Synthesis of C-Glycosides from S-Glycosyl Phosphorothioates

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Treatment of O-benzyl protected S-glucosyl phosphorothioates with 1,3,5-trimethoxybenzene in the presence of iodine or boron trifluoride etherate led to appropriate aryl C-betA-D-glucosides. The reaction of O-benzyl and O-acetyl-protected phosphorothioates of monosaccharides with allytrimethylsilane, using boron trifluoride etherate as activator, gave mainly or exclusively, the corresponding 3-(α-D-glycopyranosyl)-1-propenes. C-Glucosidation of furan with O-benzyl protected S-glucosyl phosphorothioate in the presence of boron trifluoride etherate afforded 2-furyl-α-C-glucoside.

Introduction

Carbon-linked glycosides, stable analogues of naturally occurring O- and N-glycosides, have become the subject of considerable interest in bioorganic and medicinal chemistry[1–5]. Several approaches to the synthesis of C-glycosides have been explored previously [2–5]. The most common method for the carbon-carbon bond formation at the anomeric center involves the coupling of carbon nucleophiles with carbohydrate-based electrophiles having diverse leaving groups e.g. lactols, lactones, anomeric esters, halides, glycosides, thioglycosides, imidates, glycals, enitols and 1,2-anhydro sugars. Furthermore, procedures employing transition metals—mediated couplings, anomeric anions and concerted reactions, such as [4+2] cycloadditions and sigmatropic rearrangement have also been used to synthesize C-glycosides. Recently, free radical chemistry has been extended to this area and to O→C-glycoside rearrangements.

Here, we present a new efficient procedure for the synthesis of C-glycosides using sugar phosphorothioates as the anomeric leaving group. In the previous papers [6,7], we have already reported the utility of S-glycosyl phosphorothioates for the efficient and rapid formation of isomeric 1,2-O-(1-cyanoethylidene)-D-glycoses and glycosyl cyanides.

Results and Discussion

The O-benzyl-protected S-α-D-glycosyl phosphorothioates (1–3) and O-acetylated S-(β-D-glycosyl)phosphorothioates (4–5), employed as electrophiles are listed in Fig. 1. The donors 1–3 were prepared from the corresponding 2,3,4,6-tetra-O-benzyl-D-glycopyranoses by Lewis acid-catalyzed reaction with ammonium salt of O,O-dialkylphosphorothioic acid [6,8], while donors 4–5 by condensation of ammonium salt of O,O-dialkylphosphorothioic acid with O-acetylated glycosyl halides [9].

Fig. 1. S-Glycosyl phosphorothioates 1–5 applied as glycosyl donors and C-glycosides formed 6, 12.
Reaction of glucosyl phosphorothioate 1 with electron rich aromatic compound such as 1,3,5-trimethoxybenzene in the presence of iodine was found to be an effective way to produce the sterically favored $\beta$-C-aryl-D-glucoside product 6 [10–13] (Figure 1), exclusively. We obtained the same expedient result in the coupling of 1,3,5-trimethoxybenzene with 1 in the presence of boron trifluoride etherate as an activator. Both reactions were performed in acetonitrile solution at room temperature for a few days with an excess (~2 equivalents) of acceptor and activator. After the usual work-up, product 6 was obtained with good yield after column chromatography.

Per-O-Benzylated and per-O-acetylated phosphorothioates 1–5 were evaluated as donors in the synthesis of C-allyl glycosides (Scheme 1). Reactions were conducted with allyltrimethylsilane in acetonitrile in the presence of boron trifluoride etherate. The amounts of the activator were adjusted according to the nature of the O-protective groups of sugar. O-Benzy protected phosphorothioates 1–3 were activated with 2 equivalents of BF$_3$·Et$_2$O and coupled with allyltrimethylsilane at room temperature to provide the corresponding 3-(O-benzyl-$\alpha$-D-glycopyranosyl)prop-1-enes 7–9 [14–20], stereoselectively. Compounds 7–9 were isolated in high yield by preparative TLC (Table 1). After successful application of O-benzylated glycosyl donors 1–3, synthesis of C-allyl glycosides from O-acetylated galactosyl 4 and glucosyl-phosphorothioate 5 was also investigated. The reaction of 4 or 5 with allyltrimethylsilane and BF$_3$·Et$_2$O (~1.5 equivalent) at room temperature did not proceed even after 10 days. Having increased the amount of BF$_3$·Et$_2$O to 10 equivalents, C-allylation with 4 and 5 occurred at room temperature, but even after several days some starting material were still present in the reaction mixture. Treatment of glycosyl donors 4 or 5 with allyltrimethylsilane and 10 equivalents of BF$_3$·Et$_2$O at 80 °C for a few hours led to 3-(O-acetylated $\alpha$- and $\beta$-glycopyranosyl)prop-1-enes 10, 11 [21–24] in 83% and 63% yield, respectively, after purification by column chromatography. A analysis of $^{13}$C NMR spectra of 10 and 11 revealed that a ~7:1 mixture of $\alpha$- and $\beta$-anomers was formed (Table 1) with preponderance of the thermodynamically more stable $\alpha$-isomer, despite the presence of the C-2-O-acetyl groups. Recrystallization of the $\alpha$/$\beta$ mixture 11 gave pure $\alpha$-anomer [21].

Table 1. Stereoselective synthesis of 3-glycopyranosyl-prop-1-enes

| Entry | Reactant | Reaction conditions | Product isolated | $\alpha/\beta$ ratio | Yield%
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<tr>
<td>1</td>
<td>1</td>
<td>4 h 20°</td>
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<td>0/1</td>
<td>84</td>
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<tr>
<td>2</td>
<td>2</td>
<td>15 min.</td>
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<td>74</td>
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<tr>
<td>3</td>
<td>3</td>
<td>20 min.</td>
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<td>0/1</td>
<td>85</td>
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<td>4</td>
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<td>3 h 80°</td>
<td>4</td>
<td>7/1</td>
<td>83</td>
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<td>5</td>
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<td>5 h 80°</td>
<td>5</td>
<td>7/1</td>
<td>63</td>
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In expanding this methodology to other C-nucleophiles, furan, a reactive electron-rich aromatic, was used as acceptor in the reaction with the glucosyl donor 1. In the presence of boron trifluoride etherate, in acetonitrile, the 2-(O-benzyl-$\alpha$-D-glycopyranosyl)furan (12) [25] (Fig. 1) was isolated in ~60% yield, after column chromatography.

In summary, the application of S-glycosyl phosphorothioates in the efficient synthesis of various C-aryl, C-allyl and C-heterocyclic glycosides has been demonstrated. Iodine was successfully employed as an activator in the conversion of S-glycosyl phosphorothioates to C-glycosylarenes, widespread in nature and having interesting physiological properties (hedamycin [26], kyanamycin.
2,4,6-Trimethoxy-1-(1'-deoxy-2',3',4',6'-tetra-O-
benzyl-β-D-glucopyranosyl) benzene (6)  
(A). To a solution of 1 (211 mg, 0.3 mmol) in 
acetonitrile (5 ml) 1,3,5-trimethoxybenzene 
(101 mg, 0.6 mmol) molecular sieves 4 Å, and sub-
limited iodine (152 mg, 0.6 mmol) were added. 
The reaction mixture was stirred for 4 d at r.t. The 
reaction mixture was diluted with CH2Cl2 (50 ml) 
and filtered through Celite. The filtrate was 

washed with Na2S2O3 (1

× 30 ml), water (1

× 20 ml), dried (MgSO4) and evaporated 
in vacuo to obtain the crude product. This product was dis-
solved with AcOEt and purified by preparative 
thin layer chromatography using benzene – Et2O 
(4:1, v/v) as the eluent.

3-(1'-Deoxy-2',3',4',6'-tetra-O-
benzyl-α-D-glucopyranosyl)prop-1-ene (7)  

To the solution of thiophosphate 1–3 (0.211 g, 0.3 mmol), in dry acetonitrile (3 ml), allyltrimeth-
ysilane (1.5 mmol, 0.24 ml) was added, then moleculer sieves 4 Å and finally BF3·Et2O 
(0.085 g, 0.08 ml, 0.6 mmol). The resulting solution 
was stirred for the time indicated in Table 1. The 
reaction mixture was diluted with CH2Cl2 (50 ml) 
and filtered through Celite. The filtrate was 

washed with satd. NaHCO3 (2 × 30 ml), water (1

× 20 ml), dried (MgSO4) and evaporated

in vacuo to obtain crude product. The oily residue was puri-
fied on silica gel column chromatography petro-
leum ether – ethyl acetate (4:1, v/v) to give 6

(0.149 g, 72%) as colourless syrup.

3-(1'-Deoxy-2',3',4',6'-tetra-O-
benzyl-α-D-glucopyranosyl)prop-1-ene (8)  

8 was obtained as colourless crystalline residue 
(0.142 g, 84.2%). M. p. 64–65 °C (after crystalliza-
tion from hexane), (lit. [16] 64–65 °C). – 13C

NMR: δ = 29.7 (C-3), 66.8, 71.0, 73.0, 73.4, 73.6, 
75.0, 75.4, 78.0, 80.0, 82.3, (pyranose-C, 4×CH2 Ph),

116.8 (C-1), 127.5–128.3 (4×Ph), 134.7 (C-2), 
138.0, 138.4, 138.7 (4 C, ipso Ph). 1H NMR: δ = 2.47 
(m, 2 H, 3-H), 3.55–3.62 (m, 8 H, 2', 3', 4', 5', 6', 6'-H), 
4.14 (m, 1 H, 1'-H), 4.44–4.95 (m, 8 H, 4×CH2 Ph), 
5.09 (m, 2 H, 1a-H, 1b-H), 5.81 (m, 1 H, 2-H), 7.01–7.31 (m, 20 H, 4×Ph). 1H NMR 
spectra are in agreement with lit. [15,16,18,19]. 13C

NMR spectra are in agreement with lit. [30].

Experimental Section

General methods

Melting points were determined with Boetius 
PHMK 05 apparatus and are uncorrected. IR 
spectra were obtained by using the Infinity MI-60 
FT-IR spectrometer. 1H, 13C and 31P NMR spectra 
were measured in CDCl3 solution on a Bruker 
DPX spectrometer operating at 250.13, 62.9 and 
101.24 MHz, respectively. The following materials 
were purchased from Aldrich Co: 1,3,5-
trimethoxybenzene, furen and boron trifluoride etherate. Preparative TLC was 
performed on 20 cm glass plates coated with 
benzene – ethyl acetate (4:1, v/v) as the eluent. 
Column chromatography was performed 
on Silica Gel 60 (E. Merck) (70–230 mesh, 
ASTM).

2,4,6-Trimethoxy-1-(1'-deoxy-2',3',4',6'-tetra-O-
benzyl-β-D-glucopyranosyl) benzene (6)

The reaction mixture was stirred for 4 d at r.t. 
The reaction mixture was diluted with CH2Cl2 (50 ml) 
and filtered through Celite. The filtrate was 

washed with satd. NaHCO3 (2 × 30 ml), water (1

× 30 ml), dried (MgSO4) and evaporated

in vacuo to obtain crude product. The oily residue was puri-
fied on silica gel column chromatography petro-
leum ether – ethyl acetate (4:1, v/v) to give 6

(0.149 g, 72%) as colourless syrup.
1 H, 2-H), 7.25–7.36 (m, 20 H, 4xPh). 1H and 13C NMR spectra are in agreement with the lit. [14].

3-(1'-Deoxy-2',3',4',6'-tetra-O-benzyl-α-D-
mannopyranosyl)prop-1-ene (9)

9 was obtained as colourless syrup (0.144 g, 85.2%). – 13C NMR: δ = 34.6 (C-3), 69.1, 71.4, 72.0, 72.2, 73.2, 73.6, 73.7, 74.8, 75.1, 76.8, (pyrano-C, 4x CH2Ph), 117.1 (C-1), 127.4–128.3 (4xPh), 134.2 (C-2), 138.2, 138.3, (4C, ipso Ph), – 1H NMR: δ = 2.40 (m, 2 H, 3-H), 3.70–3.92 (m, 6 H, 2', 3', 4', 5', 6', 6'-H), 4.11 (m, 1 H, 1'-H), 4.57–4.77 (m, 8 H, 4xCH2Ph), 5.01 (m, 2 H, 1a-H, 1b-H), 5.82 (m, 1 H, 2-H), 7.26–7.41 (m, 20 H, 4xPh).

General procedure. 3-(1'-Deoxy-2',3',4',6'-tetra-O-acetyl-D-galactopyranosyl)prop-1-ene (10, 11)

To the solution of thiophosphate 4 or 5 (0.307 g, 0.6 mmol) in acetonitrile (10 ml), allyltrimethylsilane (0.95 ml, 0.685 g, 6 mmol), molecular sieves 4 A, and finally BF3·Et2O (0.76 ml, 0.85 g, 6 mmol) in acetonitrile (10 ml), allyltrimethylsilane (0.95 ml, 0.685 g, 6 mmol), molecular sieves 4 A, and finally BF3·Et2O (0.76 ml, 0.85 g, 6 mmol) were added. The resulting solution was refluxed for 5 h (4, 5) for the times indicated in Table 1. The reaction mixture was cooled, diluted with CH2Cl2 (50 ml), filtered (Celite), and washed with CH2Cl2. The organic layer was washed with satd. NaHCO3 (2 x 30 ml) water (1 x 30 ml), and dried (MgSO4). The solvent was removed under reduced pressure, and the crude product was purified by column chromatography.

3-(1'-Deoxy-2',3',4',6'-tetra-O-acetyl-D-
galactopyranosyl)prop-1-ene (10)

Column chromatography, gradient toluene – A COEt, (1.0 – 3:1, v/v). 10 was obtained as a mixture (α/β = ~ 7:1). – IR (film): ν = 2961 (CH2), 1746 (C=O), 1643 (C=O), 1435, 1372, 1233, 1102, 1053, 984, 912 (CH3), 756, 590, 500 cm

- 13C NMR (α-anomer): δ = 20.2, 20.3, 20.4 (OA c), 30.5 (C-3), 61.1 (C-6'), 71.1 (C-1'), 67.3, 67.6, 67.8, 67.9 (C2'–C5'), 117.2 (C-1), 133.2 (C-2), 169.4, 169.5, 169.7, 170.1 (C=O); β-anomer: δ = ~ 20.0 (OA c), 35.6 (C-3) 61.3 (C-6'), 67.4, 68.8, 71.8, 73.7, 77.2 (C-1'), 117.0 (C-1), 133.0 (C-2), 169.3, 169.7, 169.9 (C=O), in agreement with the lit. [22,23]. - 1H NMR: δ = 2.08, 2.05, 2.04 (OA c), 2.29 (m, 1 H, 3'-H), 2.46 (m, 1 H, 3'-H), 4.09 (m, 2 H, 5',6'-H), 4.21 (dd, J3,2' = 7.2 Hz, J6,5' = 12.6 Hz, 1 H, 6'-H). 4.31 (ddd, J1,2' = 5.1 Hz, J1,3' = 10.5 Hz, J3,2' = 5.4 Hz, 1 H, 1'-H), 5.10–5.16 (m, 2 H, 1a-H, 1b-H), 5.22 (dd, J3,2' = 3.0 Hz, J2,3' = 9.3 Hz, 1 H, 3'-H), 5.28 (dd, J2,3' = 4.8 Hz, J2,3' = 9.3 Hz, 1 H, 2'-H), 5.42 (t, J3,4' = 3.0 Hz, J3,4' = 2.4 Hz, 1 H, 4'-H), 5.76 (m, 1 H, 2-H), in agreement with the lit. [22,23] 1H NMR spectra.

2-(1'-Deoxy-2',3',4',6'-tetra-O-benzyl-α-D-
glycero-phosphate) furan (12)

To the solution of thiophosphate 1 (0.211 g, 0.3 mmol) in dry acetonitrile (5 ml) furan (0.11 ml, 0.102 g, 1.5 mmol) was added, then molecular sieves 4 A and finally BF3·Et2O (0.11 ml, 0.128 g, 0.9 mmol). The mixture was allowed to react for 24 h at r.t. The reaction mixture was diluted with CH2Cl2 (50 ml) and filtered through Celite. The filtrate was washed with satd. NaHCO3 (2 x 30 ml), water (1 x 20 ml), dried (MgSO4) and evaporated in vacuo to obtain crude product, which was purified by column chromatography using petroleum ether – A COEt (19:1, v/v). 12 was obtained as colourless crystals (0.105 g, 59.3%). M. p. 92–3 °C, [after crystallization (hexane)], lit. [25] 92–3 °C. – 13C NMR: δ = 68.8, 70.0, 72.8, 73.2, 73.4, 75.0, 75.4, 75.6, 78.0, 79.4, 82.8 (pyrano-C, 4xCH2Ph), 110.0, 116.6 (C-3, C-4), 127.4–128.2 (4Ph), 138.1, 138.5, 138.8 (4C, ipso Ph), 142.6 (C-5), 150.7 (C-2). – 1H NMR: δ = 3.45–3.69 (m, 4
H₄, 5', 6', 6'-H), 3.88 (dd, J₁,₂ = 6.6 Hz, J₂,₃ = 9.5 Hz, 1 H, H₂-H), 4.15 (dd, J₂,₃ = 9.5 Hz, J₃,₄ = 9.2 Hz, 1 H, H₃-H), 4.94–4.36 (m, 8 H, 4×CH₂Ph), 5.05 (d, J₁,₂ = 6.6 Hz, 1 H, H₁-H), 6.28 (dd, J = 1.8 Hz, J = 3.3 Hz, 1 H, 4-H), 6.46 (d, J = 3.3 Hz, 1 H, 3-H), 7.03–7.27 (m, 20 H, 4C₆H₅), 7.36 (dd, J = 1 H, 1 H, 5-H). ¹H and ¹³C NMR are in agreement with the lit. data [25].

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