

The synthesis of ketose nucleosides, in general, have not been extensively explored. Most notable examples include psicofuranine and decoyinine which exhibit antibacterial and antitumour activity. The closely related β -D-fructose analogues of these compounds were not synthesised prior to this study. Such analogues might also be regarded as 1-substituted arabinose derivatives and hence related to 9- β -D-arabinofuranosyl adenine which is an active antiviral agent. The aim of the project was to explore synthetic routes to β -D-fructofuranosyl nucleosides with the objective of obtaining novel antiviral agents from inexpensive starting materials.

A variety of routes to β -D-fructofuranosyl imidazole and purine nucleosides have been explored which may be subdivided as follows:

i) Direct condensation of a heterocyclic base with a derivative of D-fructofuranose.

ii) Stereospecific synthesis via D-fructofuranosyl fused oxazolidine-2-thione. The direct condensation strategy involving 6-chloropurine and 1,3,4,6-tetra-O-benzoyl-D-fructofuranose in the presence of Mitsunobu reagents yielded 9- α -D-fructofuranosyl-6-chloropurine; the stereospecificity resulting from the neighbouring participation of the benzoyl group. In contrast, Mitsunobu conditions yielded anomeric mixtures when 1,3,4,6-tetra-O-benzoyl-D-fructofuranose was condensed with phenols, alcohols and primary amine. The direct condensation strategy was extended by replacing O-benzoyl protection by non participating O-benzyl groups. A variety of conditions, well known in nucleoside chemistry, were explored to condense either 2-chloro 2-O-acyl 1,3,4,6-tetra-O-benzyl-D-fructofuranosyl derivatives with purine bases. All attempts proved unsuccessful. However, application of Mitsunobu reaction involving 1,3,4,6-O-benzyl-D-fructofuranose and 6-chloropurine in the presence of DIAD and TPP gave an anomeric mixture of 9-D-fructofuranosyl-6-chloropurine which were separated by chromatography. This constitutes the first synthesis of a β -D-fructofuranosylpurine. 1,3,4,6-O-Benzyl-9- β -D-fructofuranosyladenine was synthesised by amination of the corresponding 6-chloropurine nucleoside. Removal of the protecting benzyl group was achieved by catalytic hydrogenation with palladium on charcoal using hydrazine hydrate as the hydrogen source.

A detailed study of D-fructofuranosyl oxazolidine-2-thiones proved very rewarding. Synthetic routes and reaction conditions have been developed which enable a choice of either 1',2'- or 2',3'-(6'-O)-trityl- β -D-fructofuranosyl oxazolidine-2-thiones to be obtained cheaply and in high yield. Such derivatives have the potential to be used in variety stereospecific syntheses thus providing interesting new chiral templates, which may be used for a variety of applications in

stereospecific synthesis. In adherence to the theme of synthesising β -D-fructofuranosyl purines, the oxazolidine-2-thiones were each reduced by Raney nickel and the respective oxazolidines so formed reacted with aminocynoacetamide (and amino-malononitrile). The resulting 5-amino-6'-O-trityl- β -D-fructofuranosyl imidazole-4-carboxamide and 5-amino-6'-O-trityl- β -D-fructofuranosyl imidazoles were cyclised with triethylorthoformate and acetic anhydride to yield, after deprotection, 9- β -D-fructofuranosylhypoxanthine and 6-amino-9-(β -D-fructofuranosyl)purine respectively. This route could be conveniently extend to other purines. It is stereospecific, economical and offers convenient derivatisation at any position on the sugar moiety. Thus the protection strategies discovered permit, potentially, convenient synthesis of, such as, deoxy and azido derivatives and synthetic incorporation into nucleic acids. The oxazolidine-2-thione and oxazoline derivatives also offer potential for other stereochemical modifications to made to the D-fructofuranosyl nucleus and hence may find a variety of other applications.