Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2022, **20**, 1874

Received 29th December 2021,
Accepted 7th February 2022

DOI: 10.1039/d1ob02502c

rsc.li/obc

Catalytic stereoselective synthesis of 2-deoxy α-glycosides using glycosyl *ortho*-[1-(*p*-MeOPhenyl)Vinyl]Benzoate (PMPVB) donors†

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2-Deoxy glycosyl *ortho*-[1-(*p*-MeOPhenyl)Vinyl]Benzoates (PMPVB) have been presented as stable, reactive glycosyl donors for the synthesis of 2-deoxy α-glycosides. The donors react under Brønsted acid conditions to provide the 2-deoxy-α-glycosides with very high stereocontrol. The observed high stereoselectivities were discussed with respect to the relative free energy differences between the anomeric reactive intermediates.

The 2-deoxysugars form a part of many bioactive natural products[1] and have been found to play important roles in many biological activities.[2] Consequently, the synthesis of this class of compounds has received significant attention from organic chemists in recent times.[3–5] Unusual challenges associated with the stereoselective synthesis of both 2-deoxy α- and β-glycosides include (a) the general 2-deoxy donors like the glycosyl acetimidates are very reactive, unstable and are difficult to handle, (b) lack of any functionality at C-2 that can be manipulated to control the anomeric stereochemistry makes the stereoselective construction of 2-deoxysugars, a challenging task, and (c) the formation of Ferrier byproducts. A number of direct methods are available for the synthesis of 2-deoxyglycosides based on glycosyl halides,[6–8] phosphites,[9,10] acetimidates,[11] hemiacetals,[12–14] and thioglycosides (Fig. 1).[15] However, a majority of them rely on extremely low temperatures due to the high reactivity and instability of the 2-deoxy donors or on the protecting groups to control the stereoselectivities. Other indirect methods use a stereodirecting auxiliary at C-2 that needs extra steps for the installation and removal of the same.[16,17] Recently, there has been an upsurge in the development of glycal activation methods for the *α*-selective synthesis of 2-deoxyglycosides; however, a majority of them are not compatible with less reactive acetyl/benzoyl substrates,[18–21] or use metal catalysts[22–26] that are prone to provide the undesired Ferrier byproducts.[27,28] Notwithstanding the numerous efforts, a general catalytic user-friendly method for the stereoselective construction of the 2-deoxyglycosidic bond remains a challenge. We present here 2-deoxy *ortho*-[1-(*p*-MeOPhenyl)Vinyl]Benzoates (PMPVB) donors as stable and reactive glycosyl donors for a protecting group independent stereoselective synthesis of α-2-deoxyglycosides under simple Brønsted acid catalysis. These alkene donors by virtue of their rigidity and 1,1-diphenyl substitutions[29,30] along with a *p*-methoxy group can easily react with not only strong electrophilic reagents like NIS but also can be activated under simple Brønsted acidic conditions. The ability of these donors to react with Brønsted acid makes them the first Fraser-Reid type alkene donors[31,32] that can be catalytically activated. Along with stability and reactivity, PMPVB donors allow the construction of the 2-deoxy *O*-glycosidic linkage in a highly stereoselective fashion. Here, we discuss the synthesis, reactivity, and mechanistic aspects of the glycosylation reactions. 2-Deoxy PMPVB donors are readily prepared by DCC coupling of the corresponding acid with 2-deoxy hemiacetals in excellent yields. 2-Deoxyglucose and 2-deoxygalactose donors with various protecting groups have been made, as shown in Scheme 1. All the donors with various protecting groups have been obtained as a mixture of isomers

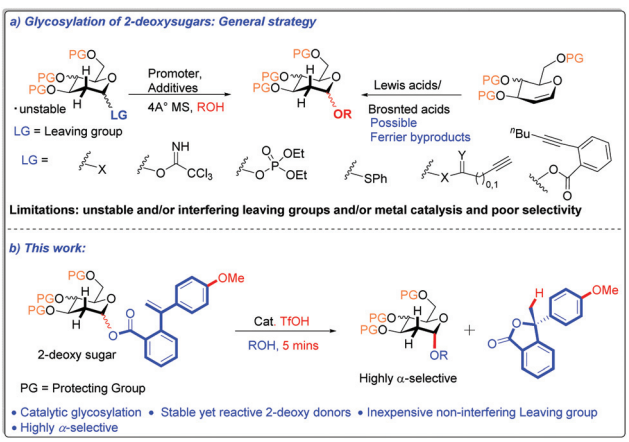

Fig. 1 a) Previous work. b) This work.

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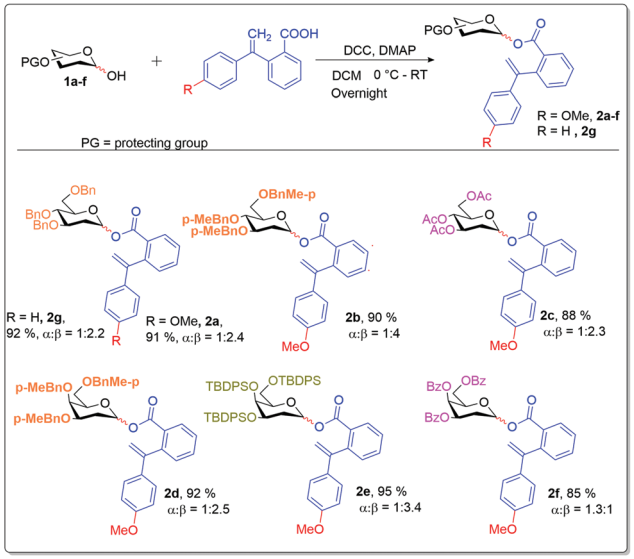
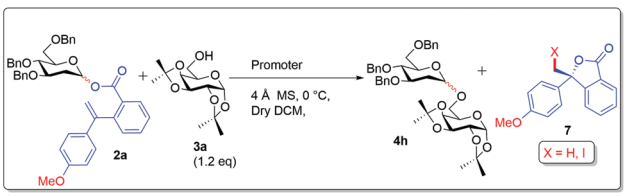
†Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ob02502c



Scheme 1 Synthesis of donors.

with β as the dominant donor except for the 2-deoxy tri-*O*-benzoyl protected galactose derived donor that is obtained with α isomer as the major product. Our study commenced with a reaction between the glucosyl donor **2a** and the acetonide acceptor **3a**. When donor **2a** (0.06 mmol) was reacted with acceptor **3a** (0.072 mmol) in dry CH_2Cl_2 (1.5 mL) at 0 °C under bistriflimide ($(CF_3SO_2)_2NH$) as the Brønsted acid catalyst (30 mol%), the reaction went to completion in just 5 min, yielding 83% of the desired disaccharide product in 1.7 : 1 (α : β) ratio (Table 1, entry 1). Since this is an alkene-based donor and can be activated under NIS/TMSOTf conditions, the same has been tried to see if the yield or selectivity could be improved. However, under NIS (1.1 equiv.) and TMSOTf (30 mol%), the reaction was slower relative to the Brønsted acidic conditions (20 min), and the yield dropped to 79% yield (1.7 : 1, α : β) (Table 1, entry 2). Also, the release of succinimide as another byproduct could also interfere in the reaction leading to poor selectivity. Intriguingly enough, when the reaction was tried with another strong acid, trifluoromethane sulfonic acid (TfOH), instead of bistriflimide, as a promoter (30 mol%), it led to 85% yield of the product with an improved anomeric ratio of 5.4 : 1 (α : β) of the products (Table 1, entry 3). The reaction was tried at various catalytic loadings to evaluate the influence of catalyst concentration on the selectivities. The donor could not be activated at 5 and 10 mol% of the triflic acid (Table 1, entries 4 and 5) even after 24 h. There is a gradual increase in the yields and selectivities when the catalytic mol % is increased from 15 to 25 (Table 1, entries 6–8) also with a drastic decrease in reaction time as well. In order to understand the influence of the –OMe group of the PMPVB donor on the outcome of the glycosylation reaction, we did another experiment taking PVB donor (**2g**) that is devoid of the methoxy group, which resulted in only 18% yield of the product with an anomeric ratio of 2.2 : 1 (α : β) after 12 h (Table 1, entry 9). In addition, a comparative study between PMPVB and PVB donors has also been performed. A mixture of 1 equiv. of donor **2a** and 1 equiv. of donor **2g** in the presence of 1 equiv. of acceptor **3a**, were reacted under the catalytic Brønsted acidic condition, where 80% of the PVB donor **2g** has been recovered, indicating little activation of the PVB donor **2g** in the presence of the PMPVB donor **2a** (refer to see ESI†) with 87% yield of desired product **4h** (α : β, 5 : 1) along with *p*-methoxy substituted cyclized adduct **7** in 94% (Scheme 5). We believe the extra stability provided by –OMe substituent *via* mesomeric effect (+M effect) leads to the intermediate **15** (Scheme 4) and hence makes the donor catalytically active unlike the unsubstituted donor. With the optimized conditions in hand, we have decided to test the protocol on other 2-deoxy PMPVB donors synthesized with variously protected acceptors (Table 2). It was interesting to note that the glycosylation of armed perbenzylated and per-*p*-methylbenzylated 2-deoxy galactosyl and glucosyl donors reacted in a highly stereoselective fashion giving rise to α isomer exclusively with good to excellent yields (**4a–f**, **4r–s**, **4u–v**, 83–92%). The high selectivities were retained even in the case of hindered and less reactive secondary acceptors as well (**4b**, **4d–e**, **4r**, **4v**). The super armed silylated 2-deoxygalactosyl donor also resulted in the glycosyl products as single isomers (α only) in excellent yields (**4j–l**; 84–91%). The peracetylated glucosyl and perbenzoylated 2-deoxygalactosyl donors also resulted selectively in α isomer with good yields (**4o–q**, **4w–x**, 80–85%) even in the case of less reactive secondary 4-OH of mannosyl acceptor (**3j**). The highly hindered mannosyl acceptor (**3j**), when reacted with perbenzylated and per-*p*-methylbenzyl protected glucosyl donors, provided the disaccharides in excellent selectivities of 14 : 1 and 14 : 1 respectively (**4m** & **4n**). A drop in selectivities

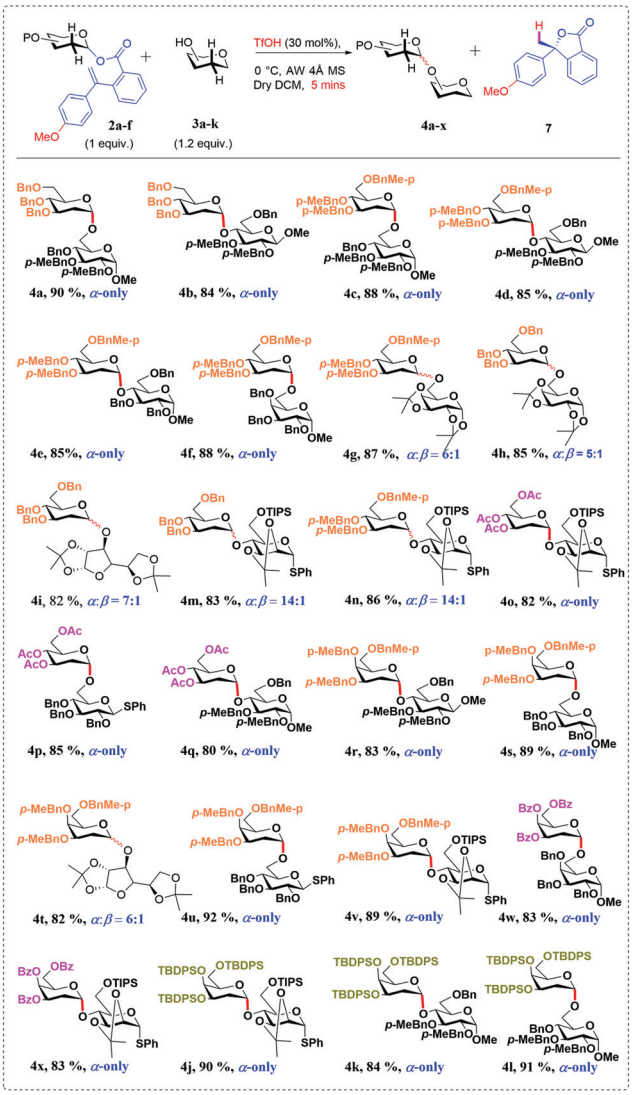
Table 1 Optimization studies



Entry	Catalyst	Amount (mol %)	Time	Yield (%)	Anomeric ratio (α : β)
1	$(CF_3SO_2)_2NH$	30	5 min	83	1.7 : 1
2	NIS (1.1 equiv.), TMSOTf	30	20 min	79	1.7 : 1
3	TfOH	30	5 min	85	5.4 : 1
4	TfOH	5	24 h	-	
5	TfOH	10	24 h	-	
6[a]	TfOH	15	5 h	64	2.7 : 1
7	TfOH	20	30 min	80	3.6 : 1
8	TfOH	25	15 min	81	4.5 : 1
9[b]	TfOH	30	12 h	18	2.2 : 1

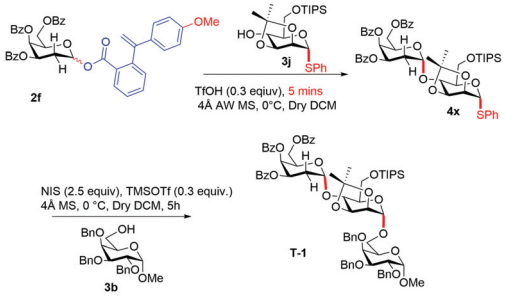
Reaction conditions: reactions were done at 0 °C in presence of activated acid-washed 4 Å MS in dry DCM medium. [a] Based on recovery of starting material. [b] **2g** donor were used.

Table 2 Substrate scope of *O*-glycosylation



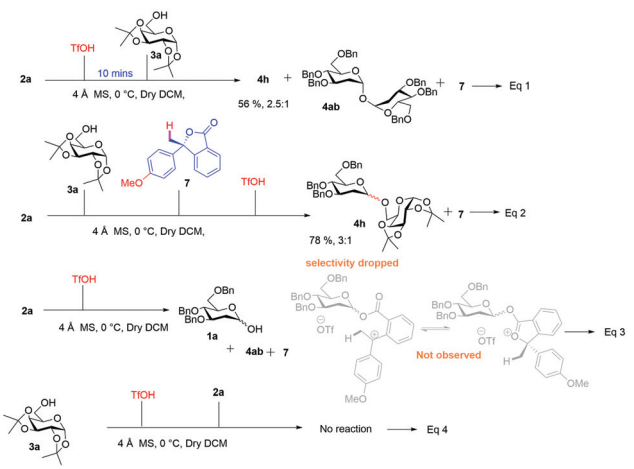
was observed when acetonide-protected acceptors **3a** & **3c** were used as acceptors (**4g–i**, **4t**; 5 : 1 to 7 : 1, α : β) in their coupling reactions with perbenzylated and per-*p*-methylbenzylated 2-deoxygalactosyl as well as glucosyl donors. Unlike the other alkene-based donors, these PMPVB donors can be activated in the presence of thioglycoside donors and the successful coupling reactions with thiomannopyranoside **3j** stands as evidence for the same. Also, one of the disaccharides (**4x**) thus synthesized has also been converted to the trisaccharide **T-1** using standard NIS/TMSOTf protocol, where trisaccharide **T-1** was also obtained as a single isomer (α only) in 76% yield (brsm) (Scheme 2).

A variety of control experiments have been performed to understand the reasons behind the observed high α-selectivity. Usually, the α-selectivity in 2-deoxyglycosides is explained *via* the corresponding oxocarbenium ions that are inherently α-directing; however, the facial selectivity usually is dependent

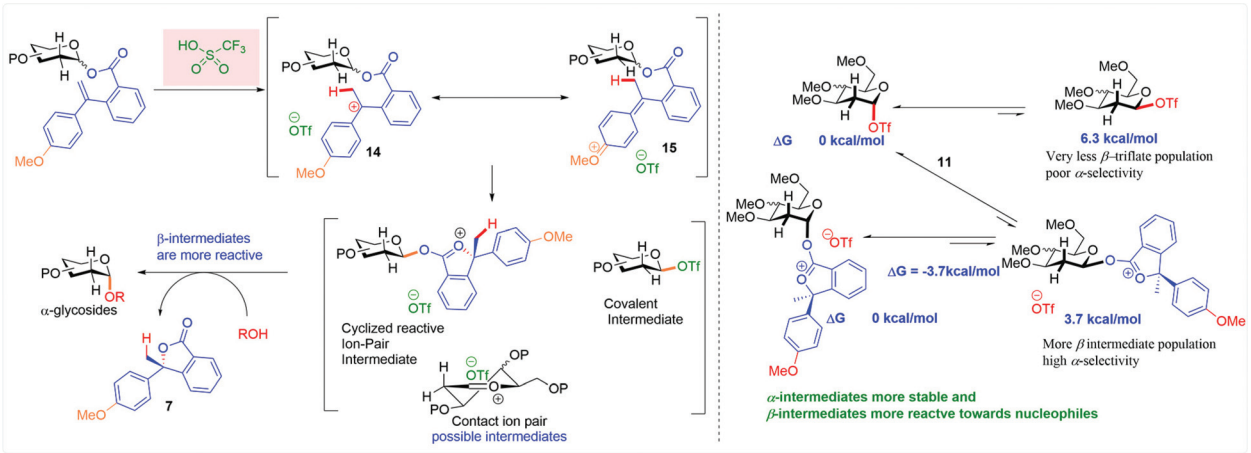


Scheme 2 Synthesis of **Gal-Man-Gal** Trisaccharide T-1.

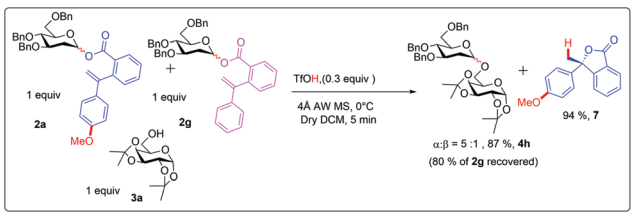
on the protecting groups on the donor. The protecting group independent high α-selectivities observed in the current protocol could arise from a possible S_N2 attack as well. With the growing body of evidence for the involvement of β-glycosyl triflates in α-selective glycosylation reactions,[33–35] invoking the naked oxocarbenium ion may no longer be a valid explanation for the anomeric selectivity. We ran a few control experiments and theoretical studies to decipher the mechanism and the possible intermediates giving rise to the observed high α-selectivities. For better comparisons, we have chosen the acetonide acceptor **3a** for the control experiments (same as the optimization studies) as this is one of the very few acceptors where the α-selectivity is relatively low. The preactivation method where the acceptor is added 10 minutes later to the addition of the catalyst led to only 56% of the product **4h** with a drop in α selectivity to 5.4 : 1 to 2.5 : 1 (Scheme 3, eqn (1)). While this experiment does not rule out the possibility of the involvement of β-glycosyl triflates as potential intermediates, this experiment suggests that it may not be the only reason for the observed high α-selectivity. The reaction, when performed with an excess amount of the cyclic byproduct **7** (1.5 equiv.) in the reaction mixture, led to a drop in the anomeric selectivity from 5.4 : 1 to 3 : 1 (α : β) and the yield from 85 to 78% (Scheme 3, eqn (2)). The drop-in selectivity and the yield could be the resultant of a slight decrease in the rate of reaction due



Scheme 3 Control experiments.



Scheme 4 Proposed mechanism and the minimum energy structures of the intermediates.



Scheme 5 Comparative study.

to the shift in the equilibrium because of the presence of **7**. Also, this experiment not only demonstrates that the by-product can react back with the oxocarbenium ion but also suggests that the cyclic intermediate **15** could be the potential intermediate affecting the stereochemical outcome of the glycosylation. The experiment performed in the absence of acceptor alcohol in order to observe the protonated intermediate only resulted in the formation of the hydrolyzed product **1a** (38%) and dimerized product **4ab** (24%) along with the byproduct **7** (91%) (Scheme 3, eqn (3)). This shows that the alkene donor once protonated is a highly unstable species and undergoes rapid cyclization followed by elimination leading to oxocarbenium ion. Surprisingly, the reaction in which the donor was added after the prior mixing of the acceptor alcohol and the catalyst did not lead to the coupled product even after 5 h (Scheme 3, eqn (4)). Presumably, the Brønsted acid catalyst is sequestered by the acceptor alcohol *via* multiple hydrogen-bonding networks. The above experiments suggest that the observed high selectivities could be arising from the S_N2 attack of the alcohol onto the more reactive protonated β-glycosylbenzofuranium intermediate or/and β-glycosyltriflate or/and the β-contact ion-pair. DFT calculations were performed using the B3LYP/6-31 g(d) level of theory on methylprotected donors to understand the relative energy differences between α and β intermediates, which revealed that the α-glycosyloxybenzofuranium intermediate is more stable by 3.7 kcal mol^{-1}. In contrast, the difference in free energies between α and β-glycosyltriflates is 6.3 kcal mol^{-1}. These calculations suggest that the β-intermediates could be significantly unstable and hence could be more reactive than their α counterparts, and the preferential attack of the *O*-nucleophiles on β-intermediates lead to the observed high α-selectivities. Based on all these observations, we propose the mechanism of the current protocol as depicted in Scheme 4.

In summary, we have demonstrated the utility of the new PMPVB donors towards the stereoselective synthesis of 2-deoxy α-glycosides. The method provides the coupled product in excellent diastereoselectivities arising from the difference in energies of the reactive intermediates. The relatively less energy difference between the α/β glycosyl benzofuranium intermediate results in an increase in the β-intermediate population that is also significantly more reactive towards nucleophiles could be the reason for the observed high α-selectivity. The high selectivities observed are independent of the protecting groups and showcased on both 2-deoxyglucosyl and 2-deoxygalactosyl donors. Extending the PMPVB donor protocol towards the synthesis of 2-deoxysugar based natural products is under progress in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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