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Stereoselective Synthesis of α-*C*-Glucosyl Serine and Alanine via a Cross-Metathesis/Cyclization Strategy

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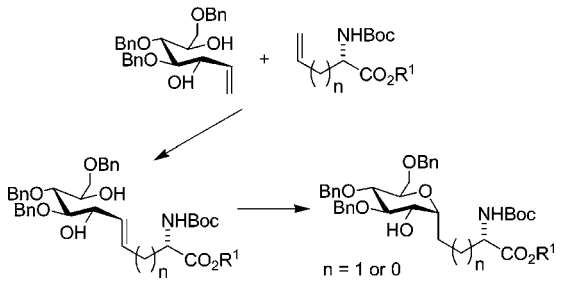
ABSTRACT



***C*-Glycosyl amino acids represent stable mimics of monomeric units within natural O-linked glycoproteins. Olefin cross-metathesis has been used to provide alkene precursors for a mercury(II)-mediated cyclization, yielding α-*C*-glucosyl serine and alanine.**

Installation of carbohydrates onto proteins is a post- and cotranslational event managed by numerous glycosyltransferases.[1] One of the most common linkages entails O-glycosylation of serine/threonine residues. Conjugation of glycosides not only confers physicochemical constraints on the protein, but the glycans serve as specific ligands for endogenous and exogenous receptors and hence mediate various biological interactions.[2]

Replacing the linking oxygen with a methylene offers a great deal of stability with minimal steric variance. These so-called C-linked glycosides are robust to degradation by glycosidases, reaction with glycosyltransferases, acid hydrolysis of the former anomeric acetal, and β-elimination from the serine.

Several syntheses of α-*C*-glycosyl serines have been reported.[3] In addition, the chain-shortened α-*C*-glycosyl alanine has been prepared, although with modest diastereoselectivity.[4]

Recently, the ruthenium-catalyzed olefin cross-metathesis, followed by hydrogenation, has been employed for the

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preparation of *C*-glycosyl amino acids, providing a rapid entry into analogues in which the intervening carbon chain contains three or more methylenes, Figure 1. Dondoni made

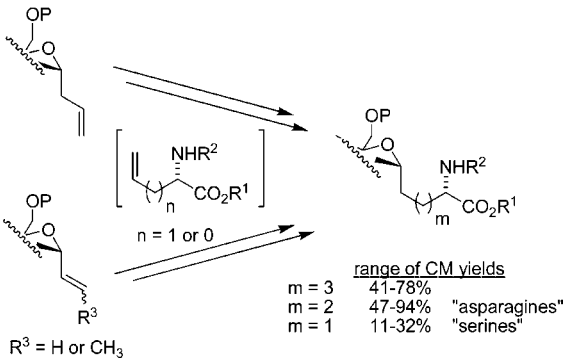

Figure 1. Summary of previous CM approaches to *C*-glycosyl amino acids.

use of benzyl-protected *C*-alkenyl glycosides and affected cross-metathesis with a vinyl oxazolidine, derived from Garner's aldehyde.[5] McGarvey has described the success of the cross-metathesis approach between *C*-alkenyl glycosides and L-allyl glycine,[6] and we have communicated the olefin cross-metathesis between *C*-allyl glycosides and L-vinyl glycines for *C*-glycosyl amino acid synthesis.[7] In each of these reports, the Grubbs' second-generation catalyst **G2**[8] was employed for the olefin cross-metathesis (CM). In our hands and in accordance with others, the linking carbon chain between the *C*-glycoside and the amino acid cannot be made shorter than three carbons without seriously diminishing the yield, yet serine mimics require only two linking methylenes. This represents a severe limitation for the preparation of C-linked glycosyl amino acids by this straightforward methodology.[9] Recognizing this limitation, Ben employed a CM strategy for several C-linked galactosyl analogues, with the exception of serine.[10]

To circumvent this limitation we considered opening the sugar to vary the reactivity for CM olefination. Specifically, as shown in Figure 2, we sought to employ the cross-metathesis methodology on the readily available gluco-heptenitol **4** and the manno stereoisomer **5** with allyl or vinyl glycine, **6** or **7**, respectively, to produce acyclic glyco-amino acid alkenes, which upon electrophilic cyclization would yield the desired *C*-glycosyl serine or alanine. Precedence

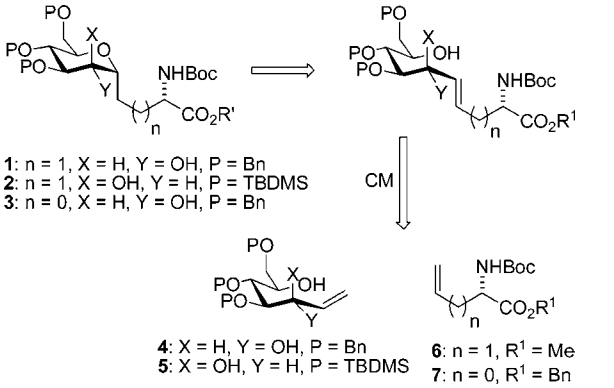

Figure 2. Retrosynthetic plan.

for this methodology has been demonstrated by Nicotra on the heptenitol **4** for the production of α-*C*-methyl glycosides.[11]

We have prepared the known gluco-heptenitol **4** in one step by addition of divinylzinc to 2,3,5-tri-*O*-benzyl arabinose.[11] The divinylzinc addition is remarkably stereoselective for the gluco isomer due to chelation control. The CM partner, allyl glycine **6**, is available via the Williams enolate[12] or by protection of the commercially available allyl glycine. A preliminary attempt at cross-metathesis using the Grubbs generation 1 catalyst **G1** [$(Cy_3P)_2(Cl_2)Ru{=}CHPh$] gave unceremoniously no CM product but rather 55% yield of **8**[13] by olefin transposition to the enol and subsequent acetal formation.

Successful cross-metathesis of **4** and **6** was accomplished using the second-generation Grubbs initiator **G2**; this provided **9** with the appropriate carbon chain length (C_{10}) for *C*-glycosyl serines. A significant amount of self-metathesis byproducts, **10** and **11**, was observed. Considering that a completely nondiscriminant metathesis reaction (i.e., rate constants for all metathesis reactions being equal) would yield only 50% of the desired product,[14] we modified the reactivity of **4** to enhance the selectivity. Using the diacetate or the bis-TMS ether of **4** gave a more selective CM reaction, but the yield did not compensate for the material loss during protection and eventual deprotection. Curiously, when the allylic hydroxyl of **4** was protected as the benzyl ether, no CM reaction was observed. This is in contrast to the structurally similar allylic pMB ether reported by Basu, which successfully undergoes CM reactions.[15] Subtle electronic and steric effects have been noted for allylic alcohols and ethers in the literature.[16]

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Table 1 illustrates the near statistical yields of metathesis

Table 1. CM of Gluco-hepetenitol and Allyl Glycine[a]

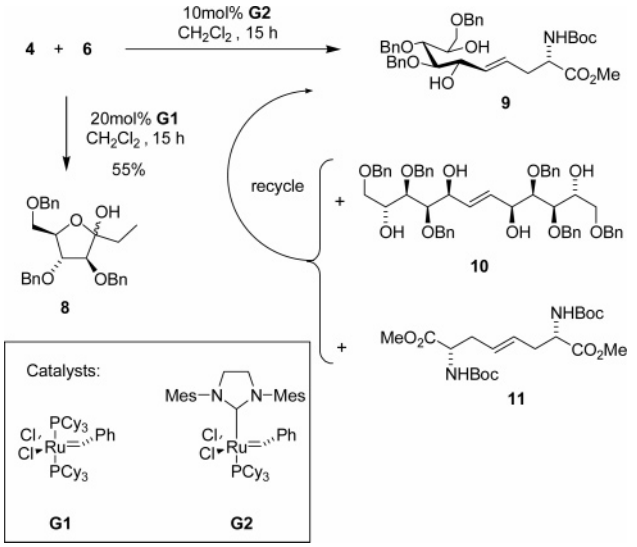
entry	ratio of **4** to **6**	yield of **9** (%)[b]	yield of homodimer **10** (%)
1	1:2	48	na
2	2:1	54	39
3	4:1	70	64

[a] All reactions were refluxed in CH_2Cl_2 for 15 h with 15 mol % **G2** catalyst. [b] All yields given were isolated from column chromatography.

products. Entry 3 represents our approach to maximizing material advancement. On the basis of consumption of **6**, a 70% yield of **9** was isolated and easily separated from the more polar homodimer **10**. This self-metathesis product could be recycled through the CM reaction with **6** (1 equiv) to give a 45% yield of **9**.

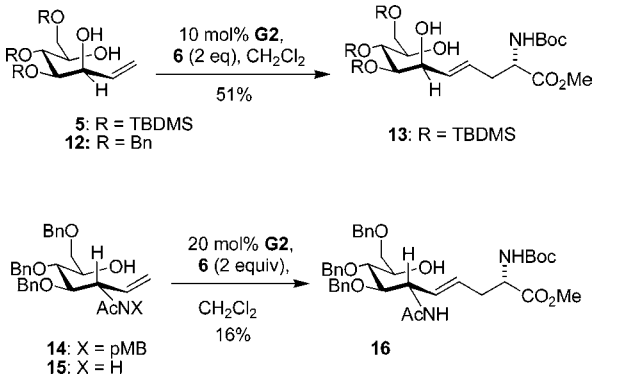
The same general CM strategy has been applied to the manno-heptenitols **5** and **12** (R = TBDMS and Bn, respectively) with allyl glycine **6** (Scheme 2). Toward that end,

Scheme 1. CM Strategy



the known tri-*O*-benzyl manno-heptene **12** was prepared by vinyl Grignard addition to 2,3,5-tri-*O*-benzyl arabinose, at low temperature as described by Nicotra.[11] The manno-heptene was produced as an inseparable diastereomeric mixture, with a manno to gluco diastereoselectivity of 2:1. Coordination of the magnesium by the carbonyl and the C-2 benzyl ether undoubtedly favors the gluco diastereomer. To minimize this chelation, we turned to the silyl ether-protected arabinose,[17] but the stereoselectivity was only marginally improved (2.5:1.0); fortunately, the separation of stereoisomers was facilitated. CM using 2 molar equiv of the allyl glycine with **5** provided **13** in 51% yield, along with the easily separable homodimers.

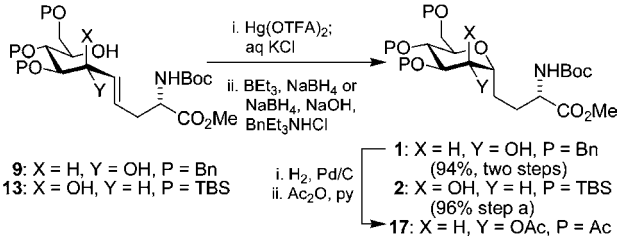
Scheme 2. CM Applied to Mannose and *N*-Acetylglucose Derivatives



Due to the importance and prevalence of many natural amino glycosides, the amino-substituted gluco-heptenitol **15**[18] was prepared in four steps from 2,3,5-tri-*O*-benzyl arabinose. In our hands, we noted the rotational isomers of the tertiary, *p*MB amide **14**; specifically, ^{1}H NMR spectroscopy revealed a doubling of many resonances.[19] Upon oxidative cleavage of the *p*-methoxybenzyl group, compound **15** appeared as a single compound by ^{1}H NMR. In view of successful CM reactions on carbamate-protected allylic amines[9] and vinyl glycines,[7] we expected a decreased reactivity for **15**, in comparison to alkene **4**, and a more selective CM. Unfortunately, **15** had rather limited reactivity, and only very low yields of CM product **16** were obtained.

Turning our attention to the cyclization step, we hoped to exploit the methodology of Nicotra for the production of C-linked glycosyl amino acids.[11] The gluco-decene **9** was successfully cyclized using mercury(II) trifluoroacetate at room temperature to give a single stereoisomer (Scheme 3).

Scheme 3. Cyclization to *C*-Glycosyl Amino Acids



Removal of mercury was uniquely and cleanly accomplished by the BEt_3, $NaBH_4$ method[20] to provide a 94% yield of **1**.

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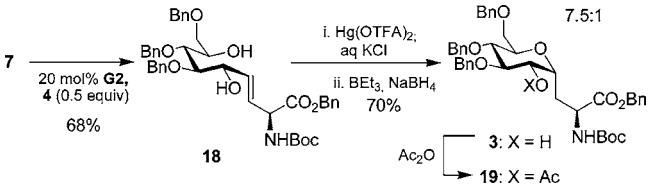
NMR evidence was initially unclear as to the "anomeric" configuration. Stereochemical assignment was possible by hydrogenolysis and acetate formation to furnish the α-*C*-glucosyl serine **17**, which was identical to material synthesized previously in our laboratory.[3i] Specifically, the ^{1}H NMR resonance for H-2 (glycoside numbering) of compound **17** in $CDCl_3$ appears as a doublet of doublets rather than a triplet, which is characteristic of the α-anomer in the $^4C_1$ conformation. The α-stereochemical preference is in accordance with Houk's inside-alkoxy model.[21]

Application of this cyclization strategy to the manno-alkene **13** also gave a single stereoisomeric organomercurial compound in 96% yield (Scheme 3). On the basis of the inside-alkoxy model, the *β*-isomer would be expected, but as Nicotra observed in his preparation of *C*-methyl mannoside, the α-isomer **2** is produced. Confirmation of this stereochemical assignment was based upon the $^1C_4$ conformation of the tetrahydropyran, as evidenced by the coupling to the proton on C-2 of $J_{1,2} = 10.4$ Hz and $J_{2,3} = 3.2$ Hz (glycoside numbering). It is possible that the allylic alcohol may interfere, leading to an intermediate epoxide, and that subsequent epoxide opening leads to a double inversion. To our dismay, attempted removal of mercury by the BEt_3 method led only to reductive elimination and recovery of alkene **13**. A low yield (29%) of **2** was achieved by $NaBH_4$ under phase transfer conditions.[22]

By direct analogy to the α-*C*-glucosyl serine synthesis, we have prepared the chain-shortened α-*C*-glucosyl alanine. As shown in Scheme 4, substituting the L-vinyl glycine **7**[23,7]

Scheme 4. Synthesis of α-*C*-Glucosyl Alanine



for the L-allyl glycine **6** in the CM reaction provided the gluco-nonene **18** in 68% yield. In this case, 2 equiv of the less reactive alkene metathesis partner **7** were used to drive the reaction to completion. Cyclization with a stoichiometric amount of Hg(II) led to a 7.5:1.0 ratio of diastereomers, which were partially separable by chromatography. The major isomer was treated with BEt_3 and $NaBH_4$ to cleanly provide **3** in a 70% overall yield for the cyclization and demercuration. Acetylation of the C-2 hydroxyl (carbohydrate numbering) pulled the H-2 NMR resonance into view downfield at δ 5.04 ppm in compound **19** in $CDCl_3$. The coupling constant ($J_{1,2}$) was measured to be 4.8 Hz, which is in agreement with Kessler's measurement of a similar α-*C*-glucosyl alanine.[4a]

The acetylation of the C-2 hydroxyl highlights the potential to vary the functionality at this position in both the serine and alanine mimics. As this position maintains key steric and electronic interactions with the peptide backbone in glycoproteins,[24] we will be exploring the conformational effects upon functional group variation at C-2.

In summary, the CM/cyclization strategy provides a rapid entry to α-*C*-glucosyl serine and alanine with high stereoselectivity. However, the methodology is not applicable to *C*-mannose derivatives due to the reductive elimination during mercury removal and does not allow direct formation of 2-*N*-acetyl-2-deoxyglucosyl derviatives due to poor CM participation.

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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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