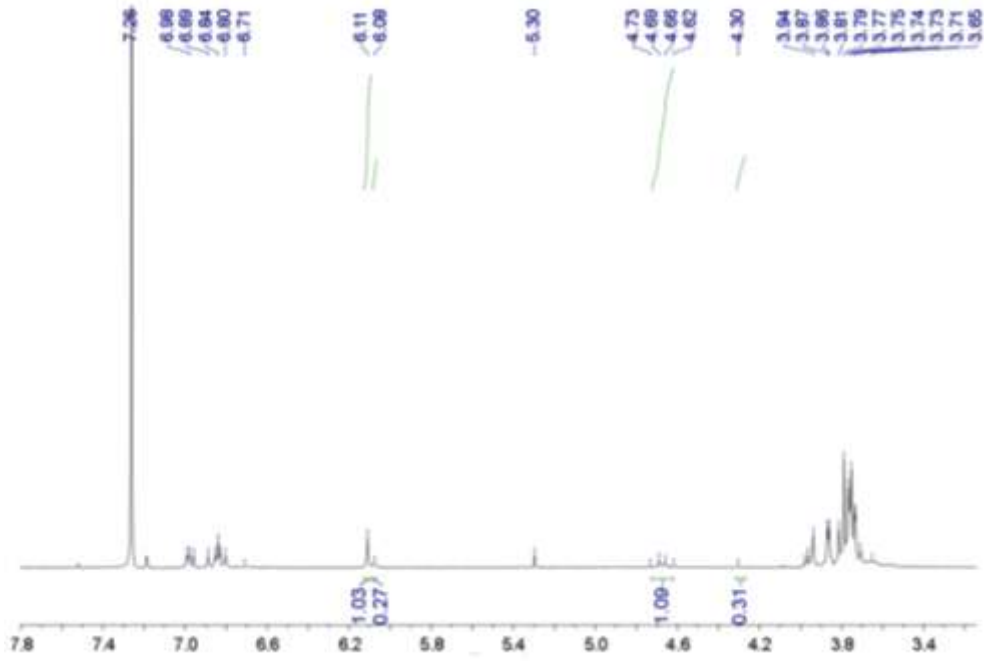


Figure S15. ^{1}H NMR spectrum (400 MHz, chloroform-*d*, 25 °C) of the mixture of 1.00 mM **2** and **3**. The association constant $K_{a,2\bullet3}$ value calculated from integrations of complexed and uncomplexed peaks of H_{11} of **2** is $[(1.03/1.34) \times 1.00 \times 10^{-3}]/[(1 - 1.03/1.34) \times 1.00 \times 10^{-3}]^2 = 1.44 \times 10^4\ M^{-1}$. The association constant $K_{a,2\bullet3}$ value calculated from integrations of complexed and uncomplexed peaks of H_{12} of **3** is $[(1.18/1.49) \times 1.00 \times 10^{-3}]/[(1 - 1.18/1.49) \times 1.00 \times 10^{-3}]^2 = 1.59 \times 10^4\ M^{-1}$. Therefore, $K_{a,2\bullet3} = (1.44 \times 10^4 + 1.59 \times 10^4)/2 = 1.52\ (\pm 0.075) \times 10^4\ M^{-1}$.

*6. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, room temperature) of **4***

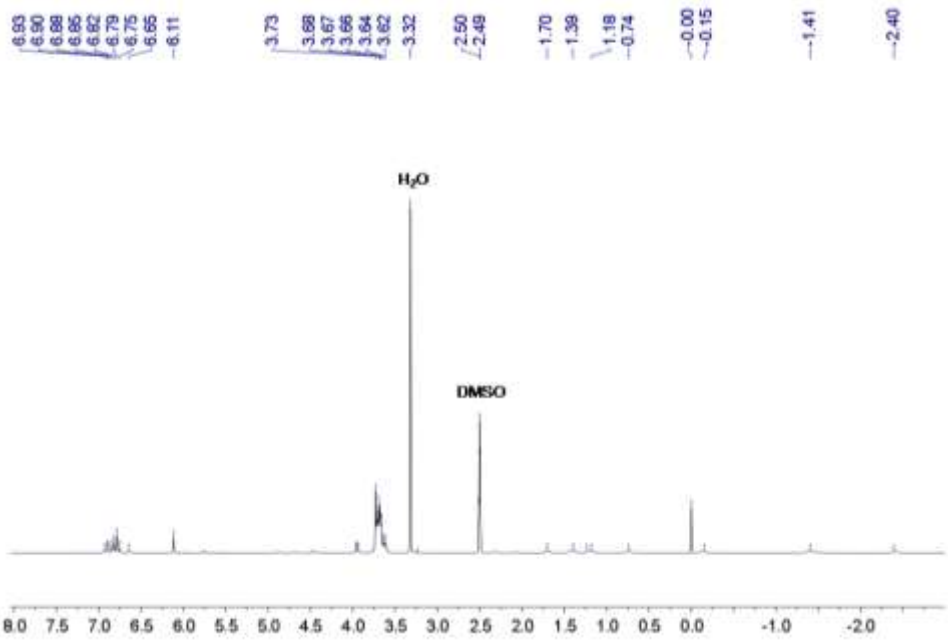


Figure S16. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, room temperature) of **4**.

7. *References*:

S1. K. R. Sathisha, S. A. Khanum, J. N. N. S. Chandra, F. Ayisha, S. Balaji, G. K. Marathe, S. Gopal and K. S. Rangappa, *Bioorg. Med. Chem.*, 2011, **19**, 211–220.