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Note

A simple one-pot method for the synthesis of partially protected mono- and disaccharide building blocks using an orthoesterification–benzylation–orthoester rearrangement approach

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Abstract

A simple one-pot method is reported for making partially protected glycosyl acceptors from *O*-methyl or *S*-alkyl/aryl glycosides of D-glucose, D-galactose, D-arabinose, L-rhamnose, L-fucose and lactose via orthoester formation, benzylation and selective hydrolysis.

Keywords: Orthoester; Benzylation; Rearrangement; One-pot reaction

A basic challenge in oligosaccharide synthesis is the preparation of partially protected building blocks where the protecting groups can be manipulated such that each can be selectively removed during the course of the synthetic route. In connection with the synthesis of various biologically active oligosaccharides, we had a need for a practical approach to partially protected building blocks. In the present note we describe a simple one-pot method for the synthesis of some useful glycosyl acceptors and donors based on an orthoesterification–benzylation–orthoester rearrangement approach.

The well-known formation of cyclic orthoesters involving *cis*-hydroxyl groups and selective rearrangement thereof, has been successfully used as the key reaction in this strategy. A selection of methyl glycopyranosides (Table 1) were treated with triethylorthoacetate and catalytic *p*-toluenesulfonic acid in dry acetonitrile[1] to form the corresponding orthoesters, which were then benzylated[2] in the same pot to protect the remaining free hydroxyl groups (Scheme 1).[†] The reaction mixture was diluted with dichloromethane and shaken with 1M HCl solution to effect orthoester rearrangement, giving the expected products.[4] The same approach could also be applied for the thioglycosides, but it worked equally well only when *N,N*-dimethylformamide has been used as solvent, as noted previously[5] (Table 1, entries 5–7).

In conclusion, we have shown that a number of useful glycosyl building blocks can be derived from *O*-methyl or *S*-alkyl/aryl glycosides by executing several reaction steps in a single pot and purifying only at the final stage by flash chromatography. The strategy significantly reduces the time for making these building blocks, and overall yields are higher compared to those obtained by stepwise reactions. Scale-up reactions have been performed with compounds **1**, **3** and **10**, which showed that this procedure can be applied on a 10-g (50 mmol) scale (Table 1).

1. Experimental

1.1. General procedure

1.1.1. Methyl glycosides. To a suspension of the methyl glycoside (1 mmol) in dry MeCN (10 mL), triethylorthoacetate (1.5 mmol) was added, followed by addition of a catalytic amount of *p*-TsOH. The mixture was allowed to stir for 45–60 min. After complete conver-

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† For the two-pot synthesis of the corresponding 2,4-di-*O*-benzoyl derivative, see Ref. 3.

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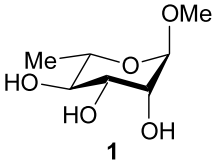
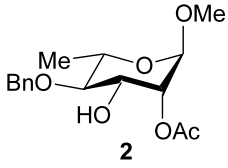
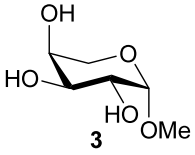
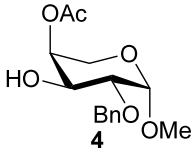
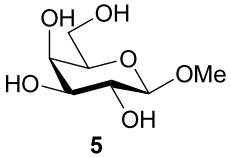
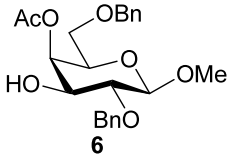
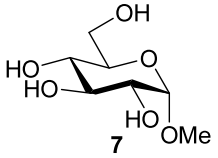
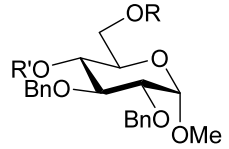
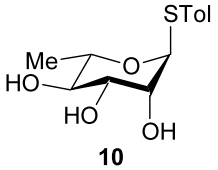
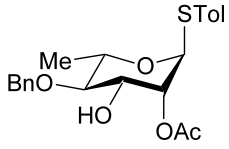
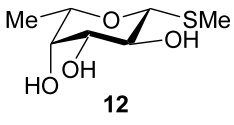
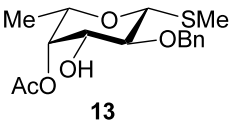
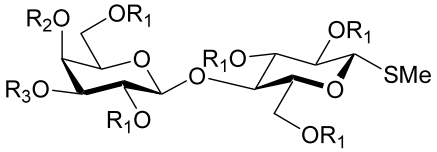
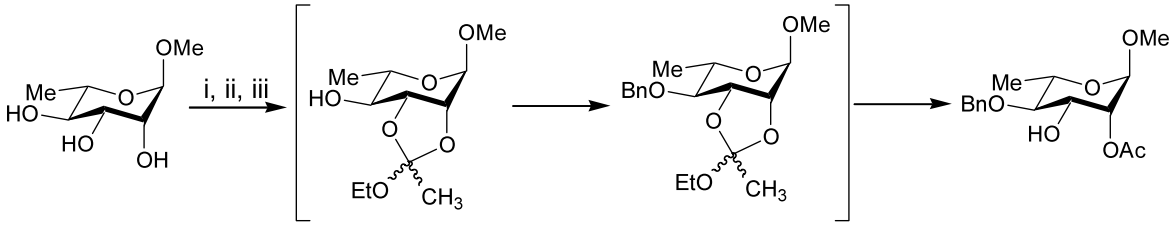
Table 1
Results obtained from the one-pot reactions with various sugars

Entry	Reactant	Product	Yield[a]	Comments
1.	 **1**	 **2**	86% 83% (60 mmol scale)	Compound **2** might be utilized for the synthesis of rhamnogalacturonan fragments found in plant cell wall extracellular matrix.[11]
2.	 **3**	 **4**	72% 70% (65 mmol scale)	Compound **4** might be a useful precursor for plant saponin synthesis.[12]
3.	 **5**	 **6**	74%	Compound **6** could be used for the synthesis of *Trypanosoma cruzi* mucin oligosaccharides.[13]
4.	 **7**	 **8a** R = Ac, R' = H **8b** R = H, R' = Ac	87% **8a:8b** = 7:3	Compounds **8a** and **8b** could be utilized as glycosyl acceptors for amylopectin branch point synthesis.[14]
5.	 **10** Tol = *p*-tolyl	 **11** Tol = *p*-tolyl	78% 74% (45 mmol scale)	Compound **11** has been successfully utilized in this lab for the synthesis of a tetrasaccharide related to *E. coli* K-12 *O*-antigen.[15]
6.	 **12**	 **13**	75%	Compound **13** might be useful for the synthesis of NOD-factor IX, where fucose is a non-terminal sugar.[16]
7.	 **14** R_1, R_2, R_3 = H (reactant) **15** R_1=Bn, R_2=Ac, R_3=H (product)		72%	Compound **15** might be a useful precursor of sialylated lactoside based on the ganglioside GM_3 structure.[17]

[a] Unless otherwise stated, yields refer to reactions performed on a 1 mmol scale.



Scheme 1. (i) Triethyl orthoacetate, *p*-TsOH, CH_3CN; (ii) BnBr, NaH; (iii) 1 N HCl.

sion thin layer chromatography (TLC) [2:1 *n*-hexane–EtOAc], Et_3N was added to neutralize the solution. NaH (1.5 mmol, 60% dispersion in mineral oil) was added, followed by BnBr [1.2 mmol (2.2 mmol for glucose derivative)], and the mixture was allowed to stir for 1 h at room temperature. When TLC (3:1 *n*-hexane–EtOAc) showed complete conversion, MeOH (1 mL) was carefully added to destroy excess NaH, and the mixture was diluted with CH_2Cl_2 (20 mL). The organic layer was shaken with M HCl (3 × 15 mL), followed by washing with satd $NaHCO_3$ solution (3 × 15 mL) and water (3 × 15 mL). Finally the organic layer was separated, dried (Na_2SO_4) and evaporated to syrup. The crude product was purified by flash chromatography using 2:1 *n*-hexane–EtOAc as eluent. The yields are given in Table 1.

1.1.2. *S*-Alkyl/aryl glycosides. The same experimental procedure described for *O*-glycosides (above) was followed, except that *N,N*-dimethylformamide has been used as solvent instead of MeCN.[5]

Compounds **2**,[6] **6**,[7] **8a**[8,9] and **8b**[10] are known; specific rotation and NMR data were in accord with the literature. Specific rotation, NMR and HRMS data of new compounds **4**, **11**, **13** and **15** are given below.

1.2. Methyl 4-*O*-acetyl-2-*O*-benzyl-β-L-arabinopyranoside (4)

$[\alpha]_D^{23}$ +125.1° (*c* 2.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.26 (m, 5 H, aromatic protons), 5.14 (m, 1 H, H-4), 4.73, 4.64 (2d, 2 H, C*H*$_2$Ph), 4.67 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1), 4.11 (m, 1 H, H-3), 3.75 (dd, 1 H, $J_{5a,5b}$ 12.9 Hz, H-5a), 3.71 (dd, 1 H, $J_{1,2}$, $J_{2,3}$ 9.9 Hz, H-2), 3.62 (dd, 1 H, $J_{5a,5b}$, H-5b), 3.33 (s, 3 H, O–C*H*$_3$), 2.60 (bs, 1 H, O*H*), 2.11 (s, 3 H, COC*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0 (*C*OCH$_3$), 138.1, 128.5, 128.0 (aromatic carbons), 98.2 (C-1), 76.6, 72.9, 71.3, 67.0, 60.2, 55.4 (OC*H*$_3$), 20.9 (CO*C*H$_3$). HRMS: Calcd for $C_{15}H_{24}NO_6$ (M+NH_4): 314.1598; found: *m/z* 314.1597.

1.3. *p*-Tolyl 2-*O*-acetyl-4-*O*-benzyl-1-thio-α-L-rhamnopyranoside (11)

$[\alpha]_D^{23}$ −148.1° (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.45–7.12 (m, 9 H, aromatic protons), 5.42 (dd, 1 H, $J_{1,2}$ 1.6 Hz, $J_{2,3}$ 2.8 Hz, H-2), 5.41 (d, 1 H, $J_{1,2}$, H-1), 4.93, 4.77 (2d, 2 H, *J* 11.2 Hz, C*H*$_2$Ph), 4.30 (m, 1 H, H-5), 4.12 (dd, 1 H, $J_{2,3}$, $J_{3,4}$ 9.6 Hz, H-3), 3.50 (t, 1 H, $J_{3,4}$, H-4), 3.19 (bs, 1 H, O*H*), 2.34 (s, 3 H, S–PhC*H*$_3$), 2.17 (s, 3 H, COC*H*$_3$), 1.42 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6 (*C*OCH$_3$), 137.9, 137.5, 132.0, 129.8 129.6, 128.2, 127.6 (aromatic carbons), 85.9 (C-1), 81.4, 74.9, 74.2, 70.3, 68.4, 20.8 (CO*C*H$_3$), 20.8 (S–C_6H_4–CH$_3$), 17.6 (C–*C*H$_3$). HRMS: Calcd for $C_{22}H_{30}NO_5S$ (M+NH_4): 420.1839; found: *m/z* 420.1843.

1.4. Methyl 4-*O*-acetyl-2-*O*-benzyl-1-thio-β-L-fucopyranoside (13)

$[\alpha]_D^{23}$ −11.3° (*c* 1.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.23 (m, 5 H, aromatic protons), 5.02 (d, 1 H, $J_{3,4}$ 3.2 Hz, H-4), 4.87, 4.67 (2d, 2 H, *J* 10.4 Hz, C*H*$_2$Ph), 4.27 (d, 1H, $J_{1,2}$ 9.6 H$_z$, H-1) 3.70 (dd, 1 H, $J_{2,3}$ 9.2 Hz, $J_{3,4}$, H-3), 3.51 (q, 1 H, $J_{5,6}$ 6.4 Hz, H-5), 3.44 (t, 1 H, $J_{1,2}$ 9.2 Hz, $J_{2,3}$, H-2), 3.01 (bs, 1 H, O*H*), 2.20 (s, 3 H, S–C*H*$_3$), 2.10 (s, 3 H, COC*H*$_3$), 1.11 (d, 3 H, $J_{5,6}$ 6.4 Hz, H-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2 (*C*OCH$_3$), 137.8, 128.2, 128.0, 127.7 (aromatic carbons), 84.9 (C-1), 78.1, 75.2, 73.2, 72.9, 72.7, 20.6 (CO*C*H$_3$), 16.3 (S–*C*H$_3$), 12.8 (C–*C*H$_3$). HRMS: Calcd for $C_{16}H_{26}NO_5S$ (M+NH_4): 344.1526; found: *m/z* 344.1528.

1.5. Methyl 4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (15)

$[\alpha]_D^{23}$ +21.3° (*c* 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.47–7.22 (m, 25 H, aromatic protons), 5.37 (dd, 1 H, $J_{4',5'}$ 3 Hz, H-4′), 5.15–4.27 (10d, 10 H, 5 C*H*$_2$Ph), 4.51 (d, 1 H, $J_{1',2'}$ 6.2 Hz, H-1′), 4.41 (d, 1 H, $J_{1,2}$ 6.6 Hz, H-1), 4.11 (dd, 1 H, $J_{2',3'}$ 6.4 Hz, H-3′), 3.87–3.81 (m, 3 H, H-5′, H-6′$_a$, H-6′$_b$), 3.70–3.61 (m, 2 H, H-4, H-5), 3.59–3.43 (m, 3 H, H-2, H-2′, H-3), 3.40 (m, 2 H, H-6$_a$, H-6$_b$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9 (*C*OCH$_3$), 139.1, 138.3, 138.2, 137.9, 137.8, 128.3–127.2, 102.3 (C-1′), 84.4 (C-1), 85.1, 80.2, 79.9, 76.0, 75.9, 75.3, 75.2, 73.2, 72.9, 72.5, 71.8, 69.5, 67.2, 20.5(CO*C*H$_3$), 12.3 (S–*C*H$_3$). HRMS: Calcd for

$C_{50}H_{60}NO_{11}S$ $(M+NH_4)$: 882.3882; found: *m/z* 882.3887.

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