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Synthesis of a polymerizable, bivalent glycan mimetic of the HIV envelope spike gp120

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ABSTRACT

A synthetic study on the creation of a bivalent, ROMP capable monomer has the ability to be polymerized into the corresponding neo-glycopolymer mimetic of the surface glycans on gp120 envelope spike of the HIV virus. In our approach, we have developed a new strategy for orthogonally attaching both the terminal Manα(1-2)Man disaccharide unit of the D1 arm of $Man_9GlcNAc_2$ of HIV gp120 and the terminal Manα1-2 unit of its D2 arm to a bivalent scaffold to produce the corresponding polymerizable monomer. The Manα1-2 saccharide moieties were assembled using a nickel catalyst, $Ni(4\text{-}F\text{-}PhCN)_4(OTf)_2$, to activate trihaloacetimidate donors under a mild and operationally simple procedure.

Human immunodeficiency virus (HIV) has evolved into one of the most threatening global viruses since its first isolation in 1983. Despite extensive research efforts in more than two decades, the conception of a synthetic HIV vaccine capable of eliciting broadly-neutralizing antibodies, has thus far proven elusive.[1] A principal explanation for this phenomenon focuses on the heavily glycosylated viral envelope, comprised of oligosaccharide fragments, which may disguise the virion from immune responses if they are recognized as 'self',[2] the virus also utilizes its 'glycan shield' to prevent protein-specific antibodies from binding to the inner protein core.[3] The isolation of carbohydrate-specific broadly-neutralizing antibody 2G12, capable of binding to HIV gp120's surface oligosaccharides,[4,5] suggests that the carbohydrate shield of HIV could be considered as a potential target for neutralization.[6] This elucidation inspired the use of glycan antigens toward the development of potential vaccines. Along with the 2G12 antibody, several other carbohydrate-specific broadly-neutralizing antibodies (bnAbs) have been characterized from HIV-infected individuals, including PG9, PG16, PGT121–123, PGT125–128, and PGT135.[1,7] Extensive studies on the binding between HIV gp120 and these bnAbs have resolved crystal structures that commonly show strong binding affinities between these antibodies and a terminal Manα(1-2)Man disaccharide motif on the D1 arm of the *N*-linked $Man_9GlcNAc_2$ unit (**1**, Fig. 1) of gp120. The crystal structure of 2G12 in particular revealed that approximately 85% of the contact with gp120 was through this terminal disaccharide unit,[6,8,9] and that its unusual Fab domain-swapped structure provided for additional multivalent binding sites.[6,10] This discovery suggests that a majority of the binding event may be conserved upon utilization of only a fraction of the $Man_9GlcNAc_2$ epitope. Our objective is to develop a glycan mimetic of HIV gp120 that potentially binds to glycan-specific bnAbs; this synthetic mimetic could subsequently be investigated for use as a potential HIV vaccination strategy.

To date, a number of scaffolds have been utilized to mimic the multivalent glycan surface of HIV gp120 such as galactose moieties,[11] cyclic peptides,[12] cholic acid[13], PNA,[14] RNA,[15] dendrimers,[16] and Qβ phage.[17] Each of these recent strategies used either a significant portion of the $Man_9GlcNAc_2$ unit or $Man_9GlcNAc_2$ in its entirety as their potential antigen.[18] Our strategy as illustrated in Figure 1, employs just two arms of the $Man_9GlcNAc_2$ glycan, D1 and D2, which constitute a large majority of the overall interaction between the 2G12 antibody and gp120. By assimilating the D1 Manα(1-2)Man disaccharide and the mannose terminus of the D2 arm into one epitope, it is hypothesized that a considerable overall interaction may be conserved without the necessity of preparing larger fragments of $Man_9GlcNAc_2$ oligosaccharide. This strategy will be accomplished through the use of bivalent, ROMP-capable linker possessing orthogonal functionalities (Fig. 1).[19] With sequential positioning of each saccharide unit onto this linker through an amide bond formation and a 'click' reaction[20] with an azide unit, respectively, two simplified fragments of the natural $Man_9GlcNAc_2$ glycan were bound to a single scaffold to afford the corresponding monomer **2** (Fig. 1). The distance between the C1-anomeric carbons in the mannose units has been

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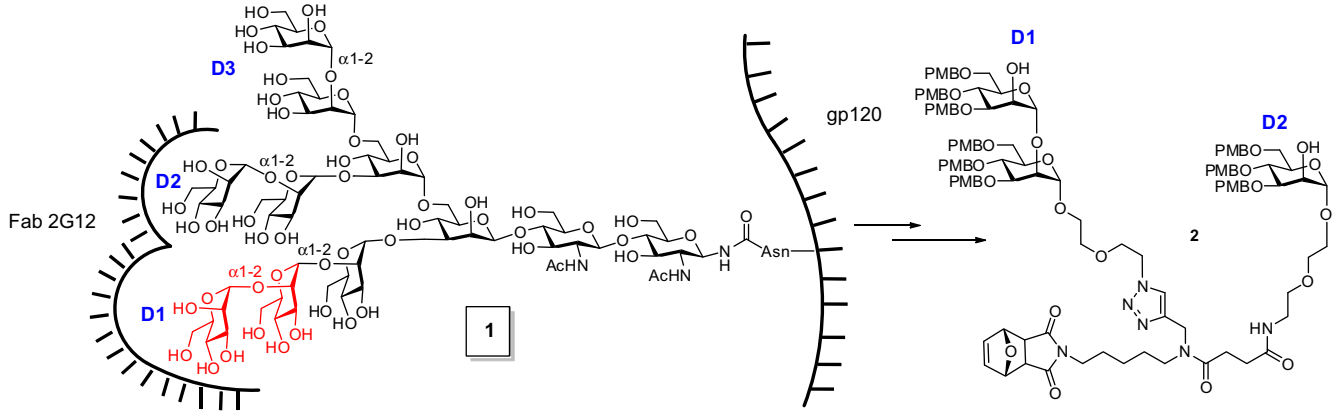


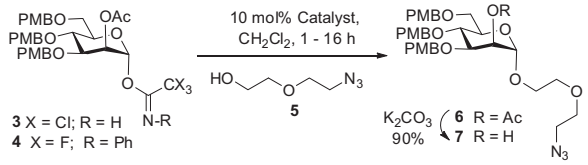
Figure 1. Simplification of $Man_9GlcNAc_2$ oligosaccharide to polymerizable, bivalent glycan monomer.

measured to be 11.5 Å.[21] For comparison, the distance between the two saccharide moieties in monomer **2** (Fig. 1) has been calculated using solid state 3D-modeling software to be ~13 Å, placing the glycans within a suitable proximity to each other to undergo 'force affinity' to their respective receptors brought on by the flexible, bivalent tethered linker. Furthermore, we selected the norbornene-based linker because it has been reported that this scaffold increases the structural rigidity of the resultant neo- glycopolymer.[22] Importantly, this polymerizable linker is also endowed with a bicyclic strained ring system that can be then opened with Grubbs I/III catalysts via a ring-opening metathesis polymerization (ROMP)[23–26] in order to polymerize the synthetic glycan mimetic of HIV gp120 and promote multivalent binding.

This Letter details the synthesis of our target epitope by presenting a monomer **2** (Fig. 1) containing a D-mannosyl monosaccharide unit and a Manα(1-2)Man disaccharide covalently bound to the polymerizable linker as proof of concept. In order to accomplish this, the traditional Lewis acid (TMSOTf) and the $Ni(4\text{-F-PhCN})_4(OTf)_2$ catalyst recently developed in our lab[27] were compared in the trihaloacetimidate glycosylation reactions. Our results demonstrate the ability of $Ni(4\text{-F-PhCN})_4(OTf)_2$ as an efficient catalyst for activating an acetimidate donor under a mild and operationally simple procedure. The construction of target monomer **2** (Fig. 1) required a preparation of the two glycan fragments, each bearing a functional group that could be sequentially coupled to the bivalent, polymerizable scaffold. In our design, *para*-methoxybenzyl (PMB) ether protecting groups were chosen for the substrate hydroxyl groups at C-3, -4, and -6 positions because post-polymerization hydrogenation allows for their removal and a reduction of the residual alkenes of the polymer to be achieved simultaneously. An acetyl protecting group was chosen for the C-2 hydroxyl group, so that it could be selectively removed and subsequently serve as an acceptor for another coupling iteration to produce the corresponding disaccharide. This synthetic sequence maximized efficiency as the glycosyl donor was readily converted to the acceptor. Additionally, two different imidates were employed in this sequence to investigate an optimal donor species.

With this approach in mind, the first step of the synthesis was the establishment of monosaccharide **7**, a mimetic of the terminus of the D2 arm. Linker **5** (Table 1) presents a terminal azide,[28] which upon reduction to the corresponding amine may facilitate an amide coupling to the carboxylic acid of the bivalent scaffold **13** (Scheme 3). Accordingly, coupling of linker **5** with Schmidt's trichloroacetimidate[29,30] donor **3** was mediated by 10 mol % TMSOTf (Table 1, entry 1), providing the desired glycoside product **6** in 70% yield. We next attempted to substitute TMSOTf for $Ni(4\text{-F-PhCN})_4(OTf)_2$ (entry 2), previously described by the Nguyen group to be successful in the

Table 1
Glycosylation of azide linker with trihaloacetimidates



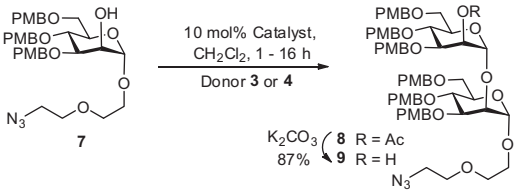
Entry	Donor	Catalyst	Temp (°C)	Time (h)	Yield[a] (%)
1	**3**	TMSOTf	−40	1	71
2	**3**	$Ni(4\text{-F-PhCN})_4(OTf)_2$	25	3	70
3	**3**	TMSOTf	25	1.5	Decomposition
4	**4**	TMSOTf	−40	5	59
5	**4**	$Ni(4\text{-F-PhCN})_4(OTf)_2$	25	16	60
6	**4**	$Ni(4\text{-F-PhCN})_4(OTf)_2$	35	16	65

[a] Isolated yield.

formation of 1,2-*cis*-2-aminoglycosides.[27] This nickel catalyst efficiently activated trichloroacetimidate donor **3** at 25 °C, providing **6** in a similar yield (70%, entry 2). In comparison, use of TMSOTf to mediate the coupling at 25 °C (entry 3) only resulted in decomposition of carbohydrate coupling partners. This result suggests that $Ni(4\text{-F-PhCN})_4(OTf)_2$ is a much milder activating reagent than air- and moisture-sensitive TMSOTf in the promotion of the glycosylation at a more green and economical temperature. The nickel catalyst is also effective at facilitating the glycosylation of **5** with *N*-phenyl trifluoroacetimidate **4** (entry 5), although the reaction took longer to reach completion. Subsequent removal of the C2-acetyl group with K_2CO_3 produced acceptor **7** in 90% yield, prepared for another coupling iteration with donors **3** and **4** to generate disaccharide.

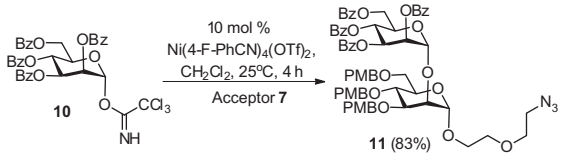
The advantage of the $Ni(4\text{-F-PhCN})_4(OTf)_2$ catalyst over the conventional Lewis acid (e.g., TMSOTf) for imidate glycosylation was further demonstrated in the preparation of Manα(1-2)Man disaccharide **8** (Table 2). The TMSOTf-mediated glycosylation of acceptor **7** with trichloroacetimidate donor **3** resulted in only a 17% yield of desired disaccharide **8** (entry 1); many different side products were observed including the formation of an orthoester, the [1,3]-rearrangement of trichloroacetimidate **3** to the trichloroacetamide, as well as a partial removal of the acid-labile PMB groups due to the acidic nature of TMSOTf. On the other hand, use of 10 mol % $Ni(4\text{-F-PhCN})_4(OTf)_2$ catalyst (entry 3) improved the yield

Table 2
Formation of the Manα(1-2)Man disaccharide

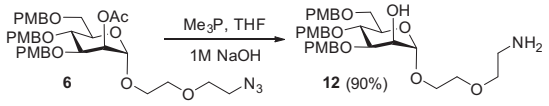


Entry	Donor	Catalyst	Temp (°C)	Time (h)	Yield[a] (%)
1	**3**	TMSOTf	−40	1	17
2	**3**	TMSOTf	25	1	Decomposition
3	**3**	TMSOTf	25	4	30
4	**4**	Ni(4-F-PhCN)$_4$(OTf)$_2$	25	16	39
5	**4**	Ni(4-F-PhCN)$_4$(OTf)$_2$	35	16	58

[a] Isolated yield.



Scheme 1. Nickel-catalyzed coupling with electron-deficient donor.



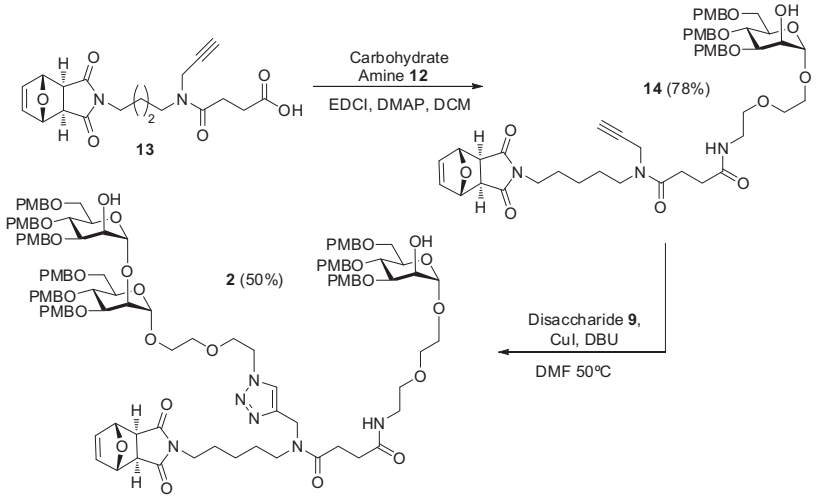
Scheme 2. One-pot hydrolysis of acetyl and reduction of azide.

of the product **8** (17% → 30%), but undesired [1,3]-rearrangement trichloroacetamide was still observed in the coupling event.[31] In order to prevent the trichloroacetamide byproduct, donor **4**, *N*-phenyltriflouroacetimidate,[32] was employed (entries 4 and 5). When Ni(4-F-PhCN)$_4$(OTf)$_2$ was utilized and the coupling reaction was heated to 35 °C, a significant improvement in formation of the desired disaccharide **8** (58%, entry 5) was observed. Subsequent removal of the C2-acetyl group furnished the terminal Manα(1-2)Man disaccharide **9** of the D1 arm of $Man_9GlcNAc_2$ moiety, which could then be 'clicked' to scaffold **13** (Scheme 3).[19,33]

In addition to effectively activating the PMB-ether protected donors **3** and **4** (Tables 1 and 2), Ni(4-F-PhCN)$_4$(OTf)$_2$ catalyst was also suitable for activating perbenzoylated trichloroacetimidate donor **10** to give disaccharide **11** (Scheme 1) in 83% yield. This result suggests that the nickel catalyst is more effective at activating electron-deficient imidate donor **10** than its electron-donating counterparts **3** and **4** (Table 2).

Next, was the creation of the terminal monosaccharide **12** of the D2 arm unit (Scheme 2). This was achieved in a one-pot reaction by simultaneously subjecting **6** to a Staudinger reduction of the azide functionality to the corresponding amine,[34] and a hydrolysis of the C2-acetyl protecting group, providing a 90% yield of **12** (Scheme 2).

With both glycans in hand, each with their respective linker-conjugate functionality, they were sequentially coupled to the bivalent polymerizable backbone **13**[19,33] to complete our preliminary target epitope **2** (Scheme 3). We selected norbornene-based scaffold **13** because it has been used to generate bivalent-brush polymers for drug-delivery applications[19b,d] and to mimic the native-like, multivalent motif found on chondroitin sulfate proteoglycans.[22] In our approach, the newly-formed terminal monosaccharide amine **12** was then coupled to the carboxylic acid on **13** under standard EDCI-mediated conditions, leading to the formation of **14** in 78% yield (Scheme 3). Next, a survey of Sharpless–Huisgen copper(I)-catalyzed cycloaddition conditions[20,35] with the terminal D1 arm disaccharide **9** was carried out. After gauging the efficiency of reactions with a number of Cu(I) sources, additives, and solvents, it was determined that optimal treatment of triazole **14** with disaccharide **9** using CuI and DBU in DMF at 50 °C generated the corresponding monomer **2** possessing a polymerizable backbone in 50% yield (Scheme 3) as the final product. We have determined that varying the amount of Grubbs I or III catalysts (0.5–5.0 mol %) led to a series of neo-glycopolymers from the norbornene-based scaffold with controllable molecular weights (M_n) and narrow polydispersities (PDI).[36] We have also determined that lowering the catalyst concentration produced glycopolymers with long chain lengths.[36] Longer polymers with narrower polydispersities might be advantageous for biological activity.[37] The most suitable length with the strongest avidity would be determined in subsequent biological studies.[38] Recent results have also illustrated that some of the bnAbs such as PG9 and PG16 require part of peptide segment of



Scheme 3. Completion of the bivalent, polymerizable glycan monomer.

the antigen to bind to.[15,39,40] We envision that this peptide portion could be coupled to glycopolymers generated from monomer **2** (Scheme 3) by investigating end-functionalization of the polymers during the quenching stage of ROMP with an amine group, which will subsequently serve as an attachment point.[22]

In summary, we have developed a new strategy for orthogonally attaching both the terminal Manα(1-2)Man disaccharide unit of the D1 arm of $Man_9GlcNAc_2$ and the terminal Manα1-2 unit of its D2 arm to a bivalent scaffold to produce the corresponding polymerizable monomer **2**. The Manα1-2 saccharide moieties were prepared in good yield via the $Ni(4\text{-F-PhCN})_4(OTf)_2$-mediated trihaloacetimidate glycosylation reactions. The ring-opening metathesis polymerization (ROMP) of monomer **2** and subsequent binding studies of its corresponding neo-glycopolymers with the 2G12 and several other bnAbs are under investigation and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.016.

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