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AUG 08 1997

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Supporting Information

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Dialkylzinc Additions to 4-Acetoxy-1,3-dioxanes: A Highly Stereoselective Route to Protected *anti*-1,3-Diols.

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Supporting Information

General Experimental Information.

All moisture and air-sensitive reactions were carried out in flame or oven-dried glassware using magnetic stirring under a positive pressure of nitrogen or argon gases. Reaction solvents were distilled or obtained from an alumina filtration system when necessary.¹ Thin layer chromatography was performed on Whatman silica gel PE SIL G/UV or Macherey-Nagel silica gel SIL G/UV (0.25 mm) plates. Concentration in vacuo was done using a Büchi rotary evaporator. Flash chromatography was performed on EM Science 230-400 mesh silica gel. Melting points were determined using an Electrothermal apparatus and are reported uncorrected. Infrared spectra were recorded on a MIDAC Grams/Prospect FT-IR. NMR spectra were measured on GE QE300, GN500, and Ω500, and Bruker DRX400 and DRX500 MHz FT-NMR instruments. Proton NMR spectra were referenced to residual solvent: CDCl₃ (7.26 ppm). Carbon NMR spectra were recorded in ppm relative to the solvent signal: CDCl₃ (77.00 ppm). Mass spectral data was obtained on Finnigan MAT95 and 7070 instruments using EI or CI methods. Elemental analyses were performed by MHW Laboratories of Phoenix, AZ.

Initial experiments using diethylzinc were performed using a 1 *M* hexane solution purchased from Aldrich Chemical Company. Neat Et₂Zn, purchased from Strem Chemicals Inc., was used in the preparation of the functionalized dialkylzinc reagents. Dimethylzinc was purchased from Fluka as a 2 *M* toluene solution. Trimethylsilyl trifluoromethanesulfonate

¹ Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J., *Organometallics*, 1996, 15, 1518-1520.

(TMSOTf) was prepared from trifluoromethanesulfonic acid and allyltrimethylsilane² or tetramethylsilane³ and stored over poly(4-vinylpyridine) under Ar.

A General Procedure for the coupling of dialkylzinc reagents with (2S*, 4R*, 6S*)-4-acetoxy-2-*t*-Butyl-6-hexyl-1,3-dioxane (2): Preparation of (2R*, 4S*, 6S*)-2-*t*-Butyl-4-ethyl-6-hexyl-1,3-dioxane (4a). A flame-dried 10 mL round-bottomed flask was charged with 0.216 g (0.753 mmol) 4-acetoxy-1,3-dioxane **2** and 3 mL CH₂Cl₂ and cooled to -78 °C in a dry ice/acetone bath. Et₂Zn (1.51 mL, 1.51 mmol, 1 *M* in hexane) was added via syringe, followed by 205 µL (1.13 mmol) TMSOTf. The reaction was stirred at -78 °C for 2 hr and then quenched with Et₃N and sat'd NaHCO₃ and warmed to rt. The organic layer was washed with ice-cold 1 *N* NaHSO₄, sat'd NaHCO₃, dried over MgSO₄, and concentrated. The residual oil was purified by flash chromatography (SiO₂, 20% CH₂Cl₂/hexanes) to give 0.176 g (91%) of a clear oil as a 51:1 mixture of diastereomers: R_f 0.29 (30% CH₂Cl₂/hexanes); FT-IR (neat) 2956, 2933, 2861, 1462, 1360, 1218, 1136, 1078, 1000 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.29 (s, 1 H), 3.91 (ddd, *J* = 10.7, 5.8, 5.8 Hz, 1 H), 3.67 (m, 1 H), 1.99 (m, 1 H), 1.74 (ddd, *J* = 12.5, 12.5, 6.1 Hz, 1 H), 1.45 (m, 4 H), 1.29 (m, 8 H), 0.93 (t, *J* = 7.4 Hz, 3 H), 0.89 (s, 9 H), 0.85 (t, *J* = 7.5 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃, DEPT) *C* 34.0; CH 99.4, 73.2, 71.6; CH₂ 36.0, 31.6, 28.9, 24.8, 24.5, 23.4, 22.3; CH₃ 24.4 (3), 13.8, 10.1; HRMS (CI/isobutane) calcd for [C₁₆H₃₂O₂+H]⁺ 257.2480, found 257.2470. Anal. calcd. for C₁₆H₃₂O₂: C, 74.94; H, 12.58. Found: C, 75.27; H, 12.39.

(2R*,4S*,6S*)-2-*t*-Butyl-6-hexyl-4-methyl-1,3-dioxane (4c). Reaction according to the above protocol using 0.156 g (0.544 mmol) **2** and 0.55 mL (1.09 mmol, 2 *M* in toluene) dimethylzinc in the presence of 148 µL TMSOTf yielded 0.119 mg (90%) of a clear oil as a single diastereomer after purification by flash chromatography (30% CH₂Cl₂/hexanes): R_f 0.68

² (a) Morita, T.; Okamoto, Y.; Sakurai, H. *Synthesis* **1981**, 745-746. (b) Olah, G. A.; Husain, A.; Balaram Gupta, B. G.; Salem, G. F.; Narang, S. C. *J. Org. Chem.* **1981**, *46*, 5212-5214.

³ Demuth, M.; Mikhail, G. *Synthesis* **1982**, 827-828.

(10% EtOAc/hexanes); FT-IR (neat) 2954, 2932, 2860, 1460, 1378, 1147, 1076, 1000 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 4.36 (s, 1 H), 5.27 (dq, $J = 6.7, 6.7$ Hz, 1 H), 3.71 (m, 1 H), 1.75 (ddd, $J = 12.1, 6.1$ Hz, 1 H), 1.53-1.24 (m, 11 H), 1.31 (d, $J = 6.9$ Hz, 3 H), 0.88 (s, 12 H); ^{13}C NMR (75 MHz, CDCl_3 , DEPT) C 34.7; CH 99.6, 71.3, 67.7; CH_2 36.2, 35.4, 31.9, 29.3, 25.1, 22.6; CH_3 24.7 (3), 17.3, 14.1; HRMS (CI/isobutane) calcd for $[\text{C}_{15}\text{H}_{30}\text{O}_2 + \text{H}]^+$ 243.2324, found 243.2323. Anal. calcd. for $\text{C}_{15}\text{H}_{30}\text{O}_2$: C, 74.32; H, 12.47. Found: C, 74.49; H, 12.43.

(2*S,4*R**,6*S**)-2-*t*-Butyl-4-isopropyl-6-hexyl-1,3-dioxane (4d).** 4-Acetoxy-1,3-dioxane **2** (99.2 mg, 0.346 mmol) was treated with 0.10 mL (0.70 mmol) $i\text{-Pr}_2\text{Zn}^4$ and 76 μL (0.419 mmol) TMSOTf according to the general protocol above to yield 0.103 g (90%) of a clear oil as a single diastereomer after purification by flash chromatography (SiO_2 , 20% $\text{CH}_2\text{Cl}_2/\text{hexanes}$): R_f 0.45 (30% $\text{CH}_2\text{Cl}_2/\text{hexanes}$); FT-IR (neat) 2957, 2929, 2864, 1464, 1219, 1133, 1119, 1046, 999 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 4.28 (s, 1 H), 3.63 (m, 1 H), 3.45 (ddd, $J = 10.4, 5.2, 1.6$ Hz, 1 H), 2.26 (m, 1H), 1.64 (ddd, $J = 13.6, 11.2, 6.0$ Hz, 1 H), 1.55 (m, 1 H), 1.50-1.34 (m, 10H), 0.96 (d, $J = 6.4$ Hz, 3 H), 0.89 (s, 12 H), 0.84 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3 , DEPT) C 43.5; CH 95.7, 78.0, 72.8, 36.8; CH_2 44.5, 40.9, 40.9, 38.8, 35.5, 33.5; CH_3 35.2 (3), 31.2, 30.8, 26.7; HRMS (CI/isobutane) calcd for $[\text{C}_{17}\text{H}_{34}\text{O}_2 + \text{H}]^+$ 271.2637, found 271.2636. Anal. calcd. for $\text{C}_{17}\text{H}_{34}\text{O}_2$: C, 75.50; H, 12.67. Found: C, 75.61; H, 12.56.

(2*S,4*S**,6*S**)-2-*t*-Butyl-4-decyl-6-hexyl-1,3-dioxane (4e).** A 100 mL Schlenk flask was charged with 2.02 mL (10.69 mmol) 1-decene and 15 mL THF under Ar. $\text{BH}_3 \cdot \text{SMe}_2$ (0.35 mL, 3.56 mmol) was added via syringe and the resulting clear solution was stirred at rt for 16 hr. The solvent and volatiles were distilled under vacuum (0.2 mm Hg, 0 $^\circ\text{C}$ to rt, 6 hr). The resulting clear oil was dissolved in 10 mL dry hexanes and cooled in an ice bath. Et_2Zn (0.73 mL, 7.13 mmol) was added and the mixture was stirred at 0 $^\circ\text{C}$ for 30 min. The volatiles were

⁴ Rathke, M. W.; Yu, H. *J. Org. Chem.* **1972**, *37*, 1732-1734.

removed under vacuum and the excess Et_2Zn was distilled (0.2 mm Hg, 25 °C, 3 hr). The resulting brown oil was diluted with 3 mL dry hexanes to make a 1.8 M solution.

4-Acetoxy-1,3-dioxane **2** (0.100 g, 0.349 mmol) was treated with 0.58 mL Dec_2Zn (1.05 mole, 1.8 M in hexanes) and 95 μL (0.524 mmol) TMSOTf according to the above protocol to yield 88.3 mg (69%) of a clear oil as a single diastereomer after purification by flash chromatography (SiO_2 , 15% CH_2Cl_2 /hexanes then 20%): R_f 0.48 (30% CH_2Cl_2 /hexanes); FT-IR (neat) 2928, 2856, 1463, 1361, 1217, 1134, 1119, 1078, 1047, 998 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 4.30 (s, 1 H), 4.01 (m, 1 H), 3.68 (m, 1 H), 1.97 (m, 1 H), 1.73 (ddd, $J = 12.5, 12.5, 6.2$ Hz, 1 H), 1.56-1.20 (m, 28 H), 0.88 (s, 15 H); ^{13}C NMR (125 MHz, CDCl_3 , DEPT) C 34.8; CH 99.7, 71.9, 71.8; CH_2 36.3, 34.5, 31.9, 31.8, 30.7, 29.6 (3), 29.5, 29.3, 29.2, 25.8, 25.1, 22.7, 22.6; CH_3 24.7 (3), 14.1 (2); HRMS (CI/isobutane) calcd for $[\text{C}_{24}\text{H}_{48}\text{O}_2+\text{H}]^+$ 369.3732, found 369.3731.

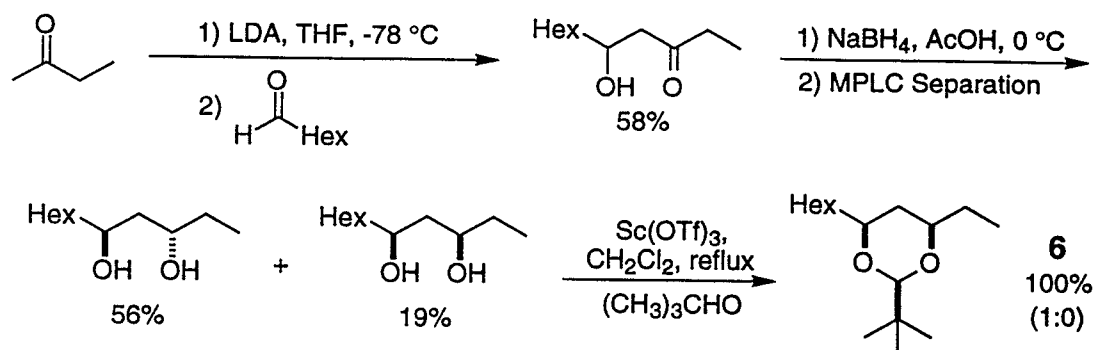
(2S*,4S*,6S*)-2-*t*-Butyl-4-(4'-chlorobutyl)-6-hexyl-1,3-dioxane (4f). A flame-dried 25 mL Schlenk flask was purged with Ar and charged with ca. 4 mg CuI (1 mole %) and 0.32 mL (2.62 mmol) 4-chloro-1-iodobutane. Et_2Zn (0.40 mL, 3.93 mmol) was added via syringe, and the resulting gray slurry was stirred at 50 °C for 18 hr. The Schlenk flask was then evacuated (0.1 mm Hg) and heated at 50 °C for 2 hr to distill off excess Et_2Zn . The dialkylzinc (reddish gray oil) was dissolved in 3 mL CH_2Cl_2 and reacted with 0.150 g (0.524 mmol) **2** and 115 μL (0.628 mmol) TMSOTf according to the general protocol to yield 0.137 g (82%) of a clear oil as a single diastereomer after purification by flash chromatography (SiO_2 , 20% CH_2Cl_2 /hexanes then 30%): R_f 0.17 (10% CH_2Cl_2 /hexanes); FT-IR (neat) 2932, 2860, 1483, 1460, 1360, 1216, 1123, 1075, 997 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.29 (s, 1 H), 4.01 (dddd, $J = 5.4, 5.4, 5.4, 5.4$ Hz, 1 H), 3.67 (m, 1 H), 3.55 (t, $J = 6.7$ Hz, 2H), 2.05 (m, 1 H), 1.80 (m, 3 H), 1.60-1.28 (m, 13 H), 0.88 (s, 12 H); ^{13}C NMR (125 MHz, CDCl_3 , DEPT) C 34.9; CH 99.8, 71.8, 71.5; CH_2 45.0, 36.3, 34.4, 32.3, 31.8, 29.9, 29.2, 25.1, 23.1, 22.6; CH_3 24.7 (3), 14.1; HRMS (CI/isobutane) calcd for $[\text{C}_{18}\text{H}_{35}\text{ClO}_2-\text{H}]^+$ 317.2247, found 317.2251.

(2*S,4*S**,6*S**)-2-*t*-Butyl-4-(ethoxybutyrate)-6-hexyl-1,3-dioxane (4g).** A 25 mL Schlenk flask was charged with 0.507 g (2.10 mmol) ethyl 4-iodobutyrate and 2 mg (0.011 mmol) CuI. Et₂Zn (0.32 mL, 3.1 mmol) was added via syringe, and the resulting slurry was stirred at 50 °C for 18 hr. Excess Et₂Zn was distilled off under vacuum (0.1 mm Hg, 50 °C, 3 hr). The resulting black oil was treated with 0.150 g, (0.524 mmol) **2** and 115 μL (0.628 mmol) TMSOTf according to the above protocol to yield 0.139 g (77%) of a clear oil as a single diastereomer after purification by flash chromatography (SiO₂, 50% CH₂Cl₂/hexanes then 5% EtOAc/hexanes): R_f 0.22 (10% EtOAc/hexanes); FT-IR (neat) 2952, 2932, 2862, 1738, 1460, 1373, 1167, 1124, 1074, 1040, 998 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.29 (s, 1 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 4.02 (dddd, *J* = 5.4, 5.4, 5.4, 5.4 Hz, 1 H), 3.66 (m, 1 H), 2.34 (m, 2H), 2.05 (dddd, *J* = 14.0, 10.0, 10.0, 4.5 Hz, 1 H), 1.80 (m, 1 H), 1.77 (ddd, *J* = 12.8, 12.8, 6.1 Hz, 1 H), 1.63 (m, 1 H), 1.49 (m, 1 H), 1.40-1.21 (m, 14 H), 0.88 (s, 12 H); ¹³C NMR (125 MHz, CDCl₃, DEPT) C 173.6, 34.8; CH 99.7, 71.8, 71.4; CH₂ 60.2, 36.2, 34.4, 33.9, 31.8, 30.0, 29.2, 25.0, 22.6, 21.3; CH₃ 24.7 (3), 14.2, 14.1; HRMS (CI/isobutane) calcd for [C₂₀H₃₈O₄+H]⁺ 343.2848, found 343.2843.

(2*S,4*S**,6*S**)-4-(3-Benzoyloxypropyl)-2-*t*-Butyl-6-hexyl-1,3-dioxane (4h).** A 50 mL Schlenk flask was charged with 0.226 g (1.40 mmol) allyl benzoate and 3 mL Et₂O and cooled in an ice bath. Et₂BH (0.14 mL, 98 mg, 1.4 mmol) was added via syringe and the solution was stirred at rt for 3 hr. The solvents were removed under reduced pressure (0.1 mm Hg, 0 °C, 30 min). After cooling in an ice bath, Et₂Zn (0.29 mL, 2.8 mmol) was added via syringe, and the resulting solution was stirred at 0 °C for 30 min. Excess Et₂Zn was distilled off under vacuum (0.1 mm Hg, 0 °C to rt., 3 hr). The oil was treated with 0.100 g, (0.349 mmol) **2** and 76 μL (0.093 mmol) TMSOTf according to the above protocol to yield 0.0748 g (55%) of a clear oil as a 18:1 ratio of diastereomers after purification by flash chromatography (SiO₂, 50% CH₂Cl₂/hexanes then 5% EtOAc/hexanes): FT-IR (neat) 3065, 2954, 2930, 2860, 1721, 1603,

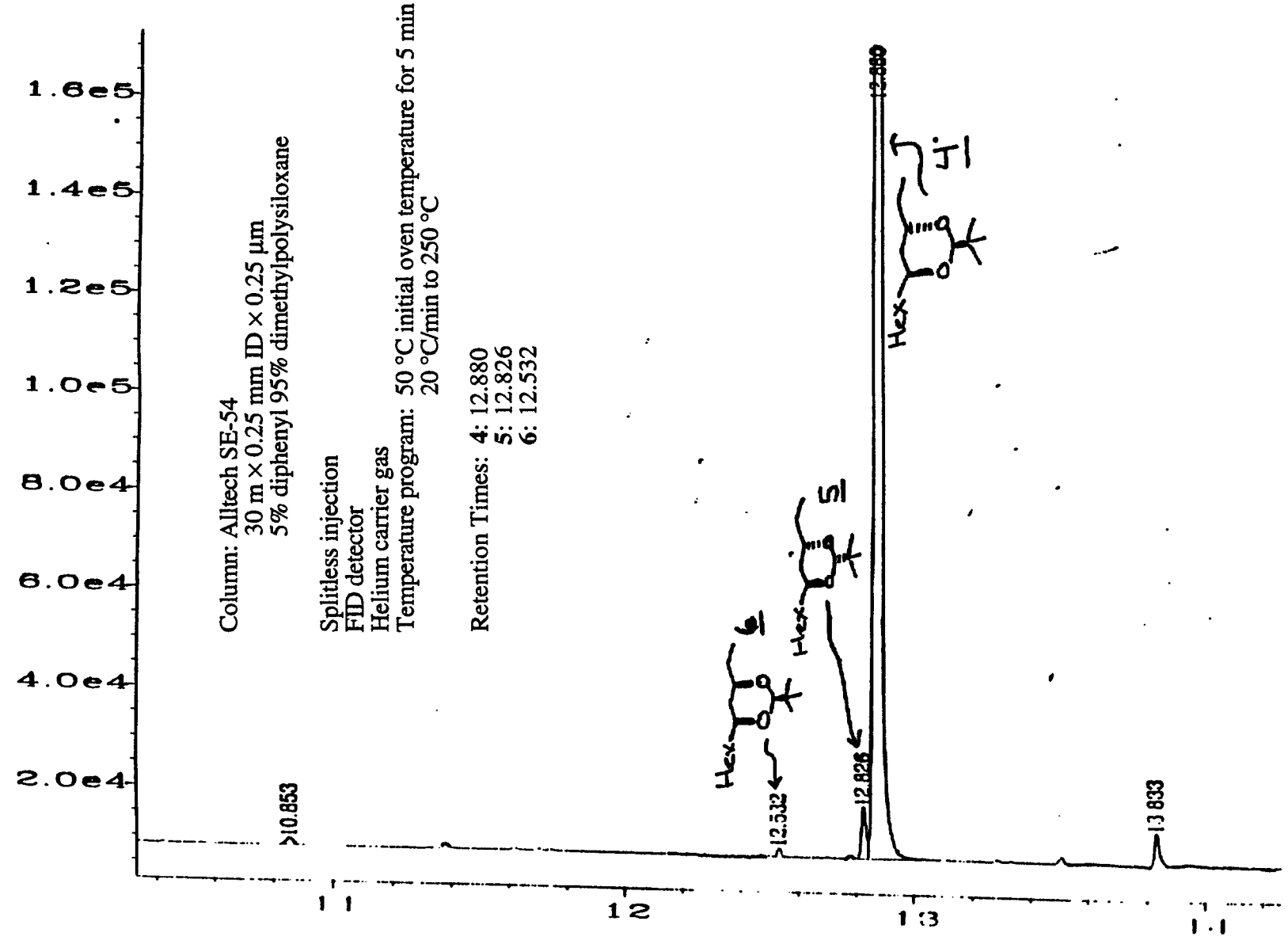
1585, 1453, 1403, 1360, 1315, 1274, 1050, 997 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.06 (dd, J = 8.4, 1.2 Hz, 2 H), 7.56 (tt, J = 7.6, 1.2 Hz, 1 H), 7.44 (t, J = 7.6 Hz, 2 H), 4.38 (m, 2 H), 4.32 (s, 1 H), 4.09 (dddd, J = 5.2, 5.2, 5.2, 5.2 Hz, 1 H), 3.69 (m, 1 H), 2.19 (dddd, J = 15.1, 10.3, 10.3, 4.8 Hz, 1 H), 1.93 (m, 1 H), 1.80 (m, 2 H), 1.50 (m, 2 H), 1.42-1.28 (m, 10 H), 0.89 (s, 12 H); ^{13}C NMR (125 MHz, CDCl_3 , DEPT) C 166.6, 130.4, 34.8; CH 132.8, 129.5, 128.3, 99.7, 71.8, 71.2; CH_2 64.8, 36.2, 34.5, 31.8, 29.2, 27.2, 25.2, 25.0, 22.6; CH_3 24.6 (3), 14.0; HRMS (CI/isobutane) calcd for $[\text{C}_{24}\text{H}_{38}\text{O}_4+\text{H}]^+$ 391.2848, found 391.2840. Anal. calcd. for $\text{C}_{24}\text{H}_{38}\text{O}_4$: C, 73.81; H, 9.81. Found: C, 73.65; H, 10.11.

(2S*,4S*,6S*)-2-*t*-Butyl-4-(3'-*t*-butyldimethylsilyloxypropyl)-6-hexyl-1,3-dioxane (4i). A 25 mL Schlenk flask was charged with 0.242 g (1.40 mmol) 3-*t*-butyldimethylsilyloxy-1-propene under Ar. Et_2BH (0.20 mL, 145 mg, 2.1 mmol) was added via syringe and the solution was stirred at rt for 18 hr. The solvents were removed under reduced pressure (0.2 mm Hg, 25 °C, 2 hr). After cooling in an ice bath, Et_2Zn (0.29 mL, 2.8 mmol) was added via syringe, and the resulting solution was stirred at 0 °C for 45 min. Excess Et_2Zn was distilled off under vacuum (0.2 mm Hg, 50 °C, 5 hr). The black oil was treated with 0.100 g, (0.349 mmol) **2** and 76 μL (0.093 mmol) TMSOTf according to the above protocol to yield 0.117 g (83%) of a clear oil as a 13:1 ratio of diastereomers after purification by flash chromatography (SiO_2 , 20% CH_2Cl_2 /hexanes then 30%): FT-IR (neat) 2952, 2930, 2858, 1463, 1380, 1360, 1254, 1101, 1000, 836 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.30 (s, 1 H), 4.02 (dddd, J = 5.2, 5.2, 5.2, 5.2 Hz, 1 H), 3.65 (m, 3 H), 2.05 m, 1 H), 1.76 (ddd, J = 13.1, 13.1, 6.2 Hz, 1 H), 1.63 (m, 1 H), 1.55-1.28 (m, 13 H), 0.88 (s, 12 H), 0.87 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (125 MHz, CDCl_3 , DEPT) C 34.8, 18.3; CH 99.7, 71.8, 71.7; CH_2 62.9, 36.3, 34.6, 31.9, 29.2, 29.1, 27.0, 25.0, 22.62; CH_3 26.0 (3), 24.70 (3), 14.0, -5.3 (2); HRMS (CI/isobutane) calcd for $[\text{C}_{23}\text{H}_{48}\text{O}_3\text{Si}+\text{H}]^+$ 401.3451, found. Anal. calcd. for $\text{C}_{24}\text{H}_{38}\text{O}_4$: C, 68.94; H, 12.07. Found: C, 69.09; H, 12.10.

Scheme 1. Synthesis of *Syn* Standard Acetal (6).**(2*R**,4*R**,6*S**)-2-*t*-Butyl-4-ethyl-6-hexyl-1,3-dioxane (6).**

A 10 mL round-bottomed flask was charged with 0.10 g (0.531 mmol) **6**, 6 mL CH₂Cl₂, and 9 mg (0.019 mmol) Sc(OTf)₃. The mixture was refluxed through a Soxhlett extractor containing 4Å MS for 4 hr, and then washed with water, dried over MgSO₄, and concentrated. The residual oil was purified by flash chromatography (SiO₂, 20% CH₂Cl₂/hexanes) to give 0.141 g (100%) of a clear oil as a single diastereomer: *R*_f 0.49 (30% CH₂Cl₂/hexanes); FT-IR (neat) 2956, 2931, 2858, 1483, 1463, 1379, 1363, 1217, 1121, 1089, 1055, 1005 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.05 (s, 1 H), 3.47 (m, 1 H), 3.39 (m, 1 H), 1.53 (m, 2 H), 1.41 (m, 4 H), 1.28 (m, 8 H), 0.93 (t, *J* = 7.6 Hz, 3 H), 0.90 (s, 9 H), 0.89 (t, *J* = 7.2 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃, DEPT) *C* 34.9; CH 106.7, 77.4, 76.1; CH₂ 36.9, 36.0, 31.9, 29.3, 29.0, 25.1, 22.6; CH₃ 24.8 (3), 14.1, 9.5; HRMS (CI/isobutane) calcd for [C₁₆H₃₂O₂+H]⁺ 257.2480, found 257.2471. Anal. calcd. for C₁₆H₃₂O₂: C, 74.94; H, 12.58. Found: C, 75.33; H, 12.70.

GC Trace of Crude Product of the Reaction of Et₂Zn with 2 (Equation 1)



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