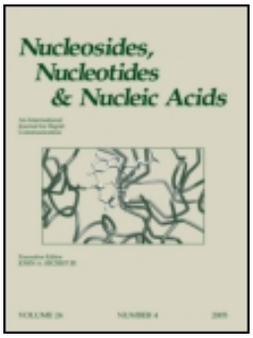

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SYNTHESIS OF NOVEL HYDROXYMETHYL SUBSTITUTED ANALOGUES RELATED TO CARBOVIR AND NEPLANOCIN A

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ABSTRACT

Two enantiomerically pure hydroxymethyl substituted cyclopentene nucleoside analogues (**42** and **53**) related to carbovir and neplanocin A, respectively, were prepared from the chiral pool of iridoid glucosides. In addition two saturated hydroxymethylated analogues (**44** and **45**) were obtained from a protected intermediate.

INTRODUCTION

During the last three decades carbocyclic nucleoside analogues have been recognized as potent and increasingly important antiviral agents. Carbocyclic analogues of active nucleosides frequently appear to be inactive, which may in part be due to the lack of the anomeric effect and the interactions between the ring-oxygen and the hydroxyl groups present. Nevertheless, in recent years several carbocyclic analogues with altered carbon-skeletons and unusual substitution patterns (Figure 1) have been found to

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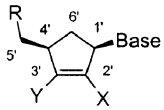
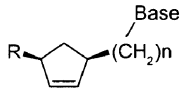
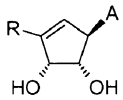


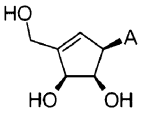
1 Base = G, R = OH, X = Y = H
4a Base = G, R = CH_2OH, X = Y = H
4b Base = G, R = $CH(OH)CH_2OH$, X = Y = H
5a Base = G, R = OH, X = F, Y = H
5b Base = G, R = OH, X = H, Y = Cl
6 Base = A or G, R = OH, X = H, Y = CH_2OH



7a Base = A, n = 0, R = OH
7b Base = A, n = 0, R = NHOH
7c Base = A, n = 0, R = $NHCOCH(CH_3)NH_2$
8 Base = A or G, n = 1, R = CH_2OH



3 R = CH_2OH
14 R = H
15a R = CH_3
15b R = CH_2F
15c R = CH_2Cl
15d R = CH_2OCH_3
15e R = CH_2SCH_3
16a R = CH_2CH_2OH
16b R = $CH(OH)CH_3$
16c R = $CH(OH)CH_2CH_3$
17a R = $CH{=}CH_2$
17b R = $CH(OH)CH{=}CH_2$
17c R = $CH(OH)C{\equiv}CH$
17d R = CH=CHCOOEt
17e R = CH=CHCN
18a R = COOH
18b R = $COOCH_3$
18c R = $CONH_2$
18d R = $CONHCH_3$



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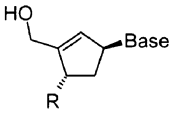
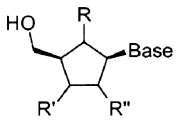
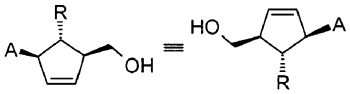


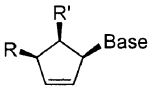
22a Base = A, R = H
22b Base = G, R = OH
22c Base = A or G, R = CH_2OH



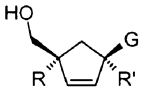
25a Base = A or G, R = H, R' = α-CH_2OH, R" = H
25b Base = A or G, R = H, R' = β-CH_2OH, R" = H
26 Base = A or G, R = H, R' = H, R" = α-CH_2OH
27a Base = A or G, R = H, R' = α-CH_2OH, R" = α-F
27b Base = A or G, R = H, R' = α-CH_2OH, R" = β-F
27c Base = A or G, R = α-F, R' = α-CH_2OH, R" = H
27d Base = A or G, R = β-F, R' = α-CH_2OH, R" = H



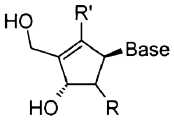
2 R = CH_2OH
13 R = H



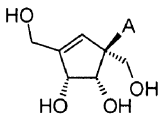
9 Base = A or G, R = H, R' = CH_2OH
10 Base = A, R = R' = CH_2OH



11 R = H, R' = CH_2OH
12a R = Me, R' = H
12b R = C_9H_{19}, R' = H
12c R = Bn, R' = H



20 Base = G, R = β-F, R' = H
21 Base = A, R = α-OH, R' = OMe



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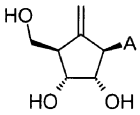

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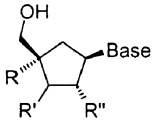
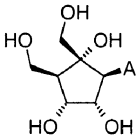


28a Base = G, R = OH, R' = α-CH_2OH, R" = H
28b Base = G, R = F, R' = α-CH_2OH, R" = H
29 Base = A or G, R = CH_2OH, R' = H, R" = OH
30a Base = A, R = CH_2OH, R' = α-OH, R" = H
30b Base = A, R = CH_2OH, R' = β-OH, R" = H



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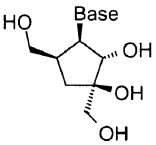

32a Base = 6-OMe-purine
32b Base = 6-Me_2N-purine

Figure 1. Carbocyclic nucleoside analogues related to **1-3** (A = adenine-9-yl, G = guanine-9-yl).

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possess activity against a number of viral infections[1]. Particularly the anti-HIV active carbovir **(1)**[2] and (-)-BCA **(2)**[3], but also the antitumoral neplanocin A **(3)**[4] still attract considerable synthetic interest[5,6] as does the development of enantioselective preparative methodologies towards carbocyclic nucleoside analogues[7–9]. Since the enantioselective synthesis[10] of 1, its pure enantiomer[11] and a number of base-modified analogues[12] including the anti-HIV agent Ziagen®[13], have been reported. In addition the 5-homologues **4a** and **4b** (the latter as two racemates) as well as the halogenated **5a** and **5b**, and the hydroxymethyl substituted 6 have been prepared[14–18]. Also 5′-hetero compounds[19–21] (**7a–c**) and analogues (**8**) with a 1′-methylene bridge[22] have appeared. Racemic analogues having a transposed[23] (i.e., **9**) or an additional hydroxymethyl group[24] (i.e., **10** and **11**) as well as optically pure 4′-alkylated analogues[25] (**12a–c**) have been synthesized. Compound **13** may be regarded either as an L-type analogue of carbovir (**1**) or as an 2′-nor-analogue of (-)-BCA (**2**)[26]. Likewise, many analogues of neplanocin A (**3**) have appeared in recent years. Hence, both the corresponding antileishmanial 5′-nor-compound[27,28] (**14**), the antiviral 5-substituted analogues (**15a–e**)[29], saturated homologues (**16a–c**)[29–31] as well as unsaturated 5-homologues (**17a–e**)[29,31,32], and 5′-carboxylic acid derivatives (**18a–d**) have been reported[33]. The enantiomer[34] of 3 as well as its diepimer[5] (**19**) have also been prepared. Other modifications seen in neplanocin A analogues include fluorination[35] (i.e., racemic **20**), methoxy substitution[36] (i.e., racemic **21**), deoxygenation[37,38] (i.e., **22a–b**), hydroxymethylation[18,39] (i.e., **22c** and **23**) and transposition of the double bond[40] (i.e., **24**). Introduction of hydroxymethyl groups instead of hydroxyls has become a common approach to obtain increased structural diversity of carbocyclic nucleoside analogues. Examples are compounds **25a–28b**[41–47], whereas compounds **29–32b** contain an extra hydroxymethyl group[40,48,49].

Only a few previous reports on the use of iridoid glucosides as cyclopentanoid building blocks in syntheses of nucleoside analogues have appeared[50–52]. In the present work either catalpol (**33**), or more conveniently its cinnamoyl ester **34**, was selected as a readily available starting material[53]. Preliminary investigations had shown that these iridoids after only a few modification and protection steps (i.e., to give **35**) could be converted into a partially protected cyclopentanoid polyol (**36**) using an ozonolytic procedure (Scheme 1)[54]. The polyol (**36**) was envisaged to be a potential intermediate in the synthesis of novel hydroxymethyl substituted analogues related to carbovir (**1**) and neplanocin A (**3**), which we report here.

RESULTS AND DISCUSSION

Initial attempts to perform either selective acylation or silylation of the primary hydroxyl groups in triol **36** resulted in rather complex mixtures of

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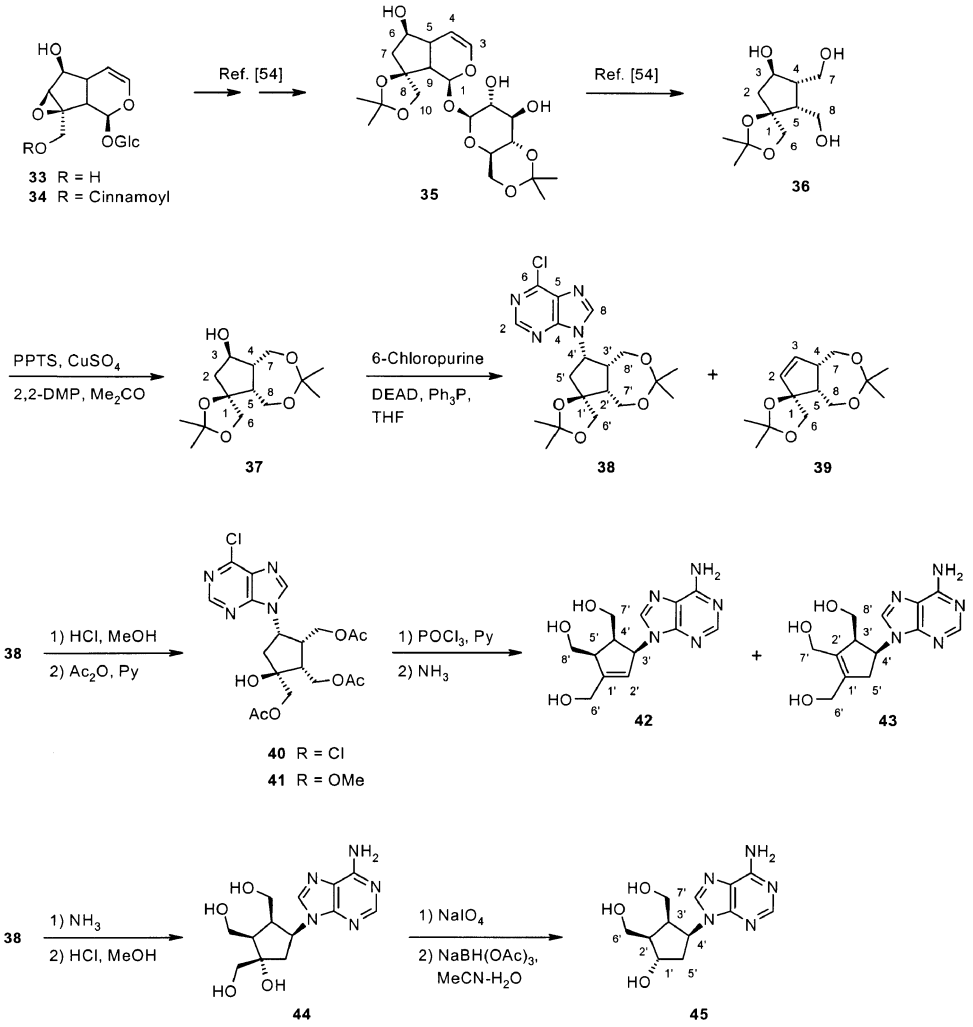

Scheme 1. Synthesis of nucleoside analogues from iridoid-derived building blocks.

mono-, di- and fully protected products. In order to overcome this obstacle, triol **36** was subjected to acetonation with 2,2-dimethoxypropane (2,2-DMP) under mild conditions, which provided diacetonide **37** in good yield (82%). The nucleoside base was introduced by way of a Mitsunobu reaction of alcohol **37** with 6-chloropurine (Scheme 1.). But in addition to the desired product (**38**) a substantial amount of elimination product (**39**) was also obtained (ca. 1:1 ratio). When polymer-bound triphenylphosphine was employed and no nucleophile was added under Mitsunobu conditions, dehydration of **37** to **39** could be accomplished in good yield (74%). It should be noted that the above seven-membered acetonides seem quite stable towards prolonged reaction time in neutral to weakly acidic conditions, and

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they may be purified by vacuum liquid chromatography (VLC) using TLC-mesh silica even when eluents without added base are employed. To be able to introduce a double bond between C-1′ and C-5′ in the cyclopentane moiety (in **38**) by dehydration of the tertiary alcohol, the isopropylidene protecting groups were exchanged for acyl groups at the primary positions. This was performed as a one-pot hydrolysis-acetylation procedure. However, due to a competing methanolysis of the 6-chloro functionality in the purine moiety, the desired product (**40**) and the 6-methoxypurine derivative (**41**) were obtained in a 5:1 ratio. Dehydration of triacetate **40** was best achieved with phosphorus oxychloride in pyridine at room temperature. Even though the reaction proceeded sluggishly under these conditions, a higher selectivity for the less substituted olefin was observed as compared to e.g., thionyl chloride in pyridine-dichloromethane at low temperature, where the selectivity was reverse (i.e., the precursor of **43** was predominant). Subsequently, the inseparable olefinic product mixture was simultaneously deacylated and converted into the adenine nucleoside analogues **42** and **43** by ammonolysis. The former compound could be obtained in essentially isomer-free state by repeated reverse-phase chromatography. Structurally, compound **42** is related to the (inactive) carbovir analogue **6**[18]. Also a uracil substituted 7′-homologue of **42** has been reported (no biological data were given)[50]. So far, only a mixture of **42** and **43** has been examined for antiviral activity, and it was found to be inactive against HIV and HSV-1.

The intermediate **38** was further elaborated into saturated nucleoside analogues **44** and **45** (Scheme 1). First, diacetonide **38** was ammonolyzed to give the corresponding adenine diacetonide that was hydrolyzed directly to yield bis(hydroxymethyl) substituted carbocyclic deoxyadenosine **44** in 84% yield. Next, periodate oxidation of the vicinal diol functionality to give the corresponding ketone proved somewhat problematic as the keto compound was prone to undergo -elimination of the purine moiety during chromatography. To avoid alkaline conditions (also promoting β-elimination) during reduction, we used sodium triacetoxyborohydride together with acetonitrile as co-solvent[55]. Thus, when the ketone, prepared in aqueous solution at 0°C, was added directly to a cooled suspension of $NaBH(OAc)_3$ in acetonitrile, the -hydroxy compound (**45**) was obtained as the only product in 77% yield. The 2′- and/or the 3′-hydroxymethyl group probably participating[56] to give the observed stereospecificity. A NOESY experiment corroborated the stereochemistry of analogue **45** (as shown in Figure 2.). Strong interactions were seen between H-1′ and the two H-6′ while the H-1′/H-2′ interaction was weak and both the H-1′/H-4′ and H-1′/H-3′ interactions were practically absent. Moreover, H-4′ exhibited strong interactions with H-2′ and H-3′ as well as medium interactions with the protons at C-5′. The three large to medium coupling constants (10.8, 9.2 and 7.6 Hz) for H-4′ together with the size of the coupling constants for H-1′ (9.0, 6.7 and 2.9 Hz) indicates that an envelope conformation with the adenine substituent in a pseudoequatorial position is

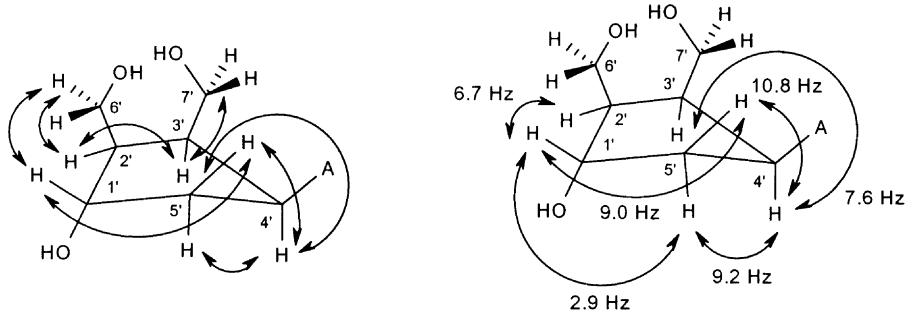
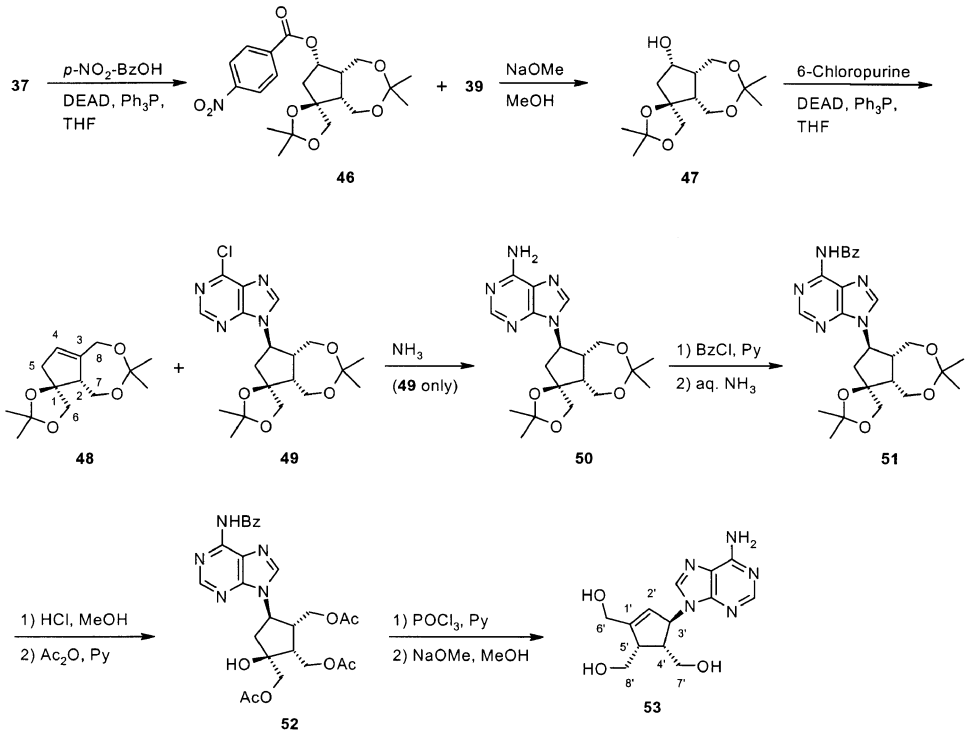


Figure 2. Correlations (left) obtained for compound **45** from a NOESY experiment (in CD_3OD, 400 MHz). Selected coupling constants pointing to an envelope conformation.

predominating (Figure 2.). To our knowledge, only one compound of closely related structure has been reported so far, namely the 6′--hydroxymethyl carbocyclic thymidine, which was studied for its effect on the stability of DNA/RNA duplexes[57].

Finally, the synthesis of a bis(hydroxymethyl)-analogue (**53**) of neplanocin A (**3**) was undertaken (Scheme 2.). The protected cyclopentanol **37** from above was subjected to Mitsunobu inversion using **4**-nitrobenzoic acid



Scheme 2. Synthesis of a bis(hydroxymethyl)-analogue of neplanocin A.

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as nucleophile, and this yielded the expected 4-nitrobenzoate **46** together with the elimination product **39** (83% and 14%, respectively). Deacylation of **46** followed by introduction of the purine moiety via a Mitsunobu coupling with 6-chloropurine resulted only in a low yield (approx. 15%) of the desired product (**49**) while the main product (59%) was an olefin (**48**). Ammonolysis of the slightly impure 6-chloropurine derivative (**49**) afforded the crystalline adenine compound (**50**), which subsequently was N^6-benzoylated[58] to give **51**. Acid hydrolysis followed by acetylation furnished triacetate **52**. Dehydration of the tertiary alcohol in triacetate **52** was accomplished with phosphorus oxychloride. Only one elimination product was obtained, and this was deprotected with methanolic sodium methoxide at slightly elevated temperature for 5 hours (a long reaction time[59] and the necessity for heating[60] have been reported for N^6-debenzoylation) to give neplanocin A analogue **53**. The analogues **44** and **45** as well as cyclopentene **53** have been submitted to biological evaluation, which will be reported in due course.

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EXPERIMENTAL SECTION

General Experimental Procedures. PPTS (pyridinium ***p***-toluenesulphonate) and DEAD (diethyl azodicarboxylat) were purchased from Aldrich Chemical Co.; 2,2-DMP (2,2-dimethoxypropane), $POCl_3$, $NaIO_4$, BzCl, and 6-chloropurine were from Fluka Chemie AG, while Ph_3P was from Merck. Acetone was distilled and then stirred with $CaCl_2$, filtered, and stored over 3Å molecular sieves. THF was freshly distilled from Na. All concentrations were performed ***in vacuo***. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the Microanalytical Department at the H. C. Ørsted Institute (University of Copenhagen). Melting points are uncorrected. TLC was performed on Merck Si gel 60 F_{254} aluminum sheets with detection by charring with H_2SO_4 or by UV light when applicable. MPLC was performed on Merck Lobar Lichroprep RP_{18} columns (size B or C). Vacuum liquid chromatography (VLC) was performed on predried (120°C; > 24 h) Merck Si gel 60H; the column size is given as height × diameter (cm). NMR spectra were recorded on Varian Inova 500 and Mercury 300 or Bruker Avance 400 spectrometers. Chemical shifts are given in ppm, using the solvent peaks as internal standards (D_2O : $\delta_H = 4.75$, CD_3OD : $\delta_H = 3.31$, $\delta_C = 49.0$, DMSO-d_6 : $\delta_H = 2.50$, $\delta_C = 39.5$, $CDCl_3$: $\delta_H = 7.27$, $\delta_C = 77.0$). Coupling constants (***J***-values) are given in hertz (Hz). The subscripts a and b indicate the low field and high field protons, respectively, in methylene groups. Primes (′) are used to denote the cyclopentanoid moities of the nucleoside analogues. For all compounds, ^{1}H NMR signals were assigned by COSY experiments, while ^{13}C NMR signals were assigned from HSQC and HMBC spectra. HRFAB-MS were recorded on a JEOL JMS-AX505W instrument using a bis(hydroxyethyl)disulfide

matrix. Carbocyclic nucleoside analogues were tested against HIV and HSV-1 at the Department of Virology, The Danish Serum Institute, Copenhagen[61–63].

(1*S*,3*R*,4*S*,5*R*)-1,6:7,8-bis-*O*-Isopropylidene-1,4,5-tris-hydroxymethyl-cyclopentane-1,3-diol (37). Acetonide **36**[54] (4.47 g, 19.3 mmol) was treated with 2,2-DMP (2.36 mL, 19.3 mmol) in dry acetone (130 mL) in the presence of anhydrous $CuSO_4$ (2.36 g) and PPTS (0.236 g). After 1 h at room temperature, Et_3N (4 mL) was added, and the volume was reduced to ca. 50 mL, which was mixed with silica gel 60 (17 g, 0.040–0.063 mm) and more Et_3N (1 mL) was added. The solvent was evaporated *in vacuo*, and then the resulting silica gel was loaded onto a VLC column (7 × 7 cm). Gradient elution with hexane, and then hexane–Me_2CO (10:1 to 4:1) yielded diacetonide **37** (4.30 g, 82%): mp 84–85° (hexane–Me_2CO); $[\alpha]^{21}{}_D$ − 3.0° (*c* 0.73, MeOH); ^{1}H NMR (CD_3OD, 500 MHz): δ 4.14 (1H, d, *J* = 9.0 Hz, H-6a), 4.11 (1H, dt, *J* = 8.1, 2 × 5.5 Hz, H-3), 3.79 (1H, dd, *J* = 12.4, 3.4 Hz, H-7a), 3.69 (1H, d, *J* = 9.0 Hz, H-6b), 3.66 (1H, dd, *J* = 12.4, 4.5 Hz, H-8a), 3.62 (2H, m, H-7b and H-8b), 2.29 (1H, br dt, *J* = 2 × 7.5, 4.5 Hz, H-5), 2.26 (1H, dd, *J* = 14.5, 8.1 Hz, H-2a), 2.19 (1H, m, H-4), 1.84 (1H, br dd, J = 14.5, 5.5 Hz, H-2b), 1.37, 1.35, 1.32, 1.27 (each 3H, s, 2 × (**CH$_3$**)$_2$C<); ^{13}C NMR (CD_3OD, 75 MHz): δ 109.3, 102.7 (2 × (**CH**$_3$)$_2$**C** <), 88.8 (C-1), 71.4 (C-3), 70.6 (C-6), 61.5 (C-7), 60.4 (C-8), 52.0 (C-4), 51.6 (C-5), 47.1 (C-2), 27.3, 27.0, 25.3, 24,5 (2 × (**C**H$_{3<}$)$_2$C <); *anal.* C 61.57%, H 9.07%, calcd for $C_{14}H_{24}O_5$ (Mw 272.34), C 61.74%, H 8.88%.

(1*S*, 2*R*, 3*R*, 4*S*)-1,6:7,8-bis-*O*-Isopropylidene-4-(6-chloro-purin-9-yl)-1,2, 3-tris-hydroxymethyl-cyclopentanol (38). To a solution of cyclopentanol **37** (1.28 g, 4.70 mmol), $Ph_3$3P (2.47 g, 2 × 4.70 mmol) and 6-chloropurine (1.45 g, 2 × 4.70 mmol) in dry THF (20 mL) was slowly added a solution of DEAD (1.42 mL, 1.95 × 4.70 mmol) in dry THF (5 mL). The mixture was kept at room temperature for 17 h, when the reaction mixture was concentrated. The residue was dissolved in CH_2Cl_2 (15 mL) and loaded onto a VLC column (5 × 5 cm). Gradient elution with hexane and then hexane-Me_2CO (50:1 to 8:1) yielded impure fractions of **39** (0.73 g) and **38** (1.15 g), which were purified by repeated VLC to give almost pure **39** (hexane–Me_2CO 100:1, 0.56 g, 47%, see below for characterization) and **38** (hexane–Me_2CO 10:1, 0.87 g, 45%). Diacetonide **38**: mp 153–154 °C (hexane–Me_2CO); $[\alpha]^{21}{}_D$ − 60.5° (*c* 0.65, MeOH); ^{1}H NMR (CD_3OD, 500 MHz): δ 8.74 (1H, s, H-2), 8.68 (1H, br s, H-8), 5.36 (1H, dt, *J* = 11.8, 2 × 8.1 Hz, H-4′), 4.39, 4.04 (each 1H, d, *J* = 9.0 Hz, 2 × H-6′), 3.97 (1H, dd, *J* = 13.0, 6.8 Hz, H-7a′), 3.89 (1H, dd, *J* = 13.0, 3.8 Hz, H-7b′), 3.42 (1H, dd, *J* = 12.8, 6.8 Hz, H-8a′), 3.33 (1H, br d, *J* = 12.8 Hz, H-8b′), 3.08 (1H, dd, *J* = 13.5, 11.8 Hz, H-5a′), 2.95 (1H, m, H-3′), 2.52 (1H, dd, *J* = 13.5, 8.1 Hz, H-5b′), 2.45 (1H, dt, *J* = 2 × 6.8, 3.8 Hz, H-2′), 1.42, 1.39 (each 3H, s, (**CH$_3$**)$_2$C<), 1.20 (6H, s,

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($C\mathbf{H_3})_2C<$); ^{13}C NMR (CD_3OD, 75 MHz): δ 153.9 (C-6), 152.8 (C-2), 151.1 (C-4), 147.8 (C-8), 132.5 (C-5), 109.9, 103.0 ($2 \times (CH_3)_2\mathbf{C}<$), 88.0 (C-1′), 71.0 (C-6′), 60.8 (C-7′), 60.4 (C-8′), 56.6 (C-4′), 52.8 (C-2′), 46.2 (C-3′), 41.2 (C-5′), 27.2, 27.1, 25.4, 23.9 ($2 \times (CH_3)_2C<$); *anal.* C 55.92%, H 6.03%, N 13.70% calcd for $C_{19}H_{25}N_4O_4Cl$ (Mw 408.89), C 55.81%, H 6.16%, N 13.70%.

(1*S*, 4*S*, 5*R*)-1,6:7,8-bis-*O*-Isopropylidene-1,4,5-tris-hydroxymethyl-cyclopent-2-enol (39). To cyclopentanol **37** (0.65 g, 2.39 mmol), Ph_3P (1.59 g, 2×2.39 mmol; polymer-bound, Aldrich, 3 mmol P/g resin) in dry THF (20 mL) was added DEAD (0.41 mL, 1.1×2.39 mmol) in THF (5 mL). After 24 h more DEAD (0.20 mL) was added, and the mixture was kept at room temperature for an additional 4 days. Then EtOAc (150 mL) was added and the resin subsequently filtered off on a bed of Na_2SO_4. Concentration yielded a residue, which was purified on a VLC column (5×5 cm). Elution with hexane and then hexane–Me_2CO (100:1) gave **39** (0.45 g, 74%): mp 36 – 37 °C (hexane–Me_2CO); $[\alpha]^{21}{}_D$ +105° (*c* 0.84, MeOH); ^1H NMR (CD_3OD, 500 MHz): δ 5.83 (2H, s, H-2 and H-3), 4.53 (1H, d, $J = 9.0$ Hz, H-6a), 4.00 (1H, dd, $J = 13.2$, 3.4 Hz, H-8a), 3.88 (1H, dd, $J = 13.2$, 2.4 Hz, H-8b), 3.73 (1H, d, $J = 9.0$ Hz, H-6b), 3.58 (1H, dd, $J = 12.4$, 4.7 Hz, H-7a), 3.33 (1H, dd, $J = 12.4$, 11.1 Hz, H-7b), 2.93 (1H, ddd, $J = 11.1$, 7.6, 4.7 Hz, H-4), 2.28 (1H, br dt, $J = 7.6, 2 \times 2.8$ Hz, H-5), 1.40, 1.38, 1.34, 1.26 (each 3H, s, $2 \times (C\mathbf{H_3})_2C<$); ^{13}C NMR (CD_3OD, 75 MHz): δ 137.7 (C-2), 134.3 (C-3), 108.8, 103.1 ($2 \times (CH_3)_2\mathbf{C}<$), 93.7 (C-1), 71.2 (C-6), 64.9 (C-7), 59.2 (C-8), 51.6 (C-5), 49.6 (C-4), 27.1, 26.5, 25.3, 24.2 ($2 \times (\mathbf{C}H_3)_2C<$); *anal.* C 65.79%, H 9.00%, calcd for $C_{14}H_{22}O_4$ (Mw 254.32), C 66.12%, H 8.72%.

(1*S*, 2*R*, 3*R*, 4*S*)-6,7,8-Tri-*O*-acetyl-4-(6-chloro-purin-9-yl)-1,2,3-tris-hydroxymethyl-cyclopentanol (40) and (1*S*, 2*R*, 3*R*, 4*S*)-6,7,8-tri-*O*-acetyl-4-(6-methoxy-purin-9-yl)-1,2,3-tris-hydroxymethyl-cyclopentanol (41). Diacetonide **38** (0.79 g) was dissolved in MeOH (35 mL), and aqueous 12M HCl (0.5 mL) was added slowly. After the mixture was stirred at room temperature for 3 h, more 12M HCl (0.25′ mL) was added. Upon a further 3 h, pyridine (2 mL) was added to the reaction mixture, and after concentration *in vacuo*, the residue was dried on an oil-pump for 0.5 h. The residue was dissolved in pyridine–CH_2Cl_2 (1:1, 30 mL), and upon cooling of the mixture to 0°C, Ac_2O (15 mL) was added. After 3 h, excess Ac_2O was quenched with ice (10 g). Then EtOAc (150 mL) was added, and the organic layer was separated and subsequently washed with saturated aqueous $NaHCO_2$ (3×25 mL). Each of the washings was extracted back with EtOAc (2×50 mL). The combined EtOAc phases were dried (Na_2SO_4) and then concentrated. The residue was purified on a VLC column (4×4 cm). Gradient elution with hexane and then hexane–Me_2CO (4:1 to 2:1) afforded **40** (0.66 g, 75%) followed by **41** (0.13 g, 15%). Triacetate **40**: white foam, $[\alpha]^{24}{}_D$ – 30.5° (*c* 0.90, MeOH); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.76 (1H, s,

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H-2), 8.14 (1H, s, H-8), 5.46 (1H, ddd, $J = 11.5$, 8.5, 7.8 Hz, H-4′), 4.44 (1H, dd, $J = 12.0$, 7.2 Hz, H-7a′), 4.41 (1H, dd, $J = 12.0$, 7.0 Hz, H-7b′), 4.39, 4.31 (each 1H, d, $J = 11.5$ Hz, 2 × H-6′), 4.02 (1H, dd, $J = 12.0$, 5.0 Hz, H-8a′), 3.76 (1H, dd, $J = 12.0$, 8.5 Hz, H-8b′), 3.42 (1H, dq, $J = 3 \times 8.5$, 5.0 Hz, H-3′), 3.05 (1H, dd, $J = 13.3$, 11.5 Hz, H-5a′), 2.76 (1H, q-like, $J = 7.3$ Hz, H-2′), 2.53 (1H, br s, 1′-OH), 2.38 (1H, dd, $J = 13.3$, 7.8 Hz, H-5b′), 2.18, 2.11, 1.74 (each 3H, s, 3 × OCOC**H$_3$**); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.8, 170.4, 169.8, (3 × **C**OCH$_3$), 152.3 (C-6), 151.7 (C-2), 151.3 (C-4), 144.9 (C-8), 131.9 (C-5), 78.9 (C-1′), 67.8 (C-6′), 60.9 (C-7′), 60.6 (C-8′), 55.6 (C-4′), 49.3 (C-2′), 41.9 (C-3′), 39.3 (C-5′), 20.9, 20.8, 20.3 (3 × CO**C**H$_3$); *anal.* C 49.89%, H 5.11%, N 12.10% calcd for $C_{19}H_{23}N_4O_7Cl$ (Mw 454.87), C 50.17%, H 5.10%, N 12.32%. 6-methoxypurin-9-yl derivative **41**: white foam, $[\alpha]^{25}_{D} - 36.5°$ (*c* 0.59, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.55 (1H, s, H-2), 8.05 (1H, br s, H-8), 4.21 (3H, s, 6-OCH$_3$), 5.43 (1H, ddd, $J = 11.5$, 8.5, 8.0 Hz, H-4′), 4.47, 4.42 (each 1H, dd, $J = 11.9$, 7.3 Hz, 2 × H-7′), 4.39, 4.31 (each 1H, d, $J = 11.5$ Hz, 2 × H-6′), 3.98 (1H, dd, $J = 12.0$, 5.5 Hz, H-8a′), 3.78 (1H, dd, $J = 12.0$, 8.5 Hz, H-8b′), 3.41 (1H, dq, $J = 3 \times 8.5$, 5.5 Hz, H-3′), 3.06 (1H, dd, $J = 13.2$, 11.5 Hz, H-5a′), 2.75 (1H, q-like, $J = 7.3$ Hz, H-2′), 2.62 (1H, br s, 1′-OH), 2.36 (1H, dd, $J = 13.2$, 8.0 Hz, H-5b′), 2.17, 2.10, 1.77 (each 3H, s, 3 × OCOC**H$_3$**); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.8, 170.4, 169.9 (3 × **C**OCH$_3$), 161.1 (C-6), 152.4 (C-4), 152.0 (C-2), 141.8 (C-8), 121.8 (C-5), 54.3 (6-O**C**H$_3$), 79.0 (C-1′), 67.9 (C-6′), 61.1 (C-7′), 60.7 (C-8′), 55.3 (C-4′), 49.3 (C-2′), 41.9 (C-3′), 39.4 (C-5′), 20.9, 20.8, 20.4 (3 × CO**C**H$_3$); *anal.* C 53.17%, H 5.76%, N 12.36% calcd for $C_{20}H_{26}N_4O_8$ (Mw 450.45), C 53.33%, H 5.82%, N 12.44%.

(3*S*, 4*R*, 5*S*)-3-(6-Amino-purin-9-yl)-4,5-bis-hydroxymethyl-cyclopent-1-enyl]-methanol (42). Triacetate **40** (0.66 g, 1.45 mmol) was dissolved in dry CH_2Cl_2 (20 mL), and upon cooling to 0°C, pyridine (4 mL) followed by a solution of $POCl_2$ (1.33 mL in 4 mL CH_2Cl_2) were added. After 48 h at room temperature, EtOAc (150 mL) was added. Excess $POCl_3$ was quenched by a slow addition of saturated aqueous $NaHCO_3$ (15 mL) under cooling to 0°C. Then H_2O (10 mL) was added, and the organic layer was separated and subsequently washed with more H_2O (10 mL) and dried (Na_2SO_4). Concentration of the EtOAc phase yielded a residue that was dissolved in CH_2Cl_2 (3 mL) and loaded onto a VLC column (3 × 3 cm). Elution with hexane and then hexane−Me_2CO (10:1 to 2:1) gave a slightly impure mixture of elimination products (0.39 g, 61%; HRES-MS$^+$ $[M+H]^+$ 437.1265, calcd for $C_{19}H_{22}N_4O_6Cl$ 437.1228) followed by recovered **40** (85 mg, 13%). An aliquot of the elimination products (0.28 g) was dissolved in THF (2 mL), and then liquid NH_3 (20 mL) was added. This solution was placed in a tube in a sealed steel vessel and was heated to 60°C for 5 days. After evaporation of the solvents, the resulting residue was purified on an RP-18 column (size B), which was eluted with H_2O−MeOH mixtures (1:0 to 5:1). This afforded a

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5:1-mixture of cyclopentene triols **42** and **43** (0.17 g, 91%); HRFAB-MS$^+$ $[M+H]^+$ 292.1380, calcd for $C_{13}H_{18}N_5O_3$ 292.1409. Repeated rechromatography (H_2O-MeOH 7:1) afforded a pure sample of **42**: white hygroscopic foam, $[\alpha]^{20}_D$ $-33.4°$(*c* 0.50, MeOH); ^{1}H NMR (d_6-DMSO, 500 MHz): δ 8.16 (1H, s, H-8), 8.14 (1H, s, H-2), 7.17 (2H, br s, 6-NH_2), 5.74 (1H, br s, H-2′), 5.55 (1H, br d, $J = 7.7$ Hz, H-3′), 4.93 (1H, t, $J = 5.0$ Hz, 6′-OH), 4.78 (1H, t, $J = 4.5$ Hz, 8′-OH), 4.51 (1H, t, $J = 5.0$ Hz, 7′-OH), 4.28, 4.14 (each 1H, dd, $J = 15.0$, 5.0 Hz, 2 × H-6′), 3.66, 3.61 (each 1H, dt, $J = 11.1$, 2 × 4.5 Hz, 2 × H-8′), 3.28, 3.14 (each 1H, m, 2 × H-7′), 2.89 (1H, m, H-4′), 2.82 (1H, m, H-5′); ^{13}C NMR (d6-DMSO, 75 MHz): δ 155.9 (C-6), 152.1 (C-2), 150.0 (C-4), 139.8 (C-8), 118.4 (C-5), 154.2 (C-1′), 121.4 (C-2′), 59.2 (C-6′), 59.0 (C-8′), 58.4 (C-3′), 57.7 (C-7′), 48.1 (C-5′), 46.4 (C-4′); *anal.* C 52.14%, H 5.92%, N 23.35% calcd for $C_{13}H_{17}N_5O_3 \cdot 1/2H_2O$ (Mw 291.31), C 51.99%, H 6.04%, N 23.32%. [(3′*R*,4′*S*)-4-(6-Amino-purin-9-yl)-2′,3′-bis-hydroxymethyl-cyclopent-1′-enyl]-methanol (**43**): ^{1}H NMR (d_6-DMSO, 500 MHz): δ 8.14 (1H, s, H-2), 8.06 (1H, s, H-8), 7.16 (2H, br s, 6-NH_2), 5.15 (1H, q-like, $J = 7.6$ Hz, H-4′), 4.72 (1H, t, $J = 5.2$ Hz, 6′-OH), 4.68 (1H, t, $J = 5.3$ Hz, 7′-OH), 4.34 (1H, t, $J = 4.5$ Hz, 8′-OH), 4.20-4.00 (4H, m, 2 × H-6′ and 2 × H-7′), 3.22-3.14 (2H, m, 2 × H-8′), 3.20 (1H, obsc., H-3′), 3.11 (1H, br dd, $J = 15.8$, 8.0 Hz, H-5a′), 2.86 (1H, dd, $J = 15.8$, 8.0 Hz, H-5b′); ^{13}C NMR (d_6-DMSO, 75 MHz): δ 155.9 (C-6), 152.0 (C-2), 149.6 (C-4), 140.4 (C-8), 118.6 (C-5), 137.8 (C-2′), 136.2 (C-1′), 58.7 (C-8′), 56.7 (C-6′), 55,7 (C-7′), 53.9 (C-4′), 51.4 (C-3′), 37.9 (C-5′).

(1*S*, 2*R*, 3*R*, 4*S*)-4-(6-Amino-purin-9-yl)-1,2,3-tris-hydroxymethyl-cyclopentanol (44). Diacetonide **38** (0.80 g) was treated with NH_3–THF (10:1, 22 mL) in a steel vessel at 60°C for 48 h. The solvents were allowed to evaporate, and the residue was then dissolved in MeOH (40 mL) with 12M aqueous HCl (0.6 mL) and stirred for 12 h at 4 °C. The mixture was allowed to warm to room temperature when more 12M aqueous HCl (0.5 mL) and H_2O (10 mL) were added. After an additional 3 h, the mixture was neutralized with aqueous saturated $NaHCO_3$. The MeOH was removed *in vacuo*, and the residual aqueous solution was then applied to an RP-18 column (size C). Gradient elution with H_2O–MeOH mixtures (1:0 to 8:1) yielded tetrol **44** (0.51 g, 84%). An analytical sample was obtained upon VLC with $CHCl_3$–MeOH mixtures: white foam, $[\alpha]^{21}_D$ $-34.9°$ (*c* 0.41, MeOH); ^{1}H NMR (d_6-DMSO, 500 MHz): δ 8.19 (1H, s, H-2), 8.11 1H, s, H-8), 7.12 (2H, br s, 6-NH2), 5.20 (1H, ddd, $J = 11.5$, 8.5, 8.0 Hz, H-4′), 4.75 (1H, t, $J = 5.0$ Hz, 6′-OH), 4.66 (1H, t, $J = 5.5$ Hz, 7′-OH), 4.34 (1H, t, $J = 5.0$ Hz, 8′-OH), 3.76, 3.70 (each 1H, dt, $J = 10.9$, 5.0 Hz, 2 × H-6′), 3.57 (2H, m, 2 × H-7′), 3.20 (1H, ddd, $J = 11.0$, 7.7, 5.0 Hz, H-8a′), 3.06 (1H, dt, $J = 11.0$, 2 × 5.0 Hz, H-8b′), 2.81 (1H, m, H-3′), 2.65 (1H, dd, $J = 12.8$, 11.5 Hz, H-5a′), 2.22 (1H, dt, $J = 7.7$, 2 × 6.0 Hz, H-2′), 1.96 (1H, dd, $J = 12.8$, 8.0 Hz, H-5b′); ^{13}C NMR (d_6-DMSO, 75 MHz): δ 155.9 (C-6), 152.1 (C-2), 150.1

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(C-4), 140.1 (C-8), 119.0 (C-5), 79.8 (C-1′), 65.4 (C-6′), 57.7 (C-7′), 57.5 (C-8′), 53.5 (C-4′), 52.0 (C-2′), 44.4 (C-3′), 40.9 (C-5′); HRFAB-MS$^+$ $[M+H]^+$ 310.1468, calcd for $C_{13}H_{20}N_5O_4$ 310.1515.

(1*S*, 2*R*, 3*R*, 4*S*)-4-(6-Amino-purin-9-yl)-2,3-bis-hydroxymethyl-cyclopentanol (45). Tetrol **44** (158 mg, 0.511 mmol) was treated with $NaIO_4$ (118 mg, 0.552 mmol) in H_2O (10 mL) at 0°C for 0.5 h. This reaction mixture was then added to a suspension of $NaBH(OAc)_3$ (1.015 g, 4.79 mmol) in MeCN (50 mL) at 0°C. After 1 h, the cooling bath was removed, and after an additional 2 h the reaction mixture was concentrated with MeOH twice. The residue was dissolved in EtOH–MeOH–Et_3N (4:4:1, 9 mL) and loaded onto a VLC column (4 × 4 cm). Elution with hexane, $CHCl_3$, and then with $CHCl_3$–MeOH (10:1 to 3:1) yielded impure **45** (227 mg), which was chromatographed on an RP-18 column (size B); elution with H_2O–MeOH (1:0, 10:1 to 5:1) afforded triol **45** (110 mg, 77%): white hygroscopic foam; $[\alpha]^{21}{}_D - 35.2°$ (*c* 0.64, MeOH); ^{1}H NMR (d_4-methanol, 400 MHz): δ 8.28 (1H, s, H-2), 8.20 (1H, s, H-8), 5.32 (1H, ddd, $J = 10.8$, 9.2, 7.6 Hz, H-4′), 4.37 (1H, ddd, $J = 9.0$, 6.7, 2.9 Hz, H-1′), 3.92 (1H, dd, $J = 10.8$, 5.3 Hz, H-6a′), 3.87 (1H, dd, $J = 10.8$, 7.9 Hz, H-6b′), 3.53, 3.18 (each 1H, dd, $J = 11.7$, 4.1 Hz, 2 × H-7′), 3.02 (1H, ddd, $J = 13.4$, 10.8, 9.0 Hz, H-5a′), 2.74 (1H, m, H-3′), 2.38 (1H, m, H-2′), 2.14 (1H, ddd, $J = 13.4$, 9.2, 2.9 Hz, H-5b′); ^{1}H NMR (d_6-DMSO, 500 MHz): δ 8.16 (1H, s, H-2), 8.11 (1H, s, H-8), 7.15 (2H, br s, 6-NH_2), 5.14 (1H, br q-like, $J = 9.4$ Hz, H-4′), 4.75 (1H, t, $J = 5.1$ Hz, 1′-OH), 4.56 (1H, t, $J = 4.5$ Hz, 7′-OH), 4.54 (1H, t, $J = 4.5$ Hz, 6′-OH), 4.12 (1H, m, H-1′), 3.67 (2H, m, 2 × H-6′), 3.26, 3.02 (each 1H, dt, $J = 11.1$, 2 × 4.5 Hz, 2 × H-7′), 2.81 (1H, ddd, $J = 12.8$, 10.7, 8.1 Hz, H-5a′), 2.56 (1H, m, H-3′), 2.18 (1H, m, H-2′), 1.95 (1H, ddd, $J = 12.8$, 9.0, 2.6 Hz, H-5b′); ^{13}C NMR (d_6-DMSO, 75 MHz): δ155.8 (C-6), 152.0 (C-2), 149.8 (C-4), 140.0 (C-8), 118.7 (C-5), 70.7 (C-1′), 59.7 (C-6′), 56.9 (C-7′), 54.5 (C-4′), 52.4 (C-2′), 44.4 (C-3′), 38.4 (C-5′); HRFAB-MS$^+$ $[M+H]^+$ 280.1427, calcd for $C_{12}H_{18}N_5O_3$ 280.1409; *anal.* C 48.28%, H 6.31%, N 23.38% calcd for $C_{12}H_{17}N_5O_3{\cdot}H_2O$ (Mw 279.30), C 48.48%, H 6.44%, N 23.56%.

(1*S*, 3*S*, 4*S*, 5*R*)-1,6:7,8-bis-*O*-Isopropylidene-3-*O*-(4′-nitrobenzoyl)-1,4,5-tris-hydroxymethyl-cyclopentane-1,3-diol (46). Diacetonide **37** (3.39 g, 12.45 mmol), Ph_3P (4.89 g, 1.5 × 12.45 mmol) and *p*-NO_2-BzOH (3.12 g, 1.5 × 12.45 mmol) were dissolved in dry THF (100 mL), and then DEAD (2.74 mL, 1.4 × 12.45 mmol) in THF (5 mL) was added dropwise to the ice-cooled mixture. After 0.5 h, the cooling bath was removed, and the mixture was stirred for an additional 17 h at room temperature. The mixture was concentrated, and the residue was dissolved in CH_2Cl_2 (20 mL) and loaded onto a VLC column (7 × 7 cm). Elution with hexane and then hexane–Me_2CO (150:1 to 20:1) afforded successively cyclopentene **39** (0.44 g,

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14%) and **46** (4.34 g, 83%). Ester **46**: white foam; $[\alpha]^{21}{}_{D} \sim 0°$ (*c* 1.2, MeOH); ^{1}H NMR (CD_3OD, 500 MHz): δ 5.60 (1H, br q-like, $J = 7.3$ Hz, H-3), 4.41, 3.91 (each 1H, d, $J = 9.0$ Hz, 2 × H-6), 3.92 – 3.85 (3H, m, H-7a and 2 × H-8), 3.81 (1H, dd, $J = 12.8$, 4.0 Hz, H-7b), 2.69 (1H, dq-like, $J = 3 \times 7.5$, 4.0 Hz, H-4), 2.47 (1H, dd, $J = 14.5$, 7.7 Hz, H-2a), 2.30 (1H, m, H-5), 2.13 (1H, dd, $J = 14.5$, 7.0 Hz, H-2b), 1.38, 1.37, 1.30, 1.23 (each 3H, s, 2 × (C**H$_3$**)$_2$C<), 8.32, 8.24 (each 2H, br d, $J = 9.0$ Hz, *p*-NO_2-**Ph**-CO); ^{13}C NMR (CD_3OD, 75 MHz): δ 165.7 (*p*-NO_2-Ph-**C**O), 152.0, 136.9, 131.8, 124.6 (*p*-NO_2-**Ph**-CO), 109.4, 102.9 (2 × $(CH_3)_2$**C**<), 88.1 (C-1), 76.8 (C-3), 71.6 (C-6), 60.7 (C-8), 60.6 (C-7), 51.9 (C-5), **46.4** (C-4), 44.9 (C-2), 27.1, 27.0, 25.4, 24.2 (2 × (**C**H_3)$_2$C<); *anal.* C 59.89%, H 6.41%, N 3.35% calcd for $C_{21}H_{27}NO_8$ (Mw 421.45), C 59.85%, H 6.46%, N 3.32%.

(1*S*, 3*S*, 4*S*, 5*R*)-1,6:7,8-bis-*O*-Isopropylidene-1,4,5-tris-hydroxymethyl-cyclopentane-1,3-diol (47). The ester **46** (4.11 g, 9.75 mmol) was dissolved in MeOH (100 mL) and 1M methanolic NaOMe (3 mL) was added. After 1 h at room temperature, the mixture was neutralized with HOAc (0.15 mL) and then concentrated. The residue was dissolved in EtOAc (100 mL), and HOAc (50 μL) followed by Et_3N (2 mL) were added. The mixture was then washed with H_2O (25 mL), dried (Na_2SO_4) and concentrated. The residue was suspended in CH_2Cl_2 (30 mL) and loaded onto a VLC column (6 × 7 cm). Elution with hexane followed by hexane–Me_2CO (30:1 to 5:1) gave alcohol **47** (2.55 g, 96%): white foam; $[\alpha]^{21}{}_{D}$ +48.3° (*c* 0.60, MeOH); ^{1}H NMR (CD_3OD, 500 MHz): δ 4.44 (1H, d, $J = 9.0$ Hz, H-6a), 4.39 (1H, dt, $J = 8.5$, 2 × 7.3 Hz, H-3), 3.93, 3.85 (each 1H, dd, $J = 13.0$, 3.4 Hz, 2 × H-8), 3.83 (1H, d, $J = 9.0$ Hz, H-6b), 3.77 (1H, dd, $J = 12.8$, 5.4 Hz, H-7a), 3.73 (1H, dd, $J = 12.8$, 10.0 Hz, H-7b), 2.38 (1H, m, H-4), 2.16 (1H, dd, $J = 14.1$, 7.3 Hz, H-2a), 2.16 (1H, obsc., H-5), 1.85 (1H, dd, $J = 14.1$, 8.5 Hz, H-2b), 1.35, 1.34, 1.31, 1.30 (each 3H, s, 2 × (C**H$_3$**)$_2$C<); ^{13}C NMR (CD_3OD, 75 MHz): δ108.9, 102.9 (2 × $(CH_3)_2$**C** <), 88.3 (C-1), 72.6 (C-6), 72.1 (C-3), 61.1 (C-7), 60.3 (C-8), 51.7 (C-5), 48.0 (C-4), 47.3 (C-2), 27.2, 26.8, 25.3, 24.5 (2 × (**C**H_3)$_2$C<); *anal.* C 61.58%, H 8.86%, calcd for $C_{14}H_{24}O_5$ (Mw 272.34), C 61.74%, H 8.88%.

(1*S*, 2*R*, 3*R*, 4*R*)-1,6:7,8-bis-*O*-Isopropylidene-4-(6-amino-purin-9-yl)-1,2,3-tris-hydroxymethyl-cyclopentanol (50). To a solution of alcohol **47** (1.98 g, 7.27 mmol), Ph_3P (3.81 g, 2 × 7.27 mmol) and 6-chloropurine (2.25 g, 2 × 7.27 mmol) in dry THF (20 mL) was slowly added a solution of DEAD (2.17 mL, 1.9 × 7.27 mmol) in dry THF (5 mL). The mixture was kept at room temperature for 1.5 h and subsequently at 4 °C for 22 h, at which point the reaction mixture was concentrated. The residue was dissolved in CH_2Cl_2 (15 mL) and loaded onto a VLC column (6 × 5 cm). Gradient elution with hexane and then hexane–Me_2CO (50:1 to 8:1) yielded impure fractions of **48** (1.69 g) and **49** (0.88 g), which were purified by repeated VLC to give

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pure **48** (hexane–Me_2CO 100:1, 1.10 g, 59%), slightly impure **49** (hexane–Me_2CO 10:1, 0.51 g, 17%; still contaminated with a small amount of hydrazine diethyldicarboxylate), and recovered **47** (hexane–Me_2CO 10:1, 86 mg, 4%). (1*S*, 2*R*)-1,6:7,8-Bis-*O*-isopropylidene-1,2,3-tris-hydroxymethyl-cyclopent-3-enol (**48**): colorless syrup; $[\alpha]^{24}{}_D$+23.6° (*c* 1.1, MeOH); ^{1}H NMR (CD_3OD, 500 MHz): δ 5.48 (1H, m, H-4), 4.24 (1H, ddq, $J = 13.7$, 3.0, 3×1.5 Hz, H-8a), 4.02 (1H, d, $J = 9.0$ Hz, H-6a), 4.00 (1H, d, $J = 13.7$ Hz, H-8b), 3.81 (1H, dd, $J = 11.5$, 5.1 Hz, H-7a), 3.70 (1H, dd, $J = 11.5$, 10.7 Hz, H-7b), 3.70 (1H, d, $J = 9.0$ Hz, H-6b), 2.97 (1H, m, H-2), 2.63 (1H, ddt, $J = 16.4$, 3.8, 2×2.1 Hz, H-5a), 2.51 (1H, ddt, $J = 16.4$, 2.6, 2×1.3 Hz, H-5b), 1.37, 1.35, 1.34, 1.33 (each 3H, s, $2 \times (\mathbf{CH_3})_2C<$); ^{13}C NMR ($CD_3OD$, 75 MHz): δ 144.4 (C-3), 124.1 (C-4), 109.7, 103.6 ($2 \times (CH_3)_2\mathbf{C}<$), 90.4 (C-1), 71.6 (C-6), 62.2 (C-8), 61.8 (C-7), 56.3 (C-2), 45.5 (C-5), 27.1, 26.8, 25.2, 24.8 ($2 \times (\mathbf{C}H_3)_2C<$); *anal.* C 65.94%, H 8.99%, calcd for $C_{14}H_{22}O_4$ (Mw 254.32), C 66.12%, H 8.72%. Diacetonide **49**: ^{1}H NMR (CD_3OD, 500 MHz): δ 8.75 (1H, s, H-2), 8.74 (1H, s, H-8), 5.47 (1H, ddd, $J = 10.9$, 8.1, 4.3 Hz, H-4′), 4.20, (1H, d, $J = 9.4$ Hz, H-6a′), 3.95 (1H, dd, $J = 13.2$, 2.1 Hz, H-8a′), 3.90 (1H, d, $J = 9.4$ Hz, H-6b′), 3.72 (1H, dd, $J = 12.4$, 10.2, H-7a′), 3.64 (1H, br dd, $J = 12.4$, 4.5 Hz, H-7b′), 3.49 (1H, dd, $J = 13.2$, 3.8 Hz, H-8b′), 2.81 (1H, m, H-3′), 2.72 (1H, dd, $J = 14.9$, 10.9 Hz, H-5a′), 2.50 (1H, m, H-2′), 2.28 (1H, ddd, $J = 14.9$, 4.3, 1.7 Hz, H-5b′), 1.48, 1.45, 1.39, 1.33 (each 3H, s, $2 \times (\mathbf{CH_3})_2C<$); ^{13}C NMR ($CD_3OD$, 75 MHz): δ 153.5 (C-6), 152.9 (C-2), 151.2 (C-4), 147.1 (C-8), 132.1 (C-5), 110.5, 103.2 ($2 \times (CH_3)_2\mathbf{C}<$), 89.3 (C-1′), 69.3 (C-6′), 60.6 (C-7′), 60.5 (C-8′), 54.8 (C-4′), 53.4 (C-2′), 52.4 (C-3′), 44.1 (C-5′), 27.5, 26.9 25.2, 24.6 ($2 \times (\mathbf{C}H_3)_2C<$); FAB-MS$^+$ $[M+H]^+$ 409.16, calcd for $C_{19}H_{26}N_4O_4Cl$ 409.16. An aliquot of **49** (386 mg, 0.94 mmol) was treated with NH_3 (20 mL) in THF (5 mL) at 60°C for 3 days. The solvents were allowed to evaporate, and the residue was dissolved in EtOAc (10 mL) and loaded onto a VLC column (4×4 cm). Elution with hexane and then hexane–Me_2CO (3:1 to 1.5:1) afforded (adenin-9-yl)-derivative **50** (326 mg, 89%): mp 218–220°C (hexane–Me_2CO); $[\alpha]^{24}{}_D$ −23.9° (*c* 0.60, MeOH); ^{1}H NMR (CD_3OD, 500 MHz): (8.35 (1H, s, H-2), 8.21 (1H, s, H-8), 5.29 (1H, ddd, $J = 10.2$, 8.1, 4.3 Hz, H-4′), 4.18 (1H, d, $J = 9.4$ Hz, H-6a′), 3.94 (1H, dd, $J = 12.8$, 2.6 Hz, H-8a′), 3.88 (1H, d, $J = 9.4$ Hz, H-6b′), 3.71 (1H, dd, $J = 12.6$, 10.0 Hz, H-7a′), 3.63 (1H, dd, $J = 12.6$, 4.5 Hz, H-7b′), 3.47 (1H, dd, $J = 12.8$, 4.0, H-8b′), 2.77 (1H, m, H-3′), 2.67 (1H, dd, $J = 14.9$, 10.2 Hz, H-5a′), 2.47 (1H, m, H-2′), 2.18 (1H, ddd, $J = 14.9$, 4.3, 1.7 Hz, H-5b′), 1.45, 1.43, 1.37, 1.33 (each 3H, s, $2 \times (\mathbf{CH_3})_2C<$); ^{13}C NMR ($CD_3OD$, 75 MHz): δ 157.3 (C-6), 153.7 (C-2), 151.0 (C-4), 141.4 (C-8), 119.8 (C-5), 110.4, 103.1 ($2 \times (CH_3)_2\mathbf{C}<$), 89.3 (C-1′), 69.5 (C-6′), 60.6 (C-7′), 60.5 (C-8′), 53.9 (C-4′), 53.3 (C-2′), 52.2 (C-3′), 44.5 (C-5′), 27.5, 26.9, 25.2, 24.6 ($2 \times (\mathbf{C}H_3)_2C<$); *anal.* C 58.63%, H 6.99%, N 17.92% calcd for $C_{19}H_{27}N_5O_4$ (Mw 389.46), C 58.60%, H 6.99%, N 17.98%.

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(1*S*, 2*R*, 3*R*, 4*R*)-6,7,8-Tri-*O*-acetyl-4-(6-benzamido-purin-9-yl)-1,2,3-tris-hydroxymethyl-cyclopentanol (52). (Adenin-9-yl)-derivative **50** (205 mg, 0526 mmol) was dissolved in pyridine (3 mL), and upon cooling to 0°C, BzCl (125 μL, 2 × 0526 mmol) in pyridine (0.5 mL) was added dropwise. After 0.5 h at 0°C the cooling bath was removed. Upon an additional 1.5 h the mixture was cooled to 0°C, and then H_2O (0.5 mL) was added. After a further 5 min, 25% aqueous ammonia (1 mL) was added. The mixture was then stirred for 0.5 h at 0°C followed by 15 min at room temperature, when EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (50 mL) were added. The organic layer was washed with H_2O (2 × 25 mL), dried (Na_2SO_4) and concentrated with toluene. The residue was dissolved in CH_2Cl_2 (4 mL) and loaded onto a VLC column (4 × 3 cm). Elution with hexane, and then with hexane−Me_2CO (5:1 to 3:1) gave an impure fraction of **51** (237 mg), which was rechromatographed to give almost pure **51** (205 mg, 79%): ^{1}H NMR (CD_3OD, 500 MHz): δ 8.72 (1H, s, H-2), 8.63 (1H, s, H-8), 8.09 (2H, br d, J = 7.3 Hz, NH-CO-**Ph**), 7.66 (1H, br t, J = 7.3 Hz, NH-CO-**Ph**), 7.57 (2H, br t, J = 7.3 Hz, NH-CO-**Ph**), 5.47 (1H, ddd, J = 10.7, 8.0, 4.0 Hz, H-4′), 4.20 (1H, d, J = 9.4 Hz, H-6a′), 3.97 (1H, dd, J = 13.0, 2.6 Hz, H-8a′), 3.91 (1H, d, J = 9.4 Hz, H-6b′), 3.74 (1H, dd, J = 12.6, 10.2 Hz, H-7a′), 3.65 (1H, dd, J = 12.6, 4.3 Hz, H-7b′), 3.51 (1H, dd, J = 13.0, 3.9 Hz, H-8b′), 2.81 (1H, m, H-3′), 2.73 (1H, dd, J = 15.4, 10.7 Hz, H-5a′), 2.50 (1H, m, H-2′), 2.27 (1H, ddd, J = 15.4, 4.0, 1.3 Hz, H-5b′), 1.48, 1.45, 1.40, 1.34 (each 3H, s, 2 × (C**H$_3$**)$_2$C<); ^{13}C NMR (CD_3OD, 75 MHz):δ 168.1 (Ph-**C**O-NH), 153.9 (C-4), 153.1 (C-2), 150.9 (C-6), 144.7 (C-8), 124.7 (C-5), 135.0, 133.8, 129.7, 129.4 (**Ph**-CO-NH), 110.4, 103.2 (2 × (CH$_3$)$_2$**C**<), 89.3 (C-1′), 69.4 (C-6′), 60.6 (C-7′), 60.5 (C-8′), 54.2 (C-4′), 53.4 (C-2′), 52.4 (C-3′), 44.2 (C-5′), 27.5, 26.9, 25.2, 24.6 (2 × (**C**H$_3$)$_2$C<); HRFAB-MS$^+$ [M+H]$^+$ 494.2420, calcd for $C_{26}H_{32}N_5O_5$ 494.2403. An aliquot of **51** (154 mg) was treated with 12M aqueous HCl (0.14 mL) in MeOH (7 mL) for 3 h at room temperature, when additional 12M aqueous HCl (0.14 mL) was added. After a further 3.5 h at room temperature, pyridine (1 mL) was added, and the mixture concentrated. The residue was dried on an oil-pump for 0.5 h, and then it was partially dissolved in pyridine−CH_2Cl_2 (3:2, 5 mL). After addition of Ac_2O (3 mL) the mixture was kept at room temperature for 2 h, when ice and saturated aqueous $NaHCO_3$ (25 g and 50 mL, respectively) were added. Then EtOAc (100 mL) was added, and the organic layer was washed with more saturated $NaHCO_3$ (25 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was subsequently concentrated with toluene and CH_2Cl_2. The residue (190 mg) was dissolved in CH_2Cl_2 (4 mL) and loaded onto a VLC column (3.5 × 3 cm). Elution with hexane, and then hexane−Me_2CO (4:1 to 1:1) afforded triacetate **52** (127 mg, 76%): $[\alpha]^{20}_D$ +7.9° (c 0.89, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.73 (1H, s, H-2), 8.24 (1H, s, H-8), 8.01 (2H, br d, J = 7.5 Hz, NH-CO-**Ph**), 7.59 (1H, br t, J = 7.5 Hz, NH-CO-**Ph**), 7.49 (2H, br t, J = 7.5 Hz, NH-CO-**Ph**), 4.94 (1H, ddd, J = 11.8, 9.6, 3.4 Hz,

H-4′), 4.37 (1H, d, $J = 11.6$ Hz, H-6a′), 4.22 (3H, m, H-7a and $2 \times$ H-8′), 4.11 (1H, d, $J = 11.6$ Hz, H-6b′), 4.10 (1H, dd, $J = 12.4$, 4.5 Hz, H-7b′), 3.50 (1H, m, H-3′), 2.72 (1H, dd, $J = 15.6$, 11.8 Hz, H-5a′), 2.68 (1H, m, H-2′), 2.33 (1H, ddd, $J = 15.6$, 3.4, 1.8 Hz, H-5b′), 2.14, 2.11, 1.81 (each 3H, s, $3 \times$ OCOC**H$_3$**); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9, 170.5, 170.0 ($3 \times CH_3$-**C**O), 164.8 (Ph-CO), 151.6 (C-2), 150.3 (C-4), 150.0 (C-6), 143.4 (C-8), 123.4 (C-5), 133.3, 132.9, 128.8, 127.9 (**Ph**-CO), 80.3 (C-1′), 67.3 (C-6′), 63.0 (C-8′), 61.0 (C-7′), 58.2 (C-4′), 49.3 (C-2′), 45.4 (C-3′), 42.0 (C-5′), 21.1, 20.8, 20.6 ($3 \times$ **C**H$_3$-CO); HRFAB-MS$^+$ [M+H]$^+$ 540.2048, calcd for $C_{26}H_{30}N_5O_8$ 540.2094.

[(3*R*, 4*R*, 5*S*)-3-(6-Amino-purin-9-yl)-4,5-bis-hydroxymethyl-cyclopent-1-enyl]-methanol (53). Triacetate **52** (92 mg, 0.171 mmol) was dissolved in dry CH_2Cl_2–pyridine (2:1, 6 mL). After cooling to 0 °C, $POCl_3$ (160 μL, 10×0.171 mmol) in dry CH_2Cl_2 (1 mL) was added, and the cooling bath removed. After 23 h at room temperature more $POCl_3$ (80 μL, 5×0.171 mmol) was added. The mixture was kept at room temperature for 2 days more when it was poured into ice–saturated aqueous $NaHCO_3$ (15 g and 30 mL, respectively) under stirring. The resulting mixture was extracted with EtOAc (2×50 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated. The residue was concentrated successively with toluene and CH_2Cl_2, and was then dissolved in CH_2Cl_2 (4 mL) and loaded onto a VLC column (3.5×3 cm). Elution with hexane and then with hexane-Me_2CO (5:1 to 3.5:1) gave almost pure elimination product (34 mg), which was treated with 0.1M NaOMe–MeOH (5 mL) for 3.5 h at room temperature followed by 1.5 h at 45°C. Then HOAc (50 μL) followed by Et_3N (50 μL) were added. The mixture was concentrated, and the residue was dissolved in saturated aqueous $NaHCO_3$ (3 mL) and loaded onto an RP-18 column (size B), which was eluted with H_2O–MeOH (1:0, 6:1 and 5:1) to give triol **53** (17 mg, 34%): white solid; $[\alpha]^{20}_D - 126°$ (*c* 0.53, MeOH); ^{1}H NMR (D_2O, 500 MHz): δ 8.06 (1H, s, H-8), 8.05 (1H, s, H-2), 5.79 (1H, br s, H-2′), 5.38 (1H, dm, $J = 8.1$ Hz, H-3′), 4.27, 4.23 (each 1H, br d, $J = 15.4$ Hz, $2 \times$ H-6′), 3.88 (1H, dd, $J = 11.5$, 7.9 Hz, H-7a′), 3.75 (2H, m, $2 \times$ H-8′), 3.73 (1H, dd, $J = 11.5$, 6.0 Hz, H-7b′), 3.07 (1H, m, H-5′), 2.74 (1H, dq-like, $J = 3 \times 8.0$, 6.0 Hz, H-4′); ^{13}C NMR (CD_3OD, 75 MHz): δ157.3 (C-6), 153.5 (C-2), 150.7 (C-4), 141.1 (C-8), 120.3 (C-5), 151.8 (C-1′), 125.9 (C-2′), 63.1 (C-3′), 61.1 (C-7′), 60.8 (C-6′ and C-8′), 54.0 (C-4′), 49.7 (C-5′); HRFAB-MS$^+$ [M+H]$^+$ 292.1388, calcd for $C_{13}H_{18}N_5O_3$ 292.1409.

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