Enantioselective Synthesis and Conformational Study of Cyclohexene Carbocyclic Nucleosides

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Enantioselective synthesis of a new family of unsaturated six-membered carbocyclic nucleosides using (*R*)-(−)-carvone as starting material is described. Introduction of the base moiety via Mitsunobu reaction proceeded regio- and stereoselectively and with good chemical yield, while the Pd-coupling approach failed. ^{1}H NMR study and molecular modeling show the adenine compound exists in an equilibrium of $^3H_2$ and $^2H_3$ conformers (ratio 7:3) in favor of the 3′-endo half-chair conformation, with the base oriented in a pseudoaxial position. This conformational preference can be explained by the $\pi \rightarrow \sigma^*_{C1'-N1}$ interaction involving the antibonding orbital of the C1′−N bond.

Introduction

Most antiviral compounds belong to the nucleoside field, and the development of new modified nucleosides as antiviral agents has remained a very active field of research. One particularly interesting domain of antiviral nucleoside research is that of carbocyclic nucleosides. In these nucleoside analogues the ring oxygen atom is replaced by a methylene group. Due to the absence of the ring oxygen atom, the anomeric effect as well as the gauche effects of O-4′ with 3′-OH and/or 2′-OH are removed. This research has led to the discovery of potent and selective antiviral agents.[1] Our current work has been focusing on six-membered carbocyclic nucleosides and is based on the discovery that the hexitol nucleosides **1** (Figure 1) were found to exhibit antiviral activity.[2] We synthesized their carbocyclic congeners **2**, but these compounds did not demonstrate antiviral activity.[3] From a conformational point of view, this different biological behavior was initially explained by the fact that these two families exist in opposite chair conformations. In addition to anomeric effects and gauche effects, steric effects play an important role in the conformational preference of these nucleoside analogues. Indeed, the hexitol nucleosides **1** exist predominantly in the $^1C_4$ conformation, with the base occupying an axial position, while their carbocyclic congeners **2a** adopt the opposite $^4C_1$ conformation having the base in an equatorial position. The hexitol nucleoside can be considered as a mimic of a furanose nucleoside frozen in the 3′-endo conformation. In an attempt to force the carbocyclic congeners of

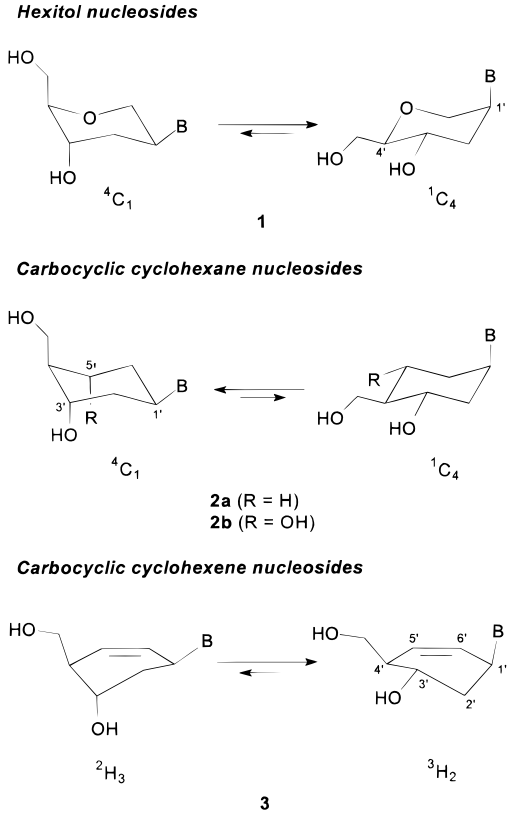

Figure 1. Conformational equilibrium of anhydrohexitol, cyclohexane, and cyclohexene nucleoside analogues.

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hexitol nucleosides into the $^1C_4$ conformation, we introduced an additional α-oriented hydroxyl group at C5′ (**2b**), but according to ^{1}H NMR analysis, the $^4C_1$ conformation with equatorial base is still preferred, despite the presence of three axial substituents. Likewise, compounds **2b** did not show antiviral activity.[3b]

The antiviral activity of a nucleoside analogue is the result of a complex interaction with several metabolic viral/human enzymes. It is generally accepted that the structural and conformational requirements of nucleosides to function as substrates or inhibitors for the different metabolic enzymes may be different. We, recently cocrystallized the antiviral hexitol nucleoside **1** in the active site of herpes virus type 1 thymidine kinase and observed a chair inversion[2c] when the nucleoside analogue is bound in the active site of the enzyme ($^1C_4$ is the energetically most stable conformation in solution, while in the crystal form of the enzyme the compound is bound in the $^4C_1$ conformation). Moreover, as oligonucleotides composed of **1** hybridize with RNA and DNA only when the monomeric nucleotides adopt the $^1C_4$ conformation,[2d] we expect that this conformation might be important for the hexitol nucleotides to be recognized by viral DNA polymerases. It can therefore be advantageous for antiviral activity if a nucleoside can adopt several conformations that are interconvertable. In this way, the conformation can adapt to different enzymatic requirements. To reduce the energy difference between different conformers of carbocyclic six-membered nucleosides, so that interconversion is facilitated, we introduced a double bond in the six-membered ring and obtained a carbocyclic cyclohexene nucleoside **3**.[3d] Not only are cyclohexene derivatives such as **3** more flexible than cyclohexanes **2**, molecular mechanics calculations show that the energy difference between the $^3H_2$ and $^2H_3$ conformations of the cyclohexene nucleoside **3** is low (1.6 kJ/mol) and that the half-chair conformation with the base in a pseudoaxial position ($^3H_2$) is preferred. This conformation is a good mimic of the geometry of the active hexitol nucleoside **1** in its $^1C_4$ form. Moreover, the electron-rich double bond may function as a mimic of the furanose oxygen atom. As shown in Figure 2, the $^3H_2$ and $^2H_3$ conformations of **3** might mimic the C3′-endo and C2′-endo conformations of a furanose nucleoside, respectively. In summary, such cyclohexene nucleoside may be considered as the best six-membered-ring mimic of a natural furanose nucleoside.

We hereby report the enantioselective synthesis and the conformational analysis of this new series of six-membered cyclohexene nucleosides **3**.

Results and Discussion

Recently, we developed an enantioselective approach to the synthesis of six-membered carbocyclic nucleosides of type **2b** (R = OH) starting from (*R*)-(−)-carvone[3b] (**4**, Scheme 1). The key step involved hydroboration of the exo double bond of cyclohexene **6b** to afford hydroxymethyl-substituted **7b** with the correct stereochemistry at C4. Precursor **6a** provided us with an ideal starting material for the synthesis of **3** as it has (1) a protected hydroxyl group at C3, (2) a protected hydroxyl substituent at C1, which at a final stage can be used to introduce a base moiety with retention of the configuration using Pd-chemistry, and (3) a free hydroxyl group at C5, which could be used to introduce the double bond.

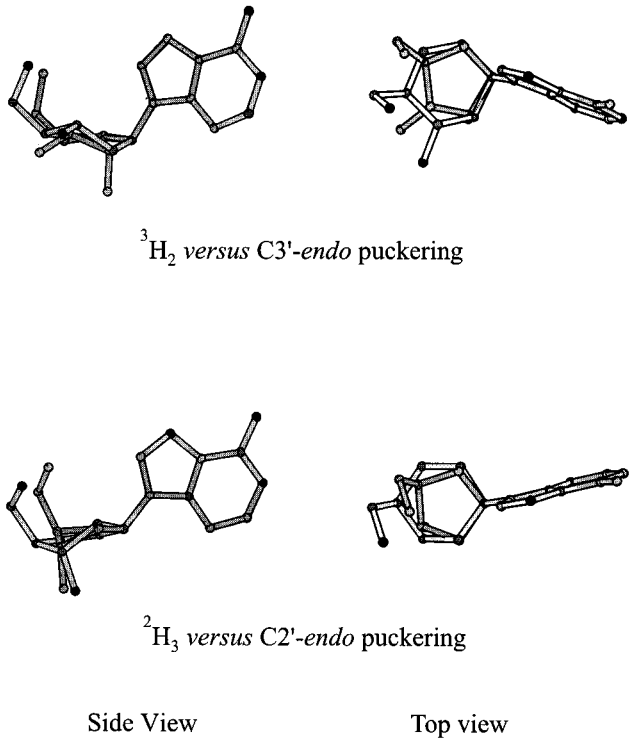

Figure 2. Comparison between the two lowest energy half-chair conformations ($^3H_2$ and $^2H_3$) of a cyclohexene nucleoside with a normal nucleoside with its sugar moiety modeled in the two most common puckering conformations (C3′-endo and C2′-endo). $^3H_2$ versus 3′-endo and $^2H_3$ versus 2′-endo. The base is adenine. Figure produced with a locally modified version of Molscript.[24]

The most straightforward approach seemed to introduce the C5−C6 double bond via conversion of the OH at C5 into a suitable leaving group, followed by a regioselective elimination. The latter might be achieved via a E_2-type elimination reaction by treatment with base, which requires a neighboring hydrogen trans to the leaving group, only available on C6. To explore this strategy, alcohol **6a** was converted into diol **7a** via hydroboration using 9-BBN in THF as described for **7b**.[3b] The reaction gave **7a** as the major isomer, together with a small amount of epimer **8a**. The β-stereochemistry at C4 was easily established by NMR spectrometry. Selective protection of the primary hydroxyl group of **7a** (TBDMSCl, imidazole, DMF) gave **9** (Scheme 2), and the leaving group was introduced (MsCl, Et_3N, dichloromethane) to give **10**. However, upon treatment of mesylate **10** with DBU[4] in toluene, cyclohexene **11** was not formed. More vigorous reaction conditions (KOH, H_2O−THF),[5] likewise, failed to yield the unsaturated compound **11**. Direct elimination of the 5-OH of **9** under

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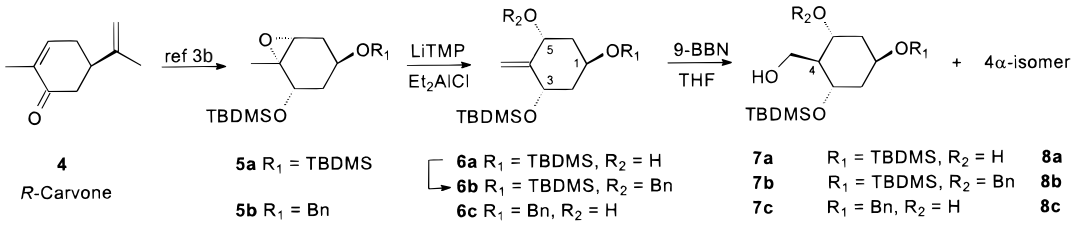
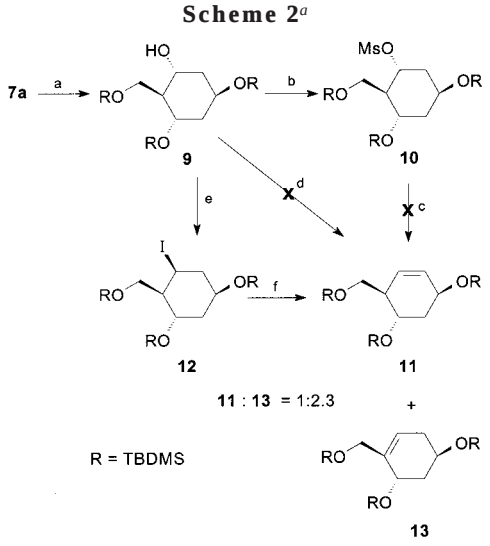
Scheme 1



Scheme 2[a]



[a] Key: (a) TBDMSCl (1.2 equiv), imidazole (2 equiv), DMF, rt, 48% starting from **6a**; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 93%; (c) DBU, toluene, or KOH, H_2O/THF; (d) DEAD, PPh_3, THF; (e) I_2, PPh_3, imidazole, toluene, reflux, 34%; (f) DBU, toluene, reflux, 68%.

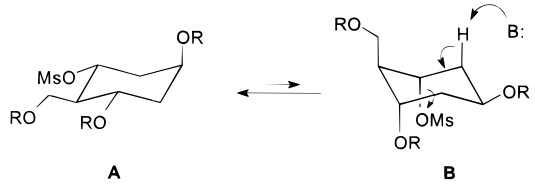


Figure 3. Conformational equilibrium disfavors elimination reaction.

Mitsunobu conditions (DEAD, PPh_3, THF)[6] was also unsuccessful. These failures might be explained by the too high activation energy to interconvert the preferred chair conformation **A** of **10** (Figure 3) into **B**, required for an anti E_2 elimination reaction. Therefore, **9** was converted into the β-iodide **12** (I_2, PPh_3, imidazole, toluene),[7] with inversion of the stereochemistry at C5, followed by treatment with DBU in refluxing toluene. This reaction resulted in an inseparable mixture (yield 68%) of cyclohexenes **11** and **13** in a 1:2.3 ratio, respectively, in favor of the undesired regioisomer.

As the previous approach failed, we turned to a new synthetic strategy, i.e., the construction of an allylic acetate of type **A** or **B** (Figure 4) as intermediate for the Pd coupling reaction to introduce the base moiety.[8] It can be expected that the C1-substituted product **C** would

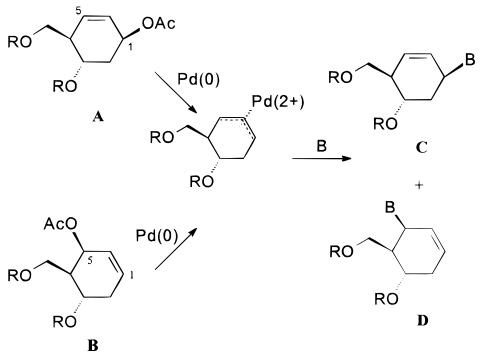


Figure 4. Mechanism of Pd(0) coupling reaction that may yield the desired compound C.

predominate over product **D** due to the presence of the β-oriented substituent at C_4. This effect is well-known in five-membered ring systems,[9] but has not yet been well studied in six-membered rings. We tried this approach via intermediate **B**.

Diol **14**[3b] (Scheme 3) was protected as cyclic acetal **15** (2,2-dimethoxypropane, PPTS, acetone−THF),[10] the Bn group was removed (10% Pd on carbon, $HCOONH_4$, MeOH, reflux)[11] to give alcohol **16**, and oxidation of the C5-OH (PDC, dichloromethane)[12] provided ketone **17**. Cleavage of the TBDMS ether using tetrabutylammonium fluoride (TBAF)[13] in THF led mainly to diol **18**. However, under neutral reaction conditions (KF, 18-crown-6, THF)[14] the desired enone **19** was isolated in 62% yield; the β-hydroxy ketone intermediate **20** could not be detected. The critical reduction of enone **19** to the corresponding allylic alcohol **22** with β-oriented OH at C5 proved to be problematic, leading almost exclusively to the α-isomer **21** under the applied reaction conditions

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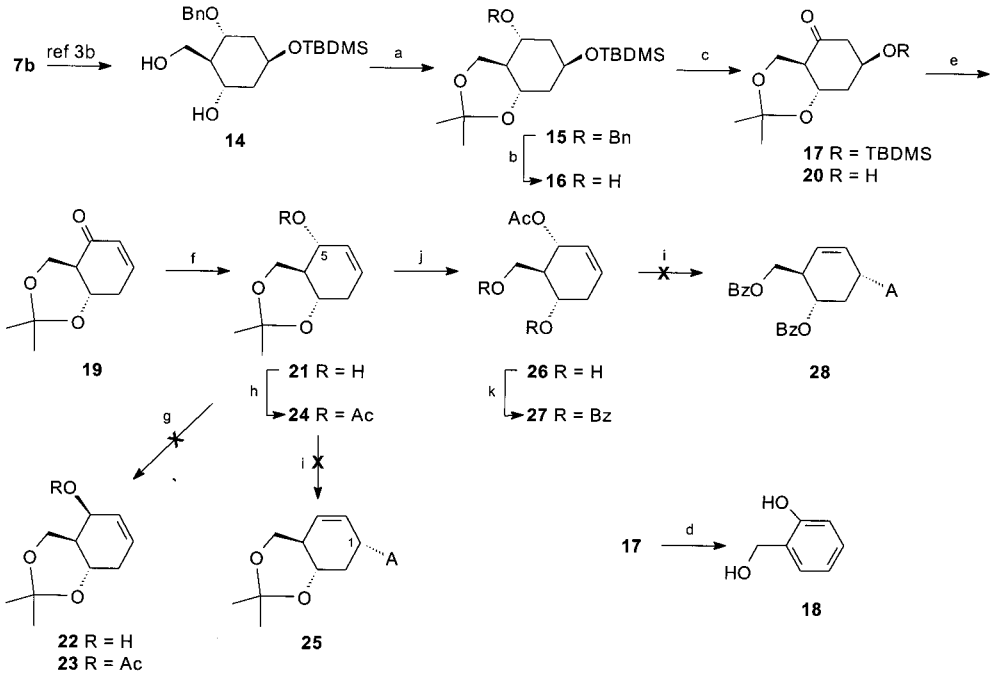
Scheme 3[a]



[a] Key: (a) $(CH_3)_2C(OCH_3)_2$, PPTS, acetone/THF (1:2), rt, 94%; (b) Pd−C (10%), $HCOONH_4$, MeOH, reflux, 100%; (c) PDC, CH_2Cl_2, rt, 94%; (d) TBAF, THF, rt; (e) KF, 18-Crown-6, THF, rt, 62% **19**; (f) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 90%; (g) PPh_3, DEAD, AcOH, THF; (h) Ac_2O, DMAP, CH_2Cl_2, 0 °C, 95%; (i) adenine, NaH, $Pd(PPh_3)_4$, DMF/THF; (j) PPTS, MeOH, rt, 59%; (k) Bz_2O, DMAP, CH_2Cl_2, 0 °C, 95%.

($NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH[15] and 9-BBN, THF[16]). In an attempt to invert the stereochemistry at C5 of α-alcohol **21**, the latter was subjected to a Mitsunobu-type reaction (DEAD, PPh_3, AcOH), but the desired β-acetate **23** was not formed. However, compound **21** might be used to synthesize the α-analogue of the aforementioned cyclohexene nucleoside, interesting for conformational analysis as well as for determination of antiviral activity.

The intended Pd coupling reaction was investigated on the α-acetate **24**, easily prepared from **21** (Ac_2O, DMAP, dichloromethane). When **24** was treated with the anion (NaH) of adenine in the presence of tetrakis(triphenylphosphine)palladium(0)[9] in DMF−THF, only **24** was recovered and no trace of the 1α-adenine **25** could be detected. Reasoning that this failure might be due to the rigidity of the cyclic acetal present, **24** was treated with PPTS[17] in MeOH to give diol **26**, which was then converted into the corresponding dibenzoate **27** (Bz_2O, DMAP, dichloromethane). However, upon subjection of **27** to the same reaction conditions for coupling as applied above to **24**, the expected 1α-adenine product **28** could not be isolated.

The above failure having exhausted the possibilities of the Pd coupling strategy, the most reliable alternative for the introduction of the base moiety seemed via a Mitsunobu reaction, i.e., by substitution with inversion of the configuration of an α-oriented hydroxyl group at C1. Therefore, we had to synthesize an appropriately protected precursor **7c**. Epoxide **5b** (Scheme 1, R_1 = Bn) was converted into **6c** under the reported conditions[3b] (LiTMP and Et_2AlCl in benzene−toluene 1:1) in 79% yield. Hydroboration of **6c** with 9-BBN in THF afforded **7c** as the major isomer (74%), together with its epimer **8c** (20%). Similar to the configurational assignment of **7a** and **7b**, the β-stereochemistry at C4 of **7c** was established by ^{1}H NMR. The primary hydroxyl group of **7c** was selectively protected using 1.2 equiv of TBDMSCl and imidazole in DMF to give **29** (70%, Scheme 4), followed by conversion of the free alcohol at C5 into the corresponding mesylate **30** by treatment with MsCl and Et_3N in dichloromethane. Hydrogenolytic cleavage of the benzyl ether at C1 using 20% $Pd(OH)_2$ on carbon in the presence of cyclohexene[18] in MeOH gave **31** in low yield (21%), which could be improved to 76% by the use of 10% Pd on carbon and $HCOONH_4$[11] in refluxing MeOH. Oxidation of alcohol **31** using PDC in dichloromethane gave a mixture of ketone **32** and enone **33** in a combined yield of 39%. However, using MnO_2[19] in dichloromethane, an incomplete but clean reaction took place. The ketone **32** was not isolated, enone **33** was obtained in 48% yield, and recovered **31** (47%) could be recycled. Finally, enone **33** was reduced using $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ in MeOH and gave the desired α-alcohol **34** as a single isomer in almost quantitative yield. The stereochemistry of **34** was confirmed by ^{1}H NMR spectral data. In $CDCl_3$, conformation **A** (Figure 5), with the three substituents in a pseudoaxial position, predominates due to intramolecular hydrogen bonding between the C1−OH and C3−OTBDMS groups, while in DMSO-d_6 it adopts conformation **B**. This reflects the much lower axial−equatorial energy differences in cyclohexenes as compared to the corresponding cyclohexanes.

With key intermediate **34** in hand, the base moiety (adenine) was introduced under Mitsunobu reaction

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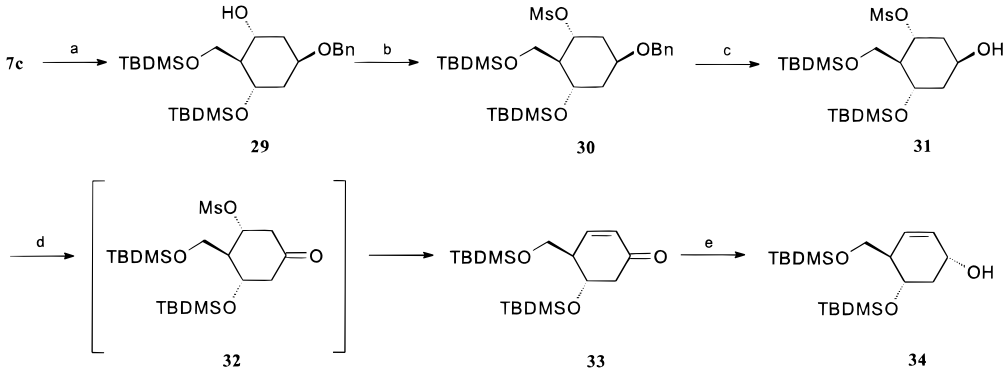
Scheme 4[a]



[a] Key: (a) TBDMSCl (1.2 equiv), imidazole (1.5 equiv), DMF, rt, 70%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 92%; (c) Pd−C (10%), $HCOONH_4$, MeOH, reflux, 76%; (d) MnO_2, CH_2Cl_2, rt, 48% and 47% recovery of **31**; (e) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C → rt, 91%.

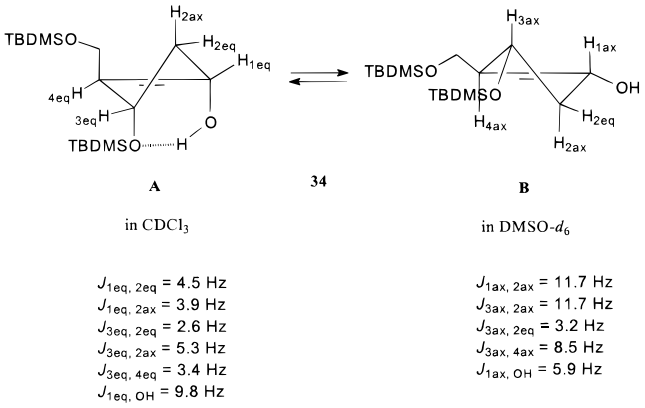


Figure 5. ^{1}H NMR experiment demonstrates the solvent-dependent conformational equilibrium of compound **34**.

conditions. Upon treatment of **34** with adenine in the presence of DEAD and PPh_3 in dioxane at room temperature for 1 day, **35a** was isolated in 66% yield, together with 17% of its N_7-isomer **35b** (Scheme 5). Complete deprotection of **35a** using TBAF in THF at room temperature afforded the desired cyclohexene carbocyclic nucleoside **36** in almost quantitative yield. However, the compound was contaminated with tetrabutylammonium salts that could not be removed by standard chromatographic techniques. Recently, Parlow et al.[20] described a workup procedure to remove tetrabutylammonium salts by the direct addition to the reaction mixture of mixed ion-exchange resins Amberlite 15 and Amberlite 15 in the Ca^{2+} form. Applied to the above TBAF reaction, a complex mixture was obtained, giving **36** in low yield. To avoid the use of TBAF, we turned to Megron's method:[21] compound **35a** was treated with potassium *tert*-butoxide in DMF at room temperature. However, only a complex reaction mixture was obtained, due to the strong basic character of the reaction conditions. Finally, **35a** was treated with a 3:1 mixture of TFA and H_2O at room temperature, which smoothly gave **36** in 54% overall yield starting from **34**. According to our experience, this is the best procedure to cleave TBDMS ethers of this type of compound. Finally, **36** was purified by reversed-phase HPLC for analysis and determination of biological activity.

Recently, we reported[3a] a synthesis of cyclohexane carbocyclic nucleosides **2a**. However, the synthetic approach was not enantioselective and **2a** was obtained as a racemic mixture of its D- and L-form. The separation of both isomers proved to be not easy.[3c] The above intermediate **36** (Scheme 5) gave us the opportunity to obtain as yet **2a** (B = adenine) in enantiopure form via reduction of the double bond. Thus, **36** was hydrogenated using H_2 under atmospheric pressure in the presence 10% palladium on carbon in MeOH at room temperature to afford D-**2a** in 75% yield. The spectral data of D-**2a** were superimposable with those of a DL mixture of **2a**. The enantiomeric purity of D-**2a** was examined by HPLC on a chiral column. The separation of a DL mixture of **2a** together with the HPLC profile of D-**2a** synthesized by the above approach is depicted in ref 3c. Its enantiomeric purity proved to be 99%, at the same time establishing the high enantiomeric purity of **36**.

Conformational Study

Conformational analysis of **36** was carried out using computational methods and ^{1}H NMR study. Molecular mechanics calculations were performed using MacroModel[22] with AMBER* as force field and H_2O as solvent. The global energy minimum was found to be the $^3H_2$ half-chair conformation with the adenine base moiety orienting in a pseudoaxial position (Figure 1). The energy difference between the most stable $^3H_2$ and $^2H_3$ conformations is 1.6 kJ/mol, corresponding to a ratio of about 7:3, respectively, of these two conformers. The calculated coupling constants (Boltzmann averaged over all 84 conformations within 50 kJ/mol of the global minimum) are in good agreement with the experimental values (solvent DMSO). (calcd: $J_{1',2'eq} = 4.9$ Hz, $J_{1',2'ax} = 4.9$ Hz, $J_{2'eq,3'} = 3.0$ Hz, $J_{2'ax,3'} = 9.2$ Hz; exptl: $J_{1',2'eq} = 4.9$ Hz, $J_{1',2'ax} = 5.3$ Hz, $J_{2'eq,3'} = 2.9$ Hz, $J_{2'ax,3'} = 9.3$ Hz). This result confirms the expected easy interconversion among the different conformers in a six-membered carbocyclic nucleoside by the introduction of a double bond in the ring.

The conformation of a nucleoside is determined by competing steric and stereoelectronic effects. In the case of hexitol nucleosides **1** and their saturated carbocyclic congeners **2**, the conformations are mainly controlled by steric effects such as 1,3-diaxial repulsions. Because the

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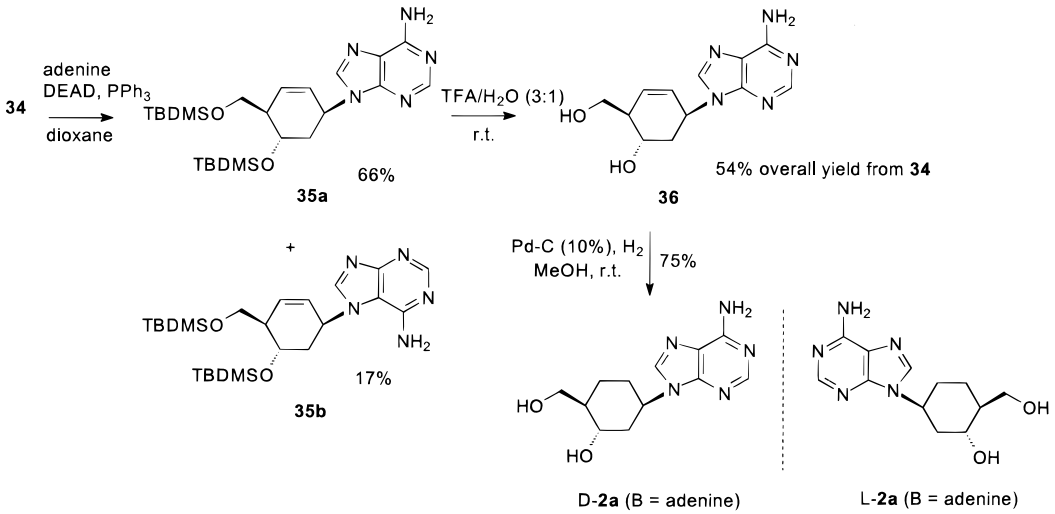
(21) Megron, G.; Vasquezy, F.; Galderon, G.; Cruz, R.; Gavino, R.; Islas, G. *Synth. Commun.* **1998**, *26*(16), 3021−3027.
(22) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

Scheme 5



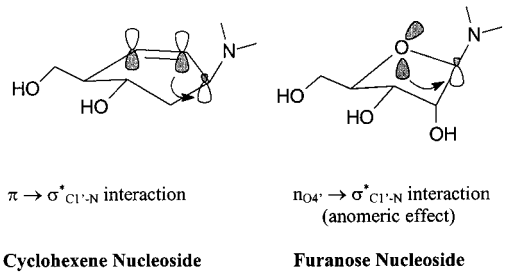


Figure 6. Comparison of anomeric effect in furanose nucleosides with $\pi \rightarrow \sigma^*_{C1'-N}$ effect in cyclohexene nucleosides.

axial free electron pair of the ring oxygen atom in **1** is smaller than the axial hydrogen in the corresponding position in **2**, compound **1** favors the $^1C_4$ conformation and compound **2** the $^4C_1$ conformation. As a consequence, the axial position of the base predominates in **1**, while their carbocyclic congeners **2** have an equatorially positioned base moiety. The conformation of the cyclohexene nucleosides **3**, which can be considered as a mimic of furanose nucleosides in which the ring oxygen atom is replaced by a double bond, is controlled by steric effects and by the $\pi \rightarrow \sigma^*_{C1'-N}$ interaction between the C5′−C6′ double bond and the heterocyclic aglycon (Figure 6). The $\pi \rightarrow \sigma^*_{C1'-N}$ effect is based on a similar principle as the anomeric effect and can be explained as an overlap between the antibonding of C1′−N and the orbitals of the π bond. In a 2′-deoxyfuranose nucleoside, the anomeric effect favors the N-conformation while the gauche effect (O4′−C4′−C3′−O) favors the S conformation. In the cyclohexene nucleosides, the anomeric effect is taken over by the $\pi \rightarrow \sigma^*_{C1'-N}$ interaction. This interaction drives the $^3H_2 \rightleftarrows {}^2H_3$ equilibrium toward the $^3H_2$ conformation, in which the base moiety is pseudoaxially oriented. Such an effect has been well studied in a 2′,3′-unsaturated pentopyranosyl nucleoside system.[23] The absence of a ring oxygen atom in **3** facilitates conformational studies due to the loss of the gauche effect. The pseudo-half-chair conformation of **3**, due to the presence of the double bond, also diminishes 1,3-diaxial repulsion as found with hexitol nucleosides. The energy difference between the conformations with equatorially and axially oriented base in the carbocyclic six-membered ring is therefore significantly reduced and the interconversion among them in a biological system might be easily possible.

The determination of the antiviral activity of **36** is in progress and will be published separately.

Conclusion

We have developed an enantioselective approach toward the synthesis of cyclohexene carbocyclic nucleosides starting from (*R*)-carvone **4**. The synthetic methodology makes use of a Mitsunobu reaction as the key step to introduce the heterocyclic base moiety. The reaction proved to be efficient as well as regio- and stereoselective, while the commonly applied palladium-mediated coupling strategy was unsuccessful. ^{1}H NMR and computation results show that in solution the synthesized adenine derivative **36** exists predominantly in a $^3H_2$ half-chair conformation with the adenine base orienting in a pseudoaxial position. The energy difference between $^3H_2$ and $^2H_3$ is, however, low. This compound may therefore be considered as an ideal mimic of a furanose nucleoside, showing two low energy conformations with a preference for the "3′-endo conformation". This is also the preferred conformation of a hexitol nucleoside, in the $^1C_4$ conformation. Moreover, the easy interconversion among both conformers might be an essential factor for antiviral activity.

Experimental Section

All analytical methods are previously described.[3b]

(1*R*,3*S*,5*R*)-5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2-methylenecyclohexanol (6c). A solution of 2,2,6,6-tetramethylpiperidine (TMP, 27.3 mL, 162 mmol) in dry benzene (80 mL) and dry toluene (80 mL) was cooled to 0 °C under N_2, and a solution of *n*-BuLi in hexane (1.6 M, 64.8 mL, 162 mmol) was added dropwise. The resulting mixture was stirred at 0 °C for 10 min, and a solution of Et_2AlCl (1.8 M, 90 mL, 162 mmol) in toluene was slowly added over a period of 1 h. The reaction was stirred for an additional 30 min. A solution of **5b** (14.1 g, 40.5 mmol) in benzene (30 mL) was added slowly. 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

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(24) Kraulis, P. J. *J. Appl. Crystallogr.* **1991**, *24*, 946−950.

with H_2O and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (*n*-hexanes−EtOAc 10:1) to give **6c** (10.2 g, 71%) as a light-yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.92 (s, 9H), 1.90 (m, 4H), 2.69 (d, 1H, J = 7.3 Hz, OH), 4.05 (m, 1H), 4.45 (m, 2H), 4.58 (s, 2H), 5.05 (s, 1H), 5.07 (s, 1H), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.1 (q), 18.0 (s), 25.7 (q), 40.7 (t), 40.9 (t), 70.4 (d and t, overlapped), 70.8 (d), 71.3 (d), 107.1 (t), 127.5 (d), 128.4 (d), 138.7 (s), 150.7 (s).

(1*R*,2*S*,3*S*,5*R*)-5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2-hydroxymethyl-cyclohexanol (7c) and Its Epimer 8c. To a solution of **6c** (10.8 g, 31.03 mmol) in dry THF (80 mL) at 0 °C under N_2 was added slowly a solution of 9-BBN in THF (0.5 M, 155 mL, 77.58 mmol). The reaction mixture was slowly warmed to room temperature overnight. The reaction was cooled to 0 °C and treated sequentially with EtOH (30 mL), a 2 N NaOH solution (60 mL), and a 35% H_2O_2 solution (60 mL) under stirring. The resulting mixture was stirred at room temperature for 24 h and then poured into a mixture of EtOAc (300 mL) and H_2O (300 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, and concentrated. The crude product was separated on silica gel (*n*-hexanes−EtOAc 5:1, then 1:1) to yield **7c** (8.4 g, 74%) and epimer **8c** (2.28 g, 20%) as a light-yellow oils.

7c: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (2s, 6H), 0.91 (s, 9H), 1.52 (ddd, 1H, J = 13.1, 10.1, 2.8 Hz), 1.54 (ddd, 1H, J = 13.1, 10.1, 3.1 Hz), 1.69 (tdd, 1H, J = 10.0, 7.5, 4.1 Hz), 2.10 (dt, 1H, J = 13.1, 4.1 Hz), 2.16 (dt, 1H, J = 13.1, 4.1 Hz), 2.71 (s, 1H), 3.11 (s, 1H), 3.78 (dd, 1H, J = 10.1, 7.5 Hz), 3.85 (td, 1H, J = 10.0, 4.2 Hz), 3.86 (m, 1H), 3.97 (br-td, 1H, J = 10.1, 4.1 Hz), 4.04 (br-dd, 1H, J = 10.1, 4.1 Hz), 4.51 (s, 2H), 7.26−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.0 (q), −4.3 (q), 17.8 (s), 25.7 (q), 38.1 (t), 38.4 (t), 53.2 (d), 63.4 (t), 68.0 (d), 69.4 (d), 70.3 (t), 72.4 (d), 127.4 (d), 127.6 (d), 128.4 (d), 138.7 (s); LISMS (THGLY) 367 $(M+H)^+$; HRMS calcd for $C_{20}H_{35}O_4Si$ $(M + H)^+$ 367.2305, found 367.2341.

8c: ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.85 (s, 9H), 1.40−1.87 (m, 3H), 2.25 (dm, 1H, J = 13.2 Hz), 2.48 (dm, 1H, J = 13.2 Hz), 3.69−4.20 (m, 6H), 4.33 (m, 1H), 4.53 (d, 1H, J = 11.7 Hz), 4.62 (d, 1H, J = 11.7 Hz), 7.33 (m, 5H), 8.79 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.6 (q), −5.0 (q), 21.9 (s), 25.5 (q), 39.2 (2t, overlapped), 45.9 (d), 61.3 (t), 69.0 (d), 69.4 (d), 70.4 (t), 70.8 (d), 127.6 (d), 127.7 (d), 128.4 (d), 138.6 (s); LISMS (THYLY) 367 $(M + H)^+$; HRMS calcd for $C_{20}H_{35}O_4Si$ $(M + H)^+$ 367.2305, found 367.2335.

(1*R*,2*R*,3*S*,5*S*)-5-Benzyloxy-3-(*tert*-butyldimethylsilyloxy)-2-(*tert*-butyldimethylsilyloxymethyl)cyclohexanol (29). To a solution of **7c** (2.5 g, 6.83 mmol) in DMF (50 mL) at room temperature were added imidazole (930 mg, 13.66 mmol) and TBDMSCl (1.23 g, 8.2 mmol) in portions. The reaction was stirred at room temperature overnight and quenched with ice. The resulting mixture was evaporated to remove DMF, and the residue was partitioned between EtOAc and H_2O. The layers were separated, and the aqueous layer was extracted with EtOAc (2×). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (*n*-hexanes−EtOAc 5:1) to yield **29** (2.28 g, 70%) as a light-yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.05, 0.06, 0.09 (3s, 12H), 0.89, 0.91 (2s, 18H), 1.53 (m, 2H), 1.72 (qd, 1H, J = 9.5, 4.4 Hz), 2.11 (m, 2H), 3.67 (t, 1H, J = 9.5 Hz), 3.78 (td, 1H, J = 9.5, 4.4 Hz), 3.87 (m, 1H), 4.01 (m, 1H), 4.16 (dd, 1H, J = 9.5, 4.4 Hz), 4.46 (d, 1H, J = 15.2 Hz), 4.48 (d, 1H, J = 15.2 Hz), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.7 (q), −5.1 (q), −4.3 (q), 17.8, 18.0 (2s), 25.7 (2q), 37.0 (t), 38.4 (t), 52.2 (d), 66.2 (t), 67.2 (d), 70.1 (t and d overlapped), 72.4 (d), 127.3 (d), 127.4 (d), 128.4 (d), 138.9 (s); LISMS (GLY): 481 $(M+H)^+$; HRMS cald for $C_{26}H_{49}O_4Si_2$ $(M + H)^+$ 481.3169, found 481.3199.

(1*R*,2*R*,3*S*,5*S*)-5-Benzyloxy-2-(*tert*-butyldimethylsilyloxymethyl)-3-(*tert*-butyldimethylsilyloxy)-1-methanesulfonyloxycyclohexane (30). To a solution of **29** (5.4 g, 11.25 mmol) in CH_2Cl_2 (120 mL) at 0 °C was added triethylamine (7.8 mL, 56.25 mmol), followed by dropwise addition of MsCl (1.3 mL, 16.87 mmol). The reaction was stirred at 0 °C for 1 h and treated with ice. The resulting mixture was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic layers were washed with a diluted HCl solution, H_2O, and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (*n*-hexanes−EtOAc 5:1) to afford **30** (5.81 g, 92%) as a white solid: mp 100−101 °C; ^{1}H NMR ($CDCl_3$) δ 0.08 (2s, 12H), 0.89 (s, 9H), 0.90 (s, 9H), 1.43 (ddd, 1H, J = 13.9, 10.0, 2.8 Hz), 1.62 (tt, 1H, J = 10.2, 2.0 Hz), 1.71 (ddd, 1H, J = 12.8, 10.6, 2.2 Hz), 2.24 (br-*d*, 1H, J = 13.9 Hz), 2.69 (br-*d*, 1H, J = 12.8 Hz), 3.01 (s, 3H), 3.74 (dd, 1H, J = 9.9, 2.2 Hz), 3.89 (m, 1H), 3.91 (dd, 1H, J = 9.9, 1.8 Hz), 4.19 (td, 1H, J = 10.0, 4.7 Hz), 4.45 (d, 1H, J = 12.0 Hz), 4.57 (d, 1H, J = 12.0 Hz), 5.13 (td, 1H, J = 10.6, 4.8 Hz), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.6 (q), −5.3 (q), −4.6 (q), −3.7 (q), 17.9 (s), 25.8 (q), 35.5 (t), 38.5 (t), 38.8 (q), 51.8 (d), 56.9 (t), 65.1 (d), 70.1 (t), 72.0 (d), 77.5 (d), 127.4 (d), 128.4 (d), 138.5 (s); LISMS(GLY/NBA) 559 $(M + H)^+$; HRMS calcd for $C_{27}H_{51}O_6SSi_2$ $(M + H)^+$ 559.2945, found 559.2979. Anal. Calcd for $C_{27}H_{50}O_6SSi_2$: C, 58.02; H, 9.02. Found: C, 57.96; H, 8.82.

(1*S*,3*R*,4*R*,5*S*)-4-*tert*-Butyldimethylsilyloxymethyl-5-*tert*-butyldimethylsilyloxy-3-methanesulfonyloxycyclohexanol (31). A mixture of **30** (3.5 g, 6.27 mmol), Pd/C (10%, 4.4 g), and $HCOONH_4$ (2.2 g) in MeOH (100 mL) was refluxed, and 2 × 1.1 g of $HCOONH_4$ was added every 3 h. The reaction was refluxed until all the starting material was consumed (total 14 h). After being cooled to room temperature, the reaction mixture was filtered through Celite and the residue was washed with CH_2Cl_2 (3×). The filtrate was concentrated to afford crude **31** (2,83 g, 97%) as a white solid, which was used as such for the next step: mp 135−137 °C; ^{1}H NMR ($CDCl_3$) δ 0.08, 0.09 (2s, 12H), 0.89 (s, 9H), 0.92 (s, 9H), 1.43−1.68 (m, 3H), 1.83 (ddd, 1H, J = 13.2, 10.6, 2.8 Hz), 2.07 (br-d, 1H, J = 13.2 Hz), 2.44 (br-d, 1H, J = 13.2 Hz), 3.02 (s, 3H), 3.72 (dd, 1H, J = 10.0, 2.4 Hz), 3.90 (dd, 1H, J = 10.0, 2.4 Hz), 4.19 (td, 1H, J = 10.6, 4.1 Hz), 4.26 (m, 1H), 5.14 (td, 1H, J = 10.6, 4.7 Hz); ^{13}C NMR ($CDCl_3$) δ −5.6 (q), −5.3 (q), −4.7 (q), −3.8 (q), 17.9 (s), 25.8 (q), 38.8 (q), 38.9 (t), 40.8 (t), 51.7 (d), 57.1 (t), 64.9 (d), 65.5 (d), 77.3 (d); LISMS (GLY/NBA) 469 $(M + H)^+$; HRMS calcd for $C_{20}H_{45}O_6SSi_2$ $(M + H)^+$ 469.2475, found 469.2453. Anal. Calcd for $C_{20}H_{44}O_6SSi_2$: C, 51.24; H, 9.46. Found: C, 51.24; H, 9.36.

(4*R*,5*S*)-4-*tert*-Butyldimethylsilyloxymethyl-5-*tert*-butyldimethylsilyloxycyclohex-2-en-1-one (33). A mixture of crude **31** (2.83 g, 6.27 mmol) and MnO_2 (13.6 g, 156.8 mmol) in dry CH_2Cl_2 (100 mL) was stirred vigorously at room temperature for 21 h. The reaction mixture was filtered through Celite and washed with CH_2Cl_2. The filtrate was concentrated, and the residue was chromatographed on silica gel (*n*-hexanes−EtOAc 5:1, then 1:2) to yield starting material **31** (1.56 g, 53%) and enone **33** (920 mg, 40% over two steps) as a light-yellow oil (solid upon storing in the refrigerator): ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 12H), 0.89 (s, 18H), 2.50 (m, 1H), 2.46 (dd, 1H, J = 16.1, 10.6 Hz), 2.72 (dd, 1H, J = 16.1, 4.8 Hz), 3.73 (dd, 1H, J = 9.9, 5.6 Hz), 3.85 (dd, 1H, J = 9.9, 4.4 Hz), 4.09 (ddd, 1H, J = 10.6, 8.1, 4.8 Hz), 6.06 (dd, 1H, J = 10.2, 2.6 Hz), 6.88 (dd, 1H, J = 10.2, 2.6 Hz); ^{13}C NMR ($CDCl_3$) δ −5.6 (q), −5.5 (q), −5.1 (q), −4.4 (q), 17.8 (s), 18.2 (s), 25.6 (q), 25.8 (q), 47.1 (t), 48.0 (d), 61.8 (t), 68.0 (d), 130.2 (d), 150.6 (d), 199.0 (s); LISMS (THGLY/NBA) 371 $(M + H)^+$; HRMS calcd for $C_{19}H_{39}O_3Si_2$ $(M + H)^+$ 371.2438, found 371.2432.

(1R,4*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldimethylsilyloxymethyl)cyclohex-2-en-1-ol (34). To a solution of **33** (920 mg, 2.49 mmol) in MeOH (35 mL) at room temperature under N_2 was added $CeCl_3 \cdot 7H_2O$ (1.39 g, 3.73 mmol). The mixture was stirred for 0.5 h, and a clear solution was obtained. $NaBH_4$ (113 mg, 2.99 mmol) was added in portions and H_2 evolved. The reaction mixture was stirred for 1 h and quenched with H_2O. The mixture was stirred for 15 min and concentrated. The residue was diluted with EtOAc, washed with H_2O and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel (*n*-hexanes−EtOAc 10:1) to give **34** (844 mg, 91%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H),

0.10 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 1.94 (ddd, 1H, J = 13.7, 5.3, 3.9 Hz), 1.99 (ddd, 1H, J = 13.7, 4.5, 2.6 Hz), 2.36 (m, 1H), 2.94 (d, 1H, J = 9.8 Hz), 3.38 (dd, 1H, J = 10.1, 7.8 Hz), 3.56 (dd, 1H, J = 10.1, 5.0 Hz), 4.09 (pseudo sext, 1H, J = 9.8, 4.5, 4.0, 3.9 Hz), 4.20 (pseudo pent, 1H, J = 5.3, 3.4, 2.6 Hz), 5.61 (dd, 1H, J = 10.0, 3.9 Hz), 5.95 (ddd, 1H, J = 10.0, 4.0, 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ −5.5 (q), −5.4 (q), −4.9 (q), −4.8 (q), 18.0 (s), 18.3 (s), 25.8 (q), 25.9 (q), 35.6 (t), 46.5 (d), 63.5 (t), 64.8 (d), 67.7 (d), 127.0 (d), 131.1 (d); LISMS (THGLY/NBA) 373 $(M + H)^+$; HRMS calcd for $C_{19}H_{40}O_3Si_2$ $(M + H)^+$ 373.2594, found 373.2626. Anal. Calcd for $C_{19}H_{39}O_3Si_2$: C, 61.23; H, 10.82. Found: C, 61.34; H, 10.83.

9-[(1*S*,4*R*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-(*tert*-butyldimethylsilyloxymethyl)-2-cyclohexenyl]adenine (35a). To a mixture of **34** (660 mg, 1.774 mmol), adenine (480 mg, 3.55 mmol), and PPh_3 (931 mg, 3.55 mmol) in dry dioxane (20 mL) under N_2 at room temperature was added a solution of DEAD (565 μL, 3.55 mmol) in dry dioxane (10 mL) over a period of 45 min. The reaction mixture was stirred at room temperature overnight and concentrated, and the residue was chromatographed on silica gel (CH_2Cl_2−MeOH 50:1, then 20:1) to yield crude **35a** (960 mg) as a yellow foam: ^{1}H NMR ($CDCl_3$) δ −0.12 (s, 3H), −0.06 (s, 3H), 0.10 (s, 3H), 0.11 (s, 3H), 0.83 (s, 9H), 0.94 (s, 9H), 2.01−2.25 (m, 2H), 2.32 (m, 1H), 3.73 (dd, 1H, J = 9.9, 4.8 Hz), 3.82 (dd, 1H, J = 9.9, 4.4 Hz), 3.97 (ddd, 1H, J = 10.2, 7.0, 4.0 Hz), 5.37 (m, 1H), 5.73 (s, 2H), 5.88 (ddd, 1H, J = 9.9, 3.7, 2.5 Hz), 6.06 (ddd, 1H, J = 9.9, 2.2, 1.1 Hz), 7.86 (s, 1H), 8.39 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.5 (q), −5.4 (q), −5.0 (q), −4.6 (q), 17.8 (s), 18.3 (s), 25.6 (q), 25.9 (q), 36.5 (t), 47.2 (d), 49.6 (d), 62.9 (t), 64.5 (d), 120.2 (s), 124.4 (d), 134.9 (d), 139.9 (d), 149.8 (s), 153.0 (d), 155.5 (s); LISMS (THGLY/NBA) 490 $(M + H)^+$; HRMS calcd for $C_{24}H_{44}N_5O_2Si_2$ $(M + H)^+$ 490.3034, found 490.3058.

9-[(1*S*,4*R*,5*S*)-5-Hydroxy-4-hydroxymethyl-2-cyclohexenyl]adenine (36). Crude **35a** was treated with TFA−H_2O (3:1, 40 mL) at room temperature overnight. The reaction mixture was concentrated and coevaporated with toluene (2×). The residue was chromatographed on silica gel (CH_2Cl_2−MeOH 20:1, then 5:1) to afford **36** (149 mg, 54% over two steps): mp 90−92 °C; ^{1}H NMR (CD_3OD) δ 2.01−2.33 (m, 3H), 3.80 (d, 2H, J = 4.8 Hz), 3.84 (m, 1H), 5.33 (m, 1H), 5.94 (ddd, 1H, J = 9.9, 3.7, 2.6 Hz), 6.13 (ddd, 1H, J = 9.9, 2.5, 1.4 Hz), 8.09 (s, 1H), 8.21 (s, 1H); ^{13}C NMR (CD_3OD) δ 37.3 (t), 47.9 (d), 51.1 (d), 63.1 (t), 64.7 (d), 120.6 (s), 125.3 (d), 136.1 (d), 141.6 (d), 150.4 (s), 153.7 (d), 157.5 (s); UV λ_{max} (MeOH) = 260 nm; LISMS (THGLY/NBA) 262 $(M + H)^+$; HRMS calcd for $C_{12}H_{16}N_5O_2$ $(M + H)^+$ 262.1304, found 262.1359. Anal. Calcd for $C_{12}H_{15}N_5O_2 \cdot 0.7H_2O$: C, 52.62; H, 6.04; N, 25.57. Found: C, 52.62; H, 5.95; N, 25.77.

9-[(1*R*,3*S*,4*R*)-3-Hydroxy-4-hydroxymethylcyclohexanyl]adenine (2a). A mixture of **36** (45 mg, 0.17 mmol) and Pd/C (10%, 40 mg) in MeOH (5 mL) was stirred under H_2 at room temperature for 24 h. The reaction mixture was cooled to room temperature, filtered through Celite, and washed with MeOH. The filtrate was concentrated, and the residue was purified by reversed-phase HPLC (5% CH_3CN in H_2O) to yield **2a** (35 mg, 78%) as a white foam: ^{1}H NMR (CD_3OD) δ 1.71 (m, 1H), 1.87−2.18 (m, 5H), 2.39 (m, 1H), 3.69 (dd, 1H, J = 14.0, 7.3 Hz), 3.74 (dd, 1H, J = 14.0, 6.9 Hz), 4.12 (m, 1H), 4.87 (m, 1H, overlapped with HOD), 8.18 (s, 1H), 8.21 (s, 1H); ^{13}C NMR (CD_3OD) δ 22.6 (t), 28.7 (t), 36.1 (t), 53.6 (d), 51.9 (d), 63.3 (t), 68.4 (d), 120.4 (s), 141.1 (d), 150.6 (s), 153.5 (d), 157.4 (s); LISMS (THGLY/NBA) 264 $(M + H)^+$; HRMS calcd for $C_{12}H_{18}N_5O_2$ $(M + H)^+$ 264.1460, found 264.1449.

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