Stereoselective Synthesis of Novel Types of Cyclopropyl Carbocyclic Nucleosides Containing Quaternary Stereogenic Centers

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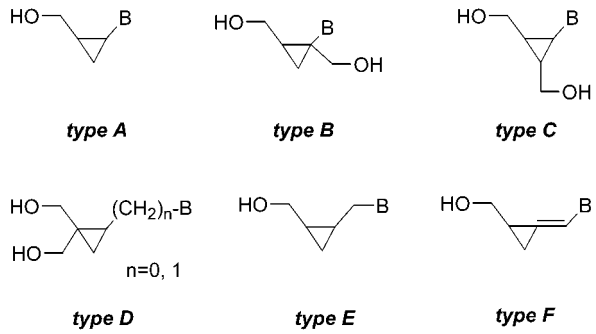
Versatile and stereocontrolled synthetic entries to novel types of cyclopropyl carbocyclic nucleosides are described. The target products have been synthesized from suitable cyclopropane precursors obtained, in turn, from olefinic compounds derived from D-glyceraldehyde as a chiral precursor. Selective manipulation of the functional groups has allowed the preparation of enantiopure nucleosides, some of them displaying opposite chirality. All these molecules contain a quaternary stereogenic carbon at C-1 or C-3 of the cyclopropane ring and bear an amino, a hydroxymethyl, or a methyl group as an additional substituent. In one instance, thymine is directly linked to the cyclopropane. A methylene unit serves as the spacer in the other synthesized nucleosides.

Introduction

The discovery of the potent antileukemic (−)-arysteromycin,[1] a naturally occurring nucleoside analogue in which a methylene group has replaced the ring oxygen atom, marked a new field in synthetic and bio-organic chemistry. In general, carbocyclic nucleosides are more resistant to enzymatic hydrolysis and degradation than classic nucleosides, and this property confers on them a promising usefulness in the search for new therapeutic agents. Several natural or designed carbocyclic nucleosides have shown, indeed, antineoplasic or antiviral activity, and these properties have stimulated synthetic chemists to develop new and efficient methods to prepare novel nucleosides in order to test their biological activities.[2] Thus, different sized carbocyclic nucleosides containing cyclohexane, cyclopentane, cyclobutane, or cyclopropane rings have been prepared. Regarding the cyclopropyl derivatives, several structural modifications have been made in order to improve or enhance the antiviral activity found for some of them. Chart 1 summarizes the most significant structural types of cyclopropyl carbocyclic nucleosides described by other authors.

One of the most usual modifications is the incorporation of a second hydroxymethyl group, either in a geminal position at C-3 (type B) or C-1 (type D) of the cyclopropane ring or in a vicinal position at C-2 (type C).[3] A new compound of type B has been prepared showing an antiviral activity 40 times more potent and better selectivity than acyclovir.[4] Moreover, the inclusion of other substituents such as halogen atoms has also been considered.[5] The introduction of spacers, i.e., additional CH_2 units between the heterocyclic base[6] or the hydroxymethyl group at C-1[7] and the cyclopropane, has also been investigated. Spacered cyclopropyl nucleosides of types D ($n = 1$) and E are more flexible than those of type A avoiding the high rigidity that seems to be unfavorable either for the interaction with phosphorylating enzymes or for interaction of the corresponding triphosphate with viral DNA polymerases.[8] Very recently, methylenecyclopropane analogues of purine nucleosides (type F) have been described as potent antiviral agents of broad selectivity.[9]

Chart 1



Therefore, the acknowledgment of the interest of these products has prompted chemists to develop synthetic

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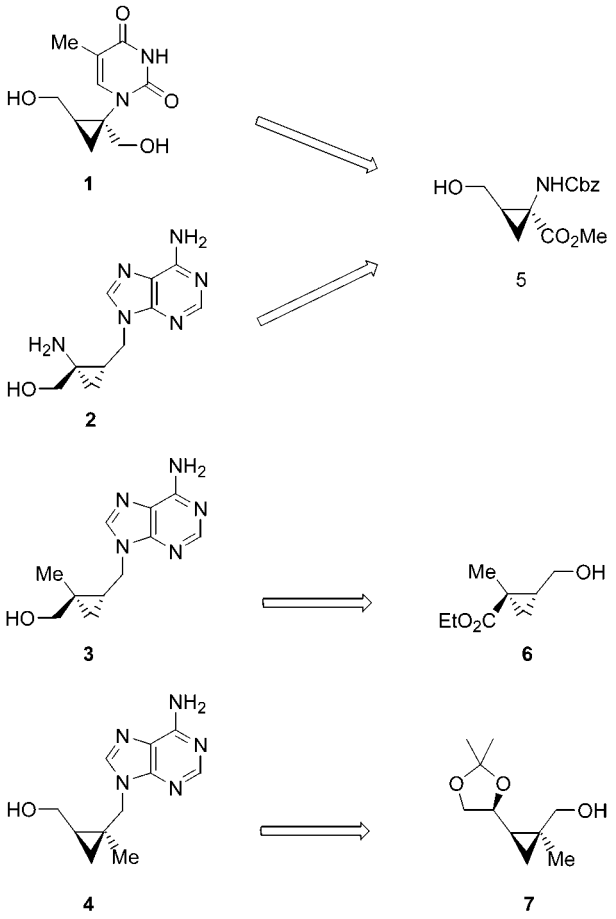
Scheme 1



approaches leading to different kinds of cyclopropyl nucleosides, in enantiomerically pure form or as racemates.[3−7,9,10] However, the protocols employed usually involve long synthetic sequences and cyclopropanation methods that often display low stereoselectivity.

We describe in this paper the easy and efficient stereoselective syntheses of the new cyclopropyl nucleosides **1**−**4** (Scheme 1). The synthetic strategy is based on the selective manipulation of functional groups starting from suitable cyclopropane derivatives and it provides a versatile entry to several types of nucleosides with different substituents and with controlled stereochemistry. The four compounds **1**−**4** bear a *gem*-disubstitution at C-1 (compounds **2** and **3**) or at C-3 (compounds **1** and **4**). In **2**, such a substitution contains a *β*-amino alcohol function. Furthermore, whereas the base is directly linked to the cyclopropane in **1**, adenine is spacered from the carbocyclic ring by a methylene group in **2**−**4**. It is noteworthy that chirality of **1** and **4** is opposite at C-3 with respect to **2** and **3**. Moreover, in **2** and **3**, the hydroxymethyl group and the base are in a trans disposition. The cyclopropane derivatives **5**−**7** are the key precursors to the target molecules, and they have been synthesized, in turn, through the highly stereoselective cyclopropanation of convenient chiral olefins prepared from D-glyceraldehyde acetonide, which is the primary source of chirality.

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Results and Discussion

(−)-(*Z*)-2,3-Methanohomoserine, **5**, previously synthesized in our laboratory on a multigram scale,[11] is the common precursor to nucleosides **1** and **2** that display different chirality. The synthetic routes leading to these products are shown in Scheme 2. The strategies to introduce the heterocyclic base are different. For **1**, the thymine ring is constructed around an amino group already present in the precursor **5**. In contrast, in the synthesis of **2** the introduction of the adenine core involves the nucleophilic displacement of mesylate from the intermediate **12**.[12]

For the synthesis of **1**, the methyl ester **5** was reduced with $LiBH_4$ to afford diol **8**,[13] which was protected as a TBDMS diether. Then, the amine was deprotected by hydrogenolysis of the benzyl carbamate, in the presence of $Pd(OH)_2$ on charcoal as a catalyst, to afford compound **10**. Creation of the thymine heterocycle was accomplished according to the standard methodology[14] through the reaction of **10** and 3-methoxy-2-methylacryloyl isocyanate. This reagent was generated in situ from 3-methoxy-2-methylacryloyl chloride and silver isocyanante. Cyclization of the acryloyl urea to the thymine ring and deprotection of diol was achieved in one single step by treatment of **11** with 0.2 M HCl to afford nucleoside **1** in 16% overall yield from **5**.

The synthetic route for nucleoside **2** involved mesylation of alcohol **5** to give **12**, which was reacted with adenine in the presence of K_2CO_3 and 18-crown-6 in DMF as a solvent, at 80 °C for 10 h, to provide isomer-free compound **13** in 47% yield. The N-9-alkylated derivative was produced as the major compound along with the N-7 regioisomer (85:15 ratio) when NaH was used as a base even in the presence of a crown ether. The structures were assigned by ^1H and ^{13}C NMR and by comparison of the spectra with those of similar compounds in the literature.[15] The structural homogeneity of **13** was assessed by TLC and by its ^{13}C NMR spectrum showing one only set of signals. Finally, subsequent reduction of the methyl ester to give **14** followed by catalytic hydrogenation of the Cbz protecting group afforded nucleoside **2** in 27% overall yield from **5**. UV of **2** (λ_{max} 256, ϵ 14 000) compares well with that of adenosine (λ_{max} 260, ϵ 15 000) in good agreement with the structure of the N-9 regioisomer.

The synthesis of nucleoside **3** is outlined in Scheme 3. Cyclopropanation of (*E*)-pentenoate **15** and subsequent hydrolysis of the acetonide provided compound **16**, as previously described by us.[16] Cleavage of the diol by the action of $NaIO_4$ afforded aldehyde **17** that was reduced to alcohol **6**. This product is the key intermediate in the preparation of **3**. Reaction of **6** with mesyl chloride in the presence of triethylamine gave a mesylate that was made to react with adenine under the conditions described above. In this way, compound **18** was obtained in 55%

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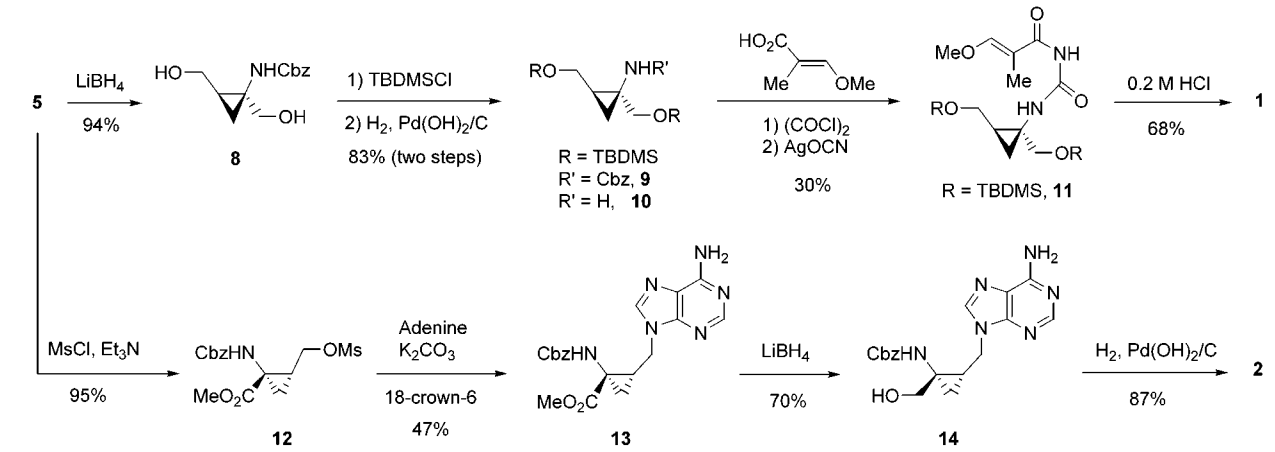
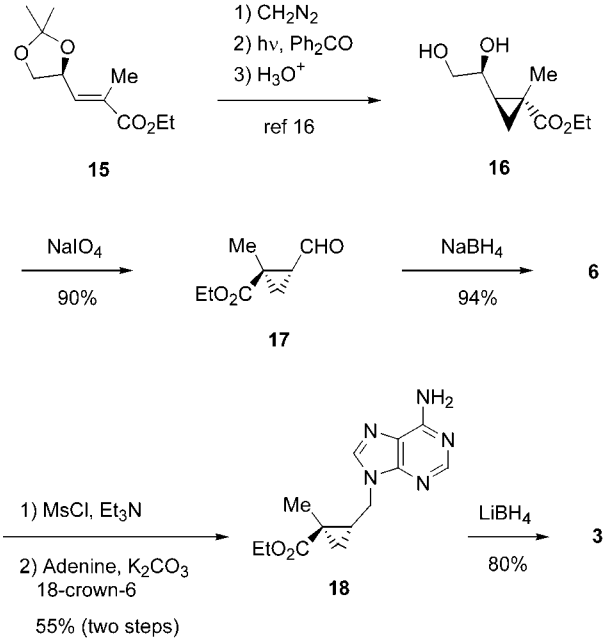
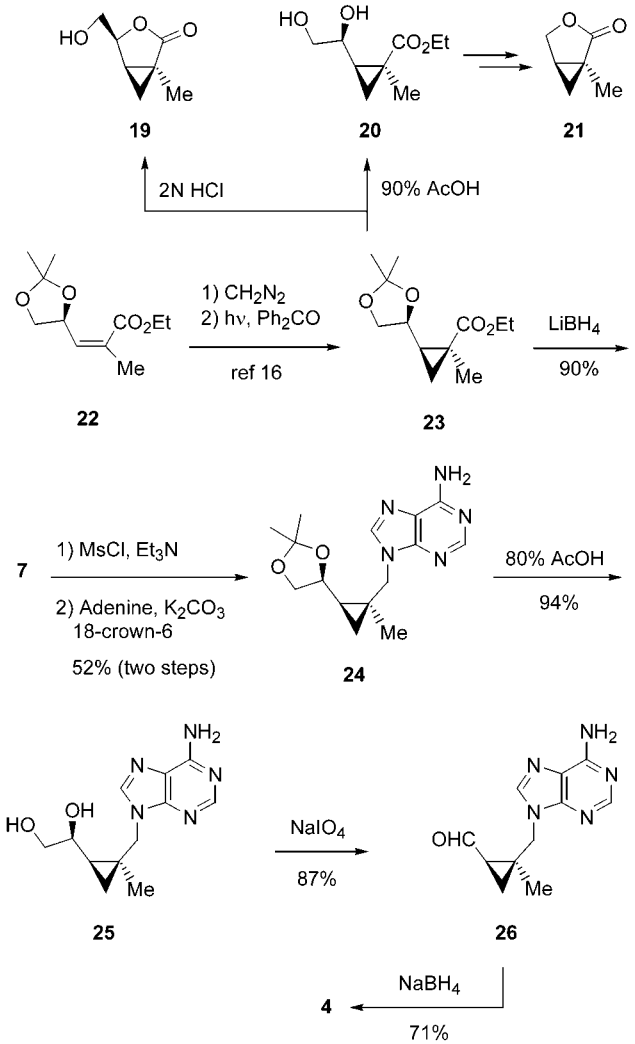
Scheme 2



Scheme 3



Scheme 4



yield for the two steps. Reduction of the methyl ester with $LiBH_4$ furnished nucleoside **3** in 37% overall yield from diol **16**.

The synthesis of nucleoside **4** was envisioned from (*Z*)-pentenoate **22** (Scheme 4). Following the methodology of our laboratory, cyclopropane **23** was obtained in 65% yield.[16] The order of manipulation of the functional groups was crucial for success. Thus, starting from **23**, attempts to transform the diol function into a hydroxymehyl group failed in the deprotection step since hydrolysis of the acetonide with 2 M HCl led to lactone **19**. The use of 90% acetic acid allowed the preparation of diol **20** without cyclization. Nevertheless, lactone **21** was obtained after oxidative cleavage of **20** and subsequent reduction of the resulting aldehyde.[17] Lactones **19** and **21** remained unaltered under several reaction conditions, being unsuitable to achieve the synthetic goal. Therefore, the methyl ester in **23** was reduced to the primary alcohol **7**, and then the adenine core was introduced as described above for the synthesis of **2** and **3**. From compound **24**, the synthesis of **4** was successfully achieved through hydrolysis of the ketal and oxidation of the resultant diol **25** to aldehyde **26**. Subsequent reduction with $NaBH_4$ to alcohol led to nucleoside **4** in 26% yield from precursor **23**.

In conclusion, we have synthesized several types of nucleosides, in enantiomerically pure form, from easily available cyclopropane derivatives. The synthetic routes presented herein involve simple chemical transformations of functional groups, and they are also useful for

(17) For a very related case, see: Martín-Vilà, M.; Hanafi, N.; Jiménez, J. M.; Álvarez-Larena, A.; Piniella, J. F.; Branchadell, V.; Oliva, A.; Ortuño, R. M. *J. Org. Chem*. **1998**, *63*, 3581.

the preparation of nucleosides containing bases other than adenine and thymine. The antiviral and the antitumoral biological activities of the synthesized products is being investigated and results will be published elsewhere.

Experimental Section

Flash column chromatography was carried out on silica gel (240−400 mesh) or on Baker silica gel (400 mesh) for acid-sensitive products. Melting points were determined on a hot stage apparatus and are uncorrected. Distillation of small amounts of material was effected in a bulb-to-bulb distillation apparatus, with oven temperatures (ot) being reported. Signals in IR spectra are reported in cm^{-1}. In 250-MHz ^1H and in 62.5-MHz ^{13}C NMR spectra, chemical shifts are given on the δ scale. Coupling constants (J) are given in Hz. Electron impact mass spectra were recorded at 70 eV.

(1*S*,2*R*)-1-*N*-Benzyloxycarbonylamino-1,2-bis(*tert*-butyldimethylsilyloxymethyl)cyclopropane, 9. DMAP (1.1 g, 9.3 mmol) and *tert*-butyldimethylsilyl chloride (0.9 g, 4.6 mmol) were successively added to a stirred and ice-cooled solution of diol **8**[13] (390 mg, 1.5 mmol) in anhydrous dichloromethane under nitrogen atmosphere. After 5 min, the mixture was stirred at rt for 15 h. Then solvent was removed at reduced pressure, and the residue was chromatographed on Baker silica (2:1 hexanes−ether) to afford 0.7 g (89% yield) of diether **9** as an oil: $[\alpha]_D$ +21.6 (*c* 1.80, $CHCl_3$); IR (film) 3500−2900 (broad), 1733, 1494, 1468, 1255, 1223; ^1H NMR ($CDCl_3$) −0.01 (s, 6H), 0.04 (s, 6H), 0.76 (m, 1H), 0.84 (s, 9H), 0.87 (s, 9H), 0.96, (m, 1H), 1.26 (m, 1H), 3.30 (d, J = 10.2, 1H), 3.39 (dd, J = 10.9, J' = 9.5, 1H), 3.91 (complex absorption, 2H), 5.06 (s, 2H), 5.50 (broad s, 1H), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) −5.46, −5.37, −5.14, 15.47, 18.18, 18.27, 23.36, 25.92, 38.50, 63.52, 66.12, 66.35, 127.94, 128.44, 136.67, 156.58. Anal. Calcd for $C_{25}H_{45}NO_4Si_2$: C, 62.58, H, 9.45, N, 2.92. Found: C, 62.66; H, 9.53; N, 2.95.

(1*S*,2*R*)-1-Amino-1,2-bis(*tert*-butyldimethylsilyloxymethyl)cyclopropane, 10. Carbamate **9** (300 mg, 0.6 mmol) in MeOH (10 mL) was hydrogenated under 4 atm of pressure for 17 h in the presence of 20% $Pd(OH)_2/C$ (27 mg). The mixture was filtered through Celite, and the solvent was removed under reduced pressure. The residue was chromatographed on Baker silica gel to furnish amine **10** (199 mg, 92% yield) as a colorless oil: $[\alpha]_D$ +9.52 (*c* 2.05, $CHCl_3$); IR (film) 3500−2700 (broad); ^1H NMR ($CDCl_3$) 0.02 (s, 6H), 0.03 (s, 6H), 0.38 (dd, J = 5.8, J' = 5.1, 1H), 0.56 (dd, J = 8.4, J' = 5.1, 1H), 0.87 (s, 18H), 0.94 (m, 1H), 2.03 (broad s, 2H), 3.42 (s, 1H), 3.43 (s, 1H), 3.68 (dd, J = 10.9, J' = 8.0, 1H), 3.85 (dd, J = 10.9, J' = 5.1, 1H); ^{13}C NMR ($CDCl_3$) −5.23, −5.11, 15.44, 18.33, 24.30, 25.94, 39.30, 62.68, 71.06. Anal. Calcd for $C_{17}H_{39}NO_2Si_2$: C, 59.07; H, 11.37; N, 4.05. Found: C, 59.28; H, 11.55; N, 4.00.

(1′*S*,2′*R*)-(*Z*)-1-[1′,2′-Bis(dihydroxymethyl)cyclopropyl]-5-methyl-(1*H*)-pyrimidine-2,4-dione, 1. Oxalyl chloride (120 μL, 1.4 mmol) was added dropwise to an ice-cooled and stirred solution of 3-methoxy-2-methylacrylic acid (146 mg, 1.3 mmol) in anhydrous benzene (8 mL). After the mixture was stirred at rt for 1 h, dry silver cyanate (380 mg, 2.5 mmol) was added, and the mixture was heated to reflux for 30 min under nitrogen atmosphere. Then the mixture was cooled to rt and added dropwise to a solution of amine **10** (199 mg, 0.6 mmol) in anhydrous dichloromethane (4 mL), cooled at −78 °C, under nitrogen atmosphere. The resultant mixture was stirred at −78 °C for 30 min and at 0 °C for 3 h. The solvent was removed, and the residue was chromatographed on Baker silica (mixtures of hexanes−ether as eluents) to afford 85 mg (30% yield) of (1′*S*,2′*R*)-(*E*)-1-(3-methoxy-2-methylacryloyl)-3-[1′,2′-bis(*tert*-butyldimethylsilyloxymethyl)cyclopropyl]urea, **11**, as a colorless oil that was identified by its spectroscopic data: IR (film) 3500−3000 (broad), 1689, 1662, 1010; ^1H NMR ($CDCl_3$) −0.02 (s, 6H), −0.03 (s, 6H), 0.68 (dd, J = 6.6, J' = 5.8, 1H), 0.87 (s, 9H), 0.98 (s, 9H), 1.01 (dd, J = 8.8, J' = 5.8, 1H), 1.25 (m, 1H), 1.73 (s, 3H), 3.57−3.76 (complex absorption, 4H), 3.82 (s, 3H), 7.32 (broad s, 1H), 9.04 (broad s, 1H); ^{13}C NMR ($CDCl_3$) −5.24, −5.19, 8.79, 14.88, 18.26, 23.18, 25.93, 25.96, 29.65, 37.93, 61.44, 62.91, 65.36, 106.80, 154.09, 158.35, 168.45.

Compound **11** (85 mg, 0.2 mmol) in (10:1) 0.2 M HCl−EtOH (11 mL) was heated to reflux overnight. The solvents were evaporated to dryness affording a dark and very dense oil which was purified by successive elutions through a C_{18} reversed-phase cartridge (water) and on silica gel (8:1 EtOAc−MeOH) to give the thymine derivative **1** (28 mg, 68% yield): crystals; mp 180−182 °C (MeOH−EtOAc); $[\alpha]_D$ -44.0 (*c* 0.50, MeOH); IR (KBr) 3600−3200 (broad), 1689, 1670; ^1H NMR (methanol-d_4) 0.89 (dd, J = 6.6, J' = 5.8, 1H), 1.20 (dd, J = 9.5, J' = 5.8, 1H), 1.56 (m, 1H), 1.86 (s, 3H), 3.05 (d, J = 11.7, 1H), 3.20−3.43 (complex absorption, 2H), 4.12 (d, J = 11.7, 1H), 7.34 (s, 1H); ^{13}C NMR (D_2O) 12.03, 14.91, 25.47, 49.00, 61.30, 66.17, 111.67, 145.40, 153.78, 167.66. Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.15; H, 6.18; N, 12.57.

Methyl (1*S*,2*R*)-1-*N*-Benzyloxycarbonylamino-2-methanesulfonyloxycyclopropanecarboxylate, 12. Freshly distilled TEA (415 μL, 3.0 mmol) and mesyl chloride (275 μL, 3.0 mmol) were successively added to a stirred and ice-cooled solution of alcohol **5**[11] (415 mg, 1.5 mmol) in dry dichloromethane (10 mL) under nitrogen atmosphere. After the mixture was stirred at 0 °C for 10 min, water (6 mL) was added, and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 6 mL), the combined organic extracts were dried ($MgSO_4$), and solvent was removed at reduced pressure. The residue was chromatographed (2:1 hexanes−EtOAc) to afford mesylate **12** (502 mg, 95% yield): crystals; mp 56−58 °C (EtOAc−pentane); $[\alpha]_D$ −7.7 (*c* 1.30, $CHCl_3$); IR (KBr) 3303 (broad, 1754, 1698; ^1H NMR (acetone-d_6) 1.29 (dd, J = 7.4, J' = 5.4, 1H), 1.66 (dd, J = 9.4, J' = 5.4, 1H), 2.20 (dddd, J = 9.4, J' = 7.4, J'' = 7.3, J''' = 7.1, 1H), 3.09 (s, 3H), 3.65 (s, 3H), 4.21 (dd, J = 11.0, J' = 7.1, 1H), 4.41 (dd, J = 11.0, J = 7.3, 1H), 5.10 (coalescent AB system, J = 11.2, 2H), 7.07 (broad s, 1H), 7.34 (complex absorption, 5H); ^{13}C NMR (acetone-d_6) 20.03, 25.49, 36.49, 38.44, 51.87, 65.98, 68.88, 127.56, 127.74, 128.28, 137.06, 156.91, 171.81. Anal. Calcd for $C_{15}H_{19}NO_7S$: C, 50.41; H, 5.36, N, 3.92; S, 8.97. Found: C, 50.34; H, 5.40; N, 3.90; S, 8.84.

Methyl (1*S*,2*R*)-2-(6-Amino-9*H*-purinylmethyl)-1-(*N*-benzyloxycarbonylamino)cyclopropanecarboxylate, 13. A solution of mesylate **13** (286 mg, 0.8 mmol) in anhydrous DMF (5 mL) was added to a mixture of adenine (113 mg, 0.8 mmol), 18-crown-6 (211 mg, 0.8 mmol), and K_2CO_3 (121 mg, 0.9 mmol) in anhydrous DMF (8 mL) under nitrogen atmosphere. After being stirred at 80 °C for 15 h, the reaction mixture was cooled to rt, brine (15 mL) was added, and extractions with EtOAc (5 × 10 mL) were performed. The combined organic extracts were dried ($MgSO_4$), and solvents were removed at reduced pressure. The residue was chromatographed on silica gel (mixtures of dichloromethane−MeOH as eluents) to afford 149 mg (47% yield) of compound **13** as a colorless oil: $[\alpha]_D$ +10.7 (*c* 0.75, MeOH); IR (film) 3324, 1724, 1644, 1598; ^1H NMR ($CDCl_3$) 1.23 (m, 1H), 1.93 (complex absorption, 2H), 3.59 (s, 3H), 4.07 (dd, J = 14.6, J' = 9.5, 1H), 4.45 (dd, J = 14.6, J' = 2.9, 1H), 5.19 (s, 2H), 6.00 (s, 2H), 7.32−7.39 (complex absorption, 5H), 7.78 (s, 1H), 8.33 (s, 1H), 8.60 (broad s, 1H); ^{13}C NMR ($CDCl_3$) 20.32, 27.83, 38.33, 43.00, 52.65, 66.78, 119.70, 127.79, 127.94, 128.41, 136.61, 140.29, 149.64, 152.73, 155.82, 157.55, 172.40. Anal. Calcd for $C_{19}H_{20}N_6O_4$: C, 57.57; H, 5.09; N, 21.20. Found: C, 57.19; H, 5.31; N, 21.53.

(1*S*,2*R*)-2-(6-Amino-9*H*-purinylmethyl)-1-*N*-benzyloxycarbonylamino-2-hydroxymethylcyclopropane, 14. A 1 M solution of $LiBH_4$ (1.4 mL, 1.4 mmol) was added to a stirred solution of compound **13** (139 mg, 0.4 mmol) in anhydrous THF (10 mL) cooled at −78 °C under nitrogen atmosphere. The resultant mixture was stirred at rt for 20 h. MeOH was then slowly added to destroy excess hydride, and solvents were removed at reduced pressure. The residue was poured into water (6 mL) and ethyl acetate (6 mL), and the layers were separated. The aqueous phase was extracted with EtOAc (5 × 6 mL), the combined organic phases were dried ($MgSO_4$),

and solvent was evaporated. The residue was eluted (water) through a C_{18} reversed-phase cartridge to afford pure alcohol **14** (116 mg, 90% yield): crystals; mp 152−154 °C (MeOH−H_2O); $[\alpha]_D$ +24.0 (*c* 1.00, MeOH); IR (KBr) 3500−2900 (broad), 3329, 1710, 1650, 1601, 1508; ^{1}H NMR (methanol-d_4) 0.83 (dd, $J = 6.6$, $J' = 5.8$, 1H), 1.07 (dd, $J = 9.5$, $J' = 5.8$, 1H), 1.59 (m, 1H), 3.47−3.57 (complex absorption, 2H), 4.25 (d, $J = 7.3$, 2H), 5.05 (s, 2H), 7.31−7.35 (complex absorption, 5H), 8.21 (s, 1H), 8.46 (s, 1H); ^{13}C NMR (methanol-d_4) 15.79, 22.96, 40.82, 44.54, 66.46, 67.60, 119.80, 128.87, 129.03, 129.48, 138.10, 142.64, 149.72, 153.49, 155.62, 159.06. Anal. Calcd for $C_{19}H_{20}N_6O_4$: C, 58.69; H, 5.47; N, 22.18. Found: C, 58.52; H, 5.31; N, 23.01.

(1*S*,2*R*)-2-(6-Amino-9*H*-purinylmethyl)-1-amino-2-hydroxymethylcyclopropane, 2. Working as described above for the hydrogentation of carbamate **9**, pure product **2** was prepared in 87% yield after elution (water) through a C_{18} reversed-phase cartridge: crystals; mp 197−199 °C (MeOH−H_2O); $[\alpha]_D$ +22.5 (*c* 0.80, MeOH); IR (KBr) 3600−2600 (broad), 3329, 1646, 1601, 1515; ^{1}H NMR (methanol-d_4) 0.63 (t, $J = 5.1$, 1H), 0.84 (dd, $J = 9.5$, $J' = 5.1$, 1H), 1.39 (m, 1H), 3.34 (s, 2H), 4.27 (dd, $J = 8.0$, $J' = 7.3$, 1H), 4.45 (dd, $J = 14.6$, $J' = 5.8$, 1H), 8.18 (s, 1H), 8.49 (s, 1H); ^{13}C NMR (methanol-d_4) 15.65, 23.03, 41.14, 44.15, 70.08, 120.10, 142.57, 150.69, 153.68, 157.27. Anal. Calcd for $C_{10}H_{14}N_6O$: C, 51.27; H, 6.02; N, 35.87. Found: C, 51.08; H, 6.28; N, 36.04.

Ethyl (1*R*,2*R*)-2-Hydroxymethyl-1-methylcyclopropanecarboxylate, 6. $NaIO_4$ (884 mg, 4.2 mmol) was added to a stirred and ice-cooled solution of diol **16**[16] (600 mg, 3.2 mmol) in 10:3 THF−H_2O (13 mL), and the resultant mixture was stirred for 10 min. The produced precipitate was filtered off, and most of THF was removed at reduced pressure. Then 5 mL of water was added, and the aqueous solution was extracted with dichloromethane (4 × 10 mL). The combined organic extracts were dried ($MgSO_4$), and solvent was removed to afford ethyl (1*R*,2*R*)-2-formyl-1-methylcyclopropanecarboxylate, **17** (456 mg, 91% yield), as a highly volatile liquid that was identified by their spectroscopic data: $[\alpha]_D$ −231.2 (*c* 1.47, $CHCl_3$); IR (film) 1729, 1708; ^{1}H NMR ($CDCl_3$) 1.21 (t, $J = 7.3$, 3H), 1.39 (s, 3H), 1.46 (dd, J =6.6, $J' = 4.4$, 1H), 1.67 (dd, $J = 8.8$, $J' = 4.4$, 1H), 2.47 (m, 1H), 4.10 (q, $J = 7.3$, 2H), 9.45 (d, $J = 4.4$, 1H); ^{13}C NMR ($CDCl_3$) 13.71, 14.00, 21.39, 29.45, 35.21, 61.32, 172.70, 198.75; MS *m*/*z* 157 (M + 1, 1), 110 (52), 83 (100), 55 (58).

A mixture of **17** (450 mg, 2.9 mmol) and $NaBH_4$ (142 mg, 3.7 mmol) in absolute ethanol (5 mL) was stirred at 0 °C for 20 min. The solvent was evaporated to dryness, the residue was slowly poured into saturated aqueous NH_4Cl (2 mL), and the solution was extracted with dichloromethane (4 × 10 mL). The combined organic phases were dried ($MgSO_4$), and solvent was removed. The residue was chromatographed on silica gel (1:4 hexanes−EtOAc) to afford alcohol **6** as an oil (430 mg, 94% yield): ot 65−70 °C (0.1 Torr); $[\alpha]_D$ −40.5 (*c* 1.08, $CHCl_3$); IR (film) 3718−3064, 1722; ^{1}H NMR ($CDCl_3$) 0.50 (dd, $J = 6.6$, $J = 4.4$, 1H), 1.18 (t, $J = 7.3$, 3H), 1.29 (s, 3H), 1.35 (dd, $J = 8.0$, $J = 4.4$, 1H), 1.74 (m, 1H), 3.46 (dd, $J = 11.7$, J =8.0, 1H), 3.76 (dd, $J = 11.7$, $J' = 5.8$, 1H), 4.05 (q, $J = 7.3$, 2H); ^{13}C NMR ($CDCl_3$) 13.65, 14.06, 20.21, 22.65, 28.33, 60.62, 62.03, 175.61. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.78; H, 8.87.

Ethyl (1*R*,2*R*)-2-(6-Amino-9*H*-purinylmethyl)-1-methylcyclopropanecarboxylate, 18. Following the same protocols as described above for the preparation of **12** and **13**, compound **18** was synthesized from **6** in 55% yield for the two steps: crystals; mp 139−141 °C (CH_2Cl_2−pentane); $[\alpha]_D$ −29.2 (*c* 0.68, $CHCl_3$); IR (KBr) 3276, 1715, 1680, 1609; ^{1}H NMR ($CDCl_3$) 0.73 (dd, J =5.9, $J' = 4.4$, 1H), 1.20 (t, $J = 7.3$, 3H), 1.41 (s, 3H), 1.48 (dd, $J = 9.5$, $J' = 4.4$, 1H), 2.02 (m, 1H), 4.08 (q, $J = 7.3$, 2H), 4.23 (complex absorption, 2H), 5.90 (broad s, 2H), 7.84 (s, 1H), 8.33 (s, 1H); ^{13}C NMR ($CDCl_3$) 14.09, 14.15, 21.15, 23.36, 25.15, 43.18, 61.03, 119.53, 139.67, 150.06, 153.06, 155.53. Anal. Calcd for $(C_{13}H_{17}N_5O_2)\cdot{}^1/_2H_2O$: C, 54.92; H, 6.38; N, 24.63. Found: C, 55.00; H, 6.11; N, 24.48.

(1*R*,2*R*)-2-(6-Amino-9*H*-purinylmethyl)-1-hydroxymethylcyclopropane, 3. To a solution of **18** (200 mg, 0.7 mmol) in anhydrous THF (20 mL) cooled at −78 °C was added a 2 M solution of $LiBH_4$ in THF (1.5 mL, 2.9 mmol) under nitrogen atmosphere. The mixture was allowed to reach rt and then was heated to reflux for 24 h. The reaction mixture was cooled to rt, and MeOH, water, and EtOAc were successively added. Layers were separated, and the aqueous phase was extracted with EtOAc (6 × 10 mL). The combined organic phases were dried ($MgSO_4$), and solvents were removed at reduced pressure to afford **3** (136 mg, 80% yield). The analytical sample was prepared by further purification on preparative TLC (9:1 dichloromethane−MeOH): crystals; mp 147−150 °C (MeOH−CH_2Cl_2−pentane); $[\alpha]_{280}$ +2217.9 (*c* 1.32, MeOH); IR (KBr) 3349 (broad), 1667, 1614; ^{1}H NMR (methanol-d_4) 0.51 (t, $J = 5.0$, 1H), 0.83 (dd, $J = 8.8$, $J' = 5.0$, 1H), 1.34 (s, 3H), 1.42 (m, 1H), 3.29 (d, $J = 11.1$, 1H), 3.52 (d, $J = 11.1$, 1H), 4.35−4.38 (m, 2H), 8.42 (s, 1H), 8.57 (s, 1H); ^{13}C NMR (methanol-d_4) 13.99, 14.74, 20.21, 22.40, 43.62, 69.47, 118.36, 140.60, 150.75, 151.93, 155.60; HRMS calcd for $C_{11}H_{15}N_5O$ (M) 233.1277, found 233.1287; calcd for $C_{11}H_{14}N_5$ (M − OH) 216.1249, found 216.1233.

(1*S*,2*R*,4′*S*)-1-Methyl-2-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)hydroxymethylcyclopropane, 7. Compound **23**[16] was reduced, according to the same procedure as described above for the reduction of **18**, to afford alcohol **7** in 90% yield: oil; ot 60−70 °C (0.01 Torr); $[\alpha]_D$ −29.4 (*c* 1.22, $CHCl_3$); IR (film) 3113−3716; ^{1}H NMR ($CDCl_3$) 0.57 (t, $J = 5.2$, 1H), 0.66 (dd, $J = 8.1$, $J' = 4.8$, 1H), 0.82 (m, 1H), 1.13 (s, 3H), 1.32 (s, 3H), 1.41 (s, 3H), 3.39 (d, $J = 11.3$, 1H), 3.62−3.73 (complex absorption, 2H), 3.84 (m, 1H), 4.12 (dd, $J = 7.9$, $J' = 5.7$, 1H); ^{13}C NMR ($CDCl_3$) 16.35, 22.18, 22.63, 25.75, 26.46, 26.77, 66.91, 70.04, 77.18, 108.61. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.29; H, 9.74.

(1*S*,2*R*,4′*S*)-2-(6-Amino-9*H*-purinylmethyl)-1-(2′,2′-dimethyl-1′,3′-dioxolan-4′-yl)-2-methylcyclopropane, 24. Following the same procedures as described above for the preparation of **12** and **13**, compound **24** was synthesized in 52% yield for the two steps: crystals; mp 153−155 °C (MeOH−CH_2Cl_2−pentane); $[\alpha]_D$ −13.3 (*c* 0.75, $CHCl_3$); IR (KBr) 1667, 1595, 1579; ^{1}H NMR ($CDCl_3$) 0.74 (dd, $J = 7.5$, $J' = 3.8$, 1H), 0.91−1.03 (complex absorption, 2H), 1.01 (s, 3H), 1.36 (s, 3H), 1.42 (s, 3H), 3.65 (t, $J = 7.7$, 1H), 4.06−4.25 (complex absorption, 3H), 4.38 (d, $J = 14.3$, 1H), 5.84 (broad s, 2H), 7.89 (s, 1H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$) 16.20, 20.86, 23.25, 25.82, 26.66, 27.23, 47.72, 70.14, 74.95, 109.28, 119.29, 140.40, 150.52, 152.96, 155.52. Anal. Calcd for $C_{15}H_{21}N_5O_2$: C, 59.39; H, 6.98; N, 23.09. Found: C, 59.44; H, 7.23; N, 23.28.

(1*S*,2*R*,1′*S*)-2-(6-Amino-9*H*-purinylmethyl)-1-(1′,2′-dihydroxyethyl)-2-methylcyclopropane, 25. A solution of compound **24** (181 mg, 0.6 mmol) in 80% acetic acid (10 mL) was stirred at rt for 24 h and then evaporated to dryness under reduced pressure. The residue was purified by elution (MeOH) through a C_{18} reversed-phase cartridge to afford diol **25** (146 mg, 94% yield) as a foam unsuitable for microanalysis: $[\alpha]_D$ +4.3 (*c* 2.34, $CHCl_3$); IR (film) 3320, 3177 (broad), 1647, 1600; ^{1}H NMR (methanol-d_4) 0.72 (dd, $J = 8.4$, $J' = 4.7$, 1H), 0.97−1.14 (complex absorption, 2H), 1.06 (s, 3H), 3.64−3.76 (complex absorption, 3H), 4.19 (d, $J = 14.3$, 1H), 4.61 (d, $J = 14.3$, 1H), 8.28 (s, 1H), 8.29 (s, 1H); ^{13}C NMR (methanol-d_4) 16.14, 21.28, 22.50, 28.70, 48.25, 66.92, 71.61, 118.70, 141.85, 150.14, 152.67, 156.27; MS *m*/*z* 263 (M, 2), 246 (4), 232 (30), 202 (10), 136 (100), 108 (27).

(1*R*,2*S*)-2-(6-Amino-9*H*-purinylmethyl)-1-formyl-2-methylcyclopropane, 26. Diol **25** was cleaved according to the same oxidative method as described above for the synthesis of **17**. Thus, aldehyde **26** resulted in 87% yield: crystals; mp 145−148 °C (MeOH−CH_2Cl_2−pentane); $[\alpha]_D$ −128.0 (*c* 0.93, $CHCl_3$); IR (KBr) 1695, 1647, 1600; ^{1}H NMR ($CDCl_3$) 1.11 (s, 3H), 1.18 (dd, $J = 7.9$, $J' = 5.0$, 1H), 1.73 (t, $J = 5.0$, 1H), 2.07 (m, 1H), 4.32 (d, $J = 14.7$, 1H), 4.45 (d, $J = 14.7$, 1H), 5.99 (broad s, 2H), 7.70 (s, 1H), 8.32 (s, 1H), 9.97 (d, $J = 3.0$, 1H); ^{13}C NMR ($CDCl_3$) 22.57, 22.60, 31.34, 35.26, 45.34, 119.17, 140.25, 150.39, 152.92, 155.68, 200.66; HRMS Calcd for $C_{11}H_{13}N_5O$ (M) 231.1120, obsd 231.1116; calcd for $C_{11}H_{13}N_3O$ (M − NH_2) 203.1059, obsd 203.1085.

(1*R*,2*S*)-2-(6-Amino-9*H*-purinylmethyl)-2-methylhydroxymethylcyclopropane, 4. The reduction of **26** was

achieved following the same procedure as described above for the synthesis of **6**. Thus, nucleoside **4** was prepared in 71% yield: crystals; mp 200−201 °C (MeOH−CH_2Cl_2−pentane); $[\alpha]_{300}$ −117.8 (*c* 0.14, MeOH); IR (KBr) 3502−2727 (broad), 1681, 1614, 1571; ^{1}H NMR (methanol-d_4) 0.72 (m, 2H), 1.02 (s, 3H), 1.27 (m, 1H), 3.67 (dd, J = 12.0, J' = 9.7, 1H), 4.08 (dd, J = 12.0, J' = 5.2, 1H), 4.39 (m, 2H), 8.28 (s, 1H), 8.42 (s, 1H); ^{13}C NMR (methanol-d_4) 15.20, 20.76, 21.92, 27.81, 46.97, 61.67, 118.77, 142.48, 149.87, 152.55, 156.35; HRMS calcd for $C_{11}H_{15}N_5O$ (M) 233.1277, obsd 233.1282; calcd for $C_{10}H_{12}N_5$ (M − CH_2OH) 202.1093, obsd 202.1097.

(1*S*,5*R*,4*S*)-4-Hydroxymethyl-1-methyl-3-oxabicyclo-[3,1,0]hexan-2-one, 19. A solution of acetonide **23** (94 mg, 0.4 mmol) in 3 mL of 2 N HCl was stirred at rt for 1.5 h and then diluted with EtOH, and solvents were removed under reduced pressure. The residue was chromatographed on silica gel (1:4 hexane/EtOAc) to afford pure **19** (45.5 mg, 78% yield): crystals; mp 67−70 °C (EtOAc−pentane); $[\alpha]_D$ −79.4 (*c* 0.71, $CHCl_3$); IR (film) 3494, 3276 (broad), 1778; ^{1}H NMR ($CDCl_3$) 0.93 (dd, J = 7.5, J' = 5.0, 1H), 1.09 (t, J = 4.7, 1H), 1.39 (s, 3H), 2.01 (m, 1H), 2.09 (broad s, 1H), 3.71 (m, 2H), 4.64 (m, 1H); ^{13}C NMR ($CDCl_3$) 14.03, 15.49, 23.70, 24.50, 63.06, 78.35, 177.89. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 58.76; H, 7.14.

Ethyl (1*S*,2*R*,1′*S*)-2-(1′,2′-Dihydroxyethyl)-1-methyl-cyclopropanecarboxylate, 20. Following a similar procedure as described above for **19** but stirring acetonide **23** with 90% AcOH for 4 h, diol **20** was obtained as a yellowish oil (200 mg, 76% yield) whose spectroscopic data follow: IR (film) 3044−3711 (broad), 1722 ^{1}H NMR ($CDCl_3$) 0.87 (dd, J = 8.6, J = 4.5, 1H), 1.09 (m, 1H), 1.19−1.24 (complex absorption, 6H),1.43 (dd, J = 6.8, J = 4.5, 1H), 3.49 (m, 2H), 3.66 (dt, J = 7.2, J' = 3.2, 1H), 4.09 (q, J = 7.2, 2H); ^{13}C NMR ($CDCl_3$) 14.13, 19.57, 21.02, 23.74, 31.82, 61.00, 66.40, 70.35, 174.7.

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Supporting Information Available: Physical constants and spectroscopic data of compounds **11**, **17**, **19**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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