Efficient Carbohydrate Synthesis by Controlled Inversion Strategies

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Abstract

The Lattrell-Dax method of nitrite-mediated substitution of carbohydrate triflates is an efficient method to generate structures of inverse configuration. In this study it has been demonstrated that a neighboring equatorial ester group plays a highly important role in this carbohydrate epimerization reaction, inducing the formation of inversion compounds in good yields. Based on this effect, efficient synthetic routes to a range of carbohydrate structures, notably β-D-mannosides and β-D-talosides, were designed. By use of the ester activation effect for neighboring groups, a double parallel as well as a double serial inversion strategy was developed.

Keywords: Carbohydrate Chemistry, Carbohydrate Protection, Epimerization, Inversion, Dynamic, Regioselective Control, Neighboring Group Participation
List of publications

I. Solvent-Dependent, Kinetically Controlled Stereoselective Synthesis of 3- and 4-Thioglycosides
Zhichao Pei, Hai Dong and Olof Ramström

II. Stereospecific Ester Activation in Nitrite-Mediated Carbohydrate Epimerization
Hai Dong, Zhichao Pei and Olof Ramström

III. Reagent-Dependent Regioselective Control in Multiple Carbohydrate Esterifications
Hai Dong, Zhichao Pei, Styrbjörn Byström and Olof Ramström
*Manuscript*

IV. Efficient Synthesis of β-D-Mannosides and β-D-Talosides by Double Parallel or Double Serial Inversion
Hai Dong, Zhichao Pei, Marcus Angelin, Styrbjörn Byström and Olof Ramström
*Manuscript*
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Abbreviations

Ac     Acetyl group
AcCl   Acetic chloride
Ac2O   Acetic anhydride
aq     aqueous
Bn     Benzyl group
BnBr   Benzyl bromide
Bz     Benzoyl group
BzCl   Benzoyl chloride
Bu2SnO Dibutyltin oxide
DMF    Dimethylformamide
equiv. equivalent
Gal    Galactoside
Glc    Glucoside
h      hour
Man    Mannoside
NGP    Neighboring group participation
NMR    Nuclear magnetic resonance
rt     room temperature
T      Temperature
Tal    Taloside
TBA    Tetrabutylamonium
TEA    Triethylamine
Tf2O   trifluoroacetic anhydride
py.    pyridine
1 Introduction

1.1 Carbohydrate Synthesis in Biology

Carbohydrates are one of the largest classes of naturally occurring substances, often found in conjunction with other large bimolecular such as lipids or proteins (Figure 1). This class of compounds has been attracting an increasing amount of attention up to today, on account of playing essential roles in diverse biological processes. Specific protein-carbohydrate interactions constitute the underlying aspects of these important processes, including cell differentiation, cell adhesion, immune response, trafficking and tumor cell metastasis, occurring through glycoprotein, glycolipid, and polysaccharide entities at cell surfaces, and lectins, proteins with carbohydrate-binding domains.\(^{1-3}\) Carbohydrates with medicinal uses include heparin, which is the most widely used anticoagulant, antibiotics and vaccines.\(^{4, 5}\) Uncovering the contributions of carbohydrates to cell biology would greatly facilitate advancements in science and medicine. However, the functions of carbohydrates in biology have not been extensively studied due both to the more complex structures of oligosaccharides and to a lack of general methods for synthesizing and analyzing these molecules.

![glycolipid (galactosyl cerebroside)](image)

![blood group antigen H](image)

![glycoprotein (O-glycosidic)](image)

Figure 1. Natural carbohydrate containing entities.\(^{6}\)

One important case is β-mannoside synthesis. The β-mannopyranosidic linkage is a common structural element in a wide range of natural products.\(^{7-10}\) This biologically important and widespread class of structures contains, as relevant component, β-D-Man\(\beta\) units, for example present as a central component in the ubiquitous N-glycan core structure of glycoproteins,\(^{7}\) and makes part of a range of fungal and bacteria (Figure 2).\(^{11, 12}\) The chemical synthesis of this 1,2-cis-mannosidic linkage is, however, especially difficult. The α-mannosidic linkage is strongly favored because of the concomitant occurrence of both the α-directing anomeric effect and the repulsion between the axial C-2 substituent and the approaching nucleophile. Moreover, neighboring group participation of a 2-acyl substituent leads to α-mannosides only.
The other important case is thiosaccharides synthesis. Thiosaccharides, where an exocyclic oxygen is replaced by a sulfur functionality, constitute an increasingly important group of compounds in glycochemistry, possessing unique characteristics compared to their oxygen-containing counterparts (Figure 3). These compounds are often used as efficient glycoside donors and acceptors in oligosaccharide and neoglycoconjugate synthesis, because the thiolate is a potent nucleophile and a weak base that reacts easily and selectively with soft electrophiles. Furthermore, the resulting thioglycosides and S-linked conjugates possess increased resistance to degradation by glycosidases potentiating their use as efficient building blocks in drug design and therapeutics.

1.2 Carbohydrate Epimerization

Initially, we focused on developing convenient routes to 3- and 4-thioglycosides of the galacto-type, starting from free galactoside or glucoside (Figure 4). In order to obtain the
3-thio-galactoside 2 or the 4-thio-galactoside 4, it was thus necessary to choose reasonable protection strategies and epimerization routes.

Figure 4. Design of synthesis routes to methyl 3- and 4-thiogalactosides.\(^{24}\)

Epimerization of carbohydrate structures to the corresponding epi-hydroxy stereoisomers is an efficient means to generate compounds with inverse configuration that may otherwise be cumbersome to prepare. Several different synthetic methods have been developed, including protocols based on the Mitsunobu reaction,\(^{25}\) sequential oxidation/reduction routes,\(^{26}\) as well as enzymatic methods,\(^{27}\) all of which with their respective advantages and shortcomings.

### 1.3 Lattrell-Dax Carbohydrate Epimerization

A common route to stereocenter inversion in carbohydrate chemistry involves the triflation of a given hydroxyl group, followed by substitution using a variety of nucleophilic reagents (Figure 5). This method was used by Dax and co-workers who first reported that glycoside triflate displacement by nitrite ion, a reaction first found by Lattrell and Lohaus,\(^{28}\) produced carbohydrates with inverse hydroxyl configuration under very mild
conditions. Due to its efficient and convenient character, we thus preferred to use the Lattrell-Dax carbohydrate epimerization method. Despite its reported efficiency, the Lattrell-Dax method has unfortunately not been extensively adopted, likely because of difficulties in predicting the outcome for specific structures.

Binkley reported a simple technique for converting methyl 2,6-dideoxy-β-D-arabinohexopyranosides into the corresponding ribo- and lyxo-isomers through internal triflate displacement by a neighboring benzoyl group and a direct inversion method through triflate displacement by nitrite ion when neighboring participation could not take place (Figure 6). He further reported that the inversion reaction appeared to be related to the configuration, but no explanation was given.

In a more recent study, von Itzstein and co-workers needed to perform a 3-position glycoside inversion reaction when they developed a new approach toward the synthesis of lactose-based S-linked sialylmimetics of α-(2,3)-linked sialosides. Their strategy however failed when they chose a glycoside where one hydroxyl group in 3-position was free and the other positions protected with benzyl groups (Figure 7). Interestingly, they obtained a satisfactory result when the 2-position benzyl group was replaced with a benzoyl group. It clearly showed that the choice of protecting group was crucial to inverting the configuration at the 3-position of the galactose ring.
In light of these studies, a tentative conclusion can be given: the choice and the configuration of the neighboring protecting group of the triflate are crucial for the reactivity in the Lattrell-Dax inversion. An equatorial trans-configuration is favored for the inversion. However, by coincidence the trans-configuration is also favored for the neighboring group participation. Thus, a question can be put forward: can the neighboring ester group activate the nitrite inversion process via a neighboring group participation mechanism?

1.4 Neighboring Group Participation

The neighboring group participation mechanism requires two conditions: a neighboring ester group and trans-configuration. For example, in the course of 3- and 4-thioglycoside synthesis, a solvent-dependent kinetically controlled stereoselective mechanism was found (Figure 8).

![Figure 8](image)

Figure 8. Solvent-dependent kinetically controlled stereoselective mechanism: a) kinetic control in toluene; b) neighboring group participation in DMF.

In the polar solvent DMF, the neighboring group participation reaction took place immediately. However, in the nonpolar solvent toluene the neighboring group participation is restrained. This indicated that neighboring group participation is favored in polar solvents. Further analysis showed that the products of the neighboring group participation always were compounds where the ester group is in axial position and the hydroxyl group is in equatorial position. For the Lattrell-Dax nitrite-mediated inversion, it was obvious that the ester group always remained in the same position and the hydroxyl group was generated on the carbon atom directly connected to the triflate group. Thus, it appeared as
if neighboring group participation did not occur. Why is it then important to have a neighboring ester group for the Lattrell-Dax inversion? Furthermore, how does this ester group activate the inversion reaction?

1.5 Design of Synthetic Strategies

To investigate the effect of the protecting group pattern to the inversion reaction, a series of galacto- and gluco-type derivatives, where one hydroxyl group in the 2, 3, or 4-position was free and the other positions were separately protected with acetyl, benzoyl, and benzyl/benzylidene groups, respectively, were chosen for further evaluation (Figure 9).

These compounds were to be subjected to conventional triflation by triflic anhydride, followed by treatment with potassium nitrite in DMF. It was expected that in all cases good inversion yields would be obtained with neighboring ester groups, whereas the inversion would be inefficient with benzyl groups.

To further analyze and explore the effect of the neighboring ester group configuration of triflate on the reactivity, other systems were designed. To avoid effects from the 2- and 6-positions and to isolate the effects arising from ester groups in the 3- and 4-positions, the
2- and 6-positions were protected with benzyl ether groups (Figure 10). Thus, a range of compounds where one of the hydroxyl groups in the 3- or 4-position is protected with an acetyl group had to be prepared and subsequently tested in the Lattrell-Dax epimerization reaction. However, all above mentioned compounds must first be synthesized. Therefore the first challenge was to develop efficient regioselective protection schemes.
2 Regioselective Carbohydrate Protections

2.1 Traditional Protection Strategies

Regioselectivity is a prominent challenge in carbohydrate chemistry since carbohydrates contain several hydroxyl groups of similar reactivity. Selective protecting groups and efficient protecting group strategies are therefore of crucial importance to efficiently obtain desired carbohydrate structures. With modern protecting groups there is the potential of fulfilling every possible protection pattern. However, a good protecting group strategy remains a central challenge in carbohydrate chemistry. The most common protecting groups for hydroxyl functions are esters, ethers, and acetals. Carbohydrate hydroxyl groups differ somewhat in reactivity depending on whether they are anomeric, primary or secondary, and also depending on their configurations. These differences in reactivity can sometimes be utilized so that a desired protection pattern can be achieved in few steps without the use of more complex reaction sequences.\(^{(34, 35)}\) A carbohydrate protection strategy was designed for acquiring the desired glycoside derivatives via the use of esterification, benzylaion, etherification, or comprehensive use of all these means.

2.1.1 Esterification

Methyl 2,3,6-tri-\(O\)-benzoyl galactoside 14 could be simply synthesized by a one-step esterification process, starting from galactoside 1 (Scheme 1).

\[
\text{HO-} \quad \text{OH} \quad \text{OMe} \\
\text{HO} \quad \text{OH} \quad \text{OMe}
\]

\[
\begin{align*}
\text{BzCl} & \quad \text{py, CH}_2\text{Cl}_2 \\
\text{-40 °C} & \quad \text{60%}
\end{align*}
\]


As for methyl 2,3,6-tri-\(O\)-benzoyl glucoside 15, it was envisaged that a good inversion yield could be obtained by the Lattrell-Dax method, resulting in efficient synthesis of 15 via the epimerization of galactoside 14. In addition, glucoside 15 can also be synthesized through a more complex route based on acyl group migration.\(^{(36)}\)

2.1.2 Benzylation

The glycoside derivatives 11, 13, 17 could be synthesized by benzylation methods. Starting from galactoside 1, the 4,6-\(O\)-benzylidene 24 was produced first, then directly reacted with benzyl bromide in the presence of sodium hydride, producing 4,6-\(O\)-benzylidene-2-\(O\)-benzyl galactoside 13 in 30% total yield (Scheme 2). Higher yield of 13 could be obtained by a more complex synthesis route, where the hydroxyl group in 3-
position of 24 was first protected with a \( p \)-methyl-benzyl group via regioselective organotin-mediated benzylation, followed by protection of the hydroxyl group in the 2-position with a benzyl group via the general benzylation method, and finally the \( p \)-methyl-benzyl group in the 3-position was removed by oxidation.


Starting from glucoside 3, the 4,6-\( O \)-benzylidene 25 could be produced by the same method, then 4,6-\( O \)-benzylidene-3-\( O \)-benzyl glucoside 11 was obtained through the same as above mentioned tin oxide benzylation method (Scheme 3). The lower yield was caused by the similar reactivity between the 2- and 3-positions of 25.

Scheme 3. Synthesis of compounds 11 and 17.

When the above reaction mixture containing 25 was directly benzylated, the 4,6-\( O \)-benzylidene-2,3-di-\( O \)-benzyl glucoside 26 was produced in a very high yield. After the benzylidene ring being opened by reduction, the 2,3,6-tri-\( O \)-benzyl glucoside 17 was finally obtained in 80% yield.

2.1.3 Combination of Esterification and Benzylation

Most of the glycoside derivatives were synthesized using a combination of esterification and benzylation reactions. Some required only a few steps, whereas others were more cumbersome. For synthesis of the 4,6-\( O \)-benzylidene-3-\( O \)-benzoyl glucoside 10, it was known that compound 25 was easily produced by one step benzylidenelation in light of Scheme 3. Starting from compound 25, the glucoside 10 was then conveniently obtained by benzoylation (Scheme 4).
The syntheses of methyl 2,4,6-tri-\(O\)-acetyl galactoside 8 and methyl 2,4,6-tri-\(O\)-benzoyl galactoside 12 were somewhat more complex. The hydroxyl group in the 3-position of galactoside 1 was first protected with a benzyl group by regioselective tin oxide benzylation, and then the obtained 26 was acylated in the presence of pyridine in methanol. Finally after removing the benzyl group in the 3-position by a catalytic hydrogenation process, the methyl galactosides 8 or 12 were acquired in high yield (Scheme 5).

It proved most difficult to synthesize the glycoside derivatives where one of the hydroxyl groups in the 3- or 4-position was protected with an acetyl group whereas the 2- and 6-position were blocked with benzyl groups. The methyl 4-\(O\)-acetyl-2,6-di-\(O\)-benzyl galactoside 18 could however be relatively easily obtained in 70% total yield via a one-pot reaction (Scheme 6).
Starting from the obtained compound 18, and removing the acetyl group, then the 2,6-di-\(O\)-benzyl galactoside 31 could be easily changed into 2,3,6-tri-\(O\)-benzyl galactoside 16 or 3-\(O\)-acetyl-2,6-di-\(O\)-benzyl galactoside 19 by organotin methods (Scheme 7).

![Scheme 7. Syntheses of compound 16 and 19.](image)

The 3-\(O\)-acetyl-2,6-di-\(O\)-benzyl glucoside 21 could be acquired via the epimerization of 19 (Figure 11). The 4-\(O\)-acetyl-2,6-di-\(O\)-benzyl glucoside 20 could be produced via acetyl group migration of 21. Furthermore, the 4-\(O\)-acetyl-2,6-di-\(O\)-benzyl guloside 22 could be acquired via the epimerization of 20 and the 3-\(O\)-acetyl-2,6-di-\(O\)-benzyl guloside 23 could be produced via neighboring group participation of 20.

![Figure 11. Synthesis approach to 20, 21, 22, 23.](image)
2.2 Organotin Protection Strategies

2.2.1 Organotin Monoprotection

For obtaining mono-substituted compounds in one or a few steps, the use of organotin reagents such as tributyltin oxide or dibutyltin oxide\(^{38}\) provide useful means to efficient regioselective acylations\(^{39-42}\), alkylations\(^{39, 43-45}\), silylations\(^{46}\), sulfonylations\(^{39, 47, 48}\), and glycosylations\(^{49-51}\). Stannylene acetals are easily prepared, and generally lead to intermediate structures with predictable reactivities. In these reactions, stoichiometric amounts of organotin reagent are normally used. Several acylation and benzylaition examples have been given in the above syntheses.

2.2.2 Organotin Multiple Esterification

However, of particular importance in this respect is the possibility of acquiring multiple protections in single step processes, and so far no efficient, general methods have been developed. Interestingly, a protocol was recently described where products with one or two free hydroxyl groups were produced by use of excess organotin reagent\(^{52}\). This potentially general approach is very convenient and efficient for multiple protection schemes. Combining this organotin method with the Lattrell-Dax (nitrite-mediated) carbohydrate epimerization method\(^{53}\), very convenient and highly efficient methods to modify carbohydrate structures that traditionally require many steps\(^{36, 54}\), can be developed. For example, the syntheses of 2,4,6-tri-O-acetyl (or benzoyl) galactoside \(8\) (or \(12\)) and 2,3,6-tri-O-benzoyl galactoside (or glucoside) \(14\) (or \(15\)), which can be used to synthesize 3- and 4-thioglycosides, normally require many steps in light of the above (Scheme 5), or the literature\(^{36}\). For this reason, is it possible that they are produced in high yield via the convenient organotin multiple esterification?

In order to advance the organotin-mediated multiple carbohydrate protection method, a study of regioselective single-step acylations of unprotected pyranosides was initiated. The unprotected glycoside was first treated with excess amount (2-3 equivalents) of dibutylinoxide, producing a stannylene intermediate that was not isolated. This intermediate was subsequently treated with the acylation reagent to yield the protected products in a one-pot process (Figure 12).

![Figure 12](image_url)  
Figure 12. Example of organotin-mediated multiple carbohydrate esterification.
During this study it was however found that the multiple esterification processes were highly dependent on the acyl reagent used. Different protection patterns could be acquired from the same starting material by control of temperature, acyl reagents, reagent mole ratio, and solvent polarity (Scheme 8, 9, 10).

Scheme 8. Multiple benzoylation controlled by temperature and reagent mole ratio.

In the course of these studies (Scheme 8), it was found that the benzoyl group can migrate to 3- and 4-position from 2- and 3-position at high temperature. Thus temperature could be used for dynamic migration control.

Scheme 9. Multiple esterifications controlled by acyl reagents and solvents.

In light of the tentative organotin benzoyl group migration mechanism suggested, the resulting tin alkoxide intermediate is able to attack the acyl carbonyl group. It is however reasonable to assume that acyl regents in general are able to migrate under the same conditions. And yet, different from benzoyl chloride and acetyl chloride, it was found that the migration could only be observed with acetyl chloride at room temperature, whereas acetyl anhydride proved inefficient in this reaction (Scheme 9).
On the other hand, since no migration resulted with whether acetic anhydride or benzoyl chloride at room temperature, it is apparent that the results controlled by acyl reagents, where the 3,6-position protected product 37 was obtained with acetic anhydride whereas the 2,6-position protected product 38 was obtained with benzoyl chloride at room temperature, were not brought about by the organotin acyl group migration mentioned above (Scheme 9).

Scheme 10. Multiple esterifications controlled by solvent polarity.

Good selectivity was always obtained when the esterification reactions were done in a more polar solvent (Scheme 10). The reason is likely due to decreased reactivity of the esterification reagent from solvent-induced destabilization of the stannylene intermediates. If the experiments were performed in polar solvents, higher yields of 15 and 38 would be acquired.
3 Stereospecific Ester Activation

3.1 Effects in Lattrell-Dax Epimerization

All the glycoside derivatives, which were designed to explore the effect of the neighboring group on the Lattrell-Dax epimerization, were synthesized via the use of esterification, benzylolation or organotin methods. It was hypothesized that, whenever the triflate group is in 2-, 3-, or 4-position of these pyranosides, good inversion yields would be obtained with neighboring ester groups, whereas poor inversion yields or complex mixtures would be obtained with neighboring benzyl groups. Furthermore, good inversion yields would be obtained with only neighboring equatorial ester groups, and it would be inefficient with neighboring axial ester groups. Our first approach was to investigate the effect of the protecting group pattern to the inversion reaction.

3.1.1 Effects of Protection Patterns

Initially, glycoside derivatives carrying a triflate group in the 3-position, were subjected to the test. In order to compare the effects of different ester groups, two types of ester-protected galactopyranosides (8, 12) were synthesized.

![Scheme 11. Epimerization of glycosides where one hydroxyl group in 3-position is free.](image)

As can be seen (Scheme 11), good yields were in these cases obtained only on the condition that esters were chosen as protecting groups, benzoyl groups being slightly less activating than the acetyl counterparts. When the ester protecting groups were replaced by benzyl/benzylidene groups, a mixture of different products was instead obtained.

Similar results were obtained from the epimerization of glycopyranosides where the hydroxyl group in the 4-position was unprotected, and all other positions were protected with either benzoyl or benzyl groups (Scheme 12). Only when an ester group was present at the carbon adjacent to the carbon atom carrying the leaving triflate group did the
reaction proceed smoothly, the axially oriented triflate being less reactive than the equatorial leaving group.

Scheme 12. Epimerization of glycosides where one hydroxyl group in 4-position is free.

In contrast to this effect, no efficient reaction occurred when benzyl groups were employed where compound mixtures were instead rapidly obtained. These results suggest that a neighboring ester group is able to induce or activate the inversion reaction, whereas an ether derivative is unable to produce this effect. The results also show that the inversion reaction proceeded smoothly regardless of the triflate configuration.

Scheme 13. Epimerization of glycosides where one hydroxyl group in 2-position is free.

Further tests were performed for glucopyranosides where the hydroxyl groups in the 2-position was free (Scheme 13). Instead of observing the inversion behavior in the 3- and 4-positions of the hexopyranosides, the 2- and 3-positions were probed (2,3-trans). The results also indicated that the ester-protecting group would prove efficient in inducing the inversion, whereas the corresponding ether protecting group would fail to produce this effect. The ester-protected glucopyranoside compound 10 afforded the inversion mannopyranoside product 43 in good yields, whereas the ether-protected compound 11
proved inefficient. In this case, slightly longer reaction times were, however, necessary due to the lower reactivity of the 2-OTf derivative.

3.1.2 Effects of Neighboring Group Configurations

It was demonstrated that a neighboring ester group was essential for the reactivity of the nitrite-mediated triflate inversion from the above experiments. To further analyze these findings and explore the effects of the neighboring ester group configurations of triflate on the reactivity, glycoside derivatives 18 to 23, where to avoid the effects from the 2- and 6-positions and to isolate the effects arising from ester groups in the 3- and 4-positions, the 2- and 6-positions were protected with benzyl ether groups, were subsequently tested in the nitrite-mediated inversion reactions. The experimental results presented in Table 1 clearly indicate that the configuration of the neighboring ester group was decisive for the reactivity of the epimerization reaction. Good inversion yields depended mainly on the relative configurations between the two groups, and only with the ester group in the equatorial position, whatever the configuration of the triflate, did the reaction proceed smoothly, whereas a neighboring axial ester group proved inefficient.

Table 1. Epimerization reaction studied.

<table>
<thead>
<tr>
<th>entry</th>
<th>Reactant</th>
<th>Time(h)</th>
<th>product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>3</td>
<td>44</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>4</td>
<td>21</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>0.5</td>
<td>22</td>
<td>69</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>1.5</td>
<td>19</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>4</td>
<td>20</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>23</td>
<td>3</td>
<td>45</td>
<td>–</td>
</tr>
</tbody>
</table>

Rapid internal triflate displacements by neighboring acetyl or benzoyl groups have been mentioned above when the ester group and the leaving group have trans-diaxial relationships. This leads to products where the configuration is retained, thus excluding
these combinations from the present investigation. This internal displacement is indicative of the fast formation of an intermediate acyloxonium carbocation, stabilized by polar solvent. In our cases, compounds 20 and 21 hold 3,4-trans configurations in diequatorial relationships, where the internal triflate displacement by the neighboring ester group is considerably less efficient. Contrary to this situation, compounds 19 and 22 hold 3,4-cis configurations, where the ester groups are in the equatorial positions, a structural situation largely excluding the conventional neighboring group participation.\(^{(59, 60)}\)

### 3.2 Neighboring Group Participation

The results obtained seem to point to the importance of a neighboring group (acyloxonium) effect, where compounds 20 and 21 (3,4-trans) expressed a higher reactivity as a result of activation from the neighboring ester group in inducing the inversion reaction compared to compounds 19 and 22 (3,4-cis). This is reflected in the longer reaction times for the 3,4-cis compounds, as displayed in Table 1. However, acyloxonium formation is still unlikely to be the sole explanation of the results, contradictory to the results for two reasons: first, starting compounds 14, 19, and 22 all have a cis relationship between the ester and the leaving group, which largely disqualifies acyloxonium formation;\(^{(59, 60)}\) and second, formation of a carbocation intermediate would result in a nucleophilic displacement from the triflate face of the compound leading to retention (double inversion) of configuration rather than single inversion (Figure 13).

![Figure 13. Comparison of nitrite-mediated inversion with neighboring group participation](image_url)
However, that acyloxonium formation is important in the trans-configuration cases was further supported by studies with added water. Thus, compounds 20 and 21, both with 3,4-trans-diequatorial relationships, mainly yielded compounds 19 and 22 from reaction with potassium nitrite in dry DMF (Table 2). If on the other hand wet DMF was used, compounds 18 and 23 were instead obtained as the main products. This suggests acyloxonium formation to the five-membered-ring intermediate, which rapidly collapses in the presence of water to produce the axial ester and the equatorial hydroxyl group. These results are indicative of (partial) acyloxonium formation in the trans-configuration cases, but that the nitrite ion is unable to open the five-membered ring from either the triflate face or from attacking the carbonyl cation, as has been suggested for water. More importantly, the ester group is, therefore, likely to induce or stabilize the attacking nitrite ion regardless of the trans- or cis-configurational relationships.

Table 2. Water effects in studied nitrite-mediated inversion reactions.

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Nucleophile</th>
<th>product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Structure of reactant 20]</td>
<td>KNO₂</td>
<td>[Structure of product 22]</td>
<td>69</td>
</tr>
<tr>
<td>[Structure of reactant 20]</td>
<td>H₂O</td>
<td>[Structure of product 23]</td>
<td>70</td>
</tr>
<tr>
<td>[Structure of reactant 21]</td>
<td>KNO₂</td>
<td>[Structure of product 19]</td>
<td>72</td>
</tr>
<tr>
<td>[Structure of reactant 21]</td>
<td>H₂O</td>
<td>[Structure of product 18]</td>
<td>70</td>
</tr>
</tbody>
</table>

i: Tf₂O, py, CH₂Cl₂, -20 °C-10 °C, 2h, ii: KNO₂, 50°C, DMF, 0.5-1.5h, or H₂O, rt, DMF, 6h

The effects observed for the ether-protected carbohydrates are likely a result of their lower degree of positive charge destabilization than the corresponding ester groups, leading to side reactions such as ring contraction and elimination. (61, 62)

3.3 Conclusion

In conclusion, it has been demonstrated that esters play highly important roles in the Lattrell-Dax reaction, facilitating nitrite-mediated carbohydrate epimerizations. Despite the higher reactivity of carbohydrate triflates protected with ether functionalities, these compounds proved inefficient in these reactions, where mixtures of compounds were rapidly obtained. Neighboring ester groups, on the other hand, could induce the formation of inversion compounds in good yields. The reactions further demonstrated stereospecificity, inasmuch as axially oriented neighboring ester groups were unproductive.
and only equatorial ester groups induced the nucleophilic displacement reaction. These findings expand the utility of this highly useful reaction in carbohydrate synthesis as well as for other compound classes.
4 Synthesis of β-D-Mannosides and β-D-Talosides

4.1 Introduction

It has been demonstrated that a neighboring equatorial ester group plays a highly important role in the Lattrell-Dax (nitrite-mediated) carbohydrate epimerization reaction, inducing the formation of inversion compounds in good yields. These studies suggested that new, efficient synthetic methods to complex glycosides would be feasible under the guidance of this principle, where the activating ester groups should be able to control the inversion of two neighboring positions simultaneously. Thus, we next attempted to meet the synthetic challenges of β-D-mannoside synthesis.

In consequence to these synthetic challenges, several different synthetic methods have been developed for β-mannoside synthesis. These include Koenigs-Knorr coupling methods using insoluble silver salt promoters blocking the α-face of mannosyl halides, sequential oxidation/reduction routes use of 2-oxo and 2-oximinoglycosyl halides, use of intermolecular or intramolecular, SN2 reactions and intramolecular aglycon delivery method, inversion of configuration of α-mannosyl triflate donors, epimerization of β-glucopyranosides to β-mannopyranosides through SN2 reactions, as well as enzymatic methods, all of which with their respective advantages and short-comings. The 1,2-cis-glycosidic linkage is present also in β-D-talopyranosides. However interesting, recently evaluated for their intriguing H-bonding motifs, these structures have been less investigated in part due to their cumbersome synthesis.

Based on multiple regioselective acylation via the respective stannylene intermediates, followed by the ester-activated inversion, novel and efficient methods to synthesizing β-D-mannopyranoside and β-D-talopyranoside derivatives can be designed.

4.2 Double Parallel Inversion

The glycoside derivatives 32, 34, 36, 37 and 39, which were synthesized by the one-pot organotin multiple esterification strategy, were chosen as starting materials (Figure 14).

The taloside derivatives can be acquired starting from 34 and 36 via the inversion of the 2-position, or starting from 37 via the double parallel inversion of 2- and 4-positions, if the equatorial ester group in the 3-position is able to activate the epimerization of the neighboring 2- and 4-positions at the same time (Figure 15). On the other hand, the
mannoside derivatives can be acquired starting from 32 and 39 via the same double parallel inversion strategy.

![Chemical structures](image)

Figure 15. Double parallel inversion.

In order to evaluate whether an equatorial ester group in the 3-position would be able to activate the epimerization of the neighbouring 2- and 4-positions at the same time, a series of inversion reactions was probed (Scheme 14). Galacto- and gluco-type derivatives 32, 37 and 39 where the 3- and 6-positions were protected with acetyl groups and the other two positions left unprotected were subjected to conventional triflation by triflic anhydride followed by treatment with tetrabutylammonium nitrite in acetonitrile or toluene at 50 °C. In acetonitrile, when methyl 3,6-di-\textit{O}-acetyl glucopyranoside 37 was used as reactant, methyl 3,6-di-\textit{O}-acetyl talopyranoside 47 was obtained in 85% yield. In contrast, the double inversion of methyl 3,6-di-\textit{O}-acetyl galactopyranoside 39 was not successful and a very complex mixture was produced. It was hypothesized that this effect is likely due to acetyl group migration and neighboring group participation from the 3-\textit{O}-acetyl group. If this explanation would be valid, the products produced would constitute an inversed-type mixture, that is to say, only the free methyl β-D-talopyranoside would be obtained if the inversed mixture was not isolated but directly deprotected under basic conditions. The experimental results showed that only one compound was obtained following deprotection of the complex mixture, indicating that this hypothesis was indeed valid.

![Scheme 14](image)

Scheme 14. Double parallel inversion reagent and conditions.
It is however well known that benzoyl groups are less reactive than acetyl counterparts to migration, as well as for neighboring group participation. In addition, neighboring group participation is disfavored in non-polar solvent.\(^{(24,53)}\) Thus, in order to avoid these side reactions, both these approaches were tested. On the one hand, reactions with methyl glucoside 37 and methyl galactoside 39 were performed in the non-polar solvent toluene; on the other hand, the inversion of methyl 3,6-di-O-benzoyl galactopyranoside 32 was attempted in acetonitrile. For comparison, the triflate of methyl galactoside 39 reacting with tetrabutylammonium acetate in acetonitrile was also tested. When methyl glucoside 37 was inversed at 50 °C in toluene, the reaction time had to be prolonged to twelve hours to obtain product 47 in 85% yield. This result indicates, as expected, that the reactivity was decreased in non-polar solvent. In addition, both these approaches proved successful for the double inversion of the methyl galactosides, efficiently reducing the neighboring group participation.

### 4.3 Double Serial Inversion

During this epimerization process, it was found that the reactivity in the 4-position was however much higher than in the 2-position. At room temperature, the epimerization reaction in the 4-position occurred instantaneously, completed within ten to twenty minutes, whereas in the 2-position the epimerization reaction proceeded very slowly under these conditions. This result incited us to make use of the reactivity difference between the different positions to develop a new method, stepwise inversion of the hydroxyl groups amounting to a double serial inversion protocol, by which carbohydrate structures where one position is a hydroxyl group and the other positions were protected with ester groups could be obtained.

![Figure 16. Double serial inversion](image)

Using the same initial step for the double serial inversion strategy, from methyl glucoside 37, the 2,4-triflate intermediates 50 could be produced via a triflation process (Scheme 15). The 4-triflates of these intermediates were subsequently inversed to the corresponding 4-O-acetyl intermediates 51 by substitution with tetrabutylammonium acetate, followed by inversion of the 2-position by tetrabutylammonium nitrite, to yield a mixture of methyl
3,4,6-tri-\(O\)-acetyl taloside 53 and methyl 2,3,6-tri-\(O\)-acetyl taloside 54. Conversely, when the 2,4-triflates of intermediates 50 were first inverted to the corresponding 4-hydroxyl groups intermediates 52 via the use of tetrabutylammonium nitrite, directly followed by inversion of the 2-position by tetrabutylammonium acetate, in this case, however, product 54 could not be formed, likely due to the steric effect of the nucleophilic reagent.

![Scheme 15. Double serial inversion from 37.](image)

Starting from methyl glucoside 39, the 2,4-triflate intermediate 55 could be produced as well (Scheme 16). The 4-triflate of this intermediate was subsequently inverted to the corresponding 4-\(O\)-acetyl intermediates 56 by substitution with tetrabutylammonium acetate, followed by inversion of the 2-position by tetrabutylammonium nitrite, to yield methyl 3,4,6-tri-\(O\)-acetyl mannoside 58. When the intermediates 55 were first inverted to the corresponding 4-hydroxyl groups intermediates 57 via the use of tetrabutylammonium nitrite, directly followed by inversion of the 2-position by tetrabutylammonium acetate, methyl 2,3,6-tri-\(O\)-acetyl mannoside 59 was efficiently produced.

![Scheme 16. Double serial inversion from 39.](image)

In addition, due to the fact that methyl glucoside 3 was produced in a lower yield (70%) than methyl galactoside 1 (90%), following the double serial inversion strategy, an
alternative, more high-yielding, synthetic route to methyl taloside could be devised starting from methyl galactoside 1 instead of methyl glucoside 3. Thus, compound 39 acquired from methyl galactoside 1 by organotin method, could be inversed to the intermediate 50 via intermediate 55 (Scheme 17). As a result, the use of methyl glucoside 2 could be avoided and the overall yield increased.

Scheme 17. Alternative double serial inversion strategy to intermediate 50

4.4 Remote Group Participation

When the inversion of intermediate 56 was performed in acetonitrile, a mixture of methyl mannosides 58 (60%) and 60 (40%) was obtained due to the neighboring group participation. Thus, to avoid neighboring participation, a high yield of methyl mannoside 58 could only be obtained in non-polar solvent. It is however more difficult to explain how the mixture of methyl talosides 53 and 54 was generated. Changing the acetyl groups for benzoyl groups proved inefficient, and the inversion of the 2-position of methyl 3,4,6-tri-O-benzoyl galactoside 34 in acetonitrile resulted in a mixture of methyl talosides 61 and 62.

Scheme 18. Epimerization by neighboring and remote group participation.

In order to further analyze this reaction, methyl 3,4,6-tri-O-benzoyl galactoside 34 and methyl 3,4,6-tri-O-acetyl galactoside 36 was tested in the more polar solvent DMF. The
experimental results indicate that the formation of methyl talosides 53 and 61, where the hydroxyl group in the 2-position is unprotected, were more favored in non-polar solvent (50%, 80%) and less favored in polar solvent (45%, 40%), whereas the formation of methyl talosides 54 and 62, where the hydroxyl group in 4-position is free, were more favored in polar solvent (55%, 60%) and less favored in non-polar solvent (50%, 20%). As a comparison, starting from intermediate 50, it was expected that the fully protected methyl taloside would be produced via the use of five equivalents of tetrabutylammonium acetate. However, the same mixture of methyl talosides 53 (52%) and 54 (48%) was produced.

All of these results support a 4-position participation mechanism, where a six-membered ring is generated first, and then opened by trace water to produce either a free 4-hydroxyl group or a free 2-hydroxyl group in a reaction that is favored by polar solvents (Figure 17). The direct nitrite competition reaction resulted in that the 2-hydroxyl group products (53, 61) were favored in less polar solvents. In combination with the steric effects of the nucleophilic reagent, this also explains why a mixture of methyl talosides 53 and 54 were primarily obtained when tetrabutylammonium acetate was employed as a nucleophilic reagent.

![Figure 17. Remote group participation.](image)

To further support this mechanism, the triflate of methyl taloside 36 was directly tested in wet acetonitrile at 50 °C for 20 hours. As a result, a complex mixture was obtained, not only including methyl talosides 53 and 54. However, these experimental results also showed that the nucleophilic reagent tetrabutylammonium nitrite/acetate play an important role for the remote group participation. The test for neighboring group participation of intermediate 56 also supported this result. When the intermediate 56 was directly subjected to reaction in wet acetonitrile at 50 °C for 20 hours, a very low conversion was recorded; whereas with two equivalents of tetrabutylammonium nitrite, talosides 58 and 60 were obtained in 60% and 40% yield during the same reaction time. The experimental results indicate that not only the neighboring ester group can activate the nitrite-mediate epimerization but also suggest that the nitrite ion can activate the neighbouring or remote group participation.
4.5 Conclusion

In conclusion, novel and convenient double parallel- and double serial inversion methods have been developed, by which methyl β-D-mannosides and methyl β-D-talosides have been efficiently synthesized in very high yields at very mild conditions in few steps. By use of the reactivity difference of the hydroxyl groups or the neighboring/remote group participation between the 2- and 3-position / 2- and 4-positions, a range of methyl β-D-mannoside and methyl β-D-taloside derivatives could be easily synthesized. It was found that not only the neighboring ester group can active the nitrite-mediate epimerization but also that the nitrite ion can activate the neighboring or remote group participation. The results also indicate that an ester group can, either in parallel or serially, induce its two neighboring groups in the epimerization reaction.
5 General Conclusions

The effects of neighboring group on Lattrell-Dax epimerization have been explored. Based on this effect, efficient synthetic routes to β-D-mannosides and β-D-talosides, from the corresponding β-D-galactosides and β-D-glucosides, have been designed. During this research, reagent-dependent regioselective organotin multiple carbohydrate esterifications were also developed.

- It has been demonstrated that organotin-mediated multiple carbohydrate esterifications can be controlled by the acylating reagent and the solvent polarity. When acetyl chloride is used, the reactions are under thermodynamic control, whereas when acetic anhydride is employed, kinetic control takes place. Very good selectivity can furthermore be obtained in more polar solvents. These results can be used in the efficient preparation of prototype carbohydrate structures.

- It has been demonstrated that a neighboring ester group was essential for the reactivity of the Lattrell-Dax nitrite-mediated triflate inversion. Furthermore, a good inversion yield also depended on the relative configuration of the neighboring ester group to the triflate. Only with the ester group in the equatorial position, whatever the configuration of the triflate, did the reaction proceed smoothly, whereas a neighboring axial ester group proved largely inefficient.

- Based on the efficient multiple carbohydrate esterifications and Lattrell-Dax carbohydrate epimerization, novel and convenient double parallel- and double serial inversion methods have been developed, by which methyl β-D-mannosides and methyl β-D-talosides have been efficiently synthesized in very high yields at very mild conditions in few steps. The results also indicate that an ester group can, either in parallel or serially, induce its two neighboring groups in the epimerization reaction.

- It was found that neighboring group- or remote group participation could easily take place if a five-membered or six-membered ring is generated between the neighboring or remote ester group and the carbon atom carrying the triflate group in more polar solvent. Further, not only the neighboring ester group can active the nitrite-mediate epimerization but the nitrite ion can also activate the neighboring or remote group participation.
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Appendix

The following is a description of my contributions to papers I-IV.

Paper I: I performed labwork and wrote parts of the article.

Paper II: I performed labwork and wrote the article.

Paper III: I performed labwork and wrote the article.

Paper IV: I performed labwork and wrote the article.
Reference


Danishefsky, S. J.; Hu, S.; Cirillo, P. F.; Eckhardt, M.; Seeberger, P. H., A highly convergent total synthetic route to glycopeptides carrying a high-mannose core.


