One Pot Conversion of Ketoses into Sugar β-Peptides via a Ritter Reaction

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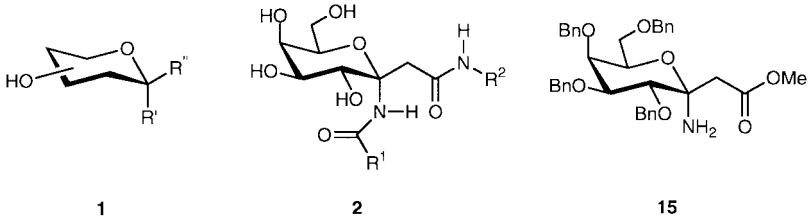
Abstract: α-D-*Galacto*-2-deoxy-oct-3-ulopyranosonic acids can be converted into unnatural glycopeptides via a one pot intramolecular Ritter reaction. Initially, the ketopyranoside reacts under Lewis acid catalyzed conditions with a nitrile (aromatic or aliphatic) to form a glycosylimino anhydride intermediate which can be isolated. Exposure of this intermediate to simple primary amines or amino acids produces novel sugar-β-peptides. Three different nitriles and three different amines have been used to generate 6 sugar β-peptides to demonstrate the generality of this reaction.

Key words: carbohydrates, combinatorial chemistry, glycopeptides, glycosylamides

Molecular recognition of carbohydrates by proteins plays an important role in many cellular processes and underlies a significant pharmaceutical potential.[1] Due to the low affinity of monovalent protein-carbohydrate interactions, novel glycomimetics with enhanced binding affinities are high in demand for the drug discovery process. In addition, carbohydrate-based scaffolds[2] and sugar-amino acid hybrids[3] have been used to mimick peptides and also have been shown to influence the pharmacokinetic and dynamic properties of pharmaceutically active compounds.[4] α,α-Disubstituted pyran amides **1** projecting functional groups in both α- and β-directions (Figure 1), appeared to us to be useful molecular probes to study carbohydrate protein recognition because of two reasons. First of all, many carbohydrate-binding proteins (with the exception of glycosidases) recognize monosaccharidic α- or β-glycosides equally[5] and secondly, carbohydrate-protein recognition may be dominated through amide bonds present in the sugar.[6] Ideally, the synthesis of compounds such as **1** should be general, allowing the implementation of combinatorial synthesis[7] for library preparation.

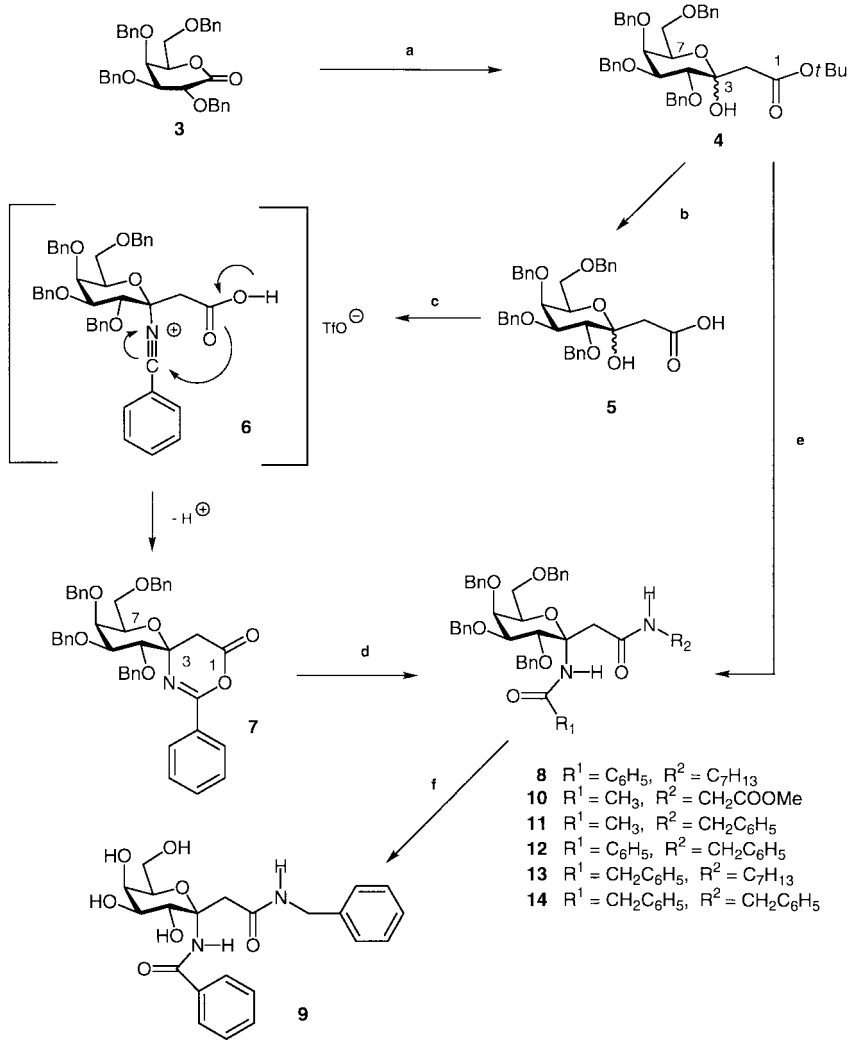
In this paper we report a stereoselective synthesis of a series of anomerically branched galactosyl amides having the general structure **2**, which contains a β-peptidic linkage. The synthesis (Scheme) started from the readily available lactone **3**.[8] Reaction of *tert*-butylacetate enolate with lactone **3** at –78 °C led to ketose **4** in 84% yield. Addition of a second enolate was not observed. Compound **4** exists entirely in the pyranose form ($CDCl_3$, room temperature, 360 MHz NMR).[9] Removal of the *tert*-butyl group and treatment of the ketose **5** with trimethylsilyl-trifluoromethanesulfonate and benzonitrile (PhCN) in dichloromethane (CH_2Cl_2) gave the spiro dihydrooxazinone **7**[10] (92%) after 10 minutes. The formation of **7** can be explained by irreversible intramolecular trapping of the initially formed nitrilium ion **6** by the free carboxylic acid and represents a modified Ritter reaction.[11] To our knowledge, this is the first reported Ritter reaction on sugar ketoses with intramolecular carboxylic acid delivery, although an intermolecular version on sugar aldoses has been described.[12] The cyclic imino anhydride **7** was stable to the work-up conditions (aqueous sodium bicarbonate) and purification (flash-chromatography on silica gel). However, when **7** was treated with cycloheptylamine, the diamide **8** (containing a sugar β-amino acid core) was isolated in 90% yield as the only product.[13] The stereochemistry of **8** was unambiguously established by NMR spectroscopy. The two amide protons (Figure 2) were easily distinguished as a singlet and a doublet (J = 7.4 Hz). The former was subjected to a one-dimensional TROESY experiment,[14,15] whereby the resonance was excited by a 240 ms selective e-burp1 pulse.[16] Inter-proton effects were observed both to H-5 and H-7 (2.5% and 0.5% NOE, respectively measured relative to the amide resonance integral, Figure 2). The observation of these ROEs is only compatible with an axial orientation of the anomeric amide group.

Once the stereochemistry of the sugar-β-peptide **8** was deduced, we focused on a one-pot conversion of the ketose **4** to the diamide **8**. Removal of the *tert*-butyl group in **4** with trifluoroacetic acid generated **5** in situ. After solvent



1 2 15

Figure 1 General structures of α,α-disubstituted pyrans as molecular probes for carbohydrate binding proteins. R' and R'' in **1** represent side chains which may enhance the binding affinity with a protein at the periphery of the sugar binding site. Structure **2** represents a novel functionalized β-peptidic scaffold. Compound **15** is a highly hindered amine which is resistant to acylation.



Scheme a) $LiCH_2COOtBu$ (4 eq.), THF, 78°C→rt, 1h, 84%; b) TFA/CH_2Cl_2 (1:1), O °C→rt, 1.5 h, quant.; c) TMSOTf (3.5 eq.), PhCN (10 eq.), CH_2Cl_2, O °C, 10 min, 92%; d) $C_7H_{13}NH_2$ (10 eq.), CH_2Cl_2, 90%; e) TFA/CH_2Cl_2 (1:1), O °C→rt, 1.5h, codistillation with toluene, then TMSOTf (3.5 eq.), R^1CN (10 eq.), CH_2Cl_2, O °C, 1.5 h, then R_2NH_2 (10 eq.), CH_2Cl_2, rt, 1.5 h, 60-70%; f) **12**, C/$Pd(OH)_2$, H_2, MeOH, quant.

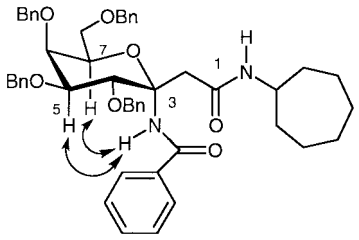


Figure 2 Conformationally relevant ROE interactions observed for **8**.

removal, **5** was treated with trimethylsilyl-trifluoromethanesulfonate and PhCN in CH_2Cl_2 for 2 h at 0 °C followed by quenching the reaction mixture with excess cycloheptylamine which produced **8** directly in an overall yield of 71%. In order to demonstrate the generality of the reaction we then treated the ketose **5** with two other nitriles, acetonitrile and phenylacetonitrile, and quenched the reaction with three different amines, namely glycine methylester, benzylamine, and cycloheptylamine. In all cases, we obtained the desired β-peptidic sugar diamides **10**–**14** as single stereoisomers in 60–70% overall isolated yield (see NMR data in Table).[20] The new stereochemistry in each of **10**–**14** was verified as described for **8**, using the 1D-TROESY NMR technique. Hydrogenolysis of **12** led to **9** in quantitative yield, an example of a deprotected sugar β-peptide.

The present "Ritter"-based method is very effective for generating glycosylamides which are not acessible by acylation of glycosylamines. For example, attempts to acylate the amine **15**.[17] prepared from the corresponding anomeric azide by hydrogenation using activated amino acid esters failed.[18] The commercial availability of large numbers of nitriles and amines suggests that the one-pot reaction presented here should be attractive for the preparation of β-peptidic sugar diamide libraries. Furthermore, the highly functionalized α,α-disubstituted pyran scaffold **2** with its rigid β-sugar amino acid core might also find use in peptide mimetic[2,3] and β-peptide synthesis.[19]

Table Characteristic ^{1}H NMR- (360 MHz, $CDCl_3$, rt, TMS) and high resolution MS-data (HRMS) for the compounds **8**,**10-14**.

comp.	^{1}H NMR H-4 /^{3}J	^{1}H NMR H-6 /^{3}J	^{1}H NMR NH	HRMS $[M+Na]^+$ (calc.)	HRMS $[M+Na]^+$ (found)
8	4.21 (d) J =9.3 Hz	4.08 (dd) J =2.4 Hz, <1 Hz	6.75 (s) 6.57 (d)	819.39852	819.40140
10	4.35 (d) J = 9.6 Hz	4.1 (s, br.)	7.35 (dd) 6.08 (s)	733.31010	733.31350
11	4.16 (d) J= 9.7 Hz	4.06 (d) J =2.4 Hz	7.03 (dd) 6.05 (s)	751.33592	751.33750
12	4.31 (d) J = 9.7 Hz	4.10 (d) J =2.4 Hz	7.09 (dd) 6.85 (s)	813.35157	813.35290
13	3.97 (d) J = 9.5 Hz	4.10 (d) J =2.6 Hz	6.50 (d) 6.04 (s)	833.41417	833.41430
14	4.06 (d) J = 9.5 Hz	4.10 (d) J =2.4 Hz	7.00 (dd) 6.09 (s)	827.36722	827.36760

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(9) Characteristic data for compound **4**: ^{1}H NMR (360 MHz, $CDCl_3$, r.t., TMS): δ = 5.43 (s, br., 1H, OH), 4.00 (dd, $^3J(H_6,H_7)$ = 1.2 Hz, $^3J(H_5,H_6)$ = 2.8 Hz, 1H, H-6), 3.75 (d, $^3J(H_4,H_5)$ = 9.8 Hz, 1H, H-4).

(10) Characteristic data for compound **7**: ^{1}H NMR (360 MHz, $CDCl_3$, r.t., TMS): δ = 4.67 (ddd, $^3J(H_6,H_7) \sim 1$ Hz, $^3J(H_7,H_{8a})$ = 7.9 Hz, $^3J(H_7,H_{8b})$ = 5.5 Hz, 1H, H-7), 4.12 (dd, $^3J(H_5,H_6)$ = 2.4 Hz, 1H, H-6), 4.06 (dd, $^3J(H_4,H_5)$ = 9.9 Hz, 1H, H-5), 4.02 (d, 1H, H-4), 3.65 (dd, $^2J(H_{8a},H_{8b})$ = 9.1 Hz, 1H, H-8a), 3.56 (dd, 1H, H-8b), 2.89 (d, $^2J(H_{2a},H_{2b})$ = 16.3 Hz, 1H, H-2a), 2.73 (d, 1H, H-2b). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C, TMS): δ = 164.9 (C=O), 152.3 (C=N), 88.9 (C-3), 80.5, 80.5, 74.8, 71.0 (C-4, C-5, C-6, C-7), 38.3 (C-2). IR (CH_2Cl_2): 1798, 1674, 1199, 1099 cm^{-1}. HRMS (ES, $[M+Na]^+$) calc. 706.27807, found 706.27842.

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(17) Characteristic data for compound **15**: ^{1}H NMR (360 MHz, $CDCl_3$, r.t., TMS): δ = 3.96 (dd, $^3J(H_6,H_7)$ = 1.2 Hz, $^3J(H_5,H_6)$ = 2.8 Hz, 1H, H-6), 3.83 (d, $^3J(H_4,H_5)$ = 9.8 Hz, 1H, H-4), 2.1-2.0 (s, br., 2H, NH_2).

(18) Attempted acylation of the amine **15** was performed with 3 equiv of a 1:1 mixture containing 1-hydroxybenzotriazole and Fmoc-L-Ala-OPfp in a 1:1 mixture of DMF and CH_2Cl_2 over a period of 48 hours. No product formation was observed and the ketose **16** was isolated after aqueous work up and chromatography.

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(20) Typical procedure for the one pot synthesis of a sugar β-peptide: Ketol **5** (0.1 mmol) was dissolved in 1:1 mixture containing trifluoroacetic acid and dichloromethane (4 mL) at 0 °C for 90 min. The solvent was removed under reduced pressure and codistilled with toluene (2 × 10 mL) to dryness. The oily residue was redissolved in dichloromethane (2 mLl) trimethylsilyl trifluoromethanesulfonate (0.35 mmol) and nitrile (1 mmol) were added at 0°C. After 90 min. the amine component (1 mmol) was added and the reaction was stirred for an additional 90 min at 0°C. Aqueous work up with sodium bicarbonate followed by chromatographic purification afforded the sugar β-peptide in 60-70% yield.

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