

Synthesis of Cyclobutane Lignans via an Organic Single Electron Oxidant-Electron Relay System

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General Methods

Infrared (IR) spectra were obtained using a Jasco 260 Plus Fourier transform infrared spectrometer. Proton and carbon magnetic resonance spectra (¹H NMR and ¹³C NMR) were recorded on a Bruker model DRX 400, DRX 500, or a Bruker AVANCE III 600 CryoProbe (¹H NMR at 400 MHz, 500 MHz or 600 MHz and ¹³C NMR at 101, 126, or 151 MHz) spectrometer with solvent resonance as the internal standard (¹H NMR: CDCl₃ at 7.24 ppm; ¹³C NMR: CDCl₃ at 77.0 ppm). ¹H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddt = doublet of doublet of triplets, ddd = doublet of doublet of doublets, dddd = doublet of doublet of doublet of doublets m = multiplet, brs = broad singlet), coupling constants (Hz), and integration. Mass spectra were obtained using a Micromass (now Waters Corporation, 34 Maple Street, Milford, MA 01757) Quattro-II, Triple Quadrupole Mass Spectrometer, with a Z-spray nano-Electrospray source design, in combination with a NanoMate (Advion 19 Brown Road, Ithaca, NY 14850) chip based electrospray sample introduction system and nozzle. Cyclic voltammograms were obtained with a platinum disc working electrode, Ag/AgCl reference electrode, a platinum wire auxillary, and CHI-760 potentiostat using 1 mM solutions of analyte in acetonitrile with 0.1 M tetrabutylammonium perchlorate as supporting electrolyte. Thin layer chromatography (TLC) was performed on SiliaPlate 250 μm thick silica gel plates provided by Silicycle. Visualization was accomplished with short wave UV light (254 nm), aqueous basic potassium permanganate solution, or cerium ammonium molybdate solution followed by heating. Flash chromatography was performed using SiliaFlash P60 silica gel (40-63

μm) purchased from Silicycle. Tetrahydrofuran, diethyl ether, dichloromethane, and toluene were dried by passage through a column of neutral alumina under nitrogen prior to use. Irradiation of photochemical reactions was carried out using a 15W PAR38 blue LED floodlamp purchased from EagleLight (Carlsbad, CA), with borosilicate glass vials purchased from Fisher Scientific. All other reagents were obtained from commercial sources and used without further purification unless otherwise noted.

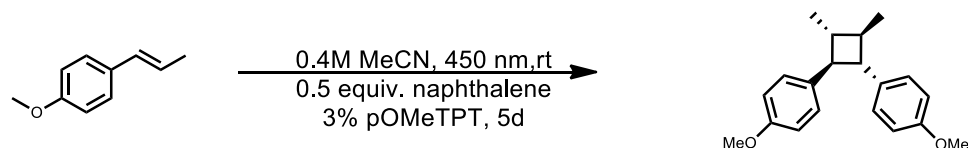
Preparation of terminal and β-methyl styrenes

To an ice-cold mixture of $[\text{Ph}_3\text{PCH}_3]^+\text{Br}^-$ (7.2 g, 20.2 mmol) or $[\text{Ph}_3\text{PCH}_2\text{CH}_3]^+\text{Br}^-$ (7.5g, 20.2 mmol) in THF (155 mL) was added BuLi (in hexanes, 19.4 mmol). The mixture was stirred at the same temperature for 2 h, and a solution of aldehyde (15.5 mmol) in THF (1 mL) was added at -78 °C. The mixture was slowly warmed to room temperature over the course of 3 hours. The reaction was diluted with 15 mL of D.I. water. The resulting mixture was extracted with chloroform twice. The combined extracts were dried over MgSO_4 , and concentrated to leave a solid, which was purified by chromatography on silica gel. The ^1H and ^{13}C NMR spectrum was identical with that reported. β-methyl substituted styrenes were prepared similarly and then isomerized to the *trans* by known procedures.¹

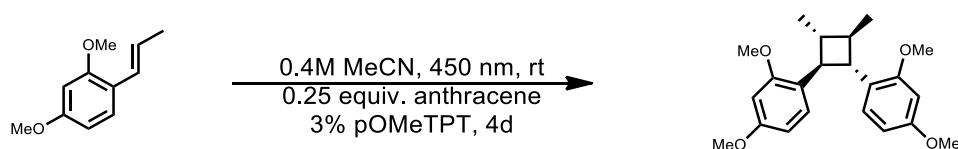
General Procedure A. To a flame-dried two dram vial equipped with a magnetic stir bar was added the terminal styrene (1.0 equiv.), *p*-OMe TPT (3 mol%), and electron relay (0.25-0.5 equiv). The vial was purged with N_2 and sparged acetone was added to achieve a concentration of 0.4 M with respect to substrate, then sealed with a septum screwcap and Teflon tape. The reaction was irradiated with a 450 nm bulb and stirred at the indicated temperature and time period. Upon completion, the reaction was quenched with small amounts of TEMPO, diluted with diethyl ether, and filtered through a short cotton plug. The solution was dry loaded further purified by flash column chromatography with acetone/hexanes as the eluent mixture.

General Procedure B. To a flame-dried two dram vial equipped with a magnetic stir bar was added the substituted styrene (1.0 equiv.), *p*-OMe TPT (3-5 mol%) and electron relay (0.25-0.5 equiv). The vial was purged with N_2 and diluted with freeze-pump-thawed acetonitrile to a concentration of 0.4 M with respect to substrate, then sealed with a septum screwcap and Teflon tape. The reaction was irradiated with a 450 nm bulb and stirred the indicated time period. Upon completion, the reaction was

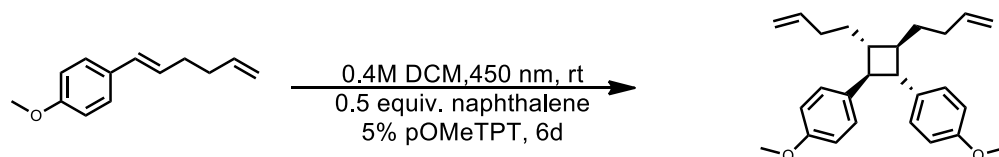
diluted with diethyl ether, and filtered through a short cotton plug. The solution was dry loaded further purified by flash column chromatography with acetone/hexanes as the eluent mixture.



4,4'-(3,4-Dimethylcyclobutane-1,2-diyl)bis(methoxybenzene) (Table 1, Entry 1) The dimer was prepared according to General Procedure **B** using 104 μ L of 4-methoxy- β -methylstyrene, 44.8 mg of naphthalene, and 10.2 mg of p-OMe TPT. Reaction was carried out at room temperature and purified via flash chromatography. Reaction time was 5 days. Yield was 56 mg (54%) of the desired adduct as a clear oil. Characterizations matched literature.² **¹H NMR** (400 MHz, CDCl₃) δ 7.17 (d, 8.8 Hz, 4H), 6.87, (d, J = 8.8 Hz, 4H), 9.80 (s, 6H), 2.84 (dd, J = 3.2, 5.6 Hz, 2H), 1.88 (m, 2H), 1.22 (d, J = 6.0 Hz, 6H). **¹³C NMR** (400 MHz, CDCl₃) δ 157.94, 135.92, 127.71, 113.69, 55.23, 52.47, 43.20, 18.86.

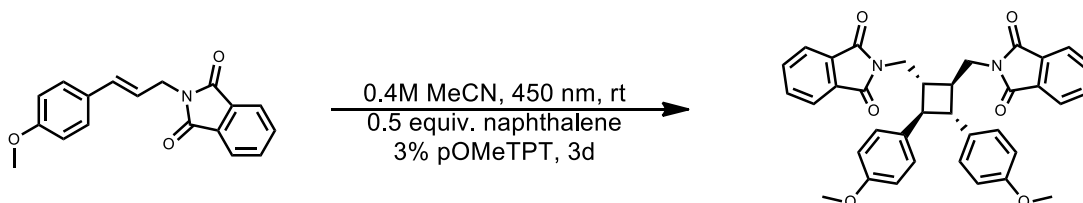


4,4'-(3,4-Dimethylcyclobutane-1,2-diyl)bis(1,3-dimethoxybenzene) (Table 1, Entry 2) The dimer was prepared according to General Procedure **B** using 106 mg of 2,4-dimethoxy- β -methylstyrene, 26.7 mg of anthracene, and 8.8 mg of p-OMe TPT. Reaction was carried out at room temperature and purified via flash chromatography. Reaction time was 4 days. Yield was 50 mg (47%) of the desired adduct as a clear oil. **¹H NMR** (400 MHz, CDCl₃) δ 7.21 (d, J = 12.0 Hz, 2H), 6.45 (dd, J = 2.0, 8.0 Hz, 2H), 6.39 (d, J = 2.4 Hz, 2H), 3.78 (s, 6H), 3.690 (s, 6H), 3.26 (dd, J = 3.6, 5.6 Hz, 2H), 1.76 (d, 5.2 Hz, 2H), 1.17 (d, J = 5.6 Hz, 6H). **¹³C NMR** (400 MHz, CDCl₃) δ 158.75, 158.47, 127.74, 125.01, 103.73, 98.20, 55.30, 55.10, 44.88, 43.43, 19.20. **MS** (+ESI) Calculated m/z for $[M+H]^+$ = 357.20, Found m/z for $[M+H]^+$ = 357.25. **IR** (Thin Film, cm⁻¹): 3050, 2998, 2950, 2861, 2851, 1611, 1585, 1506, 1455, 1438, 1294, 1264, 1208. **TLC** 2% acetone/ 98% Hexanes. CAM stains dark blue.



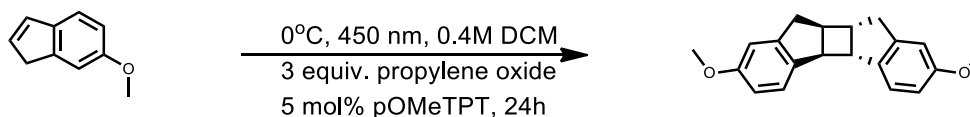
4,4'-(3,4-Di(but-3-en-1-yl)cyclobutane-1,2-diyl)bis(methoxybenzene) (Table 1, Entry 3) The dimer was prepared according to General Procedure **B** using 112.8 mg of (*E*)-1-(hexa-1,5-dien-1-yl)-4-

methoxybenzene, 38.2 mg of naphthalene, and 14.6 mg of *p*-OMe TPT. Reaction was carried out at room temperature and purified via flash chromatography. Reaction time was 6 days. Yield was 52 mg (42%) of the desired adduct as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.14 (d, *J* = 6 Hz, 2H) 6.83 (d, *J* = 6 Hz, 2H) 5.81-5.74 (m, 2H), 4.92 (s, 2H), 4.90 (d, *J* = 4 Hz, 2H), 3.78 (s, 6H), 2.81 (dd, *J* = 2.0, 4.0 Hz, 2H), 2.030 (m, 6H), 1.78-1.67 (m, 4H). ¹³C NMR (400 MHz, CDCl₃) δ 157.91, 138.81, 136.01, 127.93, 114.34, 113.61, 55.18, 52.11, 45.37, 35.28, 31.52. MS (+ESI) Calculated *m/z* for [M+H]⁺ = 377.24, Found *m/z* for [M+H]⁺ = 377.27. IR (Thin Film, cm⁻¹): 3073, 2997, 2914, 2831, 2547, 2359, 1639, 1611, 1581, 1511, 1455, 1440, 1301, 1247. TLC 2% acetone/ 98% Hexanes.



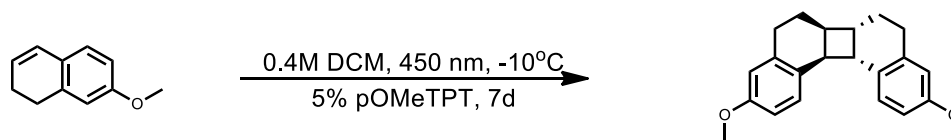
2,2'-((3,4-Bis(4-methoxyphenyl)cyclobutane-1,2-diyl)bis(methylene))bis(isoindoline-1,3-dione)

(Table 1, Entry 4) The dimer was prepared according to General Procedure B using 117 mg of (*E*)-2-(3-(4-methoxyphenyl)allyl)isoindoline-1,3-dione, 36 mg of naphthalene, and 6 mg of *p*-OMe TPT. Reaction was carried out at room temperature and purified via flash chromatography. Reaction time was 4 days. Yield was 62 mg (53%) of the desired adduct as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.72–7.70 (m, 4H), 7.64–7.62 (m, 4H), 7.12 (d, *J* = 8.8 Hz, 4H), 6.72 (d, *J* = 8.8 Hz, 4H), 3.93–3.82 (dq, *J* = 4.8, 14.0 Hz, 4H), 3.0 (dd, *J* = 3.2, 9.2 Hz, 2H), 2.57 (m, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 168.47, 158.20, 133.68, 132.00, 127.91, 123.08, 113.74, 55.17, 48.38, 43.14, 40.50. MS (+ESI) Calculated *m/z* for [M+H]⁺ = 587.12 Found *m/z* for [M+H]⁺ = 587.21. IR (Thin Film, cm⁻¹): 3056, 2933, 2836, 2360, 1771, 1715, 1612, 1513, 1429, 1395, 1265, 1248. TLC 20% acetone/ 80% Hexanes. CAM stains dark blue

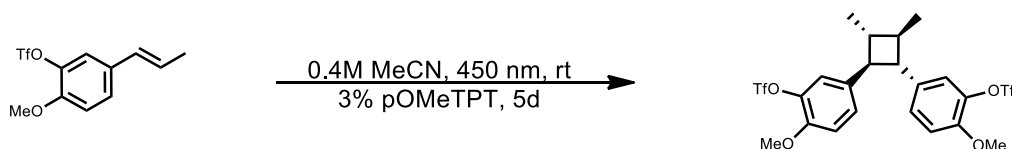


2,7-dimethoxy-4b,4c,9,9a,9b,10-hexahydrocyclobuta[1,2-*a*:4,3-*a'*]diindene (Table 1, Entry 5) The dimer was prepared according to General Procedure A using 140 μL mg of 6-methoxyindene, 210 μL of propylene oxide, and 24 mg of *p*-OMe TPT. Reaction was carried out in sparged dry dichloromethane at –10 °C, and purified via flash chromatography. Reaction time was 24 hours. Yield was 104 mg (71%) of the desired adduct as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, *J* = 8

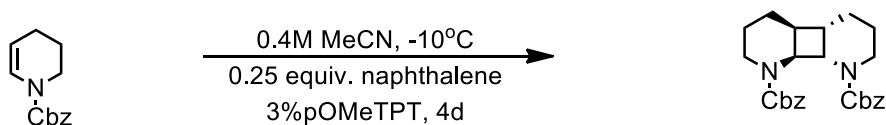
Hz, 2H), 6.87 (s, 2H), 6.85 (d, $J = 8.0$ Hz, 2H), 3.85 (s, 6H), 3.64 (d, $J = 8.0$ Hz, 2H), 3.2 (dd, $J = 16.4$, 7.2 Hz, 2H), 2.94 (d, $J = 16.0$ Hz, 2H), 2.82-2.79 (m, 2H). ^{13}C NMR (400 MHz, CDCl_3) δ 159.11, 145.60, 138.77, 125.61, 113.11, 110.29, 55.38, 53.16, 43.79, 39.51. **MS** (+ESI) Calculated m/z for $[\text{M}+\text{H}]^+ = 293.15$, Found m/z for $[\text{M}+\text{H}]^+ = 293.16$. **IR** (Thin Film, cm^{-1}): 2939, 2905, 2836, 1601, 1579, 1247. **TLC** 2% acetone/ 98% Hexanes. CAM stains dark blue



3,10-dimethoxy-5,6,6a,6b,7,8,12b,12c-octahydrodibenzo[*a,i*]biphenylene (Table 1, Entry 6) The dimer was prepared according to General Procedure B using 104 mg of 7-methoxy-1,2-dihydronaphthalene, and 7.3 mg of *p*-OMe TPT. Reaction was carried out in sparged dry dichloromethane at -10°C , and purified via flash chromatography. Reaction time was 7 days. Yield was 65 mg (63%) of the desired adduct as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 6.97 (d, $J = 8.4$ Hz, 2H), 6.77 (dt, $J = 2.0, 9.6, 17.2$ Hz, 4H), 3.82 (s, 6H), 3.20 (dd, $J = 5.2, 8.0$ Hz, 2H), 2.95 (m, 2H), 2.80-2.72 (dt, $J = 4.4, 9.6, 15.2$ Hz, 2H), 2.51 (m, 2H), 1.91-1.86 (m, 2H), 1.79-1.76 (m, 2H) ^{13}C NMR (400 MHz, CDCl_3) δ 157.62, 139.51, 132.94, 128.67, 113.88, 111.89, 55.27, 43.88, 35.35, 28.19, 26.81. **MS** (+ESI) Calculated m/z for $[\text{M}+\text{H}]^+ = 321.16$, Found m/z for $[\text{M}+\text{H}]^+ = 321.17$. **IR** (Thin Film, cm^{-1}): 3052, 3000, 2924, 2847, 2359, 1608, 1576, 1499, 1265. **TLC** 5% acetone/ 95% Hexanes.

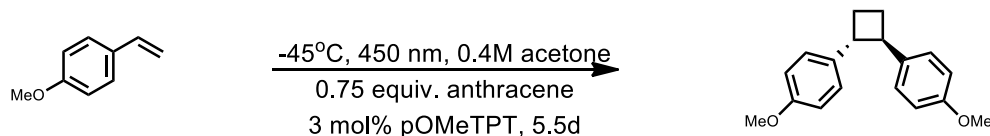


(3,4-dimethylcyclobutane-1,2-diyl)bis(2-methoxy-5,1-phenylene) bis(trifluoromethanesulfonate) (Table 1, Entry 7) The dimer was prepared according to General Procedure B using 118.4 mg of (*E*)-2-methoxy-5-(prop-1-en-1-yl)phenyl trifluoromethanesulfonate, and 5.8 mg of *p*-OMe TPT. Reaction was carried out at room temperature and purified via flash chromatography. Reaction time was 6 days. Yield was 40 mg (34%) of the desired adduct as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 7.12 (dd, $J = 1.2, 5.6$ Hz, 2H), 7.02 (d, $J = 1.2$ Hz, 2H), 6.96 (d, $J = 5.6$ Hz, 2H), 3.89 (s, 6H), 2.76 (dd, $J = 2.0, 3.6$ Hz, 2H), 1.86-1.83 (m, 2H), 1.20 (d, $J = 4.0$ Hz, 6H). ^{13}C NMR (400 MHz, CDCl_3) δ 149.74, 138.67, 136.13, 127.21, 120.57, 113.13, 56.24, 52.18, 42.97, 18.60. **MS** (+ESI) Calculated m/z for $[\text{M}+\text{H}_2\text{O}]^+ = 611.53$. Found m/z for $[\text{M}+\text{H}_2\text{O}]^+ = 611.03$. **IR** (Thin Film, cm^{-1}): 3014, 2952, 2923, 2866, 2847, 1621, 1576, 1514, 1455, 1423, 1375, 1294, 1277, 1248, 1211. **TLC** 5% acetone/ 95% Hexanes. CAM stains dark blue.

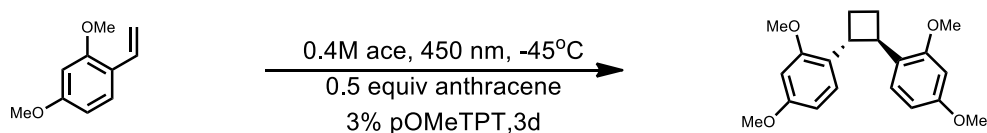


Dibenzyl octahydrocyclobuta[1,2-*b*:4,3-*b'*]dipyridine-1,8(8*aH*,8*bH*)-dicarboxylate (Table 1, Entry 8)

The dimer was prepared according to General Procedure **B** using 130 mg of benzyl 3,4-dihydropyridine-1(2H)-carboxylate, 19.2 mg of naphthalene, and 8.8 mg of *p*-OMe TPT. Reaction was carried out in degassed acetonitrile (freeze/pump/thaw method) at -10 °C, and purified via flash chromatography. Reaction time was 4 days. Yield was 104 mg (80%) of the desired adduct as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.33 (m, 10 H), 6.86-6.72 (rotamers, 2 s, 1H), 5.19-5.09, (m, 4H), 4.83 (br s, 1H), 4.06 (br d, *J* = 12.4 Hz, 1H), 3.58 (q, *J* = 5.2, 11.2 Hz, 2H), 2.83 (br t, *J* = 12.4, 24.4 Hz, 1H), 2.03-1.26 (m, 12H). ¹³C NMR (400 MHz, CDCl₃) δ 155.74, 153.63, 152.99, 136.94, 136.43, 128.38, 127.68, 122.25, 121.65, 116.06, 115.39, 67.40, 67.25, 66.97, 53.52, 42.03, 41.89, 40.13, 25.99, 25.82, 25.52, 25.41, 23.18, 22.93, 21.40, 19.53, 19.37. MS (+ESI) Calculated *m/z* for [M+H]⁺ = 435.53 Found *m/z* for [M+H]⁺ = 435.22. IR (Thin Film, cm⁻¹): 3055, 2939, 2862, 1698, 1455, 1407, 1348, 1311, 1263. TLC 5% acetone/ 95% Hexanes. CAM stains dark blue.

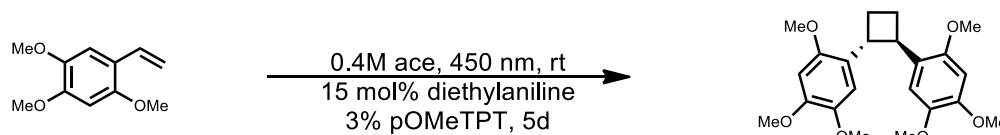


1,2-Bis(4-methoxyphenyl)cyclobutane (Table 2, Entry 1) The dimer was prepared according to General Procedure **A** using 134 mg of 4-methoxystyrene, 133.5 mg of anthracene, and 14.6 mg of *p*-OMe TPT. Reaction was carried out at -45 °C, and purified via flash chromatography. Reaction time was 5.5 days. Yield was 108 mg (80%) of the desired adduct as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.18 (d, *J* = 12.0 Hz, 4H), 6.86 (d, *J* = 16.0 Hz, 4H), 3.8 (s 6H), 3.47 (m, 2H), 2.32-2.25 (m, 2H), 2.13-2.07 (m, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 157.98, 136.87, 127.59, 113.72, 55.28, 47.78, 26.03. MS (+ESI) Calculated *m/z* for [M+H]⁺ = 269.15, Found *m/z* for [M+H]⁺ = 269.07. IR (Thin Film, cm⁻¹): 2938, 2833, 1611, 1580, 1511, 1462, 1440, 1301, 1247. TLC 2% acetone/ 98% Hexanes. CAM stains blue.

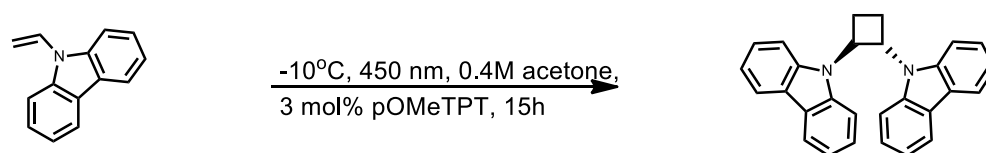


1,2-Bis(2,4-dimethoxyphenyl)cyclobutane (Table 2, Entry 2) The dimer was prepared according to

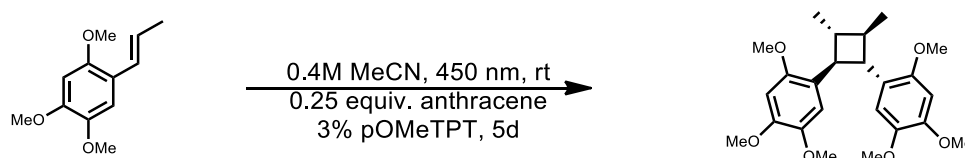
General Procedure A using 115 mg of 2,4-dimethoxystyrene, 62.3 mg of anthracene, and 10.2 mg of *p*-OMe TPT. Reaction was carried out at -45°C , and purified via flash chromatography. Reaction time was 3 days. Yield was 108 mg (82%) of the desired adduct as a clear oil. **^1H NMR** (400 MHz, CDCl_3) δ 7.22 (d, $J = 8.0$ Hz, 2H), 6.47 (d, $J = 2.0$ Hz, 2H), 6.44 (s, 2H), 3.87 (br dd, $J = 8.0, 16.0$, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.37-2.32 (ddd, $J = 4.8, 6.8, 11.6$ Hz, 2H) 1.96-1.86 (ddd, $J = 4.0, 8.0, 15.6$ Hz, 2H). **^{13}C NMR** (400 MHz, CDCl_3) δ 158.91, 158.12, 127.48, 125.64, 103.66, 98.24, 55.29, 55.21, 39.95, 27.17. **MS** (+ESI) Calculated m/z for $[\text{M}+\text{H}]^+ = 329.17$, Found m/z for $[\text{M}+\text{H}]^+ = 329.12$. **IR** (Thin Film, cm^{-1}): 2936, 2866, 2834, 2360, 2341, 2065, 1613, 1585, 1506, 1456, 1437, 1290, 1260, 1208. **TLC** 5% acetone/ 95% Hexanes. CAM stains dark blue.



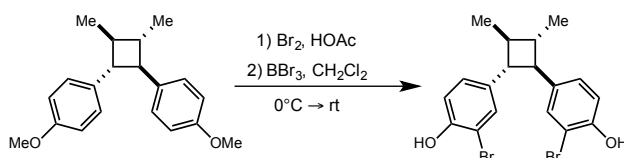
1,2-Bis(2,4,5-trimethoxyphenyl)cyclobutane (Pellucidin A) (Table 2, Entry 3) The dimer was prepared according to General Procedure A using 116 mg of 2,4,5-trimethoxystyrene, 14 μL of diethylaniline, and 8.8 mg of *p*-OMe TPT. Reaction was carried out at room temperature, and purified via flash chromatography. Reaction time was 5 days. Yield was 42.3 mg (36%) of the desired adduct as a white solid. **^1H NMR** (400 MHz, CDCl_3) δ 6.98 (s, 2H), 6.48 (s, 2H), 3.86 (s, 6H), 3.85 (s, 6H), 3.75 (s, 6H), 2.32-2.27 (m, 2H), 1.96-1.92 (m, 2H). **^{13}C NMR** (400 MHz, CDCl_3) δ 151.11, 148.60, 143.11, 124.64, 111.88, 97.81, 56.61, 56.56, 56.23, 40.47, 27.04. **MS** (+ESI) Calculated m/z for $[\text{M}+\text{H}]^+ = 389.17$, Found m/z for $[\text{M}+\text{H}]^+ = 389.17$. **IR** (Thin Film, cm^{-1}): 2988, 2935, 1715, 1523, 1462, 1440, 1349, 1227. **TLC** 15% acetone/ 85% Hexanes. CAM stains dark blue. X-ray level crystals were obtained by dissolving 20mg of material in 1.5mL acetone and layering 10 mL hexanes overtop. **Crystal Data:** $\text{C}_{22}\text{H}_{24}\text{O}_6$, $M = 384.41$, $0.4 \times 0.05 \times 0.05\text{mm}^3$, tricyclic, space group P-1, $a=5.0348(4)$, $b=14.3242(9)$, $c= 15.1715(10)$ Å, $\alpha= 115.546(5)$ $\beta= 90.919(6)$, $\gamma= 98.363(6)^{\circ}$, $V= 972.89(12)$ Å³, $Z= 2$, $T=100$ K, 8212 reflections collected, 3264 unique [$R_{\text{int}} = 0.0934$]. The refinement (259 variables, 0 restrictions) based on F^2 converged with $R = 0.0622$, $R_w = 0.1319$, and $\text{GOF} = 1.010$ using 3264 independent reflections with [$I \geq 2\sigma(I)$].



1,2-Di(9H-carbazol-9-yl)cyclobutane (Table 2, Entry 4) The dimer was prepared according to General Procedure **A** using 154 mg of N-vinyl Carbazole, and 11.7 mg of p-OMe TPT. Reaction was purified via filtration through a short plug of silica. No further purification was required, Reaction time was 15 hours. Yield was 150 mg of the desired adduct as a white solid. (97%). Analytical data for N-vinyl carbazole dimer matches literature reports:³ **¹H NMR** (400 MHz, CDCl₃) δ 8.07 (d, J = 8.0 Hz, 4H), 7.576 (d, J = 8.4 Hz, 4H), 7.38 (t, J = 7.2 Hz, 15.6 Hz, 4H), 7.20 (t, J = 8.0, 14.8 Hz, 4H), 6.29 (dd, 8.4 Hz, 17.2 Hz, 2H), 3.12 (m, 2H), 2.74 (m, 2H) **¹³C NMR** (400 MHz, CDCl₃) δ 139.94, 125.76, 123.58, 120.49, 119.33, 109.65, 54.45, 20.89. **IR** (Thin Film, cm⁻¹): 3049, 1623, 1595, 1482, 1451, 1334, 1264, 1210.

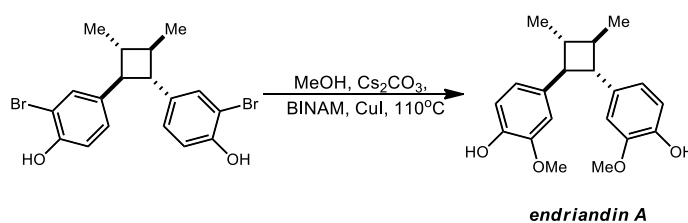


2,4,5-trimethoxy- β -methylstyrene Dimer The dimer was prepared according to General Procedure **B** using 104 mg of 2,4,5-trimethoxy- β -methylstyrene, 22 mg of anthracene, and 7.3 mg of p-OMe TPT. Reaction was carried out in at room temperature and purified via flash chromatography. Reaction time was 4 days. Yield was 52 mg (50%) of the desired adduct as a white solid. **¹H NMR** (400 MHz, CDCl₃) δ 6.94 (s, 2H), 6.46 (s, 2H), 3.86 (s, 6H), 3.85 (s, 6H), 3.69 (s, 6H), 3.27 (dd, J = 3.2, 8.8 Hz, 2H), 1.77 (dd, J = 5.2, 16.4 Hz, 2H), 1.18 (d, J = 5.2 Hz, 6H). **¹³C NMR** (400 MHz, CDCl₃) δ 151.67, 147.53, 143.11, 123.90, 112.22, 97.85, 56.74, 56.60, 56.21, 45.38, 43.51, 19.11. **MS** (+ESI) Calculated m/z for [M+H]⁺ = 416.22, Found m/z for [M+H]⁺ = 417.26. **IR** (Thin Film, cm⁻¹): 3055, 2951, 2832, 2359, 1669, 1608, 1508, 1464, 1438, 1396, 1371, 1318, 1266, 1206. **TLC** 10% acetone/ 90% Hexanes. CAM stains dark blue.



Bromination⁴ and demethylation⁵ were conducted according to literature procedures. Anethole dimer was stirred in acetic acid at 0 °C. Br₂ was added dropwise and the reaction was stirred at room temperature for 30 minutes. The reaction was quenched with Na₂S₂O₅, extracted with DCM, washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude material was then stirred in

anhydrous DCM at 0 °C. BBr₃ was added dropwise and the reaction was stirred at 0 °C for 2 h. The reaction was then allowed to stir overnight. Upon completion of the reaction, the mixture was cooled to 0 °C, quenched with H₂O, extracted with DCM, washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude material was purified by column chromatography yielding 128 mg, (80% yield) over two steps. ¹H NMR (400 MHz, CDCl₃) δ 7.27 (d, *J* = 2.0 Hz, 2H), 7.03 (dd, *J* = 2.0, 8.4 Hz, 2H), 6.93 (d, 8.4 Hz, 2H), 5.69 (s, 2H), 2.72 (dd, *J* = 3.6, 6.0 Hz, 2H), 1.81 (dd, *J* = 1.2, 1.6 Hz, 2H), 1.17 (d, *J* = 5.6 Hz, 6H). ¹³C NMR (400 MHz, CDCl₃) δ 150.60, 136.99, 129.94, 127.63, 115.92, 110.18, 52.23, 43.19, 18.67. TLC 20% acetone/ 80% Hexanes. CAM stains dark blue.



Endiadrin A: The copper-catalyzed methoxylation was conducted using a modified literature procedure⁶ as follows: a scintillation vial was charged with the substrate (158 mg, 1 eq), Cs₂CO₃ (0.481g, 4 eq), CuI (28 mg, 0.4 eq), and BINAM (42 mg, 0.4 eq) in a glove box. To the vial was added sparged MeOH (2.5 mL, 0.15M) and the reaction mixture was stirred at 110 °C for 40 hours. The reaction mixture was allowed to cool to room temperature and the crude mixture was diluted with water and quenched with 3M HCl at 0 °C. The aqueous layer was then extracted with DCM multiple times and the organics were dried over MgSO₄, and concentrated. The crude product was purified by column chromatography to yield 93 mg (77%) of the desired product as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 6.89 (d, *J* = 8.0 Hz, 2H), 6.77 (dd, *J* = 1.6, 8.4 Hz, 2H), 6.71 (s, 2H), 5.55 (s, O-H, 2H), 3.86 (s, 6H), 2.80 (dd, *J* = 3.2, 5.6 Hz, 2H), 1.86 (d, *J* = 4.8 Hz), 1.22 (d, *J* = 5.6 Hz, 6H). ¹³C NMR (400 MHz, CDCl₃) δ 146.31, 143.87, 135.77, 119.28, 114.16, 109.38, 55.79, 53.16, 42.94, 18.82. **MS** (+ESI) Calculated *m/z* for [M+H]⁺ = 329.17 Found *m/z* for [M+H]⁺ = 329.13. **IR** (Thin Film, cm⁻¹): 3525, 3055, 3004, 2946, 2918, 2862, 2061, 1856, 1611, 1514, 1463, 1452, 1431, 1371, 1264, 1239, 1208. **TLC** 20% acetone/ 80% Hexanes. CAM stains dark blue.

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