Acid Promoted Prins Cyclizations of Enol Ethers to form Tetrahydropyrans

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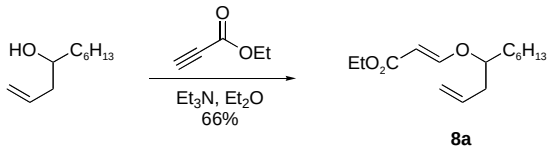
Supporting Information:

Representative experimental procedures and spectral data for **3**, **8a-g**, **9a-g**, **10a-g**, **11**, **14**, **16-19**, **23-33** are provided. Molecules **38-47** were generated in the course of structure determinations and their corresponding spectral data are included. This material is available free of charge via the Internet at http://pubs.acs.org.

General Procedures. Unless noted otherwise, materials were obtained from commercially available sources and used without further purification. All reaction solutions and mixtures were stirred using a magnetic stirrer and teflon coated stirbar, unless otherwise noted. All Prins cyclization reactions were conducted in flame-dried or oven-dried glassware under an atmosphere of dry nitrogen. Dichloromethane and triethylamine were distilled from CaH_2. Ether and tetrahydrofuran were distilled from sodium benzophenone ketyl.

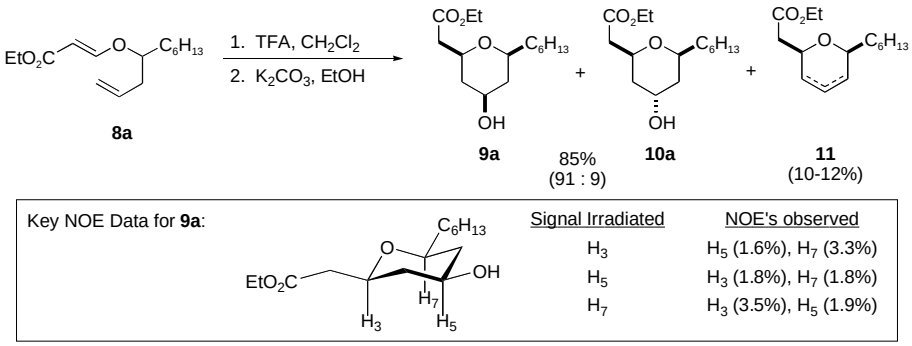
^{1}H NMR spectra were measured at 250, 400, and 500 MHz on Bruker DPX-250, DPX-400, and DRX-500 NMR instruments, respectively. Chemical shifts are reported in d with coupling constants reported in Hz. Residual chloroform (d 7.26 ppm), benzene (d 7.15 ppm), and acetone (d 2.05 ppm) were used as internal references for spectra measured in these solvents. ^{13}C NMR spectra were measured at 75, 100, or 125 MHz on Bruker DPX-250, DPX-400, and DRX-500 NMR instruments, respectively. Chloroform-d (d 77.0 ppm), benzene-d_6 (d 128.0 ppm), acetone-d_6 (d 29.8 ppm) were used as internal references for spectra measured in these solvents. Infrared spectra were measured with a Perkin-Elmer 1600 Series FT-IR spectrometer using thin film samples on NaCl plates. High resolution mass spectra were measured at 70 eV on a Kratos VG 70-250-S or Kratos MS-30 instruments at the The Ohio State University Mass Spectrometry Laboratory.

Analytical thin layer chromatography (TLC) was performed using EM Science Silica Gel 60 F_{254} glass plates coated with a 0.25 mm thickness of silica gel containing PF254 indicator. Compounds were visualized with UV light, *p*-anisaldehyde stain, or phosphomolybdic acid in EtOH. Flash chromatography was performed on SAI Silica Gel (Flash, 32-63 mm).

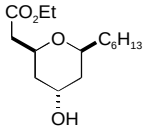


8a

Ethyl (*E*)-3-(1-decen-4-yl)oxy-2-propenoate (8a). To a yellow solution of ethyl propiolate (5.85 mL, 38.4 mmol) in Et_2O (160 mL) at room temperature was added Et_3N (8.05 mL, 57.8 mmol), resulting in the formation of a cloudy, light orange solution. After 10 min, 1-decen-4-ol was cannulated as a solution in Et_2O (10 mL) into the reaction solution, causing it to become cloudy, dark orange in appearance. Residual 1-decen-4-ol was transferred with Et_2O (2x10 mL). After being stirred for 2 d at room temperature, the reaction solution was concentrated. The residue was dissolved in CH_2Cl_2 and loaded onto 250 g of silica gel packed with hexanes. Fractions were then eluted (hexanes and then 2-10% EtOAc/hexanes) to afford desired enol ether **8a** (2.44 g, 25%), along with impure enol ether **8a** (5.05 g) and unreacted 1-decen-4-ol (0.56 g, 9%). Impure enol ether **8a** was purified by flash chromatography over 400 g of silica gel (2.5-5% EtOAc/hexanes) to yield enol ether **8a** (4.05 g, 41%). Overall yield of enol ether **8a** is 6.49 g (66%). Data for enol ether **8a**: ^{1}H NMR (400 MHz, $CDCl_3$) d 7.47 (d, 12.4 Hz, 1H), 5.76-5.66 (m, 1H), 5.19 (d, *J* = 12.4 Hz, 1H), 5.08-5.03 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.88 (dddd or app. quint, *J* = 6.1 Hz, 1H), 2.34-2.26 (m, 2H), 1.59-1.48 (m, 2H), 1.38-1.20(m, 11H), 0.83 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 168.0, 162.3, 133.0, 118.1, 96.9, 83.3, 59.5, 38.5, 33.7, 31.5, 29.0, 25.0, 22.4, 14.2, 13.9; IR (thin film, neat): 3084, 2931, 2860, 1708, 1643, 1619, 1466, 1372, 1326, 1284, 1202, 1132, 1049, 996, 955, 920, 832, 744, 726 cm^{-1}; HRMS calcd for $C_{15}H_{26}O_3Na$ (M^+) 277.1774, found 277.1787.

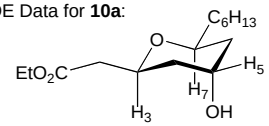


Ethyl ((*2S*, 4R*, 6S)-6-hexyl-4-hydroxytetrahydropyran-2-yl)-acetate (9a).** To a solution of enol ether **8a** (1.21 g, 4.76 mmol) in CH_2Cl_2 (48 mL) cooled to 0 °C in a round bottom flask was added trifluoroacetic acid (3.7 mL, 48 mmol) along the wall of the flask. The cooling bath was removed two minutes after the addition of trifluoroacetic acid was complete. After 35 minutes, the reaction solution was carefully poured into saturated aqueous $NaHCO_3$ (250 mL). CH_2Cl_2 (50 mL) was added, and this resulting mixture was stirred vigorously for 10 minutes. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to yield a pale yellow oil. This crude material was dissolved in ethanol (48 mL), and then K_2CO_3 (0.33 g, 2.4 mmol) was added. This reaction mixture was stirred for 19 h at room temperature, and then concentrated. The residue was dissolved in water (25 mL), brine (25 mL), and EtOAc (25 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (1 x 50 mL, 2 x 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford 1.22 g of a yellow oil. This crude material was purified by flash chromatography over 122 g of silica gel (10%-25% EtOAc/hexanes) to yield tetrahydropyran **9a** (0.795 g, 61%) along with a mixture of tetrahydropyrans **9a** and **10a** (0.289 g, 22%, 6:1 molar ratio by ^{1}H NMR, respectively), tetrahydropyran **10a** (0.026 g, 2%), and a mixture of dihydropyran **11** and an impurity (0.065 g, 1:1 molar ratio by ^{1}H NMR). It is notable that use of four equivalents of TFA gave similar results with longer reaction times, and reduction of the TFA to only two equivalents gave reduced yields of tetrahydropyrans. Data for tetrahydropyran **9a**: ^{1}H NMR (400 MHz, C_6D_6) d 3.96 (q, *J* = 7.1 Hz, 2H), 3.77 (dddd, *J* = 11.3, 7.7, 5.5, 2.0 Hz, 1H), 3.55 (dddd or app. tt, *J* = 10.9, 4.7 Hz, 1H), 3.12 (dddd, *J* = 11.2, 7.5, 4.5, 2.0 Hz, 1H), 2.55 (dd, *J* = 15.2, 7.8 Hz, 1H), 2.24 (dd, *J* = 15.2, 5.4 Hz, 1H), 2.14 (br s, 1H-OH), 1.84 (dddd or app. ddt, *J* = 12.1, 4.3, 2.1 Hz, 1H), 1.73 (dddd or app. ddt, *J* = 12.3, 4.3, 2.1 Hz, 1H), 1.58-1.21 (m, 10H), 1.13 (ddd or app. dt, *J* = 11.9, 11.3 Hz, 1H), 1.11 (ddd or app. dt, *J* = 12.2, 11.2 Hz, 1H), 0.97 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) d 170.9, 75.9, 72.4, 67.9, 60.2, 41.5, 41.3, 36.4, 32.2, 29.7, 25.9, 23.0, 14.3, 14.2; IR (thin film, neat): 3407, 2925, 2858, 1729, 1713, 1455, 1371, 1332, 1310, 1265, 1192, 1142, 1080, 1030, 934, 895, 862, 834, 789, 727 cm^{-1}; HRMS calcd for $C_{15}H_{28}O_4Na$ (M^+) 295.1880, found 295.1885. (Note: COSY and NOE data collected in C_6D_6.)



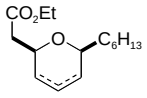
10a

Key NOE Data for **10a**:



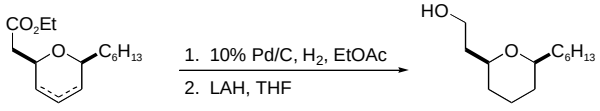
Signal Irradiated	NOE's observed
H_3	H_7 (2.1%)
H_5	$H_{4\text{-eq}}/H_{6\text{-eq}}$ (2.0%), $H_{4\text{-ax}}$ (1.5%), $H_{6\text{-ax}}$ (1.7%)
H_7	H_3 (2.4%)

Ethyl ((*2S*, 4S*, 6S)-6-hexyl-4-hydroxytetrahydropyran-2-yl)-acetate (10a).** Data for tetrahydropyran **10a**: ^{1}H NMR (400 MHz, acetone-d_6) d 4.20 (dddd, *J* = 11.6, 7.9, 5.7, 2.1 Hz, 1H), 4.15 (m, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.74 (m, 1H), 3.70 (d, *J* = 2.9 Hz, 1H-OH), 2.35 (dd, *J* = 14.7, 7.9 Hz, 1H), 2.30 (dd, *J* = 14.8, 5.6 Hz, 1H), 1.67 (dddd or app. ddt, *J* = 13.4, 2.9, 2.2 Hz, 1H), 1.61 (dddd or app. ddt, *J* = 13.5, 3.0, 2.1 Hz, 1H), 1.42-1.23 (m,, 12H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, acetone-d_6) d 171.5, 72.2, 69.5, 64.4, 60.4, 42.3, 39.5, 39.2, 37.0, 32.6, 26.2, 23.2, 14.6, 14.3 (Note, one -CH_2- signal in this ^{13}C spectrum is either overlapping with another -CH_2- signal or is buried under the -CD_3 signal of the solvent); IR (thin film from CH_2Cl_2): 3444, 2929, 2863, 1736, 1468, 1380, 1342, 1292, 1232, 1196, 1162, 1067, 1034, 994 cm^{-1}; HRMS calcd for $C_{15}H_{28}O_4Na$ (M^+) 295.1880, found 295.1893. (Note: COSY and NOE data collected in acetone-d_6.)



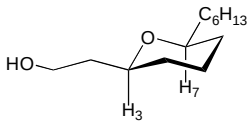
11

Ethyl ((*2R*, 6S)-6-hexyl-3,4-dihydropyran-2-yl)-acetate** and **ethyl ((*2S*, 6S**)-6-hexyl-4,5-dihydropyran-2-yl)-acetate (11).** Data for dihydropyrans **11**: HRMS calcd for $C_{15}H_{26}O_3Na$ (M^+) 277.1774, found 277.1783.



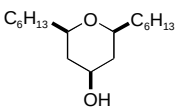
11 **38**

Key NOE Data for **38**:



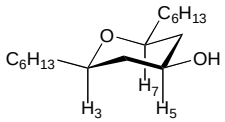
Signal Irradiated	NOE's observed
H_3	H_7 (2.0%)
H_7	H_3 (2.2%)

Ethyl ((*2S*, 6S)-6-hexyl-tetrahydropyran-2-yl)-acetate (38).** Data for tetrahydropyran **38**: ^{1}H NMR (400 MHz, $CDCl_3$) d 3.80-3.76 (m, 2H), 3.56 (dddd or app. tdd, *J* = 9.1, 3.1, 2.1 Hz, 1H), 3.34-3.28 (m, 1H), 2.51 (br s, 1H-OH), 1.85-1.63 (m, 3H), 1.59-1.13 (m, 15H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 79.1, 78.2, 62.1, 37.9, 36.5, 31.8, 31.7, 31.4, 29.3, 25.6, 23.5, 22.6, 14.1, ; IR (thin film from $CDCl_3$): 3409, 2931, 2857, 1456, 1441, 1376, 1344, 1327, 1259, 1196, 1145, 1082, 1054 cm^{-1}; HRMS calcd for $C_{13}H_{26}O_2Na$ (M^+) 237.1825, found 237.1819. (Note: NOE data collected in $CDCl_3$.)



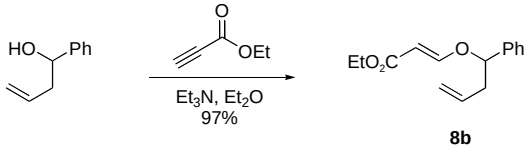
3

Key Coupling Constants for **3**:



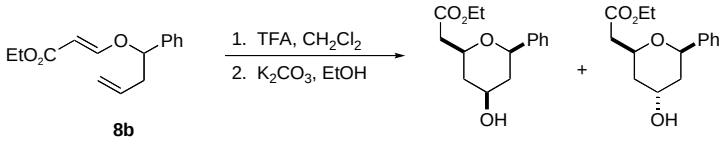
J (H_3-$H_{4\text{-ax}}$) = J (H_7-$H_{6\text{-ax}}$) = 11.2 Hz
J (H_5-$H_{4\text{-ax}}$) = J (H_5-$H_{6\text{-ax}}$) = 11.0 Hz

(2,4,6-*cis*)-2,6-dihexyl-4-hydroxytetrahydropyran (3). Data for tetrahydropyran **3**: ^{1}H NMR (400 MHz, $CDCl_3$) d 3.76 (dddd or app. tt, J = 11.0, 4.8 Hz, 1H), 3.25-3.20 (m, 2H), 1.92 (ddd, J = 12.1, 4.7, 2.0 Hz, 2H), 1.60-1.52 (m,2H), 1.46-1.27 (m, 18H), 1.11 (ddd or app. dt, J = 12.3, 11.2 Hz, 2H), 0.88 (t, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) d 75.5, 68.5, 41.5, 36.1, 31.8, 29.2, 25.6, 22.6, 14.1, ; IR (thin film from $CDCl_3$): 3358, 2928, 2856, 1466, 1370, 1326, 1261, 1141, 1082, 1048, 899, 849, 724 cm^{-1}; HRMS calcd for $C_{17}H_{34}O_2Na$ (M^+) 293.2451, found 293.2466.



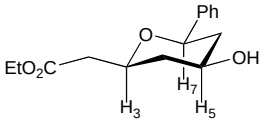
8b

Ethyl (*E*)-3-(1-phenyl-3-buten-1-yl)oxy-2-propenoate (8b). Enol ether **8b** was prepared in 97% yield from 1-phenyl-3-buten-1-ol and ethyl propiolate using the procedure described for the synthesis of enol ether **8a**. Data for enol ether **8b**: ^{1}H NMR (400 MHz, $CDCl_3$) d 7.42 (d, J = 12.5 Hz, 1H), 7.26-7.15 (m, 5H), 5.67-5.57 (m, 1H), 5.13 (d, J = 12.5 Hz, 1H), 5.00-4.96 (m, 2H), 4.78 (dd, J = 7.5, 5.7 Hz, 1H), 4.03-3.95 (m, 2H), 2.63-2.55 (m, 1H), 2.47-2.40 (m, 1H), 1.10 (qd, J = 7.1, 1.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 167.5, 161.2, 139.4, 132.8, 128.5, 128.1, 126.0, 118.1, 98.4, 83.7, 59.5, 41.6, 14.1; IR (thin film, neat): 3084, 3037, 2978, 2943, 2908, 1713, 1643, 1625, 1496, 1455, 1367, 1326, 1284, 1196, 1132, 1044, 997, 961, 920, 832, 761, 703 cm^{-1}; HRMS calcd for $C_{15}H_{18}O_3Na$ (M^+) 269.1148, found 269.1139.



8b **9b** 77% (95 : 5) **10b**

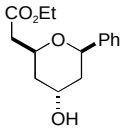
Key NOE Data for **9b**:



Signal Irradiated	NOE's observed
H_3	H_5 (1.5%), H_7 (3.2%)
H_5	H_3 (1.6%), H_7 (1.7%)
H_7	H_3 (3.3%), H_5 (1.7%)

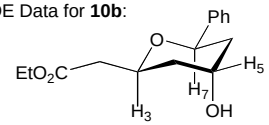
Ethyl ((*2S*, 4S*, 6R)-4-hydroxy-6-phenyltetrahydropyran-2-yl)-acetate (9b).** Tetrahydropyrans **9b** and **10b** were prepared from enol ether **8b** using the procedure described for synthesis of tetrahydropyrans **9a** and **10a**. Data for tetrahydropyran **9b**: ^{1}H NMR (500 MHz, C_6D_6) d 7.29-7.28 (m, 2H), 7.16-7.14 (m, 2H), 7.08-7.05 (m, 1H), 4.14, (dd, J = 11.4, 1.6 Hz, 1H), 3.91 (qd, J = 7.1, 1.8 Hz, 2H), 3.85 (dddd, J = 11.2, 7.4, 5.6, 1.8 Hz, 1H), 3.56 (dddd or app. tt, 10.9, 4.6 Hz, 1H), 2.61 (dd, J = 15.3, 7.5 Hz, 1H), 2.28 (dd, J = 15.3, 5.5 Hz, 1H), 1.93 (ddd, J = 12.6, 4.3, 2.2 Hz, 1H), 1.91 (br s, 1H), 1.85 (ddd, J = 12.2, 4.6, 2.3 Hz, 1H), 1.35 (ddd or app. dt, J = 12.0, 11.5 Hz, 1H), 1.17 (ddd or app. dt, J = 11.7, 11.4 Hz, 1H), 0.91 (t, J = 7.1

Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) d 170.8, 142.8, 128.4, 127.5, 126.1, 77.6, 72.8, 67.9, 60.3, 43.4, 41.4, 40.8, 14.2; IR (thin film, neat): 3419, 3065, 3031, 2976, 2943, 2921, 2865, 1730, 1497, 1453, 1392, 1370, 1326, 1309, 1270, 1210, 1187, 1149, 1077, 1066, 1027, 988, 933, 878, 756, 700 cm^{-1}; HRMS calcd for $C_{15}H_{20}O_4Na$ (M^+) 287.1254, found 287.1252. (Note: COSY and NOE data collected in C_6D_6.)



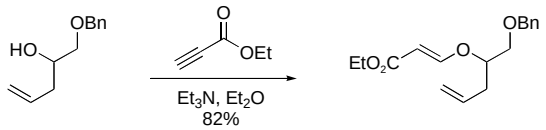
10b

Key NOE Data for **10b**:



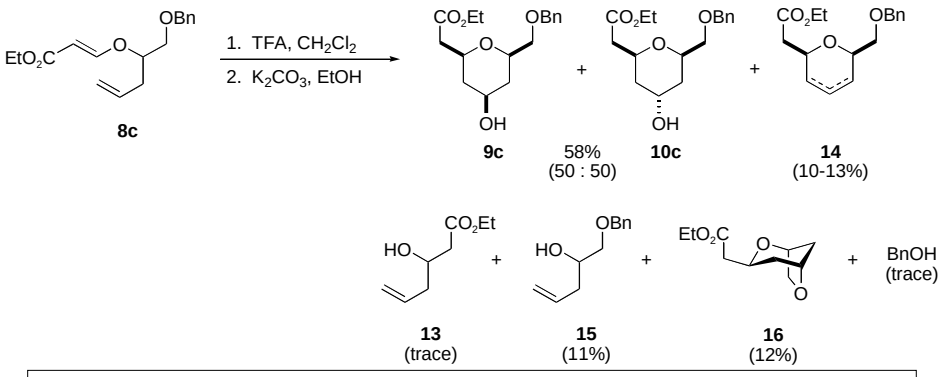
Signal Irradiated	NOE's observed
H_3	H_7 (2.0%)
H_5	$H_{4\text{-eq}}/H_{6\text{-ax}}$ (1.8%), $H_{4\text{-ax}}$ (1.0%), $H_{6\text{-eq}}$ (0.9%)
H_7	H_3 (1.8%)

Ethyl ((*2S*, 4R*, 6R)-4-hydroxy-6-phenyltetrahydropyran-2-yl)-acetate (10b).** Data for tetrahydropyran **10b**: ^{1}H NMR (250 MHz, C_6D_6) d 7.37-7.34 (m, 2H), 7..20-7.01 (m, 3H), 4.98, (dd, *J* = 11.4, 2.0 Hz, 1H), 4.57 (dddd, *J* = 11.4, 7.6, 5.6, 2.0 Hz, 1H), 3.92 (q, *J* = 7.1 2H), 3.86-3.75 (m, 1H), 2.60 (dd, *J* = 15.1, 7.5 Hz, 1H), 2.39 (dd, *J* = 15.1, 5.6 Hz, 1H), 1.67 (ddd, *J* = 13.8, 5.0, 2,5 Hz, 1H), 1.51 (ddd, *J* = 13.7, 5.1, 2.8 Hz, 1H), 1.37-1.23 (m, 3H), 0.91 (t, *J* = 7.1 Hz, 3H); IR (thin film from C_6D_6): 3452, 3065, 2976, 2921, 1735, 1497, 1453, 1370, 1337, 1298, 1270, 1215, 1187, 1160, 1082, 1060, 1027, 983, 922, 850, 756, 700 cm^{-1}; HRMS calcd for $C_{15}H_{20}O_4Na$ (M^+) 287.1254, found 287.1248. (Note: COSY and NOE data collected in C_6D_6 at 500 MHz.)

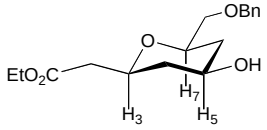


8c

Ethyl (*E*)-3-(1-benzyloxy-4-penten-2-yl)oxy-2-propenoate (8c). Enol ether **8c** was prepared in 82% yield from 1-benzyloxy-4-penten-2-ol and ethyl propiolate using the procedure described for the synthesis of enol ether **8a**. Data for enol ether **8c**: ^{1}H NMR (400 MHz, $CDCl_3$) d 7.57 (d, *J* = 12.4 Hz, 1H), 7.34-7.24 (m, 5H), 5.78-5.68 (m, 1H), 5.28 (d, *J* = 12.4 Hz, 1H), 5.12-5.07 (m, 2H), 4.51 (s, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.10 (dddd or app. qd, *J* = 6.2, 3.8 Hz, 1H), 3.56 (dd, *J* = 10.6, 3.8 Hz, 1H), 3.51 (dd, *J* = 10.6, 6.3 Hz, 1H), 2.39 (ddd or app td, *J* = 6.7, 1.1 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 167.8, 162.4, 137.6, 132.5, 128.3, 127.6, 127.5, 118.4, 97.5, 81.9, 73.3, 71.1, 59.5, 35.5, 14.3; IR (thin film, neat): 3084, 3025, 2978, 2931, 2908, 2860, 1954, 1896, 1713, 1696, 1643, 1631, 1496, 1455, 1367, 1326, 1284, 1202, 1132, 1049, 996, 955, 920, 832, 738, 697 cm^{-1}; HRMS calcd for $C_{17}H_{22}O_4Na$ (M^+) 313.1410, found 313.1405.

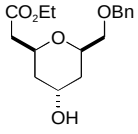


Key NOE Data for **9c**:



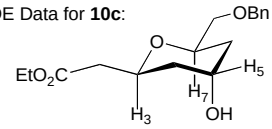
Signal Irradiated	NOE's observed
H_3	H_5 (1.9%), H_7/H_8 (3.5%)
H_5	H_3 (2.0%), H_7/H_8 (1.6%)
H_7/H_8	H_3 (3.4%), H_5 (1.0%)

Ethyl ((*2S*, 4S*, 6R)-4-hydroxy-6-(benzyloxy)methyltetrahydropyran-2-yl)-acetate (9c).** Tetrahydropyrans **9c** and **10c** were prepared from enol ether **8c** using the procedure described for synthesis of tetrahydropyrans **9a** and **10a**. Data for tetrahydropyran **9c**: ^{1}H NMR (400 MHz, C_6D_6) d 7.28-7.27 (m, 2H), 7.19-7.15 (m, 2H), 7.10-7.07 (m, 1H), 4.38, 4.34 (AB q, *J* = 12.2 Hz, 2H), 3.93 (qd, *J* = 7.1, 1.5 Hz, 2H), 3.74 (dddd, *J* = 11.3, 7.4, 5.6, 1.8 Hz, 1H), 3.52 (dddd or app. tt, *J* = 10.9, 4.6 Hz, 1H), 3.46-3.41 (m, 2H), 3.32 (dd, 12.7, 7.2 Hz, 1H), 2.55 (dd, *J* = 15.3, 7.6 Hz, 1H), 2.31 (br s, 1H), 2.23 (, dd, *J* = 15.3, 5.4 Hz, 1H), 1.84-1.78 (m,, 2H), 1.21 (ddd or app. dt, *J* = 12.0, 11.1 Hz, 1H), 1.14 (ddd or app. dt, *J* = 12.0, 11.3 Hz, 1H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) d 171.0, 139.3, 128.7, 128.0, 127.8, 75.7, 73.6, 73.5, 72.8, 67.7, 60.5, 41.5, 41.2, 38.2, 14.4; IR (thin film from C_6D_6): 3442, 3063, 3030, 2984, 2939, 2919, 2863, 1732, 1496, 1454, 1372, 1332, 1306, 1266, 1192, 1156, 1100, 1028, 950, 861, 822, 739, 699 cm^{-1}; HRMS calcd for $C_{17}H_{24}O_5Na$ (M^+) 331.1516, found 331.1541. (Note: COSY and NOE data collected in C_6D_6.)



10c

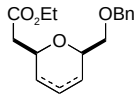
Key NOE Data for **10c**:



Signal Irradiated	NOE's observed
H_3	H_7 (3.9%)
H_5/OCH_2CH_3	$H_{4\text{-eq}}/H_{6\text{-eq}}$ (3.0%), $H_{4\text{-ax}}$ (2.2%), $H_{6\text{-ax}}$ (2.2%)
H_7	H_3 (3.9%)

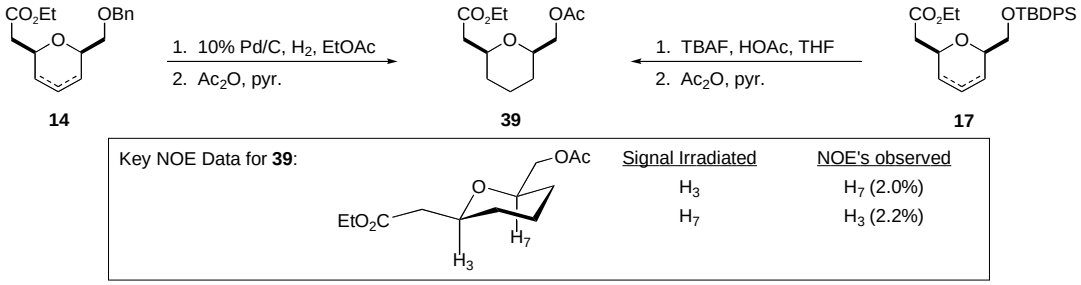
Ethyl ((*2S*, 4R*, 6R)-4-hydroxy-6-(benzyloxy)methyltetrahydropyran -2-yl)-acetate (10c).** Data for tetrahydropyran **10c**: ^{1}H NMR (400 MHz, C_6D_6) d 7.29-7.27 (m, 2H), 7.18-7.15 (m, 2H), 7.10-7.06 (m, 1H), 4.47 (dddd, *J* = 11.6, 7.6, 5.7, 1.9 Hz, 1H), 4.41, 4.37 (AB q, *J* = 12.2 Hz, 2H), 4.22 (dddd, *J* = 11.8, 5.2, 4.7, 1.9 Hz, 1H), 3.98 (m, 1H), 3.94 (qd, *J* = 7.2, 1.1 Hz, 2H), 3.45 (dd, *J* = 10.3, 5.5 Hz, 1H), 3.36 (dd, *J* = 10.3, 4.6 Hz, 1H), 2.53 (dd, *J* = 15.1, 7.8 Hz, 1H), 2.43 (br s, 1H), 2.25 (dd, *J* = 15.1, 5.4 Hz, 1H), 1.60-1.57 (m, 2H), 1.39 (ddd or app. td, *J* = 11.7, 2.5 Hz, 1H), 1.26 (ddd or app. td, *J* = 11.3, 2.6 Hz, 1H), 0.94 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) d 171.4, 139.5, 128.6, 128.4, 127.7, 73.9, 73.4, 71.9, 69.1, 64.2, 60.5, 41.9, 38.5, 35.4, 14.4; IR (thin film from C_6D_6): 3450, 3062, 3029, 2980, 2915, 2871, 1736, 1496, 1454, 1382, 1370, 1343, 1290, 1236, 1199, 1164, 1097, 1064, 1028, 993, 924, 855, 739, 699

cm^{-1}; HRMS calcd for $C_{17}H_{24}O_5Na$ (M^+) 331.1516, found 331.1528. (Note: COSY and NOE data collected in C_6D_6.)

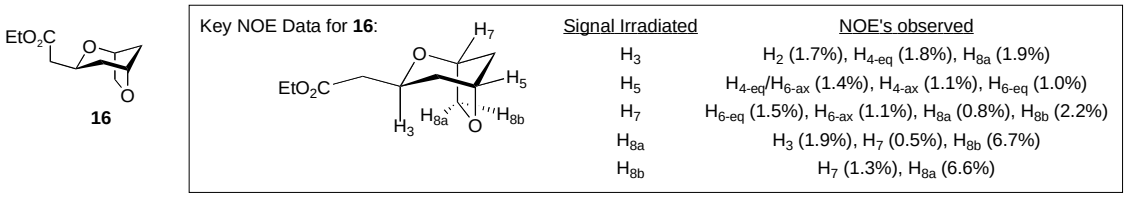


14

Ethyl ((*2R*, 6R)-6-(benzyloxy)methyl-3,4-dihydropyran -2-yl)-acetate** and **ethyl ((*2S*, 6R**)-6-(benzyloxy)methyl-4,5-dihydropyran -2-yl)-acetate (14).** Data for dihydropyrans **14**: IR (thin film, neat): 3032, 2981, 2900, 2860, 1738, 1651, 1625, 1496, 1454, 1430, 1392, 1371, 1345, 1277, 1248, 1171, 1094, 1028, 938, 859, 803, 737, 698 cm^{-1}; HRMS calcd for $C_{17}H_{22}O_4Na$ (M^+) 313.1410, found 313.1418.

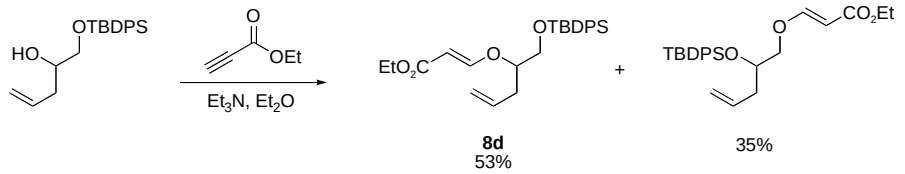


Ethyl ((*2S*, 6R)-6-(acetoxy)methyltetrahydropyran -2-yl)-acetate (39).** Data for tetrahydropyran **39**: ^{1}H NMR (400 MHz, $CDCl_3$) d 4.13 (q, *J* = 7.1 Hz, 2H), 4.05-3.98 (m, 2H), 3.78 (dddd, *J* = 11.2, 7.2, 6.0, 1.8 Hz, 1H), 3.59 (dddd, *J* = 11.5, 6.2, 4.4, 1.9 Hz, 1H), 2.56 (dd, *J* = 15.1, 7.3 Hz, 1H), 2.38 (dd, *J* = 15.1, 6.0 Hz, 1H), 2.04 (s, 3H), 1.90-1.84 (m, 1H), 1.67-1.62 (m, 1H), 1.61-1.49 (m, 2H), 1.30-1.18 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 171.2, 170.9, 75.6, 74.4, 67.2, 60.3, 41.6, 30.8, 27.2, 22.8, 20.9, 14.2; IR (thin film from $CDCl_3$): 2931, 2860, 1737, 1443, 1373, 1343, 1284, 1237, 1196, 1161, 1090, 1044 cm^{-1}; HRMS calcd for $C_{12}H_{20}O_5Na$ (M^+) 267.1203, found 267.1217. (Note: COSY and NOE data collected in $CDCl_3$.)

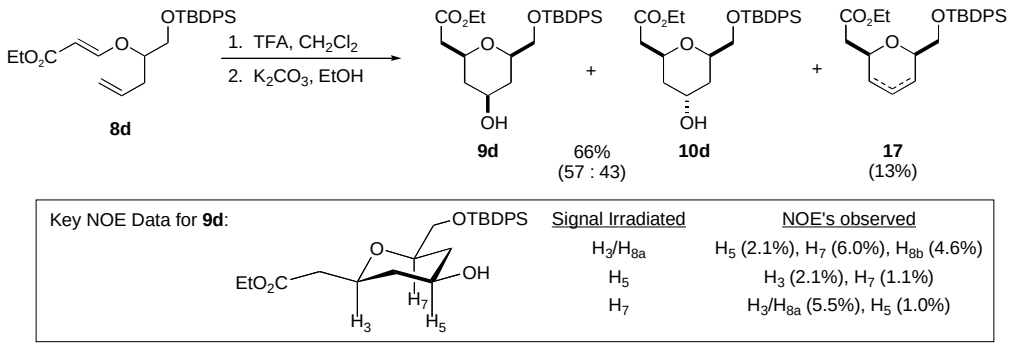


Ethyl ((*1S*, 3S*, 5R)-(2,6-dioxabicyclo-[3.2.1]-oct-3-yl))-acetate (16).** Data for bicycle **16**: ^{1}H NMR (400 MHz, $CDCl_3$) d 4.52 (dd or app. t, *J* = 5.5 Hz, 1H), 4.47 (m, 1H), 4.40-4.34 (m, 1H), 4.19 (d, *J* = 10.0 Hz, 1H), 4.16-4.09 (m, 2H), 3.79 (dd, *J* = 10.0, 3.0 Hz, 1H), 2.48 (dd, *J* = 14.9, 7.7 Hz, 1H), 2.40 (dd, *J* = 14.9, 5.2 Hz, 1H), 1.86-1.80 (m, 2H), 1.79-1.70 (m, 1H), 1.38 (dd, *J* = 12.6, 11.2 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 170.9, 75.3, 73.9, 71.2, 67.2, 60.5, 41.1, 38.4, 37.7, 14.2; IR (thin film from $CDCl_3$): 2956, 2883, 1736,

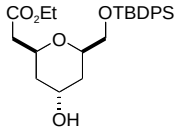
1472, 1446, 1370, 1320, 1300, 1286, 1273, 1232, 1203, 1162, 1144, 1088, 1062, 1050, 1028, 1001, 979, 963, 936, 904, 861, 838, 816, 789 cm^{-1}; HRMS calcd for $C_{10}H_{16}O_4Na$ (M^+) 223.0941, found 223.0949. (Note: COSY and NOE data collected in $CDCl_3$.)



Ethyl (*E*)-3-(1-*tert*-butyldiphenylsilyloxy-4-penten-2-yl)oxy-2-propenoate (8d). Enol ether **8d** was prepared in 53% yield from 1-*tert*-butyldiphenylsilyloxy-4-penten-2-ol and ethyl propiolate using the procedure described for the synthesis of enol ether **8a**. Data for enol ether **8d**: ^{1}H NMR (400 MHz, $CDCl_3$) d 7.71-7.66 (m, 4H), 7.62 (d, *J* = 12.3 Hz, 1H), 7.47-7.37 (m, 6H), 5.78-5.68 (m, 1H), 5.29 (d, *J* = 12.3 Hz, 1H), 5.12-5.07 (m, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.08-4.02 (m, 1H), 3.75-3.68 (m, 2H), 2.37 (t, *J* = 6.7 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) d 167.9, 163.1, 135.5, 132.9, 132.8, 132.7, 129.78, 129.77, 127.7, 118.3, 97.2, 83.9, 65.3, 59.5, 35.2, 26.7, 19.1, 14.4; IR (thin film, neat): 3072, 3037, 2954, 2931, 2860, 1708, 1643, 1472, 1425, 1390, 1367, 1326, 1284, 1202, 1132, 1114, 1049, 996, 955,920, 826, 803, 744, 703, 614 cm^{-1}; HRMS calcd for $C_{26}H_{34}O_4SiNa$ (M^+) 461.2119, found 461.2139.

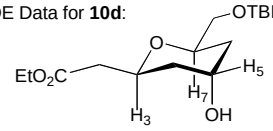


Ethyl ((*2S*, 4S*, 6R)-4-hydroxy-6-(*tert*-butyldiphenylsilyl)oxy-tetrahydropyran-2-yl)-acetate (9d).** Tetrahydropyrans **9d** and **10d** were prepared from enol ether **8d** using the procedure described for synthesis of tetrahydropyrans **9a** and **10a**. Data for tetrahydropyran **9d**: ^{1}H NMR (400 MHz, C_6D_6) d 7.86-7.77 (m, 4H), 7.31-7.18 (m, 6H), 4.01-3.89 (m, 2H), 3.75-3.69 (m, 1H), 3.73 (dd, *J* = 10.6, 5.6 Hz, 1H), 3.61 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.41 (dddd or app. tdd, *J* = 11.0, 6.3, 4.6 Hz, 1H), 3.35 (dddd, *J* = 11.5, 5.5, 4.4, 1.6 Hz, 1H), 2.52 (dd, *J* = 15.4, 7.5 Hz, 1H), 2.20 (dd, *J* = 15.4, 5.4 Hz, 1H), 1.72 (app. dd, *J* = 12.1, 3.5 Hz, 2H), 1.16 (s, 9H), 1.12 (ddd or app. q, *J* = 11.7 Hz, 1H), 1.02 (ddd or app. dt, *J* = 12.0, 11.4 Hz, 1H), 0.94 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) d 170.9, 136.38, 136.36, 134.40, 134.37, 130.21, 130.18, 128.5, 76.9, 72.7, 67.9, 67.7, 60.5, 41.6, 41.3, 37.8, 27.3, 19.8, 14.5; IR (thin film from CH_2Cl_2/acetone-d_6): 3412, 3071, 3048, 2961, 2932, 2857, 1738, 1589, 1472, 1463, 1428, 1391, 1372, 1330, 1306, 1264, 1191, 1153, 1136, 1113, 1029, 946, 860, 824, 802, 741, 703 cm^{-1}; HRMS calcd for $C_{26}H_{36}O_5SiNa$ (M^+) 479.2224, found 479.2234. (Note: COSY and NOE data collected in C_6D_6.)



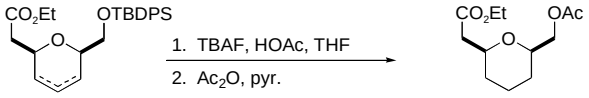
10d

Key NOE Data for **10d**:



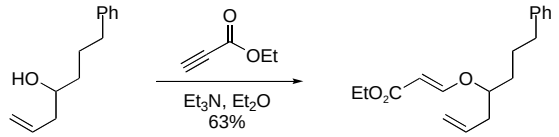
Signal Irradiated	NOE's observed
H_3	H_7 (3.9%), $H_{4\text{-eq}}$/$H_{6\text{-eq}}$ (2.0%)
H_5	$H_{4\text{-eq}}$/$H_{6\text{-eq}}$ (3.6%), $H_{4\text{-ax}}$ (2.5%), $H_{6\text{-ax}}$ (2.6%)
H_7	H_3 (4.1%), $H_{4\text{-eq}}$/$H_{6\text{-eq}}$ (1.8%), $H_{6\text{-ax}}$ (0.8%)

Ethyl ((*2S*, 4R*, 6R)-4-hydroxy-6-(*tert*-butyl-diphenylsilyl)oxytetrahydropyran-2-yl)-acetate (10d).** Data for tetrahydropyran **10d**: ^{1}H NMR (400 MHz, C_6D_6) d 7.85-7.79 (m, 4H), 7.29-7.20 (m, 6H), 4.42 (dddd, *J* = 11.5, 7.6, 5.5, 1.8 Hz, 1H), 4.08 (m, 1H), 4.02-3.90 (m, 2H), 3.81 (m, 1H), 3.71 (dd, *J* = 10.6, 5.4 Hz, 1H), 3.64 (dd, *J* = 10.6, 4.4 Hz, 1H), 2.51 (dd, *J* = 15.2, 7.6 Hz, 1H), 2.20 (dd, *J* = 15.2, 5.5 Hz, 1H), 1.47-1.40 (m, 2H), 1.34 (ddd, *J* = 13.8, 11.5, 2.6 Hz, 1H), 1.22-1.13 (m, 1H), 1.17 (s, 9H), 1.02 (ddd or app. dt, *J* = 12.0, 11.4 Hz, 1H), 0.94 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 171.2, 135.7, 135.6, 133.8, 133.7, 129.51, 129.50, 127.5, 72.4, 68.3, 67.1, 64.3, 60.4, 41.4, 38.1, 34.6, 26.8, 19.3, 14.2; IR (thin film from $CDCl_3$): 3436, 3072, 3048, 2954, 2931, 2860, 1737, 1472, 1425, 1390, 1296, 1273, 1196, 1161, 1138, 1114, 1067, 1026, 1008, 938, 820, 797, 744, 703 cm^{-1}; HRMS calcd for $C_{26}H_{36}O_5SiNa$ (M^+) 479.2224, found 479.2229. (Note: COSY and NOE data collected in C_6D_6.)



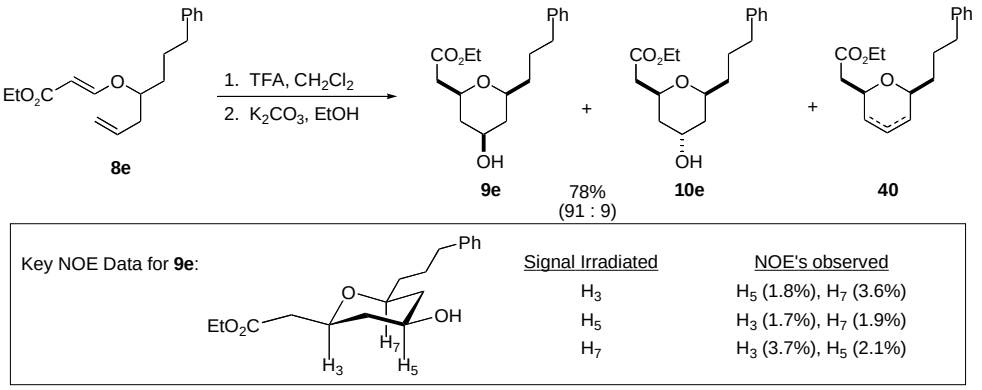
17 **39**

Ethyl ((*2R*, 6R)-6-(*tert*-butyl-diphenylsilyl)oxy-3,4-dihydropyran-2-yl)-acetate** and **ethyl ((*2S*, 6R**)-6-(*tert*-butyl-diphenylsilyl)oxy-4,5-dihydropyran-2-yl)-acetate (17).** Data for dihydropyran **17**: HRMS calcd for $C_{26}H_{34}O_4SiNa$ (M^+) 461.2119, found 461.2110. Data for tetrahydropyran **39**: (vide supra).

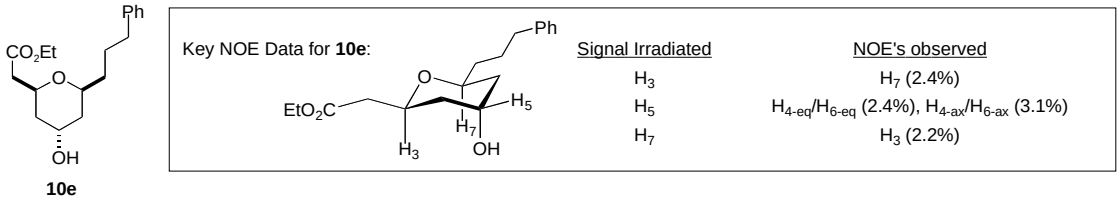


8e

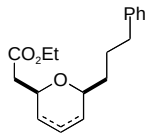
Ethyl (*E*)-3-(7-phenyl-1-hepten-4-yl)oxy-2-propenoate (8e). Enol ether **8e** was prepared in 63% yield from 1-phenyl-3-buten-1-ol and ethyl propiolate using the procedure described for the synthesis of enol ether **8a**. Data for enol ether **8e**: ^{1}H NMR (400 MHz, $CDCl_3$) d 7.50 (d, *J* = 12.4 Hz, 1H), 7.30-7.26 (m, 2H), 7.20-7.15 (m, 3H), 5.78-5.68 (m, 1H), 5.24 (d, *J* = 12.4 Hz, 1H), 5.11-5.06 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.94 (dddd or app. quint, *J* = 5.8 Hz, 1H), 2.62 (t, *J* = 7.0 Hz, 2H), 2.39-2.30 (m, 2H), 1.77-1.59 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 168.1, 162.3, 141.8, 132.9, 128.4, 128.3, 125.9, 118.4, 97.2, 83.2, 59.7, 38.6, 35.6, 33.4, 26.9, 14.4; IR (thin film, neat): 3084, 3025, 2978, 2943, 2860, 1708, 1643, 1619, 1496, 1455, 1367, 1326, 1284, 1202, 1132, 1044, 997, 955, 920, 832, 750, 703 cm^{-1}; HRMS calcd for $C_{18}H_{24}O_3Na$ (M^+) 311.1618, found 311.1604.



Ethyl ((*2S*, 4R*, 6S)-4-hydroxy-6-(3-phenyl)propyl-tetrahydropyran-2-yl)-acetate (9e).** Tetrahydropyrans **9e** and **10e** were prepared from enol ether **8e** using the procedure described for synthesis of tetrahydropyrans **9a** and **10a**. In one run, dihydropyrans **40**, contaminated with impurities, were isolated in 6% yield. Data for tetrahydropyran **9e**: ^{1}H NMR (400 MHz, C_6D_6) d 7.19-7.05 (m, 5H), 3.95 (q, *J* = 7.1 Hz, 2H), 3.70 (dddd, *J* = 11.3, 7.9, 5.3, 1.9 Hz, 1H), 3.47 (dddd or app. tt, *J* = 10.9, 4.7 Hz, 1H), 3.08-3.02 (m, 1H), 2.53 (dd, *J* = 15.2, 7.9 Hz, 1H), 2.46 (t, *J* = 7.6 Hz, 2H), 2.21 (dd, *J* = 15.2, 5.3 Hz, 1H), 1.80-1.67 (m, 3H), 1.63-1.45 (m, 3H), 1.37-1.24 (m, 1H), 1.07 (ddd or app. dt, *J* = 11.7, 11.4 Hz, 1H), 1.02 (ddd or app. dt, *J* = 12.0, 11.3 Hz, 1H), 0.94 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) d 170.9, 142.8, 128.7, 128.5, 126.0, 75.6, 72.4, 67.8, 60.2, 41.41, 41.36, 41.1, 36.1, 35.8, 27.8, 14.2; IR (thin film from C_6D_6): 3412, 3082, 3061, 3029, 2987, 2955, 2934, 2859, 1733, 1605, 1493, 1451, 1398, 1371, 1334, 1307, 1265, 1190, 1142, 1094, 1030, 860, 802, 749, 701 cm^{-1}; HRMS calcd for $C_{18}H_{26}O_4Na$ (M^+) 329.1723, found 329.1718. (Note: COSY and NOE data collected in C_6D_6.)

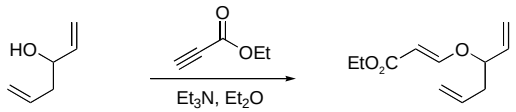


Ethyl ((*2S*, 4S*, 6S)-4-hydroxy-6-(3-phenyl)propyl-tetrahydropyran-2-yl)-acetate (10e).** Data for tetrahydropyran **10e**: ^{1}H NMR (400 MHz, acetone-d_6) d 7.26-7.23 (m, 2H), 7.19-7.18 (m, 2H), 7.15-7.12 (m, 1H), 4.22 (dddd, *J* = 11.5, 8.0, 5.6, 2.2 Hz, 1H), 4.16-4.14 (m, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.80 (dddd, *J* = 10.9, 6.6, 4.6, 2.1 Hz, 1H), 3.71 (d, *J* = 2.9 Hz, 1H-OH), 2.65-2.53 (m, 2H), 2.36 (dd, *J* = 14.8, 8.0 Hz, 1H), 2.31 (dd, *J* = 14.8, 5.5 Hz, 1H), 1.78-1.57 (m, 4H), 1.47-1.29 (m, 4H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) d 170.9, 142.9, 128.8, 128.5, 125.9, 71.6, 68.8, 64.4, 60.1, 41.8, 38.7, 38.5, 36.1, 36.0, 27.7, 14.2; IR (thin film from acetone-d_6): 3434, 3029, 2987, 2923, 2859, 1733, 1605, 1493, 1451, 1382, 1344, 1291, 1238, 1195, 1180, 1153, 1094, 1062, 1030, 924, 749, 701 cm^{-1}; HRMS calcd for $C_{18}H_{26}O_4Na$ (M^+) 329.1723, found 329.1701. (Note: COSY and NOE data collected in acetone-d_6.)



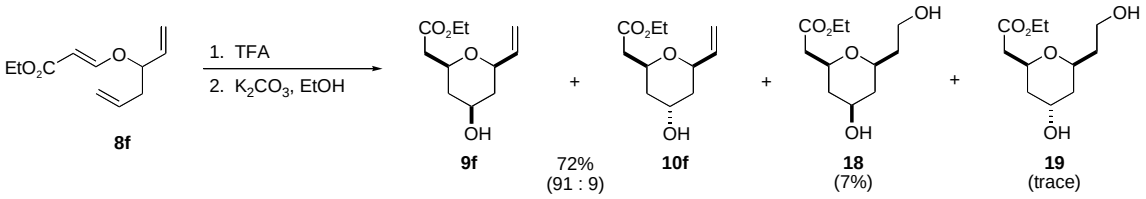
40

Ethyl ((*2R*, 6S)-6-(3-phenyl)propyl-3,4-dihydropyran-2-yl)-acetate** and **ethyl ((*2S*, 6S**)-6-(3-phenyl)propyl-4,5-dihydropyran-2-yl)-acetate (40).** Data for tetrahydropyran **40**: HRMS calcd for $C_{18}H_{24}O_3Na$ (M^+) 311.1618, found 311.1610.



8f

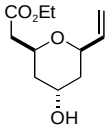
Ethyl (*E*)-3-(1,5-hexadien-3-yl)oxy-2-propenoate (8f). Enol ether **8f** was prepared in 82-90% yield from 1,5-hexadien-3-ol and ethyl propiolate using the procedure described for the synthesis of enol ether **8a**. Data for enol ether **8f**: ^{1}H NMR (400 MHz, $CDCl_3$) d 7.47 (d, J = 12.4 Hz, 1H), 5.77-5.67 (m, 2H), 5.26-5.22 (m, 2H), 5.23 (d, J = 12.4 Hz, 1H), 5.11-5.06 (m, 2H), 4.32 (ddd or app. q, J = 6.5 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 2.47-2.32 (m, 2H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 167.7, 161.2, 135.7, 132.6, 118.2, 118.1, 98.0, 82.8, 59.6, 39.1, 14.2; IR (thin film, neat): 3084, 2978, 2943, 2908, 1713, 1643, 1625, 1467, 1443, 1425, 1367, 1326, 1284, 1196, 1132, 1049, 991, 955, 926, 832, 744, 685 cm^{-1}; HRMS calcd for $C_{11}H_{16}O_3Na$ (M^+) 219.0992, found 219.0998.



8f → **9f** 72% (91 : 9) **10f** + **18** (7%) + **19** (trace)

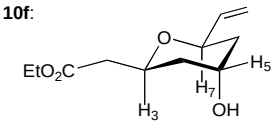
Ethyl ((*2S*, 4S*, 6R)-6-ethenyl-4-hydroxytetrahydropyran-2-yl)-acetate (9f).** To neat enol ether **8f** (0.1322 g, 0.674 mmol) cooled to 0 °C in a round bottom flask was added trifluoroacetic acid (2.7 mL) along the wall of the flask. The cooling bath was removed three minutes after the addition of trifluoroacetic acid was complete. After 1 h, the reaction solution was carefully poured into saturated aqueous $NaHCO_3$. CH_2Cl_2 was added, and this resulting mixture was stirred vigorously for 10 minutes. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to yield an oil. This crude material was dissolved in ethanol (6.7 mL), and then K_2CO_3 (0.047 g, 0.34 mmol) was added. This reaction mixture was stirred for 16.5 h at room temperature, and then concentrated. The residue was dissolved in water, brine, and EtOAc. The layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford 0.1338 g of a yellow oil. This crude material was purified by flash chromatography over 30 g of silica gel (2%-3%-4%-5%-10% MeOH/CH_2Cl_2) to yield tetrahydropyran **9f** (104 mg, 72%) plus minor impurities including tetrahydropyran **10f (9f**:**10f**, 91:9), diol **18** (11.1 mg, 7%), and diol **19**. Cyclization of enol ether **8f** under the conditions used for the synthesis of tetrahydropyran **8a**

afforded tetrahydropyran **9f** (32-34%) along with tetrahydropyran **10f** (3-4%, contaminated with another molecule), diol **18** (8-9%), and diol **19** (4-6%). Data for tetrahydropyran **9f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddd, J = 17.3, 10.6, 5.3 Hz, 1H), 5.18 (ddd or app. dt, J = 17.3, 1.5 Hz, 1H), 5.05 (ddd or app. dt, J = 10.6, 1.4 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.84-3.74 (m, 3H), 2.59 (dd, J = 15.3, 7.4 Hz, 1H), 2.59 (s, 1H-OH), 2.40 (dd, J = 15.3, 5.9 Hz, 1H), 1.99-1.93 (m, 2H), 1.25-1.13 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 137.9, 115.0, 75.9, 72.0, 67.4, 60.4, 41.0, 40.28, 40.27, 14.0; IR (thin film from $CDCl_3$): 3436, 3082, 2983, 2942, 2920, 2871, 1732, 1648, 1448, 1408, 1370, 1326, 1309, 1266, 1246, 1192, 1160, 1071, 1028, 1004, 926, 893, 862, 839, 806, 671 cm^{-1}; HRMS calcd for $C_{11}H_{18}O_4Na$ (M^+) 237.1097, found 237.1103.



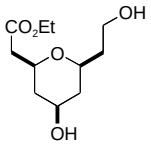
10f

Key Coupling Constants for **10f**:



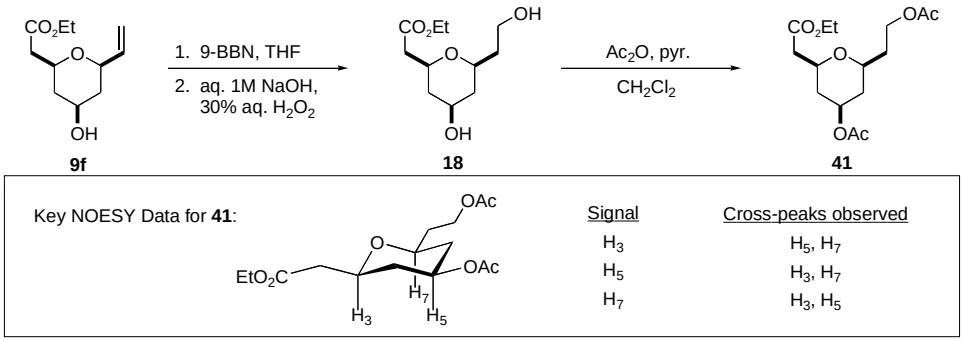
J (H_3-$H_{4\text{-ax}}$) = 11.6 Hz
J (H_7-$H_{6\text{-ax}}$) = 11.5 Hz
J (H_5-$H_{4\text{-ax}}$) = 2.7 Hz
J (H_5-$H_{6\text{-ax}}$) = 2.6 Hz

Ethyl ((*2S*, 4R*, 6R)-6-ethenyl-4-hydroxytetrahydropyran-2-yl)-acetate (10f).** Data for tetrahydropyran **10f**: ^{1}H NMR (400 MHz, C_6D_6) δ 5.80 (ddd, J = 17.3, 10.7, 5.0 Hz, 1H), 5.26 (ddd or app. dt, J = 17.3, 1.7 Hz, 1H), 4.97 (ddd or app. dt, J = 10.7, 1.6 Hz, 1H), 4.42 (dddd, J = 11.6, 7.6, 5.6, 2.0 Hz, 1H), 4.37 (m, 1H), 3.94 (q, J = 7.1 Hz, 2H), 3.71 (dddd or app. quint, J = 2.9 Hz, 1H), 2.54 (dd, J = 15.0, 7.6 Hz, 1H), 2.22 (15.0, 5.6 Hz, 1H), 1.42-1.35 (m, 2H), 1.26 (ddd, J = 13.9, 11.5, 2.6 Hz, 1H), 1.18 (ddd, J = 13.8, 11.6, 2.7 Hz, 1H), 0.94 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 170.7, 139.8, 113.9, 72.3, 68.7, 64.1, 60.1, 41.7, 38.5, 38.1, 14.2; IR (thin film from CH_2Cl_2): 3451, 3082, 2982, 2917, 1732, 1644, 1418, 1371, 1298, 1235, 1197, 1174, 1094, 1061, 1030, 992, 925, 864 cm^{-1}; HRMS calcd for $C_{11}H_{18}O_4Na$ (M^+) 237.1097, found 237.1113. COSY and NOESY data collected in C_6D_6.)

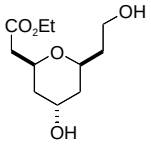


18

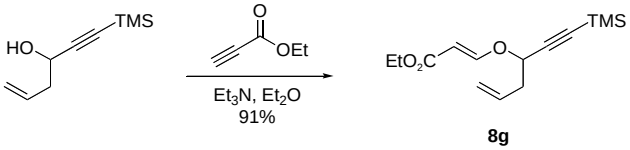
Ethyl ((*2S*, 4R*, 6S)-6-(2-hydroxy)ethyl-4-hydroxytetrahydropyran-2-yl)-acetate (18).** Data for tetrahydropyran **18**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (q, J = 7.1 Hz, 2H), 3.89-3.79 (m, 2H), 3.76 (t, J = 5.4 Hz, 2H), 3.61 (dddd, J = 9.3, 8.2, 3.1, 1.7 Hz, 1H), 2.56 (dd, J = 15.3, 8.6 Hz, 1H), 2.45 (dd, J = 15.3, 4.5 Hz, 1H), 2.05 (br s, 2H), 2.00 (dddd or app. tt, J = 12.2, 4.6, 2.3 Hz, 1H), 1.93 (dddd or app. tt, J = 12.3, 4.6, 2.3 Hz, 1H), 1.86-1.67 (m, 2H), 1.33-1.25 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.24 (ddd or app. dt, J = 11.9 Hz, 11.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1(s), 76.1(d), 72.3(d), 67.5(d), 61.3(t), 60.8(t), 41.0(t), 40.9(t), 40.4(t), 37.7(t), 14.1(q); IR (thin film, neat): 3400, 2942, 2875, 1731, 1448, 1374, 1309, 1268, 1190, 1150, 1082, 1029, 967, 861, 800 cm^{-1}; HRMS calcd for $C_{11}H_{20}O_5Na$ (M^+) 255.1203, found 255.1213.



Ethyl ((*2S*, 4R*, 6S)-4-acetoxy-6-(2-acetoxy)ethyltetrahydropyran-2-yl)-acetate (41).** Data for tetrahydropyran **41**: ^{1}H NMR (400 MHz, $CDCl_3$) d 4.90 (dddd or app. tt, *J* = 11.2, 4.8 Hz, 1H), 4.17-4.06 (m, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.81 (dddd, *J* = 11.4, 7.8, 5.5, 2.0 Hz, 1H), 3.50 (dddd, *J* = 11.2, 6.4, 4.5, 1.9 Hz, 1H), 2.54 (dd, *J* = 15.1, 7.9 Hz, 1H), 2.39 (dd, *J* = 15.1, 5.3 Hz, 1H), 2.04-1.94 (m, 2H), 2.02 (s, 3H), 2.02 (s, 3H), 1.86-1.71 (m, 2H), 1.30 (ddd or app. dt, *J* = 11.9, 11.5 Hz, 1H), 1.26 (ddd or app. dt, *J* = 12.2, 11.5 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 170.9, 170.6, 170.3, 72.1, 72.0, 69.8, 60.8, 60.5, 41.1, 36.9, 36.7, 34.8, 21.2, 20.9, 14.1; IR (thin film from $CDCl_3$): 2959, 2872, 1739, 1454, 1372, 1241, 1193, 1160, 1108, 1085, 1072, 1029 cm^{-1}; HRMS calcd for $C_{15}H_{24}O_7Na$ (M^+) 339.1414, found 339.1412. (Note: NOESY data collected in $CDCl_3$.)

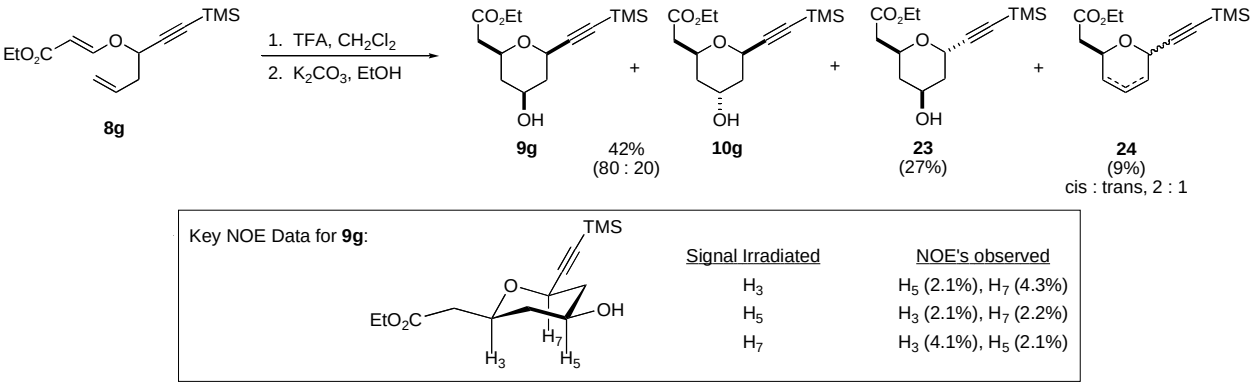


Ethyl ((*2S*, 4S*, 6S)-6-(2-hydroxy)ethyl-4-hydroxytetrahydropyran-2-yl)-acetate (19).** Data for tetrahydropyran **19**: HRMS calcd for $C_{11}H_{20}O_5Na$ (M^+) 255.1203, found 255.1205.

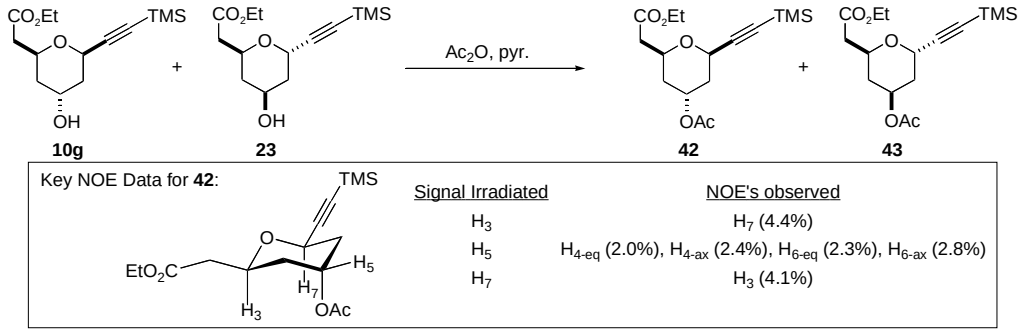


Ethyl (*E*)-3-(1-trimethylsilyl-5-hexen-1-yn-3-yl)oxy-2-propenoate (8g). To a solution of ethyl propiolate (1.5 mL, 15 mmol) in Et_2O (24 mL) at room temperature was added Et_3N (2.0 mL, 14 mmol), resulting in the formation of a cloudy, yellow mixture. After 10 min, 1-trimethylsilyl-5-hexen-1-yn-3-ol was cannulated as a solution in Et_2O (14 mL) into the reaction mixture. Residual 1-trimethylsilyl-5-hexen-1-yn-3-ol was transferred with Et_2O (2x5 mL). After being stirred for 5 h at room temperature, the orange-brown reaction mixture was diluted with EtOAc (100 mL), washed three times with aqueous 1M $KHSO_4$, washed once with saturated aqueous $NaHCO_3$, washed once with brine, dried over Na_2SO_4, filtered, and concentrated to afford 2.39 g of a brownish-orange oil. This crude material was purified by flash chromatography over 250 g of silica gel (3% EtOAc/hexanes) to yield desired enol ether **8g** (2.34 g, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) d 7.59 (d, *J* = 12.5 Hz, 1H), 5.85-5.75 (m, 1H), 5.35 (d, *J* = 12.5 Hz, 1H), 5.19-

5.13 (m, 2H), 4.54 (t, *J* = 6.5 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.61-2.50 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) d 167.5, 160.0, 131.8, 118.9, 100.8, 99.0, 93.9, 71.2, 59.7, 39.6, 14.3, –0.4; IR (thin film, neat): 3083, 2981, 2958, 2901, 2173, 1711, 1642, 1625, 1443, 1369, 1324, 1284, 1250, 1187, 1130, 1050, 1016, 988, 954, 925, 845, 760 cm^{-1}; HRMS calcd for $C_{14}H_{22}O_3SiNa$ (M^+) 289.1230, found 289.1249.

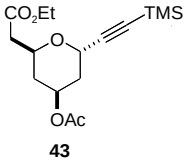


Ethyl ((*2S*, 4S*, 6R)-6-(2-trimethylsilyl)ethynyl-4-hydroxytetrahydropyran-2-yl)-acetate (9g).** Tetrahydropyrans **9g**, **10g**, and **23** and dihydropyrans **24** were prepared from enol ether **8g** using the procedure described for synthesis of tetrahydropyrans **9a** and **10a**. Tetrahydropyrans **10g** and **23** were formed as an inseparable mixture, and therefore had to be converted to their corresponding acetates to be individually characterized. Data for tetrahydropyran **9g**: ^{1}H NMR (400 MHz, C_6D_6) d 3.94 (dd, *J* = 11.7, 2.2 Hz, 1H), 3.90-3.82 (m, 2H), 3.67-3.61 (m, 1H), 3.31 (dddd or app. ddt, *J* = 15.6, 10.9, 4.6 Hz, 1H), 2.53 (dd, *J* = 15.7, 7.4 Hz, 1H), 2.16 (dd, *J* = 15.7, 5.5 Hz, 1H), 1.97 (ddd, *J* = 10.4, 4.4, 2.1 Hz, 1H), 1.70 (ddd or app. dt, *J* = 12.3, 2.3 Hz, 1H), 1.58 (dd, *J* = 12.1, 11.6 Hz, 1H), 1.06 (dd, *J* = 11.9, 11.4 Hz, 1H), 0.90 (t, *J* = 7.1 Hz, 3H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) d 170.6, 105.0, 88.8, 72.7, 66.9, 66.8, 60.4, 41.9, 41.0, 40.4, 14.1, –0.2; IR (thin film, neat): 3440, 2960, 2184, 1732, 1448, 1370, 1327, 1251, 1190, 1150, 1068, 1033, 845, 761, 702, 666 cm^{-1}; HRMS calcd for $C_{14}H_{24}O_4SiNa$ (M^+) 307.1336, found 307.1356. (Note: COSY and NOE data collected in C_6D_6.)



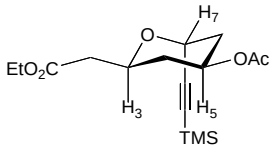
Ethyl ((*2S*, 4S*, 6R)-4-acetoxy-6-(2-trimethylsilyl)ethynyltetrahydropyran-2-yl)-acetate (42).** Data for tetrahydropyran **42**: ^{1}H NMR (250 MHz, C_6D_6) d 4.91 (dddd or app. quint, *J* = 2.9 Hz, 1H), 4.57 (dd, *J* = 11.8, 2.3 Hz, 1H), 4.21 (dddd, *J* = 11.5, 7.7, 5.4, 2.1 Hz, 1H), 3.84 (q, *J* =7.1 Hz, 2H), 2.46 (dd, *J* = 15.6, 7.6 Hz, 1H), 2.06 (dd, *J* = 15.6, 5.3 Hz, 1H), 1.89 (ddd, *J* = 14.4, 5.0, 2.6 Hz, 1H), 1.69 (ddd, *J* = 14.4, 11.7, 2.8 Hz, 1H), 1.59-1.50 (m, 1H), 1.54 (s, 3H),

1.06 (dddd or app. ddt, *J* = 14.3, 11.7, 2.8 Hz, 1H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) d 170.7, 170.1, 103.7, 89.8, 69.7, 66.8, 63.8, 60.6, 40.9, 36.1, 34.5, 21.2, 14.1, –0.2; IR (thin film from $CDCl_3$): 2959, 2902, 2856, 2185, 1739, 1369, 1295, 1250, 1199, 1164, 1062, 1022, 971, 846, 760 cm^{-1}; HRMS calcd for $C_{16}H_{26}O_5SiNa$ (M^+) 349.1442, found 349.1441. (Note: COSY and NOE data collected in C_6D_6.)



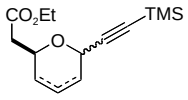
43

Key NOE Data for **43**:



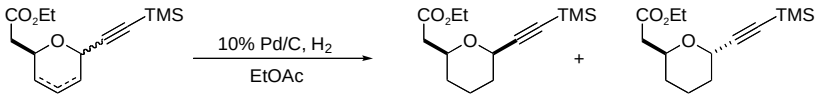
Signal Irradiated	NOE's observed
H_3	H_5 (2.1%), H_7 (0.3%)
H_5	$H_{4\text{-eq}}$ (2.1%), $H_{4\text{-ax}}$ (0.7%), $H_{6\text{-eq}}$/OAc-Me (2.9%), $H_{6\text{-ax}}$ (0.5%), H_7 (0.5%)
H_7	H_3 (0.6%), H_5 (0.5%), $H_{6\text{-eq}}$/OAc-Me (1.9%), $H_{6\text{-ax}}$ (2.7%)

Ethyl ((*2S*, 4S*, 6S)-4-acetoxy-6-(2-trimethylsilyl)ethynyltetrahydropyran-2-yl)-acetate (43).** Data for tetrahydropyran **43**: ^{1}H NMR (400 MHz, $CDCl_3$) d 5.20 (dddd or app. tt, *J* = 11.2, 4.7 Hz, 1H), 4.79 (dd, *J* = 5.5, 1.6 Hz, 1H), 4.39 (dddd, *J* = 11.3, 7.6, 5.4, 2.1 Hz, 1H), 4.20-4.07 (m, 2H), 2.53 (dd, *J* = 15.0, 7.6 Hz, 1H), 2.43 (dd, *J* = 15.0, 5.4 Hz, 1H), 2.10 (dddd or app. ddt, *J* = 12.2, 4.4, 2.1 Hz, 1H), 2.03 (dddd or app. ddt, *J* = 12.4, 4.3, 2.1 Hz, 1H), 2.01 (s, 3H), 1.73 (ddd, *J* = 12.2, 11.6, 5.6 Hz, 1H), 1.30 (ddd or app. q, *J* = 11.7 Hz, 1H), 1,24 (t, *J* = 7.1 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) d 170.3, 170.1, 102.2, 92.6, 67.4, 67.3, 64.6, 60.5, 41.1, 36.9, 35.5, 21.2, 14.2, –0.2; IR (thin film from $CDCl_3$): 2959, 2902, 2162, 1739, 1449, 1369, 1312, 1238, 1199, 1164, 1136, 1073, 1051, 1005, 948, 903, 846, 760 cm^{-1}; HRMS calcd for $C_{16}H_{26}O_5SiNa$ (M^+) 349.1442, found 349.1438. (Note: COSY and NOE data collected in $CDCl_3$.)



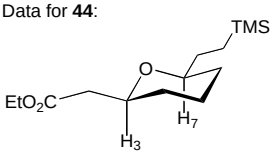
24

Ethyl ((*2,6-cis*)-6-(2-trimethylsilyl)ethynyldihydropyran-2-yl)-acetate and **ethyl ((*2,6-trans*)-6-(2-trimethylsilyl)ethynyldihydropyran-2-yl)-acetate (24).** Data for dihydropyrans **24**: HRMS calcd for $C_{14}H_{22}O_3SiNa$ (M^+) 289.1230, found 289.1219.



24 **44** **45**

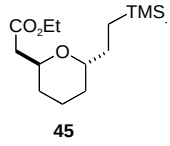
Key NOE Data for **44**:



Signal Irradiated	NOE's observed
H_3	H_7 (3.0%)
H_7	H_3 (3.2%)

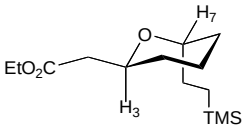
Ethyl ((*2S*, 6R)-6-(2-trimethylsilyl)ethynyltetrahydropyran-2-yl)-acetate (44).** Data for tetrahydropyran **44**: ^{1}H NMR (400 MHz, $CDCl_3$) d 4.14 (q, *J* = 7.1 Hz, 2H), 3.78-3.71 (m, 1H), 3.22-3.15 (m, 1H), 2.53 (dd, *J* = 14.8, 7.8 Hz, 1H), 2.38 (dd, *J* = 14.8, 5.7 Hz, 1H), 1.83 (br d, *J* = 13.2 Hz, 1H), 1.64-1.43 (m, 4H), 1.39-1.05 (m, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.58 (ddd, *J* =

14.3, 12.6, 4.6 Hz, 1H), 0.41 (ddd, *J* = 14.3, 12.8, 4.9 Hz, 1H), –0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) d 171.6, 80.5, 74.6, 60.3, 41.9, 31.4, 30.7, 30.6, 23.5, 14.2, 12.2, –1.8; IR (thin film from CH_2Cl_2): 2934, 2860, 1738, 1440, 1372, 1343, 1281, 1248, 1183, 1132, 1074, 1037, 861, 836, 754, 690 cm^{-1}; HRMS calcd for $C_{14}H_{28}O_3SiNa$ (M^+) 295.1700, found 295.1697. (Note: COSY and NOE data collected in $CDCl_3$.)



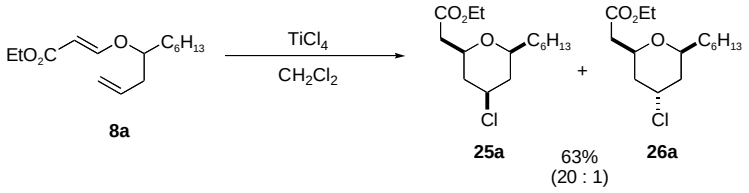
45

Key NOE Data for **45**:



Signal Irradiated	NOE's observed
H_3	none
H_7	none

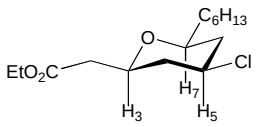
Ethyl ((*2S*, 6S)-6-(2-trimethylsilyl)ethynyltetrahydropyran-2-yl)-acetate (45).** Data for tetrahydropyran **45**: ^{1}H NMR (400 MHz, C_6D_6) d 4.32-4.26 (m, 1H), 3.99 (q, *J* = 7.2 Hz, 2H), 3.56-3.50 (m, 1H), 2.64 (dd, *J* = 14.5, 8.6 Hz, 1H), 2.20 (dd, *J* = 14.5, 5.4 Hz, 1H), 1.75-1.65 (m, 1H), 1.57-1.24 (m, 5H), 1.09-1.00 (m, 2H), 0.98 (t, *J* = 7.1 Hz, 3H), 0.76 (ddd, *J* = 14.4, 12.7, 4.2 Hz, 1H), 0.41 (ddd, *J* = 14.4, 12.8, 4.9 Hz, 1H), 0.03 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6) d 171.0, 73.6, 68.1, 60.1, 39.5, 30.1, 29.7, 27.8, 18.8, 14.3, 12.4, –1.7; IR (thin film, neat): 2933, 2870, 1738, 1462, 1445, 1369, 1288, 1248, 1209, 1176, 1139, 1096, 1041, 900, 859, 836, 761, 691 cm^{-1}; HRMS calcd for $C_{14}H_{28}O_3SiNa$ (M^+) 295.1700, found 295.1706. (Note: COSY and NOE data collected in C_6D_6.)



8a **25a** **26a**

63% (20 : 1)

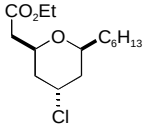
Key NOE Data for **25a**:



Signal Irradiated	NOE's observed
H_3	H_5 (1.6%), H_7 (3.3%)
H_5	H_3 (1.5%), H_7 (1.5%)
H_7	H_3 (3.5%), H_5 (1.7%)

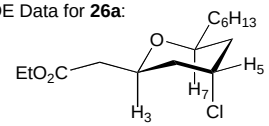
Ethyl ((*2R*, 4R*, 6S)-4-chloro-6-hexyltetrahydropyran-2-yl)-acetate (25a).** To a clear and colorless solution of enol ether **8a** (91.4 mg, 0.359 mmol) in CH_2Cl_2 (2.4 mL) cooled to –45 °C was added 1.0 M $TiCl_4$ in CH_2Cl_2 (0.96 mL) along the wall of the flask. The addition of $TiCl_4$ caused the solution to change from colorless to yellow to orange. The cooling bath was allowed to warm to –7 °C over 2.5 h, and then was replaced with a 0 °C, ice-water bath. After being stirred at 0 °C for 2.75 h, 1.0 M $TiCl_4$ in CH_2Cl_2 (0.96 mL) was added. After an additional hour at 0 °C, the cooling bath was removed. The reaction solution was stirred at room temperature for 3 d, and then water was added. The mixture was extracted with CH_2Cl_2 (3x). The combined extracts were dried over Na_2SO_4, filtered, and concentrated to yield an oil. This crude material was purified by flash chromatography over silica gel (3.5-15% EtOAc/hexanes) to yield desired tetrahydropyran **25a** (60%), along with tetrahydropyran **26a** (3%). Data for tetrahydropyran **25a**: ^{1}H NMR (400 MHz, $CDCl_3$) d 4.13 (q, *J* = 7.1 Hz, 2H), 4.01 (dddd or app. tt, *J* = 11.8, 4.5 Hz, 1H), 3.75 (dddd, *J* = 11.2, 7.7, 5.6, 1.9 Hz, 1H), 3.29 (dddd, *J* = 11.6, 6.0, 4.4, 1.9 Hz, 1H), 2.56 (dd, *J* = 15.2, 7.8 Hz, 1H), 2.39 (dd, *J* = 15.2, 5.5 Hz, 1H), 2.18 (dddd or app. ddt, *J* = 12.5, 4.2,

2.0 Hz, 1H), 2.10 (dddd or app. ddt, *J* = 12.7, 4.2, 2.0 Hz, 1H), 1.55-1.44 (m, 1H), 1.52 (ddd or app. dt, *J* = 12.0, 11.8 Hz, 1H), 1.47 (ddd or app. dt, *J* = 12.2, 11.8 Hz, 1H), 1.42-1.18 (m, 9H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 170.8, 76.9, 73.1, 60.5, 55.3, 42.2, 41.9, 41.0, 35.7, 31.7, 29.1, 25.3, 22.5, 14.2, 14.0; IR (thin film, neat): 2950, 2930, 2858, 1738, 1465, 1446, 1393, 1373, 1337, 1298, 1260, 1197, 1181, 1148, 1081, 1030, 942, 861, 773, 725 cm^{-1}; HRMS calcd for $C_{15}H_{27}O_3ClNa$ (M^+) 313.1541, found 313.1530. (Note: COSY and NOE data collected in $CDCl_3$.)



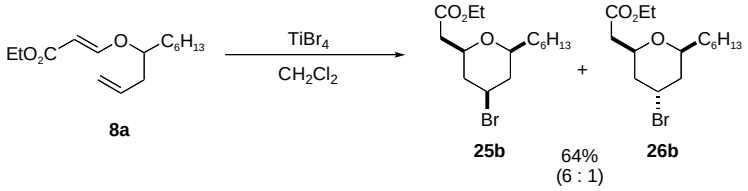
26a

Key NOE Data for **26a**:



Signal Irradiated	NOE's observed
H_3	H_7 (3.0%)
H_5	$H_{4\text{-eq}}/H_{6\text{-eq}}$ (3.1%), $H_{4\text{-ax}}/H_{6\text{-ax}}$ (3.6%)
H_7	H_3 (3.2%)

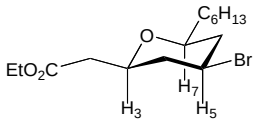
Ethyl ((*2R*, 4S*, 6S)-4-chloro-6-hexyltetrahydropyran-2-yl)-acetate (26a).** Data for tetrahydropyran **26a**: ^{1}H NMR (400 MHz, $CDCl_3$) d 4.57 (dddd or app. quint, *J* = 3.0 Hz, 1H), 4.30 (dddd, *J* = 11.0, 8.1, 5.5, 2.1 Hz, 1H), 4.16 (qd, *J* = 7.1, 1.0 Hz, 2H), 3.86-3.81 (m, 1H), 2.52 (dd, *J* = 14.8, 8.2 Hz, 1H), 2.38 (dd, *J* = 14.8, 5.2 Hz, 1H), 1.94 (ddd, *J* = 14.1, 4.6, 2.1 Hz, 1H), 1.87 (ddd, *J* = 14.2, 4.6, 2.0 Hz, 1H), 1.73 (ddd, *J* = 14.2, 11.0, 3.3 Hz, 1H), 1.65 (ddd, *J* = 14.3, 11.0, 3.3 Hz, 1H), 1.51-1.20 (m, 10H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 170.9, 71.8, 68.6, 60.5, 56.5, 41.2, 39.0, 38.8, 35.7, 31.8, 29.2, 25.3, 22.6, 14.2, 14.1; IR (thin film, neat): 2954, 2929, 2858, 1738, 1465, 1433, 1378, 1345, 1326, 1298, 1273, 1200, 1158, 1069, 1031, 942, 860, 834, 726 cm^{-1}; HRMS calcd for $C_{15}H_{27}O_3ClNa$ (M^+) 313.1541, found 313.1546. (Note: COSY and NOE data collected in $CDCl_3$.)



8a **25b** **26b**

64% (6 : 1)

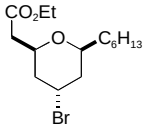
Key NOE Data for **25b**:



Signal Irradiated	NOE's observed
H_3	H_5/OCH_2CH_3 (1.7%), H_7 (3.5%)
H_5/OCH_2CH_3	H_3 (1.8%), H_7 (1.6%)
H_7	H_3 (3.7%), H_5/OCH_2CH_3 (1.8%)

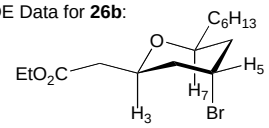
Ethyl ((*2R*, 4R*, 6S)-4-bromo-6-hexyltetrahydropyran-2-yl)-acetate (25b).** To a clear and colorless solution of enol ether **8a** (133 mg, 0.523 mmol) in CH_2Cl_2 (3.5mL) cooled to –78°C was added 1 M $TiBr_4$ in CH_2Cl_2 (4.8 mL) along the wall of the flask. The addition of $TiBr_4$ caused the solution to change from colorless solution to deep orange mixture. The cooling bath was allowed to warm to –45 °C over 3 h, and then was replaced with a 0 °C, ice-water bath. Warming the reaction mixture resulted in dissolution of solid material and a color change from orange to deep blood red. After being stirred at 0 °C for 1.75 h, the reaction solution was poured into saturated aqueous $NaHCO_3$ (20 mL). This mixture was diluted with CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (10 mL), and then stirred vigorously for 15 min. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined extracts were dried over Na_2SO_4, filtered, and concentrated to yield 148 mg of an oil. This crude material was purified by flash chromatography over 30 g of silica gel (4-10% EtOAc/hexanes) to yield desired

tetrahydropyran **25b** (55%), along with tetrahydropyran **26b** (9%). Data for tetrahydropyran **25b**: ^{1}H NMR (400 MHz, $CDCl_3$) d 4.18-4.10 (m, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.74 (dddd, *J* = 11.2, 7.6, 5.6, 2.0 Hz, 1H), 3.29 (dddd, *J* = 11.0, 6.0, 4.5, 1.9 Hz, 1H), 2.55 (dd, *J* = 15.2, 7.7 Hz, 1H), 2.38 (dd, *J* = 15.2, 5.5 Hz, 1H), 2.28 (dddd or app. ddt, *J* = 12.6, 4.2, 2.0 Hz, 1H), 2.20 (dddd or app. ddt, *J* = 12.8, 4.2, 2.0 Hz, 1H), 1.70 (ddd or app. dt, *J* = 12.1, 11.5 Hz, 1H), 1.66 (ddd or app. dt, *J* = 12.3, 11.3 Hz, 1H), 1.54-1.48 (m, 1H), 1.42-1.19 (m, 9H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 170.7, 77.7, 73.9, 60.5, 46.1, 43.0, 42.8, 40.9, 35.7, 31.7, 29.1, 25.3, 22.5, 14.2, 14.0; IR (thin film, neat): 2950, 2929, 2854, 1740, 1462, 1446, 1398, 1372, 1329, 1286, 1260, 1196, 1148, 1084, 1031, 945, 860, 711 cm^{-1}; HRMS calcd for $C_{15}H_{27}O_3BrNa$ (M^+) 357.1036, found 357.1042. (Note: COSY and NOE data collected in $CDCl_3$.)



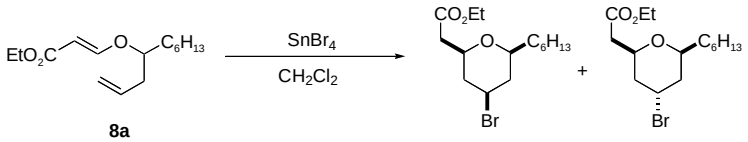
26b

Key NOE Data for **26b**:



Signal Irradiated	NOE's observed
H_3	H_7 (3.4%)
H_5	$H_{4\text{-eq}}/H_{6\text{-eq}}$ (3.0%), $H_{4\text{-ax}}/H_{6\text{-ax}}$ (3.8%)
H_7	H_3 (3.3%)

Ethyl ((*2R*, 4S*, 6S)-4-bromo-6-hexyltetrahydropyran-2-yl)-acetate (26b).** Data for tetrahydropyran **26b**: ^{1}H NMR (400 MHz, $CDCl_3$) d 4.70 (dddd or app. quint, *J* = 3.0 Hz, 1H), 4.31 (dddd, *J* = 10.7, 8.0, 5.6, 2.0 Hz, 1H), 4.15 (qd, *J* = 7.1, 1.8 Hz, 2H), 3.87-3.82 (m, 1H), 2.52 (dd, *J* = 14.8, 8.1 Hz, 1H), 2.39 (dd, *J* = 14.8, 5.3 Hz, 1H), 2.02 (ddd, *J* = 14.4, 4.4, 2.0 Hz, 1H), 1.95 (ddd, *J* = 14.5, 4.3, 2.0 Hz, 1H), 1.76 (ddd, *J* = 14.3, 10.9, 3.4 Hz, 1H), 1.68 (ddd, *J* = 14.4, 10.9, 3.5 Hz, 1H), 1.52-1.22 (m, 10H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 170.8, 72.4, 69.2, 60.4, 50.0, 41.0, 39.4, 39.2, 35.5, 31.8, 29.1, 25.3, 22.5, 14.2, 14.0; IR (thin film, neat): 2954, 2930, 2858, 1738, 1732, 1463, 1453, 1434, 1378, 1345, 1325, 1301, 1270, 1247, 1202, 1156, 1069, 1029, 940, 859, 834, 726, 697 cm^{-1}; HRMS calcd for $C_{15}H_{27}O_3BrNa$ (M^+) 357.1036, found 357.1042. (Note: COSY and NOE data collected in $CDCl_3$.)

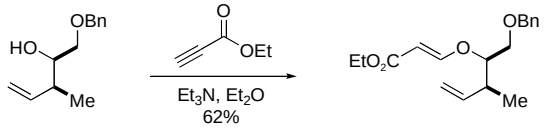


8a **25b** **26b**

69% (5 : 1)

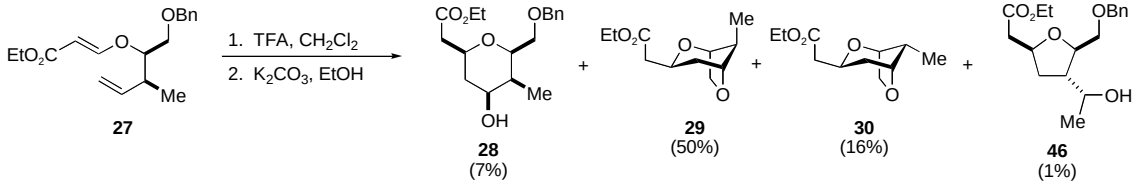
Ethyl ((*2R*, 4R*, 6S)-4-bromo-6-hexyltetrahydropyran-2-yl)-acetate (25b)** and **ethyl ((*2R*, 4S*, 6S**)-4-bromo-6-hexyltetrahydropyran-2-yl)-acetate (26b).** To a clear and colorless solution of enol ether **8a** (120.5 mg, 0.474 mmol) in CH_2Cl_2 (3.2mL) cooled to –78°C was added 1 M $SnBr_4$ in CH_2Cl_2 (4.8 mL) along the wall of the flask. The addition of $TiBr_4$ did not cause any significant change in color or appearance. The acetone cooling bath was allowed to warm to –45 °C over 3 h, and then was replaced with a 0 °C, ice-water bath. The water cooling bath was allowed to warm to 13 °C over 2.75 h, and then was removed. After being stirred at room temperature for 2.5 d, the reaction solution was poured into saturated aqueous $NaHCO_3$ (40 mL). This mixture was diluted with CH_2Cl_2 (5 mL), and then stirred vigorously for 10 min. The resulting emulsion was diluted further with CH_2Cl_2 and brine, and filtered through

filter paper in a Buchner funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined extracts were dried over Na_2SO_4, filtered, and concentrated to yield 117 mg of a yellow oil. This crude material was purified by flash chromatography over 24 g of silica gel (5-7.5% EtOAc/hexanes) to yield desired tetrahydropyran **25b** (57%), along with tetrahydropyran **26b** (12%).



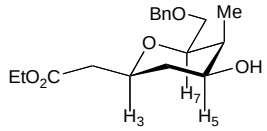
27

Ethyl (*E*)-3-((*2R*, 3S)-1-benzyloxy-3-methyl-4-penten-2-yl)oxy-2-propenoate (27).** Enol ether **27** was prepared in 62% yield from (*2R*, 3S**)-1-benzyloxy-3-methyl-4-penten-2-ol (19% recovered after purification) and ethyl propiolate using the procedure described for the synthesis of enol ether **8a**. Data for enol ether **27**: ^{1}H NMR (400 MHz, $CDCl_3$) d 7.58 (d, *J* = 12.3 Hz, 1H), 7.34-7.24 (m, 5H), 5.69 (ddd, *J* = 17.2, 10.3, 7.7 Hz, 1H), 5.30 (d, *J* = 12.3 Hz, 1H), 5.08-5.02 (m, 2H), 4.50 (s, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.90 (ddd or app. td, *J* = 6.8, 3.1 Hz, 1H), 3.62 (dd, *J* = 10.7, 3.1 Hz, 1H), 3.50 (dd, 10.7, 7.0 Hz, 1H), 2.52 (ddq, *J* = 7.6, 6.8, 6.8 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 168.0, 163.3, 138.8, 137.7, 128.3, 127.6, 127.5, 115.9, 97.3, 86.4, 73.3, 70.4, 59.5, 39.4, 15.4, 14.3; IR (thin film, neat): 3084, 3025, 2978, 2931, 2872, 1708, 1643, 1496, 1455, 1367, 1320, 1284, 1226, 1202, 1132, 1049, 996, 955, 920, 832, 739, 697 cm^{-1}; HRMS calcd for $C_{18}H_{24}O_4Na$ (M^+) 327.1567, found 327.1575.



27 | **28** (7%) | **29** (50%) | **30** (16%) | **46** (1%)

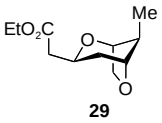
Key NOE Data for **28**:



Signal Irradiated	NOE's observed
H_3	H_5 (1.0%), H_7 (3.1%)
H_5	H_3 (1.6%), H_6 (2.9%), H_7 (2.7%)
H_7	H_3 (6.8%), H_5 (3.8%)
H_{8a}	C_6-Me (1.2%)
C_6-Me	$H_{4\text{-}ax}$ (3.3%), H_6 (1.4%), H_{8a} (1.6%), H_{8b} (2.0%)

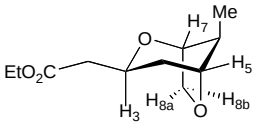
Ethyl ((*2S*, 4S*, 5S*, 6R)-4-hydroxy-6-(benzyloxy)methyl-5-methyltetrahydropyran-2-yl)-acetate (28).** Tetrahydropyran **28** was prepared from enol ether **27** using the procedure described for synthesis of tetrahydropyrans **9a** and **10a**. Data for tetrahydropyran **28**: ^{1}H NMR (400 MHz, $CDCl_3$) d 7.37-7.25 (m, 5H), 4.59, 4.48 (ABq, *J* = 12.0 Hz, 2H), 4.12 (qd, *J* = 7.1, 1.4 Hz, 2H), 3.92 (ddd or app. dt, *J* = 11.6, 4.8 Hz, 1H), 3.82 (dddd, *J* = 11.3, 7.0, 6.1, 2.3 Hz, 1H), 3.64 (ddd, *J* = 6.8, 5.4, 1.7 Hz, 1H), 3.55 (dd, *J* = 10.0, 6.7 Hz, 1H), 3.44 (dd, *J* = 10.0, 5.5 Hz, 1H), 2.62 (dd, *J* = 15.2, 7.1 Hz, 1H), 2.43 (dd, *J* = 15.2, 6.0 Hz, 1H), 2.03-1.97 (m, 1H), 1.76-1.71 (m, 1H), 1.71 (br s, 1H-OH), 1.43 (ddd or app. dt, *J* = 12.0, 11.8 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 170.9, 138.2, 128.3, 127.7, 127.6, 77.8, 73.3, 72.7, 70.7, 70.4, 60.5, 41.0, 35.9, 34.7, 14.2, 4.8; IR (thin film from $CDCl_3$):

3440, 3033, 2977, 2920, 2864, 1732, 1494, 1466, 1455, 1370, 1302, 1269, 1206, 1156, 1099, 1026, 947, 856, 738, 698 cm^{-1}; HRMS calcd for $C_{18}H_{26}O_5Na$ (M^+) 345.1672, found 345.1666. (Note: COSY and NOE data collected in $CDCl_3$.)



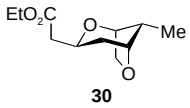
29

Key NOE Data for **29**:



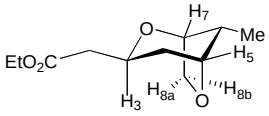
Signal Irradiated	NOE's observed
H_3	none
$H_{4\text{-}ax}$	C_6-Me (1.3%)
H_6	H_5 (1.2%), H_{8b} (0.6%)
$H_{8a}/OC\underline{H}_2CH_3$	none
H_{8b}	H_6 (0.7%), H_7 (1.0%), $H_{8a}/OC\underline{H}_2CH_3$ (4.6%)
C_6-Me	$H_{4\text{-}ax}$ (2.3%), H_6 (6.3%)

Ethyl ((*1S*, 3S*, 5R*, 8S)-(8-methyl-2,6-dioxabicyclo-[3.2.1]-oct-3-yl))-acetate (29).** Data for bicycle **29**: ^{1}H NMR (400 MHz, C_6D_6) d 4.20 (dd, *J* = 7.6, 4.5 Hz, 1H), 4.14-4.07 (m, 1H), 3.94 (q, *J* = 7.1 Hz, 2H), 3.93 (d, *J* = 9.9 Hz, 1H), 3.31 (dq, or app. quintet, *J* = 6.1 Hz, 1H), 3.12 (dd, *J* = 10.3, 4.6 Hz, 1H), 2.66 (dd, *J* = 15.3, 7.0 Hz, 1H), 2.36 (dd, *J* = 15.3, 6.0 Hz, 1H), 2.20-2.12 (m, 1H), 1.57 (ddd, *J* = 11.9, 8.6, 4.5 Hz, 1H), 1.32 (ddd or app. dt, *J* = 11.8, 9.7 Hz, 1H), 1.05 (d, *J* = 6.3 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) d 170.7, 84.8, 77.5, 76.4, 73.9, 60.2, 48.6, 39.9, 32.7, 15.5, 14.1; IR (thin film from $CDCl_3$): 2979, 2935, 2847, 1734, 1449, 1389, 1367, 1334, 1296, 1258, 1236, 1220, 1192, 1159, 1094, 1039, 995 cm^{-1}; HRMS calcd for $C_{11}H_{18}O_4Na$ (M^+) 237.1097, found 237.1100. (Note: COSY and NOE data collected in C_6D_6.)



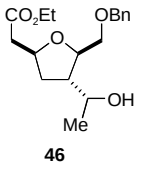
30

Key NOE Data for **30**:



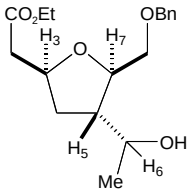
Signal Irradiated	NOE's observed
H_3	H_{8a} (1.5%)
$H_{4\text{-}ax}$	H_5 (0.8%), H_6 (0.8%)
H_5	$H_{4\text{-}eq}$ (0.9%), $H_{4\text{-}ax}$ (0.8%), H_6 (0.4%), C_6-Me (0.5%)
H_6	$H_{4\text{-}ax}$ (0.9%), H_5 (0.4%), H_7 (0.5%)
H_7	H_6 (0.5%), C_6-Me (0.7%)
H_{8b}	$H_{8a}/OC\underline{H}_2CH_3$ (6.4%), C_6-Me (0.9%)
C_6-Me	H_5 (0.7%), H_7 (0.8%), H_{8b} (0.9%)

Ethyl ((*1S*, 3S*, 5R*, 8R)-(8-methyl-2,6-dioxabicyclo-[3.2.1]-oct-3-yl))-acetate (30).** Data for bicycle **30**: ^{1}H NMR (400 MHz, $CDCl_3$) d 4.36-4.29 (m, 1H), 4.20-4.09 (m, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.89 (dd, *J* = 10.3, 3.1 Hz, 1H), 2.49 (dd, *J* = 14.9, 7.6 Hz, 1H), 2.41 (dd, *J* = 14.9, 5.3 Hz, 1H), 2.01 (dd, *J* = 13.9, 7.0 Hz, 1H), 1.88 (ddd or app. dt, *J* = 12.9, 4.5 Hz, 1H), 1.43 (dd, *J* = 12.5, 11.2 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 171.0, 80.3, 79.0, 69.1, 66.4, 60.5, 43.6, 41.0, 39.0, 14.6, 14.2; IR (thin film from $CDCl_3$): 2935, 2880, 1740, 1477, 1460, 1384, 1367, 1296, 1263, 1198, 1154, 1110, 1072, 1055, 1033, 929, 896, 853 cm^{-1}; HRMS calcd for $C_{11}H_{18}O_4Na$ (M^+) 237.1097, found 237.1094. (Note: COSY and NOE data collected in $CDCl_3$.)



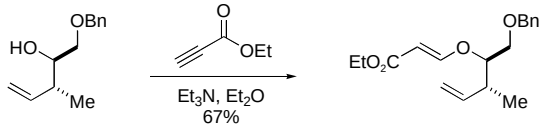
46

Key NOE Data for **46**:



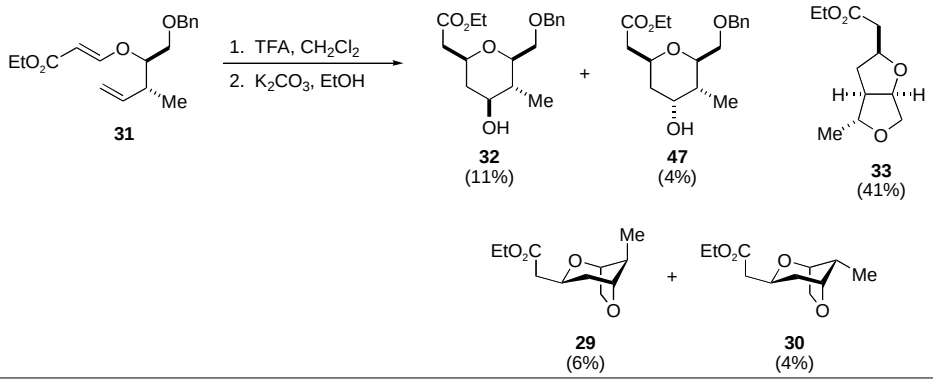
Signal Irradiated	NOE's observed
H_3	H_7 (0.7%)
H_6	H_4's (2.0%), H_7 (0.9%)
H_7	H_3 (1.4%), H_6 (1.5%)
C_6-Me	H_4's (3.5%), H_5 (2.3%), H_6 (2.5%)

Ethyl ((*2R*, 3R*, 5R)-3-(1-hydroxy)ethyl-5-(benzyloxy)methyltetrahydrofuran-2-yl)-acetate (46).** Data for tetrahydrofuran **46**: ^{1}H NMR (400 MHz, $CDCl_3$) d 7.37-7.11 (m, 5H), 4.61, 4.57 (ABq, *J* = 11.9 Hz, 2H), 4.35 (dddd or app. quint, *J* = 6.9 Hz, 1H), 4.13 (qd, *J* = 7.1, 0.9 Hz, 2H), 3.88 (ddd or app. td, *J* = 7.5, 4.2 Hz, 1H), 3.73 (dd, *J* = 9.2, 4.2 Hz, 1H), 3.65 (dq, *J* = 8.6, 6.1 Hz, 1H), 3.47 (dd, *J* = 9.2, 7.6 Hz, 1H), 2.58 (dd, *J* = 15.2, 6.8 Hz, 1H), 2.40 (dd, *J* = 15.3, 6.8 Hz, 1H), 2.01 (dddd or app. quint, *J* = 8.4 Hz, 1H), 1.89-1.79 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.19 (d, *J* = 6.1 Hz, 3H); HRMS calcd for $C_{18}H_{26}O_5Na$ (M^+) 345.1672, found 345.1678. COSY and NOE data collected in $CDCl_3$.)

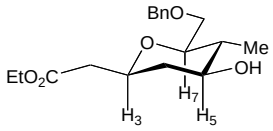


31

Ethyl (*E*)-3-((*2R*, 3R)-1-benzyloxy-3-methyl-4-penten-2-yl)oxy-2-propenoate (31).** Enol ether **31** was prepared in 67% yield from (*2R*, 3R**)-1-benzyloxy-3-methyl-4-penten-2-ol (22% recovered after purification) and ethyl propiolate using the procedure described for the synthesis of enol ether **8a**. Data for enol ether **31**: ^{1}H NMR (400 MHz, $CDCl_3$) d 7.59 (d, *J* = 12.3 Hz, 1H), 7.36-7.26 (m, 5H), 5.80-5.71 (m, 1H), 5.32 (d, *J* = 12.3 Hz, 1H), 5.09-5.04 (m, 2H), 4.53, 4.50 (ABq, *J* = 12.8 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.00-3.96 (m, 1H), 3.59 (dd, *J* = 10.6, 3.7 Hz, 1H), 3.53 (dd, *J* = 10.6, 6.8 Hz, 1H), 2.59-2.51 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 168.0, 163.3, 138.2, 137.7, 128.3, 127.6, 127.5, 116.1, 97.3, 86.2, 73.3, 70.4, 59.5, 39.5, 16.0, 14.3; IR (thin film, neat): 3072, 3025, 2978, 2931, 2907, 2872, 1708, 1643, 1496, 1455, 1420, 1367, 1320, 1284, 1226, 1202, 1132, 1049, 1002, 955, 926, 832, 738, 697 cm^{-1}; HRMS calcd for $C_{18}H_{24}O_4Na$ (M^+) 327.1567, found 327.1562.

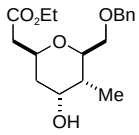


Key NOE Data for **32**:

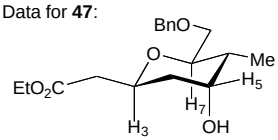


Signal Irradiated	NOE's observed
H_3	H_5 (1.5%), H_7 (2.9%)
$H_{4\text{-ax}}$	H_6 (1.5%)
H_5	H_3 (1.9%), C_6-Me (2.1%), H_7 (1.3%)
H_7	H_3 (3.3%), H_5 (1.8%), C_6-Me (1.6%)
C_6-Me	H_5 (2.6%), H_7 (2.5%)

Ethyl ((*2S*, 4S*, 5R*, 6R)-4-hydroxy-6-(benzyloxy)methyl-5-methyltetrahydropyran-2-yl)-acetate (32).** Tetrahydropyran **32** was prepared from enol ether **31** using the procedure described for synthesis of tetrahydropyrans **9a** and **10a**. Data for tetrahydropyran **32**: ^{1}H NMR (400 MHz, $CDCl_3$) d 7.34-7.25 (m, 5H), 4.63, 4.51 (ABq, *J* = 12.2 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.84 (dddd, *J* = 11.4, 7.1, 6.0, 1,9 Hz, 1H), 3.65 (dd, *J* = 11.0, 2.2 Hz, 1H), 3.54 (dd, *J* = 11.0, 4.8 Hz, 1H), 3.39 (ddd, *J* = 10.8, 10.1, 4.7 Hz, 1H), 3.19 (ddd, *J* = 10.1, 4.7, 2.2 Hz, 1H), 2.67 (dd, *J* = 15.4, 7.1 Hz, 1H), 2.44 (dd, *J* = 15.4, 6.1 Hz, 1H), 2.04 (ddd, *J* = 12.3, 4.7, 1.8 Hz, 1H), 1.61 (br s, 1H), 1.58-1.50 (m, 1H), 1.35 (ddd or app. dt, *J* = 12.1, 11.3 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 171.0, 138.4, 128.3, 127.7, 127.5, 81.1, 73.4, 72.2, 70.6, 60.5, 41.1, 40.5, 39.9, 14.2, 12.6; IR (thin film): 3446, 3087, 3070, 3033, 2979, 2914, 2870, 1730, 1496, 1453, 1372, 1317, 1258, 1209, 1149, 1100, 1084, 1051, 1024, 954, 910, 856, 737, 699 cm^{-1}; HRMS calcd for $C_{18}H_{26}O_5Na$ (M^+) 345.1672, found 345.1683. (Note: COSY and NOE data collected in $CDCl_3$.)

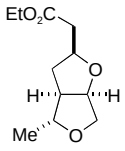


Key NOE Data for **47**:



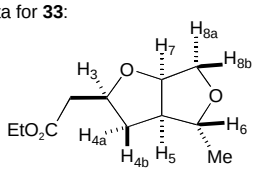
Signal Irradiated	NOE's observed
H_3	H_7 (3.0%)
H_5	$H_{4\text{-eq}}/H_6$ (3.7%), $H_{4\text{-ax}}$ (2.8%), C_6-Me (1.6%)
H_7	H_3 (2.9%), C_6-Me (1.3%)
C_6-Me	H_5 (2.1%), H_7 (2.1%)

Ethyl ((*2S*, 4R*, 5R*, 6R)-4-hydroxy-6-(benzyloxy)methyl-5-methyltetrahydropyran-2-yl)-acetate (47).** Data for impure tetrahydropyran **47**: HRMS calcd for $C_{18}H_{26}O_5Na$ (M^+) 345.1672, found 345.1683. (Note: COSY and NOE data collected in $CDCl_3$.)



33

Key NOESY Data for **33**:



Signal	Cross-peaks observed
H_3	H_{4a} (s), H_{4b} (m), H_5 (m), H_7 (m)
H_5	H_3 (w), H_6 (w), H_7 (m), C_6-Me (s)
H_7	H_3 (m), H_5 (m), H_{8a} (m), H_{8b} (w), C_6-Me (w)
H_{8a}	H_7 (m), H_{8b} (s), C_6-Me (m)
C_6-Me	H_5 (m), H_6 (m), H_7 (w), H_{8a} (m)

s=strong, m=medium, w=weak

Ethyl ((*1S*, 3R*, 5S*, 6S)-(6-methyl-2,7-dioxabicyclo-[3.3.0]-oct-3-yl))-acetate (33).** Data for bicycle **33**: ^{1}H NMR (400 MHz, $CDCl_3$) d 4.57 (ddd, *J* = 7.0, 5.0, 2.0 Hz, 1H), 4.26 (dddd or app. ddt, *J* = 9.0, 7.0, 6.2 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.94 (dd, *J* = 10.4, 4.9 Hz, 1H), 3.86-3.80 (m, 2H), 2.70 (dd, *J* = 15.6, 7.1 Hz, 1H), 2.52 (dd, *J* = 15.6, 6.1 Hz, 1H), 2.46-2.40 (m, 1H), 2.30 (ddd, *J* = 12.4, 9.0, 6.1 Hz, 1H), 1.39 (ddd, *J* = 12.4, 9.0, 5.6 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.16 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) d 171.1, 85.4, 81.6, 78.2, 72.3, 60.6, 51.7, 40.2, 36.5, 19.2, 14.2; IR (thin film from $CDCl_3$): 2967, 2934, 2869, 1734, 1463, 1447, 1387, 1371, 1338, 1317, 1295, 1257, 1197, 1165, 1094, 1078, 1029, 980, 937, 910, 861 cm^{-1}; HRMS calcd for $C_{11}H_{18}O_4Na$ (M^+) 237.1097, found 237.1092. (Note: COSY and NOESY data collected in acetone-d_6.)