Nucleic Acid Related Compounds. **81**. Syntheses of 9-(3-deoxy-β-D-*threo*-pentofuranosyl)adenine, the Core Nucleoside of the Extraordinarily Selective Antibiotic Agrocin 84, and Simplified Structural Component Analogues†

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Dedicated to the memory of Professor Roland K. Robins

Alternative syntheses of 9-(3-deoxy-β-D-*threo*-pentofuranosyl)adenine (**4**), the core nucleoside of agrocin 84 [and its 2'-deoxy *threo* isomer **5**] were devised: (1) direct conversion of 9-(β-D-arabinofuranosyl)adenine into 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine and regioselective opening of its oxirane ring with sodium borohydride to give **4** and **5** (~7.5:1); (2) treatment of adenosine with sodium hydride and 2,4,6-triisopropylbenzenesulfonyl chloride, and subjection of the resulting 2'(3')-sulfonates to the reductive [1,2]-hydride shift rearrangement with lithium triethylborohydride to give **4** and **5** (~2:1); and (3) subjection of the phenoxythiocarbonyl esters of 9-[2(3),5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-arabinofuranosyl]adenine to Barton deoxygenation, and deprotection to give **4** and 2'-deoxyadenosine (~5:1). Methods (2) and (3) gave lower yields. Syntheses of simplified 6-*N*- and 5'-*O*-adenosine phosphoramidate model compounds were explored to examine potential access to such features in the structure proposed for agrocin 84.

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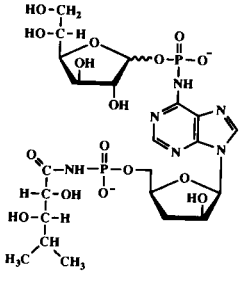
Agrocin 84 is an extraordinarily selective antibiotic produced by *Agrobacterium tumefaciens* K 84. Its proposed structure **1** contains elements of an adenine nucleotide analogue [1-3]. It inhibits nucleic acid [3-5] and protein [3,5] biosynthesis and prevents the attachment of virulent *A. tumefaciens* strains to host plant cells [6]. It is considered to be bacteriostatic [6] and inhibits virulent bacterial growth [4,7]. Sensitivity of *A. tumefaciens* to agrocin 84 is conferred by genes on the tumor-inducing plasmid [8] which also govern virulence, [9-11] nopaline metabolism, [12,13] and host specificity [14-16].



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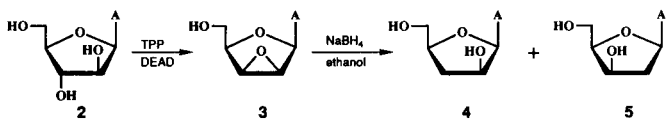
The first synthesis of the core nucleoside of agrocin 84, 9-(3-deoxy-β-D-*threo*-pentofuranosyl)adenine, and its regioisomer, 9-(2-deoxy-β-D-*threo*-pentofuranosyl)adenine, was reported by Goodman and coworkers [17]. This and other multistage methods [17-19] gave low overall yields. We reported the [1,2]-hydride shift rearrangement of 3'-*O*-tosyladenosine to give 9-(3-deoxy-β-D-*threo*-pentofuranosyl)adenine [20]. Although this final step proceeded well (82%), the synthesis included the specific preparation of 3'-*O*-tosyladenosine.

We now report three procedures which give different regioselectivities and utilize different nucleosides. Treatment of 9-(β-D-arabinofuranosyl)adenine (**2**) (Scheme 1) with triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) [21,22] gave 9-(2,3-anhydro-β-D-lyxofuranosyl)-adenine (**3**). Our solvent choice was dimethylformamide since **3** was obtained in repeatably high yields with no troublesome side products [23]. Our repetition of the reported procedure (dioxane at 70° for 50 minutes [22]) gave **3** in lower yields, and similar results were obtained with acetonitrile. This approach [22] is convenient since no protection of the 5'-OH group is needed. Treatment of **3** with excess sodium borohydride in 98% ethanol at reflux gave 9-(3-deoxy-β-D-*threo*-pentofuranosyl)adenine (**4**, 84%) and 9-(2-deoxy-β-D-*threo*-pentofuranosyl)adenine (**5**, 11%). Analogous treatment of **3** with sodium borohydride in *tert*-butyl alcohol/methanol [24] also gave **4** as the predominant product, but unreacted **3** always remained. Separation of **3** and **4** was effected readily by ion-exchange chromatography on Dowex 1 x 2(OH^-) resin [25].

Scheme 1

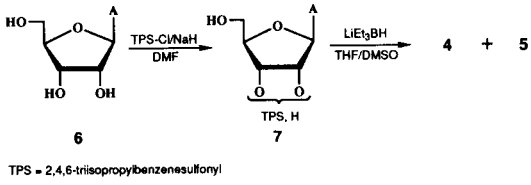


2 **3** **4** **5**

Treatment of adenosine (**6**) (Scheme 2) with sodium hydride and 2,4,6-triisopropylbenzenesulfonyl chloride (TPS-Cl) in dimethylformamide gave the 2'-*O*- and 3'-*O*-

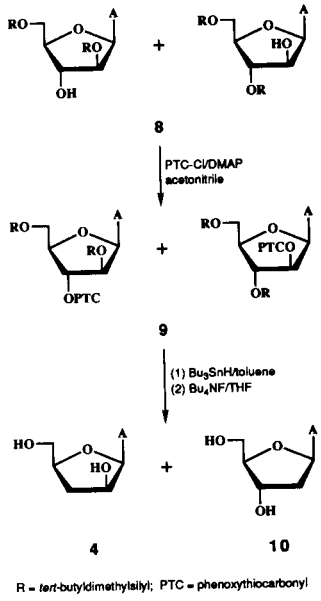
(2,4,6-triisopropylbenzenesulfonyl)adenosines (**7**, 80%), whose separation was difficult. Treatment [20] of this mixture with lithium triethylborohydride in dimethylsulfoxide/tetrahydrofuran gave **4**/**5** (2:1, 52%).

Scheme 2



Protection of 9-(β-D-arabinofuranosyl)adenine (**2**) with *tert*-butyldimethylsilyl chloride and silver nitrate in pyridine gave the 2′,5′- and 3′,5′-bis-*O*-silylated intermediates **8** (Scheme 3) (~10:3, ^{1}H nmr) [26]. Treatment of **8** with phenyl chlorothionocarbonate (PTC-Cl) and 4-dimethylaminopyridine (DMAP) gave the silylated 3′- and 2′-*O*-phenoxythiocarbonyl mixture **9**. Deoxygenation of **9** with tributylstannane and α,α′-azobisisobutyronitrile (AIBN) in toluene at 75° [27,28], deprotection with tetrabutylammonium fluoride, and separation on Dowex 1 x 2(OH$^-$) resin gave 9-(3-deoxy-β-D-*threo*-pentofuranosyl)adenine (**4**, 37% overall from **2**) and 2′-deoxyadenosine (**10**) in a ratio of ~5:1.

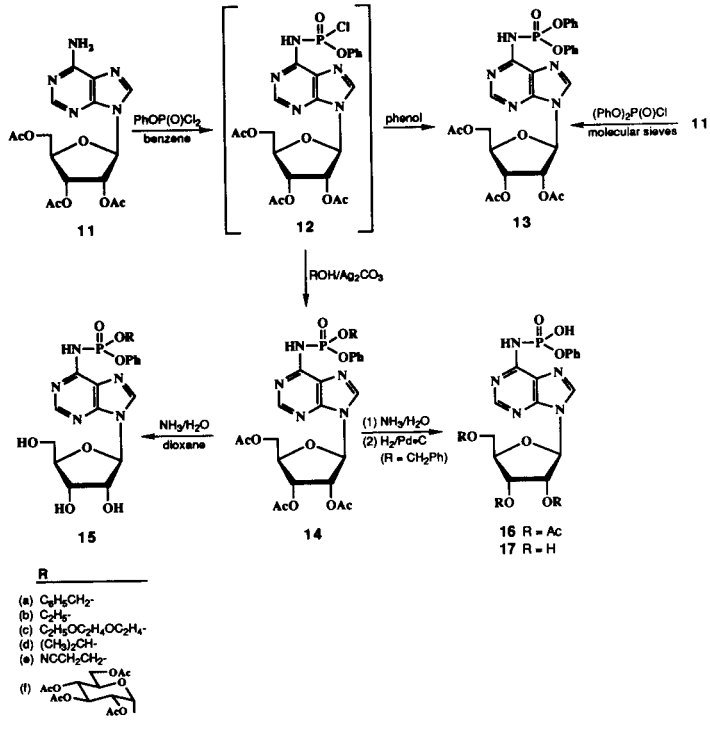
Scheme 3



Pfleiderer and coworkers treated 3′,5′-di-*O*-acetyl-2′-deoxyadenosine with diphenyl phosphorochloridate and obtained 6-*N*-phospho-nucleoside derivatives [29,30]. Treatment of aniline with phenyl phosphorodichloridate gave phenyl *N*-phenylphosphoramidochloridate, which converted alcohols into alkyl phenyl *N*-phenylphosphoramidates [31]. Since agrocin 84 (**1**) was postulated to have a D-glucofuranosyloxyphosphoryl substituent at N6 of the core nucleoside [1-3], we explored model reactions to evaluate conditions for possible attachment of a glucofuranosyl moiety to the 6-amino group through a phosphoramidate linkage.

Treatment of 2′,3′,5′-tri-*O*-acetyladenosine (**11**) [32] (Scheme 4) with phenyl phosphorodichloridate in refluxing benzene and addition of phenol to intermediate **12** gave 2′,3′,5′-tri-*O*-acetyl-6-*N*-(diphenylphosphoryl)adenosine (**13**, 64%). Treatment of **11** with diphenyl phosphorochloridate in refluxing benzene also gave **13** (60%). The latter yield was increased to 94% by inclusion of 4 Å molecular sieves [33], use of 8.5 equivalents of the phosphorylating agent, and extending the reflux period to 48 hours. Treatment of **11** with phenyl phosphorodichloridate and addition of benzyl alcohol to intermediate **12** gave 2′,3′,5′-tri-*O*-acetyl-6-*N*-(benzyl phenylphosphoryl)adenosine (**14a**, ≤40%). Addition of silver carbonate before the benzyl alcohol enhanced the yield to 63%. This enhancement with silver carbonate was general and gave the 2′,3′,5′-tri-*O*-acetyl-6-*N*-(alkyl phenylphosphoryl)adenosines (**14**) in yields of 58-76%. Compound **14e** had ultraviolet absorption and other data identical to those reported [29].

Scheme 4



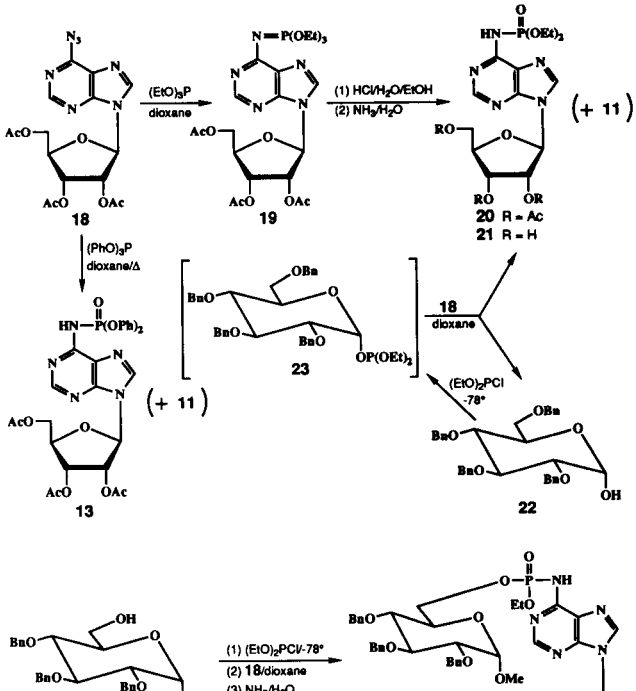
Merck 7734 silica was unsuitable for purification of these compounds, and yields were considerably lowered by chromatography over this adsorbant. The acid lability of the N-P bond of phosphoramidates (**14**) required neutralization of the silica gel by treatment with anhydrous 1,2-dimethoxyethane saturated with ammonia at 0° in order to obtain good yields. The phosphoramidates **14** were deacetylated with aqueous ammonia in dioxane [29] to give

the 6-*N*-(alkyl phenylphosphoryl)adenosines (**15**) in virtually quantitative yields. Hydrogenation of **14a** and **15a** (10% palladium·charcoal/95% ethanol) gave 2',3',5'-tri-*O*-acetyl- (**16**) and 6-*N*-(phenylphosphoryl)adenosine (**17**). The uv spectra of these compounds were similar to those of agrocin 84.

One coupling reaction of **12** with 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose [34] apparently gave **15f** (~7%) (uv and fast atom bombardment ms, insufficient material for other analyses). Further attempts to repeat couplings with this sugar or with 2,3,5,6-tetra-*O*-benzyl-D-glucofuranose failed.

Treatment of 5'-azido-5'-deoxynucleosides with phosphites had given 5'-phosphoramidate diesters [35,36], and phosphoramidate dinucleotide analogues had been obtained by treatment of 5'-azido-5'-deoxythymidine with diethyl thymidin-3'-yl phosphite [37,38]. We applied this azide-phosphite (Staudinger reaction) approach for the synthesis of nucleoside 6-phosphoramidates with the 2',3',5'-tri-*O*-acetyl derivative **18** (Scheme 5) of 6-azido-9-(β-D-ribofuranosyl)purine [39,40] as substrate.

Scheme 5



Treatment of **18** (uv max 286 nm) with triethyl phosphite in dioxane at ambient temperature resulted in a rapid shift of the uv maximum to ~269 nm. The resulting 6-phosphorimidite **19** (uv max 266 nm) was stirred with dilute ethanolic hydrochloric acid to give nearly equal amounts of 2',3',5'-tri-*O*-acetyladenosine (**11**) and 2',3',5'-tri-*O*-acetyl-6-*N*-(diethylphosphoryl)adenosine (**20**). Deacetylation of **20** gave 6-*N*-(diethylphosphoryl)adenosine (**21**).

Azidonucleoside **18** did not react readily with triphenyl phosphite in dioxane and remained at ambient temperature over a prolonged period (uv). Reflux of this mixtue for four hours gave phosphoramidate **13** plus 2',3',5'-tri-*O*-acetyladenosine (**11**). The markedly different reactivities probably result from the reduced nucleophilicity of triphenyl phosphite.

Treatment of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**22**) [41,42] with diethyl phosphorochloridite [43] at -78° was presumed to give mixed phosphite **23**. Further treatment with azidonucleoside **18** in dioxane gave 2',3',5'-tri-*O*-acetyl-6-*N*-(diethylphosphoryl)adenosine (**20**) by presumed preferential loss of the sugar alcohol **22** which was recovered quantitatively (Scheme 5). The presence of lithium chloride (to promote elimination of the ethyl group [37]) had no effect. An analogous sequence beginning with 2,3,5,6-tetra-*O*-benzyl-D-glucofuranose and diphenyl phosphorochloridite gave **13**, again with presumed loss of the sugar moiety.

Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**24**) [44] reacted smoothly with diethyl phosphorochloridite to give the mixed phosphite, which was treated with azidonucleoside (**18**) to give 2',3',5'-tri-*O*-acetyl-6-*N*-[ethyl (methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranosid-6-yl)phosphoryl]adenosine (**25**, 72%), with selective elimination of the ethyl group. Deacetylation gave 6-*N*-[ethyl (methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranosid-6-yl)phosphoryl]adenosine (**26**, 85%). The assigned structures were consistent with their ultraviolet, ^{1}H nmr, and fast atom bombardment mass spectra and elemental analyses.

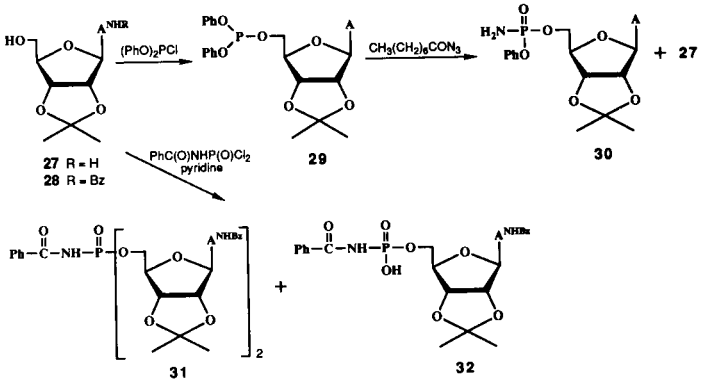
The azide-phosphite (Staudinger) procedure for the synthesis of nucleoside phosphoramidates is appealing relative to methods that employ carbodiimides, arylsulfonyl chlorides, or their derivatives [45]. The spontaneous coupling of phosphite and azide produces no activating agent by-products, the reaction is selective, and yields are usually good to high. However, only the mixed phosphite in which the carbohydrate was attached through the primary C6 coupled with the nucleoside azide to give a product that retained the carbohydrate moiety in the resulting phosphoramidate **25**.

Approaches to model compounds with a 5'-*O*-[RC(O)-NHP(O)] functionality analogous to that in agrocin 84 were briefly explored. Octanamide was chosen to mimic the D-*threo*-2,3-dihydroxy-4-methylpentanamide of the antibiotic. Octanoyl chloride and ethyl octanoate were converted to octanoyl azide [46,47]. Treatment of 2',3'-*O*-isopropylideneadenosine (**27**) with diphenyl phosphorochloridite [48] gave 2',3'-*O*-isopropylidene-5'-*O*-(diphenylphosphityl)adenosine (**29**). Phosphite **29** and octanoyl azide in refluxing ether/dioxane gave **27** and 2',3'-*O*-iso-

propylidene-5′-*O*-(phenylphosphoramidatyl)adenosine (**30**) in a ratio of ~1:1.9. No ^{1}H nmr signals for the octanoyl group were observed. Good yields of **30** were obtained when the acyl azide/phosphite ratio was 5:1.

However, treatment of 6-*N*-benzoyl-2′,3′-*O*-isopropylideneadenosine (**28**) [49] [easily prepared by Jones' transient protection [50] of **27**] with *N*-benzoyl phosphoramidodichloridate [51] gave a mixture of 6-*N*-benzoyl-5′-*O*-[(*N*-benzoyl)phosphoramidatyl]-2′,3′-*O*-isopropylideneadenosine (**32**), a nucleoside with a 5′-*O*-[ArC(O)NHP(O)] model functionality, and the bis(nucleosidyl)phosphoramidate **31**. Thus, simplified model compounds that contain primitive features of the structure proposed for agrocin 84 have been prepared. However, significant effort would be required to achieve a total synthesis of the antibiotic.

Scheme 6



EXPERIMENTAL

General Procedures.

Melting points were determined on a Reichert microstage apparatus and are uncorrected. The ^{1}H nmr spectra were recorded on Varian HA-100, Brucker WH-200, Brucker AM-300, or Brucker WH-400 spectrometers operating in the FT mode. Tetramethylsilane was used as internal reference in deuterated dimethylsulfoxide unless specified otherwise. Ultraviolet (uv) spectra of methanol solutions were recorded on a Hewlett Packard HP-8450A spectrophotometer. Mass spectra (ms) were determined by the mass spectrometery laboratory of the University of Alberta with AEI MS-50 (70 eV, direct probe, for electron impact spectra) or KRATOS/AEI MS-9 (for fast atom bombardment spectra) spectrometers. Elemental analyses were determined by the microanalytical laboratory of the University of Alberta.

Flash evaporations were effected with rotary evaporators with Dewar "Dry Ice" condensers under water or mechanical oil pump vacuum at ≤40°. Tlc was performed on Merck silica gel 60-F_{254} sheets with sample observation under uv (254 nm) light and/or by spraying with sulfuric acid/ethanol (95:5, v/v) and charring. Preparative layer chromatography (plc) was performed on glass plates coated with Merck silica gel PF_{254}. Solvents used for tlc were chloroform/methanol: (99:1, v/v), (19:1, v/v), (9:1, v/v), (4:1, v/v), and chloroform-acetone (19:1, v/v). Silica gel chromatography was performed with Mallinckrodt CC-7 (200 mesh) or Merck 7734 (100-200 mesh) silica gel. Silica gel[§] refers to Merck 7734 (100-200 mesh) silica gel soaked in anhydrous 1,2-dimethoxyethane (presaturated with ammonia at 0°) at 0° for 2 days, filtered, and dried. Anion exchange chromatography was performed on Dowex 1 x 2(OH^-) resin. All solvents and reagents were distilled prior to use. Dried solvents were stored over 4Å molecular sieves.

The ^{1}H nmr spectral abbreviations are: br = broad signal, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, 'dd' = overlapping doublet of doublets of doublets, q = quartet, s = singlet, 's' = overlapping singlets, br s = broad singlet, t = triplet, and 't' = overlapping doublet of doublets.

Mass spectral abbreviations are: C_7H_7 = benzyl and C_7H_7O = benzyloxy.

The general three step sequence for the mixed 6-*N*-phosphorylnucleosides is described for 2′,3′,5′-tri-*O*-acetyl-6-*N*-(benzyl phenylphosphoryl)adenosine (**14a**) and 6-*N*-(benzyl phenylphosphoryl)-adenosine (**15a**). Subsequent descriptions refer to Procedure A: treatment of 2′,3′,5′-tri-*O*-acetyladenosine (**11**) with phenyl phosphorodichloridate; Procedure B: reflux of the mixture after addition of silver carbonate and alcohol to the solution from Procedure A followed by filtration, evaporation of the filtrate, and chromatography of the residue on silica gel[§]; Procedure C: deacetylation with aqueous ammonia in dioxane, evaporation, and chromatography of the residue on silica gel[§].

9-(2,3-Anhydro-β-D-lyxofuranosyl)adenine (**3**).

A 267 mg (1 mmole) sample of 9-(β-D-arabinofuranosyl)adenine (**2**) was dissolved by heating with 7 ml of dry dimethylformamide. The solution was cooled to 0°, 656 mg (2.5 mmoles) of triphenylphosphine was added, and the reaction mixture was stirred for 10-15 minutes. A solution of 400 μl (2.54 mmoles) of diethyl azodicarboxylate in 7 ml of dry dimethylformamide was added over a period of 10 minutes at 0°. Stirring was continued at 0° for 15 minutes and at ambient temperature for 2 hours. Evaporation, trituration of the residue with ether, and recrystallization from methanol gave 192 mg (77%) of **3**, mp 208-210° dec, (lit mp 208-210° dec, and other physical data in harmony with those reported [52]).

9-(3-Deoxy-β-D-*threo*-pentofuranosyl)adenine (**4**) and 9-(2-deoxy-β-D-*threo*-pentofuranosyl)adenine (**5**).

Method A.

A sample of **3** (249 mg, 1 mmole) and 1.9 g (50 mmoles) of sodium borohydride were refluxed in 50 ml of 98% ethanol for 20 hours. The solution was cooled, evaporated, and the residue was dissolved in 20 ml of water. The solution was neutralized to *p*H 6 with 10% aqueous acetic acid, concentrated, and applied to a column of Dowex 1 x 2(OH^-) resin (2 x 20 cm). The column was eluted with water, the eluate was concentrated, and the residue was crystallized from methanol to give 30 mg (11%) of **5**, mp 218-220°, (lit mp 218.9-219.5° [17]); ^{1}H nmr: δ 2.3 (m, $J_{2'-2''}$ = 14.5 Hz, 1, H-2′), 2.8 (m, 1, H-2″), 3.68 (m, 2, H-5′,5″), 3.93 (m, 1, H-4′), 4.36 (m, 1, H-3′), 4.71 ("t", $J_{OH-5',5''}$ = 5.5 Hz, 1, OH-5′), 5.99 (d, $J_{OH-3'}$ = 5.6 Hz, 1, H-3′), 6.28 (dd, $J_{1'-2'}$ = 2.5 Hz, $J_{1'-2''}$ = 8.5 Hz, 1, H-1′), 7.36 (br s, 2, NH_2), 8.17 (s, 1, H-2), 8.38 (s, 1, H-8); ms: m/z 251.1018 (4.6, $M^+[C_{10}H_{13}N_5O_3]$ = 251.1015), 221.0893 (0.6, M - CH_2O), 162.0775 (57, $BHCH{=}CH_2$), 136.0609 (36, B + 2H), 135.0546 (100, B + H).

Anal. Calcd. for $C_{10}H_{13}N_5O_3$: C, 47.81; H, 5.22; N, 27.88. Found: C, 47.51; H, 5.15; N, 27.56.

Further elution of the column with methanol/water (3:7), evaporation of the eluate, and crystallization of the residue from methanol gave 210 mg (84%) of **4**, mp 198-200° (lit mp 195-196° [17]); ^{1}H nmr: δ 2.05 (m, 1, H-3'), 2.3 (m, 1, H-3''), 3.6 (m, 2, H-5',5''), 4.1 (m, 1, H-4'), 4.6 (m, 1, H-2'), 5.15 (''t'', $J_{OH-5',5''}$ = 5.0 Hz, 1, OH-5'), 5.4 (d, $J_{OH-2'}$ = 5.2 Hz, 1, OH-2'), 6.15 (d, $J_{1'-2'}$ = 5.0 Hz, 1, H-1'), 7.23 (br s, 2, NH_2), 8.14 (s, 1, H-2), 8.3 (s, 1, H-8); ms: m/z 251.1018 (6.2, M-[$C_{10}H_{13}N_5O_3$] = 251.1019), 221.0910 (8.1, M - CH_2O), 164.0574 (100, BHCHO), 162.0778 (1.8, BHCH=CH_2), 136.0616 (45, B + 2H), 135.0547 (97, B + H).

Anal. Calcd. for $C_{10}H_{13}N_5O_3$: C, 47.81; H, 5.22; N, 27.88. Found: C, 47.80; H, 5.22; N, 27.87.

Method B.

Adenosine (**6**) (534 mg, 2 mmoles) was dissolved by heating in 14 ml of dry dimethylformamide and the solution was cooled to -23° in a Dry Ice/carbon tetrachloride bath. Sodium hydride (130 mg, 5.4 mmoles) was added (50% dispersion in mineral oil washed with with dry benzene under nitrogen and transferred in ~3 ml of dry dimethylformamide at -23°) and the mixture was stirred at -23° for ~20 minutes and treated with 726 mg (2.4 mmoles) of 2,4,6-triisopropylbenzenesulfonyl chloride. Stirring at -23° was continued for 6 hours, the solution was evaporated, and the yellow oil was chromatographed on silica gel with chloroform/methanol (19:1) to give 853 mg (80%) of a mixture of 2'-*O*- and 3'-*O*-(2,4,6-triisopropylbenzenesulfonyl)adenosines (**7**); ms: m/z 533.2289 (1.4, M-[$C_{25}H_{35}N_5O_6S$] = 533.2308), 162.0776 (1.6, BHCH=CH_2), 136.0619 (100, B + 2H), 135.0544 (80, B + H).

To a cold stirred solution of this mixture (853 mg, 1.6 mmoles) of **7** in dry dimethylsulfoxide (41 ml) was added 1 *M* lithium triethylborohydride in tetrahydrofuran (20.5 ml) and stirring was continued for 2 hours in an ice-bath and 40 hours at ambient temperature. The reaction mixture was **carefully** quenched with 50 ml of water while being purged with nitrogen gas in an efficient fume hood. Concentration of the solution *in vacuo*, chromatography of the syrup on Dowex 1 x 2(OH^-) resin with water followed by methanol/water (3:7), evaporation of pooled fractions, and recrystallization of the residues from methanol gave 132 mg (17%) of **5**, mp 218-220°; and 278 mg (35%) of **4**, mp 198-200° with spectral data identical to those of Method A.

Method C.

Silylation of **2** gave 9-[2,5- and 3,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-arabinofuranosyl]adenine (**8**) [26] (~10:3). To a suspension of 496 mg (1 mmole) of **8** in 15 ml of dry acetonitrile was added 366 mg (3 mmoles) of 4-dimethylaminopyridine and 200 μl (1.45 mmoles) of phenyl chlorothionocarbonate. The solution was stirred for 15 hours at ambient temperature, evaporated, and the residue was partitioned between ethyl acetate and water. The organic phase was washed (saturated aqueous sodium bicarbonate, water, and brine), dried (sodium sulfate), and evaporated. The foam was chromatographed on silica with chloroform/methanol (97:3) to give a mixture (475 mg, 75%) of 9-[2,5-bis-*O*-(*tert*-butyldimethylsilyl)-3-*O*-phenoxythiocarbonyl-β-D-arabinofuranosyl]adenine and 9-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-2-*O*-phenoxythiocarbonyl-β-D-arabinofuranosyl]adenine (**9**).

To a solution of this mixture of **9** (475 mg, 0.75 mmole) in 8 ml of dry toluene was added 895 μl (3.32 mmoles) of tributylstannane and 95 mg (0.58 mmole) of α,α'-azobisisobutyronitrile and stirring was continued overnight with heating at 75°. Flash evaporation gave a residue which was deprotected with 1 *M* tetrabutylammonium fluoride in tetrahydrofuran (3 ml), evaporated, and partitioned between ether and water. The aqueous phase was chromatographed on Dowex 1 x 2(OH^-) resin with methanol/water (3:17) and the residue was recrystallized from ether/ethanol to give 17.5 mg (9%) of 2'-deoxyadenosine (**10**), mp 191-192° (lit mp 191-192° and spectral data in harmony with those reported [28]). Further elution with methanol/water (3:7) and recrystallization of the residue from methanol gave 88 mg (45%) of **4**, mp 198-200° and spectral data identical with those from Method A.

2',3',5'-Tri-*O*-acetyl-6-*N*-(diphenylphosphoryl)adenosine (**13**).

To a refluxing solution of 129 μl (0.86 mmole) of phenyl phosphorodichloridate in 3 ml of dry benzene was added 236 mg (0.6 mmole) of 2',3',5'-tri-*O*-acetyladenosine (**11**) and 6 ml of dry benzene. The mixture was refluxed for ~10 hours (until a clear solution resulted), 113 mg (1.2 mmoles) of phenol was added, and reflux was continued for 4 hours. Evaporation *in vacuo* and chromatography of the residue on silica gel[§] with chloroform/methanol (49:1) gave 240 mg (64%) of **13**, mp 69-71° (lit mp 78-80° [29]); uv (methanol): λ max 260 nm (ε 22,000), min 226 nm (ε 5,000); (H^+) λ max 260 nm (ε 21,000), min 230 nm (ε 4,600); (OH^-) λ max 277 nm (ε 33,000), min 238 nm (ε 5,500); ^{1}H nmr: δ 2.00, 2.05, 2.13 (3 s, 3 x 3, 3 x acetate), 4.26 (m, $J_{5'-5''}$ = 12.5 Hz, $J_{5'-4'}$ = 6.5 Hz, 1, H-5'), 4.4 (m, 2, H-4',5''), 5.64 (''t'', $J_{3'-4'}$ = 5.0 Hz, $J_{3'-2'}$ = 5.5 Hz, 1, H-3'), 6.02 (''t'', $J_{2'-3'}$ = 5.5 Hz, $J_{2'-1'}$ = 5.5 Hz, 1, H-2'), 6.3 (d, $J_{1'-2'}$ = 5.5 Hz, 1, H-1'), 7.15-7.5 (m, 10, 2 x C_6H_5), 8.62 (''s'', 2, H-2,8), 10.5 (br, 1, NH); ms: m/z (glycerol/fast atom bombardment) = 626 (MH^+).

Anal. Calcd. for $C_{28}H_{28}N_5O_{10}P$: C, 53.76; H, 4.51; N, 11.19. Found: C, 53.75; H, 4.50; N, 10.90.

2',3',5'-Tri-*O*-acetyl-6-*N*-(benzyl phenylphosphoryl)adenosine (**14a**).

To a refluxing solution of 215 μl (1.44 mmoles) of phenyl phosphorodichloridate in 10 ml of dry benzene was added 393 mg (1 mmole) of **11**. The mixture was refluxed for ~10 hours until a clear solution resulted and no **11** was observed on tlc [chloroform/methanol (19:1)] and then was cooled to ambient temperature (Procedure A). A 400 mg (1.45 mmoles) portion of silver carbonate and 207 μl (2 mmoles) of benzyl alcohol were added and the mixture was refluxed for 4 hours. The mixture was cooled, filtered, evaporated, and the residue was chromatographed on silica gel[§] with chloroform/methanol (49:1) (Procedure B). Evaporation of appropriate fractions gave 300 mg (63%) of **14a** as an amorphous solid, mp 79-81°; uv (methanol): λ max 259 nm (ε 20,200), min 234 nm (ε 13,800); (H^+) λ max 260 nm (ε 18,600), min 229 nm (ε 9,800); (OH^-) λ max 276 nm (ε 29,000), min 241 nm (ε 10,000); ^{1}H nmr: δ 2.00, 2.04, 2.13 (3 s, 3 x 3, 3 x acetate), 4.28 (m, $J_{5'-4'}$ = 6.5 Hz, $J_{5'-5''}$ = 12.5 Hz, 1, H-5'), 4.42 (m, 2, H-4',5''), 5.3 (d, $J_{H-C-O-P}$ = 7.5 Hz, 2, CH_2Ph), 5.65 (''t'', $J_{3'-4'}$ = 5.0 Hz, $J_{3'-2'}$ = 5.5 Hz, 1, H-3'), 6.04 (''t'', $J_{2'-1'}$ = 5.5 Hz, $J_{2'-3'}$ = 5.5 Hz, 1, H-2'), 6.3 (d, $J_{1'-2'}$ = 5.5 Hz, 1, H-1'), 7.18-7.5 (m, 10, 2 x C_6H_5), 8.58 (s, 1, H-2), 8.62 (s, 1, H-8), 10.28 (br, 1, NH); ms: m/z (glycerol/fast atom bombardment) = 640 (MH^+).

Anal. Calcd. for $C_{29}H_{30}N_5O_{10}P$: C, 54.46; H, 4.73; N, 10.95. Found: C, 54.76; H, 4.81; N, 10.65.

2',3',5'-Tri-*O*-acetyl-6-*N*-(ethyl phenylphosphoryl)adenosine (**14b**).

Procedure A (0.1 mmole) was followed by Procedure B with 400 mg of silver carbonate and 117 μl (2 mmoles) of ethanol. Reflux for 2 hours and purification of the residue on silica gel[§] gave 346

mg (60%) of **14b**, mp 57-59°; uv (methanol): λ max 258 nm (ε 18,100), min 225 nm (ε 4,600); (H^+) λ max 260 nm (ε 16,200), min 225 nm (ε 4,900); (OH^-) λ max 276 nm (ε 23,000), min 239 nm (ε 2,800); ^{1}H nmr: δ 1.28 (t, J = 7.5 Hz, 3, CH_2CH_3), 2.01, 2.05, 2.14 (3 s, 3 x 3, 3 x acetate), 4.26 (m, 2, CH_2CH_3), 4.35 (m, 3, H-4',5',5''), 5.65 (''t'', $J_{3'-4'}$ = 5.0 Hz, $J_{3'-2'}$ = 5.5 Hz, 1, H-3'), 6.05 (''t'', $J_{2'-3'}$ = 5.5 Hz, $J_{2'-1'}$ = 5.5 Hz, 1, H-2'), 6.3 (d, $J_{1'-2'}$ = 5.5 Hz, 1, H-1'), 7.16-7.45 (m, 5, C_6H_5), 8.58 (s, 1, H-2), 8.63 (s, 1, H-8), 10.15 (br, 1, NH); ms: m/z (glycerol-sulfolane/fast atom bombardment) = 578 (MH^+).

Anal. Calcd. for $C_{24}H_{28}N_5O_{10}P$: C, 49.92; H, 4.89; N, 12.13. Found: C, 49.69; H, 4.93; N, 11.97.

2',3',5'-Tri-*O*-acetyl-6-*N*-[2-(2-ethoxyethoxy)ethyl phenylphosphoryl]adenosine (**14c**).

Procedure A (1 mmole) was followed by Procedure B with 400 mg of silver carbonate and 300 μl (2.2 mmoles) of 2-(2-ethoxyethoxy)ethanol. Reflux for 3 hours and purification of the residue on silica gel[§] gave 513 mg (77%) of **14c**, mp 38-40°; uv (methanol): λ max 259 nm (ε 19,100), min 226 nm (ε 10,300); (H^+) λ max 260 nm (ε 19,000), min 227 nm (ε 6,500); (OH^-) λ max 276 nm (ε 27,800), min 240 nm (ε 4,500); ^{1}H nmr: δ 1.05 (t, 3, CH_2CH_3), 2.0, 2.04, 2.12 (3 s, 3 x 3, 3 x acetate), 3.44 (m, 8, 4 x CH_2), 4.3 (m, 5, H-4',5',5'', P(O)OCH_2), 5.64 (''t'', $J_{3'-4'}$ = 5.0 Hz, $J_{3'-2'}$ = 5.8 Hz, 1, H-3'), 6.03 (''t'', $J_{2'-3'}$ = 5.8 Hz, $J_{2'-1'}$ = 5.0 Hz, 1, H-2'), 6.29 (d, $J_{1'-2'}$ = 5.0 Hz, 1, H-1'), 7.15-7.5 (m, 5, C_6H_5), 8.56 (s, 1, H-2), 8.62 (s, 1, H-8), 10.1 (br, 1, NH); ms: m/z (glycerol-sulfolane/fast atom bombardment) = 666 (MH^+).

Anal. Calcd. for $C_{28}H_{36}N_5O_{12}P$: C, 50.53; H, 5.45; N, 10.52. Found: C, 50.27; H, 5.74; N, 10.21.

2',3',5'-Tri-*O*-acetyl-6-*N*-(isopropyl phenylphosphoryl)adenosine (**14d**).

Procedure A (1 mmole) was followed by Procedure B with 400 mg of silver carbonate and 153 μl (2 mmoles) of isopropyl alcohol. Reflux for 2 hours and purification of the residue on silica gel[§] afforded 302 mg (65%) of **14d**, mp 35-37°; uv (methanol): λ max 259 nm (ε 19,800), min 225 nm (ε 4,100); (H^+) λ max 260 nm (ε 20,200), min 225 nm (ε 7,000); (OH^-) λ max 276 nm (ε 27,700), min 239 nm (ε 1,100); ^{1}H nmr: δ 1.3 (d, J = 6.5 Hz, 6, CH_2Me_2), 2.0, 2.05, 2.21 (3 s, 3 x 3, 3 x acetate), 4.28 and 4.85 (m, 1, C*H*-Me_2), 4.3 (m, 3, H-4',5',5''), 5.66 (''t'', $J_{3'-2'}$ = 5.0 Hz, $J_{3'-4'}$ = 5.0 Hz, 1, H-3'), 6.04 (''t'', $J_{2'-3'}$ = 5.0 Hz, $J_{2'-1'}$ = 5.5 Hz, 1, H-2'), 6.3 (d, $J_{1'-2'}$ = 5.5 Hz, 1, H-1'), 7.1-7.6 (m, 5, C_6H_5), 8.58 (s, 1, H-2), 8.62 (s, 1, H-8), 10.08 (br, 1, NH); ms: m/z (glycerol/fast atom bombardment) = 592 (MH^+).

2',3',5'-Tri-*O*-acetyl-6-*N*-(2-cyanoethyl phenylphosphoryl)adenosine (**14e**).

Procedure A (0.1 mmole) was followed by Procedure B with 40 mg of silver carbonate and 13.7 μl (0.2 mmole) of 2-cyanoethanol. Reflux for 2 hours and purification of the residue on silica gel[§] gave 35 mg (58%) of **14e**, mp 62-64° (lit mp 62-65°), and spectral data of **14e** were in harmony with those published [29].

6-*N*-(Benzyl phenylphosphoryl)adenosine (**15a**).

A 33 mg (0.05 mmole) solution of **14a** in 80 μl of dioxane was stirred with 360 μl of concentrated aqueous ammonia at ambient temperature overnight, evaporated to dryness, and the residue chromatographed on silica gel[§] (2 x 10 cm column) with chloroform/methanol (19:1) (Procedure C). Recrystallization from chloroform with diffusion of ether gave 22 mg (83%) of **15a**, mp 79-81°; uv (methanol): λ max 261 nm (ε 20,600), min 233 nm (ε 11,800); (H^+) λ max 261 nm (ε 19,700), min 230 nm (ε 7,500); (OH^-) λ max 276 nm (ε 28,200), min 240 nm (ε 6,900); ^{1}H nmr: δ 3.77 (m, $J_{5'-5''}$ = 12.5 Hz, 2, H-5',5''), 4.0 (m, 1, H-4'), 4.2 (m, 1, H-3'), 4.63 (''dd'', $J_{2'-1'}$ = 6.0 Hz, $J_{2'-3'}$ = 4.0 Hz, $J_{2'-OH-2'}$ = 6.0 Hz, 1, H-2'), 5.2 (m, 2, OH-3', OH-5'), 5.24 (d, $J_{H-C-O-P}$ = 8.0 Hz, 2, CH_2Ph), 5.55 (d, $J_{OH-2'}$ = 6.0 Hz, 1, OH-2'), 6.0 (d, $J_{1'-2'}$ = 6.0 Hz, 1, H-1'), 7.15-7.5 (m, 10, 2 x C_6H_5), 8.56 (s, 1, H-2), 8.66 (s, 1, H-8), 10.3 (br, 1, NH); ms: m/z (glycerol/fast atom bombardment) = 514 (MH^+).

Anal. Calcd. for $C_{23}H_{24}N_5O_7P \cdot 1.25H_2O$: C, 51.54; H, 4.98; N, 13.07. Found: C, 51.59; H, 4.75; N, 13.06.

6-*N*-(Ethyl phenylphosphoryl)adenosine (**15b**).

Procedure C was applied to 90 mg (0.16 mmole) of **14b** with 180 μl of dioxane and 800 μl of aqueous ammonia to give 65 mg (93%) of **15b** after recrystallization from chloroform with diffusion of diethyl ether, mp 87-89°; uv (methanol): λ max 260 nm (ε 18,700), min 227 nm (ε 3,200); (H^+) λ max 261 nm (ε 16,500), min 228 nm (ε 4,100); (OH^-) λ max 275 nm (ε 22,000), min 239 nm (ε 2,400); ^{1}H nmr: δ 1.28 (t, J = 8.0 Hz, 3, CH_2CH_3), 3.65 (m, 2, H-5',5''), 3.95 (m, 1, H-4'), 4.25 (m, 3, H-3', CH_2CH_3), 4.61 (''dd'', $J_{2'-3'}$ = 4.5 Hz, $J_{2'-1'}$ = 5.8 Hz, $J_{2'-OH-2'}$ = 5.8 Hz, 1, H-2'), 5.24 (m, 2, OH-3', OH-5'), 5.54 (d, 1, OH-2'), 6.0 (d, $J_{1'-2'}$ = 5.8 Hz, 1, H-1'), 7.15-7.5 (m, 5, C_6H_5), 8.53 (s, 1, H-2), 8.64 (s, 1, H-8), 10.08 (br, 1, NH); ms: m/z (glycerol/fast atom bombardment) = 452 (MH^+).

Anal. Calcd. for $C_{18}H_{22}N_5O_7P \cdot 0.25H_2O$: C, 47.42; H, 4.97; N, 15.36. Found: C, 47.48; H, 4.94; N, 15.56.

6-*N*-[2-(2-Ethoxyethoxy)ethyl phenylphosphoryl]adenosine (**15c**).

Procedure C was applied to 150 mg (0.225 mmole) of **14c** with 300 μl of dioxane and 1.35 ml of aqueous ammonia to give 104 mg (86%) of **15c** after recrystallization from ethanol with diffusion of chloroform, mp 39-41°; uv (methanol): λ max 260 nm (ε 19,600), min 234 nm (ε 11,400); (H^+) λ max 260 nm (ε 18,700), min 228 nm (ε 7,600); (OH^-) λ max 276 nm (ε 26,200), min 239 nm (ε 4,900); ^{1}H nmr: δ 1.04 (t, J = 8.0 Hz, 3, CH_2CH_3), 3.52 (m, 10, 4 x CH_2, H-5',5''), 3.98 (m, 1, H-4'), 4.18 (ddd, $J_{3'-4'}$ = 4.0 Hz, $J_{3'-2'}$ = 5.0 Hz, $J_{3'-OH-3'}$ = 4.8 Hz, 1, H-3'), 4.3 (m, 2, P(O)-OCH_2), 4.6 (''dd'', $J_{2'-1'}$ = 5.8 Hz, $J_{2'-3'}$ = 5.0 Hz, $J_{2'-OH-2'}$ = 6.0 Hz, 1, H-2'), 5.15 (t, $J_{OH-5',5''}$ = 5.5 Hz, 1, OH-5'), 5.23 (d, $J_{OH-3'}$ = 4.8 Hz, 1, OH-3'), 5.5 (d, $J_{OH-2'}$ = 6.0 Hz, 1, OH-2'), 5.8 (d, $J_{1'-2'}$ = 5.8 Hz, 1, H-1'), 7.15-7.5 (m, 5, C_6H_5), 8.53 (s, 1, H-2), 8.64 (s, 1, H-8), 10.04 (br, 1, NH); ms: m/z (glycerol/fast atom bombardment) = 540 (MH^+).

Anal. Calcd. for $C_{22}H_{30}N_5O_9P \cdot 0.25H_2O$: C, 48.58; H, 5.65; N, 12.87. Found: C, 48.23; H, 5.89; N, 13.19.

6-*N*-(Isopropyl phenylphosphoryl)adenosine (**15d**).

Procedure C was applied to 100 mg (0.17 mmole) of **14d** with 190 μl of dioxane and 820 μl of aqueous ammonia to yield 70 mg (87%) of **15d** after recrystallization from ethanol with diffusion of chloroform, mp 93-95°; uv (methanol): λ max 260 nm (ε 19,200), min 225 nm (ε 2,600); (H^+) λ max 261 nm (ε 19,800), min 226 nm (ε 4,400); (OH^-) λ max 276 nm (ε 28,000), min 239 nm (ε 3,600); ^{1}H nmr: δ 1.3 (d, J = 6.5 Hz, 6, $CHMe_2$), 3.65 (m, 2, H-5',5''), 4.0 (m, 1, H-4'), 4.19 (m, 1, H-3'), 4.28 and 4.88 (m, 1, C*H*-Me_2), 4.63 (m, 1, H-2'), 5.18 (t, $J_{OH-5',5''}$ = 5.2 Hz, 1, OH-5'), 5.25 (d, $J_{OH-3'}$ = 4.5 Hz, 1, OH-3'), 5.52 (d, $J_{OH-2'}$ = 6 Hz, 1, OH-2'), 5.98 (d, $J_{1'-2'}$ = 5.5 Hz, 1, H-1'), 7.15-7.55 (m, 5, C_6H_5), 8.55 (s, 1, H-2), 8.64 (m, 1, H-8), 10.08 (br, 1, NH); ms: m/z (gly-

cerol/fast atom bombardment) = 466 (MH^+).

Anal. Calcd. for $C_{19}H_{24}N_5O_7P \cdot 0.25H_2O$: C, 48.56; H, 5.26; N, 14.90. Found: C, 48.48; H, 5.06; N, 15.20.

2',3',5'-Tri-*O*-acetyl-6-*N*-(phenylphosphoryl)adenosine (**16**).

A 30 mg (0.047 mmole) sample of **14a** was hydrogenolyzed with 10 mg of 5% palladium·carbon catalyst in 25 ml of 95% ethanol at 30 psi for 10 hours at ambient temperature in a Parr shaking apparatus. Filtration with a Celite pad, evaporation of the filtrate, and recrystallization of the residue from chloroform with diffusion of ether gave 23 mg (89%) of **16**, mp 89-91°; uv (methanol): λ max 263 nm (ε 15,600), min 229 nm (ε 2,000); (H^+) λ max 267 nm (ε 16,700), min 232 nm (ε 3,500); (OH^-) λ max 263 nm (ε 16,900), min 236 nm (ε 5,900); ^{1}H nmr: δ 2.0, 2.04, 2.11 (3 s, 3 x 3, 3 x acetate), 4.32 (m, 3, H-4', H-5',5''), 5.6 (''t'', $J_{3'-2'}$ = 5.8 Hz, $J_{3'-4'}$ = 5.5 Hz, 1, H-3'), 5.7 (br, 1, OH), 5.92 (''t'', $J_{2'-1'}$ = 5.0 Hz, $J_{2'-3'}$ = 5.8 Hz, 1, H-2'), 6.28 (d, $J_{1'-2'}$ = 5.0 Hz, 1, H-1'), 7.0-7.3 (m, 5, C_6H_5), 8.64 (s, 1, H-2), 8.67 (s, 1, H-8), 10.08 (br, 1, NH); ms: m/z (glycerol/fast atom bombardment) = 550 (MH^+).

Anal. Calcd. for $C_{22}H_{24}N_5O_{10}P \cdot 0.5H_2O$: C, 47.32; H, 4.51; N, 12.54. Found: C, 47.50; H, 4.46; N, 12.52.

6-*N*-(Phenylphosphoryl)adenosine (**17**).

A 30 mg (0.058 mmole) sample of **15a** was hydrogenolyzed with 10 mg of 10% palladium·carbon catalyst in 25 ml of 95% ethanol at 30 psi for ~10 hours at ambient temperature in a Parr shaking apparatus. Filtration with a Celite pad, evaporation, and recrystallization of the residue from ethanol by diffusion with ether afforded 18 mg (73%) of **17**, mp 159-161°; uv (methanol): λ max 263 nm (ε 16,000), min 235 nm (ε 4,200); (H^+) λ max 268 nm (ε 16,100), min 235 nm (ε 5,000); (OH^-) λ max 263 nm (ε 16,200), min 235 nm (ε 5,400); ^{1} H nmr: δ 3.63 (m, 2, H-5',5''), 3.98 (m, 1, H-4'), 4.16 (''t'', $J_{3'-2'}$ = 5.0 Hz, $J_{3'-4'}$ = 4.2 Hz, 1, H-3'), 4.52 (''t'', $J_{2'-3'}$ = 5.0 Hz, $J_{2'-1'}$ = 5.0 Hz, 1, H-2'), 4.7 (br, 4, 4 x OH), 5.95 (d, $J_{1'-2'}$ = 5.0 Hz, 1, H-1'), 6.95-7.3 (m, 5, C_6H_5), 8.58 (s, 1, H-2), 8.69 (s, 1, H-8), 9.7 (br, 1, NH); ms: m/z (glycerol/fast atom bombardment) = 424 (MH^+).

Anal. Calcd. for $C_{16}H_{18}N_5O_7P \cdot 0.5H_2O$: C, 44.45; H, 4.43; N, 16.20. Found: C, 44.32; H, 4.40; N, 15.95.

9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-6-azidopurine (**18**).

To a suspension of 250 mg (0.85 mmole) of 6-azido-9-(β-D-ribofuranosyl)purine in 2.5 ml of acetic anhydride was added 6 ml of dry pyridine dropwise with stirring. The solution was stirred overnight at ambient temperature and evaporated. Coevaporation of the residue with toluene gave a foam which was recrystallized from chloroform with diffusion of ether to give 325 mg (91%) of **18**, mp 62-64°; uv (methanol): λ max 286 nm, min 237 nm; ^{1}H nmr: δ 2.04, 2.12 (s, ''s'', 3, 6, 3 x acetate), 4.37 (m, 3, H-4',5',5''), 5.62 (''t'', $J_{3'-4'}$ = 5.5 Hz, $J_{3'-2'}$ = 5.5 Hz, 1, H-3'), 5.97 (''t'', $J_{2'-3'}$ = 5.5 Hz, $J_{2'-1'}$ = 5.2 Hz, 1, H-2'), 6.46 (d, $J_{1'-2'}$ = 5.2 Hz, 1, H-1'), 8.88 (s, 1, H-2), 10.18 (s, 1, H-8); ms: m/z 419.1189 (3.5, $M^+[C_{16}H_{17}N_7O_7]$ = 419.1187), 259.0816 (86, sugar), 133.0392 (3.5, BH - N_2), 119.0358 (1.2, BH - N_3).

Anal. Calcd. for $C_{16}H_{17}N_7O_7$: C, 45.83; H, 4.09; N, 23.38. Found: C, 45.58; H, 4.10; N, 22.99.

Treatment of **18** with Triphenyl Phosphite to give 2',3',5'-Tri-*O*-acetyl-6-*N*-(diphenylphosphoryl)adenosine (**13**) and 2',3',5'-Tri-*O*-acetyladenosine (**11**).

Reflux of a solution of 83.6 mg (0.2 mmole) of **18** in 10 ml of dry dioxane with 262 μl (1 mmole) of triphenyl phosphite for 4 hours, evaporation, and chromatography of the residue on silica gel[§] with chloroform/methanol (49:1) gave 63 mg (78%) of **13**, mp 69-71° plus **11**. Spectral data were identical to those for the previously prepared samples of **13** and **11**.

Triethyl *N*-[9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)purin-6-yl]-phosphorimidate (**19**).

A solution of 41.9 mg (0.1 mmole) of **18** in 5 ml of dry dioxane was stirred with 86 μl (0.5 mmole) of triethyl phosphite at ambient temperature for 30 minutes. Evaporation, and chromatography of the residue on silica gel[§] with chloroform/methanol (49:1) gave 54 mg (96%) of **19** as a thick syrup; uv (methanol): λ max 266 nm (ε 19,100), min 229 nm (ε 3,600); (H^+) λ max 266 nm (ε 18,400), min 230 nm (ε 4,000); (OH^-) λ max 267 nm (ε 18,300), min 234 nm (ε 4,500); ^{1}H nmr: δ 1.3 (m, 9, 3 x CH_2CH_3), 2.04, 2.08, 2.14 (3 s, 3 x 3, 3 x acetate), 4.22 (m, 9, H-4', H-5',5'', 3 x CH_2-CH_3), 5.66 (''t'', $J_{3'-4'}$ = 5.2 Hz, $J_{3'-2'}$ = 5.6 Hz, 1, H-3'), 6.08 (''t'', $J_{2'-3'}$ = 5.6 Hz, $J_{2'-1'}$ = 5.4 Hz, 1, H-2'), 6.23 (d, $J_{1'-2'}$ = 5.4 Hz, 1, H-1'), 8.3 (s, 1, H-2), 8.35 (s, 1, H-8); ms: m/z (glycerol/fast atom bombardment) = 558 (MH^+).

6-*N*-(Diethylphosphoryl)adenosine (**21**).

A solution of 54 mg (0.096 mmole) of **19** in 1.5 ml of 95% ethanol was stirred with 3 ml of 0.01 *M* hydrochloric acid for 4 days at ambient temperature, evaporated, and the residue was chromatographed by plc to give 26 mg (51%) of 2',3',5'-tri-*O*-acetyl-6-*N*-(diethylphosphoryl)adenosine (**20**), mp 34-36°; uv (methanol): λ max 261 nm (ε 14,800), min 233 nm (ε 1,800); (H^+) λ max 261 nm (ε 15,000), min 234 nm (ε 4,800); (OH^-) λ max 275 nm (ε 21,400), min 238 nm (ε 1,900); ^{1}H nmr: δ 1.23 (t, J = 6.5 Hz, 6, 2 x CH_2CH_3), 2.02, 2.04, 2.12 (3 s, 3 x 3, 3 x acetate), 4.02 (m, 4, 2 x CH_2CH_3), 4.32 (m, 3, H-4',5',5''), 5.64 (''t'', $J_{3'-2'}$ = 5.0 Hz, $J_{3'-4'}$ = 5.6 Hz, 1, H-3'), 6.04 (''t'', $J_{2'-3'}$ = 5.0 Hz, $J_{2'-1'}$ = 5.8 Hz, 1, H-2'), 6.24 (d, $J_{1'-2'}$ = 5.8 Hz, 1, H-1'), 8.4 (s, 1, H-2), 8.48 (s, 1, H-8), 9.62 (br, 1, NH); ms: m/z (glycerol/fast atom bombardment) = 530 (MH^+). An essentially equivalent amount of 2',3',5'-tri-*O*-acetyladenosine (**11**) also was produced (uv).

Procedure C was applied to 200 mg (0.378 mmole) of **20** with 1 ml of dioxane and 2.5 ml of aqueous ammonia. The residue was chromatographed on silica gel[§] with chloroform/methanol (99:1) and recrystallized from chloroform with diffusion of ether to give 140 mg (70%) of **21**, mp 59-61°; uv (methanol): λ max 260 nm (ε 14,600), min 226 nm (ε 1,700); (H^+) λ max 260 nm (ε 15,000), min 228 nm (ε 5,000); (OH^-) λ max 276 nm (ε 21,400), min 238 nm (ε 1,900); ^{1}H nmr: δ 1.23 (m, 6, 2 x CH_3), 3.1-4.2 (m, 8, 2 x CH_2, H-3', H-4',5',5''), 4.6 (m, 1, H-2'), 5.2 (m, 2, OH-3',5'), 5.51 (d, $J_{OH-2'}$ = 5.8 Hz, OH-2'), 5.8 (d, $J_{1'-2'}$ = 6.0 Hz, 1, H-1'), 8.46 (s, 1, H-2), 8.61 (s, 1, H-8), 9.54 (br, 1, NH); ms: m/z (glycerol-sulfolane/fast atom bombardment) = 404 (MH^+).

Anal. Calcd. for $C_{14}H_{22}N_5O_7P \cdot 0.25H_2O$: C, 41.23; H, 5.56; N, 17.17. Found: C, 41.27; H, 5.44; N, 16.83.

Treatment of 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranose (**22**) with Diethyl Phosphorochloridite and 9-(2,3,5-Tri-*O*-acetyl-β-D-ribofuranosyl)-6-azidopurine (**18**).

A solution of 108 mg (0.2 mmole) of **22** in 5 ml of dry tetrahydrofuran was cooled to -78° and 70 μl (0.4 mmole) of diisopropylethylamine and 45 μl (0.31 mmole) of diethyl phosphorochloridite were added. Stirring was continued for 45 minutes at -78° to produce **23**, and 41.9 mg (0.1 mmole) of **18** was added. The solution was allowed to warm gradually, dry dioxane (10 ml) was added at 0°, and the mixture was stirred overnight at ambient tempera-

ture. Evaporation, and chromatography of the residue on silica gel[§] with chloroform/methanol (99:1) gave 33 mg (62%) of 2',3',5'-tri-*O*-acetyl-6-*N*-(diethylphosphoryl)adenosine (**20**) with spectral properties identical to the previously prepared sample.

6-*N*-[Ethyl (methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranosid-6-yl)-phosphoryl]adenosine (**26**).

A solution of 46.4 mg (0.1 mmole) of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**24**) in 5 ml of dry tetrahydrofuran was cooled to -78° and 34.8 μl (0.2 mmole) of diisopropylethylamine and 43.5 μl (0.3 mmole) of diethyl phosphorochloridite were added. Stirring was continued at -78° for 1 hour and 20.9 mg (0.05 mmole) of **18** was added. The mixture was allowed to gradually warm to 0°, 5 ml of dry dioxane was added, and the solution was stirred overnight at ambient temperature. Evaporation and chromatography of the residue on silica gel[§] with chloroform/methanol (99:1) gave 34 mg (72%) of 2',3',5'-tri-*O*-acetyl-6-*N*-[ethyl (methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranosid-6-yl)-phosphoryl]adenosine (**25**); uv (methanol): λ max 258 nm, min 227 nm; (H^+) λ max 259 nm, min 228 nm; (OH^-) λ max 277 nm, min 236 nm; ^1H nmr: δ 1.2 (m, 3, CH_2CH_3), 2.0, 2.02, 2.12 (3 s, 3 x 3, 3 x acetate), 3.33-4.9 (m, 21), 5.64 (''t'', $J_{3'-4'}$ = 4.5 Hz, $J_{3'-2'}$ = 5.8 Hz, 1, H-3'), 6.04 (''t'', $J_{2'-3'}$ = 5.8 Hz, $J_{2'-1'}$ = 5.0 Hz, 1, H-2'), 6.28 (d, $J_{1'-2'}$ = 5.0 Hz, 1, H-1'), 7.2-7.5 (m, 15, 3 x C_6H_5), 8.4 (s, 1, H-2), 8.66 (s, 1, H-8), 10.82 (br, 1, NH); ms: m/z (glycerol-sulfolane/fast atom bombardment) = 948 (MH^+).

Procedure C was applied to 61 mg (0.064 mmole) of **25** with 800 μl of dioxane and 3 ml of aqueous ammonia to give 45 mg (85%) of **26** after recrystallization from chloroform with diffusion of ether, mp 82-84°; uv (methanol): λ max 260 nm (ε 14,400), min 226 nm (ε 1,800); (H^+) λ max 261 nm (ε 15,300), min 230 nm (ε 9,700); (OH^-) λ max 277 nm (ε 21,000), min 236 nm (ε 13,900); ^1H nmr: δ 1.2 (t, J = 7.0 Hz, 3, CH_2CH_3), 3.3 (s, 3, $-OCH_3$), 3.4-3.84 (m, 6), 3.9-4.42 (m, 6), 4.52-4.92 (m, 8), 5.2 (t, $J_{OH-5',5''}$ = 5.2 Hz, 1, OH-5'), 5.25 (d, $J_{OH-3'}$ = 5.0 Hz, 1, OH-3'), 5.51 (d, $J_{OH-2'}$ = 5.8 Hz, 1, OH-2'), 5.98 (d, $J_{1'-2'}$ = 6.0 Hz, 1, H-1'), 7.2-7.5 (m, 15, 3 x C_6H_5), 8.42 (s, 1, H-2), 8.62 (s, 1, H-8), 9.66 (br, 1, NH); ms: m/z (glycerol-sulfolane/fast atom bombardment) = 822 (MH^+).

Anal. Calcd. for $C_{40}H_{48}N_5O_{12}P \cdot H_2O$: C, 57.21; H, 6.00; N, 8.34. Found: C, 57.24; H, 5.77; N, 8.49.

5'-*O*-(Diphenylphosphityl)-2',3'-*O*-isopropylideneadenosine (**29**).

To a suspension of 307 mg (1 mmole) of 2',3'-*O*-isopropylideneadenosine (**27**) in 10 ml of dry methylene chloride were added 170 μl (2 mmoles) of dry pyridine and 172 μl (1.2 mmoles) of diphenyl phosphorochloridite. Stirring was continued for 1 hour at ambient temperature, 2 ml of water was added, and the mixture was evaporated. The residue was coevaporated several times with toluene and extracted with chloroform. The extract was washed (2% aqueous acetic acid, saturated aqueous sodium bicarbonate, water, and brine), dried (sodium sulfate), and evaporated. The residue was chromatographed on silica gel with chloroform/methanol (99:1) to give a solid, 392 mg (75%), which was recrystallized from ethanol with diffusion of ether to give **29**, mp 78-80°; uv (methanol): λ max 258 nm; ^1H nmr: δ 1.34, 1.56 (2 s, 2 x 3, CMe_2), 4.34 (m, 3, H-4',5',5''), 5.1 (dd, $J_{3'-4'}$ = 5.8 Hz, $J_{3'-2'}$ = 5.0 Hz, 1, H-3'), 5.5 (dd, $J_{2'-1'}$ = 4.0 Hz, $J_{2'-3'}$ = 5.0 Hz, 1, H-2'), 6.23 (d, $J_{1'-2'}$ = 4.0 Hz, 1, H-1'), 6.95-7.4 (m, 12, 2 x C_6H_5, NH_2), 8.12 (s, 1, H-2), 8.32 (s, 1, H-8); ms: m/z 430.1275 (100, M - C_6H_5O [$C_{19}H_{21}N_5O_5P$] = 430.1279), 164.0572 (3.2, BHCHO), 162.0776 (0.8, $BHCH{=}CH_2$), 136.0622 (22, B + 2H), 135.0546 (6.7, B + H).

5'-*O*-(Phenylphosphoramidatyl)-2',3'-*O*-isopropylideneadenosine (**30**).

A solution of ~169 mg (~1 mmole) of octanoyl azide in 10 ml of ether was added to a solution of 104.6 mg (0.2 mmole) of **29** in 10 ml of dry dioxane, the mixture was refluxed for 10 hours, and evaporated. Chromatography of the residue on silica gel with chloroform/methanol (49:1) gave 20 mg (32%) of 2',3'-*O*-isopropylideneadenosine (**27**). Further elution gave 60 mg (65%) of a solid which was recrystallized from chloroform with diffusion of ether to give **30**, mp 90-92°; uv (methanol): λ max = 259 nm (ε 15,400), min 225 nm (ε 2,100); (H^+) λ max 257 nm (ε 13,900), min 229 nm (ε 3,100); (OH^-) λ max 259 nm (ε 16,000); ^1H nmr: δ 1.34, 1.55 (2 s, 2 x 3, CMe_2), 4.3 (m, 3, H-2',3',4'), 5.05 (m, 1, H-5'), 5.17 (d, J_{H-N-P} = 6.5 Hz, 2, NH_2), 5.4 (m, 1, H-5''), 6.21 (d, $J_{1'-2'}$ = 2.5 Hz, 1, H-1'), 7.1-7.5 (m, 7, C_6H_5, 6-NH_2), 8.16 (s, 1, H-2), 8.33 (s, 1, H-8); ms: m/z (glycerol/fast atom bombardment) = 463 (MH^+).

Anal. Calcd. for $C_{19}H_{23}N_6O_6P$: C, 49.35; H, 5.01; N, 18.18. Found: C, 48.94; H, 5.07; N, 18.16.

6-*N*-Benzoyl-2',3'-*O*-isopropylideneadenosine (**28**).

A 307 mg (1 mmole) sample of **27** was subjected to conditions described for 2'-deoxyadenosine [50] to give 378 mg (92%) of **28**, mp 138-140° (lit mp 132-133° [49]); uv (methanol): λ max = 280 nm (ε 20,100), min 243 nm (ε 7,000); ms: m/z 411.1553 (8.1, M^+ [$C_{20}H_{21}N_5O_5$] = 411.1543), 381.1431 (2.6, M - CH_2O), 164.0572 (19, BHCHO).

Anal. Calcd. for $C_{20}H_{21}N_5O_5$: C, 58.39; H, 5.15; N, 17.02. Found: C, 58.09; H, 5.06; N, 16.92.

6-*N*-Benzoyl-5'-*O*-[(*N*-benzoyl)phosphoramidatyl]-2',3'-*O*-isopropylideneadenosine (**32**).

A solution of 411 mg (1 mmole) of **28** in 15 ml of dry pyridine was treated with 238 mg (1 mmole) of *N*-benzoyl phosphoramidodichloridate [51], stirred for 1 hour at ambient temperature, and evaporated. The residue was coevaporated with toluene, chromatographed on silica gel[§] with chloroform/methanol (24:1), and recrystallized from chloroform with diffusion of ether to give 50 mg (5%) of the bis-nucleosidylphosphoramidate **31**, mp 135-137°; uv (methanol): λ max = 230 nm (ε 37,200) and 280 nm (ε 36,000), min 253 nm (ε 22,000); (H^+) λ max 289 nm (ε 38,000), min 264 nm (ε 22,000); (OH^-) λ max 305 nm (ε 21,800), min 262 nm (ε 15,200); ^1H nmr: δ 1.29, 1.54 (2 ''s'', 2 x 6, 2 x CMe_2), 4.28 (m, 4, 2 x H-5',5''), 4.45 (m, 2, 2 x H-4'), 5.1 (m, 2, 2 x H-3'), 5.44 (m, 2, 2 x H-2'), 6.31 (''t'', $J_{1'-2'}$ = 2.2 Hz, 2, 2 x H-1'), 7.5-8.1 (m, 15, 3 x C_6H_5), 8.61, 8.63, 8.68, 8.71 (4 s, 4, 2 x H-2, 2 x H-8), 10.12 (''s'', 2, 2 x 6-NH), 11.21 (br, 1, NH); ms: m/z (glycerol/fast atom bombardment) = 988 (MH^+).

Anal. Calcd. for $C_{47}H_{46}N_{11}O_{12}P \cdot 2H_2O$: C, 55.13; H, 4.92; N, 14.74. Found: C, 54.93; H, 4.80; N, 15.05.

Further elution with chloroform/methanol (4:1) gave 260 mg of solid title compound **32** [contaminated with **31**]; ^1H nmr (400 MHz): δ 1.3, 1.53 (2 s, 2 x 3, CMe_2), 4.0 (m, 2, H-5',5''), 4.38 (m, 1, H-4'), 5.06 (m, 1, H-3'), 5.48 (m, 1, H-2'), 6.32 (d, 1, H-1'), 7.44-8.2 (m, 10, 2 x C_6H_5), 9.64 (br s, 1, 6-NH), 11.21 (br, 2, NH, OH); ms: m/z (glycerol/fast atom bombardment) = 595 (MH^+). Compound **32** was not obtained pure.

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REFERENCES AND NOTES

† For the previous paper in this series see reference 53.

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[1] W. P. Roberts, M. E. Tate and A. Kerr, *Nature (London)*, **265**, 379 (1977).

[2] M. E. Tate, P. J. Murphy, W. P. Roberts and A. Kerr, *Nature (London)*, **280**, 697 (1979).

[3] R. J. Thompson, R. H. Hamilton and C. F. Pootjes, *Antimicrob. Agents Chemother.*, **16**, 293 (1979).

[4] P. K. Das, M. Basu and G. C. J. Chatterjee, *J. Antibiot.*, **31**, 490 (1978).

[5] B. A. McCardell and C. F. Pootjes, *Antimicrob. Agents Chemother.*, **10**, 498 (1976).

[6] V. A. Smith and J. Hindley, *Nature (London)*, **276**, 498 (1978).

[7] A. Kerr and K. Htay, *Physiol. Plant Pathol.*, **4**, 37 (1974).

[8] G. Engler, M. Holsters, M. Van Montagu, J. Schell, J. P. Hernalsteens and R. Schilperoort, *Mol. Gen. Genet.*, **138**, 345 (1975).

[9] B. Watson, T. C. Currier, M. P. Gordon, M.-D. Chilton and E. W. Nester, *J. Bacteriol.*, **123**, 255 (1975).

[10] C. I. Kado, Beltsville Symp. Agri. Res. I. Virology in Agriculture, J. A. Romberger, J. D. Anderson and R. L. Powell, eds, Allanheld, Osmun and Co., New York, 1977, pp 247-266.

[11] I. Zaenen, N. Van Larebeke, H. Teuchy, M. Van Montagu and J. Schell, *J. Mol. Biol.*, **86**, 109 (1974).

[12] G. T. Hayman and S. K. Farrand, *Mol. Gen. Genet.*, **223**, 465 (1990).

[13] A. L. Montoya, M.-D. Chilton, M. P. Gordon, D. Sciaky and E. W. Nester, *J. Bacteriol.*, **12**, 101 (1977).

[14] J. E. Loper and C. I. Kado, *J. Bacteriol.*, **139**, 591 (1979).

[15] A. R. Anderson and L. W. Moore, *Phytopathology*, **69**, 320 (1979).

[16] P. J. Murphy, M. E. Tate and A. Kerr, *Eur. J. Biochem.*, **115**, 539 (1981).

[17] A. P. Martinez, W. W. Lee and L. Goodman, *J. Org. Chem.*, **31**, 3263 (1966).

[18] R. Mengel and H. Wiedner, *Chem. Ber.*, **109**, 1395 (1976).

[19] M. Ikehara, Y. Nakahara and S. Yamada, *Chem. Pharm. Bull.*, **19**, 538 (1971).

[20] F. Hansske and M. J. Robins, *J. Am. Chem. Soc.*, **105**, 6736 (1983).

[21] O. Mitsonobu, *Synthesis*, 1 (1981).

[22] R. Mengel and M. Bartke, *Angew. Chem., Int. Ed. Engl.*, **17**, 679 (1978).

[23] R. D. Guthrie, I. D. Jenkins and R. Yamasaki, *J. Chem. Soc., Chem. Commun.*, 784 (1980).

[24] K. Soai, A. Ookawa, H. Oyamada and M. Takase, *Heterocycles*, **19**, 1371 (1982).

[25] C. A. Dekker, *J. Am. Chem. Soc.*, **87**, 4027 (1965).

[26] K. K. Ogilvie, G. H. Hakimelahi, Z. A. Proba and D. P. C. McGee, *Tetrahedron Letters*, 1997 (1982).

[27] M. J. Robins and J. S. Wilson, *J. Am. Chem. Soc.*, **103**, 932 (1982).

[28] M. J. Robins, J. S. Wilson and F. Hansske, *J. Am. Chem. Soc.*, **105**, 4059 (1983).

[29] R. Charubala and W. Pfleiderer, *Heterocycles*, **15**, 761 (1981).

[30] R. Charubala, W. Bannwarth and W. Pfleiderer, *Liebigs Ann. Chem.*, 65 (1980).

[31] W. Zielinski and Z. Lesnikowski, *Synthesis*, 185 (1976).

[32] P. A. Lyon and C. B. Reese, *J. Chem. Soc., Perkin Trans. I*, 2645 (1974).

[33] M. J. Robins and E. M. Trip, *Biochemistry*, **12**, 2179 (1973).

[34] J. Honeyman, Methods in Carbohydrate Chemistry, Vol **II**, R. L. Whistler and M. L. Wolfrom, eds, Academic Press, New York, 1963, pp 95-99.

[35] W. Freist, K. Schattka, F. Cramer and B. Jastorff, *Chem. Ber.*, **105**, 991 (1972).

[36] V. Kvita and G. Baschang, *Helv. Chim. Acta.*, **55**, 2683 (1972).

[37] R. L. Letsinger and G. A. Heavner, *Tetrahedron Letters*, 147 (1975).

[38] S. Zie and L. E. Orgel, *Nucleic Acids Res.*, **15**, 1699 (1987).

[39] J. A. Johnson, Jr., H. J. Thomas and H. J. Schaeffer, *J. Am. Chem. Soc.*, **80**, 699 (1958).

[40] R. Wetzel and F. Eckstein, *J. Org. Chem.*, **40**, 658 (1975).

[41] J. S. Brimacombe, Methods in Carbohydrate Chemistry, Vol **VI**, R. L. Whistler and J. N. BeMiller, eds, Academic Press, New York, 1972, pp 376-378.

[42] C. P. J. Glaudemans and H. G. Fletcher, Methods in Carbohydrate Chemistry, Vol **VI**, R. L. Whistler and J. N. BeMiller, eds, Academic Press, New York, 1972, pp 373-376.

[43] V. J. Gloede, M. Mikolajczyk, A. Lopusinki and J. Omelanczuk, *J. Prakt. Chem.*, **316**, 703 (1974).

[44] A generous gift from N. Le and R. U. Lemieux, University of Alberta.

[45] S. A. Narang, *Tetrahedron*, **39**, 3 (1983).

[46] P. A. S. Smith, *Org. React.*, **3**, 337 (1946).

[47] W. Lwowski and S. Linke, *Liebigs Ann. Chem.*, 8 (1977).

[48] J. P. Forsman and D. Lipkin, *J. Am. Chem. Soc.*, **75**, 3145 (1953).

[49] S. Chladek and J. Smrt, *Collect. Czech. Chem. Commun.*, **29**, 214 (1964).

[50] G. S. Ti, B. L. Gaffney and R. A. Jones, *J. Am. Chem. Soc.*, **104**, 1316 (1982).

[51] A. W. Titherley and E. Worrall, *J. Chem. Soc.*, 1143 (1909).

[52] M. J. Robins, Y. Fouron and R. Mengel, *J. Org. Chem.*, **39**, 1564 (1974).

[53] M. J. Robins, S. F. Wnuk, K. B. Mullah, N. K. Dalley, C.-S. Yuan, Y. Lee and R. T. Borchardt, *J. Org. Chem.*, submitted.