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STEREOSELECTIVE SYNTHESIS OF α-LINKED SACCHARIDES BY USE OF PER O-BENZYLATED 2-PYRIDYL 1-THIO HEXOPYRANOSIDES AS GLYCOSYL DONORS AND METHYL IODIDE AS AN ACTIVATOR

Hari Babu Mereyala* and G Venugopal Reddy
National Chemical Laboratory, Poona 411 008, India

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Abstract A new, practical, stereoselective glycosidation methodology is described where per O-benzylated 2-pyridyl 1-thio-α/β-hexopyranosyl donors of D-gluco- (**1**), D-galacto- (**2**), D-manno- (**3**) and L-rhamno- (**4**) configurations have been efficiently coupled with diverse sugar alcohols (**6,8-11**) on activation by methyl iodide to obtain the α-linked disaccharides (**7,12-19**). Coupling of donor **1** with the disaccharide acceptor **20** and the disaccharide donor **5** with **8** to obtain α-linked trisaccharides **21** and **22** is also described. A possible mechanism for the α-selectivity is also discussed.

Introduction : Stereoselective synthesis of α-linked oligosaccharides (1,2-cis, D-gluco-, D-galacto-) is of paramount importance as they are constituents of many biologically active glycoconjugates.[1] As a consequence much effort is currently directed to the efficient and stereocontrolled synthesis of such saccharides[2]. In presence of a C-2 participating group the resulting glycoside is 1,2-trans; however a non-participating group at C-2 gives predominantly 1,2-cis glycosides[3]. Amongst the most satisfactory methods developed so far the 'in-situ' anomerisation (of per O-benzylated α-glycosylbromide) procedure of Lemieux et al., has gained practical utility[2a-c]. Various other methods involving use of β -N-methylacetimidolyl-[2d], n-pentenyl-[2i,j], β-thiocyano-[2k], α-fluoro-[2g,h], alkyl-[4a-c], aryl-[2f,4d-f], and heteroaryl thioglycosyl[4g-j] donors to achieve α-selectivity have also been described[5]. Earlier, activation of various thioglycopyranosyl donors by N-bromosuccinimide[2e], bromine[1d], thiophilic metal salts[1d,4g], strong methylating agents such as methyl triflate[6] and dimethyl (methylthio-) sulfonium triflate (DMTST)[7] has resulted in the formation of saccharides with not so good α-selectivity. In spite of these developments the existing methods leave a considerable margin for improvement in terms of i) formation of unstable per O-benzylated glycosyl halides, ii) acidic/basic reaction media, iii) use

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* Present address : Indian Institute of Chemical Technology, Hyderabad 500 007, India

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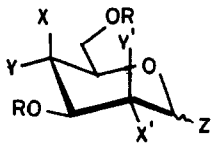
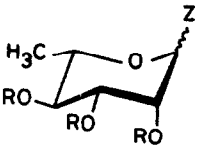
of toxic reagents, iv) critical preparation of anomerically pure glycosyl donors and v) diastereoselectivity. A new practical α-glycosidation methodology has been developed by use of per O-benzylated 2-pyridyl 1-thio hexopyranosides as donors and methyl iodide as an activator[8].

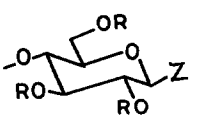
Results and Dicussion : Per O-benzylated 2-pyridyl 1-thio- α/β -D-gluco- (**1**) and -D-galacto- (**2**) and -D-manno- (**3**) pyranoside donors were prepared in good yield from the corresponding 2,3,4,6-tetra-O-benzyl-hexopyranosides on reaction with 2,2'-dipyridyl disulfide/nBu_3P. 2-Pyridyl 2,3,4-tri-O-benzyl 1-thio-α /β -L-rhamnopyranoside (**4**) and 2-pyridyl heptabenzyl 1-thio- β-D-maltoside (**5**) were prepared by deacetylation and benzylation of the corresponding per O-acetylated derivatives **4a** and **5a** respectively. **4a** and **5a** were themselves derived from the reaction of α-acetobromorhamnose[9] and α-acetobromomaltose[9] with 2-mercaptopyridine.





4, 4a

1	R = Bn; X, Y' = H; X', Y = OBn	b)	Z = OCH_3
1 a	R = Ac; X, Y' = H; X', Y = OAc	c)	Z = OiPr
2	R = Bn; Y, Y' = H; X, X' = OBn	d)	Z = Ot-Bu
2 a	R = Ac; Y, Y' = H; X, X' = OAc	e)	Z = OH
3	R = Bn; X, X' = H; Y, Y' = OBn		Z = 2-S.Py
4	R = Bn		
4 a	R = Ac		
5	R = Bn; X, Y' = H; X ' = OBn	Y =	
5 a	R = Ac; X, Y' = H; X' = OAc		



1 and **2** have been activated by several alkylating agents and coupled with simple alcohols to obtain the α-linked alkyl glycosides **1b-d** and **2b-d** respectively. Reaction conditions for the development of the new glycosideation method were established based on the study of a) role of activator, b) effect of solvent, c) rate of reaction of pri., sec. and tert. alcohols and d) temperature. a) role of activator : Glycosyl donor **1** was reacted in dichloromethane at 50°C with equimolar amount of methanol and was activated by 3 mole equivalents of several alkylating agents such as methyl iodide, n-butyl iodide, n-butyl bromide and methyl triflate to obtain methyl 2,3,4,6-tetra-O-benzyl-D-glucopyranoside (**1b**) (Table 1). Anomeric ratio of **1b-d** and **2b-d** was determined by ^{1}H-n.m.r and HPLC. Methyl iodide was found to be the ideal activator in terms of rate of reaction and diastereoselectivity. Large excess of methyl iodide also has been used in these reactions without affecting the yields. Use of stronger alkylating agents such as methyl

triflate resulted in decomposition giving **1b** in lower yields (entry iv). b) effect of solvent: Glycosidation of **1** with methanol was carried out in various solvents such benzene, dichloromethane, chloroform, N,N-dimethylformamide and tetrahydrofuran using methyl iodide (3 mole equivalents) as an activator (Table 2). Dichloromethane was found to be the suitable solvent in terms of good solubility, yields and stereoselectivity (entry ii). Use of DMF and THF resulted in the isolation of hydrolysis product **1e** along with **1b** due to adventitious water present in the solvent (entry iv, v). Solvent effect on the stereochemical outcome of the reaction was studied by use of t-butanol (1 mole equivalent) as an acceptor as it closely represents the reactivity of a sugar alcohol to obtain t-butyl 2,3,4,6-tetra-O-benzyl-D-glucopyranoside (**1d**) (Table 2). Anomeric ratio (α/β) of **1d** was over 8 in benzene and dichloromethane while 6 in DMF and THF. c) rate of glycosidation of primary, secondary and tert-alcohols : Methanol, isopropyl alcohol and tert-butyl alcohol (equimolar) were severally reacted with **1** in CH_2Cl_2 at 50°C to obtain the corresponding alkyl glycosides **1b-d** and the reactivity of alcohols was found in the order MeOH, iPrOH, tBuOH (Table 3). A similar reactivity was observed for glycosidation of **2** to obtain the alkyl galactosides **2b-d**. α-Diastereoselectivity was higher for the galactosides **2b-d** compared to the glucosides **1b-d**.

Table 1 Glycosidation of **1** with MeOH (1 mole equivalent) by Use of Various Alkylating Agents (CH_2Cl_2 at 50°C)

Entry	Activator (3 mole equivalents)	Time (h)	% yield **1b** (α/β)
i	MeI	22	95 (6/1)
ii	nBuI	72	30 (6/1) 55% of **1** recovered
iii	nBuBr	72	No reaction, 95% of **1** recovered
iv	MeOTf	24 at 25°C	20 (4/1) decomposition

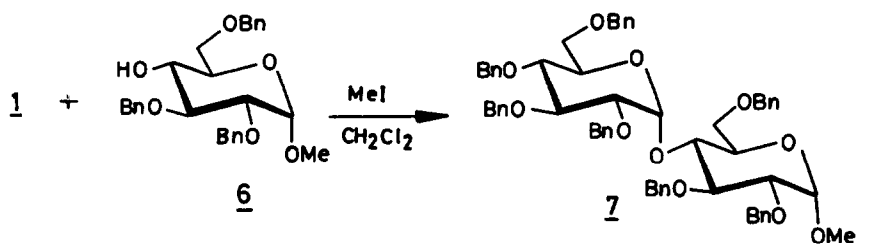
Table 2 Effect of Solvent in Glycosidation of **1** (0.25 M) with t-BuOH (equimolar) (MeI, 3 mole equivalents)

Entry	Solvent	Time (h)/Temp 0°C	% Yield **1d** (α/β)
i	C_6H_6	48 / 80	80, (85/15)
ii	CH_2Cl_2	48 / 50	82, (89/11)
iii	$CHCl_3$	48 / 70	65, (80/20)
iv	DMF	34 / 25	15, (65/35) and 40% of **1e**
v	THF	36 / 70	25, (70/30) and 45% of **1e**

Table 3 Rate of Glycosidation of **1** and **2** with Various Alcohols (1 mole equivalent) in CH_2Cl_2 at 50°C having 3 mole equivalents of Methyl Iodide

Entry	Glycosyl donor	Alcohol	Time (h)	Product	% yield (α/β)
i	1	MeOH	22	**1b**	95 (65/35)
ii	1	iPrOH	34	**1c**	85 (82/18)
iii	1	tBuOH	48	**1d**	82 (89/11)
iv	2	MeOH	23	**2b**	96 (72/28)
v	2	iPrOH	36	**2c**	87 (87/13)
vi	2	tBuOH	48	**2d**	80 (91/9)

After establishing the optimum reaction conditions for glycosidation, stage is now set for application of this methodology for the synthesis of oligosaccharides. Methyl 2,3,6-tri-O-benzyl-α-D-glucopyranoside (**6**)[10] which has earlier been reported[2d] to resist glycosidation under halide-ion catalysed glycosidations was chosen as the glycosyl acceptor and was reacted with **1** in dichloromethane at 50°C (having 3% methyl iodide) and 4A molecular sieves to afford (62h) the α-linked disaccharide **7** in good yield (82%) (Scheme-1).

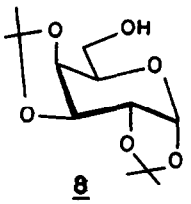


Scheme 1

Synthesis of various α-linked di- and trisaccharides was also carried out by this method. Thus donors **1** and **2** were severally coupled with the glycosyl acceptors such as 1,2:3,4-di-O-isopropylidene-α-D-galactopyranoside (**8**) and 1,2:5,6-di-O-isopropylidene-α-D-glucofuranoside (**9**) to obtain the corresponding α-linked disaccharides **12-15** respectively, coupling of **2** with 1,2:5,6-di-O-isopropylidene-α-D-galactofuranoside (**10**) gave **16**; similarly coupling of the glycosyl donor **3** with **8** gave the α-linked disaccharide **17**. Lower yields of furanosaccharides (**13 ,15,16**) (56-67%) compared to the pyranosaccharides (72-87%) (**12,14,17-19**) is due to their decomposition during silica gel chromatography. Coupling of 2-pyridyl 1-thio rhamnopyranosyl donor (**4**) with **8** and **11** gave the corresponding α-linked

(1,2-trans) disaccharides **19** and **21** respectively. Thus, D-manno- (**3**) and L-rhamno- (**4**) donors lead to the formation of 1,2-trans disaccharides **17-19**, which are also the products arising from neighbouring group assisted glycosidation procedure. Formation of α-glycosidic linkage was based on the relative chemical shifts in ^{1}H and ^{13}C-n.m.r spectra and positive specific rotations and finally by comparison of such data with the reported values (Table-4). Use of anomerically pure **1** and **2** in these reactions did not alter the stereoselectivity or yield of products.

Synthesis of α-linked trisaccharides : The efficacy of this methodology was also demonstrated by the synthesis of α-linked trisaccharide derivative of Panose (**21**)[12]. The glycosyl donor (**1**) was coupled with the acceptor **20**[12] to obtain the trisaccharide **21** as a crystalline solid. Physical characteristics of **21** are in agreement with the reported data (Table-4). The genarality of this method was also illustrated by coupling the disaccharide donor (**5**) with **8** to obtain the α-linked trisaccharide **22** in good yield. Formation of α-linkage was evident from its spectral data.



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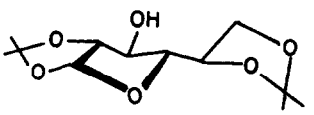

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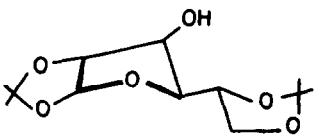

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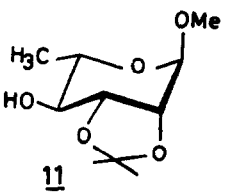

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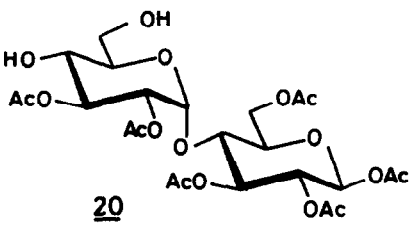

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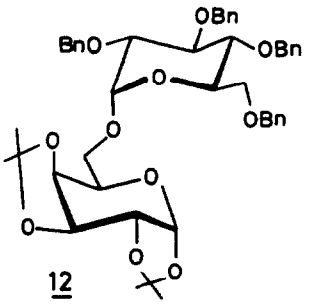
Mechanism : Electrophilic activation of 2-pyridyl 1-thioglycoside Iα by methyl iodide leads to the formation of N-methyl quaternary thiopyridinium glycoside **23** which by resonance stabilizes to form the sulfenium salt **24** (Scheme-2). **24** loses the acidic anomeric proton to form the carbanion **25** which could be represented by **25a** where the lone pair of electrons on the anomeric carbon align antiperiplanar to the oxygen lone pair[13e,f]. **25a** can further stabilize to form **26**. Protonation of either **25a** or **26** leads preferentially to the formation of β-glycoside sulfenium salt **27** due to its stabilization by reverse anomeric effect[13]. **27** undergoes a fast S_N2 nucleophilic displacement to give α-linked glycoside (**28**). N-Methyl 2-thiopyridone (**29**)[14] and its salt **30**[14] were isolated during these reactions indicating the neutralization of the hydroiodic acid liberated. Alternatively α-glycosides may also result via the classical glycosyl cation/ion pair mechanism[1].



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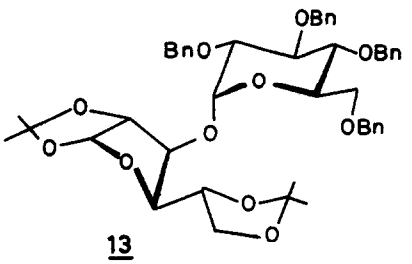

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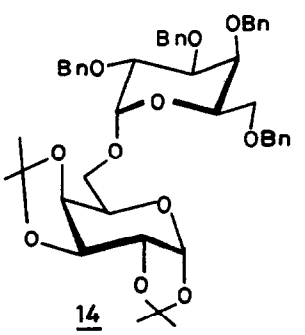

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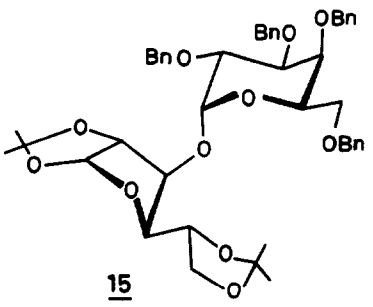

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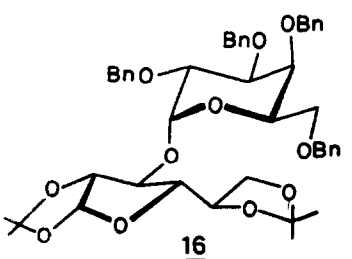

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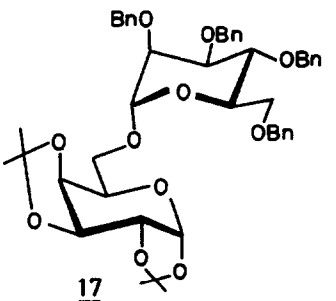

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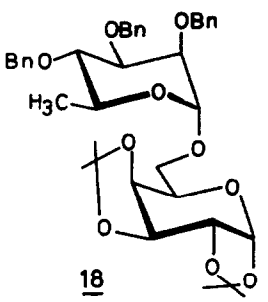

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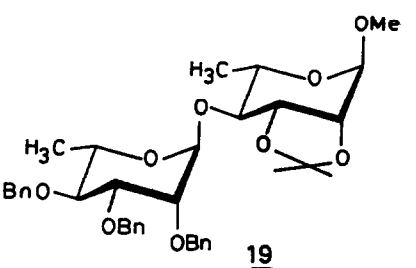

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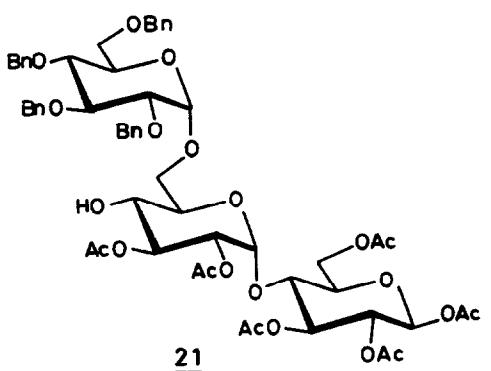

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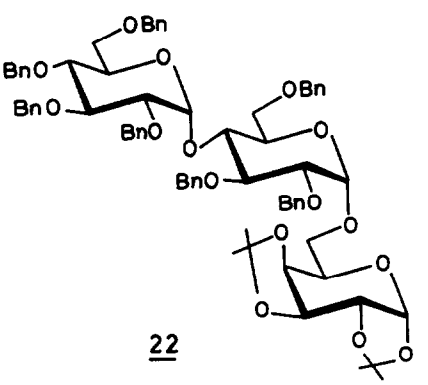

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Scheme 1

MECHANISM FOR α- GLYCOSIDATIONS

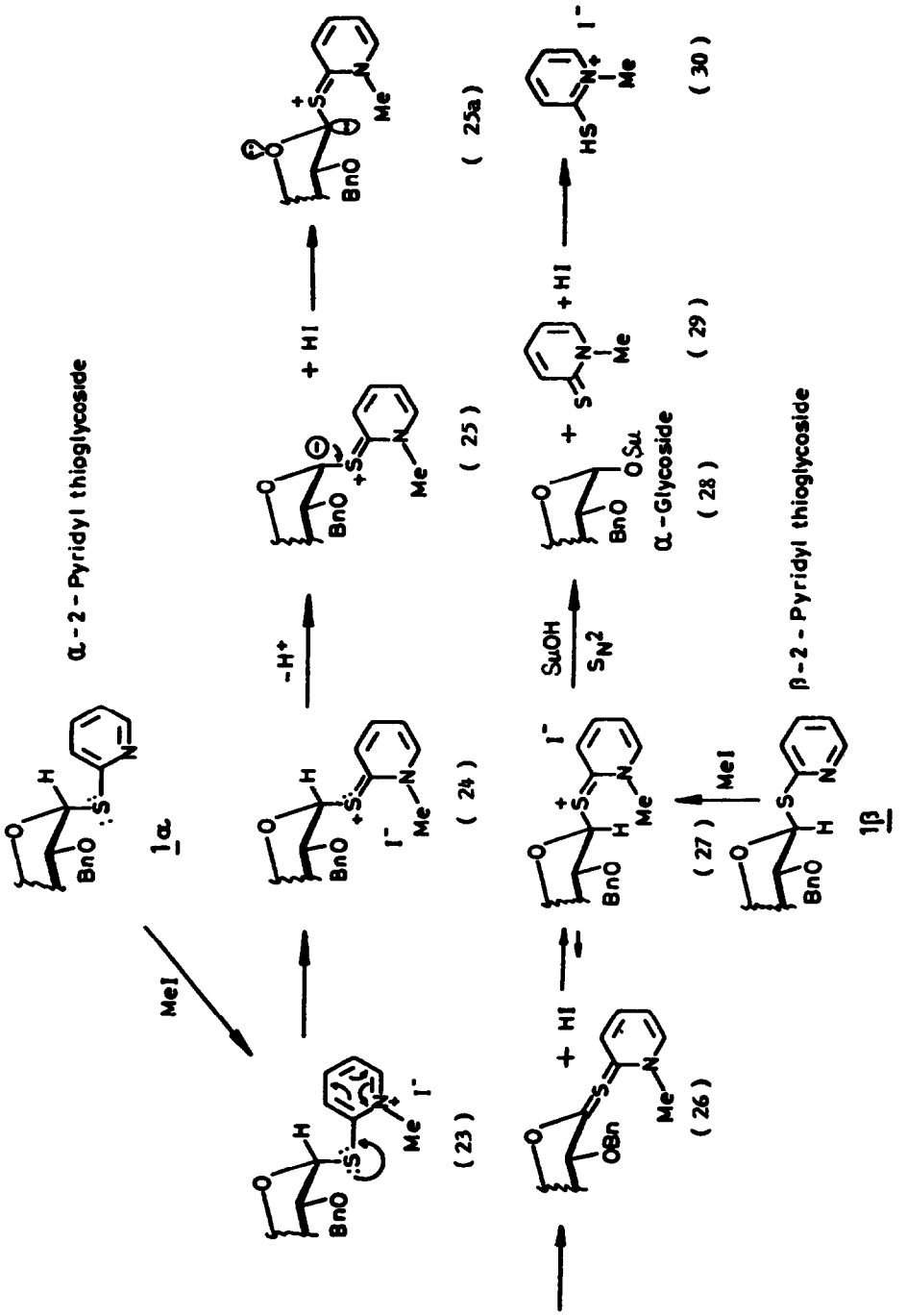

Table 4 : Physical Data of α-Linked Saccharides

Entry	Saccha-ride	Reaction time (h)	% yield	m.p. °C	Selected n.m.r data ^1H, δ ppm, (J in Hz) H-1	H-1'/-1"	^{13}C, δ ppm C-1	C-1'/-1"	[α] Deg $CHCl_3$ observed	lit.	Ref.
i	7	62	82	syrup	5.65(4)	a	96.5	97.6	+48 e,f	+48	2d
ii	12	72	87	syrup	5.48(5)	a	96.5	97.2	+10 g,h	+10.1	2a
iii	13	72	56	91[b]	5.86(4)	5.24(4)/	104.9	97.7	+46 g,h	+46	2a
iv	14	48	81	syrup	5.48(5)	a	96.2	97.5	+51 i,j	+2	9
v	15	72	62	syrup	5.72(4)	5.28(4)/	105.2	98.9	+32.7 k,l	+33	2d
vi	16	72	67	120	5.80(4)	a	-	-	+37 m,n	+36.8	2a
vii	17	55	60	syrup	5.47(4.5)	a	-	-	+39 e,n	-	-
viii	18	48	78	syrup	5.32(4.5)	a	96.4	98.3	-47 e,f	-	-
ix	19	48	72	syrup	5.35(brs)	5.28(brs)/	97.6	98.4	-23.9 e,f	-	-
x	21	48	62	151[d]	5.71(8)	a	91.6	96.3/98.2	+51.3 e,n	+53	10
xi	22	52	65	syrup	5.67(3.6)	a/5.5(4)	96.2	96.2/96.1	+25.2 e,n	-	-

a - signal burried; b - lit. m.p. 90-91°C; c - lit. m.p. 120-121°C; d - lit. m.p. 152-153°C; e - c 1.0; f - 27°C;
g - c 2.0; h - 24°C; i - c 0.9; j - 22°C; k - c 1.1; l - 20°C; m - c 0.8; n - 25°C

These overall transformations involve conversion of the α/β donor (1) to the more reactive β-donor (onium salt) **27** and the driving force for such transformation is derived through the formation of stable intermediates **25a** and **27**. In summary, the thermodynamically more stable axially linked O-glycosides are the products of methyl iodide activation method of 2-pyridyl 1-thioglycopyranosides.

Experimental

Melting points were determined in open capillaries and are uncorrected. ^{1}H-n.m.r (90 MHz, 300 MHz) and ^{13}C-n.m.r (22.63 MHz, 75 MHz) spectra were recorded on Bruker WH-90 or Varian MSL 300 instruments in $CDCl_3$ using TMS as internal standard. Optical rotations were recorded on a JASCO DIP181 digital polarimeter using sodium vapour lamp. HPLC was performed on HP 3330A Waters Associates, M 440 absorbance detector using acetonitrile/water (70/30) as eluant with a flow rate of 2 ml/min using RCM C-18 column. Column chromatography was performed on silica gel (60-120 mesh) (Acme). T.l.c was performed on silica gel G (acme) with detection by spraying a solution of 2% phosphomolybdic acid and 1% $Ce_2SO_4.4H_2O$ in 20% H_2SO_4 and heating to ca. 140°C. All the reactions were carried out with anhydrous solvents. Distilled methyl iodide was used in all the reactions.

General Procedures

Synthesis of per O-acetylated 2-pyridyl-1-thio-β-D-hexopyranoside : To a solution of 2-mercaptopyridine (0.12 mole) in dry acetone (200 ml) was added anhydrous K_2CO_3 (0.12 mole) and stirred at 40°C for 30 min. Then α-acetobromohexose (0.1 mole) dissolved in dry toluene (150 ml) was added and stirred for 2 h. The reaction mixture was diluted with toluene (150 ml), organic phase was washed with water, 1% aq.KOH, water, dried (anhyd.Na_2SO_4) and the solvent was removed on rotary evaporator to yield the per O-acetylated 2-pyridyl-1-thio-β-D-hexopyranosides in 85-95% yields.

Synthesis of per O-benzylated 2-pyridyl-1-thio-β-D-hexopyranoside : Method A : Per O-acetylated 2-pyridyl-1-thio-β-D-hexopyranoside (5 mmol) was deacetylated in dry methanol (15 ml) containing catalytic amount of sodium methoxide (50 mg, Na metal in 5 ml methanol) at room temperature for 2 h and then carefully neutralized with IR 120 H^+ resin. The resin was filtered off and solvent removed to obtain a syrupy deacetylated 2-pyridyl-1-thio-β-D-hexopyranoside in quantitative yield. It was dried at 60°C (2 h) in high vacuum, dissolved in dry DMF (5 ml) and added to hexane washed NaH (25 mmol) in DMF (5 ml) at 0°C, stirred for 30 min and benzyl bromide (24 mmol) was added slowly to the reaction mixture and the reaction was brought to room temperature gradually (1 h). When the t.l.c indicated completion of the reaction (1 h) excess of NaH was decomposed by addition of methanol (1 ml), it was diluted with water (200 ml) and extracted into CH_2Cl_2 (100 ml). The organic phase was washed with water, dried (anhy. Na_2SO_4) and evaporated to

yield a syrup which was purified by filtration on a bed of silica gel (60-120 mesh, hexane/ethyl acetate 10/1) to yield (80-87%) the per O-benzylated 2-pyridyl-1-thio-β-D-hexopyranoside.

Method B : To a solution of 2,3,4,6-tetra-O-benzyl hexopyranoside (2 mmol) in dry CH_2Cl_2 (10 ml) at room temperature was added 2,2'-dithiodipyridine (2.2 mmol), followed by nBu_3P (2.2 mmol) under nitrogen atmosphere. When the t.l.c indicated completion of the reaction (30 min) it was concentrated to 3 ml and was column chromatographed (SiO_2, hexane/ethyl acetate, 8/1.5) to obtain anomeric mixture of per O-benzylated 2-pyridyl-1-thio-α/β-D-hexopyranoside in 85-90% yield.

A typical experimental procedure for glycosidations : In an oven dried round bottom flask was taken per O-benzylated 2-pyridyl-1-thio-α/β-D-hexopyranoside (1 mmol) in dry CH_2Cl_2 (4 ml) (0.25 M) having 3% methyl iodide and reacted with the alcohol (1 mmol) in presence of powdered molecular sieves (4A, 200 mg) at 50°C (external, oil bath temperature) for 22-72 h. After completion of the reaction, it was filtered on a bed of celite, washed with CH_2Cl_2 and evaporated to dryness. The residue so obtained was purified by column chromatography on silica gel (60-120 mesh) to obtain the α-linked saccharides in good yield (70-90%).

2-Pyridyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-glucopyranoside (1). Method A : Compound **1a** (7.4 g, 16.7 mmol) was deacetylated to give 2-pyridyl-1-thio-β-D-glucopyranoside (4.3 g, 16.7 mmol) as a syrup and was subsequently benzylated to obtain **1** as a low melting solid (8.8 g, 87%), m.p. 74-76°C, $[\alpha]_D$ + 8.8° (c 2.0, $CHCl_3$). Anal. Calcd. for $C_{39}H_{39}NO_5S$: C, 73.93; H, 6.16; N, 2.21; S, 5.05. Found : C, 74.12; H, 6.21; N, 2.20; S, 5.03%. ^{1}H-n.m.r (δ ppm, J in Hz) : 3.4-3.7 (m, 4H, H-2,5,6,6'), 4.33-4.85 (m, 10H, H-3,4 and OCH_2.Phx4), 5.31 (d, 1H, $J_{1,2}$= 9, H-1), 6.78-8.50 (m, 24H, aromatic). ^{13}C-n.m.r (δ in ppm) (22.63 MHz, : 69.3 (C-6), 73.5, 75.1, 75.5, 75.8 (OCH_2Phx4), 78.3, 79.6, 81.2, 84.1 (C-2,3,4,5), 87.0 (C-1), 120.5-138.5 (aromatic); **Method B :** (1) (α/β, 2/3) : ^{1}H-n.m.r : (selected data, δ in ppm, J in Hz) (90 MHz) : 5.31 (d, 2/3H, $J_{1,2}$= 9, H-1β), 6.62 (d, 1/3H, $J_{1,2}$= 5, H-1α).

2-Pyridyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-galactopyranoside (2). Method A : Compound **2a** (6.64 g, 15 mmol) was deacetylated to give 2-pyridyl-1-thio-β-D-galactopyranoside as a syrup (3.36 g, 15 mmol) and was benzylated subsequently to obtain **2** (3.15 g, 82%) as a crystalline solid, m.p. 82-84°C, $[\alpha]_D$ +2.76° (c 1.0, $CHCl_3$). Anal.Calcd.for $C_{39}H_{39}NO_5S$: C, 73.93; H, 6.16; N, 2.21; S, 5.05. Found : C, 73.91; H, 6.19; N, 2.24; S, 5.07%. ^{1}H-n.m.r (δ ppm, J in Hz) (90 MHz) : 3.50-4.25 (m, 3H, H-5,6,6'), 4.3-5.1 (m, 11H, H-2,3,4 and OCH_2Phx4), 5.26 (d, 1H, $J_{1,2}$= 10, H-1), 6.72-8.50 (m, 24H, aromatic). ^{13}C-n.m.r (δ ppm) (22.63 MHz) : 69.1, 73.1, 73.8, 74.4, 74.9, 75.8, 77.3, 78.7 (C-2,3,4,5,6 and OCH_2Phx4), 84.6 (C-1), 120.2-139.0 (aromatic). **Method B : 2** (α/β, 1/1) (syrup) : Reaction of **2e** (1.1 g, 2 mmol) in CH_2Cl_2 (10 ml) with 2,2'-dithiodipyridine and nBu_3P afforded **2** (α/β, 1/1) (0.94 g, 80%) as a syrup. ^{1}H-n.m.r (δ ppm, J in Hz) (selected data) (90 MHz) : 5.26 (d, 1/2H, $J_{1,2}$= 10, H-1β), 6.46 (d, 1/2H, $J_{1,2}$= 5, H-1α).

2-Pyridyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (1a) : The reaction of α-acetobromoglucose (12.3 g, 30 mmol) with 2-mercaptopyridine, K_2CO_3 in acetone/toluene afforded **1a** (10 g, 72%) as yellow needles after recrystallization from hexane-dichloromethane, m.p. 120-123°C, $[\alpha]_D$ - 2.9° (c 1.1, $CHCl_3$). Anal. Calcd. for $C_{19}H_{23}NO_9S$: C, 51.70; H, 5.21; N, 3.17; S, 7.25. Found : C, 51.69; H, 5.23; N, 3.15; S, 7.21%. ^{1}H-n.m.r (δ ppm, J in Hz) (90 MHz) : 1.94, 2.00, 2.04 (4s, 12H, CH_3COx4), 3.6-4.4 (m, 3H, H-5,6,6'), 4.8-5.6 (m, 3H, H-2,3,4), 5.75 (d, 1H, $J_{1,2}$= 10, H-1), 6.9-8.5 (m, 4H, SPy). ^{13}C-n.m.r (δ ppm): (22.63 MHz) : 20.2 (CH_3COx4), 71.7 (C-6), 68.1, 69.2, 73.8, 75.6 (C-2,3,4,5), 81.3 (C-1), 120.0-155.0 (SPy), 169.0-170.0 (CH_3COx4).

2-Pyridyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-galactopyranoside (2a) : Reaction of α-acetobromogalactose (3.6 g, 8.7 mmol) with 2-mercaptopyridine/K_2CO_3 in acetone-toluene afforded **2a** (2.63 g, 85%) as a syrup. $[\alpha]_D$ -2.0° (c 1.0, $CHCl_3$). Anal. Calcd. for $C_{19}H_{23}NO_9S$: C, 51.70; H, 5.21; N, 3.17; S, 7.25. Found : C, 51.61; H, 5.23; N, 3.18; S, 7.21%. ^{1}H-n.m.r (δ in ppm, J in Hz) (90 MHz) : 1.97 (s, 6H, CH_3COx2), 2.04, 2.17 (2s, 6H, CH_3COx2), 4.00-4.45 (m, 3H, H-5,6,6'), 5.18 (dd, 1H, $J_{2,3}$= 10, $J_{3,4}$= 3.5, H-3), 5.35 (t, 1H, $J_{1,2}$= 10, H-2), 5.47 (br.s, 1H, H-4), 5.88 (d, 1H, H-1), 7.0-8.5 (m, 4H, SPy).

Methyl 2,3,4,6-tetra-O-benzyl-D-glucopyranoside (1b) : Reaction of **1** with methanol for 22 h afforded **1b** as a syrup (95%) (α/β, 65/35 by ^{1}H-n.m.r and HPLC). (See general procedure)

Isopropyl 2,3,4,6-tetra-O-benzyl-D-glucopyranoside (1c) : Reaction of **1** with isopropyl alcohol for 34 h afforded **1c** as a syrup (α/β, 82/18 by ^{1}H-n.m.r and HPLC). ^{1}H-n.m.r (δ in ppm, J in Hz) (90 MHz) : 1.08, 1.14, 1.16, 1.18, 1.22 (d, 6H, $OCHMe_2$), 3.0-5.1 (m, 16H, H-1,2,3,4,5,6,6', $OCHMe_2$, CH_2Phx4), 7.0-7.9 (m, 20H, aromatic). ^{13}C-n.m.r (δ in ppm) (22.63 MHz) : (α/β) 21.5, 22.4, 23.4, 23.9 ($OCHMe_2$), 69.2, 69.7, 70.5, 73.2, 73.7, 75.3, 75.8, 78.4, 80.5, 82.4 (C-2,3,4,5,6,6' and CH_2Ph), 95.3 (C-1), 102.5 (C-1), 120.0-139.5 (aromatic).

t.Butyl 2,3,4,6-tetra-O-benzyl-D-glucopyranoside (1d) : Reaction of **1** with t.butanol for 48 h yielded **1d** (82%) as a syrup, $[\alpha]_D$ + 37.8° (c 1.0, $CHCl_3$) (α/β, 89/11 by ^{1}H-n.m.r and HPLC). ^{1}H-n.m.r (δ in ppm, J in Hz) (90 MHz) : 1.20, 1.24 (2s, 9H, CMe_3, α/β), 3.00-4.95 (m, 14H, H-2,3,4,5,6,6' and OCH_2Phx4), 5.08 (d, 0.9H, $J_{1,2}$= 3.5, H-1), 6.9-7.7 (m, 20H, aromatic).

Methyl 2,3,4,6-tetra-O-benzyl-D-galactopyranoside (2b) : Reaction of **2** with methanol for 23 h afforded **2b** as a syrup (α/β, 72/28, ^{1}H-n.m.r and HPLC). ^{1}H-n.m.r (δ in ppm, J in Hz) (90 MHz) (selected data) : 3.32, 3.52 (2s, 3H, OCH_3).

Isopropyl 2,3,4,6-tetra-O-benzyl-D-galactopyranoside (2c) : Reaction of **2** with isopropanol for 36 h afforded **2b** as a syrup (α/ , 87/13, ^{1}H-n.m.r and HPLC), $[\alpha]_D$ +33.8° (c 1.0, $CHCl_3$). ^{1}H-n.m.r (δ in ppm, J in Hz) (90 MHz) (α/β) : 1.15, 1.19, 1.21, 1.25 (2d, 6H, $CHMe_2$), 3.26-5.26 (m, 15H, H-1,2,3,4,5,6,6' and OCH_2Phx4), 7.0-7.6 (m, 20H, aromatic).

t.Butyl 2,3,4,6-tetra-O-benzyl-D-galactopyranoside (2d) : Reaction of **2** with t-butanol for 48 h afforded **2d** as a syrup (α/β, 91/9, ^{1}H-n.m.r and HPLC), $[\alpha]_D$ + 38.8° (c 1.2, $CHCl_3$), ^{1}H-n.m.r (δ in ppm, J in Hz) (90 MHz) : 1.22, 1.26 (2s, 9H, CMe_3, α/β), 3.22-5.06 (m, 14H, H-2,3,4,5,6,6' and OCH_2Phx4), 5.14 (d, 1H, $J_{1,2}$= 3, H-1), 6.9-7.4 (m, 20H, aromatic). ^{13}C-n.m.r (δ in ppm) (22.63 MHz) (α/β) : 28.9, 29.2 (CMe_3), 69.2, 69.5, 73.2, 73.4, 73.7, 75.0, 75.8, 77.1, 79.5 (C-2,3,4,5,6,6' and CH_2Phx4), 92.6 (C-1), 127.0-139.5 (aromatic).

2-Pyridyl 2,3,4,6-tetra-O-benzyl-1-thio-α/β-D-mannopyranoside (3) : 2,3,4,6-Tetra-O-benzyl-D-mannose (1 g, 1.8 mmol) was reacted with 2,2'-dithiodipyridyl (0.43 g, 1.98 mmol) and nBu_3P (0.48 g, 1.98 mmol) to afford **3** (0.98 g, 82%) as a syrup (α/β, 1/1). Anal. Calcd. for $C_{39}H_{39}NO_5S$: C, 73.93; H, 6.16; N, 2.21; S, 5.05. Found : C, 73.91; H, 6.18; N, 2.18; S, 5.03%. ^{1}H-n.m.r (90 MHz) (δ in ppm, J in Hz) : 3.55-5.0 (m, 14H, H-2,3,4,5,6 and OCH_2Phx4), 5.6 (d, 1/2H, $J_{1,2}$= 1.8, H-1β), 6.44 (d, 1/2H, $J_{1,2}$= 0.4, H-1α), 7.0-8.5 (m, 24H, aromatic).

2-Pyridyl 2,3,4,-tri-O-benzyl-1-thio-α/β-L-rhamnopyranoside (4) : α-Acetobromorhamnose (3.1 g, 8.8 mmol) and 2-mercaptopyridine were reacted to obtain 2-pyridyl 2,3,4-tri-O-acetyl-1-thio-α/β-L-rhamnopyranoside (**4a**) (2.5 g, 75%, α/β, 1/1) as a syrup. Anal. Calcd. for $C_{17}H_{21}NO_7S$: C, 53.24; H, 5.53; N, 3.65; S, 8.36. Found : C, 53.46; H, 5.49; N, 3.67; S, 8.31%. ^{1}H-n.m.r (90 MHz) (δ in ppm, J in Hz) : 1.22, 1.29 (2d, 3H, $J_{5,6}$= 6.2, H-6), 1.95-2.20 (6s, 9H, $OCOCH_3$x3), 3.6-3.8, 4.05-4.30 (m, 1H, H-5), 5.0-5.7 (m, 3H, H-2,3,4), 6.12 (d, 1/2H, $J_{1,2}$= 1.8, H-1), 6.51 (d, 1/2H, $J_{1,2}$= 3.1, H-1), 7.0-8.5 (m, 4H, SPy). (**4α**) (2.5 g, 6.8 mmol) was deacetylated and benzylated to obtain **4** (2.72 g, 75%) (α/β, 1/1), and the anomeric mixture was separated by silica gel column chromatography (60-120 mesh, hexane/EtOAc, 4/1) to obtain **4** (α) (1.3 g) as a syrup, $[\alpha]_D$ - 44.3° (c 1.0, $CHCl_3$). Anal. Calcd. for $C_{32}H_{33}NO_4S$: C, 72.72; H, 6.29; N, 2.65; S, 6.07. Found : C, 72.65; H, 6.23; N, 2.63; S, 6.02%. ^{1}H-n.m.r (90 MHz) (δ in ppm, J in Hz) : 1.34 (d, 3H, $J_{5,6}$= 6.2, H-6), 3.6-5.1 (m, 10H, H-2,3,4,5 and OCH_2Phx3), 6.48 (d, 1H, $J_{1,2}$= 2.8, H-1), 7.0-8.5 (m, 18H, aromatic); and **4** (β) (1.32 g) as a syrup. $[\alpha]_D$ + 17.7° (c 1.2, $CHCl_3$). Anal. Found: C, 72.69; H, 6.22; N, 2.66; S, 6.01%. ^{1}H-n.m.r (90 MHz) (δ in ppm, J in Hz) : 1.36 (d, 3H, $J_{5,6}$= 6.2, H-6), 3.10-5.28 (m, 10H, H-2,3,4,5 and OCH_2Phx3), 5.68 (d, 1H, $J_{1,2}$= 1.4, H-1), 7.0-8.6 (m, 19H, aromatic).

2-Pyridyl 2,3,6-tri-O-benzyl-4-O-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)-1-thio-α-D-glucopyranoside (5) : α-Acetobromomaltose[9] (3.8 g, 5.4 mmol) was reacted with 2-mercaptopyridine to afford 2-pyridyl 2,3,6-tri-O-acetyl)-1-thio-β-D-glucopyranoside (**5a**) as a yellow crystalline solid, m.p. 110-113°C. $[\alpha]_D$ +50.5° (c 1.0, $CHCl_3$). Anal.Calcd. for $C_{31}H_{39}NO_{17}S$: C, 50.98; H, 5.39; N, 1.89; S, 4.39, Found : C, 51.08; H, 5.37; N, 1.89; S, 4.39%. ^{1}H-n.m.r (δ in ppm, J in Hz) (300 MHz) : 1.99, 2.04, 2.05 x 2, 2.06, 2.07, 2.10 (6s, 21H, $OCOCH_3$x7), 3.8-5.5 (m, 13H, H-2,3,4,5,6,1',2',3',4',5',6'), 5.85 (d, 1H, $J_{1,2}$= 10.2, H-1), 7.0-8.5 (m, 4H, SPy), ^{13}C-n.m.r (22.63 MHz) (δ in ppm) (selected data) : 80.9 (C-1), 95.3 (C-1'). **5a** (2.75 g) was deacetylated and benzylated to give **5** (2.0 g, 61%) as a colourless syrup.

(δ in ppm, J in Hz) : 1.98-2.06 (4s, 18H, $OCOCH_3$x6), 5.71 (d, 1H, $J_{1,2}$= 8, H-1); ^{13}C-n.m.r (75 MHz) (δ in ppm) (selected data) : 91.6, 96.3, 98.2 (C-1, 1', 1").

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)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranoside (27) : The coupling of **5** (0.36 g, 0.33 mmol) with **13** (0.1 g, 0.4 mmol) (52 h) gave **27** (0.15 g, 65%) as a syrup after column chromatographic purification (SiO_2, hexane/EtOAc/diethyl ether, 5/0.6/2), $[\alpha]_D$ + 25.2° (c 1.0, $CHCl_3$), Anal. Calcd. for $C_{73}H_{82}O_{16}$: C, 72.14; H, 6.80, Found : C, 72.01; H, 6.91%. ^{1}H-n.m.r (300 MHz) (δ in ppm, J in Hz) : 1.30, 1.45, 1.57, 1.60 (4s, 12H, $O_2C\underline{Me}_2$ x2), 3.3-5.1 (m, 19H, pyranosidic), 5.5 (d, 1H, $J_{1,2}$= 5, H-1), 5.67 (d, 1H, $J_{1"2"}$= 3.6, H-1"), 7.0-7.4 (m, 35H, aromatic), ^{13}C-n.m.r (75 MHz) (δ in ppm) (selected data) : 24.5, 24.7, 25.9, 26.0 (4s, $O_2C\underline{Me}_2$x2), 96.1, 96.4, 96.8 (3d, C-1, 1', 1"), 108.3, 109.0 (2s, $O_2\underline{C}Me_2$x2).

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