Tetrahedron Letters, Vol. 34, No. 38, pp. 6119-6122, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

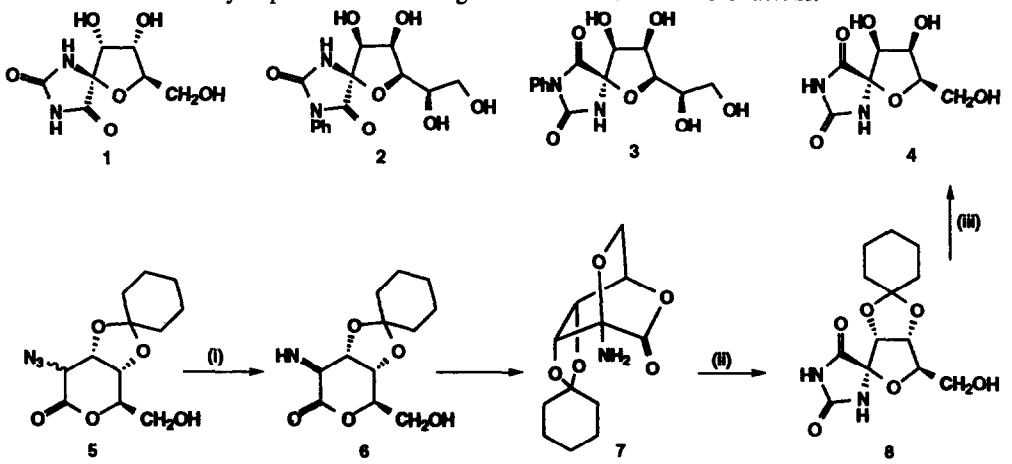
ANOMERIC SPIROHYDANTOINS OF MANNOFURANOSE: APPROACHES TO NOVEL ANOMERIC AMINO ACIDS BY AN OXIDATIVE RING CONTRACTION

Jonathan W. Burton,[a] Jong Chan Son,[a] Antony J. Fairbanks,[a] Sik-man S. Choi,[a] Helen Taylor,[a,b] David J. Watkin,[b] Bryan G. Winchester[c] and George W. J. Fleet[a]*

[a]Dyson Perrins Laboratory, Oxford Centre for Molecular Sciences, South Parks Road, Oxford OX1 3QY UK
[b]Chemical Crystallography Laboratory, Oxford University, 9 Parks Road, Oxford OX1 3PD UK
[c]Institute of Child Health, University of London, 30 Guilford Street, London WC1N 1EH

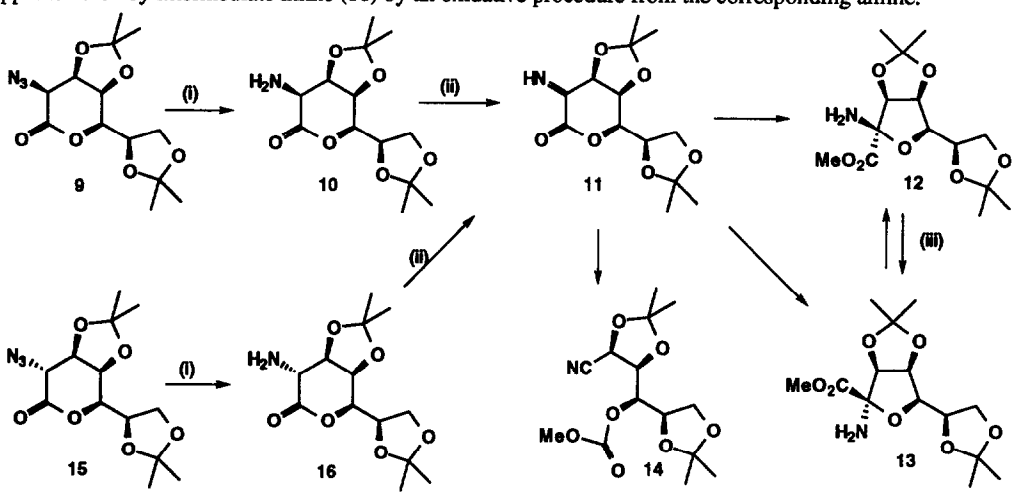
Abstract: Bromine-induced oxidative ring contraction of an α-amino-δ-lactone gave a mixture of α-aminotetrahydrofurancarboxylic esters which may allow the preparation of stable amino acid derivatives at the anomeric position of mannofuranose. The synthesis of N-phenylhydantoins at the anomeric position of mannofuranose is reported.

Isopropylidene derivatives of heptonolactones[1] have provided a set of intermediates which have been used in the synthesis of highly functionalised targets with up to seven adjacent functional groups and five contiguous chiral centres. These acetonides provide relatively easy access to highly substituted piperidines,[2] pyrrolizidines,[3] pyrrolidines,[4] alexines,[5] complex 2,5-disubstituted tetrahydrofurans,[6] highly functionalised cyclopentanes by reductive[7] or other[8] aldol condensations, and tetrahydropyrans and cyclohexanes.[9] Hydantocidin (1), with a spirohydantoin at the anomeric position of D-ribose, was isolated from *Streptomyces hygroscopicus* SANK 63584[10] and found to have potent herbicidal and plant growth regulatory activity.[11] A number of synthetic approaches to hydantocidin and its stereoisomers[12] and to some deoxyhydantocidins[13] have been described. Although no mode of action for hydantocidin has yet been proposed, it may be that spirohydantoins of other sugars also possess interesting biological properties; this paper reports the synthesis of N-phenylhydantoins of mannofuranose (2) and (3), the first examples of such derivatives of a hexose, *via* a procedure in which the key step is an oxidative ring contraction of an α-amino-δ-lactone.



Scheme 1. (i) TPAP, morpholine-N-oxide, MeCN (ii) KCNO, AcOH; then *tert*-BuOK, DMF (iii) aq. CF_3CO_2H

Tetra-*n*-propyl-ammonium perruthenate (TPAP) in the presence of morpholine-N-oxide is a selective reagent for the oxidation of alcohols to the corresponding carbonyl compounds.[14] However, the epimeric azidoalcohols (5) with TPAP gave the bicyclic aminolactone (7); this is a non-oxidative transformation of the azide to the imine (6) which is then trapped intramolecularly by the hydroxymethyl group to give (7). Treatment of (7) with potassium cyanate, followed by *tert*-butoxide, afforded the spirohydantoin (8) which, on removal of the ketal protecting group by acid hydrolysis, yielded 1-*epi*hydantocidin (4) [Scheme 1].[15] Attempts to extend this approach to the preparation of mannofuranose spirohydantoins, such as (2) and (3), by reaction of the azides (9) and (15) with TPAP and other procedures[16] failed, probably because of the ease of alternative elimination reactions derived from the removal of the proton at C-2. It was therefore decided to approach the key intermediate imine (11) by an oxidative procedure from the corresponding amine.

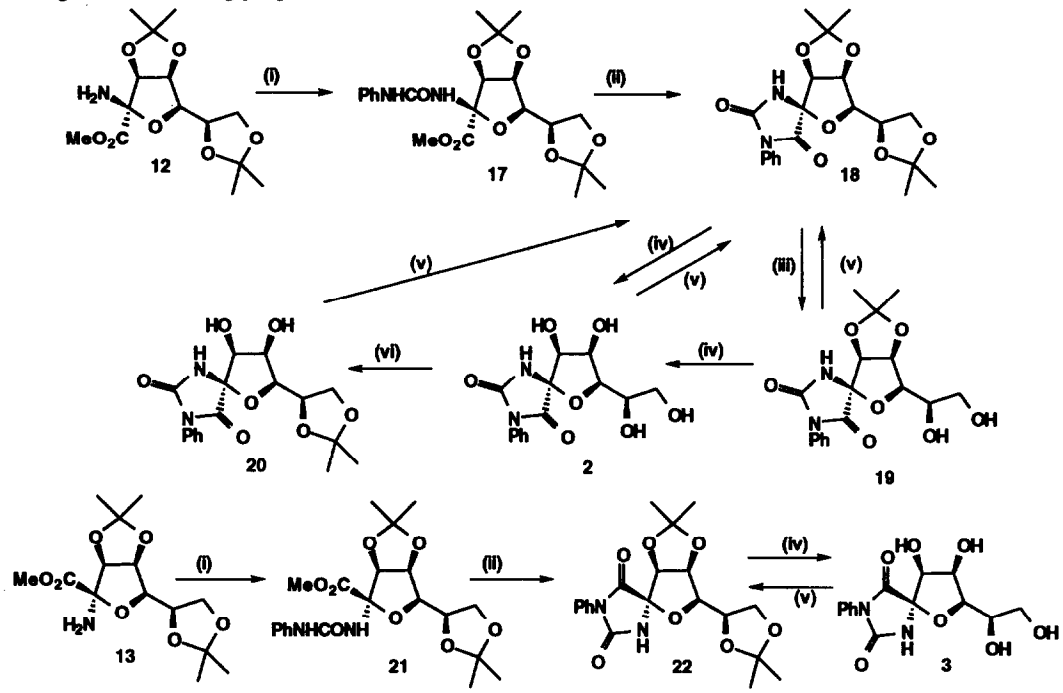


Scheme 2 (i) H_2, Pd black, EtOAc (ii) Br_2, NaOAc, MeOH; then Et_3N (iii) MeOH

Hydrogenation of the azidolactone (9) in ethyl acetate in the presence of palladium black gave the corresponding amine (10),[17] m.p. 145-147°C, $[\alpha]_D^{25}$ +56.2 (*c* 1.1, $CHCl_3$), in 94% yield [Scheme 2]. Oxidation of the amine (10) with bromine in methanol in the presence of sodium acetate, followed by addition of triethylamine gave three products, all of which could plausibly be formed from an intermediate imine (11). The major product was the amine ester (12), a colourless oil, $[\alpha]_D^{20}$ -4.0 (*c* 0.5, $CHCl_3$), formed in 60% yield; the more polar epimeric amine (13), m.p. 102-104°C, $[\alpha]_D^{20}$ +70.1 (*c* 0.5, acetonitrile) was isolated in 17% yield. Both (12) and (13) are the result of a formal oxidative ring contraction of aminolactone (10) via the imine (11) which undergoes nucleophilic attack at the lactone carbonyl followed by migration of the ring oxygen to the carbon of the imine. The nitrile (14), m.p. 109-110°C, $[\alpha]_D^{20}$ +53.5 (*c* 0.8 $CHCl_3$), isolated in 17% yield, was formed by further oxidation of the imine (11) to the N-bromoimine, followed by methanol attacking as a nucleophile at the lactone carbonyl with concommitant ring opening and loss of bromide ion. Bromine oxidation of the amine (16), m.p. 124-127°C, $[\alpha]_D^{25}$ +87.6 (*c* 0.8, $CHCl_3$), obtained in 98% yield from hydrogenation of the azide (15), gave the same three compounds in the same proportions, indicating that a common intermediate such as (11) is involved in both reactions.

The epimeric aminoesters (12) and (13) are slowly interconverted on standing in methanol to give an equilibrium mixture of the two compounds in a ratio of approximately 5:1, but otherwise they are at least

moderately stable. It is clear that (12) and (13) are suitable intermediates for incorporating amino acids at the anomeric position of sugars into novel peptides. Such materials may also provide an interesting set of analogues of N-linked glycoprotein mimics.



Scheme 3. (i) PhNCO, THF (ii) MeOH (iii) 80% aq. AcOH (iv) 40% aq. CF_3CO_2H (v) Me_2CO, conc. H_2SO_4 (vi) Me_2CO, CSA

The aminoesters (12) and (13) were converted into the spirohydantoins (2) and (3) [Scheme 3]. Reaction of (12) with phenyl isocyanate afforded the urea (17), m.p. 215-217°C, $[\alpha]_D^{20}$ -26.8 (*c* 0.6, acetonitrile), in 97% yield. The urea (17), on standing in methanol, spontaneously cyclised to the fully protected hydantoin (18), m.p. 215-217°C, $[\alpha]_D^{20}$ +59.9 (*c* 0.8, $CHCl_3$), in 88% yield. Mild hydrolysis of (18) by aqueous acetic acid removed the side chain acetonide to give the monoacetonide (19), m.p. 145-147°C, $[\alpha]_D^{20}$ +49.6 (*c* 0.4, $CHCl_3$), in 92% yield. Hydrolysis of either the diacetonide (18) or of the monoacetonide (19) by aqueous trifluoroacetic acid gave the unprotected phenylhydantoin (2), m.p. 204-207°C, $[\alpha]_D^{20}$ +20.2 (*c* 0.6, methanol), in 90% and 96% yields respectively. Reaction of (2) with acetone in the presence of camphor sulphonic acid gave the kinetic monoacetonide (20), m.p. 154-156°C, $[\alpha]_D^{25}$ +30.0 (*c* 1.2, acetonitrile), in 86% yield. The unprotected hydantoin (2) as well as the two monoacetonides (19) and (20) were all converted into the diacetonide (18) by treatment with acetone in the presence of concentrated sulphuric acid in yields of 88%, 99% and 99%. The very high yields for the deacetonation and for the reprotection of the diol units provides very strong evidence for the integrity of the spirohyantoin moiety of the mannofuranose under these sets of conditions. The structure of the unprotected phenylhydantoin (2) was firmly established by single crystal X-ray structural analysis.[18]

The aminoester (13) also reacted with phenyl isocyanate to form a urea (21), m.p. 182-184°C, $[\alpha]_D^{20}$ +106.9 (*c* 0.5, DMSO), in 85% yield. Cyclisation of (21) to the spirohydantoin (22), m.p. 170-174°C,

$[\alpha]_D^{20}$ +84.4 (c 0.4, $CHCl_3$), in methanol occurred in 88% yield but was much slower than the conversion of the epimeric urea (17) to (2). Both of the ketal protecting groups were removed from (22) by hydrolysis with aqueous trifluoroacetic acid to give the unprotected hydantoin (3), m.p. 169-171°C, $[\alpha]_D^{20}$ -1.9 (*c* 0.4, methanol), in 98% yield; on treatment with acetone and concentrated sulphuric acid, (3) was reconverted to the diacetonide (22) in 85% yield, strongly suggesting that again the spirohydantoin moiety in the anomeric position of mannofuranose is stable to such acid treatment.

The stability of the two epimeric hydantoins (2) and (3) under the conditions for the hydrolytic removal of the acetonides in their preparation and in various other isopropylidenation reactions is noteworthy and is in contrast to our experience of hydantocidin (1) and epihydantocidin (4).[17] It appears that (2) and (3) are not significantly epimerised under the conditions reported in this paper, nor have we found any evidence for the formation of mannopyranose analogues. We are actively pursuing unambiguous approaches to spirohydantoins of pyranose sugars in order to determine whether the stability of the 5,5-spiro system is thermodynamic or kinetic in origin. Whatever the outcome of these investigations, such materials may well have effects on mannosidases and other enzymes, and the biological effects of these materials will be reported elsewhere.[19]

REFERENCES

1. Bichard, C. J. F., Fairbanks, A. J., Fleet, G. W. J., Ramsden, N. G., Vogt, K., Doherty, O., Pearce, L., Watkin, D. J., *Tetrahedron: Asymm.*, 1991, **2**, 901; Beacham, A. R., Bruce, I., Choi, S., Doherty, O., Fairbanks, A. J., Fleet, G. W. J., Skead, B. M., Peach, J. M., Saunders, J., Watkin, D. J., *Tetrahedron: Asymm.*, 1991, **2**, 883.
2. Bruce, I., Fleet, G. W. J., Cenci di Bello, I., Winchester, B., *Tetrahedron*, 1992, **48**, 10191
3. Fairbanks, A. J., Fleet, G. W. J.,, Jones, A. H., Bruce, I., Al Daher, S., Cenci di Bello, I., Winchester, B., *Tetrahedron*, 1991, **47**, 131.
4. Myerscough, P. M., Fairbanks, A. J., Jones, A. H., Choi, S. S., Fleet, G. W. J., Al-Daher, S. S., Cenci di Bello, I., Winchester, B., *Tetrahedron*, 1992, **48**, 10177
5. Choi, S., Bruce, I., Fairbanks, A. J., Fleet, G. W. J., Jones, A. H., Nash, R. J., Fellows, L. E., *Tetrahedron Lett.*, 1991, **32**, 5517.
6. Choi, S. S., Myerscough, P. M., Fairbanks, A. J., Skead, B. M., Bichard, C. J. F., Mantell, S. J., Fleet, G. W. J., Saunders, J., Brown, D., *J. Chem. Soc., Chem. Commun.*, **1992**, 1605; Wheatley, J. R., Bichard, C. J. F., Mantell, S. J., Son, J. C., Hughes, D. J., Fleet, G. W. J., Brown, D., *J .Chem. Soc., Chem. Commun.*, **1993**, in press.
7. Elliott, R. P., Fleet, G. W. J., Pearce, L., Smith, C., Watkin, D. J., Tetrahedron *Lett.*, 1991, **32**, 6227.
8. Fairbanks, A. J., Elliott, R. P., Smith, C., Taylor, H., Lamont, R. B., Watkin, D. J., Winchester, B. G., Fleet, G. W. J., in preparation.
9. Skead, B. M., Fleet, G. W. J., Saunders, J., Lamont, R. B., accompanying paper.
10. Haruyama, H., Takayama, T., Kinoshita, T., Kondo, M., Nakajima, M., Haneishi, T., *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1637; Nakajima, M., Itoi, K., Takamatsu, Y., Kinoshita, T., Okazaki, T., Kawakubo, K., Shindo, M., Honma, T., Tohjigamori, M., Haneishi, T., *J. Antibiot.*, **44**, 293 (1991).
11. Mizukai, K., Mio, S., Kawakubo, K., Honma, T., Shindo, M., *Chem. Abs.*, **114**, 81826 (1991); S. Mirza, *Chem. Abs.*, **114**, 8356 (1991).
12. Mio, S., Ichinose, R., Goto, K., Sugai, S., Sato, S., *Tetrahedron*, **47**, 2111 (1991); Mio, S., Kumagawa, Y., Sugai, S., *Tetrahedron*, **47**, 2133 (1991);Mio, S., Ueda, M., Hamura, M., Kitagawa, J., Sugai, S., *Tetrahedron*, **47**, 2145 (1991); Mio, S., Shiraishi, M., Sugai, S., Haruyana, H., Sato, S., *Tetrahedron*, **47**, 2121 (1991).
13. Mio, S., Sugai, S.,*Sankyo Kenkyusho Nenpo*, **43**, 133, (1991); Mio, S., Sano, H., Shindou, M., Honma, T., Sugai, S., *Agric. Biol. Chem.*, **55**, 1105 (1991).
14. Griffith, W. P., Ley, S. V., *Aldrichimica Acta*, 23, 13 (1990).
15. Fairbanks, A. J., Ford, P. S., Watkin, D. J., Fleet, G. W. J., *Tetrahedron Lett.*, 1993, **34**, 3327.
16. Fleet, G. W. J., Bruce, I., Girdhar, A., Haraldsson, M., Peach, J. M., Watkin, D. J., *Tetrahedron*, 1990, **46**, 19.
17. Spectrocopic and microanalytical data consistent with the proposed structures have been obtained for all new compounds reported in this paper.
18.The structure of the phenylhydantoin (2) was determined by X-ray crystallographic analysis.

19. Support from SERC (to AJF), Oxford Centre for Molecular Sciences (to JCS) and the AIDS Committee of the Medical Research Council (SSC) is gratefully acknowledged.

(Received in UK 7 June 1993; accepted 23 July 1993)