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Directed, Iterative, Stereoselective Synthesis of Oligosaccharides by Use of Suitably 2-O-Substituted 2-Pyridyl 1-Thioglycopyranosides on Activation by Methyl Iodide

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Key words : Reiterative α-glycosidation; 2-pyridyl-1-thioglycopyranosides; armed-disarmed phenomena

Abstract The title synthesis is described by the proven methyl iodide activation procedure to obtain the α-linked oligosaccharides.

Introduction : Stereoselective formation of O-glycosidic linkages constitute one of the salient problems attacked by carbohydrate chemists in recent years[1]. Remarkable progress has been made and more efficient methods have been devised[1,2]. General protocol for oligosaccharide synthesis involves either a step-wise or a convergent (block) approach. Efficiency of any such method ultimately depends upon the ability to replace the anomeric substituent at the reducing end of the growing oligosaccharide chain without affecting the preformed glycosidic bonds and the protecting groups. A conceptually new glycosidation procedure termed 'armed-disarmed' phenomena has been developed by Fraser-Reid et al, from the observation that reactivity of n-pentenyl glycosides could be controlled by the substituent C-2 (OAc > OBn) when activated by iodonium sym. dicollidine perchlorate (IDCP)[3]. Since, the discovery of 'armed-disarmed' phenomena, this effect has also been observed for phenyl thioglycosides by van Boom et al[4], and for glycals by Danishfesky et al[5,6]. Now, we report that simultaneous activation of 2-O-benzyl-(**1**) and 2-O-acetyl-(**5**) substituted derivatives of 2-pyridyl 1-thioglycopyranoside with methyl iodide result in the formation of the disaccharide **7** and no self-condensation product of **5** was observed.

Results and Discussion : Earlier, we have described that 2-O-benzyl substituted 2-pyridyl 1-thioglycopyranoside donor **1** on activation by methyl iodide couples with alcohols to

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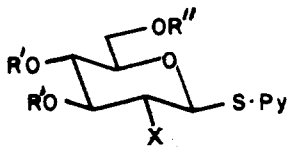
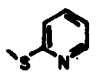
form alkyl α-glycosides[2]. However, under similar reaction conditions, reaction of the 2-O-acetyl substituted 2-pyridyl 1-thioglycopyranoside **4** with simple alcohols (CH_3OH, C_2H_5OH, 48 h) has resulted in the recovery (95%) of the starting material **4**. Hence, an evaluation of the rates of glycosidation of some 2-pyridyl 1-thioglycopyranosides **1–4** possessing commonly used C-2 protecting groups was carried out to understand their reactivity pattern.



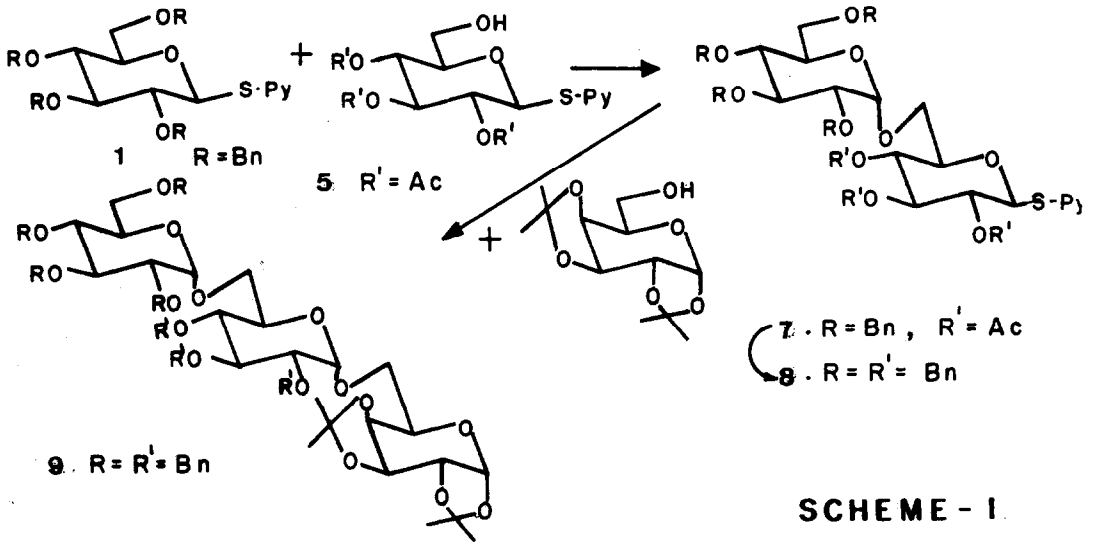
1	R', R'' = Bn,	X = OBn
2	R', R'' = Ac,	X = NHAc
3	R', R'' = Bz,	X = OBz
4	R', R'' = Ac,	X = OAc
5	R' = Ac, R'' = H,	X = OAc
6	R' = Ac, R'' = TBDMS,	X = OAc

S·Py = 

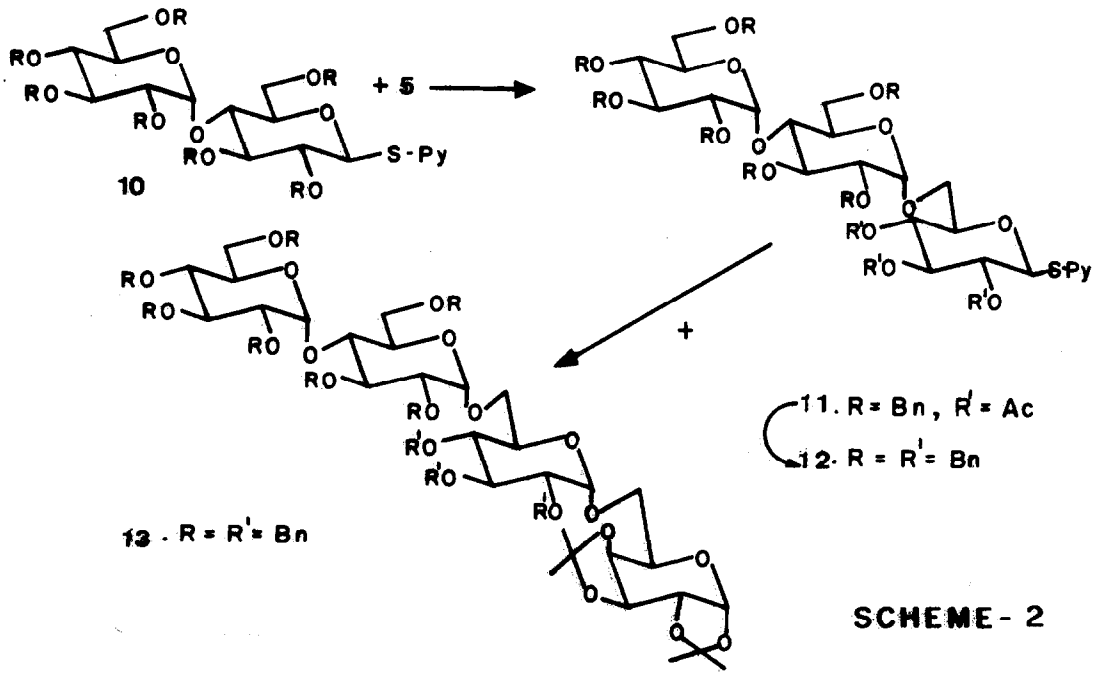
Thus, glycosidation[2] of **1–4** with equimolar amount of methanol in dichloromethane containing methyl iodide at 50°C has resulted in the isolation of the corresponding methyl 2,3,4,6-tetra-O-benzyl-α/β-D-glucopyranoside (20 h, 85% yield), methyl 2-acetamido-2-deoxy-3,4,6-tri-O-acetyl-β-D-glucopyranoside (36 h, 72%), methyl 2,3,4,6-tetra-O-benzoyl-β-D-glucopyranoside (72 h, 68%)[7] and in the recovery (72 h, 90%) of **4**. The glycosidation as well as hydrolysis rates were found to be in the order 2-O-Bn > -NHAc >-OBz >-OAc. Hydrolysis of **1–4** was affected in 1% aq. DMF containing 5% methyl iodide at 50°C (2-16 h) to obtain the corresponding reducing sugars (60-95% yield), thereby resulting in the development of a new mild hydrolysis method.

These significant differences in the rates of glycosidation of **1–4** indicated the potential of 2-pyridyl 1-thioglycosides in the development of yet another 'armed-disarmed' glycosidation methodology. The disarmed glycosyl acceptor **5** required for coupling was synthesised from **4** by sequential deacetylation, selective 6-O-silylation, acetylation and desilylation. **5** was partenered with the armed donor **1** in dichloromethane at 50°C (36 h) to obtain the α-linked disaccharide **7** in 68% yield (Scheme 1). Formation of **7** was evident from the appearance of three singlets in the ^{1}H-n.m.r. at δ 2.01, 2.03 and 2.05 for the acetyl groups, a doublet at δ 5.72 ($J_{1,2}$ = 9 Hz) for H-1 and twenty aromatic protons. The ^{13}C-n.m.r. spectrum showed C-1 and C-1' at δ 81.7 and 96.9 respectively indicating the formation of **7**. Reiterative glycosidation of **7** was possible only after the acetyl groups were replaced by benzyl groups to obtain **8**, and by further glycosidation with 1,2:3,4-di-O-isopropylidene galactose[8] to obtain the trisaccharide **9**. **9** was characterized from the ^{1}H and ^{13}C-n.m.r. data. Efficiency of this reiterative glycosidation process was also demonstrated by use of the disaccharide (armed donor) such as 2-pyridyl 2,3,6-tri-O-4-

O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-1-thio-β-D-glucopyranoside **10**[2b]. The glycoside coupling of **10** with the disarmed acceptor **5** gave the trisaccharide **11** in 64% yield. For further reiterative glycosidation **11** was deacetylated and benzylated to **12** and coupled with 1,2:3,4di-O-isopropylidene galactose to obtain the α-linked tetrasaccharide **13** in 57% yield (Scheme 2). **13** was characterised from the ^{1}H and ^{13}C-n.m.r. data.



SCHEME - 1



SCHEME - 2

Experimental : Melting points were determined in open capillaries; the values are uncorrected. Analytical thin layer chromatography (TLC) was performed on Merck pre-coated glass plates (silica gel 60, F-254, 0.25 mm thickness). Preparative column chromatography was performed on silica gel (60-120 mesh) (Acme). Optical rotations were recorded on a JASCO DIP 181 digital polarimeter. All the reactions were performed in oven dried (140°C) glassware. Dichloromethane was distilled from anhydrous P_2O_5 and stored over 4-A molecular sieves. Distilled methyl iodide was used in all the reactions.

2-Pyridyl 2,3,4-tri-O-acetyl-1-thio-β-D-glucopyranoside (5) : **4** (2.1 g, 4.75 mmol) was deacetylated with cat. $NaOCH_3$ in dry methanol (5 ml) at room temperature (2 h). The reaction mixture was carefully neutralised with IR 120 H^+ resin. The resin was filtered off and the methanolic solution was concentrated to obtain the 2-pyridyl-1-thio-β-D-glucopyranoside, which was dissolved in dry pyridine (5 ml), cooled to 0° and t-butyl dimethylsilyl chloride (0.88 g, 5.86 mmol) was added under stirring. The selective 6-O-silylation was complete in 30 min, as indicated by the appearance of a single faster moving spot (t.l.c., hexane-ethyl acetate, 1:2). To the same pot of reaction was added acetic anhydride (0.77 ml, 7.03 mmol) and stirring continued for 4 h at room temperature. The reaction mixture was poured into ice water and extracted with dichloromethane (100 ml). The organic layer was washed with water and evaporated to dryness to afford a syrup. The syrup was filtered on a bed of silica gel (hexane-ethyl acetate, 2:1) to obtain a solid which was recrystallized from dry ether to obtain **6** (2.36 g, 75% yield from **4**) as a yellowish crystalline solid,, m.p. 99-100°C, $[\alpha]_D$ +5.6° (c 1.0, $CHCl_3$). Anal. Calcd. for $C_{23}H_{35}O_8NSSi$: C, 53.76; H, 6.87; N, 2.73; S, 6.24. Found : C, 53.74; H, 6.82; N, 2.68; S, 6.19%. ^{1}H-n.m.r. (δ in ppm, J in Hz) (90 MHz) : 0.83 (s, 9H, t-BuMe$_2$Si), 2.01, 2.04 (2s, 9H, OCOCH$_3$x3), 3.70-5.60 (m, 6H, H-2,3,4,5,6,6'), 5.76 (d, 1H, $J_{1,2}$ = 10, H-1), 7.00-8.50 (m, 4H, SPy). **6** was treated with 2% p-toluene sulfonic acid in methanol (10 ml) for 1 h strictly at -5°C for affecting desilylation. The reaction mixture was then neutralized with basic ion-exchange resin (Tulsion A-36 MP). The resin was filtered off and the filtrate so obtained was concentrated to obtain a solid (90%) which was recrystallized from hexane-ether to obtain **5** as a yellowish crystalline solid, m.p. 139-141°C, $[\alpha]_D$ +13° (c 1.0, $CHCl_3$). Anal. Calcd. for $C_{17}H_{21}O_8NS$: C, 51.12; H, 5.30; N, 3.51; S, 8.01. Found : C, 51.07; H, 5.24; N, 3.48; S, 7.92%. ^{1}H-n.m.r. (δ in ppm, J in Hz) (90 MHz) : 2.01, 2.03 (2s, 9H, OCOCH$_3$x3), 3.44-3.88 (m, 3H, H-5,6,6'), 4.88-5.50 (m, 3H, H-2,3,4), 5.75 (d, 1H, $J_{1,2}$ = 10, H-1), 6.80-8.50 (m, 4H, SPy).

2-Pyridyl 2,3,4-tri-O-acetyl-6-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-1-thio-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (7) : The saccharide coupling of donor 1 (0.64 g, 1 mmol) with the acceptor **5** (0.48 g, 1.2 mmol) in dry dichloromethane (8 ml containging 3% methyl iodide) in presence of powdered molecular sieves 4A (200 mg) for 36 h was affected to obtain the disaccharide **7** (0.6 g, 66%) as a syrup after column chromatographic purification (SiO_2, hexane-ethyl acetate, 1:1), $[\alpha]_D$ + 20.2° (c 1.0, $CHCl_3$) . Anal. Calcd. for $C_{51}H_{55}NO_{13}S$: C, 66.36; H, 6.01; N, 1.51; S, 3.47. Found : C, 66.32; H, 6.03;

N, 1.49; S, 3.42%. ^{1}H-n.m.r. (δ in ppm, J in Hz) (300 MHz) : 2.01, 2.03, 2.05 (3S., 9H, $OCOCH_3$x3), 3.45-5.40 (m, 22H), 5.72 (d, 1H, $J_{1,2}$ = 9, H-1), 6.80-8.50 (m, 24H, aromatic). ^{13}C-n.m.r. (δ in ppm) (75 MHz) selected data : 20.1 (3q, $OCOCH_3$x3), 81.7 (d, C-1), 96.9 (d, C-1'), 120.0-155.0 (aromatic), 169.4, 170.4x2 (2s, $OCOCH_3$x3).

2-Pyridyl 2,3,4-tri-O-benzyl-6-O-(2,3,4,6-tetra-O-benzyl- α -D-glucopyranosyl)-1-thio- β -D-glucopyranoside (8) : 7 (0.46 g, 0.5 mmol) was deacetylated with cat. $NaOCH_3$ in methanol (5 ml) at room temperature for 1 h. The reaction mixture was carefully neutralized with dry carbon dioxide and evaporated to dryness. The resulting crude residue was benzylated using benzyl bromide (0.29 ml, 2.5 mmol), NaH (7.2 mg, 3 mmol) in dry DMF (5 ml) for 1 h at room temperature to obtain **8** (0.45 g, 85%) as a syrup after filtration on a bed of silica gel (5 g, hexane-ethyl acetate, 8/1), $[\alpha]_D$ +35.8° (c 1.0, $CHCl_3$). Anal. Calcd. for $C_{66}H_{67}NO_{10}S$: C, 74.33; H, 6.33; N, 1.31; S, 3.01. Found : C, 74.28; H, 6.29; N, 1.29; S, 2.98%. ^{1}H-n.m.r. (δ in ppm, J in Hz) (300 MHz) : 3.45-5.05 (m, 27H), 5.4 (d, 1H, $J_{1,2}$ = 9, H-1), 6.8-8.5 (m, 39 H, aromatic), ^{13}C-n.m.r. (δ in ppm) (75 MHz) selected data : 97.0 (d, C-1'), C-1 (overlapped).

O-(2,3,4,6-Tetra-O-benzyl- α -D-glucopyranosyl)-(1-6)-O-(2,3,4-tri-O -benzyl- α -D-glucopyranosyl)-(1-6)-1,2:3,4-di-O-isopropylidene-α -D-galactopyranoside (9) : The saccharide coupling of **8** (0.22 g, 0.2 mmol) with diacetone galactose[8] (0.064 g, 0.24 mmol) in CH_2Cl_2 and powdered molecular sieves at 50° for 29 h afforded **9** (0.156 g, 64%) as a syrup after column chromatographic purification (SiO_2, hexane, diethyl ether, ethyl acetate, 6:2:1), $[\alpha]_D$ +46.8° (c 1.0, $CHCl_3$), Anal. Calcd. for $C_{73}H_{82}O_{16}$: C, 72.14; H, 6.18. Found : C, 72.10; H, 6.16%. ^{1}H-n.m.r. (δ in ppm, J in Hz) (300 MHz) : 1.33, 1.37, 1.51 (merged), 1.57 (4s, 12H, O_2CMe_2x2), 3.40-5.10 (m, 34 H), 5.51 (d, 1H, $J_{1,2}$ = 5.3, H-1), 7.00-7.50 (m, 35H, aromatic); ^{13}C-n.m.r. (δ in ppm) (75 MHz) selected data : 24.6, 24.8, 26.0x2 (4q, O_2CMe_2x2), 96.2, 96.4, 97.3 (3d, C-1,1',1"), 108.1, 108.5 (2s, O_2CMe_2x2), 127.0-138.8 (aromatic).

O-(2,3,4,6-Tetra-O-benzyl- α -D-glucopyranosyl)-(1-4)-O-(2,3,6-tri-O-benzyl- α -D-glucopyranosyl)-(1-6)-2-pyridyl 2,3,4-tri-O-acetyl-1-thio-β -D-glucopyranoside (11) : The saccharide coupling of **10** (1.07 g, 1 mmol) with the acceptor **5** (0.48 g, 1.2 mmol) in CH_2Cl_2 (10 ml having 3% methyl iodide) gave (44 h) the trisaccharide **11** (0.73 g, 54%) as a colourless syrup after column chromatographic purification (SiO_2, hexane-ethyl acetate, 2:1), $[\alpha]_D$ +44.7° (c 1.0, $CHCl_3$), Anal. Calcd. for $C_{78}H_{83}NO_{18}S$: C, 69.14; H, 6.17; N, 1.03; S, 2.37. Found : C, 69.13; H, 6.14; N, 1.01; S, 2.32%. ^{1}H-n.m.r. (δ in ppm, J in Hz) (300 MHz) : 2.01, 2.04, 2.08 (3s, 9H, $OCOCH_3$x3), 3.38-5.40 (m, 33H), 5.61 (d, 1H, $J_{1",2"}$ = 3.6, H-1"), 5.67 (d, 1H, $J_{1,2}$ = 10, H-1), 6.8-8.5 (m, 39H, aromatic); ^{13}C-n.m.r. (δ in ppm) (75 MHz) selected data : 20.5 (3q, $OCOCH_3$x3), 96.6, 96.7 (2d, C-1', C-1"), 169.3, 170.1x2 (3s, $O.CO.CH_3$x3).

O-(2,3,4,6-Tetra-O-benzyl- α -D-glucopyranosyl)-(1-4)-O-(2,3,6-tri-O-benzyl- α -D-glucopyranosyl)-(1-6)-2-pyridyl 2,3,4-tri-O-benzyl-1-thio-β -D-glucopyranoside (12) : **11** (0.67 g, 0.5 mmol) was deacetylated in cat. $NaOCH_3$ in methanol (5 ml) and carefully neutralized

with IR 120 H^+ resin. The resin was filtered off and methanol removed on rotary evaporator. The resulting residue was dried perfectly on high vacuum and benzylated (BnBr, 0.29 ml, 2.5 mmol; NaH, 7.2 mg, 3 mmol) in dry DMF (4 ml) at room temperature for 2 h to obtain **12** (0.55 g, 75%) as a colourless syrup after filtration on a bed of silica gel (hexane-ethyl acetate, 2:1), $[\alpha]_D$ +43° (c 1.0, $CHCl_3$), Anal. Calcd. for $C_{93}H_{95}NO_{15}S$: C, 74.47; H, 6.38; N, 0.93; S, 2.14. Found : C, 74.41; H, 6.32; N, 0.91; S, 2.12%. ^{1}H-n.m.r. (δ in ppm, J in Hz) (300 MHz) : 3.2-5.0 (m, 36H), 5.13 (d, 1H, $J_{1',2'}$ = 3.6, H-1'), 5.37 (d, 1H, $J_{1,2}$ = 10, H-1), 5.67 (d, 1H, $J_{1'',2''}$ = 3.67, H-1''), 6.9-8.5 (m, 54H, aromatic). ^{13}C-n.m.r. (δ in ppm) (75 MHz) selected data : 96.7, 96.9 (2d, C-1,1'').

O-(2,3,4,6-Tetra-O-benzyl- α -D-glucopyranosil)-(1-4)-O-(2,3,6-tri-O-benzyl- α -D-glucopyranosyl)-(1-6)-O-(2,3,4-tri-O-benzyl- α -D-glucopyranosyl) – (1-6)-1,2:3,4-di-O-isopropylidene- α -D-galactopyranoside (13) : The saccharide coupling of **12** (0.3 g, 0.1 mmol) with diacetone galactose (0.12 g, 0.12 mmol) in CH_2Cl_2 at 50°C for 22 h provided **13** (0.19 g, 57%) as a syrup after purification by colum chromatography (SiO_2, hexane-ethyl acetate, 4:1), $[\alpha]_D$ +26° (c 1.0, $CHCl_3$), Anal. Calcd. for $C_{100}H_{110}O_{21}$: C, 72.85; H, 6.73. Found : C, 72.81; H, 6.71%. ^{1}H-n.m.r. (δ in ppm, J in Hz) (300 MHz) : 1.27, 1.33, 1.45, 1.55 (4s, 12H, $O_2C\underline{Me}_2$x2), 3.38-5.00 (m, 44H), 5.13 (d, 1H, $J_{1'',2''}$ = 3.6, H-1''), 5.56 (d, 1H, $J_{1''',2'''}$ = 4, H-1'''), 5.67 (d, 1H, $J_{1,2}$ = 6, H-1), 5.7 (d, 1H, $J_{1',2'}$ = 3.6, H-1'), 7.15-7.45 (m, 50H, aromatic). ^{13}C-n.m.r. (δ in ppm) (75 MHz) selected data : 24.5, 24.8, 25.9x2 (4q, $O_2C\underline{Me}_2$x2), 96.8 (d, C-1), 96.2, 96.3, 96.4 (3d, C-1',1'',1'''), 126.7-128.2 (aromatic).

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