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SPIROCYCLIC PEPTIDES AT THE ANOMERIC POSITION OF MANNOFURANOSE

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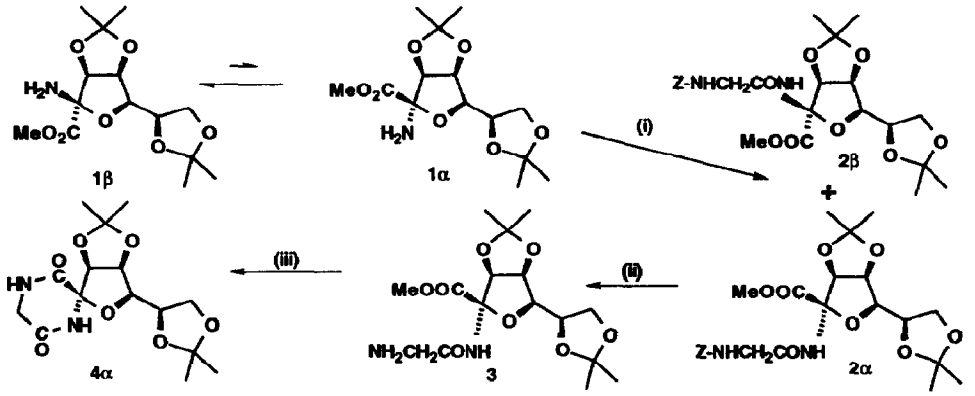
Abstract: The first syntheses of two diketopiperazine peptides containing an α-amino in which the α-carbon is also the anomeric carbon of a carbohydrate are described; studies on the kinetic and thermodynamic stability of the spirocyclic dipeptides are reported.

The preceding paper reported that the thermodynamically more stable amino ester **1β** largely isomerises to the more nucleophilic amine **1α** before reacting with Z-glycine [Z=$PhCH_2OCO$], activated by treatment with DCC and 1-hydroxybenzotriazole, to give the dipeptide **2α** in 72% yield, together with 7% of the epimeric **2β** [Scheme 1].[1] Removal of the Z-protecting group by hydrogenolysis in the presence of palladium black in methanol gave the amine **3**, m.p. 155-157°C, $[\alpha]_D^{20}$ +100.8 (*c* 0.25, MeOH), 91% yield, which on reaction with potassium *tert*-butoxide in tetrahydrofuran gave the spiro compound **4α** as an amorphous solid, $[\alpha]_D^{20}$ +113.5 (*c* 1.0, MeOH), in 89% yield.

This is the first example of a cyclic peptide at the anomeric position of a carbohydrate.

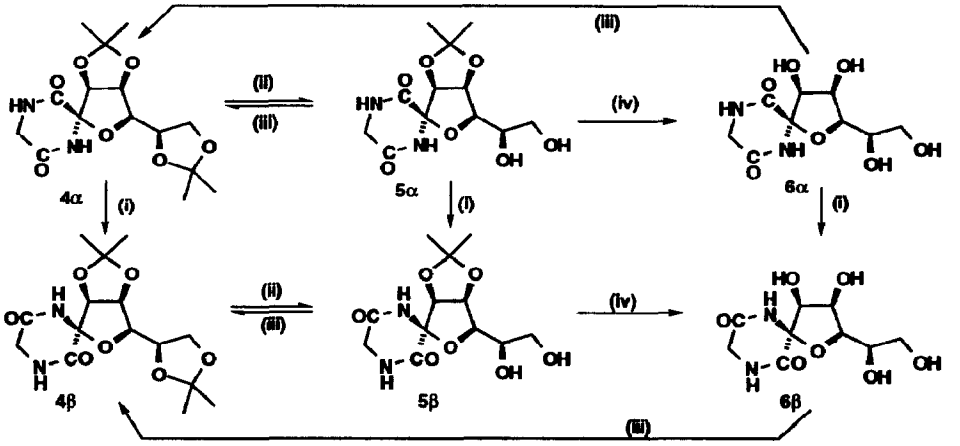


Scheme 1: (i) DCC, 1-hydroxybenzotriazole, Z-$NHCH_2COOH$ (ii) H_2, Pd, MeOH (iii) *tert*-BuOK, THF

Studies on the chemical and stereochemical stability of the diketopiperazine **4α** were conducted to establish features of the stability of both the anomeric configuration and of furanose-pyranose interconversions [Scheme 1]. Thus hydrolysis of **4α** under mild conditions with acetic acid in methanol resulted in removal of the side chain acetonide to give the diol **5α**, m.p. 125°C (dec.), $[\alpha]_D^{20}$ +120.5 (c 1.0, MeOH), in 88% yield. Further hydrolysis of the monoisopropylidene derivative **5α** with aqueous trifluoroacetic acid gave the deprotected material **6α**, m.p. 190°C (dec.), $[\alpha]_D^{20}$ +2.0 (*c* 0.1, MeOH), in 92% yield. Both **5α** and **6α** were converted into **4α** by treatment with dimethoxypropane in acetone in the presence of tosic acid in 100% and 90% yields, respectively.

The ease of establishing an equilibrium at the anomeric positions of **4**, **5** and **6** was studied. Reaction of **4α** with potassium *tert*-butoxide in dimethylformamide at 100°C for 12 h gave **4β**, $[\alpha]_D^{20}$ +96 (*c* 0.5, MeOH), in 87% yield. Similar treatment of **5α** gave **5β**, m.p. 216-218°C, $[\alpha]_D^{20}$ +88.8 (*c* 0.5, MeOH) in

88% yield where 6α gave unprotected 6β, m.p. 151-153°C, $[\alpha]_D^{20}$ +10.8 (*c* 0.5, MeOH) in 90% yield. The anomeric configuration of 4α and 4β was determined by measurements of inter-proton distances from quantitative analysis of 500 MHz NMR NOE data.[2] For 4α, NOEs are oberved for NH..H2, corresponding to a distance of 3.2 Å, and for NH..H4. For 4β no NH..H2 NOE is observed but an NOE is seen between the NH and one of the ketal methyl resonances. This is only consistent with 4α having a cis H2/NH relationship and 4β having a trans H2/NH configuration.



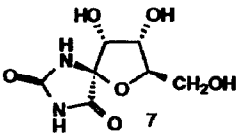
Scheme 2: (i) *tert*-BuOK, DMF (ii) MeCOOH, H_2O (iii) $Me_2C(OMe)_2$, *p*-Me-C_6H_4-SO_3H (iv) CF_3COOH, H_2O

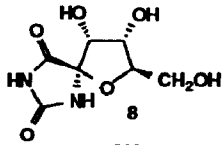
The acetonide protecting groups in 4β were sequentially removed by aqueous acetic acid to give 5β in 85% yield and by aqueous trifluoroacetic acid to give the spirotetraol 6β in 80% yield.Both 5α and 6α were converted into 4α by treatment with dimethoxypropane in acetone in the presence of tosic acid in 100% and 90% yields, respectively.

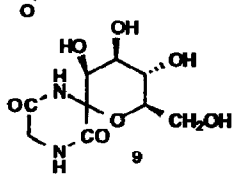
Spiropeptides such as **6** should provide an interesting new set of materials with carbohydrate recognition sites built into novel peptide structure. The materials are remarkably stable to acid and to base. In summary, this paper shows:

(i) there is no epimerisation of the anomeric position in the spiro mannofuranose cyclic peptides **4,5** and **6** under acidic conditions that are strong enough to remove both acetonides. (ii) strongly basic conditions cause efficient epimerisation of the kinetic α-spiropeptides to the thermodynamically more stable β isomers. (iii) the β-isomers are more stable when the anomeric nitrogen substituent is *cis*, rather than trans, to the 2,3-diol unit; this is consistent with the greater stability of epihydantocidin **8** to hydantocidin **7**.[3]

(iv) there is no evidence that any mannopyranose isomers, such as **9**, were formed at any stage of the reactions. Whether the lack of any mannopyranose forms is a kinetic or thermodynamic phenomenon is under investigation.[4]







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