De Novo Asymmetric Synthesis of Daumone via a Palladium Catalyzed Glycosylation

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Experimental Section:

General Methods and materials: ^1H and ^{13}C spectra were recorded on Joel 270 and Varian 600 spectrometers. Chemical shifts were reported relative to internal tetramethylsilane (δ 0.00 ppm) or CDCl_3 (δ 7.26 ppm) or CD_3OD (δ 4.87 ppm) for ^1H and CDCl_3 (δ 77.1 ppm) or CD_3OD (δ 49.15 ppm) for ^{13}C . Optical rotations were measured with a Jasco DIP-370 digital polarimeter in the solvent specified. Infrared (IR) spectra were obtained on a Prospect MIDAC FT-IR spectrometer. Flash column chromatography was performed on ICN reagent 60 (60-200 mesh) silica gel. Analytical thin-layer chromatography was performed with precoated glass-backed plates (Whatman K6F 60Å, F₂₅₄) and visualized by quenching of fluorescence and by charring after treatment with *p*-anisaldehyde or phosphomolybdic acid or potassium permanganate stain. R_f values were obtained by elution in the stated solvent ratios (v/v). Ether, THF, methylene chloride and triethylamine were dried by passing through activated alumina (8 x 14 mesh) column with argon gas pressure. Commercial reagents were used without purification unless otherwise noted. Air and/or moisture-sensitive reactions were carried out under an atmosphere of argon/nitrogen using oven/flamed-dried glassware and standard syringe/septa techniques.

1-(*tert*-butyldimethylsilyloxy)-pen-4-yne (9**)¹:**

To a magnetically stirred solution of 4-pentynol **9** (5.0 g, 59.4 mmol) and imidazole (10.1 g, 148.6 mmol) in dry DMF (100 ml), was added dropwise *tert*-butyldimethylsilyl chloride (9.4 g, 62.4 mmol) in DMF (50 ml) over 10 min at 0 °C under an atmosphere of nitrogen. The reaction mixture was warmed to room temperature and stirred over night. Water (300 ml) was added and then the reaction mixture was extracted with Et₂O (3 x 300 ml), dried (Na₂SO₄), and evaporated under reduced pressure to leave light yellow oil. The crude product was purified using silica gel flash chromatography eluting with 5% EtOAc/Hexane to give TBS-ether **10** (11.8 g, 147.1, 99%) as a colorless oil: *R_f* (30% EtOAc/hexane) = 0.89; IR (thin film, cm⁻¹) 3314, 2954, 2930, 2858, 1473, 1256, 1106, 835, 776; ¹H NMR (600 MHz, CDCl₃) δ 3.68 (t, *J* = 6.6 Hz, 2H), 2.26 (td, *J* = 7.2, 2.4 Hz, 2H), 1.90 (t, *J* = 2.4, 1H), 1.71 (tt, *J* = 7.2, 6.6 Hz, 2H), 0.89 (s, 9H), 0.05 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 84.3, 68.3, 61.5, 31.6, 26.0, 18.4, 14.9, -5.3.

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¹Muir, J. C.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin Trans.* **2002**, 1, 2243.

(+/-)-7-(*tert*-butyldimethylsilyloxy)-hept-3-yne-2-ol (10**):**

A solution of BuLi in hexane (24.71 ml, 59.3 mmol) was added dropwise to the magnetically stirred solution of TBS-ether **10** (11.8 g, 59.3 mmol) in dry THF (59.3 ml) at -78 °C under the atmosphere of argon. After 30 min, acetaldehyde (1.54 g, 35.1 mmol) was added and stirred for 10 min at 0 °C and then the resulting solution was warmed to room temperature for 50 min. 100 ml of CH₂Cl₂ was added to the reaction mixture followed by addition of 100 ml of pH = 7.0 phosphate buffer. The aqueous phase was separated and extracted with CH₂Cl₂ (3 x 100 ml). The combined organic phase was dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 6% EtOAc/hexane to give propargyl alcohol **11** (8.4 g, 34.6 mmol, 98%): light yellow oil; *R_f* (20% EtOAc/hexane) = 0.42; IR (thin film, cm⁻¹), 3364, 2953, 2930, 2858, 1740, 1472, 1254, 1103, 1071, 835, 775; ¹H NMR (600 MHz CDCl₃) δ 4.65 (qd, *J* = 6.6, 1.8 Hz, 1H), 3.64 (t, *J* = 6.0 Hz, 2H), 2.24 (td, *J* = 7.2, 1.8 Hz, 2H), 1.66 (tt, *J* = 7.2, 6.6 Hz, 2H), 1.38 (d, *J* = 6.6 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 84.0, 82.5, 61.6, 58.4, 31.7, 25.9, 24.7, 18.3, 15.1, -5.0. ms submitted. CIHRMS: Calculated for [C₁₃H₂₆O₂SiNa⁺]: 265.1594, Found: 265.1630.

7-(*tert*-butyldimethylsilyloxy)-hept-3-yne-2-one (8):

To a solution of alcohol **11** (2 g, 8.23 mmol) in THF (82.3 ml), was added activated MnO₂ (10 g) and left to stir for 30 h, the reaction mixture was filtered and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 5% EtOAc/hexane to yield propargyl ketone **8** (1.96 g, 8.13 mol, 98%): *R_f* (30% EtOAc/hexane) = 0.85; IR (thin film, cm⁻¹) 2955, 2930, 2858, 2210, 1678, 1472, 1226, 1103, 966, 8345, 775; ¹H NMR (600 MHz, CDCl₃) δ 3.64 (t, *J* = 6.0 Hz, 2H), 2.40 (t, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 1.71 (tt, *J* = 7.2, 6.0 Hz, 2H), 0.84 (s, 9H), 0.02 (s, *J* = 0.05 Hz, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 184.5, 93.5, 81.4, 61.1, 32.6, 30.7, 25.8, 18.2, 15.3, -5.4.

(*R*)-7-(*tert*-butyldimethylsilyloxy)-hept-3-yne-2-ol (11**):**

To a 20 ml flask was added propargyl ketone **8** (704 mg, 2.92 mmol), CH₂Cl₂ (1.48 ml), formic acid/triethylamine (1:1, 5.38 ml) and Noyori asymmetric transfer hydrogenation catalyst (*S*)-Ru(η^6 -mesitylene)-(*R,R*)-TsDPEN (8.9 mg, 0.5 mol%). The resulting solution was stirred at room temperature for 24 h. Water (10 ml) was added to dilute and extracted with EtOAc (3 x 20 ml). The combined organic layers were washed with saturated NaHCO₃, dried over Na₂SO₄, and concentrated under reduced pressure to afford crude oil. The crude product was purified by silica gel flash chromatography eluting with 6% EtOAc/hexane to give propargyl alcohol (+) **11** (605 mg, 2.49 mmol, 86%): colorless oil; R_f (20% Et₂O/hexane) = 0.42; $[\alpha]_D^{25} = +16$ ($c = 1.1$, CH₂Cl₂); IR (thin film, cm⁻¹) 3346, 2954, 2930, 2858, 1739, 1472, 1253, 1103, 1070, 835, 775; ¹H NMR (600 MHz CDCl₃) δ 4.43 (qd, $J = 6.0, 1.8$ Hz, 1H), 3.64 (t, $J = 6.0$ Hz, 2H), 2.71 (s, 1H), 2.22 (td, $J = 7.2, 1.8$ Hz, 2H), 1.63 (tt, $J = 7.2, 6.0$ Hz, 2H), 1.34 (d, $J = 6.0$ Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 83.8, 82.5, 61.5, 58.2, 31.6, 25.9, 24.7, 18.3, 15.0, -5.3. CI HRMS: Calculated for [C₁₃H₂₆O₂SiNa⁺]: 265.1594, Found: 265.1630.

(R)-7-(tert-butyldimethylsilyloxy) –heptan-2-ol (6):

To a solution of propargyl alcohol **11** (2 g, 8.23 mmol) in dry EtOAc (33 ml), was carefully added Pd/C (5 mg) and the resulting suspension was stirred under H₂ (1 atm) for 5 min at room temperature. The catalyst was filtered off through a short pad of Celite, contrated under reduced pressure to afford colorless oil. The crude product was purified by silica gel flash chromatography eluting with 6% EtOAc/hexane to give alcohol **6** (1.73 g, 6.75 mmol, 82%): colorless oil; R_f (20% Et₂O/hexane) = 0.40; $[\alpha]^{25}_D = +8$ ($c = 1.0$, CH₂Cl₂); IR (thin film, cm⁻¹) 3363, 2929, 2857, 1472, 1254, 1096, 835, 774; ¹H NMR (600 MHz, CDCl₃) δ 3.74 (ddq, $J = 6.0, 6.0, 6.0$, 1H), 3.56 (t, $J = 6.6$ Hz, 2H), 1.85(s, 1H), 1.49 (m, 2H), 1.43 (m, 2H), 1.39 (m, 2H), 1.31(m, 2H), 1.14 (d, $J = 6.0$ Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 68.0, 63.2, 39.4, 32.8, 26.0, 25.9, 25.6, 23.5, 18.4, -5.3. CIHRMS: Calculated for [C₁₃H₃₀O₂Si + Na]⁺: 269.1907, Found: 269.1903.

(S)-1-(2-Furyl)-ethanol (12**)²:**

To a 25 ml flask was added furan ketone **7** (800 mg, 7.27 mmol), CH₂Cl₂ (3.7 ml), formic acid/triethylamine (1:1, 9.71 ml) and Noyori asymmetric transfer hydrogenation catalyst (*R*)-Ru(η^6 -mesitylene)-(*S*, *S*)-TsDPEN (22.2 mg, 0.5 mol%). The resulting solution was stirred at room temperature for 24 h. The reaction mixture was diluted with water (10 ml) and extracted with EtOAc (3 x 25 ml). The combined organic layers were washed with saturated NaHCO₃, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 30% EtOAc/hexane to give furan alcohol **12** (745 mg, 6.76 mmol, 93%): colorless oil; *R_f* (30% EtOAc/hexane) = 0.41; $[\alpha]_D^{25} = +21$ (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3360, 2980, 2935, 1668, 1505, 1467, 1370, 1229, 1149, 1007, 877, 734; ¹H NMR (600 MHz CDCl₃) δ 7.30 (d, *J* = 1.8, 1H), 6.26 (dd, *J* = 3.0, 1.8 Hz, 1H), 6.15 (d, *J* = 3.0, 1H), 4.78 (dq, *J* = 6.6, 6.6 Hz, 1H), 3.11 (s, 1H), 1.46 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 157.7, 141.6, 109.9, 104.9, 63.3, 21.1.

² Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori R. *Org. Lett.*, **2000**, 2, 1749.

(2S)-6-Hydroxy-2-methyl-2H-Pyran-3(6H)-one (13):

Compound furan alcohol **12** (8.30 g, 74.1 mmol), 184.5 mL of THF, and 61.5 mL of H₂O were added to a round bottom flask and cooled to 0 °C. Solid NaHCO₃ (12.4 g, 148.2 mmol), NaOAc•3H₂O (10.1 g, 74.1 mmol), and NBS (13.1 g, 74.1 mmol) were added to the solution and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with saturated NaHCO₃ (200 mL), extracted (3 x 200 mL) with Et₂O, dried (Na₂SO₄), concentrated under reduced pressure and purified by silica gel chromatography eluting with 25% EtOAc/hexane to give pyranone **13** (8.56 g, 67.4 mmol, 91%): *R_f* (60% EtOAc/hexane) = 0.29; $[\alpha]_D^{25} = +44$ (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3381, 2988, 2942, 1692, 1447, 1373, 1232, 1021, 937; ¹H NMR (600 MHz, CDCl₃) major isomer δ 6.82 (dd, *J* = 10.2, 3.0 Hz, 1H), 5.96 (d, *J* = 10.2, 1H), 5.48 (d, *J* = 3.0 Hz, 1H), 3.99 (q, *J* = 7.2 Hz, 1H), 1.23 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) major isomer δ 197.6, 145.3, 126.6, 87.2, 74.8, 15.1.

(2*S*, 6*S*)-tert-butyl -5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yl carbonate (5):

Pyronone alcohol **13** (5.5 g, 42.9 mmol) was dissolved in CH₂Cl₂ (42 mL) and the solution was cooled to -78 °C. A CH₂Cl₂ (2 mL) solution of (Boc)₂O (13.46 g, 51.6 mmol) and a catalytic amount of DMAP (524.2 mg, 4.76 μmol) was added to the reaction mixture. The reaction was stirred for 1 h at -78 °C, and quenched with 200 mL of saturated NaHCO₃, extracted with Et₂O (3 x 200 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 6% EtOAc/hexane to give 7.62 g (33.5 mmol, 78%) of two diastereomers of Boc-protected pyranone **5α** and **5β** in 3:1: *R_f* (20% Et₂O/hexane) = 0.58; [α]²⁵_D = + 98 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2984, 2942, 1752, 1703, 1371, 1273, 1254, 1153, 938, 838; ¹H NMR (600 MHz, CDCl₃) δ 6.78 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.22 (d, *J* = 3.6 Hz, 1H), 6.09 (d, *J* = 10.2 Hz, 1H), 4.53 (q, *J* = 6.6 Hz, 1H), 1.40 (s, 9H), 1.28 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (150.8 MHz, CDCl₃) δ 195.5, 151.7, 140.9, 128.2, 89.1, 83.3, 72.0, 27.5, 15.1; CIHRMS Calculated for [C₁₁H₁₆O₅Na⁺]: 251.0890, Found: 251.0883.

(2*S*, 6*R*)-6-((*R*)-7'-(*tert*-butyldimethylsilyloxy)heptan-2'-yloxy)-2-methyl-2H-pyran-3(6H)-one (4):

To a solution of pyranone **5** (473 mg, 2.07 mmol) and alcohol **6** (430 mg, 1.74 mmol) in dry CH₂Cl₂ (1 mL), was added a CH₂Cl₂ (1 mL) solution of Pd₂(DBA)₃•CHCl₃ (43.9 mg, 2.5 mol%) and PPh₃ (45.6 mg, 10 mol%) at 0 °C under argon atmosphere. After stirring for 3 h at 0 °C to room temperature, the reaction mixture was quenched with 15 mL of saturated NaHCO₃, extracted (3 x 25 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 4% EtOAc/hexane to give pyranone **4** (656 mg, 1.64 mmol, 94%): *R_f* (20% EtOAc/hexane) = 0.64; [α]_D²⁵ = + 13 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2930, 2857, 1701, 1463, 1375, 1254, 1097, 1023, 836; ¹H NMR (600 MHz, CDCl₃) δ 6.77 (dd, *J* = 10.2, 3.6 Hz, 1H), 6.04 (d, *J* = 10.2 Hz, 1H), 5.25 (d, *J* = 3.6 Hz, 1H), 4.56 (q, *J* = 6.6 Hz, 1H), 3.89 (ddq, *J* = 6.0, 6.0, 6.0 Hz, 1H), 3.58 (t, *J* = 6.6 Hz, 2H), 1.58 (m, 2H) 1.49 (m, 2H), 1.47 (m, 2H), 1.41 (m, 2H), 1.35 (d, *J* = 6.6 Hz, 3H), 1.17 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 197.2, 144.2, 127.1, 90.8, 73.8, 70.4, 63.2, 37.3, 32.8, 26.0, 25.8, 25.6, 19.5, 18.3, 15.2, -5.3; CIHRMS: Calculated for [C₁₉H₃₆O₄SiNa⁺]: 379.2275, Found: 379.2277.

(1*S*, 3*S*, 5*R*, 6*R*)-5-((*R*)-7'-(*tert*-butyldimethylsilyloxy)heptan-2'-yloxy)-3-methyl-4,7-dioxa-bicyclo[4.1.0]heptan-2-one (14):

To the solution of pyranone **4** (440 mg, 1.18 mmol) in methanol (3.93 ml) at 0 °C, 30% aqueous hydrogen peroxide (0.553 ml, 4.7 mmol) was added dropwise, followed by aqueous sodium hydroxide (0.236 ml, 0.5 M). The reaction mixture was warmed to room temperature. After stirring for 5 h, the reaction mixture was quenched using saturated sodium bisulfite (5 ml), extracted with diethyl ether (5 x 20 mL). The extracts were washed with saturated NaHCO₃ (25 ml), dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 4% EtOAc/hexane to give 656 mg (1.64 mmol, 94%) of epoxy-enone **14**: *R_f* (20% EtOAc/hexane) = 0.62; [α]_D²⁵ = - 103 (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 2930, 2858, 1726, 1463, 1380, 1254, 1143, 1094, 1057, 833; ¹H NMR (600 MHz, CDCl₃) δ 5.28 (d, *J* = 0.6 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 1H), 3.86 (ddq, *J* = 6.0, 6.0, 6.0 Hz, 1H), 3.60 (t, *J* = 6.6 Hz, 2H), 3.48 (dd, *J* = 4.2, 0.6 Hz, 1H), 3.42 (d, *J* = 4.2 Hz, 1H), 1.54 (m, 2H), 1.51 (m, 2H), 1.37 (d, *J* = 6.6 Hz, 3H), 1.32 (m, 2H), 1.24 (m, 2H), , 1.20 (d, *J* = 7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 203.3, 91.3, 73.7, 71.9, 63.1, 54.3, 53.0, 37.1, 32.8, 26.0, 25.8, 25.5, 19.2, 18.4, 16.8, -5.2; CIHRMS: Calculated for [C₁₉H₃₆O₅SiNa⁺]: 395.2224, Found: 379.2228.

(1*R*, 2*S*, 3*S*, 5*R*, 6*R*)-5-((*R*)-7'-(*tert*-butyldimethylsilyl)heptan-2'-yloxy)-3-methyl-4, 7-dioxabicyclo[4.1.0]heptan-2-ol (15):

A CH₂Cl₂ (0.46 mL) solution of epoxy enone **14** (181 mg, 0.46 mmol) and CeCl₃/MeOH (0.3 mL, 0.4 M) was cooled to -78 °C. NaBH₄ (38.4 mg, 10.2 mmol) was added and the reaction mixture was stirred at -78 to -20 °C for 4 h. The reaction mixture was diluted with ether (5 mL) and quenched with 2.5 mL of saturated NaHCO₃, extracted (3 x 5 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 20% EtOAc/hexane to give 170 mg (0.43 mmol, 93%) of epoxy alcohol **15**: *R_f* (40% EtOAc/hexane) = 0.34; $[\alpha]_D^{25} = -54$ (*c* = 1.0, CH₂Cl₂); IR (thin film, cm⁻¹) 3441, 2930, 2857, 1463, 1387, 1254, 1097, 1055, 834; ¹H NMR (600 MHz, CDCl₃) δ 5.02 (s, 1H), 3.84 (ddq, *J* = 6.0, 6.0, 6.0 Hz 1H), 3.60 (t, *J* = 6.6 Hz, 2H), 3.59-3.55 (m, 1H), 3.50 (m, 1H), 3.26 (d, *J* = 3.6 Hz, 1H), 3.05 (d, *J* = 3.6 Hz, 1H), 1.61-1.53 (m, 2H) 1.52 (m, 2H), 1.49-1.40 (m, 2H), 1.38-1.31 (m, 2H), 1.23 (d, *J* = 6.6 Hz, 3H), 1.16 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 92.5, 73.1, 68.0, 65.6, 63.3, 56.0, 50.6, 37.3, 32.8, 26.0, 25.8, 25.5, 19.4, 18.4, 18.3, -5.2; CIHRMS: Calculated for [C₁₉H₃₈O₅SiNa⁺]: 397.2380, Found: 397.2386.

(2*R*, 3*R*, 5*R*, 6*S*)-2-((*R*)-7'-(*tert*-butyldimethylsilyloxy)heptan-2'-yloxy)-tetrahydro-6-methyl-2H-pyran-3,5-diol (16**):**

To a solution of epoxy ketone **14** (35 mg, 0.09 mmol) in dry THF (0.15 ml) at -78°C , was added dropwise the suspension solution of LiAlH_4 (6.8 mg, 0.18 mmol) in dry THF (0.15 ml) under argon atmosphere. After stirring 2 h, the resulting solution was warmed to the room temperature and LiAlH_4 (6.8 mg, 0.18 mmol) in dry THF (0.15 ml) was added dropwise again, keeping reaction over night. Water (1 ml) was added dropwise with cooling. Then the mixture was extracted with EtOAc (3 x 3 ml), dried (Na_2SO_4), concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexane to give 30.5 mg (0.078 mmol, 86%) of epoxy alcohol **15**: R_f (50% EtOAc/hexane) = 0.21; $[\alpha]_D^{25} = -67$ ($c = 1.0$, CH_2Cl_2); IR (thin film, cm^{-1}) 3360, 2929, 2857, 1463, 1378, 1255, 1098, 1028, 984, 835; ^1H NMR (600 MHz, CD_3OD) δ 4.69 (s, 1H), 3.83 (ddq, $J = 6.0, 6.0, 6.0$ Hz, 1H), 3.76 (m, 1H), 3.69 (t, $J = 6.6$ Hz, 2H), 3.66 (m, 1H), 3.56 (ddd, $J = 11, 11, 4.2$ Hz, 1H), 2.00 (ddd, $J = 13.2, 3.6, 3.6$ Hz, 1H), 1.82 (ddd, $J = 13.2, 11.4, 3$ Hz, 1H), 1.58 (m, 2H), 1.51 (m, 2H), 1.43 (m, 2H), 1.34 (m, 2H), 1.26 (d, $J = 6.6$ Hz, 3H), 1.17 (d, $J = 6.0$ Hz, 3H), 0.95 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (150 MHz, CD_3OD) δ 96.3, 72.5, 71.2, 70.0, 68.8, 63.1, 38.6, 36.1, 34.0, 27.1, 26.7, 26.6, 19.5, 19.3, 18.3, -4.9; CIHRMS: Calculated for $[\text{C}_{19}\text{H}_{40}\text{O}_5\text{SiNa}^+]$: 399.2537, Found: 399.2539.

(2*S*, 3*R*, 6*R*)-6-((*R*)-7'-(tert-butyldimethylsilyl)heptan-2'-yloxy)-tetrahydro-2-methyl-2H-pyran-3-ol (16D₂):

To a solution of epoxy ketone **14** (10 mg, 0.02 mmol) in dry THF (0.03 ml) at -78°C , was added dropwise the suspension solution of LiAlH_4 (1.5 mg, 0.04 mmol) in dry THF (0.03 ml) under argon atmosphere. After stirring 2 h, the resulting solution was warmed to the room temperature and LiAlH_4 (1.5 mg, 0.04 mmol) in dry THF (0.03 ml) was added dropwise again, keeping reaction over night. Water (0.5 ml) was added dropwise with cooling. Then the mixture was extracted with EtOAc (3 x 1 ml), dried (Na_2SO_4), concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 50% EtOAc/hexane to give 6.6 mg (0.017 mmol, 84%) of epoxy alcohol **15**: R_f (50% EtOAc/hexane) = 0.21; IR (thin film, cm^{-1}) 3394, 2929, 2857, 1463, 1381, 1255, 1096, 1047, 1013, 835; ^1H NMR³ (600 MHz, CD_3OD) δ 4.69 (s, 1H), 3.83 (ddq, $J = 6.0, 6.0, 6.0$ Hz, 1H), 3.76 (dd, $J = 1.8, 3.0$ Hz 1H), 3.69 (t, $J = 6.6$ Hz, 2H), 3.66 (m, 1H), 2.00 (d, $J = 3.0$ Hz, 1H), 1.58 (m, 2H) 1.51 (m, 2H), 1.43 (m, 2H), 1.34 (m, 2H), 1.26 (d, $J = 6.6$ Hz, 3H), 1.17 (d, $J = 6.0$ Hz, 3H), 0.95 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (150 MHz, CD_3OD) 97.7, 72.5, 71.2, 70.1, 63.1, 38.6, 34.0, 27.1, 26.7, 26.6, 19.5, 19.3, 18.3, -5.0; CIHRMS: Calculated for $[\text{C}_{19}\text{H}_{38}\text{D}_2\text{O}_5\text{SiNa}^+]$: 401.2663, Found: 401.2674.

³ Compared to the ^1H and ^{13}C NMR of compound 16, We found two protons missed at the position of δ 3.56 and 1.82, and two carbons missed at the position of δ 68.8 and 36.2.

(2*R*, 3*R*, 5*R*, 6*S*)-2-((*R*)-7'-hydroxyheptan-2'-yloxy)-tetrahydro-6-methyl-2H-pyran-3,5-diol (17**):**

To a solution of TBS-ether **16** (120 mg, 0.307 mmol) in dry THF (0.307 ml), TBAF (0.35 ml, 0.353 mmol) was added at room temperature under the Argon atmosphere. After 24 h, the reaction mixture was dried with a little silica gel under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 3% MeOH/EtOAc to give triol **17** (83 mg, 0.30 mmol, 98%); a colorless oil, $R_f = 0.48$ (10% MeOH/EtOAc); $[\alpha]_D^{25} = -79$ ($c = 1.01$, MeOH); IR (thin film, cm^{-1}) 3350, 2967, 2932, 2860, 1453, 1378, 1125, 1100, 1027, 983; ^1H NMR (600 MHz, CD_3OD) δ 4.61 (s, 1H), 3.75 (ddq, $J = 6.0, 6.0, 6.0$ Hz, 1H), 3.73-3.72 (m, 1H), 3.63-3.57 (m, 1H), 3.52 (t, $J = 7.2$ Hz, 2H), 3.48 (ddd, $J = 11, 11, 4.2$ Hz, 1H), 1.91 (ddd, $J = 13.2, 3.6, 3.6$ Hz, 1H), 1.73 (ddd, $J = 13.2, 11.4, 3$ Hz, 1H), 1.54-1.49 (m, 2H), 1.46-1.43 (m, 2H), 1.38-1.33 (m, 2H), 1.19 (d, $J = 6.0$ Hz, 3H), 1.09 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 97.6, 72.5, 71.3, 70.0, 68.4, 63.0, 38.5, 36.1, 33.7, 27.0, 26.8, 19.5, 18.2; CIHRMS: Calculated for $[\text{C}_{13}\text{H}_{26}\text{O}_5\text{Na}^+]$: 285.1672, Found: 285.1668.

(-)-6*R*-(tetrahydro-3'*R*, 5'*R*-dihydroxy-6'*S*-methyl-2*H*-pyran-2'*R*-yloxy) heptanoic acid (1**):**

To a stirred solution of triol **17** (70.0 mg, 0.253 mmol) in saturated NaHCO₃ (1.25 mL) was added KBr (3.0 mg, 0.252 mmol) and TEMPO (2.55 mg, 0.016 mmol) at 0°C. Then a solution of NaOCl (0.94 ml, 0.8 M) was added dropwise. The reaction mixture was allowed to stir for 48 h at 0°C, washed with CH₂Cl₂ to remove TEMPO and some other byproducts. The aqueous layer was acidified to pH = 1-2 by using 2 N HCl and then concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 5% MeOH/EtOAc to give acid **1** (45 mg, 0.154 mmol, 61%); colorless syrup, R_f = 0.45 (10% MeOH/EtOAc); $[\alpha]_D^{25}$ = - 85 (c = 1.15, MeOH); IR (thin film, cm⁻¹) 3394, 2924, 2854, 1730, 1460, 1379, 1103, 1026, 980; ¹H NMR (600 MHz, CD₃OD) δ 4.65 (s, 1H), 3.79 (ddq, J = 6.0, 6.0, 6.0 Hz, 1H), 3.73-3.72 (m, 1H), 3.65-3.51 (m, 1H), 3.52 (ddd, J = 11, 11, 4.2 Hz, 1H), 2.31 (t, J = 7.8 Hz, 2H), 1.95 (ddd, J = 13.2, 3.6, 3.6 Hz, 1H), 1.77 (ddd, J = 13.2, 11.4, 3 Hz, 1H), 1.66-1.57 (m, 2H), 1.53-1.49 (m, 2H), 1.43 (m, 2H), 1.23 (d, J = 6.0 Hz, 3H), 1.13 (d, J = 6.0 Hz, 3H); ¹³C NMR (150 MHz, CD₃OD) δ 176.4, 96.4, 71.2, 70.0, 68.8, 67.2, 36.8, 34.8, 33.8, 25.2, 24.9, 18.1, 16.9; CIHRMS: Calculated for [C₁₃H₂₄O₆Na⁺]: 299.1465, Found: 299.1467.

(2*S*, 3*S*, 6*R*)-6-((*R*)-7'-(*tert*-butyldimethylsilyloxy)heptan-2'-yloxy)-3,6-dihydro-2-methyl-2H-pyran-3-ol (18):

A solution of pyranone **4** (200 mg, 0.536 mmol) in dry CH_2Cl_2 (0.54 mL) and $\text{CeCl}_3/\text{MeOH}$ (0.54 mL) was cooled to -78°C . NaBH_4 (22.2 mg, 0.59 mmol) was added and the reaction mixture was stirred for 3 h at the temperature of -78 to -20°C . The resulting solution was diluted with ether (3 mL) and was quenched with 5 mL of saturated NaHCO_3 , extracted (3 x 5 mL) with Et_2O , dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 25% EtOAc /hexane to give 157 mg (0.42 mmol, 78%) of allylic alcohol **18**: R_f (30% EtOAc /hexanes) = 0.34; colorless oil; $[\alpha]_D^{25} = -42$ ($c = 0.47$, CH_2Cl_2); IR (thin film, cm^{-1}) 3424, 2930, 2896, 2858, 1463, 1379, 1254, 1096, 1031, 1002, 834; ^1H NMR (600 MHz, CD_3Cl) δ 5.92 (d, $J = 10.2$ Hz, 1H), 5.71 (dd, $J = 10.2$, $J = 1.8$ Hz, 1H), 5.02 (d, $J = 1.8$ Hz, 1H), 3.83 (m, 2H), 3.74 (qd, $J = 8.4$, 6.0 Hz, 1H), 3.61 (t, $J = 6.6$ Hz, 2H) 1.61 (m, 2H), 1.57-1.50 (m, 2H), 1.45-1.43 (m, 2H), 1.36-1.32 (m, 2H), 1.31 (d, $J = 6.0$ Hz, 3H), 1.13 (d, $J = 6.0$ Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, CD_3Cl) δ 133.3, 127.5, 92.0, 73.2, 70.0, 69.9, 68.2, 63.3, 37.5, 33.0, 26.1, 25.9, 25.7, 19.9, 18.0, -5.2; CIHRMS: Calculated for $[\text{C}_{19}\text{H}_{36}\text{O}_4\text{SiNa}^+]$: 379.2275, Found: 379.2287.

(2*R*, 3*R*, 4*R*, 5*S*, 6*S*)-2-((*R*)-7'-(*tert*-butyldimethylsilyloxy)heptan-2'-yloxy)-tetrahydro-6-methyl-2H-pyran-3,4,5-triol (20**):**

To a *t*-butanol, acetone (0.45 mL, 1:1, 1 M) solution of allylic alcohol **18** (165 mg, 0.44 mmol) at 0 °C was added a solution of (50% w/v) of *N*-methyl morpholine *N*-oxide/water (0.23 mL). Crystalline OsO₄ (1.14 mg, 1 mol %) was added and the reaction was stirred for 12 h. The reaction mixture was concentrated and was pipetted directly on to a silica gel column using a small amount of CH₃OH (0.6 mL) in three portions. Impurities were eluted with ether and the product was eluted with 90% EtOAc/Hexane. Pure fractions were combined and concentrated to afford triol **20** 171.8 mg (0.42 mmol, 96%): *R_f* (80% EtOAc/hexane) = 0.44; [α]_D²⁵ = - 54 (*c* = 1.03, MeOH); IR (thin film, cm⁻¹) 3388, 2930, 2858, 1463, 1384, 1254, 1095, 1045, 982, 833; ¹H NMR (600 MHz, CDCl₃) δ 4.85 (d, *J* = 1.8 Hz, 1H), 4.52-4.22 (br, 3H), 3.84 (m, 1H), 3.72 (m, 2H), 3.66 (dd, *J* = 6.6, 9.0 Hz, 1H), 3.58 (t, *J* = 6.6 Hz, 2H), 3.47-3.43 (m, 1H), 1.49 (t, *J* = 6.6, 2H), 1.41 (m, 2H) 1.39-1.34 (m, 2H), 1.29 (m, 2H), 1.27 (d, *J* = 6.6 Hz, 3H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 97.2, 72.9, 72.1, 72.0, 71.8, 68.4, 63.3, 37.2, 32.8, 26.1, 25.9, 25.6, 18.9, 18.4, 17.6, -5.2; CIHRMS: Calculated for [C₁₉H₄₀O₆SiNa⁺]: 415.2486, Found: 415.2487.

(2*R*, 3*R*, 4*R*, 5*S*, 6*S*)-2-((*R*)-7'-hydroxyheptan-2'-yloxy)-tetrahydro-6-methyl-2H-pyran-3, 4, 5-triol:

To a solution of TBS-ether **20** (145 mg, 0.354 mmol) in dry THF (0.35 ml), TBAF (0.403 ml, 0.106 mmol) was added at room temperature under the atmosphere of argon. After 24 h, the reaction mixture was dried with a little silica gel under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 10% MeOH/EtOAc to give alcohol (102.3 mg, 0.347 mmol, 98%); a colorless oil, $R_f = 0.28$ (20% MeOH/EtOAc); $[\alpha]_D^{25} = -74$ ($c = 0.50$, MeOH); IR (thin film, cm^{-1}) 3361, 2967, 2931, 2860, 1453, 1380, 1124, 1044, 981; ^1H NMR (600 MHz, CD_3OD) δ 4.86 (d, $J = 1.8$ Hz 1H), 3.82 (m, 1H), 3.80 (dd, $J = 3.0, 1.8$ Hz, 1H), 3.73-3.68 (m, 2H), 3.61 (t, $J = 6.6$ Hz, 2H) 3.44 (dd, $J = 9.3, J = 9.3$ Hz, 1H), 1.64-1.58 (m, 2H), 1.53-1.49 (m, 2H), 1.47-1.45 (m, 2H), 1.44-1.41 (m, 2H), 1.31 (d, $J = 6.6$ Hz, 3H), 1.19 (d, $J = 6.0$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 99.0, 74.1, 73.0, 72.9, 72.6, 70.1, 63.0, 38.4, 33.7, 27.0, 26.7, 19.4, 18.1; CIHRMS: Calculated for $[\text{C}_{13}\text{H}_{26}\text{O}_6\text{Na}^+]$: 301.16219, Found: 301.1626.

(*R*)-6-(tetrahydro-3'*R*, 4'*R*, 5'*S*-trihydroxy-6'*S*-methyl-2H-pyran-2'*S*-yloxy) heptanoic acid (21**):**

To a stirred solution of alcohol (75.0 mg, 0.254 mmol) in saturated NaHCO₃ (1.26 mL) was added KBr (3.1 mg, 0.252 mmol) and TEMPO (2.57 mg, 0.016 mmol) at 0°C. Then a solution of NaOCl (0.95 ml, 0.8 M) was added dropwise. The reaction mixture was allowed to stir for 36 h at 0°C, washed with CH₂Cl₂ to remove TEMPO and some other byproducts. The aqueous layer was acidified to pH = 1-2 by using 2 N HCl and then concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 10% MeOH/EtOAc to give acid **21** (43.4 mg, 0.140 mmol, 55%); colorless syrup, R_f = 0.26 (20% MeOH/EtOAc); $[\alpha]_D^{25}$ = - 73 (c = 0.75, MeOH); IR (thin film, cm⁻¹) 3372, 2967, 2931, 2860, 1709, 1452, 1381, 1235, 1094, 1047, 981; ¹H NMR (600 MHz, CD₃OD) δ 4.82 (d, J = 1.8 Hz, 1H), 3.80 (ddq, J = 6.0, 6.0, 6.0 Hz, 1H), 3.75 (dd, J = 3.0, 1.8 Hz, 1H), 3.68-3.64 (m, 2H), 3.44 (dd, J = 9.6, 9.6 Hz, 1H), 2.32 (t, J = 7.2 Hz, 2H) 1.65-1.62 (m, 2H), 1.59-1.55 (m, 2H), 1.52-1.47 (m, 2H), 1.44-1.37 (m, 2H), 1.31 (d, J = 6.0 Hz, 3H), 1.19 (d, J = 6.0 Hz, 3H); ¹³C NMR (67.5 MHz, CD₃OD) δ 178.0, 98.9, 74.1, 72.9, 72.8, 71.7, 72.6, 70.2, 38.1, 35.2, 26.3, 19.3, 18.1; CIHRMS: Calculated for [C₁₃H₂₄O₇Na⁺]: 315.1414, Found: 315.1419.

(2*S*, 3*R*, 6*R*)-6-((*R*)-7'-(tert-butyldimethylsilyl)heptan-2'-yloxy)-tetrahydro-2-methyl-2H-pyran-3-ol:

To a CH₂Cl₂ (2.3 mL, 0.1 M) solution of allylic alcohol (86 mg, 0.23 mmol) *o*-nitrobenzenesulfonylhydrazide (NBSH) (468 mg, 2.3 mmol) was added followed by triethylamine (0.39 mL, 2.76 mmol) and the reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with ether (10 mL) and was quenched with 5 mL of satd aq NaHCO₃, extracted (3 x 10 mL) with Et₂O, dried (Na₂SO₄), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 25% EtOAc/hexane to give 85 mg (0.225 mmol, 98%) of alcohol: *R*_f(30% EtOAc/hexane) = 0.31; [α]²⁵_D = - 92 (*c* = 0.705, CH₂Cl₂); IR (thin film, cm⁻¹) 3369, 2929, 2857, 1463, 1383, 1255, 1097, 1049, 991, 835; ¹H NMR (600 MHz, CD₃Cl) δ 4.86 (s, 1H), 3.74 (ddq, *J* = 6.0, 6.0, 6.0 Hz, 1H), 3.63 (qd, *J* = 9.0, 6.0 Hz, 1H), 3.61 (t, *J* = 6.6 Hz, 2H), 3.26 (m, 1H), 1.85-1.81 (m, 2H), 1.78-1.741(m, 2H), 1.61-1.57 (m, 2H), 1.56-1.50 (m, 2H), 1.45-1.43 (m, 2H), 1.36-1.31 (m, 2H), 1.24 (d, *J* = 6.0 Hz, 3H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ¹³C NMR (67.5 MHz, CD₃Cl) δ 92.8, 72.4, 70.7, 69.7, 63.5, 37.5, 32.9, 30.2, 27.8, 26.1, 26.0, 25.7, 19.1, 18.4, 17.9, -5.1; CIHRMS: Calculated for [C₁₉H₄₀O₄SiNa⁺]: 383.2580, Found: 383.2594.

(2*S*, 3*R*, 6*R*)-6-((*R*)-7'-hydroxyheptan-2'-yloxy)-tetrahydro-2-methyl-2H-pyran-3-ol

To a solution of TBS-ether (130 mg, 0.345 mmol) in dry THF (0.345 ml), TBAF (0.375 ml, 0.379 mmol) was added at room temperature under the argon atmosphere. After 24 h, the reaction mixture was dried with a little silica gel under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 80% EtOAc/hexane to give compound diol (86 mg, 0.335 mmol, 97%); a colorless oil, R_f = 0.31 (80% EtOAc/hexane); $[\alpha]_D^{25}$ = - 113 (c = 1.01, MeOH); IR (thin film, cm^{-1}) 3361, 2932, 2861, 1452, 1377, 1117, 1047, 1025, 984; ^1H NMR (600 MHz, CD_3OD) δ 4.90 (s, 1H), 3.81 (ddq, J = 6.0, 6.0, 6.0 Hz, 1H), 3.69(qd, J = 9.0, 6.0 Hz, 1H), 3.60 (t, J = 6.6 Hz, 2H), 3.19 (m, 1H), 1.84-1.82 (m, 2H), 1.91-1.79 (m, 2H), 1.65-1.60 (m, 2H), 1.56-1.50 (m, 2H), 1.49-1.42 (m, 2H), 1.24 (d, J = 6.0 Hz, 3H), 1.16 (d, J = 6.0 Hz, 3H); ^{13}C NMR (67.5 MHz, CD_3OD) δ 94.4, 72.9, 72.0, 71.1, 63.1, 38.6, 33.7, 31.3, 28.5, 27.1, 26.9, 19.5, 18.5; CIHRMS: Calculated for $[\text{C}_{13}\text{H}_{26}\text{O}_4\text{Na}^+]$: 269.1723, Found: 269.1721.

(R)-6-(tetrahydro-5'R-hydroxy-6' S -methyl-2H-pyran-2' R -yloxy) heptanoic acid

(19):

To a stirred solution of compound **18** (56 mg, 0.215 mmol) in saturated NaHCO₃ (1.06 mL) was added KBr (2.6 mg, 0.215 mmol) and TEMPO (2.2 mg, 0.014 mmol) at 0°C. Then a solution of NaOCl (0.81 mL, 0.8 M) was added dropwise. The reaction mixture was allowed to stir for 12 h at 0°C, washed with CH₂Cl₂ to remove TEMPO and some other byproducts. The aqueous layer was acidified to pH = 1-2 by using 2 N HCl and then concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography eluting with 80% EtOAc/hexane to give acid **19** (43 mg, 0.155 mmol, 72%); colorless syrup, R_f = 0.73 (10% MeOH/EtOAc); $[\alpha]_D^{25}$ = - 117 (c = 0.2, MeOH); IR (thin film, cm⁻¹) 3393, 2962, 2935, 2866, 1709, 1454, 1377, 1229, 1118, 1049, 986; ¹H NMR (600 MHz, CD₃OD) δ 4.89 (s, 1H), 3.80 (ddq, J = 6.0, 6.0, 6.0, 1H), 3.67 (qd, J = 9.0, 6.0, 1H), 3.20-3.16 (m, 1H), 2.34 (t, J = 7.2 Hz, 2H), 1.82-1.77 (m, 3H), 1.69-1.43 (m, 3H), 1.56-1.43 (m, 3H), 1.38-1.33 (m, 3H), 1.24 (d, J = 6.0 Hz, 3H), 1.14 (d, J = 6.0 Hz, 3H); ¹³C NMR (67.5 MHz, CD₃OD) δ 178.4, 94.5, 73.1, 71.9, 71.2, 38.4, 35.7, 31.4, 28.5, 26.7, 26.5, 19.4, 18.5; CIHRMS: Calculated for [C₁₃H₂₄O₅Na⁺]: 283.1516, Found: 283.1515.