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METHYL 2,3,4,6-TETRA-O-(4-METHOXYBENZYL)-1-THIO-ß-D-GLUCOPYRANOSIDE - A NOVEL REAGENT FOR α-GLYCOSYLATION TOWARDS NITROPHENYL OR BENZYL GLYCOSIDES

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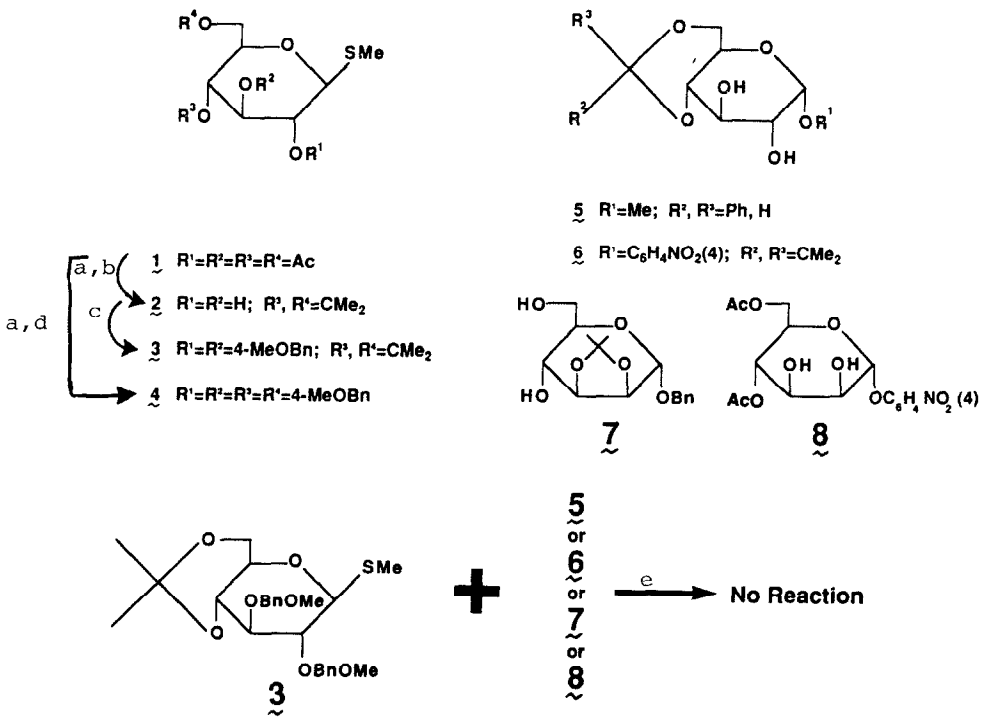
Abstract: A stereoselective synthesis of α-D-glucopyranosyl linked oligosaccharides containing an anomeric 4-nitrophenyl or benzyl group was accomplished through the use of methyl 2,3,4,6-tetra-O-(4-methoxybenzyl)-1-thio-ß-D-glucopyranoside (**4**) as a key glycosyl donor.

The envelope glycoprotein of the human immunodeficiency virus (HIV) is a surface glycoprotein which plays an important role in viral adhesion and the initiation of infection through interaction with the CD_4 glycoprotein of T-lymphocytes[1-5]. It has been reported that cultivation of the virus in the presence of inhibitors of early oligosaccharide processing (glucosidase inhibitors) of gp120 interferes with HIV infectivity[6]. Kojibiose, Glcα1→2Glc and Nigerose, Glcα1→3Glc are known to be inhibitors respectively for glucosidase I and glucosidase II[7,8]. Therefore, we have initiated a program on the synthesis of p-nitrophenyl derivatives of α-glucopyranosyl linked oligosaccharides for employment in inhibition studies. Moreover, these p-nitrophenyl glycosides will be unique chromogenic substrates for a search of new, if any, endoglycosidases[9] that are involved in the processing of these glycoproteins. In addition, these p-nitrophenyl glycosides can be employed for immunological studies after reduction of their nitro group and subsequently covalent linked to a protein.

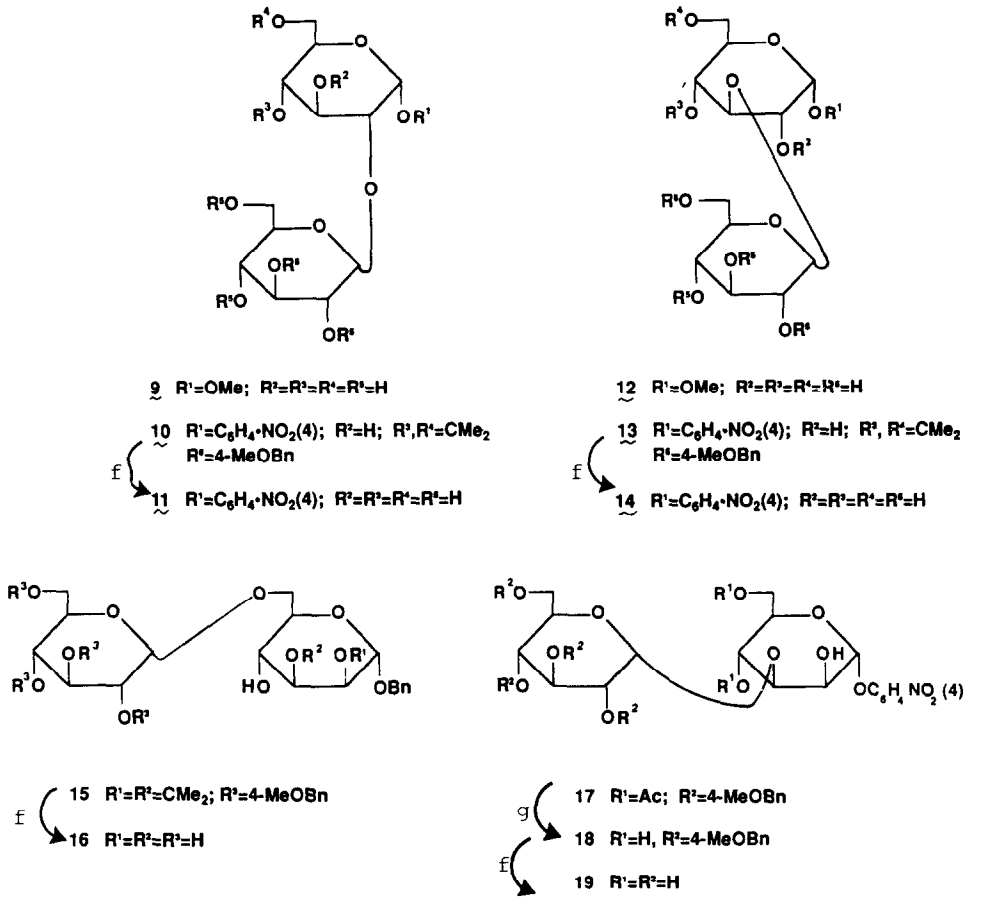
The syntheses of α-D-glucopyranosyl oligosaccharides has involved the use of fully benzylated halides, thioalkyl, trichloroacetimidate, fluoride, and xanthate derivatives[10-17] as glycosyl donors. All of these agents possess benzyl as a non-participating protecting group which necessitates hydrogenolysis for its removal. Therefore, the synthesis of oligosaccharides containing either the p-nitrophenyl or benzyl anomeric group is not practical. In our continuous effort to seek out new and more economical reaction schemes we have been successful in the development of a new glycosyl donor, methyl 2,3,4,6-tetra-O-(4-methoxybenzyl)-1-thio-ß-D-glucopyranoside (**4**) which conveniently affords our desired α-D-glucopyranosyl linked oligosaccharides.

We have already accomplished the synthesis of α-linked glycosylated oligosaccharides containing p-



Reagents: a, MeOH-MeONa; b, DMP-DMF-ptSA; c, NaH-MeOBnCl
d, KOH-MeOBnCl-Crown ether; e, $CuBr_2$-Bu_4NBr

nitrophenyl or benzyl aglycon by employing methyl 3,4-O-isopropylidene-2-O-(4-methoxybenzyl)-1-thio-ß-L-fucopyranoside[18] and methyl 3,4-O-isopropylidene-2,6-di-O-(4-methoxybenzyl)-1-thio-ß-D-galactopyranoside[19] as glycosyl donors. On the basis of these results, our initial scheme incorporated the synthesis and use of methyl 4,6-O-isopropylidene-2,3-di-O-(4-methoxybenzyl)-1-thio-ß-D-glucopyranoside (**3**). The thioglycoside **3** was prepared in three steps from methyl 2,3,4,6-tetra-O-acetyl-1-thio-ß-D-glucopyranoside[20] (**1**). Compound **1** after de-O-acetylation with methanolic sodium methoxide, was treated with 2,2-dimethoxypropane in DMF in the presence of p-toluenesulfonic acid to furnish methyl 4,6-O-isopropylidene-1-thio-ß-D-glucopyranoside **2** in 75% yield. Alkylation of **2** (NaH-DMF, 4-$MeOC_6H_4CH_2Cl$) afforded **3** in 75.3% yield. However, the crucial glycosylation of **3** with methyl 4,6-O-benzylidene-α-D-glucopyranoside (**5**), p-nitrophenyl 4,6-O-isopropylidene-α-D-glucopyranoside (**6**), benzyl 2,3-O-isopropylidene-α-D-mannopyranoside (**7**), and p-nitrophenyl 4,6-di-O-acetyl-α-D-mannopyranoside (**8**), when performed in presence of $CuBr_2$-Bu_4NBr[21] in $Cl(CH_2)_2$ Cl-DMF did not proceed toward the formation of corresponding α-linked glycosyl disaccharides. These results are in agreement with the hypothesis advanced by Fraser-Reid, which suggests that 1,3-cyclic acetals might be deactivating the



Reagents: f, $CHCl_3$-TFA-H_2O; g, MeOH-MeONa

anomeric center of a glycosyl donor **3** and cause it to behave as a disarmed donor by torsional effects[22].

We next became interested in examining the glycosylating capability of **4** which was obtained from **1** in two steps. Thus, compound **1**, after de-O-acetylation, on treatment with 4-methoxybenzyl chloride in THF in the presence of potassium hydroxide and 18-Crown-6 ether[23] gave **4** $[\alpha]_D$ + 13° (c 1.3, $CHCl_3$) in 64% yield. The glycosyl donor **4** (5.3 g, 7.7 mmol) on reaction with p-nitrophenyl 4,6-O-isopropylidene α-D-glucopyranoside (3 g, 5.9 mmol) in 5:1 (v/v) dichloroethane-N,N-dimethylformamide (120 ml) in the presence of $CuBr_2$-Bu_4NBr (11.8 mmol each) and 4A° molecular sieves (12 g) for 2 days gave the α1→3 linked disaccharide **13** (2.1 g, 43.4%) and the α1→2 linked disaccharide **10** (1.6 g, 38.1%), respectively, after silica gel column chromatography using 25-35% ethyl acetate in hexane as eluent. The removal of both protecting groups, e.g. 4-methoxybenzyl and isopropylidene, of compounds **10** and **13** was achieved in one step ($CHCl_3$-TFA-H_2O), to provide the final disaccharides Glcα1→2Glcα→OC_6H_4-p-NO_2 (**11**) and

Glcα1→3Glcα→OC_6H_4-p-NO_2 (**14**). Structural confirmation of the final products was accomplished through ^{13}C and ^1H n.m.r. spectroscopy[24]. The reaction of donor **4** with p-nitrophenyl 4,6-di-O-acetyl-α-D-mannopyranoside (**8**), resulted in the formation of the major 1→3 linked compound **18**, after de-O-acetylation (30%), and a 1→2 linked compound (5%, $[\alpha]_D$ + 78° ($CHCl_3$). A similar condensation of methyl 4,6-O-benzylidene-α-D-glucopyranoside (**5**) and benzyl 2,3-O-isopropylidene-α-D-mannopyranoside (**7**) with donor **4** afforded the α-linked D-glucopyranosyl derivatives which, after deprotection, provided methyl 2-O-α-D-glucopyranosyl-α-D-glucopyranoside (**9**; 68.5%), methyl 3-O-α-D-glucopyranosyl-α-D-glucopyranoside (**12**; 71.3%), benzyl 6-O-α-D-glucopyranosyl-α-D-mannopyranoside (**16**; 80.8%), and p-nitrophenyl 3-O-α-D-glucopyranosyl-α-D-mannopyranoside (**19**; 73.8%).

In summary, we have developed a novel glucosylating reagent which affords an efficient scheme for the synthesis of α-D-glucopyranosyl linked oligosaccharides.

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24. All products listed gave satisfactory elemental analysis. Data for compounds are given below as follows: Compound no., yield (%), values of $[\alpha]_D$ measured at 25° ± 3° for solutions in (a) $CHCl_3$ (b) H_2O. Compound **2** (75), -52° (c 1.1, a), ^{1}H-n.m.r. ($CDCl_3$): 1.43 and 1.50 (each s, 3 H, CMe), 2.20 (s, 3 H, SMe), 4.32 (d, J = 9 Hz, 1 H, H-1); Compound **3** (76), +5 (c 1.4, a), ^{1}H n.m.r. ($CDCl_3$): 1.40 and 1.47 (each s, 3 H, CMe), 2.17 (s, 3 H, SMe), 3.75 (bs, 6 H, 2 x OMe), 4.30 (d, J = 9 Hz, 1 H, H-1), 6.76 (d, J = 9 Hz, 4 H, arom.), 7.21 (d, J = 9.5 Hz, 4 H, arom.); Compound **4** (64), +13 (c 1.3, a), ^{1}H n.m.r. ($CDCl_3$): 2.17 (s, 3 H, SMe), 3.73 (bs, 12 H, 4 x OMe), 4.25 (d, J = 9 Hz, 1 H, H-1), 6.70-7.30 (m, 16 H, arom.); Compound **6** (90), +207 (c 1.0, a), ^{1}H n.m.r. ($CDCl_3$): δ 1.40 and 1.50 (each s, 3 H, CMe), 5.58 (d, J = 3 Hz, 1 H, H-1), 7.13 (d, J = 9 Hz, 2 H, arom.), 8.17 (d, J = 9 Hz, 2 H, arom.); Compound **10** (38), +80.2 (c 1.4, a), ^{1}H n.m.r. ($CDCl_3$): 1.41 and 1.48 (each s, 3 H, CMe), 3.77 (bs, 12 H, 4 x OMe), 5.53 (d, J = 3 Hz, 1 H, H-1), 6.67-7.30 (m, 18 H, arom.), 8.07 (d, J = 9 Hz, 2 H, arom.); Compound **11** (53), +182 (c 0.6, b); Compound **13** (44), +130.6 (c 1.1, a), ^{1}H n.m.r. ($CDCl_3$): 1.33 and 1.42 (each s, 3 H, CMe), 3.77 (bs, 12 H, 4 x OMe), 5.31 (d, J = 3 Hz, 1 H, H-1'), 5.53 (d, J = 3 Hz, 1 H, H-1), 6.63-7.60 (m, 18 H, arom.), 8.08 (d, J = 9 Hz, 2 H, arom.); Compound **14** (72.5), +220.2 (c 0.5, b); Compound **16** (81), +77 (c 0.2, b); Compound 18 (30), +75 (c 1.6, a), ^{1}H n.m.r. ($CDCl_3$): 3.75 (bs, 12 H, 4 x OMe), 6.70-7.30 (m, 18 H, arom.), 8.17 (d, J = 9 Hz, 2 H, arom.). Compounds **9** and **12** are known in the literature[25].
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26. This publication is Part LXXXVII of Synthetic Studies in Carbohydrates, for Part LXXXVI, see Khan, S.; Matta, K.L. Carbohydr. Res. 1992, submitted.

TABLE I ^{13}C and ^{1}H n.m.r. data[a,b] (proposed assignment)

Residue	Compound	^{13}C-n.m.r. C-1	C-2	C-3	C-4	C-5	C-6	OMe/$CH_2C_6H_5$
Glcα1→2	**9**	95.55	70.85	71.70	68.56	70.46	59.56	
Glcα-OMe		95.42	76.43	70.46	68.43	70.30	59.35	53.83
Glcα1→3	**12**	98.43	70.74	71.86	68.84	70.67	59.36	
Glcα-OMe		98.00	68.97	78.76	68.41	70.35	59.36	54.00
Glcα1→2	**11**	95.12	71.63	71.76	68.39	70.91	59.38	
Glcα-OC_6H_4-p-NO_2		93.08	73.78	70.29	68.11	70.10	59.23	
Glcα1→3	**14**	98.26	71.65	71.88	68.54	70.84	59.42	
Glcα-OC_6H_4-p-NO_2		95.76	68.66	78.55	68.43	70.71	59.01	
Glcα1→6	**16**	98.62	70.13	70.75	68.52	69.87	59.51	68.67
Manα-OBn		96.85	69.04	70.48	64.55	72.14	65.44	
Glcα1→3	**19**	99.58	71.43	71.86	68.43	70.77	59.60	
Manα-OC_6H_4-p-NO_2		96.64	68.62	77.20	64.69	72.78	59.48	

Compound	Selected ^{1}H n.m.r. Data
9	5.13 (d,J=3.7 Hz, 1H, H-1), 5.08 (d,J=3.4 Hz, 1H, H-1'), 3.50 (s, 3H, OMe)
12	5.10 (d,J=3.6 Hz, 1H, H-1), 5.06 (d,J=3.0 Hz, 1H, H-1'), 3.48 (s, 3H, OMe)
11	8.30 (d,J=9.3 Hz, 2H, arom.), 7.37 (d,J=9.5 Hz, 2H, arom.), 6.06 (d,J=3.4 Hz, 1H, H-1), 5.14 (d,J=3.9 Hz, 1H, H-1')
14	8.30 (d,J=9.3 Hz, 2H, arom.), 7.34 (d,J=9.5 Hz, 2H, arom.), 5.87 (d,J=3.7 Hz, 1H, H-1), 5.44 (d,J=3.5 Hz, 1H, H-1')
16	7.50 (bs, 5H, arom.), 5.01 (d,J=4.1 Hz, 1H, H-1)
19	8.26 (d,J-8.2 Hz, 2H, arom.), 7.30 (d,J=8.3 Hz, 2H, arom.), 5.78 (s, 1H, H-1), 5.37 (d,J=4.1 Hz, 1H, H-1')

[a]For solution in D_2O with acetone as the internal standard. [b]Aromatic carbon resonances are not shown.