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Synthesis of Transition State Analogue Inhibitors for Purine Nucleoside Phosphorylase and *N*-Riboside Hydrolases

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Abstract—Syntheses of the 'Immucillins', potent aza-*C*-nucleoside inhibitors of purine nucleoside phosphorylase are reported as well as those of 5-deoxy-, 5-deoxyfluoro- and 2-deoxy- analogues and others having modified bases.

Introduction

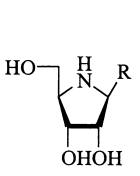
Nucleoside processing enzymes are ubiquitous and essential to provide precursors for RNA and DNA synthesis and energy metabolism. Examples of these enzymes include purine nucleoside phosphorylase and a number of nucleoside *N*-riboside hydrolases and transferases.

A genetic deficiency of purine nucleoside phosphorylase (PNP) in humans results in the selective depletion of T-cells.[1,2] PNP is the only enzyme which degrades 2′-deoxyguanosine in T-cells, and when not degraded, 2′-deoxyguanosine is converted instead to 2′-deoxyguanosine triphosphate (dGTP), which accumulates. High levels of dGTP cause an allosteric inhibition of ribonucleotide diphosphate reductase which prevents the normal DNA replication required for clonal expansion of T-cell populations.[3–5]

Undesirable activation of T-cells is associated with a number of human disease states including psoriasis, rheumatoid arthritis, T-cell lymphomas, transplant tissue rejection and possibly other autoimmune disorders. Consequently PNP inhibition has become a target for drug design.[6,7]

Nucleoside *N*-riboside hydrolases (nucleoside hydrolases) are also of potential interest to the medicinal chemist. These enzymes are found in protozoan parasites but are not known to exist in mammalian cells.[8] Protozoa have lost the capacity for de novo purine biosynthesis and rely completely on salvage pathways to recover these bases from the host for DNA and RNA synthesis.[9] In designing inhibitors, it has to be born in mind that the nucleoside hydrolases present in such protozoan parasites can vary in their substrate specificity and in their mechanisms of hydrolysis.[10–13] For example, purine salvage in the trypanosome *Crithidia fasciculata* involves two distinct nucleoside hydrolases[14,15] while a third nucleoside hydrolase has been found in *Trypanosoma brucei brucei*.[16] Nevertheless, the apparently specific role for these enzymes in the protozoa suggests they may be suitable targets for antibiotic design.

The transition states characterised to date for reactions promoted by PNP and nucleoside hydrolase enzymes have similar features. Kinetic isotope effect studies on PNP from calf spleen have been used to predict a transition state structure in which the enzyme stabilises a ribooxocarbenium ion and also assists the purine to become a leaving group by electron-withdrawing interactions.[17] Nucleoside hydrolase transition states also feature incipient ribooxocarbenium ions, but the proportion of the activation energy derived from protonation or other activation of the purine leaving group varies depending upon the enzyme.[8,12,13]



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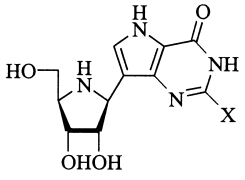

2 X = H
3 X = NH_2

From analysis of these results we predicted that 1,4-dideoxy-1,4-imino-D-ribitol compounds **1**, which will be

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Table 1. K_i values (nM) for binding of compounds **2** and **3** with two PNP's and two nucleoside hydrolase isozymes

Compound	Human PNP K_i (nM)	Bovine PNP K_i (nM)	IAG nucleoside hydrolase K_i (nM)	IU nucleoside hydrolase K_i (nM)
2	0.072	0.023	24	42
3	0.029	0.030	110	84

largely protonated at pH 7 (pK_a=6.5),[18] will be potent transition state analogue inhibitors of both PNP and nucleoside hydrolases. Preliminary studies on the synthesis and biological activity of nucleoside hydrolase inhibitors **1** (R=substituted aromatic)[13,19,20] led to the conclusion that for more potent inhibition of these enzymes the R group needed to better mimic the purine base of the substrate; and the same was expected to be the case for PNP from evaluation of the enzyme transition state by studies of the kinetic isotope effects.[17] Consequently we have synthesised the iminoribitol *C*-glycosides **2** and **3** (the 'Immucillins'), which emerged as exceedingly potent inhibitors of both bovine and human PNP as well as two nucleoside hydrolases with different substrate specificities, the IAG and IU nucleoside hydrolases from *Trypanosoma brucei brucei* and *Crithidia fasciculata*, respectively (Table 1).[21,22] In addition, the 5′-phosphates of **2** and **3** are potent inhibitors of phosphoribosyltransferases.[23–25]

These Immucillins have considerable potential for the control of T-cell proliferative disorders such as psoriasis, rheumatoid arthritis, T-cell lymphomas and transplant tissue rejection as well as antibiotics for protozoan parasite infections such as malaria, trypanosomiasis and sleeping sickness.

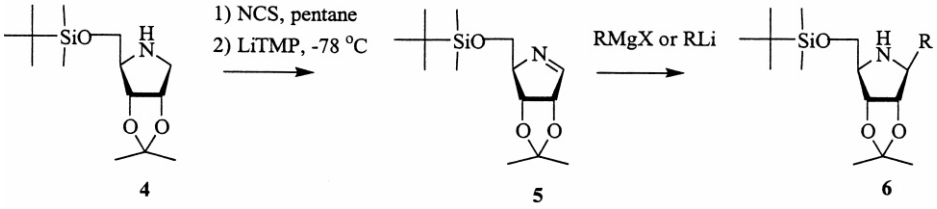
We present here the first report of the synthesis of **2** and **3** as well as some close analogues. The full biological properties of these compounds are reported elsewhere.[21,22]

Results and Discussion

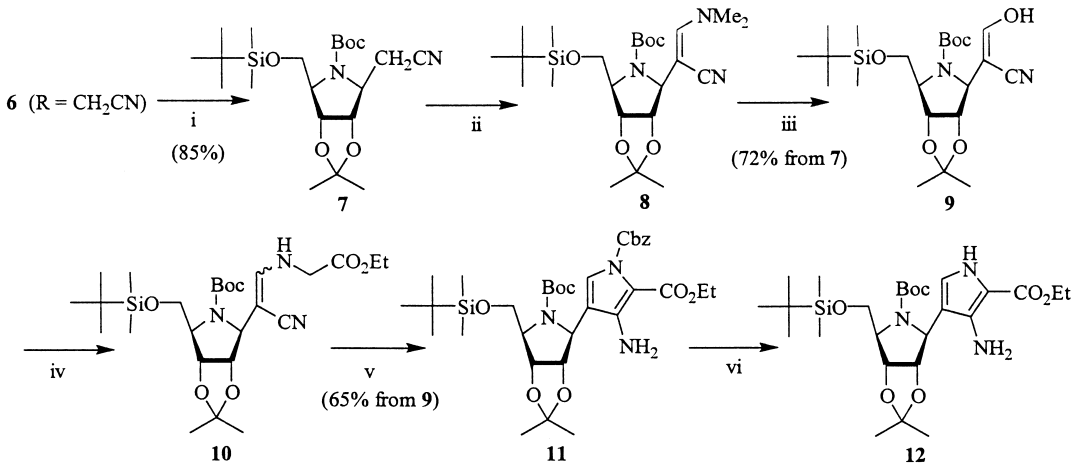
Our previous syntheses of compounds belonging to set **1** utilised additions of organometallic species to the imine **5** (Scheme 1), which is generated from the iminoribitol derivative **4**.[19,26] Others have claimed an alternative facile synthesis of some (1*S*)-aryl-1,4-dideoxy-1,4-imino-D-ribitols by the addition of organometallic compounds to a 2,3,5-tri-*O*-protected-D-ribofuranose derivative followed by oxidation of the 1,4-diol product and then reductive amination of the resultant 1,4-dicarbonyl compound to give (1*S*)-aryl-1,4-dideoxy-1,4-imino-D-ribitol compounds.[27] However, further investigations have revealed that these compounds have, in fact, the L-*lyxo* stereochemistry[28] and consequently this chemistry is not suitable for our purposes. Conceivably, the target aza-*C*-nucleosides **2** and **3** could be prepared using the methodology indicated in Scheme 1, i.e. by adding a suitable lithiated 9-deazapurine derivative to the imine **5**. However, we decided that assembling the 9-deazapurines on a preformed aza-*C*-glycoside offered a more established route to the proposed inhibitors. Such an approach has been successful in the synthesis of 9-deazainosine, 9-deazaguanosine and 9-deazaadenosine.[29–31] A direct synthesis of 9-deazaguanosine by an acid-catalyzed reaction between 9-deazaguanine and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose has been described,[32] and some aza-*C*-glycosides have been prepared by employing Lewis acid catalyzed conditions,[33,34] but these approaches did not appear appropriate for the synthesis of aza-*C*-nucleosides.

Addition of lithiated acetonitrile to imine **5** afforded the cyanomethyl *C*-glycoside derivative **6** (R=CH_2CN). Variable amounts of disubstituted acetonitrile were also produced following deprotonation of the active methylene moiety in **6** and subsequent addition of the derived anion to imine **5**. This could be minimised by conducting the reaction under dilute conditions with an excess of the lithiated acetonitrile. The iminoribitol nitrogen atom of **6** was protected as the Boc carbamate to give **7** and treatment of this with Bredereck's reagent afforded enamine **8**. Mild acid hydrolysis gave **9**, which was allowed to react with ethyl glycinate to give enamines **10**. The NMR spectra of **8** and **9** indicated they were each single isomers whereas **10** was a mixture of diastereoisomers. Protection of the enamine nitrogen atom was required in order to effect a cyclisation to the pyrrole, and when **10** was treated with excess benzyl chloroformate and DBU the pyrrole **11** was produced (Scheme 2). Hydrogenolysis of **11** readily afforded pyrrole **12**, from which the two target compounds **2** and **3** were derived (Scheme 3).

Treatment of **12** with formamidine acetate generated the deazapurine aza-*C*-glycoside **13**, which was deprotected with TFA to give the target deazainosine analogue **2** (74% yield from **11**). Alternatively, treatment of **12** with benzoyl isothiocyanate followed by methyl iodide and DBU afforded the isothiourea **14**, which when allowed to react with ammonia in methanol in a sealed tube at 100°C gave **15** along with lesser amounts of **16**. Again, deprotection was



Scheme 1.

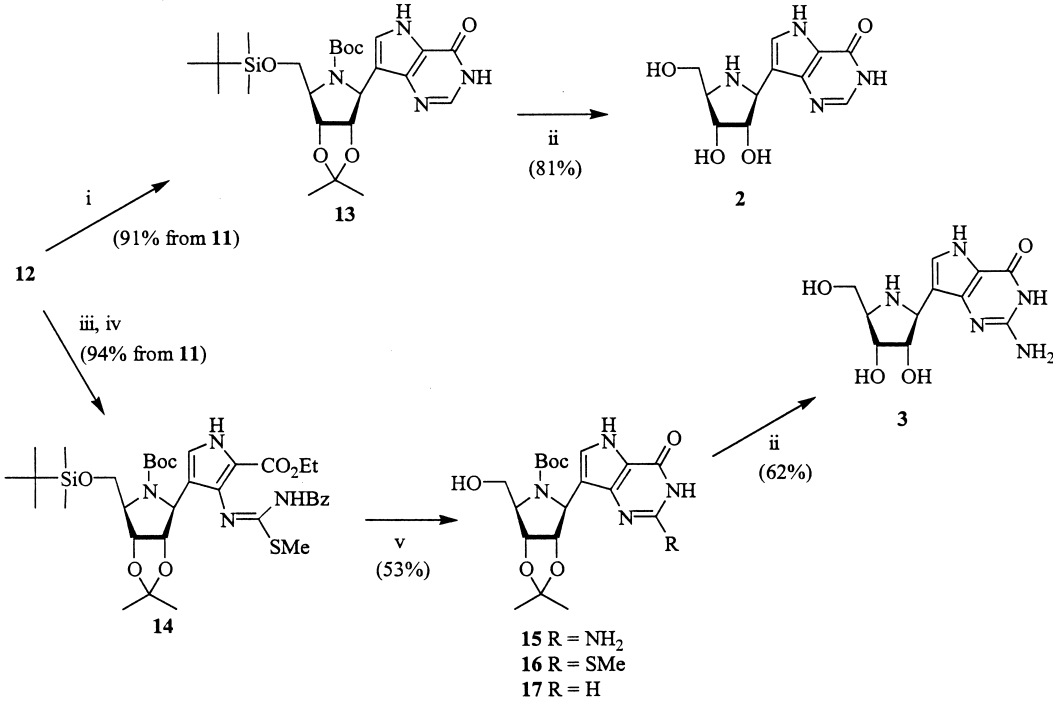


Scheme 2. Reagents: (i) $(Boc)_2O$, CH_2Cl_2; (ii) $^tBuOCH(NMe_2)_2$, DMF, 70°C; (iii) THF, HOAc, H_2O; (iv) $H_2NCH_2CO_2Et{\cdot}HCl$, NaOAc, MeOH; (v) $ClCO_2Bn$, DBU, CH_2Cl_2, reflux; (vi) H_2, Pd/C, EtOH.

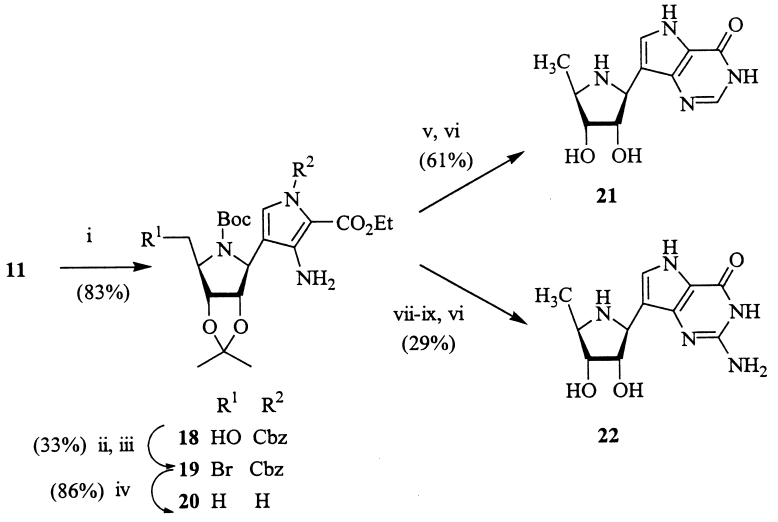
effected with TFA to give the deazaguanosine analogue **3** (32% yield from **11**).

We were also interested in probing the structure–activity relationships of these novel and potent inhibitors of nucleoside metabolism. In the first instance we focussed on the 5′-position of the aza-*C*-nucleosides with the intention of preparing 5′-deoxy and 5′-deoxyfluoro analogues. However, attempts to effect various S_N1- or S_N2-like reactions at C-5′ of **17** or its 5′-*O*-mesylate derivative were unsuccessful with the deazapurine moiety appearing to participate in the reaction. In consequence, the protected pyrrole **11** was used to prepare 5′-deoxy analogues. Desilylation of **11** and mesylation of the resulting alcohol **18** followed by displacement of the 5′-sulfonyloxy group with bromide ions afforded the 5′-bromo-5′-deoxy derivative **19** (Scheme 4). Hydrogenolysis of this material gave the 5′-deoxy compound **20** with the pyrrole moiety *N*-deprotected. This was then converted into the 5′-deoxy-9-deaza-inosine and -guanosine analogues **21** and **22** by use of the methods employed to prepare **2** and **3**.

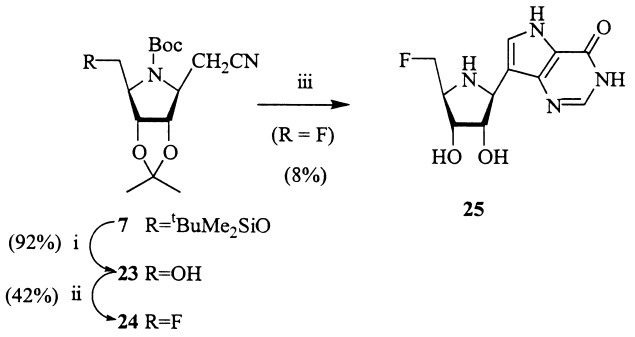
When alcohol **18** was treated with DAST a mixture of products, which did not contain fluorine was formed and appeared to result from participation of the pyrrole moiety. However, when alcohol **23** obtained by desilylation of **7** was allowed to react with DAST, the 5-deoxy-5-fluoro derivative **24** was produced. The acetonitrile component of **24** was then elaborated, as outlined in Schemes 2 and 3, for the synthesis of **2** to produce the 5′-deoxyfluoro-9-deazainosine analogue **25** (Scheme 5).



Scheme 3. Reagents: (i) $H_2NCH{=}NH.HOAc$, EtOH, reflux; (ii) TFA; (iii) BzNCS, CH_2Cl_2; (iv) DBU, MeI, CH_2Cl_2; (v) NH_3, MeOH, 100°C.

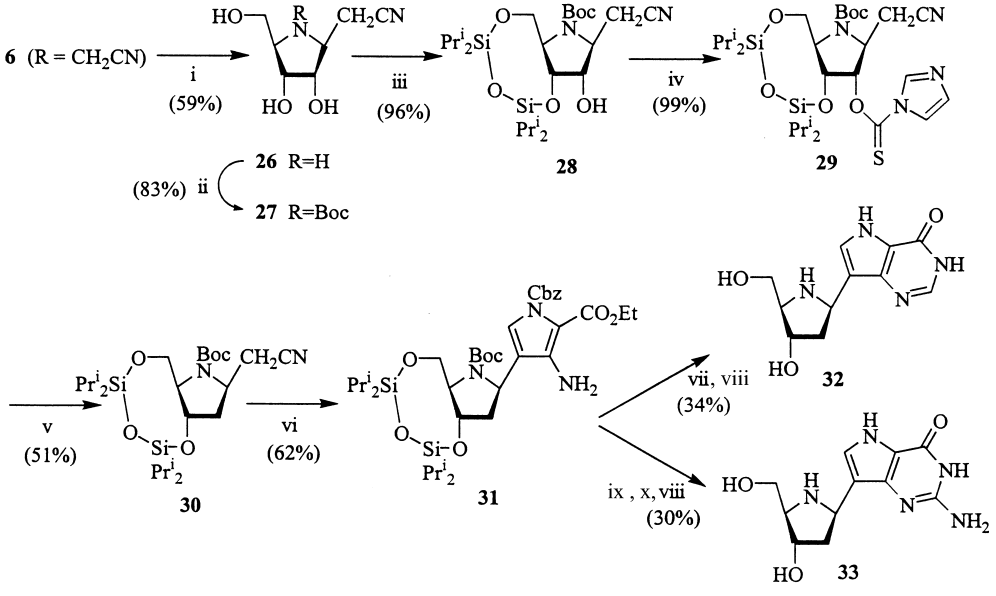


Scheme 4. Reagents: (i) Bu_4NF; (ii) MsCl, DMAP, Et_3N; (iii) Bu_4NBr; (iv) H_2, Pd/C, Et_3N, EtOH; (v) $H_2NCH{=}NH.HOAc$, EtOH, reflux; (vi) TFA; (vii) BzNCS, CH_2Cl_2; (viii) DBU, MeI, CH_2Cl_2; (ix) NH_3, MeOH, 100°C.

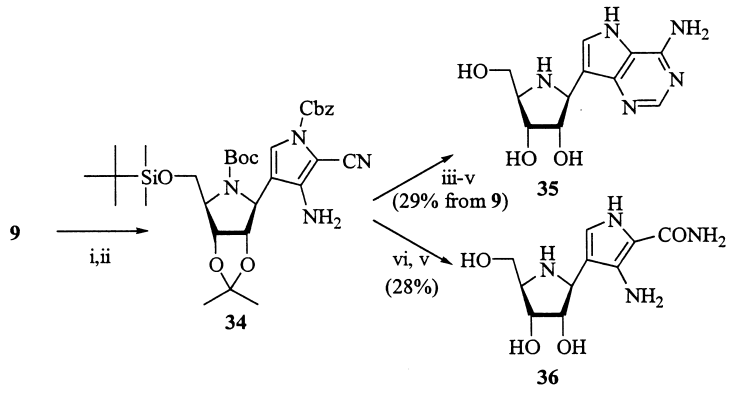


Scheme 5. Reagents: (i) Bu_4NF; (ii) DAST, CH_2Cl_2; (iii) reagents (ii)–(vi) in Scheme 2, then (i) and (ii) in Scheme 3.

The 2′-deoxy analogues of **2** and **3** were also required for structure–activity studies as transition state analogue inhibitors, particularly because PNP accepts purine 2′-deoxynucleosides as substrates.[35] As a result of the difficulties encountered when attempting modifications at C-5 when the deazapurine moiety was present, we chose to deoxygenate at C-2 prior to formation of the deazapurine. This was achieved by deprotection of **6** (R=CH_2CN) to afford **26** followed by reprotection to give **27** and then **28** (Scheme 6); deoxygenation was effected by radical reduction of the imidazolethiocarbamate **29** resulting in **30**. Elaboration of the deazapurine moieties was carried out as described above for the synthesis of **2** and **3** (Schemes 2 and 3) affording **32** and **33**.



Scheme 6. Reagents: (i) TFA; (ii) $(Boc)_2O$; (iii) $O[(^iPr)_2SiCl]_2$, imidazole, DMF; (iv) $(Imidazolyl)_2C{=}S$; (v) Bu_3SnH; (vi) reagents (ii)–(v) in Scheme 2; (vii) reagents (i) and (ii) in Scheme 3; (viii) Bu_4NF; (ix) H_2, Pd/c; (x) reagents (iii)–(v) and (ii) in Scheme 3.



Scheme 7. Reagents: (i) H_2NCH_2CN, NaOAc, MeOH; (ii) DBU, BnOCOCl, CH_2Cl_2; (iii) H_2, Pd/C, EtOH; (iv) $H_2NCH{=}NH$, EtOH; (v) aq. TFA; (vi) aq. H_2O_2, DMSO.

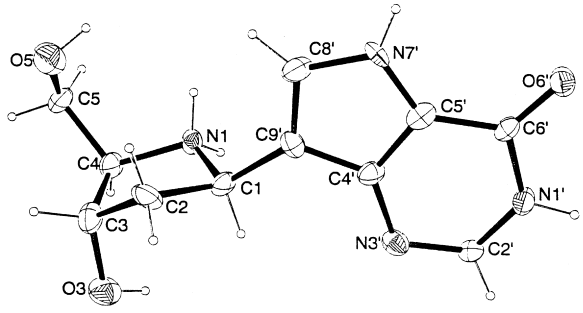


Fig. 1. ORTEP diagram of (1*R*)-1-(9-deazahypoxanthin-9-yl)-1,2,4-trideoxy-1,4-imino-D-*erythro*-pentitol hydrochloride (**32·HCl**)

The 9-deazaadenosine analogue **35** was prepared by way of the pyrrole **34** and condensation with formamidine acetate. Hydrolysis of the cyano group of **34** afforded the corresponding amide and hence **36**, a monocyclic analogue of the deazahypoxanthine derivative **2** (Scheme 7).

An X-ray diffraction analysis of **32·HCl** (Fig. 1) confirmed its structure providing proof that the product derived by the addition of lithioacetonitrile to imine **5** [i.e. **6** (R=CH_2CN)] possessed the required β-stereochemistry. The independent molecules are bound into a three dimensional lattice by at least six hydrogen bonds which involve N-1, O-5 as parent donors to one Cl^-, N-1′ as a donor to another Cl^- and O-6′, N-3′ and O-3 acting as acceptors. The five-membered ring (N-1,C-1–C-4) adopts an envelope conformation [ϕ 66(1)°][36] with the 'flap atom' C-2 0.67(1) Å from the plane of the other four. The fused five- and six-membered rings are coplanar (mean deviation 0.012 Å) with O-6′ and C-1 0.06(1) and 0.09(1) Å, respectively, from the plane. There are no significant deviations from the expected bond lengths and angles.

Experimental

General

NMR spectra were recorded on a Bruker AC-300 instrument at 300 MHz (^{1}H) or 75 MHz (^{13}C). Normally, spectra were measured in $CDCl_3$ with Me_4Si as internal reference; when D_2O was the solvent acetone (δ ^{1}H, 2.20; ^{13}C, 33.2) was used as internal reference. High resolution accurate mass determinations were performed by Hort Research Ltd on a VG70-250S double focusing, magnetic sector mass spectrometer under chemical ionisation conditions using isobutane or ammonia as the ionising gas, or under high-resolution FAB conditions in a glycerol or nitrobenzyl alcohol matrix. Melting points were determined on a Reichert hot stage microscope and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 automatic polarimeter and are given in units of 10^{-1}deg cm^2 g^{-1}. Aluminium-backed silica gel sheets (Merck or Reidel de Haen) were used for thin layer chromatography. Column chromatography was performed on silica gel (230–400 mesh, Merck). Chromatography solvents were distilled prior to use.

7-*O*-*tert*-Butyldimethylsilyl-2,3,6-trideoxy-3,6-imino-4,5-*O*-isopropylidene-D-*allo*-heptononitrile (6, R=CH_2CN). A solution of the iminoribitol compound **4**[19] (2.0 g, 7.0 mmol) in pentane (40 mL) was stirred with *N*-chlorosuccinimide (1.2 g, 9.0 mmol) for 1 h. The solids and solvent were removed, the residue was dissolved in dry THF (40 mL) and the solution was cooled to −78°C. Lithium tetramethylpiperidide (25 mL, 0.4 M in THF) was added dropwise and the resulting solution was then added via cannula to one of lithiated acetonitrile [prepared by the dropwise addition of acetonitrile (2.08 mL, 40 mmol) to a solution of butyllithium (29.8 mL, 41.8 mmol) in dry THF (50 mL) at −78°C, followed by stirring for 45 min and then addition of tetramethylpiperidine (0.67 mL, 4 mmol)] at −78°C. The reaction mixture was stirred for 10 min then quenched carefully with acetic acid (4 mL) and partitioned between water and chloroform. The organic phase was dried, concentrated, and chromatographed to afford nitrile **6** (R=CH_2CN) (0.83 g, 2.5 mmol, 36%) as a syrup. ^{1}H NMR δ 4.47 (1H, dd, $J_{4,5}$=6.6, $J_{5,6}$=3.8 Hz, H-5), 4.30 (1H, dd, $J_{3,4}$=4.6 Hz, H-4), 3.74 (1H, dd, $J_{6,7}$=3.9, $J_{7,7'}$=10.2 Hz, H-7), 3.66 (1H, dd, $J_{6,7'}$=5.2 Hz, H-7′), 3.40 (1H, m, H-3), 3.30 (1H, m, H-6), 2.68, 2.58 (2H, 2 dd, $J_{2,2'}$=16.7, $J_{2,3}$=5.3, $J_{2',3'}$=6.9 Hz, H-2,2′), 1.51, 1.32 (6H, 2s, CCH_3), 0.91 [9H, s, $C(CH_3)_3$], 0.08 (6H, s, $SiCH_3$). ^{13}C NMR δ 117.5 (C-1), 113.7 (C), 84.5 (C-4), 82.3 (C-5), 65.4 (C-6), 64.5 (C-7), 60.7 (C-3), 27.2, 25.0 [$C(CH_3)_2$], 25.8 [$C(CH_3)_3$], 22.4 (C-2), 18.2 [$C(CH_3)_3$], −5.5, −5.6 ($SiCH_3$). HRMS (MH^+) calcd for $C_{16}H_{31}N_2O_3Si$: 327.2104; found: 327.2091.

***N-tert*-Butoxycarbonyl-7-*O-tert*-butyldimethylsilyl-2,3,6-trideoxy-3,6-imino-4,5-*O*-isopropylidene-D-*allo*-heptononitrile (7).** A solution of **6** (R=CH_2CN) (0.80 g, 2.45 mmol) in CH_2Cl_2 (20 mL) containing di-*tert*-butyl dicarbonate (0.59 g, 2.7 mmol) was stirred at room temperature for 16 h. The solution was concentrated and the residue chromatographed to afford the Boc derivative **7** (0.89 g, 2.09 mmol, 85%) as a syrup. ^{1}H NMR δ 4.68–4.51 (2H, m, H-4,5), 4.16–3.71 (4H, m, H-3,6,7,7′), 2.95–2.66 (2H, m, H-2,2′), 1.48 [9H, s, $OC(CH_3)_3$], 1.46, 1.34 [6H, 2s, $C(CH_3)_2$], 0.91 [9H, s, $SiC(CH_3)_3$], 0.09, 0.08 (6H, 2s, $SiCH_3$). ^{13}C NMR δ 117.2 (C-1), 112.1 (C), 84.0 and 82.9, 81.8 and 81.1 (C-4,5),[37] 66.2 and 65.9, 61.7 and 61.4 (C-3,6), 63.2 and 62.9 (C-7), 28.2 [$OC(CH_3)_3$], 27.1, 25.1 [$C(CH_3)_2$], 25.9 [$SiC(CH_3)_3$], 21.3 and 20.5 (C-2), 18.3 [$SiC(CH_3)$], −5.5 ($SiCH_3$). HRMS (MH^+) calcd for $C_{21}H_{39}N_2O_5Si$: 427.2628; found: 427.2606.

(1*S*)-1-(3-Amino-*N*-benzyloxycarbonyl-2-ethoxycarbonylpyrrol-4-yl)-*N-tert*-butoxycarbonyl-5-*O-tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (11). *tert*-Butoxy-bis(*N*,*N*-dimethylamino)methane (1.5 mL, 7.28 mmol) was added to a solution of **7** (0.88 g, 2.07 mmol) in DMF (5 mL) and the mixture was heated at 65–70°C for 1 h. Toluene (20 mL) was added and the solution was washed (×3) with water, dried and concentrated to dryness. The residue of crude **8** was dissolved in THF/acetic acid/water (1:1:1 v/v/v, 40 mL) at room temperature and after 1.5 h, chloroform (50 mL) was added and the mixture was washed with water (×2), aqueous sodium bicarbonate, dried and evaporated to dryness. Chromatography of the residue gave the hept-1-enitol derivative **9** (0.68 g, 1.5 mmol, 72%) as a syrup. ^{1}H NMR δ 7.13 (1H, d, J=12.6 Hz, H-1), 4.92, 4.83 (2H, 2d, $J_{4,5}$=5.7 Hz, H-4,5), 4.77 (1H, s, H-3), 4.02 (1H, m, H-6), 3.73–3.51 (2H, m, H-7,7′), 1.49 [9H, s, $OC(CH_3)_3$], 1.46, 1.34 [6H, 2s, $C(CH_3)_2$], 0.91 [9H, s, $SiC(CH_3)_3$], 0.10 (6H, s, $SiCH_3$). ^{13}C NMR δ 162.7 (C-1), 118.8, 112.1, 90.2 and 83.2 (C), 82.7, 82.1 (C-4,5), 66.2 (C-6), 62.4 (C-7), 59.1 (C-3), 28.3 [$OC(CH_3)_3$], 27.1, 25.1 [$C(CH_3)_2$], 26.0 [$SiC(CH_3)_3$],18.4 [$SiC(CH_3)_3$], −5.3 ($SiCH_3$).

Ethyl glycinate hydrochloride (5.0 g, 35.8 mmol) and sodium acetate (6.0 g, 73 mmol) were added to a stirred solution of **9** (3.82 g, 8.4 mmol) in methanol (80 mL). Stirring was continued at room temperature for 16 h and the solvent was removed. Chromatography of the residue gave *N-tert*-butoxycarbonyl-7-*O-tert*-butyldimethylsilyl-2-cyano-1,2,3,6-tetradeoxy-1-*N*-(ethoxycarbonylmethylamino)-3,6-imino-4,5-*O*-isopropylidene-D-*allo*-hept-1-enitol (**10**) (3.46 g, 6.42 mmol) as a mixture of isomers. A solution of this material (3.46 g, 6.42 mmol) in dry CH_2Cl_2 (80 mL) containing 1,8-diazabicyclo[5.4.0]undec-7-ene (18 mL, 116 mmol) and benzyl chloroformate (8.8 mL, 43 mmol) was heated under reflux for 4 h, cooled and washed with dilute aqueous HCl, aqueous sodium bicarbonate, dried and concentrated. Chromatography of the residue afforded pyrrole derivative **11** (3.68 g, 5.47 mmol, 65% from **9**). ^{1}H NMR (d_6-Benzene) δ 7.23–7.00 (5H, m, Ar), 5.16 and 5.10 (1H, d, J=12.2 Hz, $ArCH_2$), 4.94 (1H, s, H-1), 4.65 and 4.53 (1H, d, $J_{2,3}$=5.3 Hz, H-2,3), 4.35 (1H, bs), 4.09 (2H, dd, J=7.1 Hz, CH_2CH_3), 3.59–3.41 (2H, m), 1.43, 1.17 [6H, 2s, $C(CH_3)_2$], 1.35 [9H, s, $OC(CH_3)_3$], 0.95 (3H, t, CH_2CH_3), 0.87 [9H, s, $SiC(CH_3)_3$], −0.03, −0.05 (6H, 2s, $SiCH_3$). ^{13}C NMR δ 161.9, 151.1, 147.3, 135.7 (C), 125.3 (C-5′), 117.4, 111.9, 105.5 (C), 83.9, 82.7 (C-2,3), 80.5 [$OC(CH_3)_3$], 69.6, 67.1 (C-1,4), 69.1 ($ArCH_2$), 63.4, 59.7 (C-5, CH_2CH_3), 28.3 [$OC(CH_3)_3$], 27.7, 25.6 [$C(CH_3)_2$], 26.1 [$SiC(CH_3)_3$],18.5 [$SiC(CH_3)$], 14.5 (CH_2CH_3). HRMS (M^+) calcd for $C_{34}H_{51}N_3O_9Si$: 673.3395; found: 673.3432.

(1*S*)-*N-tert*-Butoxycarbonyl-5-*O-tert*-butyldimethylsilyl-1-(9-deazahypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (13). A solution of **11** (1.84 g, 2.73 mmol) in ethanol (30 mL) was stirred with 10% Pd/C (0.1 g) in an atmosphere of hydrogen for 3 h. The solids and solvent were removed and the residual **12** was dissolved in ethanol (40 mL) containing formamidine acetate (1.40 g, 13.4 mmol) and the solution was heated under reflux for 16 h. The solvent was removed and chromatography of the residue gave the deazahypoxanthine derivative **13** (1.3 g, 2.5 mmol, 91%) as a syrup. ^{1}H NMR δ 8.22 (1H, bs, H-2′), 7.33 (1H, bs, H-8′), 5.35 (1H, bs, H-1), 5.20 (1H, bs, H-2 or 3), 4.86 (1H, d, J=5.6 Hz, H-2 or 3), 4.11 (1H, bs, H-4), 3.72 (2H, bs, H-5a,5b), 1.55, 1.35 [6H, 2s, $C(CH_3)_2$], 1.46 [9H, bs, $OC(CH_3)_3$], 0.91[9H, s, $SiC(CH_3)_3$], 0.09 (6H, s, CH_3). ^{13}C NMR δ 155.5, 154.6 and 143.2 (C), 141.1 and 127.8 (CH), 118.2, 117.2 and 111.9 (C), 84.6 and 82.7 (C-2,3), 80.2 [$OC(CH_3)_3$], 66.5 (C-4), 62.8 (C-5), 61.5 (C-1), 28.5[$OC(CH_3)_3$], 27.5, 25.5 [$C(CH_3)_2$], 25.9 [$SiC(CH_3)_3$],18.3 [$SiC(CH_3)$], −5.3 $Si(CH_3)$. HRMS (MH^+) calcd for $C_{25}H_{41}N_4O_6Si$: 521.2795; found: 521.2780.

(1*S*)-1-(9-Deazahypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol hydrochloride (2·HCl). Compound **13** (0.475 g, 0.91 mmol) in trifluoroacetic acid (20 mL) was allowed to stand at room temperature overnight. The solution was concentrated, and the residue, dissolved in water, was washed with chloroform (×2) and the water was evaporated. The residue was dissolved in aqueous methanol (1:1) and treated with Amberlyst A21 base resin until the solution had pH ~7. The solids and solvent were removed and the residue was dissolved in water, treated with excess aqueous HCl and then lyophilised. Trituration of the residue with ethanol gave the salt **2·HCl** as a white crystalline solid (0.225 g, 0.74 mmol, 81%). Recrystallised from 90% ethanol it had mp >300°C (with darkening) $[\alpha]_D$=−0.50 (c=1.6, H_2O). IR (cm^{-1}) 3400–2750, 1708, 1632, 1560, 1478, 1190, 1022. ^{1}H NMR (D_2O with DCl) δ 9.04 (1H, s, H-2′), 8.00 (1H, s, H-8′), 5.00 (1H, d, $J_{1,2}$=9 Hz, H-1), 4.71 (1H, dd, $J_{2,3}$=5.4 Hz, H-2), 4.44 (1H, dd, $J_{3,4}$=3.2 Hz, H-3), 3.96 (m, H-5a,5b), 3.90 (1H, m H-4). ^{13}C NMR δ 155.4 (C), 148.0 (C-8′), 135.0 (C), 133.5 (C-2′), 121.4 and 107.5 (C), 76.7 (C-2), 73.3 (C-3), 68.8 (C-4), 61.4 (C-5), 58.1 (C-1). HRMS (M^+) calcd for $C_{11}H_{14}N_4O_4$: 266.1015; found: 266.1004.

(1*S*)-1-(9-Deazaguanin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol hydrochloride (3·HCl). A solution of **11** (0.158 g, 0.235 mmol) in ethanol (5 mL) was stirred with 10% Pd/C (0.02 g) in an atmosphere of hydrogen for 3 h. The solids and solvent were removed and to a solution of the residual pyrrole derivative **12** (0.12 g) in CH_2Cl_2 (10 mL) at 0°C was added a solution (0.8 mL) of benzoyl isothiocyanate in dichloromethane (0.38 mL in 10 mL). After 0.5 h, the solution was warmed to room temperature and 1,8-diazabicyclo[5.4.0]undec-7-ene (80 μL) and methyl iodide

(100 μL) were added. After another 0.5 h the reaction solution was chromatographed directly on silica gel affording (1*S*)-1-[3-(*N*-benzoyl-*S*-methylisothiocarbamoyl)-imino-2-ethoxycarbonylpyrrol-4-yl]-*N*-*tert*-butoxycarbonyl-5-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (**14**) (0.16 g, 0.223 mmol). A solution of this material (0.20 g, 0.279 mmol) in methanol saturated with ammonia (20 mL) was heated in a sealed tube at 95°C for 16 h. The solvent was removed and chromatography of the residue afforded (1*S*)-1-(9-deazaguanin-9-yl)-*N*-*tert*-butoxycarbonyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (**15**) (0.064 g, 0.12 mmol), which was dissolved in trifluoroacetic acid (3 mL) and allowed to stand at room temperature for 16 h. The solvent was removed and a solution of the residue in aqueous methanol (10 mL) (1:1 v/v) was treated with Amberlyst A21 base resin until the solution was pH~7. The solids and solvent were removed and a solution of the residue in water was treated with excess HCl and then concentrated to dryness. Trituration with ethanol gave **3·HCl** (0.024 g, 0.075 mmol, 32% from **11**) as a white solid, which darkened at ca. 260°C but did not melt below 300°C $[\alpha]_D=-0.62$ ($c=1.0$, H_2O). IR (cm^{-1}) 3400–2750, 1709, 1570, 1400, 1125, 1080. ^1H NMR (D_2O with DCl) δ 7.71 (1H, s, H-8′), 4.86 (1H, d, $J_{1,2}=9.1$ Hz, H-1), 4.65 (1H, dd, $J_{2,3}=5.0$ Hz, H-2), 4.40 (1H, dd, $J_{3,4}=3.2$ Hz, H-3), 3.94 (2H, m, H-5a,5b), 3.87 (1H, m, H-4). ^{13}C NMR δ 156.6, 153.6 and 136.0 (C), 132.1 (C-8′), 115.0 and 105.4 (C), 76.4 (C-2), 73.4 (C-3), 68.6 (C-4), 61.5 (C-5), 58.2 (C-1). HRMS (M^+) calcd for $C_{11}H_{16}N_5O_4$: 282.1202; found: 282.1204.

(1*S*)-1-[3-Amino-*N*-benzyloxycarbonyl-2-ethoxycarbonyl-pyrrol-4-yl]-5-bromo-*N*-*tert*-butoxycarbony1-1,4,5-trideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (19). Tetrabutylammonium fluoride (2.0 mL, 1 M in THF) was added to a solution of **11** (1.06 g, 1.58 mmol) in THF (10 mL). After 1 h toluene (30 mL) was added and the solution was washed with water (×2) and processed normally. Chromatography of the crude product afforded (1*S*)-1-[3-amino-*N*-benzyloxycarbonyl-2-ethoxycarbonylpyrrol-4-yl]-*N*-*tert*-butoxycarbony1-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (**18**) (0.734 g, 1.31 mmol). 4-*N*,*N*-Dimethylaminopyridine (0.02 g, 0.16 mmol), triethylamine (0.45 mL, 6.0 mmol) and then methanesulfonyl chloride (0.10 mL, 1.29 mmol) were added to **18** (0.45 g, 0.80 mmol) in CH_2Cl_2 (10 mL). After 1 h, the solution was processed and the crude product in toluene (10 mL) containing tetrabutylammonium bromide (1.55 g, 4.8 mmol) was heated at 100°C for 2 h. The cooled solution was washed with water, dried and concentrated to dryness. Chromatography of the residue afforded the bromide **19** (0.277 g, 0.44 mmol, 28% from **11**) as a syrup. ^1H NMR δ 7.36 (5H, m, Ar), 7.00 (1H, d, $J=0.8$ Hz, H-5′), 5.54 (2H, bs, NH_2), 5.34, 5.30 (2H, 2d, $J=12.3$ Hz, $ArCH_2$), 5.00 (1H, bs), 4.85–4.78 (2H, m), 4.26 (1H, m), 4.19 (2H, q, $J=7.1$ Hz, CH_2CH_3), 3.40 (1H, m), 3.04 (1H, m), 1.50, 1.36 (6H, 2s, CCH_3), 1.45 [9H, s, $C(CH_3)_3$], 1.22 (3H, t, $J=7.1$ Hz, CH_2CH_3). ^{13}C NMR δ 161.6, 154.9, 150.5, 146.2 and 134.9 (C), 128.7, 128.4 and 124.6 (CH), 116.6, 112.5 and 105.1 (C), 83.7 and 83.1 (CH), 81.7 (C), 69.3 (CH_2), 66.3 (CH), 60.0 (CH_2), 58.8 (CH), 32.0 (CH_2), 28.3 [$C(CH_3)_3$], 27.3 and 25.4 [$C(CH_3)_2$], 14.4 (CH_2CH_3). HRMS (MH^+) calcd for $C_{28}H_{37}BrN_3O_8$: 622.1764; found: 622.1752.

(1*S*)-1-(9-Deazahypoxanthin-9-yl)-1,4,5-trideoxy-1,4-imino-D-ribitol hydrochloride (21·HCl). A solution of **19** (0.27 g, 0.43 mmol) in ethanol (10 mL) containing triethylamine (0.186 mL, 1.37 mmol) was stirred under hydrogen with 20% $Pd(OH)_2/C$ (0.10 g) for 16 h. The solids and solvent were removed and chromatography of the residue afforded **20** (0.153 g, 0.37 mmol, 86%) as a syrup. ^1H NMR δ 6.47 (1H, bs, H-5′), 5.03 (1H, s), 4.98 (2H, bs, NH_2), 4.84, 4.49 (2H, 2d, $J=5.5$ Hz), 4.30 (2H, q, $J=7.1$ Hz, CH_2CH_3), 4.14 (1H, m), 1.49, 1.34 (3H each, 2s, CCH_3), 1.45 [9H, s, $OC(CH_3)_3$], 1.34 (3H, t, CH_2CH_3), 1.15 (3H, d, $J=7.1$ Hz, H-5). ^{13}C NMR δ 154.9 (C), 119.6 (CH), 113.0, 111.9 and 106.5 (C), 86.2 and 84.3 (CH), 80.1 (C), 60.8 (CH), 59.5 (CH_2), 59.1 (CH), 28.4 [$C(CH_3)_3$], 27.4, 25.6, 19.9 and 14.7 (CH_3). Treatment of **20** (0.075 g, 0.18 mmol) with formamidine acetate, trifluoroacetic acid and then hydrochloric acid as described above in the preparation of **2·HCl** led to **21·HCl** (0.033 g, 0.11 mmol, 61%) as a solid. ^1H NMR 500 MHz, D_2O, δ 8.82 (1H, s, H-2′), 7.93 (1H, s, H-8′), 4.96 (1H, d, $J_{1,2}=8.5$ Hz, H-1), 4.82 (1H, dd, $J_{2,3}=5.1$ Hz, H-2), 4.30 (1H, t, H-3), 3.87 (1H, dq, $J_{3,4}=4.1$, $J_{4,5}=7.3$ Hz, H-4), 1.53 (3H, d, H-5abc). ^{13}C NMR δ 155.6 (C), 147.1 (C-2′), 137.4 (C), 132.6 (C-8′), 121.0 and 108.2 (C), 76.5 (C-3), 75.6 (C-2), 63.1 (C-4), 58.2 (C-1), 18.1 (C-5). HRMS (M^+) calcd for $C_{11}H_{15}N_4O_3$: 251.1144; found: 251.1131.

(1*S*)-1-(9-Deazaguanin-9-yl)-1,4,5-trideoxy-1,4-imino-D-ribitol hydrochloride (22·HCl). Treatment of **20** (0.075 g, 0.18 mmol) sequentially with benzoyl isothiocyanate, methyl iodide and DBU, ammonia in methanol, trifluoroacetic acid and then hydrochloric acid as described above in the preparation of **3·HCl** afforded **22·HCl** (0.016 g, 0.053 mmol, 29%) as a solid. ^1H NMR (D_2O) δ 7.69 (1H, s, H-8′), 4.82 (1H, d, $J_{1,2}=8.8$ Hz, H-1), 4.24 (1H, t, $J=4.3$ Hz, H-3), 3.82 (1H, m, H-4), 1.50 (3H, d, $J_{4,5}=7.1$ Hz, H-5). The resonance for H-2 was beneath the HOD peak at δ 4.6. ^{13}C NMR δ 156.5, 153.5 and 135.8 (C), 131.7 (C-8), 114.9 and 105.6 (C), 76.7 and 75.7 (C-2,3), 63.4 and 58.1 (C-1,4), 18.4 (C-5). HRMS (M^+) calcd for $C_{11}H_{16}N_5O_3$: 266.1253; found: 266.1249.

***N*-*tert*-Butoxycarbonyl-2,3,6,7-tetradeoxy-7-fluoro-3,6-imino-4,5-*O*-isopropylidene-D-*allo*-heptononitrile (24).** A solution of the silylated nitrile **7** (1.7 g, 4.0 mmol) in THF (10 mL) was treated with tetrabutylammonium fluoride (6 mL, 1 M in THF) for 1 h. The solution was concentrated to dryness and chromatography of the residue afforded alcohol **23** (1.15 g, 3.68 mmol). Diethylaminosulfur trifluoride (0.46 mL, 3.5 mmol) was added to this material (0.84 g, 2.69 mmol) in CH_2Cl_2 (20 mL). After 6 h, methanol (1 mL) was added and the solution was concentrated to dryness. Chromatography of the residue gave fluoro-compound **24** (0.36 g, 1.15 mmol, 42%) as a syrup. ^1H NMR δ 4.77 (1H, d, $J=5.8$ Hz), 4.65–4.06 (5H, m), 2.86–2.60 (2H, m), 1.49 [12H, s, $C(CH_3)_3$), CH_3], 1.34 (3H, s, CH_3). ^{13}C NMR δ 153.4, 116.9 and 112.6 (C), 83.1(d, $J_{C,F}=170$ Hz, C-7), 83.9, 82.8 and 81.2, 80.5 (C-4,5), 64.4, 61.4(C-3,6), 28.2 [$C(CH_3)_3$], 27.0 and 24.5 (CH_3), 21.2 and 20.5 (C-2).[37] HRMS (MH^+) calcd for $C_{15}H_{24}FN_2O_4$: 315.1720; found: 315.1695.

(1*S*)-1-(9-Deazahypoxanthin-9-yl)-1,4,5-trideoxy-5-fluoro-1,4-imino-D-ribitol hydrochloride (25·HCl). Treatment of

24 (0.36 g, 1.15 mmol) sequentially with *tert*-butoxybis-(dimethylamino)methane, aq. acetic acid, ethyl glycinate, DBU and benzyl chloroformate, hydrogen and Pd/C, formamidine acetate, trifluoroacetic acid and then hydrochloric acid as described above in the preparation of **2·HCl** from **7** afforded the fluorinated deazahypoxanthine compound **25·HCl** (0.027 g, 0.089 mmol, 8%) as a solid. ^{1}H NMR (D_2O) δ 8.57 (1H, s, H-2′), 7.86 (1H, s, H-8′), 5.04 (1H, d, $J_{1,2}$=8.3 Hz, H-1), 4.90 (2H, d, $J_{H,F}$=45.1 Hz, H-5a,5b), 4.60 (1H, t, J=4.5 Hz, H-3), 4.10 (1H, dd, $J_{3,4}$=3.2 Hz, $J_{4,F}$=28.8 Hz, H-4). ^{13}C NMR δ 156.2 (C), 146.8 (C-2′), 140.4 (C), 132.6 (C-8′), 121.2 and 108.4 (C), 83.0 ($J_{C,F}$=169 Hz, C-5), 76.1 (C-2), 72.7 (C-3), 66.4 ($J_{C,F}$= 17.9 Hz, C-4), 59.0 (C-1). HRMS (M^+) calcd for $C_{11}H_{14}FN_4O_3$: 269.1050; found: 269.1051.

2,3,6-Trideoxy-3,6-imino-D-*allo*-heptononitrile (26). A solution of **6** (R=CH_2CN) (1.93 g, 5.9 mmol) in trifluoroacetic acid (20 mL) was allowed to stand at room temperature overnight. The reaction mixture was concentrated in vacuo and a solution of the residue in water (50 mL) was washed with chloroform (2×50 mL) and the aqueous layer concentrated to afford the unprotected **26** as the trifluoroacetic acid salt (1.0 g, 3.5 mmol, 59%). ^{1}H NMR (D_2O) δ 3.89 (1H, t, J=5.3 Hz, H-5), 3.78 (1H, t, $J_{3,4}$=6.3 Hz, H-4), 3.56 (1H, dd, J=11.8, 5.6 Hz, H-7a), 3.54 (1H, dd, J=11.8, 5.6 Hz, H-7b), 3.34 (1H, q, J=7.0 Hz, H-3), 3.18 (1H, q, J=5.1 Hz, H-6), 2.72 (2H, dd, $J_{2,2'}$=17.3 Hz, $J_{2,3}$=7.1 Hz, $J_{2',3}$=5.3 Hz, H-2,2′). ^{13}C NMR δ 121.4 (CN), 77.1 (C-4), 74.3 (C-5), 67.2 (C-6), 64.2 (C-7), 60.4 (C-3), 23.1 (C-2). HRMS (M^+) calcd for $C_7H_{12}N_2O_3$: 172.0848; found: 172.0839.

***N-tert*-Butoxycarbonyl-2,3,6-trideoxy-3,6-imino-D-*allo*-heptononitrile (27).** A solution of crude **26** (1.0 g, 3.5 mmol) in methanol (20 mL) containing di-*tert*-butyl dicarbonate (2.09 g, 9.6 mmol) was adjusted to neutral pH by the addition of triethylamine, stirred at room temperature for 16 h and concentrated in vacuo. Chromatography of the residue afforded carbamate **27** (0.80 g, 2.9 mmol, 83%) as an oil. ^{1}H NMR ($CDCl_3$) 4.18–4.11 (2H, m, H-4,5), 3.80–3.45 (4H, m, H-3,6,7,7′), 2.80–2.46 (2H, m, H-2,2′), 1.47 [9H, s, $C(CH_3)_3$]. ^{13}C NMR δ 74.0 (C-4), 71.5 (C-5), 66.1 (C-6), 62.7 (C-7), 58.9 and 58.3 (C-3), 28.2 [$C(CH_3)_3$], 21.1 (C-2).[37] HRMS (MH^+) calcd for $C_{12}H_{20}N_2O_5$: 272.1372; found: 272.1379.

***N-tert*-Butoxycarbonyl-2,3,6-trideoxy-3,6-imino-5,7-*O*-(1,1,3,3-tetraisopropyldisiloxa-1,3-diyl)-D-*allo* heptononitrile (28).** 1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (0.9 mL, 2.8 mmol) was added dropwise to a solution of **27** (0.8 g, 2.9 mmol) and imidazole (0.70 g, 10.3 mmol) in DMF (10 mL) at 0°C. The resulting solution was allowed to warm to room temperature, diluted with toluene (150 mL), washed with water (3×25 mL), dried and concentrated. Chromatography of the resulting residue afforded the disilyloxy derivative **28** (1.4 g, 2.7 mmol, 96%) an oil. ^{1}H NMR δ 4.62 (1H, dd, J=6.5, 4.8 Hz, H-5), 4.23 (1H, dd, J=11.4, 3.8 Hz, H-4), 4.00 (3H, m, H-3,7,7′), 3.65 (1H, m, H-6), 2.99, 2.66 (2H, 2brs,H-2,2′), 1.46 (9H, s, [$C(CH_3)_3$], 1.07–1.01 [28H, m, $CH(CH_3)_2$]. ^{13}C NMR δ 154.9 (CO), 117.3 (C-1), 81.2 [$C(CH_3)_3$], 73.8 (C-4), 73.8 (C-5), 63.5 (C-6), 63.5 (C-7), 60.8 (C-3), 28.2 [$C(CH_3)_3$], 21.4 (C-2), 17.2, 17.1, 17.0 and 16.9 [$CH(CH_3)_2$], 13.2, 13.1, 12.7 and 12.6 [$CH(CH_3)_2$]. HRMS (MH^+) calcd for $C_{24}H_{47}N_2O_6Si_2$: 515.2973; found: 515.2999.

***N-tert*-Butoxycarbonyl-2,3,6-trideoxy-4-*O*-[imidazole-(thiocarbonyl)]-3,6-imino-5,7-*O*-(1,1,3,3-tetraisopropyldisiloxa-1,3-diyl)-D-*allo*-heptononitrile (29).** A solution of **28** (1.5 g, 2.9 mmol) in toluene (20 mL) containing thiocarbonyldiimidazole (90%, 0.9 g, 4.5 mmol) was stirred at 90°C for 2 h. The solution was concentrated and chromatographed to afford ester **29** (1.8 g, 99%) as an oil. ^{1}H NMR ($CDCl_3$) 8.33, 7.62, 7.06 (3H, 3s, Im), 5.90 (1H, d, J=4.6 Hz, H-4), 4.91 (1H, dd, J=7.9, 4.6 Hz, H-5), 4.30–4.22 (3H, m, H-3,7,7′), 3.75 (1H, brs, H-6), 2.82 (2H, m, H-2,2′), 1.49 [9H, s, $C(CH_3)_3$], 1.09–0.94 [28H, m, $CH(CH_3)_2$]. ^{13}C NMR δ 183.2 (C=S), 154.9 (C=O), 136.8, 131.1 and 118.0 (Im), 117.1 (C-1), 83.3 (C-4), 82.1 [$C(CH_3)_3$], 76.0 (C-5), 63.8 (C-6), 59.2 (C-3), 28.3 [$C(CH_3)_3$], 21.7 (C-2), 17.4, 17.2, 17.1 and 16.8 [$CH(CH_3)_2$], 13.2, 13.1, 12.7, 12.6 [$CH(CH_3)_2$]. HRMS (MH^+) calcd for $C_{28}H_{49}N_4O_6SSi_2$: 625.2911; found: 625.2850.

***N-tert*-Butoxycarbonyl-2,3,4,6-tetradeoxy-3,6-imino-5,7-*O*-(1,1,3,3-tetraisopropyldisiloxa-1,3-diyl)-D-*ribo*-heptononitrile (30).** To a solution of **29** (1.8 g, 2.9 mmol) in toluene (50 mL), tri-*n*-butyltin hydride (1.0 mL) was added and the mixture was heated at 80°C for 3 h, cooled, concentrated and the residue was chromatographed to afford the deoxy compound **30** (0.74 g, 1.48 mmol, 51%) as an oil. ^{1}H NMR ($CDCl_3$) 4.72 (1H, dd, J=12.0, 7.1 Hz, H-5), 4.20 (2H, 2 dd, J=11.1, 4.0 Hz, H-7,7′), 3.80 (1H, brs, H-3), 3.66 (1H, m, H-6), 2.63–2.59 (2H, m, H-2,2′), 2.20–2.17 (2H, m, H-4,4′), 1.47 [9H, s, $(C(CH_3)_3$], 1.08–1.00 [28H, m, $CH(CH_3)_2$]. ^{13}C NMR δ 154.9 (CO), 117.6 (C-1), 81.0 [$C(CH_3)_3$], 73.1 (C-5), 67.5 (C-6), 64.5 (C-7), 59.2 (C-3), 28.3 [$C(CH_3)_3$], 21.7 (C-2), 17.4, 17.2, 17.1, 16.8 [$CH(CH_3)_2$], 13.2, 13.1, 12.7, 12.6 [($CH(CH_3)_2$]. HRMS (MH^+) calcd for $C_{24}H_{47}N_2O_5Si_2$: 499.3024; found: 499.3024.

(1*R*)-1-[3-Amino-1-*N*-benzyloxycarbonyl-2-ethoxycarbonyl-pyrrol-4-yl]-*N-tert*-butoxycarbonyl-1,2,4-trideoxy-1,4-imino-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxa-1,3-diyl)-D-*erythro*-pentitol (31). To a solution of **30** (0.74 g, 1.5 mmol) in DMF (10 mL), *tert*-butoxy-bis(dimethylamino)methane (1.5 mL, excess) was added and the solution heated at 65–70°C for 1 h. Toluene (50 mL) was then added and the solution was washed with water (3×20 mL), dried and concentrated to dryness. The residue was dissolved in THF/acetic acid/water (1:1:1 v/v/v, 40 mL) at room temperature. After 1.5 h, chloroform (50 mL) was added and the mixture was washed with water (2×20 mL), aqueous sodium bicarbonate, and then dried and evaporated to dryness. Chromatography of the residue afforded the analogue of enol **9** (0.68 g, 94%) as an oil. To this material in methanol (10 mL) were added ethyl glycinate hydrochloride (0.90 g, 6.5 mmol) and sodium acetate (1.0 g, 12.2 mmol). The mixture was stirred at room temperature for 16 h and concentrated to dryness. Chromatography of the residue gave the analogue of enamine **10** (0.80 g, 100%) as a diastereomeric mixture. A solution of this material in dry CH_2Cl_2 (20 mL) containing 1,8-diazabicyclo[5.4.0]-undec-7-ene (3.6 mL, 24 mmol) and benzyl chloroformate

(1.7 mL, 11.9 mmol) was heated under reflux overnight, cooled and washed with dilute aqueous HCl, aqueous sodium bicarbonate, dried and concentrated. Chromatography of the residue afforded pyrrole derivative **31** (0.70 g, 94 mmol, 62% from **30**) as an oil. ^{1}H NMR ($CDCl_3$) 7.40–7.35 (5H, m, Ar), 7.04 (1H, s, H-5′), 5.82 (2H, brs, NH_2), 5.29 (2H, d, J=1.4 Hz, CH_2Ar), 4.97 (1H, brd, J=8.3 Hz, H-3), 4.82 (1H, m, H-4), 4.22 (2H, q, J=7.1 Hz, CH_2CH$_3$), 4.01 (1H, dd, J=11.1, 4.4 Hz, H-5a), 3.70 (1H, td, J=9.3, 4.4 Hz, H-5b), 3.49 (1H, m, H-1), 2.47–2.19 (2H, m, H-2), 1.46 [9H, s,C(CH$_3$)$_3$], 1.04–0.98 [28H, m, CH(CH$_3$)$_2$]. ^{13}C NMR δ 161.6, 154.9, 150.3, 147.2 and 134.9 (C), 128.5, 128.3 and 125.4 (CH), 118.7, 104.6 (C), 81.0 [*C*(CH$_3$)$_3$], 74.8 (C-3), 69.0 (CH$_2$Ar), 66.3 (C-4), 65.3 (C-5), 59.7 (*C*H$_2$CH$_3$), 50.8 (C-1), 38.4 (C-2), 28.3 [C(*C*H$_3$)$_3$], 17.5, 17.4, 17.2, 17.0 [CH(*C*H$_3$)$_2$], 13.4, 13.2, 13.0, 12.5 [*C*H(CH$_3$)$_2$]. HRMS (M^+) calcd for $C_{37}H_{59}N_3O_9Si_2$: 745.3790; found: 745.3748.

(1*R*)-1-(9-Deazahypoxanthin-9-yl)-1,2,4-trideoxy-1,4-imino-D-*erythro*-pentitol hydrochloride (32·HCl). A solution of **31** (0.28 g, 0.38 mmol) in ethanol (10 mL) was stirred with formamidine acetate (0.50 g, 4.8 mmol) under reflux for 8 h. The solvent was removed and chromatography of the residue gave (1*R*)-*N*-*tert*-butoxycarbonyl-1,2,4-trideoxy-1-(9-deazahypoxanthin-9-yl)-1,4-imino-3,5-*O*-(1,1,3,3-tetraisopropyldisiloxa-1,3-diyl)-D-*erythro*-pentitol (120 mg, 53%). A solution of this material in trifluoroacetic acid (2 mL) was allowed to stand at room temperature overnight then concentrated and a solution of the residue in water was washed (×2) with chloroform and then evaporated. The residue was dissolved in THF and treated with tetrabutylammonium fluoride trihydrate (200 mg) and stirred for 1 h. The solvent was evaporated and chromatography gave a residue which was redissolved in methanolic HCl, the resulting precipitate was filtered to afford the salt **32·HCl** as a white solid (37 mg, 0.15 mmol, 34% from **31**) which darkened but did not melt below 300°C. ^{1}H NMR (D_2O) δ 8.65 (1H, s, H-2′), 7.80, (1H, s, H-8′), 5.26 (1H, dd, J=12.1, 6.4 Hz, H-1), 4.57 (1H, m H-3), 3.87 (3H, m, H-4, H-5a,5b), 2.60 (1H, ddd, J=14.3, 12.2, 5.7 Hz, H-2a), 2.69 (1H, dd, J=14.3, 6.4 Hz, H-2b). ^{13}C NMR δ 153.7 (C), 144.6 (C-2′), 135.9 (C), 130.4 (C-8′), 118.6 and 107.6 (C), 71.5 (C-3), 69.1 (C-4), 59.3 (C-5), 53.4 (C-1), 38.8 (C-2). HRMS (M^+) calcd for $C_{11}H_{15}N_4O_3$: 251.1144; found: 251.1143.

(1*R*)-1-(9-Deazaguanin-9-yl)-1,2,4-trideoxy-1,4-imino-D-*erythro*-pentitol hydrochloride (33·HCl). A solution of **31** (0.78 g, 1 mmol) in ethanol (10 mL) was stirred with 10% Pd/C (100 mg) in an atmosphere of hydrogen for 1.5 h. The solids and solvent were removed to afford a residue (0.62 g) which was dissolved in dichloromethane (10 mL) at 0°C and a solution (4.8 mL) of benzoyl isothiocyanate in dichloromethane (0.30 mL in 10 mL) was added. After 0.5 h, the solution was warmed to room temperature and 1,8-diazabicyclo[5.4.0]undec-7-ene (320 μL) and methyl iodide (700 μL) were added. After another 0.5 h the reaction solution was chromatographed directly affording the analogue of **14** (0.67 g, 91%). A solution of this material in methanol saturated with ammonia (20 mL) was heated in a sealed tube at 105°C for 16 h. The solvent was removed and chromatography of the residue afforded the analogue of **15** (0.30 g, 56%) as an oil. A solution of this material in trifluoroacetic acid (5 mL) was allowed to stand at room temperature for 16 h. The solvent was removed and the residue was dissolved in THF, treated with tetrabutylammonium fluoride trihydrate (200 mg) and stirred for 1 h. The solvent was removed and the residue was dissolved in methanol (5.0 mL) and acetyl chloride (0.75 mL) was added dropwise and the mixture allowed to stand at room temperature for 16 h when ether (25 mL) was added and the resulting crystals were removed to afford the deoxynucleoside analogue **33** as the solid hydrochloride salt (89 mg, 0.30 mmol, 30% from **31**), which did not melt below 300°C. ^{1}H NMR (D_2O) δ 7.63 (s, H-8′). 5.14 (1H, dd, J=12.2, 6.3 Hz, H-1), 4.55 (1H, brt, J=2.9 Hz, H-3), 3.88 (m, 3H, H-4,5a,5b), 2.63 (1H ddd, J=14.1, 12.3, 5.7 Hz, H-2a),), 2.69 (1H dd, J=14.3, 6.3 Hz, H-2b). ^{13}C NMR δ 153.9, 150.9 and 132.4 (C), 129.8 (C-8′), 112.3 and 104.4 (C), 71.4 (C-3), 69.0 (C-4), 59.3 (C-5), 53.2 (C-1), 38.6 (C-2). HRMS (M^+) calcd for $C_{11}H_{16}N_5O_3$: 266.1253; found: 266.1262.

(1*S*)-1-(9-Deazaadenin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol hydrochloride (35·HCl). Enol **9** (0.20 g, 0.44 mmol) was treated as described above in the conversion of **9** into **2** via **11** and **13**, except that aminoacetonitrile hydrochloride was used in place of ethyl glycinate, to give, by way of **34**, the hydrochloride **35** (0.039 g, 0.13 mmol, 29%) as a solid. ^{1}H NMR (D_2O) δ 8.45 (1H, s, H-2′), 8.06 (1H, s, H-8′), 5.02 (1H, d, $J_{1,2}$=8.8 Hz, H-1), 4.80 (1H, dd, $J_{2,3}$=4.9 Hz, H-2), 4.47 (1H, dd, J=3.5, 4.8 Hz, H-3), 3.98 (2H, m, H-5a,5b), 3.93 (1H, m, H-4). ^{13}C NMR δ 152.1 (C), 146.2 (C-2′), 140.7 (C), 135.3 (C-8′), 115.4 and 107.7 (C), 76.0 (C-2), 73.1 (C-3), 68.4 (C-4), 61.3 (C-5), 58.3 (C-1). HRMS (M^+) calcd for $C_{11}H_{16}N_5O_3$: 266.1253; found: 266.1264.

(1*S*)-1-(3-Amino-2-carboxamidopyrrol-4-yl)-1,4-dideoxy-1,4-imino-D-ribitol (36). Hydrogen peroxide (0.5 mL) was added dropwise to a solution of **34** (90 mg, 0.14 mmol) and potassium carbonate (50 mg) in DMSO (1.0 mL) and stirred for 10 min. The mixture was diluted with water (50 mL), extracted with ethyl acetate (3×20 mL), and the combined organic layers were dried, concentrated and chromatographed to give a product (20 mg) which was dissolved in trifluoroacetic acid (1 mL) and the solution was allowed to stand at room temperature for 16 h. The solvent was removed and the residue in water (20 mL) was washed with CH_2Cl_2 (2×5 mL). The aqueous layer was evaporated and chromatography afforded the pyrrole C-nucleoside **36** (10 mg, 0.04 mmol, 28%) as an oil. ^{1}H NMR (D_2O) δ 6.98 (1H, s, H-5′), 4.26–4.12 (3H, m, H-1,2,3), 3.78 (2H, d, J=5.1 Hz, H-5a,5b), 3.39 (1H, d, $J_{1,2}$=4.8 Hz, H-4). ^{13}C NMR D_2O δ 168.7, 141.0 and 126.2 (C), 124.1 (C-5′), 113.2 (C), 77.6 (C-2), 74.4 (C-3), 67.7 and 59.3 (C-1,4), 64.0 (C-5). HRMS (MH^+) calcd for $C_{10}H_{17}N_4O_4$: 257.1250; found: 257.1253.

X-Ray single crystal analysis data

Compound **32·HCl**, $C_{11}H_{14}N_4O_3$·HCl, had monoclinic space group $P2_1$ (4),[38] a=6.3458(14), b=6.3655(14), c=15.129(3) Å; β=96.11(3)°; V=607.6(2) Å^3; Z=2; D_c=1.562 g cm^{-3}; T=158(2) K; λ (MoKα)=0.71073 Å;

μ=0.326 mm^{-1}. Data were collected on a Siemens P4 diffractometer with SMART CCD detector on a crystal of poor quality (fractured) 0.80×0.29×0.04 mm; 34068 reflections were collected in a triclinic cell and converted on solution to a final monoclinic cell [4293 reflections merged to 1609 unique reflections ($6.46<2\theta<52.7°$) of which 1578 had $I>2\sigma(I)$]. The absorption (SADABS) ratio of minimum:maximum transmission was 1.0:0.280. The structure was solved by direct methods[39] and refined on F^2 using all data[40] to give R_1, wR_2=0.092, 0.246. The absolute configuration was not determined. All hydrogens atoms were included but not refined in calculated positions (0.84–1.0 Å as defined[40]) with constrained thermal isotropic parameters (1.2 times parent C, O or N equivalent values). Protonation at N-1 was established by the stereochemistry and distances of hydrogen bond contacts. Possible rotational disorder of the hydrogen atom on O-3 could not be modelled. The final maximum shift/error was 0.00, and the final difference map excursions were around +1.88 (near O-3) and −0.52 e Å^{-3}.

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