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4′- and 1′-Methyl-Substituted 5′-Norcarbanucleosides

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5′-Norcarbocyclic nucleosides have been found to possess a variety of meaningful biological properties. Derivatives of these compounds possessing substituents at the hydroxyl and heterocyclic ring bearing carbon atoms have not been described. As entries into these compounds, the 4′- and 1′-methyl derivatives of 5′-noraristeromycin (**2** and **3**) have been prepared from a common cyclopentyl precursor **8**. The synthetic methods developed are adaptable to 5′-norcarbanucleosides possessing a variety of heterocyclic bases and in the L-like configuration. In turn, the products from such syntheses will lend themselves to a number of structural and biochemical investigations relevant to carbanucleosides in general. Compounds **2** and **3** lack antiviral properties and were not cytotoxic.

Introduction

As part of our ongoing research into the biological properties of 5′-norcarbanucleosides (as represented by the adenine derivative **1**, Figure 1),[1] a synthetic means adaptive to various C-4′ and C-1′ substituents from a common precursor was desired. Such compounds were seen as not only specifically relevant to the 5′-nor studies but also to carbanucleosides in general.[2−7] To develop a synthetic plan, the C-4′ and C-1′ methyl derivatives of both D-like (**2** and **3**, respectively) and L-like 5′-noraristeromycin were set as the prototype target compounds. The results of this effort are reported here.

Results and Discussion

A retrosynthetic analysis to **2** suggested that readily available[1c,8] (−)-(1*S*,4*R*)-4-hydroxy-2-cyclopenten-1-yl acetate (**4**) could serve as the starting point. Thus, treatment of **4** with *tert*-butyldimethylsilyl chloride (Scheme 1) gave the *O*-silylated compound **5**. This product was converted into **7** by, first, deacetylation to **6**[9] followed by oxidation with pyridinium chlorochromate (PCC). When enone **7** was subjected to reaction with methyllithium, the 1,2-adduct **8**[10] was obtained (*vide infra* for structure assignment). Desilylation of **8** produced **9**, which was selectively acetylated to provide allylic acetate **10**. A Pd-(0)-mediated coupling between **10** and the sodium salt of adenine[11] provided **11**. Dihydroxylation of **11** with osmium tetraoxide/*N*-methylmorpholine *N*-oxide gave the desired **2**.

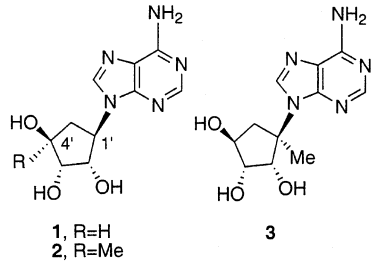

FIGURE 1. 5′-Noraristeromycins.

The structure of **2** was assigned using 2-D NMR spectroscopy. DQ-COSY was employed to determine the chemical shifts of the cyclopentyl protons. This was followed by a NOESY experiment to ascertain the ster-

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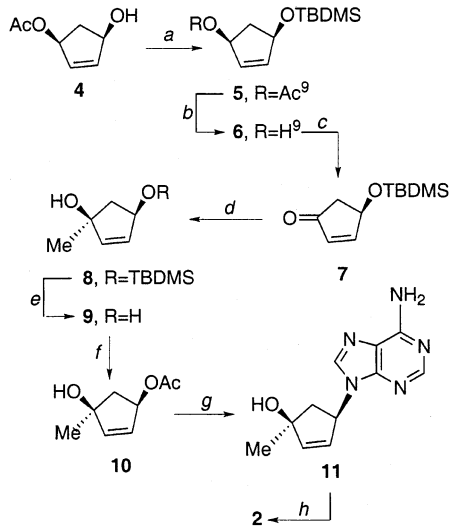
SCHEME 1[a]



[a] Reagents: (a) TBDMSCl, imidazole;[9] (b) K_2CO_3 in MeOH; (c) PCC, (d) MeLi; (e) Bu_4NF; (f) Ac_2O, pyridine; (g) $Pd_2(dba)_3$·$CHCl_3$ and 1,3-dppp in THF combined with adenine/NaH in DMF; (h) OsO_4, NMO. TBDMS = *t*-$BuMe_2Si$.

TABLE 1. NOE Enhancements Observed in 2

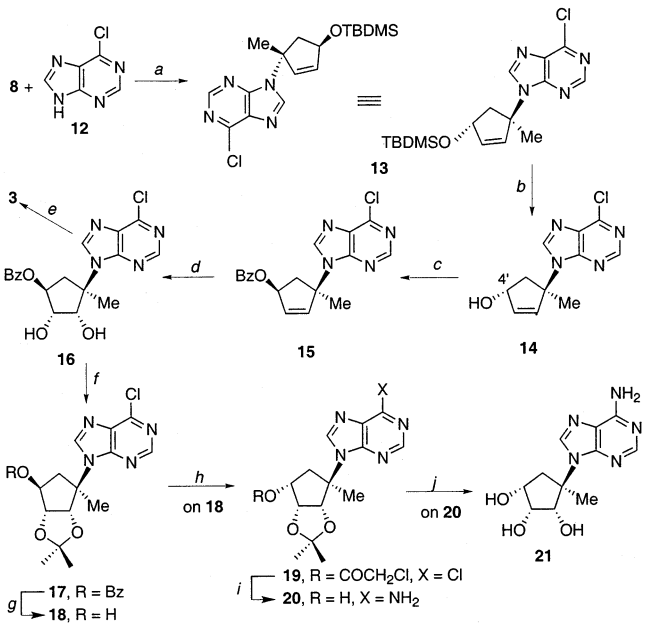
protons	% enhancement
4′-Me (δ 1.22), $H_α$−5′ (δ 2.40)	10.3
H-1′ (δ 4.70), H-5′$_α$ (δ 2.40)	7.1
H-3′$_β$ (δ 3.51), H-2′$_β$ (δ 4.65)	7.3
H-3′$_β$ (δ 3.51), H-5′$_β$ (δ 1.82)	3.6
H-2′$_β$ (δ 4.65), H-5′$_β$ (δ 1.82)	3.4
H-3′$_β$ (δ 3.51), H-1′$_α$ (δ 4.70)	none observed
H-2′$_β$ (δ 4.65), H-1′$_α$ (δ 4.70)	none observed

eochemical configuration. In this manner, a correlation existed between the C-4′ methyl protons (δ 1.22) and the H-5′$_α$ (δ 2.40)[12] (Table 1). Had the product been epimeric at C-4′ ("up" methyl group) there would have been a correlation between the methyl protons with H-5′$_β$ (δ 1.82) and H-3′$_β$ (δ 3.51), which was not observed. The α-configuration of the C-4′ methyl apparently arose due to the presence of the bulky TBDMS on the top face of **7** (Scheme 1) that influenced the stereochemistry of the methyllithium reaction.[10]

The configuration of the 2′,3′-diol of **2** was established by NOE correlations between H-3′$_β$ (δ 3.51) and H-5′$_β$ (δ 1.82) and between H-2′$_β$ (δ 4.65) and H-5′$_β$ (δ 1.82) (Table 1). Further support was seen by the lack of NOE enhancement between H-1′ and either H-2′ or H-3′ as a result of their *trans* relationship.

A retrosynthetic pathway to **3** suggested that **8** (Scheme 1), which had been employed in the preparation of **2**, could serve as its precursor. In that regard, subjecting **8** to a Mitsunobu reaction with 6-chloropurine (**12**)[13] yielded **13** (Scheme 2). Desilylation of **13** provided **14**. Inversion of the C-4′ center of **14** was accomplished by a second Mitsunobu reaction with benzoic acid[14] to give **15**. Dihydroxylation of **15** to the "down" diol[15] **16** was followed by ammonolysis to **3**.

SCHEME 2[a]



[a] Reagents: (a) Ph_3P/DlAD, THF; (b) K-10 clay, EtOAc/MeOH/H_2O (1:6:2); (c) $PhCO_2H$, DlAD, PPh_3; (d) OsO_4, NMO; (e) NH_3 in MeOH; (f) acetone, 2,2-dimethoxypropane, H^+; (g) KCN, MeOH; (h) $ClCH_2CO_2H$, DlAD, PPh_3, (i) NH_3 in MeOH; (j) dilute HCl.

The most striking feature of the NMR of **3** was that its 1′-methyl group appeared as a singlet downfield (δ 1.70) relative to the 4′-methyl group of **2** (δ 1.22), due apparently to the anisotropic effect of the adenine ring on the 1′-methyl substituent. The stereochemical assignment for the 1′-methyl in **3** arose by correlating the confirmed structure of **2** with the common precursor **8**, incorporating the known inversion of configuration that accompanies the Mitsunobu reaction[16] (leading to **13** and step c of Scheme 2) and the documented preference for dihydroxylation *trans* to the hetereocyclic base[15] (step d of Scheme 2).

The C-4′ epimeric derivative of **3** (**21**, Scheme 2) was prepared from **16** by, first, isopropylidenation to **17** followed by removal of the benzoyl group to **18**. The Mitsunobu reaction of **18** with chloroacetic acid[17] produced **19**. Ammonolysis of **19** (to **20**) with subsequent deprotection gave **21**. Compound **21** was desired to serve as a representative of the epi 5′-nor series where some biological activity has been found.[18]

The enantiomers of **2** and **3** would be available by beginning with the enantiomer of **4**[19] and following

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Schemes 1 and 2 (as a representative, see the Experimental Section for *ent*-**2**). Also, the means illustrated herein for achieving **2** and **3** and their enantiomers can be used to readily[20−22] obtain 5′-norcarbanucleosides with heterocyclic moieties other than adenine.

Compounds **2**, **3**, and **21** were evaluated for antiviral activity toward the following viruses: hepatitis B, influenza A, influenza B, parainfluenza-3, respiratory syncytial, varicella zoster (TK^+ and TK^-), cytomegalo, vesicular stomatitis, coxsackie B4, reo, herpes simplex 1 (TK^+ and TK^-) and 2, human immunodeficiency, vaccinia, and cowpox. No activity was found for any of the compounds, nor was there any cytotoxicity to the viral host cells.[23]

Experimental Section

Materials and Methods. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were determined at 250 and 62.5 MHz, respectively. 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), t (triplet), m (multiplet), and br (broad). Optical rotations were determined using the sodium-D line. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm silica gel 60-F_{254} precoated silica gel plates with visualization by irradiation with a UV lamp or exposure to iodine vapor. Column chromatography was performed on 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.

(1*R*,4*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-hydroxycyclopent-2-ene (6). To a suspension of K_2CO_3 (5.18 g, 37.54 mmol) in MeOH (100 mL) was added **5**[9] (8.0 g, 31.25 mmol) followed by stirring at room temperature for 30 min. The solvent was removed under reduced pressure and the residue dissolved in ether (300 mL) and the ether solution washed with brine (3 × 100 mL), dried (Na_2SO_4), and evaporated. The residue was purified via column chromatography eluting with hexanes/EtOAc (4:1) to afford 6.32 g (94.5%) of **6** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.003 (s, 6H), 0.81 (s, 9H), 1.42 (dt, 1H, J = 4.5, 9.1 Hz), 2.12 (s, 1H), 2.58 (dt, 1H, J = 6.9, 9.2 Hz), 4.49 (t, 1H, J = 5.8 Hz), 4.55 (t, 1H, J = 5.2 Hz), 5.78 (d, 1H, J = 4.5 Hz), 5.84 (d, 1H, J = 4.5 Hz); ^{13}C NMR ($CDCl_3$) δ −4.0, 18.8, 26.0, 45.2, 75.6, 75.9, 136.4, 137.3. Anal. Calcd for $C_{11}H_{22}O_2Si$: C, 61.63; H, 10.34. Found: C, 61.33; H, 10.39.

(1*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]cyclopent-2-en-4-one (7). To a stirred suspension of pyridinium chlorochromate (17.13 g, 79.5 mmol, 2.0 equiv) in dry CH_2Cl_2 (250 mL) was added dropwise a solution of **6** (8.4 g, 39.25 mmol) in CH_2Cl_2 (40 mL). After 14 h, Et_2O (750 mL) was added, and the reaction mixture was filtered through silica gel. The filtrate was concentrated *in vacuo*. The crude material was chromatographed (9:1 hexanes/EtOAc) to afford 7.0 g (84.13%) of **7** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 6H), 0.91 (s, 9H), 2.25 (dd, 1H, J = 1.7, 18.1 Hz), 2.71 (dd, 1H, J = 5.9, 18.1 Hz), 4.99 (m, 1H), 6.18 (d, 1H, J = 5.4 Hz), 7.46 (dd, 1H, J = 1.9, 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ −4.5, 18.3, 26.1, 45.2, 71.1, 134.6, 164.1, 206.7. Anal. Calcd for $C_{11}H_{20}O_2Si$·0.25EtOAc: C, 61.49; H, 9.46. Found: C, 61.67; H, 9.29.

(1*R*,4*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-methylcyclopent-2-en-4-ol (8). To a solution of compound **7** (5.86 g, 27.64 mmol) in anhydrous ether (100 mL) at −40 °C was added MeLi (24 mL, 1.4 M) via syringe over a period of 20 min. The reaction mixture was stirred at −40 °C for 3 h and then quenched with saturated solution of NH_4Cl (50 mL). The organic layer was separated; the aqueous layer was extracted with ether (3 × 50 mL); the organic layers were combined, dried (Na_2SO_4), and evaporated to dryness; and the residue was purified via column chromatography eluting with hexanes/EtOAc (4:1) to afford 3.8 g (60%) of **8** as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.91 (s, 9H), 1.33 (s, 3H), 1.8 (dd, 1H, J = 9.3, 17.9 Hz), 2.3 (m, 1H), 2.56 (brs, 1H), 4.80 (brs, 1H), 5.76 (dd, 1H, J = 2.0, 5.7 Hz), 5.88 (d, 1H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$) δ −4.0, 18.3, 26.2, 27.4, 51.5, 76.2, 81.7, 135.3, 141.1. Anal. Calcd for $C_{12}H_{24}O_2Si$·0.25H_2O: C, 61.88; H, 10.60. Found: C, 61.67; H, 10.29.

(1*S*,4*R*)-1-Methylcyclopent-2-ene-1,4-diol (9). A solution of **8** (1.83 g, 8.0 mmol) in anhydrous THF (50 mL) and Bu_4NF (1.0 M solution in THF, 15 mL, 15 mmol) was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure, and the residue was purified via column chromatography eluting with EtOAc/MeOH (49:1) to afford 0.57 g (62.3%) of **9** as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 3H), 1.82 (dd, 1H, J = 2.4, 14.3 Hz), 2.37 (m, 1H), 3.0 (brs, 2H), 4.70 (m, 1H), 5.83 (dd, 1H, J = 3.7, 5.5 Hz), 5.87 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 27.4, 50.2, 76.8, 82.1, 135.0, 142.1. Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.27; H, 8.52.

(1*R*,4*S*)-4-Hydroxy-4-methyl-2-cyclopenten-1-yl Acetate (10). To a chilled stirred solution of **9** (0.8 g, 7.0 mmol) in dry CH_2Cl_2 (25 mL) were added pyridine (0.66 g, 8.58 mmol) and Ac_2O (0.9 g, 9.24 mmol). The reaction mixture was stirred overnight at room temperature. Then it was treated with saturated $NaHCO_3$ solution (50 mL), stirred vigorously with ice-cold 1 N HCl (50 mL) and brine (2 × 50 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified via column chromatography, eluting with hexanes/EtOAc (1:4) to give 0.85 g (77.62%) of **10** as a colorless syrup: ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.91 (dd, 1H, J = 3.6, 14.5 Hz), 2.03 (s, 3H), 2.46 (m, 1H), 3.00 (m, 1H), 5.55 (m, 1H), 5.84 (dd, 1H, J = 2.1, 5.5 Hz), 6.00 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.1, 27.4, 51.3, 77.0, 82.2, 135.0, 142.2, 170.2. Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.43; H, 7.85.

(1′*R*,4′*S*)-4′-Methyl-1′-(6-amino-9*H*-purin-9-yl)cyclopent-2′-en-4′-ol (11). To a suspension of adenine (680 mg, 5.04 mmol) in dry DMF (30 mL) was added NaH (135 mg, 5.34 mmol, 95% dry powder), and the mixture was heated to 70 °C with stirring for 30 min. To this suspension was added a solution of a complex generated by the addition of tris(dibenzylideneacetone)dipalladium(0)·$CHCl_3$ (20 mg, 0.02 mmol) and 1,3-bis(diphenyl)phosphinopropane (30 mg, 0.072 mmol) to 720 mg (4.62 mmol) of allylic acetate **10** in dry THF (30 mL) with stirring for 15 min. The resulting mixture was stirred at 60 °C for 2 days. The volatiles were removed by rotary evaporation. The residue was then purified via column chromatography eluting with CH_3OH/CH_2Cl_2 (1:4). The fractions containing product were combined and the solvent was removed under reduced pressure to give 342 mg (32.2%) of **11** as a white solid: mp 122.4 °C; ^{1}H NMR (DMSO-d_6) δ 1.34 (s, 3H), 2.15 (dd, 1H, J = 7.0, 14.1 Hz), 2.40 (t, 1H, J = 13.3 Hz), 4.70 (brs, 1H), 5.36 (m, 1H), 5.68 (dd, 1H, J = 2.3, 5.3 Hz), 6.15 (m, 1H), 7.29 (s, 2H), 8.11 (s, 1H), 8.12 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 27.7, 47.0, 57.8, 80.1, 119.0, 128.6, 139.6, 143.6, 148.7, 152.0, 156.0. Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.28. Found: C, 57.25; H, 5.59; N, 30.17.

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(1′*R*,2′*S*,3′*S*,4′*S*)-4′-Methyl-1′-(6-amino-9*H*-purin-9-yl)cyclopentane-2′,3′,4′-triol (2). To a solution of **11** (200 mg, 0.87 mmol) in THF/H_2O (10:1, 20 mL) was added a 50% aqueous solution of *N*-methylmorpholine *N*-oxide (0.26 mL, 1.13 mmol) and OsO_4 (25 mg). The reaction mixture was stirred at room temperature for 24 h until TLC showed no remaining starting material. The solvent was removed by rotary evaporation, and the residue was coevaporated with EtOH (3 × 50 mL) to give a gummy material. This crude material was purified by column chromatography (eluent EtOAc/MeOH, 4:1) to afford **2** (161 mg, 70.2%) as a white solid: mp 202−203 °C; $[\alpha]^{25}_D$ −4.0 (*c* 0.81, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.22 (s, 3H), 1.82 (dd, 1H, J = 4.4, 14.2 Hz), 2.40 (t, 1H, J = 10.95 Hz), 3.51 (d, 1H, J = 2.1 Hz), 4.65 (t, 1H, J = 2.4 Hz), 4.70 (m, 1H), 4.95 (d, 1H, J = 2.2 Hz), 5.03 (d, 1H, J = 4.3 Hz), 5.56 (s, 1H), 7.30 (s, 2H), 8.11 (s, 1H), 8.15 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.5, 42.8, 59.3, 77.4, 77.5, 79.0, 119.1, 140.0, 149.1, 151.9, 156.1. Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 49.98; H, 5.64; N, 26.34.

(1′*S*,2′*R*,3′*R*,4′*R*)-4′-Methyl-1′-(6-amino-9*H*-purin-9-yl)cyclopentane-2′,3′,4′-triol (*ent*-2). Beginning with (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate[19] (enantiomer of **4**) and following Schemes 1 and 2 produced *ent*-**2**: mp 202−203 °C; $[\alpha]^{25}_D$ +3.9 (*c* 0.76, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.21 (s, 3H), 1.82 (dd, 1H, J = 4.4, 14.2 Hz), 2.40 (t, 1H, J = 10.96 Hz), 3.51 (d, 1H, J = 2.1 Hz), 4.65 (t, 1H, J = 2.4 Hz), 4.70 (m, 1H), 4.96 (d, 1H, J = 2.2 Hz), 5.03 (d, 1H, J = 4.3 Hz), 5.56 (s, 1H), 7.29 (s, 2H), 8.11 (s, 1H), 8.15 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.4, 42.8, 59.3, 77.4, 77.4, 79.0, 119.1, 140.0, 149.1 151.9, 156.1. Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 49.96; H, 5.66; N, 26.33.

(1′*R*,4′*R*)-4′-[(*tert*-Butyldimethylsilyl)oxy]-1′-methyl-1′-(6-chloro-9*H*-purin-9-yl)-2′-cyclopentene (13). A solution of triphenyphosphine (8.10 g, 30.81 mmol) in dry THF (100 mL) was cooled to −20 °C (dry ice bath), and diisopropyl azodicarboxylate (6.1 mL, 30.81 mmol) was added over a period of 10 min. This mixture was stirred at −20 °C for 20 min to yield a white precipitate of the triphenylphosphine−diisopropyl azodicarboxylate complex. To this latter complex as a suspension were added 6-chloropurine (4.40 g, 28.46 mmol) and a solution of **8** (5.40 g, 23.7 mmol) in dry THF (30 mL). The cooling bath was removed, and the reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the residue was purified via column chromatography eluting with hexanes/EtOAc (3:1) to afford 2.60 g (30%) of **13** as a white solid: mp 154.6 °C; ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 6H), 0.82 (s, 9H), 1.90 (s, 3H), 2.17 (d, 1H, J = 13.9 Hz), 2.87 (dd, 1H, J = 6.67, 13.94 Hz), 4.90 (d, 1H, J = 4.5 Hz), 6.12 (d, 1H, J = 4.6 Hz), 6.18 (dd, 1H, J = 4.6, 5.53 Hz), 8.02 (s, 1H), 8.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −4.5, 18.3, 26.0, 28.2, 48.2, 71.1, 77.3, 132.9, 134.3, 140.2, 143.4, 151.4, 151.5, 152.0. Anal. Calcd for $C_{17}H_{25}N_4OClSi$: C, 55.95; H, 6.90; N, 15.35. Found: C, 55.89; H, 6.96; N, 15.29.

(1′*R*,4′*R*)-1′-Methyl-1′-(6-chloro-9*H*-purin-9-yl)-2′-cyclopenten-4′-ol (14). A mixture of **13** (1 g, 2.74 mmol) and K-10 clay (1.37 g) in EtOAc/MeOH/H_2O (45 mL) (1:6:2) were stirred at 75 °C for 8 h. The reaction mixture was then filtered through Celite and washed with MeOH. The combined filtrates were concentrated and the residue coevaporated (3×) with EtOAc/toluene (1:2) under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (1:1) to afford **14** (490 mg, 71%) as a white solid: mp 165.5−166.8 °C; ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3H), 2.41 (d, 1H, J = 12.81 Hz), 2.79 (dd, 1H, J = 5.7, 12.82 Hz), 4.39 (d, 1H, J = 5.9 Hz), 4.71 (d, 1H, J = 5.2 Hz), 6.12 (d, 1H, J = 4.8 Hz), 6.19 (dd, 1H, J = 4.7, 5.54 Hz), 8.22 (s, 1H), 8.74 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.3, 41.7, 67.7, 75.7, 132.9, 134.3, 144.0, 144.2, 151.3, 151.5, 152.1. Anal. Calcd for $C_{11}H_{11}N_4OCl$: C, 52.70; H, 4.42; N, 22.35. Found: C, 52.52; H, 4.54; N, 22.39.

(1′*S*,4′*R*)-4′-Methyl-4′-(6-chloro-9*H*-purin-9-yl)-2′-cyclopenten-1′-yl Benzoate (15). A solution of triphenylphosphine (2.02 g, 7.68 mmol) in dry THF (50 mL) was cooled to −20 °C, and diisopropyl azodicarboxylate (1.56 mL, 7.68 mmol) was added over a period of 10 min. This mixture was stirred at −20 °C for 20 min to yield a white precipitate of triphenylphosphine−diisopropyl azodicarboxylate complex. To this latter complex as a suspension were added a solution of **14** (1.60 g, 6.40 mmol) in dry THF (20 mL) and benzoic acid (939 mg, 7.68 mmol). The cooling bath was removed, and the reaction mixture was stirred at room temperature for 2 h. After evaporation of the reaction mixture to dryness, the residue was purified via flash chromatography eluting with hexanes/EtOAc (3:1) to afford **15** (1.55 g, 67%) as a white solid: mp 171.3−172.1 °C; ^{1}H NMR ($CDCl_3$) δ 1.89 (s, 3H), 2.57 (d, 1H, J = 13.16 Hz), 2.87 (dd, 1H, J = 5.98, 13.20 Hz), 4.95 (d, 1H, J = 4.5 Hz), 6.06 (d, 1H, J = 5.4 Hz), 6.28 (dd, 1H, J = 4.8, 5.4 Hz), 7.43 (t, 2H, J = 7.6 Hz), 7.55 (d, 1H, J = 7.5 Hz), 8.03 (d, 2H, J = 7.7 Hz), 8.42 (s, 1H), 8.74 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.9, 48.2, 71.4, 75.1, 128.6 (2C), 129.9 (2C), 130.7, 131.5 (2C), 133.3 (2C), 139.8, 144.7, 150.6, 151.6, 166.2. Anal. Calcd for $C_{18}H_{15}N_4O_2Cl$: C, 60.94; H, 4.26; N, 15.79. Found: C, 60.61; H, 4.53; N, 15.91.

(1′*S*,2′*R*,3′*S*,4′*R*)-2′,3′-Dihydroxy-4′-methyl-4′-(6-chloro-9*H*-purin-9-yl)cyclopent-1′-yl Benzoate (16). To a solution of **15** (1.00 g, 2.82 mmol) in THF/H_2O (9:1, 60 mL) was added a 50% aqueous solution of *N*-methylmorpholine *N*-oxide (1.3 mL, 5.64 mmol) and OsO_4 (40 mg). Following stirring at room temperature for 24 h, the solvent was removed by rotary evaporator and the residue coevaporated with EtOH (3 × 50 mL) to give a gummy material. This crude material was purified by flash chromatography (eluent EtOAc/hexanes, 3:2) to afford **16** (905 mg, 82.3%) as a white solid: mp 181.4−182.3 °C; ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 3H), 2.09 (d, 1H, J = 13.57 Hz), 2.85 (dd, 1H, J = 6.3, 13.57 Hz), 3.41 (brs, 1H) 4.21 (brs, 1H), 4.36 (d, 2H, J = 8.47 Hz) 4.68 (d, 1H, J = 6.1 Hz), 7.35 (t, 2H, J = 7.7 Hz), 7.51 (d, 1H, J = 7.68 Hz), 7.96 (d, 2H, J = 7.8 Hz), 8.22 (s, 1H), 8.64 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.6, 44.7, 67.6, 75.2, 78.7, 80.7, 128.8 (2C), 130.1 (2C), 133.1, 133.6, 145.3, 150.6, 151.4, 152.1, 152.4, 167.1. Anal. Calcd for $C_{18}H_{17}N_4O_4Cl$: C, 55.61; H, 4.41; N, 14.41. Found: C, 55.74; H, 4.52; N, 14.28.

(1′*R*,2′*S*,3′*R*,4′*S*)-1′-Methyl-1′-(6-amino-9*H*-purin-9-yl)cyclopentane-2′,3′,4′-triol (3). A solution of **16** (100 mg, 0.26 mmol) in dry MeOH (40 mL) was saturated with NH_3. This mixture was heated in a Parr stainless steel sealed reaction vessel at 120 °C for 24 h. After being cooled to room temperature, the reaction mixture was evaporated to dryness and the residue purified by flash chromatography using EtOAc/MeOH (5:1) to afford **3** (50 mg, 73.3%) as a white solid: mp 221.4−222.5 °C; $[\alpha]^{22}_D$ + 41.57 (*c* 0.14, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.70 (s, 3H), 1.97 (d, 1H, J = 12.80 Hz), 2.95 (dd, 1H, J = 5.6, 12.90 Hz), 3.46 (brs, 1H) 4.05 (d, 1H, J = 5.4 Hz), 4.37 (brs, 1H), 4.57 (d, 1H, J = 4.1 Hz), 4.85 (brs, 1H), 5.08 (d, 1H, J = 4.1 Hz), 7.18 (s, 2H), 8.16 (s, 1H), 8.20 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 26.5, 43.1, 65.2, 75.1, 77.2, 79.5, 119.4, 140.4, 149.7, 151.7, 156.0. Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 50.01; H, 5.73; N, 26.21.

(1′*S*,2′*R*,3′*S*,4′*R*)-2′,3′-(Isopropylidenedioxy)-4′-methyl-4′-(6-chloro-9*H*-purin-9-yl)cyclopent-1′-yl Benzoate (17). Compound **16** (1.00 g, 2.57 mmol) was dissolved in a solution of dry acetone (30 mL) and 2,2-dimethoxypropane (10 mL). To this was added *p*-toluenesulfonic acid (150 mg) and the reaction mixture stirred at room temperature for 12 h. The mixture was then brought to pH 7 with NH_4OH. Following this, the acetone was evaporated under vacuum. The residue was dissolved in EtOAc (100 mL), and this solution was washed with brine (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrate was concentrated under vacuum to give a crude residue, which was purified by column chromatography (eluent EtOAc/hexanes, 1:3) to afford **17** (892 mg, 81.1%) as a white solid: mp 165.4−166.7 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3H), 1.42 (s, 3H), 1.87 (s, 3H), 2.42 (d, 1H, J = 12.87 Hz), 2.80 (dd, 1H, J = 5.7, 13.00 Hz), 4.75 (d, 1H, J = 5.46 Hz), 4.92 (d, 1H, J = 5.44 Hz), 5.13

(d, 1H, J = 8.82 Hz), 7.38 (t, 2H, J = 7.9 Hz), 7.50 (d, 1H, J = 7.88 Hz), 7.98 (d, 2H, J = 8.10 Hz), 8.36 (s, 1H), 8.78 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.4, 27.2, 27.3, 44.8, 68.6, 77.8, 86.2, 87.4, 111.7, 128.6 (2C), 129.9 (2C), 131.3, 133.1, 133.2, 145.2, 150.9, 152.0 (2C), 166.2. Anal. Calcd for $C_{21}H_{21}N_4O_4Cl$: C, 58.81; H, 4.94; N, 13.06. Found: C, 58.74; H, 4.92; N, 13.08.

(1′*R*,2′*S*,3′*R*,4′*S*)-2′,3′-(Isopropylidenedioxy)-1′-methyl-1′-(6-chloro-9*H*-purin-9-yl)cyclopentan-4′-ol (18). To a solution of **17** (850 mg, 1.98 mmol) in MeOH was added four drops of H_2O and a catalytic amount of KCN (40 mg). The mixture was stirred at room temperature for 2.5 h. After evaporation of the reaction mixture to dryness, the residue was purified via flash chromatography (eluent hexanes/EtOAc, 1:1) to afford **18** (580 mg, 90.10%) as a white solid: mp 174.2−175.1 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 3H), 1.43 (s, 3H), 1.79 (s, 3H), 2.32 (d, 1H, J = 12.86 Hz), 2.70 (dd, 1H, J = 5.6, 13.08 Hz), 3.72 (brs, 1H), 4.74 (d, 1H, J = 5.08 Hz), 4.90 (d, 1H, J = 5.05 Hz), 5.15 (d, 1H, J = 8.56 Hz), 8.07 (s, 1H), 8.63 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.4, 26.3, 26.7, 42.6, 68.1, 77.7, 86.4, 87.0, 111.7, 131.9, 146.1, 150.6, 151.7, 151.8. Anal. Calcd for $C_{14}H_{17}N_4O_3Cl$: C, 51.78; H, 5.28; N, 17.25. Found: C, 51.74; H, 5.22; N, 17.08.

(1′*R*,2′*R*,3′*S*,4′*R*)-2′,3′-(Isopropylidenedioxy)-4′-methyl-4′-(6-chloro-9*H*-purin-9-yl)cyclopent-1′-yl Chloroacetate (19). To a solution of **18** (250 mg, 0.77 mmol) in anhydrous toluene (30 mL) were added triphenylphosphine (405 mg, 1.54 mmol) and dry chloroacetic acid (146 mg, 1.54 mmol). To this stirred solution diisopropyl azodicarboxylate (0.31 mL, 1.54 mmol) was added dropwise, causing a slightly exothermic reaction. The resulting pale yellow solution was stirred at room temperature for 16 h. The volatile components were then removed *in vacuo*, and the residue was purified via flash chromatography eluting with hexanes/EtOAc (3:1) to afford **19** (220 mg, 71.20%) as a white solid: mp 161.8−162.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 3H), 1.41 (s, 3H), 1.86 (s, 3H), 2.43 (d, 1H, J = 12.85 Hz), 2.80 (dd, 1H, J = 5.65, 13.07 Hz), 4.07 (s, 2H), 4.70 (d, 1H, J = 5.45 Hz), 4.87 (d, 1H, J = 5.44 Hz), 5.08 (d, 1H, J = 8.82 Hz), 8.34 (s, 1H), 8.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.5, 26.3, 26.5, 37.4, 44.8, 68.6, 77.5, 84.6, 87.6, 111.1, 132.2, 145.6, 151.5, 152.1, 152.4, 166.4. Anal. Calcd for $C_{16}H_{18}N_4O_4Cl_2$: C, 47.89; H, 4.52; N, 13.96. Found: C, 47.63; H, 4.54; N, 13.99.

(1′*R*,2′*S*,3′*R*,4′*R*)-2′,3′-(Isopropylidenedioxy)-1′-methyl-1′-(6-amino-9*H*-purin-9-yl)cyclopentan-4′-ol (20). Employing the same ammonolysis procedure that produced **3**, compound **19** (200 mg, 0.5 mmol) afforded 90 mg (77.57%) of **20** as white crystals: mp 195.7−196.8 °C; ^{1}H NMR (DMSO-d_6) δ 1.15 (s, 3H), 1.17 (s, 3H), 1.73 (s, 3H), 2.44 (d, 1H, J = 13.08 Hz), 2.75 (dd, 1H, J = 5.70, 13.00 Hz), 4.04 (d, 1H, J = 5.65 Hz), 4.52 (d, 1H, J = 5.10 Hz), 5.14 (d, 1H, J = 5.20 Hz), 5.34 (brs, 1H), 7.15 (s, 2H), 8.10 (s, 1H), 8.13 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 24.3, 25.8, 26.7, 43.0, 67.6, 75.0, 83.0, 86.0, 111.7, 119.3, 140.2, 149.6, 151.6, 155.9. Anal. Calcd for $C_{14}H_{19}N_5O_3$: C, 55.07; H, 6.27; N, 22.94. Found: C, 54.94; H, 6.22; N, 22.74.

(1′*R*,2′*S*,3′*R*,4′*R*)-1′-Methyl-1′-(6-amino-9*H*-purin-9-yl)-cyclopentane-2′,3′,4′-triol (21). The compound **20** (80 mg, 0.26 mmol) was dissolved in 0.5 N HCl in MeOH (25 mL). This reaction mixture was stirred for 30 min at room temperature and the solution evaporated under reduced pressure to yield a residue that was azeotroped with MeOH. The resultant residue was dissolved in MeOH, and the pH adjusted to 7 by treating the solution with IRA 400 (basic) resin. The resin was removed by filtration and washed with MeOH. The combined filtrates were evaporated under reduced pressure to produce a residue that was purified by column chromatography using EtOAc/MeOH (4:1) as eluent to give **21** (55.00 mg, 79.14%) as a white crystalline solid: mp 212.5−213.4 °C; $[\alpha]^{22}_D$ −18.23 (*c* 0.12, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.68 (s, 3H), 1.94 (d, 1H, J = 12.70 Hz), 2.97 (dd, 1H, J = 5.5, 12.80 Hz), 3.68 (brs, 1H) 4.00 (d, 1H, J = 5.2 Hz), 4.21 (brs, 1H), 4.61 (d, 1H, J = 4.2 Hz), 4.93 (brs, 1H), 5.11 (d, 1H, J = 4.2 Hz), 7.16 (s, 2H), 8.14 (s, 1H), 8.19 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 26.5, 43.0, 65.1, 75.1, 77.1, 79.4, 119.4, 140.4, 149.7, 151.6, 156.0. Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 50.02; H, 5.54; N, 26.39.

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