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Construction of a τ-Galactosyl Histidine Moiety

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Abstract: Reaction of 2,3,4,6-tetra-*O*-acetylgalactosylbromide (2) and Cbz-His-OMe (3) in dioxane at reflux, led to the formation of *N*α-carbobenzyloxy-*N*τ-(2,3,4,6-tetra-*O*-acetyl-β-*D*-galactopyranosyl)-histidine methyl ester (4) in 15% yield. © 1998 Elsevier Science Ltd. All rights reserved.

Glycosylation of peptides and proteins occurs most frequently at the side chains of Ser and Thr (*O*-glycosylation) or Asn (*N*-glycosylation). More unusual glycosidic linkages between carbohydrates and peptides are constantly being discovered.[1] For example, the theonellamides are a family of cyclic peptides, with antifungal activity, which contain a β-glycopyranosyl unit attached to the π-nitrogen of a τ-histidinoalanine residue.[2,3] In a histidine side chain where there is no substituent at the τ-position, this is also a possible site for glycosylation (*e.g.*, compound **1**). We wish to report herein, the formation of a such a τ-galactosylhistidine residue.

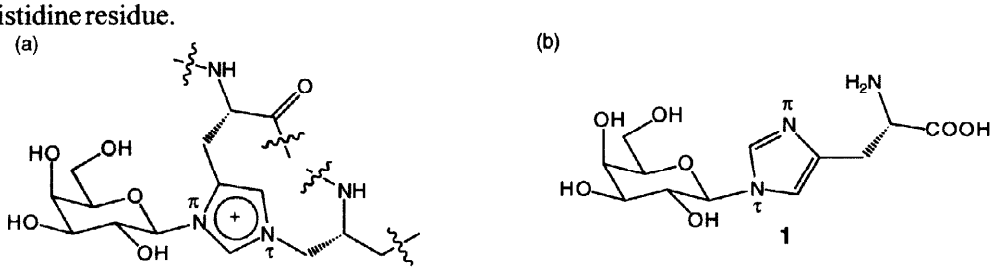
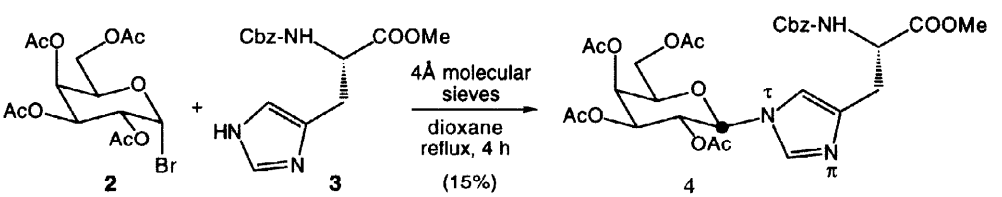


Figure 1. (a) π–(β-*D*-galactosyl)-τ–histidinoalanine moiety of theonellamide A;
(b) τ–(β-*D*-galactosyl)histidine

Reaction of galactosyl bromide **2**[4] with 2.0 equivalents of Cbz-His-OMe (**3**)[5] in dioxane at reflux, in the presence of 4Å molecular sieves, led to the formation of a number of compounds derived from either **2** or **3**. A single product appeared to have incorporated both the galactose and histidine reactants.[6] Mass spectrometry of this product revealed an ion at m/z 633 suggesting a 1:1 adduct; high resolution data was consistent with the molecular formula $C_{29}H_{35}N_3O_{13}$.



Scheme 1. Formation of the τ-Galactosyl Histidine Adduct

There are two issues to consider regarding the structure of the adduct. Firstly, the site of glycosylation on the imidazole ring (π and τ regioisomers). Secondly, the stereochemistry at the anomeric centre (•) of the galactose moiety (α and β anomers). A series of NMR experiments confirmed that the single adduct possessed a β-glycosidic linkage to the τ-nitrogen of the imidazole, as depicted in Scheme 1.

Given the propensity of acetyl protecting groups at C-2 to undergo neighbouring group participation,[7] blocking the lower face of the pyranose ring, we proposed that the product was the β-anomer. The reverse anomeric effect[8] may also be invoked to explain high β-selectivity. The ^1H and ^{13}C NMR data for the crucial region of the glycoside is summarized in Table 1. The numbering scheme is based on the

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convention used in nucleoside chemistry, whereby the atoms in the heterocycle are numbered 1-5 and the carbons in the sugar are numbered 1'-6'. The anomeric carbon of the galactose unit (C1') was readily assigned to the signal at δ84.1 ppm in the ^{13}C NMR spectrum. In the HMQC experiment, this signal showed a crosspeak with a signal at δ5.17 in the ^{1}H NMR spectrum. The doublet at δ5.17 was therefore assigned to H1'. The stereochemistry of the glycosidic linkage was confirmed to be β, based on the magnitude of the coupling constant between H1' and H2', which is consistent with a diaxial relationship between the two protons on the pyranose ring.

Table 1. Chemical Shift Data

Position	δ(H)	δ(^{13}C)
2	7.51 (s)	136.8
4	-	138.3
5	6.88 (s)	114.5
1'	5.17 (J = 10 Hz)	84.1
2'	5.46 (J = 10 Hz)	67.8

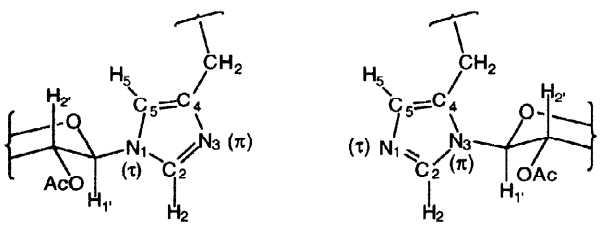

Figure 2. Partial Structures for the Two Regioisomers

Partial structures for the two regioisomers are given in Figure 2. The key evidence, which supports the τ-regiosiomer, comes from the HMBC experiment. The signal at 5.17 ppm (H1') shows a crosspeak with the signals for C2 (136.8 ppm) and C5 (114.5 ppm). In the case of the π-regioisomer, crosspeaks would be observed with C2 (136.8 ppm) and C4 (138.3 ppm). This clearly distinguishes between the two possibilities.

In summary, we have reported the first synthesis of a glycosidic linkage to a histidine residue, and have determined the regiochemistry and stereochemistry of the adduct.

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