Enantioselective Approach to the Synthesis of Cyclohexane Carbocyclic Nucleosides

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(R)-(−)-Carvone was used as starting material for the synthesis of a new series of 2-(hydroxymethyl)-cyclohexane-1,3-diol nucleosides. The enantioselective precursors of the nucleoside analogues were obtained via a stereo- and regioselective hydroboration reaction. The compounds have equatorial oriented base moieties despite the presence of three other axial substituents.

Introduction

Naturally occurring and synthetic carbocyclic nucleosides are of broad interest as antiviral agents and as building blocks for oligonucleotides.[1,2] Their therapeutic advantages may be attributed to their better chemical and enzymatic stability as well as to their different stereoelectronic properties. The difference is due to the replacement of the ring-oxygen atom by a methylene group and, hence, to the loss of the anomeric center. Compared with the knowledge on five-membered ring carbocyclic nucleosides, little is known about the conformational preference and biological activity of six-membered ring analogues. Recently we synthesized a series of modified nucleosides with general formula **1** (Figure 1).[3] These nucleosides can be considered as carbocyclic congeners of the anhydrohexitol nucleosides **2**.[4] While the latter show potent antiviral activity,[4] the carbocyclic analogues **1** were devoid of this activity.[3] A striking difference between both series is that the base moieties of the anhydrohexitol nucleosides are axially oriented, while the same bases are equatorially oriented in the case of the carbocyclic analogues. To further study this structure−activity relationship, we decided to synthesize cyclohexane nucleosides of type **3**. The additional hydroxyl group may induce an inversion of conformation when compared with compounds of structure **1**. The synthetic strategy should take into account that we should be able to further modify compound **3** in a stereospecific manner. Indeed, compound **3** (where R = H) is achiral but becomes chiral when one of the secondary hydroxyl groups becomes substituted or replaced by, for example, a halogen. The enantioselective approach presented in this work starts from *(R)*-(−)-carvone and

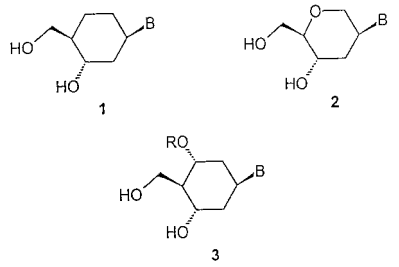
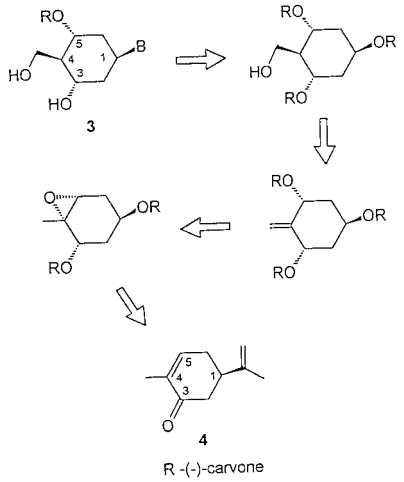


Figure 1.

involves a stereoselective hydroboration of a 2-methylenecyclohexane-1,3-diol with anti-selectivity, a regioselective desilylation reaction, and a Mitsunobu type introduction of heterocyclic rings.

(*R*)-(−)-carvone (**4**, Scheme 1) is an inexpensive and useful chiral starting material, as illustrated by the

Scheme 1



asymmetric synthesis of (−)-hirsutene and its derivatives.[5] Its structural features make it ideally suited for the stereocontrolled synthesis of **3**; i.e., (1) a cyclohexane ring is already present, (2) a chiral center at C1 allows stereospecific introduction of the base moiety via transformation of the isopropenyl substituent into a hydroxyl

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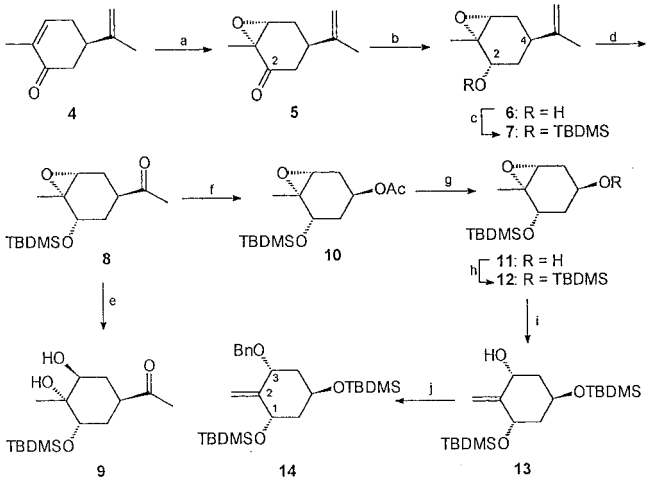
Scheme 2[a]



[a] (a) H_2O_2/NaOH, MeOH, 83%; (b) L-Selectride, THF, −65 °C; (c) TBDMSCl, imidazole, DMF, 93% from **5**; (d) 1% OsO_4/KIO_4, THF, H_2O, rt, 83%; (e) CF_3CO_3H, NaH_2PO_4, CH_2Cl_2, 0 °C, 78%; (f) *m*-CPBA, $CHCl_3$, pH = 8 buffer solution, rt, 73%; (g) K_2CO_3, MeOH, 73%; (h) TBDMSCl, imidazole, DMF, 80%; (i) LiTMP/Et_2AlCl, benzene, 0 °C, 100%; (j) NaH, BnBr, TBAI, THF, rt.

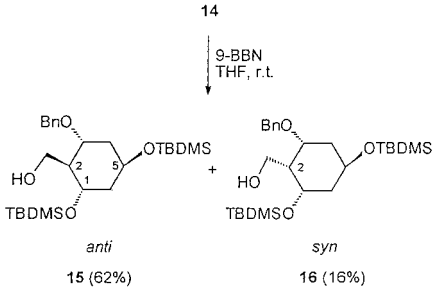
group, subsequent inversion of the configuration, and Mitsunobu reaction, (3) an enone group allows the introduction of a 1,3-diol function with the correct cis stereochemistry via stereoselective epoxidation of the double bond and reduction of the carbonyl group, and (4) a methyl group is present at C4 that can be hydroxylated via regioselective opening of the epoxide to give an exocyclic double bond, followed by hydroboration. However, the success of this approach is crucially dependent on the stereochemical outcome of the latter reaction.

Results and Discussion

Epoxide **5** (Scheme 2) was obtained by a known regio- and stereospecific epoxidation of (*R*)-(−)-carvone (**4**) in 83% yield after distillation.[6] Stereoselective reduction of the carbonyl group to obtain **6** was achieved using L-Selectride in THF at −65 °C.[7] The enantiomeric excess at C2 was more than 90%, as established by ^{1}H NMR analysis, and the minor isomer was easily removed by chromatography. Protection of the hydroxyl group as TBDMS ether under standard conditions[8] gave **7** in 93% combined yield over two steps.

Oxidative degradation of the isopropenyl side chain at C4 with retention of configuration to the corresponding acetate **10** can be carried out by an established procedure[9] involving sequential ozonolysis of the double bond, followed by Criegee rearrangement of the so-obtained methoxy hydroperoxide intermediate. However, the reactivity of the present epoxide moiety and scale limitations of the ozonolysis reaction hampered the preparation

Scheme 3



of larger amounts of **10**. We therefore decided to first convert the isopropenyl double bond to give the corresponding ketone **8** by oxidative C=C bond cleavage using OsO_4 and $NaIO_4$.[10] This reaction could easily be performed on large scale and proceeded in 83% yield. Upon applying Baeyer−Villiger reaction conditions (CF_3CO_3H in the presence of NaH_2PO_4)[11] to **8**, diol **9** was obtained in 78% yield instead of the desired **10**. To avoid epoxide opening, the reaction was repeated under neutral conditions. The oxidation was performed using *m*-CPBA in the presence of a phosphate buffer pH = 8,[12] giving acetate **10** in 73% yield. Hydrolysis of the acetate under basic conditions (Na_2CO_3 in MeOH) gave **11**. The hydroxyl group was protected as TBDMS ether using TBDMSCl and imidazole in DMF to afford **12** in 58% combined yield over two steps. Finally, the desired allylic alcohol intermediate **13** with an exo double bond was obtained in virtually quantitative yield via regioselective opening of epoxide **12** by treatment with LiTMP/Et_2AlCl[13] at −65 °C for 3 h, and the alcohol function was protected as the benzyl ether using BnBr, NaH, and tetrabutylammonium iodide (TBAI)[14] in THF to give **14**. ^{1}H NMR analysis showed the latter to exist in a chair conformation with the C3−OTBDMS and C1−OBn substituents in an equatorial position and the C5−OTBDMS group occupying an axial position.

The utility of the present reaction scheme is largely dependent on the success of the regio- and stereoselective transformation of the exo double bond at C2 of **14** into a *β*-hydroxymethyl group (Scheme 3). Hydroboration of 2-methylenecyclohexanol derivatives is known to proceed with good regioselectivity (with the borane attacking the double bond from the least hindered site), but with poor stereoselectivity.[15] The stereoselectivity for the syn isomer can be increased by the use of catalysts such as $Rh(PPh_3)_3Cl$.[15] However, enhancement of the selectivity for the desired anti isomer has so far not been successful. Hydroboration of 2-methylenecyclohexane-1,3-diol derivatives as **14** has not been studied yet. One would expect that introduction of an additional neighboring

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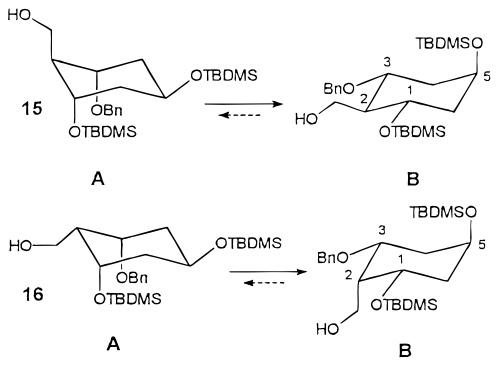


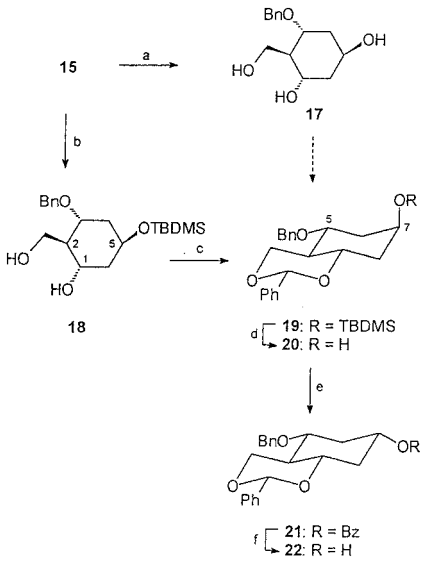
Figure 2.

α-substituent would lead to preferential attack of the borane from the *β*-side and hence to an increase in syn selectivity. Contrary to this expectation, upon treatment of **14** with 9-BBN in THF at room temperature followed by oxidation with hydrogen peroxide, the desired anti isomer **15** was obtained as major product (63% starting from **13**) and the syn isomer **16** as minor compound (16%). To the best of our knowledge, this is the first example of the hydroboration of a 2-methylenecyclohexanediol derivative proceeding with good anti selectivity. Whether the observed preferential attack of the borane on the double bond from the α-side is due either to complexation of the reagent involving the oxygen atoms of the two neighboring groups or to steric hindrance of the bulky OTBDMS group in axial position at C5 is not clear and deserves further investigation. The two diastereomers could easily be separated by chromatography.

Assignment of the relative configuration at C2 of **15** and **16** was accomplished by ^{1}H NMR analysis. The spectrum of **15** showed hydrogen H5 at $\delta = 4.19$ ppm as a pentaplet resulting from four approximately equal coupling constants $^3J_{4,5} = {}^3J_{5,6} \cong 2.4$ Hz and H2 at $\delta =$ 1.68 ppm as a triplet of triplets including two large diaxial coupling constants $^3J_{1,2} = {}^3J_{2,3} \cong 11.0$ Hz. These data are predictive for a chair conformation **B** (Figure 2) with the C2-CH_2OH group in an equatorial position and anti to the substituents at C1 and C3. On the other hand, the spectrum of **16** showed H5 at $\delta = 4.14$ ppm as a pentaplet with $^3J_{4,5} = {}^3J_{5,6} \cong 3.2$ Hz and H2 at $\delta =$ 2.61 ppm as a pentaplet resulting from four medium coupling constants $^3J_{1,2} = {}^3J_{2,3} \cong 5.5$ Hz. These data equally suggest a chair conformation **B,** but with the C2-CH_2OH group axial and syn to the substituents at C1 and C3. This conformation avoids steric clashs between the C1-OTBDMS and the C3-OBn groups. Thus, both isomers seem to exist in solution predominantly in a chair conformation with the C5-OTBDMS in an axial position.

After having obtained the key intermediate **15**, the further synthetic strategy leading to the target compounds is the formation of a cyclic acetal, inversion of the configuration at C7, and introduction of the base moieties via Mitsunobu type reaction (Scheme 4). When **15** was treated with excess TBAF[8] in THF, to simultaneously deprotect the hydroxyl groups at C1 and C5, the reaction proved quite sluggish and triol **17** was isolated in low yield. Increasing the amount of TBAF and prolonging the reaction time did not improve the yield. We, therefore, decided to deprotect the C1 and C5 hydroxyl group in a stepwise manner and we expected the axially oriented C5-OTBDMS group to be more reactive than the C1-OTBDMS group occupying an

Scheme 4[a]



[a] (a) TBAF (excess), THF, rt, 32%; (b) TBAF (1 equiv), THF, rt, 93%; (c) $PhCH(OMe)_2$, PTSA, dioxane, 90%; (d) TBAF, THF, 93%; (e) benzoic acid, DEAD, PPh_3, dioxane; (f) K_2CO_3, MeOH, 72% from **20**.

equatorial position. However, when **15** was treated with 1 equiv of TBAF in THF at room temperature for 3 h, diol **18** was isolated in 93% yield as the sole product, the equatorial TBDMS group thus having been removed much faster. This is probably due to neighboring group participation of the C2-CH_2OH group through intramolecular hydrogen bond formation which accelerates the cleavage of the Si−O bond upon attack by fluoride anion (Figure 3).

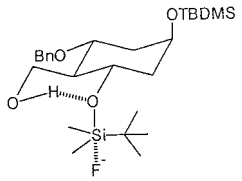


Figure 3.

The structure of **18** was confirmed by ^{1}H NMR in DMSO-d_6. The signal at $\delta = 4.52$ ppm appears as a doublet with $J = 5.1$ Hz (attributed to the C1-OH substituent). Upon irradiation of H5 the signal remained unchanged, while irradiation of H1 resulted in the collapse of the signal to a singlet.

Diol **18** was then protected as cyclic benzylidene acetal by treatment with benzaldehyde dimethyl acetal[16] in 1,4-dioxane in the presence of PTSA as a catalyst to give **19** as a single isomer in 90% yield. The formation of **19** delivers additional proof for the structure of the starting diol **18**. Cleavage of the C7-OTBDMS group using TBAF in THF now proceeded smoothly and afforded alcohol **20** (93%). The configuration of **20** was additionally verified by X-ray analysis (Figure 4). It showed the trans-fused cyclohexane and 1,3-dioxane rings both to exist in a chair conformation, with the C7-OH in an axial position and the C5-OBn substituent in an equatorial position. These results confirmed the configuration as established above

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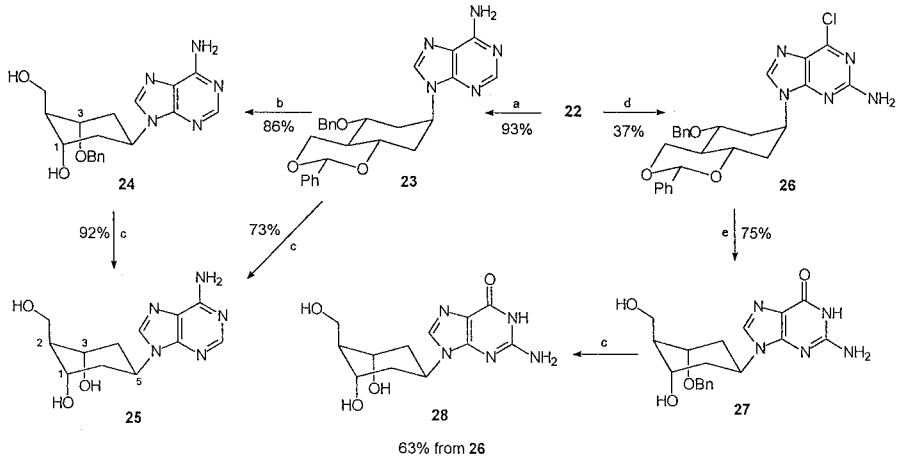
Scheme 5[a]



[a] (a) adenine, DEAD/PPh_3, dioxane, rt; (b) 80% HOAc, 60 °C; (c) $Pd(OH)_2$/C, cyclohexene, MeOH, reflux; (d) chloro-2-aminopurine, DEAD/PPh_3, dioxane, rt; (e) CF_3COOH/H_2O (3:1), rt.

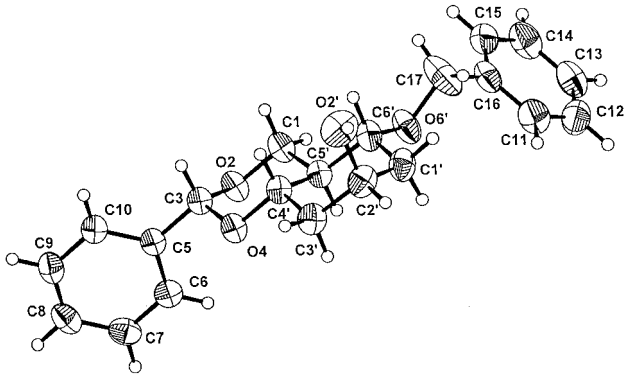


Figure 4. Molecular structure with atom labeling scheme. Displacement ellipsoids are plotted at the 40% probability level. H atoms are drawn as small circles of arbitrary radius.

for **15**. It further showed the single isolated isomer of the benzylidene acetal **20**, with the phenyl group in an equatorial position, to be the thermodynamically more stable compound.

The inversion of the configuration at C7 was accomplished by treatment of **20** with DEAD and PPh_3 in 1,4-dioxane in the presence of PhCOOH,[17] followed by base-catalyzed hydrolysis. This afforded the α-alcohol **22** in 78% combined yield. The α-configuration at C7 was confirmed by comparison of the ^{1}H NMR spectra of **20** and the benzoate intermediate **21**. The equatorial hydrogen H7 in **20** appeared at $\delta = 4.34$ ppm as a poorly resolved multiplet with $\sum^3J = 18$ Hz as a result of four equatorial−equatorial and equatorial−axial coupling constants of ±4.5 Hz with the hydrogens on C6 and C8. However, in **21** the signal for H7 appeared at $\delta = 5.06$ ppm as a triplet of triplets including two large diaxial coupling constants of 11.7 Hz, indicating the axial position of H7 and thus the α-configuration at C7.

Finally, introduction of the adenine and guanine bases in the β-position at C7 was accomplished using a second Mitsunobu type reaction (Scheme 5). Upon treatment of alcohol **22** with adenine base in the presence of DEAD and PPh_3, **23** could be isolated. Subsequent acid hydrolysis of the benzylidene acetal using 80% HOAc, followed by careful chromatographic purification, gave pure adenine derivative **24** in 70% combined yield over the two steps. The guanine derivative **27** was obtained in a similar way, i.e., reaction of **22** with 2-amino-6-chloropurine under Mitsunobu type conditions, followed by treatment with $CF_3COOH-H_2O$ 3:1[18] at room temperature for 4 days. These acidic conditions converted the 2-amino-6-chloropurine base into a guanine and simultaneously hydrolyzed the benzylidene acetal. Pure **27** was isolated in a moderate yield (27% starting from **22**). The chiral nucleoside derivatives **24** and **27**, with a free C1-OH and a protected C3-OH, are valuable precursors for the synthesis of a variety of chiral six-membered carbocyclic nucleosides containing, for example, a double bond, an epoxide ring, a fluorine substituent, or with altered stereochemistry.

To be able to evaluate the above adenine and guanine derivatives for their antiviral activity and to study their conformation in solution, the benzyl group of **24** and **27** was removed by hydrogenolysis using $Pd(OH)_2$ on carbon and cyclohexene[19] in MeOH to give the free triol **25** and **28**, respectively. Applying the same reaction conditions directly to **23** resulted in the simultaneous removal of the acetal and benzyl functions and equally resulted in the formation of **25**. Upon removal of the benzyl group the chirality is lost and **25** and **28** are achiral, possessing a plane of symmetry. This facilitated their conformational analysis by ^{1}H NMR, which led to a remarkable result. Indeed, in the spectrum recorded in DMSO-d_6 as solvent, H5 of **25** appeared at $\delta = 4.98$ ppm as a triplet of triplets with two large diaxial coupling constants $^3J_{4a,5} \cong {}^3J_{5,6a} = 9.3$ Hz and two small axial equatorial coupling constants $^3J_{4e,5} \cong {}^3J_{5,6e} = 4.5$ Hz. The protons H1 ≡ H3 appeared at $\delta = 3.92$ ppm as a triplet of doublets with coupling constants $^3J_{1,6e} \cong {}^3J_{1,6a} = 3.7$ Hz and $^3J_{1,2} = 5.2$ Hz. From this it can be concluded that **25** exists predominantly in a chair conformation with the adenine base at C5 in an equatorial position, at the expense of three axial substituents at C1, C2, and C3. A similar observation was made for the guanine derivative **28**.

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Conclusion

We have successfully developed an enantioselective approach to the synthesis of six-membered carbocyclic nucleosides starting from (*R*)-(−)-carvone. The key steps involve the regio- and stereoselective hydroboration of the double bond of a 2-methylenecyclohexane-1,3-diol derivative and the introduction of the base, illustrated using adenine and guanine, via Mitsunobu reaction. The so-obtained achiral nucleosides **25** and **28** (Scheme 5) showed no antiviral activity,[20] which confirms the previously reported observation that an axially oriented base moiety is a prerequisite for this activity.[4] The chiral precursors **24** and **27**, with differently substituted hydroxyl groups at C1 and C3, are versatile intermediates for the synthesis of other six-membered carbocyclic nucleosides with potential antiviral activity.

Experimental Section

Liquid secondary ion mass spectra (LSIMS) were obtained using glycerol (GLY) or thioglycerol (THGLY) or 3-nitrobenzyl alcohol (NBA) as matrix. High performance liquid chromatography (HPLC) was performed with a Gilson model 303 pump and model 802c manometric module and a Pharmacia LKB-Uvicord SII UV detector with a fixed wavelength (254 nm) or a Waters R400 differential refractometer. Separations were carried out on a Rogel RP column (24 × 2.5 cm) or a Bio-Sil D 90-10 silica column (25 × 1.0 cm). All other analytical methodes were described previously.

(1*R*,4*R*,6*R*)-4-Isopropenyl-1-methyl-7-oxabicyclo[4.1.0]-heptan-2-one (5). To a solution of (*R*)-(−)-carvone (**4**, 50 g, 0.33 mol) in MeOH (300 mL) at −15 °C was added dropwise a 35% H_2O_2 aqueous solution (200 mL), followed by addition of a NaOH aqueous solution (6 M, 28 mL) over a period of 1 h. The reaction was stirred at 0 °C for 3 h and poured into ice−water. The mixture was extracted with Et_2O (3×). The combined extracts (600 mL) were washed with brine, dried over Na_2SO_4, and concentrated. The resulting colorless oil was distilled under vacuum (82 °C/0.24 mmHg) to yield **5** (45.28 g, 83%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.70 (s, 3H), 1.89 (ddd, 1H, J = 14.7, 11.0, 1.2 Hz), 2.05 (dd, 1H, J = 17.4, 11.4 Hz), 2.36 (br d, 1H, J = 14.7 Hz), 2.57 (ddd, 1H, J = 17.5, 4.6, 1.3 Hz), 2.71 (m, 1H), 3.42 (dd, 1H, J = 2.0, 1.1 Hz), 4.71 (br s, 1H), 4.78 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.2 (q), 22.6 (q), 30.7 (t), 37.0 (d), 43.8 (t), 60.7 (s), 63.3 (d), 112.4 (t), 148.3 (s), 207.4 (s); LISMS (THGLY + Girard's reagent P) 300 $(M + 134)^+$.

(1*S*,2*S*,4*S*,6*R*)-4-Isopropenyl-1-methyl-7-oxabicyclo[4.1.0]-heptan-2-ol (6). To a solution of **5** (25 g, 0.15 mol) in dry THF (200 mL) under N_2 at −70 °C was added a solution of L-Selectride in THF (1 M, 180 mL, 0.18 mol). During the addition, the reaction temperature should not exceed −65 °C. The reaction was stirred at −70 °C for an additional 1.5 h and treated carefully with NH_4Cl solution. The resulting mixture was warmed to room temperature and stirred overnight. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3×). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (hexanes−EtOAc 5:1, then 1:1) to give crude **6** (30 g) as a light yellow oil which was still contaminated with borane side products. The crude **6** was used directly in the next step without further purification. An analytical sample was obtained by HPLC purification on silica gel column (hexanes−EtOAc 1:1): ^{1}H NMR ($CDCl_3$) δ 0.91 (m, 1H), 1.32 (m, 1H), 1.43 (s, 3H), 1.69 (m, 1H), 1.70 (s, 3H), 2.19 (m, 2H), 2.30 (d, 1H, J = 10.4 Hz, OH), 3.30 (m, 1H), 3.92 (ddd, 1H, J = 10.4, 3.7, 2.2 Hz), 4.68 (s, 1H), 4.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.0 (q), 23.6 (q), 32.1 (t), 33.6 (d), 37.8 (t), 61.9 (s), 65.2 (d), 70.0 (d), 111.5 (t), 150.0 (s); LISMS (THGLY + NaOAc) 171 $(M + Na)^+$; HRMS calcd for $C_{10}H_{16}O_2Na$ $(M + Na)^+$ 191.1048, found 191.1017.

(1*S*,2*S*,4*R*,6*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-isopropenyl-1-methyl-7-oxabicyclo[4.1.0.]heptane (7). To a solution of the crude **6** (30 g, 0.15 mol) in dry DMF (200 mL) at room temperature were added imidazole (20.4 g, 0.3 mol) and TBDMSCl (27.1 g, 0.18 mol) in portions. The reaction was stirred at room temperature overnight and quenched with crushed ice. The resulting mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (hexanes−EtOAc 10:1) to afford **7** (39.52 g, 93%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.92 (s, 9H), 1.32 (s, 3H), 1.46−1.73 (m, 2H), 1.73 (s, 3H), 1.84 (ddd, 1H, J = 14.0, 6.5, 3.5 Hz), 2.05 (dd, 1H, J = 14.0, 5.5 Hz), 2.33 (m, 1H), 3.10 (dd, 1H, J = 3.5, 1.2 Hz), 3.93 (dd, 1H, J = 6.5, 5.5 Hz), 4.63 (s, 1H), 4.80 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −4.7 (q), −4.4 (q), 17.9 (s), 20.9 (q), 21.5 (q), 25.7 (q), 29.0 (d), 33.6 (t), 35.1 (t), 59.1 (s), 60.6 (d), 69.1 (d), 109.4 (t), 148.0 (s); LISMS (THYLY + NaOAc) 305 $(M + Na)^+$; HRMS calcd for $C_{16}H_{30}O_2$-Na $(M + Na)^+$ 305.1913, found 305.1887.

(1*S*,2*S*,4*R*,6*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-acetyl-1-methyl-7-oxabicyclo[4.1.0.]heptane (8). To a mixture of **7** (23.5 g, 0.083 mol) in THF (200 mL) and water (200 mL) at room temperature was added a 1% OsO_4 aqueous solution (24 mL). After stirring for 30 min, KIO_4 (48 g, 0.20 mol) was added in portions. The resulting mixture was stirred vigorously at room temperature for 2 days. The mixture was filtered and the separated aqueous phase was extracted with ethyl acetate (3×). The combined organic layers were washed with $NaHSO_3$ (1 N), water, and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (hexanes−EtOAc 5:1) to provide **8** (19.5 g, 83%) as a dark oil: ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.29 (s, 3H), 1.60−2.10 (m, 4H), 2.13 (s, 3H), 2.74 (m, 1H), 3.08 (dd, 1H, J = 3.3, 1.4 Hz), 3.82 (dd, 1H, J = 7.6, 4.3 Hz); ^{13}C NMR ($CDCl_3$) δ −4.7 (q), −4.5 (q), 17.9 (s), 20.5 (q), 24.8 (t), 25.7 (q), 27.8 (q), 31.4 (t), 43.0 (d), 59.4 (s), 60.3 (d), 68.9 (d), 210.8 (s); LISMS (THGLY) 285 $(M + H)^+$; HRMS calcd for $C_{15}H_{29}O_3Si$ $(M + H)^+$ 285.1886, found 285.1848.

(1*S*,2*S*,4*R*,6*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-acetyloxy-1-methyl-7-oxabicyclo[4.1.0.]heptane (10). To a vigorously stirring mixture of **8** (19.5 g, 0.068 mol) in $CHCl_3$ (200 mL) and a pH = 8 sodium phosphate buffer solution (0.1 M, 200 mL) at 0 °C was added *m*-CPBA (70% purity, 33.8 g, 0.136 mol) protionwise. The resulting mixture was stirred from 0 °C to room temperature overnight. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with $NaHSO_3$ (1 N), $NaHCO_3$ (2 N), water, and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (hexanes−EtOAc 5:1) to afford **10** (14.85 g, 73%) as a light-yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 1.39 (s, 3H), 1.58−2.04 (m, 3H), 2.03 (s, 3H), 2.10 (dd, 1H, J = 10.3, 5.1 Hz), 3.01 (d, 1H, J = 4.4 Hz), 4.15 (dd, 1H, J = 10.3, 5.1 Hz), 4.96 (m, 1H); ^{13}C NMR ($CDCl_3$) δ −4.7 (q), −4.3 (q), 18.1 (s), 19.7 (q), 21.2 (q), 25.8 (q), 29.4 (t), 32.6 (t), 58.9 (d), 60.0 (s), 68.2 (d), 69.0 (d), 170.1 (s); LISMS (NBA) 301 $(M + H)^+$; HRMS calcd for $C_{15}H_{29}O_4Si$ $(M + H)^+$ 301.1835, found 301.1828.

(1*R*,3*R*,5*S*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-6-methyl-7-oxabicyclo[4.1.0.]heptan-3-ol (11). A mixture of **10** (11.5 g, 0.038 mol) and K_2CO_3 (26.5 g, 0.19 mol) in MeOH (200 mL) was stirred at room temperature for 12 h. The mixture was filtered and the filtrate was concentrated. The residue was dissolved into EtOAc (300 mL), washed with saturated NH_4-Cl, water, and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (hexanes−EtOAc 5:1, then 1:1) to give **11** (7.15 g, 73%) as a light-yellow oil: ^{1}H

(20) Compounds **25** and **28** were tested for their antiviral activity against herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), vaccinia virus, vesicular stomatitis virus, Coxsackie virus B4, respiratory syncytial virus (RSV), parainfluenza-3 virus, reovirus-1, Sindbis virus, and Punta Toro virus; for their cytoxicity in E_6SM cell cultures, Hela cell cultures, and Vero cell cultures; and for inhibitory activity against replication of HIV-1 (III_B) and HIV-2 (ROD) in MT-4 cells.

NMR ($CDCl_3$) δ 0.09 (s, 3H), 0.11 (s, 3H), 0.91 (s, 9H), 1.38 (s, 3H), 1.52−2.13 (m, 4H), 3.03 (d, 1H, J = 4.0 Hz), 4.04 (br s, 1H), 4.30 (dd, 1H, J = 9.9, 5.5 Hz); ^{13}C NMR ($CDCl_3$) δ −4.7 (q), −4.2 (q), 18.1 (s), 19.9 (q), 25.8 (q), 32.6 (t), 35.8 (t), 59.3 (d), 60.1 (s), 65.6 (d), 68.0 (d); LISMS (THGLY) 259 $(M + H)^+$; HRMS calcd for $C_{13}H_{26}O_3Si$ $(M + H)^+$ 259.1729, found 257.1730.

(1*S*,2*S*,4*R*,6*R*)-2,4-Bis(*tert*-butyldimethylsilyloxy)-1-methyl-7-oxabicyclo[4.1.0.]heptane (12). To a solution of **11** (7.0 g, 0.027 mol) in dry DMF (100 mL) at room temperature under nitrogen were added imidazole (3.67 g, 0.054 mol) and TBDMSCl (4.90 g, 0.032 mol) sequentially. The resulting solution was stirred at room temperature overnight. After addition of water, the resulting mixture was concentrated. The residue was taken up into EtOAc (300 mL), washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified on silica gel (hexanes−EtOAc 10:1) to afford **12** (8.0 g, 80%) as a light-yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.08 (s, 3H), 0.11 (s, 3H), 0.88 (s, 9H), 0.92 (s, 9H), 1.38 (s, 3H), 1.41−1.88 (m, 3H), 1.98 (dd, 1H, J = 15.7, 4.4 Hz), 3.02 (d, 1H, J = 4.3 Hz), 3.96 (m, 1H), 4.30 (dd, 1H, J = 9.8, 5.1 Hz); ^{13}C NMR ($CDCl_3$) δ −4.9 (q), −4.7 (q), −4.2 (q), 18.0 (s), 18.1 (s), 20.0 (q), 25.7 (q), 25.9 (q), 33.3 (t), 36.3 (t), 59.4 (d), 60.0 (s), 66.2 (d), 68.6 (d); LISMS (THGLY) 373 $(M + H)^+$; HRMS calcd for $C_{19}H_{41}O_3Si_2$ $(M + H)^+$ 373.2594, found 373.2591.

(1*R*,3*S*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-2-methylenecyclohexanol (13). A solution of 2,2,6,6-tetramethylpiperidine (TMP, 9.05 mL, 53.76 mmol) in dry benzene (60 mL) was cooled to 0 °C under N_2 and a solution of *n*-BuLi in hexane (2.5 M, 21.5 mL, 53.76 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 10 min, a solution of Et_2AlCl (1.8 M, 30 mL, 54 mmol) in toluene was slowly added, and the reaction was stirred for 30 min. A solution of **12** (5 g, 13.44 mmol) in benzene (20 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 3 h and then poured into an ice cold NH_4Cl solution (300 mL). A 3 N HCl solution was added until a clear emulsion was obtained. The layers were separated, and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (hexanes−EtOAc 10:1) to give **13** (5 g, 100%) as a light-yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.08 (s, 6H), 0.90 (s, 9H), 0.91 (s, 9H), 1.66 (m, 2H), 1.90 (m, 2H), 2.42 (d, 1H, J = 7.2 Hz, OH), 4.28 (m, 1H), 4.43 (m, 2H), 5.01 (br s, 1H), 5.07 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.1 (q), −5.0 (q), 18.0 (s), 18.2 (s), 25.8 (q), 44.1 (t), 44.5 (t), 65.0 (d), 69.6 (d), 70.4 (d), 105.0 (t), 152.2 (s); LISMS (NBA) 373 $(M + H)^+$; HRMS calcd for $C_{19}H_{41}O_3Si_2$ $(M + H)^+$ 373.2594, found 373.2576.

(1*S*,3*R*,5*R*)-3-Benzyloxy-1,5-bis(*tert*-butyldimethylsilyloxy)-2-methylenecyclohexane (14). NaH (80% suspension, 835 mg, 27.82 mmol) was added to a solution of **13** (6.9 g, 18.55 mmol) in dry THF (60 mL) at room temperature under nitrogen. The mixture was stirred for 0.5 h, followed by addition of BnBr (2.65 mL, 22.25 mmol) and tetrabutylammonium iodide (TBAI, 103 mg). The reaction was stirred at room temperature overnight. Crushed ice was added and the mixture was stirred at room temperature for 0.5 h and then poured into EtOAc (400 mL), washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (hexanes−EtOAc 20:1) to give **14** (8.7 g) as a light-yellow oil which was not pure and was used as such in the next reaction: ^{1}H NMR ($CDCl_3$) δ −0.08 (s, 3H), −0.05 (s, 3H), −0.02 (s, 3H), 0.00 (s, 3H), 0.76 (s, 9H), 0.84 (s, 9H), 1.30−1.45 (m, 2H), 1.83−2.06 (m, 2H), 4.04 (br dd, 1H, J = 11.0, 4.7 Hz), 4.09 (m, 1H), 4.32 (br dd, 1H, J = 11.0, 4.7 Hz), 4.43 (d, 1H, J = 12.0 Hz), 4.62 (d, 1H, J = 12.0 Hz), 5.06 (br s, 2H), 7.12−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.0 (q), −4.9 (q), 17.9 (s), 18.4 (s), 25.7 (q), 25.9 (q), 42.0 (t), 45.1 (t), 66.2 (d), 68.5 (d), 71.4 (d), 74.7 (t), 102.4 (t), 127.5 (d), 128.3 (d), 138.8 (s), 152.6 (s); LISMS (THGLY + NaOAc) 485 $(M + H)^+$; HRMS calcd for $C_{26}H_{46}O_3Si_2Na$ $(M + Na)^+$ 485.2883, found 485.2892.

(1*S*,2*S*,3*R*,5*R*)-3-Benzyloxy-1,5-bis(*tert*-butyldimethylsilyloxy)-2-(hydroxymethyl)cyclohexane (15). To a solution of crude **14** (8.7 g, 18.55 mmol) in dry THF (60 mL) at 0 °C under nitrogen was added dropwise a solution of 9-BBN in THF (0.5 M, 74.2 mL, 37.1 mmol). The reaction was slowly warmed to room temperature overnight. The reaction was cooled to 0 °C and treated sequentially with EtOH (7 mL), a 2 N NaOH solution (14 mL), and a 35% H_2O_2 solution while stirring. The resulting mixture was stirred at room temperature for 23 h and then poured into a mixture of EtOAc (150 mL) and water (150 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. The crude product was separated on silica gel (hexanes−EtOAc 20:1, then 1:1) to yield **15** (5.5 g, 62% starting from **13**) as a colorless oil and the epimer **16** (1.4 g, 16%) as a light-yellow oil.

15: ^{1}H NMR ($CDCl_3$) δ 0.06 (2s, 9H), 0.08 (s, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 1.40 (td, 1H, J = 11.0, 2.4 Hz), 1.46 (td, 1H, J = 11.0, 2.4 Hz), 1.68 (tt, 1H, J = 11.0, 4.0 Hz), 1.93 (br d, 1H, J = 11.0 Hz), 2.17 (br d, 1H, J = 11.0 Hz), 2.82 (dd, 1H, J = 7.0, 4.0 Hz, OH), 3.71 (td, 1H, J = 11.0, 4.1 Hz), 3.78 (dt, 1H, J = 10.6, 4.0 Hz), 3.84 (td, 1H, J = 11.0, 4.0 Hz), 3.92 (ddd, 1H, J = 10.6, 7.0, 4.0 Hz), 4.19 (m, 1H), 4.44 (d, 1H, J = 11.6 Hz), 4.64 (d, 1H, J = 11.6 Hz), 7.28−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.1 (q), −5.0 (q), −4.3 (q), 17.8 (s), 25.6 (q), 25.7 (q), 37.7 (t), 42.6 (t), 53.2 (d), 63.3 (d), 66.5 (d), 67.8 (d), 70.7 (t), 75.6 (t), 127.9 (d), 128.1 (d), 128.6 (d), 138.1 (s); LISMS (THGLY) 481 $(M + H)^+$; HRMS calcd for $C_{26}H_{49}O_4Si_2$ $(M + H)^+$ 481.3169, found 481.3167.

16: ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.85 (s, 9H), 0.90 (s, 9H), 1.53 (ddd, 1H, J = 13.0, 11.5, 2.9 Hz), 1.68 (m, 2H), 1.80 (dt, 1H, J = 13.0, 4.2 Hz), 2.61 (app pent, 1H, J = 5.9 Hz), 3.41 (dd, 1H, J = 7.3, 4.9 Hz, OH), 3.91 (ddd, 1H, J = 11.5, 4.4, 3.2 Hz), 3.92 (ddd, 1H, J = 11.2, 7.3, 4.9 Hz), 4.14 (app pent, 1H, J = 3.2 Hz), 4.24 (ddd, 1H, J = 10.2, 5.9, 5.4 Hz), 4.52 (d, 1H, J = 11.7 Hz), 4.60 (d, 1H, J = 11.7 Hz), 7.25−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −4.8 (q), −4.6 (q), 18.1 (s), 18.2 (s), 25.9 (q), 26.0 (q), 34.7 (t), 38.0 (t), 45.7 (d), 58.7 (d), 66.4 (d), 69.1 (d), 70.9 (t), 74.5 (d), 127.8 (d), 128.6 (d), 138.5 (s); LISMS (THYLY) 481 $(M + H)^+$; HRMS calcd for $C_{26}H_{49}O_4Si_2$ $(M + H)^+$ 481.3169, found 481.3120.

(1*S*,2*R*,3*R*,5*S*)-3-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-2-hydroxymethyl-cyclohexanol (18). A solution of TBAF in THF (1.0 M, 8.23 mL, 8.23 mmol) was added dropwise to a solution of **15** (4.0 g, 8.23 mmol) in THF (30 mL) and the reaction was stirred at room temperature for 3 h. TLC showed the completion of the reaction. Ice was added and the mixture was poured into ethyl acetate (200 mL), washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (hexanes−EtOAc 5:1, then 1:1) to yield **18** (2.84 g, 93%) as a light-yellow oil: ^{1}H NMR ($CDCl_3$) δ −0.01 (s, 6H), 0.82 (s, 9H), 1.29−1.46 (m, 2H), 1.63 (m, 1H), 1.92 (m, 1H), 2.08 (m, 1H), 2.95 (br s, 2H, 2OH), 3.54 (td, 1H, J = 10.4, 4.0 Hz), 3.76 (dd, 1H, J = 10.7, 4.7 Hz), 3.85 (td, 1H, J = 10.5, 4.2 Hz), 4.00 (dd, 1H, J = 10.7, 4.7 Hz), 4.15 (m, 1H), 4.33 (d, 1H, J = 11.4 Hz), 4.55 (d, 1H, J = 11.4 Hz), 7.22−7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.0 (q), −4.9 (q), 17.9 (s), 25.8 (q), 37.6 (t), 41.7 (t), 52.2 (d), 64.3 (t), 66,3 (d), 68.8 (d), 70.9 (t), 74.5 (d), 127.9 (d), 128.0 (d), 128.5 (d), 138.1 (s); LISMS (GLY) 367 $(M + H)^+$; HRMS cald for $C_{20}H_{35}O_4Si$ $(M + H)^+$ 367.2304, found 367.2346.

(2*R*,5*R*,7*R*,9*S*,10*S*)-5-Benzyloxy-7-(*tert*-butyldimethylsilyloxy)-2-phenylhexahydrobenzo[1.3]dioxine (19). A solution of **18** (2.93 g, 8.0 mmol), $PhCH(OMe)_2$ (1.44 mL, 9.6 mmol), and *p*-toluenesulfonic acid monohydrate (PTSA, 76 mg, 0.4 mmol) in dry dioxane (35 mL) was stirred at room temperature for 24 h and then poured into EtOAc (300 mL), washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (hexanes−EtOAc 20:1) to afford **19** (9.2 g, 90%) as a light-yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 6H), 0.84 (s, 9H), 1.34−1.64 (m, 2H), 1.80−2.03 (m, 2H), 2.14 (m, 1H), 3.46 (td, 1H, J = 10.7, 4.0 Hz), 3.53 (t, 1H, J = 11.0 Hz), 3.87 (td, 1H, J = 10.5, 4.3 Hz), 4.23 (m, 1H), 4.32 (d, 1H, J = 11.8 Hz), 4.49 (dd, 1H, J = 11.0, 4.3 Hz), 4.54 (d, 1H, J = 11.8 Hz), 5.47 (s,

1H), 7.20−7.48 (m, 10H); ^{13}C NMR ($CDCl_3$) δ −4.5 (q), 18.5 (s), 26.3 (q), 38.9 (t), 39.0 (t), 47.0 (d), 67.0 (d), 70,4 (t), 71.2 (t), 73.1 (d), 76.2 (d), 102.2 (d), 126.7 (d), 128.2 (d), 128.3 (d), 128.8 (d), 128.9 (d), 129.3 (d), 138.9 (s), 139.0 (s); LISMS (GLY) 455 $(M + H)^+$; HRMS calcd for $C_{27}H_{39}O_4Si$ $(M + H)^+$ 455.2618, found 455.2610.

(2*R*,5*R*,7*R*,9*S*,10*S*)-5-Benzyloxy-2-phenylhexahydrobenzo[1.3]dioxin-7-ol (20). A solution of TBAF in THF (1.0 M, 13.92 mL, 13.92 mmol) and **19** (2.10 g, 4.64 mmol) in THF (50 mL) was stirred at room temperature overnight. After standard workup, **20** (1.47 g, 93%) was obtained as a white solid after purification on silica gel (hexanes−EtOAc 1:1): mp 158−159 °C; ^{1}H NMR ($CDCl_3$) δ 1.44−1.78 (m, 3H), 1.95 (qd, 1H, J = 10.4, 4.4 Hz), 2.08 (m, 1H), 2.31 (m, 1H), 3.56 (td, 1H, J = 10.4, 4.3 Hz), 3.66 (t, 1H, J = 10.4 Hz), 3.98 (td, 1H, J = 10.4, 4.3 Hz), 4.34 (m, 1H), 4.39 (d, 1H, J = 11.7 Hz), 4.56 (dd, 1H, J = 10.4, 4.4 Hz), 4.62 (d, 1H, J = 11.7 Hz), 5.52 (s, 1H), 7.24−7.51 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 37.6 (t), 37.9 (t), 46.4 (d), 66.1 (d), 69,8 (t), 70.9 (t), 72.8 (d), 75.1 (d), 101.7 (d), 126.2 (d), 127.6 (d), 127.7 (d), 128.3 (d), 128.4 (d), 128.9 (d), 138.4 (s); LISMS (GLY) 341 $(M + H)^+$; HRMS calcd for $C_{21}H_{25}O_4$ $(M + H)^+$ 341.1753, found 341.1745. Anal. Calcd for $C_{21}H_{24}O_4$: C 74.09, H 7.11; Found: C 73.97, H 7.40.

(2*R*,5*R*,7*S*,9*S*,10*S*)-5-Benzyloxy-2-phenylhexahydrobenzo[1.3]dioxin-7-ol (22). A solution of benzoic acid (939 mg, 7.69 mmol) and DEAD (1.21 mL, 7.69 mmol) in dry dioxane (20 mL) was added dropwise to a solution of **20** (1.72 g, 5.06 mmol) and PPh_3 (1.99 g, 7.69 mmol) in dioxane (40 mL) at room temperature under N_2. The reaction mixture was stirred overnight and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexanes−EtOAc 5:1) to yield the crude **21** (2.3 g) as a white solid which was used directly in the next step: ^{1}H NMR ($CDCl_3$) δ 1.54−2.11 (m, 3H), 2.45 (m, 1H), 2.71 (m, 1H), 3.25 (td, 1H, J = 10.9, 4.1 Hz), 3.58 (td, 1H, J = 10.9, 4.0 Hz), 3.59(t, 1H, J = 10.3 Hz), 4.39 (d, 1H, J = 11.7 Hz), 4.59 (dd, 1H, J = 10.3, 4.3 Hz), 4.68 (d, 1H, J = 11.7 Hz), 5.06 (tt, 1H, J = 11.7, 4.7 Hz), 5.52 (s, 1H), 7.24−7.62 (m, 13H), 8.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 36.5 (t), 36.8 (t), 45.4 (d), 67.9 (d), 69,9 (t), 70.7 (t), 73.1 (d), 75.6 (d), 101.7 (d), 126.1 (d), 127.7 (d), 127.9 (d), 128.3 (d), 128.4 (d), 128.5 (d), 128.9 (d), 129.6 (d), 130.1 (s), 133.2 (d), 137.9 (s), 138.1 (s), 165.8 (s).

The crude **21** (2.3 g) was treated with K_2CO_3 (4 g) in MeOH (40 mL) and THF (40 mL) at room temperature overnight. After workup and chromatography on silica gel (hexanes−EtOAc 5:1, then 1:2), **22** (1.24 g, 72% over two steps) was obtained as a white solid; mp 130−132 °C; ^{1}H NMR ($CDCl_3$) δ 1.26−1.70 (m, 3H), 1.93 (qd, 1H, J = 10.6, 4.4 Hz), 2.31 (m, 1H), 2.52 (m, 1H), 3.12 (td, 1H, J = 10.6, 4.1 Hz), 3.44 (td, 1H, J = 10.6, 4.0 Hz), 3.55 (t, 1H, J = 10.6 Hz), 3.69 (m, 1H), 4.38 (d, 1H, J = 12.0 Hz), 4.56 (dd, 1H, J = 10.6, 4.4 Hz), 4.64 (d, 1H, J = 12.0 Hz), 5.46 (s, 1H), 7.25−7.51 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 40.1 (t), 40.5 (t), 45.2 (d), 65.6 (d), 70.0 (t), 70.5 (t), 73.3 (d), 75.8 (d), 101.7 (d), 126.2 (d), 127.6 (d), 127.8 (d), 128.3 (d), 128.5 (d), 129.0 (d), 138.1 (s); LISMS (THGLY) 341 $(M + H)^+$; HRMS calcd for $C_{21}H_{25}O_4$ $(M + H)^+$ 341.1753, found 341.1758.

(2*R*,5*R*,7*R*,9*S*,10*S*)-7-Adenin-9-yl-5-benzyloxy-2-phenylhexahydrobenzo[1.3]dioxine (23). To a suspension of **22** (160 mg, 0.47 mmol), adenine (127 mg, 0.94 mmol), and PPh_3 (246 mg, 0.94 mmol) in dry dioxane (13 mL) at room temperature under nitrogen was added a solution of DEAD (154 μL, 0.94 mmol) in dry dioxane (7 mL) over a period of 1 h. The resulting mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and the residue was directly chromatographed on silica gel (CH_2Cl_2−MeOH 50:1 to 20:1) to afford **23** (200 mg, 93%) as a white solid: mp 186−188 °C; ^{1}H NMR ($CDCl_3$) δ 1.93−2.24 (m, 3H), 2.77 (m, 1H), 3.06 (m, 1H), 3.51 (td, 1H, J = 11.0, 4.0 Hz), 3.61 (t, 1H, J = 11.0 Hz), 3.78 (td, 1H, J = 11.0, 4.0 Hz), 4.45 (d, 1H, J = 12.0 Hz), 4.60 (dd, 1H, J = 11.0, 4.4 Hz), 4.64 (d, 1H, J = 12.0 Hz), 5.09 (m, 1H), 5.47 (s, 1H), 5.83 (br s, 2H), 7.24−7.50 (m, 10H), 7.74 (s, 1H), 8.38 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 34.0 (t), 34.8 (t), 46.2 (d), 50.4 (d), 69.8 (t), 71.3 (t), 72.2 (d), 75.0 (d), 101.9 (d), 120.3 (s), 126.3 (d), 128.1 (d), 128.4 (d), 128.6 (d), 128.9 (d), 129.3 (d), 137.8 (s), 138.1 (s), 138.9 (d), 150.5 (s), 153.2 (d), 155.8 (s); UV λ_{max}(MeOH) = 262 nm; LISMS (THGLY) 458 $(M + H)^+$; HRMS calcd for $C_{26}H_{28}N_5O_3$ $(M + H)^+$ 458.2192, found 458.2191.

(1*S*,2*R*,3*R*,5*S*)-5-Adenin-9-yl-3-benzyloxy-2-(hydroxymethyl)cyclohexanol (24). A mixture of **23** (214 mg, 0.47 mol) in 80% HOAc aqueous solution was heated at 60 °C for 8 h and concentrated. The residue was coevaporated with toluene and purified by chromatography eluting with CH_2Cl_2−MeOH (50:1 and 10:1) to afford **24** (150 mg, 86%) as a white solid: ^{1}H NMR (DMSO-d_6, exchanged with D_2O) δ 1.96 (m, 3H), 2.37 (m, 2H), 3.57 (d, 2H, J = 5.5 Hz), 3.90 (m, 2H, overlapped with DOH peak), 4.53 (s, 2H), 4.98 (m, 1H), 7.20−7.40 (m, 5H), 8.15 (s, 2H); ^{13}C NMR (DMSO-d_6, exchanged with D_2O) δ 32.4 (t), 36.1 (t), 46.7 (d), 47.9 (d), 59.3 (t), 66.0 (d), 70.1 (t), 74.5 (d), 119.2 (s), 127.4 (d), 127.7 (d), 128.3 (d), 138.9 (s), 139.5 (d), 149.5 (s), 152.3 (d), 156.1 (s); UV λ_{max}(MeOH) = 262 nm; LISMS (THGLY) 370 $(M + H)^+$; HRMS calcd for $C_{19}H_{24}N_5O_3$ $(M + H)^+$ 370.1879, found 370.1848.

5-(6-Aminopurin-9-yl)-2-(hydroxymethyl)cyclohexane-1,3-diol (25). A mixture of **24** (110 mg, 0.3 mmol) and 20% $Pd(OH)_2$ on carbon (220 mg) in cyclohexene (6 mL) and MeOH (12 mL) was refluxed for 2 days and then cooled to room temperature, diluted with MeOH, and filtered through Celite. The filtrate was concentrated to yield **25** (77 mg, 92%) as a white solid. Compound **25** can also be prepared directly from **23** using the same procedure in 73% yield. An analytical sample was obtained by RP HPLC purification on Rogel column eluting with H_2O−CH_3CN (96:4): mp 224−226 °C; ^{1}H NMR (DMSO-d_6, exchanged with D_2O) δ 1.78 (m, 1H), 1.87 (ddd, 2H, J = 13.6, 5.9, 4.4 Hz), 2.30 (ddd, 2H, J = 13.6, 9.4, 2.9 Hz), 3.55 (m, 2H, overlapped with DOH peak), 3.92 (dt, 2H, J = 5.2, 3.7 Hz), 4.98 (tt, 1H, J = 9.3, 4.5 Hz), 8.11 (s, 1H), 8.19 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 35.8 (t), 46.5 (d), 49.1 (d), 59.6 (t), 66.8 (d), 119.1 (s), 139.6 (d), 149.4 (s), 152.2 (d), 156.1 (s); UV λ_{max}(MeOH) = 262 nm; LISMS (THGLY) 280 $(M + H)^+$; HRMS calcd for $C_{12}H_{18}N_5O_3$ $(M + H)^+$ 280.1410, found 280.1401. Anal. Calcd for $C_{12}H_{17}N_5O_3 \cdot 1.5\ H_2O$: C 47.05, H 6.58, N 22.86; Found: C 47.40, H 6.44, N 22.96.

(2*R*,5*R*,7*R*,9*S*,10*S*)-7-Guanin-9-yl-5-benzyloxy-2-phenylhexahydrobenzo[1.3]dioxine (26). Compound **26** was prepared from 2-amino-6-chloropurine and **22** as described for the synthesis of **23** in 37% yield: ^{1}H NMR ($CDCl_3$) δ 1.89−2.20 (m, 3H), 2.75 (m, 1H), 2.87 (m, 1H), 3.45 (td, 1H, J = 10.6, 4.0 Hz), 3.58 (t, 1H, J = 11.0 Hz), 3.67 (m, 1H), 4.46 (d, 1H, J = 11.9 Hz), 4.58 (dd, 1H, J = 11.0, 4.4 Hz), 4.59 (d, 1H, J = 11.9 Hz), 4.91 (m, 1H), 5.20 (s, 2H, NH2), 5.44 (s, 1H), 7.26−7.48 (m, 10H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 34.0 (t), 34.6 (t), 46.4 (d), 50.6 (d), 69.9 (t), 71.6 (t), 72.3 (d), 75.0 (d), 102.1 (d), 126.0 (s), 126.5 (d), 128.4 (d), 128.7 (d), 129.1 (d), 129.5 (d), 137.9 (s), 138.2 (s), 140.7 (d), 152.1 (s), 154.2 (s), 159.3 (s); LISMS (THGLY) 492 $(M + H)^+$; HRMS calcd for $C_{26}H_{27}N_5O_3$-Cl $(M + H)^+$ 492.1802, found 492.1810.

(1*S*,3*R*,4*R*,5*S*)-5-Guanin-9-yl-3-benzyloxy-2-(hydroxymethyl)cyclohexanol (27). A solution of **26** (54 mg, 0.11 mol) in CF_3COOH−H_2O (3:1, 4 mL) was stirred at room temperature for 4 days. The solution was concentrated and the residue was coevaporated with toluene and then treated with ammonium methanol and concentrated to yield **27** (45 mg), which was used as such in the next reaction: ^{1}H NMR (DMSO-d_6) δ 1.86 (m, 1H), 1.96 (m, 2H), 2.85 (m, 2H), 3.56 (br t, 2H), 4.46 (d, 1H, J = 5.1 Hz, exchangeable with D_2O), 4.53 (s, 2H), 4.67 (br t, 1H, OH, exchangeable with D_2O), 4.80 (m, 1H), 6.59 (s, 2H, NH_2, exchangeable with D_2O), 7.34 (m, 5H), 7.78 (s, 1H), 10.73 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ 32.3 (t), 36.1 (t), 45.3 (d), 47.0 (d), 58.8 (t), 65.5 (d), 69.8 (t), 74.1 (d), 116.4 (s), 127.1 (d), 127.4 (d), 128.0 (d), 135.5 (d), 138.6 (s), 150.6 (s), 153.2 (s), 156.7 (s); UV λ_{max}(MeOH) = 256 nm; LISMS (THGLY) 386 $(M + H)^+$; HRMS calcd for $C_{19}H_{24}N_5O_4$ $(M + H)^+$ 386.1828, found 386.1812.

5-Guanin-9-yl-2-(hydroxymethyl)cyclohexane-1,3-diol (28). The crude **27** (45 mg) was refluxed with 20% $Pd(OH)_2$ on carbon (100 mg) in cyclohexene (2.5 mL) and MeOH (5 mL) overnight. The reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was

concentrated and the residue was chromatographed on a short pad of silica gel (CH_2Cl_2−MeOH 2:1) to afford **28** (33 mg, 63% over two steps) as a white solid.

An analytic sample was prepared by RP HPLC purification on Rogel column eluenting with H_2O−CH_3CN (96:4): mp >270 °C; ^{1}H NMR (DMSO-d_6) δ 1.73−1.92 (m, 3H), 2.16 (m. 2H), 3.56 (t, 2H, J = 4.4 Hz), 3.96 (m, 2H), 4.59 (t, 1H, J = 4.4 Hz, exchangeable with D_2O), 4.84 (m, 1H), 4.95 (d, 1H, J = 5.9 Hz, OH, exchangeable with D_2O), 6.37 (s, 2H, NH_2, exchangeable with D_2O), 7.83 (s, 1H), 10.50 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ 36.2 (t), 45.5 (d), 49.2 (d), 59.6 (t), 66.8 (d), 116.7 (s), 135.9 (d), 150.9 (s), 153.4 (s), 157.1 (s); UV λ_{max}(MeOH) = 256 nm; LISMS (THGLY) 296 $(M + H)^+$; HRMS calcd for $C_{12}H_{18}N_5O_4$ $(M + H)^+$ 296.1359, found 296.1349. Anal. Calcd for $C_{12}H_{17}N_5O_4 \cdot 2\ H_2O$: C 43.50, H 6.39, N 21.14; Found: C 44.04, H 6.33, N 20.95.

X-ray Diffraction Studies.[21] Colorless single crystals were grown by slow evaporation from a hexanes−EtOAc solution at room temperature. Crystal data: $C_{21}H_{24}O_4$, MW = 340.4, monoclinic, $P2_1$, a = 8.372(5) Å, b = 5.475(5) Å, c = 19.470(5) Å, β = 91.970(5), V = 892(1) Å^3, Z = 2, D_c = 1.268 Mg/m^3, $F(000)$ = 364, μ = 0.700 mm^{-1}, λ = 1.54178 Å, T = 293(2) K, crystal size 0.40 × 0.35 × 0.20 mm.

Data Collection. A crystal was mounted on a Siemens P4 four-circle diffractometer with graphite monochromator and Cu Kα radiation. Cell parameters were calculated from the least-squares fitting for 35 high-angle reflections (2θ > 30°). Omega scans for several intense reflections indicated acceptable crystal quality. Data were collected from 4.54 to 134.10° 2θ at 293(2) K. The index range was, $-10 < h < 10$, $-5 < k < 6$, $-23 < l < 23$. Scan width for data collection was 0.94° in ω (plus $\alpha 1 - \alpha 2$ dispersion) with a variable scan rate between 1 and 60°/min. The three standards, collected every 100 reflections, showed no significant trends. Lorentz and polarization corrections were applied to 2881 reflections.

An empirical absorption correction (the method of North[22]) was applied. A total of 3423 unique reflections (R_{int} = 0.0190) were used in further calculations.

Structure Refinement. The structure was solved by direct methods using SIR92.[23] Full-matrix least-squares anisotropic refinement on F^2 for all non-hydrogen atoms yielded $R[I > 2\sigma(I)] = 0.032$ at convergence with GOF on F^2 = 1.049; extinction coefficient, 0.060(2); largest peak and hole, 0.133 and −0.105 e Å^3. Hydrogen atoms were placed in idealized positions with isotropic displacement parameters fixed at 1.3 times the value of the attached atom and were constrained to ride on their parent atoms. PARST (Nardelli)[24] and PLATON (Spek[25]) were used for geometry calculations.

Both the dioxane and the cyclohexane ring have a chair conformation with puckering parameters according to Cremer and Pople:[26] $\boldsymbol{Q}_t$ = 0.579(1) Å, θ = 177.7(1)° and $\boldsymbol{Q}_t$ = 0.560 Å, θ = 178.3(2). The intermolecular hydrogen bond network consists of O2′−H21′···O2 $(-1 + x, y, z)$ interactions.

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Supporting Information Available: ^{13}C NMR for compounds **5**, **7**, **8**, **10**−**16**, **18**−**25**, and **28** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(21) The authors have deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2, 1EZ, UK.

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