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Stereoselective *cis* glycosylation of 2-*O*-allyl protected glycosyl donors by intramolecular aglycon delivery (IAD)

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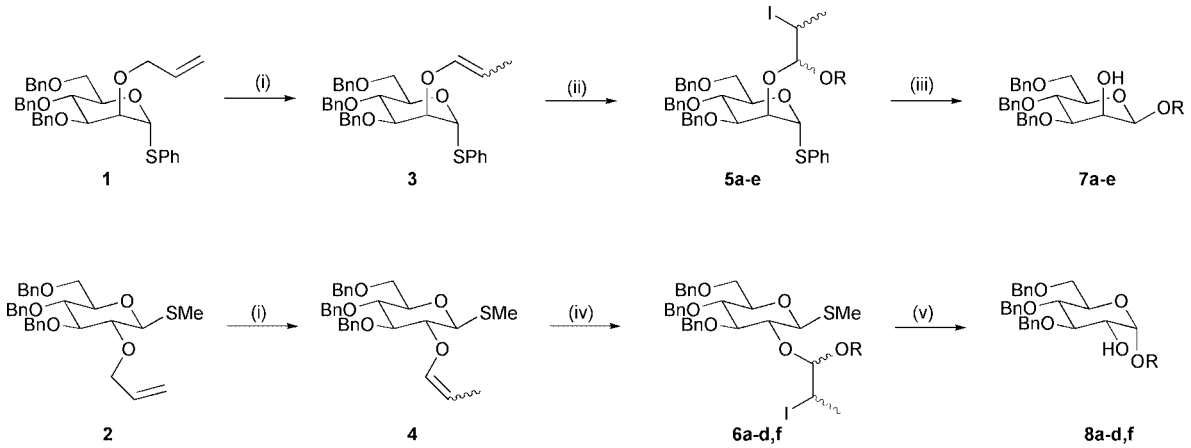
2-*O*-Allyl protected glycosyl donors may be glycosylated stereoselectively *via* a three step sequence involving double bond isomerization, *N*-iodosuccinimide mediated tethering to a glycosyl acceptor and subsequent intramolecular glycosylation (intramolecular aglycon delivery, IAD).

Stereoselective intramolecular glycosylation of glycosyl acceptors temporarily tethered to the 2-hydroxy group of the glycosyl donor is a synthetically useful technique allowing access to a range of *cis*-1,2-glycosides which can otherwise be problematic to synthesise. A number of methods have been developed for the temporary linking of donor and acceptor prior to glycosylation.[1–4] Modification of the donor 2-hydroxy protecting group commonly provides a tethering site. Thus the Hindsgaul approach involves Tebbe methylenation of a 2-*O*-acetate to produce a vinyl ether which is then coupled with the acceptor using acid catalysis to produce a mixed ketal.[3] Alternative methodology developed by Ogawa and co-workers employs oxidation of a *p*-methoxybenzyl (PMB) protecting group, which allows linking of donor and acceptor as a mixed acetal.[4] We would herein like to report the first use of the 2-*O*-allyl protecting group as the means of tethering donor to acceptor. It was envisaged that Wilkinson's catalyst mediated isomerisation of the double bond would efficiently produce a vinyl ether, which could then be subjected to tethering with *N*-iodosuccinimide (NIS) and subsequent intramolecular glycosylation according to our recently reported procedure.[5]

The 2-*O*-allyl protected glycosyl donors **1** and **2**, which are readily available through standard manipulations,† were isomerized using a combination of Wilkinson's catalyst and n-butyllithium according to a procedure recently reported by Boons and Isles.[6] This straightforward method proceeded extremely efficiently to yield the enol ethers **3** and **4** respectively in quantitative yield (Scheme 1). NIS mediated tethering was then undertaken for both *manno* and *gluco* donors **3** and **4** with a series of alcohols (ROH, Table 1) in the presence of 4 Å molecular sieves.‡ In all cases tethering proceeded efficiently in either THF or 1,2-dichloroethane (DCE) as solvent to yield mixed acetal intermediates **5a–e**, **6a–d**,**f** as diastereomeric mixtures.§ Subsequent intramolecular glycosylation proved more sluggish than we had previously experienced.[5] In the case of the less reactive anomeric thiophenyl *manno* mixed acetals **5a–e**, efficient reaction required the addition of silver triflate and more protracted reaction times at either room temperature or higher. However in all cases intramolecular glycosylation occurred in a stereospecific fashion to furnish the corresponding β-mannosides **7a–e**. The more reactive thiomethyl *gluco* mixed acetals **6a-d**,**f** were efficiently activated by the addition of methyl triflate, yielding α-glucosides **8a–d**,**f** again as single anomers following work-up.¶‖

Attention then turned to the potential one-pot reaction, whereby tethering and glycosylation are achieved in a single reaction vessel. Unlike our previous results[5] which were obtained with the Hindsgaul mixed ketal system, attempted one-pot glycosylation of donors **3** and **4** with an excess of cyclohexanol (typically 3 equivalents) produced anomeric mixtures, clearly indicating competitive intermolecular reaction by the excess of acceptor in solution. In order to find a solution to this problem, and also to overcome the sluggishness of the thiophenyl *manno* glycosylation reaction, attention turned to the use of the readily available thiomethyl substituted *manno* glycosyl donor **9**.† Isomerisation of **9** proceeded efficiently to yield the enol ethers **10** which were subsequently examined as



Scheme 1 *Reagents and conditions*: (i) $(Ph_3P)_3RhCl$, *n*-BuLi, THF, reflux, > 99%; (ii) ROH, *N*-iodosuccinimide, 4 Å molecular sieves, 1,2-dichloroethane, −40 °C to RT, 76–100%; (iii) *N*-iodosuccinimide, AgOTf, 2,6-di-*tert*-butyl-4-methylpyridine, 4 Å molecular sieves, 1,2-dichloroethane, RT (or 50 °C), 59–81%; (iv) ROH, *N*-iodosuccinimide, 4 Å molecular sieves, 1,2-dichloroethane, −40 °C to RT, 63–98%; (v) MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, 1,2-dichloroethane, RT, 65–77%.

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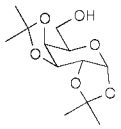
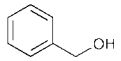
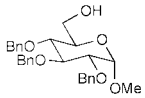
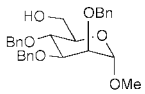
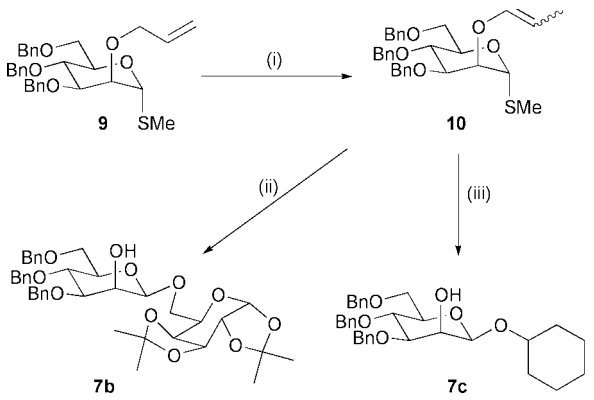
Table 1 Yields for tethering and glycosylation

Alcohol ROH	Product/yield of mixed acetals	Product/yield of glycosylation[7]
MeOH	**5a**/93% **6a**/98%	**7a**/77% **8a**/65%
	**5b**/95% **6b**/84%	**7b**/81% **8b**/70%
	**5c**/76% **6c**/80%	**7c**/68% **8c**/77%
	**5d**/ > 99% **6d**/95%	**7d**/76% **8d**/67%
	**5e**/90%	**7e**/57%
	**6f**/63%	**8f**/72%



Scheme 2 *Reagents and conditions*: (i) $(Ph_3P)_3RhCl$, *n*-BuLi, THF, reflux, > 99%; (ii) diacetone galactose, *N*-iodosuccinimide, 4 Å molecular sieves, CH_3CN, −40 °C to RT, then MeOTf, 72%; (iii) cyclohexanol, *N*-iodosuccinimide, 4 Å molecular sieves, 1,2-dichloroethane, −40 °C to RT, then MeOTf, 67%.

substrates for tethering and glycosylation. Conditions initially employed for the one-pot reactions of **10**, involving NIS mediated tethering with cyclohexanol and subsequent glycosylation by the addition of methyl triflate to the reaction mixture, again resulted in the formation of anomeric mixtures. The β : α ratio could be increased from 2 : 1 to a respectable 5 : 1 by simple dilution of the reaction mixture once tethering was complete before the addition of the methyl triflate, but α products could not be entirely eliminated. However by the use of an excess of glycosyl donor any competing intermolecular reaction could be avoided. Thus reaction of the donor **10** (2.0 equivalents) with either diacetone galactose or cyclohexanol (in acetonitrile and 1,2-dichloroethane respectively) produced the corresponding β-mannosides **7b** and **7c** as single anomers in 72% and 67% yield respectively (Scheme 2).

In summary we have demonstrated that 2-*O*-allyl protected glycosyl donors may be employed for the synthesis of a variety of *cis*-1,2-glycosides. Of particular note is that isomerization of the allyl group is a very efficient process, and is superior to the often troublesome and messy Tebbe methylenation reaction. In addition the use of an excess of glycosyl donor allows both tethering and glycosylation to be performed in a single reaction vessel, obviating the need for handling of sensitive mixed acetal intermediates. Further investigations into the use of allyl derived enol ethers for *cis* glycosylation procedures, particularly employing hindered secondary carbohydrate glycosyl acceptors are currently in progress, and the results will be reported in due course.

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Notes and references

† 2-*O*-Allyl protected donor **1** was prepared from the corresponding 2-*O*-acetate[5] *via* deprotection with sodium methoxide in methanol and allylation with sodium hydride and allyl bromide in DMF. 2-*O*-Allyl protected donors **2** and **9** were prepared from the corresponding 2-*O*-acetyl-1-bromo and 2-*O*-acetyl-1-chloro glycosides respectively by reaction with dimethyl disulfide and butyllithium in THF followed by allylation as above.[8] Full experimental details will be published in due course.

‡ Typical procedure for *manno*/*S*-phenyl tethering: the vinyl ether (0.15 mmol), the alcohol (3 equiv.) and powdered 4 Å molecular sieves (*ca*. 500 mg) were stirred in 3.5 ml dry DCE under argon at −40 °C. NIS (2.5 equiv.) was added and the mixture was allowed to warm slowly to room temperature. After 16 h, dichloromethane was added, the mixture was filtered through Celite®, washed with aqueous sodium thiosulfate, dried, filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography to give the mixed acetal as a clear oil.

§ No attempt was made at separation, and the mixtures were used as such for subsequent glycosylation.

¶ In line with our previous observations, the oxonium ion produced after aglycon delivery may be trapped, either by any available alcohol in solution or alternatively by succinimide. Simple treatment of the crude reaction mixture with either aqueous TFA or aqueous lithium hydroxide respectively efficiently hydrolyses these trapped products, typically increasing the yield of glycosylated product by 10–15%.

‖ Typical procedure for *manno*/*S*-phenyl glycosylation: the mixed acetals (0.1 mmol), NIS (5 equiv.), silver triflate (1 equiv.), 2,6-di-*tert*-butyl-4-methyl pyridine (DTBMP) (5 equiv.) and powdered 4 Å molecular sieves (*ca*. 250 mg) were dissolved in dry DCE under argon. The solution was then stirred at room temperature (or 50 °C) until TLC indicated disappearance of the starting material. TFA (10 ml), methanol (4 ml) and water (2 ml) were added and the solution was stirred for a further 1–4 h. Dichloromethane was added, the mixture filtered through Celite®, washed with saturated aqueous sodium bicarbonate and the aqueous layers were re-extracted with dichloromethane. The combined organic extracts were washed with aqueous sodium thiosulfate, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography to give the pure β-mannoside.

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7 Data for β-mannosides **7a**–**d** and α-glucosides **8a**–**d** was consistent with that reported by us previously.[5] Selected data for **7e**: a white solid, mp 105–108 °C (Et_2O–petrol), $[\alpha]_D^{22}$ +22.2 (*c*, 0.91, $CHCl_3$), [lit.[1b] $[\alpha]_D^{25}$ +24.0 (*c*, 1.0, $CHCl_3$); **8f**: a colourless oil, $[\alpha]_D^{22}$ +65.5 (*c*, 1.1, $CHCl_3$), (HRMS+H^+: 897.4229. $C_{55}H_{61}O_{11}$ requires: 897.4214).
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