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MILD AND SELECTIVE *O*-GLYCOSYLATIONS OF PRIMARY ALCOHOLS WITH THE THIOGLUCOSAMINIDE DERIVATIVE PROMOTED BY *N*-IODOSUCCINIMIDE AND HBF_4-ADOSROBED ON SILICA GEL

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Dedicated to Professor Akira Suzuki on the occasion of his 80th birthday

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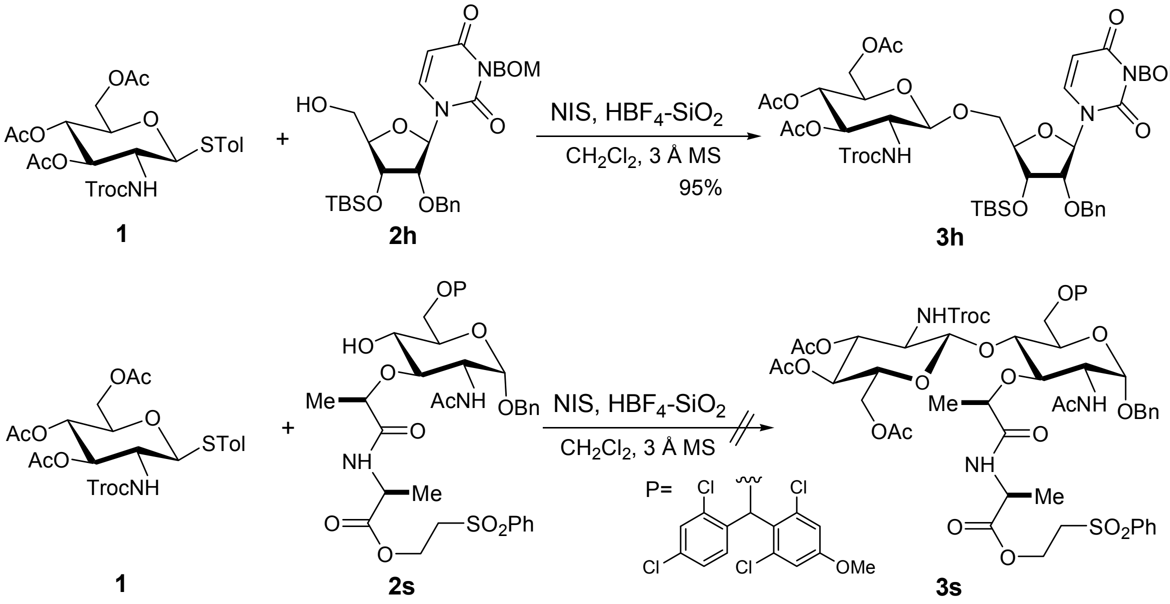
Abstract – Selective glycosylations of *primary* alcohols with the thioglucosaminide **1** are achieved by using NIS and HBF_4-SiO_2. HBF_4-SiO_2 is a mild Brønsted acid which requires *primary* alcohols or *phenols* to effectively activate **1** with NIS at rt. A wide range of functional groups are tolerated under these conditions.

Drug design in recent years has attempted to explore new chemical spaces resulting in more complex and larger molecular weight molecules. These molecules often possess limited water solubility. In general, these poorly soluble active new chemical entities present problems in drug administration and formulation.[1] Prodrug strategy has employed to improve the solubility profile of molecules, resulting in increase of the intestinal absorption of poorly water-soluble hydrophobic compounds.[2] Glycosylation is one of the approaches for increasing water solubility and cellular uptake; a number of examples of the enhancement in the solubility and efficacy of natural products *via* glycosylation have been reported.[3] However, rational attempts to improve the oral absorption of poorly soluble active new chemical entities by glycosylation(s) are complicated by the fact that the mechanisms by which new molecules are transported from the gastro intestine to the blood are unknown. In addition, extensive regeneration studies of inactive glycosyl prodrugs by the cellular enzymatic reaction of glycosidase (enzyme specific activation) or hydrolysis *in vivo* are necessary. To date, glucuronide-, glucosyl- and galactosyl-prodrug approaches have been applied to known chemical entities, and their transport and regeneration mechanisms at specific sites have been well studied.[4] Although glucosaminyl or *N*-acetyl-glucosaminyl prodrugs are known to exhibit beneficial physicochemical properties (i.e. shorter half-live of hydrolysis (at pH 7.4), and susceptibility to β-D-*N*-acetyl-glucosaminidase),[5] applications of these prodrug systems to complex molecules have been limited due in part to lack of robust selective glycosylations with glucosamine derivatives. Herein, we report a mild and selective glycosylation of *primary* alcohols with thioglucosaminide with *N*-Troc (2,2,2-trichloroethoxycarbonyl) group using NIS (*N*-iodosuccinimide) and HBF_4-SiO_2.

Thioglycosaminide with *N*-Troc such as **1** has been widely utilized in synthesis of *N*-acetylglucosamine-containing glycoconjugates.[6] The thioglycoside **1** is generally coupled to *primary* or *secondary* alcohols in good to excellent yields using a combination of NIS and TfOH[7] or other variations of triflate sources.[8] The Troc group is reliably deprotected *via* a wide range of reductive elimination conditions (i.e. Zn, Cd, or In in the presence of a mild Brønsted acid).[9] Although reported *O*-glycosylation conditions for **1** are useful for acyl- or benzyl-protected glycosyl acceptors, application of glycosylation of **1** using NIS and strong Brønsted acids or strong acid salts to glycosyl acceptors possessing acid sensitive groups (i.e. silyl or Boc group) generally requires laborious optimization efforts. In our hands, the NIS/TfOH promoted glycosylation of **2h** with **1** gave the desired product **3h** in poor yield due to desilylation of **2h** or **3h** (Scheme 1).[10] In addition, no reliable condition for selective glycosylations with **1** against *primary* alcohols of polyol molecules has been reported to date. In our investigations of an alternative acid which can promote glycosylation of **2h** with **1** and NIS, we observed that HBF_4-absorbed on silica gel (HBF_4-SiO_2)[11] efficiently catalyzed the reaction to furnish **3h** in over 95% yield within 3 h at rt. On the other hand, the glycosylation of the *secondary* alcohol **2s** with **1** did not

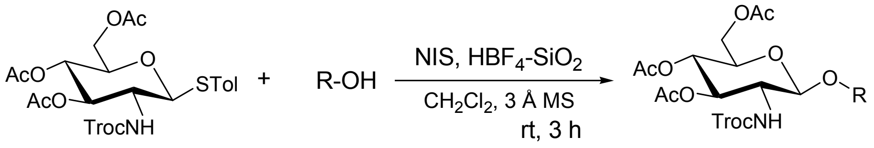


Scheme 1. Investigation of a mild Brønsted acid to promote glycosylations of **1**.

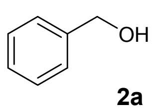
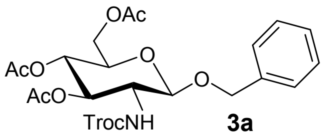
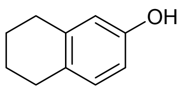
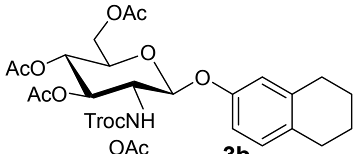
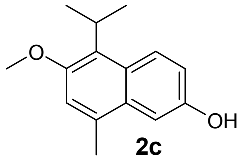
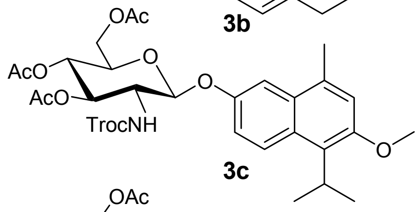
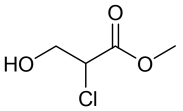
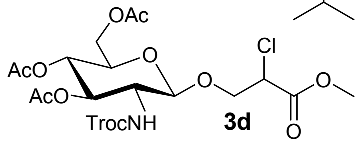
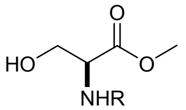
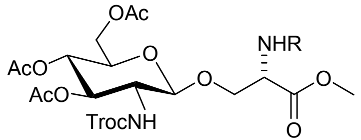
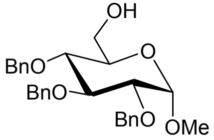
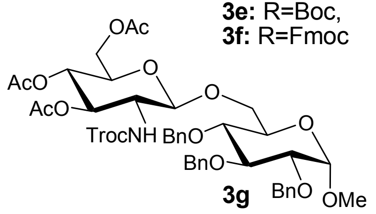
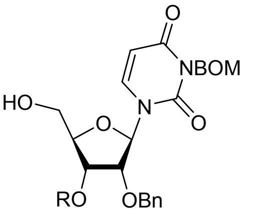
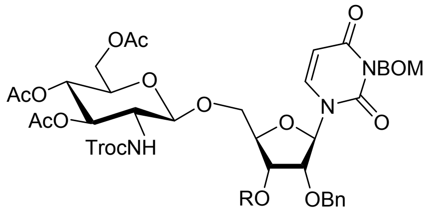
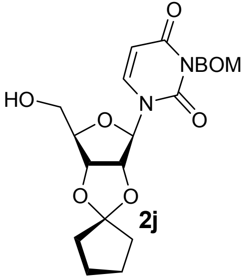
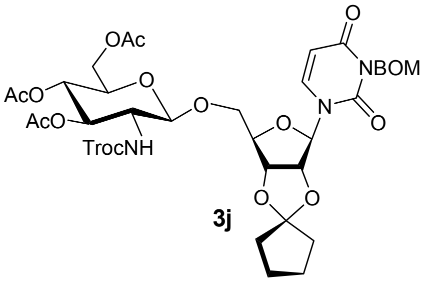
provide the disaccharide **3s** under the same conditions even after prolonged reaction time. Interestingly, **1** and **2s** could be recovered as their intact forms in almost quantitative yields (Scheme 1).[12] The glycosyl donor **1** is activated by using a NIS/TfOH condition in the absence of acceptor alcohols to furnish the corresponding anomeric alcohol. Thus, an unusual reaction mechanism, the *primary* alcohol **2h** efficiently participates in the process of activation of **1**, observed in Scheme 1 may be attributed to the preferential glycosylation of the *primary* alcohol and tolerance of the silyl group in these reactions. Indeed, HBF_4-SiO_2 1) no longer shows a strong Brønsted acid characteristic as observed for HBF_4•OEt_2 in aprotic solvents, 2) does not catalyze the cleavage of acetal, and acid sensitive ether and Boc groups at ambient temperatures, 3) has a strong affinity for alcohols, but a weak affinity for carbonyls,[13] and 4) does not cause HBF_4 leaching from silica gel during the reactions or by washing with organic solvents including MeOH.[14] Thus, such a strongly bound HBF_4 on SiO_2 serves as a moderate to weak Brønsted acid.[15]

In order to generalize the use of NIS/HBF_4-SiO_2 for selective glycosylations with **1**, a wide range of model donor molecules, *primary*, *secondary* and phenolic alcohols, were examined. In these experiments, acceptors (3~5 equiv against **1**), NIS (2 equiv against **1**), 3 Å MS (~two times its weight in **1**),[16] and HBF_4-SiO_2 (0.8 mmol/g, 2 equiv against **1**) were employed in the reactions in CH_2Cl_2 at rt. Selected examples are summarized in Table 1 and 2. All *primary* and phenolic alcohols investigated were glycosylated to furnish the corresponding β-glycosides within 3 h. Reaction rates of the phenols **2b** and **2c** were faster than those of benzyl alcohol (**2a**) and alkanols (entries 1–8 in Table 1). Glycosylations of structurally simple alcohols **2a**–**c** resulted in the formation of corresponding β-glycosides **3a**–**c** in greater than 95% yields. The β-hydroxy ester **2d** and serine derivatives, **2e** and **2f**, were coupled with **1**, and the desired products **3d**, **3e**, and **3f** were isolated with good to moderate yields (entries 4, 5). The Boc group of **2e** was stable under these conditions, however, the isolated yield of **3e** was 30% (>95% yield based on recovering **2e**) due in part to the attenuated nucleophilicity of the hydoxy group of **2e** by forming a hydrogen bond with the neighboring group. Similarly, glycosylation of the Fmoc-protected serine **2f** yielded **3f** in 50 % yield. The *primary* alcohols of the pyranose and furanose derivatives **2g**, **i**, **j** were efficiently coupled with **1** to yield the corresponding β-linked disaccharides **3g**, **i**, **j**, respectively (entries 6–8). As observed in the reaction of **2s** with **1** in Scheme 1, *secondary* alcohols showed poor reactivity against **1** under the HBF_4-SiO_2 promoted glycosylation conditions (Table 2). Glycosylation of 2-proponol (**2k**) with **1** provided the β-linked glycoside **3k** in less than 30% yield after 15 h (entry 9); no detectable amount of **3k** was identified on TLC within 1 h. However, trace amounts of **3k** was formed after 3 h. Less than 5% of the β-cholesteryl glycoside was isolated after 15 h (entry 10). The threonine derivative **2m** and *secondary* alcohols of the pyranose and furanose derivatives **2n**–**p** did not provide detectable amounts of the corresponding products on TLC even after 15 h (entries 11–13).

Table 1. NIS/HBF$_4$-SiO$_2$ promoted glycosylations of **1** with *primary* alcohols.[17]

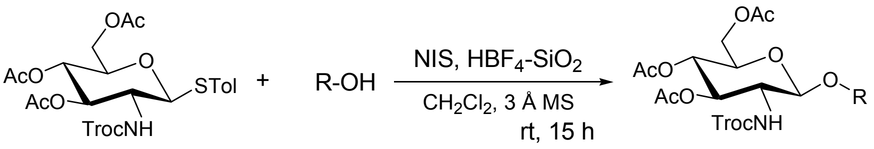


1 **2a~j** **3a~j**

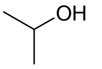
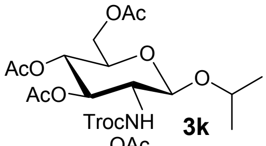
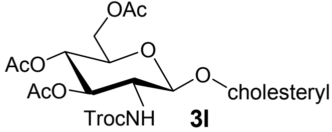
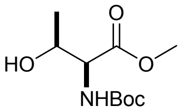
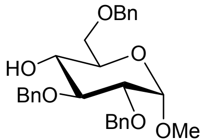
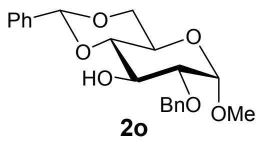
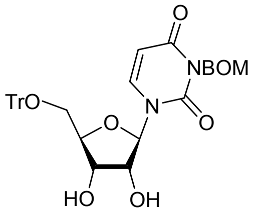
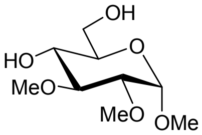
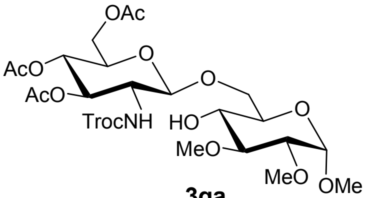
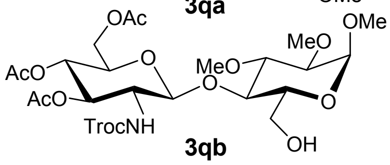
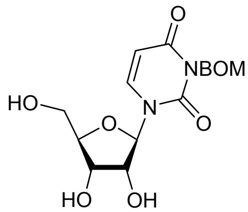
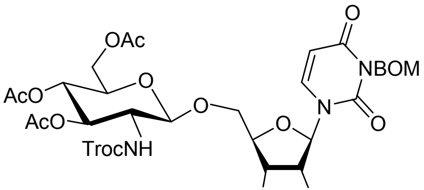
entry	acceptor	product	yield (%)
1	 **2a**	 **3a**	>95
2	 **2b**	 **3b**	>95
3	 **2c**	 **3c**	>95
4	 **2d**	 **3d**	85
5	 **2e:** R=Boc, **2f:** R=Fmoc	 **3e:** R=Boc, **3f:** R=Fmoc	**3e:** 30 (>95)[a] **3f:** 55 (>95)[a]
6	 **2g**	 **3g**	87
7	 **2h:** R=TBS, **2i:** R=Me	 **3h:** R=TBS, **3i:** R=Me	**3h:** >95 **3i:** >95
8	 **2j**	 **3j**	>95

[a] Yield based on recovering starting material.

Table 2. NIS/HBF_4-SiO_2 promoted glycosylations of **1** with *secondary* alcohols or a diol or a triol.

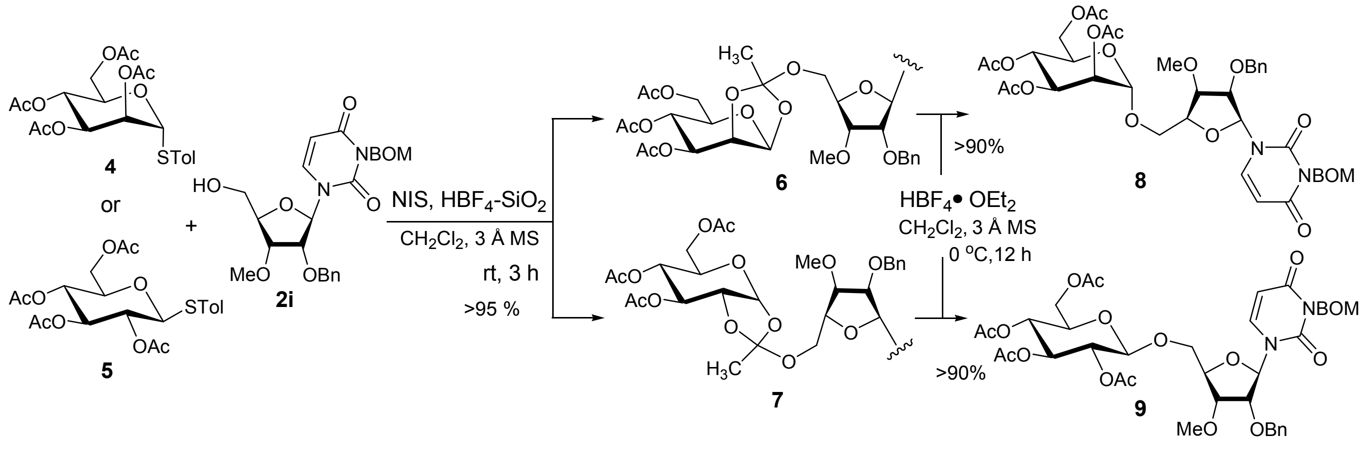


1 **2k~r** **3k~r**

entry	acceptor	product	yield (%)
9	 **2k**	 **3k**	<30
10	cholesterol **2l**	 **3l**	<5
11	 **2m**	–	–
11	 **2n**	–	–
12	 **2o**	–	–
13	 **2p**	–	–
14	 **2q**	 **3qa** 7 : 1  **3qb**	70 (**3qa**) 10 (**3qb**)
15	 **2r**	 **3r**	72 (**3r**) 18 (other regioisomers)

Having considered the observation in which *secondary* alcohols are not effectively coupled with **1** under the NIS/HBF_4-SiO_2 conditions, we explored selectivities (*primary* vs. *secondary* alcohol) of glycosylations of a diol and a triol such as **2q** and **2r**. Glycosylation of **2q** furnished a 7:1 mixture of β-glycosides, **3qa** and **3qb**, in 80% yield (entry 14). Similar selectivity against the *primary* alcohol was observed in glycosylation of **2r**, and the disaccharide **3r** was isolated in 72% yield (entry 15). In both cases the over-reaction products were not isolated and the regioisomer is the only byproduct in these reactions. It is worthwhile mentioning that the product selectivities of the reaction with **2q** and **2r** were not improved by shortening the reaction time (3 h) or lowering the reaction temperatures (-20–0 °C). Less *primary*/*secondary* selectivities observed in glycosylations of the glucose and ribose derivatives, **2q** and **2r**, are not clear. Nonetheless, we observed useful level of selectivity against *primary* alcohol in glycosylation of a diol and a triol.

The NIS/HBF_4-SiO_2 promoted selective glycosylations of *primary* alcohols observed for **1** were applicable to the other tolyl thioglycosides such as **4** and **5**. However, the orthoesters **6** and **7** were formed in almost quantitative yields within 10 min,[18] and **6** and **7** were not rearranged to the corresponding glycosides **8** and **9** even after 15 h. Isolated **6** and **7** could be completely converted to **8** and **9**, respectively, *via* HBF_4•OEt_2 in CH_2Cl_2 (Scheme 2). The experimental data summarized in Scheme 2 confirm that HBF_4-SiO_2 is a mild Brønsted acid and acid-sensitive orthoesters **6** and **7** are not hydrolyzed by HBF_4-SiO_2.



Scheme 2. NIS/HBF_4-SiO_2 promoted glycosylations of **4** and **5**.

In conclusion, we have demonstrated NIS/HBF_4-SiO_2 promoted selective glycosylations of *primary* alcohols with thioglucosaminide **1**. Interestingly, HBF_4-SiO_2 requires the thioglycosides (glycosyl acceptors) and *primary* or phenolic alcohols to efficiently activate NIS.[19] As demonstrated in Scheme 1 and 2, a wide range of functional groups are tolerated under NIS/HBF_4-SiO_2 promoted glycosylation conditions. Although mechanism of the reactions associated with HBF_4-SiO_2 is far from understood, beneficial features of NIS/HBF_4-SiO_2 described above can be applied to selective glycosylations of *primary* alcohols of target molecules, which are difficult to be glycosylated selectively using previously reported conditions.[6]

ACKNOWLEDGEMENTS

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10. *p*-Tolylsulfenyl trifluoromethanesulfonate (*p*-TolSOTf) was effective in promoting the glycosylation of **2h** with **1**. However, addition of $ScCO_3$ was indispensable to avoid desialylation of the TBS group, see: M. Kurosu and K. Li, *J. Org. Chem.*, 2008, **73**, 9767.
11. Anhydrous HBF_4 on SiO_2 can readily be obtained by a simple procedure of mixing SiO_2 with ~48% aq. HBF_4 and subsequent removal of H_2O, and is not hygroscopic.

    Preparation of HBF_4-SiO_2: To a magnetically stirred suspension of silica gel (20 g, 230–400 mesh) in Et_2O (100 mL), HBF_4 (48% in water, 2.1 mL, 16 mmol) was added at rt. After 3 h, the mixture was concentrated and the residue was dried under high vacuum (1~5 mmHg) at 110 °C for 72 h to give anhydrous HBF_4-SiO_2 (HBF_4: 0.8 mmol/g). Titration studies of the recovered HBF_4-SiO_2 and washing solvents supported that negligible amounts of HBF_4 from SiO_2 are leached during the reactions or washing.
12. In our laboratory, the glycopeptide core of lipid II **3s** has been synthesized *via* NIS/$AgBF_4$ in CH_2Cl_2. Under these conditions a gram quantity of **3s** was synthesized with >80 % yield (based on **2s**).
13. Taking advantage of strong affinity of HBF_4-SiO_2 against *primary* or phenolic alcohols, we have used HBF_4-SiO_2 as an affinity matrix for separating *primary* or phenolic alcohols out of crude materials.
14. Titrations were performed with an analytical 0.1 N NaOH solution and phenolphtalene as an indicator.
15. Recently, HBF_4-SiO_2 was demonstrated for synthesis of acetals from aldehydes or thiiranes from oxiranes, see: (a) V. T. Kamble, B. P. Bandgar, N. S. Joshi, and V. S. Jamode, *Synlett*, 2006, 2719; (b) B. P. Bandgar, P. V. Abasaheb, V. T. Kamble, and J. V. Totre, *J. Mol. Catal. A: Chem.*, 2007, **273**, 114. For a study of glycosylations with thioglycosides promoted by NIS and $HClO_4$-SiO_2, see: (c) B. Mukhopadhyay, B. Collet, and R. A. Field, *Tetrahedron Lett.*, 2005, **46**, 5923.
16. MS 3 Å is not indispensable. In order not to obtain inconsistent results caused by adventitious water, activated MS 3 Å (~two times its weight in **1**) was added in all reactions.
17. The following example represents typical experimental procedure: To a stirred suspension of **2i** (282 mg, 0.6 mmol), **1** (117 mg, 0.2 mmol) and 3Å MS (550 mg) in dry CH_2Cl_2 (10 mL) under N_2

atmosphere was added NIS (45 mg, 0.2 mmol) and HBF_4-SiO_2 (250 mg, 0.2 mmol). After 3 h at rt, the reaction mixtures were filtrated and washed with EtOAc (5 mL). The combined organic phase was evaporated *in vacuo*. Purification by silica gel chromatography (hexanes/EtOAc = 2/1) gave the **3i** (178 mg, 96 %). Data for **3i**: $[\alpha]^{20}_{D}$ +37° (c 1.0, $CHCl_3$); IR (film): 1746, 1710, 1666, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 1H), 7.43-7.28 (m, 10H), 5.97 (s, 1H), 5.80 (d, J = 8.0 Hz, 1H), 5.48 (s, 2H), 5.17 (m, 2H), 5.09 (m, 1H), 4.88 (d, J = 12.4 Hz, 1H), 4.81 (d, J = 12.4 Hz, 1H), 4.73 (m, 1H), 4.72 (s, 2H), 4.60 (d, J = 8.8 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.33-4.26 (m, 3H), 4.10 (dd, J = 2.0, 12.4 Hz, 1H), 4.03 (d, J = 3.6 Hz, 1H), 3.75-3.69 (m, 3H), 3.63 (m, 1H), 3.24 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.9, 169.5, 163.0, 154.2, 151.0, 139.1, 138.0, 137.5, 128.6, 128.5, 128.2, 127.9, 101.8, 101.1, 95.5, 89.2, 80.5, 78.8, 76.5, 74.6, 72.3, 72.1, 71.9, 70.3, 68.4, 67.5, 61.9, 58.2, 56.6, 20.9, 20.8, 20.7; HRMS (ESI) Calcd. for $C_{40}H_{46}C_{l3}N_3NaO_{16}$ $(M + Na)^+$: 952.1841, found: 952.1848.

18. The formation of orthoesters has previously been reported with a number of different glycosyl donors which contain a 2-*O*-acetyl group, see: A. H. Harreus and H. Kunz, *Liebigs Ann. Chem.*, 1986, 717.
19. The reaction mechanism of the HBF_4-SiO_2 promoted glycosylations with **1** and NIS remains far from understood. However, we speculate that *primary* alcohols interact with HBF_4-SiO_2 and alcohol protons would activate NIS by coordination with the imido carbonyl of NIS.