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Stereocontrolled Transformation of Nitrohexofuranoses into Cyclopentylamines via 2-Oxabicyclo[2.2.1]heptanes: Incorporation of Polyhydroxylated Carbocyclic β-Amino Acids into Peptides

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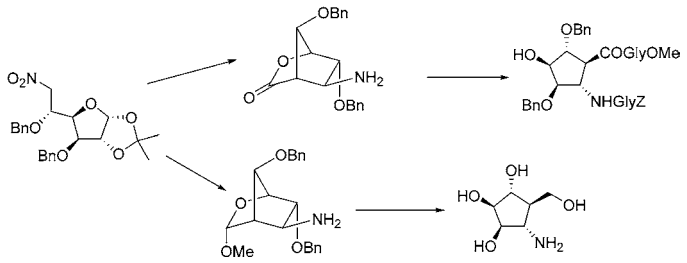
ABSTRACT



A promising new strategy for the transformation of nitrohexofuranoses into cyclopentylamines, based on intramolecular cyclization followed by controlled opening of the resulting 2-oxabicyclo[2.2.1]heptane derivatives, allowed the first total synthesis of a carbocyclic β-amino acid and its incorporation into peptides. This strategy also afforded a new route to cyclopentylamines with well-known glycosidase inhibition properties.

The biological functions and pharmacological limitations of natural peptides have in recent years prompted intense work on the preparation of analogues with pharmacological advantages.[1] Particularly interesting are oligomers of β-amino acids, which have pharmacologically interesting properties associated with their resistance to enzymatic degradation and which tend to be more rigid than α-peptides.[2] Accordingly, there has recently been much interest in the enantioselective synthesis of β-amino acids,[3,4] including water-soluble hydroxylated[5] or aminated[6] derivatives of sugar β-amino acids (a class of carbopeptoids[7]). Major contributions to this field by Kessler, Fleet, and others have resulted in the preparation of a plethora of oxetose, furanose, and pyranose amino acids and in their assembly as peptides that adopt interesting secondary structures.[8]

(1) For reviews, see: (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 717. (b) Kirshenbaum, K.; Zuckermann, R. N.; Dill, K. A. *Curr. Opin. Struct. Biol.* **1999**, *9*, 530. (c) Stigers, K. D.; Soth, M. J.; Nowick, J. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 714. (d) Andrews, M. J. L.; Tabor, A. B. *Tetrahedron* **1999**, *55*, 11711. (e) Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131.

(2) For a recent review on β-peptides which includes references to work by the Seebach and the Gellman groups, the most active in this field, see: Cheng, R. P.; Gellman, S. H.; DeGrado, W. *Chem. Rev.* **2001**, *101*, 3219.

(3) For a recent book, see: *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997.

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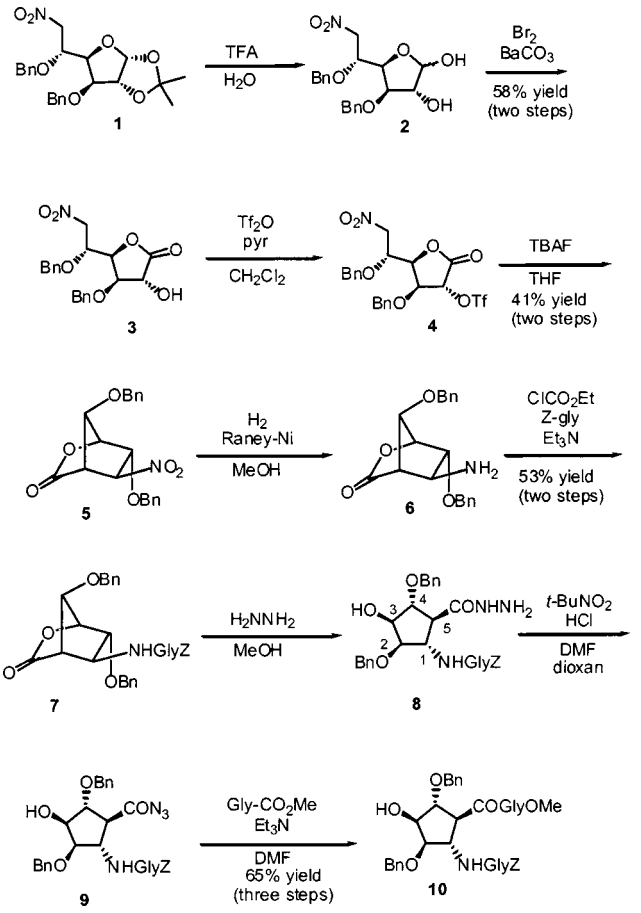
The conversion of sugars into carbocycles is another area that has attracted considerable attention,[9] and the pharmacological promise of carbasugars[10] has prompted the development of several approaches to the synthesis of optically pure carbasugars from sugars and other chiral sources.[11] In fact, particular attention has been paid to amino carbasugars such as **17**, a mannosidase inhibitor, and other inhibitors of glycosidases,[12] due to their potential for the treatment of diseases involving carbohydrate metabolism or glycoprotein-mediated processes[13] (diabetes, cancer, viral infections, etc.). Similar work on polyhydroxylated cycloalkyl amino acids has been much less abundant: as far as we know, the preparation of this kind of compounds from sugars has been limited to the preparation of a polyhydroxylated cyclohexane α-amino acid and two polyhydroxylated cyclopentane α-amino acids,[14] and neither total nor partial synthesis of similar *β*-amino acids has been reported.

This paper reports preliminary results on the synthesis of polyhydroxylated alicyclic *β*-amino acids from sugars, illustrated by the easy transformation of glucofuranose derivative **1** into a tripeptide containing a polyhydroxylated cyclopentane *β*-amino acid via the corresponding lactone (Scheme 1).

Scheme 1. Synthesis of Peptides Containing Alicyclic *β*-Amino Acids



Reaction of the easily prepared nitroglucofuranose derivative **1**[15] with trifluroacetic acid and water, followed by anomeric oxidation[16] of the resulting hydroxy lactol **2** with bromine and barium carbonate, afforded the lactone **3** as a yellow oil (58% yield from **1**). Reaction of **3** with triflic anhydride in pyridine furnished the corresponding triflate **4**, which when treated with TBAF in THF readily underwent intramolecular displacement of the triflate group by the carbanion α to the nitro group, affording the bicyclic *β*-nitrolactone **5**, in 41% yield from **3** ($[\alpha]^{20}_D$ −35 (*c* 0.85 in chloroform)). Subsequent selective reduction of the nitro group of **5** by catalytic hydrogenation with Raney nickel yielded the desired amino derivative **6**. As the lactone of a polyhydroxylated cyclopentane *β*-amino acid, we aimed to

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(8) For a recent review on sugar amino acids, see: Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491.

(9) For reviews on the preparation of carbocycles from carbohydrates, see: (a) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779. (b) Fraser-Reid, B.; Tsang, R. In *Strategies and Tactics in Organic Synthesis*; Academic Press: New York, 1989; Vol. 2, Chapter 4.

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(12) For two recent reviews on inhibitors of glicosidases, see: (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron*: *Asymmetry* **2000**, *11*, 1645. (b) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515. Recent selected articles in this field: (c) Uchida, C.; Ogawa, S. *Recent Res. Dev. Pure Appl. Chem.* **1999**, *3*, 161. (d) Leroy, E.; Reymond, J.-L. *Org. Lett.* **1999**, *1*, 775. (e) Boss, O.; Leroy, E.; Blaser, A.; Reymond, J.-L. *Org. Lett.* **2000**, *2*, 151. (f) Kleban, M.; Hilgers, P.; Greul, J. N.; Kugler, R. D.; Li, Jing; P., Sylviane; V., Pierre; Jager, V. *ChemBioChem* **2001**, *2*, 365. (g) Greul, J. N.; Kleban, M.; Schneider, B.; Picasso, S.; Jager, V. *ChemBioChem* **2001**, *2*, 368.

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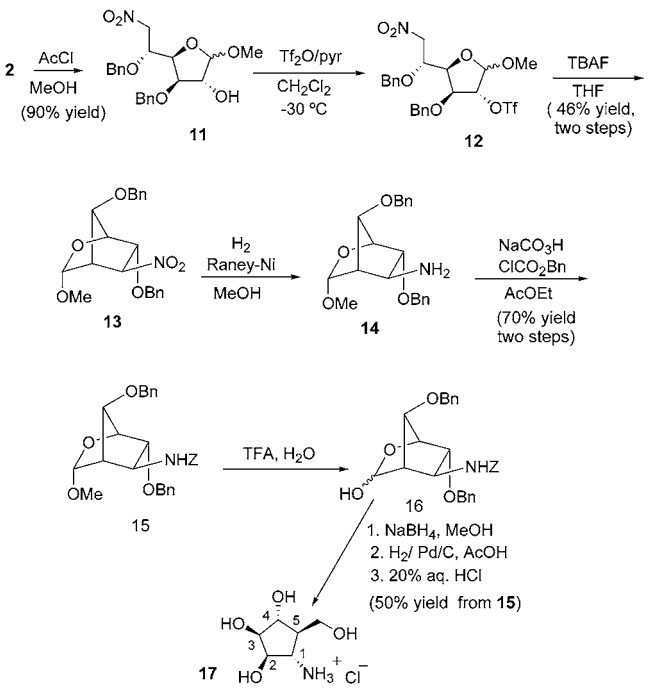
(14) (a) Fairbanks, A. J.; Hui, A.; Skead, B. M.; de Q. Lilley, P. M.; Lamont, B.; Storer, R.; Saunders: J.; Watkin, D. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1994**, *35*, 8891. (b) Hui, A.; Fairbanks, A. J.; Nash, R. J.; de Q. Lilley, P. M.; Storer, R.; Watkin, D. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1994**, *35*, 8895.

(15) Compound **1** was easily prepared by ozonolysis of the corresponding azide, which was obtained from D-glucose, as per: Fleet, G. W. J.; Carpenter, N. M.; Petursson, S.; Ramsden, N. G. *Tetrahedron Lett.* **1990**, *31*, 409−412.

(16) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 327.

Scheme 2. Synthesis of Polyhydroxylated Cyclopentylamine **17**



use this compound as the basis for the construction of peptides containing this β-amino acid.

Freshly isolated **6** was subjected to peptide coupling with ethyl chloroformate, triethylamine and benzyloxycarbonylglycine, giving the expected dipeptide **7**. Treatment of **7** with hydrazine in methanol gave hydrazide **8**, and this unstable gum was directly reacted with *tert*-butyl nitrite and HCl. The resulting acyl azide **9** in turn directly reacted with methoxycarbonylglycine and triethylamine giving tripeptide **10** (65% yield from **7**, $[\alpha]^{20}_D$ −3.2 (*c* 1.05 in methanol)).

A slight modification of the above route to alicyclic β-amino acids allowed us to obtain the cyclopentylamine **17**. Reaction of α-hydroxy furanoside **2** with acetyl chloride in methanol provided **11** in 90% yield as a 1:1 epimeric mixture, and the C_2 hydroxy group of this compound was converted into an OTf leaving group as before by reaction with triflic anhydride in pyridine (Scheme 2). Treatment of the resulting mixture of compounds **12** with TBAF afforded the bicycle **13** in 46% yield from **11** ($[\alpha]^{20}_D$ −47.2 (*c* 1 in chloroform)). The stereochemisty of **13**, firmly established by X-ray crystallography (Figure 1),[17] suggests it must have been formed by an intramolecular cyclization of the β isomer of compound **12**. Catalytic hydrogenation of **13** using Raney nickel gave amine **14**, which was directly treated with benzyl chloroformate and sodium bicarbonate to obtain bicycle **15** in 70% yield from **13** ($[\alpha]^{20}_D$ −32.2 (*c* 1.2 in chloroform)). Subsequent hydrolysis of acetal **15** with trifluoroacetic acid was followed by the immediate reduction with $NaBH_4$ of the implicit carbonyl group of the resulting bicyclic hemiacetal **16** ($[\alpha]^{20}_D$ +103.64 (*c* 2.2 in methanol)). The resulting cyclopentanoid was directly transformed into amino carbasugar hydrochoride **17** by removal of the benzyl and Z protecting groups by hydrogenation using Pd/C as the catalyst and subsequent addition of hydrochloric acid (50% overall yield from **15**).

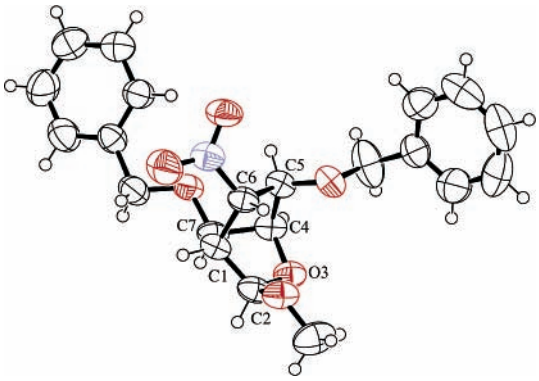


Figure 1. Molecular structure of compound **13** in the solid state.

In summary, we have developed a promising new strategy for the transformation of nitrosugars into carbasugars which allowed us to carry out the first total synthesis of a polyfunctionalized cyclopentane β-amino acid with total stereochemical control and incorporate it into a peptide. This intramolecular α-alkylation of nitrosugars also provided a convenient new route to the powerful glycosidase inhibitor **17**, selective oxidation of which at its primary alcohol should constitute an alternative path to polyhydroxylated cyclopentane β-amino acids.

We are currently applying this strategy systematically to other sugars studying the preparation and properties of homo- and heteropeptides derived from the resulting cycloalkane β-amino acids.

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Supporting Information Available: Experimental procedures for all compounds and spectroscopic data for compounds **1**, **3**, **5**−**7**, **10**, **11**, **13**, **15**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Crystallographic data for the structure of compound **13** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-205610. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax (+44)1223-336-033; e-mail deposit@ccdc.cam.ac.uk).