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Preliminary communication

A novel promoter for the efficient construction of 1,2-*trans* linkages in glycoside synthesis, using thioglycosides as glycosyl donors

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In the block synthesis[1] of oligosaccharides, most manipulations of protecting groups may be conducted on smaller rather than on larger fragments. The latter will be necessary when monomer units are added sequentially to the growing chain. Block synthesis may create problems, in that the conversion of an intermediate oligosaccharide into a glycosyl donor is required.

The glycosyl donors most widely used in the synthesis of glycosides are glycosyl halides, but the conversion of an oligosaccharide into such a derivative may be difficult[2]. Ideally, the anomeric substitutent of a block to be used as a glycosyl donor should be sufficiently stable to withstand manipulations of protecting groups elsewhere in the molecule or during glycosylation by another block, and have reactivity sufficient to permit its use as a glycosyl donor directly or after selective activation.

Such glycosyl donors as glycosyl halides, 1,2-ortho-esters, imidates, and glycosyl acetates only partially fulfil these requirements. However, the anomeric substituent of an alkyl (aryl) 1-thioglycoside is stable to various manipulations of protecting groups and to glycosylation elsewhere in the molecule[3–5] using standard methods, *e.g.*, silver triflate-promoted reactions with glycosyl halides[5]. Thioglycosides can be converted into glycosyl donors[6–9] by conversion into glycosyl bromides[3] or glycosyl fluorides[4], and activation by methyl trifluoromethanesulfonate (methyl triflate)[5]. The latter reagent, although it generates efficient glycosyl donors, has two disadvantages, namely, the health hazard involved in its routine handling and the possibility of competing methylation of the hydroxyl group instead of glycosylation.

We now report on a novel promoter for the activation of anomeric thioalkyl (aryl) groups in glycoside synthesis and demonstrate its potential in the construction of 1,2-*trans*-glycosidic linkages in (1→2)-, (1→3)-, (1→4)-, and (1→6)-linked disaccharides.

The regiospecific activation of a sulfur centre should require the use of a soft Lewis acid. Alkylsulfenylation of the sulfur could prevent *O*-alkylation, and the electrophilic intermediate would contain a leaving group better than the alkylsulfonium group. Dimethyl(methylthio)sulfonium tetrafluoroboronate[10] reacts rapidly with dimethyl sulfide[11] and has many synthetic applications[12,13] and, in pilot experiments, it was effec-

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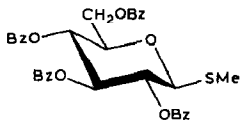
tive in activating alkyl 1-thioglycoside donors. Since triflates are excellent leaving-groups in glycosylation reactions[14–18], the tetrafluoroboronate anion was replaced by triflate. Thus, dimethyl(methylthio)sulfonium triflate (DMTST)[19] was found to be most efficient in promoting glycosylation reactions. The crystalline compound could be stored *in vacuo* over P_4O_{10} without significant decomposition for ~2 weeks, or even longer in dichloromethane.

The addition of DMTST (4–5 equiv.) to a mixture of the thioglycoside (1.2 equiv.) and the alcohol (1 equiv.) in dichloromethane, in the presence of 4 Å molecular sieves at 20°, followed by column chromatography of the products on silica gel, afforded the disaccharide derivatives in high yield. The method is illustrated in Table I with glycosyl donors having a participating 2-substituent, leading to 1,2-*trans* substituents. A benzoyl group at position 2 results in higher yields than when O-2 is acetylated[20, 21] (*cf.* entries 1–6 with 7). The reactions were faster than methyl triflate-promoted glycosylations. The method is compatible with the presence of acid-labile groups in the glycosyl donor (entry 6) as well as in the glycosyl acceptor (entries 3 and 4). High yields were obtained even in the glycosylations of unreactive, secondary hydroxyl groups (entries 2–4). Using the *N*-phthaloyl derivative **9**, an efficient synthesis of a protected 2-amino-deoxy-β-D-glucosylated product was accomplished (entry 8).



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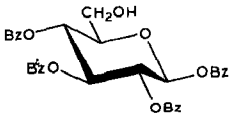

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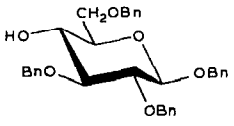

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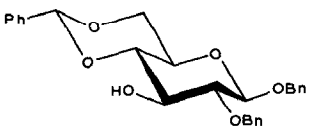

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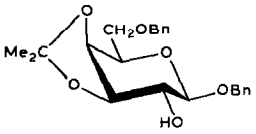

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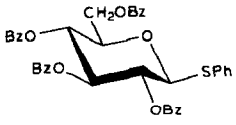

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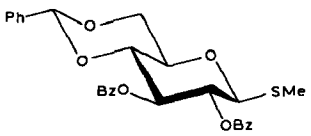

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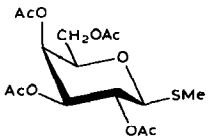

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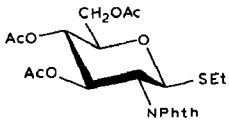

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The following disaccharide derivatives were prepared: 1,2,3,4-tetra-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-β-D-glucopyranose (entries 1 and 5), benzyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-β-D-glucopyranoside (entry 2), benzyl 2-*O*-benzyl-4,6-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-β-D-glucopyranoside (entry 3), benzyl 6-*O*-benzyl-3,4-*O*-isopropyli-

TABLE I

YIELDS AND SELECTED PHYSICAL PROPERTIES FOR β-D-LINKED DISACCHARIDES

Entry	*Thioglycoside*[a]	*Alcohol*[b]	*Reaction time (h)*	*Product yield (%)*	*M.p. (degrees)*	$[\alpha]_D^{20}$ *($CHCl_3$) (degrees)*	*Selected n.m.r. parameters ($CDCl_3$)*
1	1[c]	2[d]	1	92[e]	218–219	+16	C-1 92.8 ($J_{C-1,H-1}$ 168 Hz), C-1′ 100.4 p.p.m. ($J_{C-1',H-1'}$ 168 Hz)
2	1	3[24]	6	85[e]	–	–9	C-1 102.5 ($J_{C-1,H-1}$ 160 Hz), C-1′ 100.4 p.p.m. ($J_{C-1',H-1'}$ 166 Hz)
3	1	4[25]	4	88[e]	86–87	–17	H-1′ 5.26 p.p.m. ($J_{C-1',H-1'}$ 8 Hz), C-1 99.9 p.p.m.
4	1	5[26]	2	86[e]	89–90	+26	($J_{C-1,H-1}$ 162 Hz) C-1′ 101.1 p.p.m. ($J_{C-1',H-1'}$ 164 Hz)
5	6[27]	2	20	93[e]	entry 1		entry 1
6	7[f]	2	2	91[e]	232–233	–1	H-1 6.17 ($J_{1,2}$ 8 Hz), H-1′ 4.93 p.p.m. ($J_{1',2'}$ 7.5 Hz)
7	8[28]	5	5 min	79[e]	53–54	–4	C-1 100.4 ($J_{C-1,H-1}$ 159 Hz), C-1′ 101.6 p.p.m. ($J_{C-1',H-1'}$ 164 Hz)
8	9	2	1	90[e]	239–240	–12	C-1 92.5 ($J_{C-1,H-1}$ 171 Hz), C-1′, 97.8 p.p.m. ($J_{C-1',H-1'}$ 170 Hz)

[a] In CH_2Cl_2. [b] The ratio of donor to acceptor was 1.2:1. [c] Prepared by benzoylation of methyl 1-thio-β-D-glucopyranoside[22], it had m.p. 101–102°, $[\alpha]_D^{20}$ +33° (*c* 1, chloroform). [d] M.p. 179–181°, $[\alpha]_D^{20}$ –15° (*c* 0.9, chloroform)[23]. [e] All new products gave satisfactory elemental (C,H) analyses. [f] M.p. 170–171° $[\alpha]_D^{20}$ +17° (*c*, chloroform)[23].

dene-2-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-β-D-galactopyranoside (entry 4), 1,2,3,4-tetra-*O*-benzoyl-6-*O*-(2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-β-D-glucopyranosyl)-β-D-glucopyranose (entry 6), benzyl 6-*O*-benzyl-3,4-*O*-isopropylidene-2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-galactopyranoside (entry 7), and 1,2,3,4-tetra-*O*-benzoyl-6-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-β-D-glucopyranose (entry 8).

The glycosylation procedure described is potentially more advantageous than existing methods for the synthesis of glycosides containing 1,2-*trans* substituents.

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