been formed with very high purity (above 99%). On the other hand, the selectivities for the natural diol **9** were 9:100 (**8**:**9**) from **4a** and 6:100 from **4b**.[21] The NMR absorption at δ 0.92, assignable to the C-21 CH_3 group in **8**, supports the conclusion that the unnatural epimer had been formed from the (*E*) isomer **2**. The product **9** obtained from the (*Z*) isomer **4a,b** showed the corresponding NMR absorption at δ 1.03, which is reasonable for a natural epimer.[22]

These stereospecific reactions can be understood by the following mechanism. Formation of π-allylpalladium formate **10** takes place from the (*E*) isomer **3** by the attack of Pd(0) from the bottom side, with inversion, to give an α-oriented palladium species. The complex **10** has a stable syn form,[23] and the concerted decarboxylation–hydride transfer of **11** takes place from the α-side, with retention, to give the unnatural configuration **6** (Scheme IV). On the other hand, the (*Z*) isomer **5** affords the π-allylpalladium formate **12**, which has the anti form[23] and a large steric repulsion between the methyl and the side chain. Therefore, transformation from the unstable anti **12** to the stable syn form **15** takes place by rotation of σ-allylpalladium **13** prior to the hydride transfer **16**. At the same time, by this rotation, Pd moves to the β-side **14**, and hence the hydride transfer **16** takes place from the β-side to give the natural configuration **7** (Scheme V). The somewhat lower selectivity observed for the natural isomer **7** is understandable because the hydride transfer from the α-side takes place to give **6** to a small extent before the rotation (**13** → **14**).

The method described in this paper offers a convenient preparative method for the natural and unnatural C-20 epimers of steroids from easily available C-20 keto steroids as a common starting material. In addition, the cis and trans side-chain units can be prepared from the same acetylenic compound.[24] This novel method suggests that the palladium-catalyzed regio- and stereospecific hydrogenolysis of allylic carbonates with formate should become a powerful synthetic tool.

Supplementary Material Available: Experimental procedures for main steps and compound characterization data (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(21) The unnatural isomer **8** as the minor product from **5a** was isolated by increasing the ratio of **8**:**9** to 2:8 using 5 equiv of HCO_2H and Et_3N instead of 2 equiv and identified by its NMR spectrum and LC retention time with **8** obtained from **3**.

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Synthesis of Carbon-Linked Glycopeptides as Stable Glycopeptide Models

Carolyn R. Bertozzi, Paul D. Hoeprich, Jr.,† and Mark D. Bednarski*

Department of Chemistry, University of California, Berkeley, California 94720, and Applied Biosystems, 850 Lincoln Centre Drive, Foster City, California 94404

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Summary: A *C*-glycosyl analog of β-Gal-*O*-Ser has been synthesized and incorporated by automated solid-phase peptide synthesis into a hydrolytically stable, α-helical *C*-glycopeptide.

Protein glycosylation plays a decisive role in intercellular recognition phenomena such as tumor cell metastasis,[1] viral adhesion and infection,[2] and leukocyte trafficking.[3,4] Oxygen-linked glycopeptides in particular have been implicated in the resistance of the proteins to proteolytic degradation[5] and the introduction of conformational restraints on the peptide backbone.[6] The potential of glycopeptides as therapeutic agents has attracted much attention in recent years due to reports of dramatic changes in the activity, stability, and metabolism of glycosylated peptide drugs.[7]

The construction of O-linked glycopeptides by the assembly of glycosylated amino acids presents a challenge to the synthetic chemist due to the sensitivity of the glycosidic bond to the acidic and basic conditions which are used in both solution and solid-phase peptide synthesis.[8] This problem has been addressed by the development of new protecting groups and solid-phase supports that can be cleaved under mild conditions.[9-11] However, O-linked glycopeptides are also subject to both chemical and enzymatic deglycosylation in vivo, an inherent limitation of these materials as potential drugs.

† Applied Biosystems.

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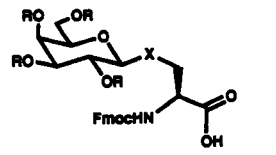
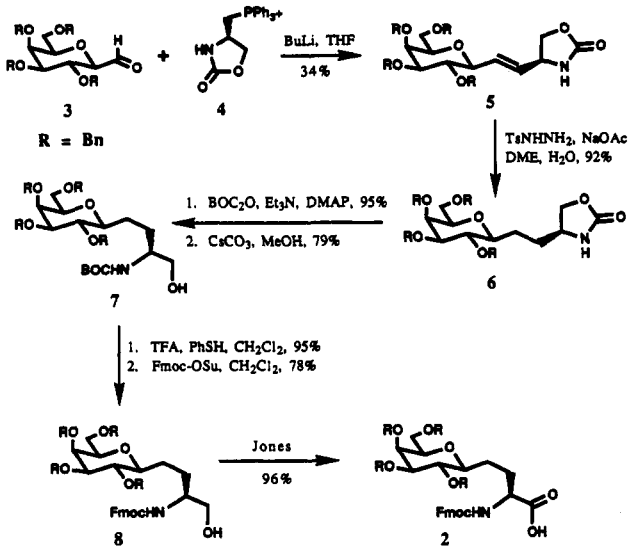


1: X ≡ O (β-Gal-*O*-Ser)
2: X = CH_2 (β-Gal-CH_2-Ser)

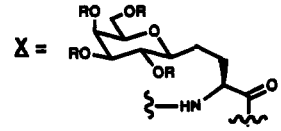
Figure 1.

Scheme I



Herein we report a method for the synthesis of stable glycopeptide analogs by the incorporation of *C*-glycosyl amino acids into solid-phase peptide synthesis. Several different O-linked glycosylation forms have been reported. These structures include GalNAc-*O*-Ser,[12] Man-*O*-Ser,[13] Xyl-*O*-Ser,[14] GlcNAc-*O*-Ser,[15] and Gal-*O*-Ser.[16] As an example of the use of our method, we report the synthesis of compound **2** (β-Gal-CH_2-Ser, Figure 1), a *C*-glycosyl analog of galactose β-linked to serine (β-Gal-*O*-Ser, **1**). Because the labile glycosidic carbon–oxygen bond has been replaced with a stable carbon–carbon bond, the resulting *C*-glycopeptide is stable to all reagents used in both solution and solid-phase peptide synthesis, and is not subject to deglycosylation in vivo.

Ac-YKAAAAKAAXAKAAAAK-NH_2



X = Ala (11)

9: R = Bn
10: R = H

Figure 2.

Furthermore, a detailed conformational analysis around the anomeric linkage of *C*-glycosides has been accomplished by examining the coupling constants of the protons on the *C*-glycosyl side chain.[17] *C*-Glycosyl saccharides have been found to adopt solution conformations similar to their oxygen-linked counterparts, suggesting that *C*-glycosides can serve as biologically active carbohydrate analogs.[18] In considering *C*-glycopeptides as biologically active glycopeptide mimics, the effects of C-glycosylation on the conformation of the peptide backbone must be evaluated. We have incorporated compound **2** by solid-phase synthesis into a 17-amino acid α-helical peptide to address the effect of C-glycosylation on a peptide with well-characterized secondary structure.[19]

Compound **2** was synthesized as outlined in Scheme I.[20,21] The β-linked stereochemistry at the anomeric center derives from the previously described aldehyde **3**,[22] and the L-stereochemistry of the α-amino acid derives from Wittig reagent **4**, a β-alanyl anion equivalent described by Sibi and Renhowe.[23] The key coupling step involves the reaction of compound **3** with compound **4** to afford a 15:1 mixture of trans/cis olefins **5** in a combined yield of 34%.[24] We have recently described a general method for the

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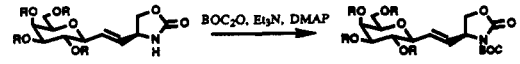

synthesis of α- and β-*C*-glycosyl aldehydes.[22,25] The reaction of these aldehydes with compound **4** is therefore a general method for the synthesis of *C*-glycosyl amino acid analogs of the other O-linked structures.

Subsequent reduction of the olefin with diimide[26] afforded the *C*-glycosyl oxazolidinone **6**, which was protected with a *tert*-butoxycarbonyl (BOC) group and cleaved with $CsCO_3$[27] to give the protected amino alcohol **7**. For compatibility with Fmoc-based automated peptide synthesis,[28] the BOC group was replaced with Fmoc by treatment of compound **7** with trifluoroacetic acid followed by *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (Fmoc-OSu) to give compound **8**. Jones oxidation of compound **8** gave the Fmoc-protected amino acid **2** which was incorporated into an automated peptide synthesizer to provide the protected *C*-glycopeptide **9** (Figure 2). Deprotection of compound **9** by catalytic hydrogenolysis (H_2, 10% Pd/C) afforded the desired *C*-glycopeptide **10**, which was purified by reversed-phase HPLC.

The alanine-based sequence of peptide **10** was designed by Baldwin and co-workers to assess the helix-forming tendencies of amino acids at position X.[29] The α-helix content of *C*-glycopeptide **10** was measured by the mean residue ellipticity at 222 nm ($[\theta]_{222}$) and compared to the alanine-substituted peptide **11**. Under the conditions used (see supplementary material), peptide **11** contains 40% α-helix ($[\theta]_{222} = -12\,194 \pm 500$ deg cm^2 dmol^{-1}) whereas glycopeptide **9** is only 18% α-helical ($[\theta]_{222} = -5349 \pm 500$ deg cm^2 dmol^{-1}). Therefore, substitution of only one C-glycosyl unit has a strong destabilizing effect on the helix.

Similar results have been reported previously for both N-linked[30] and O-linked[31] glycopeptides. In these studies, glycosylation of small peptides led to a large reduction in helicity and an absence of ordered structure. This effect can result from unfavorable steric interactions, limitation of the conformational space of the glycosyl side chain,[32] and disruption of hydrogen bonding in the helix backbone.[33,34] The similar helix-breaking effects of both C- and O-glycosylation raises the possibility that C-linked and O-linked carbohydrates exert similar conformational restrictions on a peptide backbone.

The incorporation of these *C*-glycosyl amino acids into pharmacologically active peptides may have a dramatic effect on their activity and metabolism. We are currently investigating the biological and conformational properties of *C*-glycosyl analogs of other commonly found *O*-glycopeptides. A detailed analysis of the conformational effects of glycosylation with respect to carbohydrate structure and chemical linkage (O-linked vs C-linked) will be the subject of further reports.

Acknowledgment. We thank Professor Mukund P. Sibi (North Dakota State University) for a detailed procedure for the synthesis of compound **4** and William R. Kobertz (UC Berkeley) for his contribution to the synthesis of compound **3**. M.D.B. thanks the American Cancer Society for a Junior Faculty Award and Eli Lilly for a Junior Investigator Award. C.R.B. thanks Eli Lilly for an ACS Medicinal Chemistry Fellowship and AT&T Bell Laboratories for a GRPW grant. This research was supported by National Institutes of Health award No. R29 GM43037-02.

Supplementary Material Available: Experimental procedures and spectral and analytical data for compounds **2**, **4**, and **5–10** and circular dichroism procedures and spectra for *C*-glycopeptide **10** and peptide **11** (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Five-Membered Ring Annulation via Propargyl- and Allylsilanes

Rick L. Danheiser,* Brian R. Dixon, and Robert W. Gleason†

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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Summary: Allyl- and propargylsilanes can serve as three-carbon components in a [3 + 2] annulation strategy for the synthesis of five-membered carbocycles and heterocycles.

The reaction of allenylsilanes with electron-deficient compounds constitutes a powerful method for the synthesis of five-membered carbocycles and heterocycles.[1,2] In this paper we now report the extension of this [3 + 2] annulation strategy to include two new classes of unsaturated organosilanes: *allyl-* and *propargylsilanes*.

Electrophilic substitution reactions of propargylsilanes have received considerable attention in recent years, and the application of this chemistry to the synthesis of substituted allenes is now well-documented.[3] Our prior experience with allenylsilane chemistry suggested to us that

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