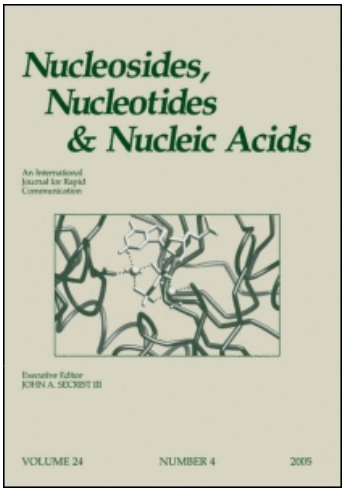

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Synthetic Strategies Towards the Synthesis of 1-(2,4-Dideoxy-4-C-hydroxymethyl-α-L-Lyxopyranosyl)base Nucleosies.

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SYNTHETIC STRATEGIES TOWARDS THE SYNTHESIS OF 1-(2,4-DIDEOXY-4-C-HYDROXYMETHYL-α-L-LYXOPYRANOSYL)BASE NUCLEOSIDES.

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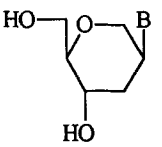
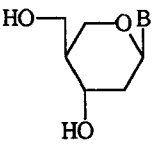
Abstract: A synthetic strategy towards the synthesis of 1-(2,4-dideoxy-4-C-hydroxymethyl-α-L-lyxopyranosyl)thymine by the formation and opening of a 3,4-anhydropentopyranose sugar is described.

1,5-Anhydrohexitol nucleosides (1) in which the natural furanosyl sugar has been replaced by a six membered ring are promising antiviral agents[1,2]. To invesitgate the structure activity relationship and effect upon the strong hybridisation properties observed by 1',5'-anhydrohexitol nucleic acids incorporated within oligonucleotides[3], a series of 1-(2,4-dideoxy-4-C-hydroxymethyl-α-L-lyxopyranosyl)nucleosides (2) were desired.



(1)

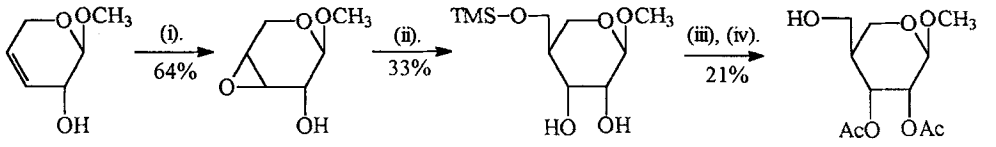


(2)

B = Heterocyclic Base eg thymine or adenosine.

The key to this synthesis involves the introduction of a hydroxymethyl moiety onto the C4-carbon of a pyranose sugar. This has previously been achieved by displacement of a C4-O-triflate group by the sodium salt of diethylmalonate[4] and via the formation of a C4-exocyclic vinylic intermediate by either a Peterson olefination or Wittig reaction upon the C4-ketone[4]. In this synthesis the use of an epoxide intermediate was investigated.

Reaction of the 3,4-vinyl-pentapyranoside (**3**) with meta-choroperoxybenzoic acid resulted in the formation of a mixture of the β-D- (**4**) and α-L-methyl-3,4-anhydropentapyranoses in a ratio of 6:2 respectively. These isomers could be separated by column chromatography. The methyl 3,4-anhydro-β-D-anhydropentopyranose (**4**) upon reaction with the higher order cuprate of trimethylsilylmethyllithium ($(TMS\text{-}Si)_2Cu(CN)Li_2$) gave the desired methyl-4-deoxy-4-trimethylsilylmethyl-α-L-lyxopyranoside (**5**) in moderate yield. Methyl-3-deoxy-3-trimethylsilylmethyl-β-D-xylopyranoside and unreacted starting material were also recovered. Upon protection, bromination followed by oxidative cleavage of the silyl group gave the desired 4-deoxy-4-hydroxymethyl-α-L lyxopyranoside structure (**6**) which can be further converted into the nucleoside.



(3) (4) (5) (6)

Reagents: i. mCPBA, CH_2Cl_2. ii. $((CH_3)_3SiCH_2)_2Cu(CN)Li_2$, $Ti(OiPr)_4$, THF; H_2O. iii. Ac_2O, Pyr. iv. KBr, AcO-OH, AcOH; $HClO_4$.

In summary, this paper reports a strategy for the introduction of a hydroxymethyl moiety onto the C4-position of an α-L-lyxopyranoside sugar by means of an epoxide. These methods have not yet been fully optimised, full results and procedures will be published at a future date.

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