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Note

Synthesis of galactosyl phosphate diester derivatives of nucleosides

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The important role of glycosyl esters of nucleoside pyrophosphates in carbohydrate metabolism is well known. Many sugar nucleotides have been synthesized and have also been widely utilized as donors or substrates for glycosyltransferases in a variety of biochemical studies. Some glycosyl phosphate triesters of nucleosides have been reported as lipophilic, macrophage-targeted carriers because of their structural relationship to membrane components [1–3]. Van Boom et al. described the design, synthesis, and biological activity of analogues of uridine 5′-(α-D-glucopyranosyl diphosphate) and found that the synthetic analogues exerted an inhibitory effect on the biosynthesis of glycolipids [4]. Several stable analogues of CMP-Kdo have been shown to be potential inhibitors of biosynthesis of bacterial lipopolysaccharides (LPS) [5,6]. Recently, Henin et al. [7] reported the synthesis of lipophilic glycosyl phosphate triester derivatives of AZT and found their antiviral activity in the micromolar range to be comparable to that of AZT. Ikeda et al. [8] stated that CMP-sialic acid analogues exhibit antiviral activity against HIV and show little or no cytotoxicity.

We considered whether the glycosyl residue in glycosyl nucleosides phosphate diesters could be used as a site-directing moiety towards glycosyl-binding proteins. In this way some glycosylated antitumor or antiviral nucleotides might be expected to have a higher therapeutic index together with lesser side effects and toxicity. We have reported the synthesis by phosphite triester methodology [9] of glycosyl phosphate diesters of adenosine as model compounds. In this paper, a series of galactosyl phosphate diester derivatives of 9-β-D-arabinofuranosyladenine (AraA) and 1-β-D-arabinofuranosylcytosine (AraC) are synthesized.

The target compounds **6a–6h** were synthesized according to Scheme 1. 3-Benzyloxy-1-propanol or 6-benzyloxy-1-hexanol were condensed with tetra-*O*-acetyl-α-

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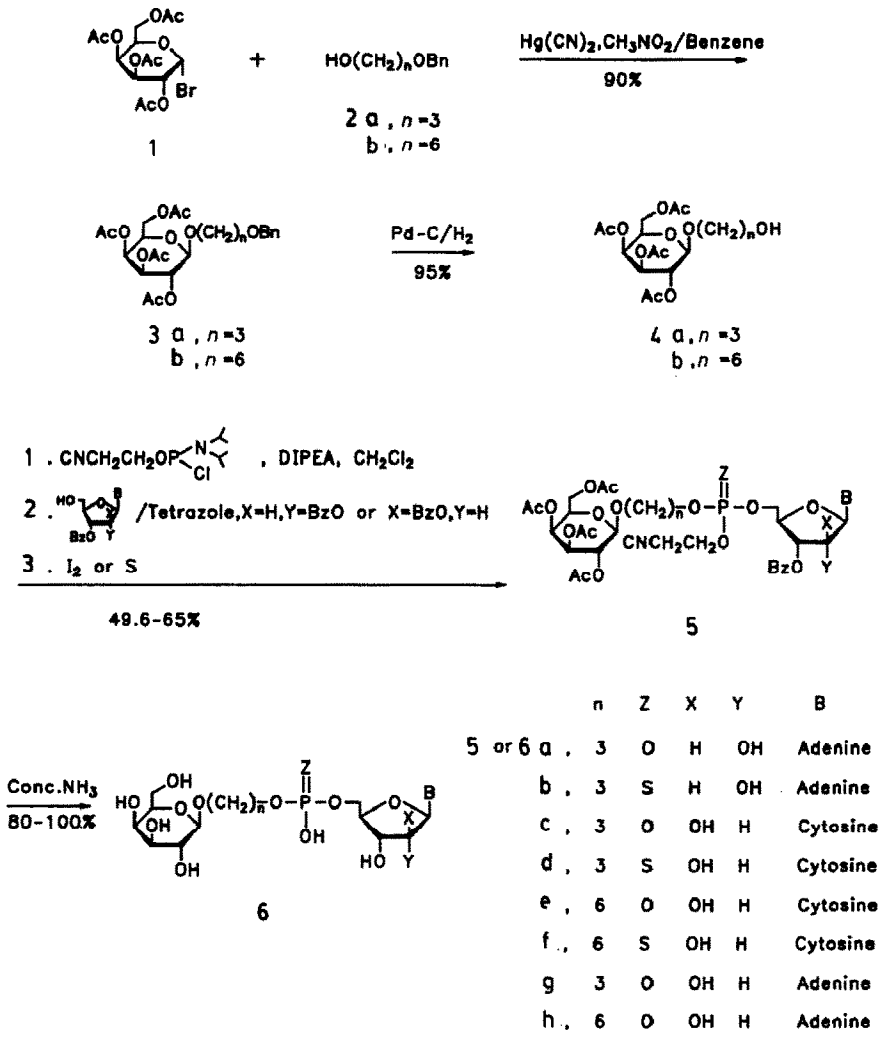
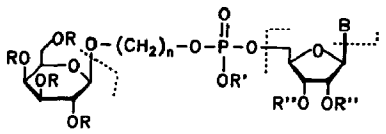


Scheme 1.

D-galactosyl bromide (**1**) in the presence of $Hg(CN)_2$ to give the benzyloxyalkyl galactosides **3a** or **3b** in 90 and 71% yields, respectively. Compounds **3a** and **3b** were identified as the β anomers by ^1H NMR ($J_{1,2}$ 7 Hz). After catalytic hydrogenolysis over Pd–C, **4a** and **4b** were obtained in 95 and 97% yield. Formation of the glycosyl phosphate triesters and glycosyl thiophosphate triester nucleosides **5a–5h** was accomplished by phosphite triester methodology. The ω-hydroxyalkylgalactosides **4a** or **4b** were treated with 2-cyanoethyl *N,N*-diisopropylchlorophosphoramidite in the presence of diisopropylethylamine (DIPEA) under an atmosphere of dry N_2. The active phosphite intermediate, without further purification, was condensed with the appropriate nucleosides in the presence of tetrazole in CH_3CN or CH_2Cl_2 and the products were subjected to oxidation or



Scheme 2.

thiation by I_2 or S, respectively, to give the corresponding galactosyl phosphate triester or thiophosphate triester nucleotides **5a–5h** in 49–65% yields. The ^{31}P NMR spectra of **5a–5h** showed that all were mixture of diastereo-isomers in a 1 : 1 ratio. After deprotection with concd NH_3 and purification by Sephadex-G15 chromatography, compounds **6a–6h** were obtained in yields of 90–100%.

The FABMS of **5a–5h** or **6a–6h** showed peaks of protonated molecular ions ($M^+ + H$) and their characteristic fragment-ions (base, nucleoside, and sugar moieties), Scheme 2 shows the main fragmentation modes.

For example, FABMS of **5a** exhibited ions at *m/z* 1205 ($M^+ + H$), 344 (base + 2H) and 331 (sugar part). The structure identification was also supported by ^1H and ^{31}P NMR.

All of the compounds were tested against human immunodeficiency virus (HIV) and human cytomegalovirus (HCMV). None of the samples were active in the HIV assay. Compounds **6c**, **6d** and **6e** were active in the HCMV assay: the IC_{50} for anti-HIMV activity were 0.2, 0.95, and 0.1 μM, respectively. It appears that the length of the alkyl side chain influences the anti-HCMV activity. A comparative test demonstrated that the potency of **6c** and **6e** was less than that of AraC (the reference standard), while the cytotoxicity was not decreased.

1. Experimental

General methods.—All evaporations were conducted in a rotary evaporator under diminished pressure. TLC was conducted on silica gel F_{254} by developing with 5 : 1 $CHCl_3$–acetone. Column chromatography was performed on silica gel (100–200 mesh, purchased from Qing Dao Chemical Company, China). ^1H NMR spectra were recorded with FX-90 Q and VXR 300 spectrometers, with Me_4Si as internal standard. ^{31}P NMR spectra were recorded with a VXR 300 spectrometer with 85% H_3PO_4 as the external standard. A ZAB-HS source was used for fast-atom bombardement (FAB) mass spectra. UV spectra were recorded with a DU-7 spectrophotometer. Microanalyses were obtained using a Perkin–Elmer 240c elemental analyser.

3-Hydroxypropyl tetra-O-acetyl-β-D-galactopyranoside (**4a**) *and 6-hydroxyhexyl tetra-O-acetyl-β-D-galactopyranoside* (**4b**).—A mixture of tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**1** 7.87 g, 17.03 mmol) in $MeNO_2$ (60 mL) and benzene (60 mL) containing $Hg(CH)_2$ (5.25 g) and anhyd $CaSO_4$ (3 g) was stirred at room temperature with 3-benzyloxy-1-propanol (3.33 g, 20.06 mmol) or 6-benzyoxy-1-hexanol (4.17 g, 20.06 mmol) for 12 h. After filtration, the filtrate was washed

successively with 10% KI, satd aq $NaHCO_3$, and water. The solution was dried (Na_2SO_4), then purified by silica gel-column chromatography with elution by 2:1 ether–petroleum ether to give syrupy **3a** or **3b** in 90% yield.

Compounds **3a** (8.94 g, 18.02 mmol) and **3b** (9.69 g, 18.02 mmol) in EtOH (60 mL) were catalytically hydrogenolyzed (10% Pd–C, 15 g) at 3 atm during 5 h and purified by column chromatography on silica gel to give **4a** and **4b**, respectively, in 95% yields.

4a: mp 83–86°C; ^{1}H NMR ($CDCl_3$), δ 5.39 (d, 1 H, $J_{3,4}$ 3.3 Hz, H-4), 5.2 (dd, 1 H, $J_{1,2}$ 7.8, $J_{2,3}$ 10.5 Hz, H-2), 5.02 (dd, 1 H, H-3), 4.49 (d, 1 H, H-1), 4.14–4.18 (m, 2 H, H-6,6′), 4.01–4.04 (m, 2 H, $-CH_2OH$), 3.93–3.95 (m, 1 H, H-5), 3.68–3.74 (m, 4 H, $-OCH_2CH_2-$), 1.98–2.12 (4s, 12 H, CH_3CO-). Anal. Calcd for $C_{17}H_{26}O_{11}$: C, 50.25; H, 6.40. Found: C, 50.07; H, 6.36.

4b: syrup; ^{1}H NMR ($CDCl_3$): δ 5.35 (dd, 1 H, H-4), 5.14–5.20 (m, 1 H, H-2), 4.96–5.01 (m, 1 H, H-3), 4.42 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 4.06–4.16 (m, 2 H, H-6,6′), 3.41–3.47 (m, 1 H, H-5), 3.83–3.89 (m, 2 H, $-CH_2-$), 3.58–3.62 (m, 2 H, $-CH_2-$), 1.98–2.12 (4s, 12 H, CH_3CO-); 1.3–1.7 (m, 8 H, $-CH_2-$). Anal. Calcd for $C_{20}H_{32}O_{11}$: C, 53.57; H, 7.19. Found: c, 53.48; c, 7.20.

N^6,N^6-*Dibenzoyl-9-(2,3-di-*O*-benzoyl-β-*D*-galactopyranosyl)adenine 5′-[(prop-3-yl tetra-*O*-acetyl-β-*D*-galactopyranoside)-1-yl] 2-cyanoethylphosphate* (**5a**) *and* N^6-*benzoyl-9-(2,3-di-*O*-benzoyl-β-*D*-galactopyranosyl)adenine 5′-[(prop-3-yl tetra-*O*-acetyl-β-*D*-galactopyranoside)-1-yl] 2-cyanoethylthio-phosphate* (**5b**).—Compounds **4a** (203 mg, 0.5 mmol) or **4b** (224 mg, 0.5 mmol) were dissolved into a solution of diisopropylethylamine (174 μL) in CH_2Cl_2 (5 mL), and then 2-cyanoethyl *N*,*N*-diisopropylaminochlorophosphoramidite (167 μL) was added at room temperature during 10 min under N_2. After 15 min, TLC showed that the reaction was complete. The mixture was diluted with CH_2Cl_2 (15 mL) and washed with 10% $NaHCO_3$ and water. The solution was dried (Na_2SO_4) and evaporated to dryness. The residue and *N*,*N*-dibenzoyl-9-(2,3-di-*O*-benzoyl-β-D-ribofuranosyl) adenine (330 mg, 0.48 mmol) [*N*-benzoyl-9-(2,3-di-*O*-benzoyl-β-D-ribofuranosyl)adenine was used for the synthesis of **5b**] was dissolved in CH_2Cl_2 (10 mL), and a solution of tetrazole (80 mg) in MeCN (5 mL) was added. The mixture was stirred at room temperature for 15 h and oxidized by stirring with iodine solution (sulfurization for synthesis of **5b** by S in toluene (2 mL)). The solution was diluted with CH_2Cl_2 (15 mL) and washed with satd Na_2SO_3, $NaHCO_3$, and water, and then dried (Na_2SO_4). After filtration, the solution was concentrated and applied to silica gel column eluting with a mixture of 6:5:1 cyclohexane–CH_2Cl_2–acetone (in the synthesis of **5b** 9:1 $CHCl_3$–acetone was used) to give **5a** or **5b** as white powders.

5a: 65% yield; UV, λ_{max}^{EtOH} 276, 233 nm; FABMS, 1205 ($M^+ + H$); ^{31}P NMR ($CDCl_3$): −1.5 ppm; ^{1}H NMR ($CDCl_3$): nucleotide, δ 8.76, 8.50 (2s, 2 H, H-2,8), 7.4–8.1 (m, 20 H, Bz), 6.64 (m, 1 H, H-1′), 6.1–6.4 (m, 2 H, H-2′,3′), 4.76 (m, 1 H, H-4′), 4.58 (m, 2 H, H-5′a,5′b), 2.68–2.9 (m, 2 H, $-OCH_2CH_2CN$); galactose, δ 5.44 (m, 1 H, H-4), 5.24–5.0 (m, 2 H, H-3,2), 4.58 (m, 1 H, H-1), 3.6–4.4 (m, 9 H, H-5,6a,6b, $-CH_2-$), 2.0–4.2 (4s, 12 H, CH_3CO-), 1.32 (m, 2 H, $-CH_2-$).

5b: 50% yield; UV, λ_{max}^{EtOH} 277.3, 229.8 nm; FABMS, 1116 ($M^+ + H$); ^{31}P NMR ($CDCl_3$): 66.04 ppm; ^{1}H NMR ($CDCl_3$): nucleotide, δ 8.83, 8.48 (2s, 2 H, H-2,8),

7.35–8.06 (m, 15 H, Bz), 6.61–6.67 (dd, 1 H, $J_{1',2'}$, 6.3 Hz, H-1'), 6.17 (d, 1 H, H-2'), 6.04 (m, 1 H, H-3'), 4.72 (m, 1 H, H-4'), 4.5 (m, 2 H, H-5'a,5'b), 4.3 (m, 2 H, $-CH_2CH_2CN$), 2.80 (m, 2 H, $-CH_2CH_2CN$); galactose, δ 5.34–5.39 (m, 1 H, H-4), 5.15–5.12 (m, 1 H, H-2), 5.0–5.07 (m, 1 H, H-3), 4.53 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1), 4.1–4.4 (m 5 H, H-5, $-CH_2-$), 1.96–2.15 (4s, 12 H, CH_3CO-), 1.2–1.4 (m, 2 H, $-CH_2-$).

N-Benzoyl-1-(2,3-di-O-benzoyl-β-D-arabinofuranosyl)cytosine 5'-[(prop-3-yl tetra-O-acetyl-β-D-galactopyranoside)-1-yl] 2-cyanoethyl phosphate (**5c**) *and* N-*benzoyl-1-(2,3-di-O-benzoyl-β-D-arabinofuranosyl)cytosine 5'-[(prop-3-yl tetra-O-acetyl-β-D-galactopyranoside)-1-yl] 2-cyanoethyl thiophosphate* (**5d**).—The procedure was same as in the synthesis of **5a** and **5b** but using *N*-benzoyl-1-(2,3-di-*O*-benzoyl-β-D-arabinofuranosyl) cytosine instead of *N*,*N*-dibenzoyl-9-(2,3-di-*O*-benzoyl-β-D-arabinofuranosyl)adenine.

5c: 50% yield, UV, λ_{max}^{EtOH} 303.7, 263.4, 234.7 nm; FABMS: 1076 ($M^+ + H$): ^{31}P NMR ($CDCl_3$, δ): −2.73 ppm; ^1H NMR ($CDCl_3$): nucleotide, δ 8.8–8.9 (m, 1 H, –NH), 8.07 (d, 1 H, H-5), 7.5 (m, 15 H, Bz), 6.6 (d, 1 H, H-6), 5.92 (d, 1 H, $J_{1',2'}$, 3.3 Hz,), 5.48 (m, 1 H, H-2'), 5.37 (m, 1 H, H-3'), 4.54 (m, 2 H, H-5'a,5'b), 4.20–4.25 (m, 1 H, H-4'), 2.6–2.8 (m, 2 H, $-CH_2-$); galactose, δ 4.98–5.18 (m, 3 H, H-4,2,3), 4.45 (dd, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 4.06–4.17 (m, 6 H, $-CH_2-$), 3.88–3.96 (m, 2 H, H-6a,6b), 3.61 (m, 1 H, H-5), 1.96–2.13 (4s, 12 H, CH_3CO-), 1.2–1.3 (m, 2 H, $-CH_2-$).

5d: 53% yield; UV, λ_{max}^{EtOH} 302.1, 262.8, 234.7 nm; FABMS: 1092 ($M^+ + H$); ^{31}P NMR 66.6, 65.36 ppm; ^1H NMR ($CDCl_3$); nucleotide, δ 8.52 (m, 1 H, NH), 8.42 (d, 1 H, H-5), 7.8–8.2 (m, 15 H, Bz), 6.68 (d, 1 H, H-6), 6.04–6.08 (m, 1 H, H-1'), 5.4–5.6 (m, 2 H, H-2',3'), 4.6 (m, 2 H, H-5'a,5'b), 4.2 (m, 1 H, H-4'), 2.6–2.8 (m, 2 H, $-CH_2-$); galactose, δ 5.08–5.12 (m, 3 H, H-2,3,4), 4.5 (m, 1 H, H-1), 4.1–4.3 (m, 6 H, $-CH_2-$), 3.9–4.0 (m, 2 H, H-6a,6b), 3.6–3.7 (m, 1 H, H-5), 1.96–2.2 (4s, 12 H, CH_3CO-), 1.3 (m, 2 H, $-CH_2-$).

N-Benzoyl-1-(2,3-di-O-benzoyl-β-D-arabinofuranosyl)cytosine 5'-(hex-6-yl tetra-O-acetyl-β-D-galactopyranoside)-1-yl] 2-cyanoethyl phosphate (**5e**) *and* N-*benzoyl-1-(2,3-di-O-benzoyl-β-D-arabinofuranosyl)cytosine 5'-[(hex-6-yl tetra-O-acetyl-β-D-galactopyranoside)-1-yl] 2-cyanoethyl thiophosphate* (**5f**).—The procedure was same as in the synthesis of **5c** and **5d** but using 6-hydroxyhexyl tetra-*O*-acetyl-β-D-galactopyranoside **4b** instead of 3-hydroxypropyl tetra-*O*-acetyl-β-D-galactopyranoside **4a**.

5e: 50% yield; UV, λ_{max}^{EtOH} 349.8, 263.1, 236 nm; FABMS: 1120 ($M^+ + H$); ^{31}P NMR ($CDCl_3$): −7.0 ppm; ^1H NMR ($CDCl_3$): nucleotide, δ 9.1 (m, 1 H, NH), 8.5 (d, 1 H, H-5), 6.6 (d, 1 H, H-6), 6.0 (d, 1 H, $J_{1',2'}$ 2.7 Hz, H-1'), 5.4–5.6 (m, 2 H, H-2',3'), 4.6 (m, 2 H, H-5'a,5'b), 4.2 (m, 1 H, H-4'), 2.7 (m, 2 H, $-CH_2-$); galactose, δ 5.0–5.3 (m, 3 H, H-4,2,3), 4.5 (m, 1 H, H-1), 4.0–4.2 (m, 6 H, $-CH_2-$), 3.88–3.98 (m, 2 H, H-6a,6b), 3.6 (m, 1 H, H-5), 1.96–2.13 (4s, 12 H, CH_3CO-), 1.2 (m, 8 H, $-CH_2-$).

5f: 53% yield; UV, λ_{max}^{EtOH} 349.8, 263.1, 236 nm; FABMS: 1136 ($M^+ + H$); ^{31}P NMR ($CDCl_3$): 68.52 ppm; ^1H NMR ($CDCl_3$): nucleotide, δ 8.5 (d, 1 H, H-5), 6.7 (d, 1 H, H-6), 6.06 (d, 1 H, $J_{1',2'}$ 3.6 Hz, H-1'), 5.4–5.6 (m, 2 H, H-2',3'), 4.6 (m, 2 H,

H-5'a,5'b), 4.2 (m, 1 H, H-4'), 2.7–2.9 (m, 2 H, $-CH_2-$); galactose, δ 5.0–5.3 (m, 3 H, H-4,3,2), 4.5 (m, 1 H, H-1), 4.0–4.2 (m, 6 H, $-CH_2-$), 3.8–4.0 (m, 2 H, H-6a,6b), 3.5–3.6 (m, 1 H, H-5), 2.0–2.2 (4s, 12 H, CH_3CO-), 1.3–1.8 (m, 8 H, $-CH_2-$).

N^6-Benzoyl-9-(2,3-di-O-benzoyl-β-D-arabinofuranosyl)adenine 5'-[(prop-3-yl tetra-O-acetyl-β-D-galactopyranoside)-1-yl] 2-cyanoethylphosphate (**5g**) *and N^6-benzoyl-9-(2,3-di-O-benzoyl-β-D-arabinofuranosyl)adenine 5'-[(hex-6-yl tetra-O-acetyl-β-D-galactopyranoside)-1-yl] 2-cyanoethyl phosphate* (**5h**).—The procedure for synthesis of **5g** was same as that for **5a** but using N^6-benzoyl-9-(2,3-di-*O*-benzoyl-β-D-arabinofuranosyl)adenine instead of N^6,N^6,dibenzoyl-9-(2,3-di-*O*-benzoyl-β-D-arabinofuranosyl)adenine. For **5h**, the procedure was the same as in the synthesis of **5e** but N^6-benzoyl-9-(2,3-di-*O*-benzoyl-β-D-arabinofuranosyl)adenine was used instead of N^4-benzoyl-1-(2,3-di-*O*-benzoyl-β-D-arabinofuranosyl)cytosine.

5g: 52.7% yield, UV, λ_{max}^{EtOH} 278.6, 233.1 nm; FABMS: 1101 ($M^+ + H$); ^{31}P NMR ($CDCl_3$): −7.27 ppm; ^1H NMR ($CDCl_3$): nucleotide, δ 9.02, 8.47 (2s, 2 H, H-2,8); 7.39–8.13 (m, 15 H, Bz), 6.9 (m, 1 H, H-1'), 5.96–6.02 (m, 2 H, H-2',3'), 4.61–4.69 (m, 1 H, H-4'), 4.44–4.56 (m, 2 H, H-5'a,5'b), 2.7–2.8 (m, 2 H, $-CH_2-$); galactose, δ 5.37 (m, 1 H, H-4), 5.0–5.2 (m, 2 H, H-2,3), 4.58 (m, 1 H, H-1), 3.6–4.4 (m, 9 H, H-5,6a,6b, $-CH_2-$), 1.97–2.14 (4s, 12 H, CH_3CO-), 1.43 (m, 2 H, $-CH_2-$).

5h: 52.6% yield; UV, λ_{max}^{EtOH} 279.3, 233.1 nm; FABMS: 1143 ($M^+ + H$); ^{31}P NMR ($CDCl_3$): −2.15, −1.07 ppm; ^1H NMR ($CDCl_3$): nucleotide, δ 8.92 (s, 1 H, H-8), 8.64 (s, 1 H, H-2), 7.4–8.2 (m, 15 H, Bz), 6.9 (m, 1 H, H-1'), 6.0–6.12 (m, 2 H, H-2',3'), 4.6–4.7 (m, 3 H, H-4',5'a,5'b), 2.68–2.9 (m, 2 H, $-CH_2-$); galactose, δ 5.1–5.5 (m, 3 H, H-2,3,4), 4.5 (m, 1 H, H-1), 3.6–4.4 (m, 9 H, H-5,6a,6b, $-CH_2-$), 1.96 –2.2 (4s, 12 H, CH_3CO-), 1.2–1.8 (m, 8 H, $-CH_2-$).

9-β-D-Ribofuranosyladenine 5'-[(prop-3-yl β-D-galactopyranoside)-1-yl]phosphate (**6a**) *and 9-β-D-ribofuranosyladenine 5'-[(prop-3-yl β-D-galactopyranoside)-1-yl]thiophosphate* (**6b**).—Compound **5a** (200 mg, 0.16 mmol) was dissolved into concd NH_4OH (10 mL), the solution was heated at 50°C in a sealed tube for 20 h. The solution was evaporated to remove NH_3 and the aqueous solution was extracted with $CHCl_3$ and applied to a column of Sephadex G-15 and eluted with water. Lyophilization gave 90 mg (96%) of **6a** as a white powder. By using the same procedure, **6b** was obtained in 76.5% yield. This procedure was also used for synthesis of **6c–6h**.

6a: UV, $\lambda_{max}^{95\%EtOH}$ 261.1 nm, FABMS: 568 ($M^+ + H$); ^{31}P NMR, −2.8 ppm, ^1H NMR (D_2O): nucleotide, δ 8.26, 8.06 (2s, 2 H, H-2,8), 5.93 (d, 1 H, $J_{1',2'}$ 5.1 Hz, H-1'), 4.59 (m, 1 H, H-2'), 4.32 (m, 1 H, H-3'), 4.17 (m, 1 H, H-4'), 3.89 (m, 2 H, H-5'a,5'b); galactose, δ 4.05 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 3.23–3.28 (m, 1 H, H-2), 3.35–3.44 (m, 3 H, H-2,6a,6b), 3.50–3.55 (m, 2 H, H-4,5), 3.63–3.71 (m, 4 H, $-CH_2-$), 1.60–1.65 (m, 2 H, $-CH_2-$).

6b: UV, $\lambda_{max}^{95\%EtOH}$ 261.4 nm; FABMS: 585 ($M^+ + H$); ^{31}P NMR: 56. 13 ppm; ^1H NMR (D_2O): nucleotide, δ 8.33, 8.03, (2 s, 2 H, H-2,8), 5.92 (d, 1 H, $J_{1',2'}$ 5.1 Hz, H-1'), 4.58 (m, 1 H, H-2'), 4.33 (m, 1 H, H-3'), 4.19 (m, 1 H, H-4'), 3.96 (m, 2 H, H-5'a,5'b); galactose, δ 4.08 (d, 1 H, $J_{1,2}$ 8.4 Hz, H-1), 3.68–3.75 (m, 5 H, H-4, $-CH_2-$), 3.36–3.43 (m, 1 H, H-3), 3.28 (m, 1 H, H-2), 3.14–3.18 (m, 2 H, H-6a,6b), 2.74–2.78 (m, 1 H, H-5), 1.6–1.8 (m, 2 H, $-CH_2-$).

1-β-D-Arabinofuranosylcytosine 5'-[(prop-3-yl β-D-galactopyranoside)-1-yl]phosphate (**6c**) *and 1-β-D-arabinofuranosylcytosine 5'-(prop-3-yl β-D-galactopyranoside)-1-yl thiophosphate* (**6d**).

6c: 100% yield, UV, $\lambda_{max}^{95\%EtOh}$ 271 nm; FABMS: 544 ($M^+ + H$); ^{31}P NMR (D_2O): −2.7 ppm; ^1H NMR (D_2O): nucleotide, δ 7.68 (d, 1 H, $J_{5,6}$ 8.1 Hz, H-6), 5.88 (d, 1 H, $J_{5,6}$ 8.1 Hz, H-5), 6.01 (d, 1 H, $J_{1',2'}$ 5.4 Hz, H-1'), 4.21–4.27 (m, 6 H, H-5'a,5'b, $-CH_2-$), 3.85–3.92 (m, 3 H, H-2',3',4'); galactose, δ 4.14 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 3.2–3.8 (m, 5 H, H-2,3,4,6a,6b), 3.2 (m, 4 H, $-CH_2-$), 2.8 (m, 1 H, H-5), 1.71–1.75 (m, 2 H, $-CH_2-$).

6d: 100% yield; UV, $\lambda_{max}^{95\%EtOH}$ 2.73.6 nm; FABMS: 559 ($M^+ + H$), 581 ($M^+ + Na$); ^{31}P NMR (D_2O); 54 ppm; ^1H NMR (Me_2SO-d_6): nucleotide, δ 7.92 (d, 1 H, $J_{5,6}$ 7.8 Hz, H-6), 6.78 (b, 2 H, N-H), 6.06 (d, 1 H, $J_{1',2'}$ 3.9 Hz, H-1'), 5.77 (d, 1 H, H-5), 3.8–4.1 (m, 7 H, H-2',5'a,5'b, $-CH_2-$), 3.6 (m, 1 H, H-4'), 3.3 (m, 1 H, H-3'), 1.24 (m, 2 H, $-CH_2-$); galactose, δ 3.8–4.1 (m, 3 H, H-1, H-6a,6b), 3.50–3.52 (m, 1 H, H-2), 3.18–3.38 (m, 3 H, H-3,4,5).

1-β-D-Arabinofuranosylcytosine 5'-(hex-6-yl β-D-galactopyranoside)-1-yl phosphate (**6e**) *and 1-β-D-arabinofuranosylcytosine 5'-[(hex-6-yl β-D-galactopyranoside)-1-yl]thiophosphate* (**6f**).

6e: 96% yield: UV, $\lambda_{max}^{95\%EtOH}$ 272.7 nm; FABMS: 586 ($M^+ + H$); ^{31}P NMR (D_2O): 3.10 ppm; ^1H NMR (D_2O): nucleotide, δ 7.68 (d, 1 H, $J_{5,6}$ 7.8 Hz, H-6), 5.90 (d, 1 H, H-5), 6.07 (d, 1 H, $J_{1',2'}$ 5.4 Hz, H-1'), 4.26–4.29 (m, 1 H, H-2'), 4.01–4.05 (m, 1 H, H-3'), 3.89–3.90 (m, 3 H, H-4',5'a,5'b); galactose δ 4.18 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1'), 3.68–3.73 (m, 1 H, H-4), 3.60–3.56 (m, 1 H, H-5), 3.43–3.51 (m, 2 H, H-2,3), 3.30–3.33 (m, 1 H, H-6a), 3.16–3.20 (m, 1 H, H-6b), 3.4–3.8 (m, 4 H, $-CH_2-$), 1.16–1.45 (m, 8 H, $-CH_2-$).

6f: 78% yield; UV, $\lambda_{max}^{95\%EtOH}$ 276.0 nm; FABMS: 602 ($M^+ + H$); ^{31}P NMR (D_2O): 53.3 ppm; ^1H NMR (D_2O): nucleotide, δ 7.66 (d, 1 H, $J_{5,6}$ 7.2 Hz, H-6), 5.87 (d, 1 H, H-5), 6.02 (d, 1 H, $J_{1',2'}$ 4.8 Hz, H-1'), 4.24 (m, 1 H, H-4'), 3.9–4.01 (m, 4 H, H-2',3',5'a,5'b); galactose, δ 4.14 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 3.3–3.7 (m, 7 H, H-2,3,4, $-CH_2-$), 3.13–3.15 (m, 2 H, H-6a,6b), 2.75 (m, 1 H, H-5), 1.1–1.3 (m, 4 H, $-CH_2-$), 1.4–1.5 (m, 4 H, $-CH_2-$).

9-β-D-Arabinofuranosyladenine 5'-[(prop-3-yl β-D-galactopyranoside)-1-yl]phosphate (**6g**) *and 9-β-D-arabinofuranosyladenine 5'-[(hex-6-yl β-D-galactopyranoside)-1-yl]phosphate* (**6h**).

6g: 79% yield; UV, $\lambda_{max}^{95\%EtOH}$ 259.1 nm; FABMS: 568 ($M^+ + H$); ^{31}P NMR (D_2O): 0.1 ppm; ^1H NMR (D_2O): nucleotide, δ 8.11 (s, 1 H, H-2), 7.8 (s, 1 H, H-8); 6.09 (d, 1 H, $J_{1',2'}$ 5.4 Hz, H-1'), 4.4 (m, 1 H, H-2'), 4.2 (m, 2 H, H-3',4'), 3.93 (m, 2 H, H-5'a,5'b); galactose δ 4.04 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 3.24–3.69 (m, 7 H, H-2,3,4, $-CH_2-$), 3.08–3.13 (m, 2 H, H-6a,6b), 2.73–2.78 (m, 1 H, H-5), 1.6–1.8 (m, 2 H, $-CH_2-$).

6h: 100% yield; UV, $\lambda_{max}^{95\%EtOH}$ 259.1 nm; FABMS: 610 ($M^+ + H$); ^{31}P NMR (D_2O): 0.1 ppm; ^1H NMR (D_2O): nucleotide, δ 8.23 (s, 1 H, H-2), 8.06 (s, 1 H, H-8), 6.23–6.28 (d, 1 H, $J_{1',2'}$ 6.31 Hz, H-1'), 4.2–4.6 (m, 3 H, H-2',3',4'), 3.94 (m, 2 H, H-5'a,5'b); galactose δ 4.08 (d, 1 H, $J_{1,2}$ 7.2 Hz, H-1), 3.27–3.71 (m, 7 H, H 2, H-2,4, $-CH_2-$), 3.16–3.27 (m, 2 H, H-6a,6b), 2.7–2.8 (m, 1 H, H-5), 1.23–1.24 (m, 4 H, $-CH_2-$), 0.90–0.91 (m, 4 H, $-CH_2-$).

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