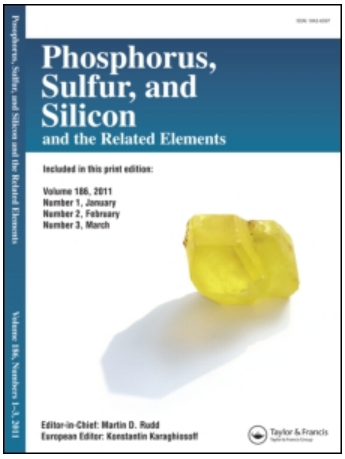

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A STEREOSELECTIVE SYNTHESIS OF TWO 2-DEOXY-3-PHOSPHASUGARS EPIMERIC AT PHOSPHORUS

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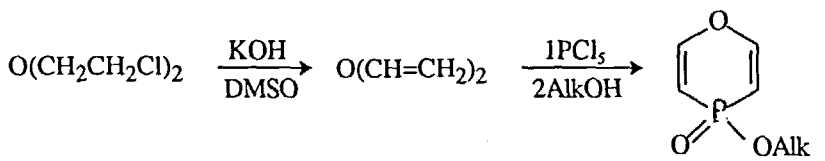
Abstract A synthetic route to 2-deoxy-3-phosphasugar derivatives utilising a stereoselective addition of a phosphinate to an aldehyde is described.

Monosaccharides are fundamental building blocks in all living systems. They are also stereochemically complex and not often targets of total synthesis with some notable and marvellously elegant exceptions [1]. Their biological ubiquity suggests that heterosugars should be attractive targets as biologically active molecules, particularly those that are isosteric or nearly so. Phosphasugars have attracted considerable attention over the past twenty years, particularly by Japanese [2] and more recently Polish [3] workers who have synthesised a wide range of derivatives in which the hemiacetal oxygen or C, of an existing sugar was replaced by P(O)R. The substituent, R, is often aryl or alkyl which would diminish any isosteric behaviour but which is synthetically more convenient. The best replacement for CHOH would be HP(O) but it would be technically difficult to carry this group through a synthesis. However, the conversion AlkOP(O)→HP(O) is known [4] and the ester group is more easily handled. We wished to development methods for the synthesis of phosphapentoses and hexoses in which CHOH was replaced by AlkOP(O) as a first step to isosteric phosphasugars, few of which are known. Initially we sought to use Sharpless's powerful stereoselective epoxidation route beginning with the readily available heterocyclic [5] (Figure 1)



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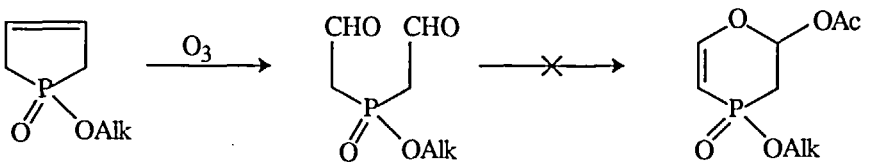
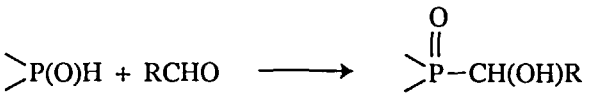
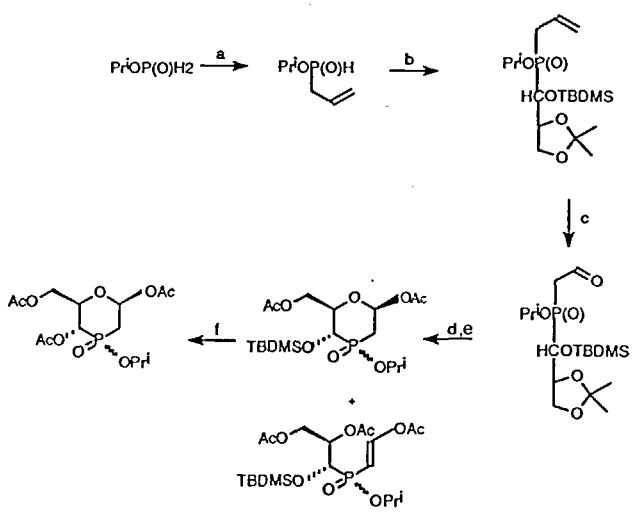
but this molecule turns out to be essentially inert under any of the oxidative conditions we examined. Attempts to prepare mono-unsaturated precursors eg



were also unsuccessful and we decided to examine the stereochemical consequences of the addition reaction:



in the hope of being able to control the stereochemical outcome by varying the substituents on the two components. After much trial and error, a successful pathway has been found and is outlined in the Scheme.



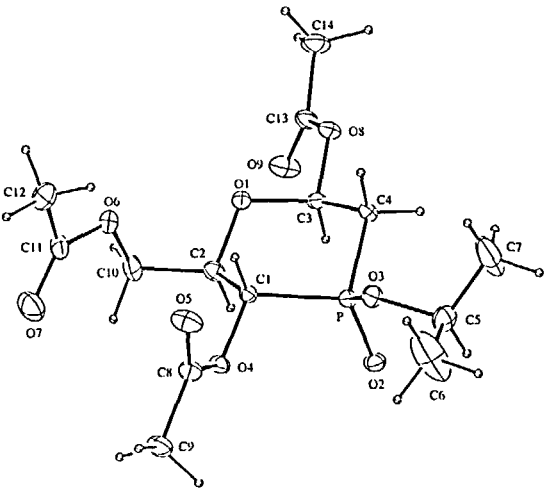
SCHEME a.Et_3N,CH_2=$CHCH_2Br$ b.Et_3N,(R)glyceraldehyde acetonide, t-BuMe_2SiCl
c.O_3,Me_2S d. CF_3CO_2H,H_2O,THF e. Ac_2O,Py,DMAP f. KF,18-crown-6,Ac_2O

Though chromatographic separations are necessary the route has a reasonable overall yield (20-30% based on R-glyceraldehyde) and optical purity is good, so it provides a practical route to 0.5-1.0g quantities of pure P-epimers as their acetates.

An interesting feature of the reaction sequence is the high stereoselectivity in the addition of the phosphinate to the aldehyde. Since we could only detect two P-epimers by

TLC and ^{31}P nmr we assume an *ee* of ≥95%. No steric preference occurs at phosphorus. Though the intermediate in the addition appears less crowded in the enantiomer leading to the S-isomer, such a high stereoselectivity seems surprising. Selectivity at C in the acetates is reasonably attributable to base-catalysed epimerisation to give the more stable equatorial acetate.

Overall stereochemistry in the sequence is confirmed by an X-ray structure of the only crystalline product obtained.



We hope to extend this study to other pentoses and hexoses and to a clearer understanding of the origins of selectivity in the addition step. We have examined many other additions with very little evidence of substantial selectivity.[6]

ACKNOWLEDGEMENT

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