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ANOMERIC SPIROEPOXIDES DERIVED FROM FRUCTOPYRANOSE, AND THE SYNTHESIS OF NEW FRUCTOPHOSPHONIC ACIDS

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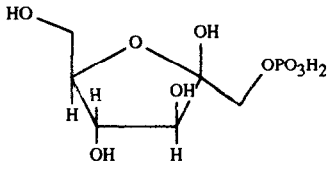
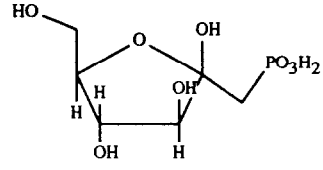
Summary: The synthesis of D-fructose 1-deoxy 1-phosphonic acid (2) is described utilising the reaction of diethyl trimethylsilyl phosphite with a novel spiro anomeric epoxide, derived from fructose.

The synthesis of phosphonate analogues of biologically active phosphates has received much interest[1,2]. Since the carbon-phosphorus bond of phosphonates is incapable of being hydrolysed by the 'ordinary' enzymes involved in phosphate cleavage, several mechanistic possibilities exist for metabolic regulation by these compounds. To date the synthesis of carbohydrate phosphate analogues has largely concentrated on isosteric phosphonates, in which a methylene group replaces the alkoxy-O-atom of the parent phosphate. A general approach to the syntheis of isosteric phosphonate analogues of ketose-1-phosphates has been described[3] from 1-deoxy-1-nitro-aldoses. However, despite their similar size to phosphates, one possible limitation of isosteric phosphonates is their reduced acidity[4].

Vasella et al. have shown[5] that non-isosteric glycosyl phosphonates, in which the phosphorous atom is bound directly to the carbohydrate residue, are isopolar to the corresponding glycosylphosphates. We now describe the synthesis of the non-isosteric analogue (2) of D-fructose 1-phosphate (1).



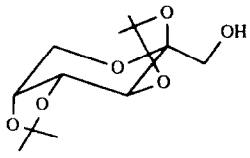
(1)



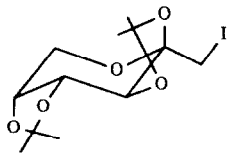
(2)

The most commonly used method for the synthesis of phosphonates is the Arbuzov reaction[6] on the appropriate alkyl halide. Readily available 2,3:4,5-di-O-isopropylidene-β-D- fructopyranose (3)[7], on treatment with iodine, triphenylphosphine and imidazole in refluxing toluene, gave directly 1-deoxy-1-iodo-2,3:4,5-di-O-isopropylidene-β-fructopyranose (4) in 80% yield. However, Arbuzov reaction of (4) in refluxing

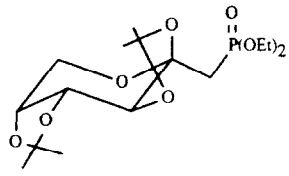
triethyl phosphite did not yield the phosphonate (5) presumably due to steric hindrance.



(3)

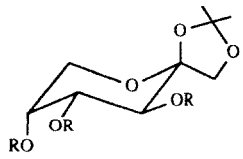


(4)



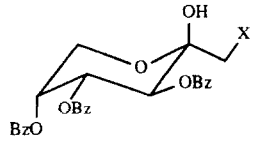
(5)

To overcome this problem a more reactive precursor was required. The reaction of diethyl trimethylsilyl phosphite with simple epoxides in the presence of Lewis acids has been shown to give phosphonates in good yields[8]. We now report the synthesis of a novel spiro anomeric epoxide (12) and its reaction with diethyl trimethylsilyl phosphite to afford exclusively a primary phosphonate. The synthesis of a spiro anomeric epoxide derived from D-glucose which has recently been published[9] prompts disclosure of our work.



(6) R = H

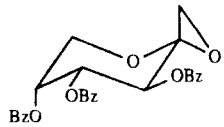
(7) R = Bz



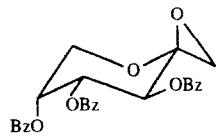
(8) X = OH

(9) X = OTs

(10) X = I



(11)



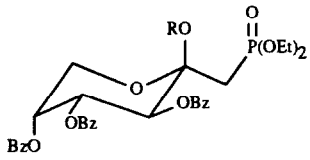
(12)

Treatment of 1,2-O-isopropylidene-β-D-fructopyranose (6)[10] with three equivalents of benzoyl chloride in pyridine gave the tribenzoyl ester (7). The isopropylidene protecting group was removed by hydrolysis with 50% aq. trifluoroacetic acid to give the corresponding diol (8) as a single anomer with β-configuration in an overall yield of 75%. The primary hydroxyl group in (8) was selectively esterified with *p*-toluenesulfonyl chloride in pyridine to give the primary tosylate (9) in 94% yield. The anomeric hydroxyl group was deprotonated on treatment with sodium hydride in THF and internal displacement of the tosyl group

led to the formation of an inseparable anomeric mixture of spiro epoxides (11) and (12), α:β ratio 45:55, in 87% yield, due to competing, reversible tetrahydropyran ring opening.

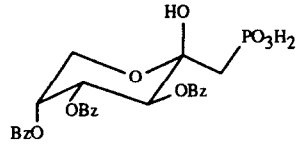
To obtain the required epoxide as a single anomer, neutral conditions for ring closure were required to prevent ring opening of the carbohydrate. Reaction of the tosylate (9) with potassium iodide in DMF afforded the primary iodide (10) which on treatment with silver(I)oxide, to facilitate iodide removal[11], in THF gave exclusively the spiro epoxide with β-configuration (12)[12] in 69% overall yield from (9).

The configuration at C-2 was deduced from n.O.e. measurements. After irradiation of the C-1 methylene group, a n.O.e. was observed for the proton on C-3, but there was no effect on the protons on C-4 or C-6, indicating the β-configuration.



(13) R = TMS

(14) R = H



(15)

The ring opening of epoxide (12) with diethyl trimethylsilyl phosphite occurred exclusively at the least hindered C-1 position to give a single primary phosphonate with β-configuration (13)[13] in 93% yield. The configuration was again deduced by n.O.e. measurements and was confirmed by X-ray crystallography[14].

Desilylation of (13) was achieved using tetrabutyl ammonium fluoride in THF to give the free alcohol (14).Transesterification of the ethyl esters with trimethylsilyl bromide in dichloromethane followed by hydrolysis gave the phosphonic acid (15) in 88% yield from (13). The benzoyl ester protecting groups were cleaved on treatment with sodium hydroxide in anhydrous methanol to give, after passage through an acidic ion-exchange column D-fructose 1-deoxy 1-phosphonic acid(2), as a mixture of α- and β-furanose and pyranose forms in D_2O (^{13}C and ^{31}P NMR).

The reactivity and chemistry of the iodomethylpyranose (10) and the spiroepoxides (11) and (12) will be reported in a further paper.

New compounds were characterized by elemental analysis and/or high resolution mass measurement of a homogeneous sample. Fructophosphonic acid (2) showed the correct molecular ion (low resolution FABMS).

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12. Data for (12): ^{1}H NMR ($CDCl_3$) δ(ppm) 2.89(1H, d, H-1, $J_{1,1'}$ -3.9Hz), 3.12(1H, d, H-1', $J_{1',1}$ -3.9Hz), 4.20(1H, dd, H-6, $J_{6,6'}$ -13.0Hz, $J_{6,5}$ 1.5Hz), 4.29(1H, bd, H-6', $J_{6',6}$ -13.0Hz), 5.87(2H, m, H-4 and H-5), 6.37(1H, d, H-3, $J_{3,4}$ 11.9Hz) and 7.23-8.17(15H, m, ArH).

13. Data for (13):^{1}H NMR ($CDCl)_3$ δ(ppm) 0.33(9H, s, $(CH_3)_3Si$), 1.24(6H, m, $(CH_3CH_2O)_2$), 2.39(1H, dd, H-1 $J_{1,1'}$ -15.2Hz, $J_{1,P}$ 20.6Hz), 2.54(1H, dd, H-1', $J_{1',1}$ -15.2Hz, $J_{1',P}$ 18.7Hz), 4.04(1H, dd, H-6, $J_{6,6'}$ -12.1Hz, $J_{6,5}$ 0.5Hz), 4.12(4H, m, $(CH_3CH_2O)_2$), 4.26(1H, bd, H-6', $J_{6,6'}$ -12.1Hz), 5.70(1H, dd, H-4, $J_{4,3}$ 10.1Hz, $J_{4,5}$ 3.3Hz), 5.77(1H, m, H-5), 6.41(1H, d, H-3, $J_{3,4}$ 10.1Hz) and 7.21-8.28(15H, m, ArH). ^{13}C NMR ($CDCl_3$) δ(ppm) 164.3, 164.1, 163.3 (3 x s, C=O), 131.4, 131.3, 128.4, 128.0, 127.9, 127.4, 126.7, 126.6, 126.4 (9 x d, ArCH), 97.0 (s, C-2), 69.2(d), 68.5(d), 68.3(d), 60.5(t), 60.4(t), 60.0(t), 36.05(td, C-1, $^1J_{C,P}$ 138.8Hz), 16.4(qd, CH_3CH_2O, $^3J_{C,P}$ 4.5Hz) and 16.3(qd, CH_3CH_2O, $^3J_{C,P}$ 6.6Hz)

14. X-ray crystallographic data and experimental details will appear in a full paper.

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