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Spirodiketopiperazines at the Anomeric position of Mannopyranose: Novel N-Linked Glycopeptides Incorporating an α-amino acid at the Anomeric Position of Mannopyranose

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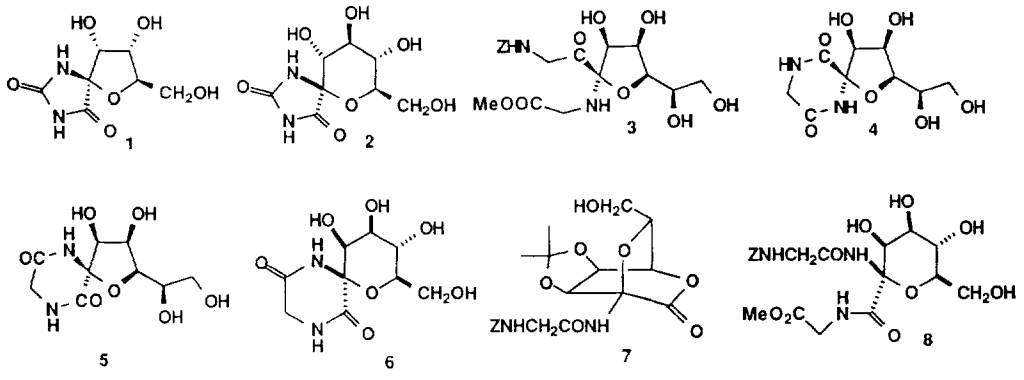
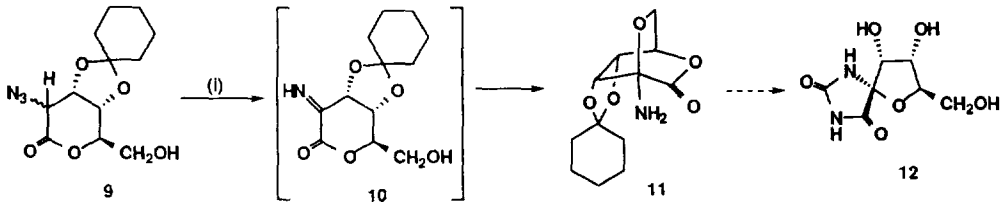
Abstract: The first synthesis of a spirodiketopiperazine at the anomeric carbon of a pyranose sugar is described; an N-acylated bicyclic amino [2.2.2] lactone provides access to a new class of glycopeptide analogues of pyranoses and determines the anomeric configuration of the spirodiketopiperazine. The mannopyranose may be equilibrated to the more stable furanose form.

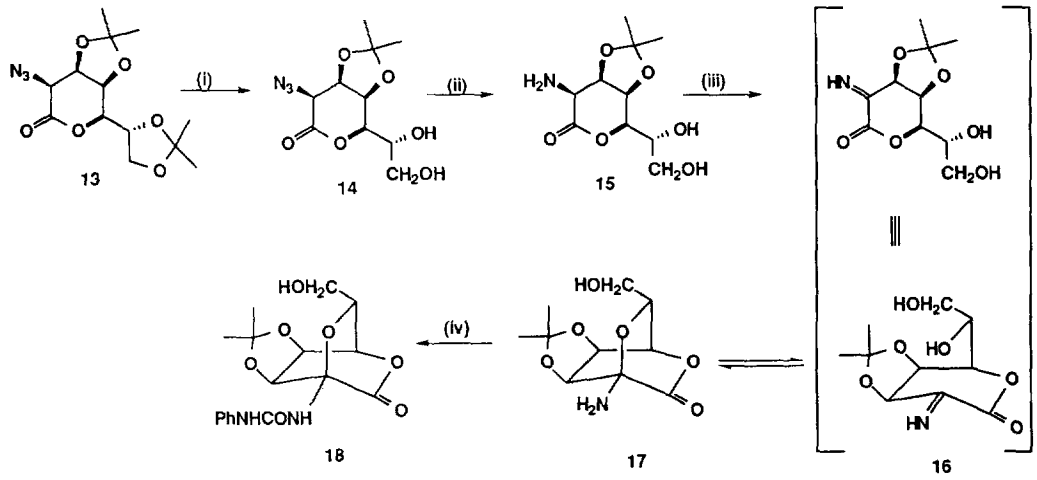
The herbicidal properties[1] of the natural product hydantocidin **1**[2] have stimulated considerable interest in both the synthesis of **1** itself[3] and of a wide range of analogues,[4] almost all[5] of which have contained the sugar moiety in a furanose form.[6] The only example of a deprotected pyranose analogue of hydantocidin, the glucopyranose **2**, has been shown to be a powerful inhibitor of glycogen phosphorylase.[7] Carbohydrate analogues possessing both an N-acyl group and a carbonyl function at the anomeric carbon are chemically quite stable in regard to both the anomeric configuration and the ring size of the sugar.[8] Oligopeptides, in which the anomeric carbon of a sugar is one of the α-amino acid constituents, form an interesting set of novel N-linked glycopeptides; for example tripeptides incorporating mannofuranose, such as **3**, and the spirocyclic diketopiperazine **4** have been prepared.[9] Diketopiperazines have a number of potential chemotherapeutic applications.[10] However, the spirodiketopiperazines of mannofuranose appear to be more stable than the pyranose isomers; treatment of **4** with potassium *tert*-butoxide in dimethyl formamide merely induces equilibration to the more stable anomer **5**.[11] This paper reports the synthesis of the mannopyranose **6** *via* an N-acylated bicyclic lactone **7** in which the configuration at the anomeric centre has been clearly defined; the bicyclic lactone **7** may also be used in an approach to novel N-linked glycopeptides such as **8** in which the anomeric carbon of mannopyranose is one of the α-amino acid constituents.





Scheme 1 (i) TPAP, NMO, MeCN, room temp., 60%

The key step in a recent synthesis of 5-*epi*-hydantocidin **12** was the transformation of the azidolactones **9** into the bicyclic amine **11** by tetra-*n*-propyl ammonium perruthenate (TPAP) in the presence of morpholine-N-oxide [Scheme 1].[12] TPAP induced the conversion of the azide function in **9** to an imine **10** which underwent intramolecular nucleophilic addition by the primary hydroxyl group to give the stable amine **11**; in this case the equilibrium between the imine **10** and the amine **11** strongly favours the bicyclic system. Structures such as **11** are attractive for the synthesis of spiro derivatives of pyranose sugars since the pyranose ring has been formed and the configuration at the anomeric position of the pyranose ring has been already defined by the bicyclic structure; however, *ribo*pyranose structures were not isolated during the conversion of **11** to **12**.[13]

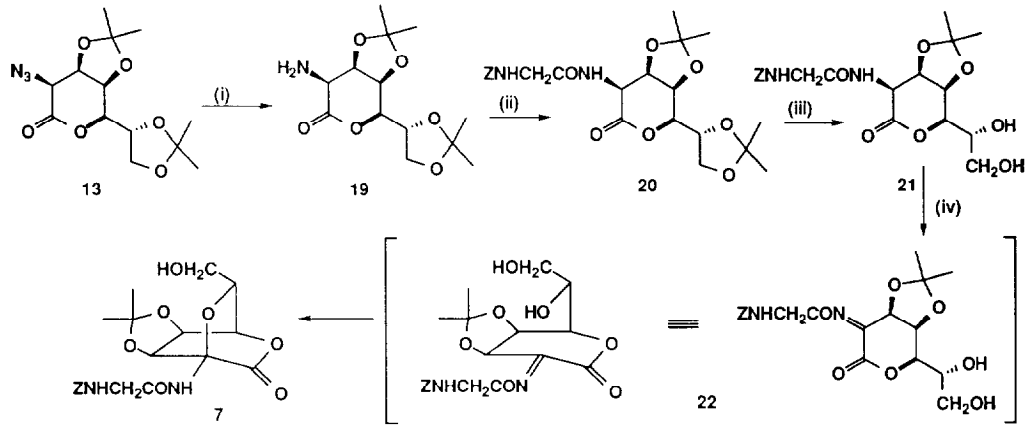


Scheme 2 (i) MeCOOH:H_2O, 1:1 (ii) H_2, Pd, EtOAc (iii) N-bromosuccinimide, MeCOONa, MeCN (iv) PhNCO

A similar approach [Scheme 2] was first adopted for the synthesis of the mannopyranose structures **6** and **8**. Removal of the side chain acetonide in the azidolactone **13**[14] gave the diol **14**[15] [92% yield]. All attempts to convert **14** directly by treatment with TPAP into the bicyclic amine **17** failed. Accordingly, the azide **14** was reduced to the corresponding amine **15** by hydrogenation in ethyl acetate in the presence of palladium black [quantitative yield]. Oxidation of **15** with N-bromosuccinimide in acetonitrile in the presence of sodium acetate gave a imine **16** which could be trapped intramolecularly by the C-6 hydroxyl group of the sugar to afford the bicyclic amine **17**: however, unlike the stable bicyclic amine **11** obtained in Scheme 1, **17** was difficult to isolate and handle. Probably steric crowding between the isopropylidene protecting group and the hydroxymethyl group in the bicyclic structure **17** causes the imine **16** to be more favoured in comparison to the equilibrium of **10** with **11**.

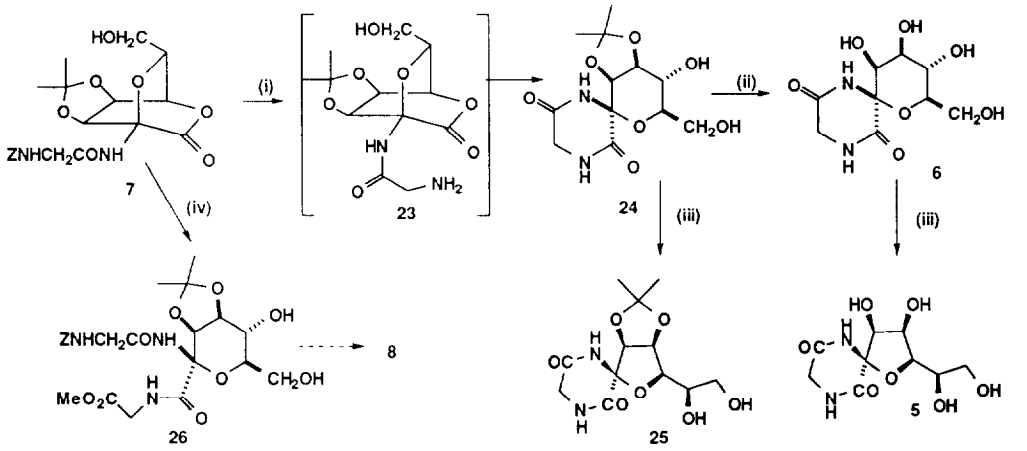
Additionally, attempts to derivatise the amine **17** gave complex reaction mixtures. Thus reaction of **17** with phenyl isocyanate gave only 21% of the phenyl urea **18**; all attempts to couple **17** with ZglyOH were unsuccessful. The problem in these reactions may be that there is a significant amount of the imine form **16**

present which can undergo faster and competitive reactions to those of the bicyclic amine **17**. Acylation of the imino function to give, for example, **22** would be expected to stabilise the acylated bicyclic form **7** so that acylation of the amine **15** prior to oxidation should allow access to stable bicyclic amidolactones.



Scheme 3: (i) H_2, Pd, EtOAc, 79% (ii) ClCOOEt, pyridine, MeCN:THF, 1:1, 86% (iii) MeCOOH:H_2O, 1:1, 100% (iv) N-bromophthalimide, MeCOONa, MeCN, 54%

Hydrogenation of the protected azide **13** [Scheme 3] gave an amine **19**[8] [79% yield] which was treated with ZglyOH, ethyl chloroformate and pyridine in acetonitrile:tetrahydrofuran [1:1] to give the dipeptide **20** [86% yield]. Aqueous acetic acid caused removal of the side chain acetonide from **20**, m.p. 200-202°C, $[\alpha]_D^{20}$ +98.9 (*c*, 1.00 in $CHCl_3$), to afford the diol **21**, m.p. 162°C, $[\alpha]_D^{25}$ +105.9 (*c*, 1.00 in MeOH), in quantitative yield. Although oxidation of **21** with N-bromosuccinimide in acetonitrile in the presence of sodium acetate formed the required bicyclic lactone **7**, it was not possible to free **7** from succinimide; thus N-bromophthalimide was used as the oxidant to give the key intermediate lactone **7**, m.p. 226-228°C, $[\alpha]_D^{22}$ +23.4 (*c*, 1.00 in MeOH), [27% yield, 54% based on unrecovered starting material]. The yield of the oxidation step is unsatisfactorily low and further studies to optimise this step are in progress.



Scheme 4: (i) H_2, Pd, MeOH (ii) CF_3COOH:H_2O, 3:2 (iii) *tert*-BuOK, DMF (iv) $MeOOCCH_2NH_3^+Cl^-$, MeCOONa, DMF

Hydrogenation of **7** in methanol in the presence of palladium black [Scheme 4] induced removal of the Z-protecting group to the free amine **23** which spontaneously cyclised to give the spirodiketopiperazine **24**, m.p. 125-127°C, $[\alpha]_D^{22}$ +45.2 (*c*, 0.66 in MeOH) [78% yield]. Removal of the acetonide in **24** by acid

hydrolysis gave the target unprotected spirodiketopiperazine of mannopyranose **6**[16,17] [100% yield], the first example of a spiro derivative of mannopyranose. Reaction of **24** with potassium *tert*-butoxide in dimethyl formamide gave the mannofuranose **25** in 92% yield; similar equilibration of the unprotected mannopyranose **6** gave the mannofuranose isomer. It is thus clear that the mannofuranose in which the nitrogen is *cis* to the diol unit is the thermodynamically stable form of all the pyranose and furanose isomers of the anomeric spirodiketopiperazines.

The bicyclic lactone **7** could be directly opened with methyl glycinate hydrochloride and sodium acetate in dimethyl formamide to give the tripeptide **26**, m.p. 80-81°C, $[\alpha]_D^{22}$ -3.5 (*c*, 1.00 in $CHCl_3$), [62% yield] in which the α-carbon of the middle constituent amino acid is the anomeric position of mannopyranose. Deprotection of **26** by aqueous hydrolysis to give peptides such as **8** is currently under investigation. This novel class of N-linked glycopeptide analogues provides a set of compounds in which the epitope of the pyranose carbohydrate is kept, allowing the full recognition of the sugar moiety by an enzyme or receptor and in which a very large diversity of compounds may easily be made by virtue of the formation of amide bonds.

In summary, this paper has provided the first examples of the preparation of derivatives of *pyranoses* in which the anomeric position of the sugar contains both amino and carbonyl functions. Such moieties may readily be incorporated into spirodiketopiperazines and many other substituents with control of the stereochemistry at the fully substituted anomeric position. The following paper[18] reports the synthesis by a similar strategy of a spirodiketopiperazine of glucopyranose, which is a specific inhibitor of glycogen phosphorylase.[19]

REFERENCES

1. Takahasi, S., Nakajima, M., Kinoshita, T., Haruyama, H., Sugai, S., Honma, T., Sato, S., Haneishi, T., *ACS Symp. Ser.*, 1994, **551**, 74.
2. Nakajima, M., Itoi, K., Takamatsu, Y., Kinoshita, T., Okazaki, T., Kawakubo, K., Shindou, M., Honma, T., Tohjigamori, M., Haneishi, T., *J. Antibiot.*, 1991, **44**, 293; Haruyama, H., Takayama, T., Kinoshita, T., Kondo, M., Nakajima, M., Haneishi, T., *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1637.
3. Mio, S., Ichinose, R., Goto, K., Sugai, S. *Tetrahedron*, 1991, **47**, 2111; Mio, S., Kumagawa, Y., Sugai, S., *Tetrahedron*, 1991, **47**, 2133; Matsumoto, M., Kirihara, M., Yoshino, T., Katoh, T., Terashima, S., *Tetrahedron Lett.*, 1993, **34**, 6289; Chemla, P., *Tetrahedron Lett.*, 1993, **34**, 7391; Harrington, P. M., Jung, M. E., *Tetrahedron Lett.*, 1994, **35**, 5145.
4. Hanessian, S., Sanceau, J.-Y., Chemla, P., *Tetrahedron*, 1995, **51**, 6669; Sano, H., Sugai, S., *Tetrahedron Asymm.*, 1995, **6**, 1143; Sano, H., Sugai, S., *Tetrahedron*, 1995, **51**, 4635; Sano, H., Mio, S., Tsukaguchi, N., Sugai, S., *Tetrahedron*, 1995, **51**, 1387.
5. Dondoni, A., Scherrmann, M.-C., Marra, A., Delaine, J.-L., *J. Org. Chem.*, 1994, **59**, 7517.
6. Brandstetter, T. W., Kim, Y., Son, J. C., Lilley, P. M. De Q., Watkin, D. J., Johnson, L. N., Oikonomakos, N. G., Fleet, G. W. J., *Tetrahedron Lett.*, 1995, **36**, 2149.
7. Bichard, C. J. F., Mitchell, E. P., Wormald, M. R., Watson, K. A., Johnson, L. N., Zographos, S. E., Koutra, D. D., Oikonomakos, N. G., Fleet, G. W. J., *Tetrahedron Lett.*, 1995, **36**, 2145.
8. Burton, J. W., Son, J. C., Fairbanks, A. J., Choi, S. S., Taylor, H., Watkin, D. J., Winchester, B. G., Fleet, G. W. J., *Tetrahedron Lett.*, 1993, **34**, 6119.
9. Estevez, J. C., Estevez, R. J., Ardron, H., Wormald, M. R., Brown, D., Fleet, G. W. J., *Tetrahedron Lett.*, 1994, **35**, 8885.
10. Prasad, C., *Peptides*, 1995, 16, 151.
11. Estevez, J. C., Ardron, H., Wormald, M. R., Brown, D., Fleet, G. W. J., *Tetrahedron Lett.*, 1994, **35**, 8889.
12. Fairbanks, A. J., Fleet, G. W. J., *Tetrahedron*, 1995, **51**, 3881.
13. Fairbanks, A. J., Ford, P. S., Watkin, D. J., Fleet, G. W. J., *Tetrahedron Lett.*, 1993, **34**, 3327.
14. Bruce, I., Fleet, G. W. J., Girdhar, A., Haraldsson, M., Peach, J. M., Watkin, D. J., *Tetrahedron*, 1990, **46**, 19.
15. Spectroscopic and/or microanalytical data consistent with each proposed structure have been obtained for all new compounds in this paper.
16. Selected data for **6**: m.p. 225-226°C; $[\alpha]_D^{21}$ +50.0 (*c*, 0.36 in D_2O); ν_{max} (KBr): 3366, 3288 (NH, OH), 1695, 1667 (C=O, amide) cm^{-1}; δ_H (D_2O): 3.53 (1H, ddd, J_{2,CH_2OH} 2.3 Hz, J_{2,CH_2OH} 6.0 Hz, $J_{2,3}$ 9.7 Hz, H-2), 3.60 (1H, p.t, H-3), 3.67 (1H, dd, J_{gem} 12.4 Hz, 0.5 x CH_2OH), 3.83 (1H, dd, 0.5 x CH_2OH), 3.88 (1H, d, $J_{9,9'}$ 18.4 Hz, H-9), 4.10 (1H, d, $J_{5,4}$ 3.7 Hz, H-5), 4.24 (1H, d, H-9'), 4.43 (1H, dd, $J_{4,3}$ 9.4 Hz, H-4); δ_C (D_2O): 44.8, 61.3 (2 x t, C-9, CH_2OH), 66.7, 69.6, 71.9, 76.8 (4 x d, C-2, C-3, C-4, C-5), 83.4 (s, C-6), 166.4, 171.7 (2 x s, 2 x C=O).
17. The anomeric configurations of the spiropyranose derivatives were established from 2D NOESY spectra; details will be given in the full paper.
18. Krulle, T. M., Watson, K. A., Gregoriuo, M., Johnson, L. N., Crook, S., Watson, D. J., Griffiths, R. C., Nash, R. J., Tsitsanou, K. E., Zographos, S. E., Oikonomakos, N., Fleet, G. W. J., accompanying paper.
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