Pergamon

Bioorganic & Medicinal Chemistry 7 (1999) 2599–2606

BIOORGANIC & MEDICINAL CHEMISTRY

Transition State Analogue Inhibitors of Protozoan Nucleoside Hydrolases

Richard H. Furneaux, [a] Vern L. Schramm [b] and Peter C. Tyler [a,*]

[a]*Carbohydrate Chemistry, Industrial Research Limited, PO Box 31310, Lower Hutt, New Zealand*
[b]*Department of Biochemistry, Albert Einstein College of Medicine, Bronx, NY 10461, USA*

Received 27 May 1999; accepted 6 July 1999

Abstract—Protozoan parasites are unable to synthesize purines de novo and must rely on purine salvage pathways for their requirements. Nucleoside hydrolases, which are not found in mammals, function as key enzymes in purine salvage in protozoa. Inhibition of these enzymes may disrupt purine supply and specific inhibitors are potential therapeutic agents for the control of protozoan infections. A series of 1,4-dideoxy-1,4-imino-D-ribitols bearing *C*-bonded aromatic substituents at C-1 have been synthesized, following carbanion additions to the imine **2**, and tested as potential nucleoside hydrolase inhibitors. Nucleoside analogues **8**, **11**, **14**, **17**, **20**, **24**–**26**, **28** exhibit K_i values in the range 0.2–22 μM against two representative isozymes of protozoan nucleoside hydrolases.

Introduction

Infections due to protozoan parasites are a continuing health problem world-wide with more than two billion people estimated to be infected by these organisms. Approximately two million deaths per year, largely of infants, result from malaria alone.[1] Protozoan parasites are devoid of the capacity for de novo purine biosynthesis and rely completely on salvage pathways for their purine requirements.[2] Nucleoside hydrolases provide a pathway for obtaining purines by nucleoside salvage in several protozoa whose pathways of purine salvage have been characterized.[3] These enzymes are not found in mammals, but they are widely distributed in bacteria, yeast and protozoa.[4,5] Inhibitors for these enzymes have potential as antimicrobials in purine auxotrophs, especially the protozoan parasites.

Two isozymes of protozoan nucleoside hydrolases have been characterized.[3,6–12] Nonspecific enzymes, the 'IU-nucleoside hydrolases'[5] from *Crithidia fasciculata* and *Leishmania major* are examples of the first type. The enzymes catalyze the hydrolysis of all commonly occurring purine and pyrimidine nucleosides, and also *p*-nitrophenyl β-D-ribofuranoside. Catalysis occurs by promoting the formation of a ribofuranose-based oxocarbenium ion transition state with modest assistance from activation of the leaving group. The ribooxocarbenium ion is promoted by conformational distortion of the sugar using protein contacts and a catalytic site Ca^{2+} to permit both the ring oxygen and the 5′-hydroxymethyl oxygens' unshared electrons to participate in the cleavage of the sugar-base bonds. The 'IAG nucleoside hydrolase' from *Trypanosoma brucei brucei* is representative of the second isozyme type which comprise purine-specific hydrolases.[3,6,12] These enzymes obtain a significant part of their catalytic efficiency from protonation of the leaving group. Both classes of hydrolase enzymes utilize mechanisms which involve transition states appreciably stabilized by contributions from the ribofuranose based oxocarbenium ion. This led to the prediction that 1,4-dideoxy-1,4-imino-D-ribitol derivatives **3**, which will be partially *N*-protonated at pH 7 ($pK_a = 6.5$),[13] would be good transition state analogue inhibitors of the nucleoside hydrolases.

We have reported some preliminary investigations into the synthesis[14] and testing[15] of iminoribitol derivatives **3** which revealed potent (nM) inhibitors, e.g. **4** and **5** (Scheme 1), of the IU nucleoside hydrolase, but none of the compounds tested had K_i values better than 12 μM against the IAG nucleoside hydrolase. Since this latter class of enzyme has a higher catalytic efficiency in those parasites that have been studied,[3,6,8] the discovery of more efficient inhibitors of the IAG type of enzyme could be of importance. We present here further attempts at the design and synthesis of compounds to act as inhibitors of nucleoside hydrolases—particularly

Key words: Antibiotics; antiparasitics; enzyme inhibitors; nucleosides.
* Corresponding author. Fax: +64-4-569-0055; e-mail: p.tyler@irl.cri.nz

0968-0896/99/$ - see front matter
PII: S0968-0896(99)00210-2

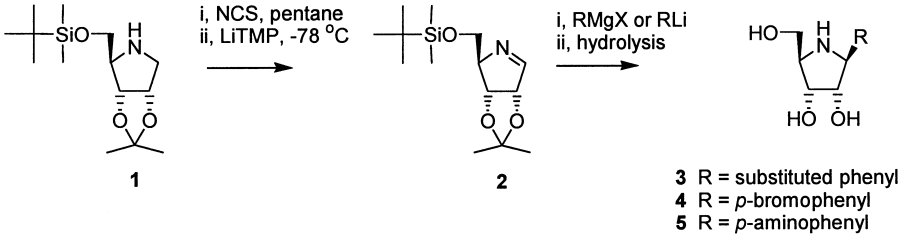
the IAG class of enzyme. Selected biological data are given; a more detailed analysis is presented elsewhere.[16]

Results and Discussion

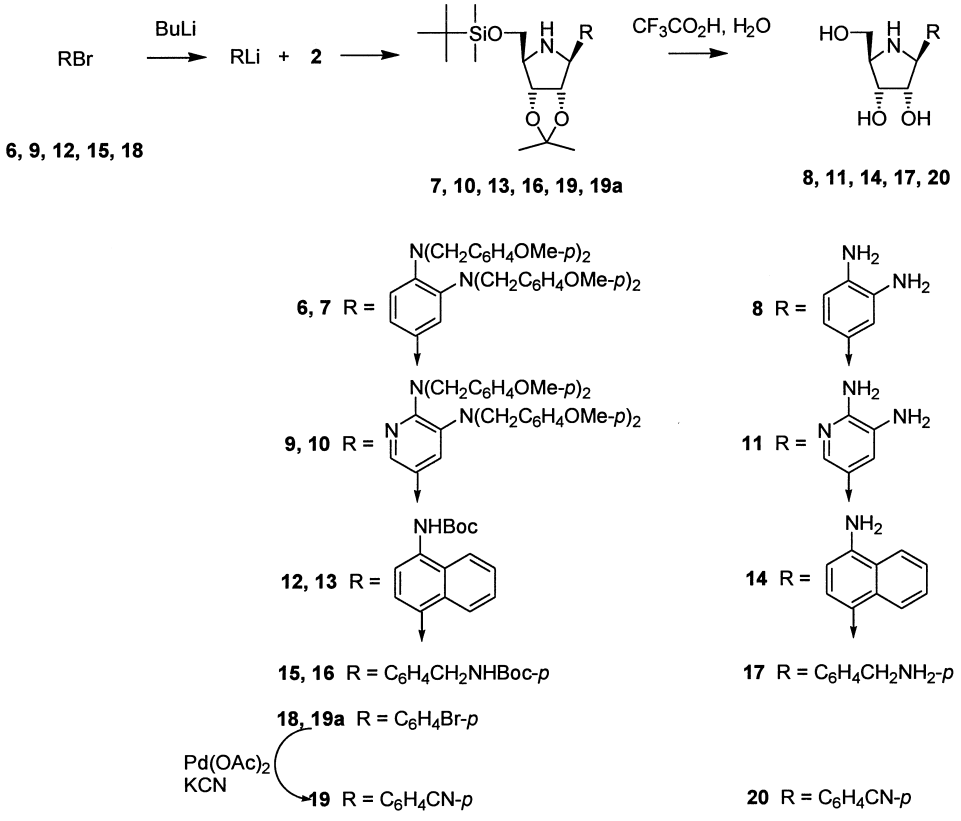
A facile synthesis of some (1*S*)-1-aryl-1,4-dideoxy-1,4-imino-D-ribitols has been claimed[17] following the addition of organometallic *C*-nucleophiles to 2,3,5-tri-*O*-substituted-D-ribofuranose derivatives, oxidation of the C-1 and C-4 hydroxy groups in the products, and then reductive amination of the resultant 1,4-dicarbonyl compounds. While further investigations confirmed that these products had the required 1,4-dideoxy-1,4-imino-pentitol structures, they also revealed that they had the all-*cis* β-L-*lyxo*-configuration[18] and were thus unsuitable for use in the current work.

Our previous syntheses of (1*S*)-1-aryl-1,4-dideoxy-1,4-imino-D-ribitols (**3**) utilized additions of organometallic species to the imine **2** which was generated from the iminoribitol derivative **1** (Scheme 1).[14,19] We have continued this approach in the synthesis of new analogues. Compounds selected for synthesis and testing were designed to have basic sites in the aryl residues available for protonation by the enzyme, and to have 'aglycons' with greater similarities to those of the natural substrates of the enzymes. These were expected to have enhanced affinity for the IAG nucleoside hydrolase as this enzyme is believed to utilize two enzymatic general acids to protonate the purine and thus facilitate the nucleoside hydrolysis.[6] Initially compounds **8**, **11**, **14**, **17** and **20** (Scheme 2) were chosen for these reasons and because they were synthetically accessible.

The precursors of compounds **8**, **11**, **14** and **17**, i.e. **7**, **10**, **13** and **16**, respectively, were made by additions of lithiated aryls produced from the corresponding aryl bromides **6**, **9**, **12** and **15** to the imine **2** (Scheme 2). The *p*-cyanophenyl precursor **19** was derived from the known *p*-bromo-analogue **19a**[14] [made from *p*-dibromobenzene (**18**) and **2**] by treatment with palladium acetate and



Scheme 1. General route to the (1*S*)-1-aryl-iminoribitols.



Scheme 2. Synthesis of the (1*S*)-1-aryl-iminoribitols.

potassium cyanide. The preparations of the aryllithium reagents, their additions to imine **2** and the deprotection of the products to give the required **8**, **11**, **14**, **17** and **20** are detailed in the Experimental section. The stereochemistry at C-1 of the products obtained by additions to imine **2** is inferred by analogy with that of the compound produced by use of phenylmagnesium bromide with this imine. NMR NOE interactions between H-1 and H-4 and between phenyl protons and H-2 established the β-(*S*)-stereochemistry.[19]

When tested against the two classes of nucleoside hydrolases (Table 1) compounds **8**, **11**, **14**, **17** and **20** proved to be inferior to **4** and **5** against the IU hydrolase and, apart from the 4-cyanophenyl derivative **20**, not clearly better against the purine specific IAG hydrolase.

Table 1. Inhibition of nucleoside hydrolases by (1*S*)-aryl-imino-D-ribitols[a]

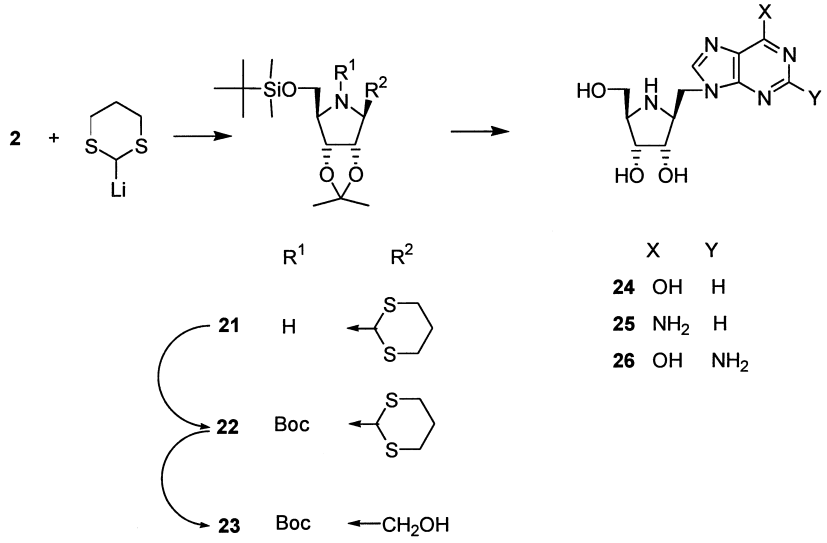
Compound	IU nucleoside hydrolase K_i (μM)	IAG nucleoside hydrolase K_i (μM)
4	0.028	115
5	0.03	12
8	0.21	>2
11	0.94	>30
14	0.43	>50
17	5.0	>2
20	0.92	3.4

[a] Inhibition constants for **4**, **5**, **11** and **14** have been reported.[15,16] The remainder are reported here for the first time.

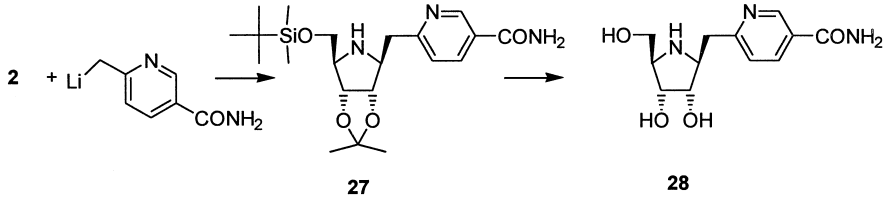
Consequently we decided to synthesize iminoribitol derivatives with 'aglycons' that resemble more closely the substrate bases inosine, adenosine and guanosine. Since the iminoribitol **2** cannot usefully be linked directly through the vinylic position to N-9 of a purine as the resulting aminal would be expected to be too susceptible to hydrolysis, the methylene-bridged compounds **24**–**26**, and also **28**, were selected as targets. For the preparation of the first three of these the alcohol **23**, made by addition of lithiated 1,3-dithiane to imine **2** to give **21** followed by *N*-protection to **22**, hydrolysis of the dithiane and reduction of the derived aldehyde (Scheme 3) was the key compound. Conversion of the alcohol **23** to the triflate or mesylate ester and displacement of the sulfonyloxy leaving groups with 6-chloropurine, adenine or 6-chloroguanine, followed by de-*O*-protection and hydrolysis of the halides, gave the nucleoside analogues **24**–**26**. Similar homonucleosides,[20] and homoazasugars (2,5-dideoxy-2,5-diiminohexitols)[21] have been reported previously.

The methylene-bridged analogue **28** was prepared via the protected derivative **27** by use of **2** and lithiated 6-methylnicotinamide (Scheme 4).

When tested for inhibition of the IU and IAG nucleoside hydrolases (Table 2) each compound generally showed similar inhibitory properties against both the isozyme representatives, the IU and IAG hydrolases, but with much less potency against the former than did **4** and **5**. However, improved inhibition against the IAG



Scheme 3. General route to the (1*S*)-1-aryl-iminoribitols. Reagents: (a) $(^tBuO)_2CO$, CH_2Cl_2; (b) $(CF_3CO_2)_2Hg$, $CaCO_3$, MeCN–H_2O; (c) $NaBH_4$; (d) RSO_2Cl, base; (e) 6-chloropurine or 6-chloroguanine; (f) CF_3CO_2H–H_2O.



Scheme 4. Synthesis of nicotinamide-based analogue **28**.

Table 2. Inhibition of nucleoside hydrolases by homo-aza-*C*-nucleosides[a]

Compound	IU nucleoside hydrolase K_i (μM)	IAG nucleoside hydrolase K_i (μM)
24	5.4	3.6
25	21	13
26	22	5
28	5.2	2.3

[a] Inhibition constants are from ref 16.

nucleoside hydrolase was observed—particularly with **24**, **26** and **28**.

Conclusion

A number of (1*S*)-1-(purin-9-yl)methyl and -aryl-1,4-dideoxy-1,4-imino-D-ribitols have been synthesized and tested against two representative protozoan nucleoside hydrolases. Compounds **20**, **24**, **26** and **28** bind as well as substrate (K_i values 2–5 μM) to the IAG nucleoside hydrolase. It is not obvious why **20** and **28** are the most potent inhibitors of the IAG nucleoside hydrolase, however both have aglycones that contain sites to accept hydrogen bonds from the enzymatic general acids. Investigations are continuing to find inhibitors of equivalent potency to those already discovered for the IU enzyme.

Experimental

NMR spectra were recorded on a Bruker AC-300 instrument at 300 MHz (^{1}H) or 75 MHz (^{13}C) in $CDCl_3$ unless otherwise stated with TMS as internal reference. In D_2O acetone was used as internal reference. High-resolution accurate mass determinations were performed by Hort Research Limited on a VG70-250S double focussing magnetic sector mass spectrometer under chemical ionization conditions using isobutane or ammonia as the ionizing gas, or under high-resolution FAB conditions in a glycerol or nitrobenzyl alcohol matrix. Elemental analyses were performed by the Campbell Laboratory, Otago University. Melting points (mp) were determined on a Reichert hot stage microscope and are uncorrected. Aluminum-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. The imine **2** was prepared as described[14] and was used directly without isolation.

4-Bromo-1,2-bis[di-(4-methoxybenzyl)amino]benzene (6). Sodium hydride (60%, 1.72 g, 43 mmol) was added to a stirred solution of 1,2-diamino-4-bromobenzene[22] (1.0 g, 5.3 mmol) in DMF (20 mL) followed by 4-methoxybenzyl chloride (5.8 mL, 32 mmol). The mixture was stirred at room temperature for 2 days and then quenched with ethanol (5 mL). Chloroform (50 mL) was added and the solution was washed with water (×2) and processed to give a crude residue which, after chromatography, afforded **6** as a syrup (1.9 g, 2.8 mmol, 53%); ^{1}H NMR δ 7.1–6.6 (19H, m, Ar), 4.36, 4.34 (8H, 2s, $ArCH_2$), 3.84, 3.83 (12H, 2s, OCH_3); ^{13}C NMR δ 158.72, 158.68, 144.78 and 142.25 (C), 130.52 (CH), 129.76, 129.68, 125.1, 124.8, 123.53 and 115.07 (C), 113.63 and 113.57 (CH), 55.24 (CH_2), 52.95 and 52.7 (CH_3); HRMS (MH^+) calcd for $C_{38}H_{40}{}^{79}BrN_2O_4$: 667.2171; found: 667.2156.

5-Bromo-2,3-bis[di-(4-methoxybenzyl)amino]pyridine (9). Ferric chloride (0.2 g, 1.2 mmol) and activated charcoal (0.3 g) were added to a suspension of 2-amino-5-bromo-3-nitropyridine (1.0 g, 4.6 mmol) in methanol (40 mL) and the mixture was heated under reflux. Hydrazine hydrate (1.0 mL) was added and reflux was continued for 3 h. The mixture was cooled, filtered and the filtrate was evaporated to give a white solid (0.94 g). Sodium hydride (60%, 1.7 g, 42 mmol) was added to a stirred solution of this material in DMF (20 mL), followed by 4-methoxybenzyl chloride (5.8 mL, 32 mmol), and the mixture was stirred at room temperature for 16 h and quenched by the addition of ethanol (5 mL). Chloroform (50 mL) was added and the solution was washed with water (×2) and processed to give a crude residue which, after chromatography, afforded **9** as a syrup (3.52 g, 5.3 mmol, 87%); ^{1}H NMR δ 7.95 (1H, d, J = 2.1 Hz, Ar), 7.04–6.75 (17H, m, Ar), 4.59, 4.22 (4H each, 2s, $ArCH_2$), 3.77, 3.76 (6H each, 2s, OCH_3); ^{13}C NMR δ 158.9, 158.6 and 152.5 (C), 140.8 (CH), 137.9 (C), 131.2, 130.6, 130.4 and 130.1 (CH), 128.6 (C), 113.74 and 113.69 (CH), 111.7 (C), 55.2 (CH_3), 51.8 and 50.6 (CH_2); HRMS (MH^+) calcd for $C_{37}H_{39}{}^{79}BrN_3O_4$: 668.2124; found: 668.2136.

4-Bromo-*N*-(*tert*-butoxycarbonyl)-1-naphthylamine (12). A solution of 4-bromo-1-naphthylamine (1.0 g, 4.5 mmol) in 1,2-dichloroethane (20 mL) containing *N,N*-diisopropylethylamine (1.57 mL, 9.0 mmol) and di-*tert*-butyl dicarbonate (1.5 g, 6.9 mmol) was heated under reflux. After 4 h, more di-*tert*-butyl dicarbonate (4.0 g, 18.3 mmol) was added and refluxing was continued for 16 h. The solution was washed with HCl (2 M), aqueous $NaHCO_3$ and processed normally. The solid residue was triturated with petroleum ether to give **12** (1.16 g, 3.6 mmol, 80%). Recrystallized from petroleum ether it had mp 138–140°C; ^{1}H NMR δ 8.14 (1H, dd, J = 7.3, 1.8 Hz, Ar), 7.75 (1H, dd, J = 7.7, 2.0 Hz, Ar), 7.64 (2H, m, Ar), 7.44 (2H, m, Ar), 6.74 (1H, s, NH), 1.44 (9H, s, CH_3); ^{13}C NMR δ 153.4, 133.1 and 132.4 (C), 129.9, 128.2, 127.4, 126.9 and 121.0 (CH), 119.2, 118.2 and 81.2 (C), 28.5 [$C(CH_3)_3$]. Anal. calcd for $C_{15}H_{16}BrNO_2$: C, 55.92; H, 5.01; Br, 24.80; N, 4.35. Found: C, 56.22; H, 4.79; Br, 24.77; N, 4.54.

4-Bromo-(*N*-*tert*-butoxycarbonyl)benzylamine (15). Di-*tert*-butyl dicarbonate (6.0 g, 27.5 mmol) and *N,N*-diisopropylethylamine (4.8 mL, 27.6 mmol) were added to a stirred suspension of 4-bromobenzylamine hydrochloride (5.1 g, 22.9 mmol) in dichloromethane (40 mL). After 2 h the solution was washed with HCl (2 M), aq $NaHCO_3$ and processed normally to give a syrup. Trituration with petroleum ether afforded crystalline **15** (3.3 g, 11.5 mmol, 50%). Recrystallized from petroleum ether it had mp 92–93°C; ^{1}H NMR δ 7.44, 7.14 (2H, 2d, J = 8.4 Hz, Ar), 4.87 (1H, bs, NH), 4.25 (2H, d, J = 5.9 Hz, CH_2); ^{13}C NMR δ

155.8 and 138.1 (C), 131.7 and 129.1 (CH), 121.1 (C), 44.1 (CH_2), 28.4 [C(CH_3)]$_3$. Anal. calcd for $C_{12}H_{16}BrNO_2$: C, 50.37; H, 5.64; Br, 27.92; N, 4.89. Found: C, 50.53; H, 5.69; Br, 27.94; N, 5.11.

(1*S*)-5-*O*-*tert*-Butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-1-{3,4-bis[di-(4-methoxybenzyl)amino]phenyl}-D-ribitol (7). A solution of **6** (0.92 g, 1.38 mmol) in ether (15 mL) and THF (5 mL) was cooled to −40°C and butyllithium (0.96 mL, 1.25 mmol) was added. The solution was cooled further to −78°C and a cold (−78°C) solution of imine **2**,[14] prepared from **1** (0.175 g, 0.61 mmol), was added by cannula. After 0.5 h, water was added, the mixture was extracted with chloroform and processed normally. Chromatography afforded **7** as a syrup (0.183 g, 0.21 mmol, 34%); ^{1}H NMR δ 6.95–6.67 (19H, m, Ar), 4.39–4.16 (10H, m, H-2,3, *N*-CH_2), 3.96 (1H, d, J = 4.8 Hz, H-1), 3.79–3.65 (2H, m, H-5,5′), 3.683, 3.679 (6H, 2s, OCH_3), 3.18 (1H, m, H-4), 1.49 and 1.26 [6H, 2s, C(CH_3)$_2$], 0.81 [9H, s, C(CH_3)$_3$], 0.05, 0.04 [6H, 2s, Si(CH_3)$_2$]; ^{13}C NMR δ 158.6, 143.5, 142.8 and 134.8 (C), 130.6, 130.5, 122.0, 120.5 and 120.4 (CH), 114.0 (C), 113.5 and 113.4 (CH), 87.8 (C-2), 81.8 (C-3), 67.8 (C-1), 65.7 (C-4), 63.6 (C-5), 55.2 (OCH_3), 53.3 and 53.2 (NCH_2O) 27.6 and 25.5 [C(CH_3)2], 26.0 [C(CH_3)$_3$], 18.4 [C(CH_3)$_3$], −5.3 [Si(CH_3)$_2$]; HRMS (MH^+) calcd for $C_{52}H_{68}N_3O_7Si$: 874.4827. Found: 874.4852.

(1*S*)-5-*O*-*tert*-Butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-1-{2,3-bis[di-(4-methoxybenzyl)amino]-5-pyridyl}-D-ribitol (10). A solution of **9** (1.2 g, 1.8 mmol) in ether (30 mL) was cooled to −40°C and butyllithium (1.35 mL, 1.75 mmol) was added dropwise. After 0.5 h, the solution was cooled to −78°C and a solution of imine **2**[14] prepared from **1** (0.16 g, 0.56 mmol) was added by cannula. After 0.5 h, water was added, the mixture was extracted with chloroform and processed normally. Chromatography afforded **10** (0.23 g, 0.26 mmol, 46%); ^{1}H NMR δ 7.89 (1H, d, J = 1.7 Hz, Ar), 6.99–6.65 (17H, m, Ar), 4.55 (4H, 2dd, *N*-CH_2), 4.35 (1H, dd, J = 4.9, 7.0 Hz, H-3), 4.21–4.09 (5H, m, H-2, *N*-CH_2), 3.97 (1H, d, J = 8.5 Hz, H-1), 3.76 (2H, m, H-5,5′), 3.69, 3.68 (6H, 2s, OCH_3), 3.21 (1H, dd, J = 4.9, 8.8 Hz, H-4), 1.50, 1.26 [6H, 2s, C(CH_3)$_2$], 0.81 [9H, s, C(CH_3)$_3$], 0.06, 0.04 [6H, 2s, Si(CH_3)$_2$]; ^{13}C NMR δ 158.5, 158.3 and 153.5 (C), 138.6 (CH), 136.7 and 130.9 (C), 130.4 and 130.0 (CH), 129.0 (C), 127.4 (CH), 113.9 (C), 113.4 and 113.3 (CH), 87.2 (C-3), 81.5 (C-2), 65.5 (C-4), 65.3 (C-1), 63.6 (C-5), 55.04 and 55.0 (CH_3), 52.0 and 50.5 (CH_2), 27.4 and 25.2 [C(CH_3)$_2$], 25.8 [C(CH_3)$_3$], 18.1 [C(CH_3)$_3$], −5.5 [Si(CH_3)$_2$]; HRMS (MH^+) calcd for $C_{51}H_{67}N_4O_7Si$: 875.4779. Found: 875.4784.

(1*S*)-1-[(*N*-*tert*-Butoxycarbonylamino)naphthalen-4-yl]-5-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (13). Butyllithium (2.95 mL, 4.6 mmol) was added to a solution of **12** (0.84 g, 2.6 mmol) in THF (5 mL) at −78°C. After 2 h, a solution of imine **2**,[14] prepared from **1** (0.175 g, 0.61 mmol), was added by cannula. After 0.5 h, water was added, the mixture was extracted with chloroform and processed normally. Chromatography afforded **13** (0.213 g, 0.40 mmol, 66%); ^{1}H NMR δ 8.28 (1H, dd, J = 2.1, 6.7 Hz, Ar), 7.81 (1H, dd, J = 3.0, 7.4 Hz, Ar), 7.71 (1H, d, J = 7.9 Hz, Ar), 7.62 (1H, d, J = 7.9 Hz, Ar), 7.44 (2H, m, aromatic), 6.78 (1H, s, NH), 4.82 (1H, d, $J_{1,2}$ = 4.4 Hz, H-1), 4.44 (1H, dd, $J_{2,3}$ = 6.9 Hz, H-2), 4.38 (1H, dd, $J_{3,4}$ = 5.0, Hz, H-3), 3.84 (1H, dd, $J_{4,5}$ = 3.8, $J_{5,5'}$ = 10.1 Hz, H-5), 3.68 (1H, dd, $J_{4,5'}$ = 6.3 Hz, H-5′), 3.37 (1H, m, H-4), 1.56, 1.22 [6H, 2s, C(CH_3)$_2$], 1.46 [9H, s, C(CH_3)$_3$], 0.83 [9H, s, C(CH_3)$_3$], 0.05, 0.04 [6H, 2s, Si(CH_3)$_2$]; ^{13}C NMR δ 153.7, 134.1, 132.5, 132.2 and 127.1 (C), 126.1, 125.8, 124.9, 123.2, 121.1 and 118.7 (CH), 113.8 (C), 87.0 (C-2), 81.6 (C-3), 80.6 (C), 65.7 (C-4), 64.5 (C-5), 64.2 (C-1), 28.4 [C(CH_3)$_3$], 27.7 and 25.5 [C(CH_3)$_2$], 26.0 [C(CH_3)$_3$], 18.4 [C(CH_3)$_3$], −5.2 and −5.3 [Si(CH_3)$_2$]; HRMS (MH^+) calcd for $C_{29}H_{45}N_2O_5Si$: 529.3098. Found: 529.3110.

(1*S*)-1-[*N*-(4-*tert*-Butoxycarbonylamino)methyl]phenyl-5-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (16). Butyllithium (2.6 mL, 3.9 mmol) was added to a solution of **15** (0.64 g, 2.2 mmol) in THF (10 mL) at −78°C and after 0.5 h a solution of imine **2**,[14] prepared from **1** (0.16 g, 0.56 mmol), was added by cannula to the resulting suspension. After 0.5 h, water was added, the mixture was extracted with chloroform and processed normally. Chromatography afforded **16** (0.055 g, 0.11 mmol, 20%); ^{1}H NMR δ 7.37, 7.25 (4H, 2d, J = 8.2 Hz, Ar), 4.85 (1H, bs, NH), 4.49 (1H, dd, $J_{2,3}$ = 7.0, $J_{3,4}$ = 4.7 Hz, H-3), 4.40 (1H, dd, $J_{1,2}$ = 5.3 Hz, H-2), 4.29 (2H, d, J = 5.7 Hz, CH_2), 4.17 (1H, d, H-1), 3.87 (1H, dd, $J_{4,5}$ = 3.7, $J_{5,5'}$ = 10.2 Hz, H-5), 3.76 (1H, dd, $J_{4,5'}$ = 5.3 Hz, H-5′), 3.34 (1H, dd, H-4), 1.58, 1.33 [6H, 2s, C(CH_3)$_2$], 1.46 [9H, s, C(CH_3)$_3$], 0.91 [9H, s, C(CH_3)$_3$], 0.08 [6H, Si(CH_3)$_2$]; ^{13}C NMR δ 155.8, 140.6 and 138.1 (C), 127.7 and 126.8 (CH), 114.1 (C), 87.6 (C-2), 81.8 (C-3), 67.7 (C-1), 65.6 (C-4), 63.8 (C-5), 44.4 (CH_2), 28.4 and 25.9 [C(CH_3)$_3$], 27.5 and 25.4 [C(CH_3)$_2$], 18.3 [C(CH_3)$_3$], −5.4 [Si(CH_3)$_2$].

(1*S*)-1-(3,4-Diaminophenyl)-1,4-dideoxy-1,4-imino-D-ribitol (8). A solution of **7** (0.175 g, 0.20 mmol) in trifluoroacetic acid (10 mL) was allowed to stand at room temperature for 24 h and then evaporated to dryness. A solution of the residue in water was extracted (×2) with chloroform and the aqueous phase was concentrated to dryness. The residue in water was eluted through a column of Amberlyst A26 base resin. Evaporation of the eluant afforded **8** (0.018 g, 0.075 mmol, 37%); ^{1}H NMR (D_2O) δ 6.94–6.76 (3H, m, Ar), 4.11–3.93 (2H, m, H-2,3), 3.90 (1H, d, $J_{1,2}$ = 7.1 Hz, H-1), 3.79 (2H, m, H-5,5′), 3.25–3.17 (1H, m, H-4); ^{13}C NMR δ 137.1 and 134.6 (C), 122.1, 120.4 and 119.0 (CH), 79.2 and 74.9 (C-2,3), 67.9 and 67.4 (C-1,4), 64.7 (C-5); HRMS (MH^+) calcd for $C_{11}H_{18}N_3O_3$: 240.1348. Found: 240.1342.

(1*S*)-1-(2,3-Diamino-5-pyridyl)-1,4-dideoxy-1,4-imino-D-ribitol (11). Acidic deprotection of **10** (0.14 g, 0.16 mmol) was carried out as described above in the formation of **8** to give **11** (0.02 g, 0.08 mmol, 50%); ^{1}H NMR (D_2O) δ 7.54, 7.12 (2H, 2d, J = 1.8 Hz, Ar), 4.04–3.98 (2H, m, H-2,3), 3.87 (1H, d, $J_{1,2}$ = 7.4 Hz, H-1), 3.72 (2H, 2d, $J_{4,5}$ = 5.4 Hz, H-5,5′), 3.17 (1H, dd, $J_{3,4}$ = 9.0 Hz, H-4); ^{13}C NMR δ 151.6 (C), 139.2 (CH), 132.2 and 129.8 (C), 125.0 (CH), 78.8 and 74.9 (C-2,3), 67.6 (C-4), 65.5 (C-1), 65.1 (C-5); HRMS (MH^+) calcd for $C_{10}H_{17}N_4O_3$: 241.1301. Found: 241.1307.

(1*S*)-(1-Aminonaphthalen-4-yl)-1,4-dideoxy-1,4-imino-D-ribitol (14). Acidic deprotection of **13** (0.21 g, 0.40 mmol) was carried out as described above in the formation of **8** to give **14** (0.03 g, 0.11 mmol, 28%); ^{1}H NMR (MeOH-d_4) δ 8.16 (1H, d, J = 8.4 Hz, Ar), 8.05 (1H, d, J = 8.5 Hz, Ar), 7.67–7.44 (3H, m, Ar), 6.85 (1H, d, J = 7.9 Hz, Ar), 5.06 (1H, d, $J_{1,2}$ = 6.8 Hz, H-1), 4.43 (1H, dd, $J_{2,3}$ = 5.3 Hz, H-2), 4.19 (1H, t, H-3), 3.82 (2H, d, H-5,5′), 3.51 (1H, dd, J = 4.3, 8.7 Hz, H-4); ^{13}C NMR δ 145.9 and 134.4 (C), 127.5, 126.3 and 125.5 (CH), 125.4 (C), 124.2 and 123.5 (CH), 122.7 (C), 109.7 (CH), 76.8 (C-2), 73.4 (C-3), 66.3 (C-4), 62.7 (C-1), 61.5 (C-5); HRMS (MH^+) calcd for $C_{15}H_{18}N_2O_3$: 274.1317. Found: 274.1312.

(1*S*)-1-(4-Aminomethyl)phenyl-1,4-dideoxy-1,4-imino-D-ribitol (17). Acidic deprotection of **16** (0.055 g, 0.11 mmol) was carried out as described above in the formation of **8** to give **17** (0.025 g, 0.10 mmol, 90%); ^{1}H NMR (D_2O) δ 7.50 (4H, m, Ar), 4.09 (5H, br s, H-1,2,3, $ArCH_2$), 3.80 (2H, m, H-5,5′), 3.25 (1H, m, H-4); ^{13}C NMR (142.4 and 138.4°C), 131.3 and 130.5 (CH), 79.3 and 74.8 (C-2,3), 67.8 (C-1), 67.5 (C-4), 64.9 (C-5), 46.0 ($ArCH_2$); HRMS (MH^+) calcd for $C_{12}H_{19}N_2O_3$: 239.1396. Found: 239.1370.

(1*S*)-5-*O*-*tert*-Butyldimethylsilyl-1-(4-cyanophenyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (19). Argon was bubbled through a solution of (1*S*)-1-(4-bromophenyl)-5-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol[14] (**19a**, 0.68 g, 1.54 mmol) in HMPA (10 mL) containing palladium acetate (0.070 g, 0.31 mmol) and potassium cyanide (0.50 g, 7.7 mmol) for 0.5 h, and then the solution was heated at 75°C under argon for 3 h. Toluene was added and the mixture was washed with $NaHCO_3$ (aq), water and processed normally to give, following chromatography, **19** as a syrup (0.351 g, 0.90 mmol, 58%); ^{1}H NMR δ 7.62, 7.55 (4H, 2d, J = 8.3 Hz, Ar), 4.46 (1H, dd, $J_{2,3}$ = 6.9, $J_{3,4}$ = 4.2 Hz, H-3), 4.34 (1H, t, H-2), 4.23 (1H, d, $J_{1,2}$ = 5.4 Hz, H-1), 3.84 (1H, dd, $J_{4,5}$ = 4.0, $J_{5,5'}$ = 10.2 Hz, H-5), 3.72 (1H, dd, $J_{4,5'}$ = 6.0 Hz, H-5′), 3.41 (1H, m, H-4), 1.59, 1.33 (6H, 2s, CH_3), 0.90 [9H, s, $C(CH_3)_3$], 0.08 [6H, $Si(CH_3)_2$]; ^{13}C NMR δ 147.2 (C), 132.2 and 127.1 (CH), 118.8, 114.1 and 111.0 (C), 87.1 (C-2), 81.7 (C-3), 67.5 (C-1), 65.3 (C-4), 64.4 (C-5), 27.4 and 25.3 [$C(CH_3)_2$], 25.8 [$C(CH_3)_3$], 18.2 [$C(CH_3)_3$], −5.5 [$Si(CH_3)_2$]; HRMS (MH^+) calcd for $C_{21}H_{33}N_2O_3Si$: 389.2260. Found: 389.2223.

(1*S*)-1-(4-Cyanophenyl)-1,4-dideoxy-1,4-imino-D-ribitol (20). A solution of **19** (0.22 g, 0.57 mmol) in THF: water:trifluoroacetic acid (15 mL, 10:4:1 v/v/v) was heated under reflux for 3 h and then concentrated to dryness. The residue in water was extracted (×2) with chloroform, concentrated to dryness, then redissolved in water and the solution was treated with Amberlyst A21 base resin to neutral pH. Lyophilization afforded **20** (0.12 g, 0.51 mmol, 89%); ^{1}H NMR (D_2O) δ 7.73, 7.55 (4H, 2d, J = 8.2 Hz, Ar), 4.13 (1H, d, $J_{1,2}$ = 7.3 Hz, H-1), 4.04 (2H, m, H-2,3), 3.72 (2H, m, H-5,5′), 3.27 (1H, dd, J = 5.8, 9.6 Hz, H-4); ^{13}C NMR δ 147.5 (C), 135.5 and 130.7 (CH), 122.3 and 113.3 (C), 79.1 and 74.6 (C-2,3), 67.6 and 67.5 (C-1,4), 64.7 (C-5); HRMS (MH^+) calcd for $C_{12}H_{15}N_2O_3$: 235.1083. Found: 235.1080.

6-*O*-*tert*-Butyldimethylsilyl-2,5-dideoxy-2,5-imino-3,4-*O*-isopropylidene-D-allose propane-1,3-diyl dithioacetal (21). Butyllithium (19.6 mL, 27.4 mmol) was added to a solution of 1,3-dithiane (3.63 g, 30.2 mmol) in THF (50 mL) at −20°C and after 0.5 h the solution was cooled to −78°C and added by cannula to a solution of imine **2**,[14] prepared from **1** (2.5 g, 8.7 mmol). After 0.5 h, water was added, the mixture was extracted with chloroform and processed normally. Chromatography afforded **21** as a syrup (2.72 g, 6.7 mmol, 77%); ^{1}H NMR δ 4.50 (1H, dd, $J_{2,3}$ = 4.8, $J_{3,4}$ = 7.0 Hz, H-3), 4.34 (1H, dd, $J_{4,5}$ = 4.5 Hz, H-4), 4.06 (1H, d, J = 7.0 Hz, H-1), 3.69 (1H, dd, $J_{5,6}$ = 3.9, $J_{6,6'}$ = 10.3 Hz, H-6), 3.60 (1H, dd, $J_{5,6'}$ = 4.9 Hz, H-6′), 3.17 (1H, m, H-5), 2.87–2.71 (4H, m, SCH_2), 2.05, 1.86 (2H, 2m, CH_2), 1.45, 1.27 [6H, 2s, $C(CH_3)_2$], 0.83 [9H, s, $C(CH_3)_3$], 0.05 [6H, $Si(CH_3)_2$]; ^{13}C NMR δ 113.5 (C), 83.4 (C-3), 81.7 (C-4), 67.0 (C-2), 65.3 (C-5), 63.7 (C-6), 49.8 (C-1), 29.3 and 29.0 (SCH_2), 27.3 and 25.3 [$C(CH_3)_2$], 25.8 [$C(CH_3)_3$ and CH_2], 18.1 [$C(CH_3)_3$], −5.5 and −5.6 [$Si(CH_3)_2$]; HRMS (MH^+) calcd for $C_{18}H_{36}NO_3S_2Si$: 406.1906. Found: 406.1898.

***N*-*tert*-Butoxycarbonyl-6-*O*-*tert*-butyldimethylsilyl-2,5-dideoxy-2,5-imino-3,4-*O*-isopropylidene-D-allose propane-1,3-diyl dithioacetal (22)**. A solution of **21** (1.0 g, 2.47 mmol) in dichloromethane (20 mL) containing di-*tert*-butyl dicarbonate (0.81 g, 3.71 mmol) was stirred at room temperature for 2 days, and then concentrated to dryness. Chromatography afforded **22** as a syrup (1.17 g, 2.32 mmol, 94%); ^{1}H NMR δ 4.79, 4.65 (2H, 2m, H-3,4), 4.37–4.14 (2H, m, H-1,2), 4.03 (1H, m, H-5), 3.80–3.58 (2H, m, H-6,6′), 3.12–2.70 (4H, m, SCH_2), 2.11–1.90 (2H, m, CH_2), 1.47 [12H, s, CH_3, $C(CH_3)_3$], 1.33 (3H, s, CH_3), 0.90 [9H, s, $C(CH_3)_3$], 0.08 [6H, $Si(CH_3)_2$]; ^{13}C NMR δ 154.8 and 111.6 (C), 82.6 and 81.7 (C-3,4), 80.1 (C), 66.6 (C-2), 66.4 (C-5), 63.1 (C-6), 46.7 (C-1), 28.2 [$C(CH_3)_3$], 27.3 and 25.4 (CH_2), 27.1 and 25.2 [$C(CH_3)_2$], 25.8 [$C(CH_3)_3$], 18.2 [$C(CH_3)_3$], −5.4 and −5.5 [$Si(CH_3)_2$]; HRMS (MH^+) calcd for $C_{23}H_{44}NO_5S_2Si$: 506.2430. Found: 506.2427.

***N*-*tert*-Butoxycarbonyl-6-*O*-*tert*-butyldimethylsilyl-2,5-dideoxy-2,5-imino-3,4-*O*-isopropylidene-D-allitol (23)**. Calcium carbonate (3.4 g) was added to a stirred solution of **22** (0.34 g, 0.67 mmol) in 5% aqueous MeCN (15 mL) followed by mercury(II) trifluoroacetate (3.47 g, 8.1 mmol) and the mixture was stirred for 4 h. Chloroform (50 mL) was added and the mixture was filtered through Celite, washed with aqueous $NaHCO_3$ and processed to give a syrup which was dissolved in ethanol and sodium borohydride (0.1 g, 2.6 mmol) was added. After 1 h the solution was partitioned between chloroform and water and the organic layer was processed normally to give, after chromatography, **23** as a syrup (0.194 g, 0.46 mmol, 69%); ^{1}H NMR δ 4.77–4.32 (3H, m), 4.14 (1H, m), 4.07–3.58 (5H, m), 1.47, 1.38 (6H, 2s, CH_3), 1.45, 0.89 [9H, s, $C(CH_3)_3$], 0.08 (6H, s, CH_3); ^{13}C NMR δ 111.4 (C), 81.9 and 81.6 (CH), 81.4 and 80.8 (CH), 80.5 and 80.1 (C), 66.5 (CH), 66.2 and 65.7 (CH), 64.6 and 63.7 (CH_2), 63.5 and 62.9 (CH_2), 28.2 [$C(CH_3)_3$], 27.4 and 25.4 [$C(CH_3)_2$], 25.8 [$C(CH_3)_3$], 18.4 [$C(CH_3)_3$], −5.7 [$Si(CH_3)_2$]; HRMS (MH^+) calcd for $C_{20}H_{40}NO_6Si$: 418.2625. Found: 418.2610.

1,2,5-Trideoxy-1-(hypoxanthin-9-yl)-2,5-imino-D-allitol (24). To a solution of **23** (0.05 g, 0.12 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.123 g, 0.6 mmol) in CH_2Cl_2 (3 mL) at 0°C was added trifluoromethanesulfonic anhydride (0.040 mL, 0.24 mmol). After 0.5 h the solution was washed with HCl (2 M), aqueous $NaHCO_3$ and processed normally. 6-Chloropurine (0.074 g, 0.48 mmol) and potassium carbonate (0.066 g, 0.48 mmol) were added to a solution of the crude product in DMF (3 mL) and the mixture was stirred at room temperature for 0.5 h. Chloroform (10 mL) was added, the solution was washed (×2) with water and processed normally to give, after chromatography, *N*-*tert*-butoxycarbonyl-6-*O*-*tert*-butyldimethylsilyl-1-(6-chloropurin-9-yl)-1,2,5-trideoxy-2,5-imino-3,4-*O*-isopropylidene-D-allitol (0.035 g, 0.063 mmol, 52%). This material was dissolved in trifluoroacetic acid (3 mL) and the solution was allowed to stand for 6 h. Water (1 mL) was added and the solution was left at room temperature for 16 h and then concentrated to dryness. The residue was dissolved in water and extracted (×2) with chloroform and the aqueous phase was concentrated to dryness. The residue in water was treated with Amberlyst A21 base resin until the solution was neutral, and then the solids and solvent were removed to give **24** as a solid (0.009 g, 0.032 mmol, 51%); ^{1}H NMR (D_2O) δ 8.19, 8.17 (2H, 2s, Ar), 4.51 (1H, dd, J = 14.5, 5.4 Hz, H-1), 4.39 (1H, dd, J = 7.5 Hz, H-1′), 3.90 (2H, m, H-3,4), 3.69–3.54 (3H, m, H-2,6,6′), 3.16 (1H, dd, J = 9.0, 4.6 Hz, H-5); ^{13}C NMR δ 161.5 and 152.0 (C), 148.7 and 145.3 (CH), 126.2 (C), 76.2 and 74.6 (C-3,4), 67.1 (C-5), 64.6 (C-6), 64.2 (C-2), 49.1 (C-1); HRMS (MH^+) calcd for $C_{11}H_{16}N_5O_4$: 282.1202. Found: 282.1196.

1-(Adenin-9-yl)-1,2,5-trideoxy-2,5-imino-D-allitol (25). Methanesulfonyl chloride (0.037 mL, 0.48 mmol) was added to a solution of **23** (0.10 g, 0.24 mmol) and *N,N*-diisopropylethylamine (0.21 mL, 1.2 mmol) in CH_2Cl_2 (5 mL) and after 1 h the solution was washed with HCl (2 M), aqueous $NaHCO_3$ and processed normally. Adenine (0.13 g, 0.96 mmol) and potassium carbonate (0.132 g, 0.96 mmol) were added to a solution of the crude residue in DMF (4 mL) and the mixture was stirred at 100°C for 6 h. Chloroform (15 mL) was added and the mixture was washed (×4) with water, and processed normally to give, after chromatography, 1-(adenin-9-yl)-*N*-*tert*-butoxycarbonyl-6-*O*-*tert*-butyldimethylsilyl-1,2,5-trideoxy-2,5-imino-3,4-*O*-isopropylidene-D-allitol (0.054 g, 0.10 mmol, 41%). This material was dissolved in trifluoroacetic acid (3 mL) and allowed to stand for 16 h. It was processed as described above for **24** to give **25** as a solid (0.02 g, 0.071 mmol, 71%); ^{1}H NMR (D_2O) δ 8.16, 8.14 (2H, 2s, Ar), 4.45 (1H, dd, J = 5.7, 14.5 Hz, H-1), 4.32 (1H, dd, J = 7.3 Hz, H-1′), 3.91 (2H, m, H-3,4), 3.68 (1H, dd, $J_{5,6}$ = 4.9, $J_{6,6'}$ = 11.6 Hz, H-6), 3.61 (1H, dd, $J_{5,6'}$ = 5.6 Hz, H-6′), 3.52 (1H, m, H-2), 3.15 (1H, m, H-5); ^{13}C NMR δ 158.1 (C), 155.1 (CH), 151.7 (C), 145.2 (CH), 120.9 (C), 76.3 and 74.7 (C-3,4), 66.7 (C-5), 64.8 (C-6), 64.1 (C-2), 49.0 (C-1); HRMS (MH^+) calcd for $C_{11}H_{17}N_6O_3$: 281.1362. Found: 281.1374.

1,2,5-Trideoxy-1-(guanin-9-yl)-2,5-imino-D-allitol (26). The alcohol **23** (0.10 g, 0.24 mmol) was treated as described above in the preparation of **25** except that 6-chloroguanine was used in place of adenine. This afforded **26** as a solid (0.025 g, 0.084 mmol, 35%); ^{1}H NMR (D_2O) δ 7.80 (1H, s, Ar), 4.48 (2H, m, H-1,1′), 4.05 (2H, m, H-3,4), 3.92–3.70 (3H, m, H-2,6,6′), 3.58 (1H, m, H-5); ^{13}C NMR δ 142.9 (CH), 74.6 and 73.6 (C-3,4), 67.9 and 64.1 (C-2,5), 62.3 (C-6), 46.3 (C-1); HRMS (MH^+) calcd for $C_{11}H_{17}N_6O_4$: 297.1311. Found: 297.1331.

6-*O*-*tert*-Butyldimethylsilyl-1-(5-carboxamido-2-pyridyl)-1,2,5-trideoxy-2,5-imino-3,4-*O*-isopropylidene-D-allitol (27). A solution of lithium tetramethylpiperidide (LiTMP) in THF (10.5 mL, 9.6 mmol) was added to a suspension of 6-methylnicotinamide (0.218 g, 1.6 mmol) in THF (15 mL) at −78°C and the mixture was stirred at −30°C for 0.5 h. The resulting solution was cooled to −78°C and a solution of imine **2**,[14] prepared from **1** (0.23 g, 0.80 mmol), was added by cannula. After 0.5 h, water was added, the mixture was extracted with chloroform and processed normally. Chromatography afforded **27** as a syrup (0.227 g, 0.54 mmol, 67%); ^{1}H NMR δ 8.90 (1H, d, J = 1.8 Hz, Ar), 8.03 (1H, dd, J = 2.1, 8.0 Hz, Ar), 7.25 (1H, d, J = 7.6 Hz, Ar), 6.51 (2H, s, NH_2), 4.38 (1H, dd, $J_{3,4}$ = 6.9, $J_{4,5}$ = 4.5 Hz, H-4), 4.27 (1H, dd, $J_{2,3}$ = 5.2 Hz, H-3), 3.71 (1H, dd, $J_{5,6}$ = 4.0, $J_{6,6'}$ = 10.3 Hz, H-6), 3.63 (1H, dd, $J_{5,6'}$ = 4.9 Hz, H-6′), 3.48 (1H, m, H-2), 3.21–3.12 (2H, m, H-1, H-5), 2.92 (1H, dd, J = 8.3, 14.2 Hz, H-1′), 1.45, 1.26 [6H, 2s, $C(CH_3)_2$], 0.82 [9H, s, $C(CH_3)_3$], 0.05 [6H, $Si(CH_3)_2$]; ^{13}C NMR δ 167.7 and 162.7 (C), 148.1 and 135.8 CH), 127.0 (C), 123.3 (CH), 113.8 (C), 85.1 (C-3), 82.0 (C-4), 65.4 (C-5), 63.9 (C-2), 63.6 (C-6), 41.9 (C-1), 27.4 and 25.4 [$C(CH_3)_2$], 25.8 [$C(CH_3)_3$], 18.2 [$C(CH_3)_3$], −5.4, −5.5 [$Si(CH_3)_2$]; HRMS (MH^+) calcd for $C_{21}H_{36}N_3O_4Si$: 422.2475. Found: 422.2503.

1-(5-Carboxamido-2-pyridyl)-1,2,5-trideoxy-2,5-imino-D-allitol (28). Compound **27** (0.11 g, 0.26 mmol) was deprotected in trifluoroacetic acid and processed further as described above in the preparation of **24** to give **28** as a solid (0.053 g, 0.20 mmol; 77%); ^{1}H NMR (D_2O) δ 8.86 (1H, s, Ar), 8.18 (1H, dd, J = 2.2, 8.1 Hz, Ar), 7.53 (1H, d, J = 8.1 Hz, Ar), 4.00 (1H, t, J = 5.5 Hz, H-4), 3.88 (1H, t, J = 6.5 Hz, H-3), 3.74 (2H, m, H-6,6′), 3.48 (1H, m, H-2), 3.28, 3.07 (2×1H, dd, $J_{1,1'}$ = 14.0, $J_{1,2}$ = 5.4, $J_{1',2}$ = 8.5 Hz, H-1,1′), 3.18 (1H, m, H-5); ^{13}C NMR δ 173.2 and 164.3 (C), 150.4, 139.6 (CH), 130.0 (C), 126.9 (CH), 77.4 (C-3), 74.2 (C-4), 67.0 (C-5), 64.8 (C-2), 63.9 (C-6), 42.4 (C-1); HRMS (MH^+) calcd for $C_{12}H_{18}N_3O_4$: 268.1297. Found: 268.1283.

Acknowledgements

The authors thank Dr. Robert W. Miles for the unpublished data of Tables 1 and 2, Dr. Herbert Wong for an excellent NMR service and Professor Robin Ferrier for assisting with the preparation of the manuscript. This work was supported by research grants from the National Institutes of Health, USA, and the Foundation for Research Science and Technology, New Zealand.

References

1. Miller, L. H. *Science* **1992**, *257*, 36.
2. Hammond, D. J.; Gutteridge, W. E. *Mol. Biochem. Parasitol.* **1984**, *13*, 243.

3. Estupinan, B.; Schramm, V. L. *J. Biol. Chem.* **1994**, *269*, 23068.
4. Berens, R. L.; Marr, J. J.; LaFon, S. W.; Nelson, D. J. *Mol. Biochem. Parasitol.* **1981**, *3*, 187.
5. Berens, R. L.; Krug, E. C.; Marr, J. J. In *Biochemistry and Molecular Biology of Parasites*, Marr, J. J., Muller, M., Eds.; Academic: New York, 1995; pp 89–117.
6. Parkin, D. W. *J. Biol. Chem.* **1996**, *271*, 21713.
7. Mazzella, L. J.; Parkin, D. W.; Tyler, P. C.; Furneaux, R. H.; Schramm, V. L. *J. Am. Chem. Soc.* **1996**, *118*, 2111.
8. Parkin, D. W.; Horenstein, B. A.; Abdulah, D. R.; Estupinan, B.; Schramm, V. L. *J. Biol. Chem.* **1991**, *266*, 20658.
8. Gopaul, D. N.; Meyer, S.; Degano, M.; Sacchettini, J. C.; Schramm, V. L. *Biochemistry* **1996**, *35*, 5963.
10. Shi, W.; Schramm, V. L.; Almo, S. C. *J. Biol. Chem.* **1999**, *274*, 2114.
11. Degano, M.; Almo, S. C.; Sacchettini, J. C.; Schramm, V. L. *Biochemistry* **1998**, *37*, 6277.
12. Pellé, R.; Schramm, V. L.; Parkin, D. W. *J. Biol. Chem.* **1998**, *273*, 2118.
13. Horenstein, B. A.; Schramm, V. L. *Biochemistry* **1993**, *32*, 7089.
14. Furneaux, R. H.; Limberg, G.; Tyler, P. C.; Schramm, V. L. *Tetrahedron* **1997**, *53*, 2915.
15. Parkin, D. W.; Limberg, G.; Tyler, P. C.; Furneaux, R. H.; Chen, X.-Y.; Schramm, V. L. *Biochemistry* **1997**, *36*, 3528.
16. Miles, R. W.; Tyler, P. C.; Evans, G. B.; Furneaux, R.H.; Parkin, D. W.; Schramm, V. L. *Biochemistry* **1999**, *38*, in press.
17. Yokoyama, M.; Akiba, T.; Ochiai, Y.; Momotake, A.; Togo, H. *J. Org. Chem.* **1996**, *61*, 6079.
18. Momotake, A.; Mito, J.; Yamaguchi, K.; Togo, H.; Yokoyama, M. *J. Org. Chem.* **1998**, *63*, 7207.
19. Horenstein, B. A.; Zabinski, R. F.; Schramm, V. L. *Tetrahedron Lett.* **1993**, *34*, 7213.
20. Hossain, N.; Blaton, N.; Peeters, O.; Rozenski, J.; Herdewijn, P. A. *Tetrahedron* **1996**, *52*, 5563.
21. Wong, C.-H.; Provencher, L.; Porco, J. A., Jr.; Jung, S.-H.; Wang, Y.-F.; Chen, L.; Wang, R.; Steensma, D. H. *J. Org. Chem.* **1995**, *60*, 1492.
22. Sato, N.; Kuriyama, H.; Agoh, M. *Eur. Pat. Appl.* **1988**, 252,507.