Electronic Supplementary Material (ESI) for ChemComm.

Investigation of Oxidopyrylium-Alkene [5+2] Cycloaddition Conjugate Addition Cascade (C^3) Sequences

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Supporting Information – Experimental

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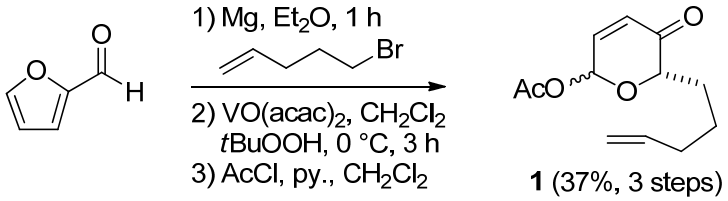
GENERAL METHODS

All reactions were carried out under Ar atmosphere in oven-dried glassware. Diethyl ether (Et_2O) was dried over pressed Na. All other commercially available anhydrous solvents and reagents were used as received. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was distilled immediately prior to use. Thin layer chromatography was performed with glass or aluminum plates (silica gel F_{254}, Art 5715, 0.25 mm), visualized by fluorescence quenching under UV light, and stained with potassium permanganate. Flash column chromatography was performed with silica gel 60 (200-400 mesh) as described by Still.[1] Mass spectral data was acquired using positive mode Electrospray Ionization (ESI+) and a high resolution Time of Flight (TOF) mass spectrometer. Infrared spectra were acquired on a FTIR spectrometer and were reported as wavenumbers (cm^{-1}). ^1H NMR spectra were acquired at 400 or 500 MHz and ^{13}C NMR spectra were acquired at 100 MHz or 125 MHz where noted. ^1H and ^{13}C NMR chemical shifts are reported as in ppm, (δ) relative to the residual solvent peaks. ^1H NMR coupling constants (*J*) are reported in Hertz (Hz), and multiplicities are indicated as follows: s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), td (triplet of doublets), ddt (doublet of doublet of triplets), dq (doublet of quartets), qq (quartet of quartets), m (multiplet), app. (apparent). Based on intensity in the ^{13}C spectra, both magnetic and chemical shift equivalent peaks are noted in parentheses.

[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

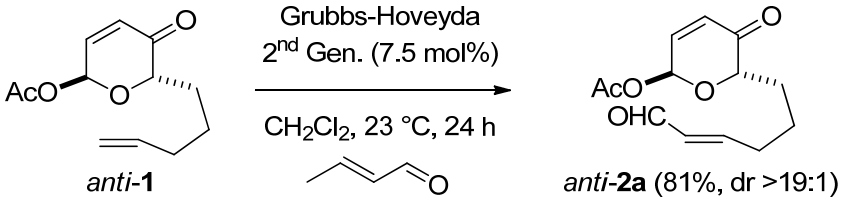
PREPARATION AND CHARACTERIZATION OF ACETOXYPYRANONES 1, 2a-f



Acetoxypyranone[2] 1: To a flame-dried, 2-neck, round bottom flask was added Mg turnings (2.50 g, 102 mmol, 1.50 equiv.), backfilled with Ar, and allowed to stir vigorously overnight. To the flask was then added anhydrous Et_2O (40 mL) and a condenser. Next, ~10% of 5-bromo-1-pentene (8.0 mL, 68 mmol, 1.1 equiv.) was added through a pressure equalizing addition funnel followed by I_2. Upon initiation, remaining 5-bromo-1-pentene was added dropwise over 10 min. The resulting solution was refluxed for 1 h, diluted with anhydrous Et_2O (120 mL), and cooled to 0 °C. Furfural (5.2 mL, 63 mmol, 1.0 equiv.) was added and the resulting solution was allowed to stir at 23 °C for 1 h at which point the reaction was quenched with sat. aq. NH_4Cl (75 mL). The reaction was stirred for 10 min and was extracted with Et_2O (200 mL). The combined organic solution was washed sequentially with sat. aq. NH_4Cl (100 mL), H_2O (100 mL), and brine (100 mL), dried with Na_2SO_4, filtered, and concentrated. The crude product was distilled under vacuum (80 °C, 1 mm Hg) to afford the alcohol **S1** (not shown) as a colorless oil (7.18 g, 43.2 mmol, 70%). To a solution of **S1** (7.18 g, 43.2 mmol, 1.0 equiv.) in CH_2Cl_2 (430 mL) was added $VO(acac)_2$ (1.15 g, 4.32 mmol, 0.1 equiv.). The solution was cooled to 0 °C and 5.5 M *t*BuOOH in decane (11.8 mL, 65 mmol, 1.5 equiv.) was added slowly. The reaction was allowed to warm to 23 °C and stirred for 3 h, quenched with sat. aq. $Na_2S_2O_3$ (200 mL), and stirred for 1 h. The resulting emulsion was diluted with CH_2Cl_2 (400 mL), filtered over Celite to remove suspended solids, and separated. The resulting aqueous solution was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic solution was washed with sat. aq. $Na_2S_2O_3$ (2 x 200 mL), dried with Na_2SO_4, filtered, and concentrated to provide crude hydroxypyranone **S2** (not shown). To a solution of **S2** (~43 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (110

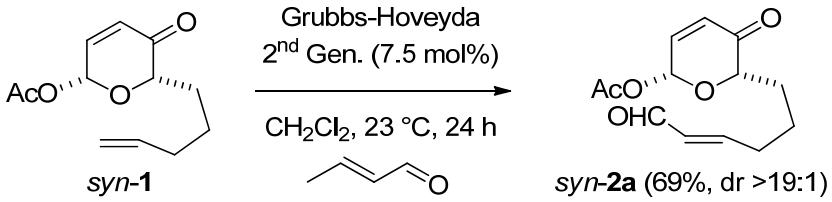
[2] Woodall, E. L.; Simanis, J. A.; Hamaker, C. G.; Goodell, J. R.; Mitchell, T. A. *Org. Lett.* **2013**, *15*, 3270-3273.

mL) was added pyridine (7.0 mL, 87 mmol, 2.0 equiv.) followed by acetyl chloride (4.5 mL, 52 mmol, 1.2 equiv.) at 0 °C. The resulting solution was allowed to warm to 23 °C and stirred for 2 h. The solution was washed with ice cold sat. aq. NaCl (2 x 50 mL), dried with Na_2SO_4, filtered, and concentrated to provide crude **1** as a mixture of diastereomers (dr 2.4:1.0). Purification by flash column chromatography (hexanes:Et_2O 75:25) delivered *anti*-**1** as a yellow oil (4.07 g, 18.1 mmol, 42%, dr >19:1), *anti*-**1**/*syn*-**1** mixture as a yellow oil (1.0 g, 4.5 mmol, 10%, dr 2.3:1.0), and *syn*-**1** as a yellow oil (1.3 g, 5.8 mmol, 13%, dr >19:1): *anti*-**1: R_f =** 0.28 (hexanes:Et_2O 75:25); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 10.3, 3.7 Hz, 1H), 6.49 (d, *J* = 3.7 Hz, 1H), 6.20 (d, *J* = 10.3 Hz, 1H), 5.83-5.75 (m, 1H), 5.03-4.98 (m, 1H), 4.97-4.94 (m, 1H), 4.47 (dd, *J* = 7.6, 3.9 Hz, 1H), 2.13 (s, 3H), 2.09-2.04 (m, 2H), 1.99-1.92 (m, 1H), 1.78-1.71 (m, 1H), 1.55-1.48 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.6, 169.7, 141.7, 138.4, 128.8, 115.0, 87.3, 75.9, 33.6, 29.3, 24.1, 21.1. *syn*-**1: R_f =** 0.20 (hexanes:Et_2O 75:25); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.84 (dd, *J* = 10.4, 2.7 Hz, 1H), 6.54 (dd, *J* = 2.7, 1.2 Hz, 1H), 6.21 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.82-5.74 (m, 1H), 5.03-4.99 (m, 1H), 4.97-4.95 (m, 1H), 4.21 (dd, *J* = 7.6, 6.4 Hz, 1H), 2.13 (s, 3H), 2.12-2.04 (m, 2H), 1.88-1.83 (m, 2H), 1.65-1.48 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.7, 169.5, 142.9, 138.2, 128.6, 115.2, 87.8, 79.7, 33.5, 32.4, 24.7, 21.2. All other spectral data was consistent with previously published data.[2]

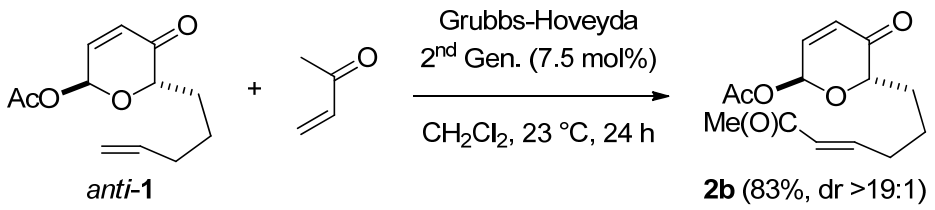


anti-**Acetoxypyranone 2a:** A solution of *anti*-**1** (1.70 g, 7.58 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (39 mL) was degassed for 10 min by bubbling Ar *via* balloon. Crotonaldehyde (3.1 mL, 37.9 mmol, 5.0 equiv.) and Grubbs-Hoveyda 2nd generation catalyst (357 mg, 0.57 mmol, 0.075 equiv.) were added sequentially. The reaction was degassed for an additional 10 min. The reaction was allowed to stir at 23 °C for 24 h and concentrated. Purification by flash column chromatography (hexanes:EtOAc 80:20 to

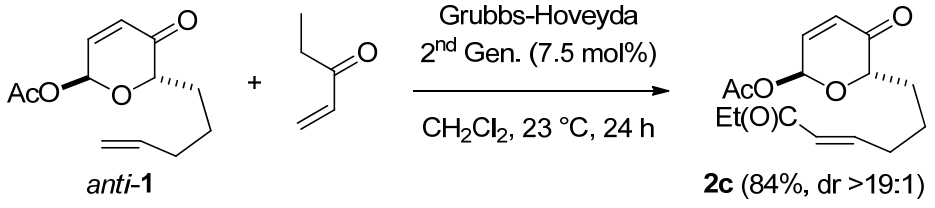
70:30) delivered *anti*-**2a** as a brown oil (1.55 g, 6.14 mmol, 81%, dr >19:1): $\mathbf{R_f}$ = 0.23 (hexanes:EtOAc 70:30); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.50 (d, *J* = 7.8 Hz, 1H), 6.90 (dd, *J* = 10.2, 3.9 Hz, 1H), 6.83 (dt, *J* = 15.7, 6.7 Hz, 1H), 6.50 (d, *J* = 3.9 Hz, 1H), 6.22 (d, *J* = 10.2 Hz, 1H), 6.12 (ddt, *J* = 15.7, 7.8, 1.5 Hz, 1H), 4.49 (dd, *J* = 7.3, 3.9 Hz, 1H), 2.38-2.34 (m, 2H), 2.13 (s, 3H), 2.02-1.95 (m, 1H), 1.85-1.77 (m, 1H), 1.67-1.61 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.2, 194.0, 169.6, 157.9, 141.8, 133.3, 128.6, 87.0, 75.5, 32.4, 29.1, 23.0, 21.0; All other spectral data was consistent with previously published data.[2]



syn-**Acetoxypyranone 2a:** A solution of *syn*-**1** (400 mg, 1.78 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (9.0 mL) was degassed for 10 min by bubbling Ar *via* balloon. Crotonaldehyde (735 µL, 8.9 mmol, 5.0 equiv.) and Grubbs-Hoveyda 2nd generation catalyst (84 mg, 0.13 mmol, 0.075 equiv.) were added sequentially. The reaction was degassed for an additional 10 min. The reaction was allowed to stir at 23 °C for 24 h and concentrated. Purification by flash column chromatography (hexanes:EtOAc 80:20 to 70:30) delivered *syn*-**2a** as a brown oil (309 mg, 1.23 mmol, 69%, dr >19:1): $\mathbf{R_f}$ = 0.19 (hexanes:EtOAc 70:30); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.53 (d, *J* = 7.8 Hz, 1H), 6.89 (dd, *J* = 10.4, 2.4 Hz, 1H), 6.85 (dt, *J* = 15.7, 6.8 Hz, 1H), 6.57 (dd, *J* = 2.4, 1.6 Hz, 1H), 6.25 (dd, *J* = 10.4, 1.5 Hz, 1H), 6.15 (ddt, *J* = 15.7, 7.8, 1.5 Hz, 1H), 4.22 (dd, *J* = 8.6, 4.9 Hz, 1H), 2.44-2.38 (m, 2H), 2.15 (s, 3H), 2.00-1.89 (m, 2H), 1.78-1.67 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.0, 193.9, 169.1, 157.6, 143.5, 133.3, 128.6, 87.9, 79.0, 32.2, 31.6, 23.5, 21.0; All other spectral data was consistent with previously published data.[2]

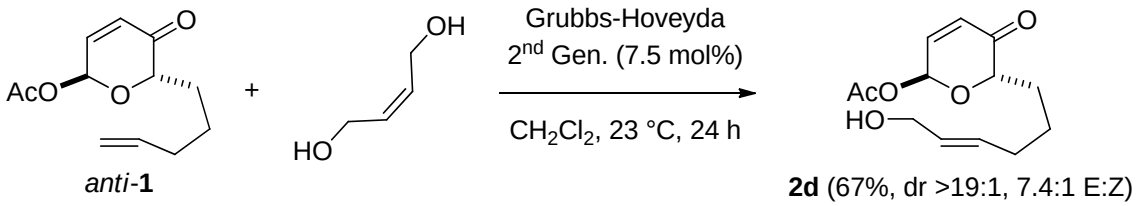


anti-**Acetoxypyranone 2b:** A solution of *anti*-**1** (1.0 g, 4.46 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (10.0 mL) was degassed for 5 min by bubbling Ar *via* balloon. Next, 3-Buten-2-one (2.24 mL, 26.8 mmol, 6.0 equiv.) and Grubbs-Hoveyda 2nd generation catalyst (209.6 mg, 0.33 mmol, 0.075 equiv) were added sequentially. The reaction was backfilled with Ar, degassed for an additional 5 min, and allowed to stir at 23 °C for 24 h at which point the reaction was concentrated *via* rotary evaporation. Purification by flash column chromatography (hexanes:EtOAc 80:20 to 70:30) delivered *anti*-**2b** as an olive green oil (983 mg, 4.34 mmol, 83%, dr >19:1): $\mathbf{R_f}$ = 0.23 (hexanes:EtOAc 70:30); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 10.2, 3.8 Hz, 1H), 6.77 (dt, *J* = 15.9, 6.8 Hz, 1H), 6.49 (d, *J* = 3.8 Hz, 1H), 6.21 (d, *J* = 10.2 Hz, 1H), 6.07 (dt, *J* = 15.9, 1.5 Hz, 1H), 4.47 (dd, *J* = 7.4, 3.7 Hz, 1H), 2.27-2.22 (m, 2H), 2.23 (s, 3H), 2.13 (s, 3H), 2.00-1.93 (m, 1H), 1.82-1.74 (m, 1H), 1.63-1.57 (m, 2H); **^{13}C NMR** (125 MHz,$CDCl_3$) δ 198.7, 195.3, 169.7, 147.6, 141.8, 131.8, 128.8, 87.2, 75.7, 32.3, 29.3, 27.0, 23.4, 21.1; **IR (film) ν_{max}** 1751, 1695, 1672, 1626, 1215 cm^{-1}; **ESI-HRMS** calcd for $C_{14}H_{18}O_5$ $[M+Na]^+$ 289.1052, found 289.1048.



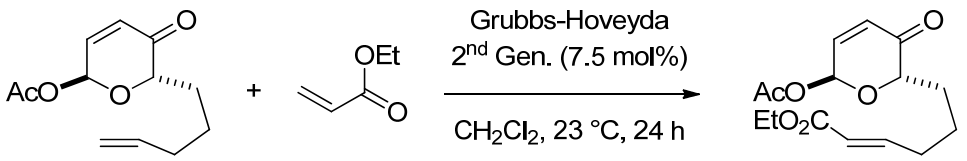
anti-**Acetoxypyranone 2c:** A solution of *anti*-**1** (500 mg, 2.23 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (11.0 mL) was degassed for 5 min by bubbling Ar *via* balloon. Next, 1-penten-3-one (1.33 mL, 13.4 mmol, 6.0 equiv) and Grubbs-Hoveyda 2nd generation catalyst (105 mg, 0.167 mmol, 0.075 equiv) were added sequentially. The reaction was backfilled with Ar, degassed for an additional 5 min, and allowed to stir at 23 °C for 24 h at which point the reaction was concentrated *via* rotary evaporation. Purification by

flash column chromatography (hexanes:EtOAc 70:30) delivered *anti*-**2c** as an brown oil (526 mg, 1.88 mmol, 84%, dr >19:1): $\mathbf{R_f}$ = 0.30 (hexanes:EtOAc 70:30); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 10.2, 3.7 Hz, 1H), 6.80 (dt, *J* = 15.9, 6.8 Hz, 1H), 6.49 (d, *J* = 3.7 Hz, 1H), 6.21 (d, *J* = 10.2 Hz, 1H), 6.10 (dt, *J* = 15.9, 1.5 Hz, 1H), 4.47 (dd, *J* = 7.3, 4.0 Hz, 1H), 2.56 (q, *J* = 7.3 Hz, 2H), 2.25-2.20 (m, 2H), 2.13 (s, 3H), 2.00-1.92 (m, 1H), 1.82-1.73 (m, 1H), 1.63-1.55 (m, 2H), 1.09 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz,$CDCl_3$) δ 201.2, 195.4, 169.6, 146.2, 141.8, 130.6, 128.7, 87.2, 75.7, 33.4, 32.2, 29.3, 23.4, 21.1, 8.3; **IR (film)** ν_{max} 1752, 1695, 1671, 1629, 1174 cm^{-1}; **ESI-HRMS** calculated for $C_{15}H_{20}O_5$ $[M+Na]^+$ 303.1208, found 303.1197.



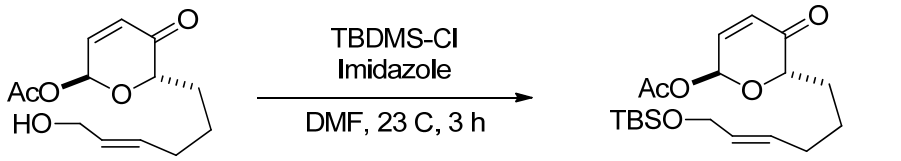
anti-**1** **2d** (67%, dr >19:1, 7.4:1 E:Z)

anti-**Acetoxypyranone 2d:** To a vial was added *anti*-**1** (400 mg, 1.78 mmol, 1 equiv), followed by anhydrous CH_2Cl_2 (9 mL) and cis-2-butene-1,4-diol (880 μL, 10.7 mmol, 6 equiv.). The resulting solution was then degassed by bubbling argon gas for 5 min. Next, Grubbs-Hoveyda second generation catalyst was added (84 mg, 0.134 mmol, 0.075 equiv). The reaction was backfilled with Ar, degassed for an additional 5 min, and allowed to stir at 23 °C for 24 h at which point the reaction was concentrated *via* rotary evaporation. Purified by flash column chromatography (hexanes:EtOAc 50:50) to afford **2d** as a yellow oil (303 mg, 1.19 mmol, 67%) as a 7.4:1 mixture of *E*:*Z* stereoisomers as determined by ^{1}H NMR; characterization data for *E*-**2d**: $\mathbf{R_f}$ = 0.28 (hexanes:EtOAc 50:50); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 10.3, 3.8 Hz, 1H), 6.49 (d, *J* = 3.8 Hz, 1H), 6.20 (d, *J* = 10.30 Hz, 1H), 5.70-5.62 (m, 2H), 4.47 (dd, *J* = 7.6, 3.9 Hz, 1H), 4.08 (m, 2H), 2.13 (s, 3H), 2.10-2.03 (m, 2H) 2.00-1.90 (m, 1H), 1.79-1.71 (m, 1H), 1.55-1.48 (m, 2H), 1.28 (br. s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 195.6, 169.7, 141.7, 132.5, 129.7, 128.8, 87.2, 75.8, 63.7, 31.9, 29.2, 24.3, 21.0; **IR (film)** ν_{max} 3439, 1750, 1694, 1217 cm^{-1}; **ESI-HRMS** calculated for $C_{13}H_{18}O_5$ $[M+Na^+]$ 277.1052, found 277.1064.



anti-**1** **2e** (90%, dr >19:1)

***anti*-Acetoxypyranone 2e:** A solution of *anti*-**1** (850 mg, 3.79 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (9.5 mL) was degassed for 10 min by bubbling Ar *via* balloon. Ethyl acrylate (2.43 mL, 22.8 mmol, 6.0 equiv) and Grubbs-Hoveyda 2nd generation catalyst (178 mg, 0.266 mmol, 0.075 equiv) were added sequentially. The reaction was backfilled with Ar, allowed to stir at 23 °C for 24 h, and concentrated *via* rotary evaporation. Purification by flash chromatography (hexanes:Et_2O 70:30) delivered *anti*-**2e** as a yellow oil (1.02 g, 3.44 mmol, 91%, dr >19:1): $\mathbf{R_f}$ = 0.32 (hexanes:EtOAc 80:20); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.93 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.89 (dd, *J* = 10.1, 3.8 Hz, 1H), 6.49 (d, *J* = 3.8 Hz, 1H), 6.21 (d, *J* = 10.1 Hz, 1H), 5.82 (dt, *J* = 15.6, 1.6 Hz, 1H), 4.47 (dd, *J* = 7.5, 3.9 Hz, 1H), 4.18 (app. q, *J* = 7.2 Hz, 2H), 2.25-2.19 (m, 2H), 2.13 (s, 3H), 1.97-1.92 (m, 1H), 1.81-1.72 (m, 1H), 1.63-1.55 (m, 2H), 1.28 (app. t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.1, 169.4, 166.5, 148.3, 141.6, 128.5, 121.7, 86.9, 75.5, 60.1, 31.8, 29.0, 23.1, 20.9, 14.2. All spectral data was consistent with previously published data.[2]

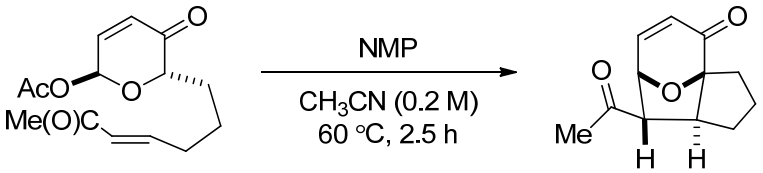


anti-**2d** (dr >19:1, 7.4:1 E:Z) **2f** (60%, dr >19:1, 10:1 E:Z)

***anti*-Acetoxypyranone 2f:** To a vial was added dimethylformamide (3.5 ml), followed by tert-butyldimethylsilylchloride (226 mg, 1.18 mmol, 1.5 equiv) and *N*,*N*-Diisopropylethylamine (205 µl, 1.18 mmol, 1.5 equiv). To this solution was then added *anti*-acetoxypyranone **2d** (200 mg, 0.786 mmol, 1 equiv.) as a suspension in DMF (2 mL) dropwise. The flask was then backfilled with argon, capped, and allowed to stir 3 h at which point monitoring by TLC (hexanes:EtOAc 50:50) showed complete consumption of starting material. The reaction was then diluted with DI water (5 mL), and extracted with

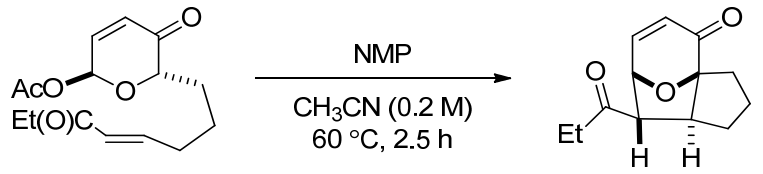
diethyl ether (3 x 15 mL). Organics were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *via* rotary evaporation. Purified by flash column chromatography (hexanes:EtOAc 80:20) to afford **2f** as a clear colorless oil (173 mg, 0.469 mmol, 60%) in an 10:1 mixture of *E*:*Z* stereoisomers as determined by NMR; characterization data for *E*-**2f**: $\mathbf{R_f}$ = 0.77 (hexanes:EtOAc 50:50); **^{1}H NMR** (400 MHz , $CDCl_3$) δ 6.87 (dd, *J* = 10.0, 3.6 Hz, 1H), 6.49 (d, *J* = 3.6 Hz, 1H), 6.19 (d, *J* = 10.0 Hz, 1H), 5.65-5.49 (m, 2H), 4.46 (dd, *J* = 7.5, 3.8 Hz, 1H), 4.10 (m, 2H), 2.12 (s, 3H), 2.08-1.99 (m, 2H), 1.99-1.87 (m, 1H), 1.80-1.65 (m, 1H), 1.53-1.46 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.5, 169.5, 141.5, 130.5, 129.7, 128.7, 87.1, 75.8, 63.9, 31.9, 29.2, 26.0(3), 24.3, 20.9, 18.4, -5.1(2); **IR (film)** ν_{max} 1756, 1700, 1217 cm^{-1}; **ESI-HRMS** calculated for $C_{19}H_{32}O_5Si$ [$M+Na^+$] 391.1917, found 391.1915.

PREPARATION AND CHARACTERIZATION OF [5+2] CYCLOADDUCTS 3b,c,f,e



anti-**2b** **3b** (87%)

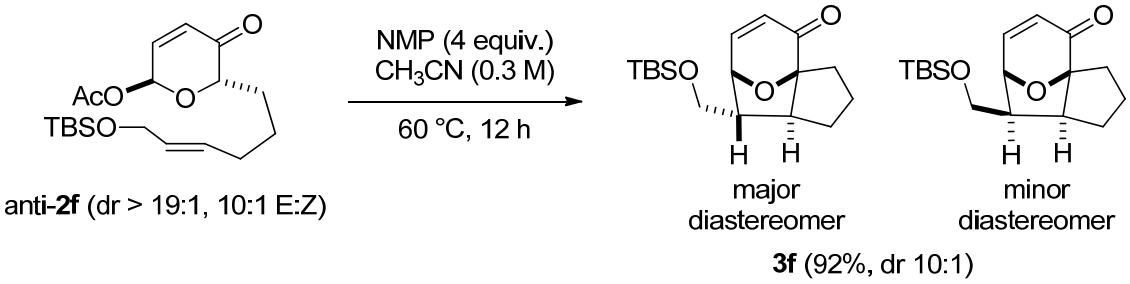
Methyl-ketone cycloadduct 3b: To a solution of *anti*-**2b** (792 mg, 2.97 mmol, 1.0 equiv) in CH_3CN (15 mL) was added *N*-methylpyrrolidine (1.24 mL, 11.9 mmol, 4.0 equiv). The reaction was allowed to stir for 2.5 h at 60 °C and then concentrated. Purification by flash column chromatography (hexanes:EtOAc 70:30) afforded **3b** as a white solid (535 mg, 2.59 mmol, 87%, dr >19:1): $\mathbf{R_f}$ = 0.32 (hexanes:EtOAc 70:30); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 9.8, 4.4 Hz, 1H), 6.02 (d, *J* = 9.8 Hz, 1H), 4.96 (dd, *J* = 6.0, 4.4 Hz, 1H), 3.22 (dd, *J* = 7.2, 6.0 Hz, 1H), 2.62-2.58 (m, 1H), 2.31-2.25 (m, 1H), 2.21 (s, 3H), 2.10-1.98 (m, 1H), 1.96-1.84 (m, 2H), 1.80-1.71 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 205.3, 196.6, 150.0, 127.0, 98.4, 76.5, 65.3, 47.7, 31.9, 30.2, 29.9, 25.8; **IR (film) ν_{max}** 1700, 1687, 1053 cm^{-1}; **ESI-HRMS** calculated for $C_{12}H_{14}O_3$ $[M+H]^+$ 207.1021, found 207.1028.



anti-**2c** **3c** (85%)

Ethyl-ketone cycloadduct 3c: To a solution of *anti*-**2c** (100 mg, 0.357 mmol, 1.0 equiv) in CH_3CN (1.8 mL) was added *N*-methylpyrrolidine (150 µL, 1.43 mmol, 4.0 equiv). The reaction was allowed to stir for 3 h at 60 °C and then concentrated *via* rotary evaporation. Purification by flash column chromatography (hexanes:EtOAc 70:30) afforded **3c** as a white solid (66.5 mg, 0.302 mmol, 85%): $\mathbf{R_f}$ = 0.39 (hexanes:EtOAc 70:30); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 9.8, 4.4 Hz, 1H), 6.03 (d, *J* = 9.8 Hz, 1H), 4.96 (dd, *J* = 6.0, 4.4 Hz, 1H), 3.22 (dd, *J* = 7.2, 6.0 Hz, 1H), 2.60 (ddd, *J* = 7.4, 7.2, 3.4 Hz, 1H), 2.51 (dq, *J* = 14.5, 7.3 Hz, 1H), 2.50 (dq, *J* = 14.5, 7.2 Hz, 1H), 2.32-2.24 (m, 1H), 2.05-1.84 (m,

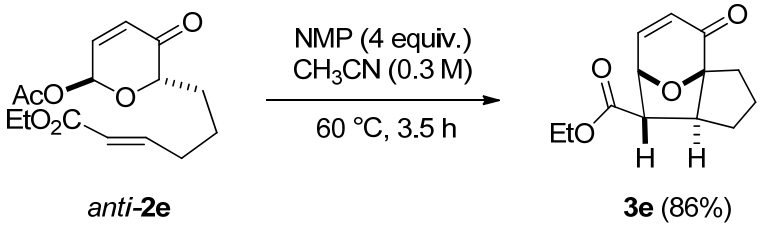
3H), 1.79-1.69 (m, 2H), 1.06 (dd, J = 7.3, 7.2 Hz, 3H); **^{13}C NMR** (100 MHz,$CDCl_3$) δ 208.1, 196.7, 150.1, 126.9, 98.4, 76.6, 64.3, 47.9, 36.0, 31.9, 30.2, 25.8, 7.6; **IR (film) ν_{max}** 1697, 1035 cm^{-1}; **ESI-HRMS** calculated for $C_{13}H_{16}O_3$ $[M+Na]^+$ 243.0997, found 243.1002.



anti-**2f** (dr > 19:1, 10:1 E:Z)

3f (92%, dr 10:1)

Silyl-ether cycloadduct 3f: To a vial containing *anti*-acetoxypyranone **2f** (173 mg, 0.469 mmol, 1 equiv.) was added CH_3CN (4.7 mL), and then *N*-methylpyrrolidine (195 μL, 1.88 mmol, 4 equiv.). The resulting solution was allowed to stir for 12 h at 60 °C at which point monitoring by TLC (hexanes:EtOAc 70:30) showed complete consumption of starting material. The reaction was concentrated *via* rotary evaporation, and purified by flash column chromatography (hexanes:EtOAc 95:5) to afford **3f** as a clear colorless oil (134 mg, 0.434 mmol, 92%) in an 10:1 mixture of diastereomers as determined by NMR; characterization data for **major** diastereomer: $\mathbf{R_f}$ = 0.76 (hexanes:EtOAc 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.14 (dd, J = 9.8, 4.3 Hz, 1H), 6.08 (d, J = 9.8 Hz, 1H), 4.84 (dd, J = 6.0, 4.3 Hz, 1H), 3.75 (dd, J = 10.3, 6.0 Hz, 1H), 3.40 (dd, J = 10.3, 9.6 Hz, 1H), 2.49-2.42 (m, 1H), 2.26-2.15 (m, 1H), 1.95-1.90 (m, 1H), 1.87-1.80 (m, 3H), 1.75-1.64 (m, 2H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.4, 150.6, 128.0, 98.3, 77.9, 64.0, 54.5, 47.6, 31.4, 30.2, 26.0(3), 25.8, 18.2, -5.3, -5.4; **IR (film) ν_{max}** 1700, 1086 cm^{-1}; **ESI-HRMS** calculated for $C_{17}H_{29}O_3Si$ $[M+H]^+$ 309.1886, found 309.1889.

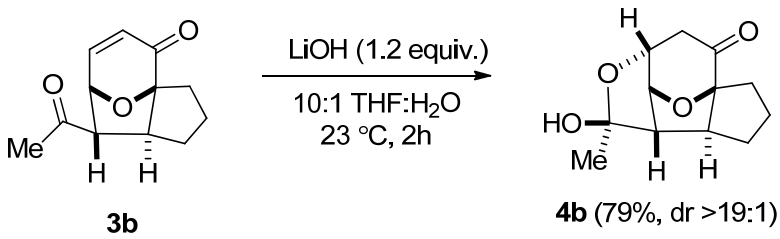


anti-**2e** **3e** (86%)

Ethyl-ester cycloadduct 3e: To a vial containing *anti*-acetoxypyranone **2e** (1.02 g, 3.44 mmol, 1 equiv.) was added CH_3CN (11.5 mL). To this solution was added *N*-methylpyrrolidine (1.43 mL, 13.8 mmol, 4 equiv.). The vial was then capped and allowed to stir for 3.5 h at 60 °C at which point monitoring by aliquot NMR showed complete consumption of starting material. The reaction was concentrated *via* rotary evaporation, and purified by flash column chromatography (hexanes:EtOAc 80:20) to give **3e** as a yellow oil (702 mg, 2.97 mmol, 86%): $\mathbf{R_f}$ = 0.35 (hexanes:EtOAc 80:20) **^{1}H NMR**: (400 MHz, $CDCl_3$) δ 7.11 (dd, *J* = 9.8, 4.3 Hz, 1H), 6.03 (d, *J* = 9.8, 1H), 4.96 (dd, *J* = 6.4, 4.3 Hz, 1H), 4.11 (app. dq, *J* = 14.4, 7.2, 2H), 2.19-2.12 (m, 2H), 3.08 (dd, *J* = 6.6, 6.4, 1H), 2.67 (ddd, *J* = 9.0, 6.6, 3.3 Hz, 1H), 2.26-2.18 (m, 1H), 2.01-1.92 (m, 1H), 1.90-1.80 (m, 2H), 1.72-1.63 (m, 2H), 1.22 (t, *J* = 7.2, 3H). All additional spectral data was consistent with previously published data.[3]

[3] Burns, N. Z.; Witten, M. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 14578-14581

STEPWISE PREPARATION AND CHARACTERIZATION OF [5+2] C^3 CYCLOADDUCTS 4b-e



3b **4b** (79%, dr >19:1)

Methyl-lactol 4b: To a vial was added methyl-ketone cycloadduct **3b** (30 mg, 0.145 mmol, 1.0 equiv.) followed by THF (2 mL) and H_2O (200 μL). To this solution was added LiOH (4.2 mg, 0.17 mmol, 1.2 equiv.). The reaction was capped and allowed to stir for 2 h at room temperature. The reaction was then acidified with addition of 1 N HCl, diluted with brine (2 mL), and extracted with EtOAc (2 x 3 mL). Organics were combined, and concentrated *via* rotary evaporation. Purification by flash chromatography (hexanes:EtOAc 70:30) afforded lactol **4b** as a white solid (25.7 mg, 0.116 mmol, 80%, dr >19:1): $\mathbf{R_f}$ = 0.32 (hexanes:EtOAc 60:40); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.35 (dd, *J* = 6.9, 6.1 Hz, 1H), 4.63 (ddd, *J* = 6.9, 4.3, 1.8 Hz, 1H), 2.70 (br. s, 1H), 2.69 (dd, *J* = 16.1, 4.3 Hz, 1H), 2.47 (dd, *J* = 16.2, 1.8 Hz, 1H), 2.44 (dd, *J* = 6.1, 2.8 Hz, 1H), 2.25-2.22 (m, 1H), 2.15 (ddd, *J* = 9.5, 7.3, 2.8 Hz, 1H), 2.05-1.98 (m, 1H), 1.95-1.87 (m, 1H), 1.79-1.74 (m, 2H), 1.57-1.50 (m, 1H), 1.47 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 211.2, 104.2, 99.9, 84.2, 73.1, 58.0, 52.1, 41.0, 33.5, 32.3, 27.2, 24.2; **IR (film)** $\mathbf{\nu_{max}}$ 3442, 1713, 1151 cm^{-1}; **ESI-HRMS** calculated for $C_{12}H_{16}O_4Na$ $[M+Na]^+$ 247.0946, found 247.0948. Subjection of a concentrated solution of methyl-lactol **4b** in chloroform to vapor diffusion of hexanes over several days at ambient temperature provided a crystalline solid which was subjected to crystallographic analysis *via* x-ray diffraction (Figure S1).

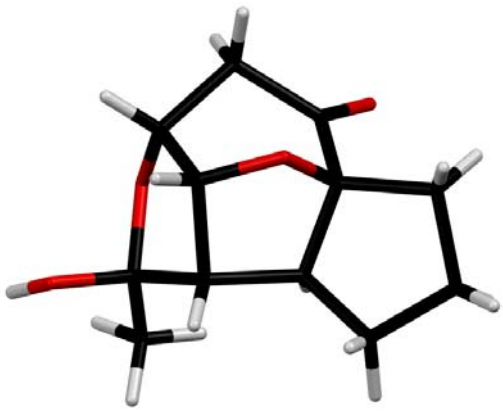
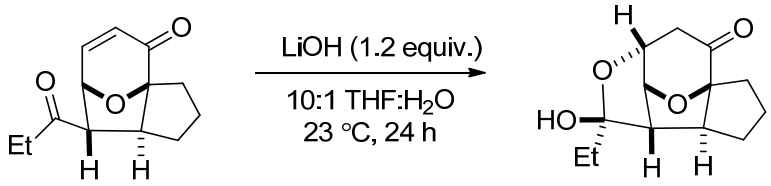


Figure S1. Connectivity Diagram of Methyl-Lactol **4b** obtained by X-Ray Crystallographic Analysis



3c **4c** (42%, dr >19:1)

Ethyl-lactol 4c: To a vial was added methyl-ketone cycloadduct **3c** (53 mg, 0.241 mmol, 1.0 equiv.) followed by THF (2.2 mL) and H_2O (220 μL). To this solution was added LiOH (20 mg, 0.481 mmol, 2 equiv.). The reaction was capped and allowed to stir for 24 h at room temperature. The reaction was then acidified with addition of 1 N HCl, diluted with brine (5 mL), and extracted with EtOAc (2 x 5 mL). Organics were combined, dried over Na_2SO_4 and concentrated *via* rotary evaporation. Purification by flash chromatography (hexanes:EtOAc 80:20) afforded lactol **4c** as a white solid (23.9 mg, 0.100 mmol, 41%, dr >19:1): $\mathbf{R_f}$ = 0.19 (hexanes:EtOAc 70:30); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.36 (dd, *J* = 7.1, 5.9 Hz, 1H), 4.67 (ddd, *J* = 7.1, 4.3, 1.8 Hz, 1H), 2.71 (dd, *J* = 16.1, 4.3 Hz, 1H), 2.49 (dd, *J* = 16.1, 1.8 Hz, 1H), 2.48 (dd, *J* = 5.9, 2.8 Hz, 1H), 2.30-2.21 (m, 1H), 2.15 (ddd, *J* = 9.4, 7.2, 2.8 Hz, 1H), 2.09-2.01 (m, 2H), 1.98-1.89 (m, 1H), 1.86-1.75 (m, 3H), 1.71-1.62 (m, 1H), 1.61-1.50 (m, 1H), 0.99 (t, 7.6 Hz, 3H); **^{13}C NMR** (100 MHz,$CDCl_3$) δ 211.3, 106.9, 99.9, 83.8, 73.1, 56.1, 51.4, 41.2, 33.6, 32.4, 30.6, 27.2, 8.6; **IR (film)** $\mathbf{\nu_{max}}$ 3368, 1728, 1147 cm^{-1}; **ESI-HRMS** calculated for $C_{13}H_{18}O_4$ $[M+Na]^+$ 261.1102, found

261.1102 Subjection of a solution of ethyl-lactol **4c** in dichloromethane to slow evaporation over several days at ambient temperature provided a single crystal suitable for X-ray diffraction analysis (Figure S2).

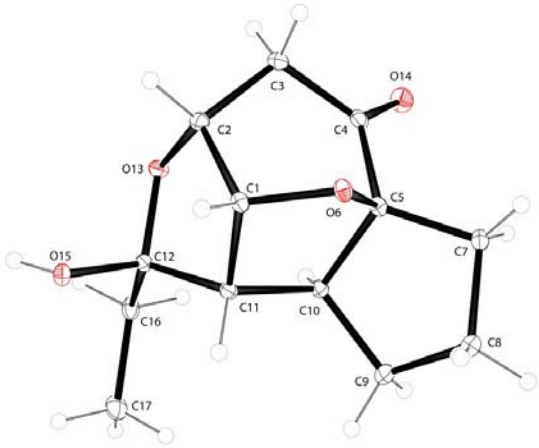
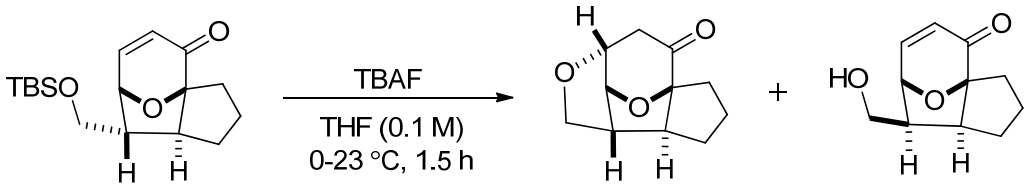


Figure S2. ORTEP Diagram of Ethyl-Lactol **4c**
(Displacement Ellipsoids at 50% Probability; H Atoms Drawn at Arbitrary Size)



3f (dr 8.8:1) **4d** (75%) *exo*-**3d** (trace)

Bis-ether 4d: To a vial was added silyl-ether cycloadduct **3f** (133 mg, 0.431 mmol, 1 equiv) and THF (4.3 mL). The resulting solution was cooled to 0 °C, at which point TBAF (860 µL, 0.862 mmol, 2 equiv) was added. The vial was then capped and allowed to warm to room temperature while stirring. After 1.5 h TLC (hexanes:EtOAc 70:30) showed complete consumption of starting material at which point the reaction was diluted with diethyl ether (10 mL), and washed with sat. aq. NH_4Cl (2 x 10 mL). The resulting organic fraction was then dried with $MgSO_4$, filtered, and concentrated *via* rotary evaporation. The crude mixture was purified by flash column chromatography (hexanes:EtOAc 70:30 to 50:50) to afford desired compound **4d** as a white solid (62.5 mg, 0.322 mmol, 75%): $\mathbf{R_f}$ = 0.46 (hexanes:EtOAc 50:50); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.09 (dd, *J* = 7.3, 6.3 Hz, 1H), 4.43 (ddd, *J* = 7.3, 4.3, 1.8 Hz, 1H),

3.80 (d, *J* = 9.3 Hz, 1H), 3.63 (dd, *J* = 9.3, 3.9 Hz, 1H), 2.68 (dd, *J* = 16.1, 4.3 Hz, 1H), 2.55 (ddd, *J* = 6.3, 3.9, 2.7 Hz, 1H), 2.50 (dd, *J* = 16.1, 1.8 Hz, 1H), 2.31-2.23 (m, 1H), 2.20 (ddd, *J* = 9.4, 6.9, 2.7 Hz, 1H), 2.11-1.98 (m, 1H), 1.97-1.85 (m, 1H), 1.84-1.70 (m, 2H), 1.65-1.50 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 211.2, 100.2, 83.9, 72.9, 70.2, 56.1, 50.1, 41.9, 33.6, 32.4, 27.0; **IR (film)** ν_{max} 1717, 1042 cm^{-1}; **ESI-HRMS** calculated for $C_{11}H_{14}O_3$ $[M+Na]^+$ 217.0841, found 217.0849. Trace amount of impure enone-alcohol *exo*-**3d** from multiple reactions was collected as a yellow oil, and was repurified by flash column chromatography (hexanes:EtOAc 40:60) to afford material suitable for characterization; ***exo*-3d**: $\mathbf{R_f}$ = 0.24 (hexanes:EtOAc 40:60); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 9.7, 4.5 Hz, 1H), 6.00 (d, *J* = 9.7 Hz, 1H), 4.84 (d, *J* = 4.5 Hz, 1H), 3.85 (dd, *J* = 10.0, 5.3 Hz, 1H), 3.63 (dd, *J* = 10.0, 9.8 Hz, 1H), 2.53-2.48 (m, 1H), 2.38-2.31 (m, 2H), 1.82-1.64 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.7, 152.0, 126.2, 99.1, 78.5, 62.5, 46.5, 46.1, 29.9, 28.2, 26.3; **IR (film)** $\boldsymbol{\nu_{max}}$ 3472, 1684 cm^{-1}; **ESI-HRMS** calculated for $C_{11}H_{14}O_3$ $[M+H]^+$ 195.1021, found 195.1024. Subjection of a solution of bis-ether **4d** in hexanes to slow evaporation over several days at ambient temperature provided a single crystal suitable for X-ray diffraction analysis (Figure S3).

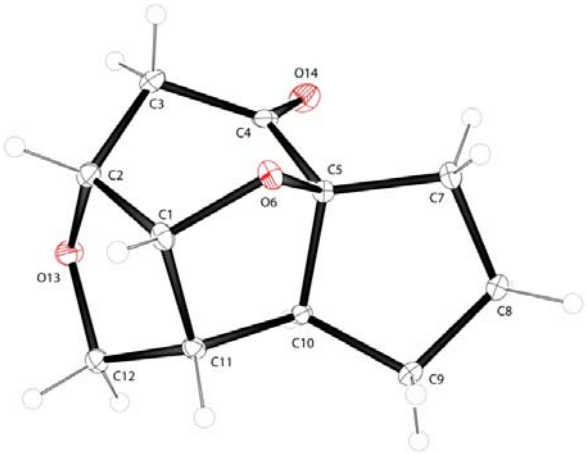
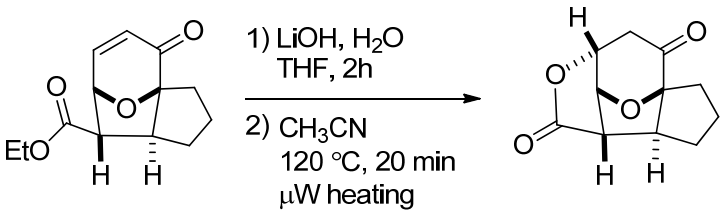


Figure S3. ORTEP Diagram of Bis-ether **4d**
(Displacement Ellipsoids at 50% Probability; H Atoms Drawn at Arbitrary Size)



3e **4e** (36%, dr > 19:1)

Lactone 4e: Ester-cycloadduct **3e** (702 mg, 2.97 mmol, 1 equiv.) was suspended in H_2O (15 mL). To this mixture was added LiOH (285 mg, 11.9 mmol, 4 equiv.). The reaction was then stirred at room temperature for 3 h at which point monitoring my TLC (hexanes:EtOAc 70:30) showed complete consumption of starting material. The solution was then extracted with EtOAc to remove organic impurities, acidified using 1 N HCl to pH ~3, at which point acid cycloadduct was extracted with EtOAc (3 x 35 mL). Combined organic fractions were then dried over Na_2SO_4, filtered, and concentrated *via* rotary evaporation to provide carboxylic acid **S3** (not shown) as an impure pale yellow solid (728 mg). A solution of crude carboxylic acid **S3** (100 mg, ~0.48 mmol, 1.0 equiv) in CH_3CN (1 mL) was heated at 120 °C in a microwave reactor for 20 min and then concentrated *via* rotary evaporation. Purification by flash column chromatography (CH_2Cl_2:acetone 95:5) afforded **4e** as a pale yellow solid (36.3 mg, 0.174 mmol, 36%): $\mathbf{R_f}$ = 0.84 (CH_2Cl_2:acetone 90:10); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.39 (dd, *J* = 7.7, 7.0 Hz, 1H), 5.14 (ddd, *J* = 7.7, 5.9, 1.3 Hz, 1H), 2.93 (dd, *J* = 7.0, 1.8 Hz, 1H), 2.91 (dd, *J* = 17.0, 5.9 Hz, 1H), 2.69 (dd, *J* = 17.0, 1.3 Hz, 1H), 2.53 (app. td, *J* = 8.8, 1.8 Hz, 1H), 2.41-2.32 (m, 1H), 2.28-2.18 (m, 1H), 2.05-1.76 (m, 3H), 1.65-1.55 (m, 1H); **^{13}C NMR** (100 MHZ, $CDCl_3$) δ 207.7, 175.1, 100.2, 78.9, 75.8, 54.2, 47.8, 40.9, 33.8, 31.6, 26.7; **IR (film) ν_{max}** 1765, 1722, 1025 cm^{-1}; **ESI-HRMS** calculated for $C_{11}H_{13}O_4$ $[M+H]^+$ 209.0814, found 209.0814. Subjection of a concentrated solution of lactone **4e** in EtOAc to vapor diffusion of hexanes over several days at ambient temperature provided a single crystal suitable for X-ray diffraction analysis (Figure S4).

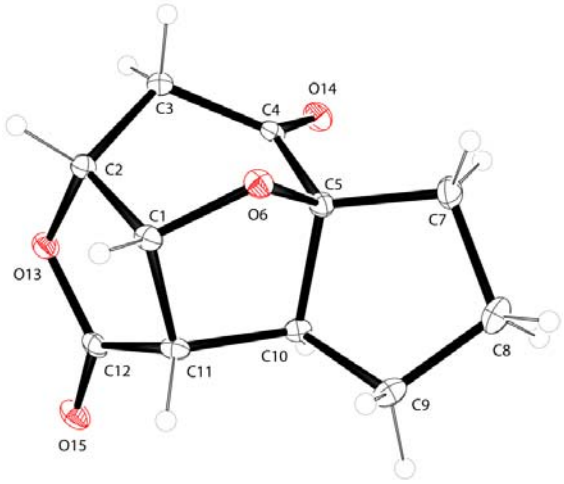
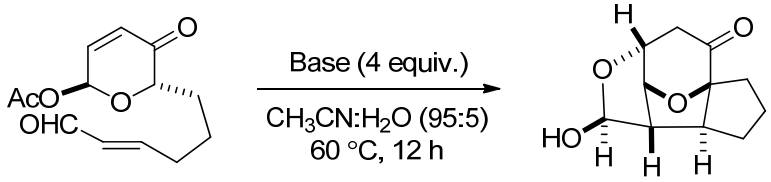


Figure S4. ORTEP Diagram of Lactone **4e**
(Displacement Ellipsoids at 50% Probability; H Atoms Drawn at Arbitrary Size)

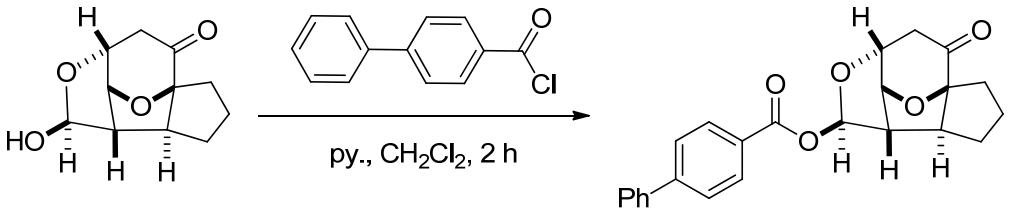
TANDEM PREPARACTION, AND CHARACTERIZATION OF CYCLOADDUCTS 4a-d, f-m

General Procedure for Synthesis of Lactol 4a by Tandem [5+2] C^3 of 2a (Table 1):



2a **4a**

To a solution of **2a** (100 mg, 0.40 mmol, 1.0 equiv.) in 95:5 CH_3CN:H_2O (3.8 mL CH_3CN, 200 μL H_2O) was added appropriate base (1.60 mmol, 4.0 equiv.; in the case of DBU: 0.40 mmol, 1 equiv.). The reaction was allowed to stir for 12 h at 60 °C (in the case of entry 8: 23 °C) and then concentrated *via* rotary evaporation. Purification by flash chromatography (hexanes:EtOAc 70:30) afforded lactol **4a** as a pale orange oil (dr >19:1): $\mathbf{R_f}$ = 0.08 (hexanes:EtOAc 70:30); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.31 (dd, *J* = 6.7, 6.0 Hz, 1H), 5.27 (br. s, 1H), 4.68 (ddd, *J* = 6.7, 4.2, 1.9 Hz, 1H), 3.33 (br. s, 1H), 2.70 (dd, *J* = 16.1, 4.2 Hz, 1H), 2.54 (dd, *J* = 6.0, 2.8 Hz, 1H), 2.48 (dd, *J* = 16.1, 1.9 Hz, 1H), 2.24-2.18 (m, 1H), 2.12 (ddd, *J* = 9.3, 6.7, 2.8 Hz, 1H), 2.06-1.99 (m, 1H), 1.93-1.85 (m, 1H), 1.80-1.72 (m, 2H), 1.59-1.53 (m, 1H); **^{13}C NMR** (125 MHZ, $CDCl_3$) δ 211.1, 99.7, 99.6, 82.7, 72.9, 55.8, 53.0, 41.2, 33.4, 32.3, 27.0; **IR (film)** ν_{max} 3419, 1724, 1010 cm^{-1}; **ESI-HRMS** calculated for $C_{11}H_{14}O_4Na$ $[M+Na]^+$ 233.0790, found 233.0785. See Table 1 in text for reported yields.



4a **S4** (26%, dr >19:1)

Lactol ester S4: Lactol ester **S4** was synthesized in order to afford a derivative of lactol **4a** that would form suitable crystals for X-ray crystallographic analysis. To a solution of lactol **4a** (27 mg, 0.13 mmol,

1.0 equiv) in CH_2Cl_2 (320 µL) was added pyridine (20 µL, 0.25 mmol, 2.0 equiv) and then biphenyl-4-carbonyl chloride (33 mg, 0.15 mmol, 1.2 equiv) at 0 °C. The resulting solution was allowed to warm to 23 °C, stirred for 2 h, and diluted with CH_2Cl_2 (5 mL). The solution was washed with ice cold sat. aq. NaCl (2 x 2 mL), dried with Na_2SO_4, filtered, and concentrated *via* rotary evaporation. Purification by flash column chromatography (hexanes:EtOAc 90:10) afforded **S4** as a white solid (13 mg, 0.34 mmol, 26%, dr >19:1): $\mathbf{R_f}$ = 0.56 (hexanes:EtOAc 70:30); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.08-8.05 (m, 2H), 7.68-7.66 (m, 2H), 7.63-7.61 (m, 2H), 7.49-7.46 (m, 2H), 7.43-7.40 (m, 1H), 6.39 (s, 1H), 5.44 (dd, *J* = 7.2, 6.0 Hz, 1H), 4.83 (ddd, *J* = 7.2, 4.2, 1.9 Hz, 1H), 2.82 (dd, *J* = 6.0, 2.8 Hz, 1H), 2.75 (dd, *J* = 16.4, 4.2 Hz, 1H), 2.64 (dd, *J* = 16.4, 1.9 Hz, 1H), 2.36-2.27 (m, 2H), 2.19-2.12 (m, 1H), 1.99-1.92 (m, 1H), 1.87-1.79 (m, 2H), 1.69-1.62 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 209.8, 165.4, 146.4, 140.0, 130.4(2), 129.1(2), 128.51, 128.47, 127.44(2), 127.29(2), 99.95, 99.89, 82.1, 74.7, 54.9, 53.0, 41.0, 33.5, 32.3, 27.0; **IR (film) ν_{max}** 1766, 1714, 1225, 1174, 843, 744, 691 cm^{-1}; **ESI-HRMS** calculated for $C_{24}H_{23}O_5$ $[M+H]^+$ 391.1545, found 391.1550. Subjection of lactol ester **S4** to slow evaporation in CH_2Cl_2 over several days at ambient temperature provided a single crystal suitable for X-ray crystallographic analysis (Figure S5).

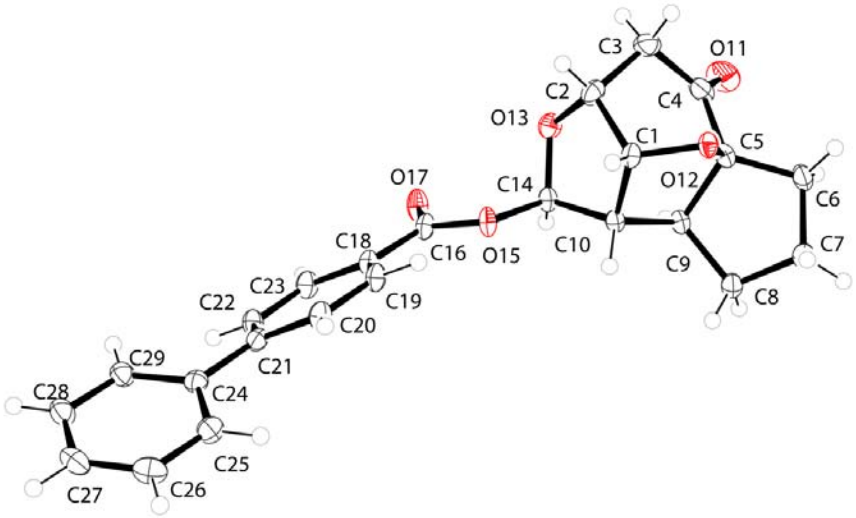
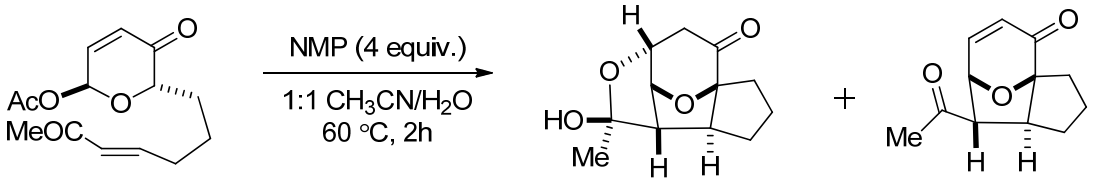
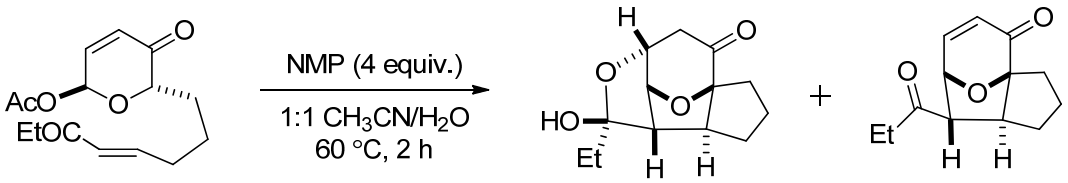


Figure S5. ORTEP Diagram of Lactol Ester **S4**
(Displacement Ellipsoids at 50% Probability; H Atoms Drawn at Arbitrary Size)



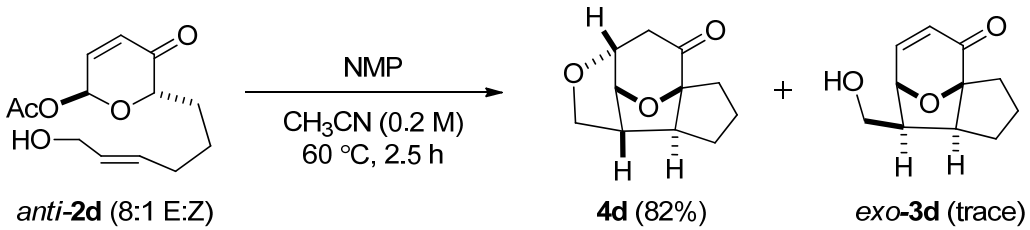
anti-**2b** **4b** (75%, dr >19:1) **3b** (6%)

Methyl-lactol 4b: To a solution of *anti*-acetoxypyranone **2b** (100 mg, 0.375 mmol, 1.0 equiv.) in 1:1 CH_3CN:H_2O (1 mL CH_3CN, 1 mL H_2O) was added *N*-methylpyrrolidine (156 µL, 1.50 mmol, 4.0 equiv.). The reaction was allowed to stir for 2 h at 60 °C. The reaction was then concentrated *via* rotary evaporation. Purification by flash chromatography (hexanes:EtOAc 60:40) afforded lactol **4b** as a white solid (62.9 mg, 0.28 mmol, 75%, dr >19:1): $\mathbf{R_f}$ = 0.32 (hexanes:EtOAc 60:40). A small amount of unreacted cycloadduct intermediate **3b** was also collected (6.5 mg, 0.024 mmol, 6%). All spectral data matched that of **4b** prepared from **3b**; see above for characterization data.



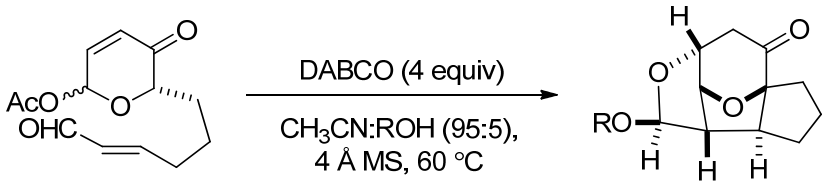
anti-**2c** **4c** (64%, dr >19:1) **3c** (16%)

Ethyl-lactol 4c: To a solution of *anti*-acetoxypyranone **2c** (100 mg, 0.357 mmol, 1.0 equiv.) in 1:1 CH_3CN:H_2O (0.9 mL CH_3CN, 0.9 mL H_2O) was added *N*-methylpyrrolidine (150 µL, 1.43 mmol, 4.0 equiv.). The reaction was allowed to stir for 2 h at 60 °C. The reaction was then concentrated *via* rotary evaporation. Purification by flash chromatography (hexanes:EtOAc 80:20) afforded lactol **4c** as a white solid (54.7 mg, 0.230 mmol, 64%, dr >19:1): $\mathbf{R_f}$ = 0.19 (hexanes:EtOAc 70:30). A small amount of unreacted cycloadduct intermediate **3c** was also collected (12.4 mg, 0.056 mmol, 16%). All spectral data matched that of **4c** prepared from **3c**; see above for characterization data.

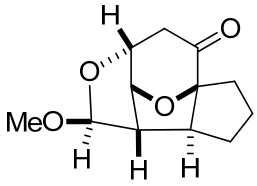


Bis-ether 4d: To a vial was added *anti*-acetoxypyranone **2d** (120 mg, 0.472 mmol, 1 equiv.) and CH_3CN (4.7 mL). Next was added *N*-methylpyrrolidine (195 µL, 1.88 mmol, 4 equiv). The vial was then capped and stirred at 60 °C for 8 h until monitoring by TLC (hexanes:EtOAc 70:30) showed complete consumption of starting material. The reaction was then concentrated *via* rotary evaporation. The crude mixture was purified by flash column chromatography (hexanes:EtOAc 70:30 to 50:50) to afford compound **4d** as a white solid (75.6 mg, 0.389 mmol, 82%, dr >19:1), and trace amount of impure enone-alcohol *exo*-**3d** as a yellow oil. All spectral data matched that of *exo*-**3d** and **4d** prepared from **3f**; see above for characterization data.

General Procedure for Synthesis of Lactols 4f-m:

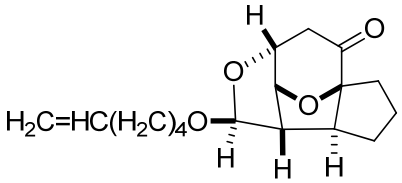


To a solution of acetoxypyranone **2a** (125 mg, 0.50 mmol, 1.0 equiv, dr ~2-3:1) in anhydrous CH_3CN (5 mL) was added activated 4 Å molecular sieves. Next, the appropriate alcohol (2 equiv.) was added, followed by DABCO (222 mg, 1.98 mmol, 4.0 equiv). The reaction backfilled with Ar, sealed, and allowed to stir for at 60 °C until complete consumption of starting material (reaction time denoted below, and in table 4), after which point the reaction was concentrated *via* rotary evaporation. The crude reaction mixture was then purified by flash column chromatography to deliver pure lactols **4f-m**.



4f (63%, dr >19:1)

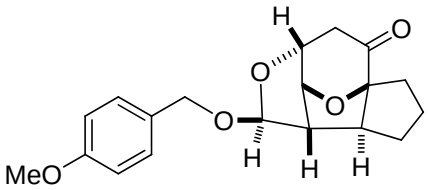
Lactol 4f: According to the general procedure, **2a** (125 mg, 0.50 mmol, 1.0 equiv, dr 2.4:1) was reacted with DABCO (222 mg, 1.98 mmol, 4.0 equiv). Synthesis of **4f** deviated from the general procedure by utilizing 95:5 CH_3CN:MeOH (4.75 mL CH_3CN, 250 μL MeOH) and 3 Å molecular sieves. The reaction was stirred for 6 hr at 60 °C, and then concentrated *via* rotary evaporation. Purification by flash column chromatography (hexanes:EtOAc 95:5) afforded **4f** as a pale yellow oil (70 mg, 0.31 mmol, 63%, dr >19:1): $\mathbf{R_f}$ = 0.56 (hexanes:EtOAc 70:30); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.24 (dd, *J* = 6.8, 6.0 Hz, 1H), 4.76 (s, 1H), 4.56 (ddd, *J* = 6.8, 4.4, 1.9 Hz, 1H), 3.29 (s, 3H), 2.71 (dd, *J* = 16.1, 4.4 Hz, 1H), 2.54-2.50 (m, 2H), 2.26-2.20 (m, 1H), 2.17-2.13 (m, 1H), 2.07-2.00 (m, 1H), 1.93-1.87 (m, 1H), 1.81-1.74 (m, 2H), 1.59-1.54 (m, 1H); **^{13}C NMR** (125 MHZ, $CDCl_3$) δ 210.8, 105.8, 99.5, 82.7, 72.5, 55.1, 54.5, 53.0, 41.2, 33.4, 32.3, 26.9; **IR (film) ν_{max}** 2934, 1728, 1094, 1027 cm^{-1}; **ESI-HRMS** calculated for $C_{12}H_{16}O_4$ $[M+Na]^+$ 247.0946, found 247.0945.



4g (53%, dr >19:1)

Lactol 4g: According to the general procedure, **2a** (125 mg, 0.50 mmol, 1.0 equiv, dr 2.4:1) was reacted with DABCO (222 mg, 1.98 mmol, 4.0 equiv), and 5-hexen-1-ol (120 μL, 0.99 mmol, 2 equiv.). The reaction was stirred for 6 hr at 60 °C, and then concentrated *via* rotary evaporation. Purification by flash column chromatography (hexanes:EtOAc 90:10) afforded **4g** as a colorless oil (77 mg, 0.26 mmol, 53%, dr >19:1): $\mathbf{R_f}$ = 0.83 (hexanes:EtOAc 70:30); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.79 (ddt, *J* = 17.0, 10.2, 6.7, 1H), 5.25 (dd, *J* = 6.6, 6.0 Hz, 1H), 5.02-4.93 (m, 2H), 4.86 (s, 1H), 4.55 (ddd, *J* = 6.6, 4.4, 2.0 Hz, 1H),

3.61 (dt, *J* = 9.7, 6.7 Hz, 1H), 3.34 (dt, *J* = 9.7, 6.7 Hz, 1H), 2.71 (dd, *J* = 16.1, 4.4 Hz, 1H), 2.51 (dd, *J* = 16.1, 2.0 Hz, 1H), 2.51 (dd, *J* = 6.0, 2.8 Hz, 1H), 2.26-2.20 (m, 1H), 2.15 (ddd, *J* = 9.3, 6.8, 2.8 Hz, 1H), 2.08-2.00 (m, 3H), 1.94-1.87 (m, 1H), 1.81-1.73 (m, 2H), 1.60-1.52 (m, 3H), 1.44-1.38 (m, 2H); **^{13}C NMR** (125 MHZ, $CDCl_3$) δ 211.0, 138.8, 114.7, 104.7, 99.6, 83.0, 72.5, 67.2, 55.3, 53.0, 41.3, 33.56, 33.45, 32.3, 29.1, 27.0, 25.6; **IR (film) ν_{max}** 2936, 1729, 1640, 1100, 1065 cm^{-1}; **ESI-HRMS** calculated for $C_{17}H_{24}O_4$ $[M+Na]^+$ 315.1572, found 315.1568.



4h (62%, dr >19:1)

Lactol 4h: According to the general procedure, **2a** (125 mg, 0.50 mmol, 1.0 equiv, dr 3.3:1) was reacted with DABCO (222 mg, 1.98 mmol, 4.0 equiv), and 4-methoxy benzyl alcohol (124 μL, 1.00 mmol, 2.0 equiv.). The reaction was stirred for 1 hr at 60 °C, and then concentrated *via* rotary evaporation. Purification by flash column chromatography (hexane:EtOAc 80:20) afforded **4h** as a white solid (101 mg, 0.306 mmol, 62%, dr >19:1): $\mathbf{R_f}$ = 0.65 (hexane:EtOAc 70:30); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (app. d, *J* = 8.6 Hz, 2H), 6.90 (app. d, *J* = 8.6 Hz, 2H), 5.31 (dd, *J* = 6.5, 6.3 Hz, 1H), 4.97 (s, 1H), 4.62 (ddd, *J* = 6.5, 4.1, 2.0 Hz, 1H), 4.60 (d, *J* = 11.5 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 3.83 (s, 3H), 2.75 (dd, *J* = 16.1, 4.1 Hz, 1H), 2.57 (dd, *J* = 6.3, 2.8 Hz, 1H), 2.56 (dd, *J* = 16.1, 2.0 Hz, 1H), 2.29-2.24 (m, 1H), 2.17 (ddd, *J* = 9.3, 6.8, 2.8 Hz, 1H), 2.09-2.00 (m, 1H), 1.96-1.88 (m, 1H), 1.83-1.75 (m, 2H), 1.62-1.53 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 211.0, 159.5, 129.8(2), 129.7, 114.0(2), 103.5, 99.6, 82.9, 72.6, 68.5, 55.4, 55.2, 53.0, 41.3, 33.5, 32.4, 27.0; **IR (film) ν_{max}** 1721, 1612, 1246, 828 cm^{-1}; **ESI-HRMS** calculated for $C_{19}H_{22}O_5$ $[M+Na]^+$ 353.1365, found 353.1351. Subjection of a concentrated solution lactol **4h** in EtOAc to slow evaporation over several days at ambient temperature provided a single crystal suitable for X-ray crystallographic analysis (Figure S6).

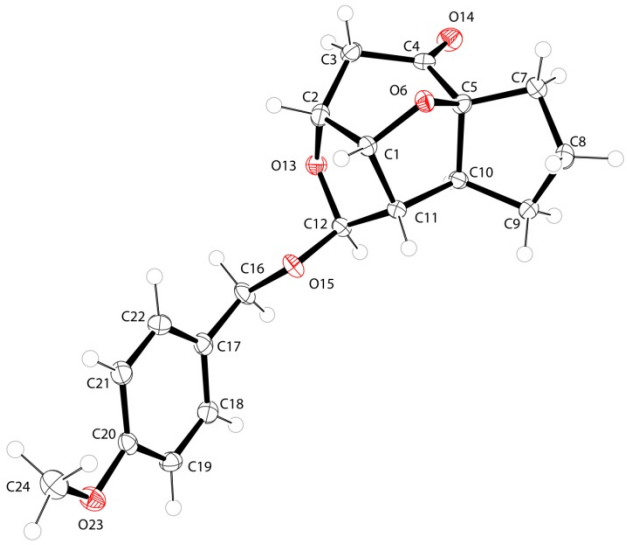
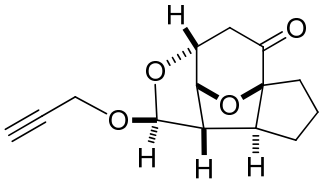
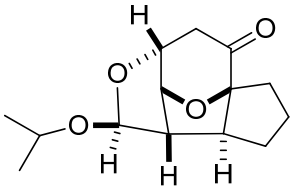


Figure S6. ORTEP Diagram of Lactol **4h**
(Displacement Ellipsoids at 50% Probability; H Atoms Drawn at Arbitrary Size)



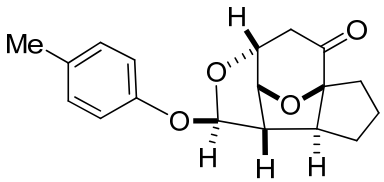
4i (57%, dr >19:1)

Lactol 4i: According to the general procedure, **2a** (125 mg, 0.50 mmol, 1.0 equiv, dr 2.0:1) was reacted with DABCO (222 mg, 1.98 mmol, 4.0 equiv), and propargyl alcohol (59 µL, 1.0 mmol, 2.0 equiv). The reaction was stirred for 2.5 hr at 60 °C, and then concentrated *via* rotary evaporation. Purification by flash column chromatography (hexane:EtOAc 90:10) afforded **4i** as colorless oil (69.6 mg, 0.280 mmol, 57%, dr >19:1): $\mathbf{R_f}$ = 0.65 (hexane:EtOAc 60:40); **^{1}H NMR** (400MHz, $CDCl_3$) δ 5.27 (dd, *J* = 7.0, 6.0 Hz, 1H), 5.08 (s, 1H), 4.59 (ddd, *J* = 7.0, 4.2, 2.0 Hz, 1H), 4.19 (dd, *J* = 15.8, 2.4 Hz, 1H), 4.15 (dd, *J* = 15.8, 2.4 Hz, 1H), 2.72 (dd, *J* = 16.1. 4.2 Hz, 1H), 2.57 (dd, *J* = 6.0, 2.8 Hz, 1H), 2.53 (dd, *J* = 16.1, 2.0 Hz, 1H), 2.42 (t, *J* = 2.3 Hz, 1H), 2.28-2.15 (m, 2H), 2.13-2.04 (m, 1H), 1.97-1.85 (m, 1H), 1.85-1.72 (m, 2H), 1.62-1.53 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 210.6, 103.0, 99.5, 82.5, 79.2, 74.6, 72.9, 55.0, 53.8, 52.8, 41.1, 33.4, 32.2, 26.9; **IR (film)** $\mathbf{\nu_{max}}$ 1726, 1023 cm^{-1}; **ESI-HRMS** calculated for $C_{14}H_{16}O_4$ $[M+Na]^+$ 271.0946, found 271.0945.



4j (53%, dr >19:1)

Lactol 4j: According to the general procedure, **2a** (125 mg, 0.50 mmol, 1.0 equiv, dr 3.3:1) was reacted with DABCO (222 mg, 1.98 mmol, 4.0 equiv), and isopropanol (77 μL, 1.00 mmol, 2.0 equiv). The reaction was stirred for 4 hr at 60 °C, and then concentrated *via* rotary evaporation. Purification by flash column chromatography (hexane:EtOAc 90:10) afforded **4j** as a white solid (66.2 mg, 0.262 mmol, 53%, dr >19:1): $\mathbf{R_f}$ = 0.76 (hexane:EtOAc 70:30); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.27 (dd, *J* = 6.8, 6.2 Hz, 1H), 4.98 (s, 1H), 4.56 (ddd, *J* = 6.8, 4.1, 2.0 Hz, 1H), 3.84 (qq, *J* = 6.24, 6.16, 1H), 2.71 (dd, *J* = 16.0, 4.1 Hz, 1H), 2.50 (dd, *J* = 16.0, 2.0 Hz, 1H), 2.47 (dd, *J* = 6.2, 2.8 Hz, 1H), 2.28-2.20 (m, 1H), 2.15 (ddd, *J* = 9.2, 6.6, 2.8 Hz, 1H), 2.08-1.99 (m, 1H), 1.96-1.85 (m, 1H), 1.81-1.72 (m, 2H), 1.60-1.56 (m, 1H), 1.15 (d, *J* = 6.24, 3H), 1.11 (d, *J* = 6.16, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 211.2, 102.8, 99.5, 83.1, 72.2, 68.8, 55.6, 53.1, 41.3, 33.5, 32.4, 27.0, 23.7, 21.8; **IR (film)** $\mathbf{\nu_{max}}$ 1720, 1013, 989 cm^{-1}; **ESI-HRMS** calculated for $C_{14}H_{20}O_4$ $[M+Na]^+$ 275.1259, found 275.1262.



4l (20%, dr >19:1)

Lactol 4l: According to the general procedure, **2a** (125 mg, 0.50 mmol, 2.4 equiv, dr 2.0:1) was reacted with DABCO (222 mg, 1.98 mmol, 4.0 equiv), and *p*-Cresol (105 μL, 1.00 mmol, 2.0 equiv). The reaction was stirred for 1.5 hr at 60 °C, and then concentrated *via* rotary evaporation. Purification by flash column chromatography (hexane:EtOAc 90:10) afforded **4l** as a white solid (30 mg, 0.100 mmol, 20%, dr >19:1): $\mathbf{R_f}$ =0.79 (hexane:EtOAc 70:30); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.06 (app. d, *J* = 8.4, 2H), 6.86

(app. d, J = 8.4, 2H), 5.54 (s, 1H), 5.43 (dd, J = 7.1, 6.0 Hz, 1H), 4.70 (ddd, J = 7.1, 4.3, 1.9 Hz, 1H), 2.77 (dd, J = 6.0, 2.8 Hz, 1H), 2.73 (dd, J = 16.1, 4.3 Hz, 1H), 2.55 (dd, J =16.1, 1.9 Hz, 1H), 2.31-2.23 (m, 5H), 2.14-2.05 (m, 1H), 2.00-1.90 (m, 1H), 1.86-1.76 (m, 2H), 1.68-1.59 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 210.7, 154.4, 131.7, 130.1(2), 116.6(2), 103.4, 99.7, 82.8, 73.4, 55.3, 53.1, 41.2, 33.5, 32.4, 27.0, 20.7; **IR (film) ν_{max}** 1722, 1508, 985, 814 cm^{-1}; **ESI-HRMS** calculated for $C_{18}H_{20}O_4$ $[M+Na]^+$ 323.1259, found 323.1258. Subjection of lactol **4l** to slow evaporation in acetone over several days at ambient temperature provided a single crystal suitable for X-ray crystallographic analysis (Figure S7).

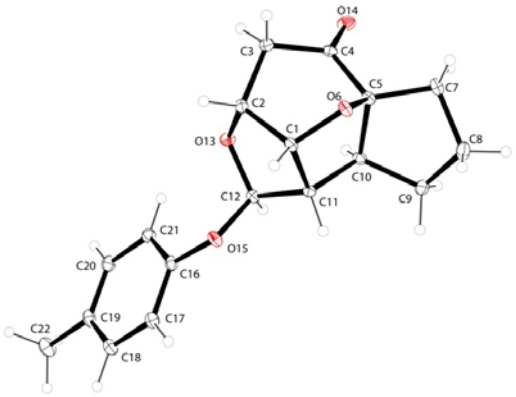
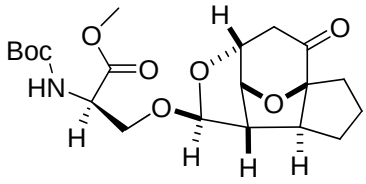


Figure S7. ORTEP Diagram of Lactol **4l**
(Displacement Ellipsoids at 50% Probability; H Atoms Drawn at Arbitrary Size)



4m (73%, dr >19:1)

Lactol 4m: According to the general procedure, **2a** (125 mg, 0.50 mmol, 2.4 equiv, dr 2.0:1) was reacted with DABCO (222 mg, 1.98 mmol, 4.0 equiv), and Boc-L-serine methyl ester (205 µL, 1.00 mmol, 2.0 equiv). The reaction was stirred for 2 hr at 60 °C, and then concentrated *via* rotary evaporation. Purification by flash column chromatography (hexane:EtOAc 70:30) afforded **4m** as purple oil (150 mg,

0.365 mmol, 73%, dr = 1:1; inseparable): $\mathbf{R_f}$ = 0.49 (hexane:EtOAc 60:40); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.44 (d, *J* = 8.5 Hz, 1H), 5.27 (d, 8.8 Hz, 1H), 5.21 (t, *J* = 6.6, 1H), 5.15 (t, *J* = 6.6 Hz, 1H), 4.85 (s, 1H), 4.83 (s, 1H), 4.63-4.58 (m, 1H), 4.50-4.35 (m, 3H), 3.99 (dd, *J* = 9.9, 3.4 Hz, 1H), 3.90-3.78 (m, 2H), 3.75 (d, J = 2.2 Hz, 6H), 3.61 (dd, *J* = 10.0, 3.4 Hz, 1H), 2.72 (dd, *J* = 9.0, 4.2 Hz, 1H), 2.68 (dd, *J* = 9.0, 4.2 Hz, 1H), 2.55-2.45 (m, 4H), 2.28-2.18 (m, 2H), 2.17-2.08 (m, 2H), 2.08-1.98 (m, 2H), 1.96-1.84 (m, 2H), 1.83-1.70 (m, 4H), 1.62-1.50 (m, 2H), 1.45 (s, 18H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 210.64, 210.60, 171.1, 171.0, 155.5, 155.4, 105.3, 104.7, 99.6, 99.5, 82.51, 82.50, 80.24, 80.16, 72.82, 72.81, 68.1, 67.2, 54.99, 54.97, 54.0, 53.8, 52.9, 52.8, 52.6, 52.5, 41.1(2), 33.4(2), 32.3(2), 28.4(6), 26.9(2); **IR (film)** $\mathbf{\nu_{max}}$ 3354, 1714, 1161 cm^{-1}, **ESI-HRMS** calculated for $C_{20}H_{30}NO_8$ $[M+H]^+$ 412.1971, found 412.1972.

CONFORMATIONAL ANALYSIS OF CYCLOADDUCT, HYDRATE, AND HEMIACETAL INTERMEDIATES

Conformation searches cycloadducts **3a-c**, proposed hydrate intermediates **9a-c**, and (*R*)- and (*S*)-hemiacetals **S5** were performed. Initial structures were generated utilizing a systematic conformation searching approach, and minimized with the MMFF94 force field using the Spartan '02 software package (Wavefunction, Inc.). Multiple representative low energy conformers generated from the search were transferred to the Gaussian '03 software package (Gaussian, Inc.), and geometries were optimized using Density Functional Theory (DFT) at the B3LYP level of theory, and a 6-31G** basis set with d(6) Cartesian diffuse functions. The conductor polarized continuum model (CPCM) was used to account for acetonitrile solvation effects on conformational energies. All relative energy values are reported in $kcalmol^{-1}$.

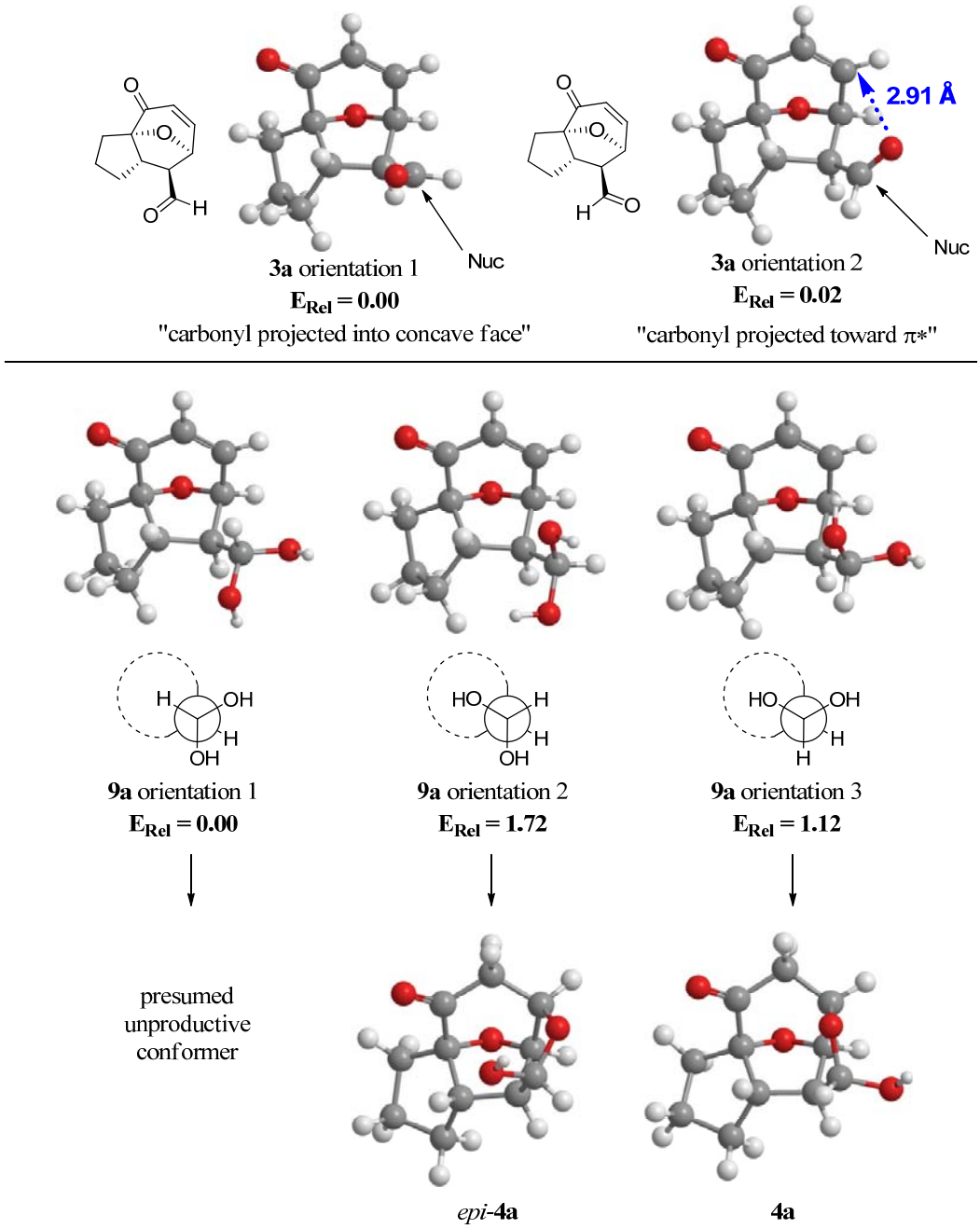


Figure S8. Relative Energy Values of Cycloadduct **3a**, Hydrate Intermediate **9a**, and Lactol **4a** Conformers

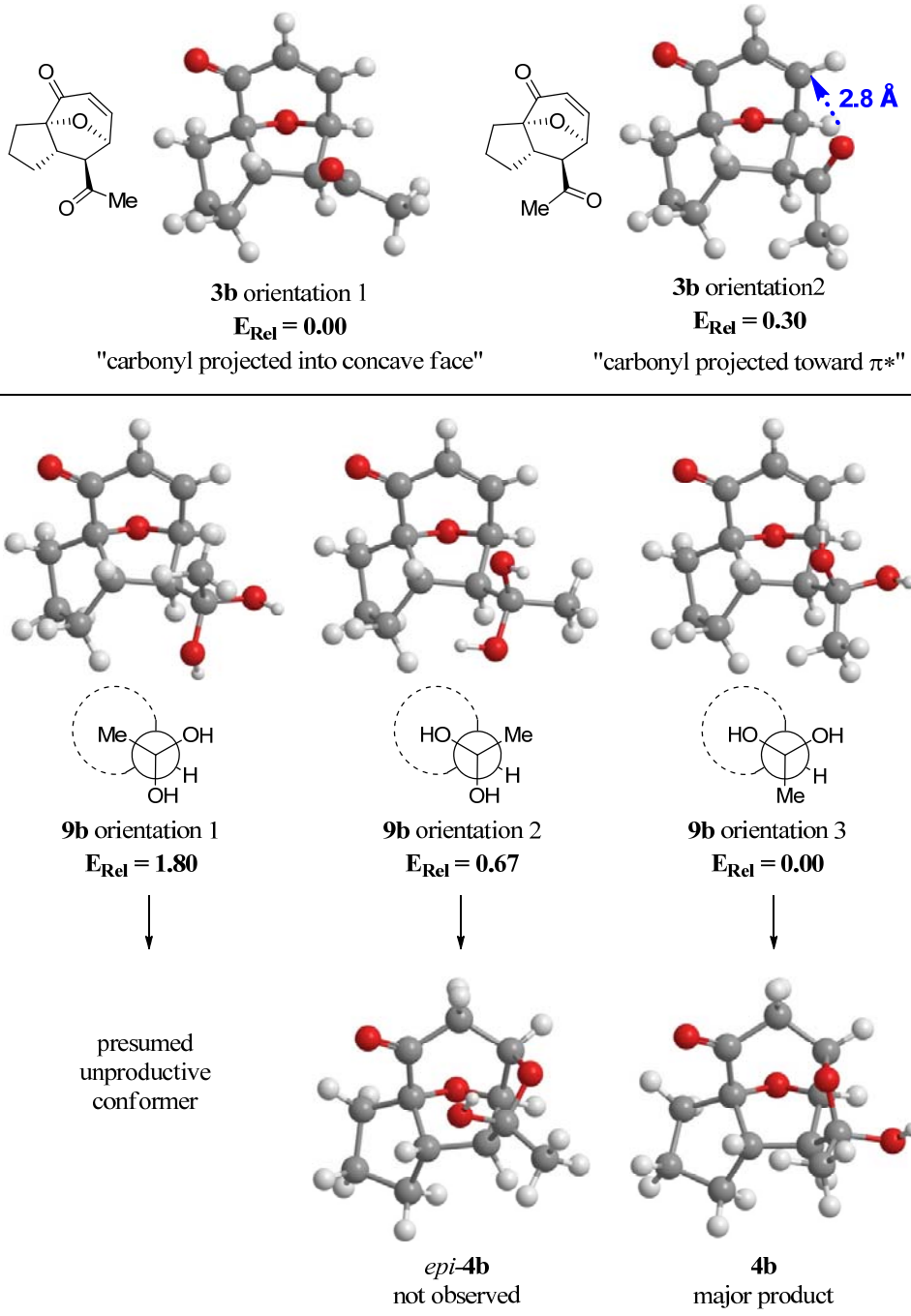
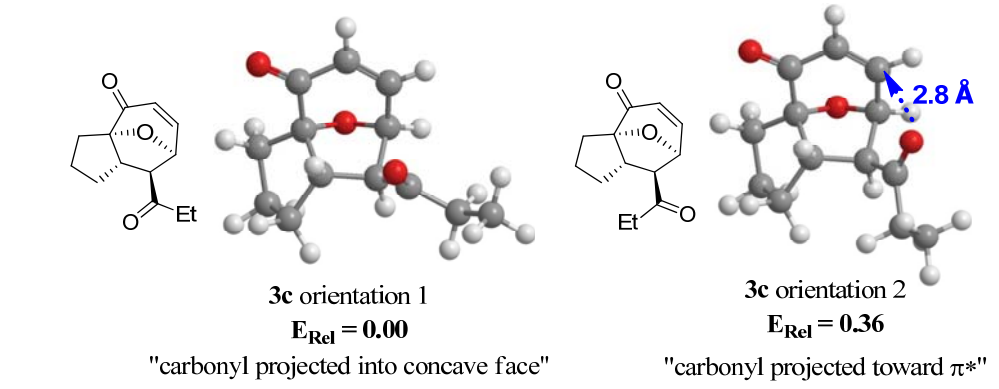
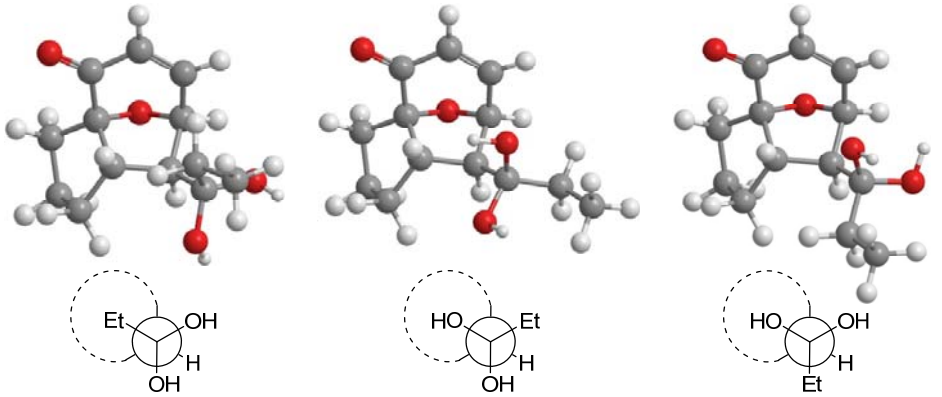


Figure S9. Relative Energy Values of Cycloadduct **3b**, Hydrate Intermediate **9b**, and Lactol **4b** Conformers



3c orientation 1
E_{Rel} = 0.00
"carbonyl projected into concave face"

3c orientation 2
E_{Rel} = 0.36
"carbonyl projected toward π*"

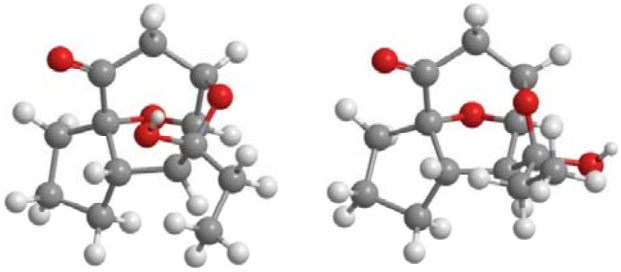


9c orientation 1
E_{Rel} = 1.49

9c orientation 2
E_{Rel} = 0.00

9c orientation 3
E_{Rel} = 0.83

presumed unproductive conformer



epi-**4c**
not observed

4c
major epimer

Figure S10. Relative Energy Values of Cycloadduct **3c**, Hydrate Intermediate **9c**, and Lactol **4c** Conformers

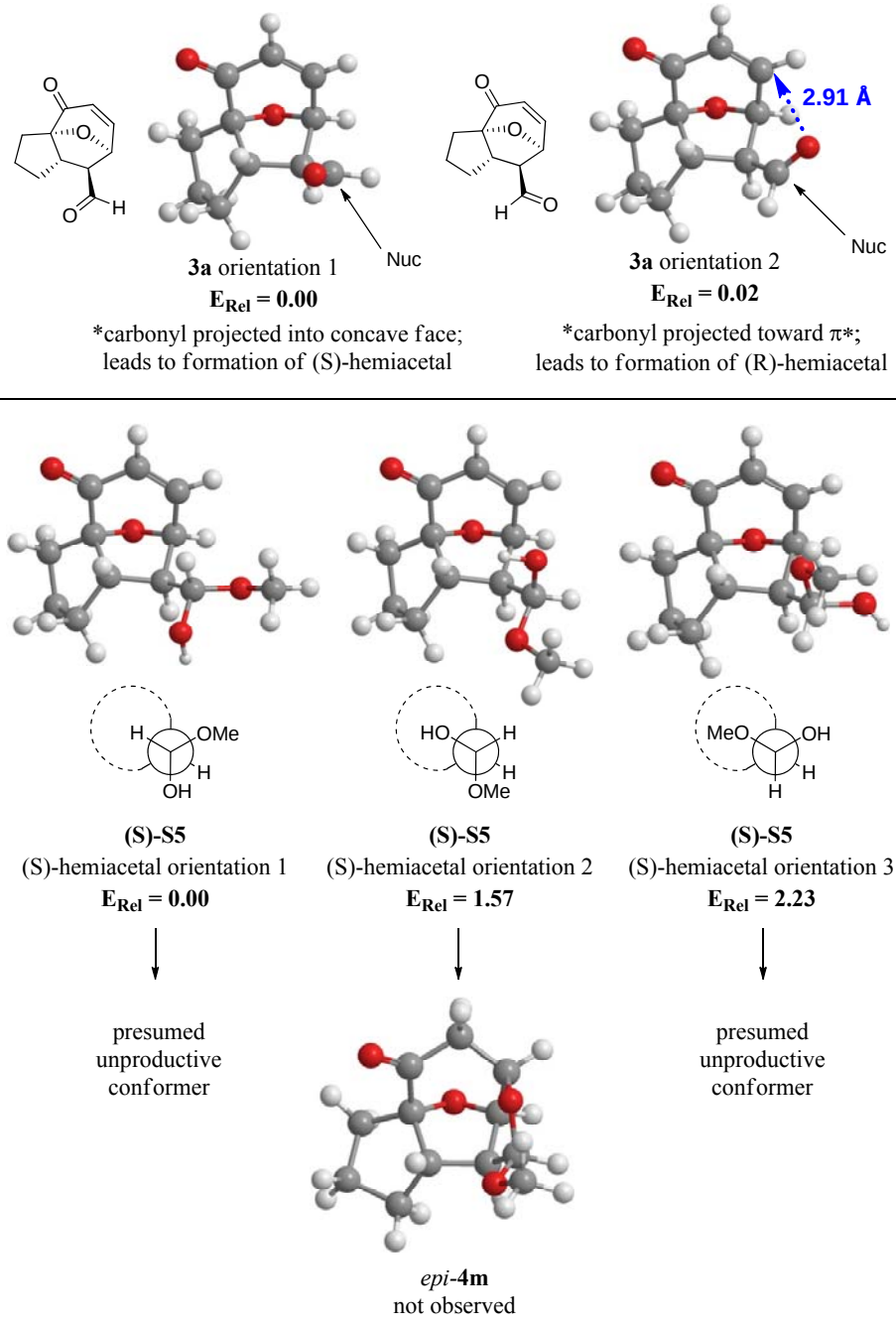


Figure S11. Relative Energy Values of (S)-hemiacetal Intermediate **S5** Derived from Addition of Methanol to **3a** Orientation 1

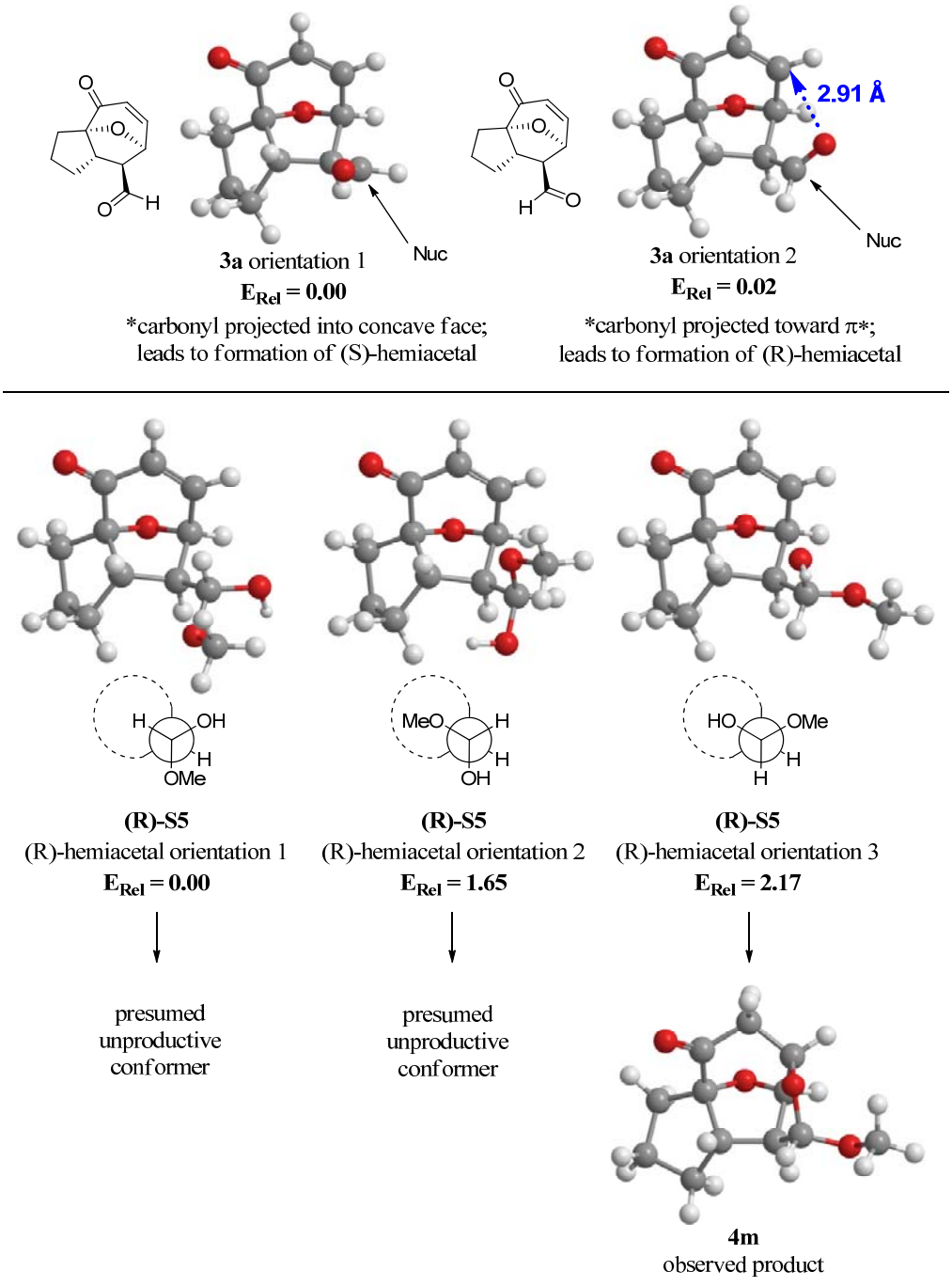


Figure S12. Relative Energy Values of (R)-hemiacetal Intermediate **S5** Derived from Addition of Methanol to **3a** Orientation 2

ADDITIONAL X-RAY CRYSTALLOGRAPHY ACQUISITION PARAMETERS AND DATA

X-ray crystallographic studies were performed at Illinois State University on a Bruker APEX II CCD diffractometer at 100(2) K using MoKα radiation (λ = 0.71073 Å). All crystals were mounted on a polyamide loop using mineral oil. The data were processed using the Bruker SAINT software package and were corrected for absorption using the SADABS. Structures were solved by direct methods using either SIR92[4] or SHELXS-97.[5] The data were refined using SHELXL-97 within the WINGX[6] software package. All non-H atoms were refined anisotropically. Hydrogen atoms attached to carbon were assigned positions based on the geometries of their attached carbons. Hydroxyl hydrogens were assigned positions based on the Fourier difference map. See **Table S1** for final refinement parameters.

[4] Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Crystallogr.* **1993,** *26*, 343.
[5] Sheldrick GM (1997) SHELX 97, program for crystal structure refinement; University of Göttingen, Germany
[6] Farrugia, L. J. *J. Appl. Cryst.* **1999,** *32*, 837.

Table S1: Crystallographic Data

	4c	**4d**	**4e**	**4h**	**4l**	**S4**
CCDC deposit number	1003498	1003499	1003500	1003501	1003502	1003601
Empirical formula	$C_{13}H_{18}O_4$	$C_{11}H_{14}O_3$	$C_{11}H_{12}O_4$	$C_{19}H_{22}O_5$	$C_{18}H_{20}O_4$	$C_{24}H_{22}O_5$
Formula weight	238.27	194.22	208.21	330.37	300.34	390.42
crystal size (mm)	0.206×0.173×0.059	0.164×0.157×0.085	0.239×0.235×0.120	0.238×0.132×0.041	0.303×0.124×0.106	0.255×0.174×0.150
Temperature (K)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)
crystal system	tetragonal	orthorhombic	monoclinic	monoclinic	monoclinic	monoclinic
space group	$I4_1/a$	$P2_12_12_1$	$P2_1/c$	Pc	$P2_1$	$P2_1/n$
a (Å)	23.3014(13)	7.1815(2)	11.8981(3)	16.831(4)	9.8857(3)	8.2563(4)
b (Å)	23.3014(13)	8.0509(2)	9.1977(2)	8.3170(19)	7.1169(2)	12.5278(7)
c (Å)	8.5463(5)	15.9570(5)	8.6578(2)	11.555(3)	10.7398(4)	18.4201(10)
β (°)	90	90	97.9810(10)	100.853(4)	93.306(2)	94.169(3)
V (Å^3)	4640.3(5)	922.59(4)	938.29(4)	1588.6(6)	754.35(4)	1900.21(17)
Z / Z'	16 / 1	4 / 1	4 / 1	4 / 2	2 / 1	4 / 1
ρ_{calcd} (g/cm^3)	1.364	1.398	1.474	1.381	1.322	1.365
μ (mm^{-1})	0.100	0.101	0.113	0.099	0.093	0.095
F(000)	2048	416	440	704	320	824
Data / restraints / parameters	2369 / 0 / 159	1161 / 0 / 127	1922 / 0 / 136	3040 / 2 / 435	2190 / 1 / 200	4036 / 0 / 262
R_1: [$I > 2\sigma(I)$] / all	0.0337 / 0.0391	0.0293 / 0.0307	0.0334 / 0.0347	0.0280 / 0.0339	0.0274 / 0.0281	0.0407 / 0.0433
wR_2: [$I > 2\sigma(I)$] / all	0.0854 / 0.0896	0.0738 / 0.0752	0.0836 / 0.0847	0.0656 / 0.0680	0.0703 / 0.0709	0.1062 / 0.1083
GOF on F^2	1.042	1.056	1.054	1.033	1.035	1.056
Largest peak/hole (e/Å^3)	0.331 / –0.237	0.272 / –0.171	0.041 / –0.177	0.155 / –0.184	0.233 / –0.156	0.486 / –0.244