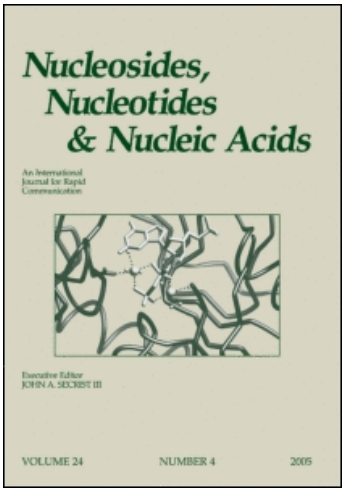

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Synthesis of 1-[cis-2-Hydroxy-cis-3-(hydroxymethyl)-cyclobutyl]thymine, a Novel Method for the Synthesis of Cyclobutyl Nucleosides and Related Compounds

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SYNTHESIS OF 1-[CIS-2-HYDROXY-CIS-3-(HYDROXYMETHYL)-CYCLOBUTYL]THYMINE, A NOVEL METHOD FOR THE SYNTHESIS OF CYCLOBUTYL NUCLEOSIDES AND RELATED COMPOUNDS

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Abstract. Syntheses of 1-[cis-2-hydroxy-cis-3-(hydroxymethyl)cyclobutyl]thymine (**1**) and related compounds by a novel method are reported. Coupling of 3-benzyloxymethyl-1-cyclobutene (**2**) with silylated thymine in the presence of NIS, followed by treatment with DBU, basic hydrolysis and catalytic hydrogenation produced the target compound (**1**) and its isomer (**12**).

Oxetanocin A, the first natural oxetanosyl-*N*-glycoside was found to exhibit antiviral activity against human immunodeficiency virus type 1 (HIV-1) in vitro.[1] Several carbocyclic analogues of oxetanocin, such as cyclobut-A and cyclobut-G, have been synthesized by several independent laboratories and have shown potent antiviral activity against herpesvirus (including cytomegalovirus) and HIV.[2-7] With regard to the antiviral activity, it appears that the presence of the 2'-hydroxymethyl group is not necessary because both 2'-dehydroxymethylcyclobut A and SQ-32,829 (FIG. 1) showed significant activity against HIV-1[8] and herpes simplex viruses,[9] respectively. In order to study the relationship between chemical structure and biological activity of this class of compounds and to develop a new strategy for the synthesis of cyclobutyl nucleosides, 1-[cis-2-hydroxy-cis-3-(hydroxymethyl)-cyclobutyl]-thymine (**1**) and related compounds were synthesized.

Recently, Jacobs et al.[9] and Slusarchyk et al.[10] reported that purine and pyrimidine cyclobutane nucleosides were synthesized from 3-benzyloxymethyl-1-cyclobutene (**2**) by first epoxidation of the cyclobutene derivative **2** to the corresponding cis- and trans-epoxide and then condensation of the isolated trans-epoxide with the respective purine and pyrimidine bases in the presence of NaH/18-crown-6. The two epoxides are similar in physical

This paper is dedicated to the memory of Professor Roland K. Robins.

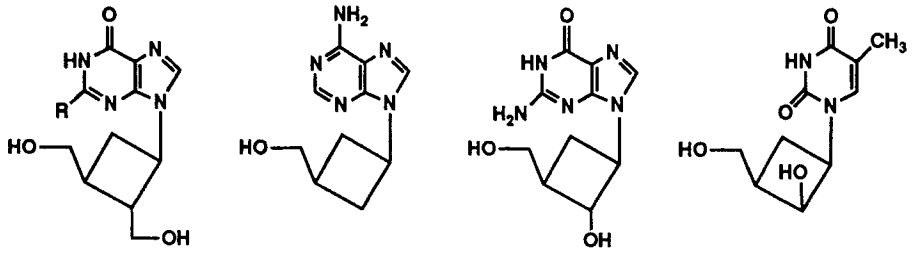
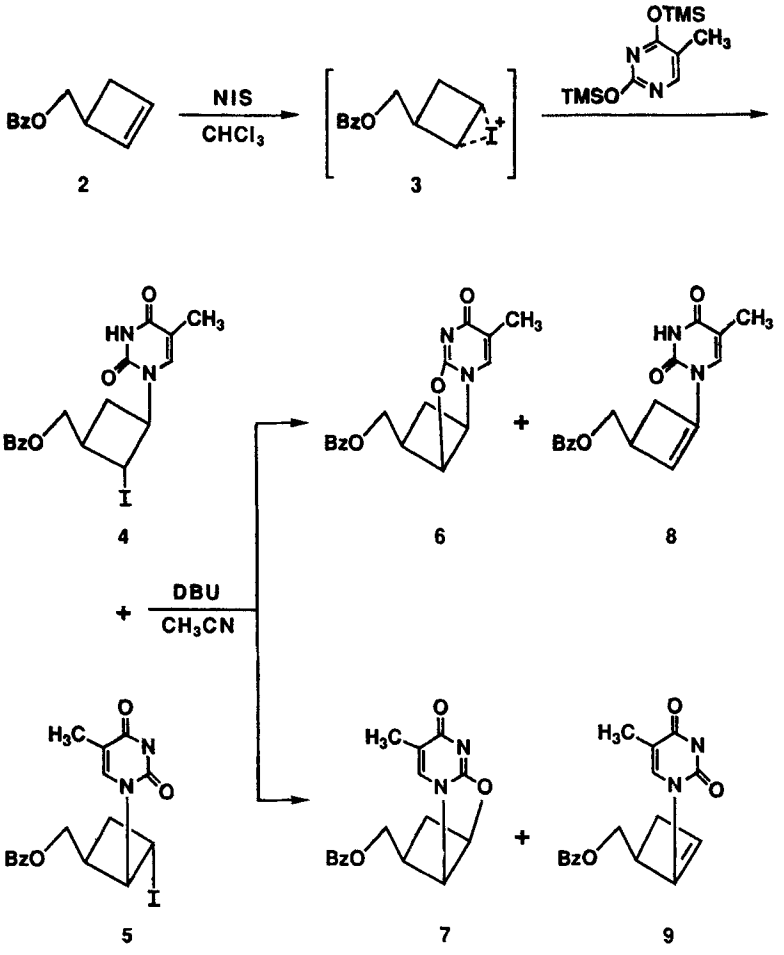


FIG. 1

properties and had to be separated by a combination of flash chromatography and preparative HPLC.[9] Recently, Jung et al.[11] also reported the synthesis of carbovir by treatment of cyclopentene with a nitrogen nucleophile in the presence of DMTSF, followed by an elimination reaction. Since the reaction of a double bond with *N*-iodosuccinimide (NIS) and a nucleophile resulted in formation of a trans-1,2-addition product,[12,13] it was anticipated that reaction of the cyclobutene derivative **2** with NIS, followed by condensation with the silylated base, would produce the corresponding cyclobutyl nucleoside. Reaction of 3-benzyloxymethyl-1-cyclobutene (**2**) with *N*-iodosuccinimide (NIS) and silylated thymine in refluxing chloroform yielded the desired cyclobutyl nucleoside **4** as major product. A small amount of compound **5**, resulting from N-1 attack at the double bond position alpha to the benzyloxymethyl group, was also obtained. The regio- and stereoselectivity observed in this reaction are a consequence of the sterically favored α-face approach by NIS. The resulting α-iodonium ion intermediate **3** is then attacked from the opposite side (β-face) by the silylated thymine to give compounds **4** and **5**. The nucleophilic attack occured mainly at the position beta to the benzyloxymethyl group to form compound **4**, since attack at the α-position is hindered by steric interaction with the benzyloxymethyl group. Compounds **4** and **5** could not be clearly separated by either fractional recrystallization or silica gel chromatography. However, treatment of the mixture of **4** and **5** with DBU in anhydrous acetonitrile gave the corresponding anhydro derivatives **6** and **7**, which were easily separated by silica gel chromatography, and a pair of unsaturated nucleosides **8** and **9** (SCHEME 1).

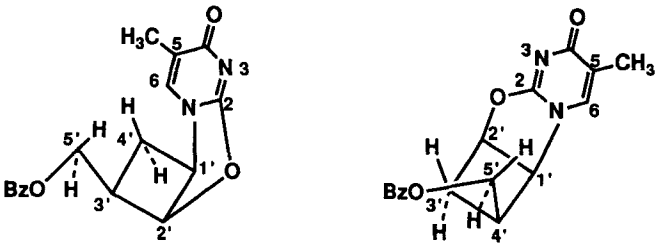
The structures of compounds **6** and **7** were assigned by ^{1}HNMR and mass spectra. The multiplet at δ 5.19-5.23 ppm was assigned to the 1'-proton, which is split by 2'-H (1 H) and 4'-H (2 H), and the triplet (overlapped dd, $J_{2',1'} = J_{2',3'} = 5.2$ Hz) at δ 4.62-4.67 ppm was assigned to the 2'-proton, which is split by 1'-H (1 H) and 3'-H (1 H), in compound **6**. The triplet (overlapped dd, $J_{1',2'} = J_{1',4'} = 6.7$ Hz) and the multiplet at δ 5.37-5.43 ppm and



Bz = $C_6H_5CH_2$

SCHEME 1

δ 4.74-4.80 ppm were assigned to the 1'-proton, which is split by 2'-H (1 H) and 4'-H (1 H), and to the 2'-proton, which is split by 1'-H (1 H) and 3'-H (2 H), in compound **7**, respectively. A visual examination of the molecular model of compounds **6** and **7** (FIG. 2) reveals that the up-positions of 4'- and 5'-hydrogens of compound **6** were in the cone of positive shielding from the 2,3 and 5,6 double bonds of the base. Therefore, they would have lower chemical shift values than those of the 4'- and 5'-hydrogens which are at down-positions.[14] The multiplets at δ 2.26 ppm and 2.45 ppm were assigned to the 4'-up-proton



6 7

FIG. 2

and the 4'-down-proton in **6**, respectively. The multiplets at δ 3.38 ppm and 3.61 ppm were assigned to the corresponding 5'-up-proton and the 5'-down-proton in **6**. The up-position of 3'-hydrogen in compound **7** was also in the cone of positive shielding from the 2,3 and 5,6 double bonds of the base. The multiplets at δ 2.24 ppm and 2.65 ppm were assigned to the respective 3'-up-proton and the 3'-down-proton in **7**. However, the up-position of 5'-hydrogen was out of the positive shielding area, thus there was only a minor difference in chemical shift values between 5'-protons. The partial ^{1}HNMR spectra (δ 2-6) of compounds **6** and **7** are shown in FIG. 3.

Compounds **8** and **9** could not be separated by silica gel chromatography. Their structures were tentatively determined by ^{1}HNMR and mass spectra. The molecular weights of the unsaturated nucleosides **8** and **9**, which were determined by mass spectroscopy, are equivalent to the products produced by elimination of one molecule of HI from compounds **4** and **5**. An intense peak at *m/e* 173 is characteristic of the unsaturated carbocycle and an another intense peak *m/e* 127 represents the base plus one hydrogen. The ^{1}HNMR spectra of the mixture of compounds **8** and **9** showed there are two vinylic proton peaks at δ 6.05 and 6.13, respectively, and the signals of 1'-protons had disappeared. This suggests that the 1'-hydrogens in compounds **4** and **5**, which were more acidic than those of 3'-hydrogen in compound **4** and 3'-hydrogen in compound **5**, were eliminated with the adjacent iodine atoms to form the respective unsaturated nucleosides **8** and **9** in the presence of the strong basic catalyst DBU. Hydrolysis of compounds **6** and **7** with 1 N sodium hydroxide in 50% ethanol afforded the corresponding 2-hydroxy-cyclobutylnucleosides **10** and **11**. Deblocking of **10** and **11** by catalytic hydrogenation gave the target compound **1** and its isomer **12** (SCHEME 2) .

Compounds **1** and **12** were tested against HIV-1 in vitro and were found to be not active at 100 μM.

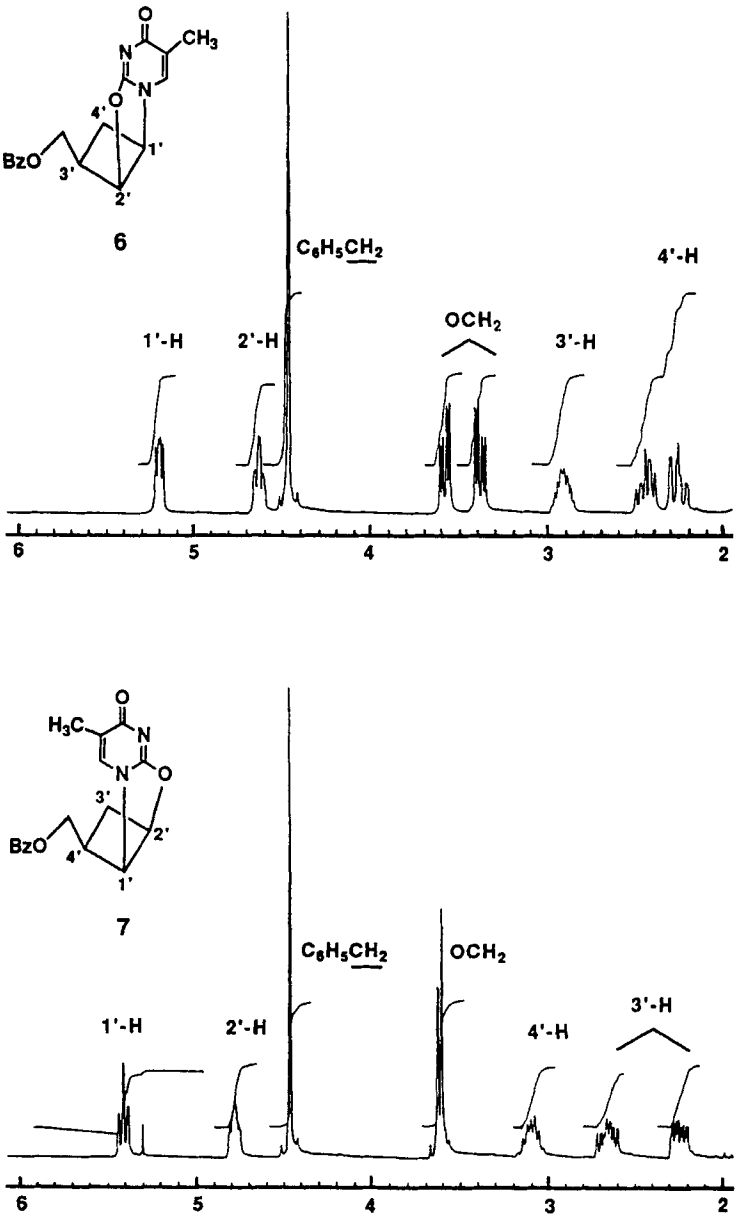
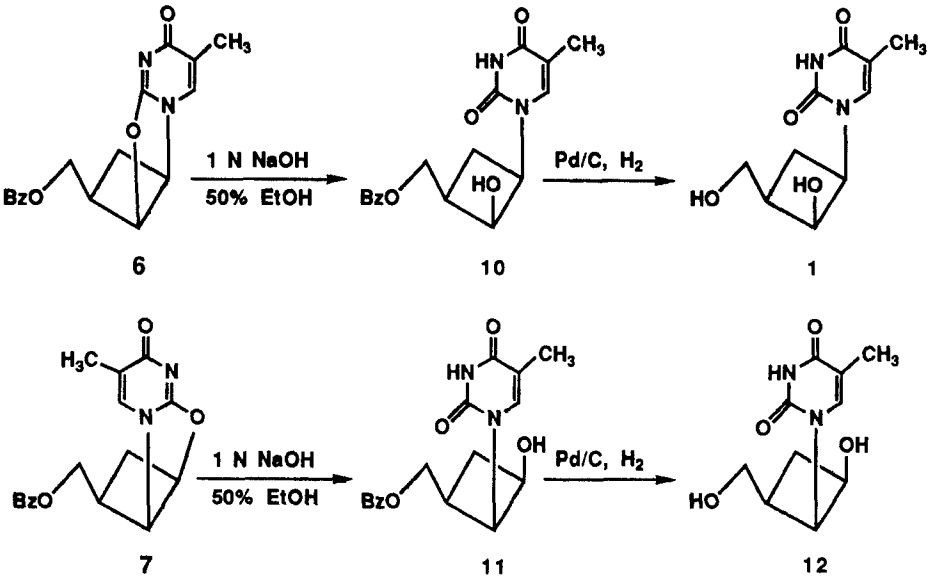


FIG. 3



SCHEME 2

EXPERIMENTAL SECTION

Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian EM-390 (90 MHz) NMR spectrometer or a Bruker WM-250B (250 MHz) spectrometer with Me_4Si as the internal reference. The UV spectra were recorded on a Beckman-25 spectrophotometer. The mass spectra were provided by the Mass Spectrometry Facility, Comprehensive Cancer Center, Yale Medical School. Column chromatography was done with Merck silica gel 60, 230-400 mesh. Thin-layer chromatography was performed with Merck silica gel 60 F_{254} TLC plate, and spots were visualized by UV light or spraying with concentrated H_2SO_4, followed by heating. Elemental analyses were carried out by the Baron Consulting Co., Orange, CT.

1-[cis-3-(Benzyloxymethyl)-trans-2-iodo-cyclobutyl]thymine (4) and 1-[cis-4-(Benzyloxymethyl)-trans-2-iodo-cyclobutyl]thymine (5).

To 7.56 g (60 mmol) of thymine were added 300 mL of 1,1,1,3,3,3,-hexamethyldisilazane and 6 mL of chlorotrimethylsilane. The reaction mixture was refluxed for 16 h. Removal of the excess reagent by rotary evaporation in vacuo provided silylated thymine as a colorless oil, which was then treated with 300 mL of ethanol-free chloroform, 8.8 g (39 mmol) of *N*-iodosuccinimide and 5.25 g (30 mmol) of 3-benzyloxymethyl-1-cyclobutene

at 60 °C with stirring overnight. An additional 3 g (13 mmol) of *N*-iodosuccinimide was added to the reaction mixture and stirred at 60 °C for another 4 h. The cooled reaction mixture was diluted with 200 mL of chloroform, washed with 5 N $Na_2S_2O_3$ solution and water, dried over anhydrous sodium sulfate, and filtered. After removal of the solvent, the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH, 15:1, v/v, R_f 0.58) to give 3.9 g (31%) of product as a mixture of compounds **4** and **5** with a ratio of 2.5:1 (estimated by ^{1}HNMR). Compound **4**: ^{1}HNMR ($CDCl_3$) δ 1.95 (s, 3H, 5-CH_3), 2.43-2.85 (m, 3H, 3'-H and 4'-H), 3.55-3.80 (m, 2H, OCH_2), 4.60 (s, 2H, $ArCH_2$), 4.95-5.05 (m, 1H, 2'-H), 5.10 (m, 1H, 1'-H), 7.10 (s, 1H, 6-H), 7.30-7.38 (m, 5H, ArH), 9.45 (s, 1H, 3-NH, D_2O exchangeable). Compound **5**: ^{1}HNMR ($CDCl_3$) δ 1.85 (s, 3H, 5-CH_3), 2.40-2.80 (m, 3H, 3'-H and 4'-H), 3.40-3.50 (m, 2H, OCH_2), 4.70 (s, 2H, $ArCH_2$), 4.90-5.15 (m, 2H, 1'-H and 2'-H), 7.18 (s, 1H, 6-H), 7.30-7.40 (m, 5H, ArH), 9.40 (s, 1H, 3-NH, D_2O exchangeable).

2,2'-Anhydro-1-[cis-3-(benzyloxymethyl)-cyclobutyl]thymine (6) and 2,2'-Anhydro-1-[cis-4-(benzyloxymethyl)-cyclobutyl]thymine (7).

To a stirred solution of compounds **4** and **5** (3.4 g, 8 mmol) in 8 mL of anhydrous acetonitrile was added dropwise 1.8 g (11.8 mmol) of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) at 0-5 °C. The reaction mixture was stirred at room temperature until TLC showed the starting materials had disappeared (about 36 h). The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column (CH_2Cl_2/MeOH, 15:1, v/v) to give 3 fractions:

Compound **6** (1.0 g, 42%), obtained from the second fraction as white crystals: mp 187-188 °C; TLC R_f 0.34; UV (MeOH) λ_{max} 262 nm, shoulder at 230 nm, λ_{min} 220 nm; ^{1}HNMR ($CDCl_3$) δ 1.91 (s, 3H, 5-CH_3), 2.26 (m, 1H, 4'-H_A), 2.45 (m, 1H, 4'-H_B), 2.90-2.94 (m, 1H, 3'-H), 3.38 (m, 1H, OCH_A), 3.61 (m, 1H, OCH_B), 4.48 (s, 2H, $ArCH_2$), 4.62-4.67 (t, 1H, 2'-H, $J_{2',1'} = J_{2',3'} = 5.2$ Hz), 5.19-5.23 (m, 1H, 1'-H), 7.04 (s, 1H, 6-H), 7.19-7.33 (m, 5H, ArH). Anal. Cacld. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.72; H, 5.78; N, 9.43.

Compound **7** (0.39 g, 16%), obtained from the third fraction as white crystals: mp 185-186 °C; TLC R_f 0.25; UV (MeOH) λ_{max} 262 nm, shoulder at 230 nm, λ_{min} 220 nm; ^{1}HNMR ($CDCl_3$) δ 1.91 (s, 3H, 5-CH_3), 2.24 (m, 1H, 3'-H_A), 2.65 (m, 1H, 3'-H_B), 3.05-3.12 (m, 1H, 4'-H), 3.57-3.62 (m, 2H, OCH_2), 4.46 (s, 2H, $ArCH_2$), 4.74-4.80 (m, 1H, 2'-H), 5.37-5.43 (t, 1H, 1'-H, $J_{1',2'} = J_{1',4'} = 6.7$ Hz), 7.00 (s, 1H, 6-H), 7.22-7.35 (m, 5H, ArH). Anal. Cacld. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.00; H, 5.79; N, 9.62.

Compounds **8** and **9** (0.55 g, 23%), obtained from the first fraction as a foam: TLC R_f 0.63; ^{1}HNMR ($CDCl_3$) δ 6.05 (d, 1H, vinylic) and 6.13 (d, 1H, vinylic); MS *m/e* 299 (M^+ + 1), 173 (carbocycle +1), 127 (thymine + 1).

1-[cis-3-(Benzyloxymethyl)-cis-2-hydroxy-cyclobutyl]thymine (10).

A suspension of compound **6** (0.50 g, 1.7 mmol) in 4.3 mL of 1 N sodium hydroxide and 65 mL of 50% ethanol was stirred at room temperature until a clear solution was formed. The reaction mixture was stirred for an additional 4 h, then adjusted to pH ~7 with HOAc/EtOH (1:1, v/v). The solution was evaporated under reduced pressure until a white solid appeared. The resulting white solid was collected by filtration, washed with water, dried, and recrystallized from ethanol to give 0.44 g (83%) of product: mp 74-75 °C; TLC R_f 0.62 (CH_3CN/MeOH, 20:1, v/v); UV (MeOH) λ_{max} 272 nm, λ_{min} 236 nm; ^{1}HNMR ($CDCl_3$) δ 1.70 (br s, 1H, 2'-OH, D_2O exchangeable), 1.91 (s, 3H, 5-CH_3), 2.23-2.56 (m, 3H, 3'-H and 4'-H), 3.56-3.58 (d, 2H, OCH_2), 4.48-4.51 (m, 1H, 2'-H), 4.54 (s, 2H, $ArCH_2$), 4.81-4.89 (m, 1H, 1'-H), 7.25 (s, 1H, 6-H), 7.28-7.38 (m, 5H, ArH), 9.31 (s, 1H, 3-NH, D_2O exchangeable). Anal. Cacld. for $C_{17}H_{20}N_2O_4 \cdot H_2O$: C, 61.06; H, 6.63; N, 8.38. Found: C, 60.95; H, 6.27; N, 8.52.

1-[cis-4-(Benzyloxymethyl)-cis-2-hydroxy-cyclobutyl]thymine (11).

This compound was synthesized from **7** (0.31 g, 1.0 mmol) by the same procedure described for compound **8**. Yield: 0.28 g (85%) as a foam; TLC R_f 0.62 (CH_3CN/MeOH, 20:1, v/v); UV (MeOH) λ_{max} 274 nm, λ_{min} 238 nm; ^{1}HNMR ($CDCl_3$) δ 1.80 (s, 3H, 5-CH_3), 2.30-2.50 (m, 3H, 3'-H and 4'-H), 3.50-3.70 (d, 3H, OCH_2 and 2'-OH, D_2O exchangeable), 4.50 (s, 2H, $ArCH_2$), 4.60-4.75 (m, 2H, 1'-H and 2'-H), 7.15 (s, 1H, 6-H), 7.25-7.40 (m, 5H, ArH), 9.90 (s, 1H, 3-NH, D_2O exchangeable). Anal. Cacld. for $C_{17}H_{20}N_2O_4 \cdot 0.25\ H_2O$: C, 63.63; H, 6.44; N, 8.73. Found: C, 63.80; H, 6.87, N, 8.69.

1-[cis-2-Hydroxy-cis-3-(hydroxymethyl)cyclobutyl]thymine (1).

A mixture of compound **10** (0.20 g, 0.63 mmol), 0.15 g of 10% Pd/C in 50 mL of anhydrous ethanol was shaken under 50 psi of hydrogen pressure at room temperature overnight. The reaction mixture was filtered, washed with ethanol, and the combined filtrate and washings were evaporated under reduced pressure to give an oil residue, which was co-evaporated with chloroform and ethyl acetate several times and recrystallized from a mixture of chloroform and ethyl acetate to afford 0.13 g (91%) of product as white crystals: mp 176-178 °C; TLC R_f 0.20 (CH_2Cl_2/MeOH, 10:1, v/v); UV (CH_3OH) λ_{max} 276 nm (ε 9515), λ_{min} 240 nm; UV (0.01 N HCl) λ_{max} 277 nm (ε 9709), λ_{min} 241 nm; UV (0.01 N NaOH) λ_{max} 275 nm (ε 8544), λ_{min} 241 nm; ^{1}HNMR ($CDCl_3$) δ 1.80 (s, 3H, 5-CH_3),

1.95-2.05 (m, 1H, 4-H_A), 2.15-2.23 (m, 1H, 4-H_B), 2.41-2.58 (m, 1H, 3'-H), 3.41-3.52 (m, 2H, 3'-CH_2), 4.08-4.15 (m, 1H, 2'-H), 4.68 (t, 1H, 3'-COH, D_2O exchangeable), 4.78-4.89 (m, 1H, 1'-H), 5.24 (d, 1H, 2'-OH, D_2O exchangeable), 7.60 (s, 1H, 6-H), 12.1 (s, 1H, 3-NH, D_2O exchangeable); MS *m/e* 227 (M^+ + 1), 127 (thymine + 1). Anal. Cacld. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.39. Found: C, 52.84; H, 6.50; N, 12.05.

1-[cis-2-Hydroxy-cis-4-(hydroxymethyl)cyclobutyl]thymine (12).

This compound was synthesized from **11** (0.20 g, 0.63 mmol) by the same procedure described for compound **1**. Yield: 0.13 g (88%) as white crystals; mp 176-178 °C; TLC R_f 0.20 (CH_2Cl_2/MeOH, 20:1, v/v); UV (CH_3OH) λ_{max} 274 nm (ε 8437), λ_{min} 238 nm; UV (0.01 N HCl) λ_{max} 276 nm (ε 10106), λ_{min} 240 nm; UV (0.01 N NaOH) λ_{max} 275 nm (ε 9550), λ_{min} 240 nm; ^{1}HNMR (DMSO-d_6) δ 1.80 (s, 3H, 5-CH_3), 1.95-2.05 (m, 1H, 3'-H_A), 2.15-2.23 (m, 1H, 3'-H_B), 2.41-2.58 (m, 1H, 4'-H), 3.41-3.52 (m, 2H, 4'-CH_2), 4.08-4.15 (m, 1H, 2'-H), 4.68 (t, 1H, 4'-COH, D_2O exchangeable), 4.55-4.62 (m, 1H, 1'-H), 5.11 (d, 1H, 2'-OH, D_2O exchangeable), 7.48 (s, 1H, 6-H), 10.8 (s, 1H, 3-NH, D_2O exchangeable); MS *m/e* 227 (M^+ + 1), 127 (thymine + 1). Anal. Cacld. for $C_{10}H_{14}N_2O_4 \cdot 0.5\ H_2O$: C, 51.05; H, 6.42; N, 11.92. Found: C, 51.14; H, 6.71; N, 11.56.

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