

Lipase Mediated Resolution of 4-TMS-3-butyn-2-ol and Use of the Mesylate Derivatives as a Precursor to a Highly Stereoselective Chiral Allenylindium Reagent.

James A. Marshall*, Harry R. Chobanian, and Mathew M. Yanik

Department of Chemistry, University of Virginia

PO Box 400319, Charlottesville, VA 22904

jam5x@virginia.edu

Supporting Information

General. Unless otherwise stated all reactions were performed in flame dried glassware under an atmosphere of nitrogen or argon. Anhydrous THF, diethyl ether, and dichloromethane were purified by pressure filtration through activated alumina. The InI (99.999 % anhydrous beads) was purchased from Aldrich Chemical Company, Inc., 1001 West St. Paul Avenue, Milwaukee, WI 53233.

(3*S*,4*R*)-(-)-4-Cyclohexyl-3-methyl-1-trimethylsilyl-but-1-yn-4-ol (10a). The standard procedure with cyclohexanecarboxaldehyde (104 μ L, 0.86 mmol), Pd(OAc)₂ (12.3 mg, 0.055 mmol), PPh₃ (14.4 mg, 0.055 mmol), TMSmesylate (*R*)-**9** (250 mg, 1.10 mmol), InI (294 mg, 1.20 mmol) in THF (3 mL) and HMPA (1 mL) at 0 °C for 2 h gave 155 mg (75%) of alcohol **10a** as a single diastereomer: $[\alpha]_D^{20}$ -14.0 ($c = 2.02$, CHCl₃); IR (film) ν 3486, 2168 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.05 (s, 1H), 2.77 (m, $J = 4.5$ Hz, 1H), 1.90 (d, $J = 13.0$ Hz, 1H), 1.78-1.61 (m, 5 H), 1.40-1.02 (m, 9H), 0.14 (s, 9H);

^{13}C NMR (125 MHz, CDCl_3) δ 107.6, 87.5, 78.5, 47.7, 31.0, 29.7, 27.8, 26.4, 26.3, 26.0, 18.0, 0.14. Anal. Calcd for $\text{C}_{14}\text{H}_{26}\text{OSi}$: C, 70.52; H, 10.99. Found: C,; H,.

(3R,4S)-(-)-2,4-dimethyl-6-trimethylsilyl-5-hexyn-3-ol (10b). The standard procedure with isobutyraldehyde (103 μL , 1.13 mmol), $\text{Pd}(\text{OAc})_2$ (15.2 mg, 0.068 mmol), PPh_3 (17.7 mg, 0.068 mmol), TMSmesylate (*R*)-**9** (300 mg, 1.35 mmol), InI (359 mg, 1.49 mmol) in THF (3 mL) and HMPA (1 mL) at 0 °C for 2 h gave 200 mg (89%) of alcohol **10b** and its syn diastereomer as a 98:2 inseparable mixture: $[\alpha]_D^{20}$ -5.50 (c = 2.21, CHCl_3); IR (film) ν 3466, 2173 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.04 (m, 1H), 2.71 (m, 1H), 1.76 (m, J = 6.5 Hz, 1H), 1.65 (d, J = 6.5 Hz, 1 H), 1.21 (d, J = 7.0 Hz, 3H), 0.13 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 107.5, 86.5, 79.3, 31.8, 31.6, 19.6, 18.1, 17.4, 0.13. Anal. Calcd for $\text{C}_{11}\text{H}_{22}\text{OSi}$: C, 66.60; H, 11.18. Found: C,; H,.

(3S,4R)-(-)-3-Methyl-6-phenyl-1-trimethylsilyl-1-hexyn-4-ol (10c). The standard procedure with hydrocinnamaldehyde (123 mg, 0.94 mmol), $\text{Pd}(\text{OAc})_2$ (12.3 mg, 0.055 mmol), PPh_3 (14.4 mg, 0.055 mmol), TMSmesylate (*R*)-**9** (250 mg, 1.10 mmol), InI (294 mg, 1.20 mmol) in THF (3 mL) and HMPA (1 mL) at 0 °C for 2 h gave 146 mg (69%) of alcohol **10c** as a single diastereomer: $[\alpha]_D^{20}$ -7.0 (c = 1.66, CHCl_3); IR (film) ν 3432, 2182, 1597, 1466 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.25 (m, 5H), 3.41 (s, 1H), 2.83 (m, 1H), 2.71 (m, 1H), 2.57 (m, 1H), 1.85 (m, 3H), 1.20 (d, J = 7.0 Hz, 3H) 0.16 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.9, 128.4, 128.3, 125.8, 108.1, 87.1, 73.3, 36.7, 34.3, 32.0, 17.3, 0.13. Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{OSi}$: C, 73.79; H, 9.29. Found: C,; H,.

(3S,4R)-(-)-3-Methyl-1-trimethylsilyl-1-decyn-4-ol (10d) Standard Procedure For Silylated Allenyl Indium Additions to Aldehydes. To a solution of THF (3 mL) and HMPA (1 mL) was added heptanal (105 μL , 0.75 mmol) followed by $\text{Pd}(\text{OAc})_2$ (10.1

mg, 0.045 mmol) and PPh₃ (11.8 mg, 0.045 mmol). Upon complete dissolution of the PPh₃ the solution was cooled to 0 °C. InI beads (283 mg, 1.17 mmol) were pulverized in a mortar and added to the solution followed by TMSmesylate (*R*)-**9** (200 mg, 0.90 mmol). The solution was then stirred at 0 °C for 15 min before being warmed to rt. Upon completion of the reaction as judged by TLC analysis, the reaction mixture was quenched with 10% HCl (10 mL) and diluted with Et₂O. The Et₂O solution was separated, dried over MgSO₄, and concentrated under reduced pressure. The residue was chromatographed on silica gel (10:1 hexanes/Et₂O) to give 145 mg (80%) of alcohol **10d** and its syn diastereomer as a 99:1 inseparable mixture: $[\alpha]_D^{20} -10.1$ ($c = 2.14$, CHCl₃); IR (film) ν 3432, 2174, 1946 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.38 (t, $J = 4.0$ Hz, 1H), 2.55 (m, $J = 4.5$ Hz, 1H), 1.78 (s, 1H), 1.64 – 1.30 (m, 10 H), 1.20 (d, $J = 7.5$ Hz, 3H), 0.88 (t, $J = 7.5$ Hz, 3H), 0.15 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 107.6, 87.5, 74.2, 35.0, 34.1, 31.7, 29.2, 25.6, 22.6, 17.4, 14.1, 0.13. Anal. Calcd for C₁₄H₂₈OSi: C, 69.93; H, 11.74. Found: C,; H,.

(3*S*,4*R*)-(-)-3-Methyl-1-trimethylsilyl-1-decyn-5-en-4-ol (10e). The standard procedure for allenyl indium additions was employed with (*E*)-2-heptenal (84 mg, 0.75 mmol), Pd(OAc)₂ (10.1 mg, 0.045 mmol), PPh₃ (11.8 mg, 0.045 mmol), TMSmesylate (*R*)-**9** (200 mg, 0.90 mmol), InI (239 mg, 0.99 mmol) in THF (3 mL) and HMPA (1 mL) at 0 °C for 2 h to give 130 mg (73%) of alcohol **10e** and its syn diastereomer as a 99:1 inseparable mixture: $[\alpha]_D^{20} -0.27$ ($c = 2.43$, CHCl₃); IR (film) ν 3530, 2165 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.71 (m, $J = 6.9$ Hz, 1H), 5.42 (m, $J = 7.2$ Hz, 1H), 3.86 (t, $J = 6.9$ Hz, 1H), 2.55 (m, $J = 7.2$ Hz, 1 H), 2.05 (q, $J = 6.9$ Hz, 3H), 1.34 (m, 4H), 1.15 (dd, $J = 6.9, 1.2$ Hz, 3H), 0.89 (t, $J = 6.9$ Hz, 3H), 0.15 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 134.2, 129.6, 107.6, 87.5, 75.6, 34.7, 31.9, 31.2, 22.2, 16.9, 13.9, 0.10. Anal. Calcd for C₁₄H₂₆OSi: C, 70.52; H, 10.99. Found: C,; H,.

(3*S*,4*R*)-(+)-3-Methyl-6-phenyl-1-hexyn-4-ol (11c). The standard procedure with hydrocinnamaldehyde (74 mg, 0.68 mmol), Pd(OAc)₂ (7.6 mg, 0.034 mmol), PPh₃ (8.9 mg, 0.034 mmol), mesylate (*R*)-**1** (100 mg, 0.67 mmol), InI (177 mg, 0.73 mmol) in THF (2 mL) and HMPA (0.7 mL) at 0 °C for 2 h gave 75 mg (71%) of alcohol **11c** and its syn diastereomer as an inseparable 77:23 mixture: $[\alpha]_D^{20} +5.2$ ($c = 3.00$, CHCl₃); IR (film) ν 3426, 2327 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.26 (m, 5H), 3.47 (s, 1H), 2.83 (m, 1H), 2.71 (m, 1H), 2.56 (m, 1H), 2.15 (d, $J = 7.5$ Hz, 1H), 1.87 (m, 3H) 1.23 (d, $J = 7.0$ Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 141.8, 128.4, 128.3, 125.8, 87.9, 73.4, 71.1, 36.8, 33.0, 32.0, 17.3. Anal. Calcd for C₁₃H₁₆O: C, 82.94; H, 8.57. Found: C,; H,.

(2*S*,3*S*,4*S*)-(+)-2-(*tert*-Butyldimethylsilyloxy)-4-methyl-1-trimethylsilyl-5-hexyn-3-ol (13a). The standard procedure for was employed with aldehyde (*S*)-**12** (180 mg, 0.96 mmol), Pd(OAc)₂ (12.3 mg, 0.055 mmol), PPh₃ (14.4 mg, 0.055 mmol), TMSmesylate (*R*)-**9** (250 mg, 1.13 mmol), InI (294 mg, 1.20 mmol) in THF (3 mL) and HMPA (1 mL) at 0 °C for 2 h to give 257 mg (87%) of an inseparable 90:10 mixture of alcohols **13a** and **13b**: $[\alpha]_D^{20} +10.4$ ($c = 2.26$, CHCl₃); IR (film) ν 3563, 2182 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.93 (m, 1H), 3.17 (q, $J = 6.0$ Hz, 1H), 2.66 (m, 1H), 2.56 (d, $J = 4.2$ Hz, 1H), 1.24 (d, $J = 7.2$ Hz, 3H), 1.16 (d, $J = 6.0$ Hz, 3H), 0.90 (s, 9 H), 0.15 (s, 6 H), 0.09 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 107.7, 86.5, 77.8, 70.0, 29.8, 25.8, 19.9, 18.0, 0.14, -4.1, -4.8. Anal. Calcd for C₁₆H₃₄O₂Si₂: C, 61.08; H, 10.89. Found: C,; H,.

(2*S*,3*R*,4*R*)-(+)-2-(*tert*-Butyldimethylsilyloxy)-4-methyl-1-trimethylsilyl-5-hexyn-3-ol (14). The standard procedure was employed with aldehyde (*S*)-**12** (180 mg, 0.96 mmol), Pd(OAc)₂ (12.3 mg, 0.055 mmol), PPh₃ (14.4 mg, 0.055 mmol), TMSmesylate (*S*)-**9** (250 mg, 1.13 mmol), InI (294 mg, 1.20 mmol) in THF (3 mL) and

HMPA (1 mL) at 0 °C for 2 h to give 218 mg (74%) of a single diastereomer **14**: $[\alpha]_D^{20} +36.1$ ($c = 2.66$, CHCl_3); IR (film) ν 3353, 2165 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.69 (m, 1H), 3.08 (s, 1H), 3.00 (m, 1H), 1.71 (s, 1H), 1.25 (d, $J = 7.5$ Hz, 3H), 1.23 (d, $J = 6.0$ Hz, 3H), 0.89 (s, 9H), 0.15 (s, 9H) 0.09 (d, $J = 8.5$ Hz, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 106.9, 87.9, 78.7, 70.2, 29.7, 25.8, 20.3, 18.1, 0.13, -4.25, -4.92. Anal. Calcd for $\text{C}_{16}\text{H}_{34}\text{O}_2\text{Si}_2$: C, 61.08; H, 10.89. Found:

(2S,3R,4R)-(+)-2-(tert-Butyldimethylsilyloxy)-4-methyl-1-trimethylsilyl-5-hexyn-3-ol (13a and 13b) and (2S,3R,4R)-(+)-2-(tert-Butyldimethylsilyloxy)-4-methyl-1-trimethylsilyl-5-hexyn-3-ol (14). The standard procedure was employed with aldehyde (*S*)- **12** (300 mg, 1.60 mmol), $\text{Pd}(\text{OAc})_2$ (21.3 mg, 0.095 mmol), PPh_3 (24.9 mg, 0.095 mmol), TMSmesylate (*R,S*)-**9** (424 mg, 1.90 mmol), InI (502 mg, 2.00 mmol) in THF (6 mL) and HMPA (2 mL) 0 °C for 2 h to give 353 mg (70%) of a separable 50:47:3 mixture of alcohols **13a** and **14**. Alcohol **13a** contained 3% of the syn,syn diastereomer **13b**: **13a**: $[\alpha]_D^{20} +14.6$ ($c = 3.57$, CHCl_3), **14**: $[\alpha]_D^{20} +36.2$ ($c = 3.71$, CHCl_3).

(2R,3S,4S)-(+)-1-(tert-Butyldimethylsilyloxy)-2,4-dimethyl-6-trimethylsilyl-5-hexyn-3-ol (16). The standard procedure was employed with aldehyde (*R*)-**15** (190 mg, 0.94 mmol), $\text{Pd}(\text{OAc})_2$ (12.3 mg, 0.055 mmol), PPh_3 (14.4 mg, 0.055 mmol), TMSmesylate (*R*)-**9** (250 mg, 1.13 mmol), InI (294 mg, 1.20 mmol) in THF (3 mL) and HMPA (1 mL) at 0 °C for 2 h to give 217 mg (71%) of a single diastereomer **16**: $[\alpha]_D^{20} +0.56$ ($c = 1.80$, CHCl_3); IR (film) ν 3501, 2182 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ

3.71 (m, 2H), 3.54 (d, $J = 4.5$ Hz, 1H), 3.32 (m, 1H), 2.70 (m, 1H), 1.95 (m, 1H), 1.26 (d, $J = 7.5$ Hz, 3H), 0.90 (s, 9H), 0.86 (d, $J = 6.5$ Hz, 3H) 0.15 (s, 9H). 0.08 (d, $J = 2.5$ Hz, 6 H); ^{13}C NMR (125 MHz, CDCl_3) δ 107.7, 86.1, 78.4, 67.9, 38.9, 31.4, 25.8, 23.3, 18.2, 17.6, 13.5, 0.21. Anal. Calcd for $\text{C}_{17}\text{H}_{36}\text{O}_2\text{Si}_2$: C, 62.13; H, 11.04. Found:

(2*R*,3*R*,4*R*)-(+)-1-(*tert*-Butyldimethylsilyloxy)-2,4-dimethyl-6-trimethylsilyl-5-hexyn-3-ol (17). The standard procedure was employed with aldehyde (*R*)-**15** (171 mg, 0.85 mmol), $\text{Pd}(\text{OAc})_2$ (11.2 mg, 0.050 mmol), PPh_3 (13.1 mg, 0.050 mmol), TMSmesylate (*S*)-**9** (225 mg, 1.00 mmol), InI (266 mg, 1.10 mmol) in THF (3 mL) and HMPA (1 mL) at 0 °C for 2 h to give 200 mg (72%) of a single diastereomer **17**: $[\alpha]_{\text{D}}^{20} +4.20$ ($c = 2.46$, CHCl_3); IR (film) ν 3536, 2147 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.61 (m, 2H), 2.68 (d, $J = 6.5$ Hz, 1H), 2.33 (d, $J = 5.0$ Hz, 1H), 1.77 (m, 1H), 1.64 (d, $J = 6.5$ Hz, 1H), 1.17 (d, $J = 7.0$ Hz, 3H), 0.92 (d, $J = 7.0$ Hz, 3H), 0.86 (s, 9H), 0.14 (s, 9H), 0.04 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ 108.5, 86.2, 75.3, 66.7, 38.1, 31.8, 25.8, 23.3, 18.2, 17.6, 10.4, 0.14. Anal. Calcd for $\text{C}_{17}\text{H}_{36}\text{O}_2\text{Si}_2$: C, 62.13; H, 11.04. Found: