SYNTHESIS OF 2'-[F-18]FLUORO-2'-DEOXY-ß-D-ARABINOFURANOSYL NUCLEOSIDES

T.J. Mangner[1], R. Klecker[2], L. Anderson[2] and A. Shields[3]

[1]Children's Hospital of Michigan, PET Center, Wayne State University, 3901 Beaubien Blvd, Detroit, MI 48201, [2]U.S. Food and Drug Administration, Laboratory of Clinical Pharmacology, Rockville, MD 20850, [3]Karmanos Cancer Institute, Harper Hospital, Wayne State University, Detroit, MI 48201.

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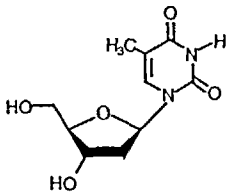
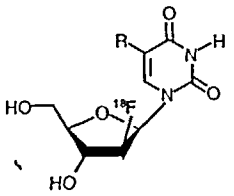
As part of an ongoing effort to develop PET imaging agents for use in tumor detection and/or to monitor response to chemotherapy, several 2'-[F-18]fluoro-2'-deoxy-β-D-arabinofuranosyl nucleosides were prepared: **1a** (FAU), **1b** (FMAU) and **1c** (FIAU). These analogs of thymidine are substrates for thymidine kinase, a key enzyme of DNA synthesis.



Thymidine

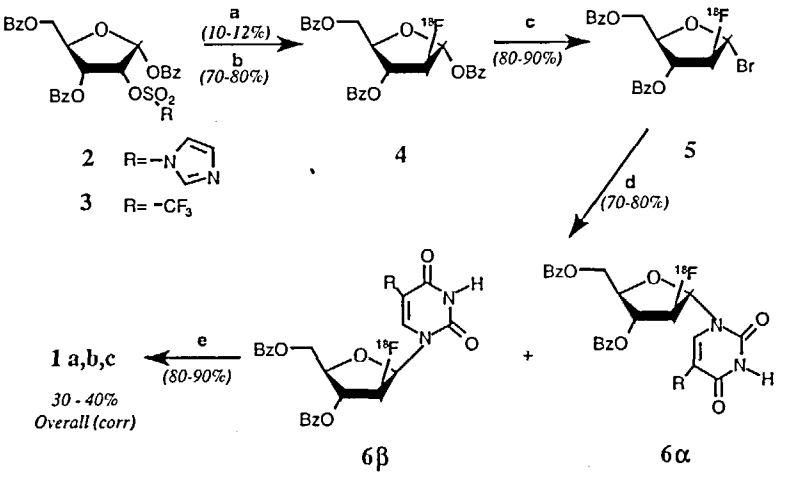


1a R= -H
1b R= -CH_3
1c R= -I

The overall synthetic approach to these compounds is based on that published by Howell et al (1, 2) for the unlabelled compounds (Scheme 1). Initially, the tribenzoylated [F-18]fluorinated arabinose 4 was prepared in low yield (10 - 12% decay corrected) from the sulfonyl imidazole 2 with [F-18]fluoride and KHF_2 in butanediol at 160°C for 20 min. Use of the triflate 3, however, with kryptofix-assisted radiofluorination, proved to be a more efficient approach to 4. After examining a variety of polar, aprotic solvents (MeCN, DMF, DMSO) and reaction temperatures for the nucleophilic radiofluorination of the triflate 3, reaction conditions were developed ([F-18]fluoride/KRP/K_2CO_3 in DMF for 5 min at 150°C) that consistently provide 4 in radiochemical yields of 70 - 80% (decay corrected). Following the radiofluorination reaction, the DMF is evaporated and the residue, dissolved in methylene chloride, is passed through a small silica gel column to remove the kryptofix and any unreacted [F-18]fluoride. The product is then eluted from the column with a small volume of methylene chloride.

The protected [F-18]fluorinated arabinose 4 is converted to the dibenzoyl bromide 5 in excellent radiochemical yield (80 - 90% corr) by treatment with HBr/AcOH in CH_2Cl_2 for 10 min at 125°C. Following the bromination, evaporation of the CH_2Cl_2 at 125°C and final removal of any residual traces of HBr and acetic acid with the aid of a toluene azeotrope provides 5 as a dark oil ready for conversion to a number of protected arabinofuranosyl nucleoside analogs.

Scheme 1



Reaction Conditions: a) (with 2) [F-18]fluoride, KHF_2, in butanediol, 160°C for 20 min; b) (with 3) [F-18]fluoride, KRP 2.2.2, K_2CO_3, in DMF, 150°C for 5 min; c) HBr/AcOH in CH_2Cl_2, 125°C for 10 min; d) bis(Me3Si)uracil (a) or bis(Me3Si)thymine (b) or bis(Me3Si)-5-iodouracil (c) in $CHCl_3$, 150°C for 30 min; e) NaOMe/MeOH in MeCN, 20°C for 10 min, followed by semi-prep HPLC (C-18, 10% EtOH).

Condensation of 5 with several bis(trimethylsilyl)pyrimidines give the corresponding dibenzoyl arabino nucleosides 6 a,b,c as a mixture of the α and β isomers in excellent radiochemical yields. The ratio of β to α is dependent on the polarity of the reaction solvent. In line with a published report (2), when the condensation of 5 with a silylated uracil is carried out in MeCN (at 150°C for 30 min), the ratio of the desired β isomer to the unwanted α isomer is approximately 3 to 1. Under similar conditions in methylene chloride, this ratio increases to 4 to 1, and in chloroform (the solvent currently being employed) this ratio is approximately 8 to 1. Following the condensation reaction, 6 (as an isomeric mixture) is isolated by passing the reaction mixture through a small silica gel column, washing the column with methylene chloride and eluting the product with chloroform containing 1% ethanol. The chloroform is then removed by evaporation and crude 6 is dissolved in MeCN for the final deprotection reaction.

The benzoyl groups of the isomeric mixture **6** are cleanly removed by treatment with sodium methoxide (0.5M in MeOH) in MeCN (20°C for 10 min) to give, in excellent yield (80 - 90% corr), the corresponding mixture of α and β isomers of **1**. The desired β isomer is then isolated by semi-prep HPLC (C-18, 10% EtOH) in a decay-corrected overall radiochemical yield of 30 - 40% from [F-18]fluoride.

Each of these compounds have been prepared several times for initial imaging studies. In a typical synthesis, approximately 20 mCi of labelled product is obtained starting from approximately 200 mCi of [F-18]fluoride. Currently, the synthetic sequence takes a total of 3.5 hours, owing primarily to the time required for the bromination and condensation reactions. Efforts are currently underway to reduce the overall synthesis time and complexity by exploring alternative routes from **4** to **6**.

References

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