Efficient Stereoselective Glycosylations of Alcohols by Sugar Perpivalates: The First Use of 1-O-Pivaloylated Glycosyl Donors

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Abstract: 1-*O*-Pivaloyl glycosides were shown to be efficient glycosyl donors by using the perpivaloylated derivatives of lactose, galactose and glucose in the direct $ZnCl_2$-promoted glycosylations of various alcohols. The corresponding glycosides were isolated in good yields and β-selectivity.

Key words: carbohydrates, glycolipids, glycosyl donors, glycosylations, stereoselective synthesis

The stereoselective formation of glycosidic bonds is a crucial process in most oligosaccharide and glycoconjugate syntheses.[1,2] A wide variety of glycosylation methods have been developed to address the challenges of an efficient (i.e., high-yielding, regio- and stereoselective) reaction between a glycosyl donor and a glycosyl acceptor.[3] In this research area, the development of general and simple modes of glycosylation of lipids (ceramide and its analogues, steroids, long-chain fatty alcohols, etc.) is of continuous interest in view of the biological relevance of glycolipids[4] and numerous applications thereof, for example in the field of biosensing.[5]

Alkyl glycosides are most commonly prepared by the well-established Koenigs–Knorr reaction[6] of *O*-acetyl-protected glycosyl bromides and alkanols, in the presence of promoters such as silver or mercury salts. Alternatively, for the glycosylation of alcohols with lower nucleophilicity (e.g. ceramide and long-chain fatty alcohols), a variety of glycosyl donors have been used, including glycosyl trichloroacetimidates,[7] thioglycosides,[8] glycosyl fluorides (for both chemical[9] and enzymatic[10] syntheses), iodides,[11] and others.[12] Among the plethora of glycosyl donors, sugar peracetates are frequently seen as the benchmark[13,14] due to their stability and ease of preparation (one-step reaction from an unprotected sugar). The activation of these compounds can be achieved in the presence of a Lewis acid (such as $SnCl_4$, $BF_3{\cdot}Et_2O$, $ZnCl_2$ or TMSOTf), and the products are preferentially 1,2-*trans*-glycosides, as a result of the anchimeric assistance of the C-2 acetoxy group.

However, the yields of glycosylations by sugar peracetates are frequently modest (30–40%), due to the formation of orthoesters[15] in a side-reaction that is common for glycosyl donors bearing an acetyl group at C-2. To avoid such orthoester formation, this acetyl group is often replaced by a sterically more demanding benzoyl or pivaloyl group.[16,17]

In the course of our on-going studies on the synthesis[18] of ganglioside analogues for various applications on surfaces[19] or in solution,[20] a highly efficient preparation of ω-functionalized alkyl lactosides was required. Such lactosides are particularly useful as starting compounds for the chemoenzymatic syntheses of various ganglioside structures with a specifically designed aglycone. The functionalized aglycone allows the carbohydrates to be attached to various solid[18c,19] and molecular[20] scaffolds, while the lactose moiety – as a structural part of the human gangliosides – represents an excellent starting point from which enzymes are able to construct the target oligosaccharides.[18a] However, unlike in the syntheses of, for example, glucosides and galactosides, glycosylations of fatty alcohols by fully or partially acetylated lactose donors are largely ineffective in terms of yields and β-selectivity.[1,14] In addition, the preparation of an efficient lactose donor[21] may be laborious. This therefore leaves a demand for a simple and high-yielding method.

Here we report a convenient procedure for the direct high-yield glycosylation of ω-functionalized alcohols through the use of perpivaloylated sugars (including lactose) as glycosyl donors. This procedure combines the ease of preparation of peracylated glycosyl donors with the advantageous use of *O*-pivaloyl protection at C-2. To the best of our knowledge, this is also the first report on the use of glycosyl donors with other than acetyl/benzoyl-derived 1-*O*-acyl protection.

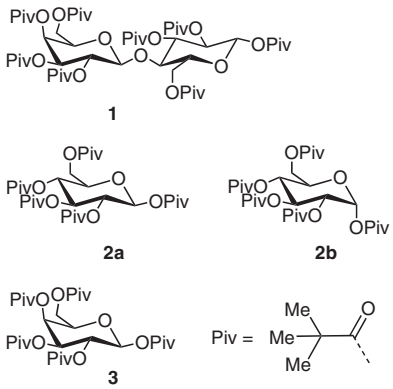

Figure 1 Perpivaloylated glycosyl donors used in this study

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In this study, perpivaloylated derivatives of lactose, glucose and galactose were used (Figure 1). β-Lactose octapivalate (**1**) was prepared by reaction of lactose with trimethylacetyl chloride in pyridine for five days at 80 °C; shorter reaction times led to an incomplete pivaloylation. β-Glucose pentapivalate (**2a**) was obtained in a similar fashion. The formation of **2a** has been reported in a triethylamine-catalyzed reaction of glucose and trimethylacetyl chloride in CH_2Cl_2.[17] However, in our hands this procedure led to the isolation of the thermodynamically more stable α-anomer of glucose pentapivalate (**2b**).[22] β-Galactose pentapivalate (**3**) is commercially available.

Zinc chloride has been reported to be the promoter of choice for the glycosylations of ω-bromoalcohols with peracetylated sugars.[14] In view of this, we initially examined the zinc(II) chloride-promoted reaction of β-lactose octapivalate (**1**) with commercially available 11-bromoundecanol (**4a**, Scheme 1). Thus, **1** and **4a** (1.3 equiv) were dissolved in anhydrous toluene and, upon addition of $ZnCl_2$, the reaction mixture was heated at 65 °C for one hour. No reaction took place, thus indicating much lower reactivity of an anomeric pivalate as compared to the corresponding acetate. Overnight heating of the reaction mixture at this temperature yielded the expected 11-bromoundecyl lactoside **5a**, but only as an inseparable mixture of α- and β- anomers (1:1 as determined by ^{1}H NMR spectroscopy).

Nevertheless, compound **5a** (as an α/β mixture) was isolated in an excellent overall yield of 93% and no byproducts common for the glycosylations of peracetylated sugars (such as an orthoester, 2-O-deacylated glycosides or anomeric chloride) were detected in the reaction mixture.

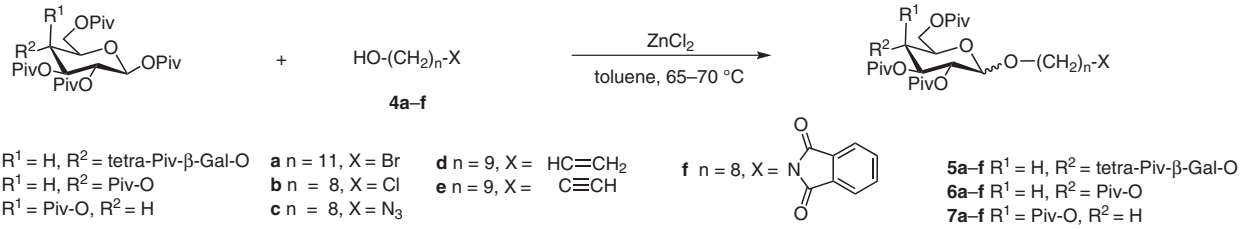
Lewis acids have been shown to epimerize β-glycosides to more stable α-anomers, and we considered that this process was very likely to occur under the applied reaction conditions. In order to optimize the synthesis of β-glycosides, the reaction between **1** and **4a** was followed by NMR in C_6D_6; this led to the development of reaction conditions that gave maximum yield and high stereoselectivity. With reaction conditions of 70 °C, 1.5 equivalents of **4a** and 1.5 equivalents of $ZnCl_2$, the complete disappearance of the starting lactose octapivalate was observed after 5.5 hours, and β-lactoside **5a** was formed as the major product with only 5% of the α-anomer. With this information in hand, we performed a series of preparative glycosylations of various alcohols (**4a**–**f**) with **1** as a glycosyl donor.[23] As can be seen in Table 1, in all cases the β-anomers of the resulting lactosides **5a**–**f** could be isolated in good to excellent yields (entries 1–6).

Table 1 $ZnCl_2$-Promoted Glycosylations of Alcohols by Sugar Perpivalates in Toluene

Entry	Donor	Acceptor (equiv)	$ZnCl_2$ (equiv)	Temp (°C)	Time (h)	Ratio α/β[a]	Yield (%)[b]
1	**1**	**4a** (1.5)	1.5	70	6	92% β	89
2	**1**	**4b** (1.5)	1.5	70	5	98% β	91
3	**1**	**4c** (1.5)	1.5	70	5	98% β	90
4	**1**	**4d** (1.5)	1.5	70	5	95% β	87
5	**1**	**4e** (1.5)	1.5	70	6	95% β	85
6	**1**	**4f** (1.5)	1.5	70	6.5	88% β	77
7	**2a**	**4a** (1.3)	1.3	65	2	95% β	90
8	**2a**	**4b** (1.3)	1.3	65	1.5	99% β	93
9	**2a**	**4d** (1.3)	1.3	65	1.5	98% β	91
10	**2a**	**4e** (1.3)	1.3	65	2	95% β	89
11	**3**	**4a** (1.1)	1	65	1.5	only β	95
12	**3**	**4b** (1.1)	1	65	1.5	only β	99
13	**3**	**4c** (1.1)	1	65	1.5	only β	98
14	**3**	**4d** (1.1)	1	65	1.5	only β	98
15	**3**	**4e** (1.1)	1	65	1.5	only β	97
16	**2b**	**4b** (1.3)	2	65→90	18	1:1	–

[a] In crude product, as determined by NMR spectroscopy (^{1}H and HSQC data).
[b] Isolated yield of the β-glycoside.

Subsequently, we explored the glycosylating properties of perpivaloylated β-glucose (**2a**) and β-galactose (**3**) derivatives. As in the case of lactose **1**, the optimum reaction conditions were established by performing the glycosylations in an NMR tube in C_6D_6. The monosaccharides proved to be more reactive glycosyl donors in comparison with the lactose octapivalate: couplings involving **2a** and **3** required smaller amounts of the promoter and shorter reaction times. The relative reactivities of the studied compounds were determined to be galactose > glucose > lactose. Thus, glycosylations of the alcohols **4a**–**e** with the galactose donor **3** were complete in 1.5 hours, and the corresponding galactosides **7a**–**e** were obtained as exclusive-



Scheme 1 Sugar perpivalates in $ZnCl_2$-promoted glycosylations

ly β-anomers and isolated in nearly quantitative yields (Table 1, entries 11–15).

From the comparison of reaction conditions applied in this study (Table 1) with those reported for sugar peracetates[14] it can be concluded that the reactivity of glycosyl pivalates is generally lower than those of analogous 1-*O*-acetyl glycosides. However, the use of perpivaloylated saccharides for the glycosylation of ω-functionalized fatty alcohols can avoid numerous complications that are characteristic of couplings involving peracetates, while at the same time preserving the ease of preparation of peracylated sugar derivatives and the β-selectivity of the coupling reaction as a result of the anchimeric assistance of an acyl group at the C-2 position.

It has been shown for the glucose and galactose peracetates that the β-anomers are much more reactive than the corresponding α-anomers.[24] Since the geometries of the sugar rings in peracetylated and perpivaloylated glucose are very similar, an analogous relative reactivity was expected in the case of sugar perpivalates. Indeed, the α-anomer of pentapivaloyl glucose (**2b**) was only poorly reactive. Glycosylations with **2b** as a donor (e.g. Table 1, entry 16) required at least two equivalents of $ZnCl_2$, the complete transformation of the starting material could be achieved only in ≥18 hours and the resulting glucosides were mixtures of α- and β-anomers at all stages of the reaction.

A nice feature of the reaction procedure[23] is that it does not require an aqueous work-up, and the highly apolar product (due to a number of trimethylacetyl groups) can be easily separated from the excess of alcohol on a silica column. Essentially anhydrous conditions (with regard to both toluene and $ZnCl_2$) were crucial to achieve high β-selectivities; however, the use of molecular sieves should be avoided.

In conclusion, we have demonstrated that 1-*O*-pivaloyl glycosides can be activated by a Lewis acid to serve as glycosyl donors. An efficient glycosylation procedure was developed and successfully applied to the stereoselective synthesis of various ω-functionalized alkyl 1,2-*trans*-glycosides in high yields (77–99%). Application of a perpivalate instead of peracetate appears to be especially beneficial in the case of lactose, given the considerably higher yields of the lactosides presented in this study in comparison with those reported previously (cf. e.g. 42–47% for 8-bromooctyl lactosides,[14] 56% for 10-undecenyl lactoside[18c]). The application of anomeric pivalates as glycosyl donors is thus worth further exploration, especially regarding their use with other promoters and glycosyl acceptors; such investigations are currently underway in our laboratory.

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(22) Data for **2b**: ^{1}H NMR (400 MHz, C_6D_6): δ = 6.52 (d, *J* = 3.8 Hz, 1 H), 5.82 (t, *J* = 9.8 Hz, 1 H), 5.28 (t, *J* = 9.9 Hz, 1 H), 5.23 (dd, *J* = 10.0, 3.8 Hz, 1 H), 4.21–4.28 (m, 2 H), 4.08–4.14 (m, 1 H), 1.16 (s, 9 H), 1.12 (s, 9 H), 1.12 (s, 9 H), 1.09 (s, 9 H), 1.08 (s, 9 H); ^{13}C NMR (100 MHz, C_6D_6): δ = 177.8, 177.2, 176.9, 176.8, 175.9, 89.5, 71.4, 70.5, 70.3, 68.5, 62.4, 39.4, 39.3, 39.2 (2 C, peaks overlap), 39.1, 27.7, 27.6, 27.5, 27.5, 27.4.

(23) Typical glycosylation procedure: To a solution of lactose octapivalate **1** (1 g, 0.99 mmol) and 8-chlorooctan-1-ol (**4b**; 243 μL, 1.48 mmol) in anhydrous toluene (10 mL), was added $ZnCl_2$ (0.2 g, 1.48 mmol, which was dried in vacuo at 120 °C for at least 1 h prior to use) and the resulting suspension was stirred at 70 °C for 5 h. After cooling, the reaction mixture was diluted with EtOAc (10 mL), and solid $NaHCO_3$ (2 g) and H_2O (0.5 mL) were added portion-wise with stirring. After the formation of gas stopped (~20 min), the solution was filtered over Hyflo. The precipitate was washed thoroughly with EtOAc. The combined organic phase was evaporated in vacuo and the residue was purified by silica gel column chromatography (EtOAc–petroleum ether, 1:7) to give 8-chlorooctyl lactoside **5b** (0.97 g, 0.9 mmol, 91%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.36 (d, *J* = 2.3 Hz, 1 H), 5.18 (t, *J* = 9.5 Hz, 1 H), 5.09 (dd, *J* = 10.5, 8.0 Hz, 1 H), 4.96 (dd, *J* = 10.5, 3.5 Hz, 1 H), 4.79 (dd, *J* = 9.7, 7.9 Hz, 1 H), 4.50 (d, *J* = 7.8 Hz, 1 H), 4.47–4.56 (m, 1 H), 4.44 (d, *J* = 8.0 Hz, 1 H), 4.18 (dd, *J* = 12.0, 5.0 Hz, 1 H), 4.04–4.11 (m, 1 H), 3.95–4.03 (m, 1 H), 3.88–3.94 (m, 1 H), 3.85 (t, *J* = 9.5 Hz, 1 H), 3.67–3.75 (m, 1 H), 3.47 (t, *J* = 6.8 Hz, 2 H), 3.44–3.53 (m, 1 H), 3.33–3.41 (m, 1 H), 1.65–1.75 (m, 2 H), 1.48 (t, *J* = 6.4 Hz, 2 H), 1.32–1.42 (m, 2 H), 1.22–1.28 (m, 6 H), 1.21 (s, 9 H), 1.19 (s, 9 H), 1.17 (s, 9 H), 1.15 (s, 9 H), 1.11 (s, 9 H), 1.11 (s, 9 H), 1.05 (s, 9 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.7, 177.5, 177.2, 177.0, 176.7, 176.5, 175.9, 100.7, 100.0, 73.7, 73.3, 71.7, 71.6, 71.4, 71.3, 69.6, 68.8, 66.8, 61.7, 61.3, 44.9, 38.9–38.6 (7 C, peaks overlap), 32.5, 29.4, 29.0, 28.7, 27.3, 27.2, 27.1, 27.0 (3 C, peaks overlap), 26.9, 26.7, 25.8.

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