

**Optically Active Calixarenes Conducted by Methylene Substitution**

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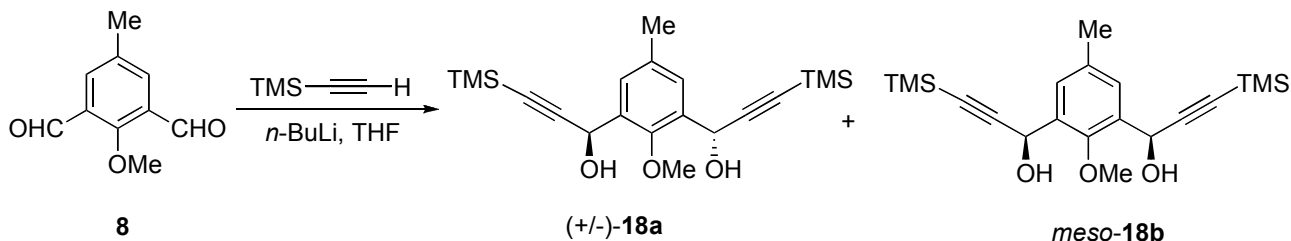
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## General Experimental

All reactions were run using either oven-dried or flame-dried glassware under an inert atmosphere of argon. Chemicals used were reagent grade and used as supplied except where noted. The following solvents were distilled from the listed drying agents: Tetrahydrofuran (Na, benzophenone), diethyl ether (Na, benzophenone), toluene (Na), dichloromethane (CaH<sub>2</sub>). Anhydrous 1,2 dichloroethane was purchased from Aldrich and used under atmosphere of argon. Molecular sieves (4Å) 1/16" pellets were dried in oven over 2-3 days at 125-140°C prior to use. Silver nitrate (99.9995 % Ag) was purchased from Strem chemicals. Chromatographic purifications were performed on Merck silica gel grade (230-400 mesh) by step gradient elution method starting from 5 % ethyl acetate / hexanes unless otherwise mentioned and TLC's were performed on plastic baked TLC plates from Silicycles. The general solvent systems used were either a combination of ethyl acetate / hexanes or dichloromethane / hexanes unless otherwise specified. Compounds were visualized by dipping in solution of KMnO<sub>4</sub> followed by heating with a heat-gun. <sup>1</sup>H NMR data obtained either on a Varian 300 MHz or 500 MHz instrument are reported in parts per million (δ) relative to tetramethyl silane (0.00 ppm) or chloroform (7.24 ppm) for spectra run in CDCl<sub>3</sub> and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets) and br (broad). <sup>13</sup>C NMR data were obtained on the Varian 300 MHz or 500 MHz instruments respectively and are reported in δ relative to CDCl<sub>3</sub> (77 ppm). Infrared spectra were recorded on Perkin Elmer FT IR instrument and the peaks are reported in cm<sup>-1</sup> with indicated relative intensities: s (strong), m (medium), w (weak), brs (broad and strong). 1-D NOE experiments and NOESY experiments were performed on a Varian 600 MHz NMR instrument. Mass spectral data and elemental analysis were obtained from Michigan State University Biochemistry Mass spectrometry facility and in-house facility. The mass spectra were obtained using direct probe EI using chloroform as solvent on JEOL AX-505 double focusing mass spectrometer, FAB conditions using 2-Nitrobenzyl alcohol as solvent on JEOL HX-110 double focusing mass spectrometer in the positive ionization mode. Data are reported in the form of m/z (intensity relative to base peak = 100). 2,6-diformyl-4-methyl anisole was prepared by Swern oxidation of 2,6-bis-hydroxymethyl-4-methyl anisole following literature procedure<sup>1</sup>. The synthesis of carbene complex **13a** was reported in an earlier communication.<sup>2</sup> Organo-lithium reagents were purchased from Aldrich and titrated to a known concentration following the procedure of Gilman.<sup>3</sup> The indicated reaction temperatures are of the oil bath temperature monitored by a digital temperature controller. The reactions were often monitored for completion by quenching an aliquot of the reaction mixture in ether/water and ethereal layer was subjected to GC/MS analyses on Saturn 2000R mass spectrometer and 3800GC using chrome-pack

capillary column. Melting points were recorded on Thomas Hoover capillary melting point apparatus using 1.5-1.8×90mm capillary tubes. Optical rotation measurements were made on a Perkin Elmer 141 polarimeter at 589 nm (Sodium D Line) using 1dm cells. Specific rotations are reported in degrees per decimeter at 25°C and the concentration is given in grams per 100 mL.

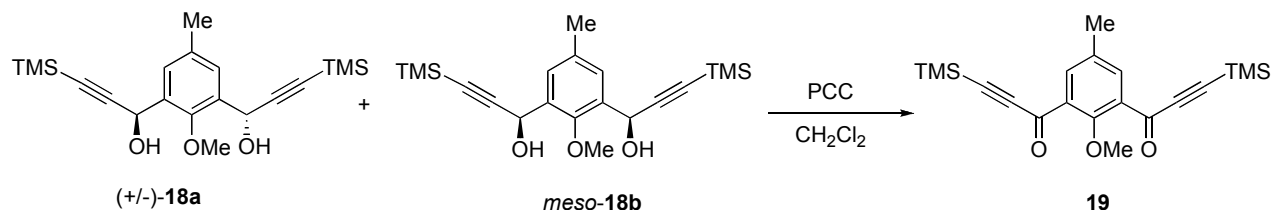
#### Synthesis of the bis-Propargyl Alcohols *rac*-**18a** and *meso*-**18b**.



To a flame dried 50 mL round bottomed flask was added trimethyl silyl acetylene (0.63 mL, 4.48 mmol) and 10 mL of tetrahydrofuran under an argon atmosphere and the solution cooled to  $-78^{\circ}\text{C}$ . *n*-Butyl lithium (2.8 mL, 4.48 mmol, 1.6 M in hexanes) was dispensed into the flask via syringe at  $-78^{\circ}\text{C}$  and the resulting solution was warmed to room temperature while stirring for another 1h. The aldehyde **8**<sup>1</sup> (0.356 g, 2.0 mmol) was added at  $0^{\circ}\text{C}$  and the mixture was left to stir at room temperature for 12h. Water (10 mL) was added and the organic layer extracted with methylene chloride (100 mL). After drying over anhydrous magnesium sulfate, the solvent was removed from the organic layer under vacuum and the crude product purified by silica-gel chromatography (15 % ethyl acetate / hexanes) to afford the two diastereomers **18a** (0.197 g, 0.365 mmol, 18 %) and **18b** (0.67 g, 1.24 mmol, 62 %) as white solids in combined 80 % yield. ( $\pm$ )-2,6-bis(-3-hydroxy-1-trimethylsilylpropynyl)-4-methylanisole **18a**: mp  $97\text{--}100^{\circ}\text{C}$ ,  $R_f$  (3/1 hexanes/ ethylacetate) = 0.40. Spectral data for *rac*-**18a**:  $^1\text{H}$ NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.15 (s, 18H), 2.34 (s, 3H), 2.66 (d, 2H,  $J$  = 6.3 Hz), 3.99 (s, 3H), 5.64 (d, 2H,  $J$  = 6.3 Hz), 7.37 (s, 2H);  $^{13}\text{C}$ NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  -0.25, 20.97, 60.58, 63.77, 91.31, 105.26, 129.34, 133.84, 134.72 (1  $\text{sp}^2$  C not located); IR ( $\text{CDCl}_3$ ) 3393, 2961, 2901, 2837, 2174, 1481, 1437, 1408, 1250  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) 374  $\text{M}^+$  (28), 357 (100), 73 (36), HRMS calcd for  $\text{C}_{20}\text{H}_{30}\text{O}_3\text{Si}_2$   $m/z$  374.1734, measd 374.1736. *Meso*-2,6-bis(-3-hydroxy-1-trimethylsilylpropynyl)-4-methylanisole **18b**: mp  $103\text{--}105^{\circ}\text{C}$ ,  $R_f$  (3/1 hexanes/ ethylacetate) = 0.30. Spectral data for *meso*-**18b**:  $^1\text{H}$ NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.15 (s, 18H), 2.34 (s, 3H), 2.66 (d, 2H,  $J$  = 6.0 Hz), 3.95 (s, 3H), 5.65 (d, 2H,  $J$  = 6.0 Hz), 7.38 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  -0.25, 20.97, 60.53, 63.66, 91.33, 105.20, 129.28, 133.87, 134.75 (1  $\text{sp}^2$  C not located); IR ( $\text{CDCl}_3$ ) 3405, 2961, 2174, 1481, 1437, 1250  $\text{cm}^{-1}$ ; mass

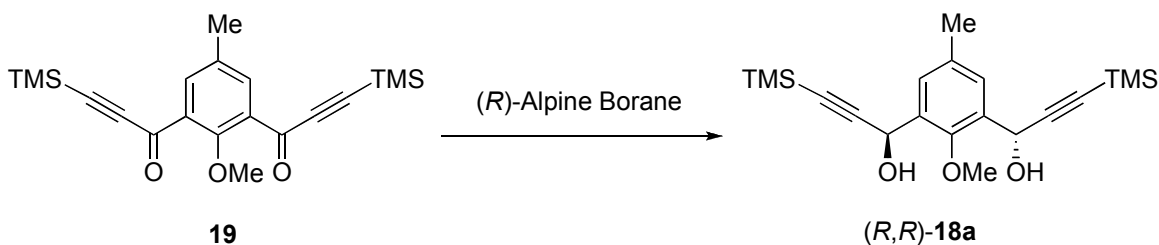
spectrum  $m/z$  (% rel intensity) 374  $M^+$  (28), 357 (100), 154 (16), 136 (16), 73 (40); HRMS calcd for  $C_{20}H_{30}O_3Si_2$   $m/z$  374.1734, measd 374.1736.

#### Oxidation of racemic and meso diols **18a** and **18b** to the diyne **19**.



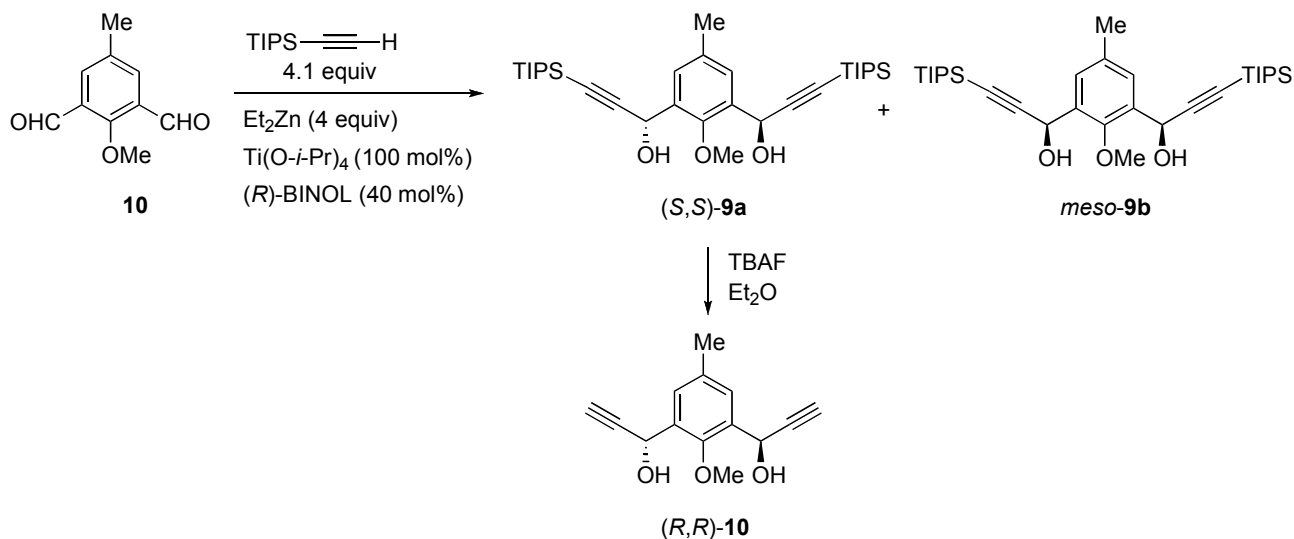
To a mixture of bis-propargyl alcohols  $(+/-)\text{-}\mathbf{18a}$  and  $\text{meso-}\mathbf{18b}$  (7.42 g, 20 mmol) in 60 mL of dichloromethane was added 4Å MS (2.7 g) and Celite (2.7 g) and then pyridinium chlorochromate (2.71 g) was slowly added and the resultant dark brown slurry was stirred at rt for 12h. Filtration of the reaction mixture over a pad of silica-gel and removal of the solvent under reduced pressure afforded the diyne **19** (6.46 g, 17.4 mmol, 87 %) as a yellow oil;  $R_f$  (hexanes / ethylacetate = 95/5) = 0.20. Spectral data for **19**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  0.27 (s, 18H), 2.37 (s, 3H), 3.90 (s, 3H), 7.91 (s, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  0.75, 20.59, 64.10, 100.07, 102.64, 131.75, 133.37, 137.35, 158.82, 176.08; IR ( $\text{CDCl}_3$ ) 2963, 2151, 1653, 1570, 1472, 1421, 1307  $\text{cm}^{-1}$ . mass spectrum ( $m/z$ , % rel.intensity) 371 ( $M^+ + 1$ , 60), 307 (28), 273 (20), 154 (100), 136 (72), 107 (20), HRMS calc'd for  $C_{20}H_{36}O_3Si_2$  371.1499 meas'd 371.1501.

#### Asymmetric Reduction of diyne **19** with (*R*)-Alpine Borane.



To a solution of diynone **19** (2.05 g, 5.5 mmol) in tetrahydrofuran (1.1 M) was added (*R*)-Alpine borane (4 equiv) and the resultant solution was stirred at ambient temperature for 6 h. After the indicated time period, solvent was removed under reduced pressure by applying a water aspirator. The resultant mixture was heated to 40 °C for 20 min to afford a thick reddish oil, which was subsequently dissolved in anhydrous ether (10-15 mL). Ethanolamine (2-3 mL) was added dropwise at 0 °C to facilitate the formation of the borane-ethanolamine adduct that precipitates as a light yellow solid. This mixture was then filtered over a medium porosity glass funnel packed with Celite and the solid was repeatedly washed with ether (50 mL). Removal of the solvent from the filtrate under reduced pressure afforded the crude alkynol that was purified by silica-gel chromatography to afford (*R,R*)-**18a** in 76 % yield (1.55 g, 4.18 mmol). None of the *meso*-**18b** was observed by TLC. The enantiomeric enrichment of (*R,R*)-**18a** was determined to be >99.5% ee upon desilylation to (*S,S*)-**10** in 90 % yield [(*R,R*)-**10** not seen in the HPLC trace].

#### Synthesis of the bis-Propargyl Alcohols (*S,S*)-**9a** and *meso*-**9b**.

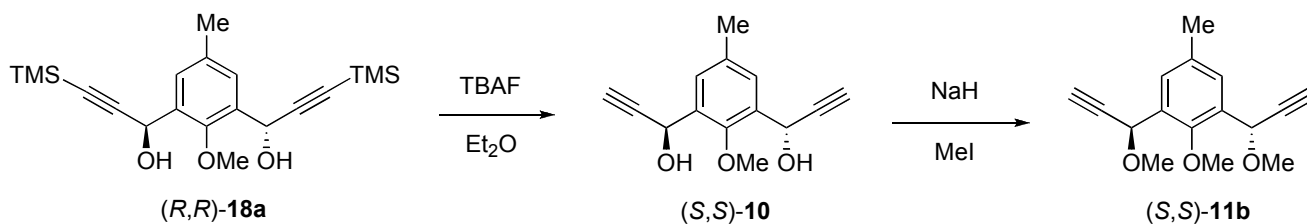


The following procedure was modified from that reported by Pu et.al<sup>4</sup> so as to avoid the use of extremely pyrophoric neat diethyl zinc. Diethyl zinc [1.1 M in toluene] was purchased from Sigma-Aldrich and used under an atmosphere of dry argon. Into a clean flame dried three necked round bottomed flask fitted with a reflux condenser and filled with argon was added triisopropylsilyl acetylene (9.9 mL, 44 mmol) under argon. Toluene (18 mL) and diethyl zinc (1.1 M in toluene, 36 mL, 39.6 mmol) were added and the resulting solution was refluxed for 6 h upon which time the resulting solution turned grey in color. (*R*)-BINOL (1.14 g, 4 mmol) in dichloromethane (40 mL) was

pre-dried over anhydrous 4Å molecular sieves and added to this grey solution and stirred for 15 min. Titanium *iso*-propoxide (3 mL, 10 mmol) was then transferred to the flask via syringe. The solution turned deep red and stirring was continued for another 1h. Aldehyde **8**<sup>1</sup> (1.78 g, 10 mmol) in dichloromethane (40 mL) was added and the reaction was monitored by thin-layer chromatography for completion. Saturated aqueous ammonium chloride (50 mL) was added to quench the reaction. Extraction with dichloromethane (60 mL), drying over anhydrous magnesium sulfate, and evaporation of the solvent resulted in a mixture of products as a yellow oil that were separated by column chromatography (5% to 15% ethylacetate / hexanes) on silica gel to afford the major diastereomer (*S,S*)-**9a** (3.03 g, 5.6 mmol, 56%) and the minor diastereomer *meso*-**9b** (2.28 g, 4.2 mmol, 42%). Specific rotation for (*S,S*)-**9a**:  $[\alpha]_D -22.7$  (*c* 1.06 CHCl<sub>3</sub>). The (*R,R*)-**9a** was prepared accordingly using the (*S*)-enantiomer of 1,1'-Binaphthol or by reduction of **19** with (*R*)-Alpine borane as described above.

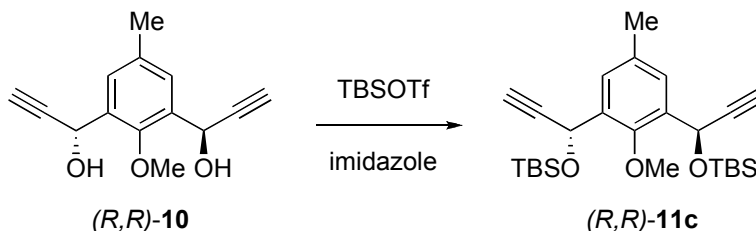
The optical purity of **9a** was measured after desilylation to the diol **10**. A sample (*R,R*)-**9a** (3.03 g, 5.6 mmol) was subjected to desilylation by treatment with 5 equiv of tetrabutyl ammonium fluoride (1 M in THF) in 60 mL of ether. The mixture was stirred at room temperature until consumption of the starting material was complete as indicated by TLC. The final product was purified by silica-gel chromatography (10% to 50% ethyl acetate/hexanes) to afford (*S,S*)-**10** (1.07 g, 4.65 mmol, 83%) as a crystalline white solid. The optical purity was determined to be 99.2% ee by HPLC analysis by comparison of retention times with that of (*R,R*)-**10** prepared in a similar manner from (*S,S*)-**9a** (Chiralcel OD Column, 94:6 hexane:*i*-PrOH to 85:15 hexane:*i*-PrOH, 254 nm). *R*<sub>t</sub> for (*S,S*)-**10** = 47.60 min; *R*<sub>t</sub> for (*R,R*)-**10** = 53.79 min. Spectral data for **10**: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz) δ 2.34 (s, 3H), 2.58 (d, 2H, *J* = 5.7 Hz), 2.63 (d, 2H, *J* = 1.3 Hz), 3.94 (s, 3H), 5.68 (d, 2H, *J* = 5.4 Hz), 7.42 (s, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ 20.94, 59.76, 63.77, 74.65, 83.61, 129.26, 133.58, 135.02, 152.78; IR (CHCl<sub>3</sub>) 3350, 3289, 2925, 2800, 2090, 1481 cm<sup>-1</sup>; mass spectrum *m/z* (% rel intensity) 230 (54), 213 (100), 197 (60), 115 (34). Anal calcd for C<sub>14</sub>H<sub>14</sub>O<sub>3</sub> C, 73.03; H, 6.13. Found C, 73.08; H, 6.33. Specific rotation of (*S,S*)-**10**:  $[\alpha]_D -20.5$  (*c* 0.66 CHCl<sub>3</sub>).

## Preparation of the bis-Propargyl Ether (*S,S*)-11b.



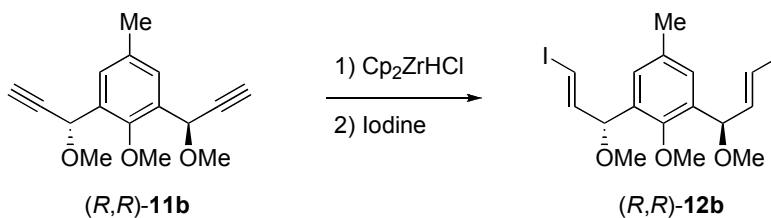
The diynol (*R,R*)-**18a** was desilylated according to the procedure described above for **9a** and gave (*S,S*)-**10** in 90% yield. To a pre-weighed flame dried three necked 100 mL round bottomed flask was added 350 mg (8.75 mmol) sodium hydride (60% dispersion in oil) and pentane (10 mL) was added. The resulting slurry was stirred at ambient temperature for 15 minutes. Most of the pentane was carefully removed using a syringe such that the NaH precipitate was not disturbed and the residual solvent was removed under vacuum to afford 210 mg of sodium hydride. Tetrahydrofuran (30 mL) was added to this flask under argon and then (*S,S*)-**10** (0.782 g, 3.4 mmol) was slowly added over 5 minutes. Upon completion of the addition, the yellow slurry was stirred for another 45 min. Iodomethane (0.70 mL, 11.2 mmol) was added and the reaction was allowed to stir overnight. Ether (25 mL) was added and the reaction was worked up by addition of saturated aqueous ammonium chloride solution (15 mL). The product was extracted with ether (100 mL) and the organic layer was washed with water (100 mL). After drying over anhydrous magnesium sulfate and removal of ether under reduced pressure, the product was purified by silica gel chromatography (15% ethylacetate/hexanes) to afford 0.87 g (3.36 mmol, 99%) of (*S,S*)-**11b** as a colorless oil;  $R_f = 0.37$  (hexanes / ethyl acetate = 85 / 15). Spectral data for (*S,S*)-**11b**:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 500MHz)  $\delta$  2.33 (s, 3H), 2.58 (d, 2H,  $J = 2.5$  Hz), 3.44 (s, 6H), 3.83 (s, 3H), 5.34 (d, 2H,  $J = 2.5$  Hz), 7.44 (s, 2H);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  20.92, 56.35, 63.60, 67.05, 75.14, 81.68, 129.93, 131.40, 134.59, 153.19; IR ( $\text{CH}_2\text{Cl}_2$ ) 3297, 3053, 2992, 2939, 2903, 2824, 2114, 1728, 1662, 1593, 1481, 1435, 1331, 1261; mass spectrum FAB in NBA  $m/z$  (% rel.intensity) 258 (60), 227 (100), 154 (100), 136 (100), 107 (35), 77 (30), HRMS calc'd for  $\text{C}_{16}\text{H}_{18}\text{O}_3$   $m/z$  258.1256, measd 258.1257.  $[\alpha]_D +16.8$  ( $c$  0.5  $\text{CHCl}_3$ ) on material prepared from (*S,S*)-**10** that was >99.5% ee.

### Preparation of the bis-Propargyl Silyl Ether (*R,R*)-11c.



To a solution of the alkynol (*R,R*)-10 (99.2% ee, 0.735 g, 3.2 mmol) in 35 mL of dichloromethane was added imidazole (0.522 g, 7.7 mmol) followed by TBSOTf (1.6 mL, 7.04 mmol) at 0 °C. The reaction mixture was subsequently warmed to room temperature and stirred for 24 h. Addition of water (50 mL), extraction of the organic layer with dichloromethane and removal of the solvent under reduced pressure afforded the bis-propargyl TBS ether (*R,R*)-11c in 92 % yield (1.35 g, 2.92 mmol) as a white solid; mp 124-126°C. Spectral data for (*R,R*)-11c: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ 0.08 (s, 6H), 0.16 (s, 6H), 0.88 (s, 18H), 2.32 (s, 3H), 2.47 (d, 2H, J = 2.4 Hz), 3.82 (s, 3H), 5.71 (d, 2H, J = 2.1 Hz), 7.39 (s, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ -4.90, -4.57, 18.23, 21.32, 25.77, 58.93, 63.03, 72.95, 82.57, 128.34, 134.38, 134.47; IR (neat) 3436, 3277, 2951, 2928, 2899, 2859, 2112, 1644, 1473, 1252 cm<sup>-1</sup>; mass spectrum *m/z* (% rel.intensity) 458 (M<sup>+</sup> not found), 443 (M<sup>+</sup>-CH<sub>3</sub>, 2), 401 (100), 330 (9), 256 (17). Specific rotation: [α]<sub>D</sub><sup>20</sup> +1° (c 1.57 CHCl<sub>3</sub>) on material prepared from (*R,R*)-10 that was 99.2% ee.

### Preparation of bis-Vinyl Iodide (*R,R*)-12b.



Newly purchased or freshly prepared<sup>5</sup> Schwartz reagent (1.14 g, 4.40 mmol) and a stir bar were placed in flame-dried 100 mL round bottom flask under nitrogen and shielded from light with foil and then 10 mL of freshly distilled CH<sub>2</sub>Cl<sub>2</sub> was added. Diyne (*R,R*)-11b (454 mg, 1.76 mmol) was diluted with 10 mL of CH<sub>2</sub>Cl<sub>2</sub> and added *via* syringe in one portion. The reaction mixture was allowed to stir at room temperature for 15 min, after which it was placed in an ice bath, and an iodine solution (1.35 g, 5.30 mmol in 40 mL of CH<sub>2</sub>Cl<sub>2</sub>) was added drop wise *via* syringe until the reaction mixture turned orange in color (usually about 80% of iodine is added at that point). The bath was then removed, and reaction mixture stirred for another 15 minutes, and then poured into 50 mL of saturated aqueous NaHSO<sub>3</sub> and diluted with 150 mL of 10% ethyl acetate in hexane. The resulting two-phase





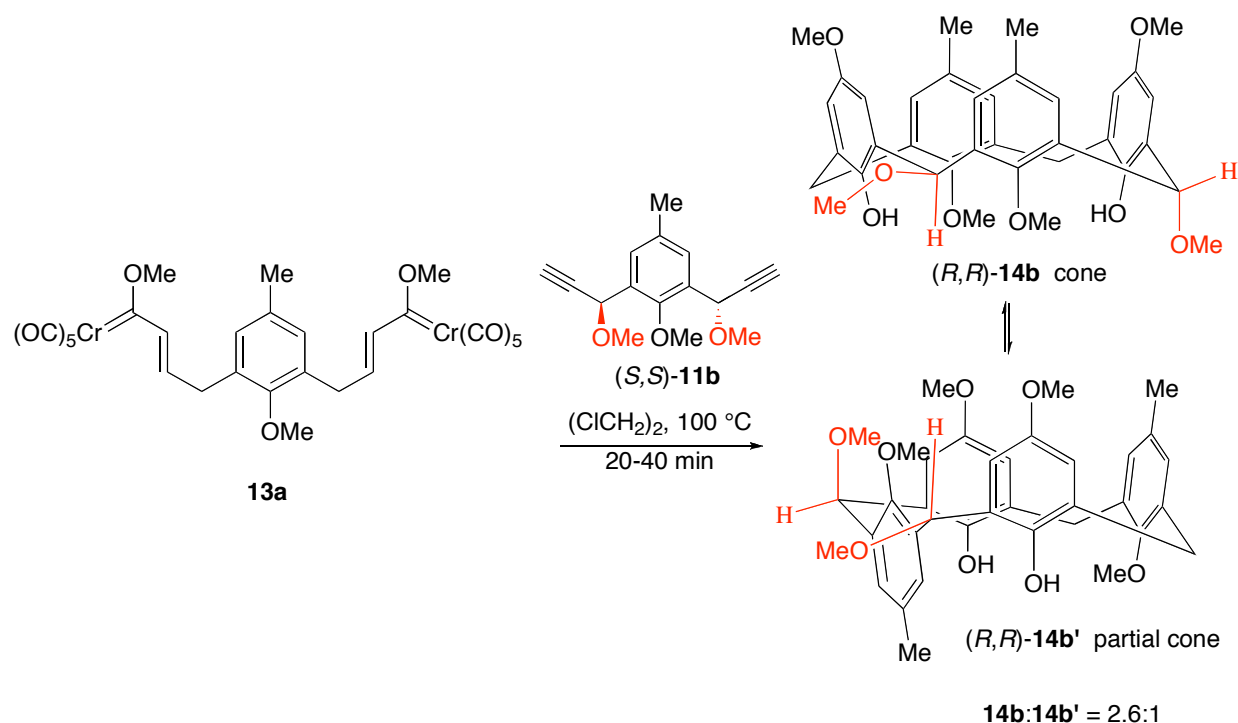
Celite, the solvent was removed and crude product was purified by silica gel chromatography (15% ethyl acetate/hexanes) to give carbene complex (*R,R*)-**13b** in 24 % yield (0.162 g, 0.22 mmol) as a red oil;  $R_f = 0.44$  (20% ethyl acetate in hexanes). Spectral data for (*R,R*)-**13b**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  2.26 (s, 3H), 3.33 (s, 6H), 3.76 (s, 3H), 4.73 (s, 6H), 5.09 (s, 2H), 6.11 (d, 2H,  $J = 11.5$  Hz), 7.10 (s, 2H), 7.54 (d, 2H,  $J = 14.5$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  20.85, 56.95, 63.06, 66.58, 76.22, 129.08, 131.13, 132.09, 135.34, 142.12, 153.68, 216.43, 223.98, 337.19; IR (neat) 2934, 2828, 2060, 1927, 1605, 1452, 1226  $\text{cm}^{-1}$ . mass spectrum  $m/z$  (% rel intensity) 730  $\text{M}^+$  (10), 699 (10), 590 (45), 450 (100), 154 (80), HRMS calcd for  $\text{C}_{30}\text{H}_{26}\text{Cr}_2\text{O}_{15}$   $m/z$  730.0082, meas 730.0084. The carbene complex (*S,S*)-**13b** was prepared in a similar manner from (*S,S*)-**12b** and the following specific rotation was taken on (*S,S*)-**13b**:  $[\alpha]_D -69$  ( $c$  1.22,  $\text{CHCl}_3$ ).

*Procedure B: Addition of *t*-butyl lithium to  $\text{Cr}(\text{CO})_6$  and bis-vinyl iodide (*R,R*)-**12b**.* To a solution of vinyl iodide (*R,R*)-**12b** (0.651 g, 1.26 mmol, 99.5% ee,) and chromium hexacarbonyl (1.11 g, 5.04 mmol) in tetrahydrofuran (55 mL) under argon at  $-78^\circ\text{C}$  was added *t*-butyllithium (4 eq, 1.7 M in pentane) and the reaction mixture was stirred at  $-78^\circ\text{C}$  for 30 min. The resulting deep red solution was warmed to room temperature and stirred for 3 h. The solvent was evaporated under vacuum and 50 mL of a 1:1 mixture of water/dichloromethane was added and then trimethyloxonium tetrafluoroborate (6.5 eq) was added and the mixture stirred for 30 min. The organic layer (150 mL) was washed with water (2 x 50 mL) and dried over anhydrous magnesium sulfate. After filtration through Celite, the solvent was removed and crude product was purified by silica gel chromatography (15% ethyl acetate/hexanes) to give carbene complex (*R,R*)-**13b** in 24 % yield (0.224 g, 0.31 mmol) as a red oil.

*Procedure C: Addition of the bis-vinyl lithium from (*R,R*)-**12b** to  $\text{Cr}(\text{CO})_6$ .* Bis-iodide (*R,R*)-**12b** (463 mg, 0.90 mmol) was placed in 100 mL flame-dried round-bottom flask equipped with a stir bar under nitrogen, and dissolved in the Trapp solvent,<sup>6</sup> prepared by mixing freshly distilled THF (10 mL), diethyl ether (10 mL) and pentane (2.5 mL). The mixture was cooled to  $-117^\circ\text{C}$  by immersing the flask into a diethyl ether/liquid nitrogen bath and then *tert*-butyllithium solution (2.11 mL, 1.7 M in pentane, 3.60 mmol) was slowly added drop wise over 10 minutes. The reaction mixture was stirred for an additional 20 minutes at the same temperature, and then *quickly* transferred *via* a large diameter ( $\sim 3$  mm) Teflon cannula into a 250 mL round-bottomed flask containing a stirred solution of chromium hexacarbonyl (792 mg, 3.60 mmol) in 30 mL of THF which was immersed in a warm ( $40^\circ\text{C}$ ) water bath. The bath was removed after 5 min resulting in the formation of a yellow-orange solution which was allowed to stir for an additional 30 minutes. After the addition of 0.5 mL of water, the mixture was evaporated to dryness by a water aspirator and then dried in vacuo ( $\sim 0.05$  mm Hg, oil pump) for 45 min. The resulting orange solid was

dissolved in a mixture of freshly distilled  $\text{CH}_2\text{Cl}_2$  (30 mL) and deionized water (20 mL) and then trimethyloxonium tetrafluoroborate (866 mg, 5.85 mmol) was added in one portion with vigorous stirring. The stirring was continued for another 30 min, after which the reaction mixture was diluted with 100 mL of ether and washed consecutively with 50 mL of saturated aqueous sodium bicarbonate, water, and brine. The resulting organic phase was dried over  $\text{MgSO}_4$ , filtered through Celite, evaporated to dryness, and the crude product was purified by column chromatography (silica gel, 15% ethyl acetate in hexane) to give 235 mg (0.32 mmol, 36%) of (*R,R*)-**13b** as a dark-red oil.

**General Procedure for the Synthesis of Calixarenes:** Illustrated for the Preparation of 5,17-dimethyl-2(*S*),8(*S*),11,23,26,28-hexamethoxy-25,27-dihydroxycalix[4]arene (*R,R*)-**14b**.

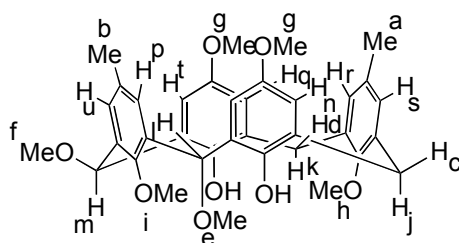


A mixture of carbene complex **13a**<sup>2</sup> (0.161 g, 0.24 mmol) and diyne (*S,S*)-**11b** (0.082 g, 0.32 mmol, >99% ee) in 96 mL of 1,2-dichloroethane was introduced into a 250 mL pear shaped single-necked flask in which the 14/20 joint was replaced by a T-shaped high vacuum Teflon valve. The solution was deoxygenated by the freeze-thaw method (3 cycles,  $-196$  to  $25\text{ }^\circ\text{C}$ ) and then backfilled with argon at ambient temperature. The flask was sealed and then heated at  $100\text{ }^\circ\text{C}$  20-40 min during which time the deep red solution turned yellow. The flask was cooled to room temperature and the yellow solution was stirred overnight exposed to air to facilitate demetalation. The solvent was removed from the resulting dark brown mixture and the residue was dissolved in ethyl acetate (50

mL) and then filtered through a short pad of silica gel. The silica gel pad was rinsed several times with ethyl acetate and the combined organic layer was stripped of solvent to give the crude calixarene. TLC analysis of the crude material revealed only one spot corresponding to the product and examination of the crude  $^1\text{H}$  NMR indicated no other side products. Purification of the product by silica-gel chromatography (50% ethyl acetate/hexanes) afforded the calixarene (*R,R*)-**14b** was obtained in 32% yield (46 mg, 0.077 mmol) as a 2.6/1 mixture of inseparable conformers as a light-yellow solid, mp >320° (dec),  $R_f$  = 0.22 (3/1 hexanes/ethyl acetate). TLC analysis of the crude material revealed only one spot corresponding to the product and examination of the crude  $^1\text{H}$  NMR indicated no other side products. However, it may be possible that a small amount of the calix[8]arene was formed that could not be detected either by TLC or crude  $^1\text{H}$  NMR analysis (See Mass spectral data below). Spectral data for (*R,R*)-**14b**: major conformer **14b**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$  2.10 (s, 3H), 2.12 (s, 3H), 3.35 (d, 2H,  $J$  = 13.5 Hz), 3.41 (s, 3H), 3.47 (s, 3H), 3.78 (s, 6H), 3.94 (s, 3H), 3.99 (s, 3H), 4.10 (d, 1H,  $J$  = 13.0 Hz), 4.39 (d, 1H,  $J$  = 13.0 Hz), 5.06 (s, 1H), 6.01 (s, 1H), 6.61 (d, 1H,  $J$  = 3.0 Hz), 6.65 (d, 1H,  $J$  = 2.0 Hz), 6.73 (s, 1H), 6.77 (s, 2H), 6.85 (s, 1H), 6.93 (s, 1H), 6.97 (d, 1H,  $J$  = 2.5 Hz), 7.07 (s, 1H), 7.78 (s, 1H); minor conformer **14b'**:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 600 MHz)  $\delta$  2.31 (s, 3H), 2.38 (s, 3H), 3.34 (s, 3H), 3.36 (s, 3H), 3.38 (s, 3H), 3.43 (s, 3H), 3.52 (s, 3H), 4.12 (d, 1H,  $J$  = 11.5 Hz), 5.13 (s, 1H), 6.35 (s, 1H), 6.64 (1H overlapping with Ar-H's of major), 6.87 (s, 1H), 7.09 (s, 1H), 7.16 (d, 1H,  $J$  = 2.0 Hz), 7.40 (s, 1H), 7.59 (broad peak undefined no. of H). Three of the methylene hydrogens, one methoxy and two aromatic hydrogens of the minor isomer are not detectable possibly due to overlap of chemical shifts with those from the major isomer.  $^{13}\text{C}$  NMR (125 MHz) (on a mixture of the two conformers)  $\delta$  20.85, 20.89, 20.92, 21.20, 29.68, 31.44, 31.71, 32.05, 37.78, 55.71, 55.74, 55.78, 57.16, 57.28, 57.30, 57.75, 60.99, 62.96, 63.66, 64.26, 73.33, 81.73, 87.93, 107.68, 108.32, 109.84, 112.78, 113.49, 114.14, 114.89, 115.52, 126.30, 127.01, 128.35, 128.46, 128.83, 128.91, 129.31, 129.45, 129.96, 130.01, 130.06, 130.11, 130.18, 130.94, 131.20, 132.34, 132.63, 132.85, 133.10, 133.38, 133.45, 134.13, 134.46, 134.59, 134.74, 135.46, 136.55, 144.41, 145.89, 146.04, 146.30, 151.33, 151.71, 151.76, 151.80, 152.62, 152.93, 153.01, 153.24 (one aryl carbon not located); IR ( $\text{CH}_2\text{Cl}_2$ ) 3328, 2936, 2829, 2247, 1607, 1461, 1435  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel.intensity) 600  $\text{M}^+$  (40), 569 (18), 537 (35), 505 (60), 307 (36), 154 (100), HRMS calcd for  $\text{C}_{36}\text{H}_{40}\text{O}_8$   $m/z$  600.2720, measd 600.2730; Specific rotation:  $[\alpha]_D -11.6$  ( $c$  0.94,  $\text{CHCl}_3$ ). The calix[8]arene is present to only a very small extent as indicated by the relative ratio of the intensities of the peaks in the mass spectrum (40/0.1).

From an extensive analysis of the 1D-NOE and NOESY experiments, the major and minor isomers were deduced to be the cone and partial cone. From the 1D NOE experiment, peaks due to chemical exchange (Phased

positive) in addition to the cross peaks (Phased negative) from the major isomer were observed upon selective irradiation of the hydrogens present in the minor isomer suggesting the possibility of inter-conversion of the two isomers. This result was substantiated by the presence of exchange peaks in the NOESY spectrum.



Cone conformer **14b**

Table 2. Results of NOE Experiment on Major conformer of **14b**<sup>a</sup>

Chemical shift	Proton Irradiated	NOE Observed	Chemical shift	Proton Irradiated	NOE Observed
2.08 (s)	a	r,s	5.03 (s)	l	e, p, s
2.10 (s)	b	u,p	5.98 (s)	m	f, i
3.31 (d)	c	---	6.58 (d)	n	c, g
3.35 (d)	d	---	6.64 (d)	o	l
3.38 (s)	e	---	6.71 (s)	p	b, l
	f	---	6.74 (s)	q	d, g
3.44 (s)	g	NR	6.74 (s)	r	a, d
3.75 (s)	h	NR	6.82 (s)	s	a
3.91 (s)	i	m	6.94 (d)	t	d
3.97 (s)	j	c, -OH	7.05 (s)	u	b
4.11 (d)	k	d			
4.34 (d)					

<sup>a</sup> The closeness of the chemical shifts of the methylene hydrogens and overlap with those of the minor isomer does not permit accurate assignments of NOE effects

HPLC Analysis revealed the presence of two closely spaced peaks (99.5:0.5 hexanes: *i*-PrOH to 95:5 hexanes: *i*-PrOH, flow rate 0.5 mL/min, 254 nm, retention times major = 36.38 min, minor = 38.62, ratio of major / minor = 2.04/1).

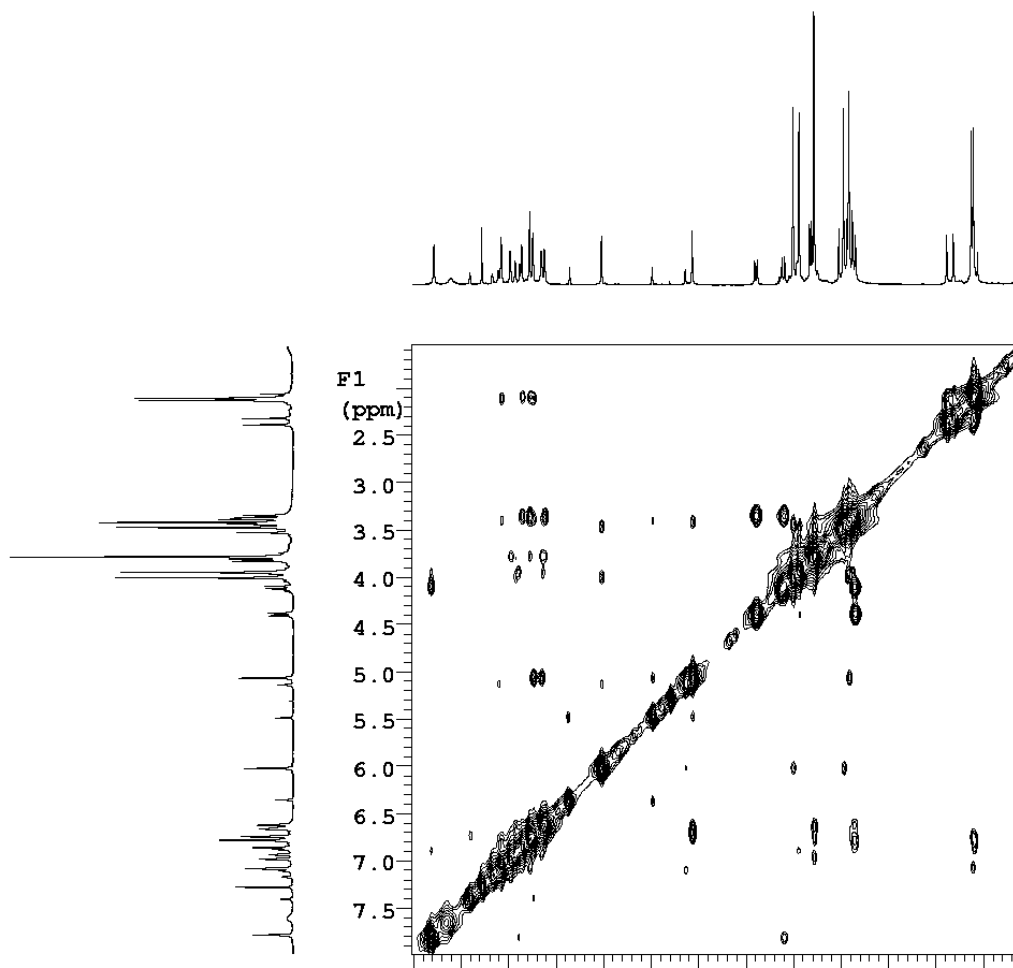


Figure 1. NOESY of mixture of major and minor conformers of **14b** in CDCl<sub>3</sub> at 25°C.

Although a precise assignment of all the protons and their through space interactions with the neighboring protons could not be made either by NOE or by NOESY on the minor isomer, a tentative assignment as the partial cone conformer is based on the 1D-NOE observations shown in Figure 2.

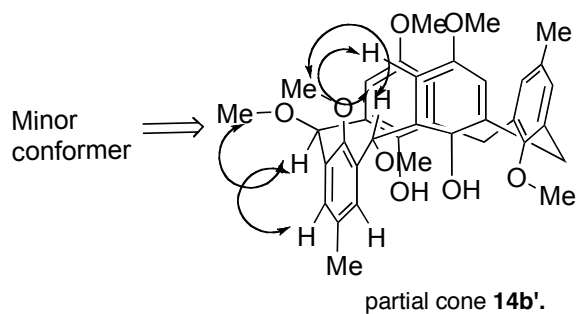
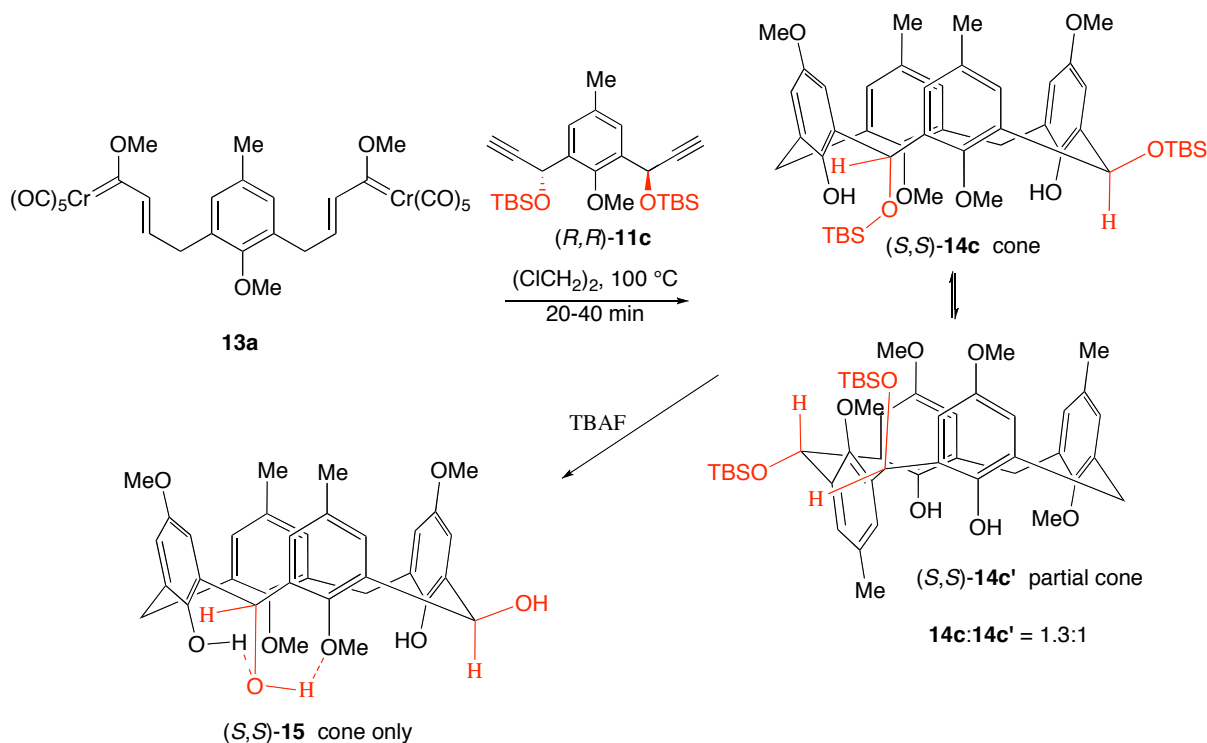


Figure 2. Structure of Minor isomer of **14b**.

Preparation of 5,17-dimethyl-11,23,26,28-tetramethoxy-2(*R*),8(*R*)-tert-butyldimethylsilyloxy-25,27-dihydroxycalixarene (*S,S*)-**14c** and 5,17-dimethyl-11,23,26,28-tetramethoxy-2(*R*),8(*R*),25,27-tetrahydroxycalixarene (*S,S*)-**15**.



Following the general procedure described above for the preparation of (*R,R*)-**14b**, carbene complex **13a**<sup>2</sup> (0.21 g, 0.23 mmol) was reacted with diene (*R,R*)-**11c** (99.2% ee, 0.059 g, 0.23 mmol) in 90 mL of 1,2-dichloroethane. The crude product was purified on silica gel with 15% ethyl acetate/hexanes to give the chiral calixarene (*S,S*)-**14c** as a 1.3:1 mixture of two inseparable conformers in 13 % yield (0.038 g, 0.0498 mmol),  $R_f = 0.39$  (85/15 hexanes/ethyl acetate). These conformers were tentatively assigned as the cone (major) and partial cone (minor). Complete spectral data and structure elucidation was carried out on the desilylated derivative (*S,S*)-**15**. The chiral calix[4]arene **14c** (0.024 g, 0.28 mmol) was dissolved in 10 mL of anhydrous ether and *tetra*-butyl ammonium fluoride (0.5 mL, 0.5 mmol) was added. The resulting slurry was stirred at ambient temperature for 3-4 h. After aqueous workup, drying the organic layer over anhydrous magnesium sulfate and concentration under vacuum, the crude product was purified on a silica-gel column by elution with 50% ethyl acetate/hexanes to give a 56% yield (0.015 g, 0.0265 mmol) of (*S,S*)-**15** as an oil and as a single conformer. The structure of this conformer was ascertained by NOESY to be the cone conformer. Spectral data for (*S,S*)-**15**:  $R_f = 0.3$  (1/1 hexanes/ethyl acetate); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$  2.04 (s, 3H), 2.07 (s, 3H), 3.29 (d, 1H,  $J = 13.0$  Hz), 3.37 (d, 1H,  $J = 14.0$  Hz), 3.74 (s, 3H), 3.77 (s, 3H), 3.98 (s, 3H), 4.04 (s, 3H), 4.05 (d, 1H,  $J = 13.5$  Hz), 4.31 (d, 1H,  $J = 12.5$  Hz), 5.55

(dd, 2H,  $J = 24.0, 11.0$  Hz ), 6.32 (s, 1H), 6.57 (d, 1H,  $J = 2.0$  Hz), 6.62 (s, 2H), 6.67 (d, 1H,  $J = 3.0$  Hz), 6.74 (d, 1H,  $J = 2.0$  Hz), 6.81 (d, 1H,  $J = 2.0$  Hz), 6.98 (d, 1H,  $J = 2.0$  Hz), 7.05 (d, 1H,  $J = 3.5$  Hz), 7.32 (s, 1H), 7.76 (s, 1H) (OH proton not located);  $^{13}\text{C}$  NMR (125 MHz)  $\delta$  20.90, 20.97, 30.78, 31.93, 55.79, 55.83, 63.84, 64.53, 65.16, 79.64, 106.94, 112.64, 114.49, 114.54, 126.65, 128.56, 129.41, 129.54, 129.57, 130.31, 131.86, 132.09, 132.43, 133.14, 133.56, 134.41, 135.17, 136.49, 144.65, 146.39, 150.41, 151.03, 152.37, 153.00; IR (neat) 3360, 2924, 2850, 1650, 1590, 1481  $\text{cm}^{-1}$ ; mass spectrum  $m/z$  (% rel intensity) (FAB in NBA) 572  $\text{M}^+$  (0.2), 460 (8.4), 307 (76), 107 (36), HRMS calcd for  $\text{C}_{34}\text{H}_{36}\text{O}_8$   $m/z$  572.2410, meas 572.2408. Specific rotation:  $[\alpha]_{\text{D}} +2.7$  ( $c$  0.34,  $\text{CHCl}_3$ ).

### Structure Elucidation by NOESY in $\text{CDCl}_3$

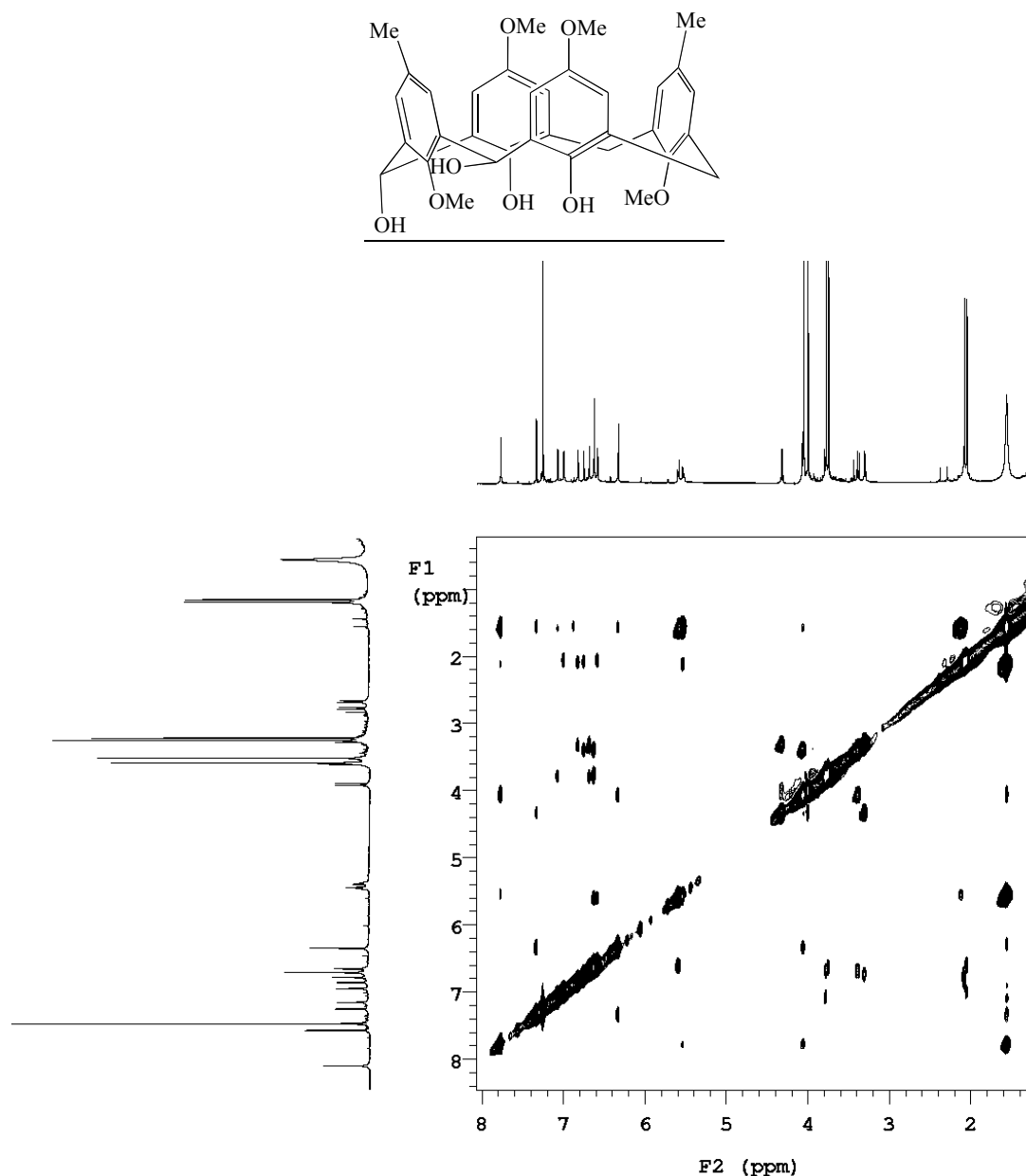
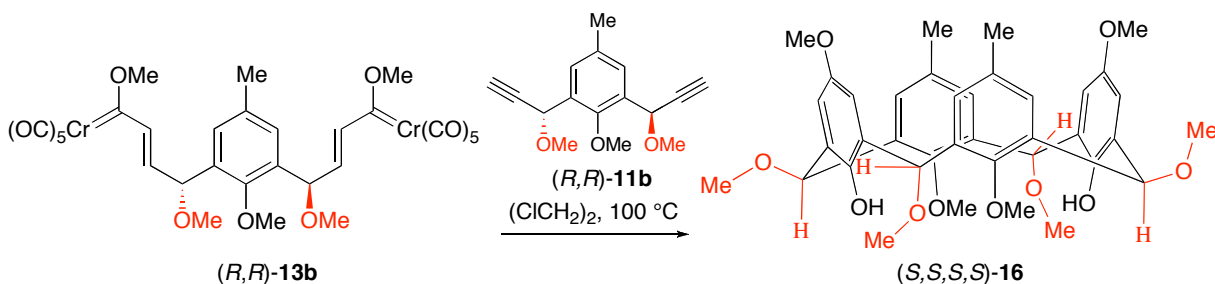


Figure 3. NOESY of **15** in  $\text{CDCl}_3$  at 25  $^{\circ}\text{C}$

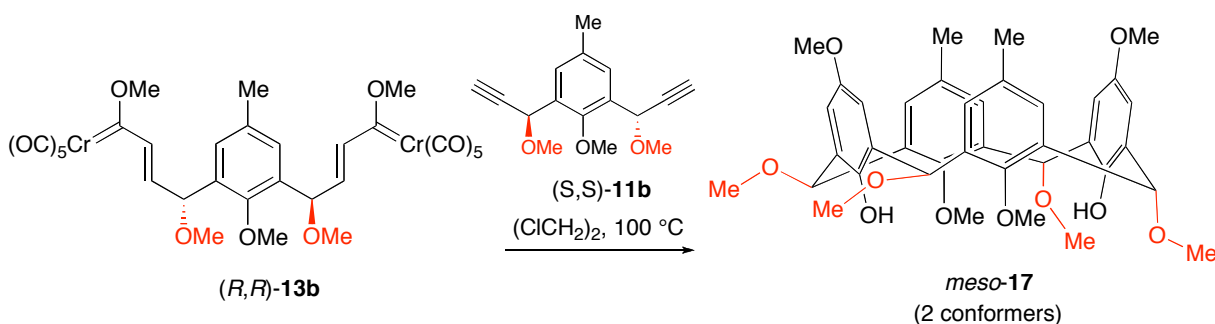


**Preparation of 5,17-dimethyl-2(*S*),8(*S*),11,14(*S*),20(*S*),23,26,28-octamethoxy-25,27-dihydroxycalixarene (*S,S,S,S*)-16.**



The reaction of bis carbene complex (*R,R*)-13b (0.158 g, 0.216 mmol) with the diyne (*R,R*)-11b (0.056 g, 0.216 mmol) in 86 mL of 1,2-dichloroethane was carried out with the general procedure described above for the preparation of (*R,R*)-14b. The reaction mixture was heated to 100 °C for 30 min. Workup according to the general procedure gave the crude calixarene which was purified by flash chromatography on silica gel with 25% ethyl acetate/hexanes as eluent to give a 30 % yield (0.043 g, 0.065 mmol) of (*S,S,S,S*)-16 as powdery white solid; mp 83-86 °C, *R<sub>f</sub>* = 0.32 (3/1 hexanes/ethyl acetate). TLC analysis of the crude material revealed only one spot corresponding to the product and examination of the crude <sup>1</sup>H NMR indicated no other side products. Spectral data for (*S,S,S,S*)-16: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 600 MHz) δ 2.12 (s, 6H), 3.40 (s, 6H), 3.43 (s, 6H), 3.67 (s, 6H), 3.99 (s, 6H), 5.05 (s, 2H), 6.08 (s, 2H), 6.39 (d, 2H, *J* = 3.0 Hz), 6.69 (s, 2H), 6.87 (d, 2H, *J* = 3.0 Hz), 7.15 (s, 2H) (2 OH protons not located); <sup>13</sup>C NMR (125 MHz) δ 20.99, 29.69, 55.78, 57.03, 57.49, 64.18, 72.89, 89.39, 110.61, 114.49, 126.28, 127.89, 129.44, 131.21, 132.85, 134.17, 136.91, 146.41, 152.02 (1 sp<sup>2</sup> C not located); IR (CHCl<sub>3</sub>) 3343, 2930, 2826, 1609, 1483, 1345 cm<sup>-1</sup>; mass spectra *m/z* (% rel intensity) 660 M<sup>+</sup> (56), 629 (20), 597 (60), 565 (100), 535 (20), 149 (60), HRMS calcd for C<sub>38</sub>H<sub>44</sub>O<sub>10</sub> *m/z* 660.2929, measd 660.2934. Anal calcd for C<sub>38</sub>H<sub>44</sub>O<sub>10</sub>: C, 69.07; H, 6.71. Found C, 69.43; H, 7.14. [α]<sub>D</sub> +25.1 (c 0.695, CDCl<sub>3</sub>). The amount of any calix[8]arene that could be present is appreciably small as indicated by relative intensities (56/0.06) of *m/z* ions corresponding to the monomer and dimer in the mass spectrum.

**Preparation of 5,17-dimethyl-2(R),8(R),11,14(S),20(S),23,26,28-octamethoxy-25,27-dihydroxycalix[4]arene *meso*-17.**



The reaction of chiral bis-carbene complex  $(R,R)\text{-13b}$  (0.206 g, 0.24 mmol, 94% ee) with alkyne  $(S,S)\text{-11b}$  (0.073 g, 0.24 mmol) in 96 mL of 1,2-dichloroethane was carried according to the general procedure described above for the preparation of  $(R,R)\text{-14b}$ . The reaction mixture was heated at 100 °C for 8h. Purification of the crude product by silica-gel chromatography (50% ethyl acetate/hexanes) afforded the calix[4]arene *meso*-17 in 26 % yield (0.018 g, 0.028 mmol) as a light yellow solid and as a 1:1 mixture of two inseparable conformers; mp > 284 °C (dec),  $R_f$  = 0.62 (1/1 hexanes/ethyl acetate). The structure of neither of these conformers was assigned. The following data was collected on the mixture of the two conformers. Spectral data for *meso*-17:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  2.14 (s, 6H), 2.36 (s, 6H), 3.34 (s, 6H), 3.39 (s, 6H), 3.40 (s, 6H), 3.42 (s, 6H), 3.47 (s, 6H), 3.79 (s, 6H), 3.80 (s, 6H), 3.83 (s, 3H), 3.89 (s, 3H), 4.98 (s, 2H), 5.06 (s, 2H), 5.47 (s, 2H), 5.49 (s, 2H), 6.28 (s, 2H), 6.64 (s, 1H), 6.89 (d, 2H,  $J$  = 3.0 Hz), 6.93 (s, 2H), 6.95 (s, 2H), 6.99 (s, 2H), 7.04 (d, 2H,  $J$  = 2Hz), 7.15 (d, 2H,  $J$  = 2.5 Hz), 7.27 (s, 2H), 7.42 (d, 2H,  $J$  = 2 Hz) (One hydroxyl group of one of the conformers not located);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  20.85, 21.22, 29.69, 55.63, 55.75, 55.82, 56.96, 57.12, 57.57, 57.75, 63.75, 63.84, 72.92, 73.34, 81.40, 81.56, 108.07, 108.34, 109.88, 110.01, 126.02, 129.26, 129.68, 129.96, 130.66, 131.04, 131.21, 132.28, 132.35, 132.81, 134.07, 134.91, 135.59, 135.72, 143.69, 151.28, 153.25, 153.82; IR ( $\text{CHCl}_3$ ) 3345, 2928, 2826, 1774, 1605, 1481, 1465, 1433  $\text{cm}^{-1}$ ; mass spectrum (FAB in NBA)  $m/z$  (% rel intensity) 660  $\text{M}^+$  (40), 565 (100), 391 (20), 257 (28), 154 (84), calcd for  $\text{C}_{38}\text{H}_{44}\text{O}_{10}$   $m/z$  660.2934 measd 660.2932.  $[\alpha]_D$  0.0 ( $c$  0.834,  $\text{CHCl}_3$ ). No detectable amount of a calix[8]arene was observed by mass spectra. Based on DEPT and HMQC experiments, the calix[4]arene **17** was determined to exist as a (1:1) mixture of two conformers in solution (For HMQC See details below).

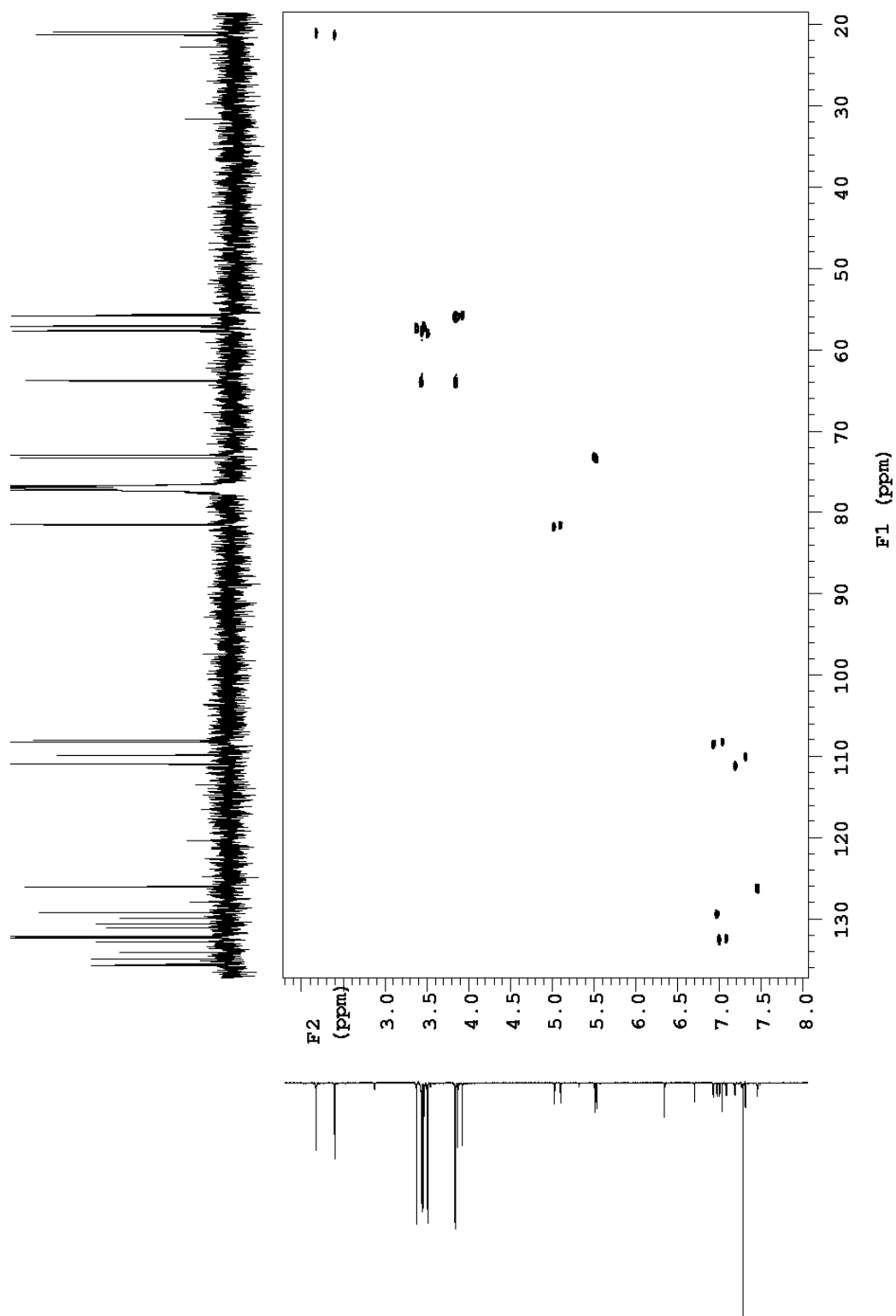


Figure 4. HMQC of **17** in  $\text{CDCl}_3$  at  $25^\circ\text{C}$ .

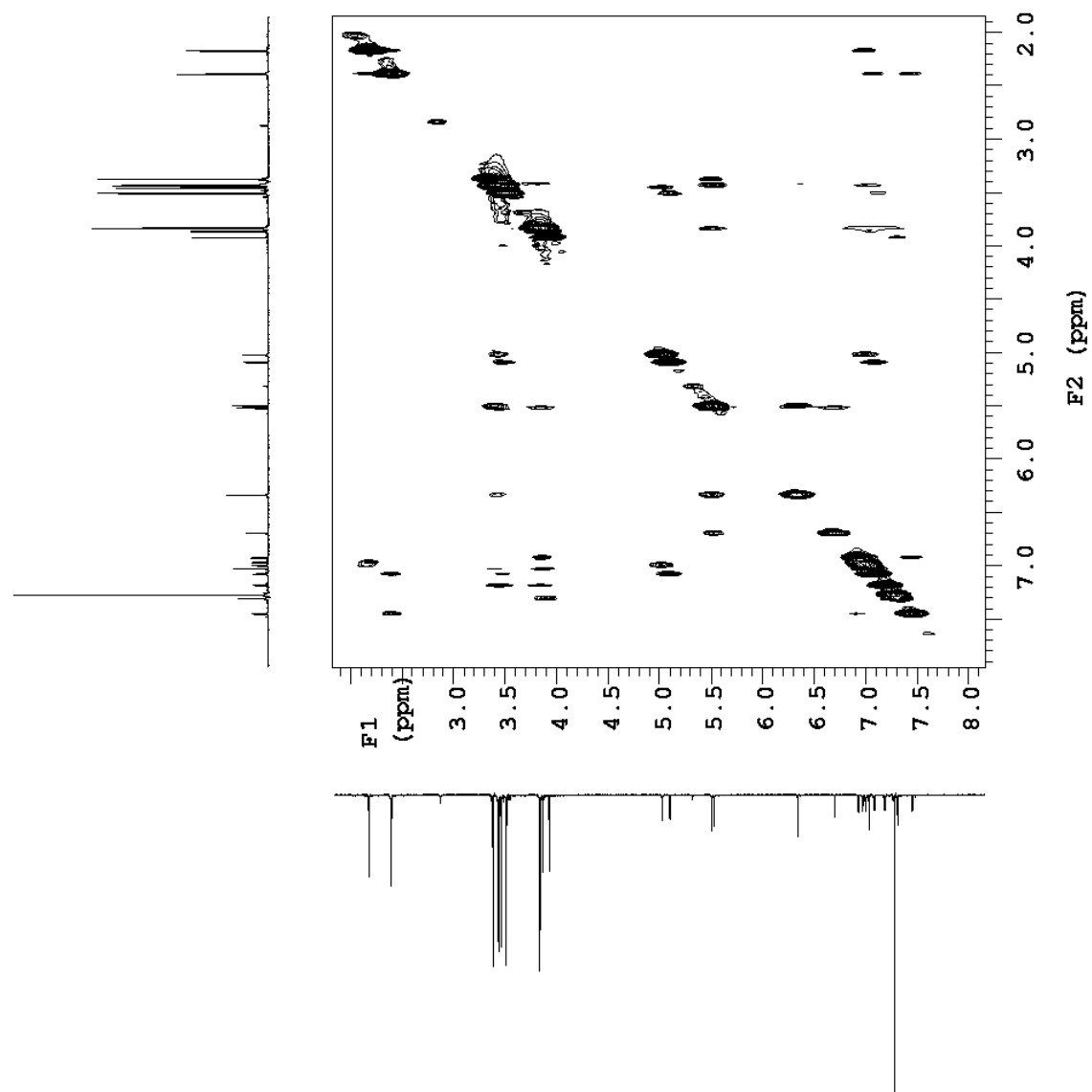
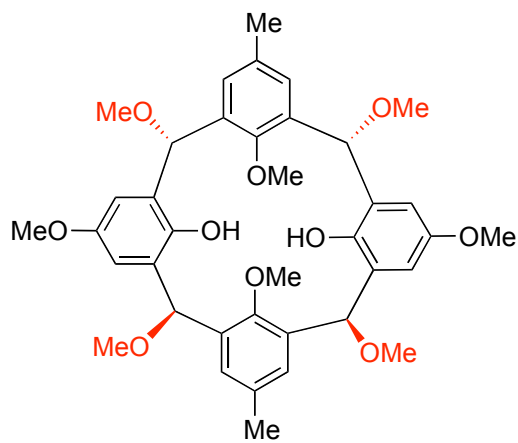


Figure 5. NOESY of 17 in CDCl<sub>3</sub> at 25°C

The structures of the two conformers could not be precisely assigned by 1D-NOE / NOESY experiments but the chemical shifts of the protons corresponding to each isomer were identified (See Table 3 and 4 below).



**17**

Table 3. Results from the 1D-NOE / NOESY experiments for Unknown Conformer **17a**

Chemical Shift	No of Protons	NOE Observed	Chemical shift	No of protons	NOE Observed
2.14 (s)	6H	ND	4.98 (s)	2H	6.96, 3.42
3.40 (s)	6H	ND	5.49 (s)	2H	6.66, 3.80, 3.40
3.42 (s)	6H	ND	6.66 (s)	2H	5.49
3.80 (s)	6H	ND	6.93 (s)	2H	No NOE
3.83 (s)	3H	6.99	6.96 (s)	2H	2.14, 4.99
3.89 (s)	3H	7.27	6.99 (s)	2H	3.83, 3.40
			7.27(s)	2H	3.80, 3.89

Table 4. Results from the 1D-NOE / NOESY experiments for Unknown Conformer **17b**

Chemical Shift	No of Protons	NOE Observed	Chemical shift	No of protons	NOE Observed
2.36 (s)	6H	ND	5.06 (s)	2H	3.47, 7.05
3.34 (s)	6H	ND	5.47 (s)	2H	3.34, 3.39, 6.30
3.39 (s)	6H	ND	6.30 (s)	2H	3.39, 5.47
3.47 (s)	6H	ND	6.89 (s)	2H	3.80, 7.41
3.80 (s)	6H	ND	7.05 (s)	2H	2.36, 3.47, 5.06
			7.16 (s)	2H	3.39, 3.47, 3.80
			7.41 (s)	2H	2.36, 6.89

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