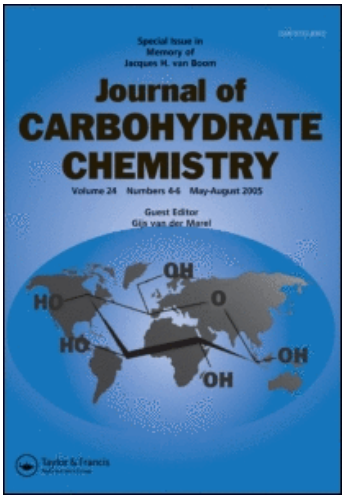

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COMMUNICATION

CHEMOSELECTIVE GLYCOSYLATION BASED ON DIFFERENCE IN THE REACTIVITIES OF ETHYL AND *p*-TOLYL THIOGLYCOSIDES

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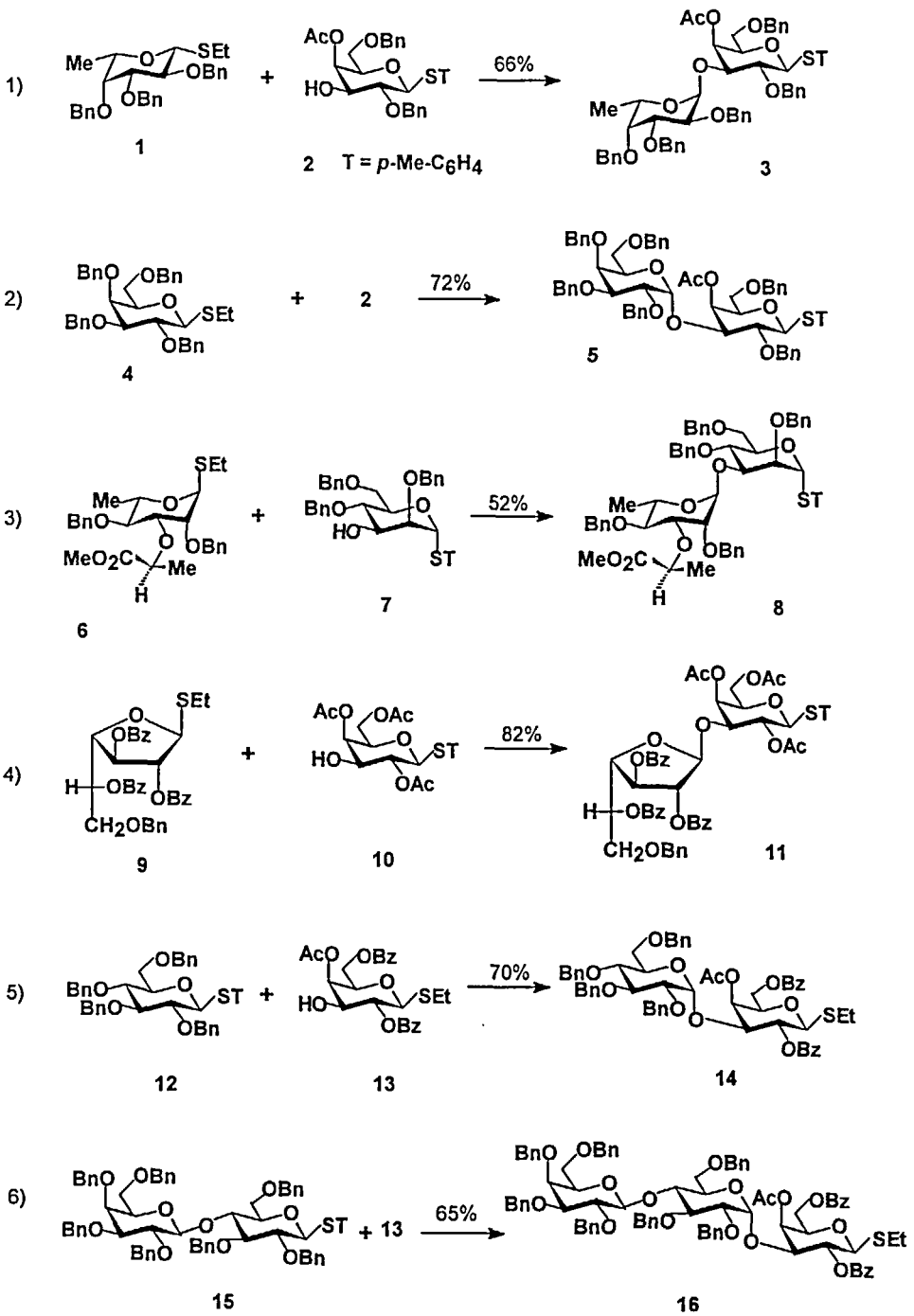
Thioglycosides are very useful glycosyl donors for the synthesis of oligosaccharides.[1] Frequent use of these donors is due to their ease of preparation, stability and capability of reaction in the presence of a variety of promoters like iodonium dicollidine perchlorate,[2] *N*-iodosuccinimide–triflic acid (NIS-TfOH),[3] dimethyl-(methylthio)sulfonium triflate,[4] methyl triflate,[5] etc. to form glycosidic bonds. In addition, the armed - disarmed glycosylation strategy[6] was also successfully applied and it was claimed that 2-*O*-substituents play the greater role in activating or deactivating a donor molecule. Thus coupling of an ethyl thioglycoside donor having a 2-*O*-benzyl substituent with an ethyl thioglycoside acceptor having a 2-*O*-acyl protecting group, proceeds with high chemoselectivity to give the desired product in good yield.[2,3] There are also reports on the concept of active and latent thioglycosyl donors[7] caused by activation or deactivation of the anomeric center. The enhanced reactivities of *p*-acetamidophenyl and ethyl thioglycoside in comparison to *p*-nitrophenyl thioglycoside are also examples of anomeric activation and deactivation.[8] More recently, it was

reported[9] that the bulky dicyclohexylmethyl thioglycoside donors are much less reactive than the ethyl thioglycosides and this strategy was applied to chemoselective glycosylation utilising donors and acceptors both having either 2-*O*-benzyl or 2-*O*-acyl substituents.

In a previous communication,[10] we had shown that the donor ethyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-fucopyranoside (**1**) reacted with the acceptor *p*-tolyl 4-*O*-acetyl-2,6-di-*O*-benzyl-1-thio-β-D-galactopyranoside (**2**) to give exclusively the *p*-tolyl thioglycoside of the disaccharide **3** (Equation 1).The self coupling product of **2** was not detected at all. It was possible that the higher reactivity of the ethyl thioglycoside compared to the *p*-tolyl thioglycoside was because of the higher electron withdrawing effect of the tolyl compared to the ethyl group. However, it was not possible to make a firm conclusion from the above finding alone because the donor was an L-fucose derivative which is known to be more reactive than the corresponding donor of D-galactose. In the present communication we report the synthesis of some oligosaccharides utilizing the same strategy in order to establish the usefulness of chemoselective glycosylation based on the differences in the reactivities of ethyl and *p*-tolyl thioglycosides. It was considered that taking the donor and the acceptor from the same sugar would make a better comparison. Accordingly, the perbenzylated ethyl thioglycoside of D-galactopyranose[11] (**4**) was allowed to react with **2**[10] in presence of NIS-TfOH. The product was exclusively the *p*-tolyl thioglycoside of the disaccharide **5** (Equation 2). The electron withdrawing nature of the benzene ring may have hindered the formation of the intermediate sulfonium ion during glycosylation. In another experiment, where the reaction was conducted with a CHMeCOOMe group at the 3-position of the donor **6** and the acceptor **7** had no acetyl protected hydroxyl group (compare Equations 1 and 2), the *p*-tolyl thioglycoside of the disaccharide[12] **8** (Equation 3) was the major product. This showed that the presence of acetyl group at the 4-position of **2** has no deactivating effect. A similar effect was also observed in the preparation of **11,** where the donor is a furanoside[13] (Equation 4). However, when perbenzylated *p*-tolyl thioglycosides **12**[14] and **15**[14] were allowed to react with ethyl 4-*O*-acetyl-2,6-di-*O*-benzoyl-1-thio-β-D-galactopyranoside (**13**), the resulting products were the ethyl thioglycosides of the disaccharide **14** and the trisaccharide **16**, respectively (Equations 5 and 6). Obviously, the formation of the products in these two cases was governed by the arming and disarming effects of the 2-*O*-substituents[6] and not



by the higher electronegativity of the *p*-tolyl moiety. The acceptor **13** was prepared from ethyl 1-thio-β-D-galactopyranoside[15] by its reaction with triethyl orthoacetate[16] followed by benzoylation of the resulting orthoester and regioselective opening with aqueous acetic acid[16].

The present communication, provides more data to show the importance of an electronic effect at the anomeric center and suggests that it has a definite directive influence. Chemoselective glycosylation can therefore be achieved when an ethyl thioglycoside donor is allowed to react with a *p*-tolyl thioglycoside acceptor, provided both the reactants have similar 2-*O*-substituents. When the 2-*O*-substituents are different, the course of the reaction is guided by the activating effect of the 2-*O*-substituent.

EXPERIMENTAL

General Methods. All reactions were monitored by TLC on silica gel G (E. Merck). Column chromatography was performed using 100-200 mesh silica gel (SRL, India). All solvents were dried and/or distilled before use, and all evaporations were conducted below 50°C under diminished pressure unless otherwise stated. Melting points were determined using a Fisher-Johns apparatus and are uncorrected. Optical rotations were measured at 24 °C with a Perkin-Elmer 241 MC polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded (internal standard tetramethylsilane) with a Jeol FX100 and Bruker 300 MHz spectrometer, using $CDCl_3$ as the solvent unless stated otherwise.

Method of Glycosylation. A mixture of ethyl thioglycoside donor (0.3 mmol), *p*-tolyl thioglycoside acceptor, (0.2 mmol), and 4Å molecular sieves (200 mg) in CH_2Cl_2 (5 mL) was stirred for 6 h at 25 °C. The mixture was then cooled to 0 °C and NIS (0.22 mmol) and TfOH (0.1 mmol) were added. Stirring was continued for 45 min at 0 °C. The solution was then diluted with CH_2Cl_2, filtered and washed successively with aq Na_2CO_3, M $Na_2S_2O_3$ and water. The organic layer was dried (Na_2SO_4), concentrated to a syrupy product.

***p*-Tolyl 2,3,4,6-Tetra-*O*-benzyl-α-D-galactopyranosyl-(1→3)-4-*O*-acetyl-2,6-di-*O*-benzyl-β-D-galactopyranoside (5).** The crude product was purified by column chromatography using 10:1 toluene-EtOAc yielding pure **5** (105 mg, 66%): $[\alpha]_D^{25}$ +47.7°

(*c* 6.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.94 (s, 3H, $COCH_3$), 2.41 (s, 3H, $SC_6H_4CH_3$), 4.62 (d, 1H, J=9.9 Hz, H-1), 5.38 (m, 1H, H-4), 5.66 (d, 1H, J=3.0 Hz, H-1'), 7.13-7.57 (m, 34H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 21.1 ($SC_6H_4CH_3$), 21.4 (CH_3CO), 65.6, 69.2, 72.6, 72.9, 73.4, 73.5, 74.5, 74.6, 75.1, 76.0, 76.2, 76.4, 78.1, 80.1, 81.8, 88.3 (C-1), 92.9 (C-1'), 127.3-138.8 (aromatic carbons), 170.2 (CH_3CO).

Anal. Calcd for $C_{63}H_{66}O_{11}S$: C, 73.37; H, 6.45. Found: C, 73.15; H, 6.62.

***p*-Tolyl 2,4-Di-*O*-benzyl-3-*O*-[(*R*)-1-(methoxycarbonyl)ethyl]-α-L-rhamnopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (8).** Column chromatography of the crude product with toluene-EtOAc gave **8** (225 mg, 52%) as a glass: $[\alpha]_D^{25}$ +47.8° (*c* 0.18, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.15 (d, 3H, J=6 Hz, H-6'), 1.34 (d, 3H, J=5 Hz, $OCHCH_3COOCH_3$), 2.24 (s, 3H, $SC_6H_4\ CH_3$), 3.31 (s, 3H, $COOCH_3$), 5.23 (s, 1H, H-1'), 5.48 (s, 1H, H-1), 6.94-7.28 (m, 29H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 18.1 (C-6'), 18.9 ($OCHCH_3COOCH_3$), 21.1 ($CH_3C_6H_4S$), 51.7 ($COOCH_3$), 68.2, 71.8, 72.4, 72.9, 73.3, 73.6, 73.8, 74.2, 74.9, 79.2, 80.1, 85.4 (C-1), 93.6 (C-1'), 127.2-138.1 (aromatic carbons), 172.9 ($COOCH_3$).

Anal. Calcd for $C_{58}H_{64}O_{10}S$: C, 73.08; H, 6.77. Found: 73.25; H, 6.91.

Ethyl 4-*O*-Acetyl-2,6-di-*O*-benzyl-1-thio-β-D-galactopyranoside (13). To a stirred suspension of ethyl 1-thio-β-D-galactopyranoside (1.2g, 5.4 mmol) in CH_3CN (40 mL) were added at room temperature *p*-toluenesulfonic acid (60 mg) and triethyl orthoacetate (1.5 mL, 8.1 mmol) and the mixture was stirred for 45 min. The reaction was quenched with Et_3N and the solution was concentrated to a syrup which was treated at 0 °C under N_2 with benzoyl chloride (2.5 mL) and pyridine (10 mL) and the mixture was stirred for 5 h. Methanol (1 mL) was added to decompose the excess of benzoyl chloride, and the solution, diluted in CH_2Cl_2 (200 mL), was washed in succession with M hydrochloric acid (100 mL), saturated aq $NaHCO_3$ (100 mL) and water (100 mL). The organic phase was dried (Na_2SO_4) and concentrated to a syrup which was dissolved in 80% aq acetic acid (10 mL) and stirred for 30 min at room temperature. Solvents were removed by evaporation under reduced pressure and the glassy crude product was purified by column chromatography with 5:2 toluene-EtOAc to afford **13** (1.14 g, 45%): $[\alpha]_D^{25}$ –10.7 (*c* 0.17, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, J=7.5 Hz, SCH_2CH_3), 2.21 (s, 3H, $COCH_3$), 2.73 (m, 2H, SCH_2CH_3), 4.68 (d, 1H, J=9.9 Hz, H-1), 5.32 (t, 1H, J=9.6 Hz, H-2), 5.54 (d, 1H, J=3.0, H-4), 7.36-8.06 (m, 10H, aromatic protons); ^{13}C NMR

($CDCl_3$) δ 14.9 (SCH_2CH_3), 20.8 (SCH_2CH_3), 24.5 ($COCH_3$), 62.3 (C-6), 70.0, 71.7, 72.4, 74.8, 83.7 (C-1), 128.3-133.4 (aromatic carbons), 166.0, 166.5 (COC_6H_5), 171.0 ($COCH_3$).

Anal. Calcd for $C_{24}H_{26}O_8S$: C, 60.75, H, 5.52. Found: C, 60.60, H, 5.65.

Ethyl 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl-(1→3)-4-*O*-acetyl-2,6-di-*O*-benzoyl-1-thio-β-D-galactopyranoside (14). Purification of the crude product was effected by column chromatography with 10:1 toluene-EtOAc giving **14** (81 mg, 70%): $[\alpha]_D^{25}$ +70.3° (*c* 3.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.35 (t, 3H, J=7.2 Hz, SCH_2CH_3), 1.92 (s, 3H, CH_3CO), 2.73 (q, 2H, SCH_2CH_3), 4.24 (d, 1H, J=11.4 Hz, H-1), 5.19 (d, 1H, J=3 Hz, H-1'), 5.59 (t, 1H, H-2), 5.72 (m, 1H, J=3 Hz, H-4), 7.16-7.61 (m, 30H, aromatic protons); ^{13}C NMR ($CDCl_3$) δ 14.9 (SCH_2CH_3), 20.4 (SCH_2CH_3), 24.4 (CH_3CO), 62.3 (C-6'), 65.1 (C-6), 68.3, 68.9, 70.6, 73.3, 73.4, 74.3, 74.8, 75.5, 77.4, 79.1, 81.4, 84.3 (C-1), 93.2 (C-1'), 127.1-138.4 (aromatic carbons), 165.2, 166.0 (C_6H_5CO), 170.4 (CH_3CO).

Anal. Calcd for $C_{58}H_{60}O_{13}S$: C, 69.86; H, 6.06. Found: C, 69.71, H, 6.27.

Ethyl 2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl-(1→3)-4-*O*-acetyl-2,6-di-*O*-benzoyl-β-D-galactopyranoside (16). The crude reaction mixture was chromatographed with 6:1 toluene-EtOAc to afford **16** (72 mg, 65%): $[\alpha]_D^{25}$ +124.2° (*c* 1.67, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.21 (t, J=7.5 Hz, SCH_2CH_3), 1.89 (s, 1H, CH_3CO), 2.65 (q, 2H, SCH_2CH_3), 4.23 (d, 1H, J=11.7 Hz, H-1), 4.61 (d, 1H, J=8.1 Hz, H-1''), 5.38 (t, 1H, H-2), 5.6 (d, 1H, H-1'), 7.02-7.39 (m, 45H, aromatic protons); ^{13}C NMR δ 14.9 (SCH_2CH_3), 20.6 (SCH_2CH_3), 24.4 (CH_3CO), 62.5, 66.8, 67.9, 68.1, 69.6, 70.3, 71.3, 72.5, 72.9, 73.0, 73.3, 73.4, 73.6, 74.6, 74.7, 75.0, 77.0, 78.5, 79.4, 79.8, 82.5, 84.1 (C-1), 96.0 (C-1'), 103.1 (C-1''), 127.4-138.9 (aromatic carbons), 165.4, 166.0 (C_6H_5CO), 170.2 (CH_3CO).

Anal. Calcd for $C_{85}H_{88}O_{18}S$: C, 71.41; H, 6.20. Found: 71.60, H, 6.38.

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