Pentenyl Ribosides: New Reagents for Purine Nucleoside Synthesis†

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Protected pent-4-enyl ribosides and deoxyribosides were synthesized as reagents for the preparation of nucleosides and deoxynucleosides. Reaction of pent-4-enyl 2′,3′,5′-tri-*O*-benzoyl-D-*erythro*-pentofuranoside with five nucleobases in the presence of *N*-iodosuccinimide/trifluoromethanesulfonic acid (NIS/TfOH) produced the *N*-9-β-nucleosides in 50–70% yields. Pent-4-enyl-2′-deoxy-3′,5′-di-*O*-*p*-toluyl-α-D-*erythro*-pentofuranoside coupled with 6-chloropurine in the presence of iodonium dicollidine perchlorate (IDCP) to produce a mixture of deoxynucleoside isomers (N-9, N-7, α, β) in 91% yield. Under the same conditions, coupling of 6-chloropurine with pent-4-enyl 2′-deoxy-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-D-*erythro*-pentofuranoside produced only N-9α and N-9β products in 40% total yield. The N-9β nucleoside was the only product of the reaction of 6-chloropurine with pent-4-enyl 2′-*O*-benzoyl-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)-D-*erythro*-pentofuranoside in the presence of NIS/TfOH. Pent-4-enyl ribosides appear to be useful reagents for the synthesis of ribo- and deoxyribonucleosides under mild (NIS/TfOH) or neutral (IDCP) conditions.

Synthetic procedures for the construction of nucleosides and nucleoside analogs are important for the preparation of antiviral agents, carcinogen–DNA adducts, etc. One strategy for nucleoside construction involves condensation of a heterocyclic base with an activated ribosyl unit.[1] The most common ribosyl donors are halides and acetates which couple with metalated[2] or trimethylsilylated bases.[3] Ribosyl halides are limited in utility because they are rather unstable, and basic conditions are required for some of the condensation reactions.[4] Ribosyl acetates are more useful reagents since the development of silyl esters of strong acids as catalysts for their condensation with trimethylsilylated bases. However, these reagents can lead to sluggish and low-yield reactions.[5]

Fraser-Reid and colleagues have described a novel route of coupling glycosyl units to oxygen nucleophiles in which pentenyl glycosides are activated by reaction with iodonium complexes.[6] They have demonstrated the utility of this reaction for oligosaccharide and glycopeptide synthesis and Pale and Whitesides have extended it to glycosyl phosphate synthesis.[7] Pentenyl glycosides are useful reagents for chemical synthesis because they are indefinitely stable and can be activated under mildly acidic or neutral conditions. We have investigated the possibility that activation of pentenyl ribosides can be used for the construction of nucleosides by synthesizing several pentenyl ribose and deoxyribose derivatives and developing conditions for their coupling with purine bases. No attempts were made to couple these reagents to pyrimidine bases. The results suggest that condensation of pentenyl ribosides with purine bases is a facile reaction that provides a new strategy for nucleoside construction.

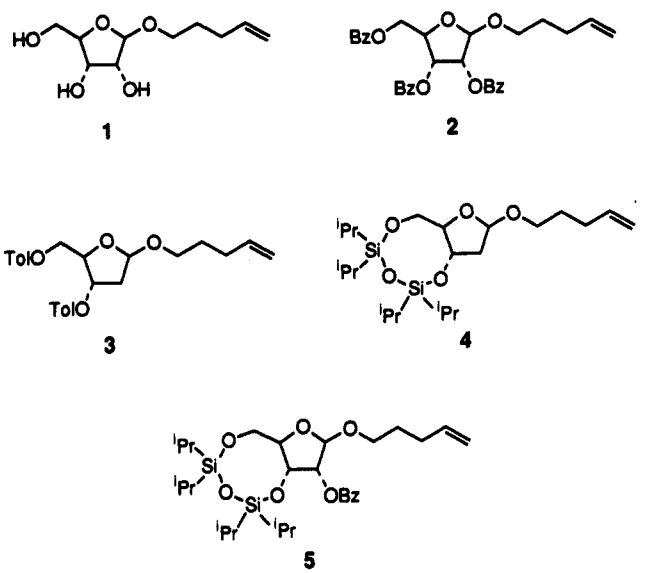

Figure 1. Structures of pentenyl ribosides.

Results

Fischer glycosylation of ribose with an excess of 4-pentenol in the presence of camphorsulfonic acid produced pent-4-enyl β-D-*erythro*-pentofuranoside (1) in 86% yield (Figure 1). The presence of the pentenyl group was indicated by the $ABMX_2$ pattern of the olefinic H4 proton at ~5.7 ppm in the ^1H NMR spectrum. The existence of the sugar ring in the furanose as opposed to pyranose configuration was verified by comparison of its ^{13}C NMR spectrum to those of methyl pyranosides and furanosides (Table I). The chemical shift of C-4′ corresponded closely to those of methyl furanosides and was very different than those of methyl pyranosides. Furthermore, the ^{13}C chemical shifts suggested 1 was produced primarily in the β configuration.

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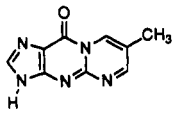
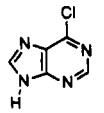
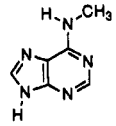
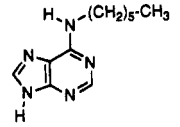
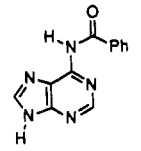
Table I. ^{13}C Chemical Shifts of Methyl and Pentenyl Glycosides[a]

sugar	C-1′	C-2′	C-3′	C-4′	C-5′
methyl β-D-ribopyranoside	103.1	71.0	68.6	68.6	63.9
methyl α-D-ribopyranoside	100.4	69.2	70.4	67.4	60.8
methyl β-D-ribofuranoside	109.0	75.3	71.9	83.9	63.9
methyl α-D-ribofuranoside	104.2	72.1	70.8	85.5	62.2
pentenyl β-D-ribofuranoside 1	107.5	75.5	71.7	83.9	63.5

[a] Chemical shifts for methyl glycosides from references.

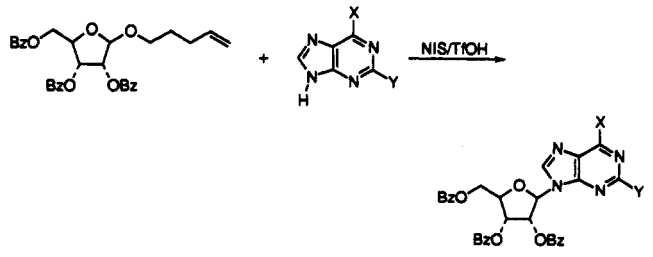
Table II. Coupling of Purines to 1

base	% yield[a]
	60
	53
	65
	70
	50

[a] Yields are reported for the N-9 coupling product. A small of N-7 coupling product was detected with 6-chloropurine.

Reaction of 1 with benzoyl chloride produced pent-4-enyl 2′,3′,5′-tri-*O*-benzoyl-β-D-*erythro*-pentofuranoside (2), which was isolated in 69% yield following column chromatography. The 2′-benzoyl group decreases the reactivity of the pentenyl acetal toward sources of iodonium ion so NIS/TfOH was used as a catalyst for reaction of 2 with purine bases. Fraser-Reid has previously shown that NIS/TfOH is an effective catalyst for reactions of 2′-acylated pentenyl glycosides.[8]

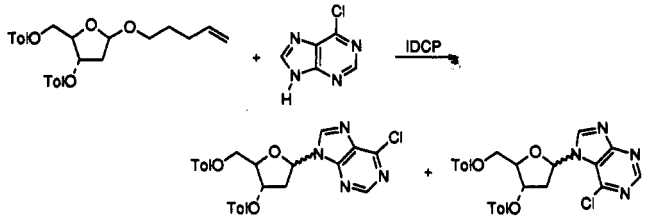
Addition of TfOH to acetonitrile solutions containing 2, various purines, and NIS effected rapid coupling to form the nucleosides (eq 1) (Table II). Good yields were



obtained with 6-chloropurine, 7-methylpyrimido[1,2-*a*]-purin-10(3*H*)-one, N^6-methyladenine, N^6-hexyladenine, and N^6-benzoyladenine. The major reaction products were tribenzoylated nucleosides substituted at N-9. Structural assignments were made by comparison of the NMR spectra of isolated products to those reported in the literature. A small amount of N-7 coupling product was formed with 6-chloropurine (5%). The stereochemistry at the ribosyl carbon was β in all cases as expected from the use of the 2′-benzoyl protecting group.[9] Varying amounts of the hydrolysis product 2′,3′,5′-tri-*O*-benzoylribose were detected in reactions with different bases. It was a minor product with the bases listed in Table II but was the major product when attempts were made to couple guanine or 7-methylguanine with 2.

Pent-4-enyl 2′-deoxy-3′,5′-di-*O*-*p*-toluyl-D-*erythro*-pentofuranoside (3) was prepared as a potential deoxyribosyl donor. Fischer glycosylation of 2′-deoxyribose and toluyl protection followed the procedures described for 2. The α and β anomers of 3 were produced in approximately equal amounts and were separated by column chromatography. The isolated α compound was a powder whereas the β compound was a wax. Their stereochemistry was assigned by ^1H NMR. The 2″ proton of the α anomer exhibited an upfield chemical shift of ~0.2 ppm relative to the β anomer. Either the mixture of anomers or the purified α compound was used for coupling reactions with identical results.

The absence of an acyl group at the 2 position of 3 enhanced its reactivity to iodonium ion sources so iodonium dicollidine perchlorate (IDCP)[10] was used as catalyst. Reaction of 3 with 6-chloropurine in acetonitrile was complete in 2 h at room temperature. Four coupling products were detected that were identified by NMR as the 9-α- (17%), 9-β- (35%), 7-α- (14%), and 7-β-6-chloropurine deoxyribosides (25%) (eq 2). The same



distribution of products was observed when either 3α or the mixture of anomers was used for condensation.

To investigate the effect of the protecting groups on the stereochemistry of deoxyribosyl coupling, pent-4-enyl 2′-deoxy-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-D-*erythro*-pentofuranoside (4) was prepared as another potential deoxyribosyl donor. Reaction of 4 with 6-chloropurine was effected with IDCP and gave equal amounts of α and β coupling products in 40% total yield. Surprisingly only N-9 products were detected.

The stereochemistry of deoxynucleoside synthesis with 3 and 4 suggested deoxyribosyl transfer occurs by an S_N1 mechanism and that direct deoxynucleoside synthesis from either pentenyl deoxyriboside would be of limited utility. An alternate approach to deoxynucleoside synthesis is to use a ribosyl equivalent that can be selectively deprotected for deoxygenation after coupling. Therefore, pent-4-enyl 2′-*O*-benzoyl-3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-β-D-*erythro*-pentofuranoside (5) was synthesized.

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Reaction of **5** with 6-chloropurine in the presence of NIS/TfOH occurred *instantaneously* at room temperature and generated the 9-β-diastereomer as the major product in 60% isolated yield. A small amount of the 7-β-diastereomer (10%) was also isolated but neither α-diastereomer was detected.

Discussion

The present results indicate that pentenyl ribosides are potentially useful reagents for the synthesis of purine nucleosides. The starting materials are readily prepared and indefinitely stable. Their stability contrasts with that of ribosyl halides, which readily decompose on storage and handling. Coupling of purines to pentenyl ribosides is catalyzed by NIS/TfOH, a relatively mild reagent that does not cause loss of acid-sensitive protecting groups.[8] The main products are the N-9 nucleosides. The major side reaction to coupling is hydrolysis which was relatively unimportant with several purines but which predominated in reactions with poorly nucleophilic purines.

Coupling of purines to pentenyl deoxyribosides was effected under neutral conditions by treatment with IDCP. The stereochemistry of coupling indicated an S_N1 process via an oxonium ion intermediate. This implies pentenyl deoxyribosides will be of limited utility for direct deoxynucleoside synthesis because of the lack of stereochemical control in the coupling step. However, this problem can be circumvented by use of **5** which bears a 2-acyl group that directs nucleophile addition to the β face of the sugar and prevents α attack. Selective deoxygenation by photosensitized electron-transfer[11] or removal of the 2′-acyl protecting group followed by Barton deoxygenation[12] should extend the chemistry to the synthesis of purine deoxyribosides.

Fraser-Reid and colleagues have demonstrated the utility of pentenyl glycosides for the construction of complex carbohydrates[13] and glycopeptides.[14] The present results demonstrate that this chemistry can be extended to the construction of nucleosides and that purine bases are compatible with the catalysts developed for carbohydrate synthesis. There are limitations to the application of this methodology to a broad range of purines and to deoxynucleoside synthesis. However, the ease of preparation, storage, and activation of pentenyl ribosides suggests they should find application in the synthesis of nucleosides.

Experimental Section

N^6-Methyladenine, N^6-hexyladenine, and N^6-benzoyladenine were purchased from Sigma Chemical Co. (St. Louis, MO). 6-Chloropurine, ribose, 2′-deoxyribose, 4-pentenol, benzoyl chloride, toluyl chloride, TPDSCl, and camphorsulfonic acid were obtained from Aldrich Chemical Co (Milwaukee, WI). 7-Methylpyrimido[1,2-*a*]purin-10(3*H*)-one was synthesized by reaction of 2-methyl-1,1,3,3-tetraethoxypropane with guanine as described.[15] IDPC was prepared as described.[15]

NMR spectra were recorded at room temperature in $CDCl_3$ on a Bruker AC300, 300-MHz Bruker instrument. Chemical shifts are reported relative to tetramethylsilane as internal standard.

I. Synthesis of Pentenyl Riboside Donors. Pent-4-enyl β-D-*erythro*-Pentofuranoside (1). To 1.249 g of ribose (8.32 mmol) dissolved in 15–20 mL of 4-pentenol was added 2.3 mL of 1% (±)-10-camphorsulfonic acid in pentenol (0.05 g/mL). After 15 min, the reaction was quenched with 0.46 g of $AgCO_3$. The reaction mixture was filtered and evacuated to remove pentenol. The pentenol was recovered by washing with cold 1 N HCl followed by distillation. Protection of the hydroxyls of **1** was usually done without further purification. However, the unprotected product was isolated as an oil in 86% yield to characterize it. ^{1}H NMR δ 5.77 (m, 1, H_4), 4.98 (m, 2, H_5), 4.91 (s, 1, $H_{1'}$), 4.28–3.37 (m, 10, H_1, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'S}$, $H_{5'R}$, 3 OH), 2.07 (m, 2, H_3), 1.63 (m, 2, H_2); ^{13}C NMR δ 137.8 (C4), 115.1 (C5), 107.5 (C1′), 83.9 (C4′), 75.5 (C2′),71.7 (C3′), 67.9 (C1), 63.5 (C5′), 30.1, 28.7 (C2, C3).

Pent-4-enyl 2′,3′,5′-Tri-*O*-benzoyl-β-D-*erythro*-pentofuranoside (2). Acylation of the pentenyl riboside (6.46 mmol, 1.41 g) with an excess of benzoyl chloride (4 mL) in pyridine (10 mL) was allowed to proceed overnight. The reaction mixture was extracted with ether and the ether was washed with water, dilute H_2SO_4, and sodium carbonate. It was dried with magnesium sulfate and the solvent was evaporated. The residue was subjected to open column chromatography (hexane–ethyl acetate, 100/3). The fully protected sugar **2** was recovered as a viscous oil in 69% overall yield. ^{1}H NMR δ 8.04, 8.00, 7.81 (3 × d, 6, phenyl protons ortho to the carbonyl group), 7.43 (m, 9, phenyl protons para and meta to the carbonyl group), 5.85 (dd, 1, $H_{3'}$, J = 4.8 Hz, 6.7 Hz), 5.75 (m, 1, H_4), 5.66 (d, 1, $H_{2'}$, J = 4.8 Hz), 5.22 (s, 1, $H_{1'}$), 4.97 (m, 2, H_5), 4.70 (m, 2, $H_{5'}$, $H_{4'}$), 4.50 (dd, 1, $H_{5''}$, J = 12.9, 6.6 Hz), 3.60 (m, 2, H_1), 2.07 (m, 2, H_3), 1.62 (m, 2, H_2); ^{13}C NMR δ 166.2, 165.4, 165.3 (3 × C(O), benzoyl), 137.9 (C4), 133.4, 133.3, 133.1, 129.8, 129.7, 129.3, 129.0, 128.9, 128.4, 128.3 (benzoyl), 115.0 (C5), 105.6 (C1′), 78.8 (C4′), 75.6 (C3′), 72.6 (C2′), 67.8 (C1), 65.0 (C5′), 30.1, 28.5 (C2, C3). Anal. Calcd for $C_{31}H_{29}O_8$ (529.57): C, 70.31; H, 5.52; O, 24.17. Found: C, 70.14; H, 5.63; O, 23.77.

Pent-4-enyl 2′-Deoxy-3′,5′-di-*O*-*p*-toluyl-D-*erythro*-pentofuranoside (3). Deoxyribose (4.16 mmol, 0.56 g) was dissolved in 5 mL of 4-pentenol. To this solution was added 1.15 mL of 1% (±)-10-camphorsulfonic acid (0.05 g/mL). After addition of the acid, the reaction proceeded smoothly and was stopped with 0.23 g of $AgCO_3$ after 20–25 min (the formation of the pentenyl deoxyriboside was not complete but the reaction was stopped to prevent any pyranose formation). Protection of the free hydroxyls of the α- and β-pentenyl riboside mixture (0.319 g; 1.58 mmol) was performed with *p*-toluyl chloride (3.5 mmol, 0.5 mL) in freshly distilled pyridine (~4 mL). The addition was done with cooling and the reaction was allowed to stand at room temperature overnight. The reaction mixture was extracted with ether and worked up as described for **2**.

A silica gel column was run to separate the anomers (hexane–ethyl acetate, 30/1). **3α** was isolated as a flocculent powder in 38% overall yield: ^{1}H NMR δ 7.95, 7.89 (2 × d, 4, phenyl protons ortho to the carbonyl group), 7.19 (m, 4, phenyl protons meta to the carbonyl group), 5.70 (m, 1, H_4), 5.40 (m, 1, $H_{3'}$), 5.25 (dd, 1, $H_{1'}$, J = 0.9, 5.1 Hz), 4.95 (m, 2, H_5), 4.65–4.45 (m, 3, $H_{5'}$, $H_{5''}$, $H_{4'}$), 3.60 (m, 2, H_1), 2.45 (m, 1, $H_{2'}$), 2.40, 2.39 (2 × s, 6, CH_3), 2.15 (m, 3, $H_{2''}$, H_3), 1.65 (m, 2, H_2); ^{13}C NMR δ 166.5 (C(O), toluyl), 138.2 (C4), 143.9, 143.7, 129.8, 129.7, 129.1, 127.1 (toluyl), 114.7 (C5), 103.8 (C1′), 81.0 (C4′), 74.6 (C3′), 66.8 (C1), 64.3 (C5′), 39.3 (C2′), 30.3, 28.9 (C2, C3), 21.6 (CH_3). Anal. Calcd for $C_{26}H_{30}O_6$ (438.53): C, 71.21; H, 6.90; O, 21.89. Found: C, 71.13; H, 6.93; O, 21.57.

3β was isolated as a wax in 42% overall yield. ^{1}H-NMR δ 7.94, 7.89 (2 × d, 4, phenyl protons ortho to the carbonyl group), 7.20 (m, 4, phenyl protons meta to the carbonyl group), 5.75 (m, 1, H_4), 5.60 (m, 1, $H_{3'}$), 5.32 (dd, 1, $H_{1'}$, J = 2.4, 5.4 Hz), 4.95 (m,

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2, H_5), 4.5 (m, 3, $H_{5'}$, $H_{5''}$, $H_{4'}$), 3.60 (m, 2, H_1), 2.55 (m, 1, $H_{2'}$), 2.42, 2.40 (2 × s, 6, CH_3), 2.35 (m, 3, $H_{2''}$), 2.10 (m, 2, H_3), 1.65 (m, 2, H_2); ^{13}C NMR δ 166.1, 165.9 (C(O), toluyl), 138.0 (C4), 143.8, 143.6, 129.7, 129.6, 129.0, 127.1, 126.8 (toluyl), 114.6 (C5), 104.6 (C1'), 81.7 (C4'), 75.5 (C3'), 67.4 (C1), 65.1 (C5'), 39.2 (C2'), 30.1, 28.6 (C2, C3), 21.5 (CH_3). Anal. Calcd for $C_{26}H_{30}O_6$ (438.53): C, 71.21; H, 6.90; O, 21.89. Found: C, 71.32; H, 7.14; O, 21.55.

Pent-4-enyl 2'-Deoxy-3',5'-di-*O*-TPDS-D-*erythro*-pentofuranoside (4). Vacuum-dried 1 (4.16 mmol, 0.56 g) was dissolved in 8 mL of pyridine and 1.1 equiv (1.45 mL) of 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TPDSCl) was added with cooling. The reaction was left overnight. After aqueous workup, the ether extract was dried with magnesium sulfate and evaporated to an oil. The mixture of anomers of 4 was recovered in 95% overall yield: ^1H NMR δ 5.3 (m, 1, H_4), 4.95 (m, 3, H_5, $H_{1'}$), 4.6 (m, 0.5, $H_{3'}$), 4.35 (m, 0.5, $H_{3'}$), 4.0–3.2 (m, 4, H_1, $H_{5'S}$, $H_{4'}$, $H_{5'R}$), 2.1 (m, 2, H_3), 1.9–2.5 (m, 2, $H_{2'}$, $H_{2''}$), 1.6 (m, 2, H_2), 1.0 (m, 28, isopropyl); ^{13}C NMR δ 138.1β, 138.1 (C4), 114.7 (C5), 102.8, 102.3β (C1'), 84.7, 81.7β (C4'), 74.3, 71.8β (C3'), 67.2β, 66.6 (C1), 66.5, 62.3β (C5'), 42.1, 40.8β (C2'), 30.4, 28.9 (C2, C3), 17.6, 17.4, 17.3, 17.1, 17.0 (CH_3, isopropyl), 13.4, 13.2, 12.9, 12.6 (CH, isopropyl). Anal. Calcd for $C_{22}H_{44}O_5Si_2$ (444.76): C, 59.41; H, 9.97; Si, 12.63. Found: C, 59.29; H, 9.57; Si, 12.48.

Pent-4-enyl 3',5'-Di-*O*-TPDS-β-D-*erythro*-pentofuranoside. Simultaneous protection of both 3' and 5' hydroxyls of 1 using the TPDS group was carried out as follows. After several evaporations from pyridine, the pentenyl ribose reaction mixture (8.32 mmol) was dissolved in 10 mL of pyridine, and 2.9 mL of TPDSCl (1.1 equiv) was added with cooling. The reaction mixture was allowed to warm to room temperature. After 6 h, the reaction was quenched, worked up, and dried overnight. Open column chromatography on ammonia-impregnated silica gel (Mallinckrodt 100–200 Mesh-6447) was performed (hexane–ethyl acetate, 40/3). The fractions containing the desired compound were condensed and dried. The protected sugar was isolated as an oil in 53% overall yield (starting from ribose): ^1H NMR δ 5.78 (m, 1, H_4), 4.98 (m, 2, H_5), 4.89 (s, 1, $H_{1'}$), 4.50 (t, 1, $H_{3'}$, J = 5.4 Hz), 4.04 (d, 1, $H_{2'}$, J = 3.7 Hz), 3.85 (m, 3, $H_{5'}$, $H_{4'}$, $H_{5''}$), 3.49 (m, 2, H_1), 2.96 (s, 1, OH), 2.09 (m, 2, H_3), 1.62 (m, 2, H_2), 1.03 (m, 28, isopropyl); ^{13}C NMR δ 138.0 (C4), 114.8 (C5), 106.2 (C1'), 82.5 (C4'), 75.8 (C3'), 75.0 (C2'), 67.0 (C1), 66.2 (C5'), 30.2, 28.7 (C2, C3), 17.5, 17.4, 17.1, 16.9 (CH_3, isopropyl), 13.3, 12.9, 12.6 (CH, isopropyl).

Pent-4-enyl 2'-*O*-Benzoyl-3',5'-di-*O*-TPDS-β-D-*erythro*-pentofuranoside (5). To the vacuum-dried residue of 3',5'-*O*-TPDS-pentenyl ribose (1.62 g, 3.52 mmol) were added 30 mL of anhydrous CH_3CN, 1.04 mg (8.5 mmol) of 4-(dimethylamino)-pyridine, and 710 μL (6.1 mmol; 869 mg) of benzoyl chloride. The reaction was stirred overnight. After aqueous workup, the fully protected ribose 5 was purified by open column chromatography (hexane–THF, 100/2). The fractions containing the desired product were pooled and evaporated to an oil (overall yield starting with ribose: 23%): ^1H NMR δ 8.04, 8.00, 7.81 (3 × d, 6, phenyl protons ortho to the carbonyl group), 7.43 (m, 9, phenyl protons para and meta to the carbonyl group), 5.85 (dd, 1, $H_{3'}$, J = 4.8, 6.7 Hz), 5.75 (m, 1, H_4), 5.66 (d, 1, $H_{2'}$, J = 4.8 Hz), 5.22 (s, 1, $H_{1'}$), 4.97 (m, 2, H_5), 4.70 (m, 2, $H_{5'}$, $H_{4'}$), 4.50 (dd, 1, $H_{5''}$, J = 12.9, 6.6 Hz), 3.60 (m, 2, H_1), 2.07 (m, 2, H_3), 1.62 (m, 2, H_2), 1.04 (m, 28, isopropyl); ^{13}C NMR 165.6 (C(O), benzoyl), 138.0 (C4), 133.0, 130.1, 129.8, 129.5, 128.3 (benzoyl), 114.8 (C5), 104.4 (C1'), 82.1 (C4'), 77.3 (C3'), 73.4 (C2'), 67.3 (C1), 65.1 (C5'), 30.2, 28.7 (C2, C3), 17.5, 17.4, 17.1, 17.0, 16.8 (CH_3, isopropyl), 13.3, 13.2, 12.8, 12.6 (CH, isopropyl). Anal. Calcd for $C_{29}H_{48}O_7Si_2$ (564.87): C, 61.66; H, 8.57. Found: C, 62.38; H, 8.59.

II. Coupling Reactions. Procedure A: In a flame-dried pear-shaped 5-mL flask was stirred 0.06 mmol of 2 (31.0 mg), 0.02 mmol of the nucleobase of interest, 0.06 mmol of *N*-iodosuccinimide (12.2 mg), and activated 4-Å molecular sieves in 2 mL of freshly distilled acetonitrile. After 5 min, 0.06 mmol of triflic acid (5.4 μL) was added to this suspension. The reaction was stirred for 40 min and 20 μL was analyzed by HPLC [Beckman Ultrasphere C_{18} 5 μm, 10 × 250 mm: water–methanol, 50% methanol (0–5 min), 50–100% methanol (5–15 min), 100% methanol (15–25 min), 100–50% methanol (25–35 min). Flow rate: 4 mL/min], with diode array UV detection and integration (Hewlett-Packard Chemstations 1040A and 9153C). The percentage conversion was estimated at 254 nm, where the absorbances of the bases were maximal. The percentage conversion estimated by HPLC was determined to be the same as the isolated yield in a large-scale reaction with 6-chloropurine. Procedure B was identical to procedure A except for the amount of 2 (0.03 mmol instead of 0.06 mmol).

6-Chloro-9-(2',3',5'-tri-*O*-benzoyl-β-D-pentofuranosyl)-purine was synthesized by procedure A and isolated as a white solid after chromatographic purification (t_R 17.1 min): ^1H NMR δ 8.59 (s, 1, H-8 purine), 8.26 (s, 1, H-2 purine), 8.05, 8.00, 7.90 (3 × d, 6, phenyl protons ortho to the carbonyl group), 7.56 (m, 3, phenyl protons para to the carbonyl group), 7.39 (m, 6, phenyl protons meta to the carbonyl group), 6.43 (d, 1, $H_{1'}$, J = 5.0 Hz), 6.39 (t, 1, $H_{2'}$, J = 5.4 Hz), 6.22 (t, 1, $H_{3'}$, J = 5.3 Hz), 4.92 (dd, 1, $H_{5'}$, J = 12.1 Hz, 3.2 Hz), 4.84 (m, 1, $H_{4'}$), 4.68 (dd, 1, $H_{5''}$, J = 12.1 Hz, 4.1 Hz); thermospray MS M + 1 = 599.

6-Chloro-7-(2',3',5'-tri-*O*-benzoyl-β-D-pentofuranosyl)-purine was also isolated as a white solid after purification (t_R 16.7 min): ^1H NMR δ 8.90 (s, 1, H-8 purine), 8.67 (s, 1, H-2 purine), 8.09, 7.94, 7.92, (3 × d, 6, phenyl protons ortho to the carbonyl group), 7.48 (m, 3, phenyl protons para and meta to the carbonyl group), 7.01 (d, 1, $H_{1'}$, J = 5.4 Hz), 6.0 (t, 1, $H_{2'}$, J = 5.5 Hz), 5.95 (t, 1, $H_{3'}$, J = 4.8 Hz); 4.89 (m, 2, $H_{4'}$, $H_{5'}$), 4.75 (dd, 1, $H_{5''}$, J = 13.3, 4.3 Hz); thermospray MS M + 1 = 599.

3-(2',3',5'-Tri-*O*-benzoyl-β-D-*erythro*-pentofuranosyl)-7-methyl-10-oxo-9,10-dihydropyrimido[1,2-*a*]purine was synthesized following procedure A and isolated as a yellowish solid after purification (t_R 16.2 min): ^1H NMR δ 9.03 (bs, 1, H-8 purine), 8.86 (bs, 1, H-6 purine) 8.38 (b s, 1, H-2 purine), 8.02, 7.97, 7.88 (3 × d, 6, phenyl protons ortho to the carbonyl group), 7.44 (m, 9, phenyl protons para and meta to the carbonyl group), 6.60 (d, 1, $H_{1'}$, J = 5.3 Hz), 6.26 (t, 1, $H_{2'}$, J = 5.8 Hz), 6.13 (t, 1, $H_{3'}$, J = 5.7 Hz), 4.92 (dd, 1, $H_{5'}$, J = 11.5 Hz, 3.1 Hz), 4.81 (m, 1, $H_{4'}$), 4.75 (dd, 1, $H_{5''}$, J_5 = 11.6, 4.9 Hz); thermospray MS M + 1 = 646.

N^6-Methyl-2',3',5'-tri-*O*-benzoyladenosine was synthesized following procedure A and isolated as a white solid after purification (t_R 16.6 min): ^1H NMR δ 8.58 (bs, 1, $HNCH_3$), 8.11 (s, 1, H-8 purine), 7.89 (s, 1, H-2 purine), 8.06, 8.01, 7.88 (3 × d, 6, phenyl protons ortho to the carbonyl group), 7.49 (m, 9, phenyl protons para and meta to the carbonyl group), 6.39 (d, 1, $H_{1'}$, J = 5.4 Hz), 6.21 (t, 1, $H_{2'}$, J = 5.7 Hz), 6.07 (t, 1, $H_{3'}$, J = 5.1 Hz), 4.93 (dd, 1, $H_{5'}$, J = 12.3 Hz, 2.8 Hz), 4.83 (m, 1, $H_{4'}$), 4.66 (dd, 1, $H_{5''}$, J = 12.6, 3.9 Hz), 3.59 (d, 3, CH_3); thermospray MS M + 1 = 594.

N^6-Hexyl-2',3',5'-tri-*O*-benzoyladenosine was synthesized following procedure B and isolated as a white solid after purification (t_R 18.8 min): ^1H NMR δ 8.30 (s, 1, H-8 purine), 8.08, 7.97, 7.91 (3 × d, 6, phenyl protons ortho to the carbonyl group), 7.89 (s, 1, H-2 purine), 7.49 (m, 9, phenyl protons para and meta to the carbonyl group), 6.40 (d, 1, $H_{1'}$, J = 5.3 Hz), 6.34 (t, 1, $H_{2'}$, J = 5.6 Hz), 6.24 (t, 1, $H_{3'}$, J = 5.2 Hz), 4.87 (dd, 1, $H_{5'}$, J = 12.0, 3.2 Hz), 4.79 (m, 1, $H_{4'}$), 4.68 (dd, 1, $H_{5''}$, J = 12.0 Hz, 4.1 Hz), 3.59 (b s, 2, CH_2 a), 1.64 (m, 2, CH_2 b), 1.31 (m, 6, CH_2 c–e), 0.86 (bt, 3, CH_3); thermospray MS M + 1 = 664.

N^6,2',3',5'-Tetra-*O*-benzoyladenosine was synthesized following procedure B and isolated as a white solid after purification (t_R 16.7 min): ^1H NMR δ 8.63 (s, 1, H-8 purine), 8.24 (s, 1, H-2 purine), 8.08, 8.05, 8.00, 7.90 (4 × d, 8, phenyl protons ortho to the carbonyl group), 7.47 (m, 12, phenyl protons para and meta to the carbonyl group), 6.49 (d, 1, $H_{1'}$, J = 5.4 Hz), 6.38 (t, 1, $H_{2'}$, J = 5.6 Hz), 6.13 (t, 1, $H_{3'}$, J = 5.3 Hz), 4.92 (dd, 1, $H_{5'}$, J = 12.1, 3.1 Hz), 4.84 (m, 1, $H_{4'}$), 4.70 (dd, 1, $H_{5''}$, J = 12.1, 4.1 Hz); thermospray MS M + 1 = 684.

6-Chloro-9-(2'-deoxy-3',5'-di-*O*-TPDS-D-*erythro*-pentofuranosyl)purine. Ninety-one milligrams (0.2 mmol) of 4, 61.8 mg (0.4 mmol) of 6-chloropurine, and activated 4-Å molecular sieves were mixed with 7 mL of freshly distilled acetonitrile. To this solution was added 100 mg (0.22 mmol) of iodonium dicollidine perchlorate (IDCP). The reaction was stirred for 2 h abd then worked up as described above. Two major peaks were purified on HPLC [Beckman Ultrasphere C_{18} 5 μm, 10 × 250 mm; water–methanol: 50% methanol (0–5 min), 50–100% methanol (5–15 min), 100% methanol (15–25 min), 100–50% methanol (25–35 min). Flow rate: 4 mL/min]. N-9β was obtained in 20% yield (t_R 20.3 min): ^1H NMR δ 8.75 (m, 1, H-8 purine),

8.65 (m, 1, H-2 purine), 6.48 (dd, 1, $H_{1'}$, J = 3.3, 7.2 Hz), 4.71 (m, 1, $H_{3'}$), 4.13 (m, 1, $H_{4'}$), 4.05 (dd, 1, $H_{5''}$, J = 3.8, 7.9 Hz), 3.77 (dd, 1, $H_{5'}$, J = 8.2, 10.8 Hz), 2.95 (m, 1, $H_{2'}$), 2.68 (dt, 1, $H_{2''}$, J = 3.6, 14.5 Hz), 0.99 (m, 28, isopropyl); thermospray MS M + 1 = 513. N-9α was obtained in 20% yield (t_R 20.7 min): ^{1}H NMR δ 8.69 (m, 1, H-8 purine), 8.34 (m, 1, H-2 purine), 6.33 (dd, 1, $H_{1'}$, J = 3.0, 6.6 Hz), 4.91 (m, 1, $H_{3'}$), 4.03 (m, 2, $H_{5'5''}$), 3.89 (m, 1, $H_{4'}$), 2.70 (m, 1, $H_{2'}$), 2.67 (d, 1, $H_{2''}$, J = 6.8 Hz), 1.04 (m, 28, isopropyl); thermospray MS M + 1 = 513.

6-Chloro-9-(2′-*O*-benzoyl-3′,5′-di-*O*-TPDS-D-*erythro*-pentofuranosyl)purine. One hundred and thirteen milligrams (0.2 mmol) of **5**, 0.22 mmol of 6-chloropurine, 45 mg (0.22 mmol) of NIS, and 4-Å molecular sieves were mixed with 5 mL of freshly distilled acetonitrile. To this solution, was added 18 mL (0.2 mmol) of TfOH. The reaction mixture was immediately worked up as described above.

Purification of 6-chloro-9-(2′-*O*-benzoyl-3′,5′-TPDS-β-D-*erythro*-pentofuranosyl)purine and its N-7 isomer was accomplished by HPLC (Dynamax preparative silica column; 2% 2-propanol in dichloromethane). N-9β was obtained in 60% yield (t_R 8.4 min): ^{1}H NMR δ 8.71 (s, 1, H-8 purine), 8.34 (s, 1, H-2 purine), 8.06 (d, 2, phenyl protons ortho to the carbonyl group, J = 7.8 Hz), 7.48 (m, 3, phenyl protons para and meta to the carbonyl group), 6.21 (s, 1, $H_{1'}$), 5.98 (d, 1, $H_{2'}$, J = 5.4 Hz), 5.14 (dd, 1, $H_{3'}$, J = 5.5, 8.5 Hz), 4.18 (m, 2, $H_{5'}$, $H_{4'}$), 4.07 (dd, 1, $H_{5''}$, J = 13.6 Hz, 3.5 Hz), 1.03 (m, 28, isopropyl). N-7β was obtained in 10% yield (t_R 11.5 min): ^{1}H NMR δ 8.91 (s, 1, H-8 purine), 8.87 (s, 1, H-2 purine), 8.08 (d, 2, phenyl protons ortho to the carbonyl group, J = 7.0 Hz), 7.53 (m, 3, phenyl protons para and meta to the carbonyl group), 6.67 (s, 1, $H_{1'}$), 5.84 (d, 1, $H_{2'}$, J = 4.7 Hz), 4.66 (dd, 1, $H_{3'}$, J = 4.7, 9.0 Hz), 4.33 (m, 2, $H_{5'}$, $H_{4'}$), 4.08 (dd, 1, $H_{5''}$, J = 12.5 Hz, 2.5 Hz), 0.98 (m, 28, 2-propyl).

6-Chloro-9-(2′-deoxy-3′,5′-di-*O*-*p*-toluyl-β-D-*erythro*-pentafuranosyl)purine (and isomers). Forty-four milligrams (0.1 mmol) of **3**α, 0.2 mmol of the nucleobase of interest, and activated 4-Å molecular sieves were mixed with 3 mL of freshly distilled acetonitrile. To this solution was added 59 mg (0.13 mmol) of iodonium dicollidine perchlorate was added. The reaction was stirred for 2 h and then diluted with dichloromethane and filtered. The organic phase was washed with 1 M H_2SO_4, saturated K_2CO_3, and brine. After drying over $MgSO_4$, the filtrate was evaporated to dryness. N-9 and N-7 coupling products were separated and purified by preparative TLC followed by HPLC separation of the anomers (Dynamax Silica column; 5% 2-propanol in dichloromethane). N-9β was obtained in 35% yield (t_R 26.3 min): ^{1}H NMR δ 8.69 (s, 1, H-8 purine), 8.34 (s, 1, H-2 purine), 6.54 (t, $H_{1'}$, J = 7 Hz). N-9α was obtained in 17% yield (t_R 22.5 min): ^{1}H NMR δ 8.6 (s, 1, H-8 purine), 8.4 (s, 1, H-2 purine), 6.7 (d, $H_{1'}$, J = 4.5 Hz). N-7β was obtained in 25% yield (t_R 32.2 min): ^{1}H NMR δ 8.92 (s, 1, H-8 purine), 8.73 (s, 1, H-2 purine), 6.90 (t, $H_{1'}$, J = 5.7 Hz). N-7α was obtained in 14% yield (t_R 29.5 min): ^{1}H NMR δ 8.92 (s, 1, H-8 purine), 8.6 (s, 1, H-2 purine), 6.95 (d, $H_{1'}$, J = 4.6 Hz).

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Supplementary Material Available: Copies of ^{1}H NMR spectra of **1**–**5** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.