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Pivaloyl-protected glucosyl iodide as a glucosyl donor for the preparation of β-*C*-glucosides

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ABSTRACT

A method for the selective synthesis of β-*C*-glucosides using α-*D*-tetra-*O*-pivaloylglucosyl iodide as a glucosyl donor is reported. Its diastereoselectivity differs from that of the respective acetyl-protected glucosyl bromide, as it reported in the literature under similar reaction conditions. The concentration of the catalyst, the solvent and the type of additive used are crucial factors that determine the reaction selectivity. This method has been applied in a short synthesis of dapagliflozin. The stability of α-*D*-tetra-*O*-pivaloylglucosyl iodide in $CDCl_3$ and THF at reflux was also studied. All side products in the coupling and decomposition reactions were isolated and characterized, and possible pathways for their formation are proposed.

Introduction

C-Glycosides are an important class of naturally occurring and synthetic products with applications as potent pharmaceutical compounds [1]. As they are less vulnerable to metabolic processes, in contrast to *O*-glycosides, many *C*-glycosides have been proven to be good drug candidates and inhibitors of carbohydrate processing enzymes. Among them, a number of gliflozins, which act as selective sodium-glucose transporter-2 (SGLT2) inhibitors, have attracted interest as alternative therapeutics for glycemic control in a glucose-dependent but insulin independent manner [2]. Currently, several gliflozins, such as ertugliflozin (**1**), dapagliflozin (**2**) and canagliflozin (**3**) are on the market for the treatment of type 2 diabetes (Fig. 1).

However, despite their importance, the stereoselective, synthesis of *C*-glycosides remains a challenge and this topic has evoked growing interest [3]. The construction of the key anomeric C—C bond involves approaches that generate nucleophilic, electrophilic or radical character on the C1 center, whereas glycals, glycosyl halides, thioglycosides, anomeric trichloroacetimidates, glycosyl acetates, glyconolactones and glycosyl stannanes have been used as glucosyl donors [4]. Perhaps, the most common approach involves nucleophilic addition of an organometallic reagent to a glycosyl bromide often catalyzed by Ni, Co, Pd and Fe complexes [5].

Glycosyl iodides, in contrast to the respective bromides, have been seldom used as glycosyl donors in general, and much less for the synthesis of *C*-glycosides. This is probably due to the long held belief that glycosyl iodides are too difficult to prepare, and too unstable, to be useful glycosyl donors [6]. Only in the 21st century was it discovered that "disarmed" glycosyl iodides such as glucose derivatives **4** and **5** (Fig. 1) are stable compounds while the respective "armed" (**6**) and "super armed" (R = $SiMe_3$) glycosyl iodides can be prepared *in situ* [7]. Our interest in the development of new methods to synthesize gliflozins [8] prompted us to investigate the possibility to prepare β-*C*-aryl glycosides, such as dapagliflozin using glucosyl iodides **4**–**6** as glucosyl donors.

Results and discussion

We commenced our work with the reaction of pivaloyl-protected glucosyl iodide **4** and excess phenyl magnesium bromide **7** (R = Ph; 2.5 equiv.). Without the presence of any catalyst, only 2-deoxyglucoside **11** and glucal **12** were isolated in low yields (Table 1, Entry 1). Using catalytic CuI in THF in the presence of LiCl (2 equiv.) and TMEDA (5 mol%), none of the desired *C*-glucoside was formed and traces of the elimination product **10** were isolated (Entry 2). Also, the reaction between **4** and 2.5 equivalents of **7** (R = Ph) in the presence of 10 mol% PEPPSI-iPr gave only trace

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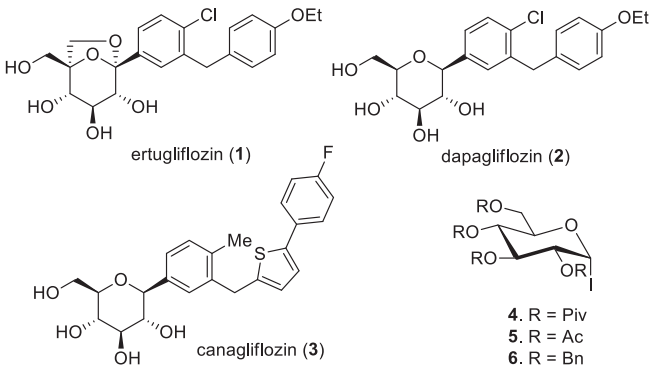


Fig. 1. Structure of selected gliflozins and protected glucosyl iodides.

amounts of **10** (Entry 3). Encouraging results were obtained when we applied the catalytic conditions introduced by Reymond, Cossy and co-workers [5b] and the reaction between **4** and **7** (R = Ph; 1:2.5 M ratio) with 5 mol% $Co(acac)_3$ and 5 mol% TMEDA in THF afforded the desired phenyl *β*-*C*-glucoside **8a** in 42% yield together with *α*-*C*-glucoside **9a** and compound **10** in 7% and 8% yields, respectively (Table 1, Entry 4).

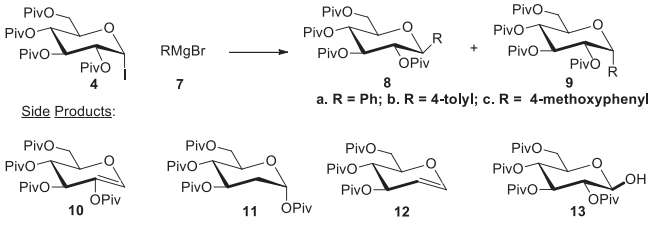
In order to optimize the yields of desired phenyl *β*-*C*-glucoside **8a**, a number of experiments were carried out. It was found that keeping the same reaction conditions and changing the solvent to toluene, 1,4-dioxane or ethyl ether did not give **8a** but small amounts of the elimination product **10** (Entries 5 and 6). Interestingly, using THF as the solvent and replacing the TMEDA additive with Et_3N (5 mol%) or DABCO (5 mol%), resulted in a reversal of the reaction stereoselectivity and phenyl *α*-*C*-glucoside **9a** was formed, but in lower yields together with products **10**, **11**, and **12** (Entries 7 and 8). Running the reaction in THF at reflux or doubling the amount of the $Co(acac)_3$ catalyst caused no change to the results (Entries 9 and 10). However, the use of 10 mol% of TMEDA suppressed the formation of desired phenyl *β*-glucoside **8a**, while at the same time increasing the yield of elimination product **10** (Entry 11). Once again, the role of TMEDA was proven crucial, since its absence (Entry 12) led to the formation of **8a** and **9a** in very low yields together with trace amounts of products **11** and **12**. Finally, reducing the equivalents of the Grignard reagent resulted in a dramatically different reaction pathway and only trace amounts of elimination product **10** were detected (Entry 13).

Having established the optimum conditions leading to the desired phenyl *β*-glucoside **8a** (Entry 4), we considered that the moderate yields are due to the unreactive starting *α*-glucosyl iodide **4** and/or its partial decomposition to some of the side products during the work-up. Thus, it was proposed that the yields of **8a** would be increased upon prolonged reaction times. Indeed, after 4 days of reaction between **4** and **7** (R = Ph) at 25 °C (1:2.5 M ratio) with 5 mol% $Co(acac)_3$ and 5 mol% TMEDA in THF, the desired phenyl *β*-glucoside **8a** was isolated chromatographically in 63% yield (entry 14). Interestingly, this result was reproducible on multi-gram scales.

High *β*-selectivity and better yields have been obtained from analogous reactions of the respective tetra-*O*-pivaloyl-*α*-*D*-glucosyl bromide using organozinc reagents as nucleophiles [5c]. However, our method is much simpler with regard to the reaction conditions, reagents availability and sensitivity, and experimental and safety precautions.

To our surprise, peracetylated glucosyl iodide **5** (Fig. 1) under the established reaction conditions did not give any phenyl *α*- or *β*-*C*-glucoside, but 2,3,4,6-tetraacetyl-*O*-glucopyranose (37%)

Table 1
Optimization study and reactions of pivaloyl-protected glucosyl iodide with Grignard reagents



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Entry	R	Reaction Conditions	Products (%)
1	Ph	Et_2O, 25 °C, 12 h	**11** (2), **12** (3)
2	Ph	CuI (5 mol%), LiCl (2 equiv.), TMEDA (5 mol%), THF, 25 °C, 12 h	**10** (5)
3	Ph	PEPPSI-IPr (10 mol%), TMEDA (5 mol%), THF, 25 °C, 12 h	**10** (3)
4	Ph	$Co(acac)_3$ (5 mol%), TMEDA (5 mol%), THF, 25 °C, 12 h	**8a** (42), **9a** (7), **10** (8)
5	Ph	$Co(acac)_3$ (5 mol%), TMEDA (5 mol%), Toluene, 25 °C, 48 h	**10** (10%)
6	Ph	$Co(acac)_3$ (5 mol%), TMEDA (5 mol%), Dioxane, 25 °C, 48 h	**10** (4)
7	Ph	$Co(acac)_3$ (5 mol%), Et_3N (5 equiv.), THF, 25 °C, 12 h	**9a** (24), **10** (10), **11** (7), **12** (5)
8	Ph	$Co(acac)_3$ (5 mol%), DABCO (5 eqiv.), THF, 25 °C, 12 h	**9a** (27), **10** (10), **11** (7), **12** (6)
9	Ph	$Co(acac)_3$ (5 mol%), TMEDA (5 mol%), THF, 60 °C, 12 h	**8a** (42), **9a** (7), **10** (8)
10	Ph	$Co(acac)_3$ (10 mol%), TMEDA (5 mol%), THF, 25 °C, 12 h	**8a** (42), **9a** (7), **10** (8)
11	Ph	$Co(acac)_3$ (5 mol%), TMEDA (10 mol%), THF, 25 °C, 12 h	**8a** (27), **9a** (15), **10** (17)
12	Ph	$Co(acac)_3$ (5 mol%), no additive, THF, 25 °C, 12 h	**8a** (2), **9a** (3), **11** (1), **12** (5)
13	Ph[a]	$Co(acac)_3$ (5 mol%), TMEDA (5 mol%), THF, 25 °C, 12 h	**10** (3)
14	Ph	$Co(acac)_3$ (5 mol%), TMEDA (5 mol%), THF, 25 °C, 4 d	**8a** (63), **9a** (9), **10** (10)
15	allyl	$Co(acac)_3$ (5 mol%), TMEDA (5 mol%), THF, 25 °C, 4 d	**10** (41)
16	*n*-butyl	$Co(acac)_3$ (5 mol%), TMEDA (5 mol%), THF, 25 °C, 4 d	**11** (8), **12** (48)
17	cyclohexyl	$Co(acac)_3$ (5 mol%), TMEDA (5 mol%), THF, 25 °C, 4 d	**11** (7), **12** (33)
18	2-tolyl	$Co(acac)_3$ (5 mol%), TMEDA (5 mol%), THF, 25 °C, 4 d	**10** (64), **13** (28)
19	4-tolyl	$Co(acac)_3$ (5 mol%), TMEDA (5 mol%), THF, 25 °C, 4 d	**8b** (38), **9b** (19), **10** (4), **12** (5)
20	4-anisyl	$Co(acac)_3$ (5 mol%), TMEDA (5 mol%), THF, 25 °C, 2 d	**8c** (35), **10** (1), **12** (3)
21	vinyl	$Co(acac)_3$ (5 mol%), TMEDA (5 mol%), THF, 25 °C, 2 d	**10** (19), **12** (13), **13** (2)

[a] 1.5 equiv. of PhMgBr.

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together with the elimination product **10** (9%) were isolated. Similarly from the perbenzylated glucosyl iodide **6** (prepared *in situ*), 2,3,4,6-tetrabenzyl-*O*-glucopyranose was isolated (15%) from a complex mixture of products.

Comparing our results to those reported by Reymond, Cossy and co-workers [5b] in analogous reactions where the respective peracetylated glucosyl bromide was used as a glucosyl donor, it is interesting to note the reverse diastereoselectivity obtained. Reymond and Cossy reported an α/β 3:1 diastereoselectivity with preference for the α-anomer whereas we obtained an α/β 1:6.3 ratio with preference for the β-anomer. This might be due to either different protecting groups or replacement of the bromine atom by iodine. Additional mechanistic studies are needed to shed light on these results. Another interesting point in our results is the inversion of diastereoselectivity when we switched the additive from TMEDA to Et_3N or DABCO. No β-anomer was isolated in these cases and only α-anomer together with significant amounts of side products were formed.

To develop further the reaction, a number of Grignard reagents were used instead of PhMgBr. Although it has been reported that the "armed" per-*O*-benzylated galactopyranosyl iodide analogous to **6** undergoes an S_N2 displacement of iodide by allyl magnesium bromide [7b], affording the respective *C*-glycoside, no α- or β-*C*-glucoside was obtained when we attempted the reactions of **4** with allyl, *n*-butyl or cyclohexyl magnesium bromides under the optimum conditions established for PhMgBr (Entries 15–17).

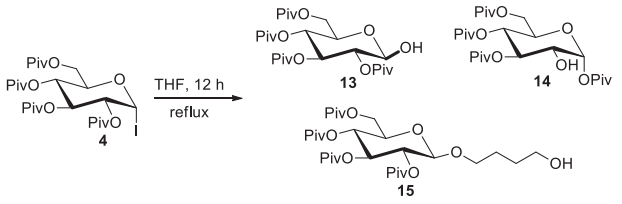
o-Tolyl magnesium bromide gave none of the *C*-glucosylation product and the elimination product **10** was obtained in 64% yield together with 2,3,4,6-tetrapivaloyl-*O*-glucopyranose (**13**, 28%), possibly due to steric reasons (Entry 18). However, the reaction of *p*-tolyl magnesium bromide led to the formation of both α- and β-*C*-glucosides but in lower diastereoselectivity (α/β, 1:2), together with the known side products (Entry 19). Interestingly, 4-anisyl magnesium bromide led to exclusive formation of the β-*C*-glucoside in moderate yield, together with the known side products, but the vinyl magnesium bromide gave none of the *C*-glucoside (Entries 20, 21).

Furthermore, we studied the stability of glucosyl iodide **4**. It is a solid (m.p. 140–142 °C) and can be stored in the refrigerator for months without decomposition as determined by NMR. Also, it is similarly stable in the air at room temperature as a solid under light protection. A solution of **4** in $CDCl_3$ at room temperature was followed by ^1H NMR and after 22 days, it was completely decomposed to products **13** and **14** in roughly equally amounts.

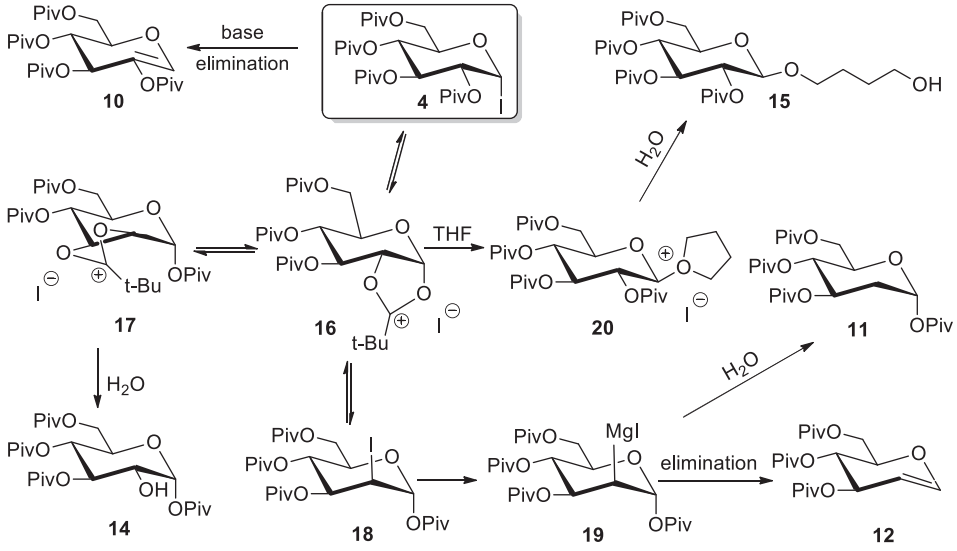
In addition, heating a solution of **4** in THF at reflux for 12 h (Scheme 1) resulted in appreciable decomposition and the already mentioned compounds **13** and **14** were formed in 5% and 2% yields, respectively, together with compound **15** (58%) and unchanged staring material (12%).

All compounds **8**, **9**, **10**, **12** and **13** [5c,5f,9–11] are known and their structure was assigned on the basis of their ^1H and ^{13}C NMR spectra, which were in good agreement with those reported in the literature. Both β- and α-anomers **8** and **9**, are easily discerned from their 1-H and aromatic chemical shifts (500 MHz, $CDCl_3$). Exemplifying for **8a**, the 1-H signal appeared as a doublet at δ 4.41 (J = 9.3 Hz, axial disposition) whereas in **9a** it appeared at δ 5.37 (d, J = 5.3 Hz, equatorial disposition). Also interestingly, the aromatic protons in **8a** are almost equivalent and appeared as a narrow multiple centered at δ 7.31, whereas in **9a** the signal of deshielded *ortho*-protons (δ 7.61) is distinct from those *meta*- (δ 7.38) and *para*-protons (δ 7.32). Glucosides **11**, **14** and **15** are new compounds and their structure assignment was easily made by comparison of their NMR spectra with those of the respective known acetates, which are very similar [12–14]. Their α- (compounds **11** and **14**) and β-anomeric structure (compound **15**) was deduced from the 1-H signal in the ^1H NMR spectra, which appeared at δ 6.23, d, J = 2.8 Hz for **11**, at δ 6.21, d, J = 3.8 Hz for **14** (both indicating equatorial disposition) and δ 4.48, d, J = 8.0 Hz for **15** (axial disposition).

Side product **13** formed in the coupling reactions is apparently a decomposition product of iodide **4** by water, whereas the formation of compounds **10**, **11** and **12** is caused by side-reactions of Grignard reagents or the additive with iodide **4**, as shown in Scheme 2. By the action of a base (Grignard reagent or additive) an elimination reaction in **4** occurs, affording compound **10**. Iodide **4** is evidently in equilibrium with intermediate **16** as previously



Scheme 1. Decomposition products of **4** in THF at reflux.



Scheme 2. Possible reaction pathways leading to side and decomposition products.

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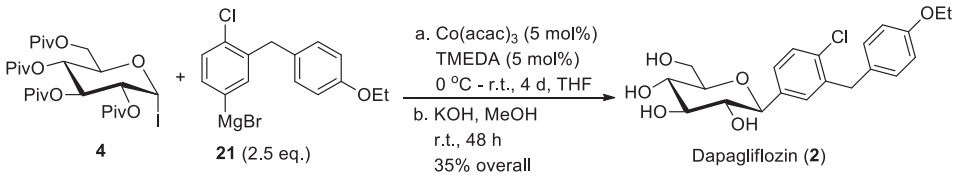

Scheme 3. Preparation of dapagliflozin.

reported for acylated glucosyl halides [5c]. Further opening of the dioxolane ring in **16** by attack of the iodide anion to C-2 gives intermediate iodide **18**, which is subsequently converted to the respective Grignard reagent **19** by metallation with magnesium or transmetallation with RMgBr. This intermediate can be transformed into glucal **12** by an elimination reaction or decomposed by water during the work-up leading to the deoxy derivative **11**.

Upon heating iodide **4** in THF at reflux, intermediate **16** is further transformed to intermediate **17**, by neighboring group participation (Scheme 2). Addition of water to **17** leads to the formation of **14**, with simultaneous migration of the pivaloyl group to the 1-position. The reaction of water with intermediate **17** at C-2 is not favored since the respective hydroxyl group should be in an axial disposition. Glucoside **15** –the main decomposition product in THF at reflux– is presumably generated by nucleophilic attack of THF to intermediate **16** and further oxonium cleavage by water, which is supported by its β-anomeric structure.

Having established a method for the β-C-glucosylation of pivaloyl-protected glucosyl iodide **4**, we proceeded in the synthesis of dapagliflozin **2** from **4**. Thus, treatment of **4** with Grignard reagent **21** [8a] and catalytic amounts of $Co(acac)_3$ (5 mol%) and TMEDA (5 mol%) in THF for four days led to the formation of pivaloyl-protected dapagliflozin. Its further methanolysis with KOH gave the desired product **2** in 35% overall yield (Scheme 3), with analytical and spectral data identical to those reported in the literature [5c].

Conclusion

In conclusion, we have described a method for the synthesis of β-*C*-glucosides using α-*D*-tetra-*O*-pivaloylglucosyl iodide as a glucosyl donor. It is noteworthy that its diastereoselectivity differs from that of the respective acetyl-protected glucosyl bromide, as reported in the literature under similar reaction conditions. The concentration of the catalyst, the solvent and the type of additive used are crucial factors that determine the reaction selectivity. The above method may find application in the short synthesis of gliflozins, as demonstrated by the synthesis of dapagliflozin. The stability of α-*D*-tetra-*O*-pivaloylglucosyl iodide in $CDCl_3$ and THF at reflux was also studied. All side products in the coupling and decomposition reactions were isolated and characterized, and possible pathways for their formation are proposed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152173.

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