Adenosine Deaminase Inhibitors: Synthesis and Biological Evaluation of Unsaturated, Aromatic, and Oxo Derivatives of (+)-*erythro*-9-(2′*S*-Hydroxy-3′*R*-nonyl)adenine [(+)-EHNA]

Palle V. P. Pragnacharyulu,* Vaibhav Varkhedkar, Mark A. Curtis, I. F. Chang, and Elie Abushanab*

Department of Chemistry, University of Rhode Island, Kingston, Rhode Island 02881-0809

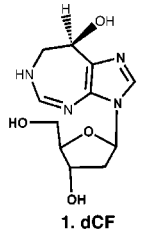
Received June 12, 2000

The synthesis and biological evaluation of three classes of chain-modified derivatives of (+)-EHNA are described. Among the 5′,6′-unsaturated derivatives, the *Z*-isomer was the most potent inhibitor of adenosine deaminase (ADA) but 3-fold less active than (+)-EHNA. Several 9-aralkyladenines (ARADs) have been prepared, and their inhibitory activity was determined. A minimum of two carbon atoms separating the aromatic ring from the adenine-bearing carbon (C-3′) was found to be essential for ADA activity equal to or slightly greater than that of (+)-EHNA. Finally, replacement of the C-5′ carbon with an oxygen resulted in reduced potency.

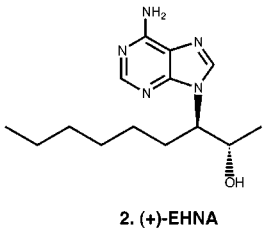
Introduction

Adenosine deaminase (ADA, adenosine aminohydrolase, EC 3.5.4.4) catalyzes the hydrolytic deamination of adenosine and 2′-deoxyadenosine to inosine and 2′-deoxyinosine, respectively. Inhibition of ADA activity has significant physiological consequences due to accumulation of these substrates. ADA inhibition leads to adenosine receptor-mediated effects on neurological,[1] vascular,[2,3] and blood platelet functions.[4] It also potentiates the cardio- and neuroprotective effects of adenosine against ischemia/reperfusion injury.[5−7] As a chemotherapeutic strategy, ADA inhibition potentiates 2′-deoxyadenosine-mediated lymphotoxicity in the treatment of some leukemias[8,9] and could block the inactivation of cytotoxic and antiviral adenosine analogues that are substrates of ADA.[10,11]

Potent ADA inhibitors fall into two classes: purine ribosides or 2′-deoxyribosides, in which the hydrated heterocycle resembles the putative transition state,[12] and compounds that have adenine or a modified congener attached to a hydrohobic substitutent at N-9.[13] 2′-Deoxycoformycin (**1**, dCF, pentostatin) belongs to the former class, and *erythro*-9-(2′*S*-hydroxy-3′*R*-nonyl)-adenine (**2**, EHNA) is the most potent example of the latter. The long and nearly irreversible inhibition of



1. dCF



2. (+)-EHNA

intercellular ADA[14] offers a likely explanation for toxicities observed with dCF therapy. EHNA, on the other hand, is rapidly metabolized,[15,16] and its shorter duration of action allows faster recovery of enzymatic activity. A shorter-acting ADA inhibitor than dCF could permit a controlled duration of chemotherapeutic efficacy while avoiding toxicities associated with long-term inhibition of ADA. Attractive targets would be analogues that are 1−2 orders of magnitude more potent than (+)-EHNA.

Racemic EHNA was designed by Schaeffer on the basis of extensive structure−activity relationship (SAR) studies.[17] Later work has shown that the ADA inhibitory activity resides mostly with the 2′*S*,3′*R*-*erythro*-enantiomer, (+)-EHNA.[18−21] The SAR studies suggested distinct binding pockets for the 1′-methyl and 2′-hydroxy groups and the hydrophobic alkyl chain.[22] The restrictive nature of these binding sites has been confirmed by the synthesis of C-1′ and nor-C-1′ derivatives of (+)-EHNA[23] and 3-deaza-(+)-EHNA.[24] On the other hand, not much work has been done to study the requirements on the terminal end of the alkyl chain where metabolic hydroxylation is likely to take place. Earlier studies in monkeys[15] and mice[16] revealed the formation of several metabolites which were tentatively identified as hydroxylated derivatives. We reported the synthesis of such hydroxylated (+)-EHNA derivatives and their evaluation with calf intestinal ADA.[25] These compounds were found to be less active than (+)-EHNA, which could be due to the interaction of polar hydroxyl groups with the enzyme. We also reported the biological evaluation of various (+)-EHNA derivatives having hydrophobic substituents at the chain terminus.[26] These derivatives had comparable ADA inhibitory activity to (+)-EHNA and were shown to have beneficial effect in ischemia.[26]

Although ADA interaction with a tight-binding transition-state inhibitor has been obtained by X-ray analysis,[27] no comparable data for a semi-tight-binding inhibitor such as EHNA are available. Neither the conformation nor its binding site have been elucidated. To better assess the role of the alkyl chain in ADA inhibition, we decided to study the affects of conformation on activity. Thus, a series of compounds having unsaturation in the alkyl chain were designed. The site

* Correspondence to: Prof. Elie Abushanab, 462 Montana Luna Ct., Escondido, CA 92025. Tel: (760) 741-5702. E-mail: vabu@home.com.

10.1021/jm0002533 CCC: $19.00
Published on Web 11/10/2000

of unsaturation was chosen between the 5′- and 6′-carbon atoms because of synthetic expediency. The biological evaluation of these compounds showed the *Z*-geometry to be associated with potent activity. Incorporation of this geometry in an aromatic ring with an alkyl substituent was then undertaken. The length and position of the alkyl chain were designed in such a way to maintain the nine-carbon chain length of the parent compound. Finally, the isosteric substitution of C-5′ with oxygen in (+)-EHNA and the most active 9-aralkyladenine (ARAD, **11h**) were chosen for further SAR studies.

In this paper a full account of the syntheses and biological evaluation of 5′,6′-unsaturated (+)-EHNA,[28] ARADs,[29] and their 5′-oxo isosteres are reported.

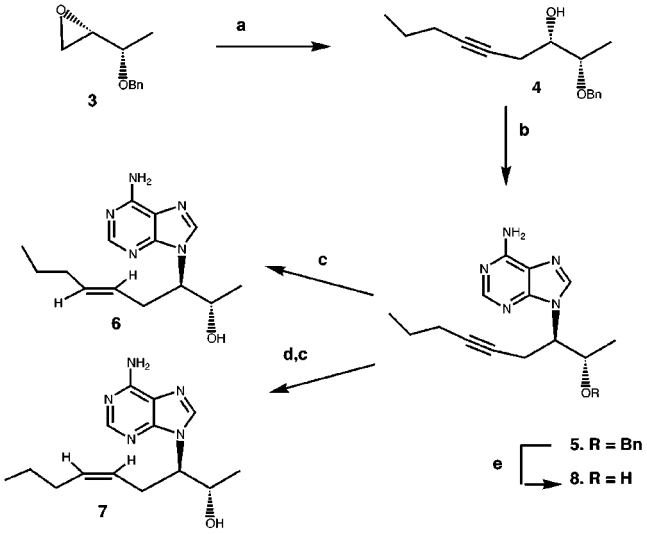
Chemistry

Unsaturated Derivatives. The reaction of epoxide **3**[30] with 1-pentynyllithium gave alcohol **4**. Construction of the purine ring has been previously accomplished by a rather lengthy procedure through the intermediacy of an amine.[25] A more recent approach to 9-substituted purine rings made use of the Mitsunobu reaction between an already formed purine and an alcohol.[11] Application of this strategy to condense **4** with adenine was unsuccessful and resulted, instead, in forming what is believed to be olefinic products as suggested by TLC analysis. On the other hand, condensation of **4** with 6-chloropurine furnished a product that could not be obtained in pure form due to its similar chromatographic behavior to dihydrodiisopropyl azodicarboxylate, a byproduct in the Mitsunobu reaction. However, ^{1}H NMR analysis of the crude product clearly showed the formation of a chloropurine derivative as evidenced by two singlets at δ 8.0 and 8.33 corresponding to H-2 and H-8, respectively. Ammonolysis of the crude product allowed the isolation of a compound that proved to be an 85:15 mixture of N-9:N-7 isomers. Separation of these isomers was accomplished by preparative thin-layer chromatography, which furnished the pure N-9 isomer **5** whose structural assignment was derived from UV analysis. [Compound **5** showed maximum absorption at 262 nm which is similar to that for adenosine (λ_{max} = 259.4 nm).]

Intermediate **5** was successfully converted to three different derivatives (**6**−**8**). The synthetic routes are depicted in Scheme 1. The *E*-isomer **6** was obtained by treatment of **5** with sodium/liquid ammonia, which resulted in the simultaneous reduction of the triple bond and cleavage of the benzyl ether. On the other hand, partial catalytic hydrogenation over Lindlar's catalyst followed by sodium/liquid ammonia reductive cleavage of the benzyl group gave the *Z*-isomer **7**. Finally, the acetylenic compound **8** was prepared by selective debenzylation of **5** using calcium/liquid ammonia with concomitant formation of minor amounts of **6**.[31]

ARADs. As can be seen in Scheme 2, the first step involved the opening of epoxide **3** with the anion of a suitable aryl or aralkyl unit to give alcohols **9a**−**h**. This reaction was accomplished by choosing either a Grignard or an organolithium reagent based on the convenience of its preparation. As described above, incorporation of the purine ring made use of the Mitsunobu reaction which took place with inversion of configuration at C-3′. The resultant 9-aralkyl-6-chloropurine derivatives could not be purified because of reasons described earlier, and after partial purification, they were subjected to ammonolysis to obtain the corresponding 6-amino derivatives **10a**−**h**. The target compounds **11a**−**h** were obtained by reductive debenzylation in good yield.

Scheme 1[a]



[a] (a) *n*-BuLi, 1-pentyne, Li_2CuCl_4, THF, −30 °C, 88%; (b) i. 6-chloropurine, PPh_3, DIAD, THF, reflux, 24 h, ii. NH_3, 90 °C, 27% (two steps); (c) Na/NH_3, toluene, −78 °C, 80%; (d) Lindlar's catalyst, toluene, H_2, 99%; (e) Ca/NH_3, toluene, −78 °C, 30% (**8**), 20% (**6**).

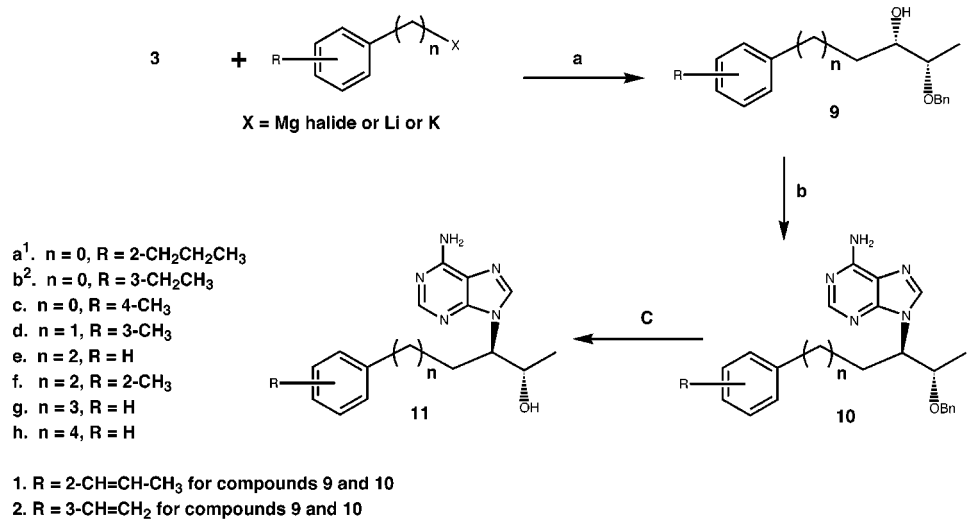
5′-Oxo Isosteres. As can be seen in Scheme 3, the first step involved the opening of epoxide **3** with the anion of either *n*-butanol or 2-phenethanol to give alcohols **12a**,**b**, respectively. The incorporation of the adenine ring followed procedures outlined earlier to give compounds **13a**,**b**. The target compounds **14a**,**b** were obtained by reductive debenzylation in good yield.

Results and Discussion

The ADA inhibitory activity of all the compounds was determined following procedures described earlier.[25] All 5′,6′-dehydro derivatives **6**−**8** have higher K_i values than (+)-EHNA. The *Z*-isomer **7** is the most active one in the series and is 3-fold less active than EHNA itself. It is 13 and 50 times more active than the corresponding *E*-isomer **6** and acetylene derivative **8**, respectively. This can be attributed to distance-related hydrophobic interactions between the terminus and the purine ring which are optimal in the *Z*-isomer.

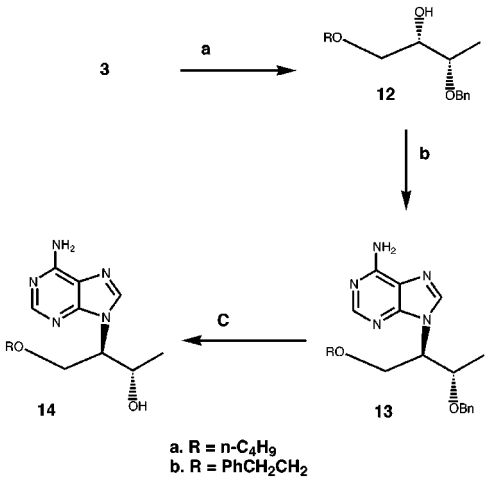
The ADA inhibitory activity data of the ARAD **11a**−**h** aromatic ring plays a significant role in ligand−enzyme binding. With only one carbon (**11a**−**c**) much reduced activity is observed. This finding corroborates similar results obtained by pulse ultrafiltration screens for receptor binding, a recently described technique to identify homologues with the highest affinity for a receptor.[32] Increasing the distance by one (**11d**), two (**11e**,**f**), three (**11g**), and four (**11h**) carbon atoms imparted activity similar to or greater than that of (+)-EHNA, **11f** (n = 2) being the most potent derivative described.

Scheme 2[a]



[a] (a) BF_3-Et_2O or Li_2CuCl_4, THF, −78 °C; (b) i. 6-chloropurine, PPh_3, DIAD, THF, reflux, ii. NH_3, 90 °C; (c) $Pd(OH)_2$, C_6H_{12}, reflux.

Scheme 3[a]



[a] (a) ROH (R = Bu), NaOH, 120 °C, 1 h or ROH (R = $PhCH_2CH_2OH$), NaOH, *t*-BuOH, 120 °C, 12 h; (b) i. 6-chloropurine, PPh_3, DIAD, THF, reflux, 12 h, ii. NH_3, 85 °C; (c) $Pd(OH)_2$, C_6H_{12}, EtOH, reflux, 48 h.

Table 1. Inhibition Constants for Various Chain-Modified Derivatives of (+)-EHNA with Calf Intestinal ADA[a]

compd	K_i (nM)	compd	K_i (nM)
2 [(+)-EHNA]	1.13	**11d**	1.02
6	50.7	**11e**	0.89
7	3.74	**11f**	0.51
8	188	**11g**	0.76
11a	302	**11h**	0.95
11b	133	**14a**	123.4
11c	302	**14b**	93.1

[a] Steady-state inhibition of ADA was measured at 30 °C after a 5-min preincubation with the inhibitor. K_i values are the means of two runs.

Replacement of C-5′ with oxygen to make oxo-EHNAs (**14a**,**b**) resulted in decreased activity. It is interesting to note that this activity is consistently ∼100-fold less than that of their carbon counterparts (**2** and **11g**).

The newly described conformationally restricted analogues of EHNA give an opportunity to probe further the binding requirements for ADA. This is currently being pursued by a molecular modeling/synthesis approach.

Experimental Section

Melting points were determined on a Buchi 535 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer model 141 automatic digital-readout polarimeter. ^{1}H NMR spectra were recorded on either a Varian EM 390 or Bruker AM-300 spectrometer using $CDCl_3$ as solvent and Me_4Si (TMS) as an internal standard. UV absorption spectra were recorded with a Beckman DU-64 spectrophotometer. All moisture-sensitive reactions were performed using flame-dried glassware and all evaporations were performed under reduced pressure. Plates (1.0 and 2.0 mm) used were coated with silica gel PF254 containing $CaSO_4$. Thin-layer chromatography was performed on precoated silica gel plates (60-F254, 0.2 mm) manufactured by EM Science, Inc., and short-wave ultraviolet light (254 nm) was used to detect the UV-absorbing compounds. Silica gel (Merck grade 60, 230−400 mesh, 60 Å) suitable for column chromatography was purchased from Aldrich. All solvent proportions are by volume unless stated otherwise. Sodium sulfate was used for all dryings. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ.

(2*S*,3*S*)-2-Benzyloxynon-5-yn-3-ol (4). To a stirred solution of 1-pentyne (1.02 g, 15 mmol) in dry THF (40 mL) at −78 °C under nitrogen was added *n*-butyllithium (4.5 mL, 2.5 M solution in hexanes, 12 mmol). After the mixture was stirred for 2 h, epoxide **3** (1.07 g, 6 mmol) in dry THF (20 mL) was added dropwise. The reaction mixture was stirred at −78 °C for an additional 3 h and at room temperature overnight and evaporated. Water (20 mL) was added to the reaction mixture, which was subsequently washed with ether (3 × 50 mL). The combined organic layers were washed with brine and dried. The viscous material obtained after solvent removal was chromatographed on a silica gel column with hexanes−ethyl acetate (10:1) to give **4** (1.3 g, 88%): ^{1}H NMR δ 0.80 (t, J = 6.0 Hz, 3H), 1.20 (d, J = 6.0 Hz, 3H), 1.25−1.50 (m, 2H), 2.00−2.30 (m, 2H), 2.33−2.60 (m, 3H, 1H D_2O exchangeable), 3.40−3.90 (m, 2H), 4.60 (AB q center, Δ_{AB} = 18.0 Hz, J_{AB} = 9 Hz, 2H), 7.25−7.40 (m, 5H).

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)-2-benzyloxynon-5-yne (5). To a stirred solution of **4** (1.23 g, 5 mmol), 6-chloropurine (1.55 g, 10 mmol) and triphenylphosphine (TPP; 2.62 g, 10 mmol) in dry THF (100 mL) was added DIAD (2.02 g, 10 mmol) in dry THF (20 mL). The mixture was refluxed for 24 h and the solvent was removed. The residue was chromatographed on a silica gel column (ethyl acetate−hexanes 1:1). The chloropurine derivative was contained in the ethyl acetate fraction along with dihydro DIAD impurities, as shown by its ^{1}H NMR spectrum. This mixture was dissolved in liquid ammonia (20 mL) and heated at 90 °C in a steel bomb for 24 h. After cooling, excess ammonia was allowed to evaporate. The residue was

taken up in CH_2Cl_2 (50 mL) and washed with water (2 × 5 mL). The organic layer was dried and evaporated to give **5** as a white solid: $[\alpha]_D^{25}$ +49° (*c* 0.2, $CHCl_3$); ^{1}H NMR δ 0.80 (t, J = 6.0 Hz, 3H), 1.0−1.50 (m, 5H), 1.80−2.05 (m, 2H), 2.85−3.10 (m, 2H), 4.10 (dt, 1H), 4.40−4.90 (m, 1H), 4.50 (AB q center, Δ_{AB} = 22 Hz, J_{AB} = 11.0 Hz, 2H), 6.60 (bs, D_2O exchangeable, 2H), 7.10−7.40 (m, 5H), 8.0 (s, 1H), 8.33 (s, 1H). Anal. ($C_{21}H_{25}N_5O$) C, H, N.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)non-5*E*-en-2-ol (6). To liquid ammonia (15 mL) at −78 °C was added Na metal until the solution turned blue. To this was added the benzyl derivative **5** (100 mg, 0.27 mmol) in toluene (5 mL) and the mixture was stirred vigorously at the same temperature for 2 h. NH_4Cl (100 mg) and MeOH (1 mL) were and the reaction mixture was allowed to warm to room temperature. The solvents were evaporated to dryness under reduced pressure and the residue was extracted with CH_2Cl_2 (3 × 20 mL). Which was subsequently washed with water (2 × 5 mL), dried and evaporated. The product obtained was purified by preparative TLC (ethyl acetate) to give **6** (60 mg, 80%): $[\alpha]_D^{25}$ +130°; ^{1}H NMR δ 0.74 (t, J = 7.2 Hz, 3H), 1.14−1.25 (m, 2H), 1.78−1.85 (m, 2H), 2.59−2.80 (m, 2H), 4.22 (ddd, J = 10.5, 3.9, 2.1 Hz, 1H), 4.33 (dq, J = 6.3, 2.0, 1H), 5.10−5.30 (m, 2H), 5.60 (bs, 1H D_2O exchangeable), 5.88 (bs, 2H, D_2O exchangeable), 7.70 (s, 1H), 8.30 (s, 1H). Anal. ($C_{14}H_{21}N_5O$) C, H, N.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)non-5*Z*-en-2-ol (7). To compound **5** (75 mg, 0.2 mmol) in toluene (5 mL) was added Lindlar's catalyst (20 mg) and the mixture was stirred under hydrogen atmosphere overnight. The catalyst was filtered off and the toluene solution was evaporated to dryness. The residue obtained was charged on a silica gel column and eluted with ethyl acetate to give the olefinic material (70 mg, 92%) as a gum: ^{1}H NMR δ 0.80 (t, J = 6.0 Hz, 3H), 1.0−1.40 (m, 5H), 1.90−2.50 (m, 2H), 2.70−3.0 (m, 2H), 3.80−4.10 (m, 1H), 4.20−4.60 (m, 3H), 4.90−5.60 (m, 2H), 6.0 (bs, 2H, D_2O exchangeable) 7.10−7.40 (m, 5H), 7.90 (s, 1H), 8.33 (s, 1H). It was used as such in the next reaction.

The above material (70 mg, 0.175 mmol) was debenzylated to give **7** (40 mg, 75%) following the procedure described for the preparation of **6**: $[\alpha]_D^{25}$ +16.5° (*c* 0.26, $CHCl_3$); ^{1}H NMR δ 0.70 (t, J = 7.4 Hz, 3H), 0.90−1.20 (m, 2H), 1.36 (d, J = 6.5 Hz, 3H), 1.65 (m, 2H), 2.55−2.65 (m, 1H), 2.85−3.00 (m, 1H), 4.17 (dq, J = 12.0, 3.5, 3.0 Hz, 1H), 4.35 (doublet of AB quartet, J = 12.0, 6.0, 1.5 Hz, 1H), 5.15−5.25 (m, 1H), 5.35−5.45 (m, 1H), 5.82 (bs, 2H, D_2O exchangeable), 7.70 (s, 1H), 8.32 (s, 1H). Anal. ($C_{14}H_{21}N_5O$) C, H, N.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)nonan-5-yn-2-ol (8). To liquid ammonia (15 mL) at −78 °C was added Ca metal (11 mg) and the solution turned blue. To this, was added the benzyl derivative **5** (45 mg, 0.125 mmol) in toluene (5 mL) and the mixture was stirred vigorously at the same temperature for 2 h. After the addition of NH_4Cl and MeOH, the reaction mixture was allowed to warm to room temperature. The solvents were evaporated to and the residue was extracted with CH_2Cl_2 (3 × 20 mL) which was washed with water (2 × 5 mL), dried and evaporated. The product **8** (10 mg, 30%) obtained was purified by preparative TLC by eluting with MeOH−CH_2Cl_2 (1:10): ^{1}H NMR δ 0.86 (t, J = 7.0 Hz, 3H), 1.34 (d, J = 6.6 Hz, 3H), 1.41 (sextet, J = 7.3, 7.3, 7.2 Hz, 2H), 2.0 (tt, J = 7.0, 2.4, 2.2 Hz, 2H), 2.70 (dd, J = 5.6, 2.4 Hz, 1H), 2.75 (dd, J = 5.5, 2.4 Hz, 1H), 4.30 (dq, J = 2.4 Hz, 1H), 4.40 (dq, J = 13.8, 7.3, 1.7, 1H), 5.85 (bs, 1H, D_2O exchangeable), 6.05 (bs, 2H, D_2O exchangeable), 7.90 (s, 1H), 8.30 (s, 1H); HRMS calcd for $C_{14}H_{19}N_5O$ 274.1656, found 274.1667.

Compound **6** (7 mg, 20%) and the starting material **5** (15 mg, 33%) were also isolated.

Opening of Epoxide 3 with Aryllithium Salts (Procedure A). To a cold (−78 °C) stirred solution of aromatic halide (2 equiv) was slowly added *n*-butyllithium (2 equiv). This was stirred at the same temperature for 0.5 h at which time a solution of epoxide **3** (1 equiv) in dry THF was added followed by the slow addition of $BF_3{\cdot}Et_2O$ (3 equiv). The stirring was continued for an additional 3 h. The reaction mixture was allowed to warm to room temperature and was further stirred overnight. Quenching with saturated aqueous ammonium chloride (4 mL) was followed by concentrating and dilution with Et_2O (200 mL). The ether layer was washed sequentially with brine (2 × 20 mL) and distilled water (20 mL). The organic phase was dried and evaporated to yield the crude product. This was placed on a silica gel column and elution with hexanes−ethyl acetate (10:1) yielded the desired product.

Opening of Epoxide 3 with Aralkyl Grignard Reagents (Procedure B). To a mechanically stirred mixture of Mg metal (2 equiv) and one crystal of iodine in a minimal amount of anhydrous Et_2O was added dropwise a solution of the aralkyl halide (2 equiv) in anhydrous Et_2O. When the reaction became vigorous, it was cooled in an ice bath while the remaining halide was added slowly. When all of the Mg had reacted, the solution was cooled (−78 °C) and mechanically stirred for 15 min. A solution of LiCl (0.2 equiv) and $CuCl_2$ (0.1 equiv) in dry THF (2 mL) was added followed immediately by addition of the epoxide **3** (1 equiv) in anhydrous Et_2O. The reaction mixture was stirred at −78 °C for 5 h then allowed to slowly warm to room temperature and stirred overnight. Subsequent workup was identical to the procedure described earlier.

(2*S*,3*S*)-2-(Benzyloxy)-4-(2-prop-2-enylphenyl)butan-3-ol (9a). This compound was made from 3-(2-bromophenyl)-prop-2-ene using procedure A in 67% yield as a gum: $[\alpha]_D^{25}$ +12.8° (*c* 1.485, CH_2Cl_2); ^{1}H NMR δ 1.20 (d, J = 6 Hz, 3H), 1.50−1.90 (m, 3H, 1H D_2O exchangeable), 2.70−2.90 (m, 2H), 3.25−3.80 (m, 2H) 4.55 (AB quartet center, Δ_{AB} = 21 Hz, J_{AB} = 12 Hz, 2H), 5.50−7.30 (m, 11H). Anal. ($C_{20}H_{24}O_2$) C, H.

(2*S*,3*S*)-2-(Benzyloxy)-4-(3-ethenylphenyl)butan-3-ol (9b). This compound was prepared from 3-bromostyrene using procedure A in 81% yield as a gum: $[\alpha]_D^{25}$ +1.3° (*c* 0.875, CH_2Cl_2); ^{1}H NMR δ 1.30 (d, J = 6 Hz, 3H), 2.60−3.0 (m, 2H, 1H D_2O exchangeable), 3.30−3.90 (m, 2H), 4.55 (AB q center, Δ_{AB} = 24 Hz, J_{AB} = 12 Hz, 2H), 5.25 (d, J = 10 Hz, 1H), 5.75 (d, J = 18 Hz, 1H), 6.77 (dd, J = 18, 10 Hz, 1H), 7.0−7.60 (m, 9H). Anal. ($C_{19}H_{22}O_2$) C, H.

(2*S*,3*S*)-2-(Benzyloxy)-4-(4-methylphenyl)butan-3-ol (9c). This compound was prepared from 4-bromotoluene in 82% yield using procedure B: $[\alpha]_D^{25}$ +34.4° (*c* 1.155, $CHCl_3$); ^{1}H NMR δ 1.20 (d, J = 6 Hz, 3H), 2.25 (s, 3H), 2.56−2.85 (m, 3H), 3.13−3.78 (m, 2H), 4.16−4.73 (m, 2H), 7.03 (s, 4H), 7.28 (s, 5H). Anal. ($C_{19}H_{22}O_2$) C, H.

(2*S*,3*S*)-2-(Benzyloxy)-5-(3-methylphenyl)pentan-3-ol (9d). To a stirred solution of *m*-xylene (3.6 g, 33.7 mmol) and KO*t*-Bu (3.78 g, 33.7 mmol) in dry THF under nitrogen was added *n*-butyllithium (13.5 mL, 2.5 M in hexanes). The mixture then stirred at −78 °C for 5 min and to it was added epoxide **3** (2.0 g, 11.2 mmol) and Li_2CuCl_4 (0.1 mmol). The stirring was continued for an additional 4 h. The work up was carried out as in procedure A to obtain **9d** in 60% yield: $[\alpha]_D^{25}$ +16.9° (*c* 1.285, $CHCl_3$); ^{1}H NMR δ 1.2 (d, J = 6 Hz, 3H), 1.55−1.76 (m, 2H), 2.30 (s, 3H), 2.43−3.03 (m, 3H), 3.3−3.55 (m, 2H), 4.27−4.77 (J_{AB} = 12 Hz, 2H), 6.86−7.45 (m, 9H). Anal. ($C_{19}H_{24}O_2$) C, H.

(2*S*,3*S*)-2-(Benzyloxy)-6-phenylhexan-3-ol (9e). This compound was prepared from 2-phenyl-1-bromoethane using procedure B in 82% yield as a clear gummy liquid: $[\alpha]_D^{25}$ +25.4° (*c* 1.625, CH_2Cl_2); ^{1}H NMR δ 1.15 (d, J = 6 Hz, 3H), 1.30−1.90 (m, 4H), 2.45−2.7 (m, 2H, 1H D_2O exchangeable), 3.25−3.50 (m, 2H), 4.45 (AB q center, Δ_{AB} = 24 Hz, J_{AB} = 12 Hz, 2H), 7.0−7.40 (m, 10H). Anal. ($C_{19}H_{24}O_2$) C, H.

(2*S*,3*S*)-2-(Benzyloxy)-6-(2-methylphenyl)hexan-3-ol (9f). This compound was prepared from 2-(2-methylphenyl)-1-chloroethane using procedure B in 58% yield as a clear gummy liquid: $[\alpha]_D^{25}$ +20.75° (*c* 4.02, CH_2Cl_2). Anal. ($C_{20}H_{26}O_2$) C, H.

(2*S*,3*S*)-2-(Benzyloxy)-7-phenylheptan-3-ol (9g). This compound was prepared from 3-phenyl-1-bromopropane using procedure B in 84% yield as a clear gummy liquid: $[\alpha]_D^{25}$ +19.76° (*c* 1.675, CH_2Cl_2); ^{1}H NMR δ 1.10 (d, J = 6 Hz, 3H), 1.20−1.65 (m, 6H), 2.35−2.60 (m, 2H, 1H D_2O exchangeable), 3.05−3.40 (m, 4H), 4.45 (AB q center, Δ_{AB} = 24 Hz, J_{AB} = 12 Hz, 2H), 6.95−7.30 (m, 10H). Anal. ($C_{20}H_{26}O_2$) C, H.

(2*S*,3*S*)-2-(Benzyloxy)-8-phenyloctan-3-ol (9h). This compound was prepared from 4-phenyl-1-chlorobutane using procedure B in 80% yield as a clear gum: $[\alpha]_D^{25}$ +19.78° (*c* 1.39, CH_2Cl_2). Anal. ($C_{21}H_{29}O_2$) C, H.

Preparation of Compound 10 (Procedure C). To a solution of the alcohol **9** (1 equiv), TPP (2 equiv), and 6-chloropurine (2 equiv) in dry THF was slowly added DIAD (2 equiv). The resulting mixture was stirred at reflux, under nitrogen, overnight. After cooling and concentrating, the residue was applied to a short silica column and eluted with Et_2O. The combined Et_2O fractions were concentrated to about 100 mL and washed with brine (2 × 20 mL) and distilled water (20 mL). The organic layer was then dried and concentrated to give the crude product. This material was partially purified by silica gel chromatography [hexanes−EtOAc (10:1→ 1:10)] and was placed in liquid ammonia and heated in a bomb at 90 °C overnight. Cooling, evaporation of the ammonia, dilution with CH_2Cl_2 (50 mL), washing with distilled water (3 × 5 mL), and evaporation of the organic layer gave a residue which was chromatographed on a silica column (hexanes−EtOAc) to obtain the desired product.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)-2-(benzyloxy)-4-(2-prop-2-enylphenyl)butane (10a). This compound was prepared from alcohol **9a** in 9% overall yield: $[\alpha]_D^{25}$ +120.9° (*c* 0.67, CH_2Cl_2); ^{1}H NMR δ 1.20 (d, J = 6 Hz, 3H), 1.50−1.80 (m, 3H), 2.30−2.60 (m, 3H), 2.80−3.50 (m, 1H), 4.55 (AB q center, Δ_{AB} = 18 Hz, J_{AB} = 12 Hz, 2H), 5.35−6.40 (m, 2H, 2H D_2O exchangeable), 6.80−7.40 (m, 9H), 8.0 (s, 1H), 8.30 (s, 1H). Anal. ($C_{25}H_{27}N_5O$) C, H, N.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)-2-(benzyloxy)-4-(3-ethenylphenyl)butane (10b). This product was obtained from **9b** in 11.4% yield as a white solid: mp 116−118 °C; $[\alpha]_D^{25}$ +142.8° (*c* 0.83, CH_2Cl_2); ^{1}H NMR δ 1.35 (d, J = 6 Hz, 3H), 3.30−3.70 (m, 2H), 4.0−4.20 (m, 1H), 4.55 (AB q center, Δ_{AB} = 24 Hz, J_{AB} = 12 Hz, 2H), 4.60−4.90 (m, 1H), 5.10 (d, J = 10 Hz, 1H), 5.50 (d, J = 18 Hz, 1H), 6.50 (dd, J = 18 Hz, 10 Hz, 1H), 6.70−7.20 (m, 4H, 2H D_2O exchangeable), 7.30−7.50 (m, 5H), 7.26 (s, 5H), 7.80 (s, 1H), 8.30 (s, 1H). Anal. ($C_{24}H_{25}N_5O$) C, H, N.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)-2-(benzyloxy)-4-(4-methylphenyl)butane (10c). This compound was prepared in 14.5% yield from **9C** following procedure C: mp 144−146 °C; $[\alpha]_D^{25}$ +106.4° (*c* 1.91, CH_2Cl_2); ^{1}H NMR δ 1.20 (d, J = 6 Hz, 3H), 2.16 (s, 3H), 3.20−3.43 (m, 2H), 3.88−4.76 (m, 4H), 5.81 (bs, 2H), 6.83 (s, 4H), 7.26 (s, 5H), 7.68 (s, 1H), 8.23 (s, 1H). Anal. ($C_{23}H_{25}N_5O$) C, H, N.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)-2-(benzyloxy)-5-(3-methylphenyl)pentane (10d). This compound was prepared from alcohol **9d** in 30% overall yield: mp 155−157 °C; $[\alpha]_D^{25}$ +52.5° (*c* 0.415, $CHCl_3$); ^{1}H NMR δ 1.20 (d, J = 6 Hz, 3H), 2.25 (s, 3H), 2.30−2.48 (m, 4H), 3.70−4.03 (m, 1H), 4.18−4.68 (m, 3H), 5.93 (bs, 2H), 6.66−7.40 (m, 9H), 7.91 (s, 1H), 8.33 (s, 1H). Anal. ($C_{24}H_{27}N_5O$) C, H, N.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)-2-(benzyloxy)-6-phenylhexane (10e). This compound was prepared from **9e** in 13% overall yield as a white solid: mp 139−140 °C; $[\alpha]_D^{25}$ +80.7° (*c* 1.97, CH_2Cl_2); ^{1}H NMR δ 1.20 (d, J = 6 Hz, 3H), 1.30−1.70 (m, 2H), 1.95−2.30 (m, 2H), 2.60 (t, J = 8 Hz, 2H), 3.70−3.95 (m, 1H), 4.40 (AB q center, Δ_{AB} = 24 Hz, J_{AB} = 12 Hz, 2H), 4.45−4.70 (m, 1H) 6.35 (m, 2H, 2H D_2O exchangeable), 6.95−7.35 (m, 10H), 7.90 (s, 1H), 8.30 (s, 1H). Anal. ($C_{24}H_{27}N_5O$) C, H, N.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)-2-(benzyloxy)-6-(2-methylphenyl)hexane (10f). This compound was prepared from **9f** in 18% overall yield as a white solid: mp 141−142 °C; $[\alpha]_D^{25}$ +76.5° (*c* 0.23, CH_2Cl_2). Anal. ($C_{25}H_{29}N_5O$) C, H, N.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)-2-(benzyloxy)-7-phenylheptane (10g). This compound was prepared from **9g** in 8.3% overall yield as a white solid: mp 102−103 °C; $[\alpha]_D^{25}$ +65.41° (*c* 1.405, CH_2Cl_2); ^{1}H NMR δ 0.90−1.30 (m, 2H), 1.10 (d, J = 6 Hz, 3H), 1.35−1.70 (m, 2H), 1.90−2.25 (m, 2H), 2.35−2.60 (m, 2H), 3.70−3.95 (m, 1H), 4.55 (AB q center, Δ_{AB} = 24 Hz, J_{AB} = 12 Hz, 2H), 4.40−4.70 (m, 1H) 6.55 (bs, 2H, 2H D_2O exchangeable), 6.90−7.35 (m, 10H), 7.90 (s, 1H), 8.30 (s, 1H). Anal. ($C_{24}H_{27}N_5O$) C, H, N.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)-2-(benzyloxy)-8-phenyloctane (10h). This compound was prepared from **9h** in 28% overall yield as a white solid: $[\alpha]_D^{25}$ +19.78° (*c* 0.665, CH_2Cl_2). Anal. ($C_{24}H_{27}N_5O$) C, H, N.

Debenzylation of Compounds 10 (Procedure D). A mixture of the adenine derivative **10** (1 equiv), $Pd(OH)_2$/C (equal in weight to the starting material) in ethanol (20 mL) and cyclohexene (10 mL) was stirred at reflux overnight then allowed to cool to room temperature. The mixture was then filtered and the solution was concentrated under reduced pressure. The residue was placed on a silica gel column and eluted with EtOAc (50 mL) and then with EtOAc:MeOH (10:1) to yield the desired product.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)-4-(2-propylphenyl)butan-2-ol (11a). This compound was prepared from **10a** in 91% yield: mp 181−182 °C; $[\alpha]_D^{25}$ +377.0° (*c* 0.29, EtOH); ^{1}H NMR δ 0.80 (t, J = 9 Hz, 3H), 1.15−1.60 (m, 5H), 2.30 (t, J = 9 Hz, 2H), 3.10−3.40 (m, 2H), 3.75 (bs, 2H D_2O exchangeable), 7.25 (s, 1H), 8.10 (s, 1H). Anal. ($C_{19}H_{23}N_5O$) C, H.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)-4-(3-ethylphenyl)butan-2-ol (11b). This compound was prepared from **10b** in 90% yield: mp 157−158 °C; $[\alpha]_D^{25}$ +143.0° (*c* 1.115, EtOH); ^{1}H NMR δ 1.05 (t, J = 8 Hz, 3H), 1.35 (d, J = 6 Hz, 3H), 2.45 (q, J = 8 Hz, 2H), 3.20 (d, J = 6 Hz, 3H), 4.20−4.60 (m, 2H), 4.95 (bs, 2H, 1H D_2O exchangeable), 6.50−7.20 (m, 4H, 2H D_2O exchangeable), 7.50 (s, 1H), 8.20 (s, 1H). Anal. ($C_{17}H_{21}N_5O$) C, H, N.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)-4-(4-methylphenyl)butan-2-ol (11c). This compound was prepared in 65% yield from **10c**: mp 156−158 °C; $[\alpha]_D^{25}$ +247.7° (*c* 0.17, $CHCl_3$); ^{1}H NMR δ 1.33 (d, J = 6 Hz, 3H), 2.16 (s, 3H), 3.16 (d, J = 7.5 Hz, 2H), 4.05−4.50 (m, 3H), 5.80 (bs, 2H), 6.40−6.90 (dd, J_{AB} = 9 Hz, 4H), 7.98 (s, 1H), 8.16 (s, 1H). Anal. ($C_{16}H_{19}N_5O$) C, H, N.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)-5-(3-methylphenyl)pentan-2-ol (11d). This compound was prepared from **10d** in 62% yield: mp 146−148 °C; $[\alpha]_D$+55.9° (*c* 0.315, $CHCl_3$); ^{1}H NMR δ 1.21 (d, J = 6 Hz, 3H), 2.28 (s, 3H), 2.33−2.68 (m, 4H), 4.03−4.46 (m, 2H), 4.95 (bs, 1H), 6.50 (bs, 2H), 6.75−7.09 (m, 4H), 7.76(s, 1H), 8.26 (s, 1H). Anal. ($C_{17}H_{21}N_5O$) C, H, N.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)-6-phenylhexane-2-ol (11e). This compound was prepared from **10e** in 98% yield: mp 153−154 °C; $[\alpha]_D^{25}$ +51.0° (*c* 0.36, EtOH); ^{1}H NMR δ 1.15 (d, J = 6 Hz, 3H), 1.20−1.60 (m, 2H), 1.70−2.20 (m, 2H), 2.40−2.70 (m, 2H), 3.95−4.50 (m, 2H D_2O exchangeable), 6.60−7.25 (m, 7H, 2H D_2O exchangeable), 7.80 (s, 1H), 8.20 (s, 1H). Anal. ($C_{17}H_{21}N_5O$) C, H, N.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)-6-(2-methylphenyl)hexan-2-ol (11f). This compound was prepared from **10f** in 71% yield as a white solid: mp 153−155 °C; $[\alpha]_D^{25}$ +33.6° (*c* 1.155, EtOH); ^{1}H NMR δ 1.15 (d, J = 6 Hz, 3H), 1.20−1.55 (m, 2H), 1.75−2.25 (m, 2H), 2.15 (s, 3H), 2.40−2.70 (m, 2H), 3.95−4.50 (m, 2H, D_2O exchangeable), 6.65−7.25 (m, 6H, 2H D_2O exchangeable), 7.80 (s, 1H), 8.20 (s, 1H). Anal. ($C_{18}H_{23}N_5O$) C, H, N.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)-7-heptan-2-ol (11 g). This compound was prepared from **10g** in 92% yield: $[\alpha]_D^{25}$ +37.4° (*c* 0.39, EtOH); ^{1}H NMR δ 0.90−1.70 (m, 7H), 1.70−2.10 (m, 2H), 2.10−2.50 (m, 2H), 3.94−4.40 (m, 2H), 4.80 (bs, 1H D_2O exchangeable), 6.60−7.20 (m, 7H, 2H D_2O exchangeable), 7.75 (s, 1H), 8.10 (s, 1H). Anal. ($C_{18}H_{23}N_5O$) C, H, N.

(2*S*,3*R*)-3-(6-Aminopurin-9-yl)-8-phenyloctan-2-ol (11h). This compound was prepared from **10h** in 89% yield: $[\alpha]_D^{25}$ +49.6° (*c* 0.365, EtOH); ^{1}H NMR δ 0.85−1.65 (m, 9H), 1.65−2.05 (m, 2H), 2.05−2.5 (m, 2H), 3.95−4.45 (m, 2H), 4.80 (bs, 1H D_2O exchangeable), 6.65−7.25 (m, 7H, 2H D_2O exchangeable), 7.75 (s, 1H), 8.10 (s, 1H). Anal. ($C_{17}H_{21}N_5O$) C, H, N.

(2*S*,3*S*)-3-*O*-Benzyl-1-*O*-*n*-butylbutane-1,2,3-triol (12a). *n*-BuOH (3.1 mL, 33.71 mmol), NaOH (0.45 g, 11.24 mmol) and water (0.45 mL) were mixed and refluxed for 30 min. To this solution was added epoxide **3** (1 g, 5.62 mmol), and the resulting solution was refluxed for 1 h. *n*-BuOH was removed, and the residue was diluted with water (50 mL) and extracted

with Et_2O (3 × 50 mL). Drying and evaporation of Et_2O gave **12a** (1.3 g, 5.16 mmol, 92%). An analytical sample was obtained by column chromatography using hexanes−EtOAc (9:1) as eluent: $[\alpha]_D^{25}$ +33.3° (*c* 0.75, CH_2Cl_2); ^{1}H NMR δ 0.90 (d, 3H, J = 6 Hz), 1.10−1.70 (m, 7H), 2.70 (brs, 1H, D_2O exchangeable), 3.30−3.80 (m, 6H), 4.50−4.80 (dd, J = 6, 18 Hz, 2H), 7.30 (s, 5H). Anal. ($C_{15}H_{24}O_3$) C, H.

(2*S*,3*S*)-3-*O*-Benzyl-1-*O*-(2-phenethyl)butane-1,2,3-triol (12b). Phenethyl alcohol (4.04 mL, 33.72 mmol), NaOH (0.45 g, 11.24 mmol), *t*-BuOH (4.0 mL) and water (0.45 mL) were mixed and refluxed for 30 min. To this mixture was added epoxide **3** (1 g, 5.62 mmol), and the reaction mixture was refluxed overnight. After removal of the solvent, the residue was diluted with water (50 mL) and extracted with Et_2O (3 × 50 mL). Drying and removal of Et_2O gave **12b** (1.44 g, 4.8 mmol, 85%). An analytical sample was obtained by column chromatography using hexanes−EtOAc (9:1) as eluent: $[\alpha]^{25}_D$ +25.87° (*c* 1.875, CH_2Cl_2); ^{1}H NMR δ 1.20 (d, 3H, J = 6 Hz), 2.50 (brs, 1H, D_2O exchangeable), 2.80 (t, 2H), 3.40−3.80 (m, 6H), 4.30−4.80 (dd, J = 9, 21 Hz), 7.10−7.50 (m, 10H). Anal. ($C_{19}H_{24}O_3$) C, H.

(2*R*,3*S*)-2-(6-Aminopurin-9-yl)-3-*O*-benzyl-1-*O*-*n*-butylbutane-1,3-diol (13a). To a mixture of the 6-chloropurine (1.23 g, 7.94 mmol), TPP (2.08 g, 7.94 mmol) and compound **12a** in dry THF (20 mL) was slowly added DIAD (1.41 g, 7.94 mmol). The procedure followed was identical to that described for the preparation of compound **10** using the Mitsunobu reaction followed by ammonolysis. Recrystallization from Et_2O and hexane gave an analytical sample (262 mg, 0.71 mmol, 18%): $[\alpha]_D^{25}$ +35.7° (*c* 0.70, CH_2Cl_2); mp 126.5−127.5 °C; ^{1}H NMR δ 0.85 (d, 3H, J = 6 Hz), 1.10 (d, 3H, J = 6 Hz), 1.10−1.65 (m, 4H), 3.20−3.48 (m, 8H), 5.85 (s, 2H, D_2O exchangeable), 7.30 (s, 5H), 8.0 (s, 1H), 8.35 (s, 1H); UV λ_{max} 259.0 @ pH 1 (ϵ 6293.0), λ_{max} 260.0 @ pH 13 (ϵ 6340.9). Anal. ($C_{20}H_{27}N_5O_2$) C, H, N.

(2*R*,3*S*)-2-(6-Aminopurin-9-yl)-3-*O*-benzyl-1-*O*-(2-phenethyl)butane-1,3-diol (13b). The procedure was identical to that described for the preparation of **10**. Recrystallization from Et_2O and hexane gave an analytical sample (385 mg, 0.92 mmol, 25%): $[\alpha]_D^{25}$ +23.87° (*c* 0.75, CH_2Cl_2); mp 90−94.5 °C; ^{1}H NMR δ 1.10 (d, 3H, J = 6 Hz), 2.60−2.80 (t, 2H), 3.50−4.90 (m, 8H), 5.70 (s, 2H, D_2O exchangeable), 7.0−7.50 (m, 10H), 7.75 (s, 1H), 8.30 (s, 1H); UV λ_{max} 259.2 @ pH 1 (ϵ 13160.8), λ_{max} 260.0 @ pH 13 (ϵ 12447.6). Anal. ($C_{24}H_{27}N_5O_2$) C, H, N.

(2*R*,3*S*)-2-(6-Aminopurin-9-yl)-1-*O*-*n*-butylbutane-1,3-diol (14a). Compound **13a** (250 mg, 0.68 mmol), absolute EtOH (25 mL), cyclohexene (25 mL), and $Pd(OH)_2$/C (500 mg) were mixed and refluxed for 48 h. The catalyst was filtered and the solvent was removed. The analytical sample (121 mg, 0.435 mmol, 64%) was obtained by column chromatography using hexanes−EtOAc (1:4): $[\alpha]_D^{25}$ +65.88° (*c* 1.70, CH_2Cl_2); mp 115.8−118.5 °C; ^{1}H NMR δ 0.85 (t, 3H), 1.22−1.29 (m, 2H), 1.35 (d, 3H, J = 6.5 Hz), 1.43−1.50 (m, 2H), 3.29−3.47 (m, 2H), 3.88−4.0 (m, 2H), 4.38−4.43 (m, 1H), 4.45−4.49 (m, 1H), 5.60−5.90 (br s, 2H, D_2O exchangeable), 6.44 (s, 2H, D_2O exchangeable), 7.95 (s, 1H), 8.31 (s, 1H); ^{13}C NMR δ 13.72, 19.17, 20.72, 62.51, 67.98, 68.52, 71.42, 119.72, 141.63, 149.41, 152.14, 155.78. Anal. ($C_{13}H_{21}N_5O_2$) C, H, N.

(2*R*,3*S*)-2-(6-Aminopurin-9-yl)-1-*O*-(2-phenethyl)butane-1,3-diol (14b). Compound **13b** (250 mg, 0.6 mmol), absolute EtOH (25 mL), cyclohexene (25 mL), and $Pd(OH)_2$/C (500 mg) were mixed and refluxed for 48 h. The catalyst was filtered and the solvent was removed. The analytical sample (123.6 mg, 0.38 mmol, 63%) was obtained by column chromatography using hexanes−EtOAc (1:4): $[\alpha]_D^{25}$ +55° (*c* 0.7, CH_2Cl_2); mp 84.5−85.7 °C; ^{1}H NMR δ 1.31 (d, 3H, J = 6.5 Hz), 2.77−2.82 (t, 2H), 3.52−3.71 (m, 2H), 3.86−4.01 (m, 2H), 4.31−4.35 (m, 1H), 4.39−4.42 (m, 1H), 5.45−5.55 (br s, 2H, D_2O exchangeable), 6.28 (s, 2H, D_2O exchangeable), 7.08−7.28 (m, 5H), 7.77 (s, 1H). Anal. ($C_{17}H_{21}N_5O_2$) C, H.

Biological Evaluation. All the derivatives of EHNA reported herein were evaluated as ADA inhibitors using the protocol described earlier.[25]

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JM0002533