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Synthesis of (1→4)-Linked 2-Deoxy-2-fluoroglucose Oligomers. 1

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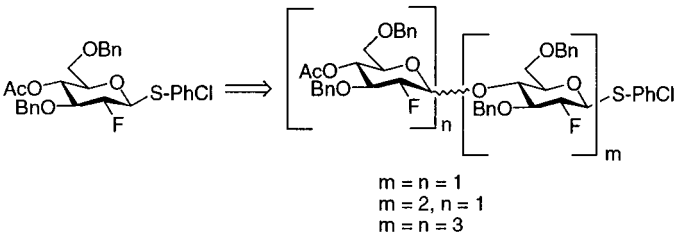
ABSTRACT



Thioglycosides of natural monosaccharides are readily converted into their corresponding chlorides by diphenylchlorosulfonium chloride. This reagent can likewise effect the conversion of the more stable 4-chlorophenylthio 2-deoxy-2-fluoroglucose derivatives into chloride glycosyl donors. On the basis of this activation strategy, it was possible to assemble unnatural oligosaccharides composed of 2-fluorodeoxy sugars.

Starch primarily consists of two glucan fractions, namely, linear amylose which is composed of α-(1→4)-linked glucose moieties and amylopectin which additionally contains α-(1→6)-linked glucose branches.[1] The amylose fraction crystallizes in polymorphic forms known as the A and B forms, both of which are right-handed double helices.[2] A third form, V-amylose, is found in the non-A and non-B segments of amylose and is folded into a left-handed single-helical motif. The helix of V-amylose contains six glucose units per turn with a pitch height of approximately 8 Å.[3]

The properties of V-amylose closely resemble those of the cyclodextrins and, in particular, α-cyclodextrin which may be viewed as a mimetic of a single V-amylose turn.[4] Glucose residues in both of these structures are in the syn orientation, and the helical structure is stabilized by inter-glucose hydrogen bonds between $O(3)_n-O(2)_{n+1}$. Additional stability to the V-amylose helix is provided by $O(6)_n-O(2)_{n+6}$ hydrogen bond formation between the turns.[5] This helical arrangement provides a relatively hydrophobic interior cavity which is suited for the inclusion of substances and may be exploited for the purpose of drug delivery.[6] As the fluorine nucleus displays a wide chemical shift range in its NMR spectra, it seemed reasonable to us that installation of this reporter into the glucose residues[7] of α-(1→4)-linked oligmers may prove useful in studying maltooligosaccharide complexes. We report herein the preparation of (1→4)-linked 2-fluorodeoxyglucose (2-FDG) blocked donors/acceptors, which are suitable for the preparation of larger 2-FDG-based oligomers.

Surprisingly, there are few reports regarding the use of 2-fluorodeoxyhexosyl donors in oligosaccharide synthesis,[8] and to date, we are not aware of any reports on the assembly of simple 2,2′-difluoro-disaccharides nor of 2-deoxy-2-

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(1) Collins, P. M.; Ferrier, R. J. *Monosaccharides, Their Chemistry and Their Roles in Natural Products*; John Wiley & Sons: Chichester, 1995; Chapter 8.

(2) Imberty, A.; Chanzy, H.; Perez, S.; Buleon, A.; Tran, V. *J. Mol. Biol.* **1988**, *201*, 365−378.

(3) Murphy, V. G.; Zaslow, B.; French, A. D. *Biopolymers* **1975**, *14*, 1487−1501.

(4) Hinrichs, W.; Buttner, G.; Steifa, M.; Betzel, C.; Zabel, V.; Pfannemuller, B.; Saenger, W. *Science* **1987**, *238*, 205−208.

(5) Gessler, K.; Uson, I.; Takaha, T.; Krauss, N.; Smith, S. M.; Okada, S.; Sheldrick, G. M.; Saenger, W. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 4246−4251.

(6) Molteni, L. In *Drug Carriers in Biology and Medicine*; Gregoriadis, G., Ed.; Academic Press: London, 1979; pp 107−125.

(7) For a comprehensive review on fluorosugars, see: Tsuchiya, T. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 91−277.

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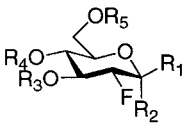

	R_1	R_2	R_3	R_4	R_5
1	OAc	H	Ac	Ac	Ac
2	H	Br	Ac	Ac	Ac
3a	H	S-PhCl	Ac	Ac	Ac
3b	S-PhCl	H	Ac	Ac	Ac
4a	H	S-PhCl	H	H	H
4b	S-PhCl	H	H	H	H
5a	H	S-PhCl	H	PhCH	
5b	S-PhCl	H	H	PhCH	
6a	H	S-PhCl	Bn	PhCH	
6b	S-PhCl	H	Bn	PhCH	
7a	H	S-PhCl	Bn	H	Bn
7b	S-PhCl	H	Bn	H	Bn
8a	H	S-PhCl	Bn	Ac	Bn
8b	S-PhCl	H	Bn	Ac	Bn
9a	H	Cl	Bn	Ac	Bn
9b	Cl	H	Bn	Ac	Bn

Figure 1.

fluorohexose oligomers. Compound **1** (Figure 1) was the starting point for the present synthetic work, and this material was readily accessible from 1,3,4,6-tetra-*O*-acetyl-β-D-mannopyranose[9] following published procedures.[10] Thioglycosylation of **1** with 4-chlorothiophenol in the presence of boron trifluoride diethyl etherate (8 equiv) gave α-thioglycoside **3a** (70%).[11] De-*O*-acetylation of this thioglycoside with sodium methoxide in methanol provided triol **4a**, which was reacted with benzaldehyde dimethyl acetal (catalytic amount of *p*-toluenesulfonic acid) to give **5a** (75%). Etherification of the remaining hydroxyl moiety with sodium hydride and benzyl bromide in tetrahydrofuran at 60 °C gave fully protected **6a** (72%), which was then subjected to reductive ring opening conditions[12] to provide di-*O*-benzyl thioglycoside **7a** (80%). Acetylation of the free 4-OH group furnished **8a**. Synthesis of the corresponding β-thioglycoside **8b** required the conversion of **1** to bromide **2**,[13] which was then reacted under phase-transfer conditions[14] with 4-chlorothiophenol to give **3b** (91%). The β-thioglycoside **3b** was then subjected to the same sequence of events as **3a** to give successively **4b** (quantitative), **5b** (76%), **6b** (95%), and finally **7b** (95%). The latter compound was then acetylated to provide fully protected fluorodeoxyglucose derivative **8b**. Both **8a** and **8b** were readily converted to their corresponding chlorides **9a** and **9b** upon treatment with diphenylchlorosulfonium chloride.[15] Reaction of **8a** under these conditions provided the chloride mixture **9b**/**9a** (11:1), whereas **8b** gave **9a** as the sole product. Thus, conversion presumably proceeds by inversion at the anomeric center. The result observed with **8b** was totally unexpected as β-thioglycosides of natural sugars typically provide a mixture of α:β chlorides.[16] We next studied the glycosyl donor protential of chlorides **9a** and **9b**. Reaction of chloride **9a** with acceptor **7b** failed to proceed under halide ion conditions[17] or in the presence of mercury bromide.[18] Glycosylation of **7b** (1 equiv) with **9a** (1 equiv) did proceed, however, using silver trifluoromethanesulfonate/2,6-di-*tert*-butylpyridine[19] in chloroform−toluene 4:1 to provide a mixture of **10** and **12** (**10**:**12** = 40:60) in 65% yield (Figure 2). Reaction of this same acceptor with chloride **9b** provided **10** and **12** in a 45:55 ratio.[20] Silver promotion of the reaction between **7b** and **9a** in either acetonitrile or tetrahydrofuran as solvent was remarkably sluggish, and even donor **2** has been noted to be reasonably stable to typical glycosylation conditions.[8e] Glycosidation was therefore effected under forced conditions as follows: The reaction mixture in acetonitrile−toluene 3:2 was concentrated under reduced pressure (<40 °C) and coevaporated with toluene several times. After workup and purification by silica gel column chromatography, **10** and **12** were obtained in 83% combined yield (**10**:**12** = 62:38). Silver-promoted glycosylation of the 4-OH of a glucose acceptor with a 2-deoxy-2-fluoromannosyl donor has previously been reported to proceed with preferential α-stereoselectivity.[8b] The poor stereoselectivity observed with the 2-deoxy-2-fluoroglucosyl donors reported herein is potentially related to the nature and reactivity of the fluoroglycosyl oxocarbonium intermediate. The product distribution obtained seems to be consistent with an S_N1-type reaction mechanism; however, further studies are required in order to gain an understanding of the precise mechanistic details.

The latter reaction conditions were selected for the subsequent assembly of (1→4)-linked 2-deoxy-2-fluoroglucose oligomers. Thus, disaccharide **10** was de-*O*-acetylated to give glycosyl acceptor **11**, and reaction of this compound with chloride **9a** under the aforementioned forced conditions provided both the α- and β-trisaccharides **13** and **16** (85% combined yield, **13**:**16** = 54:46). Compound **13** was then de-*O*-acetylated to give the trisaccharide glycosyl acceptor **15**, while the trisaccharide glycosyl donor **14** was prepared under the conditions used to generate chloride **9a**. Again, glycosylation of compound **15** with **14** was effected using

(8) (a) Vass, G.; Rolland, A.; Cleophax, J.; Mercier, D.; Quiclet, B,; Gero, S. D. *J. Antibiot.* **1979**, *32*, 670−672. (b) Ogawa, T.; Takahashi, Y. *J. Carbohydr. Chem.* **1983**, *2*, 461−467. (c) Shelling, J. G.; Dolphin, D.; Wirz, P.; Cobbledick, R. E.; Einstein, F. W. B. *Carbohydr. Res.* **1984**, *132*, 241−259. (d) McCarter, J. D.; Adam, M. J.; Braun, C.; Namchuk, M.; Tull, D.; Withers, S. G. *Carbohydr. Res.* **1993**, *249*, 77−90. (e) McCarter, J. D.; Yeung, W.; Chow, J.; Dolphin, D.; Withers, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 5792−5797.

(9) Pozgay, V.; Glaudemans, P. J.; Robbins, J. B.; Schneerson, R. *Tetrahedron* **1992**, *48*, 10249−10264.

(10) Kovac, P. *Carbohydr. Res.* **1986**, *153*, 168−170.

(11) Thioglycoside formation is slow, however, long reaction times leads to the formation of **3b** (~15% after 10 days).

(12) Garegg, P. J.; Hultberg, H. *Carbohydr. Res.* **1981**, *93*, C10−C11.

(13) Adamson, J.; Foster, A. B.; Westwood, J. H. *Carbohydr. Res.* **1971**, *18*, C10−C11.

(14) (a) Dess, D.; Kleine, H. P.; Weinberg, D. V.; Kaufman, R. J.; Sidhu, R. S. *Synthesis* **1981**, 883−885. (b) Rothermel, J.; Faillard, H. *Biol. Chem. Hoppe-Seyler* **1989**, *370*, 1077−1084.

(15) Sugiyama, S.; Diakur, J. M. *Org. Lett.* **2000**, *2*, 2713−2715.

(16) Kovac, P.; Lerner, L. *Carbohydr. Res.* **1988**, *184*, 87−112.

(17) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056−4062.

(18) Helferich, B.; Wedemeyer, K. F. *Liebigs Ann. Chem.* **1949**, *563*, 139−145.

(19) Hanessian, S.; Banoub, J. *Carbohydr. Res.* **1977**, *53*, C13−C16.

(20) Reaction of **7a** with **2** under the same conditions proceeds to give the corresponding disaccharides in 74% yield (α:β = 4.5/1).

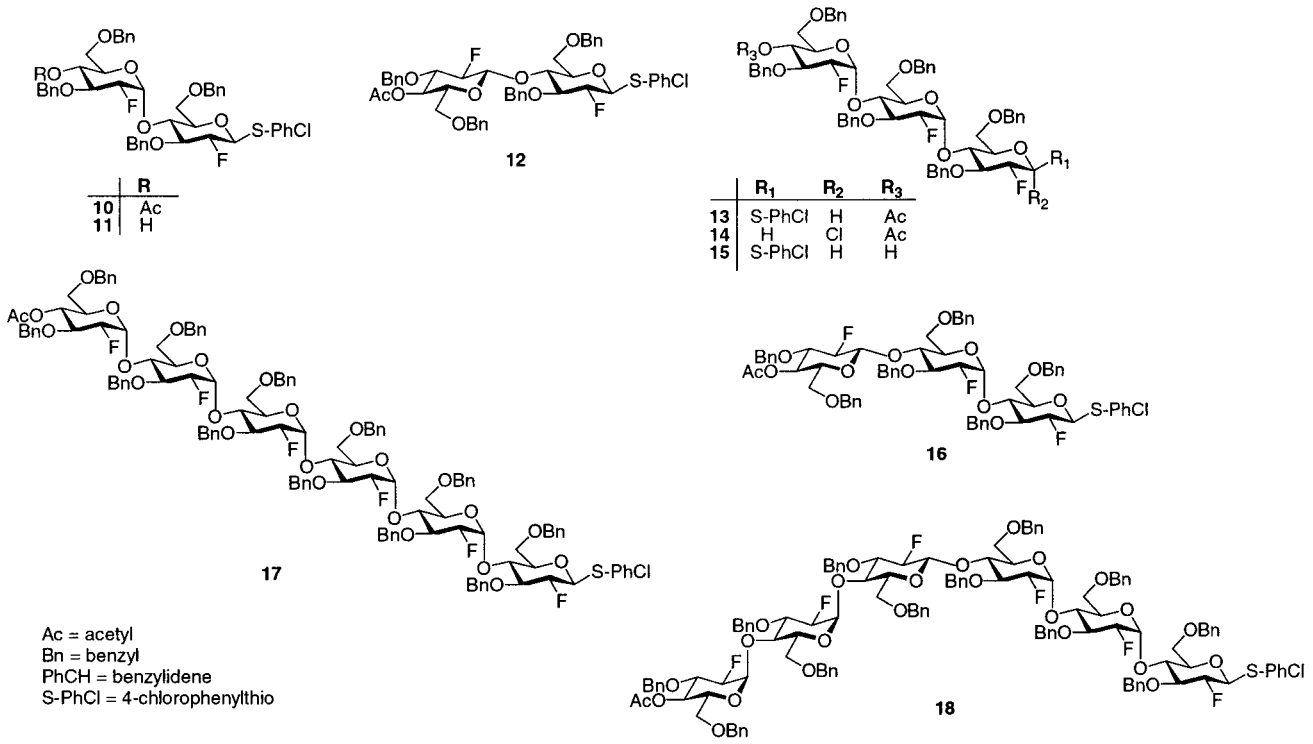

Figure 2.

the forced conditions to provide α- and *β*-hexasaccharides **17** and **18**, respectively (54% combined yield, **17**:**18** = 3:2).

In summary, we have extended the application of the conversion of thioglycosides into their corresponding glycosyl chlorides with diphenylchlorosulfonium chloride to include the generation of 2-deoxy-2-fluoroglucose donors. Control over stereoselectivity during glycosylation with 2-deoxy-2-fluoroglycosyl donors **9a** and **9b** proved to be challenging, nevertheless, the assembly of novel (1→4)-linked 2-deoxy-2-fluoroglucose oligomers using the resulting glycosyl chlorides has been demonstrated. These reported donors may be employed in the preparation of fluoromalto- and fluorocellulo-oligosaccharides or, potentially, other modified oligosaccharides. The deprotected 2-deoxy-2-fluoromaltohexose may prove useful in subsequent ^{19}F NMR complexation studies, while the blocked hexasaccharide **17** may be useful in the preparation of a fluorinated α-cyclodextin. Future efforts in our laboratory will be directed to both of these ends.

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Supporting Information Available: Spectral data for compounds **3**−**18** and the experimental details for the glycosylation reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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