Supporting Information

Ruthenium- and Palladium-Catalyzed Enyne Cycloisomerizations: Differentially Stereoselective Syntheses of Bicyclic Structures

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Materials and Methods. All reactions were performed under an argon atmosphere unless otherwise noted. Catalysts $[CpRu(CH_3CN)_3]PF_6$ and $Pd_2dba_3 \cdot CHCl_3$ was prepared according to literature procedures.[1] Acetone was freshly distilled from anhydrous calcium sulfate prior to its use in reactions. 1,2-Dichloroethane was distilled from calcium hydride. All other solvents were purified by passing through activated alumina columns. *N,N*-dimethylpropylene urea, diisopropylamine, hexamethylphosphoramide, and hexamethyldisilazane were each distilled from calcium hydride before use. Isobutyraldehyde was distilled prior to use. All other reagents were used as received. Commercially available chemicals were purchased from either Sigma-Aldrich Chemical Company (Milwaukee, WI), Alfa Aesar (Ward Hill, MA), Acros Organics (Pittsburgh, PA), TCI America (Portland, OR), or GFS Chemicals (Columbus, OH). Analytical thin-layer chromatography (TLC) was performed on 0.2 mm coated silica gel plates (EM 60-F254). Visualization was accomplished with UV light and exposure to either anisaldehyde or $KMnO_4$ solution followed by heating. Flash chromatography was performed using Silicycle silica gel (230-400 mesh). ^1H spectra were acquired on either a Varian Mercury 400 (at 400 MHz) or a Inova Unity 500 (at 500 MHz) and are reported relative to $SiMe_4$ (δ 0.00). ^{13}C spectra were acquired on either a Varian Mercury 400 (at 100 MHz) or a Inova Unity 500 (at 125 MHz) and are reported relative to $SiMe_4$ (δ 0.0). All IR spectra were obtained on sodium chloride plates with a Thermo Scientific Nicolet IR100. Mass spectrometry data were acquired by the Vincent Coates Foundation Mass Spectrometry Laboratory, Stanford University Mass Spectrometry (http://mass-spec.stanford.edu) on a Micromass Q-Tof API-US mass spectrometer (Waters Corporation, Milford, MA).

Enyne Cycloisomerizations

General procedure for the ruthenium-catalyzed cycloisomerizations: To a solution of the enyne substrate in acetone (0.1 M) at 23 °C under argon was added $CpRu(CH_3CN)_3PF_6$ (3-20 mol %, in general 5 mol %). The resulting mixture was stirred at room temperature for the time provided, at which point the solvent was removed via rotary evaporation. The residue was diluted in the minimum amount of CH_2Cl_2/Et_2O (1:1) and passed through a small plug of silica gel (Et_2O eluent). The filtrate was concentrated in vacuo, and the residue was further purified by flash chromatography to afford the bicyclic adduct.

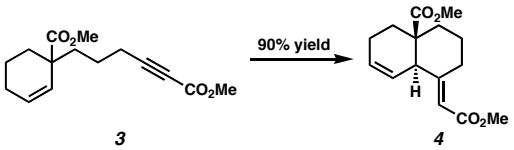
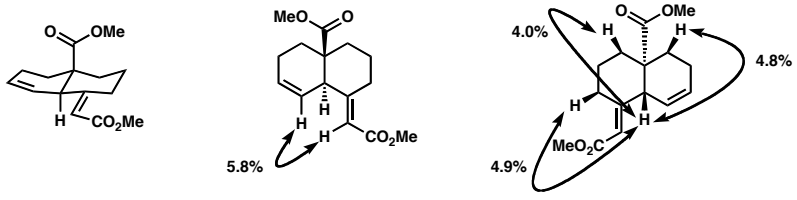
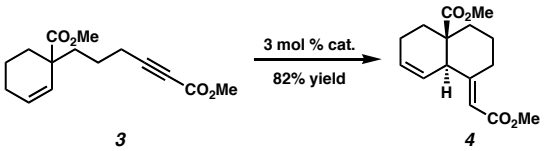


Table 1, entry 1. According to the general procedure, 20.0 mg **3** (0.0757 mmol) and 1.6 mg $CpRu(CH_3CN)_3PF_6$ (0.00379 mmol) were stirred in 757 μl acetone for 3 h. Purification of the residue by flash chromatography (9:1 hexanes/EtOAc eluent) afforded **4** (17.9 mg, 90% yield, R_F = 0.47 in 2:1 hexanes/Et_2O) as a colorless oil.

Bicycle 4: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (br d, *J* = 10.2 Hz, 1H), 5.81 (s, 1H), 5.76-5.69 (m, 1H), 4.05-3.98 (m, 1H), 3.68 (s, 3H), 3.59 (s, 3H), 2.90 (br s, 1H), 2.19-1.92 (comp m, 4H), 1.91-1.80 (comp m, 2H), 1.69 (ddd, *J* = 6.2, 12.2, 12.2 Hz, 1H), 1.53 (dt, *J* = 3.6, 13.6 Hz, 1H), 1.39 (ddq, *J* = 3.4, 6.2, 17.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 167.8, 160.8, 127.2, 125.4, 112.9, 51.7, 51.3, 51.1, 49.4, 37.4, 34.8, 30.1, 24.8, 23.4; IR (film) 2947, 1740, 1717, 1193, 1155 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{15}H_{20}O_4 + Na]^+$: 287.1259, found 287.1258.

NOE analysis:





According to the general procedure, 20.0 mg **3** (0.0757 mmol) and 1.0 mg $CpRu(CH_3CN)_3PF_6$ (0.00227 mmol) were stirred in 757 μl acetone for 3 h. Purification of the residue by flash chromatography (9:1 hexanes/EtOAc eluent) afforded **4** (16.4 mg, 82% yield) as a colorless oil.

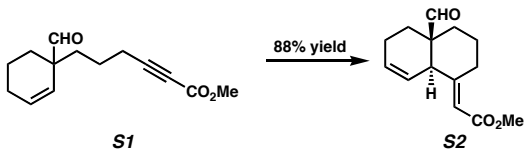
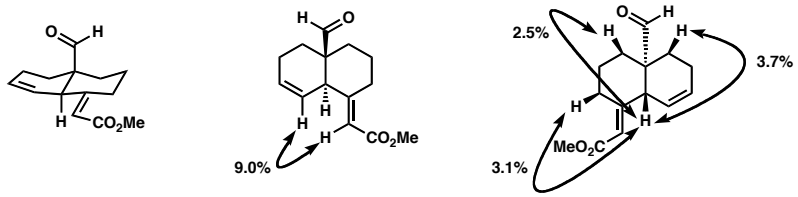
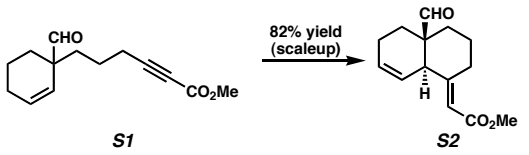


Table 1, entry 2. According to the general procedure, 20.0 mg **S1** (0.0854 mmol) and 1.9 mg $CpRu(CH_3CN)_3PF_6$ (0.00427 mmol) were stirred in 854 μl acetone for 2 h. Purification of the residue by flash chromatography (11:1 hexanes/EtOAc eluent) afforded bicycle **S2** (17.5 mg, 88% yield, R_F = 0.45 in 4:1 hexanes/EtOAc) as a colorless oil.

Bicycle S2: ^{1}H NMR (400 MHz, C_6D_6) δ 9.58 (s, 1H), 5.84 (s, 1H), 5.56 (d, *J* = 10.4 Hz, 1H), 5.48-5.42 (m, 1H), 4.26 (br d, *J* = 12.7 Hz, 1H), 3.37 (s, 3H), 2.46 (br s, 1H), 1.77 (br d, *J* = 13.0 Hz, 1H), 1.73-1.54 (comp m, 3H), 1.50 (dt, *J* = 5.5, 13.1 Hz, 1H), 1.07-0.98 (m, 1H), 0.78 (dt, *J* = 5.5, 13.0 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 206.0, 166.4, 160.6, 130.0, 124.9, 113.3, 51.3, 50.5, 47.9, 35.2, 33.0, 30.4, 24.7, 22.6; IR (film) 2934, 1717, 1640, 1193, 1161 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{14}H_{18}O_3 + Na]^+$: 257.1154, found 257.1153.

NOE analysis:





Prepatory scale example. According to the general procedure, 230 mg **S1** (0.981 mmol) and 21.3 mg $CpRu(CH_3CN)_3PF_6$ (0.0491 mmol) were stirred in 9.81 mL acetone for 2 h. Purification of the residue by flash chromatography (11:1 hexanes/EtOAc eluent) afforded bicycle **S2** (189 mg, 82% yield).

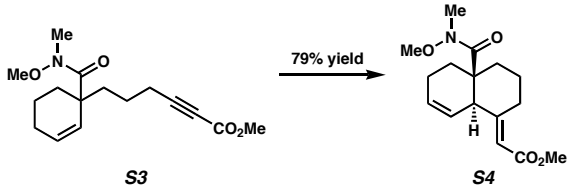
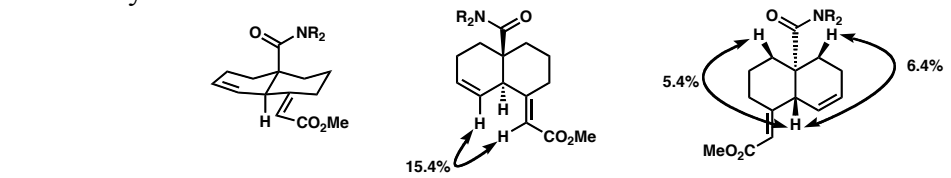


Table 1, entry 3. According to the general procedure, 20.0 mg **S3** (0.0682 mmol) and 1.5 mg $CpRu(CH_3CN)_3PF_6$ (0.00341 mmol) were stirred in 682 μl acetone for 3 h. Purification of the residue by flash chromatography (2:1 hexanes/EtOAc eluent) afforded bicycle **S4** (15.7 mg, 79% yield, R_F = 0.22 in 2:1 hexanes/EtOAc) as a colorless oil.

Bicycle S4: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.99 (d, *J* = 10.3 Hz, 1H), 5.89 (s, 1H), 5.73-5.68 (m, 1H), 4.05 (br d, *J* = 14.5 Hz, 1H), 3.65 (app. s, 6H), 3.12 (s, 3H), 2.83 (br s, 1H),

2.48 (dd, *J* = 5.1, 13.4 Hz, 1H), 2.48-2.41 (m, 1H), 2.15-2.08 (m, 1H), 2.06-1.82 (comp m, 3H), 1.66 (dt, *J* = 5.5, 12.9 Hz, 1H), 1.53-1.38 (comp m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 168.0, 161.6, 126.4, 126.2, 112.6, 60.5, 52.6, 52.3, 50.9, 34.9, 33.8, 32.7, 30.0, 24.3, 23.9; IR (film) 2928, 1714, 1655, 1158 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{16}H_{23}NO_4 + Na]^+$: 316.1525, found 316.1524.

NOE analysis:



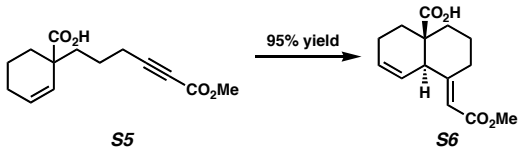
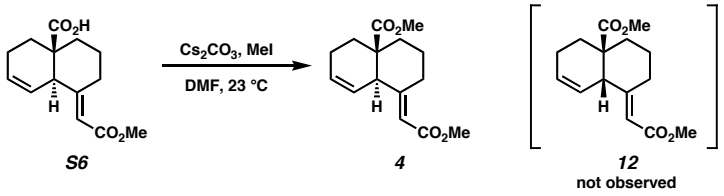


Table 1, entry 4. According to the general procedure, 22.8 mg **S5** (0.0911 mmol) and 2.0 mg $CpRu(CH_3CN)_3PF_6$ (0.00456 mmol) were stirred in 799 μl acetone for 3 h. Purification of the residue by flash chromatography (2:1 hexanes/EtOAc eluent) afforded bicycle **S6** (21.6 mg, 95% yield, R_F = 0.21 in 2:1 hexanes/EtOAc) as a white semisolid.

Bicycle S6: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (d, *J* = 10.3 Hz, 1H), 5.77 (s, 1H), 5.77-5.72 (m, 1H), 4.02 (br d, *J* = 11.8 Hz, 1H), 3.68 (s, 3H), 2.91 (br s, 1H), 2.21-2.09 (comp m, 4H), 1.90-1.82 (comp m, 2H), 1.75-1.68 (m, 1H), 1.58-1.47 (comp m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 167.8, 160.4, 127.5, 125.1, 113.0, 51.1, 50.9, 49.0, 37.4, 34.8, 30.0, 24.6, 23.3; IR (film) 2947, 1710, 1195, 1161 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{14}H_{18}O_4 + Na]^+$: 273.1103, found 273.1100.



Confirmation of stereochemistry of S6: Bicyclic adduct **S6** was methylated under standard conditions (MeI, Cs_2CO_3, DMF). Only diastereomer **4**, and not **12**, was observed.

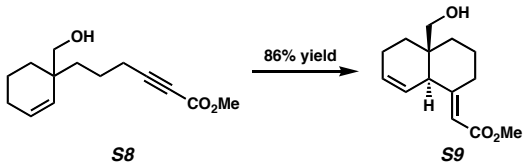
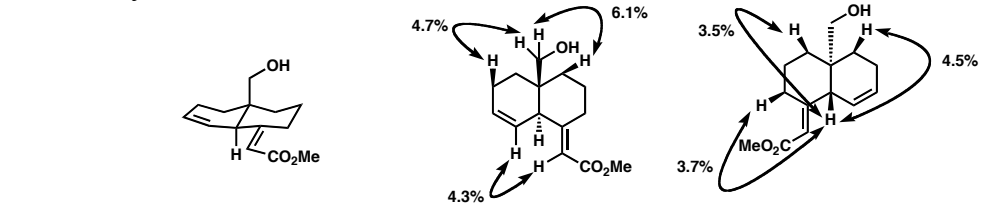


Table 1, entry 5. According to the general procedure, 20.0 mg **S8** (0.0846 mmol) and 3.7 mg $CpRu(CH_3CN)_3PF_6$ (0.00846 mmol) were stirred in 846 μl acetone for 6 h.

Purification of the residue by flash chromatography (3:1 hexanes/EtOAc eluent) afforded bicycle **S9** (17.1 mg, 86% yield, R_F = 0.47 in 2:1 hexanes/acetone) as a colorless oil.
Bicycle S9: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82-5.76 (m, 1H), 5.60 (br d, *J* = 10.1 Hz, 1H), 5.51 (s, 1H), 3.95 (br d, *J* = 11.4 Hz, 1H), 3.69 (s, 3H), 3.43 (br s, 2H), 2.91 (br s, 1H), 2.20-2.02 (comp m, 2H), 1.97-1.68 (comp m, 5H), 1.39 (ddd, *J* = 7.0, 12.1, 12.1 Hz, 1H), 1.22 (app. dt, *J* = 4.5, 13.0 Hz, 1H), 1.12 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 162.7, 129.2, 124.5, 112.0, 59.4, 51.2, 50.5, 41.0, 33.9, 31.4, 30.8, 23.6, 22.6; IR (film) 3442, 2932, 1718, 1638, 1160, 1024 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{14}H_{20}O_3 + Na]^+$: 259.1310, found 259.1308.
NOE analysis:



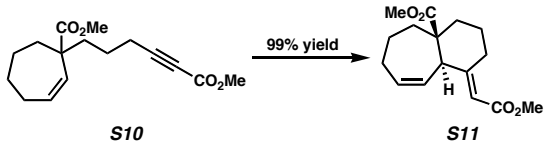
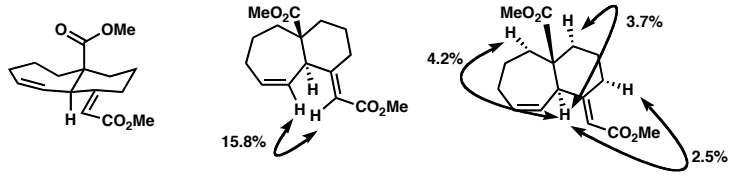


Table 1, entry 6. According to the general procedure, 21.0 mg **S10** (0.0754 mmol) and 1.6 mg $CpRu(CH_3CN)_3PF_6$ (0.00377 mmol) were stirred in 750 μl acetone for 3 h. Purification of the residue by flash chromatography (3:1 hexanes/Et_2O eluent) afforded **S11** (21.0 mg, 99% yield, R_F = 0.35 in 7:3 hexanes/Et_2O) as a colorless oil.
Bicycle S11: ^{1}H NMR (500 MHz, C_6D_6) δ 6.22 (s, 1H), 6.16-6.15 (m, 1H), 4.44-4.39 (m, 1H), 3.43 (s, 3H), 3.22 (s, 3H), 2.85 (s, 1H), 1.82-1.74 (comp m), 1.53-1.36 (comp m, 5H), 1.27-1.21 (m, 1H), 1.17-1.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 167.6, 161.9, 130.7, 113.4, 91.9, 51.9, 51.4, 51.0, 47.4, 42.7, 38.3, 29.4, 28.0, 23.4, 22.4; IR (film) 2944, 1722, 1633, 1434, 1373, 1262, 1157 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{16}H_{22}O_4 + Na]^+$: 301.1416, found: 301.1404.
NOE analysis:



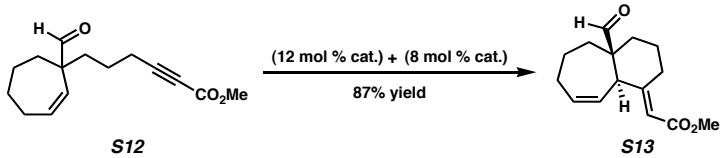
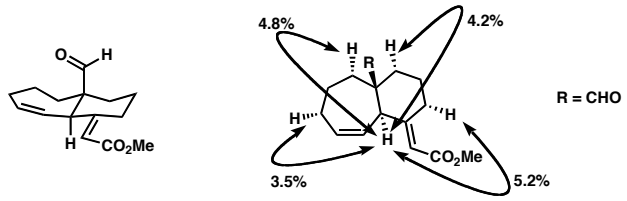


Table 1, entry 7. To a solution of enyne **S12** (30.0 mg, 0.121 mmol) in 1.00 mL acetone at 23 °C under argon was added $CpRu(CH_3CN)_3PF_6$ (6.3 mg, 0.0145 mmol). The resulting mixture was stirred at room temperature for 3 h, at which point additional

$CpRu(CH_3CN)_3PF_6$ (4.2 mg, 0.00968 mmol) was added, and the reaction stirred at room temperature for another 2 h. The reaction was worked up according to the general procedure. Purification of the residue by flash chromatography (4:1 hexanes/Et_2O eluent) afforded **S13** (26.0 mg, 87% yield, R_F = 0.20 in 9:1 hexanes/Et_2O) as a colorless oil.

Bicycle S13: ^{1}H NMR (500 MHz, $CHCl_3$) δ 9.54 (s, 1H), 5.98-5.96 (m, 2H), 3.90 (dt, *J* = 4.6, 14.3 Hz, 1H), 3.70 (s, 3H), 3.32 (br s, 1H), 2.24-2.19 (comp m, 2H), 2.14 (ddd, *J* = 2.4, 7.5, 14.4 Hz, 1H), 1.97-1.90 (comp m, 2H), 1.81-1.71 (comp m, 2H), 1.59-1.54 (m, 1H), 1.50-1.40 (comp m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2, 167.1, 161.1, 132.1, 127.7, 114.0, 55.4, 51.1, 47.0, 39.2, 30.1, 28.4, 23.0, 21.8; IR (film) 2934, 1719, 1638, 1435, 1372, 1192, 1159 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{15}H_{20}O_3 + Na]^+$: 271.1310, found: 271.1300.

NOE analysis:



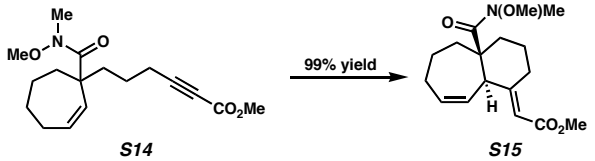
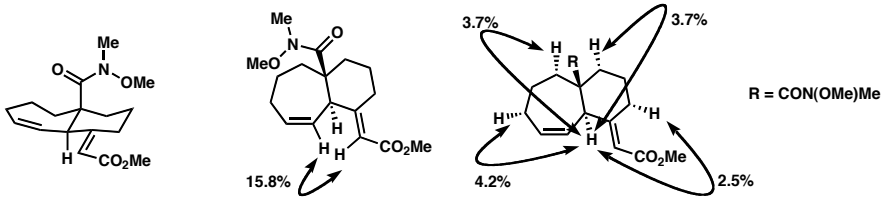
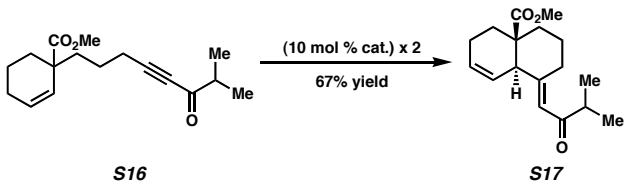


Table 1, entry 8. According to the general procedure, 22.0 mg **S14** (0.0716 mmol) and 1.8 mg $CpRu(CH_3CN)_3PF_6$ (0.00357 mmol) were stirred in 800 μl acetone for 4 h. Purification of the residue by flash chromatography (7:3 hexanes/EtOAc eluent) afforded **S15** (22.0 mg, 99% yield, R_F = 0.35 in 7:3 hexanes/EtOAc) as a colorless oil.

Bicycle S15: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.08-6.04 (m, 1H), 5.96 (s, 1H), 5.68-5.63 (m, 1H), 3.94-3.90 (m, 1H), 3.92 (dt, *J* = 3.5, 16.0 Hz, 1H), 3.66 (s, 3H), 3.63 (s, 3H), 3.14 (s, 1H), 3.12 (s, 3H), 2.33-2.26 (comp m, 3H), 2.24-2.13 (comp m, 1H), 2.07-2.00 (comp m, 1H), 1.89-1.74 (comp m, 3H), 1.61-1.49 (comp m, 2H), 1.45-1.35 (comp m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 167.8, 163.1, 131.0, 127.8, 112.5, 60.5, 55.0, 50.8, 49.7, 38.9, 34.7, 33.7, 29.3, 28.4, 22.5, 22.3; IR (film) 2931, 1715, 1648, 1434, 1371 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{17}H_{25}NO_4 + Na]^+$: 330.1681, found 330.1678.

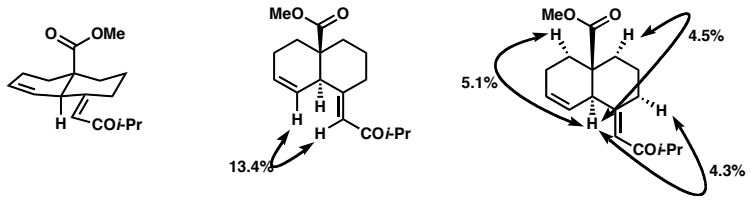
NOE analysis:

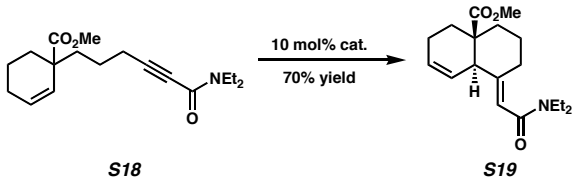




S16 *S17*

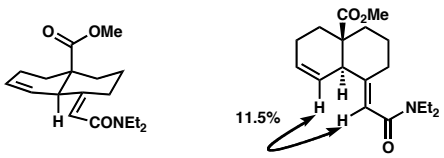
Table 1, entry 9. To a solution of enyne **S16** (20.0 mg, 0.0724 mmol) in 724 μl acetone at 23 °C under argon was added $CpRu(CH_3CN)_3PF_6$ (3.1 mg, 0.00724 mmol). The resulting mixture was stirred at room temperature for 3 h, at which point additional $CpRu(CH_3CN)_3PF_6$ (3.1 mg, 0.00724 mmol) was added, and the reaction stirred at room temperature for another 3 h. The reaction was worked up according to the general procedure. Purification of the residue by flash chromatography (3:1 hexanes/Et_2O eluent) afforded **S17** (13.3 mg, 67% yield, R_F = 0.40 in 7:3 hexanes/Et_2O) as a colorless oil.
Bicycle S17: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22 (s, 1H), 5.89 (d, *J* = 11.5 Hz, 1H), 5.77-5.75 (m, 1H), 3.87-3.83 (m, 1H), 3.60 (s, 3H), 2.93 (br s, 1H), 2.67 (septet, *J* = 7.0 Hz, 1H), 2.18-2.21 (comp m, 2H), 2.03-1.96 (comp m, 1H), 1.90-1.77 (comp m, 2H), 1.7 (ddd, *J* = 5.68, 12.3, 12.7 Hz, 1H), 1.52 (dt, *J* = 3.9, 13.6 Hz, 1H), 1.39-1.29 (m, 1H), 1.11 (dd, *J* = 4.3, 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 174.4, 158.2, 127.2, 120.3, 51.5, 51.3, 49.3, 41.9, 37.35, 34.7, 30.2, 24.9, 23.3, 18.5, 18.3; I R (film) 2930, 1740, 1686, 1618, 1451, 1162 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{17}H_{24}O_3 + Na]^+$: 299.1623, found: 299.1610.
NOE analysis:





S18 *S19*

Table 1, entry 10. According to the general procedure, 21.0 mg **S18** (0.0688 mmol) and 3.0 mg $CpRu(CH_3CN)_3PF_6$ (0.00688 mmol) were stirred in 690 μl acetone for 3 h at 40 ºC. Purification of the residue by flash chromatography (3:2 hexanes/EtOAc eluent) afforded **S19** (15.1 mg, 70% yield, R_F = 0.15 in 3:2 hexanes/Et_2O) as a colorless oil.
Bicycle S19: ^{1}H NMR (500 MHz, C_6D_6) δ 6.11 (s, 1H), 5.94 (d, *J* = 11.5 Hz, 1H), 5.63-5.60 (br m, 1H), 3.54 (app. d, *J* = 14.0 Hz, 1H), 3.38-3.21 (comp m, 4H), 3.23 (s, 3H), 3.17-3.11 (m, 1H), 2.62 (br s, 1H), 2.01-1.81 (comp m, 5H), 1.55-1.50 (br m, 1H), 1.40-1.30 (comp m, 3H), 1.04 (t, *J* = 6.5 Hz, 3H), 0.89, (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 147.1, 126.6, 125.9, 117.0, 51.5, 50.2, 48.1, 42.3, 39.0, 37.3, 34.5, 31.0, 24.7, 23.4, 14.5, 13.2; IR (film) 3251, 2934, 1727, 1451, 1242, 1199 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{18}H_{27}NO_3 + Na]^+$: 328.1889, found: 328.1874.
NOE analysis:



(The trans relationship in **S19** was assigned based on both analogy and the similarities in ^{1}H spectra to bicycles **4** and **S17**.)

General procedure for the palladium-catalyzed cycloisomerizations: To a solution of the enyne substrate and formic acid (2 equiv) in 49:1 DCE/CH_3CN (0.025 M) under argon was added $Pd_2dba_3{\cdot}CHCl_3$ (4 mol%). The resulting mixture was heated to 40 °C and stirred for the time provided. Upon completion of the reaction, the solution was cooled to room temperature and partitioned between EtOAc and saturated $NaHCO_3$. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography provided the bicyclic adduct.

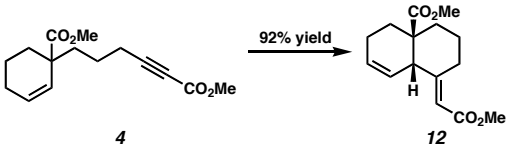
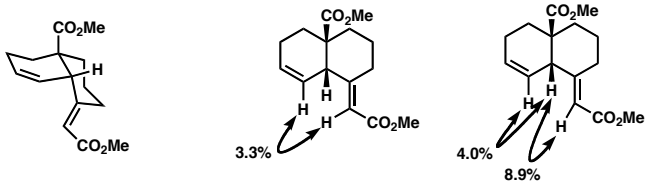


Table 2, entry 1. According to the general procedure, 20.0 mg **4** (0.0757 mmol), 5.7 µl HCO_2H (0.151 mmol), and 3.1 mg $Pd_2dba_3{\cdot}CHCl_3$ (0.00303 mmol) were stirred in 2.97 mL DCE and 60.6 µl CH_3CN for 4 h. Purification of the residue by flash chromatography (2 flashes: 1) 11:1 hexanes/EtOAc eluent; 2) 2:1 CH_2Cl_2/hexanes eluent) afforded bicycle **12** (18.3 mg, 92% yield, R_F = 0.48 in 4:1 hexanes/EtOAc) as a colorless oil.

Bicycle 12: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77-5.73 (m, 1H), 5.72 (s, 1H), 5.50-5.45 (m, 1H), 3.68 (s, 3H), 3.67 (s, 3H), 3.40 (br s, 1H), 2.94-2.86 (br m, 1H), 2.74-2.65 (br m, 1H), 2.13-2.08 (comp m, 2H), 1.89 (ddd, J = 3.3, 6.8, 10.9 Hz, 1H), 1.75-1.62 (comp m, 4H), 1.60-1.50 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 167.3, 163.6, 127.85, 127.80, 116.1, 52.2, 51.1, 48.5, 46.6, 30.4, 28.6, 27.3, 23.7, 22.8; IR (film) 2948, 1728, 1644, 1435, 1231 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{15}H_{20}O_4 + Na]^+$: 287.1259, found 287.1256.

NOE analysis:



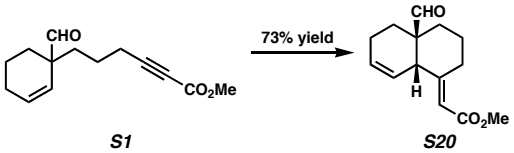
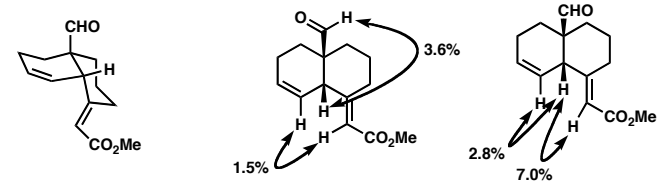
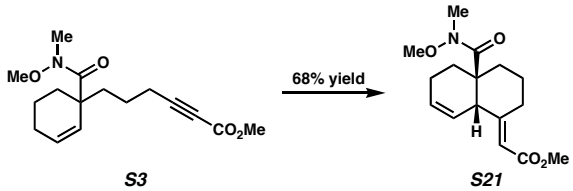


Table 2, entry 2. According to the general procedure, 32.0 mg **S1** (0.137 mmol), 10.3 μl HCO_2H (0.274 mmol), and 5.6 mg $Pd_2dba_3{\cdot}CHCl_3$ (.00548 mmol) were stirred in 5.37 mL DCE and 110 μl CH_3CN for 5 h. Purification of the residue by flash chromatography (solvent system eluent) afforded bicycle **S20** (23.2 mg, 73% yield, R_F = 0.27 in 9:1 hexanes/EtOAc) as a colorless oil.

Bicycle S20: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.44 (s, 1H), 5.83-5.78 (m, 1H), 5.73 (s, 1H), 5.57-5.53 (m, 1H), 3.68 (s, 3H), 3.16 (br s, 1H), 2.86-2.74 (comp m, 2H), 2.14-2.08 (comp m, 2H), 1.76-1.65 (comp m, 2H), 1.63-1.52 (comp m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6, 167.1, 162.5, 129.0, 127.0, 116.3, 51.2, 51.1, 44.9, 28.2, 27.5, 25.3, 23.0, 22.2; IR (film) 2934, 1719, 1643, 1435, 1155 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{14}H_{18}O_3 + Na]^+$: 257.1154, found 257.1148.

NOE analysis



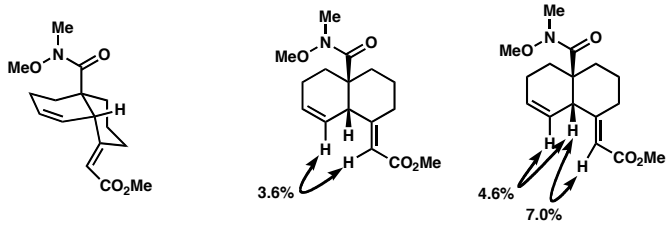


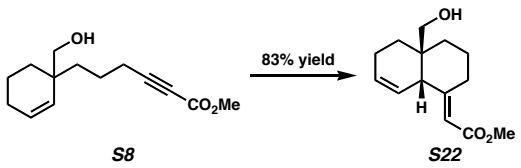
S3 *S21*

Table 2, entry 3. According to the general procedure, 20.0 mg **S3** (0.0682 mmol), 5.1 μl HCO_2H (0.136 mmol), and 2.8 mg $Pd_2dba_3{\cdot}CHCl_3$ (0.00273 mmol) were stirred in 2.67 mL DCE and 54.6 μl CH_3CN for 15 h. Purification of the residue by flash chromatography (4:1 hexanes/EtOAc eluent) afforded bicycle **S21** (13.6 mg, 68% yield, R_F = 0.62 in 1:1 hexanes/EtOAc) as a colorless oil.

Bicycle S21: ^{1}H NMR (500 MHz, C_6D_6) δ 6.06 (s, 1H), 5.55 (app. s, 2H), 3.80 (br s, 1H), 3.37 (s, 3H), 3.27-3.18 (m, 1H), 2.88 (s, 3H), 2.85-2.76 (m, 1H), 2.78 (s, 3H), 1.99-1.91 (m, 1H), 1.88-1.64 (comp m, 5H), 1.58-1.48 (comp m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 167.5, 164.7, 128.7, 127.5, 116.6, 60.3, 51.1, 50.2, 46.9, 34.3, 30.4, 28.7, 26.1, 24.0, 23.3; IR (film) 2938, 1716, 1643, 1156 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{16}H_{23}NO_4 + Na]^+$: 316.1525, found 316.1524.

NOE analysis:



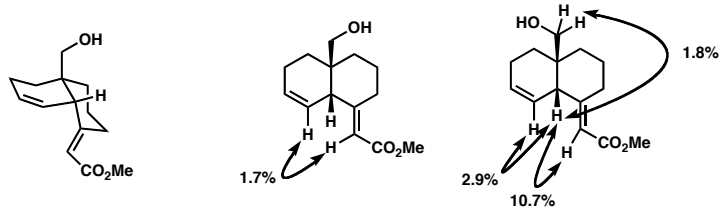


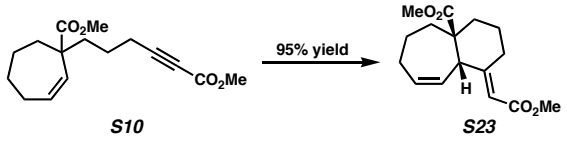
S8 *S22*

Table 2, entry 5. According to the general procedure, 20.0 mg **S8** (0.0846 mmol), 6.4 μl HCO_2H (0.169 mmol), and 3.5 mg $Pd_2dba_3{\cdot}CHCl_3$ (0.00338 mmol) were stirred in 3.32 mL DCE and 67.7 μl CH_3CN for 2.5 h. Purification of the residue by flash chromatography (3:1 hexanes/EtOAc eluent) afforded bicycle **S22** (16.6 mg, 83% yield, R_F = 0.38 in 2:1 hexanes/acetone) as a colorless oil.

Bicycle S22: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78-5.74 (m, 1H), 5.69 (s, 1H), 5.36 (app. dq, *J* = 2.3, 10.0 Hz, 1H), 3.68 (s, 3H), 3.46 (ABq, *J* = 10.9 Hz, Δν = 29.2 Hz, 2H), 3.21 (app. dt, *J* = 4.3, 13.9 Hz, 1H), 2.68 (br s, 1H), 2.35 (br dt, *J* = 4.3, 13.9 Hz, 1H), 2.14-2.02 (comp m, 2H), 1.68-1.48 (comp m, 4H), 1.48-1.41 (comp m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 165.1, 128.1, 128.0, 115.5, 68.4, 51.1, 47.4, 39.2, 28.3, 27.3, 26.9, 22.4, 22.3; IR (film) 3422, 2936, 1717, 1639, 1169, 1132 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{14}H_{20}O_3 + Na]^+$: 259.1310, found 259.1312.

NOE analysis:





S10 *S23*

Table 2, entry 6. According to the general procedure, 21.0 mg **S10** (0.0754 mmol), 5.7 μl HCO_2H (0.151 mmol), and 3.1 mg $Pd_2dba_3{\cdot}CHCl_3$ (0.00300 mmol) were stirred in 2.94 mL DCE and 60.3 μl CH_3CN for 3 h. Purification of the residue by flash chromatography (4:1 PhH/$CHCl_3$ eluent) afforded bicycle **S23** (20.0 mg, 95% yield, R_F = 0.30 in 4:1 PhH/$CHCl_3$) as a colorless oil.

Bicycle S23: ^{1}H NMR (500 MHz, C_6D_6) δ 6.08 (s, 1H), 5.70-5.65 (m, 1H), 5.49-5.23 (m, 1H), 3.71 (d, *J* = 6.5 Hz, 1H), 3.40 (s, 1H), 3.29 (s, 1H), 2.59-2.55 (br m, 1H), 1.99-1.93 (comp m, 1H), 1.86-1.70 (comp m, 3H), 1.60-1.36 (comp m, 7H); ^{13}C NMR (125 MHz, C_6D_6) δ 176.0, 166.9, 160.0, 132.5, 129.9, 116.4, 53.0, 51.3, 50.5, 51.2, 36.4, 35.1, 29.1, 27.9, 23.4, 22.7; IR (thin film) 2946, 1722, 1647, 1435, 1237, 1150 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{16}H_{22}O_4 + Na]^+$: 301.1416, found: 301.1411.

NOE analysis:

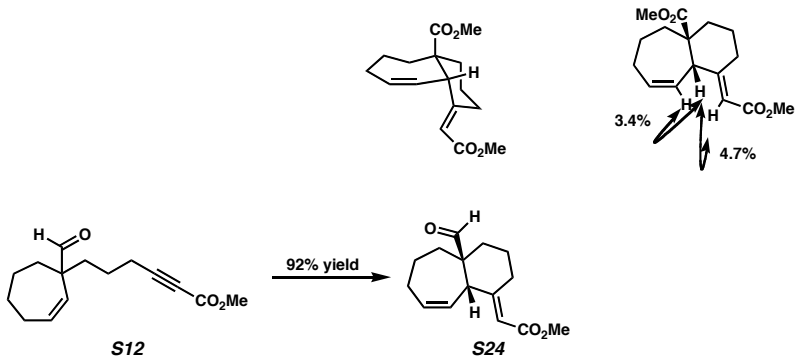
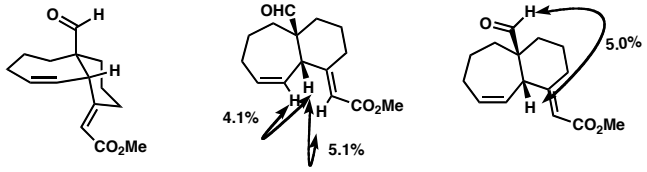


Table 2, entry 7. According to the general procedure, 25.0 mg **S12** (0.101 mmol), 7.5 μl HCO_2H (0.200 mmol), and 4.1 mg $Pd_2dba_3{\cdot}CHCl_3$ (0.00403 mmol) were stirred in 3.96 mL DCE and 80.8 μl CH_3CN for 4 h. Purification of the residue by flash chromatography (4:1 PhH/$CHCl_3$ eluent) afforded bicycle **S24** (23.3 mg, 92% yield, R_F = 0.45 in 4:1 PhH/$CHCl_3$) as a colorless oil.

Bicycle S24: ^{1}H NMR (500 MHz, C_6D_6) δ 9.45 (s, 1H), 5.89-5.85 (m, 1H), 5.82 (s, 1H), 5.49 (dd, *J* = 6.5, 11.1 Hz, 1H), 3.70 (s, 3H), 3.45 (d, *J* = 6.6 Hz, 1H), 3.32 (dt, *J* = 4.5, 13.5 Hz, 1H), 2.49 (ddd, *J* = 4.5, 10.5, 13.6 Hz, 1H), 2.19-2.12 (comp m, 1H), 2.10-2.03 (comp m, 1H), 1.92 (ddd, *J* = 3.2, 8.2, 14.3 Hz, 1H), 1.81-1.51 (comp m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.5, 167.1, 159.4, 133.6, 128.1, 116.0, 55.7, 51.1, 48.9, 32.8, 31.8, 28.8, 27.9, 22.8, 21.7; IR (thin film) 3017, 2935, 1722, 1647, 1436, 1153 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{15}H_{20}O_3 + Na]^+$: 271.1310, found: 271.1309.

NOE analysis:



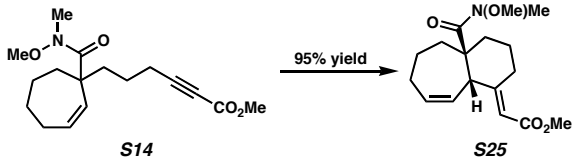
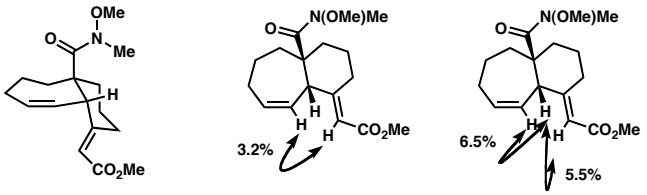
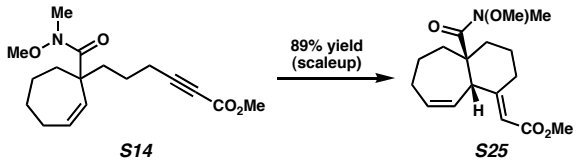


Table 2, entry 8. According to the general procedure, 22.0 mg **S14** (0.0716 mmol), 5.4 μl HCO_2H (0.143 mmol), and 3.0 mg $Pd_2dba_3{\cdot}CHCl_3$ (0.00286 mmol) were stirred in 2.81 mL DCE and 57.2 μl CH_3CN for 2.5 h. Purification of the residue by flash chromatography (7:3 hexanes/EtOAc eluent) afforded bicycle **S25** (20.8 mg, 95% yield, R_F = 0.20 in 17:3 hexanes/EtOAc) as a colorless oil.

Bicycle S25: ^{1}H NMR (500 MHz, C_6D_6) δ 6.23 (s, 1H), 5.81-5.71 (comp m, 2H), 3.98 (d, *J* = 6.6 Hz, 1H), 3.74-3.70 (m, 1H), 3.42 (s, 3H), 2.94 (s, 3H), 2.84 (s, 3H), 2.47-2.41 (s, 1H), 2.09-2.00 (comp m, 3H), 1.92-1.85 (comp m, 2H), 1.76-1.64 (comp m, 2H), 1.62-1.36 (comp m, 5H); ^{13}C NMR (125 MHz, C_6D_6) δ 177.2, 167.6, 160.0, 131.1, 117.0, 116.2, 92.4, 60.2, 55.3, 52.0, 51.0, 34.8, 34.2, 32.7, 29.5, 29.0, 24.1, 22.8; IR (thin film)

2933, 1716, 1645, 1358, 1147, 1001 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $[C_{17}H_{25}NO_4 + Na]^+$: 330.1681, found 330.1669.
NOE analysis:





Prepatory scale example. According to the general procedure, 200 mg **S14** (0.651 mmol), 49.0 μl HCO_2H (1.30 mmol), and 26.9 mg $Pd_2dba_3{\cdot}CHCl_3$ (0.0260 mmol) were stirred in 25.5 mL DCE and 521 μl CH_3CN for 4 h. Purification of the residue by flash chromatography (7:3 hexanes/EtOAc eluent) afforded bicycle **S25** (177 mg, 89% yield).

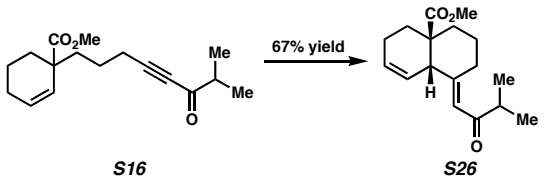
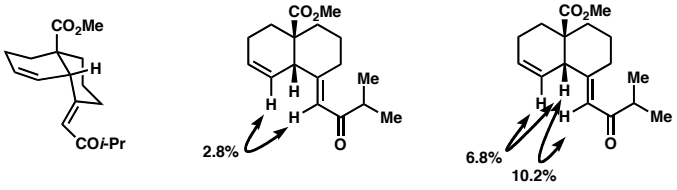
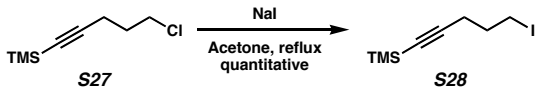


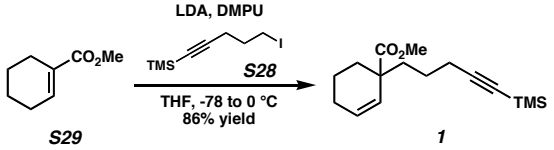
Table 2, entry 9. According to the general procedure, 20.0 mg **S16** (0.0724 mmol), 5.2 μl HCO_2H (0.146 mmol), and 3.0 mg $Pd_2dba_3{\cdot}CHCl_3$ (0.00289 mmol) were stirred in 2.86 mL DCE and 57.9 μl CH_3CN for 12 h. Purification of the residue by flash chromatography (4:1 PhH/$CHCl_3$ eluent) afforded bicycle **S26** (13.4 mg, 67% yield, R_F = 0.45 in 4:1 hexanes/Et_2O) as a colorless oil.
Bicycle S26: ^1H NMR (500 MHz, $CDCl_3$) δ 6.12 (s, 1H), 5.79-5.75 (m, 1H), 5.52-5.49 (m, 1H), 3.86 (s, 3H), 3.40 (s, 1H), 2.89 (br s, 1H), 2.10 (br m, 3H), 1.92-187 (m, 1H), 1.78-1.45 (comp m, 7H), 1.09, (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.8, 177.1, 161.0, 128.0, 127.5, 123.2, 52.0, 48.5, 46.7, 41.8, 30.0, 28.8, 27.3, 23.8, 22.6, 18.40, 18.35; HRMS (ESI^+) *m/z* calc'd for $[C_{17}H_{24}O_3 + Na]^+$: 299.1623, found: 299.1618.
NOE analysis:



Substrate Syntheses

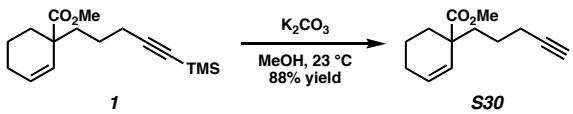


A solution of chloride **S27** (4.00 mol, 20.5 mmol) and NaI (7.69 g, 51.3 mmol) in 41.8 mL acetone was refluxed for 23 h. The mixture was then cooled to room temperature and partitioned between hexanes (250 mL) and water (100 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The iodide (5.46 g, quantitative yield, R_F = 0.75 in 9:1 hexanes/Et_2O) was sufficiently pure to be used in subsequent transformations without further purification. Spectroscopic analysis of iodide **S28** agreed with literature data.[2]



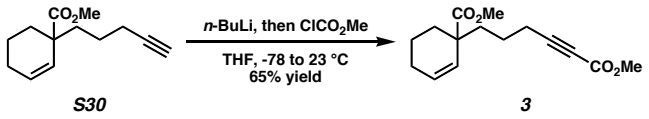
Deconjugative alkylation was performed according to a modified procedure described by Kuwajima and Urabe.[3] To a solution of *i*-Pr_2NH (1.13 mL, 8.09 mmol) in 14.7 mL THF at –78 °C was added *n*-BuLi (3.37 mL, 2.4 M in hexanes, 8.09 mmol) dropwise. The solution of LDA was stirred at –78 °C for 5 min and at 0 °C for 15 min. It was then cooled to –78 °C, and DMPU (1.07 mL, 8.82 mmol) was added. The resulting mixture was stirred for 30 min, and then **S29** (1.00 mL, 7.35 mmol) was introduced. After 20 min, **S28** (2.04 mL, 9.56 mmol) was added, and the reaction was stirred at –78 °C for 15 min, at which point it was warmed to 0 °C. After 2 h, the reaction mixture was quenched with saturated NH_4Cl (75 mL) and extracted with Et_2O (3 x 75 mL). The combined organic layers were washed with saturated $NaHCO_3$ (50 mL), then brine (50 mL), dried over $MgSO_4$, and concentrated to an oil. Purification by flash chromatography (19:1 hexanes/Et_2O eluent) provided ester **1** (1.76 g, 86% yield, R_F = 0.47 in 9:1 hexanes/EtOAc) as a colorless oil.

Ester 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (app. dt, *J* = 3.5, 10.2 Hz, 1H), 5.69 (d, *J* = 10.2 Hz, 1H), 3.68 (s, 3H), 2.18 (t, *J* = 7.2 Hz, 2H), 2.18-2.12 (m, 1H), 2.04-1.90 (comp m, 2H), 1.76-1.40 (comp m, 7H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 129.8, 129.0, 107.2, 84.9, 52.1, 46.9, 39.5, 30.9, 25.1, 24.1, 20.4, 19.9, 0.3; IR (film) 2952, 2175, 1732, 1250, 843 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{16}H_{26}O_2Si + Na]^+$: 301.1600, found 301.1598.



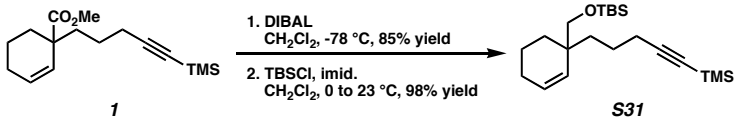
To a solution of ester **1** (767 mg, 2.75 mmol) in 18.3 mL MeOH at 23 °C was added K_2CO_3 (456 mg, 3.30 mmol). The resulting mixture was maintained at room temperature for 8 h, at which point a mixture of saturated $NaHCO_3/H_2O$ was added (2:1, 75 mL). The organic solvent was removed via rotary evaporation, and the residue was extracted with

Et_2O (2 x 100 mL). The organic phases were combined, washed with brine (75 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (15:1 hexanes/Et_2O eluent) to afford ester **S30** (500 mg, 88% yield, R_F = 0.37 in 9:1 hexanes/Et_2O) as a colorless oil.



To a solution of ester **S30** (446 mg, 2.16 mmol) in 18.0 mL THF at –78 °C was added *n*-BuLi (987 μl, 2.3 M in hexanes, 2.27 mmol) dropwise, and the resulting mixture was stirred at –78 °C for 1 h. Methyl chloroformate (434 μl, 5.62 mmol) was then introduced slowly, and the reaction was maintained at –78 °C for 1 h. The mixture was then allowed to gradually warm to room temperature, stirred for 5 min, and then it was quenched with saturated NH_4Cl (50 mL) and extracted with Et_2O (3 x 60 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (4:1 hexanes/Et_2O eluent) to provide ester **3** (292 mg, 65% yield, R_F = 0.42 in 4:1 hexanes/EtOAc) as a colorless oil.

Ester 3: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (app. dt, *J* = 3.8, 10.1 Hz, 1H), 5.67 (d, *J* = 10.1 Hz, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 2.31 (t, *J* = 7.0 Hz, 2H), 2.15 (ddd, *J* = 2.3, 6.3, 12.7 Hz, 1H), 2.04-1.90 (comp m, 2H), 1.77-1.48 (comp m, 6H), 1.42 (ddd, *J* = 3.1, 10.8, 13.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 154.4, 129.34, 129.31, 89.3, 73.3, 52.8, 52.2, 46.9, 39.4, 30.9, 25.1, 23.0, 19.8, 19.3; IR (film) 2951, 2237, 1718, 1258 cm^{-1}; Anal. calc'd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; O, 24.21. Found: C, 67.99; H, 7.43.

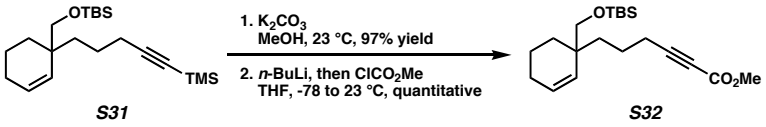


To a solution of ester **1** (496 mg, 1.78 mmol) in 9.52 mL CH_2Cl_2 at –78 °C was added DIBAL (5.34 mL, 1.0 M in toluene, 5.34 mmol) dropwise over 3 min. The resulting mixture was maintained at –78 °C for 1 h, at which point EtOAc (1.56 mL, 16.0 mmol) was added. The reaction was stirred for 5 min, and then saturated sodium potassium tartrate solution and EtOAc (50 mL each) were added, and the mixture was allowed to warm to room temperature and stirred vigorously. Once the phases were clear (approx. 4 h), the mixture was partitioned, and the aqueous phase was extracted with EtOAc (75 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The oil was purified by flash chromatography (8:1 hexanes/EtOAc eluent) to afford the desired alcohol (380 mg, 1.52 mmol, R_F = 0.39 in 4:1 hexanes/EtOAc), which was taken directly to the subsequent transformation.

To a solution of the alcohol (380 mg, 1.52 mmol) in 10.1 mL CH_2Cl_2 at 0 °C was added imidazole (207 mg, 3.04 mmol), followed by TBSCl (274 mg, 1.82 mmol). The mixture was allowed to warm to room temperature and stirred. After 5 h, the reaction was quenched at 0 °C with water (40 mL), and it was extracted with CH_2Cl_2 (2 x 75 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated to an oil.

Purification by flash chromatography (50:1 hexanes/EtOAc eluent) provided silyl ether **S31** (544 mg, 98% yield, R_F = 0.85 in 9:1 hexanes/EtOAc) as a colorless oil.

Silyl ether S31: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (app. dt, *J* = 3.7, 10.2 Hz, 1H), 5.40 (d, *J* = 10.2 Hz, 1H), 3.32 (ABq, *J* = 9.6 Hz, Δν = 28.5 Hz, 2H), 2.18 (t, *J* = 6.7 Hz, 2H), 1.96-1.90 (comp m, 2H), 1.61-1.34 (comp m, 8H), 0.89 (s, 9H), 0.14 (s, 9H), 0.02 (app. s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 128.2, 108.1, 84.4, 68.9, 39.5, 36.8, 29.5, 26.1, 25.6, 23.6, 21.0, 19.1, 18.5, 0.4, -5.26, -5.29; IR (film) 2953, 2932, 2175, 1250, 1087, 841 cm^{-1}.

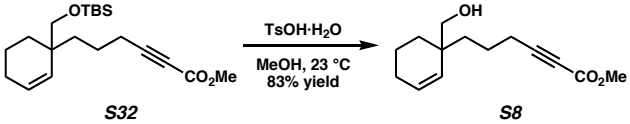


S31 *S32*

To a solution of **S31** (544 mg, 1.49 mmol) in 14.9 mL MeOH at 23 °C was added K_2CO_3 (247 mg, 1.79 mmol). The resulting mixture was maintained at room temperature for 8 h, at which point a mixture of saturated $NaHCO_3/H_2O$ was added (2:1, 75 mL). The organic solvent was removed via rotary evaporation, and the residue was extracted with Et_2O (2 x 100 mL). The organic phases were combined, washed with brine (75 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (50:1 hexanes/EtOAc eluent) to afford the desired alkyne (423 mg, 97% yield, R_F = 0.29 in hexanes) as a colorless oil.

To a solution of the alkyne (423 mg, 1.45 mmol) in 12.1 mL THF at –78 °C was added *n*-BuLi (809 μl, 2.15 M in hexanes, 1.74 mmol) dropwise, and the resulting mixture was stirred at –78 °C for 1 h. Methyl chloroformate (291 μl, 3.77 mmol) was then introduced slowly, and the reaction was maintained at –78 °C for 1 h. The mixture was then allowed to gradually warm to room temperature, stirred for 5 min, and then it was quenched with saturated NH_4Cl (50 mL) at 0 °C and extracted with Et_2O (3 x 60 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (50:1 hexanes/EtOAc eluent) to provide ester **S32** (508 mg, quantitative yield, R_F = 0.48 in 9:1 hexanes/EtOAc) as a pale yellow oil.

Ester S32: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (app. dt, *J* = 3.7, 10.2 Hz, 1H), 5.39 (d, *J* = 10.2 Hz, 1H), 3.75 (s, 3H), 3.31 (ABq, *J* = 9.6 Hz, Δν = 24.6 Hz, 2H), 2.30 (t, *J* = 7.2 Hz, 2H), 1.96-1.91 (comp m, 2H), 1.60-1.32 (comp m, 8H), 0.88 (s, 9H), 0.02 (app. s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 132.2, 128.6, 90.2, 73.0, 68.7, 52.8, 39.4, 36.8, 29.6, 26.1, 25.6, 22.6, 19.7, 19.1, 18.5, -5.30, -5.33; IR (film) 2951, 2930, 2238, 1719, 1255 cm^{-1}.

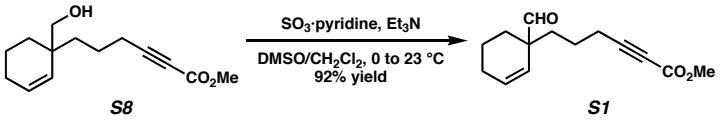


S32 *S8*

To a solution of silyl ether **S32** (508 mg, 1.45 mmol) in 14.5 mL MeOH at 23 °C was added $TsOH·H_2O$ (5.5 mg, 0.0290 mmol), and the resulting mixture was stirred for 18 h. The reaction was quenched with saturated $NaHCO_3$ (30 mL), and the organic solvent was

removed via rotary evaporation. The residue was extracted with Et_2O (2 x 75 mL), and the combined organic phases were washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc eluent) afforded alcohol **S8** (284 mg, 83% yield, R_F = 0.15 in 4:1 hexanes/EtOAc) as a colorless oil.

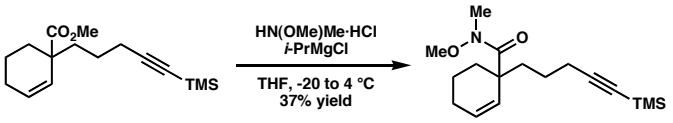
Alcohol S8: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (app. dt, *J* = 3.8, 10.2 Hz, 1H), 5.36 (d, *J* = 10.2 Hz, 1H), 3.75 (s, 3H), 3.43 (dd, *J* = 3.8, 10.7 Hz, 1H), 3.36 (dd, *J* = 6.6, 10.7 Hz, 1H), 2.31 (t, *J* = 7.0 Hz, 2H), 1.99-1.93 (comp m, 2H), 1.70-1.54 (comp m, 2H), 1.50-1.40 (comp m, 3H), 1.35 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 131.3, 130.7, 89.8, 73.2, 69.6, 52.8, 39.7, 37.0, 29.5, 25.2, 22.6, 19.7, 19.3; IR (film) 3417, 2934, 2236, 1713, 1256 cm^{-1}; Anal. calc'd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; O, 20.31. Found: C, 70.99; H, 8.46.



S8 *S1*

To a solution of alcohol **S8** (199 mg, 0.842 mmol) in 4.21 mL CH_2Cl_2 and 2.10 mL DMSO at 0 °C was added Et_3N (353 µl, 2.53 mmol). After 1 min, a solution of SO_3·pyridine (201 mg, 1.26 mmol) in 2.10 mL DMSO was added dropwise, and the resulting mixture was stirred 10 min at 0 °C and 1.5 h at 23 °C. The reaction was then quenched at 0 °C with water (30 mL) and extracted with Et_2O (3 x 40 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (9:1 hexanes/EtOAc eluent) provided aldehyde **S1** (181 mg, 92% yield, R_F = 0.27 in 4:1 hexanes/EtOAc) as a colorless oil.

Aldehyde S1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.42 (s, 1H), 6.01 (app. dt, *J* = 3.8, 10.1 Hz, 1H), 5.46 (d, *J* = 10.1 Hz, 1H), 3.76 (s, 3H), 2.34 (t, *J* = 6.9 Hz, 2H), 2.04-1.94 (comp m, 3H), 1.72-1.50 (comp m, 6H), 1.45 (ddd, *J* = 3.2, 10.7, 13.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 154.4, 132.7, 126.2, 89.0, 73.5, 52.8, 50.9, 35.2, 27.5, 25.0, 22.4, 19.4, 19.1; IR (film) 2939, 2236, 1716, 1257, 1075 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{14}H_{18}O_3 + Na]^+$: 257.1154, found 257.1150.

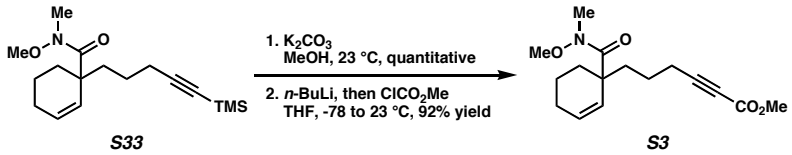


1 *S33*

Weinreb amide **S33** was synthesized according to the procedure of Williams et al.[4] To a stirring suspension of ester **1** (246 mg, 0.883 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (129 mg, 1.32 mmol) in 1.77 mL THF at –20 °C was added *i*-PrMgCl (1.33 mL, 2.0 M in THF, 2.65 mmol) dropwise. The resulting mixture was stirred at –20 °C for 30 min and at 4 °C for 30 h, at which point it was quenched with saturated NH_4Cl (50 mL) and extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification

of the residue by flash chromatography (8:1 hexanes/EtOAc eluent) afforded amide **S33** (100 mg, 37% yield, R_F = 0.39 in 4:1 hexanes/EtOAc) as a colorless oil.

Amide S33: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (d, *J* = 10.3 Hz, 1H), 5.75 (app. dt, *J* = 3.4, 10.3 Hz, 1H), 3.63 (s, 3H), 3.16 (s, 3H), 2.38 (ddd, *J* = 2.9, 6.1, 7.9 Hz, 1H), 2.19 (t, *J* = 7.2 Hz, 2H), 2.00-1.95 (comp m, 2H), 1.83 (dt, *J* = 4.8, 12.9 Hz, 1H), 1.74-1.67 (m, 1H), 1.64-1.38 (comp m, 4H), 1.23 (ddd, *J* = 3.1, 11.6, 12.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 130.7, 128.2, 107.5, 84.7, 60.8, 47.7, 38.2, 34.0, 31.6, 25.2, 24.0, 20.5, 20.0, 0.4; IR (film) 2958, 2937, 2174, 1643, 1249, 842 cm^{-1}.

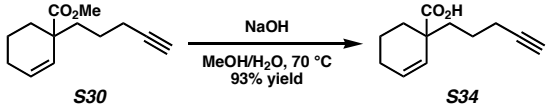


S33 *S3*

To a solution of amide **S33** (100 mg, 0.325 mmol) in 2.17 mL MeOH at 23 °C was added K_2CO_3 (53.9 mg, 0.390 mmol). The resulting mixture was stirred at 23 °C for 12 h, at which point it was diluted with EtOAc (50 mL) and washed with saturated $NaHCO_3/H_2O$ (2:1, 25 mL). The aqueous phase was extracted with EtOAc (25 mL), and the combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (7:1 hexanes/EtOAc eluent) to provide the desired alkyne (76.8 mg, quantitative yield, R_F = 0.31 in 4:1 hexanes/EtOAc) as a colorless oil, which was taken directly to the subsequent transformation.

To a solution of the alkyne (76.8 mg, 0.325 mmol) in 2.71 mL THF at –78 °C was added *n*-BuLi (160 μl, 2.13 M in hexanes, 0.341 mmol) dropwise, and the resulting mixture was stirred at –78 °C for 1 h. Methyl chloroformate (65.3 μl, 0.845 mmol) was then introduced slowly, and the reaction was maintained at –78 °C for 1 h. The mixture was then allowed to gradually warm to room temperature, stirred for 5 min, and then it was quenched with saturated NH_4Cl (20 mL) at 0 °C and extracted with EtOAc (3 x 30 mL). The organic phases were combined, washed with brine (25 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (3:1 hexanes/EtOAc eluent) to provide ester **S3** (88.1 mg, 92% yield, R_F = 0.37 in 2:1 hexanes/EtOAc) as a colorless oil.

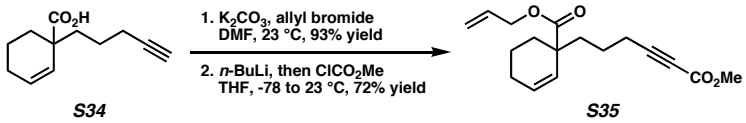
Ester S3: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (d, *J* = 10.2 Hz, 1H), 5.75 (app. dt, *J* = 3.0, 10.2 Hz, 1H), 3.75 (s, 3H), 3.62 (s, 3H), 3.16 (s, 3H), 2.36 (ddd, *J* = 2.0, 2.9, 5.3 Hz, 1H), 2.30 (t, *J* = 7.1 Hz, 2H), 2.00-1.95 (comp m, 2H), 1.82 (dt, *J* = 5.2, 12.8 Hz, 1H), 1.74-1.45 (comp m, 5H), 1.27-1.19 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 154.4, 130.3, 128.4, 89.7, 73.2, 60.8, 52.8, 47.6, 38.2, 34.0, 31.6, 25.1, 23.0, 19.9, 19.4; IR (film) 2938, 2236, 1715, 1640, 1258, 1076 cm^{-1}; Anal. calc'd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77; O, 21.82. Found: C, 65.32; H, 7.81; N, 4.80.



S30 *S34*

To a solution of ester **S30** (500 mg, 2.42 mmol) in 4.84 mL MeOH was added 1 N NaOH (aq., 7.26 mL). The mixture was heated to 70 °C and stirred. After 4 h, the reaction was

cooled to 0 °C, diluted with Et_2O (75 mL), and acidified by slow addition of 1 N HCl. Once acidic, the mixture was partitioned, and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, and concentrated to an oil. Purification by flash chromatography (3:1 hexanes/EtOAc eluent) afforded carboxylic acid **S34** (430 mg, 93% yield, R_F = 0.05 in 9:1 hexanes/EtOAc) as a colorless oil.

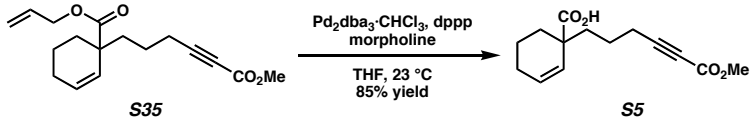


S34 *S35*

To a solution of acid **S34** (376 mg, 1.96 mmol) in 19.6 mL DMF at 23 °C was added K_2CO_3 (650 mg, 4.70 mmol), then allyl bromide (509 µl, 5.88 mmol). The reaction mixture was maintained at 23 °C for 45 min, at which point it was quenched with saturated NH_4Cl (50 mL) at 0 °C. The mixture was extracted with Et_2O (2 x 75 mL), and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (24:1 hexanes/Et_2O eluent) to afford the desired allyl ester (426 mg, 93% yield, R_F = 0.77 in 2:1 hexanes/EtOAc) as a colorless oil, which was taken directly to the subsequent transformation.

To a solution of the alkyne (416 mg, 1.79 mmol) in 14.9 mL THF at –78 °C was added *n*-BuLi (783 µl, 2.4 M in hexanes, 1.88 mmol) dropwise, and the resulting mixture was stirred at –78 °C for 1 h. Methyl chloroformate (359 µl, 4.65 mmol) was then introduced slowly, and the reaction was maintained at –78 °C for 1 h. The mixture was then allowed to gradually warm to room temperature, stirred for 5 min, and then it was quenched with saturated NH_4Cl (50 mL) at 0 °C and extracted with Et_2O (3 x 60 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (11:1 hexanes/EtOAc eluent) to provide ester **S35** (372 mg, 72% yield, R_F = 0.30 in 9:1 hexanes/EtOAc) as a colorless oil.

Ester S35: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (dddd, *J* = 5.6, 10.5, 11.2, 16.1 Hz, 1H), 5.80 (app. dt, *J* = 3.5, 10.1 Hz, 1H), 5.66 (d, *J* = 10.1 Hz, 1H), 5.30 (d, *J* = 16.1 Hz, 1H), 5.21 (d, *J* = 10.5 Hz, 1H), 4.62-4.53 (comp m, 2H), 3.74 (s, 3H), 2.30 (t, *J* = 7.1 Hz, 2H), 2.15 (ddd, *J* = 2.8, 6.7, 13.2 Hz, 1H), 2.03-1.90 (comp m, 2H), 1.75 (ddd, *J* = 5.4, 11.7, 13.1 Hz, 1H), 1.71-1.48 (comp m, 5H), 1.42 (ddd, *J* = 3.2, 10.9, 13.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 154.4, 132.4, 129.4, 129.3, 118.2, 89.2, 73.3, 65.4, 52.8, 46.9, 39.4, 30.8, 25.1, 22.9, 19.8, 19.2; IR (film) 2950, 2237, 1719, 1255, 1176 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{17}H_{22}O_4 + Na]^+$: 313.1416, found 313.1420.

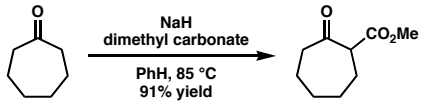


S35 *S5*

Deallylation was performed according to the procedure described by Sato and coworkers.[5] A flame-dried flask was charged with $Pd_2dba_3{\cdot}CHCl_3$ (14.9 mg, 0.0144 mmol) and dppp (17.8 mg, 0.0432 mmol). It was dissolved in 4.80 mL THF (degassed

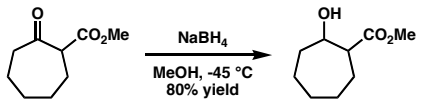
via bubbling with argon for 20 min), and the resulting mixture was stirred at 23 °C for 10 min (reaction mixture turned pale orange in color). The catalyst solution was transferred via syringe to a solution of ester **S35** (278 mg, 0.959 mmol) and morpholine (101 μl, 1.15 mmol) in 4.80 mL THF (degassed). The reaction mixture was maintained at 23 °C for 2 h, at which point it was diluted with EtOAc (100 mL) and washed with saturated NH_4Cl (50 mL). The aqueous phase was extracted with EtOAc (50 mL), and the combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, and concentrated to an oil. Purification by flash chromatography (2:1 hexanes/EtOAc eluent) afforded carboxylic acid **S5** (205 mg, 85% yield, R_F = 0.22 in 2:1 hexanes/EtOAc) as a colorless oil.

Acid S5: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (app. dt, *J* = 3.7, 10.3 Hz, 1H), 5.67 (d, *J* = 10.3 Hz, 1H), 3.76 (s, 3H), 2.33 (t, *J* = 7.1 Hz, 2H), 2.15 (ddd, *J* = 2.8, 6.5, 9.6 Hz, 1H), 2.06-1.93 (comp m, 2H), 1.81-1.74 (m, 1H), 1.74-1.56 (comp m, 5H), 1.45 (ddd, *J* = 3.4, 10.6, 13.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.3, 154.4, 130.0, 128.7, 89.2, 73.3, 52.8, 46.6, 39.2, 30.6, 25.0, 22.9, 19.7, 19.3; IR (film) 2951, 2238, 1715, 1258, 1076 cm^{-1}.



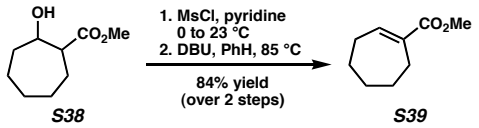
S36 *S37*

To a suspension of washed sodium hydride (10.2 g, 60% dispersion in mineral oil, 255 mmol, 3 x 20 mL hexanes wash) in 160 mL benzene was added dimethyl carbonate (15.4 mL, 182 mmol) dropwise via syringe. The resulting mixture was heated at reflux for 1 h. A solution of cycloheptanone (**S36**, 12.0 mL, 91.1 mmol) in 12.0 mL benzene was then added via syringe, and the reaction mixture was heated at reflux. After 3 h, the heterogeneous mixture was cooled to room temperature and quenched with AcOH (16 mL). The mixture was diluted with water (200 mL) and extracted with EtOAc (3 x 150 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to an oil. Purification by flash chromatography (4:1 hexanes/EtOAc eluent) provided ketoester **S37** (14.1 g, 91% yield, R_F = 0.45 in 4:1 hexanes/EtOAc) as a pale yellow oil.



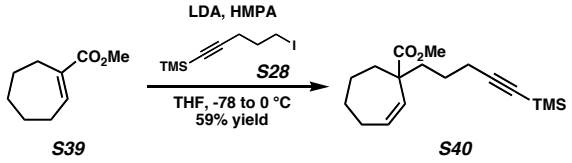
S37 *S38*

To a solution of **S37** (10.0 g, 59.0 mmol) in 236 mL MeOH at -45 °C was added $NaBH_4$ (3.12 g, 76.7 mmol) in four portions over 10 minutes. The resulting mixture was stirred at -45 °C for 20 min, at which point it was quenched by the slow addition of saturated NH_4Cl (100 mL). The volatile material was removed via rotary evaporation, and the residue was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to an oil. Purification by flash chromatography (3:2 hexanes/EtOAc eluent) afforded alcohol **S38** (8.16 g, 80% yield, R_F = 0.40 in 3:2 hexanes/EtOAc) as a pale yellow oil.



To a solution of alcohol **S38** (4.12 g, 23.9 mmol) in 79 mL pyridine at 0 °C was added methanesulfonyl chloride (5.55 mL, 71.8 mmol). The resulting mixture was stirred at 0 °C for 30 min, and then it was allowed to warm to room temperature and stirred for an additional 4 h. The solution was then cooled to 0 °C, diluted with 200 mL EtOAc, and quenched with water (100 mL). 2.0 M HCl (100 mL) was added, the phases were separated, and the organic layer was washed with 2.0 M HCl (100 mL). The aqueous phases were extracted with 100 mL EtOAc, and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated to an oil. The crude mesylate (R_F = 0.10 in 4:1 hexanes/Et_2O) was taken immediately to the subsequent transformation.

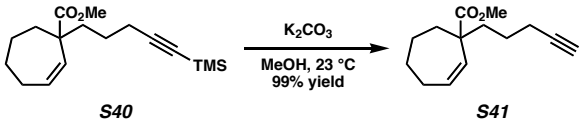
To a solution of the mesylate (23.9 mmol) in 12.0 mL PhH at room temperature was added DBU (7.15 mL, 47.8 mmol). The reaction mixture was heated to reflux and stirred for 8 h. The solution was then cooled to room temperature, diluted with Et_2O (100 mL), and washed with saturated $NaHCO_3$ (75 mL). The aqueous layer was extracted with Et_2O (100 mL), and the combined organic phases were washed with 100 mL brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (17:3 hexanes/Et_2O eluent) provided ester **S39** (3.11 g, 84% yield over 2 steps, R_F = 0.75 in 4:1 hexanes/Et_2O) as a pale yellow oil. Spectroscopic data for **S39** were identical to literature values.[6]



Deconjugative alkylation was performed according to a modified procedure described by Kuwajima and Urabe.[3] To a solution of *i*-Pr_2NH (1.52 mL, 10.8 mmol) in 6.31 mL THF at –78 °C was added *n*-BuLi (4.50 mL, 2.4 M in hexanes, 10.8 mmol) dropwise. The solution of LDA was stirred at –78 °C for 5 min and at 0 °C for 15 min. It was then cooled to –78 °C, and HMPA (2.05 mL, 11.8 mmol) was added. The resulting mixture was stirred for 30 min, and then **S39** (1.50 mL, 9.82 mmol) was introduced. After 20 min, **S28** (2.72 mL, 12.8 mmol) was added, and the reaction was stirred at -78 °C for 15 min, at which point it was warmed to 0 °C. After 2 h, the reaction mixture was quenched with saturated NH_4Cl (75 mL) and extracted with EtOAc (3 x 75 mL). The combined organic layers were washed with saturated $NaHCO_3$ (50 mL), then brine (50 mL), dried over $MgSO_4$, and concentrated to an oil. Purification by flash chromatography (23:2 hexanes/Et_2O eluent) provided ester **S40** (1.69 g, 59% yield, R_F = 0.50 in 93:7 hexanes/Et_2O) as a colorless oil.

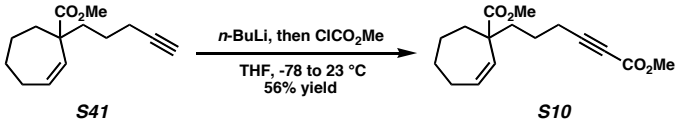
Ester S40: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (dt, *J* = 5.2, 12 Hz, 1H), 5.65 (d, *J* = 11.6 Hz, 1H), 3.70 (s, 3H), 2.20 (t, *J* = 7.1 Hz, 2H), 2.14-2.10 (m, 2H), 1.81-1.68 (comp m, 5H), 1.58-1.41 (comp m, 5H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 133.7,

132.5, 117.0, 107.0, 84.5, 52.2, 39.3, 35.1, 28.1, 27.1, 25.7, 24.1, 20.4, 0.20; IR (film) 2928, 2174, 1731, 1452, 1249, 843 cm^{-1}.



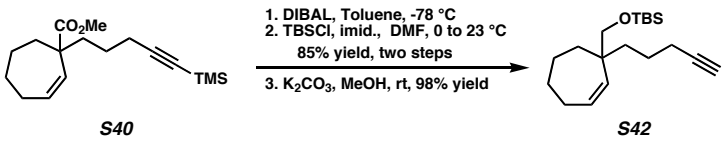
To a solution of ester **S40** (266 mg, 0.909 mmol) in 6.06 mL MeOH at 23 °C was added K_2CO_3 (151 mg, 1.09 mmol). The resulting mixture was maintained at room temperature for 12 h, at which point saturated $NaHCO_3$ was added. The organic solvent was removed via rotary evaporation, and the residue was extracted with CH_2Cl_2 (2 x 100 mL). The organic phases were combined, washed with brine (75 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (19:1 hexanes/ Et_2O eluent) to afford ester **S41** (200 mg, 99% yield, R_F = 0.37 in 19:1 hexanes/ Et_2O) as a colorless oil.

Ester S41: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (dt, *J* = 6.0, 11.7 Hz, 1H), 5.62 (d, *J* = 11.6 Hz, 1H), 3.68 (s, 3H), 2.16 (dt, *J* = 2.9, 7.3 Hz, 2H), 2.13-2.08 (comp m, 2H), 1.78-1.65 (comp m, 6H), 1.60-1.41 (comp m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 133.5, 132.5, 84.0, 68.6, 52.1, 39.5, 35.2, 28.1, 27.5, 27.0, 25.8, 23.8, 18.9; IR (film) 3304, 2927, 1729, 1452, 1211 cm^{-1}.

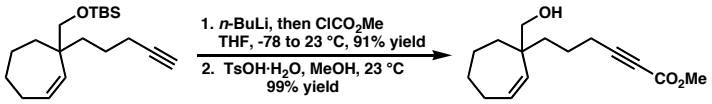


To a solution of ester **S41** (200 mg, 0.908 mmol) in 908 μL THF at –78 °C was added *n*-BuLi (397 μl, 2.4 M in hexanes, 0.953 mmol) dropwise, and the resulting mixture was stirred at –78 °C for 1 h. Methyl chloroformate (156 μl, 2.00 mmol) was then introduced slowly, and the reaction was maintained at –78 °C for 1 h. The mixture was then allowed to gradually warm to room temperature, and quenched with saturated NH_4Cl (50 mL) at 0 °C and extracted with EtOAc (3 x 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (4:1 hexanes/ Et_2O eluent) to provide ester **S10** (141 mg, 56% yield, R_F = 0.15 in 17:3 hexanes/EtOAc) as a colorless oil.

Ester S10: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86-5.81 (m, 1H), 5.59 (d, *J* = 11.7 Hz, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 2.31 (t, *J* = 7.0 Hz, 2H), 2.11-2.09 (m, 2H), 1.95 (m, 1H), 1.76-1.50 (comp m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 154.2, 133.2, 132.8, 89.1, 73.2, 52.7, 52.0, 39.3, 35.2, 28.0, 27.0, 25.7, 23.1, 19.1; IR (film) 2927, 2237, 1717, 1434, 1256, 1077 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $[C_{16}H_{22}O_4 + Na]^+$: 301.1416, found 301.1406.



To a solution of ester **S40** (378 mg, 1.36 mmol) in 7.27 mL toluene at –78 °C was added DIBAL (4.07 mL, 1.0 M in toluene, 4.07 mmol) dropwise. The resulting mixture was maintained at –78 °C for 1 h, at which point EtOAc (1.20 mL, 12.2 mmol) was added. The reaction was stirred for 5 min, and then saturated sodium potassium tartrate solution and EtOAc (50 mL each) were added, and the mixture was allowed to warm to room temperature and stirred vigorously for 12 h. The mixture was partitioned, and the aqueous phase was extracted with EtOAc (75 mL). The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo to provide the alcohol as a colorless oil which was taken directly to the subsequent transformation.
To a solution of the alcohol (378 mg, 1.36 mmol) in 4.53 mL DMF at 0 °C was added imidazole (139 mg, 2.04 mmol), followed by TBSCl (307 mg, 2.04 mmol). The mixture was allowed to warm to room temperature and stirred. After 8 h, the reaction was quenched at 0 °C with saturated NH_4Cl (40 mL), and it was extracted with Et_2O (2 x 75 mL). The organic phases were combined, dried over $MgSO_4$, and concentrated to an oil. Purification by flash chromatography (9:1 hexanes/Et_2O eluent) provided the silyl ether (438 mg, 85% yield over two steps, R_F = 0.94 in 4:1 hexanes/Et_2O) as a colorless oil.
To a solution of the ether (623 mg, 1.64 mmol) in 10.9 mL MeOH at 23 °C was added K_2CO_3 (273 mg, 1.98 mmol). The resulting mixture was maintained at room temperature for 12 h, at which point saturated $NaHCO_3$ was added. The organic solvent was removed via rotary evaporation, and the residue was extracted with CH_2Cl_2 (2 x 100 mL). The organic phases were combined, washed with brine (75 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (19:1 hexanes/Et_2O eluent) to afford ether **S42** (494 mg, 98% yield, R_F = 0.63 in 19:1 hexanes/Et_2O eluent) as a colorless oil.
Ether S42: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (dt, *J* = 6.0, 12.9 Hz, 1H), 5.35 (d, *J* = 12.0 Hz), 3.40 (d, *J* = 9.4 Hz, 1H), 3.30 (d, *J* = 9.6 Hz, 1H), 2.1-2.09 (comp m, 4H), 1.94 (t, *J* = 2.5 Hz, 1H), 1.72-1.67 (comp m, 2H), 1.62-1.41 (comp m, 8H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0, 130.8, 117.0, 84.9, 68.2, 68.0, 35.7, 33.1, 28.5, 28.2, 26.0, 24.8, 23.3, 19.4, 18.3; IR (film) 2927, 2856, 1467, 1253, 1086 cm^{-1}.

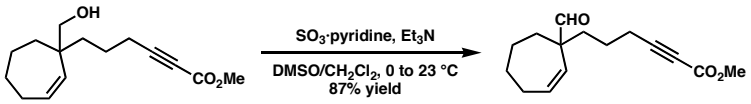


S42 *S43*

To a solution of alkyne **S42** (475 mg, 1.55 mmol) in 15.5 mL THF at –78 °C was added *n*-BuLi (969 μl, 2.4 M in hexanes, 2.33 mmol) dropwise, and the resulting mixture was stirred at –78 °C for 1 h. Methyl chloroformate (282 μl, 3.64 mmol) was then introduced slowly, and the reaction was maintained at –78 °C for 1 h. The mixture was then allowed to gradually warm to room temperature, and quenched with saturated NH_4Cl (70 mL) at 0 °C and extracted with EtOAc (3 x 80 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (19:1 hexanes/Et_2O eluent) to provide the ester (516 mg, 91% yield, R_F = 0.50 in 19:1 hexanes/EtOAc) as a colorless oil.
To a solution of the silyl ether (1.45 mmol, 516 mg) in 14.2 mL MeOH at 23 °C was added TsOH·H_2O (5.4 mg, 0.0283 mmol), and the resulting mixture was stirred for 24 h. The reaction was quenched with saturated $NaHCO_3$ (30 mL), and the organic solvent was

removed via rotary evaporation. The residue was extracted with EtOAc (3 x 75 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (1:1 hexanes/Et_2O eluent) afforded alcohol **S43** (354 mg, quantitative yield, R_F = 0.10 in 19:1 hexanes/Et_2O) as a colorless oil.

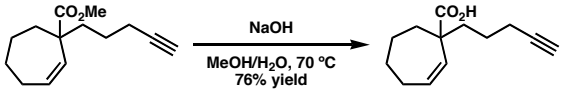
Alcohol S43: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (dt, *J* = 6.1, 11.8 Hz, 1H), 5.33 (d, 1H, *J* = 11.8 Hz, d), 3.76 (s, 3H), 3.50 (d, *J* = 11.0 Hz, 1H), 3.43 (d, *J* = 11.0 Hz, 1H), 2.33 (t, *J* = 6.6 Hz, 2H), 2.18-2.12 (m, 2H), 1.73 (app. quintet, *J* = 5.8 Hz, 2H), 1.63-1.46 (comp m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 135.8, 132.5, 89.8, 68.9, 52.6, 44.9, 36.3, 33.0, 31.6, 28.4, 28.0, 24.6, 22.4, 19.5; IR (film) 3417, 2921, 2236, 1714, 1435, 1257, 1076 cm^{-1}.



S43 *S12*

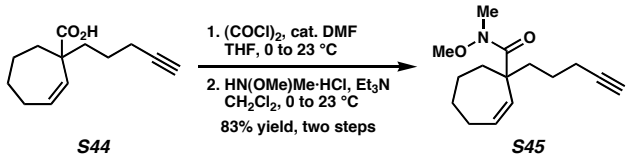
To a solution of alcohol **S43** (354 mg, 1.41 mmol) in 3.53 mL CH_2Cl_2 and 1.76 mL DMSO at 0 °C was added Et_3N (590 μl, 4.23 mmol). A solution of SO_3·pyridine (337 mg, 2.12 mmol) in 1.76 mL DMSO was added dropwise, and the resulting mixture was stirred 30 min at 0 °C and 1.5 h at 23 °C. The reaction was then quenched at 0 °C with water (150 mL) and extracted with Et_2O (3 x 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (3:1 hexanes/Et_2O eluent) provided aldehyde **S12** (285 mg, 89% yield, R_F = 0.65 in 11:9 hexanes/Et_2O) as a colorless oil.

Aldehyde S12: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 ((s, 1H), 6.02 (dt, *J* = 5.9, 12.1 Hz, 1H), 5.55 (d, *J* = 11.8 Hz, 1H), 3.76 (s, 3H), 2.34 (t, *J* = 6.9 Hz, 2H), 2.23-2.08 (m, 2H), 1.81-1.45 (comp m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 135.0, 88.8, 73.4, 58.4, 55.5, 52.7, 35.0, 32.0, 28.3, 27.2, 25.0, 22.5, 19.2; IR (film) 2927, 2237, 1717, 1435, 1258, 1076, 752 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{15}H_{20}O_3 + Na]^+$: 299.1620, found: 299.1621.



S41 *S44*

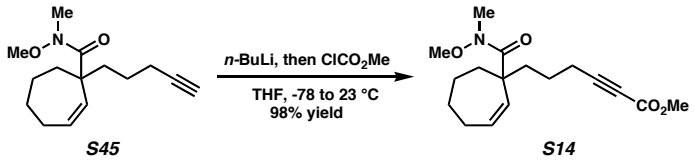
To a solution of ester **S41** (500 mg, 2.66 mmol) in 5.30 mL MeOH was added 1 N NaOH (aq., 8.00 mL). The mixture was heated to 70 °C and stirred. After 48 h, the reaction was cooled to 0 °C, diluted with Et_2O (75 mL), and acidified by slow addition of 1 N HCl. Once acidic, the mixture was partitioned, and the aqueous phase was extracted with Et_2O (2 x 50 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, and concentrated to an oil. Purification by flash chromatography (1:1 hexanes/Et_2O eluent) afforded carboxylic acid **S44** (587 mg, 76% yield, R_F = 0.35 in 1:1 hexanes/Et_2O) as a colorless oil.



To a solution of acid **S44** (340 mg, 1.65 mmol) in 8.25 mL THF at 0 °C was added oxalyl chloride (698 μl, 8.25 mmol), followed by DMF (1 drop, ~10 μl). The resulting mixture was stirred 5 min at 0 °C and 1 h at 23 °C, and then the volatile materials were removed via rotary evaporation. The residue was azeotroped from benzene (10 mL) three times via rotary evaporation, and the crude acid chloride was taken immediately to the subsequent transformation.

To a solution of *N,O*-dimethylhydroxylamine hydrochloride (805 mg, 8.25 mmol) and Et_3N (2.30 mL, 16.5 mmol) in 8.25 mL CH_2Cl_2 at 0 °C was added a solution of the crude acid chloride in 8.25 mL CH_2Cl_2 via cannula. The reaction mixture was allowed to warm to room temperature and stirred 12 h, at which point it was partitioned between CH_2Cl_2 (150 mL) and saturated NH_4Cl (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL), dried over Na_2SO_4, and concentrated to an oil. Purification of the residue by flash chromatography (7:3 hexanes/EtOAc eluent) provided amide **S45** (340 mg, 83% yield, R_F = 0.20 in 4:1 hexanes/EtOAc) as a colorless oil.

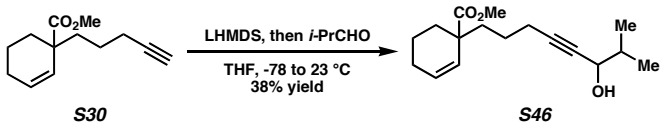
Amide S45: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (dt, *J* = 5.2, 11.4 Hz, 1H), 5.61 (d, *J* = 11.4 Hz, 1H), 3.60 (s, 3H), 3.15 (s, 3H), 2.19-2.05 (m, 5H), 2.03-1.93 (comp m, 2H), 1.82-1.71 (comp m, 3H), 1.62-1.39 (comp m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 129.9, 84.4, 68.5, 60.2, 51.1, 39.5, 35.4, 33.9, 28.6, 26.69, 26.66, 23.6, 19.0; IR (film) 3301, 2932, 1644, 1456, 1349, 1004 cm^{-1}.



To a solution of amide **S45** (289 mg, 1.16 mmol) in 11.5 mL THF at –78 °C was added *n*-BuLi (508 μl, 2.4 M in hexanes, 1.22 mmol) dropwise, and the resulting mixture was stirred at –78 °C for 1 h. Methyl chloroformate (180 μl, 2.32 mmol) was then introduced slowly, and the reaction was maintained at –78 °C for 1 h. The mixture was then allowed to gradually warm to room temperature, and quenched with saturated NH_4Cl (50 mL) at 0 °C and extracted with EtOAc (3 x 50 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (3:2 hexanes/EtOAc eluent) to provide amide **S14** (350 mg, 98% yield, R_F = 0.15 in 17:3 hexanes/EtOAc) as a colorless oil.

Amide S14: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (dt, *J* = 6.0, 11.6 Hz, 1H), 5.58 (d, *J* = 11.6 Hz, 1H), 3.75 (s, 3H), 3.58 (s, 3H), 3.15 (s, 3H), 2.31 (t, *J* = 7.2 Hz, 2H), 2.13 (dt, *J* = 5.0, 13.3 Hz, 1H), 2.09-2.06 (m, 2H), 2.01- 1.93 (m, 1H), 1.80-1.70 (comp m, 3H), 1.64-1.53 (comp m, 3H), 1.49-1.40 (comp m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 154.3, 135.9, 130.1, 89.5, 73.1, 60.2, 52.6, 51.2, 39.3, 35.3, 33.8, 28.6, 26.7, 26.6, 22.8,

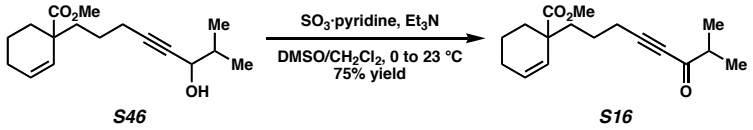
19.3; IR (film) 2931, 2234, 1715, 1644, 1435, 1257 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $[C_{17}H_{25}NO_4 + Na]^+$: 330.1681, found: 330.1680



A stock solution of 1.0 M LHMDS was prepared as follows: To a solution of hexamethyldisilazane (1.00 mL, 4.80 mmol) in 2.80 mL THF at –78 °C was added *n*-BuLi (2.00 mL, 2.4 M in hexanes, 4.80 mmol) dropwise. The solution of LHMDS was stirred at –78 °C for 5 min and at 0 °C for 15 min. The required amount of the 1.0 M LHMDS solution was then transferred via syringe to the reaction mixture.

To a solution of alkyne **S30** (350 mg, 1.70 mmol) in 15.0 mL THF at –78 °C was added LHMDS (1.87 mL, 1.0 M in THF, 1.87 mmol) dropwise, and the resulting mixture was stirred at –78 °C for 30 min. Isobutyraldehyde (233 μl, 2.55 mmol) was then introduced slowly, and the reaction was maintained at –78 °C for 45 min, then quenched with saturated NH_4Cl (70 mL) and extracted with EtOAc (3 x 80 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (7:3 hexanes/Et_2O eluent) to provide alcohol **S46** (181 mg, 38% yield, R_F = 0.15 in 9:1 hexanes/EtOAc) as a colorless oil.

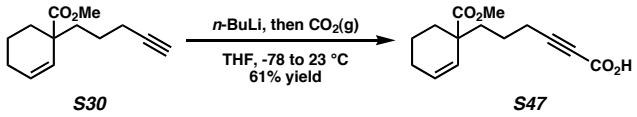
Alcohol S46: ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (dt, *J* = 3.8, 10.0 Hz, 1H), 5.70 (d, *J* = 11.0 Hz, 1H), 4.15 (dt, *J* = 2.2, 6.0 Hz, 1H), 3.68 (s, 3H), 2.20 (dt, *J* = 1.9, 6.8), 2.15 (dt, *J* = 2.5, 6.2 Hz, 1H), 2.04-1.92 (m, 2H), 1.84 (app. sextet, *J* = 5.9 Hz, 1H), 1.77-1.41 (comp m, 9H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 129.5, 128.9, 85.7, 80.3, 68.2, 52.0, 46.8, 39.4, 34.7, 30.9; IR (film) 3400, 2954, 2870, 1729, 1461, 1024 cm^{-1}.



To a solution of alcohol **S46** (158 mg, 0.568 mmol) in 1.42 mL CH_2Cl_2 and 710 μL DMSO at 0 °C was added Et_3N (238 μl, 1.70 mmol). A solution of SO_3·pyridine (135 mg, 0.851 mmol) in 710 μL DMSO was added dropwise, and the resulting mixture was stirred 30 min at 0 °C and 1.5 h at 23 °C. The reaction was then quenched at 0 °C with water (150 mL) and extracted with Et_2O (3 x 150 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (9:1 hexanes/EtOAc eluent) provided ketone **S16** (117 mg, 75% yield, R_F = 0.30 in 7:3 hexanes/Et_2O) as a colorless oil.

Ketone S16: ^1H NMR (500 MHz, $CDCl_3$) δ 5.81 (dt, *J* = 3.4, 10.1 Hz, 1H), 5.68 (d, *J* = 10.5 Hz, 1H), 3.68 (s, 3H), 2.61 (septet, *J* = 6.6 Hz, 2H) 2.17-2.13 (m, 1H), 2.03-1.92 (m, 2H), 1.75 (dt, *J* = 5.4, 12.7, 1H), 1.70 (m, 6H), 1.43 (app. t, *J* = 11.0 Hz, 1H), 1.19 (d, *J* = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 176.4, 129.2, 129.1, 94.3, 80.0, 52.0

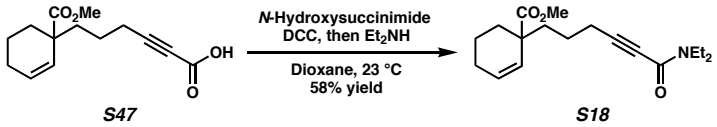
46.7, 43.1, 39.3, 30.8, 24.9, 23.1, 19.7, 19.4, 18.0; IR (film) 2938, 2210, 1730, 1674, 1194 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $[C_{17}H_{24}O_3 + Na]^+$: 299.1623, found: 299.1609.



S30 *S47*

To a solution of alkyne **S30** (395 mg, 1.91 mmol) in 16.0 mL THF at –78 °C was added *n*-BuLi (2.01 mmol, 2.4 M in hexanes, 0.836 mL) dropwise, and the resulting mixture was stirred at –78 °C for 1 h. The nitrogen line was then replaced by a carbon-dioxide balloon fitted with a 9-inch needle, the septa was pierced with a second outlet needle, and CO_2 was bubbled into the reaction mixture for 30 min at -78 ºC, and then the mixture was allowed to gradually warm to room temperature. After 30 min of bubbling at room temperature, the outlet needle was removed and stirring continued for 2 h. The reaction was then cooled to 0 ºC, quenched with saturated NH_4Cl (50 mL), and extracted with EtOAc (3 x 50 mL). The organic phases were combined, washed with 1 M KH_2PO_4, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (30:19:1 EtOAc/hexanes/AcOH eluent) to provide acid **S47** (290 mg, 61% yield, R_F = 0.25 in 4:1 EtOAc/hexanes) as a colorless oil.

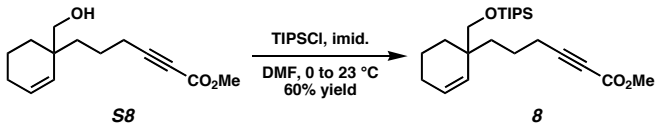
Acid S47: ^1H NMR (500 MHz, $CDCl_3$) δ 5.82 (dt, *J* = 4.0, 10.6 Hz, 1H); 5.68 (d, *J* = 9.8 Hz, 1H), 3.69 (s, 3H), 2.34 (t, *J* = 7.3 Hz, 2H), 2.18-2.13 (m, 1H), 1.78-1.41 (comp m, 9H), 1.31 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 129.3, 129.1, 91.7, 86.4, 85.9, 52.2, 46.8, 39.2, 30.8, 25.0, 22.8, 19.7, 19.2.



S47 *S18*

To a solution of acid **S47** (280 mg, 1.12 mmol) in 11.2 mL dioxane at 23 °C was added *N*-hydroxysuccinimide (142 mg, 1.23 mmol), then DCC (243 mg, 1.18 mmol). Solids immediately precipitated, and the resulting suspension was maintained at 23 ºC for 2 h, at which point Et_2NH (116 µl, 1.12 mmol) was added. After 18 h, the reaction mixture was diluted with Et_2O and filtered through Celite. The filtrate was concentrated and purified by flash chromatography (1:1 EtOAc/hexanes) to provide amide **S18** (197 mg, 58% yield, R_F = 0.45 in 1:1 EtOAc/hexanes) as a colorless oil.

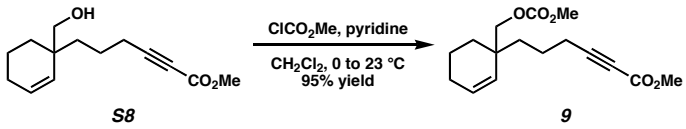
Amide S18: ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (dt, *J* = 3.2, 10.4 Hz, 1H), 5.68 (d, *J* = 10.0 Hz, 1H), 3.69 (s, 1H), 3.57 (q, *J* = 7.2 Hz, 2H), 3.41 (q, *J* = 7.2 Hz, 2H), 2.34 (t, *J* = 7.0 Hz, 2H), 2.19-2.13 (m, 1H), 2.00-1.96 (m, 2H), 1.79-1.38 (comp m, 7H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 154.1, 129.2, 129.1, 91.1, 74.7, 52.0, 46.7, 43.5, 39.4, 39.1, 30.9, 24.5, 23.1, 19.7, 19.4, 14.4, 12.9; IR (film) 2936, 1729, 1626, 1427, 1278, 1173 cm^{-1}; HRMS (ESI^+) *m/z* calc'd for $[C_{18}H_{27}NO_3 + Na]^+$: 328.1889, found 328.1889.



S8 *8*

To a solution of alcohol **S8** (21.6 mg, 0.0914 mmol) and imidazole (18.6 mg, 0.274 mmol) in 914 μl DMF at 0 °C was added TIPSCl (29.3 μl, 0.137 mmol). The reaction was stirred 5 min at 0 °C, then allowed to warm to room temperature and stirred. After 32 h, the mixture was quenched at 0 °C with H_2O (20 mL), and then extracted with Et_2O (2 x 20 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$, and concentrated to an oil. Purification by flash chromatography (30:1 hexanes/EtOAc eluent) provided silyl ether **8** (21.6 mg, 60% yield, R_F = 0.69 in 4:1 hexanes/EtOAc) as a pale yellow oil.

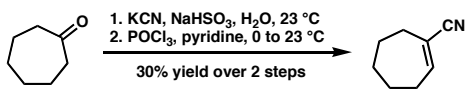
Silyl ether 8: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (app. dt, *J* = 3.7, 10.2 Hz, 1H), 5.41 (d, *J* = 10.2 Hz, 1H), 3.75 (s, 3H), 3.44 (ABq, *J* = 9.5 Hz, Δν = 27.2 Hz, 2H), 2.30 (t, *J* = 7.0 Hz, 2H), 1.97-1.91 (comp m, 2H), 1.62-1.52 (comp m, 5H), 1.51-1.44 (comp m, 2H), 1.43-1.34 (m, 1H), 1.08-1.02 (comp m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 132.3, 128.6, 90.2, 73.0, 69.2, 52.7, 39.8, 36.8, 29.6, 25.6, 22.7, 19.8, 19.2, 18.3, 12.2; IR (film) 2942, 2866, 2238, 1720, 1255 cm^{-1}.



S8 *9*

To a solution of alcohol **S8** (14.5 mg, 0.0614 mmol) in 614 ml CH_2Cl_2 at 0 °C was added methyl chloroformate (14.2 μl, 0.184 mmol), followed by pyridine (13.9 μl, 0.172 mmol). The resulting mixture was stirred at 0 °C for 45 min, at which point it was allowed to gradually warm to room temperature, and then water (20 mL) was added. The solution was extracted with Et_2O (2 x 20 mL), and the combined organic phases were washed with brine (15 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (9:1 hexanes/EtOAc eluent) to afford carbonate **9** (17.2 mg, 95% yield, R_F = 0.39 in 4:1 hexanes/EtOAc) as a pale yellow oil.

Carbonate 9: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (app. dt, *J* = 3.8, 10.2 Hz, 1H), 5.37 (d, *J* = 10.2 Hz, 1H), 4.00 (d, *J* = 10.5 Hz, 1H), 3.89 (d, *J* = 10.5 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 2.31 (t, *J* = 7.2 Hz, 2H), 2.04-1.89 (comp m, 2H), 1.65-1.41 (comp m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 154.4, 130.3, 130.1, 89.6, 73.3, 73.2, 55.0, 52.8, 37.9, 36.9, 29.5, 25.2, 22.5, 19.5, 18.8; IR (film) 2952, 2236, 1749, 1716, 1440, 1259 cm^{-1}.

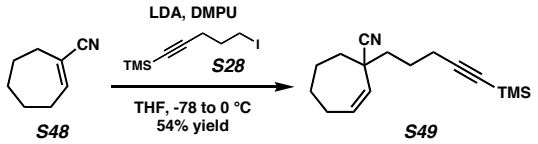


S36 *S48*

To a stirring solution of cycloheptanone (**S36**, 5.00 mL, 47.4 mmol) and KCN (3.31 g, 50.9 mmol) in 23.7 mL H_2O at 23 °C (maintained with an external water bath) was added a solution of $NaHSO_3$ (9.68 g, 50.9 mmol) in 23.7 mL H_2O dropwise over 5 min. The

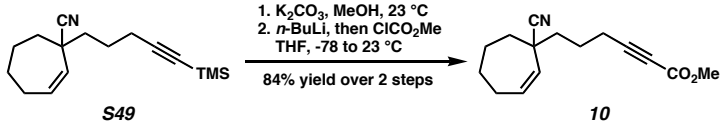
resulting heterogeneous mixture was stirred at 23 °C for 12 h. The reaction mixture was then filtered, and the solids were thoroughly washed with Et_2O (200 mL). The filtrate layers were separated, and the aqueous phase was extracted with Et_2O (2 x 75 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, and concentrated to an oil. The residue was purified by flash chromatography (5:1 hexanes/EtOAc eluent) to afford the desired cyanohydrin (2.77 g, ~80% pure, R_F = 0.16 in 2:1 hexanes/Et_2O), which was taken directly to the subsequent transformation.

To a solution of the cyanohydrin in 49.3 mL pyridine at 0 °C was added $POCl_3$ (11.6 mmol, 125 mmol) dropwise. The resulting mixture was stirred 10 min at 0 °C, and then it was allowed to warm to room temperature and stirred for an additional 5 h. The reaction was quenched at 0 °C by the dropwise addition of water (~30 mL), and then it was partitioned between CH_2Cl_2 (200 mL) and 1 N HCl (200 mL). The aqueous phase was extracted with CH_2Cl_2 (100 mL), and the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (9:1 hexanes/Et_2O eluent) provided nitrile **S48** (1.71 g, 30% yield over 2 steps, R_F = 0.58 in 4:1 hexanes/EtOAc) as a colorless oil. Spectroscopic analysis for nitrile **S48** was in agreement with the literature data.[6]



To a solution of *i*-Pr_2NH (156 μl, 1.11 mmol) in 1.00 mL THF at –78 °C was added *n*-BuLi (463 μl, 2.4 M in hexanes, 1.11 mmol) dropwise. The solution of LDA was stirred at –78 °C for 5 min and at 0 °C for 15 min. It was then cooled to –78 °C, and DMPU (146 μl, 1.21 mmol) was added. The resulting mixture was stirred for 30 min, and then a solution of nitrile **S48** (122 mg, 1.01 mmol) in 1.02 mL THF was introduced. After 20 min, iodide **S28** (279 μl, 1.31 mmol) was added, and the reaction was stirred at –78 °C for 10 min, at which point it was warmed to 0 °C. After 2 h, the reaction mixture was quenched with saturated NH_4Cl (30 mL) and extracted with Et_2O (3 x 40 mL). The combined organic layers were washed with saturated $NaHCO_3$ (30 mL), then brine (30 mL), dried over $MgSO_4$, and concentrated to an oil. Purification by flash chromatography (14:1 hexanes/Et_2O eluent) provided nitrile **S49** (140 mg, 54% yield, R_F = 0.53 in 4:1 hexanes/Et_2O) as a colorless oil.

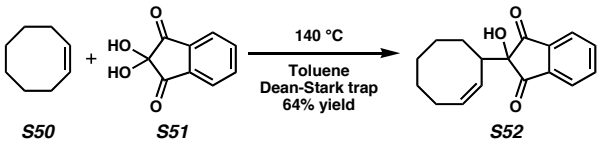
Nitrile S49: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (ddd, *J* = 5.5, 7.5, 11.0 Hz, 1H), 5.50 (d, *J* = 11.0 Hz, 1H), 2.39-2.17 (comp m, 2H), 2.29 (t, *J* = 6.7 Hz, 2H), 2.08-1.85 (comp m, 3H), 1.84-1.68 (comp m, 5H), 1.62 (ddd, *J* = 3.2, 10.7, 13.1 Hz, 1H), 1.46-1.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 131.6, 122.3, 106.4, 85.6, 41.6, 39.9, 36.3, 27.8, 27.2, 26.5, 24.1, 20.1, 0.3; IR (film) 2932, 2175, 1249, 843, 760 cm^{-1}.



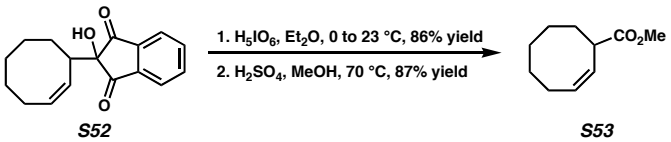
To a solution of nitrile **S49** (140 mg, 0.540 mmol) in 2.93 mL MeOH at 23 °C was added K_2CO_3 (89.6 mg, 0.648 mmol). The resulting mixture was maintained at room temperature for 5 h, at which point a mixture of saturated $NaHCO_3/H_2O$ was added (2:1, 75 mL). The solution was extracted with Et_2O (2 x 100 mL), and the organic phases were combined, washed with brine (75 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (14:1 hexanes/Et_2O eluent) to afford the desired alkyne (R_F = 0.47 in 9:1 hexanes/EtOAc) as a colorless oil, which was taken directly to the subsequent transformation.

To a solution of the alkyne (assume 0.540 mmol) in 5.40 mL THF at –78 °C was added *n*-BuLi (282 μl, 2.3 M in hexanes, 0.648 mmol) dropwise, and the resulting mixture was stirred at –78 °C for 1 h. Methyl chloroformate (108 μl, 1.40 mmol) was then introduced slowly, and the reaction was maintained at –78 °C for 1 h. The mixture was then allowed to gradually warm to room temperature, stirred for 5 min, and then it was quenched with saturated NH_4Cl (50 mL) and extracted with Et_2O (3 x 60 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (8:1 hexanes/EtOAc eluent) to provide ester **10** (111 mg, 84% yield over 2 steps, R_F = 0.42 in 4:1 hexanes/EtOAc) as a colorless oil.

Ester 10: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (ddd, *J* = 5.5, 7.5, 11.1 Hz, 1H), 5.47 (d, *J* = 11.1 Hz, 1H), 3.76 (s, 3H), 2.45-2.40 (comp m, 2H), 2.39-2.29 (m, 1H), 2.21 (ddt, *J* = 2.5, 7.5, 16.0 Hz, 1H), 2.07-1.74 (comp m, 8H), 1.60 (ddd, *J* = 3.5, 11.0, 14.5 Hz, 1H), 1.45-1.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 136.8, 131.2, 122.0, 88.3, 73.7, 52.9, 41.5, 39.9, 36.3, 27.7, 27.2, 26.5, 23.1, 18.9; IR (film) 2931, 2237, 1715, 1259 cm^{-1}; HRMS (ESI$^+$) *m/z* calc'd for $[C_{15}H_{19}NO_2 + Na]^+$: 268.1313, found 268.1313.



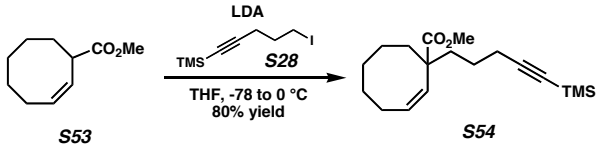
Cyclooctene **S52** was synthesized according to the procedure described by Gill and coworkers.[7] A solution of cyclooctene (**S50**, 1.10 mL, 8.43 mmol) and ninhydrin (**S51**, 500 mg, 2.81 mmol) in 50 mL toluene was heated to reflux with azeotropic removal of water using a Dean-Stark apparatus. The solution went from a dark green color to pale green, indicating consumption of the trione produced in situ. After 40 h, the reaction mixture was cooled to room temperature, and the solvent was removed via rotary evaporation. Purification of the residue by flash chromatography (3:1 hexanes/EtOAc eluent) afforded **S52**[7] (487 mg, 64% yield, R_F = 0.40 in 2:1 hexanes/EtOAc) as a pale yellow solid.



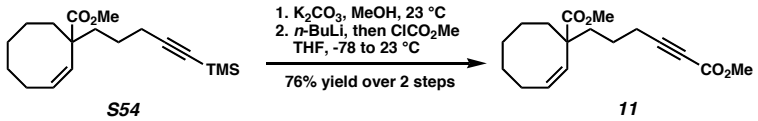
Oxidative cleavage was performed according to the procedure of Gill et al.[7] To a solution of alcohol **S52** (487 mg, 1.80 mmol) in 18.0 mL Et_2O at 0 °C was added periodic

acid (841 mg, 3.69 mmol) portionwise over 2 min. The resulting suspension was allowed to gradually warm to room temperature, being careful to prevent a sudden exothermic event by routinely cooling as the H_5IO_6 was dissolving. After stirring 5 h at 23 °C, the reaction mixture was filtered through a plug of celite (Et_2O eluent), and the filtrate was concentrated in vacuo. Purification by flash chromatography (4:1 CH_2Cl_2/hexanes → 2:1 hexanes/EtOAc eluent) afforded the desired carboxylic acid (237 mg, 86% yield, R_F = 0.36 in 2:1 hexanes/EtOAc) as a pale yellow oil, which was taken directly to the subsequent transformation.

To a solution of the carboxylic acid (237 mg, 1.54 mmol) in 7.70 mL MeOH at 23 °C was added conc. H_2SO_4 (52.0 μl). The solution was heated to 70 °C and stirred for 2 h, at which point it was cooled to 0 °C and quenched with saturated $NaHCO_3$ (40 mL). The mixture was extracted with Et_2O (2 x 75 mL), and the combined organic phases were washed with brine (40 mL), dried over $MgSO_4$, and concentrated to an oil. Purification of the residue by flash chromatography (19:1 hexanes/Et_2O eluent) provided ester **S53** (232 mg, 87% yield, R_F = 0.85 in 2:1 hexanes/EtOAc) as a pale yellow oil. Spectroscopic analysis of ester **S53** agreed with literature data.[8]



To a solution of *i*-Pr_2NH (170 μl, 1.21 mmol) in 3.00 mL THF at –78 °C was added *n*-BuLi (483 μl, 2.4 M in hexanes, 1.16 mmol) dropwise. The solution of LDA was stirred at –78 °C for 5 min and at 0 °C for 15 min. It was then cooled to –78 °C, and a solution of ester **S53** (176 mg, 1.05 mmol) in 2.25 mL THF was introduced. The mixture was stirred at –78 °C for 1 h, and then it was warmed to 0 °C and stirred for an additional 10 min to ensure deprotonation. The reaction mixture was cooled back to –78 °C, iodide **S28** (262 μl, 1.26 mmol) was added, and the reaction was stirred at –78 °C for 15 min, at which point it was warmed to 0 °C. After 2 h, the reaction mixture was quenched with saturated NH_4Cl (40 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ (30 mL), then brine (30 mL), dried over $MgSO_4$, and concentrated to an oil. Purification by flash chromatography (29:1 hexanes/EtOAc eluent) provided ester **S54** (257 mg, 80% yield, R_F = 0.46 in 9:1 hexanes/Et_2O) as a colorless oil.



To a solution of ester **S54** (340 mg, 1.11 mmol) in 9.27 mL MeOH at 23 °C was added K_2CO_3 (289 mg, 2.09 mmol). The resulting mixture was maintained at room temperature for 11 h, at which point a mixture of saturated $NaHCO_3/H_2O$ was added (2:1, 50 mL). The organic solvent was removed via rotary evaporation, and the residue was extracted with Et_2O (2 x 100 mL). The organic phases were combined, washed with brine (75 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash

chromatography (19:1 hexanes/Et_2O eluent) to afford the desired alkyne (R_F = 0.49 in 9:1 hexanes/EtOAc) as a pale yellow oil, which was taken directly to the subsequent transformation.

To a solution of the alkyne (assume 1.11 mmol) in 9.25 mL THF at –78 °C was added *n*-BuLi (488 μl, 2.4 M in hexanes, 1.17 mmol) dropwise, and the resulting mixture was stirred at –78 °C for 1 h. Methyl chloroformate (223 μl, 2.89 mmol) was then introduced slowly, and the reaction was maintained at –78 °C for 1 h. The mixture was then allowed to gradually warm to room temperature, stirred for 5 min, and then it was quenched with saturated NH_4Cl (50 mL) and extracted with Et_2O (3 x 60 mL). The organic phases were combined, washed with brine (50 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (10:1 hexanes/EtOAc eluent) to provide ester **11** (247 mg, 76% yield over 2 steps, R_F = 0.25 in 9:1 hexanes/EtOAc) as a colorless oil.

Ester 11: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61 (d, *J* = 11.8 Hz, 1H), 5.56 (ddd, *J* = 7.1, 8.7, 11.8 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 2.30 (t, *J* = 7.1 Hz, 2H), 2.27-2.19 (m, 1H), 2.18-2.05 (comp m, 2H), 1.84-1.47 (comp m, 10H), 1.44-1.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 154.4, 133.0, 128.9, 89.3, 73.3, 52.8, 52.2, 52.0, 41.1, 35.5, 27.1, 25.5, 24.4, 24.3, 23.0, 19.2; IR (film) 2949, 2236, 1720, 1257 cm^{-1}.

References

[1] a) Ruthenium catalyst: Trost, B. M.; Older, C. M. *Organometallics* **2002**, *21*, 2544-2546. b) Palladium catalyst: Ukai, T.; Kawazura, H.; Ishii, Y. *J. Organomet. Chem.* **1974**, *65*, 253-266.

[2] Bräse, S.; Wertal, H.; Frank, D.; Vidovic, D.; de Meijere, A. *Eur. J. Org. Chem*. **2005**, *19*, 4167-4178.

[3] Kuwajima, I.; Urabe, H. *Org. Synth*. **1988**, *66*, 87.

[4] Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. –H.; Grabowski, E. J. J. *Tetrahedron Lett*. **1995**, *36*, 5461-5464.

[5] Okamoto, S.; Ono, N.; Tani, K.; Yoshida, Y.; Sato, F. *J. Chem. Soc., Chem. Commun*. **1994**, 279-280.

[6] Pawlak, J. L.; Berchtold, G. A. *J. Org. Chem*. **1988**, *53*, 4063-4069.

[7] Gill, G. B.; Idris, M. S. H.; Kirollos, K. S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2355-2365.

[8] Whitesell, J. K.; Helbling, A. M. *J. Org. Chem*. **1980**, *45*, 4135-4139.