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Graphical Abstract

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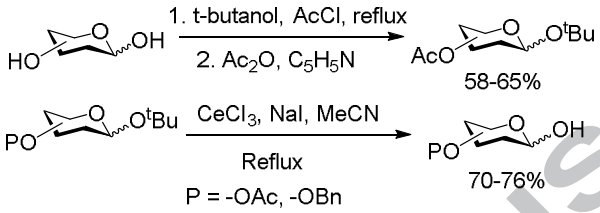

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The tertiary-butyl group: Selective protection of the anomeric centre and evaluation of its orthogonal cleavage

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ABSTRACT

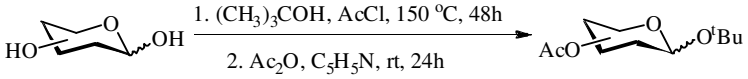
The tertiary-butyl group has not been examined extensively as a protecting group. In this work, we describe the synthesis of tert-butyl glycosides via the Fischer glycosylation protocol. Furthermore, its utility as a temporary anomeric protecting group was evaluated. A range of differentially protected monosaccharides was used to investigate the stability of the tert-butyl group upon the introduction of other protecting groups; and compatibility of its cleavage in the presence of the latter.

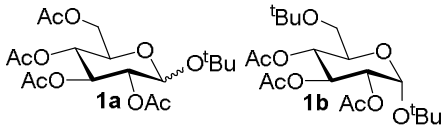
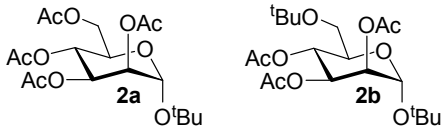
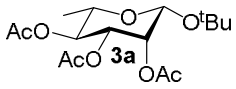
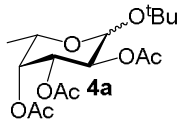
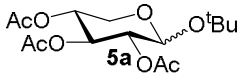
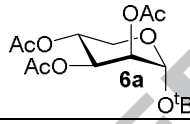
Carbohydrates are well known for their complexity and diversity in nature.[1] This facilitates their roles in biological systems and hence makes them attractive synthetic targets for a variety of medicinal purposes.[2,3] In constructing mimics of naturally occurring glycoconjugates and oligosaccharides, glycoside bond formation is a common challenge.[1,4] Consequently, there is always a demand for alternative glycosylation strategies and a critical step in such techniques is the choice of protection for the anomeric centre on the donor molecule. Some anomeric protecting groups are bifunctional since they can also act as a leaving group upon activation to facilitate glycosylation.[5] More commonly however, the anomeric protection is removed, subsequent to which an appropriate leaving group is installed. In this latter case, an ideal candidate should be: (1) selectively and easily installed; (2) stable to further modifications on the molecule and; (3) deprotected relatively easily, yielding the hemiacetal while preserving the remaining groups.[6]

Currently, there are a number of anomeric protecting groups that are employed in oligosaccharide synthesis. Some of the more popular ones include the *O*-methyl,[7] *O*-allyl,[8] *p*-methoxyphenyl,[9] *p*-nitrobenzyl,[10] *n*-pentenyl,[11] TMSEt,[12] thioglycosides,[13] *O*-benzyl,[14] and more recently the *N,O*-dimethylhydroxylamine,[15] and the 1-methyl 1'-cyclopropylmethyl.[16] Each of these has their relative advantages and associated drawbacks. The lack of an ideal anomeric protecting group is what spurs research in this area. One of the major problems encountered with many of these groups involves the need to perform multistep protocols to allow for their installation with differential protection around the molecule.[17] Depending on the nature of the reactions involved, this can result in a significantly low overall yield. Among the groups listed, the methyl, allyl and benzyl allow for selective introduction on a free sugar via a Fischer glycosylation pathway. This acid catalyzed reaction in the presence of excess alcohol is attractive and indispensable, due to its anomeric selectivity.[18]

The tert-butyl group, like most ethers, is stable to many conditions encountered. It can however be cleaved under milder conditions when compared to other alkyl ethers. Despite this, it is not among the more popular protecting groups.[19] Its utility has been demonstrated for the protection of alcohols in non-carbohydrate systems, using isobutylene together with different combinations of reagents such as: (1) $BF_3.Et_2O$, H_3PO_4;[20] (2) Amberlyst H-15;[21] (3) H_2SO_4;[22] as well as using t-BuOC(=NH)CCl_3 and $BF_3.Et_2O$.[23] The systems protected include cyclic ketones, halohydrins, acetylenic alcohols, esters and ethers. Various methods have also been developed for its selective cleavage under acidic conditions. Some of these include: (1) anhydrous CF_3COOH;[24] (2) HBr/AcOH;[25] (3) TBDMSOTf;[26] (4) HCO_2H;[27] and $CeCl_3$/NaI.[28] There exist very little precedent for its usage in carbohydrate derivatives. In most cases, tert-butanol has been employed as an acceptor in evaluating new glycosylation protocols. Lindberg described the synthesis of a tert-butyl glucoside via the Koenigs-Knorr method of glycosylation using $Hg(O_2CCH_3)_2$ as the promoter.[29] Further work done in investigating the action of strong acids on these acetylated glucosides indicated that selective deprotection of the tert-butyl group was achieved using BCl_3 in moderate yields.[30] A similar study was also undertaken using instead silver salicylate as the promoter, and selective cleavage of the glycoside was achieved with CF_3COOH.[31] Other activators also investigated include: Ag_2O;[29] HgO;[32] and $Hg(CN)_2$/$HgBr_2$.[33]

Table 1
Synthesis of Tert-butyl Glycosides



Entry	Substrate	Product	Yield %	Ratio α:β
1	D-Glucose		58 (**1a**) 8 (**1b**)	3:1 (**1a**) α exclusively
2	D-Mannose		65 (**2a**) 10 (**2b**)	α exclusively
3	L-Rhamnose		61	β exclusively
4	L-Fucose		64	0.7: 1
5	D-Xylose		65	1: 0.5
6	D-Lyxose		61	α exclusively

In glycosylations which employ the anomeric acetate as a leaving group, the formation of ortho esters inevitably results in low yields of the target glycoside.[34] Pavia et al. described the synthesis of tert-butyl glycosides in yields of 60-90% using isobutylene on acetylated reducing sugars.[35] Cleavage of the glycosides was effected using $FeCl_3$, both in the presence and absence of acetic anhydride.[35]

We report herein a straightforward synthesis of tert-butyl glycosides via the Fischer glycosylation method; using tert-butyl alcohol with catalytic amounts of Lewis acid. Its stability under conditions necessary for the introduction of common protecting groups was also investigated. Furthermore, we evaluated its selective removal in the presence of these protecting group patterns. To the best of our knowledge this is the first report: (i) detailing the synthesis of tert-butyl glycosides using the Fischer glycosylation; and (ii) functionalizes the remaining hydroxyls on the tert-butyl glycoside beyond an ester protection and testing for the latter's orthogonal cleavage.

The impact of temperature, time, equivalents of catalyst, as well as the volume of the alcohol were examined. Below 150 °C, extended reaction times (> 48h) were required for solubilization of the free sugar. Refluxing beyond 48h did not yield any appreciable improvement in product yield. The deoxy sugars, L-Rha and L-Fuc, were the most soluble in the tert-butanol followed by D-Xyl. D-Glc demonstrated a much lower solubility than D-Man and as a result, a larger volume of the alcohol was required for solvation. The other sugars exhibited poor solubility in the t-BuOH. In an attempt to facilitate their dissolution and hence reaction, an equal volume of DMF was added. With D-Gal, D-Maltose and D-Gentiobiose, homogenous solutions were formed within 2 h. However, with D-GlcNAc and D-$GlcNH_2$.HCl, no apparent solubilization was observed, even when DMSO was used instead. This is not surprising as solubility problems exist with these sugars even with the simpler alcohols.[36]

Acetylation of the crude mixture was undertaken to aid in purification of anomers (Table 1).[37] The α anomer of the glucopyranoside **1a** was the major product, with minor quantities of the β anomer and furanosides being detected. Recrystallization from methanol afforded the pure β anomer. The mannoside, **2a**, was obtained exclusively in the α configuration. It is likely that the bulkiness of the tert-butyl group destabilizes the *cis*-glycosidic linkage, a common observation with D-Man.[38] Interestingly, both these hexopyranoses yielded the 1,6 di-substituted compound, **1b** and **2b** respectively. Such products have never been reported under typical Fischer conditions. A plausible explanation revolves around the stability of a tert-butyl carbocation which is unfavourable with the simple commonly used alcohols. Nucleophilic attack by the 6-OH on the cation is facilitated because of the former's sterically accessible nature.

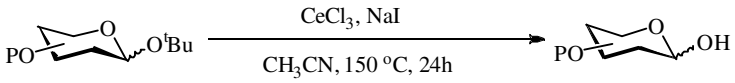
Table 2

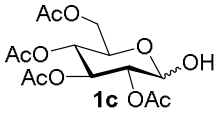
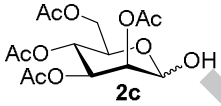
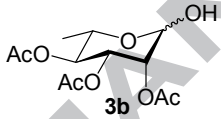
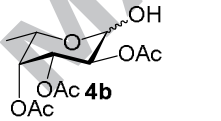
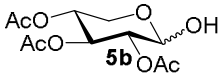
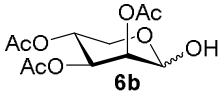
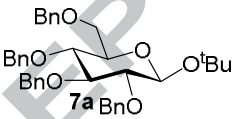
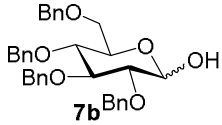
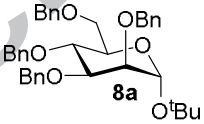
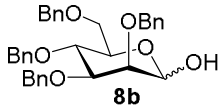
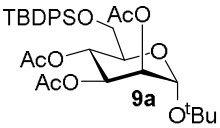
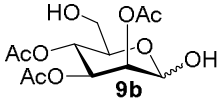
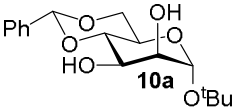
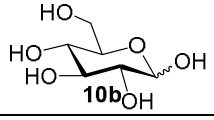
Deprotection Conditions Attempted

No Reaction	Non-selective Cleavage
$InCl_3$/TMSCl; NBS; $ZnCl_2$; ZnI_2; VCl_3; NaOH; NaH; KOH; $KB(CH_3)_3H$; TBAF; CH_3COOH; CCl_3COOH; $Cu(OTf)_2$; LiCl; HCl.	BCl_3; $BF_3.OEt_2$; TMSOTf; TfOH; NIS/TMSOTf; $SnCl_4$; $FeCl_3$; $AlBr_3$; $AlCl_3$; CF_3COOH; HBr/AcOH.

Table 3

Cleavage of Tert-butyl Glycosides

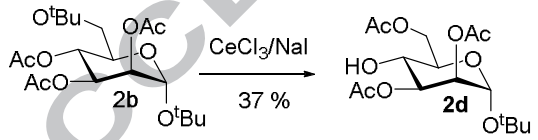


Entry	Substrate	Product	Yield %
1	**1a**	 **1c**	70
2	**2a**	 **2c**	72
3	**3a**	 **3b**	76
4	**4a**	 **4b**	74
5	**5a**	 **5b**	75
6	**6a**	 **6b**	65
7	 **7a**	 **7b**	73
8	 **8a**	 **8b**	74
9	 **9a**	 **9b**	60
10	 **10a**	 **10b**	65

The rhamnopyranoside, **3a**, was obtained exclusively as the β anomer in 61 % yield. L-Fuc yielded both anomers with the β being higher yielding. Xyloside, **5a** was obtained in 43 % yield of the α isomer and 22 % of the β. The resulting glycoside of D-Lyx, **6a**, was produced only as the α anomer. Though the D-Gal was soluble in the t-BuOH/DMF system, no reaction occurred. For the disaccharides, hydrolysis of the glycoside bond took precedence over formation of the Fischer product. Significant amounts of glucose were produced indicating that hydrolysis was faster than glycoside formation. Glycosides **1a**-**6a** were obtained in yields ranging from 58-65 % (Table 1). These lower than usual yields (for a Fischer Glycosylation) are likely due to the lability of the existing tert-butyl protection under these conditions, arising as a result of the stability of the tertiary carbocation.[39]

Deacetylation of compounds **1a** and **2a** was performed using K_2CO_3 in methanol to give the free sugar, which was then further functionalized. Substrates: **7a**, **8a**, **9a**, and **10a,** were synthesized from the resulting glycosides.[40] We were pleased to observe the stability of the tert-butyl group under conditions necessary for the introduction of *O*-Benzyl, *O*-Benzylidene and silyl protecting groups. A variety of reagents were evaluated in order to achieve selective cleavage of the tert-butyl group (Table 2). Even though the tert-butyl protection is well known to be highly resistant toward strong basic conditions, we speculated that isobutylene liberation may have been favoured in this case.[40] Some of the reagents produced no observable reactions while others, though deprotecting the tert-butyl group, also caused removal of other protecting groups present.

Bartoli and co-workers described the $CeCl_3$/NaI protocol for the deprotection of tert-butyl ethers from a range of aliphatic and aromatic systems.[28] Employing these reaction conditions gave no reaction after 24 h. Cerium is highly oxophilic and owing to the number of oxygen atoms on the sugar, excess cerium chloride was added to compensate for this.[28] We also found that using the fully hydrated $CeCl_3.7H_2O$ gave very sluggish reactions and as such, the anhydrous form was used.[28] After 24 h almost complete conversion of starting material was observed. Leaving the reaction for a further 12 h resulted in no significant progression. An examination was also undertaken to assess which of the tert-butyl groups from **2b** would be the most reactive under these conditions. Results indicated that the primary tert-butyl was selectively removed; however 4→6 *O*-acyl migration took place subsequently under these conditions (Scheme 1). This type of migration is known to occur under both acidic and basic conditions.[41]



Scheme 1: Tert-butyl cleavage and 4→6 *O*-acyl migration

Per-*O*-acetylated derivatives **1a-6a** were deprotected selectively to their corresponding hemiacetals in good yields of over 70% (Table 3). Benzylated substrates **7a** and **8a** gave slightly higher yields of deprotection. Unfortunately, these conditions proved to be too harsh for both the benzylidene acetal **9a** as well as the silyl ether **8a**. Similar to Pavia's method of tert-butyl introduction using a glycosyl acetate;[35] an alternative route to synthesizing tert-butyl glycosides of the insoluble sugars was demonstrated with D-Glc.NH_2.[40] This pathway utilized Schmidt's trichloroacetimidate protocol.[42]

As a result of the above observation, we also attempted to remove a silyl group from a protected monosaccharide (Scheme 2). Compound **11a** was subjected to the same deprotection conditions and desilylation was observed selectively in over 70 % yield. With base labile groups present on a compound, it provides a mild route to silyl ether deprotection. This is especially advantageous since the existing strongly basic conditions may deprotect the anomeric acetate.[43]

Reagents and conditions: $CeCl_3$, NaI, CH_3CN, 100 °C

Scheme 2: Desilylation using $CeCl_3$/NaI

Two possible mechanisms are likely. The first being the proposal by Bartoli and co-workers in which an iodide ion attacks the tertiary carbon resulting in tert-butyl iodide as the byproduct.[28] A second pathway may exist with carbohydrates, which involves iodide attacking the anomeric centre of **13**, instead of the tertiary carbon, to yield the glycosyl halide **14** (Figure 1). Under these conditions the glycosyl halide will readily hydrolyze to yield the hemiacetal, **15**.[44] We estimate that the relative stability of the glycosyl cation will be greater than the tertiary cation and hence our thoughts are more in favour with the latter mechanism for these glycosides.

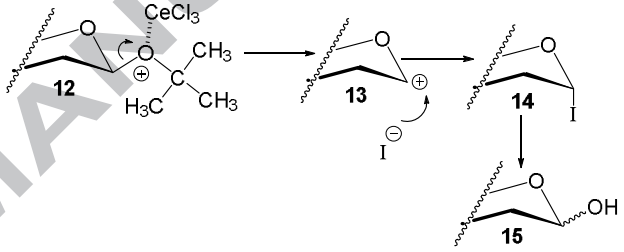


Figure 1: Proposed mechanism of anomeric tert-butyl cleavage

In summary, we have successfully demonstrated an efficient method for the synthesis of tert-butyl glycosides. This route is advantageous as it allows for selective installation on an unprotected monosaccharide. Our method of deprotection allows for selective cleavage with both acetate and benzyl protecting groups present. It is a relatively cheap and simple procedure that does not require any aqueous work up. Furthermore, in light of the results obtained from the silylated substrate, we present a method that selectively removes silyl ethers and which is also orthogonal to both the acetate and benzyl groups.

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Supplementary data

Supplementary data (NMR data and spectra data) associated with this article can be found….

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- Synthesis of tert-butyl glycosides in a single step from the free sugars
- Addition of popular protecting groups at other positions in tert-butyl glycosides
- Deprotection conditions of anomeric tert-butyl group investigated
- Tert-butyl group removal is compatible with acetate and benzyl groups