Supporting Information

Facile Entry to the Tetracyclic 5-7-6-3 Tigliane Ring System

Timo V. Ovaska* Sarah E. Reisman, and Meghan A. Flynn

Department of Chemistry, Connecticut College, 270 Mohegan Avenue, New London, CT 06320

tvova@conncoll.edu

Experimental

^{1}H and ^{13}C NMR spectra were obtained with a 250 MHz Bruker AC-250 NMR spectrometer except for the analysis of compound **16** which was done using a 500 MHz Bruker DMX 500 NMR spectrometer. All chemical shifts are reported relative to tetramethylsilane at δ = 0.00 ppm. Product mixtures were analyzed by gas chromatography using an HP5890 series II gas chromatograph with a 25 m HP-1 cross linked methyl silicone fused–silica capillary column (0.32 mm x 1.05 μM film thickness). Mass spectra were obtained by an HP5971 series Mass Selective Detector at 70eV with a 25 m HP-1 cross linked methyl silicone fused-silica capillary column (0.32 mm x 1.05 μm film thickness. High-resolution mass spectroscopic molecular weights for previously unreported compounds were obtained at the University of Illinois (at Urbana-Champaign) Mass Spectroscopic laboratory. IR spectra were obtained by a Perkins Elmer 1600 series FT-IR spectrometer. Optical rotations were measured using a Jasco P-1010 digital polarimeter at 589 nm. All operations involving organolithiums were performed in flame-dried glassware using standard syringe/cannula techniques under an atmosphere of dry nitrogen or argon. The concentration of commercial of alkyllithium solutions was determined prior to use by titration with standard 2-butanol in xylene using 1,10-phenanthroline as indicator following the method of Watson and Eastham.[1] Diethyl ether and THF were distilled from dark-purple solutions of sodium/benzophenone. Diphenyl

ether was distilled over sodium and stored over activated molecular sieves. All glassware used for the tandem cyclization/Clasisen rearrangement reaction was base-washed (aq. NaOH) prior to use. Dilute solutions (~0.1 M) of MeLi catalyst used for these reactions were prepared by dissolving commercially available MeLi solutions in anhydrous phenetole.

(1'S, 5'S) Methyl 2-(5'-*tert*-butyldimethylsilyloxy)cyclopent-2'-enyl)acetate (8). To a solution of 2.00 g of (1'S, 5'S) methyl 2-(5'-hydroxycyclopent-2-enyl)acetate dissolved in 20 mL of distilled DCM was added 4.34 mL (3.15 g, 31.1 mmol) of triethylamine while stirring under nitrogen at room temperature. To the resulting solution was then added 4.27 g (28.3 mmol) of TBDMSCl, followed by 70 mg (catalytic) of DMAP. The reaction mixture was allowed to stir at room temperature under nitrogen atmosphere for 96 hours before it was quenched by the addition of distilled water. The layers were separated, the aqueous layer was washed with four 15 mL portions of DCM, and the combined organic layers were dried over anhydrous magnesium sulfate. The crude product was purified by column chromatography (10% EtOAc/Hexanes) to give 1.38 g (40%) of pure clear oil. $[\alpha]^{20} = -28.5°$ (c= 1.10 CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 5.57-5.67 (m, 1H), 4.44-4.51 (m, 1H), 3.63 (s, 3H), 3.00-3.04 (m, 1H), 2.60 (dd, J=16.4, J=7.6 Hz, 1H), 2.43-2.54 (m, 1H), 2.24 (dd, J=16.4, J=7.6 Hz, 1H), 2.15-2.25 (m, 1H), 0.84 (s, 9H), -0.00 (d, J=5.5 Hz, 6H) ppm. ^{13}C NMR ($CDCl_3$) δ 173.9, 132.5, 128.7, 72.9, 51.3, 45.5, 41.1, 32.9, 25.8, 16.0, -4.8, -5.1 ppm. IR: 3058, 2953, 2857, 1740, 1472, 1436, 1363, 1258, 1167, 1110, 1041, 837, 776 cm^{-1}. Mass spectroscopic molecular weight calculated for $C_{14}H_{26}OSi$ 270.1651, found 270.1654.

(1'S, 2'S) Methyl 2-[2'-(*tert*-butyldimethylsilyloxy)cyclopentyl]acetate. To a suspension of 23.0 mg of palladium on activated carbon in 15 mL of distilled THF was added 291 mg (1.05 mmol) of **8**, and the resulting suspension was purged with H_2 for 5-10 minutes. After this time, the suspension was allowed to stir vigorously under a hydrogen atmosphere for an additional 2 hours. The reaction was stopped by removing the catalyst by filtration through a pad of celite, and isolated by evaporation under reduced pressure to quantitatively yield 293 mg of the desired product (100 %) in an analytically pure form. $[\alpha]^{21} = +39.4°$ (c=1.10 CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 4.15-4.20 (m,

[1] Watson, S.C.; Eastham, J.F. *J. Organomet. Chem.* **1967**, *9*, 165.

1H), 3.65 (s, 3H), 2.50 (dd, J=16.1, 7.5 Hz, 1H), 2.26 (dd, J=16.0, J=7.0 Hz, 1H), 1.30–2.06 (m, 6H), 0.87-0.93 (m, 1H), 0.84 (s, 9H), -0.018 (d, J=7.1 Hz, 6H) ppm. ^{13}C NMR ($CDCl_3$) δ 174.3, 74.6, 51.3, 41.8, 35.0, 34.1, 28.8, 25.8, 26.6, 21.7, -4.6 ppm. IR (neat) 2955, 2857, 1739, 1472, 1436, 1362, 1257, 1173, 1055, 1022, 837, 776, 740 cm^{-1}. Mass spectroscopic molecular weight calculated for $C_{15}H_{25}OSi$ (M^+–CH_3) 257.1573, found 257.1577.

(1'S, 2'S) 2-[2'-(*tert*-Butyldimethyl-silyloxy)cyclopentyl]acetaldehyde (9). To a solution of 942 mg (3.46 mmol) of (1'S, 2'S) methyl 2-[2'-(*tert*-butyldimethylsilyloxy)-cyclopentyl]acetate dissolved in 47.5 mL of dry toluene cooled to -85°C was slowly added 4.28 mL of 20% DIBAL-H in toluene dropwise via cannula over a 30 minute period while stirring under nitrogen. The reaction mixture was allowed to stir at -85°C for an additional two hours, after which time GC analysis of an aliquot removed from the reaction mixture indicated that all the starting material had been consumed. The reaction mixture was then poured into 70 mL of 20% aqueous acetic acid, an additional 20 mL of ether was added, the layers were separated, and the aqueous layer was extracted with four 20 mL portions of ether. The combined organic layers were dried over anhydrous magnesium sulfate and, following filtration, the solvents were evaporated under reduced pressure to give 765 mg (91.2 %) of the crude aldehyde. This product was judged to be sufficiently pure by NMR and was used without further purification for the next step. $[\alpha]^{22} = +41.7°$ (c=0.72 in CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 9.78 (d, J=2.2 Hz, 1H), 4.14-4.27 (m, 1H), 3.58-3.68 (m, 1H), 2.67 (ddd, J=7.2, J=1.6, J=8.7 Hz, 1H), 2.14-2.46 (m, 2H), 1.31-1.90 (m, 5 H), 0.84 (s, 9H), -0. 02 (d, J=7.0 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$) δ 203.1, 74.7, 44.5, 39.7, 34.8, 26.9, 25.8, 21.7,18.0, -4.5, -4.9 ppm. IR (neat) 2956, 2712, 1726, 1472, 1361, 1255, 1057, 836, 775, 739 cm^{-1}. Mass spectroscopic molecular weight calculated for $C_{12}H_{25}OSi$ (M^+– CH_3) 227.1467, found 227.1463.

(1S, 2S)-1-*tert*-Butyldimethylsilyloxy-2-(2-propynyl)cyclopentane. To a solution of 115 mg (0.834 mmol) of anhydrous potassium carbonate dissolved in 3mL of "superdry" MeOH was added 101 mg (0.417 mmol) of **9**, followed by addition of 120 mg (0.625 mmol) of dimethyl-1-diazo-2-oxopropylphosphonate while stirring under nitrogen. The reaction mixture was allowed to stir at room temperature for one hour at which point the reaction was judged to be complete by TLC. The reaction mixture was then diluted with

10% Et_2O/pentane, the layers were separated, and the aqueous layer was extracted with three 10 mL portions of the same solvent mixture. The combined organic layers were dried over anhydrous magnesium sulfate and the solvents were removed by evaporation under reduced pressure. The crude product was further purified by column chromatography (10% EtOAc/Hex, Rf=0.18) to give 87.7 mg (88.4 %) of the desired alkyne as a clear oil. $[\alpha]^{22}$ = +48.4° (c=0.74 in CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 4.11-4.15 (m, 1H), 3.72-3.82 (m, 1H), 2.3 (ddd, J=10.1, J=7.4, J=2.6 Hz, 1H), 2.14 (ddd, J=9.8, J=7.2, J=2.7 Hz, 1H), 1.88 (t, J=2.6 Hz, 1H), 1.22-1.96 (m, 6H), 0.85 (s, 9H), 0.025 (d, J=3.5 Hz, 6H) ppm. ^{13}C NMR ($CDCl_3$) δ 84.9, 75.4, 67.7, 42.5, 34.9, 28.5, 25.8, 21.7, 18.5, 18.0, -4.5, -4.9 ppm. IR (neat) 3313, 2956, 2857, 2118, 1472, 1362, 1256, 1151 1056, 1015, 836, 775, 626 cm^{-1}. Mass spectroscopic molecular weight calculated for $C_{13}H_{25}OSi$ (M^+–CH_3) 223.1518, found 223.1516.

(**1S, 2S)-2-(2-Propynyl)cyclopentanol**. To a solution of 248 mg (1.04 mmol) of (1S, 2S)-1-*tert*-butyldimethylsilyloxy-2-(2-propynyl)cyclopentane in 5 mL of distilled THF was added 4.00 mL of 1M TBAF in THF (4.00 mmol), and the reaction was allowed to stir under nitrogen overnight. Most of the THF was then removed by evaporation under reduced pressure and the residue was taken up in 7 mL of H_2O and 10 mL of diethyl ether. The layers were separated and the aqueous layer was extracted twice with 10 mL portions of diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, the solvent was removed by evaporation under reduced pressure, and the crude product was purified by column chromatography (20 % EtOAc/Hexanes, Rf = 0.22) to give 113 mg (88.0 %) of the acetylenic alcohol as a clear oil. $[\alpha]^{22}$ = +115.2° (c=.50 in CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 4.23-4.30 (m, 1H), 2.30-2.38 (m, 2H), 1.95 (t, J=2.7, 1H), 1.38-2.02 (m, 8H) ppm. ^{13}C NMR ($CDCl_3$) δ 83.9, 74.3, 68.7, 44.5, 34.5, 28.8, 22.1, 18.3 ppm. IR (neat) 3300, 2958, 2116, 1430, cm^{-1}.

S-2-(2-Propynyl)cyclopentanone (11). To a solution of 385 mg (3.06 mmol) of oxalyl chloride dissolved in 25 mL of anhydrous DCM at -78°C under nitrogen was slowly added 489 mg (6.25 mmol) of DMSO diluted in 4 mL of DCM via cannula while stirring. Gas evolution was immediately evident, and upon completion of the addition, the reaction mixture was allowed to stir an additional 15 minutes before 303 mg (2.44mmol) of (1S, 2S)-2-(2-propynyl)cyclopentanol in 5 mL of DCM was added slowly via cannula.

After 1 h of stirring at –78 °C, 689 mg of freshly distilled triethylamine was added, and the reaction mixture was allowed to stir an additional hour at this temperature. After warming to 0 °C, the solvents were removed by evaporation under reduced pressure. The resulting salts were removed by filtration and washed with several portions of Et_2O. The crude product was isolated by evaporation of the solvents under reduced pressure and purified by column chromatography (50% DCM/Hexanes, Rf=0.14) to give 257 mg (86.0 %) of ketone **11** as a clear oil. [α] = –270.1° (c=0.95 in CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 2.48-2.57 (m, 1H), 2.20-2.40 (m, 4H), 2.00-2.13 (m, 2H), 1.92 (t, J=2.5 Hz, 1H), 1.75-1.85 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$)δ 218.8, 81.7, 69,4, 47.6, 38.0, 28.6, 20.4, 18.5 ppm. IR (neat): 3459, 3288, 2965, 2118, 1740, 1453, 1157 cm^{-1}.

(–)-2-(2-Propynyl)-1-(4,7,7-trimethylbicyclo[4.1.0]hept-2-ene-3-yl)cyclopentanol (14). In a flame dried 50 mL round bottomed flask, 305 mg (0.619 mmol) of anhydrous cerium trichloride (dried under vacuum at 140 °C for 12 h prior to use) was suspended in 3 mL of distilled THF, and the resulting slurry was stirred for 1 hour under argon. In a separate flame-dried 25 mL round bottomed flask, 442 mg of vinyl bromide **3** (1.238 mmol,) in 10 mL of Et_2O at -78°C was treated 1.16 mL (2.476 mmol, 2.14M) of t-BuLi. The resulting solution was first stirred at -78°C for 30 minutes, then at 0°C for an additional 15 minutes. The resulting vinyllithium solution was then recooled to -78°C and rapidly added via cannula to a – 78 °C slurry of cerium trichloride, and the resulting heterogeneous mixture was stirred at this temperature for 1 hour. A solution of 65.3 mg (0.619 mmol) of **11** in 3 mL of THF was then added via cannula to the reaction mixture over a 30 minute period at -78°C. The resulting mixture was stirred for 2 hours, after which time the reaction was judged to be complete by TLC. The reaction was then quenched with 0.5 mL of distilled water, most of the solvents were removed under reduced pressure and the residue was taken up in 20 mL of ether and 15 mL of distilled water. The layers were separated and the aqueous layer was extracted with three 15 mL portions of ether. The combined organic layers were dried over anhydrous magnesium sulfate, followed by filtration and solvent evaporation under reduced pressure. The crude product was then purified by column chromatography to give 0.113 mg (81.9%) of **14** as a viscous oil. $[\alpha]^{21}$ = -51.2° (c=1.02 in CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 5.79–5.82 (m, 1 H), 1.50–2.45 (m, 6 H), 1.94 (t, J= 2.6 Hz, 1 H), 0.85–1.27 (m, 9 H), 1.10 (d, J=7.5 Hz, 3 H), 1.06 (s, 3 H), 0.86, 3 H) ppm. ^{13}C NMR ($CDCl_3$)δ 143.9, 121.3, 84.7, 84.3, 68.7, 45.6,

40.5, 30.5, 29.7, 29.6, 27.8, 23.5, 23.5, 21.9, 21.3, 20.7, 18.5, 15.5 ppm. IR (neat) 3496, 3309, 2954, 2872, 2116, 1448, 1374, 1262, 1008. 877, 834, 628 cm^{-1}. Mass spectroscopic molecular weight calculated for $C_{18}H_{24}$ (M^{+}–H_2O) 240.1878, found 240.1873.

(+)–1,1,8-trimethyl-1a,1b,2,3,4,4a,5,6,7,8,9,9a-dodecahydro-1H-cyclopropa- [3.4]-benzo[1,2-e]azulene (16). In a dry 5 mL two-necked flask, 26.3 mg (0.102 mmol) of **14** was dissolved in 1 mL of diphenyl ether and the resulting solution and heated to 180°C under nitrogen in an oil bath. To the solution was added 0.062 mL (0.0102 mmol, 0.165 M) of methyllithium dropwise, and the reaction mixture was heated thereafter at 185°C for 1 hour. After cooling, the reaction mixture was chromatographed on silica eluting with 5% ethyl acetate in hexanes to give 19.9 mg (76.1%) of the desired tetracyclic product as a viscous oil. $[\alpha]^{22} = +69.1°$ (c=0.92 in CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 3.47 (dd, J=12.5, 4.8 Hz, 1 H), 3.20–3.25 (m, 1 H), 3.13–3.19 (m, 1 H), 2.62–2.68 (m, 1 H), 2.59 (dd, J=17.7, 3.7 Hz, 1 H), 2.44 (dd, J=17.1, 12.2 Hz, 1 H), 2.35–2.42 (m, 3 H), 2.03 (ddd, J=14.4, 9.2, 5.9 Hz, 1 H), 1.94 (app. sextet, J=6.4 Hz, 1 H), 1.67 (app.heptet, J=6.3 Hz, 1 H), 1.54–1.58 (m, 1 H), 1.34–1.43 (m, 1 H), 1.26–1.34 (m, 1 H), 1.24 (d, 7.1 Hz, 3 H), 1.02 (s, 3 H), 1.00 (s, 3 H), 0.86 (dt, J=9.2, 4.3 Hz, 1 H), 0.73 (dd, J=9.2, 6.7 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$) δ 212.3, 138.9, 135.0, 50.3, 49.0, 41.4, 39.5, 38.4, 34.9, 33.9, 30.8, 30.3, 30.1, 25.8, 22.2, 21.2, 18.4 ppm. IR (neat) 2946, 2863, 1709, 1450, 1373, 1297, 1242, 1182, 1060, 803 cm^{-1}. Mass spectroscopic molecular weight calculated for $C_{18}H_{26}O$ 258.1984, found 258.1984.