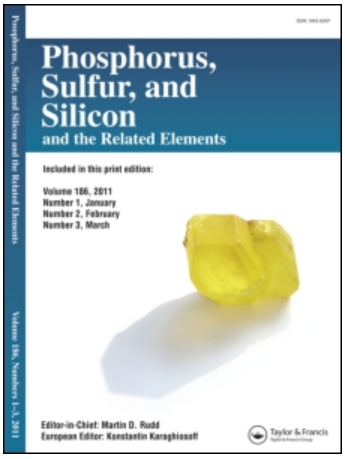

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Enantioselective Syntheses of the Methylene- and Fluoromethylene-Phosphonate Analogues of 3-Phospho-D-Glyceric Acid

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ENANTIOSELECTIVE SYNTHESES OF THE METHYLENE- AND FLUOROMETHYLENE-PHOSPHONATE ANALOGUES OF 3-PHOSPHO-D--GLYCERIC ACID

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The racemic methylene analogue of 3-phospho-D-glyceric acid[1-4] has been shown to be a viable substrate for the combined action of 3-phosphoglycerate kinase, PGK, and glyceraldehyde 3-phosphate dehydrogenase, GPD. We have shown that replacement of CH_2 by CHF or CF_2 in a variety of nucleotide analogues[4,5] can lead to improved performance as enzyme substrates or inhibitors. We have therefore undertaken enantiospecific syntheses of the methylene- and fluoromethylene-analogues of 3-phospho-D-glyceric acid to investigate their interaction with PGK and GPD and explore whether the fluorine atom in the latter can mimic an oxygen lone-pair in binding to enzymes.

The syntheses utilise C-4 of a D-pentose precursor as the source of C-2 in the phosphoglycerate analogue. Later stages in the synthesis may be adapted to make analogues of 3-phospho-D-glycerol and or D-glyceraldehyde 3-phosphate.

The D-pentose (ribose and lyxose are used) is appropriately protected, oxidised, and condensed with tetraethyl lithiofluoromethylenebis-phosphonate[6-8] to give a fluorovinylphosphonate, exclusively as the (*E*)-isomer. Stereoselective reduction gives predominantly a single diastereoisomer product which, after deprotection, oxidation of the *vic*-diol, and de-esterification of the phosphonate ester, provides the requisite 4-fluoro-2-(*R*)-hydroxy-4-phosphonobutanoic acid product.

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