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A C_2 -SYMMETRIC POOL BASED SYNTHESIS OF THE FURANOSIDE OF HYGROMYCIN A

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Abstract — The readily available and inexpensive D-tartaric acid serves as the chiral building block for synthesis of the furanoside of hygromycin A. Key to our successes in the asymmetric synthesis of the furanose segment was the melding of several key reactions, such as the successful application of the monosilylation of C_2 -symmetric diol, diastereocontrolled di(2-propenyl)zinc addition to the aldehyde, and TMSCl-MeOH promoted desilylation, acetal-cleavage, and intramolecular esterification in one-step.

Hygromycin A **1** was shown to have a relative broad spectrum of activity such as activity against Gram-positive and Gram-negative bacterial and high hemagglutination inactivation activity and high antitreponemal activity.¹ The complex structure of hygromycin A is composed of three distinct domains, namely the furanose unit **2**, the phenol unit **3**, and the aminocyclitol unit **4**, that are revealed by retrosynthetic cleavage of the indicated bonds in **1** (Figure 1). Despite the unique structure and interesting

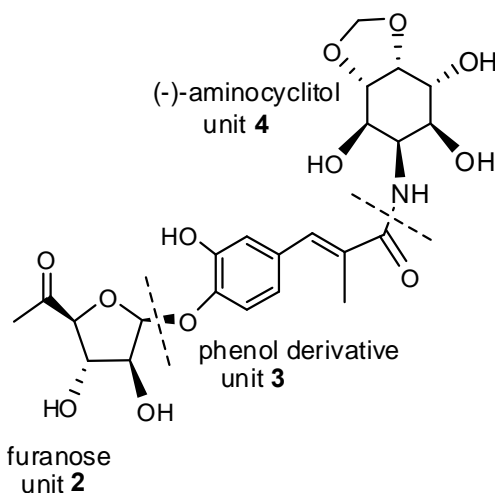
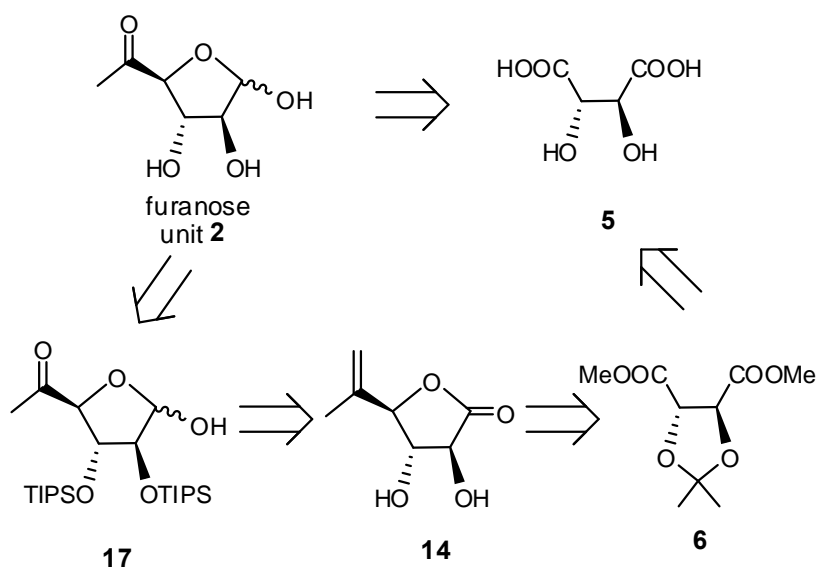


Figure 1. Structure of hygromycin A (**1**)

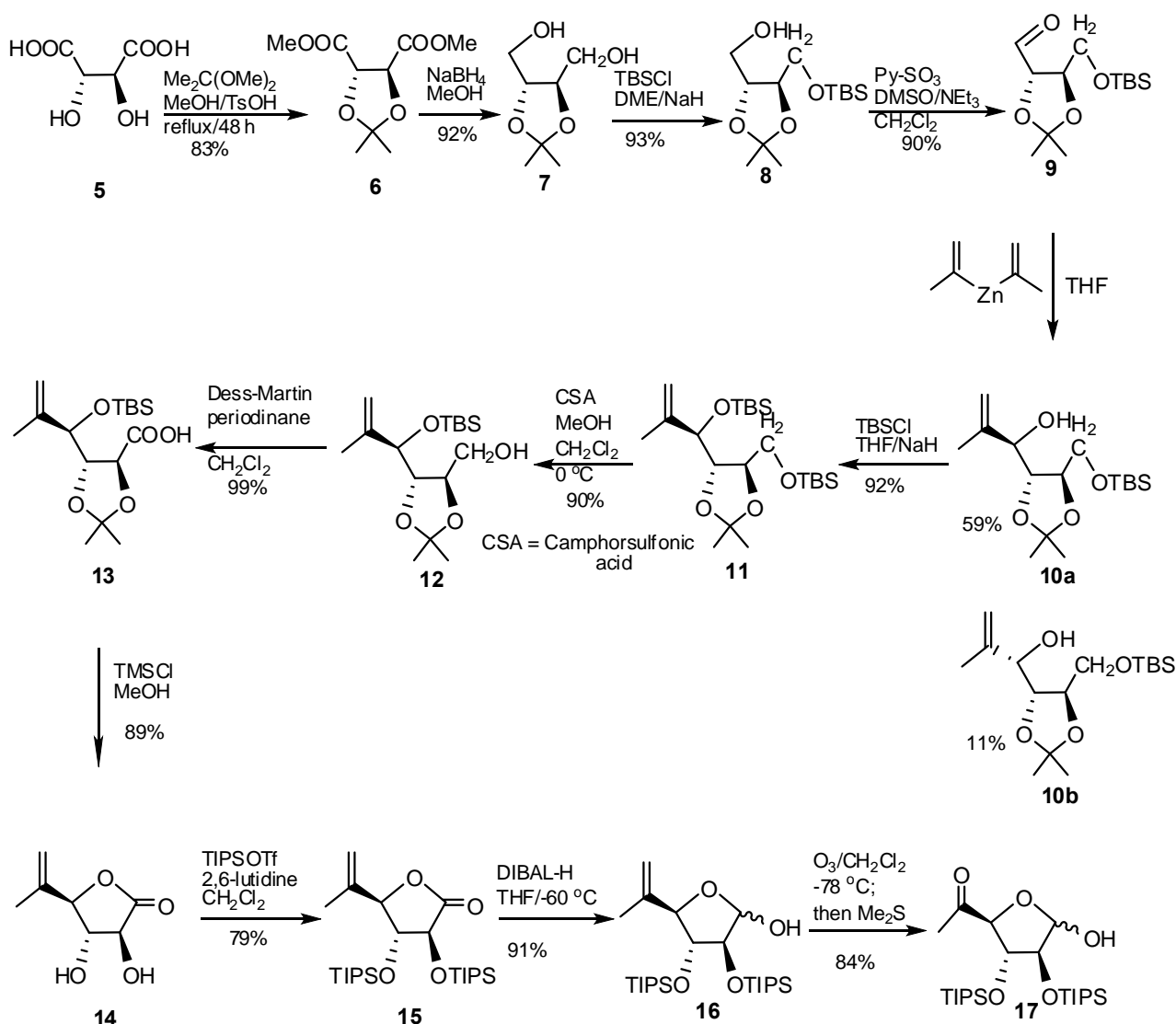
biological activities, limited enantioselective syntheses of the furanose unit **2** have been reported. Asymmetric synthesis of furanose derivative from D-arabinose² and D-glucose derivative appeared in the literature.³ On the other hand, an elegant synthesis of C-2-epi-furanoside employed a desymmetrization of meso-type enedibenzoate has been reported by Trost et al in 2002.⁴ We have previously described a flexible synthetic strategy that leads from a C_2 -symmetric L-tartaric acid to many aminocyclitol analogues.⁵ The successful creation of this convenient general strategy illustrates the importance of C_2 symmetry element on the development of new strategies for the asymmetric synthesis of natural products. To further evaluate the capacity of C_2 -symmetric chiral substrates we developed a new approach to the furanose unit **2** based upon the utilization of the readily available and inexpensive D-tartaric acid as a chiral building block. Scheme 1 outlines, in retrosynthetic format, the overall plan for the construction of the furanose unit **2** starting from D-tartaric acid **5**. Thus, furanose unit **2** was expected to arise from bis(triisopropylsiloxy)furanose **17**. The origins of **17** were then traced to 2,3-dihydroxy-4-(2-propenyl)- γ -butyrolactone **14**. Finally, **14** was envisioned to arise from the tartaric acid-derived isopropylidene tartrate **6** by standard functional-group manipulations.



Scheme 1

Following the reported procedures, the synthesis commenced with the commercially available D-tartaric acid **5** or its derivative dimethyl 2,3-*O*-isopropylidene tartrate **6** (Scheme 2). Reduction of tartrate **6** with NaBH_4 , followed by a monosilylation of the hydroxyl group, afforded the desired silyloxy alcohol **8** in a 93% yield.⁶ Subsequent oxidation with dimethyl sulfoxide-pyridine-sulfur trioxide proceeded without complication to give silyloxy aldehyde **9** in a 90% yield.⁷ Controlled coupling of aldehyde **9** with di(2-propenyl)zinc in THF solution at -78°C gave a chromatographically separable mixture of allylic alcohols

10a and **10b** in 70% yield with >6:1 diastereoselectivity.⁸ Silylation of the secondary hydroxyl group in **10a** with *t*-butyldimethylchlorosilane led to disilyl ether **11** in 92% yield. Notably, the *t*-butyldimethylsilyl (TBS) protecting group onto the primary hydroxyl was surprisingly labile under mild acidic conditions, and was efficiently removed by a catalytic amount of camphorsulfonic acid at 0 °C in 1:1 methanol-CH₂Cl₂ leading to a 90% yield of alcohol **12**. Surprisingly, the treatment of alcohol **12** with Dess-Martin periodinane⁹ in CH₂Cl₂ produced carboxylic acid **13** instead of the aldehyde in 99% yield. The stage was set for removal of the protecting groups and effecting the direct coupling of acid with hydroxyl group. Gratifyingly, exposing **13** to trimethylchlorosilane in methanol at room temperature for



Scheme 2

3 h smoothly and cleanly effected the desired desilylation, acetal-cleavage, and intramolecular esterification in one-step to give dihydroxy- γ -butyrolactone **14** in 89% isolated yield. Finally, triisopropylsilyl

protection of the diol in **14**,² followed by DIBAL-H promoted reduction of lactone and ozone-mediated oxidative cleavage of carbon-carbon double bond provided the desired furanose **17** as an anomeric mixture, which served as an important furanose unit for hygromycin A synthesis.² This synthesis based on a C_2 -symmetric pool of chiral substrates requires 12 steps from cheap D-tartaric acid to give furanose **17** in 17.2% overall yield.

In summary, this C_2 -symmetric chiral pool synthesis represents a new approach to the furanose unit **2**. The successful creation of this synthetic strategy illustrate the importance of the presence of a C_2 symmetry element within the chiral pool. Key to our successes in the synthesis was the melding of several key reactions, such as the successful application of the monosilylation of C_2 -symmetric diol, diastereocontrolled di(2-propenyl)zinc addition to the aldehyde, and TMSCl-MeOH promoted desilylation, acetal-cleavage, and intramolecular esterification in one-step.

EXPERIMENTAL

Dichloromethane was distilled from P_2O_5 prior to use. THF and DME were distilled from Na prior to use. Commercially available TBSCl, TIPSOTf, and DIBAL-H were used as received. Chromatography was performed on silica gel 60 (230-400 mesh). All reactions were carried out under an atmosphere of argon. 1H and ^{13}C NMR spectra were recorded on a Varian VXR-400 MHz spectrometer at ambient temperature. High-resolution mass spectra were determined on a Jeol JMS-HX 110 spectrometer. Optical rotations were obtained on an Optical Activity AA-100 polarimeter.

Dimethyl 2,3-*O*-isopropylidene tartrate (6).^{5,10} D-tartaric acid **5** (101 g, 673 mmol) was added to a solution of MeOH (40 mL) and *p*-toluenesulfonic acid (400 mg, 2.1 mmol) in dimethoxypropane (190 mL) at room temperature. After stirring for 1.5 h at reflux, an additional dimethoxypropane (95 mL) was added to the reaction mixture, then stirred for an additional 12 h at reflux. Any volatile compounds (dimethoxypropane, and MeOH) was removed by simple distillation and the resulting crude product was washed with saturated aqueous potassium carbonate (2x30 mL). After drying, solvent evaporation, and distillation at reduced pressure, dimethyl tartrate **6** (121.9 g, 558.6 mmol, 83%) was obtained as a colorless oil: bp 110-112 °C (2 mm), [lit.,¹ bp 100-110 (0.7 mm); lit.,² bp 82-90 (0.02 mm)]; R_f = 0.5 (hexane:EtOAc 3:1); 1H NMR (400 MHz, $CDCl_3$): δ 4.76 (s, 2H), 3.78 (s, 6H), 1.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0 (C), 113.8 (C), 76.9 (CH), 52.7 (CH_3), 26.2 (CH_3, CH_3).

2,3-*O*-Isopropylidene-D-threitol (7).¹¹ To a solution of D-tartrate **6** (9.34 g, 42.8 mmol) in MeOH (150 mL) at 0 °C was slowly added $NaBH_4$ (3.24 mL, 85.7 mmol) over 15 min. After stirring 2 h at room temperature, the resulting mixture was cooled to 0 °C. The reaction was carefully quenched with brine (20 mL) and the resulting suspension was stirred for 1 h before it was filtered through a pad of Celite, concentrated in vacuo, and extracted with EtOAc (3x100 mL). After drying ($MgSO_4$) and solvent

evaporation, the residue was flash chromatographed with EtOAc to give threitol **7** (6.38 g, 39.4 mmol, 92%), $R_f = 0.5$ (silica gel, EtOAc); $[\alpha]_D^{25} +4.3^\circ$ (c 1.4, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 4.01-3.99 (m, 2H), 3.81-3.78 (m, 2H), 3.70-3.66 (m, 2H), 1.42 (s, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 109.3, 78.1, 62.0, 27.0; IR (film cm^{-1}) ν 3408, 2936, 1087, 883; HRMS (EI) m/e : Calcd for $\text{C}_7\text{H}_{14}\text{O}_4$: 162.0893. Found 162.0887.

((4R,5R)-5-((tert-Butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (8).¹¹ To a suspension consisting of NaH (576 mg, 24.0 mmol) and DME (10 mL) at 0 °C was added a solution of threitol **7** (2.33 g, 14.4 mmol) in DME (30 mL). After 5 min at 0 °C, a solution of TBSCl (2.17 g, 14.4 mmol) in DME (20 mL) was added dropwise and the reaction mixture was stirred at room temperature for 4 h. The reaction was carefully quenched with water (30 mL) and extracted with EtOAc (3x50 mL). After drying (MgSO_4) and solvent evaporation, the residue was flash chromatographed with 15:1 hexane:EtOAc to give silyloxy alcohol **8** (3.69 g, 13.4 mmol, 93%), $R_f = 0.5$ (silica gel, hexane:EtOAc 5:1); $[\alpha]_D^{25} +5.6$ (c 1.8, CHCl_3); $^1\text{H NMR}$ (400MHz, CDCl_3): δ 3.97 (dt, $J = 8.0, 4.4$ Hz, 1H), 3.88-3.83 (m, 2H), 3.78-3.62 (m, 3H), 2.35 (dd, $J = 8.0, 4.4$ Hz, 1H), 1.40 (s, 3H), 1.38 (s, 3H), 0.88 (s, 9H), 0.07 (s, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 109.0, 80.0, 78.0, 63.6, 62.7, 27.0, 26.8, 25.8$ (3C), 18.2, -5.5, -5.6; IR (film cm^{-1}) ν 3454, 2955, 1254, 1084, 833; HRMS (FAB) m/e : Calcd for $\text{C}_{13}\text{H}_{29}\text{O}_4\text{Si}$: 277.1835. Found 277.1828.

(4S,5R)-5-(((tert-Butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (9).^{4,5,6} To a solution of $\text{Py}\cdot\text{SO}_3$ (6.92 g, 43.5 mmol) in CH_2Cl_2 (15 mL) at room temperature was added DMSO (7.5 mL, 105 mmol) and Et_3N (7.5 mL, 54 mmol). The mixture was cooled to 0 °C and added a solution of silyloxy alcohol **8** (3.00 g, 10.9 mmol) in CH_2Cl_2 (60 mL). The mixture was stirred at 0 °C for 4 h followed by dropwise addition of water (30 mL) and extracted with CH_2Cl_2 (3x50 mL). After drying (MgSO_4) and solvent evaporation, the residue was flash chromatographed with 15:1 hexane:EtOAc to give silyloxy aldehyde **9** (2.68 g, 9.81 mmol, 90%), $R_f = 0.5$ (silica gel, hexane:EtOAc 3:1) $[\alpha]_D^{25} -24$ (c 3.0, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 9.74 (d, $J = 1.6$ Hz, 1H), 4.31 (dd, $J = 7.2, 1.6$ Hz, 1H), 4.10 (dt, $J = 7.2, 4.4$ Hz, 1H), 3.79 (dd, $J = 4.4, 1.6$ Hz, 2H), 1.45 (s, 3H), 1.39 (s, 3H), 0.87 (s, 9H), 0.06 (s, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 200.7, 111.4, 82.0, 77.6, 62.9, 26.8, 26.3, 25.8$ (3C), 18.3, -5.4, -5.5; IR (film cm^{-1}) ν 1737, 1255, 1084, 838; HRMS (FAB) m/e : Calcd for $\text{C}_{13}\text{H}_{27}\text{O}_4\text{Si}$: 275.1679. Found 275.1667.

(R)-1-((4R,5R)-5-((tert-Butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylprop-2-en-1-ol (10a) and **(S)-1-((4R,5R)-5-((tert-Butyldimethylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylprop-2-en-1-ol (10b)**. To a solution of silyloxy aldehyde **9** (2.38 g, 8.65 mmol) in THF (30 mL) at -78 °C was added di(2-propenyl)zinc in THF (86.5 mL, 0.4 M, 34.6 mmol) over 20 min. After stirring for an additional 1 h at -78 °C, the solution was then allowed to warm to room temperature and

stirred for an additional 9 h. The mixture was carefully quenched with H₂O, filtered through Celite to remove solids, concentrated in vacuo, and extracted with EtOAc (3x50 mL). After drying (MgSO₄) and solvent evaporation, the residue was flash chromatographed with 12:1 hexane:EtOAc to give allylic alcohol **10a** and **10b** (1.92 g, 6.06 mmol, 70%). The title compound as a >6:1 mixture of diastereomers as determined by NMR integration of the olefinic protons: 5.09 (s, ~0.859H) and 5.01 (s, ~0.141H) (1H total).

10a: $R_f = 0.60$ (hexane:EtOAc 5:1); $[\alpha]_D^{25} -3.1$ (c 1.3, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 5.09 (s, 1H), 4.96 (s, 1H), 4.13 (d, $J=4.4$ Hz, 1H), 3.99-3.93 (m, 2H), 3.76-3.66 (m, 2H), 3.20 (s, 1H), 1.77 (s, 3H), 1.40 (s, 3H), 1.38 (s, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 143.5, 112.8, 108.9, 79.3, 78.6, 74.9, 63.9, 26.9, 26.8, 25.8$ (3C), 18.5, 18.3, -5.5, -5.6; IR (film cm⁻¹) ν 3455, 2955, 1651, 1373, 1254, 1079, 837; HRMS (FAB) m/e : Calcd for C₁₆H₃₃O₄Si : 317.2148 found 317.2139.

10b: $R_f = 0.58$ (hexane:EtOAc 5:1); $[\alpha]_D^{25} +10.0$ (c 1.2, CHCl₃); ¹H NMR (400MHz, CDCl₃): δ 5.01 (s, 1H), 4.93 (s, 1H), 4.10-4.03 (m, 2H), 3.96-3.92 (m, 1H), 3.70 (d, $J = 4.8$ Hz, 2H), 2.53 (d, $J = 6.4$ Hz, 1H), 1.77 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H), 0.87 (s, 9H), 0.04 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 144.5, 112.9, 109.4, 79.2, 78.0, 75.1, 63.4, 27.3, 27.2, 25.9$ (3C), 18.5, 18.3, -5.4, -5.5; IR (film cm⁻¹) ν 3484 ,2931, 1650, 1373, 1254, 1082, 838; HRMS (FAB) m/e : Calcd for C₁₆H₃₃O₄Si: 317.2149. Found 317.2162.

tert-Butyl((4R,5S)-5-((R)-1-(tert-butyldimethylsilyloxy)-2-methylallyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)dimethylsilane (11). To a suspension consisting of NaH (385 mg, 16.0 mmol) and THF (10 mL) at 0 °C was added a solution of allylic alcohol **10a** (1.69 g, 6.03 mmol) in THF (20 mL). After 5 min at 0 °C, a solution of TBSCl (1.45 g, 9.63 mmol) in THF (15 mL) was added dropwise and the reaction mixture was stirred at room temperature for 2 h. The reaction was carefully quenched with water (25 mL) and extracted with CH₂Cl₂ (3x50 mL). After drying (MgSO₄) and solvent evaporation, the residue was flash chromatographed with 35:1 hexane:EtOAc to give disilyl ether **11** (2.12 g, 5.55 mmol, 92%), $R_f = 0.67$ (hexane:EtOAc 30:1); $[\alpha]_D^{25} +4.0$ (c 2.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 5.01 (s, 1H), 4.91 (s, 1H), 4.12 (d, $J = 5.6$ Hz, 1H), 4.05-4.02 (m, 1H), 3.97 (q, $J = 7.2$ Hz, 1H), 3.81 (dd, $J = 11.2, 2.4$ Hz, 1H), 3.57 (dd, $J = 11.2, 4.0$ Hz, 1H), 1.73 (s, 3H), 1.38 (s, 6H), 0.88 (s, 18H), 0.06 (s, 3H), 0.04 (s, 6H), 0.00 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 144.9, 113.2, 108.9, 79.4, 77.1, 76.9, 64.1, 27.4, 27.2, 25.9$ (3C), 25.8 (3C), 18.4, 18.3, 18.2, -4.7, -4.8, -5.3, -5.4; IR (film cm⁻¹) ν 2931, 1651, 1378, 1254, 1081, 837; HRMS (FAB) m/e : Calcd for C₂₂H₄₇O₄Si₂: 431.3013. Found 431.3001.

((4R,5S)-5-((R)-1-(tert-Butyldimethylsilyloxy)-2-methylallyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-methanol (12). To a solution of disilyl ether **11** (1.88 g, 4.36 mmol) in MeOH:CH₂Cl₂ 1:1 (30 mL) at 0 °C was added CSA (203 mg, 0.87 mmol). After stirring for an additional 3 h at 0 °C, the reaction mixture was quenched with saturated aqueous sodium carbonate and extracted with EtOAc (3x30 mL). After

drying (MgSO_4) and solvent evaporation, the residue was flash chromatographed with 8:1 hexane:EtOAc to give alcohol **12** (1.24 g, 3.92 mmol, 90%). $R_f = 0.45$ (hexane:EtOAc 5:1); $[\alpha]_D^{25} +6.9^\circ$ (c 1.6, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.02 (s, 1H), 4.93 (s, 1H), 4.10-4.06 (m, 2H), 3.85 (t, $J = 6.4$ Hz, 1H), 3.78 (ddd, $J = 8.4, 5.2, 3.2$ Hz, 1H), 3.59 (ddd, $J = 12.0, 7.6, 3.2$ Hz, 1H), 1.99 (dd, $J = 7.6, 5.2$ Hz, 1H), 1.73 (s, 3H), 1.39 (s, 6H), 0.87 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 144.7, 113.7, 109.1, 79.3, 77.6, 77.5, 63.6, 27.2$ (2C), 25.9 (3C), 18.2, 18.1, -4.7, -4.9; IR (film cm^{-1}) ν 3484, 2932, 1651, 1254, 1073, 837; HRMS (FAB) m/e : Calcd for $\text{C}_{16}\text{H}_{33}\text{O}_4\text{Si}$: 317.2148. Found 317.2154.

(4S,5S)-5-((R)-1-(tert-Butyldimethylsilyloxy)-2-methylallyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (13). Dess-Martin periodinane (1.18 g, 2.78 mmol) was added to a solution of alcohol **12** (293 mg, 0.93 mmol) in CH_2Cl_2 (15 mL). Stirring at room temperature for 12 h, filtration through Celite, evaporation, and flash chromatography (2:1 hexane:EtOAc), acid **13** (303 mg, 0.92 mmol, 99%) was obtained. $R_f = 0.73$ (hexane:EtOAc 1:1); $[\alpha]_D^{25} +3.8^\circ$ (c 1.3, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.05 (s, 1H), 4.96 (s, 1H), 4.47 (d, $J = 6.0$ Hz, 1H), 4.32 (t, $J = 6.0$ Hz, 1H), 4.17 (d, $J = 6.0$ Hz, 1H), 1.76 (s, 3H), 1.46 (s, 3H), 1.38 (s, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): $\delta = 175.0, 143.9, 114.1, 111.9, 80.2, 77.2, 75.6, 26.9, 25.8$ (3C), 25.6, 18.2 (2C), -4.7, -5.0; IR (film cm^{-1}) ν 3076, 2932, 1726, 1654, 1382, 1256, 1084, 838; HRMS (FAB) m/e : Calcd for $\text{C}_{16}\text{H}_{31}\text{O}_5\text{Si}$: 331.1941. Found 331.1947.

(3S,4S,5S)-3,4-Dihydroxy-5-(prop-1-en-2-yl)dihydrofuran-2(3H)-one (14). To a solution of acid **13** (1.59 g, 4.89 mmol) in MeOH (30 mL) was added TMSCl (3 mL, 24.0 mmol). After stirring for an additional 3 h at room temperature, the reaction mixture was quenched with saturated aqueous sodium carbonate (10 mL) and extracted with EtOAc (3x50 mL). After drying (MgSO_4) and solvent evaporation, the residue was flash chromatographed with 2:1 hexane:EtOAc to give dihydroxy- γ -butyrolactone **14** (678 mg, 4.35 mmol, 89%). $R_f = 0.75$ (EtOAc); $[\alpha]_D^{20} +21.3^\circ$ (c 0.8, CH_3OH); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.15 (s, 1H), 5.07 (s, 1H), 4.57 (d, $J = 8.8$ Hz, 1H), 4.54 (d, $J = 8.8$ Hz, 1H), 4.21 (t, $J = 8.8$ Hz, 1H), 1.76 (s, 3H); ^{13}C (100 MHz, CDCl_3): δ 174.6, 138.7, 116.1, 83.2, 76.4, 74.7, 17.1; IR (film cm^{-1}) ν 3385, 2923, 1773, 1308, 1145, 964; HRMS (EI) m/e : Calcd for $\text{C}_7\text{H}_{10}\text{O}_4$: 158.0579. Found 158.0582.

(3S,4R,5R)-5-(Prop-1-en-2-yl)-3,4-bis((triisopropylsilyl)oxy)dihydrofuran-2(3H)-one (15). To a solution of dihydroxy- γ -butyrolactone **14** (420 mg, 2.66 mmol) in CH_2Cl_2 (10 mL) were added 2,6-lutidine (1.42 g, 13.3 mmol) and TIPSOTf (2.44 g, 7.97 mmol). After stirring for an additional 3 h at room temperature, the reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL) with CH_2Cl_2 (3x30 mL). After drying (MgSO_4) and solvent evaporation, the residue was flash chromatographed with 30:1 hexane:EtOAc to give disilyl ether **15** (988 mg, 2.10 mmol, 79%). $R_f = 0.63$ (hexane:EtOAc 30:1); $[\alpha]_D^{25} -13.1$ (c 7.5, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 5.10 (d, $J = 0.8$ Hz,

1H), 5.01 (d, $J = 0.8$ Hz, 1H), 4.60 (d, $J = 4.0$ Hz, 1H), 4.34 (d, $J = 4.0$ Hz, 1H), 4.29 (dd, $J = 4.0, 4.0$ Hz, 1H), 1.77 (s, 3H), 1.23-1.01(m, 42H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 173.8, 139.3, 115.7, 87.8, 77.8, 76.6, 18.0$ (6C), 17.7, 12.8 (6C), 12.6 (6C); IR (film cm^{-1}) ν 2945, 2868, 1798, 1463, 1140, 883, 683; HRMS (ESI) m/e : Calcd for $\text{C}_{25}\text{H}_{50}\text{O}_4\text{Si}_2$: 470.3242. Found 470.3260.

(3S,4R,5R)-5-(Prop-1-en-2-yl)-3,4-bis((triisopropylsilyl)oxy)tetrahydrofuran-2-ol (16). To a solution of disilyl ether **15** (405 mg, 0.86 mmol) in CH_2Cl_2 (5 mL) at -60 °C was added DIBAL-H (2.2 mL, 20% in hexane, 2.2 mmol) over 15 min. The mixture was stirred at -60 °C for 1 h followed by dropwise addition of water (1 mL). After stirring for an additional 30 min at -60 °C, the solution was added saturated aqueous sodium carbonate (5 mL) and allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (3x10 mL). After drying (MgSO_4) and solvent evaporation, the residue was flash chromatographed with 20:1 hexane:EtOAc to give hemiacetal **16** (370 mg, 0.78 mmol, 91%). The title compound as a >5.5:1 mixture of diastereomers as determined by NMR integration of the anomeric protons: 5.19 (dd, $J = 0.8, 11.6$ Hz, 0.152H) and 5.48 (dd, $J = 12.8, 3.2$ Hz, 0.848H) (1 H total). $R_f = 0.65$ (hexane:EtOAc 10:1); α -**16** ^1H NMR (400 MHz, CDCl_3): δ 5.19 (dd, $J = 0.8, 11.6$ Hz, 1H), 5.05 (s, 1H), 4.85 (s, 1H), 4.63 (s, 1H), 4.17 (d, $J = 0.8$ Hz, 1H), 4.13 (d, $J = 0.8$ Hz, 1H), 3.72 (d, $J = 11.6$ Hz, 1H), 1.75 (s, 3H), 1.15-0.98 (m, 42H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 142.2, 112.7, 104.1, 91.2, 82.0, 81.0, 19.0, 17.9$ (12C), 12.1 (6C); β -**16** ^1H NMR (400 MHz, CDCl_3): δ 5.48 (dd $J = 12.8, 3.2$ Hz, 1H), 5.13 (s, 1H), 4.85 (s, 1H), 4.26 (s, 1H), 4.23 (s, 1H), 3.98 (dd, $J = 3.2, 0.8$ Hz, 1H), 3.64 (d, $J = 12.8$ Hz, 1H), 1.75 (s, 3H), 1.15-0.98 (m, 42H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 142.4, 112.1$ (br), 98.5, 88.3, 79.7, 78.3, 19.3, 18.0 (12C), 12.5 (3C), 12.2 (3C); IR (film cm^{-1}) ν 2945, 2868, 1650, 1464, 1126, 1068, 883, 682; HRMS (ESI) m/e : Calcd for $\text{C}_{25}\text{H}_{51}\text{O}_4\text{Si}_2$: 471.3320. Found 471.3340.

1-((2S,3R,4S)-5-Hydroxy-3,4-bis((triisopropylsilyl)oxy)tetrahydrofuran-2-yl)ethanone (17).² A solution of hemiacetal **16** (367 mg, 0.78 mmol) in dry CH_2Cl_2 (10 mL) was cooled to -78 °C and ozone was bubbled through until a blue color appeared. The excess ozone was removed by a flow of dry N_2 and quenched by Me_2S (1 mL). The resulting mixture was allowed to warm to room temperature and was stirred for 12 h. After concentration on a rotary evaporator the residue was flash chromatographed with 20:1 hexane:EtOAc to give furanose **17** (309 mg, 0.66 mmol, 84%). The title compound as a >6.5:1 mixture of diastereomers as determined by NMR integration of the anomeric protons: 5.25 (d, $J = 12.8$ Hz, 0.132H) and 5.60 (d, $J = 13.2, 2.8$ Hz, 0.868H) (1 H total). $R_f = 0.61$ (hexane:EtOAc 10:1); α -**17** ^1H NMR (400MHz, CDCl_3): δ 5.25 (d, $J = 12.8$ Hz, 1H), 4.52 (s, 1H), 4.49 (s, 1H), 4.08 (s, 1H), 4.03 (d, $J = 12.8$ Hz, 1H), 2.21 (s, 3H), 1.16-1.00 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 209.0, 105.0, 91.8, 81.0, 78.9, 26.5, 17.7$ (3C), 17.8 (3C), 11.9 (6C), 11.8 (6C); β -**17** ^1H NMR (400MHz, CDCl_3): δ 5.60 (d, $J = 13.2, 2.8$ Hz, 1H), 4.56 (s, 1H), 4.12 (s, 1H), 3.89 (dd, $J = 1.2, 2.8$ Hz, 1H), 3.65 (d, $J = 13.2$ Hz, 1H), 2.25 (s, 3H), 1.16-1.00 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 209.4, 100.1, 89.8, 80.5, 76.2, 27.0, 17.9$ (6C), 12.2

(12C); IR (film cm^{-1}) ν 3524, 2946, 1719, 1420, 683; HRMS (EI) m/e : Calcd for $\text{C}_{24}\text{H}_{50}\text{O}_5\text{Si}_2$: 474.3196. Found 474.3193.

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