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Synthesis of 4-Substituted Carbocyclic 2,3-Dideoxy-3-C-hydroxymethyl Nucleoside Analogues as Potential Anti-viral Agents

Johanna Wachtmeister, Anna Mühlman, Björn Classon and Bertil Samuelsson*#

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, S-106 91 Stockholm, Sweden.

#Address also: Astra Hässle AB, Medicinal Chemistry, S-431 83 Mölndal, Sweden.

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Abstract: The synthesis of two carbocyclic guanosine analogues with an electronegative fluoro or hydroxy substituent in the 4-position is described. The cyclopentanols **17a** and **18** were synthesized from enantiomerically pure 3S,4S-bis(hydroxymethyl)cyclopentanone ethylene glycol ketal (**7**) via a number of key steps involving stereospecific reduction of the keto function and a dihydroxylation of the C-4 methylene. Substitution of the tertiary C-4 hydroxyl group in **16** with fluorine using bis-(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor™) and coupling of the cyclopentanol-moiety with 2-amino-6-chloropurine using the Mitsunobu procedure gave compounds **3** and **4** which have been evaluated as potential anti-viral agents.

Keywords: nucleosides, reduction, hydroxylation, halogenation, Mitsunobu reaction

INTRODUCTION

Carbocyclic nucleoside analogues belong to a class of compounds that has attracted major interest in identifying effective drugs against human immunodeficiency virus (HIV) and other viruses.[1-4] One potential therapeutic advantage of carbocyclic nucleosides compared with the furanose nucleoside analogues is their increased metabolic stability to phosphorylase and hydrolase enzymes, which cleave the glycosidic linkage of nucleosides. We and others have previously described the synthesis and discovery of the potent broad spectrum anti-viral agent 2,3-dideoxy-3-*C*-hydroxymethyl cytidine (**1**) (Figure 1).[5-8] The carbocyclic guanosine analogue (**2**) was subsequently synthesized but notably showed no anti-viral activity.[9] In the present work the syntheses and anti-viral evaluation of C-3 hydroxymethyl substituted carbocyclic nucleoside analogues **3** and **4**, having a C-4 hydroxyl (**3**) or a C-4 fluorine substituent (**4**), are described.

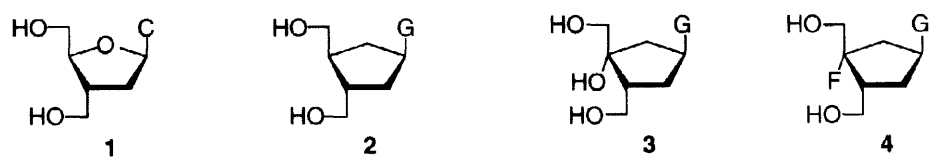

Figure 1

Electronegative substituents in the C-4 position of carbocyclic nucleoside analogues have been shown to promote anti-viral activity (Figure 2).[10] Notably, Borthwick *et al.* have shown that compounds **5** and **6** have good activity against HSV-1 and HSV-2.

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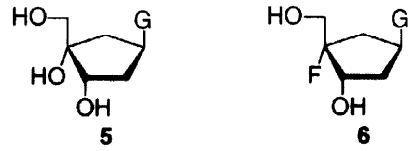
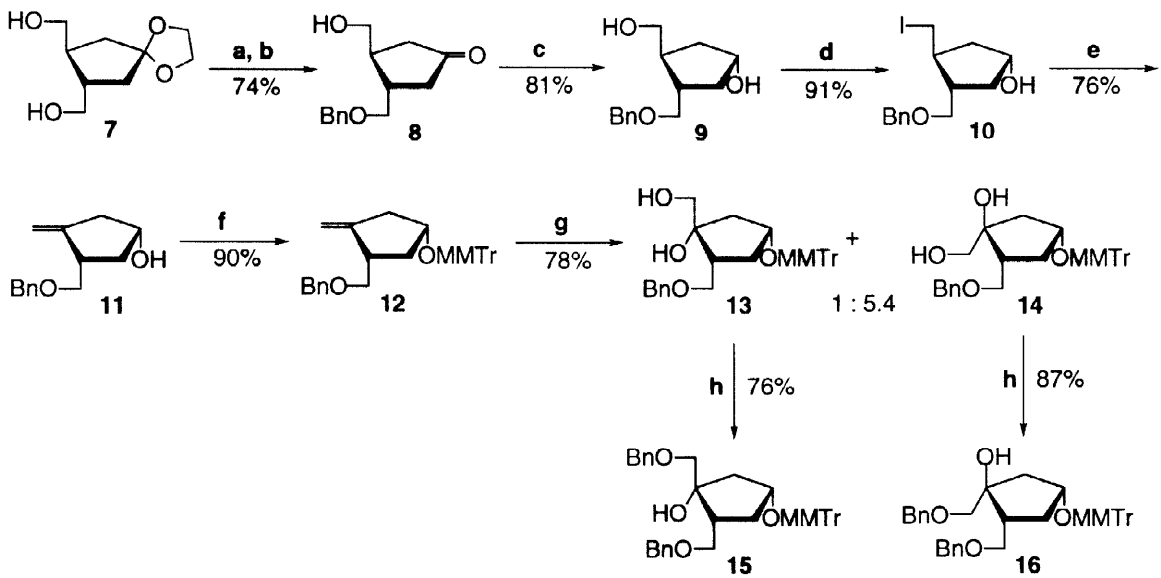


Figure 2

RESULTS AND DISCUSSION

Chemistry. 3*S*,4*S*-Bis(hydroxymethyl)cyclopentanone ethylene glycol ketal (**7**)[11] was monobenzylated using phase transfer conditions with benzyl bromide, 5% aqueous NaOH, tetrabutylammonium hydrogen sulphate and triethylamine in refluxing dichloromethane.[12] The crude product was hydrolyzed in dioxane-water containing *p*-toluene sulphonic acid at 70 °C to give ketone **8** in 74% yield (Scheme 1). Stereoselective reduction of the ketone with tetramethylammonium triacetoxyborohydride (15 equiv.) in acetone-acetonitrile 1:1 containing acetic acid (60 equiv.) gave diol **9** in 81% yield after 2 days.[13,14] The other isomer could not be detected. The use of other solvents such as 2-propanol or THF gave lower yields and longer reaction times, but without affecting the stereoselectivity.



Scheme 1: (a) BnBr, $QHSO_4$, NaOH, Et_3N, CH_2Cl_2, reflux; (b) pTsOH, dioxane, H_2O, 50 °C; (c) $Me_4NBH(OAc)_3$, acetone, CH_3CN, HOAc; (d) ICH_2CH_2I, PPh_3, THF; (e) DBU, toluene, 95 °C; (f) MMTrCl, DMAP, Et_3N, CH_2Cl_2, reflux; (g)K_2OsO_4 x $2H_2O$, *N*-methylmorpholine-*N*-oxide, THF, H_2O; (h) NaH, BnBr, DMF, -78 °C.

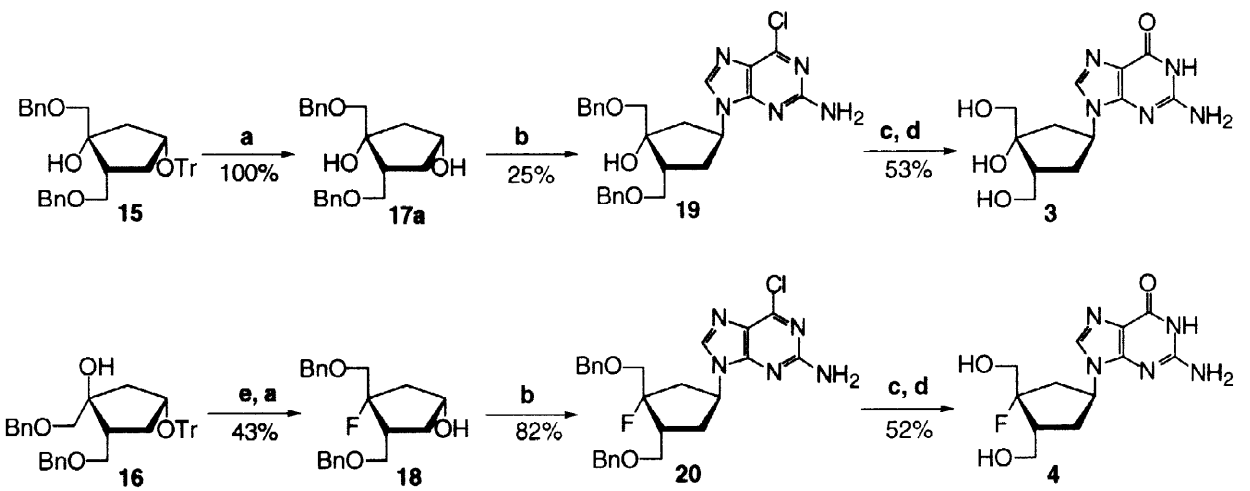
Selective iodination of compound **9** was initially attempted using iodine, triphenylphosphine and imidazole in toluene-acetonitrile 2:1.[15-17] This method, however, gave a mixture of **10** and the diiodinated compound. Using other solvents, temperatures and equivalents of reagents failed to provide only the monoiodinated product **10**, indicating an exceptionally S_N2 reactive secondary hydroxyl at C-1. Selective replacement of the primary hydroxyl group in compound **9** by iodine was, however, accomplished using 1,2-

diiodoethane and triphenylphosphine in THF, which after a 6 days reaction time gave iodide **10** in 91% yield.[18]

Elimination of HI from **10** using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene at 95 °C for 18 hours gave the olefin **11** in 76% yield.[19] Higher reaction temperature or the use of silver fluoride in pyridine gave lower yields of the olefin **11**. Tritylation of **11** using monomethoxytrityl chloride, 4-(dimethylamino)pyridine (DMAP) and triethylamine in refluxing dichloromethane gave **12** in 90% yield.[20]

Dihydroxylation of the olefinic bond using potassium osmate dihydrate and *N*-methylmorpholine-*N*-oxide in THF-water 3:1 gave two diastereomers which were separated by column chromatography to furnish **13** and **14** in 12% and 66% yield respectively (see Configuration Assignment).[21,22] The product distribution reflects the preferential approach of the osmium oxidant from the sterically less hindered β-face. The primary hydroxyls in **13** and **14** were selectively benzylated using benzyl bromide and sodium hydride in DMF to give **15** and **16** in 76% and 87% yield, respectively.[23]

Detritylation of **15** using *p*-toluenesulfonic acid in aqueous dichloromethane gave the diol **17a** in quantitative yield (Scheme 2). Fluorination of **16** using diethylaminosulphur trifluoride (DAST) and pyridine in dichloromethane gave a mixture of products,[10,24-26] which was detritylated, as described above, to give fluoride **18** in 25% yield. The fluorination of **16** could be improved using bis-(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor™) giving **18** in 43% yield. [27,28]



Scheme 2: (a) pTsOH, CH_2Cl_2, H_2O; (b) PPh_3-DIAD, 2-amino-6-chloropurine, THF; (c) 80% HCOOH, 80 °C then 25% NH_4OH, MeOH; (d) H_2, Pd-black, MeOH, H_2O; (e) Deoxofluor™, pyridine, CH_2Cl_2.

The carbocyclic nucleoside analogues were synthesized by coupling **17a** and **18** with 2-amino-6-chloropurine using the Mitsunobu reaction [triphenylphosphine-diisopropyl azodicarboxylate (DIAD)] to give **19** and **20** in 25% and 82% yield respectively.[29] The low yield (25%) in the coupling of the purine base with **17a** is attributed to competing side reactions of the tertiary hydroxyl group. Treatment of **19** and **20** with 80% formic acid at 80 °C followed by 25% ammonium hydroxide in methanol,[30] and hydrogenation of the benzyl groups using Pd-black in methanol-water 10:1 gave the final products **3** and **4** in 53% and 52% yield, respectively.

Configuration Assignments. The configurations of **9**, **17a** and **17b** were determined on the basis on COSY and NOESY experiments (Figure 3). In **9** the chemical shifts for H-2$_\alpha$ and H-2$_\beta$ were well resolved and significant nOes were found between H-1 and H-2$_\beta$ as well as between H-3 and H-2$_\beta$. Weaker nOes were also found between the C-3 benzyloxymethyl protons and H-2$_\alpha$. This indicates a *cis*-relationship between the C-1 hydroxyl group and the C-3 benzyloxymethyl, confirming the (*S*)-stereochemistry at C-1.

In **17b** the chemical shifts for H$_{5\alpha}$ and H$_{5\beta}$ were also well resolved and significant nOes were found between H-1 and H-5$_\beta$ and also between the C-4 benzyloxymethyl protons and H-5$_\alpha$, indicating a 4(*S*)-stereochemistry. The H-5$_\alpha$ and H-5$_\beta$ chemical shifts were less well resolved in **17a**. In spite of this fact, significant nOes were found between H-1 and H-5$_\beta$ and also between H-5$_\beta$ and the C-4 benzyloxymethyl protons. This indicates a *cis*-relationship between the C-4 benzyloxymethyl and the C-1 hydroxyl group in **17b** and a *trans*-relationship in **17a**.

The ^{1}H NMR spectrum of **18** resembles that of **17a**, but in a NOESY experiment no nOes were detected. However in **20**, by selective irradiation of H$_3$, nOe was found to the C-4 benzyloxymethyl protons indicating a *cis*-relationship, and thus that the fluorine substitution had occurred via inversion of configuration at C-4. No nOes were found between the C-3- and C-4-benzyloxymethyl protons in compound **20**.

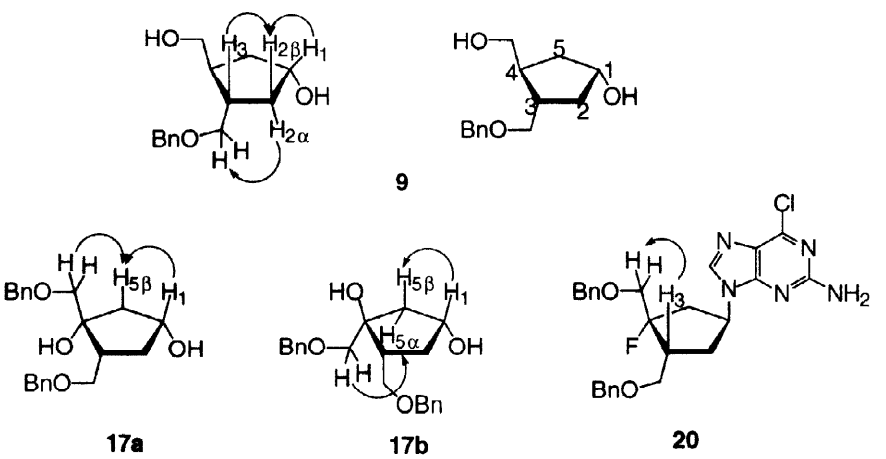


Figure 3

Biological Results. Compounds **3** and **4** were tested in an XTT assay for anti HIV-1 activity and cytopathic effects[31] (and in a similar assay for anti HSV-1 effect)[32] but were found to be inactive in these assays.

EXPERIMENTAL SECTION

General procedures. All solvents were distilled prior to use. Thin layer chromatography was performed using silica gel 60 f-254 (Merck) plates with detection by UV, charring with 8% sulphuric acid or a mixture of 4-methoxybenzaldehyde-sulphuric acid-acetic acid-EtOH (5:7:2:186). Column chromatography was performed on silica gel (Matrix Silica Si 60A, 35-70 μm, Amicon). Organic phases were dried over anhydrous sodium sulphate. Concentrations were performed under reduced pressure. NMR spectra were recorded on a

JEOL GSX-270 instrument, shifts are given in ppm downfield from tetramethylsilane in $CDCl_3$ and DMSO-D_6. Accurate mass measurements were recorded on a JEOL SX 102 Mass Sprectrometer / MS-MP7000 Data system.

(3*S*,4*S*)-3-(Benzyloxymethyl)-4-(hydroxymethyl)cyclopentanone (8). To a stirred solution of (3*S*,4*S*)-bis(hydroxymethyl)cyclopentanone ethyleneglycol ketal (**7**) (6.05 g, 32.1 mmol) in CH_2Cl_2 (400 mL) was added triethylamine (0.3 mL), followed by tetrabutylammonium hydrogen sulphate (2.18 g, 6.42 mmol) and 5% aqueous NaOH (40 mL). The mixture was heated to reflux and benzyl bromide (11.4 mL, 96.3 mmol) was added. After 40 h the aqueous phase was removed and the organic layer was washed with water (2x). The water phase was extracted with CH_2Cl_2 (2x) and the combined organic layer was dried and concentrated. The crude (3*S*,4*S*)-3-(benzyloxy)methyl-4-(hydroxymethyl)cyclopentanone ethyleneglycolketal was dissolved in dioxane (400 mL) and water (40 mL), *p*-toluene sulphonic acid (1.0 g) was added and the mixture was heated to 70 °C. After 1.3 h saturated aqueous $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3x). The combined organic layer was dried concentrated and purified by column chromatography (toluene-EtOAc 2:1, 1:1) to give **8** (5.58 g, 23.8 mmol) as a light yellow oil in 74%; $[\alpha]_D$ +50.5 (*c* 1.16, $CHCl_3$). NMR ($CDCl_3$) δ_H: 1.95-2.09 (2H, m), 2.24-2.47 (4H, m), 3.14 (1H, s), 3.44-3.73 (4H, m), 4.55 (2H, s), 7.13-7.44 (5H, m); δ_C: 40.9, 41.9, 42.0, 43.8, 65.3, 72.8, 73.6, 127.9, 128.0, 128.6, 137.3, 216.3. Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.73; H, 7.70.

(1*S*,3*S*,4*S*)-3-(Benzyloxymethyl)-4-(hydroxymethyl)cyclopentanol (9). To a stirred solution of **8** (5.86 g, 25.0 mmol) in acetone-acetonitrile 1:1 (600 mL) under argon, HOAc (90 mL, 1.5 mol) was added dropwise. Tetramethylammonium triacetoxyborohydride (98.7 g, 375 mmol) was added in one portion and the mixture was stirred at ambient temperature for 2 days, before successive addition of saturated aqueous NH_4Cl (250 mL), 1 M potassium tartrate (200 mL), saturated aqueous $NaHCO_3$ (200 mL) and EtOAc (250 mL). The mixture was stirred for 1 h before the phases were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layer was dried concentrated and purified by column chromatography (toluene-EtOAc 1:2, 1:3, 1:4) to give **9** (4.80 g, 20.3 mmol) as a white solid in 81% yield. A small portion was recrystallized from CH_2Cl_2-hexane to give white needle shaped crystals; melting point 77 °C; $[\alpha]_D$ -6.5 (*c* 1.27, $CHCl_3$). NMR ($CDCl_3$): δ_H: 1.36-1.47 (2H, m), 1.75-1.84 (1H, m), 1.99-2.15 (2H, m), 2.16-2.35 (1H, m), 3.02 (2H, s), 3.35-3.44 (2H, m), 3.53-3.64 (2H, m), 4.18-4.26 (1H, m), 4.56 (2H, s), 7.22-7.40 (5H, m); δ_C: 38.8, 39.6, 42.6, 44.6, 66.5, 72.2, 73.5, 74.3, 127.8, 127.9, 128.5, 137.4. Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.12; H, 8.51.

(1*R*,3*S*,4*S*)-3-(Benzyloxymethyl)-4-(iodomethyl)cyclopentanol (10). To a stirred solution of triphenylphosphine (31.9 g, 121.8 mmol) and 1,2-diiodoethane (29.2 g, 103.5 mmol) in THF (250 mL) under an argon atmosphere was added **9** (4.80 g, 20.3 mmol). After 6 days the successive addition of saturated aqueous $NaHCO_3$, (300 mL), 0.1 M $Na_2S_2O_3$ (100 mL) and toluene (250 mL) was followed by stirring for an additional hour, separation of the phases and extraction of the aqueous layer with toluene (3x). The combined organic layer was dried, concentrated and immediately purified by column chromatography (toluene-EtOAc 10:1) to give **10** (6.37 g, 18.4 mmol) as a yellow oil in 91% yield; $[\alpha]_D$ +26.3 (*c* 0.90,

$CHCl_3$). NMR ($CDCl_3$): δ_H: 1.47 (1H, ddd, J=4.3, 10.4 and 13.3 Hz), 1.63 (1H, ddd, J=1.9, 3.7 and 13.9 Hz), 1.92-2.03 (2H, m), 2.15 (1H, ddd, J=4.9, 10.8 and 13.9 Hz), 2.24-2.29 (1H, m), 3.02 (1H, s), 3.27 (1H, dd, J=6.4 and 9.7 Hz), 3.36 (1H, dd, J=5.4 and 9.7 Hz), 3.41 (1H, dd, J=4.2 and 9.0 Hz), 3.56 (1H, dd, J=3.7 and 9.0 Hz), 4.18-4.26 (1H, m), 4.56 (2H, s), 7.22-7.40 (5H, m); δ_C: 14.8, 39.2, 41.7, 44.0, 44.4, 72.4, 72.8, 73.3, 127.6, 127.8, 128.4, 137.6. Anal. Calcd. for $C_{14}H_{19}O_2I$: C, 48.57; H, 5.53. Found: C, 48.57; H, 5.43.

(1*R*,3*S*)-3-(Benzyloxymethyl)-4-methylenecyclopentanol (11). To a stirred solution of **10** (2.73 g, 7.89 mmol) in dry toluene (250 mL) under an argon atmosphere was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2.36 mL, 15.8 mmol). The mixture was heated to 95 °C for 18 h, before it was washed with saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc (2x) and the combined organic layer was dried and concentrated to give **11** (1.31g, 5.98 mmol) as a yellow oil in 76% yield. No further purification was made due to instability of the product. $[\alpha]_D$ +33.9 (*c* 0.81, $CHCl_3$). NMR ($CDCl_3$): δ_H: 1.74 (1H, ddt, J=3.0, 3.1 and 14.4 Hz), 2.20 (1H, ddd, J=5.3, 9.7 and 14.4 Hz), 2.41 (1H, dd, J=2.8 and 16.9 Hz), 2.54 (1H, dd, J=3.4 and 16.9 Hz), 2.66-2.87 (1H, m), 3.32 (1H, s) 3.58 (2H, d, J=4.4 Hz), 4.18-4.20 (1H, m), 4.54 (2H, s), 5.01 (2H, d, J=28.6 Hz); 7.20-7.40 (5H, m); δ_C: 39.4, 41.7, 44.5, 71.4, 73.5 (2 C), 107.6, 127.6, 127.8, 128.4, 137.6, 151.3.

(1*R*,3*S*)-3-(Benzyloxymethyl)-1-(4-methoxyphenyldiphenylmethoxy)-4-methylenecyclopentane (12). To a stirred solution of **11** (1.30 g, 5.96 mmol) in CH_2Cl_2 (200 mL) under an argon atmosphere was added monomethoxytrityl chloride (2.53 g, 8.19 mmol), 4-dimethylaminopyridine (30 mg, 0.24 mmol) and triethylamine (1.24 mL, 8.90 mmol). The mixture was refluxed for 3 days, before it was washed with saturated aqueous NH_4Cl (3x). The aqueous layer was extracted with CH_2Cl_2 (1x) and the organic layer was dried, concentrated and purified by column chromatography (toluene) to give **12** (2.63g, 5.36mmol) as a colorless syrup in 90% yield; $[\alpha]_D$ +20.7 (*c* 0.92, $CHCl_3$). NMR ($CDCl_3$): δ_H: 1.40-1.52 (1H, dt, J=8.2 and 13.0 Hz), 1.77 (1H, dt, J=6.6 and 13.0 Hz), 1.91 (1H, dd, J=6.2 and 16.3 Hz), 2.09 (1H, ddd, J=2.2, 7.4 and 16.3 Hz), 2.42-2.60 (1H, m), 3.40 (1H, dd, J=6.1 and 8.9 Hz), 3.55 (1H, dd, J=8.0 and 8.9 Hz), 3.76 (3H, s); 4.02 (1H, p, J=7.0 Hz), 4.48 (2H, s), 4.75 (2H, d, J=11.0 Hz), 6.81 (2H, d, J=9.0 Hz), 7.14-7.50 (17H, m); δ_C: 37.7, 41.0, 41.4, 55.1, 73.0, 73.8, 74.2, 86.6, 106.8, 113.0, 126.7, 127.4, 127.5, 127.7, 128.2, 128.4, 130.3, 136.8, 138.5, 145.6, 150.3, 158.5. Anal. Calcd. for $C_{34}H_{34}O_3$ x $1H_2O$: C, 80.28; H, 7.13. Found: C, 80.51; H, 6.89.

(1*R*,3*R*,4*R*)-3-(Benzyloxymethyl)-4-(hydroxymethyl)-1-(4-methoxyphenyldiphenylmethoxy)-4-cyclopentanol (13) and (1*R*,3*R*,4*S*)-3-(Benzyloxymethyl)-4-(hydroxymethyl)-1-(4-methoxyphenyldiphenylmethoxy)-4-cyclopentanol (14). To a cold, stirred solution of **12** (3.20 g, 6.52 mmol) and 4-methylmorpholine-*N*-oxide (1.52 g, 13.0 mmol) in THF-H_2O 3:1 (30 mL) under an argon atmosphere, was added potassium osmate dihydrate (239 mg, 0.65 mmol). The mixture was stirred at ambient temperature for 24 h, before the reaction was quenched by the addition of $NaHSO_3$ (s) (0.9 g) and the stirring was continued for 15 min. The mixture was concentrated, dissolved and extracted in EtOAc-H_2O. The organic layer was dried, concentrated and purified by column chromatography (toluene-EtOAc 3:1) to give

the two alcohols **13** (413 mg, 0.79 mmol, 12%), **14** (2.25 g, 4.28 mmol, 66%) as colorless syrups and unreacted **12** (430 mg, 0.88 mmol, 13%). **13**: $[\alpha]_D$ -2.4 (*c* 1.1, $CHCl_3$). NMR ($CDCl_3$): δ_H: 1.40-1.6 (4H, m), 1.65-1.80 (1H, m), 3.12 (1H, s); 3.25-3.55 (4H, m), 3.60 (1H, t, J=4.5 Hz), 3.73 (3H, s), 3.98 (1H, p, J=6.4 Hz), 4.47 (2H, d, J=3.0 Hz), 6.80 (2H, d, J=9.1 Hz), 7.14-7.50 (17H, m); δ_C: 36.1. 44.7, 45.5, 55.1, 68.9, 69.1, 72.7, 73.4, 79.9, 87.0, 113.1, 126.8, 127.8, 127.9, 128.4, 128.5, 130.4, 136.6, 137.2, 145.3, 158.5. HRMS calcd. For $C_{34}H_{36}O_5$+Na: 547.2460. Found 547.2507. **14**: $[\alpha]_D$ +5.7 (*c* 1.2, $CHCl_3$). NMR ($CDCl_3$): δ_H: 1.03 (1H, dt, J=5.8 and 14.0 Hz), 1.42 (2H, dq, J=4.1 and 8.5 Hz), 1.73-1.91 (1H, m), 1.91-2.05 (1H, m), 2.70 (1H, s), 3.30-3.39 (3H, m), 3.48 (1H, t, J=4.5 Hz), 3.63 (1H, dd, J=5.4 and 11.3 Hz), 3.75 (3H, s), 4.24 (1H, p, J=6.0 Hz), 4.48 (2H, s), 6.80 (2H, d, J=9.1 Hz), 7.14-7.50 (17H, m); δ_C: 35.7. 42.6, 47.5, 55.1, 66.3, 71.9, 72.8, 73.6, 81.5, 86.8, 113.1, 126.8, 127.8, 128.0, 128.1, 128.4, 128.6, 130.4, 136.7, 137.1, 145.4, 158.5. HRMS calcd. For $C_{34}H_{36}O_5$+Na: 547.2460. Found 547.2467. Due to instability of the alcohols **13** and **14**, no elemental analysis of these compounds gave satisfying results.

(1*R*,3*R*,4*R*)-3,4-Bis(benzyloxymethyl)-1-(4-methoxyphenyldiphenylmethoxy)-4-cyclopentanol (15). To a stirred suspension of NaH (95%) (28 mg, 1.11 mmol) in DMF (2 mL) under an argon atmosphere was added **13** (291 mg, 0.55 mmol) in DMF (4 mL). The mixture was cooled to –70 °C and benzyl bromide (67 μL, 0.58 mmol) in DMF (2 mL) was added dropwise during 10 min. After 1 h the ice bath was removed and stirring continued at ambient temperature for 19 h before MeOH (0.5mL) and H_2O (10 mL) were added. The mixture was extracted with EtOAc (3x), dried, concentrated and purified by column chromatography (toluene-EtOAc 20:1) to give **15** (258 mg, 0.42 mmol) as a colorless syrup in 76% yield; $[\alpha]_D$ +3.2 (*c* 0.6, $CHCl_3$). NMR ($CDCl_3$): δ_H: 1.42-1.69 (4H, m), 1.84-1.97 (1H, m), 3.15 (1H, s), 3.19 (1H, d, J=9.1 Hz), 3.32 (1H, d, J=9.1 Hz), 3.46 (1H, dd, J=6.2 and 9.9 Hz), 3.66 (1H, dd, J=6.0 and 9.9 Hz), 3.75 (3H, s), 4.02 (1H, p, J=7.1 Hz), 4.41 (4H, s), 6.80 (2H, d, J=9.0 Hz), 7.14-7.50 (21H, m); δ_C: 36.4, 42.9, 45.2, 55.1, 70.5, 73.1, 73.2, 73.4, 75.7, 80.0, 87.0, 113.1, 126.7, 127.3, 127.5, 127.8, 128.3, 128.5, 130.4, 136.6, 138.2, 138.4, 145.3, 158.5. HRMS calcd. For $C_{41}H_{42}O_5$+Na: 637.2930. Found 637.2933.

(1*R*,3*R*,4*S*)-3,4-Bis(benzyloxymethyl)-1-(4-methoxyphenyldiphenylmethoxy)-4-cyclopentanol (16). Compound **16** was prepared from **14** (1.94 g, 3.69 mmol) in the same manner as described for compound **15** to afford the title compound as a colorless syrup in 87% yield (1.97 g, 3.20 mmol); $[\alpha]_D$ +8.2 (*c* 0.9, $CHCl_3$). NMR ($CDCl_3$): δ_H: 1.37 (1H, ddd, J=5.8, 8.3 and 13.5 Hz), 1.45-1.61 (2H, m), 1.81 (1H, dt, J=7.9 and 13.5 Hz), 1.98 (1H, p, J=7.3 Hz), 2.56 (1H, s); 3.31-3.56 (4H, m), 3.77 (3H, s), 4.22 (1H, p, J=7.0 Hz), 4.48 (2H, s), 4.50 (2H, s), 6.80 (2H, d, J=9.0 Hz), 7.14-7.50 (17H, m); δ_C: 36.2, 44.4, 47.1, 55.2, 70.7, 72.7, 73.0, 73.6, 74.2, 80.1, 86.7, 113.0, 126.7, 127.5, 127.5, 127.6, 127.8, 128.3, 128.5, 130.4, 136.9, 138.1, 138.4, 145.6, 158.5. HRMS calcd. For $C_{41}H_{42}O_5$+Na: 637.2930. Found 637.2900.

(1*R*,3*R*,4*R*)-3,4-Bis(benzyloxymethyl)-1,4-cyclopentanediol (17a). To a stirred solution of **15** (258 mg, 0.42 mmol) in CH_2Cl_2 (13 mL) was added *p*-toluenesulfonic acid (32 mg) and H_2O (3 drops). After 2.5 h at ambient temperature the mixture was washed with saturated aqueous $NaHCO_3$, the

aqueous layer was extracted with CH_2Cl_2 (2x) and the combined organic layer was dried, concentrated and purified by column chromatography (toluene-EtOAc 2:1) to give **17a** as a colorless syrup(146 mg, 0.42 mmol) in quantitative yield; $[\alpha]_D$ +4.1 (*c* 0.7, $CHCl_3$). NMR ($CDCl_3$): δ_H: 1.72 (1H, ddd, J=2.2, 8.0 and 14.4 Hz), 1.91-1.94 (2H, m), 2.04-2.34 (2H, m), 2.90 (1H, s, br), 3.40 (1H, d, J=9.2 Hz), 3.50 (1H, s, br), 3.57 (1H, d, J=9.2 Hz), 3.63-3.75 (2H. m), 4.20-4.31 (1H, m), 4.49 (2H, s), 4.54 (2H, d, J=4.0 Hz), 7.17-7.40 (10H, m); δ_C: 38.5, 43.6, 46.6, 70.3, 71.9, 73.2, 73.3, 75.1, 82.1, 127.5, 127.6, 128.2, 128.3, 137.9, 138.1. Anal. Calcd. For $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.42; H, 7.49. Due to the gradual decomposition of compounds 13-16 a small portion of **16** was detritylated as above to give **17b**, to be able to compare it with **17a** in the configurational assignments. $[\alpha]_D$ +14.5 (*c* 1.0, $CHCl_3$). NMR ($CDCl_3$): δ_H: 1.50 (1H, ddd, J=1.9, 3.8 and 13.9 Hz), 1.60 (1H, dd, J=3.5 and 14.5 Hz), 2,12-2.23 (2H, m), 2.45 (1H, dt, J=7.7 and 13.9 Hz), 2.72 (1H, s, br), 3.13 (1H, s, br), 3.41-3.56 (4H, m), 4.37 (2H, d, J=1.83 Hz), 4.43 (2H, d, J=1.83 Hz), 7.23-7.34 (10 H, m); δ_C: 38.8, 48.0, 48.3, 70.7, 71.1, 73.6, 73.7, 74.2, 81.6, 128.1, 128.2, 128.6, 137.5, 137.7. Anal. Calcd. For $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.39; H, 7.51.

(1*R*,3*R*,4*R*)-3,4-Bis(benzyloxymethyl)-4-fluoro-1-cyclopentanol (18). To a stirred solution of bis-(2-methoxyethyl)aminosulphur trifluoride (140 mg, 0.68 mmol) and pyridine (60 μL, 0.73 mmol) in CH_2Cl_2 (9 mL) under an argon atmosphere at -78 °C, **16** (346 mg, 0.56 mmol) in CH_2Cl_2 (6 mL) was added dropwise during 10 min. The mixture was allowed to reach room temperature and after 18h saturated aqueous $NaHCO_3$ (10 mL) was added. TLC indicated the formation of 1 main product and 4 byproducts. The mixture was washed with H_2O (2x), the aqueous layer was extracted with CH_2Cl_2 (3x), the combined organic layer was dried and concentrated. The crude mixture was dissolved in CH_2Cl_2 (17 mL) and *p*-toluensulfonic acid (100 mg) and H_2O (10 drops) was added. After stirring for 2 days at ambient temperature the mixture was washed with saturated aqueous $NaHCO_3$, the aqueous layer was extracted with CH_2Cl_2 (2x) and the combined organic layer was dried, concentrated and purified by column chromatography (toluene-EtOAc 3:1) to give **18** as a light yellow syrup (83 mg, 0.24 mmol) in 43% yield; $[\alpha]_D$ +5.5 (*c* 1.0, $CHCl_3$). NMR ($CDCl_3$): δ_H: 1.55-1.76 (1H, m), 2.00 (1H, s, br), 2.07-2.38 (4H, m); 3.43-3.79 (4H, m), 4.20-4.31 (1H, m), 4.48 (2H, s), 4.56 (2H, d, J=7.0 Hz), 7.20-7.40 (10 H, m); δ_C: 38.6, 44.0 (d, $J_{C,F}$=20.2 Hz), 45.1 (d, $J_{C,F}$=22.0 Hz), 69.2 (d, $J_{C,F}$=9.1 Hz), 71.0, 72.8 (d, $J_{C,F}$=29.4 Hz), 73.2, 73.5, 104.9 (d, $J_{C,F}$=179.7 Hz), 127.5, 127.6, 128.3, 138.0, 138.1. Anal. Calcd. for $C_{21}H_{25}O_3F$: C, 73.23; H, 7.32. Found: C, 73.07; H, 7.44.

(1*S*,3*R*,4*R*)-2-Amino-9-[3,4-bis(hydroxymethyl)-4-hydroxycyclopentyl]-9*H*-purine-6(1*H*)-one (3). To a stirred solution of triphenylphosphine (165 mg, 0.63 mmol) in THF (4 mL) under an argon atmosphere at 0 °C, diisopropylazodicarboxylate (DIAD) was added dropwise during 5 min. The mixture was stirred for 30 min to yield a white precipitate of thiphenylphosphine-DIAD complex. A suspension of 2-amino-6-chloropurine (107 mg, 0.63 mmol) and **17a** (146 mg, 0.42 mmol) in THF (6 mL) was added and the mixture was stirred for 15 h at ambient temperature, concentrated and purified by column chromatography (toluene-EtOAc 2:1, 2:3, 1:2) to give **19** as a light yellow syrup (53 mg, 0.107 mmol) in 25% yield. NMR ($CDCl_3$): δ_H: 2.08-2.25 (1H, m), 2.30-2.55 (3H, m), 2.60-2.80 (1H, m), 3.45-3.72 (5H, m), 5.05 (1H, p, J=6.8 Hz), 5.15 (2H, s), 7.20-7.40 (10 H, m), 7.81 (1H, s); δ_C: 33.8, 42.9, 43.9, 53.3, 69.2,

73.5, 74.6, 81.1, 125.8, 127.6, 127.8, 127.9, 128.4, 137.6, 137.9, 141.3, 151.2, 153.6, 158.7. Unreacted **17a** (31 mg, 0.091 mmol, 22%) was also recovered. A solution of **19** (53 mg, 0.107 mmol) in 80% formic acid (3 mL) was stirred at 80 °C for 2 h. The mixture was concentrated and dissolved in MeOH (3 mL) and 25% NH_4OH (0.4 mL) and stirred overnight before it was concentrated. A suspension of the crude product and a catalytic amount of Pd-black in MeOH-H_2O 10:1 was hydrogenated at ambient pressure overnight, filtered through a pad of celite and concentrated. The mixture was purified by column chromatography (EtOAc-MeOH-H_2O 7:2:1) and on a BioGel® P-2 column to give **3** as a white hygroscopic solid (18 mg, 0.057 mmol) in 53% yield; $[\alpha]_D$ +5.0 (*c* 0.4, H_2O).NMR (DMSO-D_6): δ_H: 1.86-2.23 (4H, m), 2.31 (1H, p, J=6.2 Hz), 3.30-3.68 (4H, m), 4.47 (1H, s), 4.55 (1H, s), 4.89 (1H, p, J=6.8 Hz), 4.99 (1H, s), 6.45 (2H, s) 7.81 (1H, s); δ_C: 35.0, 43.9, 44.8, 51.2, 60.4, 65.9, 80.8, 116.6, 135.3, 150.9, 153.2, 156.8. Anal. Calcd. for ($C_{12}H_{17}N_5O_4$ x $4H_2O$) C, 39.23; H, 6.86; N, 19.23. Found: C, 39.42; H, 6.57; N, 19.06.

(1*S*,3*R*,4*R*)-2-Amino-9-[3,4-bis(hydroxymethyl)-4-fluorocyclopentyl]-9*H*-purine-6(1*H*)-one (4). Compound **4** was prepared from **18** (113 mg, 0.33 mmol) in the same manner as described for compound **3** (above) via compound **20** which was isolated in 82% yield as a light yellow syrup (132 mg, 0.27 mmol). NMR ($CDCl_3$): δ_H: 2.20-2.33 (2 H, m), 2.54-2.72 (2H, m), 2.91 (1H, dtt, J=7.1, 9.5 and 27.5 Hz); 3.50 (1H, ddd, J=2.0, 6.8 and 8.8 Hz), 3.69-3.77 (2H, m), 3.84 (1H, dd, J=10.5 and 11.1 Hz), 4.50 (2H, dd, J=11.9 and 19.3 Hz), 4.59 (2H, dd, J=12.0 and 23.2 Hz), 4.99 (2H, s, br), 4.98-5.07 (1H, m), 7.27-7.37 (10 H, m), 7.83 (1H, s); δ_C: 34.5, 41.7 (d, $J_{C,F}$=22.0 Hz), 43.5 (d, $J_{C,F}$=18.3 Hz), 53.0, 68.5 (d, $J_{C,F}$=9.2 Hz), 71.6, (d, $J_{C,F}$=29.3 Hz), 73.2, 73.5, 104.0 (d, $J_{C,F}$=179.7 Hz), 125.7, 127.5, 127.6, 127.8, 128.3, 128.4, 137.6, 138.0, 141.1, 151.2, 153.4, 158.7. Unreacted **18** (20 mg, 0.058 mmol, 17%) was also recovered. The title compound was afforded in 52% yield as a white hygroscopic solid (44 mg, 0.139 mmol); $[\alpha]_D$ +12.0 (*c* 0.5, H_2O). NMR (DMSO-D_6): δ_H: 1.98-2.20 (2H, m), 2.26-2.49 (2H, m), 2.61 (1H, p, J=6.4 Hz), 3.17-3.72 (4H, m), 4.70 (1H, s), 4.86 (1H, p, J=6.9 Hz), 5.24 (1H, s), 6.50 (2H, s) 7.83 (1H, s); δ_C: 34.5, 41.6 (d, $J_{C,F}$=22.0 Hz), 45.0 (d, $J_{C,F}$=18.4 Hz), 51.0, 59.5 (d, $J_{C,F}$=12.8 Hz), 63.8, (d, $J_{C,F}$=27.4 Hz), 105.4 (d, $J_{C,F}$=179.6 Hz), 116.8, 135.4, 150.9, 153.3, 156.8. Anal. Calcd. for $C_{12}H_{16}N_5O_4F$ x $4H_2O$: C, 39.42; H, 6.80; N, 18.91. Found: C, 39.41; H, 6.45; N, 18.93.

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