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Tetrahedron Letters 44 (2003) 7601–7605

TETRAHEDRON LETTERS

Glycosylation with 2′-thio-*S*-acetyl participation

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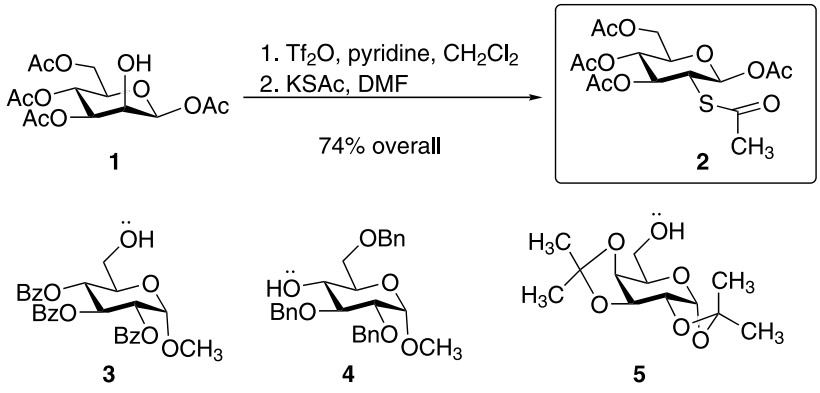
Received 10 July 2003; revised 13 August 2003; accepted 15 August 2003

Abstract—The reaction of 1,2,3,4,6-penta-*O*,*S*,*O*,*O*,*O*-acetyl-2-thio-β-D-glucopyranose with glycosyl acceptors in the presence of trimethylsilyl triflate leads to the β-disaccharides exclusively, owing to especially avid anchimeric assistance by the 2-thio-*S*-acetyl group. Optional reductive removal of –SAc with Ra–Ni gives the corresponding 2′-deoxy-β-disaccharides.

The stereochemistry of disaccharide formation can be effectively controlled by a participating group located near C-1 of the glycosylation donor.[1–3] For example, 2-*O*-acetyl-, 2-acetamido-2-deoxy-, and 2-deoxy-2-phthalimido glucopyranosyl donors are commonly observed to give β-disaccharide products by way of presumed cyclized intermediates. Subsequent transformation of the participating group can give rise to 2′-modified disaccharides, including 2′-amino, 2′-deoxy, and others. We report some glycosylations with the new 2-thio-*S*-acetyl glucopyranosyl donor **2**, which evidently reacts by participation of the thioester carbonyl oxygen,[4] and provides 2′-thio-*S*-acetyl β-disaccharides that have potential for further transformation to the corresponding 2′-deoxy, 2′-thio, and 2′-thio-*S*-substituted derivatives.

Pure β-donor[5] **2** was prepared efficiently in two steps from 1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranose[6] **1** by triflation at O-2,[7] and then replacement of triflate by reaction with potassium thioacetate[8] (Scheme 1). Glycosylation of three acceptors was examined. The primary alcohol **3**[9] was selected because it gives a mixture of α/β-disaccharides when steric and/or conformational effects determine the donor stereoselectivity,[10,11] and thus might be used as an indicator of participation. The secondary alcohol **4**[12] is more hindered than **3**, and reacts very slowly with weak donor species.[13] The commercially available and commonly used galactose-derived acceptor **5** was tried because it would lead to the known 2′-deoxy disaccharide **10** upon reductive removal of the participating group.



Scheme 1.

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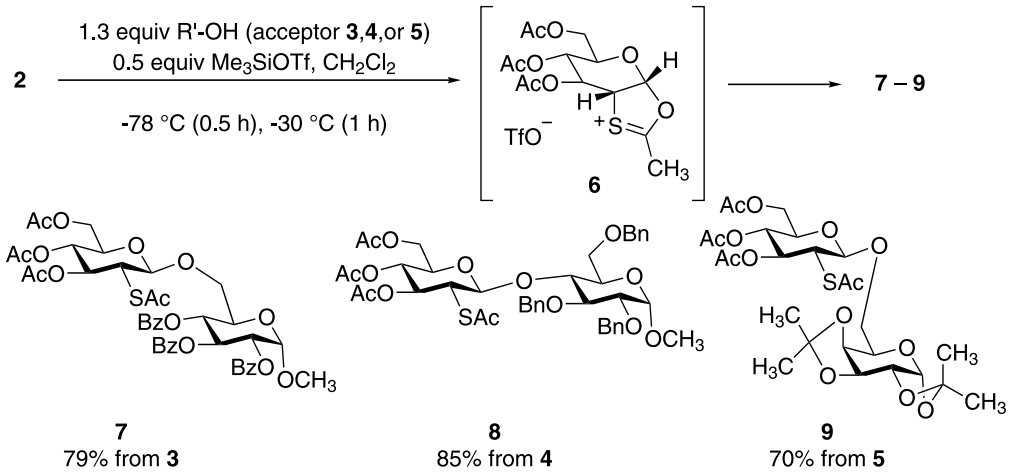
doi:10.1016/j.tetlet.2003.08.063



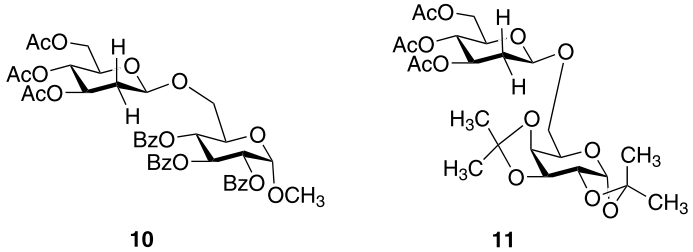
Scheme 2.

Reaction of donor **2**, as the limiting reagent, with the acceptors **3**–**5** was carried out in dichloromethane solution with 0.5 equiv. of trimethylsilyl triflate as the activator[14] (Scheme 2). With all three acceptors, reaction commenced at −78°C, but only proceeded about halfway, according to TLC analysis. Raising the temperature to −30°C led to complete consumption of the donor **2**. Efficient and highly stereoselective glycosylation of the acceptor took place in each case, affording after chromatography the respective β-disaccharides **7**–**9** in the yields shown. The corresponding α-isomers were not detected by NMR or TLC in the crude product mixture. Mass spectral and ^{1}H and ^{13}C NMR analysis confirmed the structures, and the anomeric stereochemistry is indicated by *J* for H-1′/H-2′ (9.0, 9.0, and 10 Hz, respectively).

Two of the disaccharides were treated with excess Raney nickel in ethanol solution at room temperature to afford the corresponding 2′-deoxy β-disaccharides **10** and **11** in the yields shown. As expected, **11** proved to be identical with the literature compound,[15] according to its ^{1}H NMR spectrum at 500 MHz. The structure of the triacetate/tribenzoate **10**, whose ^{1}H NMR spectrum closely resembles that of the corresponding disaccharide hexaacetate,[16] was further corroborated by conversion to the hexaacetate itself (NaOMe, MeOH; then Ac_2O, pyridine, DMAP; 90% overall), and then comparison of its ^{1}H NMR spectrum with the reported values.

The disarmed[17,18] donor **2** exhibits high stereoselectivity and remarkable reactivity at −78°C. Presumably the trimethylsilyl triflate activator removes the C-1 acetoxy by *O*-silylation at the low temperature to afford the cyclized intermediate **6**, which then kinetically glycosylates the acceptor at the same temperature. Triflic acid, which forms as the result of partial glycosylation of the hydroxyl-bearing acceptor, is then available to serve as the (somewhat weaker) activator after trimethylsilyl triflate is consumed, necessitating the increase in bath temperature to about −30°C. Anomerization of the donor[10] is not observed. The glycosylation is complete under conditions that are apparently milder than those reported for similar donors with 2-acetoxy[19] (**12**) and 2-acetamido-2-deoxy[20] (**13**) participating substituents.

The reactivity of the three anomeric acetate donors **2**, **12**, and **13** (see structures below) toward trimethylsilyl triflate was more directly compared under glycosylation conditions similar to those used for the formation of disaccharide **9**. Treatment of **11** with 0.5 equiv. of trimethylsilyl triflate and 1.3 equiv. of acceptor **5** at −78°C for 0.5 h, and then −30°C for 3 h led to no detectable disaccharide formation, as determined by comparison of the ^{1}H NMR spectrum of the crude reaction mixture with the spectrum reported for the authentic expected disaccharide.[21] Furthermore, the known coupled orthoester,[22] which is isomeric with the disaccharide and might form under these conditions via a cyclized intermediate, was also not detected (no 3H s at 1.72 ppm[23]). Rather, the crude reaction mixture consisted primarily of unreacted, non-anomerized, donor and acceptor, according to ^{1}H NMR and TLC analysis. Treatment of **13** with 2.0 equiv. of trimethyl-

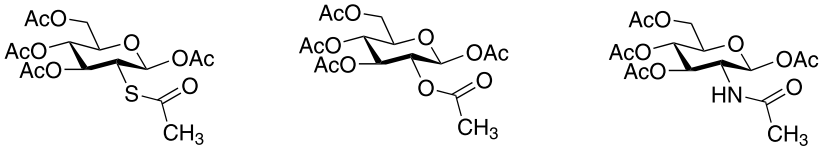


silyl triflate at −78 and −30°C in the absence of acceptor led to no reaction, according to TLC analysis. Further stirring for 1 h at 0°C likewise caused no cyclization, and after aqueous bicarbonate quench the starting donor **13** was recovered in high yield. Neither formation of the known oxazoline nor amide *C*-silylation[24] was observed, although transient amide *O*-silylation[25] might have gone undetected.

What is the source of the reactivity of **2** as a glycosyl donor? Compared with the 2-acetoxy substitutent of **12**, the 2-thio-*S*-acetyl substituent (–SAc) of donor **2** has greater electron density on the carbonyl oxygen, as evidenced by the expected bond length[26] and infrared stretching frequency of C=O.[27] Donor **2** also possesses two considerably longer C–S single bonds compared with C–O of **12**.[28] On the other hand, the inductive effects[29] of –SAc and –OAc substituents are quite similar, according to their σ_I values. Therefore, greater electron density on the carbonyl oxygen and greater C–S bond lengths relative to C–O may be cited as possible factors contributing to the reactivity of **2**. The corresponding 2-acetamido donor **13**, by contrast, should benefit from its high amide carbonyl electron density and lower –NAc inductive effect, and yet is relatively unreactive. This may be due to competing *O*-silylation at the NC=O, its most Lewis basic site, which might be expected to slow *O*-cyclization, even in the presence of 2 equiv. of trimethylsilyl triflate. The shorter C–N single bond lengths[30] of **13** relative to C–S of **2** may also play a role.

ionization at C-1 were the only consideration. In other words, –SAc should be the better participating neighboring group (by Lewis basicity), but should 'disarm' the donor by induction to an extent similar to –OAc. The same argument can be used to rule out initial formation of an intermediate anomeric triflate.[31] Third, the –NHAc of **13** is known to cyclize in the presence of trimethylsilyl triflate to form the stable and characterizable oxazoline. The –SAc of **2** ought to cyclize by an analogous process, and other carbonyl-bearing donor 2-substituents,[1,2] including –OCOPh[32] and –OCO_2-(*p*-ClC_6H_4),[33] are thought to behave in comparable fashion. Participation by the –SAc sulfur atom to form an *S*-acetyl-episulfonium intermediate is unlikely due its poor Lewis basicity.[34]

2′-Deoxy-β-pyranoside substructures occur within the oligosaccharide portion of a variety of natural products, and their stereoselective synthesis is of continuing interest.[2,10] 2′-Thiopyranosides have likewise been *S*-glycosylated[35,36] and *S*-alkylated[37] to make enzyme-resistant thio analogues of oligosaccharides, among other applications.[38] The use of 2-thio-*S*-acetyl as a participating group in β-glycosylations potentially expands the range of 2′-thio sugars and *S*-derivatives that are easily accessible. Despite the availability of many alternative β-directing donor 2-substituents, its use may also offer some advantage in the stereoselective synthesis of 2′-deoxy-β-disaccharides where, for example, one can take advantage of its facile participation at low temperature.[39]



2	**12**	**13**
forms glycosides at -78 and -30 °C	no reaction at -30 °C	no reaction at 0 °C
C=O 1.20 Å	C=O 1.18 Å	C=O 1.21 Å
S–CO 1.76 Å	O–CO 1.35 Å	N–CO 1.34 Å
C–SAc 1.81 Å	C–OAc 1.43 Å	C–NHAc 1.45 Å
IR 1708 cm^{-1}	IR 1747 cm^{-1}	IR 1656 cm^{-1}
σ_I (-SAc) = 0.39	σ_I (-OAc) = 0.38	σ_I (-NHAc) = 0.28

Several lines of circumstantial evidence point to actual participation at C-1 by the carbonyl oxygen of –SAc. First, the glycosylations of **2** are highly β-stereoselective, and in no case, including the reaction leading to **7**, could we detect the α-linked disaccharide. Some α-disaccharide might have been expected had the reaction proceeded through an oxocarbenium intermediate.[11] Second, the rapid rate of reaction of the donor **2** at −78°C relative to the 2-*O*-acetyl version **11** suggests that the cyclization rather than formation of an oxocarbenium ion is rate-determining, as the respective oxocarbenium ions should form at comparable rates if

Acknowledgements

We are grateful to Merck & Co. and Vela Pharmaceuticals Inc. for financial support. We thank Etzer Darout for the control reaction of **13** with trimethylsilyl triflate, and Professor Joseph A. Potenza for assistance with the Cambridge Crystallographic Data Base search.

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39. Characterization of new compounds. Compound **2**: mp 117.5–118.5°C; ^{1}H NMR [500 MHz, $CDCl_3$, δ (multipl., *J* in Hz, integr.)] 5.79 (d, 9.5, 1H), 5.27 (dd, 9.0, 11.5, 1H), 5.05 (t, 10, 1H), 4.28 (dd, 4.0, 12.5, 1H), 4.06 (dd, 2.0, 12.5, 1H), 3.81 (ddd, 2.0, 4.0, 10.0, 1H), 3.69 (dd, 9.5, 11.5, 1H), 2.27 (s), 2.02 (s), 1.98 (s), 1.95 (s); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 192.25, 170.59, 169.90, 169.42, 168.74, 92.02, 72.55, 70.98, 68.81, 61.53, 47.07, 30.65, 20.68 (2 C's), 20.53, 20.48; LC–MS *m*/*z* 429.0 MNa^+. Compound **7**: colorless oil; ^{1}H NMR 7.94 (d, 7.0, 2H), 7.90 (d, 7.0, 2H), 7.82 (d, 7.5, 2H), 7.49 (app q, 7.5, 2H), 7.39 (t, 7.5, 1H), 7.35 (app q, 7.5, 4H), 7.25 (t, 7.5, 2H), 6.14 (t, 9.5, 1H), 5.48 (t, 10.0, 1H), 5.30 (dd, 11.5, 9, 1H), 5.23–5.28 (m, 2H), 5.05 (t, 9.5, 1H), 4.73 (d, 9.0, 1H), 4.26–4.30 (m, 2H), 4.05–4.11 (m, 2H), 3.71–3.76 (m, 2H), 3.61 (dd, 9.0, 11, 1H), 3.50 (s, 3H), 2.36 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H); ^{13}C NMR 133.03, 129.87, 129.77, 129.60, 129.22, 129.01, 128.91, 128.43, 128.37, 128.21, 101.15, 96.84, 71.94, 71.63, 71.03, 70.50, 69.48, 69.36, 68.62, 68.30, 62.00, 55.54, 48.39, 30.63, 20.63, 20.55; LC–MS *m*/*z* 875.0 MNa^+. Compound **8**: colorless oil; ^{1}H NMR 7.21–7.39 (m, 15H), 4.90–4.98 (m, 3H), 4.74 (d, 11.5, 1H), 4.70 (d, 12.5, 1H), 4.69 (d, 12, 1H), 4.56 (d, 12, 1H), 4.55 (d, 3.5, 1H), 4.48 (d, 9.0, 1H), 4.39 (d, 12.0, 1H), 4.10 (dd, 4.5, 12, 1H), 3.91 (t, 10, 1H), 3.86 (dd, 12, 2.5, 1H), 3.80 (t, 9.5, 1H), 3.79 (dd, 11, 2.5, 1H), 3.62 (br app t, 9.5, 2H), 3.44–3.49 (m, 2H), 3.34 (s, 3H), 3.26 (ddd, 2.5, 4.5, 13.0, 1H), 2.25 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 1.92 (s, 3H); ^{13}C NMR 192.38, 170.66, 170.03, 169.46, 139.45, 138.26, 137.69, 128.64, 128.49, 128.29. 128.21, 128.18, 128.06, 128.03, 127.71, 127.32, 127.09, 99.34, 98.35, 80.03, 78.83, 75.91, 74.98, 73.43, 71.63,

71.27, 69.45, 69.34, 68.17, 61.87, 55.33, 48.82, 30.67, 20.62, 20.57, 20.53; LC–MS m/z 832.9 MNa^+. Compound **9**: colorless oil; ^1H NMR 5.44 (d, 4.5, 1H), 5.20 (dd, 9.0, 11.5, 1H), 5.00 (t, 9, 1H), 4.69 (d, 10.0, 1H), 4.56 (dd, 1.5, 10.0, 1H), 4.23–4.28 (m, 2H), 4.15 (dd, 2.0, 5.0, 1H), 4.09 (dd, 2.0, 11.5, 1H), 3.96 (dd, 1.5, 11.5, 1H), 3.87–3.90 (m, 1H), 3.63–3.68 (m, 2H), 3.55 (dd, 9.0, 11.5, 1H), 2.29 (s, 3H), 2.04 (s, 3H), 1.96 (s, 6H), 1.48 (s, 3H), 1.39 (s, 3H), 1.28 (s, 6H); ^{13}C NMR 192.91, 170.63, 170.09, 169.47, 109.23, 108.56, 101.59, 96.14, 71.52, 71.24, 71.02, 70.56, 70.34, 69.51, 69.32, 67.69, 61.99, 48.35, 30.63, 26.02, 25.86, 24.99, 24.26, 20.70, 20.56, 20.54. LC–MS m/z 629.1 MNa^+. Compound **10**: colorless oil; ^1H NMR (CD_3OD) 7.22–7.51 (m, 10H), 7.74–7.88 (m, 5H), 5.99 (t, 10.0, 1H), 5.50 (t, 10.0, 1H), 5.25 (dd, 4.0, 10.5, 1H), 5.16 (d, 4.0, 1H), 4.98 (ddd, 5.5, 7.5, 13.0, 1H), 4.80 (1H partially obscured by HOD), 4.55 (dd, 2.0, 9.5, 1H), 4.24 (ddd, 2.5, 5.5, 10.0, 1H), 4.16 (dd, 6.4, 11.5, 1H), 3.98 (dd, 2.5, 11.5, 2H), 3.70 (dd, 6.0, 11.5, 1H), 3.61 (ddd, 2.0, 5.0, 10, 1H), 3.45 (s, 3H), 2.26 (ddd, 2.0, 5.0, 12.0, 1H), 1.94 (s, 3H), 1.94 (s, 3H), 1.93 (s, 3H), 1.57 (app q, 9.5, 1H); ^{13}C NMR (CD_3OD) 171.23, 170.57, 170.44, 166.12, 165.80, 165.59, 133.57, 133.50, 133.34, 129.59, 129.53, 129.34, 129.18, 129.14, 128.5, 128.41, 128.32, 100.23, 97.22, 71.98, 71.85, 70.99, 70.61, 69.71, 69.45, 68.90, 68.40, 62.42, 54.88, 35.88, 19.61, 19.48 (2 C's); LC–MS m/z 801.1 MNa^+.