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Stereoselective approach to *C*-glycosylasparagines

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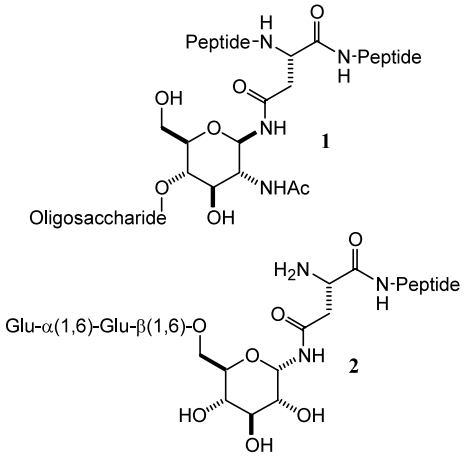
Abstract—In this paper we describe a simple and efficient approach to *N*-glycopeptide analogues that incorporate a ketomethylene unit in place of a native amide link. Key C–C bond forming steps involve the stereocontrolled addition of a functionalised allylsilane to activated sugar derivatives and the asymmetric phase-transfer alkylation of a glycine imine. Utility of this chemistry is demonstrated by the synthesis of a *C*-analogue of the glycopeptide core found in nephritogenoside. Regioselective ozonolysis of a 1,5-diene is also described.

The development of methods for the generation of synthetic constructs which incorporate both amino acid and carbohydrate elements is attracting increasing attention.[1] This is in part due to their potential as mimics of natural glycopeptides[2] and also because the functionality resident in these materials is well-suited to automated combinatorial diversification.[3] For some time we have been interested in the development of synthetic approaches towards both carbohydrate[4] and peptide[5] fragments in which heteroatoms found in the native structures have been replaced by carbon. In this paper we outline the development of a simple stereoselective route to *N*-glycosylasparagine-like structures which incorporate an all-carbon connection between the amino acid and carbohydrate units.



N-Glycopeptides are the most common type of glycopeptide found in nature and it has been estimated that almost half of all natural proteins may contain this structural element.[6] The most common *N*-glycopeptide link found involves the amino acid asparagine connected to a polysaccharide via the amide side-chain. In most cases these glycopeptides contain a common core in which the first sugar unit attached is a β-linked *N*-acetyl glucosamine (i.e. **1**),[2,7] however an increasing number of *N*-glycosylasparagines involving alternative carbohydrate attachments have been isolated and characterised.[1b] Perhaps most notable amongst this latter group is nephritogenoside **2**, an *N*-glycopeptide isolated from the glomerular basement membrane of rats.[8] This glycopeptide has been shown to induce glomerulonephritis and this activity coupled with its unusual structure has resulted in the development of a number of synthetic approaches to this natural product.[9]

It has long been recognised that the replacement of peptide bonds with their ketomethylene isosteres can lead to bio-active compounds with improved metabolic stability.[10,11] Replacement of the amide link in *N*-glycosylasparagines by this type of isostere (e.g. **3**) appears equally attractive as this minimal modification changes the chemistry of both amide and the glycosidic bonds, and hence should result in materials that are resistant to hydrolysis at both these sites. However, although a number of methods have been developed for the synthesis of *C*-glycosylasparagines, to date, work in this area has focused primarily on alternative amide isosteres.[2,12]

In an effort to develop a general synthetic approach to ketomethylene *C*-glycosylasparagines of type **3**, we con-

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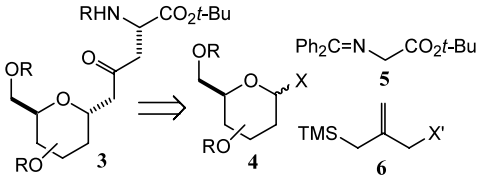
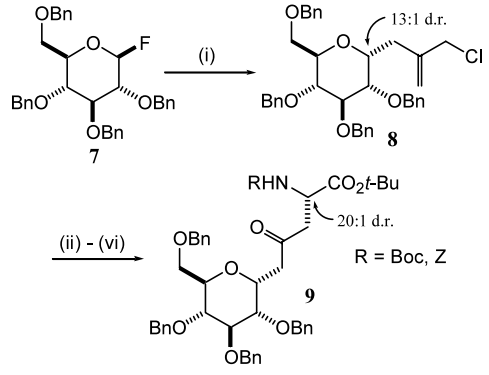
sidered the possibility of using a bifunctional fragment **6** as a means of connecting a sugar derivative **4** to a glycine derivative **5**. This seemed like an attractive approach to targets of this type as there is precedent for good stereocontrol in the two carbon–carbon bond forming steps involved, and because the chemistry required should be compatible with a range of different sugar substrates **4**.



We considered that the best strategy for connecting these three fragments would involve initial coupling of a sugar derivative **4** with allylsilane **6**, followed by alkylation with the glycine imine **5**. In order to test this hypothesis we first investigated the synthesis of **9**, a protected *C*-analogue of the glycopeptide core found in nephritogenoside **2** (Scheme 1).

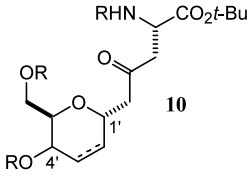
The addition of simple allylsilanes to sugar derived oxonium ions is known to proceed via axial attack, and generally delivers good stereoselectivity for the α-*C*-glycoside with D-glucose derivatives. After surveying a range of C-1 activation methods we established that, in our hands, glycosyl fluoride **7** provided the most effective glucosyl donor for reaction with allylsilanes of type **6**.[13] Using this approach, reaction of **7** with commercially-available 2-chloromethyl-3-trimethylsilylpropene provided the *C*-glycoside **8** in good yield and with high selectivity for the desired α-isomer. Chloride **8** was then converted into the corresponding iodide which proved to be an excellent substrate for the asymmetric PTC alkylation using glycine imine **5**.[14] For this latter process we employed *O*-benzyl-*N*-(9-anthracenylmethyl)-dihydrocinchonidinium bromide as the phase-transfer catalyst as we have previously established that this quaternary ammonium salt generally gives high selectivity for (*S*)-amino acid derivatives in reactions of this type.[15] Hydrolysis of the resulting imine, *N*-protection with either Boc or Z, and oxidative cleavage of the alkene then provided the target *C*-glycoside **9** in good overall yield.



Scheme 1. *Reagents and conditions*: (i) 2-chloromethyl-3-trimethylsilylpropene (1.5 equiv.), $BF_3{\cdot}OEt_2$ (1.1 equiv.), CH_3CN, −30°C (64%); (ii) NaI, acetone; (iii) **5**, *O*-benzyl-*N*-(9-anthracenylmethyl)dihydrocinchonidinium bromide (10 mol%), 9 M aq. KOH, PhMe, rt; (iv) 15% aq. citric acid, THF, rt; (v) BnOCOCl, Et_3N, CH_2Cl_2, 0°C–rt (58% overall), or Boc_2O, Et_3N, CH_2Cl_2, 0°C–rt (50% overall); (vi) O_3, $CDCl_3$, −50°C; Ph_3P, rt (93% R = Z, 94% R = Boc).

Thus this sequence of reactions constitutes a short (6 step) highly stereoselective route to the fully-protected *C*-analogue of the glycopeptide core found in nephritogenoside **2**. The chemistry involved should be compatible with a range of glycosyl fluorides and hence should allow access to a range of novel *C*-linked glycopeptide structures.

In an effort to probe the scope of this chemistry further we have also investigated synthesis of *C*-linked glycopeptides of type **10**.

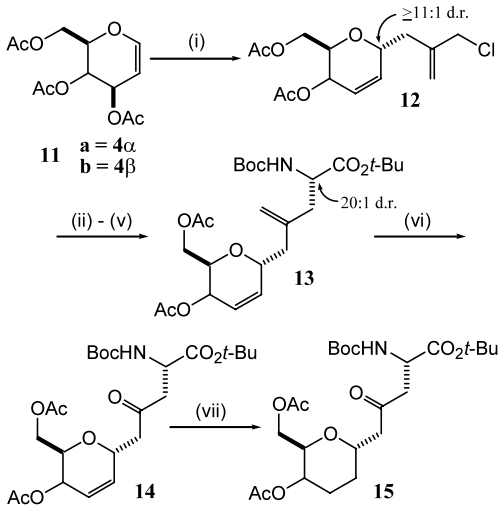


These structures lack the C-2′ and C-3′ substituents found in native *N*-glycopeptides, but retain the key C-4′ and C-6′ hydroxyl functions, the positions at which additional sugar units are usually attached.[2] We believe that compounds of this type have significant potential as simplified glycopeptide mimics as they contain all the functionality required for incorporation into more complex glycopeptide fragments but avoid problems associated with the need to differentiate between secondary hydroxyl groups. We envisaged that compounds of this type should be accessible from the commercially-available tri-*O*-acetyl glucals **11a** and **11b**.

It was found that glucals **11a** and **11b** could be coupled with 2-chloromethyl-3-trimethylsilylpropene in excellent yield using $Yb(OTf)_3$ catalysis.[16] As expected, good selectivity for the α-product **12** was obtained in both cases. Conversion to the corresponding iodides followed by asymmetric phase-transfer alkylation, hydrolysis and Boc-protection gave intermediates **13** in good overall yields (Scheme 2).[14]

It is interesting to note that although the phase-transfer alkylation step required the use of 9M aqueous potassium hydroxide, no hydrolysis of the *O*-acetyl groups could be detected. Presumably this is because the phase-transfer catalysts employed do not extract hydroxide ion into the organic phase to any significant extent,[17] and thus the two-phase nature of the reaction enables even primary acetates to survive.

Next we required oxidative cleavage of the 1,1-disubstituted alkene in the presence of a 1,2-disubstituted alkene. It was anticipated that this should be possible



Scheme 2. *Reagents and conditions*: (i) 2-chloromethyl-3-trimethylsilylpropene (1.2 equiv.), $Yb(OTf)_3$ (10 mol%), CH_2Cl_2, rt (**12a**, 96%, **12b**, 87%); (ii) NaI, acetone; (iii) **5**, *O*-benzyl-*N*-(9-anthracenylmethyl)dihydrocinchonidinium bromide (10 mol%), 9 M aq. KOH, PhMe, rt; (iv) 15% aq. citric acid, THF, rt; (v) Boc_2O, Et_3N, CH_2Cl_2, 0°C–rt (**13a**, 55% overall, **13b**, 71% overall); (vi) O_3, $CDCl_3$, −50°C; Ph_3P, rt (**14a**, 70%, **14b**, 84%); (vii) H_2, 10% Pd/C, EtOAc, rt (**15a**, 77%, **15b**, 77%).

via ozonolysis since reaction at the 1,2-disubstituted alkene should be disfavoured on both steric and electronic grounds. This did indeed prove to be the case, however low temperature and carefully-controlled delivery of ozone were necessary in order to obtain good yields of the desired products **14**. Finally, hydrogenation of the remaining alkene furnished the target compounds **15a** and **15b**.

This latter sequence of reactions helps to establish the generality of this approach to *C*-glycosylasparagines and demonstrates that good stereoselectivity can be obtained with a number of different substrates.

For all the substrates studied, the stereochemistry of the *C*-glycoside bond is readily confirmed by ^1H NMR analysis. The stereochemistry assigned to C-2 of the amino acid moiety is based on the well-established stereochemical course of glycine imine alkylations involving *O*-benzyl-*N*-(9-anthracenylmethyl)dihydrocinchonidinium bromide.[14,15]

In conclusion, we have developed a simple, stereoselective approach to ketomethylene isosteres of *N*-glycosylasparagines. This chemistry should allow access to a wide range of novel glycopeptide-based materials and further developments in this area will be reported in due course.

Acknowledgements

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