Synthesis of *C*-Glycosyltetrazoles Related to 3-Deoxy-D-*arabino*-heptulosonic Acid 7-Phosphate (DAHP); Potential Inhibitors of Early Steps in the Shikimate Pathway

J. Grant Buchanan,†[a] Andrew P. W. Clelland,[a] Trevor Johnson,[b] Robert A. C. Rennie[b] and Richard H. Wightman*[a]

[a] *Department of Chemistry, Heriot-Watt University, Riccarton, Edinburgh, EH14 4AS, UK*
[b] *Corporate Carbohydrate Group, ICI plc, The Heath, Runcorn, Cheshire, WA7 4QE, UK*

Treatment of 3,4,5,7-tetra-*O*-acetyl-2,6-anhydro-D-*glycero*-D-*galacto*-heptononitrile **16** with diazabicycloundecene (DBU) formed 4,5,7-tri-*O*-acetyl-2,6-anhydro-3-deoxy-D-*arabino*-hept-2-enononitrile **22**, which on treatment with ammonium azide gave the corresponding unsaturated tetrazole **23**. Stereoselective catalytic reduction of **23** and subsequent deacetylation produced 5-(2-deoxy-β-D-*arabino*-hexopyranosyl)tetrazole **24**, which was converted in two steps into its 6-phosphate **10**.

Reaction of 4,5,7-tri-*O*-acetyl-2,6-anhydro-3-deoxy-D-*manno*-heptononitrile **27** with ammonium azide, followed by deacetylation, gave 5-(2-deoxy-α-D-*arabino*-hexopyranosyl)tetrazole **29** (81% overall), which was converted into its 6-phosphate **11**.

When 4,5,7-tri-*O*-acetyl-2,6-anhydro-2-bromo-3-deoxy-D-*gluco*-heptononitrile **31** was treated with methanol and 2,6-lutidine, methyl 3,4,6-tri-*O*-acetyl-1-cyano-2-deoxy-β-D-*arabino*-hexopyranoside **34** was obtained (40%) together with the α-anomer **35** (11%). Cycloaddition of **34** with azide ion, followed by sequential treatment with base and with acid, gave 2-deoxy-1-tetrazol-5-yl-α-D-*arabino*-hexopyranose **12** (54% overall).

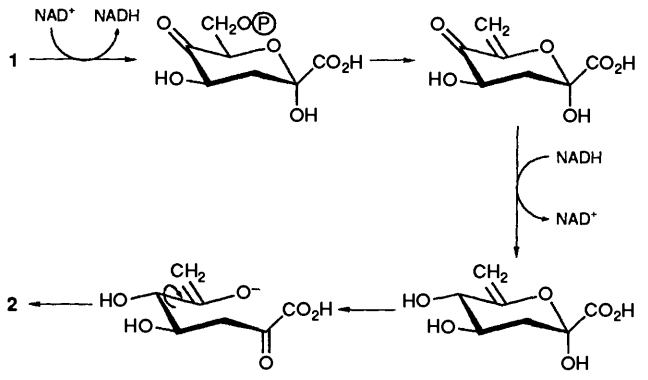
Treatment of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-*lyxo*-hexopyranose **38** with trimethylsilyl cyanide and boron trifluoride in nitromethane gave 4,5,7-tri-*O*-acetyl-2,6-anhydro-3-deoxy-D-*talo*-heptononitrile **40** (53%), together with the D-*galacto*-epimer **39** (17%). Cycloaddition of **39** and **40** with azide ion and subsequent deprotection gave 5-(2-deoxy-β-D-*lyxo*-hexopyranosyl)tetrazole **13** and the α-D-*lyxo*-isomer **14** respectively in good yields. Reaction of nitrile **40** with *N*-bromosuccinimide formed 4,5,7-tri-*O*-acetyl-2,6-anhydro-2-bromo-3-deoxy-D-*galacto*-heptononitrile **43** (63%), which with methanol and 2,6-lutidine was converted into the methyl β-D-glycoside **44**. Cycloaddition of **44** with azide ion, deacetylation, and hydrolysis led to 2-deoxy-1-tetrazol-5-yl-α-D-*lyxo*-hexopyranose **15**.

None of the *C*-glycosyltetrazoles were strong inhibitors of dehydroquinate synthase from *E. coli*.

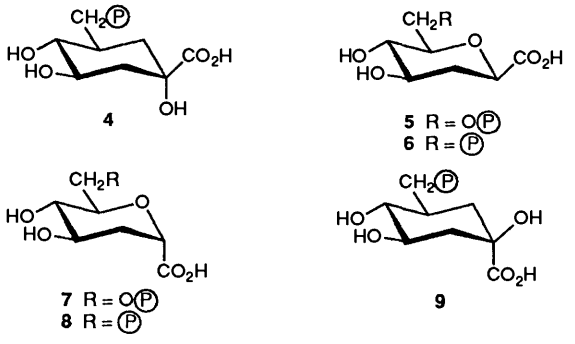
The first step in the shikimate pathway,[1] by which aromatic amino acids are produced in plants and microorganisms, involves the condensation of D-erythrose 4-phosphate and phosphoenolpyruvate to produce 3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate **1** (DAHP). DAHP is then converted into 3-dehydroquinate **2** (DHQ) the first carbocyclic compound of the pathway, by the enzyme DHQ synthase (EC 4.6.1.3). This enzyme, as purified from *Escherichia coli*, is a relatively small protein of 362 amino acid residues,[2] although in many lower eukaryotes dehydroquinate synthase activity is part of a multifunctional protein, the appropriate segment of which has been shown, in the case of *Saccharomyces cerevisiae*, to have considerable homology with the *E. coli* enzyme.[3] DHQ synthase is dependent for activity on the presence of zinc ions[4,5] and nicotinamide adenine dinucleotide (NAD^+).[2,5] The requirement for NAD^+ is not immediately evident, since the overall reaction catalysed is redox-neutral, but can be accounted for by the mechanism in Scheme 1, which is essentially that proposed in 1963 by Sprinson and co-workers.[6] Recently, in elegant and incisive studies, Knowles and co-workers have probed the mechanism of Scheme 1 by the use of a series of substrate analogues, which, on account of their structural variations, can only proceed partially along the reaction pathway.[7,8] This work has shown the validity of the proposals in Scheme 1 and has led to the suggestion that the role of the enzyme may be at best minimal in the later stages of the process, with intermediate **3** being released from the enzyme and undergoing spontaneous rearrangement to DHQ **2**.[8] This idea, which circumvents the problem of how such a small enzyme could perform all the individual steps of Scheme 1, is supported by the work of Bartlett and Satake, who generated intermediate **3** photochemically, and showed its stereospecific rearrangement to DHQ **2**.[9]

During their work, Knowles and co-workers prepared a number of inhibitors of DHQ synthase, including the carbocyclic phosphonate **4**[7] and the 2-deoxy-analogue **5**.[8] Frost and

† *Present address:* School of Chemistry, University of Bath, Bath, BA2 7AY, UK.

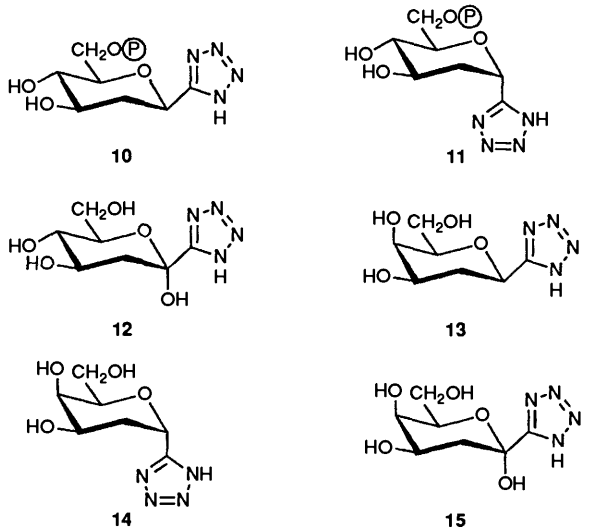


Scheme 1



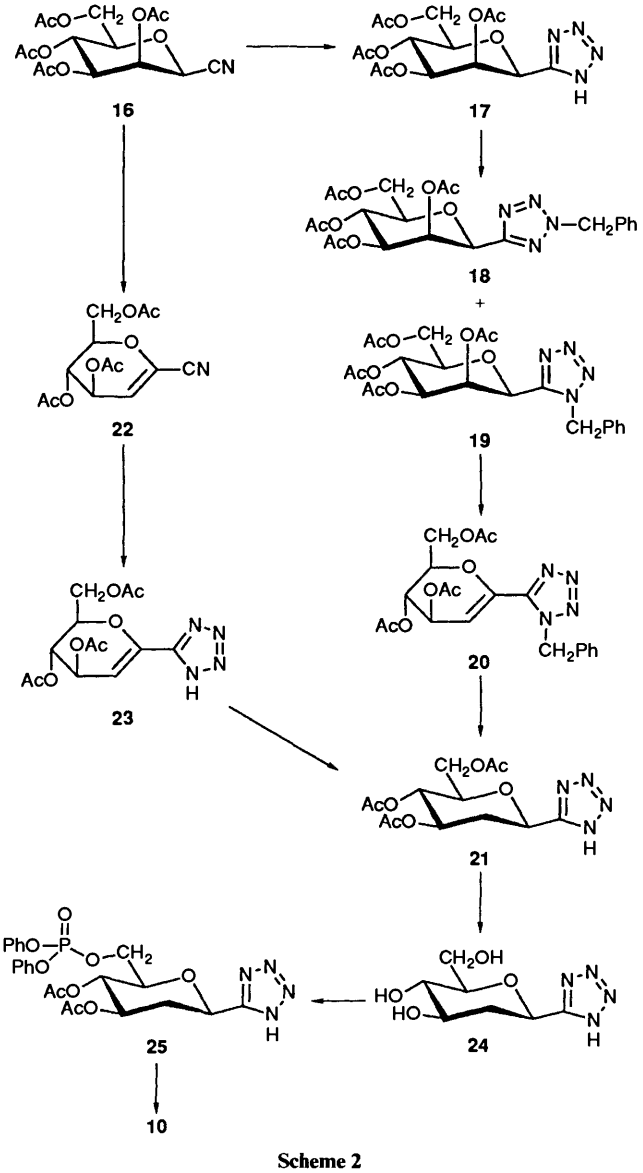
co-workers have reported that the anomer **7** is a somewhat more powerful inhibitor of *E. Coli* DHQ synthase than is **5**.[10] The same workers have also prepared the anomeric phosphonates **6** and **8**; the α-carboxy compound **8** was a competitive inhibitor of DHQ synthase from both *E. coli*[10] and *Pisum sativum*,[11] whilst the β-carboxy anomer **6** was not inhibitory. The same group has also reported that the anomer **9** related to **4** is also an inhibitor of DHQ synthase; this result had been predicted on the basis of computational modelling and the K_i values of **4** and **9** were found to be very comparable.[12,13]

It is well established that a number of commercial herbicidal compounds act by inhibition of amino acid biosynthesis, and indeed the broad-spectrum herbicide *N*-phosphonomethylglycine (glyphosate) has as its primary target a later step in the shikimate pathway to the aromatic amino acids.[14] We have been interested in the synthesis of analogues of DAHP **1** as potential herbicidal agents, and, since it is well established that a



tetrazole unit can act as an isopolar and isosteric replacement for the carboxy group,[15] we have addressed the synthesis of tetrazole analogues of **1**. The inhibitory activity of the analogues **7**–**9**, with α-carboxy groups, led us to propose as initial targets both the analogues **10** and **11** of 2-deoxy-DAHP. In this paper we report the synthesis of **10** and **11**, together with the analogue **12** of 3-deoxy-D-*arabino*-heptulosonic acid. We also describe related compounds **13**–**15** with epimeric stereochemistry at the position where, in DAHP **1**, oxidation–reduction occurs in the conversion into DHQ **2**.

We envisaged that a stereoselective route to the 2′-deoxy-β-D-glycosyltetrazole **10** could rely, for correct establishment of stereochemistry, on the reduction of a 1′,2′-ene. As a precursor to such an alkene we were attracted to the β-D-mannopyranosyl cyanide **16**, recently prepared by Köll and Fortsch by reductive dehydration of the corresponding nitromethyl compound using phosphorus trichloride in pyridine,[16] since generation of a glycal from such a compound by *trans*-diaxial elimination of acetic acid should be favourable. Glycopyranosyl cyanides can be converted into the corresponding tetrazoles by cycloaddition with azide[17] and, in our first approach to **10**, nitrile **16** was converted smoothly into tetrazole **17** (Scheme 2) by treatment with sodium azide and ammonium chloride in dimethyl formamide (DMF). It was felt that protection of the acidic tetrazole



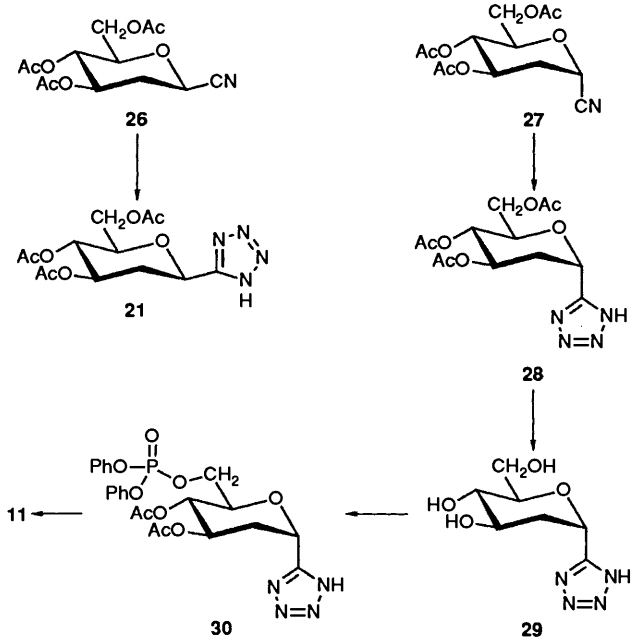
Scheme 2

ring would be necessary before base-catalysed elimination, and thus **17** was treated with benzyl bromide and triethylamine. It has been reported that alkylation of tetrazoles with an electron-donating substituent at C-5 gives predominantly the 1,5-disubstituted product, but this conclusion can be affected by steric factors.[18] In the case of **17**, two products were produced in a ratio of *ca.* 2:1 (70% combined yield). The major product was assigned as the 1,5-disubstituted tetrazole **19** on the basis of ^{1}H NMR spectroscopic data; the benzylic methylene group in **19** appeared as an AB double doublet, indicative of restricted rotation, whilst in the minor isomer **18** the corresponding signal was a singlet. Additionally, the anomeric proton (1′-H) in **19** was somewhat shielded (0.26 ppm), due to the proximity of the phenyl group, as compared with the equivalent signal from **18**.

When the 1,5-disubstituted tetrazole **19** was treated with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in dichloromethane, the alkene **20** was produced, but only in poor yield. The isomer **18** was inert to the same conditions, and this difference in behaviour can be ascribed to the greater stabilization of an incipient carbanion at C-1′ in isomer **19**. Alkene **20** could be hydrogenated readily, with concomitant hydrogenolysis of the *N*-benzyl group, to give the crystalline 2′-deoxy-β-D-*arabino*-hexopyranosyltetrazole **21** in 92% yield. The stereochemistry at C-1′ in **21** was clear from the ^{1}H NMR spectrum in which the signal of 1′-H displayed a large (12.0 Hz) *trans*-diaxial coupling with the axial proton at C-2′.

A better route to the tetrazole **21** could be developed by carrying out the elimination prior to formation of the tetrazole. Thus, treatment of nitrile **16** with DBU formed the α,β-unsaturated nitrile **22** cleanly. Attempts at reduction of the alkene unit of **22** were unsuccessful, but it was found that treatment of **22** with ammonium azide produced the unsaturated tetrazole **23** with no competing cycloaddition to the alkenyl unit. Subsequent catalytic hydrogenation of **23** then gave **21** in good yield.

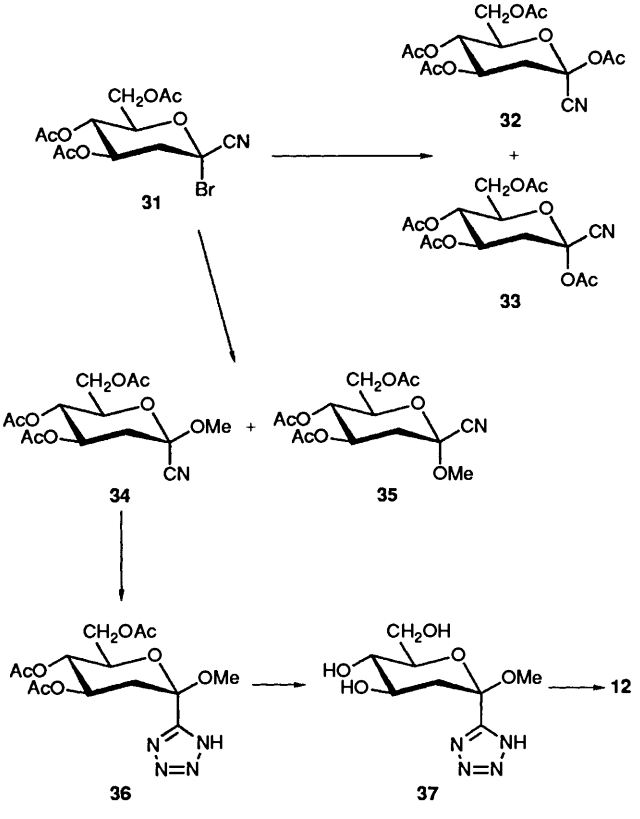
Deacetylation of **21** with sodium methoxide in methanol gave the crystalline triol **24** in high yield. Treatment of this with two equivalents of diphenyl phosphorochloridate in pyridine, followed by acetylation, led to isolation of the 6′-*O*-diphenyl phosphate **25** in *ca* 20% yield. A second equivalent of the phosphorylating reagent was necessary in this step, presumably due to transient phosphorylation of the tetrazole ring. Hydrogenolysis of **25** over platinum oxide, followed by Zemplen deacetylation, then led to the DAHP analogue **10** (71%).



Scheme 3

We have previously reported the preparation of the separable isomers **26** and **27** from 1,3,4,6-tetra-*O*-acetyl-α-D-*arabino*-hexopyranose.[19] The β-nitrile **26** provided an alternative high-yielding route to the β-tetrazole **21** by cycloaddition with ammonium azide (Scheme 3). The α-nitrile **27** in the same way gave rise to the epimeric tetrazole **28** in 90% yield, although it was observed that this cycloaddition proceeded at a significantly slower rate than the other cases above. The α-tetrazole **28** was converted into DAHP analogue **11** *via* the intermediacy of **29** and **30**, by methods analogous to those used in the epimeric series. The stereochemistry at the anomeric centre of compounds in the two series was evident from the magnitudes of the coupling constants shown by the anomeric proton.

For the preparation of analogue **12**, the bromonitrile **31**[19] provided a convenient starting material (Scheme 4). Treatment of **31** with silver acetate in acetic acid-acetic anhydride[20] gave a



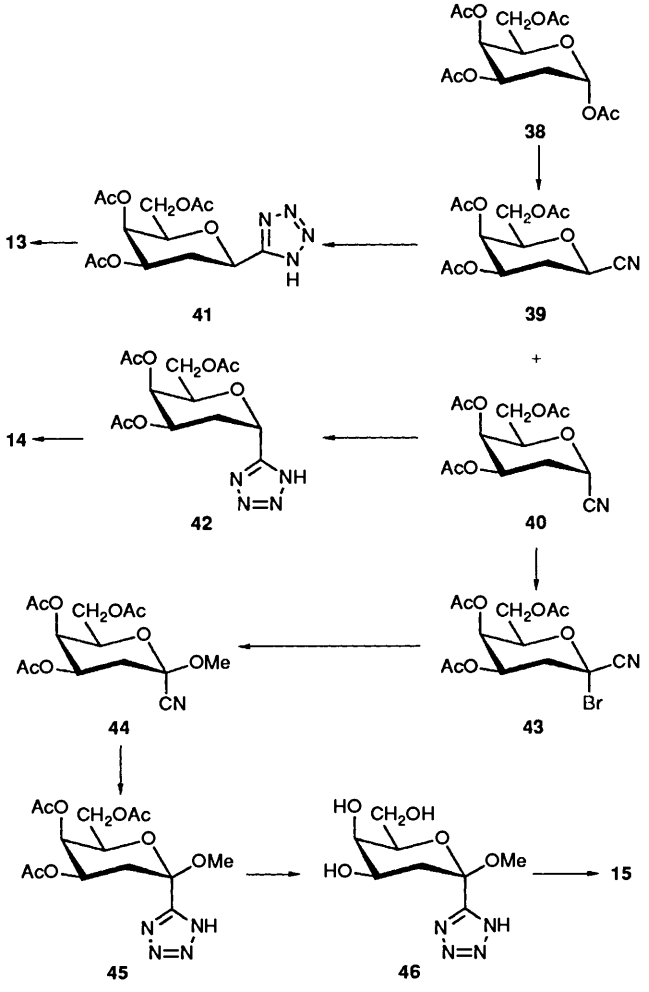
Scheme 4

mixture of the two α-acetoxy nitriles **32** and **33** in a ratio of 5:2. The stereochemistry of these compounds was clear from the proton-coupled ^{13}C NMR spectrum of **32**, which displayed a three-bond heteronuclear coupling of 7.78 Hz between the nitrile carbon and the axial hydrogen at C-2, such a value being typical of a *trans*-diaxial relationship between these atoms.[20–22] Thus the major product of this reaction is formed with inversion of configuration. However, attempts to convert **32** and **33** into tetrazoles were unsuccessful, leading to a range of uncharacterised products.

More success was achieved by reaction of **31** with methanol containing 2,6-lutidine, which led to the slow formation of the methyl glycosides **34** and **35** in a ratio of *ca.* 4:1 (51% combined yield). Attempts to accelerate this reaction by the addition of silver triflate led to the formation of an ortholactone.[19] Again configurations of **34** and **35** could be assigned from ^{13}C–^{1}H coupling constants ($^3J_{CN,H\text{-}2ax}$ 7.5 Hz for **34**, 1.5 Hz for **35**), and the reaction thus proceeds with predominant inversion of configuration. The axial nitrile group in **34** underwent slow but

clean cycloaddition with ammonium azide in DMF at 70 °C to give tetrazole **36** in 90% yield, and this could be deacetylated by sodium methoxide in methanol to give triol **37**. When the ^1H NMR spectrum of **37** was recorded in D_2O, it became apparent that slow hydrolysis was occurring, leading to the production of methanol. It was subsequently found that when **37** was left to stand for several days in aqueous solution it was converted into the ketose **12** in good yield. This rapid hydrolysis, without added acid, presumably involves intramolecular catalysis by proton donation from the tetrazole ring to the methoxy group. The observed three-bond coupling of 3.4 Hz between the tetrazole carbon and the axial proton at C-2 strongly implies that **12** has the indicated configuration at the anomeric centre, as would be expected at equilibrium after mutarotation had been permitted to occur. Unfortunately, attempts at phosphorylation of both **37** and **12** were unsuccessful, with a range of unidentified products being formed in each case.

Routes to the analogues **13**–**15** of D-*lyxo*-configuration were developed along similar lines (Scheme 5). Thus, treatment of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-*lyxo*-hexopyranose **38**[23] with trimethylsilyl cyanide and boron trifluoride–diethyl ether in nitromethane[24] gave a separable mixture of the 2,6-anhydro-



Scheme 5

D-*galacto*-heptononitrile **39** and its D-*talo*-epimer **40** in a ratio of *ca.* 1:3 (70% combined yield). Nitriles **39** and **40** were converted into tetrazoles **41** and **42** respectively in good yield; again it was noted that a longer reaction time was needed in the case of α-nitrile **40**. Deacetylation of **41** and **42** produced the triols **13** and **14** respectively. Treatment of the α-nitrile **40** with *N*-bromosuccinimide and dibenzoyl peroxide in refluxing carbon tetrachloride[21] led to the somewhat unstable bromo nitrile **43** in 63% yield. This reaction, involving the abstraction of an equatorial hydrogen, proceeded slowly;[19] the stereochemistry of **43**, with bromine axial, is assigned based on precedent.[19,21] Reaction of **43** with methanol and 2,6-lutidine gave methyl glycoside **44** in moderate yield; none of the epimer could be isolated in this series, and the α-orientation of the nitrile in **44** was confirmed by ^{13}C NMR spectroscopic data ($^3J_{CN,H\text{-}2ax}$ 7.6 Hz, $^3J_{CN,H\text{-}2eq}$ 2.1 Hz). Cycloaddition to the axial nitrile was again slow but efficient, and the resultant tetrazole **45** was deacetylated under Zemplen conditions to give triol **46** ($^3J_{tetrazole\text{-}C,H\text{-}2ax}$ 5.2 Hz). As in the isomeric series above, **46** underwent slow hydrolysis in aqueous solution to give the ketose **15**, in the proton-coupled ^{13}C NMR spectrum of which the tetrazole carbon (δ 158.7) appeared as a broad singlet, indicating that the tetrazole ring occupied an equatorial position.

Each of the deprotected tetrazole analogues **10**–**15** were evaluated as inhibitors of DHQ synthase from *E. coli*, but none of them showed significant inhibition at sub-millimolar concentrations. The non-phosphorylated analogues **12**–**15**, **24** and **29** were also subjected to herbicidal and anti-bacterial screening but were without significant activity.

Experimental

NMR spectra were recorded on Bruker WP 200SY, WP 360 and AM 500 instruments, with $CDCl_3$ as solvent unless otherwise stated. *J* Values are given in Hz. Mass spectrometry was performed using VG updated MS9 and VG ZAB-E high resolution EI/CI/FAB instruments. Specific rotations were measured at room temperature using a Bendix-NPL 143D automatic polarimeter (path length 1 cm); units for $[\alpha]_D$-values are 10^{-1} deg cm^2 g^{-1}.

Column chromatography was carried out using Kieselgel H type 60 (Merck); an external pressure was applied to the top of columns. Light petroleum refers to the fraction of boiling range 40–60 °C. Melting points were determined on an Electrothermal Mk II apparatus in capillaries and are uncorrected. Organic extracts were dried over anhydrous magnesium sulfate.

5-(2,3,4,6-*Tetra*-O-*acetyl*-β-D-*mannopyranosyl*)*tetrazole* **17**.—A solution of heptononitrile **16**[16] (6.5 g, 16 mmol), sodium azide (1.56 g, 24 mmol), and ammonium chloride (1.27 g, 24 mmol) in DMF (30 cm^3) was maintained at 70 °C for 24 h. The residual syrup after evaporation was dissolved in water (10 cm^3). Addition of aqueous acetic acid (10%; 5 cm^3) gave a white precipitate which was filtered to yield *tetrazole* **17** (4.9 g, 67%), m.p. 194–196 °C, $[\alpha]_D$ −40.4 (*c* 1.1, CH_3CN); δ_H(200 MHz; CD_3OD) 1.97, 1.99, 2.00 and 2.07 (each 3 H, s, OAc), 4.12 (1 H, m, 5′-H), 4.21 (1 H, dd, J_{gem} 12.47, $J_{6'a,5'}$ 2.25, 6′$_a$-H), 4.38 (1 H, dd, $J_{6'b,5'}$ 5.22, 6′$_b$-H), 5.3–5.45 (2 H, m, 3′, 4′-H), 5.55 (1 H, d, $J_{1',2'}$ 1.43, 1′-H) and 5.75 (1 H, dd, $J_{2',3'}$ 3.03, 2′-H); δ_C(50 MHz; CD_3OD) 20.2, 20.5 and 20.6 (×2) (CO*Me*), 63.7 (C-6′), 66.9, 70.7, 72.6, 72.8, 77.9, 154.8 (C-5), 171.2, 171.4, 171.5 and 172.4 (*C*OMe); *m/z* 400 (M^+) and 358 ($M^+ - N_3$) (Found: C, 44.8; H, 5.0; N, 13.8. $C_{15}H_{20}N_4O_9$ requires C, 45.00; H, 5.05; N, 14.00%).

5-(2,3,4,6-*Tetra*-O-*acetyl*-β-D-*mannopyranosyl*)-2-*benzyl*- **18** *and* -1-*benzyltetrazole* **19**.—Triethylamine (1.8 cm^3) and benzyl bromide (1.5 cm^3, 12.6 mmol) were added to a solution of tetrazole **17** (4.9 g, 12 mmol) in acetone (25 cm^3). The mixture was stirred for 3 h at room temperature, filtered, and evaporated. The residue was partitioned between water (100 cm^3) and ether (3 × 100 cm^3). The organic layer was washed with dil. hydrochloric acid, dried and evaporated. The residue was chromatographed on silica with toluene–diethyl ether (10:1) as eluent to yield firstly the 2-*benzyltetrazole* **18** (1.4 g, 23%), m.p.

154–156 °C, $[\ddot{\alpha}]_D$ −33.7 (*c* 1.25, CH_2Cl_2); δ_H(200 MHz) 1.90, 2.00, 2.07 and 2.08 (each 3 H, s, OAc), 3.85 (1 H, ddd, $J_{5',4'}$ 9.82, $J_{5',6'a}$ 5.65, $J_{5',6'b}$ 2.48, 5'-H), 4.22 (1 H, dd, J_{gem} 12.44, 6'$_b$-H), 4.33 (1 H, dd, 6'$_a$-H), 5.08 (1 H, d, $J_{1',2'}$ 1.19, 1'-H), 5.21 (1 H, dd, $J_{3',4'}$ 10.05, $J_{3',2'}$ 3.31, 3'-H), 5.38 (1 H, t, *J* 10.0, 4'-H), 5.75 (3 H, m, 2'-H, CH_2Ph) and 7.3 (5 H, m, Ph); δ_C(50 MHz) 20.4, 20.5, 20.6 and 20.7 (CO*Me*), 56.9 (*C*H_2Ph), 62.6 (C-6'), 65.7, 68.4, 71.7, 72.0, 77.0, 128.1, 128.4, 128.9, 132.8, 161.9 (C-5), 169.5, 169.9 (× 2) and 170.6 (*C*OMe); *m/z* 490 (M^+) and 448 ($M^+ - CH_2CO$) (Found: C, 54.2; H, 4.9; N, 11.2. $C_{22}H_{26}N_4O_9$ requires C, 53.87; H, 5.35; N, 11.42%).

Further elution then gave the 1-*benzyltetrazole* **19** (2.8 g, 47%), m.p. 120–122 °C, $[\alpha]_D$ −67.2 (*c* 1.22, CH_2Cl_2); δ_H(200 MHz) 1.98 and 2.00 (each 3 H, s, OAc), 2.08 (6 H, s, 2 × OAc), 3.77 (1 H, dt, $J_{5',4'}$ 9.9, $J_{5',6'}$ 4.10, 5'-H), 4.25 (2 H, d, 6'-H_2), 4.92 (1 H, d, $J_{1',2'}$ 1.28, 1'-H), 5.12 (1 H, dd, $J_{3',4'}$ 10.12, $J_{3',2'}$ 3.26, 3'-H), 5.33 (1 H, t, *J* 10.0, 4'-H), 5.75 (2 H, AB system, J_{gem} 14.8, CH_2Ph), 5.90 (1 H, dd, 2'-H) and 7.3 (5 H, m, Ph); δ_C (50 MHz) 20.4 (× 2), 20.55 and 20.6 (CO*Me*), 52.0 (CH_2Ph), 62.4 (C-6), 65.2, 68.2, 71.2, 71.6, 77.0, 127.7, 128.9, 129.0, 133.6, 149.7 (C-5) and 169.4, 169.5, 169.9 and 170.3 (*C*OMe); *m/z* 490 (M^+) 448 ($M^+ - CH_2CO$) and 417 ($M^+ - CH_2OAc$) (Found: C, 54.2; H, 4.9; N, 11.2. $C_{22}H_{26}N_4O_9$ requires C, 53.87; H, 5.35; N, 11.42%).

5-(3,4,6-*Tri*-O-*acetyl*-2-*deoxy*-1,2-*didehydro*-D-arabino-*hexopyranosyl*)-1-*benzyltetrazole* **20**.—A solution of compound **19** (1.5 g, 3.1 mmol) and DBU (1 cm^3, 6.7 mmol) in dichloromethane (15 cm^3) was stirred for 3 d at room temperature. The residue after evaporation was partitioned between water (100 cm^3) and diethyl ether (3 × 100 cm^3). The dried organic extracts were evaporated and the residue was chromatographed on silica with toluene–diethyl ether (10:1) as eluent to yield *alkene* **20** (0.32 g, 24%) as a clear syrup, $[\alpha]_D$ −49.5 (*c* 0.89, $CHCl_3$); δ_H(200 MHz) 2.03, 2.07 and 2.08 (each 3 H, s, OAc), 4.35 (3 H, m, 5'-H, 6'-H_2), 5.29 (1 H, dd, $J_{4',5'}$ 7.4, $J_{4',3'}$ 5.8, 4'-H), 5.50 (1 H, dd, $J_{3',2'}$ 3.6, 3'-H), 5.75 (2 H, AB system, *J* 14.97, CH_2Ph) and 6.10 (1 H, d, 2'-H); δ_C(50 MHz) 20.5, 20.6 and 20.7 (CO*Me*), 52.5 (*C*H_2Ph), 60.8 (C-6'), 66.2, 66.8, 75.7, 104.8 (C-2'), 127.3, 128.7, 129.0, 134.2, 141.4 (C-1'), 148.5 (C-5), 169.3, 169.9 and 170.2 (*C*OMe); *m/z* 431 (MH^+), 388 ($M^+ - CH_2CO$) and 268 (M^+ − HOAc − OAc − Ac) [Found: (M^+ − HOAc − OAc − Ac) 268.0957. $C_{14}H_{12}N_4O_2$ requires 268.0960].

5-(3,4,6-*Tri*-O-*acetyl*-2-*deoxy*-β-D-arabino-*hexopyranosyl*)-*tetrazole* **21**.—(*a*) A solution of alkene **20** (0.32 g) in ethyl acetate (10 cm^3) was hydrogenated at 1 atm. for 2 h with palladium-on-charcoal (5%; 50 mg) as catalyst. The solution was filtered through Celite and evaporated. Crystallization of the residue from diethyl ether–light petroleum gave *tetrazole* **21** (0.23 g, 92%), m.p. 147–149 °C, $[\alpha]_D$ −17.1 (*c* 1.00, MeOH); δ_H(360 MHz) 2.01 (1 H, q, *J* 12, 2'$_{ax}$-H), 2.04, 2.07 and 2.08 (each 3 H, s, OAc), 2.81 (1 H, ddd, J_{gem} 13.1, $J_{2'eq,3'}$ 5.04, $J_{2'eq,1'}$ 2.30, 2'$_{eq}$-H), 3.87 (1 H, ddd, $J_{5',4'}$ 9.93, $J_{5',6'a}$ 4.93, $J_{5',6'b}$ 2.39, 5'-H), 4.22 (1 H, dd, J_{gem} 12.47, 6'$_b$-H), 4.28 (1 H, dd, 6'$_a$-H), 5.07 (1 H, t, $J_{4',5'}$ ~ $J_{4',3'}$ 9.7, 4'-H), 5.08 (1 H, dd, $J_{1',2'ax}$ 12.0, 1'-H) and 5.21 (1 H, ddd, $J_{3',2'ax}$ 11.41, 3'-H); δ_C(50 MHz) 20.6, 20.7 and 20.8 (CO*Me*), 35.0 (C-2'), 62.6 (C-6'), 68.7, 69.1, 70.9, 76.6 (C-1'), 155.9 (C-5) and 169.9, 170.3 and 171.3 (*C*OMe); *m/z* (CI, NH_3) 360 ($M^+ + NH_4$) and 343 (MH^+) (Found: C, 45.3; H, 5.2; N, 16.1. $C_{13}H_{18}N_4O_7$ requires C, 45.61; H, 5.31; N, 16.37%).

(*b*) Alkene **23** (75 mg) in ethyl acetate (3 cm^3) was hydrogenated at 1 atm for 6 h using Pd/C (10%; 10 mg) as catalyst. Filtration through Celite, evaporation, and chromatography of the residue on silica with ethyl acetate as eluent gave compound **21** (53 mg, 70%), with properties as for material prepared in (*a*).

(*c*) A solution of β-nitrile **26**[19] (2.2 g, 7.4 mmol), sodium azide (0.72 g, 11 mmol) and ammonium chloride (0.6 g, 11 mmol) in DMF (15 cm^3) was maintained at 70 °C for 24 h, and then evaporated. The residue in water (100 cm^3) was acidified with dil. hydrochloric acid (2 mol dm^{-3}; 50 cm^3) and extracted with ethyl acetate (3 × 100 cm^3). Evaporation of the dried organic extracts, and chromatography of the residue on silica with ethyl acetate as eluent gave compound **21** (2.25 g, 90%), with properties as for material prepared in (*a*).

4,5,7-*Tri*-O-*acetyl*-2,6-*anhydro*-3-*deoxy*-2,3-*didehydro*-D-arabino-*heptononitrile* **22**.—A solution of tetra-*O*-acetyl nitrile **16** (2.0 g, 5.6 mmol) and DBU (0.85 cm^3, 5.6 mmol) in dichloromethane (100 cm^3) was stirred at room temperature for 24 h, and then evaporated to dryness. The residue was dissolved in water (100 cm^3) and extracted with diethyl ether (3 × 100 cm^3). The dried organic extracts were evaporated, and the residue was chromatographed on silica with toluene–diethyl ether (10:1) as eluent. After evaporation of product fractions, crystallization of the residue from diethyl ether gave *unsaturated nitrile* **22** (1.0 g, 60%), m.p. 79–81 °C, $[\alpha]_D$ −46.6 (*c* 1.10, $CHCl_3$); δ_H(200 MHz) 2.04, 2.05 and 2.06 (each 3 H, s, OAc) 4.1–4.5 (3 H, m, 6-H, 7-H_2), 5.20 (1 H, t, $J_{5,6}$ ~ $J_{5,4}$ ~ 5.5, 5-H), 5.35 (1 H, dd, $J_{4,3}$ 3.7, 4-H) and 5.70 (1 H, d, 3-H); δ_C(50 MHz) 20.5 (× 3) (CO*Me*), 60.2 (C-7), 65.6, 65.8, 75.7, 112.2 (C-3), 112.7 (C-1), 130.2 (C-2) and 169.1, 169.6 and 170.2 (*C*OMe); *m/z* 298 (MH^+) and 238 (M^+ − OAc) (Found: C, 52.3; H, 5.0; N, 4.7. $C_{13}H_{15}NO_7$ requires C, 52.53; H, 5.10; N, 4.71%).

5-(3,4,6-*Tri*-O-*acetyl*-2-*deoxy*-1,2-*didehydro*-D-arabino-*hexopyranosyl*)*tetrazole* **23**.—A solution of unsaturated nitrile **22** (150 mg, 0.5 mmol), sodium azide (48 mg, 0.75 mmol) and ammonium chloride (41 mg, 0.75 mmol) was heated at 70 °C with stirring for 24 h, and then evaporated. The residue was partitioned between water (20 cm^3) and ethyl acetate (3 × 20 cm^3). The dried organic extracts were evaporated and the residue was chromatographed on silica with ethyl acetate as eluent to give *alkenyltetrazole* **23** (100 mg, 58%) as a colourless syrup, $[\alpha]_D$ −42.7 (*c* 1.34, MeOH); δ_H(200 MHz) 2.09, 2.10 and 2.12 (each 3 H, s, OAc), 4.3–4.6 (3 H, m, 5'-H, 6'-H_2), 5.35 (1 H, dd, $J_{4',5'}$ 7.1, $J_{4',3'}$ 5.7, 4'-H), 5.55 (1 H, dd, $J_{3',2'}$ 3.7, 3'-H) and 6.21 (1 H, d, 2'-H); *m/z* (FAB) 363 (MNa^+), 341 (MH^+) and 281 (M^+ − OAc) (Found: MH^+, 341.1097. $C_{13}H_{17}N_4O_7$ requires 341.1097).

5-(2-*Deoxy*-β-D-arabino-*hexopyranosyl*)*tetrazole* **24**.—A solution of triester **24** (0.23 g) in methanolic sodium methoxide [25 cm^3; from sodium (16 mg)] was maintained for 2 h at room temperature and then evaporated. The residue in water (10 cm^3) was passed through a column of Amberlite IR 120 (H^+), and appropriate fractions were lyophilized to yield the *triol* **24** (0.14 g, 95%), m.p. 221–224 °C, $[\alpha]_D$ +30.6 (*c* 1.00, water); δ_H(360 MHz; D_2O) 1.88 (1 H, q, *J* 12, 2'$_{ax}$-H), 2.57 (1 H, ddd, J_{gem} 12.85, $J_{2'eq,3'}$ 5.00, $J_{2'eq,1'}$ 2.28, 2'$_{eq}$-H), 3.45 (1 H, t, 4'-H), 3.64 (1 H, ddd, $J_{5',4'}$ 9.74, $J_{5',6'a}$ 5.89, $J_{5,6'b}$ 2.32, 5'-H), 3.82 (1 H, dd, J_{gem} 12.32, 6'$_a$-H), 3.94 (1 H, ddd, $J_{3',2'ax}$ 11.4, 3'-H), 3.99 (1 H, dd, 6'$_b$-H) and 5.16 (1 H, dd, $J_{1',2'ax}$ 11.91, $J_{1',2'eq}$ 2.32, 1-H); *m/z* (FAB) 255 (MK^+) 239 (MNa^+) and 217 (MH^+) (Found: C, 39.0; H, 5.6; N, 25.4. $C_7H_{12}N_4O_4$ requires C, 38.88; H, 5.61, N, 25.92%).

5-(3,4-*Di*-O-*acetyl*-2-*deoxy*-6-O-*diphenoxyphosphinoyl*-β-D-arabino-*hexopyranosyl*)*tetrazole* **25**.—A solution of diphenyl phosphorochloridate (0.06 cm^3, 0.28 mmol) in pyridine (1 cm^3) was added over 2 h to a solution of triol **24** (30 mg, 0.14 mmol) in pyridine (1 cm^3) at 0 °C. The mixture was maintained at room temperature for 8 h, when acetic anhydride (2 cm^3) was added. After a further 12 h, the mixture was poured into water (15 cm^3), stirred for 1 h, and extracted with ethyl acetate (3 × 15 cm^3).

The combined organic extracts were washed with dil. hydrochloric acid (2 × 10 cm^3) and water (10 cm^3), dried and evaporated. Chromatography on silica with toluene–ethyl acetate (4:1) as eluent afforded the *phosphate* **25** (14 mg, 19%) as an oil, $[\alpha]_D$ +9.8 (*c* 0.82, $CHCl_3$); δ_H(200 MHz) 1.60 (1 H, q, *J* 12.5, 2′$_{ax}$-H), 2.06 and 2.10 (each 3 H, s, OAc), 2.75 (1 H, ddd, J_{gem} 13.14, $J_{2'eq,3'}$ 4.70, $J_{2'eq,1'}$ 2.50, 2′$_{eq}$-H), 3.80 (1 H, ddd, $J_{5',4'}$ 9.77, $J_{5',6'a}$ 4.90, $J_{5',6'b}$ 2.43, 5′-H), 4.4 (2 H, m, 6′-H_2), 4.87 (1 H, dd, $J_{1',2'ax}$ 11.87, 1′-H), 4.99 (1 H, t, *J* 9.6, 4′-H), 5.18 (1 H, ddd, $J_{3',2'ax}$ 11.34, $J_{3',4'}$ 9.48, 3′-H) and 7.1–7.3 (10 H, m, Ph); *m/z* (FAB) 555 (MNa^+), 533 (MH^+) and 283 [$M^+ - PO_2(OPh)_2$] [Found: MH^+ (FAB) 533.1437. $C_{23}H_{26}N_4O_9P$ requires 533.1437].

5-(2-*Deoxy*-6-O-*phosphono*-β-D-arabino-*hexopyranosyl*)-*tetrazole* **10**.—A solution of **25** (10 mg) in methanol (4 cm^3) was hydrogenated at 1 atm and room temperature over PtO_2 (5 mg) for 3 h. The solution was filtered and the catalyst was washed with methanol (4 cm^3). Methanolic sodium methoxide solution [from sodium (0.5 mg) in methanol (0.7 cm^3)] was added and the mixture was stirred for 4 h. The solution was passed through a column of Amberlite IR 120 (H^+) and evaporated to yield the *phosphate* **10** (4.0 mg, 71%) as an amorphous solid; δ_H(200 MHz; D_2O) 1.84 (1 H, q, *J* 12, 2′$_{ax}$-H), 2.47 (1 H, ddd, J_{gem} 13.0, $J_{2'eq,3'}$ 5.0, $J_{2'eq,1'}$ 2.0, 2′$_{eq}$-H), 3.47 (1 H, t, *J* 9.2, 4′-H), 3.65 (1 H, m, 5′-H), 3.86 (1 H, ddd, $J_{3',4'}$ 9.3, $J_{3',2'ax}$ 11.3, 3′-H), 4.1 (2 H, m, 6′-H_2) and 5.06 (1 H, br d, $J_{1',2'ax}$ 10.0, 1′-H); δ_P(81 MHz; D_2O) 1.69 [Found: MH^+ (FAB) 297.0600. $C_7H_{14}N_4O_7P$ requires 297.0600].

5-(3,4,6-*Tri*-O-*acetyl*-2-*deoxy*-α-D-arabino-*hexopyranosyl*)-*tetrazole* **28**.—The α-nitrile **27** [19] (3.2 g, 11 mmol) was processed as in the preparation of the β-tetrazole **21** from the β-nitrile **26** (see above), but with a reaction time of 4 days, to yield the α-*tetrazole* **28** (3.29 g, 90%) as a syrup, $[\alpha]_D$ +56.2 (*c* 1.59, MeOH); δ_H(200 MHz) 2.04, 2.07 and 2.10 (each 3 H, s, OAc), 2.33 (1 H, ddd, J_{gem} 13.7, $J_{2'ax,3'}$ 10.11, $J_{2'ax,1'}$ 5.72, 2′$_{ax}$-H), 2.81 (1 H, ddd, $J_{2'eq,3'}$ 4.9, $J_{2'eq,1'}$ 3.2, 2′-$_{eq}$-H), 3.83 (1 H, ddd, $J_{5',4'}$ 8.5, $J_{5',6'a}$ 4.5, $J_{5',6'b}$ 2.7, 5′-H), 4.15 (1 H, dd, J_{gem} 12.4, 6′$_b$-H), 4.38 (1 H, dd, 6′$_a$-H), 5.08 (1 H, t, $J_{4',3'}$ 8.5, 4′-H), 5.40 (1 H, ddd, 3′-H) and 5.58 (1 H, dd, 1′-H); δ_C(50 MHz) 20.6, 20.7 and 20.8 (CO*Me*), 31.4 (C-2′), 61.6 (C-6′), 65.4, 68.4, 68.6, 72.2, 156.7 (C-5) and 169.8, 170.0 and 171.0 (*C*OMe); *m/z* (FAB) 365 (MNa^+), 343 (MH^+), 301 ($MH^+ - N_3$) and 283 (M^+ − OAc) (Found: MH^+ 343.122. $C_{13}H_{19}N_4O_7$ requires 343.125).

5-(2-*Deoxy*-α-D-arabino-*hexopyranosyl*)*tetrazole* **29**.—The tri-*O*-acetyl derivative **28** (2.6 g) was treated as for the β-anomer **21** above to yield *triol* **29** (1.47 g, 90%), m.p. 139–140 °C, $[\alpha]_D$ +73.0 (*c* 0.95, H_2O); δ_H(200 MHz; D_2O) 2.11 (1 H, ddd, J_{gem} 13.9, $J_{2'ax,3'}$ 11.6, $J_{2'ax,1'}$ 6.1, 2′$_{ax}$-H), 2.68 (1 H, ddd, $J_{2'eq,3'}$ 4.8, $J_{2'eq,1'}$ 1.4, 2′$_{eq}$-H), 3.16 (1 H, ddd, $J_{5',4'}$ 9.6, $J_{5',6'a}$ 5.1, $J_{5',6'b}$ 2.3, 5′-H), 3.40 (1 H, t, *J* 9.4, 4′-H), 3.65–3.85 (3 H, m, 3′-H, 6′-H_2) and 5.50 (1 H, br d, 1′-H); *m/z* (FAB) 239 (MNa^+) and 217 (MH^+) [Found: MH^+ (FAB) 217.0937. $C_7H_{13}N_4O_4$ requires 217.0937].

5-(3,4-*Di*-O-*acetyl*-2-*deoxy*-6-O-*diphenoxyphosphinoyl*-α-D-arabino-*hexopyranosyl*)*tetrazole* **30**.—The α-tetrazole **29** (0.1 g, 0.46 mmol) was treated as in the preparation of the β-anomer **25** above to yield *diphenyl phosphate* **30** (52 mg, 21%) as a syrup, $[\alpha]_D$ +18.8 (*c* 1.54, $CHCl_3$); δ_H(200 MHz) 2.04 and 2.05 (each 3 H, s, OAc), 2.25 (1 H, ddd, J_{gem} 13.8, $J_{2'ax,3'}$ 9.5, $J_{2'ax,1'}$ 5.4, 2′$_{ax}$-H), 2.95 (1 H, dt, $J_{2'eq,3'} \sim J_{2'eq,1'}$ 4.4, 2′-$_{eq}$-H), 3.85 (1 H, dt, $J_{5',6'a} \sim J_{5',4'} \sim$ 8.0, $J_{5',6'b}$ 1.85, 5′-H), 4.22 (1 H, ddd, $J_{6'b,P}$ 19.0, J_{gem} 12.3, 6′$_b$-H), 4.55 (1 H, dt, $J_{6',P} \sim J_{6'a,5'}$ 8.2, 6′$_a$-H), 4.85 (1 H, t, $J_{4',3'} \sim$ 7.8, 4′-H), 5.19 (1 H, ddd, 3′-H) and 5.36 (1 H, t, 1′-H); δ_C(50 MHz) 20.6 and 20.7 (CO*Me*), 30.6 (C-2′), 64.9, 67.9, 68.2 (d, $^3J_{C,P}$ 7.2, C-6′), 68.5, 73.8, 119.9, 125.7, 129.9, 150.1 (d), 150.3 (d), 154.5 (C-5) and 169.3 and 169.8 (*C*OMe); *m/z* (FAB) 1065 ($2M^+$ + H), 555 (MNa^+), 533 (MH^+) and 283 [$M^+ - PO_2(OPh)_2$] [Found: MH^+ (FAB) 533.1437. $C_{23}H_{26}N_4O_9P$ requires 533.1437].

5-(2-*Deoxy*-6-O-*phosphono*-α-D-arabino-*hexopyranosyl*)-*tetrazole* **11**.—The α-tetrazole **30** (30 mg) was treated as described in the preparation of the β-anomer **10** (above) to give the *monophosphate* **11** (10 mg, 60%) as a solid foam; δ_H(200 MHz; D_2O) 2.10 (1 H, m, 2′$_{ax}$-H), 2.70 (1 H, ddd, J_{gem} 14.0, $J_{2'eq,3'}$ 4.6, $J_{2'eq,1'}$ 1.5, 2′$_{eq}$-H), 3.25 (1 H, m, 5′-H), 3.49 (1 H, t, $J_{4',5'} \sim J_{4',3'}$ 9.2, 4′-H), 3.73 (1 H, ddd, $J_{3',2'ax}$ 11, 3′-H), 4.0–4.1 (2 H, m, 6′-H_2) and 5.50 (1 H, br d, *J* ~ 5, 1′-H); δ_P(81 MHz; D_2O) 1.41; *m/z* (FAB) 335 (MK^+), 297 (MH^+) and 217 ($M^+ - PO_3$) [Found: MH^+ (FAB) 297.0600. $C_7H_{14}N_4O_7P$ requires 297.0600].

1,3,4,6-*Tetra*-O-*acetyl*-1-*cyano*-2-*deoxy*-β- **32** *and* -α-D-arabino-*hexopyranose* **33**.—Silver acetate (0.3 g, 1.8 mmol) was added to a solution of bromonitrile **31** [19] (0.5 g, 1.3 mmol) in acetic acid (6 cm^3) and acetic anhydride (1.5 cm^3). The mixture was heated under reflux for 1 h, cooled, filtered and evaporated. The residue was triturated with ice–water, stored at room temperature for 1 h, and extracted with chloroform (3 × 20 cm^3). The organic extracts were washed with aq. sodium hydrogen carbonate (20 cm^3) and water (200 cm^3), dried, and evaporated. The residue was chromatographed on silica with toluene–diethyl ether (10:1) as eluent to give, after crystallization from diethyl ether–hexane, the β-*glycosyl acetate* **32** (0.25 g, 53%), m.p. 129–131 °C, $[\alpha]_D$ +59.0 (*c* 1.0, $CHCl_3$); δ_H(200 MHz) 2.05, 2.07, 2.10 and 2.19 (each 3 H, s, OAc), 2.1 (1 H, m, 2$_{ax}$-H), 2.80 (1 H, dd, J_{gem} 13.1, $J_{2eq,3}$ 5.1, 2$_{eq}$-H), 4.1 (2 H, m, 5-, 6$_a$-H), 4.41 (1 H, dd, *J* 12.8 and 4.55, 6$_b$-H), 5.07 (1 H, t, *J* 9.6, 4-H) and 5.30 (1 H, ddd, $J_{3,2ax}$ 11.6, $J_{3,4}$ 9.37, 3-H); δ_C(50 MHz) 20.2 (× 2), 20.3 and 20.5 (CO*Me*), 38.4 (C-2), 60.7 (C-6), 66.8, 67.7, 72.7, 89.4 (C-1), 113.0 (CN, $^3J_{C,H}$ 7.78), 166.3, 169.2 (× 2) and 169.9 (*C*OMe); *m/z* 358 (MH^+) and 298 (M^+ − OAc) (Found: C, 50.9; H, 5.6; N, 4.0. $C_{15}H_{19}NO_9$ requires C, 50.41; H, 5.37; N, 3.92%).

Further elution of the column and crystallization from diethyl ether–hexane afforded the α-*glycosyl acetate* **33** (0.1 g, 22%), m.p. 139–140 °C, $[\alpha]_D$ +61.3 (*c* 0.87, $CHCl_3$); δ_H(200 MHz) 2.04 (6 H, s, OAc), 2.08 and 2.20 (each 3 H, s, OAc), 2.28 (1 H, dd, J_{gem} 13.6, $J_{2ax,3}$ 11.0, 2$_{ax}$-H), 2.80 (1 H, dd, $J_{2eq,3}$ 4.9, 2$_{eq}$-H), 3.95 (1 H, ddd, $J_{4,5}$ 9.82, $J_{5,6a}$ 4.51, $J_{5,6b}$ 2.23, 5-H), 4.06 (1 H, dd, J_{gem} 12.6, 6$_b$-H), 4.30 (1 H, dd, 6$_a$-H), 5.10 (1 H, t, *J* 9.6, 4-H) and 5.20 (1 H, ddd, 3-H) (Found: C, 50.7; H, 5.4; N, 3.9. $C_{15}H_{19}NO_9$ requires C, 50.41; H, 5.37; N, 3.92%).

Methyl 3,4,6-*Tri*-O-*acetyl*-1-*cyano*-2-*deoxy*-β- **34** *and* -α-D-arabino-*hexopyranoside* **35**.—To a solution of bromonitrile **31** (2.0 g, 5.3 mmol) in dichloromethane (2 cm^3) was added methanol (20 cm^3) followed by 2,6-lutidine (1.9 cm^3). The solution was stirred at room temperature for 5 days and evaporated. The residue was partitioned between water (100 cm^3) and dichloromethane (3 × 100 cm^3). The dried organic extracts were evaporated and the residue was chromatographed on silica, with toluene–diethyl ether (10:1) as eluent, to afford firstly, after crystallization from diethyl ether–light petroleum, the β-glycoside **34** (0.7 g, 40%), m.p. 110–111 °C, $[\alpha]_D$ +55.7 (*c* 1.37, $CHCl_3$); δ_H(200 MHz) 1.95 (1 H, dd, J_{gem} 13.3, $J_{2ax,3}$ 11.8, 2$_{ax}$-H), 2.00, 2.03 and 2.06 (each 3 H, s, OAc), 2.55 (1 H, dd, $J_{2eq,3}$ 5.15, 2$_{eq}$-H), 3.58 (3 H, s, OMe), 3.95 (1 H, ddd, $J_{5,4}$ 9.8, $J_{5,6a}$ 4.34 $J_{5,6b}$ 2.27, 5-H), 4.12 (1 H, dd, J_{gem} 12.55, 6$_b$-H), 4.30 (1 H, dd, 6$_a$-H), 5.00 (1 H, t, *J* 9.65, 4-H) and 5.22 (1 H, ddd, 3-H); δ_C(50 MHz) 20.5 (× 3) (CO*Me*), 39.4 (C-2), 53.9 (OMe), 61.4 (C-6), 67.9, 68.6, 72.5, 95.9 (C-1), 114.1 (CN, $^3J_{C,H}$ 7.5) and 169.6 (× 2) and 170.3 (*C*OMe) (Found: C, 51.2; H, 6.1; N, 4.4. $C_{14}H_{19}NO_8$ requires C, 51.05; H, 5.83; N, 4.25%).

Further elution of the column yielded the α-*glycoside* **35** (0.19

g, 11%) as a syrup, $[\alpha]_D$ +46.0 (*c* 1.33, $CHCl_3$); δ_H(200 MHz) 2.03, 2.04 and 2.10 (each 3 H, s, OAc), 2.15 (1 H, dd, J_{gem} 13.1, $J_{2ax,3}$ 11.2, 2_{ax}-H), 2.61 (1 H, dd, $J_{2eq,3}$ 5.25, 2_{eq}-H), 3.50 (3 H, s, OMe), 3.85 (1 H, ddd, $J_{5,4}$ 10.05, $J_{5,6a}$ 5.0, $J_{5,6b}$ 2.3, 5-H), 4.08 (1 H, dd, J_{gem} 12.4, 6_b-H), 4.25 (1 H, dd, 6_a-H), 5.03 (1 H, t, *J* 9.75, 4-H) and 5.25 (1 H, ddd, 3-H); δ_C(50 MHz) 20.55, 20.6 and 20.7 (CO*Me*), 39.0 (C-2), 52.6 (OMe), 61.7 (C-6), 67.7, 68.1, 69.9, 94.7 (C-1), 114.6 (CN, $^3J_{C,H}$ 1.5) and 169.5, 169.8 and 170.4 (*C*OMe) [Found: (M^+ − OMe) 298.0914. $C_{13}H_{16}NO_7$ requires 298.0927].

Methyl 3,4,6-*Tri*-O-*acetyl*-2-*deoxy*-1-*tetrazol*-5-*yl*-β-D-arabino-*hexopyranoside* **36**.—Nitrile **34** (0.50 g, 1.5 mmol), sodium azide (0.143 g, 2.2 mmol) and ammonium chloride (0.12 g, 2.2 mmol) were heated in DMF (5 cm^3) at 70 °C for 3 days. The mixture was evaporated and the residue was chromatographed on silica, with ethyl acetate as eluent, to yield the *tetrazole* **36** (0.51 g, 90%) as a colourless syrup, $[\alpha]_D$ +34.5 (*c* 0.87, MeOH); δ_H(200 MHz; CD_3OD) 1.93, 1.97 and 2.07 (each 3 H, s, OAc), 2.10 (1 H, dd, J_{gem} 12.6, $J_{2ax,3}$ 11.65, 2_{ax}-H), 3.05 (1 H, dd, $J_{2eq,3}$ 5.1, 2_{eq}-H), 3.14 (3 H, s, OMe), 3.81 (1 H, dt, $J_{5,4} \sim J_{5,6a} \sim J_{5,6b} \sim 2.8$, 5-H), 4.26 (1 H, dd, J_{gem} 12.4, 6_a-H), 4.34 (1 H, dd, 6_b-H), 4.83 (1 H, ddd, $J_{3,4}$ 9.35, 3-H) and 5.05 (1 H, t, 4-H); δ_C(50 MHz) 20.6, 20.7 and 20.8 (CO*Me*), 36.9 (C-2), 50.8 (OMe), 62.2 (C-6), 68.7, 69.3, 71.9, 96.6 (C-1), 157.6 (tetrazole-C) and 169.9, 170.5 and 171.2 (*C*OMe); *m/z* (FAB) 395 (MNa^+) and 373 (MH^+) [Found: MNa^+ (FAB) 395.1180. $C_{14}H_{20}N_4NaO_8$ requires 395.1179].

Methyl 2-*Deoxy*-1-*tetrazol*-5-*yl*-β-D-arabino-*hexopyranoside* **37**.—A solution of triester **36** (0.32 g) in methanol (5 cm^3) was treated with a solution of sodium (23 mg) in methanol (35 cm^3). The mixture was stirred at room temperature for 2 h and then passed down a column of Amberlite IR 120 (H^+). The solvent was evaporated to afford the *triol* **37** (182 mg, 86%) as a solid foam, $[\alpha]_D$ + 36.8 (*c* 1.96, MeOH); δ_H(200 MHz; CD_3OD) 2.05 (1 H, dd, J_{gem} 13.0, $J_{2ax,3}$ 11.5, 2_{ax}-H), 2.78 (1 H, dd, $J_{2eq,3}$ 4.86, 2_{eq}-H), 3.22 (1 H, ddd, $J_{5,4}$ 9.64, $J_{5,6a}$ 5.03, $J_{5,6b}$ 2.32, 5-H), 3.33 (3 H, s, OMe), 3.36 (1 H, t, *J* 9.6, 4-H), 3.58 (1 H, ddd, 3-H), 3.75 (1 H, dd, J_{gem} 11.9, 6_a-H) and 3.90 (1 H, dd, 6_b-H); δ_C(50 MHz; CD_3OD) 40.7 (C-2), 50.9 (OMe), 62.7 (C-6), 70.6, 72.4, 78.3, 97.9 (C-1) and 157.5 (tetrazole-C); *m/z* (FAB) 269 (MNa^+), 247 (MH^+), 215 (M^+ − OMe) and 177 (M^+ − CHN_4) (Found: MH^+ 247.1042. $C_8H_{15}N_4O_5$ requires 247.1042).

2-*Deoxy*-1-*tetrazol*-5-*yl*-α-D-arabino-*hexopyranose* **12**.—A solution of the glycoside **33** (0.10 g) in water (10 cm^3) was left to stand for 5 days at room temperature, and then evaporated to yield the *hexose* **12** (66 mg, 70%) as a solid foam, $[\alpha]_D$ +40.0 (*c* 1.13, H_2O); δ_H(200 MHz; D_2O) 1.75 (1 H, dd, J_{gem} 13.15, $J_{2ax,3}$ 11.7, 2_{ax}-H), 2.45 (1 H, dd, $J_{2eq,3}$ 5.0, 2_{eq}-H), 3.43 (1 H, t, *J* 9.35, 4-H), 3.8 (3 H, m, 5-H, 6-H_2) and 3.99 (1 H, ddd, 3-H); δ_C(50 MHz; D_2O) 41.2 (C-2), 60.3 (C-6), 67.9, 70.2, 73.4, 92.9 (C-1) and 158.5 (tetrazole-C, $^3J_{C,H}$ 3.4); *m/z* (FAB) 255 (MNa^+) 233 (MH^+) 215 (M^+ − OH) and 163 (M^+ − CHN_4) (Found: MH^+, 233.0886. $C_7H_{13}N_4O_5$ requires 233.0886).

4,5,7-*Tri*-O-*acetyl*-2,6-*anhydro*-3-*deoxy*-D-galacto- **39** *and* -D-talo-*heptononitrile* **40**.—To a stirred solution of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-*lyxo*-hexopyranose **38**[23] (4.0 g, 12 mmol) in nitromethane (80 cm^3) was added trimethylsilyl cyanide (4 cm^3, 30 mmol), followed by boron trifluoride–diethyl ether (0.5 cm^3). After 3 h, the mixture was evaporated and the residue was partitioned between water (100 cm^3) and diethyl ether (3 × 100 cm^3). The organic extracts were washed with water (100 cm^3), dried and evaporated to give a yellow syrup which was chromatographed on silica, with toluene–diethyl ether (10:1) as eluent to give the D-talo-*heptononitrile* **40** (1.9 g, 53%), m.p. 138–140 °C, $[\alpha]_D$ +92.5 (*c* 1.06, $CHCl_3$); δ_H(200 MHz) 2.01 (1 H, m, 3_{eq}-H), 2.02, 2.08 and 2.15 (each 3 H, s, OAc), 2.37 (1 H, dt, *J* 12.5 and 5.7, 3_{ax}-H), 4.1–4.3 (3 H, m, 6-H, 7-H_2), 5.04 (1 H, dd, $J_{2,3ax}$ 5.7, $J_{2,3eq}$ 1.3, 2-H), 5.27 (1 H, ddd, $J_{4,3ax}$ 12.4, *J* 4.7 and 3.0, 4-H) and 5.40 (1 H, m, 5-H); δ_C(50 MHz) 20.5 (× 3) (CO*Me*), 28.2 (C-3), 61.6 (C-7), 63.4, 65.7, 66.2, 72.4, 116.1 (C-1), and 169.5, 169.8 and 170.3 (*C*OMe); *m/z* 300 (MH^+), 256 (M^+ − Ac), 240 (M^+ − OAc) and 226 (M^+ − CH_2OAc) (Found: C, 52.3; H, 5.9; N, 4.7. $C_{13}H_{17}NO_7$ requires C, 52.16; H, 5.73; N, 4.68%).

Further elution then yielded the D-galacto-*heptononitrile* **39** (0.61 g, 17%) as a colourless syrup, $[\alpha]_D$ +40.6 (*c* 1.01, $CHCl_3$); δ_H(200 MHz) 2.03, 2.08 and 2.18 (each 3 H, s, OAc), 2.10 (1 H, m, 3_{eq}-H), 2.32 (1 H, q, *J* 12.5, 3_{ax}-H), 3.87 (1 H, br t, *J* 6, 6-H), 4.10 (2 H, d, *J* 6, 7-H_2), 4.45 (1 H, dd, $J_{2,3ax}$ 12.2, $J_{2,3eq}$ 2.4, 2-H), 5.00 (1 H, ddd, $J_{4,3ax}$ 12.2, $J_{4,3eq}$ 4.8, $J_{4,5}$ 3.0, 4-H) and 5.30 (1 H, br d, *J* 3, 5-H); δ_C(50 MHz) 20.6 (× 3) (CO*Me*), 29.6 (C-3), 61.8 (C-7), 63.7, 65.2, 67.6, 75.2, 116.2 (C-1) and 169.7, 170.9 and 170.3 (*C*OMe); *m/z* 300 (MH^+), 256 (M^+ − Ac), 240 (M^+ − OAc) and 226 (M^+ − CH_2OAc) [Found: (M^+ − Ac) 256.0816. $C_{11}H_{14}NO_6$ requires 256.0821].

5-(3,4,6-*Tri*-O-*acetyl*-2-*deoxy*-β-D-lyxo-*hexapyranosyl*)*tetrazole* **41**.—The D-*galacto*-heptononitrile **39** (0.232 g, 0.78 mmol) was treated as in the preparation of tetrazole **21** (above) to yield β-*tetrazole* **41** (0.210 g, 79%), m.p. 146–148 °C, $[\alpha]_D$ +26.4 (*c* 1.0, MeOH); δ_H(200 MHz) 2.04, 2.10 and 2.13 (each 3 H, s, OAc), 2.17 (1 H, q, *J* 12.5, $2'_{ax}$-H), 2.5 (1 H, m, $2'_{eq}$-H), 4.1 (2 H, m, 5′-, $6'_a$-H), 4.30 (1 H, dd, *J* 13.0 and 8.6, $6'_b$-H), 5.08 (1 H, dd, $J_{1',2'ax}$ 11.9, $J_{1',2'eq}$ 2.53, 1′-H), 5.18 (1 H, ddd, *J* 12.2, 4.8 and 3.0, 3′-H) and 5.42 (1 H, d, *J* 2.75, 4′-H); *m/z* (FAB) 365 (MNa^+), 343 (MH^+), 301 (MH^+ − CH_2CO), 283 (M^+ −OAc) and 273 (M^+ − CHN_4) (Found: C, 46.0; H, 5.4; N, 16.4. $C_{13}H_{18}N_4O_7$ requires C, 45.61; H, 5.31; N, 16.37%).

5-(2-*Deoxy*-β-D-lyxo-*hexopyranosyl*)*tetrazole* **13**.—The tri-*O*-acetyl derivative **41** (0.13 g) was treated as in the synthesis of **24** (above) to afford the *triol* **13** (70 mg, 85%), m.p. 176–178 °C, $[\alpha]_D$ +53.3 (*c* 0.90, MeOH); δ_H(200 MHz; D_2O) 1.95 (1 H, q, *J* 12, $2'_{ax}$-H), 2.25 (1 H, dddd, J_{gem} 12.6, $J_{2'eq,3'}$ 4.7, $J_{2'eq,1'}$ 2.8, $J_{2'eq,4'}$ 0.8, $2'_{eq}$-H), 3.7–3.8 (3 H, m, 5′-, $6'\text{-H}_2$), 3.85 (1 H, br d, *J* ~ 3, 4-H), 4.02 (1 H, ddd, $J_{3',2'ax}$ 11.8, $J_{3',4'}$ 3.05, 3′-H) and 5.01 (1 H, dd, $J_{1',2'ax}$ 11.9, 1′-H); *m/z* (FAB) 239 (MNa^+) and 217 (MH^+) (Found: C, 38.8; H, 5.7; N, 25.3. $C_7H_{12}N_4O_4$ requires C, 38.88; H, 5.61; N, 25.92%).

5-(3,4,6-*Tri*-O-*acetyl*-2-*deoxy*-α-D-lyxo-*hexopyranosyl*)*tetrazole* **42**.—The D-*talo*-heptonitrile **40** (4.4 g, 15 mmol) was treated as in the preparation of tetrazole **21**, but with a reaction time of 5 d, to yield α-*tetrazole* **42** (3.5 g, 70%) as a colourless syrup, $[\alpha]_D$ +82.5 (*c* 1.69, MeOH); δ_H(500 MHz) 1.95, 1.97 and 2.15 (each 3 H, s, OAc), 2.45 (2 H, m, $2'\text{-H}_2$), 3.85 (1 H, br t, 5′-H), 4.02 (1 H, dd, J_{gem} 11.6, $J_{6'a,5'}$ 5.7, $6'_a$-H), 4.28 (1 H, dd, $J_{6'b,5'}$ 6.8, $6'_b$-H), 5.2 (2 H, m, 3′-, 4′-H) and 5.50 (1 H, t, *J* 4.4, 1′-H); δ_C(50 MHz) 20.5, 20.6 and 20.8 (CO*Me*), 27.6 (C-2′), 61.7 (C-6′), 66.4, 66.7 (× 2), 70.5, 157.4 (C-5) and 170.3, 170.4 and 171.0 (*C*OMe); *m/z* (FAB) 365 (MNa^+), 343 (MH^+), 301 (MH^+ − CH_2CO) and 283 (M^+ − OAc) [Found: MH^+ (FAB) 343.1279. $C_{13}H_{19}N_4O_7$ requires 343. 1254].

5-(2-*Deoxy*-α-D-lyxo-*hexopyranosyl*)*tetrazole* **14**.—Tri-*O*-acetyl derivative **42** (1.8 g) was deacetylated and processed as in the preparation of **24** (above) to give *triol* **42** (0.8 g, 71%) as a syrup, $[\alpha]_D$ +0.5 (*c* 1.85, H_2O); δ_H(500 MHz; D_2O) 2.45 (1 H, ddd, J_{gem} 13.7, $J_{2'ax,3}$ 12.1, $J_{2'ax,1}$ 6.24, $2'_{ax}$-H), 2.55 (1 H, dd, $J_{2'eq,3'}$ 5.0, $J_{2'eq,1'} \sim 0$, $2'_{eq}$-H), 3.50 (1 H, dd, *J* 7.5, 4.0, 5′-H), 3.80 (1 H, dd, *J* 11.8, 4.2, $6'_a$-H), 3.9 (2 H, m, 4′-, $6'_b$-H), 4.03 (1 H, ddd, $J_{3',4'}$ 3.0, 3′-H) and 5.65 (1 H, br d, *J* ~ 6, 1′-H); δ_C(50

MHz; D_2O), 27.8 (C-2′), 61.3 (C-6′), 64.8, 66.1, 67.0, 74.7 and 155.8 (C-5); *m/z* (FAB) 239 (MNa^+) and 217 (MH^+) [Found: MH^+ (FAB) 217.0918. $C_7H_{13}N_4O_4$ requires 217.0937].

4,5,7-*Tri*-O-*acetyl*-2,6-*anhydro*-2-*bromo*-3-*deoxy*-D-galacto-*heptononitrile* **43**.—*N*-Bromosuccinimide (1.47 g, 8.3 mmol) and dibenzoyl peroxide (0.26 g, 1.0 mmol) were added to a solution of the D-*talo*-heptononitrile **40** (1.88 g, 6.3 mmol) in carbon tetrachloride (80 cm^3). The mixture was heated under reflux for 5 d, with addition of further portions (0.26 g each) of dibenzoyl peroxide at 1 d intervals, then cooled, filtered and evaporated. The residue was chromatographed on silica with toluene–diethyl ether (10:1) as eluent to yield the *2-bromo compound* **43** (1.50 g, 63%), as a clear syrup, $[\alpha]_D$ +126.1 (*c* 0.15, $CHCl_3$), which decomposed slowly on standing; δ_H(200 MHz) 2.03, 2.10 and 2.18 (each 3 H, s, OAc), 2.60 (1 H, dd, *J* 12.5 and 6.5, 3_{eq}-H), 2.66 (1 H, dd, *J* 13.5 and 11, 3_{ax}-H), 4.0–4.4 (3 H, m, 6-H, 7-H_2) and 5.3–5.5 (2 H, m, 4-, 5-H); δ_C(50 MHz) 20.4 (3 × CO*Me*), 39.5 (C-3), 60.6 (C-7), 64.4, 65.6, 73.5, 95.9 (C-2), 115.1 (C-1) and 169.4, 169.6 and 170.1 (*C*OMe); *m/z* 298 (M^+ − Br) [Found: (M^+ − Br) 298.0905. $C_{13}H_{16}NO_7$ requires 298.0928].

Methyl 3,4,6-*Tri*-O-*acetyl*-1-*cyano*-2-*deoxy*-β-D-lyxo-*hexopyranoside* **44**.—Methanol (15 cm^3) and 2,6-lutidine (1.5 cm^3) were added with stirring to a solution of bromonitrile **43** (1.51 g, 4.0 mmol) in dichloromethane (2 cm^3). After 5 d at room temperature, the solvents were evaporated and the residue was partitioned between water (100 cm^3) and dichloromethane (3 × 100 cm^3). The organic layer was washed with water (100 cm^3), dried and evaporated, and the residue was chromatographed on silica, with toluene–diethyl ether (20:1) as eluent to give the *methyl glycoside* **44** (0.53 g, 41%) as a clear syrup, $[\alpha]_D$ +66.4 (*c* 1.43, $CHCl_3$); δ_H(200 MHz) 2.02, 2.09 and 2.15 (each 3 H, s, OAc), 2.0–2.3 (2 H, m, 2-H_2), 3.65 (3 H, s, OMe), 4.20 (3 H, app. s, 5-H, 6-H_2), 5.25 (1 H, ddd, $J_{3,2ax}$ 12.1, $J_{3,2eq}$ 5.65, $J_{3,4}$ 3.0, 3-H) and 5.39 (1 H, d, 4-H); δ_C(50 MHz) 20.5 (3 × CO*Me*), 35.0 (C-2), 53.8 (OMe), 61.1 (C-6), 64.6, 66.7, 71.9, 96.6 (C-1), 114.3 (CN, $^3J_{C,H}$ 7.6) and 169.4, 169.8 and 170.1 (*C*OMe); *m/z* 303 (M^+ − CN), 298 (M^+ − OMe), 256 (M^+ − CH_2OAc) and 227 (M^+ − OAc − Ac) [Found: (M^+ − OAc − Ac) 227.0786. $C_{10}H_{13}NO_5$ requires 227.0794].

Methyl 3,4,6-*Tri*-O-*acetyl*-2-*deoxy*-1-*tetrazol*-5-*yl*-β-D-lyxo-*hexopyranoside* **45**.—The methoxy nitrile **44** (0.53 g, 1.61 mmol) was treated as in the preparation of the D-*arabino* analogue **36** (see above) to yield the *tetrazole* **45** (0.50 g, 84%) as a syrup, $[\alpha]_D$ +36.5 (*c* 0.80, $CHCl_3$); δ_H(200 MHz) 2.53 (1 H, t, *J* 12.5, 2_{ax}-H), 2.66 (1 H, dd, J_{gem} 12.9, $J_{2eq,3}$ 4.96, 2_{eq}-H), 3.40 (3 H, s, OMe), 4.05–4.35 (3 H, m, 5-H, 6-H_2), 5.22 (1 H, ddd, $J_{3,2ax}$ 12.2, $J_{3,4}$ 2.9, 3-H) and 5.39 (1 H, br d, *J* ~ 2, 4-H); δ_C(50 MHz) 20.6 (3 × CO*Me*), 32.1 (C-2), 50.6 (OMe), 61.7 (C-6), 65.3, 67.5, 71.0, 97.0 (C-1), 157.3 (tetrazole-C, $^3J_{C,H}$ 5.1) and 170.2, 170.3 and 171.0 (*C*OMe); *m/z* (FAB) 395 (MNa^+), 373 (MH^+) and 303 (M^+ − CHN_4) [Found: MNa^+ (FAB) 395.1179. $C_{14}H_{20}N_4NaO_8$ requires 395.1179].

Methyl 2-*Deoxy*-1-*tetrazol*-5-*yl*-β-D-lyxo-*hexopyranoside* **46**.—A solution of the triacetate **45** (0.45 g, 1.2 mmol) in methanol (2 cm^3) was treated with methanolic sodium methoxide [from sodium (35 mg) in methanol (50 cm^3)]. After 2 h, the mixture was passed down a column of Amberlite IR 120 (H^+) resin and evaporated to give the *triol* **46** (0.24 g, 80%) as a syrup, $[\alpha]_D$ +73.0 (*c* 1.32, MeOH); δ_H(200 MHz, D_2O) 2.22 (1 H, t, *J* 12.3, 2_{ax}-H), 2.62 (1 H, dd, J_{gem} 12.7, $J_{2eq,3}$ 4.7, 2_{eq}-H), 3.21 (3 H, s, OMe), 3.5 (1 H, m, 5-H) and 3.6–3.9 (4 H, m, 3-, 4-H, 6-H_2); δ_C(50 MHz; CD_3OD) 35.1 (C-2), 50.7 (OMe), 62.9 (C-6), 68.1, 68.2, 77.0, 98.2 (C-1) and 157.6 (tetrazole-C, $^3J_{C,H}$ 5.2); *m/z* (FAB) 269 (MNa^+), 247 (MH^+), 215 (M^+ − OMe) and 177 (M^+ − CHN_4) [Found: MH^+ (FAB) 247.1042. $C_8H_{15}N_4O_5$ requires 247.1042].

2-*Deoxy*-1-*tetrazol*-5-*yl*-α-D-lyxo-*hexopyranose* **15**.—A solution of the glycoside **46** (0.17 g) in water (5 cm^3) was maintained at room temperature for 14 d, and then evaporated to afford the *hexose* (112 mg, 70%) as a syrup, $[\alpha]_D$ +28.2 (*c* 0.71, H_2O); δ_H(200 MHz; D_2O) 1.95 (1 H, t, *J* 12.5, 2_{ax}-H), 2.22 (1 H, dd, J_{gem} 13.1, $J_{2eq,3}$ 5.0, 2_{eq}-H), 3.7–3.9 (3 H, m, 5-H, 6-H_2) and 4.1–4.3 (2 H, m, 3-, 4-H); δ_C(50 MHz; D_2O) 35.6 (C-2), 61.3 (C-6), 64.9, 72.5, 93.0 (C-1) and 158.7 (tetrazole-C, $^3J_{C,H}$ ~ 0) [Found: MH^+ (FAB) 217.0886. $C_7H_{13}N_4O_4$ requires 217.0937].

Enzyme Assay.[25]—The assay solution contained aqueous solutions of tris hydrochloride (pH 7.2; 0.1 mol dm^{-3}; 0.5 cm^3), cobalt(II) sulfate (0.1 mol dm^{-3}; 0.005 cm^3), NAD^+ 0.02 mol dm^{-3}; 0.005 cm^3), DAHP (4 mmol dm^{-3}, 0.025 cm^3) and dihydroquinase (EC 4.2.1.10) from *E coli*[4] (60 m units cm^{-3}; 0.005 cm^3). DHQ Synthase from *E. coli*[26] (0.01 cm^3) was added and the solution made up to 1 cm^3 with deionised water. The production of 3-dehydroshikimate was monitored at 234 nm. The assay was repeated with different concentrations of tetrazoles **10–15** present (0.1, 1.0 and 10 mmol dm^{-3} final concentration).

Acknowledgements

We are greatly indebted to Professor J. R. Coggins, University of Glasgow, for his assistance with the measurements of enzyme inhibition, which were carried out in Professor Coggins' laboratory. We thank ICI plc for the provision of a studentship (to APWC), and SERC for data obtained at the Mass Spectrometry Service Centre, University College Swansea (Director, Dr. J. A. Ballantine), and the High Resolution NMR Service Centre, University of Edinburgh (Director, Dr. I. H. Sadler).

References

1 U. Weiss and J. M. Edwards, *The Biosynthesis of Aromatic Compounds*, Wiley, New York, 1980; B. Ganem, *Tetrahedron*, 1978, **34**, 3353; P. M. Dewick, *Nat. Prod. Rep.*, 1992, **9**, 153, and earlier reviews in this series.
2 G. Millar and J. R. Coggins, *FEBS Lett.*, 1986, **200**, 11.
3 K. Duncan, R. M. Edwards and J. R. Coggins, *Biochem. J.*, 1987, **246**, 375.
4 J. M. Lambert, M. R. Boocock and J. R. Coggins, *Biochem. J.*, 1985, **226**, 817.
5 S. L. Bender, S. Mehdi and J. R. Knowles, *Biochemistry*, 1989, **28**, 7555.
6 P. R. Srinavasan, J. Rothschild and D. B. Sprinson, *J. Biol. Chem.*, 1963, **238**, 3176.
7 S. L. Bender, T. Widlanski and J. R. Knowles, *Biochemistry*, 1989, **28**, 7560.
8 T. Widlanski, S. L. Bender and J. R. Knowles, *Biochemistry*, 1989, **28**, 7572.
9 P. A. Bartlett and K. Satake, *J. Am. Chem. Soc.*, 1988, **110**, 1628.
10 S. Myrvold, L. M. Reimer, D. L. Pompliano and J. W. Frost, *J. Am. Chem. Soc.*, 1989, **111**, 1861.
11 D. L. Pompliano, L. M. Reimer, S. Myrvold and J. W. Frost, *J. Am. Chem. Soc.*, 1989, **111**, 1866.
12 L. T. Piehler, J.-L. Montchamp, J. W. Frost and C. J. Manly, *Tetrahedron*, 1991, **47**, 2423.
13 For other work on inhibitors of DHQ synthase see: P. Le Marechal, C. Froussios, M. Level and R. Azerad, *Carbohydr. Res.*, 1981, **94**, 1; N. Nikolaides and B. Ganem, *Tetrahedron Lett.*, 1989, **30**, 1461.
14 G. M. Kishore and D. M. Shah, *Ann. Rev. Biochem.*, 1988, **57**, 627, and refs. therein.
15 *E.g.* P. F. Juby and T. W. Hudyma, *J. Med. Chem.*, 1969, **12**, 396; J. M. Essery, *J. Med. Chem.*, 1969, **12**, 703; J. S. Morley, *J. Chem. Soc. C*, 1969, 809; G. P. Ellis and D. Shaw, *J. Med. Chem.*, 1972, **15**, 865; R. L. Buchanan and V. Sprancmanis, *J. Med. Chem.*, 1973, **16**, 174.

16 P. Köll and A. Fortsch, *Carbohydr. Res.*, 1987, **171**, 301.
17 I. Farkas, I. F. Szabó and R. Bognár, *Carbohydr. Res.*, 1977, **56**, 404.
18 R. A. Henry and W. G. Finnegan, *J. Am. Chem. Soc.*, 1954, **76**, 923.
19 J. G. Buchanan, A. P. W. Clelland, R. H. Wightman, T. Johnson and R. A. C. Rennie, *Carbohydr. Res.*, 1992, in the press.
20 L. Somsák, G. Batta and I. Farkas, *Carbohydr. Res.*, 1984, **132**, 342.
21 L. Somsák, G. Batta and I. Farkas, *Carbohydr. Res.*, 1983, **124**, 43.
22 C.-H. Wang and C. A. Kingsbury, *J. Org. Chem.*, 1975, **40**, 3811; K. Luthman, M. Orbe, T. Waglund and A. Claesson, *J. Org. Chem.*, 1987, **52**, 3777; H. Hori, T. Nakajima, Y. Nishida, H. Ohrui and H. Meguro, *Tetrahedron Lett.*, 1988, **29**, 6317; S. Prytulla, J. Lauterwein, M. Klessinger and J. Thiem, *Carbohydr. Res.*, 1991, **215**, 345.
23 D. M. Ciment and R. J. Ferrier, *J. Chem. Soc.*, 1966, 441.
24 *c.f.* F. G. de las Heras and P. Fernández-Resa, *J. Chem. Soc., Perkin Trans. 1*, 1982, 903.
25 G. R. Welch and F. H. Gaertner, *Arch. Biochem. Biophys.*, 1976, **172**, 476.
26 J. W. Frost, J. L. Bender, J. T. Kadonaga and J. R. Knowles, *Biochemistry*, 1984, **23**, 4470.

Paper 2/03945A
Received 23*rd July* 1992
Accepted 30*th July* 1992