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Solution-Phase Hexasaccharide Synthesis Using Glucosyl Iodides

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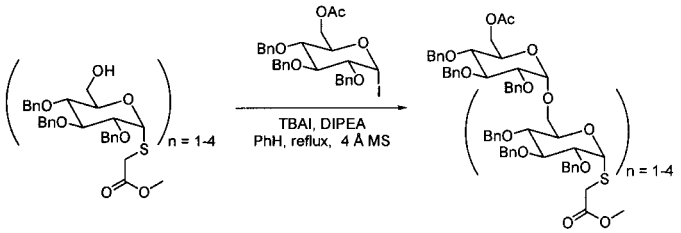
ABSTRACT



Oligosaccharides composed of 1,6-glucosyl residues have been prepared from glucosyl iodides. The reactions are highly stereoselective, giving the α-glycosides as the only isolated products in yields ranging from 84% to 94%. Oligomer synthesis can take place in an iterative 1 + 1 + 1 fashion or in a convergent manner where dimer iodides serve as donors for higher order acceptors.

Many strategies are available for the construction of *O*-glycosidic linkages as a result of the early work of Fischer,[1] Köenigs and Knorr,[2] Helferich and Olst,[3] Lemieux,[4] and Paulsen[5] and the more recent work of Schmidt,[6] Kahne,[7] Danishefsky,[8] Seeberger,[9] and others.[10] Glycosyl halides are among the most useful donors; however, they have not been widely employed in the construction of higher order oligosaccharides. Because recent studies[11,12] have shown that iodide donors offer advantages over bromides in terms of reaction times, efficiencies, and stereochemical outcomes, we decided to probe the utility of glycosyl iodides in solution-phase oligosaccharide synthesis.

We have found that the most practical way of generating glycosyl iodides is through the reaction of glycosyl acetates with iodotrimethylsilane.[13] The byproduct, trimethylsilyl acetate, can be removed through rotoevaporation, yielding the iodide without need of further purification. However, the emergence of glycosyl iodides as viable glycosyl donors has prompted other groups to devise new preparative methods including the use of solid supported diphenylphosphine and molecular iodine[12c] or in situ generation of anhydrous hydroiodic acid from thiolacetic acid and molecular iodine.[14]

Our glycosylation studies involve a modification of the in situ anomerization conditions established for glycosyl bromides in the pioneering work of Lemieux and co-workers.[15] A combination of glycosyl iodide and tetrabutyl-

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(2) Köenigs, W.; Knorr, E. *Chem. Ber.* **1901**, *34*, 957.
(3) Helferich, B.; Ost, W. *Chem. Ber.* **1962**, *95*, 2612.
(4) Lemieux, R. U.; Hendricks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056.
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(11) (a) Bhat, A. S.; Gervay-Hague, J. *Org. Lett.* **2001**, *3*, 2081. (b) Hadd, M. J.; Gervay, J. *Carbohydr. Res.* **1999**, *320*, 61. (c) Gervay, J. *Org. Synth.: Theory Appl.* **1998**, *4*, 121−153. (d) Gervay, J.; Hadd, M. J. *J. Org. Chem.* **1997**, *62*, 6961.
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ammonium iodide (TBAI) in the presence of suitable nucleophiles quickly yields highly α-selective *C*-, *N*-, and *O*-glycosides through what is believed to be an S_N2-like reaction.[11b] In all of these reactions, glycosyl iodides offer clear advantages over glycosyl bromides including increased stereoselectivity and faster reaction times.

It seemed plausible that the unique reactivity of glycosyl iodides would be useful in extended oligosaccharide syntheses, which can proceed in one of two directions. The chain can grow through elongation of the reducing end via glycosyl donor activation and subsequent acceptor addition (Figure 1, Eq. I). Alternatively the nonreducing end of the growing

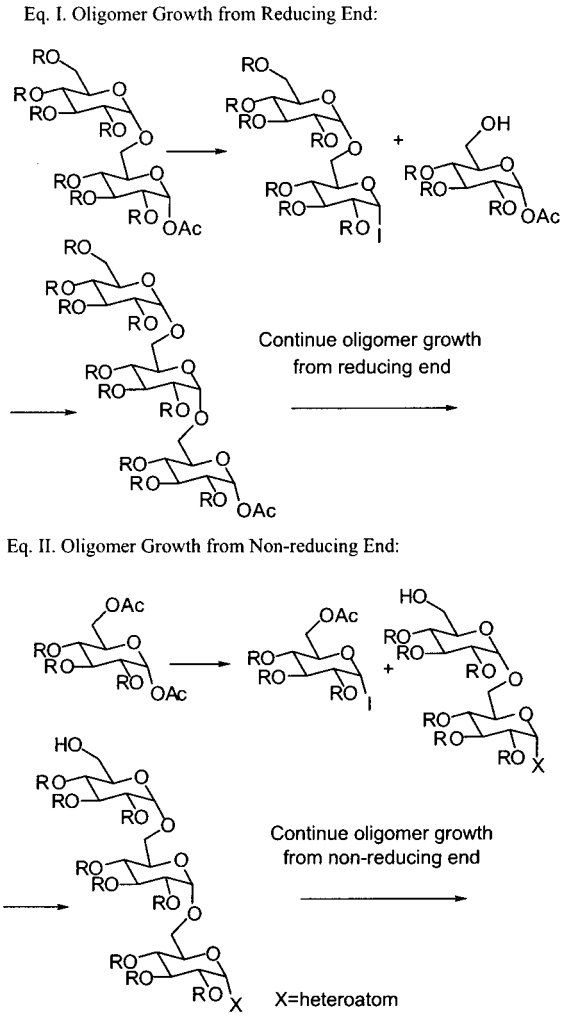

Figure 1. Potential glycosylation stategies.

chain can serve as the acceptor when presented with glycosyl donor (Figure 1, Eq. II). We were mindful of the susceptibility of the glycosidic linkage[11a] to the action of TMSI, so the latter route was first investigated.

This design strategy required the use of an orthogonally functionalized monomer unit onto which the growing chain could be anchored. After achieving oligosaccharide synthesis, it would be desirable to have the reducing end amenable to further elaboration. To this end, the thioglycolate group seemed an appropriate choice (Figure 2). For example,

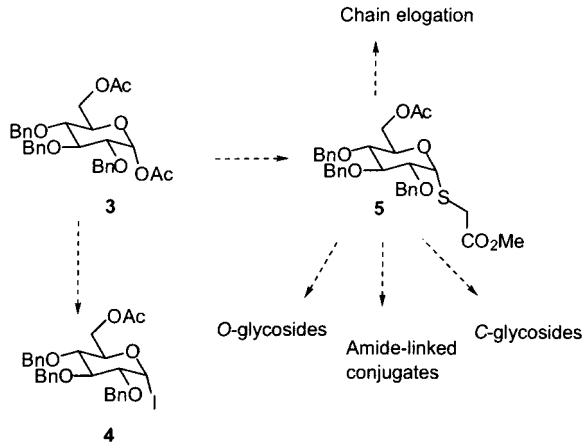

Figure 2. Orthogonally functionalized monomer units.

conversion of the ester functionality to an acid would allow conjugation through amide formation. Alternatively, the thioglycoside could be activated to yield *O*-glycosides, or perhaps it could be used in a Ramberg−Bäcklund-type rearrangement, as recently demonstrated by Franck[16] and Taylor.[17] For the internal building blocks, we would require a substrate that could be selectively activated at the anomeric center with a C-6 protecting group that could be removed after coupling. With these objectives in mind, 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-glucopyranose (**3**) was chosen as the central building block. Reaction of this compound with TMSI would yield the glycosyl iodide (**4**) as an essential donor building block. Alternatively **3** could be reacted to afford the thioglycolate **5** as the reducing-end anchor.

The synthesis of central building block **3** was quickly realized in two steps through known transformations. Commercially available α-*O*-methyl-D-glucopyranose (**1**) was converted to perbenzylated sugar **2** through the action of excess NaH, BnBr, and catalytic TBAI in DMF (Scheme 1). According to methodology developed by Kong and coworkers,[18] perbenzylated α-*O*-methyl glucopyranose (**2**) dissolved in a mixture of Ac_2O/HOAc (2:1) was treated with freshly fused $ZnCl_2$ in Ac_2O/HOAc (2:1) to afford the 1,6-di-*O*-acetyl monosaccharide (**3**).[19] Addition of 1.1 equiv of TMSI to a solution of **3** dissolved in dry CH_2Cl_2 provided the desired α-1-iodo 6-*O*-acetyl-2,3,4-tri-*O*-benzylglucopyranosyl iodide **4** in quantitative yield, as determined by ^1H

(14) Chervin, S. M.; Abada, P.; Koreeda, M. *Org. Lett.* **2000**, *2*, 369.
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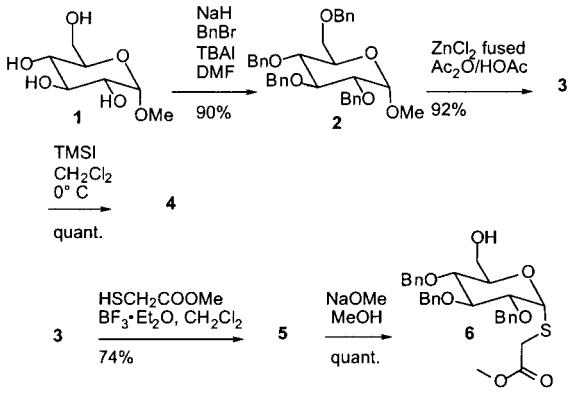
(19) This sequence of reactions has been performed on large scale (20 g).

Scheme 1. Synthesis of Monomer Units

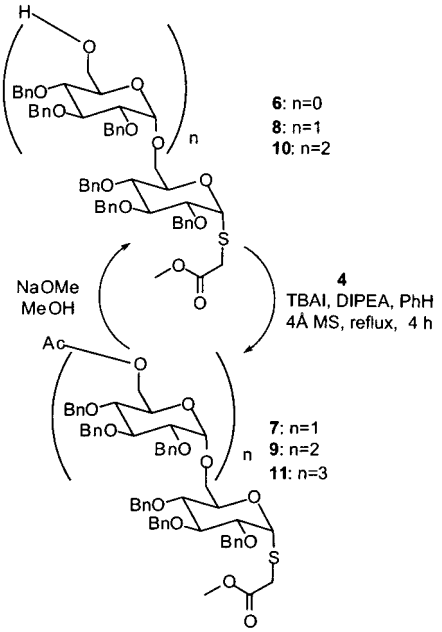


NMR.[20] In this transformation, it was important to use flame-dried glassware and an inert atmosphere (argon). Chilling the mixture in an ice bath throughout the course of the reaction also prevented formation of side products, as TMSI is also known to cleave benzyl ethers.[21]

Treatment of compound **3** with excess $BF_3{\cdot}Et_2O$ in the presence of methyl thioglycolate provided thioglycoside **5** in 74% yield. Saponification of **5** quickly afforded the glycosyl acceptor **6**, which would serve as the terminal building block.

Glycosyl donor **4** was typically used immediately after synthesis. However, **4** stored in the freezer under argon in anhydrous benzene remained stable even after 1 month, as monitored by ^{1}H NMR. In a typical glycosylation experiment, **4** was cannulated into a stirring solution of glycosyl acceptor **6**, TBAI, DIPEA, and 4 Å molecular sieves (Scheme 2). The reaction mixture was refluxed for 4 h under a positive argon

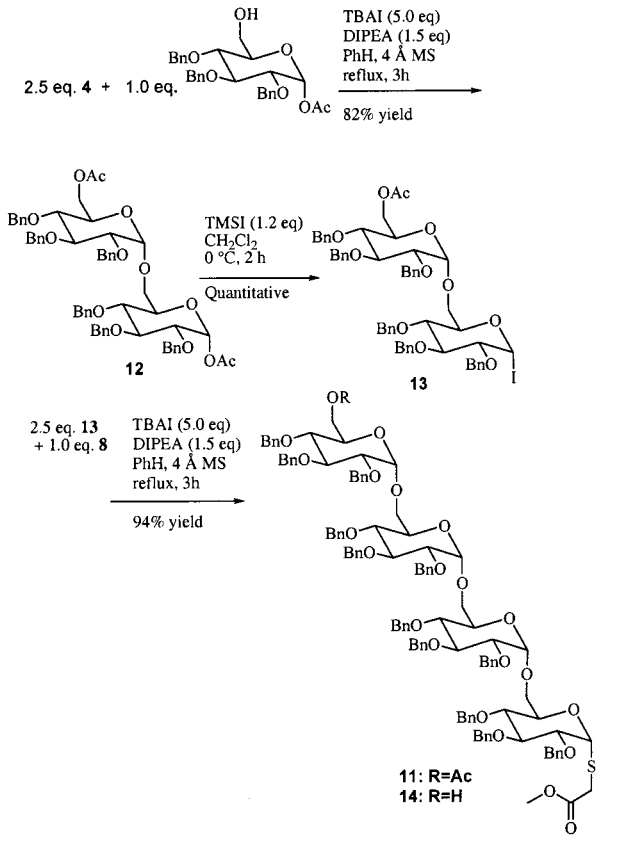
Scheme 2. 1 + 1 Iterative Oligosaccharide Synthesis



pressure. Only α-linked disaccharide **7** was isolated in 88% yield after silica gel column chromatography. The stereochemical outcome was established through a combination of NMR (C_6D_6) methods, which clearly showed the anomeric proton as a doublet at δ 4.97 ppm, with a coupling constant of 3.4 Hz. The assignment was further corroborated by ^{13}C NMR giving a diagnostic anomeric peak at δ 97.66 ppm. No evidence for β-glycoside formation was detected. Deacetylation of **7** gave **8**, and repetition of the glycosylation procedure afforded trisaccharide **9** in 92% yield.[22] Repeating the deacetylation and glycosylation steps on **9** afforded tetrasaccharide **11**.[23] These glycosylations were performed in the absence of ambient light to prevent the formation of radical intermediates.[24,25] On the basis of our earlier studies, we believe that the high α-selectivity is due to S_N2-like displacement of the more reactive β-iodide.

Encouraged by the high efficiency of the 1 + 1 interative process we next investigated a more convergent approach. A disaccharide glycosyl donor (**13**) was prepared as shown in Scheme 3. Glycosylation of **13** with the disaccharide

Scheme 3. 2 + 2 Oligosaccharide Synthesis

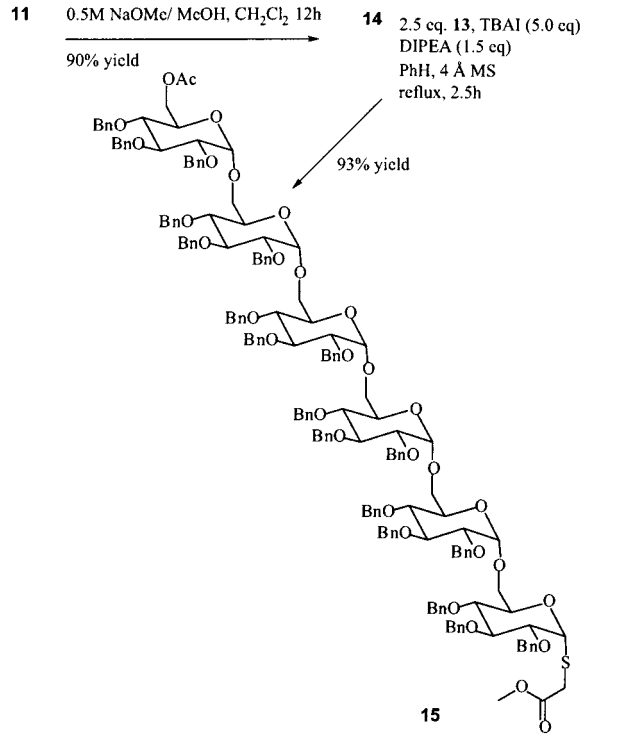


thioglycolate acceptor afforded the tetrasaccharide (**11**) in 94% yield. The tetrasaccharide was then converted to an acceptor through hydrolysis of the C-6′ acetate functionality

(20) Characteristic peak in ^{1}H NMR (DRX500, 500 MHz, C_6D_6) δ 6.78, d, J = 3.3 Hz.

(21) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761.

Scheme 4. 2 + 4 Oligosaccharide Synthesis



to afford **14**, which was subsequently reacted with **13** to afford the hexasaccharide **15** in 93% yield (Scheme 4).[26]

It is notable that relatively simple di-*O*-acetate precursors can be employed as fundamental building blocks for oligosaccharide synthesis. Moreover, there appears to be little difference in relative reactivity between monomer and dimer donors. Similarly monomer, dimer, and tetramer acceptors react equally well suggesting that this methodology may be applicable to a variety of systems.

Currently, 2.5 equivalents of donor is required to achieve high conversion. The byproduct is the 2-benzyloxyglycal resulting from elimination of HI.[27] It is possible that this will not be a universal problem, as we have already shown that mannosyl iodides do not undergo elimination.[11b] Nonetheless, future investigations include establishing methods for the use of stoichiometric glycosyl donor.

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(22) ^{1}H NMR (DRX500, 500 MHz, C_6D_6) δ 5.97 (d, 1H, J = 5.5 Hz, H-1A), 5.27 (d, 1H, J = 3.1 Hz, H-1B), 5.12 (d, 1H, J = 3.3 Hz, H-1C), 1.78 (s, 3H, $COCH_3$). ^{13}C NMR (DRX500, 125 MHz, C_6D_6) δ 97.71 (C-1C), 97.20 (C-1B), 82.92 (C-1A), 14.81 ($COCH_3$).

(23) ^{1}H NMR (DRX500, 500 MHz, C_6D_6) δ 5.97 (d, 1H, J = 5.6 Hz, H-1A), 5.32 (d, 1H, J = 3.4 Hz, H-1B), 5.30 (d, 1H, J = 3.4 Hz, H-1C), 5.14 (d, 1H, J = 3.6 Hz, H-1C), 1.78 (s, 3H, $COCH_3$). ^{13}C NMR (DRX500, 125 MHz, C_6D_6) δ 97.78 (C-1D), 97.56 (C-1C), 97.28 (C-1B), 82.93 (C-1A), 20.44 ($COCH_3$).

(24) Araki, Y.; Endo, T.; Tanji, M.; Nagasawa, J.; Ishido, Y. *Tetrahedron Lett.* **1987**, *28*, 5853.

(25) Axon, J. R.; Beckwith, A. L. J. *J. Chem. Soc., Chem. Commun.* **1995**, 549.

(26) ^{1}H NMR (DRX500, 500 MHz, C_6D_6) δ 5.97 (d, 1H, J = 5.5 Hz, H-1A), 5.36 (d, 1H, J = 3.5 Hz, H-1B), 5.34 (apparent t, 2H, J = 4.6, 3.9 Hz, H-1D, H-1C), 5.32 (d, 1H, J = 3.5 Hz, H-1E), 5.15 (d, 1H, J = 1.8 Hz, H-1F), 1.78 (s, 3H, $COCH_3$). ^{13}C NMR (DRX500, 125 MHz, C_6D_6) δ 97.79 (C-1F), 97.66 (C-1E), 97.63 (C-1D), 97.61 (C-1C), 97.27 (C-1B), 82.95 (C-1A), 20.44 ($COCH_3$).

(27) 2-Benzyloxyglycals of both monomer and dimer iodides are formed. The elimination products have characteristic NMR peaks: ($CDCl_3$) ^{1}H δ 6.27 ppm, (s, H-1); ^{13}C δ 127 ppm (C-1).