Synthesis of 2-deoxy-α- and -β-D-*arabino*-hexopyranosyl phosphonic acids and related compounds; analogues of early intermediates in the shikimate pathway

Nigel J. Barnes,[a] Mark A. Probert[b] and Richard H. Wightman *,[b]

[a] *Zeneca Agrochemicals, Jealott's Hill Research Station, Bracknell, Berkshire RG42 6ET, UK*
[b] *Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh EH14 4AS, UK*

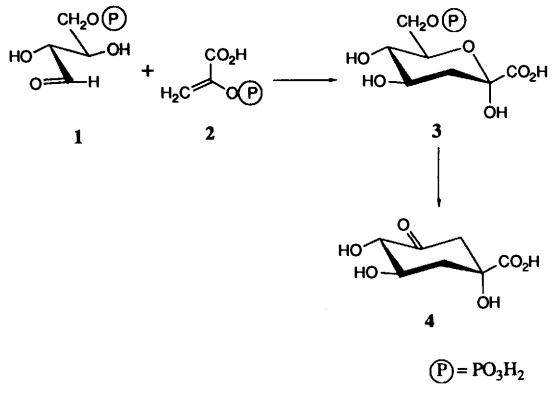
Treatment of 1-*O*-acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hexopyranose 18 with trimethyl phosphite in the presence of trimethylsilyl triflate gave a separable mixture of dimethyl (3,4,6-tri-*O*-benzyl-α-D-*arabino*-hexopyranosyl)phosphonate 19 (35%) and the β-anomer 20 (60%). The diethyl analogue of compound 20 could be prepared stereoselectively from tributyl (3,4,6-tri-*O*-benzyl-2-deoxy-β-D-*arabino*-hexopyranosyl)stannane 21 and diethyl chlorophosphate.

Reaction of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-D-*arabino*-hexopyranose 23 with trimethyl phosphite and trimethylsilyl triflate gave dimethyl (3,4,6-tri-*O*-acetyl-2-deoxy-α-D-*arabino*-hexopyranosyl)phosphonate 25 and the β-anomer 27 with some α-selectivity. Deprotection of compounds 25 and 27 gave the phosphonic acids 11 and 12 respectively. The esters 25 and 27 could be converted into methyl 3,4,6-tri-*O*-acetyl-2-deoxy-1-(dimethoxyphosphoryl)-β-D-*arabino*-hexopyranoside 31 by free-radical bromination followed by methanolysis, and diethyl [3,4,6-tri-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-D-*arabino*-hex-1-enopyranosyl)phosphonate 33 was prepared by interaction of the 1-lithioglucal with diethyl chlorophosphate.

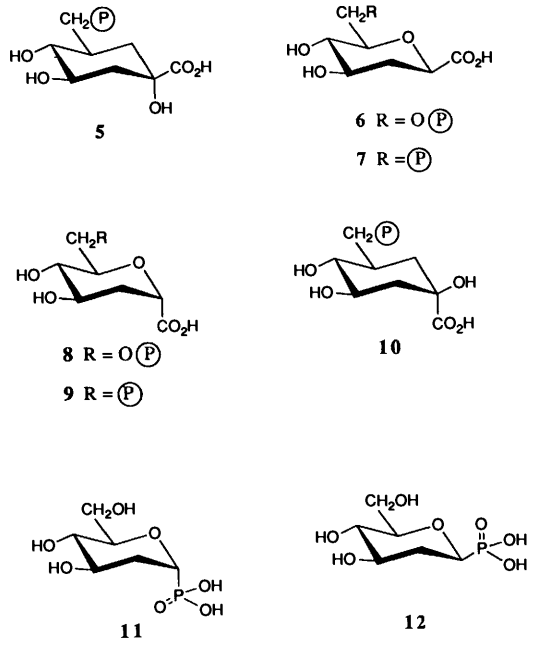
Metallation of stannane 21 and reaction with methyl chloroformate gave methyl 2,6-anhydro-4,5,7-tri-*O*-benzyl-3-deoxy-D-*gluco*-heptonate 35 which could be alkylated with *tert*-butyl bromoacetate to give, after deprotection, 3,7-anhydro-3-carboxy-2,4-dideoxy-D-*gluco*-octonic acid 14.

Introduction

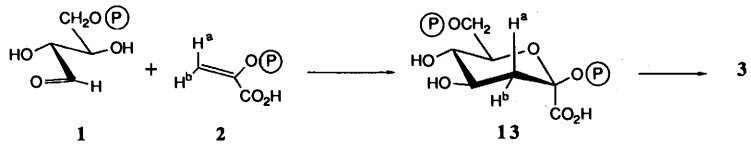
The initial stages in the shikimate pathway [1] for the biosynthesis of aromatic amino acids in plants and microorganisms involve the condensation of phosphoenolpyruvate (PEP, **2**) and D-erythrose 4-phosphate **1** to produce 3-deoxy-D-*arabino*-hept-2-ulopyranosonic acid 7-phosphate (DAHP, **3**), which is then converted into 3-dehydroquinate (DHQ, **4**), the first carbocyclic compound of the pathway. The mechanism for the conversion of DAHP **3** into DHQ **4** by DHQ synthase (EC 4.6.1.3) in *Escherichia coli* has been much clarified in recent years by, in particular, elegant studies from Knowles' laboratory which have demonstrated the inherent simplicity of what is at first sight a complex transformation.[2,3]



Since inhibition of the shikimate pathway offers a means to obtaining herbicidal compounds,[4] we have been interested in the synthesis of analogues of DAHP **3** which could act as inhibitors of DHQ synthase and/or DAHP synthase (EC 4.1.2.15). We have earlier described the preparation of some *C*-glycosyl tetrazoles structurally related to DAHP,[5] and we now describe the synthesis of some glycosyl phosphonates. Since DAHP analogues **5**[2] and **6**,[3] and compounds **8**,[6] **9**[6] and **10**[7] with an α-carboxy group, are all inhibitors of DHQ synthase (the β-carboxy analogue **7** being non-inhibitory[6]), we wished to prepare both the anomers **11** and **12**. We here describe the synthesis of compounds **11** and **12**, together with some approaches to related phosphonates.

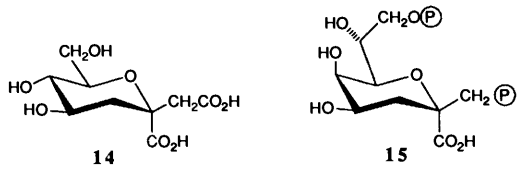


The mechanism for formation of DAHP catalysed by DAHP synthase remains unclear, although proposals have been made.[1] Any mechanism must take account of two longstanding observations; C–C bond formation takes place on the *si*-face of



Scheme 1

PEP **2**,[8] and the reaction occurs with cleavage of the C–O bond of PEP, not the P–O linkage.[9] We considered that these and other observations could be accommodated by a mechanism (Scheme 1) in which condensation of compounds **1** and **2** could lead [either by synchronous bond formation, or in a stepwise process where C–C bond formation precedes C–O linkage, but without free rotation about the C(2)–C(3) bond] to the β-glycosyl phosphate **13** as an intermediate. This could be expected to undergo hydrolysis to DAHP **3** with C–O cleavage. We wished to prepare stable analogues of the proposed intermediate **13**, and as an initial target in this area we report the synthesis of the diacid **14**. The likelihood that the mechanism of Scheme 1 has validity for DAHP biosynthesis is strongly supported by elegant work reported by Baasov and co-workers during the course of our studies;[10] they demonstrated that for the closely related formation of KDO 8-phosphate from D-arabinose 5-phosphate and PEP, catalysed by KDO 8-phosphate synthase, the phosphonate **15** isosteric with the comparable intermediate of type **13** is the most potent inhibitor so far reported for the enzyme.



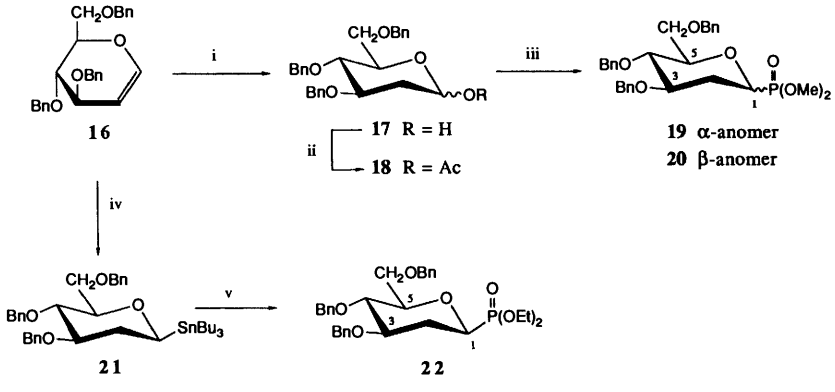
Results and discussion

For the preparation of the phosphonic acids **11** and **12**, we first investigated the use of O-benzylated intermediates (Scheme 2). Addition of hydrogen chloride to tri-*O*-benzyl-D-glucal **16**, and subsequent hydrolysis of the resultant glycosyl chloride in aq. acetone gave 3,4,6-tri-*O*-benzyl-2-deoxy-D-*arabino*-hexopyranose **17**, which could be acetylated to give the 1-*O*-acetyl compound **18** in high yield. Vasella and co-workers have reported the preparation of glycosyl phosphonates by treatment of 1-*O*-acetylglycoses with trimethyl phosphite in the presence of trimethylsilyl triflate, (TMSOTf)†[11] and the application of this method to acetate **18** gave the separable anomers **19** and **20** in 95% yield, and with a selectivity of ~1.7:1 in favour of the β-anomer **20**. The structures of compounds **19** and **20**, and of other similar anomeric pairs described below, follow from a number of self-consistent patterns in their NMR data, most of which have been commented on before by other workers.[11,12] Thus the α-anomer **19** showed the signal for 1-H (equatorial proton) at lower field (δ 4.35) than was observed for the axial proton of compound **20** (δ ~3.7). In the ^{13}C NMR data, α-anomer **19** showed C-1 at higher field[13] (δ_C 67.5) and with a smaller value[14] of $^1J_{C,P}$ (158.9 Hz) than was observed for the β-anomer **20** (δ_C 71.3, $^1J_{C,P}$ 173.4 Hz). Additionally in β-anomer **20** the signals for C-3 and C-5 showed substantial three-bond couplings (19.6 and 17.2 Hz) to the *trans*-coplanar phosphorus.[15] We have also found that, for any anomeric pair, the ^{31}P NMR signal occurs at lower field in the α-anomer (**19**, δ_P 24.3; **20**, δ_P 21.2).

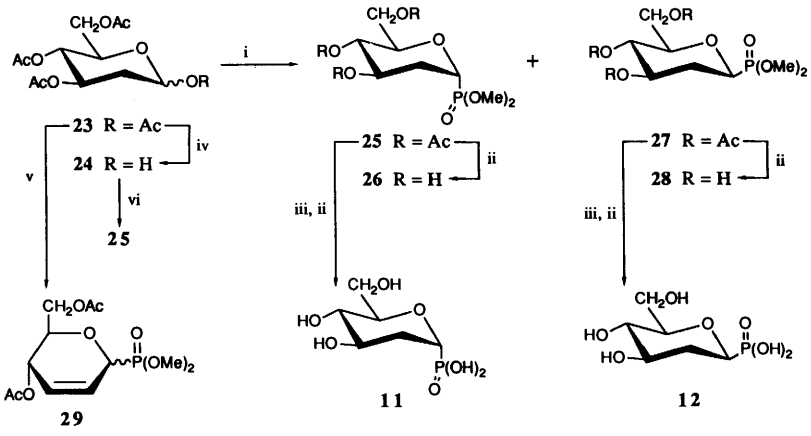
We also investigated a stereoselective route to the β-configured phosphonate. The glycosylstannane **21** was prepared as described by Sinaÿ and co-workers[16] by treatment of tribenzyl-D-glucal **16** with HCl in toluene and reaction of the α-glycosyl chloride with tributylstannyllithium[17] in tetrahydrofuran (THF). We observed that for success in this preparation it was necessary to make the tributylstannyllithium by reaction of bis(tributyltin) with butyllithium; if instead the reagent was prepared by treatment of tributylstannane in THF with lithium diisopropylamide (LDA), then significant amounts of butyl 3,4,6-tri-*O*-benzyl-2-deoxy-α,β-D-*arabino*-hexopyranoside were isolated, presumably as a result of reductive cleavage of THF by the tributylstannane and subsequent reaction of butoxytributyltin with the glycosyl chloride. Treatment of the stannane **21** with butyllithium and reaction of the resultant β-glycosyllithium species with diethyl chlorophosphate gave the phosphonate **22** as a pure β-anomer, but in rather poor yield. The stereochemistry of compound **22** followed from its NMR data (*e.g.*, C-1, δ_C 71.7, $^1J_{C,P}$ 172.4 Hz; C-3 and C-5, $^3J_{C,P}$ 20.0 and 17.4 Hz; δ_P 20.57).

O-Acetyl protection could also be used (Scheme 3). When tetra-*O*-acetyl-2-deoxy-D-*arabino*-hexopyranose **23** was treated with trimethyl phosphite and TMSOTf the two anomers **25** and **27**, which were separable by chromatography, were produced in high yield, and with a selectivity of 2:1 in favour of the α-anomer **25**. The same product ratio was found independently of whether the precursor **23** was an anomeric mixture (α:β, 1:2) from acetylation of 2-deoxy-D-glucose, or the pure-α-anomer, prepared by the method of Giese.[18] This

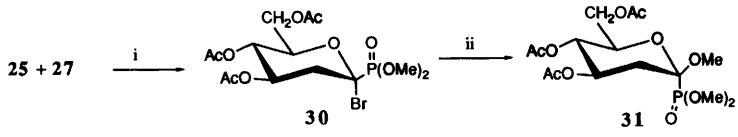
† Triflate = trifluoromethanesulfonate.



Scheme 2 *Reagents:* i, HCl, toluene; then acetone–water; ii, Ac_2O, C_5H_5N; iii, $P(OMe)_3$, TMSOTf; iv, HCl, toluene; then Bu_3SnLi, THF; v, BuLi, $ClPO(OEt)_2$



Scheme 3 *Reagents:* i, $P(OMe)_3$, TMSOTf; ii, NaOMe, MeOH; iii, TMSBr, CH_2Cl_2; iv, NH_3, THF–MeOH; v, $HPO(OMe)_2$, $BF_3{\cdot}Et_2O$; vi, CCl_3CN, NaH; then $P(OMe)_3$, TMSOTf



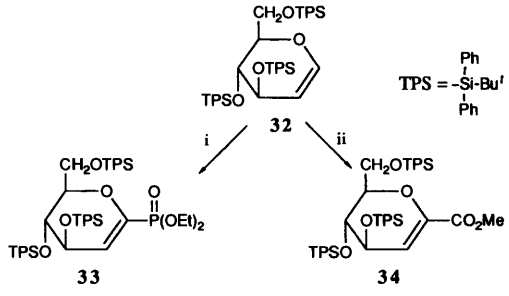
Scheme 4 *Reagents and conditions:* i, NBS, CCl_4, *hv*; ii, MeOH, 2.6-lutidine

selectivity can be compared with the weak β-selectivity when using the O-benzylated precursor **18**. Similar observations have been made by previous workers,[12] and rationalized in terms of the formation and equilibration of intermediate triflates, and of the trimethoxyphosphonium salts derived from them; the β-triflates should react more rapidly with trimethyl phosphite to give α-phosphonium salts, but subsequent equilibration of phosphonium salts should favour the β-anomers by the reverse anomeric effect, and this equilibration should be more rapid for O-benzylated substrates.

The use of a trichloroacetimidate intermediate[19] was also investigated. Selective deacetylation of compound **23** by ammonia in THF–methanol[20] gave compound **24**, which on treatment with sodium hydride and trichloroacetonitrile, followed by trimethyl phosphite,[12] gave only the α-anomer **25**, but the yield was poor despite some experimentation. When the glycosyl acetate **23** was treated with dimethyl hydrogen phosphite and boron trifluoride–diethyl ether, the phosphonates **25** and/or **27** were not obtained, but instead the alkenyl phosphonate **29** (α : β, 1 : 2) was formed. This observation can be rationalized as proceeding through the intermediacy of tri-*O*-acetyl-D-glucal, since reaction of this under similar conditions is known to give compound **29** with a similar anomeric ratio.[21]

Although triacetates **25** and **27** could be cleanly deacetylated under Zemplen conditions to give the triols **26** and **28**, subsequent demethylation proved unrewarding. Therefore to prepare the free phosphonic acids, the dimethyl phosphonates **25** and **27** were each first treated with trimethylsilyl bromide (TMSBr) to effect demethylation, followed by deacetylation using sodium methoxide in methanol. The phosphonic acids **11** and **12** could then each be isolated in high yield after ion-exchange chromatography. The stereochemistry of these, and of triols **26** and **28**, was again clear using the NMR criteria mentioned above; additionally, in these deacetylated compounds it was possible to observe in the ^1H NMR spectra of the α-anomers **26** and **11** a large (~33 Hz) three-bond proton–phosphorus coupling[11,22] in the signals for the axial hydrogen at C-2. For each of the β-anomers **12** and **28**, 2-H^{ax} displayed a much smaller coupling to phosphorus (~9.5 Hz), but a substantial coupling (~11.5 Hz) to 1-H.

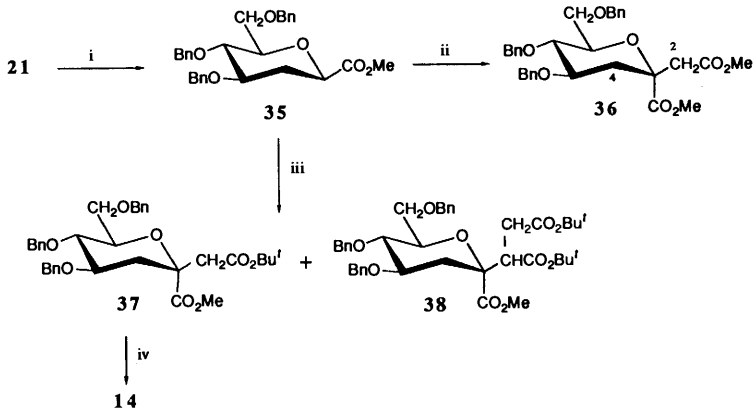
It was possible to photobrominate[23] the mixed phosphonates **25** and **27** to give the bromo derivative **30** (Scheme 4). Although this compound could be isolated and shown to be the expected α-bromide (for 2-H^{ax}, $^3J_{H,P}$ = 6.7 Hz), it proved to be somewhat unstable. Reaction of crude bromide **30** directly with methanol and 2,6-dimethylpyridine (2,6-lutidine), however, led to the isolation of the methyl glycoside **31** in 51% overall yield. The stereochemistry of product **31** is supported by the absence, in the ^{13}C NMR spectrum, of observable coupling between C-3 and C-5 and phosphorus. Our aim in making glycoside **31** had been to attempt its hydrolysis to give a phosphonate analogue of DAHP **3** by a method possibly applicable to phosphonate analogues of other 3-deoxy-2-ulosonic acids. However, various attempts to achieve this objective proved abortive, as did alternative synthetic approaches, and the stability of such phosphonate analogues must remain questionable.



Scheme 5 *Reagents:* i, Bu^{t}Li, $ClPO(OEt)_2$; ii, Bu^{t}Li, $ClCO_2Me$

We have also prepared the unsaturated glycosyl phosphonate **33** in moderate yield by vinylic deprotonation of the glucal derivative **32** by *tert*-butyllithium, followed by reaction with diethyl chlorophosphate (Scheme 5). The use of *tert*-butyldiphenylsilyl (TPS) protection in glycal **32** was occasioned by the observations from Friesen's laboratory that use of silicon-based protecting groups that have C–H bonds α- to silicon can lead to unwanted deprotonation in these locations as well as at the vinylic position,[24] and by the unsuitability of benzyl protection with *tert*-butyllithium as base.[25] We had hoped that compound **33** could be used as a precursor for the β-phosphonate **12** by stereoselective hydrogenation, but attempts at reduction of compound **33** were not fruitful. Reaction of the lithio-derivative of compound **32** with methyl chloroformate gave the enoate **34** (59%).

The *C*-glycoside target **14** was prepared as indicated in Scheme 6. Lithiation of the glycosylstannane **21**[16] and addition of the glycosyllithium species to excess of methyl chloroformate gave the ester **35**, the stereochemistry of which was evident from



Scheme 6 *Reagents:* i, BuLi, THF, $ClCO_2Me$; ii, $NaN(TMS)_2$, THF, $BrCH_2CO_2Me$; iii, $NaN(TMS)_2$, $BrCH_2CO_2Bu^t$; iv, NaOH, aq. MeOH; TFA; H_2, Pd/C, MeOH

^1H NMR data. Attempted reduction of the enoate **34** to give an analogous saturated system was unsuccessful. Treatment of ester **35** with sodium bis(trimethylsilyl)amide followed by methyl bromoacetate gave the diester **36** in moderate yield. The stereochemistry of the alkylation was clear from nuclear Overhauser effect (NOE) measurements, in which irradiation of the axial proton at C-4 caused significant enhancements of the signals for both the diastereotopic hydrogens at C-2. Since the separation of compound **36** from residual starting material **35** and other by-products was difficult on a large scale, the alkylation was repeated using *tert*-butyl bromoacetate. The diester **37** was obtained in a somewhat poorer yield, but was readily separated by chromatography from by-products, which included the triester **38**, isolated in 11% yield. Interestingly, NMR spectroscopy showed compound **38** to be a pure stereoisomer. Conventional deprotection of the diester **37** then led to the target **14** in high yield.

Experimental

IR spectra were recorded on a Perkin-Elmer FT-IR 1600 instrument. Mass spectra were obtained from updated VG-MS 9, VG ZABE high-resolution EI/CI/FAB, JEOL DX303 and VG AutospecQ spectrometers. NMR spectra were recorded on Bruker WP 200SY and AC 400 spectrometers, using $CDCl_3$ as solvent unless otherwise stated. Coupling constants (J) are quoted in Hz.

Specific rotations were performed on a Bendix-NPL 143D automatic polarimeter (path length 1 cm); units for $[\alpha]_D$ values are 10^{-1} deg cm^2 g^{-1}. Mps were determined using an Electrothermal MK II melting point apparatus and are uncorrected.

Column chromatography was carried out using Sorbsil C60 40/60H (Prolabo); an external pressure was applied to the top of the columns. Light petroleum refers to material of boiling range 40–60 °C. Organic extracts were dried using anhydrous sodium sulfate.

3,4,6-Tri-*O*-benzyl-2-deoxy-α,β-D-*arabino*-hexopyranose 17

Dry hydrogen chloride gas was bubbled for 20 min through a solution of tri-*O*-benzyl-D-glucal **16**[26] (2.5 g) in dry toluene (15 cm^3) at 0 °C after which nitrogen was passed for a further 20 min. The resulting solution was evaporated under reduced pressure to give a pale yellow syrup, which was dissolved in a mixture of acetone (20 cm^3) and water (5 cm^3). After 48 h, the solution was poured into dichloromethane and extracted with saturated aq. sodium hydrogen carbonate. The organic fraction was dried, and evaporated under reduced pressure to give a yellow syrup, which was chromatographed on silica, with toluene–ethyl acetate (3:1) as eluent, to give the 2-*deoxysugar* **17** (1.69 g, 65%), mp 99–103 °C; ν_{max}(KBr)/cm^{-1} 3380, 3080, 3060, 3020, 2920, 2900 and 2860; δ_H(200 MHz) 1.5 (1 H, m, 2-H^{ax}), 2.2–2.4 (1 H, m, 2-H^{eq}), 3.1 (1 H, br s, OH), 3.5 (1 H, m, 4-H), 3.7 (2 H, m, 6-H_2), 4.0–4.15 (2 H, m, 3- and 5-H), 4.4–4.75 (~5 H, m, CH_2Ph and 1-H of β-anomer), 4.86 (0.25 H, d, J 11, CH_2Ph, β-anomer), 4.90 (0.75 H, d, J 11, CH_2Ph, α-anomer), 5.37 (0.75 H, br s, 1-H, α-anomer) and 7.3 (15 H, m, Ph); δ_C(50 MHz) (signals for α-anomer) 35.5 (C-2), 69.4 (C-6), 70.7, 77.0 and 78.6 (C-3, -4 and -5), 71.7, 73.4 and 74.8 (3 × CH_2Ph), 127.5–128.3 (Ph) and 138.0–138.6 (C-1 of Ph) (Found: C, 74.4; H, 7.0. $C_{27}H_{30}O_5$ requires C, 74.63; H, 6.96%).

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-α,β-D-*arabino*-hexopyranose 18

A solution of the hemiacetal **17** (729 mg, 1.7 mmol) in a mixture of pyridine (1 cm^3) and acetic anhydride (0.26 cm^3, 2.5 mmol) was stirred at room temperature for 24 h. Ice was added and the mixture was stirred for 30 min, after which the solution was poured into dichloromethane and washed successively with water, dil. hydrochloric acid (1 mol dm^{-3}) and saturated aq. sodium hydrogen carbonate. The organic layer was dried, and evaporated under reduced pressure to give the 1-O-*acetyl compound* **18** (0.8 g, 100%) as a syrup, α:β 3:2; ν_{max}(KBr)/cm^{-1} 3080, 3060, 3020, 2920, 2860 and 1750; δ_H(200 MHz) 1.7–1.9 (1 H, m, 2-H^{ax}), 2.05 (1.8 H, s, OAc, α-anomer), 2.10 (1.2 H, s, OAc, β-anomer), 2.25–2.45 (1 H, m, 2-H^{eq}), 3.4–4.0 (5 H, m, 3-, 4-, 5-H and 6-H), 4.4–4.7 (5 H, m, CH_2Ph), 4.88 (0.4 H, d, J 10.6, CH_2Ph, β-anomer), 4.90 (0.6 H, d, J 10.7, CH_2Ph, α-anomer), 5.68 (0.4 H, dd, $J_{1,2ax}$ 10.06, $J_{1,2eq}$ 2.18, 1-H, β-anomer), 6.25 (0.6 H, dd, J 3.21 and 1.47, 1-H, α-anomer) and 7.3 (15 H, m, Ph) (Found: C, 73.2; H, 6.8. $C_{29}H_{32}O_6$ requires C, 73.08; H, 6.78%).

Dimethyl (3,4,6-tri-*O*-benzyl-2-deoxy-α- and -β-D-*arabino*-hexopyranosyl)phosphonates 19 and 20

1-*O*-Acetyl compound **18** (172 mg, 0.36 mmol) was dissolved in dry dichloromethane (5 cm^3) and the solution was treated with distilled trimethyl phosphite (0.1 cm^3, 0.87 mmol) and then with TMSOTf (0.1 cm^3, 0.54 mmol) at 0 °C. After 15 min the solution was maintained at room temperature for 24 h. Water (1 cm^3) was added and the mixture was stirred for a further 30 min after which the solution was poured into ethyl acetate (100 cm^3) and washed successively with saturated aq. sodium hydrogen carbonate and brine. The organic fraction was dried, and evaporated under reduced pressure to give a pale yellow syrup, which was chromatographed on silica, with toluene–ethyl acetate (1:3) as eluent, to give first the α-anomer **19** (66 mg, 35%) as an oil, $[\alpha]_D$ +32.8 (*c* 1.22, $CHCl_3$); δ_H(200 MHz) 1.9–2.1 (1 H, m, 2-H^{ax}), 2.4 (1 H, m, 2-H^{eq}), 3.75 and 3.80 (each 3 H, d, $^3J_{H,P}$ 10.5, CH_3OP), 3.7–4.0 (4 H, m, 4-, 5-H and 6-H_2), 4.1 (1 H, m, 3-H), 4.35 (1 H, m, 1-H), 4.5–4.7 (5 H, m, CH_2Ph), 4.78 (1 H, d, CH_2Ph) and 7.3–7.5 (15 H, m, Ph); δ_C(50 MHz) 28.89 (C-

2), 52.7 (d, $^2J_{C,P}$ 7, CH_3OP), 53.72 (d, $^2J_{C,P}$ 6.85, CH_3OP), 67.5 (d, $^1J_{C,P}$ 158.9, C-1), 68.62 (C-6), 71.67, 73.20 and 73.77 (CH_2Ph), 75.53 and 75.79 (each d, $^3J_{C,P}$ 3.4, C-3, -5), 76.65 (C-4), 128.0 (Ph) and 138.0 (C-1 of Ph); δ_P(81 MHz) 24.29; *m/z* 435 (M − CH_2Ph)$^+$ [Found: (M − CH_2Ph)$^+$, 435.1578. $C_{22}H_{28}O_7P$ requires *m/z*, 435.1573].

Further elution gave the β-*isomer* **20** (114 mg, 60%) as an oil, $[\alpha]_D$ +13.1 (*c* 1.07, $CHCl_3$); δ_H(200 MHz) 1.7–1.95 (1 H, m, 2-H^{ax}), 2.45 (1 H, m, 2-H^{eq}), 3.4 (1 H, m, 5-H), 3.52 (1 H, t, *J* 9, 4-H), 3.6–3.85 (4 H, m, 1-, 3-H and 6-H_2), 3.80 and 3.82 (each 3 H, d, $^3J_{H,P}$ 10.5, CH_3OP), 4.4–4.7 (5 H, m, CH_2Ph), 4.90 (1 H, d, *J* 11, CH_2Ph) and 7.3–7.5 (15 H, m, Ph); δ_C(50 MHz) 31.03 (C-2), 53.43 (d, $^2J_{C,P}$ 6.3, CH_3OP), 53.79 (d, $^2J_{C,P}$ 6.8, CH_3OP), 69.06 (C-6), 71.21, 73.14 and 75.06 (CH_2Ph), 71.27 (d, $^1J_{C,P}$ 173.4, C-1), 77.64 (C-4), 80.28 (d, $^3J_{C,P}$ 19.6, C-3/5), 88.68 (d, $^3J_{C,P}$ 17.2, C-5/3), 128.0 (Ph) and 138.0 (C-1 of Ph); δ_P(81 MHz) 21.23; *m/z* 526 (M^+) and 435 (M − CH_2Ph)$^+$ (Found: M^+, 526.2100. $C_{29}H_{35}O_7P$ requires M, 526.2120).

Diethyl (3,4,6-tri-*O*-benzyl-2-deoxy-β-D-*arabino*-hexopyranosyl)phosphonate 22

A solution of the glycosylstannane **21**[16] (0.25 g, 0.35 mmol) in dry THF (5 cm^3) was treated with butyllithium in hexane (0.26 cm^3, 0.42 mmol) at −78 °C. After 2 min diethyl chlorophosphate (0.07 cm^3, 0.42 mmol) was added and the solution was stirred for a further 30 min before being quenched by aq. ammonium chloride. The mixture was partitioned between water and diethyl ether, with the organic phase then being washed with further aq. ammonium chloride. Evaporation of the dried ether layers under reduced pressure gave a yellow syrup, which was chromatographed on silica, with toluene–ethyl acetate (1 : 3) as eluent, to give the β-*phosphonate* **22** (51 mg, 26%) as a syrup, $[\alpha]_D$ +6.85 (*c* 1.60, $CHCl_3$); δ_H(200 MHz) 1.25 (6 H, m, CH_3CH_2OP), 1.74 (1 H, quintet, *J* ~ 10, 2-H^{ax}), 2.35 (1 H, m, 2-H^{eq}), 3.33 (1 H, dt, $J_{5,4}$ 9.4, $J_{5,6}$ 3.0, 5-H), 3.47 (1 H, t, *J* 9.3, 4-H), 3.6–3.8 (4 H, m, 1- and 3-H and 6-H_2), 4.1–4.3 (4 H, m, $MeCH_2OP$), 4.5–5.0 (6 H, 3 AB systems, CH_2Ph) and 7.2–7.4 (15 H, m, Ph); δ_C(50 MHz) 16.4 (CH_3CH_2OP), 31.4 (C-2), 62.77 (d, $^2J_{C,P}$ 5.9, CH_2OP), 63.06 (d, $^2J_{C,P}$ 7.1, CH_2OP), 69.34 (C-6), 69.34 (CH_2Ph), 71.43 (CH_2Ph), 71.69 (d, $^1J_{C,P}$ 172.4, C-1), 73.25 (CH_2Ph), 77.91 (C-4), 80.69 (d, $^3J_{C,P}$ 20.0, C-3/5), 81.11 (d, $^3J_{C,P}$ 17.4, C-5/3), 127–129 (Ph) and 138.3 (C-1 of Ph); δ_P(81 MHz) 20.57 (Found: C, 66.8; H, 7.2; P, 5.6. $C_{31}H_{39}O_7P$ requires C, 67.12; H, 7.10; P, 5.58%).

Dimethyl (3,4,6-tri-*O*-acetyl-2-deoxy-α- and -β-D-*arabino*-hexopyranosyl)phosphonate 25 and 27

A solution of the tetra-*O*-acetyl compound **23** (3.2 g, 9.6 mmol) in dry dichloromethane (60 cm^3) was treated with trimethyl phosphite (2.7 cm^3, 23 mmol) and TMSOTf (2.7 cm^3, 14.4 mmol) at 0 °C. After 15 min the solution was allowed to warm to room temperature and was stirred for a further 24 h. Water (5 cm^3) was added and after 30 min the mixture was added to ethyl acetate (100 cm^3) and washed successively with saturated aq. sodium hydrogen carbonate and brine. The organic fraction was dried, and evaporated under reduced pressure to give a pale yellow syrup, which was chromatographed on silica with toluene–ethyl acetate (1 : 3) as eluent to give, first, the α-*anomer* **25** (2.35 g, 64%) as a syrup, $[\alpha]_D$ +9.5 (*c* 1.88, $CHCl_3$); ν_{max}(film)/cm^{-1} 2940, 2840, 1730, 1250 and 1050; δ_H(400 MHz) 2.0–2.1 (1 H, m, 2-H^{ax}), 2.03, 2.04 and 2.06 (each 3 H, s, OAc), 2.41 (1 H, ddt, *J* 14.1, 6.7 and 4.7, 2-H^{eq}), 3.82 and 3.85 (each 3 H, d, $^3J_{H,P}$ 10.6, CH_3OP), 4.04 (1 H, dd, J_{gem} 11.9, $J_{6a,5}$ 2.3, 6-H^a), 4.27–4.35 (2 H, m, 1- and 5-H), 4.38 (1 H, dd, J_{gem} 11.9, $J_{6b,5}$ 5.9, 6-H^b), 4.88 (1 H, t, $J_{4,3}$ = $J_{4,5}$ = 7.5, 4-H) and 5.29 (1 H, dt, $J_{3,2ax}$ = $J_{3,4}$ = 8.8, $J_{3,2eq}$ 4.55, 3-H); δ_C(50 MHz) 20.61, 20.65 and 20.84 (CH_3CO_2), 28.45 (d, $^2J_{C,P}$ 2.5, C-2), 52.95 (d, $^2J_{C,P}$ 6.85, CH_3OP), 53.55 (d, $^2J_{C,P}$ 6.75, CH_3OP), 61.78 (C-6), 66.9 (d, $^1J_{C,P}$ 152, C-1), 68.05 (C-4), 68.50 and 73.22, (C-3 and -5), 169.7 (× 2) and 170.4 (CH_3CO_2); δ_P(81 MHz) 24.38 (Found: C, 43.7; H, 6.3; P, 7.6. $C_{14}H_{23}O_{10}P$ requires C, 43.98; H, 6.0; P, 8.1%).

Further elution of the column gave the β-*anomer* **27** (1.17 g, 32%) as an oil, $[\alpha]_D$ +73.3 (*c* 1.86, $CHCl_3$); ν_{max}(film)/cm^{-1} 2940, 2840, 1730, 1250 and 1050; δ_H(200 MHz) 1.9–2.1 (1 H, m, 2-H^{ax}), 2.02, 2.03 and 2.08 (each 3 H, s, CH_3CO_2), 2.40 (1 H, br d, J_{gem} 12, 2-H^{eq}), 3.6 (1 H, ddd, $J_{5,6a}$ 5.0, $J_{5,6b}$ 2.4, $J_{5,4}$ 9.3, 5-H), 3.83 and 3.85 (each 3 H, d, $^3J_{H,P}$ 10.6, CH_3OP), 3.90 (1 H, dt, $J_{1,2ax}$ ~ $^2J_{H,P}$ ~ 12.5, $J_{1,2eq}$ ~ 2, 1-H), 4.15 (1 H, dd, J_{gem} 12.4, $J_{6b,5}$ 2.4, 6-H^b), 4.25 (1 H, dd, J_{gem} 12.4, $J_{6a,5}$ 4.9, 6-H^a) and 4.9–5.1 (2 H, m, 3- and 4-H); δ_C(50 MHz) 20.47, 20.66 and 21.05 (CH_3CO_2), 30.96 (C-2), 53.4 (d, $^2J_{C,P}$ 6.55, CH_3OP), 53.8 (d, $^2J_{C,P}$ 6.8, CH_3OP), 62.98 (C-6), 68.77 (C-4), 71.36 (d, $^1J_{C,P}$ 175, C-1), 71.4 (d, $^3J_{C,P}$ 20.6, C-3/5), 77.75 (d, $^3J_{C,P}$ 13.6, C-5/3) and 169.56, 170.10 and 170.49 (CH_3CO_2); δ_P(81 MHz) 21.37 (Found: C, 43.7; H, 6.3; P, 7.7%).

Stereospecific synthesis of α-anomer 25

A solution of 3,4,6-tri-*O*-acetyl-2-deoxy-D-*arabino*-hexopyranose **24**[20] (0.194 g, 0.67 mmol) and trichloroacetonitrile (0.23 cm^3, 2.3 mmol) in dry dichloromethane (10 cm^3) was added to oil-free sodium hydride (60% dispersion; 26 mg, 0.65 mmol) at room temperature. The mixture was stirred for 1 h, and then was treated with a solution of trimethyl phosphite (0.16 cm^3, 1.4 mmol) in dichloromethane (10 cm^3) followed by the addition of TMSOTf (0.16 cm^3, 0.8 mmol). After 1 h the solution was diluted with dichloromethane (25 cm^3) and washed successively with saturated aq. sodium hydrogen carbonate, water and brine. The organic fraction was dried, and evaporated under reduced pressure to give a brown syrup, which was chromatographed on silica, with toluene–ethyl acetate (1 : 3) as eluent, to give the α-phosphonate **25** (48 mg, 19%), with properties as reported above.

Dimethyl (2-deoxy-α-D-*arabino*-hexopyranosyl)phosphonate 26

The tri-*O*-acetyl compound **25** (106 mg, 0.28 mmol) as a solution in dry methanol (5 cm^3) was treated with a solution of sodium methoxide in methanol prepared by the addition of sodium (20 mg) to dry methanol (5 cm^3). The solution was stirred at room temperature for 2 h and evaporated under reduced pressure. The resulting syrup was dissolved in water (10 cm^3) and the solution was passed through a column of Amberlite IR-120 (H^+) resin. Evaporation of the eluate under reduced pressure gave the *triol* **26** (69.6 mg, 98%) as a syrup, $[\alpha]_D$ +15.3 (*c* 1.57, CH_3OH); δ_H(200 MHz; CD_3OD) 1.88 (1 H, dddd, $^3J_{H,P}$ 35.4, J_{gem} 13.95, $J_{2ax,3}$ 10.75, $J_{2ax,1}$ 7.1, 2-H^{ax}), 2.23 (1 H, ddt, J_{gem} 13.7, $J_{2eq,3}$ = $^3J_{H,P}$ = 5.0, $J_{2eq,1}$ 2.5, 2-H^{eq}), 3.22 (1 H, t, $J_{4,3}$ ~ $J_{4,5}$ ~ 8.4, 4-H), 3.6–3.8 (3 H, m, 5-H and 6-H_2), 3.81 and 3.86 (each 3 H, d, $^3J_{H,P}$ 10.55, CH_3OP), 3.98 (1 H, ddd, $J_{3,2ax}$ 10.7, $J_{3,4}$ 8.2, $J_{3,2eq}$ 4.8, 3-H) and 4.38 (1 H, ddd, $^2J_{H,P}$ 12.1, $J_{1,2ax}$ 7.1, $J_{1,2eq}$ 2.4, 1-H); δ_C(50 MHz; CD_3OD) 32.8 (C-2), 53.45 (d, $^3J_{C,P}$ 6.9, CH_3OP), 54.4 (d, $^3J_{C,P}$ 7.1, CH_3OP), 62.9 (C-6), 70.0 (d, $^1J_{C,P}$ 157.0, C-1) and 69.7, 72.7 and 79.1 (C-3, -4, -5); δ_P(81 MHz; CD_3OD) 26.7 (Found: C, 37.0; H, 6.5. $C_8H_{17}O_7P$ requires C, 37.51; H, 6.69%).

Dimethyl (2-deoxy-β-D-*arabino*-hexopyranosyl)phosphonate 28

A solution of the tri-*O*-acetyl compound **27** (120 mg, 0.32 mmol) in methanol (5 cm^3) was treated as described above for the α-anomer to give the *triol* **28** (76 mg, 93%) as a syrup, $[\alpha]_D$ +55.5 (*c* 1.14, CH_3OH); δ_H(200 MHz; CD_3OD) 1.51 (1 H, ddt, J_{gem} ~ $J_{2ax,3}$ ~ 12.6, $J_{2ax,1}$ 11.3, $^3J_{H,P}$ 9.8, 2-H^{ax}), 1.95 (1 H, ddt, J_{gem} 12.6, $J_{2eq,3}$ ~ $J_{2eq,1}$ ~ 1.6, $^3J_{H,P}$ 5.05, 2-H^{eq}), 3.0–3.1 (2 H, m), 3.4–3.7 (3 H, m), 3.64 and 3.65 (each 3 H, d, $^3J_{H,P}$ 10.6, CH_3OP) and 3.81 (1 H, ddd, $^2J_{H,P}$ 12.6, $J_{1,2ax}$ 11.2, $J_{1,2eq}$ 2.0, 1-H); δ_C(50 MHz; CD_3OD) 32.47 (C-2), 53.85 and 54.09 (each d, $^2J_{C,P}$ 6.80, CH_3OP), 60.78 (C-6), 69.0 (d, $^1J_{C,P}$ 172.7, C-1), 70.5 (C-4), 71.0 (d, $^3J_{C,P}$ 20.35, C-3/5) and 81.5 (d, $^3J_{C,P}$ 16.6, C-5/3) (Found: C, 37.3; H, 6.5%).

2-Deoxy-α-D-*arabino*-hexopyranosylphosphonic acid 11

A solution of the dimethyl phosphonate **25** (1.13 g, 2.96 mmol) in dry dichloromethane (40 cm^3) at 0 °C was treated with TMSBr (1.56 cm^3, 11.8 mmol). After 4 h, methanol (10 cm^3) was added. The solution was stirred for a further 30 min, evaporated under reduced pressure and the residue was taken up in water (40 cm^3); the solution was evaporated under reduced pressure to give a pale brown syrup. This residue as a solution in dry methanol (40 cm^3) was treated with a solution of sodium methoxide in methanol (20 cm^3) [from sodium (340 mg)]. The solution was stirred at room temperature overnight, and evaporated under reduced pressure. The residue was taken up in water (40 cm^3) and the solution was passed through a column of Amberlite IR-120 (H^+) resin. Evaporation of the eluate gave a brown foam. A solution of this material in water (5 cm^3) was applied to a column of Dowex 1-X8 [previously washed with formic acid (1 mol dm^{-3}) and then with deionized water until the eluate was neutral]. The column was eluted with deionized water and then with aq. formic acid (0.8 mol dm^{-3}). Evaporation of the acidic eluate gave the *phosphonic acid* **11** (573 mg, 85%) as a foam, $[\alpha]_D$ +37.9 (*c* 1.03, CH_3OH); δ_H(200 MHz; CD_3OD) 1.86 (1 H, dddd, $^3J_{H,P}$ 31.1, J_{gem} 13.8, $J_{2ax,3}$ 10.3, $J_{2ax,1}$ 6.9, 2-H^{ax}), 2.31 (1 H, dddd, J_{gem} 13.9, $^3J_{H,P}$ 7.9, $J_{2eq,3}$ 4.68, $J_{2eq,1}$ 2.9, 2-H^{eq}), 3.23 (1 H, t, $J_{4,3} \sim J_{4,5} \sim$ 8.2, 4-H), 3.6–3.9 (3 H, m, 5-H and 6-H_2), 4.03 (1 H, ddd, $J_{3,2eq}$ 10.2, $J_{3,4}$ 7.95, $J_{3,2eq}$ 4.7, 3-H) and 4.19 (1 H, ddd, $^2J_{H,P}$ 12.3, $J_{1,2ax}$ 7.85, $J_{1,2eq}$ 3.0, 1-H); δ_C(50 MHz; CD_3OD) 32.4 (d, $J_{C,P}$ 3.2, C-2), 62.89 (C-6), 69.91 (d, $^1J_{C,P}$ 156, C-1) and 69.54, 72.59 and 78.93 (C-3, -4, -5); δ_P(81 MHz; CD_3OD) 22.16 (Found: C, 31.3; H, 5.8. $C_6H_{13}O_7P$ requires C, 31.58; H, 5.75%).

2-Deoxy-β-D-*arabino*-hexopyranosylphosphonic acid 12

The β-phosphonate **27** (304 mg, 0.80 mmol) was treated as described above for the α-anomer with TMSBr (1.56 cm^3) to give the β-*phosphonic acid* **12** (173 mg, 94%) as a foam, $[\alpha]_D$ +16.9 (*c* 0.84, CH_3OH); δ_H(200 MHz; CD_3OD) 1.68 (1 H, dq, $J_{gem} = J_{2ax,1} = J_{2ax,3}$ = 12.0, $^3J_{H,P}$ 9.5, 2-H^{ax}), 2.17 (1 H, ddd, J_{gem} 12.8, *J* 2.5 and 1.8, 2-H^{eq}), 3.1–3.35 (2 H, m, 3- and 5-H), 3.5–3.8 (3 H, m, 1- and 4-H and 6-H^a) and 3.89 (1 H, dd, J_{gem} 11.8, $J_{6b,5}$ 1.8, 6-H^b); δ_C(50 MHz; CD_3OD) 34.85 (C-2), 62.97 (C-6), 72.95 (d, $^1J_{C,P}$ 167.9, C-1), 73.02 (C-4), 73.4 (d, $^3J_{C,P}$ 19.2, C-3/5) and 83.36 (d, $^3J_{C,P}$ 15.9, C-5/3); δ_P(81 MHz; CD_3OD) 19.9 (Found: C, 31.5; H, 5.8%).

Dimethyl (4,6-di-*O*-acetyl-2,3-dideoxy-α,β-D-erythro-hex-2-enopyranosyl)phosphonate 29

A solution of the tetra-*O*-acetyl compound **23** (1.86 g, 5.6 mmol) in a mixture of dimethyl hydrogen phosphite (20 cm^3) and boron trifluoride–diethyl ether (1 cm^3, 8.1 mmol) was stirred at 60 °C for 2 h. The reaction mixture was poured into dichloromethane, which was then washed successively with aq. sodium hydrogen carbonate, water and brine and dried. Evaporation under reduced pressure gave a yellow syrup, which was chromatographed on silica with toluene–ethyl acetate (1:2) as eluent to give the alkene **29**[21] (1.036 g, 57%) as a syrup, α:β, 1:2; ν_{max}(film)/cm^{-1} 3000, 2960, 2860, 1740, 1230 and 1030; δ_H(200 MHz) 2.1 (6 H, 4 s, CH_3CO_2), 3.7–3.9 (6 H, 4 d, CH_3OP), 4.2–4.4 (3 H, m, 5-H and 6-H_2), 4.6–4.8 (1 H, m, 1-H), 5.2–5.4 (1 H, m, 4-H) and 5.85–6.2 (2 H, m, 2-, 3-H); δ_C(50 MHz) for α-anomer: 20.7 (CH_3CO_2), 51.8 and 53.6 (each d, $^2J_{C,P}$ 5.9, CH_3OP), 62.8 (C-6), 63.7 (C-4), 64.3 (d, $^3J_{C,P}$ 2.2, C-5), 72.1 (d, $^1J_{C,P}$ 181.1, C-1), 127.2 (d, $^3J_{C,P}$ 7.1, C-3), 127.2 (d, $^2J_{C,P}$ 11.2, C-2) and 169.8 and 170.4 (CH_3CO_2); for β-anomer: 20.5 (CH_3CO_2), 52.7 (d, $^2J_{C,P}$ 7.5, CH_3OP), 53.9 (d, $^2J_{C,P}$ 6.8, CH_3OP), 62.5 (C-6), 70.0 (d, $^1J_{C,P}$ 157.4, C-1), 70.2 (C-4), 73.8 (d, $^3J_{C,P}$ 19.7, C-5), 124.3 (C-3), 126.8 (d, $^2J_{C,P}$ 11.4, C-2) and 170.0 and 170.4 (CH_3CO_2); *m/z* 323 $(MH)^+$ and 263 $(M - AcO)^+$; *m/z* (FAB) 323 $(M + H)^+$ [Found: $M - OAc)^+$, 263.0678. Calc. for $C_{10}H_{16}O_6P$: *m/z*, 263.0685].

Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-1-dimethoxyphosphoryl-β-D-*arabino*-hexopyranoside 31

A mixture of phosphonates **25** and **27** (358 mg, 0.94 mmol) and *N*-bromosuccinimide (NBS) (167 mg, 0.94 mmol) in dry tetrachloromethane (5 cm^3) was stirred under irradiation from a large tungsten lamp, the progress of the reaction being monitored by TLC. On completion the mixture was filtered and the yellow solid residue was washed with dry tetrachloromethane. The combined organic filtrates were evaporated under reduced pressure at room temperature to give the crude bromo compound **30** as a yellow syrup [chromatography at this stage, with toluene–ethyl acetate (1:2) as eluent] gave bromide **30** (~25%) as a syrup which darkened on storage; δ_H(200 MHz) 1.97 (3 H, s, OAc), 2.01 (6 H, s, OAc), 2.32 (1 H, ddd, J_{gem} 13.8, $J_{2ax,3}$ 10.9, $^3J_{H,P}$ 6.7, 2-H^{ax}), 2.75 (1 H, dd, J_{gem} 13.8, $J_{2eq,3}$ 5.15, 2-H^{eq}), 3.87 and 3.90 (each 3 H, d, $^3J_{H,P}$ 10.5, CH_3OP), 4.07 (1 H, dd, J_{gem} 12.5, $J_{6a,5}$ 2.1, 6-H^a), 4.18 (1 H, dt, $J_{5,4}$ 10.1, $J_{5,6b}$ 3.7, $J_{5,6a} \sim {}^4J_{H,P} \sim$ 2.0, 5-H), 4.33 (1 H, ddd, J_{gem} 12.5, $J_{6b,5}$ 3.7, $^5J_{H,P}$ 0.5, 6-H^b), 5.09 (1 H, t, *J* 9.9, 4-H) and 5.42 (1 H, dddd, $J_{3,2ax}$ 10.9, $J_{3,4}$ 9.8, $J_{3,2eq}$ 5.15, $^4J_{H,P}$ 1.15, 3-H)].

A solution of this syrup in methanol (2 cm^3) containing 2,6-lutidine (0.33 cm^3, 0.95 mmol) was stirred at room temperature overnight, evaporated under reduced pressure and partitioned between dichloromethane and water. The organic extracts were washed with water, dried, and evaporated under reduced pressure to give a syrup, which was chromatographed on silica, with toluene–ethyl acetate (1:2) as eluent, to give the *glycoside* **31** (0.199 g, 51%) as a syrup, $[\alpha]_D$ +18.2 (*c* 0.88, $CHCl_3$); δ_H(200 MHz) 2.04, 2.06 and 2.08 (each 3 H, s, OAc), 2.05 (1 H, m, 2-H^{ax}), 2.47 (1 H, dt, J_{gem} 14.3, $J_{2eq,3} \sim {}^3J_{H,P} \sim$ 5.8, 2-H^{eq}), 3.50 (3 H, s, OMe), 3.80 and 3.83 (each 3 H, d, *J* 10.5, POMe), 4.13 (1 H, dd, J_{gem} 12.0, $J_{6a,5}$ 2.9, 6-H^a), 4.21 (1 H, dd, J_{gem} 11.9, $J_{6b,5}$ 4.3, 6-H^b), 4.30 (1 H, m, 5-H), 5.04 (1 H, t, *J* 8.85, 4-H) and 5.33 (1 H, dt, $J_{3,4} = J_{3,2ax}$ = 8.8, $J_{3,2eq}$ 5.7, 3-H); δ_C(50 MHz) 20.53 and 20.75 (CH_3CO_2), 33.35 (d, $^2J_{C,P}$ 14.7, C-2), 50.20 (d, $^3J_{C,P}$ 6.3, OMe), 53.57 and 54.06 (each d, $^2J_{C,P}$ 6.85, CH_3OP), 62.56 (C-6), 68.48 (C-4), 68.88, 72.18 (C-3 and -5), 98.99 (d, $^1J_{C,P}$ 203.6, C-1) and 169.7, 169.9 and 170.4 (CH_3CO_2); δ_P(81 MHz) 17.3 (Found: C, 43.8; H, 6.2. $C_{15}H_{25}O_7P$ requires C, 43.69; H, 6.12%).

Diethyl [3,4,6-tri-*O*-(*tert*-butyldiphenylsilyl)-2-deoxy-D-*arabino*-hex-1-enopyranosyl]phosphonate 33

A solution of the glucal derivative **32**[24] (1.417 g, 1.67 mmol) in dry THF (9 cm^3) was treated with a solution of *tert*-butyllithium in pentane (5.9 cm^3, 10.03 mmol) at −78 °C and the mixture was then warmed to 0 °C for 1 h. After the mixture had been cooled to −78 °C, diethyl chlorophosphate (1.45 cm^3, 10.03 mmol) was added to the stirred mixture. After 15 min, the reaction was quenched by the addition of aq. ammonium chloride and the mixture was partitioned between diethyl ether and water. The ether layer was washed with brine, dried, and evaporated under reduced pressure to give a yellow oil, which was chromatographed on silica with toluene–ethyl acetate (5:1) as eluent to give the unsaturated phosphonate **33** (0.79 g, 47%) as an oil, $[\alpha]_D$ −25.7 (*c* 1.05, $CHCl_3$); δ_H(200 MHz) 0.75, 0.90 and 1.0 (each 9 H, 3 s, Bu^t), 1.30 (6 H, 2 t, *J* 7.0, CH_3CH_2OP), 3.70 (1 H, dd, J_{gem} 11.4, $J_{6a,5}$ 4.3, 6-H^a), 3.85 (1 H, dt, $J_{3,2}$ 5.3, $J_{3,4}$ 2.0, $^4J_{H,P}$ 2.0, 3-H), 3.93 (1 H, m, 4-H), 4.02–4.23 (5 H, m, 6-H^b, CH_3CH_2OP), 4.33 (1 H, m, 5-H), 5.68 (1 H, ddd, $^3J_{H,P}$ 11.3, $J_{2,3}$ 5.3, $J_{2,4}$ 1.6, 2-H) and 7.2–7.6 (30 H, m, Ph); δ_C(50 MHz) 16.1 and 16.2 (CH_3CH_2OP), 18.7, 18.9 and 18.95 (Me_3CSi), 26.6 and 26.7 (Me_3CSi), 61.8 (C-6), 62.5 (d, $^2J_{C,P}$ 6.0, CH_3CH_2OP), 62.6 (d, $^2J_{C,P}$ 6.2, CH_3CH_2OP), 64.3 (d, $^3J_{C,P}$ 13.6, C-3/5), 69.4 (C-4), 80.5 (d, $^3J_{C,P}$ 8.5, C-5/3), 112.8 (d, $^2J_{C,P}$ 21.0, C-2), 127.5 and 129.5 (Ph), 132.8 (C-1 of Ph), 135.5 (Ph) and 144.5 (d, $^1J_{C,P}$ 220, C-1); δ_P(81 MHz) 9.64.

Methyl 2,6-anhydro-4,5,7-tri-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-D-arabino-hept-2-enonate 34

A solution of the protected glucal **32** (4.425 g, 5.2 mmol) in dry

THF (30 cm^3) was treated with a solution of *tert*-butyllithium in pentane (6.2 cm^3, 10.5 mmol) at −78 °C. The mixture was warmed to 0 °C for 1 h and then was cannulated into a stirred solution of methyl chloroformate (2.4 cm^3, 31.1 mmol) in THF (10 cm^3) at −78 °C. After 30 min, the reaction was quenched by the addition of aq. ammonium chloride and was partitioned between diethyl ether and water. The ether layer was washed with brine, dried, and evaporated under reduced pressure to give a yellow oil, which was chromatographed on silica with toluene as eluent to give the enoate **34** (2.81 g, 59%) as an oil, $[\alpha]_D$ −24.5 (*c* 0.98, $CHCl_3$); ν_{max}(film)/cm^{-1} 3070, 2960, 2930, 2900, 2860, 1710 and 1646; δ_H(200 MHz) 0.72, 0.90 and 1.00 (each 9 H, 3 s, Bu^t), 3.7–4.1 (4 H, m, 5-, 6-H and 7-H_2), 3.83 (3 H, s, CH_3O), 4.52 (1 H, m, 4-H), 5.68 (1 H, dd, $J_{3,4}$ 5.35, $J_{3,5}$ 1.56, 3-H) and 7.15–7.6 (30 H, m, Ph); δ_C(50 MHz) 18.7 and 19.0 (Me_3CSi), 26.6 and 26.7 (Me_3CSi), 52.0 (CH_3O), 61.6 (C-7), 65.3, 69.5 and 80.9 (C-4, -5, -6), 108.0 (C-3), 127.6–129.6 (Ph), 132.1 (C-1 of Ph), 135.5 (Ph), 142.1 (C-2) and 163.3 (C-1).

Methyl 2,6-anhydro-4,5,7-tri-*O*-benzyl-3-deoxy-D-*gluco*-heptonate 35

A solution of glycosylstannane **21** [16] (4.324 g, 6.12 mmol) in dry THF (50 cm^3) was treated with a solution of butyllithium in hexane (4.1 cm^3, 7.38 mmol) at −78 °C for 10 min. The resulting yellow solution was transferred by cannula into a solution of methyl chloroformate (4.7 cm^3, 60.83 mmol) in THF (20 cm^3) at −78 °C. After 1 h the reaction mixture was quenched by the addition of aq. ammonium chloride, warmed to room temperature, and extracted with diethyl ether. The organic phase was washed with more aq. ammonium chloride followed by brine, dried, and evaporated under reduced pressure to give a yellow oil, which was chromatographed on silica, with hexane–ethyl acetate (4:1) as eluent, to give the *anhydroaldonate* **35** (1.53 g, 53%) as a syrup, $[\alpha]_D$ +11.9 (*c* 1.01, $CHCl_3$); ν_{max}/cm^{-1} 3080, 3060, 3020, 2900, 2970 and 1730; δ_H(200 MHz) 1.74 (1 H, q, *J* 12.3, 3-H^{ax}), 2.52 (1 H, ddd, J_{gem} 12.8, $J_{3eq,4}$ 4.9, $J_{3eq,2}$ 2.1, 3-H^{eq}), 3.48 (1 H, m, 6-H), 3.52 (1 H, t, *J* 9.3, 5-H), 3.6–3.8 (3 H, m, 4-H, 7-H_2), 3.78 (3 H, s, OMe), 4.04 (1 H, dd, $J_{2,3ax}$ 12.3, $J_{2,3eq}$ 2.09, 2-H), 4.5–4.95 (6 H, 3 AB systems, CH_2Ph) and 7.3 (15 H, m, Ph); δ_C(50 MHz) 33.8 (C-3), 52.3 (CH_3O), 68.9 (C-7), 71.4 and 73.4 (CH_2Ph), 74.4 (C-4), 75.1 (C-2), 77.6 (C-5), 79.2 and 80.4 (C-4, -6), 127–129 (Ph), 138.1 (C-1 of Ph) and 170.4 (CO) (Found: C, 73.0; H, 6.8. $C_{29}H_{32}O_6$ requires C, 73.09; H, 6.77%).

Methyl 3,7-anhydro-5,6,8-tri-*O*-benzyl-2,4-dideoxy-3-methoxycarbonyl-D-*gluco*-octonate 36

A solution of ester **35** (80 mg, 0.17 mmol) in dry THF (5 cm^3) was added dropwise to a stirred solution of sodium bis(trimethylsilyl)amide (0.34 mmol) in dry THF (5 cm^3) at −78 °C. After 30 min, methyl bromoacetate (0.1 cm^3, 1.06 mmol) was added and the mixture was stirred at −78 °C for a further 15 min. The reaction was quenched with aq. ammonium chloride and the mixture was partitioned between diethyl ether and water. The ethereal layer was washed successively with aq. ammonium chloride and brine, dried, and evaporated under reduced pressure to give a pale yellow syrup, which was purified by HPLC [Dynamax 6 mm column; hexane–ethyl acetate (4:1), 12.5 cm^3 min^{-1}] to give the *diester* **36** (45 mg, 48%) as an oil, $[\alpha]_D$ +40.0 (*c* 1.15, $CHCl_3$); δ_H(270 MHz) 1.69 (1 H, dd, J_{gem} 13.1, $J_{4ax,5}$ 11.6, 4-H^{ax}), 2.74 (1 H, dd, J_{gem} 13.1, $J_{4eq,5}$ 4.35, 4-H^{eq}), 2.80 (1 H, d, J_{gem} 14.0, 2-H^a), 2.85 (1 H, d, J_{gem} 14.0, 2-H^b), 3.68 (3 H, s, CH_3O), 3.70–3.90 (5 H, m, 5-, 6-, 7-H and 8-H_2), 3.73 (3 H, s, CH_3O), 4.5–4.75 (5 H, m, CH_2Ph), 4.88 (1 H, d, *J* 10, CH_2Ph) and 7.3–7.5 (15 H, m, Ph); δ_C(50 MHz) 37.4 (C-4), 45.1 (C-2), 51.8 and 52.4 (CH_3O), 69.1 (C-8), 71.8, 73.3 and 750 (CH_2Ph), 76.2, 77.0, 77.6 and 78.1 (C-3, 5, 6 and 7), 127.7–128.4 (Ph), 138.5 (C-1 of Ph) and 169.5 and 172.1 (CO) (Found: C, 69.8; H, 6.6. $C_{32}H_{36}O_8$ requires C, 70.06; H, 6.61%).

Further elution of the column gave residual starting material (12.5 mg, 16% recovery).

***tert*-Butyl 3,7-anhydro-5,6,8-tri-*O*-benzyl-2,4-dideoxy-3-methoxycarbonyl-D-*gluco*-octonate 37 and *tert*-butyl 4,8-anhydro-6,7,9-tri-*O*-benzyl-3-*tert*-butoxycarbonyl-2,3,5-trideoxy-4-methoxycarbonyl-D-*gluco*-nononate 38**

A solution of ester **35** (434 mg, 0.91 mmol) in dry THF (20 cm^3) was added dropwise to a stirred solution of sodium bis(trimethylsilyl)amide (1.1 mmol) in dry THF (20 cm^3) at −78 °C. After 30 min, *tert*-butyl bromoacetate (0.37 cm^3, 2.29 mmol) was added and the mixture was stirred at −78 °C for a further 15 min. The reaction was quenched with aq. ammonium chloride and the solution was partitioned between diethyl ether and water. The ethereal layer was washed successively with aq. ammonium chloride and brine, dried, and evaporated under reduced pressure to give a pale yellow syrup, which was chromatographed on silica, with light petroleum–ethyl acetate (7:1) as eluent to give first the *triester* **38** (67.4 mg, 10.5%) as a syrup, $[\alpha]_D$ +25.4 (*c* 0.59, $CHCl_3$); δ_H(200 MHz) 1.42 and 1.44 (each 9 H, s, Me_3CO), 1.58 (1 H, dd, J_{gem} 13.1, $J_{5ax,6}$ 11.2, 5-H^{ax}), 2.51 (1 H, dd, J_{gem} 13.1, $J_{5eq,6}$ 4.81, 5-H^{eq}), 2.62 (1 H, dd, J_{gem} 17.0, $J_{2a,3}$ 4.3, 2-H^a), 2.72 (1 H, dd, J_{gem} 17.0, $J_{2b,3}$ 10.7, 2-H^b), 3.30 (1 H, dd, $J_{3,2b}$ 10.7, $J_{3,2a}$ 4.20, 3-H), 3.4–3.5 (2 H, m, 7- and 8-H), 3.65–3.8 (3 H, m, 6-H and 9-H_2), 3.72 (3 H, s, OMe), 4.5–4.9 (6 H, 3 AB systems, CH_2Ph) and 7.2–7.4 (15 H, m, Ph); δ_C(50 MHz) 27.8 and 28.0 (Me_3CO), 32.4 and 33.0 (C-2, -5), 49.8 (C-3), 52.3 (CH_3O), 69.2 (C-9), 71.7, 73.2 and 75.0 (CH_2Ph), 76.1, 77.6 and 78.5 (C-6, -7, -8), 80.1 and 80.7 (Me_3CO), 81.3 (C-4), 127.4–128.3 (Ph), 138.5 (C-1 of Ph) and 169.5, 171.1 and 171.7 (CO) (Found: C, 69.6; H, 7.4. $C_{41}H_{52}O_{10}$ requires C, 69.85; H, 7.45%).

Further elution of the column gave the diester **37** (173 mg, 32%), $[\alpha]_D$ +33.8 (*c* 0.71, $CHCl_3$); δ_H(200 MHz) 1.43 (9 H, s, Me_3CO), 1.65 (1 H, dd, J_{gem} 12.9, $J_{4ax,5}$ 11.5, 4-H^{ax}), 2.69 (1 H, dd, J_{gem} 12.9, $J_{4eq,5}$ 4.56, 4-H^{eq}), 2.70 (1 H, d, J_{gem} 14.1, 2-H^a), 2.74 (1 H, d, J_{gem} 14.1, 2-H^b), 3.65–3.80 (5 H, m), 3.72 (3 H, s, CH_3O), 4.50–4.72 (5 H, m, CH_2Ph), 4.87 (1 H, d, *J* 10.5, CH_2Ph) and 7.2–7.4 (15 H, m, Ph); δ_C(50 MHz) 28.0 (Me_3CO), 37.4 (C-4), 46.7 (C-2), 52.2 (CH_3O), 69.2 (C-8), 71.7, 73.4 and 74.9 (CH_2Ph), 76.0, 77.8 and 78.2 (C-5, -6, -7), 81.2 (C-3), 127.4–129.7 (Ph), 138.5 (C-1 of Ph) and 168.1 and 172.1 (CO); *m/z* 533 (M − Bu^t)$^{\cdot+}$ and 499 (M − Bn)$^+$ [Found for (M − Bu^t)$^+$: *m/z* 533.2180. $C_{31}H_{33}O_8$ requires *m/z* 533.2175. Found for (M − $PhCH_2$)$^+$, *m/z* 499.2337. $C_{28}H_{35}O_8$ requires *m/z* 499.2332].

3,7-Anhydro-3-carboxy-2,4-dideoxy-D-*gluco*-octonic acid 14

A solution of diester **37** (277 mg, 0.47 mmol) in methanol (10 cm^3) and aq. sodium hydroxide (10% w/v; 2 cm^3) was heated under reflux for 2.5 h and was then evaporated under reduced pressure to give a yellow syrup, which was partitioned between hydrochloric acid (1 mol dm^{-3}) and dichloromethane. The organic layer was washed with water and evaporated under reduced pressure. The residue was maintained in trifluoroacetic acid (TFA) (2 cm^3) at 0 °C for 1 h. Evaporation under reduced pressure gave a yellow oil, which was dissolved in methanol (20 cm^3) and hydrogenated at 1 atm overnight with palladium-on-charcoal (5%; 140 mg) as catalyst. Filtration of the suspension and concentration of the filtrate under reduced pressure gave compound **14** (108 mg, 92%) as a syrup, $[\alpha]_D$ + 46.15 (*c* 0.84, CH_3OH); δ_H(200 MHz; CD_3OD) 1.61 (1 H, dd, J_{gem} 12.9, $J_{4ax,5}$ 11.9, 4-H^{ax}), 2.53 (1 H, dd, J_{gem} 12.9, $J_{4eq,5}$ 4.7, 4-H^{eq}), 2.72 (1 H, d, *J* 14.9, 2-H^a), 2.78 (1 H, d, *J* 14.9, 2-H^b), 3.23 (1 H, t, $J_{6,5}$ = $J_{6,7}$ = 9.2, 6-H) and 3.54–3.85 (4 H, m, 5- and 7-H and 8-H_2); δ_C(50 MHz; CD_3OD) 40.9 (C-4), 45.8 (C-2), 62.8 (C-8), 70.9, 72.6 and 78.5 (C-5, -6, -7), 78.9 (C-3) and 173.3 and 175.5 (CO); *m/z* (FAB) 251 (MH)$^{\cdot+}$ and 273 (MNa)$^+$ [Found: MH$^+$ (FAB), 251.0742. $C_9H_{15}O_8$ requires *m/z* 251.0767].

Acknowledgements

We thank SERC/EPSRC and Zeneca Agrochemicals for financial support under the CASE Scheme. We are also grateful for access to EPSRC central facilities for high-resolution NMR spectroscopy (University of Warwick) and mass spectrometry (University of Wales, Swansea).

References

1 E. Haslam, *Shikimic Acid: Metabolism and Metabolites*, Wiley, Chichester, 1993; P. M. Dewick, *Nat. Prod. Rep.*, 1995, **12**, 101, and earlier annual reviews in this series.
2 S. L. Bender, T. Widlanski and J. R. Knowles, *Biochemistry*, 1989, **28**, 7560.
3 T. Widlanski, S. L. Bender and J. R. Knowles, *Biochemistry*, 1989, **28**, 7572.
4 G. M. Kishore and G. M. Shah, *Annu. Rev. Biochem.*, 1988, **57**, 627, and refs. therein.
5 J. G. Buchanan, A. P. W. Clelland, T. Johnson, R. A. C. Rennie and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2593.
6 S. Myrvold, L. M. Reimer, D. L. Pompliano and J. W. Frost, *J. Am. Chem. Soc.*, 1989, **111**, 1861.
7 L. T. Piehler, J.-L. Montchamp, J. W. Frost and C. J. Manly, *Tetrahedron*, 1991, **47**, 2423.
8 H. G. Floss, D. K. Onderka and M. Carroll, *J. Biol. Chem.*, 1972, **247**, 736.
9 A. B. DeLeo and D. B. Sprinson, *Biochem. Biophys. Res. Commun.*, 1968, **32**, 373; H. Nagano and H. Zalkin, *Arch. Biochem. Biophys.*, 1970, **138**, 58.
10 S. Sheffer-Dee-Noor, V. Belakhov and T. Baasov, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 1583, and refs. therein.
11 R. Meuwly and A. Vasella, *Helv. Chim. Acta*, 1986, **69**, 25; K. Wallimann and A. Vasella, *Helv. Chim. Acta*, 1990, **73**, 1359.
12 K. Briner and A. Vasella, *Helv. Chim. Acta*, 1987, **70**, 1341; A. Vasella and R. Wyler, *Helv. Chim. Acta*, 1991, **74**, 451.
13 K. Bock and C. Pedersen, *Adv. Carbohydr. Chem. Biochem.*, 1983, **41**, 27.
14 *e.g.*, M. M. Vaghefi, R. J. Bernacki, N. K. Dalley, B. E. Wilson and R. K. Robins, *J. Med. Chem.*, 1987, **30**, 1383.
15 G. W. Buchanan and J. H. Bowen, *Can. J. Chem.*, 1977, **55**, 604; J. Thiem and B. Meyer, *Org. Magn. Reson.*, 1978, **11**, 50.
16 P. Lesimple, J.-M. Beau and P. Sinaÿ, *Carbohydr. Res.*, 1987, **171**, 289.
17 W. C. Still, *J. Am. Chem. Soc.*, 1978, **100**, 1481.
18 B. Giese, S. Gilges, K. S. Gröninger, C. Lamberth and T. Witzel, *Liebigs Ann. Chem.*, 1988, 615.
19 For a review, see R. R. Schmidt and W. Kinzy, *Adv. Carbohydr. Chem. Biochem.*, 1994, **50**, 21.
20 J. Fiandor, M. T. Garcia-Lopéz, F. G. de las Heras and P. P. Méndez-Castrillón, *Synthesis*, 1985, 1121.
21 H. Paulsen and J. Thiem, *Chem. Ber.*, 1973, **106**, 3850.
22 *e.g.* L. Evelyn, L. D. Hall, P. R. Steiner and D. H. Stocker, *Org. Magn. Reson.*, 1973, **5**, 121; J. R. Neeser, J. M. J. Tronchet and E. Cherollais, *Can. J. Chem.*, 1983, **61**, 2112.
23 L. Somsák and R. J. Ferrier, *Adv. Carbohydr. Chem. Biochem.*, 1991, **49**, 37, and refs. therein.
24 R. W. Friesen, C. F. Sturino, A. K. Daljeet and A. Kolaczewska, *J. Org. Chem.*, 1991, **56**, 1944.
25 P. Lesimple, J.-M. Beau, G. Jaurand and P. Sinaÿ, *Tetrahedron Lett.*, 1986, **27**, 6201.
26 I. D. Blackburn, P. M. Fredericks and R. D. Guthrie, *Aust. J. Chem.*, 1976, **29**, 381.

Paper 5/05418D
Received 14*th August* 1995
Accepted 30*th August* 1995