ChemComm

exo-Glycal approaches to *C*-linked glycosyl amino acid synthesis

Andrew D. Campbell,[a] Duncan E. Paterson,[a] Tony M. Raynham[b] and Richard J. K. Taylor[a]*

[a] *Department of Chemistry, University of York, Heslington, York, UK YO10 5DD. E-mail: rjkt1@york.ac.uk*
[b] *Roche Discovery Welwyn, Welwyn Garden City, Hertfordshire, UK AL7 3AY*

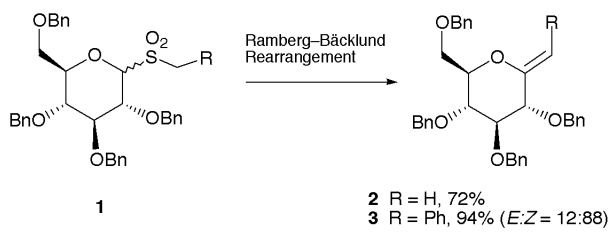
Received (in Cambridge, UK) 22nd June 1999, Accepted 8th July 1999

Two novel routes to *C*-linked glycosyl amino acids are described; the first involves elaboration of an *exo*-glycal and subsequent Ramberg–Bäcklund rearrangement of a sulfone intermediate to give, after functional group manipulation, a protected *C*-glycosyl serine, while the second uses hydroboration–Suzuki coupling of the same *exo*-glycal to produce ultimately the corresponding *C*-glycosyl asparagine analogue.

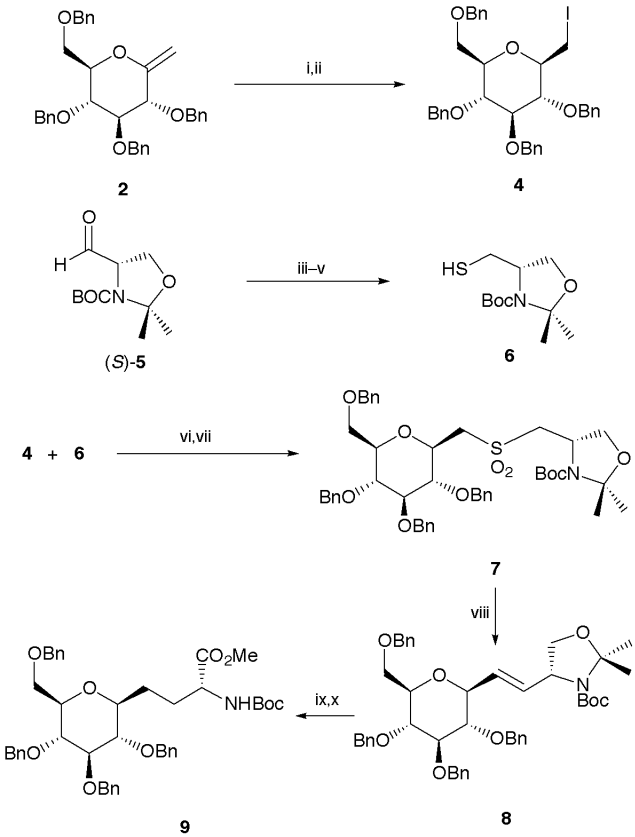
Glycopeptides and glycoproteins are of great current interest from the viewpoints of structure elucidation, molecular recognition, biological function and chemical synthesis.[1] Replacement of the glycosidic oxygen by carbon gives the corresponding *C*-glycoside analogues (glycopeptidomimetics), compounds which are particularly valuable for biological studies because of their hydrolytic stability. The recent publications in this area[1,2] prompt us to disclose our own results. We have recently established that the Ramberg–Bäcklund rearrangement of *S*-glycoside dioxides provides a versatile route to di-, tri- and tetra-substituted *exo*-glycals[3] which are themselves useful intermediates for the preparation of more elaborate *C*-glycosides.[4] Scheme 1 illustrates this methodology with a glucose-derived sulfone: the Meyers variant[5] of the Ramberg–Bäcklund rearrangement is used to convert the sulfones **1** directly into the corresponding *exo*-glycals **2** or **3** without competing 1,2-glycal formation. We have gone on to apply this methodology to the synthesis of *C*-linked disaccharides such as β,β-*C*-trehalose and methyl *C*-gentiobioside.[6]

We now report the application of this methodology to the construction of *C*-linked glycopeptidomimetics. Initial studies (Scheme 2) were concerned with the synthesis of the *C*-glucosyl serine analogue **9**. The key starting material, iodide **4**, was readily prepared from *exo*-glycal **2** by stereoselective 9-BBN hydroboration–oxidation[7] followed by iodination.[6] Thiol **6** was the required coupling partner. We were surprised to discover that this useful building block had not been reported previously but it was easily obtained from the Garner aldehyde (*S*)-**5**[8] by reduction followed by Mitsunobu displacement using thioacetic acid and then treatment with sodium methoxide.† Alkylation of thiol **6** using iodide **4** followed by oxidation of the resulting sulfide produced sulfone **7** {$[\alpha]_D$ −30.1 (*c* 0.57, $CHCl_3$) [HRMS (FAB+): Found: 838.3601. $C_{46}H_{57}NO_{10}SNa$ requires 838.3608 (0.9 ppm error)]}. This sulfone was then treated under Chan's tandem halogenation–Ramberg–Bäcklund conditions[5b] to produce the *E*-alkene **8** (*J* 15.6 Hz) in 37% unoptimised yield. Alkene reduction was efficiently achieved using diimide generated *in situ* and the amino acid was unmasked using a one-pot hydrolysis–oxidation procedure.[9] Diazomethane esterification gave the target *C*-glycosyl serine derivative **9** {$[\alpha]_D$ −8.2 (*c* 1.45, $CHCl_3$) [HRMS (FAB+): Found: 762.3614. $C_{44}H_{53}NO_9Na$ requires 762.3618 (0.6 ppm error)]}.

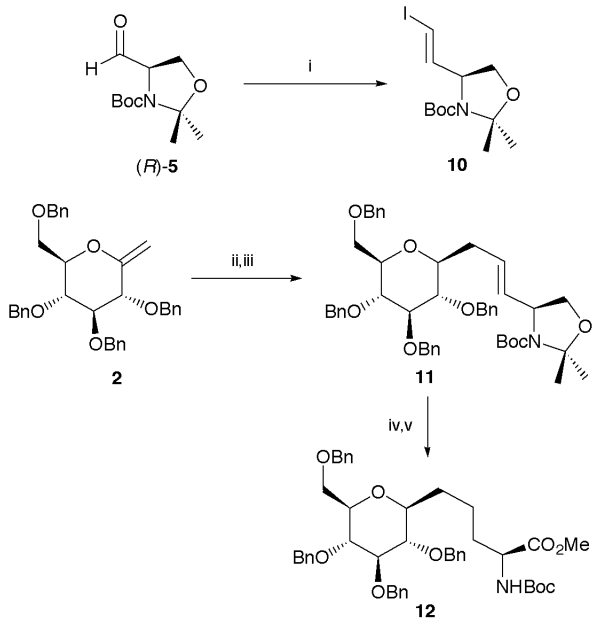
The second target was the *C*-glycosyl asparagine analogue **12** depicted in Scheme 3. In principle, this compound could be made *via* the methodology outlined in Scheme 2 simply by using the higher homologue of iodide **4**[6] or of thiol **6**. However, we decided to investigate an alternative approach based on the Suzuki coupling procedure developed by Johnson and Johns[10] but not previously applied to *C*-glycosyl amino acid synthesis (Scheme 3). For this route we required vinyl iodide **10** which has been described but *via* a rather lengthy route.[11] An improved route to **10** was developed: treatment of the Garner aldehyde (*R*)-**5**‡ with $CHI_3/CrCl_2$[12] produced **10** exclusively as the *E*-isomer {$[\alpha]_D$ −80.8 (*c* 1.76, $CHCl_3$); lit.,[11] −75.3 (*c* 1.9, $CHCl_3$)}. Hydroboration of *exo*-glycal **2** followed by Suzuki coupling with vinyl iodide **10** gave alkene **11** in moderate yield but with complete control over 'anomeric' configuration and alkene geometry (*J* 15.5 Hz). Diimide reduction followed by treatment with Jones' reagent and then diazomethane, as before,



Scheme 1



Scheme 2 *Reagents and conditions*: i, 9-BBN, then H_2O_2, NaOH; ii, PPh_3, imidazole, I_2, 80% (ref. 6); iii, $NaBH_4$; iv, PPh_3, diisopropyl azodicarboxylate, AcSH; v, NaOMe, 38% for 3 steps; vi, K_2CO_3, MeCN–MeOH, reflux; vii, MCPBA, Na_2HPO_4, 66% for 2 steps; viii, CBr_2F_2, KOH–Al_2O_3, Bu^{t}OH, 60 °C, 37%; ix, $TsNHNH_2$, NaOAc, 85 °C, 82%; x, Jones' reagent (1 M), then CH_2N_2, 60%.



Scheme 3 *Reagents and conditions*: i, CHI_3, $CrCl_2$, THF, 60%; ii, 9-BBN; iii, **10**, $PdCl_2(dppf)\cdot CHCl_3$, aq. K_3PO_4, DMF, 48%; iv, $TsNHNH_2$, NaOAc, 85 °C, 78%; v, Jones' reagent (1 M), then CH_2N_2, 56%.

gave the protected *C*-glycosyl amino acid **12** in good yield. All data correlated well with those reported in a previous synthesis of **12** by Dondoni *et al.*[2a] {*e.g.* $[\alpha]_D$ +6.25 (*c* 0.8, $CHCl_3$); lit.,[2a] +6.2 (*c* 0.7, $CHCl_3$) [HRMS (FAB+): Found: 776.3783. $C_{45}H_{55}NO_9Na$ requires 776.3775 (1.2 ppm error)]} and thus confirmed the expected[7,10] β-selectivity of the hydroboration step.

In summary, we have devised two new, versatile routes to glycopeptidomimetics which join together the individual sugar and amino acid units to produce exclusively β-stereoisomers at the 'anomeric' centre. We have also established that the Ramberg–Bäcklund rearrangement of *S*-glycoside dioxides is a general procedure which can be utilised for the synthesis of *exo*-glycals,[3] *C*-linked disaccharides,[6] and now in this work, *C*-linked glycosyl amino acids. We are currently optimising the above procedures and extending the methodology to more challenging targets.

We are grateful to the BBSRC and the University of York for studentships (A. D. C. and D. E. P., respectively). We would also like to thank Roche Discovery Welwyn for CASE support (A. D. C.).

Notes and references

† All new compounds were fully characterised spectroscopically and by HRMS/elemental analysis.

‡ The enantiomeric Garner aldehyde (*R*)-**5** was used in this route because full data is available for diastereoisomer **12**.

1 For a comprehensive review, see C. M. Taylor, *Tetrahedron*, 1998, **54**, 11317.
2 For more recent work in this area, see (*a*) A. Dondoni, A. Marra and A. Massi, *J. Org. Chem.*, 1999, **64**, 933; (*b*) R. N. Ben, A. Orellana and P. Arya, *J. Org. Chem.*, 1998, **63**, 4817; D. Urban, T. Skrydstrup and J.-M. Beau, *Chem. Commun.*, 1998, 955; (*c*) T. Fuchss and R. R. Schmidt, *Synthesis*, 1998, 753; (*d*) F. Burkhart, M. Hoffmann and H. Kessler, *Angew. Chem., Int. Ed. Engl.*, 1997, **36,** 1191.
3 F. K. Griffin, P. V. Murphy, D. E. Paterson and R. J. K. Taylor, *Tetrahedron Lett.*, 1998, **39**, 8179; see also P. S. Belica and R. W. Franck, *Tetrahedron Lett.*, 1998, **39**, 8225.
4 M.-L. Alcaraz, F. K. Griffin, D. E. Paterson and R. J. K. Taylor, *Tetrahedron Lett.*, 1998, **39**, 8183.
5 (*a*) C. Y. Meyers, A. M. Malte and W. S. Matthews, *J. Am. Chem. Soc.*, 1969, **91**, 7510; (*b*) T.-L. Chan, S. Fong, Y. Li, T.-O. Man and C. D. Poon, *Chem. Commun.*, 1994, 1771.
6 F. K. Griffin, D. E. Paterson and R. J. K. Taylor, *Angew. Chem., Int. Ed.*, 1999, in the press.
7 T. V. RajanBabu and G. S. Reddy, *J. Org. Chem.*, 1986, **51**, 5458.
8 P. Garner and J. M. Park, *J. Org. Chem.*, 1987, **52**, 2361; A. D. Campbell, T. M. Raynham and R. J. K. Taylor, *Synthesis*, 1998, 1707.
9 A. Dondoni, A. Marra and A. Massi, *Tetrahedron*, 1998, **54**, 2827.
10 C. R. Johnson and B. A. Johns, *Synlett*, 1997, 1406.
11 G. Reginato, A. Mordini and M. Caracciolo, *J. Org. Chem.*, 1997, **62**, 6187.
12 K. Takai, K. Nitta and K. Utimoto, *J. Am. Chem. Soc.*, 1986, **108**, 7408.

Communication 9/05014K