Anal. Calcd for $C_{10}H_{13}N_4O_8P \cdot 0.5H_2O$: C, 33.62; H, 3.95; N, 15.69. Found: C, 33.57; H, 3.86; N, 15.64.

**Registry No.**—**5**, 55555-55-0; **5** triacetate, 55530-09-1; **6**, 55555-56-1; **6** triacetate, 55530-10-4; **7**, 55530-11-5; **7** triacetate, 55530-12-6; **7** triacetate ½ HBr, 55530-13-7; **8**, 55530-14-8; **8** triacetate, 55530-15-9; **8** triacetate ½ HBr, 55530-16-0; **9**, 55530-17-1; **10**, 55555-57-2; **11**, 55530-18-2; **12**, 55530-19-3; **13**, 17434-53-6; **14**, 55530-20-6; **15**, 55530-21-7; **16**, 55555-58-3; **17**, 55530-22-8; **18**, 55530-23-9; **19**, 55530-24-0; **20**, 55530-25-1; tri-*O*-acetyl-β-L-arabinopyranosyl bromide, 14227-90-8; bis(trimethylsilyl)uracil, 10457-14-4; tri-*O*-acetyl-α-L-lyxopyranosyl bromide, 55555-59-4; bis(trimethylsilyl)cytosine, 18037-10-0; 1,2,3,4-tetra-*O*-acetyl-α-L-arabinopyranose, 17080-99-8; tetra-*O*-acetyl-α-L-lyxopyranose, 2595-11-1; $N^6$-benzoyladenine, 4005-49-6; $N^6$-benzoyl-9-(2,3,4-tri-*O*-acetyl-α-L-lyxopyranosyl)adenine, 55530-26-2; 2,2-dimethoxypropane, 77-76-9; phosphoryl chloride, 10025-87-3; 2,6-dichloropurine, 1839-23-2.

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# Synthesis of 5-Vinyluridine and 5-Vinyl-2′-deoxyuridine as New Pyrimidine Nucleoside Analogs


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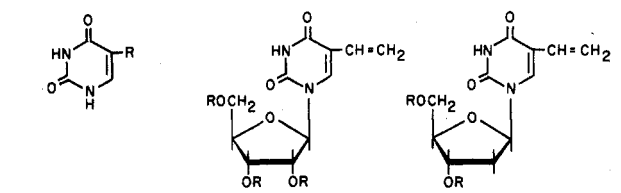
5-Formyluracil condensed smoothly with carbethoxymethylenetriphenylphosphorane to give *trans*- and *cis*-3-(5-uracilyl)acrylic acid ethyl ester (**3**). The analogous reaction, using methylenetriphenylphosphorane leading to 5-vinyluracil (**1**), failed. Alternatively, 5-chloromethyluracil was converted to the phosphonium salt **4** by reaction with triphenylphosphine. **4** readily condensed with paraformaldehyde in the presence of base to afford **1** in good yield. Condensation of the trimethylsilyl derivative of **1** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in the presence of stannic chloride gave, after deblocking, 5-vinyluridine (**7**). Similarly, condensation of the trimethylsilyl derivative **5** with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl chloride, followed by transesterification with sodium methoxide, gave 5-vinyl-2′-deoxyuridine (**10**) and its α anomer **11**. The anomeric configuration was determined by NMR spectroscopy.


In view of the antiviral activity of 5-ethyl-2′-deoxyuridine,[1,2] which has been reported to be comparable to that of 5-iodo-2′-deoxyuridine[1,3] vs. Herpes Simplex and Vaccinia viruses, and that of other 5-alkylpyrimidine nucleosides,[4,5] it appeared worthwhile to synthesize 5-vinyluridine (**7**) and 5-vinyl-2′-deoxyuridine (**10**), whose 5 substituent has a van der Waals radius in-between that of the methyl and ethyl groups.

Although the necessary intermediate **1** had previously been prepared by dehydration[6] of 5-(1-hydroxyethyl)uracil, decarboxylation[7] of 3-(5-uracilyl)propenoic acid, and also by the base-catalyzed condensation[8] of 2-dimethoxymethyl-3-methoxybutyrate with urea, the yields were very low. Since a larger amount of **1** was needed for the synthesis of nucleosides, we sought to develop an improved procedure for the preparation of **1**.

Initially, we attempted the synthesis of **1** by condensation of methylenetriphenylphosphorane with 5-formyluracil (**2**), which was obtained by the oxidation of 5-hydroxymethyluracil.[9] However, this procedure failed to furnish **1** under a variety of experimental conditions. The failure of **2** to undergo Wittig reaction with methylenetriphenylphosphorane parallels the observation made by other workers,[10,11] when only trace amounts of 6-vinylpyrimidines were obtained by condensation of this relatively unstable ylide with 6-formylpyrimidines. Satisfactory results were



obtained, however, when an ylide stabilized by conjugation was used in the Wittig reaction of **2**. Thus, condensation of **2** with carbethoxymethylenetriphenylphosphorane in DMF, at room temperature, proceeded smoothly to yield 70% of the (4:3) *trans*- and *cis*-3-(5-uracilyl)acrylic acid ester (**3**). The identity of each component in the mixture was determined by the different coupling constants of the vinyl protons.

Alternatively, the procedure similar to that described by Klein and Fox,[11] for the synthesis of 6-vinyluracil, was chosen for the preparation of **1**. 5-Chloromethyluracil, which was readily prepared from 5-hydroxymethyluracil by treatment with concentrated HCl,[12] afforded, upon reaction with triphenylphosphine in DMF, under nitrogen, 5-uracilylmethyltriphenylphosphonium chloride (**4**). The phosphonium salt **4** reacted with paraformaldehyde in DMF in the presence of excess sodium ethoxide to give 5-vinyluracil (**1**) in good yield. While this work was in progress, an interesting synthetic procedure for the preparation of **1** appeared in the literature.[13]

For the preparation of nucleosides, **1** was converted to its trimethylsilyl derivative (**5**) by reaction with hexamethyldisilazane in the presence of a catalytic amount of ammonium sulfate.[14] Condensation of the crude **5** with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in 1,2-dichloroethane, at room temperature, in the presence of stannic chloride[15] gave 2′,3′,5′-tri-*O*-benzoyl-5-vinyluridine (**6**). The blocked nucleoside (**6**) was purified by silica gel chromatography. Removal of the protecting benzoyl groups from **6**, by treatment with sodium methoxide in methanol, afforded 5-vinyluridine (**7**). It is generally recognized that condensation of the protected ribofuranosyl 1-*O*-acetate with trimethylsilylpyrimidines by the procedure of Niedballa and Vorbrüggen[15] leads almost exclusively to the corresponding β-nucleosides. The NMR spectrum of **7** showed the coupling constant $J_{1',2'}$ = 3 Hz, a value somewhat indicative of the β configuration.[16] The β configuration of **7** was further substantiated by the difference in the chemical shifts ($\Delta\delta$) of the methyl signals of the isopropylidine derivative of **7**, which is 0.20, as reported by Imbach and his coworkers[17,18] ($\Delta\delta < 0.15$ for the α anomer and >0.15 for the β anomer).

Treatment of 2,4-bis(trimethylsilyloxy)-5-vinylpyrimidine (**5**) with 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl chloride[19] in dry benzene at 0–5° for 2 hr, and then at room temperature for 8–10 hr under nitrogen, in the presence of stannic chloride furnished a 40% yield of the blocked nucleosides **8** and **9**, with an anomeric ratio of β/α = 3:1. A large portion of the β anomer (**8**) was separated from the mixture by fractional crystallization and the remaining mixture, containing α and β anomers, was resolved by chromatography on a dry silica gel column using benzene–ethyl acetate (7:3) as the eluent.

Transesterification of **8** by sodium methoxide in methanol furnished the desired 5-vinyl-2′-deoxyuridine (**10**). Assignment of the β configuration to **10** was made on the basis of the NMR spectrum, wherein the anomeric proton appeared as the characteristic triplet.[20,21] Similarly, deblocking of the protected nucleoside **9** by sodium methoxide in methanol afforded 1-(2-deoxy-α-D-*erythro*-pentofuranosyl)-5-vinyluracil (**11**). In the NMR spectrum of **11**, the anomeric proton appeared as a pair of doublets,[20,21] supporting the α configuration of the nucleoside.

The site of glycosidation of the nucleosides (**7**, **10**, and **11**) was assigned at N-1 on the basis of the uv spectra. While the uv spectra of N-1 substituted uracil derivatives show little change when compared at pH 7 or pH 12, the N-3 substituted uracil derivatives at pH 12 undergo a strong bathochromic shift of the maxima and an increase in the extinction coefficient.[14,22] The uv spectra of the compounds **7**, **10**, and **11** remained unchanged at pH 7 or 12, supporting the above conclusion.

## Experimental Section

**General Procedure.** Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Uv spectra were measured on a Cary Model 14 spectrophotometer, and NMR spectra on Varian A-60 and XL-100 spectrometers using $Me_4Si$ as internal standard. The mass spectra were recorded on a CEC 21-491 double-focusing mass spectrometer using an ionization voltage of 70 eV. Thin layer chromatography was performed on silica gel N-HR/$uv_{254}$ precoated plastic sheets (Brinkman); the spots were detected by uv absorbance or by spraying with 10% (v/v) sulfuric acid–ethanol and heating. Column chromatography was done on silica gel (60–200 mesh), J. T. Baker No. 3405. 5-Hydroxymethyluracil was purchased from Raylo Chemicals Limited, Edmonton, Alberta. Microanalyses were performed by Robertson Laboratory, Florham Park, N.J.

***trans*- and *cis*-3-(5-Uracilyl)acrylic Acid Ethyl Ester (3).** Anhydrous 5-formyluracil[8] (1.20 g, 0.0086 mol) was suspended in 50 ml of dry DMF and to this was added 4.50 g (0.0129 mol) of carbethoxymethylenetriphenylphosphorane. The reaction mixture was stirred at room temperature for 20 hr, at which time TLC, using benzene–ethyl acetate (3:7), showed essentially the disappearance of 5-formyluracil. The DMF was evaporated and the product was crystallized from absolute ethanol, yielding 1.26 g (70%) of the analytically pure **3** as colorless crystals: mp 215–216°; $\lambda_{max}$ (MeOH) 299 nm (ε 14,651), 261 (10,255); $\lambda_{min}$ (MeOH) 275 (9441), 227 (ε 2767).

The NMR spectrum of the crystalline **3** showed it to be a mixture of the cis and trans isomers in the ratio of 3:4. Some of the trans isomer was separated from the mixture by fractional crystallization from ethanol: mp 258–259°; NMR (DMSO-$d_6$) δ 1.25 (t, 3, $OCH_2CH_3$), 4.17 (q, 2, $OCH_2CH_3$), 6.86 and 7.45 (two AB doublets, 2, $J_{trans}$ = 16.5 Hz, CH=CH), 8.08 (s, 1, H-6), 11.45 (br, 2, 2NH's).

No attempt was made to isolate the cis isomer from the mixture. However, the NMR signals corresponding to the cis isomer of the mixed spectrum can be described as follows: NMR (DMSO-$d_6$) δ 1.23 (t, 3, $OCH_2CH_3$), 4.17 (q, 2, $OCH_2CH_3$), 5.88 and 6.90 (two AB doublets, 2, $J_{cis}$ = 12.5 Hz, CH=CH), 8.75 (s, 1, H-6), 11.40 (br, 2, 2NH's).

Anal. Calcd for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.76; N, 13.33. Found: C, 51.18; H, 4.75; N, 13.05.

**5-Uracilylmethyltriphenylphosphonium Chloride (4).** To a suspension of 5-chloromethyluracil[11] (8.50 g, 0.0527 mol) in 100 ml of dry DMF was added 20.00 g (0.0763 mol) of triphenylphosphine. The mixture was stirred at 100° under nitrogen for 16 hr. A clear solution thus obtained was then evaporated to dryness. The residue was triturated with anhydrous ether to remove the unreacted triphenylphosphine. The product was obtained as a colorless, crystalline solid, yield 21.50 g (96%). Recrystallization from absolute ethanol gave the analytical sample: mp 287–288°; $\lambda_{max}$ (MeOH) 274 nm (ε 10,717), 267 (11,644), $\lambda_{min}$ (MeOH) 247 (6595).

Anal. Calcd for $C_{23}H_{20}N_2O_2PCl \cdot 1.5H_2O$: C, 61.40; H, 5.11; N, 6.22; Cl, 7.89. Found: C, 61.73; H, 5.31; N, 6.09; Cl, 8.13.

**5-Vinyluracil (1).** A mixture of the phosphonium chloride **4** (6.50 g, 0.0154 mol, dried over $P_2O_5$ at 110° for 10 hr) and paraformaldehyde (2.7 g, 0.0900 mol, dried over $P_2O_5$ at 50° for 12 hr) was suspended in 300 ml of dry DMF. To the stirred suspension was added dropwise under nitrogen a solution of sodium ethoxide (prepared from 1.60 g of sodium metal in 100 ml of absolute ethanol). The addition of the sodium ethoxide led to the dissolution of most of the solid, although a clear solution could not be obtained. After a few minutes, the reaction mixture became turbid as a precipitate formed. After all the sodium ethoxide was added (20 min), the thick suspension was stirred at room temperature under nitrogen for 18 hr. The reaction mixture was then warmed to 50–60° for 20 min, cooled to room temperature, and evaporated to dryness. The solid material was taken up in 400 ml of MeOH, neutralized with Dowex 50 ($H^+$) resin, and filtered. The clear solution was evaporated to dryness and the residue was triturated with ether to remove triphenylphosphine oxide. The crude material thus obtained was 1.90 g (89%). After two recrystallizations from water, 1.69 g of **1** was obtained (80% yield). The analytical sample was prepared by pouring the material in a small amount of water on a dry silica gel column, eluting with ethyl acetate, and finally crystallization from

water: mp 250–285° (lit.[6] mp 248° dec, lit.[7] mp 230–270°); $\lambda_{max}$ (MeOH) 288 nm ($\epsilon$ 8452), 238 (13714), $\lambda_{min}$ (MeOH) 259 ($\epsilon$ 4398); mass spectrum *m/e* 138 ($M^+$), 139 ($M^+ + 1$); NMR (DMSO-$d_6$) $\delta$ 5.06 (2 d, 1, $J_{AC}$ = 11, $J_{BC}$ = 3 Hz, H-C), 5.94 (2 d, 1, $J_{AB}$ = 18, $J_{BC}$ = 3 Hz, H-B), 6.40 (2 d, 1, $J_{AB}$ = 18, $J_{AC}$ = 11 Hz, H-A), 7.58 (s, 1, H-6), 11.12 (s, 2, 2 NH).

Anal. Calcd for $C_6H_6N_2O_2$: C, 52.20; H, 4.39; N, 20.30. Found: C, 52.14; H, 4.53; N, 20.11.

**2,4-Bis(trimethylsilyloxy)-5-vinylpyrimidine (5).** A mixture of well-dried **4** (1.65 g, 0.0120 mol), hexamethyldisilazane (35 ml), and 30 ml of dry benzene was heated under reflux in the presence of anhydrous ammonium sulfate (0.03 g). After 6–7 hr, a clear solution resulted. The solvents were evaporated in vacuo and the oily product was coevaporated with dry toluene. The crude trimethylsilyl derivative (**5**) thus obtained was utilized directly for condensation with protected sugars.

**2',3',5'-Tri-*O*-benzoyl-5-vinyluridine (6).** To a solution of **5** [prepared from 0.67 g (0.0049 mol) of **1**] and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-$\beta$-D-ribofuranose (3.00 g, 0.0059 mol) in 50 ml of dry 1,2-dichloroethane was added slowly a solution of 0.2 ml of stannic chloride[12] in 15–20 ml of 1,2-dichloroethane. The reaction mixture was stirred at room temperature for 16 hr under anhydrous conditions. TLC of the mixture using benzene–ethyl acetate (7:1) showed the presence of essentially one major spot ($R_f$ 0.69) in addition to some unreacted sugar. The solution was extracted with saturated aqueous sodium bicarbonate and three times with water, and dried over anhydrous sodium sulfate. The solvent was removed by evaporation and the crude **6** was purified on a dry silica gel column, eluting with benzene–ethyl acetate (7:1). After evaporation, **6** was obtained as a colorless foam. Crystallization from absolute ethanol gave 1.65 g (58%) of the analytically pure **6**, mp 141–142°.

Anal. Calcd for $C_{32}H_{26}N_2O_9$: C, 65.98; H, 4.47; N, 4.81. Found: C, 65.96; H, 4.64; N, 4.76.

**5-Vinyluridine (7).** A solution of **6** (0.89 g, 0.0015 mol) and sodium methoxide (0.15 g, 0.0028 mol) in 100 ml of methanol was stirred at room temperature for 45 min. It was then neutralized with Dowex 50 ($H^+$) resin and filtered, and the resin was washed with methanol. The combined filtrate was evaporated and the residue was crystallized from ethanol, giving 0.37 g (89%) of **7**: mp 160–165° sintered, 255–260° dec; $\lambda_{max}$ (MeOH) 291 nm ($\epsilon$ 9450), 237 (11,285), $\lambda_{min}$ (MeOH) 259 (3983); NMR (DMSO-$d_6$) $\delta$ 5.12 (2 d, 1, $J_{AC}$ = 11, $J_{BC}$ = 3 Hz, H-C), 5.78 (d, 1, $J_{1',2'}$ = 3 Hz, H-1'), 5.88 (2 d, 1, $J_{AB}$ = 18, $J_{BC}$ = 3 Hz, H-B), 6.38 (2 d, 1, $J_{AB}$ = 18, $J_{AC}$ = 11 Hz, H-A), 8.20 (s, 1, H-6), 11.40 (s, 1, NH).

Anal. Calcd for $C_{11}H_{14}N_2O_6$: C, 48.89; H, 5.19; N, 10.37. Found: C, 48.79; H, 5.34; N, 10.17.

**1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-$\beta$-D-*erythro*-pentofuranosyl)-5-vinyluracil (8) and 1-(2-Deoxy-3,5-di-*O*-*p*-toluoyl-$\alpha$-D-*erythro*-pentofuranosyl)-5-vinyluracil (9).** A solution of the trimethylsilyl derivative **5** [prepared from 1.65 g (0.0120 mol) of **1**] and 2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranosyl chloride[17] [obtained from 6.50 g (0.0169 mol) of methyl-2-deoxy-3,5-di-*O*-*p*-toluoyl-D-*erythro*-pentofuranoside[17]] in 150 ml of dry benzene was kept in ice under a nitrogen atmosphere. To this cooled solution was added slowly 0.4 ml of stannic chloride in 100 ml of dry benzene over a period of 20 min. About 100 ml of anhydrous 1,2-dichloroethane was also added to the reaction mixture. The mixture was stirred for 2–3 hr at 0–5° and then at room temperature for 8–10 hr. The solution was extracted with saturated aqueous sodium bicarbonate and twice with water, and dried over anhydrous sodium sulfate. TLC of the mixture using benzene–ethyl acetate (7:3) showed essentially two major products with $R_f$ values 0.45 and 0.53, together with some minor products. The mixture was evaporated to dryness, giving a colorless foam, which was dissolved in 300 ml of acetone and then evaporated to approximately 10 ml when crystallization started. Methanol (10–15 ml) was added and the crystals were filtered. TLC of this crystalline material, in the above solvent system, showed it to be the $\beta$ anomer **8** (0.90 g, $R_f$ 0.53). The mother liquor containing the $\alpha$ and $\beta$ anomers was chromatographed on a dry silica gel column, eluting with benzene–ethyl acetate (7:3). The first fraction containing the $\beta$ anomer was evaporated, furnishing the crystalline material, which was recrystallized from methanol to yield 0.86 g of **8**. Thus the pure $\beta$ anomer **8** was obtained in a total yield of 1.76 g (30%), mp 172–173°.

Anal. Calcd for $C_{27}H_{26}N_2O_7$: C, 66.12; H, 5.31; N, 5.71. Found: C, 66.11; H, 5.49; N, 5.65.

Evaporation of the second fraction gave the crystalline $\alpha$ anomer **9**, which was recrystallized from ethanol, 0.53 g (9%), mp 136–137°.

Anal. Calcd for $C_{27}H_{26}N_2O_7$: C, 66.12; H, 5.31; N, 5.71. Found: C, 65.91; H, 5.53; N, 5.54.

**5-Vinyl-2'-deoxyuridine (10).** To a suspension of compound **8** (0.40 g, 0.0008 mol) in 100 ml of dry methanol was added a freshly prepared solution of sodium methoxide (0.15 g of sodium in 50 ml of methanol). The mixture was stirred at room temperature for 2 hr, neutralized with Dowex 50 ($H^+$) resin, and filtered, and the resin was washed with methanol. The combined filtrates were evaporated to dryness. The residue was triturated with ether to remove the methyl *p*-toluate. This procedure yielded 0.16 g (76%) of the deblocked nucleoside **10**. Recrystallization from absolute ethanol gave the analytical sample: mp 230–235° with effervescence, 260–265° dec; $\lambda_{max}$ (MeOH) 292 nm ($\epsilon$ 9190), 238 (12,253), $\lambda_{min}$ (MeOH) 260 (4021); NMR (DMSO-$d_6$) $\delta$ 5.14 (2 d, 1, $J_{AC}$ = 11, $J_{BC}$ = 3 Hz, H-C), 5.90 (2 d, 1, $J_{AB}$ = 18, $J_{BC}$ = 3 Hz, H-B), 6.18 (t, 1, $J_{1',2'}$ = 6.5 Hz, H-1'), 6.42 (2 d, 1, $J_{AB}$ = 18, $J_{AC}$ = 11 Hz, H-A), 8.14 (s, 1, H-6), 11.40 (br, 1, NH).

Anal. Calcd for $C_{11}H_{14}N_2O_5$: C, 51.96; H, 5.51; N, 11.02. Found: C, 51.69; H, 5.74; N, 10.72.

**1-(2-Deoxy-$\alpha$-D-*erythro*-pentofuranosyl)-5-vinyluracil (11).** A suspension of 0.24 g (0.0005 mol) of **9** in 50 ml of dry methanol was treated with sodium methoxide (0.08 g of sodium in 50 ml of methanol). After 2 hr of stirring at room temperature, the solution was neutralized with Dowex 50 ($H^+$) resin, filtered, and evaporated. Trituration of the residue with ether gave 0.10 g (80%) of **11**. An analytical sample was prepared by recrystallization from ethanol: mp 235–240° with effervescence, 260–265° dec; $\lambda_{max}$ (MeOH) 292 nm ($\epsilon$ 9024), 239 (11,698), $\lambda_{min}$ (MeOH) 260 ($\epsilon$ 4177); NMR (DMSO-$d_6$) $\delta$ 5.12 (2 d, 1, H-C), 5.88 (2 d, 1, H-B), 6.14 (d of d, 1, $J_{1',2',2''}$ = 2.5 and 7.0 Hz, H-1'), 6.42 (2 d, 1, H-A), 8.06 (s, 1, H-6), 11.38 (br, 1, NH).

Anal. Calcd for $C_{11}H_{14}N_2O_5$: C, 51.96; H, 5.51; N, 11.02. Found: C, 51.69; H, 5.78; N, 10.72.

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**Registry No.**—**1**, 37107-81-6; *cis*-**3**, 55520-59-7; *trans*-**3**, 55520-60-0; **4**, 55520-61-1; **5**, 55520-62-2; **6**, 55520-63-3; **7**, 55520-64-4; **8**, 55520-65-5; **9**, 55520-66-6; **10**, 55520-67-7; **11**, 55520-68-8; 5-formyluracil, 1195-08-0; 5-chloromethyluracil, 3590-48-5; triphenylphosphine, 603-35-0; hexamethyldisilazane, 999-97-3; 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-$\beta$-D-ribofuranose, 6974-32-9; 2-deoxy-3,5-di-*O*-*p*-toluoyl-$\alpha$-D-*erythro*-pentofuranosyl-5-vinyluracil, 3601-89-6.

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