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Reaction of Glyconitriles with Organometallic Reagents: Access to Acyl β-*C*-Glycosides

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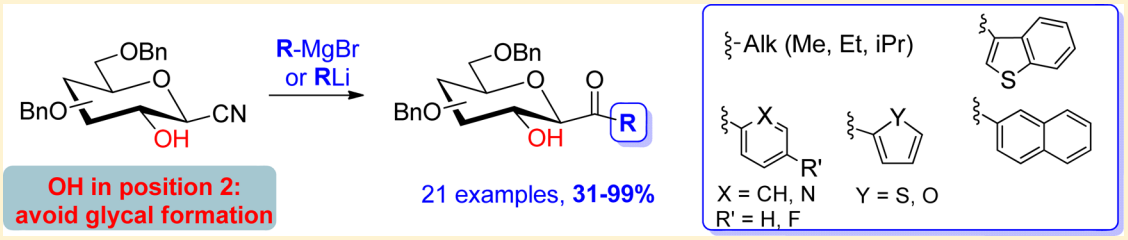
Supporting Information



ABSTRACT: A new strategy for the synthesis of acyl β-*C*-glycosides is described. The reactivity of glyconitriles toward organometallic reagents such as organomagnesium or organolithium derivatives was studied, affording acyl β-*C*-glycosides in moderate to good yields. In this study, glycal formation was efficiently prevented by deprotonating the hydroxyl group in position 2 of the glyconitriles during the process.

INTRODUCTION

Glycoconjugates, such as glycoproteins and glycolipids, are major components of the outer surface of mammalian cells and are fundamental to many important biological processes including inflammation, signal transduction, fertilization, immune response and cell−cell, bacterium−cell, or virus−cell recognition.[1]

In glycoconjugates, carbohydrates are generally covalently linked to the aglycone (lipid or protein) through an oxygen atom. However, due to the hydrolytic lability of the glycoside bond, the use of carbohydrate-derived molecules as drugs could be limited. Several research groups are focusing their attention on the development of stable mimics such as *C*-glycosides, which are inert to hydrolysis by glycosidases, and numerous methods have been developed for the synthesis of *C*-glycosides.[2]

As part of an ongoing program on the preparation of new *C*-galactoside analogues of complex bioactive galactosides, we investigated a strategy involving the synthesis of a *C*-galactosyl ketone as a key intermediate; such carbonyl group could be easily modified to original *C*-glycoconjugates. Furthermore, interesting biological activity of naturally acyl *C*-glycosides has been previously described.[3] We focused our attention on developing a direct method for the synthesis of *C*-glycosyl ketones. The most described methods to prepare acyl *C*-glycosides are highlighted on Scheme 1. The first approach consists of adding a C1-metalated-glycosyl nucleophile either to an aldehyde[4] followed by the oxidation of the corresponding alcohol or to an electrophilic acylating reagent (Scheme 1a).[5] Following this method, the *C*-glycosyl ketones are, in general, isolated in low to moderate overall yields and the scope is limited. Another strategy is based on the addition of a nucleophile to 1-formyl-*C*-glycoside[6] followed by the oxidation of the corresponding alcohol (Scheme 1b). In most examples, the main difficulty relies on the synthesis of the *C*-glycosyl aldehyde. Indeed during its preparation, either formation of byproducts due to oxidation of protective groups,[7] β-elimination product of a benzyloxy[8] or an azide[9] group in position 2 or acid formation,[10] or presence of an anomeric mixture during the oxidation step[8] have been observed lowering the overall yield and limiting their use. In order to isolate pure *C*-glycosyl aldehyde and particularly the β anomer, several research groups have introduced in the anomeric position a masked formyl group such as thiazole,[11] benzothiazole[12] or dithiane.[13] In 2005, Dondoni et al. have taken advantage of this strategy and reported a general synthesis of β-*C*-glycosyl ketones from β-*C*-glycosyl benzothiazole (Scheme 1c).[14] However, this method requires to unmask the carbonyl group, by use of toxic mercury salt. In 2012, a β-selective *C*-glycosylation was reported by Liu et al.[15] who described the first NHC-catalyzed acyl anion addition to the anomeric carbon of 2-nitroglycal leading to the corresponding acyl-*C*-glycoside (not illustrated on Scheme 1). However, this Stetter-type

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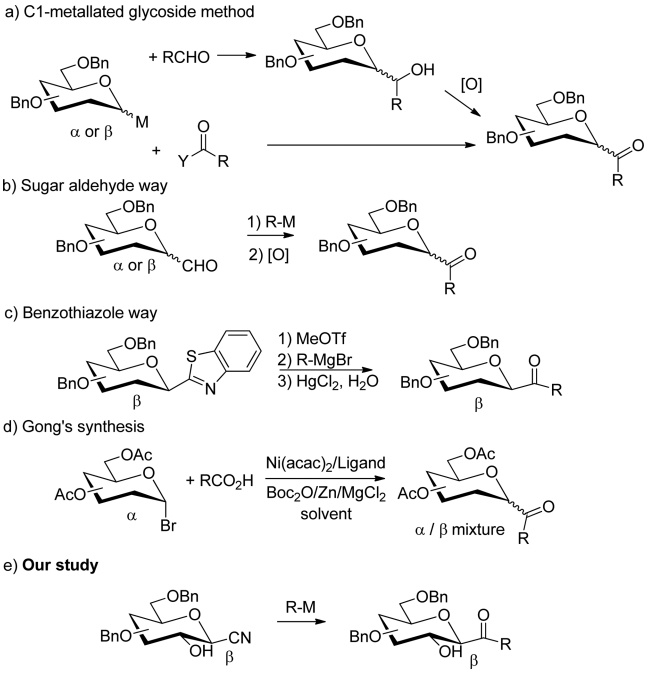
Scheme 1. General Strategies to Access Acyl-*C*-glycosides



reaction was only limited to 2-formylpyridine and quinoline derivatives.

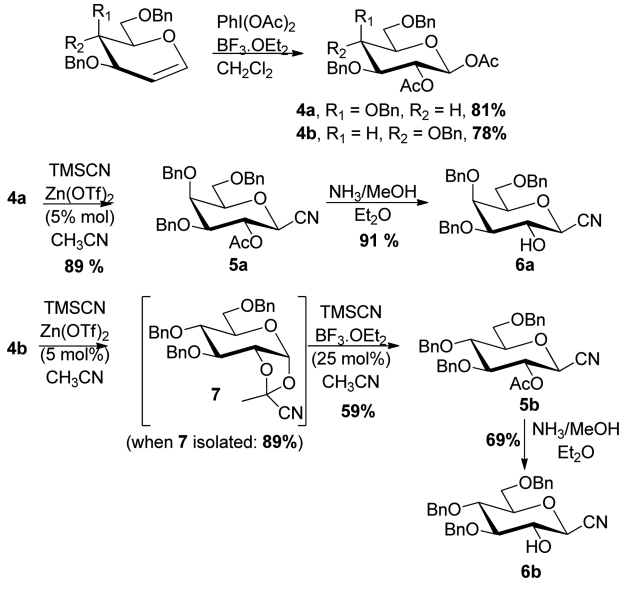
In the course of our study, Gong et al. described the synthesis of *C*-acyl glycosides from the Ni-catalyzed coupling between glycosyl bromides and carboxylic acids or anhydrides (Scheme 1d).[16] To date, this method is the most direct synthesis of acyl-*C*-glycosides; however with the exception of the mannose series a mixture of α/β-*C*-glycosides ketones was systematically obtained. Most of these reported methods present several drawbacks (poor yields, epimerization, use of toxic reagents...); therefore, the development of new strategies for the synthesis of such *C*-glycoside ketone remains of major importance. Herein, we report an alternative method and describe the first study on addition of organometallic reagents to *C*-glycosyl cyanide leading to acyl *C*-glycosides (Scheme 1e).

RESULTS AND DISCUSSION

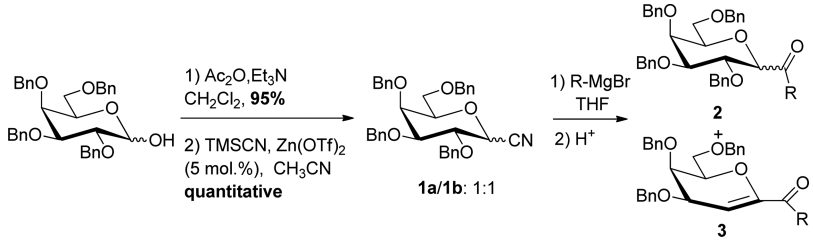
We first examined the reactivity of 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl cyanide **1** with organomagnesium reagents. Galactonitrile **1** were prepared by treatment of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-galactose[17] with 4 equiv of TMSCN in the presence of zinc triflate (0.05 equiv) in acetonitrile leading to a separable 1:1 mixture of α anomer **1a** and β anomer **1b** in quantitative yield by adapting a procedure described by de Las Heras[18] (Scheme 2). When a solution of ethylmagnesium bromide (1.25 equiv) was added to galactonitrile **1a** or **1b**, the corresponding 3,4,6-tri-*O*-benzyl-D-galactal cyanide (obtained by elimination of a benzyloxy group) was observed as the major product whereas the keto-*C*-glycosides **2** and **3** were the minor ones (Scheme 2). When β-*C*-galactosyl cyanide **1b** was reacted with either 1.25 or 3 equiv of phenylmagnesium bromide an inseparable 1:1 mixture of ketones **2** and **3** was obtained in 60% yield after hydrolysis. In the same conditions, α anomer **1a** yielded glycal **3** as the major product (**2**/**3** ratio, 1:2, Scheme 2). The formation of glycal products can be explained by the presence of the nitrile group which increases the lability of the anomeric hydrogen, facilitating then the elimination reaction.

To avoid the formation of glycal ketone **3**, we investigated the possibility of using a glyconitrile containing a hydroxyl group in position 2. The deprotonation of hydroxyl group during the organometallic process should prevent the elimination. To the best of our knowledge, only one similar strategy was reported to date. Knapp, while synthesizing ezomycins, described the addition of a dithioacetal organolithium derivative to a galactosyl cyanide bearing two hydroxyl groups in positions 2 and 3.[19] Our intent was to study the general outcome of organometallic addition reactions involving C-3, C-4 and C-6-protected glyconitrile bearing a free hydroxyl at C-2. 3,4,6-Tri-*O*-benzyl-β-D-galactosyl and β-D-glucosyl cyanides **6** have already been reported by Wadouachi et al.,[20] but in our hands, this method did not allow isolating derivatives **6** in high overall yield from the corresponding 3,4,6-tri-*O*-benzyl-D-glycal. We then opted for another three-step sequence (Scheme 3). The reaction between glycals and the diacetoxy-

Scheme 3. Synthesis of the 3,4,6-Tri-*O*-benzyl-β-D-galactosyl and β-D-Glucosyl Cyanides 6



Scheme 2. Reactivity of 2,3,4,6-Tetra-*O*-benzyl-1-cyano-1-deoxy-D-galactose with Organomagnesium Reagents



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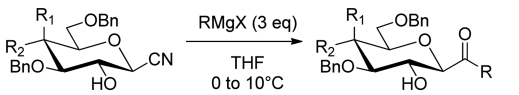
iodobenzene in the presence of a Lewis acid such as $BF_3{\cdot}OEt_2$ under the same conditions as described by Gin et al.[21] led to diacetates **4a** and **4b** in 81 and 78% yield, respectively. As observed by Gin et al. diacetate **4b** was always obtained in a mixture with the α-manno isomer (*gluco*/*manno*: 87:13); however compound **4b** could be easily isolated by column chromatography on silica. The introduction of the anomeric nitrile group was performed under the same conditions described in Scheme 2. Conversion of diacetate **4a** was complete after 45 min of reaction (estimated by TLC) and the corresponding galactonitrile **5a** was isolated in 89% yield. The ^{1}H NMR spectrum of compound **5a** showed a doublet at 4.09 ppm with a coupling constant of 10.1 Hz ($^3J_{H1-H2}$), which is characteristic of the β-configuration of *C*-galactosides. Under the same reaction conditions, diacetate **4b** gave the 1,2-*O*-cyanoethylidene glucose derivative **7** as the sole product of the reaction in 89% yield and no trace of **5b** was detected. Its structure was confirmed by ^{1}H and ^{13}C NMR analysis (Scheme 3).[22] The ^{1}H NMR spectrum presented a doublet at 5.82 ppm with a coupling constant of 5.2 Hz ($^3J_{H1-H2}$), which is characteristic of the α-configuration and the ^{13}C NMR spectrum showed signals at 98.8 and 117.1 ppm which were respectively attributed to CN group and the quaternary $C(CH_3)$ (CN) carbons; the signal of the carbonyl group of the acetate was not detected.[23]

The isomerization of compound **7** was then attempted by allowing the reaction mixture to stir at room temperature for 72 h but only 9% of glucosyl cyanide **5b** was isolated. In order to improve the isomerization step, boron trifluoride diethyl ether complex (0.25 equiv) was added to the reaction mixture, after formation of compound **7** (checked by TLC), but in that case only 15% of cyanide **5b** was isolated after 24 h. Optimization of the isomerization step was achieved by adding TMSCN (3 equiv) and $BF_3{\cdot}OEt_2$ (0.25 equiv) to the solution once compound **7** was formed (checked by TLC) resulting in the isolation of glucosyl cyanide **5b** in a 59% yield. The acetate group of the two glycosyl cyanides **5** was then removed under classical conditions to lead to the desired 3,4,6-tri-*O*-benzyl-β-D-galactosyl and β-D-glucosyl cyanides **6** (Scheme 3).

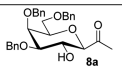
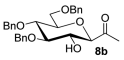
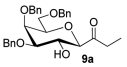
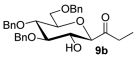
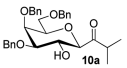
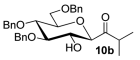
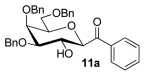
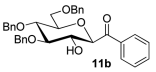
With glycosyl cyanides **6** in hand, we first examined their reactivity toward Grignard reagents. Initial attempts using galactosyl cyanide **6a** and three equivalents of commercially available solution of methylmagnesium bromide at low temperature (below −10 °C), led to the formation of acyl *C*-glycosides in very low yield. When the reaction was performed between 0 and 10 °C for 1.5 h, ketone **8a** was obtained in a moderate yield of 55% although starting material was totally consumed (estimated by TLC and ^{1}H NMR of the crude product) (Table 1, entry 1). The addition of various organomagnesium reagents to glycosyl cyanide **6** was then evaluated. Except for the addition of ethylmagnesium bromide to galactosyl cyanide **6a** and phenylmagnesium bromide to glucosyl cyanide **6b** (Table 1, entries 3 and 8) for which the yields were higher (>60%), the reactions between the different organomagnesium reagents and either galactosyl cyanide **6a** or glucosyl cyanide **6b** led to the corresponding ketones in the same range of yield (around 50%, entries 1−2 and 4−7). It is noteworthy that an extended reaction time led, in some cases, to a decrease of the yield due to the formation of the glycal analogue, as a byproduct, as confirmed by the presence of a doublet at 6.00 ppm on the ^{1}H NMR spectrum, characteristic of the H-2 of the glycal. In addition, when vinyl- or ethynylmagnesium bromide was added, no reaction was observed with glycosyl cyanide **6**.

Table 1. Addition of Grignard Reagent to Glycosyl Cyanides 6



6a, R_1 = OBn, R_2 = H
6b, R_1 = H, R_2 = OBn

8-11a, R_1 = OBn, R_2 = H
8-11b, R_1 = H, R_2 = OBn

Entry	Glycosyl cyanide	Glycosyl ketone	Yield (%)
1	**6a**	 **8a**	55
2	**6b**	 **8b**	53
3	**6a**	 **9a**	66
4	**6b**	 **9b**	51
5	**6a**	 **10a**	49
6	**6b**	 **10b**	49
7	**6a**	 **11a**	43
8	**6b**	 **11b**	61

The reactivity of glycosyl cyanide **6** toward organolithium reagents was then explored. The optimized conditions involved the addition of 3 equiv of organolithium reagents (commercially available or freshly prepared) in THF at −78 °C and then stirring of the reaction mixture at −40 °C until completion (checked by TLC). In these conditions, addition of commercial methyl or ethyllithium solutions to glucosyl cyanides **6b** offered the corresponding ketones **8b** and **9b** in 48% and 61% yield respectively (Table 2, entries 1 and 2).

When phenyllithium, 4-fluorophenyllithium and 2-naphtyllithium were used, ketones **11-13** were isolated in good to excellent yields (entries 3−8). Addition of aryl- or heteroaryllithium reagents to the galactosyl cyanide **6a** afforded the corresponding acyl *C*-glycosides in good yields for 1-naphtalene, 2-thiophene and 3-benzothiophene compounds (entries 9−10 and 13) and in modest yields for pyridine and furan derivatives (entries 11−12). It is noteworthy that ketone **16a** seemed to be unstable which did not allow to isolate it in high purity. Furthermore, no reaction occurred when acetylide lithium reagents were used.

In general, the *C*-glycosyl ketones were isolated in higher yield when organolithium reagents were used compared to organomagnesium reagents. In the latter case, some unidentified byproducts were formed probably due to a higher reaction

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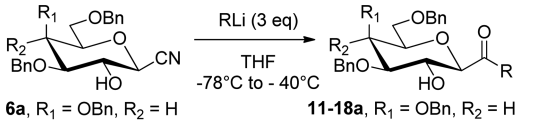
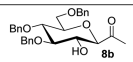
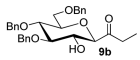
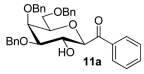
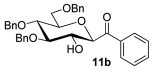
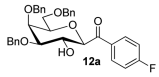
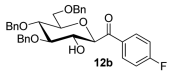
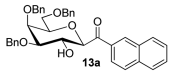
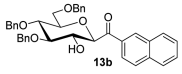
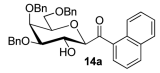
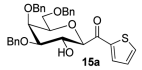
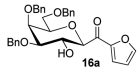
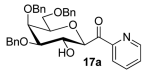
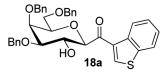
Table 2. Addition of Organolithium Reagents to Glycosyl Cyanides 6



6a, R_1 = OBn, R_2 = H
6b, R_1 = H, R_2 = OBn

11-18a, R_1 = OBn, R_2 = H
8, 9, 11-13b, R_1 = H, R_2 = OBn

Entry	Glycosyl cyanide	Glycosyl ketone	Yield (%)
1[a]	**6b**	 **8b**	48
2[a]	**6b**	 **9b**	61
3[a]	**6a**	 **11a**	99
4[a]	**6b**	 **11b**	69
5[b]	**6a**	 **12a**	66
6[b]	**6b**	 **12b**	56
7[b]	**6a**	 **13a**	73
8[b]	**6b**	 **13b**	51
9[b]	**6a**	 **14a**	72
10[b]	**6a**	 **15a**	79
11[b]	**6a**	 **16a**	36
12[b]	**6a**	 **17a**	31
13[b]	**6a**	 **18a**	67

[a]Commercial organolithium solution. [b]Freshly prepared organolithium solution.

temperature. In addition, a wide range of acyl β-*C*-glycosides could be obtained with the organolithium reagents.

CONCLUSION

In summary, we described a new direct access to different acyl β-*C*-glycosides from glyconitriles. This work constitutes the first general study on the reactivity of glyconitriles toward organomagnesium or organolithium compounds. The addition of various organomagnesium and organolithium to either galactosyl or glucosyl cyanides led to the corresponding acyl β-*C*-glycosides in moderate to good yields. This route to access β-*C*-glycosyl ketones is highly competitive with the reported methods, as it allows to synthesize β-*C*-glycosyl ketones in a stereoselective manner and good overall yield, with the whole process only requiring four steps from the corresponding glycal without using any toxic heavy metal. Furthermore, compared to the aldehyde homologue, the glyconitriles were highly stable and could be handled for a long time even at room temperature. Further functionalization of carbonyl group could allow the access of new *C*-glycosides, which are considered as stable analogues of biologically relevant *O*-arylglycosides.[24]

EXPERIMENTAL SECTION

General Information. All air- and moisture-sensitive reactions were carried out in anhydrous solvent under argon using flame-dried glassware. Diethyl ether, dichloromethane and THF were dried over activated neutral alumina column under nitrogen. Dry methanol was distilled in the presence of sodium and dry acetonitrile was distilled over CaH_2 under argon. Boron trifluoride diethyl etherate complex was distilled prior to use. TLC and column chromatography were respectively performed on Alugram SIL G/UV 254 silica gel sheets and on silica gel 60 (40−63 μm). ^{1}H and ^{13}C NMR spectra were respectively recorded at 400 and 100.6 MHz. The chemical shifts (δ) are expressed in part per million (ppm) relative to Me_4Si and the coupling constants (J) in Hertz. The splitting patterns were designated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Proton and carbon assignments were established using COSY, HSQC, HMBC and DEPT-Q experiments. High-resolution mass spectra were recorded on a Q-Tof mass spectrometer. 3,4,6-Tri-*O*-benzyl-D-glucal and D-galactal were prepared following described methods.[25] Commercial organomagnesium[26] or alkyllithium[27] reagents were titrated just prior to use and aryllithium reagents were prepared by lithium/bromine exchange from the corresponding aryl bromide or by following known procedures.[28]

*1,2-Di-O-acetyl-3,4,6-tri-O-benzyl-β-D-galactopyranose (**4a**).*[21] Boron trifluoride diethyl etherate (2.6 mL, 20.8 mmol, 0.25 equiv) was added to a solution of 3,4,6-tri-*O*-benzyl-D-galactal (33.4 g, 80.1 mmol) and iodobenzene diacetate (31.3 g, 87.4 mmol, 1.1 equiv) in dry DCM (800 mL) at −60 °C. The reaction was stirred at this temperature for 45 min then warmed to −25 °C and stirred for another 1h30. The solution was cooled to −45 °C. Triethylamine (60 mL) and an aqueous saturated ammonium chloride solution (600 mL) were added successively. The layers were partitioned and the aqueous layer was extracted with DCM (2 × 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was recrystallized in EtOH (400 mL) to give **4a** (34.72 g, 64.9 mmol, 81%) as white needles: mp 81−82 °C; R_f = 0.22 (cyclohexane/EtOAc 8:2); $[\alpha]_D^{25}$= +24.9 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.22 (m, 15H), 5.58 (d, 1H, J = 8.2 Hz), 5.48 (dd, 1H, J = 10.0, 8.2 Hz), 4.93 (d, 1H, J = 11.5 Hz), 4.67 (d, 1H, J = 12.2 Hz), 4.59 (d, 1H, J = 11.5 Hz), 4.51 (d, 1H, J = 12.2 Hz), 4.45 (d, 1H, J = 11.6 Hz), 4.40 (d, 1H, J = 11.6 Hz), 4.00 (d, 1H, J = 2.6 Hz), 3.69−3.73 (m, 1H), 3.64 (dd, 1H, J = 8.9, 7.5 Hz), 3.58 (dd, 1H, J = 8.9, 5.5 Hz,), 3.58 (dd, 1H, J = 10.0, 2.6 Hz), 1.99 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 169.5, 169.4, 138.2, 137.7, 137.6, 128.4, 128.2, 128.0, 127.9, 127.8, 127.6, 127.4, 92.6, 74.6, 74.3, 73.5, 72.2, 72.1, 70.3, 67.8, 20.9, 20.8.

*1,2-Di-O-acetyl-3,4,6-tri-O-benzyl-β-D-glucopyranose (**4b**).*[21] Following the procedure described aboved, 3,4,6-tri-*O*-benzyl-D-glucal (2 g, 4.8 mmol) led to **4b** (1.87 g, 3.5 mmol, 78%) as a yellow oil after purification by chromatography eluting with dichloromethane/Acetone (100:1 to 50:1). R_f = 0.60 (dichloromethane/acetone 5:1); $[\alpha]_D^{25}$ = +24.9 (c 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.22 (m, 15H), 5.61 (d, 1H, J = 8.2 Hz), 5.11 (dd, 1H, J = 9.2, 8.2 Hz), 4.80 (d, 1H, J = 11.4 Hz), 4.77 (d, 1H, J = 10.9 Hz), 4.67 (d, 1H, J = 11.4 Hz), 4.62 (d, 1H, J = 12.0 Hz), 4.54 (d, 1H, J = 10.9 Hz), 4.49 (d, 1H, J = 12.0 Hz), 3.80 (dd, 1H, J = 9.2, 9.1 Hz), 3.75−3.79 (m, 2H), 3.70 (dd, 1H, J = 9.2, 9.1 Hz), 3.60 (ddd, 1H, J = 9.2, 3.3, 2.2 Hz), 2.08 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 169.5, 169.4, 138.1, 138.0, 137.8, 128.5, 128.4 (3C), 127.9 (2C), 127.8, 127.9, 127.7, 92.3, 82.8, 77.2, 75.8, 75.2, 75.1, 73.6, 72.2, 68.1, 20.9, 20.8.

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*2-O-Acetyl-3,4,6-tri-O-benzyl-β-D-galactopyranosyl cyanide (**5a**).* To a stirred solution of diacetate **4a** (5.13 g, 9.60 mmol) and trimethylsilyl cyanide (5.5 mL, 40.2 mmol, 4.2 equiv) in dry acetonitrile (96 mL) was added zinc trifluoromethanesulfonate (0.21 g, 0.58 mmol, 0.06 equiv) in one portion at rt. The reaction mixture was stirred for 40 min, then a saturated aqueous solution of $NaHCO_3$ (100 mL) was added, followed by DCM (100 mL). The aqueous solution was extracted with DCM (2 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude residue as an orange oil. Further purification by flash chromatography (Pet.Ether/EtOAc 9:1 to 8:2) afforded **5a** (4.28 g, 8.52 mmol, 89% yield) as a yellow oil. R_f = 0.16 (cyclohexane/EtOAc 8:2); $[\alpha]_D^{25}$ = +8.8 (*c* 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.24 (m, 15H), 4.92 (d, 1H, *J* = 11.5 Hz), 4.66 (d, 1H, *J* = 12.2 Hz), 4.55 (d, 1H, *J* = 11.5 Hz), 4.52 (d, 1H, *J* = 12.2 Hz), 4.46 (d, 1H, *J* = 11.7 Hz), 4.41 (d, 1H, *J* = 11.7 Hz), 4.22 (dd, 1H, *J* = 10.1, 9.8 Hz), 4.09 (d, 1H, *J* = 10.1 Hz), 3.96 (d, 1H, *J* = 2.7 Hz), 3.61−3.52 (m, 3H), 3.49 (dd, 1H, *J* = 9.8, 2.7 Hz), 2.06 (s, 3H); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 168.8, 137.9, 137.5, 137.4, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.5, 115.1, 80.3, 78.6, 74.8, 73.7, 72.8, 72.2, 68.3, 68.2, 67.0, 20.6; HRMS (CI^+, NH_3 CH_4) Calcd for $C_{30}H_{32}NO_6$ $[M + H]^+$ 502.2230, found 502.2253.

*2-O-Acetyl-3,4,6-tri-O-benzyl-β-D-glucopyranosyl cyanide (**5b**).* Under argon, to a solution of diacetate **4b** (3.7 g, 6.90 mmol) in dry CH_3CN (60 mL) was added zinc trifluoromethanesulfonate (161 mg, 0.44 mmol, 0.06 equiv) and TMSCN (3.8 mL, 30.2 mmol, 4.4 equiv). The mixture was stirred at room temperature for 40 min before adding another portion of TMSCN (2.8 mL, 22 mmol, 3 equiv) and $BF_3{\cdot}OEt_2$ (233 μL, 1.84 mmol, 0.25 equiv). The resulting mixture was stirred at room temperature for 18 h then washed with saturated aqueous solution of $NaHCO_3$ and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and then concentrated under reduced pressure. Purification by column chromatography, eluting with cyclohexane/EtOAc (95:5 to 90:10) gave **5b** (2.0 g, 4.06 mmol, 59%) as a yellow oil. R_f = 0.38 (cyclohexane/EtOAc 8:2). $[\alpha]_D^{25}$ = −41.0 (*c* 1, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.14 (m, 15H), 5.28 (dd, 1H, *J* = 10.3, 9.3 Hz), 4.79 (d, 1H, *J* = 11.8 Hz), 4.77 (d, 1H, *J* = 10.9 Hz), 4.66 (d, 1H, *J* = 11.1 Hz), 4.59 (d, 1H, *J* = 11.8 Hz), 4.54 (d, 1H, *J* = 10.9 Hz), 4.52 (d, 1H, *J* = 11.1 Hz), 4.12 (d, 1H, *J* = 10.3 Hz), 3.72 (dd, 1H, *J* = 9.3, 5.2 Hz), 3.71 (dd, 1H, *J* = 7.6, 2.2 Hz), 3.70 (dd, 1H, *J* = 7.6, 4.9 Hz), 3.61 (dd, 1H, *J* = 9.3, 9.3 Hz), 3.46 (ddd, 1H, *J* = 8.6, 5.2, 2.2 Hz), 1.99 (s, 3H); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 168.9, 137.8, 137.7, 137.6, 128.6 (2C), 128.5 (2C), 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.6, 115.1, 83.2, 80.3, 77.5, 75.5, 75.4, 73.7, 70.5, 68.1, 66.7, 20.7; HRMS (ESI) Calcd for $C_{30}H_{32}NO_6$ $[M + H]^+$ 502.2224, found 502.2227.

*3,4,6-Tri-O-benzyl-1,2-O-(1-cyanoethylidene)-α-D-glucopyranose (**7**).* Under argon, to a solution of diacetate **4b** (250 mg, 0.46 mmol) in dry acetonitrile (5 mL) was added zinc trifluoromethanesulfonate (10 mg, 0.028 mmol, 0.06 equiv) and TMSCN (235 μL, 1.88 mmol, 4.1 equiv). The mixture was stirred at room temperature for 50 min. When the reaction is complete, the mixture was diluted with EtOAc (5 mL) and washed with $NaHCO_3$ (5 mL). The resulting mixture was extracted with EtOAc (3 × 15 mL) and the organic layers were dried over $MgSO_4$ and concentrated under a vacuum. Purification by column chromatography, eluting with cyclohexane/EtOAc: 95:5 afforded **7** as colorless oil (220 mg, 0.44 mmol, 89%). R_f = 0.63 (cyclohexane/EtOAc 8:2); $[\alpha]_D^{25}$ = +8 (*c* 2.7, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.14 (m, 15H), 5.82 (d, 1H, *J* = 5.2 Hz), 4.66 (d, 1H, *J* = 12.1 Hz), 4.57 (d, 1H, *J* = 12.5 Hz), 4.56 (d, 1H, *J* = 12.1 Hz), 4.50 (d, 1H, *J* = 11.3 Hz), 4.49 (d, 1H, *J* = 12.5 Hz), 4.44 (dd, 1H, *J* = 5.2, 3.1 Hz), 4.32 (d, 1H, *J* = 11.3 Hz), 3.90 (dd, 1H, *J* = 3.1, 3.1 Hz), 3.73−3.69 (m, 2H), 3.62 (dd, 2H, *J* = 5.5, 2.7 Hz), 1.84 (s, 3H); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 137.9, 137.6, 137.2, 128.6, 128.5, 128.4, 128.3, 128.2 (2C), 128.1 (2C), 128.0, 127.9 (2C), 127.8, 127.7, 127.6, 127.5, 117.1, 98.8, 98.5, 73.5, 72.6, 72.0, 70.6, 68.9, 68.8, 68.5, 24.7; HRMS (CI) Calcd for $C_{30}H_{32}NO_6$ $[M + H]^+$ 502.2230, found 502.2269.

*3,4,6-Tri-O-benzyl-β-D-galactopyranosyl cyanide (**6a**).*[20] To a solution of compound **5a** (12.9 g, 25.7 mmol) in dry diethyl ether (16.0 mL) was added a saturated solution of ammonia in MeOH (193 mL) at rt. The reaction mixture was stirred for 24 h (until TLC indicated complete conversion). Solvents were removed under reduced pressure and the residue was crystallized in EtOH to give galactonitrile **6a** (10.7 g, 23.3 mmol, 91%) as a white solid. R_f = 0.16 (cyclohexane/EtOAc 4:1); mp 83−84 °C ; $[\alpha]_D^{25}$ = +6.3 (*c* 0.7, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.24 (m, 15H), 4.85 (d, 1H, *J* = 11.4 Hz), 4.72 (d, 1H, *J* = 11.8 Hz), 4.59 (d, 1H, *J* = 11.8 Hz), 4.55 (d, 1H, *J* = 11.4 Hz), 4.47 (d, 1H, *J* = 11.7 Hz), 4.41 (d, 1H, *J* = 11.7 Hz), 4.22 (ddd, 1H, *J* = 10.0, 9.3, 3.8 Hz), 3.96 (d, 1H, *J* = 10.0 Hz), 3.93 (d, 1H, *J* = 2.8 Hz), 3.58−3.50 (m, 3H), 3.34 (dd, 1H, *J* = 9.3, 2.8 Hz), 2.89 (d, 1H, *J* = 3.8 Hz); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 138.0, 137.4 (2C), 128.6, 128.4, 128.3, 128.1, 128.0, 127.9 (2C), 127.8, 127.7, 116.4, 82.4, 78.3, 74.7, 73.6, 72.6, 72.4, 69.0, 68.4, 68.2; HRMS (CI^+, NH_3 CH_4) Calcd for $C_{28}H_{33}N_2O_5$ $[M + NH_4]^+$ 477.2389, found 477.2393.

*3,4,6-Tri-O-benzyl-β-D-glucopyranosyl cyanide (**6b**).*[20] Following the procedure described previously, acetate **5b** (3.60 g, 7.17 mmol) led to gluconitrile **6b** (2.27 g, 4.9 mmol, 69%) as a slightly green oil after purification by column chromatography (cyclohexane/EtOAc 95/5 to 90:1). R_f = 0.3 (cyclohexane/EtOAc 4:1); $[\alpha]_D^{25}$ = +29.6 (*c* 0.7, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.14 (m, 15H), 4.87 (d, 1H, *J* = 11.5 Hz), 4.81 (d, 1H, *J* = 11.5 Hz), 4.79 (d, 1H, *J* = 11.1 Hz), 4.59 (d, 1H, *J* = 11.8 Hz), 4.54 (d, 1H, *J* = 11.1 Hz), 4.51 (d, 1H, *J* = 11.8 Hz), 3.97 (d, 1H, *J* = 10.1 Hz), 3.74 (ddd, 1H, *J* = 10.1, 6.2, 4.0 Hz), 3.70−3.66 (m, 2H), 3.60 (dd, 1H, *J* = 9.2, 9.2 Hz), 3.46 (dd, 1H, *J* = 9.2, 6.2 Hz), 3.41 (ddd, 1H, *J* = 9.2, 3.7, 2.4 Hz), 3.01 (d, 1H, *J* = 4.0 Hz); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 138.1, 137.7, 137.6, 128.7, 128.5, 128.1 (2 C), 128.0 (2 C), 127.9 (2 C), 127.8, 116.3, 85.2, 80.0, 76.7, 75.6, 75.2, 73.7, 72.0, 68.9, 68.2; HRMS (ESI) Calcd for $C_{28}H_{30}NO_5$ $[M + H]^+$ 460.2118, found 460.2126.

Addition of Organometallic Reagents to Glycosyl Cyanide 6.

Procedure A: Organomagnesium Reagents. To a solution of glycosyl cyanide (1 equiv) in dry THF (0.2 mmol/mL) under argon at 0 °C was added a solution of commercial organomagnesium bromide reagent (3 equiv). The reaction mixture was allowed to warm to 10 °C over 1h30. TLC (cyclohexane/EtOAc 8:2) indicated completion of the reaction. At 0 °C, the solution was diluted with dichloromethane and an aqueous saturated ammonium chloride solution was then added. The reaction mixture was stirred at rt for 20 min and then extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Further purification by flash chromatography (cyclohexane/EtOAc) was performed.

Procedure B: Organolithium Reagents. To a solution of glycosyl cyanide (1 equiv) in dry THF (0.2 mmol/mL) under argon at −78 °C was added a solution of commercial or prepared organolithium reagent (3 equiv). The reaction mixture was allowed to warm to −40 °C and stirred at this temperature for 16 h (TLC (cyclohexane/EtOAc 8:2) indicated completion of the reaction). The solution was cooled to −78 °C and a 1 M solution of H_3PO_4 was then added. The reaction mixture was stirred at rt for 6 h then extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Further purification by flash chromatography (cyclohexane/EtOAc) was performed.

*1-((2R,3R,4R,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxytetrahydro-2H-pyran-2-yl)ethanone (**8a**).* Following procedure A, the reaction between galactosyl cyanide **6a** (150.2 mg, 0.327 mmol) and a commercial solution of methylmagnesium bromide in ether (2 M, 490 μL, 0.981 mmol) led to **8a** (85.7 mg, 0.180 mmol, 55%) as a colorless liquid. R_f = 0.15 (cyclohexane/EtOAc 4:1). $[\alpha]_D^{25}$ = +17.4 (*c* 0.25, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.24 (m, 15H), 4.91 (d, 1H, *J* = 11.5 Hz), 4.81 (d, 1H, *J* = 12.0 Hz), 4.74 (d, 1H, *J* = 12.0 Hz), 4.59 (d, 1H, *J* = 11.5 Hz), 4.49 (d, 1H, *J* = 11.9 Hz), 4.45 (d, 1H, *J* = 11.9 Hz), 4.19 (dd, 1H, *J* = 9.4, 9.3 Hz), 3.90 (d, 1H, *J* = 2.9 Hz), 3.66−3.61 (m, 2H), 3.56 (d, *J* = 9.4 Hz), 3.59−3.51 (m, 1H), 3.48 (dd, *J* = 9.3, 2.9 Hz), 3.34 (bs, 1H), 2.27 (s, 3H); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 209.7, 138.5, 138.4, 137.8, 128.4 (2C), 128.2

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(2C), 128.1 (2C), 127.8, 127.7, 127.6, 83.0 82.8, 77.8, 74.7, 73.7, 73.5, 72.9, 69.1, 69.0, 26.9; HRMS (CI^+, NH_3 CH_4) Calcd for $C_{29}H_{36}NO_6$ $[M + NH_4]^+$ 494.2543, found 494.2562.

*1-((2R,3R,4S,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxytetrahydro-2H-pyran-2-yl)ethanone (**8b**).* Following procedure A, the reaction between glucosyl cyanide **6b** (250 mg, 0.54 mmol) and a solution of methylmagnesium bromide in ether (2.85 M, 570 μL, 1.62 mmol) led to **8b** (136.4 mg, 0.287 mmol, 53%) as a colorless oil. Following procedure B, the reaction between glucosyl cyanide **6b** (200 mg, 0.44 mmol) and a solution of methyllithium in diethyl ether (1.24 M, 1.05 mL, 1.3 mmol) afforded **8b** (100.1 mg, 0.21 mmol, 48%) as a colorless oil. R_f = 0.35 (cyclohexane/EtOAc 7:3); $[\alpha]_D^{25}$ = +0.34 (*c* 0.56, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.08 (m, 15H), 4.94 (d, 1H, *J* = 11.2 Hz), 4.78 (d, 1H, *J* = 11.1 Hz), 4.76 (d, 1H, *J* = 11.1 Hz), 4.52 (d, 1H, *J* = 12.1 Hz), 4.49 (d, 1H, *J* = 11.2 Hz), 4.48 (d, 1H, *J* = 12.1 Hz), 3.72 (ddd, 1H, *J* = 10.2, 8.2, 1.8 Hz), 3.68 (dd, 1H, *J* = 11.1, 1.6 Hz), 3.62 (dd, 1H, *J* = 11.1, 4.2 Hz), 3.50−3.42 (m, 4H), 3.30 (d, 1H, *J* = 1.8 Hz), 2.24 (s, 3H); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 210.1, 138.7, 138.1 (2C), 128.4, 128.0 (2C), 127.9 (2C), 127.8, 127.7 (3C), 85.8, 82.3, 79.3, 76.9., 75.4, 75.1, 73.5, 72.8, 69.1, 27.1; HRMS (FD) Calcd for $C_{29}H_{32}O_6Na$ $[M + Na]^+$ 499.2091, found 499.2078.

*1-((2R,3R,4R,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxytetrahydro-2H-pyran-2-yl)propan-1-one (**9a**).* Following procedure A, the reaction between galactosyl cyanide **6a** (45.0 mg, 0.098 mmol) and a commercial solution of ethylmagnesium bromide in THF (1.7 M, 200 μL, 0.340 mmol) led to **9a** (31.7 mg, 0.065 mmol, 66%) as a colorless oil. R_f = 0.24 (cyclohexane/EtOAc 8:2); $[\alpha]_D^{25}$ = +59.5 (*c* 0.136, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.23 (m, 15H), 4.92 (d, 1H, *J* = 11.5 Hz), 4.83 (d, 1H, *J* = 12.0 Hz), 4.75 (d, 1H, *J* = 12.0 Hz), 4.59 (d, 1H, *J* = 11.5 Hz), 4.49 (d, 1H, *J* = 11.9 Hz), 4.45 (d, 1H, *J* = 11.9 Hz), 4.19 (ddd, 1H, *J* = 9.4, 9.3, 1.8 Hz), 3.90 (d, 1H, *J* = 2.9 Hz), 3.65−3.59 (m, 2H), 3.58 (d, 1H, *J* = 9.3 Hz), 3.52−3.57 (m, 1H), 3.48 (dd, 1H, *J* = 9.4, 2.9 Hz), 3.41 (d, 1H, *J* = 1.8 Hz), 2.79 (dq, 1H, *J* = 19.1, 7.2 Hz), 2.60 (dq, 1H, *J* = 19.1, 7.2 Hz), 1.02 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 212.3, 138.5 (2C), 137.9, 128.4 (2C), 128.2 (2C), 127.8, 127.6 (2C), 82.8, 82.6, 77.8, 74.7, 73.8, 73.6, 72.9, 69.2 (2C), 32.4, 6.8; HRMS (CI^+, NH_3 CH_4) Calcd for $C_{30}H_{38}NO_6$ $[M + NH_4]^+$ 508.2699, found 508.2713.

*1-((2R,3R,4S,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxytetrahydro-2H-pyran-2-yl)propan-1-one (**9b**).* Following procedure A, the reaction between glucosyl cyanide **6b** (250 mg, 0.54 mmol) and a commercial solution of ethylmagnesium bromide THF (1.6 M, 1 mL, 1.6 mmol) afforded **9b** (135.1 mg, 0.275 mmol, 51%) as a slightly yellow oil. Following procedure B, the reaction between glucosyl cyanide **6b** (200 mg, 0.44 mmol) and a solution of ethyllithium in benzene (0.43 M, 3 mL, 1.3 mmol) gave **9b** (131.7 mg, 0.269 mmol, 61%) as a colorless oil. R_f = 0.33 (cyclohexane/EtOAc 7:3); $[\alpha]_D^{25}$ = +14.0 (*c* 0.59, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.10 (m, 15H), 4.99 (d, 1H, *J* = 11.3 Hz), 4.84 (d, 1H, *J* = 12.8 Hz), 4.82 (d, 1H, *J* = 12.8 Hz), 4.58 (d, 1H, *J* = 12.3 Hz), 4.57 (d, 1H, *J* = 11.3 Hz), 4.54 (d, 1H, *J* = 12.3 Hz), 3.78 (dd, 1H, *J* = 8.9, 8.0 Hz), 3.75 (dd, 1H, *J* = 10.9, 1.7 Hz), 3.68 (dd, 1H, *J* = 10.9, 3.7 Hz), 3.62−3.48 (m, 4H), 3.35 (br s, 1H), 2.76 (dq, 1H, *J* = 18.7, 7.2 Hz), 2.63 (dq, 1H, *J* = 18.7, 7.2 Hz), 1.06 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 212.6, 138.8, 138.1 (2C), 128.4, 128.0 (3C), 127.8 (3C), 127.7 (2C), 85.9, 81.9, 79.3, 76.9, 75.4, 75.2, 73.5, 72.9, 69.1, 32.6, 6.9; HRMS (CI^+, NH_3 CH_4) Calcd for $C_{30}H_{38}NO_6$ $[M + NH_4]^+$ 508.2699, found 508.2694.

*1-((2R,3R,4R,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxytetrahydro-2H-pyran-2-yl)-2-methylpropan-1-one (**10a**).* Following procedure A, the reaction between galactosyl cyanide **6a** (250 mg, 0.54 mmol) and a commercial solution of isopropylmagnesium bromide in THF (1 M, 1.7 mL, 1.7 mmol) afforded **10a** (134 mg, 0.266 mmol, 49%) as a colorless oil. R_f = 0.36 (cyclohexane/EtOAc 7:3); $[\alpha]_D^{25}$ = +19.5 (*c* 0.58, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45−7.31 (m, 15H), 4.93 (d, 1H, *J* = 11.6 Hz), 4.84 (d, 1H, *J* = 12.1 Hz), 4.75 (d, 1H, *J* = 12.1 Hz), 4.57 (d, 1H, *J* = 11.6 Hz), 4.48 (d, 1H, *J* = 12.0 Hz), 4.45 (d, 1H, *J* = 12.0 Hz), 4.22 (ddd, 1H, *J* = 9.4, 9.3, 1.5 Hz), 3.90 (d, 1H, *J* = 2.9 Hz), 3.66−3.61 (m, 2H), 3.56 (d, 1H, *J* = 9.4 Hz), 3.59−3.52 (m, 1H), 3.49 (d, 1H, *J* = 1.5 Hz), 3.48 (dd, 1H, *J* = 9.3, 2.9 Hz), 3.21 (qq, 1H, *J* = 7.1, 6.8 Hz), 1.10 (d, 3H, *J* = 7.1 Hz), 1.06 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 215.4, 138.6, 138.5, 137.9, 128.5 (2C), 128.3, 128.2 (2C), 127.9, 127.7 (2C), 127.6, 82.8, 81.4, 77.9, 74.7, 73.9, 73.6, 73.1, 69.4, 69.3, 36.8, 18.4, 17.2; HRMS (ESI) Calcd for $C_{31}H_{36}NaO_6$ $[M + Na]^+$ 527.2404, found 527.2385.

*1-((2R,3R,4S,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxytetrahydro-2H-pyran-2-yl)-2-methylpropan-1-one (**10b**).* Following procedure A, the reaction between glucosyl cyanide **6b** (250 mg, 0.540 mmol) and a commercial solution of isopropylmagnesium bromide in THF (1 M, 1.7 mL, 1.7 mmol) led to **10b** (133.5 mg, 0.265 mmol, 49%) as a colorless oil. R_f = 0.36 (cyclohexane/EtOAc 7:3); $[\alpha]_D^{25}$ = +3.6 (*c* 0.68, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.18 (m, 15H), 4.99 (d, 1H, *J* = 11.3 Hz), 4.84 (d, 1H, *J* = 12.8 Hz), 4.82 (d, 1H, *J* = 12.8 Hz), 4.58 (d, 1H, *J* = 12.3 Hz), 4.57 (d, 1H, *J* = 11.3 Hz), 4.54 (d, 1H, *J* = 12.3 Hz), 3.78 (dd, 1H, *J* = 8.9, 8.0 Hz), 3.75 (dd, 1H, *J* = 10.9, 1.7 Hz), 3.68 (dd, 1H, *J* = 10.9, 3.7 Hz), 3.60−3.50 (m, 4H), 3.35 (br s, 1H), 3.23 (qq, 1H, *J* = 7.1, 6.9 Hz), 1.14 (d, 3H, *J* = 7.1 Hz), 1.09 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 215.7, 138.8, 138.1 (2C), 128.4, 128.0 (2C), 127.8 (2C), 127.7 (2C), 127.6, 85.9, 80.7, 79.4, 76.9, 75.5, 75.2, 73.4, 73.1, 69.1, 37.0, 18.4, 17.3; HRMS (ESI) Calcd for $C_{31}H_{36}NaO_6$ $[M + Na]^+$ 527.2404, found 527.2400.

*((2R,3R,4R,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxytetrahydro-2H-pyran-2-yl)-(phenyl)methanone (**11a**).* Following procedure A, the reaction between galactosyl cyanide **6a** (150.0 mg, 0.326 mmol) and a commercial solution of phenylmagnesium bromide in diethyl ether (2 M, 490 μL, 0.980 mmol) led to **11a** (76.1 mg, 0.141 mmol, 43%) as a white solid. Following procedure B, the reaction between galactosyl cyanide **6a** (159.3 mg, 0.347 mmol) and a commercial solution of phenyllithium in THF (0.75 M, 1.5 mL, 1.125 mmol) gave **11a** (186 mg, 0.345 mmol, 99%) as white needles. R_f = 0.22 (cyclohexane/EtOAc 8:2); mp 90.7−91.2 °C; $[\alpha]_D^{25}$ = −4.2 (*c* 0.404, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.08−8.06 (m, 2H), 7.55−7.50 (m, 1H), 7.42−7.24 (m, 17H), 4.96 (d, 1H, *J* = 11.5 Hz), 4.83 (d, 1H, *J* = 12.1 Hz), 4.80 (d, 1H, *J* = 12.1 Hz), 4.62 (d, 1H, *J* = 11.5 Hz), 4.59 (ddd, 1H, *J* = 9.7, 9.3, 2.9 Hz), 4.46 (d, 1H, *J* = 11.7 Hz), 4.40 (d, 1H, *J* = 11.7 Hz), 4.31 (d, 1H, *J* = 9.3 Hz), 4.00 (d, 1H, *J* = 2.6 Hz), 3.81 (ddd, 1H, *J* = 6.2, 6.2, 0.8 Hz), 3.62 (dd, 1H, *J* = 9.7, 2.6 Hz), 3.61 (dd, 1H, *J* = 9.7, 6.2 Hz), 3.55 (dd, 1H, *J* = 9.7, 6.2 Hz), 2.83 (d, 1H, *J* = 2.9 Hz); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 196.4, 138.5, 138.3, 137.9, 135.1, 133.5, 129.8, 128.5, 128.4, 128.3, 128.1 (2C), 127.8, 127.7, 127.6 (2C), 82.9, 81.5, 78.7, 76.7, 74.6, 73.6, 72.8, 69.3, 68.7; HRMS (CI^+, NH_3 CH_4) Calcd for $C_{34}H_{38}NO_6$ $[M + NH_4]^+$ 556.2699, found 556.2703.

*((2R,3R,4S,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxytetrahydro-2H-pyran-2-yl)-(phenyl)methanone (**11b**).* Following procedure A, the reaction between glucosyl cyanide **6b** (250 mg, 0.54 mmol) and a commercial solution of phenylmagnesium bromide in THF (1.5 M, 1.1 mL, 1.65 mmol) afforded **11b** (177.4 mg, 0.33 mmol, 61%) as a white solid. Following procedure B, the reaction between glucosyl cyanide **6b** (200 mg, 0.44 mmol) and a commercial solution of phenyllithium in dibutyl ether (1.5 M, 0.87 mL, 1.3 mmol) gave **11b** (162 mg, 0.301 mmol, 69%) as a white solid. R_f = 0.45 (cyclohexane/EtOAc 7:3); mp 78−79 °C; $[\alpha]_D^{25}$ = +26.9 (*c* 0.89 CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.00−7.95 (m, 2H), 7.52−7.50 (m, 1H), 7.36−7.30 (m, 3H), 7.29−7.14 (m, 14H), 4.96 (d, 1H, *J* = 11.1 Hz), 4.83 (d, 1H, *J* = 11.0 Hz), 4.82 (d, 1H, *J* = 11.1 Hz), 4.51 (d, 1H, *J* = 11.0 Hz), 4.45 (d, 1H, *J* = 12.2 Hz), 4.39 (d, 1H, *J* = 12.2 Hz), 4.30 (d, 1H, *J* = 9.1 Hz), 4.11 (dd, 1H, *J* = 9.1 Hz, 8.8 Hz), 3.74−3.64 (m, 3H), 3.55 (dd, 1H, *J* = 10.6, 5.3 Hz), 3.51 (dd, 1H, *J* = 9.0, 9.0 Hz), 2.87 (br s, 1H); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 196.7, 138.7, 138.1 (2C), 135.1, 133.7, 129.7, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6 (2C), 85.7, 80.3, 80.0, 76.7, 75.4, 75.1, 73.3, 72.4, 69.2; HRMS (ESI) Calcd for $C_{34}H_{34}NaO_6$ $[M + Na]^+$ 561.2248, found 561.2256.

*((2R,3R,4R,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxytetrahydro-2H-pyran-2-yl)-(4-fluorophenyl)methanone (**12a**).* Following procedure B, the reaction between galactosyl cyanide **6a**

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J. Org. Chem. 2016, 81, 2364−2371

(251.4 mg, 0.547 mmol) and a freshly prepared solution of 4-fluorophenyllithium in THF (2.45 mL, 1.64 mmol) gave **12a** (201.2 mg, 0.361 mmol, 66%) as a white solid. R_f = 0.24 (cyclohexane/EtOAc 8:2); mp 104−105 °C; $[\alpha]_D^{25}$ = −3.7 (*c* 0.378, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.10 (m, 2H), 7.41−7.24 (m, 15H), 7.00−6.95 (m, 2H), 4.96 (d, 1H, *J* = 11.4 Hz), 4.82 (d, 1H, *J* = 12.4 Hz), 4.79 (d, 1H, *J* = 12.4 Hz), 4.61 (d, 1H, *J* = 11.4 Hz), 4.67 (ddd, 1H, *J* = 9.4, 9.3, 2.9 Hz), 4.46 (d, 1H, *J* = 11.7 Hz), 4.42 (d, 1H, *J* = 11.7 Hz), 4.24 (d, 1H, *J* = 9.3 Hz), 3.99 (d, 1H, *J* = 2.7 Hz), 3.79 (dd, 1H, *J* = 6.2, 6.1 Hz), 3.63−3.59 (m, 2H), 3.53 (dd, 1H, *J* = 9.7, 6.0 Hz), 2.83 (d, 1H, *J* = 2.9 Hz); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 194.9, 165.9 (d, *J* = 255.9 Hz), 138.4, 138.2, 137.8, 132.7 (d, *J* = 9.6 Hz), 131.3 (d, *J* = 2.9 Hz), 128.5, 128.4, 128.3, 128.1, 127.8 (2C), 127.7, 127.6, 115.4 (d, *J* = 21.7 Hz), 82.8, 81.9, 78.7, 74.6, 73.6, 73.5, 72.8, 69.3, 68.7; HRMS (FD+) Calcd for $C_{34}H_{33}FO_6$ $[M]^+$ 556.2261, found 556.2287.

((2R,3R,4S,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxytetrahydro-2H-pyran-2-yl)-(4-fluorophenyl)methanone (***12b***). Following procedure B, the reaction between glucosyl cyanide **6b** (200 mg, 0.44 mmol) and a freshly prepared solution of 4-fluorophenyllithium in THF (7.2 mL, 1.3 mmol) led to compound **12b** (136.2 mg, 0.245 mmol, 56%) as a brown solid. R_f = 0.45 (cyclohexane/EtOAc: 8:2); mp 73−74 °C; $[\alpha]_D^{25}$ = −5.8 (*c* 0.64 CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.08 (m, 2H), 7.42−7.21 (m, 15H, H_{Ar}), 7.05−7.00 (m, 2H), 5.03 (d, 1H, *J* = 11.1 Hz), 4.89 (d, H, *J* = 10.9 Hz), 4.88 (d, 1H, *J* = 11.1 Hz), 4.57 (d, H, *J* = 10.9 Hz), 4.52 (d, 2H, *J* = 11.9 Hz), 4.46 (d, 2H, *J* = 11.9 Hz), 4.31 (d, 1H, *J* = 9.2 Hz), 4.16 (ddd, 1H, *J* = 9.2, 9.0, 2.9 Hz), 3.76−3.72 (m, 3H), 3.60 (dd, 1H, *J* = 10.5 Hz, 5.8 Hz), 3.56 (dd, 1H, *J* = 10.2 Hz, 8.6 Hz), 2.97 (d, 1H, *J* = 2.9 Hz); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 195.3, 166.1 (d, *J* = 254.2 Hz), 138.7, 138.0 (2C), 137.5, 132.6 (d, *J* = 9.6 Hz), 131.5, 128.5 (2C), 128.4, 128.1, 128.0, 127.9, 127.8, 127.7 (2C), 115.8 (d, *J* = 21.9 Hz), 85.7, 80.3, 80.2, 77.4, 75.5, 75.2, 73.4, 72.3, 69.3; HRMS (ESI) Calcd for $C_{34}H_{34}FO_6$ $[M + H]^+$ 557.2334, found 557.2323.

((2R,3R,4R,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxytetrahydro-2H-pyran-2-yl)-(naphthalen-2-yl)methanone (***13a***). Following procedure B, the reaction between galactosyl cyanide **6a** (251.0 mg, 0.546 mmol) and a freshly prepared solution of naphthalen-2-yllithium in THF (2.6 mL, 1.639 mmol) gave **13a** (234.0 mg, 0.397 mmol, 73%) as a white solid. R_f = 0.24 (cyclohexane/EtOAc 8:2); mp 133.5−134 °C; $[\alpha]_D^{25}$ = −43.1 (*c* 0.418, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.06 (d, 1H, *J* = 8.7 Hz), 7.81 (d, 1H, *J* = 7.8 Hz), 7.78 (d, 1H, *J* = 8.9 Hz), 7.62 (d, 1H, *J* = 8.2 Hz), 7.56 (dd, 1H, *J* = 7.8, 7.2 Hz), 7.43−7.23 (m, 16H), 4.99 (d, 1H, *J* = 11.2 Hz), 4.83 (s, 2H), 4.67 (dd, 1H, *J* = 9.4, 9.3 Hz), 4.64 (d, 1H, *J* = 11.2 Hz), 4.48 (d, 1H, *J* = 11.7 Hz), 4.42 (d, 1H, *J* = 11.7 Hz), 4.40 (d, 1H, *J* = 9.4 Hz), 4.04 (d, 1H, *J* = 2.6 Hz), 3.81 (dd, 1H, *J* = 6.2, 6.1 Hz), 3.66 (dd, 1H, *J* = 9.3, 2.6 Hz), 3.64 (dd, 1H, *J* = 9.7, 6.2 Hz), 3.59 (dd, 1H, *J* = 9.7, 6.1 Hz), 2.85 (br s, 1H); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 196.3, 138.5, 138.3, 137.8, 135.7, 132.5, 132.4, 132.1, 130.0, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8 (2C), 127.7 (2C), 127.6 (2C), 126.4, 124.9, 83.0, 82.2, 78.7, 74.7, 73.7, 73.6, 72.8, 69.4, 68.9; HRMS (FD^+) Calcd for $C_{38}H_{36}O_6$ $[M]^+$ 588.2512, found 588.2499.

((2R,3R,4S,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxytetrahydro-2H-pyran-2-yl)-(naphthalen-2-yl)methanone (***13b***). Following procedure B, the reaction between glucosyl cyanide **6b** (200 mg, 0.44 mmol) and a freshly prepared solution of naphthalen-2-yllithium in THF (6.8 mL, 1.3 mmol) led to compound **13b** (132.1 mg, 0.225 mmol, 51%) as a brown solid. R_f = 0.4 (cylohexane/EtOAc 8:2); mp 79−80 °C; $[\alpha]_D^{25}$ = −10.4 (*c* 0.56, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (br s, 1H), 8.05 (dd, 1H, *J* = 8.8, 1.6 Hz), 7.86−7.78 (m, 3H), 7.61−7.57 (m, 1H), 7.48−7.46 (m, 1H), 7.44−7.21 (m, 15H), 5.06 (d, 1H, *J* = 11.2 Hz), 4.91 (d, 1H, *J* = 10.9 Hz), 4.90 (d, 1H, *J* = 11.2 Hz), 4.60 (d, 1H, *J* = 10.9 Hz), 4.51 (d, 1H, *J* = 12.1 Hz), 4.49 (d, 1H, *J* = 9.3 Hz), 4.47 (d, 1H, *J* = 12.1 Hz), 4.24 (ddd, 1H, *J* = 9.3, 8.9, 2.7 Hz), 3.85−3.77 (m, 3H), 3.63 (dd, 1H, *J* = 11.0, 5.9 Hz), 3.60 (dd, 2H, *J* = 9.5, 9.5 Hz), 3.04 (d, 1H, *J* = 2.7 Hz);); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 196.9, 138.9, 138.2 (2C), 136.1, 132.6, 132.5, 130.2, 129.0, 128.6 (2C), 128.5 (2C), 128.3, 128.1 (2C), 128.0, 127.8 (2C), 127.7, 126.8, 124.9, 85.9, 80.5 (2C), 77.6, 75.6, 75.3, 73.6, 72.6, 69.5; HRMS (ESI) Calcd for $C_{38}H_{37}O_6$ $[M + H]^+$ 589.2585, found 589.2576.

((2R,3R,4R,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxytetrahydro-2H-pyran-2-yl)-(naphthalen-1-yl)methanone (***14a***). Following procedure B, the reaction between galactosyl cyanide **6a** (255.5 mg, 0.556 mmol) and a freshly prepared solution of naphthalen-1-yllithium in THF (2.5 mL, 1.668 mmol) led to compound **14a** (237.0 mg, 0.403 mmol, 72%) as an orange oil. R_f = 0.4 (cyclohexane/EtOAc 7:3); $[\alpha]_D^{25}$ = +0.6 (*c* 0.53, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, 1H, *J* = 8.6 Hz), 8.07 (dd, 1H, *J* = 7.3, 1.2 Hz), 7.95 (d, 1H, *J* = 8.2 Hz), 7.83 (dd, 1H, *J* = 8.1, 1.3 Hz), 7.55 (ddd, 1H, *J* = 8.6, 6.8, 1.5 Hz), 7.49 (ddd, 1H, *J* = 8.1, 6.8, 1.2 Hz), 7.41−7.24 (m, 14H), 7.20−7.16 (m, 2H), 4.94 (d, 1H, *J* = 11.6 Hz), 4.79 (s, 2H), 4.62 (dd, 1H, *J* = 9.4, 9.3 Hz), 4.62 (d, 1H, *J* = 11.6 Hz), 4.43 (d, 1H, *J* = 9.3 Hz), 4.38 (d, 1H, *J* = 11.8 Hz), 4.33 (d, 1H, *J* = 11.8 Hz), 3.98 (d, 1H, *J* = 2.8 Hz), 3.77 (dd, 1H, *J* = 6.2, 6.0 Hz), 3.62 (dd, 1H, *J* = 9.4, 2.8 Hz), 3.55 (dd, 1H, *J* = 9.9, 6.0 Hz), 3.52 (dd, 1H, *J* = 9.9, 6.2 Hz), 3.07 (br s, 1H); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 200.4, 138.5, 138.3, 137.8, 133.8, 133.3, 133.0, 130.8, 130.0, 128.4 (2C), 128.3, 128.2, 128.1, 128.0, 127.7 (3C), 127.6 (2C), 126.3, 125.8, 124.1, 83.0, 81.9, 78.6, 74.5, 73.6, 73.4, 72.7, 69.2, 69.1; HRMS (FD^+) calculated for $C_{38}H_{36}O_6$ $[M]^+$ 588.2512, found 588.2562.

((2R,3R,4R,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxytetrahydro-2H-pyran-2-yl)-(thiophen-2-yl)methanone (***15a***). Following procedure B, the reaction between galactosyl cyanide **6a** (154.4 mg, 0.336 mmol) and a prepared solution 2-thienyllithium in THF (1.4 mL, 1.092 mmol) afforded **15a** (144.3 mg, 0.265 mmol, 79%) as a yellow thick oil. R_f = 0.23 (cyclohexane/EtOAc 8:2); $[\alpha]_D^{25}$ = +4.5 (*c* 0.312, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, 1H, *J* = 3.9, 1.1 Hz), 7.61 (dd, 1H, *J* = 4.9, 1.1 Hz), 7.71−7.24 (m, 15H), 7.00 (dd, 1H, *J* = 4.9, 3.9 Hz), 4.96 (d, 1H, *J* = 11.5 Hz), 4.84 (d, 1H, *J* = 12.1 Hz), 4.78 (d, 1H, *J* = 12.1 Hz), 4.61 (d, 1H, *J* = 11.1 Hz), 4.49 (dd, 1H, *J* = 9.5, 9.4 Hz), 4.49 (d, 1H, *J* = 11.9 Hz), 4.45(d, 1H, *J* = 11.9 Hz), 4.12 (d, 1H, *J* = 9.4 Hz), 3.97 (d, 1H, *J* = 2.7 Hz), 3.78 (dd, 1H, *J* = 6.4, 6.2 Hz), 3.63 (dd, 1H, *J* = 9.5, 6.4 Hz), 3.58 (dd, 1H, *J* = 9.5, 6.2 Hz), 3.55 (dd, 1H, *J* = 9.5, 2.7 Hz), 3.13 (br s, 1H); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 196.4, 138.5, 138.3, 137.8, 135.1, 133.5, 128.5, 128.4, 128.3, 128.2, 128.1(2C), 127.8, 127.7, 127.6 (2C), 82.8, 81.5, 78.7, 74.6, 73.6 (2C), 72.8, 69.3, 68.7; HRMS (FD^+) Calcd for $C_{32}H_{33}O_6S$ $[M + H]^+$ 545.1998, found 545.2002.

((2R,3R,4R,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxytetrahydro-2H-pyran-2-yl)-(furan-2-yl)methanone (***16a***). Following procedure B, the reaction between galactosyl cyanide **6a** (151.8 mg, 0.330 mmol) and a freshly prepared solution of furan-2-yllithium in THF (1.2 mL, 0.972 mmol) gave **16a** (62.7 mg, 0.119 mmol, 36%) as a slightly orange oil. R_f = 0.12 (cyclohexane/EtOAc 8:2); $[\alpha]_D^{25}$ = +17.1 (*c* 0.24, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 1H, *J* = 1.6 Hz), 7.57 (d, 1H, *J* = 3.7 Hz), 7.40−7.20 (m, 15H), 6.43 (dd, 1H, *J* = 3.7, 1.6 Hz), 4.94 (d, 1H, *J* = 11.5 Hz), 4.82 (d, 1H, *J* = 12.0 Hz), 4.77 (d, 1H, *J* = 12.0 Hz), 4.61 (d, 1H, *J* = 11.5 Hz), 4.49 (d, 1H, *J* = 11.7 Hz), 4.46 (dd, 1H, *J* = 9.4, 9.4 Hz), 4.45 (d, 1H, *J* = 11.7 Hz), 4.10 (d, 1H, *J* = 9.4 Hz), 3.95 (d, 1H, *J* = 2.8 Hz), 3.75 (dd, 1H, *J* = 6.5, 5.9 Hz), 3.66 (dd, 1H, *J* = 9.5, 6.5 Hz), 3.57 (dd, 1H, *J* = 9.4, 2.8 Hz), 3.52 (dd, 1H, *J* = 9.5, 5.9 Hz); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 190.3, 140.9, 138.5, 138.3, 137.8, 135.6, 135.0, 128.5, 128.4, 128.2, 128.1, 127.8 (2C), 127.8, 127.7, 127.6, 82.8 (2C), 78.3, 76.7, 74.5, 73.6, 72.9, 69.3 (2C); HRMS (FD^+) Calcd for $C_{32}H_{33}O_7$ $[M + H]^+$ 529.2226, found 529.2195.

((2R,3R,4R,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxytetrahydro-2H-pyran-2-yl)-(pyridin-2-yl)methanone (***17a***). Following procedure B, the reaction between galactosyl cyanide **6a** (152.8 mg, 0.333 mmol) and a freshly prepared solution of 2-pyridyllithium in THF (1.4 mL, 1.078 mmol) led to **17a** (55.7 mg, 0.103 mmol, 31%) as an orange oil. R_f = 0.12 (cyclohexane/EtOAc 8:2); $[\alpha]_D^{25}$ = +16.0 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (ddd, 1H, *J* = 4.8, 1.7, 1.1 Hz), 8.04 (ddd, 1H, *J* = 7.8, 1.1, 1.1 Hz), 7.79 (ddd, 1H, *J* = 7.8, 7.6, 1.7 Hz), 7.43 (ddd, 1H, *J* = 7.6, 4.8, 1.2 Hz), 7.39−7.21 (m, 15H), 5.17 (d, 1H, *J* = 9.5 Hz), 4.92 (d, 1H, *J* = 11.6 Hz), 4.79 (d, 1H, *J* = 11.9 Hz), 4.75 (d, 1H, *J* = 11.9 Hz), 4.63 (d, 1H, *J* = 11.6 Hz), 4.45 (d, 1H, *J* = 11.7 Hz), 4.43 (dd, 1H, *J* = 9.5,

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J. Org. Chem. 2016, 81, 2364−2371

9.4 Hz), 4.38 (d, 1H, J = 11.7 Hz), 4.01 (dd, 1H, J = 2.8, 0.9 Hz), 3.80 (ddd, 1H, J = 6.4, 6.2, 0.9 Hz), 3.66 (dd, 1H, J = 9.4, 2.8 Hz), 3.62 (dd, 1H, J = 9.5, 6.2 Hz), 3.59 (dd, 1H, J = 9.5, 6.4 Hz); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 196.0, 152.8, 148.7, 138.6, 138.3, 137.9, 137.2, 128.4, 128.3 (2C), 128.2, 128.1 (2C), 127.8, 127.7, 127.6 (3C), 127.4, 127.2, 123.3, 84.1 (2C), 78.3, 74.5, 73.6, 73.4, 72.6, 68.9 (2C); HRMS (FD$^+$) Calcd for $C_{33}H_{34}NO_6$ $[M + H]^+$ 540.2386, found 540.2408.

*((2R,3R,4R,5S,6R)-4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-3-hydroxytetrahydro-2H-pyran-2-yl)-(benzo[b]thiophen-3-yl)-methanone (**18a**).* Following procedure B, the reaction between galactosyl cyanide **6a** (255.4 mg, 0.556 mmol) and a freshly prepared solution of benzo[b]thiophen-3-yllithium in THF (2 mL, 1.886 mmol) led to compound **18a** (250.6 mg, 0.372 mmol, 67%) as an orange oil. R_f = 0.3 (cyclohexane/EtOAc 8:2); $[\alpha]_D^{25}$ = +5.6 (c 0.27, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.81 (d, 1H, J = 8.1 Hz), 7.52 (d, 1H, J = 8.1 Hz), 7.44−7.25 (m, 18H), 4.99 (d, 1H, J = 11.4 Hz), 4.84 (d, 1H, J = 12.3 Hz), 4.81 (d, 1H, J = 12.3 Hz), 4.63 (d, 1H, J = 11.4 Hz), 4.57 (ddd, 1H, J = 9.4, 9.3, 2.7 Hz), 4.54 (d, 1H, J = 11.8 Hz), 4.49 (d, 1H, J = 11.8 Hz), 4.23 (d, 1H, J = 9.3 Hz), 4.02 (d, 1H, J = 2.7 Hz), 3.84 (dd, 1H, J = 6.5, 6.1 Hz), 3.73 (dd, 1H, J = 9.5, 6.5 Hz), 3.62 (dd, 1H, J = 9.4, 2.7 Hz), 3.61 (dd, 1H, J = 9.5, 6.1 Hz), 2.96 (d, 1H, J = 2.6 Hz); ^{13}C NMR (100,6 MHz, $CDCl_3$) δ 189.7, 140.2, 138.5 (2C), 138.3, 137.8, 134.7, 128.5, 128.4 (2C), 128.2, 128.1, 127.8, 127.7 (2C), 127.6, 127.5, 125.7, 125.6, 122.6, 114.6, 82.5, 81.5, 78.7, 74.7, 73.7, 73.6, 72.9, 68.6, 68.4; HRMS (FD$^+$) Calcd for $C_{36}H_{34}O_6S$ $[M]^+$ 594.2076, found 594.2126.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02853.

^{1}H and ^{13}C NMR spectra for compounds **5**−**7** and ketones **8**−**18**. (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683−720.

(2) (a) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545−8599. (b) Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, 1995. (c) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Tarrytown, NY, 1995. (d) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700−717. (e) Smoliakova, I. P. *Curr. Org. Chem.* **2000**, *4*, 589−608. (f) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913−9959.

(3) (a) Disadee, W.; Mahidol, C.; Sahakitpichan, P.; Sitthimonchai, S.; Ruchiwarat, S.; Kanchanapoon, T. *Phytochemistry* **2012**, *74*, 115−122. (b) Wu, Q.; Cho, J.-G.; Lee, D.-S.; Lee, D.-Y.; Song, N.-Y.; Kim, Y.-C.; Lee, K.-T.; Chung, H.-G.; Choi, M.-S.; Jeong, T.-S.; Anh, E.-M.; Kim, G.-S.; Baek, N.-I. *Carbohydr. Res.* **2013**, *372*, 9−13.

(4) For 1-metallated-glycosyl addition to aldehydes, see: (a) Lesimple, P.; Beau, J.-M. *Bioorg. Med. Chem.* **1994**, *2*, 1319−1330. (b) Frey, O.; Hoffmann, M.; Wittmann, V.; Kessler, H.; Uhlmann, P.; Vasella, A. *Helv. Chim. Acta* **1994**, *77*, 2060−2069. (c) Mazéas, D.; Skrydstrup; Beau, J.-M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 909−912.

(5) (a) Belosludtev, Y. Y.; Bhatt, R. K.; Falck, J. R. *Tetrahedron Lett.* **1995**, *36*, 5881−5882. (b) DeShong, P.; Soli, E. D.; Slough, G. A.; Sidler, D. R.; Elango, E.; Rybczynski, P. J.; Vosejpka, L. J. S.; Lessen, T. A.; Le, T. X.; Anderson, G. B.; von Philipsborn, W.; Vöhler, M.; Rentsch, D.; Zerbe, O. *J. Organomet. Chem.* **2000**, *593*−*594*, 49−62.

(6) For nucleophile addition to *C*-glycosyl aldehyde, see: (a) Picard, J.; Lubin-Germain, N.; Uziel, J.; Augé, J. *Synthesis* **2006**, 979−982. (b) Kolympadi, M.; Fontanella, M.; Venturi, C.; André, S.; Gabius, H.-J.; Jiménez-Barbero, J.; Vogel, P. *Chem. - Eur. J.* **2009**, *15*, 2861−2873. (c) Geng, Y.; Kumar, A.; Faidallah, H. M.; Albar, H. A.; Mhkalid, I. A.; Schmitt, R. R. *Bioorg. Med. Chem.* **2013**, *21*, 4793−4802.

(7) Dondoni, A.; Marra, A.; Scherrmann, M.-C. *Tetrahedron Lett.* **1993**, *34*, 7323−7326 and references cited therein.

(8) Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. R. *Tetrahedron Lett.* **1992**, *33*, 737−740.

(9) Bertozzi, C. R.; Bednarski, M. R. *Tetrahedron Lett.* **1992**, *33*, 3109−3112.

(10) Petrušová, M.; BeMiller, J. N.; Krihová, A.; Petruš, L. *Carbohydr. Res.* **1996**, *295*, 57−67.

(11) Dondoni, A.; Scherrmann, M.-C. *Tetrahedron Lett.* **1993**, *34*, 7319−7322.

(12) Dondoni, A.; Marra, A. *Tetrahedron Lett.* **2003**, *44*, 13−16.

(13) Sánchez, M. E. L.; Michelet, V.; Besnier, I.; Genet, J. P. *Synlett* **1994**, 705−708.

(14) Dondoni, A.; Catozzi, N.; Marra, A. *J. Org. Chem.* **2005**, *70*, 9257−9268.

(15) Vedachalam, S.; Tan, S. M.; Teo, H. P.; Cai, S.; Liu, X.-W. *Org. Lett.* **2012**, *14*, 174−177.

(16) (a) Zhao, C.; Jia, X.; Wang, X.; Gong, H. *J. Am. Chem. Soc.* **2014**, *136*, 17645−17651. (b) Jia, X.; Zhang, X.; Qian, Q.; Gong, H. *Chem. Commun.* **2015**, *51*, 10302−10305.

(17) Kulkarni, S. S.; Gervay-Hague, J. *Org. Lett.* **2006**, *8*, 5765−5768.

(18) De las Heras, F. G.; Fernández-Resa, P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 903−907. Procedure was modified by changing BF_3·OEt_2 by $Zn(OTf)_2$ and nitromethane by acetonitrile.

(19) Knapp, S.; Shieh, W.-C.; Jaramillo, C.; Trilles, R. V.; Nandan, S. R. *J. Org. Chem.* **1994**, *59*, 946−948.

(20) Benksim, A.; Beaupère, D.; Wadouachi, A. *Org. Lett.* **2004**, *6*, 3913−3915.

(21) Shi, L.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 6939−6940.

(22) Myers, R. W.; Lee, Y. C. *Carbohydr. Res.* **1986**, *154*, 145−163.

(23) For characteristic signals in NMR, see for example: Betaneli, V. I.; Ott, A. Y.; Brukhanova, O. V.; Kochetkov, N. K. *Carbohydr. Res.* **1988**, *179*, 37−50.

(24) For example, see: (a) Katsuno, K.; Fujimori, Y.; Takemura, Y.; Hiratochi, M.; Itoh, F.; Komatsu, Y.; Fujikura, H.; Isaji, M. *J. Pharmacol. Exp. Ther.* **2007**, *320*, 323−330. (b) Kadam, R. U.; Garg, D.; Schwartz, J.; Visini, R.; Sattler, M.; Stocker, A.; Darbre, T.; Reymond, J.-L. *ACS Chem. Biol.* **2013**, *8*, 1925−1930.

(25) (a) Czechura, P.; Tam, R. Y.; Dimitrijevic, E.; Murphy, A. V.; Ben, R. N. *J. Am. Chem. Soc.* **2008**, *130*, 2928−2929. (b) Zhao, J.-Z.; Wei, S.-Q.; Ma, X.-F.; Shao, H.-W. *Carbohydr. Res.* **2010**, *345*, 168−171.

(26) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188−196.

(27) Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281−283.

(28) (a) Jones, E.; Moodie, I. M. *Org. Synth.* **1970**, *50*, 104−106. (b) Malmberg, H.; Wilsson, M. *Tetrahedron* **1986**, *42*, 3981−3986.

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