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2'-Spirocyclopropyl-carbocyclic Nucleoside as a Novel Scaffold for Potent Anti-HCV Agents

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The discovery of 2'-spirocyclopropyl-ribocytidine (*J. Med. Chem.* **2010**, *53*, 8150-8160) as a potent inhibitor of RNA synthesis by NS5B (IC_{50} = 7.3 μM), the RNA polymerase encoded by hepatitis C Virus (HCV), has led to the synthesis and biological evaluation of several carbocyclic versions of 2'-spiropropyl-nucleosides. The cyclopentenol intermediate **7** was successfully constructed *via* ring-closing metathesis (RCM) from divinyl **6**. Spirocyclopropanation of enone **8** was effected by using (2-chloroethyl)-dimethylsulfonium iodide and potassium *tert*-butoxide to form the desired intermediate **9**. The synthesized nucleoside analogues **21**-**24** were assayed for their ability to inhibit HCV RNA replication in a subgenomic replicon Huh7 cell line. Among them, the cytosine nucleoside analogue **22** exhibited significant anti-HCV activity (EC_{50} = 18.2 μM).

Key Words : Anti-HCV agent, Ring-closing metathesis, 2'-Spirocarbocyclic nucleoside

Introduction

Hepatitis C virus (HCV) infection is a leading cause of chronic hepatitis, liver cirrhosis and hepatoma carcinoma.[1] However, there is no effective chemotherapy for the treatment of HCV infection except immunotherapy using ribavirin in combination with interferon-α, which leads to a sustained virological response in only about half of the patients treated.[2]

To date, despite extensive exploration of many novel scaffolds,[3] including carbocyclic derivatives,[4] only two different classes of potent HCV nucleosides have progressed. The first such class of HCV nucleoside inhibitors (NIs) encompasses 2'-modified ribonucleoside derivatives, with 2'-β-*C*-methyl analogues being particularly important. Among these derivatives, 2'-methylcytidine[5] **1** and 2'-methyl-2'-fluorocytidine[6] **2** led to the most promising HCV NIs (Figure 1). Through further modification of these derivatives, 2'-deoxy-2'-spirocyclopropylcytidine[7] **3** was discovered as a new member of the class of 2'-modified nucleoside derivatives that have HCV inhibiting properties. Compound **3** is a novel potent (EC_{50} = 7.3 mM) and selective (CC_{50} > 98.4 μM) inhibitor of the HCV NS5B RNA-dependent RNA polymerase, a clinically validated target for HCV treatment.

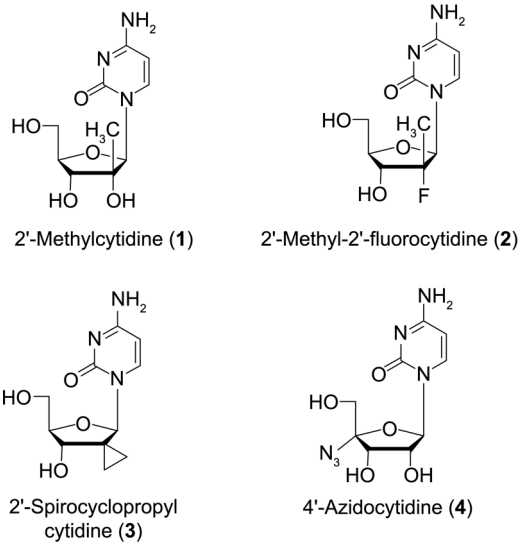


Figure 1. Structures of potent anti-HCV agents.

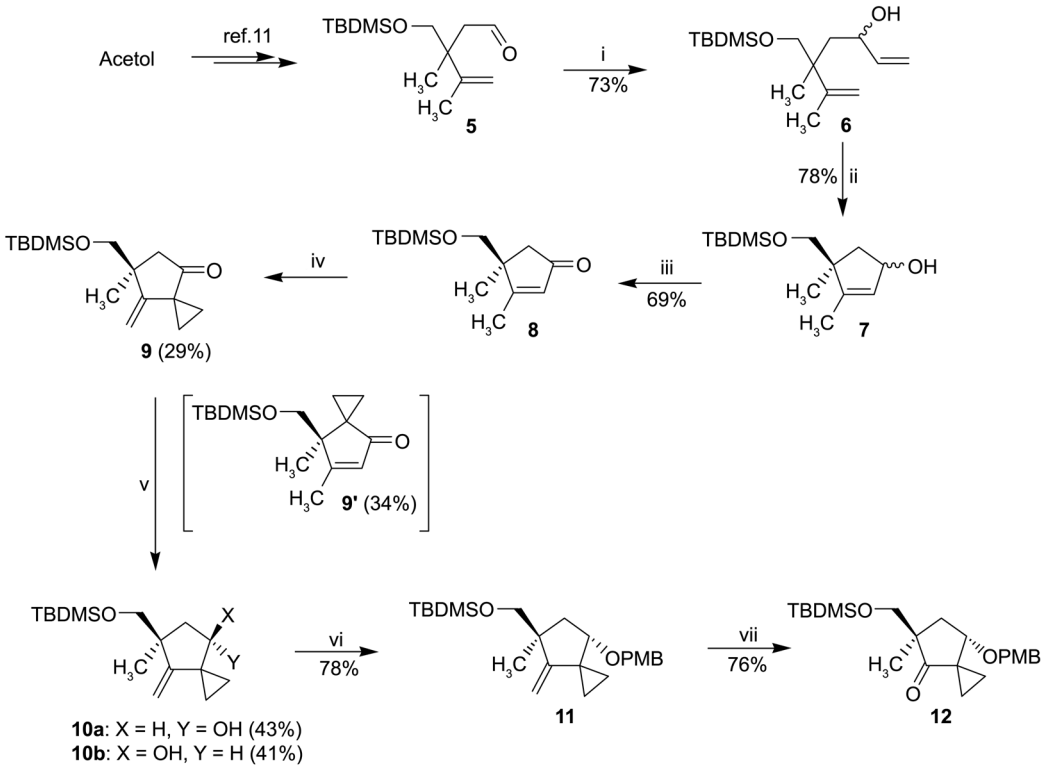
The 4'-modified ribonucleoside derivatives are the second distinct structural class of HCV NIs. Various substituents at the 4'-position of the sugar are accommodated by NS5B polymerase.

Modeling studies demonstrated the presence of a narrow, relatively hydrophobic 4'-pocket that can accommodate these substitutions, contributing to the observed enhancement in potency.[8] For example, 4'-azidocytidine[9] **4** showed excellent anti-HCV activity in the genotype 1b subgenomic replicon system.

Natural as well as synthetic carbocyclic nucleosides[10] are well known for their interesting biological activities, including antitumor and antiviral activities against a wide variety of RNA and DNA viruses. Carbocyclic nucleosides are chemically more stable and are subject to the action of the enzymes that cleave the glycosyl linkage in conventional nucleosides.

Result and Discussion

On the basis of these findings that 2'- or 4'-modified ribonucleoside derivatives exhibited excellent anti-HCV activities, we have synthesized novel classes of nucleosides comprising 4'-methyl-2'-spirocyclopropyl carbocyclic nucleoside analogues. The target compounds were prepared as shown in Scheme 1 from the key starting material **5**, which was readily synthesized according to our previous published



Scheme 1. Synthesis of spirocyclopropyl cyclopentanone intermediate.

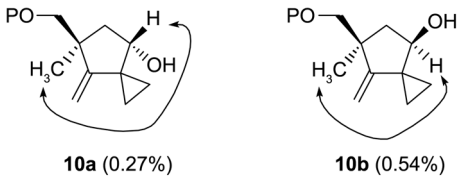
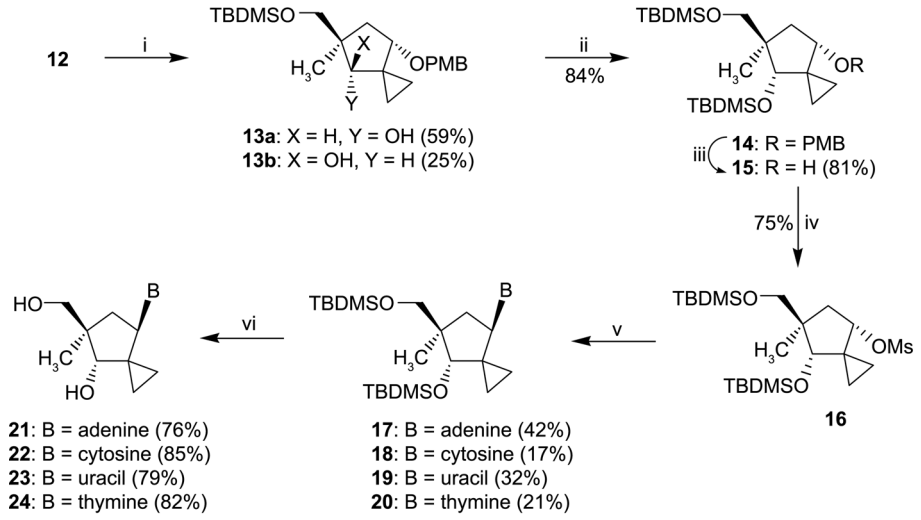


Figure 2. NOE differences between the proximal hydrogens of **10a** and **10b**.

procedure.[11] The aldehyde **5** was treated with vinyl Grignard reagent to form divinyl **6**. Without separation of diastereomeric mixture, divinyl **6** was subjected to ring-closing metathesis (RCM) conditions[12] using 2nd generation Grubbs catalyst to provide the cyclopentenols **7** as a diastereomeric mixture, which was then oxidized to enone derivative **8**. Spirocyclopropylation of enone **8** was effected by using (2-chloroethyl)-dimethylsulfonium iodide[13] and potassium *tert*-butoxide to form two isomers **9** (29%) and **9'** (34%), respectively. Reduction of ketone **9** with $LiAlH_4$ gave two diastereomeric secondary alcohols **10a** and **10b**. The availability of both stereoisomers in pure condition allowed for confirmation of the stereochemical configuration by NOE methods (Figure 2). As expected, NOE enhancements were found between the *cis*-oriented hydrogens. Upon irradiation of C_6-CH_3, a weak NOE pattern was observed at the proximal hydrogen of compound **10a** [C_4-H (0.27%)] versus those of compound **10b** [C_4-H (0.54%)]. The secondary hydroxyl group of **10a** was protected as a temporary *p*-methoxy benzyl ether (PMB) by reaction[14] with PMBCl and NaH in DMF to afford the protected olefin **11**. The exomethylene of **11** was treated with ozone in methylene chloride at −78 °C, followed by the decomposition of the ozonide by dimethylsulfide (DMS) to give the ketone **12**.

Reaction of reduction reagent ($LiAlH_4$) with cyclopentanone **12** proceeded from the less hindered face of the substrate to provide a mixture of cyclopentanols **13a** (59%) and **13b** (25%) (Scheme 2). In order to unambiguously confirm the stereochemistry, NOE analysis was performed on **13a** and **13b**. Upon irradiation of C_7-H, a strong NOE pattern was observed at the proximal hydrogen of compound **13a** [C_4-H (0.67%)] versus those of compound **13b** [C_4-H (0.42%)] (Figure 3). Hydroxyl functional group of **13a** was protected with *t*-butyldimethylsilyl chloride (TBDMSCl) to give compound **14**. Oxidative deprotection of the PMB ether moiety of **14** was effected with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[15] in methylene chloride with a small amount of water to give the alcohol **15**, which was transformed into mesylate **16** to prepare for direct S_N2 displacement involving a series of nucleoside bases.[16] The protected spirocarbanucleosides **17**-**20** were obtained with modest efficiency by direct condensation of **16** with sodium salts of adenine, cytosine, uracil and thymine. Although a small quantity of the N^3-isomer (less than 6%) of the adenine base was present, they were readily differentiated



Scheme 2. Synthesis of target 4'-methyl-2'-spirocyclopropyl nucleoside analogues.

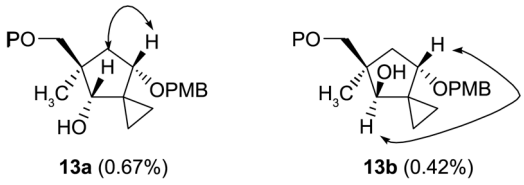


Figure 3. NOE differences between the proximal hydrogens of **13a** and **13b**.

[UV(MeOH) λ_{max} 279 nm].[17] Also, O_2-isomers of pyrimidine bases such as 2-*O*-cyt, 2-*O*-ura, 2-*O*-thy are readily differentiated by the UV data.[18] Finally, global deprotection of intermediates **17-20** with TBAF efficiently produced the targets 4'-methyl-2'-spirocyclopropylnucleosides **21-24**.

The synthesized nucleoside analogues mentioned above were assayed for their ability to inhibit HCV RNA replication in a subgenomic replicon Huh7 cell line.[19] This system is composed of a human hepatocarcinoma cell line supporting HCV replication. These cells contain an HCV subgenomic replicon RNA encoding a luciferase reporter gene as a marker. The antiviral potency of these analogues against the HCV replicon is expressed as EC_{50}, which was quantified by a luciferase assay after a two-day incubation period with the compounds. To confirm the anti-HCV potency of compounds, subgenomic replicon RNA levels were quantified by real-time RT-PCR analysis. In addition, the associated cytotoxicity was evaluated in a tetrazolium (XTT)-based assay. As shown in Table 1, the cytosine nucleoside analogue **22** showed significant anti-HCV activity. However, nucleoside analogues **23** and **24** did not show anti-HCV activity or cytotoxicity at concentrations of up to 50 μM.

In summary, based on the potent anti-HCV activity of 4'-branched nucleoside and 2'-spirocyclopropyl nucleoside analogue, we have designed and successfully synthesized

Table 1. Anti-HCV activity of the newly synthesized compounds

Compound No.	Anti-HCV EC_{50} (μM)	Cytotoxicity CC_{50} (μM)
21	39.2	41.3
22	**18.2**	42.5
23	> 50	> 50
24	> 50	> 50
2′-*C*-Me-C	4.6	> 50

2'-*C*-Me-C: 2'-*C*-Methylcytidine (Fig. 1). EC_{50} (μg/mL): concentration required to inhibit the replication of HCV in Huh-7 cell. CC_{50} (μg/mL): concentration required to reduce cell viability

novel 4'-methyl-2'-spirocarbocyclic nucleoside analogues starting from acetol. 2'-Spiroribonucleoside analogue[7] **3** and 4'-azidoribonucleoside analogue[9] **4** were found to inhibit HCV with an EC_{50} = 7.3 μM and 1.28 μM, respectively. Taking these data into account, the proposed 4'-pocket in the active site of the RNA polymerase encoded by HCV is sensitive to electronic changes in the 4'-substituent, especially when such changes involve increasing the van der Waals radius or changing the projection angle of the 4'-substituent into the pocket.

Experimental Section

Melting points were determined on a Mel-temp II laboratory device and are uncorrected. NMR spectra were recorded on a JEOL 300 Fourier transform spectrometer (JEOL, Tokyo, Japan); chemical shifts are reported in parts per million (δ) and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublets). UV spectra were obtained on a Beckman DU-7 spectrophotometer (Beckman, South Pasadena, CA, USA). The elemental analyses were performed using a Perkin-Elmer 2400 analyzer (Perkin-Elmer, Norwalk, CT, USA).

TLC was performed on Uniplates (silica gel) purchased from Analtech Co. (7558, Newark, DE, USA). All reactions were carried out in an atmosphere of nitrogen unless otherwise specified. Dry dichloromethane, benzene and pyridine were obtained by distillation from CaH_2. Dry THF was obtained by distillation from Na and benzophenone immediately prior to use.

(*rel*)-(3*R* and *3S*,5*S*)-5-(*t*-Butyldimethylsilanyloxymethyl)-5,6-dimethyl-hepta-1,6-dien-3-ol (6): To a solution of **5** (2.5 g, 9.75 mmol) in dry THF (25 mL) was slowly added vinylMgBr (11.7 mL, 1.0 M solution in THF) at –78 °C. After 5 h, saturated NH_4Cl solution (12 mL) and water (70 mL) were added sequentially, and the reaction mixture was slowly warmed to rt. The mixture was extracted with EtOAc (70 mL) two times. The combined organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:12) to give **6** (2.02 g, 73%) as colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.96-5.85 (m, 1H), 5.30-5.14 (m, 2H), 4.72-4.64 (m, 2H), 3.92 (m, 2H), 3.71 (dd, *J* = 10.4, 6.8 Hz, 2H), 1.69 (s, 3H), 1.46-1.39 (m, 2H), 1.29 (s, 3H), 0.83 (m, 9H), 0.01 (m, 6H).

(*rel*)-(1*R* and 1*S*,4*S*)-4-(*t*-Butyldimethylsilyloxymethyl)-3,4-dimethyl-cyclopent-2-enol (7): To a solution of **6** (1.22 g, 4.30 mmol) in dry benzene (10 mL) was added 2nd generation Grubbs catalyst (63 mg 0.075 mmol). The reaction mixture was refluxed overnight and cooled to room temperature. The mixture was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give cyclopentenol **7** (860 mg, 78%) as a diastereomeric mixture. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.41-5.38 (m, 2H), 4.08 (m, 2H), 3.79-3.53 (m, 4H), 1.95 (m, 2H), 1.79-1.74 (m, 5H), 1.65 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H), 0.82 (m, 18H), 0.01 (m, 12H).

(±)-4-(*t*-Butyldimethylsilanyloxymethyl)-3,4-dimethyl-cyclopent-2-enone (8): A mixture of allylic alcohol **7** (1.37 g, 5.34 mmol) and manganese (IV) dioxide (1.28 g, 14.8 mmol) in CCl_4 (20 mL) was stirred at 65 °C. Additional manganese (IV) dioxide (214 mg, 2.47 mmol) was added each hour and the progress of the reaction was monitored by TLC (EtOAc/hexane, 1:30). The resultant mixture was filtered through a pad of Celite and washed with ethyl acetate. The filtrate and washes were concentrated *in vacuo* to give a residue that was purified by silica gel column chromatography (EtOAc/hexane, 1:30) to give α,β-unsaturated ketone derivative **8** (937 mg, 69%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.79 (d, *J* = 5.2 Hz, 1H), 3.77 (d, *J* = 10.6 Hz, 1H), 3.47 (d, *J* = 10.7 Hz, 1H), 2.88 (d, *J* = 8.8 Hz, 1H), 2.57 (d, *J* = 8.9 Hz, 1H), 1.77 (s, 3H), 1.31 (s, 3H), 0.82 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.4, 161.9, 117.3, 75.2, 53.0, 41.5, 25.3, 21.3, 18.4, 16.8, -5.7; Anal. Calcd. for $C_{14}H_{26}O_2Si$: C, 66.09; H, 10.30. Found: C, 66.13; H, 10.26.

(±)-6-(*t*-Butyldimethylsilanyloxymethyl)-6-methyl-7-methylene-spiro[2.4]heptan-4-one (9); and (±)-7-(*t*-butyldimethylsilanyloxymethyl)-6,7-dimethyl-spiro[2.4]hept-5-en-4-one (9'): A solution of bicyclic enone **8** (346 mg, 1.36 mmol) in *t*-butyl alcohol (4.0 mL) was added to a stirred mixture of potassium *t*-butoxide (615 mg, 5.5 mmol) in *t*-butyl alcohol (4.0 mL). After the mixture was stirred at room temperature for 20 min, potassium iodide (455 mg, 2.75 mmol) and (2-chloroethyl)dimethylsulfonium iodide (640 mg, 2.55 mmol) were added in portions under a stream of nitrogen. The mixture was stirred at room temperature for 1.5 h, diluted with saturated NH_4Cl solution (20 mL), and extracted with ether (3 × 30 mL). The combined organic layer was washed with brine, dried under anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography (EtOAc/hexane, 1:25) on silica gel to give ketones **9** (110 mg, 29%) and **9'** (129 mg, 34%) as colorless oil. Spectral date for **9**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.71 (br s, 1H), 4.61 (br s, 1H), 3.65 (d, *J* = 9.4 Hz, 1H), 3.44 (d, *J* = 9.5 Hz, 1H), 2.88 (d, *J* = 8.8 Hz, 1H), 2.57 (d, *J* = 8.9 Hz, 1H), 1.31 (s, 3H), 1.20-0.91 (m, 4H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 210.7, 167.2, 95.4, 77.0, 47.7, 39.5, 32.6, 25.5, 20.7, 18.3, 10.8, 9.4, -5.2; Anal. Calcd. for $C_{16}H_{28}O_2Si$: C, 68.52; H, 10.06. Found: C, 68.47; H, 10.11. Spectral data for **9'**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.87 (s, 1H), 3.75 (d, *J* = 9.2 Hz, 1H), 3.62 (d, *J* = 9.3 Hz, 1H), 1.74 (s, 3H), 1.28 (s, 3H), 1.16-0.89 (m, 4H), 0.81 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.2, 156.4, 123.5, 69.4, 56.2, 40.6, 25.3, 22.0, 18.7, 12.8, 11.1, 9.8, -5.5; Anal. Calcd. for $C_{16}H_{28}O_2Si$: C, 68.52; H, 10.06. Found: C, 68.55; H, 10.04.

(*rel*)-(4*S*,6*R*)-6-(*t*-Butyldimethylsilanyloxymethyl)-6-methyl-7-methylenespiro[2.4]heptan-4-ol (10a) and (*rel*)-(4*R*,6*R*)-6-(*t*-butyldimethylsilanyloxymethyl)-6-methyl-7-methylene-spiro[2.4]heptan-4-ol (10b): A 1.0 M solution of lithium aluminum hydride in ether (0.6 mL, 0.6 mmol) was added to a solution of ketone **9** (129 mg, 0.46 mmol) in ether (5 mL). The mixture was stirred at room temperature (rt) for 40 min. To the cooled reaction mixture was added a solution of H_2O/THF (1:9) (6.0 mL), and the mixture was stirred at room temperature for 45 min and filtered through a pad of Celite. The residue was thoroughly washed with ether, and the filtrate and the washes were combined and concentrated. The residual oil was purified by column chromatography (EtOAc/hexane, 1:15) on silica gel to give alcohol **10a** (55.8 mg, 43%) and **10b** (53 mg, 41%) as colorless oils. Compound **10a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.74 (d, *J* = 2.1 Hz, 1H), 4.66 (d, *J* = 2.2 Hz, 1H), 3.69 (d, *J* = 9.6 Hz, 1H), 3.48 (d, *J* = 9.6 Hz, 1H), 3.27 (dd, *J* = 6.8, 4.8 Hz, 1H), 1.50 (dd, *J* = 8.8, 6.8 Hz, 1H), 1.44 (dd, *J* = 8.9, 4.8 Hz, 1H), 1.22 (s, 3H), 0.94-1.19 (m, 4H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.4, 106.4, 86.0, 75.1, 44.3, 32.3, 25.6, 19.2, 18.3, 11.0, 8.8, -5.5; Anal. Calcd. for $C_{16}H_{30}O_2Si$: C, 68.03; H, 10.70. Found: C, 67.95; H, 10.65; Compound **10b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.75 (d, *J* = 1.9 Hz, 1H), 4.63 (d, *J* = 2.0 Hz, 1H), 3.71 (d, *J* = 10.1 Hz, 1H), 3.46 (d, *J* = 9.9 Hz, 1H), 3.21 (dd, *J* = 6.8, 4.4 Hz, 1H), 1.56 (dd, *J* = 8.8, 6.7 Hz, 1H), 1.41 (m, 1H), 1.24 (s, 3H), 1.18-0.88 (m, 4H), 0.81 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5, 108.4, 84.7, 74.8, 46.0, 33.5, 25.3, 19.3, 18.5, 10.8, 8.9, -5.3; Anal. Calcd. for $C_{16}H_{30}O_2Si$: C, 68.03; H, 10.70. Found: C, 68.09; H, 10.73.

(*rel*)-(5*S*,7*S*)-6-*t*-Butyl-[7-(4-methoxybenzyloxy)-5-methyl-4-methylenespiro[2.4]hept-5-ylmethoxy]-dimethylsilane (11): NaH (60% in mineral oil, 1.66 g, 41.6 mmol) was added portion-wise to a cooled (0 °C) solution of **10a** (9.79 g, 34.67 mmol) in DMF (100 mL) and *p*-methoxybenzyl chloride (5.17 mL, 38.13 mmol) in anhydrous DMF (50 mL). The reaction mixture was stirred at rt overnight. The solvent was quenched with H_2O, removed under reduced pressure and extracted with EtOAc (2 × 100 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give **11** (10.88 g, 78%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27-7.23 (m, 2H), 6.91-6.83 (m, 2H), 4.75 (d, *J* = 2.0 Hz, 1H), 4.64 (br s, 1H), 4.44 (s, 2H), 3.82 (s, 3H), 3.67 (d, *J* = 9.8 Hz, 1H), 3.49 (d, *J* = 9.8 Hz, 1H), 2.86 (dd, *J* = 6.2, 5.0 Hz, 1H), 1.39 (dd, *J* = 10.6, 8.8 Hz, 1H), 1.23 (dd, *J* = 10.7, 6.8 Hz, 1H), 1.27 (s, 3H), 1.19-0.95 (m, 4H), 0.81 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.6, 159.3, 131.2, 129.0, 116.3, 102.5, 89.3, 75.3, 45.7, 42.3, 30.8, 25.3, 19.0, 18.5, 10.6, 8.9, -5.4; Anal. Calcd. for $C_{24}H_{38}O_3Si$: C, 71.59; H, 9.51. Found: C, 71.63; H, 9.46.

(*rel*)-(5*S*,7*S*)-5-(*t*-Butyldimethylsilanyloxymethyl)-7-(4-methoxybenzyloxy)-5-methyl-spiro[2.4]heptan-4-one (12): A solution of compound **11** (3.87 g, 9.62 mmol) in anhydrous CH_2Cl_2 (50 mL) was cooled to −78 °C, and ozone gas was then bubbled into the reaction mixture until a blue color persisted for 10 minutes. The reaction mixture was degassed with nitrogen, and dimethyl sulfide (2.97 mL, 40.41 mmol) was slowly added at −78 °C. The mixture was stirred for 1 h at −78 °C under argon gas and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:12) to give compound **12** (2.96 g, 76%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28-7.24 (m, 2H), 6.93-6.85 (m, 2H), 4.65 (s, 2H), 3.97 (d, *J* = 9.9 Hz, 1H), 3.82 (d, *J* = 9.8 Hz, 1H), 3.78 (s, 3H), 3.39 (dd, *J* = 5.8, 4.2 Hz, 1H), 2.26 (dd, *J* = 10.8, 8.2 Hz, 1H), 2.09 (dd, *J* = 10.8, 6.7 Hz, 1H), 1.28 (s, 3H), 1.16-0.91 (m, 4H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.2, 159.7, 132.5, 130.5, 117.7, 73.8, 73.1, 69.8, 53.1, 37.5, 28.5, 25.6, 18.4, 16.3, 11.2, 9.2, -5.6; Anal. Calcd. for $C_{23}H_{36}O_4Si$: C, 68.27; H, 8.97. Found: C, 68.33; H, 8.91.

(*rel*)-(4*S*,5*S*,7*S*)-5-(*t*-Butyldimethylsilanyloxymethyl)-7-(4-methoxybenzyloxy)-5-methyl-spiro[2.4]heptan-4-ol (13a) and (*rel*)-(4*R*,5*S*,7*S*)-5-(*t*-butyldimethylsilanyloxymethyl)-7-(4-methoxybenzyloxy)-5-methyl-spiro[2.4]heptan-4-ol (13b): Compounds **13a** and **13b** were synthesized from **12** using a similar procedure as described for **10a** and **10b**. Spectral data for **13a**: yield 59%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25-7.20 (m, 2H), 6.89-6.84 (m, 2H), 4.65 (s, 2H), 3.77 (s, 3H), 3.70 (d, *J* = 8.8 Hz, 1H), 3.61 (d, *J* = 8.9 Hz, 1H), 3.22 (s, 1H), 2.87 (m, 1H), 1.62 (dd, *J* = 10.2, 8.4 Hz, 1H), 1.49 (dd, *J* = 10.3, 6.6 Hz, 1H), 1.13 (s, 3H), 1.13-0.89 (m, 4H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.5, 131.8, 129.7, 119.2, 77.2, 75.4, 71.4, 35.8, 31.2, 29.4, 25.6, 18.4, 15.7, 10.6, 8.8, -5.3; Anal. Calcd. for $C_{23}H_{38}O_4Si$: C, 67.94; H, 9.42. Found: C, 67.89; H, 9.37; Spectral data for **13b**: yield 25%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26-7.19 (m, 2H), 6.90-6.85 (m, 2H), 4.64 (s, 2H), 3.79 (s, 3H), 3.73 (d, *J* = 9.0 Hz, 1H), 3.61 (d, *J* = 8.9 Hz, 1H), 3.20 (s, 1H), 2.87 (m, 1H), 1.63 (dd, *J* = 10.6, 8.5 Hz, 1H), 1.50 (dd, *J* = 10.5, 6.8 Hz, 1H), 1.17 (s, 3H), 1.17-0.91 (m, 4H), 0.81 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.7, 132.1, 130.3, 118.4, 78.5, 74.3, 70.8, 36.5, 31.2, 28.7, 25.4, 18.5, 14.9, 10.8, 8.9, −5.6; Anal. Calcd. for $C_{23}H_{38}O_4Si$: C, 67.94; H, 9.42. Found: C, 67.97; H, 9.46.

(*rel*)-(4*S*,5*S*,7*S*)-4-(*t*-Butyldimethylsilanyloxy)-5-(*t*-butyldimethylsilanyloxymethyl)-7-(4-methoxy benzyloxy)-5-methyl-spiro[2.4]heptanes (14): TBDMSCl (1.16 g, 7.71 mmol) was added slowly to a solution of **13a** (2.85 g, 7.02 mmol) and imidazole (0.72 g, 10.52 mmol) in CH_2Cl_2 (150 mL) at 0 °C, and stirred for 5 h at the same temperature. The solvent was evaporated under reduced pressure. The residue was dissolved in water (150 mL) and extracted with diethyl ether (150 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:18) to give compound **14** (3.07 g, 84%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27-7.21 (m, 2H), 6.93-6.87 (m, 2H), 4.65 (s, 2H), 3.82 (s, 3H), 3.75 (d, *J* = 9.2 Hz, 1H), 3.56 (d, *J* = 9.1 Hz, 1H), 3.19 (s, 1H), 2.85 (m, 1H), 1.84 (dd, *J* = 10.8, 8.8 Hz, 1H), 1.62 (dd, *J* = 10.7, 6.8 Hz, 1H), 1.19 (s, 3H), 1.17-0.91 (m, 4H), 0.82 (s, 18H), 0.02 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.1, 132.7, 129.9, 118.7, 79.6, 75.1, 71.4, 37.2, 33.5, 29.5, 25.7, 25.1, 18.8, 13.5, 11.2, 9.2, −5.7; Anal. Calcd. for $C_{29}H_{52}O_4Si_2$: C, 66.87; H, 10.06. Found: C, 66.91; H, 10.12.

(*rel*)-(4*S*,6*S*,7*S*)-7-(*t*-Butyldimethylsilanyloxy)-6-(*t*-butyldimethylsilanyloxymethyl)-6-methyl-spiro[2.4]heptan-4-ol (15): To a solution of compound **14** (1.41 g, 2.71 mmol) in CH_2Cl_2/H_2O mixture (12 mL, 20:1 v/v) was added DDQ (672 mg, 3.69 mmol) and the mixture was stirred for 4 h at room temperature. Saturated $NaHCO_3$ (3 mL) was added to quench the reaction and further diluted with water (50 mL). The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give compound **15** (879 mg, 81%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.70 (d, *J* = 9.1 Hz, 1H), 3.58 (d, *J* = 9.0 Hz, 1H), 3.24 (m, 1H), 3.19 (s, 1H), 1.62 (dd, *J* = 10.8, 8.6 Hz, 1H), 1.52 (dd, *J* = 10.8, 6.8 Hz, 1H), 1.15 (s, 3H), 1.18-0.90 (m, 4H), 0.81 (s, 18H), 0.01 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 84.5, 72.5, 70.6, 36.7, 32.9, 31.1, 25.5, 18.3, 15.2, 10.8, 8.8, -5.3; Anal. Calcd. for $C_{21}H_{44}O_3Si_2 \cdot 0.5$ EtOAc: C, 61.10; H, 10.87. Found: C, 61.08; H, 10.89.

(*rel*)-(4*S*,6*S*,7*S*)-7-(*t*-Butyldimethylsilanyloxy)-6-(*t*-butyldimethylsilanyloxymethyl)-6-methylspiro[2.4]heptyl-4-methansulfonate (16): A solution of **15** (240 mg, 0.6 mmol) and Et_3N (0.252 mL, 1.8 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C and treated dropwise with MsCl (96 μL, 1.2 mmol).

The reaction mixture was stirred for 4 h, allowed to warm to rt, quenched with saturated $NaHCO_3$ solution (1.0 mL), and further diluted with water (80 mL). The mixture was extracted with Et_2O (3 × 80 mL). The combined organic phases were dried and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to give compound **16** (879 mg, 75%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.81 (dd, *J* = 5.0, 2.8 Hz, 1H), 3.72 (d, *J* = 9.2 Hz, 1H), 3.61 (d, *J* = 9.3 Hz, 1H), 3.21 (s, 1H), 3.01 (s, 3H), 1.64 (dd, *J* = 10.8, 8.7 Hz, 1H), 1.50 (dd, *J* = 10.9, 6.8 Hz, 1H), 1.17 (s, 3H), 1.21-0.92 (m, 4H), 0.81 (m, 18H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 83.7, 71.2, 69.5, 38.7, 37.2, 30.4, 28.4, 25.6, 18.6, 15.7, 12.1, 9.5, −5.6.

(*rel*)-(4*S*,6*S*,7*S*)-9-[7-(*t*-Butyldimethylsilanyloxy)-6-(*t*-butyldimethylsilanyloxymethyl) 6-methylspiro[2.4]hept-4-yl] adenine (17): To a mixture of NaH (12 mg, 0.5 mmol) and adenine (67 mg, 0.5 mmol) in DMF (5.5 mL), the mesylate **16** (153 mg, 0.32 mmol) dissolved in DMF (2.0 mL) was added. The reaction mixture was brought to 80 °C, stirred for 12 h, allowed to cool to rt, quenched with saturated $NaHCO_3$ (1.0 mL) solution, and further diluted with water (50 mL). The mixture was extracted with ether (3 × 50 mL). The combined ether layers were dried and concentrated to leave a residue that was purified by silica gel column chromatography (EtOAc/hexane, 1:1) to give compound **17** (69 mg, 42%) as a white solid. mp 189-192 °C; UV (MeOH) λ_{max} 261.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.28 (s, 1H), 8.16 (s, 1H), 3.76 (d, *J* = 10.2 Hz, 1H), 3.69-3.61 (m, 2H), 3.20 (s, 1H), 1.90 (dd, *J* = 11.2, 8.8 Hz, 1H), 1.61 (dd, *J* = 11.2, 6.8 Hz, 1H), 1.28 (s, 3H), 1.12-0.93 (m, 4H), 0.82 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.2, 152.3, 145.7, 132.4, 119.4, 86.1, 70.7, 57.6, 39.3, 29.7, 27.7, 25.6, 18.6, 15.7, 10.0, 8.6, −5.3; Anal. Calcd. for $C_{26}H_{47}N_5O_2Si_2$: C, 60.30; H, 9.15; N, 13.52. Found: C, 60.25; H, 9.11; N, 13.47.

(*rel*)-(4*S*,6*S*,7*S*)-1-[7-(*t*-Butyldimethylsilanyloxy)-6-(*t*-butyldimethylsilanyloxymethyl) 6-methylspiro[2.4]hept-4-yl] cytosine (18): Similar coupling conditions as described for adenine synthesis **17** were used for the preparation of the cytosine analogue from mesylate **16**. Yield 17%; mp 160-162 °C; UV (MeOH) λ_{max} 272.0 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04 (d, *J* = 5.6 Hz, 1H), 6.09 (d, *J* = 5.7 Hz, 1H), 3.71 (d, *J* = 10.2 Hz, 1H), 3.65 (d, *J* = 10.3 Hz, 1H), 3.60 (m, 1H), 3.22 (s, 1H), 1.89 (dd, *J* = 10.8, 8.9 Hz, 1H), 1.72 (dd, *J* = 10.7, 6.8 Hz, 1H), 1.35 (s, 3H), 1.19-0.90 (m, 4H), 0.81 (m, 18H), 0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.8, 163.2, 157.7, 99.6, 86.4, 70.6, 60.2, 39.6, 30.5, 28.3, 25.7, 18.8, 15.8, 12.3, 9.2, −5.6; Anal. Calcd. for $C_{25}H_{47}N_3O_3Si_2 \cdot 0.5$ EtOAc: C, 60.28; H, 9.50; N, 8.81. Found: C, 60.31; H, 9.48; N, 8.79.

(*rel*)-(4*S*,6*S*,7*S*)-1-[7-(*t*-Butyldimethylsilanyloxy)-6-(*t*-butyldimethylsilanyloxymethyl) 6-methylspiro[2.4]hept-4-yl] uracil (19): Uracil nucleoside analogue was synthesized from mesylate **16** using a similar procedure as described for **17**. Yield 32%; mp 154-156 °C; UV (MeOH) λ_{max} 262.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.48 (br s, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 5.74 (d, *J* = 8.1 Hz, 1H), 3.76 (d, *J* = 10.4 Hz, 1H), 3.63-3.58 (m, 2H), 3.22 (s, 1H), 1.87 (dd, *J* = 10.7, 8.7 Hz, 1H), 1.69 (dd, *J* = 10.8, 6.6 Hz, 1H), 1.23 (s, 3H), 1.17-0.89 (m, 4H), 0.82 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.9, 150.5, 141.6, 102.4, 85.6, 71.3, 62.2, 40.0, 31.2, 29.8, 25.4, 18.5, 14.7, 11.7, 9.3, −5.4; Anal. Calcd. for $C_{25}H_{46}N_2O_4Si_2$: C, 60.68; H, 9.37; N, 5.66. Found: C, 60.75; H, 9.41; N, 5.70.

(*rel*)-(4*S*,6*S*,7*S*)-1-[7-(*t*-Butyldimethylsilanyloxy)-6-(*t*-butyldimethylsilanyloxymethyl) 6-methylspiro[2.4]hept-4-yl] thymine (20): Thymine nucleoside analogue was prepared from mesylate **16** using a similar procedure as described for **17**. Yield 21%; mp 161-163 °C; UV (MeOH) λ_{max} 267.5 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.45 (s, 1H), 6.98 (s, 1H), 3.76 (d, *J* = 10.4 Hz, 1H), 3.70-3.65 (m, 2H), 3.25 (s, 1H), 1.96 (s, 3H), 1.86 (dd, *J* = 10.7, 8.6 Hz, 1H), 1.71 (dd, *J* = 10.8, 6.7 Hz, 1H), 1.31 (s, 3H), 1.21-0.99 (m, 4H), 0.82 (m, 18H), 0.01 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.8, 163.2, 157.7, 99.6, 86.4, 70.6, 60.2, 39.6, 30.5, 28.3, 25.7, 18.8, 15.8, 12.9, 12.3, 9.2, −5.6; Anal. Calcd. for $C_{26}H_{48}N_2O_4Si_2$: C, 61.37; H, 9.51; N, 5.51. Found: C, 61.42; H, 9.45; N, 5.49.

(*rel*)-(4*S*,6*S*,7*S*)-9-[7-(Hydroxy)-6-(hydroxymethyl)-6-methylspiro[2.4]hept-4-yl] adenine (21): To a solution of protected adenine analogue **20** (240 mg, 0.463 mmol) in cosolvent (7.0 mL, THF/CH_3CN = 1:1) was added TBAF (1.39 mL, 1.0 M solution in THF) at 0 °C. The mixture was stirred for 36 h at room temperature and then concentrated. The residue was purified by silica gel column chromatography (MeOH/CH_2Cl_2, 1:4) to give **21** (101 mg, 76%) as a white solid. mp 236-239 °C; UV (H_2O) λ_{max} 260.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.21 (s, 1H), 7.85 (s, 1H), 7.18 (br d, 2H, D_2O exchangeable), 4.97 (d, *J* = 4.8 Hz, 1H, D_2O exchangeable), 4.85 (t, *J* = 4.8 Hz, 1H, D_2O exchangeable), 3.79 (dd, *J* = 8.8, 6.8 Hz, 1H), 3.44 (d, *J* = 10.0 Hz, 1H), 3.38 (d, *J* = 10.1 Hz, 1H), 3.19 (s, 1H), 1.86 (dd, *J* = 10.2, 8.8 Hz, 1H), 1.76 (dd, *J* = 10.2, 6.8 Hz, 1H), 1.18 (s, 3H), 1.12-0.90 (m, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 156.4, 152.3, 148.8, 140.2, 119.3, 85.4, 68.3, 56.9, 37.6, 28.4, 27.2, 15.4, 11.2, 8.8; Anal. Calcd. for $C_{14}H_{19}N_5O_2$: C, 58.12; H, 6.62; N, 24.21. Found: C, 58.08; H, 6.57; N, 24.19.

(*rel*)-(4*S*,6*S*,7*S*)-1-[7-(Hydroxy)-6-(hydroxymethyl)-6-methylspiro[2.4]hept-4-yl] cytosine (22): Similar coupling conditions as described for adenine synthesis **21** were used for the preparation of cytosine analogue. Yield 85%; mp 169-171 °C; UV (H_2O) λ_{max} 271.0 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.87 (d, *J* = 6.1 Hz, 1H), 7.06 (br d, 2H, D_2O exchangeable), 6.12 (d, *J* = 6.0 Hz, 1H), 4.99 (d, *J* = 4.4 Hz, 1H, D_2O exchangeable), 4.78 (t, *J* = 4.3 Hz, 1H, D_2O exchangeable), 3.61 (d, *J* = 10.2 Hz, 1H), 3.52 (d, *J* = 10.1 Hz, 1H), 3.42 (d, *J* = 10.0 Hz, 1H), 3.21 (s, 1H), 1.66 (dd, *J* = 10.6, 8.7 Hz, 1H), 1.52 (dd, *J* = 10.6, 6.8 Hz, 1H), 1.17 (s, 3H), 1.11-0.87 (m, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 166.5, 164.7, 155.2, 99.1, 83.6, 68.5, 55.5, 36.3, 30.2, 27.9, 14.5, 11.6, 9.0; Anal. Calcd. for $C_{13}H_{19}N_3O_3 \cdot 1.0$ MeOH: C, 56.54; H, 7.79; N, 14.13. Found: C, 56.49; H, 7.82; N, 14.11.

(*rel*)-(4*S*,6*S*,7*S*)-1-[7-(Hydroxy)-6-(hydroxymethyl)-6-methylspiro[2.4]hept-4-yl] uracil (23): Uracil analogue **23**

was prepared under similar coupling conditions as described for adenine synthesis **21**. Yield 79%; mp 178-180 °C; UV (H_2O) λ_{max} 263.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.68 (d, J = 8.0 Hz, 1H), 5.69 (d, J = 8.0 Hz, 1H), 4.97 (br s, 1H, D_2O exchangeable), 4.77 (t, J = 4.5 Hz, 1H, D_2O exchangeable), 3.64 (d, J = 10.4 Hz, 1H), 3.56 (d, J = 10.4 Hz, 1H), 3.48 (dd, J = 6.8, 4.4 Hz, 1H), 3.20 (s, 1H), 1.68 (dd, J = 10.6, 8.6 Hz, 1H), 1.48 (dd, J = 10.7, 6.5 Hz, 1H), 1.32 (s, 3H), 1.19-0.91 (m, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 164.7, 151.5, 143.2, 101.3, 85.1, 67.8, 55.3, 35.8, 28.3, 27.3, 15.2, 12.2, 8.9; Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.59; H, 6.78; N, 10.49.

(*rel*)-(4*S*,6*S*,7*S*)-1-[7-(Hydroxy)-6-(hydroxymethyl)-6-methylspiro[2.4]hept-4-yl] thymine (24): Final thymine nucleoside analogue was obtained using similar coupling conditions as described for adenine synthesis **21**. Yield 82%; mp 166-168 °C; UV (H_2O) λ_{max} 267.5 nm; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.51 (s, 1H), 5.01 (d, J = 4.4 Hz, 1H, D_2O exchangeable), 4.81 (br s, 1H, D_2O exchangeable), 3.70 (d, J = 10.7 Hz, 1H), 3.61 (d, J = 10.6 Hz, 1H), 3.51 (br s, 1H), 3.23 (s, 1H), 1.92 (s, 3H), 1.72 (dd, J = 10.7, 8.7 Hz, 1H), 1.55 (dd, J = 10.8, 6.7 Hz, 1H), 1.23 (s, 3H), 1.15-0.89 (m, 4H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 165.2, 151.7, 139.2, 109.3, 86.4, 68.3, 54.5, 36.3, 28.8, 27.4, 16.2, 12.5, 11.3, 9.2; Anal. Calcd. for $C_{14}H_{20}N_2O_4 \cdot 0.5$ MeOH: C, 58.76; H, 7.48; N, 9.45. Found: C, 58.82; H, 7.51; N, 9.43.

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