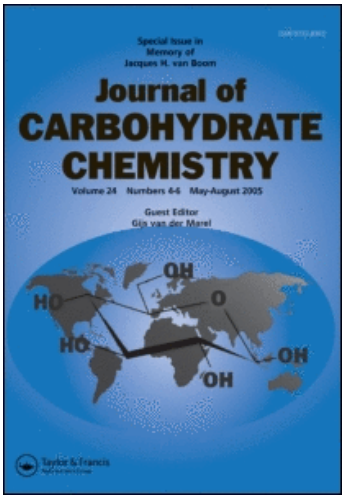

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Palladium-Catalyzed Glycosylation Reaction: *De-Novo* Synthesis of Trehalose Analogues

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Palladium-Catalyzed Glycosylation Reaction: *De-Novo* Synthesis of Trehalose Analogues

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The unnatural L-1,1-α-disaccharides were synthesized from acylfurans using a palladium-catalyzed glycosylation reaction. The 1,1-α-*manno*-disaccharides were achieved in six total steps starting from an acylfuran. The overall efficiency of this protocol was the use of highly diastereoselective palladium-catalyzed glycosylation, reduction, and dihydroxylation.

Keywords Trehalose, *Manno*-trehalose, Palladium, Glycosylation, α-1,1-Disaccharides

INTRODUCTION

Because of their uncommon structure, the 1,1-glycosidically linked trehalose disaccharides serve many unique biological functions in mycobacteria. For example, mycobacteria contain high levels of unsubstituted trehalose **1**, which perform various biological roles.[1] Most bacteria use various forms of trehalose disaccharides for many functions, such as an osmoprotectant, as a thermoprotectant, and for preventing aggregation of proteins.[2] It is becoming increasingly clear that acylated trehalose sugars play an important role in the infection process.[3]

Besides the *gluco*/*gluco*-form of trehalose, some stereoisomeric forms are also known. Trehalose-based galactose-containing oligosaccharides were found in *Mycobacterium smegmatis*; in addition, mannopyranosyl-substituted

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This paper is dedicated to Prof. Denis W. H. MacDowell during the year of his 80th birthday.
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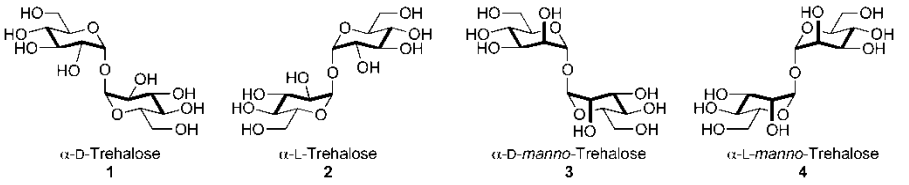
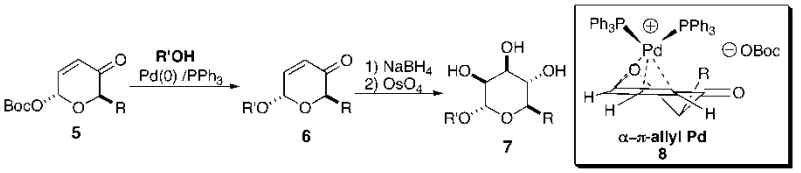


Figure 1: D- and L-trehalose and their *manno*-isomers.

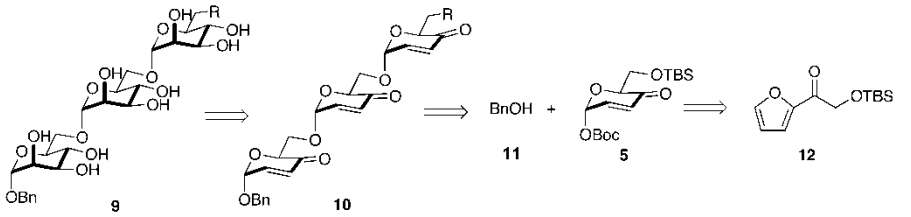
trehaloses of unknown function were found in *M. bovis* BCG.[4,5] In addition to its role in biological function, the unique structural feature of the trehalose disaccharides serves as a challenge for carbohydrate synthesis.

Typically, the 1,1-glycosidic linkage of trehalose **1** is prepared by a glycosylation of mixtures of *C*-1 anomeric alcohols; this, however, proceeds with poor α/β-anomeric control. More recently, Bertozzi has developed a method of preparing α/α-trehaloses via the acid-catalyzed decomposition of mixed acetal.[6] While this method solves the problem associated with stereocontrol, it can suffer from low yields (40%–70%). Thus, there is still a need for new synthetic methods applicable for the assembly of the trehalose 1,1-glycosidic linkage. Herein we describe our approach to trehalose analogs. This occurs via a palladium-catalyzed bis-glycosylation of water to prepare a bis-pyranone intermediate, which in turn can be converted into various trehalose analogs with minimal use of protecting groups (Fig. 1).

Recently we developed a highly diastereoselective palladium-catalyzed glycosylation reaction (Sch. 1).[7] Specifically, it converts 2-substituted 6-*t*-butoxycarboxy-2H-pyran-3(6H)-ones (**5**) into 2-substituted 6-alkoxy-2H-pyran-3 (6H)-ones (**6**) with complete retention of configuration.[8] When the glycosylation reaction is followed by a diastereoselective reduction and dihydroxylation, *manno*-sugars result. In contrast to typical glycosylation reactions,[9] this Pd π-allyl reaction proceeds under possibly the mildest reaction conditions and with almost complete stereocontrol. Our approach is equally amenable to the preparation of either D- or L-1,1-disaccharides, because it relies upon the catalytic asymmetric synthesis of furan alcohols, which in turn are converted into pyranones via the Achmatowicz reaction.[10,11] As such, this method allows for the *de novo* asymmetric synthesis of sugars.[12]



Scheme 1: Palladium-catalyzed glycosylation reaction.



Scheme 2: De novo oligosaccharide synthesis.

More recently we demonstrated that this diastereoselective palladium-catalyzed glycosylation reaction can be used for oligosaccharide synthesis.[12] Thus, when the glycosylation reaction was used iteratively, a tris-pyranone **10** was prepared. When this was followed by the highly stereoselective postglycosylation transformations (**10** to **9**), a rather efficient oligosaccharide synthesis resulted (Sch. 2).[7]

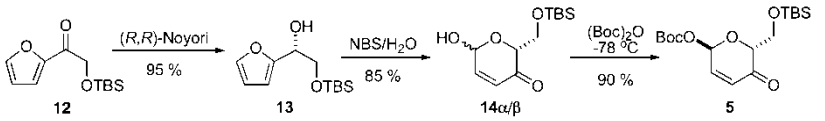
RESULTS AND DISCUSSION

Our glycosyl donor, pyranone **5**, was easily prepared from acyl furan **12** by means of a Noyori reduction (**12** to **13**),[13] Achmatowicz reaction (**13** to **14**), which was followed by a selective hemiacetal protection (**14** to **5**, Sch. 3). We have found that the more reactive axial anomeric alcohols can be selectively acylated at $-78^{\circ}C$ (>20:1). Alternatively, a 1:1 mixture of anomers can be produced when the acylation is performed at $0^{\circ}C$.

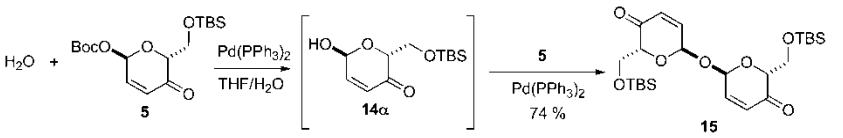
Pyranone **5** was dimerized by means of a bis-palladium glycosylation reaction. The first glycosylation reaction (5 mol% palladium/10 mol% PPh_3) was performed using water (1.2 equiv.) as nucleophile to generate anomeric alcohol **14α** (~70%) along with the dimeric pyranone (~30%), both as single diastereomers. While the anomeric alcohol **14α** cannot be purified without isomerization of the anomeric center, crude **14α** can be used as a nucleophile in the second glycosylation reaction with an additional 1.2 equiv. of **5** under identical conditions (5 mol% palladium/10 mol% PPh_3).[a] Thus this sequential glycosylation reaction yielded the 1,1-α-glycoside **15** in 74% yield (Sch. 4).

The first trehalose analog was prepared by subsequent bis-functionalizations of the bis-pyranone **15**. The 1,1-glycoside **15** was subjected to the diastereoselective reduction (**15** to **16**) and oxidation (**16** to **17**) to convert to 1,1-α-*manno*-disaccharide **17**. The bis-1,2-reduction of disaccharide **15** with $NaBH_4$ ($-78^{\circ}C$ in CH_2Cl_2/CH_3OH) gave alcohol **16** in 82% yield. Subsequent tandem double bond oxidation with OsO_4/NMO ($0^{\circ}C$ in CH_2Cl_2/H_2O)

[a]The solvent THF appears to be critical for the first glycosylation reaction, whereas the second reaction can be preformed in either THF or CH_2Cl_2.



Scheme 3: Synthesis of pyranone and glycosylation reaction.



Scheme 4: Synthesis of 1,1-disaccharide.

afforded the 1,1-di-α-L-mannose **17** in 86% yield. Important to the successful execution of this process, both reactions must occur with exceedingly high diastereocontrol (Sch. 5).

The bis-2,3-dideoxy-trehalose **18** was also prepared by employing a bis-diimide reduction on the 1,1-linked di-pyran **16**. In practice, **18** was prepared by an exhaustive reduction of allylic alcohols **16**, using excess triethylamine and *o*-nitrophenylsulfonylhydrazide as a diimide precursor (Sch. 6).[b,14]

In summary, we have synthesized unnatural 1,1-α-*manno*-disaccharide as a trehalose analogue from furan alcohol by the use of a palladium-catalyzed glycosylation reaction. This new route was also used for the preparation of 2,3-dideoxy-disaccharides as trehalose analogues. The 1,1-α-*manno*-disaccharides were achieved in six total steps starting from achiral acylfuran.

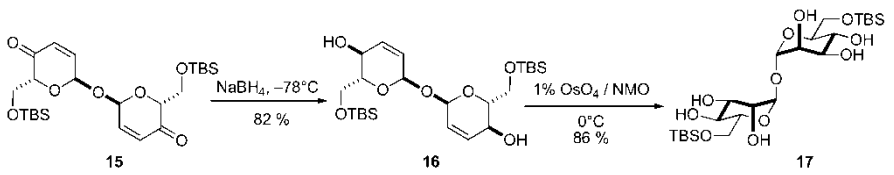
This efficient three-step protocol for the synthesis of trehalose analogues utilizes a palladium-catalyzed glycosylation reaction, diastereoselective reduction, and diastereoselective oxidation.

EXPERIMENTAL

General Methods

Liquid chromatography was performed using flash chromatography of the indicated solvent system on ICN reagent silica gel 60 (60–200 mesh). Ether, tetrahydrofuran, methylenechloride, and methanol were dried by passing through activated alumina column with argon gas pressure. Hexanes refer to the petroleum fraction bp 40–60°C. Commercial reagents were used without

[b]We have found *o*-nitrophenylsulfonylhydrazide/triethylamine to be an excellent diimide precursor, ideal for reducing pyrans of this type; see ref. 14.

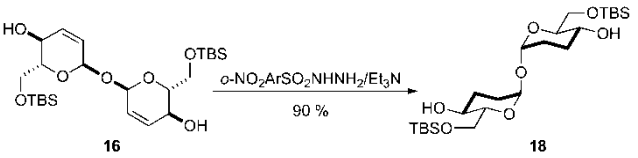


Scheme 5: Diastereoselective conversion to 1,1-α-*manno*-disaccharide.

purification unless otherwise noted. ^{1}H and ^{13}C spectra were recorded on Joel 270 and Varian 600 spectrometers. Chemical shifts are reported relative to internal tetramethylsilane (δ 0.00 ppm) or $CDCl_3$ (δ 7.26 ppm) for ^{1}H and $CDCl_3$ (δ 77.0 ppm) for ^{13}C. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon/nitrogen using oven-dried glassware and standard syringe/septa techniques. Melting points are uncorrected.

(5S)-1-Hydroxy-5-tert-butyldimethylsilanyloxymethyl-5H-pyran-4-(1H)-one (14α/β)

(1*S*)-1-(2′-Furyl)-2-*tert*-butyldimethylsilanyloxyethan-1-ol (1.69 g, 6.97 mmol), 12 mL of THF, and 3 mL of H_2O were added to a round bottom flask and cooled to 0°C. Solid $NaHCO_3$ (1.17 g, 13.9 mmol), $NaOAc \cdot 3H_2O$ (0.950 g, 6.98 mmol), and NBS (1.24 g, 6.97 mmol) were added to the solution and the mixture was stirred for 1 hr at 0°C. The reaction was quenched with satd. aq. $NaHCO_3$ (15 mL), extracted (3×25 mL) with Et_2O, dried (Na_2SO_4), concentrated under reduced pressure, and purified by silica gel chromatography eluting with 20% EtOAc/hexanes to give (5*S*)-1-Hydroxy-5-*tert*-butyldimethylsilanyloxymethyl-5*H*-pyran-4-(1*H*)-one **14α/β** 1.71 g (6.62 mmol, 85%): R_f (40% Et_2O/hexanes) = 0.40; IR (thin film, cm^{-1}) 3388, 2951, 2929, 2884, 2858, 1699, 1464, 1256; ^{1}H NMR (270 MHz, $CDCl_3$) δ major isomer 6.93 (dd, $J = 10.3$, 3.3 Hz, 1H), 6.12 (dd, $J = 10.4$, 0.6 Hz, 1H), 5.79 (dd, $J = 5.1$, 3.1 Hz, 1H), 4.59 (dd, $J = 5.0$, 2.8 Hz, 1H), 4.02 (dd, $J = 11.2$, 5 Hz, 1H), 3.93 (dd, $J = 11.2$, 2.0 Hz, 1H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) major isomer δ 194.9, 145.9, 128.1, 88.1, 76.7, 63.5, 25.8(3C), 18.5, −5.2, −5.3; CIHRMS Calcd for $[(C_{12}H_{22}O_4Si)+H]^+$: 259.1366. Found 259.1366; Anal. Calcd for C, 55.79; H, 8.59. Found: C, 55.86; H, 8.45.



Scheme 6: Synthesis of 2,3-deoxy-1,1-trehalose.

*(1S,5S)-Carbonic acid tert-butyl ester 5-(tert-butyl-dimethyl-silanyloxymethyl)-4-oxo-2,3-dihydro-6H-pyran-6-yl ester (**5**)*

(5*S*)-1-Hydroxy-5-*tert*-butyldimethylsilanyloxymethyl-5*H*-pyran-4-(1*H*)-one **14α/β** (2.58 g, 10 mmol) was dissolved in CH_2Cl_2 (8 mL) and the solution was cooled to −78°C. A CH_2Cl_2 (2 mL) solution of $(Boc)_2O$ (2.61 g, 12 mmol) and a catalytic amount of DMAP (122 mg, 1 μmol) was added to the reaction mixture. The reaction was stirred for 1 hr at −78°C. The reaction was quenched with 50 mL of satd. aq. $NaHCO_3$, extracted (3 × 50 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 6% EtOAc/hexanes to give 2.93 g (8.20 mmol, 90%) of (1*S*,5*S*)-Carbonic acid *tert*-butyl ester 5-(*tert*-butyl-dimethyl-silanyloxymethyl)-4-oxo-2,3-dihydro-6*H*-pyran-6-yl ester **5**: R_f (20% Et_2O/hexanes) = 0.70; $[\alpha]_D^{21} = +47.7$ (c = 1.5, CH_2Cl_2); IR (thin film, cm^{-1}) 2956, 2932, 2858, 1754, 1703, 1472, 1371, 1277, 1257; ^1H NMR (270 MHz, $CDCl_3$) δ 6.88 (dd, $J = 10.2$, 3.7 Hz, 1H), 6.45 (d, $J = 3.5$ Hz, 1H), 6.23 (d, $J = 10.2$ Hz, 1H), 4.54 (dd, $J = 3.5$, 3.3 Hz, 1H), 4.05 (d, $J = 3.5$ Hz, 1H), 4.03 (d, $J = 3.5$ Hz, 1H), 1.51 (s, 9H), 0.84 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 193.6, 151.7, 141.4, 129.2, 89.1, 83.5, 77.7, 62.6, 27.6 (3C), 25.8 (3C), 18.2, −5.3 (2C); CIHRMS Calcd for $[C_{17}H_{30}O_6Si+Na]^+$: 381.1716. Found: 381.1716.

*(1′R,5′S,1R,5S)-1′,1-Bis-5-(tert-butyl-dimethyl-silanyloxymethyl)-1H-pyran-4-one (**15**)*

A THF (0.3 mL) solution of compound **5** (200 mg, 0.55 mmol) and water (12 μL, 0.67 mmol) was cooled to 0°C. A THF (0.2 mL) solution of $Pd_2(DBA)_3 \cdot CHCl_3$ (14 mg, 2.5 mol%) and PPh_3 (12 mg, 10 mol%) was added to the reaction mixture at 0°C. The reaction mixture was stirred at 0°C for 1 hr. The solvent of the reaction mixture was concentrated under reduced pressure. A crude NMR spectrum revealed formation of 30% dimmer and 60% anomeric alcohols. Then the reaction mixture was reacted with compound **5** (240 mg, 0.67 mmol) in THF (0.3 mL) by adding a THF (0.2 mL) solution of $Pd_2(DBA)_3 \cdot CHCl_3$ (14 mg, 2.5 mol%) and PPh_3 (12 mg, 10 mol%) at 0°C. The reaction mixture was quenched with 5 mL of satd. aq. $NaHCO_3$, extracted (3 × 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 10% EtOAc/hexanes to give 205 mg (0.413 mmol, 74%) of **15**: R_f (20% EtOAc/hexanes) = 0.56; $[\alpha]_D^{21} = +73.6$ (c = 1.0, CH_2Cl_2); IR (thin film, cm^{-1}) 2929, 2359, 1699, 1253, 1133, 1037, 836; ^1H NMR (600 MHz, $CDCl_3$) δ 6.85 (dd, $J = 10.2$, 3.0 Hz, 2H), 6.15 (d, $J = 10.2$ Hz, 2H), 5.78 (d, $J = 4.2$ Hz, 2H), 4.47 (dd, $J = 5.4$, 2.4 Hz, 2H), 4.08 (dd, $J = 11.4$, 2.4 Hz, 2H), 4.00 (dd, $J = 11.4$, 5.4 Hz, 1H), 4.04 (m, 2H), 0.86 (s, 18H), 0.06

(s, 6H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.9(2C), 142.9(2C), 128.6(2C), 89.7(2C), 76.5(2C), 62.4(2C), 25.8(6C), 18.2(2C), −5.35(2C), −5.33(2C); CIHRMS Calcd for $[C_{24}H_{42}O_7Si_2+Na]^+$: 521.2361. Found: 521.2365.

*(1′R,5′S,1R,5S)-1′,1-Bis-5-(tert-butyl-dimethyl-silanyloxymethyl)-1H-pyran-4-ol (**16**)*

A CH_2Cl_2 (1 mL) solution of compound 1,1-bis-pyranone **15** (250 mg, 0.5 mmol) and MeOH (1 mL) was cooled to −78°C. $NaBH_4$ (76 mg, 2.0 mmol) was added, and the reaction mixture was stirred at −78°C for 3 hr. The reaction mixture was diluted with ether (10 mL) and was quenched with 5 mL of satd. aq. $NaHCO_3$, extracted (3 × 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 20% EtOAc/hexanes to give 206 mg (0.41 mmol, 82%) of **16**: R_f (30% EtOAc/hexanes) = 0.42; $[\alpha]_D^{21} = +15.2$ (c = 2, CH_2Cl_2); IR (thin film, cm^{-1}) 3442, 2929, 1462, 1255, 1043, 838; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.86 (dd, J = 10.2, 1.2 Hz, 2H), 5.62 (ddd, J = 10.2, 1.8, 1.8 Hz, 2H), 5.24 (dd, J = 10.2, 1.8 Hz, 2H), 4.07 (d, J = 7.0 Hz, 2H), 3.77 (dd, J = 10.2, 5.4 Hz, 2H), 3.70 (dd, J= 10.2, 5.4 Hz, 2H), 3.62 (ddd, J = 11.4, 5.4, 5.4 Hz, 2H), 0.80 (s, 18H), 0.004 (s, 6H), 0.00 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 133.0(2C), 125.7(2C), 90.1(2C), 70.7(2C), 66.6(2C), 65.1(2C), 25.8(6C), 18.2(2C), −5.4(2C), −5.5(2C); CIHRMS Calcd for $[C_{24}H_{46}O_7Si_2Na^+]$: 525.2674. Found: 525.2670.

*5-(tert-Butyl-dimethyl-silanyloxymethyl)-bis-1′,1-α-L-mannose (**17**)*

To a CH_2Cl_2, (0.4 mL, 0.5M) solution of allyl alcohol **16** (100 mg, 0.19 mmol) at 0°C was added a solution of (50% w/v) of N-methyl morpholine N-oxide/water (0.2 mL). Crystalline OsO_4 (0.5 mg, 1 mol %) was added and the reaction was stirred for 12 hr. The reaction mixture was concentrated and was pipetted directly onto a silica gel column using a small amount of CH_2Cl_2 (0.6 mL) in three portions. Impurities were eluted with ether and the product was eluted with MeOH/ether (2:98 to 4:96). Pure fractions were combined and concentrated to afford 1,6-bis-α-L-mannose 97 mg (0.17 mmol, 86%) of **17**: R_f (10% MeOH/Ether) = 0.30; $[\alpha]_D^{21} = -43.8$ (c = 2, CH_2Cl_2); IR (thin film, cm^{-1}) 3442, 2929, 1462, 1255, 1043, 838; ^{1}H NMR (600 MHz, $CDCl_3$+CD_3OD) δ 4.96 (m, 2H), 3.92 (m, 6H), 3.76 (dd, J = 10.2, 1.8 Hz, 2H), 3.71 (dd, J = 10.2, 5.4 Hz, 2H), 3.67 (d, J = 1.2 Hz, 2H), 3.56 (dd, J = 9.6, 2.4 Hz, 2H), 3.54 (d, J = 9.6 Hz, 1H), 3.51 (d, J = 9.6 Hz, 1H), 3.39 (m, 2H), 0.77 (s, 9H), 0.76 (s, 9H), −0.04 (s, 6H), −0.03 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 94.8(2C), 72.9(2C), 71.9(2C), 70.4(2C), 68.5(2C), 63.5(2C), 25.7(6C), 18.1(2C), −5.3(2C), −5.4(2C); CIHRMS Calcd for $[C_{24}H_{50}O_{11}Si_2Na^+]$: 593.2783. Found: 593.2773.

*5-(tert-Butyl-dimethyl-silanyloxymethyl)-bis-1′,1-α-L-2,3-deoxy-Trehalose (**18**)*

To a CH_2Cl_2 (1.5 mL, 0.1M) solution of allylic alcohol **16** (80 mg, 0.104 mmol) *o*-nitrobenzenesulfonylhydrazide (NBSH) (388 mg, 1.91 mmol) was added followed by triethylamine (30 μL, 0.836 mmol), and the reaction mixture was stirred at rt for 12 hr. The reaction mixture was diluted with ether (10 mL) and was quenched with 5 mL of satd. aq. $NaHCO_3$, extracted (3×5 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 30% EtOAc/hexanes to give 72 mg (0.14 mmol, 90%) of **18**: R_f(50% EtOAc/hexanes) = 0.44; $[\alpha]_D^{21} = -45.3$ (c = 0.3, CH_2Cl_2); IR (thin film, cm^{-1}) 3452, 2927, 1462, 1456, 1258, 1049, 836; ^1H NMR (600 MHz, $CDCl_3$) δ 4.97 (d, $J = 3.0$ Hz, 2H), 3.75 (dd, $J = 10.2$, 5.4 Hz, 2H), 3.63 (dd, $J = 9.6$, 3.0 Hz, 1H), 3.61 (dd, $J = 9.6$, 3.0 Hz, 1H), 3.54 (ddd, $J = 10.2$, 4.8, 4.8 Hz, 2H), 3.46 (ddd, $J = 8.4$, 4.8, 4.8 Hz, 2H), 3.24 (s, 2H), 1.84–1.64 (m, 8H), 0.82 (s, 18H), 0.02 (s, 6H), 0.01 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 91.0(2C), 71.4(2C), 66.4(2C), 28.5(2C), 25.81(2C), 25.80(6C), 18.2(2C), −5.5(2C), −5.6(2C); CIHRMS Calcd for $[C_{24}H_{50}O_7Si_2Na^+]$: 529.2992. Found: 529.2982.

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