Stereoselective Synthesis of Novel Aristeromycin Analogues as Potential Antiviral Agents

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Abstract: A series of 3′-methyl-branched and purine-modified analogues of aristeromycin were synthesized via the SN_2 displacement of a key triflate, which was prepared from a readily available enantiopure building block in eight steps. The synthesized compounds were evaluated as potential antiviral agents against important viruses. Only the 2,6-diaminopurine derivative exhibited moderate activity against vesicular stomatitis virus.

Key words: synthesis, carbanucleosides, nucleobases, S_N2 displacement, antiviral activity

Nucleoside analogues constitute an important class of therapeutic agents in the treatment of cancers and viral infections. Among them, aristeromycin (Figure 1), the natural carbocyclic analogue of adenosine isolated from *Streptomyces citricolor*,[1–3] has elicited numerous biological studies due to its potent antiviral activities. The antiviral activities have been correlated with its inhibitory effects toward the cellular enzyme *S*-adenosylhomocysteine (AdoHcy) hydrolase,[4–8] which is essential for viral mRNA capping of most animal-infecting DNA and RNA viruses.[9,10] However, the high cytotoxicity of aristeromycin has greatly hindered its therapeutic application.[11,12] In order to overcome this disadvantage for the development of chemotherapeutic agents, chemical modifications have been carried out on the carbasugar as well as on the base. As part of these efforts, aristeromycin derivatives containing a methyl group at the C2′-, C4′- and C5′- positions of the carbasugar moiety have been synthesized.[13–15] Recently, a series of adenosine analogues substituted at the ribose ring with a methyl group have been synthesized and evaluated for antitumor activity.[16] From this study, 3′-C-methyladenosine (3′-Me-Ado, Figure 1) has emerged as an active derivative, and the structure–activity correlation studies have pointed out that its structure is crucial for the antitumor activity.[16] In connection with these facts, we reported in a preliminary communication an original synthetic pathway to the carbasugar analogue, (–)-3′-methylaristeromycin, with the aim of studying in the near future its biological potential (**1**, Figure 1).[17] Modifications of the heterocyclic base moiety of carbocyclic nucleosides may also lead to significant changes in the spectrum of their biological activities.[18–20] On the basis of these relevant properties, and as a logical continuation of our research into the preparation and pharmacological evaluation of novel carbanucleosides, we report here as a full paper the synthesis of five 3′-methyl-branched and purine modified aristeromycin analogues **2**–**6** (Figure 1), based on the same synthetic pathway, and their antiviral evaluation. Except for the adenine carbocyclic derivative **1**, previously described by our group, all the target compounds are hitherto unknown.

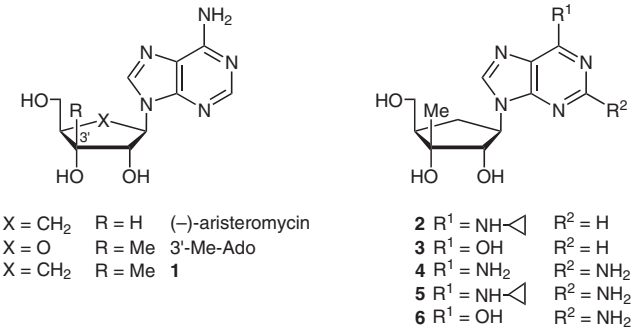

Figure 1 Aristeromycin and its modified analogues

The starting material was enantiopure ethyl (1*S*,4*R*)-4-hydroxy-2-methylcyclopent-2-ene-1-carboxylate [(–)-**7**], obtained through enzymatic kinetic resolution[21] of the corresponding racemic **7** (Scheme 1). Osmium tetroxide catalyzed *cis*-dihydroxylation of protected ester **8** (TBSCl, imidazole, DMF)[22] yielded 86% of the expected diol **9** as the major product, along with a small amount of the β-face stereoisomer **9′** (10:1 ratio). Column chromatography on silica gel readily afforded pure **9**. The alcohol functionalities of **9** were protected as the corresponding 2′,3′-*O*-isopropylidene (acetonide) derivative **10** and stereochemical confirmation was carried out at this stage by NOESY technique (Figure 2). A NOE effect for one methyl of acetonide (δ = 1.49), C*H*CO_2Et (δ = 2.95) and C*H*OTBS (δ = 4.12–4.23 partially overlapped) established the *cis* spatial orientation of these protons.

Treatment of **10** with tetrabutylammonium fluoride in tetrahydrofuran at room temperature afforded **11** in 88% yield (Scheme 2). Attempts to invert the alcohol configuration of **11** through a Mitsunobu reaction[23] with acetic acid failed. Probably depending on the high degree of steric hindrance, no reaction occurred even if the reaction

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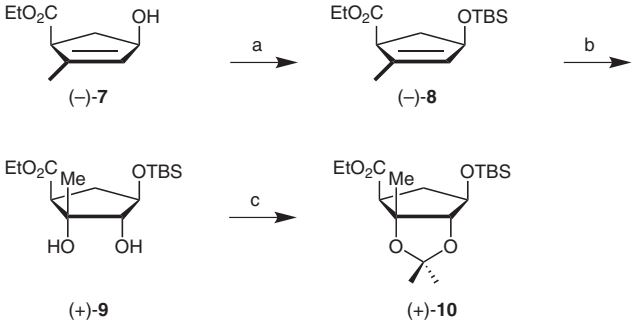


Scheme 1 *Reagents and conditions:* (a) TBSCl, imidazole, DMF, 12 h, r.t., 90%; (b) OsO_4 (cat.), NMO, acetone–H_2O (3:1), 24 h, r.t., 86%; (c) 2-methoxypropene, CSA (cat.), THF, 3 h, r.t., 93%.

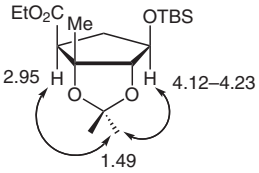
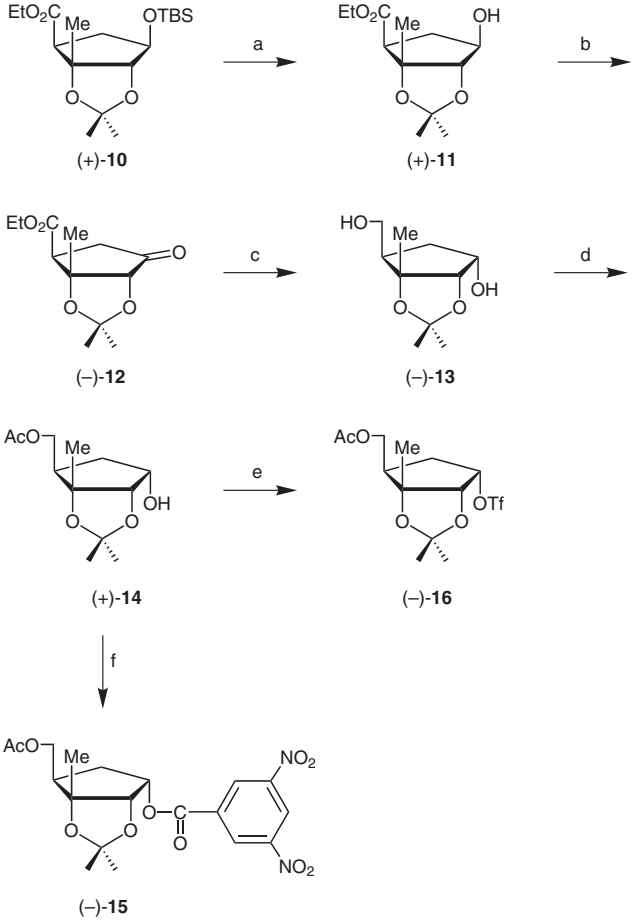


Figure 2 NOE of (+)-**10**

mixture was heated at reflux. Faced with this unfortunate step, we decided to invert the hydroxyl function of **11** following a two-step procedure. First, oxidation of **11** with tetrapropylammonium perruthenate[24] in the presence of *N*-methylmorpholine *N*-oxide gave **12** in 85% yield, which was later reacted with lithium aluminum hydride to give the diol **13** with 91% yield as the only product. Afterwards, protection of the primary alcohol in **13** was achieved by enzymatic transesterification with vinyl acetate using *Candida antartica lipase* (Novozym® 435) to give the monoacetylated derivative **14** regioselectively and in 95% yield. At this stage, the stereostructure of **14** was unequivocally determined by single crystal X-ray crystallography of the corresponding 3,5-dinitrobenzoate **15** (Figure 3). Mitsunobu condensation of 6-chloropurine with **14** in the presence of triphenylphosphine and diisopropyl azodicarboxylate, to give the corresponding purine derivative failed. As previously, in the attempts to invert the hydroxyl group of **11**, no reaction occurred. With this unexpected outcome, we therefore decided to first prepare the corresponding triflate **16**, and then look at the S_N2 displacement of this secondary triflate with the sodium salt of nucleobases, adapting the protocol developed by Robins.[25] For this purpose, **14** was treated with trifluoromethanesulfonyl chloride and 4-dimethylaminopyridine in dichloromethane at 0 °C to provide **16** in 92% yield.

The S_N2 displacement of triflate **16** with the sodium salt of 6-chloropurine provided the protected 6-chloropurine derivative **17** in 63% yield (Scheme 3). Construction of the 6-cyclopropylaminopurine derivative **18** was accomplished using the following one-pot two-step sequence: (i) conversion of the 6-chloro group into 6-cyclopropylamino group with cyclopropylamine in methanol at 50 °C and (ii) evaporation in vacuo of the reaction mixture and



Scheme 2 *Reagents and conditions:* (a) TBAF, THF, 1 h, r.t., 88%; (b) TPAP, NMO, 4 Å MS, CH_2Cl_2, 12 h, r.t., 85%; (c) $LiAlH_4$, THF, 6.5 h, –80 °C to r.t., 91%; (d) CAL-B, vinyl acetate, 5 h, r.t., 95%; (e) TfCl, DMAP, CH_2Cl_2, 15 min, 0 °C, 92%; (f) 3,5-dinitrobenzoyl chloride, Et_3N, CH_2Cl_2, 12 h, r.t., 93%.

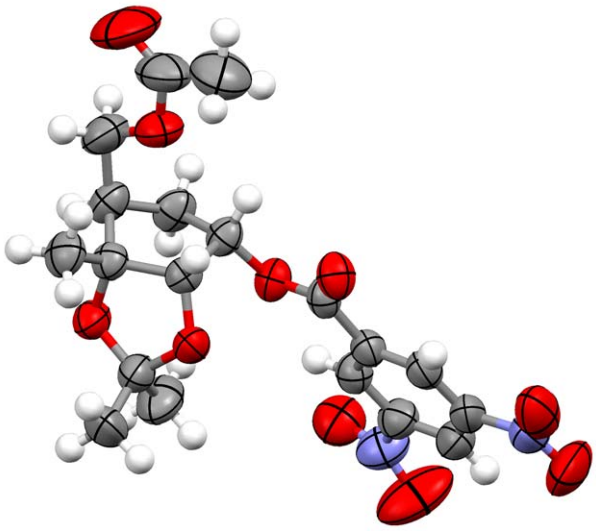
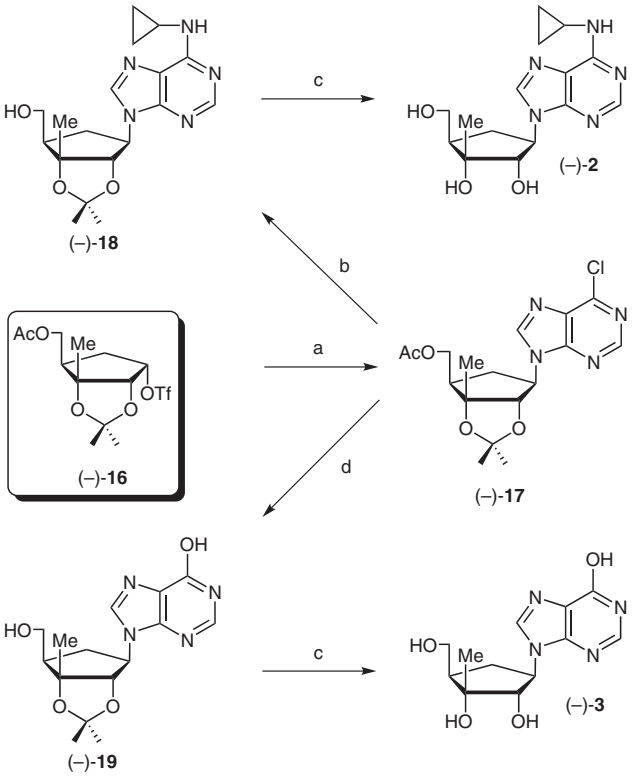


Figure 3 ORTEP projection of the molecular structure of 3,5-dinitrobenzoate (–)-**15**

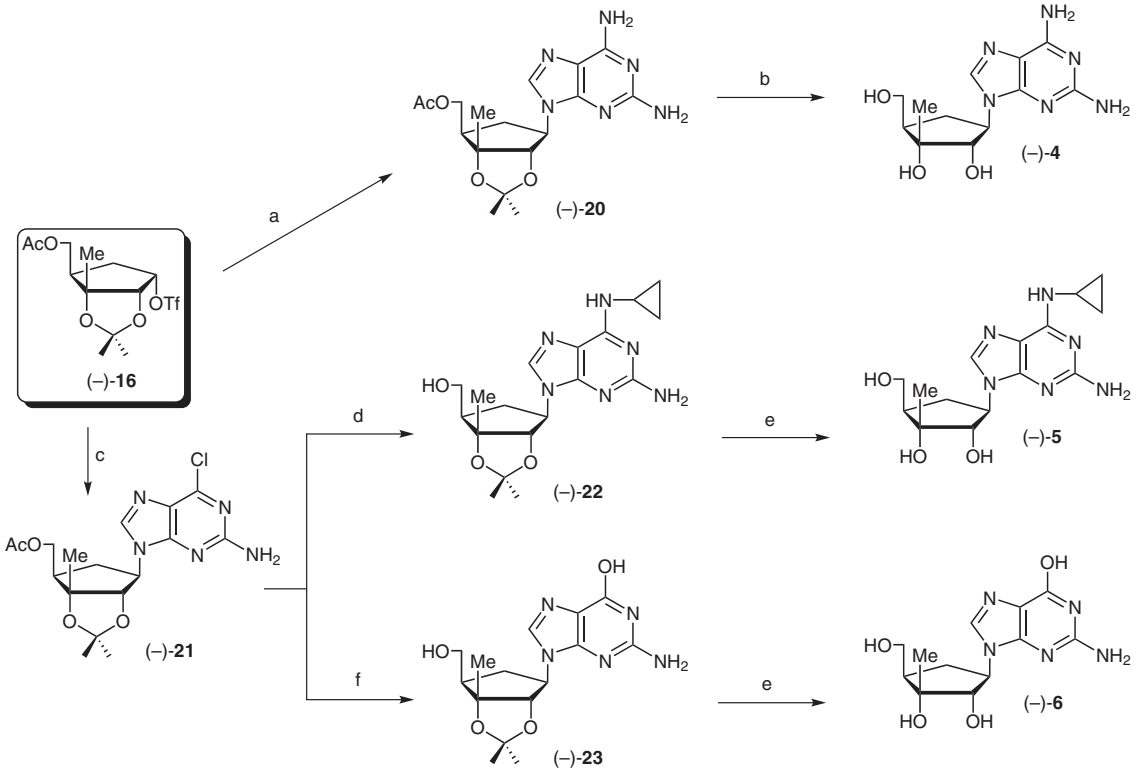
deacylation with methanolic ammonia at room temperature to provide the acetonide-protected derivative **18** in 78% yield for two steps. Subsequent treatment of the ma-



Scheme 3 *Reagents and conditions:* (a) 6-chloropurine, NaH, DMF, 2 h, 60 °C, 63%; (b) (i) cyclopropylamine, MeOH, 12 h, 50 °C; (ii) NH_3/MeOH, 12 h, r.t., 78%; (c) HCl, H_2O, 12 h, 50 °C, 87% for (–)-**2**, 86% for (–)-**3**; (d) 2-mercaptoethanol, MeONa, MeOH, 12 h, reflux, 82%.

terial with aqueous 1 M hydrochloric acid at 50 °C gave the targeted nucleoside **2** in 87% yield. Hydrolytic removal of the 6-chloro substituent required for the conversion of **17** into the hypoxanthine derivative **19** was accomplished with 2-mercaptoethanol and NaOMe in refluxing methanol.[26] Under these conditions, the acyl group was simultaneously removed with an overall yield of 82%. Finally acetonide deprotection with aqueous 1 M hydrochloric acid at 50 °C like earlier led efficiently to **3** in 86% yield.

The synthesis of 2-amino substituted targeted molecules **4**–**6** is outlined in Scheme 4. Reaction of triflate **16** with the sodium salt of 2,6-diaminopurine in dimethylformamide at 60 °C gave the protected derivative **20** in 75% yield. Deprotection of the acetonide group of **20** with trifluoroacetic acid–water (2:1) at room temperature and subsequent deprotection of the acetate group with methanolic ammonia led to **4** in 70% yield for the two steps. Preparation of **5** and **6** was subsequently accomplished in a manner similar to that developed earlier. Reaction of **16** with the sodium salt of 2-amino-6-chloropurine afforded **21** in 70% yield. Treatment of **21** with cyclopropylamine then methanolic ammonia gave **22** (76% yield), and the desired deprotected product **5** was obtained by hydrolysis with hydrochloric acid (90% yield). On the other hand, reaction of **21** with 2-mercaptoethanol afforded guanine relative **23** (87% yield), from which **6** was obtained by deprotection of the acetonide group with hydrochloric acid (76% yield). 3′-Methylaristeromycin (**1**) and the newly synthesized carbocyclic nucleosides **2**–**6** have been



Scheme 4 *Reagents and conditions:* (a) 2,6-diaminopurine, NaH, DMF, 2 h, 60 °C, 72%; (b) (i) trifluoroacetic acid–H_2O (2:1), 12 h, r.t.; (ii) NH_3/MeOH, 24 h, r.t., 74%; (c) 2-amino-6-chloropurine, NaH, DMF, 2 h, 60 °C, 70%; (d) (i) cyclopropylamine, MeOH, 12 h, 50 °C; (ii) NH_3/MeOH, 12 h, r.t., 76%; (e) HCl, H_2O, 12 h, 50 °C, 90% for (–)-**5**, 76% for (–)-**6**; (f) 2-mercaptoethanol, MeONa, MeOH, 12 h, reflux, 87%.

evaluated for their antiviral activity[27] against herpes simplex virus type 1 and type 2 (HSV-1, strain KOS and HSV-2, strain G), vaccinia virus (VV), vesicular stomatitis virus (VSV) and thymine kinase-deficient herpes simplex virus type 1 (TK- HSV-1, strain KOS, ACVr) in HEL cells cultures, VSV, Coxsackie virus B4, and respiratory syncytial virus (RSV) in HeLa cell cultures, Coxsakie virus B4, Sindbis virus and Punta Toro virus in Vero cell cultures, and feline corona virus (FIPV) feline herpes virus in CRFK cell cultures, as well as for their cytotoxicity.

No significant cytotoxicities were reported for any of the compounds. Compound **4** (EC_{50} 20 μg/mL) showed a moderate activity against vesicular stomatitis virus (HeLa cells) without toxicity up to 100 μg/mL. None of other compounds showed any antiviral activity against any of the viruses tested.

In summary, a series of 3′-methyl-branched and purine-modified analogues of aristeromycin **2–6** were synthesized by the efficient S_N2 displacement of the key triflate **16**, prepared in eight steps using a procedure recently developed in our group. All derivatives were tested against important viruses in order to determine their spectrum of antiviral activity. However, only the 2,6-diaminopurine carbocyclic nucleoside **4** displayed a moderate activity against vesicular stomatitis virus.

All air and/or water sensitive reactions were carried out under argon with anhydrous, freshly distilled solvents using standard syringe-cannula/septa techniques. All corresponding glassware was oven-dried (80 °C) and/or carefully dried in line with a flameless heat gun. All solvents were distilled under argon: THF from a blue solution of sodium-benzophenone ketyl radical prior to use; CH_2Cl_2 and DMF from CaH_2, and toluene from $LiAlH_4$. Routine monitoring of reactions was performed using Merck Silica gel 60 F_{254}, aluminum supported TLC plates; spots were visualized using a UV light and ethanolic acidic *p*-anisaldehyde solution or ethanolic phosphomolybdic solution, followed by heating. Purification by means of column chromatography was performed with silica gel 60 (230–400 mesh) and gradients of Et_2O–petroleum ether (PE, bp 40–65 °C) or CH_2Cl_2–MeOH as eluent, unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_3OD or DMSO-d_6 solutions on a Bruker AM-500, Bruker AM-400, or Bruker AM-300 spectrometer. Chemical shifts (δ) in ppm are reported using residual nondeuterated solvents as internal reference. Optical rotations were measured on a PerkinElmer 341 polarimeter. Microanalyses were performed on a Thermo Finnigan EA 1112 apparatus. Melting points are uncorrected. IR spectra were obtained as films or KBr pellets using a PerkinElmer 1600 FTIR spectrophotometer.

Ethyl (1*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-methylcyclopent-2-enecarboxylate [(–)-8]

To an ice-cold solution of alcohol (–)-**7** (5.0 g, 29.4 mmol) in DMF (40 mL) under argon was added imidazole (8.0 g, 117.5 mmol, 4.0 equiv) followed by TBSCl (6.6 g, 44.1 mmol, 1.5 equiv). After stirring at r.t. for 12 h, the solution was poured into H_2O (200 mL). The aqueous layer was extracted with Et_2O (3 × 150 mL), then the organic layers were combined, washed with H_2O (100 mL), brine (100 mL), and dried ($MgSO_4$). Concentration of the organic extracts in vacuo and purification of the residue by column chromatography gave compound (–)-**8** (7.5 g, 90%) as a clear oil; $[\alpha]_D^{25}$ –18.2 (*c* 1.0, $CHCl_3$).

IR (neat): 3055, 1729, 1215, 1150 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.48 (m, 1 H), 4.78 (m, 1 H), 4.16 and 4.11 (*AB*X_3, *J* = 13.4, 7.2, 7.2 Hz, 2 H), 3.18 (br t, *J* = 7.2 Hz, 1 H), 2.48 (ddd, *J* = 12.9, 8.9, 7.4 Hz, 1 H), 1.96 (ddd, *J* = 12.9, 7.3, 5.4 Hz, 1 H), 1.74 (q, *J* = 1.5 Hz, 3 H), 1.24 (AB*X*$_3$, *J* = 7.2 Hz, 3 H), 0.87 (s, 9 H), 0.04 (br s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3 (C), 139.9 (C), 131.8 (CH), 76.2 (CH), 60.4 (CH_2), 51.9 (CH), 38.5 (CH_2), 25.9 (3 × CH_3), 18.1 (C), 15.4 (CH_3), 14.2 (CH_3), –4.7 (2 × CH_3).

Anal. Calcd for $C_{15}H_{28}O_3Si$: C, 63.33; H, 9.92. Found: C, 63.66; H, 9.87.

Ethyl (1*S*,2*R*,3*S*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-2,3-dihydroxy-2-methylcyclopentanecarboxylate [(–)-9] and Ethyl (1*S*,2*S*,3*R*,4*R*)-4-(*tert*-Butyldimethylsilyloxy)-2,3-dihydroxy-2-methylcyclopentanecarboxylate [(–)-9′]

To an ice-cold solution of alkene (–)-**8** (5.0 g, 17.6 mmol) in acetone–H_2O (3:1, 240 mL) under argon was added a catalytic amount of OsO_4 (4% wt in H_2O). The solution turned black, then NMO (4.2 g, 35.2 mmol, 2.0 equiv) was added. After stirring at r.t. for 24 h, the solution was diluted with Et_2O (200 mL) and poured into aq Na_2SO_3 (8.8 g, 70 mmol, 4.0 equiv) cooled in an ice bath, and stirred for 30 min. The aqueous layer was extracted with Et_2O (3 × 200 mL), then the organic layers were combined, washed with H_2O (200 mL), brine (200 mL), and dried ($MgSO_4$). Concentration of the organic extracts in vacuo and purification of the residue by column chromatography gave compounds (+)-**9** (4.36 g, 78%) and (–)-**9′** (445 mg, 8%) as clear oils.

(+)-**9**

$[\alpha]_D^{25}$ +2.6 (*c* 1.0, $CHCl_3$).

IR (neat): 3433, 1742, 1223, 1139 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.18 and 4.17 (*AB*X_3, *J* = 13.4, 7.2, 7.2 Hz, 2 H), 4.02 (ddd, *J* = 8.5, 6.4, 3.5 Hz, 1 H), 3.51 (d, *J* = 3.5 Hz, 1 H), 2.91 (dd, *J* = 10.5, 8.5 Hz, 1 H), 2.28 (dt, *J* = 13.8, 8.5 Hz, 1 H), 1.83 (ddd, *J* = 13.8, 10.5, 6.4 Hz, 1 H), 1.27 (AB*X*$_3$ partially overlapped, *J* = 7.2 Hz, 3 H), 1.25 (s, 3 H), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3 (C), 83.6 (CH), 77.8 (C), 75.2 (CH), 60.7 (CH_2), 50.9 (CH), 33.1 (CH_2), 25.7 (3 × CH_3), 22.2 (CH_3), 17.9 (C), 14.3 (CH_3), –4.8 (CH_3), –4.9 (CH_3).

Anal. Calcd for $C_{15}H_{30}O_5Si$: C, 56.57; H, 9.49. Found: C, 56.85; H, 9.44.

(–)-**9′**

$[\alpha]_D^{25}$ –15.5 (*c* 1.0, $CHCl_3$).

IR (neat): 3439, 1728, 1218, 1135 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.26–4.09 (m, 3 H), 3.44 (m, 1 H), 2.68 (dd, *J* = 10.3, 7.4 Hz, 1 H), 2.29 (ddd, *J* = 14.8, 7.4, 2.3 Hz, 1 H), 2.02 (ddd, *J* = 14.8, 10.3, 5.8 Hz, 1 H), 1.38 (s, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 0.89 (s, 9 H), 0.13 (s, 3 H), 0.10 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8 (C), 79.4 (C), 77.8 (CH), 73.5 (CH), 60.7 (CH_2), 50.2 (CH), 32.3 (CH_2), 25.7 (3 × CH_3), 23.8 (CH_3), 17.9 (C), 14.3 (CH_3), –4.8 (CH_3), –5.1 (CH_3).

Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 56.57; H, 9.49. Found: C, 56.29; H, 9.56.

Ethyl (3a*R*,4*S*,6*R*,6a*S*)-6-(*tert*-Butyldimethylsilyloxy)-2,2,3a-trimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxole-4-carboxylate [(+)-10]

To an ice-cold solution of diol (+)-**9** (4.0 g, 12.6 mmol) in THF (200 mL) under argon were added 2-methoxypropene (2.4 mL, 25.1 mmol, 2.0 equiv) and a catalytic amount of CSA. The solution was stirred for 3 h at r.t.; then the mixture was poured into aq $NaHCO_3$ (100 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL),

then the organic layers were combined, washed with aq $NaHCO_3$ (100 mL), H_2O (100 mL), brine (100 mL), and dried ($MgSO_4$). Concentration of the organic extracts in vacuo and purification of the residue by column chromatography gave compound (+)-**10** (4.21 g, 93%) as a clear oil; $[\alpha]_D^{25}$ +31.7 (*c* 1.0, $CHCl_3$).

IR (neat): 1728, 1237, 1205, 1094 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.23–4.12 (m, 3 H), 3.94 (d, *J* = 1.8 Hz, 1 H), 2.95 (dd, *J* = 11.3, 7.1 Hz, 1 H), 2.32 (dt, *J* = 13.6, 7.1 Hz, 1 H), 2.06 (ddd, *J* = 13.6, 11.3, 7.1 Hz, 1 H), 1.49 (s, 3 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H), 0.88 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.2 (C), 112.0 (C), 93.5 (CH), 88.5 (C), 74.8 (CH), 60.5 (CH_2), 53.3 (CH), 36.8 (CH_2), 28.3 (CH_3), 26.8 (CH_3), 25.7 (3 × CH_3), 21.7 (CH_3), 17.9 (C), 14.3 (CH_3), –4.9 (CH_3), –5.0 (CH_3).

Anal. Calcd for $C_{18}H_{35}O_5Si$: C, 60.30; H, 9.56. Found: C, 60.19; H, 9.59.

Ethyl (3a*R*,4*S*,6*R*,6a*S*)-6-Hydroxy-2,2,3a-trimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxole-4-carboxylate [(+)-11]

To an ice-cold solution of silyl ether (+)-**10** (4.0 g, 11.2 mmol) in THF (200 mL) under argon was added a 1.0 M solution of TBAF in THF (33.5 mL, 33.5 mmol, 3.0 equiv) dropwise. After stirring for 1 h at r.t., the mixture was poured into H_2O (100 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL), then the organic layers were combined, washed with H_2O (100 mL), brine (100 mL), and dried ($MgSO_4$). Concentration of the organic extracts in vacuo and purification of the residue by column chromatography gave the alcohol (+)-**11** (2.4 g, 88%) as a clear oil; $[\alpha]_D^{25}$ +64.7 (*c* 1.0, $CHCl_3$).

IR (neat): 3409, 1744, 1261, 1074 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.17–4.06 (m, 4 H), 3.02 (dd, *J* = 8.8, 2.6 Hz, 1 H), 2.37 (ddd, *J* = 14.3, 8.8, 5.0 Hz, 1 H), 1.92 (br d, *J* = 14.3 Hz, 1 H), 1.41 (s, 3 H), 1.33 (s, 3 H), 1.27 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.7 (C), 110.3 (C), 92.6 (CH), 91.3 (C), 76.0 (CH), 61.5 (CH_2), 55.9 (CH), 34.6 (CH_2), 27.6 (CH_3), 26.2 (CH_3), 23.1 (CH_3), 14.0 (CH_3).

Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.73; H, 8.19.

Ethyl (3a*R*,4*S*,6a*R*)-2,2,3a-Trimethyl-6-oxotetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxole-4-carboxylate [(–)-12]

To an ice-cold solution of alcohol (+)-**11** (2.0 g, 8.19 mmol) in CH_2Cl_2 (100 mL) under argon was added powdered 4 Å MS (10 g) and a catalytic amount of TPAP. The solution turned deep green, then NMO (2.88 g, 24.6 mmol, 3.0 equiv) was added. After stirring at r.t. for 12 h, the solution was poured into aq Na_2SO_3 (6.2 g, 49.2 mmol, 6.0 equiv) cooled in an ice bath, and stirred for 30 min. The aqueous layer was extracted with Et_2O (3 × 100 mL), then the organic layers were combined, washed with H_2O (100 mL), brine (100 mL), and dried ($MgSO_4$). Concentration of the organic extracts in vacuo and purification of the residue by column chromatography gave the ketone (–)-**12** (1.69 g, 85%) as a clear oil; $[\alpha]_D^{25}$ –103.9 (*c* 1.0, $CHCl_3$).

IR (neat): 1736, 1714, 1251, 1076 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.13 (q, *J* = 7.1 Hz, 2 H), 4.08 (br s, 1 H), 3.21 (dd, *J* = 8.4, 2.9 Hz, 1 H), 2.72 (dd, *J* = 18.6, 8.4 Hz, 1 H), 2.46 (br d, *J* = 18.6 Hz, 1 H), 1.42 (s, 3 H), 1.40 (s, 3 H), 1.28 (s, 3 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.7 (C), 172.8 (C), 112.4 (C), 86.3 (C), 83.2 (CH), 61.3 (CH_2), 48.3 (CH), 39.3 (CH_2), 28.3 (CH_3), 28.2 (CH_3), 21.1 (CH_3), 13.9 (CH_3).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.64; H, 7.53.

(3a*S*,4*S*,6*R*,6a*R*)-6-(Hydroxymethyl)-2,2,6a-trimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-ol [(–)-13]

To a stirred solution of the keto ester (–)-**12** (1.5 g, 6.19 mmol) in THF (70 mL) under argon was slowly added at –78 °C a 1.0 M solution of $LiAlH_4$ in THF (6.2 mL, 6.19 mmol, 1.0 equiv) dropwise. After stirring for 30 min at –78 °C, another portion of $LiAlH_4$ (1.0 M solution in THF, 6.2 mL, 6.19 mmol, 1.0 equiv) was added dropwise. The mixture was stirred for 6 h and the temperature was allowed to rise slowly to 0 °C. Then, Celite (13 g) and $Na_2SO_4 \cdot 10H_2O$ (13 g) were carefully added, and the mixture was stirred for a further 1 h at r.t. Concentration of the organic extracts in vacuo and recrystallization of the residue from Et_2O–PE gave compound (–)-**13** (1.14 g, 91%); white needles; mp 74–75 °C; $[\alpha]_D^{25}$ –3.1 (*c* 1.0, $CHCl_3$).

IR (KBr): 3438, 1240, 1077 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.22–4.15 (m, 2 H), 3.64 and 3.57 (*AB*X, *J* = 10.7, 6.4, 6.4 Hz, 2 H), 2.26 (AB*X*CH_2, quint, *J* = 6.4, 6.4 Hz, 1 H), 2.02–1.91 (m, 1 H) 1.82–1.72 (m, 1 H), 1.50 (s, 3 H), 1.44 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 112.4 (C), 89.9 (C), 86.5 (CH), 70.3 (CH), 62.2 (CH_2), 48.1 (CH), 36.0 (CH_2), 27.8 (CH_3), 27.5 (CH_3), 21.6 (CH_3).

Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 58.99; H, 9.01.

[(3a*R*,4*R*,6*S*,6a*S*)-6-Hydroxy-2,2,3a-trimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]methyl Ethanoate [(+)-14]

To a stirred solution of diol (–)-**13** (1.0 g, 4.94 mmol) in vinyl acetate (100 mL) was added CAL-B (*Candida antarctica B*, Novozym® 435, Novo Nordisk A/S, 100 mg). The solution was stirred for 5 h at r.t., and then filtered through a short pad of Celite. Concentration of the filtrate in vacuo and purification of the residue by column chromatography gave compound (+)-**14** (1.15 g, 95%) as a clear oil; $[\alpha]_D^{25}$ –3.9 (*c* 1.0, $CHCl_3$).

IR (neat): 3402, 1732, 1229, 1098 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.07–3.99 (m, 2 H), 3.94 and 3.84 (*AB*X, *J* = 11.3, 6.8, 5.9 Hz, 2 H), 2.25 (AB*X*CH_2, br quint, *J* = 6.5 Hz, 1 H), 1.98–1.85 (m partially overlapped, 1 H), 1.94 (s, 3 H), 1.72–1.62 (m, 1 H), 1.38 (s, 3 H), 1.32 (s, 3 H), 1.29 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6 (C), 111.9 (C), 89.2 (C), 86.1 (CH), 70.3 (CH), 63.8 (CH_2), 44.7 (CH), 35.6 (CH_2), 27.5 (CH_3), 27.2 (CH_3), 21.7 (CH_3), 20.7 (CH_3).

Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.11; H, 8.31.

(3a*S*,4*S*,6*R*,6a*R*)-6-(Acetoxymethyl)-2,2,6a-trimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl 3,5-Dinitrobenzoate [(–)-15]

To an ice-cold stirred solution of (+)-**14** (100 mg, 0.41 mmol) in anhyd CH_2Cl_2 (10 mL) was added Et_3N (172 μL, 1.23 mmol, 3.0 equiv) followed by 3,5-dinitrobenzoyl chloride (142 mg, 0.61 mmol, 1.5 equiv). The red mixture was stirred at r.t. for 12 h, then poured into H_2O (30 mL). After extraction with Et_2O (3 × 40 mL), the combined organic layers were was washed with H_2O (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification of the residue by column chromatography gave crystalline (–)-**15** (166 mg, 93%). A single crystal of (–)-**15** that was suitable for X-ray diffractometry was obtained by dissolving the chromatographically purified product in the smallest possible quantity of Et_2O in a vial, and then slowly evaporating the

solvent at r.t.; white needles; mp 96–97 °C; $[\alpha]_D^{25}$ –12.3 (*c* 1.0, $CHCl_3$).

IR (KBr): 1736, 1542, 1254 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.17 (t, *J* = 2.1 Hz, 1 H), 9.12 (d, *J* = 2.1 Hz, 2 H), 5.30–5.23 (m, 1 H), 4.49 (d, *J* = 5.4 Hz, 1 H), 4.11 and 4.02 (*AB*X, *J* = 11.5, 5.5, 4.5 Hz, 2 H), 2.54–2.43 (m, 2 H), 2.10–2.03 (m partially overlapped, 1 H), 2.07 (s, 3 H), 1.44 (s, 3 H), 1.40 (s, 3 H), 1.36 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7 (C), 162.1 (C), 148.7 (C), 133.8 (C), 129.5 (2 × CH), 122.5 (C), 112.2 (C), 89.8 (C), 84.4 (CH), 75.4 (CH), 64.1 (CH_2), 44.4 (CH_3), 32.4 (CH_2), 27.9 (CH_3), 27.8 (CH), 21.7 (CH_3), 21.0 (CH_3).

Anal. Calcd for $C_{19}H_{22}N_2O_{10}$: C, 52.06; H, 5.06; N, 6.39. Found: C, 51.92; H, 5.10; N, 6.45.

X-ray Diffraction Analysis of (–)-15

$C_{19}H_{22}N_2O_{10}$, M = 438.39 g·mol^{-1}. The colorless single crystal (crystal size : 0.3 × 0.15 × 0.15) was analyzed at 293 K with a Bruker Nonius Kappa-CCD automated four circle diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Crystal data: monoclinic, space group *C*-2, *a* = 21.6317(7) Å, *b* = 5.9730(2) Å, *c* = 18.2114(8) Å, *β* = 113.2400(10)°, *V* = 2162.10(14) Å^3, *Z* = 4, *D*x = 1.347 g/cm^3, *F*(000) = 920, and *μ*(Mo-Kα) = 1.1 cm^{-1}. 284 parameters were refined on F^2 using 2789 reflections to final indices *R*1 [$F^2 > 4\sigma(F^2)$] = 0.0558, *wR*2 [$(w = 1/[\sigma^2(F_o^2) + (0.1109\,P)^2 + 0.4306\,P)$ where $P = (F_o^2 + 2\,F_c^2)/3$] = 0.2127.[28,29]

[(3a*R*,4*R*,6*S*,6a*S*)-2,2,3a-Trimethyl-6-(trifluoromethylsulfonyloxy)tetrahydro-3a*H*-cyclopenta[*d*][1,3]dioxol-4-yl]methyl Ethanoate [(–)-16]

To an ice-cold solution of alcohol (+)-**14** (1.0 g, 4.09 mmol) in CH_2Cl_2 (75 mL) under argon was added DMAP (3.0 g, 24.6 mmol, 6.0 equiv). After 5 min, TfCl (1.1 mL, 10.2 mmol, 2.5 equiv) was added dropwise. After stirring for 15 min at 0 °C, the mixture was poured into H_2O (100 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL), and then the organic layers were combined, washed with H_2O (100 mL), brine (100 mL), and dried ($MgSO_4$). Concentration of organic extracts in vacuo and purification of the residue by column chromatography gave the triflate (–)-**16** (1.42 g, 92% yield); white needles; mp 59–60 °C; $[\alpha]_D^{25}$ –32.1 (*c* 1.0, $CHCl_3$).

IR (KBr): 1758, 1258, 1084 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.13 (ddd, *J* = 8.8, 7.0, 5.6 Hz, 1 H), 4.32 (d, *J* = 5.6 Hz, 1 H), 4.06 and 4.00 (*AB*X, *J* = 11.6, 5.0, 4.8 Hz, 2 H), 2.50 (dt, *J* = 12.5, 8.8 Hz, 1 H), 2.44–2.38 (m, 1 H), 2.05 (s, 3 H), 2.05–1.98 (m partially overlapped, 1 H), 1.46 (s, 3 H), 1.42 (s, 3 H), 1.41 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3 (C), 118.5 (q, *J* = 317 Hz, CF_3), 113.1 (C), 89.2 (C), 85.2 (CH), 84.4 (CH), 63.7 (CH_2), 44.2 (CH), 32.9 (CH_2), 27.6 (CH_3), 27.5 (CH_3), 21.6 (CH_3), 20.7 (CH_3).

Anal. Calcd for $C_{13}H_{19}F_3O_7S$: C, 41.49; H, 5.09. Found: C, 41.73; H, 5.13.

9-[(1′*R*,2′*S*,3′*R*,4′*R*)-4′-Acetoxymethyl-2′,3′-*O*-isopropylidene-3′-methylcyclopent-1′-yl]-6-chloropurine [(–)-17]

A mixture of NaH (113 mg, 2.82 mmol, 2.0 equiv) and 6-chloropurine (544 mg, 3.52 mmol, 2.5 equiv) in DMF (30 mL) was brought to 60 °C and stirred at this temperature for 2 h. The solution was cooled to 0 °C, and triflate (–)-**16** (530 mg, 1.41 mmol) in DMF (3 mL) was added dropwise. After stirring for 2 h at 60 °C, the mixture was allowed to cool to r.t. and concentrated to leave a residue that was purified by chromatography on silica gel (gradient CH_2Cl_2–MeOH) to give (–)-**17** (337 mg, 63% yield); white solid; mp 115 °C; $[\alpha]_D^{25}$ –13.7 (*c* 1.0, MeOH).

IR (KBr): 1758, 1241, 1136 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.62 (s, 1 H), 8.13 (s, 1 H), 4.82 (m, 1 H), 4.53 (d, *J* = 3.6 Hz, 1 H), 4.13 (d, *J* = 6.0 Hz, 2 H), 2.56–2.36 (m, 3 H), 1.96 (s, 3 H), 1.56 (s, 3 H), 1.43 (s, 3 H), 1.22 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6 (C), 151.4 (CH), 151.2 (C), 151.0 (C), 144.8 (CH), 132.2 (C), 113.7 (C), 90.1 (CH), 87.6 (C), 62.8 (CH_2), 60.8 (CH), 46.9 (CH), 34.1 (CH_2), 28.3 (CH_3), 26.9 (CH_3), 20.6 (2 × CH_3).

Anal. Calcd for $C_{17}H_{21}ClN_4O_4$: C, 53.62; H, 5.56; N, 14.71. Found: C, 53.99; H, 5.61; N, 15.02.

6-Cyclopropylamino-9-[(1′*R*,2′*S*,3′*R*,4′*R*)-4′-hydroxymethyl-2′,3′-*O*-isopropylidene-3′-methylcyclopent-1′-yl]purine [(–)-18]

To a solution of (–)-**17** (96 mg, 0.25 mmol) in MeOH (5 mL) under argon was added cyclopropylamine (1 mL). The mixture was brought to 50 °C, stirred for 12 h, allowed to cool to r.t. and concentrated in vacuo. The crude residue was dissolved in NH_3/MeOH (ca. 7 M, 6 mL) and the resulting mixture stirred at r.t. for 12 h. Removal of solvent and purification of the residue by chromatography on silica gel (gradient CH_2Cl_2–MeOH) gave (–)-**18** (71 mg, 78%) as a foam; $[\alpha]_D^{25}$ –14.8 (*c* 1.0, MeOH).

IR (KBr): 3368, 1245, 1139 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.36 (s, 1 H), 7.73 (s, 1 H), 6.49 (br s, 1 H, D_2O exch), 4.75 (m, 1 H), 4.53 (d, *J* = 3.4 Hz, 1 H), 3.86–3.78 (m, 1 H), 3.70–3.62 (m, 1 H), 3.50 (br s, 1 H, D_2O exch), 2.95 (m, 1 H), 2.43–2.31 (m, 3 H), 1.60 (s, 3 H), 1.48 (s, 3 H), 1.27 (s, 3 H), 0.85 (m, 2 H), 0.59 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.7 (C), 152.8 (CH), 148.9 (C), 139.2 (CH), 120.4 (C), 113.5 (C), 90.8 (CH), 88.2 (C), 61.3 (CH_2), 60.4 (CH), 50.3 (CH), 34.2 (CH_2), 28.5 (CH_3), 27.0 (CH_3), 23.5 (CH), 20.6 (CH_3), 7.2 (2 × CH_2).

Anal. Calcd for $C_{18}H_{25}N_5O_3$: C, 60.15; H, 7.01; N, 19.48. Found: C, 59.99; H, 7.08; N, 19.83.

6-Cyclopropylamino-9-[(1′*R*,2′*S*,3′*R*,4′*R*)-2′,3′-dihydroxy-4′-hydroxymethyl-3′-methylcyclopent-1′-yl] purine [(–)-2]

A solution of (–)-**18** (65 mg, 0.18 mmol) in HCl (1 M, 8 mL) was stirred at 50 °C for 12 h. The mixture was then cooled, neutralized with Amberlyst IRA-67, filtered, and concentrated. Purification of the residue by chromatography on silica gel (gradient CH_2Cl_2–MeOH) gave (–)-**2** (49 mg, 87%); white solid; mp 55 °C; $[\alpha]_D^{25}$ –26.0 (*c* 1.0, MeOH).

IR (KBr): 3462, 1263, 1088 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 8.24 (s, 1 H), 8.15 (s, 1 H), 4.86 (q, *J* = 9.6 Hz, 1 H, partially overlapped with HDO), 4.36 (d, *J* = 9.6 Hz, 1 H), 3.74 (d, *J* = 4.8 Hz, 2 H), 2.92 (m, 1 H), 2.61 (dt, *J* = 13.5, 9.6 Hz, 1 H), 2.15 (dq, *J* = 9.6, 4.8 Hz, 1 H), 2.04 (ddd, *J* = 13.5, 9.6, 4.8 Hz, 1 H), 1.36 (s, 3 H), 0.86 (m, 2 H), 0.63 (m, 2 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 157.0 (C), 153.1 (CH), 150.0 (C), 141.9 (CH), 121.1 (C), 81.0 (CH), 78.7 (C), 64.0 (CH_2), 61.7 (CH), 48.6 (CH), 30.3 (CH_2), 24.5 (CH), 21.6 (CH_3), 7.6 (2 × CH_2).

Anal. Calcd for $C_{15}H_{21}N_5O_3$: C, 56.41; H, 6.63; N, 21.93. Found: C, 56.17; H, 6.68; N, 22.11.

9-[(1′*R*,2′*S*,3′*R*,4′*R*)-4′-Hydroxymethyl-2′,3′-*O*-isopropylidene-3′-methylcyclopent-1′-yl]hypoxanthine [(–)-19]

To a solution of (–)-**17** (96 mg, 0.25 mmol) in MeOH (5 mL) under argon was added 2-mercaptoethanol (177 μL, 2.53 mmol, 10 equiv) and NaOMe (5.0 M solution in MeOH, 505 μL, 2.53 mmol, 10 equiv). The mixture was heated to reflux for 12 h, allowed to cool to r.t., and concentrated in vacuo. The residue was purified by chromatography on silica gel (gradient CH_2Cl_2–MeOH) to afford 66 mg

(82%) of (–)-**19**; white solid; mp >235 °C (dec.); $[\alpha]_D^{25}$ –8.9 (*c* 1.0, MeOH).

IR (KBr): 3444, 1443, 1239, 1089 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 12.10 (br s, 1 H, D_2O exch), 8.25 (s, 1 H), 8.05 (s, 1 H), 4.85 (m, 1 H), 4.42 (d, *J* = 4.2 Hz, 1 H), 3.60 and 3.39 (*AB*X, *J* = 10.5, 7.2, 4.8 Hz, 2 H), 3.50 (br s, 1 H, D_2O exch), 2.39–2.11 (m, 3 H), 1.44 (s, 6 H), 1.24 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 156.7 (C), 148.2 (C), 145.6 (CH), 139.4 (CH), 124.6 (C), 112.7 (C), 91.0 (CH), 87.8 (C), 60.1 (CH_2), 59.0 (CH), 50.3 (CH), 34.8 (CH_2), 28.7 (CH_3), 27.4 (CH_3), 20.8 (CH_3).

Anal. Calcd for $C_{15}H_{20}N_4O_4$: C, 56.24; H, 6.29; N, 17.49. Found: C, 55.89; H, 6.35; N, 17.76.

9-[(1′*R*,2′*S*,3′*R*,4′*R*)-2′,3′-Dihydroxy-4′-hydroxymethyl-3′-methylcyclopent-1′-yl]hypoxanthine [(–)-3]

Starting from (–)-**19** (55 mg, 0.17 mmol), compound (–)-**3** (41 mg, 86%) was prepared in the same manner as that for (–)-**2**; white solid; mp >250 °C (dec.); $[\alpha]_D^{25}$ –18.8 (*c* 1.0, DMSO).

IR (KBr): 3387, 1461, 1233, 1090 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 12.28 (br s, 1 H, D_2O exch), 8.16 (s, 1 H), 8.01 (s, 1 H), 5.06 (br s, 1 H, D_2O exch), 4.71 (q, *J* = 9.4 Hz, 1 H), 4.34 (br s, 1 H, D_2O exch), 4.07 (d, *J* = 9.4 Hz, 1 H), 3.51 and 3.44 (*AB*X, *J* = 10.5, 6.4, 5.1 Hz, 2 H), 3.36 (br s, 1 H, D_2O exch), 2.34 (dt, *J* = 13.2, 9.4 Hz, 1 H), 1.97 (AB*X*, br dq, *J* = 9.4, 5.8 Hz, 1 H), 1.70 (ddd, *J* = 13.2, 9.5, 5.8 Hz, 1 H), 1.18 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 156.8 (C), 148.8 (C), 145.2 (CH), 139.0 (CH), 124.2 (C), 79.4 (CH), 76.3 (C), 62.0 (CH_2), 58.8 (CH), 47.0 (CH), 30.2 (CH_2), 21.6 (CH_3).

Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.60; H, 5.79; N, 19.74.

9-[(1′*R*,2′*S*,3′*R*,4′*R*)-4′-Acetoxymethyl-2′,3′-*O*-isopropylidene-3′-methylcyclopent-1′-yl]-2,6-diaminopurine [(–)-20]

Starting from triflate (–)-**16** (200 mg, 0.53 mmol) and 2,6-diaminopurine (159 mg, 1.06 mmol), derivative (–)-**20** (144 mg, 72%) was prepared according to the same procedure used in the preparation of (–)-**17**; white solid; mp 151 °C; $[\alpha]_D^{25}$ –15.4 (*c* 1.0, MeOH).

IR (KBr): 3309, 1748, 1238, 1092 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.83 (s, 1 H), 6.73 (br s, 2 H, D_2O exch), 5.78 (br s, 2 H, D_2O exch), 4.73 (td, *J* = 9.8, 3.6 Hz, 1 H), 4.43 (d, *J* = 3.6 Hz, 1 H), 4.11 (d, *J* = 7.3 Hz, 2 H), 2.44–2.36 (m, 1 H), 2.29–2.22 (m, 2 H), 2.01 (s, 3 H), 1.52 (s, 3 H), 1.44 (s, 3 H), 1.26 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.4 (C), 160.1 (C), 156.2 (C), 151.5 (C), 136.3 (CH), 113.5 (C), 112.5 (C), 90.5 (CH), 87.5 (C), 62.9 (CH_2), 57.4 (CH), 46.6 (CH), 34.1 (CH_2), 28.5 (CH_3), 27.0 (CH_3), 20.7 (CH_3), 20.5 (CH_3).

Anal. Calcd for $C_{17}H_{24}N_6O_4$: C, 54.24; H, 6.43; N, 22.33. Found: C, 53.97; H, 6.48; N, 22.15.

2,6-Diamino-9-[(1′*R*,2′*S*,3′*R*,4′*R*)-2′,3′-dihydroxy-4′-hydroxymethyl-3′-methylcyclopent-1′-yl]purine [(–)-4]

To an ice-cold solution of (–)-**20** (100 mg, 0.27 mmol) in H_2O (6 mL) under argon was carefully added CF_3CO_2H (12 mL) and the mixture was stirred at r.t. for 12 h. The solvents were removed in vacuo, the crude *vic*-diol dissolved in NH_3/MeOH (ca. 7 M, 10 mL) and the mixture stirred at r.t. for 24 h. After concentration, the residue was purified by chromatography on silica gel (gradient CH_2Cl_2–MeOH) to give 57 mg (74%) of (–)-**4**; white solid; mp >220 °C (dec.); $[\alpha]_D^{25}$ –16.4 (*c* 1.0, MeOH).

IR (KBr): 3402, 1237, 1079 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 7.99 (s, 1 H), 4.72 (q, *J* = 9.5 Hz, 1 H), 4.26 (d, *J* = 9.5 Hz, 1 H), 3.72 (d, *J* = 5.3 Hz, 2 H), 2.54 (dt, *J* = 13.6, 9.5 Hz, 1 H), 2.12 (dq, *J* = 9.5, 5.3 Hz, 1 H), 1.97 (ddd, *J* = 13.6, 9.5, 5.3 Hz, 1 H), 1.34 (s, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 156.1 (C), 153.9 (C), 153.1 (C), 141.2 (CH), 113.7 (C), 80.8 (CH), 78.6 (C), 63.8 (CH_2), 61.2 (CH), 48.6 (CH), 30.0 (CH_2), 21.6 (CH_3).

Anal. Calcd for $C_{12}H_{18}N_6O_3$: C, 48.97; H, 6.16; N, 28.56. Found: C, 50.19; H, 6.12; N, 28.29.

9-[(1′*R*,2′*S*,3′*R*,4′*R*)-4′-Acetoxymethyl-2′,3′-*O*-isopropylidene-3′-methylcyclopent-1′-yl]-2-amino-6-chloropurine [(–)-21]

Starting from triflate (–)-**16** (500 mg, 1.33 mmol) and 2-amino-6-chloropurine (466 mg, 2.66 mmol), derivative (–)-**21** (366 mg, 70%) was prepared according to the same procedure used in the preparation of (–)-**17**; white solid; mp 128 °C; $[\alpha]_D^{25}$ –9.8 (*c* 1.0, MeOH).

IR (KBr): 3480, 1732, 1266, 1029 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 8.26 (s, 1 H), 6.91 (br s, 2 H, D_2O exch), 4.82 (td, *J* = 10.8, 3.6 Hz, 1 H), 4.45 (d, *J* = 3.6 Hz, 1 H), 4.11 (dd, *J* = 7.2, 2.1 Hz, 2 H), 2.47–2.25 (m, 3 H), 2.01 (s, 3 H), 1.52 (s, 3 H), 1.44 (s, 3 H), 1.26 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.4 (C), 159.6 (C), 153.8 (C), 149.6 (C), 142.1 (CH), 123.7 (C), 112.7 (C), 90.3 (CH), 87.6 (C), 62.8 (CH_2), 58.0 (CH), 46.6 (CH), 33.7 (CH_2), 28.5 (CH_3), 27.0 (CH_3), 20.7 (CH_3), 20.4 (CH_3).

Anal. Calcd for $C_{17}H_{22}ClN_5O_4$: C, 51.58; H, 5.60; N, 17.69. Found: C, 51.81; H, 5.65; N, 17.43.

2-Amino-6-cyclopropylamino-9-[(1′*R*,2′*S*,3′*R*,4′*R*)-4′-hydroxymethyl-2′,3′-*O*-isopropylidene-3′-methylcyclopent-1′-yl]purine [(–)-22]

Starting from (–)-**21** (100 mg, 0.25 mmol), derivative (–)-**22** (71 mg, 76%) was prepared according to the same procedure used in the preparation of (–)-**18**; foam; $[\alpha]_D^{25}$ –12.3 (*c* 1.0, MeOH).

IR (KBr): 3408, 1262, 1089 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.44 (s, 1 H), 6.12 (br s, 1 H, D_2O exch), 4.96 (br s, 2 H, D_2O exch), 4.62 (td, *J* = 10.6, 3.3 Hz, 1 H), 4.53 (d, *J* = 3.3 Hz, 1 H), 3.79 and 3.64 (*AB*X, *J* = 10.6, 6.4, 6.2 Hz, 2 H), 3.50 (br s, 1 H, D_2O exch), 2.92 (m, 1 H), 2.45–2.24 (m, 3 H), 1.58 (s, 3 H), 1.50 (s, 3 H), 1.30 (s, 3 H), 0.80 (m, 2 H), 0.56 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.6 (C), 156.2 (C), 150.8 (C), 136.7 (CH), 115.1 (C), 113.2 (C), 90.7 (CH), 88.2 (C), 61.4 (CH_2), 59.7 (CH), 50.3 (CH), 34.1 (CH_2), 28.5 (CH_3), 27.0 (CH_3), 23.5 (CH), 20.6 (CH_3), 7.3 (2 × CH_2).

Anal. Calcd for $C_{18}H_{26}N_6O_3$: C, 57.74; H, 7.00; N, 22.44. Found: C, 57.39; H, 6.97; N, 22.66.

2-Amino-6-cyclopropylamino-9-[(1′*R*,2′*S*,3′*R*,4′*R*)-2′,3′-dihydroxy-4′-hydroxymethyl-3′-methylcyclopent-1′-yl]purine [(–)-5]

Starting from (–)-**22** (60 mg, 0.16 mmol), compound (–)-**5** (46 mg, 90%) was prepared according to the same procedure used in the preparation of (–)-**2**; white solid; mp 96 °C; $[\alpha]_D^{25}$ –38.4 (*c* 1.0, MeOH).

IR (KBr): 3419, 1263, 1078 cm^{-1}.

^1H NMR (300 MHz, MeOH-d_4): δ = 7.76 (s, 1 H), 4.68 (q, *J* = 9.4 Hz, 1 H), 4.29 (d, *J* = 9.4 Hz, 1 H), 3.73 (d, *J* = 4.8 Hz, 2 H), 2.89 (tt, *J* = 7.0, 3.5 Hz, 1 H), 2.58 (dt, *J* = 13.5, 9.4, 1 H), 2.12 (dq,

J = 9.4, 4.8 Hz, 1 H), 2.02 (ddd, J = 13.5, 9.4, 4.8 Hz, 1 H), 1.35 (s, 3 H), 0.81 (m, 2 H), 0.59 (m, 2 H).

^{13}C NMR (75 MHz, MeOH-d_4): δ = 161.3 (C), 157.5 (C), 151.8 (C), 139.0 (CH), 115.3 (C), 80.9 (CH), 78.9 (C), 64.1 (CH_2), 61.4 (CH), 48.6 (CH), 29.9 (CH_2), 24.3 (CH), 21.5 (CH_3), 7.6 (2 × CH_2).

Anal. Calcd for $C_{15}H_{22}N_6O_3$: C, 53.88; H, 6.63; N, 25.13. Found: C, 53.45; H, 6.69; N, 24.83.

9-[(1′*R*,2′*S*,3′*R*,4′*R*)-4′-Hydroxymethyl-2′,3′-*O*-isopropylidene-3′-methylcyclopent-1′-yl]guanine [(–)-23]

Starting from (–)-**21** (100 mg, 0.25 mmol), derivative (–)-**23** (73 mg, 87%) was prepared according to the same procedure used in the preparation of (–)-**19**; foam; $[\alpha]_D^{25}$ –7.2 (*c* 1.0, MeOH).

IR (KBr): 3429, 1264, 1072 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.11 (br s, 1 H, D_2O exch), 7.82 (s, 1 H), 6.77 (br s, 2 H, D_2O exch), 4.65 (ddd, J = 11.3, 7.4, 3.8 Hz, 1 H), 4.35 (d, J = 3.8 Hz, 1 H), 3.60 and 3.39 (*AB*X, J = 10.4, 7.6, 5.1 Hz, 2 H), 3.50 (br s, 1 H, D_2O exch), 2.35–2.00 (m, 3 H), 1.43 (s, 6 H), 1.24 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 157.0 (C), 153.8 (C), 151.0 (C), 136.2 (CH), 116.9 (C), 112.5 (C), 90.9 (CH), 87.8 (C), 60.2 (CH_2), 57.9 (CH), 50.4 (CH), 35.0 (CH_2), 28.7 (CH_3), 27.2 (CH_3), 20.7 (CH_3).

Anal. Calcd for $C_{15}H_{21}N_5O_4$: C, 53.72; H, 6.31; N, 20.88. Found: C, 54.01; H, 6.26; N, 21.19.

9-[(1′*R*,2′*S*,3′*R*,4′*R*)-2′,3′-Dihydroxy-4′-hydroxymethyl-3′-methylcyclopent-1′-yl]guanine [(–)-6]

Starting from (–)-**23** (60 mg, 0.18 mmol), compound (–)-**6** (45 mg, 76%) was prepared according to the same procedure used in the preparation of (–)-**2**, except that derivative (–)-**6** was obtained as the chlorhydrate salt after concentration and crystallization from MeOH–H_2O; white solid; mp >245 °C (dec.); $[\alpha]_D^{25}$ –5.9 (*c* 1.0, H_2O).

IR (KBr): 3419, 1253, 1094 cm^{-1}.

^{1}H NMR (400 MHz, D_2O, 315 K): δ = 8.99 (s, 1 H), 4.86 (q, J = 9.4 Hz, 1 H), 4.33 (d, J = 9.4 Hz, 1 H), 3.80 and 3.70 (*AB*X, J = 11.2, 7.1, 5.3 Hz, 2 H), 2.64 (dt, J = 13.9, 9.4 Hz, 1 H), 2.25 (AB*X*, m, 1 H), 1.96 (ddd, J = 13.9, 9.4, 6.5 Hz, 1 H), 1.35 (s, 3 H).

^{13}C NMR (75 MHz, D_2O, 315 K): δ = 156.5 (2 × C), 151.8 (C), 137.9 (CH), 109.5 (C), 80.4 (CH), 78.7 (C), 63.6 (CH_2), 62.4 (CH), 48.1 (CH), 29.7 (CH_2), 21.8 (CH_3).

Anal. Calcd for $C_{12}H_{18}ClN_5O_4$: C, 43.44; H, 5.47; N, 21.11. Found: C, 43.56; H, 5.42; N, 21.43.

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