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Synthesis of ethylene isosteres of β-D-galactosyl- and β-D-glucosyl-L-asparagine

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Abstract

The Mukaiyama-type coupling of galactosyl and glucosyl aldehydes with a four-carbon atom silyl enol ether carrying the oxazolidine ring affords the corresponding sugar containing aldols (65-74%) that upon deoxygenation and oxidative cleavage of the heterocyclic ring lead to the title carbon-linked β-glycosyl amino acids.

Keywords: Amino acids and derivatives; Carbohydrates; Enol ethers; Mukaiyama reactions.

The two main classes of glycosidic linkages to proteins involve either oxygen in the side chain of serine, threonine, and hydroxylysine, or nitrogen in the side chain of asparagine. The recognition that the carbohydrates linked to the peptide backbone exert profound effects on their properties and activities has stimulated the synthesis of accurately sequenced glycopeptides for biological and structural studies [1-5]. This issue is also currently addressed by the use of peptide analogues in which *O*- and *N*-glycosidic linkages are replaced by a chemically and enzymatically stable carbon-carbon bond (*C*-glycopeptides). Key building blocks for the synthesis of these glycopeptide mimetics are carbon-linked glycosyl amino acids. While several syntheses of methylene isosteres (GlyCH_2Ser) of glycosyl serines (Gly*O*Ser) have been reported [6-15], there is only one synthesis of the ethylene isostere (Glc-$(CH_2)_2$-Asn) of an *N*-glycosyl asparagine [16]. The method involves as a key step the coupling of *N*-acetylglucosamine dianion with a glutamic acid derived monoaldehyde. The application of this method for the synthesis of deaminated compounds **2** would require the use of glycosyl dianions generated from 2-hydroxy sugars to prevent β-elimination [17]. In the event, the presence of two free hydroxy groups in the resulting coupling product would make the selective removal of the one in the side-chain quite problematic. Hence we would like to describe here a method leading to the ethylene isosteres **2** of β-*N*-galactosyl- and β-*N*-glucosyl asparagines **1** that involves as a key step the Mukaiyama-type aldol condensation [18] of β-linked formyl *C*-glycosides **3** with the silyl enol ether **4**, a novel homoalanine carbanion

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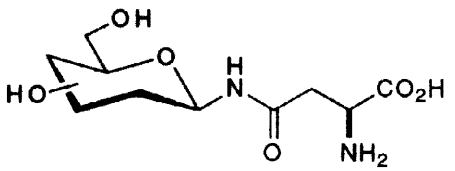
equivalent. In addition, this method offers the remarkable advantage of exploiting the existing configuration at the anomeric center of the glycosyl aldehydes **3.**



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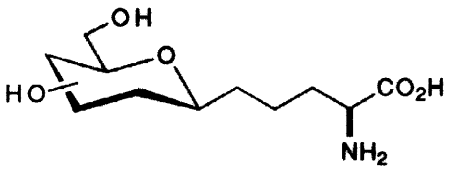

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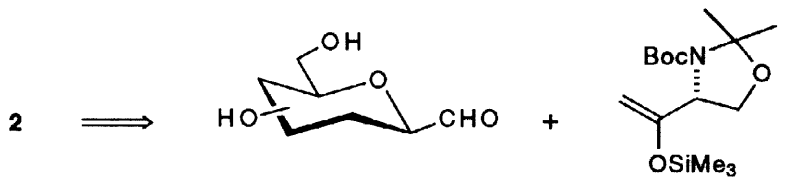
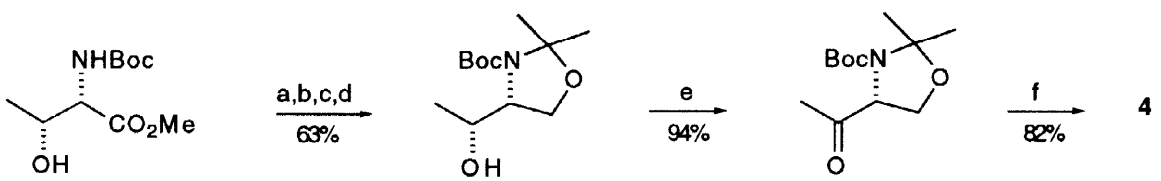


3 **4**

The multigram scale synthesis of **4** started from the known [19] methyl L-threoninate **5** which was transformed by a sequence of high yield reactions into the ketone **7** (Scheme 1).[1] The enantiomeric purity of this key intermediate was established by reduction to the alcohol **6** with sodium borohydride (ds 75%) and conversion of the latter into the Mosher ester. Silylation of the oxazolidinyl ketone **7** was readily effected using trimethylsilyl triflate (TMSOTf) and triethylamine [20] furnishing exclusively the kinetic trimethylsilyl enol ether **4** in 82% yield.[1]



5 **6** **7**

Scheme 1. Key: a, TBDMSOTf , Et_3N, DMAP, DMF, 0 °C to r. t.; b, $LiAlH_4$, THF, -50 °C; c, 2-methoxypropene, CSA, CH_2Cl_2, 0 °C to r. t.; d, *n*-Bu_4NF, THF, r. t.; e, PCC, CH_2Cl_2, 4 Å MS, r. t.; f, TMSOTf, Et_3N , CH_2Cl_2, -15 °C.

The same synthetic scheme was followed starting from either the readily available [21] *C*-galactopyranosyl aldehyde **3a** or the *C*-glucopyranosyl isomer **3b** (Scheme 2). The condensation of these aldehydes with the silyl enol ether **4** (1.5 equiv) occurred smoothly in CH_2Cl_2 at -10 °C under the agency of $ZnBr_2$ (2 equiv) as a promoter to give the corresponding aldols **8a** and **8b** as mixtures of stereoisomers[2] in 74 and 65% yield,

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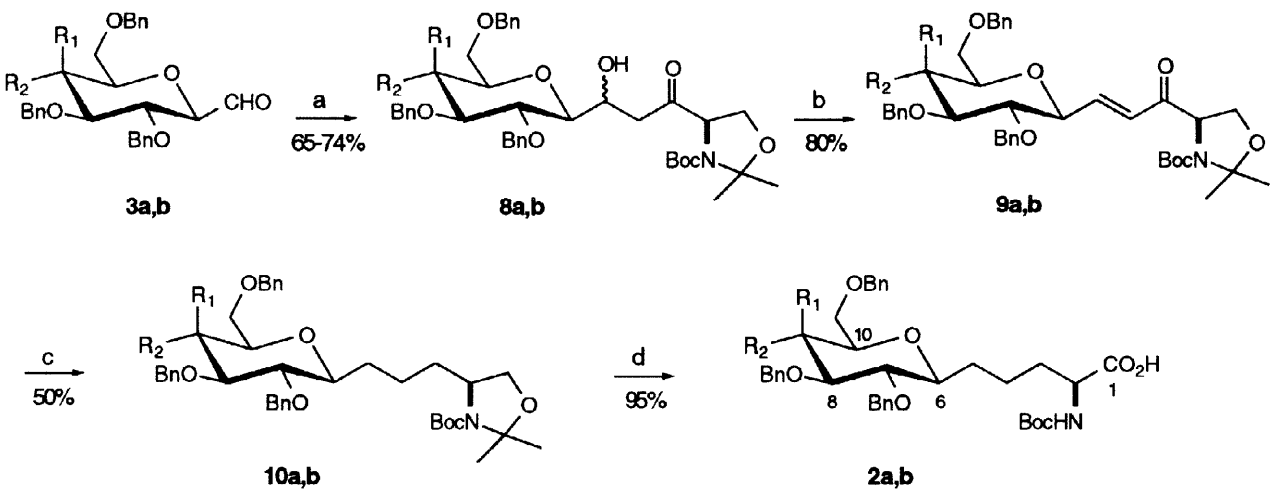
[1] **4**: mp 45-48 °C; $[\alpha]_D$ = +23.4 (*c* 0.6, $CHCl_3$). **6**: mp 87-88 °C (from cyclohexane); $[\alpha]_D$ = +24.2 (*c* 0.7, $CHCl_3$). **7**: oil, $[\alpha]_D$ = +56.9 (*c* 2.1, $CHCl_3$).

[2] Quite surprisingly the aldol **8a** was a 50:50 mixture of *syn/anti* isomers whereas **8b** was essentially constituted by a single isomer (dr ≥95 :5). **8b**: syrup, $[\alpha]_D$ = +26.0 (*c* 1.0, $CHCl_3$). **9a**: syrup, $[\alpha]_D$ = -11.9 (*c* 0.6, $CHCl_3$). **9b**: syrup, $[\alpha]_D$ = -3.2 (*c* 0.6, $CHCl_3$). **10a**: syrup, $[\alpha]_D$ = +5.9 (*c* 0.7, $CHCl_3$). **10b**: syrup, $[\alpha]_D$ = +6.2 (*c* 1.0, $CHCl_3$).

respectively. The removal of the hydroxy and carbonyl groups from these compounds was carried out by a three-step sequence involving DCC-$CuCl_2$-promoted dehydration [22,23], reduction of the α,β-enones[2] **9a** and **9b** with $NaBH_4$ and then with in situ generated diimide [24,25], and finally elimination of the hydroxy group by the Barton-McCombie radical reduction [26,27] to give **10a** and **10b**.[2] It is noteworthy that the neutral conditions under which the β-hydroxy ketones **8a** and **8b** were converted into the α,β-enones **9a** and **9b** ensured the configurational integrity of the α-carbon carrying the nitrogen atom as proved by NMR analysis. Attempts to remove both oxygen atoms by reduction of the carbonyl and then application of the Barton-McCombie deoxygenation method were unsuccessful because the treatment of the 1,3-diol intermediate with 1,1'-thiocarbonyldiimidazole led to the formation of a cyclic thiocarbonate. Having obtained the *C*-glycosides **10a** and **10b**, the conversion into the galactose β-linked amino acid **2a** (β-Gal-$(CH_2)_2$-Asn and the glucose isomer **2b** (β-Glc-$(CH_2)_2$-Asn) was straightforward through the Jones oxidative cleavage of the oxazolidine ring.[3] These hitherto unreported compounds represent ethylene isosteres of asparagine-bound *N*-glycosides **1** in which the amide group is replaced by an ethylene group.



Scheme 2. Key: *galacto* series: **3a**, **8a**, **9a**, **10a**, **2a** R_1 = OBn, R_2 = H; *gluco* series: **3b**, **8b**, **9b**, **10b**, **2b** R_1 = H, R_2 = OBn. Reagents and conditions: a, **4**, $ZnBr_2$, 4 Å MS, CH_2Cl_2, -10 °C, 9 h; b, DCC, $CuCl_2$, 4 Å MS, THF, r. t., 8 h; c, (i) $NaBH_4$, MeOH-Et_2O, 0 °C to r. t., 20 min; (ii) $TsNHNH_2$, NaOAc, DME, 85 °C, 5.5 h; (iii) 1,1'-thiocarbonyldiimidazole, DMAP, THF, reflux, 6 h; (iv) Bu_3SnH, AIBN, toluene, 85 °C, 2 h; d,1 M Jones reagent, acetone, 0 °C to r. t., 3.5 h

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[3] The *C*-glycosyl amino acids **2a** and **2b** were characterized through their methyl ester derivatives. **2a Me ester**: syrup, $[\alpha]_D$ = +6.4 (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) selected data: δ 4.98 (bd, 1 H, *J* = 8.0 Hz, NH), 4.30-4.21 (m, 1 H, H-2), 3.98 (dd, 1 H, $J_{8,9}$ = 2.6, $J_{9,10}$ = ~0.5 Hz, H-9), 3.68 (s, 3 H, OMe), 3.64 (dd, 1 H, $J_{6,7}$ = 9.0, $J_{7,8}$= 8.8 Hz, H-7), 3.57 (dd, 1 H, H-8), 3.56-3.44 (m, 3 H, H-10, 2 H-11), 3.16 (ddd, 1 H, $J_{5a,6} = J_{6,7}$ = 9.0, $J_{5b,6}$ = 2.3 Hz, H-6), 1.95-1.20 (m, 6 H, 2 H-3, 2 H-4, 2 H-5). **2b Me ester**: syrup, $[\alpha]_D$ = +6.2 (*c* 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) selected data: δ 5.04 (bd, 1 H, *J* = 8.0 Hz, NH), 4.33-4.22 (m, 1 H, H-2), 3.74-3.58 (m, 4 H, H-8, H-9, 2 H-11), 3.70 (s, 3 H, OMe), 3.36 (ddd, 1 H, $J_{9,10}$ = 9.1, $J_{10,11a}$ = 2.2, $J_{10,11b}$ = 3.5 Hz, H-10), 3.25 (dd, 1 H, $J_{6,7} = J_{7,8}$ = 9.0 Hz, H-7), 3.20 (ddd, 1 H, $J_{5a,6} = J_{6,7}$ = 9.0, $J_{5b,6}$ = 2.4 Hz, H-6), 1.88-1.72, 1.70-1.51, and 1.50-1.29 (3 m, 6 H, 2 H-3, 2 H-4, 2 H-5).

In conclusion, a viable route to glycosyl asparagine ethylene isosteres has been illustrated that relies on the use of the functionalized silyl enol ether **4** as a new homoalanine carbanion equivalent. The coupling of this reagent with sugar aldehydes occurs readily without any apparent epimerization at the formyl group and nitrogen bearing stereocenters. Given the availability of various formyl *C*-glycosides [21], this new synthetic method may be applied for the synthesis of various *C*-glycosyl amino acids with different sugar moieties.

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