

Supporting Information

Room Temperature Intramolecular Hydro-*O*-alkylation of Aldehydes: sp^3 C-H Functionalization via Tandem 1,5-Hydride Transfer/Cyclization.

Stefan J. Pastine and Dalibor Sames*

Department of Chemistry, Columbia University, New York, NY 10027

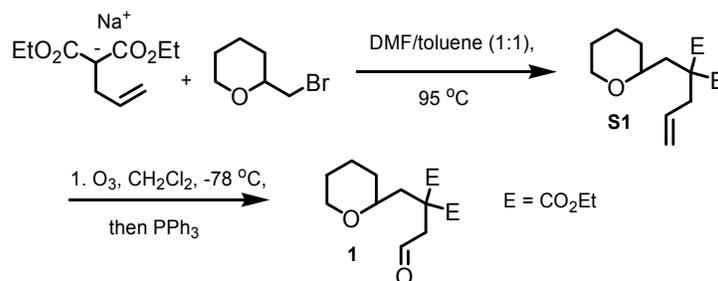
I. General.

Argon was purified by passage through Drierite. Nuclear Magnetic Resonance spectra were recorded at 300 K (unless otherwise noted) on Bruker 300 or 400 or 500 Fourier transform NMR spectrometers. Spectra recorded in $CDCl_3$ (unless otherwise noted) solutions were referenced to TMS or the solvent residual peak. DMF, THF, CH_2Cl_2 and ether used for synthesis were deoxygenated and dried via passage through a column of activated alumina.¹ IR spectra were taken neat on NaCl plates using a Perkin-Elmer 1600 FTIR spectrometer. Flash chromatography was performed on SILICYCLE silica gel (230-400 mesh). Mass spectra were recorded on a JEOL LCmate (Ionization mode: APCI+).

Quantum chemical calculations were performed using density functional theory (DFT) in Jaguar 4.1,² at the B3LYP level, with a 6-31G** basis set. Solvation was implemented using Jaguar's standard Poisson-Boltzmann dielectric continuum boundary method; settings used were for methylene chloride (keywords: espout=9.08; radprb=2.33237). Full geometry optimizations were performed first in the gas phase then with solvation for several conformers of each reactant and product, and the energies from the conformers with the lowest energies in the latter calculation were compared to estimate the free energy change of for the reaction.

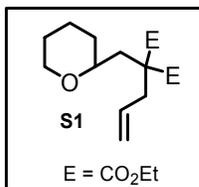
II. Synthesis of Starting Material.

Synthesis of tetrahydropyran (1)

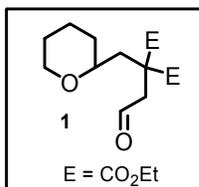


¹ Pangborn, A. B.; Giardello, M.A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J.; *Organometallics* **1996**, *15*, 1518

² Jaguar 4.1, Schrödinger, Inc., Portland, Oregon, 2000.

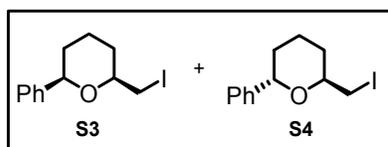
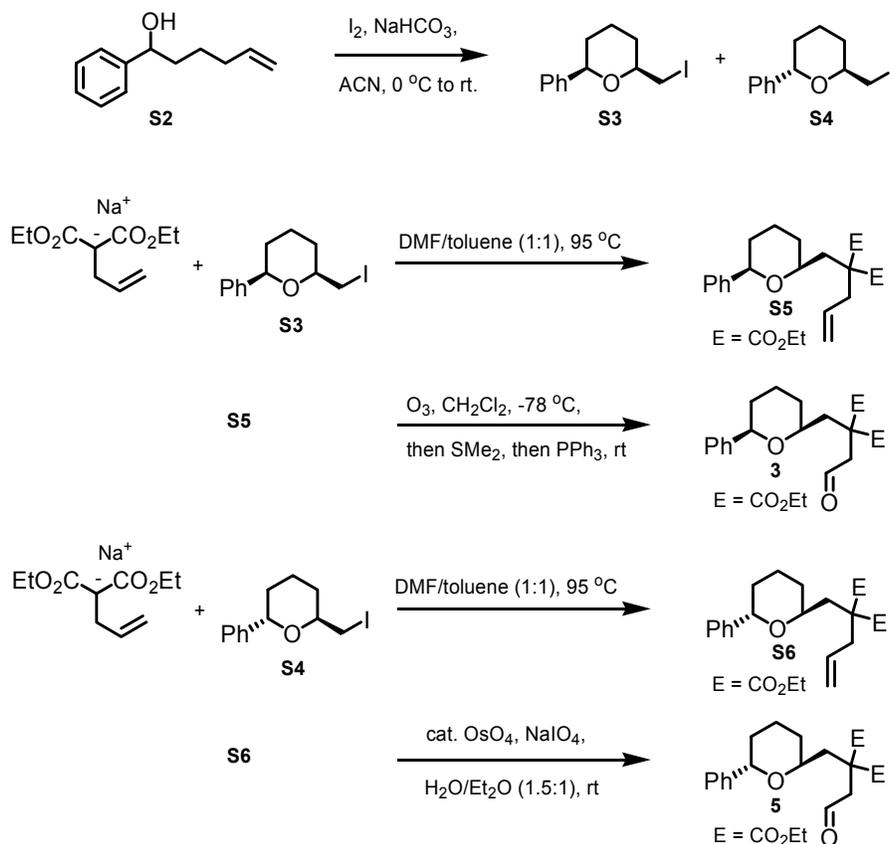


To a suspension of NaH (280 mg, 11.1 mmol, 1.1 equiv, 95% Aldrich) in 50 mL of DMF/touene (1:1) was added diethyl allylmalonate (2.0 mL, 10.1 mmol, 1.0 equiv) drop wise via syringe under argon at room temperature. After stirring for 20 minutes, 2-bromomethyl-tetrahydropyran (1.5 mL, 11.1 mmol, 1.1 equiv) was added via syringe in one portion. After stirring overnight at 95 °C, the reaction was quenched with 20 mL water and 100 mL of Et₂O and 100 mL of hexanes were added. The layers were separated and the organic layer was washed with water (3 X 10 mL), brine (20 mL), dried over Sodium Sulfate, and concentrated *in vacuo*. Purification of the crude oil via flash chromatography (Hex:EtOAc = 30:1 then 10:1) gave **S1** as a colorless oil (1.82 g, 61% yield): IR 2937, 2848, 1733, 1201, 1093, 1050 cm⁻¹; ¹H NMR (300 MHz) δ 1.24 (t, *J*_{av} = 6.4 Hz, 6H), 1.29-1.36 (m, 1H), 1.41-1.51 (m, 4H), 1.74-1.80 (m, 2H), 1.94-2.09 (m, 2H), 2.64-2.80 (m, 2H), 3.82 (dd, *J* = 11.1, 2.1 Hz, 1H), 4.10-4.21 (m, 4H), 5.06-5.11 (m, 2H), 5.61-5.70 (m, 1H); ¹³C NMR (75 MHz) δ 14.0, 23.5, 25.6, 32.3, 37.6, 38.9, 55.7, 60.9, 61.1, 68.0, 74.0, 118.7, 132.8, 171.3; MS (LR-APCI); calcd for C₁₆H₂₇O₅ 299.19, measured 299.36.



In a 250 mL round bottom flask was placed **S1** (1.5g, 5.0 mmol) and 150 mL of CH₂Cl₂. The solution was cooled to -78 °C and ozone was bubbled through the solution until a blue color appeared. Air was passed through the solution to remove the excess ozone and then triphenyl phosphine (2.8 g, 10.1 mmol, 2.1 equiv) was added. After stirring overnight at room temperature, the solvent was removed *in vacuo*. Purification of the crude residue via flash chromatography (Hex:EtOAc = 10:1 then 5:1) gave **1** as a clear oil (1.32 g, 87% yield): ¹H NMR (300 MHz) δ 1.21-1.36 (m, 7H), 1.47-1.54 (m, 4H), 1.8 (bs, 1H), 2.06-2.18 (m, 2H), 3.11 (q, *J* = 17.8 Hz, 2H), 3.20-3.34 (m, 2H), 3.93 (bd, *J* = 12.6 Hz, 1H), 4.19 (pentet, *J* = 7.0 Hz, 4H), 9.68 (s, 1H); ¹³C NMR (75 MHz) δ 13.8, 23.3, 25.5, 32.3, 39.8, 46.5, 53.2, 61.5, 61.6, 67.8, 74.2, 170.4, 170.5, 199.0; MS (LR-APCI); calcd for C₁₅H₂₅O₆ 301.17, measured 301.28.

Synthesis of tetrahydropyrans (**3**) and (**5**)

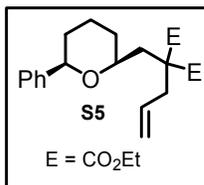


To a 500 mL round bottom flask was placed **S3** (5.8 g, 32.9 mmol), 250 mL of acetonitrile, and $NaHCO_3$ (8.3 g, 98.7 mmol, 3.0 equiv). The solution was stirred vigorously for 15 minutes and then cooled to $0\text{ }^\circ\text{C}$. Iodine (25.0 g, 98.7, 3.0 equiv) was added and the reaction was gradually allowed to warm to room temperature. After 2 hours, the reaction was quenched by the addition of saturated Na_2SO_3 . The majority of acetonitrile was removed *in vacuo*. 300 mL of ether was added and the layers separated. The aqueous layer was extracted with ether (2 X 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. One purification of the crude oil via flash chromatography (Hex:EtOAc = 140:1) gave 5.1 g of the major diastereomer **S3** (higher R_f). Three additional flash chromatographies (Hex:EtOAc = 140:1) gave additional 1.0 g of **S2** and 1.9 g of the minor diastereomer **S4**.

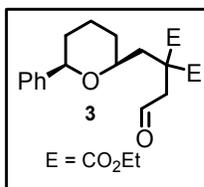
S3 (6.1 g, 61% yield, colorless oil); 1H NMR (500 MHz) δ 1.30-1.38 (m, 2H), 1.45-1.52 (m, 2H), 1.65-1.72 (m, 2H), 1.81 (bd, $J = 7.8$ Hz, 1H), 1.88 (bd, $J = 7.6$ Hz, 1H), 1.96 (bd, $J = 7.1$ Hz, 1H), 3.27 (d, $J = 2.7$ Hz, 2H), 3.49 (bs, 1H), 4.42 (d, $J = 6.7$ Hz), 7.24-7.38 (m, 5H); ^{13}C NMR (125 MHz) δ 10.3, 23.6, 31.0, 33.1, 79.8, 125.7, 127.2, 128.2, 142.8.

S4 (1.9 g, 19% yield, colorless oil); 1H NMR (400 MHz) δ 1.64-1.80 (m, 4H), 1.92-1.98 (m, 2H), 3.32-3.39 (m, 2H), 3.80-3.82 (m, 1H), 4.90 (t, $J = 5.1$ Hz, 1H), 7.24-7.26 (m,

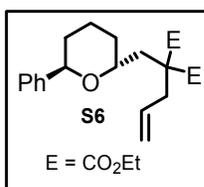
1H), 7.36 (t, $J_{av} = 7.7$ Hz, 2H), 7.44 (d, $J = 7.3$ Hz); ^{13}C NMR (100 MHz) δ 8.8, 18.8, 29.1, 29.5, 71.3, 72.9, 126.4, 127.0, 128.2, 140.9.



To a suspension of NaH (273 mg, 10.8 mmol, 1.25 equiv, 95% Aldrich) in 80 mL of DMF/touene (1:1) was added diethyl allylmalonate (1.8 mL, 8.6 mmol, 1.0 equiv) drop wise via syringe under argon at room temperature. After stirring for 20 minutes, **S3** (3.0 g, 11.1 mmol, 1.15 equiv) was added via syringe in one portion. After stirring overnight at 95 °C (reaction monitored by mass spectrometry), the reaction was quenched with 20 mL water, and 250 mL of Et₂O and 150 mL of Hexanes were added. The layers were separated and the organic layer was washed with water (3 X 20 mL), brine (20 mL), dried over MgSO₄, and concentrated *in vacuo*. Purification of the crude oil via flash chromatography (Hex:EtOAc = 30:1) gave **S5** as a colorless oil (2.83 g, 88% yield based on diethyl allylmalonate): IR 2981, 2936, 2858, 1732, 1442, 1256, 1285, 1222, 1194, 1092, 1046 cm⁻¹; ^1H NMR (500 MHz) δ 1.07 (t, $J = 7.2$ Hz, 3H), 1.15 (t, $J = 7.1$ Hz, 3H), 1.35-1.49 (m, 2H), 1.57 (bd, $J = 13.0$ Hz, 1H), 1.63-1.72 (m, 1H), 1.76 (bd, $J = 13.1$ Hz, 1H), 1.91 (bd, $J = 13.2$ Hz, 1H), 2.07 (d, $J = 14.8$ Hz, 1H), 2.18-2.22 (m, 1H), 2.67-2.71 (m, 1H), 2.76-2.80 (m, 1H), 3.60 (t, $J_{av} = 10.3$ Hz, 1H), 3.81-3.91 (m, 2H), 4.00-4.04 (m, 2H), 4.24 (d, $J = 11.2$ Hz, 1H), 5.06-5.10 (m, 2H), 5.66 (sextet, $J_{av} = 8.4$ Hz, 1H), 7.13-7.23 (m, 1H), 7.26-7.28 (m, 4H); ^{13}C NMR (125 MHz) δ 13.8, 13.9, 24.0, 31.8, 33.3, 37.5, 38.8, 55.7, 60.8, 61.0, 74.3, 79.6, 118.7, 125.9, 127.0, 127.9, 132.9, 143.2, 171.1.

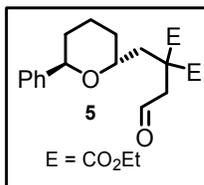


In a 250 mL round bottom flask was placed **S5** (2.2 g, 5.87 mmol) and 150 mL of CH₂Cl₂. The solution was cooled to -78 °C and ozone was bubbled through the solution until a blue color appeared. Air was passed through the solution to remove the excess ozone and then dimethyl sulfide (6.5 mL, 88.5 mmol, 15 equiv) was added. After stirring overnight at room temperature, triphenyl phosphine was added (1.0 g, 3.81 mmol, 0.65 equiv). After stirring for an additional 12 hours, the solvent was removed *in vacuo*. Purification of the crude residue via flash chromatography (Hex:EtOAc = 12:1 then 9:1) gave **3** as a clear oil (1.05 g, 48% yield): ^1H NMR (500 MHz) δ 1.14 (t, $J = 7.1$ Hz, 3H), 1.19 (t, $J = 7.1$ Hz, 3H), 1.33-1.48 (m, 2H), 1.58-1.76 (m, 3H), 1.90 (bd, $J = 13.2$ Hz, 1H), 2.22-2.29 (m, 2H), 3.05 (d, $J = 17.9$ Hz, 1H), 3.17 (d, $J = 17.9$ Hz), 3.57 (t, $J_{av} = 9.5$ Hz, 1H), 3.98-4.05 (m, 2H), 4.12 (q, $J = 7.1$ Hz, 2H), 4.20 (d, $J = 11.3$ Hz), 7.21-7.31 (m, 5H), 9.51 (s, 1H); ^{13}C NMR (125 MHz) δ 13.7, 13.8, 23.9, 31.7, 33.5, 39.6, 46.5, 53.1, 61.5, 61.6, 74.5, 79.5, 125.7, 127.1, 128.0, 143.0, 170.4, 198.8.



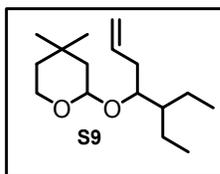
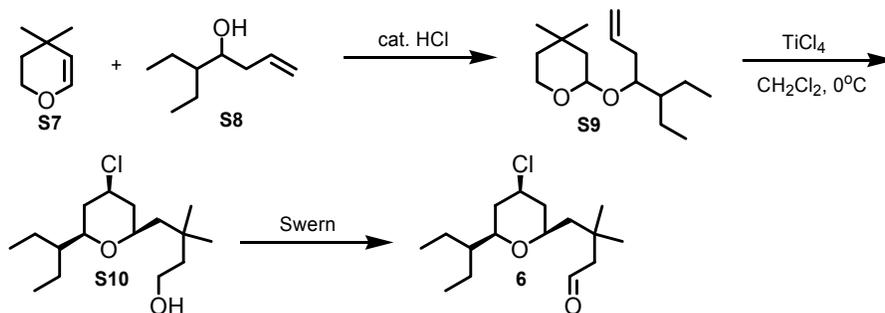
S6 was prepared in a similar manner as **S5**. A colorless oil (SiO₂, Hex:EtOAc = 30:1, 61 % yield): IR 2980, 2937, 2868, 1732, 1446, 1366, 1282, 1221, 1194, 1103, 1041, 924 cm⁻¹; ^1H NMR (500 MHz) δ 1.14 (t, $J = 7.1$ Hz, 3H), 1.21 (t, $J = 7.1$ Hz, 3H), 1.46-1.49 (m, 1H), 1.71-1.79 (m, 4H), 1.89-1.93 (m, 2H), 2.60-2.65 (m, 1H), 2.69-2.74 (m, 1H), 2.80-2.84 (m, 1H), 3.91-3.98 (m, 3H), 4.12 (q, $J = 7.1$ Hz, 2H), 4.76 (bs, 1H), 5.03-5.06 (m, 2H), 5.61 (sextet, $J_{av} = 8.4$ Hz, 1H), 7.24 (t, $J = 7.1$ Hz,

1H), 7.3-7.4 (m, 4H); ¹³C NMR (125 MHz) δ 13.8, 14.0, 19.0, 30.9, 31.0, 35.1, 36.6, 55.7, 61.0, 61.2, 67.8, 72.0, 118.8, 126.5, 126.8, 128.0, 132.8, 142.4, 171.2, 171.4.

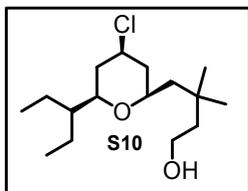


To a 150 mL round bottom flask was placed **S6** (1.05 g, 2.80 mmol), 30 mL ether, 45 mL water, and osmium tetroxide (710 μL, 0.112 mmol, 0.04 equiv, 4 % wt in water). The reaction was stirred vigorously for 15 minutes and then NaIO₄ (2.40 g, 11.2 mmol, 4.0 equiv) was added. After vigorous stirring for 43 hours, 125 mL of ether was added. The layers were separated and the aqueous layer extracted with EtOAc (50 mL). The organic layers were combined, washed with 4M NaOH (3 X 15 mL), dried with MgSO₄ and concentrated *in vacuo*. Purification of the crude oil via flash chromatography (Hex:EtOAc = 20 : 1) gave **5** as colorless oil (940 mg, 89% yield): IR 2981, 2938, 2867, 2734, 1732, 1446, 1367, 1281, 1218, 1194, 1104, 1042, 1028 cm⁻¹; ¹H NMR (500 MHz) δ 1.12-1.21 (m, 6H), 1.35-1.38 (m, 1H), 1.73-1.75 (m, 4H), 1.83-1.84 (m, 1H), 2.01 (d, *J* = 15.0 Hz, 1H), 2.74-2.78 (m, 1H), 3.03 (d, *J* = 18.1 Hz, 1H), 3.26 (d, *J* = 18.1 Hz, 1H), 3.86-3.88 (m, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.66 (bs, 1H), 7.23 (t, *J* = 6.6 Hz, 1H), 7.30-7.34 (m, 4H), 9.59 (s, 1H); ¹³C NMR (125 MHz) δ 13.7, 13.8, 19.0, 31.0, 35.7, 45.9, 53.5, 61.6, 61.7, 68.5, 72.0, 126.5, 127.0, 128.1, 142.1, 170.3, 170.4, 199.2.

Synthesis of tetrahydropyran **6**.



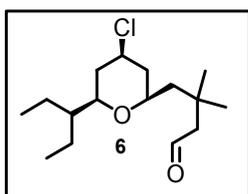
The protected alcohol **S9** was prepared by the reacting 4,4-dimethyl-2,3-dihydro-2H-pyran **S7**³ with **S8** neat in the presence of a few drops of concentrated HCl. Purification via passage the reaction through a plug of silica gel (Hex:EtOAc = 30:1) gave **S9** in 80% yield.



To **S9** (1.16 g, 4.6 mmol) in 30 mL of CH₂Cl₂ was added TiCl₄ (760 μL, 6.9 mmol, 1.5 equiv) dropwise via syringe at 0 °C. After 45 minutes, the reaction was quenched by the addition of saturated sodium bicarbonate. The layers were separated and the aqueous layer was extracted with EtOAc (3 X 40 mL). The combined organic layers were washed with brine, dried with MgSO₄, and concentrated *in vacuo*. Purification of the crude oil via flash chromatography

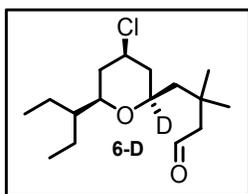
³ Murray, R. W.; Shiang, D. L.; Singh, D. L. *J. Org. Chem.* **1991**, *56*, 3677-3682.

(Hex:EtOAc = 8:1 then 5:1) gave **S10** (830 mg, 61% yield). IR 3372(br), 2961, 2933, 2875, 1466, 1380, 1386, 1155, 1078, 1037 cm^{-1} ; ^1H NMR (500 MHz) δ 0.86-0.90 (m, 6H), 0.94 (s, 3H), 0.95 (s, 3H), 1.20 (dd, $J = 14.9, 1.4$, 1H), 1.25-1.50 (m, 6H), 1.54 (dd, $J = 11.7$ Hz; $J_{\text{av}} = 2.5$ Hz, 1H) 1.58 (dd, $J = 11.7$ Hz; $J_{\text{av}} = 2.5$ Hz 1H), 1.70-1.78 (m, 2H), 1.97-2.08 (m, 3H), 3.25-3.28 (m, 1H), 3.41-3.45 (m, 1H), 3.68-3.73 (m, 2H), 3.99-4.04 (m, 1H); ^{13}C NMR (100 MHz) δ 11.4, 11.6, 21.5, 21.9, 28.4, 28.7, **32.1**, 39.2, 43.8, 44.0, 45.6, 47.3, 56.5, 59.8, 74.4, 78.4.



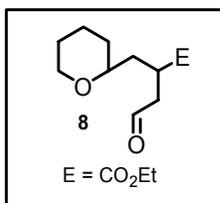
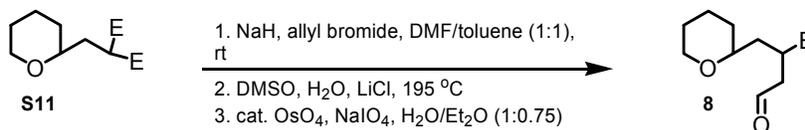
A 50 mL round bottom flask containing oxalyl chloride (290 μL , 3.30 mmol, 1.2 equiv) and 10 mL of CH_2Cl_2 was cooled to -78°C and DMSO (390 μL , 5.53 mmol, 2.0 equiv) was added dropwise via syringe. After 15 minutes, **S10** (800 mg, 2.75 mmol) was added via syringe in 20 mL of CH_2Cl_2 . After 15 minutes, triethylamine (1.9 mL, 13.8 mmol, 5.0 equiv) was added dropwise via syringe.

The reaction was allowed to gradually warm to ambient temperature overnight. Ether was added and the reaction was filtered through a pad of celite, and concentrated *in vacuo*. Purification of the residual material via flash chromatography (Hex:EtOAc = 30:1) gave **6** (750 mg, 94% yield) as a colorless oil: IR 2962, 2934, 2875, 1721, 1466, 1369, 1156, 1078, 1031 cm^{-1} ; ^1H NMR (500 MHz) δ 0.83 (q, $J_{\text{av}} = 6.9$ Hz, 6H), 1.04 (s, 3H), 1.05 (s, 3H), 1.20-1.43 (m, 6H), 1.46-1.55 (m, 2H), 1.71 (dd, $J = 14.5, 9.5$ Hz, 1H), 1.99 (ddm, $J = 17.7, 12.6$ Hz, 1H), 2.24 (dd, $J = 14.9, 3.2$ Hz, 1H), 2.41 (dd, $J = 14.9, 2.1$ Hz, 1H), 3.21 (dd, $J = 11.5, 3.7$ Hz, 1H), 3.40 (tm, $J_{\text{av}} = 10.2$ Hz, 1H), 3.95-4.01 (m, 1H), 9.79 (t, $J = 2.6$ Hz, 1H); ^{13}C NMR (125 MHz) δ 11.3, 11.6, 21.5, 21.9, 28.1, 28.7, 32.8, 39.1, 43.8, 45.5, 47.5, 54.5, 47.5, 54.6, 56.4, 73.9, 78.1, 203.5.



6-D was synthesized in the same manner as **6** by starting with 4,4-dimethyl-6-deuterio-deut-2,3-dihydro-2H-pyran² **S7-D**.² The percent deuterium was determined by the disappearance of the ^1H NMR resonance at δ 3.41; ^1H NMR (300 MHz) δ 0.84-0.90 (m, 6H), 1.08 (s, 3H), 1.09 (s, 3H), 1.22-1.46 (m, 7H), 1.55 (q, $J_{\text{av}} = 11.9$ Hz, 2H), 1.74 (d, $J = 14.7$ Hz, 1H), 1.96-2.09 (m, 2H), 2.27 (dd, $J = 14.8, 3.3$ Hz, 1H), 2.46 (dd, $J = 14.8, 2.4$ Hz, 1H), 3.21-3.26 (m, 1H), 4.01 (tt, $J = 11.7, 4.5$ Hz, 1H), 9.81 (t, $J = 2.9$ Hz).

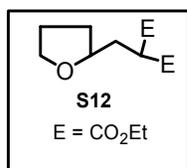
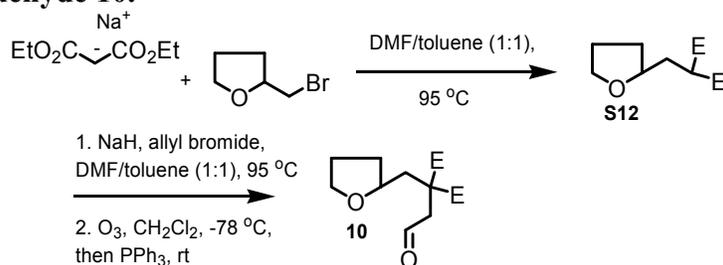
Synthesis of aldehyde **8**.



To a 150 mL round bottom flask containing **S11** (3.0 g, 11.6 mmol) and 60 mL of DMF/toluene (1:1) was added NaH (352 mg, 13.9 mmol, 1.2 equiv, 95%). The ensuing reaction was stirred for 15 min, and then allyl bromide (2.9 mL, 34.8 mmol, 3.0 equiv) was added.

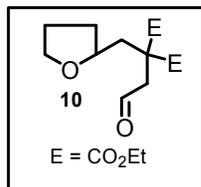
After stirring for 3 hours at room temperature, the reaction was quenched by the addition of 20 mL of water. 150 mL of ether and 30 mL of hexanes were added. The layers were separated and the organic layer was washed with water (1 X 20 mL, 2 X 10mL), brine, dried with MgSO₄, and concentrated *in vacuo*. To the resulting crude oil was added 20 mL DMSO, a few drops of water and LiCl (1.08 g, 25.5 mmol, 2.2 equiv). The mixture was heated to 195 °C for 2 hours (reaction monitored via mass spectrometry) and then 200 mL of ether, 25 mL of Hexane, 10 mL of 1M HCl, and 10 mL of water were added to the reaction. The layers were separated and the organic layer was washed with water (4 X 20 mL) and brine, dried over MgSO₄, and concentrated *in vacuo*. To the resulting crude oil was added 100 mL of distilled water and 75 mL of ether. The biphasic mixture was stirred vigorously and then OsO₄ (2.9 mL, 0.464 mmol, 0.04 equiv, 4%/wt in H₂O). After 15 minutes, NaIO₄ (9.9 g, 46.4 mmol, 4.0 equiv) was added in one portion. After stirring overnight, 100 mL Et₂O was added and the layers separated. The aqueous layer was extracted with EtOAc (2 X 25 mL). The organic layers were combined and washed with 4 M NaOH (4 X 10 mL), brine, dried over MgSO₄, and concentrated *in vacuo*. The resulting crude oil was purified via flash chromatography (Hex/EtOAc = 5:1 then 2:1) to give **8** (978 mg, 37% yield) as a colorless oil (~1:1 mixture of diastereomers); IR 2937, 2845, 1728, 1180, 1091, 1048 cm⁻¹; ¹H NMR (300 MHz) δ 1.23-1.32 (m, 4H), 1.44-1.63 (m, 5H), 1.75-1.92 (m, 2H), 2.60-2.69 (m, 1H), 2.79-2.87 (m, 1H), 3.04-3.11 (m, 1H), 3.24-3.36 (m, 2H), 3.91 (dm, *J* = 11.0 Hz, 1H), 4.10-4.18 (m, 2H) 9.70-9.72 (m, 1H); ¹³C NMR (75 MHz) δ 14.1, 23.3, 25.8, 31.9, 32.1, 35.9, 36.3, 37.9, 38.4, 44.8, 46.0, 60.6, 68.2, 74.8, 75.7, 174.6, 174.8, 200.0, 200.3.

Synthesis of aldehyde **10**.

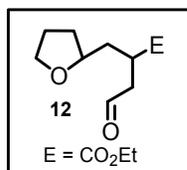


To a 500 mL round bottom flask containing 300 mL of DMF/toluene (1:1) and diethyl malonate (34.7 mL, 228 mmol, 2.0 equiv) was added NaH (5.77 g, 228 mmol, 2.0 equiv, 95%) portionwise. After stirring for 20 minutes at room temperature under argon, 2-bromomethyl-tetrahydrofuran (13 mL, 114 mmol, 1.0 equiv) was added via syringe in one portion. The resulting reaction mixture was heated to 95 °C overnight (~16 h) and quenched in a 1000 mL separatory funnel containing 100 mL water. 500 mL of ether and 250 mL hexanes were added, and the layers separated. The organic layer was washed with water (1 X 100 mL, 3 X 50 mL) and brine, dried over MgSO₄, and concentrated *in vacuo*. Vacuum distillation (~ 1 mmHg) of the residual oil through a Vigreux column (10 cm) gave **S12** (20.7 g, 74% yield, bp 104-108 °C) as a colorless oil: IR 2980, 2873, 1750, 1732, 1370, 1267, 1242, 1155, 1063, 1031 cm⁻¹; ¹H NMR (300 MHz) δ 1.24-1.29 (m, 6H), 1.45-1.56 (m, 1H), 1.82-1.90 (m, 2H), 1.94-2.18 (m, 3H), 3.55 (dd, *J* = 8.6, 6.0 Hz,

1H), 3.69 (q, $J_{av} = 7.3$ Hz, 1H), 3.79 (t, $J_{av} = 6.7$ Hz, 1H), 3.84-3.91 (m, 2H), 4.1-4.27 (m, 4H); ^{13}C NMR (75 MHz) δ 14.0, 25.5, 31.3, 34.5, 49.4, 61.3, 67.6, 76.4, 169.3, 169.5.

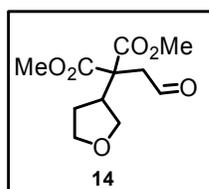
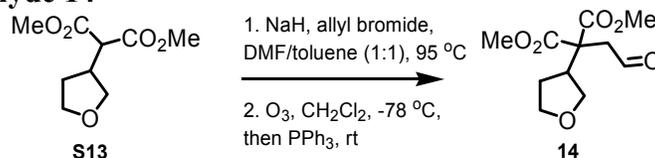


To a solution of **S12** (1.0 g, 4.09 mmol) in 50 mL of DMF/toluene under argon was added NaH (130 mg, 4.90 mmol, 1.2 equiv, 95%) portion wise. After stirring 15 minutes, allyl bromide (860 μL , 10.2 mmol, 2.5 equiv) was added and the reaction stirred for 3 hours at room temperature. The reaction was quenched by the addition of 20 mL of water. 100 mL of ether and 25 mL of hexanes were added and the layers separated. The organic layer was washed with water (4 X 10 mL) and brine, dried over MgSO_4 , and concentrated *in vacuo*. The resulting crude oil was dissolved in 100 mL of CH_2Cl_2 and the solution cooled to -78 $^\circ\text{C}$. ozone was bubbled through the solution until a blue color appeared. Air was passed through the solution to remove the excess ozone. Triphenyl phosphine was added (1.3 g, 4.91 mmol, 1.2 equiv). After stirring for 24 hours at room temperature, the solvent was removed *in vacuo*. Purification of the crude residue via flash chromatography (Hex:EtOAc = 3:1 then 2:1) gave **10** as a clear oil (500 mg, 43% yield): IR 2980, 2875, 1731, 1446, 1367, 1288, 1193, 1096, 1020, cm^{-1} ; ^1H NMR (500 MHz) δ 1.25 (t, $J = 7.1$ Hz, 6H), 1.46-1.53 (m, 1H), 1.77-1.91 (m, 2H), 2.20 (dd, $J = 14.7, 10.0$ Hz, 1H), 2.28 (dd, $J = 14.7, 2.3$ Hz, 1H), 3.12 (d, $J = 18.0$ Hz, 1H) 3.30 (d, $J = 18.0$ Hz, 1H) 3.65 (q, $J_{av} = 7.3$ Hz, 1H), 3.73 (q, $J_{av} = 7.4$ Hz, 1H), 3.84-3.89 (m, 1H), 4.15-4.23 (m, 4H), 9.73 (s, 1H); ^{13}C NMR (125 MHz) δ 13.9, 25.2, 32.5, 38.8, 46.2, 53.9, 61.7, 61.8, 67.7, 75.2, 170.4, 170.5, 199.4.



12 (~ 1:1 mixture of diastereomers) was prepared **S12** in the same manner as **8** in 30% yield for three steps: IR 2976, 2870, 2727, 1731, 1446, 1378, 1233, 1180, 1070 cm^{-1} ; ^1H NMR (500 MHz) δ 1.26 (t, $J_{av} = 7.9$ Hz, 3H), 1.43-1.50 (m, 1H), 1.63-1.70 (m, 1H), 1.83-1.95 (m, 3H), 1.97-2.04 (m, 1H), 2.67-2.74 (m, 1H), 2.84-2.91 (m, 1H), 3.03-3.07 (m, 1H), 3.67-3.72 (m, 1H), 3.80-3.87 (m, 2H), 4.13-4.18 (m, 2H), 9.75-9.76 (m, 1H); ^{13}C NMR (125 MHz) δ 14.05, 25.4, 25.5, 31.5, 31.7, 36.8, 37.0, 37.2, 37.5, 44.9, 45.6, 60.7, 67.6, 67.6, 76.3, 77.2, 174.5, 174.6, 200.1, 200.2.

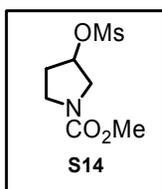
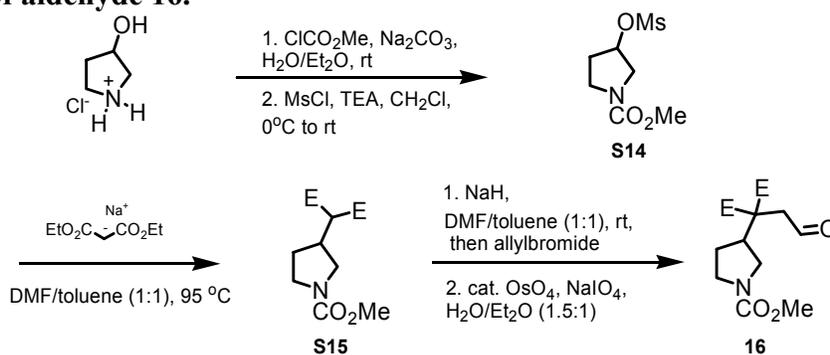
Synthesis of aldehyde **14**



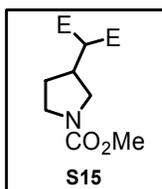
To a solution of **S13** (2.28 g, 11.3 mmol) in 50 mL of DMF/toluene under argon was added NaH (313 mg, 12.4 mmol, 1.2 equiv, 95%) portion wise. After stirring 15 minutes, allyl bromide (2.4 mL, 10.2 mmol, 2.5 equiv) was added and the reaction stirred for 3.5 hours at 95 $^\circ\text{C}$. The reaction was quenched by the addition of 20 mL of water. 175 mL of ether and 25 mL of hexanes were added, and the layers separated. The organic layer was washed with water (4 X 10 mL) and brine, dried over

MgSO₄, and concentrated *in vacuo*. The resulting crude oil was dissolved in 150 mL of CH₂Cl₂ and the solution cooled to -78 °C. Ozone was bubbled through the solution until a blue color appeared. Air was passed through the solution to remove the excess ozone. Triphenyl phosphine was added (3.5 g, 13.5 mmol, 1.2 equiv) After stirring for 24 hours at room temperature, the solvent was removed *in vacuo*. Purification of the crude residue via flash chromatography (Hex:EtOAc = 3:1 then 2:1) gave **14** as a clear oil (1.6 g, 58% yield): IR 2957, 2865, 1731, 1436, 1274, 1208, 1076, 1113, 1076 cm⁻¹; ¹H NMR (300 MHz) δ 1.64-1.74 (m, 1H), 1.88-1.97 (m, 1H), 2.89-2.92 (m, 3H), 3.58 (q, *J*_{av} = 8.0 Hz, 1H), 3.64-3.80 (m, 9H), 9.63 (m, 1H); ¹³C NMR (75 MHz) δ 27.7, 42.9, 45.6, 52.8, 56.2, 67.8, 69.2, 170.0, 170.2, 198.3.

Synthesis of aldehyde **16**.

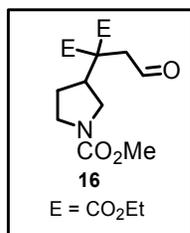


To a 250 mL round bottom flask was added 3-hydroxy-pyrrolidine hydrochloride (5.6 g, 45.3 mmol), 120 mL of ether, and 60 mL of water. The biphasic solution was stirred vigorously and Na₂CO₃ (14.4g, 136 mmol, 3 equiv) was added. After 20 minutes, methyl chloroformate (5.6 mL, 72.5 mmol, 1.6 equiv) was added. The reaction was stirred overnight and then 15 mL of 1M HCl was added. The layers were separated and the aqueous layer was extracted with EtOAc (2 X 200 mL). The combined organic layer was dried with MgSO₄ and concentrated *in vacuo*. The resulting crude oil (3.15 g, 21.7 mmol, 48% yield) was dissolved in 100 mL of CH₂Cl₂, and triethyl amine (3.3 mL, 23.9 mmol, 1.1 equiv) was added. The solution was cooled to 0 °C under argon and methane sulfonyl chloride (1.85 mL, 23.9 mmol, 1.1 equiv) was added via syringe. The reaction was allowed to gradually warm to ambient temperature and stirred overnight. 60 mL of water was added and the layers separated. The aqueous layer was extracted with CH₂Cl₂ (2 X 100 mL). The combined organic layers were dried with MgSO₄ and concentrated *in vacuo*. Purification of the crude oil via flash chromatography (100% EtOAc) gave **S14** (4.6 g, 95% yield) as a colorless oil: ¹H NMR (300 MHz) δ 2.12-2.18 (m, 1H), 2.23-2.30 (m, 1H), 3.05 (s, 3H), 3.48-3.63 (m, 3H), 3.71 (s, 3H), 3.71-3.78 (m, 1H), 5.27 (bs, 1H).



To a 150 mL round bottom flask containing 80 mL of DMF/toluene (1:1) and diethyl malonate (6.1 mL, 39.9 mmol, 2.0 equiv) was added NaH (1.0 g, 39.9 mmol, 2.0 equiv, 95%) portion wise. After stirring for 20 minutes at room temperature under argon, **S14** (4.45 g, 19.9 mmol, 1.0 equiv) in 15 mL of toluene was added via syringe in one portion. The resulting reaction mixture was heated to 95 °C overnight and quenched in a 1000

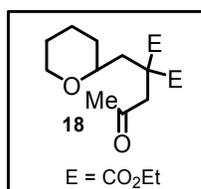
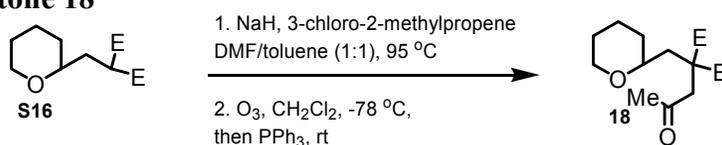
mL separatory funnel containing 100 mL water. 300 mL of ether and 100 mL hexanes were added and the layers separated. The organic layer was washed with water (1 X 40 mL, 3 X 20 mL) and brine, dried over MgSO₄ and concentrated *in vacuo*. Purification of the crude oil via flash chromatography (Hex:EtOAc = 3:1) gave **S15** (3.28 g, 55% yield) as a colorless oil: IR 2983, 2878, 1732, 1708, 1370, 1452, 1392, 1177, 1029 cm⁻¹; ¹H NMR (300 MHz) δ 1.22-1.28 (m, 6H), 1.61-1.68 (m, 1H), 2.07 (bs, 1H), 2.75-2.83 (m, 1H), 3.05 (q, *J*_{av} = 10.6 Hz, 1H), 3.23-3.33 (m, 1H), 3.44-3.56 (m, 1H), 3.65 (s, 3H), 3.68-3.71 (m, 1H), 4.13-4.22 (m, 4H).



To a solution of **S15** (1.93 g, 6.40 mmol) in 40 mL of DMF/toluene under argon was added NaH (194 mg, 12.4 mmol, 1.2 equiv, 95%) portion wise. After stirring 15 minutes, allyl bromide (1.6 mL, 19.2 mmol, 3.0 equiv) was added and the reaction stirred for 3.5 hours at room temperature. The reaction was quenched by the addition of 15 mL of water. 150 mL of EtOAc and 50 mL of hexanes were added and the layers separated. The organic layer was washed with water (4 X 10 mL)

and brine, and concentrated *in vacuo*. To the resulting crude oil was added 50 mL ether and 75 mL water. To the vigorously stirred biphasic mixture was added OsO₄ (1.6 mL, 0.256 mmol, 0.04 equiv, 4%/wt in H₂O). After 15 minutes, NaIO₄ (5.5 g, 25.6 mmol, 4.0 equiv) was added in one portion. After stirring for 24 hours 100 mL Et₂O was added and the layers separated. The aqueous layer was extracted with EtOAc (2 X 50 mL). The organic layers were combined and washed with 4 M NaOH (4 X 10 mL) and brine, dried over MgSO₄, and concentrated *in vacuo*. The resulting crude oil was purified via flash chromatography (Hex/EtOAc = 1:1) to give **16** (950 mg, 45% yield) as a colorless oil; IR 2983, 1731, 1709, 1454, 1393, 1271, 1196, 1132, 1018 cm⁻¹; ¹H NMR (500 MHz) δ 1.24 (t, *J* = bd Hz, 6H), 1.71-1.77 (m 1H), 1.93-2.04 (m, 1H), 2.82-2.93 (m, 1H), 2.92 (d, *J* = 1.1 Hz, 2H), 3.16-3.28 (m, 2H), 3.49-3.62 (m, 2H), 3.65 (s, 3H), 4.20 (q, *J* = 7.1 Hz, 4H), 9.66 (t, *J* = 1.3 Hz, 1H); ¹³C NMR (125 MHz) δ 13.8, 26.6, 27.5, 41.5, 42.3, 45.1, 45.4, 45.7, 46.9, 47.4, 52.2, 55.6, 61.9, 155.1, 169.2, 198.0. The ¹³C NMR is a mixture of rotamers.

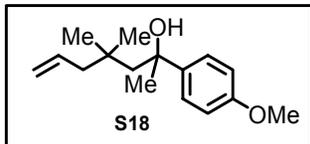
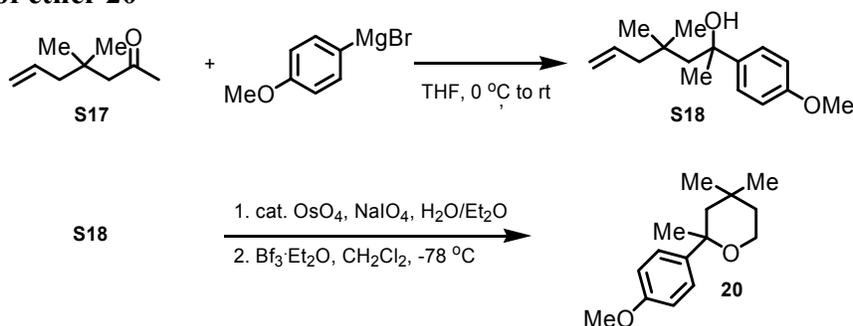
Synthesis of ketone 18



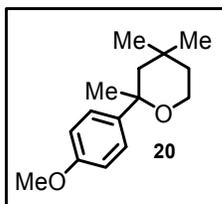
To a solution of **S16** (725 mg, 2.81 mmol) in 20 mL of DMF/toluene under argon was added NaH (92 mg, 3.65 mmol, 1.3 equiv, 95%) in one portion. After stirring 15 minutes, 3-chloro-2-methylpropene (1.1 mL, 11.2 mmol, 4.0 equiv) was added and the reaction stirred for 6 hours at room temperature. The reaction was quenched by the addition of 5 mL of water. 100 mL of ether and 10 mL of hexanes were added and the layers separated. The organic layer was washed with water (4 X 5 mL) and brine, dried over MgSO₄, and concentrated *in vacuo*. The resulting crude oil was dissolved in 75 mL of CH₂Cl₂ and the solution cooled to -78 °C. Ozone was bubbled through the solution until a

blue color appeared. Air was passed through the solution to remove the excess ozone. Triphenyl phosphine was added (740 mg, 2.81 mmol, 1.0 equiv) After stirring for 24 hours at room temperature the solvent was removed *in vacuo*. Purification of the crude residue via flash chromatography (Hex:EtOAc = 6:1 then 3:1) gave **18** as a clear oil (820 mg, 93% yield): IR 2981, 2937, 2647, 1732, 1442, 1366, 1296, 1198, 1092, 1050 cm^{-1} ; ^1H NMR (500 MHz) δ 1.14-1.25, (m, 7H), 1.36-1.44 (m, 2H), 1.71-1.73 (m, 1H), 1.92-1.98 (m, 1H), 2.05 (s, 3H), 2.13 (d, $J = 14.8$ Hz, 1H), 3.11-3.27 (m, 4H), 3.72-3.74 (m, 1H), 4.03-4.13 (m, 4H); ^{13}C NMR (125 MHz) δ 13.8, 23.4, 25.5, 29.9, 32.3, 39.1, 46.2, 53.5, 61.2, 67.5, 74.5, 170.6, 170.7, 205.0.

Synthesis of ether **20**



To a solution of **S17** (1.9 g, 13.5 mmol) in a 150 mL round bottom flask at 0 °C was added 4-methoxyphenylmagnesium bromide (54.2 mL, 27.1 mmol, 2.0 equiv, 2.0 M THF) via syringe. The cooling bath was removed and reaction stirred for 1.5 hours and then quenched with saturated NH_4Cl , and concentrated to remove the majority of the THF. Ether was added and the solvent decanted from the precipitate. The organic layer was washed with 35 mL water, and the aqueous layer extracted with 25 mL EtOAc. The organic layers were combined, washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification of the crude oil via flash chromatography (Hex/EtOAc = 15:1) gave **S18** (2.38 g, 75% yield) as a colorless oil. ^1H NMR (300 MHz) δ 0.72 (s, 3H), 0.79 (s, 3H), 1.54 (s, 3H), 1.72 (s, 1H), 1.87 (d, $J = 6.6$ Hz, 2H), 1.89-1.99 (m, 2H), 3.78 (s, 3H), 4.91-5.00 (m, 2H), 5.72-5.82 (m, 2H), 6.83 (d, $J = 8.3$ Hz, 2H), 7.33 (d, $J = 8.3$ Hz, 2H).



In a 200 mL round bottom flask was added **S18** (1.28 g, 5.15 mmol, 1.0 equiv), 50 mL ether, and 75 mL water. To the vigorously stirred biphasic mixture was added OsO_4 (1.3 mL, 0.206 mmol, 0.04 equiv, 4%/wt in water). After 15 minutes, NaIO_4 (4.4 g, 20.6 mmol, 4.0 equiv) was added in one portion. After 24 hours, 50 mL of ether was added and the layers separated. The aqueous layer was extracted with EtOAc (2 X 25 mL). The organic layers were combined and washed with 4 M NaOH (4 X 10 mL) and brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude oil was placed in a 100 mL round bottom flask and dissolved in 50 mL of CH_2Cl_2 . Triethylsilane

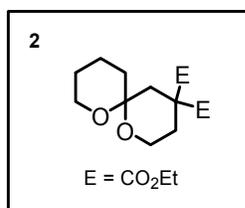
(4.1 mL, 25.8 mmol, 5.0 equiv) was added and the solution cooled to -78 °C. BF₃·Et₂O (1.3 mL, 10.3 mmol, 2.0 equiv) was added drop wise via syringe over a 5 minute period. The reaction was stirred for 5 hours while not allowing the cooling bath to surpass -10 °C, and then poured into a separatory funnel containing 50 mL of saturated bicarbonate. The layers were separated and the aqueous layer extracted with CH₂Cl₂ (2 X 30 mL). The organic layers were combined, washed with brine, dried over MgSO₄, and concentrated *in vacuo*. Purification of the resulting crude oil via flash chromatography (Hex/EtOAc = 35:1) give **20** (750 mg, 62% yield) as a colorless oil; IR 2951, 2927, 2872, 2836, 1612, 1582, 1511, 1464, 1297, 1244, 1177, 1099, 1062, 1038, 831 cm⁻¹; ¹H NMR (300 MHz) δ 0.58, (s, 3H), 0.98 (s, 3H), 1.18 (dq, *J* = 13.2, 2.2 Hz, 1H), 1.33 (s, 3H), 1.51-1.64 (m, 2H), 2.19 (dd, *J* = 14.0, 2.0 Hz), 3.72 (t, *J*_{av} = 2.7 Hz), 3.74 (d, *J* = 2.4 Hz), 6.84 (m, 2H), 7.28-7.33 (m, 2H); ¹³C NMR (100 MHz) δ 26.2, 29.0, 33.7, 35.8, 38.9, 47.0, 55.2, 59.7, 75.4, 113.4, 126.4, 138.1, 157.9.

III. General Procedure for Hydro-*O*-alkylation.

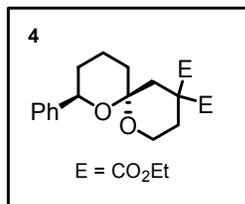
Boron trifluoride etherate was purchased from Aldrich and used as received. Older bottles of catalyst (> 1 year) could be employed with out a noticeable decrease in performance. TiF₄ was purchased from Strem and stored in a glove box. All reactions were carried out in round bottom flasks from the drawer and were not dried prior to use. Reactions run at elevated temperature were carried out in sealed tubes. All reactions were run on 0.5 mmol or 0.25 mmol scale at 0.025 M concentration of substrate. Reactions were monitored by TLC analysis using hexanes/ethyl acetate mixtures as the eluent (visualization using ceric ammonium molybdate stain). The ketal products have higher R_fs than starting materials.

General procedure for reactions with BF₃·Et₂O: In a 50 mL of round bottom flask was weighed 0.50 mmol of substrate. The flask was capped with a septum and evacuated and filled with argon three times. 20 mL of CH₂Cl₂ was added via syringe. 0.15 mmol of BF₃·Et₂O was added via a micro syringe. Reactions were monitored by TLC analysis. After completion the solvent was removed on a rotary evaporator and the crude residue purified via flash chromatography (yields given in Table 1).

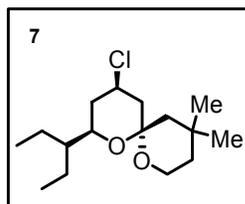
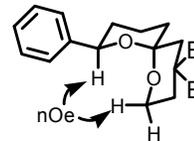
General procedure for reactions with TiF₄: In a 20 mL sealed tube was weighed 0.25 mmol of substrate on the benchtop. The tube was fitted with a septum and evacuated and filled with argon three times. 10 mL of CH₂Cl₂ was added via syringe. The septum was removed and a Teflon screw cap was replaced on the tube. The sealed tube was brought in to a glove box and TiF₄ was weighed and added to the solution (TiF₄ should have good solubility in CH₂Cl₂). The reaction was removed from the glove box and stirred at the appropriate time and temperature (Table 1). Reactions were monitored via TLC (removal of the Teflon screw cap in the ambient atmosphere). After completion, 2 mL of saturated sodium bicarbonate and 2 mL of water was added. The layers separated and the aqueous extracted with CH₂Cl₂ (2 x 5 mL). The combined organic layer was dried over MgSO₄, concentrated and purified via flash chromatography (yields given in Table 1).



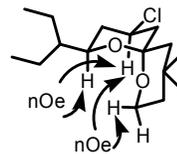
A white solid (SiO₂, Hex:EtOAc = 4:1): IR 2948, 2865, 1727, 1456, 1234, 1178, 1071, 1017, 978; ¹H NMR (500 MHz) δ 1.22 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.44-1.56 (m, 4H), 1.62-1.70 (m, 2H), 1.78-1.82 (m, 1H), 2.00 (d, *J* = 14.1 Hz), 2.31 (t, *J*_{av} = 12.7 Hz), 3.44- 3.47 (m, 1H), 3.54 (td, *J*_{1av} = 11.5 Hz and *J*_{2av} = 2.7 Hz), 3.63 (dd, *J* = 11.5, 4.4 Hz), 3.97 (td, *J*_{1av} = 12.1 Hz and *J*_{2av} = 2.0 Hz, 1H), 4.12-4.16 (m, 4H); ¹³C NMR (125 MHz) δ 13.9, 18.2, 24.7, 29.9, 34.8, 39.2, 50.2, 57.3, 60.2, 61.0, 61.5, 94.7, 170.6, 171.7; MS (LR-APCI); calcd for C₁₅H₂₅O₆ 301.17, measured 301.25.



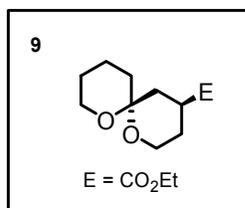
A clear oil (SiO₂, Hex:EtOAc = 5:1): IR 2979, 2947, 1733, 1441, 1312, 1242, 1172, 1097, 1012, 958; ¹H NMR (500 MHz) δ 1.02 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.42-1.59 (m, 2H), 1.66-1.74 (m, 3H), 1.78 (d, *J* = 13.2 Hz, 1H), 1.97-2.05 (m, 1H), 2.09 (d, *J* = 14.0 Hz, 1H), 2.30 (d, *J* = 13.3 Hz), 2.46 (d, *J* = 14.0 Hz), 3.67 (dd, *J* = 11.5, 5.1 Hz, 1H), 3.71-3.76 (m, 1H), 3.77-3.85 (m, 2H), 4.00 (t, *J* = 11.9 Hz, 1H), 4.09-4.21 (m, 2H), 4.56 (d, *J* = 11.4 Hz, 1H), 7.21-7.31 (m, 5H); ¹³C NMR (100 MHz) δ 13.6, 13.9, 29.9, 32.5, 34.4, 39.2, 50.2, 57.5, 60.9, 61.5, 71.6, 95.9, 126.2, 127.2, 127.9, 142.7, 170.1, 171.9; MS (LR-APCI); calcd for C₂₁H₂₉O₆ 377.20, measured 377.31.



A clear oil (SiO₂, Hex:EtOAc = 5:1): IR 2959, 2933, 2877, 1464, 1381, 1209, 1060, 1016, 977; ¹H NMR (500 MHz) δ 0.90 (t, *J*_{av} = 7.3 Hz, 9H), 1.13 (s, 3H), 1.24-1.27 (m, 3H), 1.29-1.40 (m, 2H), 1.43-1.62 (m, 6H), 2.05 (dd, *J* = 12.4, 2.1 Hz, 1H), 2.11 (dd, *J*₁ = 12.6 Hz; *J*_{2av} = 3.2 Hz), 3.51 (dd, *J*₁ = 11.2 Hz; *J*_{2av} = 4.4 Hz, 1H), 3.62-3.70 (m, 2H), 4.29-4.35 (m, 1H). ¹³C NMR (100 MHz) δ 12.1, 12.2, 22.1, 22.5, 26.8, 28.6, 34.5, 38.3, 39.4, 46.0, 47.4, 47.5, 54.5, 57.9, 71.1, 98.3; MS (LR-APCI); calcd for C₁₆H₃₀ClO₂ 289.19, measured 289.28.



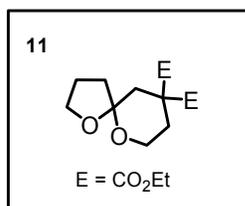
The % deuterium incorporation into the equatorial position of **7-D** was determined by the decrease in the ¹H NMR resonance at δ 3.51 and comparison to **7**. The % deuterium incorporation into the axial position of **7-D** was determined by the decrease in the ¹H NMR resonance at δ 3.62-3.70 and comparison to **7**.



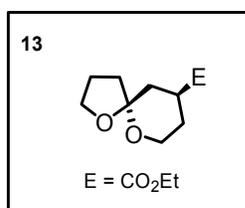
A clear oil (SiO₂, Hex:EtOAc = 2:1): Due to overlapping nOe experiments could not be used to determine the relative stereochemistry. The bis-anomeric conformation with the large ester substituent in the equatorial position represents the thermodynamic structure.⁴ By analogy to **4** and **7**, compound **9** should also possess these relationships; IR 2943, 2869, 1464, 1734, 1443, 1310, 1214,

⁴ Delongchamps, P. *Organic Chemistry Series; Vol. 1: Stereoelectronic Effects in Organic Chemistry*; Baldwin, J. E., Ed.; Pergamon Press: Oxford, 1983; pp. 5-20.

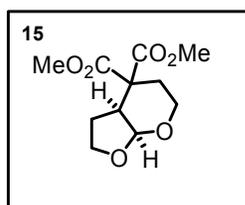
1181, 1150, 1065, 1044, 993; ^1H NMR (500 MHz) δ 1.23 (t, $J = 7.1$ Hz, 3H), 1.45- 1.59 (m, 5H), 1.62-1.71 (m, 2H), 1.80-1.85 (m, 2H), 1.90 (dm, $J = 13.2$ Hz, 1H), 2.91 (tt, $J = 3.9, 12.6$ Hz), 3.59 (dm, $J = 7.9$ Hz, 1H), 3.65 (dd, $J_1 = 11.7$ Hz ; $J_{2\text{av}} = 2.8$ Hz, 1H), 3.69 (dm, $J = 8.5$ Hz, 2H), 4.11 (q, $J = 7.1$ Hz, 2H); ^{13}C NMR (100 MHz) δ 14.1, 18.4, 25.1, 27.7, 35.4, 35.8, 37.8, 59.3, 59.2, 60.3, 60.4, 94.9, 175.0.



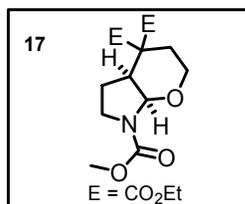
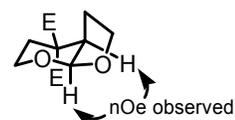
A clear oil (SiO₂, Hex:EtOAc = 5:1): IR 2981, 2895, 1734, 1442, 1367, 1310, 1242, 1093, 1021; ^1H NMR (500 MHz) δ 1.23 (t, $J = 7.2$ Hz, 3H), 1.26 (t, $J = 7.0$ Hz, 3H), 1.67-1.1.27 (m, 2H), 1.83-1.87 (m, 1H), 1.93-2.02 (m, 2H), 2.29 (d, $J = 13.2$ Hz), 2.34 (s, 2H), 3.61 (dd, $J = 11.6, 5.0$ Hz, 1H), 3.82 (t, $J_{\text{av}} = 6.9$ Hz, 2H), 4.08-4.19 (m, 3H), 4.22 (q, $J = 7.1$ Hz, 2H); ^{13}C NMR (100 MHz) δ 13.9, 23.5, 29.8, 36.9, 37.6, 51.2, 58.2, 61.1, 61.5, 67.3, 104.4, 170.5, 171.5.



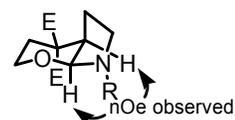
A clear oil (SiO₂, Hex:EtOAc = 2:1): nOe experiments could not be used to determine the relative stereochemistry. The bis-anomeric conformation with the large ester substituent in the equatorial position represents the thermodynamic structure.⁴ By analogy to **4** and **7**, compound **13** should also possess these relationships;; IR 2960, 2879, 1737, 1447, 1259, 1187, 1155, 1075, 1048, 1021; ^1H NMR (500 MHz) δ 1.25 (t, $J = 7.1$ Hz, 3H), 1.66- 1.76 (m, 2H), 1.81-1.98 (m, 5H), 2.02-2.07 (m, 1H), 2.89 (tt, $J = 12.5, 3.9$ Hz, 1H), 3.67 (dd, $J = 11.4, 4.7$ Hz), 3.83 (tm, $J_{\text{av}} = 12.1$ Hz, 1H), 3.89-3.92 (m, 2H), 4.13 (q, $J = 7.1$ Hz, 2H); ^{13}C NMR (100 MHz) δ 14.6, 24.1, 28.1, 36.0, 37.9, 38.1, 60.6, 60.7, 67.5, 105.4, 175.2.

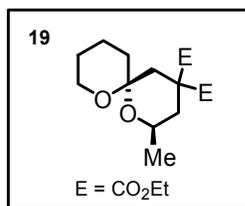


A clear oil (SiO₂, Hex:EtOAc = 5:1): The relative stereochemistry was determined by nOe experiments; IR 2956, 1732, 1436, 1256, 1201, 1134, 1067, 1092, 1067; ^1H NMR (500 MHz) δ 1.65-1.71 (m, 1H), 1.86-1.94 (m, 2H), 2.32 (td, $J_{1\text{av}} = 13.8$ Hz and $J_{2\text{av}} = 4.6$ Hz, 1H), 2.79 (tm, $J = 10.1$ Hz, 1H), 3.33 (t, $J = 12.7$ Hz, 1H), 3.74 (s, 3H), 3.77 (s, 3H), 3.83 (dd, $J = 12.5$ Hz, 4.5 Hz, 1H), 3.93 (q, $J_{\text{av}} = 8.3$ Hz, 1H), 4.15 (tm, $J_{\text{av}} = 8.4$, 1H), 5.24 (d, $J = 3.1$ Hz, 1H). ^{13}C NMR (100 MHz) δ 23.7, 25.7, 42.1, 52.8, 53.0, 54.8, 60.3, 67.5, 99.6, 170.1, 171.3; MS (LR-APCI); calcd for C₁₁H₁₇O₆ 245.10, measured 245.17.

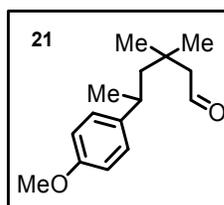


A clear oil (SiO₂, Hex:EtOAc = 3:2 then 1:1): The relative stereochemistry was determined by nOe experiments; IR 2980, 1731, 1717, 1449, 1395, 1380, 1258, 1193, 1068; ^1H NMR (300 MHz, C₆D₆, 345 K) δ 0.88-0.97 (m, 6H), 1.35-1.46 (m, 1H), 1.88 (d, $J = 14.3$ Hz, 1H), 2.27 (td, $J_{1\text{av}} = 13.8$ Hz ; $J_2 = 4.7$ Hz, 1H), 2.74-2.82 (m, 1H), 3.28 (td, $J_{1\text{av}} = 12.7$ Hz; $J_{2\text{av}} = 1.7$ Hz, 1H), 3.49 (s, 3H), 3.59 (ddd, $J = 8.0, 4.6, 1.6$ Hz, 1H), 3.85-4.01 (m, 4H), 5.65 (bs, 1H); ^{13}C NMR (75 MHz, C₆D₆, 345 K) δ 13.9, 23.3 (b), 26.6, 41.9 (b), 44.9, 52.0, 55.4, 61.2, 61.3, 61.6, 84.6, 154.9, 169.4, 170.8.





A clear oil (SiO₂, Hex:EtOAc = 5:1): The bis-anomeric conformation with the large ester substituent in the equatorial position represents the thermodynamic structure.⁴ By analogy to **4** and **7**, compound **19** should also possess these relationships; IR 2965, 2938, 2865, 1734, 1243, 1134, 1014; ¹H NMR (500 MHz) δ 1.19-1.22 (m, 10H), 1.43-1.54 (m, 4H), 1.61-1.64 (m, 1H), 1.82-1.88 (m, 1H), 1.93 (d, $J = 13.8$ Hz, 1H), 2.33 (t, $J_{av} = 14.0$ Hz, 2H), 3.42-3.44 (m, 1H), 3.48-3.52 (m, 1H), 4.01-4.07 (m, 1H), 4.11-4.23 (m, 4H); ¹³C NMR (75 MHz) δ 14.0, 18.3, 21.4, 24.8, 34.8, 36.9, 38.7, 51.1, 60.1, 61.0, 61.5, 62.0, 95.2, 170.8, 171.7.

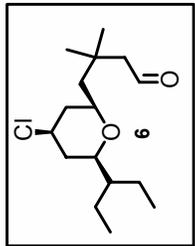
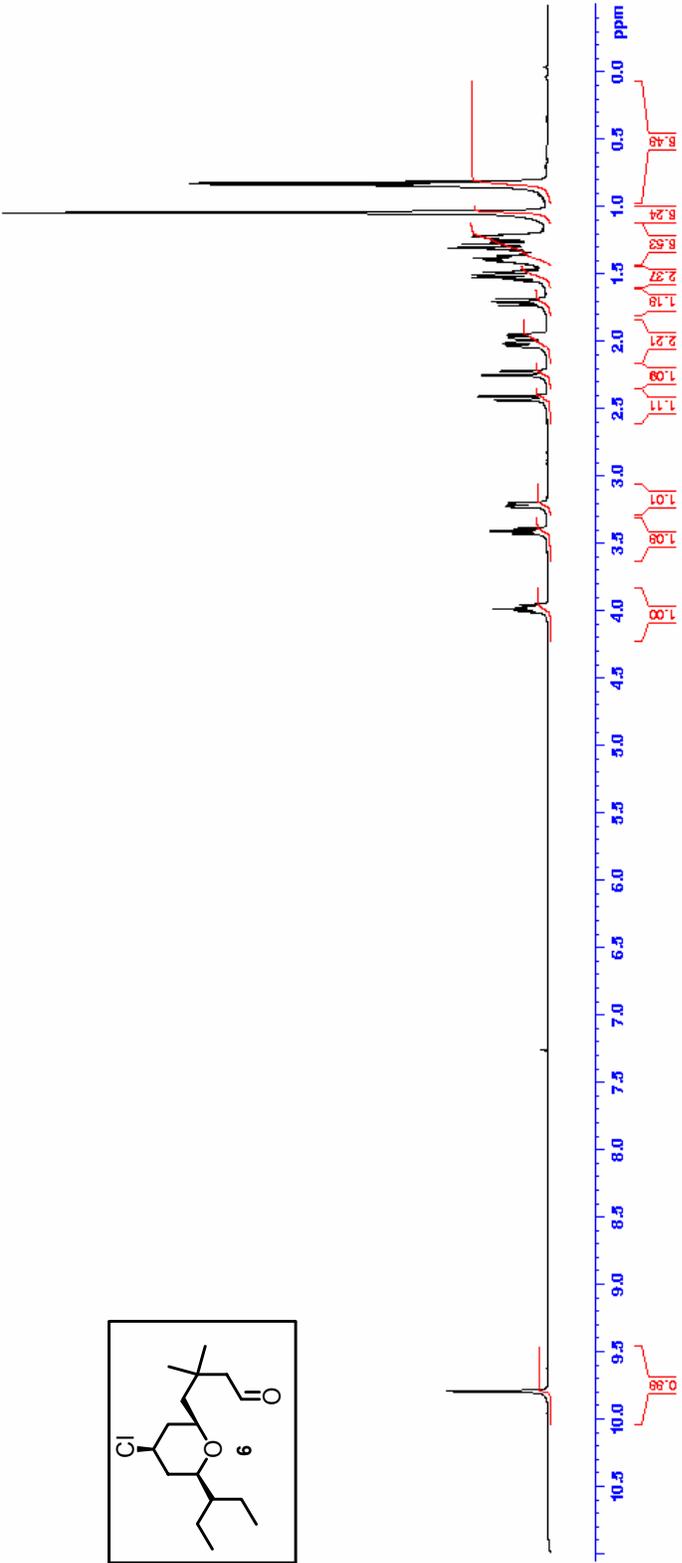


A clear oil (SiO₂, Hex:EtOAc = 6:1): IR 2958, 1719, 1612, 1512, 1466, 1247, 1178, 1036, 830; ¹H NMR (500 MHz) δ 0.95 (s, 6H), 1.21 (d, $J = 7.0$ Hz, 3H), 1.58 (dd, $J = 14.3, 3.8$ Hz, 1H), 1.86 (dd, $J = 14.2, 9.0$ Hz, 1H), 2.12 (d, $J = 2.8$ Hz, 1H), 2.82 (m, 1H), 3.77 (s, 3H), 6.82 (d, $J = 8.5$ Hz, 2H), 7.10 (d, $J = 8.5$ Hz, 2H), 9.68 (t, $J = 2.8$ Hz, 1H); ¹³C NMR (133 MHz) δ 26.0, 28.0, 28.3, 34.0, 35.6, 50.4, 55.0, 55.1, 113.8, 127.8, 140.4, 157.8, 203.4.

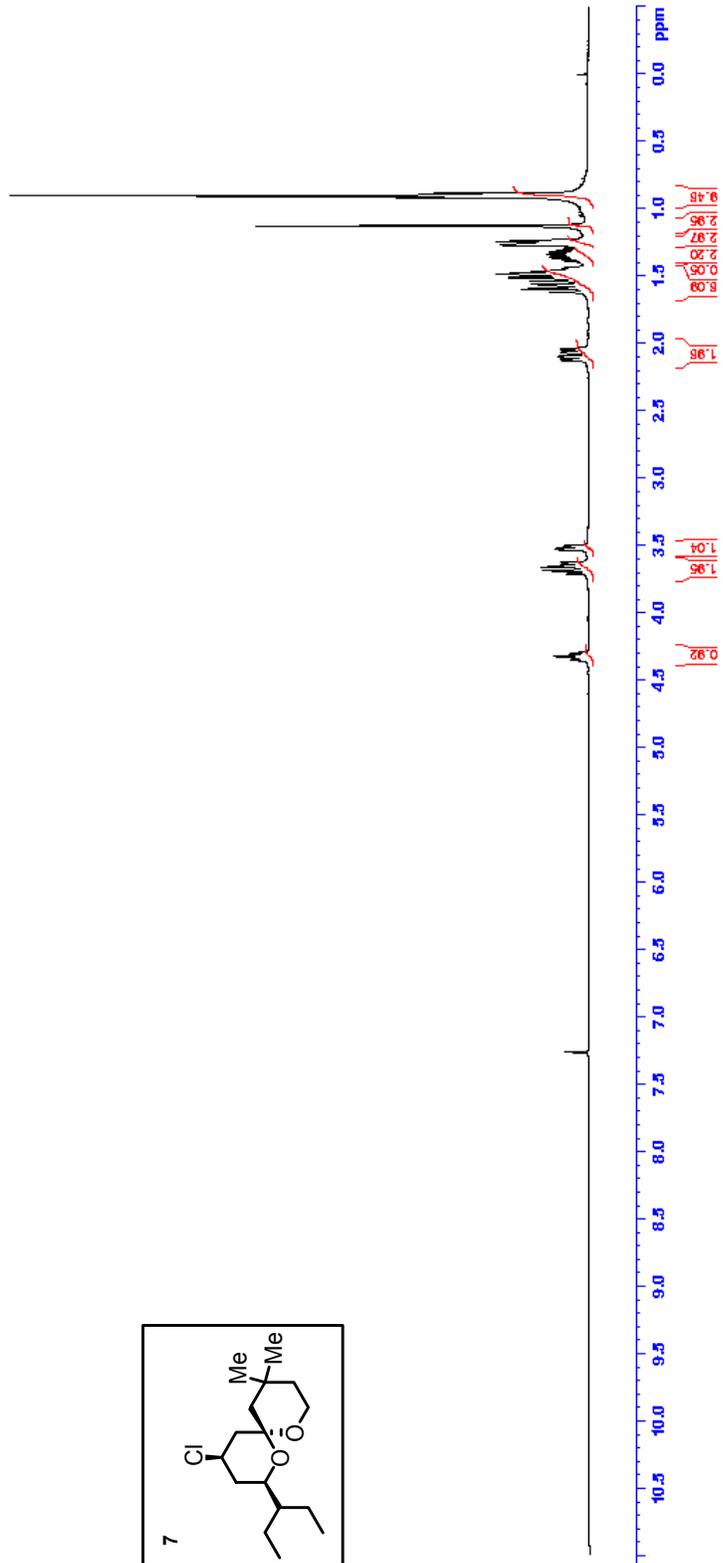
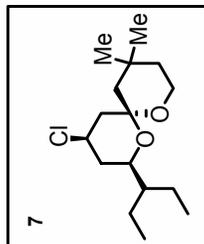
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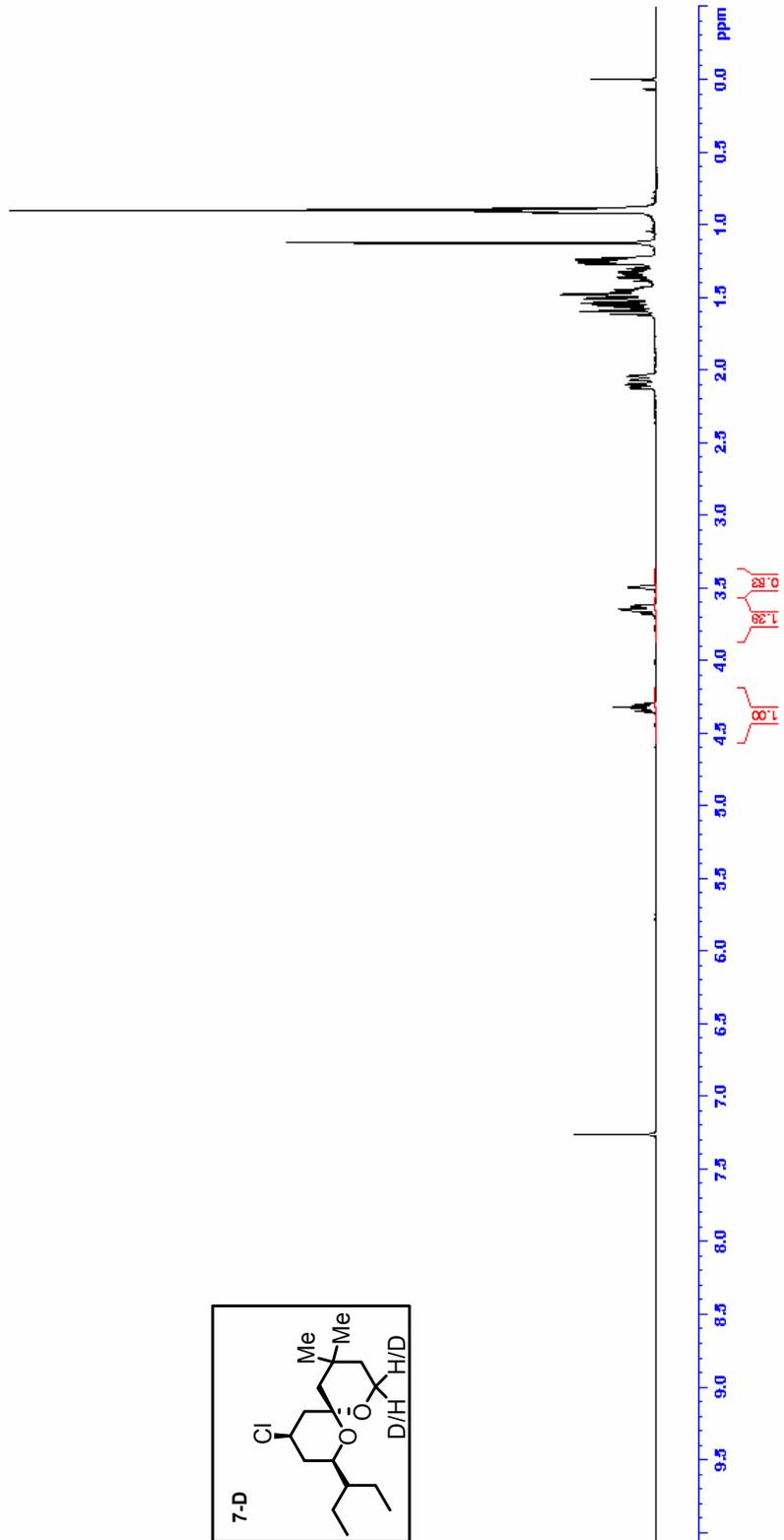
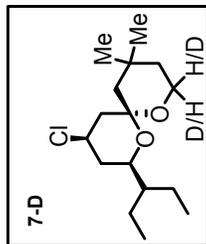
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sp-7-24
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standard proton



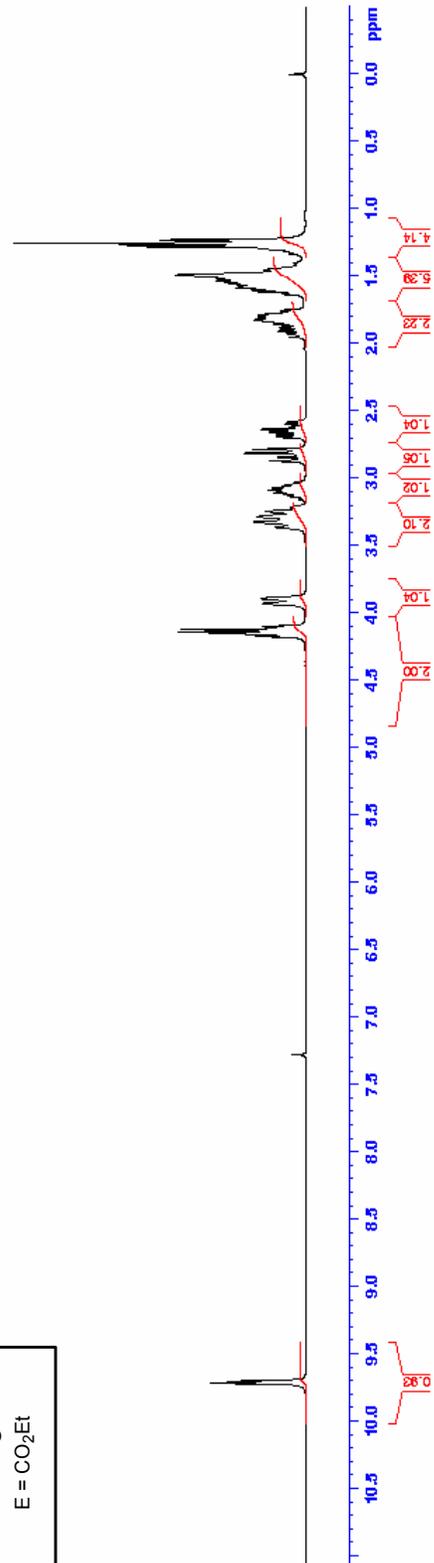
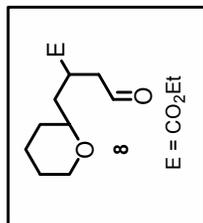
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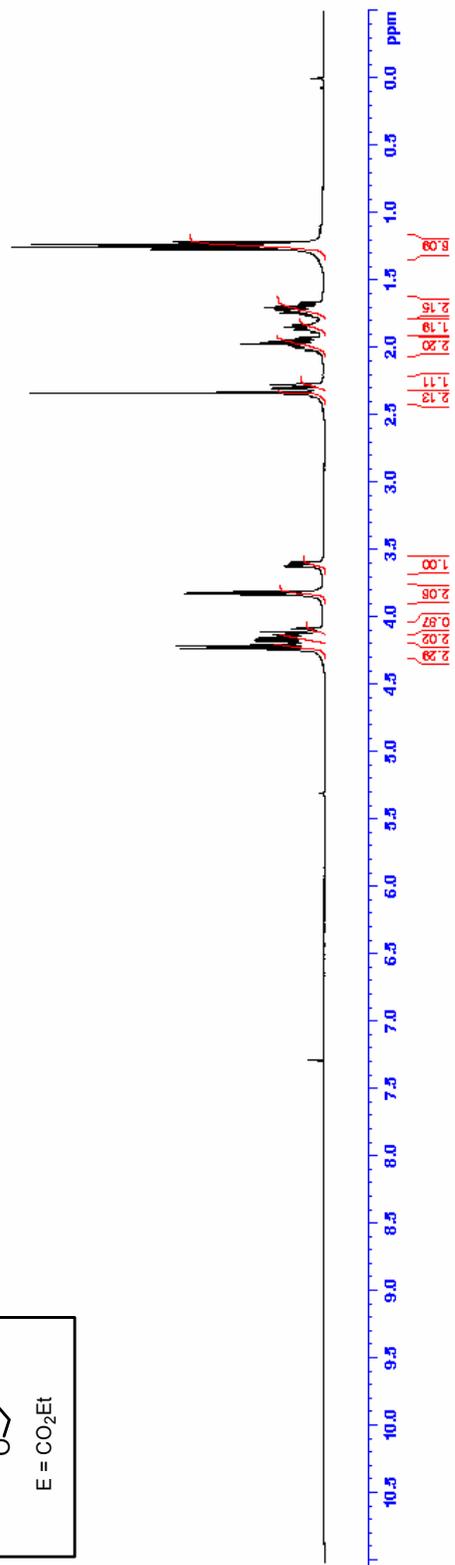
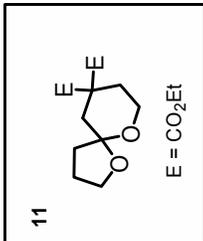
SP-7-119
300nb

9.2177
9.2024

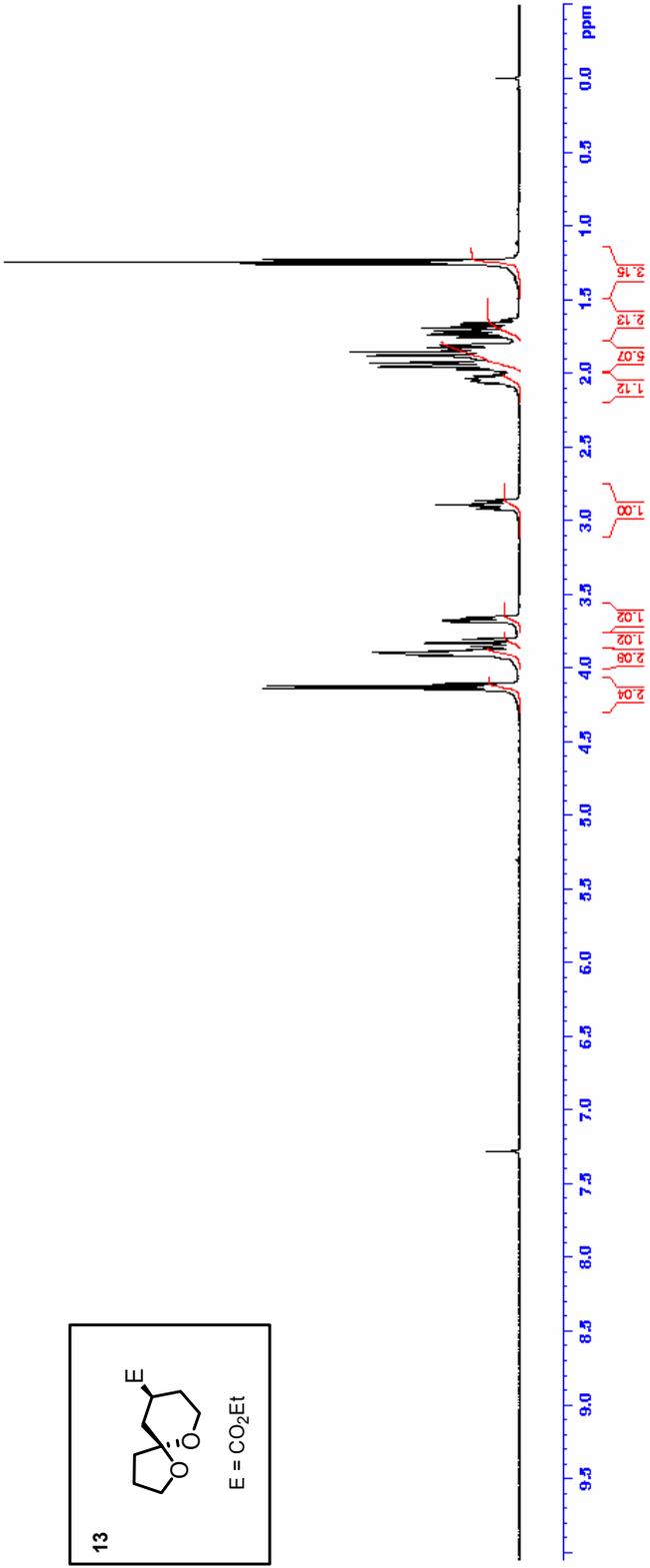
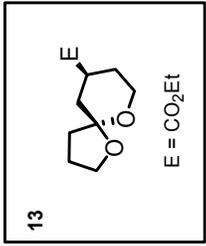
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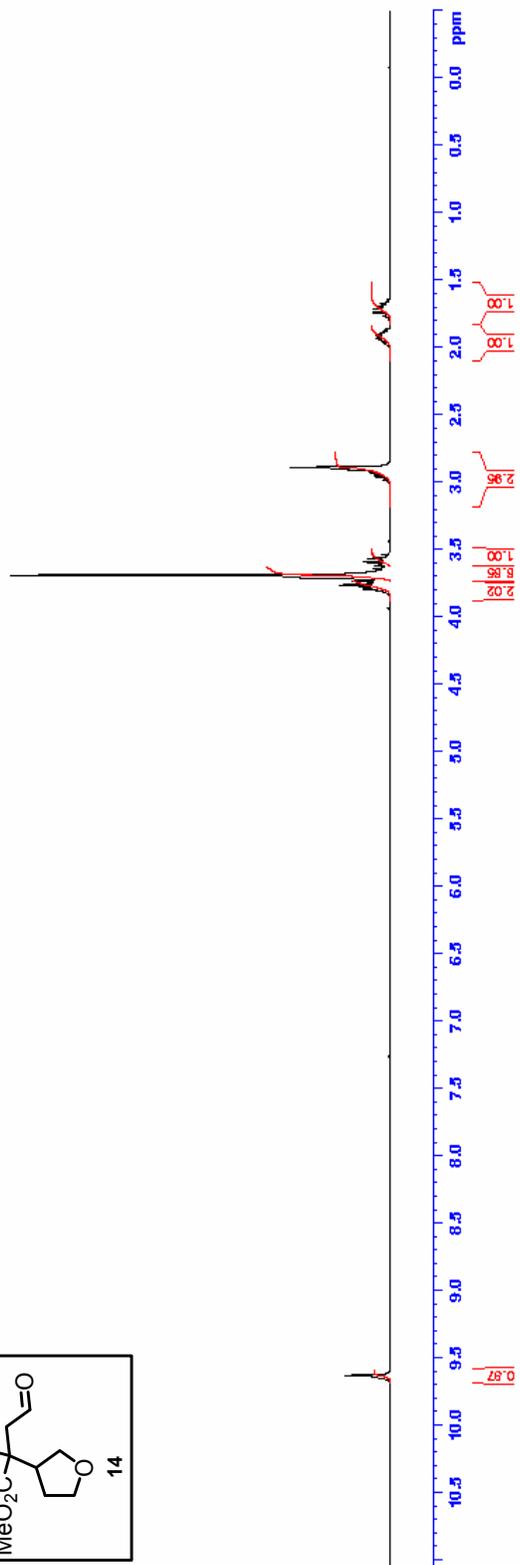
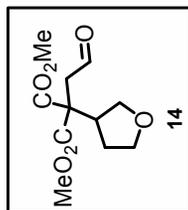
SP-6-196
500
standard proton



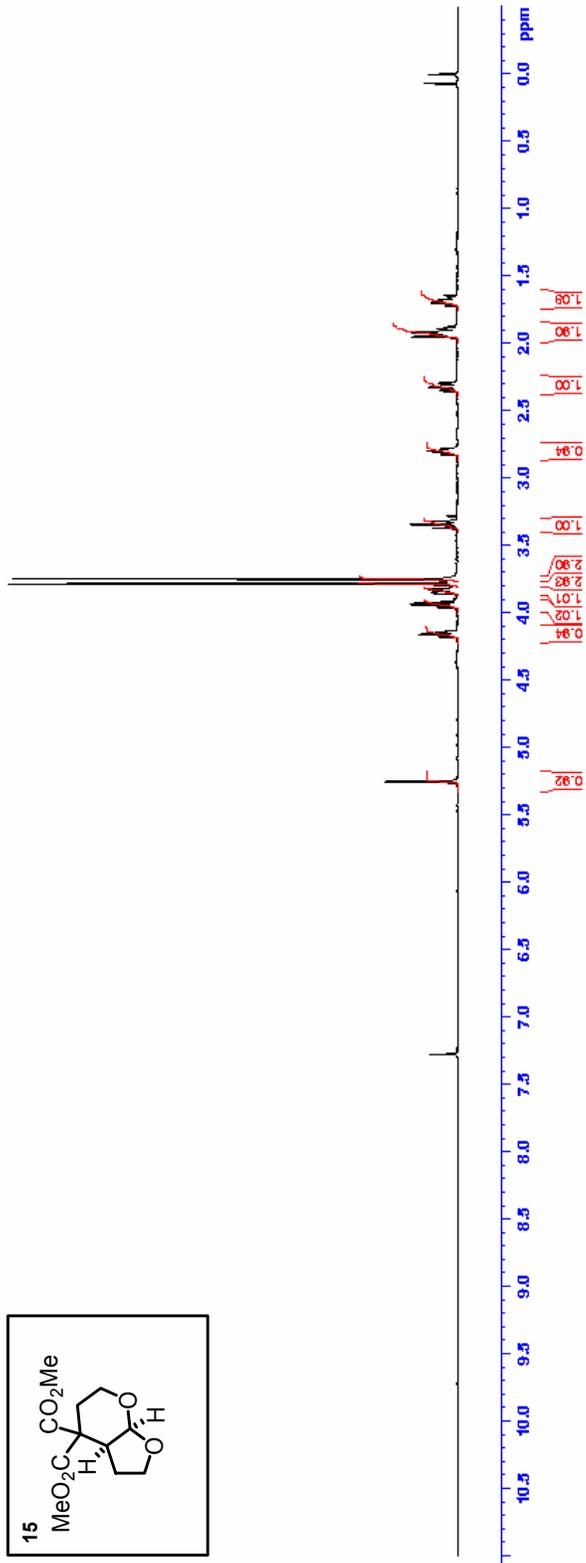
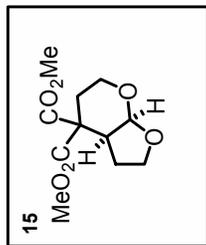
sp-7-121
 major diastereomer
 500 standard proton



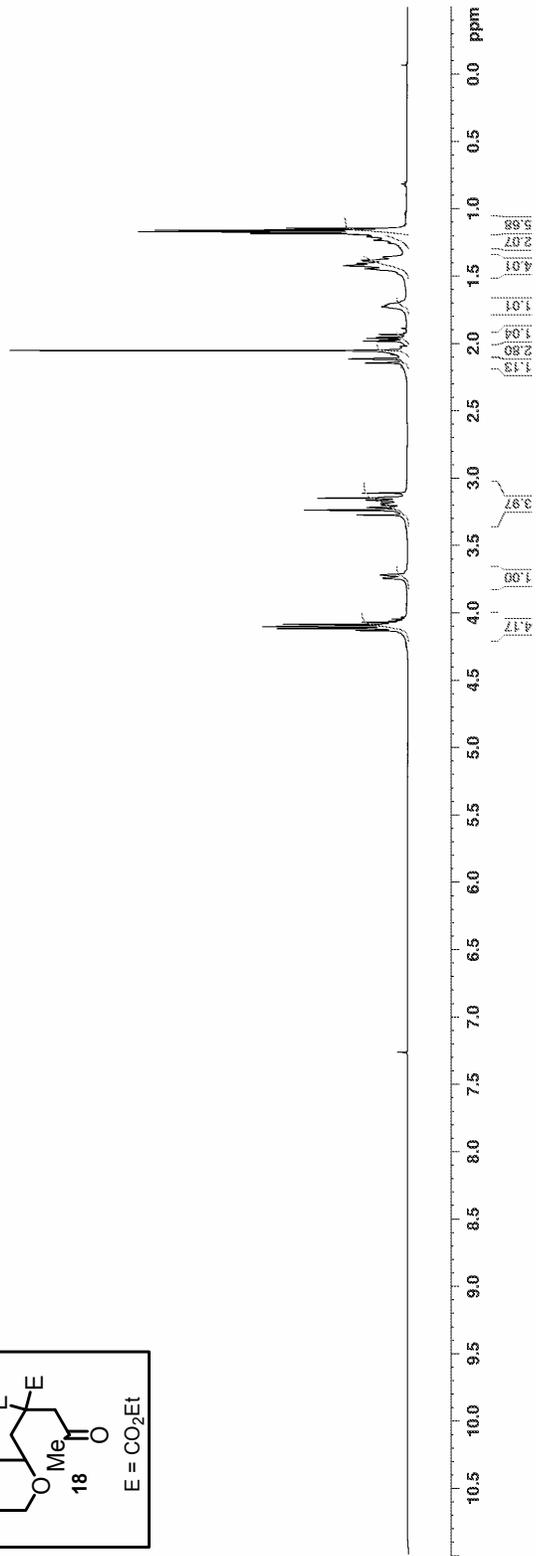
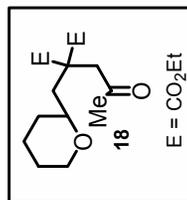
SP-6-180
300wb
proton



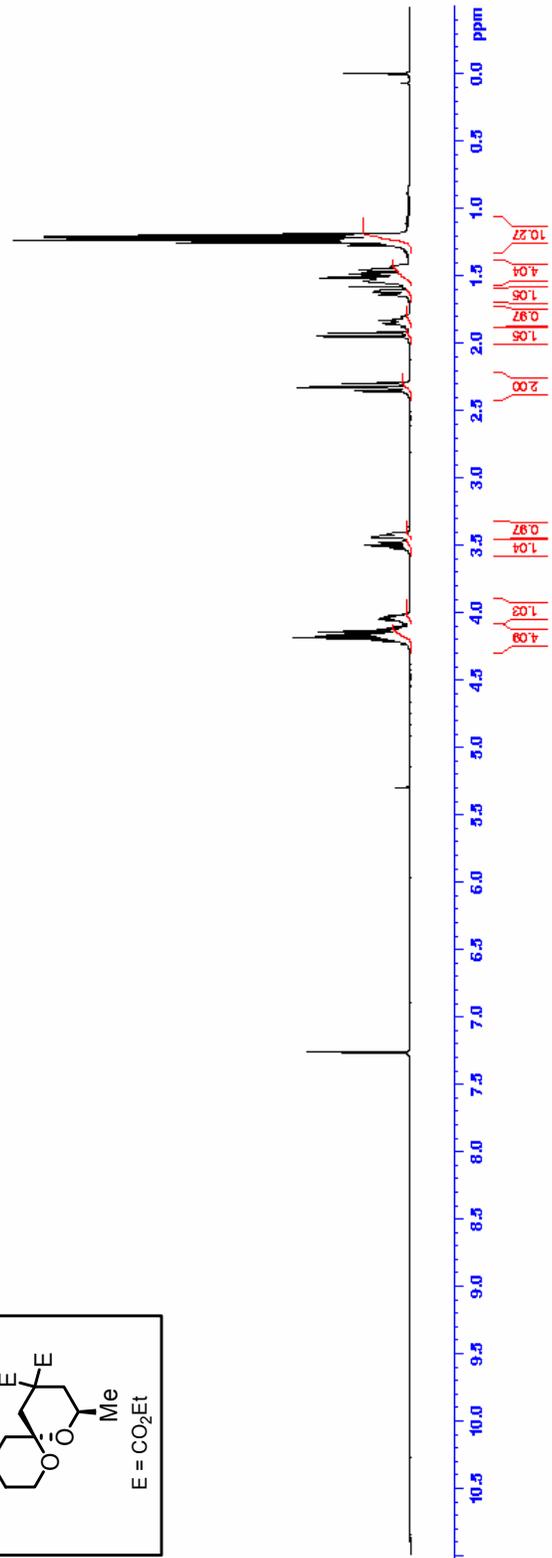
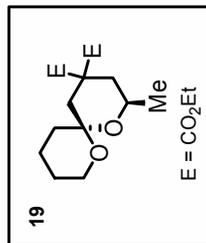
SP-6-179
500



sp-6-195
500
standard_proton



SP-6-198
500
standard proton



sp-7-125
purified aldehyde
500

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9.6780

7.1180
7.0876
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6.8133

3.7209

2.8230

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0.9551

