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Synthesis of Conformationally Locked L-Deoxythreosyl Phosphonate Nucleosides Built on a Bicyclo[3.1.0]hexane Template

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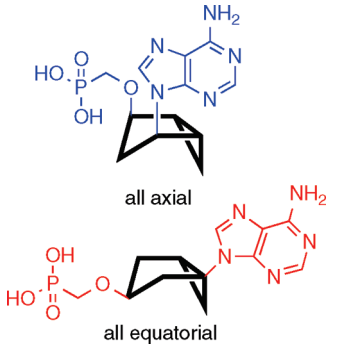

Two conformationally locked versions of L-deoxythreosyl phosphonate nucleosides (**2** and **3**) were synthesized to investigate the preference of HIV reverse transcriptase for a conformation displaying either a fully diaxial or fully diequatorial disposition of substituents. Synthesis of the enantiomeric 4-(6-amino-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-2-ol carbocyclic nucleoside precursors (diaxially disposed) proceeded straightforwardly from commercially available (1*R*,4*S*)-4-hydroxy-2-cyclopent-2-enyl-1-yl acetate employing a hydroxyl-directed Simmons−Smith cyclopropanation that culminated with a Mitsunobu coupling of the purine base. For the more complicated 1-(6-amino-9*H*-purin-9-yl)bicyclo-[3.1.0]hexan-3-ol carbocyclic nucleoside precursors (diequatorially disposed), the obligatory linear approach required the syntheses of key 1-aminobicyclo[3.1.0.]hexan-3-yl benzoate precursors that were assembled via the amide variant of the Kulinkovich reaction involving the intramolecular cyclopropanation of a substituted δ-vinylamide. Completion of the purine ring was achieved by conventional approaches but with much improved yields through the use of a microwave reactor. The syntheses of the phosphonates and the corresponding diphosphates were achieved by conventional means. None of the diphosphates, which were supposed to act as nucleoside triphosphate mimics, could compete with dATP even when present in a 10-fold excess.

Introduction

Five years ago, Herdewijn and co-workers reported the synthesis of some L-deoxythreosyl phosphonate nucleosides, among which those carrying the adenine (**1a**) and thymine (**1b**) bases proved effective against HIV-1 and HIV-2 with EC_{50} values of 2.53 and 6.59 μM, respectively.[1] This was a welcome finding since with the exception of acyclic phosphonate nucleosides, where the ribose is replaced by an alkolyalkyl moiety[2] and a couple of phosphonomethoxydihydrofuranyl nucleosides bearing the nucleobases adenine and thymine,[3] all phosphonate nucleosides built on furanose, pyranose, and

(1) Wu, T.; Froeyen, M.; Kempeneers, V.; Pannecouque, C.; Wang, J.; Busson, R.; De Clercq, E.; Herdewijn, P. *J. Am. Chem. Soc.* **2005**, *127*, 5056–5065.

(2) Holý, A.; Votruba, I.; Merta, A.; Cerny, J.; Vesely, J.; Vlach, J.; Sedivá, K.; Rosenberg, I.; Otmar, M.; Hrebabecky, H.; Trávnicek, M.; Vonkac, V.; Snoeck, R.; De Clercq, E. *Antiviral Res.* **1990**, *13*, 295–311.

(3) Kim, C. U.; Luh, B. Y.; Martin, J. C. *J. Org. Chem.* **1991**, *56*, 2642–2647.

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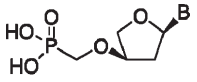
carbocyclic pseudosugars have failed to produce effective anti-HIV compounds.



1a, B = adenin-9-yl
1b, B = thymin-1-yl

Modeling of the L-deoxythreosyladenine phosphonate nucleoside (**1a**) inside the HIV reverse transcriptase (RT) domain at the 3′-end of the primer, paired with a thymidine nucleotide in the template strand, revealed that the sugar ring was puckered in the 3′-endo conformation with the 1′-(adenin-9-yl) and 3′-*O*-(phosphonomethyl) groups in a quasi-diaxial orientation.[1] A similar axial disposition of all the substituents in L-α-threofuranosyl nucleosides was also revealed by X-ray analysis and such a conformation was in addition consistent with the formation of stable duplexes in L-α-threofuranosyl-(3′→2′)-oligonucleotides (TNAs).[4]

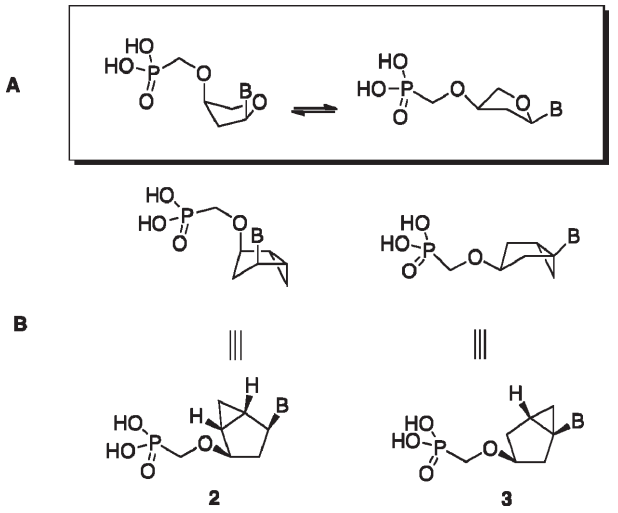


FIGURE 1. Structures of L-deoxythreosyl phosphonate nucleosides (A) and conformationally locked versions (B).

The results described above seem to indicate that the ability of the base and the *O*-phosphonomethyl groups to maintain their axial disposition is quite important for TNAs and for the anti-HIV activity of **1a** and **1b**; however, as shown in Figure 1A, the flexible nature of the 5-membered ring should allow rapid equilibration to the all-equatorial conformation which on steric grounds ought to be more stable. In order to test the preference of HIV RT for either diaxial or diequatorial disposition of substituents, we constructed conformationally rigid analogues of each conformer (**2** and **3**, Figure 1B) using the bicyclo[3.1.0]hexane scaffold that we have successfully employed to study the conformational preferences of enzymes

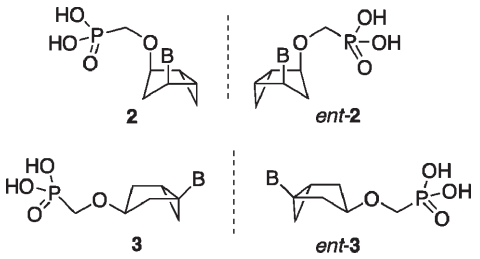


FIGURE 2. Structures of enantiomers of conformationally locked nucleosides.

for their nucleoside and nucleotide substrates.[5,6] Because the additional bulk added by the bicyclic scaffold could be sterically unfavorable at the active site of RT, we also synthesized the optical enantiomers of each of the targets to allow the base and the *O*-phosphonomethyl group to bind in a different orientation and possibly avoid unfavorable steric contacts (*ent*-**2** and *ent*-**3**, Figure 2).

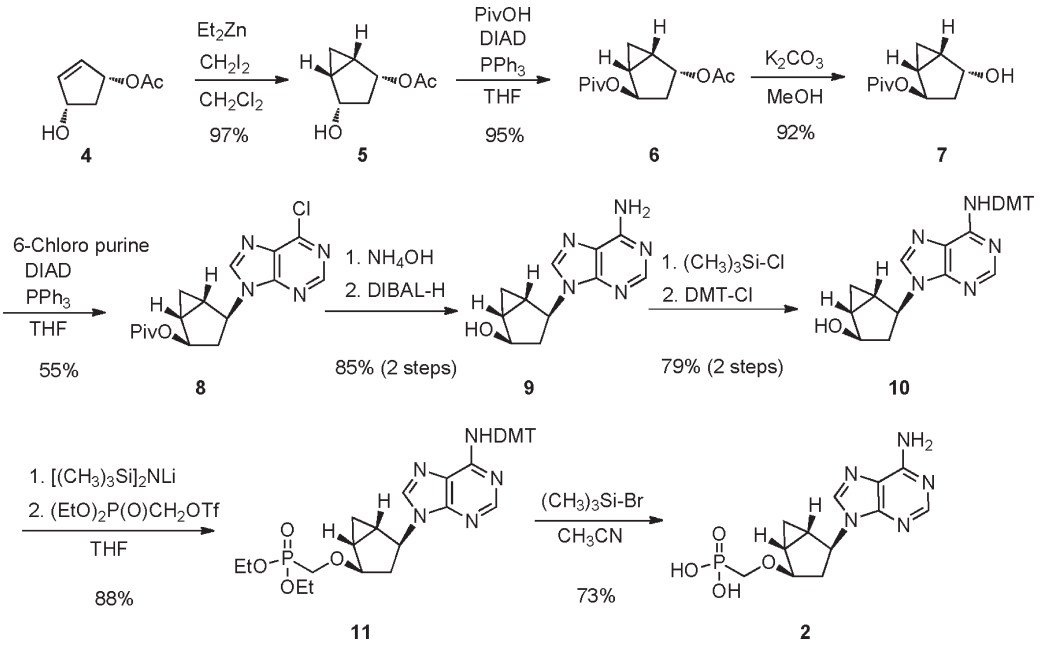
Results and Discussion

Synthesis. The synthesis of the first target phosphonate (**2**) started from commercially available (1*R*,4*S*)-4-hydroxy-2-cyclopent-2-enyl-1-yl acetate (**4**, Scheme 1), which is derived from the enzymatic hydrolysis of prochiral *cis*-1,4-diacyl-2-cyclopentendiols.[7] An ensuing hydroxyl-directed Simmons-Smith cyclopropanation provided the bicyclo[3.1.0]hexane template **5** in excellent yield. Then, reaction of the free secondary alcohol in **5** with pivalic acid under Mitsunobu conditions afforded the inverted ester in (**6**), which as reported in the literature[8] was stable under conditions that hydrolyzed the acetate moiety to give **7**. The coupling **7** with 6-chloropurine under Mitsunobu conditions gave the desired purine carbonucleoside **8** which after ammonolysis and reductive elimination of the pivaloyl protecting group led to the key conformationally locked threosyl nucleoside **9**. Employing the transient Jones silylation procedure,[9] the amino group in **9** was selectively protected with dimethoxytrityl chloride[10] to give compound **10**. Finally, the target phosphonate **2** was assembled after reaction with diethyl [(trifluoromethanesulfonyl)oxy]methanephosphonate[11] followed by deprotection with trimethylsilyl bromide.

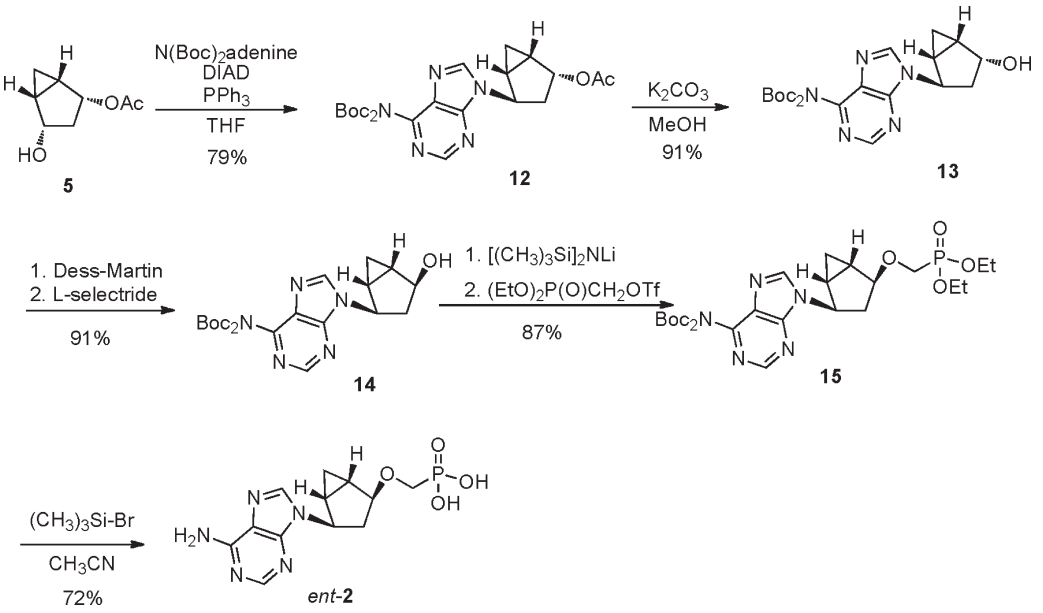
For the synthesis of the antipode (*ent*-**2**), some changes were implemented to improve yields and to reduce the number of steps (Scheme 2). Beginning with the same intermediate **5**, we performed the Mitsunobu reaction with the $N(Boc_2)$-protected adenine,[12] which resulted in a 24% increase yield of the coupled product (**12**). Selective removal of the acetate group was followed by a tandem oxidation−reduction protocol to invert the configuration of the secondary alcohol. This was more efficient than the Mitsunobu inversion used in Scheme 1. The obtained product (**14**) was

(4) Schöning, K.-U.; Scholz, P.; Guntha, S.; Wu, X.; Krishnamurthy, R.; Eschenmoser, A. *Science* **2000**, *290*, 1347–1351.
(5) Marquez, V. E. The properties of Locked Methanocarba Nucleosides in Biochemistry, Biotechnology and Medicine. In *Modified Nucleosides in Biochemistry, Biotechnology and Medicine*; Herdewijn, P., Ed.; Wiley-VCH: New York, 2008; Chapter 12, pp 307−341.
(6) Part of this work was presented as a poster at the XVIII International Round Table for Nucleosides, Nucleotides and Nucleic Acids, Kyoto, Japan, Sep 8−11, 2008: Saneyoshi, H.; Vu, B. C.; Hughes, S. H.; Boyer, P. L.; Sarafianos, S. G.; Marquez, V. E. *Nucleic Acids Symp. Ser. No. 52* **2008**, 623–624.
(7) Laumen, K; Schneider, M. *Tetrahedron Lett*. **1984**, *25*, 5875–5878.
(8) Myers, A. G.; Hammond, M; Wu, Y. *Tetrahedron Lett*. **1996**, *37*, 3083–3086.
(9) Ti, G. S.; Gaffney, B. L.; Jones, R. A. *J. Am. Chem. Soc*. **1982**, *104*, 1316–1329.
(10) Sierzchala, A. B.; Dellinger, D. J.; Betley, J. R.; Wyrzkiewicz, T. K.; Yamada, C. M.; Caruthers, M. H. *J. Am. Chem. Soc*. **2003**, *125*, 13427–13441.
(11) Xu, Y.; Flavin, M. T.; Xu, Z. *J. Org. Chem*. **1996**, *61*, 7697–7701.
(12) (a) Dey, S; Garner, P. *J. Org. Chem*. **2000**, *65*, 7697–7699. (b) Yin, X; Li, W; Schneller, S. W. *Tetrahedron Lett*. **2006**, *47*, 9187–9189.

SCHEME 1



SCHEME 2

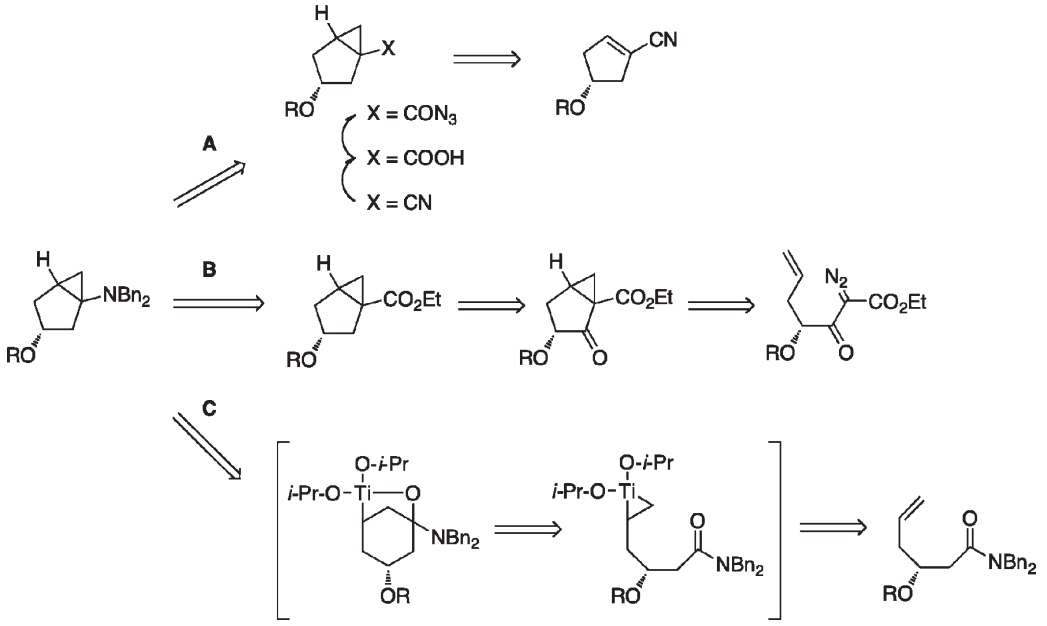


converted to the final target (*ent*-**2**) in the same manner shown in Scheme 1.

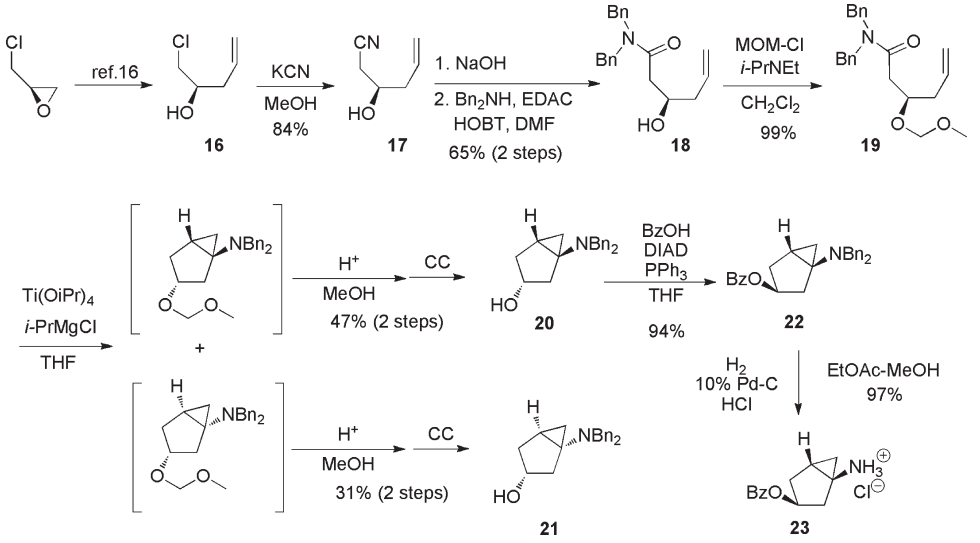
For the syntheses of compounds **3** and *ent*-**3**, we considered three possible approaches to the key bicyclic cyclopropylamine as described retrosynthetically in Scheme 3. The first route considered (A) was based on a previous synthesis of bicyclo[3.1.0]hexane nucleosides from our laboratory using a 1,3-dipolar cycloaddition of diazomethane to a hydroxyl-protected 4-hydroxycyclopent-1-enecarbonitrile to give the *cis*-fused pyrazoline intermediate, which without isolation was expected to undergo photolysis-induced nitrogen extrusion to the fused bicyclic system. Several steps to the intermediate bicyclic amine were required, including hydrolysis of the nitrile to the carboxylic acid and Curtius rearrangement of the intermediate acyl azide to the isocyanate, which could be trapped with H_2O to give the desired bicyclic cyclopropylamine. Alternatively, a carbene insertion protocol (B), also used by us in assembling the bicyclo[3.1.0]hexane system, was considered. However, the additional step of removing the carbonyl group adjacent to the fused cyclopropane made this approach less attractive. A more straightforward approach (C) based on the amide variant of the Kulinkovich reaction,[13] as developed by

(13) (a) Kunlinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Prityckaja, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244–2245. (b) Kunlinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Synthesis* **1991**, *3*, 234. (c) For a comprehensive review, see: Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789–2834.

SCHEME 3



SCHEME 4



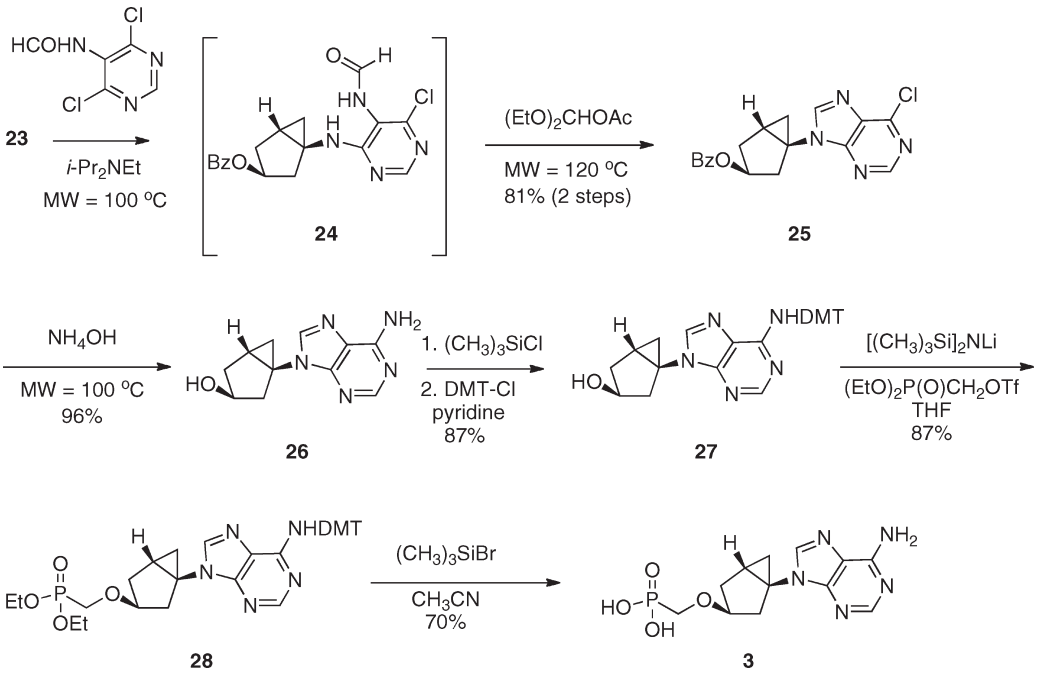
Chaplinski and de Meijere,[14] and later expanded in scope by Lee and Cha[15] to the intramolecular cyclopropanation of substitued ω-vinylamides, was able to provide the desired bicyclic cyclopropylamine in one step. This latter approach was successfully accomplished as depicted in Scheme 4.

Through a copper bromide-promoted addition,[16] (*R*)-epichlorohydrin was reacted with vinylmagnesium bromide to provide compound **16**. The ensuing nucleophilic displacement with KCN afforded the corresponding nitrile (**17**), which was hydrolyzed to the acid. Without isolation, activation of the acid with *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (EDAC) in the presence of hydroxybenzotriazole (HOBT) gave the key δ-vinyldibenzylamide (**18**) upon reaction with dibenzylamine ($HNBn_2$). Reaction of **18** with chloromethyl methyl ether produced the MOM-protected δ-vinyldibenzylamide (**19**), and the subsequent room temperature intramolecular cyclopropanation with stoichiometric amounts of $Ti(O\text{-}i\text{-}Pr)_4$ in the presence of *i*-PrMgCl in THF afforded a 1.5:1 mixture of diastereoisomers which after hydrolysis of the MOM group (**20** and **21**) were separated by columan chromatography. The required inversion of configuration of the secondary alcohol was performed by a Mitsunobu reaction with benzoic acid to give compound **22**, and generation of the required amine (**23**) was achieved by catalytic hydrogenation.

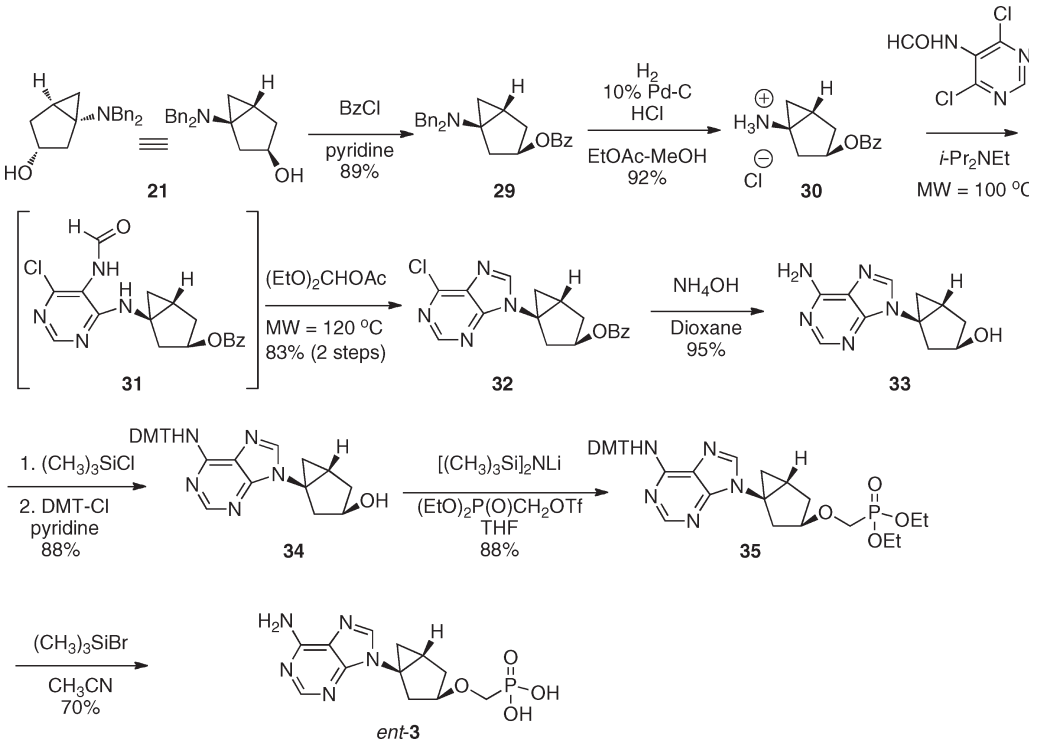
From amine **23**, the two-step construction of the purine ring was efficiently achieved (81%) by reacting first with

(14) Chaplinski, V.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 413–414.
(15) Lee, J.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 1584–1585.
(16) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2004**, *126*, 2495–2500.

SCHEME 5



SCHEME 6



N-(4,6-dichloropyrimidin-5-yl)formamide[17] in a microwave reactor for 20 min and then immediately cyclizing the transiently isolated intermediate—also in a microwave reactor for 120 min—in the presence of diethoxymethyl acetate to give compound **25** (Scheme 5). Use of the microwave for the construction of the purine ring was quite useful in terms of shortening the reaction time, avoiding prolonged heating in an oil bath, and improving the yields. Ammonolysis produced the desired adenine ring and simultaneously hydrolyzed the benzoyl ester-protecting group to give the carbocyclic nucleoside **26**. In a similar fashion, as performed for compounds **2** and *ent*-**2**, the amino group was selectively protected with dimethoxytrityl chloride and the final target phosphonate **3** was assembled

(17) Harnden, M. R.; Wyatt, P. G.; Boyd, M. R.; Sutton, D. *J. Med. Chem.* **1990**, *33*, 187–196.

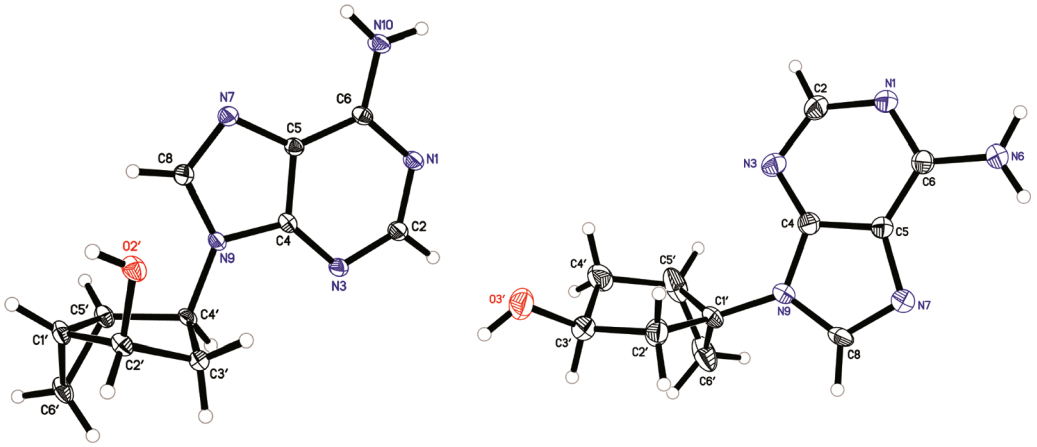


FIGURE 3. Displacement ellipsoid plot of (−)-**9** (left) and (−)-**26** (right) drawn at the 50% probability level showing, respectively, the axial and equatorial orientation of the substituents. Note that (−)-**26** crystallizes with two molecules in the asymmetric unit (one of which is disordered) plus three water molecules. In this view, the disordered molecule of (−)-**26** and the water are omitted for clarity.

TABLE 1. Optical Rotation Values for the Enantiomeric Phosphonates

phosphonate	optical rotation
diaxial phosphonate (**2**)	$[\alpha]^{20}_D = -13.5$
diaxial phosphonate (*ent*-**2**)	$[\alpha]^{20}_D = +13.5$
diequatorial phosphonate (**3**)	$[\alpha]^{20}_D = -43.4$
diequatorial phosphonate (*ent*-**3**)	$[\alpha]^{21}_D = +43.1$

after reaction with diethyl [(trifluoromethanesulfonyl)oxy]-methanephosphonate followed by deprotection with trimethylsilyl bromide.

Starting from the enantiomeric amine **21** (Scheme 4), the construction of the final target, *ent*-**3**, was achieved in a manner similar to that depicted in Scheme 6.

Syntheses of Diphosphates. The diphosphates **2**-DP, **3**-DP, and *ent*-**3**-DP were custom made from the corresponding phosphonate acids by TriLink BioTechnologies, San Diego, CA, following the procedure of Herdewijn et al.[1] The characteristics of the final products and the method of purification can be found in the Experimental Section. Unfortunately, the synthesis was unsuccessful in the case of *ent*-**2**-DP.

Structural Analysis. The optical rotation values (Table 1) as well as the crystal structures of intermediates (−)-**9** and (−)-**26** were in keeping with the structures proposed. The crystal structures of the precursors also show clearly the all-axial and all-equatorial disposition of substituents in (−)-**9** and (−)-**26**, respectively (Figure 3). Although the glycosyl bond in (−)-**9** was clearly *anti*, the crystal structure of (−)-**26** showed two conformations with the glycosyl bond in the *anti* and *syn* orientations (only the *syn* conformation is shown).

Biological Activity. All phosphonates (**2**, *ent*-**2**, **3**, and *ent*-**3**) were inactive against HIV in cell culture. Furthermore, both **2**-DP and **3**-DP incorporated into DNA only when they were the exclusive A nucleotide available; however, neither could compete with dATP even when present in a 10:1 excess. Therefore, we conclude that the bicyclo[3.1.0]hexane template mimicking a threosyl template is not recognized by cellular kinases and the resulting triphosphate mimics may have severe steric contacts with important amino acids at the active site of HIV RT (vide infra). In the case of the fully diequatorial compounds **3**-DP and *ent*-**3**-DP, the presence of the *syn* conformation, as inferred from the structure of (−)-**26**, may explain their lack of recognition. For the fully diaxial compounds **2**-DP and *ent*-**2**-DP, molecular modeling showed severe steric clashes between the fused cyclopropane ring and amino acids Y115 and M184, respectively.

Experimental Section

(1*S*,2*R*,4*S*,5*R*)-4-Hydroxybicyclo[3.1.0]hexan-2-yl Acetate (5). Over a cooling bath at 0 °C, compound **4** (3 g, 21.1 mmol) was dissolved in CH_2Cl_2 (100 mL) and treated with 1 M Et_2Zn (23.2 mL). After the mixture was stirred at 0 °C for 15 min, CH_2I_2 (3.8 mL, 46.8 mmol) and 1 M Et_2Zn−hexane (23.2 mL) were added. Fifteen minutes later, an additional amount of CH_2I_2 (3.8 mL, 46.8 mmol) was added. The reaction mixture was allowed to reach room temperature, and after being stirred for 6 h, the contents was poured onto a cold, aqueous solution of NH_4Cl (200 mL). Following the extraction with $CHCl_3$ (6 × 100 mL), the organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel with hexanes/EtOAc (100:0 → 50:50, v/v) as eluent to give **5** (3.2 g, 97%) as a syrup: $[\alpha]^{22}_D = +48.8°$ (*c* 1.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.08 (td, J = 8.3, 4.7 Hz, 1 H, H-2), 4.38 (td, J = 8.3, 4.7 Hz, 1 H, H-4), 2.42 (br s, 1 H, 3-*OH*), 2.29−2.22 (m, 1 H, H-1), 2.00 (s, 3 H, *CH*$_3$-COO), 1.70−1.57 (m, 2 H, H-3a, H-3b), 1.20−1.09 (m, 1 H, H-5), 0.91−0.88 (m, 1 H, H-6b), 0.52−0.47 (m, 1 H, H-6a); ^{13}C NMR ($CDCl_3$) δ 171.1, 73.3, 70.3, 33.1, 22.8, 21.3, 20.0, 2.4; FAB-MS *m*/*z* (relative intensity) 157.1 (MH^+, 17.8). Anal. Calcd for $C_8H_{12}O_3 \cdot 0.1H_2O$: C, 60.82; H, 7.78. Found: C, 60.72; H, 7.89.

(1*R*,2*R*,4*R*,5*S*)-4-Acetoxybicyclo[3.1.0]hexan-2-yl Pivalate (6). Compound **5** (1.3 g, 8.33 mmol), pivalic acid (1.3 g, 12.7 mmol), and PPh_3 (4.4 g, 16.8 mmol) were dissolved in THF (80 mL). The solution was cooled to 0 °C and treated with DIAD (3.2 mL, 16.5 mmol). The reaction mixture was allowed to reach room temperature and was stirred for 30 min before evaporation to dryness in vacuo. The residue was purified by column chromatography on silica gel with hexane/EtOAc (100:0 → 75:15, v/v) as eluent to give **6** (1.90 g, 95%) as a syrup: $[\alpha]^{22}_D = +74.9$ (*c* 0.72, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.44 (td, J = 8.4, 4.7 Hz, 1 H, H-4), 5.11 (d, J = 5.3 Hz, 1 H, H-2), 2.06−2.00 (m, 4 H, *CH*$_3$COO, H-3a,), 1.84−1.79 (m, 1 H, H-1), 1.54−1.44 (m, 2 H, H-3b, H-5), 1.17 (s, 9 H, (*CH*$_3$)$_3$COO), 0.63−0.58 (m, 1 H, H-6b), 0.54−0.51 (m, 1 H, H-6a); ^{13}C NMR ($CDCl_3$) δ 178.0, 171.2, 75.4, 38.6, 32.9, 27.0, 21.7, 21.1, 19.3, 5.2; FAB-MS *m*/*z* (relative intensity) 279.1 ($M + K^+$,39.4). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.20; N, 8.48.

(1*R*,2*R*,4*R*,5*S*)-4-Hydroxybicyclo[3.1.0]hexan-2-yl Pivalate (7). Compound **6** (60 mg, 0.25 mmol) was dissolved in MeOH (2.5 mL) and stirred with K_2CO_3 (35 mg, 0.25 mmol) at room temperature for 2 h. After diluting with $CHCl_3$ (15 mL), the organic layer was washed with aqueous NH_4Cl and brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was then purified by column chromatography on silica gel eluted with hexane/EtOAc (2:1, v/v) as eluent to give **7** (46 mg, 92%) as a syrup: $[\alpha]^{25}_D = +88.3$ (*c* 0.585, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.12 (d, J = 5.2 Hz, 1 H, H-2), 4.80−4.75 (m, 1 H, H-4), 1.91 (ddd, J = 14.9, 7.8, 1.1 Hz, 1 H, H-3a), 1.71−1.65 (m, 1 H, H-5), 1.52−1.48 (m, 1 H, H-1), 1.42−1.34 (m, 1 H, H-3b), 1.18 (s, 9 H, $(CH_3)_3$-COO), 0.60−0.55 (m, 2 H, H-6a, H-6b); ^{13}C NMR ($CDCl_3$) δ 178.1, 76.4, 72.5, 38.6, 35.9, 27.0, 22.0, 21.4, 4.4; FAB-MS *m*/*z* (relative intensity) 199.1 (MH^+, 13.2). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.50; H, 9.23.

(1′*R*,2′*R*,4′*S*,5′*S*)-4-(6-Chloro-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-2-yl Pivalate (8). PPh_3 (778 mg, 2.9 mmol) was dissolved in THF (10 mL) and treated with DIAD (577 μL, 2.9 mmol) at 0 °C. The mixture was stirred for 20 min, and then compound **7** (255 mg, 1.3 mmol) and 6-chloropurine (319 mg, 2.1 mmol) dissolved in THF (3 mL) were added. The mixture was stirred at room temperature for 2 h and evaporated in vacuo. The residue was purified by column chromatography on silica gel with hexane/EtOAc (50:50, v/v) as eluent to give **8** (223 mg, 55%) as a white solid: mp 237−238 °C; $[\alpha]^{21}_D = +9.9$ (*c* 0.975, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.73 (s, 1 H, H-2), 8.56 (s, 1 H, H-8), 5.30 (d, J = 5.7 Hz, 1 H, H-2′), 5.24 (d, J = 7.0 Hz, 1 H, H-4′), 2.34−2.27 (dt, J = 16.4, 6.4 Hz, 1 H, H-3′b), 2.04−1.90 (m, 3 H, H-1′, H-3′a, H-5′), 1.09 (s, 9 H, $(CH_3)_3$COO), 0.98−0.92 (m, 1 H, H-6′b), 0.39−0.35 (m, 1 H, H-6a); ^{13}C NMR ($CDCl_3$) δ 177.7, 151.7, 151.3, 150.9, 144.0, 131.6, 75.7, 55.4, 38.6, 37.5, 27.0, 23.6, 22.4, 7.0; FAB-MS *m*/*z* (relative intensity) 335.1 (MH^+, 100). Anal. Calcd for $C_{16}H_{19}ClN_4O_2$: C, 57.40; H, 5.72; N, 16.73. Found: C, 57.40; H, 5.78; N, 16.68.

(1′*R*,2′*R*,4′*S*,5′*S*)-4-(6-Amino-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-2-ol (9). Compound **8** (215 mg, 0.64 mmol) was dissolved in dioxane−NH_4OH (5 mL, 1:1, v/v) and heated in a microwave reactor (100 °C) for 10 min. The solution was then diluted with $CHCl_3$ (20 mL) and washed with brine. The organic layer was dried ($MgSO_4$) and evaporated in vacuo. The residue was immediately dissolved in CH_2Cl_2 (5 mL), and under argon it was treated with 1 M DIBAL-H in toluene (1.3 mL) at −78 °C. After being stirred for 60 min, the reaction was quenched with MeOH (1 mL) and evaporated in vacuo. The residue was redissolved in $CHCl_3$/MeOH (20 mL, 9:1, v/v) and filtered through a pad of Celite. The solution was evaporated in vacuo, and the residue was purified by column chromatography on silica gel eluted with $CHCl_3$−MeOH (90:10, v/v, 0.5%Et_3N). Finally, the compound was precipitated with Et_2O at −78 °C to give compound **9** (126 mg, 85%) as a white solid. An analytical sample was recrystallized from EtOH: mp 209−210 °C; $[\alpha]^{22}_D = -28.3$ (*c* 0.605, MeOH); ^{1}H NMR (CD_3OD) δ 8.54 (s, 1 H, H-2), 8.21 (s, 1 H, H-8), 5.03 (d, J = 7.4 Hz, 1 H, H-4′), 4.35 (d, J = 5.3 Hz, 1 H, H-2′), 2.24−2.17 (m, 1 H, H-3′b), 1.90−1.79 (m, 3 H, H-1′, H-3′a, H-5′), 0.82−0.76 (m, 1 H, H-6′b), 0.28−0.24 (m, 1 H, H-6′a); ^{13}C NMR (CD_3OD) δ 157.3, 153.3, 150.1, 142.6, 120.1, 74.0, 57.3, 40.4, 27.4, 23.7, 7.4; FAB-MS *m*/*z* (relative intensity) 232.1 (MH^+, 100). Anal. Calcd for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.28. Found: C, 56.95; H, 5.81; N, 30.34.

(1′*R*,2′*R*,4′*S*,5′*S*)-4-(6-(Bis(4-methoxyphenyl)(phenyl)methylamino)-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-2-ol (10). Compound **9** (357 mg, 1.5 mmol) was coevaporated three times with anhydrous pyridine and finally dissolved in anhydrous pyridine (10 mL). Under an argon atmosphere, the solution was treated with $(CH_3)_3SiCl$ (292 μL, 2.3 mmol), stirred at room temperature for 5 min, and then treated with $[(MeO)Ph]_2PhCCl$ (DMTrCl, 604 mg, 1.8 mmol). After 18 h, the reaction was quenched with aqueous $NaHCO_3$ (1 mL) and evaporated in vacuo. The residue was dissolved in $CHCl_3$ (60 mL), washed with brine, dried ($MgSO_4$), and evaporated in vacuo. Purification by column chromatography on silica gel eluted with $CHCl_3$/MeOH (99:1 → 98:2, v/v, 0.5%Et_3N) gave compound **10** (653 mg, 79%) as a white foam: $[\alpha]^{22}_D = -41.0$ (*c* 0.96, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.04 (s, 1 H, H-2), 7.90 (s, 1 H, H-8), 7.34−7.19 (m, 9 H, PhH), 6.97 (s, 1 H, $(MeO)_2$Tr*NH*), 6.80−6.77 (m, 4 H, PhH), 6.65 (br s, 1 H, OH-2′), 4.81 (d, 1 H, J = 8.2 Hz, H-4′), 4.33 (br, 1 H, H-2′), 2.39−2.30 (m, 1 H, H-3′b), 2.00 (d, 1 H, J = 16.2 Hz, H-3′a), 1.86 (dt, 1 H, J = 9.0, 4.6 Hz, H-1′), 1.61 (dt, 1 H, J = 8.7, 4.3 Hz, H-5′), 0.81−0.75 (m, 1 H, H-6′b), 0.05−0.01 (m, 1 H, H-6′a); ^{13}C NMR ($CDCl_3$) δ 158.2, 154.3, 151.2, 145.3, 140.7, 137.3, 130.0, 128.7, 127.8, 126.8, 113.1, 73.2, 70.6, 58.1, 55.2, 41.2, 27.9, 23.3, 7.7; FAB-MS *m*/*z* (relative intensity) 534.2 (MH^+, 33.8). Anal. Calcd for $C_{32}H_{31}N_5O_3 \cdot 0.3H_2O$: C, 71.30; H, 5.91; N, 12.99. Found: C, 71.16; H, 5.87; N, 12.98.

Diethyl ((1′*R*,2′*R*,4′*S*,5′*S*)-4-(6-(Bis(4-methoxyphenyl)(phenyl)-methylamino)-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-2-yloxy)methylphosphonate (11). Compound **10** (59 mg, 0.10 mmol) was coevaporated four times with anhydrous toluene and dissolved in anhydrous THF (0.5 mL) under argon. The solution was treated with 1 M $[(CH_3)_3Si]_2NLi$ (LiHMDS, 133 μL) and stirred at room temperature for 5 min before the addition of trifluoromethansulfonyl diethoxy methyl phosphonate[10] (40 mg, 0.13 mmol) in anhydrous THF (1 mL). After 25 min, the reaction was quenched with aqueous $NaHCO_3$ (1 mL) and diluted with $CHCl_3$ (20 mL). The mixture was washed with brine, dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (98:2, v/v, 0.5% Et_3N) to give **11** (67 mg, 88%) as a syrup: $[\alpha]^{26}_D = -11.3$ (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.32 (s, 1 H, H-2), 8.07 (s, 1 H, H-8), 7.35−7.19 (9H, m, PhH), 6.88 (1H, br s, $(MeO)_2$Tr*NH*), 6.80−6.77 (m, 4 H, PhH), 5.10 (distorted dd, 1 H, J = 5.9, 1.7 Hz, H-4′), 4.22−4.11 (m, 5 H, $(CH_3CH_2O)_2$P, H-2′), 3.85−3.72 (m, 8 H, $(MeO)_2$TrNH, PCH_2O), 2.07−2.00 (m, 3 H, H-1′, H-3′a, H-3′b), 1.73 (dt, 1 H, J = 9.1, 3.9 Hz, H-5′), 1.37−1.27 (m, 6 H, $(CH_3$-$CH_2O)_2$P), 0.78 (dt, 1 H, J = 8.6, 6.2 Hz, H-6′b), 0.19−0.15 (m, 1 H, H-6′a); ^{13}C NMR ($CDCl_3$) δ 158.2, 154.0,. 151.8, 148.5, 145.5, 139.8, 137.5, 130.0, 128.7, 127.7, 126.6, 120.5, 113.0, 83.8 (J_{CP} = 11.0 Hz), 70.4, 62.4 (J_{CP} = 6.5 Hz), 62.1 (J_{CP} = 168.0 Hz), 55.2, 54.2, 36.6, 23.3, 23.0, 16.5 (J_{CP} = 4.2 Hz), 16.4 (J_{CP} = 4.2 Hz), 6.8; APCI-MS *m*/*z* (relative intensity) 684.3 (MH^+, 18.2). Anal. Calcd for $C_{37}H_{42}N_5O_6P \cdot 0.4H_2O$: C, 64.32; H, 6.24; N, 10.14. Found: C, 64.27; H, 6.43; N, 9.99.

((1′*R*,2′*R*,4′*S*,5′*S*)-4-(6-Amino-9*H*-purin-9-yl)bicyclo[3.1.0]-hexan-2-yloxy)methylphosphonic Acid Sodium Salt (2). Compound **11** (40 mg, 58.5 μmol) was dissolved in CH_3CN (1 mL) under argon. The solution was treated with $(CH_3)_3SiBr$ (TMSBr, 38 μL, 0.29 mmol) and stirred for 2 days at room temperature. After the solution was quenched with triethylammonium bicarbonate (TEAB) buffer (3 mL), the CH_3CN was evaporated in vacuo. The aqueous buffer solution that remained was washed three times with EtOAc and evaporated in vacuo. The residue was purified by reversed-phase chromatography (1.5 cm ×4 cm) on a C-18 silica gel column eluted with 0.1 M TEAB/CH_3CN (100:0−90:10, v/v) and further purified by reversed-phase HPLC using a similar column eluted with 0.1 M TEAB/CH_3CN (100:0 → 90:10, v/v). The desired fractions were combined, coevaporated with EtOH, and lyophilized. Finally, the compound was applied to a Dowex (Na^+) column to give compound **2** (16 mg, 73%) as a white solid: $[\alpha]^{20}_D = -13.5$ (*c* 0.45, H_2O); ^{1}H NMR (D_2O) δ 8.51 (s, 1 H, H-2), 8.14 (s, 1 H, H-8), 4.89 (distorted d, J = 5.1 Hz, 1 H, H-4′), 4.21 (distorted d, J = 3.6 Hz, 1 H, H-2′), 3.54 (dd, J = 13.0, 9.2 Hz, 1 H, P*CH*HO), 3.43 (dd, J = 13.0, 8.9 Hz, 1 H, P*CH*HO), 2.10−2.05 (m, 3 H, H-1′, H-3′a, H-3′b), 1.81 (td, J = 8.5, 4.2 Hz, 1 H, H-5′), 0.82 (dt, J = 8.5, 6.0 Hz, 1 H, H-6′b), 0.32−0.29 (m, 1 H, H-6′a); ^{13}C NMR (D_2O) δ 154.3, 151.0, 147.8, 141.6, 117.7, 83.3 (J_{CP} = 11.8 Hz), 63.7 (J_{CP} = 157.3 Hz),

55.4, 35.2, 22.5, 21.6, 5.9; ^{31}P NMR (D_2O) δ 15.8; FAB-MS m/z (relative intensity) 324.2 (MH^-, 100); HRMS (FAB) calc for ($C_{12}H_{15}N_5O_4P^-$) 324.0867 (MH^-), found 324.0850.

(1′*S*,2′*R*,4′*R*,5′*R*)-4-(6-(Bis(*tert*-butoxycarbonyl)amino)-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-2-yl Acetate (12). Compound **5** (400 mg, 2.5 mmol), *N*-(Boc)$_2$adenine (1.29 g, 3.8 mmol), and PPh_3 (1.01 g, 3.8 mmol) were dissolved in THF (25 mL). After being cooled to 0 °C, the solution was treated with DIAD (786 μL, 3.8 mmol) and stirred at the same temperature for 30 min. The reaction mixture was evaporated in vacuo, and the crude residue was purified by column chromatography on silica gel eluted with hexane/EtOAc (100:0 → 60:40%, v/v) to give compound **12** (953 mg, 79%) as a syrup: $[\alpha]^{21}_D$ = 40.8 (c 1.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.85 (s, 1 H, H-2), 8.18 (s, 1 H, H-8), 5.62 (td, J = 8.5, 4.7 Hz, 1 H, H-2′), 5.22 (d, J = 7.0 Hz, 1 H, H-4′), 2.27 (dd, J = 15.3, 8.2 Hz, 1 H, H-3′b), 2.19−2.14 (m, 1 H, H-1′), 2.06 (s, 3 H, CH_3CO), 1.96−1.88 (m, 1 H, H-3′a), 1.77−1.73 (1 m, 1 H, H-5′), 1.46 (s, 18 H, $(CH_3)_3$COCO × 2), 0.91−0.82 (m, 2 H, H-6′a, H-6′b); ^{13}C NMR ($CDCl_3$) δ 171.0, 152.8, 152.0, 150.5, 150.4, 142.4, 129.0, 83.8, 74.8, 55.4, 34.2, 27.8, 22.0, 21.0, 20.8, 6.1; FAB-MS m/z (relative intensity) 474.3 (MH^+, 65.9). Anal. Calcd for $C_{23}H_{31}N_5O_6$ 1.4H_2O: C, 55.39; H, 6.83; N, 14.04. Found: C, 55.63; H, 6.59; N, 13.63.

(1′*S*,2′*R*,4′*R*,5′*R*)-4-(6-(Bis(*tert*-butoxycarbonyl)amino)-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-2-ol (13). Compound **12** (872 mg, 1.8 mmol) was dissolved in MeOH (20 mL) and treated with K_2CO_3 (254 mg, 1.8 mmol). After the solution was stirred at room temperature for 2 h, $CHCl_3$ (150 mL) was added, and the organic layer was washed with brine and aqueous NH_4Cl, dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude material was purified by column chromatography on silica gel eluted with hexane/EtOAc (100:0 → 0:100%, v/v) to give compound **13** (722 mg, 91%) as a white foam: $[\alpha]^{21}_D$ = 26.7 (c 2.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.84 (s, 1 H, H-2), 8.19 (s, 1 H, H-8), 5.20 (d, J = 6.8 Hz, 1 H, H-4′), 4.94−4.99 (m, 1 H, H-2′), 2.27 (br, 1 H, OH-2′), 2.10 (dd, J = 15.1, 7.9 Hz, 1 H, H-3′b), 1.95 td, J = 8.6, 4.6 Hz, 1 H, H-1′), 1.78 (ddd, J = 15.4, 8.7, 7.1 Hz, 1 H, H-3′a), 1.67 (td, J = 8.6, 4.4 Hz, 1 H, H-5′), 1.45 (s, 18 H, $(CH_3)_3$COCO × 2), 0.87 (td, J = 5.9, 3.8 Hz, 1 H, H-6′b), 0.84−0.78 (m, 1 H, H-6′a); ^{13}C NMR ($CDCl_3$) δ 152.8, 151.9, 150.6, 150.2, 142.7, 129.0, 83.8, 72.0, 56.1, 36.9, 27.8, 23.3, 21.8, 5.2; FAB-MS m/z (relative intensity) 432.3 (MH^+, 92.9%). Anal. Calcd for $C_{21}H_{29}N_5O_5 \cdot 0.4H_2O$: C, 57.49; H, 6.85; N, 15.96. Found: C, 57.49; H, 6.84; N, 15.87.

(1′*S*,2′*S*,4′*R*,5′*R*)-4-(6-(Bis(*tert*-butoxycarbonyl)amino)-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-2-ol (14). Compound **13** (110 mg, 0.25 mmol) was dissolved in CH_2Cl_2 (2.5 mL) under argon. After being cooled to 0 °C, the solution was treated with the Dess−Martin periodinane reagent (162 mg, 0.37 mmol) and stirring continued for 5 h allowing the reaction to reach room temperature. EtOAc (30 mL) was added, and the combined organic solution was washed with cold, aqueous $NaHCO_3$, cold 10% aqueous $Na_2S_2O_3$, and brine. After drying ($MgSO_4$), the filtrate was evaporated in vacuo. The residue coevaporated two times with anhydrous toluene and once with anhydrous THF. Finally, under argon at −78 °C, the residue was treated with 1 M L-selectride in THF (280 μL, 0.280 mmol) for 10 min and quenched with acetone (1 mL) followed by aqueous NH_4Cl (3 mL). The mixture was extracted with EtOAc (30 mL), and the organic extract was washed with brine, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude material was purified by column chromatography on silica gel eluted with hexane/EtOAc (100:0 → 0:100%, v/v) to give compound **14** (103 mg, 94%) as a white solid: mp 173 °C-174 °C; $[\alpha]^{21}_D$ = 52.7° (c 1.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.84 (s, 1 H, H-2), 8.53 (s, 1 H, H-8), 5.07 (d, J = 8.0 Hz, 1 H, H-4′), 4.43 (d, J = 5.5 Hz, 1 H, H-2′), 4.36 (br s, 1 H, OH-2′), 2.27−2.35 (m, 1 H, H-3′b), 1.98 (d, J = 16.3 Hz, 1 H, H-3′a), 1.91 (dt, J = 8.9, 4.5 Hz, 1 H, H-1′), 1.68 (dt, J = 8.4, 4.2 Hz, 1 H, H-5′), 1.46 (s, 18 H, $(CH_3)_3$COCO × 2), 0.84−0.79 (m, 1 H, H-6′b), 0.13 (dt, J = 5.9, 3.9 Hz, 1 H, H-6′a); ^{13}C NMR ($CDCl_3$) δ 152.5, 151.2, 150.5, 150.2, 145.8, 129.4, 83.8, 73.1, 56.9, 40.3, 27.8, 27.2, 23.1, 7.4; FAB-MS m/z (relative intensity) 432.3 (MH^+, 65.9). Anal. Calcd for $C_{21}H_{29}N_5O_5$: C, 58.45; H, 6.77; N, 16.23. Found: C, 58.60; H, 6.82; N, 16.24.

Diethyl ((1′*S*,2′*S*,4′*R*,5′*R*)-4-(6-(Bis(*tert*-butoxycarbonyl)amino)-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-2-yloxy)methylphosphonate (15). Compound **14** (150 mg, 0.35 mmol) was coevaporated three times with anhydrous toluene and dissolved in THF (3.5 mL). After being cooled to −78 °C, the solution was treated with 1 M $[(CH_3)_3Si]_2NLi$ (LiHMDS in THF, 383 μL) followed by the addition of diethoxyphosphonomethyl trifluoromethanesulfonate (115 mg, 0.38 mmol) in THF (1 mL). The solution was stirred at −78 °C for 20 min, quenched by addition of aqueous NH_4Cl (1 mL), and further diluted with EtOAc (50 mL). The organic solution was washed with brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel eluted with hexane/EtOAc (100:0 → 0:100, v/v), $CHCl_3$−MeOH (98:2, v/v) to give **15** (176 mg, 87%) as a syrup: $[\alpha]^{20}_D$ = 9.8 (c 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.82 (s, 1 H, H-2), 8.68 (s, 1 H, H-8), 5.25 (d, J = 7.0 Hz, 1 H, H-4′), 4.22−4.08 (m, 5 H, $(CH_3CH_2O)_2$P, H-2′), 3.81 (dd, J = 13.8, 9.3 Hz, 1 H, PC*H*HO), 3.72 (dd, J = 13.8, 8.9 Hz, 1 H, PC*H*HO), 2.18−2.11 (m, 1 H, H-3′b), 2.07−2.02 (m, 2 H, H-1′, H-3′a), 1.71 (dt, J = 8.4, 4.4 Hz, 1 H, H-5′), 1.44 (s, 18 H, $(CH_3)_3$COCO × 2), 1.33 (t, J = 7.1 Hz, 3 H, $(CH_3CH_2O)_2$P), 1.28 (t, J = 7.1 Hz, 3 H, $(CH_3CH_2O)_2$P), 0.87−0.81 (m, 1 H, H-6′b), 0.23−0.19 (m, 1 H, H-6′a); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.1, 151.5, 150.5, 149.8, 144.9, 128.6, 83.7 (J_{CP} = 11.3 Hz), 83.5, 62.5 (J_{CP} = 5.0 Hz), 62.4 (J_{CP} = 4.9 Hz), 62.1 (J_{CP} = 168.3 Hz), 54.6, 36.7, 27.7, 23.3, 23.1, 16.41 (J_{CP} = 3.5 Hz), 16.35 (J_{CP} = 3.5 Hz), 6.8; FAB-MS m/z (relative intensity) 582.3 (MH^+, 83.4). Anal. Calcd for $C_{26}H_{40}N_5O_8P$: C, 53.69; H, 6.93; N, 12.04. Found: C, 53.56; H, 7.32; N, 11.65.

((1′*S*,2′*S*,4′*R*,5′*R*)-4-(6-Amino-9*H*-purin-9-yl)bicyclo[3.1.0]-hexan-2-yloxy)methylphosphonic Acid Sodium Salt (*ent*-2). Following the same procedure as for compound **2**, *ent*-**2** was obtained in 72% yield: $[\alpha]^{20}_D$ = 13.5 (c 0.450, H_2O). The ^{1}H NMR, ^{13}C NMR, and mass spectral data were identical to **2**.

(*R*)-3-Hydroxyhex-5-enenitrile (17). Compound **16**[16] (10 g, 82.9 mmol) was dissolved in MeOH (100 mL) and treated with KCN (5.9 g, 90.6 mmol). After being stirred and heated for 24 h at 70 °C, the solvent was removed in vacuo and the residue was dissolved in EtOAc (250 mL) and washed with aqueous NH_4Cl and brine. The organic solution was dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel eluted with hexane/EtOAc (100:0 → 70:30, v/v) to give **17** (7.7 g, 84%) as an oil: $[\alpha]^{21}_D$ = −6.8 (c 0.8, $CHCl_3$); IR (neat) 2251 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.83−5.73 (m, 1 H, H-5), 5.18−5.23 (m, 2 H, H-6a, H-6b), 3.97 (td, J = 12.1, 5.4 Hz, 1 H, H-3), 2.55 (dd, J = 16.7, 5.1 Hz, 1 H, H-2b), 2.47 (dd, J = 16.7, 6.3 Hz, 1 H, H-2a), 2.45−2.31 (m, 3 H, OH-3, H-4a, H-4b); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 132.4, 119.9, 117.4, 66.7, 40.8, 21.2. Anal. Calcd for $C_6H_9NO \cdot 0.1H_2O$: C, 63.81; H, 8.21; N, 12.40. Found: C, 63.87; H, 8.10; N, 12.32.

(*R*)-*N*,*N*-Dibenzyl-3-hydroxyhex-5-enamide (18). Compound **17** (3.0 g, 27.0 mmol) was dissolved in a mixture of 25% aqueous NaOH (50 mL) and MeOH (50 mL). The solution was stirred for 24 h at 90 °C, cooled to room temperature, and neutralized with concentrated HCl. The solution was extracted with EtOAc (2 × 200 mL), and the organic phase was dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was dissolved in anhydrous DMF (140 mL) and treated with dibenzylamine (Bn_2NH, 6.4 mL, 32.4 mmol), hydroxybenzotriazole (HOBT, 4.4 g, 32.6 mmol), and *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (10.4 g, 54.2 mmol) at 0 °C. After room temperature was reached, stirring was continued for 16 h before all the volatiles were removed in vacuo. The residue was dissolved in EtOAc (250 mL), washed with

brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product obtained was purified by column chromatography on silica gel eluted with hexane/EtOAc (100:0 → 70:30, v/v) to give **18** (5.4 g, 65%) as a solid: mp 57−58 °C; $[\alpha]^{20}_D = -43.4$ (*c* 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.13 (m, 10 H, PhH), 5.87−5.77 (m, 1 H, H-5), 5.12−5.05 (m, 2 H, H-6a, H-6b), 4.67 (d, J = 14.2 Hz, 1 H, PhC*H*H), 4.53 (1H, d, J = 14.8 Hz, 1 H, PhCH*H*), 4.38 (AB q, J = 17.0 Hz, 2 H, PhCH_2), 4.21−4.15 (m, 1 H, H-3), 2.60 (dd, J = 16.4, 2.6 Hz, 1 H, H-2b), 2.43 (dd, J = 16.4, 9.3 Hz, 1 H, H-2a), 2.31−2.38 (m, 1 H, H-4b), 2.27−2.20 (m, 1 H, H-4a); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.0, 136.7, 135.8, 134.3, 128.9, 128.5, 128.0, 127.6, 127.4, 126.3, 117.4, 67.7, 49.7, 47.9, 40.7, 38.5; FAB-MS *m*/*z* (relative intensity) 310.2 (MH^+, 83.2(. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.59; H, 7.34; N, 4.56.

(*R*)-*N*,*N*-Dibenzyl-3-(methoxymethoxy)hex-5-enamide (19). Under a blanket of argon and over a cooling bath at 0 °C, compound **18** (560 mg, 1.8 mmol) was dissolved in CH_2Cl_2 (5 mL) and treated with diisopropylethylamine (617 μL, 4.5 mmol) and methyl chloromethyl ether (MOMCl, 150 μL, 2.0 mmol). The mixture was allowed to reach room temperature and stirred for 16 h. The reaction was diluted with Et_2O (100 mL) and washed with brine and aqueous $NaHCO_3$. The ether layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel eluted with hexane/EtOAc (100:0 → 75:25, v/v) to give **19** (629 mg, 99%) as an oil: $[\alpha]^{22}_D = 5.3$ (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38−7.16 (m, 10 H, PhH), 5.87−5.77 (m, 1 H, H-5′), 5.10−5.01 (m, 2 H, H-6′a, H-6′b), 4.74−4.65 (m, 3 H, PhCH_2, OCH*H*OCH$_3$), 4.57−4.39 (m, 3 H, PhCH_2, OC*H*HOCH$_3$), 4.33−4.27 (m, 1 H, H-3), 2.71 (dd, J = 15.4, 7.5 Hz, 1 H, H-2b), 2.48 (dd, J = 15.4, 5.2 Hz, 1 H, H-2a), 2.47−2.37 (m, 2 H, H-4a, H-4b); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4, 137.3, 136.5, 134.1, 128.9, 128.5, 128.2, 127.6, 127.3, 126.5, 117.7, 96.4, 75.0, 55.6, 50.0, 48.2, 39.4, 38.2; FAB-MS *m*/*z* (relative intensity) 354.2 (MH^+, 22.2). Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.58; H, 7.64; N, 3.92.

(1*S*,3*R*,5*S*)-1-(Dibenzylamino)bicyclo[3.1.0]hexan-3-ol (20) and (1*R*,3*R*,5*R*)-1-(Dibenzylamino)bicyclo[3.1.0]hexan-3-ol (21). Compound **19** (500 mg, 1.4 mmol) was dissolved in THF (5 mL) and treated with Ti(O-*i*-Pr)$_4$ (405 μL, 1.4 mmol) followed by 2 M *i*-PrMgCl/THF (2.8 mL, 5.6 mmol) at room temperature. After 1 h, the reaction was quenched with aqueous NH_4Cl (1 mL) and diluted with EtOAc (100 mL). The entire mixture was filtered through a Celite pad and washed with aqueous $NaHCO_3$ and brine. The organic phase was dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was dissolved in 3% HCl/MeOH (20 mL) and stirred at 60 °C for 4 h. After all of the volatiles were removed in vacuo, the residue was diluted with EtOAc (200 mL) and neutralized with aqueous $NaHCO_3$ (5 mL). The organic phase was washed with brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified by column chromatography on silica gel eluted with hexane/EtOAc (100:0 → 80:20, v/v) to give **20** (195 mg, 47%) as a white solid, mp 120−121 °C, and isomer **21** (127 mg, 31%) also as a white solid.

Isomer **20**: $[\alpha]^{20}_D = -18.4$ (*c* 0.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31−7.18 (10H, m, PhH), 4.35 (distorted t, J = 6.4 Hz, 1 H, H-3), 3.77 (d, J = 13.4 Hz, 2 H, PhCH_2), 3.62 (d, J = 13.4 Hz, 2 H, PhCH_2), 2.40 (ddd, J = 13.8, 6.9, 2.2 Hz, 1 H, H-2a), 2.48 (dt, J = 14.0, 5.7 Hz, 1 H, H-4a), 1.66 (d, J = 13.9 Hz, 1 H, H-2b), 1.36 (d, J = 14.1 Hz, 1 H, H-4b), 1.10 (d, J = 2.8 Hz, 1 H, OH), 0.91−0.86 (dt, J = 9.2, 4.8 Hz, 1 H, H-5), 0.74 (pseudo t, $J \approx 4.40$ Hz, 1 H, H-6b), 0.68−0.64 (m, 1 H, H-6a); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.2, 129.0, 127.9, 126.7, 72.8, 56.9, 52.0, 37.8, 34.3, 26.4, 21.1; FAB-MS *m*/*z* (relative intensity) 294.2 (MH^+, 50.2). Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.70; H, 7.89; N, 4.78.

Isomer **21**: mp 93 °C; $[\alpha]^{20}_D = 2.4$ (*c* 0.555, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52−7.19 (m, 10 H, PhH), 3.93−3.84 (m, 1 H, H-3), 3.76 (d, J = 13.4 Hz, 2 H, PhCH_2), 3.68 (d, J = 13.4 Hz, 2 H, PhCH_2), 2.12 (dd, J = 12.0, 7.2 Hz, 1 H, H-2b), 1.98 (ddd, J = 12.0, 8.0, 1.6 Hz, 1 H, H-2a), 1.85 (dd, J = 12.3, 7.1 Hz, 1 H, H-4b), 1.31 (ddd, J = 12.8, 8.4, 4.8 Hz, 1 H, H-4a), 1.26 (d, J = 5.3 Hz, 1 H, OH), 0.87 (dt, J = 9.0, 4.6 Hz, 1 H, H-5), 0.40 (ddd, J = 8.7, 4.9, 1.1 Hz, 1 H, H-6b), 0.18 (pseudo t, $J \approx 4.7$ Hz, 1 H, H-6a); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.1, 129.0, 127.9, 126.7, 70.8, 56.9, 49.3, 36.2, 32.9, 24.4, 18.3; FAB-MS *m*/*z* (relative intensity) 294.2 (MH^+, 28.2). Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.84; H, 7.87; N, 4.84.

(1*S*,3*S*,5*S*)-1-(Dibenzylamino)bicyclo[3.1.0]hexan-3-yl Benzoate (22). A mixture of compound **20** (403 mg, 1.4 mmol), benzoic acid (418 mg, 3.4 mmol), and PPh_3 (898 mg, 3.42 mmol) was dissolved in THF (14 mL). After being cooled to 0 °C, the solution was treated with DIAD (700 μL, 3.4 mmol) and stirred for 30 min. The solvent was evaporated in vacuo, and the residue was purified by column chromatography on silica gel eluted with hexane/EtOAc (100:0 → 90:10, v/v) to give **22** (514 mg, 94%) as a white solid: mp 88−89 °C; $[\alpha]^{20}_D = -42.7$ (*c* 0.71, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06−8.04 (m, 2 H, PhH), 7.60−7.21 (m, 13 H, PhH), 4.90 (quintet, J = 7.7 Hz, 1 H, H-3), 3.79 (d, J = 13.3 Hz, 2 H, PhCH_2), 3.71 (d, J = 13.3, Hz, PhCH_2), 2.37 (dd, J = 12.4, 7.5 Hz, 1 H, H-2b), 2.20 (ddd, J = 12.3, 7.8, 1.6 Hz, 1 H, H-2a), 2.04 (dd, J = 12.6, 7.4 Hz, 1 H, H-4b), 1.66 (ddd, J = 12.8, 8.2, 4.9 Hz, 1 H, H-4a), 0.97 (dt, J = 9.0, 4.6 Hz, 1 H, H-5), 0.51 (distorted dd, J = 8.6, 4.8 Hz, 1 H, H-6b), 0.31 (t, J = 4.8 Hz, 1 H, H-6a); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.2, 140.0, 132.9, 130.4, 129.5, 129.0, 128.3, 128.0, 126.8, 73.9, 57.0, 49.4, 33.0, 30.0, 24.0, 18.9; FAB-MS *m*/*z* (relative intensity) 398.2 (MH^+, 38.2). Anal. Calcd for $C_{27}H_{27}NO_2$: C, 81.58; H, 6.85; N, 3.52. Found: C, 81.50; H, 6.91; N, 3.43.

(1*S*,3*S*,5*S*)-1-Aminobicyclo[3.1.0]hexan-3-yl Benzoate Hydrochloride (23). Compound **22** (320 mg, 0.8 mmol) was dissolved in EtOAc−MeOH (8 mL, 1:1, v/v) and treated with 2 M HCl/Et_2O (1.2 mL, 2.4 mmol) under argon. After the addition of 10 wt % Pd/C (500 mg), the argon atmosphere was replaced with H_2 gas and the mixture was stirred at room temperature for 20 h. The mixture was filtered through Celite, and the filtrate was evaporated in vacuo to give compound **23** (198 mg, 97%) as a brown solid: mp 212 °C dec; $[\alpha]^{21}_D = -11.4$ (*c* 0.45, MeOH); ^{1}H NMR (CD_3OD, 400 MHz) δ 8.02−7.98 (m, 2 H, PhH), 7.62−7.44 (m, 3 H, PhH), 4.99 (quintet, J = 7.7 Hz, 1 H, H-3), 2.76 (dd, J = 12.3, 7.3 Hz, 1 H, H-2b), 2.36 (dd, J = 12.9, 7.4 Hz, 1 H, H-4b), 2.27−2.14 (m, 2 H, H-2a, H-4a), 1.84 (dt, J = 9.4, 4.7 Hz, 1 H, H-5), 1.08 (pseudo t, $J \approx 7.8$ Hz, 1 H, H-6b), 0.87 (distorted dd, J = 6.6, 4.7 Hz, 1 H, H-6a); ^{13}C NMR (CD_3OD, 100 MHz) δ 167.3, 134.5, 131.0, 130.5, 129.6, 73.7, 39.6, 36.8, 33.7, 21.2, 14.5; FAB-MS *m*/*z* (relative intensity) 218.2 (MH^+, 100). Anal. Calcd for $C_{13}H_{16}ClNO_2 \cdot 0.5H_2O$: C, 59.43; H, 6.52; N, 5.33. Found: C, 59.45; H, 6.35; N, 5.40.

(1′*S*,3′*S*,5′*S*)-1-(6-Chloro-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-3-yl Benzoate (25). A solution of compound **23** (100 mg, 0.39 mmol) and *N*-(4,6-dichloropyrimidin-5-yl)formimidic acid (79 mg, 0.41 mmol) in 1,4-dioxane (2 mL) was treated with *i*-Pr$_2$NEt (217 μL, 1.6 mmol) and heated in a microwave reactor at 100 °C for 20 min. The mixture was evaporated in vacuo, and the residue was extracted with EtOAc (50 mL), washed with brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude **24** was then dissolved in diethoxymethyl acetate (2 mL) and heated in a microwave reactor at 120 °C for 120 min. After the volatiles were removed in vacuo, the residue was purified by column chromatography on silica gel eluted with hexane/EtOAc (100:0 → 60:40, v/v) to give **25** (113 mg, 81%) as a white solid: 92−93 °C; $[\alpha]^{21}_D = -35.4$ (*c* 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.78 (s, 1 H, H-2), 8.19 (1s, 1 H, H-8), 8.04−8.01 (m, 2 H, PhH), 7.58−7.41 (m, 3 H, PhH), 5.11 (quintet, J = 7.8 Hz, 1 H, H-3′), 2.94 (dd, J = 12.5, 7.2 Hz, 1 H, H-2′b), 2.59−2.46 (m, 3 H, H-2′a, H-4′a, H-4′b), 2.17−2.13

(m, 1 H, H-5′), 1.35 (m, 1 H, H-6′b), 1.24 (dd, J = 6.5, 5.1 Hz, 1 H, H-6′a); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.0, 152.2, 152.4, 151.2, 145.6, 133.2, 131.9, 129.6, 128.4, 72.4, 40.8, 38.2, 32.9, 21.9, 16.6; FAB-MS m/z (relative intensity) 355.1 (MH^+, 100). Anal. Calcd for $C_{18}H_{15}ClN_4O_2$: C, 60.94; H, 4.26; N, 15.79. Found: C, 60.91; H, 4.35; N, 15.83.

(1′*S*,3′*S*,5′*S*)-1-(6-Amino-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-3-ol (26). Compound **25** (80 mg, 0.23 mmol) was dissolved in mixture of dioxane and 28% NH_4OH (4 mL, 1:1, v/v) and heated in a microwave reactor at 100 °C for 40 min. After the volatiles were removed in vacuo, the residue was purified by column chromatography on silica gel eluted with EtOAc−$CHCl_3$−MeOH (100:0:0 → 0:90:10, v/v) to give **26** (50 mg, 96%) as a white solid. An analytical sample was recrystallized from EtOH: mp 191 °C; $[\alpha]^{20}_D$ = −53.6 (c 0.415, MeOH); ^{1}H NMR (CD_3OD, 400 MHz) δ 8.23 (s, 1 H, H-2), 8.17 (s, 1 H, H-8), 4.05 (quintet, J = 7.3 Hz, 1 H, H-3′), 2.62 (dd, J = 12.7, 6.7 Hz, 1 H, H-2′b), 2.24−2.09 (m, 3 H, H-2′a, H-4′a, H-4′b), 2.03−1.99 (m, 1 H, H-5′), 1.27−1.22 (m, 1 H, H-6′b), 1.10 (pseudo t, $J \approx$ 5.6 Hz, 1 H, H-6′a); ^{13}C NMR (CD_3OD, 100 MHz) δ 157.4, 153.7, 151.4, 143.0, 120.4, 71.7, 42.5, 42.2, 37.0, 23.3, 18.0; FAB-MS m/z (relative intensity) 232.1 (MH^+, 18.2). Anal. Calcd for $C_{11}H_{13}N_5O\cdot 0.7H_2O$: C, 54.18; H, 5.95; N, 28.72. Found: C, 54.16; H, 5.89; N, 28.88.

(1′*S*,3′*S*,5′*S*)-1-(6-(Bis(4-methoxyphenyl)(phenyl)methylamino)-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-3-ol (27). Compound **26** (150 mg, 0.65 mmol) was coevaporated four times with pyridine, dried *in vacuo* overnight and dissolved in anhydrous pyridine (3.2 mL). The solution was treated with $(CH_3)_3SiCl$ (247 μL, 1.9 mmol), and after 30 min of stirring it was treated with 4,4′-dimethoxytrityl chloride (242 mg, 0.68 mmol). After 1 day, the reaction was quenched with H_2O (1 mL) and evaporated in vacuo. The residue was extracted with EtOAc (50 mL) and washed with brine, aqueous $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$), filtered, and evaporated in vacuo, and the residue was purified by column chromatography on silica gel eluted with $CHCl_3$/MeOH (99:1 → 98:2, v/v, 0.5% Et_3N) to give **27** (300 mg, 87%) as a white foam: $[\alpha]^{20}_D$ = −26.6 (c 0.34, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (s, 1 H, H-2), 7.76 (s, 1 H, H-8), 7.34−7.21 (m, 9 H, PhH), 6.95 (br, 1 H, N*H*DMTr), 6.80−6.76 (m, 4 H, PhH), 6.13 (br s, 1 H, OH-3′), 4.24 (br s, 1 H, H-3′), 2.39−2.35 (m, 1 H, H-2′b), 2.27 (dd, J = 14.3, 4.6 Hz, 1 H, H-4′b), 2.20 (distorted dd, J = 14.4, 1.2 Hz, 1 H, H-2′a), 1.95−1.88 (m, 1 H, H-5′), 1.76−1.70 (m, 2 H, H-4′a, H-6′b), 0.95 (t, J = 5.3 Hz, 1 H, H-6′a); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.2, 154.2, 151.8, 148.9, 145.2, 139.8, 137.3, 130.0, 128.7, 127.8, 126.8, 121.2, 113.1, 70.6, 55.2, 45.3, 43.7, 40.3, 25.5, 25.1; FAB-MS m/z (relative intensity) 534.2 (MH^+, 16.8%); HRMS (FAB) calc for ($C_{32}H_{32}N_5O_3^+$) 534.2500 (MH^+), found 534.2534.

Diethyl ((1′*S*,3′*S*,5′*S*)-1-(6-(Bis(4-methoxyphenyl)(phenyl)-methylamino)-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-3-yloxy)methylphosphonate (28). Compound **27** (54 mg, 0.10 mmol) was dissolved in THF (0.5 mL) under argon and treated with 1 M LHMDS (111 μL) at room temperature. The mixture was stirred for 5 min and treated with diethyl [(trifluoromethanesulfonyl)-oxy]methanephosphonate (33 mg, 0.10 mmol) dissolved in THF (1 mL). After 25 min, the reaction was quenched with aqueous $NaHCO_3$ (1 mL) and diluted with $CHCl_3$ (50 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel eluted with EtOAc−$CHCl_3$−MeOH (100:0:0 → 0:99:1, v/v, 0.5% Et_3N) to give **28** (60 mg, 87%) as an oil: $[\alpha]^{20}_D$ = −26.7 (c 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (s, 1 H, H-2), 7.78 (s, 1 H, H-8), 7.34−7.20 (m, 9 H, PhH), 6.85 (br s, 1 H, N*H*DMT), 6.80−6.77 (m, 4 H, PhH), 3.84 (quintet, 1 H, J = 7.4 Hz, H-3′), 3.77 (s, 6 H, [(OCH_3)Ph]$_2$), 3.74−3.67 (m, 2 H, PCH_2O), 2.76 (dd, 1 H, J = 12.3, 6.8 Hz, H-2′a), 2.32−2.20 (m, 3 H, H-2′b, H-4′a, H-4′b), 2.01−1.97 (m, 1 H, H-5′), 1.35−1.31 (m, 6 H, ($CH_3CH_2O)_2$P), 1.26−1.21 (m, 1 H, H-6′a), 1.02 (pseudo t, 1 H, $J \approx$ 5.5 Hz, H-6′b); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.2, 154.1, 152.4, 149.7, 145.4, 139.9, 137.5, 130.0, 128.7, 127.8, 126.7, 121.0, 113.0, 80.0 (J_{CP} = 12.7 Hz), 70.5, 63.1 (J_{CP} = 168.2), 62.5 (J_{CP} = 2.5 Hz), 62.4 (J_{CP} = 2.5 Hz), 55.1, 40.3, 38.8, 33.1, 16.8, 16.4 (J_{CP} = 5.6 Hz); FAB-MS m/z (relative intensity) 684.3 (MH^+, 20.6). Anal. Calcd for $C_{11}H_{13}N_5O\cdot 0.7H_2O$: C, 63.82; H, 6.28; N, 10.06. Found: C, 63.82; H, 6.24; N, 9.87.

((1′*S*,3′*S*,5′*S*)-1-(6-Amino-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-3-yloxy)methylphosphonic Acid Sodium Salt (3). Compound **28** (43 mg, 63 μmol) was dissolved in CH_3CN (1 mL) and treated with trimethylsilyl bromide (41 μL, 0.32 mmol) under argon. The mixture was stirred at room temperature for 2 days and quenched with triethylammonium bicarbonate buffer (TEAB, 3 mL). The CH_3CN in the mixture was evaporated in vacuo, and the residue was washed with EtOAc. The aqueous phase was evaporated in vacuo and coevaporated with EtOH, and the crude obtained was purified with a C-18 column (1.5 cm × 4 cm) eluted with 0.1 M TEAB−CH_3CN (100:0 → 90:10). The product-containing fractions were coevaporated with EtOH and lyophilized. The compound was then passed through a DOWEX (Na^+) column to give compound **3** (16 mg, 70%) as the sodium salt: $[\alpha]^{20}_D$ = −43.4 (c 0.51, H_2O); ^{1}H NMR (D_2O, 400 MHz) δ 8.24 (s, 1 H, H-2), 8.23 (s, 1 H, H-8), 3.96 (quintet, 1 H, J = 7.6 Hz, H-3′), 3.60−3.51 (m, 2 H, PCH_2O), 2.80 (dd, 1 H, J = 1 H, 12.2, 6.9 Hz, H-2′a), 2.34 (dd, J = 12.6, 7.1 Hz, 1 H, H-4′a), 2.23−2.01 (m, 3 H, H-2′b, H-4′b, H-5′), 1.31 (distorted dd, 1 H, J = 8.5, 6.5 Hz, H-6′a), 1.10 (pseudo t, 1 H, $J \approx$ 5.6 Hz, H-6′b); ^{13}C NMR (D_2O, 100 MHz) δ 154.8, 151.8, 149.0, 142.5, 118.0, 79.1 (J_{CP} = 11.9 Hz), 65.4 (J_{CP} = 155.5 Hz), 39.8, 37.7, 32.2, 21.1, 15.3; ^{31}P NMR (D_2O, 100 MHz) δ 14.9; FAB-MS m/z (relative intensity) 324.1 (MH^-, 100); HRMS (FAB) calc for ($C_{12}H_{15}N_5O_4P$) 324.0867 (MH^-), found 324.0851.

(1*R*,3*R*,5*R*)-1-(Dibenzylamino)bicyclo[3.1.0]hexan-3-yl benzoate (29): yield 89%; the spectral data were identical to those of the enantiomeric compound **22**; $[\alpha]^{21}_D$ = 42.8 (c 1.06, $CHCl_3$).

(1*R*,3*R*,5*R*)-1-Aminobicyclo[3.1.0]hexan-3-yl benzoate hydrochloride (30): yield 93%; the spectral data were identical to those of the enantiomeric compound **23**; $[\alpha]^{20}_D$ = 10.9 (c 1.17, MeOH).

(1′*R*,3′*R*,5′*R*)-1-(6-Chloro-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-3-yl benzoate (32): yield 82%; the spectral data were identical to that of the enantiomeric compound **25**; $[\alpha]^{20}_D$ = 34.7 (c 1.21, $CHCl_3$).

(1′*R*,3′*R*,5′*R*)-1-(6-Amino-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-3-ol (33): yield 95%; the spectral data were identical to those of the enantiomeric compound **26**; $[\alpha]^{21}_D$ = 54.0 (c 0.40, MeOH).

(1′*R*,3′*R*,5′*R*)-1-(6-(Bis(4-methoxyphenyl)(phenyl)methylamino)-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-3-ol (34): yield 88%; the spectral data were identical to those of the enantiomeric compound **27**; $[\alpha]^{20}_D$ = 25.4 (c 0.34, $CHCl_3$).

Diethyl ((1′*R*,3′*R*,5′*R*)-1-(6-(Bis(4-methoxyphenyl)(phenyl)-methylamino)-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-3-yloxy)methylphosphonate (35): yield 84%; the spectral data were identical to those of the enantiomeric compound **28**; $[\alpha]^{20}_D$ = 25.5 (c 0.30, $CHCl_3$).

((1′*R*,3′*R*,5′*R*)-1-(6-Amino-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-3-yloxy)methylphosphonic acid sodium salt (*ent*-3): yield 70%; the spectral data were identical to those of the enantiomeric compound **3**; $[\alpha]^{21}_D$ = 43.1 (c 0.51, H_2O).

Synthesis of dDiphosphates. The diphosphates **2**-DP, **3**-DP, and *ent*-**3**-DP were custom-made from the corresponding phosphonate acids by TriLink BioTechnologies, San Diego, CA, following the procedure of Herdewijn et al.[1]

((1′*R*,2′*R*,4′*S*,5′*S*)-4-(6-Amino-9*H*-purin-9-yl)bicyclo[3.1.0]-hexan-2-yloxy)methylphosphonic diphosphoric anhydride lithium salt (2-DP): > 94% purity by AX-HPLC; the ^{1}H NMR spectrum was identical to that of **2**; ^{31}P NMR (D_2O) δ −21.91, −9.64, 10.22; ESI-MS m/z 483.9 (MH^-).

((1′*S*,3′*S*,5′*S*)-1-(6-Amino-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-3-yloxy)methylphosphonic diphosphoric anhydride (free acid, 3-DP): >96.8% purity by AX-HPLC; the ^{1}H NMR spectrum was identical to that of **3**; ^{31}P NMR (D_2O) δ −19.82, −4.50, 9.51; ESI-MS *m*/*z* 491.2 ($MH^- + Li$), 497.2 ($MH^- + Li_2$).

((1′*R*,3′*R*,5′*R*)-1-(6-Amino-9*H*-purin-9-yl)bicyclo[3.1.0]hexan-3-yloxy)methylphosphonic diphosphoric anhydride (free acid, *ent*-3-DP): >88.3% purity by AX-HPLC; the ^{1}H NMR spectrum was identical to that of **3** and *ent*-**3**; ^{31}P NMR (D_2O) δ −22.53, −4.50, 9.46; ESI-MS *m*/*z* 484.9 (MH^-).

X-ray Crystal Structure of (−)-9 and (−)-26. Single-crystal X-ray diffraction data on compounds (−)-**9** and (−)-**26** were collected at 93 and 144 K, respectively, using MoKα radiation and a Bruker APEX 2 CCD area detector. Crystals were prepared for data collection by coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was mounted on a glass rod and transferred immediately to the cold stream on the diffractometer. Corrections were applied for Lorentz, polarization, and absorption effects. The structures were solved by direct methods and refined by full-matrix least-squares on F^2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS Inc., Madison, WI). Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model (coordinate shifts of C applied to H atoms)] with C−H distance set at 0.96 Å. The absolute configuration was set on the basis of the known configuration of the starting material.

The crystal of (−)-**9** was orthorhombic in space group $P2_12_12_1$ with unit cell dimensions $a = 6.6440(5)$ Å, $b = 7.6383(5)$ Å, and $c = 21.5272(15)$ Å. Data were 98.7% complete to 29.19° θ (approximately 0.73 Å) with an average redundancy of 7.02. (−)-**9** crystallized with a single molecule in the asymmetric unit.

The crystal of (−)-**26** was monoclinic in space group *C*2 with unit cell dimensions $a = 29.496(6)$ Å, $b = 8.2267(18)$ Å, $c = 10.584(2)$ Å, and $\beta = 108.523(5)°$. Data were 97.8% complete to 29.60° θ (approximately 0.73 Å) with an average redundancy of 4.07. (−)-**26** crystallized with two molecules in the asymmetric unit plus three molecules of solvent (water). One molecule was disordered over two positions with a ratio of approximately 60:40, and one water molecule sits on a special position resulting is disorder of the solvent.

Atomic coordinates for compounds (−)-**9** and (−)-**26** have been deposited with the Cambridge Crystallographic Data Centre (deposition nos. 794726 and 794727).

Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44(0)-1223−336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of new compounds; complete crystallographic data on compounds (−)-**9** and (−)-**26**, including crystal data and structure refinement, atomic coordinates, bond lengths and angles, anisotropic displacement parameters, hydrogen coordinates and isotropic displacement parameters, torsion angles, and hydrogen bonds (Tables 1−14); corresponding X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.