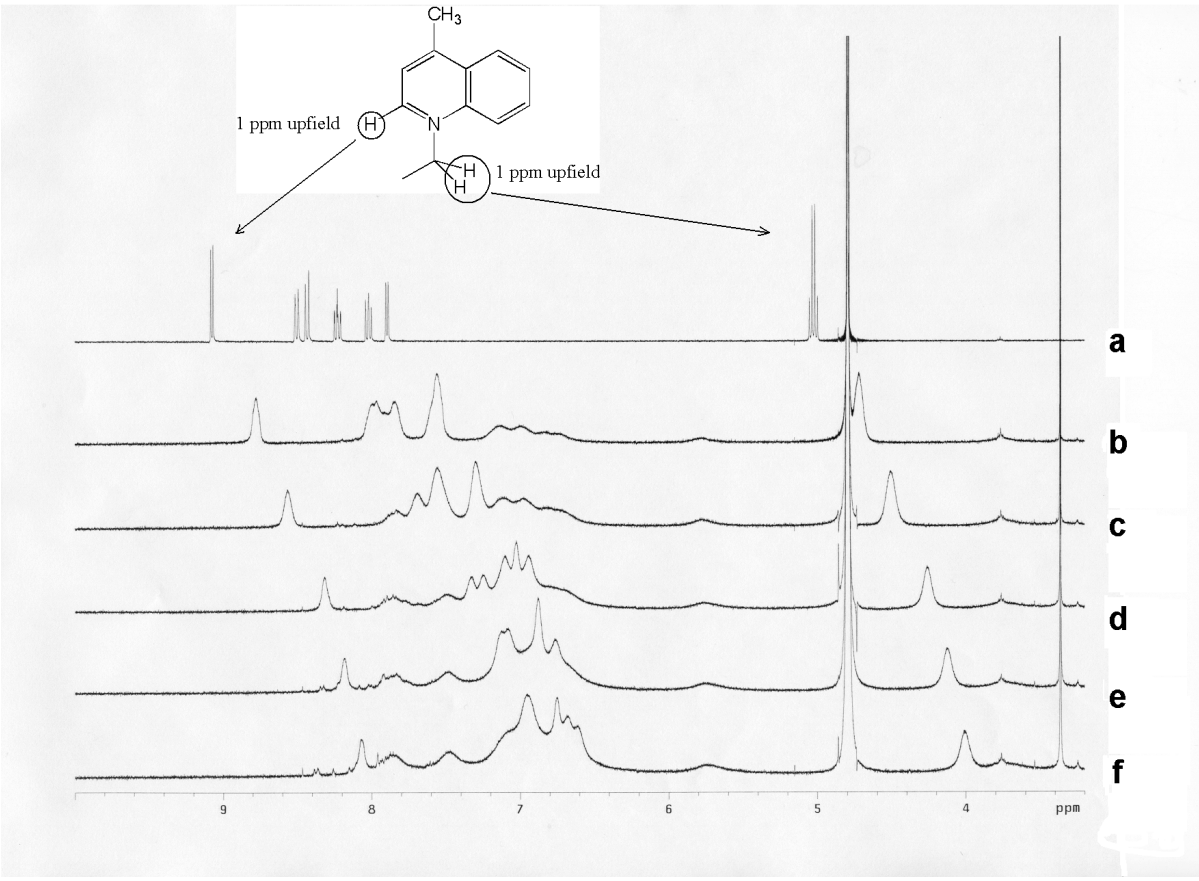
**Supporting Information**

# A Modular Molecular Tweezer Designed using CAVEAT

Haidong Huang and Dale G. Drueckhammer
Department of Chemistry, Stony Brook University, Stony Brook, NY 11794

([1]H-NMR spectra for binding experiments and experimental procedures.)




[1]H-NMR spectra (400 MHz) of **15** (14.3 mM) in $D_2O$ (0.700 mL) (**a**) and after addition of 0.200 mL increments of **11** (20 mM) in $D_2O$ (**b-f**).

**Experimental procedures**

**General.** $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian Gemini-2300 or Inova 400 spectrometer. $^{1}H$ spectra were referenced to the residual proton peak of the deuterated solvent. $^{13}C$ spectra were referenced to $CDCl_3$ (77.00 ppm). Chemicals were purchased from Aldrich and used as received. Molecular orbital calculations were performed using Gaussian03.[S1]

**cis-4-Cyclopentene-1,3-diol:** Cyclopentadiene was distilled from dicyclopentadiene. In to a solution of cyclopentadiene (0.6 mL, 7 mmol) in 50 mL methanol cooled in an ice bath, was bubbled oxygen for 5min. The light from a slide projector was directed through the flask for 4.5h with stirring. Stirring was continued without irradiation overnight. Methanol was removed, and the residue was taken up in 40ml $H_2O$ and was filtered. The water of the filtrate was removed under an air stream. The crude product was purified by column chromatography eluted by 0 to 2% methanol in ethyl acetate to give cis-4-cyclopentene-1,3-diol (120mg, 1.2 mmol). $^{1}H$ NMR ($CDCl_3$) $\delta$ 6.08 (s, 2H), 4.75 (dd, $J_1$=6 Hz, $J_2$=3 Hz), 2.82 (dt, $J_1$=12 Hz, $J_2$=6 Hz, 1H), 1.62 (dt, $J_1$=12 Hz, $J_2$=3 Hz, 1H).

***cis*-Acetic acid 4-hydroxy-cyclopent-2-enyl ester 5:** To a solution of cis-4-cyclopentene-1,3-diol (83 mg, 0.83 mmol) in anhydrous methylene chloride (150 mL) was added triethylamine (172 μL, 1.03mmol) and DMAP (101.4 mg, 0.83 mmol). A solution of acetic anhydride (78 μL, 0.83mmol) in methylene chloride (2 mL) was added dropwise and product formation was monitored by TLC. The reaction was quenched by 0.1 M HCl when diacylated products began to appear. The solution was washed with sodium bicarbonate solution (50 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate and the solvent was removed. The crude product was purified by column chromatography eluted

with 1:1 hexane/ethyl acetate to give **5** (95mg, 0.62 mmol). $^{1}$H NMR ($CHCl_3$) δ 6.13 (d, J=3 Hz, 1H), 5.97 (d, J=3 Hz, 1H), 5.48 (m, 1H), 4.72 (m, 1H), 2.81 (dt, $J_1$=12 Hz, $J_2$=6 Hz, 1H), 2.69 (s, 1H), 2.04 (s, 3H), 1.63 (dt, $J_1$=12 Hz, $J_2$=3 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 170.77, 138.46, 132.14, 77.00, 74.42, 40.26, 21.02; MS (EI) calcd for $C_7H_{10}O_3$ MW 142.1, m/z found 82 ($M^+$-AcOH).

***trans*-4-(3-Bromophenyl)-cyclopent-2-enol 7:** To a solution of 1-bromo- 3-iodobenzene (356 μL, 2.79 mmol) in anhydrous THF (5 mL), a solution of isopropylmagnesium chloride in diethyl ether (1.40 mL, 2 M, 2.8 mmol) was added dropwise. The solution was stirred at -5°C for 2h. CuCN (27 mg, 0.09 mmol) was placed in a flask flushed with $N_2$. The freshly prepared Grignard solution was transferred into the CuCN flask and the reaction was stirred for 18 min. **5** (132 g, 0.93 mmol) in THF (2 mL) was added and the resulting mixture was stirred at -5°C for 3h. The reaction was quenched by $NH_4Cl/NH_3$ buffer and extract with diethyl ether (3 × 50 mL). The organic layer was dried over magnesium sulfate and the solvent was removed. The crude product was purified by column chromatography eluted with 2:1 hexane/ethyl acetate to give **7** (137 mg, 0.57mmol). $^{1}$H NMR ($CDCl_3$) δ 7.37 (d, J=6 Hz, 1H), 7.29 (s, 1H), 7.21 (t, J=6 Hz, 1H), 7.10 (d, J=6 Hz, 1H), 6.08 (m, 1H), 6.02 (m, 1H), 5.07 (m, 1H), 4.15 (m, 1H), 2.30 (ddd, $J_1$=18 Hz, $J_2$=10 Hz, $J_3$=3 Hz, 1H), 2.10 (m, 2H); $^{13}$C NMR($CDCl_3$) δ 147.17, 138.11, 134.63, 130.06, 130.02, 129.38, 125.74, 122.59, 77.10, 49.57, 43.78. RSMS (ESI) calcd for $C_{11}H_{12}BrO$ ($MH^+$) 238.9895, m/z found 238.9888.

***trans*-Acetic acid 4-(3-bromophenyl)-cyclopent-2-enyl ester:** The reaction was performed by using the same procedure as the synthesis of **5**. The crude product was purified by column chromatography eluted with 10:1 hexanes/ethyl acetate to give *trans*-acetic acid

4-(3-bromophenyl)-cyclopent-2-enyl ester (121 mg, 0.44 mmol). $^{1}$H NMR ($CDCl_3$) δ 7.40 (d, J=6 Hz, 1H), 7.34 (s, 1H), 7.22 (t, J=6 Hz, 1H), 7.11 (d, J=6 Hz, 1H), 6.17 (m, 1H), 6.12 (m, 1H), 5.89 (m, 1H), 4.15(m, 1H), 2.44(ddd, $J_1$=18Hz, $J_2$=10Hz, $J_3$=3Hz, 1H), 2.17(m, 1H), 2.12(s, 3H). $^{13}$C NMR ($CDCl_3$) δ 170.84, 146.53, 140.51, 130.87, 130.14, 130.09, 129.59, 125.71, 122.66, 79.93, 49.58, 40.28, 21.17; MS (EI) Calcd for $C_{13}H_{13}BrO_2$ MW 280, m/z found 220 ($M^+$-AcOH).

***cis*-3,5-Bis-(3-bromophenyl)-cyclopentene 8:** The reaction was performed by using the same procedure as the synthesis of **7**. The crude product was purified by column chromatography eluted with hexanes to give **8** (135 mg, 0.36 mmol). $^{1}$H NMR (CDCl3) δ 7.37 (m, 4H), 7.20 (m, 4H), 6.98 (s, 2H), 3.97 (t, 2H), 2.92 (dt, J1=12 Hz, J2=7 Hz, 1H), 1.56 (dt, J1= 12Hz, J2= 7Hz, 1H); 13C NMR (CDCl3) δ 147.62, 135.31, 130.40, 130.05, 129.37, 125.92, 122.58, 51.13, 44.70. HRMS (EI) calcd for $C_{17}H_{14}Br_2$ 375.9463, m/z found 375.9459.

**Compound 9:** To a mixture of methyl 6-bromo-2-naphthoate **(**0.265 g, 1.0 mmol), bis(pinacolato)diborane (0.381 g, 1.5 mmol), Pd(dppf)$Cl_2$ (24 mg, 0.03 mmol), and potassium acetate (0.88 g, 3 mmol) was added anhydrous DMSO (10 mL) and the reaction was stirred at 80°C for 3 h. The resulting mixture was diluted with ethyl acetate (200 mL) and washed with water (50 mL). The organic layer was dried over magnesium sulfate and the solvent was removed. The crude product was purified by column chromatography eluted with 10:1 hexane/ethyl acetate to give **9** (180 mg, 0.59 mmol). $^{1}$H NMR ($CDCl_3$) δ 8.57 (s, 1H), 8.39 (s, 1H), 8.02 (d, 1H, J= 9Hz), 7.90 (m, 3H), 3.95 (s, 3H), 1.37 (s, 12H); $^{13}$C NMR ($CDCl_3$) δ 167.03, 135.75, 134.68, 133.92, 131.10, 130.68, 128.73, 128.22, 128.18, 125.08, 84.01, 52.10, 24.81. HRMS (ESI) ($M^+$) calcd for $C_{18}H_{21}BO_4$, 312.1647, m/z found 312.1632.

**11 Dimethyl ester:** To a mixture of **8** (100 mg, 0.27 mmol), **9** (180 mg, 0.60 mmol), $Pd(PPh_3)_4$ (68 mg) and $K_2CO_3$ (450 mg, 2.5 mmol) was added anhydrous dimethoxyethane (20 mL). The mixture was stirred at reflux for 36h. The solvent was evaporated and the residue was taken up in $CH_2Cl_2$ (50 mL) and washed with brine (20 mL). The organic layer was dried over magnesium sulfate and the solvent was removed. The crude product was purified by column chromatography eluted with 3:1 hexane/ethyl acetate to give **11** dimethyl ester (84 mg , 0.14 mmol). $^1$H NMR ($CDCl_3$) δ 8.58 (2H, s), 8.02 (4H, d, J=6 Hz), 7.94 (2H, d, J=6 Hz), 7.86 (2H, d, J=6 Hz), 7.78 (2H, J=6 Hz), 7.62 (2H, s), 7.59 (2H, d, J=6 Hz), 7.43 (2H, t, J=6 Hz), 7.37 (2H, d, J=6 Hz), 6.10 (2H, s), 4.16 (2H, t), 3.98 (6H, s), 3.08 (1H, m), 1.83 (1H, m); $^{13}$C NMR ($CDCl_3$) δ 167.16, 146.48, 140.97, 140.78, 135.73, 135.56, 131.57, 130.73, 129.79, 129.09, 128.31, 127.30, 126.97, 126.47, 126.38, 125.62, 125.49, 125.45, 52.19, 51.67, 44.77.

**Compound 11:** **11** Dimethyl ester (32 mg, 0.053 mmol) was stirred in 10 mL 0.1M KOH in 1:1(v:v) MeOH/THF solution at reflux for 12 h. The solvent was removed the residue was taken up in 2 mL water and acidified with 1 M HCl. The precipitate was filtered and washed with water 3 times. The solid was dried in air to give **11** (30 mg, 0.053 mmol). $^1$H NMR ($d_6$-DMSO) δ 8.59 (2H, s), 8.24 (2H, s), 8.13 (2H, d, J=6 Hz), 8.00 (2H, d, J=6Hz), 7.94 (2H, d, J=6Hz), 7.88 (2H, d, J=6 Hz), 7.68 (4H, d, J=6 Hz), 7.48 (2H, t, J=6 Hz), 7.34 (2H, d, J=6 Hz), 6.13 (2H, s), 4.16 (2H, t, J=9 Hz), 3.08 (1H, m), 1.67 (1H, m); $^{13}$C NMR ($d_6$-DMSO) δ 167.61, 146.58, 140.04, 139.89, 135.48, 135.42, 131.46, 130.35, 130.10, 129.50, 128.66, 128.25, 127.05, 126.14, 125.76, 125.29, 125.16, 50.93, 44.35; HRMS (ESI) calcd for $C_{39}H_{29}O_4$ ($MH^+$) 561.2066 found m/z 561.2058.

**Methyl 6-bromo-5-chloro-2-naphthoate 14:** To a mixture of methyl 6-bromonaphthoate **13** (2 g, 7.54 mmol), LiCl (497 mg, 11.3 mmol), and lead acetate (5 g, 11.3 mmol) was added trifluoroacetic acid (12.5 mL). The reaction was stirred at room temperature for 1h. The solvent was removed and the residue was dissolved in 100 mL EtOAc and carefully washed with sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and the solvent was removed. The crude product was first purified by column chromatography eluted with 10:1 hexanes/ethyl acetate. The product from the column was then further purified by recrystallization from hexanes to give **14** (753 mg, 2.47 mmol). $^{1}$H NMR ($CDCl_3$) δ 8.55 (s, 1H), 8.31 (d, J=6 Hz, 1H), 8.15 (d, J=6 Hz, 1H), 7.71 (s, 2H), 3.98 (s, 3H); $^{1}$H NMR ($d_6$-DMSO) δ 8.76 (s, 1H), 8.38 (d, J=6 Hz, 1H), 8.22 (d, J=6 Hz, 1H), 8.19 (d, J=6 Hz, 1H), 7.90 (d, J=6 Hz, 1H), 3.99 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 166.50, 133.82, 132.19, 131.05, 131.02, 128.98, 128.39, 127.36, 125.40, 123.41, 52.44. HRMS (ESI) calcd for $C_{12}H_9O_2BrCl$ ($MH^+$) 298.9474, found m/z 298.9466.

**Methyl 5-chloro-6-iodo-2-naphthoate:** Methyl 6-bromo-5-chloro-2-naphthoate **14** (200 mg, 0.67 mmol), KI (333 mg, 2.01 mmol), CuI (10 mg, 0.052 mmol), and N,N'-dimethylethylenediamine (9 mg, 0.1 mmol) were dissolved in 1 mL anhydrous dioxane. The reaction was heated at reflux for 24 h. The mixture was quenched by 1 mL ammonia, diluted with water (20 mL), and extracted with chloroform (3 × 20 mL). The organic layer was dried over magnesium sulfate and the solvent was removed. The residue was purified by column chromatography eluted with 10:1 hexanes/ethyl acetate to yield 1:1(m:m) mixture of **14** and methyl 5-chloro-6-iodo-2-naphthoate (186 mg). The mixture was not further purified and was used directly in the next reaction.

**Compound 10:** The 1:1 mixture of **14** and methyl 5-chloro-6-iodo-2-naphthoate (186 mg, 0.27 mmol of each component) was dissolved in THF (5 mL) at -30°C. A solution of i-PrMgCl in THF (2 M, 0.15ml, 0.3mmol) was added dropwise over 5 min. The reaction was stirred for 90 min and kept at -30°C. Isopropyl pinacol borate (61 μL, 0.3 mmol) was added. The reaction was warmed to room temperature slowly and stirred overnight. The reaction was quenched by saturated ammonium chloride solution and extracted with chloroform (3 × 20 mL). The organic layers were combined, dried over magnesium sulfate and the solvent was removed. The residue was purified by column chromatography eluted with 10:1 hexanes/ethyl acetate to give **10** (91 mg, 0.27 mmol). $^{1}$H NMR ($CDCl_3$) δ 8.58 (s, 1H), 8.43 (d, 1H, J=9 Hz), 8.13 (d, 1H, J=9 Hz), 7.83 (d, 1H, J=8 Hz), 7.76 (d, 1H, J=8 Hz), 3.99 (s, 3H), 1.43 (s, 12H); $^{13}$C NMR ($CDCl_3$) δ 166.79, 138.12, 134.77, 132.91, 131.63, 130.91, 128.76, 127.32, 126.24, 125.71, 84.51, 52.34, 24.84. HRMS (ESI) calcd for $C_{18}H_{21}BClO_4$ ($MH^+$) 347.1221, found m/z 347.1213.

**Dimethyl ester of 12:** To a mixture of **8** (50 mg, 0.13 mmol), **10** (97 mg, 0.29 mmol), $Pd(PPh_3)_4$ (33 mg), $K_2CO_3$ (220 mg, 1.6 mmol) was added dimethoxyethane (5 mL). The mixture was stirred at reflux for 36 h. The mixture was diluted with 50 mL $CH_2Cl_2$ was washed with brine (30 mL). The organic was dried over magnesium sulfate and the solvent was removed. The crude product was purified by column chromatography eluted with 3:1 hexane/ethyl acetate to give **12** dimethyl ester (34 mg, 0.06 mmol). $^{1}$H NMR ($CDCl_3$) δ 8.60 (s, 2H), 8.33 (d, 2H, J=8 Hz), 8.15 (d, 2H, J=8 Hz), 7.84 (d, 2H, J=8 Hz), 7.50-7.31 (m, 10H), 6.05 (s, 2H), 4.11 (t, 2H), 4.03 (s, 6H), 3.03 (m, 1H), 1.79 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ 166.80, 145.70, 140.27, 139.93, 135.59, 133.35, 132.72, 130.95, 129.54, 129.41, 128.66, 128.26, 128.02, 127.49, 127.07, 126.68, 125.43. 52.36, 51.62, 45.17.

**Compound 12:** **12** Dimethyl ester (32mg, 0.486 mmol) was stirred in 10 mL 0.1M KOH in 1:1(v:v) MeOH/THF solution at reflux for 12 h. The solvent was removed the residue was dissolved in 2 mL water and acidified with 1 M HCl until the solution turned acidic. The precipitate was filtered and washed with water for 3 times. The solid was dried in air to give **12** (34 mg, 0.0539 mmol). $^{1}$H NMR ($d_6$-DMSO) δ 8.68 (2H, s), 8.11 (6H, m), 7.57 (2H, d, J=8 Hz), 7.39 (8H, m), 6.02 (2H, s), 4.11 (2H, t), 3.03 (1H, m), 1.62 (1H, m); $^{13}$C NMR ($d_6$-DMSO) δ 166.94, 145.54, 139.66, 139.25, 135.29, 132.55, 132.26, 130.80, 129.33, 128.96, 128.71, 128.48, 128.19, 128.06, 127.30, 127.08, 124.67, 50.67, 43.20.

**NMR Titration**

The NMR titration was performed on Varian 400 MHz NMR. 14.3 mM **15** in 700μL $D_2O$ was added into an NMR tube. 20mM potassium salts of **11** was dissolved in 1ml $D_2O$. The solution of **11** was injected into the solution of **15** at 200μL per injection from a syringe. The chemical shift change was recorded and fitted in Origin 7.0.

$$\frac{\Delta\delta}{\Delta\delta_{max}} = 1/2\left(K + 1 + \frac{K_d}{[G_o]} + \sqrt{(K+1+\frac{K_d}{[G_o]})^2 - 4K}\right)$$

Δδ: the cumulative chemical shift change

$\Delta\delta_{max}$ : maximum chemical shift change

K: the ratio of total host molecule to total guest molecule. K= $[H_0]/[G_0]$

$K_d$ : dissociation constant.

$[G_0]$: total guest molecule concentration. $[G_0]$ changes after each injection due to the dilution.

A blank titration was performed by adding $D_2O$ into the solution of **15**. Less than 0.1 ppm total chemical shifts were observed. The titration with **12** was performed at 1/3 of the

concentration above. Serious broadening was observed after the fourth injection. The binding constant was estimated by assuming that **12** can cause the same degree of chemical shift as **11**.

The host-guest complex concentration is $[HG]= [G_0] \times \Delta\delta/\Delta\delta_{max}$;

The free guest molecule concentration is $[G]= [G_0] - [HG]$;

The free host molecule concentration is $[H]= [H_0] - [HG]$

The dissociation constants were calculated from $K_d = [H] [G] / [HG]$

S1. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; 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 A.1; Gaussian, Inc.: Pittsburgh, PA, 2003.