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Potential usefulness of 4-nitrophenylthio-β-D-glycosides in the chemoselective synthesis of oligosaccharides

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Abstract. Condensation of 4-nitrophenylthio D-glycosyl acceptors with ethylthio D-glycosyl donors in the presence of thiophilic promoters IDCP and NIS/TfOH, according to the "latent-active" principle proposed by Roy *et al*, did not proceed in all cases as expected. On the other hand, replacement of the ethylthio function by an *n*-pentenyloxy group shows promise for the future chemoselective assembly of oligosaccharides.

Keywords. Chemoselective glycosylation; thiophilic promoters; alkyl (aryl) thio-glycosides; *n*-pentenyl-glycosides

1. Introduction

Recently, Roy *et al* (1992) reported that the sulfur atom in a so-called "latent" 4-nitrophenylthio-α-sialoside derivative was inert, due to the presence of the electron withdrawing nitro substituent in the thioaryl moiety, toward the thiophilic promoters dimethyl (methylthio) sulfonium triflate (DMTST) (Fügedi and Garegg 1986) and N-iodosuccinimide/triflic acid (NIS/TfOH) (Konradsson *et al* 1990; Veeneman *et al* 1990). On the other hand, transformation of the nitro group into the electron-donating NH-acetyl function by reduction and subsequent acetylation gave the corresponding "active" sialoside, which could be condensed under the influence of DMTST with a suitable acceptor leading to a mixture of anomeric sialosides in a good yield.

Earlier studies from our laboratory (Veeneman and Van Boom 1990) revealed *inter alia* (table 1, entry 1) that iodonium *sym*-dicollidine perchlorate (IDCP) mediated condensation of the partially benzoylated ethylthio-β-D-glycoside 1 ("disarmed" acceptor, Mootoo *et al* 1988) with the corresponding fully benzylated ethylthio-glycoside 10 ("armed" donor, Mootoo *et al* 1988) proceeded with a high degree of chemoselectivity to provide disaccharide 15 as a mixture of anomers. On the basis of the "latent-active" concept of Roy *et al* (1992), it was anticipated that replacement of the anomeric ethylthio function in "disarmed" or "armed" acceptors by a 4-nitrophenylthio group would widen the scope of iodonium ion promoted chemoselective glycosylations.

As part of a programme (Sliedregt *et al* 1993) to study in detail the chemoselective introduction of interglycosidic linkages using 4-nitrophenylthio-β-D-glycosides as acceptors, we present here a full report on iodonium ion promoted glycosylations of the 4-nitrophenylthio-glycosides 7–8 with the ethyl(phenyl) thio-glycosides 10–12 as well as the *n*-pentenyl-glycosides 13–14.

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2. Results and discussion

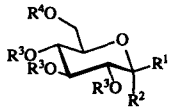
The requisite partially benzoylated and benzylated 4-nitrophenylthio acceptors 7 and 8 respectively, were readily accessible by the following procedure (Blanc-Muesser *et al* 1978; Tropper *et al* 1992).

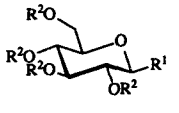
Treatment of the perbenzoylated D-gluco derivative 2 with hydrogen bromide in acetic acid gave bromide 3. Subsequent reaction of 3 with the potassium salt of 4-nitrophenylthiol for 16 h in THF afforded 4 in 63% overall yield. Zemplen debenzoylation of 4, followed by regioselective tritylation of the resulting compound 5, yielded the 6-O-trityl protected derivative 6. Benzoylation or benzylation of 6 and finally acidolysis of the dimethoxytrityl protective group of the respective fully protected intermediates furnished acceptors 7 and 8.

The results of the glycosylations of acceptors 7–8 with the ethylthio donors 10–11 are recorded in table 1. In the first experiment, the "armed" ethylthio donor 10 was coupled (entry 2) in the presence of the weak thiophilic promoter IDCP with the "more-disarmed" 4-nitrophenylthio acceptor 7. Contrary to expectation, (*cf* entry 1), a low yield of the resulting dimer 16 (anomeric mixture) was obtained. It is also apparent that the glycosylation proceeded at a much lower rate. In order to further assess the above finding, the "less-armed" acceptor 8 was condensed under identical conditions with the same donor 10. It can be seen in entry 3, that the recovery of the fully benzylated dimer 17 is even lower, but that the rate of the reaction is the same in both cases. Nonetheless, it is of interest to note that the result in entry 3 illustrates the feasibility to couple two "armed" thioglycoside species using the promoter IDCP. A similar example was also recently reported by Zegelaar-Jaarsveld *et al* (1992).

In the next stage (see entry 4), the "disarmed" ethylthio donor 11 was condensed under the influence of NIS/TfOH with the "more-disarmed" acceptor 7. In this particular case, a high yield of fully benzoylated and β-linked dimer 18 was obtained. The result in entry 4 shows for the first time that two "disarmed" thioglycosides can be condensed with a high degree of chemoselectivity. As expected, NIS/TfOH assisted condensation (entry 5) of "disarmed" 11 with the "less-armed" acceptor 8 led to a less satisfactory yield of the β-linked dimer 19.

The most striking feature of the glycosylations summarized in table 1 is the low yield of the IDCP mediated condensation of the "armed" donor 10 with the relatively

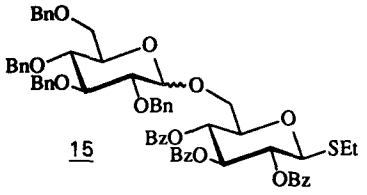
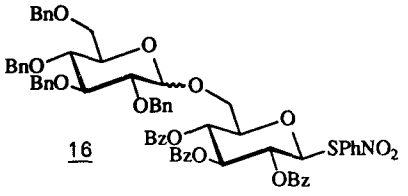
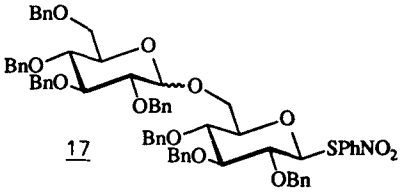
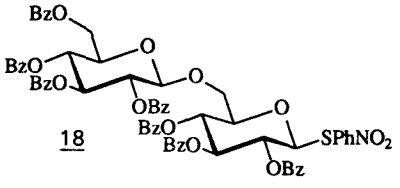
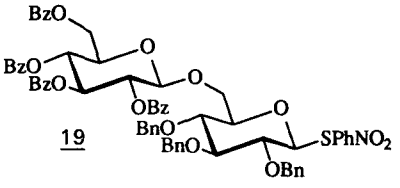


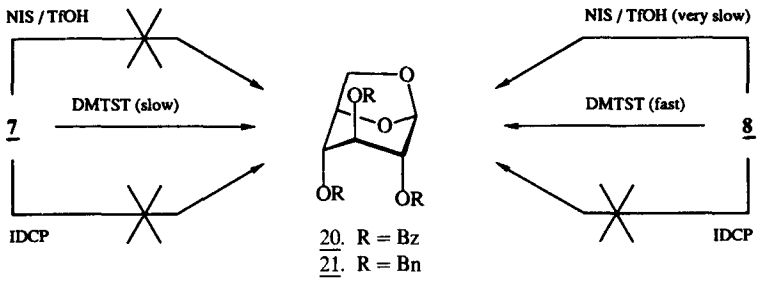


1. R^1 = SEt; R^2 = H; R^3 = Bz; R^4 = H
2. R^1 = OBz; R^2 = H; R^3 = R^4 = Bz
3. R^1 = H; R^2 = Br; R^3 = R^4 = Bz
4. R^1 = $SPhNO_2$; R^2 = H; R^3 = R^4 = Bz
5. R^1 = $SPhNO_2$; R^2 = R^3 = R^4 = H
6. R^1 = $SPhNO_2$; R^2 = R^3 = H; R^4 = DMT
7. R^1 = $SPhNO_2$; R^2 = H; R^3 = Bz; R^4 = H
8. R^1 = $SPhNO_2$; R^2 = H; R^3 = Bn; R^4 = H
9. R^1 = $SPhNO_2$; R^2 = H; R^3 = R^4 = Bn

10. R^1 = SEt; R^2 = Bn
11. R^1 = SEt; R^2 = Bz
12. R^1 = SPh; R^2 = Bz
13. R^1 = OPent; R^2 = Bn
14. R^1 = OPent; R^2 = Bz

Table 1. IDCP and NIS/TfOH promoted glycosylations of acceptors 1, 7 and 8 with ethylthio donors 10 and 11.

Entry	Donor	Acceptor	Promoter	Time	Product	Yield (α/β)
1	10	1	IDCP	1 h	 15	84% (7:1)
2	10	7	IDCP	4 h	 16	55% (4:1)
3	10	8	IDCP	4 h	 17	36% (4:1)
4	11	7	NIS TfOH	15 min	 18	88%
5	11	8	NIS TfOH	15 min	 19	47%



Scheme 1

"more-disarmed" acceptor 7 to give dimer 16 (entry 2). The low recovery of 16 may be due to concomitant cyclization of acceptor 7 into the 1,6-anhydro derivative 20 (see scheme 1). Indeed, monitoring of the glycosylation in entry 2 by TLC analysis revealed the presence of a small amount of the 1,6-anhydro sugar 20. Similar observations (i.e. formation of 21) were made in the case of the glycosylations in entries 3 and 5. Moreover, when a mixture of less reactive (Fügedi and Garegg 1986) phenylthio glycosyl donor 12 (Ferrier and Furneaux 1980) and the partially benzylated 4-nitrophenylthio acceptor 8 was treated with NIS/TfOH, the acceptor was consumed within 5 min, as evidenced by TLC analysis. Work-up and purification of the crude reaction mixture gave dimer 19 and the 1,6-anhydro derivative 21 in 23% and 44% yield, respectively.

In contrast, treatment of the individual 7 and 8 with iodonium ion promoters does not result (scheme 1) as mentioned above in the formation of the respective 1,6-anhydro sugars. Thus, treatment of 7 with either IDCP or NIS/TfOH did not lead, as gauged by TLC analysis, to any detectable amount of 20. Furthermore, the partially benzylated acceptor 8 was virtually inactive towards IDCP. However, extremely slow conversion into 21 was observed using NIS/TfOH as promoter. Surprisingly[1], DMTST mediated cyclization of 8 (see scheme 1) went to completion within 5 min to give 21 in 70% yield. As expected, partially benzoylated acceptor 7 was transformed more slowly under the same conditions into 20 (e.g. 35% of 20 was formed after 48 h).

The rapid conversion of 8 into 21 in the presence of DMTST implied that a benzylated glycoside having at C-1 a 4-nitrophenylthio group could be employed as donor in a DMTST assisted glycosylation. Indeed, condensation (table 2, entry 1) of the "less-armed" D-glycosyl donor 9 with the D-galactoside derivative 22 provided disaccharide 23 (anomeric mixture) in 75% yield (based on 22), while treatment of a mixture of 9 and acceptor 7 with DMTST afforded dimer 16 in 60% yield (entry 2).

The observed inertness of the individual acceptors 7 and 8 toward IDCP and NIS/TfOH (see scheme 1) indicates that the rapid formation of 1,6-anhydro sugars which accompanies the glycosylations recorded in table 1, and particularly so the condensation of the phenylthio glycosyl donor 12 with acceptor, 8, cannot be solely ascribed to a direct activation of the 4-nitrophenylthio acceptors by the iodonium ion promoters. A possible explanation may be that a reactive species, generated *in situ* by activation of the respective ethyl(phenyl)thio glycosyl donors by iodonium ions, may account for the conversion of the 4-nitrophenylthio-glycosides 7 and 8 into the corresponding cyclization products. In order to test this hypothesis, the anomeric ethylthio function in the benzylated and benzoylated glycosyl donors 10 and 11 was replaced by an *n*-pentenyloxy group (i.e. compounds 13 and 14). The results of the condensations of 4-nitrophenylthio acceptors 7 and 8 with the *n*-pentenyl donors 13 and 14 are presented in table 3.

It is evident from the results recorded in table 3, that replacement of the ethylthio group by an *n*-pentenyloxy function has a beneficial effect, apart from the condensation in entry 3 (*cf* entry 4 in table 1), on the glycosylation process. In addition, it was established that the glycosylations recorded in table 3 proceeded without any

[1] In this respect it is of interest to note that the reported (Roy *et al* 1992) inactivity of a 4-nitrophenylthio-α-sialoside with regard to DMTST is probably due to the presence of the additional electron-withdrawing carboxylic ester function at the anomeric centre.

Table 2. DMTST promoted glycosylations of acceptors 22 and 7 with 4-nitrophenylthio donor 9.

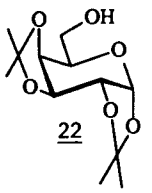
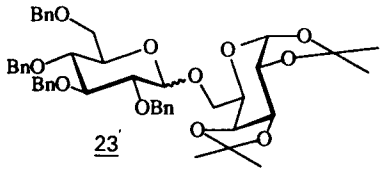
Entry	Acceptor	Time	Product	Yield (α/β)
1	 22	1 h	 23	75% (2:1)
2	7	1 h	16	60% (7:5)

Table 3. IDCP and NIS/TfOH promoted glycosylations of 4-nitrophenylthio acceptors 7 and 8s with *n*-pentenyl donors 13 and 14.

Entry	Donor	Acceptor	Promoter	Time	Product	Yield (α/β)
1	13	7	IDCP	16 h	16	76% (5:1)
2	13	8	IDCP	16 h	17	64% (5:1)
3	14	7	NIS/TfOH	15 min	18	77%
4	14	8	NIS/TfOH	5 min	19	74%

detectable cyclization of the acceptor molecules. The latter observation endorses the assumption that an undefined reactive species may be responsible for the undesired activation of 4-nitrophenylthio acceptors 7 and 8 in the iodonium ion promoted condensations with ethyl(phenyl)thio donors 10 – 12.

3. Experimental

3.1 *General procedures*

Reactions were performed at room temperature, unless stated otherwise. Pyridine was dried by refluxing with CaH_2 (5 g/l) and then distilled. Dichloromethane, 1,2-dichloroethane (DCE) and toluene were distilled from P_2O_5. DMF was stirred overnight with CaH_2, and then distilled under reduced pressure. Ether and THF were distilled from $LiAlH_4$. Methanol was dried by refluxing with magnesium methoxide and then distilled. Pyridine, dichloromethane, DCE and DMF were stored over molecular sieves 4 Å (Janssen) and methanol over molecular sieves 3 Å (Janssen). Toluene and ether were stored over sodium wire. Schleicher and Schüll DC Fertigfolien F 1550 LS 254 were used for TLC analysis. All sugar compounds were visualized by UV light (254 nm) and by charring with conc. sulfuric acid/methanol

(2:8, v/v). Sugar compounds containing 4-nitrophenyl functions were visualized by UV light (366 nm). Optical rotations were recorded with a Perkin – Elmer 241 polarimeter. Column chromatography was performed on silica gel 60, 230–400 mesh (Merck). Gelfiltration was performed on Sephadex LH-20 (Pharmacia). ^{1}H NMR spectra (200 MHz) and ^{13}C NMR spectra (50·1 MHz) were recorded with a Jeol JNM-FX 200 spectrometer. ^{1}H NMR spectra (300 MHz) were recorded with a Bruker WM-300 spectrometer. Chemical shifts (δ) are given in ppm relative to TMS as an internal standard.

3.2 *4-Nitrophenyl 2,3,4,6-tetra-O-benzoyl-1-thio-β-D-glucopyranoside* (4)

To a solution of 1,2,3,4,6-penta-O-benzoyl-β-D-glucopyranose (2) (7·0 g; 10 mmol) in dry dichloromethane (80 ml) was added a solution of hydrogen bromide in acetic acid (6·7 M, 15 ml; 0·10 mol). After stirring for 1 h, TLC analysis (dichloromethane/acetone 98:2, v/v) showed complete conversion into the bromide 3. The mixture was poured into ice-water (400 ml) and extracted with dichloromethane (300 ml). The solution in dichloromethane was washed with water (2 × 300 ml) and a cold (5°C) aq. solution of $NaHCO_3$ (1 M; 300 ml), dried ($MgSO_4$), concentrated, and coevaporated with dry toluene (2 × 50 ml).

Potassium hydride (0·60 g; 15 mmol) was dissolved in freshly distilled THF (50 ml). To this solution was added, under stirring, 4-nitrophenylthiol (2·3 g; 15 mmol). The dark red mixture was stirred for 2 h. Next, a solution of the crude glycosyl bromide in freshly distilled THF (50 ml) was added. The mixture was left stirring overnight. The mixture was taken up in ethylacetate (200 ml), washed with aq. $NaHCO_3$ (1 M; 200 ml), and water (200 ml), dried ($MgSO_4$), concentrated *in vacuo*. The crude product was purified by silica gel column chromatography, using *n*-hexane/diethylether (2:1 → 1:4, v/v) as eluent.

Yield: 4.6 g (6.3 mmol, 63%). $[\alpha]_D^{20} + 9°$ (*c* 1·0, $CHCl_3$). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 62·8 (C-6), 69·1, 70·1, 73·6, 76·3 (C-2, 3, 4, 5), 84·2 (C-1), 123·5 ($\underline{C}H_{arom}$ phenyl), 128·1–133·4 ($\underline{C}H_{arom}$), 141·6, 146·5 (2 × $\underline{C}_q$ phenyl), 164·8 165·0, 165·5, 165·6 (4 × $\underline{C}$ = O benzoyl). ^{1}H NMR ($CDCl_3$): δ 4·27–4·35 (*m*, 1 H, H-5), 4·51 (*dd*, 1 H, H-6a, J_{5-6a} 6·4 Hz, J_{6a-6b} 12·3 Hz), 4·73 (*dd*, 1 H, H-6b, J_{5-6b} 2·6 Hz), 5·20 (*d*, 1 H, H-1, J_{1-2} 10·0 Hz), 5·56 (*t*, 1 H, H-2, J_{2-3} 9·3 Hz), 5·64 (*t*, 1 H, H-4, J_{4-5} 9·7 Hz), 5·99 (*t*, 1 H, H-3, J_{3-4} 9·5 Hz), 7·23–8·08 (m, 20 H, $C\underline{H}_{arom}$).

3.3 *Nitrophenyl 1-thio-β-D-glucopyranoside* (5)

Compound 4 (3·7 g; 5·0 mmol) was taken up in a solution of potassium *t*-butoxide (0·5 g) in dry methanol (50 ml). After stirring for 6 h, TLC analysis (*n*-hexane/ethylacetate 1:1, v/v and ethylacetate/methanol 92:8, v/v) showed conversion of 4 into one product. The mixture was neutralized with acetic acid, concentrated and coevaporated with toluene (2 × 25 ml). The crude product was dissolved in methanol, and silica gel (5 g) was added. The solvent was evaporated, and the resulting powder was dried *in vacuo* for 16 h. The dry powder was applied to a column of silica gel, using ethylacetate/methanol (100:0 → 90:10, v/v) as eluent. The pure product was obtained as an oil.

Yield: 1·5 g (4·7 mmol, 94%). ^{13}C{^{1}H} NMR ($CDCl_3/CD_3OD$): δ 61·4 (C-6), 69·3, 72·0, 77·8, 79·8 (C-2, 3, 4, 5), 86·1 (C-1), 123·7, 128·7 ($\underline{C}H_{arom}$), 144·0, 145·9 ($\underline{C}_q$ phenyl).

3.4 *4-Nitrophenyl 2,3,4-tri-O-benzoyl-1-thio-β-D-glucopyranoside* (7)

Compound 5 (0·63 g; 2·0 mmol) was dissolved in dry pyridine (25 ml). To this solution was added 4,4'-dimethoxytrityl chloride (0·74 g; 2·2 mmol). After stirring for 4 h, TLC analysis (*n*-hexane/ethylacetate 1:1, v/v and ethylacetate/methanol 92:8, v/v) showed complete conversion of 5 into one product. Benzoyl chloride (0·76 ml; 6·6 mmol) was added and stirring was continued overnight. Methanol (1 ml) was added and the reaction mixture was concentrated *in vacuo*. The residue was taken up in ethylacetate (50 ml), washed with aq. $NaHCO_3$ (1 M; 50 ml), and water (50 ml), dried ($MgSO_4$) and concentrated to an oil. The crude product was dissolved in a solution of para-toluenesulfonic acid monohydrate (0·02 g/ml; 50 ml) in dichloromethane/methanol (7:3, v/v). After 5 min. TLC analysis (*n*-hexane/diethylether 1:3, v/v) revealed the formation of 7 to be complete. The mixture was taken up in dichloromethane (50 ml), washed with aq. $NaHCO_3$ (1 M; 50 ml) and water (50 ml), dried ($MgSO_4$) and concentrated. Pure 7 was obtained after silica gel column chromatography, using *n*-hexane/diethylether (3:1 → 1:3, v/v) as eluent.

Yield: 0·81 g (1·3 mmol, 64%). $[\alpha]_D^{20} + 9°$ (*c* 1·0, $CHCl_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 61·1 (C-6), 68·9, 70·2, 73·6, 79·0 (C-2,3,4,5) 84·4 (C-1), 123·7 ($\underline{C}H_{arom}$ phenyl), 128·1–133·5 ($\underline{C}H_{arom}$), 128·4 ($\underline{C}_q$ benzoyl), 142·2, 146·4 (2 × $\underline{C}_q$ phenyl), 164·8, 165·5, 165·6 (3 × $\underline{C}$=O benzoyl). ^1H NMR ($CDCl_3$): δ 3·91–3·97 (*m*, 3 H, H-5,6a,6b), 5·23 (*d*, 1 H, H-1, J_{1-2} 10·0 Hz), 5·55 (*m*, 2 H, H-2, H-4) 6·02 (*t*, 1 H, H-3, $J_{2-3} \approx J_{3-4}$ 9·5 Hz), 7·22–7·96 (*m*, 15 H, $C\underline{H}_{arom}$), 7·60 (*d*, 2 H, $C\underline{H}_{arom}$ phenyl, *J* 9·0 Hz), 8·15 (*d*, 2 H $C\underline{H}_{arom}$ phenyl).

3.5 *4-Nitrophenyl 2,3,4-tri-O-benzyl-1-thio-β-D-glucopyranoside* (8)

The product 6, obtained by treatment of 5 with 4,4'-dimethoxytrityl chloride as described above, was dissolved in dry DMF (50 ml). To this solution were added at 0°C, benzyl bromide (0·86 ml; 7·2 mmol) and sodium hydride (80%, 0·33 g; 11 mmol). After TLC analysis (*n*-hexane/diethylether 1:3, v/v) had shown complete conversion into one product, the reaction was stopped by the addition of methanol (1 ml). The mixture was taken up in diethylether (200 ml), washed with water (100 ml), aq. $NaHCO_3$ (1 M; 100 ml) and water (100 ml), dried over $MgSO_4$ and concentrated to an oil. The crude product was dissolved in a solution of para-toluenesulfonic acid monohydrate (0·02 g/ml; 50 ml) in dichloromethane/methanol (7:3, v/v). After 5 min, TLC analysis (*n*-hexane/diethylether 1:3, v/v) revealed the formation of 8 to be complete. The mixture was taken up in dichloromethane (50 ml), washed with aq. $NaHCO_3$ (1 M; 50 ml) and water (50 ml), dried ($MgSO_4$) and concentrated. Pure 8 was obtained after silica gel column chromatography, using *n*-hexane/diethylether (3:1 → 1:2, v/v)as eluent.

Yield: 0·69 g (1·2 mmol, 59%). $[\alpha]_D^{20} -7°$ (*c* 1·0, $CHCl_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 60·3(C-6), 75·0, 75·5, 75·6(3 × $\underline{C}H_2$ benzyl), 77·3, 79·9, 80·7, 85·6 (C-2,3,4,5) 86·3 (C-1), 123·9 ($\underline{C}H_{arom}$ phenyl), 126·0–128·9 ($\underline{C}H_{arom}$), 137·6, 137·9, 138·2 (3 × $\underline{C}_q$ benzyl), 144·5, 146·0 (2 × $\underline{C}_q$ phenyl). ^1H NMR ($CDCl_3$): δ 3·50–3·91 (*m*, 6 H, H-2,3,4,5,6a,6b), 4·90 (*d*, 1 H, H-1, J_{1-2} 9·8 Hz), 4·64–4·92 (*m*, 6 H, 3 × $C\underline{H}_2$ benzyl), 7·29–7·32 (*m*, 15 H, $C\underline{H}_{arom}$), 7·50 (*d*, 2 H, $C\underline{H}_{arom}$ phenyl, *J* 9·0 Hz), 8·11 (*d*, 2 H, $C\underline{H}_{arom}$ phenyl).

3.6 *4-Nitrophenyl 2,3,4-tri-O-benzoyl-6-O-(2,3,4,6-tetra-O-benzyl-α/β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (16)*

Method A: Using ethyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside (10) as donor. A mixture of 7 (72 mg; 114 μmol), 10 (80 mg; 137 μmol) and powdered molecular sieves (4 Å) in DCE/diethylether (1:5, v/v; 6·0 ml) was stirred for 1 h under nitrogen atmosphere. To this mixture was added IDCP (110 mg; 0·23 mmol). After stirring for 4 h, TLC analysis (dichloromethane/acetone 98:2, v/v) showed complete conversion of the acceptor. The mixture was filtered, taken up in ethylacetate (25 ml), and washed with aq. $Na_2S_2O_3$ (1 M; 25 ml), aq. $NaHCO_3$ (1 M; 25 ml), and water (25 ml), dried ($MgSO_4$), and concentrated to an oil. The product was purified by silica gel column chromatography, using *n*-hexane/ethylacetate (4:1 → 1:2, v/v) as eluent, followed by Sephadex LH-20 chromatography, using dichloromethane/methanol (1:1, v/v) as eluent. Yield: 72 mg (62 μmol, 55%, α/β 4:1).

Method B: Using pent-4-enyl 2,3,4,6-tetra-O-benzyl-β-D-glucopyranoside (13) as donor. A mixture of 7 (129 mg; 205 μmol) and 13 (146 mg; 240 μmol) was treated with IDCP as described in method A. The acceptor was completely converted after 16 h. The crude product was purified by silica gel column chromatography, followed by Sephadex LH-20 chromatography. Yield: 179 mg (155 μmol, 76%, α/β 5:1).

$^{13}C\{^1H\}$ NMR ($CDCl_3$): (α-isomer) δ 66·8, 68·2 (C-6, C-6'), 69·1, 70·0, 70·1, 73·8, 77·4, 80·1, 81·9 (C-2, 3, 4, 5, C-2', 3' 4', 5'), 73·1, 73·6, 74·8, 75·6 (4 × $\underline{C}H_2$ benzyl), 85·0 (C-1), 97·2 (C-1'), 123·8 ($\underline{C}H_{arom}$ phenyl) 127·4–133·5 ($\underline{C}H_{arom}$), 137·7, 138·0, 138·7 ($\underline{C}_q$ benzyl), 142·4, 146·4 (2 × $\underline{C}_q$ phenyl), 164·9, 165·5 ($\underline{C}=O$ benzoyl). (β-isomer) δ 104·0 (C-1'). ^1H NMR ($CDCl_3$): (α-isomer) δ 3·45–3·65, 3·83–4·08 (2 × *m*, 8 H, H-2, 3, 4, 6a, 6b, H-6'a, 6'b), 4·20 (*ddd*, 1 H, H-5, J_{5-6a} 7·9 Hz, J_{5-6b} 1·9 Hz), 4·38–5·61 (*m*, 8 H, 4 × $C\underline{H}_2$ benzyl), 4·67 (*d*, 1 H, H-1', J_{1-2}, 3·6 Hz), 5·12 (*d*, 1 H, H-1, J_{1-2} 10·1 Hz), 5·46 (*t*, 1 H, H-4, J_{4-5} 9·8 Hz), 5·53 (*t*, 1 H, H-2, J_{2-3} 9·5 Hz), 5·93 (*t*, 1 H, H-3, J_{3-4} 9·7 Hz), 7·01-8·10 (*m*, 39 H, $C\underline{H}_{arom}$). (β-isomer) δ 4·49 (*d*, H-1', J_{1-2}, 7·8 Hz), 5·21 (*d*, H-1, J_{1-2} 10·0 Hz).

3.7 *4-Nitrophenyl 2,3,4-tri-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl-α/β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (17)*

Method A: Using ethyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside (10) as donor. A mixture of 8 (87 mg; 148 μmol) and 10 (103 mg; 175 μmol) was treated with IDCP as described for the preparation of 16. The acceptor was completely converted after 4 h. The crude product was purified by silica gel column chromatography, using *n*-hexane/ethylacetate (4:1 → 1:1, v/v) as eluent, followed by Sephadex LH-20 chromatography. Yield: 60 mg (54 μmol, 36%, α/β 4:1).

Method B: Using pent-4-enyl 2,3,4,6-tetra-O-benzyl-β-D-glucopyranoside (13) as donor. A mixture of 8 (97 mg; 165 μmol) and 13 (122 mg; 200 μmol) was treated with IDCP as described for the preparation of 16. The acceptor was completely converted after 16 h. The crude product was purified by silica gel column chromatography, followed by Sephadex LH-20 chromatography. Yield: 117 mg (105 μmol, 64%, α/β 5:1).

$^{13}C\{^1H\}$ NMR ($CDCl_3$): (α-isomer) δ 66·3, 68·3 (C-6, C-6'), 70·1, 77·5, 78·8, 80·1, 80·7, 81·8, 86·2 (C-2, 3, 4, 5, C-2', 3', 4', 5'), 72·8, 73·3, 74·9, 75·0, 75·6, 75·7 ($\underline{C}H_2$ benzyl), 86·5 (C-1), 97·3 (C-1'), 124·0 ($\underline{C}H_{arom}$ phenyl) 127·5–129·1 ($\underline{C}H_{arom}$), 137·5, 137·8, 138·0, 138·2, 138·7 ($\underline{C}_q$ benzyl), 144·3, 146·0 ($\underline{C}_q$ phenyl). (β-isomer) δ 104·0 (C-1'). ^1H NMR

($CDCl_3$): (α-isomer) δ 3·36 (*dd*, 1 H, H-2, J_{2-3} 8·5 Hz), 3·51–3·97 (*m*, 11 H, H-3, 4, 5, 6a, 6b, H-2', 3', 4', 5', 6'a, 6'b), 4·79 (*d*, 1 H, H-1, J_{1-2} 9·8 Hz), 4·91 (*d*, 1 H, H-1', $J_{1'-2'}$ 4·0 Hz), 4·39–5·06 (*m*, 14 H, 7 × C<u>H</u>$_2$ benzyl), 7·01–7·41 (m, 35 H, C<u>H</u>$_{arom}$), 7·56 (*d*, 2 H, C<u>H</u>$_{arom}$ phenyl, *J* 9·0 Hz), 8·14 (*d*, 2 H, C<u>H</u>$_{arom}$ phenyl).

3.8 *N-iodosuccinimide/triflic acid solution (NIS/TfOH)*

N-iodosuccinimide (1·8 mol eq. based on acceptor) was taken up in DCE/ether (1:1, v/v; 2·0 ml). Triflic acid (0·2 mol eq. based on acceptor) was added under nitrogen atmosphere via syringe. The resulting solution was used immediately.

3·9 *4-Nitrophenyl 2,3,4-tri-O-benzoyl-6-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (<u>18</u>)*

<u>*Method A*</u>: Using ethyl 2,3,4,6 tetra-O-benzoyl-1-thio-β-D-glucopyranoside (<u>11</u>) as donor. A mixture of <u>7</u> (163 mg; 259 μmol) and <u>10</u> (199 mg; 311 μmol) and powdered molecular sieves (4 Å) in dry DCE (3·0 ml) was stirred for 1 h under nitrogen atmosphere. To this mixture was added the above mentioned solution of NIS/TfOH at 0°C via syringe. After 15 min, TLC analysis (dichloromethane/acetone 98:2, v/v) showed the absence of acceptor <u>7</u>. The reaction was stopped by the addition of triethylamine. The mixture was filtered, taken up in ethylacetate (25 ml), and washed with aq. $Na_2S_2O_3$ (1 M; 25 ml), aq. $NaHCO_3$ (1 M; 25 ml) and water (25 ml), dried ($MgSO_4$), and concentrated to an oil. The product was purified by silica gel column chromatography, using *n*-hexane/ethylacetate (4:1 → 1:2, v/v) as eluent, followed by Sephadex LH-20 chromatography. Yield: 278 mg (230 μmol, 88%).

<u>*Method B*</u>: Using pent-4-enyl 2,3,4,6 tetra-*O*-benzoyl-β-D-glucopyranoside (<u>14</u>) as donor. A mixture of <u>7</u> (134 mg; 213 μmol) and <u>14</u> (174 mg; 263 μmol) was treated with NIS/TfOH at 0°C as described in method A. The acceptor was completely converted after 15 min. The crude product was purified by silica gel column chromatogaphy, followed by Sephadex LH-20 chromatography. Yield: 198 mg (164 μmol, 77%).

$[\alpha]_D^{20}$ + 34° (*c* 1·1, $CHCl_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 62·3 (C-6'), 68·9 (C-6), 69·3, 69·4, 70·2, 71.7, 72·4, 72·7, 73·7, 77·8, (C-2, 3, 4, 5, C-2', 3', 4', 5',), 84·7 (C-1), 101·5 (C-1'), 123·9 (<u>C</u>H$_{arom}$ phenyl) 128·2–133·5 (<u>C</u>H$_{arom}$), 142·2, 146·6 (2 × <u>C</u>$_q$ phenyl), 164·9, 165·0, 165·2, 165·4, 165·7, 165·9 (<u>C</u> = O benzoyl). ^1H NMR ($CDCl_3$): δ 3·94 (*dd*, 1 H, H-6a, J_{6a-6b} 11·6 Hz), 4·10–4·15 (*m*, 2 H, H-6b, H-5'), 4·28 (*ddd*, 1 H, H-5, J_{5-6a} 7·5 Hz, J_{5-6b} 2·2 Hz), 4·38 (*dd*, 1 H, H-6'a, $J_{5'-6'b}$ 4·5 Hz, $J_{6'a-6'b}$ 12·3 Hz), 4·74 (*dd*, 1 H, H-6'b, $J_{5'-6'b}$ 2·9 Hz) 4·99 (*d*, 1 H, H-1', $J_{1'-2'}$ 7·9 Hz), 5·10 (*d*, 1 H, H-1, J_{1-2}, 10·0 Hz), 5·34 (*t*, 1 H, H-4, J_{4-5} 9·8 Hz), 5·47 (*t*, 1 H, H-2, J_{2-3} 9·5 Hz), 5·58 (*dd*, 1 H, H-2', $J_{2'-3'}$ 9·7 Hz), 5·72 (*t*, 1 H, H-4', $J_{4'-5'}$ 9·7 Hz), 5·91 (*t*, 1 H, H-3'. $J_{3'-4'}$ 9·7 Hz), 5·98 (*t*, 1 H, H-3, J_{3-4} 9·4 Hz), 7·18–8·12 (*m*, 39 H, C<u>H</u>$_{arom}$).

3.10 *4-Nitrophenyl 2,3,4-tri-O-benzyl-6-O-(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (<u>19</u>)*

<u>*Method A*</u>: Using ethyl 2,3,4,6 tetra-O-benzoyl-1-thio-β-D-glucopyranoside (<u>11</u>) as donor. A mixture of <u>8</u> (184 mg; 313 μmol) and <u>11</u> (270 mg; 421 μmol) was treated with NIS/TfOH at 0°C as described for the preparation of <u>18</u>. After 15 min, the acceptor

had disappeared on TLC. The crude product was purified by silica gel column chromatography, using *n*-hexane/ethylacetate (4:1 → 1:2, v/v) as eluent, followed by Sephadex LH-20 chromatography. Yield: 171 mg (147 μmol, 47%).

Method B: Using pent-4-enyl 2,3,4,6 tetra-O-benzoyl-β-D-glucopyranoside (14) as donor. A mixture of 8 (101 mg; 172 μmol) and 14 (142 mg; 214 μmol) was treated with NIS/TfOH at 0°C as described for the preparation of 18. The reaction was complete after 5 min. The crude product was purified by silica gel column chromatography, followed by Sephadex LH-20 chromatography. Yield: 149 mg (128 μmol, 74%).

Method C: Using phenyl 2,3,4,6 tetra-O-benzoyl-1-thio-β-D-glucopyranoside (12) as donor. A mixture 8 (201 mg; 342 μmol) and 12 (282 mg; 409 μmol) was treated with NIS/TfOH at 0°C as described for the preparation of 18. After 5 min, the acceptor had disappeared. The mixture was applied to silica gel column chromatography, followed by Sephadex LH-20 chromatography. Yield of 19: 91 mg (78 μmol, 23%). Yield of 21: 65 mg (150 μmol, 44%). In addition, 178 mg of donor 12 was recovered (258 μmol, 63%).

$[\alpha]_D^{20} + 4°$ (C 1·6, $CHCl_3$). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 62·8 (C-6'), 68·0 (C-6) 69·5, 71·7, 72·3, 72·7, 77·1, 78·2, 80·1, 85·7 (C-2,3,4,5,C-2',3',4',5'), 74·7, 75.3, 75·5 (3 × $\underline{C}H_2$ benzyl), 86·3 (C-1), 101·2 (C-1'), 123·9 ($\underline{C}H_{arom}$ phenyl) 127·5–133·3 ($\underline{C}H_{arom}$), 137·5, 137·7, 138·1 (3 × $\underline{C}_q$ benzyl), 143·9, 146·2 (2 × $\underline{C}_q$ phenyl), 164·9, 165·0, 165·7 ($\underline{C}$ = O benzoyl). ^1H NMR ($CDCl_3$): δ 3·46 (*dd*, 1 H, H-2, J_{2-3} 8·7 Hz), 3·49 (*t*, 1 H, H-4, J_{4-5} 8·7 Hz), 3·58 (*m*, 1 H, H-5), 3·65 (*t*, 1 H, H-3, J_{3-4} 8·8 Hz), 3·79 (*dd*, 1 H, H-6'a, $J_{5'-6'a}$ 4·7 Hz, J_{6a-6b} 11·0 Hz), 4·09 (*m*, 1 H, H-5'), 4·20 (*dd*, 1 H, H-6b, J_{5-6b} 1·7 Hz), 4·46 (*dd*, 1 H, H-6'a, $J_{5'-6'a}$ 4·8 Hz, $J_{6'a-6'b}$ 12·3 Hz), 4·41–4·84 (*m*, 7 H, 3 × $C\underline{H}_2$ benzyl, H-6'b), 4·72 (*d*, 1 H, H-1, J_{1-2} 9·8 Hz) 4·85 (*d*, 1 H, H-1', $J_{1'-2'}$, 7·8 Hz), 5·61 (*dd*, H, H-2', $J_{2'-3'}$, 9·6 Hz), 5·71 (*t*, 1 H, H-4', $J_{4'-5'}$, 9·8 Hz), 5·88 (*t*, 1 H, H-3', $J_{3'-4'}$, 9·6 Hz), 7·11–7·95 (*m*, 35 H, $C\underline{H}_{arom}$), 7·55 (*d*, 2 H, $C\underline{H}_{arom}$ phenyl, *J* 9·0 Hz), 8·13 (*d*, 2 H, $C\underline{H}_{arom}$ phenyl).

3.11 *Dimethyl(methylthio)sulfonium triflate (DMTST) stock solution (0·5 M)*

Methyl trifluoromethanesulfonate (1·1 ml; 10 mmol) was added to a solution of dimethyl disulfide (0·9 ml; 10 mmol) in dry DCE (20 ml) under a blanket of nitrogen. The mixture was stirred for 48 h. The resulting stock solution was stored under nitrogen atmosphere at −20°C.

3.12 *1,6-Anhydro-2,3,4-tri-O-benzoyl-β-D-glucopyranose (20)*

A mixture of 7 (314 mg; 499 μmol) and powdered molecular sieves (4 Å) in DCE (2·0 ml) was stirred for 1 h under nitrogen atmosphere. The stock solution of DMTST in DCE (0·5 M, 4·0 ml; 2·0 mmol) was added. After 48 h, the reaction was stopped by the addition of triethylamine. The mixture was filtered, taken up in ethylacetate (25 ml), washed with aq. $NaHCO_3$ (1 M; 25 ml) and water (25 ml), dried ($MgSO_4$), and concentrated to an oil. The product was purified by silica gel column chromatography, using *n*-hexane/ethylacetate (4:1 → 1:1, v/v) as eluent, followed by Sephadex LH-20 chromatography.

Yield: 83 mg (175 μmol, 35%). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 65·5 (C-6), 69·0, 69·7, 70·1, 73·8 (C-2,3,4,5), 99·4 (C-1), 128·3–133·6 ($\underline{C}H_{arom}$), 164·9, 165·0 (3 × $\underline{C}$ = O benzoyl).

3.13 *1,6-Anhydro-2,3,4-tri-O-benzyl-β-D-glucopyranose (21)*

Compound 8 (294 mg; 500 μmol) was treated with DMTST as described for the preparation of 20. After 5 min, TLC analysis (dichloromethane/acetone 98:2, v/v) showed full conversion of the starting compound. After work-up, the crude product was purified by silica gel column chromatography, using *n*-hexane/ethylacetate (4:1 → 1:1, v/v) as eluent, followed by Sephadex LH-20 chromatography.

Yield: 169 mg (391 μmol, 78%). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 65·2 (C-6), 71·0, 71·6, 71·8 (3 × $\underline{C}H_2$ benzyl), 74·2, 75·9, 76·0, 76·6 (C-2,3,4,5), 100·4 (C-1), 127·6–129·6 ($\underline{C}H_{arom}$), 137·7 ($\underline{C}_q$ benzyl).

3.14 *4-Nitrophenyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside (9)*

Compound 5 (0·63 g; 2·0 mmol) was dissolved in dry DMF (50 ml). To this solution were added, at 0°C, benzyl bromide (1·1 ml; 9·6 mmol) and sodium hydride (80%, 0·42 g; 14 mmol). After TLC analysis (*n*-hexane/diethylether 1:3, v/v), has shown complete conversion into one product, the reaction was stopped by the addition of methanol (1 ml). The mixture was taken up in diethylether (200 ml), washed with water (100 ml), aq. $NaHCO_3$ (1 M; 100 ml), and water (100 ml), dried over $MgSO_4$ and concentrated to an oil. The crude product was purified by silica gel column chromatography, using *n*-hexane/ethylacetate (4:1 → 1:1, v/v) as eluent.

Yield: 1·10 g (1·6 mmol, 81%). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 68·7 (C-6), 73·1, 74·7, 75·2, 75·5 (4 × $\underline{C}H_2$ benzyl), 77·4, 78·8, 80·4, 85·4 (C-2,3,4,5), 86·3 (C-1), 123·5 ($\underline{C}H_{arom}$ phenyl), 127·4–129·2 ($\underline{C}H_{arom}$), 137·4, 137·6, 137·7, 138·0 ($\underline{C}_q$ benzyl), 144·1, 145·8 ($\underline{C}_q$ phenyl).

3.15 *1,2,3,4-Di-O-isopropylidene-6-O-(2,3,4,6-tetra-O-benzyl-α/β-D-glucopyranosyl)-α-D-galactopyranose (23)*

A mixture of 1,2:3,4-di-O-isopropylidene-α-D-galactose (22) (65 mg; 250 μmol), 9 (203 mg; 299 μmol) and powdered molecular sieves (4 Å) in DCE (2·0 ml) was stirred for 1 h under nitrogen atmosphere. The stock solution of DMTST in DCE (0·5 M, 2·0 ml; 1·0 mmol) was added. After 30 min, TLC analysis (*n*-hexane/ethylacetate 1:1, v/v) indicated the absence of both donor and acceptor, the reaction was stopped by the addition of triethylamine. The mixture was filtered, taken up in ethylacetate (25 ml), washed with aq. $NaHCO_3$ (1 M; 25 ml) and water (25 ml), dried ($MgSO_4$), and concentrated to an oil. The product was purified by silica gel column chromatography, using *n*-hexane/ethylacetate (4:1 → 1:1, v/v) as eluent.

Yield: 147 mg (188 μmol, 75%, α/β 2:1). $^{13}C\{^1H\}$ NMR ($CDCl_3$): (α-isomer) δ 96·2 (C-1'), 96·9 (C-1), (β-isomer) δ 96·9 (C-1), 104·3 (C-1').

3.16 *4-Nitrophenyl 2,3,4-tri-O-benzoyl-6-O-(2,3,4,6-tetra-O-benzyl-α/β-D-glucopyranosyl-1-thio-β-D-glucopyranoside (16)*

A mixture of 7 (157 mg; 249 μmol) and 9 (200 mg; 295 μmol) was coupled under the agency of DMTST as described for the preparation of 23. After 30 min, TLC analysis showed the absence of donor 9. After work-up, the crude product was purified by silica gel column chromatography, followed by Sephadex LH-20 chromatography.

Yield: 173 mg (150 μmol, 60%, α/β 7:5).

4. Conclusions

The results presented in this paper indicate that iodonium ion mediated glycosylation of 4-nitrophenylthio-glycosides is not in complete agreement with the "latent-active" principle proposed by Roy *et al* (1992). On the other hand, iodonium ion promoted condensation of *n*-pentenyl-glycosides instead of ethyl(phenyl)thio-glycosides promises to be a valuable asset for the future assembly of oligosaccharides by the "latent-active" concept. Further, it was found that a properly protected 4-nitrophenylthio-glycoside, in contrast with the assumption of Roy *et al* (1992), may serve as donor in a DMTST assisted glycosylation (see examples in table 2).

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