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First enantioselective synthesis of (−)-neplanocin F

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Abstract—(−)-Neplanocin F, the natural isomer of a component of the neplanocin family was enantioselectively synthesized starting from D-γ-ribonolactone. The synthetic approach was based on the preparation of a suitable carbocyclic precursor bearing three hydroxyl groups orthogonally protected. The key steps of the synthesis were the regioselective protection of a secondary allylic alcohol over a homoallylic one and the coupling of the nucleobase with a triflate intermediate.
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1. Introduction

The neplanocin derivatives are an important class of naturally occurring carbocyclic nucleosides isolated from *Ampullariella regularis*.[1] To date, five distinct components were identified: (−)-neplanocin A (**1**), (−)-neplanocin B (**2**), (−)-neplanocin C (**3**), (−)-neplanocin D (**4**) and (−)-neplanocin F (**5**) (Fig. 1). Among these, (−)-neplanocin A received greater attention due to its interesting biological properties[2] and numerous syntheses of neplanocin A[3] as well as its analogues were published.[4] Conversely, only two syntheses of neplanocin F, the allylic rearranged isomer of (−)-neplanocin A, were reported including the total synthesis as a racemate[5] of (+/−)-neplanocin F as well as the enantioselective synthesis of its unnatural (+) enantiomer.[6] In order to evaluate the biological properties of such carbanucleoside against emerging pathogens, its enantioselective synthesis was reconsidered. In addition, (−)-neplanocin F could be considered as an attractive template giving an access, through appropriate chemical modifications, to new series of nucleoside derivatives displaying potential biological properties. In this paper, results concerning the optimization of the enantioselective synthesis of (−)-neplanocin F are presented.

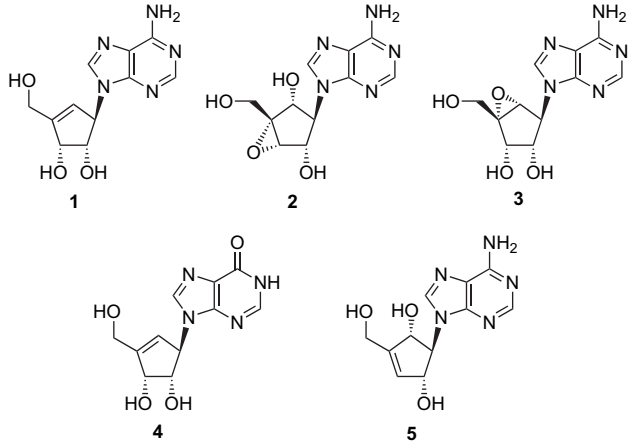

Figure 1. Naturally occuring carbocyclic nucleosides from the neplanocin family.

2. Results and discussion

2.1. Retrosynthetic pathway

The synthesis of the natural isomer of (−)-neplanocin F (**5**) was envisioned via S_N2 coupling of the heterocyclic nucleobase with a suitable carbocyclic intermediate bearing appropriate protective groups (Fig. 2). Such an intermediate can be obtained from (4*R*,5*R*)-4,5-isopropylidene-2-cyclopentenone (**6**). Compound **6** is readily prepared from commercially available D-γ-ribonolactone following previously established procedures.[7] The cyclopentenone **6** was extensively used as chiral starting material in organic synthesis.[8] Indeed, numerous natural and unnatural products, such as carbocyclic nucleosides,[9] were prepared from this cyclopentenone derivative. For our part, compound **6** seemed to us as the ideal precursor for the synthesis of the carbocyclic intermediate in which the hydroxyl group at C-5 was free, while the other hydroxyl groups (at C-1, C-4 and C-6) remained protected. Introduction of the base and removal of the protective groups should finally afford (−)-neplanocin F (**5**).

Keywords: Neplanocin; Carbocyclic nucleosides; Enantioselective synthesis.
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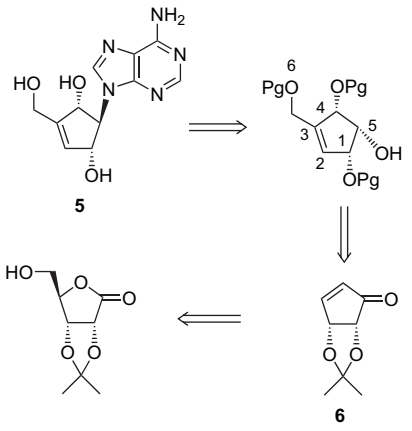
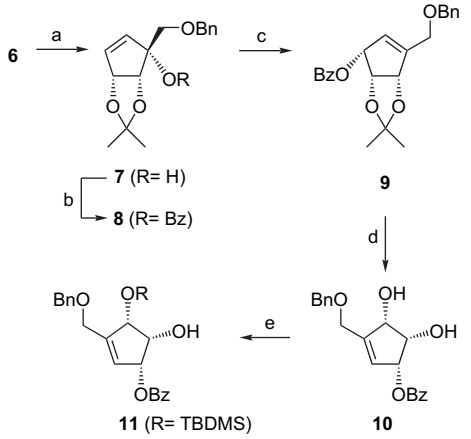


Figure 2. Retrosynthetic pathway. Pg=various protective groups.

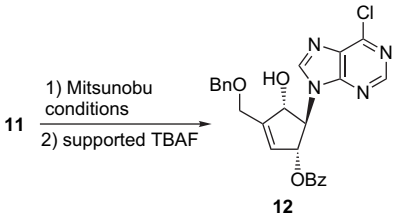
2.2. Synthesis

Addition of the carbanion (Scheme 1), generated in situ from $BnOCH_2SnBu_3$ and *n*-butyllithium in dry THF at −78 °C, to compound **6** gave cyclopentenyl alcohol **7** stereoselectively by an 1,2-addition mechanism. The stereochemistry of **7** may be explained by a nucleophilic attack from the less hindered β-face due to the presence of the isopropylidene group.[10] ^1H and ^{13}C NMR spectra were in accordance with the presence of an unique epimer (the stereoisomer resulting from a α-nucleophilic attack was not detected). The alcohol **7** was then protected using benzoyl chloride in pyridine at room temperature. From benzoate **8**, the carbocyclic frame of the natural isomer of (−)-neplanocn F can be readily obtained following a [3,3]-sigmatropic rearrangement.[11] Thus, treatment of the allylic ester **8** with a catalytic amount of $PdCl_2[CH_3CN]_2$ and *p*-benzoquinone in dry THF under reflux provided the regioisomer **9**.[12] Cleavage of the acetonide group via treatment with acetic acid at 60 °C gave the desired diol **10** in good yield. Nevertheless, the benzoate group of compound **10** has a tendency to migrate on standing for long time at room temperature and therefore it must be kept at −20 °C. At this stage of the synthesis, the selective protection of the allylic alcohol of **10** was the key step for the synthesis of the target molecule. Owing to the presence of the benzyl and benzoyl protective groups, the orthogonal *tert*-butyldimethylsilyl group was chosen. Thus, treatment of compound **10** with *tert*-butyldimethylsilyl triflate and 2,6-lutidine in dry CH_2Cl_2 at −78 °C gave **11**.[13] The structure of compound **11** was confirmed by ^1H NMR and ^1H–^1H COSY experiments as well as with selective irradiation of protons H-1, H-2, H-4 and H-5.



Scheme 1. Reagents and conditions: (a) $BnOCH_2SnBu_3$, *n*-BuLi, THF, −78 °C, 74%; (b) BzCl, pyridine, rt, 72%; (c) $PdCl_2[CH_3CN]_2$, *p*-benzoquinone, THF, 85 °C, 82%; (d) AcOH (50%)/H_2O, 60 °C, 80% and (e) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C to rt, 78%.

Once the synthesis of the suitable carbocyclic intermediate bearing appropriate protective groups **11** was achieved, introduction of the base (6-chloropurine) was attempted via a Mitsunobu-type reaction (Scheme 2), which was successfully employed to provide carbocyclic nucleosides.[14] Different reaction conditions (Table 1) were attempted. As the coupling product was inseparable from the attendant hydrazine generated from DIAD,[15] a silyl group deprotection of the latter using polymer supported TBAF in THF was undertaken providing compound **12**.



Scheme 2. Reagents and conditions: see Table 1.

However, the Mitsunobu conditions did not give the desired product with satisfactory yields. The best result (entry 7) was obtained when DIAD (3 equiv) was added over a mixture of PPh_3 (3 equiv) and 6-chloropurine (3 equiv) in dry THF at 0 °C and under an argon atmosphere. After 30 min, a solution of **11** in THF was added and the reaction was heated at 55 °C for 24 h. After work-up and purification by column chromatography, the crude material was dissolved in THF and treated with polymer supported TBAF in THF for 90 min to afford after purification compound **12** with 20% yield. As an alternative attempt, we have tried to activate the homoallylic hydroxyl group by means of its triflate in order to introduce the base via a nucleophilic substitution, however without success (data not shown). Therefore, at this stage

Table 1. Mitsunobu coupling conditions between **11** and 6-chloropurine

Entry	Mitsunobu conditions[a]	Time and temperature	Yield (%)
1	A	24 h at rt	No coupling
2	A	96 h at rt	14
3	A	48 h at 50 °C	14
4	A	24 h at 75 °C	14
5	A[b]	24 h at 75 °C	12
6	B	72 h at rt	19
7	B	24 h at 55 °C	20
8	A[c]	10 min at 80 °C	No coupling

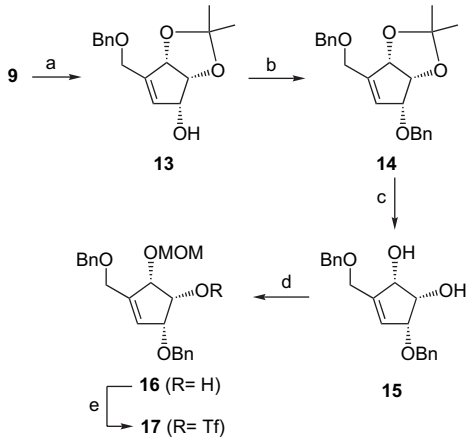
Yields of compound **12** after TBDMS group deprotection.

[a] *Method A*: DIAD (3 equiv) was added over the mixture formed by PPh_3 (3 equiv), 6-chloropurine (3 equiv) and alcohol **11** (1 equiv) in dry THF, at 0 °C under argon; *Method B*: DIAD (3 equiv) added over the mixture formed by PPh_3 (3 equiv) and 6-chloropurine (3 equiv) in THF, at 0 °C under argon. After 30 min at 0 °C, **11** (1 equiv) in THF was added.

[b] Reaction was carried out in 1,4-dioxane.

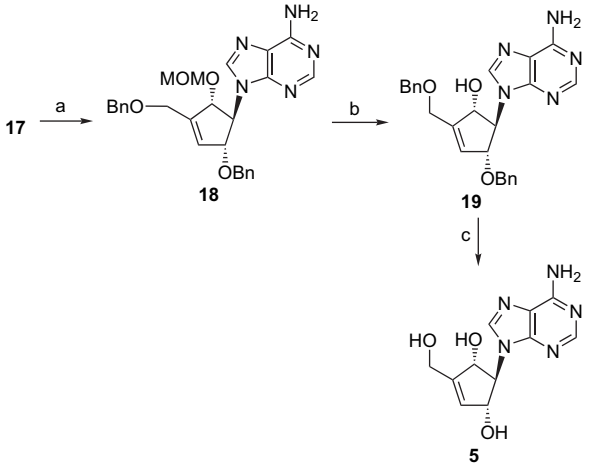
[c] Microwave was used (1 bar, 40 W). The reaction was performed in a sealed tube (Pyrex).

of the synthesis, compound **12** seemed not to be the ideal carbocyclic precursor for the synthesis of (−)-neplanocin F. Thus, the synthesis of such a precursor was reconsidered from compound **9**. The modifications envisioned were the introduction of a benzyl group at C-1 position as well as the selective protection of the allylic alcohol after acetonide removal. In this regard, compound **9** (Scheme 3) was treated with NaOH in methanol giving **13** after purification by column chromatography.



Scheme 3. Reagents and conditions: (a) NaOH (1%) in MeOH, rt, 90%; (b) BnBr, NaH, DMF, rt, 88%; (c) AcOH (60%)/H_2O, 50 °C, 93%; (d) (i) $HC(OCH_3)_3$, $Ce(NH_4)_2(NO_3)_6$, CH_2Cl_2, rt; (ii) DIBAL-H, toluene, −78 °C, 60% overall yield and (e) Tf_2O, DMAP, CH_2Cl_2, 0 °C, 97%.

Compound **13** was converted into **14** using standard conditions. The cleavage of the acetonide group was accomplished by treatment of **14** with acetic acid at 50 °C for 16 h to afford in quantitative yield the diol **15**. The selective protection of the allylic hydroxyl position of the resulting diol **15** was achieved following a procedure recently reported.[6] Such an approach is based upon the preparation of an orthoester intermediate from the corresponding diol with trimethyl orthoformate followed by reductive cleavage with DIBAL-H in methylene chloride at low temperature. Under these conditions, compound **16** was obtained in 60% yield. The position of the MOM protective group at the allylic position was confirmed by selective irradiation of the protons of the cyclopentene ring. Mitsunobu-type reaction was envisioned between the precursor **16** and 6-chloropurine but gave the coupling product with low yields (≈30%). Our data are not in agreement with those previously reported in the lit. 6. To overcome these low yields in the coupling reaction, we attempted a nucleophilic displacement on an activated sugar precursor with the heterocyclic base. Thus, compound **16** was treated with Tf_2O[16] and DMAP in dry CH_2Cl_2 to afford **17** in good yield after purification by silica gel column chromatography. Thereafter, treatment of **17** (Scheme 4) with K_2CO_3, adenine and a catalytic amount of 18-crown-6 ether in dry DMF[17] under an argon atmosphere at 60 °C for 3 h afforded the N-9 alkylated compound **18** without a trace of the undesired N-7 isomer as by-product, as established by ^{1}H NMR and UV spectra. From compound **18**, the deprotection of MOM ether group can give access to subsequent functionalizations of this allylic position. The selective MOM group removal[6] was carried out with diluted TFA in methylene chloride providing **19** in 75% yield. Finally, compound **19** was fully deprotected by treatment with boron trichloride in methylene chloride affording the target molecule (−)-neplanocin F (**5**). The ^{1}H NMR was superimposable with that previously reported for the racemic product[5] as well as for the unnatural enantiomer.[6] The optical rotation value was in agreement with the one previously reported.[18]



Scheme 4. Reagents and conditions: (a) K_2CO_3, 18-crown-6 ether, DMF, 60 °C, 60%; (b) TFA (18%)/CH_2Cl_2, 75% and (c) (i) BCl_3, CH_2Cl_2, −78 °C; (ii) MeOH, −78 °C, 84% overall yield.

In conclusion, the efficient synthesis of natural isomer (−)-neplanocin F (**5**) was realized from 2,3-*O*-isopropylidene-D-1,4-ribonolactone in 15 steps. The synthetic methodology can give an access, through appropriate functionalizations to new series of carbanucleosides. Further investigations are in progress in our laboratory.

3. Experimental

3.1. General

All moisture-sensitive reactions were carried out in oven-dried glassware under an argon atmosphere. Unless otherwise noted, chemicals were commercially available and used without further purification. Solvents were distilled before use. Tetrahydrofuran was distilled from sodium/benzophenone, methylene chloride was distilled from phosphorous pentoxide. Anhydrous *N*,*N*-dimethylformamide and pyridine were used as supplied from Fluka.

Nuclear magnetic resonance spectra were recorded using a Bruker AC-300 MHz or Bruker AC-400 MHz spectrometer. Chemicals shifts are reported in parts per million relative to TMS as an internal standard. The ^{1}H NMR spectra are referenced with respect to $CDCl_3$ at 7.26 ppm or to DMSO-d_6 at 2.50 ppm. ^{13}C NMR spectra were fully decoupled and referenced to $CDCl_3$ at 77.0 ppm or to DMSO-d_6 at 39.5 ppm. Splitting patterns are designated as follows: s, singlet; d, doublet; q, quadruplet; dd, doublet of doublets and m, multiplet. Melting points were taken on a Büchi-545 capillary melting point apparatus and are uncorrected. Column chromatography was carried out on Silica Gel 60 (Merck, Art. 9385). Reverse phase (C18) purification was performed by

Silica Merck LiChroprep RP-18. UV spectra were recorded on an Uvikon 931 (Kontron) spectrophotometer. Mass spectra were recorded on a JEOL SX 102 in FAB positive-ion or negative-ion mode. The matrix was a mixture (50:50, v/v) of glycerol and thioglycerol (GT). Specific rotations were measured on a Perkin Elmer model 341 spectropolarimeter (path length 1 cm). Elemental analyses were performed by The Service de Microanalyses du CNRS, Division de Vernaison (France).

3.1.1. (−)-(1*S*,4*R*,5*R*)-1-[(Benzyloxy)methyl]-4,5-(isopropylidenedioxy)-3-cyclopenten-1-ol (7). To a stirred solution of Bu_3SnCH_2OBn[19] (64 g, 2 equiv) in freshly distilled THF (470 mL) was added *n*-butyllithium (73 mL, 1.5 equiv) at −78 °C and the resulting solution was stirred for 20 min. To this mixture was added **6** (11.91 g, 77.337 mmol) in freshly distilled THF (234 mL) at −78 °C and the mixture was stirred for 1 h and 20 min. The reaction was quenched with a saturated ammonium chloride solution (100 mL), then diluted with diethyl ether (700 mL), washed successively with water (300 mL), brine (300 mL), dried (Na_2SO_4) and concentrated to dryness under reduced pressure. The residue was purified by column chromatography using petroleum ether/ethyl acetate (8:2–6:4, v/v) to give **7** as a colourless syrup (15.84 g, 74% yield): R_f (petroleum ether/ethyl acetate; 8:2 v/v) 0.26; $[\alpha]_D^{20}$ −95 (*c* 1.0, $EtOH_{abs}$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29–7.37 (m, 5H, Ar*H*), 5.95 (dd, 1H, *J*=1.7, 7.5 Hz, *H*3), 5.79 (d, 1H, *J*=7.25 Hz, *H*2), 5.07 (dd, 1H, *J*=1.65, 5.45 Hz, *H*4), 4.59 (s, 2H, CH_2), 4.54 (d, 1H, *J*=5.45 Hz, *H*5), 3.59 (d, 1H, *J*=9.46 Hz, CH_2O), 3.47 (d, 1H, *J*=9.47 Hz, CH_2O), 3.21 (br s, 1H, O*H*), 1.47 (s, 3H, CH_3), 1.42 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.97 (*C*q), 136.96 (*C*3), 132.96 (*C*2), 128.39 (*Ar*H×2), 127.69 (*Ar*H×2), 127.60 (*Ar*H), 112.60 (*C*q), 83.87 (*C*4), 81.71 (*C*q), 80.42 (*C*5), 73.97 (*C*H_2), 73.60 (*C*H_2), 27.72 (*C*H_3), 26.60 (*C*H_3); FABMS (<0) *m*/*z* 275 $[M-H]^-$. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.24; H, 7.26.

3.1.2. (−)-(1*S*,4*R*,5*R*)-1-Benzoyloxy-1-[(benzyloxy)methyl]-4,5-(isopropylidenedioxy)-3-cyclopentene (8). To a stirred solution of **7** (7.4 g, 27 mmol) in dry pyridine (90 mL) was added dropwise benzoyl chloride (4.7 mL, 40.5 mmol) and the resulting solution was stirred overnight at room temperature. The solvent was removed and the residue was partitioned between CH_2Cl_2 (100 mL) and water (100 mL). The organic layer was washed with brine (100 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography using dichloromethane/ethyl acetate (99:1, v/v) to give **8** as a colourless syrup (7.38 g, 72% yield): R_f (dichloromethane) 0.63; $[\alpha]_D^{20}$ −58 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95–7.98 (m, 2H, Ar*H*), 7.45–7.50 (m, 1H, Ar*H*), 7.33–7.38 (m, 2H, Ar*H*), 7.16–7.26 (m, 5H, Ar*H*), 6.12 (d, 1H, *J*=6.0 Hz, *H*2), 6.02 (dd, 1H, *J*=1.5, 6.0 Hz, *H*3), 5.04 (d, 1H, *J*=0.86, 5.5 Hz, *H*4), 4.85 (d, 1H, *J*=5.5 Hz, *H*5), 4.45 (s, 2H, CH_2), 3.90 (q, 2H, *J*=9.5 Hz, CH_2), 1.27 (s, 3H, CH_3), 1.24 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.5 (*C*=O), 136.7 (*C*q), 133.6 (*C*3), 132.6 (*C*2), 131.7 (*Ar*H), 129.7 (*C*q), 128.7 (*Ar*H×2), 127.3 (*Ar*H×2), 127.1 (*Ar*H×2), 126.6 (*Ar*H×2), 126.4 (*Ar*H), 111.2 (Cq), 88.2 (*C*q), 82.9 (*C*4), 80.0 (*C*5), 72.5 (*C*H_2), 70.5 (*C*H_2), 26.6 (*C*H_3), 26.1 (*C*H_3); FABMS (>0) *m*/*z* 381 $[M+H]^+$. Anal. Calcd for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.74; H, 6.63.

3.1.3. (−)-(1*R*,4*S*,5*S*)-1-Benzoyloxy-3-[(benzyloxy)methyl]-4,5-(isopropylidenedioxy)-2-cyclopentene (9). A mixture of **8** (6.88 g, 18.1 mmol) under argon, $PdCl_2[CH_3CN]_2$ (470 mg, 1.81 mmol) and *p*-benzoquinone (1.55 g, 14.5 mmol) in freshly distilled THF (335 mL) was heated under reflux for 24 h. The reaction mixture was cooled to room temperature and filtered through a Celite pad. The solvent was concentrated to dryness under reduced pressure. The residue was purified by column chromatography using petroleum ether/diethyl ether (6:4, v/v) to give **9** as a colourless syrup (5.65 g, 82% yield); $[\alpha]_D^{20}$ −9.9 (*c* 1.0, $EtOH_{abs}$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98–8.04 (m, 2H, Ar*H*), 7.19–7.53 (m, 8H, Ar*H*), 5.86 (d, 1H, *J*=1.64 Hz, *H*2), 5.54 (dd, 1H, *J*=2.0, 3.5 Hz, *H*1), 4.94–5.01 (m, 2H, *H*4, *H*5), 4.54 (s, 2H, CH_2), 4.10–4.24 (m, 2H, CH_2), 1.29 (s, 3H, CH_3), 1.28 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.06 (*C*=O), 146.0 (*C*q), 137.9 (*C*q), 132.9 (*Ar*H), 130.0 (*C*q), 129.8 (*Ar*H×2), 128.4 (*Ar*H×2), 128.3 (*Ar*H×2), 127.7 (*Ar*H×2), 127.7 (*Ar*H), 126.4 (*C*2), 113.0 (*C*q), 83.0 (*C*4), 77.4 (*C*5), 75.8 (C1), 73.0 (*C*H_2), 66.6 (*C*H_2), 27.4 (*C*H_3), 26.8 (*C*H_3); FABMS (>0) *m*/*z* 381 $[M+H]^+$. Anal. Calcd for $C_{23}H_{24}O_5$: C, 72.61; H, 6.36. Found: C, 72.47; H, 6.51.

3.1.4. (−)-(1*R*,4*S*,5*S*)-1-Benzoyloxy-3-[(benzyloxy)methyl]-2-cyclopentene-4,5-diol (10). A solution of **9** (8.25 g, 21.71 mmol) in acetic acid (163 mL) and water (43 mL) was heated at 50 °C during 3 h. The solvent was evaporated and the residue was partitioned between CH_2Cl_2 (150 mL) and aqueous $NaHCO_3$ (50 mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to dryness. The residue was purified by column chromatography using diethyl ether to give **10** as a colourless syrup (5.89 g, 80% yield): R_f (diethyl ether) 0.32; $[\alpha]_D^{20}$ −52 (*c* 1.0, $EtOH_{abs}$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.00–8.24 (m, 2H, Ar*H*), 7.20–7.50 (m, 8H, Ar*H*), 6.00–6.10 (m, 1H, *H*2), 5.70–5.79 (m, 1H, *H*1), 4.52 (s, 2H, CH_2), 4.41–4.49 (m, 1H, *H*4), 4.35–4.41 (m, 1H, *H*5), 4.20 (s, 2H, CH_2), 2.66 (br s, 1H, O*H*), 2.55 (br s, 1H, O*H*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.06 (*C*=O), 148.03 (*C*q), 137.65 (*C*q), 133.26 (*Ar*H), 129.82 (*C*q), 128.53 (*Ar*H×2), 128.45 (*Ar*H×2), 127.93 (*Ar*H×2), 127.82 (*Ar*H×2), 126.73 (*C*2), 76.23 (*C*1), 73.82 (*C*4), 73.23 (*C*H_2), 71.09 (*C*5), 67.21 (*C*H_2); FABMS (>0) *m*/*z* 341 $[M+H]^+$, 93 (100%). Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.58; H, 5.92. Found: C, 70.25; H, 5.99.

3.1.5. (−)-(1*R*,4*S*,5*S*)-1-Benzoyloxy-3-[(benzyloxy)methyl]-4-{[*tert*-butyl(dimethyl)silyl]oxy}-2-cyclopenten-5-ol (11). A magnetically stirred solution of **10** (2.29 g, 6.74 mmol) in dry CH_2Cl_2 (49 mL) was cooled to −78 °C and a solution containing freshly distilled 2,6-lutidine (1.7 mL, 14.57 mmol) and *tert*-butyldimethylsilyltrifluoromethane sulfonate (1.6 mL, 6.95 mmol) in dry CH_2Cl_2 (11 mL) was added slowly dropwise over a 15-min period. After 1 h at −78 °C, the reaction mixture was allowed to reach room temperature and stirred continually overnight. The reaction was quenched with absolute EtOH (11 mL). The solvent was evaporated and the residue was partitioned between CH_2Cl_2 (100 mL) and water

(50 mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to dryness. The residue was purified by column chromatography using petroleum ether/diethyl ether (1:1, v/v) to give **11** as a colourless syrup (2.392 g, 78% yield): R_f (petroleum ether/diethyl ether; 1:1, v/v) 0.52; $[\alpha]_D^{20}$ −51.4 (*c* 1.05, $EtOH_{abs}$); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, 2H, *J*=8.35 Hz, Ar*H*), 7.10–7.88 (m, 8H, Ar*H*), 5.88 (d, 1H, *J*=1.43 Hz, *H*2), 5.48 (dd, 1H, *J*=2.06, 4.29 Hz, *H*1), 4.44 (d, 1H, *J*=5.22 Hz, *H*4), 4.39 (s, 2H, CH_2), 4.20–4.31 (m, 1H, *H*5), 4.00 (s, 2H, CH_2), 2.58 (br s, 1H, O*H*), 0.76 (s, 9H, 3×CH_3), 0.00 (s, 3H, SiCH_3), −0.012 (s, 3H, SiCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.05 (*C*═O), 147.17 (*C*q), 137.75 (*C*q), 132.99 (*Ar*H×2), 130.07 (*C*q), 129.77 (*Ar*H×2), 128.46 (*Ar*H×2), 128.30 (*Ar*H×2), 127.84 (*Ar*H×2), 127.01 (*C*2), 76.17 (*C*1), 73.67 (*C*4), 72.95 (*C*H_2), 71.07 (*C*5), 66.54 (*C*H_2), 25.72 (3×*C*H_3), 18.12 (*C*q), −4.76 (Si*C*H_3), −4.90 (Si*C*H_3); FABMS (>0) *m*/*z* 455 $[M+H]^+$, 93 (100%). Anal. Calcd for $C_{26}H_{34}O_5Si$: C, 68.69; H, 7.54. Found: C, 68.48; H, 7.79.

3.1.6. (−)-9-[(1*R*,2*S*,5*R*)-2-Benzoyloxy-4-(benzyloxy)-methyl-5-hydroxy-cyclopent-3-en-1-yl]-6-chloropurine (12). To a stirred solution, at 0 °C, of triphenylphosphine (1.13 g, 4.32 mmol) and 6-chloro-9*H*-purine (667 mg, 4.32 mmol) under argon in dry THF (25 mL) was added DIAD (850 μL, 4.32 mmol). The solution was stirred at room temperature for 30 min and a solution of **11** (656 mg, 1.44 mmol) in dry THF (5 mL) was added dropwise. The reaction mixture was stirred at 55 °C overnight. The solvent was removed under vacuum and the residue was purified by column chromatography using petroleum ether/ethyl acetate (2.5:1, v/v) to give the protected 6-chloronucleoside contaminated with hydrazine by-product. The compound was added to TBAF supported on silica (2.6 g, 2.88 mmol) [1.1 mmol F^-/g of resin] in dry THF (15 mL). The reaction was stirred at room temperature for 2 h and filtered through a Celite pad. The solvent was removed under vacuum and the residue was purified by column chromatography using diethyl ether to give **12** as a white solid (120 mg, 20% yield from **11**): R_f (diethyl ether) 0.43; UV (EtOH, 96%) λ_{max}=264.4 nm (ε=8287); $[\alpha]_D^{20}$ −187 (*c* 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.60 (s, 1H, *H*2), 7.98–8.04 (m, 3H, *H*8 and Ar*H*), 6.9–7.6 (m, 8H, Ar*H*), 6.21 (s, 1H, *H*3′), 5.93 (d, 1H, *J*=3.5 Hz, *H*5′), 5.60 (d, 1H, *J*=5.5 Hz, *H*2′), 4.99 (t, 1H, *J*=6.0 Hz, *H*1′), 4.29 (d, 1H, *J*=12.0 Hz, CH_2), 4.14 (d, 1H, *J*=12.0 Hz, CH_2), 3.92 (d, 1H, *J*=13.0 Hz, CH_2), 3.71 (d, 1H, *J*=13.0 Hz, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.6 (*C*═O), 151.9 (*C*2), 151.5 (*C*q), 151.1 (*C*q), 145.2 (*C*8), 144.1 (*C*3′), 141.6 (*C*q), 136.6 (*C*q), 133.5 (*Ar*H), 129.8 (*Ar*H×2), 129.3 (*C*q), 128.5 (*C*q), 128.4 (*Ar*H×2), 128.2 (*Ar*H×2), 128.0 (*Ar*H×2), 127.7 (*Ar*H), 75.8 (*C*1′), 75.4 (*C*5′), 73.1 (*C*H_2), 66.8 (*C*2′), 65.9 (*C*H_2); FABMS (>0) *m*/*z* 477 $[M+H]^+$.

3.1.7. (−)-(1*R*,4*S*,5*S*)-3-[(Benzyloxy)methyl]-4,5-(isopropylidenedioxy)-2-cyclopenten-1-ol (13). To a solution of **9** (6.66 g, 17.5 mmol) at room temperature in methanol (85 mL) was added a 1% NaOH solution (350 mL) in methanol and the resulting mixture was stirred for 90 min. The solvent was removed under vacuum and the residue was partitioned between ethyl acetate (200 mL) and water (300 mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography using petroleum ether/ethyl acetate (1:1, v/v) to give **13** as an oil (4.35 g, 90% yield): R_f (petroleum ether/ethyl acetate; 1:1, v/v) 0.31; $[\alpha]_D^{20}$ −41.4 (*c* 1.0, $EtOH_{abs}$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28–7.43 (m, 5H, Ar*H*), 5.83 (s, 1H, *H*2), 4.99 (d, 1H, *J*=5.5 Hz, *H*4), 4.79 (t, 1H, *J*=5.5 Hz, *H*5), 4.58 (s, 3H, *H*1, CH_2), 4.18 (s, 2H, CH_2), 2.72 (br s, 1H, O*H*), 1.44 (s, 3H, CH_3), 1.42 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.5 (*C*q), 136.9 (*C*q), 131.4 (*C*2), 128.4 (*Ar*H×2), 127.7 (*Ar*H×2), 127.6 (*Ar*H), 111.5 (*C*q), 82.9 (*C*4), 77.7 (*C*5), 73.3 (*C*1), 72.9 (*C*H_2), 66.2 (*C*H_2), 27.6 (*C*H_3), 26.6 (*C*H_3); FABMS (>0) *m*/*z* 277 $[M+H]^+$; Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.19; H, 7.45.

3.1.8. (−)-(1*R*,4*S*,5*S*)-1-Benzyloxy-3-[(benzyloxy)-methyl]-4,5-(isopropylidenedioxy)-2-cyclopentene (14). To a stirred suspension of NaH (66 mg, 1.51 mmol, mineral oil dispersion, 55–65%) in dry DMF (1.1 mL) was added, at 0 °C and under argon, **13** (300 mg, 1.08 mmol) in dry DMF (1 mL). The resulting yellow solution was stirred at 0 °C for 5 min and benzyl bromide (180 μL, 1.51 mmol) was added dropwise. After 1 h at room temperature, the reaction was cooled down at 0 °C and quenched by addition of an aqueous saturated NH_4Cl solution (2 mL). The mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine (5×20 mL), dried (Na_2SO_4) and concentrated to dryness under reduced pressure. The residue was purified by column chromatography using petroleum ether/ethyl acetate (4:1, v/v) to give **14** as a colourless oil (350 mg, 88% yield): R_f (petroleum ether/ethyl acetate; 4:1, v/v) 0.26; $[\alpha]_D^{20}$ +2.0 (*c* 1, $CHCl_3$), lit.[6] $[\alpha]_D^{24}$ −3.8 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.15–7.31 (m, 10H, 2×Ar*H*), 5.72 (d, 1H, *J*=1.0 Hz, *H*2), 4.83 (d, 1H, *J*=5.0 Hz, *H*4), 4.74 (d, 1H, *J*=5.0 Hz, *H*5), 4.73 (d, 1H, *J*=12.0 Hz, OCH_2), 4.53 (d, 1H, *J*=12.0 Hz, OCH_2), 4.46 (s, 2H, CH_2), 4.30 (m, 1H, *H*1), 4.08 (s, 2H, CH_2), 1.37 (s, 3H, CH_3), 1.32 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.1 (*C*q), 138.4 (*C*q), 138.1 (*C*q), 128.84 (*C*2), 128.39 (ArH×2), 128.05 (ArH×2), 127.70 (ArH×2), 127.66 (ArH×2), 112.4 (*C*q), 82.9 (*C*4), 79.7 (*C*1), 78.0 (*C*5), 72.8 (*C*H_2), 71.8 (O*C*H_2), 66.4 (*C*H_2), 27.6 (*C*H_3), 26.8 (*C*H_3).

3.1.9. (−)-(1*R*,4*S*,5*S*)-1-Benzyloxy-3-[(benzyloxy)-methyl]-2-cyclopentene-4,5-diol (15). A solution of **14** (2.43 g, 6.6 mmol) in acetic acid (18 mL) and water (12 mL) was heated at 50 °C for 16 h. The solvent was evaporated and the residue was partitioned between CH_2Cl_2 (100 mL) and aqueous $NaHCO_3$ (50 mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to dryness under reduced pressure. The residue was purified by column chromatography using ethyl acetate/petroleum ether (2:1, v/v) to give **15** as a white solid (2.01 g, 93% yield): R_f (ethyl acetate/petroleum ether; 2:1, v/v) 0.46; mp 59–61 °C (lit. mp 57–58 °C); $[\alpha]_D^{20}$ −32 (*c* 1, $CHCl_3$), lit.[6] $[\alpha]_D^{24}$ +15.3 (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.17–7.34 (m, 10H, 2×Ar*H*), 5.81 (s, 1H, *H*2), 4.60 (q, 2H, *J*=11.5 Hz, OCH_2), 4.48 (s, 2H, CH_2), 4.28 (m, 2H, *H*1, *H*4), 4.17 (d, 1H, *J*=5.0 Hz, *H*5), 4.12 (s, 2H, CH_2), 2.76 (s, 2H, 2×O*H*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.0 (*C*q), 138.0

(*C*q), 137.6 (*C*q), 128.5 (*Ar*H×2), 128.4 (*Ar*H×2), 128.0 (*Ar*H×2), 127.9 (*Ar*H×2), 127.7 (*Ar*H×2), 126.6 (*C*2), 79.9 (*C*1), 74.3 (*C*4), 73.0 (O*C*H_2), 72.1 (*C*H_2), 70.6 (*C*5), 66.8 (*C*H_2); FABMS (>0) *m*/*z* 327 $[M+H]^+$. Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.54; H, 6.82.

3.1.10. (−)-(1*R*,4*S*,5*S*)-1-Benzyloxy-3-[(benzyloxy)-methyl]-4-[(methoxy)methoxy]-cyclopent-2-en-5-ol (16). A solution of diol **15** (2.01 g, 6.16 mmol) in anhydrous CH_2Cl_2 (100 mL) was treated with trimethyl orthoformate (2.0 mL, 18.5 mmol) in the presence of ceric ammonium nitrate (236 mg, 0.43 mmol) under argon. The reaction mixture was stirred at room temperature for 3 h. The solution was cooled at −78 °C and a 1.5 M solution of DIBAL-H in toluene (61.5 mL, 92.3 mmol) was added. The mixture was stirred for 1 h and then cooled down in an ice bath. After 10 min, the mixture was carefully added to an aqueous 1.0 M HCl solution (100 mL). An aqueous saturated solution of sodium and potassium tartrate (150 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2×100 mL) and the combined organic layers were washed with brine (2×100 mL). The aqueous phase was extracted again with EtOAc (2×100 mL) and the combined organic layers were washed with brine (2×100 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by column chromatography using diethyl ether/petroleum ether (4:1, v/v) to afford **16** as a solid (1.34 g, 60% yield): R_f (diethyl ether/petroleum ether; 4:1, v/v) 0.28; $[\alpha]_D^{20}$ −66.7 (*c* 0.93, $CHCl_3$), lit.[6] $[\alpha]_D^{24}$ +31.4 (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24–7.29 (m, 10H, 2×Ar*H*), 5.89 (s, 1H, *H*2), 4.76 (d, 1H, *J*=6.5 Hz, OCH_2O), 4.68 (d, 1H, *J*=12.0 Hz, OCH_2), 4.62 (d, 1H, *J*=6.5 Hz, OCH_2O), 4.58 (d, 1H, *J*=12.0 Hz, OCH_2), 4.41–4.50 (m, 2H, CH_2), 4.30 (d, 1H, *J*=5.0 Hz, *H*4), 4.14–4.19 (m, 2H, *H*1, *H*5), 4.09 (s, 2H, CH_2), 3.31 (s, 3H, CH_3), 2.90 (br s, 1H, O*H*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.9 (*C*q), 138.2 (*C*q), 137.9 (*C*q), 128.8 (*Ar*H), 128.4 (*Ar*H×3), 127.8 (*Ar*H×3), 127.79 (*C*2), 127.74 (*Ar*H×3), 96.6 (O*C*H_2O), 79.5 (*C*1), 78.5 (*C*4), 72.8 (O*C*H_2), 72.1 (*C*H_2), 71.3 (*C*5), 66.9 (*C*H_2), 55.8 (*C*H_3); FABMS (<0) *m*/*z* 369 $[M-H]^-$. Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.47; H, 7.32.

3.1.11. (−)-(1*R*,4*S*,5*S*)-1-Benzyloxy-3-[(benzyloxy)-methyl]-4-[(methoxy)methoxy]-5-(trifluoro-methanesulfonate)-2-cyclopentene (17). To a solution of **16** (500 mg, 1.34 mmol) and DMAP (1.65 g, 13.5 mmol) at 0 °C and under argon in dry CH_2Cl_2 (150 mL) was added trifluoromethanesulfonic anhydride (680 μL, 4.04 mmol). The cloudy mixture was stirred at 0 °C for 30 min and poured into saturated $NaHCO_3$ solution (150 mL). The aqueous phase was extracted with CH_2Cl_2 (2×150 mL) and the combined organic phases were washed with an aqueous saturated $NaHCO_3$ solution (2×100 mL), brine (2×100 mL), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by column chromatography using diethyl ether/petroleum ether (4:1, v/v) gave **17** as a colourless syrup (661 mg, 97% yield): R_f (diethyl ether/petroleum ether; 4:1, v/v) 0.44; $[\alpha]_D^{20}$ −47 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.30 (m, 10H, 2×Ar*H*), 5.86 (m, 1H, *H*2), 5.22 (t, 1H, *J*=5.0 Hz, *H*5), 4.51–4.71 (m, 5H, H4, OCH_2, OCH_2O), 4.45 (s, 2H, CH_2), 4.35 (m, 1H, *H*1), 4.09 (s, 2H, CH_2), 3.31 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −75.0 (s, SO_2CF_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.3 (*C*q), 136.6 (*C*q), 136.4 (*C*q), 127.45 (*C*2), 126.93 (*Ar*H×2), 126.87 (*Ar*H×2), 126.84 (*Ar*H×2), 126.77 (*Ar*H×2), 117.5 (q, *J*=315 Hz, *C*F_3), 95.1 (O*C*H_2O), 84.5 (*C*5), 76.8 (*C*4), 75.6 (*C*1), 72.0 (*C*H_2), 71.7 (O*C*H_2), 65.0 (*C*H_2), 55.0 (*C*H_3); FABMS (>0) *m*/*z* 503 $[M+H]^+$.

3.1.12. (−)-9-[(1*R*,2*S*,5*R*)-2-Benzyloxy-4-(benzyloxy)-methyl-5-(methoxy)methoxy-cyclopent-3-en-1-yl]-6-aminopurine (18). To a solution of **17** (100 mg, 0.20 mmol) in dry DMF (2 mL) was added successively K_2CO_3 (88 mg, 0.63 mmol), adenine (62 mg, 0.45 mmol) and 18-crown-6 ether (20 mg, 0.07 mmol). The mixture was heated at 60 °C for 3 h and poured into brine (50 mL) and ethyl acetate (50 mL). The aqueous phase was extracted with ethyl acetate (3×50 mL) and the combined organic phases were washed with brine (5×50 mL), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by column chromatography using ethyl acetate/methanol (96:4, v/v) gave **18** as a colourless syrup (58 mg, 60% yield): R_f (ethyl acetate/methanol; 9:1 v/v) 0.32; mp 114–116 °C; UV (EtOH, 96%) λ_{max}=260.0 nm (ε=10,844); $[\alpha]_D^{20}$ −21 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.19 (s, 1H, *H*2), 7.62 (s, 1H, *H*8), 7.00–7.29 (m, 10H, 2×Ar*H*), 6.01 (br s, 3H, *H*4′, NH_2), 5.10 (d, 1H, *J*=5.5 Hz, *H*5′), 4.96 (d, 1H, *J*=5.5 Hz, *H*2′), 4.64 (t, 1H, *J*=6.0 Hz, *H*1′), 4.30–4.6 (m, 6H, 3×CH_2), 4.05–4.19 (m, 2H, CH_2), 3.01 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.8 (*C*q), 152.6 (*C*2), 149.8 (*C*q), 143.1 (*C*3′), 140.8 (*C*8), 137.9 (*C*q), 137.6 (*C*q), 128.4 (*Ar*H×2), 128.3 (*Ar*H×2), 128.1 (*Ar*H×2), 127.8 (*Ar*H×2), 127.7 (*C*q), 127.6 (*Ar*H×2), 120.3 (*C*q), 96.8 (*C*H_2), 82.6 (*C*5′), 82.5 (*C*2′), 72.7 (*C*H_2), 71.8 (*C*H_2), 70.5 (*C*1′), 66.1 (*C*H_2), 55.4 (*C*H_3); FABMS (>0) *m*/*z* 488 $[M+H]^+$ (100%). Anal. Calcd for $C_{27}H_{29}N_5O_4$: C, 66.51; H, 6.00; N, 14.36. Found: C, 66.17; H, 6.20; N, 14.38.

3.1.13. (−)-9-[(1*R*,2*S*,5*R*)-2-Benzyloxy-4-(benzyloxy)-methyl-5-hydroxy-cyclopent-3-en-1-yl]-6-aminopurine (19). To a solution of **18** (84 mg, 0.17 mmol) in CH_2Cl_2 (3.6 mL) was added dropwise TFA (0.81 mL). The solution was stirred at room temperature for 48 h, then poured into an aqueous saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness. Purification by column chromatography using ethyl acetate/methanol (96:4, v/v) gave **19** as a white solid (57.6 mg, 75% yield): R_f (ethyl acetate/methanol, 9:1) 0.36; mp 160–161 °C (lit. mp 157–158 °C); UV (EtOH, 96%) λ_{max}=262.0 nm (ε=17,283); $[\alpha]_D^{20}$ −30 (*c* 2.0, DMSO), lit.[6] $[\alpha]_D^{24}$ +42.2 (*c* 0.8, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.30 (s, 1H, *H*2), 8.09 (s, 1H, *H*8), 7.08–7.38 (m, 12H, 2×Ar*H*, NH_2), 5.98 (s, 1H, *H*4′), 5.74 (d, 1H, *J*=7.0 Hz, O*H*), 4.99–5.03 (m, 1H, *H*2′), 4.95 (d, 1H, *J*=6.0 Hz, *H*5′), 4.62–4.66 (m, 1H, *H*1′), 4.56 (s, 1H, OCH_2), 4.55 (s, 1H, OCH_2), 4.44 (s, 2H, CH_2), 4.14 (s, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 65.3 (CH_2), 69.4 (*C*H_2), 70.5 (*C*1′), 71.2 (O*C*H_2), 75.0 (*C*2′), 81.2 (*C*5′), 118.9 (*C*q), 124.7 (*C*q), 126.7 (*Ar*H×2), 126.9 (*Ar*H×2), 127.0 (*Ar*H×2), 127.4 (*Ar*H×2), 127.7 (*Ar*H×2), 137.5 (*C*q), 137.7 (*C*q), 140.5 (*C*8), 144.4 (*C*3′), 148.9 (*C*q), 151.5 (*C*2), 155.5 (*C*q); FABMS (>0) *m*/*z* 444 $[M+H]^+$. Anal. Calcd for

$C_{25}H_{25}N_5O_3 \cdot 0.3H_2O$: C, 66.89; H, 5.75; N, 15.60. Found: C, 66.88; H, 5.74; N, 15.50.

3.1.14. (−)-9-[(1*R*,2*S*,5*R*)-2,5-Dihydroxy-4-(hydroxyl)-methyl-cyclopent-3-en-1-yl]-6-aminopurine (5). Under argon, to a solution of **19** (146 mg, 0.33 mmol) in anhydrous methylene chloride (25 mL), at −78 °C was added 2.6 mL (2.63 mmol) of a 1.0 M solution of BCl_3 in heptane. The reaction mixture was stirred at −78 °C for 5 h and then for 1 h at −45 °C. The mixture was cooled again to −78 °C, then MeOH (6.5 mL) was added and the mixture was stirred at −78 °C for an additional hour. The reaction was allowed to reach room temperature and the solvent was evaporated. Methanol (4×20 mL) was added and evaporated after each addition. The residue was purified by reverse phase column chromatography (C18 octadecyl), eluting with water, to give **5** as a white solid after lyophilization (72 mg, 84% yield): R_f (*i*-PrOH/H_2O/NH_4OH, 7:2:1) 0.60; mp 221–223 °C (lit.[18] mp 223 °C); UV (H_2O) λ_{max}=259.3 nm (ε=12,454); $[\alpha]_D^{20}$ −7.2 (*c* 0.8, H_2O), lit.[18] $[\alpha]_D^{20}$ −6.6 (*c* 0.8, H_2O); ^1H NMR (DMSO-d_6, 400 MHz) δ 8.70 (s, 1H, *H*2), 8.49 (s, 1H, *H*8), 5.70 (d, 1H, *J*=1.5 Hz, *H*3′), 4.88–4.98 (m, 2H, *H*2′, *H*5′), 4.49 (t, 1H, *J*=6.65 Hz, *H*1′), 4.14 (d, 1H, *J*=16.0 Hz, CH_2), 4.03 (d, 1H, *J*=15.5 Hz, CH_2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 151.0 (*C*q), 149.3 (*C*q), 147.3 (*C*3′), 145.4 (*C*2), 144.5 (*C*8), 126.8 (*C*q), 119.1 (*C*q), 76.3 (*C*5′), 75.2 (*C*2′), 74.4 (*C*1′), 58.1 (*C*H_2); HRMS: calcd for $C_{11}H_{14}N_5O_3$ 264.1097. Found 264.1089.

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