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5′-Noraristeromycin derivatives isomeric to aristeromycin and 2′-deoxyaristeromycin

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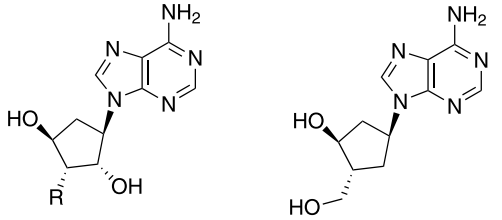
Abstract—A straightforward synthesis of (1*S*,2*R*,3*R*,4*R*)-4-(6-aminopurin-9-yl)-2-hydroxymethylcyclopentane-1,3-diol (**2**), an isomer of aristeromycin, and its 2′-deoxy derivative **3** from readily available disubstituted cyclopentenes is presented. An antiviral analysis of **2** showed it to have significant activity versus Epstein–Barr virus (IC_{50} 0.62 μg/mL in the Elisa assay) and to be free of cytotoxicity effects against the host cells. In a much less comprehensive antiviral analysis, **3** also was active towards Epstein–Barr (IC_{50} 7.58 μg/mL in the Elisa assay) but this was accompanied by cellular toxicity.

1. Introduction

Oligonucleotides possessing carbanucleoside monomeric units have received little attention.[1,2] Such derivatives would be expected to render, among other properties, nuclease stability[3] to the oligos in which they are incorporated and may have a role to play in nanotechnology.[4] As an outgrowth of our antiviral studies with 5′-nor carbanucleosides (for example, 5′-noraristeromycin, **1**)[5] (Fig. 1) we became interested in their inclusion in oligomers.[6] However, as a consequence of lacking the C-5′ methylene in the nucleoside monomer, such oligos would have shortened internucleotide phosphate bonds. As a consequence, oligomeric structural perturbations would arise that would be difficult to correlate with the customary furanose-based oligomers. To develop 5′-nor carbanucleosides that would not offer an oligomeric product with shortened phosphorus to phosphorus distances, 3′-homo-5′-noraristeromycin (**2**) and its 2′-deoxy derivative **3** were sought. The preparation of **2** and **3** is reported. For comparative purposes to **1**, the antiviral properties of **2** are given.



1, R=OH
2, R=CH_2OH

3

Figure 1.

2. Chemistry

The synthesis of **2** was envisioned as starting with the readily available chiral hydroxyacetate **4**[7] because of its facile conversion to **5**,[8] which possesses functionality appropriately placed for the cyclopentyl component of **2**. Epoxidation of **5** gave predominantly the α-epoxide **6** (α:β, 10:1), which was based on Henbest's rule,[9] literature precedence,[10a,b] and correlation with the confirmed (vide infra) structure of **8**. Epoxide **6** was protected as its benzyl ether **7**. This was followed by reaction with adenine to provide a mixture of two regioisomers in a 3:1 ratio. Identification of the two isomers by NMR could not be achieved due to overlapping signals. However, X-ray analysis (Fig. 2) revealed **8**[10] as the major component, possibly arising as a result of the benzyl ether assisting epoxide ring opening.

Hydrogenolytic deprotection of the benzyl ether **8** under various circumstances was unsuccessful. However, treatment of **8** with boron trichloride, followed by addition of methanol to the reaction mixture and heating gave the

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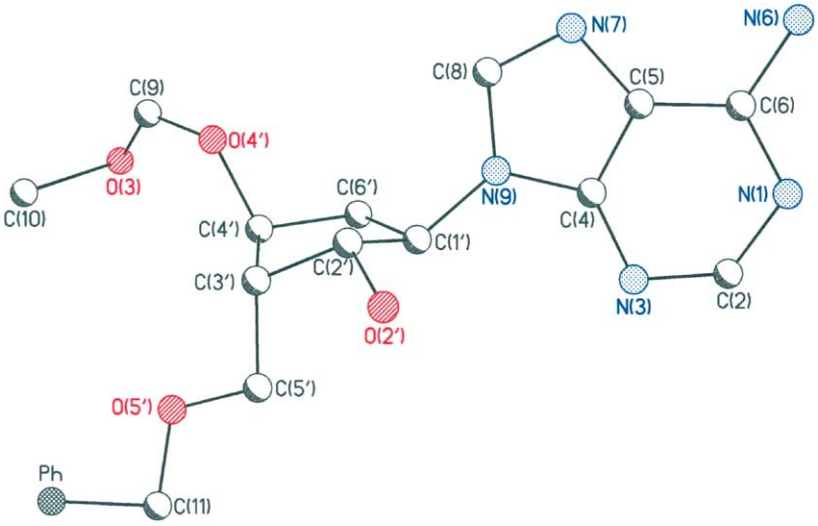


Figure 2. X-ray structure for compound **8**.

desired **2** in a very low yield as a consequence of purification difficulties.

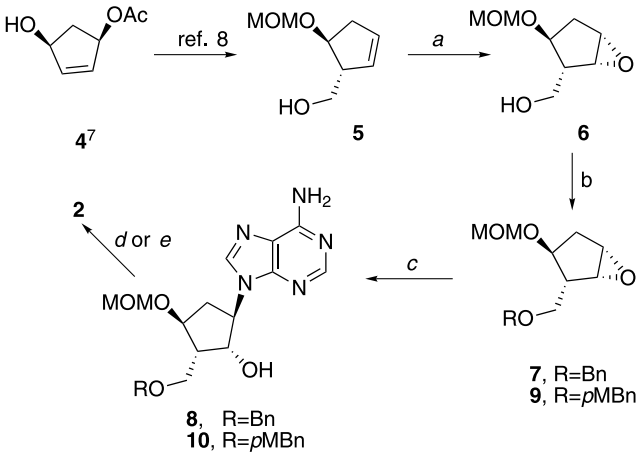
To improve the yield of **2** an alternative protection of **6** was sought. In this regard, **6** was converted to the *p*-methoxybenzyl derivative **9**. Opening of epoxide **9** with adenine provided two isomers (1.5:1). The major isomer **10** was deprotected with 10% trifluoroacetic acid followed by refluxing in 5 N hydrochloric acid to give **2** in 78% yield (compared to 10% from **8**). The NMR spectra of **2** from both methods were superimposable.

The synthesis of **3** began with the known[11] enone **11**. Using a copper promoted 1,4-addition[12] of *t*-butoxymethyl lithium, **11** was converted into **12**. L-Selectride reduction of **12** yielded alcohol **13**. Mitsunobu coupling of **13** with 6-chlorpurine produced **14**, which, upon ammonolysis and deprotection, provided the desired **3**.

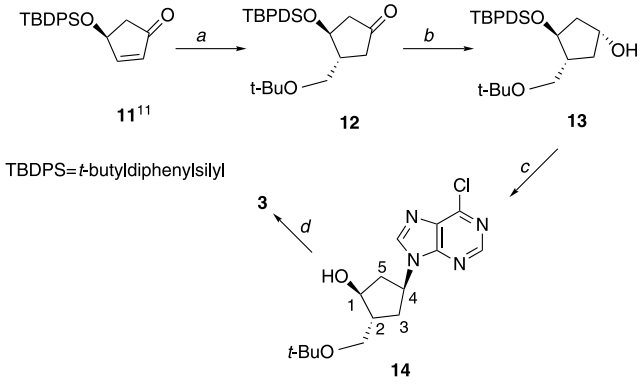
Confirmation of the structure of **14** was achieved via NMR analysis by, first, carrying-out a proton–proton COSY determination to assign the cyclopentyl ring protons. In that direction, the C-1 hydroxyl proton (3.93 ppm and identified by solvent exchange) correlated only with the H-1 (4.23 ppm). In turn, H-1 correlates with H-5 (H-5_α at 2.73 ppm and H-5_β at 2.22–2.15 ppm,) and, to a lesser degree, with H-2 (2.46 ppm). Proton-2 correlated with the two exocyclic methylene protons and the two H-3 (2.15–2.08 ppm) while H-4 (5.12 ppm) correlated with all four H-3 and H-5.

With this information available a NOESY analysis of **14** was performed: major correlations were observed between (i) H-1, H-5_α and H-4; (ii) H-4, H-3_α and the exocyclic methylene protons; and, (iii) H-2 and H-3_β.

For the previously stated purposes of this project, the synthetic methods described to **2** and **3** conveniently lend themselves to variation of the heterocyclic base unit (step d of Scheme 1 and step c of Scheme 2).



Scheme 1. Reagents: *a*, *m*CPBA, CH_2Cl_2, 84.5%; *b*, BnCl or *p*MBnCl, NaH, DMF, 82% for both; *c*, adenine, NaH, 15-C-5, 56.5% and 34%; *d*, for R=Bn, BCl_3 then MeOH, CH_2Cl_2, 10%; *e*, for R=*p*MBn, 10% TFA then 5 N HCl, CH_2Cl_2 then MeOH, 78%.



Scheme 2. Reagents: *a*, $(t\text{-}BuOCH_2)_2CuLi$, *t*-BuOMe, THF, 87%; *b*, L-selectride, THF, 79%; *c*, (i) 6-chloropurine, PPh_3, DIAD, THF; (ii) TBAF, THF, 30.5% overall for 2 steps; *d*, (i) NH_3, MeOH; (ii) TFA, H_2O, 75% overall for two steps.

3. Antiviral results

Compound **2** was subjected to antiviral analysis.[13] No activity was found except against Epstein–Barr virus (in Daudi cells: Elisa assay, IC_{50} 0.62 μg/mL; DNA hybridization assay, IC_{50} 20 μg/mL; acyclovir IC_{50} 1.7 μg/mL in both assays).[14a] Compound **2** was non-toxic to the following host cells: human foreskin fibroblast, Daudi, MA-104, MDCK, human embryonic lung, Vero, and human hepatoblastoma 2.2.15. The promising effects of **2** towards Epstein–Barr virus prompted a similar assay for **3**[13b] (in Daudi cells: Elisa assay, IC_{50} 7.58 μg/mL; DNA hybridization assay, IC_{50} 0.1 μg/mL; acyclovir IC_{50} 1.3 μg/mL in the Elisa assay and 0.4 in the DNA assay).[14a] However, **3** demonstrated significant toxicity to the Daudi cells (CC_{50} 47.1 μg/mL in both assays). Analog **3** showed no effects against the other herpes viruses.

4. Experimental

4.1. General

Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. The NMR spectra were recorded on Bruker AC 250 and AV 400 spectrometers. All ^{1}H chemical shifts are reported in δ relative to internal standard tetramethylsilane (TMS, δ 0.00). ^{13}C chemical shifts are reported in δ relative to $CDCl_3$ (center of triplet, δ 77.23) or relative to DMSO-d_6 (center of septet, δ 39.51). The spin multiplicities are indicated by the symbols s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants (J) are expressed in Hz. The X-ray analysis was conducted using a Bruker SMART APEX CCD diffractometer. The optical rotation determinations were carried out on a Jasco P1010 polarimeter and the ultraviolet spectra recorded using a Hitachi U2000 spectrophotometer. Atlantic Microlabs, Atlanta, Georgia, performed the elemental analyses. Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm Whatman Partisil R Diamond K6F plates with visualization by irradiation with a Mineral light UVGL-25 lamp or exposure to iodine vapor. Column chromatography was performed on Whatman silica gel (average particle size 5–25 μm, 60 Å) and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials. The reactions were generally carried out in a N_2 atmosphere under anhydrous conditions.

4.1.1. (1*R*,2*R*,3*S*,5*S*)-3-Methoxymethoxy-2-phenethyl-6-oxabicyclo[3.1.0]hexane (7). To an ice-cold stirring solution of **5**[8] (600 mg, 3.82 mmol) in 50 mL of CH_2Cl_2 was added a solution of *m*CPBA (4.93 g, 77% max.) in CH_2Cl_2 (30 mL). The ice bath was removed and the reaction mixture was kept at rt overnight. The reaction mixture was washed sequentially with saturated Na_2CO_3 (3×50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$), filtered and the filtrate concentrated under reduced pressure. The resultant crude material (NMR analysis indicating two products in a 10:1 ratio) was purified by silica gel column chromatography (hexanes–EtOAc, 2:1) to give **6** (the major product) as a colorless, sticky liquid (620 mg, 84.5%): ^{1}H NMR ($CDCl_3$) δ 4.59 (s, 2H), 4.00–3.88 (m, 2H), 3.67–3.50 (m, 3H), 3.38 (s, 3H), 2.65 (dd, J=7.5 Hz, 1H), 2.21 (m, 1H), 2.10 (brs, 1H), 1.69–1.78 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 96.8, 76.9, 62.5, 56.9, 55.73, 54.9, 49.0, 35.1.

To a solution of the above oil (530 mg, 3.06 mmol) in DMF (10 mL) in an ice-cooled bath were added NaH (88.23 mg, 3.70 mmol) and benzyl bromide (0.409 mL, 3.37 mmol). This mixture was stirred for 2 h at room temperature and then evaporated at reduced pressure. The residue was then diluted with EtOAc (20 mL), washed with H_2O (10 mL) and brine (10 mL) and the organic phase dried ($MgSO_4$). The drying agent was removed by filtration and the filtrate evaporated under reduced pressure to give a residue that was purified by silica gel column chromatography (hexanes–EtOAc, 10:1 to 3:1) to provide **7** (620 mg, 82%) as white solid, mp 43 °C: ^{1}H NMR ($CDCl_3$) δ 7.36–7.25 (m, 5H), 4.61 (m, 3H), 4.56 (s, 3H), 3.76–3.44 (m, 5H), 3.29 (s, 1H), 2.53 (dd, J=7.25 Hz, 1H), 2.33 (m, 1H), 1.75 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 138.5, 128.5, 127.8, 127.7, 96.5, 76.7, 73.5, 69.5, 56.9, 55.5, 55.4, 47.3, 34.9. Anal. calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; Found: C, 68.19; H, 7.66.

4.1.2. (1*R*,2*S*,3*S*,5*R*)-5-(6-Aminopurin-9-yl)-2-benzyloxymethyl-3-methoxymethoxycyclopentanol (8). A suspension of adenine (686 mg, 5 mmol) and NaH (120 mg, 5 mmol) in DMF (10 mL) was stirred at 135 °C for 15 min. To this mixture **7** (440 mg, 1.77 mmol) in DMF (10 mL) and 15-crown-5 (0.1 mL) were added at room temperature. The mixture was then heated at 135 °C for 3.5 h. The mixture was evaporated in vacuo and the residue then diluted with CH_2Cl_2 (50 mL). The new solution was washed with brine (20 mL), dried ($MgSO_4$), and evaporated to a foam (two regioisomers, 3:1 by the NMR). The resulting foam was purified very carefully by silica gel column chromatography (MeOH–CH_2Cl_2, 1:20) to give 310 mg (56.5%) of **8** as a white solid, mp 137–138 °C: ^{1}H NMR ($CDCl_3$) δ 8.31 (s, 1H), 7.89 (s, 1H), 7.26 (m, 5H), 5.70 (brs, 2H), 4.75–4.50 (m, 7H), 4.25 (q, J=6.6 Hz, 1H), 3.81 (s, 1H), 3.79 (s, 1H), 3.35 (s, 3H), 2.89 (m, 1H), 2.55 (m, 1H), 2.23 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 155.68, 152.7, 150.5, 139.7, 138.0, 128.7, 128.1, 128.0, 120.2, 95.3, 76.5, 73.7, 67.9, 62.1, 55.8, 47.9, 35.8, 18.4. Anal. calcd for $C_{20}H_{25}N_5O_4\cdot 0.25H_2O$: C, 59.41; H, 6.25; N, 17.12. Found: C, 59.38; H, 6.34; N, 17.07.

4.1.3. (1*R*,2*S*,3*S*,5*R*)-5-(6-Aminopurin-9-yl)-2-(4-methoxybenzyloxymethyl)-3-(methoxymethoxy)cyclopentanol (10). To a solution of **6** (880 mg, 5.08 mmol) in DMF (10 mL) cooled in an ice bath was added NaH (134.1 mg, 5.59 mmol). After 10 min, *p*-methoxybenzyl chloride (0.68 mL, 5.59 mmol) was added. The mixture was stirred for 2 h at room temperature and then evaporated under reduced pressure. The resultant residue was diluted with EtOAc (20 mL) and this solution washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and the filtrate concentrated in vacuo. The residue was purified by silica gel column chromatography (hexanes–EtOAc, 10:1 to 3:1) to yield **9** (620 mg, 82%) as an oil: ^{1}H NMR ($CDCl_3$) δ 7.26 (d, J=10 Hz, 2H), 6.86 (d, J=10 Hz, 2H), 4.54 (s, 2H), 4.51 (s, 2H), 3.80 (s, 3H), 3.70–3.40 (m, 5H), 3.29 (s, 3H), 2.70 (dd, J=7.5 Hz, 1H), 2.40 (m, 1H), 1.85 (m, 1H).

A suspension of adenine (1.85 g, 13.5 mmol) and NaH (240 mg, 10 mmol) in DMF (10 mL) was stirred at 130 °C for 15 min. To this, **9** (440 mg, 1.77 mmol) in DMF (10 mL) and 15-crown-5 (0.4 mL) were added at room temperature. This mixture was then heated at 130 °C for 6 h. The mixture was evaporated in vacuo and the residue diluted with EtOAc (50 mL). The new mixture was washed with brine (20 mL), dried ($MgSO_4$), and the filtrate evaporated to give a yellow foam (two regioisomers, 1.5:1 by the NMR). The major isomer was purified from the residue by silica gel column chromatography (5% MeOH in CH_2Cl_2) to give 610 mg (34%) of **10**[15] as a white solid, mp 136.3 °C: ^{1}H NMR ($CDCl_3$) δ 8.31 (s, 1H), 7.89 (s, 1H), 7.28 (d, J=10.0 Hz, 2H), 6.86 (d, J=10 Hz, 2H), 5.76 (brs, 2H), 4.67–4.60 (m, 4H), 4.55 (d, J=7.5 Hz, 2H), 4.23 (q, J=7.5 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 1H), 3.75 (s, 1H), 3.54 (s, 3H), 2.90 (m, 1H), 2.59 (m, 1H), 2.22 (m, 1H), 1.98 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 154.10, 150.5, 150.24, 147.3, 145.0, 134.26, 124.6, 124.1, 114.7, 108.6, 90.8, 72.0, 71.7, 71.1, 67.9, 62.2, 56.6, 50.3, 50.0, 47.5, 30.40. Anal. calcd for $C_{21}H_{27}N_5O_5$: C, 58.73; H, 6.34; N, 16.31. Found: C, 58.78; H, 6.31; N, 16.39.

4.1.4. (1*S*,2*R*,3*R*,4*R*)-4-(6-Aminopurin-9-yl)-2-(hydroxymethyl)cyclopentane-1,3-diol (2). (a) From **8**. To a solution of **8** (766 mg, 2 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C was added BCl_3 (7.2 mL, 1.0 M in CH_2Cl_2). This mixture was stirred at the same temperature for 2 h and MeOH (10 mL) was added dropwise. Water (10 mL) was then added and the mixture refluxed for overnight. Neutralization of the mixture with NH_4OH followed by evaporation led to a residue that was subjected to silica gel column chromatography (CH_2Cl_2–MeOH, 7:1 to 3:1) to give a white solid. Recrystallization of this material using MeOH–CH_2Cl_2 resulted in **2** (50 mg, 10%) as a white solid, mp 175.5–177 °C; $[\alpha]_D^{23.5}=-20.42$ (*c* 0.10, MeOH); uv (MeOH) λ_{max} 239 nm (ε 453.3); ^{1}H NMR (DMSO) δ 8.19 (s, 1H), 8.12 (s, 1H), 7.24 (brs, 2H), 5.22 (d, J=5 Hz, 1H), 5.13 (d, J=4.9 Hz, 1H), 4.60–4.51 (m, 2H), 4.31 (t, J=5.3 Hz, 1H), 4.04 (m, 1H), 3.69 (m, 1H), 3.53 (m, 1H), 2.60 (m, 1H), 2.10–1.95 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 155.9, 155.8, 151.9, 140.0, 119.1, 74.9, 70.4, 60.6, 58.4, 42.4, 37.9. Anal. calcd for $C_{11}H_{15}N_5O_3\cdot 0.7H_2O$: C, 47.50; H, 5.90; N, 25.19. Found: C, 47.83; H, 5.59; N, 24.96.

(b) From **10**. Compound **10** (100 mg, 2.42 mmol) was stirred in a solution of 10% trifluoroacetic acid (10 mL in CH_2Cl_2) for 20 min, during which time it became a clear pink solution. The mixture was then evaporated and the residue co-evaporated with anhydrous EtOH (3×20 mL). The material left from this process was stirred in a solution of 5 N HCl in MeOH (10 mL) at 50 °C overnight. Evaporation and then co-evaporation with MeOH (3× 20 mL) gave a yellow solid that was then dissolved in MeOH and neutralized with IRA-67 resin. Filtration, concentration of the filtrate and purification of the residue by silica gel column chromatography (5% MeOH in CH_2Cl_2) gave **2** (50 mg, 78%), whose spectral properties were identical to **2** obtained from **8**.

4.1.5. (1*R*,3*S*,4*R*)-3-(*tert*-Butyldiphenylsilyloxy)-4-(*tert*-butoxymethyl)cyclopentanol (13). Under N_2 *sec*-butyllithium solution (1.4 M in hexanes, 30 mL, 42 mmol) was added dropwise to a suspension of potassium *tert*-butoxide (4.71 g, 42.0 mmol) in anhydrous *tert*-butylmethyl ether (200 mL) at −70 °C over 5 min under N_2. After stirring 3.5 h at this temperature, a solution of LiBr (7.27 g, 82.0 mmol) in dry THF (100 mL) was added dropwise at −70 °C over 10 min. This mixture was then allowed to warm to −15 °C at which point it was stirred for 30 min. Upon re-cooling to −70 °C, a solution of $CuBr\cdot SMe_2$ (4.31 g, 20.7 mmol) in di*iso*propyl sulfide (30 mL) was added dropwise over 10 min. To this a solution of **11**[11] (4.32 g, 13.8 mmol) in dry THF (25 mL) was added dropwise over 5 min. The new reaction mixture was allowed to cool to −30 °C over 15 min and then stirred at this temperature for an additional 30 min. The reaction was then quenched with MeOH/AcOH (1:1, v/v, 25 mL), which was followed by pouring into NH_4Cl/NH_4OH solution (25 mL). After removal of the aqueous layer, the organic phase was washed with a mixture of saturated NH_4Cl and 3% NH_4OH (1:1) and then with brine. The organic layer was dried (Na_2SO_4) and then filtered and the filtrate concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15% EtOAc in hexanes) to give **12** as a colorless oil (4.81 g, 87%): ^{1}H NMR ($CDCl_3$) δ 7.74–7.40 (m, 10H), 4.38 (m, 1H), 3.13 (m, 2H), 2.50–2.06 (m, 5H), 1.09 (s, 9H), 1.03 (s, 9H).

To a solution of **12** (1.41 g, 3.5 mmol) in anhydrous THF (20 mL), was added L-selectride (3.7 mL, 1 M in THF) at −78 °C. The resulting mixture was stirred at the same temperature for 40 min and then quenched with sat. aqueous NH_4Cl solution (10 mL). Water (20 mL) was added to this and the mixture extracted with EtOAc (2×100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated and the resultant epimeric mixture (3:1 by NMR) purified by silica gel column chromatography (20% EtOAc in hexanes) to give, as the major product, **13**[16] (1.1 g, 79%) as a colorless oil. Anal. calcd for $C_{26}H_{38}O_3Si$: C, 73.19; H, 8.98; Found: C, 73.36; H, 9.07.

4.1.6. (1*S*,2*R*,4*S*)-4-(6-Aminopurin-9-yl)-2-(*tert*-butoxymethyl)cyclopentanol (14). To a stirring suspension of 6-chloropurine (0.51 g, 3.20 mmol) and triphenylphosphine (0.72 g, 3.20 mmol) in THF (20 mL) at −78 °C was added, dropwise, di*iso*propyl azodicarboxlate (0.70 g, 3.20 mmol). To this mixture was added a solution of **13** (1.17 g, 2.91 mmol) in dry THF (10 mL). The new mixture was warmed to room temperature over 2 h and stirred at this temperature overnight. Following concentration in vacuo, column chromatography (silica gel) (hexanes–EtOAc, 7:1) provided a yellow oil (750 mg). This oil (750 mg) was placed in THF (20 mL) and to this *tetra*butylammonium fluoride (2 mL of 1 M solution in THF) was added. This mixture was stirred for 2 h at room temperature. This mixture was then evaporated and the residue carefully purified by silica gel column chromatography (15% EtOAc in hexanes) to give **14** (0.2 g, 30.5%, two steps) as a white solid, mp 134–136 °C: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.74 (s, 1H), 8.34 (s, 1H), 5.12 (m, 1H), 4.23 (m, 1H), 3.93 (d, J=4.75 Hz, 1H), 3.51 (dd, J=3.75, 4.25 Hz, 1H), 3.31 (t, J=4.75 Hz, 1H), 2.73 (ddd, J=14.4, 6.68, 5.44 Hz, 1H), 2.46 (m, 1H), 2.30 (m, 1H), 2.22–2.15 (m, 1H), 2.15–2.08 (m, 1H) 1.21 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 151.5, 151.2, 146.9, 145.1, 132.6, 76.8, 73.4, 64.2, 55.0, 48.1, 36.7, 27.7.

Anal. calcd for $C_{15}H_{21}N_4O_2Cl$: C, 54.47; H, 6.53; N, 10.92; Cl, 17.25. Found: C, 54.84; H, 6.52; N, 10.55; Cl, 16.92.

4.1.7. (1*S*,2*R*,4*S*)-4-(6-Aminopurin-9-yl)-2-(hydroxymethyl)cyclopentanol (3). A solution of **14** (1.3 g, 4.3 mmol) in dry MeOH (30 mL) saturated with ammonia was kept at 120 °C for 48 h in a Parr stainless steel, sealed reaction vessel. The reaction mixture was evaporated and the resulting white foam stirred overnight in trifluoroacetic acid (20 mL, 50 v/v% in H_2O) at 50 °C. This mixture was then evaporated and the residue co-evaporated with anhydrous EtOH (3×20 mL). The new residue was purified by silica gel column chromatography (50% EtOAc in MeOH) to give **3** as a white solid (750 mg, 75%, two steps), mp 184–186 °C: $[\alpha]_D^{23.7} = +34.0$ (*c* 0.053, MeOH); uv (MeOH) λ_{max} 239 nm (ε 906.6); ^{1}H NMR (DMSO) δ 8.25 (s, 1H), 8.17 (s, 1H), 7.38 (brs, 2H), 4.93 (m, 1H), 4.71 (brs, 1H), 3.99 (q, J=4.5 Hz, 1H), 3.53–3.34 (m, 2H), 2.41 (m, 1H), 2.22–1.99 (m, 4H), 1.01 (t, J=7.0 Hz, 1H). ^{13}C NMR (DMSO) δ 155.2, 151.5, 149.1, 140.0, 118.9, 72.0, 62.1, 56.0, 52.3, 49.9, 33.8. Anal. calcd for $C_{11}H_{15}N_5O_2 \cdot 0.4H_2O$: C, 51.47; H, 6.16; N, 27.29; Found: C, 51.71; H, 6.08; N, 27.14.

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15. Confirmation of **10** as the regioisomeric form shown in Scheme 1 was achieved by its conversion to **2** whose structure was related to the X-ray analysis of **8**.
16. Compound **13** was identified as the major product based on its reaction with 6-chloropurine under Mitsunobu reaction conditions[17] to produce **14**, a structure assigned by NMR analysis (see text).
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