mixture was allowed to react at 25 °C for 30 min, at which time an orange aqueous layer separated. The mixture was extracted with 2 × 5 mL of $CHCl_3$, the combined organic extracts were washed with 5 mL of water and 10 mL of brine, dried ($MgSO_4$), and filtered, the filtrate was concentrated in vacuo to yield 4.5 mg (75%) of essentially pure **2**. The crude material could be recrystallized from CH_2Cl_2–cyclohexane to afford white feathery crystals: mp 180–182 °C; R_f 0.29 (5% CH_3OH–$CHCl_3$); $[\alpha]_D$ +116° (*c* 0.73, $CHCl_3$); ^1H NMR δ 1.34 (s, 3 H), 1.52 (s, 3 H), 1.7–2.25 (br m, 5 H), 2.3–2.6 (m, 2 H), 3.09 (d, J = 8.6 Hz, 1 H), 3.6 (m, 1 H), 3.8 (m, 1 H), 4.2 (overlapping dd, 1 H), 4.92 (s, 3 H), 5.2 (d, J = 8.6 Hz, 1 H), 5.95 (overlapping dd, 1 H), 7.1 (m, 2 H), 7.3 (m, 1 H), 7.8 (m, 1 H), 9.4 (br s, 1 H); ^{13}C NMR δ 22.2, 28.7, 29.8, 32.5, 46.2, 47.7, 49.0, 60.0, 69.4, 71.5, 83.5, 106.1, 111.3, 119.9 (2C), 122.0, 126.3, 135.2, 136.0, 165.4, 165.8; IR 3380, 3010, 2965, 2935, 1660, 1450, 1380, 1226, 1150 cm^{-1}; high-resolution mass spectral analysis for $C_{21}H_{25}N_3O_5$, calcd 399.1796, found 399.1808.

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Synthesis of Nucleotide 5′-Diphosphates from 5′-*O*-Tosyl Nucleosides

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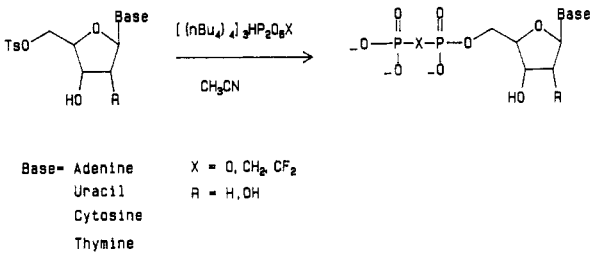
Procedures are described for the synthesis of nucleoside 5′-diphosphates, methanediphosphonates, and difluoromethanediphosphonates. The general strategy involves protection of the nucleosides as amidine, 2′,3′-methoxymethylidene, and 3′-(*tert*-butyldimethylsilyl) derivatives prior to tosylation with tosyl chloride and (*N*,*N*-dimethylamino)pyridine. Deprotection, followed by displacement of the tosyl moiety with the tris(tetra-*n*-butylammonium) pyrophosphate, methanediphosphonate, or difluoromethanediphosphonate salts gave the desired products. The ammonium salts of the nucleotides were purified by flash chromatography on cellulose or medium pressure ion-exchange chromatography on DEAE Fractogel. Syntheses are reported for UDP (**18**), CDP (**19**), TDP (**20**), GDP (**21**), ADP (**23**), 2′,3′-isopropylidene-ADP (**22**), adenosine 5′-methanediphosphonate (**24**), adenosine 5′-difluoromethanediphosphonate (**25**), and deoxyadenosine 5′-difluoromethanediphosphonate (**27**). In addition, ATP (**26**) was prepared by treatment of 5′-*O*-tosyladenosine with tetrakis(tetra-*n*-butylammonium) triphosphate. Yields for the displacement reactions ranged from 43% to 93%.

Nucleoside 5′-diphosphates are central compounds in numerous biochemical and pharmacological studies. As a result, they and their various analogues have been the targets of numerous synthetic efforts over the past 3 decades. This work has produced a large repertoire of synthetic organic and biochemical methods for the phosphorylation of nucleosides.[1] In general, nucleoside phosphorylation is achieved by nucleophilic addition of the 5′-ribosyl hydroxyl to an activated phosphate derivative. The P–O–P linkage is then generated by a variety of activation and displacement sequences at phosphorus. Although phosphorylation with electrophilic phosphorus derivatives serves in many applications, a transformation that introduces phosphorus as a nucleophile in a single step is an important alternative with numerous applications. There are few phosphorylation strategies that rely upon nucleophilic displacement at carbon for establishment of the C–O–P linkage. Reported cases include the synthesis of methanediphosphonate nucleotides and their analogues by displacements on 5′-halogen or sulfonate ester derivatives[2-5] and polymerization of O^2,5′-cyclonucleosides.[6]

Scheme I



We recently developed a single-step diphosphorylation procedure for the synthesis of various isoprenoid natural products and their analogues.[7-9] An adaptation of this approach to the phosphorylation of nucleosides is now presented.[10] The procedure utilizes a nucleophilic displacement of 5′-*O*-tosyl nucleosides by the tris(tetra-*n*-butylammonium) form of pyrophosphoric acid at room temperature as outlined in Scheme I. The resulting diphosphates are purified by a simple absorption chroma-

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tography on cellulose or by ion-exchange chromatography on DEAE Fractogel. The displacement reaction is also useful for the synthesis of isosteric methylene-bridged diphosphonate derivatives. In addition, a one-step synthesis of ATP from 5′-*O*-tosyladenosine by displacement with tetrakis(tetra-*n*-butylammonium) triphosphate is described.

Results and Discussion

Synthesis of 5′-*O*-Tosyl Nucleosides. Development of a general approach for the synthesis of nucleotides by nucleophilic displacement required suitable procedures for activation of the nucleoside 5′-hydroxyl group. Experience with isoprenoid diphosphates indicated that 5′-*O*-tosylates would be appropriate precursors.[8] However, the only activated nucleoside commercially available is 5′-*O*-tosyladenosine. Thus, an efficient synthesis of nucleoside 5′-*O*-tosylates in high yields was required. Although several groups have reported syntheses of a variety of 5′-*O*-sulfonate esters, the procedures are generally not well developed for ribonucleosides, and the overall yields for protection, sulfonation, and deprotection for ribo- and deoxyribonucleosides are typically below 50%.[11-17] We first concentrated on the synthesis of ribonucleoside 5′-*O*-tosylates. Comparative studies with the 2′,3′-*O*-phenylborate[15,18] and the 2′,3′-*O*-methoxymethylidene[19,20] protecting groups indicated that the latter were more suitable in our hands. In addition, deprotection of methoxymethylidene could be accomplished with mild acid in the presence of 5′-*O*-tosylate or diphosphate moieties.

Based on ample literature precedent[6,15,21] and initial experiments with 2′,3′-*O*-isopropylideneguanosine, we concluded that protection of the basic amino groups in guanosine and cytidine prior to tosylation would lead to enhanced yields. Ideally, an amine blocking group should be removed under conditions similar to those used to deblock the 2′,3′-hydroxyls. Therefore, the amidine moiety,[22-24] which underwent hydrolysis during removal of the 2′,3′-*O*-methoxymethylidene group by brief treatment with 0.01 N HCl/MeOH, was chosen. Conversion to the amidine group proceeded smoothly for 2′,3′-(methoxymethylidene)cytidine; however, substantial losses were incurred with 2′,3′-(methoxymethylidene)guanosine. The problem was circumvented by performing the reaction in dry acetonitrile in the presence of excess diisopropylethylamine. We assume that impurities carried from the previous step were responsible for the low yield. Analytical samples of protected ribonucleosides were readily obtained by chromatography on silica gel, although in general the materials were directly converted to the protected tosylates in order to optimize yields.

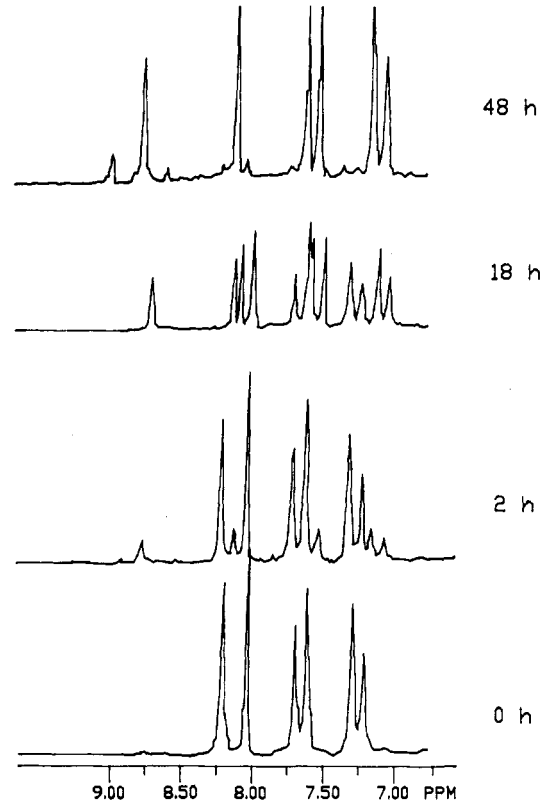

Figure 1. Progress of tosylate displacement of **12** by reagent **14**. Mixture was transferred from reaction vial under nitrogen via syringe to a dry 5-mm NMR tube; 90-MHz ^{1}H NMR data referenced to tetramethylsilane.

Our initial attempts to prepare 5′-*O*-tosylates by treatment of the blocked nucleosides with pyridine and tosyl chloride required more than 16 h. In several instances, decomposition of the protected tosylates at the long reaction times needed for complete conversion led to mediocre recoveries.[17] As a result, we developed a new procedure that has proven to be useful in our hands for the preparation of a wide variety of tosylates. Treatment of the blocked nucleosides with a 1:1 mixture of 4-(*N*,*N*-dimethylamino)pyridine (4-DMAP) and tosyl chloride in dichloromethane or chloroform provided acceptable yields of the corresponding 5′-*O*-tosylates in 6–12 h at room temperature. After purification, the protecting groups were removed by exposure to mild acid followed by a brief treatment at pH 7.5–8.0. Typical overall yields for synthesis of ribonucleoside 5′-*O*-tosylates ranged from 52% to 83% for the protection, tosylation, and deprotection steps.

Sulfonation of 2′-deoxyribonucleosides has been more extensively described in the literature.[11-14] Although several procedures for selective 5′-*O*-tosylation exist, we chose to first prepare the 3′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyribonucleosides[25-29] and employ the previously

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Table I

nucleoside	time (h)	product (X)	yield (%)[a]
5′-*O*-tosyluridine (**2**)	24	**18** (O)	58
5′-*O*-tosylcytidine (**5**)	72	**19** (O)	53
5′-*O*-tosylthymidine (**6**)	24	**20** (O)	83
5′-*O*-tosylguanosine (**9**)	4–5 days	**21** (O)	43
2′,3′-*O*-isopropylidene-5′-*O*-tosyladenosine (**11**)[b]	2	**22** (O)	93
5′-*O*-tosyladenosine[a] (**12**)	24	**23** (O)	72
	48	**24** (CH_2)	70
	66	**25** (CF_2)	54
	24	**26** (PO_4)	55
5′-*O*-tosyl-2′-deoxyadenosine (**13**)	48	**27** (CF_2)	50

[a] All yields refer to the lyophilized ammonium salts. [b] Reference 17.

described tosylation with 4-DMAP in dichloromethane. In the two cases studied (thymidine and adenosine), selective removal of the silyl protecting group in the presence of the 5′-*O*-tosylate was achieved with dilute aqueous hydrofluoric acid in acetonitrile.[30] Pure 5′-*O*-tosyl-2′-deoxyribonucleosides were obtained after flash chromatography on silica gel in overall yields of 60–70% for the protection, tosylation, and deprotection steps.

Phosphorylations. Our early experiments for conversion of the 5′-*O*-tosyl nucleosides to the corresponding diphosphates were patterned after those for the synthesis of isoprenoid diphosphates using tris(tetra-*n*-butylammonium) hydrogen pyrophosphate.[7-10] The progress of the reaction was followed by monitoring the ^1H NMR spectrum between 7 and 9 ppm, where the tosylate moiety appears as an AA′XX′ spin system.[31] A characteristic upfield shift is observed upon displacement of the tosylate anion (Figure 1). In order to achieve complete displacement in a reasonable period of time, a 0.5-fold excess of phosphorylating reagent was required at concentrations above 1 M in acetonitrile. We were surprised to encounter a dramatic difference in the rates of phosphorylation of 5′-*O*-tosyladenosine and its 2′,3′-*O*-isopropylidene derivatives (see Table I). This result is consistent with a decreased nucleophilicity for the reagent, perhaps through hydrogen bonding with exposed hydroxyls in the unprotected nucleoside. However, changes in the conformation of the ribose ring upon protection may also alter the rate of reaction. All of the nucleoside tosylates listed in Table I except for 5′-*O*-tosylguanosine (**9**) were soluble in acetonitrile containing high concentrations of the pyrophosphate salt. The sparingly soluble **9** required prolonged reaction times. When a more polar mixture consisting of 1:1 (v/v) Me_2SO and acetonitrile was employed, the rate increased for consumption of starting tosylate (24 h vs. 4–5 days). However, deleterious side reactions reduced the yield to a disappointing 24%.

Methanediphosphonate analogues of ADP (**24**, **25**) and deoxy-ADP (**27**)[32,33] were also synthesized by using the tosylate displacement protocol. Displacements of 5′-*O*-tosyl, 5′-iodo, and 5′-chloro ribonucleosides with methanediphosphonic acid and related derivatives has been reported previously.[2-5] Overall yields using these methods ranged from traces to 40% and usually required temperatures in excess of 100 °C for the displacement. Yields of purified materials using the tosylate strategy with nucleophilic tetra-*n*-butylammonium salts at room temperature were 50–70%. Thus, the procedure represents a viable alternative to existing methods for the synthesis of methylene-bridged analogues.

Our success with the diphosphates encouraged us to attempt the synthesis of nucleotide triphosphates by a similar strategy. To this end, a reagent was prepared by careful titration of a cold solution of $H_5P_3O_{10}$ (freshly prepared from $Na_5P_3O_{10}$) with aqueous tetra-*n*-butylammonium hydroxide to pH 7.0 followed by lyophilization. When the 5′-*O*-tosylates of adenosine, uridine, and cytidine were treated with this reagent, complete displacement occurred within 24 h. However, only in the case of adenosine was a pure preparation of triphosphate obtained. Although the rates for the disappearance of all tosylates were similar, the pyrimidine triphosphates were obtained in disappointingly low yields (5–30%), and substantial amounts of nonphosphorylated nucleosides were formed during the reactions. On the basis of these results, attempts to triphosphorylate the pyrimidine nucleosides were abandoned.

Purification. Two simple procedures were developed to purify the diphosphates from reaction mixtures obtained after the displacements. Both are mild and rapid and represent general methods for purification of phosphorylated materials. The first relies upon our earlier experience with the isoprenoid diphosphates and utilizes an inexpensive chromatographic step on cellulose.[7,8] The tetra-*n*-butylammonium counter ion was replaced with ammonium by cation exchange on DOWEX AG 50W-X8 resin (NH_4^+ form). After lyophilization, the ammonium salts were purified by flash cellulose chromatography using cellulose TLC to monitor the elution. All chromatographies were performed with mixtures of water, acetonitrile, and ammonium carbonate. This procedure can be easily adapted for milligram to gram scale purifications, and diphosphate ammonium salts were obtained in pure form for all of the cases presented in Table I.

A second procedure employed DEAE Fractogel, a medium pressure anion exchanger. In our hands, this material provided superior resolution and shorter elution times than existing procedures on DE 52 cellulose or DEAE Sephadex.[34-39] Authentic samples were used to identify retention volumes, and gradient protocols were developed on analytical columns prior to preparative purifications. All phosphorylated materials described in this study were easily separated with linear gradients of 0.05 M to 0.5 M ammonium bicarbonate pH 7.8 at room temperature within 2 h. This procedure did not require prior exchange of the tetra-*n*-butylammonium counter ion, and fractions were easily monitored by UV detection. Pooled fractions were dried by lyophilization, and residual ammonium carbonate was removed by lyophilization from deionized

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water after the pH was adjusted to 7.0 with carbon dioxide. Ammonium salts recovered from this procedure were also pure as judged by TLC, HPLC, and ^1H, ^{13}C, and ^{31}P NMR spectroscopy. Where available, commercial materials were used for comparisons of chromatographic properties and spectral data with synthetic materials.

Concluding Remarks. Organic-soluble salts of phosphoric and phosphonic acids are excellent reagents for synthesis of nucleotides from nucleosides in good overall yields by direct displacement at the 5' position of 5'-*O*-tosyl derivatives. This procedure complements existing synthetic and enzymatic methods based on addition of the nucleophilic 5'-hydroxyl group to activated phosphate or phosphite derivatives. The displacement approach should be useful for the synthesis of ^{32}P-labeled nucleotides in a single step and for the synthesis of nucleotide analogues where the phosphate-containing moiety must be introduced as an *intact* unit. Since the displacement reaction proceeds with inversion of configuration at primary centers,[8] it should be possible to synthesize both diastereomers of nucleotides isotopically labeled at C5' from a single nucleoside diastereomer by displacement of tosylate or by addition of the 5'-hydroxyl to phosphorus. Despite limited success with preparation of 5'-nucleotide triphosphates by direct displacement, the diphosphates may provide useful precursors to these materials by a number of proven enzymatic methods.[35,40] We also anticipate that nucleoside monophosphates can be prepared in good yields by using the displacement strategy. Finally, the activated nucleosides can be prepared and stored until needed, and the chromatographic procedures we describe give pure samples of solid ammonium salts that can be stored for extended periods at −70 °C without decomposition.

Experimental Section

Materials. Nucleosides, $H_2Na_2P_2O_7$, and $Na_5P_3O_{10}\cdot 6H_2O$ were purchased from Sigma Chemical Co., with the exception of 5'-*O*-tosyladenosine (Aldrich), and were used without purification. Nucleotides used as standards were purchased from Boehringer Mannheim Biochemicals. Pyridine hydrochloride, tetra-*n*-butylammonium hydroxide, and trimethyl orthoformate were purchased from Aldrich Chemical Co. 4-(*N*,*N*-Dimethylamino)-pyridine was purchased from Lancaster Synthesis. Dowex AG 50W-X8 cation exchange resin (100–200 mesh) was purchased from Bio Rad and dimethylformamide dimethyl acetal from Fluka Chemical Corp. All solvents used for chromatography were of reagent grade and glass distilled prior to use, except acetonitrile for flash cellulose chromatography. Dichloromethane and acetonitrile for reactions were distilled from phosphorus pentoxide. Reagent grade chloroform was glass distilled and passed through neutral alumina. Dimethylformamide was distilled from barium oxide and stored over 4-Å molecular sieves. *N*,*N*-Diisopropylethylamine was distilled from calcium hydride just prior to use. *p*-Toluenesulfonyl chloride (J. T. Baker) was dissolved in diethyl ether, washed with saturated sodium bicarbonate, dried over magnesium sulfate, and recrystallized from hexanes and diethyl ether at −20 °C.

General Methods. ^1H, ^{13}C, ^{31}P, and ^{19}F NMR spectra were recorded on Varian EM 390, SC 300, or XL 300 instruments. ^1H and ^{13}C spectra are referenced in parts per million (ppm) from internal 3-(trimethylsilyl)-1-propanesulfonic acid (TPS) or a solvent lock signal. ^{31}P and ^{19}F spectra are referenced from external phosphoric acid and trichlorofluoromethane, respectively. NMR spectra were recorded in $CDCl_3$, D_2O, CD_3CN, Me_2SO-d_6, or acetone-d_6. In the case of ^{31}P spectra, 1–2 mM concentrations of Na_2EDTA were used. All ^{13}C and ^{31}P NMR data are reported for broad-band decoupled spectra. In cases where the data was of appropriate quality, ^{13}C–P and ^{13}C–F coupling constants are stated. Infrared spectra were recorded on a Perkin-Elmer Model 299 infrared spectrophotometer calibrated with the 1601-cm^{-1} absorption of polystyrene. Absorbances are reported in wavenumbers (cm^{-1}). Ultraviolet spectra were recorded on a Guilford 2600 spectrophotometer. All wavelengths are reported in nanometers (nm). Positive fast atom bombardment (FAB) mass spectra were recorded on a VG Analytical 7070-E magnetic sector mass spectrometer operated at +5.0 kV accelerating potential and 2000 resolving power. Samples were placed in a glycerol matrix, and the data system was calibrated with the spectra of concentrated sulfuric acid. Elemental analyses were performed by Mic. Anal. of Tucson, AZ. Melting points were obtained on a Büchi melting point apparatus and are uncorrected.

Reactions that required a dry nitrogen atmosphere were performed with oven-dried glassware (140 °C). Samples were concentrated by rotary evaporation at water aspirator pressure. Solid samples were dried at reduced pressure (0.01 mmHg) at room temperature for periods of >6 h.

Analytical TLC on silica gel was performed on silica gel 60 F-254, 0.25 mm layer, 2.5 cm × 10 cm glass plates (American Scientific Products) that were visualized under UV light. Flash chromatography on 235–400-mesh silica gel 60 (J. T. Baker) was performed as described by Still.[41] Gravity flow chromatography was performed with 60–200-mesh silica gel 60 (J. T. Baker), which was slurry packed in the desired solvent.

Analytical TLC on cellulose was performed on EM Reagents F-254, 0.1-mm layer, 2.5 cm × 10 cm glass plates (American Scientific Products). These plates were visualized by either UV light or sulfosalicylic acid–ferric chloride stain. Flash cellulose chromatography was performed as described[7,8] on Whatman CF-11 fibrous cellulose.

A Waters Model 680 gradient HPLC system equipped with two M-45 pumps, a U6K injector, and a 441 UV detector was employed for the reversed-phase and anion exchange chromatography. Analytical reversed-phase chromatography was performed on either a C_{18} μBondapak (0.46 cm × 30 cm) column or a RCM-100 module cartridge. Preparative-scale reversed-phase work was performed on a Waters Prep-500 with a single reversed-phase cartridge. DEAE Fractogel (Pierce Chemical Co.) was packed into a 0.46 cm × 25 cm column (analytical) and a 2.0 cm × 30 cm column (preparative). All solvents were of HPLC grade and filtered prior to use. Ammonium bicarbonate solutions were made fresh each day by dissolving reagent-grade ammonium bicarbonate in HPLC-grade water prior to filtration.

2',3'-*O*-(Methoxymethylidene)-5'-*O*-tosyluridine (1). Uridine (1.22 g, 5.0 mmol) and 0.125 g (0.5 mmol) of pyridine-*p*-toluenesulfonic acid were stirred in tetrahydrofuran at room temperature. Trimethyl orthoformate (2.65 g, 25 mmol) was added via syringe, and the solution was stirred for 2 h. Water (450 g, 25 mmol) was then added. After 30 min, 0.5 mL of pyridine was added to quench the hydrolysis, and solvent was removed in vacuo to yield an off-white solid; TLC (R_f 0.4; 1:1 chloroform/acetone).[19]

The dry solid was dissolved in 50 mL of dichloromethane, and 0.78 g (6.5 mmol) of 4-DMAP and 1.15 g (6.0 mmol) of tosyl chloride were added as a solution in 10 mL of dichloromethane. The reaction mixture was stirred for 24 h, 60 mL of tetrahydrofuran was added, and the resulting precipitate was removed by filtration. The solution was concentrated to a foam, dissolved in 100 mL of chloroform, and extracted with three 20-mL portions of 5% sodium bicarbonate. The organic layer was dried over sodium sulfate. The solution was concentrated to yield 2.1 g (95%) of a white foam. Material for analysis was obtained by flash chromatography on silica gel: TLC (R_f 0.7; 10:1 chloroform/methanol); mp 110 °C dec; UV λ_{max} (CH_3CN) 227 (ε 19 490) 256 (12 480); ^1H NMR (300 MHz, $CDCl_3$) for diastereomer A and B 9.20 (1, s, H3), 7.86 (2, d, J = 8.3 Hz, phenyl H), 4.71 (2, d, J = 8.3 Hz, phenyl H), 7.30 (1, d, J = 8.0 Hz, H6), 6.04, 5.98 (1, s, acetal), 5.81 (1, d, J = 8.0 Hz, H5), 5.78 (1, d, J = 2.2 Hz, H1'), 5.00 (2, m, H2', H3'), 4.59 (1, m, H4'), 4.38 (2, m, H5', H5''), 3.46, 3.39 (3, s, OCH_3), 2.52 (3, s, CH_3). Anal. Calcd for $C_{18}H_{20}N_2O_9S\cdot H_2O$: C, 47.18; H, 4.80; N, 6.11. Found: C, 47.07; H, 4.31; N, 6.00.

5'-*O*-Tosyluridine (2). 2',3'-*O*-(Methoxymethylidene)-5'-*O*-tosyluridine (2.10 g, 4.7 mmol) was dissolved in 50 mL of a 1:1 (v/v) mixture of acetonitrile and 0.01 N hydrochloric acid, and

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1.0 N hydrochloric acid was added to the stirred solution until pH 2.0. The solution was stirred for 1 h, the pH was adjusted to 8 with aqueous ammonia, and stirring was continued for an additional 2 h. Acetonitrile was removed in vacuo and water was removed by lyophilization. The resulting white solid was purified by flash chromatography on silica gel, eluting with 85:15 chloroform/methanol to yield 1.63 g (87%) of a white foam: mp 112–115 °C;[15] TLC (R_f 0.3; 7:1 chloroform/methanol); IR (KBr) 1700, 1675, 1375, 1180; UV λ_{max} (CH_3CN) 226 (ϵ 17170) 262 (11120); ^1H NMR (300 MHz, Me_2SO-d_6) 11.39 (1, s, H3), 7.78 (2, d, J = 7.5 Hz, phenyl H), 7.46 (3, bd, phenyl H, H6), 5.70 (1, d, J = 4.7 Hz, H1′), 5.60 (1, d, J = 7.7 Hz, H5), 4.2–3.9 (7, m, sugar and OH's), 2.39 (3, s, CH_3); ^{13}C NMR (75 MHz, Me_2SO-d_6) 162.9, 150.5, 145.2, 140.6, 131.9, 130.1, 127.6, 101.9, 88.6, 80.7, 72.2, 69.9, 69.3, 21.0; FAB MS (glycerol) M + 1 399 (9), 156 (9), 113 (23), 93 (100, glycerol). Anal. Calcd for $C_{16}H_{18}N_2O_8S$: C, 48.24; H, 4.52; N, 7.04. Found: C, 48.75; H, 4.83; N, 6.92.

2′,3′-*O*-(Methoxymethylidene)-4-*N*-[(dimethylamino)-methylene]cytidine (3). A mixture of 2.0 g (8.24 mmol) of cytidine, 1.04 g (9.06 mmol) of pyridine hydrochloride, and 6.85 g (41 mmol) of trimethyl orthoformate was stirred in 50 mL of DMF for 48 h. Water (1 mL) was added, and the solution was stirred for 2 h. Pyridine (25 mL) was added, and solvent was removed in vacuo to yield a tacky, tan solid; TLC (R_f 0.5; 3:1 chloroform/methanol).[19]

Crude 2′,3′-*O*-(methoxymethylidene)cytidine (2.35 g, 8.24 mmol) and 1.96 g (16.5 mmol) of dimethylformamide dimethyl acetal were stirred in 20 mL DMF for 24 h. Dimethylformamide was removed in vacuo, and the final traces of solvent were removed by coevaporation with toluene to yield 2.91 g (104%) of a tacky, brown solid. Material for analysis was obtained by flash chromatography on silica gel:[22] mp 200–205 °C; TLC (R_f 0.4; 10:1 chloroform/methanol); UV λ_{max} (CH_3CN) 318 (ϵ 31000); ^1H NMR (300 MHz, $CDCl_3$) for diastereomer A and B 8.70 (1, s, H8), 7.31 (1, d, J = 7.9 Hz, H6), 5.93 (1, d, J = 7.9 Hz, H5), 5.78 (1, s, acetal), 5.40 (1, d, J = 2.9 Hz, H1′), 5.15 (2, m, H2′, H3′), 4.36 (1, m, H4′), 3.80 (2, m, H5′, H5″), 3.29 (3, s, OCH_3), 3.10 (3, s, NCH_3), 3.05 (3, s, NCH_3). Anal. Calcd for $C_{14}H_{20}N_4O_6 \cdot H_2O$: C, 46.95; H, 6.14; N, 15.64. Found: C, 47.25; H, 5.70; N, 15.63.

2′,3′-*O*-(Methoxymethylidene)-5′-*O*-tosyl-4-*N*-[(dimethylamino)methylene]cytidine (4). Crude 3 (2.80 g, 8.24 mmol) was stirred in 40 mL of dichloromethane. 4-DMAP (1.30 g, 10.7 mmol) and 1.90 g (9.9 mmol) of tosyl chloride were added as a solution in 10 mL of dichloromethane. The reaction mixture was stirred for 16 h, 50 mL of tetrahydrofuran was added, and the resulting precipitate was removed by filtration. The solution was concentrated to a foam, dissolved in 150 mL of chloroform, extracted twice with 20 mL of saturated ammonium chloride and twice with 20 mL of 5% sodium bicarbonate, and dried over anhydrous sodium sulfate. Solvent was removed in vacuo to give a tan solid which was purified by flash chromatography on silica gel to yield 2.80 g (67%) of a white foam: mp 215° C dec; TLC (R_f 0.5; acetone); UV λ_{max} (CH_3CN) 223 (ϵ 24880) 325 (20000); ^1H NMR (300 MHz, $CDCl_3$) diastereomer A and B 8.77 (1, s, H8), 7.75 (2, d, J = 8.1 Hz, phenyl H), 7.32 (3, m, phenyl H, H6), 6.00 (1, d, J = 6.6 Hz, H5), 5.87 (1, s, acetal), 5.53 (1, s, H1′), 5.19 (1, d, J = 7.3 Hz, H2′), 4.91 (1, m, H3′), 4.52 (1, m, H4′), 4.35 (2, m, H5′, H5″), 3.36 (3, s, OCH_3), 3.17 (3, s, NCH_3), 3.14 (3, s, NCH_3), 2.40 (3, s, CH_3). Anal. Calcd for $C_{22}H_{26}N_4O_8S$: C, 52.18; H, 5.14; N, 11.06. Found: C, 51.92; H, 5.14; N, 10.65.

5′-*O*-Tosylcytidine (5). Pure 4 (2.0 g, 3.95 mmol) was dissolved in 50 mL of a 1:1 (v/v) mixture of acetonitrile and 0.01 N hydrochloric acid, and 1.0 N hydrochloric acid was added to the stirred solution until pH 2.0. The solution was stirred for 24 h. The pH was adjusted to 8.0 with aqueous ammonia, and stirring was continued for an additional 2 h. Acetonitrile was removed in vacuo, and water was removed by lyophilization to yield a white powder. The solid was dissolved in a 6:4 (v/v) mixture of acetonitrile and 0.05% trifluoroacetic acid and purified by preparative reversed-phase HPLC using the same solvent. Solvent was removed to yield 1.37 g (87%) of a white powder: mp 120–122° C;[15] TLC (R_f 0.2; 5:1 chloroform/methanol); IR (KBr) 1720, 1684, 1400, 1375, 1180; UV λ_{max} (CH_3CN) 221 (ϵ 22900) 262 (9165); ^1H NMR (300 MHz, Me_2SO-d_6) 7.79 (2, d, J = 7.5 Hz, phenyl H), 7.65 (1, d, J = 7.3 Hz, H6), 7.48 (2, d, J = 7.5 Hz, phenyl H), 5.95 (1, d, J = 7.3 Hz, H5), 5.68 (1, d, J = 3.1 Hz, H1′), 4.27 (1, m, H4′), 4.1–3.6 (6, m), 2.41 (3, s, CH_3); ^{13}C NMR (75 MHz, Me_2SO-d_6) 161.8, 150.5, 145.2, 142.9, 131.9, 130.1, 127.6, 94.3, 90.3, 80.5, 72.8, 69.8, 69.0, 21.0; FAB MS (glycerol) M + 1 398 (11), 155 (6), 154 (6), 139 (9), 112 (100), 93 (28, glycerol). Anal. Calcd for $C_{16}H_{19}N_3O_7S$: C, 48.36; H, 4.79; N, 10.58. Found: C, 48.66; H, 4.82; N, 10.26.

5′-*O*-Tosylthymidine (6). A mixture of 0.48 g (1.34 mmol) of 3′-*O*-(*tert*-butyldimethylsilyl)thymidine,[25] 1.12 g (1.75 mmol) of 4-DMAP, and 0.31 g (1.61 mmol) of tosyl chloride was stirred in 25 mL of dichloromethane for 6 h. Ethyl acetate (25 mL) was added, and the resulting precipitate was removed by filtration. The solution was concentrated to a foam, dissolved in 10 mL of a 1:1 (v/v) mixture of acetonitrile and 1% hydrofluoric acid, and stirred for 6 h. The solution was neutralized with 5% sodium bicarbonate, acetonitrile was removed in vacuo, and water was removed by lyophilization to yield a white powder. The resultant solid was suspended in 9:1 chloroform/methanol, filtered, and concentrated. The residue was purified by flash chromatography on silica gel to yield 0.41 g (85%) of a white foam: mp 180 °C dec;[12] TLC (R_f 0.6; 9:1 chloroform/methanol); IR (KBr) 1720, 1750, 1350, 1280, 1175; UV λ_{max} (CH_3CN) 221 (ϵ 27000), 265 (9360); ^1H NMR (300 MHz, acetone-d_6) 9.52 (1, s, H5), 7.81 (2, d, J = 8.3 Hz, phenyl H), 7.47 (2, d, J = 8.3 Hz, phenyl H), 7.44 (1, d, J = 1.6 Hz, H6) 6.26 (1, t, J = 6.8 Hz, H1′), 4.39 (1, bq, J = 3.9 Hz, H6′), 4.29 (2, dq, J = 3.4, 10.7 Hz, H5′, H5″), 4.04 (1, q, J = 4.4 Hz, H3′), 2.44 (3, s, CH_3), 2.24 (2, m, H2′, H2″), 1.82 (3, d, J = 1.6 Hz, CH_3); ^{13}C NMR 75 MHz (Me_2SO-d_6) 163.4, 150.2, 145.0, 135.8, 131.9, 130.0, 127.5, 109.7, 83.9, 83.1, 70.1, 69.9, 38.3, 21.2, 12.2; FAB MS (glycerol) M + 1 397 (2), 303 (5), 153 (2), 127 (8), 93 (100, glycerol). Anal. Calcd for $C_{17}H_{19}N_2O_7S$: C, 51.65; H, 4.81; N, 7.09. Found: C, 51.26; H, 5.07; N, 7.01.

2′,3′-*O*-(Methoxymethylidene)-2-*N*-[(dimethylamino)-methylene]guanosine (7). To a flask that contained 566 mg (2.0 mmol) of guanosine was added via syringe 5 mL (31.0 mmol) of trimethyl orthoformate followed by 350 mg (3.0 mmol) of pyridine hydrochloride. The stirred suspension was treated with 0.7 mL of Me_2SO and stirring was continued for 48 h. The resultant cloudy suspension cleared after addition of 5 mL of methanol and 180 mg (3.3 mmol) of sodium methoxide. After 3 h, the mixture was concentrated to give a thick creamy suspension which was treated with a 1:1 diethyl ether/methanol. An off-white solid was obtained by filtration and the material was dried. TLC (R_f 0.24; 8:2 chloroform/methanol).[19]

The solid was suspended in 18 mL of acetonitrile under nitrogen and treated in sequence with 1.0 mL (6.0 mmol) of diisopropylethylamine and 0.7 mL (5.3 mmol) of dimethylformamide dimethyl acetal. After 15 h, the white suspension was concentrated to one-half volume and filtered to yield 690 mg (90%) of an off-white solid. A pure sample was obtained by chromatography on silica gel. After drying, 532 mg (70%) of a white powder was obtained: TLC (R_f 0.35; 9:1 chloroform/methanol); UV λ_{max} (CH_3CN) 237.5 (ϵ 19500), 276 (11800), 306 (18600); ^1H NMR (300 MHz, $CDCl_3$) diastereomer A and B 9.9 (1, s, H1), 8.45 (1, s, H8), 7.72, 7.68, (1, s, N=CH), 5.98, 5.91 (1, s, acetal), 6.03, 5.81, (1, d, H1′), 5.33, 5.26 (1, m, H2′), 5.13 (1, m, H3′), 4.42, 4.35 (1, d, H4′), 3.90 (1, m, H5′), 3.76 (1, m, H5″), 3.39, 3.28 (3, s, OCH_3), 3.12 (3, s, N $(CH_3)_2$), 2.98 (3, s, N $(CH_3)_2$). Anal. Calcd for $C_{15}H_{20}N_6 \cdot H_2O$: C, 45.22; H, 5.56; N, 21.1. Found: C, 44.88; H, 5.19; N, 20.69.

2′,3′-*O*-(Methoxymethylidene)-5′-*O*-tosyl-2-*N*-[(dimethylamino)methylene]guanosine (8). Protected guanosine 7 (177 mg, 0.466 mmol) was dissolved in 3.5 mL of chloroform under nitrogen before sequential addition of 115 mg (0.65 mmol) of tosyl chloride and 80 mg (0.65 mmol) of 4-DMAP. The reaction mixture was stirred for 15 h, concentrated, and purified by silica gel chromatography (2 cm × 15 cm) to yield 190 mg (80%) of a white powder: TLC (R_f 0.44; 9:1 chloroform/methanol); UV λ_{max} (CH_3CN) 229 (ϵ 18780), 242 (12321), 276 (8062), 308 (13290); ^1H NMR (300 MHz, $CDCl_3$) diastereomer A and B 9.63 (1, s, H1), 8.48 (1, s, H8), 7.70 (2, d, phenyl H), 7.54 (1, s, N=CH), 7.16 (2, d, phenyl H), 5.98, 5.92 (1, s, acetal H), 5.96, 5.86 (1, d, H1′) 5.50, 5.45 (1, dd, H2′), 5.18, 5.08 (1, dd, H3′) 4.45, 4.28 (1, q, H4′), 4.25 (1, m, H5′), 4.16 (1, m, H5″), 3.38, 3.31 (3, s, OCH_3), 3.2 (3, s, $N(CH_3)_2$), 3.09 (3, s, $N(CH_3)_2$), 2.43 (3, s, tosyl CH_3). Anal. Calcd for $C_{22}H_{26}N_6O_8S \cdot H_2O$: C, 47.82; H, 5.11; N, 15.21. Found: C, 47.89; H, 4.85; N, 15.22.

5'-O-Tosylguanosine (9). A 430-mg (0.81 mmol) sample of the fully protected guanosine tosylate 8 was dissolved in 9 mL of a 2:1 (v/v) mixture of methanol and water. To this solution was added 0.4 mL (592 mg, 5.2 mmol) of trifluoroacetic acid. After 14 h, the mixture was concentrated to 4 mL before diluting with a 2:1 (v/v) mixture of water and ethanol. The suspension was treated with 400 mg (5.0 mmol) of ammonium bicarbonate and warmed to achieve a solution which produced a fine white powder upon cooling to 4 °C. The material was recovered by filtration and was dried to yield 265 mg (75%) of a white powder judged to be >95% pure by reversed-phase HPLC (35:65 methanol/0.1% aqueous trifluoroacetic acid). A homogenous sample was obtained after purification by reversed-phase HPLC: mp 171 °C dec;[19] UV λ_{max} (CH_3CN) 225 (ε 16 240) 258 (13 100) 275 (8730); IR (KBr) 1675, 1375, 1185, 1175; ^1H NMR (300 MHz, Me_2SO-d_6) 7.77 (1, s, H8), 7.73 (2, d, J = 8.2 Hz, phenyl H), 7.37 (2, d, J = 8.2 Hz, phenyl H), 5.66 (1, d, J = 5.1 Hz, H1'), 4.38 (1, t, J = 5.0 Hz, H2'), 4.24 (2, m, H5', H5''), 4.11 (1, t, J = 4.5 Hz, H3'), 3.48 (1, q, J = 4.5 Hz, H4'), 2.36 (3, s, phenyl CH_3); ^{13}C NMR (75 MHz, Me_2SO-d_6) 156.9, 153.8, 151.3, 145.1, 135.5, 132.1, 130.1, 127.6, 118.2, 86.9, 81.2, 73.0, 70.5, 70.1, 21.1; FAB MS (glycerol) M + 1 438 (7), 284 (3), 277 (5), 194 (3), 166 (5), 152 (72), 93 (100, glycerol). Anal. Calcd for $C_{17}H_{19}N_5O_7S{\cdot}H_2O$: C, 44.83; H, 4.65; N, 15.38. Found: C, 45.10; H, 4.25; N, 15.34.

5'-O-Tosyl-3'-O-(*tert*-butyldimethylsilyl)-2'-deoxyadenosine (10). In a dry flask under nitrogen was dissolved 1 g (2.97 mmol) of 3'-O-(tert-butyldimethylsilyl)-2'-deoxyadenosine[25] in 25 mL of dichloromethane. To this solution was added 611 mg (5.0 mmol) of 4-DMAP, and the resultant mixture was cooled to 0 °C before the addition of 622 mg (3.26 mmol) of tosyl chloride in 5 mL of dichloromethane over a 15-min period. The reaction mixture was kept at 4 °C for 20 h before being warmed to room temperature for 0.5 h. Solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (4 cm × 18 cm; 98:2 chloroform/methanol) to yield 1.3 g (89%) of a white solid: mp 149–151 °C; TLC (R_f 0.32; 95:5 chloroform/methanol); UV λ_{max} (CH_3CN) 229.5 (ε 14 300), 261 (14 700); ^1H NMR (300 MHz, $CDCl_3$) 8.26 (1, s, H8), 7.91 (1, s, H2), 7.70 (2, d, J = 8.2 Hz, phenyl H), 7.24 (2, d, J = 8.2 Hz, phenyl H), 6.33 (1, t, J = 6.7 Hz, H1'), 5.84 (2, s, N6), 4.61 (1, dt, J = 6.7 Hz, J = 3.6 Hz, H3'), 4.24 (1, dd, J = 10.8 Hz, J = 4.1 Hz, H5''), 4.08 (1, dt, J = 4.3 Hz, J = 4.1 Hz, J = 3.6 Hz, H4'), 2.82 (1, dt, J = 14.1 Hz, J = 5.9 Hz, J = 6.7 Hz, H2'), 2.34 (3, s, phenyl CH_3), 2.34 (1, m, H2''), 0.87 (9, s, *t*-Bu), 0.07 (6, s, $(CH_3)_2Si$); ^{13}C NMR (75 MHz, $CDCl_3$) 155.3, 152.8, 145.0, 139.1, 132.2, 129.7, 127.8, 84.7, 84.6, 76.6, 72.3, 68.7, 40.0, 25.7, 21.7, 18.0, -4.8, -4.6. Anal. Calcd for $C_{23}H_{33}N_5O_5SSi$: C, 53.16; H, 6.40; N, 13.48. Found: C, 53.21; H, 6.30; N, 13.20.

5'-O-Tosyl-2'-deoxyadenosine (13). Tosylate **10** (1 g, 2.04 mmol) was suspended in 50 mL of acetonitrile before addition of 50 mL of 2% aqueous hydrofluoric acid. After 24 h, a homogeneous solution was obtained that was neutralized with solid ammonium bicarbonate. Acetonitrile was removed in vacuo; and water was removed by lyophilization. The resultant off-white solid was extracted with 9:1 chloroform/methanol and filtered prior to purification by flash chromatography on silica gel (5 cm × 12 cm) to yield 402 mg (73%) of a white foam: TLC (R_f 0.31; 9:1 chloroform/methanol); mp 146–148 °C;[11] UV λ_{max} 229 (ε 16 400), 267 (16 260); IR (KBr) 1675, 1450, 1375; ^1H NMR (300-MHz, CD_3CN) 8.13 (1, s, H8), 7.93 (1, s, H2), 7.60 (2, d, J = 8.2 Hz, phenyl H), 7.23 (2, d, J = 8.2 Hz, phenyl H), 6.28 (1, t, J = 6.6 Hz, H1'), 6.21 (2, s, N6), 4.53 (1, dt, J = 7.0 Hz, J = 5.1 Hz, H3'), 4.27 (1, dd, J = 11.5 Hz, J = 4.0 Hz, H5') 4.21 (1, dd, J = 11.5 Hz, J = 5.0 Hz, H5''), 4.06 (1, dt, J = 5.0 Hz, J = 4.0 Hz, H4'), 2.81 (1, dt, J = 13.7 Hz, J = 7.0 Hz, H2') 2.36 (1, m, H2''), 2.35 (3, s, phenyl CH_3); ^{13}C NMR (75 MHz, CD_3CN) 156.6, 153.4, 146.1, 140.4, 133.0, 130.5, 128.4, 126.4, 85.1, 84.9, 71.8, 70.8, 55.2, 39.4, 21.58; FAB MS (glycerol) M + 1 406 (6), 233 (3), 162 (4), 136 (100) 91 (13). Anal. Calcd for $C_{17}H_{19}N_5O_5S{\cdot}H_2O$: C, 48.22; H, 4.99; N, 16.54. Found: C, 48.24; H, 4.66; N, 16.16.

Tris(tetra-*n*-butylammonium) Hydrogen Pyrophosphate (14). A solution of 3.33 g (15.0 mmol) of disodium dihydrogen pyrophosphate in 15 mL of 10% (v/v) aqueous ammonium hydroxide was passed through a 2.5 cm × 7.0 cm (58 mequiv) column of Dowex AG 50W-X8 cation exchange resin (100–200-mesh hydrogen form). The free acid was eluted with 100 mL of deionized water, and the resulting solution (pH 1.2) was immediately titrated to pH 7.3 with 40% (wt/wt) aqueous tetra-*n*-butylammonium hydroxide. The resulting solution (approximately 150 mL total volume) was dried by lyophilization to yield 13.1 g (97%) of a hygroscopic white solid: ^1H NMR (90 MHz, D_2O) 0.83–1.01 (36, m, CH_3), 1.14–1.73 (48, m, CH_2), 3.03–3.19 (24, m, CH_2); ^{31}P NMR (121 MHz, D_2O) -1.60 (s).

The resulting hydrate from above can be purified by recrystallization. A 2.5-g portion of the white solid was partially dried by twice treating with 75 mL of acetonitrile and azeotropic removal of solvent by rotary evaporation to yield a tacky solid. This material was warmed (40 °C) in 50 mL of ethyl acetate before gravity filtration. The clear, colorless filtrate was concentrated to one-half volume by rotary evaporation and cooled to -20 °C. Short, white needles were recovered on sintered glass and washed with diethyl ether. Typical recoveries were 40–55%. The water content of the resulting hygroscopic solid was determined by ^1H NMR in C_6D_6 and it was found to contain 3 equiv of water.

Tris(tetra-*n*-butylammonium) Hydrogen Methanediphosphonate (15). A solution of 1.0 g (5.68 mmol) of methanediphosphonic acid in 20 mL of deionized water (pH 1.0) was titrated to pH 10.0 with 40% (w/w) aqueous tetra-*n*-butylammonium hydroxide. The resulting solution (approximately 32 mL total volume) was dried by lyophilization to yield 4.97 g (97%) of a hygroscopic, oily solid: ^1H NMR (300 MHz, D_2O) 0.87 (36, m, CH_3), 1.27 (24, m, CH_2), 1.84 (2, t, $J_{H,P}$ = 20.6 Hz), 3.10 (24, m, CH_2), 4.83 (1, s, OH); ^{13}C NMR (75 MHz, D_2O) 15.2, 21.3, 25.2, 31.0 (t, $J_{C,P}$ = 112.7 Hz), 60.2; ^{31}P NMR (121 MHz, D_2O) 16.07 (s).

Tris(tetra-*n*-butylammonium) Hydrogen Difluoromethanediphosphonate (16). The preparation of tetrakis(trimethylsilyl) difluoromethanediphosphonate has been reported elsewhere.[8] To 15 mL of deionized water was added 4.5 g (10.5 mmol) of the silyl phosphonate and the resulting suspension was stirred for 45 min. The phases were separated and the aqueous phase was washed with two 15-mL portions of diethyl ether. The aqueous solution (pH 1.0) was titrated to pH 7.3 with 40% aqueous tetra-*n*-butylammonium hydroxide. The resulting solution (approximately 75 mL total volume) was dried by lyophilization to yield 8.92 g (91%) of a hygroscopic white solid: ^1H NMR (300 MHz, D_2O) 0.93 (36, m, CH_3), 1.35 (24, m, CH_2), 1.63 (24, m, CH_2), 3.18 (24, m, CH_2), 4.83 (1, s, OH); ^{13}C NMR (75 MHz, D_2O) 15.1, 21.2, 25.2, 60.0, 122.7 (tt, $J_{C,P}$ = 231.0 Hz, $J_{C,F}$ = 272.7 Hz); ^{31}P NMR (121 MHz, D_2O) 5.4 (t, $J_{F,P}$ = 79.1 Hz); ^{19}F NMR (282 MHz, D_2O) 121.1 (t, $J_{F,P}$ = 80.4 Hz).

Tetrakis(tetra-*n*-butylammonium) Hydrogen Triphosphate (17). A solution of pentasodium tripolyphosphate (2 g, 4.2 mmol) in 20 mL of deionized water was passed through a 1 cm × 16 cm column (21 mequiv) of DOWEX AG 50W-X8 cation exchange resin (100–200 mesh hydrogen form) at 4 °C. The free acid was eluted with 40 mL of deionized water, and the resulting cold solution was titrated to pH 7.0 with 40% (w/v) aqueous tetra-*n*-butylammonium hydroxide. Water was removed by lyophilization to yield 2.4 g (89%) of a white solid which was stored over phosphorus pentoxide until used: ^1H NMR (90 MHz, D_2O) 0.93–1.01 (36, m, CH_3), 1.14–1.73 (48, m, CH_2), 3.03–3.19 (24, m, CH_2); ^{31}P NMR (121 MHz, D_2O) -7.74 (d, J = 20 Hz), -22.11 (t, J = 20 Hz).

A General Procedure for Preparation of 5'-Nucleoside Diphosphates. The displacement reactions were performed in oven-dried round-bottomed flasks equipped for magnetic stirring under a nitrogen atmosphere at room temperature. The nucleoside tosylates (0.1 to 0.5 mmol) were dissolved in acetonitrile to a concentration of 1.0 to 1.5 M and tris(tetra-*n*-butylammonium) hydrogen pyrophosphate (1.5 equiv) was added to the stirred solution. High concentrations of tosylate and pyrophosphate were necessary for the reactions to proceed at reasonable rates. The progress of each reaction was monitored by changes in the ^1H NMR chemical shifts for the tosylate AA'XX' spin system, where the four-line pattern for the tosylate moves upfield by approximately 0.1 ppm upon conversion to the tosylate anion (see Figure 1). Upon completion, the reaction mixture was diluted with 5–10 volumes of water and tetra-*n*-butylammonium cation was exchanged for ammonium by passing the solution through a DOWEX AG 50W-X8 column (100–200 mesh, 30 equiv, ammonium form) and eluting with 2 column volumes of deionized water. The

eluent was lyophilized, and the resultant white solid was extracted with acetonitrile/100 mM ammonium bicarbonate/concentrated ammonium hydroxide (7:3:2). The soluble material was loaded onto a CF-11 cellulose flash column (2 cm × 25 cm) and eluted with the same solvent. Cellulose TLC was employed to follow the progress of the chromatography. The fractions containing product were pooled, and acetonitrile was removed by rotary evaporation. The resulting aqueous solution was lyophilized to yield the phosphorylated nucleosides as white powders; all cellulose TLC (R_f 0.2, 7:3:2 acetonitrile/100 mM ammonium bicarbonate/concentrated ammonium hydroxide) were similar for the nucleoside diphosphates and stated when different.

An alternative workup involved dilution of the concentrated reaction mixtures with 1 mL of water and filtration through a 0.45-μm Millex filter. The resultant filtrate was purified by a linear gradient elution from a DEAE Fractogel (2 cm × 30 cm) column with ammonium bicarbonate (0.05–0.5 M), pH 7.8 at a flow rate of 1.5 mL min^{-1} over 2 h. The desired fractions were dried by lyophilization, and excess ammonium bicarbonate was removed by repeated lyophilization from deionized water after adjustment to pH 7.0 with carbon dioxide.

Uridine 5′-Diphosphate (18). Following the general procedure, 133 mg (0.33 mmol) of 5′-*O*-tosyluridine in 0.2 mL of acetonitrile and 452 mg (0.5 mmol) of tris(tetra-*n*-butylammonium) hydrogen pyrophosphate were allowed to react for 48 h to give 88 mg (58%) of a white powder.

An alternative procedure involved addition of 40 mg (0.1 mmol) of 5′-*O*-tosyluridine to a solution containing 191 mg (0.2 mmol) of tris(tetra-*n*-butylammonium) hydrogen pyrophosphate trihydrate (recrystallized) in 0.3 mL of dry acetonitrile. The stirred solution was maintained under a nitrogen atmosphere for a total of 30 h before being diluted with 1.5 mL of water and filtered prior to purification by anion exchange chromatography (DEAE Fractogel). Pooled fractions were dried by lyophilization to yield 21 mg (54%) of a fluffy white solid: ^{1}H NMR (90 MHz, D_2O) 7.98 (1, d, J = 8 Hz, H6), 5.92 (1, d, J = 5 Hz, H1′), 5.90 (1, d, J = 8 Hz, H5). 4.27 (5, m); ^{13}C NMR (75 MHz, D_2O) 163.3, 154.3, 144.7, 105.4, 91.8, 85.9 (d, $J_{C,P}$ = 9.6 Hz), 76.7, 72.1, 67.1 (d, $J_{C,P}$ = 4.9 Hz); ^{31}P NMR (121 MHz, D_2O) −5.6 (d, J = 22 Hz), −10.0 (d, J = 22 Hz).

Cytidine 5′-Diphosphate (19). Following the general procedure, 66 mg (0.66 mmol) of 5′-*O*-tosylcytidine in 0.1 mL of acetonitrile and 226 mg (0.25 mmol) of tris(tetra-*n*-butylammonium) hydrogen pyrophosphate were allowed to react for 72 h to yield 40 mg (53%) of a white powder: ^{1}H NMR (90 MHz, D_2O) 7.93 (1, d, J = 7.2 Hz, H6), 6.1 (1, d, J = 9 Hz, H5), 5.95 (1, d, J = 2.3 Hz, H1′), 4.22 (5, m); ^{13}C NMR (75 MHz, D_2O) 168.7, 160.2, 144.8, 99.5, 92.5, 85.6, 77.1, 72.0, 67.3; ^{31}P NMR (121 MHz, D_2O) −6.95 (d, $J_{P,P}$ = 21.8 Hz), −11.27 (d, $J_{P,P}$ = 21.8 Hz).

Thymidine 5′-Diphosphate (20). Following the general procedure, 40 mg (0.101 mmol) of 5′-*O*-tosylthymidine and 136 mg (0.14 mmol) of tris(tetra-*n*-butylammonium) hydrogen pyrophosphate in 0.1 mL of acetonitrile were allowed to react for 24 h to yield 38 mg (83%) of a white powder: ^{1}H NMR (90 MHz, D_2O) 7.60 (1, s, H6), 6.20 (1, t, J = 7.2 Hz, H1′), 4.1 (4, m), 2.25 (2, m, H2′), 1.76 (3, s, CH_3); ^{13}C NMR (75 MHz, D_2O) 169.3, 154.5, 140.1, 138.4, 114.5, 88.1 (d, $J_{C,P}$ = 9.0 Hz), 87.6, 73.6, 67.9 (d, $J_{C,P}$ = 3.0 Hz), 41.2; ^{31}P NMR (121 MHz, D_2O) −10.4 (d, $J_{P,P}$ = 16.9 Hz), −12 (d, $J_{P,P}$ = 16.9 Hz).

Guanosine 5′-Diphosphate (21). A. 5′-*O*-Tosylguanosine (54 mg, 0.124 mmol) was dissolved in 0.5 mL of acetonitrile, and 170 mg (0.188 mmol) of tris(tetra-*n*-butylammonium) hydrogen pyrophosphate was added. The reaction was allowed to continue 5 days before workup to yield 26 mg (43%) of a white powder.

B. The above reaction was repeated in 0.15 mL of 1:1 acetonitrile/dimethyl sulfoxide. Tosylate was consumed after 24 h, and workup yielded 16 mg (26%) of the same material: ^{1}H NMR (90 MHz, D_2O) 8.15 (1, br s, H8), 5.82 (1, d, J = 6.3 Hz, H1′), 4.18 (5, m); ^{13}C NMR (75 MHz, D_2O) 161.7, 156.8, 154.5, 140.4, 118.9, 89.8, 86.6 (d, $J_{C,P}$ = 8 Hz), 76.8, 73.2, 68.0 (d, $J_{C,P}$ = 4 Hz); ^{31}P NMR (121 MHz, D_2O) −9.36 (d, $J_{P,P}$ = 20.7 Hz), −10.36 (d, $J_{P,P}$ = 20.7 Hz).

2′,3′-*O*-Isopropylideneadenosine 5′-Diphosphate (22). 2′,3′-*O*-Isopropylidene-5′-*O*-tosyladenosine (210 mg, 0.5 mmol) was dissolved in 0.2 mL of acetonitrile before addition of 600 mg (0.655 mmol) of tris(tetra-*n*-butylammonium) hydrogen pyrophosphate. The solution was stirred for 2 h before workup to yield 206 mg (93%) of a white powder: TLC cellulose (R_f 0.15; 7:3:2 acetonitrile/100 mM ammonium bicarbonate/concentrated ammonium hydroxide); ^{1}H NMR (90 MHz, D_2O) 8.45 (1, s, H8), 8.14 (1, s, H2), 6.23 (1, d, J = 3.6 Hz, H1′), 5.4 (2, m), 4.75 (1, br s), 4.30 (2, m), 1.84 (3, s, CH_3), 1.6 (3, s, CH_3); ^{13}C NMR (75 MHz, D_2O) 157.7, 155.3, 151.1, 142.9, 120.9, 118.0, 92.7, 87.4, 86.8, 84.1, 68.3, 29.1, 27.3; ^{31}P NMR (121 MHz, D_2O) −7.27 (d, $J_{P,P}$ = 20.7 Hz), −10.35 (d, $J_{P,P}$ = 20.7 Hz).

Adenosine 5′-Diphosphate (23). Following the general procedure, 140 mg (0.33 mmol) of 5′-*O*-tosyladenosine in 0.2 mL of acetonitrile and 451 mg (0.495 mmol) of tris(tetra-*n*-butylammonium) hydrogen pyrophosphate were allowed to react for 24–48 h to give 113 mg (74%) of a white powder: ^{1}H NMR (90 MHz, D_2O) 8.45 (1, s, H8), 8.06 (1, s, H2), 6.06 (1, d, J = 6.1 Hz, H1′), 4.73 (1, m), 4.6 (1, m), 4.31 (3, m); ^{13}C NMR (75 MHz, D_2O) 158.2, 155.6, 151.5, 142.8, 121.2, 90.2, 86.4 (d, $J_{C,P}$ = 9.0 Hz), 77.3, 72.8, 67.5 (d, $J_{C,P}$ = 3.7 Hz); ^{31}P NMR 121 MHz, D_2O) −5.6 (d, $J_{P,P}$ = 21.8 Hz), −9.9 (d, $J_{P,P}$ = 21.8 Hz).

Adenosine 5′-Methanediphosphonate (24). Following the general procedure, 140 mg (0.33 mmol) of 5′-*O*-tosyladenosine in 0.2 mL of acetonitrile was allowed to react with 500 mg (0.495 mmol of tris(tetra-*n*-butylammonium) hydrogen methanediphosphonate for 48 h to yield 109 mg (72%) of a white powder: ^{1}H NMR (90 MHz, D_2O) 8.46 (1, s, H8), 8.09 (1, s, H2), 6.08 (1, d, J = 6.3 Hz, H1′), 4.76 (1, m), 4.56 (1 m), 4.43 (1, m), 4.22 (2, m), 2.2 (2, dt, $J_{H,P}$ = 19.5 Hz, $J_{H,H}$ = 6.75 Hz); ^{13}C NMR (75 MHz, D_2O) 158.3, 155.7, 151.7, 142.8, 121.3, 90.1, 86.7 (d, $J_{C,P}$ = 7.3 Hz), 77.2, 73.1, 66.4 (d, $J_{C,P}$ = 21.8 Hz), 30.4 (t, $J_{C,P}$ = 125.4 Hz); ^{31}P NMR (121 MHz, D_2O) 19.4 (d, $J_{P,P}$ = 9.5 Hz), 15.3 (d, $J_{P,P}$ = 21.8 Hz).

Adenosine 5′-Difluoromethanediphosphonate (25). Following the general procedure, 350 mg (0.33 mmol) of 5′-*O*-tosyladenosine was dissolved in 0.5 mL of acetonitrile and allowed to react with 1.17 g (1.25 mmol) of tris(tetra-*n*-butylammonium) hydrogen difluoromethanediphosphonate for 66 h. The mixture was diluted with 10 mL water before being subjected to a cation exchange (3.5 cm × 16 cm) column. After lyophilization, the sample was purified by flash cellulose chromatography (3.5 cm × 25 cm) to yield 253 mg (54%) of a white powder: TLC cellulose (R_f 0.15; 7:3:2 acetonitrile/100 mM ammonium bicarbonate/concentrated ammonium hydroxide); ^{1}H NMR (300 MHz, D_2O) 8.48 (1, s, H8), 8.16 (1, s, H2), 6.10 (1, d, J = 5.4 Hz, H1′), 4.85 (1, m), 4.66 (1, m), 4.48 (1, m), 4.43 (2, m); ^{13}C NMR (75 MHz, D_2O) 158.3, 155.7, 151.4, 142.7, 124.3 (ddt, $J_{C,P}$ = 168.6 Hz, $J_{C,P}$ = 157.5 Hz, $J_{C,F}$ = 258.8 Hz), 121.4, 90.1, 86.7 (d, $J_{C,P}$ = 7 Hz), 77.3, 73.1, 68.3 (d, $J_{C,P}$ = 6.1 Hz); ^{19}F NMR 282 MHz (D_2O) 117.6 (dd, $J_{P,F}$ = 93.6 Hz, $J_{P,F}$ = 72.8 Hz); ^{31}P NMR (121 MHz, D_2O) 3.8 (dt, $J_{P,P}$ = 52 Hz, $J_{P,F}$ = 93.6 Hz), 0.97 (dt, $J_{P,P}$ = 52.0 Hz, $J_{P,F}$ = 72.8 Hz).

Adenosine 5′-Triphosphate (26). In 0.3 mL of acetonitrile was dissolved 245 mg (0.2 mmol) of tetra-*n*-butylammonium hydrogen triphosphate prior to the addition of 42 mg (0.1 mmol) of 5′-*O*-tosyladenosine. The solution was stirred for 23 h before dilution with 1 mL water and filtration. The sample was purified by anion exchange chromatography on DEAE Fractogel to yield 31 mg (55%) of a fluffy white powder: ^{1}H NMR (300 MHz, D_2O) 8.58 (1, s, H8), 8.40 (1, s, H2), 6.10 (1, d, J = 5.3 Hz), 4.68 (1, m), 4.54 (1, m), 4.32 (1, m), 4.19 (2, m); ^{13}C NMR (75 MHz, D_2O) 152.3, 150.4, 147.8, 144.5, 120.5, 90.3, 86.6 (d, $J_{C,P}$ = 9 Hz), 77.5, 72.7, 67.7 (d, $J_{C,P}$ = 6.7 Hz); ^{31}P NMR (121 MHz, D_2O) −10.1 (d, $J_{P,P}$ = 17.9 Hz), −11.5 (d, $J_{P,P}$ = 19.5 Hz), −23.0 (dd, $J_{P,P}$ = 17.9 Hz, $J_{P,P}$ = 19.5 Hz).

2′-Deoxyadenosine 5′-Difluoromethanediphosphonate (27). Following the general procedure, 150 mg (0.37 mmol) of 5′-*O*-tosyl-2′-deoxyadenosine was dissolved in 0.3 mL of acetonitrile and allowed to react with 557 mg (0.52 mmol) of tris(tetra-*n*-butylammonium) hydrogen difluoromethanediphosphonate for 48 h. The mixture was diluted with 5 mL of water before cation exchange chromatography (3.5 cm × 13 cm column). After lyophilization, the sample was purified by flash cellulose chromatography (3.0 cm × 17 cm) to yield 95 mg (48%) of a white powder: ^{1}H NMR (300 MHz, D_2O) 8.49 (1, s, H8), 8.21 (1, s, H2), 6.49 (1, t, J = 7.1 Hz), 4.25 (4, m), 2.88 (1, m, H2′), 2.60 (1, m, H2″); ^{13}C NMR (75 MHz, D_2O) 157.6, 154.7, 150.7, 142.0, 126.2 (ddt, $J_{C,F}$ = 273.9 Hz, $J_{C,P}$ = 176.0 Hz, $J_{C,P}$ = 165.4 Hz), 121.0, 88.3 (d, $J_{C,P}$

= 7.6 Hz), 86.3, 73.7, 67.8, 41.8; ^{19}F NMR (282 MHz, D_2O) 116.7 (dd, $J_{P,F}$ = 89.1 Hz, $J_{P,F}$ = 73.3 Hz); ^{31}P NMR (121 MHz, D_2O) 3.86 (dt, $J_{P,P}$ = 51.9 Hz, $J_{P,F}$ = 73.3 Hz), 0.70 (dt, $J_{P,P}$ = 51.9 Hz, $J_{P,F}$ = 89.1 Hz).

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Registry No. 1 (*S* diastereomer), 107201-92-3; 1 (*R* diastereomer), 107269-58-9; 2, 24380-35-6; 3 (*S* diastereomer), 107201-93-4; 3 (*S* diastereomer), 107201-99-0; 4 (*S* diastereomer), 107201-94-5; 4 (*R* diastereomer), 107202-00-6; 5, 50615-57-1; 6, 7253-19-2; 7 (*S* diastereomer), 107222-38-8; 7 (*R* diastereomer), 107202-01-7; 8 (*S* diastereomer), 107201-95-6; 8 (*R* diastereomer), 107202-02-8; 9, 39947-33-6; 10, 107201-96-7; 13, 6698-29-9; 14, 76947-02-9; 15, 93978-76-8; 16, 107202-03-9; 17, 93978-77-9; 18, 58-98-0; 19, 63-38-7; 20, 491-97-4; 21, 146-91-8; 22, 36373-38-3; 23, 58-64-0; 24, 3768-14-7; 25, 107201-97-8; 26, 56-65-5; 27, 107201-98-9; 2′,3′-*O*-isopropylidene-5′-*O*-tosyladenosine, 5605-63-0; 5′-*O*-tosyladenosine, 5135-30-8; uridine, 58-96-8; cytidine, 65-46-3; 2′-(*S*)-2′,3′-*O*-(methoxymethylidene)cytidine, 107297-06-3; 3′-*O*-(*tert*-butyldimethylsilyl)thymidine, 40733-27-5; guanosine, 118-00-3; 3′-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine, 51549-31-6; 2′(*R*)-2′,3′-*O*-(methoxymethylidene)cytidine, 107297-07-4.

Scope and Limitations of the Cuprate–Acetylene–Vinyltriphenylphosphonium Bromide–Aldehyde Reaction: Synthesis of (6*Z*,9*Z*)-Heneicosadiene

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Syntheses of (6*Z*,9*Z*)-heneicosadiene, a component of the sex attractant secretion of the female arctiid moth (*Uthetheisa ornatrix*), and of triene **6**, a useful precursor for the synthesis of (8*S*)-HETE, are described using a one-pot four-component (cuprate–acetylene–vinyltriphenylphosphonium bromide–aldehyde) reaction. The use of 1-iodo-1-alkenes as an alternative to Normant's alkenylcuprate methodology is demonstrated.

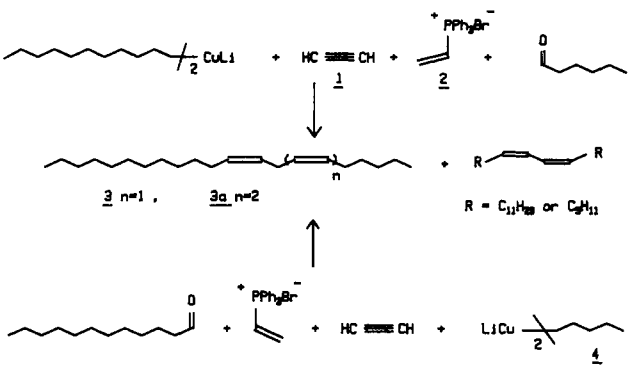
We recently described a general synthesis of 1,5-dialkylpenta-1(*Z*),4(*Z*)-dienes[1] using a one-pot four-component (cuprate–acetylene–vinyltriphenylphosphonium bromide–aldehyde) reaction. This procedure has now been applied to the syntheses of (6*Z*,9*Z*)-heneicosadiene (**3**), a component isolated from the sex attractant secretion of the female arctiid moth (*Uthetheisa ornatrix*) recently synthesized by Meinwald et al.[2] and of triene **6**, a useful precursor for the synthesis of (8*S*)-HETE.[4]

Results and Discussion

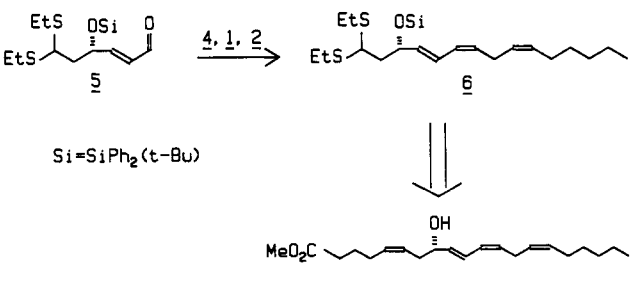
In our approach to the synthesis of (6*Z*,9*Z*)-heneicosadiene (**3**), we could envision starting from 1-undecylcuprate or 1-pentylcuprate as illustrated in Scheme I. When acetylene was introduced into a solution of 1-undecylcuprate[3] and the corresponding 1-tridecenylcuprate treated with vinyltriphenylphosphonium bromide, HMPA, and hexanal, a mixture of (6*Z*,9*Z*)-heneicosadiene (**3**), the diacetylene addition product (6*Z*,9*Z*,11*Z*)-tricosatriene, 1-tridecene, and the alkenyl cross-coupling product ($C_{11}H_{23}CH{=}CH)_2$ were obtained.

Since separation of these hydrocarbons was troublesome, the same sequence was repeated using pentylcuprate **4**.[3] The difficult part in the process was control of the amount of acetylene which added, and on a 1-mmol scale, the desired diene **3** was contaminated with 20–25% of **3a** where two molecules of acetylene had reacted with the pentylcuprate. Kugelrohr distillation gave a 40% yield of **3**, contaminated with 10% of **3a**, as determined by GC/

Scheme I



Scheme II



(1) Just, G.; O'Connor, B. *Tetrahedron Lett.* **1985**, *26*, 1799–1802.
(2) Jain, S. C.; Dussourd, D. E.; Conner, W. E.; Eisner, T.; Guerrero, A.; Meinwald, J. *J. Org. Chem.* **1983**, *48*, 2266–2270.
(3) 1-Undecylcuprate or 1-Pentylcuprate were prepared by treating the appropriate 1-bromo derivative, in THF, with *tert*-butyllithium (2 equiv) at −78 °C for 20 min followed by the addition of CuBr/SMe_2 (0.5 equiv) and stirring at −50 °C for 1 h.

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