Glycosylation with Glycosyl *p*-Bromophenyl Phthalates as New Efficient Glycosyl Donors

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The development of an efficient and stereoselective glycosylation methodology has been a major concern in synthetic organic chemistry in the past a decade due to the important biological functions of complex oligosaccharides and glycoconjugates.[1] Devising new glycosyl donors and developing new activation systems for the existing donors resulted in major advances in this area. For example, several glycosylation methodologies using the efficient glycosyl donors such as thioglycosides,[2] glycosyl sulfoxides,[3] glycals,[4] glycosyl trichloroacetimidates,[5] *n*-pentenyl glycosides,[6] and glycosyl fluorides[7] have been available. In addition, there have been recent reports regarding the development of glycosylation methods *via* new glycosyl donors and the application of existing glycosyl donors in novel activation systems.[8] However, there still remains a need for more efficient and generally applicable new glycosylation methodology.

In our previous endeavors, we reported a novel type of glycosyl donors, the 2'-(benzyloxycarbonyl)benzyl (BCB) glycoside[9] and the 2'-carboxybenzyl (CB) glycoside **A**, as shown in Figure 1 for the stereoselective β-mannopyranosylation[10] and the 2-deoxyglycosylation.[11] We applied this methodology to the synthesis of a trisaccharide[12] and tetrasaccharide.[13] More recently, we have also reported the synthesis of the glycosyl benzyl phthalate **C** and its use as a new type of glycosyl donor.[14] Although the glycosyl benzyl phthalate **C** proved to be the efficient glycosyl donor, there still remains a need for improvement. Thus, it is desirable to conduct the glycosylation more efficiently and at lower temperature in order to control the stereochemistry of the product and to keep acid-labile reactants or products intact under the acidic condition resulting from the use of TMSOTf. We envisaged that certain glycosyl aryl phthalates **D** might be more reactive than **C** so that the glycosylation might be conducted at lower temperature. Herein we describe the synthesis of a new type of glycosyl donors, the glycosyl aryl phthalate **D** and report that the glycosylation with glycosyl *p*-bromophenyl phthalates could be conducted under milder condition than that with glycosyl benzyl phthalates.

Results and Discussion

Crystalline aryl hydrogen phthalates (**1a-e**) were readily prepared in large quantities by treating the inexpensive phthalic anhydride with phenol or *p*-substituted phenols (Scheme 1). Esterification of 2,3,4,6-tetra-*O*-benzyl-D-glucose (**2**) and the phthalates **1a-d** using DCC in the presence of DMAP provided the anomeric mixture of corresponding glucopyranosyl aryl phthalates **3a-d** in good yields (Scheme 2).[15] These aryl phthalate glycosyl donors **3a-d** were stable enough to be stored at room temperature

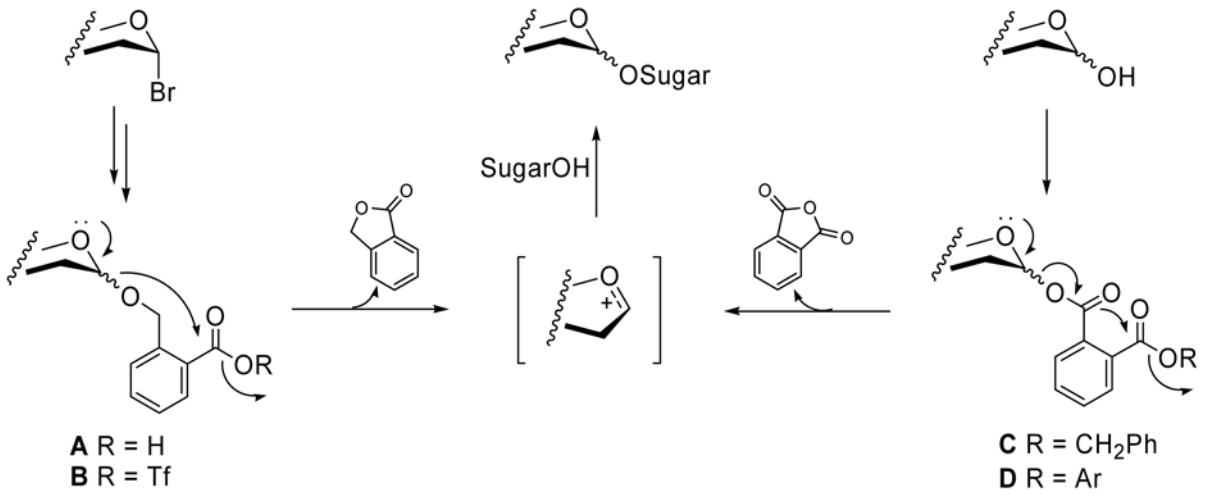
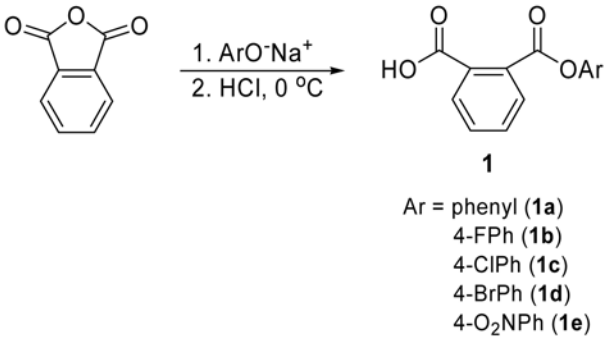


Figure 1



Scheme 1

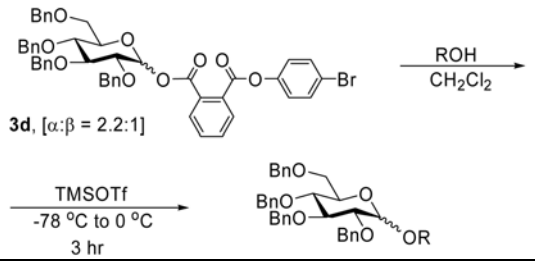
for months with no appreciable change. However, 4-nitrophenyl derivative **3e** was highly unstable and decomposed during the purification.

All donors **3a-d** were readily activated by TMSOTf in dichloromethane and were coupled with the glycosyl acceptor **4** to give the corresponding disaccharide **12** in excellent yields (Table 1). General procedure involved stirring of a solution of the phthalates **3** (1.0 equiv.), of the acceptor **4** (2.0 equiv.), and of TMSOTf (0.5 equiv.) in dichloromethane, and quenching with aqueous $NaHCO_3$. The reaction mixture was purified by column chromatography to provide a mixture of α- and β-disaccharides **12** (Scheme 2, all entries in Table 1, and entry 1 in Table 2). Among glycosyl aryl phthalates **3a-d**, 4-bromo substituted donor **3d** showed the highest reactivity.[16] Glycosylation with

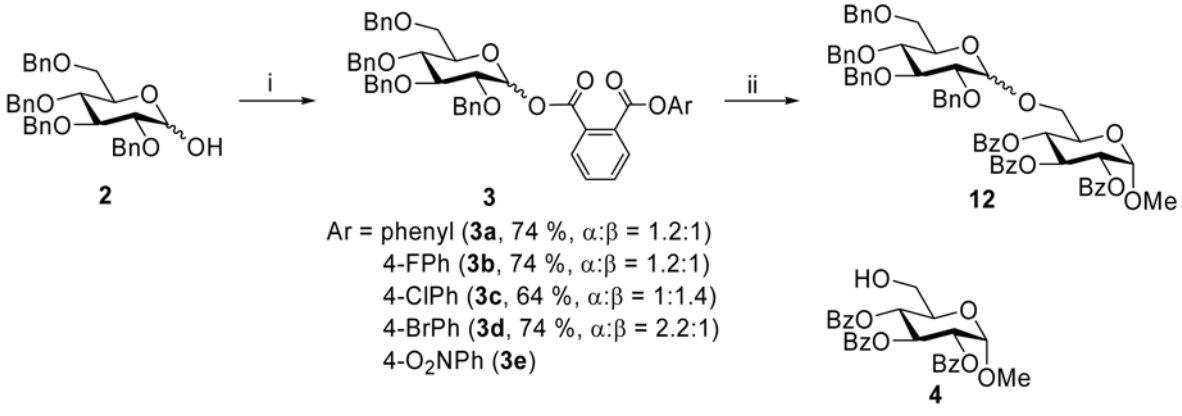
Table 1. Glycosylation for **12** with glycosyl aryl phthalates **3** and acceptor **4**

Glycosyl donor	Aryl	Reaction temp. (°C)		Time (h)	Yield (%)	Ratio (α/β)
		Starting	Completion			
3a		−10	rt	3 h	91	1.6 : 1
3b	F	−10	rt	3 h	93	1.4 : 1
3c	Cl	−20	rt	3 h	88	1.7 : 1
3d	Br	−30	0	3 h	93	1 : 1.2

Table 2. Glycosylation with glucopyranosyl *p*-bromophenyl phthalate **3d** and various glycosyl acceptors



Entry	Acceptor (ROH)	Product	TMSOTf (eq.)	Yield (%)	Ratio (α/β)
1	**4**	**12**	0.5	93	1 : 1.2
2	**5**	**13**	0.5	91	1 : 1.1
3	**6**	**14**	0.5	89	1 : 1
4	**7**	**15**	0.5	88	1.4 : 1
5	**8**	**16**	1	83	1 : 1.4
6	**9**	**17**	1	87	1 : 1
7	**10**	**18**	0.5	85	1.4 : 1
8	**11**	**19**	1	80	1 : 1

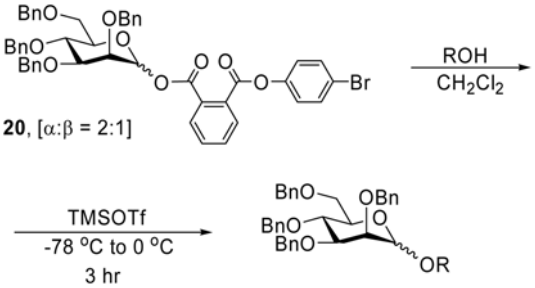


Scheme 2. Reagents and conditions: i, aryl hydrogen phthalate (**1**), DCC, DMAP (cat.), CH_2Cl_2, 0 °C to rt, 3 hr; ii, **4**, TMSOTf, CH_2Cl_2, 3 hr.

the donor **3d** virtually completed at −30 °C while other donors **3a-c** required −10 or −20 °C although the reaction temperature was raised to room temperature in order to make sure the complete conversion of reactants into products.

Based on these results, we chose the derivative **3d** as our lead donor and treated it with various glycosyl acceptors to investigate the general applicability (Table 2). Reaction of the donor **3d** with other primary alcohol acceptors **5**, **6**, **7**, and **10** similarly provided disaccharides **13** (α/β = 1 : 1.1), **14** (α/β = 1 : 1), **15** (α/β = 1.4 : 1) and **18** (α/β = 1.4 : 1) in 85-91% yields, respectively (entries 2, 3, 4, and 7 in Table 2). The glycosylation of the donor **3d** with secondary alcohol acceptors also proved to be quite efficient. Treating 1.0 equiv. of the donor **3d** with 2.0 equiv. of secondary alcohol acceptors **8**, **9**, and **11** in the presence of 1.0 equiv. of TMSOTf in dichloromethane gave disaccharides **16** (α/β = 1 : 1.4), **17** (α/β = 1 : 1), and **18** (α/β = 1 : 1) in 80-87% yields, respectively (entries 5, 6, and 8 in Table 2). These results indicated that glycosyl *p*-bromophenyl phthalates were more efficient glycosyl donors than glycosyl benzyl phthalates.[14] Additionally, new set of the glycosyl donor **20** was prepared from mannopyranose (Table 3).[17] While the glucopyranosyl donor **3d** showed no diastereoselectiviy, the glycosylation with mannopyranosyl donor **20** exhibited α-selectivity for both primary or secondary alcohol acceptors. Moderate (α/β = 2 : 1) to high (α only) α-selectivity was observed in the reaction of **20** with primary alcohol acceptors (entries 1-4, and 7 in Table 3). On the other hand, only the α-isomers were obtained when the donor **20** was reacted with the secondary alcohol acceptors **8**, **9**, and **11** to provide exclusively α-disaccharides **25**, **26**, and **28**, respectively (entries 5, 6, and 8 in Table 3).

Table 3. Glycosylation with mannopyranosyl *p*-bromophenyl phthalate **20** and various glycosyl acceptors



Entry	Acceptor (ROH)	Product	TMSOTf (eq.)	Yield (%)	Ratio (α/β)
1	**4**	**21**	0.5	91	α only
2	**5**	**22**	0.5	92	α only
3	**6**	**23**	0.5	89	2 : 1
4	**7**	**24**	0.5	92	2.4 : 1
5	**8**	**25**	1	82	α only
6	**9**	**26**	1	89	α only
7	**10**	**27**	0.5	78	2.6 : 1
8	**11**	**28**	1	84	α only

In conclusion, we have developed a new type of glycosyl donors, glycosyl aryl phthalates, and identified glucopyranosyl *p*-bromophenyl phthalate **3d** and mannopyranosyl *p*-bromophenyl phthalate **20** as the most reactive donors. Since glycosylation with these glycosyl *p*-bromophenyl phthalates could be conducted at lower temperature than that with glycosyl benzyl phthalates, control of stereochemistry in glycosylation might be easier and glycosylation with acid-labile reactants or products would be possible.

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15. **3d**: colorless oil (α/β = 2.2 : 1): R_f = 0.33 (hexane/EtOAc, 4 : 1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.58-3.87 (m, 5H), 3.91-4.02 (m, 1H), 4.36-4.74 (m, 5H), 4.77-5.01 (m, 3H), 5.88 (d, J = 7.4 Hz, 0.3H, $H_{\beta-1}$), 6.56 (d, J = 3.3 Hz, 0.7H, $H_{\alpha-1}$), 7.10-7.33 (m, 22H), 7.41-7.46 (m, 2H), 7.54-7.62 (m, 2H), 7.78-7.87 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 55.2, 67.7, 68.1, 68.5, 70.1, 73.1, 73.2, 73.4, 73.5, 75.0, 75.4, 75.7, 75.8, 76.7, 78.9, 79.8, 80.8, 81.7, 82.1, 84.8, 91.5, 95.2, 98.2, 119.2, 123.5, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 129.4, 131.6, 131.7, 131.8, 132.5, 137.6, 137.7, 137.8, 137.9, 138.6, 149.9, 164.9, 165.6; IR ($CHCl_3$, film) 3063, 3031, 2867, 1744, 1267, 1197 cm^{-1}. Anal. calcd for $C_{48}H_{43}BrO_9$: C, 68.33; H, 5.14. Found: C, 68.25; H, 5.27.

16. The reason for the higher reactivity of **3d** over **3a-c** is currently unknown.
17. **20**: colorless oil (α/β = 2 : 1): R_f = 0.28 (hexane/EtOAc, 4 : 1); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.62-3.93 (m, 4H), 4.05-4.20 (m, 2H), 4.27-4.65 (m, 5H), 4.75-4.89 (m, 3H), 5.89 (br s, 0.33H, $H_{\beta-1}$), 6.52 (br s, 0.67H, $H_{\alpha-1}$), 7.03-7.65 (m, 26H), 7.78-7.87 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 68.5, 68.7, 71.5, 71.8, 72.4, 72.8, 73.2, 73.8, 73.9, 74.0, 74.7, 75.1, 76.3, 79.1, 81.7, 93.8, 94.0, 119.0, 119.1, 123.28, 123.32, 127.4, 127.5, 127.7, 127.8, 127.9, 128.0, 128.2, 128.8, 129.0, 129.4, 129.9, 131.3, 131.4, 132.0, 132.2, 132.4, 137.6, 137.8, 137.9, 138.0, 138.1, 149.5, 149.6, 164.9, 165.6, 165.7.