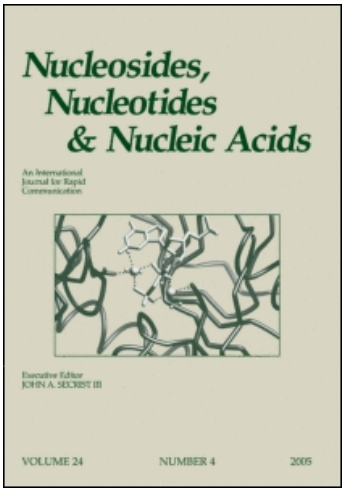

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Synthesis of Unsaturated Carboacyclic Nucleoside Analogues via Mitsunobu Reactions

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Synthesis of Unsaturated Carboacyclic Nucleoside Analogues via Mitsunobu Reactions

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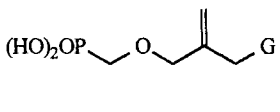
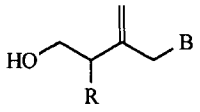
ABSTRACT: 2-Substituted allyl alcohols **9** and **14** were prepared starting from butane-1,2,4-triol and glycerol, respectively. Mitsunobu condensations of **9** and **14** with purine and pyrimidine bases, followed by deprotection, afforded a number of acyclonucleosides having 4-hydroxy-2-methylenebutyl or 3,3-bis(hydroxymethyl)-2-methylenepropyl chain.

A large number of acyclonucleosides (ACNs) have been synthesized and evaluated for antiviral activities[1-3] since acyclovir demonstrated potent activity against HSV infection.[4] Recently, (*S*)-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) was used clinically for treatment of HCMV infection, which prompted intense research activities in the area of ACNs, especially ACN phosphonates.[5-7] In addition to their broad-spectrum antiviral activities, certain ACN phosphonates demonstrated potent anticancer activities.[8-9] Clearly, ACNs and ACN phosphonates continue to add value to drug discovery. Most of the interesting ACNs such as ACV and GCV as well as 9-(2-phosphonylmethoxyethyl)adenine (PMEA) and (*R*)-9-(2-phosphonylmethoxypropyl)-adenine (PMPA) have a flexible, acyclic chain, but some ACNs were built on constrained acyclic chains.[1,10-14] Recently, 9-(2-methylene-3-phosphonylmethoxypropyl)guanine (**1**), in which guanine was attached to an allyl methylene, demonstrated potent activity against HIV.[12,15] Moreover, this compound showed lower toxicity to normal cells when compared to PMEA, which implicated a selective inhibition of the viral DNA synthesis. In order to shed more light on partially constrained ACNs, in this article we present synthesis of ACNs having 4-hydroxy-2-methylenebutyl (**2**) or 3,3-bis(hydroxymethyl)-2-methylenepropyl chain (**3**) via Mitsunobu reaction.



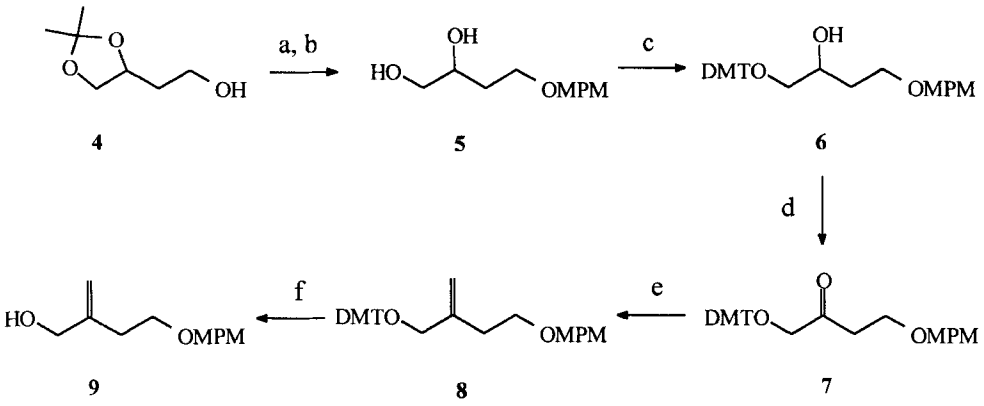
1



2 R = H
3 R = CH_2OH

Most of ACNs in which nucleoside bases are attached to an allyl methylene were synthesized via nucleophilic substitutions of allyl sulfonates or halides.[10-14,16] We attempted to use similar procedures to synthesize **2** and **3**, but found it difficult to prepare desired allyl sulfonates in good yields. Alternatively, we explored condensations of nucleoside bases with 4-(*p*-methoxybenzyloxy)-2-methylenebutanol **9** and 3,3-bis(*t*-butyldimethylsilyloxymethyl)-2-methylenepropanol **14** via Mitsunobu reaction. This approach avoided preparing allyl sulfonates or halides, and the condensations were conducted under mild conditions.

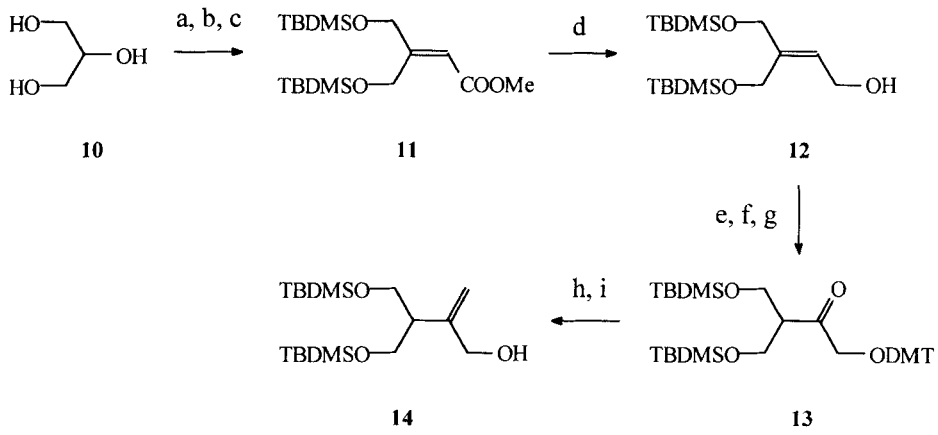
Scheme 1.



a) *p*-MeOBn-Cl, NaH, THF, r.t.; b) HCl, MeOH, r.t., 96% (two steps); c) DMT-Cl, Pyridine, r.t., 77%; d) DMSO, DCC, TFA, pyridine, r.t., 90%; e) $MePh_3PBr$, sodium *t*-pentoxide, Et_2O, –10 °C, 90%; f) TsOH, MeOH, r.t., 89%.

Compound **9** was synthesized from butane-1,2,4-triol-1,2-acetonide (**4**)[17] prepared from butane-1,2,4-triol (Scheme 1). The hydroxyl of **4** was protected with *p*-methoxybenzyl (MPM), followed by hydrolysis, to give **5**. The primary hydroxyl of **5** was selectively protected with 4,4'-dimethoxytrityl (DMT), and the resulting **6** was subjected to a mild oxidation to give the ketone **7**. Wittig reaction converted **7** to the alkene **8**, which was treated with *p*-toluenesulfonic acid to give **9**.

Scheme 2.



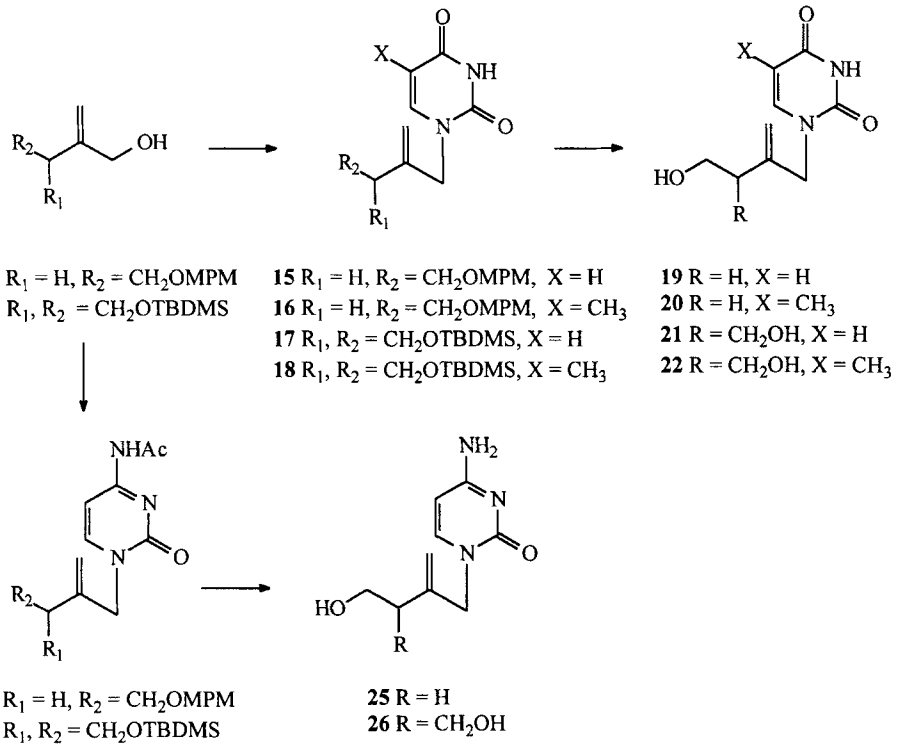
a) TBDMS-Cl, imidazole, $CHCl_3$, r.t; b) same as d in Scheme 1; c) $Ph_3PCHCOOMe$, MeOH, r.t, 91% (three steps); d) DIBAL-H, Et_2O, –78 °C, 98%; e) DMT-Cl, pyridine; f) 1. BH_3SMe_2, THF, r.t.; 2. $NaBO_3$, H_2O_2, H_2O, EtOH, r.t., g) same as b, 32.8% (three steps); h) same as e in scheme 1; i) silica gel, benzene, 72% (two steps).

Compound **14** was synthesized, in nine steps, from glycerol **10** (Scheme 2). The primary hydroxyls of **10** were selectively protected with *t*-butyldimethylsilyl (TBDMS) and the secondary hydroxyl was oxidized to give a ketone. Wittig reaction of the ketone with methyl (triphenylphosphoranylidene)acetate gave **11**, which was subjected to a selective reduction of the carboxylic ester with DIBAL-H to give **12**. After protection with DMT, **12** was subjected to hydroboration and the subsequent oxidation to give **13**. It is worth mentioning that one of the two TBDMS protecting groups was partially removed during the hydroboration and could be added back by reaction with TBDMS-Cl. Compound **13** was subjected to a Wittig reaction and the subsequent removal of DMT on silica gel[18] to give **14**.

The pyrimidine ACNs were synthesized via Mitsunobu condensations[19-20] of pyrimidine bases with the alcohols **9** and **14** (Scheme 3). Condensations were conducted in THF in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) at room temperature. When uracil and thymine were used, **15-18** were obtained in moderate to good yields. However, the Mitsunobu reaction failed to give cytidine derivatives when cytosine was used under the same conditions. Alternatively, N^4-acetylcytosine was reacted with **9** and **14** to give the desired products **23** and **24**, respectively. Treatment of **15**, **16**, and **23** with boron trifluoride at low temperature afforded the desired ACNs **19**, **20**, and, after removal of acetyl group, **25**, respectively. Treatment of **17**, **18**, and **24** with tetrabutylammonium fluoride gave the ACNs **21**, **22**, and, after deacetylation, **26**,

respectively. These acyclic nucleosides were obtained in moderate yields (30-55%) from the condensation and the subsequent deprotection.

Scheme 3.



9 R_1 = H, R_2 = CH_2OMPM
14 R_1, R_2 = $CH_2OTBDMS$

15 R_1 = H, R_2 = CH_2OMPM, X = H
16 R_1 = H, R_2 = CH_2OMPM, X = CH_3
17 R_1, R_2 = $CH_2OTBDMS$, X = H
18 R_1, R_2 = $CH_2OTBDMS$, X = CH_3

19 R = H, X = H
20 R = H, X = CH_3
21 R = CH_2OH, X = H
22 R = CH_2OH, X = CH_3

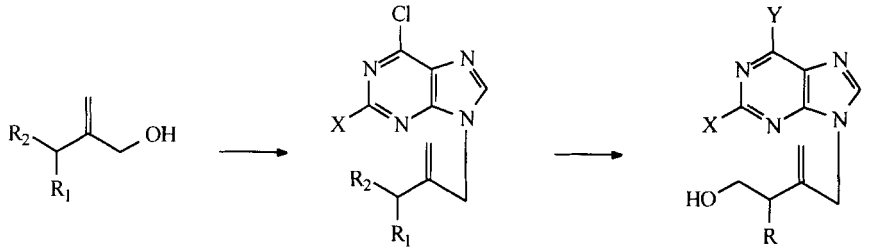
23 R_1 = H, R_2 = CH_2OMPM
24 R_1, R_2 = $CH_2OTBDMS$

25 R = H
26 R = CH_2OH

Condensations of 6-chloropurine or 2-amino-6-chloropurine with **9** and **14** under the same conditions as those of the pyrimidine bases afforded, after removal of MPM or TBDMS, **27-30** in moderate yields (31-51%), respectively (Scheme 4). Compounds **27-30** were treated with 2-mercaptoethanol in the presence of sodium methoxide[21] to give the desired ACNs **31-34**, respectively. Treatment of **27** and **29** with ammonia in methanol at 100 °C in a steel bomb afforded the ACNs **35** and **36**, respectively.

In summary, we have reported synthesis of two series of new ACNs in which the nucleoside bases were attached to an allyl methylene via Mitsunobu reactions. When compared with other procedures reported for similar compounds,[11-13] the Mitsunobu condensations afforded the ACNs in better yields and avoided preparing allyl sulfonates or halides which could be troublesome owing to instability to hydrolysis. Also, Mitsunobu reaction is useful for preparation of allyl ACNs containing all the common nucleoside bases.

Scheme 4.



9 $R_1 = H$, $R_2 = CH_2OMPM$
14 $R_1, R_2 = CH_2OTBDMS$

27 $R_1 = H$, $R_2 = CH_2OH$, $X = H$
28 $R_1 = H$, $R_2 = CH_2OH$, $X = NH_2$
29 $R_1, R_2 = CH_2OH$, $X = H$
30 $R_1, R_2 = CH_2OH$, $X = NH_2$

31 R = H, X = H, Y = OH
32 R = H, $X = NH_2$, Y = OH
33 $R = CH_2OH$, X = H, Y = OH
34 $R = CH_2OH$, $X = NH_2$, Y = OH
35 R = H, X = H, $Y = NH_2$
36 $R = CH_2OH$, X = H, $Y = NH_2$

Experimental

Proton NMR spectra were recorded on a 300 MHz spectrometer and chemical shifts are reported in δ values (parts per million) with tetramethylsilane (TMS) as the internal standard. Elemental analysis data were obtained from NuMega Resonance Labs, San Diego. Melting points were measured with a capillary melting points apparatus and are uncorrected. Anhydrous solvents containing <0.005% water were purchased from Fluka or Aldrich and used directly without further treatment. Thin layer chromatography plates and silica gel for column chromatography were supplied by ICN.

(*p*-Methoxybenzyloxy)-2-hydroxybutanol (5). To a solution of butane-1,2,4-triol-1,2-acetonide **4** (5.40 g, 37 mmol) in anhydrous THF (300 mL) under argon was added NaH (60 % in mineral oil, 2.22 g, 55.5 mmol) in portions, and the mixture was stirred at room temperature for 15 min, followed by addition of *p*-methoxybenzyl chloride (6.95 g, 44.4 mmol). The resulting mixture was refluxed for 3 h, cooled, diluted with ethyl acetate, washed with brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in MeOH (200 mL) and 37 % hydrochloric acid (0.25 mL) was added. The reaction mixture was stirred at room temperature for 1 h, neutralized with solid $NaHCO_3$, and concentrated to dryness. The residue was purified by chromatography on silica (5 % MeOH in CH_2Cl_2) to give 8.1 g (96 %) of **5** as a syrup; ^1H NMR ($CDCl_3$) δ 7.36, 6.99 (AA'BB', 4H, ArH), 4.57 (s, 2H, $ArCH_2$), 4.01 (m, 1H, H2), 3.91 (s, 3H, OMe), 3.57-3.82 (m, 4H, 1-CH_2, 4-CH_2), 2.55 (br, 2H, 2OH), 1.78-2.00 (m, 2H, 3-CH_2).

1-(4,4'-Dimethoxytrityloxy)-4-(*p*-methoxybenzyloxy)butan-2-ol (6). A solution of **5** (1.83 g, 8.1 mmol) and 4,4'-dimethoxytrityl chloride (2.88 g, 8.5 mmol) in CH_2Cl_2 (20

mL) and pyridine (5 mL) was stirred at room temperature for 24 h, diluted with ethyl acetate, washed with brine, dried (Na_2SO_4), and concentrated to dryness. Chromatography on silica (20 % EtOAc in hexanes) gave 3.38 g (77%) of **6** as a syrup; ^{1}H NMR ($CDCl_3$) δ 7.25-7.50 (m, 13H, ArH), 6.85-6.95 (m, 4H, ArH), 4.45 (s, 2H, $ArCH_2$), 4.04 (m, 1H, H2), 3.86 (s, 3H, OMe), 3.85 (s, 6H, 2OMe), 3.64 (m, 2H, 1-CH_2), 3.15 (d, J = 5.7 Hz, 2H, 4-CH_2), 2.92 (d, J = 3.3 Hz, 1H, OH), 1.84 (m, 2H, 3-CH_2).

1-(4,4'-Dimethoxytrityloxy)-4-(*p*-methoxybenzyloxy)butan-2-one (7). To a solution of **6** (3.3 g, 6.25 mmol) in anhydrous DMSO (30 mL) under argon were added DCC (3.87 g, 18.75 mmol), pyridine (0.5 mL, 6.25 mmol), and trifluoroacetic acid (0.24 mL, 3.15 mmol). The reaction mixture was stirred at room temperature for 15 h, diluted with ethyl acetate (200 mL) and water (50 ml), and stirred for 20 min. The organic layer was washed with water five times, and the combined aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Chromatography on silica (20 % EtOAc in hexanes) gave 2.95 g (90 %) of **7** as a syrup; ^{1}H NMR ($CDCl_3$) δ 7.25-7.51 (m, 13H, ArH), 6.85-6.95 (m, 4H, ArH), 4.47 (s, 2H, $ArCH_2$), 3.86 (s, 3H, OMe), 3.84 (s, 6H, 2OMe), 3.81 (s, 2H, 1-CH_2), 3.76 (t, J = 6.6 Hz, 2H, 4-CH_2), 2.90 (t, J = 6.6 Hz, 2H, 3-CH_2).

1-(4,4'-Dimethoxytrityloxy)-4-(*p*-methoxybenzyloxy)-2-methylenebutane (8). To a suspension of methyltriphenylphosphonium bromide (4.33 g, 12.1 mmol) in anhydrous ether (320 mL) under argon was added a solution of sodium *t*-pentoxide (1.23 g, 11.0 mmol) in benzene (11 mL). The mixture was stirred at room temperature for 5 h, and cooled to –10 °C, followed by addition of a solution of **7** (2.9 g, 5.5 mmol) in ether (20 mL). The resulting mixture was stirred at –10 to 0 °C for 2.5 h, washed with brine, dried (Na_2SO_4), and concentrated. Chromatography on silica (20 % EtOAc in hexanes) gave 2.6 g (90%) of **8** as a syrup; ^{1}H NMR ($CDCl_3$) δ 7.15-7.46 (m, 13H, ArH), 6.78-6.86 (m, 4H, ArH), 5.30 (s, 1H, =CH_2), 4.96 (s, 1H, =CH_2), 4.36 (s, 2H, $ArCH_2$), 3.79 (s, 3H, OMe), 3.78 (s, 6H, 2OMe), 3.52 (s, 2H, 1-CH_2), 3.45 (t, J = 6.9 Hz, 2H, 4-CH_2), 2.34 (t, J = 6.6 Hz, 2H, 3-CH_2).

4-(*p*-Methoxybenzyloxy)-2-methylenebutanol (9). A solution of **8** (2.9 g, 5.53 mmol) in ether (50 mL) and aqueous acetic acid (80%, 10 mL) was stirred for 1 h, and ether was evaporated. The remaining solution was stirred at room temperature for 30 min, diluted with ether (200 mL), washed with aqueous $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. Chromatography on silica (30 % EtOAc in hexanes) gave 1.1 g (89%) of **9** as a syrup; ^{1}H NMR ($CDCl_3$) δ 7.26, 6.88 (AA'BB', 4H, ArH), 5.05 (m, 1H, =CH_2), 4.92

(s, 1H, $=CH_2$), 4.46 (s, 2H, $ArCH_2$), 4.07 (d, J = 5.4, 2H, 1-CH_2), 3.80 (s, 3H, OMe), 3.58 (t, J = 6.0 Hz, 2H, 4-CH_2), 2.53 (t, J = 6.0 Hz, 1H, OH), 2.41 (t, J = 6.0 Hz, 2H, 3-CH_2).

Methyl 3,3-bis(*t*-butyldimethylsilyloxymethyl)acrylate (11). A mixture of glycerol (9.2 g, 0.1 mol) and *t*-butyldimethylsilyl chloride (31.4 g, 0.2 mol) in anhydrous pyridine (100 mL) was stirred at room temperature for 15 h, concentrated, dissolved in ethyl acetate, washed with brine, dried (Na_2SO_4), and concentrated to dryness. The resulting syrup was dissolved in DMSO (200 mL). To the solution were added DCC (61.9 g, 0.3 mol), pyridine (8.08 mL, 0.1 mol), and trifluoroacetic acid (3.9 mL, 0.05 mol). The resulting mixture was stirred at room temperature for 24 h, diluted with ethyl acetate and water, stirred for 30 min, washed with water five times. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Chromatography on silica (10 % EtOAc in hexanes) gave a ketone as a syrup, which was dissolved in methanol (300 mL). Methyl (triphenylphosphoranylidene)acetate (33.4 g, 0.1 mol) was added, and the resulting mixture was stirred at room temperature for 30 h. Solvent was evaporated and the residue was chromatographed on silica (30 % CH_2Cl_2 in hexanes) to give **11** (34.1g, 91%) as a syrup; ^{1}H NMR ($CDCl_3$) δ 5.99 (m, 1H, H2), 4.87 (m, 2H, 3-CH_2), 4.43 (m, 2H, 3-CH_2), 3.69 (s, 3H, OMe), 0.93, 0.89 (2s, 18H, 2(*t*-Bu)), 0.08, 0.06 (2s, 12H, 2$SiMe_2$).

3,3-Bis(*t*-butyldimethylsilyloxymethyl)allyl alcohol (12). To a solution of **11** (34.1 g, 91.2 mmol) in ether (350 mL) under argon was added diisobutylaluminum hydride (1 M in heptane, 200 mL). The reaction mixture was stirred at –78 °C for 2 h and then quenched by slow addition of aqueous potassium sodium tartrate. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Chromatography on silica (25 % of EtOAc in hexanes) gave 31.1 g (98 %) of **12** as a syrup. ^{1}H NMR ($CDCl_3$) δ 5.82 (t, J = 6.6 Hz, 1H, H2), 4.22 (m, 4H, 3,3-2CH_2), 4.15 (d, J = 0.6 Hz, 2H, 1-CH_2), 2.01 (t, J = 6.6 Hz, 1H, OH), 0.91, 0.90 (2s, 18H, 2(*t*-Bu)), 0.08, 0.07 (2s, 12H, 2$SiMe_2$).

1',1'-Bis(*t*-butyldimethylsilyloxymethyl)-1-(4,4'-dimethoxytrityloxy)acetone (13). A solution of **12** (31 g, 89.6 mmol), pyridine (20 mL), and 4, 4'-dimethoxytrityl chloride (36.4 g, 107.5 mmol) in CH_2Cl_2 (200 mL) was stirred at room temperature for 3 h, diluted with water (50 mL), stirred at room temperature for 20 min. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Chromatography on silica (8 % EtOAc in hexanes) gave 47.3 g (81%) of 1,1-bis(*t*-butyldimethylsilyloxymethyl)-3-(4,4'-dimethoxytrityloxy)propene as a syrup.

To a solution of 1,1-bis(*t*-butyldimethylsilyloxymethyl)-3-(4,4'-dimethoxytrityloxy)propene (12.96 g, 20 mmol) in THF (100 mL) was added BH_3-SMe_2 (2 M in THF, 20 mL, 40 mmol). The reaction mixture was stirred at room temperature for 2 h, quenched with water, made alkaline with $NaHCO_3$, concentrated in vacuo, and then dissolved in ethanol (500 mL). Water (100 mL) and $NaBO_3$ (9.18 g, 60 mmol) were added, and the mixture was stirred at room temperature for 1 h and then at 50 °C for 1 h. At 50 °C, 30% hydrogen peroxide (5 mL, 44 mmol) was added and the mixture stirred for 20 min. Ethanol was evaporated and the residue was extracted with ether. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Chromatography on silica (5 % EtOAc in hexanes) gave the hydroboration product (6.1 g, 45 %) as a syrup.

To a solution of the hydroboration product (22.3 g, 33.4 mmol) in DMSO (200 mL) were added DCC (20.7 g, 100 mmol), pyridine (2.62 mL, 33.4 mmol), trifluoroacetic acid (1.27 mL, 16.7 mmol). The mixture was stirred at room temperature for 5 h, diluted with ethyl acetate (500 mL) and water (100 mL), stirred at room temperature for 20 min. Precipitate was filtered and washed with ethyl acetate. The combined organic layer was washed with water five times, dried (Na_2SO_4), and concentrated. Chromatography on silica (3 % EtOAc in hexanes) gave 20.1 g (90 %) of **13** as a syrup; ^{1}H NMR ($CDCl_3$) δ 6.89-7.59 (m, 13H, ArH), 3.94 (s, 2H, 1-CH_2), 3.89 (s, 6H, 2OMe), 3.82 (m, 4H, 1',1'-2CH_2OSi), 3.10 (m, 1H, H1'), 0.90 (s, 18H, 2(*t*-BuSi)), 0.067 (s, 12H, 2$SiMe_2$).

3,3-Bis(*t*-butyldimethylsilyloxymethyl)-2-methylenepropanol (14). To a mixture of methyltriphenylphosphonium bromide (23.7 g, 66.3 mmol) in anhydrous ether (700 mL) under argon was added a solution of sodium *t*-pentoxide (6.99 g, 95 %, 60.2 mmol) in benzene (60 mL), and the mixture was stirred at room temperature for 5 h. To the resulting yellow mixture was added a solution of **13** (20 g, 30.1 mmol) in ether (50 mL). The reaction mixture was stirred at –10 °C for 2 h, washed with brine, dried (Na_2SO_4), and concentrated. Chromatography on silica (2 % EtOAc in hexanes) gave 18.5 g (90 %) of the Wittig reaction product.

A solution of the Wittig reaction product (16.0 g, 24.2 mmol) in dry benzene was developed on a silica gel column which was allowed to stand at room temperature for 24 h. The column was eluted with 10 % methanol in methylene chloride, and the solution was concentrated to dryness. Chromatography on silica (5 % EtOAc in hexanes) gave 7.0 g, (80 %) of **14** as a syrup; ^{1}H NMR ($CDCl_3$) δ 5.12 (s, 1H, =CH_2), 4.92 (s, 1H, =CH_2), 4.03 (d, J = 5.4 Hz, 2H, 1-CH_2), 3.80-363 (m, 4H, 3,3-2CH_2), 3.30 (t, J = 5.7 Hz, 1H, OH), 2.49 (m, 1H, H3), 0.89 (s, 18H, 2(*t*-BuSi)), 0.057 (s, 12H, 2$SiMe_2$).

General procedure I: Synthesis of acyclonucleosides having 4-hydroxy-2-methylenebutyl chain from 9 and nucleoside bases via Mitsunobu reaction. To a stirred mixture of a nucleoside base (6.0 mmol) and triphenylphosphine (6.0 mmol) in anhydrous THF (60 mL) under argon was added diethyl azodicarboxylate (DEAD, 6.0 mmol). The resulting mixture was stirred at room temperature for 10 min, and a solution of **9** (3 mmol) in THF (3 mL) was added. The resulting mixture was stirred at room temperature (3-20 h) until **9** was consumed (in case that **9** remained after overnight, thriphenylphosphine and diethyl azodicarboxylate, 6.0 mmol each, were added, and the mixture was stirred for a few more hours). After removal of solvent in vacuo, the residue was dissolved in ethyl acetate (100 mL), washed with water, dried (Na_2SO_4), and concentrated. Chromatography on silica (EtOH in CH_2Cl_2) gave a coupling product (contaminated by a small amount of DEAD), which was thoroughly dried under vacuum and dissolved in anhydrous methylene chloride (20 mL). BCl_3 (5 mL, 1.0 M in methylene chloride) was added, and the resulting mixture was stirred at –78 °C for 1-2 h, poured into methanol (100 mL) containing excess $NaHCO_3$. The mixture was stirred at room temperature for 20 min, and precipitate was filtered and washed with methylene chloride. The combined organic layer was concentrated to dryness. Chromatography on silica (EtOH in CH_2Cl_2) gave an acyclonucleoside having 4-hydroxy-2-methylenebutyl chain.

General procedure II: Synthesis of acyclonucleosides having 3,3-bis(hydroxymethyl)-2-methylenepropyl chain from 14 and nucleoside bases via Mitsunobu reaction. Condensation via Mitsunobu reaction was identical as described in general procedure I. After chromatographic purification, the coupling product from **14** and nucleoside bases was dissolved in THF (10 mL) and TBAF (1.0 M in THF, 1.5-2.5 mL) was added. The resulting solution stood at room temperature overnight and was concentrated. Chromatography on silica (MeOH in CH_2Cl_2) gave an acyclonucleoside having 3,3-bis(hydroxymethyl)-2-methylenepropyl chain.

1-(4-Hydroxy-2-methylenebutyl)uracil (19). General procedure I (from uracil) gave **19** (30 %) as a colorless solid; mp 116-117 °C (MeOH/Et_2O); ^{1}H NMR (DMSO-d_6) δ 11.29 (s, 1H, NH), 7.49 (d, J = 7.8 Hz, 1H, H6), 5.58 (d, J = 7.8Hz, 1H, H5), 4.90 (s, 1H, =CH), 4.70 (s, 1H, =CH), 4.57 (t, J = 5.1 Hz, 1H, OH), 4.24 (s, 2H, 1'-CH_2), 3.50 (dd, J = 6.6, 12.0 Hz, 2H, 4'-CH_2), 2.12 (t, J = 6.9 Hz, 2H, 3'-CH_2). Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28; Found: C, 55.04; H, 6.05; N, 14.30.

1-(4-Hydroxy-2-methylenebutyl)thymine (20). General procedure I (from thymine) gave **20** (43%) as a colorless solid; mp 121-123 °C (MeOH/Et_2O); ^{1}H NMR

(DMSO-d_6) δ 11.29 (s, 1H, NH), 7.36 (s, 1H, 6-H), 4.89 (s, 1H, =CH), 4.70 (s, 1H, =CH), 4.56 (t, J = 5.4 Hz, 1H, OH), 4.20 (s, 2H, 1'-CH_2), 3.50 (dd, J = 6.6, 12.6 Hz, 2H, 4'-CH_2), 2.11 (t, J = 6.9 Hz, 2H, 3'-CH_2), 1.73 (s, 3H, CH_3). Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.32; Found: C, 57.11; H, 6.67; N, 13.38.

1-(4-Hydroxy-2-methylenebutyl)cytosine (25). General procedure I (from N^4-acetylcytosine) gave 1-[4-(*p*-methoxybenzyloxy)-2-methylenebutyl]-N^4-acetylcytosine, which was dissolved in ammonia-saturated methanol. The resulting solution stood at room temperature for 15 h and then was concentrated to dryness. Chromatography on silica (10-15 % MeOH in CH_2Cl_2) gave **25** (40%) as a colorless solid; ^{1}H NMR (DMSO-d_6) δ 7.48 (d, J = 7.2 Hz, 1H, H6), 7.37, 7.16 (2s, 2H, NH_2), 5.70 (d J = 7.2 Hz, 1H, H5), 4.86 (s, 1H, =CH), 4.63 (s, 1H, =CH), 4.56 (t, J = 4.8 Hz, 1H, OH), 4.24 (s, 2H, 1'-CH_2), 3.50 (dd, J = 6.9, 11.8 Hz, 2H, 4'-CH_2), 2.10 (t, J = 6.9 Hz, 2H, 3'-CH_2). Anal. Calcd. for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52; Found: C, 55.35; H, 6.67; N, 21.44.

1-[3,3-Bis(hydroxymethyl)-2-methylenepropyl]uracil (21). General procedure II (from uracil) gave **21** (32 %) as a colorless solid; mp 142-143 °C; ^{1}H NMR (DMSO-d_6) δ 11.29 (s, 1H, NH), 7.46 (d, J = 7.8 Hz, 1H, H6), 5.58 (dd, J = 2.1, 7.8 Hz, 1H, H5), 4.90 (s, 1H, =CH), 4.71 (s, 1H, =CH), 4.51 (t, J = 5.1 Hz, 2H, 2OH), 4.27 (s, 2H, 1'-CH_2), 3.47 (m, 4H, 3',3'-2CH_2), 2.18 (m, 1H, H3'). Anal. Calcd. for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38; Found: C, 53.18; H, 6.22; N, 12.31.

1-[3,3-Bis(hydroxymethyl)-2-methylenepropyl]thymine (22). General procedure II (from thymine) gave **22** (33%) as a colorless solid; mp 143-144 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 11.28 (s, 1H, NH), 7.33 (d, J = 1.2 Hz, 1H, 6-H), 4.89 (s, 1H, =CH), 4.70 (s, 1H, =CH), 4.51 (t, J = 5.1 Hz, 2H, 2OH), 4.23 (s, 2H, 1'-CH_2), 3.46 (m, 4H, 3',3'-2CH_2), 2.17 (m, 1H, H3'), 1.74 (s, 3H, CH_3). Anal. Calcd. for $C_{10}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66; Found: C, 55.09; H, 6.57; N, 11.79.

1-[3,3-Bis(hydroxymethyl)-2-methylenepropyl]cytosine (26). General procedure II (from N^4-acetylcytosine) gave 1-[3,3-bis(hydroxymethyl)-2-methylenepropyl]-N^4-acetylcytosine as a colorless solid (55%), which was treated with ammonia-methanol as described for **25** to give **26** (93%) as a colorless solid; mp 162-164 °C (MeOH/Et_2O); ^{1}H NMR (DMSO-d_6) δ 7.44 (d, J = 7.2 Hz, 1H, H6), 7.09, 7.02 (2s, 2H, NH_2), 5.66 (d, J = 7.2 Hz, 1H, H5), 4.84 (s, 1H, =CH), 4.58 (s, 1H, =CH), 4.52 (t, J = 5.4 Hz, 2H, 2OH), 4.24 (s, 2H, 1'-CH_2), 3.48 (m, 4H, 3,'3'-2CH_2), 2.19 (m, 1H, H3'). Anal. Calcd. for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.65; Found: C, 53.25; H, 6.60; N, 18.58.

9-(4-Hydroxy-2-methylenebutyl)-6-chloropurine (27). General procedure I (from 6-chloropurine) gave **27** (51%) as a colorless solid; ^{1}H NMR ($CDCl_3$) δ 8.76, 8.17 (2s, 2H, H2, H8), 5.13 (s,.1H, =CH), 4.94 (s, 2H, 1'-CH_2), 4.85 (s, 1H, =CH), 3.86 (dd, J = 5.4, 7.5 Hz, 2H, 4'-CH_2), 2.31 (t, J = 5.7 Hz, 3H, 3'-CH_2, OH).

9-(4-Hydroxy-2-methylenebutyl)hypoxanthine (31). To a solution of **27** (185 mg, 0.78 mmol) in MeOH (50 mL) were added 2-mercaptoethanol (0.28 mL, 3.0 mmol) and sodium methoxide (200 mg, 4 mmol). The resulting solution was refluxed for 6 h, neutralized with acetic acid, and concentrated to dryness. Chromatography on silica (15% EtOH in CH_2Cl_2) gave 160 mg (93%) of **31** as a colorless solid; mp 183-184 °C (MeOH/Et_2O); ^{1}H NMR (DMSO-d_6) δ 12.3 (br s, 1H, NH), 8.02 (s, 2H, H2, H8), 4.90 (s, 1H, =CH), 4.74 (s, 2H, 1'-CH_2), 4.59 (t, 1H, OH), 4.55 (s, 1H, =CH), 3.50 (dd, J = 6.9, 11.7 Hz, 2H, 4'-CH_2), 2.13 (t, J = 6.9 Hz, 2H, 3'-CH_2). Anal. Calcd. for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44; Found: C, 54.38; H, 5.32; N, 25.46.

9-(4-Hydroxy-2-methylenebutyl)adenine (35). A solution of **27** (119 mg, 0.5 mmol) in ammonia-saturated methanol (50 mL) was heated in a steel bomb at 100 °C for 15 h and concentrated to dryness. Chromatography on silica (15 % MeOH in CH_2Cl_2) gave 95 mg (86%) of **35** as a colorless solid; mp 195-197 °C (MeOH/Et_2O); ^{1}H NMR (DMSO-d_6) δ 8.11, 8.07 (2s, 2H, H2, H8), 7.24 (s, 2H, NH_2), 4.89 (s, 1H, =CH), 4.73 (s, 2H, 1'-CH_2), 4.60 (t, J = 5.1 Hz, 1H, OH), 4.57 (s, 1H, =CH), 3.51 (dd, J = 6.6, 12.3 Hz, 2H, 4'-CH_2), 2.13 (t, J = 6.6 Hz, 2H, 3'-CH_2). Anal. Calcd. for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.94; Found: C, 54.72; H, 5.80; N, 32.13.

9-[3,3-Bis(hydroxymethyl)-2-methylenepropyl]-6-chloropurine (28). General procedure II (from 6-chloropurine) gave **28** (31%) as a colorless solid; ^{1}H NMR (DMSO-d_6) δ 8.78, 8.64 (2s, 2H, H2, H8), 4.93 (s, 3H, =CH, 1'-CH_2), 4.64 (s, 1H, =CH), 4.55 (t, J = 5.1 Hz, 2H, 2OH), 3.47 (m, 4H, 3', 3'-2CH_2), 2.22 (m, 1H, H3').

9-[3,3-Bis(hydroxymethyl)-2-methylenepropyl]hypoxanthine (33). A similar procedure as described for **31** gave 120 mg (92%) of **33** as a colorless solid from **28** (140 mg, 0.52 mmol); mp 206-208 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 12.35 (s, 1H, NH), 8.03, 8.01 (2s, 2H, H2, H8), 4.90 (s, 1H, =CH), 4.77 (s, 2H, 1'-CH_2), 4.57 (t, J = 5.4 Hz, 2H, 2OH), 4.54 (s, 1H, =CH), 3.48 (m, 4H, 3', 3'-2CH_2), 2.22 (m, 1H, H3'). Anal. Calcd. for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.64; N, 22.39; Found: C, 52.77; H, 5.45; N, 22.56.

9-[3,3-Bis(hydroxymethyl)-2-methylenepropyl]adenine (36). A similar procedure as described for **35** gave 90 mg (69%) of **36** as a colorless solid from **28** (140 mg, 0.52

mmol); mp 175-177 °C; ^{1}H NMR (DMSO-d_6) δ 8.11, 8.06 (2s, 2H, H2, H8), 7.24 (s, 2H, NH_2), 4.89 (s, 1H, =CH), 4.75 (s, 2H, 1'-CH_2), 4.59 (t, J = 5.4 Hz, 2H, 2OH), 4.54 (s, 1H, =CH), 3.48 (m, 4H, 2CH_2), 2.22 (m, 1H, H3'). Anal. Calcd. for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07; N, 28.10; Found: C, 52.60; H, 6.17; N, 27.85.

9-(4-Hydroxy-2-methylenebutyl)-2-amino-6-chloropurine (29). General procedure I (from 2-amino-6-chloropurine) gave **29** (38%) as a colorless solid; ^{1}H NMR (DMSO-d_6) δ 8.06 (s, 1H, H8), 6.95 (s, 2H, NH_2), 4.89 (s, 1H, =CH), 4.64 (s, 2H, 1'-CH_2), 4.59 (t, J = 5.4 Hz, OH), 4.50 (s, 1H, =CH), 3.52 (dd, J = 6.6, 12.0 Hz, 2H, 4'-CH_2), 2.14 (t, J = 6.6 Hz, 3'-CH_2).

9-(4-Hydroxy-2-methylenebutyl)guanine (32). A similar procedure as described for **31** gave 65 mg (77%) of **32** as a colorless solid from **29** (90 mg, 0.35 mmol); mp 261-263 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 10.55 (s, 1H, CONH), 7.60 (s, 1H, H8), 6.44 (s, 2H, NH_2), 4. 87 (s, 1H, =CH), 4.58 (t, J = 5.1 Hz, OH), 4.52 (s, 2H, 1'-CH_2), 4.49 (s, 1H, =CH), 3.51 (dd, J = 6.9, 12.0 Hz, 2H, 4'-CH_2), 2.12 (t, J = 6.9 Hz, 2H, 3'-CH_2). Anal. Calcd. for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.57; N, 29.77; Found: C, 50.82; H, 5.45; N, 29.60.

9-[3,3-Bis(hydroxymethyl)-2-methylenepropyl]-2-amino-6-chloropurine (30). General procedure II (from 2-amino-6-chloropurine) gave **30** (38%) as a colorless solid. ^{1}H NMR (DMSO-d_6) δ 8.04 (s, 1H, H8), 6.94 (s, 2H, NH_2), 4.91 (s, 1H, =CH), 4.67 (s, 2H, 1'-CH_2), 4.57 (m, 3H, =CH, 2OH), 3.45 (m, 4H, 3',3'-2CH_2), 2.21 (m, 1H, H3').

9-[3,3-Bis(hydroxymethyl)-2-methylenepropyl]guanine (34). A similar procedure as described for **31** gave 170 mg (74%) of **34** as a colorless solid from **30** (245 mg, 0.86 mmol), mp 273-75 °C; ^{1}H NMR (DMSO-d_6) δ 10.56 (s, 1H, CONH), 7.58 (s, 1H, H8), 6.44 (s, 2H, NH_2), 4.88 (s, 1H, =CH), 4. 54 (m, 5H, =CH, 1'-CH_2, 2OH), 3.49 (m, 4H, 3',3'-2CH_2), 2.20 (m, 1H, H3'). Anal. Calcd. for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40; Found: C, 49.60; H, 5.67; N, 26.17.

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