Studies on Nucleosides and Nucleotides. XII.[1] Carbon-Chain Extension at 5′-Position of Ribonucleosides

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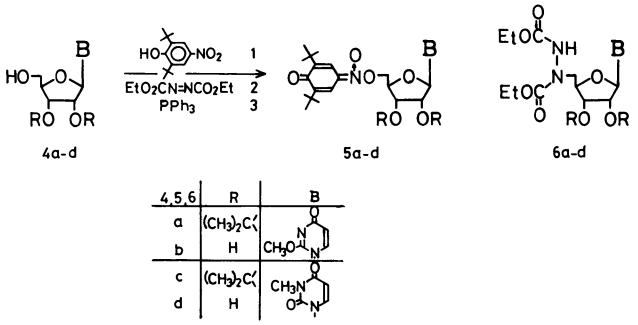
2,6-Di-*t*-butyl-4-nitrophenol reacted with O^2-methyluridine, N^3-methyluridine or 4-triazolyl-1-(β-D-ribofuranosyl)-2(1*H*)-pyrimidinone in the presence of diethyl azodicarboxylate and triphenylphosphine selectively at the 5′-position to give the corresponding 4-(nucleosid-5′-yl-*aci*-nitro)-2,6-di-*t*-butylcyclohexa-2,5-dienone (*aci*-nitro ester of nucleoside) in 39—72% yields along with varied amounts of 5′-deoxy-5′-[*N*,*N*′-bis(ethoxycarbonyl)-hydrazino]nucleosides. By comparison of the reactions of pyrimidine nucleosides having free 2′- and 3′-hydroxyl groups with those of their 2′,3′-*O*-isopropylidene derivatives, the ratio of *aci*-nitro ester to 5′-deoxy-5′-hydrazinonucleoside was affected by the protecting groups as well as the time required for the addition of diethyl azodicarboxylate to a solution of other reactants. Similarly, N^1,N^6,2′,3′-*O*-tetrabenzoyladenosine afforded the expected *aci*-nitro ester in 83% yield. The *aci*-nitro esters prepared were successfully reacted with stabilized phosphoranes such as (ethoxycarbonylmethylene)triphenylphosphorane or (acetylmethylene)triphenylphosphorane giving 1-[(*E*)-β-D-ribo-hept-5-enofuranosyl]- or 1-[(*E*)-β-D-ribo-oct-5-enofuranosyl]-pyrimidines and -purines. When the two stage reactions were carried out by one-pot procedure without isolation of *aci*-nitro esters, overall yields of alkenofuranosylpyrimidines were markedly improved.

Nucleoside antibiotics such as ezomycins, octosyl acids, and sinefungin have a common structural unit comprising higher-carbon sugars and pyrimidine or purine bases. For the synthesis of these antibiotics and their analogues from ribonucleosides, the creation of C–C bond at the 5′-position is required and nucleoside 5′-aldehyde has been generally chosen as a key intermediate. Thus, protection of 2′- and 3′-hydroxyl groups of a nucleoside, oxidation of 5′-hydroxyl group, and subsequent treatment of the resulting aldehyde with anionic species such as Wittig reagents affords the corresponding homologated nucleoside.[2,3] Because of instability of nucleoside 5′-aldehydes, however, only a limited number of oxidation process have been utilized.[2] Therefore, there are ongoing needs to develop a convenient procedure for carbon-chain extension of nucleosides.

Recently, we have reported the synthesis of *aci*-nitro esters by the reaction of alcohols with 2,6-di-*t*-butyl-4-nitrophenol (**1**), diethyl azodicarboxylate (**2**), and triphenylphosphine (**3**).[4] As a masked aldehyde, the *aci*-nitro ester prepared reacted with Wittig reagents giving the corresponding olefins.[5] The reaction would involve intermediacy of aldehyde or ketone which successively reacts with Wittig reagents. An advantage would thereby accrue to the preparation of olefins via unstable aldehydes. Further, it was found that improved yields were obtained when the sequence of reactions were carried out by one-pot procedure without isolation of *aci*-nitro ester. Application of this methodology to the synthesis of 1-[(*E*)-5-enofuranosyl]-uracils from uridine has also been shortly reported.[6]

In this paper, we wish to report the synthesis of 1-[(*E*)-5-enofuranosyl]-pyrimidine and -purine derivatives via *aci*-nitro esters.

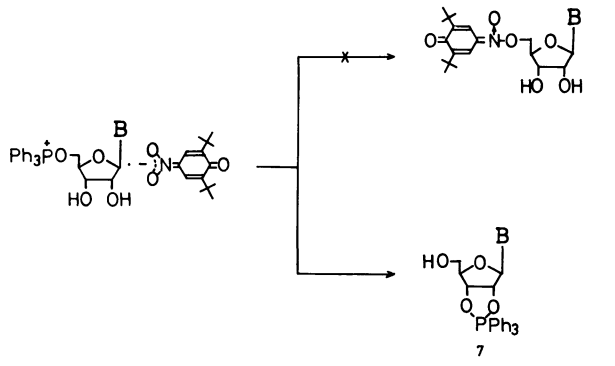
Reactions of Uridine Derivatives. When 2′,3′-*O*-isopropylideneuridine was allowed to react with **1**, **2**, and **3**, intramolecular dehydration occurred giving 2′,3′-*O*-isopropylidene-O^2,5′-cyclouridine rather than expected *aci*-nitro ester. In order to prevent the cyclouridine formation, the uracil moiety was protected by methyl group. O^2-Methyl- or N^3-methyl-2′,3′-*O*-isopropylideneuridine (**4a**, **4c**) reacted smoothly with **1** in the presence of 1.5 molar amounts of **2** and **3** at room temperature overnight to give the corresponding *aci*-nitro ester (**5a** or **5c**) in 84 or 83% yield, respectively. We did not attempt to isolate 5′-deoxy-5′-hydrazinouridine derivative (**6a**, **6c**)(vide infra).



In view of the fact that the condensation of unprotected nucleosides with carboxylic acids using **2** and **3** selectively affords 5′-*O*-acylnucleosides,[7] high regioselectivity could also be expected in the formation of *aci*-nitro esters. Thus, O^2-methyluridine (**4b**) and N^3-methyluridine (**4d**) were used as nucleoside components. When **2** (3 equiv) was added dropwise over a period of 2 h to a solution of **1** (1.5 equiv), **3** (3 equiv), and **4b**, followed by being stirred overnight, *aci*-nitro ester (**5b**) was obtained in

72% yield accompanying a trace of 5′-deoxy-5′-hydrazinouridine derivative (**6b**). Under the same conditions, **4d** afforded *aci*-nitro ester (**5d**) and 5′-deoxy-5′-hydrazinouridine derivative (**6d**) in 39 and 41% yields, respectively. In both cases, the products derived from the reaction at 2′- and/or 3′-hydroxyl group could not be obtained.

In contrast to the preparation of *aci*-nitro esters of fully protected uridines (**4a**, **4c**),[8] more than two equivalents of **2** and **3** were required for the conversion of uridines having free 2′- and 3′-hydroxyl groups. In fact, when **4b** was treated with 1 molar amount each of **1**, **2**, and **3**, the corresponding *aci*-nitro ester (**5b**) was hardly formed as monitored by TLC of the reaction mixture. These results suggest that one-equivalents of **2** and **3** were consumed by the formation of 2′,3′-*O*-(triphenylphosphoranediyl) ring.[9] The data concerning to the reaction of uridine with **2**, **3**, and an acidic component support the initial formation of 5′-*O*-(triphenylphosphonio)uridine. Thus, when carboxylic acid or phosphoric diester was used as an acidic component the corresponding 5′-*O*-substituted uridine was exclusively formed. On the other hand, with weak nucleophile such as phthalimide, intramolecular process is favorable to give O^2,5′-cyclouridine.[9b] Since uracil moiety was protected in the present reactions, it would be rational to assume that phosphonio group migration predominated over the intermolecular displacement by *aci*-nitronate anion and 2′,3′-*O*-(triphenylphosphoranediyl)-O^2-methyl- or -N^3-methyluridine (**7**) was formed.[9]



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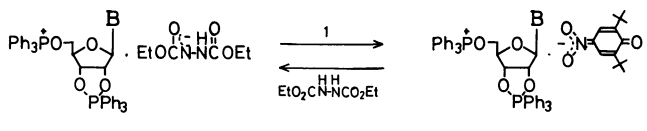
The formation of **6d** suggests that reaction mixture contains nucleoside phosphonium salts **8** and **9** in equilibrium. The reaction courses would therefore depend on the equilibrium constant and nucleophilicity of the counter anions comprising in **8** and **9**.



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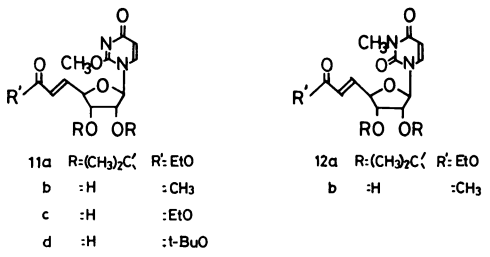
Although no kinetic data are available, the conversion of **9** to uridine 5′-*O*-*aci*-nitro ester would be rate-determining step because of low nucleophilicity of *aci*-nitronate anion. In order to suppress the formation of **6b** and **6d**, the concentration of diethyl hydrazinedicarboxylate must be minimized. This requirement could be satisfied at least at an early stage of the reaction by slow addition of **2** to a solution of other reactants.[10] In fact, when **2** was added dropwise within 0.5 h to a solution of **1**, **3**, and **4b**; **5b** and **6b** were obtained in 47 and 30% yields, respectively. When **4d** was used, the yield of **6d** was increased to 76%.

Next, the reaction of uridine 5′-*aci*-nitronates with Wittig reagents was examined. When *aci*-nitro ester (**5a** or **5c**) was treated with 2 molar amounts of (ethoxycarbonylmethylene)triphenylphosphorane (**10**) in benzene under reflux for 8 h, 1-[(*E*)-5,6-dideoxy-7-ethoxy-2,3-*O*-isopropylidene-β-D-ribo-hept-5-eno-1,4-furanosid-7-ulosyl]-O^2-methyl- or -3-methyluracil (**11a** or **12a**) was obtained in 81 or 70% yield, respectively. Under similar conditions, the reaction of *aci*-nitro ester (**5b** or **5d**) with (acetylmethylene)triphenylphosphorane (**13**) completed within 2 h to give 1-[(*E*)-5,6,8-trideoxy-β-D-ribo-oct-5-eno-1,4-furanosid-7-ulosyl]-O^2-methyl or -3-methyluracil (**11b** or **12b**) in 66 or



11a R=(CH3)2C(, R'=EtO
b :H :CH3
c :H :EtO
d :H :t-BuO

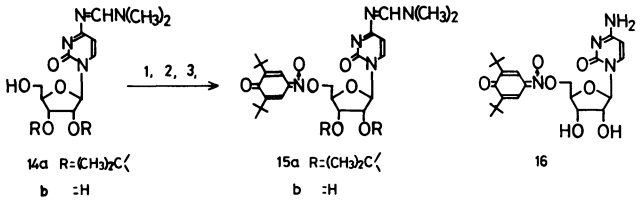
12a R=(CH3)2C(, R'=EtO
b :H :CH3

50% yield, respectively. ^{1}H-NMR spectroscopy showed that **11a** was pure *E*-isomer, $C_{5'}$H and $C_{6'}$H appearing as sharp double doublets at 7.06 and 6.03 ppm with $J_{5',6'}$=16.7 Hz, $J_{4',5'}$=5.5 Hz, and $J_{4',6'}$= 1.5 Hz. Similarly, the ^{1}H-NMR spectrum of **11b**, **12a**, and **12b** showed similar pattern of signals as shown in experimental section.

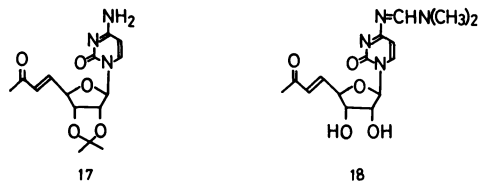
It was found that overall yields of enofuranosyluracils were improved by one-pot procedure without isolation of *aci*-nitro ester. Thus, to a solution of **4b**, **1**, and **3** in THF was added **2** in THF at room temperature for 2 h. The reaction mixture was stirred overnight and **13** in benzene was added. The resulting solution was successively refluxed for 2 h giving **11b** in 73% yield. By the same procedure, **4d** afforded **12b** in 43% yield. When **4b** was allowed to react with **1**, **2**, and **3**, followed by **10** or (*t*-butoxycarbonylmethylene)triphenylphosphorane by one-pot procedure, the second step completed in 3 h giving the expected 1-[(*E*)-β-D-ribo-hept-5-enofuranos-

yl]-uracils (**11c**, **11d**) in 70% yield.

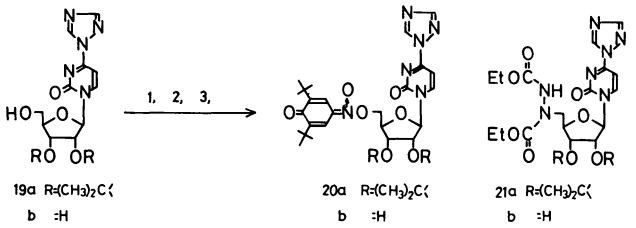
Reactions of Cytidine Derivatives. Similar to the case of 2′,3′-*O*-isopropylideneuridine, the reaction of N^4-benzoyl-2′,3′-*O*-isopropylidenecytidine with **1**, **2**, and **3** quantitatively gave N^4-benzoyl-2′,3′-*O*-isopropylidene-O^2,5′-cyclocytidine. This result suggests that both hydrogen atoms of the amino group should be substituted to prevent undesirable cyclization. Thus, the cytosine moiety was protected by dimethylaminomethylene group. When N^4-dimethylaminomethylene-2′,3′-*O*-isopropylidenecytidine (**14a**) reacted with **1** by the use of 1.5 molar amounts of **2** and **3**, the corresponding *aci*-nitro ester (**15a**) was obtained in 54% yield. The reaction of N^4-dimethylaminomethylenecytidine (**14b**) with **1** (1.5 equiv), **2** (3 equiv), and **3** (3 equiv) afforded *aci*-nitroester (**15b**) in 32% yield accompanying with deprotected product (**16**; 14%).



When **15a** was treated with **13** in THF under reflux for 6.5 h, no N^4-dimethylaminomethylene-1-[(*E*)-5,6,8-trideoxy-2,3-*O*-isopropylidene-β-D-ribo-oct-5-eno-1,4-furanosid-7-ulosyl]-2(1*H*)-pyrimidinone could be isolated but N^4-amino-1-[(*E*)-5,6,8-trideoxy-2,3-*O*-isopropylidene-β-D-ribo-oct-5-eno-1,4-furanosid-7-ulosyl]-2(1*H*)-pyrimidinone (**17**) was obtained in 18% yield. On the other hand, the reaction of **15b** with **13** gave N^4-dimethylaminomethylene-1-[(*E*)-5,6,8-trideoxy-β-D-ribo-oct-5-eno-1,4-furanosid-7-ulosyl]-2(1*H*)-pyrimidinone (**18**) in 31% yield. No deprotected product could be isolated.

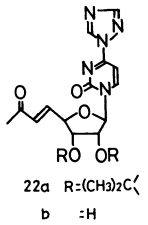


As the dimethylaminomethylene group was obviously inadequate for the present purpose because of instability, 4-triazolyl-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-2(1*H*)-pyrimidinone (**19a**) was used. Compound **19a** was readily prepared from 2′,3′-*O*-isopropylideneuridine by the modification of Reese's procedure.[11] The transformation of the triazolyl group into various functional groups involving amino group has been demonstrated.[12] Therefore, carbon-chain extension of **19a** is synthetically useful because a variety of pyrimidinenucleosides would be prepared from a single precursor. The reaction of **19a** with two equivalents of **1**, **2**, and **3** resulted in the formation of the corresponding *aci*-nitro ester (**20a**) and 5′-deoxy-5′-hydrazino derivative (**21a**) in 61 and 20% yields, respectively, while the reaction of 4-triazolyl-1-(β-D-ribofuranosyl)-2(1*H*)-pyrimidinone (**19b**) with two equivalents of **1**, **2**, and **3** exclusively gave *aci*-nitro ester (**20b**) in 71% yield without detectable formation of hydrazino derivative (**21b**).



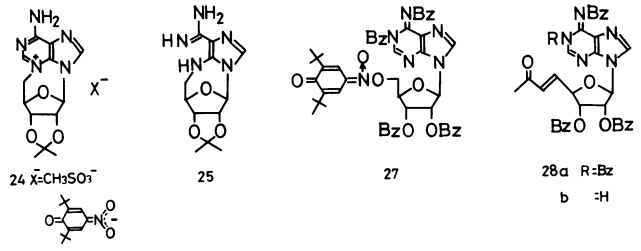
Similar to the case of uridine derivatives, the *aci*-nitro ester derived from the reaction at 2′- and/or 3′-hydroxyl group could not be detected.

The reaction of **13** with **20a** or **20b** afforded the corresponding (*E*)-olefins (**22a** or **22b**) in 61 or 77% yield, respectively. By a one-pot reaction, **19b** afforded **22b** in 68% yield.



Reactions of Adenosine Derivatives. When N^6-dimethylaminomethylene-2′,3′-*O*-isopropylideneadenosine (**23**) was allowed to react with two equivalents of **1**, **2**, and **3**, expected *aci*-nitro ester could not be obtained. Examination of the crude reaction mixture by paper chromatography revealed the formation of a compound having UV_{max} (MeOH) 292 nm. Anzai has demonstrated that, by treatment with aqueous sodium hydroxide, 2′,3′-*O*-isopropylidene-N^3,5′-cycloadenosine (**24**; $X^- = CH_3SO_3^-$) converted into N^5,5′-anhydro-5-amino-4-amidino-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)imidazole (**25**) which exhibits UV_{max} (MeOH) 290 nm.[13] Thus, the results obtained could be explained by assuming the initial formation of **24** (X^-=2,6-di-*t*-butyl-4-nitrophenoxide anion) which decomposed into **25** during manipuration. In order to prevent the undesirable cyclization, N^1,N^6,2′,3′-*O*-tetrabenzoyladenosine (**26**) was used where nucleophilicity of N^3-position was decreased by the electron-withdrawing group. When **26** was allowed to react with **1** in the presence of **2** and **3**, the corresponding *aci*-nitro ester (**27**) was obtained in 83% yield. When **27** was treated with **13** in THF

under reflux for 8 h, N^1,N^6-dibenzoyl-9-[(*E*)-2,3-di-*O*-benzoyl-β-D-ribo-oct-5-eno-1,4-furanosid-7-ulosyl]-adenine (**28a**) and N^6-benzoyl-9-[(*E*)-2,3-di-*O*-benzoyl-β-D-ribo-oct-5-eno-1,4-furanosid-7-ulosyl]-adenine (**28b**) were obtained in 19 and 36% yields, respectively.



Conclusion. The reaction of nucleosides with **1**, **2**, and **3** resulted in the formation of the corresponding *aci*-nitro esters. The condensation selectively took place at 5′-hydroxyl group, no protection at 2′- and 3′-hydroxyl groups being required. A serious side reaction is the competitive formation of 5′-deoxy-5′-hydrazino nucleosides. However the formation of the side products could be partly suppressed by a slow addition of **2**. Although no explanation can be offered at the present stage of investigation, a comparison of reactions of nucleosides having free 2′- and 3′-hydroxyl groups with those of 2′,3′-*O*-isopropylidene nucleosides revealed that the protecting group might influence the reactivity of the intermediary phosphonium salts. Thus, the isopropylidene group of uridine derivatives (**4a**, **4c**) facilitated the *aci*-nitro ester formation, while the reverse was found for **19a**. The yield of 5′-deoxy-5′-hydrazinouridines was also affected by manner of protection of uracil moiety. Since *aci*-nitro esters can be utilized as masked aldehydes, the conversion of uridine, cytidine, and adenosine derivatives into *aci*-nitro esters and subsequent reaction with stabilized phosphoranes provides a convenient procedure for the preparation of the corresponding carbon-chain extended nucleosides.

Experimental

Methods. Preparative layer chromatography (PLC) was carried on 20 cm×30 cm glass coated with Merck silica gel PF_{254}. Kiesel-gel 60 (Merck, mesh 70—220) was used for column chromatography (5 cm×30 cm). ^{1}H-Nuclear magnetic resonance (NMR) spectra were measured on Hitachi R-20 (60 MHz) or JEOL GX-270 (270 MHz) spectrometer using tetramethylsilane as internal standard. Ultraviolet absorption spectra were obtained with a Hitachi EPS-3T recording spectrometer. Elemental analyses were obtained from Institute of Physical and Chemical Research, Wako, Saitama.

The nucleosidic starting materials, O^2-methyl-2′,3′-*O*-isopropylideneuridine (**4a**),[14] N^3-methyl-2′,3′-*O*-isopropylideneuridine (**4c**),[3b] O^2-methyluridine (**4b**),[8] N^3-methyluridine (**4d**),[3b] N^4-dimethylaminomethylene-2′,3′-*O*-isopropylidenecytidine (**14a**),[15] N^4-dimethylaminomethylenecytidine (**14b**),[15] 4-triazolyl-1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-2(1*H*)-pyrimidinone (**19a**),[11] 4-triazolyl-1-(β-D-ribofuranosyl)-2(1*H*)-pyrimidinone (**19b**),[11] N^6-dimethylaminomethylene-2′,3′-*O*-isopropylideneadenosine (**23**),[15] and N^1,N^6,2′,3′-*O*-tetrabenzoyladenosine (**26**)[16] were prepared by known procedures or their modifications.

Preparations of *aci*-Nitro Ester. Preparations of 5a and 5c. A solution of **2** (261 mg, 1.5 mmol) in THF (1 ml) was added dropwise over a period of 1 h to a mixture of uridine derivative (**4a** or **4c**, 298 mg, 1 mmol), **1** (375 mg, 1.5 mmol), and **3** (393 mg, 1.5 mmol) in THF (3 ml). The solution gradually colored red-orange on addition of **2** and kept stirring at room temperature overnight. The **5a** was separated by PLC ($CHCl_3$:EtOAc: MeOH=10:5:1) in 84% yield: red-orange oily semisolid; ^{1}H-NMR ($CDCl_3$)[17] δ=1.29 and 1.30 (18H, s, *t*-Bu), 1.38 and 1.60 (6H, s, isopropylidene CH_3), 4.06 (3H, s, OCH_3), 4.37 (1H, dd, 4′-H), 4.58 and 4.67 (2H, dd, $J_{5'a,4'}$=4.3 Hz, $J_{5'b,4'}$=5.9 Hz, $J_{5'a,5'b}$=12.0 Hz, 5′-H), 4.82 (1H, dd, $J_{2',3'}$=6.6 Hz, $J_{3',4'}$=3.3 Hz, 3′-H), 4.89 (1H, dd, $J_{1',2'}$=2.3 Hz, 2′-H), 5.85 (1H, d, 1′-H), 5.99 (1H, d, $J_{5,6}$=7.6 Hz, 5-H), 7.41 (1H, d, 6-H), and 7.36 and 7.54 (2H, d, quinone H).

5c was isolated by PLC (benzene:EtOAc=10:1) in 83% yield: red-orange oil; ^{1}H-NMR ($CDCl_3$) δ=1.29 (18H, s, *t*-Bu), 1.36 and 1.56 (6H, s, isopropylidene CH_3), 3.31 (3H, s, NCH_3), 4.37 (1H, m, 4′-H), 4.62 and 4.63 (2H, d, $J_{4',5'}$=6.3 Hz, 5′-H), 4.95 (1H, dd, $J_{3',4'}$=4.0 Hz, $J_{2',3'}$=6.4 Hz, 3′-H), 5.12 (1H, dd, $J_{1',2'}$=1.6 Hz, 2′-H), 5.53 (1H, d, 1′-H), 5.77 (1H, d, $J_{5,6}$=7.9 Hz, 5-H), 7.20 (1H, d, 6-H), and 7.35 and 7.59 (2H, d, quinone H).

Preparations of 5b and 5d. A mixture of **1** (375 mg, 1.5 mmol), **3** (786 mg, 3 mmol), and uridine derivative (**4b** or **4d**, 256 mg, 1 mmol) in THF (3 ml) was stirred and a solution of **2** (261 mg, 1.5 mmol) in THF (1 ml) was added over a period of 1 h at room temperature. After 3 h, **2** (1.5 mmol) in THF (1 ml) was further added for 1 h. The nucleoside (**4b** or **4d**) dissolved on addition of **2** and the solution gradually colored red-orange. After the solution kept stirring overnight, the residue was evaporated under reduced pressure. The residue was purified by column chromatography ($CHCl_3$:MeOH=10:1) to afford **5b** or **5d** in 72 or 39% yield. **5b**: red-orange semisolid; ^{1}H-NMR (60 MHz, DMSO-d_6) δ=1.22 and 1.27 (18H, s, *t*-Bu), 3.91 (3H, s, OCH_3), 5.41 and 5.63 (2H, d, 2′-, 3′-OH), 5.79 (1H, d, $J_{1',2'}$=5.2 Hz, 1′-H), 5.90 (1H, d, $J_{5,6}$=8.4 Hz, 5-H), 7.30 and 7.58 (2H, d, quinone H), and 7.73 (1H, d, 6-H). **5d**: red-orange semisolid; ^{1}H-NMR (60 MHz, $CDCl_3$) δ=1.31 (18H, s, *t*-Bu), 3.31 (3H, s, NCH_3), 5.72 (1H, s, 1′-H), 5.80 (1H, d, $J_{5,6}$=7.6 Hz, 5-H), 7.45 (1H, d, 6-H), and 7.36 and 7.55 (2H, d, quinone H).

In the case of the preparation of **5d**, a side product (**6d**) was obtained in 41% yield (oil; UV_{max} (MeOH) 265 nm, UV_{min} 235 nm; ^{1}H-NMR (60 MHz, $CDCl_3$) δ=1.24 (6H, t, $-CH_2\underline{CH_3}$), 3.27 (3H, s, OCH_3), 5.70 (1H, d, 1′-H), 5.80 (1H, d, $J_{5,6}$=8.5 Hz, 5-H), 7.45 (1H, d, 6-H), and 7.63 (1H, br s, NH).

In a similar reaction, when **2** (3 mmol) was added to the THF solution of **1**, **3**, and **4b** or **4d** within 0.5 h, the undesirable products, 5′-deoxy-5′-hydrazino derivatives (**6b** or **6d**) was obtained in 30 or 76% yield, respectively. The **6b** was recrystallized from CH_3CN and melted at 147—149 °C (UV_{max} (MeOH) 235, 250 (sh) nm, UV_{min} 215 nm; ^{1}H-NMR (60 MHz, DMSO-d_6) δ=1.17 (6H, t, $-CH_2\underline{CH_3}$), 5.24 and

5.56 (2H, d, 2'-, 3'-OH), 5.70 (1H, d, $J_{1',2'}$=4.4 Hz, 1'-H), 5.88 (1H, d, $J_{5,6}$=7.8 Hz, 5-H), 7.75 (1H, d, 6-H), and 9.58 (1H, br s, NH)).

Preparation of 15a. By a similar procedure described in the preparation of **5a** and **5c**, **14a** (389 mg, 1.24 mmol) reacted with 1.5 equivalents of **1**, **2**, and **3**. The **15a** was isolated by the use of column chromatography ($CHCl_3$:EtOAc:MeOH=12:5:1) in 54% yield (orange oil; ^{1}H-NMR ($CDCl_3$) δ=1.27 and 1.29 (18H, s, *t*-Bu), 1.36 and 1.55 (6H, s, isopropylidene CH_3), 3.15 and 3.18 (6H, s, $-N(CH_3)_2$), 4.43 (1H, m, 4'-H), 4.68 and 4.79 (2H, dd, $J_{5'a,4'}$=7.2 Hz, $J_{5'b,4'}$=4.9 Hz, $J_{5'a,5'b}$=12.0 Hz, 5'-H), 5.06 (1H, dd, $J_{3',4'}$=3.3 Hz, $J_{2',3'}$=6.3 Hz, 3'-H), 5.27 (1H, d, 2'-H), 5.50 (1H, s, 1'-H), 6.04 (1H, d, $J_{5,6}$=7.3 Hz, 5-H), 7.39 (1H, d, 6-H), 7.36 and 7.59 (2H, d, quinone H), and 8.81 (1H, s, =CH–).

Preparations of 15b and 16. For the reaction of **14b** (420 mg, 1.53 mmol), 1.5 equivalents of **1** and 3 equivalents of **2** and **3** were used. **15b** and **16** were isolated by column chromatography ($CHCl_3$:MeOH=12:1) in 36 and 14% yields, respectively. **15b**: orange oil; ^{1}H-NMR ($CDCl_3$) δ=1.26 and 1.30 (18H, s, *t*-Bu), 3.13 and 3.20 (6H, s, $-N(CH_3)_2$), 4.1—4.3 (3H, m, 4'-H, 5'-H), 4.4—4.6 (2H, m, 2'-H, 3'-H), 4.74 and 4.79 (2H, d, 2'-, 3'-OH), 5.82 (1H, d, $J_{1',2'}$=3.3 Hz, 1'-H), 6.07 (1H, d, $J_{5,6}$=7.3 Hz, 5-H), 7.35 and 7.53 (2H, d, quinone H), 7.70 (1H, d, 6-H), and 8.73 (1H, s, =CH–).

Preparations of 20a and 20b. When **19a** (282 mg, 0.84 mmol) reacted with 2 equivalents of **1**, **2**, and **3**, **20a** and 5'-deoxy-5'-hydrazino derivative (**21a**) were isolated by the use of column chromatography ($CHCl_3$:MeOH=15:1) in 61 and 20% yields, respectively. **20a**: orange oil; ^{1}H-NMR (60 MHz, $CDCl_3$) 1.26 (18H, s, *t*-Bu), 1.36 and 1.60 (6H, s, isopropylidene CH_3), 5.68 (1H, s, 1'-H), 7.02 (1H, d, $J_{5,6}$=8.0 Hz, 5-H), 7.26 and 7.48 (2H, d, quinone H), 8.00 (1H, d, 6-H), and 8.06 and 9.15 (2H, s, triazole H). **21a**; oil; ^{1}H-NMR (60 MHz, CD_3OD) δ=1.23 (6H, t, $-CH_2\underline{CH_3}$), 1.32 and 1.52 (6H, s, isopropylidene CH_3), 5.83 (1H, s, 1'-H), 7.02 (1H, d, $J_{5,6}$=7.6 Hz, 5-H), 8.36 (1H, d, 6-H), and 8.26 and 9.30 (2H, s, triazole H).

Compound **19b** (210 mg, 0.71 mmol) was allowed to react with 2 equivalents of **1**, **2**, and **3** by the same procedure described in the preparation of **5b** and **5d**. The reaction mixture being stirred for 2 d, the residue obtained by the removal of THF was applied to a silica-gel column and eluted with a mixture of $CHCl_3$–EtOAc–MeOH (10:5:1) giving 71% yield of **20b**; orange oil; ^{1}H-NMR (60 MHz, $CDCl_3$) δ=1.33 (18H, s, *t*-Bu), 5.90 (1H, s, 1'-H), 7.05 (1H, d, $J_{5,6}$=7.0 Hz, 5-H), 7.30 and 7.58 (2H, d, quinone H), 8.30 (1H, d, 6-H), and 8.06 and 9.20 (2H, s, triazole H). A 20% of the starting material **19b** was recovered.

Preparation of 27. A solution of **2** (94 mg, 0.64 mmol) in THF (2 ml) was added dropwise over a period of 1 h to a mixture of **26** (203 mg, 0.3 mmol), **1** (149 mg, 0.6 mmol), and **3** (156 mg, 0.6 mmol) in THF (3 ml). The reaction mixture was kept stirring at room temperature for 2 d. After being evaporated, the residue was purified by PLC (benzene:EtOAc=10:1) giving **27** in 83% yield: orange oil; ^{1}H-NMR ($CDCl_3$) δ=1.24 and 1.27 (18H, s, *t*-Bu), 4.7—4.8 (2H, m, 5'-H), 4.94 (1H, m, 4'-H), 6.17—6.26 (2H, m, 2'-H, 3'-H), 6.39 (1H, d, $J_{1',2'}$=4.3 Hz, 1'-H), 7.2—8.0 (22H, m, aromatic and quinone H), and 8.25 and 8.67 (2H, s, purine H).

Reaction of *aci*-Nitro Esters with Wittig Reagents. Preparations of 11a and 12a. One mmol of **5a** or **5c** in benzene (10 ml) was treated with 2 molar amounts of **10** under reflux for 8 h and then evaporated. The **11a** and **12a** were isolated by the column chromatography using $CHCl_3$–MeOH (10:1) in 81 and 70% yields, respectively. **11a**: oil; ^{1}H-NMR (60 MHz, $CDCl_3$) δ=1.29 (3H, t, $-CH_2\underline{CH_3}$), 1.38 and 1.60 (6H, s, isopropylidene CH_3), 4.01 (3H, s, OCH_3), 6.00 (1H, d, $J_{5,6}$=8.0 Hz, 5-H), 6.05 (1H, d, 6'-H), 6.98 (1H, dd, $J_{5',6'}$=15.0 Hz, $J_{4',5'}$=4.8 Hz, 5'-H), and 7.36 (1H, d, 6-H). **12a**: oil; ^{1}H-NMR (60 MHz, $CDCl_3$) δ=1.29 (3H, t, $-CH_2\underline{CH_3}$), 1.38 and 1.59 (6H, s, isopropylidene CH_3), 3.31 (3H, s, NCH_3), 4.23 (2H, q, $-CH_2-$), 5.70 (1H, d, $J_{1',2'}$=1.5 Hz, 1'-H), 5.81 (1H, d, $J_{5,6}$=8.1 Hz, 5-H), 6.03 (1H, dd, $J_{4',6'}$=1.2 Hz, 6'-H), 7.06 (1H, dd, $J_{5',6'}$=16.7 Hz, $J_{4',5'}$=5.5 Hz, 5'-H), and 7.33 (1H, d, 6-H).

The **11a** was treated with 80% acetic acid under reflux for 2 h and then evaporated. The residue was purified by column chromatography (EtOAc) to quantitatively give 1-[(*E*)-5,6-dideoxy-7-ethoxy-β-D-ribo-hept-5-eno-1,4-furanosid-7-ulosyl]uracil; mp 163—165 °C; UV_{max} (MeOH) 263 nm, UV_{min} 241 nm; ^{1}H-NMR (60 MHz, CD_3OD) δ=1.28 (3H, t, $-CH_2\underline{CH_3}$), 5.75 (1H, d, $J_{5,6}$=7.6 Hz, 5-H), 5.83 (1H, d, $J_{1',2'}$=3.0 Hz, 1'-H), 6.10 (1H, dd, $J_{4',6'}$=1.2 Hz, 6'-H), 7.07 (1H, dd, $J_{5',6'}$=15.5 Hz, $J_{4',5'}$=5.2 Hz, 5'-H), and 7.58 (1H, d, 6-H); Found: C, 50.00; H, 5.16; N, 8.97%. Calcd for $C_{13}H_{16}N_2O_7$: C, 50.00; H, 5.16; N, 8.97%.[18]

Preparations of 11b and 12b. Similar to the case of preparations of **11a** and **12a**, **11b** and **12b** were obtained in 66 and 50% yields, respectively. The **11b** was recrystallized from EtOH, mp 189—190 °C; UV_{max} (H_2O) 228, 250 (sh) nm; ^{1}H-NMR (60 MHz, DMSO-d_6) δ=2.28 (3H, s, $COCH_3$), 3.92 (3H, s, OCH_3), 5.92 (1H, d, $J_{5,6}$=7.6 Hz, 5-H), 6.20 (1H, d, 6'-H), 7.00 (1H, dd, $J_{5',6'}$=16.0 Hz, $J_{4',5'}$=5.6 Hz, 5'-H), and 7.73 (1H, d, 6-H); Found: C, 52.28; H, 5.71%. Calcd for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44%. The **12b** was recrystallized from EtOH, mp 128—130 °C; UV_{max} (H_2O) 219, 260 nm, UV_{min} 250 nm; ^{1}H-NMR (60 MHz, $CDCl_3$) δ=2.30 (3H, s, $COCH_3$), 3.30 (3H, s, NCH_3), 5.83 (1H, d, $J_{5,6}$=8.0 Hz, 5-H), 6.35 (1H, d, 6'-H), 6.91 (1H, dd, $J_{5',6'}$=16.0 Hz, $J_{4',5'}$=4.5 Hz, 5'-H), and 7.38 (1H, d, 6-H); Found: C, 52.20; H, 5.44; N, 9.50%. Calcd for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.46%.

Preparation of 11b by One-Pot Reaction. To a solution of **4b** (256 mg, 1 mmol), **1** (377 mg, 1.5 mmol), and **3** (786 mg, 3 mmol) in THF (3 ml) was added **2** (261 mg, 1.5 mmol) in THF (1 ml) at room temperature for 1 h. The reaction mixture being stirred for 3 h, **2** (1.5 mmol) in THF (1 ml) was further added for 1 h. To the solution kept stirring overnight, **13** (636 mg, 2 mmol) in benzene (10 ml) was added. The resulting solution was refluxed for 3 h and evaporated under reduced pressure. The residue was purified by column chromatography ($CHCl_3$:MeOH=7:1) to give **11b** in 73% yield.

Preparations of 17 and 18. A THF solution of **15a** (437 mg, 0.80 mmol) and **13** (234 mg, 0.80 mmol) was refluxed for 7.5 h and then evaporated under reduced pressure. The residue was purified by PLC ($CHCl_3$:MeOH=9:1) to give **17** in 18% yield: oil; UV_{max} (MeOH) 271 nm; ^{1}H-NMR ($CDCl_3$) δ=1.35 and 1.57 (6H, s, isopropylidene CH_3), 2.26 (3H, s, $COCH_3$), 4.66 (1H, m, 4'-H), 4.98 (1H, m, 3'-H), 5.21 (1H, d, $J_{2',3'}$=6.0 Hz, 2'-H), 5.49 (1H, s, 1'-H), 5.88 (1H, d, $J_{5,6}$=7.3 Hz, 5-H), 6.24 (1H, d, 6'-H), 6.95 (1H, dd, $J_{5',6'}$=16.1 Hz, $J_{4',5'}$=6.4 Hz, 5'-H), and 7.30 (1H, d, 6-H).

The **15b** (209 mg, 0.38 mmol) in THF (8 ml) was treated with **13** (239 mg, 0.81 mmol) under reflux for 5 h and then evapotated. The **18** was isolated by column chromatography using $CHCl_3$–MeOH (8:1) in 31% yield; oil; UV_{max} (MeOH) 319 nm, UV_{min} 261 nm; ^{1}H-NMR ($CDCl_3$–CD_3OD) δ=2.35 (3H, s, $COCH_3$), 3.17 and 3.22 (6H, s, $N(CH_3)_2$), 3.94 (1H, m, 3′-H), 4.18 (1H, d, $J_{2',3'}$=5.4 Hz, 2′-H), 4.66 (1H, m, 4′-H), 5.82 (1H, s, 1′-H), 6.44 (1H, dd, $J_{4',6'}$=1.4 Hz, 6′-H), 6.18 (1H, d, $J_{5,6}$=7.2 Hz, 5-H), 6.95 (1H, dd, $J_{5',6'}$=16.3 Hz, $J_{4',5'}$=5.0 Hz, 5′-H), 7.71 (1H, d, 6-H), and 8.87 (1H, s, =CHN–).

Preparations of 22a and 22b. A solution of *aci*-nitro ester [**20a** (76 mg, 0.13 mmol) or **20b** (230 mg, 0.43 mmol)] and **13** (2 equiv) in THF (7 ml) was refluxed for 7 h. After the solvent was removed, the residue was purified by column chromatography. For the reaction of **20a**, elution with $CHCl_3$–MeOH (15:1) gave **22a** as an oil in 61% yield; UV_{max} (MeOH) 313 nm, UV_{min} 282 nm; ^{1}H-NMR ($CDCl_3$) δ=1.38 and 1.67 (6H, s, isopropylidene CH_3), 2.30 (3H, s, $COCH_3$), 4.78 (1H, m, 4′-H), 5.02 (1H, m, 3′-H), 5.23 (1H, d, $J_{2',3'}$=6.3 Hz, 2′-H), 5.74 (1H, s, 1′-H), 6.25 (1H, dd, $J_{4',6'}$=1.0 Hz, 6′-H), 6.94 (1H, dd, $J_{5',6'}$=16.2 Hz, $J_{4',5'}$=6.6 Hz, 5′-H), 7.09 (1H, d, $J_{5,6}$=7.3 Hz, 5-H), 7.96 (1H, d, 6-H), and 8.15 and 9.26 (2H, s, triazole H).

For the reaction of **20b**, elution with EtOAc–MeOH (8:1) afforded a 77% yield of **22b** which was recrystallized from $CHCl_3$–MeOH: mp 208—209 °C; UV_{max} (MeOH) 217, 251, 316 nm, UV_{min} 233, 280 nm; ^{1}H-NMR ($CDCl_3$) δ=2.32 (3H, s, $COCH_3$), 3.93 (1H, dd, $J_{3',4'}$=4.8 Hz, $J_{4',5'}$=7.7 Hz, 4′-H), 4.18 (1H, dd, $J_{2',3'}$=3.4 Hz, 2′-H), 4.57 (1H, dd, 3′-H), 5.85 (1H, d, $J_{1',2'}$=0.6 Hz, 1′-H), 7.03 (1H, d, $J_{5,6}$=7.7 Hz, 5-H), 6.29 (1H, d, 6′-H), 7.07 (1H, dd, $J_{5',6'}$=16.1 Hz, 5′-H), 8.41 (1H, d, 6-H), and 8.43 and 9.46 (2H, s, triazole H); Found; C, 49.90; H, 4.52; N, 20.73%. Calcd for $C_{14}H_{15}N_5O_5$: C, 50.45; H, 4.54; N, 21.01%.

Preparations of 28a and 28b. A THF (7 ml) solution of **27** (228 mg, 0.25 mmol) and **13** (148 mg, 0.5 mmol) was refluxed for 7.5 h and then evaporated. The residue was purified by PLC (benzene:EtOAc=5:1 and $CHCl_3$:MeOH=20:1) to give **28a** and **28b** in 19 and 36% yields, respectively. **28a**: mp 112—115 °C; UV_{max} (MeOH) 232, 277 nm, UV_{min} 219, 267 nm; ^{1}H-NMR ($CDCl_3$) δ=2.29 (3H, s, $COCH_3$), 5.03 (1H, dd, $J_{3',4'}$=5.9 Hz, $J_{4',5'}$=5.6 Hz, 4′-H), 6.04 (1H, dd, $J_{2',3'}$=5.6 Hz, 3′-H), 6.4—6.5 (2H, m, 1′-H, 2′-H), 6.38 (1H, d, 6′-H), 7.02 (1H, dd, $J_{5',6'}$=16.2 Hz, 5′-H), and 8.25 and 8.68 (2H, s, purine H). **28b**: oil; UV_{max} (MeOH) 232, 282 nm, UV_{min} 257 nm; ^{1}H-NMR ($CDCl_3$) δ=2.32 (3H, s, $COCH_3$), 5.08 (1H, dd, $J_{3',4'}$=5.3 Hz, $J_{4',5'}$=5.6 Hz, 4′-H), 6.09 (1H, dd, $J_{2',3'}$=5.6 Hz, 3′-H), 6.5—6.6 (2H, m, 1′-H, 2′-H), 6.57 (1H, d, 6′-H), 7.06 (1H, dd, $J_{5',6'}$=16.2 Hz, 5′-H), 8.31 and 8.84 (2H, s, purine H), and 9.29 (1H, br s, NH).

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