JOC*Note*

An Expeditious and Efficient Procedure for the Synthesis of Unsaturated Acyclonucleosides of *Z* Configuration Related to D4T

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Abstract: Enantiopure 2,5-dihydrofuran derivatives were prepared from (*S*)-glycidol through a new reaction sequence involving epoxide opening with a vinylcuprate, selenium-induced cyclization to give exclusively the 5-*endo* product, and regioselective selenoxide elimination. Unsaturated acyclonucleosides of *Z* configuration were obtained in a straightforward manner by treating 2,5-dihydrofuran with iodotrimethylsilane in the presence of silylated purinic or pyrimidinic bases. This synthetic process involves opening of the dihydrofuran ring by trimethylsilyl iodide and substitution of iodine by the nucleic base in a single reaction step.

Unsaturated nucleosides such as d4T[1] (**1**) and neplanocin A[2] (**2**) are strong inhibitors of HIV reverse transcriptase and *S*-adenosylhomocysteine-hydrolase. Prompted by these findings and by the fact that several acyclonucleosides[3] such as acyclovir,[4] (**3**) gancyclovir[5] (**4**), and pencyclovir[6] (**5**) are currently used in the treatment of several viral diseases, different unsaturated acyclonucleosides were prepared and tested as antiviral and antitumor agents. Nucleosides **6**[7] and **7**,[8,9] conceptually derived from **1** by removing the furanose oxygen or breaking the O−C_1 bond, respectively, and **8** (R = H)[8−10] showed only weak antiviral activity. However, the presence of a phosphonate[7,11] group (**8**, R = $CH_2P(O)(OH)_2$, base = adenine) or phosphoroalaninate (**8**, R = $[CH_3O_2CCH(CH_3)NH]P(O)(OH)_2$, base = adenine)[12] in place of the free OH significantly increases the antiviral activity. Compound **8** (R = $CH_2P(O)(OH)_2$, base = thymine) has also been shown to be an inhibitor of the thymidine phosphorylase.[13] Unsaturated acyclonucleosides of *Z* configuration are currently prepared in several ways: (a) by nucleophilic substitution of appropriately protected propargyl derivatives followed by reduction,[7] (b) by selective protection of *cis*-2-butene-1,4-diols, followed by halogenation and substitution,[10,12] (c) from *cis*-1,4-dichloro-2-butene,[11] or (d) from chiral glyceraldehyde with the cis selective Horner−Emmons reaction.[8]

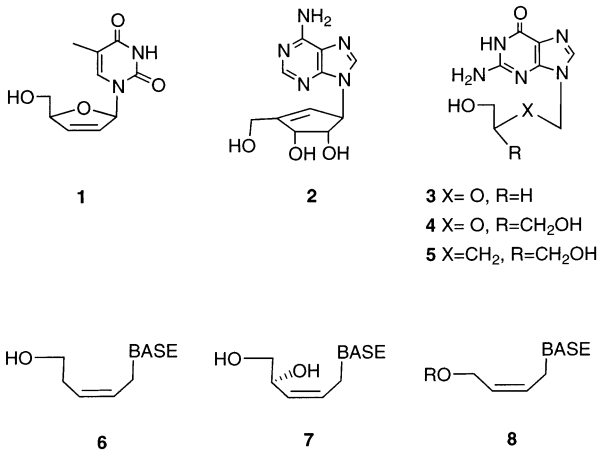

FIGURE 1.

In this Note we describe an expeditious, highly efficient and stereoselective procedure for synthesizing unsaturated acyclonucleosides of *Z* configuration from 2,5-dihydrofuran, as well as a direct method to prepare chiral enantiopure 2,5-dihydrofuran derivatives.

There are only a few examples of 2,5-dihydrofuran opening under acidic conditions. They involve the use of acetic−toluenesulfonic mixed anhydride,[14] acetyl chloride and $CoCl_2$[15] or $Mo(CO)_6$ as catalyst,[16] acetyl bromide,[17] or Et_2NSiMe_3/MeI as an equivalent of iodotrimethylsilane.[18] Iodotrimethylsilane (Me_3SiI) is a particularly

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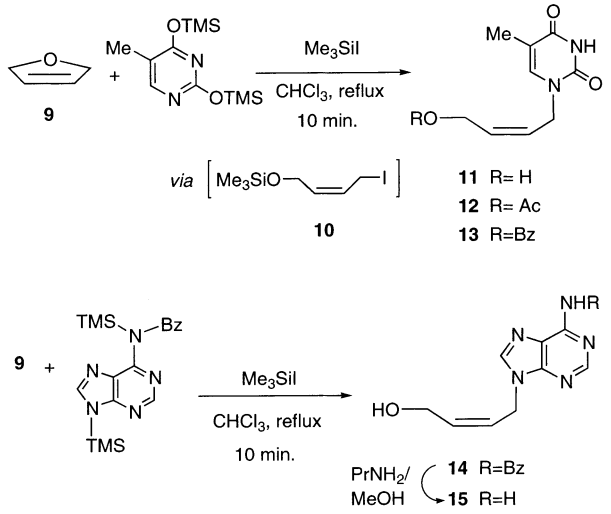
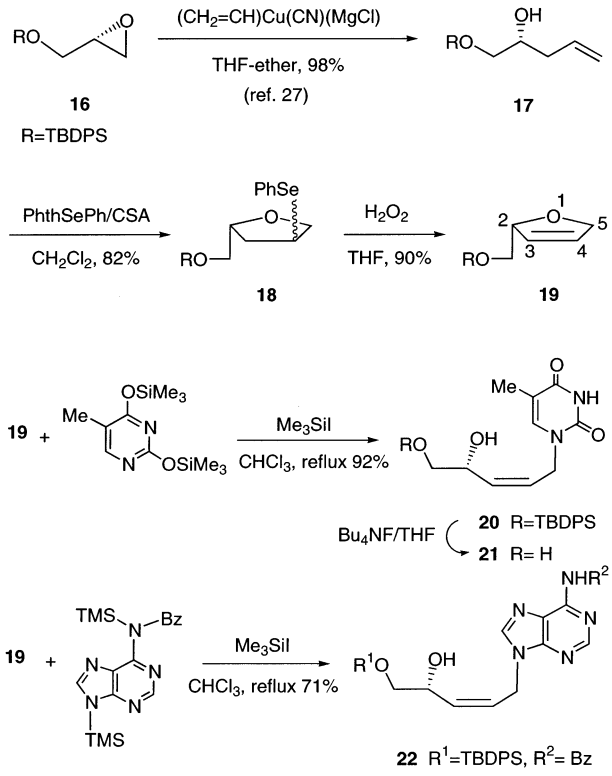
SCHEME 1



efficient reagent for ether cleavage.[19] It has also been used as a promotor in glycosylation reactions leading to oligosaccharides[20] and nucleosides,[21] as well as in the synthesis of acyclonucleosides from acyclic donors.[22] We expected that iodotrimethylsilane would open the 2,5-dihydrofuran ring to give an iododerivative that would convert to an acyclonucleoside in the presence of a purine or pyrimidine base.

Initially, we treated commercially available dihydrofuran **9** with bis(trimethylsilyl)thymine in the presence of Me_3SiI in refluxing chloroform, and we observed that compound **11** was quickly formed (Scheme 1). Although the *Z* isomer predominated, some isomerization to the *E*-alkene occurred with increasing the reaction time (ratio $Z/E = 23:1$ at 10 min and 5:1 at 30 min).[9,23] The *E* isomer was produced in a $Z/E = 20$ ratio when the reaction was performed at room temperature, but the reaction was much slower. Although previous reports stated that refluxing 2,5-dihydrofuran with Et_2NSiMe_3/MeI gave almost exclusively the *E* isomer,[18] in our case the *Z* isomer was always the major product, probably because the initially formed intermediate **10** is transformed into the nucleoside prior to isomerization. The 2,5-dihydrofuran was recovered unchanged when TMSI was replaced with TMSOTf, suggesting that intermediate **10** is initially formed. In fact, the allylic iodide **10** was detected when the reaction was conducted in the absence of the nucleic base. Although the *Z*/*E* mixture of **11** was inseparable, the acyl derivatives **12** and **13** allowed the isolation of the *Z* isomer in pure form.

SCHEME 2



Similarly, compound **14** was obtained in 60% yield starting from N^6-benzoyl-*N*,[6]9-bis(trimethylsilyl)adenine.[24] The *Z* isomer was obtained by crystallization. Deprotection of amine **14** by reaction with $PrNH_2$/MeOH provided the acyclonucleoside **15**.

We next applied this procedure to the synthesis of chiral acyclonucleosides **20** and **21** (Scheme 2). We have recently reported that the mode of cyclization of 4-pentene-1,2,3-triols can be governed by the electrophile. Thus, iodo electrophiles give the 5-*exo* cyclization involving the primary hydroxyl, while selenium electrophiles give the 5-*endo* cyclization by involving the secondary hydroxyl.[25] It is also known that selenoxide is preferentially eliminated to give C−C double bonds instead of enolethers.[26]In this context, glycidol **16** was treated with a vinylcuprate to obtain the alkenediol **17** in excellent yield.[27] Compound **17** was then reacted with phenylselenenylphthalimide (PhthSePh) in the presence of catalytic camphorsulfonic acid (CSA) to obtain the tetrahydrofuran **18**, resulting from 5-*endo* cyclization, as a 25:75 mixture of diastereomers in 82%.[25] The mixture of selenotetrahydrofurans **18** was oxidized by treatment with hydrogen peroxide to give exclusively the 2,5-

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dihydrofuran **19**.[26] The reaction of dihydrofuran **19** with bis(trimethylsilyl)thymine in the presence of Me_3SiI gave **20** in 92% yield, although the reaction rate was much slower. Treatment of compound **20** with Bu_4NF provided the acyclonucleoside **21** related to d4T (**1**) in 97% yield. The adenine derivative **22** was similarly produced in good yield, by treating **19** with N^6-benzoyl-*N*,[6]9-bis(trimethylsilyl)adenine. No traces of the *E* isomer were observed in either case.

In conclusion, a new methodology has been developed for the stereo- and regioselective synthesis of acyclonucleosides analogous to the antiviral dideoxydidehydronucleosides. The *Z*-selectivity of this process involving the intermediacy of reactive allylic iodides of *Z*-configuration is particularly noteworthy.

Experimental Section

General Procedures. Melting points are uncorrected. Optical rotations were measured at 25 °C in 10-cm cells. ^{1}H NMR and ^{13}C NMR spectra were recorded on 300 or 400 MHz (300, 75.4 and 400, 100.5 MHz, respectively) Varian equipment, with $CDCl_3$ as solvent, unless otherwise specified. Coupling constants are given in hertz (Hz). Elemental analyses were determined at the Servei de Recursos Científics (Universitat Rovira i Virgili). Flash column chromatography was performed using silica gel 60 A CC (40−63 mμ). Radial chromatography was performed on 1-, 2-, or 4-mm plates of silica gel, depending on the amount of product. Medium-pressure chromatography (MPLC) was performed using silica gel 60 A CC (6−35 mμ). Band separation was monitored by UV. TLC plates were prepared by using Kieselgel 60 PF_{254}. Solvents for chromatography were distilled at atmospheric pressure prior to use. Reaction solvents were purified and dried by using standard procedures.[28]

General Procedure for the Synthesis of Acyclonucleosides from 2,5-Dihydrofuran Derivatives. The 2,5-dihydrofuran derivative (1 mmol) in anhydrous chloroform (1 mL) was added to a solution of the silylated base (3 mmol) in anhydrous chloroform (2 mL). Then iodotrimethylsilane (1.3 mmol) was added and the reaction mixture was heated to reflux. The reaction mixture was then allowed to cool at room temperature and was poured into an aqueous solution of sodium bicarbonate. The aqueous layer was extracted with ethyl acetate, and the combination of extracts was washed with an aqueous solution of sodium thiosulfate (10%) and dried over $MgSO_4$ and the solvent was evaporated under vacuum. The residue was purified by chromatography or by crystallization to obtain the acyclonucleoside.

1-[(2′*Z*)-2′-Buten-4′-acetoxy-1′-yl]thymine (12). Starting from 2,5-dihydrofuran (**9**, 100 μL, 1.32 mmol) and bis(trimethylsilyl)thymine (3.96 mmol), the general procedure of acyclonucleoside synthesis was applied maintaining the reaction at reflux for 10 min, to obtain an inseparable mixture of **10** and the *E* isomer (ratio *Z*/*E* = 23:1). This mixture was then dissolved in anhydrous pyridine (1 mL) and treated with an excess of acetic anhydride (4 mmol). When the reaction was finished the mixture was poured into ice/water and was extracted with dichloromethane. The organic extracts were dried, evaporated under vacuum, and purified by MPLC (hexane to hexane/ethyl acetate 1:3) to obtain 241 mg (77%) of acetylated products. Crystallization of the mixture (ethyl acetate) provided compound **12** as colorless crystals (212 mg, 68%). Mp 113−115 °C. ^{1}H NMR ($CDCl_3$) δ 9.04 (s, 1H), 7.12 (q, 1H, J = 1.2 Hz), 5.80 (dtt, 1H, J = 10.8, 7.2, 1.2), 5.65 (dtt, 1H, J = 10.8, 7.2 Hz, 1.2 Hz), 4.72 (dd, 2H, J = 7.2, 1.6 Hz), 4.47 (dd, 2H, J = 7.2, 1.2 Hz), 2.09 (s, 3H), 1.92 (d, 3H, J = 1.2 Hz). ^{13}C NMR ($CDCl_3$) δ 170.9, 164.1, 150.8, 139.8, 128.5, 127.9, 111.1, 59.4, 44.3, 20.9, 12.3. Anal. Calcd for $C_{11}H_{13}N_2O_4$: C, 55.46; H, 5.88; N, 11.77. Found: C, 55.56; H, 6.02; N, 11.83.

9-[(2′*Z*)-2′-Buten-4′-hydroxy-1′-yl]- N^6-benzoyladenine (14). Starting from 2,5-dihydrofuran (**9**, 50 μL, 0.66 mmol) and (**9**) bis(trimethylsilyl)adenine (1.98 mmol), the general procedure for synthesizing acyclonucleosides was applied. The reaction was maintained for 30 min to obtain compound **14** as a mixture (ratio *Z*/*E* = 5:1). Crystallization of the mixture (methanol) provided 110 mg (54%) of compound **14** as colorless crystals. Mp 174−176 °C. ^{1}H NMR (CD_3OD) δ 8.57 (s, 1H), 8.27 (d, 2H), 8.24 (s, 1H), 7.54−7.42 (m, 3H), 5.85 (dtt, 1H, J = 11.2, 6.0, 1.6), 5.79 (dtt, 1H, J = 11.2, 6.4, 1.2), 5.35 (dd, 2H, J = 6.0, 1.2), 5.21 (dd, 2H, J = 6.4, 1.6). ^{13}C NMR (CD_3OD) δ 150.4, 148.9, 138.3, 134.6, 133.1, 130.9, 129.1, 126.4, 58.9, 48.2 (quaternary carbons not included, except carbonyl). Anal. Calcd for $C_{16}H_{15}N_5O_2$: C, 62.14; H, 4.86; N, 22.65. Found: C, 62.29; H, 5.00; N, 22.71.

9-[(2′*Z*)-2′-Buten-4′-hydroxy-1′-yl]-adenine (15).[9] Compound **14** (123 mg, 0.40 mmol) was dissolved in $PrNH_2$ (10 M in MeOH, 2.5 mL) and heated to reflux for 24 h. After evaporation the residue was purified by chromatography in a short column eluting with CH_2Cl_2/methanol 9:1 to give compound **15** as a syrup (56 mg, 69% yield). ^{1}H NMR (DMSO-d_6) δ 8.12 (s, 1H), 8.08 (s, 1H), 7.75 (br s, 2H), 5.65−5.52 (m, 2H), 4.15−4.05 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 152.0, 139.0, 131.7, 127.2, 57.0, 37.2. (quaternary carbons not included). Anal. Calcd for $C_9H_{11}N_5O$: C, 52.68; H, 5.36; N, 34.15. Found: C, 52.51; H, 5.28; N, 34.02.

(3*S*,5*R*)-3-Phenylselenenyl-5-(*tert*-butyldiphenyl)silyloxymethyl-tetrahydrofuran (18a) and (3*R*,5*R*)-3-Phenylselenenyl-5-(*tert*-butyldiphenyl)silyloxymethyl-tetrahydrofuran (18b). Compound **17** (510 mg, 1.50 mmol) was dissolved in dichloromethane (23 mL) and then camphorsulfonic acid (104 mg, 0.45 mmol) and *N*-phenylselenophthalimide (544 mg, 1.80 mmol) were added. The resulting reaction mixture was heated to reflux for 12 h and was then left to cool at room temperature and filtered over a silica gel pad and the solvent evaporated under vacuum. The residue was purified by MPLC using linear gradient (hexane to hexane/ethyl acetate 5/1), to afford compounds **18a** + **18b** as a diastereoemeric mixture (ratio 25:75) (624 mg, 84%). Both compounds were separated by radial chromatography (hexane/ethyl acetate 10:1).

18a (higher R_f): $[\alpha]^{25}_D$ −6.6 (*c* 1.70. $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.8−7.0 (m, 15H), 4.25−4.15 (m, 2H), 4.90−3.74 (m, 2H), 3.71 (dd, 1H, J = 10.8, 4.5), 3.63 (dd, 1H, J = 10.8, 4.2), 2.35 (ddd, 1H, J = 13.2, 6.9, 6.0), 2.02 (ddd, 1 H, J = 13.2, 7.5, 5.8), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$) δ: 135.7, 135.6, 134.2, 133.5, 129.7, 129.3, 129.2, 127.7, 127.6, 79.0, 74.4, 65.9, 39.3, 35.1, 26.7, 19.1. Anal. Calcd for $C_{27}H_{32}O_2SeSi$: C, 65.44; H, 6.51. Found: C, 65.53; H, 6.65.

18b: $[\alpha]^{25}_D$ +19.3 (*c* 0.914. $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.8−7.2 (m, 15H), 4.12 (dd, 1H, J = 8.4, 6.6), 4.15−4.05 (m, 1H), 3.80 (td, 1H, J = 8.4, 8.4, 1.5), 3.8−3.6 (m, 3H), 2.40 (dt, 1H, J = 12.9, 7.0), 1.88 (dtd, 1H, J = 12.9, 8.1, 1.5), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 135.7, 134.9, 134.2, 133.5, 129.7, 129.2, 127.7, 127.7, 127.6, 127.4, 79.6, 74.1, 65.9, 38.5, 35.1, 26.7, 19.1. Anal. Calcd for $C_{27}H_{32}O_2SeSi$: C, 65.44; H, 6.51. Found: C, 65.60; H, 6.51.

(5*R*)-5-(*tert*-Butyldiphenyl)silyloxymethyl-2,5-dihydrofuran (19). A mixture of compounds **18a** + **18b** (624 mg, 1.26 mmol) was dissolved in THF (8 mL) and cooled in an ice bath. Then pyridine (8 drops) and 10% H_2O_2 (2.4 mL, 7.56 mmol) were added. The reaction was stirred for 1 h and was then quenched by adding water. The reaction mixture was extracted with dichloromethane, and the organic phase was dried with magnesium sulfate and evaporated under vacuum. The residue obtained was purified by flash chromatography eluting with hexane/ethyl acetate 5:1, to obtain compound **19** as a white solid (391 mg, 92%). Mp 39−42 °C. $[\alpha]^{25}_D$ +69.3 (*c* 0.878. $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.8−7.3 (m, 10H), 5.95 (ddd, 1H, J = 6.3, 3.6, 1.8), 5.82 (ddt, 1H, J = 6.3, 2.5, 1.5), 4.91 (dddt, 1H, J = 4.8, 4.8, 3.6, 1.8, 1.5), 4.69 (ddd, 1H, J = 12.8, 2.5, 1.8), 4.63 (ddd, 1H, J = 12.8, 2.5, 1.8), 3.72 (dd, 1H, J = 10.5, 4.8), 3.68 (dd, 1H, J = 10.5, 4.8), 1.05 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 135.7, 135.6, 133.7, 133.6, 129.6 (2 C), 127.8, 127.6 (2 C), 127.4, 86.6, 75.6,

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66.5, 26.6, 19.1. Anal. Calcd for $C_{21}H_{26}O_2Si$: C, 74.51; H, 7.74. Found: C, 74.21; H, 7.84.

1-[(4′*R*)-5′-*O*-*tert*-Butyldiphenylsilyl-2′-penten-4′,5′-diol-1′-yl]thymine (20). Starting from compound **19** (110 mg, 0.32 mmol) and bis(trimethylsilyl)thymine (0.96 mmol), the general procedure of acyclonucleoside synthesis was applied maintaining the reaction at reflux for 12 h. The reaction crude was purified by radial chromatography (hexane/ethyl acetate 1:3) to obtain compound **20** as a foam (139 mg, 92%). $[\alpha]^{25}_D$ −40.4 (*c* 1.251. $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 9.99 (s, 1H), 7.7−7.3 (m, 10H), 7.01 (s, 1H), 5.66 (dd, 1H, *J* = 11.0, 7.4), 5.53 (m, 1H), 4.64 (q, 1H, *J* = 6.3, 6.3, 6.3), 4.39 (dd, 1H, *J* = 15.2, 8.4), 4.31 (ddd, 1H, *J* = 15.2, 6.0, 1.2), 3.67 (dd, 1H, *J* = 10.4, 6.8), 3.64 (dd, 1H, *J* = 10.4, 5.2), 3.37 (br s, 1H), 1.87 (s, 3H), 1.08 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 164.4, 151.2, 139.8, 135.5, 135.4, 133.7, 132.9, 132.8, 129.9, 129.8, 127.7, 126.1, 111.0, 68.3, 67.2, 44.9, 26.7, 19.1, 12.2. Anal. Calcd for $C_{26}H_{32}N_2O_4Si$: C, 67.21; H, 6.94; N, 6.03. Found: C, 67.15; H, 6.89; N, 5.98.

1-[(4′*R*)-2′-Penten-4′,5′-diol-1′-yl]thymine (21). A solution of compound **20** (120 mg, 0.26 mmol) in 2 mL of dry THF was treated with tetrabutylammonium fluoride (1 M solution in THF, 0.30 mmol) at 0 °C and under argon atmosphere. The reaction was monitored by TLC in ethyl ether/petroleum chloroform/methanol 9:1. After 2 h the reaction mixture was left to warm to room temperature, poured into a water/ice mixture, and extracted with ether. The combination of extracts was concentrated and chromatographed in a short column eluting with CH_2Cl_2/methanol 9:1 to obtain compound **21** as an oil (56 mg, 97%). $[\alpha]^{25}_D$ −19.81 (*c* 1.060. CH_3OH). ^{1}H NMR (CD_3OD) δ 7.27 (s, 1H), 5.57 (dd, 1H, *J* = 10.8, 8.0), 5.47 (m, 1H), 4.46 (q, 1H, *J* = 7.2, 7.2, 7.2), 4.40 (dd, 1H, *J* = 15.2, 7.2), 4.35 (dd, 1H, *J* = 15.2, 6.4), 3.48 (dd, 1H, *J* = 11.2, 6.8), 3.41 (dd, 1H, *J* = 11.2, 5.2), 1.79 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 164.6, 150.8, 140.3, 133.4, 125.4, 109.9, 67.4, 64.9, 44.3, 11.1. Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.19; N, 12.39. Found: C, 52.89; H, 6.08; N, 12.23.

9-[(4′*R*)-(5′-*O*-*tert*-Butyldiphenylsilyl-2′-penten-4′,5′-diol-1′-yl]-N^6-benzoyladenine (22). Starting from compound **19** (139 mg, 0.41 mmol) and bis(trimethylsilyl)-^{6}*N*-benzoyladenine (1.23 mmol), the general procedure of acyclonucleosides synthesis was applied. The reaction was maintained for 12 h and the reaction crude was purified by MPLC using linear gradient (hexane to hexane/ethyl acetate 1:2) to obtain compound **22** as a foam (168 mg, 71%). $[\alpha]^{25}_D$ −12.03 (*c* 0.910. $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.4 (s, 1H), 8.2 (d, 2H), 8.1 (s, 1H), 7.7−7.6 (m, 4H), 7.5−7.1 (m, 9H), 5.86 (dddd, 1H, *J* = 11.2, 7.2, 6.4, 1.6), 5.66 (ddt, 1H, *J* = 11.2, 11.2, 6.4, 1.2), 5.23 (ddd, 1H, *J* = 14.8, 6.4, 1.6), 5.08 (ddd, 1H, *J* = 14.8, 7.2, 1.6), 4.70 (m, 1H), 3.70 (dd, 1H, *J* = 10.4, 4.0), 3.64 (dd, 1H, *J* = 10.4, 8.), 1.08 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 175.4, 146.6, 141.4, 132.1, 137.5, 135.6, 135.5, 131.9, 130.1, 130.0, 129.8, 128.1, 127.9, 127.1, 69.3, 67.4, 47.3, 26.8, 19.2. Anal. Calcd for $C_{33}H_{35}N_5O_3Si$: C, 68.63; H, 6.07; N, 12.13. Found: C, 68.92; H, 6.17; N, 11.98.

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