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Modulation of the relative reactivities of carbohydrate secondary hydroxyl groups. Modification of the hydrogen bond network

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Abstract—An approach towards the control of the relative regioselectivity of the secondary hydroxyl groups is presented. Original protecting groups, which are capable of specific intramolecular hydrogen bonds and are likely to modulate the partial charges of the oxygen atoms, have been developed. Qualitative NMR experiments confirmed the existence of the expected hydrogen bonds and shed light on the perturbation of the cooperative intramolecular hydrogen bond network. Further reactivity studies are presented and confirm the potential of protecting group-mediated regioselective functionalization of carbohydrates.

1. Introduction

The number of therapeutic targets is expected to increase dramatically due to the completion of the human genome project. In order to screen libraries of oligosaccharides, which are potential ligands of target proteins such as lectins, one strategy is to develop suitable methods for combinatorial or parallel synthesis of such polymeric molecules. Indeed, the poor availability of naturally occurring oligosaccharides has to be balanced by synthetic approaches. This calls for efficient and regioselective coupling methods, which still require suitably protected synthons and therefore necessitate synthetic efforts for their preparation. In an attempt to decrease the number of tedious protection/deprotection transformations, one can take advantage of selective enzymes. However, this approach is restricted to particular substrates, since enzymes do not recognize some of the modified sugars.

Open glycosylation is therefore regarded as a promising alternative. However, only a few studies, which are directed toward non protected (or partially protected) donor and acceptor coupling, have been reported.[1,2] To achieve regioselective glycosylation, the relative reactivities of the free hydroxyl groups of the acceptors must be controlled. The use of Lewis acids (boron, tin) was envisioned and successfully used in the preparation of particular disaccharides.[3,4]

In this communication, we describe a new alternative approach to the control of the relative reactivities of carbohydrate secondary hydroxyl groups. In this preliminary work, we took advantage of designed protecting groups at position 6 and explored the effect of intramolecular interactions modulating the nucleophilicity of the oxygen atoms.

2. Design and synthesis of hydrogen bond acceptor protecting groups

Recent papers shed light on the intramolecular network that controls the relative reactivity of the glucose hydroxyl groups (Fig. 1).[5,6]

With this in mind, we set out to explore the role of protecting groups at position 6 that would beneficially interact with positions 3 and 4. Hopefully, this would result in a modification of the electronic distribution and consequently of the intrinsic reactivity of the interacting hydroxyl groups.

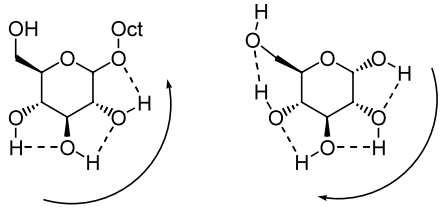

Figure 1. Glucose intramolecular H bond network in chloroform as proposed by Yoshida[5] and Davies.[6]

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Thus, novel hydrogen bond acceptor protecting groups were designed with the help of molecular modeling. For instance, a phenyl group in **1a** was substituted for a precisely positioned pyridyl ring that would hydrogen bond with the 4-OH (**1b**). The expected stability of this protecting group in acidic medium (protonation of the pyridyl group favored over cleavage of the ether bond) was balanced by the introduction of electrodonating groups, which further stabilize the corresponding tertiary carbocation (**1c**). A second pyridyl group was next added and linked to the trityl-like protecting group by means of a selected spacer (**1e**). This extra heterocycle should participate in a second hydrogen bond as suggested by molecular modeling studies. For comparison purpose, **1a** and **1d** were also prepared.

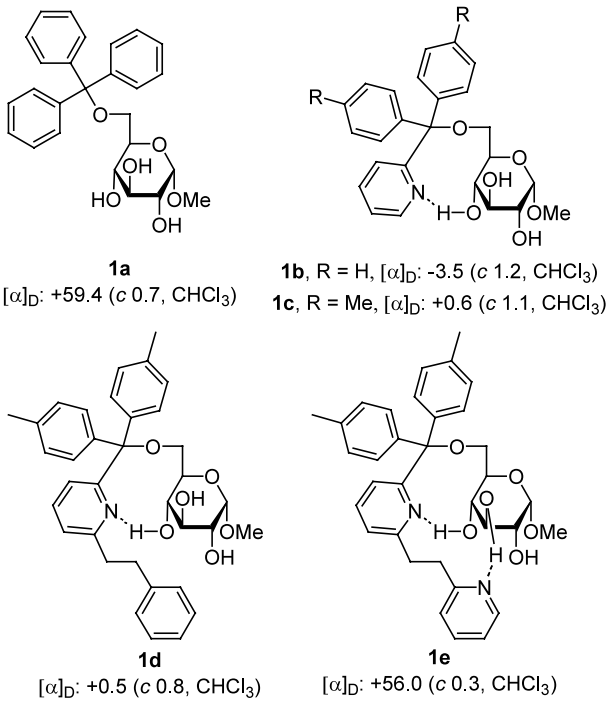
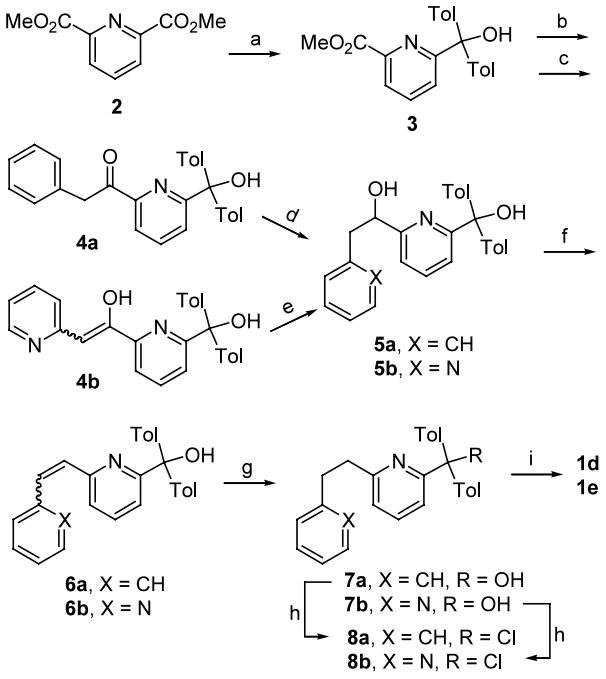


Figure 2. Selected protecting groups.

The synthesis of **1d** and **1e**, outlined in Scheme 1, began with the selective disubstitution of symmetric pyridine diester **2**. This desymmetrization was achieved under optimized temperature conditions with a reasonable yield. The appropriate lithio derivatives were next added onto the remaining ester moiety. Surprisingly, although **4a** adopted the keto form, the presence of nitrogen on the ring favored the enol form over the keto form in **4b**. As a consequence, monoaddition of 2-lithio picoline onto **3** was accomplished with a good yield (83%) while the yield for the reaction of lithio toluene with **3** gave no selectivity (35% mono addition, 35% diaddition, 30% starting material). Reductions of the ketone carbonyl of **4a** and of the enol double bond of **4b** were accomplished by hydride-mediated reduction and catalytic hydrogenation respectively yielding the diols **5a** and **5b**. Dehydration of these alcohols was next achieved by triflation and in situ elimination. Thus, on treatment with a base and $PhNTf_2$ (milder that triflic anhydride which induced partial decomposition), **5a** and **5b** were converted into the conjugated olefins **6a** and **6b** (83 and 76%). These unsaturated intermediates were isolated and then further reduced by catalytic hydrogenation to afford the advanced intermediates **7a** and **7b** in fairly good yields (94 and 72%). These alcohols were transformed into the chlorinated reagents **8a** and **8b** by treatment with a mixture of acetyl chloride and thionyl chloride. Conversion of **7a** and **7b** into their hydrochloride counterpart was a prerequisite for an efficient chlorination. These activated trityl-like moieties were reacted in situ with methyl α-D-glucopyranoside in pyridine to afford the target compounds **1d** and **1e**.



Scheme 1. *Reagents and conditions*: (a) TolMgBr (0.9 equiv.), THF, rt then TolMgBr (1.1 equiv.), −78°C, 45%; (b) toluene, *t*-BuLi, THF, −78°C then **3**, HMPT, 35% (along with 30% of **3**); (c) 2-picoline, *n*-BuLi, THF, −78°C then **3**, HMPT, 83%; (d) $LiAlH_4$, THF, 0°C, 70%; (e) H_2, 10% Pd/C, EtOH/THF, 60%; (f) NaHMDS, THF, −78°C, then $PhNTf_2$, −50°C, 83% (**6a**), 76% (**6b**); (g) H_2, 10% Pd/C, EtOH/THF, 94% (**7a**), 72% (**7b**); (h) HCl, H_2O, reflux then $SOCl_2$, AcCl; (i) pyridine, methyl α-D-glucopyranoside, 50% (**1d**, two steps), 63% (**1e**, two steps, along with **7b** 23%). Tol: *p*-tolyl.

3. Solution conformation

In order to prove that the pyridyl ring acts as suggested by the modeling, extensive NMR solution conformation studies were carried out. The hydroxy resonance is highly sensitive to his implication in hydrogen bonding. Besides, adjacent ring proton resonance is an additional indication that would infer the existence of hydrogen bonds. Fortunately, unambiguous assignments of all the peaks were made possible by COSY experiments. ^1H NMR analysis in both DMSO-d_6 and $CDCl_3$ indicated the presence of the expected specific interaction (Table 1). A closer look to the data revealed that

Table 1. Chemical shift dependence of glycoside protons

Proton	**1a** DMSO	**1b** DMSO	**1a** $CDCl_3$	**1b** $CDCl_3$	**1c** $CDCl_3$	**1d** $CDCl_3$	**1e** $CDCl_3$
H-1	4.61	4.61	4.79	4.76	4.76	4.74	4.71
H-2	3.22	3.23	3.55	3.63	3.61	3.65	3.65
H-3	3.46	3.46	**3.74**	**3.86**	**3.86**	**3.87**	**3.94**
H-4	2.95	3.00	**3.53**	**4.06**	**4.04**	**3.85**	**3.85**
H-5	3.61	3.61	3.70	3.70	3.70	3.97	3.85
H-6	3.04	3.06	**3.41**	**3.13**	**3.13**	**3.21**	**3.27**
H-6′	3.37	3.37	**3.70**	**3.70**	**3.70**	**3.41**	**3.27**
OMe	3.39	3.40	**3.43**	**3.33**	**3.33**	**3.35**	**3.35**
OH-2	4.74	4.74	2.10	2.20	2.21	2.18	2.30
OH-3	4.78	4.79	2.53	2.95	2.97	2.86	4.72
OH-4	4.82	4.90	2.62	–	–	6.72	–

although **1a** and **1b** spectra are roughly identical in DMSO-d_6, several significant variations in the chemical shifts could be measured in $CDCl_3$. For instance, the H-4 and H-3 ring proton signals shifted downfield ($\Delta\delta_{H\text{-}4}$(**1c**–**1a**) = 0.51 ppm; $\Delta\delta_{H\text{-}3}$(**1c**–**1a**) = 0.12 ppm). Similarly, the modified patterns for the H-6 and OMe signals as well as the optical rotation values (Fig. 2) strongly support a large conformational change. The coupling constant values were also useful for the determination of the geometry and therefore of the conformation adopted in chloroform.[7,8] All these data are consistent with the models proposed on Figure 3.

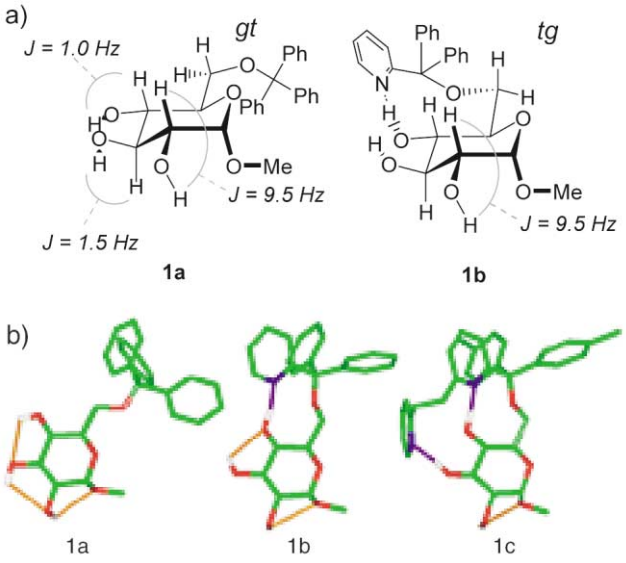


Figure 3. Proposed conformations on the basis of NMR spectroscopic data and by NMR restrained molecular modeling. *g* and *t* stand for *gauche* and *trans*.

The existence of the hydrogen bond in **1b** being established, the protecting group was further elaborated leading to **1e**. **1d** Was concomitantly used as a model for non-intramolecular hydrogen bonded OH-3.

Analysis of the ^1H spectra of chloroform solutions of **1e** and its analogue **1d** compared to those of **1a**, **1b** and **1c** showed that the previously observed hydrogen bond still exists although the chemical shift variations were less marked ($\Delta\delta_{H\text{-}4}$(**1d**–**1a**) = 0.32 ppm, $\Delta\delta_{H\text{-}4}$(**1e**–**1a**) = 0.32 ppm). When comparing **1d** to **1e**, H-3 shifted downfield by $\delta = 0.07$ ppm. The H-2 signal was displaced downfield from **1a** to **1b** by 0.08 ppm and remained roughly unchanged for **1d** and **1e**.

These observations were attributed to a reorganization of the hydroxy hydrogen bonding as illustrated in Figure 3b. Initially, OH-3 weakly hydrogen bonded with O-2 (**1a**). Owing to the intramolecular hydrogen bond with the pyridyl ring, OH-4 polarization increased. Consequently, OH-3 favored an interaction with O-4 over O-2 inducing an increase in O-2 partial charge. The extra pyridyl ring of **1e** hydrogen bonded with OH-3 whereas the phenyl counterpart **1d** cannot. Again, the significant variations of recorded optical rotation values corroborated the proposed models.

4. Relative reactivities

Our primary concern was the control of the relative reactivities of the secondary hydroxyl groups. In this context, is this established cooperative hydrogen bonding relevant to the hydroxy relative reactivities? To answer this question, the regioselectivity of the acetylation with these five triols was investigated. Solvents of different polarity and hydrogen bond properties were used to evaluate the role of the hydrogen bonding. It is worth noting that THF and dichloromethane are usual solvents for most of the glycosylation procedures and that we plan to extend this approach to open glycosylation.

The well-known higher reactivity of the 3-OH was observed whatever the protecting group (Table 2) while the reactivities for the other two-hydroxyl groups were similar in THF. As the solvent hydrophobicity increased, the amount of **9** and **11** decreased in favor of **10** (from 1:4.8:1.2 in THF to 1:11.7:1.9 in $CHCl_3$). The reactivity of the three positions was modified when the designed protecting groups acted as a hydrogen bond acceptor (in chloroform and dichloromethane). In this context, the proposed hydrogen bonding (Fig. 3b) released (O-2 not hydrogen bonded) and activated

(OH-3 hydrogen bonded with O-4) the 2-OH and 3-OH. Concomitantly, the amount of 4-OAc regio-isomers produced decreased significantly (oxygen atom not hydrogen bonded in **1a**, bonded in **1b**) in favor of the 2-OAc regioisomer. This expected deactivation resulted in a reversal of the relative reactivities of the positions 2 and 4 between **1a** and **1b** (from 1:4.6:1.1 in THF to 1:4:0.4 in $CHCl_3$). In addition, this new network remarkably deactivated the whole carbohydrate since conversions dropped down to 10% for **1b**, **1c** and **1d** and even to almost 0% with **1e** where two pyridyl rings are presumed to hydrogen bond. In contrast to the trityl group of **1a**, part of the partial charge of the hydroxyl groups is transferred to the protecting group. In this context, donor groups should be more appropriate and are presently considered.

These encouraging results were further validated with the ratios measured for the acetylation of **1c**, **1d** and **1e**. Again, dichloromethane was the best solvent in terms of regioselectivity and intrinsic reactivity. So far, we cannot decide between steric or electronic effects and both. When considering the loss of reactivity that comes with the increasing number of hydrogen bonds, one can conclude to an electronic effect. However, the presence of the pyridyl ring close to the western part of the sugar ring can also explain the decrease of the amount of **11**.

5. Conclusions

In the search for novel regioselective functionalization or glycosylation of free carbohydrates, we proposed herein a strategy relying on the control of the relative reactivities of the hydroxy groups. As a proof of concept, the effectiveness of this methodology was demonstrated in a systematic regioselectivity study using acetylation as a model reaction. These particularly protected glucopyranosides have demonstrated somewhat enhanced, though still modest, selectivity.

A first monopyridyl protecting group was designed that H-bonded with the 4-OH decreasing its reactivity. Less conclusive were the data for **1e** relative to those for **1b**. Since the ratios were identical, we cannot conclude to a positive effect. Further work is now underway to extend this study to a large panel of usual and designed protecting groups and to evaluate the potential of this strategy in open glycosylation.

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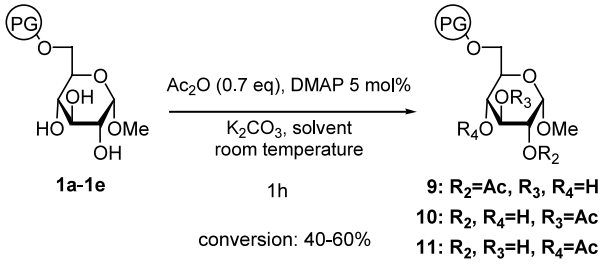
Table 2. Regioselectivity versus protecting groups



Compd	Solvent	**9**[a] (%)	**10** (%)	**11** (%)	Ratio
1a	THF	14	68	18	1:4.8:1.2
	CH_2Cl_2	13	74	13	1:5.5:1.0
	$CHCl_3$	7	80	13	1:11.8:1.0
1b	THF	15	69	16	1:4.6:1.1
	CH_2Cl_2	16	79	5	1:5.0:0.34
	$CHCl_3$[b]	19	74	7	1:3.9:0.40
1c	THF	15	73	12	1:4.8:0.8
	CH_2Cl_2	11	83	6	1:7.2:0.5
	$CHCl_3$[b]	22	71	7	1:3.2:0.35
1d	THF	17	78	5	1:4.5:0.30
	CH_2Cl_2	14	81	5	1:5.8:0.38
	$CHCl_3$[b]	7	93	<3	1:13.2:<0.1
1e	THF	13	76	11	1:5.8:0.84
	CH_2Cl_2	11	83	6	1:7.2:0.66
	$CHCl_3$	[c]	NR[c]	[c]	–

[a] Based on ^1H NMR of the crude mixture (±2%).
[b] Reacted for 6 h, 10% conversion (estimated ±5%).
[c] No reaction: reacted for 24 h, <5% conversion.

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