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A MILD GENERAL METHOD FOR THE SYNTHESIS OF α-LINKED DISACCHARIDES

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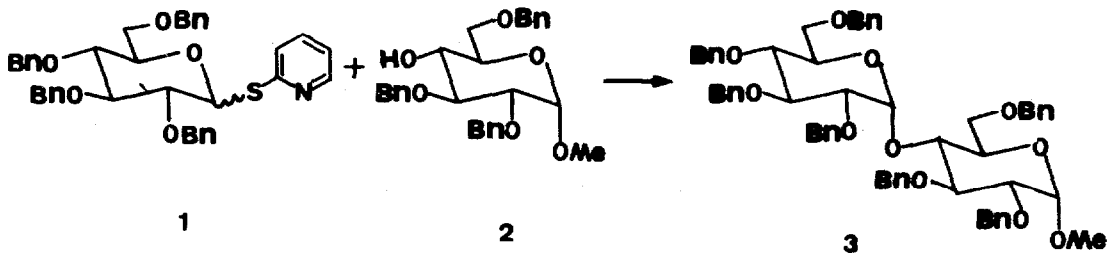
Stereoselective α-glycosylations may be achieved using stable 2-pyridyl thioglycosides (anomeric mixture) having a non-participating 2-substituent as glycosyl donor and methyl iodide as an activator.

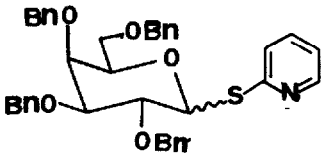
α-Linked disaccharides are of paramount importance as they are constituents of many biologically active natural prdoucts[1]. As a consequence, much effort is currently directed to the efficient and stereocontrolled synthesis of such disaccharides[2]. Present synthetic methods for construction of such molecules, inspite of some stimulating approaches[3-9] however, leave a considerable margin for improvement in terms of formation of unstable glycosyl halide (classical glycosyl donor), acidic reaction media, toxic reagents, efficiency, generality and stereoselectivity. We report herein, a mild methodology that utilizes the stable, readily available anomeric mixture (α and β) of 2-pyridyl thioglycosides[10] **1**, **4-6** with a non-participating 2-substituent as glycosyl donor and methyl iodide as an activator in presence of glycosyl acceptors **2**, **7**, **12**, r,t give rise to α-linked disaccharides. The potential of this efficacious, powerful technology is amply demonstrated herein, through the practical synthesis of ten disaccharides and a trisaccharide (Table 1). 2-Pyridyl thioglycosides have earlier been used as glycosyl donors and activation by heavy metal salts did not yield results to be of general application for widespread use in oligosaccharide synthesis[11].

In a typical procedure, 2-pyridyl 2,3,4,6-tetra-O-benzyl-1-thio-α,β-D-glucopyranoside **1**[10] (1.0 mmol) (α:β anomers 2:3 ratio) was reacted with 4-hydroxyl group of the glucopyranoside **2**[12] (1.1 mmol), which is known to resist[4] glycosidation under halide ion catalysed conditions[3], in dry methylenechloride (10 ml, having 3% methyl iodide) in presence of 4-Å molecular sieves at 50°C for three days. After work up and purification (silica gel column), methyl 2,3,6-tri-O-benzyl-4-O-(2,3,4,6-tetra-O-benzyl-α-D-glycopyranosyl)-α-D-glucopyranoside was isolated as a syrup **3**, (82%), $[\alpha]_D^{20}$ +48° (c, 1.0, $CHCl_3$)[4], (Scheme 1).



1 **2** **3**

Scheme-I



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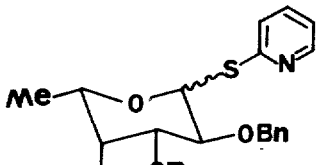

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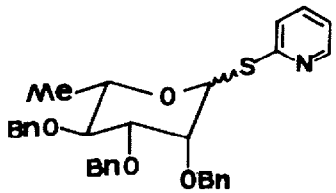

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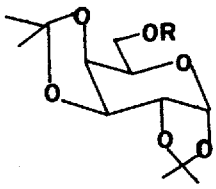
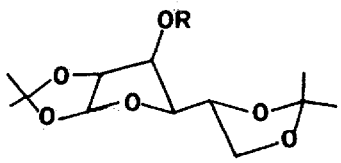




7 R = H

8 R = 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl

9 R = 2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl

10 R = 2,3,4-tri-O-benzyl-α-L-fucopyranosyl

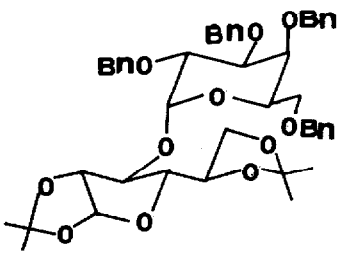
11 R = 2,3,4-tri-O-benzyl-α-L-rhamnopyranosyl

12 R = H

13 R = 2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl

14 R = 2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl

15 R = 2,3,4-tri-O-benzyl-α-L-fucopyranosyl



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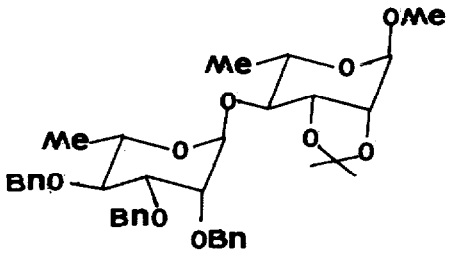

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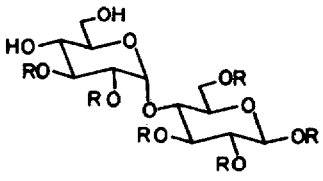
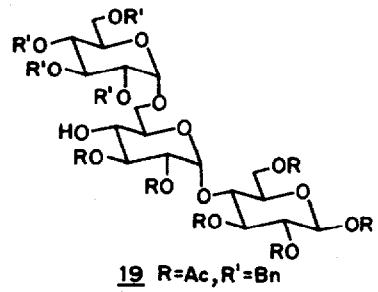


18 R = Ac



19 R=Ac, R'=Bn

The versatility and usefulness of this technology was tested in a number of demanding situations. Thus, D-gluco, D-galacto- and L-fucosylations have been performed with α-diastereoselectivity, by reaction of their corresponding pyridyl thioglycosides **1, 4** and **5** with several glycosyl acceptors (Table 1).

Table 1: Glycosidation Via Pyridyl thioglycoside Method

Entry	Glycosyl[a] Donor	Acceptor	Protected Disaccharide (m.p.)	Yield %	$[\alpha]_D$ Deg.[b] Observed	Lit. (Ref.)
i	**1**	**7**	**8** m	87	+10[c,i]	+10.1 (3)
ii	**1**	**12**	**13** (91°C) o	56	+46[c,i]	+46 (4)
iii	**4**	**7**	**9** m	81	+5.1 f,k	+2 (13)
iv	**4**	r	**16** (120°C) p	67	+37 g,j	+36.8 (3)
v	**4**	**12**	**14** m	62	+32.7 d,l	+33 (4)
vi	**5**	**7**	**10** (115-116°C) q	71	-116.5 c,j	-117 (3)
vii	**5**	**12**	**15** m	59	-96.8 c,j	-97 (3)
viii	**6**	**7**	**11** m	78	-47 e,h	s
ix	**6**	t	**17** m	72	-23.9 e,h	s

[a]Reaction time for primary alcohols as acceptors (2 days) and secondary alcohols (3 days). [b]In chloroform. [c]c 2.0. [d]c 1.1. [e]c 1.0. [f]c 0.9. [g]c 0.8. [h]27. [i]24. [j]25. [k]22. [l]20. [m]Syrup. [o]Lit. mp 90-91°C. [p]Lit. mp 120-121°C. [q]Lit. mp 115-116°C. [r]1,2:4,6-di-O-isopropylidene-D-galactofuranose. [s]On debenzylation (Pd/H_2) identical with the reported compound ref.14. [t]Methyl α-2,3-O-isopropylidene-L-rhamnoside.

Furthermore, 2-pyridyl thiorhamnoside **6** also exhibited α-selectivity (entry viii, ix), synthesis of such α-linked rhamnobioses **11** and **17** has earlier been possible only by neighbouring group assisted orthoester procedure. Panose **19**[15] a trisaccharide, which has been earlier isolated from acid hydrolyzates of amylopectin, glycogen and pullulan has been synthesized by condensation of **18** (20 h) with **1** in 62% yield $[\alpha]_D^{20}$ +51.3° (c 2.0, $CHCl_3$)[15,16].

These results revealed that preparatively satisfactory α-glycosidations can be performed under mild conditions. The prospects of affecting macrolactonisation and esterification are also evident from this methodology. Application of this methodology for the synthesis of α-linked 2-deoxydisaccharides is reported in the following paper.

Acknowledgement:

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10. Prepared essentially as anomeric mixture (ca. 2/3,α/β) on reaction of $(Py.s)_2$/n Bu_3P/CH_2Cl_2/ RT/2 h. with the corresponding 2,3,4,6- or 2,3,4-O-benzylated pyranosides.
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16. All the compounds have been characterised by comparison of ^{1}H-n.m.r., ^{13}C-n.m.r. and optical rotations. Satisfactory analytical data have been obtained for new compounds.

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