Total synthesis of hydroxymethyl isonucleosides as potential antiviral agents

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Abstract
Hydroxymethyl isodideoxynucleosides, designed as potential antiviral agents, have been synthesized through development of a multi-step procedure starting from furan and cyanovinyl acetate. Key steps in the synthesis include a Diels-Alder reaction, oxidative cleavage of alkene, a Mitsunobu reaction, stereospecific introduction of amino group and nucleobase construction.

Keywords: Total synthesis, purine and pyrimidine isonucleosides

Introduction
Isomeric dideoxynucleosides as antiviral agents have been the subject of intense investigation in our laboratory and have also been studied by others. Work in our laboratory led to the discovery of 4(S)-(adenin-9-y1)-2(S)-hydroxymethyltetrahydrofuran [(S,S)-isoddA] (1, Figure 1) which exhibits potent anti-HIV activity against HIV-1, HIV-2, and HIV-resistant strains. Its triphosphate is among the strongest known inhibitors of HIV reverse transcriptase. In the design of new structures that may have anti-HIV activity, we decided to explore analogues of this lead compound by introducing functionalized substituents into the sugar moiety. Introduction of an additional hydroxymethyl group was of interest, not only because of the observation of anti-HIV activity associated with isomeric nucleosides in which the adenine ring and the –CH₂OH have cis-1,3- and 1,2-relationships (2, Figure 1), but also because of the known antiviral activity of natural oxetanocin and its ring expanded analog which bear an additional –CH₂OH group. The molecules targeted for synthesis (3-5) are shown in Figure 1.
Results and Discussion

For the preparation of the proposed hydroxymethyl isodideoxynucleosides, the initial step of the procedure involved a Diels-Alder reaction (Scheme 1). Thus, furan 6 was treated with 1-cyanovinylacetate (7) and catalyst, zinc diiodide, and stirred at room temperature for 4 days to give an adduct 8 in high yield (70%). Adduct 8 was converted to ketone 9 by sequential treatment with 1N potassium hydroxide and formaldehyde. Ketone 9 was reduced stereoselectively to alcohol 10 by sodium borohydride in methanol in 65% yield from 8. However, direct reduction of 8 with sodium borohydride gave even higher yields of 10 (89%) and with the same stereoselectivity. Protection of compound 10 with tert-butyldimethylsilyl chloride gave intermediate 11 (83%).

An attempt to convert olefin 11 to a dialdehyde 13 in one pot, using osmium tetroxide-sodium periodate system, did not give a clean reaction. Therefore, compound 11 was converted to the dialdehyde 13 in two discrete steps. First, olefin 11 was dihydroxylated to the triol derivative 12 using catalytic amounts of osmium tetroxide and stoichiometric amounts of N-methyl morpholine N-oxide (88% yield). Purified 12 was treated with sodium periodate in tetrahydrofuran-water to give the dialdehyde 13, which was immediately reduced to the triol derivative 14 in 76% yield by sodium borohydride. Because the initial Diels-Alder reaction produced a racemic adduct 8, the sequence of reactions from 8 would produce the racemic triol derivative 14.
Intermediate 14 was protected to its ditrityl derivative 15 with trityl chloride (82%) which was desilylated using tetrabutylammonium fluoride (TBAF) in 85% yield (Scheme 2). An attempt to invert the chirality at the C-3 position of 17 using benzoic acid-PPh$_3$-DEAD was not successful probably due to the bulky trityl groups. However, under similar conditions using PPh$_3$ and I$_2$ the iodide 20 with inverted configuration at the C-3 position was produced in 87% yield. Coupling the iodide 20 with sodium azide in dimethyl sulfoxide (DMSO) gave the desired azide 22 but in moderate yields (58%). Elimination to produce an olefin byproduct 20 in 16% yield was also observed. The catalytic reduction of the azide 22 was compromised by partial removal of the trityl protection to give 56% yield of an amine 27 (Scheme 3). Thus, to avoid the problems derived from the trityl protection, the diol 14 was protected with MOMCl to give intermediate 16 which was desilylated to alcohol 18 in 79% yield from 14 (Scheme 2). Treatment of alcohol 18 under Mitsunobu conditions and in the presence of benzoic acid afforded benzoate 23, which was debenzoylated with ammonia in methanol to give the inverted alcohol 24. As previously mentioned, this conversion with inversion of stereochemistry could not be achieved with the trityl counterpart 17. Alcohol 24 was mesylated to 25 (98%) which was then treated with sodium azide in DMF to give azide 26 in 82% yield without the eliminative by-product. However,
development of the pathway utilizing the MOM protecting group was done after the total synthesis was complete with the trityl protecting group in order to have a more efficient pathway for the synthesis of the key azido intermediate.

![Scheme 2](image)

Intermediate 27, prepared from the reduction of azido compound (+) 22 (Scheme 3), was coupled with 5-amino-4,6-dichloropyrimidine\(^{16}\) to give, in 68% yield, the pyrimidine intermediate 28 which, on treatment with triethyl orthoformate in the presence of HCl, gave the 6-chloropurine derivative 29 with concomitant removal of the trityl groups (Scheme 3).
Scheme 3

Ammonolysis with methanolic ammonia gave the desired adenosine analogue 3 in 53% yield from 28. For the preparation of the uridine analogue, intermediate 27 was treated with 3-methoxyacryloyl isocyanate,\(^{17}\) freshly prepared from 3-methoxyacryloyl chloride and silver cyanate to give an acryloylurea 30, which was then cyclized to the uracil analogue 31 on treatment with ammonium hydroxide at 100 °C. Deprotection with trifluoroacetic acid gave the target uridine 4 (34% yield from 27). The cytidine analogue 5 was obtained from the uridine 31 by sequential treatment with 2,4,6-trisopropylbenzenesulfonyl chloride and ammonium hydroxide\(^{18}\) followed by deprotection with dilute HCl in 46% yield.
In summary, target compounds, 3, 4, and 5, were synthesized as racemates from the key intermediate, the tetrahydrofuran triol 14, which was obtained efficiently using a Diels-Alder pathway from basic starting compounds, furan (6) and 1-cyanovinylacetate (7). Antiviral studies of the target compounds are currently in progress.

**Experimental Section**

**General Procedures.** Melting points reported are uncorrected and were determined on an Electrothermal Engineering Ltd. melting point apparatus. Nuclear magnetic resonance spectra were recorded on Bruker Model AC300 and WM 360 systems. Ultraviolet spectra were recorded on a Varian Cary Model 3 spectrophotometer. Flash chromatography used 230-400 mesh silica gel. HPLC analyses were carried out on a Beckman-Coulter instrument with C-18 reversed-phase columns.

(±)-2-endo/exo-Acetoxy-7-oxabicyclo[2.2.1]hept-5-en-2-exo/endo-carbonitrile (8). To a mixture of furan (6) (13.2 mL, 180.15 mmol) and 1-cyanovinylacetate (7) (5.0 g, 45.00 mmol) was added zinc iodide (7.20 g, 22.56 mmol). The resulting reaction mixture was stirred at room temperature in the dark for 4 days. The catalyst was removed by filtration and the filtrate was concentrated and purified by flash chromatography (hexanes: ethyl acetate = 5:1) to give a 3:1 mixture of compound 8 as a colorless liquid in 71% yield. $^1$H NMR (CDCl$_3$) (major isomer) δ 6.64 (dd, 1H, $J = 1.27$, 5.83 Hz), 6.21 (dd, 1H, $J = 1.54$, 5.83 Hz), 5.58 (s, 1H), 5.13 (m, 1H), 2.73 (dd, 1H, $J = 4.80$, 12.70 Hz), 2.06 (s, 3H), 1.73 (d, 1H, $J = 12.70$ Hz).

(±)-7-Oxabicyclo[2.2.1]hept-5-en-2-endo-ol (10)

**Method 1.** $^9$ To a solution of compound 8 (3.6 g, 20.09 mmol) in tetrahydrofuran-water (1:1, 100 mL) was added 1N sodium hydroxide (30 mL) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 1 h and 37% formaldehyde (120 mL) was added to the reaction mixture, which was stirred at 0 °C for 10 min and extracted with chloroform (4 x 50 mL). The organic layer was dried on sodium sulfate and concentrated under reduced pressure at 35 °C. The resulting residue (compound 9) was dissolved in methanol (20 mL), to which was added sodium borohydride (1.6 g, 42.29 mmol) over 20 min at 0 °C (internal temperature), and the resulting reaction mixture was stirred for 1 h and concentrated under reduced pressure at 31 °C. The residue obtained was purified by flash chromatography (hexanes: ethyl acetate = 2:1) to give compound 10 as colorless liquid (1.46 g, 65%).

**Method 2.** To a solution of compound 8 (29 g, 162 mmol) in methanol (600 mL) at 0 °C (internal temperature) was added sodium borohydride (14 g, 370 mmol) over 20 min. The resulting reaction mixture was stirred at room temperature overnight, neutralized under ice-bath
temperatures with conc. HCl, and concentrated. The resulting residue was purified by flash chromatography (hexanes:EtOAc = 1:1) to give compound 10 (16 g, 89%) as a colorless liquid. $^1$H NMR (CDCl$_3$) $\delta$ 6.64 (dd, 1H, $J = 1.76, 5.88$ Hz), 6.39 (dd, 1H, $J = 1.29, 5.87$ Hz), 4.93 (dd, 1H, $J = 1.54, 6.49$ Hz), 4.89 (dd, 1H, $J = 1.16, 4.51$ Hz), 4.46 (m, 1H), 2.30 (ddd, 1H, $J = 4.83, 8.00, 11.90$ Hz), 1.25 (bs, 1H), 0.98 (dd, 1H, $J = 2.33, 11.91$ Hz); $^{13}$C NMR (CDCl$_3$) $\delta$ 138.48, 131.83, 79.71, 79.40, 68.74, 35.87.

(±)-2-endo-tert-Butyldimethylsilyloxy-7-oxabicyclo[2.2.1]hept-5-ene (11). To a solution of a mixture of 10 (6.0 g, 53.51 mmol) and 4-$N,N$-dimethylpyridine (300 mg, 2.46 mmol) in anhydrous pyridine (60 mL) was added tert-butyldimethylsilyl chloride (16 g, 106.15 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 24 h. The reaction was quenched by ice water (10 mL). Then, the reaction mixture was diluted with ethyl acetate (500 mL), washed with water (3 x 50 mL), and brine (2 x 50 mL). The organic layer was dried over sodium sulfate, concentrated, and separated by flash chromatography (hexanes: ethyl acetate = 40:1) to give compound 11 as a colorless liquid (10g, 83%). $^1$H NMR (CDCl$_3$) $\delta$ 6.48 (dd, 1H, $J = 1.70, 5.88$ Hz), 6.26 (dd, 1H, $J = 1.50, 5.87$ Hz), 4.88 (dd, $J = 1.64, 4.81$ Hz), 4.76 (dd, 1H, $J = 1.50, 4.44$ Hz), 4.40 (m, 1H), 2.14 (m, 1H), 0.94 (dd, 1H, $J = 2.32, 11.33$ Hz), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); $^{13}$C NMR (CDCl$_3$) $\delta$ 82.41, 78.49, 73.63, 64.85, 62.70, 37.28, 25.83, 18.08, -4.63, -5.08.

(±)-(2R/S, 3R/S, 5R/S)-3-tert-Butyldimethylsilyloxy-2,5-di(hydroxymethyl)tetrahydrofuran (14). To a solution of compound 11 (1.37 g, 6.05 mmol) in acetone (20 mL) containing N-methyl morpholine N-oxide (610 mg, 5.21 mmol) was added osmium tetroxide (48 mg, 0.19 mmol) under ice bath temperature. The solution was stirred at room temperature for 14 h. Sodium hydrosulfite (1.36 g, 7.81 mmol) was added to the reaction mixture, which was stirred at room temperature for 30 min and concentrated under reduced pressure. The residue obtained was dissolved in brine (100 mL) and extracted with chloroform (5 x 50 mL). The organic layer was dried with sodium sulfate, concentrated, and purified by flash chromatography (hexanes: ethyl acetate = 1:2) to give compound 12 (1.36 g, 86%) as a syrup. To a solution of compound 12 (900 mg, 3.03 mmol) in tetrahydrofuran-water (4:1, 50 mL) was added sodium periodate (1.98 g, 9.26 mmol) in portions at 0 °C. The resulting reaction mixture was stirred at room temperature for 1.5 h, then diluted with brine (200 mL), and extracted with chloroform (5 x 100 mL). The combined organic layer was dried on sodium sulfate and concentrated. The residue (compound 13) was dissolved in tetrahydrofuran (200 mL) and cooled to -10 °C, to which sodium borohydride (804 mg, 21.25 mmol) in methanol (10 mL) was added over 10 min. The resulting reaction was stirred at room temperature for 30 min and concentrated. The resulting residue was purified by flash chromatography (chloroform:methanol = 30:1) to give compound 14 (688 mg, 76% from 12) as colorless syrup. $^1$H NMR (CDCl$_3$) $\delta$ 4.44 (m, 1H), 4.09 (m, 1H), 3.89 (m, 1H), 3.79-3.71 (m,
3H), 3.58 (m, 1H), 3.27 (bs, 1H), 3.00 (bs, 1H), 1.80 (m, 1H), 0.87 (s, 9H), 0.07 (s, 6H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 82.49, 78.49, 73.65, 64.85, 62.70, 37.28, 25.83, 18.08, -4.63, -5.08.

(±)-(2R/S, 3R/S, 5R/S)-3-tert-Butyldimethylsilyloxy-2,5-di(trityloxymethyl)tetrahydrofuran (15). To a solution of compound 14 (910 mg, 3.47 mmol) in anhydrous pyridine (20 mL) was added trityl chloride (3.42 g, 12.27 mmol) at room temperature. The resulting reaction mixture was stirred for 18 h. Additional trityl chloride (3.00 g, 10.76 mmol) was added and the reaction was continued for 18 h and quenched by adding cold water (5 mL). The reaction mixture was diluted by ethyl acetate (500 mL), and washed with water (2 x 100 mL) and brine (2 x 100 mL). After concentration, the residue was separated by flash chromatography (hexanes: EtOAc = 40:1) to give compound 15 as white solid (2.12 g, 82%).

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.48-7.15 (m, 30H), 4.27-4.24 (m, 3H), 4.08 (m, 1H), 3.45 (m, 2H), 3.13 (dd, 1H, \(J = 4.33, 9.84\) Hz), 2.83 (dd, 1H, \(J = 4.90, 9.14\) Hz), 2.19 (m, 1H), 1.57 (m, 1H), 0.54 (s, 9H), -0.18 (s, 3H), -0.26 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 144.29, 144.25, 128.87, 128.85, 127.76, 127.69, 126.83, 126.77, 86.82, 86.38, 83.65, 72.37, 67.87, 64.34, 38.60, 25.60, 17.71, -4.82, -5.38.

(±)-(2R/S, 3R/S, 5R/S)-2,5-Di(trityloxymethyl)-3-hydroxytetrahydrofuran (17). A mixture of compound 15 (2.20 g, 2.94 mmol) and tetrabutylammonium fluoride (1.54 g, 5.89 mmol) in tetrahydrofuran (125 mL) was stirred at room temperature for 48 h. After concentration, the resulting residue was purified by flash chromatography (hexanes : EtOAc = 10:1) to give compound 17 as white foam (1.58 g, 85%).

\(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.91-7.20 (m, 30H), 4.25 (m, 1H), 4.16 (m, 1H), 3.93 (m, 1H), 3.50 (d, 2H, \(J = 5.53\) Hz), 3.45 (dd, 1H, \(J = 3.84, 10.07\) Hz), 3.26 (d, 1H, \(J = 8.65\) Hz), 3.07 (dd, 1H, \(J = 3.19, 10.11\) Hz), 2.27 (ddd, 1H, \(J = 5.71, 9.47, 13.87\) Hz), 1.73 (ddd, 1H, \(J = 1.32, 4.24, 13.79\) Hz); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 143.94, 143.49, 128.87, 127.93, 127.09, 127.00, 87.42, 86.96, 82.51, 82.41, 76.94, 72.29, 66.21, 62.91, 37.56.

(±)-(2R/S, 3R/S, 5R/S)-2,5-Di[(O-methoxymethyl)methyl]-3-hydroxy-tetrahydrofuran (18). To a solution of compound 14 (1.30 g, 4.95 mmol) in anhydrous methylene chloride (20 mL)
containing diisopropylmethylamine (3.0 mL) was added methoxymethyl chloride (1.50 mL, 19.75 mmol) slowly at 0 °C. The resulting reaction mixture was stirred at 0 °C for 1 h, to which cold water (15 mL) was added, and extracted with chloroform (3 x 15 mL). The combined organic layer was dried, concentrated, and purified by silica gel column chromatography (hexanes: EtOAc = 3:1) to give a residue (compound 16). A mixture of 16 and TBAF (2.59 g, 9.90 mmol) in tetrahydrofuran (50 mL) was stirred at room temperature for 24 h, concentrated, and purified by flash chromatography (hexanes: EtOAc = 1:1) to give compound 18 as a syrup (923 mg, 79%).

\[ \text{H NMR (CDCl}_3\text{) } \delta 4.67 \text{ (s, 2H), 4.66 (s, 2H), 4.29 (m, 1H), 4.19 (m, 1H), 3.90 (m, 1H), 3.79-3.73 (m, 2H), 3.54 (dd, 1H, } J = 2.70, 10.56 \text{ Hz), 3.39 (m, 3H), 3.38 (m, 3H), 2.37 (m, 1H), 1.92 (dd, 1H, } J = 3.32, 13.95 \text{ Hz); 3.52 (d, 1H, } J = 10.20 \text{ Hz); } 13\text{C NMR (CDCl}_3\text{) } \delta 96.80, 96.50, 82.68, 76.65, 71.72, 69.32, 66.73, 55.60, 55.29, 37.13. \]

(±)-(2R/S, 3S/R, 5R/S)-2,5-Di[(O-methoxymethyl)methyl]-3-hydroxytetrahydrofuran (24).

To a solution of compound 18 (795 mg, 3.36 mmol) in anhydrous tetrahydrofuran (20 mL) containing triphenylphosphine (1.76 g, 10.10 mmol) and benzoic acid (1.23 g, 10.07 mmol) was added DEAD (2.81 g, 16.13 mmol) in tetrahydrofuran (5 mL) through a dropping funnel over 10 min. The resulting reaction mixture was stirred at room temperature for 4 h, concentrated, and purified by flash chromatography (hexanes: EtOAc = 4:1) to give a residue (23), which was dissolved in methanolic ammonia (10 mL), heated at 90 °C for 12 h, and concentrated. The residue obtained was purified by flash chromatography (hexanes: EtOAc = 1:1) to give compound 24 as syrup (600 mg, 75%).

\[ \text{H NMR (CDCl}_3\text{) } \delta 5.17 \text{ (m, 1H), 4.66-4.63 (m, 4H), 4.35 (m, 1H), 4.30 (m, 1H), 3.95 (m, 1H), 3.67-3.62 (m, 2H), 3.56-3.51 (m, 2H), 3.37 (m, 6H), 1.97-1.93 (m, 2H); } 13\text{C NMR (CDCl}_3\text{) } \delta 96.77, 96.60, 85.36, 77.39, 74.08, 69.79, 68.08, 55.32, 55.23, 37.10. \]

(±)-(2R/S, 3S/R, 5R/S)-2,5-Di[(O-methoxymethyl)methyl]-3-O-methanesulfonyltetrahydrofuran (25).

To a solution of compound 24 (600 mg, 2.54 mmol) and triethylamine (3 mL) in anhydrous methylene chloride (40 mL) was added methanesulfonyl chloride (0.80 mL, 10.34 mmol) slowly at °C for 30 min, and diluted with cold water (100 mL) and extracted with chloroform (2 x 100 mL). The organic layer was washed with brine (80 mL), dried, concentrated, and purified by flash chromatography (hexanes: EtOAc = 1:1) to give compound 25 as a syrup (780 mg, 98%).

\[ \text{H NMR (CDCl}_3\text{) } \delta 5.17 \text{ (m, 1H), 4.66-4.63 (m, 4H), 4.35 (m, 1H), 4.22 (m, 1H), 3.68 (m, 2H), 3.55 (dd, 2H, } J = 5.71, 10.69 \text{ Hz), 3.36 (m, 2H, 3.06 (m, 3H), 2.25 (m, 1H, } J = 1.58, 5.47, 13.92 \text{ Hz), 2.07 (m, 1H, } J = 6.17, 10.26, 13.93 \text{ Hz).} \]

(±)-(2R/S, 3R/S, 5R/S)-3-Azido-2,5-di(trityloxyethyl)tetrahydrofuran (22) and cis-2,5-di-(trityloxyethyl)-2,5-dihydrofuran (21).

A mixture of compound 20 (4.0 g, 5.39 mmol) and sodium azide (1.57 g, 24.15 mmol) in anhydrous dimethyl sulfoxide (150 mL) was stirred at 40°C for 48 h, diluted with ethyl acetate (500 mL), and washed with water (3 x 50 mL). The organic layer was concentrated in vacuo and the residue was separated by flash chromatography.
(hexanes: EtOAc = 30:1) to give compound 22 as a white solid (2.06 g, 58%) and compound 21 as a glassy solid (530 mg, 16%). Compound 22: $^1$H NMR (CDCl$_3$) δ 7.50-7.19 (m, 30H), 4.12 (m 2H), 3.98 (dd, 1H, $J = 6.05, 10.40$ Hz), 3.45 (dd, 1H, $J = 5.62, 9.50$ Hz), 3.28 (dd, 1H, $J = 6.16, 9.40$ Hz), 3.22 (dd, 1H, $J = 6.80, 9.46$ Hz), 3.00 (dd, 1H, $J = 5.69, 9.36$ Hz), 2.33 (m, 1H), 1.87 (ddd, 1H, $J = 2.28, 5.52, 13.93$ Hz); $^{13}$C NMR (CDCl$_3$) δ 143.97, 143.89, 128.72, 127.80, 127.76, 127.00, 126.92, 86.99, 86.57, 81.50, 66.15, 62.60, 34.78. Compound 21: δ 7.40-7.15 (m, 30H), 5.87 (s, 2H), 4.95 (m , 2H), 3.22 (dd, 2H, $J = 4.88, 9.36$ Hz), 3.06 (dd, 2H, $J = 4.56, 9.36$ Hz); $^{13}$C NMR (CDCl$_3$) δ 144.04, 128.89, 128.73, 127.67, 126.87, 86.51, 85.73, 67.54; HRFABMS calcd for C$_{44}$H$_{39}$N$_3$O$_2$Na 680.2889, found 680.2903 (M + Na)$^+$. 

(±)-(2R/S, 3R/S, 5R/S)-3-Azido-2,5-di[(O-methoxymethyl)methyl]-tetrahydrofuran (26). A mixture of compound 25 (1.0 g, 3.18 mmol) and sodium azide (1.1 g, 16.92 mmol) in anhydrous DMF (30 mL) was heated at 80 °C for 2 days, concentrated in vacuo, and purified by flash chromatography (chloroform: methanol = 3:1) to give compound 26 (681 mg, 82%) as a syrup. $^1$H NMR (CDCl$_3$) δ 4.68 (2s, 4H), 4.21-4.15 (m, 2H), 4.02 (dd, 1H, $J = 5.89, 10.57$ Hz), 3.79-3.71 (m, 2H), 3.69-3.60 (m , 2H), 3.40 (s, 3H), 3.39 (s, 3H), 2.43 (m , 1H), 1.96 (m, 1H); $^{13}$C NMR (CDCl$_3$) δ 96.89, 96.70, 80.80, 77.06, 69.63, 66.43, 62.18, 55.42, 55.34, 34.33.

(±)-(2’R/S, 3’R/S, 5’R/S)-5-Amino-4-chloro-6-[[2’,5’-di(trityloxymethyl)tetrahydrofuran-3’-yl][amino]pyrimidine (28). A mixture of compound 22 (1.40 g, 2.13 mmol) and 10% Pd/C (235 mg) in ethanol (120 mL) was stirred in a Parr apparatus with 30 psi of hydrogen for 4 h and worked up. The residue obtained was purified by flash chromatography (chloroform: methanol = 3:1) to give compound 27 as a syrup (754 mg, 56%). A mixture of compound 27 (500 mg, 0.79 mmol) and triethylamine (2 mL) in 1-butanol (10 mL) was refluxed at 130 °C for 3 days and concentrated under reduced pressure. The residue was purified by flash chromatography (hexanes: ethylacetate = 10:1) to give compound 28 as syrup (408 mg, 68%). $^1$H NMR (CDCl$_3$) δ 7.91 (s, 1H), 7.47-7.19 (m, 30H), 6.06 (d, 1H, $J = 7.36$ Hz), 4.82 (m, 1H), 4.23 (m, 1H), 4.17 (m, 1H), 3.50 (dd, 1H, $J = 4.99, 10.32$ Hz), 3.37 (dd, 1H, $J = 3.96, 9.85$ Hz), 3.11 (dd, 1H, $J = 2.90, 10.32$ Hz), 2.56 (m, 1H), 1.87 (m, 1H), 1.57 (bs, 2H).

(±)-(2’R/S, 3’R/S, 5’R/S)-3’-(Adenin-9-yl)-2’,5’- di(hydroxymethyl)tetrahydrofuran (3). To a solution of compound 28 (300 mg, 0.40 mmol) in triethyl orthoformate (5 mL) was added conc. HCl (40 µL). The resulting reaction mixture was stirred at room temperature for 4 h and poured into sat. aqueous NaHCO$_3$ (5 mL). After concentration, the residue was purified by flash chromatography (chloroform: methanol = 30:1) to give compound 29 as a white solid. Compound 29 was dissolved in methanol (70 mL), bubbled with ammonia at −10 °C for 10 min, transferred to a steel bomb which was sealed and heated at 110 °C for 17 h. After concentration, the residue was purified by flash chromatography (pre-saturated with triethylamine) (chloroform: methanol = 10:1) to give compound 3 as a white solid (56 mg, 53%). mp 223 °C; UV $\lambda_{max}$ 260 nm (MeOH, $\varepsilon$ 11 277); $^1$H NMR (D$_2$O) δ 8.37 (s, 1H), 8.21 (s, 1H), 5.37 (m, 1H), 4.25 (m, 2H), ...
4.04 (dd, 1H, J = 2.15, 11.81 Hz), 3.86 (dd, 1H, J = 4.43, 12.62 Hz), 3.33 (dd, 1H, J = 3.67, 12.05 Hz), 3.17 (dd, 1H, J = 6.8, 12.07 Hz), 2.85 (m, 1H), 2.37 (m, 1H); \(^{13}\)C NMR (D\(_2\)O + DMSO-\(d_6\)) δ 157.20, 154.10, 150.69, 142.60, 119.63, 82.80, 80.36, 62.80, 61.24, 56.80, 34.69; HRFABMS calcd for C\(_{11}\)H\(_{16}\)N\(_5\)O\(_3\) 266.1253, found 266.1254 (M + H\(^+\)).

(±)-(2′R/S, 3′R/S, 5′R/S)-2′,5′-Di(hydroxymethyl)-3′-(uracil-1-yl)tetrahydrofuran (4). To a suspension of dried silver cyanate (0.26 g, 1.75 mmol) in anhydrous toluene (6 mL) was added freshly prepared β-methoxyacryloyl chloride (0.12 g, 0.99 mmol) at room temperature. The reaction mixture was heated under reflux at 150 °C for 30 min and cooled to room temperature. The supernatant was transferred to a solution of compound 27 (100 mg, 0.16 mmol) in anhydrous toluene (3 mL) at –10 °C over 10 min. The resulting reaction mixture was stirred at –10 °C for 1.5 h, poured into cold NaHCO\(_3\) solution, and extracted with chloroform (3 x 10 mL). The organic layer was concentrated, dissolved in ethyl alcohol (6 mL) containing ammonium hydroxide (1 mL), and heated in a sealed steel bomb at 100 °C for 12 h. After concentration, the residue was purified by flash chromatography (hexanes: ethyl acetate = 3:1 to 2:1) to give compound 31, which was dissolved in methanol (3 mL) and water (5 mL) containing trifluoroacetic acid (1 mL) and stirred at 60 °C for 5 h. After concentration and coevaporation with toluene, the resulting residue was purified by flash chromatography (chloroform: methanol = 10:1) to give compound 4 as a hygroscopic solid (13 mg, 35%). UV \(\lambda_{max}\) 260 nm (MeOH, \(\varepsilon\) 10 890); \(^1\)H NMR (D\(_2\)O) δ 7.89 (d, 1H, J = 8.08 Hz), 5.87 (d, 1H, J = 8.06 Hz), 5.35 (m, 1H), 4.18-4.13 (m, 2H), 3.99 (m, 1H), 3.79 (m, 1H), 3.66-3.60 (m, 2H), 2.64 (m, 1H), 2.07 (m, 1H); \(^{13}\)C NMR (D\(_2\)O + DMSO-\(d_6\)) δ 167.70, 153.95, 146.06, 103.25, 82.54, 80.14, 63.30, 61.21, 57.71, 33.59; HRFABMS calcd for C\(_{10}\)H\(_{15}\)N\(_2\)O\(_5\) 243.0980, found 243.0987 (M + H\(^+\)).

(±)-(2′R/S, 3′R/S, 5′R/S)-2′,5′-Di(hydroxymethyl)-3′-(cytosin-1-yl)tetrahydrofuran (5). To a solution of compound 31 (131 mg, 0.18 mmol) in anhydrous acetonitrile (10 mL) containing Et\(_3\)N (2 mL) and DMAP (89 mg, 0.73 mmol) was added 2,4,6-triisopropyl-benzenesulfonyl chloride (220 mg, 0.72 mmol) in portions at 0 °C. The resulting reaction mixture was stirred at room temperature for 3.5 h. Then, aqueous ammonia (29%, 7 mL) was added to the reaction mixture, which was stirred for 17 h, concentrated, and purified by flash chromatography (chloroform: methanol = 30:1 to 10:1). The cytidine derivative thus obtained was dissolved in methanol (5 mL) containing 5M HCl (1 mL) and stirred at room temperature for 5 h, concentrated, neutralized with potassium carbonate powder, and purified by flash chromatography (chloroform: methanol = 10:1 to 5:1) to give compound 5 (20 mg, 86%) as a white solid. mp 230-233 °C; UV \(\lambda_{max}\) 275 nm (MeOH, \(\varepsilon\) 10, 110); \(^1\)H NMR (D\(_2\)O) δ 7.78 (d, 1H, J = 7.54 Hz), 5.99 (d, 1H, J = 7.50 Hz), 5.33-4.75 (m, 1H), 4.18-4.14 (m, 1H), 4.09 (m, 1H), 3.91 (dd, 1H, J = 2.91, 12.53 Hz), 3.74 (dd, 1H, J = 4.80, 12.53 Hz), 3.53 (dd, 1H, J = 3.80, 12.26 Hz), 3.38 (dd, 1H, J = 6.71, 12.26 Hz), 2.53 (m, 1H), 2.03 (m, 1H); \(^{13}\)C NMR (D\(_2\)O + CD\(_3\)OD) δ
166.10, 158.72, 144.27, 96.01, 81.35, 78.72, 62.19, 60.23, 57.08, 32.30; HRFABMS calcd for C_{10}H_{16}N_{3}O_{4} 242.1140, found 242.1130 (M + H)^{+}.

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References

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