Supplementary Material (ESI) for Chemical Communications

Supporting Information for the Manuscript entitled:

Synthesis of Macrocyclic Terpene-Derived Hybrids

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1. General Methods

Unless noted otherwise, all manipulations were carried out under an argon atmosphere using standard Schlenk techniques. All glassware was oven dried for approximately 1 h prior to use. THF, Et_2O and 1,4-dioxane were distilled from Na benzophenone ketyl under argon. DCM was distilled from CaH_2. Other solvents were HPLC grade and were used without further purification. All reagents were obtained from commercial sources and used without further purification, unless noted otherwise. 2,2-di(2-propynyl)malonate,[1] 1,2-(bispropynyloxy)benzene,[2] 1,3-(bispropynyloxy)benzene,[2] 1,4-(bispropynyloxy)benzene,[2] 9,9-di(prop-2-ynyl)-9*H*-fluorene[3] were prepared using the reported procedures. $BF_3{\cdot}OEt_2$ was distilled from CaH_2 under vacuum prior to use. *N,N,N′,N′*-tetramethylethylendiamine was distilled from KOH. Silica-gel 60 F_{254} plates were used for TLC analysis. Flash column chromatography was performed using silica-gel (Merk, nº 9385,230-400 mesh). ^1H and ^{13}C NMR spectra were recorded at 200, 300, 400 and 500 MHz (^1H) using $CDCl_3$ as solvent and with the residual solvent signal as internal reference ($CDCl_3$, 7.25 and 77.0 ppm). The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), and br (broad). Mass spectra were recorded using the electronic impact technique with an ionization energy of 70 eV or using the atmospheric pressure chemical ionization (APCI) or electrospray (ES) chemical ionization techniques in its positive or negative modes. IR spectra were obtained on a Perkin-Elmer 681 spectrophotometer. Optical rotations were measured on a 241 MC polarimeter using a sodium lamp. Melting points were determined on a Koffler block. Elemental analyses were made with a Carlo Erba EA 1108 apparatus.

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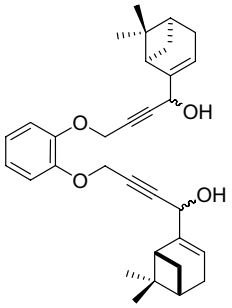
[1] D. Llerena, O. Buisine, C. Aubert and M. Malacria, *Tetrahedron* 1998, **54**, 9373.
[2] S. Braverman, M. L. Cherkinsky, M. L. Birsa, S. Tichman and I. Goldberg, *Tetrahedron Lett.* 2001, **42**, 7485.
[3] J. A. Gautier, M. Miocque and H. Moskowitz, *Bull. Soc. Chim. Fr.* 1965, 1735.

2. Experimental Procedures

2.1. General Procedure for the Preparation of Diyne-ols. A solution of the dyine, and *N,N,N′,N′*-tetramethylethylendiamine when required, in THF at -78 ºC was treated dropwise with a solution of the lithium reagent indicated below. The mixture was stirred for 30 min, and then a solution of (1*R*)-(-)-myrtenal in THF was added dropwise, via cannula. The cooling bath was removed, and the reaction mixture was stirred at room temperature until no starting material was observed by TLC analysis. Then, it was quenched with saturated aqueous NH_4Cl, and extracted with Et_2O (2 x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel chromatography of the crude product provided the desired diyne-ols.

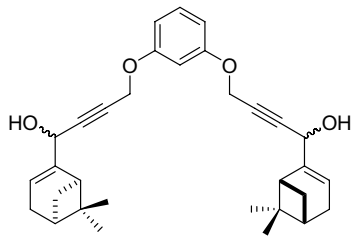
Preparation of Compound 6.



Following the general procedure, a THF (25mL) solution of 1,2-(bispropynyloxy)benzene (1.0 g, 5.37 mmol) and *N,N,N′,N′*-tetramethylethylendiamine (1.9 mL, 12.9 mmol) was treated with *n*-BuLi (8.1 mL, 12.9 mmol, 1.6 M solution in hexanes), and (1*R*)-(-)-myrtenal (1.67 mL, 10.74 mmol in 10 mL of THF). The reaction mixture was stirred for 3 h at room temperature. The crude product was purified by silica gel chromatography (hexanes/AcOEt 4:1) to give 1.9 g (73%) of **6** (mixture of diastereoisomers) as a pale yellow oil. IR (film) ν_{max} 3391, 2916, 2831, 2244, 1594, 1502, 1456, 1368, 1125, 1006 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.02 (m, 2H), 6.97

(m, 2H), 6.95 (br s, 2H), 4.79 (s, 4H), 4.74 (m, 2H), 2.42-2.16 (m, 8H), 2.07 (m, 2H), 1.82 (m, 2H), 1.26 (s, 3H), 1.24 (s, 3H), 1.14 (d, J = 8.5 Hz, 1H), 1.11 (d, J = 8.8 Hz, 1H), 0.79 (s, 3H), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 147.5 (2C), 146.0 (2C), 121.8 (2CH), 119.9 (CH), 119.5 (CH), 115.1 (CH), 114.9 (CH), 86.4 (C), 86.3 (C), 80.2 (C), 80.1 (C), 64.8 (CH), 64.5 (CH), 56.9 ($2CH_2$), 42.5 (CH), 42.4 (CH), 40.5 (2CH), 37.7 (2C), 31.6 (CH_2), 31.5 (CH_2), 30.9 ($2CH_2$), 25.8 ($2CH_3$), 20.9 (CH_3), 20.8 (CH_3); MS (ES) m/z 509.1 [M^+ + Na]; Anal. Calcd. for $C_{32}H_{38}O_4$: C, 78.98; H, 7.87; Found: C, 78.52; H, 8.02.

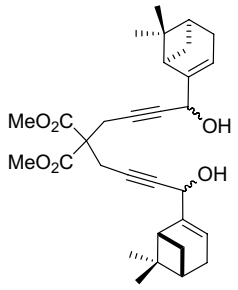
Preparation of Compound 7.



Following the general procedure, a THF solution of 1,3-(bispropynyloxy)benzene (200 mg, 1.07 mmol in 8 mL of THF) was treated with *n*-BuLi (1.5 mL, 2.35 mmol, 1.6 M solution in hexanes), and (1*R*)-(-)-myrtenal (0.33 mL, 2.14 mmol in 3 mL of THF). The reaction mixture was stirred for 2 h at room temperature. The crude product was purified by silica gel chromatography (hexanes/AcOEt 10:1 → 8:2) to give 415 mg (80%) of **7** (mixture of diastereoisomers) as a pale yellow oil. IR (film) ν_{max} 3391, 2987, 2892, 1594, 1490, 1367, 1260, 1149, 1042 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18 (t, J = 8.7 Hz, 1H), 6.59 (m, 3H), 5.63 (br s, 2H), 4.76 (br s, 2H), 4.71 (s, 2H), 4.70 (s, 2H), 2.43-2.16 (m, 8H), 2.07 (m, 2H), 1.80 (m, 2H), 1.27 (s, 3H), 1.25 (s, 3H), 1.15 (d, J = 8.9 Hz, 1H), 1.12 (d, J = 8.9 Hz, 1H), 0.79 (s, 3H), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.6 (2C), 146.0 (C), 145.9 (C), 129.7 (CH), 119.9 (CH), 119.4 (CH), 107.8

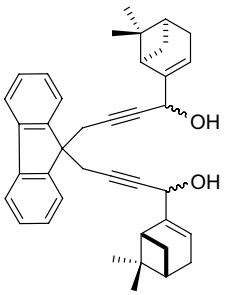
(CH), 107.7 (CH), 102.3 (CH), 86.3 (C), 86.2 (C), 80.0 (C), 79.9 (C), 64.8 (CH), 64.4 (CH), 56.0 (CH_2), 55.9 (CH_2), 42.5 (CH), 42.3 (CH), 40.5 (2CH), 37.7 (2C), 31.5 (CH_2), 31.4 (CH_2), 30.9 ($2CH_2$), 25.9 (CH_3), 25.8 (CH_3), 20.9 (CH_3), 20.8 (CH_3); MS (ES) m/z 509.1 [M^+ + Na]; Anal. Calcd. for $C_{32}H_{38}O_4$: C, 78.98; H, 7.87; Found: C, 78.81; H, 7.83.

Preparation of Compound 8.



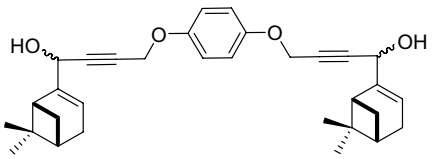
Following the general procedure, a THF solution of dimethyl 2,2-di(2-propynyl)malonate (700 mg, 3.36 mmol in 33 mL of THF) was treated with LiHMDS (16.8 mL,16.8 mmol, 1.0 M solution in THF), and (1*R*)-(-)-myrtenal (2.6 mL, 16.8 mmol). The reaction mixture was stirred for 1 h at room temperature. The crude product was purified by silica gel chromatography (hexanes/AcOEt 9:1) to give 1.17 g (68%) of **8** (mixture of diastereoisomers) as a yellow oil. IR (film) ν_{max} 3427, 2224, 1739, 1435, 1295, 1214 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.60 (br s, 2H), 4.67 (br s, 2H), 3.74 (s, 6H), 3.00 (s, 4H), 2.46-2.39 (m, 2H), 2.35-2.24 (m, 6H), 2.09 (m, 2H), 1.69 (br s, 1H), 1.58 (br s, 1H), 1.30 (s, 6H), 1.17 (d, *J* = 8.9 Hz, 1H), 1.15 (d, *J* = 8.9 Hz, 1H), 0.81 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2 (2C), 146.5 (2C), 119.7, 119.4 (2CH), 82.7 (C), 82.6 (C), 79.9(C), 79.7 (C), 65.1 (CH), 64.8 (CH), 56.6 (C), 53.1 ($2CH_3$), 42.6 (2CH), 40.6 (2CH), 37.9 (C), 37.8 (C), 31.8 (CH_2), 31.6 (CH_2), 31.0 ($2CH_2$), 26.0 ($2CH_3$), 23.0 ($2CH_2$), 21.1 (CH_3), 21.0 (CH_3); MS (ES) m/z 531.2 [M^+ + Na]; Anal. Calcd. for $C_{31}H_{40}O_6$: C, 73.20; H, 7.93; Found: C, 73.52; H, 7.58.

Preparation of Compound 9.



Following the general procedure, a THF solution of 9,9-di(prop-2-ynyl)-9*H*-fluorene (510 mg, 2.10 mmol in 13 mL of THF) was treated with LiHMDS (5.3 mL, 5.25 mmol, 1.0 M solution in THF), and (1*R*)-(-)-myrtenal (0.82 mL, 5.25 mmol). The reaction mixture was stirred for 3 h at room temperature. The crude product was purified by silica gel chromatography (hexanes/AcOEt 15:1 $\rightarrow$ 9:1) to give 688 mg (60%) of **9** (mixture of diastereoisomers) as a yellow oil. IR (film) ν_{max} 3401, 2987, 2916, 2244, 1449, 1430, 1218, 1083, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 7.3 Hz, 2H), 7.66 (m, 2H), 7.40-7.28 (m, 4H), 5.45 (m, 2H), 4.62 (br s, 2H), 2.87 (s, 2H), 2.86 (s, 2H), 2.42-2.39 (m, 2H), 2.24 (m, 6H), 2.07 (m, 2H), 1.69 (br s, 1H), 1.58 (br s, 1H), 1.28 (s, 3H), 1.26 (s, 3H), 1.12 (d, J = 8.5 Hz, 1H), 1.10 (d, J = 8.5 Hz, 1H), 0.77 (s, 3H), 0.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.6 (2C), 146.7 (C), 146.6 (C), 140.2 (2C), 127.9 (2CH), 127.2 (2CH), 123.7 (2CH), 119.8 (2CH), 119.4 (2CH), 82.8 (C), 82.7 (C), 81.4 (2C), 65.1 (2CH), 51.0 (C), 42.8 (CH), 42.7 (CH), 40.7 (2CH), 37.9 (2C), 31.9 (CH_2), 31.7 (CH_2), 31.1 (CH_2), 31.0 (CH_2), 28.1 ($2CH_2$), 26.1 ($2CH_3$), 21.1 ($2CH_3$); MS (EI) *m/z* (relative intensity) 524 [M^+ - 18] (3), 481 (3), 455 (5), 335 (14), 291 (16), 215 (23), 203 (99), 165 (100); Anal. Calcd. for $C_{39}H_{42}O_2$: C, 86.30; H, 7.80; Found: C, 86.50; H, 7.35.

Preparation of Compound 19.

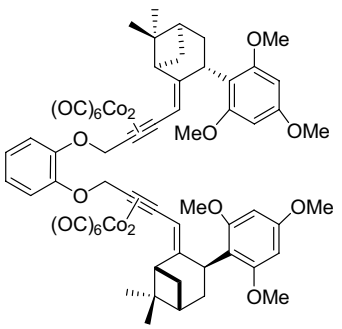


Following the general procedure, a THF solution of 1,4-(bispropynyloxy)benzene (310 mg, 2.11 mmol in 17 mL of THF) was treated with LiHMDS (5.1 mL, 5.1 mmol, 1.0 M solution in THF), and (1*R*)-(-)-myrtenal (0.8 mL, 5.1 mmol). The reaction mixture was stirred for 2 h at room temperature. The crude product was purified by silica gel chromatography (hexanes/AcOEt 10:1 $\rightarrow$ 8:2) to give 1.0 g (98%) of **19** (mixture of diastereoisomers) as a yellow oil. IR (film) ν_{max} 3400, 2916, 1628, 1505, 1366, 1203, 1112, 1022 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.89 (s, 4H), 5.62 (br s, 2H), 4.77 (br s, 1H), 4.75 (br s, 1H), 4.68 (s, 2H), 4.67 (s, 2H), 2.43-2.17 (m, 10H), 2.08 (m, 2H), 1.27 (s, 3H), 1.25 (s, 3H), 1.15 (d, J = 8.1 Hz, 1H), 1.12 (d, J = 8.3 Hz, 1H), 0.80 (s, 3H), 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.2 (2C), 146.0 (2C), 120.1 (CH), 119.5 (CH), 115.9 (2CH), 115.8 (2CH), 86.1 (C), 86.0 (C), 80.4 (C), 80.3 (C), 64.9 (CH), 64.6 (CH), 56.6 ($2CH_2$), 42.6 (CH), 42.4 (CH), 40.5 (2CH), 37.8 (2C), 31.6 (CH_2), 31.5 (CH_2), 30.9 ($2CH_2$), 25.9 ($2CH_3$), 21.0 (CH_3), 20.9 (CH_3); MS (EI) *m/z* (relative intensity) 468 [M^+ - 18] (1), 481 (3), 425 (2), 336 (5), 281 (11), 237 (27), 171 (62), 129 (100), 110 (92), 91 (99); Anal. Calcd. for $C_{32}H_{38}O_4$: C, 78.98; H, 7.87; Found: C, 79.52; H, 7.96.

2.2. General Procedure for the Intermolecular Nicholas Reaction Using 1,3,5-Trimethoxybenzene as Nucleophile. To a solution of the alkyne in DCM was added $Co_2(CO)_8$ in one portion. The deep red mixture was stirred at room temperature until no starting material was observed by TLC analysis and then cooled to the temperature

specified below. The nucleophile was added and the mixture was treated dropwise with a solution of $BF_3{\cdot}OEt_2$. When TLC analysis revealed no further progress, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and warmed to room temperature with stirring. The layers were separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography.

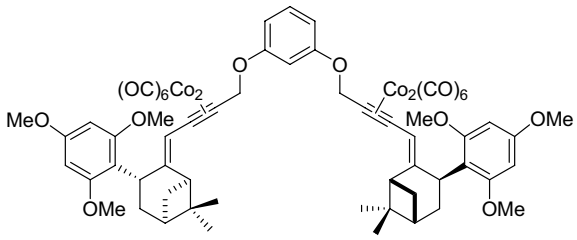
Preparation of Coumpound 10.



Following the general method, the dicobalt hexacarbonyl complex was prepared from **6** (50 mg, 0.10 mmol) and $Co_2(CO)_8$ (83 mg, 0.20 mmol) in DCM (10 mL), after 1 h of stirring. Treatment of the cobalt complex with 1,3,5-trimethoxybenzene (51 mg, 0.30 mmol) and $BF_3{\cdot}OEt_2$ (25 μL, 0.20 mmol) at –78 ºC, provided **10** after 30 min of stirring. The crude product was purified by silica gel chromatography (hexanes/AcOEt 20:1) to give a dark green oil (102 mg, 75%). IR (film) ν_{max} 2086, 2046, 2015, 1607, 1496, 1455, 1204, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (m, 4H), 6.17 (br s, 2H), 6.10 (br s, 2H), 5.75 (d, *J* = 2.4 Hz, 2H), 5.19 (s, 4H), 4.54 (ddd, *J* = 10.0, 7.1, 2.4 Hz, 2H), 3.82 (s, 12H), 3.63 (s, 6H), 3.52 (t, *J* = 5.7 Hz, 2H), 2.44 (dt, *J* = 7.1, 6.3 Hz, 2H), 2.26 (td, *J* = 12.1, 2.2 Hz, 2H), 2.10 (m, 2H), 1.84 (m, 4H), 1.35 (s, 6H), 1.07 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.8 (12C), 159.6 (2C), 159.3 (2C), 159.1 (2C), 158.3 (2C), 149.3 (2C), 122.0 (2CH), 116.5 (2CH), 114.4 (2C), 114.2 (2CH), 93.6 (2C), 91.5

(2CH), 90.3 (2CH), 87.6 (2C), 71.2 ($2CH_2$), 56.3 ($2CH_3$), 55.2 ($2CH_3$), 54.5 ($2CH_3$), 48.4 (2CH), 42.1 (2CH), 39.6 (2C), 33.4 ($2CH_2$), 31.5 (2CH), 30.5 ($2CH_2$), 27.0 ($2CH_3$), 22.6 ($2CH_3$); Anal. Calcd. for $C_{62}H_{58}Co_4O_{20}$: C, 54.80; H, 4.30; Found: C, 54.58; H, 4.22.

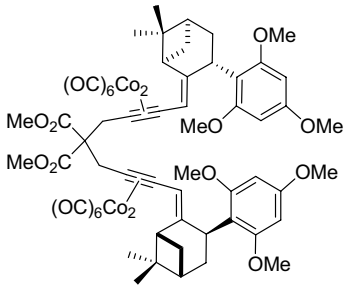
Preparation of Compound 11.



Following the general procedure, the dicobalt hexacarbonyl complex was prepared from **7** (106 mg, 0.22 mmol) and $Co_2(CO)_8$ (198 mg, 0.48 mmol) in DCM (10 mL), after 1 h of stirring. Treatment of the cobalt complex with 1,3,5-trimethoxybenzene (82 mg, 0.48 mmol) and $BF_3{\cdot}OEt_2$ (56 μL, 0.44 mmol) at –78 ºC, provided **11** after 30 min of stirring. The crude product was purified by silica gel chromatography (hexanes/AcOEt 20:1 → 10:1) to give a dark brown oil (152 mg, 51%). IR (film) ν_{max} 2086, 2046, 2014, 1739, 1606, 1592, 1490, 1455, 1204, 1152, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, *J* = 8.1 Hz, 1H), 6.56 (m, 3H), 6.20 (br s, 2H), 6.13 (br s, 2H), 5.77 (d, *J* = 2.3 Hz, 2H), 5.13 (s, 4H), 4.58 (ddd, *J* = 9.8, 7.1, 2.2 Hz, 2H), 3.84 (s, 12H), 3.66 (s, 6H), 3.45 (t, *J* = 5.6 Hz, 2H), 2.45 (dt, *J* = 7.0, 6.4 Hz, 2H), 2.30 (br t, *J* = 10.7 Hz, 2H), 2.12 (m, 2H), 1.86 (m, 4H), 1.35 (s, 6H), 1.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8 (12C), 159.8 (2C), 159.6 (2C), 159.1 (2C), 158.4 (2C), 158.3 (2C), 129.9 (CH), 114.8 (2CH), 114.2 (2C), 107.1 (2CH), 101.3 (CH), 92.6 (2C), 91.5 (2CH), 90.3 (2CH), 87.4 (2C), 69.2 ($2CH_2$), 56.3 ($2CH_3$), 55.2 ($2CH_3$), 54.5 ($2CH_3$), 48.7 (2CH), 42.1 (2CH), 39.7

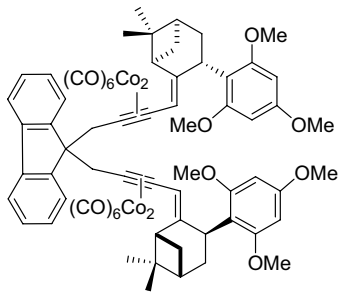
(2C), 33.6 ($2CH_2$), 31.5 (2CH), 30.5 ($2CH_2$), 27.0 ($2CH_3$), 22.6 ($2CH_3$); Compound was not stable and correct analytical data could not be obtained.

Preparation of compound 12.



Following the general procedure, the dicobalt hexacarbonyl complex was prepared from **8** (129 mg, 0.25 mmol) and $Co_2(CO)_8$ (231 mg, 0.56 mmol) in DCM (11 mL), after 1 h of stirring. Treatment of the cobalt complex with 1,3,5-trimethoxybenzene (95 mg, 0.56 mmol) and $BF_3{\cdot}OEt_2$ (71 μL, 0.56 mmol) at 0 ºC, provided **12** after 20 min of stirring. The crude product was purified by silica gel chromatography (hexanes/AcOEt 20:1 → 10:1) to give a dark green oil (161 mg, 47%). IR (KBr) ν_{max} 2084, 2045, 2012, 1734, 1607, 1455, 1204, 1154, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.14 (d, *J* = 2.0 Hz, 2H), 6.08 (d, *J* = 2.2 Hz, 2H), 5.72 (d, *J* = 2.2 Hz, 2H), 4.52 (br t, *J* = 9.4 Hz, 2H), 3.80 (s, 12H), 3.66 (s, 6H), 3.57 (s, 4H), 3.42 (s, 8H), 2.42 (br t, *J* = 11.0 Hz, 2H), 2.34 (m, 2H), 2.08 (m, 2H), 1.85 (m, 4H), 1.37 (s, 6H), 1.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1 (6C), 199.7 (6C), 170.2 (2C), 160.1 (2C), 159.6 (2C), 159.0 (2C), 158.3 (2C), 114.2 (2CH), 113.9 (2C), 92.8 (2C), 91.5 (2CH), 90.2 (2CH), 89.5 (2C), 59.0 (C), 56.0 ($2CH_3$), 55.2 ($2CH_3$), 54.4 ($2CH_3$), 52.2 ($2CH_3$), 47.3 (2CH), 42.8 ($2CH_2$), 41.9 (2CH), 39.6 (2C), 33.5 ($2CH_2$), 31.5 (2CH), 30.5 ($2CH_2$), 26.9 ($2CH_3$), 22.6 ($2CH_3$); Anal. Calcd. for $C_{61}H_{60}Co_4O_{22}$: C, 53.06; H, 4.38; Found: C, 53.20; H, 4.67.

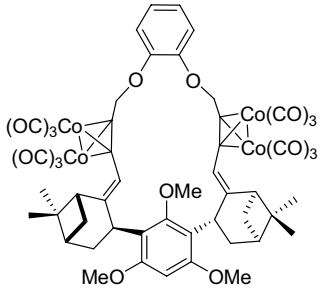
Preparation of Compound 13.



Following the general procedure, the dicobalt hexacarbonyl complex was prepared from **9** (87 mg, 0.16 mmol) and $Co_2(CO)_8$ (146 mg, 0.35 mmol) in DCM (8 mL), after 1 h of stirring. Treatment of the cobalt complex with 1,3,5-trimethoxybenzene (60 mg, 0.35 mmol) and $BF_3{\cdot}OEt_2$ (44 μL, 0.35 mmol) at –20 ºC, provided **13** after 10 min of stirring. The crude product was purified by silica gel chromatography (hexanes/AcOEt 15:1) to give a dark green oil (124 mg, 55%). IR (film) ν_{max} 2080, 2042, 2010, 1607, 1593, 1455, 1155, 1122 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 7.3 Hz, 2H), 7.11 (t, *J* = 7.3 Hz, 2H), 6.87 (t, *J* = 7.6 Hz, 2H), 6.29 (d, *J* = 2.2 Hz, 2H), 6.10 (d, *J* = 2.2 Hz, 2H), 4.76 (d, *J* = 2.2 Hz, 2H), 4.19 (td, *J* = 9.5, 2.0 Hz, 2H), 3.99 (s, 6H), 3.90 (s, 6H), 3.81 (s, 2H), 3.80 (s, 2H), 3.60 (s, 6H), 3.51 (t, *J* = 5.6 Hz, 2H), 2.26 (m, 4H), 1.95 (m, 2H), 1.66 (d, *J* = 9.0 Hz, 2H), 1.57 (br d, *J* = 7.1 Hz, 1H), 1.53 (br d, *J* = 6.6 Hz, 1H), 1.24 (s, 6H), 0.87 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9 (12C), 159.4 (2C), 158.9 (2C), 158.6 (2C), 158.0 (2C), 146.5 (2C), 141.3 (2C), 127.8 (2CH), 127.0 (2CH), 123.6 (2CH), 120.7 (2CH), 115.1 (2C), 113.6 (2CH), 93.9 (2C), 91.0 (2CH), 90.1 (2CH), 89.5 (2C), 56.2 (C), 55.8 ($2CH_3$), 55.3 ($2CH_3$), 54.5 ($2CH_3$), 47.8 ($2CH_2$), 46.7 (2CH), 41.5 (2CH), 39.3 (2C), 34.5 ($2CH_2$), 31.3 (2CH), 30.2 ($2CH_2$), 26.7 ($2CH_3$), 22.3 ($2CH_3$); Anal. Calcd. for $C_{69}H_{62}Co_4O_{18}$: C, 58.57; H, 4.42; Found: C, 58.75; H, 4.31.

2.3. General Procedure for the Intramolecular Nicholas Reaction Using 1,3,5-Trimethoxybenzene as Nucleophile. To a solution of the alkyne in DCM was added $Co_2(CO)_8$ in one portion. The deep red mixture was stirred at room temperature until no starting material was observed by TLC analysis and then cooled to the temperature specified below. At this point, the nucleophile was added and the mixture was treated dropwise with a solution of $BF_3{\cdot}OEt_2$. When TLC analysis revealed no further progress, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and warmed to room temperature with stirring. The layers were separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography.

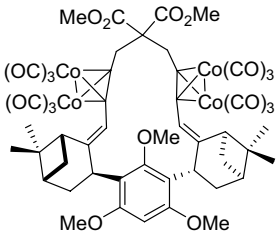
Preparation of Compound 14.



Following the general procedure, the dicobalt hexacarbonyl complex was prepared from **6** (50 mg, 0.22 mmol) and $Co_2(CO)_8$ (83 mg, 0.20 mmol) in DCM (3 mL), after 1 h of stirring. The mixture was cooled to –20 ºC and treated dropwise with a DCM (3 mL) solution of 1,3,5-trimethoxybenzene (17 mg, 0.10 mmol) and $BF_3{\cdot}OEt_2$ (25 μL, 0.20 mmol) for a 1.5 h period. The reaction mixture was stirred for 10 h at this temperature. Silica gel chromatography of the crude product (hexanes/AcOEt 20:1 → 9:1) provided two isolable pure compounds: the previously described **10** (23 mg, 17%), and **14** (14 mg, 12%, single stereoisomer), which was a dark green oil. IR (KBr) ν_{max} 2086, 2048,

2018, 1596, 1497, 1456, 1200, 1106 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.92 (d, *J* = 7.8 Hz, 1H), 6.86 (m, 1H), 6.81 (d, *J* = 4.4 Hz, 2H), 6.27 (s, 1H), 5.99 (s, 1H), 5.88 (s, 1H), 5.49 (d, *J* = 14.6 Hz, 1H), 5.37 (d, *J* = 13.7 Hz, 1H), 5.31 (d, *J* = 13.7 Hz, 1H), 5.23 (d, *J* = 14.6 Hz, 1H), 4.62 (t, *J* = 7.8 Hz, 1H), 4.27 (t, *J* = 7.3 Hz, 1H), 3.87 (s, 3H), 3.80 (m, 2H), 3.71 (s, 3H), 3.51 (s, 3H), 2.53 (m, 2H), 2.24-2.13 (m, 4H), 1.96 (dd, *J* = 12.7, 7.8 Hz, 2H), 1.81 (dd, *J* = 9.3, 5.4 Hz, 2H), 1.42 (s, 3H), 1.40 (s, 3H), 1.11 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3 (C), 163.5 (C), 158.8 (C), 157.4 (C), 156.8 (C), 149.0 (C), 148.2 (C), 121.7 (CH), 121.6 (CH), 118.8 (C), 118.6 (C), 115.2 (CH), 114.8 (CH), 114.0 (CH), 113.6 (CH), 94.2 (C), 93.6 (C), 92.6 (CH), 87.6 (C), 86.6 (C), 73.2 (CH_2), 69.7 (CH_2), 61.7 (CH_3), 56.2 (CH_3), 54.3 (CH_3), 47.9 (CH), 47.6 (CH), 42.5 (CH), 41.6 (CH), 39.7 (C), 39.1 (C), 34.2 (CH), 33.6 (CH_2), 32.1 (CH), 31.2 (CH_2), 30.3 (CH_2), 27.0 (CH_3), 26.9 (CH_3), 22.7 ($2CH_3$); Anal. Calcd. for $C_{53}H_{46}Co_4O_{17}$: C, 53.46; H, 3.89; Found: C, 53.21; H, 4.15.

Preparation of Compound 15.



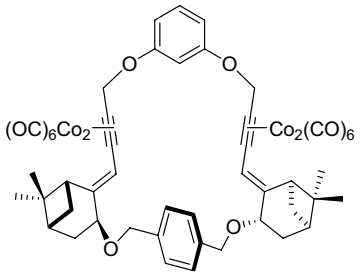
Following the general method, the dicobalt hexacarbonyl complex was prepared from **8** (131 mg, 0.26 mmol) and $Co_2(CO)_8$ (234 mg, 0.57 mmol) in DCM (3 mL), after 1 h of stirring. The mixture was cooled to 0 ºC and treated dropwise with a DCM solution (10 mL) of 1,3,5-trimethoxybenzene (44 mg, 0.26 mmol) and $BF_3{\cdot}OEt_2$ (73 μL, 0.57 mmol) for a 75 min period. The reaction mixture was stirred for 15 min at this temperature. Silica gel chromatography of the crude product (hexanes/Et_2O 20:1 → 10:1) provided two isolable pure compounds: **15** (50 mg, 16%, single stereoisomer) as a dark green oil,

and **12** (22 mg, 6%), which was described previously. IR (KBr) ν_{max} 2084, 2047, 2013, 1735, 1596, 1455, 1202, 1105 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 1H), 5.81 (d, *J* = 2.4 Hz, 1H), 5.58 (d, *J* = 2.4 Hz, 1H), 4.67 (ddd, *J* = 10.3, 7.7, 2.4 Hz, 1H), 4.21 (ddd, *J* = 10.1, 8.1, 2.2 Hz, 1H), 3.86-3.54 (m, 4H), 3.83 (s, 3H), 3.75 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 3.53 (s, 3H), 3.49 (d, *J* = 15.2 Hz, 1H), 3.18 (d, *J* = 15.2 Hz, 1H), 2.57 (m, 1H), 2.48 (m, 1H), 2.44-2.16 (m, 4H), 2.00 (dd, *J* = 7.7, 1.8 Hz, 1H), 1.96 (dd, *J* = 7.9, 1.8 Hz, 1H), 1.92 (d, *J* = 9.2 Hz, 1H), 1.72 (d, *J* = 9.3 Hz, 1H), 1.39 (s, 3H), 1.38 (s, 3H), 1.15 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2 (6C), 199.6 (6C), 170.4 (C), 170.2 (C), 163.7 (C), 161.7 (C), 160.3 (C), 157.8 (C), 157.7 (C), 119.2 (C), 118.8 (C), 114.7 (CH), 113.4 (CH), 95.0 (C), 93.1 (C), 92.2 (CH), 89.9 (C), 87.2 (C), 62.3 (CH_3), 59.2 (C), 56.2 (CH_3), 54.6 (CH_3), 52.7 (CH_3), 52.3 (CH_3), 47.4 (CH), 47.3 (CH), 45.7 (CH_2), 42.3 (2CH), 39.6 (CH_2), 39.2 (C), 38.6 (C), 33.8 (CH), 33.3 (CH_2), 33.1 (CH_2), 32.4 (CH), 31.1 (CH_2), 30.9 (CH_2), 27.1 (CH_3), 26.9 (CH_3), 22.9 (CH_3), 22.3 (CH_3); Compound was not stable and correct analytical data could not be obtained.

2.4. General Procedure for the Nicholas Reaction Using 1,4-Benzenedimethanol as Nucleophile. To a solution of the alkyne in DCM was added $Co_2(CO)_8$ in one portion. The deep red mixture was stirred at room temperature until no starting material was observed (TLC analysis), and then cooled to –20 ºC. A dioxane or DCM solution of the nucleophile was added via cannula, and finally the mixture was treated dropwise with $BF_3{\cdot}OEt_2$. The reaction mixture was stirred for 1 h, then diluted with saturated aqueous $NaHCO_3$ and warmed to room temperature. The layers were separated, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure.

Finally, the crude product was solved in AcOEt, filtered through a short pad of celite, and concentrated *in vacuo*.

Preparation of compound 17.

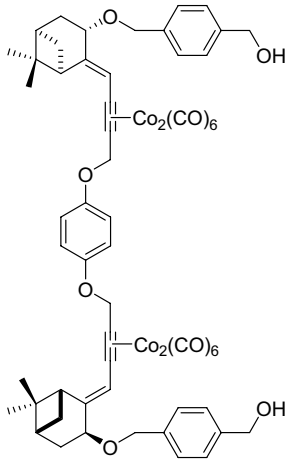


Following the general procedure, the dicobalt hexacarbonyl complex was prepared from **7** (149 mg, 0.31 mmol) and $Co_2(CO)_8$ (278 mg, 0.67 mmol) in DCM (5 mL), after 1 h of stirring. Treatment of the cobalt complex with a dioxane (2.5 mL) solution of 1,4-benzenedimethanol (43 mg, 0.31 mmol), and then with $BF_3{\cdot}OEt_2$ (83 μL, 0.65 mmol) provided **17** (290 mg, 81 %) as a dark brown oil. IR (film) ν_{max} 2930, 2091, 2052, 2023, 1595, 1146, 1076, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (s, 4H), 7.25 (m, 1H), 6.61 (m, 3H), 6.40 (s, 2H), 5.18 (s, 2H), 5.17 (s, 2H), 4.63 (d, *J* = 11.9 Hz, 2H), 4.45 (d, *J* = 11.9 Hz, 2H), 4.07 (d, *J* = 6.8 Hz, 2H), 3.00 (m, 2H), 2.08-1.98 (m, 10H), 1.34 (s, 6H), 0.70 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4 (12C), 159.7 (2C), 147.1 (2C), 137.9 (2C), 130.2 (CH), 127.9 (4CH), 125.0 (2CH), 107.2 (2CH), 101.4 (CH), 91.0 (2C), 83.6 (2C), 74.8 (2CH), 69.2 ($2CH_2$), 68.9 ($2CH_2$), 46.6 (2CH), 43.0 (2C), 40.0 (2CH), 33.2 ($2CH_2$), 26.0 ($2CH_3$*), 25.7 ($2CH_2$*), 21.7 ($2CH_3$), assignments marked with an asterisk could be interchanged; Anal. Calcd. for $C_{52}H_{44}Co_4O_{16}$: C, 53.81; H, 3.82; Found: C, 53.68; H, 3.95.

Alkyne liberation in compound 17. To a solution of **17** (230 mg, 0.20 mmol) in 8 mL of DCM at 0ºC was added an excess of TMANO (232 mg, 3.1 mmol). The mixture was

stirred for 1 h and then filtered through a pad of celite. The solvent was removed under vacuum. The crude product was purified by silica gel chromatography. (hexanes/AcOEt 20:1) to give 15 mg (13%) of a clear oil. IR (film) ν_{max} 2930, 2211, 1593, 1489, 1456, 1368, 1260, 1173, 1147, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (s, 4H), 7.16 (m, 1H), 6.63 (t, *J* = 5.2 Hz, 1H), 6.54 (dd, *J* = 8.3, 2.4 Hz, 2H), 5.35 (s, 2H), 4.82 (s, 2H), 4.81 (s, 2H), 4.65 (d, *J* = 12.0 Hz, 2H), 4.37 (d, *J* = 12.0 Hz, 2H), 4.02 (d, *J* = 7.3 Hz, 2H), 3.03 (t, *J* = 5.1 Hz, 2H), 2.41-1.97 (m, 8H), 1.67 (d, *J* = 10.0 Hz, 2H), 1.30 (s, 6H), 0.63 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4 (2C), 157.1 (2C), 137.9 (2C), 129.5 (CH), 128.3 (4CH), 107.6 (2CH), 107.4 (2CH), 103.8 (CH), 88.2 (2C), 84.3 (2C), 73.3 (2CH), 70.1 ($2CH_2$), 56.2 ($2CH_2$), 47.5 (2CH), 41.7 (2C), 39.9 (2CH), 32.2 ($2CH_2$), 27.3 ($2CH_2$*), 26.1 ($2CH_3$*), 21.9 ($2CH_3$), assignments marked with an asterisk could be interchanged; MS (EI) *m/z* (relative intensity) 588 (2), 519 (12), 331 (15), 280 (38), 171 (47), 121 (61), 104 (100), 91 (62); Anal. Calcd. for $C_{40}H_{44}O_4$: C, 81.60; H, 7.53; Found: C, 81.95; H, 7.71.

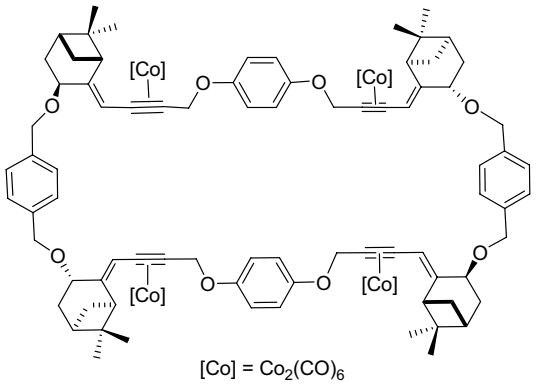
Preparation of Compound 21.



Following the general procedure, the dicobalt hexacarbonyl complex was prepared from **19** (101 mg, 0.21 mmol) and $Co_2(CO)_8$ (200 mg, 0.46 mmol) in DCM (5 mL), after 1 h

of stirring. Treatment of the cobalt complex with a dioxane (2.5 mL) solution of 1,4-benzenedimethanol (70 mg, 0.50 mmol), and then with $BF_3{\cdot}OEt_2$ (53 μL, 0.42 mmol) provided **21** (273 mg, 70%) as a dark brown oil. IR (film) ν_{max} 3401, 2971, 2090, 2050, 2014, 1505, 1218, 1075, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 4H), 6.93 (s, 8H), 6.39 (s, 2H), 5.15 (s, 4H), 4.68 (AB system, *J* = 9.4 Hz, 4H), 4.63 (d, *J* = 11.7 Hz, 2H), 4.46 (d, *J* = 11.7 Hz, 2H), 4.06 (d, *J* = 7.1 Hz, 2H), 3.03 (m, 2H), 2.35-1.96 (m, 8H), 1.59 (m, 2H), 1.33 (s, 6H), 0.70 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4 (12C), 153.0 (2C), 147.1 (2C), 137.9 (4C), 127.9 (2CH), 127.1 (2CH), 124.9 (2CH), 115.4 (4CH), 91.3 (2C), 83.6 (2C), 74.7 (2CH), 69.3 ($6CH_2$), 46.4 (2CH), 43.0 (2C), 40.0 (2CH), 33.2 ($2CH_2$), 26.0 ($2CH_2$*), 25.7 ($2CH_3$*), 21.7 ($2CH_3$), assignments marked with an asterisk could be interchanged.

Preparation of Compound 18.



Following the general procedure, the dicobalt hexacarbonyl complex **20** was prepared from **19** (48 mg, 0.10 mmol) and $Co_2(CO)_8$ (87 mg, 0.21 mmol) in DCM (3 mL), after 1 h of stirring. Treatment of the cobalt complex with a DCM (2 mL) solution of **21** (130 mg, 0.10 mmol), and then with $BF_3{\cdot}OEt_2$ (25 μL, 0.20 mmol) provided quantitatively **18** as a dark brown oil. IR (film) ν_{max} 2933, 2091, 2051, 2022, 1505, 1221, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 8H), 6.93 (s, 8H), 6.39 (s, 4H), 5.15 (s, 8H), 4.62 (d,

J = 11.7 Hz, 4H), 4.45 (d, *J* = 11.7 Hz, 4H), 4.06 (d, *J* = 6.8 Hz, 4H), 3.02 (m, 4H), 2.36-1.78 (m, 20H), 1.32 (s, 12H), 0.70 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4 (24C), 153.0 (4C), 147.1 (4C), 137.9 (4C), 127.9 (8CH), 124.9 (4CH), 115.4 (8CH), 91.3 (4C), 83.6 (4C), 74.7 (4CH), 69.3 ($4CH_2$), 69.2 ($4CH_2$), 46.5 (4CH), 43.0 (4C), 40.0 (4CH), 33.2 ($4CH_2$), 26.0 ($4CH_3$*), 25.7 ($4CH_2$*), 21.7 ($4CH_3$), assignments marked with an asterisk could be interchanged; Anal. Calcd. for $C_{104}H_{88}Co_8O_{32}$: C, 53.81; H, 3.82; Found: C, 53.60; H, 3.44.

Preparation of Compound 18 from 19 in a Single Step.

Following the general procedure, the dicobalt hexacarbonyl complex was prepared from **19** (117 mg, 0.24 mmol) and $Co_2(CO)_8$ (219 mg, 0.53 mmol) in DCM (5 mL), after 1 h of stirring. Treatment of the cobalt complex with a dioxane (2.5 mL) solution of 1,4-benzenedimethanol (33 mg, 0.24 mmol), and then with $BF_3{\cdot}OEt_2$ (64 μL, 0.50 mmol) provided quantitatively **18** (single stereoisomer) as a dark brown oil.