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Stereospecific Synthesis of 1,2-*cis* Glycosides by Allyl-Mediated Intramolecular Aglycon Delivery. 2. The Use of Glycosyl Fluorides

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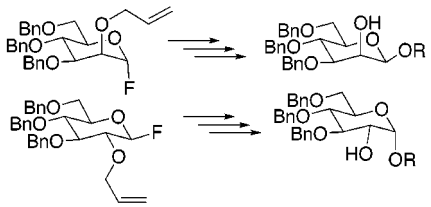
ABSTRACT



Stereospecific 1,2-*cis* glycosylation of 2-*O*-allyl-protected glucosyl and mannosyl fluorides via a sequence of allyl isomerization, *N*-iodosuccinimide-mediated tethering, and intramolecular aglycon delivery (IAD) is reported. The use of fluoride as anomeric leaving group is advantageous in that tethering efficiencies can be increased for hindered aglycon alcohols by the use of extended reaction times without competitive anomeric activation. Intramolecular glycosylation furnishes the desired α-glucosides and *β*-mannosides in an entirely stereoselective manner.

The efficient formation of 1,2-*cis* glycosidic linkages (e.g., α-*gluco*, *β*-*manno*) still represents a major challenge during oligosaccharide synthesis. One of the most appealing approaches to find a generally applicable solution to this problem is the technique of intramolecular aglycon delivery (IAD), which was originally pioneered for the synthesis of *β*-mannosides by Hindsgaul[1] and Stork[2] and more recently to greater effect by Ogawa.[3] As part of our ongoing interest in the synthesis of oligosaccharides containing 1,2-*cis* linkages, we originally reported[4] a modification of the Hindsgaul approach whereby *N*-iodosuccinimide (NIS) mediated tethering of an aglycon alcohol to a Tebbe-derived 2-*O* enol ether could be followed by in situ activation of a thioglycoside donor to yield 1,2-*cis* glycosides in a one-pot procedure. Subsequently we reported[5] the development of 2-*O*-allyl protected thioglycosides as glycosyl donors for IAD. Herein the enol ether at the 2 position of the glycosyl donor is accessed in near quantitative yield from the isomerization of a 2-*O*-allyl protecting group. However while

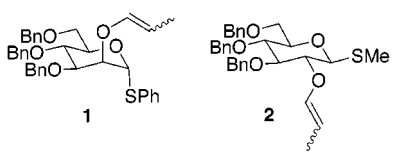


Figure 1. Thioglycoside donors bearing 2-*O*-propenyl ethers.

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(2) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087−1088. Stork, G.; La Clair, J. J. *J. Am. Chem. Soc.* **1996**, *118*, 247−248.
(3) Lergenmuller, M.; Nukada, T.; Kuramochi, K.; Dan, A.; Ogawa, T.; Ito, Y. *Eur. J. Org. Chem.* **1999**, 1367−1376. Dan, A.; Ito, Y.; Ogawa, T. *J. Org. Chem.* **1995**, *60*, 4680−4681. Ito, Y.; Ogawa, T.; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1765−1767.

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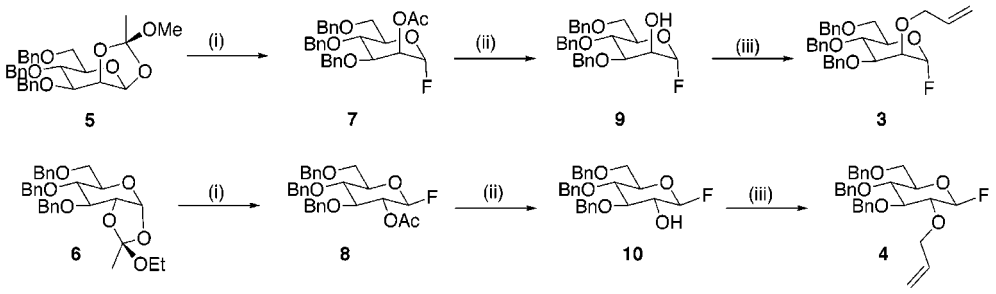
Scheme 1. Synthesis of the 2-*O*-Allyl Glycosyl Fluorides[a]



[a] (i) DAST, DCM, 0 °C, **7** 98%; (ii) ^{n}PrNH$_2$, MeOH, THF, 45 °C, **9** 99%; **10** 91% from **6**; (iii) allyl bromide, NaH, DMF, 0 °C, **3** 96%; **4** 93%.

good yields were obtained for NIS-mediated tethering of thioglycoside donors **1** and **2** (Figure 1)with a variety of simple aglycon alcohols, a limitation arose in the cases of more hindered carbohydrate alcohols, where tethering occurred more slowly.

The problem in particular was that in order to avoid competitive activation of the anomeric leaving group, the length of time that tethering could be left was limited. The situation was exacerbated in the case of the more reactive thioglycosides (such as SMe) wherein the differential in reactivity between the vinyl ether and the thioglycoside was small. Consequently in the case of hindered secondary carbohydrate alcohols, only modest to poor tethering yields were observed.

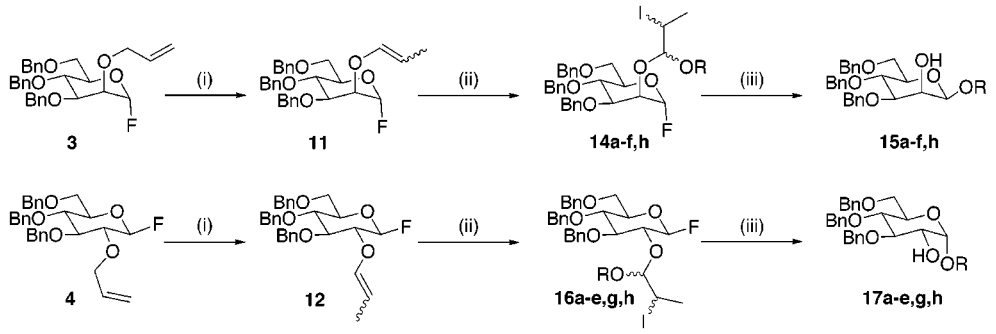
The utility of the approach was also somewhat limited by competitive intermolecular reaction during the one-pot procedure[5] when the glycosyl acceptor was present in excess. It was envisaged that the use of an orthogonal anomeric leaving group, which would not be activated under the tethering conditions, could provide a solution for the tethering of secondary carbohydrate aglycons. We herein report our findings using glycosyl fluorides as donors in the allyl-derived IAD system.

Both *manno* **3** and *gluco* **4** fluorides bearing allyl protection of the 2-hydroxyl were prepared from their respective ortho esters. Thus, DAST opening of **5**[6] and **6**[7] followed by an *n*-propylamine-mediated de-acetylation of acetates **7** and **8** and finally reprotection of OH-2 by treatment with allyl bromide and sodium hydride in DMF furnished the desired donors **3** and **4** (Scheme 1).

We were pleased to find that the isomerization following Boons' [8] protocol proceeded as smoothly as in the thioglycoside case to furnish the enol ethers **11** and **12** in excellent yields (Scheme 2). NIS-mediated tethering of the *manno* vinyl ether **11** was carried out with a variety of alcohols, **13a**−**h**, under our established reaction conditions,[9,10] and the desired mixed acetals **14a**−**f**,**h** were obtained in good to excellent yields (Table 1). Notable are the cases of the secondary carbohydrate alcohols **13e** and **13f**, and the steroid **13h**, whereby longer reaction times were now possible without activation of the glycosyl fluoride. However, in the case of the more hindered alcohols **13d**−**f**,**h** an increasing amount of the succinimide-trapped material **18** was isolated (Figure 2).

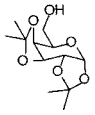
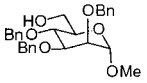
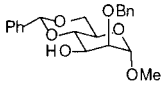
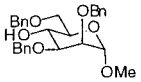
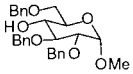
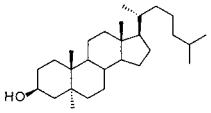
In the *gluco* series, tethering of enol ether **12** with the same series of alcohols **13a**−**h** likewise proceeded to give the mixed acetals **16a**−**e**,**g**,**h**. While excellent yields were obtained for alcohols **13a**−**c**, slightly lower yields were observed than in the *manno* series for some of the more bulky carbohydrates **13d**,**e**. Overall it is clear that tethering is

Scheme 2. Isomerization, Tethering, and IAD[a]



[a] (i) Wilkinson's catalyst, BuLi, THF, 70 °C, 96%; **3**, 98%, **4**; (ii) ROH **13a**−**h**, NIS, DCE, −40 °C → rt, 4 Å; (iii) AgOTf, DTBMP, $SnCl_2$, DCE, or MeCN, 50 °C; then TFA, H_2O or NIS, H_2O.

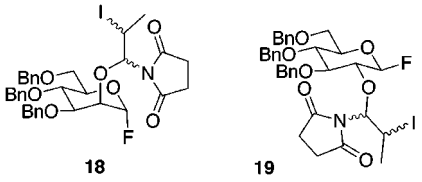
Table 1. Tethering and Glycosylation Yields

alcohol	ROH	product/yield of mixed acetals[a]	product/yield of glycosylation[c]
13a	MeOH	**14a**/97% **16a**/99%	**15a**/76%[e] **17a**/89%[e]
13b		**14b**/99% **16b**/99%	**15b**/70%[e] **17b**/66%[e]
13c		**14c**/98% **16c**/91%	**15c**/61%[d,f] **17c**/63%[d]
13d		**14d**/80% **16d**/79%	**15d**/49%,[e] 75%[d] **17d**/44%,[e] 46%[d]
13e		**14e**/83% **16e**/52%	**15e**/55%[d,f] **17e**/66%[d,g]
13f		**14f**/37%	**15f**/50%[d]
13g		**16g**/39%	**17g**/45%[d]
13h		**14h**/72% **16h**/68%[b]	**15h**/59%[d] **17h**/87%[d]

[a] Isolated yields. Reactions carried out in DCE except where otherwise stated. [b] Reaction carried out in THF. [c] Isolated yields. Acid treatment with TFA except where otherwise stated. [d] Reaction carried out in DCE. [e] Reaction carried out in acetonitrile. [f] No acid treatment. [g] Treatment with NIS, H_2O.

slightly less efficient in the *gluco* series. In the case of the steroid **13h**, which was only partially soluble in DCE, a change of solvent to THF for tethering was required in order to obtain acceptable yields. Again some succinimide-trapped material **19** was observed in the cases of the more hindered alcohols.

Activation of glycosyl fluorides is generally carried out by the use of some form of Lewis acid.[11] However the mixed acetal tether, which itself could be susceptible to Lewis acid catalyzed cleavage, must remain intact for IAD to operate and crucially ensure complete stereoselectivity. Several different reaction conditions often employed for the activation



18 **19**

Figure 2. Succinimide-trapped species.

of glycosyl fluorides were investigated, including Cp_2HfCl_2/$AgClO_4$/DTBMP,[12] $BF_3.OEt_2$,[13] and $BF_3.OEt_2$/DTBMP. While some of the desired products were usually observed, in these cases product formation was accompanied by hydrolysis of the tether to various extents, the formation of α/β mixtures of products (presumably arising from intermolecular glycosylation following the hydrolysis of the tether), or occasionally the formation of an intractable mixture of products. However, optimum results were obtained using tin(II) chloride, in combination with silver triflate and the hindered base 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP). Heating to 50 °C ensured that the reaction proceeded at an efficient rate. Thus, tethered materials treated under these conditions[14] furnished the desired β-mannosides **15a**−**f**,**h** and α-glucosides **17a**−**e**,**g**,**h** stereospecifically as the pure 1,2-*cis* anomers in all cases.

The efficiency of glycosylation was found to be solvent dependent. For example, it was observed that while the glycosylation of the *manno* mixed acetals **14c** in acetonitrile was sluggish, and occurred concomitantly with partial hydrolysis of the tether, an otherwise identical experiment employing dichloroethane (DCE) as solvent proceeded very quickly (ca. 2 h), with no hydrolysis; subsequent glycosylation reactions were therefore carried out in DCE.

Recently the question as to the possible fate of the oxonium ion produced after intramolecular glycosylation has arisen in the Ogawa/Ito PMB system.[15] In our earlier work on the thioglycosides,[5] byproducts were observed after glycosylation that were subsequently identified as mixed acetals. These presumably arise from trapping out of the oxonium ion produced after glycosylation reaction, by an

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(6) Zhang, Y. M.; Mallet, J.-M.; Sinaÿ, P. *Carbohydr. Res.* **1992**, *236*, 73−88.

(7) Lichtentaler, F. W.; Schneider-Adams *J. Org. Chem.* **1994**, *59*, 6728−6734.

(8) Boons, G.-J.; Isles, S. *J. Org. Chem.* **1996**, *61*, 4262−4271.

(9) **Typical procedure for tethering:** NIS (3 equiv) and powdered 4 Å molecular sieves were stirred in 1 mL of dry DCE under argon at −40 °C. The alcohol (1.5−3 equiv) was added by cannula under argon in 1.5 mL of dry DCE. The vinyl ether (0.1 mmol) was added by cannula under argon in 1.5 mL of dry DCE, and the mixture was allowed to warm slowly to room temperature. After 1−24 h, the mixture was diluted with dichloromethane, washed with aqueous sodium thiosulfate, dried, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography to give the mixed acetals as a colorless oil.

(10) Thieme, J.; Karl, H.; Schwenter, J. *Synthesis* **1978**, 696−698.

(11) Toshima, K. *Carbohydr. Res.* **2000**, *327*, 15−26.

(12) Matsumoto, T.; Maeta, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1988**, *29*, 3567−3570.

(13) Nicolaou, K. C.; Chucholowski, A.; Dolle, R. E.; Randall, J. L. *J. Chem. Soc., Chem. Commun.* **1984**, 1155−1156.

(14) **Typical procedure for glycosylation:** 2,6-Di-*tert*-butyl-4-methylpyridine (DTBMP) (2 equiv), silver triflate (2 equiv), anhydrous tin(II) chloride (2 equiv), and powdered 4 Å molecular sieves were stirred in 1 mL of dry DCE under argon at 50 °C. The mixed acetals (0.1 mmol) were added by cannula under argon in 3 mL of dry DCE, and the reaction was stirred at 50 °C until TLC indicated disappearance of starting material. TFA (2 mL) and water (1 mL) were added, and the solution was stirred for a further 30 min. Diethyl ether was added, and the mixture was filtered through Celite, washed with saturated aqueous bicarbonate and brine, dried, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography to give the pure 1,2-*cis* glycoside.

(15) Ito, Y.; Ando, H.; Wada, M.; Kawai, T.; Ohnish, Y.; Nakahara, Y. *Tetrahedron* **2001**, *57*, 4123−4132.

external alcohol acting as a nucleophile. Treatment of the crude reaction mixture with TFA during workup resulted in the hydrolysis of any such mixed acetals and an increased the yield of the desired 1,2-*cis* glycoside.

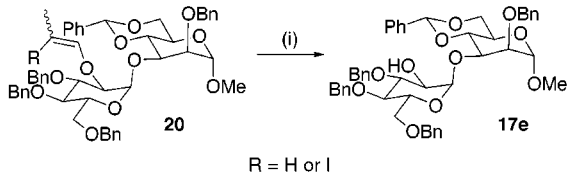
Again, during the course of this work it was found that byproducts (which were more prevalent in the *gluco* than the *manno* series) were observed by TLC. Treatment of these reaction byproducts with TFA yielded further 1,2-*cis* glycoside product. However it was noted that this byproduct hydrolysis was faster than we had observed previously. Therefore, in the case of alcohol **13e**, which possesses an acid-sensitive protecting group which may be cleaved by acid treatment, rather than adopting this acid workup procedure to optimize the yield of disaccharide product, we investigated the identity of this so-called "trapped" material. Rather surprisingly these minor byproducts were identified as the enol ethers **20**.[16]

Treatment of these enol ethers **20** with NIS/H_2O rapidly resulted in the formation of the desired glycoside **17e**, without any cleavage of the acid-sensitive 4,6-benzylidene protection (Scheme 3).

In summary we have demonstrated that glycosyl fluorides can be used as glycosyl donors for the allyl-mediated IAD approach to 1,2-*cis* glycosides and that tethering and intramolecular glycosylation may be achieved for a variety of alcohols. The use of glycosyl fluorides is advantageous in that tethering efficiency can be increased in the case of bulky secondary carbohydrate alcohols by the use of extended

(16) It is not yet entirely clear exactly how **20** (R = H) is formed, since this formally requires loss of I^+ from the oxonium ion produced after intramolecular glycosylation.

Scheme 3[a]



[a] (i) NIS, THF, H_2O then Et_3N.

reaction times. However, although the method efficiently provides β-mannosides, the use of 3-fold excesses of glycosyl acceptor and NIS means that other methods are currently more efficient for the synthesis of α-glucosides. Further investigations into the use of allyl-derived IAD, with the aim of increasing the efficiency of tethering and glycosylation steps, are currently in progress and will be reported in due course.

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Supporting Information Available: Full characterization and spectral data for compounds **3**, **4**, **7**−**12**, **15a**−**f**,**h**, and **17a**−**e**,**g**,**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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