Cesium Trifluoroacetate or Silver Oxide Mediated Acyl Migration for the Construction of Disaccharide Building Blocks

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Abstract: A convenient method for the selective differentiation of the 2-OH and 3-OH of pyranosides, based on the CsO_2CCF_3- or Ag_2O-mediated acyl migration, has been established. The 2-OH and 3-OH can be sequentially glycosylated by the desired carbohydrate generating disaccharides of biological interest. A mechanism involving either acid- or base-assisted acyl migration is proposed.

Key words: ABO blood group antigens, silver oxide, cesium trifluoroacetate, acyl migration, migration mechanisms

Carbohydrates are widely recognized for their remarkable biological relevance. Thus, the synthesis of oligosaccharides has long been a goal pursued by many researchers.[1] For example, the minimal determinant oligosaccharides of the ABO blood group antigens play essential roles in blood transfusion, cell differentiation, and cell recognition, and are, therefore, the focus of great interest (Figure 1).[2] Research in these areas requires access to these oligosaccharides, which has been accomplished via chemical synthesis[3] or biosynthesis.[4] For the approach using chemical synthesis, regioselective protection and glycosylation of both O-2 and O-3 hydroxy groups of the core galactopyranose are the crucial steps that often require tedious protection and deprotection processes. Unlike the O-4 and O-6 hydroxy groups that can be readily protected using benzylidene, a multistep process is often needed for regioselective exposure of the desired O-2 or O-3 hydroxy groups, and the following glycosylation to take place. Hence, for the synthesis of oligosaccharides, such as the oligosaccharides of the ABO blood group antigen, it is preferable that such a multistep process can be as concise as possible.

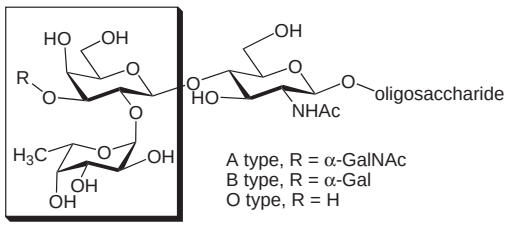
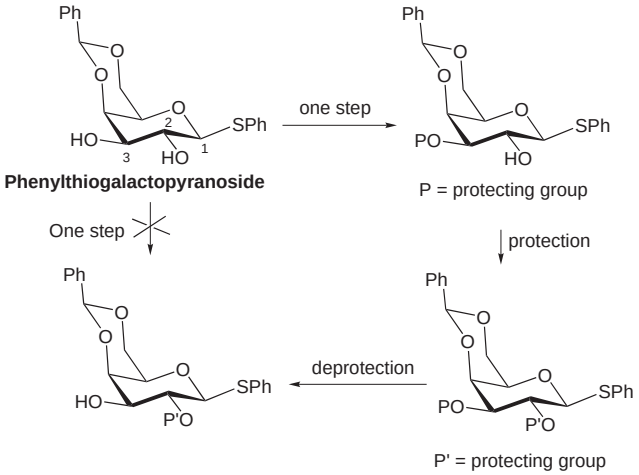


Figure 1 Examples of carbohydrate blood group antigens.

Among these multistep processes, differentiation of the equatorial O-2/O-3 *trans*-diol is one of the most challenging tasks in carbohydrate protecting group manipulation. The presence of vicinal axial heteroatoms, such as O and S, will enhance the nucleophilicity of the corresponding vicinal equatorial OH. For instance, the 3-OH in β-D-*galacto* configurations will be more nucleophilic than the 2-OH. Such an enhanced nucleophilicity has led to the development of many methods for the differentiation of 2-OH and 3-OH, like metal-mediated protection,[5] direct acylation,[6] reductive cleavage,[7] and enzyme catalysis[8] (Scheme 1). On the other hand the regioselective exposure of 3-OH is rather indirect often involving sequential protection and deprotection. To alleviate such an inconvenience and to facilitate oligosaccharide synthesis, we wish to report a facile acyl migration that will allow regioselective exposure of the desired hydroxyl groups in a *trans*-diol configuration and the application of such acyl migration to the synthesis of disaccharides.



Scheme 1 Strategy for the differentiation of O-2/O-3 on galactopyranose

Recently, Ye and co-workers reported a method for the regioselective protection of 2-OH or 3-OH where the selectivity seems to be governed by differences in the pyranose scaffold.[9] However, no detailed explanation to predict the regioselectivity was given. In the mean time, we discovered that, in the presence of Lewis acids (or bases) and catalyst, an acyl group can migrate from the 3-OH to the 2-OH of a *galacto*-configured disaccharide as shown in the transformation from **1**[5a] to **2**[5a] (Table 1). To make such

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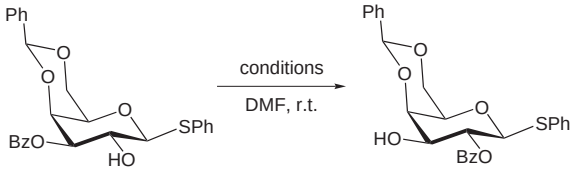
an acyl migration compatible with acid- or base-labile functional groups we have also examined various Lewis acids and bases for their capability of initiating acyl migration. We found Ag_2O and CsO_2CCF_3 were the best Lewis base and acid for performing acyl migration (Table 1, entries 1 and 10). We have also discovered that the presence of tetrabutylammonium iodide (TBAI) as a catalyst is important. Without the catalyst (TBAI) the migration occurs at a much slower rate (Table 1, entry 13), however, TBAI alone cannot trigger the acyl migration (Table 1, entry 14). We reasoned that protection of the hydroxy group vicinal to an axial group, for example, the 3-OH of benzylidene-protected phenylthiogalactoside, is kinetically controlled. Migration of the acyl group to the other hydroxy group (for example, the 2-OH of compound **1**) is thermodynamically controlled, and is governed by the steric hindrance of the axial group (for example, the 4-OR of compound **2**).

Acyl migration is a common phenomenon that has been observed in carbohydrate chemistry.[10] For example, Bourne[11] reported that alkaline hydrolysis (aq NaOH) of 2-*O*-benzoyl-α-D-glucoside could give the 3-*O*-benzoated isomer. Similarly, 3-*O*-benzoyl-β-D-galactoside could be converted into the 2-*O*-benzoated isomeric product by acyl migration under alkaline conditions (pyridine, NaOMe or NaOH),[12] however, pyridine is harmful and toxic which may cause environmental problems. Moreover, a long reaction time is usually required for the acyl migration to go to completion (seven days). Other alkalis, such as NaOMe and NaOH, may be not suitable when the substrates contain base-sensitive functionalities. In contrast, application of a Lewis base (Ag_2O) and Lewis acid (CsO_2CCF_3) proved to be a good solution to circumvent these problems. The convenience and simplicity of employing Ag_2O- and CsO_2CCF_3-mediated acyl migration as well as the good yields of desired products render this protocol more attractive and applicable.

Besides the benzoyl group, the migration protocol can also be applied to other acyl groups, such as 4-chlorobenzoyl, 4-methoxybenzoyl, decanoyl, and acetyl groups (Table 2). Under the optimized conditions [Ag_2O (1 equiv)/TBAI (0.1 equiv) or CsO_2CCF_3 (1 equiv)/TBAI (0.1 equiv)], the (substituted and unsubstituted) benzoyl group seems to be more susceptible to migration than the acetyl counterpart under similar conditions. It should be noted that temperatures higher than those indicated in Table 2 led to complicated results, for example, the 2,3-diacyl and 2,3-diol products could be generated; longer

Table 1 Conditions Examined for Optimizing Acyl Migration

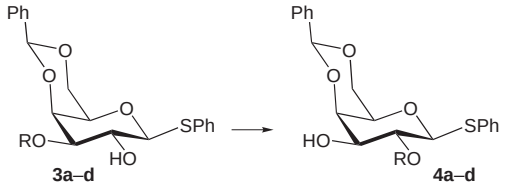


1 **2**

Entry	Reagent (equiv)	Catalyst (equiv)	Time (h)	Products	Yields (%)
1	Ag_2O (1)	TBAI (0.1)	48	**2**	**95**
2	Ag_2CO_3 (1)	TBAI (0.1)	8	**2**	40
3	AgOTf (1)	TBAI (0.1)	48	N.R.[a]	–
4	ZnI_2 (1)	TBAI (0.1)	48	**2**	30
5	$Cu(OAc)_2$ (1)	TBAI (0.1)	72	**2**	24
6	$ZnCl_2$ (1)	TBAI (0.1)	72	**2**	13
7	$FeCl_3$ (1)	TBAI (0.1)	72	N.R.	–
8	$FeCl_2$ (1)	TBAI (0.1)	72	N.R.	–
9	BaO (1)	TBAI (0.1)	72	**2**	50
10	CsO_2CCF_3 (1)	TBAI (0.1)	72	**2**	**67**
11	CuCl (1)	TBAI (0.1)	72	**2**	33
12	$Cu(OTf)_2$ (1)	TBAI (0.1)	72	N.R	–
13	Ag_2O (1)	–	72	**2**	30
14	–	TBAI (1)	72	**2**	N.R.

[a] No reaction.

Table 2 Migration of Different Acyl Groups[a]



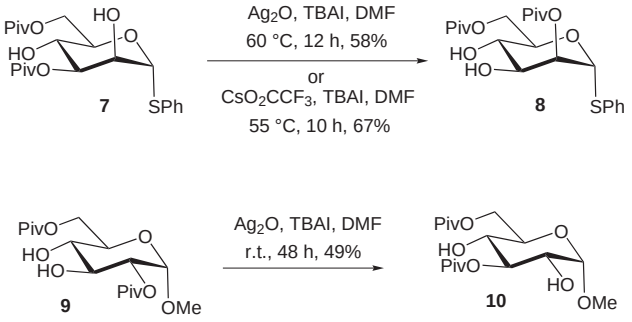
Compd	R	Method	Temp	Time (h)	Yield (%)
3a	4-ClBz	A	75 °C	7	80
		B	75 °C	8	83
3b	4-MeOBz	A	40 °C	10	77
		B	50 °C	12	79
3c	$C_9H_{19}CO$	A	60 °C	7	76
		B	50 °C	12	76
3d	Ac	A	r.t.	48	68
		B	45 °C	24	71

[a] Method A: Ag_2O, TBAI, DMF; Method B: CsO_2CCF_3, TBAI, DMF.

reaction times caused the same problem. Therefore, the reaction was monitored by TLC and quenched immediately when a side-product appeared. Typically, the regioisomers formed were more polar than the starting materials so they could be easily separated by column chromatography.

Differentiation of the O-2 or O-3 hydroxy groups on benzylidene-protected α-D-glucoside can be achieved in a similar fashion (Table 3). For the α-D-glucoside scaffold the 2-OH is kinetically favored, while the 3-OH is thermodynamically more stable. The tosyl group failed to undergo migration (**5e**), which may, in part, explain the results observed by Ye; the tosyl and acyl groups appear to have the opposite regioselectivity. We propose that, initially, both tosyl and acyl groups favor the formation of kinetic products then the acyl groups migrate to the thermodynamically more favored hydroxy group.

Interestingly, moderate to excellent selectivity for the acyl migration was obtained even when pyranoses containing multiple hydroxy groups were employed (Scheme 2). For example, the 3-*O*-pivaloyl group compound **7** migrates predominately to the 2-OH, suggesting that 4-OH is sterically more hindered. The 2-*O*-pivaloyl group of compound **8** migrates to the 3-OH, affording the more stable regioisomer. We attempted to optimize the reaction conditions, however, in both cases, heating the reaction to higher temperatures generated complicated results.

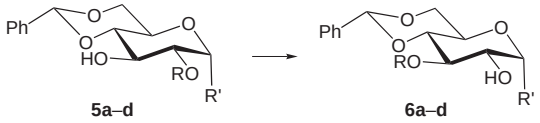


Scheme 2 Migration of acyl groups on pyranoses with diols

In the absence of steric preference as in compound **11**, a mixture of starting material and migrated compound **12** (1:1 ratio) was obtained when Ag_2O/TBAI was used to effect migration at room temperature (30 hours), although it was found that 2-OH is more reactive toward benzoylation (Scheme 3).[9]

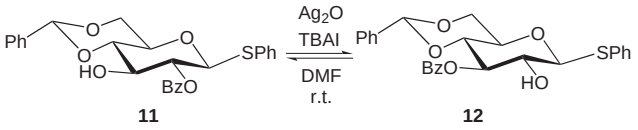
It was suggested that the acyl migration might proceed through an intermediate cyclic orthoester.[11] The formation of such a transitory intermediate would initiated by

Table 3 Migration of Acyl Groups on Benzylidene-Protected α-D-Glucoside



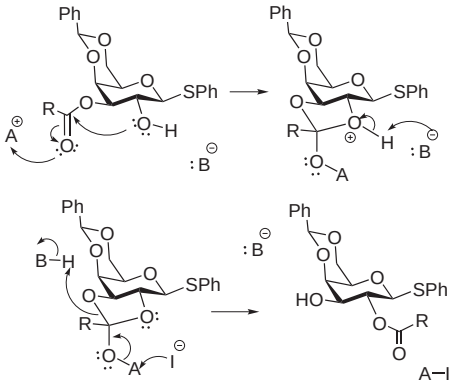
Compd	R	R′	Method[a]	Temp	Time (h)	Yield (%)
5a	Bz	OMe	A	75 °C	7	74
			B	50 °C	17	78
5b	Ac	OMe	A	r.t.	48	60
			B	r.t.	24	67
5c	Bz	SPh	A	r.t.	48	70
5d	Ac	SPh	A	50 °C	24	71
			B	50 °C	12	72
5e	Ts	OMe	A	60 °C	48	–
			B	60 °C	48	–

[a] Method A: Ag_2O, TBAI, DMF; Method B: CsO_2CCF_3, TBAI, DMF.



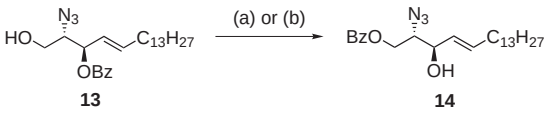
Scheme 3 Acyl migration on glucopyranose

nucleophilic addition of the hydroxyl group at C-2 to the vicinal carbonyl functionality. Then ring scission would give the more stable acyl group at C-2. Based on this mechanism, we proposed a possible involvement of iodide (from TBAI) to explain our acyl migration (Scheme 4). In the proposed mechanism, the iodide functions as a catalyst and facilitates the orthoester ring scission, which leads to the migrated product.



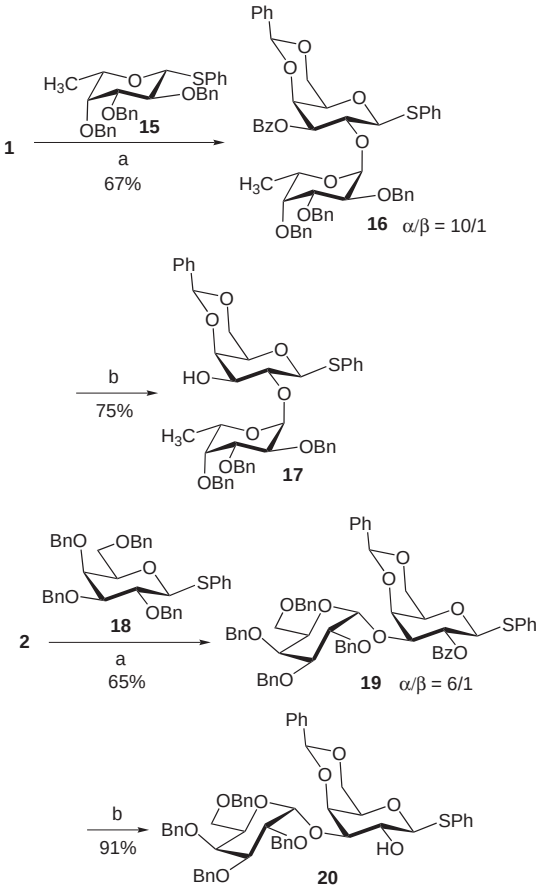
Scheme 4 Proposed mechanism of acyl migration

After the successful acyl migration in pyranosides, we proceeded to investigate the compatibility of other substrate such as sphingosine derivative **13**[13] under similar conditions (Scheme 5). The desired product **14** was obtained in good yields (77% and 74%, respectively) under both conditions; any unreacted starting material was recovered.



Scheme 5 3,1-Acyl migration on sphingosine. *Reagents and conditions*: (a) Ag_2O (1 equiv), TBAI (0.1 equiv), DMF, r.t., 20 h, yield: 77%; (b) CsO_2CCF_3 (1 equiv), TBAI (1 equiv), DMF, 50 °C, 6 h, yield: 74%.

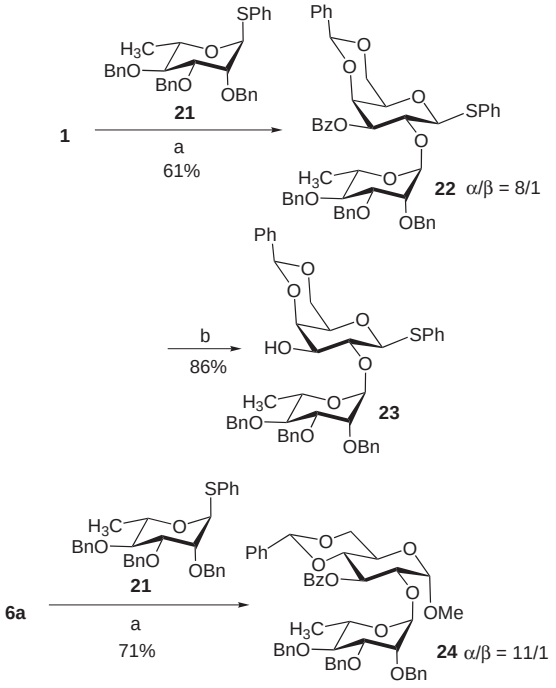
Having achieved the regioselective acyl migration, we began to explore its application in the synthesis of several biologically important disaccharides, for example, the minimal determinant oligosaccharides of the ABO blood group antigen. As shown in Scheme 6, the 2-OH and 3-OH can be glycosylated leading to the synthesis of various disaccharides. Compound **16**, precursor of an O-type antigen, can be prepared by the glycosylation of **1** with **15**.[14] One of the advantages of using the acyl group is that it can be easily removed allowing further glycosylation if necessary. For example, hydrolysis of the benzoyl group of compound **16** yields **17**. Further glycosylation of the 2-OH with a glycosyl donor like **18**[14] will lead to the synthesis of a B-type antigen.



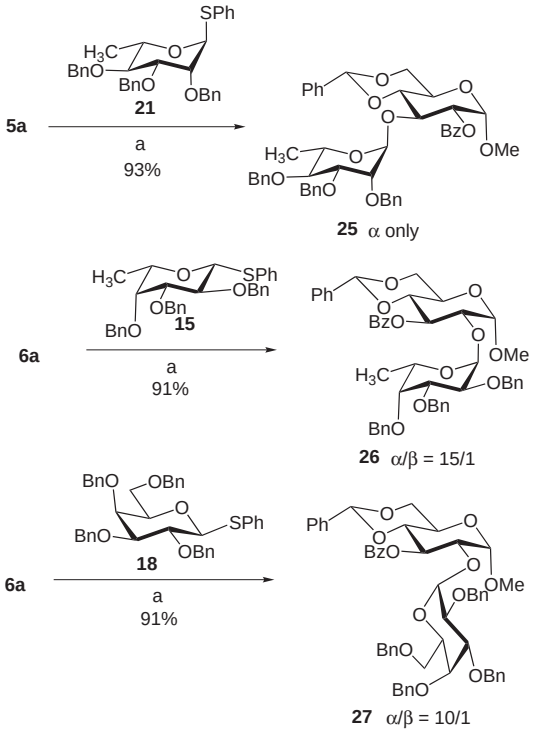
Scheme 6 *Reagents and conditions*: (a) PhSCl, AgOTf, 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), molecular sieves (AW300), CH_2Cl_2, –78 °C; (b) LiOH, H_2O, THF, r.t.

Glycosylation using rhamnose and other carbohydrate moieties has also been successfully attempted (Schemes 7 and 8). Even though both donors (**15**, **18**, and **21**) and acceptors (**1** and **2**) in one-pot glycosylation reactions are thioglycosides, the chemoselective glycosylation was achieved successfully in the presence of PhSCl/AgOTf as promoter, affording good yields of disaccharides as an α/β-anomeric mixture. Pure α-anomers were obtained by recrystallization from diethyl ether–hexane (1:3). Notably, such disaccharide products contain an anomeric phenylthio group that can serve as a glycosyl donor, thus broadening the application of this procedure.

In conclusion, we have developed two general and comparable protocols for the differentiation of 2,3-*trans*-diol in various pyranoses, which will allow further modifications such as glycosylation of desired carbohydrates.[15,16] To demonstrate the building block synthesis, several disaccharides were prepared. Another advantage of our acyl migration protocol is the use of acyl groups that can be removed conveniently, thus allowing further modifications if desired. In addition, our protocols can be applied to the



Scheme 7 *Reagents and conditions*: (a) PhSCl, AgOTf, DTBMP, molecular sieves (AW300), CH_2Cl_2, –78 °C; (b) LiOH, H_2O, THF, r.t.



Scheme 8 *Reagents and conditions*: (a) PhSCl, AgOTf, DTBMP, molecular sieves (AW300), CH_2Cl_2, –78 °C.

3,1-acyl migration of sphingosine. The mechanism for the acyl migration has been elaborated, which may clarify the role of TBAI and the effect of DMF. Furthermore, the extension of acyl migration methodology to other poly-hydroxyl substrates has also been undertaken.

Acknowledgment

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(15) **Acyl Migration Using Ag_2O; General Procedure**. A solution of starting material (0.12 mmol) and TBAI (4.2 mg, 0.012 mmol), Ag_2O (0.12 mmol) in anhyd DMF (5 mL) was stirred at the indicated temperature. The reaction was monitored by TLC. When the side product appeared, the reaction mixture was subsequently filtered then concentrated. The filtrate was subject to flash column chromatography to yield the desired product. The unreacted starting material was recovered.
(16) **Acyl Migration Using CsO_2CCF_3; General Procedure**. A mixture of starting material (0.20 mmol), CsO_2CCF_3 (0.20 mmol), and TBAI (8 mg, 0.02 mmol) in anhyd DMF (10 mL) was stirred at the indicated temperature. The reaction was monitored by TLC. When the side product appeared, the reaction mixture was filtered then concentrated. The filtrate was subject to flash column chromatography to yield the desired product. The unreacted starting material was recovered.