Exploring Structure−Activity Relationships of Transition State Analogues of Human Purine Nucleoside Phosphorylase

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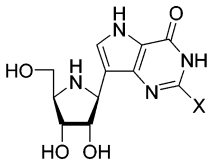
The aza-C-nucleosides, Immucillin-H and Immucillin-G, are transition state analogue inhibitors of purine nucleoside phosphorylase, a therapeutic target for the control of T-cell proliferation. Immucillin analogues modified at the 2′-, 3′-, or 5′-positions of the azasugar moiety or at the 6-, 7-, or 8-positions of the deazapurine, as well as methylene-bridged analogues, have been synthesized and tested for their inhibition of human purine nucleoside phosphorylase. All analogues were poorer inhibitors, which reflects the superior capture of transition state features in the parent immucillins.

Introduction

Purine nucleoside phosphorylase (PNP) has been identified as a therapeutic target for the control of T-cell proliferative disorders such as organ transplant rejection, T-cell cancers, rheumatoid arthritis, psoriasis, and some other autoimmune diseases.[1−5] We have used knowledge of the transition state characteristics of the phosphorolysis catalyzed by bovine PNP[6−8] to design and synthesize transition state analogue inhibitors.[9−11] Immucillin-H **1** and Immucillin-G **2** are exceedingly potent inhibitors of bovine and human PNP[12,13] as well as PNP from *Plasmodium falciparum*[14] and *Mycobacterium tuberculosis*.[15] Immucillin-H has been shown to inhibit the proliferation of human T lymphocytes[16−18] and has entered clinical trials for the control of T-cell malignancies.



1 X=H
2 X=NH_2

We report here the synthesis and structure−activity relationships of some immucillin analogues applied to human PNP.

Results and Discussion

The immucillins were designed to possess features of the transition state of the enzyme-catalyzed reaction, and X-ray crystallography of the inhibitors bound in the active site of bovine[19,20] and *Mycobacterium tuberculosis*[21] PNP's has revealed a network of many hydrogen bonds between inhibitor and enzyme. It is likely, therefore, that disruption of any one of these hydrogen bonds will lead to reduced binding to the enzyme. However, we wished to explore the consequences of functional group changes in the hope that additional or altered binding modes to the human enzyme might be discovered.

Modifications of the Iminoribitol Moiety. Some analogues of **1** modified in the iminoribitol moiety, namely the 2′-deoxy-, 5′-deoxy- and 5′-deoxy-5′-fluoro derivatives, have been described.[10] For this study we wished to focus on the synthesis of derivatives modified at the 2′- and 3′-positions. The protected immucillin derivative **3** is readily available,[11] and mild acid hydrolysis followed by treatment with di-*tert*-butyl dicarbonate afforded triol **4** which was tritylated to give diol **5** (Scheme 1). This diol could be monoprotected with moderate regioselectivity using stannylene methodology[22] generating the allyl ethers **6** and **7**, and the 4-methoxybenzyl ethers **8** and **9** with the 2-*O*-ethers predominating in each case by a ratio of ∼2:1. The regioisomers were distinguished by 2D-NMR experiments on the isomers and/or their derived monoacetates. The 2-*O*-allyl ether **6** was readily converted into the 3-*O*-(4-methoxybenzyl) derivative **9**.

Deoxygenation of the 2-*O*-(4-methoxybenzyl) ether **8** was achieved by treatment with thiocarbonyl diimidazole followed by tributyltin hydride (Scheme 2), and the 3′-deoxy product was deprotected by acid hydrolysis to give 3′-deoxy-immucillin-H **10**. *O*-Methylation of the 3-*O*-allyl derivative **7** followed by deprotection afforded 2′-*O*-methyl-immucillin-H **11**. Oxidation of **9** followed by reduction with sodium borohydride generated the 2′-epimer as the only product. Acid hydrolysis then gave the *arabino*-immucillin-H **12**.

Several attempts were made to introduce fluorine at the 2′-position by treating **7**, **9**, their 2′-epimers, or the derived ketones with DAST, but no discrete products could be obtained. Consequently the 2-deoxy-2,2-difluoroiminoribitol derivative **13** (Scheme 3) was prepared with the intention of converting it into the corresponding immucillin analogue. The parent iminoribitol **14**[23,24] was selectively functionalized via the tetraisopropyldisiloxane derivative **15** to the alcohol **16**. Oxidation of this

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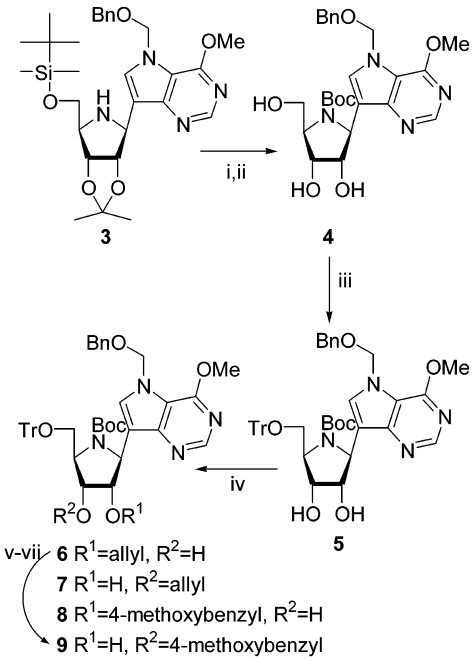
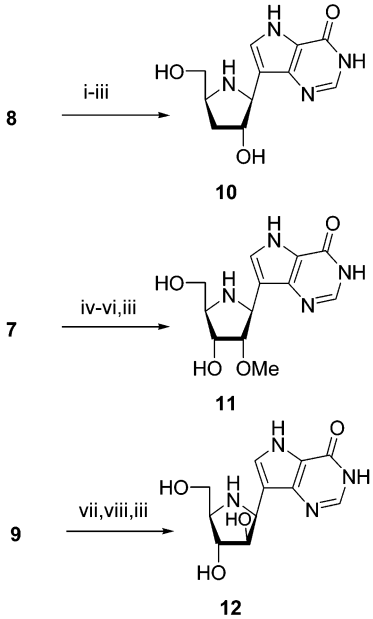
Scheme 1[a]



[a] Reagents: i, aq TFA, THF; ii, $(Boc)_2O$, Et_3N; iii, TrCl, $^iPr_2NEt$, DMAP, CH_2Cl_2; iv, Bu_2SnO, toluene, reflux, then Bu_4NBr and allyl bromide or 4-MeO-benzyl chloride; v, NaH, 4-MeO-benzyl chloride, DMF; vi, DABCO, $(Ph_3P)_3RhCl$, EtOH, reflux; vii, HgO, $HgCl_2$, aq acetone.

Scheme 2[a]

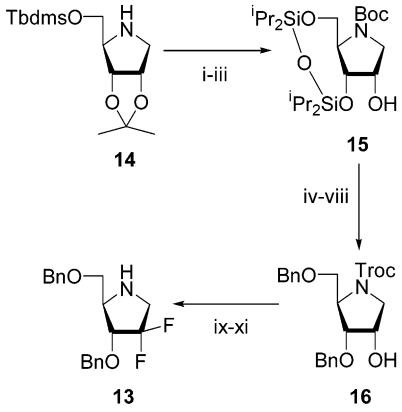


[a] Reagents: i, thiocarbonyldiimidazole; ii, Bu_3SnH; iii, concd HCl, reflux; iv, NaH, MeI; v, DABCO, $(Ph_3P)_3RhCl$, EtOH, reflux; vi, HgO, $HgCl_2$, aq acetone, vii, DMSO, TFAA, CH_2Cl_2, −70 °C, then Et_3N, viii, $NaBH_4$, EtOH.

alcohol to the ketone and treatment with DAST afforded the difluoroiminoribitol **13**. Generation of a 1,*N*-imine from this material was possible using standard techniques[10,11] but it was unstable, and attempts to add a 9-lithio-9-deazapurine derivative or lithiated acetonitrile to it did not afford discrete products.

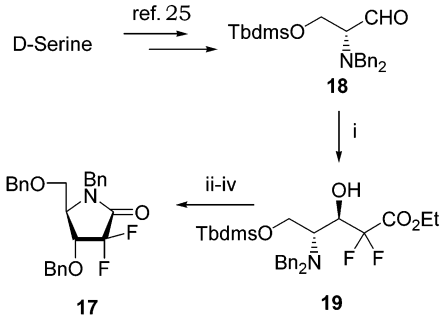
The difluoropentonolactam **17** was then prepared (Scheme 4) from D-serine via the known aldehyde **18**.[25] The addition of organometallic reagents to **18** is known

Scheme 3[a]



[a] Reagents: i, aq TFA; ii, $(Boc)_2O$; iii, $TipsCl_2$, imid.; iv, MomBr, $^iPr_2NEt$; v, Bu_4NF; vi, NaH, BnBr; vii, TFA, H_2O, THF; viii, Cl_3CCH_2OCOCl, Et_3N; ix, TFAA, DMSO, Et_3N; x, DAST; xi, Zn, HOAc.

Scheme 4[a]



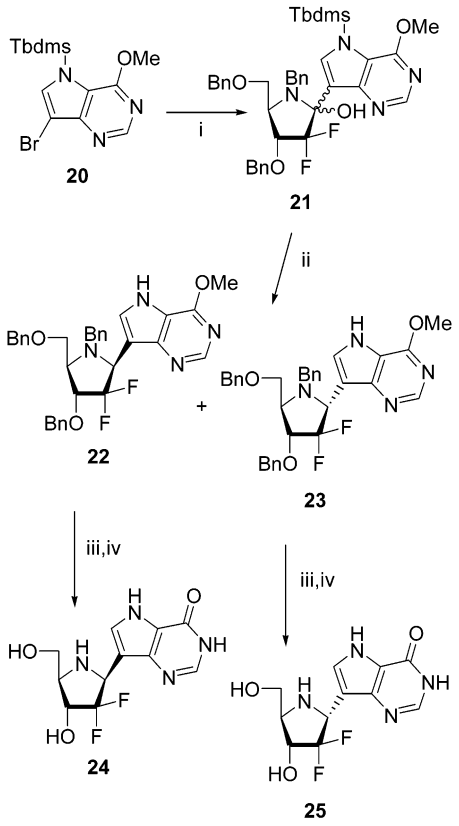
[a] Reagents: i, $BrCF_2CO_2Et$, Zn, THF; ii, H_2, Pd/C; iii, aq TFA; iv, NaH, BnBr.

to be highly stereoselective affording products with the desired anti stereochemistry.[26] When a Reformatsky reaction employing ethyl bromodifluoroacetate was applied to this aldehyde under standard conditions[27] only one product, **19**, was obtained in moderate yield. Deprotection and then benzylation of the resulting lactam gave **17**.

Lithiation of the 9-bromo-9-deazahypoxanthine derivative **20**[11] by bromine−lithium exchange and then addition of lactam **17** to the reaction mixture afforded a product, presumably **21** (Scheme 5). Reduction of this crude material using sodium cyanoborohydride afforded a separable mixture of **22** and **23** in a 1:3 ratio as well as some recovered lactam. The minor isomer, when deprotected by hydrogenolysis and acid hydrolysis, gave 2′-deoxy-2′,2′-difluoro-immucillin-H **24**. The stereochemistry of this compound was confirmed by NMR experiments whereby a NOESY pulse sequence showed correlations between H-1′ and H-4′ as well as between H-3′ and H-5′. The other isomer, **25**, demonstrated NOESY correlations between H-1′ and H-3′ as well as H-3′ and H-5′. These experiments provide evidence for the stereochemistry at C-1′ and C-3′.

Modification of the Deazapurine Moiety. The 6-*O*-methyl- and 7-*N*-methyl-immucillin derivatives **26** and **27** were prepared from **28**[11] by selective hydrolysis, and methylation followed by acid hydrolysis, respectively (Scheme 6). Treatment of immucillin-H **1** with di-*tert*-butyl dicarbonate and acetylation gave triacetate **29**, which, after exposure to Lawesson's reagent followed

Scheme 5[a]



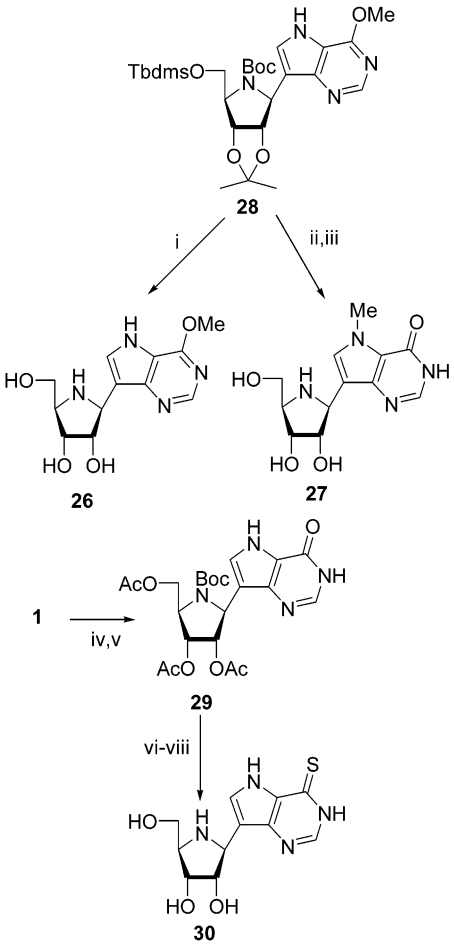
[a] Reagents: i, BuLi, THF, −70 °C, then **17**; ii, $NaBH_3CN$, HOAc, MeOH; iii, H_2, Pd/C; iv, aq HCl, MeOH.

by saponification and acid hydrolysis afforded the 6-thioimmucillin **30**.

When the fully protected derivative **31**[11] was allowed to react with *n*-butyllithium at −70 °C and then quenched with CD_3OD, deuterium incorporation was observed by ^1H NMR spectroscopy only at H-8 (Scheme 7). Similar treatment of a 6-chloropurine riboside derivative, but with LDA as base, has shown that both the 2- and 8-positions of the purine were readily lithiated.[28] Consequently it might have been expected that lithiation of the 9-deazapurine derivative **31** would occur at *C*-2 rather than the observed *C*-8. The 8-lithio intermediate was allowed to react with methyl iodide to give **32**, which on hydrogenolysis and acid hydrolysis afforded 8-methylimmucillin-H **33**. Similarly, treatment of the 8-lithio derivative with *N*-fluorobenzenesulfonimide generated an 8-fluoro derivative, but the strong acid conditions required for deprotection resulted in partial hydrolysis of the heteroaryl fluoride moiety. The alternative 6-*O*-*tert*-butyl compound **34** was prepared in an analogous manner to the 6-*O*-methyl derivative **31**, and successfully converted into the 8-fluoro derivative **35** as above. Hydrogenolysis and a mild acid hydrolysis then afforded **36**. The 8-trimethylsilyl derivative **37** was synthesized in order to block the 8-position from lithiation. However, treatment of this material with *n*-butyllithium at −70 °C did not result in any detectable *C*-2 lithiation and under more forcing conditions resulted only in degradation.

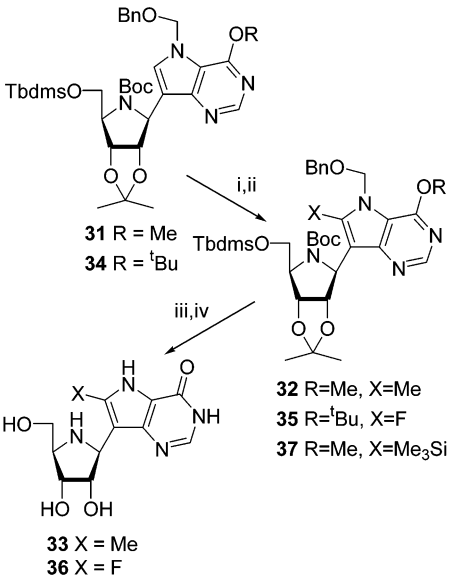
Synthesis of "Methylene-Bridged" Analogues. Addition of lithiated *tert*-butyl acetate to the imine **38** successfully afforded the adduct **39** (Scheme 8). With a

Scheme 6[a]



[a] Reagents: i, MeOH, 2 M aq HCl; ii, NaH, MeI; iii, MeOH, concd aq HCl, reflux; iv, $(Boc)_2O$; v, Ac_2O, py; vi, Lawesson's reagent, toluene, reflux; vii, NH_3/MeOH; viii, 1 M aq HCl.

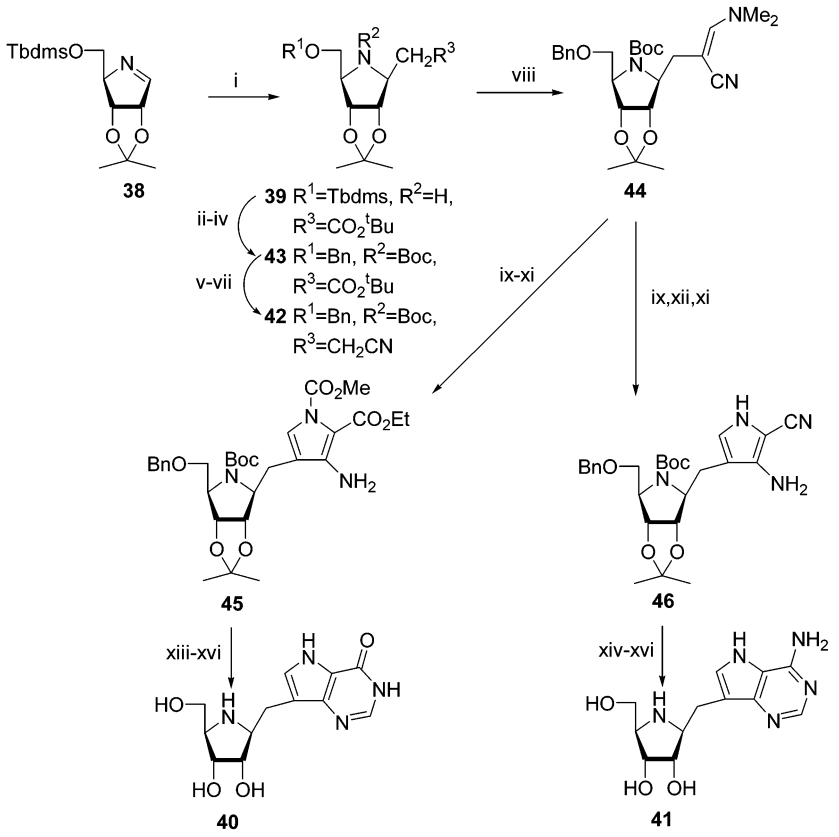
Scheme 7[a]



[a] Reagents: i, BuLi, THF, −70 °C; ii, MeI or $(PhSO_2)_2NF$ or Me_3SiCl, HMPA; iii, H_2, Pd/C; iv, MeOH, concd aq HCl, reflux, (for **33**), or MeOH, 2 M aq HCl (for **36**).

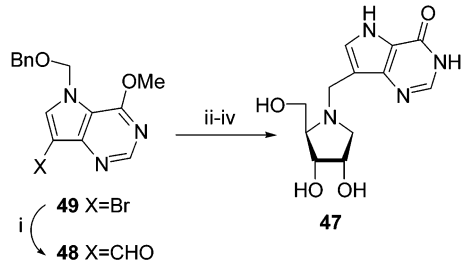
view toward synthesizing immucillins **40** and **41** with a methylene bridge between the deazapurine and iminoribitol moieties, **39** was converted into the propioni-

Scheme 8[a]



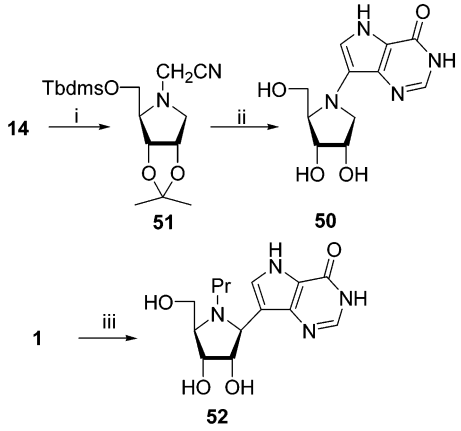
[a] Reagents: i, LDA, $CH_3CO_2{}^tBu$; ii, $(Boc)_2O$; iii, Bu_4NF; iv, NaH, BnBr; v, DIBAH; vi, MsCl, $^iPr_2NEt$; vii, KCN, DMF; viii, $^tBuOCH(NMe_2)_2$, DMF; ix, THF, HOAc, H_2O; x, NaOAc, $H_2NCH_2CO_2Et$, MeOH; xi, DBU, MeOCOCl, then, for **46**, MeOH; xii, NaOAc, H_2NCH_2CN, MeOH; xiii, K_2CO_3, MeOH; xiv, formamidine, EtOH, reflux; xv, H_2, $Pd(OH)_2/C$, EtOH, xvi, 2 M aq HCl.

Scheme 9[a]



[a] Reagents: i, BuLi, DMF; ii, $NaBH_3CN$, **14**, MeOH; iii, H_2, Pd/C, EtOH; iv, concd HCl; MeOH, reflux.

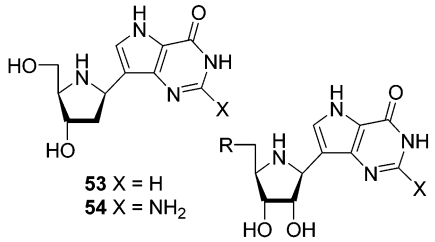
Scheme 10[a]

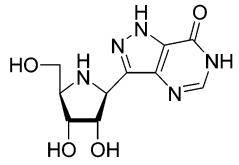


[a] Reagents: i, $^iPr_2NEt$, $BrCH_2CN$; ii, as in Scheme 8 for the conversion of **42** to **40**; iii, H_2, Pd/C, EtCHO.

trile derivative **42** via **43**. This was then functionalized to the enamine **44** and then pyrroles **45** and **46**, using standard methods,[10] from which the methylene bridged immucillins **40** and **41** were obtained. The *N*-linked methylene-bridged compound **47** was readily prepared (Scheme 9) by a reductive amination applied to the 9-deaza-9-formylpurine **48**, itself available from **49**.[11] The compound **50** with the iminoribitol directly *N*-linked to the 9-deazapurine, was synthesized (Scheme 10) from the acetonitrile adduct **51** using the standard chemistry for building up a 9-deazapurine moiety, but in poor overall yield. A standard reductive amination between immucillin-H **1** and propionaldehyde has afforded the *N*-propyl immucillin **52**.

Biological Results. While some preliminary assays of immucillin analogues against bovine PNP have been reported, it is of more interest to study the clinically relevant human PNP as presented here. We have recently reported on the inhibitory properties of the 2′-deoxy, **53** and **54**, and 5′-modified **55**−**57** derivatives against bovine PNP.[10,19] In these cases the 2′-deoxy inhibitors **53** and **54** showed good activity, as might be expected since 2′-deoxy nucleosides are excellent substrates for the enzyme, whereas changes at the 5′-position proved deleterious to binding. This is perhaps not surprising since the X-ray crystal structure of bovine PNP complexed with **1** showed the 5′-hydroxy group engaged in a strong hydrogen bonding pattern with enzyme and the 4′-nitrogen.[20] This pattern of activity of the 2′- and 5′-modified compounds is repeated for the human enzyme except that the 2′-deoxy-immucillins





58

were slightly poorer inhibitors than the parent compounds (Table 1). Other changes engendered at the 2′-position such as inversion of stereochemistry **12**, methyl ether formation **11**, and fluorination **24**, as well as 3′-deoxygenation **10**, all resulted in relatively poor inhibition compared to the extremely potent immucillin-H **1** and immucillin-G **2**. The 2′,2′-difluoro derivative **24** appeared to decompose in the presence of the enzyme but this was not further investigated.

In the cases of the immucillins modified in the deazapurine ring, the 6-*O*-methyl **26** and 7-*N*-methyl derivatives **27** exhibited a ∼100 fold loss of activity, whereas the 6-thio derivative **30** suffered a ∼400-fold loss of activity. Substitution at the 8-position (compounds **33** and **36**) again reduced activity, although the 8-fluoro derivative **36** was <10 times less active. The 8-aza compound **58**[30] on the other hand retained most of the activity of the parent compound.

At the transition state of nucleoside phosphorolysis catalyzed by PNP there is reduced bond order between the ribose and the departing purine. Synthesis of analogues with greater distance between the ribose mimic and the deazapurine explored this feature of the transition state. Such "methylene-bridged" analogues **40** and **47** were not an improvement. The *N*-linked **50** and *N*-propyl **52** derivatives were exceedingly poor inhibitors in comparison to **1** and **2**.

Conclusion

Immucillin analogues modified in the iminoribitol and deazapurine moieties as well as "methylene-bridged" derivatives have been prepared and assayed as inhibitors of human purine nucleoside phosphorylase. All were poorer inhibitors than the potent transition state analogues **1** and **2**.

Experimental Section

General Methods. Aluminum-backed silica gel sheets (Merck or Riedel de Haen) were used for TLC. Column chromatography was performed on silica gel (230−400 mesh, Merck). Chromatography solvents were distilled prior to use. Anhydrous solvents were obtained from Aldrich or Acros. NMR spectra were recorded at 300 MHz (^{1}H) and 75 MHz (^{13}C) in $CDCl_3$ with tetramethylsilane as internal standard unless otherwise indicated.

Human PNP and Assays. The cDNA for human PNP was inserted into a pCRT7/NT-TOPO vector and expressed in *E. coli* with an N-terminal His-tag. Protein was purified to >98% homogeneity and used as the His-tagged product. Full characterization of the human enzyme will be reported elsewhere.

Table 1. Inhibition of Human PNP by Immucillins[a]

compd	K_i, nM	K_i*, nM	compd	K_i, nM	K_i*, nM
1	3.3 ± 0.2	0.056 ± 0.015	**40**	250 ± 7	ND
2	0.54 ± 0.1	0.042 ± 0.006	**41**	>30 000	ND
10	9.5 ± 1.6	ND	**47**	2.84 ± 0.06	ND
11	5.9 ± 1.4	ND	**50**	12 700 ± 1700	ND
12	3.5 ± 0.3	ND	**52**	415 ± 86	ND
24	1.4 ± 0.2	ND	**53**	0.25 ± 0.06	ND
26	4.7 ± 0.5	ND	**54**	0.22 ± 0.02	ND
27	4.7 ± 0.3	ND	**55**	25 ± 7	ND
30	24.7 ± 1.1	ND	**57**	81 ± 5	7 ± 2
33	10.1 ± 1.6	ND	**58**	1.4 ± 0.2	0.18 ± 0.02
36	5.6 ± 0.7	0.39 ± 0.02			

[a] K_i is the initial rate constant and K_i* is the equilibrium dissociation constant obtained after slow-onset inhibition.[12] ND indicates that no slow-onset phase was observed.

Assays used inosine and inorganic phosphate as substrates. The hypoxanthine product was converted to uric acid in a coupled assay that detects the UV absorbance of uric acid at 293 nm. Details of the assay and experimental determination of K_i and K_i^* have been described.[12]

(1*S*)-1-(7-*N*-Benzyloxymethyl-9-deaza-6-*O*-methylhypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-1,4-dideoxy-1,4-imino-D-ribitol (4). A solution of **3**[11] (2.25 g, 5.1 mmol) in THF (30 mL), trifluoroacetic acid (4 mL), and water (12 mL) was heated under reflux for 1.5 h and then concentrated to dryness. The crude residue in methanol (20 mL) was treated with triethylamine (1.43 mL, 10.3 mmol) and di-*tert*-butyl dicarbonate (1.67 g, 7.7 mmol). After 1 h the solution was concentrated to dryness and chromatography afforded **4** as a syrup (2.28 g, 4.56 mmol, 88%). ^{1}H NMR (at 50 °C after D_2O shake) δ 8.24 (bs, 1H), 7.40 (bs, 1H), 7.32−7.25 (m, 5H), 5.72−5.65 (m, 2H), 4.70 (d, J = 7.6 Hz, 1H), 4.65 (s, 1H), 4.55−4.46 (m, 2H), 4.21 (s, 1H), 4.15−4.10 (m, 1H), 4.07 (s, 3H), 3.99 (s, 1H), 3.66 (d, J = 12.2 Hz, 1H), 1.13 (bs, 9H); ^{13}C NMR (at 50 °C) δ 157.1, 149.7, 148.1, 137.6, 132.9, 129.1, 128.6, 128.3, 117.0, 80.5, 77.7, 76.9, 74.1, 71.1, 68.4, 63.6, 60.4, 54.3, 28.9. HRMS (MH^+) calcd for $C_{25}H_{33}N_4O_7$: 501.2349. Found: 501.2388.

(1*S*)-1-(7-*N*-Benzyloxymethyl-9-deaza-6-*O*-methylhypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-1,4-dideoxy-1,4-imino-5-*O*-triphenylmethyl-D-ribitol (5). A solution of **4** (1.74 g, 3.48 mmol) in dichloromethane (20 mL) containing *N*,*N*-diisopropylethylamine (2.4 mL, 13.8 mmol), 4-(dimethylamino)pyridine (0.13 g, 1.06 mmol), and chlorotriphenylmethane (1.17 g, 4.2 mmol) was allowed to stand at room temperature for 16 h. Additional chlorotriphenylmethane (1.0 g, 3.6 mmol) was added, and after a further 6 h, the solution was washed with water and aq $NaHCO_3$ and processed normally. Chromatography afforded **5** (2.27 g, 3.06 mmol, 88%) as a colorless foam. ^{1}H NMR (C_6D_6 at 70 °C) δ 8.40 (s, 1H), 7.56 (d, J = 1.1 Hz, 1H), 7.39−7.35 (m, 6H), 7.05−6.90 (m, 14H), 5.46 (d, J = 6.8 Hz, 1H), 5.24 (s, 2H), 5.03 (dd, J = 6.7, 4.3 Hz, 1H), 4.54 (bs, 1H), 4.46 (d, J = 4.0 Hz, 1H), 4.11 (s, 2H), 3.76 (s, 3H), 3.60 (dd, J = 9.4, 5.7 Hz, 1H), 3.35 (dd, J = 9.4, 3.3 Hz, 1H), 3.22 (bs, 1H), 1.42 (s, 9H); ^{13}C NMR (C_6D_6 at 70 °C) δ 156.7, 156.5 (C), 149.8 (CH), 149.6, 144.7, 137.8 (C), 132.1 (CH), 118.7, 116.1, 87.6, 79.8 (C), 77.8 (CH), 77.2 (CH_2), 74.3 (CH), 70.2 (CH_2), 67.0 (CH), 64.5 (CH_2), 61.6 (CH), 53.2, 28.6 (CH_3), some aromatic signals were obscured by the solvent. HRMS (MH^+) calcd for $C_{44}H_{47}N_4O_7$: 743.3445. Found: 743.3419.

1(*S*)-2-*O*-Allyl-1-(7-*N*-benzyloxymethyl-9-deaza-6-*O*-methylhypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-1,4-dideoxy-1,4-imino-5-*O*-triphenylmethyl-D-ribitol (6) and 1(*S*)-3-*O*-Allyl-1-(7-*N*-benzyloxymethyl-9-deaza-6-*O*-methylhypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-1,4-dideoxy-1,4-imino-5-*O*-triphenylmethyl-D-ribitol (7). A solution of **5** (1.9 g, 2.56 mmol) in toluene (50 mL) was heated under reflux with dibutyltin oxide (0.64 g, 2.57 mmol) in a Dean−Stark apparatus for 1 h, tetrabutylammonium bromide (0.82 g, 2.55 mmol) and allyl bromide (4 mL, 46.2 mmol) were added, refluxing was continued for 4 h, and then the solution was concentrated to dryness. Chromatography of the residue

afforded the 2-ether **6** (1.14 g, 1.46 mmol, 57%) followed by the 3-ether **7** (0.61 g, 0.78 mmol, 30%) as syrups. For **6**; ^{1}H NMR (C_6D_6 at 70 °C) δ 8.57 (s, 1H), 7.61−7.57 (m, 7H), 7.15−6.99 (m, 14H), 5.79−5.68 (m, 1H), 5.55 (d, J = 3.6 Hz, 1H), 5.32 (d, J = 10.4 Hz, 1H), 5.14 (dd, J = 17.2, 1.6 Hz, 1H), 5.05 (d, J = 10.4 Hz, 1H), 4.96−4.92 (m, 3H), 4.34−4.29 (m, 1H), 4.18 (d, J = 1.7 Hz, 2H), 4.16−4.03 (m, 3H), 3.85 (dd, J = 9.4, 3.8 Hz, 1H), 3.80 (s, 3H), 2.55 (d, J = 5.7 Hz, 1H), 1.30 (s, 9H); ^{13}C NMR (C_6D_6 at 70 °C) δ 156.6, 155.8(C), 150.2 (CH), 149.9, 145.0, 138.0 (C), 135.1, 133.7 (CH), 116.9 (CH_2), 116.5, 87.6 (C), 82.1 (CH), 79.5 (C), 77.4 (CH_2), 72.1 (CH), 71.3, 70.3 (CH_2), 64.8 (CH), 63.2 (CH_2), 58.7 (CH), 53.0, 28.6 (CH_3). HRMS (MH^+) calcd for $C_{47}H_{51}N_4O_7$: 783.3758. Found: 783.3795. For **7**; ^{1}H NMR (C_6D_6 at 70 °C) δ 8.49 (s, 1H), 7.55 (s, 1H), 7.48 (d, J = 7.5 Hz, 6H), 7.12−6.97 (m, 14H), 5.93−5.82 (m, 1H), 5.45 (d, J = 5.4 Hz, 1H), 5.29−5.23 (m, 4H), 5.17 (d, J = 10.4 Hz, 1H), 5.05 (d, J = 10.4 Hz, 1H), 4.57−4.49 (m, 2H), 4.21−4.08 (m, 3H), 4.04 (bs, 1H), 3.88−3.79 (m, 1H), 3.77 (s, 3H), 3.65 (dd, J = 9.4, 3.8 Hz, 1H), 1.34 (s, 9H); ^{13}C NMR (C_6D_6 at 70 °C) δ 156.6, 156.1 (C), 150.0 (CH), 149.7, 144.9, 137.9 (C), 135.6, 133.3 (CH), 116.7 (CH_2), 116.3, 87.5 (C), 80.6 (CH), 79.5 (C), 77.3 (CH_2), 75.4 (CH), 71.5, 70.2, 63.8 (CH_2), 63.6, 61.6 (CH), 53.0, 28.6 (CH_3). HRMS (MH^+) calcd for $C_{47}H_{51}N_4O_7$: 783.3758. Found: 783.3741.

(1*S*)-1-(7-*N*-Benzyloxymethyl-9-deaza-6-*O*-methylhypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-1,4-dideoxy-1,4-imino-2-*O*-(4-methoxybenzyl)-5-*O*-triphenylmethyl-D-ribitol (8) and (1*S*)-1-(7-*N*-Benzyloxymethyl-9-deaza-6-*O*-methylhypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-1,4-dideoxy-1,4-imino-3-*O*-(4-methoxybenzyl)-5-*O*-triphenylmethyl-D-ribitol (9). A solution of **5** (0.50 g, 0.67 mmol) in benzene (15 mL) was treated as described above in the preparation of **6** and **7** except that 4-methoxybenzyl chloride (0.18 mL, 1.33 mmol) was used in place of allyl bromide, and the reaction was heated under reflux for 18 h. Chromatography afforded the 2-ether **8** (0.377 g, 0.44 mmol, 65%) followed by the 3-ether **9** (0.143 g, 0.17 mmol, 25%) as syrups. For the 2-ether **8**; ^{1}H NMR (500 MHz) (DMSO-d_6 at 90 °C) δ 8.23 (s, 1H), 7.49 (s, 1H), 7.40−7.37 (m, 6H), 7.30−7.22 (m, 12H), 7.15−7.10 (m, 4H), 6.72 (d, J = 8.5 Hz, 2H), 5.61 (d, J = 10.4 Hz, 1H), 5.35 (d, J = 10.4 Hz, 1H), 5.00 (d, J = 5.1 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.49−4.46 (m, 2H), 4.43 (d, J = 12.0 Hz, 1H), 4.37 (d, J = 12.0 Hz, 1H), 4.34 (d, J = 12.0 Hz, 1H), 4.06 (s, 3H), 4.94−4.91 (m, 1H), 3.70 (s, 3H), 3.58 (dd, J = 9.4, 6.9 Hz, 1H), 3.40 (dd, J = 9.4, 4.1 Hz, 1H), 1.18 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 158.9, 155.9, 154.9, 149.3, 148.7, 144.1, 137.5, 130.4, 129.4, 128.7, 128.5, 128.2, 127.9, 127.7, 127.3, 115.2, 113.6, 86.4, 79.5, 79.0, 77.2, 70.8, 69.7, 64.1, 62.0, 57.1, 55.3, 53.7, 28.2. HRMS (MH^+) calcd for $C_{52}H_{55}N_4O_8$: 863.4020. Found: 863.4052. For the 3-ether **9** ^{1}H NMR (C_6D_6 at 70 °C) δ 8.51 (s, 1H), 7.55 (s, 1H), 7.51−7.44 (m, 6H), 7.29 (d, J = 8.6 Hz, 2H), 7.11−6.90 (m, 14H), 6.83−6.75 (m, 2H), 5.49 (d, J = 5.3 Hz, 1H), 5.28 (m, 2H), 5.16 (d, J = 10.4 Hz, 1H), 4.71−4.67 (m, 3H), 4.54 (bs, 1H), 4.17 (s, 2H), 3.88−3.81 (m, 1H), 3.78 (s, 3H), 3.66 (dd, J = 9.4, 3.8 Hz, 1H), 3.37 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (C_6D_6 at 70 °C) δ 160.1, 156.6, 156.1 (C), 150.0 (CH), 149.7, 144.9, 137.9, 117.9 (C), 114.5 (CH), 87.5 (C), 80.3 (CH), 79.6 (C), 77.3 (CH_2), 75.3 (CH), 72.3, 70.3, 63.8 (CH_2), 63.5, 61.6 (CH), 55.0, 53.0, 28.6 (CH_3) some aromatic peaks were obscured by the solvent. HRMS (MH^+) calcd for $C_{52}H_{55}N_4O_8$: 863.4020. Found: 863.4014.

(1*S*)-1-(7-*N*-Benzyloxymethyl-9-deaza-6-*O*-methylhypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-1,4-dideoxy-1,4-imino-3-*O*-(4-methoxybenzyl)-5-*O*-triphenylmethyl-D-ribitol (9). Sodium hydride (0.117 g, 60%, 2.9 mmol) was added slowly to a solution of the 2-*O*-allyl compound **6** (1.14 g, 1.46 mmol) and 4-methoxybenzyl chloride (0.3 mL, 2.1 mmol) in DMF (15 mL), and the mixture was stirred at room temperature for 4 h. A little ethanol was added followed by toluene (30 mL), and the mixture was washed with water. Normal processing afforded a syrup which was dissolved in a mixture of ethanol (30 mL), benzene (9 mL), and water (3 mL). DABCO (0.326 g, 2.91 mmol) and tris(triphenylphosphine)rhodium(I) chloride (0.15 g, 0.16 mmol) were added, and the resulting solution was heated under reflux for 4 h. The same quantities of reagents were added again, and refluxing was continued for another 4 h. The solution was concentrated to dryness and the residue was dissolved in 10 % aq acetone (30 mL). Yellow mercuric oxide (1.0 g, 4.6 mmol) and mercuric chloride (0.6 g, 2.2 mmol) were added to the stirred solution, and after 1 h the same quantities of reagents were added again. After another 1 h the mixture was concentrated to dryness. Chloroform (100 mL) was added, and the mixture was filtered. The filtrate was washed twice with water and processed normally to give, after chromatography, **9** as a syrup (1.02 g, 1.18 mmol, 81%) with the same ^{1}H and ^{13}C NMR spectra described above.

(1*S*)-1-(9-Deazahypoxanthin-9-yl)-1,3,4-trideoxy-1,4-imino-D-*erythro*-pentitol Hydrochloride (10·HCl). A solution of the 2-*O*-(4-methoxybenzyl) derivative **8** (0.36 g, 0.418 mmol) in toluene (5 mL) containing thiocarbonyl diimidazole (0.148 g, 0.83 mmol) was heated under reflux for 1 h. Tributyltin hydride (1.2 mL, 4.45 mmol) was added directly to the refluxing solution, and refluxing was continued for 1 h. The solution was concentrated to dryness, the residue was dissolved in acetonitrile (10 mL), and this solution was washed twice with light petroleum. The acetonitrile phase was concentrated to dryness and chromatography afforded a colorless foam (0.204 g). This material was suspended in concentrated HCl (5 mL), and the mixture was heated under reflux for 1 h, cooled, and concentrated to dryness. The residue was redissolved in water, and this solution was washed twice with chloroform. The aqueous phase was concentrated to dryness and chromatography (CH_2Cl_2/MeOH/a NH_3 5:4:1) afforded a syrup which was treated with 2M aq HCl (2 mL) and the solution was lyophilized to give **10·HCl** as a white solid (0.065 g, 0.22 mmol, 52%) which decomposed at ∼270 °C without melting. ^{1}H NMR (D_2O) δ 7.95 (s, 1H), 7.68 (s, 1H), 4.95−4.84 (m, 2H), 4.24−4.17 (m, 1H), 3.97 (dd, J = 12.6, 3.8 Hz, 1H), 3.83 (dd, J = 12.6, 6.7 Hz, 1H), 2.50−2.40 (m, 1H), 2.34−2.25 (m, 1H); ^{13}C NMR (D_2O) δ 157.5, 146.0 (C), 145.3, 131.4 (CH), 120.4, 110.8 (C), 76.2, 63.8 (CH), 63.1 (CH_2), 62.7 (CH), 36.6 (CH_2). HRMS (MH^+) calcd for $C_{11}H_{15}N_4O_3$: 251.1144. Found: 251.1133.

(1S)-1-(9-Deazahypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-2-*O*-methyl-D-ribitol (11). Sodium hydride (0.03 g, 60%, 0.75 mmol) was added to a solution of the 3-*O*-allyl derivative **7** (0.20 g, 0.26 mmol) and methyl iodide (32 μL, 0.51 mmol) in DMF (3 mL), and the mixture was stirred at room temperature for 1 h. A small amount of ethanol was added followed by toluene (15 mL), and the solution was washed twice with water and processed normally. The crude product in ethanol (5 mL), benzene (1.5 mL), and water (0.5 mL) was treated with DABCO (0.06 g, 0.53 mmol) and tris(triphenylphosphine)-rhodium(I) chloride (0.05 g, 0.054 mmol), and the solution was heated under reflux for 8 h. Additional reagents as above were added, and reflux was continued for 2 h. The solution was concentrated to dryness and redissolved in 10% aq acetone (10 mL). Yellow mercuric oxide (0.30 g) and mercuric chloride (0.25 g) were added to the stirred solution, and after 1 h the mixture was concentrated to dryness. Chloroform (50 mL) was added, the solids were removed, and the filtrate was washed with water and processed normally followed by chromatography to give 0.12 g of syrupy material. This was dissolved in concentrated HCl (10 mL), and the solution was heated under reflux for 1 h then concentrated to dryness. A solution of the residue in water was washed twice with chloroform, and the aq phase was evaporated to dryness. Chromatography of the residue (MeOH:$CHCl_3$:concentrated aq NH_3 100:100:1) afforded **11** as an amorphous powder (0.025 g, 0.09 mmol, 34%). ^{1}H NMR (D_2O) δ 7.97 (s, 1H), 7.62 (s, 1H), 4.57 (d, J = 8.2 Hz, 1H), 4.41 (dd, J = 5.2, 4.3 Hz, 1H), 4.18 (dd, J = 8.2, 5.3 Hz, 1H), 3.86−3.76 (m, 2H), 3.45 (dd, J = 9.1, 4.8 Hz, 1H), 3.41 (s, 3H); ^{13}C NMR (D_2O) δ 158.1, 146.3 (C), 145.0, 131.0 (CH), 120.7, 115.8 (C), 87.0, 72.9, 68.2 (CH), 64.1 (CH_2), 60.8 (CH_3), 58.1 (CH). HRMS (MH^+) calcd for $C_{12}H_{17}N_4O_4$: 281.1250. Found: 281.1249.

(1S)-1-(9-Deazahypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-arabinitol (12). A solution of DMSO (0.24 mL, 3.38 mmol)

in dichloromethane (10 mL) was cooled to −70 °C, and trifluoroacetic anhydride (0.24 mL, 1.73 mmol) was added to the stirred solution. After 10 min a solution of the 3-*O*-methoxybenzyl ether **9** (0.31 g, 0.36 mmol) in dichloromethane (5 mL) was added followed by triethylamine (0.4 mL, 5.4 mmol) after a further 15 min. The solution was allowed to warm to room temperature and processed normally. The crude product in methanol (5 mL) was cooled to 0 °C, and sodium borohydride (0.1 g, 2.5 mmol) was added to the stirred solution. After 30 min the solution was concentrated to dryness, and chromatography afforded a syrup, presumably (1*S*)-1-(7-*N*-benzyloxymethyl-9-deaza-6-*O*-methylhypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-1,4-dideoxy-1,4-imino-3-*O*-(4-methoxybenzyl)-5-*O*-triphenylmethyl-D-arabinitol (0.22 g, 0.255 mmol, 70%). Some of this material (0.16 g, 0.186 mmol) was dissolved in concentrated HCl, and the solution was heated under reflux for 1 h and then concentrated to dryness. Chromatography (CH_2Cl_2/MeOH/aq NH_3 5:4:1) afforded **12** as a solid (0.038 g, 0.143 mmol, 77%) which decomposed at ∼210 °C without melting. ^{1}H NMR (D_2O) δ 7.86 (s, 1H), 7.57 (s, 1H), 4.68 (d, J = 3.8 Hz, 1H), 4.30 (dd, J = 3.8, 1.5 Hz, 1H), 4.10 (dd, J = 4.2, 1.5 Hz, 1H), 3.93 (dd, J = 11.8, 5.0 Hz, 1H), 3.86 (dd, J = 11.8, 6.8 Hz, 1H), 3.36−3.31 (m, 1H); ^{13}C NMR (D_2O) δ 157.7, 145.6 (C), 144.8, 131.7 (CH), 119.9, 113.1 (C), 81.5, 80.9, 69.1 (CH), 64.2 (CH_2), 59.9 (CH). HRMS (MH^+) calcd for $C_{11}H_{15}N_4O_4$: 267.1093. Found: 267.1092.

3,5-Di-*O*-benzyl-1,4-dideoxy-1,4-imino-*N*-(2,2,2-trichloroethoxycarbonyl)-D-ribitol (16). A solution of **14**[24] (2.41 g, 8.4 mmol) in 10% aq trifluoroacetic acid (30 mL) was allowed to stand at room temperature for 16 h and then was concentrated to dryness. A solution of the residue in methanol (30 mL) was treated with triethylamine (2.3 mL, 16.6 mmol) and then di-*tert*-butyl dicarbonate (2.38 g, 10.9 mmol), and after standing at room temperature for 2 h the solution was concentrated to dryness. Chromatography of the residue afforded *N*-*tert*-butoxycarbonyl-1,4-dideoxy-1,4-imino-D-ribitol (1.68 g, 86%). A cold (−20 °C) solution of this material (2.16 g, 9.27 mmol) and imidazole (3.78 g, 55.6 mmol) in dry *N*,*N*-dimethylformamide (25 mL) was treated with 1,3-dichlorotetraisopropyldisiloxane (3.11 mL, 9.73 mmol), and after 0.5 h the solution was allowed to warm to room temperature. Toluene (40 mL) was added, and the solution was washed twice with water. Normal processing followed by chromatograpgy gave **15** (4.02 g, 82%). Bromomethyl methyl ether (1.2 mL, 14.7 mmol) was then added to a solution of this material (2.25 g, 4.74 mmol) in THF (30 mL) containing diisopropylethylamine (5.0 mL, 28.7 mmol), and the mixture was heated under reflux for 1 h and cooled, and then methanol (20 mL) and tetrabutylammonium fluoride (15 mL, 1 M in THF) were added. After 16 h, the solution was concentrated to dryness. A solution of the crude material in dry DMF (10 mL) was treated with benzyl bromide (2.0 mL, 16.7 mmol) and sodium hydride (0.6 g, 60%, 15.6 mmol), and the mixture was stirred for 2 h. The reaction was quenched with a little methanol, toluene (30 mL) was added, and the solution was washed (×2) with water. Normal processing and chromatography afforded syrupy 3,5-di-*O*-benzyl-*N*-*tert*-butoxycarbonyl-1,4-dideoxy-1,4-imino-2-*O*-methoxymethyl-D-ribitol (1.71 g, 78%). A solution of this material (1.6 g, 3.5 mmol) in THF (20 mL), water (10 mL), and TFA (10 mL) was heated under reflux for 1.5 h and then concentrated to dryness. The residue was dissolved in methanol (20 mL) containing triethylamine (2.4 mL, 17.3 mmol), and then trichloroethyl chloroformate (0.75 mL, 5.4 mmol) was added slowly with stirring. After 1 h, chloroform (30 mL) was added, and the solution was processed normally followed by chromatography to give title compound **16** as a syrup (1.58 g, 3.23 mmol, 92%). ^{1}H NMR δ 7.35−7.23 (m, 10H), 4.84−4.53 (m, 4H), 4.46 (s, 2H), 4.42−4.32 (m, 1H), 4.15−4.09 (m, 1H), 4.02 (m, 1H), 3.80−3.50 (m, 4H), 2.66 (t, J = 7.9 Hz, 1H); ^{13}C NMR (many of the peaks are doubled due to slow interconversion of rotamers) δ 153.6 and 153.4, 138.4 and 138.3, 137.5, 129.0, 128.8, 128.7, 128.4, 128.2, 128.1, 128.0, 96.1 and 95.9, 81.3 and 80.4, 75.3 and 75.2, 73.8, 72.7 and 72.5, 69.4 and 68.9, 69.0 and 68.2, 61.5 and 61.1, 52.7 and 52.3. HRMS (MH^+) calcd for $C_{22}H_{25}NO_5{}^{35}Cl_2{}^{37}Cl$: 490.0769. Found: 490.0757.

3,5-Di-*O*-benzyl-1,2,4-trideoxy-2,2-difluoro-1,4-imino-D-*erythro*-pentitol (13). A solution of **16** (1.0 g, 2.04 mmol) in dichloromethane (20 mL) containing DMSO (1.0 mL, 14 mmol) was cooled to −70 °C, and trifluoroacetic anhydride (1.0 mL, 7.2 mmol) was added slowly. After 0.5 h at −70 °C, triethylamine (2.0 mL, 15 mmol) was added, and the solution was warmed to ambient temperature, then processed normally. DAST (1.5 mL, 11.4 mmol) was added to the crude product in dry chloroform (20 mL), and the solution was heated under reflux for 4 h, then washed with aq $NaHCO_3$ and processed normally. Chromatography afforded a syrup (0.94 g) which was stirred with zinc dust (1.0 g) in acetic acid (30 mL) for 1 h. The solids and solvent were removed, and the residue in chloroform was washed with aq $NaHCO_3$ and dried and concentrated to dryness. Chromatography gave syrupy title compound **13** (0.535 g, 1.61 mmol, 78%). ^{1}H NMR δ 7.37−7.23 (m, 10H), 4.83 (d, J = 11.6 Hz, 1H), 4.52−4.40 (m, 3H), 3.88−3.78 (m, 1H), 3.65−3.61 (m, 1H), 3.54−3.49 (m, 1H), 3.35 (dt, J = 13.3, 6.9 Hz, 1H), 3.23−3.08 (m, 2H); ^{13}C NMR δ 138.2, 137.8 (C), 128.8, 128.5, 128.4, 128.2, 128.1 (CH), 80.4, (dd, $J_{C,F}$ = 29, 18 Hz, CH), 73.7, 73.2, 68.7 (CH_2), 63.3 (d, $J_{C,F}$ = 6 Hz, CH), 53.9 (t, $J_{C,F}$ = 28 Hz, CH_2). HRMS (MH^+) calcd for $C_{19}H_{22}F_2NO_2$: 334.1619. Found: 334.1611.

4-Amino-4-*N*-benzyl-3,5-di-*O*-benzyl-2,4-dideoxy-2,2-difluoro-D-*erythro*-pentonolactam (17). To a stirred suspension of zinc dust (2.73 g, 41.7 mmol) in THF (100 mL) was added 1,2-dibromoethane (0.273 mL, 3.17 mmol), and the mixture was briefly heated to reflux. After the mixture was cooled to 40 °C, chlorotrimethylsilane (0.35 mL, 2.76 mmol) was added, and the stirred mixture was maintained at ∼40 °C for 10 min before being cooled to room temperature. Ethyl bromodifluoroacetate (4.35 mL, 33.9 mmol) was added to the stirred mixture with cooling to keep the reaction temperature ≤30 °C. When the exothermic reaction was complete, the mixture was stirred at room temperature for 0.5 h and then cooled to 0 °C. A solution of **18**[25] (crude product from oxidation of the corresponding propan-1-ol derivative; 4.35 g, 11.3 mmol) in THF (15 mL) was added, and the resulting mixture was allowed to warm to room temperature and stirred for 16 h. Ether (200 mL) was added, and the mixture was washed with water and filtered through a pad of Celite. Normal processing and chromatography gave, presumably, ethyl 4-amino-4-*N*,*N*-dibenzyl-5-*O*-*tert*-butyldimethylsilyl-2,4-dideoxy-2,2-difluoro-D-*erythro*-pentanoate **(19)** (2.32 g, 4.6 mmol). A solution of this material (1.0 g, 1.97 mmol) in ethanol (30 mL) was stirred under hydrogen in the presence of 10% Pd/C (0.5 g) for 1 h. The solids and solvent were removed, and the residue was dissolved in 25% aq trifluoroacetic acid (10 mL). After 3 h, the solution was concentrated to dryness, and a solution of the residue in THF (10 mL) and DMF (2.5 mL) was treated with benzyl bromide (1.17 mL, 9.8 mmol) and sodium hydride (0.40 g, 60%, 10 mmol). The mixture was stirred at room temperature for 16 h and then quenched carefully with ethanol. Chloroform (100 mL) was added, and normal processing followed by chromatography afforded syrupy title compound **17** (0.50 g, 1.14 mmol). ^{1}H NMR δ 7.39−7.05 (m, 15H), 5.05 (d, J = 15.2 Hz, 1H), 4.83 (d, J = 11.5 Hz, 1H), 4.51 (d, J = 11.5 Hz, 1H), 4.37 (d, J = 12.0 Hz, 1H), 4.28 (d, J = 11.9 Hz, 1H), 4.22−4.13 (m, 1H), 3.91 (dd, J = 15.2, 1.5 Hz, 1H), 3.50 (m, 1H), 3.43 (m, 1H), 3.34 (m, 1H); ^{13}C NMR δ 163.3 (t, $J_{C,F}$ = 30 Hz, C), 137.4, 136.9, 135.0 (C), 129.3, 129.0, 128.7, 128.6, 128.5, 128.4, 128.3 (CH), 115.6 (t, $J_{C,F}$ = 255 Hz, C), 74.5 (dd, $J_{C,F}$ = 25, 17 Hz, CH), 73.6, 73.5, 64.7 (CH_2), 58.3 (d, $J_{C,F}$ = 7.0 Hz, CH), 44.8 (CH_2). HRMS (MH^+) calcd for $C_{26}H_{26}F_2NO_3$: 438.1881. Found: 438.1886.

(1*S*)-1-(9-Deazahypoxanthin-9-yl)-1,2,4-trideoxy-2,2-difluoro-1,4-imino-D-*erythro*-pentitol Hydrochloride (24·HCl). A solution of **20**[11] (2.6 g, 7.6 mmol) in ether (100 mL) and anisole (35 mL) was cooled to −70 °C, and butyllithium (4.8 mL, 7.6 mmol) was added. After 10 min, a solution of lactam **17** (1.6 g, 3.66 mmol) in ether (10 mL) was added, and the resulting solution was stirred at −40 °C for 30 min before

water was added. Normal processing afforded a syrup which was dissolved in methanol (50 mL) and acetic acid (1 mL), and sodium cyanoborohydride (1 g) was added to the stirred solution. After 1 h, the solution was partitioned between chloroform and aq sodium bicarbonate. The organic phase was processed normally, and then chromatography gave first recovered lactam **17** (0.45 g, 1.03 mmol) and then the *C*-1 epimer **23** of the desired product (0.81 g, 1.42 mmol) followed by **22** (0.261 g, 0.46 mmol). A solution of this material **22** (0.17 g, 0.3 mmol) in ethanol (10 mL) with 10% Pd/C (200 mg) was stirred under H_2 for 3 days. The solids and solvent were removed, and chromatography of the residue afforded fully debenzylated material (0.015 g). A solution of this material in methanol (3 mL) and concentrated aq HCl (3 mL) was heated under reflux for 3 h and then concentrated to dryness. The residue was redissolved in water and lyophilized to give title compound **24**·HCl as an amorphous solid (0.015 g, 0.047 mmol). ^{1}H NMR (D_2O) δ 8.33 (s, 1H), 7.84 (d, J = 2.1 Hz, 1H), 5.44 (dd, J = 19.1, 8.2 Hz, 1H), 4.60−4.52 (m, 1H), 4.07−3.95 (m, 2H), 3.92−3.84 (m, 1H); ^{13}C NMR δ 154.5 (C), 144.3 (CH), 140.6 (C), 131.2 (d, J = 4.7 Hz, CH), 118.3, 100.9 (C), 70.8 (dd, J = 33, 18.9 Hz, CH), 63.9 (CH), 58.3 (CH_2), 55.7 (dd, J = 34.8, 25.9 Hz, CH). HRMS (MH^+) calcd for $C_{11}H_{13}F_2N_4O_3$: 287.0956. Found: 287.0934.

(1*S*)-1-(9-Deaza-6-*O*-methylhypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol Bis-Hydrochloride (26·2HCl). A solution of **28**[11] (0.395 g, 0.94 mmol) in methanol (6 mL) and 2 M aq HCl (6 mL) was allowed to stand at room temperature for 4 h and was then concentrated to dryness. The residue was recrystallized from aq acetone to give **26·2HCl** as a white solid (0.20 g, 0.57 mmol, 60%) which charred at 240 °C without melting. ^{1}H NMR (D_2O) δ 8.87 (s, 1H), 8.22 (s, 1H), 5.08 (d, J = 9.0 Hz, 1H), 4.79 (dd, J = 9.0, 4.9 Hz, 1H), 4.47 (dd, J = 4.7, 3.1 Hz, 1H), 4.35 (s, 3H), 3.99−3.92 (m, 3H); ^{13}C NMR δ 162.1 (C), 149.4 (CH), 141.0 (C), 137.2 (CH), 119.5, 106.3 (C), 76.6, 73.5, 68.8 (CH), 61.5 (CH_2), 59.3 (CH_3), 58.2 (CH). Anal. calcd for $C_{12}H_{18}Cl_2N_4O_4$: C, 40.81; H, 5.14; Cl, 20.08; N, 15.86. Found: C, 41.06; H, 5.10; Cl, 19.85; N, 15.86.

(1*S*)-1-(9-Deaza-7-*N*-methylhypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol Hydrochloride (27·HCl). A stirred solution of **28**[11] (0.43 g, 0.80 mmol) in THF (10 mL) containing methyl iodide (75 μL, 1.20 mmol) was cooled in an ice bath while sodium hydride (0.050 g, 60%, 1.25 mmol) was added, and then the mixture was stirred at room temperature for 1 h. Normal processing and chromatography afforded a syrup (0.427 g). This material in methanol (4 mL) and concentrated HCl (4 mL) was heated under reflux for 2 h and then concentrated to dryness. The solid residue was recrystallized from aq acetone to give **27**·HCl as a white solid (0.188 g, 0.59 mmol, 73%) which charred at ∼270 °C without melting. ^{1}H NMR (D_2O) δ 7.89 (s, 1H), 7.54 (s, 1H), 4.87 (d, J = 8.2 Hz, 1H), 4.41 (t, J = 4.4 Hz, 1H), 3.98−3.91 (m, 5H), 3.87−3.80 (m, 1H) one of the signals was obscured by the HOD peak; ^{13}C NMR (D_2O) δ 155.7, 144.1 (C), 143.0, 133.5 (CH), 118.3, 106.6 (C), 73.8, 71.0, 65.6 (CH), 59.0 (CH_2), 57.0 (CH), 36.3 (CH_3). Anal. Calcd for $C_{12}H_{17}ClN_4O_4$: C, 45.50; H, 5.41; Cl, 11.19; N, 17.69. Found: C, 45.68; H, 5.52; Cl, 11.37; N, 17.62.

(1*S*)-2,3,5-Tri-*O*-acetyl-*N*-*tert*-butoxycarbonyl-1-(9-deazahypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol (29). Di-*tert*-butyl dicarbonate (2.0 g, 9.2 mmol) and triethylamine (1.5 mL, 20.5 mmol) were added to a solution of **1**·HCl[11] (1.5 g, 4.96 mmol) in water (20 mL) and methanol (40 mL). After 30 min the solution was concentrated to dryness. Pyridine (10 mL) and acetic anhydride (15 mL) were added to the residue, and the resulting solution was allowed to stand at room temperature for 16 h. The solution was poured onto water (200 mL), and after 30 min the mixture was extracted twice with chloroform. The combined extracts were processed normally followed by chromatography to give **29** as a foam (1.42 g, 2.89 mmol, 58%). ^{1}H NMR δ 7.66 (bs, 1H), 7.31 (d, J = 2.6 Hz, 1H), 5.95 (bs, 1H), 5.63 (t, J = 3.8 Hz, 1H), 5.19 (bs, 1H), 4.67 (bs, 1H), 4.48 (dd, J = 11.4, 3.8 Hz, 1H), 4.20 (bs, 1H), 2.14 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 1.46 (bs, 9H); ^{13}C NMR δ 170.7, 170.1, 155.0, 154.5, 142.8 (C), 140.5, 127.5 (CH), 118.1, 114.7, 81.2 (C), 75.1, 72.2 (CH), 62.6 (CH_2), 60.6, 57.0 (CH), 28.3, 20.8 (CH_3). Anal. Calcd for $C_{22}H_{28}N_4O_9$: C, 53.65; H, 5.73; N, 11.38. Found: C, 53.99; H, 5.65; N, 11.20.

(1*S*)-1-(9-Deaza-6-thiohypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol Hydrochloride (30·HCl). A solution of **29** (0.215 g, 0.437 mmol) and Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] (0.265 g, 0.65 mmol) in dry toluene (15 mL) was heated under reflux for 1.5 h. The cooled solution was washed with water and processed normally followed by chromatography to give, presumably, the 6-thio analogue (0.22 g). This material was dissolved in 2 M NH_3 in methanol (15 mL), and the solution was stored at room temperature for 18 h before being concentrated to dryness. Chromatography of the residue gave deacetylated material (0.11 g) which was dissolved in 1 M aq HCl (5 mL). After 2 h the solution was lyophilized to give **30**·HCl as a pale yellow solid (0.087 g, 0.273 mmol, 62%) which decomposed at ∼250 °C without melting. ^{1}H NMR (D_2O) δ 8.19 (s, 1H), 7.95 (s, 1H), 4.99 (d, J = 8.2 Hz, 1H), 4.83 (dd, J = 8.2, 4.9 Hz, 1H), 4.49 (t, J = 4.4 Hz, 1H), 4.04−3.98 (m, 2H), 3.93−3.88 (m, 1H); ^{13}C NMR (D_2O) δ 167.6 (C), 142.6 (CH), 139.5 (C), 133.1 (CH), 129.7, 108.0 (C), 73.7, 71.0, 65.6 (CH), 59.0 (CH_2), 57.0 (CH). Anal. Calcd for $C_{11}H_{15}ClN_4O_3S$: C, 41.44; H, 4.74; Cl, 11.12; N, 17.58; S, 10.06. Found: C, 41.42; H, 4.87; Cl, 10.74; N, 16.99; S, 9.89.

7-*N*-Benzyloxymethyl-9-bromo-6-*O*-*tert*-butyl-9-deazahypoxanthine. A mixture of 6-chloro-9-deazapurine[29] (5.0 g, 32.6 mmol) and benzyl chloromethyl ether (6.0 mL, 43.1 mmol) in THF (100 mL) was stirred in an ice bath while sodium hydride (1.7 g, 60%, 42.4 mmol) was added portionwise. When the addition was complete, the mixture was stirred for 1 h, and then *tert*-butyl alcohol (20 mL) and *N*,*N*-dimethylformamide (20 mL) were added followed by more sodium hydride (1.5 g, 60%, 37.5 mmol). The cooling bath was removed, and the mixture was stirred at room temperature for 18 h and then diluted with chloroform and washed twice with water. Normal processing afforded a dark syrup which was dissolved in chloroform (50 mL), and the resulting solution was stirred in an ice bath while NBS was added until TLC analysis indicated complete conversion to a less polar product. Chromatography then afforded the title compound as a white solid (5.8 g, 14.9 mmol, 46%). Recrystallized from ethyl acetate/petroleum ether it had mp 91−93 °C; ^{1}H NMR δ 8.55 (s, 1H), 7.41 (s, 1H), 7.34−7.20 (m, 5H), 5.73 (s, 2H), 4.48 (s, 2H), 1.69 (s, 9H); ^{13}C NMR δ 156.3 (C), 151.1 (CH), 148.7, 137.1 (C), 131.4, 128.9, 128.4, 127.8 (CH), 117.0, 92.6, 84.0 (C), 77.6, 70.5 (CH_2), 29.0 (CH_3). Anal. Calcd for $C_{18}H_{20}BrN_3O_2$: C, 55.40; H, 5.17; N, 10.77. Found: C, 55.46; H, 5.18; N, 10.80.

(1*S*)-1-(7-*N*-Benzyloxymethyl-6-*O*-*tert*-butyl-9-deazahypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-5-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (34). *n*-Butyllithium (2.9 mL, 2.4 M, 6.96 mmol) was added to a stirred solution of 7-*N*-benzyloxymethyl-9-bromo-6-*O*-*tert*-butyl-9-deazahypoxanthine (2.7 g, 6.9 mmol) in anisole (20 mL) and ether (40 mL) at −60 °C, and then a solution of imine **38**[11] (1.6 g, 5.6 mmol) in ether (5 mL) was added. The resulting solution was allowed to warm to 10 °C and washed with water. Normal processing afforded a crude syrup which was dissolved in chloroform (20 mL) containing di-*tert*-butyl dicarbonate (1.05 g, 4.8 mmol). After 0.5 h, the solution was concentrated to dryness and after chromatography **34** was obtained as a syrup (2.17 g, 3.12 mmol, 56%). ^{1}H NMR (C_6D_6) δ 8.65 (s, 1H), 7.52 (s, 1H), 7.07−7.02 (m, 5H), 5.91 (bs, 1H), 5.74 (bs, 1H), 5.62 (bs, 1H), 5.38 (bs, 1H), 5.20−5.05 (m, 1H), 4.52 (bs, 1H), 4.30−4.05 (m, 3H), 3.94 (bs, 1H), 1.57 (s, 3H), 1.56 (s, 9H), 1.41 (s, 9H), 1.30 (s, 3H), 0.97 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (C_6D_6) δ 156.2, 154.6 (C), 149.8 (CH), 149.2, 137.8 (C), 134.6 (CH), 131.9, 116.9, 115.5, 111.8 (C), 85.4 and 84.2, 83.9 and 83.2 (CH), 82.3, 79.4 (C), 77.0, 69.8 (CH_2), 67.5 (CH), 63.1 (CH_2), 61.6 (CH), 28.6, 28.5, 27.7, 26.2, 25.5 (CH_3), 18.6 (C), −4.9, −5.1 (CH_3) some aromatic signals were obscured by the solvent. HRMS (MH^+) calcd for $C_{37}H_{57}N_4O_7Si$: 697.3997. Found: 697.3989.

(1*S*)-1-(7-*N*-Benzyloxymethyl-6-*O*-*tert*-butyl-9-deaza-8-fluorohypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-5-O-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (35). *n*-Butyllithium (1.2 mL, 2.4M, 2.88 mmol) was added to a stirred solution of **34** (1.25 g, 1.80 mmol) in THF (30 mL) at −70 °C. After 10 min, *N*-fluorobenzenesulfonimide (1.42 g, 4.5 mmol) was added to the red/brown solution which resulted in an immediate decolorization to a yellow solution. After 20 min, water was added, and the solution was extracted with chloroform and processed normally to give, after chromatography, **35** as a syrup (0.67 g, 0.94 mmol) followed by recovered **34** (0.40 g, 0.57 mmol). For **35**, ^{1}H NMR (C_6D_6) δ 8.58 (s, 1H), 7.12−7.00 (m, 5H), 5.7−5.1 (m, 5H), 4.8−4.05 (m, 5H), 1.55 (s, 9H), 1.54 (s, 3H), 1.39 (s, 9H), 1.27 (s, 3H), 1.01 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (C_6D_6) δ 155.3, 154.4 (C), 150.3 (CH), 147.7, 137.7, 112.0, 110.7 (C), 85.3, 83.8 (CH), 82.5, 79.6 (C), 72.4, 70.5 (CH_2), 67.1 (CH), 63.0 (CH_2), 59.3 (CH), 28.6, 28.5, 27.8, 26.2, 25.6 (CH_3), 18.6 (C), −4.8, −5.0 (CH_3) some aromatic signals were obscured by the solvent. HRMS (MH^+) calcd for $C_{37}H_{56}FN_4O_7Si$: 715.3902. Found: 715.3916.

(1*S*)-1-(9-Deaza-8-fluorohypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol Hydrochloride (36·HCl). Tetrabutylammonium fluoride (1 M in THF, 5 mL) was added to a solution of **35** (0.20 g, 0.28 mmol) in methanol (5 mL) and THF (5 mL). After 18 h, toluene (20 mL) was added, and the solution was washed twice with water, dried and concentrated to dryness. A solution of the crude residue in ethanol (10 mL) containing 10% Pd/C (0.2 g) was stirred in a hydrogen atmosphere for 2 d. The solids and solvent were removed, and chromatography of the residue afforded two compounds, the more polar of which appeared by NMR to have lost the *tert*-butyl group. A solution of this mixture (0.102 g) in methanol (2 mL) and 2 M aq HCl (2 mL) was allowed to stand at room temperature for 2.5 h and then concentrated to dryness. The residue was recrystallized from aq acetone to give **36**·HCl as a cream solid (0.043 g, 0.13 mmol, 46%) which charred at ∼250 °C without melting. ^{1}H NMR (D_2O) δ 8.04 (s, 1H), 4.97−4.88 (m, 2H), 4.48 (t, J = 4.1 Hz, 1H), 4.05−3.99 (m, 2H), 3.89 (dd, J = 9.1, 4.6 Hz, 1H); ^{13}C NMR (D_2O) δ 157.2, 155.2 (d, J = 250 Hz), (C), 146.6 (CH), 146.2 (d, J = 9.2 Hz), 113.1, 89.5 (d, J = 6.6 Hz), (C), 74.9, 73.3, 68.2 (CH), 61.6 (CH_2), 57.7 (CH). Anal. Calcd for $C_{11}H_{14}ClFN_4O_4$: C, 41.20; H, 4.40; Cl, 11.05; N, 17.47. Found: C, 41.01; H, 4.37; Cl, 11.11; N, 17.17.

(1*S*)-1-(9-Deaza-8-methylhypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol Hydrochloride (33·HCl). *n*-Butyllithium (0.40 mL, 2.4M, 0.96 mmol) was added to a stirred solution of **31** (0.29 g, 0.44 mmol) in THF (7 mL) at −70 °C. After 10 min, methyl iodide (0.25 mL, 4.0 mmol) was added, and 10 min later the reaction was quenched with water. Normal processing followed by chromatography afforded 1-(*S*)-1-(7-*N*-benzyloxymethyl-9-deaza-8-methyl-6-*O*-methylhypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-5-O-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol **(32)** as a syrup (0.164 g, 0.25 mmol, 55%). ^{1}H NMR (C_6D_6 at 70 °C) δ 8.66 (s, 1H), 7.10−7.00 (m, 5H), 5.70 (d, J = 5.9 Hz, 1H), 5.57 (s, 1H), 5.52 (d, J = 5.0 Hz, 1H), 5.39 (d, J = 10.9 Hz, 1H), 5.32 (d, J = 10.9 Hz, 1H), 4.56−4.44 (m, 2H), 4.25 (s, 2H), 4.06 (dd, J = 8.2, 4.3 Hz, 1H), 3.77 (s, 3H), 2.63 (s, 3H), 1.58 (s, 3H), 1.40 (s, 9H), 1.32 (s, 3H), 1.03 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (C_6D_6 at 70 °C) δ 155.4, (C), 149.7 (CH), 149.5, 143.0, 138.3, 116.0, 114.3, 111.8 (C), 85.5, 84.6 (CH), 79.5 (C), 74.4, 70.1 (CH_2), 68.5 (CH), 63.6 (CH_2), 61.6 (CH), 52.9, 28.7, 28.0, 26.3, 25.8 (CH_3), 18.7 (C), 10.8, −4.8, −4.9 (CH_3). Some aromatic signals were obscured by the solvent. A solution of this material in ethanol (5 mL) containing 10% Pd/C (0.1 g) was stirred in a hydrogen atmosphere for 2 d. The solids and solvent were removed, and a solution of the residue in methanol (3 mL) and concd HCl (3 mL) was heated under reflux for 2 h. The solution was concentrated to dryness, and trituration of the residue with ethanol afforded **33**·HCl as a white solid (0.061 g, 0.19 mmol, 76%) which charred at ∼260 °C without melting. ^{1}H NMR (D_2O) δ 8.46 (s, 1H), 4.96 (dd, J = 9.4, 4.6 Hz, 1H), 4.89 (d, J = 9.5 Hz, 1H), 4.51 (m, 1H), 4.07 (m, 2H), 3.96 (m, 1H), 2.54 (s, 3H); ^{13}C NMR (D_2O) δ 155.7 (C), 146.2 (CH), 145.7, 141.3, 119.4, 104.8 (C), 75.7, 73.8, 68.6 (CH), 61.9 (CH_2), 59.4 (CH), 14.5 (CH_3). Anal. Calcd for $C_{12}H_{17}ClN_4O_4$: C, 45.50; H, 5.41; Cl, 11.19; N, 17.69. Found: C, 45.38; H, 5.41; Cl, 11.50; N, 17.80.

(1*S*)-1-(7-*N*-Benzyloxymethyl-9-deaza-6-*O*-methyl-8-trimethylsilylhypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-5-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (37). *n*-Butyllithium (2.0 mL, 1.3 M in hexanes, 2.6 mmol) was added to a stirred solution of **31** (0.75 g, 1.15 mmol) in THF (15 mL) at −70 °C. After 15 min, HMPA (0.57 mL) was added followed by chlorotrimethylsilane (0.63 mL, 5.0 mmol), and 45 min later the reaction was quenched with water. Normal processing followed by chromatography gave **37** as a syrup (0.447 g, 0.62 mmol, 54%). ^{1}H NMR (C_6D_6 at 70 °C) δ 8.64 (s, 1H), 7.10−7.02 (m, 5H), 5.76 (d, J = 2.9 Hz, 1H), 5.72 (d, J = 10.5 Hz, 1H), 5.61 (d, J = 10.5 Hz, 1H), 5.50 (d, J = 5.9 Hz, 1H), 5.40 (dd, J = 5.5, 2.8 Hz, 1H), 4.89 (dd, J = 10.6, 9.4 Hz, 1H), 4.49 (dd, J = 10.6, 4.7 Hz, 1H), 4.34−4.25 (m, 3H), 3.74 (s, 3H), 1.58 (s, 3H), 1.30 (s, 9H), 1.29 (s, 3H), 1.07 (s, 9H), 0.71 (s, 9H), 0.24 (s, 6H); ^{13}C NMR (C_6D_6 at 70 °C) δ 156.4, 155.2, 150.0 (C), 149.5 (CH), 146.3, 138.5, 120.3, 112.2 (C), 85.8, 84.4 (CH), 79.6 (C), 76.8, 70.3 (CH_2), 68.0 (CH), 63.8 (CH_2), 62.9 (CH), 53.1, 28.8, 28.3, 26.6, 26.0 (CH_3), 19.0 (C), 2.5, −4.4, −4.6 (CH_3). Some aromatic signals were obscured by the solvent. HRMS (MH^+) calcd for $C_{37}H_{59}N_4O_7Si_2$: 727.3922. Found: 727.3921.

(1*S*)-5-*O*-*tert*-Butyldimethylsilyl-1-*tert*-butoxycarbonylmethyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (39). *tert*-Butyl acetate (40 mL, 297 mmol) was added dropwise to a stirred solution of LDA (200 mL, 1.5 M, 300 mmol) in diethyl ether such that the reaction temperature was maintained below −65 °C. The resulting solution was left to stir for 20 min after which time a solution of imine **38**[11] (17.0 g, 60 mmol) was added at such a rate that the reaction temperature was maintained below −65 °C, and the resulting solution was then allowed to warm to room temperature. The reaction was quenched by the addition of saturated aq ammonium chloride (200 mL), and the organic layer was separated and processed normally. Chromatography then afforded **39** as an oil (15.7 g, 39 mmol, 65%). ^{1}H NMR δ 4.31 (dd, J = 7.0, 4.6 Hz, 1H), 4.18 (t, J = 6.1 Hz, 1H), 3.71 (dd, J = 10.2, 4.1 Hz, 1H), 3.57 (dd, J = 10.2, 5.7 Hz, 1H), 3.32 (quintet, J = 5.0 Hz), 3.15 (1H, q, J = 4.7 Hz), 2.54 (dd, J = 15.9, 4.8 Hz, 1H), 2.34 (dd, J = 15.9, 8.2 Hz, 1H), 1.44 (s, 3H), 1.38 (s, 9H), 1.24 (s, 3H), 0.83 (s, 9H), 0.01 (s, 6H); ^{13}C NMR δ 171.4, 114.1 (C), 85.1, 85.2 (CH), 81.1 (C), 65.8 (CH), 64.7 (CH_2), 61.3 (CH), 39.9 (CH_2), 28.5, 27.8, 26.3, 25.8, −5.5, −5.6 (CH_3). HRMS (MH^+) calcd for $C_{20}H_{40}NO_5Si$: 402.2661. Found: 402.2676.

(1*S*)-5-*O*-Benzyl-*N*-*tert*-butoxycarbonyl-1-*tert*-butoxycarbonylmethyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (43). Di-*tert*-butyl dicarbonate (13.0 g, 60 mmol) was added, portionwise, to a stirred solution of amine **39** (15.7 g, 39 mmol) in methanol (100 mL) at room temperature. The reaction was monitored by TLC and on completion tetrabutylammonium fluoride in THF (40 mL, 1.0 M, 40 mmol) was added dropwise and the resulting solution left to stir for 14 h. The reaction was then concentrated in vacuo, the resulting residue (15 g) was dissolved in DMF (100 mL) and benzyl bromide (18.5 mL, 155 mmol) at 0 °C, and sodium hydride (2 g, 60%, 50 mmol) was added portionwise, keeping the reaction temperature ≤0 °C. The reaction mixture was allowed to warm to room temperature and then was diluted with toluene (500 mL) and washed with water and then brine and processed normally. The crude material was purified by chromatography to afford **43** as an oil (15.0 g, 31.4 mmol, 80%). ^{1}H NMR δ 7.36−7.27 (m, 5H), 4.69 (d, J 5.8 Hz, 1H), 4.56−4.52 (m, 3H), 4.35−4.01 (m, 2H), 3.60−3.46 (m, 2H), 2.85−2.49 (m, 2H), 1.46 (s, 3H), 1.43 (s, 18H), 1.31 (s, 3H); ^{13}C NMR δ 170.9, 154.1, 138.1 (C), 128.8, 128.1 (CH), 111.9 (C), 85.3, 84.7, 82.8, 82.2 (CH), 81.0, 80.4 (C), 73.9, 70.5 (CH_2), 64.7 (CH), 62.6, 62.3 (CH), 39.5, 38.5 (CH_2), 28.8, 28.5, 27.6, 25.7 (CH_3). HRMS (MH^+) calcd for $C_{26}H_{40}NO_7$: 478.2805. Found: 478.2791.

(1*S*)-5-*O*-Benzyl-*N*-*tert*-butoxycarbonyl-1-(2-cyanoethyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (42). Diisobutylaluminum hydride (1.0 M in toluene, 120 mL, 120 mmol) was added dropwise to a stirred solution of **43** (15.0 g, 39 mmol) in THF (150 mL) at 0 °C under argon. After 3 h, the reaction was quenched with water (100 mL) and diluted with toluene (500 mL). The organic layer was separated, washed with dilute HCl (10% v/v, 100 mL), water (100 mL), and brine (100 mL), and processed normally. Methanesulfonyl chloride (3.0 mL, 39 mmol) was added dropwise to a stirred solution of the crude residue (10.4 g, 36 mmol) and diisopropylethylamine (13.3 mL, 76 mmol) in dichloromethane (100 mL) at 0 °C under an inert atmosphere. The reaction was allowed to warm to rt, diluted with dichloromethane (250 mL), washed with water (100 mL) and brine (100 mL), and processed normally. The residue was dissolved in DMF (100 mL), and potassium cyanide (12.6 g, 195 mmol) was added. The resulting suspension was stirred at 80 °C for 14 h, diluted with toluene (500 mL), washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatography of the resulting residue afforded **42** as an oil (6.5 g, 15.6 mmol, 40%). ^{1}H NMR δ 7.39−7.26 (m, 5H), 4.68 (d, J = 5.7 Hz, 1H), 4.51 (dd, J = 11.8, 5.7 Hz, 2H), 4.34 (brd, J = 5.0 Hz, 1H), 3.95 (brs, 1H), 3.56 (s, 2H), 2.35 (m, 2H), 1.84 (sextet, J = 6.5 Hz, 1H), 1.60 (d, J = 5.5 Hz, 1H), 1.44 (s, 12H), 1.30 (s, 3H); ^{13}C NMR δ 154.7, 137.9 (C), 128.9, 128.3 (CH), 119.5, 112.3 (C), 84.9, 84.4, 82.6, 82.0 (CH), 79.9 (C), 73.6, 70.5 (CH_2), 65.4, 64.2 (CH), 29.7 (CH_2), 28.8, 27.7, 25.8 (CH_3), 14.6 (CH_2). HRMS (MH^+) calcd for $C_{23}H_{32}N_2O_5$: 417.2389. Found: 417.2391.

(1*S*)-5-*O*-Benzyl-*N*-*tert*-butoxycarbonyl-1-(2-cyano-3-dimethylaminoallyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (44). A solution of nitrile **42** (6.4 g, 15.4 mmol) and *tert*-butoxybis(dimethylamino)methane (15 mL, 72.6 mmol) in DMF (50 mL) was heated at 70 °C under an inert atmosphere for 72 h and then cooled to r.t., diluted with toluene (250 mL), washed with water (100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatography of the resulting residue afforded **44** as an oil (6.1 g, 12.9 mmol, 84%). ^{1}H NMR δ 7.36−7.27 (m, 5H), 6.23, 5.86 (s, 1H), 4.71 (brs, 1H), 4.51 (m, 3H), 4.23 (brs, 1H), 3.96 (m, 1H), 3.58 (m, 2H), 2.97 (s, 6H), 2.43 (m, 1H), 2.04 (m, 1H), 1.49 (s, 3H), 1.45 (s, 9H), 1.33 (s, 3H); ^{13}C NMR δ 154.7, 153.2 (C), 152.1, 151.0 (CH), 138.3 (C), 128.8, 128.2 (CH), 122.5, 112.0 (C), 84.9, 84.1, 83.0, 82.1 (CH), 80.4 (C), 73.9, 70.6 (CH_2), 69.2, 67.3, 64.4 (CH), 42.1 (CH_3), 37.0, 35.7 (CH_2), 28.8, 27.7, 25.9 (CH_3). HRMS (MH^+) calcd for $C_{26}H_{37}N_3O_5$: 471.2733. Found: 471.2709.

(1*S*)-1-(3-Amino-2-ethoxycarbonyl-1-*N*-methoxycarbonylpyrrol-4-yl)methyl-5-*O*-benzyl-*N*-*tert*-butoxycarbonyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (45). A solution of enamine **44** (260 mg, 0.55 mmol) in THF/acetic acid/water (1:1:1, v/v/v, 6 mL) was stirred at room temperature for 1.5 h. The solution was then diluted with chloroform (100 mL), washed with water (2 × 25 mL) and saturated aqueous sodium bicarbonate, and then dried and concentrated in vacuo. The crude residue was redissolved in methanol (5 mL), and sodium acetate (500 mg, 6.1 mmol) and ethyl glycinate hydrochloride (300 mg, 2.2 mmol) were added consecutively. The mixture was stirred at room temperature for 16 h and then concentrated in vacuo and partitioned between chloroform (100 mL) and water (50 mL). The organic layer was separated, washed with water (25 mL) and then brine (25 mL), dried, and concentrated in vacuo. The crude residue was redissolved in dichloromethane (5 mL) and treated with DBU (2.25 mL, 15 mmol) and then methyl chloroformate (0.6 mL, 7.6 mmol) and the resulting solution heated under reflux for 1 h. The reaction was cooled and diluted with dichloromethane (250 mL), washed with dilute aqueous HCl and aqueous sodium bicarbonate, dried, and concentrated in vacuo. Chromatography of the residue afforded **45** as a syrup (120 mg, 0.204 mmol, 37%). ^{1}H NMR δ 7.38−7.28 (m, 5H), 6.98 (brs, 1H), 5.46 (brs, 1H), 4.75 (d, J = 5.8 Hz, 1H), 4.53 (s, 2H), 4.38 (brd, J = 5.8 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 4.05 (m, 2H), 3.88 (s, 3H), 3.50 (m, 2H), 2.51 (m, 2H), 1.42 (s, 12H), 1.32 (t, J = 7.1 Hz, 3H), 1.28 (s, 3H); ^{13}C NMR δ 162.0, 154.6, 153.9, 151.6, 138.0 (C), 128.9, 128.4, 127.0 (CH), 113.5, 112.1 (C), 84.3, 83.0 (CH), 81.9 (C), 74.0, 70.4 (CH_2), 65.0, 64.3 (CH), 60.0 (CH_2), 54.1 (CH_3), 28.7 (CH_3), 28.4 (CH_2), 27.5, 25.6, 14.9 (CH_3). HRMS (MH^+) calcd for $C_{30}H_{42}N_3O_9$: 588.2921. Found: 588.2901.

(1*S*)-1-(3-Amino-2-cyanopyrrol-4-yl)methyl-5-*O*-benzyl-*N*-*tert*-butoxycarbonyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (46). A solution of the enamine **44** (6.1 g, 12.6 mmol) in THF/acetic acid/water (1:1:1, v/v/v, 45 mL) was stirred at room temperature for 1.5 h, diluted with chloroform (150 mL), washed with water (2 × 50 mL) and saturated aqueous sodium bicarbonate, dried, and concentrated in vacuo. Sodium acetate (10.0 g, 122 mmol) and aminoacetonitrile hydrochloride (8.0 g, 86.4 mmol) were added to a solution of the residue in methanol (100 mL). The mixture was stirred at room temperature for 16 h, concentrated in vacuo, and partitioned between chloroform (200 mL) and water (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried, and concentrated in vacuo. The crude residue was redissolved in dichloromethane (50 mL) and treated with DBU (15 mL, 100 mmol) and then methyl chloroformate (5 mL, 65 mmol) and the resulting solution heated under reflux for 16 h. The reaction solution was cooled and diluted with methanol (50 mL), and the resulting solution was stirred for an additional 1 h, diluted with dichloromethane (250 mL), washed with dilute aqueous HCl and aqueous sodium bicarbonate, dried, and concentrated in vacuo. Chromatography of the residue afforded **46** as a syrup (2.35 g, 4.87 mmol, 39%). ^{1}H NMR δ 8.51 (brs, 1H), 7.39−7.29 (m, 5H), 6.35 (d, J = 3.0 Hz, 1H), 4.74 (d, J = 5.9 Hz, 1H), 4.53 (s, 2H), 4.41 (d, J = 5.9 Hz, 1H), 3.95 (m, 2H), 3.58 (m, 1H), 3.53 (m, 1H), 2.71−2.36 (m, 2H), 1.45 (s, 12H), 1.28 (s, 3H); ^{13}C NMR δ 154.6, 148.9143.5, 138.1 (C), 128.9, 128.4, 122.3 (CH), 112.1, 109.3 (C), 84.4, 83.0 (CH), 80.1 (C), 74.0, 70.6 (CH_2), 65.5, 64.9 (CH), 28.8 (CH_3), 28.0 (CH_2), 27.6, 25.7 (CH_3). HRMS (MH^+) calcd for $C_{26}H_{35}N_4O_5$: 482.2529. Found: 482.2549.

(1*S*)-1-(9-Deazahypoxanthin-9-yl)methyl-1,4-dideoxy-1,4-imino-D-ribitol Bis-Hydrochloride (40·2HCl). Carbamate **45** (120 mg, 0.20 mmol) was dissolved in ethanol (5 mL), potassium carbonate (100 mg) was added, and the resulting suspension was stirred at rt for 16 h. The reaction mixture was concentrated in vacuo, the residue suspended in chloroform (50 mL) and filtered, and the filtrate concentrated in vacuo. The crude residue was redissolved in ethanol (5 mL), formamidine acetate (400 mg, 3.8 mmol) was added, and the resulting suspension was heated under reflux for 16 h. The mixture was concentrated to dryness, and chromatography of the residue afforded an oil which was not characterized but redissolved in ethanol and stirred with Pearlman's catalyst (50 mg) under a hydrogen atmosphere for 16 h. The crude reaction was filtered through Celite, 2 M HCl was added, and the resulting solution was stirred for an additional 2 h and then concentrated in vacuo to afford **40**·2HCl as the solid monohydrate (45 mg, 69%) which decomposed between 269 and 270 °C without melting. ^{1}H NMR δ 8.79 (s, 1H), 7.60 (s, 1H), 4.23 (t, J = 7.3 Hz, 1H), 4.13 (t, J = 5.3 Hz, 1H), 3.83 (m, 3H), 3.65 (q, J = 5.3 Hz, 1H), 3.20 (dq, J = 15.7, 6.9 Hz, 2H); ^{13}C NMR δ 153.1 (C), 144.3 (CH), 133.2 (C), 130.7 (CH), 118.2, 108.0 (C), 73.4, 70.44, 65.0, 62.9 (CH), 58.4, 24.2 (CH_2). HRMS (MH^+) calcd for $C_{12}H_{17}N_4O_4$: 281.1250. Found: 281.1259. Anal. Calcd for $C_{12}H_{16}N_4O_4.2HCl·H_2O$ requires C, 38.83; H, 5.43; N, 15.09; Cl, 19.10; Found C, 39.17; H, 5.42; N, 14.97; Cl, 19.15.

(1*S*)-1-(9-Deazaadenin-9-yl)methyl-1,4-dideoxy-1,4-imino-D-ribitol Tris-Hydrochloride (41·3HCl). Pyrrole **46** (100 mg, 0.20 mmol) was dissolved in ethanol (2 mL), formamidine acetate (35 mg, 0.3 mmol) was added, and the resulting suspension was heated under reflux for 16 h. The mixture was concentrated to dryness, and chromatography of the residue afforded an oil which was not characterized but redissolved in ethanol and stirred with Pearlman's catalyst (40 mg) under a hydrogen atmosphere for 16 h. The crude reaction was filtered through Celite, 2 M HCl was added, and the resulting solution was stirred for an additional 2 h and then concentrated in vacuo to afford solid **41**·3HCl (42 mg, 59%) with mp 254−257 °C. ^{1}H NMR (D_2O) δ 8.38 (s, 1H), 7.75 (s, 1H), 4.26

(t, J = 5.3 Hz), 4.16 (q, J = 5.3, 1H), 3.88 (m, 3H), 3.66 (q, J = 5.4 Hz, 1H), 3.26 (m, 2H); ^{13}C NMR δ 150.5 (C), 144.0 (CH), 136.5 (C), 132.6 (CH), 112.9, 107.3 (C), 73.4, 70.4, 65.0, 62.9 (CH), 58.4, 24.1 (CH_2). HRMS (MH^+) calcd for $C_{12}H_{18}N_5O_3$: 280.1410. Found: 280.1405. Anal. Calcd for $C_{12}H_{17}N_5O_3$.3HCl requires C, 37.08; H, 5.19; N, 18.02; Cl, 27.36. Found: C, 36.88; H, 5.25; N, 18.29; Cl, 27.19.

7-*N*-Benzyloxymethyl-9-deaza-9-formyl-6-*O*-methylhypoxanthine (48). A solution of **49**[11] (1.0 g, 2.87 mmol) in anisole (10 mL) and ether (25 mL) was cooled to −70 °C, and *n*-butyllithium (2.4 mL, 1.2 M) was added to the resulting suspension. After 10 min, dry *N*,*N*-dimethylformamide (1.1 mL, 14.2 mmol) was added to the clear solution which was stirred at −70 °C for 30 min and then quenched with water. Normal processing afforded a solid, which after trituration with ethanol gave title compound **48** as a white solid (0.67 g, 2.26 mmol, 78%) with mp 100−101 °C. ^{1}H NMR δ 10.30 (s, 1H), 8.67 (s, 1H), 8.00 (s, 1H), 7.35−7.21 (m, 5H), 5.77 (s, 2H), 4.55 (s, 2H), 4.14 (s, 3H); ^{13}C NMR δ 184.7 (CH), 157.0 (C), 153.0 (CH), 150.0 (C), 136.9 (CH), 136.5 (C), 129.0, 128.7, 128.1 (CH), 118.6, 116.7 (C), 78.3, 71.4 (CH_2), 54.3 (CH_3). HRMS (MH^+) calcd for $C_{19}H_{21}N_3O_3$ 340.1661 found: 340.1652.

***N*-(9-Deazahypoxanthin-9-yl)methyl-1,4-dideoxy-1,4-imino-D-ribitol Hydrochloride (47·HCl).** The aldehyde **48** (114 mg, 0.38 mmol) was added to a solution of **14**[24] (100 mg, 0.35 mmol) in methanol (1.5 mL), THF (0.5 mL), and acetic acid (100 μL), and the mixture was stirred for 10 min. Sodium cyanoborohydride (88 mg, 1.4 mmol) was added, and the solution was stirred for 4 h and then partitioned between chloroform and aq $NaHCO_3$. The organic layer was dried and concentrated to dryness. Chromatography of the residue afforded, presumably, *N*-(7-*N*-benzyloxymethyl-9-deaza-6-*O*-methylhypoxanthin-9-yl)methyl-5-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol as a syrup (175 mg, 0.31 mmol, 88%). A solution of this material in ethanol (5 mL) was stirred with 10% Pd/C (100 mg) in a hydrogen atmosphere for 16 h. The solids and solvent were removed, chromatography of the residue afforded a syrup (129 mg) which was dissolved in methanol (5 mL) and concentrated HCl (5 mL), and the solution was heated under reflux for 2 h. The solution was concentrated to dryness and the residue redissolved in water and lyophilized to give title compound **47**·HCl as a powder (80 mg, 0.25 mmol, 80%). ^{1}H NMR (D_2O) δ 8.57 (m, 1H), 7.78 (s, 1H), 4.66 (s, 1H), 4.56 (s, 1H), 4.29 (m, 1H), 4.13 (m, 1H), 3.76 (m, 2H), 3.61 (m, 2H), 3.34 (dd, J = 13.0, 3.4 Hz, 1H); ^{13}C NMR δ 153.6 (C), 144.8 (CH), 136.7 (C), 133.2 (CH), 118.5, 103.3 (C), 71.3, 70.3, 68.9 (CH), 57.4, 57.1, 50.1 (CH_2). HRMS (M^+) calcd For $C_{12}H_{17}N_4O_4$: 281.1250. Found: 281.1260.

5-*O*-*tert*-Butyldimethylsilyl-*N*-cyanomethyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (51). Bromoacetonitrile (1.46 mL, 20.9 mmol) and ethyldiisopropylamine (5.46 mL, 56.9 mmol) were added to a solution of **14**[24] (3.0 g, 10.45 mmol) in acetonitrile (20 mL). After 1 h, the solution was concentrated to dryness, and chromatography of the residue afforded title compound **51** as a syrup (3.4 g, 10.4 mmol, 99%). ^{1}H NMR δ 4.58 (dt, J = 6.4, 4.3 Hz, 1H), 4.20 (dd, J = 6.8, 4.2 Hz, 1H), 3.88 (d, J = 17 Hz, 1H), 3.79 (dd, J = 10.9, 3.0 Hz, 1H), 3.58 (m, 1H), 3.56 (d, J = 17 Hz, 1H), 3.19 (dd, J = 9.8, 6.1 Hz, 1H), 2.85 (m, 1H), 2.75 (dd, J = 9.8, 4.3 Hz, 1H), 1.44 (s, 3H), 1.23 (s, 3H), 0.82 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR δ 115.6, 113.6 (C), 82.2, 78.3, 68.6 (CH), 64.7, 59.3, 41.0 (CH_2), 27.6, 26.2, 25.6 (CH_3), 18.5 (C). HRMS (MH^+) calcd For $C_{16}H_{31}N_2O_3Si$: 327.2104. Found: 327.2097.

***N*-(9-Deazahypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol Hydrochloride (50·HCl).** The *N*-cyanomethyl derivative **51** (0.5 g, 1.53 mmol) was converted into the title compound by the same sequence of reactions described previously in the preparation of **1**[10] to give **50**·HCl as an amorphous powder (0.07 g, 0.23 mmol, 15%). ^{1}H NMR (D_2O) δ 8.24 (s, 1H), 7.71 (s, 1H), 4.43 (m, 1H), 4.29−4.17 (m, 2H), 3.96 (m, 1H), 3.82−3.71 (m, 3H); ^{13}C NMR δ 154.2 (C), 144.3 (CH), 133.0 (C), 124.0 (CH), 117.8, 115.9 (C), 73.4, 70.4, 68.9 (CH), 62.9, 56.1 (CH_2). HRMS (M^+) calcd For $C_{11}H_{15}N_4O_4$: 267.1093. Found: 267.1101.

(1*S*)-1-(9-Deazahypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-*N*-propyl-D-ribitol Hydrochloride (52·HCl). A solution of **1**·HCl (0.21 g, 0.69 mmol) and propionaldehyde (0.25 mL, 3.46 mmol) in water (10 mL) was stirred with 10% Pd/C (0.08 g) in a hydrogen atmosphere for 16 h, and then the solids and solvent were removed to give a white solid residue (0.24 g) of title compound **52**·HCl. This material was very hygroscopic and became an oil on exposure to air. ^{1}H NMR (D_2O) δ 8.38 (s, 1H), 7.84 (s, 1H), 4.85 (d, J = 9.7 Hz, 1H), 4.41 (dd, J = 4.4, 2.1 Hz, 1H), 3.99 (dd, J = 12.7, 4.1 Hz, 1H), 3.91 (dd, J = 12.7, 3.7 Hz, 1H), 3.83 (m, 1H), 3.36−3.19 (m, 2H), 1.74−1.52 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H) (the peaks for one proton were obscured under the HOD peak); ^{13}C NMR δ 154.4 (C), 144.3 (CH), 139.9 (C), 130.9 (CH), 118.5, 105.6 (C), 74.0, 73.7, 71.7, 64.6 (CH), 59.0, 58.5, 18.2 (CH_2), 10.5 (CH_3). HRMS (M^+) calcd For $C_{14}H_{21}N_4O_4$: 309.1563. Found: 309.1566.

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