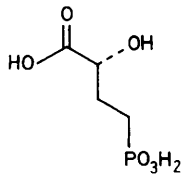
Enantiospecific Syntheses of the Methylene- and α-Fluoromethylene-Phosphonate Analogues of 3-Phospho-D-Glyceric Acid

G. Michael Blackburn* and Abdul Rashid

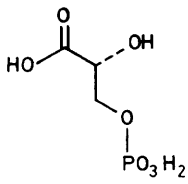
Department of Chemistry, The University, Sheffield S3 7HF, U.K.

An enantioselective synthesis is described for the preparation of 2-(*R*)-3-carboxy-3-hydroxypropane-1-phosphonic acid (**1**), an isosteric analogue of 3-phospho-D-glyceric acid (**2**), from D-lyxose; the route is extended to provide a stereoselective synthesis of one diastereoisomer of 2-(*R*)-3-carboxy-1-fluoro-3-hydroxypropane-1-phosphonic acid (**3**), of undetermined stereochemistry at C-1; these preparations provide the first examples of syntheses of phosphonate analogues of 3-phospho-D-glyceric acid having the natural configuration at C-2.

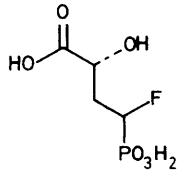
Following the synthesis of the racemic methylene analogue of 3-phospho-D-glyceric acid,[1,2] Dixon and Sparkes[2] and Orr and Knowles[3] showed it to be a viable substrate for the combined action of 3-phosphoglycerate kinase (PGK) and glyceraldehyde 3-phosphate dehydrogenase (GPD) with a comparable rate of oxidation of NADH but with a strongly pH-dependent reduction in equilibrium binding to PGK, the rate-limiting enzyme. We have demonstrated for a variety of nucleotide analogues that α-fluorination of phosphonic acids can lead to an improvement in their performance as analogues of biological phosphates.[4,5] We have also shown that both enantiomers of 2-carboxybutane-1,4-bisphosphonic acid, the bismethylene analogue of glyceric acid 2,3-bisphosphate, bind equally well to haemoglobin.[6] It therefore seemed to us that the concept of replacing the oxygen of a phosphate ester by a CHF or CF_2 group should be tested by enantiospecific synthesis which is also enantioselective with respect to the mimicry of an oxygen lone pair by a fluorine atom. We therefore determined to establish an enantiospecific route to the methylene and fluoromethylene analogues of 3-phospho-D-glyceric acid (**2**) which might also be of general applicability to the 3-phosphates of glycerol and D-glyceraldehyde. We now report some results of that work, which employs C-4 of a



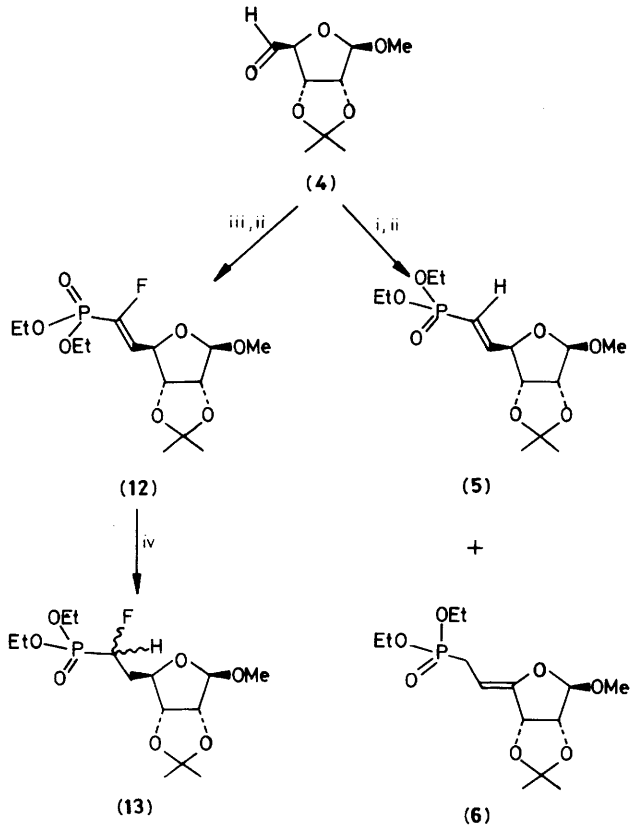
(**1**)



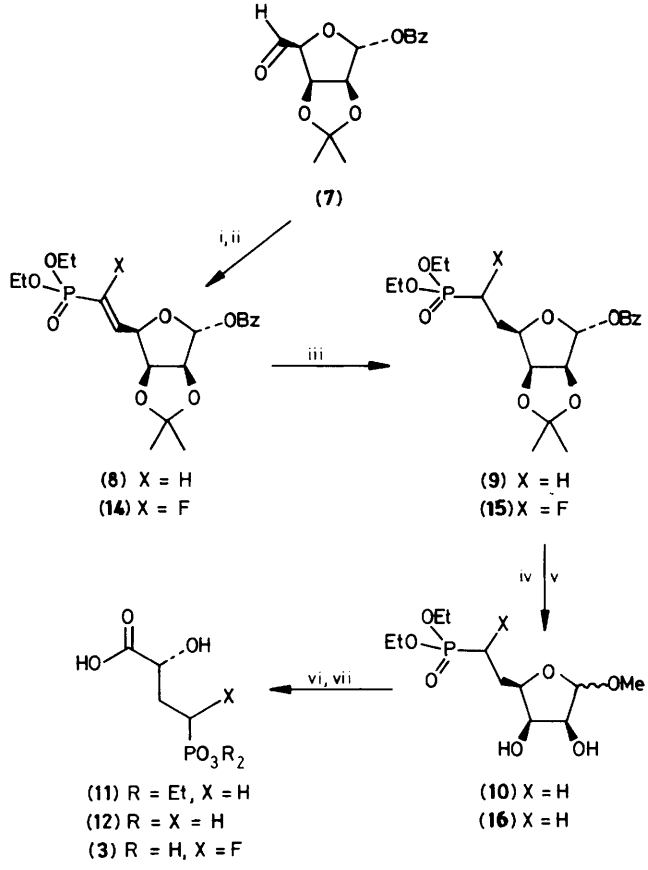
(**2**)



(**3**)



Scheme 1. *Reagents*: i, $[(EtO)_2P(O)]_2CHLi$; ii, $NaHCO_3$; iii, $[(EtO)_2P(O)]_2CFLi$; iv, H_2/PdC.



Scheme 2. *Reagents and conditions*: i, $(EtO)_2P(O)_2CXLi$; ii, $NaHCO_3$; iii, H_2/PdC; iv, CF_3COOH; v, MeOH, H^+; vi, HIO_4 pH 3.7; vii, Me_3SiI then MeOH.

D-pentose to provide the chiral centre at C-3 of the synthetic analogues (**1**) and (**3**).

The Wadsworth–Emmons condensation of methyl 2,3-*O*-isopropylidene-β-D-ribopentodialdehydo-1,4-furanoside[7] (**4**) with tetraethyl lithiomethylenebisphosphonate gave the unstable vinylphosphonate (**5**) as its (*E*)-isomer which was isolated in admixture with the rearranged phosphonate (**6**) (Scheme 1). By contrast, the same condensation reaction with 1-*O*-benzoyl 2,3-*O*-isopropylidene-α-D-*lyxo*pentodialdehydo-1,4-furanoside[8] (**7**) gave the stable vinyl phosphonate (8)† exclusively as the (*E*)-isomer, which was reduced catalytically to the phosphonate (**9**). Treatment with 90% trifluoroacetic acid followed by methanolic HCl afforded the methyl furanoside (**10**) as a mixture of α- and β-anomers. Oxidation of this mixture with an excess of sodium periodate at pH 3.7 led to the diester (**11**) which was de-esterified using iodotrimethylsilane followed by methanol[9] to give the desired product (**1**) (Scheme 2).

The condensation of (**4**) with tetraethyl lithiofluoromethylenebisphosphonate[10] provided exclusively the (*E*)-isomer of the α-fluorovinylphosphonate (**12**) which on catalytic reduction using palladium–charcoal gave the α-fluorophosphonate (**13**) as a 1:1 mixture of diastereoisomers. Attempts to achieve a stereoselective reduction using $RhCl(PPh_3)_3$ or $RuHCl(PPh_3)$ were not successful nor could the diastereoisomers be separated by chromatography.

The corresponding Wadsworth–Emmons condensation with the *lyxo*-isomer (**7**) smoothly provided the α-fluorovinylphosphonate (**14**) exclusively as the (*E*)-isomer which underwent catalytic reduction with palladium–charcoal to give the α-fluoroalkanephosphonate (**15**) as an 85:15 mixture of diastereoisomers. This stereoselectivity can be attributed to the steric hindrance provided by the proximate isopropylidene group and might well be enhanced by the use of bulkier protecting groups for the *cis*-diol in (**7**). This product was converted as before into a mixture of the α- and β-anomers of the methyl furanoside (**16**), oxidised with periodate and de-esterified to give the α-fluoromethylphosphonate (**3**) analogue of 3-phospho-D-glyceric acid (**2**). Spectroscopic analysis indicates that this contained at least 93% of the major diastereoisomer. Work is in progress to identify its stereochemistry at C-1 and evaluate its biological properties with respect to PGK and DPG.

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† All new compounds were fully characterised by spectroscopic and composition analysis and were homogeneous by h.p.l.c. or t.l.c. analysis.

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