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Syntheses of α- and β-C-Glucopyranosyl Serines from a Common Intermediate

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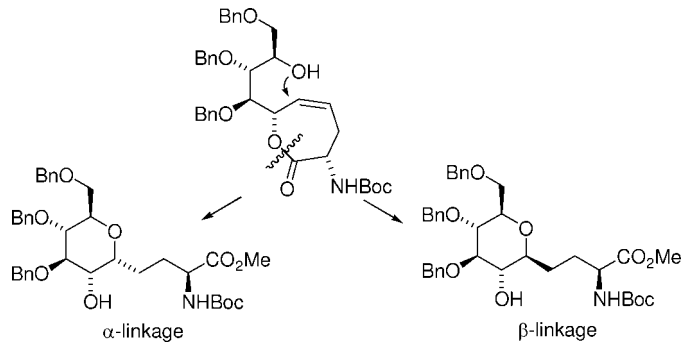
ABSTRACT



A versatile synthesis leading to either C-linked α- or β-glucopyranosyl serines is presented from a common, advanced synthetic intermediate. Cyclization of the penultimate carbinol onto the alkene and methanolysis of the lactone yields selectively the α-linkage. A transposition of these last steps leads to the β-linked isomer selectively.

Protein glycosylation, often via an oxygen linkage to serine/threonine, is of biochemical significance because it alters the physicochemical properties and activity of proteins and the carbohydrates themselves act as receptors on the cell surface.[1] Cell surface carbohydrates play important roles in the modulation of cellular interactions. Of particular interest, the α-linkage to O-GalNAc Ser/Thr, known as Tn antigen, forms the foundation for eight core structures of the heavily glycosylated proteins known as mucins. These structures are key immunological recognition features directly involved in antibody−antigen interactions, in pathogen binding, and serve as tumor markers. In addition, Hart has reviewed the significance of β-linked O-GlcNAc in cellular regulation on cytosolic and nuclear proteins and the implication of its misregulation in neurodegenerative diseases and diabetes.[2] The stereochemical aspect of the anomeric linkage (α or β) is essential to biochemical activity, and it has been shown, for example, that replacement of the natural α-O-GalNAc in mucin glycopeptides with a β-O-GalNAc results in structural disorder.[3]

Many groups have sought to mimic these glycoconjugates to better understand their glycobiology and to produce potential therapeutic agents. Toward that end, convenient syntheses of catabolically stable glycosyl amino acid mimics are desired. One approach has been the substitution of the linking oxygen with a methylene to form the so-called C-glycosides. These mimics are robust to degradation by

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glycosidases, reaction with glycosyltransferases, acid hydrolysis of the former anomeric acetal, and β-elimination from the serine.

Several syntheses of α-C-glycopyranosyl serines[4] and β-C-glycopyranosyl serines[4a,e,5] have been reported. In most cases, the stereochemistry of the C-linkage to the carbohydrate is first established with a pendant functional group, which is utilized to elaborate the amino acid moiety. The one exception being the exoalkylidene hydrogenation to afford the β-C-linkage.[5e,f] In addition to these strategies, cross-metathesis (CM) has been employed to join C-vinyl glycosides with vinyl glycine surrogates to furnish glycosyl serine mimics. In general, these have only produced low yields of CM product.[6]

Previously, we have reported the synthesis of α-C-glycosyl serine **4** through an intramolecular hydroalkoxylation of the (*E*)-4-decenoate **1**.[7] This cyclization precursor was prepared by CM of the readily available gluco-heptenitol **2** and L-allyl glycine **3**, as illustrated in Figure 1. Unfortunately, both

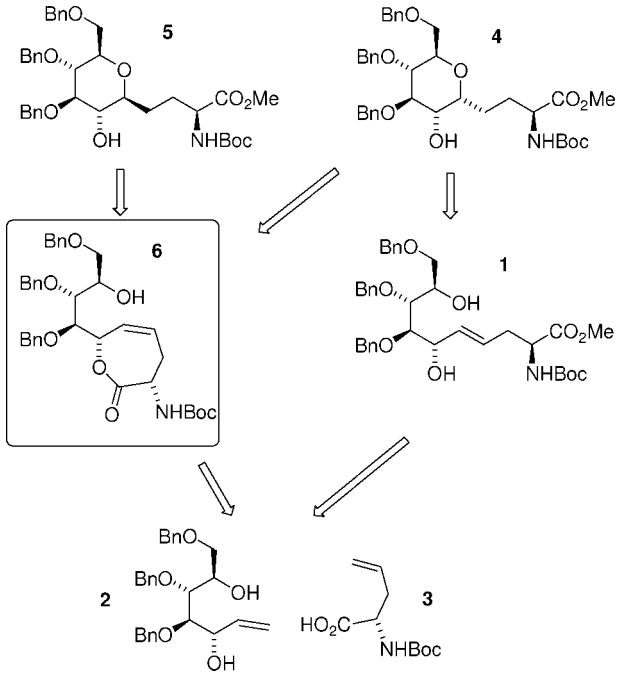
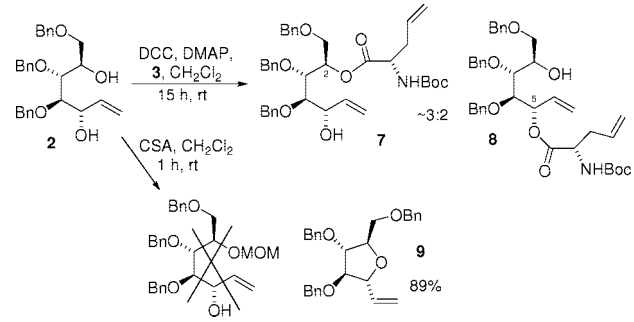


Figure 1. Retrosynthetic plan and the common intermediate.

metathesis partners are of type I[8] and thus are highly reactive, so significant amounts of the two self-metathesis products were obtained. This was circumvented by using a 4:1 ratio of the heptenitol to the allyl glycine, providing the decenoate **1** and a large amount of the easily separated heptenitol self-metathesis product. While this strategy was tenable for the readily available gluco-heptenitol **2**, it was not feasible for other heptenitols that may require greater synthetic effort. To avoid this limitation, we present here a ring-closing metathesis strategy that not only allows for a 1:1 stoichiometric ratio between the metathesis partners but also presents the option of diverting the synthesis to yield stereospecifically the α- or β-anomeric C-linkage, **4** and **5**, respectively, from the common intermediate **6**.

The known gluco-heptenitol **2** was available in one step by addition of divinylzinc to 2,3,5-tri-*O*-benzyl arabinose.[9] The divinylzinc addition is remarkably stereoselective, and the crude product is used directly in the next step. The metathesis partner, allyl glycine **3**, was produced by protection of the commercially available allyl glycine. As shown in Scheme 1, Yamaguchi or DCC-activated esterification of

Scheme 1. Nonselective Esterification of Diol **2**



the heptenitol **2** with the acid **3** yielded mixtures of products with a slight preference for the nonallylic ester **7** over the allylic ester **8** in a ~3:2 ratio by mass after separation of products. Neither Bu_2SnO[10] nor Ag_2O,[11] which are useful for selective reaction of vicinal diols, were of any use in

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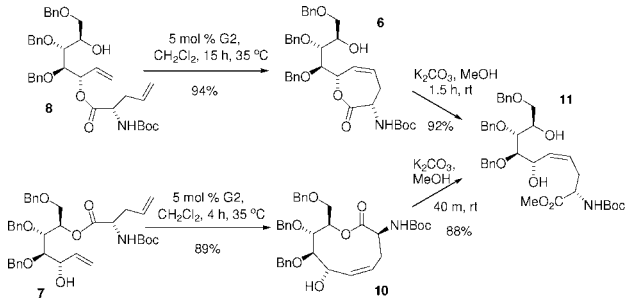
our esterification. Although we were unable to achieve a satisfactory esterification, others have shown modest selectivity for the allylic hydroxyl in reactions on diol **2** by alkylation with *p*-methoxybenzyl chloride[12] and benzoylation in a two-phase system to supply modest selectivity, 3.5:1.[13] Interestingly, Crumpstey has reported a highly selective (10:1) 3,4-dimethoxybenzylation on a structurally similar octenitol with preference for etherification of the non-allylic hydroxyl.[14] A report using trimethylorthoformate and camphorsulfonic acid followed by reduction with diisobutylaluminum hydride[15] was promising as there exhibited a preference for MOM protection of a non-allylic hydroxyl in the presence of an allyic hydroxyl, yet in our hands, the initial acid-catalyzed step of this procedure directly yielded the C-vinyl arabinose **9**[16] by S_N2 displacement at the allylic position.

With esters **7** and **8** in hand, albeit unselectively at this point, we conducted the RCM using 5 mol % of Grubbs second generation catalyst (G2) in refluxing dichloromethane (see Scheme 2). Both esters gave good yields of cyclized

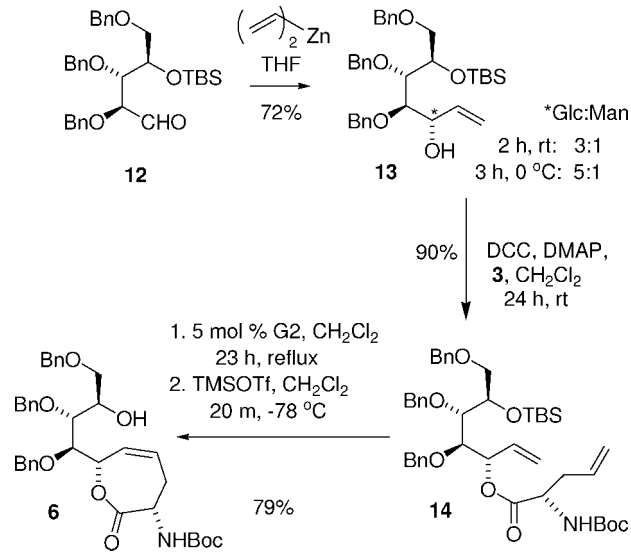
Scheme 2. RCM and Convergent Synthesis of Decenoate **11**



products. The oxepenone **6** was produced in 94% yield and the oxecenone **10** in 89% yield. Obviously, RCM of the allylic ester **8** can only afford the *Z*-geometry within the seven-membered oxepenone framework, but presumably the nonallylic ester **7** could produce a mixture of (*E*)- and (*Z*)-alkenes in the 10-membered ring; however, we observed only the *Z*-isomer. The assignment was confirmed by methanolysis of each of the lactones to yield the same acyclic (*Z*)-alkene **11**. We were surprised to find that only the *Z*-geometry of **10** was obtained in view of the mixtures observed in other RCM reactions leading to 10-membered rings, such as that found in microcarpalide syntheses.[17] Recently, a report by Mohapatra and Grubbs[18] observed the olefin geometry of nonenolides was critically dependent on the protecting groups, with allylic hydroxyl favoring the (*Z*)-alkene and PMB protection affording the *E*-isomer.

With both esters **7** and **8** leading to the same *Z*-configuration, the selectivity issues of the esterification were not of concern providing that the (*Z*)-decenoate **11** leads on the desired product. However, we were more interested in the synthetic versatility of the oxepenone **6**. The esterification selectivity issue described in Scheme 1 was avoided by an alternative route, shown in Scheme 3, through a dithioacetal

Scheme 3. Alternative Selective Synthesis of the Common Intermediate **6**



to supply the starting aldehyde **12**.[19] While reproducing the literature procedure, we explored two modifications. Attempts to prepare the initial dithioacetal via an odorless protocol[20] were unsuccessful; however, the removal of the diethyl dithioacetal using NBS, CH_3CN, and H_2O[21] nicely replaced the need for mercury salts to unmask the aldehyde of **12**. Divinylzinc addition by Nicotra's method[9] yielded the gluco-heptenitol **13** as the major isomer. Lowering the temperature of the reaction from rt to 0 °C improved the selectivity of vinyl addition from 3:1 to 5:1 in favor of the gluco-configuration over the manno-isomer. Chelation control with the adjacent benzyl ether dictates the gluco-configuration, and proof of the diastereoselection was accomplished by removal of the silyl protecting group in 85% yield using Bu_4NF to supply the aforementioned gluco-heptenitol **2**. Conversion of **13** into **6** was accomplished by esterification

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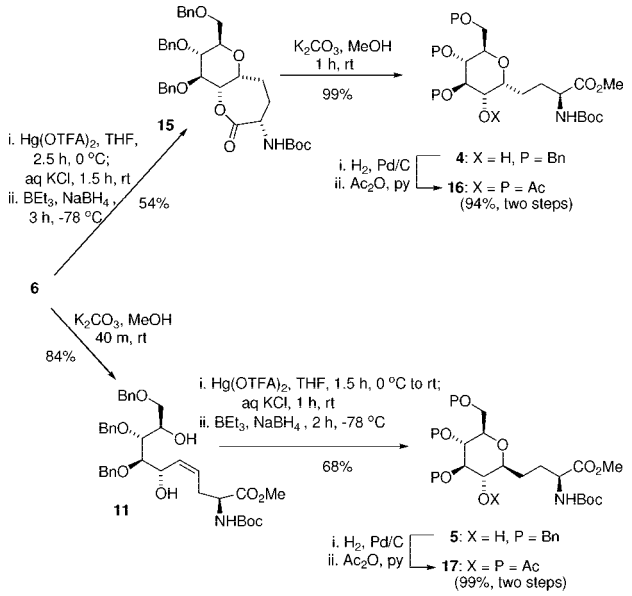
with L-allyl glycine **3**, RCM to yield the oxepenone, and TMSOTf deprotection of the silyl ether.[22]

Turning now to the key closure of the pyranosyl ring, we envisioned a mercury(II)-mediated cyclization of the penultimate carbinol onto the alkene as described in our earlier work,[7a] which was modeled after Nicotra's C-methyl glycosides.[9] As shown in Scheme 4, treatment of **6** with

Scheme 4. Divergence from **6** to Afford α- and *β*-C-Glc Ser



mercury(II) trifluoroacetate in an ice bath, followed by removal of mercury with BEt_3 and $NaBH_4$[23] produced a single stereoisomer. The stereoselectivity of the addition was controlled by the stereochemistry at the allylic position, which orients the cyclizing chain to one face of the alkene. Essentially, the lactone ring locks the allylic C−O bond into the inside alkoxy orientation that has been explanatory for other intramolecular additions to alkenes[24] (see Figure 2). Finally, methanolysis of the lactone provided the α-C-glucopyranosyl serine **4**. The stereochemical assignment was only possible by hydrogenolysis and acetate formation to furnish the tetraacetate **16**, which was identical to material synthesized by a stereochemically unambiguous route.[4i]

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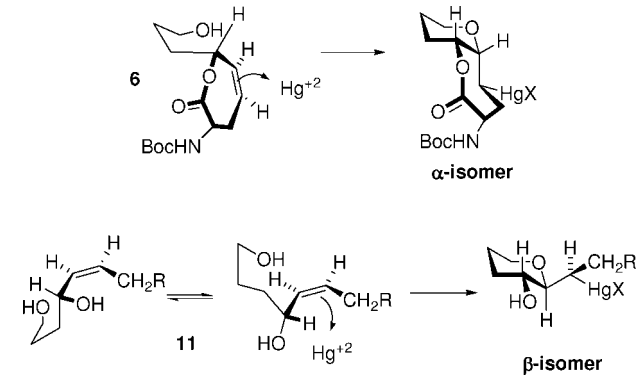

Figure 2. Suggested origin of the cyclization stereochemistry.

Specifically, the ^1H NMR resonance for H-2 (glycoside numbering) of compound **16** in $CDCl_3$ appears as a doublet of doublets ($J_{1,2}$ = 5.7 Hz) at 5.07 ppm, which is characteristic of the α-anomer in the $^4C_1$ conformation.

In contrast, when the cyclization was conducted, after methanolysis of **6**, on the aforementioned acyclic (*Z*)-alkene **11**, the *β*-C-glucopyranosyl serine **5** was observed. Presumably, the steric repulsion of the hydroxyl and the *cis*-methylene disfavors the inside alkoxy model, allowing bond rotation to position the smaller C−H bond into the plane of the double bond, giving rise to cyclization from the opposite face of the alkene, as shown in Figure 2. Confirmation of the *β*-isomer was supported by transformation to the tetraacetate and comparison to the ^1H NMR spectrum of the known compound.[4i] In particular, for compound **17** in $CDCl_3$, the NMR resonance of H-2 at δ 4.89 ppm appears as a triplet with $J_{1,2}$ = 9.6 Hz, in agreement with axial−axial coupling constants, as expected for the *β*-isomer.

In summary, the oxepenone **6** is available through a RCM strategy and can be diverted to prepare mimics of O-glycosyl serines in either anomeric configuration. From the oxepenone, hydroalkoxylation and methanolysis afford the α-C-glucopyranosyl serine, and a reversal of the sequence of the final two reactions leads to the *β*-C-glucopyranosyl serine.

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Supporting Information Available: Experimental procedures and characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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