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IMINOHEPTITOLS AS GLYCOSIDASE INHIBITORS: SYNTHESIS OF AND SPECIFIC α-L-FUCOSIDASE INHIBITION BY β-L-HOMOFUCONOJIRIMYCIN AND 1-β-C-SUBSTITUTED DEOXYMANNOJIRIMYCINS

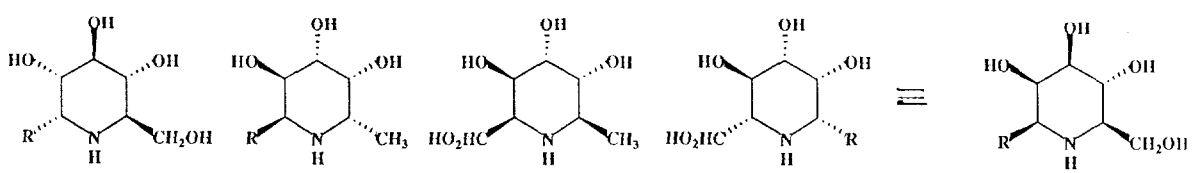
G. W. J. Fleet,[a] S. K. Namgoong,[a] C. Barker,[b] S. Baines,[b] G. S. Jacob[c] and B. Winchester[b,d]

[a]Dyson Perrins Laboratory and Oxford Centre for Molecular Sciences, Oxford University, South Parks Road, Oxford OX1 3QY, UK
[b]MRC Human Genetic Diseases Research Group, Biochemistry Department, King's College London, Campden Hill Road, London W8 7AH, UK
[c]Glycobiology Unit, Biochemistry Department, University of Oxford, Oxford OX1 3QU,
[d]Enzyme Section, Department of Clinical Biochemistry, Institute of Child Health (University of London), 30, Guilford Street, London WC1N 1EH, UK

Studies on the synthesis of, and specific α-L-fucosidase inhibition by, some 2,6-imino-2,6,7-trideoxy-iminoheptitols are described; none of the compounds showed significant mannosidase inhibition.

Both deoxynojirimycin (1) and α-homonojirimycin (2), the first example of a naturally occurring azapyranose analogue of a heptose recently isolated from Omphalea diandra L., are potent inhibitors of α-glucosidase activity.[1] Iminoheptitols such as (2) provide the opportunity for the synthesis of a class of stable aza-disaccharides such as (3) which may confer additional potency and/or specificity in comparison with the corresponding azapyranose analogues such as deoxynojirimycin; for example, the β-D-glucopyranosyl derivative (3) of α-homonojirimycin was first designed as a synthetic transition state inhibitor of α-glucosidases[2,3] and is in clinical trials in relation to the treatment of diabetes mellitus.[4]

Deoxyfuconojirimycin (DFJ) (4), readily prepared from D-lyxonolactone,[5] is a very powerful and highly specific inhibitor of a number of mammalian α-L-fucosidases; some fucosidase inhibitors may have potential as antiretroviral agents.[6] This paper describes an attempted synthesis of α-L-homofuconojirimycin (5), the azaheptose analogue of DFJ (4), which resulted in the synthesis of 6-epi-α-L-homofuconojirimycin (6); the preparations of β-L-homofuconojirimycin (7), which may also be considered as β-methyl deoxymannojirimycin, together with β-ethyl (8) and β-phenyl (9) derivatives



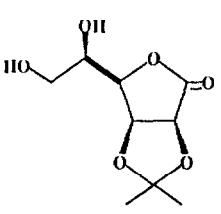
(1) R=H
(2) R=CH_2OH
(3) R=$CH_2O\beta$glucopyranosyl

(4) R=H
(5) R=CH_2OH

(6)

(7) R=Me β-L-homofuconojirimycin
(8) R=Et β-1-C-ethyl-deoxymannojirimycin
(9) R=Ph β-1-C-phenyl-deoxymannojirimycin
(10) R=H

of deoxymannojirimycin (10), are also reported. The three contiguous chiral centres bearing the the secondary hydroxyl groups on the piperidine rings of both DFJ (4) and deoxymannojirimycin (DMJ) (10) are the same and DMJ has been shown to inhibit bovine α-L-fucosidase[7] as well as mannosidase I of glycoprotein processing; this paper also examines the ability of these compounds to act as inhibitors of glycosidases.



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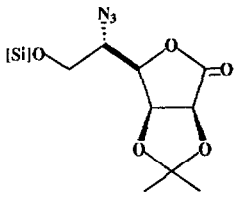

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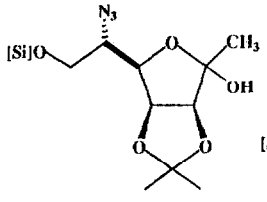

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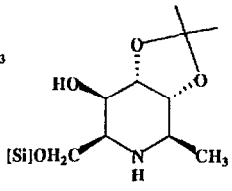

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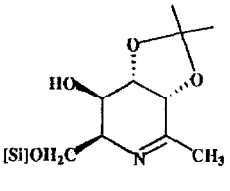

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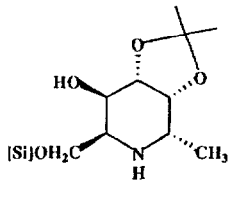

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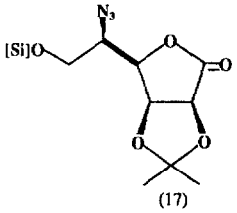

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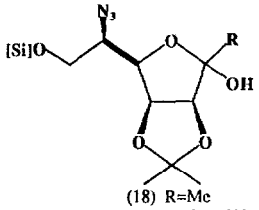
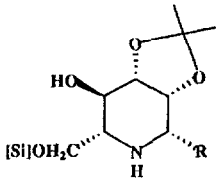


(18) R=Me
(19) R=CH=CH$_2$
(20) R=Ph



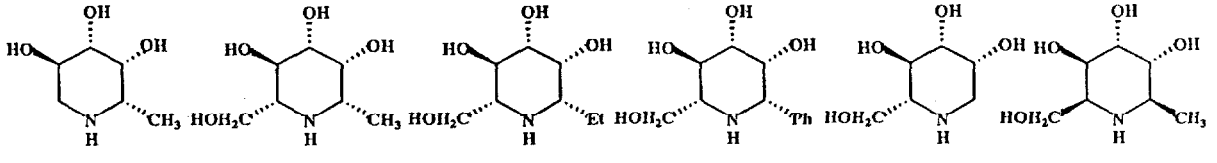
(21) R=Me
(22) R=Et
(23) R=Ph

[Si]=SiMe$_2$t-Bu

Synthetic work. The syntheses of the iminoheptitols were achieved by intramolecular reductive aminations by hydrogenation of protected 6-azido-6-deoxy-heptul-2-oses. An attempted synthesis of α-L-homofuconojirimycin (5) resulted in the preparation of the epimeric compound (6). The partially protected mannonolactone (11), m.p. 131°-132°C [lit.[8] m.p. 133°C], was reacted with tert-butylchlorodimethylsilane (in order to protect the primary hydroxyl group), esterified with trifluoromethanesulphonic anhydride and then treated with azide ion to afford the azidolactone (12) as an oil, $[\alpha]_D^{20}$ +78.5° (c, 1.56 in $CHCl_3$), [65% yield from (11)]. Reaction of (12) with methyl lithium in tetrahydrofuran gave the protected heptulose (13) [82% yield] which on hydrogenation in ethyl acetate in the presence of platinum oxide gave a single major product (14), m.p. 98°-99°C, $[\alpha]_D^{20}$ +40.7° (c, 1.17 in $CHCl_3$), in 47% yield; the approach of hydrogen to the carbon-nitrogen double bond of the intermediate imine (15) was determined by the protected hydroxymethyl substituent on the piperidine ring, rather than the isopropylidene group. The stereochemical result of the hydrogenation of the intermediate imine (15) was indicated by the coupling constants in the free base (6) [$J_{5,6}$ = 10.3 Hz] and in the hydrochloride of (6) [$J_{5,6}$ = 10.7

Hz] showing the trans-diaxial relationship betweeen H-5 and H-6. No compound corresponding to (16), which would lead to α-L-homonojirimycin (5) and which would be formed if either complexation to the free hydroxyl group or the steric bulk of the isopropylidene ketal function in (15) controlled the stereochemistry of the addition of hydrogen, was isolated from the reaction; reduction of the imine intermediate (15) appears to be determined solely by steric bulk, rather than by chelation of any of the oxygen functions to the heterogeneous catalyst.[9,10] Removal of the protecting groups in (14) by aqueous trifluoroacetic acid in quantitative yield gave (6),[11] m.p. 61°-64°C, $[\alpha]_D^{20}$ +40.3° (c, 0.90 in H_2O), which formed an easily crystallised hydrochloride, m.p. 190°-192°C.

Short syntheses of β-L-homofuconojirimycin (7) and the other 1-β-C-substituted deoxymannojirimycins (8) and (9) began from the azidolactone (17).[12] Thus addition of methyl lithium to (17) gave the adduct (18) in 72% yield which on hydrogenation in the presence of a catalyst of platinum(IV) oxide gave a single piperidine (21), m.p. 93°-94°C, $[\alpha]_D^{20}$ -47.3° (c, 1.06 in $CHCl_3$), in 86% yield. Both the silyl and isopropylidene protecting groups were removed from (21) to give β-L-homofuconojirimycin [β-1-C-methyl deoxymannojirimycin] (7),[13] m.p. 97°-98°C, $[\alpha]_D^{20}$ -21.5° (c, 1.07 in H_2O), in 95% yield. Addition of vinyl magnesium bromide to azidolactone (17) gave the monoadduct (19) (90%) which on hydrogenation gave (22), m.p. 55°-56°C, $[\alpha]_D^{20}$ -37.7° (c, 1.26 in $CHCl_3$), in 80% yield. Subsequent acid hydrolysis of (22) gave β-1-C-ethyl deoxymannojirimycin (8),[14] m.p. 54°-56°C, $[\alpha]_D^{20}$ -6.5° (c, 1.07 in H_2O), in 95% yield. Similarly, addition of phenyl magnesium bromide to (17) gave (20) (86% yield) which on hydrogenation gave (23), m.p. 86°-87°C, $[\alpha]_D^{20}$ 0.0° (c, 1.05 in $CHCl_3$), in 81% yield; hydrolytic removal of the protecting groups afforded β-1-C-phenyl deoxymannojirimycin (9),[15] m.p. 77°-79°C, $[\alpha]_D^{20}$ +62.0° (c, 0.57 in H_2O), in 90% yield. For each of the protected heptitols the small value of the coupling constant between H-1 and H-2 ($J_{1,2}$ 2.5-2.6 Hz) in contrast to that between the trans-diaxial protons, H-4 and H-5 ($J_{4,5}$ = 10.0-10.1 Hz) indicates a cis relationship between H-1 and H-2; thus the hydrogenation of the C=N proceeds consistently and exclusively from the least hindered face.



Ki for inhibition of human liver α-L-fucosidase catalysed hydrolysis of 4-umbelliferyl α-L-fucopyranoside

Glycosidase Inhibition. The compounds were assayed as inhibitors of 12 human liver glycosidases.[16] All the compounds prepared were potent and specific competitive inhibitors of human liver α-L-fucosidase (see figure); thus the introduction to DFJ (4) of an anomeric hydroxyl group with the wrong configuration to give β-L-

homonojirimycin (7) did not diminish the inhibition of α-L-fucosidase. When the methyl group in (7) was substituted for ethyl, it was found that ß-ethyl DMJ (8) was still a very powerful fucosidase inhibitor. Even ß-phenyl DMJ (9), with the methyl group substituted by a large aromatic group, is a more potent fucosidase inhibitor than is DMJ (10), where the methyl group is replaced by hydrogen. The 6-epi-α-L-homonojirimycin (6), with the correct anomeric hydroxyl group but with the wrong stereochemistry of the methyl group, is 500 times weaker an inhibitor than is (7) with the correct methyl chirality but the wrong anomeric configuration. It is noteworthy that only DMJ (10) showed any inhibition of mannosidase activity; none of the other compounds caused any significant inhibition of mannosidase activity. Since none of the alkylated deoxymannojirimycins are mannosidase inhibitors but all are fucosidase inhibitors, it is apparent that the ability of derivatives of DMJ (10) to inhibit mannosidases is highly sensitive to substituents at the C-1 position. A full account of the inhibition of glycosidases by these compounds will be published elsewhere.[17] Further attempts to synthesise α-L-homofuconojirimycin (5) are in progress.[18]

REFERENCES

1. Kite, G. C., Fellows, L. E., Fleet, G. W. J., Liu, P. S., Scofield, A. M., Tetrahedron Lett., 1988, 29, 6483.
2. Liu, P. S., J. Org. Chem., 1987, 52, 4717.
3. Anzereno, P. B., Creemer, L. J., Daniel, J. K., King, C.-H. R., Liu, P. S., J. Org. Chem., 1989, in press.
4. Rhinehart, B. L., Robinson, K. M., Liu, P. S., Payne, A. J., Wheatly, M. E., Wagner, S. R., J. Pharmacol. Exptl. Therapeut., 1987, 241, 915.
5. Fleet, G. W. J., Petursson, S., Campbell, A., Mueller, R. A., Behling, J. R., Babiak, K. A., Ng, J. S., Scaros, M. G., J. Chem. Soc., Perkin Trans. 1, 1989, 665.
6. Fleet, G. W. J., Karpas, A., Dwek, R. A., Fellows, L. E., Tyms, A. S., Petursson, S., Namgoong, S. K., Ramsden, N. G., Smith, P. W., Son, J. C., Wilson, F. X., Witty, D. R., Jacob, G. S., Rademacher, T. W., FEBS Lett., 1988, 237, 128; Karpas, A., Fleet, G. W. J., Dwek, R. A., Petursson, S., Namgoong, S. K., Jacob, G. S., Rademacher, T. W., Proc. Nat. Acad. Sci. US, 1988, 85, 9229.
7.Evans, S. V., Fellows, L. E., Shing, T. K. M., Fleet, G. W. J., Phytochemistry, 1985, 24, 1953.
8. Barker, S. A., Bourne, E. J., Pinkard, R. M., Whiffen, D. H., Chem. Ind., 1958, 758; Heilbron's Dictionary of Org. Compounds, Vol. 4, p.3629, Chapman and Hall, 1982.
9. Brown, J. M., Angew. Chem. Int. Ed. Eng., 1987, 26, 190.
10. Bartok, M., Czombos, J., Felfordi, K., Gera, L., Gondos, G., Molnar, A., Notheisz, F., Palinko, I., Wittmann, G., Zsigmond, A. G., Stereochemistry of Heterogeneous Metal Catalysis, Wiley, Chichester, 1985.
11. For (6), δ_C (D_2O): 71.82, 71.51, and 70.15 (3 x d, C-3, C-4 and C-5), 61.83 (t, C-1), 55.34 and 50.92 (2 x d, C-2 and C-6), 17.56 (q, C-7).
12. Fleet, G. W. J., Ramsden, N. G., Witty, D. R., Tetrahedron, 1989, 45, 319; Fleet, G. W. J., Ramsden, N. G., Witty, D. R., Tetrahedron Lett., 1988, 29, 2871.
13. For (7), δ_C (D_2O): 76.13, 73.17, and 68.91 (3 x d, C-2, C-3 and C-4), 61.58 (t, C-6), 60.82 and 53.08 (2 x d, C-1 and C-5), 17.13 (q, Me).
14. For (8), δ_C (D_2O): 76.21, 70.42, and 69.14 (3 x d, C-2, C-3 and C-4), 61.61 (t, C-6), 60.95 and 59.17 (2 x d, C-1 and C-5), 24.19 (t, $\underline{C}H_2Me$), 10.66 (q, Me).
15. For (9), δ_C (D_2O): 140.70 (s, Ph), 129.72, 128.58 and 127.87 (3 x d, Ph), 76.31, 74.41 and 69.10 (3 x d, C-2, C-3 and C-4), 61.78 (t, C-6), 61.54 and 61.20 (2 x d, C-1 and C-5).
16. For assay methods, see Daher, S. A., Fleet, G., Namgoong, S. K., Winchester, B., Biochem. J., 1989, 258, 613.
17. Winchester, B., Barker, C., Baines, S., Jacob, G. S., Namgoong, S. K., Fleet, G. W. J., in preparation.
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