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Stereospecific Synthesis of 1,2-*cis* Glycosides by Vinyl-Mediated IAD

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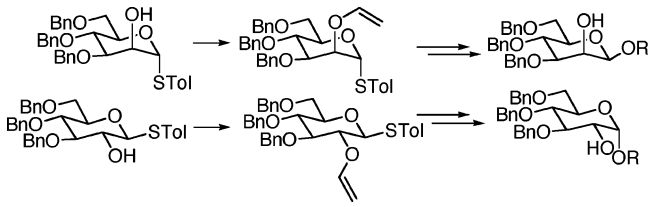
ABSTRACT



Stereospecific 1,2-*cis* glycosylation of 2-*O*-vinyl thioglycosides, synthesized from the corresponding alcohols by Ir-catalyzed transvinylation with vinyl acetate, is achieved by iodine-mediated tethering of a range of primary and secondary carbohydrate acceptors, followed by intramolecular aglycon delivery (IAD). The use of such an intramolecular glycosylation strategy furnishes the desired α-gluco and *β*-manno disaccharides in an entirely stereoselective manner.

The stereoselective synthesis of 1,2-*cis* glycosidic linkages, wherein the interglycosidic oxygen is formally *cis* to the 2-hydroxyl group of the glycosyl donor, represents a major challenge during oligosaccharide synthesis. While the use of neighboring group participation of 2-*O*-acyl-protected glycosyl donors reliably allows the synthesis of the corresponding 1,2-*trans* glycosides,[1] there is no correspondingly easy and general technique which allows the synthesis of 1,2-*cis* stereoisomers with complete stereocontrol.[2]

The recent development of several intramolecular glycosylation strategies[3] has shown promise for achieving higher levels of stereocontrol for glycoside and oligosaccharide synthesis. In particular, the intramolecular glycosylation strategy commonly referred to as intramolecular aglycon delivery (IAD), wherein the glycosyl donor and the glycosyl acceptor are linked prior to glycosylation by the 2-hydroxyl of the donor and the alcohol of the acceptor to be glycosylated, is perhaps the most predictable and reliable method of achieving 1,2-*cis* stereocontrol. This approach was originally developed specifically for the synthesis of *β*-mannosides by Hindsgaul[4] and Stork[5] and then used subsequently to greater effect by Ogawa.[6]

As part of our ongoing interest in the synthesis of oligosaccharides containing 1,2-*cis* linkages,[7] we reported the development of an IAD approach based on the use of 2-*O*-allyl-protected glycosyl donors, which allows the stereospecific synthesis of a range of 1,2-*cis* glycosides and disaccharides.[8] Studies have detailed the use of both thioglycosides[9] and glycosyl fluorides[10] as donors, and the strategy

(1) Wulff, G.; Röhle, G. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 157−170.
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(4) Barresi, F.; Hindsgaul, O. *Can. J. Chem.* **1994**, *72*, 1447−1465. Barresi, F.; Hindsgaul, O. *Synlett.* **1992**, 759−760. Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *113*, 9377−9379.
(5) 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.
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(9) Aloui, M.; Chambers, D. J.; Cumpstey, I.; Fairbanks, A. J.; Redgrave, A. J.; Seward, C. M. P. *Chem. Eur. J.* **2002**, *8*, 2608−2621. Seward, C. M. P.; Cumpstey, I.; Aloui, M.; Ennis, S. C.; Redgrave, A. J.; Fairbanks A. J. *J. Chem. Soc., Chem. Commun.* **2000**, 1409−1410.

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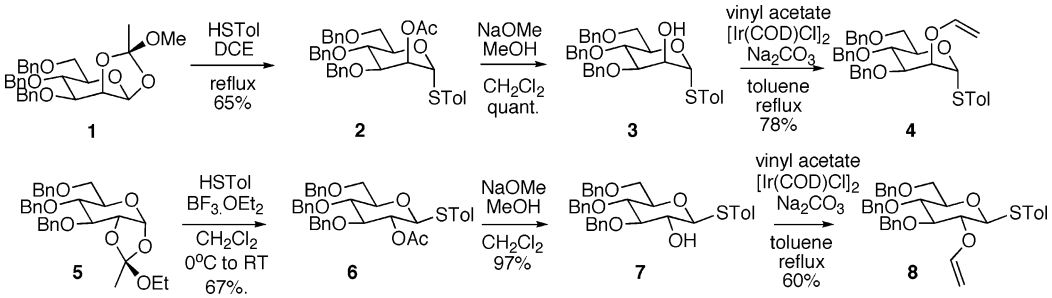
Scheme 1. Synthesis of 2-*O*-Vinyl Glycosyl Donors



has also been applied to less common 1,2-*cis* glycosides such as β-rhamnosides and α-glucofuranosides.[11]

One of the current limitations with the allyl IAD approach is the moderate efficiency of the tethering of glycosyl donor and acceptor when the acceptor is a hindered secondary carbohydrate alcohol. On the basis of previous observations of the greatly increased efficiency of mixed acetal tethering of the allyl IAD system as compared to the original Hindsgaul IAD approach, it was considered that a further increase in efficiency of tethering could be achieved by the use of 2-*O*-vinyl glycosyl donors (Figure 1). The caveat to

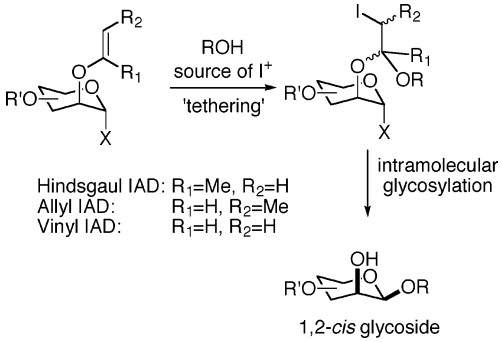


Figure 1. Comparison of Hindsgaul IAD, allyl IAD, and vinyl IAD approaches.

this approach was the relative inefficiency of the synthesis of the required vinyl ethers compared to the extremely efficient access to enol ethers derived from 2-*O*-allyl glycosyl donors by Wilkinson's catalyst mediated isomerization.[12]

Thioglycosides **3** and **7** were synthesized as potential donors for investigation of the vinyl IAD approach. Manno donor **3** was accessed from the known ortho ester **1**[13] by reaction with *p*-thiocresol to yield the acetate **2**. Deacetylation then yielded the required alcohol **3**. Similarly, the gluco donor **7** was accessed from known ortho ester **5**[14] by opening with *p*-thiocresol to yield the acetate **6** and then deacetylation to yield the alcohol **7** (Scheme 1). Both alcohols **3** and **7** were used as substrates in a search for an efficient method for the synthesis of the corresponding 2-*O*-vinyl glycosides. A variety of different literature methods for the synthesis of vinyl ethers from alcohols were investigated,[15] but none proved particularly satisfactory. The most efficient method investigated involved the use of vinyl acetate in an iridium complex catalyzed transvinylation process, as reported by Ishii.[16] Optimization of this procedure finally allowed the synthesis of the desired 2-*O*-vinyl thioglycosides **4** and **8** in 78% and 60% yields, respectively (Scheme 1).

With both vinyl ethers in hand, tethering of a variety of carbohydrate alcohols was undertaken using recently optimized conditions[17] for mixed acetal formation of iodine, and silver triflate in the presence of di-*tert*-butylmethylpyridine (DTBMP). In all cases, efficient tethering of the alcohol and the vinyl ether was observed using 1 equiv of aglycon alcohol (Table 1). Although the yield of mixed acetals was marginally lower for the hindered secondary carbohydrate alcohols (entries 4), these results were more efficient than for the corresponding mixed acetals in the allyl IAD system.[9,10]

With a selection of mixed acetals in hand, attention turned to the subsequent intramolecular glycosylation step. Mixed acetal **10a**, derived from diacetone galactose and the gluco vinyl ether **8**, was subjected to a range of activation conditions in an attempt to induce efficient intramolecular glycosylation (Table 2). Treatment with *N*-iodosuccinimide and silver triflate, in the presence of di-*tert*-butylmethylpyridine, produced only a poor yield of the desired α-gluco disaccharide **12a**, a result which contrasted with previous investigations in the allyl IAD system. The use of either more forcing reaction conditions, changes in activator to either iodine/silver triflate, dimethyl (methylthio)sulfonium triflate (DMTST),[18] *S*-(4-methoxyphenyl)benzenethiosulfinate

(10) Cumpstey, I.; Fairbanks, A. J.; Redgrave, A. J. *Monatsh. Chem.* **2002**, *133*, 449−466. Cumpstey, I.; Fairbanks, A. J.; Redgrave, A. J. *Org. Lett.* **2001**, *3*, 2371−2374.

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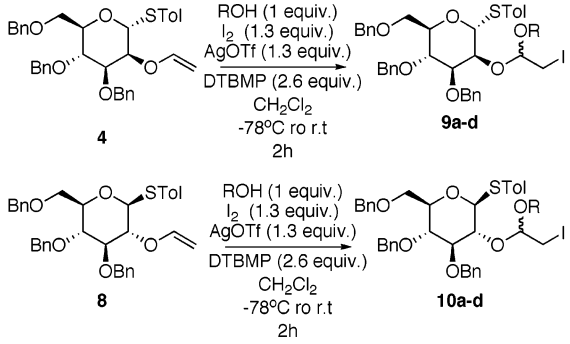
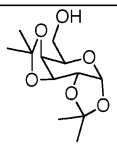
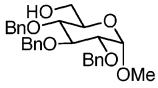
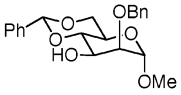
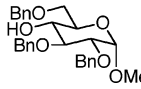
(15) Dujardin, G.; Rossignol, S.; Brown, E. *Tetrahedron Lett.* **1995**, *36*, 1653−1656. Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc.* **1957**, *79*, 2828−2833.

(16) Olimoto, Y.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2002**, *124*, 1590−1591.

(17) Cumpstey, I.; Chayajarus, K.; Fairbanks, A. J.; Redgrave, A. J.; Seward, C. M. P. *Tetrahedron: Asymmetry* **2004**, *15*, in press.

Table 1. Mixed Acetal Formation



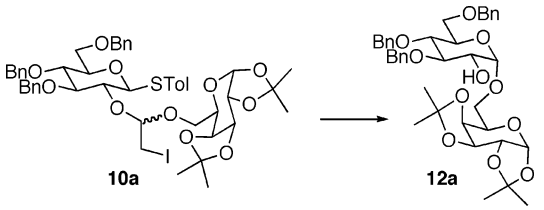
entry	alcohol ROH	product/yield of *manno* mixed acetals **9a-d**	product/yield of *gluco* mixed acetals **10a-d**
1)		**9a**/86%	**10a**/90%
2)		**9b**/79%	**10b**/81%
3)		**9c**/75%	**10c**/71%
4)		**9d**/60%	**10d**/57%

(MPBT)/triflic anhydride,[19] or 1-(benzenesulfinyl)piperidine (BSP)/triflic anhydride[20] or the use of 2,4,6-tri-*tert*-butylpyrimidine (TTBP)[21] as an alternative base all resulted in only slight alterations in yield (Table 2).

These results indicate that intramolecular glycosylation is clearly more difficult in the vinyl system than in the allyl-derived system, as may have been predicted by consideration of inductive effects on the stability of the oxonium produced after glycosylation. Previous results had confirmed that intramolecular glycosylation was more sluggish in the allyl system than in the Hindsgaul acetate/Tebbe system, again in line with inductive stabilization of the oxonium ion formed after intramolecular glycosylation. However the use of iodine and silver triflate, again in the presence of DTBMP as a base, combined with changing the reaction solvent to acetonitrile resulted in a significant improvement in the yield of glycosylated product. In this instance the α-gluco disaccharide **12a** was isolated in 51% yield.

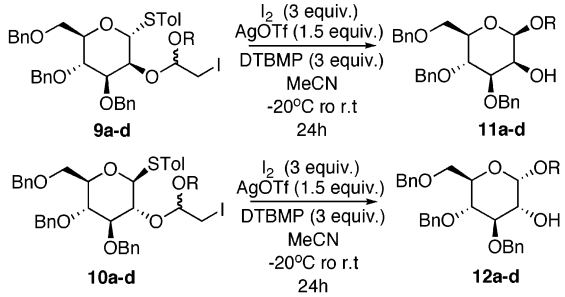
Encouraged by this result, the remaining mixed acetals in both the gluco and manno series were subjected to these specific glycosylation conditions. Moreover, an acidic work-up was employed for acetals derived from carbohydrate acceptors that did not possess acid-labile protection of other hydroxyl groups. In all cases, the 1,2-*cis* disaccharide product (**11a**−**d**, **12a**−**d**) was isolated as the sole glycosylated product, in good to moderate yield (Table 3).

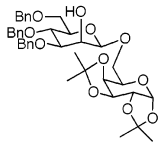
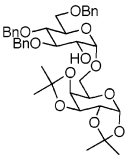
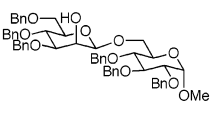
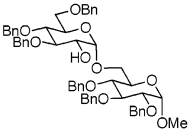
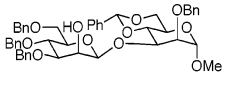
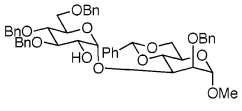
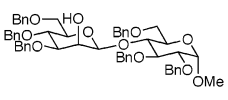
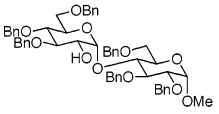
Table 2. Intramolecular Glycosylation of Mixed Acetals **10a**



entry	glycosylation conditions	yield (%)
1	NIS, AgOTf, DTBMP, DCE, RT, 72 h	16
2	NIS, AgOTf, DTBMP, DCE, 80 °C, 48 h	25
3	I_2, AgOTf, DTBMP, DCE, −78 °C to rt, 24 h	20
4	DMTST, DTBMP, CH_2Cl_2, −40 °C to rt, 2.5 h	31
5	MPBT, Tf_2O, DTBMP, CH_2Cl_2, −60 °C, 6 h	38
6	BSP, Tf_2O, TTBP, CH_2Cl_2, −60 °C to rt, 6 h	22
7	I_2, AgOTf, DTBMP, MeCN, rt, 24 h	51

Table 3. Intramolecular Glycosylation of Mixed Acetals **9a**−**d** and **10a**−**d**



entry	product/yield of β-*manno* disaccharide **11a-d**	product/yield of α-*gluco* disaccharide **12a-d**
1)	 **11a**/65%	 **12a**/51%
2)	 **11b**/79%	 **12b**/ 78%
3)	 **11c**/63%	 **12c**/55%
4)	 **11d**/52%	 **12d**/33%

Once again, the efficiency of glycosylation can be seen to be dependent on the nature of the glycosyl acceptor; more hindered glycosyl acceptors, and in particular those in which it is the 4-hydroxyl group to be glycosylated, react less efficiently. However, even for the most hindered carbohydrate glycosyl acceptors the desired 1,2-*cis* disaccharide products are formed in a totally stereoselective fashion.

In summary it has been demonstrated that the use of 2-*O*-vinyl glycosyl donors allows the synthesis of a variety of 1,2-*cis* disaccharides in good yield and most importantly with complete stereocontrol. This technique of vinyl IAD is complementary to the approach based on 2-*O*-allyl-protected donors (allyl IAD) in that it possesses the advantage of increased tethering efficiency for particularly hindered secondary carbohydrate acceptors. However, the synthesis of the corresponding glycosyl donors and the efficiency of the intramolecular glycosylation step of allyl IAD are more efficient than those so far developed for the vinyl approach. Further investigations into the use of both vinyl- and allyl-derived IAD and their applications for the synthesis of a variety of biologically important oligosaccharides are currently in progress, and the results will be reported in due course.

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Supporting Information Available: Synthetic procedures are available, together with full characterization and spectral data for compounds **1**, **2**, **4**, **6**−**8**, **9a**−**d**, **10a**−**d**, **11a**−**d**, and **12a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323−326.