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Novel conformationally restricted glycoamino acids from glyco-α-aminonitriles as potent turn mimics in peptide synthesis

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Abstract—Our previously described glycoaminocyanation procedure using $Ti(OiPr)_4$ and TMSiCN has been applied to introduce amino acid and peptide moieties on a monosaccharide. Selective reduction using $NaNH_4$–$CoCl_2$ and Pd(C), respectively, is described. Restricted conformation of the new glycoamino acids favours intramolecular cyclisation to give the corresponding oxopiperazine **5a**–**b** and **12a**–**b**. The target acyclic compound **I** was obtained when the peptide derivative was displaced from the complex using KCN. Hydrolysis of the glycospirohydantoin **18** to give the glycoamino acid **II** is also described. © 2002 Published by Elsevier Science Ltd.

More recently there has been an increased interest in unnatural α-amino acids.[1–5] A particular class within this family is the conformationally restricted amino acids, which are known as β-turn mimics.[5–7] Such compounds have been used to study enzymatic reaction mechanisms and as optically active starting materials for a variety of synthetic applications. Numerous different types of unnatural aminoacids have been reported in the last decade using a variety of synthetic approaches.[8–10] An interesting class of turn mimics is the glycoamino acids (GAAs), which are intended to function as conformationally restricted dipeptide isosters.[11–16] The GAAs described in this paper are characterised by having the amino and carboxylic acid functionalities on two distinct positions of the saccharide backbone. Recently, Steiner reported the hydrolysis of spirohydantoin derivatives of protected 4,6-dideoxy-L-talopyranoside and D-allopyranoside to obtain the corresponding α-aminoacids with one of the carbon atoms of the sugar ring being Cα.[17]

The concept of α,α-disubstituted α-aminoacids as building blocks for peptide scaffolds and conformational restrained peptidomimetics, has been applied to the synthesis of new chiral axial disymmetric compounds. Wakselman prepared various biphenyl-, binaphthyl- and 4,5-diazafluorene derivatives to study their potential to induce β-bends and $\alpha/3_{10}$ helices in peptides and to allow better control of the spatial organisation of these metal receptors in peptide supramolecular architectures.[5,18,19]

In the course of our ongoing interest in the introduction of α-aminonitriles at non-anomeric positions of monosaccharides, we have explored various stereoselective routes to new chiral sugar α-amino acids incorporating Cα as one of the carbon atoms of the sugar ring. This paper shows that the previously reported[20–23] amino cyanation procedure can provide ready access to key intermediates in routes to new GAAs derivatives of the types **I** and **II** (Fig. 1).

In keeping with our earlier work, we have introduced α-aminoacids on the saccharide moiety such that they possess an N-terminal amino group in common with standard α-aminoacids. Thus, L-alanine and glycine were firstly protected by conversion into their methyl esters using classical conditions ($(MeO)_2C(Me)_2$; HCl–

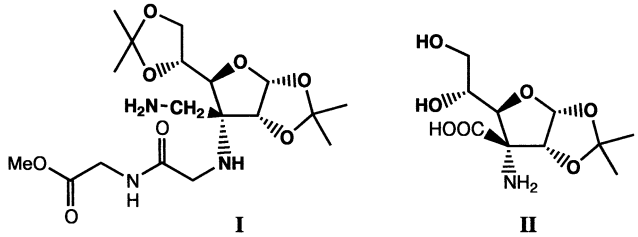

Figure 1. Target glycoamino acid structures.

Keywords: glyco-α-aminonitriles; glyco-α-amino acids; selective reduction; oxopiperazine; glycopeptides; turn mimics.

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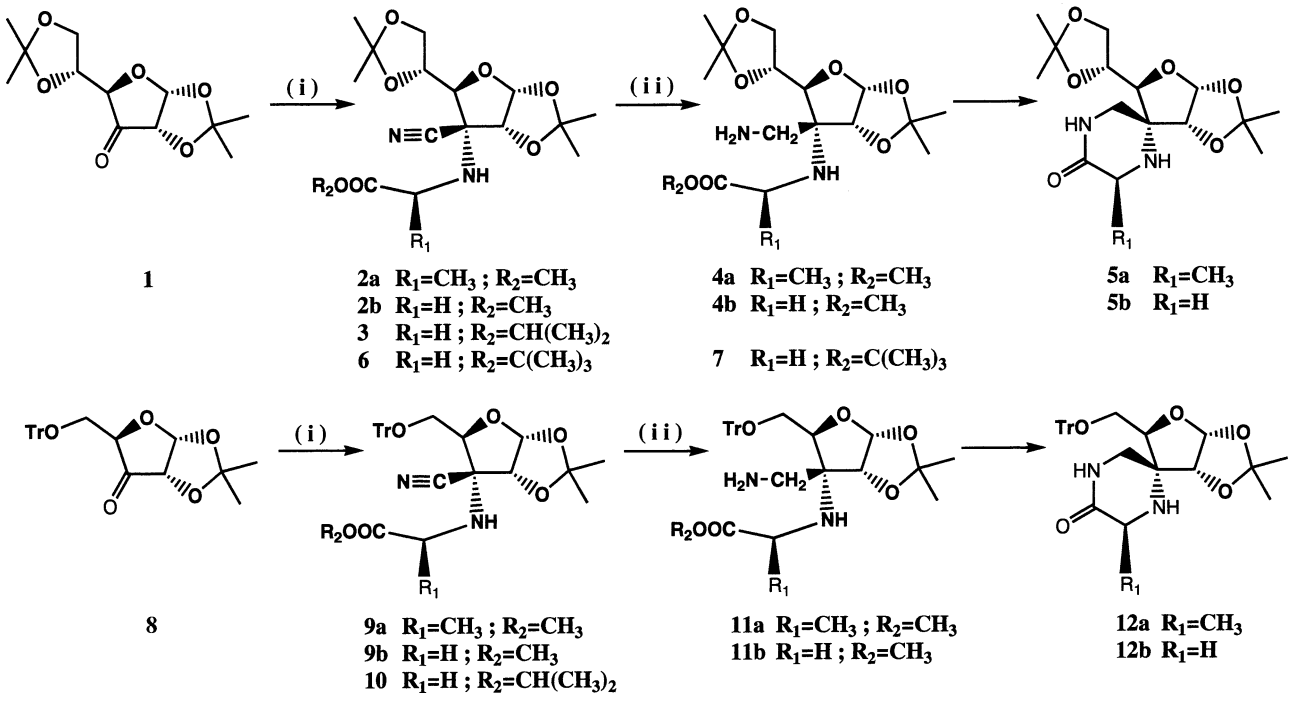


Scheme 1. *Reagents*: (i) L-Ala-OMe, HCl or L-Gly-OMe, HCl; TEA; $Ti(OiPr)_4$; MeOH then TMSiCN; (ii) $CoCl_2$; $NaBH_4$; MeOH.

H_2O) and then stereoselectively coupled with the uloses **1** and **8** using our aminocyanation procedure which employs $Ti(OiPr)_4$ as mild and effective Lewis acid catalyst. Relatively low yields of the L-alanine derivatives **2a** and **9a** (23 and 47%, respectively) were obtained. In contrast, higher yields (53 and 80%, respectively) were afforded of the glycine derivatives **2b**[24] and **9b** using the same reaction conditions.

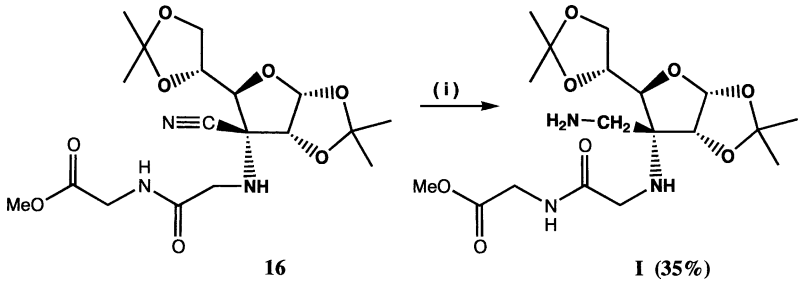
Increases in either the number of equivalents of aminoacid or that of $Ti(OiPr)_4$ did not permit an improvement in the yield. In the second case, the isopropylesters **3** (**2b**: 43%; **3**: 38%) and **10** (**9b**: 23%; **10**: 12%) were observed as by-products. Selective reduction of the CN group of **2a–b** and **9a–b** with $NaBH_4$–$Co^{II}Cl_2$ system[5] gave the corresponding amino derivatives **4a–b** and **11a–b**, which spontaneously cyclised to the corresponding oxopiperazines **5a** (75%), **5b** (78%),[25] **12a** (50%) and **12b** (60%) as outlined in Scheme 1. Removal of Co^{II} derivatives was achieved in all cases by filtration through a silica gel pad. The same strategy was applied to obtain the ulose derivative **1** starting from *t*-butyl ester protected aminoacid derivatives that are less subject to aminolysis. α-Aminonitrile **6** was obtained in 35% yield. Reduction of the CN group of **6** and subsequent cyclisation gave **5b** in 82% yield.

To avoid spontaneous intramolecular aminolysis aided by the formation of a stable pyranose ring, we chose to use the dipeptide glycylglycine in the route instead of a monomeric aminoacid. Thus, the corresponding glycopeptidonitrile **16** was obtained in 38% yield.[26]

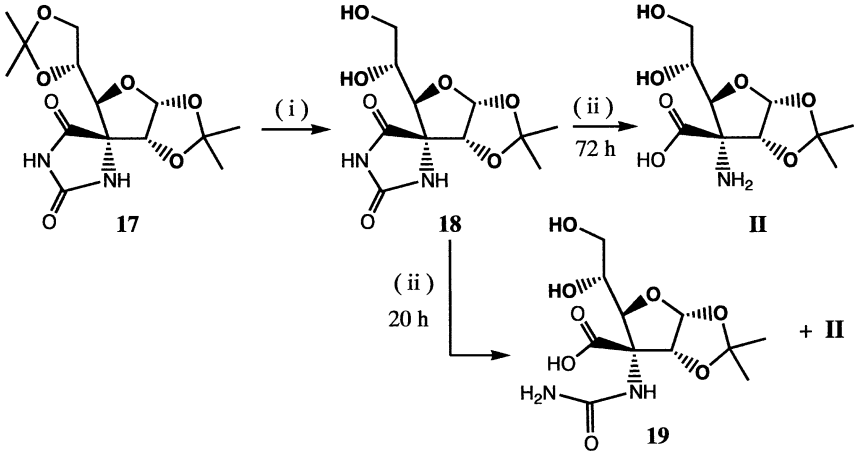
Selective reduction of the cyano groups of **16** was achieved in the same fashion as used for **2a–b** and **9a–b**. Contrary to previous experiments, the Co^{II}-glycopeptide complex of **I** appeared to be relatively stable, such that filtration through a layer of silica was found to be inefficient in removing the cobalt moiety. However, extraction using aqueous HCl (0.5N) gave exclusively the cyclic oxopiperazine **5b** in a low yield (34%). These results demonstrate the effective and selective reduction of the cyano group without affecting the carbonyl group and the capability of the subsequent amines to efficiently cyclise to give the required piperazine derivatives. It has been proposed[27] that the high reactivity is due to the formation of a cobalt–aminoacid complex involving the oxygen and nitrogen atoms of the same aminoacid unit. Two different approaches were used to access to the acyclic target compound **I**.[28]

The first protocol involves displacement of the peptide derivative from the complex by adding KCN followed by extraction into $CHCl_3$.[29] Application of this procedure to the dipeptide derivative **16** led successfully to the target compound **I** in 35% yield. The glycine and alanine derivatives **2a–b** and **9a–b**, were exclusively converted into the cyclic oxopiperzine **5a–b** and **12a–b** in high yield (60–75%).

The second route involved the selective reduction of the cyano group without formation of the Co^{II} derivative. Pd(C)-catalysed hydrogenation of **2b** in either pure MeOH or MeOH–AcOH (1:1) yielded the cyclic derivative **5b** in 44 and 57%, respectively. The Herranz method,[30] which involves hydrogenation in the presence



Scheme 2. *Reagents*: (i) $CoCl_2$; $NaBH_4$; MeOH then KCN.



Scheme 3. *Reagents and conditions*: (i) aqueous HCl (1N); (ii): $Ba(OH)_2$; H_2O reflux then Dowex 50X8-200 ion-exchange resin.

of di-*tert*-butyl-dicarbonate to give an (*N*-Boc)-protected derivative, was found to be ineffective in the this case; thus **5b** was obtained from **2b** in 71%. Compound **16** appeared to be stable during Pd(C)-catalysed hydrogenation in MeOH and a low yield (32%) of **5b** was observed (Scheme 2).

Compound **II** was synthesised via the corresponding hydantoin derivative **17**. In our previous paper we described the synthesis of novel spirohydantoins of D-allose and D-ribose derived from glyco-α-aminonitriles.[22,23] The preliminary study concerning the conversion of these derivatives into the corresponding amino acids was achieved on the partially deprotected D-allose derivative **18** which was obtained in 67% yield from **17** using aqueous 1 M HCl. Hydrolysis of the hydantoin ring with aqueous barium hydroxide (72 h; reflux) gave, after treatment of the resulting barium carboxylate derivative on Dowex 50X8-200 acidic resin, the target compound **II** in 82% yield.[31] It should be noted that a shorter reaction time led to a mixture of **II** and of the ureic derivative **19** (Scheme 3).

In conclusion, we have demonstrated that the convenient introduction of an α-aminonitrile moiety at a non-anomeric position of a monosaccharide to generate a new chiral centre (Cα) as one of the carbon atoms of the sugar ring. The nature of the restricted conformation is being evaluated. Further derivatisations are being explored using various amino acids in the aminocyanation step and in subsequent peptide coupling reactions involving **I** and **II** are in progress.

Acknowledgements

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24. *Selected spectroscopic values*: **2b** ^{1}H NMR ($CDCl_3$) δ 5.85 (d, 1H, H-1, $J_{1,2}$ 3.6 Hz), 4.66 (d, 1H, H-2), 4.30 (m, 1H, H-5, $J_{5,6b}$ 4.0 Hz), 4.11 (dd, 1H, H-6a, $J_{5,6a}$ 6.1 Hz), 3.96 (dd, 1H, H-6b, $J_{6a,6b}$ 9.0 Hz), 3.84 (d, 1H, H-4, $J_{4,5}$ 9.0 Hz), 3.70 (s, 3H, OCH_3), 3.58 (s, 2H, $\underline{CH_2}NH$), 2.93 (s, 1H, NH) 1.50 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), ^{13}C NMR ($CDCl_3$) δ 170.9 (C=O), 117.1 (CN), 114.1 ($CH_3\underline{C}CH_3$), 110.3 ($CH_3\underline{C}CH_3$), 104.4 (C-1), 82.5 (C-2), 80.8 (C-4), 75.0 (C-5), 68.0 (C-3), 67.6 (C-6), 52.1 (OCH_3), 46.5 (CH_2NH_2), 26.6 (2 CH_3), 26.5 (CH_3), 24.9 (CH_3).
25. *Selected spectroscopic values*: **5b** ^{13}C NMR ($CDCl_3$) δ 171.2 (C=O), 113.3 ($CH_3\underline{C}CH_3$), 110.4 ($CH_3\underline{C}CH_3$), 104.3 (C-1), 81.7 (C-2), 80.9 (C-4), 73.7 (C-5), 68.6 (C-6), 62.6 (C-3), 46.8 ($CH_{2\alpha}NH$), 44.1 ($CH_{2\beta}NH$), 27.1 (CH_3), 27.0 (CH_3), 26.7 (CH_3), 25.5 (CH_3).
26. *Selected spectroscopic values*: **16** ^{1}H NMR ($CDCl_3$) δ 7.60 (t, 2H, NH, $J_{NH-CH2\beta}$ 5.4 Hz), 5.80 (d, 1H, H-1, $J_{1,2}$ 3.6 Hz), 4.70 (d, 1H, H-2), 4.26 (m, 1H, H-5, $J_{5,6b}$ 4.4 Hz), 4.08 (dd, 1H, H-6a, $J_{5,6a}$ 6.2 Hz), 3.95 (d, 2H, $CH_{2\beta}$-NH), 3.90 (dd, 1H, H-6b, $J_{6a,6b}$ 9.2 Hz), 3.72 (d, 1H, H-4, $J_{4,5}$ 9.0 Hz), 3.60 (s, 3H, OCH_3), 3.50 (dd, 1H, $\underline{H\alpha gly}$, $J_{H\alpha-NH}$ 6.1 Hz), 3.36 (dd, 1H, $\underline{H\alpha' gly}$, $J_{H\alpha-H\alpha'}$ 16.7 Hz), 2.80 (dd, 1H, NH, $J_{H\alpha'-NH}$ 7.8 Hz), 1.46 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), ^{13}C NMR ($CDCl_3$) δ 170.7 (C=O), 170.3 (C=O), 117.3 (CN), 114.4 ($CH_3\underline{C}CH_3$), 110.8 ($CH_3\underline{C}CH_3$), 104.7 (C-1), 82.2 (C-2), 80.6 (C-4), 72.2 (C-5), 68.9 (C-3), 67.9 (C-6), 52.5 (OCH_3), 48.7 ($CH_{2\alpha}NH$), 41.2 ($CH_{2\beta}NH$), 26.9 (2 CH_3), 26.7 (CH_3), 25.2 (CH_3).
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28. *Selected spectroscopic values*: **I** ^{13}C NMR ($CDCl_3$) δ 173.5 (C=O), 170.7 (C=O), 112.3 ($CH_3\underline{C}CH_3$), 110.2 ($CH_3\underline{C}CH_3$), 104.5 (C-1), 83.4 (C-2), 82.0 (C-4), 73.7 (C-5), 69.1 (C-6), 67.8 (C-3), 52.6 (OCH_3), 47.2 ($CH_{2\alpha}NH$), 41.0 ($CH_{2\beta}NH$), 41.7 (CH_2NH_2), 27.2 (CH_3), 27.0 (CH_3), 26.6 (CH_3), 25.7 (CH_3).
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31. *Selected spectroscopic values*: **II** ^{13}C NMR (D_2O) δ 170.3 (C=O), 114.7 ($CH_3\underline{C}CH_3$), 106.6 (C-1), 81.3 (C-2), 78.9 (C-4), 70.9 (C-5), 67.9 (C-3), 63.5 (C-6), 25.8 (CH_3), 25.5 (CH_3).