Cascade Cyclizations and Couplings Involving Nickel Enolates

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Supporting Information

General Information. All reagents were used as received unless otherwise noted. Tetrahydrofuran (THF) was either freshly distilled from sodium/benzophenone ketyl or treated under nitrogen through a solvent purification system (Innovative Technology, Inc., Model # SPS-400-3). TMEDA (tetramethylethylenediamine) was distilled from calcium hydride. Benzaldehyde and methyl iodide were freshly distilled. Ni(COD)₂ (Strem Chemicals, Inc.; used as received) was stored and weighed in an inert atmosphere glovebox. All reactions were conducted in flame-dried glassware under an oxygen-free atmosphere of argon or nitrogen. Analytical thin layer chromatography (TLC) were performed using EM Science 0.25 mm Silica gel 60-F plates. Visualization of the developed chromatogram was accomplished with UV light and aqueous potassium permanganate, acidic *p*-anisaldehyde, or ethanolic vanillin stains. Column chromatography was done with silica gel 60 (EM Science) 0.040-0.063 mm (230-400 mesh ASTM), unless otherwise noted. ¹H and ¹³C NMR spectra were obtained in deuteriochloroform (CDCl₃), unless otherwise noted, on a Varian Unity 300, Varian Mercury 400, or Varian Unity 500 MHz instrument. Chemical shifts of ¹H NMR spectra were recorded in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet, and br = broad), coupling constant in Hertz (Hz), and integration. Chemical shifts of ¹³C NMR spectra are reported in ppm from the central peak of CDCl₃ (77.0 ppm) on the δ scale. Infrared (IR) spectra were recorded on a

Nicolet Avatar 320 FT-IR spectrometer. High Resolution mass spectra (HMRS) were obtained on a Kratos MS 80 mass spectrometer by the Central Instrumentation Facility, Department of Chemistry, Wayne State University, Detroit, Michigan. rt = room temperature, mp = melting point, h or hr = hour, min = minutes, eq = equivalents, EtOAc = ethyl acetate, Hex = hexanes, COD = 1,5-cyclooctadiene.

Compounds (in order as they appear in Table 1) **9a**, **9b**, **9a'**, **11a**, **9c**, **10a**, **10b**, **11b**, and **Table 2** (entries **1** and **4**) were formed as previously reported.¹

General Procedure for Table 1 and Table 2:

General Procedure for the Ni(COD)₂ / tmeda Promoted [3+2] Cyclization of Enals and Enones:

To a solution of Ni(COD)₂ (1 equiv) in THF (0.05 M) was added dropwise tetramethylethylenediamine (tmeda) (1 equiv) at room temperature. After stirring for 5-10 min at rt, the reaction mixture became bright yellow and was cooled to 0°C. A solution of enal or enone at 0°C (RT or warmer especially for the silane derivatives) in THF (0.05 M) was added dropwise, and the reaction mixture was stirred at 0°C and allowed to warm to room temperature or until TLC analysis indicated disappearance of the enal or enone.

Aqueous Work-up

enals (entries 1-4, and 6, Table 1): The reaction mixture was quenched with aqueous NH₄Cl / NH₄OH (pH 8) buffer and extracted twice with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated, and the

¹ Chowdhury, S. K.; Amarasinghe, K.K.D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.*, **2000**, *122*, 6775.

residue was purified by column chromatography on silica gel.

Enones (entries 8-10, Table 1): The reaction mixture was poured over a slurry of silica gel in CH₂Cl₂ in air and was stirred for 30 min, filtered, and concentrated. The residue was dissolved in THF/H₂O (9:1), *p*-toluenesulfonic acid (1 equiv) was added, and the mixture was stirred for 10 min at rt. The reaction mixture was quenched with saturated NaHCO₃ and was extracted twice with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, filtered, and concentrated, and the residue was purified by column chromatography on silica gel.

Methanol Work-up for enones (entries 5,7 and 11, Table 1): The reaction mixture was quenched with excess anhydrous methanol and stirred for 30 minutes. The reaction mixture was poured in air over a pad of silica gel wetted with ether on a cindered glass funnel and filtered with suction. The solvent was removed by rotary evaporation and the filtrate subjected to column chromatography on silica gel.

Entry 1: (3R*,5R*)-2-(Phenyl)bicyclo[3.3.0]oct-1-en-3-ol (9a)

Following the general procedure, 8-(phenyl)oct-2-en-7-ynal (135 mg, 0.681 mmol), Ni(COD)₂ (187 mg, 0.681 mmol), and tmeda (102 μ L, 0.681 mmol) were stirred for 2 h at 0°C. Product **9a** (112 mg, 82%) was obtained as colorless oil after SiO₂ chromatography (EtOAc/Hex: 1/4). ¹H NMR (400 MHz, CDCl₃) δ 7.48 (d, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.20-7.26 (m, 1H), 5.47 (d, *J* = 6.4 Hz, 1H), 3.33-3.38 (m, 1H), 2.55-2.62 (m, 1H), 2.37-2.46 (m, 1H), 1.97-2.17 (m, 5H), 1.79 (quint, *J* = 6.9 Hz, 1H), 0.95-1.06 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 156.5, 135.4, 131.8, 128.8, 127.1, 126.7, 83.3, 52.2, 40.1, 32.0, 29.6, 26.0; IR (film, cm⁻¹) 3394; HRMS (EI) *m/z*

calcd for $C_{14}H_{16}O$ $[M^+]$ 200.1197, found 200.1199. Irradiation of the methine signal at δ 5.47 ($\underline{CH}$ -OH) resulted in a 4.6 % NOE enhancement to the methylene signal at δ 1.79 ppm. Irradiation of the other methylene signal at δ 1.97-2.17 resulted in a 2.7% NOE enhancement of the methine signal at δ 3.33-3.38 ppm (bridgehead-CH), and 5.9% NOE enhancement to the methylene signal at δ 1.79 ppm.

Entry 2 : (3R*,5R*)-2-(Methyl)bicyclo[3.3.0]oct-1-en-3-ol (9b)

Following the general procedure, non-2-en-7-ynal (62 mg, 0.45 mmol), $Ni(COD)_2$ (125 mg, 0.45 mmol), and tmeda (68 μ L, 0.45 mmol) were stirred 2 h at 0°C. Product **9b** (45 mg, 72%) was obtained as colorless oil after SiO_2 chromatography (Et₂O/Hex: 1/4). 1H NMR (400 MHz, $CDCl_3$) δ 4.65 (d, J = 6.8 Hz, 1H), 3.02-3.05 (m, 1H), 2.05-2.13 (m, 2H), 1.95-2.03 (m, 2H), 1.85-1.94 (m, 2H), 1.69 (s, 3H), 1.63-1.67 (m, 1H), 1.48-1.53 (br s, 1H), 0.82-0.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 128.6, 87.1, 49.7, 40.8, 32.6, 28.6, 22.4, 12.6; IR (film, cm^{-1}) 3429; HRMS (EI) m/z calcd for $C_9H_{14}O$ $[M^+]$ 138.1044 found 138.1044. The stereochemistry was assigned by analogy to **9a**.

Entry 3 : (1R*,8R*)-7-(Phenyl)bicyclo[4.3.0]non-6-en-8-ol (9a')

Following the general procedure, 9-(phenyl)non-2-en-8-ynal (82 mg, 0.39 mmol) in THF (0.1 M, 3.8 mL), $Ni(COD)_2$ (106 mg, 0.386 mmol), and tmeda (58 μ L, 0.386 mmol) were stirred 18 h at 0°C. The reaction mixture was filtered through SiO_2 and concentrated.

Product **9a'** (33 mg, 40%) and product **11a** (15 mg, 18%) were obtained as colorless oils after SiO₂ chromatography (EtOAc/Hex, 1:9). For compound **9a'**: ¹H NMR (500 MHz, C₆D₆) δ 7.32-7.34 (m, 2H), 7.17-7.20 (m, 2H), 7.06-7.09 (m, 1H), 4.91 (d, *J* = 8.0 Hz, 1H), 2.67 (td, *J* = 14, 2 Hz, 1H), 2.54 (sext, *J* = 6.0 Hz, 1H), 1.99 (ddd, *J* = 14.0, 7.5, 1.5 Hz, 1H), 1.80-1.84 (m, 1H), 1.73 (dt, *J* = 14.0, 5.0 Hz, 1H), 1.62 (quint, *J* = 7.0 Hz, 1H), 1.47-1.53 (m, 2H), 1.28, (br s, 1H), 1.11 (tq, *J* = 3.5, 13.5 Hz, 1H), 0.94 (tq, *J* = 13.5, 4.5 Hz, 1H), 0.78 (dq, *J* = 12.5, 3.0 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 146.3, 136.2, 135.3, 128.8, 128.6, 127.0, 79.2, 45.3, 40.4, 36.0, 27.6, 26.9, 25.9; IR (film, cm⁻¹) 3387; HRMS (EI) *m/z* calcd for C₁₅H₁₈O [*M*⁺] 214.1353 found 214.1353. Irradiation of the methine signal at δ 4.91 (CH-OH) resulted in a 2.9% NOE enhancement to the methylene signal at δ 1.62 ppm. Irradiation of the other methylene signal at δ 1.99 resulted in a 2.7% NOE enhancement of the methine signal at δ 2.54 ppm (bridgehead-CH), and 12.8% NOE enhancement to the methylene signal at δ 1.62 ppm.

9c

Entry 4 : (3R*,5R*)-2-(Acetyl)bicyclo[3.3.0]oct-1-en-3-ol (9c)

Following the general procedure, 9-(oxo)dec-2-en-7-ynal (67 mg, 0.41 mmol), Ni(COD)₂ (112 mg, 0.408 mmol), and tmeda (62 μL, 0.41 mmol) were stirred 2 h at 0°C. Product **9c** (10 mg, 15%) was obtained as crystalline solid (mp. 59-60°C) after SiO₂ chromatography (EtOAc/Hex: 1/1). ¹H NMR (500 MHz, CDCl₃) δ 5.28 (d, *J* = 6.5 Hz, 1H), 3.40-3.46 (m, 1H), 2.50-2.65 (m, 2H), 2.30 (s, 3H), 2.26 (br s, 1H), 2.15-2.22 (m, 1H), 2.01-2.09 (m, 3H), 1.65-1.71 (m, 1H), 1.06-1.14 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 197.1, 174.5, 134.7, 81.8, 54.2, 37.8, 31.3, 29.3, 27.0; IR (film, cm⁻¹) 3429, 1640; HRMS (EI) *m/z*

calcd for $C_{10}H_{14}O_2$ $[M^+]$ 166.099 found 166.0991. The stereochemistry was assigned by analogy to **9a**.

Entry 5: (3R*,5R*)-2-(Trimethylsilyl)bicyclo[3.3.0]oct-1-en-3-ol (9d)

Following the general procedure, 8-trimethylsilyl-oct-2-en-7-ynal (38 mg, 0.19 mmol), $Ni(COD)_2$ (54 mg, 0.19 mmol) and tmeda (30 μ L, 0.19 mmol) were stirred for 2h at rt. The reaction mixture was subsequently heated to 45°C for 4 hours and then at 55 °C for another 4 hours. The reaction mixture was cooled to rt before anhydrous methanol (1 mL) was added and stirred for 30 min. After chromatography (EtOAc/Hex, 1:10), product **9d** (21 mg, 0.11 mmol, 55%) was obtained as a light yellow oil. A small portion (5 mg, 13%) of starting material was also recovered. 1H NMR (400 MHz, $CDCl_3$) δ 5.00 (d, J = 6.0 Hz, 1H), 3.12-3.20 (m, 1H), 2.27-2.34 (m, 1H), 2.11-2.20 (m, 1H), 1.87-2.10 (m, 4H), 1.52 (ddd, J = 13.4, 7.2, 5.6 Hz, 1H), 1.27 (br s, 1H), 0.86-0.96 (m, 1H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.5, 131.9, 87.3, 52.7, 41.8, 31.7, 29.3, 25.0, -0.5; IR (film, cm^{-1}) 3365, 1716, 1621, 1446, 1247, 838; HRMS (EI) m/z calcd for $C_{11}H_{20}OSi$ $[M^+]$ 196.1283, found 196.1284.

Entry 6 : (3R*,5R*)-2-(Phenyl)-7-oxo-bicyclo[3.3.0]oct-1-en-3-ol (9e)

Following the general procedure, 4-(3-Phenyl-prop-2-ynyloxy)-but-2-enal (72 mg, 0.36 mmol), Ni(COD)₂ (98 mg, 0.36 mmol) and tmeda (54 μ L, 0.36 mmol) were stirred for 2h at 0°C. Product **9e** (57 mg, 0.28 mmol, 78%) was obtained as a white crystalline solid (mp 76-77°C) after chromatography (EtOAc/Hex, 1:5). ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.40 (m, 2H), 7.26-7.29 (m, 3H), 5.61 (d, J = 6.0 Hz, 1H), 4.60 (d, J = 14.0 Hz, 1H), 4.42 (d, J = 14.4 Hz, 1H), 4.15-4.18 (m, 1H), 3.76-3.82 (m, 1H), 3.11 (dd, J = 10.6, 7.4 Hz, 1H), 2.14 (dd, J = 13.6, 6.4 Hz, 1H), 2.07 (br m, 1H), 1.88-1.95 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 150.8, 134.0, 133.8, 129.1, 127.8, 127.3, 83.8, 72.2, 65.4, 51.3, 37.1 IR (film, cm⁻¹) 3366, 1496, 1442, 1183, 1091, 1012; HRMS (EI) m/z calcd for C₁₃H₁₄O₂ [M⁺] 202.0994, found 202.0993.

Entry 7 : (3R*,5R*)-2,3-(Diphenyl)bicyclo[3.3.0]oct-1-en-3-ol (9f)

Following the general procedure, Ni(COD)₂ (102 mg, 0.371 mmol, 1eq.), 6 mL THF, tmeda (60 μ L, 0.40 mmol, 1eq.), and 1,8-Diphenyl-oct-2-en-7-yn-1-one (102 mg, 0.371 mmol) as a solution in 6 mL THF were stirred at 0°C→rt. After 3 hours, the reaction was

quenched with 10 mL anhydrous methanol. The reaction mixture was filtered through a pad of Celite and dried over anhydrous magnesium sulfate. Column chromatography (10:1 Hex/EtOAc) afforded the colorless oil, **9f** (43.6 mg, 0.158 mmol, 52%). ^1H NMR (400 MHz, C_6D_6): δ 7.55-7.58 (m, 2H), 7.32 (d, $J = 7.2$ Hz, 2H), 7.08-7.11 (m, 2H), 6.94-7.00 (m, 3H), 6.85 (t, $J = 7.2$ Hz, 1H), 2.78-2.86 (m, 1H), 2.29-2.40 (m, 2H), 2.12-2.18 (m, 1H), 1.96 (s, 1H), 1.82-1.90 (m, 2H), 1.61-1.73 (m, 2H), 0.85-0.96 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ 156.7, 147.8, 135.9, 133.6, 128.1, 128.05, 128.02, 126.3, 126.1, 125.9, 94.8, 51.6, 50.4, 31.8, 29.1, 25.7; IR (film, cm^{-1}): 3454(br w), 1671(m), 1600(m), 1495(m), 1446(m), 1061(m), 975(m), 909(s), 760(s), 732(s), 699(s); HRMS (EI) m/z calcd for $\text{C}_{20}\text{H}_{20}\text{O}$ [M^+] 276.1514, found 276.1514.

Entry 8: (1R*,5S*)-2,3-(Diphenyl)bicyclo[3.3.0]oct-2-en-1-ol (10a)

Following the general procedure, 1,8-(diphenyl)oct-2-en-7-yn-1-one (68 mg, 0.248 mmol), $\text{Ni}(\text{COD})_2$ (68 mg, 0.248 mmol), and tmeda (37 μL , 0.248 mmol) were stirred for 3 h at 0°C . Product **10a** (35 mg, 53%) was obtained as crystalline solid (mp $113\text{--}114^\circ\text{C}$) after chromatography (EtOAc/Hex, 1/4). ^1H NMR (500 MHz, CDCl_3) δ 7.25-7.29 (m, 5H), 7.12-7.17 (m, 5H), 3.19 (dd, $J = 17.0, 8.5$ Hz, 1H), 2.57-2.62 (m, 1H), 2.53 (dd, $J = 16.8, 3.3$ Hz, 1H), 2.19-2.26 (m, 1H), 1.87-1.92 (m, 1H), 1.76-1.83 (m, 1H), 1.61 - 1.74 (m, 2H), 1.51 (sext, $J = 6.2$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.1, 139.7, 137.2, 129.8, 128.6, 128.5, 128.1, 127.4, 127.2, 98.7, 49.0, 42.1, 39.6, 35.2, 26.0; IR (film, cm^{-1}) 3339; HRMS (EI) m/z calcd for $\text{C}_{20}\text{H}_{20}\text{O}$ [M^+] 276.1514 found 276.1517. The structure of **10a** was proven by single-crystal X-ray analysis. The author has deposited

atomic coordinates for **10a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Entry 9: (1R*,5S*)-2-Methyl-3-(phenyl)bicyclo[3.3.0]oct-2-en-1-ol (10b)

Following the general procedure, 1-(phenyl)non-2-en-7-yn-1-one (105 mg, 0.495 mmol), Ni(COD)₂ (136 mg, 0.495 mmol), and tmeda (74 μ L, 0.495 mmol) were stirred 3 h at 0°C. Product **10b** (55 mg, 52%) was obtained as crystalline solid (mp 79-80°C) after chromatography (EtOAc/hexane 1/4). ¹H NMR (500 MHz, CDCl₃) δ 7.3 - 7.37 (m, 4H), 7.23 - 7.26 (m, 1H), 3.08 (ddd, J = 16.6, 9.0, 2.0 Hz, 1H), 2.44 (sept, J = 4 Hz, 1H), 2.28 (td, J = 16.3, 2.3 Hz, 1H), 2.09-2.17 (m, 1H), 1.89-1.93 (m, 1H), 1.85 (t, J = 2.0 Hz, 3H), 1.73-1.80 (m, 3H), 1.53-1.60 (m, 1H), 1.43 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 138.2, 137.0, 136.9, 128.3, 128.0, 127.0, 98.5, 48.5, 42.2, 38.8, 35.1, 25.8, 11.4; IR (film, cm⁻¹) 3338; HRMS (EI) m/z calcd for C₁₅H₁₈O [M⁺] 214.1357 found 214.1358. Anal. calcd for C₁₅H₁₈O: C, 83.66 H, 8.90 found C, 83.88 H, 8.65.

Entry 10: 2-(2-Methylene-cyclopentyl)-1-phenyl-ethanone (11b)

Following the general procedure, (2E)-1-phenyloct-2-en-7-yn-1-one (94 mg, 0.47 mmol), Ni(COD)₂ (130 mg, 0.47 mmol), and tmeda (72 μ L, 0.47 mmol) were stirred for 3 h at

0°C. Product **11b** was obtained as a colorless oil after chromatography (EtOAc/Hex: 1/4) (25 mg, 0.23 mmol, 27%). {Full spectroscopic details available in Montgomery, J.; Oblinger, E.; Savchenko, A. *J. Am. Chem. Soc.*, **1997**, *119*(21), 4911.}

Entry 11 : (3R*,5R*)-3-(Phenyl)-2-(trimethylsilyl)bicyclo[3.3.0]oct-1-en-3-ol (9g)

Following the general procedure, Ni(COD)₂ (20.0 mg, 0.0727 mmol, 1eq.), tmeda (12 μ L, 0.397 mmol, 1eq.) in 3 mL THF, and a solution of 1-phenyl-8-trimethylsilyl-oct-2-en-7-yn-1-one (19.9 mg, 0.0735 mmol) in 2 mL THF were stirred at 65°C for 14 hours at which point the red solution had become slightly turbid. The reaction was quenched with 7 mL anhydrous methanol. The reaction mixture was filtered through a pad of Celite and dried over anhydrous magnesium sulfate. Column chromatography (10:1 Hex/EtOAc) afforded a yellow oil, **9g** (12.2 mg, 0.0448 mmol, 61%). ¹H NMR (500 MHz, CDCl₃): δ 7.42 (m, 2H), 7.31 (m, 2H), 7.21 (m, 1H), 3.23 (m, 1H), 2.25-2.43 (m, 3H), 2.10-2.17 (m, 1H), 1.96-2.06 (m, 2H), 1.82 (dd, J = 13.4, 7.8 Hz, 1H), 1.79 (s, 1H), 1.06-1.17 (m, 1H), -0.17 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 172.9, 148.0, 135.6, 127.8, 126.5, 126.0, 97.8, 52.7, 51.5, 31.7, 28.9, 25.6, 0.02; IR (film, cm⁻¹): 3474(br w), 1682(w), 1617(m), 1492(w), 1446(m), 1246(s), 835(vs), 758(s), 702(s); HRMS (EI) m/z calcd for C₁₇H₂₄OSi [M⁺] 272.1596, found 272.1595.

Entry 12 : (1R*,5S*)-3-(Phenyl)-2-(trimethylsilyl)bicyclo[3.3.0]oct-2-en-1 (10c)

A solution of **9g** (12.2 mg, 0.0448 mmol) in 10 mL CH₂Cl₂ and 1.0 gram silica gel was stirred for 8 h at room temperature. The mixture was filtered and the solvent removed *in vacuo* to give a quantitative yield of white solid **10c** (12.2 mg, 0.0448 mmol). ¹H NMR (400 MHz, CDCl₃): δ 7.26-7.32 (m, 3H), 7.16 (m, 2H), 3.06 (dd, *J* = 17.6, 8.8 Hz, 1H), 2.47-2.41 (m, 1H), 2.28 (dd, *J* = 17.8, 4.2 Hz, 1H), 2.11 (dq, *J* = 6.4, 1.6 Hz, 1H), 1.92 (m, 2H), 1.78 (m, 1H), 1.68 (sext, *J* = 6.4 Hz, 1H), 1.64 (s, 1H), 1.35 (sext, *J* = 6.8 Hz, 1H), -0.03 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 156.7, 143.0, 140.9, 128.1, 127.8, 127.3, 102.6, 52.2, 47.7, 41.5, 34.7, 26.3, 1.2; IR (CDCl₃, film, cm⁻¹): 3387(br m), 1589(w), 1489(w), 1444(m), 1246(s), 836(vs), 758(s), 699(s); HRMS (EI) *m/z* calcd for C₁₇H₂₄OSi [M⁺] 272.1596, found 272.1597.

General Procedure for Table 2: (see general procedure above)

Entry 1: (3R*,4R*,5R*)-4-Methyl-2-(phenyl)bicyclo[3.3.0]oct-1-en-3-ol

Following the general procedure, 8-(phenyl)oct-2-en-7-ynal (47 mg, 0.236 mmol), Ni(COD)₂ (65 mg, 0.236 mmol, 1 eq.), and tmeda (36 μL, 0.236 mmol, 1 eq.) were stirred

for 2 h at 0°C. Methyl iodide (44 μ L, 0.708 mmol, 3 eq.) was added dropwise and stirring at 0°C was continued 1h. Product **{Table 2, Entry 1}** (34 mg, 0.16 mmol, 68%) was obtained as crystalline solid (mp 117-118°C) after chromatography (EtOAc/Hex, 1:9). ^1H NMR (500 MHz, CDCl_3) δ 7.50 (d, J = 8.0 Hz, 2H), 7.34-7.37 (m, 2H), 7.20-7.23 (m, 1H), 5.17 (d, J = 5.5 Hz, 1H), 2.86-2.91 (m, 1H), 2.55-2.61 (m, 1H), 2.39-2.47 (m, 1H), 2.11-2.17 (m, 1H), 1.98-2.06 (m, 2H), 1.92 (sext, J = 7.0 Hz, 1H), 1.44 (br s, 1H), 1.21 (d, J = 7.0 Hz, 3H), 0.99-1.09 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3): δ 156.3, 135.7, 132.5, 128.7, 127.0, 126.6, 84.9, 58.9, 45.3, 30.6, 29.7, 26.5, 13.5; IR (film, cm^{-1}) 3364; HRMS (EI) m/z calcd for $\text{C}_{15}\text{H}_{18}\text{O}$ [M^+] 214.1357, found 214.1354. Irradiation of the methine signal at δ 5.17 (CH-OH) resulted in 6.7% NOE enhancement to the methine signal at δ 1.89-1.93 (CH-CH_3). Irradiation of the methyl signal at δ 1.21 resulted in a 2.5% NOE enhancement to the methine signal at δ 2.86-2.91 ppm (bridgehead-CH).

Entry 2: 1-Allyl-3-phenyl-1,2,4,5,6,6a-hexahydro-pentalen-2-ol

Following the general procedure, 8-(phenyl)oct-2-en-7ynal (100 mg, 0.505 mmol), $\text{Ni}(\text{COD})_2$ (140 mg, 0.505 mmol) and tmeda (76 μ L, 0.50 mmol) were stirred for 2h at 0°C. Allyl iodide (139 μ L, 1.52 mmol) was added dropwise at 0°C and the reaction mixture was stirred at the same temperature for 2 hours. Product **{Table 2, Entry 2}** (87 mg, 0.363 mmol, 72%) was obtained as a white crystalline solid (mp 97-98°C) after chromatography (EtOAc/Hex, 1:5). ^1H NMR (400 MHz, CDCl_3) δ 7.50 (d, J = 8.0 Hz, 2H), 7.36 (t, J = 7.8 Hz, 2H), 7.23 (q, J = 7.0 Hz, 1H), 5.96 (ddt, J = 17.4, 10.0, 7.2 Hz,

1H), 5.28 (d, $J = 5.6$ Hz, 1H), 5.15-5.20 (m, 1H), 5.04-5.07 (m, 1H), 2.91-2.97 (m, 1H), 2.33-2.61 (m, 4H), 1.96-2.18 (m, 3H), 1.81-1.92 (m, 1H), 1.60 (s, 1H), 0.99-1.11 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 156.2, 138.4, 135.6, 132.1, 128.7, 127.0, 126.7, 115.6, 83.6, 57.5, 50.3, 33.9, 31.4, 29.7, 26.3. IR (film, cm^{-1}) 3364, 3213, 1498, 1444, 1089, 1036, 909, 770, 690; HRMS (EI) m/z calcd for $\text{C}_{17}\text{H}_{20}\text{O}$ [M^+] 240.1514, found 240.1513. Irradiation of the methine signal at δ 5.28 (CH-OH) resulted in 4.88% NOE enhancement to the methine signal at δ 1.81-1.92 ($\text{CH-CH}_2\text{CHCH}_2$).

Experimental Scheme A: Towards product Table 2, Entry 3

Entry 3 : (3R*,4R*,5R*)-2-Phenyl-4-[benzyl]-bicyclo[3.3.0]oct-1-en-3-ol:²

(This is also a representative procedure for Scheme 8 in paper.)

In a round bottom flask under vacuum $\text{Ni}(\text{acac})_2$ (104mg, 0.404 mmol) was heated briefly with a heat gun. After cooling and establishing a positive argon atmosphere, 1 mL THF

² See leading reference Mackenzie, P.; Krysan, D.J., *J. Org. Chem.* **1990**, 55, 4229.

was added, followed by the addition of COD (198 μ L, 1.62 mmol). The solution was then cooled to -78°C in a dry ice/acetone bath to give a green slurry and DIBAL-H (1.0 M/THF, 1.01 mmol, 1.01 mL) was introduced over one hour using a syringe pump to give a reddish brown solution which was allowed to warm to 0°C over a 1 hr period. THF was removed under vacuum and the resulting yellowish brown solid was washed with 1 mL portions of cold ether until the brown residues were removed to give a yellow solid. THF (12 mL) was added, followed by the addition of tmeda (38 μ L, 0.25 mmol), and the solution was stirred for 5 min at rt. 8-(Phenyl)oct-2-en-7ynal (50 mg, 0.25 mmol) as a solution in 3mL THF was introduced via a cannula at 0°C . After 2 hours at 0°C , benzyl iodide (100 μ L, 0.757 mmol) was added and the reaction mixture was kept at the same temperature for another hour. The reaction was quenched with aqueous saturated sodium bicarbonate, extracted 3 times with ethyl acetate and dried over magnesium sulfate. After removal of solvent *in vacuo* the crude material was subjected to SiO_2 chromatography (EtOAc/Hex, 1:10). The product **{Table 2, Entry 3}** (50 mg, 68% mp $99\text{--}100^{\circ}\text{C}$) and was obtained as a white crystalline solid). ^1H NMR (400 MHz, CDCl_3): δ 7.47 (d, $J = 8.0$ Hz, 2H), 7.31-7.36 (m, 6H), 7.19-7.26 (m, 2H), 5.23 (d, $J = 6.0$ Hz, 1H), 2.97-3.1 (m, 2H), 2.88 (dd, $J = 13.4, 8.0$ Hz, 1H), 2.56 (dd, $J = 18.4, 10.4$ Hz, 1H), 2.35-2.44 (m, 1H), 2.08- 2.20 (m, 1H), 1.89-2.07 (m, 2H), 1.55-1.61 (m, 2H), 0.85 (dq, $J = 12.4, 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.3 141.8, 135.5, 132.2, 129.2, 128.7, 128.6, 127.0, 126.7, 126.1, 83.5, 57.3, 52.7, 35.5, 31.1, 29.6, 26.3; IR (film, cm^{-1}) 3323.7; HRMS (EI) m/z calcd for $\text{C}_{21}\text{H}_{22}\text{O}$ [M^+] 290.1671, found 290.1668. Irradiation of the methine signal at δ 5.23 (CH-OH) resulted in 7.8% NOE enhancement to the methine signal at δ 2.08-2.20 ($\text{CH-CH}_2\text{-Ph}$).

Entry 4: (3R*,4R*,5R*)-2-Phenyl-4-[(S*)-phenylmethanol]bicyclo[3.3.0]oct-1-en-3-ol

Following the general procedure, 8-(phenyl)oct-2-en-7-ynal (47 mg, 0.236 mmol), Ni(COD)₂ (65 mg, 0.236 mmol, 1 eq.), and tmeda (36 μ L, 0.236 mmol, 1 eq.) were stirred for 2 h at 0°C. Benzaldehyde (72 μ L, 0.708 mmol, 3 eq.) was added dropwise at 0°C and the reaction mixture was stirred at rt for 12 h. Product {**Table 2, Entry 4**} (59 mg, 0.193 mmol, 82%) was obtained as crystalline solid (mp 133-134°C) after chromatography (EtOAc/Hex, 1:6). ¹H NMR (400 MHz, CDCl₃) δ 7.44 (t, *J* = 6.4 Hz, 4H), 7.36 (t, *J* = 7.2 Hz, 4H), 7.21-7.28 (m, 2H), 5.50 (d, *J* = 5.6 Hz, 1H), 5.29 (d, *J* = 4.0 Hz, 1H), 3.93 (br s, 1H), 3.48-3.54 (m, 1H), 2.56 (dt, *J* = 18.4, 5.6, 1H), 2.28-2.39 (m, 2H), 2.14-2.19 (m, 1H), 1.92-2.00 (m, 2H), 1.37-1.44 (m, 1H), 0.61-0.72 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 157.6, 144.0, 134.9, 131.3, 128.9, 128.4, 127.2, 127.0, 126.9, 125.9, 85.1, 73.3, 56.9, 51.4, 31.8, 29.4, 25.9; IR (film, cm⁻¹) 3356; HRMS (EI) *m/z* calcd for C₂₁H₂₂O [M⁺] 306.1698, found 288.1514 [M-H₂O]⁺. The stereochemical assignment was confirmed by single crystal X-ray analysis.

Entry 5: (3R*,4R*,5R*)-2-Phenyl-4-[hydroxymethyl]bicyclo[3.3.0]oct-1-en-3-ol;

Following the general procedure, 8-(phenyl)oct-2-en-7-ynal (50 mg, 0.25 mmol), Ni(COD)₂ (70 mg, 0.25 mmol) and tmeda (38 μ L, 0.25 mmol) were stirred for 2h at 0°C. A suspension of paraformaldehyde (68mg, 0.76 mmol) in 3 mL ether was added dropwise at 0°C and the reaction mixture was stirred at the same temperature for 2 hours. The product {**Table 2, Entry 5**} (46 mg, 0.20 mmol, 80%) was obtained as a white crystalline solid (mp 132-133°C) after chromatography (EtOAc/Hex, 4:1). ¹H NMR (400 MHz, CDCl₃) δ 7.46 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 8.4 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 5.51 (d, *J* = 6.4 Hz, 1H), 3.86-3.98 (m, 2H), 3.11-3.17 (m, 1H), 2.37-3.08 (br s, 1H), 2.59 (dd, *J* = 18.8, 10.4, 1H), 2.37-2.47 (m, 1H), 1.98-2.17 (m, 4H), 0.99-1.11 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 156.6, 135.1, 131.5, 128.9, 127.0, 126.9, 84.1, 62.4, 53.3, 50.9, 30.9, 29.5, 26.2; IR (film, cm⁻¹) 3333(br), 1712, 1272, 1204, 1119, 1020, 756, 692; HRMS (EI) *m/z* calcd for C₁₅H₁₈O₂ [M⁺] 230.1307, found 230.1307. Irradiation of the methine signal at δ 5.54 (CH-OH) resulted in 6.9% NOE enhancement to the methine signal at 1.99-2.18 (CH-CH₂OH). Irradiation of the bridgehead methine at 3.15-3.21 resulted in 1.8% NOE enhancement to the CH₂OH signal at 3.91-4.02.

Entry 6 : (3R*,4R*,5R*)-2-Phenyl-4-[benzoyl]bicyclo[3.3.0]oct-1-en-3-ol:

Following the general procedure, 8-(phenyl)oct-2-en-7ynal (100 mg, 0.505 mmol), Ni(COD)₂ (140 mg, 0.505 mmol) and tmeda (76 μ L, 0.505 mmol) were stirred for 2h at 0°C. Benzoyl chloride (59 μ L, 0.505 mmol) was added dropwise at 0°C and the reaction mixture was stirred at the same temperature for 10 min. The product {Table 2, Entry 6} was obtained as a white crystalline solid (111 mg, 0.3651 mmol, 72%, mp 126-127°C) after chromatography (EtOAc/Hex, 1:5). ¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, J = 7.2 Hz, 2H), 7.59-7.62 (m, 1H), 7.52 (t, J = 7.2 Hz, 4H), 7.36 (t, J = 7.8 Hz, 2H), 7.21-7.26 (m, 1H), 5.75 (t, J = 7.0 Hz, 1H), 3.90-3.97 (m, 1H), 3.84 (t, J = 6.8 Hz, 1H), 2.66 (dd, J = 17.8, 9.8 Hz, 1H), 2.46-2.55 (m, 1H), 2.42 (d, J = 8.4 Hz, 1H), 2.02-2.23 (m, 3H), 1.09-1.20 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 200.1, 155.1, 137.4, 134.8, 133.5, 130.0, 129.0, 128.8, 128.5, 127.0, 127.0, 84.7, 57.3, 53.1, 31.3, 29.5, 26.2; IR (film, cm⁻¹) 3458, 1679, 1596, 1496, 1446, 1252, 1020; HRMS (EI) m/z calcd for C₂₁H₂₀O₂ [M]⁺ 304.1463, found 286.1358 [M-H₂O]⁺. Irradiation of the methine signal at δ 5.75 (CH-OH) resulted in 8.3% NOE enhancement to the methine signal at δ 3.84 (CH-CO-Ph).

Entry 7: 8-Phenyl-2,3,3a,3b,4,5,6,7a-octahydro-1H-7-oxa-cyclopenta[a]inden-6-ol

Following the general procedure, 8-(phenyl)oct-2-en-7ynal (50 mg, 0.25 mmol), Ni(COD)₂ (70 mg, 0.25 mmol) and tmeda (38 μ L, 0.25 mmol) were stirred for 2h at 0°C. Acrolein (51 μ L, 0.76 mmol) was added dropwise at 0°C and the reaction mixture was stirred at the same temperature for 2 hours. The product {**Table 2, Entry 7**} (47 mg, 0.18 mmol, 72%) was obtained as a white crystalline solid (mp 124-125°C) after chromatography (EtOAc/Hexane, 1:5) as a 3:2 inseparable mixture of diastereomers. ¹H NMR (400 MHz, CDCl₃) δ 7.46-7.48 (m, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.17-7.20 (m, 1H), 5.47 (d, *J* = 5.5 Hz, 0.6H), 5.33-5.34 (m, 0.6H), 5.17 (d, *J* = 4.0 Hz, 0.4H), 4.76 (t, *J* = 7.5Hz, 0.4H), 3.2-3.26 (m, 0.4H), 3.12-3.17 (m, 0.6H), 2.88 (m, 0.4H), 2.79 (m, 0.6H), 2.58-2.64 (m, 1H), 2.41-2.51 (m, 1H), 2.12-2.20 (m, 2H), 1.73-2.10 (m, 4H), 1.51-1.64 (m, 2H), 1.02-1.10 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 157.9, 157.7, 135.6, 130.1, 129.8, 128.63, 128.61, 126.93, 126.87, 126.6, 126.5, 95.6, 92.4, 88.0, 80.4, 57.1, 54.8, 43.7, 43.5, 30.8, 30.5, 30.0, 29.7, 29.2, 27.0, 26.7, 26.5, 23.2, 20.1; IR(film, cm⁻¹) 3386, 1708, 1496, 1444, 1008; HRMS (EI) *m/z* calcd for C₁₇H₂₀O₂ [M⁺] 256.1463, found 256.1458.

Experimental Scheme B: Synthesis of precursor 17 for Scheme 5

B3, 2-(4-Phenyl-but-3-ynyl)-cyclopentanone:³

The iodide **B2** (9.145 g, 35.72 mmol) was added to a solution of the pyrrolidine enamine of cyclopentanone **B1** (5.872 g, 42.86 mmol, 1.2 eq.)⁴ in dry toluene (86 mL) and the reaction mixture was heated to reflux under argon for 18 h. Water was added (10 mL), and the mixture was heated to reflux for an additional 30 min, cooled, poured into cold 10% aqueous HCl and extracted 3 x with ethyl acetate. The organic layer was washed with brine, dried over MgSO₄, and filtered. Evaporation of the solvent and purification by silica gel column chromatography (EtOAc:Hex, 1:8) gave 3.4 g (16 mmol, 45%) of **B3** as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.39 (m, 2H), 7.26-7.29 (m, 3H), 2.52 (qt, *J* = 17.2, 6.4Hz, 2H), 2.24-2.37 (m, 3H), 2.00-2.19 (m, 3H), 1.75-1.87 (m,

³ See leading reference Ghera, E., Maurya, R.; Ben-David, Y., *J. Org. Chem.*, **1988**, 53, 1912.

⁴ Preparation of **B1** done as in Murray, D.F.; Baum, M.W.; Jones, M., *J. Org. Chem.*, **1986**, 51, 1.

1H), 1.52-1.62 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 222.1, 131.7, 128.4, 127.9, 124.0, 89.5, 81.5, 48.5, 38.3, 29.7, 28.9, 21.0, 17.9 IR (film, cm^{-1}) 1735, 1490, 1202, 1156, 1070, 755, 692; HRMS (EI) m/z calcd for $\text{C}_{15}\text{H}_{16}\text{O}$ [M^+] 212.1201, found 212.1197.

B4, [2-(4-Phenyl-but-3-ynyl)-cyclopentylidene]-acetic acid ethyl ester:⁵

NaH (60% dispersion in mineral oil, 33mg, 0.84 mmol) was washed with hexanes, and the resulting powder was suspended in dry THF (2 mL) and cooled in a dry ice/acetone bath. Triethylphosphonoacetate (231 μL , 1.17 mmol) in 2mL THF was added dropwise and the reaction mixture was stirred for 30 min at rt. The mixture was cooled in a dry ice/acetone bath and a solution of 2-(4-phenyl-but-3-ynyl)-cyclopentanone in 1mL THF was added dropwise. The mixture was allowed to warm to rt while stirring over 10 h. The reaction mixture was quenched with saturated ammonium chloride and extracted 3 x with ether. The combined ether extract was washed with brine and the organic layer dried over anhydrous MgSO_4 . Evaporation of the solvent and purification by column chromatography (EtOAc:Hex, 1:10) furnished *E*-[2-(4-phenyl-but-3-ynyl)-cyclopentylidene]-acetic acid ethyl ester **B4** as a colorless oil (132 mg, 0.468 mmol, 66%) along with *Z*-[2-(4-phenyl-but-3-ynyl)-cyclopentylidene]-acetic acid ethyl ester (15 mg, 0.053 mmol, 8%). Product **B4** ^1H NMR (400 MHz, CDCl_3) δ 7.37-7.40 (m, 2H), 7.25-7.30 (m, 3H), 5.77 (q, $J = 2.4\text{Hz}$, 1H), 4.15 (q, $J = 7.6\text{ Hz}$, 2H), 2.95-3.01 (m, 1H),

⁵ See leading reference Srikrishna, A.; Kumar, P.P., *Tetrahedron*, **2000**, 56(41), 8189.

2.66-2.78 (m, 2H), 2.39-2.56 (m, 2H), 1.91-2.03 (m, 2H), 1.80-1.90 (m, 1H), 1.54-1.68 (m, 2H), 1.32-1.36 (m, 1H), 1.27 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.5, 167.2, 131.8, 128.4, 127.9, 124.0, 112.0, 89.7, 81.4, 59.8, 46.0, 33.2, 32.8, 31.5, 24.4, 17.9, 14.6; IR (film, cm^{-1}) 3390(br w), 1713(s), 1275, 1201, 1037, 758, 693; HRMS (EI) m/z calcd for $\text{C}_{19}\text{H}_{22}\text{O}_2$ [M^+] 282.1620, found 282.1612.

B5

B5, 2-[2-(4-Phenyl-but-3-ynyl)-cyclopentylidene]-ethanol:

A solution of [2-(4-phenyl-but-3-ynyl)-cyclopentylidene]-acetic acid ethyl ester (295 mg, 1.05 mmol) in 11 mL CH_2Cl_2 was cooled to -40°C before DIBAL (2.61 mL, 1 M in hexanes, 2.62 mmol) was introduced dropwise. The mixture was kept at this temperature for 30 minutes followed by the dropwise addition of 0.5 mL anhydrous methanol (CAUTION: vigorous evolution of gas). The mixture was allowed to warm to rt and was stirred with an aqueous saturated solution of sodium potassium tartarate overnight. The organic fraction was extracted 3 x with ethyl acetate and dried over anhydrous magnesium sulfate. After solvent removal by rotary evaporation, column chromatography (1:3, Hex/EtOAc) afforded **B5**, 2-[2-(4-Phenyl-but-3-ynyl)-cyclopentylidene]-ethanol, (204 mg, 0.850 mmol, 81%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.40 (m, 2H), 7.26-7.30 (m, 3H), 5.47-5.50 (m, 1H), 4.15 (d, $J = 7.2$ Hz, 2H), 2.35-2.55 (m, 4H), 2.22-2.30 (m, 1H), 1.87-1.99 (m, 2H), 1.73-1.82 (m, 1H), 1.47-1.63 (m, 3H), 1.24-1.33 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.4, 131.8, 128.4, 127.8, 124.2, 119.6, 90.4, 81.0, 61.1, 43.8, 33.5, 32.3, 29.2, 24.3, 18.0; IR (film,

cm⁻¹) 3342, 1490, 999, 755, 692; HRMS (EI) *m/z* calcd for C₁₇H₂₀O [M⁺] 240.1514, found 240.1506.

17, [2-(4-Phenyl-but-3-ynyl)-cyclopentylidene]-acetaldehyde:

A solution of 2-[2-(4-phenyl-but-3-ynyl)-cyclopentylidene]-ethanol (85mg, 0.35 mmol) in 9 mL CH₂Cl₂ was stirred while PCC (122mg, 0.567 mmol, 1.6 equiv.) was added portion wise. The reaction mixture stirred for 2 h at rt. The solvent was removed by rotary evaporation, and the crude material was loaded on a silica gel pad. After elution with CH₂Cl₂, product **B5** (65mg, 0.27 mmol, 77%) was isolated as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 9.90 (d, *J* = 8.0 Hz, 1H), 7.37-7.39 (m, 2H), 7.26-7.31 (m, 3H), 5.98-6.00 (m, 1H), 2.97-3.02 (m, 1H), 2.72-2.81 (m, 2H), 2.42-2.59 (m, 2H), 1.91-2.11(m, 3H), 1.57-1.77 (m, 2H), 1.35-1.44 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 192.1, 176.1, 131.8, 128.5, 128.0, 123.9, 123.1, 89.3, 81.6, 45.9, 32.5, 31.1, 30.8, 24.5, 17.9; IR (film, cm⁻¹) 1677, 1490, 1274, 1162, 756, 692; HRMS (EI) *m/z* calcd for C₁₇H₁₈O [M⁺] 238.1358, found 238.1357.

20, 3-Phenyl-1,2,4,5,5a,6,7,8-octahydro-cyclopenta[c]pentalen-2-ol:

Following the general procedure, [2-(4-phenyl-but-3-ynyl)-cyclopentylidene]-acetaldehyde (100 mg, 0.420 mmol), Ni(COD)₂ (116 mg, 0.420 mmol) and tmeda (64 μ L, 0.40 mmol) were stirred for 2h at room temperature. Anhydrous methanol (2 mL) was added and the reaction mixture was stirred for another 15 min. Product **15** (72 mg, 0.30 mmol, 71%) was obtained as a white crystalline solid (mp 77-78°C) after column chromatography (EtOAc/Hex, 1:5). ¹H NMR (500 MHz, CDCl₃) δ 7.45 (d, J = 7.5Hz, 2H) 7.36 (t, J = 7.5 Hz, 2H), 7.24 (q, J = 7.5Hz, 1H), 5.43 (d, J = 6.5Hz, 1H), 2.45-2.55 (m, 2H), 1.95-2.12 (m, 4H), 1.77-1.92 (m, 4H), 1.63-1.71 (m, 3H), 1.40-1.48 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 158.9, 135.2, 131.7, 128.7, 127.6, 126.9, 81.9, 66.8, 48.4, 47.3, 42.0, 36.0, 34.9, 27.6, 25.6; IR (film, cm⁻¹) 3327, 1650, 1598, 1496, 1445, 1012; HRMS (EI) m/z calcd for C₁₇H₂₀O [M⁺] 240.1514, found 240.1514. The structural assignment was confirmed by single crystal X-Ray analysis.

Figure 1: ORTEP perspective views of **20** showing the labeling system. Protons were removed for clarity. Thermal ellipsoids are drawn at a 30% probability level.

21, 1-Hydroxymethyl-3-phenyl-1,2,4,5,5a,6,7,8-octahydro-cyclopenta[c]pentalen-2-ol:

Following the general procedure, [2-(4-phenyl-but-3-ynyl)-cyclopentylidene]-acetaldehyde (71 mg, 0.30 mmol), Ni(COD)₂ (82 mg, 0.30 mmol) and tmeda (45 μ L, 0.30 mmol) were stirred for 2h at room temperature. Paraformaldehyde (81 mg, 0.89 mmol) as a slurry in ether was added dropwise and the reaction mixture was stirred at room temperature for another 4 hours. After chromatography (EtOAc/Hex, 1:5) **21** was obtained as a white crystalline solid (37 mg, 0.14 mmol, 46%). ¹H NMR (400 MHz, CDCl₃) δ 7.44 (d, J = 7.2Hz, 2H), 7.35 (t, J = 7.8 Hz, 2H), 7.21-7.26 (m, 1H), 5.41 (d, J = 5.6, 1H), 4.09 (t, J = 10.2 Hz, 1H), 3.86 (dd, J = 10.8, 6.0 Hz, 1H), 2.49 (dd, J = 9.2, 5.6 Hz, 2H), 2.11-2.22 (m, 2H), 1.89-2.05 (m, 4H), 1.66-1.80 (m, 3H), 1.49-1.61 (m, 2H), 1.39-1.46 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 160.4, 135.1, 131.5, 128.8, 127.6, 127.0, 81.2, 66.9, 60.5, 54.8, 47.0, 36.1, 35.7, 34.9, 27.6, 25.8; IR (film, cm⁻¹) 3343, 1493, 1445, 1014, 690; HRMS (EI) m/z calcd for C₁₈H₂₂O₂ [M⁺] 270.1620, found 270.1620. Irradiation of the methine signal at δ 5.41 (CH-OH) resulted in 7.6% NOE enhancement to the methine signal at δ 2.11- 2.22 (CH-CH₂OH).

Experimental Scheme C: Towards compounds leading up to 22 (Scheme 6)

C2, 6-(tert-Butyl-dimethyl-silanyloxy)-hexanoate:⁶ A solution of **C1** (2.55 g, 17.4 mmol) in 10 mL dichloromethane was added to a mixture of imidazole (2.03 g, 29.8 mmol, 1.7 eq.) and DMAP (215 mg, 1.76 mmol, 0.1 eq.) in 15 mL of freshly distilled dichloromethane and stirred at 0°C. Five minutes later, a solution of TBSCl (3.91 g, 25.9 mmol, 1.5 eq.) in 10 mL dichloromethane was added dropwise via a syringe over 10 min. The mixture was allowed to warm to rt over 3.5 hours. The reaction was quenched with 3 x 10 mL brine, extracted with dichloromethane, and dried over MgSO₄. The solvent was removed by rotary evaporation to yield **C2** as a colorless oil (4.34 g, 16.7 mmol, 96%). ¹H NMR (400 MHz, CDCl₃) δ 3.65 (s, 3H), 3.59 (t, *J* = 6.4 Hz, 2H), 2.30 (t, *J* =

⁶ For leading reference see Fujiwara, K.; Amano, A.; Tokiwano, T.; Murai, A., *Tetrahedron*, **2000**, 56(8), 1065.

8.0 Hz, 2H), 1.63 (quint, $J = 7.6$ Hz, 2H), 1.52 (quint, $J = 6.4$ Hz, 2H), 1.31-1.39 (m, 2H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR δ 174.4, 63.1, 51.6, 34.3, 32.7, 26.2, 25.6, 25.0, 18.5, -5.1; IR (film, cm^{-1}): 2929(m), 2856(m), 1741(s), 1462(m), 1436(m), 1388(w), 1361(m), 1253(s), 1200(m), 1163(m), 1097(vs), 1006(m), 830(vs), 772(vs), 663(s); HRMS (EI) m/z calcd for $\text{C}_{13}\text{H}_{28}\text{O}_3\text{Si}$ 245.1573, found: 245.1575 $[\text{M}-\text{CH}_3]^+$.

C5, Methyl 2-[4-(tert-Butyl-dimethyl-silanyloxy)-butyl]-3-hydroxy-7-phenyl-hept-6-ynoate: To a 0°C solution of diisopropylamine (1.60 mL, 11.4 mmol, 1.3 eq.) in 20 mL THF was added of n-butyl lithium (7.10 mL of 1.6 M in hexanes, 11.4 mmol, 1.3 eq.), and the mixture was stirred at this temperature for 30 min. The mixture was then cooled to -78°C for 20 min before adding a solution of **C2** (2.26g, 8.68 mmol, 1 eq.) in 3 mL THF via syringe dropwise {the most reproducible results were obtained using a syringe drive at 0.35 mL/min}. The mixture was stirred at this temperature for 35 minutes, stirred outside of the cold bath at room temperature for 1 minute, and placed back in the cold bath. A solution of **C4** (1.52g, 8.78 mmol, 1 eq.) in 5 mL THF was added via a syringe dropwise {the most reproducible results were obtained using a syringe drive at 0.20 mL/min} and the mixture stirred at -78°C for 3 more hours and TLC analysis (10:1 hexanes/ethyl acetate) shows the reaction was complete. The reaction was quenched with 25 mL of pH 8 buffer ($\text{NH}_4\text{Cl}/\text{NH}_4\text{OH}$) at -78°C and the mixture warmed to ambient temperature. The organic material was extracted with ether and dried over magnesium

sulfate. Column chromatography (hexanes:ethyl acetate, 10:1) allowed for the clean separation of a yellow oil, as a *mixture of isomers* of **C5** (2.47 g, 5.71 mmol, 66%). ¹H NMR (500 MHz, CDCl₃): δ 7.37-7.39 (m, 2H), 7.25-7.27 (m, 3H), 3.69 and 3.70 (s, 3H), 3.58 (dt, *J* = 6.4, 2.4 Hz, 2H), 2.43-2.55 (m, 4H), 1.44-1.86 (m, 9H), 1.22-1.43 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 176.4, 176.1, 131.7, 128.4, 127.8, 124.1, 89.9, 81.3, 72.1, 71.8, 63.0, 51.9, 51.8, 51.3, 51.2, 34.9, 33.6, 32.94, 32.86, 29.7, 27.0, 26.2, 25.3, 25.2, 24.3, 24.0, 19.4, 18.5, -5.07; IR (CDCl₃, film, cm⁻¹): 3456(br w), 2928(m), 2856(m), 1732(m), 1716(m), 1599(w), 1490(w), 1462(m), 1435(m), 1387(w), 1360(w), 1253(s), 1198(m), 1162(m), 1096(s), 1006(m), 976(m), 833(vs), 754(vs), 691(vs); HRMS (EI) *m/z* calcd for C₂₄H₄₀O₄Si [M⁺] 432.2696, found: 432.2693.

C6, Methyl 2-[4-(tert-Butyl-dimethyl-silanyloxy)-butyl]-7-phenyl-hept-2-en-6-ynoate:

A 15 mL round bottom flask was charged with DMAP (11 mg, 0.098mmol, 0.14eq.), 1 mL dichloromethane, and triethylamine (400 μL, 2.87 mmol, 4 eq.) and cooled to 0°C. Five minutes later, a solution of **C5** (307 mg, 0.710 mmol, 1 eq.) in 2 mL dichloromethane was cannula transferred into the mixture. After five more minutes, MsCl (130 μL, 2.87 mmol, 4 eq.) was added which made the mixture turbid and yellow. The mixture was stirred one additional hour to allow the ice bath to reach ambient temperature. The mixture was poured into 30 mL of water and the organic layer extracted with ether. The ether layer was washed with brine and followed by the addition

of and dried over magnesium sulfate. The yellow residue was taken up in 2 mL of dichloromethane and stirred at room temperature while DBU (450 μ L, 2.99 mmol, 4.2 eq.) was added dropwise over 2 minutes. The reaction was quenched after 2 hours with 4 mL of 1N HCl, washed with NaHCO₃ and brine; the organic layer dried over magnesium sulfate. Column chromatography (5:1 hexanes/ether) allowed for the clean separation of a colorless oil, **C6** (140 mg, 0.338 mmol, 56%; 8.3:1 *E:Z*, 125 mg of *E*). ¹H NMR (400 MHz, CDCl₃): δ 7.38 (m, 2H), 7.26-7.29 (m, 3H), 6.77 (t, *J* = 7.2 Hz, 1H), 3.72 (s, 3H), 3.58 (t, *J* = 5.6 Hz, 2H), 2.45 (t, *J* = 7.2 Hz, 2H), 2.36 (quint., *J* = 7.2 Hz, 2H), 1.75 (quint., *J* = 7.2 Hz, 2H), 1.40-1.56 (m, 4H), 0.88 (s, 9H), 0.03 (s, 6H); ¹³C NMR (DEPT, 100 MHz, CDCl₃): δ 168.6(C_{quat.}), 141.9(CH), 133.3(C_{quat.}), 131.7(CH), 128.4(CH), 127.9(CH), 124.0(C_{quat.}), 89.5(C_{quat.}), 81.5(C_{quat.}), 63.2(CH₂), 51.9(CH₃), 32.9(CH₂), 28.1(CH₂), 27.9(CH₂), 26.9(CH₂), 26.2(CH₃), 25.9(CH₂), 19.3(CH₃), 18.5(C_{quat.}), -5.04(CH₃); IR (film, cm⁻¹): 2949(m), 2928(m), 2858(m), 1713(s), 1644(w), 1598(w), 1490(m), 1461(m), 1434(m), 1387(w), 1360(w), 1280(m), 1253(s), 1193(m), 1096(vs), 1006(m), 835(vs), 775(s), 755(vs), 691(s); HRMS (EI) *m/z* calcd for C₂₅H₃₇O₃Si [M⁺] 413.2512, found 413.2150.

C7

C7, 2-(5-Phenyl-pent-4-ynylidene)-hexane-1,6-diol:

A 15 mL round bottom flask was charged with **C6** (530 mg of only the *E* isomer, 1.28 mmol, 1eq.) and 6 mL dichloromethane and then cooled to -40°C (dry ice in acetonitrile

bath). DIBALH (4.0 mL of a 1.0M in hexanes, 4.0 mmol, 3.1 eq.) was added via syringe and the mixture stirred 1 hour. TLC analysis (hexanes-ether, 5:1) indicated the first step of this reaction was complete. The reaction was quenched with 1 mL methanol and the reaction mixture poured into a 1:1 mixture of ethyl acetate to saturated potassium sodium tartrate and extracted with ether. The organic fraction was dried over magnesium sulfate and the solvent was removed by rotary evaporation. The crude colorless oil was subsequently taken up in 10 mL of THF and chilled to 0°C. The TBS group was removed with the addition of TBAF (2.2 mL of 1.0 M in THF, 2.2 mmol, 1.7 eq.) and stirring for 1 hour while allowing the bath to warm to room temperature. The reaction mixture was quenched with 3 mL of water and the organic material extracted with ether and dried over magnesium sulfate. Column chromatography (5% methanol in dichloromethane) afforded the clean separation of a colorless oil, **C7** (244 mg, 0.895 mmol, 70% over both steps). This compound was spectroscopically identical to the product obtain in a defined two step sequence (below).

This transformation was also done in step-wise fashion thereby confirming the combination of steps:

C6.1, 2-[4-(tert-Butyl-dimethyl-silanyloxy)-butyl]-7-phenyl-hept-2-en-6-yn-1-ol:

A 15 mL round bottom flask was charged with **C6** (78 mg, 0.19 mmol, 1eq.) and 6 mL dichloromethane and then cooled to -40°C (dry ice in acetonitrile bath). DIBALH (600

A solution of **C6.1** (47 mg, 0.12 mmol, 1 eq.) in 4 mL of THF was chilled to 0°C and treated with TBAF (150 µL of 1.0 M in THF, 0.150 mmol, 1.2 eq.) with stirring for 1 hour at 0°C followed by 30 minutes at room temperature. The reaction mixture was quenched with 2 mL of water and the organic material extracted with ether and dried over magnesium sulfate. Column chromatography (5% methanol in dichloromethane) afforded

a colorless oil, **C7** (20 mg, 0.075 mmol, 62%). ^1H NMR (500 MHz, CDCl_3): δ 7.39 (m, 2H), 7.27 (m, 3H), 5.45 (t, $J = 7.6$ Hz, 1H), 4.05 (s, 2H), 3.62 (t, $J = 6.0$ Hz, 2H), 2.42 (t, $J = 7.2$ Hz, 2H), 2.23 (q, $J = 7.2$ Hz, 2H), 2.16 (t, $J = 8.4$ Hz, 2H), 1.67 (quint., $J = 7.2$ Hz, 2H), 1.47-1.61 (m, 5H), 1.37 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 140.0, 131.7, 128.5, 127.8, 126.4, 124.2, 90.2, 81.1, 67.4, 62.9, 32.9, 28.9, 28.0, 26.8, 24.9, 19.2; IR (CDCl_3 , film, cm^{-1}): 3334(br, m), 2931(s), 2861(m), 1733 (w), 1598 (w), 1490 (m), 1457 (m), 1442(m), 1068(s), 1025(m), 913 (w), 874 (w), 756(vs), 692(s); HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{24}\text{O}_2$ $[\text{M} + \text{H}]^+$ 272.1776, found 272.1779.

22, 2-(5-Phenylpent-4-ynylidene)-hexane-1,6-dial:

A solution of PCC (490 mg, 2.27 mmol, 4.5 eq.) in 10 mL dichloromethane was stirred under a nitrogen atmosphere for 5 minutes before a solution of **C7** (136 mg, 0.499 mmol, 1 eq.) in 10 mL dichloromethane was cannula transferred in. The reaction was stirred at rt for 2 hours before being concentrated *in vacuo* to about 5 mL. The black reaction mixture was heated to 40°C then poured through a wide silica gel pad which was pre wetted with a 1% MeOH in dichloromethane. With a slight vacuum, about 300 mL of the eluent (1% MeOH in dichloromethane) helped push through the product (Caution: only the colorless material is collected.). The solvent is removed on the rotary evaporator and then on the vacuum pump to give a pure, colorless oil **22** (84.3 mg, 0.314 mmol, 63% yield). *Note that this compound is unstable so only partial characterization is given.* ^1H NMR (400 MHz, CDCl_3): δ 9.72 (s, 1H), 9.39 (s, 1H), 7.38 (m, 3H), 7.28 (m, 2H), 6.55

(t, $J = 7.2$ Hz, 1H), 2.58 (q, $J = 7.2$ Hz, 2H), 2.50 (t, $J = 7.6$ Hz, 2H), 2.42 (t, $J = 7.6$ Hz, 2H), 2.32 (t, $J = 8.0$ Hz, 2H), 1.83 (quint, $J = 7.2$ Hz, 2H), 1.70 (quint, $J = 8.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3): δ 202.3, 195.2, 155.0, 143.6, 131.7, 128.5, 128.0, 123.8, 89.0, 81.9, 43.7, 28.2, 27.8, 23.5, 21.5, 21.3, 19.3; IR (CDCl_3 , film, cm^{-1}): 2930(m), 2865(w), 2718(w), 1723(s), 1682(vs), 1640(m), 1598(w), 1490(m), 1442(m), 1290(w), 1144(w), 1069(m), 758(s), 693(s); HRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{20}\text{O}_2$ [M^+] 267.1385, found 267.1383.

Synthesis of Tricyclic Spiro Compound, 25.

25, Spirocompound:

A 25 mL round bottom flask was charged with Ni(COD)_2 (25 mg, 0.091 mmol, 1eq.) and 4 mL THF followed by the addition of TMEDA (15 μL , 0.099 mmol, 1.1eq.) and chilled to 0°C . The yellow mixture was stirred for 10 minutes before the dropwise addition of **22** (24 mg, 0.089 mmol, 1eq.) as a solution in 7 mL CH_2Cl_2 via a syringe over about 1 minute. Within 2 minutes, the reaction mixture had become an orange color and after 25 minutes the reaction had turned a deep red color. The reaction was quenched after 24 hours with pH 8 buffer. Column chromatography (hexanes: ethyl acetate, 2:1) afforded a yellow, oily solid (mp 91°C), **25** (12 mg, 0.043 mmol, 49%). ^1H NMR (400 MHz, CDCl_3): δ 7.45 (d, $J = 7.2$ Hz, 2H), 7.36 (t, $J = 7.2$ Hz, 2H), 7.22 (t, $J = 7.2$ Hz, 1H), 4.98 (s, 1H), 4.36 (t, $J = 8.8$ Hz, 1H), 3.65 (m, 1H), 2.89 (s, 1H), 2.61 (dd, $J = 18.6, 9.6$

Hz, 1H), 2.36-2.45 (m, 1H), 2.04-2.22 (m, 3H), 1.85 (br s, 1H), 1.79 (dt, $J = 11.6, 6.4$ Hz, 1H), 1.53-1.74 (m, 4H), 1.32-1.55 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3 , DEPT) δ 156.9 ($\text{C}_{\text{quat.}}$), 135.2 ($\text{C}_{\text{quat.}}$), 130.1 ($\text{C}_{\text{quat.}}$), 128.9 (CH), 126.7 (CH), 91.4 (CH), 76.5 (CH), 56.8 ($\text{C}_{\text{quat.}}$), 52.5 (CH), 31.5 (CH_2), 30.9 (CH_2), 29.8 (CH_2), 27.0 (CH_2), 26.6 (CH_2), 19.1 (CH_2); Gradient HMQC (400MHz, CDCl_3 , selected peaks, $^1\text{H} \leftrightarrow ^{13}\text{C}$): δ 7.45 $\leftrightarrow$ 128.9, 7.36 $\leftrightarrow$ 126.7, 7.22 $\leftrightarrow$ 126.7, 4.98 $\leftrightarrow$ 91.4, 4.36 $\leftrightarrow$ 76.5, 3.65 $\leftrightarrow$ 52.5, 1.65 $\leftrightarrow$ 31.5, 2.06 $\leftrightarrow$ 31.5, 1.79 $\leftrightarrow$ 27.0, 1.62 $\leftrightarrow$ 19.1; Gradient DQFCOSY (400MHz, CDCl_3 , selected peaks, $^1\text{H} \leftrightarrow ^1\text{H}$): δ 4.36 $\leftrightarrow$ 2.10;1.65, 3.65 $\leftrightarrow$ 2.61;1.79;1.36, 2.61 $\leftrightarrow$ 2.40;3.65, 2.40 $\leftrightarrow$ 2.61;2.10;2.06, 2.18 $\leftrightarrow$ 1.36;2.40, 1.79 $\leftrightarrow$ 1.36, 1.66 $\leftrightarrow$ 1.36;2.12; Gradient NOE (400MHz, CDCl_3 , selected peaks, Irradiate $\leftrightarrow$ NOE [%]): δ 7.45 $\leftrightarrow$ 4.98[3.8], 4.98 $\leftrightarrow$ 7.45[8.5] and 4.36[3.2], 4.36 $\leftrightarrow$ 4.98[0.82] and 2.11[4.1], 3.65 $\leftrightarrow$ 1.81 and 1.56 [9.8], 2.61 $\leftrightarrow$ 7.45[5.3]; IR (film, cm^{-1}): 3399(br w), 2923(vs), 1733(m), 1650(w), 1599(w), 1489(m), 1458(m), 1378(m), 1258(m), 1091(s), 1072(m), 836(m), 755(s), 690(s); LRMS (EI) m/z calcd for $\text{C}_{18}\text{H}_{22}\text{O}_2$ $[\text{M} + \text{Na}]^+$ 293.03., found 293.04. Stereochemical assignments were confirmed by single crystal X-ray analysis.

Figure 2: ORTEP perspective views of **25** showing the labeling system. Thermal ellipsoids are drawn at a 30% probability level.

Experimental Scheme D: Towards Tricyclic Compound 29 (Scheme 7)

D2, 1-(tert-Butyl-dimethyl-silanyloxy)-9-phenyl-non-8-yn-4-ol:

A 5 mL Et₂O solution of **C4** (1.37g, 7.89 mmol) was added dropwise to a -40°C solution of **D1** (10.5 mL, 0.75 M solution in hexanes, 7.88 mmol, 1 eq., FMC Corporation, Lithium division) in 20 mL diethyl ether. After 50 min, the yellow reaction mixture was warmed to 0°C. The resulting light orange reaction mixture was stirred at this temperature for 30 min followed by warming to rt with continued stirring for another 30

min. The reaction mixture was quenched with saturated aqueous ammonium chloride, and the organic material was extracted with ether and dried over anhydrous magnesium sulfate. Column chromatography (4:1 Hex/EtOAc) afforded **D2** (2.69g, 7.76 mmol, 98%) as a colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 7.38 (m, 2H), 7.25–7.29 (m, 3H), 3.67 (m, 3H), 2.72 (br s, 1H), 2.44 (t, $J = 7.0$ Hz, 2H), 1.74–1.81 (m, 1H), 1.57–1.72 (m, 6H), 1.44–1.52 (m, 1H), 0.90 (s, 9 H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 131.7, 128.4, 127.7, 124.2, 90.4, 81.0, 71.3, 63.8, 36.8, 35.2, 29.4, 26.1, 25.3, 19.7, 18.5, -5.2; IR (film, cm^{-1}) 3374 (br, w), 2928(m), 2856(m), 1599(w), 1490(m), 1462(m), 1442(m), 1254(m), 1092(m), 1069(m), 1005(m), 912 (w), 833(s), 776 (m), 754(vs), 690(vs); HRMS (EI) m/z calcd for $\text{C}_{21}\text{H}_{34}\text{O}_2\text{Si}$ [M^+] 346.2328, found 346.2328 (M^+).

D3, 1-(tert-Butyl-dimethyl-silanyloxy)-9-phenyl-non-8-yn-4-one:

A solution of dimethylsulfoxide (25 μL , 0.346 mmol) was added dropwise via syringe to a -78°C solution of oxalyl chloride (15 μL , 0.173 mmol) in 1 mL of CH_2Cl_2 . The reaction mixture was stirred at this temperature for 20 min before a solution of 1-(*t*-butyldimethylsilanyloxy)-9-phenyl-non-8-yn-4-ol (30mg, 0.087 mmol) in 1 mL CH_2Cl_2 was introduced. After stirring 40 min at -78°C , triethylamine (72 μL , 0.519 mmol) was then added and the mixture was allowed to warm to rt. The reaction mixture was quenched by pouring into a saturated solution of sodium bicarbonate. The organic material was extracted with 3x with ethyl acetate. The solvent was removed *in vacuo* and column chromatography of the resulting crude mixture (10:1 Hex/EtOAc) afforded (23

mg, 0.067 mmol, 77%) of the product **D3** as a colorless oil. ^1H NMR (500 MHz, CDCl_3): δ 7.37–7.39 (m, 2H), 7.25–7.29 (m, 3H), 3.60 (t, J = 6.0 Hz, 2H), 2.62 (t, J = 7.0 Hz, 2H), 2.52 (t, J = 7.5 Hz, 2H), 2.45 (t, J = 7.0 Hz, 2H), 1.87 (quint, J = 7.0 Hz, 2H), 1.79 (m, 2H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 210.7, 131.8, 128.4, 127.9, 124.0, 89.4, 81.5, 62.4, 41.6, 39.5, 27.0, 26.1, 22.8, 19.0, 18.5, -5.1; IR (film, cm^{-1}): 3060 (w), 2955 (s), 2932 (s), 2856 (m), 1713 (vs), 1598(w), 1489(s), 1463(m), 1442(m), 1409 (m), 1371 (m), 1255(m), 1097(m), 1028(w), 1005(w), 914 (w), 835(s), 776 (m), 756(vs), 692(vs); HRMS (EI) m/z calcd for $\text{C}_{21}\text{H}_{32}\text{O}_2\text{Si}$ 344.2172 [M^+], found 287.1465 [$\text{M} - (t\text{-butyl})$] $^+$.

D4, 3-[3-(tert-Butyl-dimethyl-silanyloxy)-propyl]-8-phenyl-oct-2-en-7-ynoic acid ethyl ester:

Sodium hydride (149 mg of 60% dispersion in oil, 3.77 mmol, 2.0 eq.) was washed with 2 x 5 mL portions of hexanes (hexane layer subsequently discarded) and the resulting powder suspended in 15 mL THF. The suspension was cooled to -78°C prior to the dropwise addition of triethyl phosphonoacetate (0.935 mL, 4.71 mmol, 2.0 eq.) in 2 mL THF and warmed to rt and stirred at this temperature for 30 min. The reaction mixture was cooled to -78°C and a solution of **D3** (650 mg, 1.88 mmol) in 2 mL THF was added dropwise over 10 min. The mixture was warmed to rt and then heated to 65°C overnight. After TLC analysis indicated the reaction was complete (4:1 Hex/EtOAc, R_f =0.68, visualized as with anisaldehyde stain), the reaction was quenched with saturated

ammonium chloride. The organic layer was extracted with ether and dried over magnesium sulfate. Column chromatography (10:1 Hex/EtOAc) of the crude material gave a colorless oil containing an *inseparable* 1:1 *E:Z* mixture of **D4** (642 mg, 1.55 mmol, 82%). ^1H NMR (500 MHz, CDCl_3): δ 7.38 (m, 2H), 7.27 (m, 3H), 5.69 (s, 1H), 4.14 (q, $J = 6.4$ Hz, 2H), 3.66 (t, $J = 6.4$ Hz, 1H), 3.62 (t, $J = 5.6$ Hz, 1H), 2.76 (t, $J = 8.0$ Hz, 1H), 2.66 (t, $J = 7.2$ Hz, 1H), 2.45 (dt, $J = 13.6, 7.2$ Hz, 2H), 2.34 (t, $J = 8.0$ Hz, 1H), 2.25 (t, $J = 8.0$ Hz, 1H), 1.79 (quint, $J = 7.6$ Hz, 2H), 1.66-1.73 (m, 2H), 1.27 (t, $J = 7.6$ Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3): δ 166.65, 166.59, 163.4, 163.3, 131.8, 128.45, 128.40, 127.88, 127.75, 124.19, 123.99, 116.2, 90.08, 89.50, 81.54, 81.20, 63.39, 62.56, 59.8, 37.63, 35.00, 32.02, 31.77, 30.9, 28.84, 28.03, 26.83, 26.2, 19.91, 19.25, 18.54, 14.6, -5.04, -5.07; IR (film, cm^{-1}): 2952 (m), 2929 (m), 2856 (m), 2253 (w), 1713 (vs), 1642 (s), 1599(w), 1490(m), 1462(m), 1442(m), 1379 (m), 1255(s), 1226 (s), 1160 (vs), 1099(vs), 1038(s), 1006(m), 965 (m), 910 (s), 834(vs), 775 (s), 756(vs), 732 (vs), 691(s); HRMS (EI) m/z calcd for $\text{C}_{25}\text{H}_{38}\text{O}_3\text{Si}$ $[\text{M}^+]$ 414.2590, found 414.2591.

D5, 3-(5-Phenyl-pent-4-ynyl)-hex-2-ene-1,6-diol:

A solution of **D4** (363 mg, 0.876 mmol, 1 eq.) in 10 mL of CH_2Cl_2 was cooled to -40°C and stirred 20 min before the dropwise addition of DIBALH (2.70 mL, 1.0 M in hexanes, 2.70 mmol, 3.1 eq.). Three hours later, TLC analysis (4:1 Hex:EtOAc; stained with vanillin) indicated the reaction was complete. At -40°C the reaction mixture was

quenched with 1 mL methanol and allowed to warm to rt. The reaction mixture was poured into a 1:1 mixture of ethyl acetate:saturated potassium sodium tartrate and stirred 15 min before extracting 3x with ether. The organic layer was dried over magnesium sulfate and the solvent removed *in vacuo* to give a yellow residue. This residue was taken up in 20 mL THF and cooled to 0°C. TBAF (2.0 mL, 0.90 M in THF, 1.8 mmol, 2.0 eq.) was added dropwise; the mixture was stirred at 0°C for 1h resulting in the reaction mixture turning from yellow to orange. The reaction was quenched with 5 mL 1.0 N HCl. The product was extracted with ether and the organic layer dried over anhydrous magnesium sulfate. Column chromatography (5% MeOH in CH₂Cl₂) afforded a yellow oil of **D5** (194.3 mg, 0.752 mmol, 86% over both steps) as an *inseparable* ~1:1 mixture of *E* and *Z* isomers. ¹H NMR (500 MHz, CDCl₃): δ 7.36-7.40 (m, 2H), 7.25-7.29 (m, 3H), 5.59 (t, *J* = 7.5 Hz, 0.5H), 5.48 (t, *J* = 7.0 Hz, 0.5H), 4.19 (d, *J* = 7.0 Hz, 1H), 4.11 (d, *J* = 7.5 Hz, 1H), 3.62 (t, *J* = 6.5 Hz, 1H), 3.56 (t, *J* = 5.5 Hz, 1H), 3.02 (br s, 1H), 2.39 (q, *J* = 6.5 Hz, 2H), 2.24-2.28 (m, 2H), 2.18 (t, *J* = 7.5 Hz, 1H), 2.0-2.3 (br s, 1H), 2.12 (t, *J* = 7.5 Hz, 1H), 1.65-1.75 (m, 4H); ¹³C NMR (125 MHz, CDCl₃): δ 143.3, 142.1, 131.7, 128.49, 128.44, 127.89, 127.81, 125.3, 125.0, 124.12, 123.99, 90.08, 89.89, 81.44, 81.27, 62.5, 61.0, 59.1, 58.4, 35.2, 32.9, 30.9, 30.3, 29.3, 27.6, 27.0, 25.6, 19.2; IR (film, cm⁻¹): 3338(br, s), 2938(s), 2868(m), 2253(w), 1663(w), 1598(w), 1490(m), 1442(m), 1379(m), 1058(s), 1004(s), 914(w), 834(vs), 756(vs), 692(vs); HRMS (EI) *m/z* calcd for C₁₇H₂₂O₂ [M-H]⁺ 258.1620, found 257.1540.

29, 5-Phenyl-1,2,3,3a,4,6,7,8-octahydro-cyclopenta[c]pentalene-3,4-diol:

Method a) **D5** $\rightarrow$ **26**, isolate, then **26** $\rightarrow$ **29**

A 25 mL round bottom flask was charged with **D5** (41.4 mg, 0.160 mmol, 1 eq.) and 5 mL of methylene chloride; the flask was cooled to 0 °C. PDC (142 mg, 0.377 mmol, 2.3 eq) was added in two equal lots with a 6 minute interval. The mixture turned from yellow to red as the reaction proceeded and warmed to room temperature where it remained stirring under nitrogen for 2 hours. TLC analysis confirmed that the reaction was complete (blue spot with vanillin stain). The reaction mixture was filtered through Celite and dried over anhydrous magnesium sulfate. Column chromatography (2:1 Hex:EtOAc) of the residue gave **26**, (40.2 mg, 0.158 mmol, 99%) as a yellow oil. Due to the *instability* of **26**, only partial characterization was possible. ^1H NMR (500 MHz, CDCl_3): δ 10.08 (d, 1H, $J=7.5$ Hz), 9.81 (s), 7.38 (m, 2H), 7.29 (m, 3H), 5.86 (d, 1H, $J=8.0$ Hz), 2.80 (t, 2H, $J=7.5$ Hz), 2.72 (d, 2H, $J=7.0$ Hz), 2.59 (t, 2H, $J=7.2$ Hz), 2.50 (t, 2H, $J=6.5$ Hz), 1.87 (quint, 2H, $J=6.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3): δ 200.1, 190.8, 164.4, 131.7, 128.5, 128.1, 123.6, 88.6, 82.2, 41.4, 30.7, 29.7, 28.3, 26.5, 19.3; IR (CDCl_3 , film, cm^{-1}): 1722(s), 1669(vs), 1490(m).

26 $\rightarrow$ **29**

To a stirring solution of Ni(COD)_2 (10 mg, 0.036 mmol, 1 eq.) and TMEDA (10 μL , 0.066 mmol, 1.8 eq.) in 5 mL THF at 0°C, **26** (9.2 mg, 0.036 mmol) was added dropwise as a solution in 2 mL of THF. Within 2 min, the yellow solution had turned color to

orange-brown, and then while warming to rt the reaction mixture became red. After 3 hours, the reaction was complete by TLC then quenched with a pH 8 buffer solution. The organic layer was extracted with ether and dried over magnesium sulfate. Column chromatography (2:1 hexanes: ethyl acetate) gave the clean separation of a light yellow oil, **29** (4.9 mg, 0.019 mmol, 53%). This material was spectroscopically identical (details follow) to the material obtained by the preferred method below.

Method b) D5 → [26(*in situ*)] → **29**

Swern oxidation of the mixture of *cis* and *trans* isomers of **D5** (40 mg, 0.155 mmol) followed by workup and solvent removal gave the crude mixture containing enyne-dial **26**. This was then introduced in the nickel cyclization using the general procedure. The crude mixture, $\text{Ni}(\text{COD})_2$ (64 mg, 0.232 mmol, 1.5 eq.) and tmeda (35 μL , 0.232 mmol) were stirred for 1.5 h at rt, followed by addition of anhydrous methanol (2 mL). Silica gel column chromatography (3:1 Hex/EtOAc) gave the product **29** with an impurity which most likely was the monocyclized compound by NMR analysis. Since the mixture could not be separated by column chromatography, the mixture was treated with excess

DIBAL at -40°C . Subsequent workup and chromatographic purification (10:1 Hex/EtOAc) afforded **29** (24mg, 0.093 mmol, 61% over 2 steps) as a white crystalline solid (mp $130\text{-}131^{\circ}\text{C}$). ^1H NMR (400 MHz, CDCl_3) δ 7.35-7.46 (m, 4H), 7.23-7.26 (m, 1H), 5.81 (d, $J = 8.0$ Hz, 1H), 4.39 (q, $J = 8.5$ Hz, 1H), 4.05 (s, 1H), 2.56-2.67 (m, 3H), 2.32 (dt, $J = 17.0, 8.5$ Hz, 1H), 1.94-2.12 (m, 4H), 1.86-1.91 (m, 1H), 1.68 (dd, $J = 11.5, 7.0$ Hz, 1H), 1.31-1.44 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 156.6, 134.4, 132.4, 128.9, 127.5, 127.2, 84.4, 77.1, 65.4, 50.0, 38.6, 35.1, 33.2, 26.6, 24.3. Irradiation of the methine signal at δ 5.81 (allylic CH-OH) resulted in 9.3% NOE enhancement to the methine signal at 2.56-2.67 (tertiary C-H). IR (film, cm^{-1}) 3388 (br m), 1497 (m), 1444 (m), 1262 (m), 1090 (s), 1065 (s), 1034 (s), 1013 (s), 909 (m), 801 (m), 769 (s), 693 (vs); HRMS (EI) m/z calcd for $\text{C}_{17}\text{H}_{20}\text{O}_2$ 256.1463 [M^+], found 256.1461. Stereochemical assignments were confirmed by single crystal X-ray analysis.

Figure 3: ORTEP perspective views of **29** showing the labeling system. Thermal ellipsoids are drawn at a 30% probability level.

Experimental procedures for compounds leading up to and including Scheme 8 are represented as that shown for Table 2, Entry 3.

^1H NMR Spectra

proton spectrum

Mercury 400 spectrometer

pulse sequence: zgpg30

Mercury 400 spectrometer

proton spectrum

Pulse Sequence: s2pul

in Benzene- d_6

11se Sequence: s2pul

AS4P047, F25-28, CDCl3

Pulse Sequence: s2pul

Mercury 400 spectrometer

Mercury 400 spectrometer

AS4P047, rearranged, CDCl₃

Pulse Sequence: s2pul

Table 2,
Entry 1

proton spectrum

Mercury 400 spectrometer

Pulse Sequence: s2pul

Table 2, Entry 6

std menthol

res=0.7Hz

sw probe

April 1 99

lock freq=1.470

new shims

Pulse Sequence: s2pul

Table 2, Entry 7

Mercury 400 spectrometer

proton spectrum

pulse sequence: zgpg30

B3

Mercury 400 spectrometer

n spectrum

Sequence: s2pul

B5

```
std menthol
res=0.7Hz
sw probe
April 1 99
lock freq=1.470
new shims
```

Pulse Sequence: s2pul

Unity 500 spectrometer

Mercury 400 spectrometer

n spectrum

Sequence: s2pul

Mercury 400 spectrometer

AS2P156, redistilled, CDCl₃

Pulse Sequence: s2pul

C2

Mercury 400 spectrometer

as 400, colorless oil, CDCl₃

Pulse Sequence: s2pul

Mercury 400 spectrometer

AS2P091, col., CDCl3

Pulse Sequence: s2pul

AS2PI71, Rf=0.21, CDCl3
Pulse Sequence: s2pul

Mercury 400 spectrometer

Mercury 400 spectrometer

AS3P049, col#3, F25-55, CDCl3

Pulse Sequence: s2pul

Unity 500 spectrometer

AS3..Guan diol, column, CDC13

Pulse Sequence: s2pul