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β-Mannosylation of *N*-acetyl glucosamine by propargyl mediated intramolecular aglycon delivery (IAD): synthesis of the *N*-glycan core pentasaccharide

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Abstract—An efficient and completely stereocontrolled synthesis of the *N*-glycan Manβ(1–4)GlcNAc disaccharide is achieved by propargyl mediated intramolecular aglycon delivery (IAD). Isomerisation of the 2-*O*-progargyl group of a *manno* thioglycoside to an allene is followed by iodonium ion mediated mixed acetal formation with the 4-OH of a protected GlcNAc derivative, and subsequent intramolecular glycosylation with complete control of anomeric stereochemistry. Access to this key disaccharide intermediate allows completion of the total synthesis of the core *N*-glycan pentasaccharide.

Control of anomeric stereochemistry during the course of a glycosylation reaction is a key consideration during the synthesis of any oligosaccharide. Whilst much work has been done to facilitate the speed of assembly of oligosaccharide structures, the issue of absolute control of anomeric stereochemistry still remains unanswered. Whilst 1,2-*trans* glycosidic linkages can usually be synthesised with high levels of stereocontrol by taking advantage of neighbouring group participation of 2-*O*-acyl protected glycosyl donors[1] the synthesis of 1,2-*cis* glycosidic linkages is considerably more difficult. The current situation is that there is still no generally applicable method available,[2] and considerable research effort continues to be focussed on the development of new and improved stereocontrolled glycosylation procedures. For example, very recently Boons and co-workers described a new and elegant approach to the synthesis of α-glucosides by the use of novel neighbouring group participation.[3] However this methodology, whilst representing an extremely welcome development is, as it stands, limited in its applicability. For example, this approach does not currently allow the formation of β-1,2-cis linkages, such as the notorious β-mannosides. Hence there is still an urgent need for the development of reliable and truly generally applicable methodology that will allow the formation of any 1,2-*cis* glycosidic linkage, irrespective of the configuration of the glycosyl donor.

Conceptually, perhaps the most elegant solution to this '1,2-*cis* glycoside problem' is to apply the technique of intramolecular aglycon delivery, or IAD, which is an intramolecular glycosylation strategy[4] wherein the glycosyl acceptor is temporarily appended to the 2-hydroxyl group of a glycosyl donor through a short linker. The first so-called 'tethering' step, that is, the linking of donor and acceptor, is followed by activation of the glycosyl donor which subsequently furnishes the 1,2-*cis* glycoside in a completely stereoselective fashion. The two key advantages of the IAD approach over other intramolecular glycosylation reactions in which the donor and acceptor are either connected by other hydroxyl groups, through longer linkers, or other remote positions, are the predictability and strict control of the anomeric stereochemistry of the product. However, even using the IAD approach, one has to be careful to avoid problems of regiochemical control, that is, ensure that only the desired hydroxyl is glycosylated,[5] and also to avoid the use of longer linkers, which can lead to undesired non-stereoselective reactions.[6]

Amongst several IAD methodologies that have been reported,[7–9] the approach developed by Ogawa and co-workers, based on the use of 2-*O*-*para*-methoxybenzyl

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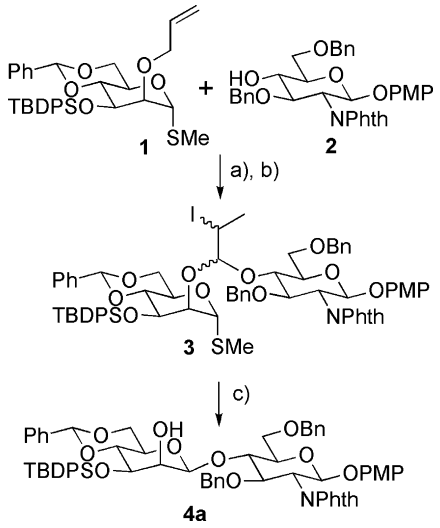
(PMB) protected glycosyl donors,[10] is the only methodology that has been really successfully applied to the syntheses of complex targets, such as the core *N*-glycan pentasaccharide. This pentasaccharide, which contains the crucial Manβ(1–4)GlcNAc linkage, can be considered a benchmark test for potential widespread utility of any 1,2-*cis* glycosylation procedure. Whilst the Ogawa approach has also been applied to the synthesis of a selection of other 1,2-*cis* glycosides, with varying degrees of success,[11] it is notable that it has not yet found routine applicability.

We recently reported the development of an allyl protecting group mediated IAD approach (allyl IAD),[12] based on either thioglycoside[13] or glycosyl fluoride donors.[14] This methodology relies on iodonium ion mediated formation of a mixed acetal between a glycosyl acceptor alcohol and an enol ether, itself derived from a 2-*O*-allyl protected glycosyl donor by Wilkinson's catalyst mediated isomerisation[15] of the double bond. However, attempted application of this methodology to the synthesis of complex oligosaccharides, such as the core *N*-glycan pentasaccharide, met with frustration. For example, although an effective intramolecular glycosylation of a fully 'armed' benzyl protected *manno*-thioglycoside was achieved with the 4-hydroxyl of a glucosamine acceptor, when this reaction sequence was attempted with the more advanced *manno*-thioglycoside **1**, using a previously applied glucosamine acceptor **2**, investigations met with considerable difficulties. Although optimised conditions[6] for mixed acetal formation allowed the synthesis of intermediate **3** in high yield, it was found that **3** resisted almost all attempts to effect intramolecular glycosylation. A variety of different conditions commonly used for thioglycoside activation were investigated. The only successful procedure involved the use of a Me_2S_2/Tf_2O mixture, as reported originally by Fügedi and Tatai,[16] together with added di-*tert*-butylmethylpyridine (DTBMP), which was found to further improve the efficiency of glycosylation.[17] However, even these conditions were only able to produce the desired β-disaccharide **4a** in 29% yield, albeit with complete control of anomeric stereochemistry (Scheme 1).

We were therefore unable to access disaccharide **4a** satisfactorily by our allyl IAD procedure. Moreover, it should also be noted at this point that the Crich direct β-mannosylation procedure does not work well with glucosamine acceptors such as **2**.[18] It was thought that the difficulty in obtaining a satisfactory yield for this step, as compared to previous intramolecular glycosylation reactions using the allyl IAD approach, could in part be due to the fact that the *manno* donor is partially 'disarmed'[19] due to torsional deactivation by the 4,6-benzylidene group. With the reasoning that an increase in stability of the oxonium ion produced subsequent to the intramolecular glycosylation step may actually facilitate the glycosylation process it was decided to investigate the use of 2-*O*-propargyl ethers for a similar intramolecular glycosylation strategy.

Although not widely used in carbohydrate chemistry, recent reports from Crich et al. have detailed the utility

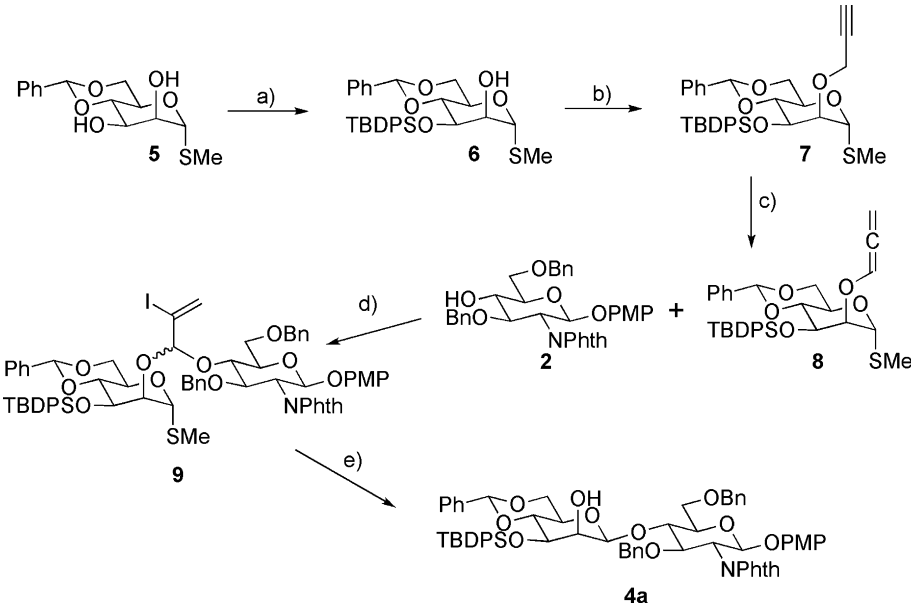


Scheme 1. Reagents and conditions: (a) $(Ph_3P)_3RhCl$, *n*-BuLi, THF, reflux, 73%; (b) **2**, I_2, AgOTf, DTBMP, CH_2Cl_2, −78 °C to rt, 64%; (c) Me_2S, Tf_2O, DTBMP, CH_2Cl_2, 0 °C–rt, 29%.

of propargyl ethers[20] as sterically unobtrusive groups for the protection of the 2-hydroxyl of *manno* thioglycosides as part of their β-mannosylation procedure. As the basis of an IAD glycosylation approach it was reasoned that base-mediated isomerisation of 2-*O*-progargyl protected glycosyl donors would allow access to 2-*O*-allenyl protected carbohydrates.[21] Such allenes could then undergo a similar sequence as had previously been applied as the basis of the allyl IAD—namely, iodonium ion catalyzed mixed acetal formation with an acceptor alcohol, and subsequent intramolecular glycosylation with complete control of stereochemistry. An envisaged advantage of the propargyl based approach over the allyl based methodology was that the oxonium ion produced subsequent to glycosylation would be stabilised by conjugation with the side-chain alkene; a factor which may facilitate aglycon delivery.

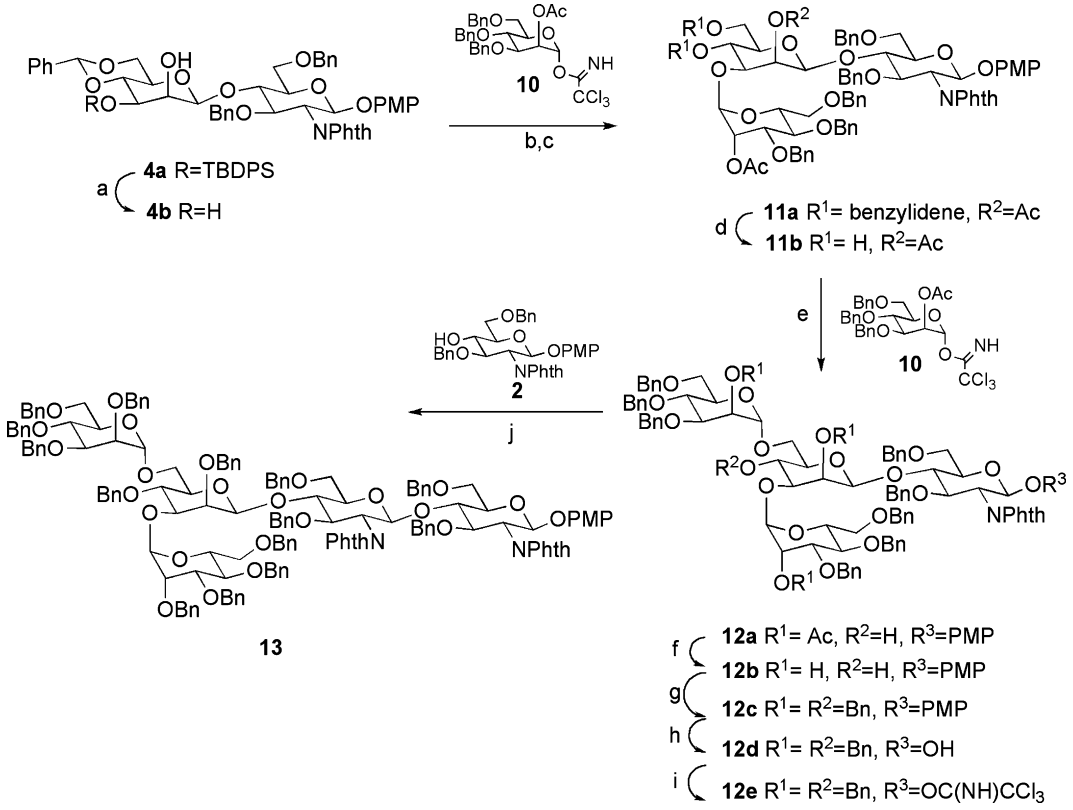
In order to investigate the feasibility of such an approach, propargyl ether **7** was synthesised by regioselective silylation of diol **5** to yield **6**, which then underwent subsequent etherification using propargyl bromide and sodium hydride in DMF to give propargyl ether **7**. Isomerisation by treatment with *t*-butoxide[22] then yielded the desired intermediate allene **8**. Iodonium ion mediated mixed acetal formation with glucosamine acceptor **2** gave mixed acetals **9** in an excellent 88% yield. Subsequent intramolecular glycosylation, using the previously optimised Fügedi activation conditions,[17] proceeded smoothly to give the desired Manβ(1–4)GlcNAc disaccharide **4a** in an excellent 81% yield, with complete stereocontrol (Scheme 2).

The above process represented a significant improvement on the allyl IAD system for glycosylation of the disarmed *manno* donor, and could be performed reliably on a significant scale. With substantial quantities of disaccharide **4a** in hand attention then turned to the completion of the total synthesis of the *N*-glycan pentasaccharide. Deprotection of the silyl group of **4a** with



Scheme 2. Reagents and conditions: (a) Bu^tPh_2SiCl, imidazole, CH_2Cl_2, rt, 84%; (b) propargyl bromide, NaH, DMF, rt, 72%; (c) Bu^tOK, Et_2O, 66%; (d) **2**, I_2, AgOTf, DTBMP, CH_2Cl_2, −78 °C to rt, 88%; (e) Me_2S, Tf_2O, DTBMP, CH_2Cl_2, 0 °C–rt, 81%.

TBAF gave diol **4b**, which was then glycosylated regioselectively at position 3 with the known trichloracetimidate donor **10**,[23] to give a trisaccharide which was immediately acetylated to give **11a**. Removal of the 4,6-benzylidene protection to yield trisaccharide diol **11b** proved slightly problematic. A simple treatment with aqueous acetic acid invariably resulted in the formation of small quantities of the 6-*O*-acetate as a side product. An optimised procedure was therefore developed involving treatment with trifluoroacetic acid in



Scheme 3. Reagents and conditions: (a) TBAF, THF, rt, 60%; (b) **10**, TMSOTf, CH_2Cl_2, −78 °C to rt; (c) Ac_2O, pyridine, rt, 86% over two steps; (d) 10% TFA in 10:1 MeCN:H_2O, 90%; (e) **10**, TMSOTf, CH_2Cl_2, −78 °C to rt, 76%; (f) K_2CO_3, MeOH, rt; (g) NaH, BnBr, DMF, rt, 77% over two steps; (h) $(NH_4)_2Ce(NO_3)_6$, toluene, MeCN, H_2O, rt, 77%; (i) Cl_3CCN, DBU, CH_2Cl_2, rt, 96%; (j) **2**, TMSOTf, CH_2Cl_2, −78 °C to rt, 85%.

aqueous acetonitrile. In this case, although some of the corresponding 6-*O*-trifluoroacetate was formed initially, this material was readily hydrolysed upon work-up, yielding diol **11b** in 90% yield. A second regioselective glycosylation reaction with donor **10** then smoothly gave tetrasaccharide **12a**. Further protecting group manipulations and activation of the anomeric centre as the trichloroacetimidate then allowed glycosylation with acceptor **2** to finally yield the desired pentasaccharide **13** (Scheme 3).

In conclusion, the development of propargyl mediated IAD appears to represent a considerable improvement over the allyl IAD approach in terms of efficiency of the intramolecular glycosylation step. The work detailed in this Letter demonstrates that an efficient intramolecular glycosylation can be achieved even using a disarmed glycosyl donor, together with a hindered *N*-acetyl glucosamine acceptor, allowing completion of the total synthesis of the core *N*-glycan pentasaccharide. Further investigations exploring the scope of use and efficiency of propargyl mediated IAD are currently in progress, and the results will be reported in due course.

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