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Catalytic Stereoselective Synthesis of β-Digitoxosides: Direct Synthesis of Digitoxin and C1′-epi-Digitoxin

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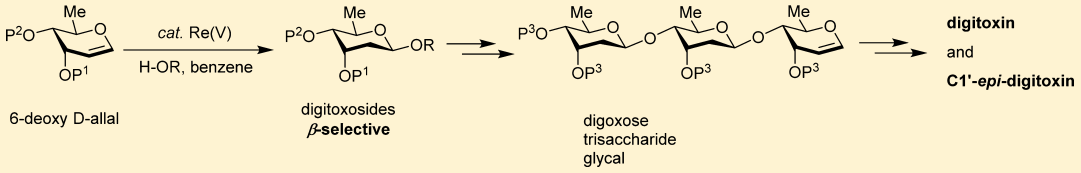
Supporting Information



ABSTRACT: A mild and atom-economic rhenium(V)-catalyzed stereoselective synthesis of β-D-digitoxosides from 6-deoxy-D-allals has been described. This β-selective glycosylation was achieved probably because of the formation of corresponding α-digitoxosides disfavored by 1,3-diaxial interaction. In addition, this method has been successfully applied to the synthesis of digitoxin trisaccharide glycal for the direct synthesis of digitoxin and C1′-epi-digitoxin.

INTRODUCTION

2-Deoxy sugars, especially 2,6-dideoxy sugars, exist in numerous bioactive natural products and clinical agents and influence their chemical, physical, and biological activities.[1] Among the naturally occurring 2,6-dideoxy sugars, β-linked digitoxosides are present in cardiac glycosides[2] involved in clinic use, such as digitoxin[3] and digoxin.[4] Digitoxin and its congeners are well-known inhibitors of the enzyme Na^+/K^+-ATPase and used for treating congestive heart failure and cardiac arrhythmia for a long period of time.[3] While their clinical use is limited because of the high toxicity, it was recently discovered that these molecules have also demonstrated interesting anticancer activity[5] and could be potential agents for neuroprotection.[6]

In previous reports, β-digitoxosides were stereoselectively prepared from various thio-digitoxoside (Hg^{2+}),[7] 6-deoxy-D-allal ($Ph_3P{\cdot}HBr$),[8] in situ generated digitoxosyl iodides,[9] digitoxosyl *o*-alkynylbenzoates (cationic Au(I)),[10] or via palladium-catalyzed glycosylation followed by functional group manipulations.[11] Despite those remarkable accomplishments, only one direct synthesis of digitoxin was achieved by McDonald and co-workers thus far,[8] in which $Ph_3P{\cdot}HBr$-catalyzed glycosylation of digitoxigenin with digoxose trisaccharide glycal afforded desired product in modest anomeric selectivity (β/α = 3/2). Other syntheses of digitoxin from the groups of Wiesner,[7] O'Doherty,[11] and Yu[10] required iterative glycosylation of costly digitoxigenin or its furan derivative[7] with various glycosyl donors, which led to the decreasing overall efficiency of the total synthesis.

In addition, extensive efforts have been reported for the preparation of analogues of digitoxin and related cardiac glycosides in order to improve their activity and/or to alleviate their side effects. Among those studies, special attention has been paid to the modification of the sugar subunit, such as neoglycorandomization,[12] regioselective acylation[13] or glycosylation[14] of parent digitoxin, replacement of the natural digoxose trisaccharide with monosaccharide moieties,[15] as well as incorporation of other type of sugars.[16] Studies of their structure−activity relationship (SAR) indicated that their antitumor activity was significantly affected by the stereochemistry and length of the sugar subunit. To further explore the role of sugar subunit and search for better analogues of digitoxin and its congeners, we initiated our effort toward the synthesis of digitoxin.

RESULTS AND DISCUSSION

Recently, transition-metal catalysis has been successfully utilized in the stereoselective synthesis of oligosaccharides/glycoconjugates including 2-deoxy sugars and has demonstrated advantages over traditional glycosylations involving stoichiometric amount of electrophilic promoters.[17,18] Among those reports, the Toste glycosylation[19] involving rhenium(V)-catalyzed stereoselective synthesis of 2-deoxy-α-glycosides from glycals bearing *equatorial* C3-substituents, such as D-glucal (**1**), D-rhamnal (**2**), and D-galactal (**3**), was particularly appealing (Scheme 1a), in that this rhenium catalysis enables direct selective formation of 2-deoxy α-glycosides (**4**) with essentially 100% atom-economic efficiency. Inspired by this report, we wonder if glycals bearing *axial* C3-substituents, such as 6-deoxy-D-allal (**5**), would be selectively converted to the corresponding β-digitoxosides (**6**) under similar Re(V) catalysis. Because of 1,3-diaxial interactions, the production of corresponding α-digitoxosides (**7**) should be disfavored (Scheme 1b).

Initially, known 3-*O*-benzyl-4-*O*-*tert*-butyldimethylsilyl-6-deoxy-D-allal (**8**)[20] was chosen to react with diacetone-D-

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Scheme 1. Re(V)-Catalyzed Stereoselective Synthesis of 2-Deoxy Glycosides from Glycals

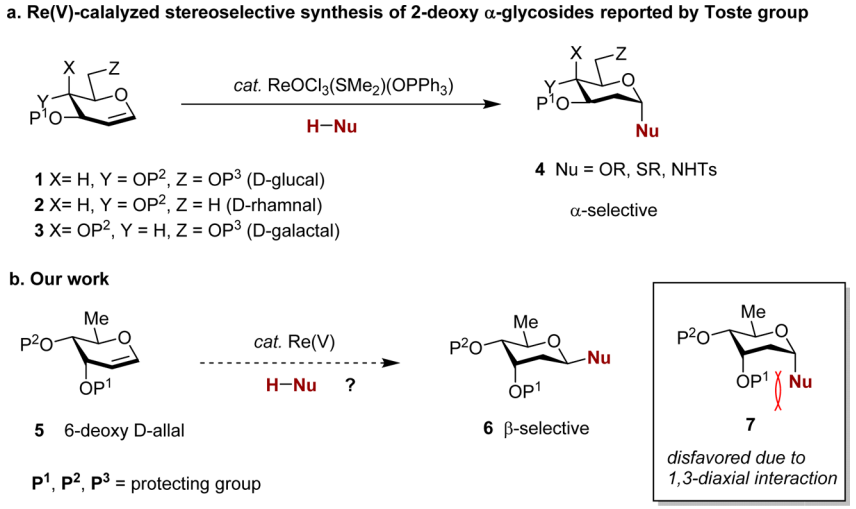
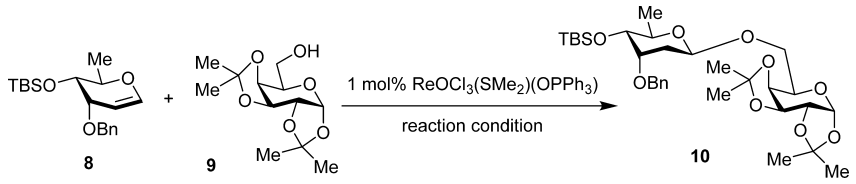


Table 1. Optimization of Re(V)-Catalyzed Stereoselective Synthesis of 2-Deoxy β-D-Digitoxoside[a]



entry	reaction condition	yield[b] (β/α)[c]
1	toluene, rt, 12 h	85%, 3.6/1
2	CH_2Cl_2, rt, 24 h	31%, 5.6/1
3	CH_3CN, rt, 24 h	21%, 4.6/1
4	Benzene, rt, 12 h	92%, 4.3/1

[a]Reactions were performed using 0.3 mmol of **8** (1.5 equiv), 0.2 mmol of **9** (1.0 equiv), and 1 mol % $ReOCl_3(SMe_2)(OPPh_3)$, in 0.5 mL of solvent at room temperature unless otherwise noted. [b]Combined isolated yield of α/β isomers. [c]α/β Ratio was determined by ^{1}H NMR analysis.

galactose (**9**) for our condition optimization (Table 1). It was found that with the use of 1 mol % $ReOCl_3(SMe_2)(OPPh_3)$ in toluene, the original optimal condition reported by Toste,[19] disaccharide **10** was produced in 85% yield (β/α = 3.6/1) (entry 1, Table 1). Use of more polar solvents, such as dichloromethane and acetonitrile, significantly dropped the yields, albeit slightly better β/α selectivity was observed (entries 2 and 3). It was found that reactions in those polar solvents were sluggish, and significant amounts of side products were detected, which was consistent with what Toste observed.[19] Finally, it was discovered that use of benzene as solvent afforded disaccharide **10** in 92% yield (β/α = 4.3/1) (entry 4).

With this optimal condition developed, we next investigated the reaction scope using various 6-deoxy-D-allals (**8** and **11**[21]) as well as primary and secondary alcohols (**9**, **12**–**13**[21]) and thiophenol as acceptors (Table 2). As shown in Table 2, a number of digitoxosides and thio-digitoxosides have been prepared in synthetically useful to excellent yields with good to excellent β-selectivity. In particular, use of thiophenol essentially gave rise to the desired thio-digitoxosides in excellent yields with complete β selectivity. In general, this type of glycosylation involving secondary alcohol acceptors generally afforded higher β/α selectivity than the use of primary alcohol acceptors. In addition, higher catalyst loading was required for secondary alcohol acceptors, probably due to their relatively lower reactivity as compared to the primary alcohols. It was found that Ferrier rearrangement[22] was the main side reaction, which competes with the desired glycosylation pathway. It is worth noting that glycosyl phenylsulfide **13** bearing C2-methoxy group serves as the precursor for its corresponding glycal and can be converted into the glycal via reductive lithiation and 1,2-elimination (vide infra). Accordingly, Re(V)-catalyzed glycosylation between 6-deoxy D-allal **8** and acceptor **13** followed by tetra-*n*-butylammonium fluoride (TBAF)-mediated desilylation afforded disaccharide **20** in 64% yield over two steps together with a small amount of α-anomer (β/α= 8.3/1).

Having established this optimal condition, we set forth to apply this method to the direct synthesis of digitoxin (Scheme 2). Accordingly, disaccharide acceptor **20** reacted with 6-deoxy D-allal **8** under Re(V) catalysis to give rise to β-linked trisaccharide **21** in 75% yield together with a small amount of its α-anomer (β/α = 7/1). Trisaccharide **21** was then subjected to TBAF-mediated desilylation to furnish desired alcohol **22** (89% yield). Next, reductive debenzylation and concomitant reductive lithiation–elimination[23] of **22** furnished the free trisaccharide glycal, which subsequently underwent global protection as its tetra-TES ether **23** (73% yield overall). Because of the insolubility of digitoxigenin in nonpolar solvent,[8] Re(V)-catalyzed glycosylation of glycal **23** with digitoxigenin (**24**) in benzene was very sluggish. Use of dichloromethane instead of benzene as solvent for this Re(V) catalysis afforded trace amount of desired product together with side products from Ferrier rearrangement.[22] Finally, employing the condition

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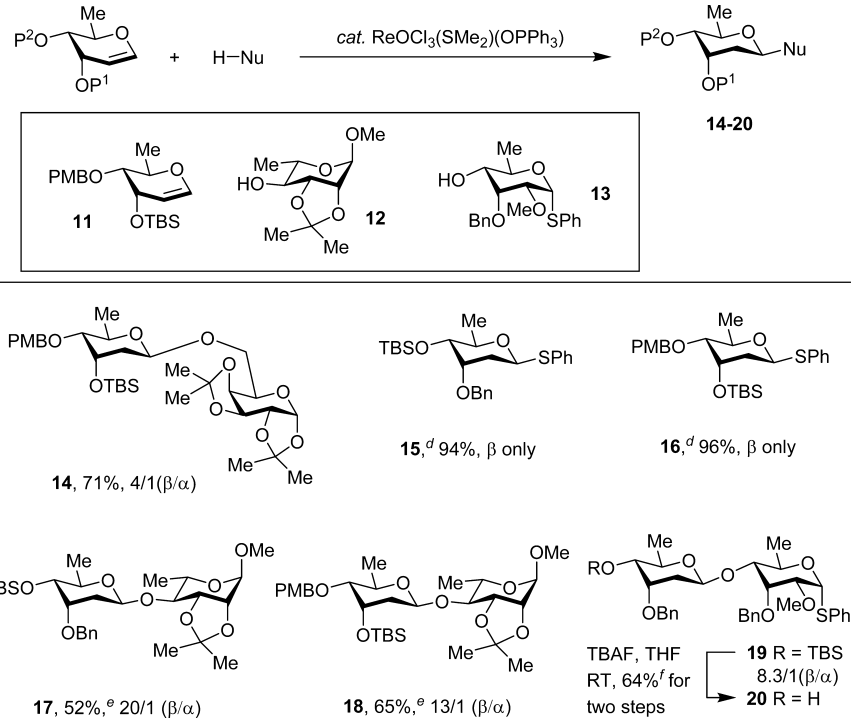
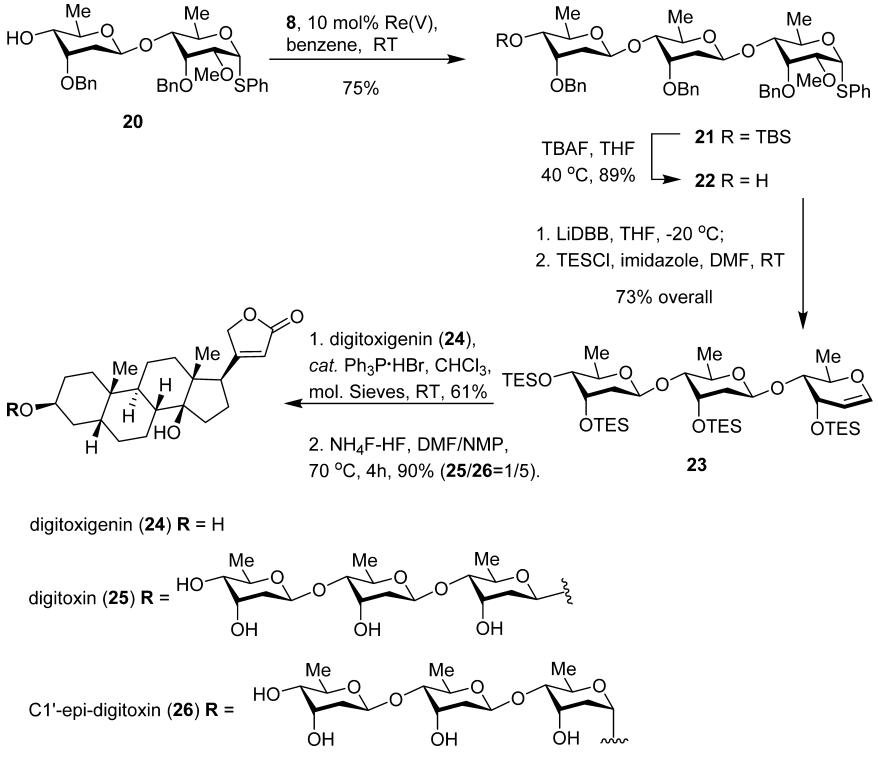
Table 2. Re(V)-Catalyzed Stereoselective Synthesis of β-D-Digitoxosides[a,b,c]



[a]Reactions were performed using glycal (1.5 equiv), acceptor (1.0 equiv), 1 mol % $ReOCl_3(SMe_2)(OPPh_3)$, in benzene at room temperature unless otherwise noted. [b]Isolated yield. [c]α/β Ratio was determined by ^1H NMR analysis. [d]Glycal (1.0 equiv) and thiophenol (1.2 equiv) were used. [e]Glycal (1.0 equiv), acceptor (1.5 equiv), and 10 mol % $ReOCl_3(SMe_2)(OPPh_3)$ were used. [f]10 mol % $ReOCl_3(SMe_2)(OPPh_3)$ was used. **20** was obtained in 64% yield over two steps (Re(V)-catalyzed glycosylation followed by TBAF-mediated desilylation).

Scheme 2. Direct Synthesis of Digitoxin



described by McDonald ($Ph_3P{\cdot}HBr$, $CHCl_3$) provided the desired glycosylation product in 61% yield as an inseparable mixture of anomers (β/α = 1/5) in which α was found to be the major compound probably due to the predominance of anomeric effect over 1,3-diaxial interaction. Subsequent global deprotection of TES ether of this anomeric mixture using $NH_4F{-}HF$ in DMF/NMP (4 h)[8] afforded a mixture of digitoxin **25** (β-isomer) and C1′-epi-digitoxin **26** (C1′-α-

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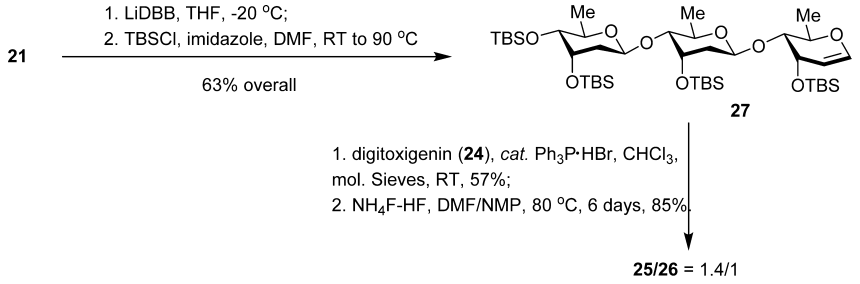
Scheme 3. Revised Synthesis of Digitoxin



isomer) in a combined 90% yield. This mixture was further separated by reverse phase HPLC (C18 column) to provide pure digitoxin **25** (β-isomer) and C1′-epi-digitoxin **26** (C1′-α-isomer).[21] Our synthetic digitoxin was identical to the digitoxin purchased from Sigma-Aldrich according to spectroscopic analysis.

Because of the fact that poor β/α ratio was obtained in the glycosylation between trisaccharide glycal **23** and digitoxigenin (**24**), we decided to prepare corresponding TBS-protected trisaccharide glycal **27** (Scheme 3). We hope that greater size of TBS ether, as compared to TES ether, would lead to more severe 1,3-diaxial interaction, which would disfavor the formation of α-anomer and thus favor the production of β-anomer. Accordingly, reductive debenzylation and concomitant reductive lithiation−elimination[23] of **21** followed by global silyl-protection afforded trisaccharide glycal tetra-TBS ether **27** (63% yield overall).[24] Next, use of the condition described by McDonald (Ph_3P·HBr, $CHCl_3$)[8] provided the glycosylation product in 57% yield (β/α = 1.4/1) in which β was found to be the major compound, probably because 1,3-diaxial interaction is prodominant over anomeric effect because of the steric bulkiness of TBS ether. Final global deprotection of TBS ether using NH_4F−HF in DMF/NMP at 80 °C (6 days)[8] furnished the desired digitoxin **25** and its C1′-epi-digitoxin (**26**) in 85% combined yield, which can be separated by reverse phase HPLC (C18 column) as previously discussed.

CONCLUSION

In conclusion, we have reported a mild and atom-economic Re(V)-catalyzed stereoselective synthesis of β-D-digitoxosides from 6-deoxy-D-allals. This β-selectivity may be resulted from the disfavored production of corresponding α-digitoxosides by 1,3-diaxial interaction. In addition, this method has been successfully applied to a direct synthesis of digitoxin, a potent cardiac glycoside, and its C1′-epimer. Synthesis of digitoxin analogues bearing diverse sugar subunits and investigations of their biological activity are currently in progress and will be reported in due course.

EXPERIMENTAL SECTION

1,5-Anhydro-3-*O*-*tert*-butyldimethylsilyl-2,6-dideoxy-4-*O*-*p*-methoxybenzyl-D-*ribo*-hex-1-enitol (11). To a solution of 1,5-anhydro-3-*O*-benzyl-D-*ribo*-hex-1-enitol[20] (1.73 g, 7.9 mmol) in 16 mL *N*,*N*-dimethylformamide cooled at 0 °C was added sodium hydride (408 mg, 10.2 mmol) portionwise. The resulting mixture was stirred at 0 °C for 45 min, and *p*-methoxybenzyl chloride (1.1 mL, 8.3 mmol) was added. The reaction mixture was warmed up and stirred at ambient temperature for 1 h. Ice-cold water was added, and the resulting mixture was extracted with EtOAc (3 × 30 mL). Combined organic extracts were washed with water (2 × 50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by silica gel flash column chromatography (toluene:EtOAc = 50:1) to afford 2.6 g (96% yield) of 1,5-anhydro-3-*O*-benzyl-4-*O*-*p*-methoxybenzyl-D-*ribo*-hex-1-enitol. Next, to 1,5-anhydro-3-*O*-benzyl-4-*O*-*p*-methoxybenzyl-D-*ribo*-hex-1-enitol (2.3 g, 6.4 mmol) in 21 mL of THF cooled at −78 °C was added LiDBB (21.3 mL, 0.4 M) dropwise. The resulting mixture was stirred for 15 min at −78 °C. Saturated sodium bicarbonate (1 mL) was added. After THF was removed under reduced pressure, the remaining aqueous mixture was extracted with EtOAc (3 × 40 mL). Combined extracts were washed sequentially with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (hexanes:EtOAc = 5:1 to 3:1) to afford 1.3 g of 1,5-anhydro-4-*O*-*p*-methoxybenzyl-D-*ribo*-hex-1-enitol (81% yield). Next, to a mixture of 1,5-anhydro-4-*O*-*p*-methoxybenzyl-D-*ribo*-hex-1-enitol (1.3 g, 5.2 mmol) in 5 mL of DMF and imidazole (1.08 g, 15.8 mmol), *tert*-butyldimethylsilyl chloride (1.59 g, 10.6 mmol) was added. The reaction mixture was stirred at room temperature for 1 h before water was added. The resulting mixture was extracted with EtOAc (3 × 30 mL), and combined organic extracts were sequentially washed with water (2 × 50 mL) and brine (25 mL), dried over anhydrous sodium sulfate, filtered, and concentrated . Crude mixture was purified by silica gel flash column chromatography (hexanes:ethyl acetate = 25:1) to access 1.8 g of 1,5-anhydro-3-*O*-*tert*-butyldimethylsilyl-2,6-dideoxy-4-*O*-*p*-methoxybenzyl-D-*ribo*-hex-1-enitol (**11**) (94% yield): $[\alpha]_D^{23}$ = 232.0° (*c* = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (ovrlp, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 6.30 (d, *J* = 5.9 Hz, 1 H), 4.78 (t, *J* = 5.9 Hz, 1 H), 4.67 (d, *J* = 11.4 Hz, 1 H), 4.39 (d, *J* = 11.4 Hz, 1 H), 4.28 (dd, *J* = 3.3, 5.7 Hz, 1 H), 4.14 (dd, *J* = 6.2, 9.7 Hz, 1 H), 3.83−3.77 (m, 3 H), 3.24 (dd, *J* = 3.5, 9.7 Hz, 1 H), 1.32 (d, *J* = 6.2 Hz, 3 H), 0.90 (s, 9 H), 0.13−0.05 (ovrlp, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.5, 145.6, 130.7, 129.7, 114.0, 102.2, 79.0, 70.7, 70.0, 60.9, 55.6, 26.2, 18.5, 18.1, −3.6, −4.0; FT-IR (thin film) 3047, 2926, 2843, 1643, 1607, 1500, 1456, 1243, 1171, 1083 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{20}H_{32}NaO_4Si$ 387.1968, found 387.1963.

Phenyl 3-*O*-benzyl-6-deoxy-2-*O*-methyl-1-thio-α-D-*ribo*-hex-opyranoside (13). To a solution of 1,2,4,6-*tetra*-*O*-acetyl-3-*O*-benzylallopyranose[25] (14.8 g, 33.8 mmol) and thiophenol (6.9 mL, 67.6 mmol) in 84 mL of dichloromethane cooled at 0 °C was added boron trifluoride diethyl etherate (8.3 mL, 67.6 mmol) dropwise. The reaction mixture was stirred at ambient temperature for 2 h before 100 mL of water was added. After separating organic layer, aqueous layer was extracted with dichloromethane (3 × 100 mL). Combined extracts were washed sequentially with water (100 mL), saturated sodium bicarbonate (200 mL) and brine (200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (toluene:EtOAc = 50:1 to 5:1) to afford 11.5 g (70% yield) of an α/β mixture of phenyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-1-thio-D-*ribo*-hexopyranoside. To this α/β mixture of phenyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-1-thio-D-*ribo*-hex-opyranoside (9.0 g, 18.4 mmol) in 37 mL of methanol was added sodium methoxide (683 μL, 3.6 mmol). The resulting mixture was stirred at ambient temperature overnight and neutralized with Dowex-50 in the H+ form. Solvent was evaporated after filtration, residue was azeotroped with toluene and redissolved in 37 mL of *N*,*N*-dimethylformamide and benzaldehyde dimethyl acetal (4.2 mL, 27.9 mmol), *p*-toluenesulfonic acid (106 mg, 0.56 mmol) was added. The reaction mixture was stirred at ambient temperature overnight.

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Saturated sodium bicarbonate (50 mL) was added, and aqueous layer was extracted with ethyl acetate (3 × 50 mL). Combined organic layers were washed sequentially with water (3 × 50 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (toluene:EtOAc = 25:1) to afford 6.5 g (78% combined yield) of an α/β mixture of phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-D-*ribo*-hexopyranoside.

To a solution of α/β mixture of phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-D-*ribo*-hexopyranoside (6.5 g, 14.4 mmol) in 47 mL of *N*,*N*-dimethylformamide cooled at 0 °C was added sodium hydride (1.14 mg, 28.5 mmol) portionwise. The resulting mixture was stirred for 45 min at 0 °C before methyl iodide (1.4 mL, 21.4 mmol) was added. The reaction mixture was stirred for 3 h, and then water (50 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were washed sequentially with water (2 × 100 mL), brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (hexanes:EtOAc = 40:1 to 1:1) to afford 3.85 g (58% yield) of phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-methyl-1-thio-α-D-*ribo*-hexopyranoside and 1.92 g (29% yield) of its corresponding β-anomer. Next, to phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-methyl-1-thio-α-D-*ribo*-hexopyranoside (3.4 g, 7.3 mmol) in 72 mL of dichloromethane and 1.5 mL of water was added trifluoroacetic acid (842 μL, 11 mmol). The reaction mixture was stirred at ambient temperature for 24 h before solid sodium bicarbonate (1.2 g, 14 mmol) was added. The resulting mixture was concentrated in vacuo and purified by silica gel flash column chromatography (hexanes:EtOAc = 10:1) to furnish 2.45 g (88% yield) of phenyl 3-*O*-benzyl-2-*O*-methyl-1-thio-α-D-*ribo*-hexopyranoside.

A mixture of phenyl 3-*O*-benzyl-2-*O*-methyl-1-thio-α-D-*ribo*-hexopyranoside (2.1 g, 5.6 mmol), 2-aminoethyl diphenyl borinate[26] (126 mg, 0.56 mmol) and *p*-toluenesulfonyl chloride (1.6 g, 8.4 mmol) in 21 mL of acetonitrile and *N*,*N*-diisopropylethylamine (1.4 mL, 8.4 mmol) was stirred at ambient temperature for 22 h. The reaction was quenched with saturated sodium bicarbonate (25 mL) and brine (20 mL), and organic layer was separated. The aqueous layer was extracted with ethyl acetate (4 × 40 mL). Combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (hexanes:EtOAc = 4:1 to 2:1) to afford phenyl 3-*O*-benzyl-2-*O*-methyl-6-*O*-*p*-toluenesulfonyl-1-thio-α-D-*ribo*-hexopyranoside. To a solution of this tosylate in 27 mL of THF cooled at 0 °C was added lithium aluminum hydride (3 mL, 4 M in diethyl ether) dropwise. The reaction mixture was refluxed for 1 h before being cooled back to 0 °C. Saturated ammonium chloride (1 mL) was added dropwise. After THF was removed under reduced pressure, the residue was diluted with methylene chloride (120 mL) and filtered through Celite. The filtrate was washed with saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (toluene:EtOAc = 10:1) to afford 1.7 g (84% over 2 steps) of phenyl 3-*O*-benzyl-6-deoxy-2-*O*-methyl-1-thio-α-D-*ribo*-hexopyranoside (**13**): $[\alpha]_D^{23}$ = 205.1° (*c* = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58–7.53 (m, 2 H), 7.48–7.43 (m, 2 H), 7.40–7.35 (m, 2 H), 7.34–7.27 (m, 3 H), 7.26–7.21 (m, 1 H), 5.54 (d, *J* = 5.5 Hz, 1 H), 5.20 (d, *J* = 11.6 Hz, 1 H), 4.58 (d, *J* = 11.6 Hz, 1 H), 4.21 (qd, *J* = 6.3, 9.7 Hz, 1 H), 4.08 (t, *J* = 2.6 Hz, 1 H), 3.68 (dd, *J* = 2.2, 5.5 Hz, 1 H), 3.54–3.48 (m, 3 H), 3.21 (ddd, *J* = 3.3, 9.7, 11.6 Hz, 1 H), 2.35 (d, *J* = 11.4 Hz, 1 H), 1.30 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.6, 138.3, 131.4, 129.2, 128.9, 128.5, 128.2, 127.1, 86.4, 80.7, 76.7, 75.2, 72.1, 57.7, 17.7; FT-IR (thin film) 3424, 2926, 1633, 1586, 1471, 1444, 1368, 1347, 1160, 1062 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{20}H_{24}NaO_4S$ 383.1293, found 383.1303.

General Procedure for Rhenium(V)-Catalyzed Synthesis of β-Digitoxosides and β-Thiodigitoxosides. *3-O-Benzyl-4-O-tert-butyldimethylsilyl-2,6-dideoxy-β-D-ribo-hexapyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranoside (**10**).* To a mixture of glycal **8** (100 mg, 0.3 mmol) and diacetone-D-galactose **9** (52 mg, 0.2 mmol) in 0.5 mL of dry benzene (0.4 M based on limiting reagent) cooled at 0 °C was added 1 mol % catalyst $ReOCl_3(SMe_2)$-$(OPPh_3)$. The resulting mixture was stirred at ambient temperature for 12 h. After 100 μL of saturated sodium bicarbonate was added, the resulting mixture was filtered through a pad of anhydrous sodium sulfate, concentrated, and purified by silica gel flash column chromatography (hexanes:EtOAc = 30:1 to 10:1) to afford **10** (109 mg, 92% combined yield) as α/β (1/4.3) mixture: $[\alpha]_D^{23}$ = −1.0° (*c* = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40–7.21 (ovrlp, 5 H, α and β), 5.55 (d, *J* = 5.0 Hz, 1 H, β), 5.50 (d, *J* = 5.0 Hz, 1 H, α), 4.89 (d, *J* = 9.5 Hz, 1 H, β), 4.81 (d, *J* = 4.2, 1 H, α) 4.69 (ovrlp, 1 H, α and β), 4.62 (d, *J* = 11.9 Hz, 1 H, β), 4.60–4.54 (ovrlp, 1 H, α and β), 4.55–451 (m, 1 H, α), 4.32–4.18 (ovrlp, 5 H, α and β), 4.06–4.01 (m, 1 H, β), 4.01–3.96 (ovrlp, 1 H, α and β), 3.96–3.90 (m, 1 H, β), 3.80–3.74 (ovrlp, 1 H, α and β), 3.72–3.69 (m, 1 H, α), 3.68–3.59 (ovrlp, 1 H, α and β), 3.41 −3.36 (ovrlp, 1 H, α and β), 2.34 − 2.29 (m, 1 H, α) 2.29–2.24 (m, 1 H, β), 1.74 − 1.69 (m, 1 H, α), 1.66–1.57 (ovrlp, 1 H, β), 1.54–1.49 (ovrlp, 3 H, α and β), 1.46–1.40 (ovrlp, 3 H, α and β), 1.32 (s, 9 H, α and β), 1.28 (s, 3 H, α), 1.24–1.17 (ovrlp, 3 H, α and β), 0.95–0.85 (ovrlp, 9 H α and β), 0.09–0.00 (ovrlp, 6 H, α and β); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.4, 139.2, 128.6, 128.5, 127.9, 127.9, 127.8, 127.7, 127.5, 109.7, 109.3, 108.9, 108.9, 98.9, 97.0, 96.7, 96.6, 76.2, 75.7, 75.3, 74.3, 72.5, 71.8, 71.2, 71.1, 71.0, 70.8, 70.7, 70.3, 68.8, 68.0, 66.2, 65.7, 64.9, 36.3, 32.8, 26.5, 26.4, 26.3, 26.2, 25.3, 25.3, 24.8, 24.8, 18.8, 18.5, 18.5, 18.4, −3.6, −3.8, −4.4, −4.5; FT-IR (thin film) 2913, 2871, 2355, 1461, 1384, 1316, 1254, 1212, 1171, 1072 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{31}H_{50}NaO_9Si$ 617.3122, found 617.3119.

*3-O-tert-Butyldimethylsilyl-2,6-dideoxy-4-O-p-methoxybenzyl-β-D-ribo-hexapyranosyl-(1→6)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranoside (**14**).* Prepared according to general procedure from compound **11** (109 mg, 0.3 mmol), diacetone-D-galactose **9** (52 mg, 0.2 mmol), and 1 mol % catalyst $ReOCl_3(SMe_2)(OPPh_3)$ at ambient temperature in 12 h. Purification by silica gel flash column chromatography (hexanes:EtOAc = 50:1 to 10:1) furnished **14** (70.6 mg, 57%) and its α-anomer (17.5 mg, 14%) (71% combined yield). The β-anomer **14** is characterized as follows: $[\alpha]_D^{23}$ = −0.8° (*c* = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25–7.20 (m, 2 H), 6.89–6.82 (m, 2 H), 5.54 (d, *J* = 5.1 Hz, 1 H), 4.88 (dd, *J* = 1.9, 9.4 Hz, 1 H), 4.61–4.54 (m, 2 H), 4.34 (d, *J* = 11.4 Hz, 1 H), 4.29 (dd, *J* = 2.4, 5.1 Hz, 1 H), 4.26–4.20 (m, 2 H), 4.04–3.96 (m, 2 H), 3.94–3.88 (m, 1 H), 3.80 (s, 3 H), 3.65 (dd, *J* = 7.1, 10.7 Hz, 1 H), 2.98 (dd, *J* = 2.4, 9.2 Hz, 1 H), 2.02 (ddd, *J* = 2.0, 4.0, 13.4 Hz, 1 H), 1.65–1.57 (ovrlp, 1 H), 1.52 (s, 3 H), 1.45 (s, 3 H), 1.32 (d, *J* = 4.2 Hz, 6 H), 1.21 (d, *J* = 6.2 Hz, 3 H), 0.91–0.85 (s, 9 H), 0.07–0.01 (ovrlp, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.5, 130.6, 129.8, 114.0, 109.6, 108.9, 98.7, 96.7, 81.1, 71.8, 71.4, 71.0, 70.7, 68.8, 68.5, 67.9, 66.1, 55.6, 39.6, 26.4, 26.3, 26.2, 25.3, 24.7, 18.6, 18.5, −4.2, −4.5; FT-IR (thin film) 2926, 2895, 2843, 1607, 1461, 1373, 1301, 1249, 1171, 1072 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{32}H_{52}NaO_{10}Si$ 647.3227, found 647.3217.

*Phenyl 3-O-benzyl-4-O-tert-butyldimethylsilyl-2,6-dideoxy-1-thio-β-D-ribo-hexapyranoside (**15**).* Prepared according to general procedure from compound **8** (70 mg, 0.21 mmol), thiophenol (26 μL, 0.25 mmol), and 1 mol % catalyst $ReOCl_3(SMe_2)(OPPh_3)$ at ambient temperature in 3 h. Purification by silica gel flash column chromatography (hexanes:EtOAc = 50:1) afforded **15** (87.5 mg, 94% yield): $[\alpha]_D^{23}$ = 39.8° (*c* = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50–7.45 (m, 2 H), 7.37–7.26 (m, 7 H), 7.25–7.21 (m, 1 H), 5.23 (dd, *J* = 1.9, 11.8 Hz, 1 H), 4.74 (d, *J* = 11.7 Hz, 1 H), 4.62 (d, *J* = 11.7 Hz, 1 H), 4.01 (dd, *J* = 6.3, 9.3 Hz, 1 H), 3.80 (q, *J* = 2.6 Hz, 1 H), 3.41 (dd, *J* = 2.7, 9.3 Hz, 1 H), 2.31–2.23 (m, 1 H), 1.85 (ddd, *J* = 2.4, 11.8, 13.8 Hz, 1 H), 1.26 (d, *J* = 6.2 Hz, 3 H), 0.92 (s, 9 H), 0.09 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.1, 135.1, 130.9, 129.1, 128.7, 127.9, 127.2, 79.8, 76.4, 75.5, 73.2, 72.9, 37.1, 26.2, 19.0, 18.4, −3.6, −4.5; FT-IR (thin film) 2947, 2871, 2843, 1581, 1467, 1352, 1249, 1202, 1124, 1088 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{25}H_{36}NaO_3SSi$ 467.2052, found 467.2054.

*Phenyl 3-O-tert-butyldimethylsilyl-2,6-dideoxy-4-O-p-methoxybenzyl-1-thio-β-D-ribo-hexapyranoside (**16**).* Prepared according to

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general procedure from compound **11** (73 mg, 0.2 mmol), thiophenol (25 μL, 0.24 mmol), and 1 mol % catalyst $ReOCl_3(SMe_2)(OPPh_3)$ at ambient temperature in 3 h. Purification by silica gel flash column chromatography (hexanes:EtOAc = 50:1) afforded **16** (91 mg, 96% yield): $[\alpha]_D^{23}$ = 37.7° (*c* = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50−7.45 (m, 2 H), 7.32−7.27 (m, 2 H), 7.25−7.20 (m, 3 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 5.23 (dd, *J* = 1.9, 11.6 Hz, 1 H), 4.57 (d, *J* = 11.2 Hz, 1 H), 4.36 (d, *J* = 11.4 Hz, 1 H), 4.26 (td, *J* = 2.1, 3.9 Hz, 1 H), 3.95 (dd, *J* = 6.2, 9.4 Hz, 1 H), 3.81 (s, 3 H), 3.00 (dd, *J* = 2.4, 9.4 Hz, 1 H), 2.04 (ddd, *J* = 2.0, 3.9, 13.5 Hz, 1 H), 1.85 (ddd, *J* = 2.2, 11.6, 13.5 Hz, 1 H), 1.24 (d, *J* = 6.2 Hz, 3 H), 0.91−0.83 (s, 9 H), 0.08−0.02 (ovrlp, 6 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.5, 134.9, 131.3, 130.5, 129.8, 129.1, 127.3, 114.0, 80.7, 79.4, 71.7, 71.4, 66.1, 55.6, 40.3, 26.2, 18.8, 18.5, −4.1, −4.5; FT-IR (thin film) 2942, 2870, 1607, 1581, 1508, 1461, 1447, 1373, 1295, 1243 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{26}H_{38}NaO_4SSi$ 497.2158, found 497.2145.

Methyl 3-O-benzyl-4-O-tert-butyldimethylsilyl-2,6-dideoxy-β-D-ribo-hexapyranosyl-(1→4)-6-deoxy-2,3-O-isopropylidene-α-L-mannopyranoside (**17**). Prepared according to general procedure from compound **8** (100 mg, 0.3 mmol), **12** (98 mg, 0.45 mmol), and 10 mol % catalyst $ReOCl_3(SMe_2)(OPPh_3)$ in 500 μL of benzene at ambient temperature in 3 days. Purification by silica gel flash column chromatography (hexanes:EtOAc = 70:1 to 20:1) afforded **17** (86 mg, 52% yield) and its α-anomer (4.4 mg). Compound **17** is characterized as follows: $[\alpha]_D^{23}$ = 6.4° (*c* = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41−7.35 (m, 2 H), 7.32 (t, *J* = 7.6 Hz, 2 H), 7.27 (ovrlp, 1 H), 5.28−5.23 (m, 1 H), 4.84 (s, 1 H), 4.70 (d, *J* = 11.9 Hz, 1 H), 4.64 (d, *J* = 11.9 Hz, 1 H), 4.15−4.09 (m, 1 H), 4.07 (d, *J* = 5.5 Hz, 1 H), 3.93−3.85 (m, 1 H), 3.76 (d, *J* = 2.8 Hz, 1 H), 3.63−3.56 (m, 2 H), 3.40−3.33 (ovrlp, 4 H), 2.22 (td, *J* = 1.7, 13.6 Hz, 1 H), 1.56−1.48 (ovrlp, 4 H), 1.34 (s, 3 H), 1.32−1.26 (m, 3 H), 1.20 (d, *J* = 6.2 Hz, 3 H), 0.95−0.87 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.3, 128.6, 127.9, 127.7, 109.5, 98.3, 97.7, 78.8, 78.8, 76.5, 76.4, 75.7, 72.4, 70.4, 64.8, 55.1, 36.5, 28.2, 26.9, 26.2, 18.8, 18.4, 17.9, −3.7, −4.4; FT-IR (thin film) 2926, 2895, 2843, 1446, 1378, 1243, 166, 1140, 1093, 1015 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{29}H_{48}NaO_8Si$ 575.3016, found 575.3029.

Methyl 3-O-tert-butyldimethylsilyl-2,6-dideoxy-4-O-p-methoxybenzyl-β-D-ribo-hexapyranosyl-(1→4)-6-deoxy-2,3-O-isopropylidene-α-L-mannopyranoside (**18**). Prepared according to general procedure from compound **11** (1.8 g, 4.9 mmol), **12** (1.6 g, 7.4 mmol), and 10 mol % catalyst $ReOCl_3(SMe_2)(OPPh_3)$ in 4.9 mL of benzene at ambient temperature in 60 h. Purification by silica gel flash column chromatography (hexanes:EtOAc = 70:1 to 20:1) afforded **18** (1.86 g, 65% yield) and its α-anomer (142 mg). The β-anomer **18** is characterized as follows: $[\alpha]_D^{23}$ = 18.3° (*c* = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26−7.21 (m, 2 H), 6.89−6.83 (m, 2 H), 5.27 (dd, *J* = 1.8, 9.5 Hz, 1 H), 4.83 (s, 1 H), 4.57 (d, *J* = 11.6 Hz, 1 H), 4.34 (d, *J* = 11.4 Hz, 1 H), 4.26 (td, *J* = 2.1, 3.9 Hz, 1 H), 4.12−4.07 (m, 1 H), 4.07−4.03 (m, 1 H), 3.87 (dd, *J* = 6.2, 9.4 Hz, 1 H), 3.80 (s, 3 H), 3.61−3.50 (m, 2 H), 3.35 (s, 3 H), 2.98 (dd, *J* = 2.5, 9.3 Hz, 1 H), 1.98 (ddd, *J* = 1.9, 3.9, 13.2 Hz, 1 H), 1.57−1.47 (ovrlp, 4 H), 1.31 (s, 3 H), 1.28 (d, *J* = 6.1 Hz, 3 H), 1.20 (d, *J* = 6.2 Hz, 3 H), 0.94−0.88 (s, 9 H), 0.10−0.07 (m, 3 H), 0.07−0.02 (m, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.5, 130.7, 129.8, 114.0, 109.4, 98.3, 97.9, 80.9, 79.4, 78.8, 76.4, 71.1, 69.0, 66.1, 64.8, 55.6, 55.1, 39.9, 28.2, 26.7, 26.1, 18.7, 18.5, 17.9, −4.1, −4.6; FT-IR (thin film) 2926, 1607, 1508, 1461, 1378, 1301, 1249, 1145, 1093, 1041 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{30}H_{50}NaO_9Si$ 605.3122, found 605.3113.

Phenyl 3-O-benzyl-2,6-dideoxy-β-D-ribo-hexapyranosyl-(1→4)-3-O-benzyl-6-deoxy-2-O-methyl-1-thio-α-D-ribo-hexopyranoside (**20**). To a solution of **8** (601 mg, 1.8 mmol) and **13**[21] (432 mg, 1.2 mmol) in 2.4 mL of benzene at 0 °C was added 78 mg (10 mol %) of catalyst $ReOCl_3(SMe_2)(OPPh_3)$. The reaction mixture was stirred for 3 days before 200 μL of saturated sodium bicarbonate was added. The resulting mixture was filtered through anhydrous sodium sulfate, concentrated in vacuo, and purified by silica gel flash column chromatography (hexanes:EtOAc = 70:1 to 5:1) to afford **19** (577 mg), its α-anomer (70 mg), and unreacted acceptor **13** (59.4 mg). The β-anomer **19** was dissolved in 3.0 mL of THF at 0 °C, and tetra-*n*-butylammonium fluoride (1.25 mL, 1 M in THF) was added. The resulting mixture was stirred overnight before saturated sodium bicarbonate was added. After THF was evaporated, the aqueous layer was extracted with ethyl acetate (3 × 15 mL). Combined organic extracts were washed sequentially with water (5 mL) and brine (2 × 10 mL), dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (toluene:EtOAc = 10:1) to afford **20** (448 mg, 64% yield over 2 steps) (75% yield based on recovered alcohol **13**). Compound **20** is characterized as follows: $[\alpha]_D^{23}$ = 167.8° (*c* = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58−7.48 (m, 4 H), 7.40−7.35 (m, 2 H), 7.35−7.29 (m, 4 H), 7.29−7.16 (ovrlp, 5 H), 5.50 (d, *J* = 5.7 Hz, 1 H), 4.90 (s, 2 H), 4.81 (dd, *J* = 1.7, 9.5 Hz, 1 H), 4.69 (d, *J* = 11.6 Hz, 1 H), 4.55−4.46 (ovrlp, 2 H), 4.32−4.26 (m, 1 H), 3.90 (d, *J* = 2.8 Hz, 1 H), 3.68−3.62 (m, 1 H), 3.60 (dd, *J* = 2.4, 5.7 Hz, 1 H), 3.38 (s, 3 H), 3.23 (dd, *J* = 2.6, 9.9 Hz, 1 H), 3.22−3.15 (m, 1 H), 2.28−2.21 (ovrlp, 2 H), 1.63−1.55 (ovrlp,1 H), 1.27 (d, *J* = 6.2 Hz, 3 H), 1.24 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.8, 139.1, 138.2, 131.2, 129.0, 129.0, 128.4, 128.2, 128.1, 127.2, 126.8, 100.0, 86.8, 81.8, 79.5, 76.5, 76.2, 74.7, 72.8, 72.1, 71.0, 64.1, 57.2, 35.0, 18.7, 17.7; FT-IR (thin film) 3445, 2916, 2874, 1643, 1586, 1498, 1451, 1368, 1321, 1171 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{33}H_{40}NaO_7S$ 603.2392, found 603.2411.

Phenyl 3-O-benzyl-4-O-tert-butyldimethylsilyl-2,6-dideoxy-β-D-ribo-hexapyranosyl-(1→4)-3-O-benzyl-2,6-dideoxy-β-D-ribo-hexapyranosyl-(1→4)-3-O-benzyl-6-deoxy-2-O-methyl-1-thio-α-D-ribo-hexopyranoside (**21**). A mixture of compound **8** (1.1 g, 3.3 mmol) and **20** (1.27 g, 2.2 mmol) was dissolved in 1.5 mL of benzene at 0 °C before 10 mol % of catalyst $ReOCl_3(SMe_2)(OPPh_3)$ was added. The reaction mixture was stirred for 60 h before 300 μL of saturated sodium bicarbonate was added. The resulting mixture was filtered through anhydrous sodium sulfate, concentrated in vacuo, and purified by silica gel flash column chromatography (hexanes:EtOAc = 30:1 to 8:1) to afford **21** (1.51 g, 75% yield) and its α-anomer (215 mg). The β-anomer **21** is characterized as follows: $[\alpha]_D^{23}$ = 133.7° (*c* = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56−7.50 (m, 4 H), 7.40−7.25 (ovrlp, 15 H), 7.23 (d, *J* = 7.5 Hz, 1 H), 7.21−7.19 (m, 1 H), 5.49 (d, *J* = 5.7 Hz, 1 H), 4.94−4.90 (m, 1 H), 4.90−4.85 (ovrlp, 3 H), 4.84 (d, *J* = 12.3 Hz, 1 H), 4.80 (d, *J* = 11.9 Hz, 1 H), 4.61 (dd, *J* = 12.2, 14.0 Hz, 2 H), 4.51−4.44 (m, 1 H), 4.30 (t, *J* = 2.4 Hz, 1 H), 4.07 (q, *J* = 2.9 Hz, 1 H), 3.98−3.90 (m, 2 H), 3.79 (q, *J* = 2.8 Hz, 1 H), 3.59 (dd, *J* = 2.6, 5.7 Hz, 1 H), 3.39−3.34 (ovrlp, 4 H), 3.21 (ddd, *J* = 2.8, 6.4, 9.5 Hz, 2 H), 2.15 (ddd, *J* = 2.1, 3.6, 13.5 Hz, 1 H), 2.01 (ddd, *J* = 2.0, 3.5, 13.7 Hz, 1 H), 1.63 (ddd, *J* = 2.5, 9.7, 13.5 Hz, 1 H), 1.60−1.54 (ovrlp, 1 H), 1.25−1.17 (ovrlp, 9 H), 0.94 (s, 9 H), 0.11 (s, 3 H), 0.10−0.09 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.0, 139.9, 139.3, 139.2, 131.2, 129.0, 128.7, 128.5, 128.2, 128.2, 128.0, 127.9, 127.8, 127.7, 127.1, 126.8, 100.4, 100.3, 86.8, 82.9, 81.9, 79.4, 76.8, 76.6, 75.8, 75.6, 74.7, 73.1, 73.1, 70.2, 68.9, 64.1, 57.1, 37.2, 37.1, 26.2, 19.0, 18.6, 18.4, 17.7, −3.6, −4.4; FT-IR (thin film) 2926, 2885, 1586, 1498, 1446, 1368, 1347, 1249, 1166, 1088 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{52}H_{70}NaO_{10}SSi$ 937.4357, found 937.4360.

2,6-Dideoxy-3,4-bis-O-(triethylsilyl)-β-D-ribo-hexapyranosyl-(1→4)-2,6-dideoxy-3-O-triethylsilyl-β-D-ribo-hexapyranosyl-(1→4)-1,5-anhydro-2,6-dideoxy-3-O-triethylsilyl-D-ribo-hex-1-enitol (**23**). To a solution of **21** (1.51 g, 1.65 mmol) in 4 mL of THF was added tetra-*n*-butylammonium fluoride (3.3 mL, 1 M in THF). The reaction mixture was heated at 40 °C for 5 h before saturated sodium bicarbonate was added. After evaporating THF, the aqueous layer was extracted with ethyl acetate (3 × 50 mL). Combined organic extracts were washed sequentially with water (2 × 50 mL), brine (2 × 50 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (hexane:EtOAc = 10:1 to 2:1) to afford alcohol **22** (1.18 g, 89% yield). To this alcohol **22** (230 mg, 0.287 mmol) in 1 mL of THF cooled at −20 °C was added LiDBB (7.1 mL, 0.4 M). The reaction mixture was stirred for 15 min at −20 °C before 500 μL of saturated sodium bicarbonate was added. The resulting mixture was concentrated and purified by silica gel flash column chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH(20/1)) to afford corresponding tetra-ol. This tetra-ol was then dissolved in

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300 μL of *N*,*N*-dimethylformamide, imidazole (196 mg, 2.9 mmol) and triethylsilyl chloride (322 μL, 1.9 mmol) were added. The reaction mixture was stirred at room temperature for 45 min before water was added. The resulting mixture was extracted with dichloromethane (4 × 15 mL), and combined organic extracts were sequentially washed with water (2 × 20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. This crude mixture was purified by silica gel flash column chromatography (hexanes:CH_2Cl_2 = 10:1 to 3:1) to provide 174.4 mg of compound **23** (73% yield over 2 steps) which is characterized as follows: $[\alpha]_D^{23}$ = 98.8° (*c* = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.29 (d, *J* = 6.1 Hz, 1 H), 4.91 (dd, *J* = 1.7, 9.4 Hz, 1 H), 4.86 (dd, *J* = 2.0, 9.4 Hz, 1 H), 4.79 (t, *J* = 5.8 Hz, 1 H), 4.30−4.25 (m, 1 H), 4.21 (dd, *J* = 3.5, 5.7 Hz, 1 H), 4.13 (dd, *J* = 6.4, 10.5 Hz, 1 H), 4.00−3.95 (m, 1 H), 3.88−3.77 (m, 2 H), 3.44 (dd, *J* = 3.5, 10.5 Hz, 1 H), 3.18 (dd, *J* = 2.4, 9.2 Hz, 1 H), 3.03 (dd, *J* = 2.8, 9.5 Hz, 1 H), 1.94−1.87 (ovrlp, 2 H), 1.71−1.64 (m, 1 H), 1.64−1.56 (ovrlp, 1 H), 1.29 (d, *J* = 6.4 Hz, 3 H), 1.15 (t, *J* = 5.9 Hz, 6 H), 1.02−0.89 (m, 36 H), 0.70−0.51 (m, 24 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.2, 103.2, 100.1, 82.9, 80.9, 75.7, 70.5, 69.6, 69.5, 69.2, 68.4, 64.4, 40.3, 39.8, 18.8, 18.3, 17.6, 7.3, 7.3, 7.2, 5.4, 5.3, 5.2; FT-IR (thin film) 2955, 2876, 1641, 1458, 1368, 1316, 1236, 1171, 1137, 1083 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{42}H_{86}NaO_9Si_4$ 869.5247, found 869.5250.

Synthesis of Digitoxin (25) and C1′-epi-Digitoxin (26). To a mixture of **23** (52 mg, 61 μmol) and digitoxigenin **24** (23 mg, 61 μmol) (this mixture was dried via azeotrope with benzene) in 2.3 mL of dry chloroform was added 23 mg of freshly activated molecular sieves. This mixture was stirred for 10 min, Ph_3P·HBr (1 mg) was then added, and the resulting mixture was stirred at ambient temperature for 1 h. TLC analysis showed the reaction was incomplete. Therefore, another batch of Ph_3P·HBr (1 mg) was added, and the reaction was continued to stir for another 2 h. The reaction mixture was quenched with saturated sodium bicarbonate (1 mL), diluted with dichloromethane (70 mL). The organic layer was washed sequentially with water (2 × 5 mL), brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (hexanes:EtOAc = 20:1 to 10:1) to afford 46 mg (61%) of the glycoconjugate as an inseparable α/β mixture. To this α/β mixture (20 mg, 16 μmol) and ammonium fluoride hydrogen fluoride (NH_4F−HF, 132 mg, 2.3 mmol) was added 1.6 mL of DMF and 1.6 mL of NMP. The resulting mixture was stirred at 70 °C for 4 h. The reaction mixture was cooled down to room temperature, and solvents were removed by air flow. The residue was diluted with dichloromethane (40 mL), and organic layer was washed sequentially with water (2 × 10 mL), brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography (CH_2Cl_2/MeOH = 50/1 to 10/1) to afford 11 mg of a mixture of **25** and **26** (90% combined yield, **25**/**26** = 1/5). This α/β mixture was further purified by reverse phase HPLC (C18 column, a gradient of 30 to 70% CH_3CN in water over 20 min) to afford pure **25** and **26**, which are characterized below.

*Digitoxin (**25**).* $[\alpha]_D^{23}$ = 21° (*c* = 0.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.87 (s, 1 H), 4.99 (dd, *J* = 1.5, 18.2 Hz, 1 H), 4.90 (dt, *J* = 2.1, 9.9 Hz, 2 H), 4.86 (dd, *J* = 1.8, 9.5 Hz, 1 H), 4.81 (dd, *J* = 1.7, 18.1 Hz, 1 H), 4.27−4.22 (m, 2 H), 4.13 (br. S., 1 H), 4.02 (br. s., 1 H), 3.83 (qd, *J* = 6.1, 9.5 Hz, 1 H), 3.80−3.73 (m, 2 H), 3.34−3.29 (m, 1 H), 3.24 (dd, *J* = 3.0, 9.3 Hz, 1 H), 3.20 (dd, *J* = 3.0, 9.4 Hz, 1 H), 3.04 (s, 1 H), 2.97 (s, 1 H), 2.80−2.74 (m, 1 H), 2.30 (br. s., 1 H), 2.19−2.02 (m, 5 H), 2.01−1.94 (m, 1 H), 1.90−1.79 (m, 2 H), 1.76−1.33 (m, 21 H), 1.29 (d, *J* = 6.2 Hz, 3 H), 1.22 (dd, *J* = 1.8, 6.2 Hz, 6 H), 0.91 (s, 3 H), 0.86 (s, 3H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.9, 174.9, 118.0, 98.6, 98.5, 95.7, 86.0, 82.9, 82.5, 73.8, 73.1, 72.9, 69.8, 68.6, 68.4, 68.4, 66.8, 66.7, 51.3, 49.9, 42.2, 40.4, 38.1, 37.5, 37.0, 36.5, 36.1, 35.5, 33.5, 30.5, 30.1, 30.1, 27.2, 27.0, 26.9, 23.9, 21.7, 21.5, 18.5, 16.1; FT-IR (thin film) 3436, 2933, 1737, 1631, 1449, 1406, 1380, 1317, 1273, 1067 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{41}H_{64}NaO_{13}$ 787.4245, found 787.4238.

*C1′-epi-Digitoxin (**26**).* $[\alpha]_D^{23}$ = 56.5° (*c* = 0.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.87 (s, 1 H), 5.02−4.96 (m, 1 H), 4.94 (d, *J* = 3.3 Hz, 1 H), 4.93−4.87 (ovrlp, 2 H), 4.81 (dd, *J* = 1.7, 18.2 Hz, 1 H), 4.25 (d, *J* = 2.8 Hz, 1 H), 4.23−4.18 (m, 1 H), 4.15−4.11 (m, 1 H), 4.09−4.02 (m, 1 H), 3.98 (br. s., 1 H), 3.83−3.73 (ovrlp, 3 H), 3.33−3.27 (m, 1 H), 3.23 (td, *J* = 2.4, 9.5 Hz, 2 H), 3.00 (s, 1 H), 2.81−2.74 (m, 1 H), 2.36 (s, 1 H), 2.19−2.02 (ovrlp, 6 H), 1.93 (td, *J* = 3.4, 14.3 Hz, 1 H), 1.91−1.79 (m, 4 H), 1.78−1.72 (m, 1 H), 1.72−1.31 (m, 17 H), 1.30−1.19 (ovrlp, 9 H), 0.91 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.9, 174.8, 118.1, 99.7, 98.5, 95.3, 85.9, 82.8, 82.7, 73.8, 73.1, 72.1, 69.8, 68.4, 68.3, 67.8, 66.7, 63.1, 51.2, 49.9, 42.1, 40.3, 38.2, 37.1, 37.0, 36.1, 36.0, 35.5, 33.5, 32.4, 30.4, 30.0, 27.2, 26.8, 24.1, 24.0, 21.6, 21.5, 18.5, 18.5, 18.1, 16.1; FT-IR (thin film) 3435, 2932, 2095, 1738, 1633, 1449, 1406, 1380, 1319, 1223 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{41}H_{64}NaO_{13}$ 787.4245, found 787.4248.

*3,4-Di-O-tert-butyldimethylsilyl-2,6-dideoxy-β-D-ribo-hexapyranosyl-(1→4)-3-O-tert-butyldimethylsilyl-2,6-dideoxy-β-D-ribo-hexapyranosyl-(1→4)-1,5-anhydro-3-O-tert-butyldimethylsilyl-2,6-dideoxy-D-ribo-hex-1-enitol (**27**).* To a solution of **21** (274 mg, 0.30 mmol) in 1.0 mL of THF cooled at −20 °C was added LiDBB (6.6 mL, 2.64 mmol). The reaction mixture was stirred at −20 °C for 15 min and then quenched with 500 μL of saturated sodium bicarbonate, concentrated, and purified by silica gel flash column chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH(20/1)). The resulting compound was dissolved in 150 μL of *N*,*N*-dimethylformamide, imidazole (306 mg, 4.5 mmol) and *tert*-butylchlorodimethylsilane (452 mg, 3.0 mmol) were added. The reaction mixture was stirred at room temperature for several hours before being heated at 50 °C for 40 h. The reaction mixture was quenched with water and extracted with dichloromethane (4 × 20 mL). The combined organic layers were sequentially washed with water (2 × 20 mL), brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (hexanes:CH_2Cl_2 = 5:1) to afford **27** and its corresponding tri-TBS protected trisaccharide glycal. This tri-TBS-protected trisaccharide glycal was resubjected for *tert*-butyldimethylsilyl-protection at 90 °C. After a total of three cycles, 160 mg (63% yield overall) of **27** as well as 28 mg of tri-TBS-protected trisaccharide glycal were obtained. Compound **27** is characterized as follows: $[\alpha]_D^{23}$ = 103.9° (*c* = 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.28 (d, *J* = 5.9 Hz, 1 H), 4.90 (dd, *J* = 1.7, 9.5 Hz, 1 H), 4.86 (dd, *J* = 1.8, 9.5 Hz, 1 H), 4.77 (t, *J* = 5.8 Hz, 1 H), 4.27−4.23 (m, 1 H), 4.19 (dd, *J* = 3.5, 5.7 Hz, 1 H), 4.13−4.06 (m, 1 H), 3.98−3.94 (m, 1 H), 3.86−3.80 (m, 1 H), 3.80−3.73 (m, 1 H), 3.43 (dd, *J* = 3.5, 10.5 Hz, 1 H), 3.16 (dd, *J* = 2.4, 9.0 Hz, 1 H), 3.04 (dd, *J* = 2.8, 9.5 Hz, 1 H), 1.93 (ddd, *J* = 1.9, 4.0, 13.3 Hz, 1 H), 1.88 (ddd, *J* = 1.8, 3.9, 13.2 Hz, 1 H), 1.69−1.59 (ovrlp, 2 H), 1.28 (d, *J* = 6.2 Hz, 3 H), 1.13 (dd, *J* = 3.0, 6.3 Hz, 6 H), 0.94−0.84 (ovrlp, 36 H), 0.11−0.02 (ovrlp, 24 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.1, 103.3, 100.0, 100.0, 82.8, 80.7, 75.7, 70.3, 69.7, 69.3, 68.6, 64.5, 40.1, 39.7, 26.4, 26.3, 26.2, 19.0, 18.7, 18.5, 18.4, 18.4, 18.4, 17.6, −3.2, −3.8, −3.8, −4.0, −4.3, −4.4, −4.4, −5.1; FT-IR (thin film) 2955, 2930, 2892, 2857, 1641, 1472, 1387, 1254, 1137, 1084 cm^{-1}; ESIHRMS $[M+Na]^+$ calculated for $C_{42}H_{86}NaO_9Si_4$ 869.5247, found 869.5267.

Synthesis of Digitoxin (25) and C1′-epi-Digitoxin (26). To a mixture of **27** (51 mg, 60 μmol) and **24** (22 mg, 60 μmol) (this mixture was dried via azeotrope with benzene) in 2.3 mL of dry chloroform was added 23 mg of activated molecular sieves. This mixture was stirred for 10 min, Ph_3P.HBr (1 mg)[5] was added, and the resulting mixture was stirred at ambient temperature for 2 h. TLC analysis showed the reaction was incomplete. Therefore, another batch of Ph_3P·HBr (3 mg) was added, and the reaction was continued to stir for another 22 h. The reaction mixture was quenched with saturated sodium bicarbonate (1 mL) and diluted with dichloromethane (70 mL). The organic layer was washed sequentially with water (2 × 5 mL), brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (hexanes:EtOAc = 20:1 to 10:1) to afford 42 mg (57%) of the glycoconjugate as an inseparable α/β mixture. To this mixture (25 mg, 20.4 μmol) and ammonium fluoride hydrogen fluoride (NH_4F−HF, 168 mg, 2.9 mmol) was added 2 mL of DMF and 2 mL of NMP. The resulting mixture was stirred at 80 °C for six days. The reaction mixture was cooled down to room temperature, and

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solvents were removed by air flow. The residue was diluted in dichloromethane (40 mL), and organic layer was washed sequentially with water (2 × 10 mL), brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 50:1 to 10:1) to afford 13.3 mg of anomeric mixture **25** and **26** (85% combined yield, **25**/**26** = 1.4/1).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds, and select ^{1}H−^{13}C HSQC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) De Lederkremer, R. M.; Marino, C. *Adv. Carbohydr. Chem. Biochem.* **2008**, *61*, 143−216. (b) Kirschning, A.; Bechthold, A. F.-W.; Rohr, J. *Top. Curr. Chem.* **1997**, *188*, 1−84. (c) Weymouth-Wilson, A. C. *Nat. Prod. Rep.* **1997**, *14*, 99−110. (d) Kahne, D. *Chem. Biol.* **1995**, *2*, 7−12. (e) Kren, V.; Martinkova, L. *Curr. Med. Chem.* **2001**, *8*, 1303−1328. (f) Kren, V.; Rezanka, T. *FEMS Microbiol. Rev.* **2008**, *32*, 858−889.

(2) (a) Newman, R. A.; Yang, P.; Pawlus, A. D.; Block, K. I. *Mol. Interventions* **2008**, *8*, 36−49. (b) Riganti, C.; Campia, I.; Kopecka, J.; Gazzano, E.; Doublier, S.; Aldieri, E.; Bosia, A.; Ghigo, D. *Curr. Med. Chem.* **2011**, *18*, 872−885.

(3) (a) Schmiedeberg, J. E. O. *Arch. Exp. Pathol. Pharmakol.* **1875**, *3*, 16. (b) Greeff, K.; Schadewaldt, H. Cardiac Glycosides Part I: Experimental Pharmacology. In *Handbook of Experimental Pharmacology*; Greeff, K., Ed.; Springer-Verlag: Berlin, 1981; Vol. *56*, p 1−12. (c) Hauptman, P. J.; Kelly, R. A. *Circulation* **1999**, *99*, 1265−1270.

(4) Eichhorn, E. J.; Gheorghiade, M. *Prog. Cardiovasc. Dis.* **2002**, *44*, 251−256.

(5) Elbaz, H. A.; Stueckle, T. A.; Tse, W.; Rojanasakul, Y.; Dinu, C. Z. *Exp. Hematol. Oncol.* **2012**, *1*, 4 DOI: 10.1186/2162-3619-1-4.

(6) Wang, J. K. T.; Portbury, S.; Thomas, M. B.; Barney, S.; Ricca, D. J.; Morris, D. L.; Warner, D. S.; Lo, D. C. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 10461−10466.

(7) Wiesner, K.; Tsai, T. Y. R.; Jin, H. *Helv. Chim. Acta* **1985**, *68*, 300−314.

(8) McDonald, F. E.; Reddy, K. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3653−3655.

(9) Tanaka, H.; Yoshizawa, A.; Takahashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 2505−2507.

(10) Ma, Y.; Li, Z.; Shi, H.; Zhang, J.; Yu, B. *J. Org. Chem.* **2011**, *76*, 9748−9756.

(11) (a) Zhou, M.; O'Doherty, G. A. *J. Org. Chem.* **2007**, *72*, 2485−2493. (b) Zhou, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 4339−4342.

(12) Langenhan, J. M.; Peters, N. R.; Guzei, I. A.; Hoffmann, F. M.; Thorson, J. S. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 12305−12310.

(13) Yoshida, K.; Furuta, T.; Kawabata, T. *Tetrahedron Lett.* **2010**, *51*, 4830−4832. (b) Ueda, Y.; Mishiro, K.; Yoshida, K.; Furuta, T.; Kawabata, T. *J. Org. Chem.* **2012**, *77*, 7850−7857.

(14) Beale, T. M.; Taylor, M. S. *Org. Lett.* **2013**, *15*, 1358−1361.

(15) (a) Fullerton, D. S.; Kihara, M.; Deffo, T.; Kitatsuji, E.; Ahmed, K.; Simat, B.; From, A. H. L.; Rohrer, D. C. *J. Med. Chem.* **1984**, *27*, 256−261. (b) Rathore, H.; From, A. H. L.; Ahmed, K.; Fullerton, D. S. *J. Med. Chem.* **1986**, *29*, 1945−1952. (c) Langenhan, J. M.; Engle, J. M.; Slevin, L. K.; Fay, L. R.; Lucker, R. W.; Smith, K. R.; Endo, M. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 670−673. (d) Wang, H.-Y. L.; Xin, W.; Zhou, M.; Stueckle, T. A.; Rojanasakul, Y.; O'Doherty, G. A. *ACS Med. Chem. Lett.* **2011**, *2*, 73−78. (e) Wang, H.-Y. L.; Wu, B.; Zhang, Q.; Kang, S.-W.; Rojanasakul, Y.; O'Doherty, G. A. *ACS Med. Chem. Lett.* **2011**, *2*, 259−263.

(16) (a) Iyer, A. K. V.; Zhou, M.; Azad, N.; Elbaz, H.; Wang, L.; Rogalsky, D. K.; Rojanasakul, Y.; O'Doherty, G. A.; Langenhan, J. M. *ACS Med. Chem. Lett.* **2010**, *1*, 326−330. (b) Wang, H.-Y. L.; Rojanasakul, Y.; O'Doherty, G. A. *ACS Med. Chem. Lett.* **2011**, *2*, 264−269. (c) McDonald, F. E.; Wu, M. *Org. Lett.* **2002**, *4*, 3979−3981.

(17) (a) Li, X.; Zhu, J. *J. Carbohydr. Chem.* **2012**, *31*, 284−324. (b) McKay, M. J.; Nguyen, H. M. *ACS Catal.* **2012**, *2*, 1563−1595.

(18) For our previous effort in this research field, see: (a) Adhikari, S.; Baryal, K. N.; Zhu, D.; Li, X.; Zhu, J. *ACS Catal.* **2013**, *3*, 57−60. (b) Adhikari, S.; Li, X.; Zhu, J. *J. Carbohydr. Chem.* **2013**, *32*, 336−359.

(19) Sherry, B. D.; Loy, R. N.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4510−4511.

(20) Baryal, K. N.; Zhu, D.; Li, X.; Zhu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 8012−8016 See Supporting Information for the preparation of compound **8**.

(21) See Supporting Information for details.

(22) (a) Ferrier, R. J. *Top Curr. Chem.* **2001**, *215*, 153−175. (b) Rosati, O.; Curini, M.; Messina, F.; Marcotullio, M. C.; Cravotto, G. *Catal. Lett.* **2013**, *143*, 169−175.

(23) Fernandez-Mayoralas, A.; Marra, A.; Trumtel, M.; Veyrières, A.; Sinaÿ, P. *Tetrahedron Lett.* **1989**, *30*, 2537−2540.

(24) This global TBS-protection was found to be very challenging. Reaction was never completed, and desired product tetra-TBS protected **27** as well as a corresponding tri-TBS protected glycal were isolated. This tri-TBS protected glycal was resubjected to TBS protection at 90 °C (TBSCl, imidazole, DMF) to afford tetra-TBS protected **27**. See Supporting Information for details. It is worth noting that use of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and 2,6-lutidine at −78 °C for global TBS-protection afforded low yield of the desired product **27** together with significant amount of side products resulted from Ferrier rearrangement.

(25) Dick, W. E., Jr.; Weisleder, D.; Hodge, J. E. *Carbohydr. Res.* **1975**, *42*, 55−63.

(26) Lee, D.; Williamson, C. L.; Chan, L.; Taylor, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 8260−8267.