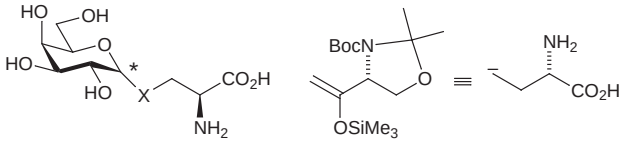
Synthesis of methylene isosteres of α- and β-D-galactopyranosyl-L-serine

Alessandro Dondoni,*† Alberto Marra and Alessandro Massi

Dipartimento di Chimica, Laboratorio di Chimica Organica, Università, 44100-Ferrara, Italy

The $BF_3{\cdot}Et_2O$ promoted coupling of tetra-*O*-benzyl-α-D-galactopyranosyl trichloroacetimidate with a silyl enol ether carrying an oxazolidine ring leads to the α-*C*-glycosylmethyl ketone (32%, 95% ds) that is converted into the title α-*C*-glycosyl amino acid by carbonyl oxygen removal (Barton–McCombie) and oxidative cleavage (Jones) of the heterocyclic ring, and into the β-isomer by anomerization and the same two-step sequence.

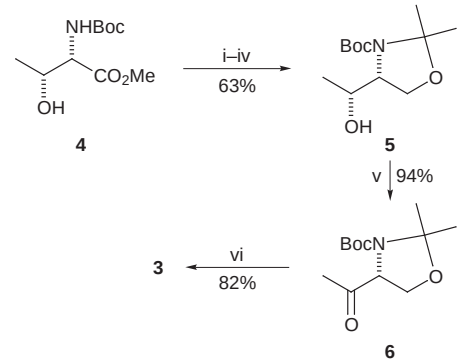
Towards a better understanding and control of the function of sugars in natural glycopeptides,[1] the synthesis of their analogues in which the sugar moieties are linked to the peptide backbone by an all-carbon chain that is resistant to chemical and enzymatic degradation is a topic of increasing importance in glycobiology and medicinal chemistry. Therefore carbon-linked glycosyl amino acids as precursors to glycopeptide mimetics are current synthetic targets in various laboratories.[2] Different syntheses of methylene isosteres of *O*-glycosyl serines have been reported[2a–c,f–h] since these sugar amino acids are the most common constituents of natural glycoproteins. The *C*-glycosylation of a suitable α-amino acid equivalent[2c] appears to be the most direct route to these compounds.[3] Therefore we describe here the synthesis of α- and β-*C*-galactosyl serine **1** (Gal-CH_2-Ser), *i.e.* the methylene isosteres of D-galactose α- and β-linked to L-serine (Gal-*O*-Ser, **2**), employing the silyl enol ether **3** as a novel homoalanine carbanion equivalent. To the best of our knowledge this is the first approach to a pair of α- and β-isomer *C*-glycosyl amino acids *via* a single synthetic scheme.



1 X = CH_2
2 X = O
3

The multigram scale synthesis of **3** started from the known[4] methyl L-threoninate **4** which was transformed by a sequence of high yielding reactions into the ketone **6** (Scheme 1).‡ The enantiomeric purity of this key intermediate was established by reduction to the alcohol **5** with sodium borohydride (75% ds) and conversion of the latter into its Mosher ester. Silylation of the oxazolidinyl ketone **6** was readily effected using TMSOTf and Et_3N[5] furnishing exclusively the kinetic trimethylsilyl enol ether **3** in 82% yield.§

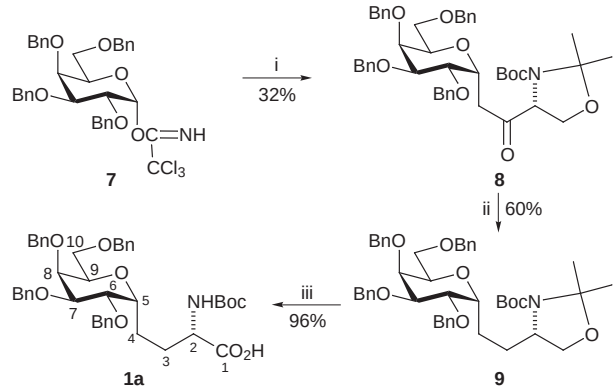
The glycosylation of the silyl enol ether **3** was carried out with the readily available electrophilic sugar tetra-*O*-benzyl α-D-galactopyranosyl trichloroacetimidate[6] **7** (Scheme 2). Unoptimized conditions involved the addition *via* syringe pumping of an Et_2O solution of **7** (2 equiv.) to silyl enol ether **3** and $BF_3{\cdot}Et_2O$ (1 equiv.) in Et_2O at −15 °C. The expected[7] major product, α-*C*-glycoside **8,** and the β-anomer **10** were isolated by column chromatography in 32% overall yield and 19:1 ratio.¶ Also isolated was the ketone **6** (45%) arising from the hydrolysis of unreacted **3**, and a mixture of anomeric galactosyl trichloroacetamides (70%). The recovery of the enantiomerically pure ketone **6** demonstrated that the configuration at the



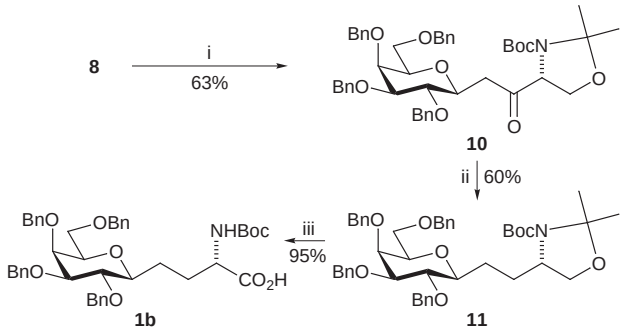
Scheme 1 *Reagents and conditions*: i, TBDMSOTf (1.2 equiv.), Et_3N, DMAP, DMF, 0 °C to room temp., 1.5 h; ii, $LiAlH_4$ (4 equiv.), THF, −50 °C, 50 min; iii, 2-methoxypropene, CSA, CH_2Cl_2, 0 °C to room temp., 1.5 h; iv, Bu_4NF, THF, room temp., 6 h; v, PCC (5 equiv.), CH_2Cl_2, 4 Å MS, room temp., 20 min; vi, TMSOTf (1.4 equiv.), Et_3N (1.6 equiv.), CH_2Cl_2, −15 °C, 1 h

stereocenter of the silyl enol ether **3** was unaffected under the glycosylation conditions. Towards the target *C*-glycosyl amino acid, the deoxygenation of the sugar ketone **8** was first carried out through the classical Barton–McCombie reduction-elimination sequence[8] affording **9** in 60% yield. Treatment of **9** with the Jones reagent induced the cleavage of the oxazolidine ring and oxidation of the alcohol in a single step to give the α-linked tetra-*O*-benzyl-*C*-galactosyl-L-serine **1a** in 96% isolated yield. This compound proved to be contaminated by *ca.* 5% (^1H NMR analysis) of the corresponding α-amino alcohol. Therefore, the amino acid **1a** was fully characterized through its methyl ester.

Guided by earlier work regarding the base-catalyzed equilibration of α-*C*-glycosides bearing a carbonyl group in the side chain,[9] the anomerization of the α-*C*-glycosylmethyl ketone **8** was carried out upon treatment with Bu^tLi in Et_2O (Scheme 3). Under these conditions a mixture of **8** and the β-anomer **10** in a



Scheme 2 *Reagents and conditions*: i, **3** (0.5 equiv.), $BF_3{\cdot}Et_2O$ (0.5 equiv.), Et_2O, −15 °C, 2 h; ii, $NaBH_4$, MeOH–Et_2O, −20 °C, 1 h, then 1,1′-thiocarbonyldiimidazole (10 equiv.), DMAP (15 equiv.), THF, reflux, 6 h, then Bu_3SnH (10 equiv.), AIBN (0.1 equiv.), toluene, 85 °C, 2 h; iii, 1 M Jones reagent (3 mol per mol of reactant), acetone, 0 °C to room temp., 3.5 h



Scheme 3 *Reagents and conditions*: i, Bu^{t}Li (1.2 equiv.), Et_2O, −78 to −20 °C, 2 h, then room temp., 2 h; ii, $NaBH_4$, MeOH–Et_2O, −20 °C, 1 h, then 1,1′-thiocarbonyldiimidazole (10 equiv.), DMAP (15 equiv.), THF, reflux, 6 h, then Bu_3SnH (10 equiv.), AIBN (0.1 equiv.), toluene, 85 °C, 2 h; iii, 1 M Jones reagent (3 mol per mol of reactant), acetone, 0 °C to room temp., 3.5 h

3:7 ratio and 90% overall yield was obtained. The isolated β-*C*-glycosylmethyl ketone **10** was subjected to the radical deoxygenation as described above for **8** to give the β-*C*-alkyl glycoside[2h] **11** (60% isolated yield). The conversion of the oxazolidine ring of this compound into the α-amino acid moiety by treatment with the Jones reagent gave the known[2b,h] β-D-linked tetra-*O*-benzyl-*C*-galactosyl-L-serine **1b** (95%). The synthesis of **1b** highlights the use of the silyl enol ether **3** as the homoalanine carbanion equivalent since a similar approach cannot be developed by using amino acid equivalents[2c,3] lacking the carbonyl group.

In conclusion, the synthesis of **1a** and **1b** demonstrates the viability of a new approach to α- and β-linked *C*-glycosyl amino acids starting from a single carbohydrate precursor. The protected hydroxy and amino groups (as *O*-benzyl and *N*-Boc derivatives) and, by contrast, the free carboxylic group constitute a synthetically convenient structure for the incorporation of these *C*-glycosyl amino acids into a peptide chain. The application of this method for the preparation of pairs of amino acids by glycosylation of the silyl enol ether **3** with other sugars is now of interest.

Notes and References

† E-mail: adn@dns.unife.it

‡ *Selected data* for **3**: $[\alpha]_D$ +23.4 (*c* 0.6); $\delta_H(C_2D_2Cl_4$, 120 °C) 4.26 (d, 1 H, *J* 1.5), 4.24 (dd, 1 H, *J* 3.5, 7.0), 4.21 (d, 1 H, *J* 1.5), 4.04 (dd, 1 H, *J* 7.0, 8.5), 3.95 (dd, 1 H, *J* 3.5, 8.5), 1.63, 1.58 (2 s, 6 H), 1.46 (s, 9 H), 0.30 (s, 9 H). For **5**: mp 87–88 °C (from cyclohexane); $[\alpha]_D$ +24.2 (*c* 0.7); $\delta_H(CDCl_3)$ 4.18–4.11, 4.00–3.77 (2 m, 4 H), 1.58 (s, 3 H), 1.50 (s, 12 H), 1.18 (d, 3 H, *J* 6.5). For **6**: $[\alpha]_D$ +56.9 (*c* 2.1); $\delta_H(C_2D_2Cl_4$, 120 °C) 4.36 (dd, 1 H, *J* 3.1, 7.2), 4.15 (dd, 1 H, *J* 7.2, 9.0), 3.95 (dd, 1 H, *J* 3.1, 9.0), 2.20 (s, 3H), 1.70, 1.57 (2 s, 6 H), 1.51 (s, 9 H). For **8**: $[\alpha]_D$ +53.3 (*c* 0.9); $\delta_H([^2H_6]$DMSO, 120 °C) 4.09 (dd, 1 H, $J_{1a,1b}$ 9.0, $J_{1a,2}$ 7.2, H-1a), 3.86 (dd, 1 H, $J_{1b,2}$ 3.2, H-1b), 2.91 (dd, 1 H, $J_{4a,4b}$ 17.0, $J_{4a,5}$ 8.2, H-4a), 2.68 (dd, 1 H, $J_{4b,5}$ 4.5, H-4b). For **9**: $[\alpha]_D$ +37.1 (*c* 0.8); $\delta_H([^2H_6]$DMSO, 160 °C) 4.02–3.73 (m, 8 H), 3.69 (dd, 1 H, *J* 4.2, 11.3), 3.65 (dd, 1 H, *J* 2.2, 8.1), 1.76–1.50 (m, 4 H). For **1a**: $\delta_H(CDCl_3)$ 5.29 (br d, 1 H, $J_{2,NH}$ 6.5, NH), 4.30–4.24 (m, 1 H, H-2), 1.99–1.84, 1.80–1.51 (2 m, 4 H, 2 H-3, 2 H-4); $\delta_C(CDCl_3)$ 176.3 (CO_2H), 155.8 (CO_2Bu^t), 53.5 (C-2), 28.3 (CH_3). For **1a Me ester**: $[\alpha]_D$ +29.0 (*c* 1.0); $\delta_H([^2H_6]$DMSO, 120 °C) 6.53 (br d, 1 H, $J_{2,NH}$ 7.5, NH), 4.06–3.84 (m, 5 H), 3.79–3.72 (m, 2 H), 3.65 (dd, 1 H, $J_{9,10b}$ 4.4, $J_{10a,10b}$ 10.8, H-10b), 3.61 (s, 3 H, OMe), 1.92–1.57 (m, 4 H). For **10**: $[\alpha]_D$ +22.4 (*c* 0.4); $\delta_H([^2H_6]$DMSO, 120 °C) 4.47 (dd, 1 H, $J_{1a,2}$ 7.8, $J_{1b,2}$ 3.8, H-2), 4.07 (dd, 1 H, $J_{7,8}$ 2.8, $J_{8,9}$ *ca.* 0.5, H-8), 4.05 (dd, 1 H, $J_{1a,1b}$ 9.0, H-1a), 3.81 (dd, 1 H, H-1b), 3.76 (dd, 1 H, $J_{6,7}$ 9.1, H-7), 3.74 (ddd, 1 H, $J_{4a,5}$ 2.5, $J_{4b,5}$ 8.8, $J_{5,6}$ 9.2, H-5), 3.69 (ddd, 1 H, $J_{9,10a}$ 6.0, $J_{9,10b}$ 6.5, H-9), 3.57 (dd, 1 H, $J_{10a,10b}$ 10.0, H-10a), 3.51 (dd, 1 H, H-10b), 2.82 (dd, 1 H, $J_{4a,4b}$ 16.1, H-4a), 2.63 (dd, 1 H, H-4b). $[\alpha]_D$ Values were measured in $CHCl_3$ at 20 ± 2 °C; ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively).

§ TMSOTf and Et_3N were added in three portions to the cooled (-15 °C) CH_2Cl_2 solution of **6** in order to avoid extensive removal of the protecting groups.

¶ The α- and β-D-configuration of *C*-glycosides **7** and **10** was proved by ^1H NMR analysis of the corresponding tetra-*O*-acetyl derivatives ($J_{5,6}$ 4.7 and 9.8, respectively, in $[^2H_6]$DMSO at 120 °C).

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