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# Glycal Scavenging in the Synthesis of Disaccharides Using Mannosyl Iodide Donors[1]

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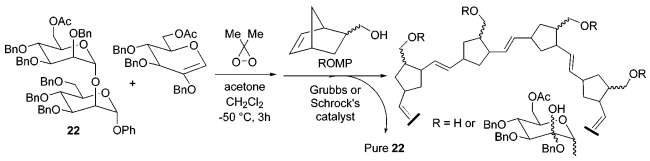


High mannose glycans composed of α (1→2) and α (1→6) branched sugars are important components of the HIV-associated envelope glycoprotein, gp120. These substructures can be efficiently prepared in solution from glycosyl iodide precursors requiring only a slight excess of the iodide donor, which offers advantages over solid-phase methods that require more than 5 equiv of donor. During the reaction, excess iodide is converted to a glycal that is not easily separated from the desired disaccharide. To overcome this difficulty, a phase-trafficking methodology that relies upon nucleophilic interception of the 1,2 anhydrosugar resulting from oxidation of the glycal has been developed.

The utility of glycosyl iodides in organic synthesis has been widely demonstrated in recent years. The reactions can be conducted under neutral conditions giving rise to highly $\beta$-selective glycosidations[2] or alternatively, in situ anomerization can be employed in α-glycosylations.[3] Although we have shown that glycosyl iodides can be effectively employed in solid-phase oligosaccharide synthesis, typically 5 equiv of the iodide is required. The preparation of appropriately protected monosaccharide building blocks is laborious and often the slow step in oligosaccharide synthesis prompting us to develop more efficient methodologies. Solution-phase reactions look promising as only a slight excess of the iodide donor is required and it is not unusual for crude reaction mixtures to have only the desired product along with glycal, which is produced by HI elimination from the excess iodide.

As a part of our program focused on developing solution-phase oligosaccharide synthesis, we have extended the glycosyl iodide studies to include the synthesis of branched mannose containing sugars. We have targeted 1→6 (**3**) and 1→2 (**4**) α-linked mannosides because these are substructures of HIV-associated high mannose N-glycans (**1**,**2**) that are implicated in the pathogenicity of this disease (Figure 1). Establishing efficient methodologies for the construction of structural subsets in addition to the parent compounds is an important step toward having materials for biological evaluation. Herein, we report our initial investigations using in situ anomerization[4,5] of mannosyl iodides en route to the targeted dimers and the development of a scavenging protocol for removing glycal byproducts.

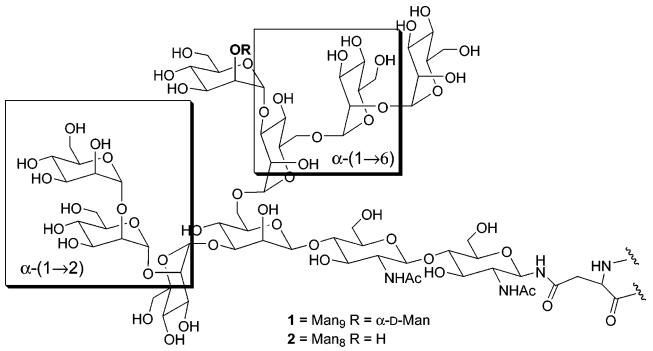


**FIGURE 1.** $Man_9$: representative high-mannose oligosaccharide of HIV-1 rgp120.

The three monomer units required for the disaccharide syntheses include 6-*O*-acetyl-2,3,4-tri-*O*-benzyl mannopyranosyl iodide (**5**) along with the differentially protected acceptors **6** and **7**, Figure 2. A phenyl moiety was introduced at the reducing end to facilitate HPLC purification of fully deprotected disaccharides.

Preparation of **5** began with formation of methyl α-D-mannopyranoside (**8**),[6] which was subsequently subjected to per-benzylation using NaH and BnBr with catalytic TBAI, to give **9**. Acid-catalyzed acetolysis of **9** using $H_2SO_4$[7] or $ZnCl_2$ [8] furnished diacetate **10**, which was converted to **5** using TMSI. Alternatively, **10** could be reacted with $BF_3{\cdot}OEt_2$ in the presence of phenol to afford **11**, which upon deacetylation provided acceptor **6**, (Scheme 1).

The primary alcohol of **6** was glycosidated under standard in situ anomerization conditions (TBAI and Hünig's base in PhH at 80 °C), with mannosyl iodide donor **5**, Scheme 2. Though the reaction provided the α-anomer **13**, we were unable to chromatographically (flash chromatography and HPLC) separate glycal **14** from the disaccharide, as both possessed very similar $R_f$ values in numerous solvent systems. However, following deacetylation of the crude mixture using an excess of NaOMe in anhydrous MeOH, the pure α-linked disaccharide **15**, verified by a large coupling $^1J_{C,H} = 169.0$ Hz,[9]

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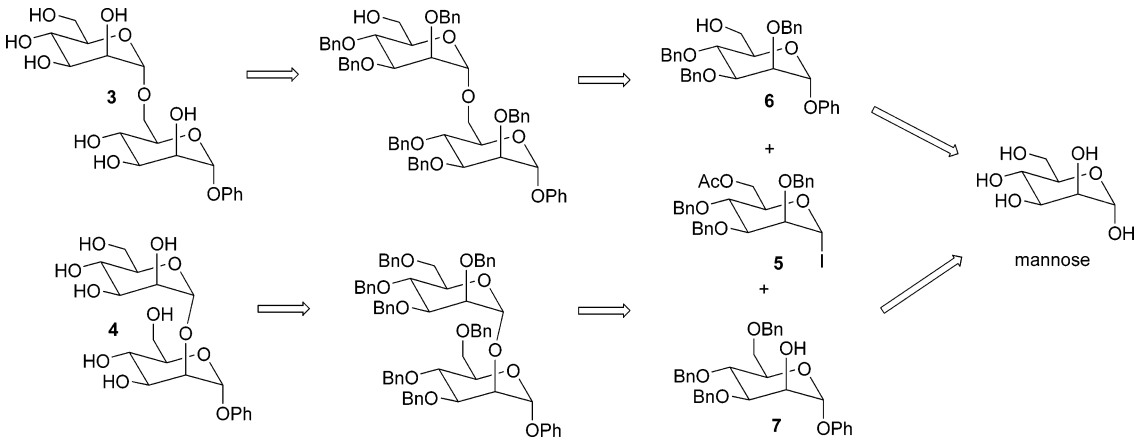
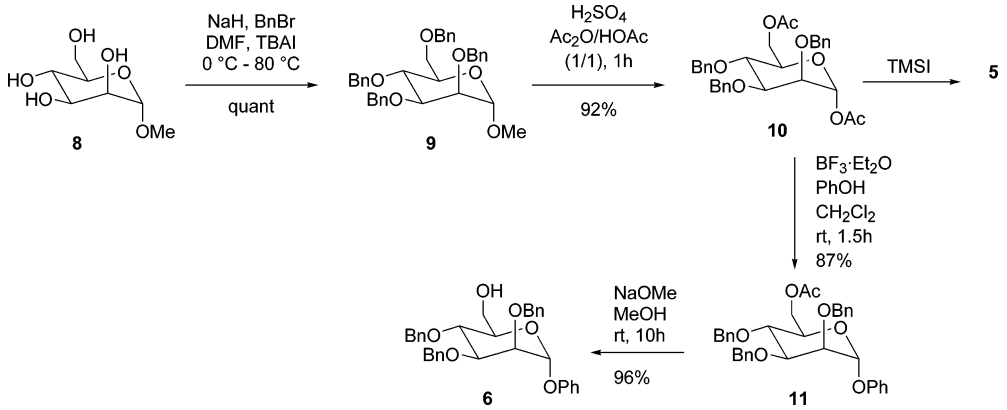
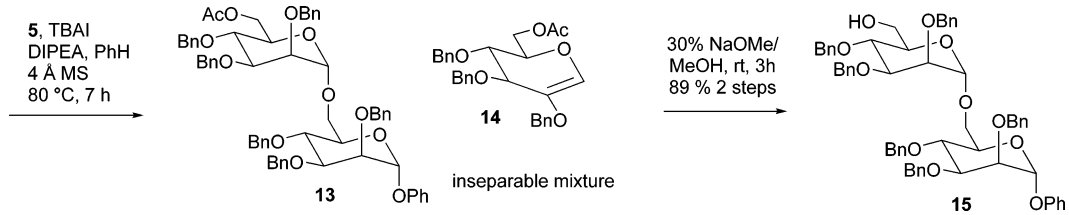



**FIGURE 2.** Retrosynthesis of targeted disaccharides.

**SCHEME 1**




**SCHEME 2**




was recovered in 89% yield over two steps. Through a combination of chemical and chromatographic means, the glycal was satisfactorily separated from the synthetic target but this protocol was far from ideal and not amenable to automated synthesis.

Having synthesized one of two targets, our attention turned toward the preparation of acceptor **7**, Scheme 3. The synthesis began with glycosidation of acetobromomannose **16**[10] with ethanol under basic conditions to give 1,2-*O*-(1-ethoxyethylidene)-3,4,6-tri-*O*-acetyl-*β*-D-mannopyranose **17**, in high yields (>90% over 2 steps) as an epimeric mixture. Removal of the acetyl groups using excess NaOMe in MeOH (to give **18**) with successive benzylation provided large quantities of the tri-*O*-benzyl ortho ester **19** in 30 min with high yields. Treatment of **19** with phenol in the presence of camphorsulfonic acid provided α-phenyl glycoside **20** (Scheme 4), which after quantitative deacetylation using catalytic NaOMe in anhydrous MeOH afforded **7**. As anticipated, glycosidation of **7** with mannosyl iodide **5** under in situ anomerization conditions produced disaccharide **22**. After aqueous workup and passage of the crude mixture through a decolorizing silica gel plug, the crude $^1$H NMR spectrum illustrated the clean conversion of the monosaccharide to the disaccharide (86% conversion to **22** based upon $^1$H NMR integrations and the amount of isolated crude material). Two major materials dominated the spectrum, the glycal **14** (H1 6.30 ppm) and the disaccharide **22** (H1′ OPh 6.10 ppm, H1″ OMan 5.43 ppm) with relative integrations of 1.7:1:1, respectively.

The $^1J_{C1,H} = 170.5$ Hz coupling confirmed the α-glycosidic linkage;[9] however, again we encountered a situation whereby the glycal was not readily separated from the disaccharide. Because chromatographic separation of deacetylated **14** and **22** is not an ideal strategy for automated procedures, we decided to explore methods for scavenging the glycal out of the mixture.

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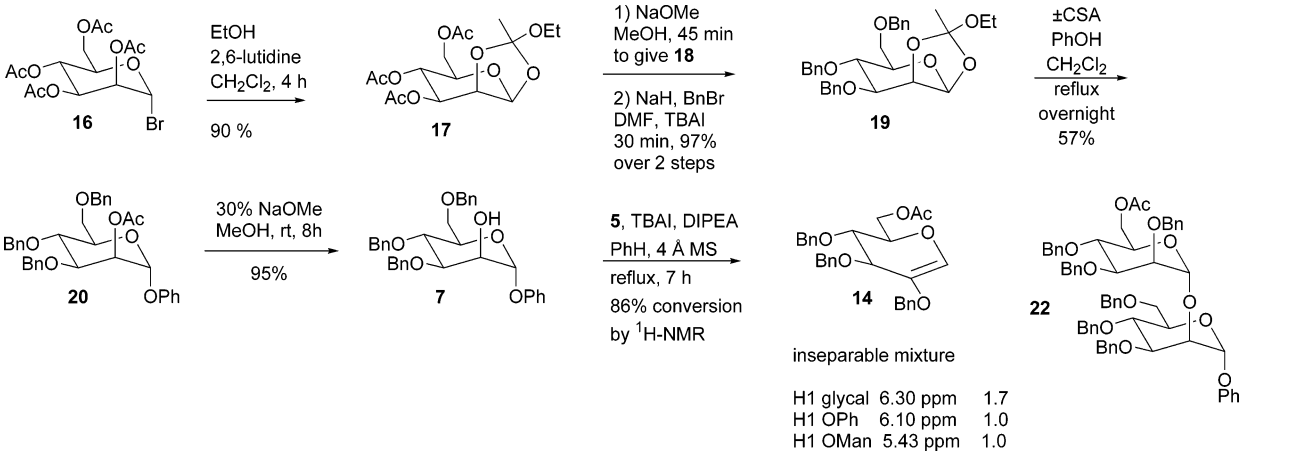
**SCHEME 3**

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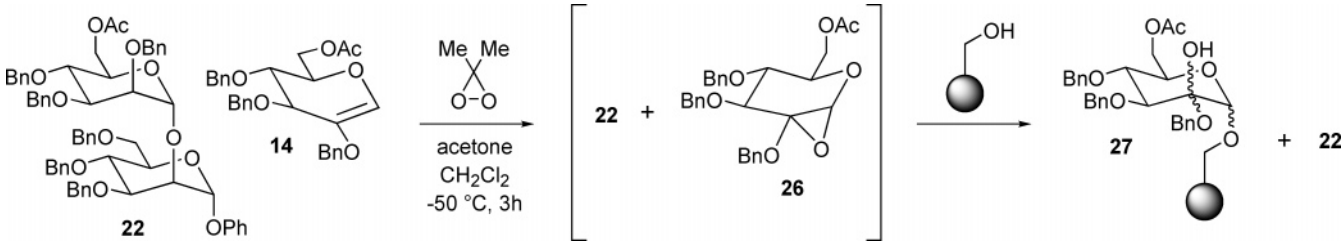


We felt that phase trafficking techniques[11,12] were ideally suited for purification of the glycal from the desired disaccharide due to their orthogonal reactivities. Phase trafficking requires the use of resins or crystallizable polymers to scavenge unwanted molecules from reactions. Whether the support is present throughout the reaction or added post-completion is dependent upon the nature of the support and the reaction. For example, divinylbenzene (DVB) cross-linked polystyrene (PS) beads, represented by a shaded ball and abbreviated as PS, offer the advantage of insolubility in most organic solvents, which facilitates removal via filtration. Various functionalities attached to PS such as nucleophiles (PS-X) allow for chemical elaboration.

Taking advantage of the electron density about the enol ether in **14**, we envisioned implementing dimethyl dioxirane (DMDO)[13] to provide a 1,2-anhydro sugar, which would be susceptible to nucleophilic attack. Adam and co-workers had previously shown that 2,3,4,6-tetra-*O*-benzyl-D-glucal **23** undergoes electrophilic epoxidation with DMDO at −20 °C in 2 h.[14] However upon warming to room temperature, only 2,3,4,6-tetra-*O*-benzyl-D-glucofuranose (**25**) with an aldehydic C-1 was seen in the $^1$H NMR spectrum. It was suggested that in order to relieve ring strain, the C-2 benzyl ether donates electrons forming the C-2 oxacarbenium (**24**), which also opens the oxirane and breaks the C-1-O-5 bond, Figure 3.

We reasoned that a similar strategy would be effective in removing the glycal from solution so long as the oxirane could be intercepted. The nucleophile would attack the highly strained and electrophilic anomeric center of **26** to immobilize the epoxidized sugar giving **27** and leaving behind only the disaccharide **22**. As **22** does not possess functionalities that react with either DMDO or the anhydro sugar, it would remain silent throughout the sequence. This strategy was reduced to practice upon treatment of the crude mixture with a 1.5 molar excess of DMDO relative to the glycal in the presence of PS−OH (1.5 molar excess to the glycal) at −50 °C for 3 h (Scheme 4), which removed 60% of the glycal as revealed by $^1$H NMR integrations.

Signs of unreacted 1,2-anhydro sugar were disclosed by the presence of ring-contracted furanosyl C-glycoside revealed through $^1$H and $^{13}$C NMR (H1 9.41 ppm, C1 196.17 ppm). The aldehydic resonance had an integration of 0.3 relative to the disaccharide (1.0). The resonance corresponding to the glycal (6.30 ppm) was also apparent in the $^1$H NMR spectrum with a relative integration of 0.4. The experiment was repeated with larger quantities of the PS-OH, in an effort to increase the concentration of nucleophilic groups capable of trapping the anhydrosugar intermediate. However, increasing the molar ratios of PS−OH to glycal to 10:1 as well as DMDO (4.5 molar excess), did not drive the reaction to 100% completion nor did it dramatically increase glycal removal (65% arrested glycal). The aldehyde and glycal were still apparent in the $^1$H NMR spectrum. Nonetheless, based upon $^1$H NMR integrations (1.7:1 to 0.4:1 glycal:disaccharide), ∼76% of the glycal had reacted with DMDO. Moreover, the disaccharide remained untouched by the mild reaction conditions as evidenced by the relative cleanliness of the TLC plate and the $^1$H NMR spectra. This initial attempt demonstrated the viability of the phase-trafficking glycal removal process.

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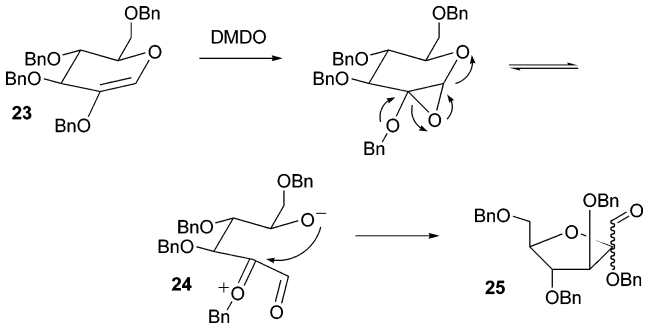
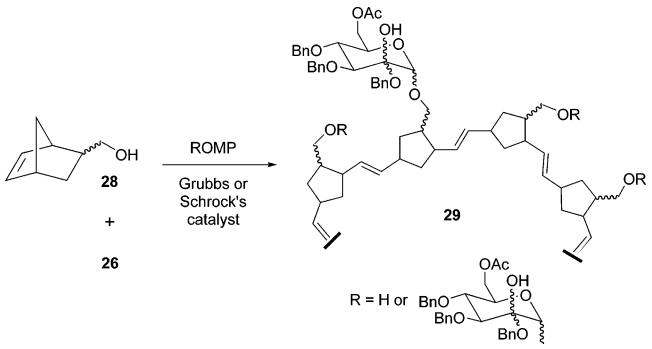



**FIGURE 3.** Rearrangement of 1,2-anhydro sugar to furanose.

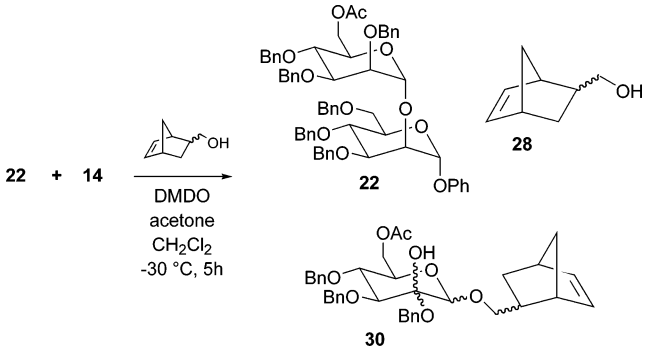
**SCHEME 5**




Departing from the polymer-bound nucleophile, we sought to employ norbornene-2-methanol **28** as a more viable solution-phase scavenger, Scheme 5. Compound **28** and its derivatives have been successfully subjected to ring opening metatheses polymerization (ROMP) in the presence of Grubbs or Schrock's catalyst to form ROMPgels.[11,15] ROMPgels are fluidic supports[11,16,17] that can be precipitated from various solvent mixtures depending upon the nature of the polymer. Numerous reagents and reactants immobilized onto ROMPgels have been employed in a myriad of chemical transformations including synthesis of oxazoles[18] and homoallylic alcohols,[19] scavenging of amines,[20] and Horner-Emmons olefinations.[11,21] Mindful of these developments, we envisioned the immediate trapping of **26** by **28** and subsequent ROMP to provide a polymer (**29**) that could be precipitated leaving behind only **22**.

We first treated **28** with a 10-fold molar excess of DMDO and no reaction was seen as monitored by TLC after 5 h at −30 °C. The norbornene olefin was left untouched even following reaction for an additional 10 h at room temperature as determined by TLC and $^1$H NMR analysis. This result alleviated concerns that **28** might interfere with the formation of **26**. We next subjected a mixture of **22** and **14** to oxidation with DMDO

**SCHEME 6**




in the presence of the solution-phase nucleophile **28** for 2 h at −30 °C, Scheme 6. After rotoevaporation, $^1$H NMR analysis of the crude mixture revealed the absence of resonances corresponding to either **14** (6.30 ppm) or the aldehyde (9.41 ppm). The spectrum was much more complicated than before, which was primarily due to the fact that eight new norbornene methyl glycosides **30** had been produced as three new stereogenic centers resulted. The presence of **30** was also indicated by the appearance of new resonances between 5.5 and 6.2 ppm. Most importantly, resonances corresponding to the anomeric protons of **22** were also observed. This experiment clearly demonstrated that a solution-phase alcohol was much more efficient at scavenging **26** than PS-alcohols.

After copolymerization of the norbornene methyl glycosides **30** with **28** using Grubbs generation I catalyst, a gelatinous film was deposited. Heterogeneous extraction of the gelatinous mass with boiling heptane provided in three 10 mL fractions **22** tainted with Grubbs catalyst and small impurities. Following flash chromatography, **22** was obtained in 80% yield from the crude phase-trafficked material.

In summary, mannosyl iodide **5** has been efficiently utilized in the construction of disaccharides **15** and **22**. The glycosidations are highly stereoselective cleanly presenting the dissacharides in excellent yields; but these reactions are plagued by the formation of glycal **14**, which is not readily separated. To overcome this difficulty, a scavenging protocol that depends on selective epoxidation of the glycal followed by nucleophilic attack was developed. A solution-phase nucleophilic scavenger **28** proved more effective toward scavenging epoxidized glycal than a comparable polymer-supported nucleophile PS-OH. The phase trafficking strategy, coupled with highly stereoselective glycosidations provides a foundation for future studies directed toward automated solution-phase synthesis of branched-chain mannose oligomers.

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**Supporting Information Available:** Experimental procedures for the synthesis of **5**, **6**, **15**, **20**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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