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Vinyl Glycosides in Oligosaccharide Synthesis (Part 1): A New Latent-Active Glycosylation Strategy.

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Abstract: We have developed a novel latent-active glycosylation strategy. This glycosylation strategy is based on isomerisation of substituted allyl glycosides to give vinyl glycosides which can subsequently be used in a Lewis acid mediated glycosylation reaction. This approach will enable complex oligosaccharides of biological importance to be prepared in a highly convergent manner.

It is now well established, that in the living cell, carbohydrates play key roles in many different processes.[1] Examples include embryogenesis, fertilisation, neuronal development, hormone activities, cell proliferation, and their organisation into specific tissues. As many of these processes involve, at some stage, the interaction between proteins and oligosaccharides,[2] an understanding of the factors which control these interactions at the molecular level is of prime importance. To elucidate the factors controlling the important carbohydrate-protein interactions, it is of the utmost importance to have sufficient amounts of pure and well-defined (poly)saccharides of different sizes. Organic synthesis provides the only means of obtaining these fragments.

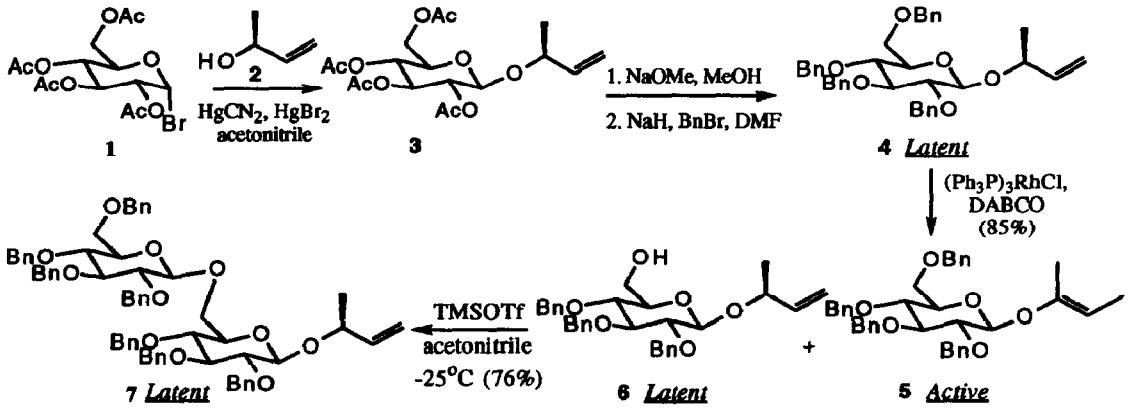
A practical difficulty in the preparation of complex oligosaccharides, is the availability of building blocks which can be readily transformed into glycosyl donors. The employment of this type of building block keeps manipulations of complex oligosaccharide fragment to a minimum and may give an opportunity of preparing oligosaccharide libraries. In this respect, thioglycosides[3] and pentenyl glycosides[4] have attracted considerable attention and these substrates may be used in a chemoselective glycosylation strategy ("armed-disarmed" approach). The chemoselective glycosylation of pentenyl and thioglycosides relies on the fact that C-2 esters deactivate (disarmed) and C-2 ethers activate (armed) the anomeric centre. Thus, the difference in reactivity between two anomeric centres of the glycosyl donor and acceptor is achieved through differential protecting groups of the 2-OH (ether/ester, armed/disarmed). Therefore the preparation of oligosaccharide donors by this approach is limited however as only very few types of protecting groups are available.[5]

A glycosylation strategy in which the reactivity of the carbohydrate units is controlled only with the anomeric group,[6] would not require differential protection and hence is more versatile and can make oligosaccharide donors of any size.

Isopropenyl glycosides, which can be prepared by reacting anomeric acetates with Tebbe's reagent, undergo glycosylation reactions with primary and secondary carbohydrate alcohols in the presence of trimethylsilyl triflate or boron trifluoride etherate.[7] Since many functional and protecting groups are sensitive towards Tebbe's reagent, this glycosylation method is not widely applicable.

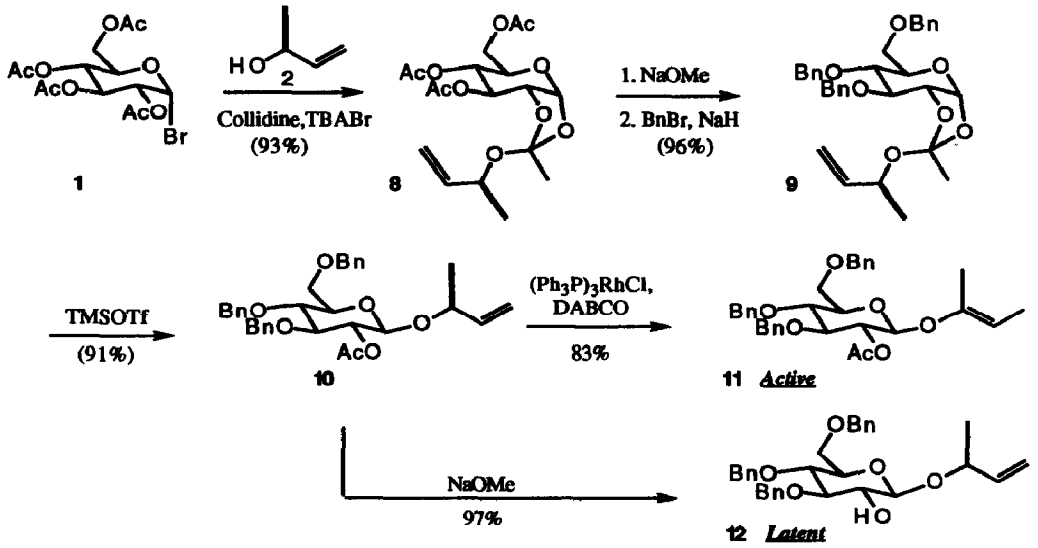
We report here a novel glycosylation strategy based on isomerisation of 3-buten-2-yl glycosides to give 2-butene-2-yl glycosides which in turn can undergo a Lewis acid-catalysed glycosylation reaction. This approach offers the possibility to control the reactivity of the anomeric centre of the carbohydrate unit by only the anomeric group (allyl *vs.* vinyl) and therefore does not require differential protection and hence is more versatile then the armed-disarmed glycosylation strategy and can now anable oligosaccharide donors of any size to be used. It should also be noted that the reaction conditions used in this approach are very suitable for oligosaccharide synthesis.

The substituted allyl glycoside **3**[8] was readily prepared from the corresponding acetoxy-bromide **1** and 3-butene-2-ol (**2**).[9] Compound **3** may undergo many different functional and protecting group manipulations. For example, deacetylation of **3** under Zémplèn conditions, followed by benzylation with benzyl bromide and sodium hydride in DMF, gave the fully benzylated allyl glycoside **4**. Glycosyl acceptor **6** was also readily prepared from compound **3** by deacetylation followed by regioselective silylation with TBDMSCl and pyridine. The obtained compound was benzylated with benzyl bromide and sodium hydride and the TBDMS protecting group was removed by treatment with a mixture of acetic acid/water. Isomerisation of the substituted anomeric allyl ethers **4**, using Wilkinson catalyst[10] (latent → active), gave the substituted vinyl glycoside **5** which, in turn, was used in a TMSOTf (0.1 equivalent)-promoted glycosylation reaction with allyl glycoside **6** to give mainly the β-linked dimer **7** in an excellent yield (76%, α/β 1/20). A slightly improved yield was obtained when the glycosylation reaction was performed in propionitrile at -60°C. Dimer **7** can be converted into a glycosyl donor by isomerisation of its allyl moiety (latent → active).



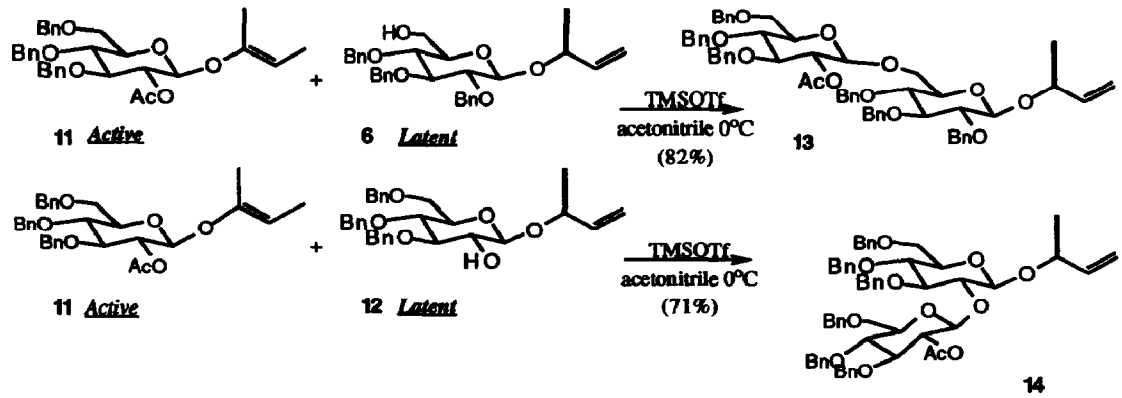
Scheme 1

The diastereochemical outcome of the above discussed glycosylation reaction is controlled by the solvent acetonitrile.[11] Another approach to control the α/β ratio of a glycosylation reaction and which leads to the formation of 1,2-*trans* glycosides is based on neighbouring group participation by the 2-hydroxyl protecting group (Koenigs-Knorr synthesis).[12] It is to be expected that a vinyl glycoside having a neighbouring participating protecting group at the 2-hydroxyl position can be obtained by isomerisation of the analogous substituted allyl glycoside. These substrates can be used as glycosyl donors in a modified Koenigs-Knorr synthesis. We have prepared the vinyl glucoside **11** which could be coupled to the glycosyl acceptors **6** and **12** (see **Scheme 2** and **3**). Thus, treatment of the bromide **1** with allyl alcohol **2** in the presence of collidine and a catalytic amount of *t*-butyl ammonium bromide gave orthoester **8** in an excellent yield. Orthoester **8** could be readily converted into the benzylated compound **9** and treatment of this compound with a catalytic amount of TMSOTf resulted in the formation of compound **10**.



Scheme 2

3-Butene-2-yl glycoside **10** could be converted into glycosyl donor **11** by isomerisation in the presence of Wilkinson catalyst and into glycosyl acceptor **12** by base-mediated removal of the acetyl protecting group. Treatment of a mixture of **11** and **6** with a catalytic amount of TMSOTf in acetonitrile at 0°C gave, as expected, pure β-linked dimer **13** in good yield. Compound **12** is a suitable glycosyl acceptor and was condensed with glycosyl donor **11** under standard coupling conditions to give dimer **14**. The dimers **13** and **14** can be converted into glycosyl donors by isomerisation of the allyl moiety.



Scheme 3

In conclusion, the glycosylation strategy described here, offers the possibility to prepare oligosaccharides by a highly convergent latent-active glycosylation approach and addresses the problems associated with the armed-disarmed glycosylation strategy. This new glycosylation procedure will be applied in the preparation of oligosaccharides of biological importance. Differently substituted vinyl glycosides will be used in the coupling reactions to widen the scope of the new glycosylation strategy.[13]

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