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Reactivity, Selectivity and Synthesis of 4-C-Silylated Glycosyl Donors and 4-Deoxy Analogues

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Abstract: A method for introducing dimethylphenylsilyl at the 4-position in carbohydrates has been developed. Two *C*-silylated glycosyl donors were prepared via levoglucosenone, starting from cellulose. The glycosylation properties were studied using three glucoside acceptors, a 3-OH, 4-OH and 6-OH. Compared with the 4-deoxy variant, it was found that the anomeric selectivity was influenced more by the C-2 substituents orientation than the silyl in the 4-position. In general, the reactivity of these donors was higher than the corresponding 4-deoxy-analogue, albeit a competition experiment showed that the introduction of a C-Si increases the relative reactivity by a modest factor of around two.

Introduction

All functional groups found on a sugar ring in the biosphere are electron withdrawing (relative to carbon), and deoxy-glycosides are therefore considered the upper limit in terms of reactivity for glycosyl donors. When the deoxy position is next to the anomeric center (on C2), the resulting donor is often uncontrollable, unstable and less selective in glycosylation reactions,[1,2] as a non-functionalized position does not have a steric influence and only little conformational influence. Consequently, it is interesting to study how electron donating groups with steric bulk can influence a glycosyl donors' reactivity and selectivity. Comparably few functional groups are electron donating relative to carbon and even fewer would be practical for use in glycosylation chemistry. Boron and silicon however are both electropositive relative to H and C, and form stable bonds with carbon.[3] Particularly, alkylated or arylated silicon are popular as *O*-protective groups because they are easily installed and removed with high degree of orthogonality. Contrary to this, the direct introduction of Si on the sugar scaffold would reverse the stereoelectronic effects compared to a protected alcohol and increase the steric rigidity from having a tetravalent group directly attached to the pyrane ring.[4] Additionally, silicon is well known to stabilize the formation of carbocations, especially in, but not limited to, their β-position.[5] Beside these interesting properties, the C-Si can be reductively cleaved to a C-H, or oxidatively cleaved to the corresponding alcohol. Hence, a silicon functions as a masked alcohol, offering the hydroxyl group with retention of stereochemistry using Fleming-Tamao oxidation[6–10] or related methods.[11]

Despite the perspectives of having silicon on a sugar scaffold, only a few sporadic examples have been reported. Pegram and Anderson introduced a C6-(dimethylphenylsilyl) via hydrosilation of the 5,6-unsaturated hexopyranoside.[12] Sinaÿ and coworkers observed a silyl-migration of a 2-*O*-TMS group to C-1 under basic conditions giving the α-D-glycopyranosyltrimethylsilane.[13] The same group later reported the use of silylmethylene radical cyclization, followed by a Tamao oxidation, for the synthesis of branched carbohydrates.[14] Grignard reactions using (phenyldimethylsilyl)methylmagnesium chloride were introduced by van Boom and coworkers for the elongation of carbohydrates.[15] This approach was later followed up by Stepowska and Zamojski.[16] Boulineay and Wei used the same reagent for epoxide-opening to yield L-hexopyranosides from pentoses.[17] Zhu and Vogel used the nucleophilic silyl reagent (phenyldimethylsilyl)dimethylzinc lithium for the conjugated addition to a carbohydrate derived enone.[18] Cen and Sauve synthesized a 2-deoxy-2-fluororibolactone via a C2-TMS intermediate, which was obtained from the silylation of the α-carbon (C-2) under basic conditions with TMSOTf as electrophile.[19] Recently, Frihed *et al.* used C-H activation to synthesize L-sugars from the corresponding 6-deoxy-L-sugars via a cyclic silyl intermediate.[20,21] Lastly, Álvarez and Pedersen synthesized C-6 silylated glycosyl donors for the study of glycosylation properties in terms of selectivity and reactivity.[22]
A common factor for most of the examples above is that the obtained silylated carbohydrate derivative are intermediates and further investigation of having a silyl incorporated has only been studied in one case.[22] No one has studied the impact of a silicon, on glycosylation reactivity and selectivity, when directly attached to the pyranose.
The lack of studies of *C*-silylated carbohydrates are striking as C-Si bond formation has received considerable attention in other natural product classes, e.g. peptide chemistry, and other areas of bio- and medicinal chemistry, examples of this are metalloprotease inhibitors[23] and pseudo-peptides.[24,25]

Results and Discussion

For the synthesis of 4-*C*-silylated glycosyl donors a broad variety of methods for introducing silicon has been tested, i.e. addition of

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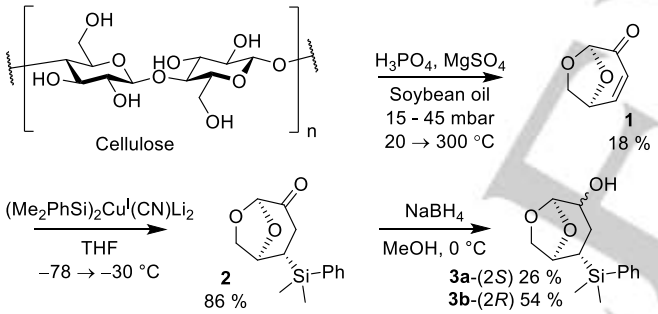
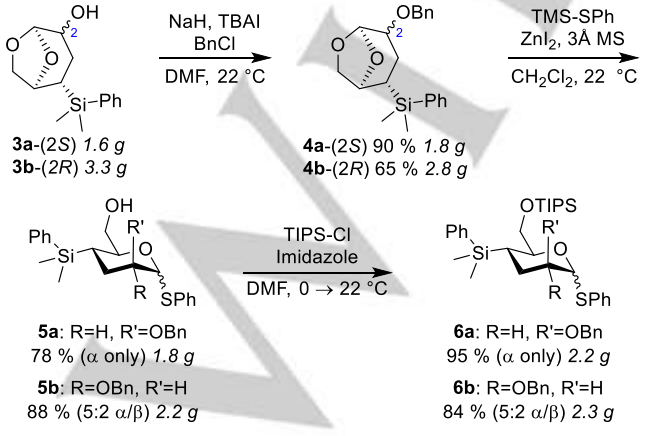
silyl lithium and metal- and Lewis-acid catalyzed silylation of double bonds.[12,14,18] However, none of these reactions successfully provided a satisfactory yield of the *C*-silylated products. The breakthrough was the use of an α,β-unsaturated ketone, D-levoglucosenone **1**, as a precursor for the *C*-silylated compounds. This compound is commercially available, but also easily synthesized via thermolytic decomposition of cellulose.[26,27] We obtained **1** from cellulose, using soybean oil as reaction medium. The product was isolated in high purity by vacuum distillation giving a yield of 18 % (Scheme 1).

Nucleophilic addition of silane to **1**, using dimethylphenylsilyl lithium in THF at -78 °C, gave both 1,2- and 1,4-addition in 34 % and 29 % yield, respectively. Exchanging the lithiated silyl nucleophile for the softer silylcuprate[28] exclusively yielded the desired 1,4-addition as a single diastereoisomer **2**. The following reduction of the ketone **2** with L-selectride delivered selectively the hydride to the *re*-face yielding **3a** as the sole product. However, a divergent synthesis strategy was desirable and reduction of **2** with $NaBH_4$ resulted in a separable 2:1 mixture of diastereoisomers. In this way, we accessed both 3-deoxy-mannose, **3a** and 3-deoxy-glucose, **3b** configurated donors. Starting from ketone **2** the 3-position could be functionalized with a benzoate ester **28** (not shown), by a protocol developed by Tomkinson and coworkers.[29,30] An example of a Fleming-Tamao oxidation was performed on the reduced 4-*C*-silylated substrate **29** to give allosan **30** (see supporting information, Scheme S1). For simplicity, we chose to continue with the 3-deoxy structures, accessing two configurations of *C*-silylated donors.



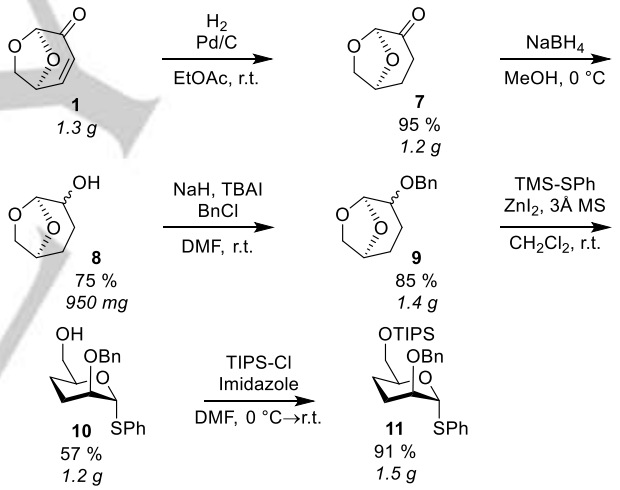
Scheme 1. Synthesis of 4-*C*-silylated carbohydrate derivatives.



Scheme 2. Synthesis of 3-deoxy-mannoside **6a** and 3-deoxy-glucoside **6b** donors from their respective 1,6-anhydro derivative.

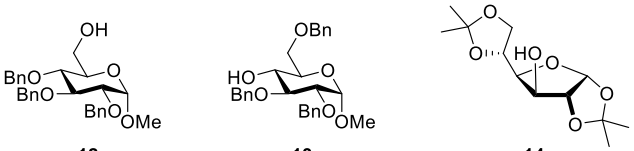
With the *C*-silylated carbohydrate scaffold, the glycosyl donor synthesis was continued. First, the hydroxyl group was benzylated to give a fully protected 1,6-anhydro sugar with the *manno*-isomer giving a high yield of 90% and the *gluco*-isomer a more modest yield of 65%. The 1,6-anhydro bridge was opened and a thiophenyl ether installed using TMSSPh in combination with ZnI_2 giving the thioglycosides in high yields and with good α-selectivity; exclusively α for **5a** and an anomeric mixture of 5:2 (α/β) for **5b**. Finally, the 6-OH were protected by TIPS groups in high yields, giving the glycosyl donors **6a** and **6b** on a gram scale. Even though 3-deoxy-glucoside donor **6b** was obtained as mixture of anomers we evaluated that their reactivity difference would be negligible. It was demonstrated by Heuckendorff *et al.* that there can be reactivity differences between restricted α- and β-thioglycosides.[31] However, this difference does not influence the stereochemical outcome of the glycosylation, because the reaction intermediate, glycosyl iodides and triflates, readily anomerizes and the initial stereochemical information is lost in the reaction.[32]

To investigate the influence of the silyl group on reactivity and selectivity in glycosylation reactions, we wished to compare the equivalent deoxy analogue. This 3,4-di-deoxy glycosyl donor **11** was synthesized from levoglucosenone **1** in five steps (Scheme 3).



Scheme 3. The 3,4-dideoxy donor **11** was successfully synthesized starting from levoglucosenone **1**.

The properties of the three donors were studied by glycosylating three model glycosyl acceptors. Glucosyl acceptor **12** being more accessible and reactive, while acceptor **13** with the 4-OH acceptor site is less nucleophilic (more electron poor[33]) and less accessible as studied by Codée and co-workers.[34,35] Acceptor **14** has the 3-OH even more sterically hindered. Three methods of activation; A, B, and C, were used (details in Table 1)



12 **13** **14**

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Figure 1. The three different glucoside-based acceptors allowed for coupling to three different positions.

A simple model alcohol mimicking a sugar alcohol, 2-methoxy ethanol, was used to study the reactivity and selectivity of glycosyl donor **6b** to give glycoside **15** (Table 1, entry 1). Immediately after addition of *N*-iodosuccinimide (NIS) at ambient temperature, the characteristic color change was observed, and TLC analysis showed full conversion of the donor material in less than 5 minutes. Glycosylation of **12** with **6b** gave disaccharide **19** in similar reaction times both in CH_2Cl_2 and CH_3CN (entries 2 and 3). Activation and glycosylation with only NIS was best for primary acceptors, such as methoxyethanol and **12**. However, couplings between the sterically demanding acceptors **13** and **14** was low yielding (see SI and Table S2).

Adding a mild Lewis or Brønsted acid and/or having a non-participating anion present could improve the reaction outcome in terms of yield or selectivity by stabilizing glycosylation intermediates after the activation by NIS. Introducing LiOTf as a mild Lewis acid (glycosylation method B) improved the outcome without affecting reaction time. Glycosylation between 3-deoxy-mannoside donor **6a** and 6-OH acceptor **12** gave **16** in 76 % yield (entry 4), compared to 55 % without the addition of LiOTf. These conditions also let donor **6a** successfully glycosylate both the secondary acceptors **13** and **14,** delivering the disaccharides **17** and **18** in decent yields with good α-selectivity.

The addition of LiOTf also lowered the reaction time between 3-deoxy-glucoside **6b** and primary acceptor **12** (Table 1, entry 5), however the selectivity in this case had changed compared to entry 2. Glycosylations with donor **6b** and the secondary acceptors **13** and **14** performed much better under these conditions, increasing the β-selectivity. Glycosylation of acceptor **12** with the 3,4-dideoxy donor **11** (entry 6) resulted in disaccharide **22** in 88 % yield and high α-selectivity. The secondary acceptors **13** and **14**, were successfully glycosylated to give **23** and **24** with similarly good α-selectivity.

Though LiOTf was a significant improvement and minimized side reactions under the glycosylation conditions, we investigated the effects of other Brønsted and Lewis acids. At room temperature weak Brønsted acids did not affect the outcome of the reactions, however addition of TfOH resulted in decomposition. Likewise, TMSOTf also led to some degradation, albeit to a lesser degree. This indicated that the 4-*C*-silylated saccharides possessed a decent Lewis acid stability at ambient temperature, while strong Brønsted acid degraded them. Whether the positive effect of LiOTf originated from the weak Lewis acidity of lithium or the counter ion, triflate is not clear from these results, but triflates are known to be beneficial for substitution reactions.[36]

Table 1. Reaction results from glycosylation between *C*-silylated donors and the different carbohydrate acceptors (for full table, see supporting information Table S2).

Entry	Conditions[a]	Donor	Acceptor	Reaction time[b]	Product	Anomeric ratio (α/β)[c]	Yield (%)[d]
1[e]	A	**6b**	methoxy-ethanol	5 min	**15**	61:39	61 (α) 39 (β)
2	A	**6b**	**12**	<9 min	**19**	76:24	66
3	A[f]	**6b**	**12**	<3 min	**19**	71:29	80
4	B	**6a**	**12**	<30 sec	**16**	93:7	76
5	B	**6b**	**12**	<3 min	**19**	60:40	72
6	B	**11**	**12**	<3min	**22**	91:9	74
7	C	**6a**	**12**	6 h	**16**	>95:<5	88
8	C	**6a**	**13**	3 h	**17**	>95:<5	73
9[e]	C	**6b**	**13**	1.8 h	**20**	71:29	54 (α) 27 (β)
10	C	**6b**	**14**	50 min	**21**	63:37	79
11	C	**11**	**14**	35 min	**24**	92:8	81

[a] Glycosylation conditions: A: Acceptor (1.5 equiv.), donor (1.0 equiv.), CH_2Cl_2, 3Å MS, ambient temperature, then NIS (1.1 equiv.); B: Acceptor (1.5 equiv.), donor (1.0 equiv.), CH_2Cl_2, 3Å MS, ambient temperature, LiOTf (15 mol%), then NIS (1.1 equiv.), C: Acceptor (1.5 equiv.), donor (1.0 equiv.), CH_2Cl_2, 3Å MS, -78 °C, then NIS (1.1 equiv.) and TMSOTf (10 mol%). [b] Based on color change of the reaction mixture and confirmed by TLC analysis. [c] Based on ^1H and ^{13}C NMR of the crude mixture. [d] Isolated yield. [e] The respective anomers were separable. [f] CH_3CN as reaction solvent.

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Glycosylation of less acid-stabile donors are preferably performed at low temperature (−78 °C with TMSOTf and NIS as, glycosylation conditions C, Table 1, entries 7-11).

Glycosylating using **6a** under conditions C led to higher yields, and better selectivity. Coupling primary acceptor **12** gave 88 % of **16** (entry 7) and the secondary acceptors **13** and **14**, gave 73 % of **17** (entry 8) and 66 % of **18** with high anomeric selectivity (>20:1 α/β). 3-Deoxy-glucoside **6b** and the secondary acceptors **13** and **14** (entries 9 and 10) showed similar good yields around 80 % and anomeric selectivity comparable to those observed with method B. Reactions between 3,4-dideoxy donor **11** and acceptor **12** and **13** were slow, and increasing the temperature to -40 °C was beneficial. Hence, acceptor **13** gave disaccharide **23** in 41 %, compared to 23 % (see SI Table S2, entries 28 and 29). Coupling to **14** was generally found to be faster and gave good yield of glycoside **24** (Table 1, entry 11). Strikingly, acceptors **12** – **14** showed a reverse tendency of reaction time contradictory to their expected nucleophilicity.

The anomeric selectivity for donor **6a** and **11** in the glycosylation reactions (Table 1) were primarily influenced by the orientation of the benzyl ether in the neighboring 2-position in line with the general observation for α-selectivity of any mannosylations. An intermediate oxocarbenium ion is expected to mainly adopt a $^4H_3$-conformation for compound **6a** and **11**, placing the silyl and the methylene substituents in sterically more favorable pseudo-equatorial positions (figure 2). Nucleophilic attack from the "α-side" on the $^4H_3$-conformation is favored and leads to the lowest energy transition state, according to Woerpel and co-workers observations.[37,38]

The 3-deoxy-glucoside **6b,** was found to be α-selective, but to a lesser degree than in **6a** and **11**, with their axial 2-benzyloxy substituent. This suggest that the oxocarbenium also adopt the $^4H_3$-conformation, placing all substituents in a sterically more favorable pseudo-equatorial position (Figure 2). The $^3H_4$-conformation suffers from a 1,3-diaxial interaction between 2-benzyloxy and 4-silyl. Nucleophilic attack from the α-face leads to a destabilizing 1,2-gauche interaction in the $^4H_3$-conformation and attack from the β–face a destabilizing 1,3-diaxial interaction between the nucleophile and the C5-methyleneoxy. Together with the observed lower selectivity therefore indicates a near equal contribution of steric influences in the transition state. Surprisingly, the bulky silyl group in the 4-position seems not to influence the glycosylation out-come much.

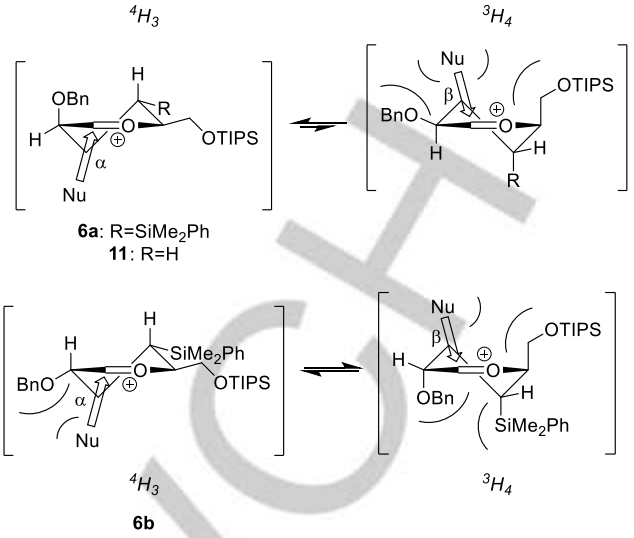

Figure 2. Suggested equilibria states of different oxocarbenium ions for the reaction between the three donors and a nucleophile.

Surprised by the small reactivity differences between a silicon group and hydrogen in the 4-position, a competition experiment using method C was performed (SI, Figure S4 and S5). This experiment showed a relative reactivity difference of approximately 1:2.5 between the 3,4-dideoxy donor **11** and 4-silyl donor **6a**. Although smaller than expected it is interesting that the bulky silyl group in the 4-position – furthest away from the reactive center – is more activating compared to the 4-deoxy analogue.

Curiously, our less successful attempts to perform the competition study directly in an NMR-tube at room temperature led us to discover and determine the major side-product pathway. The ^{13}C NMR measurements indicated the characteristics of vinylic signals around 115 ppm (SI Figure S6), originating from the rearrangement of the donor and/or products. This was not unlike vinyl furanoside **25**, L-*threo*-hex-5-enofuranoside[39,40] observed by glycosylating acceptor **12** directly with 1,6-anhydro compound **4b** (Scheme 4). This vinyl furanoside was also the sole isolated product when 3-deoxy-glucoside donor **6b** was activated with iodine and base. Oddly, when 1,6-anhydro **4b** was opened using TMSOTf instead of ZnI_2, two minor side-products, a vinyl furanoside **26** and the 6,6-bis(phenylthio)hex-2-en-1-ol **27** were isolated (SI Figure S2). This suggest that the formation of the double bond goes through a stabilized cation, allowing for isomerization of this bond into the energetically favored *E*-conformation. It also indicates that the glycosylation must occur prior to the elimination.

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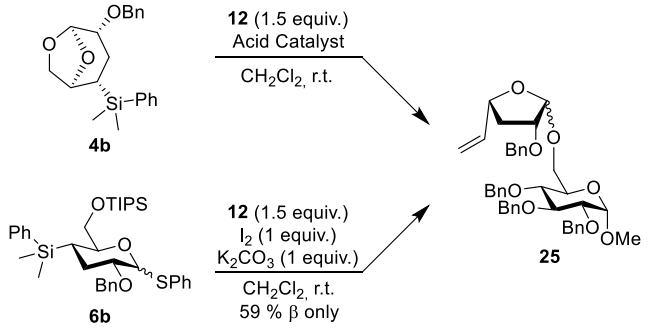

Scheme 4. Vinyl furanoside **25** was observed as the major product under some glycosylation conditions. For the glycosylation reactions of **12** with 1,6-anhydro donor **4b** the following two catalysts were used; $BF_3{\cdot}Et_2O$ (0.6 equiv), 87 % (1:7.3 α/β); TfOH (0.1 equiv), 75 % (1:13 α/β).

The mechanistic background for the formation of vinyl furanosides was not investigated in-depth. Nevertheless, our observations suggest that the β-cationic stabilization from the silyl-group results in the electrophilic substitution of an unsaturated allylic silane[5,41,42] through a two-step mechanism related to a 1,2-silyl migration or 1,3-silyl rearrangement followed by *anti*-elimination, not unlike a Peterson-olefination.[13,43,44] This would explain why inversion of the 4-position was observed. It is noteworthy that the formation of vinyl furanosides also was observed by Imperio *et al.* during their synthesis of 6-boronic acid sugar derivatives.[45] The similarity in side-product formation reveals a reduced stability of polyols containing weaker electronegative elements, both in terms of acid and base lability.

Conclusion

A method for introducing a silyl substituent in the 4-position of a carbohydrate scaffold has been developed. This mitigated the synthesis of silylated glycosides, where two thioglycosides were used as donors to investigate the reactivity and selectivity of this previously unknown class of carbohydrates. Comparing glycosylation reactions with these and a 3,4-di-deoxy donor showed that the 4-*C*-silylated donors had surprisingly similar properties in terms of selectivity. Although the relative reactivity difference was small, it is appreciably different. The introduction of C-Si bonds increased the donor reactivity outside the current limits. The silylated glycosides have good shelf-life with little to no alteration after several months of storage at room temperature. Yet, under reaction conditions, at room temperature, this compound class were shown to have a limited tolerance to strong acids and bases.

Acknowledgements

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Keywords: Silylation • Carbohydrates • Glycosylation • Reactivity • Selectivity • Levoglucosenone • Functionalization

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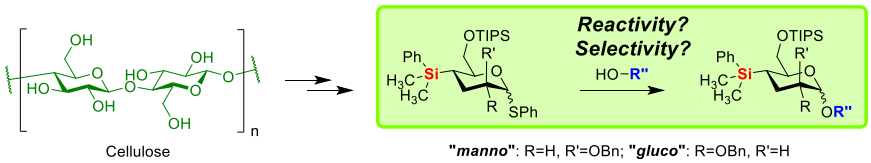

Two 4-*C*-silylated glycosyl donors have been synthesized starting from cellulose. This new class of donors showed remarkably similar selectivity to and modestly more reactivity than their 4-*C*-deoxy analogue. Allowing for very mild glycosylation reaction conditions and short reaction times.