COVER FEATURE

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Recipient of the RSC Haworth Lectureship

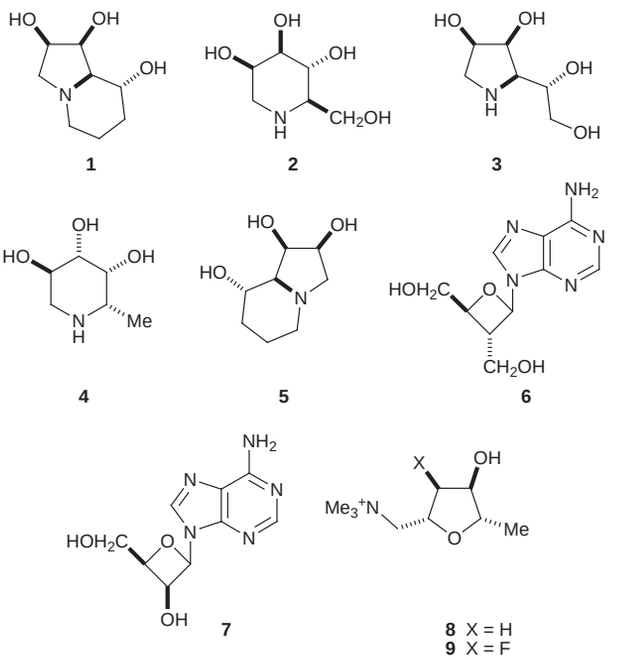
Career

Magdalene College Cambridge BA 1965, PhD 1969. Postgraduate studentship with Dr Ian Fleming. MRC Postdoctoral Fellowship 1968, Oxford, with Professor Rodney Porter and Dr Jeremy Knowles, Harvard University Fellowship and Fullbright Travel Scholarship 1972 with Professor E. J. Corey University of Oxford since 1973, currently Professor and Tutorial Fellow of St Johns College. Pfizer award for organic synthesis, 1984; Pfizer award for organic synthesis, 1985; RSC Bader Award for Organic Synthesis 1995. Author of over 290 papers and published US patents.

Research

Our first publications in carbohydrate chemistry were the total syntheses of pseudomonic acid[1] (with the side chain from L-arabinose and the tetrahydropyran ring from D-arabinose), shikimic acid[2] and swainsonine **1**[3] (from mannose), and an inelegant synthesis of deoxymannojirimycin **2**[4] from glucose. The alkaloid syntheses started a long standing collaboration initially with Linda Fellows at Kew Gardens, and continued with Rob Nash at the BBSRC Institute of Grassland and Environmental Research on the design and evaluation of amino sugar mimics. The synthetic materials DIM **3**[5] and DFJ **4**[6] were found to be very powerful and specific inhibitors of α-D-mannosidases and α-L-fucosidases respectively. Such structures possess specific recognition arising from the ring substituents and stereogenic centres, and also have a basic nitrogen which can bind in a protonated form in the active site of an enzyme; most enzymes that handle carbohydrates make or break glycosidic bonds, so it is no surprise that azasugars provide a wide ranging family of inhibitors. The ease of access to, and protection of, sugar lactones considerably simplified our approach to a number of different sugar mimics, leading to a highly efficient synthesis of both 2 and its mirror image from L- and D-gulonolactone, respectively.[7] There are interesting structure–activity relationships between enantiomeric inhibitors; thus while D-swainsonine **1** is a very potent naturally occurring α-D-mannosidase inhibitor, the synthetic L-swainsonine **5** is the most potent L-rhamnosidase inhibitor yet described.[8] We have also studied many other sugar analogues; for example, a convenient synthesis of oxetanes from γ-lactones allowed the synthesis of the natural product oxetanocin **6**[9] and the development of the analogue **7**[10] with much the same biological activity. A general synthesis of tetrahydrofuran carboxylates from both γ- and δ-lactones under either acidic or basic conditions provided an efficient synthesis of muscarine **8** and its analogues, including the fluoromuscarine **9**[11] with much the same biological properties as muscarine itself. Some of the early synthetic[12] and biological[13] work has been reviewed.

Our present projects include a range of mimics of carbohydrate containing natural products. Thus the L-rhamnose analogue **10** is just as cytotoxic as the natural product spicamycin **11**[14] and may have promise as an anti-tumour material with a highly novel mode of action. 6-C-Substituted alkylhexoses, such as the epimeric mannose compounds **12**, are a new set of carbohydrate analogues which inhibit various enzymes involved in the primary metabolism of carbohydrates.[15] Mycobacterial cell walls contain a number of carbohydrates (D-arabinofuranose, D-galactofuranose and L-rhamnose) which play no role in mammalian metabolism; thus, a new chemotherapeutic strategy for the treatment of tuberculosis, leprosy and other diseases caused by mycobacteria would involve the development of inhibitors of enzymes associated with the biosynthesis or incorporation of those sugars into the cell walls. We have reported the first inhibitors of UDP-Gal mutase and mycobacterial galactan biosynthesis by pyrrolidine analogues of galactofuranose, such as **13**;[16] divergent bicyclic lactones such as **14**[17] and **15**[18] may be useful intermediates for the



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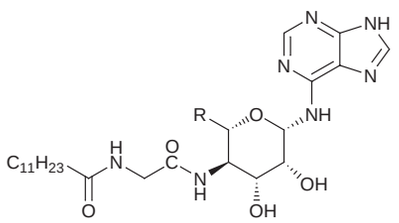
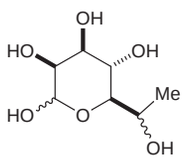
incorporation of such structural motifs into combinatorial libraries. Rigid bicyclic L-fucose mimics such as **16**[19] and **17**[20] are being used to generate potential libraries of fucosyl transferase and fucosidase inhibitors.



10: R = Me **11** R = $HOH_2C.CH(OH)$-



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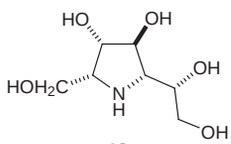

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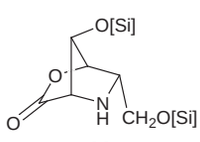

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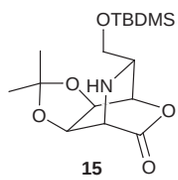

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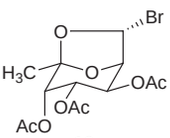

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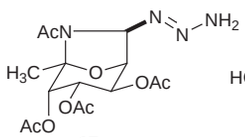

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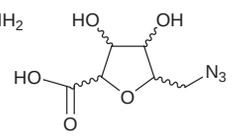

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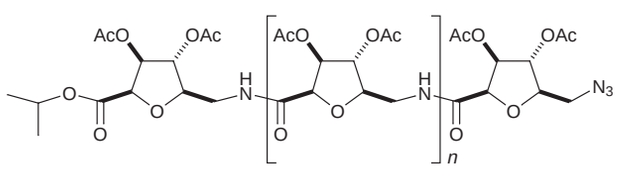
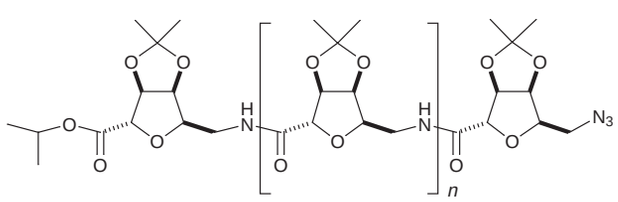
The sixteen stereoisomeric azidoacids **18** provide a family of monomers that in preliminary studies appear to generate a range of secondary structures in short peptidomimetic sequences which might lead to novel compounds with interesting biological activities. Thus the tetramer **19** and hexamer **20** form β-turn-like structures (Fig. 1),[21] whereas the octamer **21**[22] and hexadecamer **22** produce left-handed α-helices (see lower structure on cover). A prediction for the formation of right-handed α-helices by another stereoisomer is currently being tested.



19 *n* = 2 **20** *n* = 4



21 *n* = 6 **22** *n* = 14

We consider that the use of sugars to generate relatively small molecules has a number of attractions, including the particular virtue of structural diversity; the use of such materials in generating libraries has yet barely started and should produce both random and partially rational compounds with biological activity.

Acknowledgements

I am indebted to my group over the years for their enthusiasm, hard work and experimental skill, and also for most of the successful ideas; it has been a pleasure to work with them.

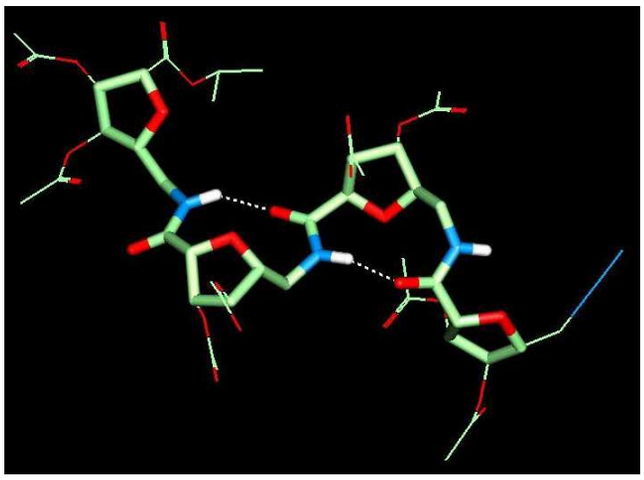


Fig. 1

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