Notes

Regioselective Coupling of Tetraalkylammonium Salts of 6-Iodo-2-aminopurine to a Cyclobutyl Triflate: Efficient Preparation of Homochiral BMS-180,194, a Potent Antiviral Carbocyclic Nucleoside

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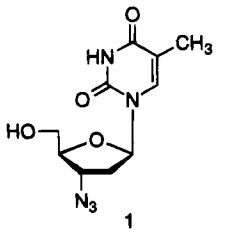
Introduction

The design and preparation of novel nucleoside analogues as antiviral agents has a well-established history in medicinal chemistry.[1] For example, modification of the carbohydrate ring of nucleosides has yielded a number of agents with inhibitory activities against the human immunodeficiency virus (HIV) and/or herpes viruses. These modified nucleosides include deoxy analogs such as AZT (**1**),[2] acyclic analogs such as acyclovir (**2**),[3] and carbocyclic analogs such as the cyclopentyl nucleosides **3**[4] and **4**,[5] and the cyclobutyl nucleoside **5** (BMS-180,194; lobucavir).[6] Carbocyclic nucleosides are of special interest in that they lack a glycosidic linkage and are therefore metabolically stable to the phosphorylases which can cleave furanose-based analogs such as **1**.[7]



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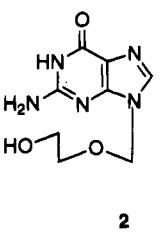

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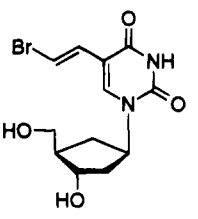

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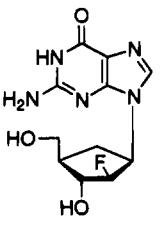

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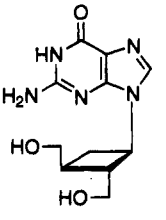

5 BMS-180,194

A crucial consideration in the synthetic strategy for the preparation of many nucleoside analogs is the manner by which the nucleobase is appended to the carbohydrate (or modified carbohydrate) moiety. The formation of a glycosidic bond has traditionally been accomplished by the general methodology of Vorbrüggen.[8] However, in the case of carbocyclic nucleosides, diverse methodologies continue to be investigated.[7,9] Conceptually, the simple alkylation of a nucleobase with a suitably activated carbocycle is a highly convergent approach, yet low yields, harsh reaction conditions, the necessity of employing a large excess of reagents in high-boiling polar solvents, and purification problems have continually plagued investigators. In particular, the regioselective N-9 alkylation of guanine or its synthetic equivalents, e.g. 6-halo- or 6-alkoxy-2-aminopurines, has represented a special synthetic challenge.[10] For example, alkylation of 6-substituted-2-aminopurines in the presence of an alkali metal carbonate or hydride with various cyclopentyl or cyclobutyl mesylates or tosylates typically requires employing 1.5–4 equiv of the purine, and the use of DMF or DMSO as solvent at elevated temperatures (75–120 °C) for extended periods (5–21 h) to provide the desired N-9-coupled purine in modest yields ranging from 18–58% (eq 1, Y = OTs or OMs).[5,6a,11,12] Milder coupling conditions have been achieved by employing a Mit-

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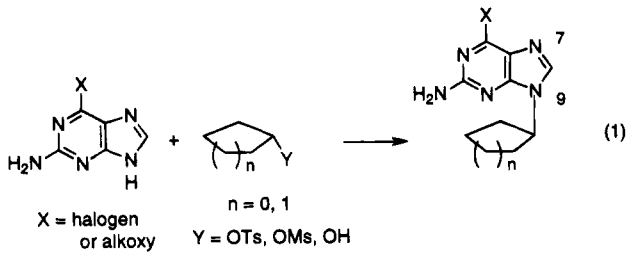
sunobu-type strategy (eq 1, Y = OH) with yields ranging from 23–78% (53% for a coupling with unsubstituted cyclobutanol), although product purification is a persistent problem.[10b,13] Due in part to the above difficulties, less convergent strategies for the preparation of carbocyclic guanine nucleosides, such as the stepwise construction of the purine ring starting from a carbocyclic primary amine, have continued to be widely employed.[14]



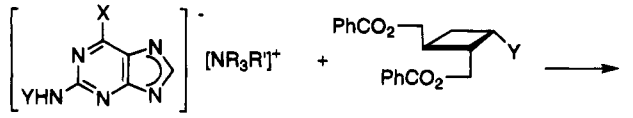
(1)

During the course of our efforts directed toward improving the synthesis of BMS-180,194 (**5**), we studied the alkylation of various salts of guanine synthons with activated cyclobutyl moieties. As described herein, we have discovered that tetraalkylammonium salts of 6-iodo-2-aminopurine couple smoothly with equimolar quantities of the corresponding protected cyclobutyl triflate at room temperature in methylene chloride to provide the corresponding N-9-coupled product in yields up to 76% following a simple extractive workup and crystallization. The N-9 to N-7 regioselectivity for this reaction was typically 93:7 prior to isolation; subsequent crystallization afforded the N-9 isomer in >99:1 regiochemical purity. This unique set of conditions offers significant advantages in terms of yield, regioselectivity, stoichiometry, mild reaction conditions, and ease of purification compared to previously published reports from this or other laboratories.[6a,10b,11,13]

Results and Discussion

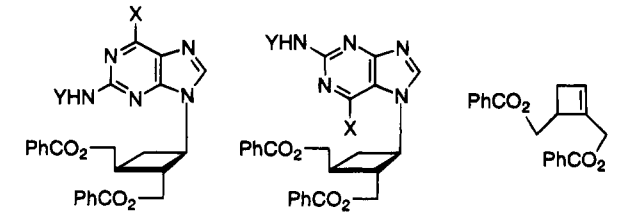
Previously[6a] we had reported that reaction of 6-(benzyloxy)-2-aminopurine with the cyclobutyl tosylate **7a** in DMF at 110 °C for 21 h in the presence of K_2CO_3 and 18-crown-6 afforded the corresponding coupled product **8a** in 51% yield following chromatography (Scheme 1). The modest yield of **8a** was subsequently found to be partially due to the formation of two side-products, the N-7 isomer **9a** and an elimination product **10**, isolated in 16 and 7% yields, respectively.[15] Our initial studies to improve the yield for this coupling centered on variation of the purine 6-substituent. Investigators at Beecham[16] had reported that the regioselectivity (N-9 vs N-7) of alkylation of 2-aminopurines with primary alkyl halides is improved by modifying the 6-substituent from methoxy to chloro or, especially, to iodo. However, reaction of either 2-amino-6-chloropurine or 2-amino-6-iodopurine with tosylate **7a** employing the above reaction

Scheme 1



6a X = OBn; R, R' = nBu, Y = H
6b X = I; R, R' = nBu, Y = H
6c X = I; R = Et, R' = Bn, Y = H
6d X = Cl; R, R' = nBu, Y = H
6e X = Cl; R, R' = nBu; Y = COiPr

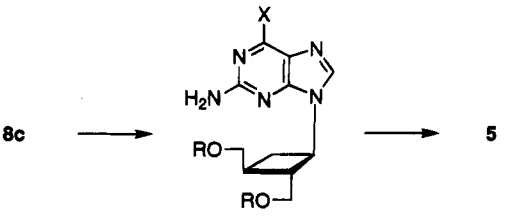
7a Y = OTs
7b Y = OTf
7c Y = ONs



8a X = OBn; Y = H
8b X = Cl; Y = H
8c X = I; Y = H
8d X = Cl; Y = COiPr

9a X = OBn; Y = H
9b X = I; Y = H
9c X = Cl; Y = COiPr

10



11a X = OMe, R = H
11b X = OH, R = Bz

conditions did not result in improved yields of the desired coupled products (**8b** and **8c**, respectively). In fact, 2-amino-6-iodopurine degraded quickly under the relatively harsh reaction conditions.

We next investigated the influence of the base used for generation of the purine anion. Kjellberg et al.[17] had reported that purine alkylations with primary alkyl halides in the presence of LiH led to improved yields of N-9 alkylated product. However, lithiation of 6-(benzyloxy)-2-aminopurine with LiH followed by reaction with tosylate **7a** (110 °C, 8 h, DMF) resulted in no improve-

(12) A specialized coupling involving a cyclopentyl π-allylpalladium complex has recently been employed to prepare unsaturated carbocycles such as carbovir in good yields: see, for example, Jung, M. E.; Rhee, H. *J. Org. Chem.* **1994**, *59*, 4719.

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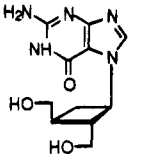
(15) Spectral data for **9a** and **10** and spectral data and an X-ray crystal structure for **12**, the N-7 isomer of **5**, are found in the supplementary material section of this journal. Compound **12** was prepared from **9a**, according to the deprotection scheme previously described[6a] for **8a**. Compound **12** was alternatively prepared from **9b** using the deprotection method described for the preparation of **5**.



12

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ment in the yield of **8a**. Since alkali metal salts of 6-substituted-2-aminopurines tend to be only partially soluble in DMF or DMSO even at elevated temperatures, we sought a purine salt form which would allow a homogeneous reaction mixture. Although tetra-*N*-alkylammonium salts of purines have been reported only rarely in the literature,[18,19] we prepared these salts to study their comparative reactivity and solubility. Thus, treatment of 6-(benzyloxy)-2-aminopurine with 1 equiv of tetra-*N*-butylammonium hydroxide in water followed by removal of solvent afforded the salt **6a** as a white amorphous powder, completely soluble in DMF. Reaction of **6a** with tosylate **7a** in DMF at 110 °C was complete after 5 h, but afforded **8a** in only 44% yield after chromatography along with **9a** (15%) and **10** (15%). We reasoned that a better leaving group might allow the alkylation to proceed under milder conditions and hence allow the use of the preferred[16] 2-amino-6-iodopurine. Therefore, we prepared the cyclobutyl triflate **7b** for use in the coupling reaction. Iodopurine tetra-*N*-butylammonium salt **6b** (1.1 equiv) reacted smoothly with triflate **7b** as a homogeneous solution in CH_2Cl_2 at room temperature to afford, following aqueous workup and crystallization, the desired N-9 isomer **8c** in 76% isolated yield with no detectable quantity of the elimination product **10**. Examination of the crude coupling product by ^1H NMR[20] revealed a N-9 to N-7 (**8c** to **9b**) regioselectivity of 93:7. Similar alkylation of the iodopurine *N*-benzyl-*N*-triethylammonium salt **6c** with the triflate **7b** afforded **8c** in 70% yield with identical regioselectivity (93:7). Alkylation of **6d**, the tetra-*N*-butylammonium salt of 6-chloro-2-aminopurine, with triflate **7b** under similar conditions afforded the corresponding N-9 product **8b** in 74% yield following chromatography; however, the regioselectivity[21] for this coupling was lower (N-9 to N-7, 80:20). Coupling of the salt **6b** with the less activated cyclobutyl *p*-nitrobenzenesulfonate **7c** was also successful at providing **8c** (64% isolated yield; N-9 to N-7, 89:11), although refluxing in acetonitrile for 8.5 h was required.

N-2-Acylated (e.g. N-2-isobutyryl) derivatives of guanine have often been employed in the preparation of guanosine analogs,[10] although the specific effect of such a substitution on the yield and regioselectivity in reactions with carbocyclic electrophiles has apparently not been studied. Alkylation of salt **6e** with **7b** furnished N-9 isomer **8d** in only 54% isolated yield with a 14% yield of N-7 isomer **9c** (80:20 regioselectivity). Thus, N-acylation of the purine offers no advantages for this type of carbocyclic coupling.

The protected nucleoside intermediate **8c** could be converted to the final product **5** in high yield by one of several methods. Treatment of **8c** with sodium methoxide in hot MeOH afforded the 6-methoxy intermediate **11a** which, following reflux in aqueous HCl, gave **5** in 93% overall yield.[22,23] Alternatively, treatment of **8c** with hot aqueous acetic acid gave the benzoyl-protected nucleoside analog **11b** in 77% yield. The benzoyl groups of **11b** were removed to provide **5** using either sodium methoxide in MeOH (79% yield) or sodium hydroxide in water (91% yield).

The enhanced solubility of the tetraalkylammonium salts of 6-iodo-2-aminopurine and other 6-substituted-2-aminopurines allow their effective use in a greater range of organic solvents than is possible with the standard alkali-metal salt forms of these purines. As demonstrated above, the selective N-9 alkylation of tetraalkylammonium salts of 6-iodo-2-aminopurine with a cyclobutyl triflate proceeds in high yield under extremely mild conditions. Furthermore, the use of essentially equimolar quantities of the purine and triflate, as well as the lack of significant side-products, allows for facile isolation of the coupled product. Multikilogram quantities of BMS-180,194 have been prepared employing these procedures.

Experimental Section

General Methods. Melting points were determined in open capillary tubes and are uncorrected. Flash chromatography was performed with E. Merck 240−400 mesh silica gel. Thin layer chromatography (TLC) was carried out with E. Merck silica gel 60F-254 plates. Solvents were concentrated under reduced pressure on a rotary evaporator. ^1H NMR spectra were recorded at 270 and 400 MHz and ^{13}C NMR at 68 MHz. Chemical shifts are expressed in δ units (parts per million) with TMS as internal reference. Elemental analyses, Karl Fischer (KF) measurements, and high-resolution FAB mass spectra were performed by the Analytical Research and Development Department, Bristol-Myers Squibb. Elemental analyses were within ±0.4% of the theoretical values. 6-(Benzyloxy)-9*H*-purin-2-amine was prepared according to a literature procedure.[24] 6-Chloro-9*H*-purin-2-amine is commercially available (Aldrich Chemical Co.).

6-Iodo-9*H*-purin-2-amine. A modification of a published procedure[25] was employed. 6-Chloro-9*H*-purin-2-amine (5.0 g, 29.5 mmol) was added to 47% HI (61 mL) chilled in an ice bath. After 1.5 h, water (61 mL) was added and the mixture was stirred in the ice-bath for 30 min. The yellow solid was filtered and the filter cake was washed with water. 6 M NaOH (7 mL) was added to the wet solid with stirring until all the solid had dissolved. The solution was added to 30 mL of boiling water containing 3 mL of AcOH. The mixture was boiled briefly and allowed to stand at rt for 1 h. The product was filtered, washed with water, and dried under vacuum to give 6-iodo-9*H*-purin-2-amine. (6.88 g, 89%) as a colorless solid: mp 240 °C dec (lit.[25] yield 25%, mp 245 °C dec). Anal. Calcd for $C_5H_4N_5I \cdot 0.014\ H_2O$: C, 22.99; H, 1.55; N, 26.81; I, 48.57 (H_2O, 0.10%). Found: C, 23.32; H, 1.52; N, 26.75; I, 48.14 (H_2O determined by KF, 0.09%).

(18) (a) Hagberg, C.-E.; Johansson, K. N.-G.; Kovacs, Z. M. I.; Stening, G. B. Eur. Pat. Appl. 55239, 1981. (b) For a description of *in situ* generated Bu_4N salts of purines, see Hakimelahi, G. H.; Khalafi-Nezhad, A. *Helv. Chim. Acta* **1989**, *72*, 1495.

(19) For the use of phase-transfer conditions for the alkylation and glycosylation of purines and purine isosteres, see (a) Seela, F.; Gumbiowski, R. *Heterocycles* **1989**, *29*, 795. (b) Seela, F.; Steker, H. *Tetrahedron Lett.* **1984**, 5017. (c) Ramzaeva, N.; Alksnis, E.; Goldberg, Y.; Lidaks, M. *Synth. Commun.* **1989**, *19*, 3121.

(20) The ratio of regioisomers was readily determined by integration of the purine C-8 proton singlets: **8c**, 8.46 ppm, and **9b**, 8.82 ppm (DMSO-d_6).

(21) For the determination of the regioselectivity of the alkylation of 6-chloro-2-aminopurine salt **6d**, a sample of the crude coupled product mixture was fully deprotected to provide the corresponding mixture of **5** and its N-7 isomer, **12**.[15] Integration of the guanine C-8 proton singlets (**5**, 7.82 ppm; **12**, 8.19 ppm; DMSO-d_6) in the ^1H NMR spectrum provided the desired ratio.

(22) For other methods for converting 6-halo-2-aminopurines to the corresponding guanine, see: Linn, J. A.; McLean, E. W.; Kelley, J. L. *J. Chem. Soc., Chem. Commun.* **1994**, 913 and references therein.

(23) An X-ray crystal structure of **5** following crystallization from H_2O−CH_3CN was obtained. Additionally, an X-ray crystal structure of the hemi-sodium salt of **5** was obtained. This salt was prepared by treatment **5** (1 mmol) with aqueous sodium hydroxide (1 mmol) to afford a clear solution which was lyophilized. The lyophilate was crystallized from MeOH to afford the hemi-sodium salt of **5**. The structures are found in the supplementary material section of this journal. The author has deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(24) Maccoss, M.; Tolman, R. L.; Wagner, A. F.; Hannah, J., European Patent Application, 184473, 1986.

(25) Koda, R. T.; Biles, J. A.; Wolf, W. *J. Pharm. Sci.* **1968**, *57*, 2056.

6-Iodo-9*H*-purin-2-amine, Ion(1−), Tetrabutylammonium (1:1) Salt (6b). Aqueous tetrabutylammonium hydroxide (1.53 M, 2.5 mL, 3.83 mmol) was added to a slurry of powdered 6-iodo-9*H*-purin-2-amine (1.0 g, 3.83 mmol) in 30 mL of CH_2Cl_2. The mixture was stirred for a few minutes and the filtrate concentrated. The residue was concentrated from toluene (3 × 10 mL) and triturated with 20 mL of Et_2O. The solid was filtered and dried over P_2O_5 under vacuum to give **6b** (1.84 g, 95%) as a colorless solid: mp. ~90 °C, crystallized from EtOAc mp 114−116 °C; ^{1}H NMR ($CDCl_3$) δ 0.95 (12H, t, J = 6 Hz), 1.32 (16H, m), 2.83 (8H, m), 7.28 (2H, s), 8.00 (1H, s); ^{13}C NMR ($CDCl_3$) δ 13.5, 19.5, 23.6, 58.2, 117.5, 135.5, 155.5, 156.9, 160.9. Anal. Calcd for $C_{21}H_{39}N_6I \cdot 0.13H_2O$: C, 49.96; H, 7.84; N, 16.65; I, 25.14 (H_2O, 0.46%). Found: C, 50.17; H, 7.92; N, 16.86; I, 25.14 (H_2O determined by KF, 0.48%).

6-Iodo-9*H*-purin-2-amine, Ion(1−), Triethyl(phenylmethyl)ammonium (1:1) Salt (6c). Benzyltriethylammonium hydroxide (24.6 mL, 43.3 mmol, 40 wt % in MeOH) was added to a suspension of 6-iodo-9*H*-purin-2-amine (10.0 g, 38.3 mmol) in 22 mL of EtOH and stirred until nearly all of the solid had dissolved. The mixture was filtered, and the filtrate was concentrated to a small volume. The residue was rapidly stirred while EtOAc (25 mL) was added in one portion. A solution was formed from which a solid precipitated. Additional EtOAc (175 mL) was added dropwise over 30 min. After precipitation was complete, the mixture was stirred for 2 h, filtered, washed with EtOAc, and dried under vacuum to give **6c** (15.16 g, 88%) as a colorless solid: mp 156−159 °C (effervesces); ^{1}H NMR (DMSO-d_6) δ 1.30 (9H, t, J = 6 Hz), 3.15 (6H, q, J = 6 Hz), 4.49 (2H, s), 5.40 (2H, br s), 7.52 (5H, s), 7.57 (1H, s); ^{13}C NMR (DMSO-d_6) δ 7.5, 52.0, 59.5, 117.9, 127.8, 129.0, 130.2, 132.5, 134.7, 154.6, 156.9, 161.7. Anal. Calcd for $C_{18}H_{25}N_5I \cdot 0.065H_2O$: C, 47.39; H, 5.54; N, 18.63; I, 28.22 (H_2O, 0.26%). Found: C, 47.45; H, 5.50; N, 18.63; I, 27.94 (H_2O determined by KF, 0.26%).

[1*S*-(1α,2β,3α)]-3-(2-Amino-6-iodo-9*H*-purin-9-yl)-1,2-cyclobutanedimethanol, Dibenzoate Ester (8c) and [1*S*-(1α,2β,3α)]-3-(2-Amino-6-iodo-7*H*-purin-7-yl)-1,2-cyclobutanedimethanol, Dibenzoate Ester (9b). Triflic anhydride (2.01 mL, 12.0 mM) dissolved in 3 mL of CH_2Cl_2 was added dropwise over 5 min to a stirred, ice cold solution of 1*S*-(1α,2β,3β)]-3-hydroxy-1,2-cyclobutanedimethanol, 1,2-dibenzoate ester[6a] (3.40 g, 10.0 mM) and pyridine (1.28 mL, 15.0 mM) in 15 mL of CH_2Cl_2. After 5 min of additional stirring, the alcohol was absent by TLC (5% THF/CH_2Cl_2, R_f 0.37). The reaction mixture was worked up below 20 °C as follows. The mixture was quenched with ice and diluted to 100 ml with CH_2Cl_2. The organic layer was washed with ice−water (2×), cold 5% $NaHSO_4$, and ice−water. The aqueous washings were back-extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and concentrated to afford triflate **7b** as a mobile oil (TLC, 20% EtOAc/hexane, R_f = 0.32). A solution of triflate **7b** in CH_2Cl_2 (5 mL) was added to a stirred, ice cold solution of the tetrabutylammonium salt **6b** (6.02 g, 12 mmol) in CH_2Cl_2 (7 mL). After 30 min, the ice bath was removed and the reaction mixture stirred overnight at rt. The reaction mixture was concentrated, and the residue was dissolved in EtOAc (50 mL) by brief heating on a steam bath. The mixture was diluted with toluene (50 mL), washed with 30% aqueous H_3PO_4 (2×), and water (6×) until tetrabutylammonium ion was absent by TLC (EtOAc, visualized with Dragendorff's reagent, R_f ca. 0.18). The organic layer was then washed with 5% $NaHCO_3$ and brine and dried ($MgSO_4$). The EtOAc solution was concentrated to afford crude **8c** (5.51 g, 95% crude yield; **8c:9b**, 93:7 as determined by ^{1}H NMR;[20] TLC, EtOAc, R_f **8c** 0.59, **9b** 0.18). The crude product was heated to boiling in 90 mL of absolute EtOH. The product formed an oil on heating which crystallized in the boiling mixture. The hot mixture was allowed to cool to rt and let stand for 4 h and at 0 °C overnight. The solid was filtered, washed with cold 95% EtOH, and dried under vacuum to afford **8c** (4.43 g, 76%) as colorless crystals: mp 148−149 °C; $[\alpha]^{22}_D$ = −20.5° (c = 1, $CHCl_3$); IR ($CHCl_3$) 1716 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.60 (3H, m), 3.32 (1H, m), 4.38−4.65 (4H, m), 4.80 (1H, m), 6.80 (2H, br s), 7.37−7.74 (8H, m), 8.03 (2H, m), 8.46 (1H, s); ^{13}C NMR (DMSO-d_6) δ 29.9, 30.5, 45.7, 47.8, 65.6, 67.5, 123.4, 128.8, 129.0, 129.1, 129.4, 129.6, 129.9, 131.1, 133.5, 133.6, 141.2, 150.2, 159.6, 165.7, 166.0; MS (CI) m/z 584 (M + H)$^+$. Anal. Calcd for $C_{25}H_{22}IN_5O_4 \cdot 0.13H_2O \cdot 0.15EtOH$: C, 51.28; H, 3.94; N, 11.82; I, 21.41 (H_2O, 0.4%). Found: C, 51.46; H, 3.75; N, 11.76; I, 21.09 (H_2O determined by KF, 0.4%). An analytical sample of **9b** (colorless crystals) was isolated by chromatography followed by crystallization from EtOH: mp 160−161 °C; $[\alpha]^{22}_D$ −14.7° (c = 1, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 2.29 (1H, ddd, J = 10, 10, 10 Hz), 2.60 (1H, m), 2.70 (1H, m), 3.39 (1H, m), 4.50 (4H, d, J = 6.5 Hz), 5.33 (1H, ddd, J = 8, 8, 8 Hz), 6.52 (2H, s), 7.39−7.70 (8H, m), 8.00 (2H, m), 8.82 (1H, s); ^{13}C NMR (DMSO-d_6) δ 29.8, 32.1, 45.1, 48.5, 64.7, 66.9, 110.8, 120.9, 128.6, 128.8, 128.9, 129.2, 129.3, 129.6, 133.3, 133.4, 147.3, 159.7, 161.3, 165.4, 165.7; Anal. Calcd for $C_{25}H_{22}IN_5O_4$: C, 51.47; H, 3.80; N, 12.01; I, 21.75. Found: C, 51.36; H, 3.70; N, 11.69; I, 22.19.

[1*R*-(1α,2β,3α)-2-Amino-9-[2,3-bis(hydroxymethyl)cyclobutyl]-6*H*-purin-6-one (5). A solution of NaOMe in MeOH (3.9 M, 5.3 mL, 20.7 mmol) was added to a suspension of **8c** (8.0 g, 13.7 mmol) in dry MeOH (40 mL). The mixture was refluxed for 1.5 h. TLC (EtOH/EtOAc 1:1, R_f 0.56) showed formation of **11a**. The solution was neutralized with 1 N HCl to pH 7, and the MeOH was removed in vacuo. The resulting aqueous mixture was further acidified with concd HCl to pH ~0.5 and the mixture was washed with CH_2Cl_2 to remove methyl benzoate. The aqueous layer was heated in a 95 °C oil bath for 3 h (TLC, THF−MeOH−concd NH_4OH 6:3:1, R_f of **5**, 0.45). The hot mixture was adjusted to pH 7 with 4 N NaOH. Crystals formed immediately. The mixture was allowed to cool to rt slowly. After standing at rt overnight, the mixture was chilled at 0 °C for 1 h, filtered, and washed with cold water. The wet product was dissolved in 65 mL of refluxing water. The solution was allowed to stand at rt for 3 h and at 0 °C for 1 h. The resulting solid was filtered, washed with cold water, and dried under vacuum over P_2O_5 to afford **5** (3.40 g, 94%, 88% corrected for H_2O) as colorless crystals: mp ~ 290 °C dec, $[\alpha]^{22}_D$ = −24.4° (c = 1, DMSO), +25.3° (c = 1, 0.1 N NaOH). ^{1}H NMR and ^{13}C NMR.[6a] Anal. Calcd for $C_{11}H_{15}N_5O_3 \cdot 1.04H_2O$: C, 46.51; H, 6.06; N, 24.65 (H_2O, 6.60%). Found: C, 46.71; H, 6.02; N, 24.88 (H_2O determined by KF, 6.62%).

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Supplementary Material Available: Physical and spectral data for **9a**, **10**, and **12**; experimental procedures for the preparation of **6e**, **7c**, **8d**, **9c**, **11a**, and **11b** (13 pages). This material is contained in libraries on microfiche, immediately following this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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