

A Concise and Modular Synthesis of Pyranicin

Nolan D. Griggs and Andrew J. Phillips*

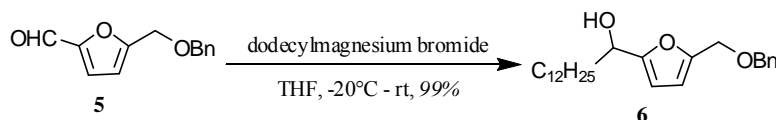
Department of Chemistry and Biochemistry, University of Colorado, Boulder, CO 80309-0215

SUPPORTING INFORMATION

General Experimental Procedures.

Unless otherwise noted, ^1H and ^{13}C NMR spectra were recorded at 25 °C on Varian Inova spectrometers operating at 500 or 400, and 125 or 100 MHz, respectively, using CDCl_3 as the solvent and internal reference. Coupling constants are reported in Hertz, Hz. All non-aqueous reactions were run in flame-dried glassware under a dry N_2 atmosphere. Toluene, THF, CH_2Cl_2 , and Et_2O were obtained from Aldrich (Pure-Pac) and further dried by passage through activated alumina as described by Bergman and Grubbs.¹ All flash chromatography was performed with normal phase silica gel (Sorbent Technologies, 32-63 μm particle size, 60 Å pore size), following the general protocol of Still.²

1-(5-(Benzyloxymethyl)furan-2-yl)tridecan-1-ol, **6**.

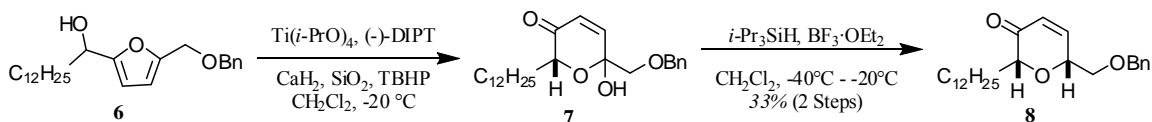


To a solution of aldehyde **5** (11.0 g, 50.9 mmol) in THF (203 mL) in a 500 mL round-bottomed flask, was added a freshly prepared solution of dodecylmagnesium bromide (56.0 mL of a 1M solution in ether, 56.0 mmol) dropwise at -20 °C. The reaction was stirred for 1h at -20 °C and was then allowed to warm to rt. The reaction was quenched with sat. NH_4Cl , diluted with water, and extracted 3x with ether. The combined organic layers were washed with brine, dried with MgSO_4 , filtered, and the solvent was removed *in vacuo*. The crude product was purified using flash column chromatography (8% EtOAc/Hex.) to yield pure alcohol **6** (19.6 g, 99%) as a clear oil. ^1H NMR (CDCl_3) δ 7.30-7.40 (m, 5H), 6.29 (d, $J=3.2$, 1H), 6.21 (d, $J=3.2$, 1H), 4.65 (t, $J=6.8$, 1H), 4.58 (s, 2H), 4.49 (s, 2H), 2.87 (br s, 1H), 1.87 (m, 2H), 1.24-1.53 (m, 20H), 0.196 (t, $J=7.0$, 3H). ^{13}C NMR (CDCl_3) δ 157.9, 151.0, 138.1, 128.7, 128.2, 127.9, 110.4, 106.5, 72.0, 67.9, 64.1, 35.8, 32.2, 30.0, 29.97, 29.93, 29.8, 29.7, 29.6, 25.8, 23.0, 14.4. IR (neat, cm^{-1}) 3410 (OH). HRMS (ESI) calc for $\text{C}_{25}\text{H}_{38}\text{O}_3\text{Na}^+$ 409.2713, found 409.2707.

(2R,6R)-6-(Benzyloxymethyl)-2-dodecyl-2H-pyran-3(6H)-one, **8**.

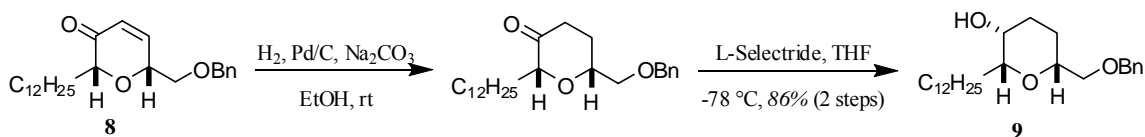
¹ a) Alaimo, P. J.; Peters, D.W.; Arnold, J.; Bergman, R.G. *J. Chem. Educ.* **2001** 78 64. b) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R.K.; Timmers, F. J. *Organometallics* **1996**, 15, 151.

² Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, 43, 2923.



To a mixture of $\text{Ti}(\text{OPr}_i)_4$ (0.76 mL, 2.59 mmol), CaH_2 (10.9 mg, 0.26 mmol), and silica gel (32 mg, 0.512 mmol) in dry CH_2Cl_2 (13 mL) at $-20\text{ }^\circ\text{C}$ was added (-)-DIPT (0.660 mL, 3.10 mmol). The mixture was stirred for 10 min, then furyl alcohol **6** (1.00 g, 2.59 mmol) was added, and the reaction was stirred an additional 10 min. The solution was cooled to $-40\text{ }^\circ\text{C}$, and TBHP (1.29 mL of a 5 M solution in decane, 6.47 mmol) was added slowly. The reaction was sealed under $\text{Ar}(\text{g})$ and allowed to stir at $-20\text{ }^\circ\text{C}$ for 8 h. The reaction was quenched with 10% aqueous tartaric acid and stirred until the solution was clear. The organic layer was separated, and the aqueous layer was extracted 3x with CH_2Cl_2 . The combined organic layers were then washed with brine, dried with MgSO_4 , filtered, and the solvent was removed *in vacuo*. The crude mixture was partially purified using flash column chromatography (15% EtOAc/Hex) to yield an inseparable mixture of the desired, unstable, hemiketal **7** (6:1 dr) and (-)-DIPT. This mixture was immediately dissolved in CH_2Cl_2 (8.6 mL) and triisopropylsilane (2.65 mL, 12.94 mmol) was added. The solution was then cooled to $-40\text{ }^\circ\text{C}$, and $\text{BF}_3\cdot\text{OEt}_2$ (175 μL , 1.42 mmol) was added dropwise. The solution was stirred at $-40\text{ }^\circ\text{C}$ for 5h, then warmed to $-20\text{ }^\circ\text{C}$ for an additional hour. The reaction was quenched with sat. NaHCO_3 , diluted with water, and extracted 3x with ether. The combined organic extracts were washed with brine, dried with MgSO_4 , filtered, and the solvent was removed *in vacuo*. The crude product was purified using flash column chromatography (8% EtOAc/Hex) yielding pure product **8** (325 mg, 33% over 2 steps) as a clear oil. ^1H NMR (CDCl_3) δ 7.31-7.42 (m, 5H), 7.08 (dd, $J=1.5, 10.3$, 1H), 6.18 (dd, $J=2.5, 10.3$, 1H), 4.65 (m, 2H), 4.54 (m, 1H), 3.99 (ddd, $J=2.0, 3.7, 7.8$, 1H), 3.75 (dd, $J=5.8, 10.0$, 1H), 3.63 (dd, $J=5.9, 10.0$, 1H), 2.00 (m, 1H), 1.69 (m, 1H), 1.21-1.54 (m, 20H), 0.91 (t, $J=7.0$, 3H). ^{13}C NMR (CDCl_3) δ 196.9, 148.9, 137.9, 128.7, 128.1, 128.0, 127.9, 80.9, 73.8, 71.4, 32.1, 29.98, 29.91, 29.8, 29.7, 29.6, 25.4, 22.9, 14.4. $[\alpha]_D^{25} +18.1$ (c 1.00, CHCl_3). IR (neat, cm^{-1}) 1693 (CO). HRMS (ESI) calc for $\text{C}_{25}\text{H}_{38}\text{O}_3\text{Na}^+$ 409.2713, found 409.2705.

(2R,3R,6R)-6-(Benzyloxymethyl)-2-dodecyltetrahydro-2H-pyran-3-ol, 9.

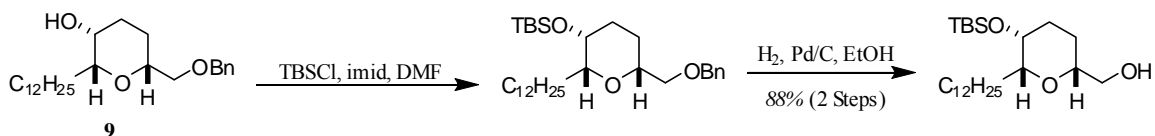


Enone **8** (550 mg, 1.43 mmol) was dissolved in dry EtOH (14 mL) in a 50 mL 2-neck flask. Na_2CO_3 (151 mg, 1.43 mmol) was added followed by 5% Pd/C (303 mg). The reaction was then evaluated, equipped with a hydrogen balloon, and was allowed to react for 1h. The solution was then diluted with ether, filtered through a plug of Celite[®], and the solvent was removed *in vacuo* to yield the desired pure ketone which was used without further purification. ^1H NMR (CDCl_3) δ 7.29-7.42 (m, 5H), 4.66 (d, $J=11.6$, 1H), 4.64 (d, $J=11.6$, 1H), 3.96 (dt, $J=4.6, 10.1$, 1H), 3.85 (dd, $J=4.3, 7.8$, 1H), 3.64 (dd, $J=5.9, 10.2$, 1H), 3.55 (dd, $J=4.7, 10.2$, 1H), 2.62 (ddd, $J=4.6, 6.6, 16.0$, 1H), 2.45 (m, 1H), 2.10 (m, 1H), 1.97 (m, 1H), 1.85 (m, 1H), 1.61 (m, 1H), 1.12-1.49 (m, 20H), 0.91 (t, $J=7.0$, 3H). ^{13}C NMR (CDCl_3) δ 209.9, 138.4, 128.6, 127.9, 127.8, 83.2, 75.3,

73.7, 72.7, 37.1, 32.1, 30.2, 29.9, 29.8, 29.7, 29.6, 28.1, 25.5, 22.9, 14.4. IR (neat, cm^{-1}) 1725 (CO). HRMS (ESI) calc for $\text{C}_{25}\text{H}_{40}\text{O}_3\text{Na}^+$ 411.2869, found 411.2867. $[\alpha]_{\text{D}} +35.2$ (c 1.00, CHCl_3).

To a solution of the crude ketone (551 mg, 1.42 mmol) in THF (14 mL) was added a 1M solution of L-Selectride (4.25 mL, 4.25 mmol) at -78 °C. The reaction was stirred for 3h, and was then allowed to warm to 0 °C. The reaction was quenched with hydrogen peroxide (30% (aq), 11 mL) followed by NaOH (2N, 55 mL) and the biphasic mixture was stirred vigorously for 1h at rt. The layers were then separated, and the aqueous layer was extracted 3x with ether. The combined organic extracts were washed with brine, dried with MgSO_4 , filtered, and the solvent was removed *in vacuo*. The crude product was purified using flash column chromatography (12% EtOAc/Hex) yielding pure product **9** (475 mg, 86% over 2 steps) as a clear oil. ^1H NMR (CDCl_3) δ 7.34 (m, 5H), 4.64 (d, $J=12.1$, 1H), 4.58 (d, $J=12.1$, 1H), 3.65 (m, 2H), 3.55 (dd, $J=6.1$, 10.2, 1H), 3.47 (dd, $J=4.4$, 10.2, 1H), 3.38 (t, $J=6.9$, 1H), 2.01 (m, 2H), 1.19-1.76 (m, 25H), 0.91 (t, $J=7.0$, 3H). ^{13}C NMR (CDCl_3) δ 138.6, 128.6, 127.9, 127.8, 80.3, 77.6, 73.6, 66.2, 32.2, 31.9, 30.8, 29.92, 29.90, 29.86, 29.84, 29.6, 25.8, 22.9, 22.6, 14.4. IR (neat, cm^{-1}) 3443 (OH). HRMS (ESI) calc for $\text{C}_{25}\text{H}_{42}\text{O}_3\text{Na}^+$ 413.3026, found 413.3019. $[\alpha]_{\text{D}} +6.7$ (c 1.00, CHCl_3).

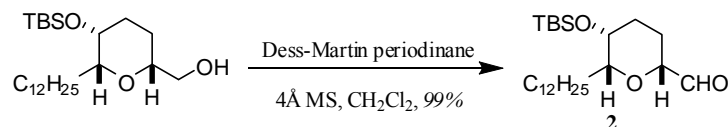
(2R,5R,6R)-5-(tert-Butyldimethylsilyloxy)-6-dodecyltetrahydro-2H-pyran-2-carbaldehyde, 2.



To a solution of alcohol **9** (475 mg, 1.22 mmol) and imidazole (248 mg, 3.65 mmol) in DMF (6 mL) was added TBSCl (202 mg, 1.4 mmol) slowly at rt. The reaction was stirred overnight, and was then diluted with water and extracted 3x with ether. The combined organic extracts were washed with brine, dried with MgSO_4 , filtered, and the solvent was removed *in vacuo* yielding pure silylated product which could be used without purification. An analytically pure sample could be obtained by flash column chromatography (2% EtOAc/Hex). ^1H NMR (CDCl_3) δ 7.36 (m, 5H), 4.65 (d, $J=12.1$, 1H), 4.57 (d, $J=12.1$, 1H), 3.62 (m, 3H), 3.46 (m, 1H), 3.29 (t, $J=6.6$, 1H), 1.90 (dd, $J=3.0$, 12.9, 1H), 1.69 (m, 3H), 1.39 (m, 22H), 0.95 (s, 9H), 0.92 (t, $J=7.0$, 3H), 0.09 (s, 3H) 0.08 (s, 3H). ^{13}C NMR (CDCl_3) δ 138.8, 128.5, 127.9, 127.6, 80.3, 74.0, 73.5, 66.8, 32.4, 32.1, 31.7, 30.0, 29.9, 29.8, 29.6, 26.1, 25.9, 23.0, 22.9, 18.4, 14.4, -4.25, -4.49. IR (neat, cm^{-1}) 2924, 2853, 1462, 1251. HRMS (ESI) calc for $\text{C}_{31}\text{H}_{56}\text{O}_3\text{SiNa}^+$ 527.3890, found 527.3873. $[\alpha]_{\text{D}} +6.02$ (c 1.00, CHCl_3).

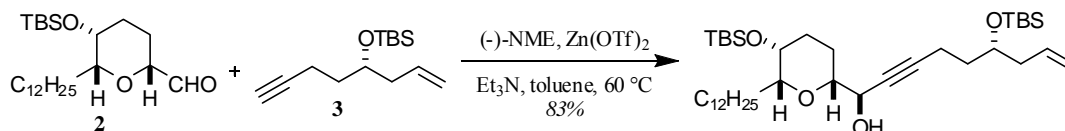
The resulting silyl ether was immediately dissolved in ethanol (10 mL) and 5% Pd/C (450 mg) was added. The flask was then equipped with a hydrogen balloon and the reaction was stirred overnight. The solution was then filtered through a plug of Celite[®], the solvent was removed *in vacuo*, and the crude product was purified using flash column chromatography (12% EtOAc/Hex) yielding pure alcohol (445 mg, 88% over 2 steps). ^1H NMR (CDCl_3) δ 3.63 (s, 1H), 3.56 (m, 2H), 3.48 (dtd, $J=1.8$, 5.3, 7.3, 1H), 3.28 (m, 1H), 2.38 (brs, 1H), 1.87 (td, $J=3.2$,

12.9, 1H), 1.66 (m, 3H), 1.19-1.49 (m, 22H), 0.92 (s, 9H), 0.89 (t, $J=7.0$, 3H), 0.07 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (CDCl_3) δ 80.2, 78.2, 66.9, 66.3, 32.4, 32.1, 31.5, 29.97, 29.90, 29.6, 26.1, 22.9, 21.8, 18.4, 14.3, -4.31, -4.55. IR (neat, cm^{-1}) 3453 (OH). HRMS (ESI) calc for $\text{C}_{24}\text{H}_{50}\text{O}_3\text{SiNa}^+$ 437.3421, found 437.3413. $[\alpha]_{\text{D}} -3.63$ (c 1.00, CHCl_3).



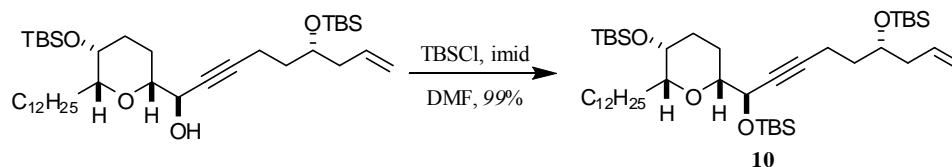
To a suspension of the alcohol obtained above (411 mg, 0.99 mmol) and activated 4Å molecular sieves (100 mg) in CH_2Cl_2 (6.6 mL) was added Dess-Martin periodinane (462 mg, 1.09 mmol) at rt. The reaction was stirred 3h at rt. The reaction was quenched with 1:1 sat. NaHCO_3 : sat. $\text{Na}_2\text{S}_2\text{O}_3$, diluted with water, and extracted 3x with ether. The combined organic extracts were washed with brine, dried with MgSO_4 , filtered, and the solvent was removed *in vacuo*. The resulting residue was taken up in ether and flushed through a plug of silica. Evaporation of the solvent gave pure product **2** (409 mg, 99%) as a clear oil. ^1H NMR (CDCl_3) δ 9.69 (s, 1H), 3.81 (dd, $J=2.5$, 11.8, 1H), 3.67 (s, 1H), 3.35 (m, 1H), 1.96 (qd, $J=3.1$, 13.1, 1H), 1.82 (dd, $J=3.5$, 12.4, 1H), 1.71 (m, 2H), 1.63 (m, 1H), 1.22-1.54 (m, 21H), 0.93 (s, 9H), 0.90 (t, $J=7.0$, 3H), 0.084 (s, 6H). ^{13}C NMR (CDCl_3) δ 203.1, 81.9, 80.5, 66.5, 32.3, 32.1, 31.3, 29.93, 29.90, 29.88, 29.85, 29.6, 26.1, 25.8, 22.9, 20.8, 18.4, 14.4, -4.28, -4.56. IR (neat, cm^{-1}) 1740 (CO). HRMS (ESI) calc for $\text{C}_{24}\text{H}_{48}\text{O}_3\text{SiNa}^+$ 435.3264, found 435.3261. $[\alpha]_{\text{D}} +31.4$ (c 1.00, CHCl_3).

(5*R*,10*S*)-10-Allyl-5-((2*R*,5*R*,6*R*)-5-(*tert*-Butyldimethylsilyloxy)-6-dodecyltetrahydro-2*H*-pyran-2-yl)-2,2,3,3,12,12,13,13-octamethyl-4,11-dioxa-3,12-disilatetradec-6-yne, **10.**



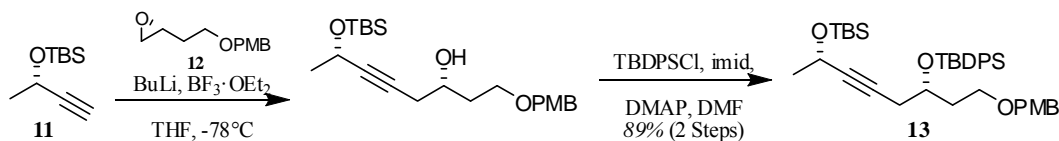
To a suspension of zinc (II) triflate (397 mg, 1.09 mmol) and (-)-*N*-methylephedrine (214 mg, 1.19 mmol) in toluene (2 mL) was added triethylamine (168 μL , 1.19 mmol) at rt. The resulting mixture was stirred at rt for 2h. The alkyne **3** (237 mg, 0.99 mmol) was then added in one portion as a solution in toluene (500 μL). The reaction was stirred for 15 min. The aldehyde **2** (410 mg, 0.99 mmol) was then added in one portion as a solution in toluene (500 μL), and the reaction was heated to 60 °C for 2h. The reaction was then cooled to rt and quenched with sat. NH_4Cl , diluted with water, and extracted 3x with ether. The organic layers were washed with brine, dried with MgSO_4 , filtered, and the solvent was removed *in vacuo*. The crude product was then purified using flash column chromatography (5% EtOAc/Hex.) to yield pure alcohol (**10**) (536 mg, 83%) as a single diastereomer. ^1H NMR (CDCl_3) δ 5.81 (m, 1H), 5.06 (m, 2H), 4.25 (qd, $J=2.0$, 8.0, 1H), 3.82 (td, $J=5.6$, 11.5, 1H), 3.63 (s, 1H), 3.34 (dt, $J=3.0$, 8.1, 1H), 3.29 (dd, $J=4.6$, 7.6, 1H), 2.89 (d, $J=2.3$, 1H), 2.29 (m, 4H), 1.91 (dd, $J=3.0$, 6.5, 1H), 1.65 (m, 6H), 1.21-1.47 (m, 21H), 0.91 (m, 21H), 0.08 (m, 12H). ^{13}C NMR (CDCl_3) δ 134.9, 117.3, 86.7, 80.9,

80.4, 77.8, 70.7, 66.7, 66.3, 42.0, 35.5, 32.3, 32.1, 31.4, 29.9, 29.88, 29.86, 29.6, 26.1, 25.9, 22.9, 21.9, 18.4, 18.3, 15.2, 14.3, -4.13, -4.28, -4.41, -4.51. IR (neat, cm^{-1}) 3448 (OH). HRMS (ESI) calc for $\text{C}_{38}\text{H}_{74}\text{O}_4\text{Si}_2\text{Na}^+$ 673.5017, found 673.5018. $[\alpha]_{\text{D}} -8.78$ (c 1.00, CHCl_3).



To a solution of the alcohol obtained above (100 mg, 0.15 mmol) and imidazole (31.4 mg, 0.46 mmol) in DMF (1 mL) was added TBSCl (26 mg, 0.16 mmol) slowly at rt. The reaction was stirred overnight. The solution was then diluted with water and extracted 3x with ether. The combined organic extracts were washed with brine, dried with MgSO_4 , filtered, and the solvent was removed *in vacuo*. The crude product was purified using flash column chromatography (1% EtOAc/Hex) yielding pure product **10** (115 mg, 99%) as a clear oil. ^1H NMR (CDCl_3) δ 5.81 (m, 1H), 5.06 (m, 2H), 4.31 (td, $J=2.0, 6.6$, 1H), 3.82 (td, $J=5.7, 11.6$, 1H), 3.59 (s, 1H), 3.31 (ddd, $J=1.9, 6.7, 11.0$, 1H), 3.21 (m, 1H), 2.25 (m, 4H), 1.87 (m, 1H), 1.66 (m, 6H), 1.23-1.46 (m, 21H), 0.84-1.01 (m, 30H), 0.04-0.16 (m, 18H). ^{13}C NMR (CDCl_3) δ 135.0, 117.2, 85.8, 80.8, 80.1, 79.6, 70.8, 67.3, 66.6, 42.0, 35.7, 32.4, 32.1, 31.6, 30.0, 29.9, 29.8, 29.6, 26.1, 26.0, 25.8, 22.9, 21.4, 18.6, 18.38, 18.30, 15.2, 14.4, -4.14, -4.36, -4.46, -4.53, -4.65. IR (neat, cm^{-1}) 2925, 2854, 1470, 1361. HRMS (ESI) calc for $\text{C}_{44}\text{H}_{88}\text{O}_4\text{Si}_3\text{Na}^+$ 787.5882, found 787.5874. $[\alpha]_{\text{D}} -16.38$ (c 1.00, CHCl_3).

(5*R*,9*S*)-9-(2-(4-Methoxybenzyloxy)ethyl)-2,2,3,3,5,12,12-heptamethyl-11,11-diphenyl-4,10-dioxo-3,11-disilatridec-6-yne, 13.

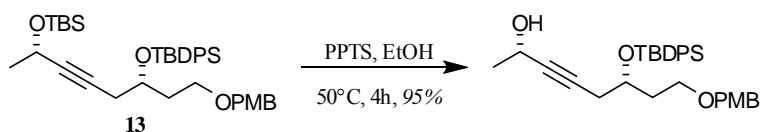


To a solution of alkyne **11** (920 mg, 4.99 mmol) in freshly distilled THF (20 mL) was added *n*-butyllithium (3.66 mL of a 1.6 M solution in hexanes, 5.49 mmol) dropwise at -78 °C. The solution was stirred for 45 min and then allowed to warm to -10 °C for 30 min, and was then cooled down to -78 °C. This solution was then transferred via cannula into a solution of epoxide **12** (1.35 g, 6.49 mmol) in THF (15 mL) at -78 °C while adding $\text{BF}_3 \cdot \text{OEt}_2$ (6.75 mL, 5.49 mmol) simultaneously. The solution was stirred at -78 °C for 1 h, and was then warmed to -20 °C for 1 h. The reaction was quenched with sat. NaHCO_3 , diluted with water, and extracted 3x with ether. The organic layers were washed with brine, dried with MgSO_4 , filtered, and the solvent was removed *in vacuo*. NMR of the crude product showed product along with unreacted epoxide, which were inseparable by practical means. Thus, the crude reaction mixture was taken on to the next step in the sequence. An analytically pure sample was obtained through flash column chromatography. ^1H NMR (CDCl_3) δ 7.27 (d, $J=8.6$, 2H), 6.90 (d, $J=8.6$, 2H), 4.53 (tq, $J=1.8, 6.3$, 1H), 4.47 (s, 2H), 3.95 (m, 1H), 3.82 (s, 3H), 3.73 (ddd, $J=4.6, 6.0, 10.5$, 1H), 3.64 (ddd, $J=4.3, 8.1, 10.5$, 1H), 3.09 (t, $J=3.8$, 1H), 2.42 (ddq, $J=1.9, 6.3, 16.6$, 2H), 1.88 (m, 2H), 1.40 (d, $J=6.5$, 3H), 0.92 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (CDCl_3) δ 159.5, 130.2,

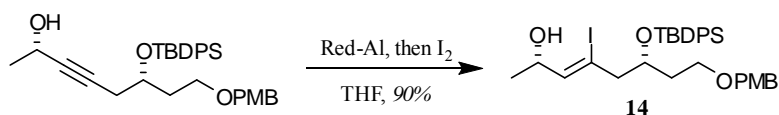
129.5, 114.0, 85.3, 80.0, 73.1, 70.0, 68.6, 59.3, 55.5, 35.5, 27.6, 26.0, 25.9, 18.5, -4.38, -4.67. IR (neat, cm^{-1}) 3449 (OH), 1612, 1513. HRMS (ESI) calc for $\text{C}_{22}\text{H}_{36}\text{O}_4\text{SiNa}^+$ 415.2275, found 415.2272. $[\alpha]_{\text{D}} -15.5$ (c 1.00, CHCl_3).

To a solution of the crude alcohol (2.00 g, 5.09 mmol), imidazole (1.04 g, 15.28 mmol), and DMAP (62 mg, 0.509 mmol) in dry DMF (12 mL) was added dropwise *tert*-butyldiphenylchlorosilane (1.44 mL, 5.60 mmol) at rt. The reaction was stirred overnight. The solution was then diluted with water and extracted 3x with ether. The combined organic extracts were washed with brine, dried with MgSO_4 , filtered, and the solvent was removed *in vacuo*. The crude product was purified using flash column chromatography (4% EtOAc/Hex) yielding pure product **13** (2.85 g, 89% over 2 steps). ^1H NMR (CDCl_3) δ 7.78 (m, 4H), 7.48 (m, 6H), 7.26 (d, $J=8.7$, 2H), 6.94 (d, $J=8.7$, 2H), 4.57 (dq, $J=4.3$, 5.7, 1H), 4.39 (m, 2H), 4.12 (m, 1H), 3.87 (s, 3H), 3.61 (td, $J=1.9$, 6.6, 2H), 2.40 (m, 2H), 2.04 (dq, $J=1.9$, 6.6, 2H), 1.45 (d, $J=6.6$, 3H), 1.16 (s, 9H), 0.99 (s, 9H), 0.19 (s, 3H) 0.17, (s, 3H). ^{13}C NMR (CDCl_3) δ 159.3, 136.19, 136.17, 134.4, 134.1, 130.9, 129.95, 129.91, 129.5, 127.89, 127.82, 127.75, 127.71, 113.9, 85.1, 80.4, 72.7, 69.4, 66.8, 59.5, 55.5, 36.4, 27.6, 27.4, 27.3, 26.2, 25.9, 19.7, 18.6, -4.22, -4.60. IR (neat, cm^{-1}) 2929, 2856, 1612, 1513, 1470. HRMS (ESI) calc for $\text{C}_{38}\text{H}_{54}\text{O}_4\text{Si}_2\text{Na}^+$ 653.3452, found 653.3452. $[\alpha]_{\text{D}} -16.24$ (c 1.00, CHCl_3).

(2*R*,6*R*,*Z*)-6-(*tert*-Butyldiphenylsilyloxy)-4-iodo-8-(4-methoxybenzyloxy)oct-3-en-2-ol, 14.



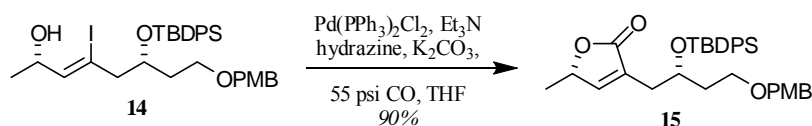
To a solution of bis-silyloxy ether **13** (2.31 g, 3.66 mmol) in ethanol (18 mL) was added pyridinium *p*-toluenesulfonate (276 mg, 1.09 mmol). The reaction was heated to 50 °C and stirred for 4h. The reaction mixture was then concentrated *in vacuo*, diluted with ether, and this suspension was diluted with water, and extracted 3x with ether. The combined organic extracts were washed with brine, dried with MgSO_4 , filtered, and the solvent was removed *in vacuo*. The crude product was purified using flash column chromatography (15% EtOAc/Hex) yielding pure product (1.80 g, 95%) as a clear oil. ^1H NMR (CDCl_3) δ 7.74 (m, 4H), 7.46 (m, 6H), 7.24 (d, $J=8.7$, 2H), 6.92 (d, $J=8.7$, 2H), 4.51 (m, 1H) 4.40 (d, $J=11.4$, 1H), 4.30 (d, $J=11.4$, 1H), 4.11 (p, $J=5.8$, 1H), 3.85 (s, 3H), 3.59 (m, 2H), 2.38 (m, 2H), 2.18 (s, 1H), 1.99 (q, $J=6.4$, 2H), 1.40 (d, $J=6.6$, 3H), 1.13 (s, 9H). ^{13}C NMR (CDCl_3) δ 159.3, 136.19, 136.18, 134.5, 133.9, 130.7, 130.0, 129.9, 129.5, 127.9, 127.8, 113.9, 84.6, 81.4, 72.7, 69.5, 66.6, 58.6, 55.5, 36.6, 27.6, 27.2, 24.7, 19.7. IR (neat, cm^{-1}) 3430 (OH), 2246, 1612, 1586, 1512. HRMS (ESI) calc for $\text{C}_{32}\text{H}_{40}\text{O}_4\text{SiNa}^+$ 539.2588, found 539.2570. $[\alpha]_{\text{D}} +9.56$ (c 1.00, CHCl_3).



To a solution of the alcohol obtained above (300 mg, 0.58 mmol) in THF (6.0 mL) was added dropwise Red-Al (283 μL of a 65% solution in hexanes, 0.92 mmol) at -10 °C. The reaction was

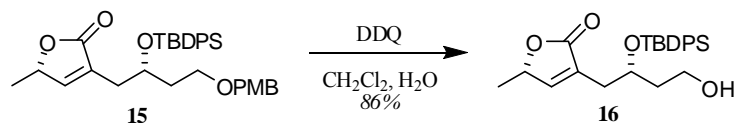
stirred at 0 °C for 24 h. The reaction was quenched with freshly distilled ethyl acetate (91 μ L, 0.92 mmol), cooled to -78 °C, and treated with a solution of iodine (221 mg, 0.871 mmol) in THF (1 mL). The reaction was allowed to warm to rt and stirred for 1h. The reaction was quenched with 1:1 sat. NaHCO₃: sat. Na₂S₂O₃, treated with sat. Rochelle's salt for 10 min, diluted with water, and extracted 3x with ether. The combined organic extracts were washed with brine, dried with MgSO₄, filtered, and the solvent was removed *in vacuo*. The crude product was purified using flash column chromatography (12% EtOAc/Hex) yielding pure product **14** (337 mg, 90%) as a clear oil. ¹H NMR (CDCl₃) δ 7.73 (dd, *J*=1.4, 8.0, 4H), 7.44 (m, 6H), 7.24 (d, *J*=8.7, 2H), 6.90 (d, *J*=8.7, 2H), 5.60 (d, *J*=7.3, 1H), 4.34 (m, 3H), 4.24 (m, 1H), 3.84 (s, 3H), 3.58 (td, *J*=6.6, 9.2, 1H), 3.49 (td, *J*=6.8, 9.3, 1H), 2.67 (m, 2H), 1.80 (m, 2H), 1.67 (s, 1H), 1.22 (d, *J*=6.4, 3H), 1.08 (s, 9H). ¹³C NMR (CDCl₃) δ 159.3, 141.1, 136.3, 136.2, 134.3, 133.9, 130.7, 130.0, 129.9, 129.5, 127.9, 127.8, 113.9, 103.8, 72.8, 72.7, 70.3, 66.6, 55.5, 52.5, 35.8, 27.3, 21.9, 19.7. IR (neat, cm⁻¹) 3413 (OH), 3068, 2929, 2855, 1612, 1586, 1512. HRMS (ESI) calc for C₃₂H₄₁O₄SiNa⁺ 667.1711, found 667.1684. [α]_D -32.2 (*c* 1.00, CHCl₃).

(5*R*)-3-((*S*)-2-(*tert*-Butyldiphenylsilyloxy)-4-(4-methoxybenzyloxy)butyl)-5-methylfuran-2(5*H*)-one, 15.



To a solution of vinyl iodide **14** (350 mg, 0.54 mmol), potassium carbonate (150 mg, 1.08 mmol), hydrazine (2 drops), and triethylamine (84 μ L, 0.59 mmol) in THF (5.5 mL) was added Pd(PPh₃)₂Cl₂ (38.1 mg, 0.054 mmol) at rt under Ar(g). The reaction was purged with CO(g) and was placed in a bomb. The pressure was adjusted to 55 psi, and the reaction was heated to an internal temperature of 45 °C. The reaction was stirred 2 days. The bomb was then slowly vented, and the solution was passed through a plug of Celite[®]. The solvent was removed *in vacuo*, and the crude product was purified using flash column chromatography (8% EtOAc/Hex) to give pure product **15** (265 mg, 90%). ¹H NMR (CDCl₃) δ 7.73 (m, 4H), 7.45 (m, 6H), 7.21 (d, *J*=8.6, 2H), 6.89 (m, 3H), 4.87 (m, 1H), 4.32 (m, 3H), 3.82 (s, 3H), 3.51 (m, 2H), 2.53 (d, *J*=4.9, 2H), 1.84 (m, 2H), 1.32 (d, *J*=6.9, 3H), 1.11 (s, 9H). ¹³C NMR (CDCl₃) δ 174.2, 159.3, 151.7, 136.16, 136.12, 134.15, 134.10, 132.4, 132.3, 130.7, 130.5, 130.04, 130.02, 129.4, 128.7, 127.9, 113.9, 77.7, 72.7, 69.7, 66.6, 55.5, 36.6, 32.6, 27.3, 19.6, 19.2. IR (neat, cm⁻¹) 1754 (CO). HRMS (ESI) calc for C₃₃H₄₀O₅SiNa⁺ 567.2537, found 567.2527. [α]_D -75.44 (*c* 1.00, CHCl₃).

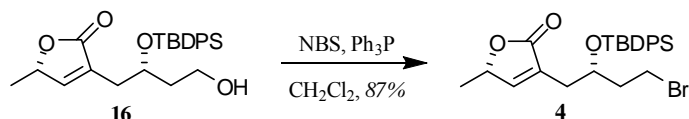
(5*R*)-3-((*S*)-2-(*tert*-Butyldiphenylsilyloxy)-4-hydroxybutyl)-5-methylfuran-2(5*H*)-one, 16.



To a solution of PMB ether **15** (350 mg, 0.64 mmol) in CH₂Cl₂ (6.1 mL) and water (306 μ L) in a 25 mL round-bottomed flask was added DDQ (219 mg, 0.96 mmol) portionwise at 0 °C. The reaction was allowed to warm to rt and stirred for 1 h. The reaction was quenched with sat.

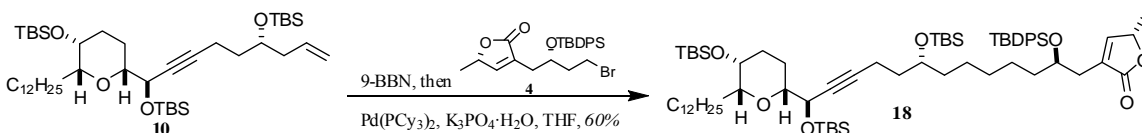
NaHCO₃, diluted with water, and extracted 3x with ether. The organic layers were washed with brine, dried with MgSO₄, filtered, and the solvent was removed *in vacuo*. The crude product was purified using flash column chromatography (30% EtOAc/Hex) yielding pure product **16** (234 mg, 86%) as a yellow oil. ¹H NMR (CDCl₃) δ 7.71 (m, 4H), 7.45 (m, 6H), 6.89 (d, *J*=1.0, 1H), 4.91 (m, 1H), 4.24 (m, 1H), 3.69 (m, 2H), 2.53 (dq, *J*=5.9, 14.9, 2H), 2.00 (brs, 1H), 1.73 (m, 2H), 1.33 (d, *J*=6.8, 3H), 1.09 (s, 9H). ¹³C NMR (CDCl₃) δ 174.3, 152.1, 136.1, 133.9, 133.7, 130.4, 130.1, 128.0, 127.9, 77.8, 70.4, 59.5, 38.5, 32.4, 27.2, 19.5, 19.1. IR (neat, cm⁻¹) 1752 (CO). HRMS (ESI) calc for C₂₅H₃₂O₄SiNa⁺ 447.1962, found 447.1955. [α]_D +10.42 (*c* 1.00, CHCl₃).

(5*R*)-3-((*S*)-4-Bromo-2-(*tert*-Butyldiphenylsilyloxy)butyl)-5-methylfuran-2(5*H*)-one, 4.



To a solution of alcohol **16** (165 mg, 0.38 mmol) and triphenylphosphine (112 mg, 0.42 mmol) in CH₂Cl₂ (3.8 mL) was added *N*-bromosuccinimide (76 mg, 0.42 mmol) slowly at 0 °C. The reaction was stirred at 0 °C for 1h. The reaction was quenched with 1:1 sat. NaHCO₃: sat. Na₂S₂O₃, diluted with water, and extracted 3x with ether. The combined organic extracts were washed with brine, dried with MgSO₄, filtered, and the solvent was removed *in vacuo*. The crude product was purified using flash column chromatography (12% EtOAc/Hex) yielding pure product **4** (164 mg, 87%) as a yellow oil. ¹H NMR (CDCl₃) δ 7.72 (m, 4H), 7.46 (m, 6H), 6.83 (d, *J*=1.2, 1H), 4.91 (dq, *J*=1.3, 6.7, 1H), 4.19 (m, 1H), 3.45 (dt, *J*=1.9, 7.1, 2H), 2.47 (d, *J*=5.9, 2H), 2.08 (qd, *J*=6.6, 13.2, 1H), 1.96 (dtd, *J*=4.9, 7.2, 12.0, 1H), 1.34 (d, *J*=6.8, 3H), 1.09 (s, 9H). ¹³C NMR (CDCl₃) δ 173.9, 152.0, 136.1, 136.0, 133.8, 133.5, 130.2, 130.1, 130.0, 128.0, 127.9, 77.8, 70.7, 39.5, 32.0, 29.9, 27.2, 19.6, 19.2. IR (neat, cm⁻¹) 1754 (CO). HRMS (ESI) calc for C₂₅H₃₁BrO₃SiNa⁺ 509.1118, found 509.1105. [α]_D +32.5 (*c* 1.00, CHCl₃).

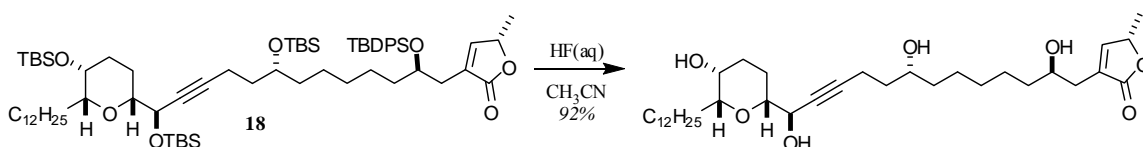
(*S*)-3-((2*R*,8*R*,13*R*)-8,13-bis(*tert*-Butyldimethylsilyloxy)-13-((2*R*,5*R*,6*R*)-5-(*tert*-butyldimethylsilyloxy)-6-dodecyltetrahydro-2*H*-pyran-2-yl)-2-(*tert*-butyldiphenylsilyloxy)tridec-11-ynyl)-5-methylfuran-2(5*H*)-one, 18.



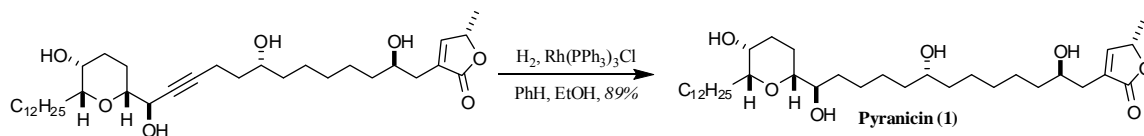
In a glove-box, to neat alkene **10** (50 mg, 0.065 mmol) in a small scintillation vial was added freshly prepared 9-BBN solution (0.5 M, 144 μL, 0.072 mmol made from 9-BBN dimer and degassed THF). The solution was stirred overnight. The resulting trialkylborane solution was then transferred to a vial containing Pd(PCy₃)₂ (8.7 mg, 0.013 mmol) and K₃PO₄·H₂O (20 mg, 0.085 mmol). A solution of bromide **4** (38.2 mg, 0.078 mmol) in THF (100μL) was then added. The reaction was stirred at rt for 24h. The vial was then removed from the glove-box, and the solution was then diluted with hexanes, filtered through a plug of Celite(R), and the solvent was removed *in vacuo*. The crude product was purified using flash column chromatography (3%

EtOAc/Hex) yielding pure product **18** (46 mg, 60%) as a yellow oil. ^1H NMR (CDCl_3) δ 7.68 (m, 4H), 7.43 (m, 6H), 6.94 (d, $J=0.7$, 1H), 4.91 (m, 1H), 4.31 (d, $J=6.7$, 1H), 4.04 (m, 1H), 3.68 (m, 1H), 3.59 (s, 1H), 3.31 (ddd, $J=1.5$, 6.7, 10.7, 1H), 3.21 (dd, $J=3.5$, 8.4, 1H), 2.46 (m, 2H), 2.23 (dd, $J=7.2$, 13.0, 2H), 1.87 (m, 1H), 1.65 (m, 7H), 1.29-1.41 (m, 36H), 1.07 (s, 9H), 0.92 (m, 27H), 0.09 (m, 18H). ^{13}C NMR (CDCl_3) δ 174.2, 151.4, 136.1, 136.0, 134.3, 130.9, 129.93, 129.90, 127.8, 86.0, 80.8, 80.1, 79.4, 71.9, 71.7, 71.2, 67.3, 66.7, 37.1, 36.6, 36.0, 32.4, 32.1, 32.0, 31.6, 30.0, 29.9, 29.6, 27.2, 26.1, 26.0, 25.9, 25.2, 22.9, 21.4, 19.5, 19.1, 18.6, 18.39, 18.31, 15.1, 14.4, -4.1, -4.2, -4.4, -4.5, -4.6. IR (neat, cm^{-1}) 2926, 1855, 1761 (CO). HRMS (ESI) calc for $\text{C}_{69}\text{H}_{120}\text{O}_7\text{Si}_4\text{Na}^+$ 1195.8003, found 1195.7992. $[\alpha]_D -5.82$ (c 1.00, CHCl_3).

Pyranicin, 1.



To a solution of silyl ether **18** (28 mg, 0.024 mmol) in acetonitrile (2.5 mL) in a teflon vial was added HF (100 μL , 48% aq. sol.). The reaction was stirred at rt overnight. The reaction was quenched with sat. NaHCO_3 , diluted with water, and extracted 3x with EtOAc. The combined organic layers were then washed with brine, dried with MgSO_4 , filtered, and concentrated to give the crude tetraol. Purification using flash column chromatography (90% EtOAc/Hex) gave the desired tetraol product (13 mg, 92%) as a clear oil. ^1H NMR (CDCl_3) δ 7.22 (d, $J=1.3$, 1H), 5.09 (m, 1H), 4.29 (d, $J=7.1$, 1H), 3.87 (m, 1H), 3.76 (m, 1H), 3.66 (m, 1H), 3.41 (m, 2H), 2.75 (m, 1H), 2.56 (m, 1H), 2.41 (m, 4H), 2.18 (s, 1H), 2.05 (m, 1H), 1.86 (brs, 1H), 1.72 (m, 3H), 1.64 (m, 3H), 1.49 (m, 4H), 1.46 (d, $J=6.8$, 3H), 1.38 (m, 27H), 0.90 (t, $J=6.8$, 3H). ^{13}C NMR (CDCl_3) δ 174.9, 152.1, 131.3, 86.8, 80.9, 80.5, 78.2, 71.2, 70.0, 69.9, 66.1, 66.0, 37.4, 37.3, 35.8, 33.6, 32.1, 31.7, 30.6, 29.9, 29.88, 29.86, 29.80, 29.5, 25.7, 25.69, 25.65, 22.9, 21.4, 19.3, 15.6, 14.3. IR (neat, cm^{-1}) 3399 (OH), 2923, 2852, 1739, 1456. HRMS (ESI) calc for $\text{C}_{35}\text{H}_{60}\text{O}_7\text{Li}^+$ 599.4494, found 599.4520. $[\alpha]_D +2.24$ (c 1.00, CHCl_3).



To a degassed solution of the tetraol alkyne obtained above (5.0 mg, 0.0084 mmol) in benzene (1.2 mL) and EtOH (1.2 mL) was added Wilkinson's catalyst (7.8 mg, 0.0084 mmol). The solution was frozen (N_2), evacuated, and then purged with hydrogen. The reaction was stirred under a balloon of hydrogen for 14 h. The reaction was then purged with argon, the solvent was removed *in vacuo*, and the crude product was purified using flash column chromatography (EtOAc) to yield pure pyranicin **1** (4.5 mg, 89%). ^1H NMR (CDCl_3) δ 7.22 (d, $J=1.0$, 1H), 5.09 (m, 1H), 3.88 (m, 1H), 3.63 (m, 2H), 3.48 (m, 1H), 3.37 (dd, $J=5.7$, 7.6, 1H), 3.22 (ddd, $J=2.0$, 6.9, 9.6, 1H), 2.56 (m, 1H), 2.43 (m, 1H), 2.03 (m, 1H), 1.74-1.24 (m, 47H), 1.46 (d, $J=6.8$, 3H), 0.91 (t, $J=6.9$, 3H). ^{13}C NMR (CDCl_3) δ 174.9, 152.1, 131.4, 81.4, 80.2, 78.2, 74.2, 72.0, 70.1, 66.3, 37.49, 37.57, 37.52, 33.6, 32.4, 32.1, 31.8, 30.7, 29.90, 29.89, 29.87, 29.85, 29.83, 29.80, 29.7, 29.5, 25.85, 25.81, 25.74, 25.5, 22.9, 21.8, 19.3, 14.3. IR (neat, cm^{-1}) 3390 (OH), 2924,

2853, 1740, 1516, 1463, 1260. HRMS (ESI) calc for $C_{35}H_{64}O_7Na^+$ 619.4544, found 619.4551.
[α]_D +24.8 (*c* 0.20, CHCl₃), +8.8 (*c* 0.20, MeOH).