Diastereoselective Additions of Nucleophiles to a-Acetoxy Ethers Using the a-(Trimethylsilyl)benzyl Auxiliary

Scott D. Rychnovsky and Jennifer Cossrow

General Experimental Details. All moisture and air–sensitive reactions were carried out in flame-dried glassware using magnetic stirring under a positive pressure of argon. Concentration of organic solutions was accomplished by rotary evaporation. Thin layer chromatography was performed on Whatman silica gel PE SIL G/UV (0.25 mm) plates. Eluted plates were visualized using cerric ammonium molybdate, *p*-anisaldehyde or potassium permanganate TLC stains. Flash column chromatography was performed on EM Science 230–400 mesh silica gel. All commercial reagents were used as received with the following exceptions: Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was prepared according to Demuth, and stored over polyvinyl pyridine.[1] Tetrahydrofuran, methylene chloride, and toluene were obtained from an alumina filtration system according to the method described by Grubbs.[2]

Optical rotations were measured using a JASCO DIP-370 digital polarimeter; concentration *c* is reported in g/100 mL. Infrared spectra were recorded on a MIDAC Grams/Prospect FT-IR spectrometer. NMR spectra were recorded on 400 MHz or 500 MHz Bruker instruments. ^{1}H NMR spectra were recorded in ppm and were referenced to residual solvent peaks. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet), coupling constant(s) in Hertz (Hz), and integration. Multiplets (m) are reported over the range (ppm) at which they appear at the indicated field strength. ^{13}C NMR spectra were recorded in ppm relative to the solvent signals. Capillary GC analysis was performed on Hewlett Packard Model 6890 and 5890 instruments with a 30m PhMe–Silicon column and a 20m b-cyclodextrin, permethylated hydroxypropyl column, respectively. Mass spectral data was obtained on a Micromass 7070E–HF or a MicroMass LCT Electrospray spectrometer. Combustion analyses were performed by M-H-W Laboratories (Phoenix, AZ).

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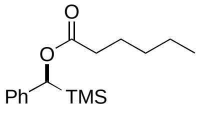
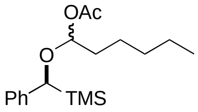
[1] Demuth, M.; Mikhail, G. *Synthesis* **1982**, 827.

[2] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.



5

Ester (*S*)-5. To a cooled (0 °C) solution of (*S*)-α-(trimethylsilyl)benzyl alcohol[3] (1.40 g, 7.74 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added pyridine (1.25 mL, 15.5 mmol, 2 equiv) and hexanoyl chloride (1.51 mL, 15.5 mmol, 2 equiv). The reaction mixture was warmed to 25 °C and stirred 18 h, whereupon the mixture was cooled to 0 °C and saturated aqueous NH_4Cl (15 mL) was added. After extraction of the aqueous layer with CH_2Cl_2 (3 x 10 mL), the combined organic layers were washed with 1N HCl (40 mL), saturated aqueous $NaHCO_3$ (40 mL), brine (40 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Flash column chromatography (5% Et_2O / hexanes) afforded the title compound as a clear oil (2.14 g, 99%). $[\alpha]^{23}_{D}$ –90.4 (*c* 0.99, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.12 (m, 5 H), 5.68 (s, 1 H), 2.38 (t, *J* = 7.4 Hz, 2 H), 1.68–1.64 (m, 2 H), 1.33–1.30 (m, 4 H), 0.89 (t, *J* = 6.9 Hz, 3 H), 0.01 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 140.2, 128.2, 126.0, 125.2, 71.3, 34.6, 31.3, 24.9, 22.3, 13.9, –3.9; IR (neat) 1738, 1248, 843 cm^{-1}; HRMS (CI / NH_3) *m/z* calcd for $C_{16}H_{26}O_2Si$ $(M)^+$ 278.1702, found 278.1697; Anal. Calcd for $C_{16}H_{26}O_2Si$: C, 69.01; H, 9.41. Found: C, 68.90; H, 9.25.



6

α-Acetoxy Ether (*S*)-6. To a cooled (–78 °C) solution of ester (*S*)-**5** (1.11 g, 4.0 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) was added DIBAL-H (8.0 mL, 1M / toluene, 8.0 mmol, 2.0 equiv) over 7 min. The solution was stirred at –78 °C for 45 min, whereupon pyridine (0.97 mL, 12.0 mmol, 3 equiv), DMAP (1.48 g, 12.0 mmol, 3 equiv), and acetic anhydride (2.26 mL, 24.0 mmol, 6 equiv) were added sequentially. The reaction mixture was stirred at –78 °C for 12.5 h, and then gradually warmed to –10 °C over a period of 5 h. The reaction was quenched at –10 °C by addition of saturated aqueous NH_4Cl (40 mL) and saturated aqueous Na^+/K^+ tartrate (45 mL) and the resultant opaque mixture was stirred vigorously at 25 °C for 3.5 h. After extraction of the aqueous layer with CH_2Cl_2 (4 x 40 mL), the combined organic layers were washed with cold (0 °C) 1M $NaHSO_4$ (2 x 50 mL), saturated aqueous $NaHCO_3$ (3 x 100 mL), brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography on deactivated

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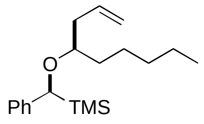
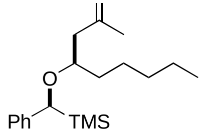
[3] Cossrow, J.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 147-150.

SiO_2 gel (5% Et_2O / hexanes) afforded a 1:1 mixture of diastereomers as a pale yellow oil (1.08 g, 84%). Data is reported for mixture of diastereomers: [a]$^{23}_{D}$ –115.2 (*c* 1.21, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) d 7.29–7.09 (m, 5 H), 5.97 (t, *J* = 6.1 Hz, 0.51 H), 5.70 (t, *J* = 5.3 Hz, 0.49 H), 4.33 (s, 0.49 H), 4.23 (s, 0.51 H), 2.05 (s, 1.47 H), 1.73–1.62 (m, 2 H), 1.38–1.23 (m, 6 H), 1.32 (s, 1.53 H), 0.91–0.85 (m, 3 H), –0.016 (s, 4.41 H), –0.023 (s, 4.59 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 171.0, 142.0, 140.7, 128.1, 127.6, 126.2, 126.0, 125.7, 125.4, 101.0, 98.5, 79.5, 75.5, 34.8, 34.7, 31.6, 23.9, 23.6, 22.5 (2), 21.3, 20.4,14.0, 13.9, 4.1; IR (neat) 1739, 1246, 843 cm^{-1}; HRMS (CI / NH_3) *m/z* calcd for $C_{16}H_{26}OSi$ $(M–C_2H_4O_2)^+$ 262.1753, found 262.1736; Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 66.89; H, 9.19.



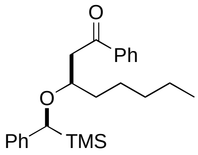
2

Ether 2. To a cooled (–78 °C) solution of a-acetoxy ether (*S*)-**6** (45 mg, 0.14 mmol, 1.0 equiv) in toluene (1.4 mL) were added allyltrimethylsilane (25 mL, 0.15 mmol, 1.1 equiv) and TMSOTf (28 mL, 0.15 mmol, 1.1 equiv). The reaction was stirred at –78 °C for 1 h whereupon saturated aqueous $NaHCO_3$ (3 mL) was added and the mixture was warmed to 25 °C. Following extraction with ethyl acetate (3 x 5 mL), the organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography (2.5% CH_2Cl_2 / hexanes) afforded the title ether as a colorless oil (39.7 mg, 93%, 44:1 mixture of diastereomers). Data is reported for the major diastereomer. [a]$^{23}_{D}$ –112.4 (*c* 0.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) d 7.28–7.12 (m, 5 H), 5.83–5.74 (m, 1 H), 4.98–4.95 (m, 2 H), 4.17 (s, 1 H), 3.33–3.29 (m, 1 H), 2.41–2.15 (m, 2 H), 1.48–1.44 (m, 2 H), 1.33–1.23 (m, 6 H), 0.89 (t, *J* = 6.9 Hz, 3 H), –0.05 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 142.4, 135.9, 127.8, 126.2, 125.4, 116.1, 77.5, 74.8, 39.2, 32.2, 31.8, 24.0, 22.7, 14.1, –3.9; IR (neat) 1642, 1247, 913, 841 cm^{-1}; HRMS (CI / NH_3) *m/z* calcd for $C_{19}H_{33}OSi$ $(M + H)^+$ 305.2301, found 305.2303; Anal. Calcd for $C_{19}H_{32}OSi$: C, 74.93; H, 10.59. Found: C, 74.76; H, 10.39.



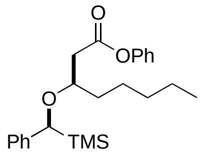
7

Ketone 7. To a cooled (–78 °C) solution of a-acetoxy ether (*S*)-**6** (67.3 mg, 0.21 mmol, 1.0 equiv) in toluene (2.1 mL) were added 2-(trimethylsilyloxy)propene (38 mL, 0.23 mmol, 1.1 equiv) and TMSOTf (42 mL, 0.23 mmol, 1.1 equiv). The reaction was stirred at –78 °C for 1 h whereupon saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was warmed to 25 °C. Following extraction with ethyl acetate (3 x 5 mL), the organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography (1–2–5% Et_2O / hexanes) afforded the title ketone as a yellow oil (46.4 mg, 69%, 67:1 mixture of diastereomers). Data is reported for the major diastereomer. $[a]^{23}_D$ –136.5 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) d 7.28–7.06 (m, 5 H), 4.15 (s, 1 H), 3.81–3.75 (m, 1 H), 2.60 (dd, *J* = 14.6, 7.5 Hz, 1 H), 2.37 (dd, *J* = 14.6, 4.9 Hz, 1 H), 2.02 (s, 3 H), 1.57–1.46 (m, 2 H), 1.33–1.23 (m, 6 H), 0.89 (t, *J* = 6.8 Hz, 3 H), –0.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) d 208.5, 141.5, 128.0, 126.2, 125.8, 75.1, 74.8, 49.0, 32.7, 32.0, 31.3, 24.1, 22.6, 14.0, –3.9; IR (neat) 1717, 1247, 841 cm^{-1}; HRMS (CI / NH_3) *m/z* calcd for $C_{18}H_{29}O_2Si$ $(M - CH_3)^+$ 305.1937, found 305.1937; Anal. Calcd for $C_{19}H_{32}O_2Si$: C, 71.19; H, 10.06. Found: C, 71.28; H, 9.96.



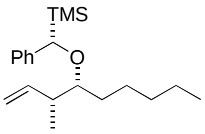
8

Ketone 8. To a cooled (–78 °C) solution of a-acetoxy ether (*S*)-**6** (68.9 mg, 0.21 mmol, 1.0 equiv) in toluene (2.1 mL) were added a-(trimethylsilyloxy)styrene (48 mL, 0.24 mmol, 1.1 equiv) and TMSOTf (41 mL, 0.24 mmol, 1.1 equiv). The reaction was stirred at –78 °C for 1 h whereupon saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was warmed to 25 °C. Following extraction with ethyl acetate (3 x 5 mL), the organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography (20–40% CH_2Cl_2 / hexanes) afforded the title ketone as a colorless oil (50 mg, 61%, >20:1 mixture of diastereomers). Data is reported for the major diastereomer. $[a]^{23}_D$ –98.8 (*c* 0.69, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) d 7.88–6.97(m, 10 H), 4.17 (s, 1 H), 3.95–3.91 (m, 1 H), 3.26 (dd, *J* = 14.5, 7.1 Hz, 1 H), 2.80 (dd, *J* = 14.5, 5.8 Hz, 1 H), 1.59–1.55 (m, 2 H), 1.41–1.26 (m, 6 H), 0.89 (t, *J* = 6.9 Hz, 3 H), –0.12 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 199.7, 141.4, 137.7, 132.7, 128.5, 128.3, 127.9, 126.2, 125.7, 75.4, 75.2, 44.1, 32.7, 32.1, 24.0, 22.6, 14.0, –4.0; IR (neat) 1683, 1247, 841 cm^{-1}; HRMS (CI / NH_3) *m/z* calcd for $C_{23}H_{31}O_2Si$ $(M – CH_3)^+$ 367.2093, found 367.2092; Anal. Calcd for $C_{24}H_{34}O_2Si$: C, 75.34; H, 8.96. Found: C, 75.25; H, 8.73.



9

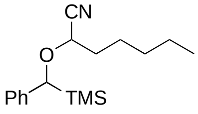
Ester 9. To a cooled (–78 °C) solution of α-acetoxy ether (*S*)-**6** (55 mg, 0.17 mmol, 1.0 equiv) and 1-phenoxy-1-(trimethylsilyloxy)ethene (53 mg, 0.26 mmol, 1.5 equiv) in toluene (1.7 mL) was added TMSOTf (77 μL, 0.43 mmol, 2.5 equiv). The reaction was stirred at –78 °C for 1 h whereupon saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was warmed to 25 °C. Following extraction with ethyl acetate (3 x 5 mL), the organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography (20–40% CH_2Cl_2 / hexanes) afforded the title ester as a pale yellow oil (49.7 mg, 73%, 78:1 mixture of diastereomers). Data is reported for the major diastereomer. $[\alpha]^{23}_{D}$ –85.4 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.20 (m, 5 H), 7.16–7.01 (m, 5 H), 4.24 (s, 1 H), 3.93–3.88 (m, 1 H), 2.73 (dd, *J* = 14.6, 7.2 Hz, 1 H), 2.59 (dd, *J* = 14.6, 5.6 Hz, 1 H), 1.64–1.60 (m, 2 H), 1.41–1.26 (m, 6 H), 0.91 (t, *J* = 6.9 Hz, 3 H), –0.02 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 150.7, 141.5, 129.3, 128.0, 126.1, 125.7, 125.6, 121.6, 75.1, 74.7, 40.4, 32.4, 32.1, 24.0, 22.6, 14.0, –3.9; IR (neat) 1761, 1247, 841 cm^{-1}; HRMS (CI / NH_3) *m/z* calcd for $C_{23}H_{31}O_3Si$ $(M – CH_3)^+$ 383.2042, found 383.2039; Anal. Calcd for $C_{24}H_{34}O_3Si$: C, 72.32; H, 8.60. Found: C, 72.44; H, 8.46.



10

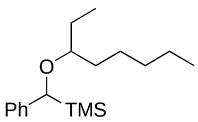
Ether 10. To a cooled (–78 °C) solution of α-acetoxy ether (*S*)-**6** (59.5 mg, 0.18 mmol, 1.0 equiv) in CH_2Cl_2 (1.8 mL) were added *E*-crotyltrimethylsilane (35 μL, 0.20 mmol, 1.1 equiv) and TMSOTf (37 μL, 0.20 mmol, 1.1 equiv). The reaction was stirred at –78 °C for 1 h whereupon saturated aqueous $NaHCO_3$ (3 mL) was added and the mixture was warmed to 25 °C. Following extraction with CH_2Cl_2 (3 x 5 mL), the organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*.

Purification by flash column chromatography (0–5% CH_2Cl_2 / hexanes) afforded the title ether as a colorless oil (45.9 mg, 78%, 22:2:1 mixture of diastereomers: See text). Data is reported for the major diastereomer. $[\alpha]^{23}_D$ –118.2 (*c* 0.815, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.28–7.14 (m, 5 H), 5.75 (ddd, *J* = 17.5, 10.4, 7.7 Hz, 1 H), 4.95–4.91 (m, 2 H), 4.18 (s, 1 H), 3.16–3.13 (m, 1 H), 2.36–2.32 (m, 1 H), 1.49–1.40 (m, 2 H), 1.32–1.23 (m, 6 H), 1.02 (d, *J* = 6.7 Hz, 3 H), 0.88 (t, *J* = 7.0 Hz, 3 H), –0.04 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 141.7, 127.8, 126.6, 125.6, 113.4, 79.5, 73.6, 40.9, 32.3, 28.8, 23.7, 22.7, 15.8, 14.1, –3.9; IR (neat) 1247, 913, 840 cm^{-1}; HRMS (CI / NH_3) *m/z* calcd for $C_{20}H_{34}OSi$ $(M)^+$ 318.2379, found 318.2382; Anal. Calcd for $C_{20}H_{34}OSi$: C, 75.40; H, 10.76. Found: C, 75.55; H, 10.96.



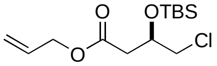
12

Ether 12. To a cooled (–78 °C) solution of α-acetoxy ether **6** (34.6 mg, 0.11 mmol, 1.0 equiv) in toluene (1.1 mL) were added trimethylsilyl cyanide (116 μL, 0.88 mmol, 8.0 equiv) and TMSOTf (49 μL, 0.27 mmol, 2.5 equiv). The reaction was stirred at –78 °C for 1 h whereupon saturated aqueous $NaHCO_3$ (3 mL) was added and the mixture was warmed to 25 °C. Following extraction with ethyl acetate (3 x 5 mL), the organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography (0–5–10% Et_2O / hexanes) afforded the title ether as a colorless oil (30 mg, 97%, 5:1 mixture of diastereomers). Data is reported for the major diastereomer. ^1H NMR (500 MHz, $CDCl_3$) δ 7.34–7.31(m, 2 H), 7.23–7.17 (m, 3 H), 4.20 (s, 1 H), 4.08 (t, *J* = 6.3 Hz, 1 H), 1.80–1.77 (m, 2 H), 1.53–1.48 (m, 2 H), 1.33–1.31 (m, 4 H), 0.90 (t, *J* = 6.8 Hz, 3 H), –2.89 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 128.3, 126.6, 126.1, 119.1, 79.7, 69.2, 33.1, 31.2, 24.2, 22.4, 13.9, –4.0; IR (neat) 1249, 843 cm^{-1}; HRMS (CI / NH_3) *m/z* calcd for $C_{15}H_{23}OSi$ $(M – C_2H_4N)^+$ 247.1518, found 247.1511; Anal. Calcd for $C_{17}H_{27}NOSi$: C, 70.53; H, 9.40. Found: C, 70.40; H, 9.27.



13

Ether 13. To a cooled (–78 °C) solution of α-acetoxy ether **6** (37.2 mg, 0.12 mmol, 1.0 equiv) in toluene (1.2 mL) were added diethylzinc (231 μL, 1M / hexanes, 2.31 mmol, 2.0 equiv) and TMSOTf (23 mL, 0.13 mmol, 1.1 equiv). The reaction was stirred at –78 °C for 1 h whereupon saturated aqueous $NaHCO_3$ (3 mL) was added and the mixture was warmed to 25 °C. Following extraction with ethyl acetate (3 x 5 mL), the organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography (0–2% Et_2O / hexanes) afforded the title ether as a colorless oil (25.4 mg, 75%, 4:1 mixture of diastereomers). Data is reported for the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) d 7.28–7.14 (m, 5 H), 4.17 (s, 1 H), 3.20–3.16 (m, 1 H), 1.47–1.40 (m, 4 H), 1.33–1.22 (m, 6 H), 0.89 (t, *J* = 6.9 Hz, 3 H), 0.85 (t, *J* = 7.4 Hz, 3 H), –0.04 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 142.6, 127.8, 126.3, 125.4, 78.8, 74.4, 32.3, 31.5, 27.1, 24.1, 22.7,14.1, 10.0, –3.9; IR (neat) 1247, 868, 841 cm^{-1}; HRMS (CI / NH_3) *m/z* calcd for $C_{17}H_{29}OSi$ $(M - CH_3)^+$ 277.1988, found 277.1993; Anal. Calcd for $C_{18}H_{32}OSi$: C, 73.90; H, 74.10. Found: C, 74.10; H, 10.88.



19

Allyl ester 19. To a cooled (–78 °C) solution of (*R*)-allyl 4-chloro-3-hydroxybutyrate[4] (2.30 g, 12.9 mmol, 1.0 equiv) in CH_2Cl_2 (65 mL) was added 2,6-lutidine (3.3 mL, 28.3 mmol, 2.2 equiv) followed by TBSOTf (4.1 mL, 18.0 mL, 1.4 equiv). The reaction was stirred at –78 °C for 1 h then at 0 °C for 20 min. Saturated aqueous NH_4Cl (70 mL) was added and the mixture was warmed to 25 °C. Following extraction with CH_2Cl_2 (5 x 15 mL), the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography (5–10% EtOAc / hexanes) afforded the title ester as a pale yellow oil (3.20 g, 85%). $[a]^{23}_{D}$ 18.17 (*c* 1.04, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) d 5.95–5.87 (m, 1 H), 5.37 (dd, *J* = 17.2, 1.4 Hz, 1 H), 5.24 (dd, *J* = 10.4, 1.1 Hz, 1 H), 4.62–4.55 (m, 2 H), 4.34–4.29 (m, 1 H), 3.53 (dd, *J* = 11.0, 4.8 Hz, 1 H), 3.50 (dd, *J* = 11.1, 6.2 Hz, 1 H), 2.73 (dd, *J* = 15.4, 4.8 Hz, 1 H), 2.56 (dd, *J* = 15.3, 7.2 Hz, 1 H), 0.87 (s, 9 H), 0.11 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 170.6, 131.9, 118.5, 69.4, 65.3, 48.0, 40.3, 25.7, 17.9, –4.7, –5.0; IR (neat) 1741, 1650, 1257, 1101, 990. 838, 779 cm^{-1}; HRMS (CI / NH_3) *m/z* calcd for $C_{13}H_{25}ClO_3Si$ $(M + H)^+$ 293.1340, found 293.1347; Anal. Calcd for $C_{13}H_{25}ClO_3Si$: C, 53.31; H, 8.60. Found: C, 53.12; H, 8.84.

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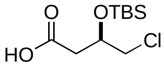
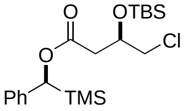
[4] Rychnovsky, S. D.; Fryszman, O.; Khire, U. R. *Tetrahedron Lett.* **1999**, *40*, 41-44.



20

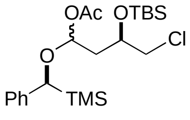
Carboxylic acid 20. To a solution of $Pd(PPh_3)_4$ (248 mg, 0.21 mL, 0.02 equiv) in CH_2Cl_2 (30 mL) was added phenylsilane (3.2 mL, 25.9 mmol, 2.4 equiv). The reddish-brown solution was stirred at 25 °C for 5 min. A solution of allyl ester **19** (3.11 g, 10.62 mmol, 1 equiv) in CH_2Cl_2 (130 mL) was added via cannula over 20 min. The reaction mixture was stirred at 25 °C for 70 min whereupon the solvent was removed *in vacuo*. The crude dark brown oil was purified by flash column chromatography (5–10% EtOAc / hexanes) to afford the title acid as a brown oil (2.49 g, 93%). [a]$^{23}_{\mathrm{D}}$ 25.14 (*c* 1.09, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) d 4.30 (dddd, J = 7.4, 7.4, 4.7, 4.7 Hz, 1 H), 3.52 (dd, *J* = 11.1, 4.8 Hz, 1 H), 3.50 (dd, *J* = 11.1, 6.6 Hz, 1 H), 2.77 (dd, *J* = 15.6, 4.5 Hz, 1 H), 2.57 (dd, *J* = 15.6, 7.4 Hz, 1 H), 0.88 (s, 9 H), 0.12 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 176.7, 69.3, 47.7, 40.0, 25.6, 17.9, –4.7, –5.0; IR (neat) 3044 (br), 1714, 1257, 1104, 958, 838, 778 cm^{-1}; HRMS (CI / NH_3) *m/z* calcd for $C_{10}H_{22}ClO_3Si$ ($(M + H)^+$ 253.1027, found 253.1034; Anal. Calcd for $C_{10}H_{21}ClO_3Si$: C, 47.51; H, 8.37. Found: C, 47.73; H, 8.18.



21

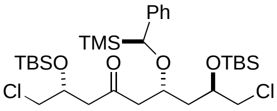
Ester 21. To a cooled (0 °C) solution of acid **20** (1.00 g, 3.95 mmol, 1.1 equiv) in CH_2Cl_2 (40 mL) was added (*S*)-a-(trimethylsilyl)benzyl alcohol (0.647 g, 3.59 mmol, 1.0 equiv), DMAP·Ts (0.105 g, 0395 mmol, 0.1 equiv), and DCC (0.823 g, 3.95 mmol, 1.1 equiv). The reaction mixture was warmed to 25 °C and stirred 21 h, whereupon the resultant white suspension was filtered through a cotton plug. The filtrate was washed with saturated aqueous NH_4Cl (2 x 40 mL), saturated aqueous $NaHCO_3$ (2 x 40 mL), and brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography (2–4% Et_2O / hexanes) afforded the title compound as a colorless oil (1.40 g, 94%). [a]$^{23}_{\mathrm{D}}$ –57.0 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) d 7.29–7.12 (m, 5 H), 5.70 (s, 1 H), 4.30 (m, 1 H), 3.55 (d, *J* = 5.3 Hz, 2 H), 2.77 (dd, *J* = 15.8, 5.8 Hz, 1 H), 2.64 (dd, *J* = 15.8, 6.3 Hz, 1 H), 0.80 (s, 9 H), 0.07 (s, 3 H), 0.02 (s, 9 H), –0.07 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 170.7, 139.8, 128.2, 126.1, 125.3, 72.0, 69.3, 48.2, 40.2, 25.6, 17.9, –3.9, –4.8, –5.1; IR (neat) 1738, 1252, 1104, 976, 839, 778 cm^{-1}; HRMS (CI / NH_3) *m/z* calcd for $C_{20}H_{35}ClO_3Si_2$ $(M)^+$ 414.1813, found 414.1817; Anal.

Calcd for $C_{20}H_{35}ClO_3Si_2$: C, 57.87; H, 8.50. Found: C, 57.88; H, 8.47.



17

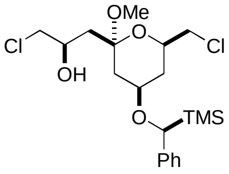
(a)-Acetoxy ether 17. To a cooled (–78 °C) solution of ester **21** (1.05 g, 2.53 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) was added DIBAL-H (5.1 mL, 1M / hexanes, 5.06 mmol, 2.0 equiv) over 4 min. The solution was stirred at –78 °C for 45 min, whereupon pyridine (0.614 mL, 7.59 mmol, 3.0 equiv), DMAP (0.936 g, 7.59 mmol, 3.0 equiv), and acetic anhydride (1.43 mL, 15.18 mmol, 6.0 equiv) were added sequentially. The reaction mixture was stirred at –78 °C for 10 h, and then gradually warmed to –10 °C over a period of 7 h. The reaction was quenched at –10 °C by addition of saturated aqueous NH_4Cl (50 mL) and saturated aqueous Na^+/K^+ tartrate (60 mL) and the resultant opaque mixture was stirred vigorously at 25 °C for 3.5 h. After extraction of the aqueous layer with CH_2Cl_2 (4 x 25 mL), the combined organic layers were washed with cold (0 °C) 1M $NaHSO_4$ (2 x 50 mL), saturated aqueous $NaHCO_3$ (3 x 50 mL), brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography on deactivated SiO_2 gel (0–2% Et_2O / hexanes) afforded a 2.4:1 mixture of diastereomers as a pale yellow oil (0.937 g, 81%). Data reported for mixture of diastereomers: $[a]^{23}_{D}$ –74.7 (*c* 1.08, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) d 7.30–7.08 (m, 5 H), 6.14 (dd, *J* = 5.8, 4.6 Hz, 0.7 H), 5.76 (t, *J* = 5.0 Hz, 0.3 H), 4.39 (s, 0.3 H), 4.26 (s, 0.7 H), 4.05–3.96 (m, 1 H), 3.53 (dd, *J* = 11.2, 4.6 Hz, 0.7 H), 3.47 (dd, *J* = 11.1, 4.6 Hz, 0.3 H), 3.45 (dd, *J* = 11.1, 5.4 Hz, 0.7 H), 3.39 (dd, *J* = 10.9, 5.6 Hz, 0.3 H), 2.14–2.02 (m, 1 H), 2.07 (s, 0.9 H), 1.95–1.86 (m, 1 H), 1.30 (s, 2.1 H), 0.90 (s, 6.3 H), 0.81 (s, 2.7 H), 0.14 (s, 2.1 H), 0.12 (s, 2.1 H), 0.07 (s, 0.9 H), –0.01 (s, 0.9 H), –0.017 (s, 2.7 H), –0.023 (s, 6.3 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 170.6, 170.4, 141.7, 140.1, 128.2, 127.7, 126.3 (2), 125.8, 125.6, 97.8, 95.5, 79.4, 76.2, 69.1, 69.0, 49.1, 49.0, 40.8, 40.6, 25.7 (2), 21.2, 20.3, 18.1, 18.0, –4.0, –4.1, –4.4, –4.5, –4.6, –5.0; IR (neat) 1743, 1248, 1109, 939, 840, 777 cm^{-1}; HRMS (electrospray) *m/z* calcd for $C_{22}H_{39}ClO_4Si_2Na$ $(M + Na)^+$ 481.1973, found 481.1971; Anal. Calcd for $C_{22}H_{39}ClO_4Si_2$: C, 57.55; H, 8.56. Found: C, 57.38; H, 8.70.



18

Ketone 18. To a cooled (–78 °C) solution of a–acetoxy ether **17** (122.0 mg, 0.27 mmol, 1.0

equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (109.0 mg, 0.53 mmol, 2.0 equiv) in CH_2Cl_2 (1.2 mL) were added a solution of silyl enol ether **15**[5] (171.5 mg, 0.53 mmol, 2.0 equiv) in CH_2Cl_2 (1.5 mL) and TMSOTf (115 mL, 0.66 mmol, 2.5 equiv). The reaction was stirred at –78 °C for 2 h whereupon saturated aqueous $NaHCO_3$ (4 mL) was added and the mixture was warmed to 25 °C. Following extraction with CH_2Cl_2 (3 x 5 mL), the organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography (0–1–1.5–2% Et_2O / hexanes) afforded the title ketone as a viscous yellow oil (131.0 mg, 76%). $[a]^{23}_{D}$ –32.9 (*c* 1.08, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) d 7.35–7.13 (m, 5 H), 4.36–4.31 (m, 1 H), 4.21 (s, 1 H), 3.99–3.91 (m, 2 H), 3.55–3.44 (m, 4 H), 2.68 (dd, *J* = 16.9, 5.6 Hz, 1 H), 2.64 (dd, *J* = 15.4, 6.2 Hz, 1 H), 2.52 (dd, *J* = 16.8, 6.4 Hz, 1 H), 2.51 (dd, *J* = 15.5, 5.5 Hz, 1 H), 2.13–2.07 (m, 1 H), 1.63 (ddd, *J* = 14.4, 6.2, 6.2 Hz, 1 H), 0.93 (s, 9 H), 0.92 (s, 9 H), 0.16 (s, 3 H), 0.13 (s, 3 H). 0.10 (s, 3 H), 0.09 (s, 3 H), 0.02 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 206.7, 141.4, 128.1, 126.3, 126.0, 76.3, 73.3, 70.7, 68.2, 50.5, 49.2, 48.7, 48.6, 40.2, 25.8, 25.7, 18.0 (2), –3.8, –4.4, –4.6, –4.7, –4.8; IR (neat) 1716, 1251, 1092, 939, 840, 778 cm^{-1}; HRMS (electrospray) *m/z* calcd for $C_{31}H_{59}Cl_2O_4Si_3$ $(M + H)^+$ 649.3098, found 649.3107. Anal. Calcd for $C_{31}H_{58}Cl_2O_4Si$: C, 57.29; H, 8.99. Found: C, 57.18; H, 9.11.



22

Acetal 22. To a cooled (0 °C) solution of ketone **18** (87.2 mg, 0.13 mmol, 1.0 equiv) in methanol (1.3 mL) was added HCl (10.7 mL, 0.25 M / MeOH, 2.68 mmol, 20 equiv) over 10 minutes. After stirring at 0 °C for 2.5 h, the reaction mixture was warmed to 25 °C and stirred for 1.5 h. The reaction was quenched at 0 °C by addition of saturated aqueous $NaHCO_3$ (12 mL). After extraction of the aqueous layer with Et_2O (5 mL) and EtOAc (3 x 5 mL), the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Flash column chromatography (5–7–10% EtOAc / hexanes) afforded the title acetal as a viscous yellow oil (35 mg, 60%). ^1H NMR (500 MHz, $CDCl_3$) d 7.30–7.11 (m, 5 H), 4.26 (s, 1 H), 4.10–4.06 (m, 1 H), 3.82–3.72 (m, 2 H), 3.64 (d, *J* = 1.4 Hz, 1 H), 3.62 (dd, *J* = 11.6, 3.9 Hz, 1

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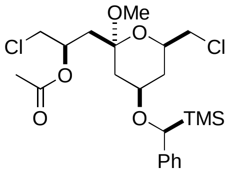
[5] Sinz, C. J.; Rychnovsky, S. D. *Tetrahedron* **2002**, *58*, 6561-6576.

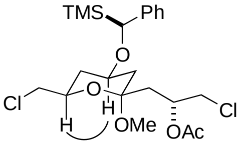
H), 3.56–3.48 (m, 3 H), 3.11 (s, 3 H), 2.11–2.05 (m, 2 H), 1.98 (ddd, *J* = 13.1, 4.7, 1.4 Hz, 1 H), 1.72 (dd, *J* = 14.4, 1.6 Hz, 1 H), 1.64 (dd, *J* = 12.9, 11.1 Hz, 1 H), 1.29 (q, *J* = 11.9 Hz, 1 H), –0.05 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 141.8, 128.1, 125.7, 125.5, 101.9, 74.5, 70.1, 69.0, 68.0, 48.9, 47.6, 47.3, 39.8, 39.2, 33.4, –4.1; IR (neat) 3502 (br), 1247, 1050, 869, 842 cm^{-1}; HRMS (electrospray) *m/z* calcd for $C_{20}H_{32}Cl_2O_4SiNa$ (M + Na)$^+$ 457.1345, found 457.1345.



23

Acetal 23. To a 25 °C solution of alcohol **22** (31.0 mg, 0.071 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) were added pyridine (58 mL, 0.71 mmol, 10 equiv), DMAP (9 mg, 0.071 mmol, 1.0 equiv), and acetic anhydride (34 mL, 0.36 mmol, 5.0 equiv). After stirring for 200 min at 25 °C, the reaction mixture was cooled to 0 °C and quenched by addition of saturated aqueous NH_4Cl (3 mL). Following extraction of the aqueous layer with CH_2Cl_2 (4 x 5 mL), the combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (5–10% EtOAc / hexanes) afforded the title acetal as a white powder (17 mg, 50%): mp = 83-85 °C; ^{1}H NMR (500 MHz, C_6D_6) d 7.18–6.98 (m, 5 H), 5.24–5.20 (m, 1 H), 4.12 (s, 1 H), 3.77 (dddd, *J* = 10.9, 10.9, 4.7, 4.7 Hz, 1 H), 3.29–3.26 (m, 2 H), 3.20–3.15 (m, 2 H), 3.04–3.03 (m, 1 H), 2.80 (s, 3 H), 2.07 (dd, *J* = 12.8, 4.7 Hz, 1 H), 1.93–1.77 (m, 2 H), 1.80–1.76 (m, 1 H), 1.65 (s, 3 H), 1.52 (dd, *J* = 12.7, 11.2 Hz, 1 H), 1.06 (q, *J* = 11.7, 1 H), 0.02 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) d 169.8, 142.8, 128.9, 126.5, 126.0, 100.9, 75.3, 72.0, 69.9, 69.4, 47.8, 47.7, 46.8, 41.4, 38.3, 34.8, 20.9, –3.6; IR (thin film) 1744, 1246, 1048, 869, 842 cm^{-1}; HRMS (electrospray) *m/z* calcd for $C_{22}H_{34}Cl_2O_5SiNa$ (M + Na)$^+$ 499.1450, found 499.1454.

Proof of stereochemistry: Coupling constant analysis and NOESY cross-peaks between the indicated axial hydrogen atoms confirmed the predicted configuration. These experiments corroborate that addition of enol silane **15** to a-acetoxy ether **17** occurred with the facial selectivity predicted by Linderman's model.



23