Diazomethyl Ketone Derivatives of Pyrimidine Nucleosides

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1,5,6,8-Tetradeoxy-8-diazo-β-D-*erythro*-7-octulofuranosylthymine (**20**) and 5,6,8-trideoxy-8-diazo-β-D-*ribo*-7-octulofuranosyluracil (**31**), pyrimidine nucleosides containing the reactive diazomethyl ketone function, were prepared from thymidine and uridine via their 5'-aldehydes **2** and **22** by the Wittig reaction with (carbalkoxymethylene)triphenylphosphoranes followed by modification of the side chains of **3**, **4**, and **23** and blocking of the acidic NH of the pyrimidine rings.

As a part of a program to develop active-site-directed, irreversible inhibitors of enzymes involved in the metabolism of pyrimidine nucleotides, we have prepared diazo ketone derivatives of thymidine and uridine, since such a functional group should react under in vivo conditions with protonated guanidine groups that act as binding points for the phosphate moieties of these nucleotides.[1] An effort was made to properly position the diazomethyl ketone group by extending the carbon chain attached to C-4 of the furanose ring of the nucleosides. To do this 1-(3-*O*-acetyl-2-deoxy-β-D-*erythro*-pento-1,5-dialdo-1,4-furanosyl)thymine[2] (**2**) was prepared by the Pfitzner–Moffatt oxidation of 3'-*O*-acetylthymidine followed by isolation of the aldehyde as the *N*,*N*'-diphenylethylenediamine derivative, although we later found that, for the purpose herein described, this step can be omitted. Reaction of **2** with (carbethoxymethylene)triphenylphosphorane gave trans olefin **3** (Scheme I) which was reduced to **6** which in turn was hydrolyzed to 1,2,5,6-tetradeoxy-1-(thymin-1-yl)-β-D-*erythro*-heptofuranuronic acid (**15**). Since attempted acylation of **15** gave a complex reaction mixture, probably due to mixed anhydride formation and subsequent reactions, **15** was converted to its benzyl ester (**16**) by treatment with thionyl chloride in excess benzyl alcohol. Treatment of **16** with 4-toluyl chloride gave a mixture of the mono- (**7**) and bis(4-toluyl) (**9**) derivatives in a ratio of about 1:2, identified by mass spectral data (M^+ of m/e 493 and 611) and chromatographic behavior and separated by dissolution of **9** in ether in which **7** is almost completely insoluble. Compound **7** was converted to the acid chloride **12** which was allowed to react with a 30-fold excess of diazomethane for 16 h at which time no **12** remained (TLC), and a major, new, NBP positive, UV absorbing spot that charred appeared on the chromatogram. The IR spectrum of this material showed a strong band at 2105 cm^{-1}, and its UV spectrum was essentially the same as that of thymidine, but the mass spectrum (field desorption) showed a molecular ion of m/e 440, indicating methylation of the diazo ketone had occurred. The ^1H NMR spectrum showed three kinds of methyl signals: δ 1.89 (s, 5-CH_3), 2.41 (s, $CH_3C_6H_4$), and 3.20 (s, NCH_3). The identity of the UV spectrum with that of thymidine indicates that N-methylation occurred principally, in keeping with previous observations.[3,4] Since diazomethyl ketone formation was accompanied by N-methylation, the bis(4-toluyl) compound **9** was reduced to the acid **10** for conversion to the acid chloride **13**, which cannot undergo N-methylation. Reaction of **13** with diazomethane gave the diazomethyl ketone **18** [m/e 545 $(M + 1)^+$], which was purified to homogeneity by dry-column chromatography but which did not crystallize and did not give acceptable elemental analyses. Analytically pure **20** was obtained by a different route. Reaction of [(carbobenzyoxy)methylene]triphenylphosphorane, prepared from benzyl bromoacetate, with **2** gave the olefin **4** which was acylated at N-3 to give **5**. Reduction of **5** gave the fully protected **11** for conversion to the acid chloride **14** for reaction with diazomethane. Treatment of the diazomethyl ketone **19**, purified by preparative TLC, with methoxide gave the target compound **20**, also purified by chromatography. In addition to **19**, a second product was isolated that appears to be the corresponding chloromethyl ketone although its instability prevented its purification.

The diazomethyl ketone derivative (**31**) of uridine was prepared by a similar sequence of reactions. 1,5,6-Trideoxy-1-(uracil-1-yl)-β-D-*ribo*-heptofuranuronic acid (**25**) was prepared from 2',3'-*O*-isopropylideneuridine **21** via the Wittig reaction with the aldehyde **22**[5,6] followed by reduction and removal of the blocking groups (Scheme II). The acid **25** was converted to its benzyl ester **26** which was benzoylated to the tribenzoyl derivative **27**. Reaction of the acid chloride **29**, prepared from **28**, with an excess of diazomethane gave **30**, which was treated with methoxide to give 5,6,8-trideoxy-8-diazo-β-D-*ribo*-7-octulofuranosyluracil (**31**), which was purified by chromatography. Again, a second, unstable product tentatively identified as the corresponding chloromethyl ketone was isolated from the reaction.

Experimental Section

All evaporations were carried out in vacuo with a rotary evaporator. Analytical samples were normally dried in vacuo over P_2O_5 at room temperature for 16 h. Analtech precoated (250 μm) silica gel G(F) plates were used for TLC analyses; the spots were detected by irradiation with a Mineralight and by charring after spraying with saturated $(NH_4)_2SO_4$. Compounds containing the acid chloride or diazomethyl ketone function were also detected with (*p*-nitrobenzyl)pyridine. All analytical samples were essentially TLC homogeneous. Melting points were determined with a Mel-Temp apparatus and are not corrected. The UV absorption spectra were determined in 0.1 N HCl (pH 1), pH 7 buffer, and 0.1 N NaOH (pH 13) with a Cary 17 spectrophotometer: the maxima are reported in nanometers ($10^{-3}\epsilon$). The NMR spectra were determined with a Varian XL-100-15 spectrometer in Me_2SO-d_6 (unless otherwise specified) with tetramethylsilane as an internal reference: chemical shifts (δ) quoted in the case of multiplets are measured from the approximate

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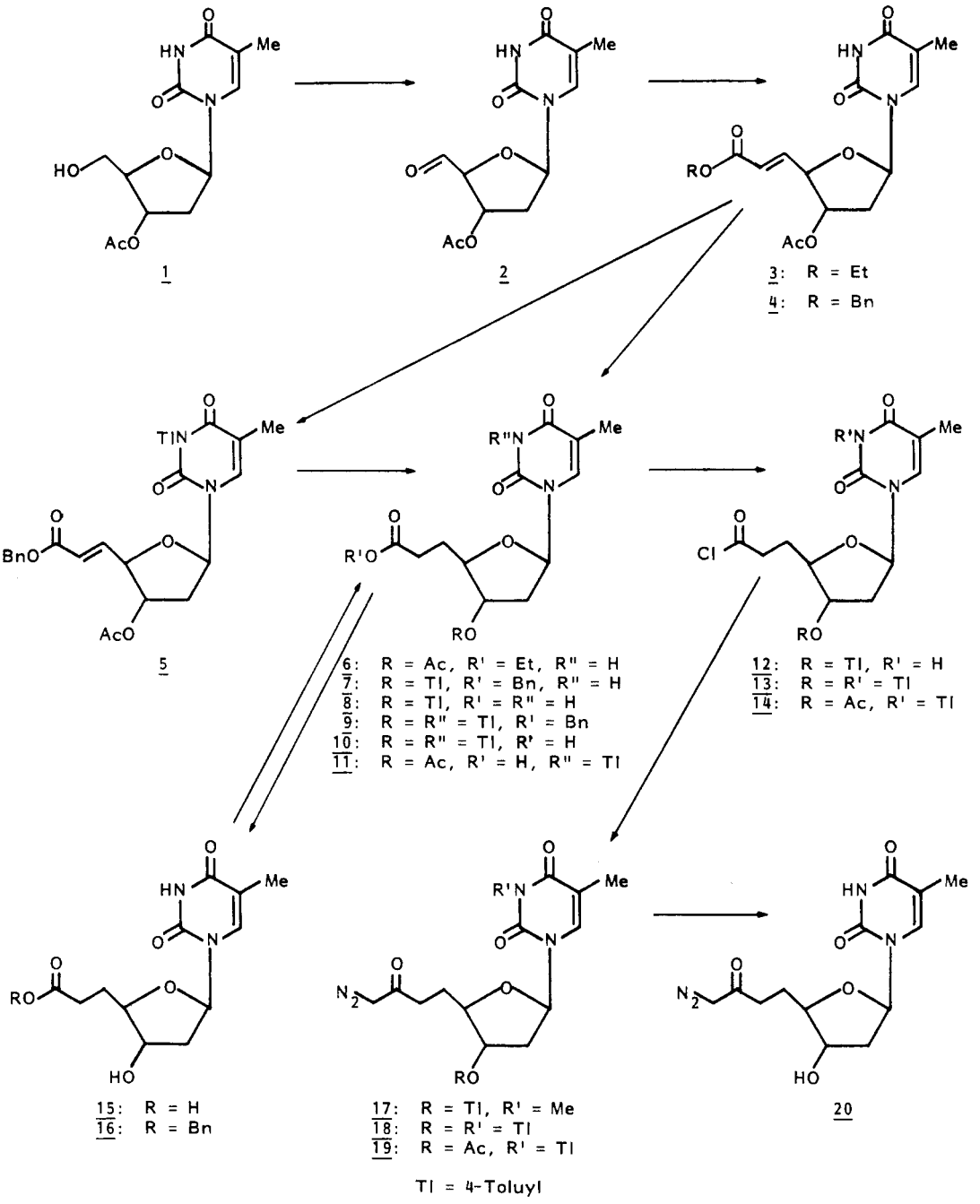
Scheme I



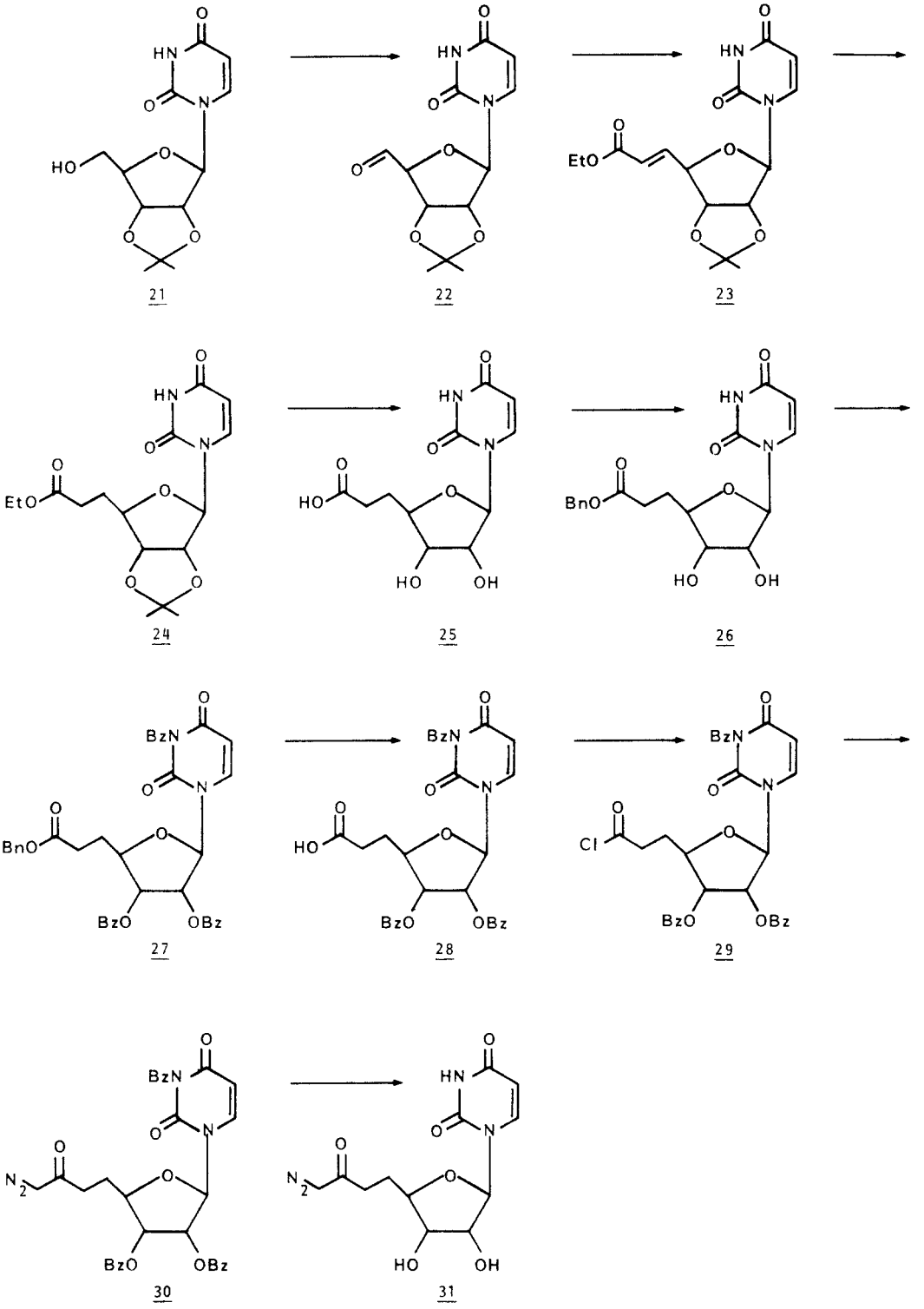
center. The mass spectral data were obtained with a Varian MAT 311A mass spectrometer in the electron-impact (EI) or field-desorption (FD) mode.

1-(3-*O*-Acetyl-2-deoxy-β-D-*erythro*-pento-1,5-dialdo-1,4-furanosyl)thymine (2). A solution of 3′-*O*-acetylthymidine (5.68 g, 20.0 mmol) and *N,N*′-dicyclohexylcarbodiimide (16.5 g, 80.0 mmol) in Me_2SO (60 mL) was diluted with dichloroacetic acid (0.8 mL, 10.0 mmol) in Me_2SO (20 mL) and stirred at ambient temperature for 3 h before oxalic acid (7.56 g, 60.0 mmol) was carefully added. After 0.5 h at ambient temperature, the resulting mixture was filtered, and the insolubles were washed with MeOH. The combined filtrate and wash was treated with dianilinoethane (6.40 g, 30.0 mmol) and kept in the dark at ambient temperature for 20 h before it was poured into aqueous 2% $NaHCO_3$ (2 L). The $CHCl_3$ extract of the resulting insoluble material was washed with two 250-mL portions of H_2O, dried with $MgSO_4$, and evaporated to an orange syrup, which crystallized from cyclohexane–ethyl acetate (3:1) as the dianilinoethane adduct, yield 1.92 g. Another crop was obtained by purification of the filtrate on a dry silica gel (Woelm) column (2 cm × 48 cm) developed in cyclohexane–ethyl acetate (3:1). The product was obtained by MeOH extraction: yield 6.62 g (total yield, 87%); mass spectrum, *m/e* 416 [$(M - HOAc)^+$], 461 [$(M - CH_3)^+$], 476 (M^+) TLC was done with $CHCl_3$–MeOH (95:5).

The free aldehyde was obtained by stirring 8.36 g (17.0 mmol) of the adduct with 24 g of Dowex 50W-X8 (H^+) ion-exchange resin (50–100 mesh) in a mixture of H_2O–THF (372 mL, 1:1) for 6 h. The resulting solution was filtered, evaporated in vacuo to remove the THF, refiltered, and evaporated to dryness. Trituration of the residue with ether gave a solid that was dried in vacuo and used immediately to prepare **4** [TLC done with $CHCl_3$–MeOH (95:5)].

Ethyl 3-*O*-Acetyl-1,2,5,6-tetradeoxy-1-(thymin-1-yl)-β-D-*erythro*-hept-5-enofuranuronate (3). A solution of 3′-*O*-acetylthymidine (284 mg, 1.0 mmol) and dicyclohexylcarbodiimide (620 mg, 3.0 mmol) in Me_2SO (2.5 mL) was treated with dichloroacetic acid (4 mL, 0.5 mmol), stirred 20 h at ambient temperature, and then neutralized with pyridine (0.04 mL) before addition of (carboxymethylene)triphenylphosphorane (349 mg, 1.0 mmol). The resulting mixture was stirred for 20 h at ambient temperature and evaporated to dryness in vacuo. The residue was purified by preparative thin-layer chromatography on

Scheme II



Brinkmann silica gel 60F-254 plates (2-mm thickness) developed in ethyl acetate–cyclohexane (2:1). The product was eluted with MeOH and rechromatogrammed as described above. A glass was obtained: yield 265 mg (75%); ^{1}H NMR δ 1.2 (t, CH_3CH_2), 1.8 (s, 5-CH_3), 2.07 (s, CH_3CO), 2.3–2.7 (m, 2 $H_{2'}$), 4.15 (m, CH_3CH_2), 4.58 (m, $H_{4'}$), 5.2 (m, $H_{3'}$), 6.07 (d, $H_{6'}$), 6.25 (t, $H_{1'}$), 7.05 (dd, $H_{5'}$), 7.6 (H_6).

[(Carbobenzyloxy)methylene]triphenylphosphorane. A solution of benzyl bromoacetate (286 mg, 1.25 mmol) and triphenylphosphene (361 mg, 1.37 mmol) in CH_3CN (20 mL) was refluxed for 0.5 h and neutralized with 1 N $NaOCH_3$ (1.25 mL). The solution was then allowed to react with the aldehyde **2** without isolation of the product [TLC with cyclohexane–ethyl acetate (9:1)].

Benzyl 3-*O*-Acetyl-1,2,5,6-tetradeoxy-1-(thymin-1-yl)-β-D-*erythro*-hept-5-enofuranuronate (4). A solution of 1-(3-*O*-acetyl-2-deoxy-β-D-*erythro*-pento-1,5-dialdo-1,4-furanosyl)thymine (**2**, 1.25 mmol) and [(carbobenzyloxy)methylene]triphenylphosphorane (1.25 mmol) in acetonitrile (20 mL) was kept 20 h at ambient temperature, evaporated to about 2 mL, and resolved by preparative thin-layer chromatography on silica gel plates (Brinkmann 60F-254, 2-mm thickness) developed in ethyl acetate. Elution of the product band with ethyl acetate gave a syrup: yield 278 mg (54%); mass spectrum, *m/e* 229 [(sugar – HOAc)$^+$], 289 [(sugar)$^+$], 354 [(M - HOAc)$^+$], 414 (M^+).

Benzyl 3-*O*-Acetyl-1,2,5,6-tetradeoxy-1-[3-(4-toluyl)thymin-1-yl]-β-D-*erythro*-hept-5-enofuranuronate (5). To a cold (ice bath) solution of benzyl 3-*O*-acetyl-1,2,5,6-tetradeoxy-1-

(thymin-1-yl)-β-D-*erythro*-hept-5-enofuranuronate (**4**; 5.73 g, 13.8 mmol) in pyridine (50 mL) was added 4-toluyl chloride (6.41 g, 41.5 mmol). After being stirred in the cold for 1 h, the solution was kept 20 h at ambient temperature. Since TLC examination showed the presence of starting compound, the solution was again chilled and treated with another 5.48 mL of 4-toluyl chloride. After another 20 h at ambient temperature, the solution was poured into saturated $NaHCO_3$ (100 mL) and the mixture extracted with $CHCl_3$ (100 mL). The $CHCl_3$ layer was washed successively with 100 mL each of saturated $NaHCO_3$, cold dilute H_2SO_4, and H_2O. After being dried with $MgSO_4$, the $CHCl_3$ solution was evaporated to dryness in vacuo. The syrup obtained was purified by dry-column chromatography on a silica gel (Woelm) column (1.5 cm × 5 cm), developed with cyclohexane–ethyl acetate. Evaporation of the MeOH extract of the product band gave a glass: yield 3.4 g (46%); ^1H NMR δ ($CDCl_3$) 1.95 (m, CH_3), 2.05 (s, $COCH_3$ of cis isomer), 2.09 (s, $COCH_3$ of trans isomer), 2.1–2.6 (m, 2 $H_{2'}$), 2.41 (s, CH_3 of toluyl), 4.6 (m, $H_{4'}$), 5.18 (m, $H_{3'}$ and CH_2), 6.22 (m, $H_{6'}$), 6.35 (m, $H_{1'}$), 7.1 (m, $H_{5'}$), 7.3 (br m, aromatic H and H_6), 8.2 (d, H_2 and H_6 of toluyl); mass spectrum (FD), *m/e* 532 (M^+), 533 [$(M + 1)^+$].

Ethyl 3-*O*-Acetyl-1,2,5,6-tetradeoxy-1-(thymin-1-yl)-β-D-*erythro*-heptofuranuronate (6). A solution of ethyl 3-*O*-acetyl-1,2,5,6-tetradeoxy-1-(thymin-1-yl)-β-D-*ribo*-hept-5-enofuranuronate (**3**; 245 mg, 0.7 mmol) in MeOH (50 mL) containing PtO_2 catalyst (55 mg) was hydrogenated at ambient temperature and 48 psi of H_2 for 20 h, filtered, and evaporated to a syrup: yield 237 mg (96%); ^1H NMR δ 1.15 (m, CH_3CH_2), 1.8 (s, 5-CH_3), 1.7–2.1 (m, 2 $H_{5'}$ and 2 $H_{6'}$), 2.04 (s, CH_3CO), 2.35 (m, 2 $H_{2'}$), 3.3 (H_2O), 3.9 (m, $H_{4'}$), 4.05 (q, CH_3CH_2), 5.05 (m, $H_{3'}$), 6.12 (t, $J_{1',2'}$ = 6 Hz, $H_{1'}$), 7.6 (m, H_6), 12.1 (br, NH); mass spectrum, *m/e* 229 (sugar), 249 [$(M - HOAc - EtO)^+$], 294 [$(M - HOAc)^+$], 354 (M^+).

3-*O*-Acetyl-1,2,5,6-tetradeoxy-1-[3-(4-toluyl)thymin-1-yl]-β-D-*erythro*-heptofuranuronic acid (11). A solution of benzyl 3-*O*-acetyl-1,2,5,6-tetradeoxy-1-[3-(4-toluyl)thymin-1-yl]-β-D-*erythro*-hept-5-enofuranuronate (**5**; 1.06 g, 1.99 mmol) in glacial acetic acid (25 mL) containing PtO_2 catalyst (200 mg) was hydrogenated at ambient temperature and atmospheric pressure until the uptake of hydrogen was complete (ca. 3 h). The solution, after filtering, was freeze-dried to a fluffy white solid: yield 826 mg (93%); TLC was done with H_2O; ^1H NMR δ 1.95 (s, 5-CH_3), 2.0 (m, 2 $H_{5'}$), 2.1 (s, CH_3CO), 2.47 (s, CH_3 of toluyl), 2.0–2.8 (m, 2 $H_{2'}$, $H_{6'}$), 4.0 (m, $H_{4'}$), 5.15 (m, $H_{3'}$), 6.18 (t, $J_{1',2'}$ = 7 Hz, $H_{1'}$), 7.45 (d, H_3 and H_5 of toluyl), 7.8 (s, H_6), 9.2 (d, H_2 and H_6 of toluyl), H of CO_2H best observed in integral; mass spectrum (FD), *m/e* 444 (M^+), 445 [$(M + 1)^+$].

1,2,5,6-Tetradeoxy-1-(thymin-1-yl)-β-D-*erythro*-heptofuranuronic acid (15). A solution of ethyl 3-*O*-acetyl-1,2,5,6-tetradeoxy-1-(thymin-1-yl)-β-D-*erythro*-hept-5-enofuranuronate (**3**; 2.4 g, 6.7 mmol) in 1 N NaOH (52 mL) was heated at 80 °C for 20 h, deionized with Amberlite IR-120 (H), evaporated to about 6 mL, and purified by preparative thin-layer chromatography on Analtech Avicel cellulose plates (1-mm thickness) developed in BuOH–HOAc–H_2O (5:2:3). The product was extracted with H_2O. Evaporation of the aqueous solution gave a syrup that was crystallized from MeOH: yield 207 mg (11%); mp 163 °C; UV λ_{max} ($10^{-3}\epsilon$) 266 nm at pH 1 (9.71), 267 at pH 7 (9.69), 266 at pH 13 (7.58); ^1H NMR δ 1.82 (s, 5-CH_3), 1.9 (m, 2 $H_{5'}$), 2.1 (t, 2 $H_{2'}$), 2.30 (q, 2 $H_{6'}$), 3.65 (m, $H_{4'}$), 4.1 (m, $H_{3'}$), 6.15 (t, $J_{1',2'}$ = 6 Hz, $H_{1'}$), 7.42 (s, H_6), 13.37 (s, ring NH); mass spectrum (FD), *m/e* 284 (M^+), 285 [$(M + 1)^+$].

Anal. Calcd for $C_{12}H_{16}N_2O_6$: C, 50.69; H, 5.67; N, 9.86. Found: C, 50.50; H, 5.80; N, 9.83.

Benzyl 1,2,5,6-Tetradeoxy-1-(thymin-1-yl)-β-D-*erythro*-heptofuranuronate (16). Thionyl chloride (0.87 mL, 12 mmol) was added to a suspension of 1,2,5,6-tetradeoxy-1-(thymin-1-yl)-β-D-*erythro*-heptofuranuronic acid (**15**; 1.72 g, 6 mmol) in benzyl alcohol (42 mL) chilled in an ice–MeOH bath. After the ice melted, the mixture was stirred overnight before it was evaporated in vacuo at 40 °C. After crystallization began, the evaporation was stopped, and two volumes of ether were added. The product was washed with ether and dried: yield 1.58 g (70%); mp 148–150 °C; UV λ_{max} ($10^{-3}\epsilon$) 267 nm (9.74) at pH 1, 7, and 13; ^1H NMR δ 1.78 (s, 5-CH_3), 2.20 (m, 2 $H_{2'}$ and CH_2CH_2), 3.67 (m, $H_{4'}$), 4.12 (m, $H_{3'}$), 4.73 (s, $CH_2C_6H_5$), 5.22 (m, OH), 6.11 (t, $H_{1'}$), 7.33 (m, C_6H_5 and H_6), 11.2 (m, NH).

A small sample was recrystallized from ethyl acetate for analysis; mp 149–151 °C.

Anal. Calcd for $C_{19}H_{22}N_2O_6 \cdot 0.2EtOAc$: C, 60.61; H, 6.02; N, 7.14. Found: C, 60.37; H, 5.99; N, 7.41.

2,5,6,8-Tetradeoxy-8-diazo-β-D-*erythro*-7-octulofuranosylthymine (20). A solution of 3-*O*-acetyl-1,2,5,6-tetradeoxy-1-[3-(4-toluyl)thymin-1-yl]-1-β-D-*erythro*-heptofuranuronic acid (**11**; 767 mg, 1.73 mmol) in thionyl chloride (25 mL) was stirred in a drybag with external cooling (ice bath) for about 7 min and then at ambient temperature for 2 h before evaporation to dryness under anhydrous conditions. The residue was dissolved in anhydrous toluene and again evaporated to dryness to remove last traces of HCl. The residue of acid chloride was treated with an ethereal solution of diazomethane (ca. 20 mL, 7.2 mmol) in the drybag. After about 0.5 h in cold, the mixture was allowed to rise to ambient temperature where it was kept for 20 h. The resulting solution evaporated to dryness in vacuo and the residue purified by preparative thin-layer silica gel chromatography (Brinkmann 60-F 254, 2-mm thickness) developed in cyclohexane–ethyl acetate (1:1). The UV absorbing bands were extracted with ethyl acetate. The blocked diazo ketone was obtained as a glass: yield 419 mg (52%); mass spectrum, *m/e* 468 (M^+). In addition to the product, a second compound that appeared to be the blocked chloro ketone was obtained: yield 83 mg (10%); mass spectrum (FD), *m/e* 458 (M^+). It gave a positive NBP test and was too unstable to purify.

A solution of blocked diazo ketone (151 mg, 0.32 mmol) in 1 mL of 1 N $NaOCH_3$ was kept at 3 °C for 20 h, neutralized with acetic acid, and purified by preparative TLC developed in $CHCl_3$–MeOH (3:1) plus 5% NH_4OH. Evaporation of a MeOH extract of the product gave a crystalline solid that was recrystallized from EtOH: yield 25 mg (25%); mp 141–143 °C dec; UV λ_{max} ($10^{-3}\epsilon$) unstable at pH 1, 271 nm at pH 7 (17.9), 13 (19.7); IR 2090 (s) cm^{-1}; ^1H NMR δ 1.1 (t, CH_3 of EtOH), 1.8 (s, 5-CH_3), 1.9 (m, 2 $H_{5'}$), 2.1 (m, 2 $H_{2'}$), 2.45 (m, 2 $H_{6'}$), 3.63 (m, $H_{4'}$), 4.08 (m, $H_{3'}$), 5.28 (m, $O_{3'}H$), 6.05 (s, $H_{8'}$), 6.15 (t, $H_{1'}$), 7.4 (s, H_6), 12.8 (br s, NH of ring); mass spectrum (FD), *m/e* 308 (M^+), 309 [$(M + 1)^+$].

Anal. Calcd for $C_{13}H_{16}N_4O_5 \cdot 0.1EtOH$: C, 50.67; H, 5.34; N, 17.90. Found: C, 50.86; H, 5.28; N, 17.73.

Ethyl 1,5,6-Trideoxy-2,3-*O*-isopropylidene-1-(uracil-1-yl)-β-D-*ribo*-heptofuranuronate (24). A solution of ethyl 1,5,6-trideoxy-2,3-*O*-isopropylidene-1-(uracil-1-yl)-β-D-*ribo*-hept-5-enofuranuronate[6] (**23**; 194 mg, 0.6 mmol) in EtOH (20 mL) containing PtO_2 (43 mg) was hydrogenated at ambient temperature and 48 psi of H_2 for 20 h, filtered, and evaporated to a syrup. A solution of the syrup in acetone was filtered and evaporated to dryness in vacuo. A white glass was obtained: yield 195 mg (ca. 100%); TLC was done with $CHCl_3$–MeOH (9:1); mass spectrum, *m/e* 243 (sugar), 309 [$(M - OEt)^+$], 339 [$(M - CH_3)^+$], 354 (M^+).

1,5,6-Trideoxy-1-(uracil-1-yl)-β-D-*ribo*-heptofuranuronic Acid (25). A solution of ethyl 1,5,6-trideoxy-2,3-*O*-isopropylidene-1-(uracil-1-yl)-β-D-*ribo*-heptofuranuronate (**24**; 8.95 g, 30.0 mmol) in 1 N H_2SO_4 (500 mL) was heated at 60 °C for 1 h, decanted from an insoluble gum, neutralized with solid $BaCO_3$, and filtered, and enough 50% NaOH solution was added to give a 0.1 N solution. After being stirred 20 h at ambient temperature, the basic solution was deionized with Amberlite IR-120 (H) ion-exchange resin and evaporated to dryness in vacuo. A 100-mL aqueous solution of the residue was absorbed on Dowex 2×8 (200–400 mesh, formate) ion-exchange resin. After elution with H_2O to remove impurities, the product was obtained by eluting the resin with 0.1 N HCOOH. Evaporation gave a syrup that crystallized on standing; yield 3.0 g (34%).

An analytical sample was obtained by recrystallization of a small amount of material from MeOH: mp 115–117 °C; TLC was done with BuOH–HOAc–H_2O (5:2:3); UV λ_{max} ($10^{-3}\epsilon$) 262 nm at pH 1 (9.85), 263 at pH 7 (9.92), 262 at pH 13 (7.37); ^1H NMR δ 1.86 and 2.25 (2 m, 2 $H_{5'}$ and 2 $H_{6'}$), 3.78 (m, $H_{3'}$ and $H_{4'}$), 4.07 (m, $H_{2'}$), 5.65 (d, H_5), 5.75 (d, $H_{1'}$), 6.5–7.0 (br, NH and OH), 7.6 (d, H_6); mass spectrum, *m/e* 112 [(base + H)$^+$], 141 [(base + H$_2$O)$^+$], 250 [$(M - 2H_2O)^+$], 251 [$(M - H_2O - OH)^+$], 268 [$(M - H_2O)^+$], 269 [$(M - OH)^+$], 287 [$(M + 1)^+$].

Anal. Calcd for $C_{11}H_{14}N_2O_7$: C, 46.15; H, 4.93; N, 9.79. Found: C, 46.07; H, 4.93; N, 9.39.

Benzyl 1,5,6-Trideoxy-1-(uracil-1-yl)-β-D-*ribo*-heptofuranuronate (26). A cold (ice bath) suspension of 1,5,6-trideoxy-1-(uracil-1-yl)-β-D-*ribo*-heptofuranuronic acid (**25**; 451 mg, 1.58 mmol) in benzyl alcohol (10 mL) was treated with $SOCl_2$ (0.29 mL, 4.00 mmol), stirred in the cold for 1 h, and then kept at ambient temperature for 20 h. The resulting solution was evaporated to dryness under high vacuum at 38–40 °C. A dioxane solution of the residue was diluted with H_2O just to turbidity and kept 20 h at ambient temperature to decompose the 2′,3′-sulfite ester. Evaporation of the solution gave a residue that was crystallized from ethyl acetate: yield 339 mg (57%); mp 126–128 °C.

An analytical sample was obtained by recrystallization of a small sample from ethyl acetate: mp 127–129 °C; TLC was done with H_2O; UV λ_{max} ($10^{-3}\epsilon$) 262 nm at pH 1 (9.76), 262 at pH 7 (9.72), 262 at pH 13 (7.95); ^1H NMR δ 1.95 (m, 2 $H_{5'}$), 2.5 (m, 2 $H_{6'}$), 3.8 (m, $H_{3'}$ and $H_{4'}$), 4.08 (q, $H_{2'}$), 5.1 (t, $O_{3'}H$ and CH_2O), 5.35 (d, $O_{2'}H$), 5.62 (d, H_5), 5.7 (d, $J_{1',2'}$ = 5 Hz, $H_{1'}$), 7.37 (s, C_6H_5), 7.59 (d, H_6); 12.33 (s, NH); mass spectrum, *m/e* 112 (base + H^+), 265 [(sugar)$^+$], 269 [(M − $C_6H_5CH_2O$)$^+$], 376 (M^+).

Anal. Calcd for $C_{18}H_{20}N_2O_7$: C, 57.44; H, 5.36; N, 7.44. Found: C, 57.29; H, 5.52; N, 7.38.

Benzyl 2,3-Di-*O*-benzoyl-1-(3-benzoyluracil-1-yl)-1,5,6-trideoxy-β-D-*ribo*-heptofuranuronate (27). A solution of benzyl 1,5,6-trideoxy-1-(uracil-1-yl)-β-D-*ribo*-heptofuranuronate (**26**; 1.44 g, 2.66 mmol) and benzoyl chloride (0.83 mL, 7.2 mmol) in pyridine (25 mL) was stirred in an ice bath for 1 h and at ambient temperature for 20 h. The solution, which was found by TLC to still contain starting compound, was again chilled, diluted with benzoyl chloride (0.83 mL), stirred at ambient temperature for 20 h, and then poured into 200 mL of ice-saturated $NaHCO_3$. The resulting mixture was extracted with $CHCl_3$ (ca. 200 mL). The $CHCl_3$ extract was washed with ice-cold dilute H_2SO_4 and then with H_2O, dried with $MgSO_4$, and evaporated to dryness in vacuo. Purification of the residue by dry-column chromatography (silica gel, Woelm; 2 cm × 48 cm column) developed in cyclohexane–ethyl acetate (1:1) gave the product as a solid: yield 1.79 g (98%); TLC was done with cyclohexane–ethyl acetate (1:1); mass spectrum, *m/e* 461 [(M − $C_6H_5CO_2H$ − C_6H_5CO)$^+$], 473 [(sugar)$^+$], 566 [(M − $C_6H_5CO_2H$)$^+$], 581 [(M − $C_6H_5CH_2O$)$^+$], 688 (M^+).

2,3-Di-*O*-benzoyl-1-(3-benzoyluracil-1-yl)-1,5,6-trideoxy-β-D-*ribo*-heptofuranuronic acid (28). A solution of benzyl 2,3-di-*O*-benzoyl-1-(3-benzoyluracil-1-yl)-1,5,6-trideoxy-β-D-*ribo*-heptofuranuronate (**27**; 780 mg, 1.13 mmol) in glacial acetic acid (25 mL) containing 30% Pd/C catalyst (200 mg) was hydrogenated at ambient temperature and atmospheric pressure, filtered, and freeze-dried to a fluffy white solid: yield 610 mg (90%); TLC was done with cyclohexane–EtOAc (1:1); mass spectrum (FD), *m/e* 599 [(M + 1)$^+$].

5,6,8-Trideoxy-8-diazo-β-D-*ribo*-7-octulofuranosyluracil (31). To 25 mL of cold $SOCl_2$ in a drybag was slowly added 2,3-di-*O*-benzoyl-1-(3-benzoyluracil-1-yl)-1,5,6-trideoxy-β-D-*ribo*-heptofuranuronic acid (**28**; 610 mg, 1.02 mmol). The resulting solution was stirred in the cold for ca. 7 min and at ambient temperature for 2 h before it was evaporated to dryness in vacuo, giving the acid chloride as a glass.

A solution of the acid chloride in ether–DMF (20 mL, 3:1) was slowly added (in the drybag) to a cold stirred solution of ethereal diazomethane (25 mL, ca. 9 mmol). The resulting solution was stirred in the cold for 1 h, kept 20 h at ambient temperature, and evaporated to dryness in vacuo. The residue was purified by preparative thin-layer chromatography (Brinkmann silica gel 60F-254, 2-mm thickness) by development with cyclohexane–ethyl acetate (1:1). The blocked nucleoside was obtained as a glass: yield 260 mg (41%); mass spectrum, *m/e* 623 [(M + 1)$^+$]. A byproduct was obtained that appears to be the chloro ketone, yield 135 mg (21%).

A solution of the blocked diazo ketone **21** (260 mg, 0.42 mmol) in 1 N methanolic $NaOCH_3$ (4 mL) was kept 20 h at 3 °C, neutralized with acetic acid, and purified by preparative TLC by development with $CHCl_3$–MeOH (3:1) plus 5% NH_4OH. The product was obtained by MeOH extraction as a hygroscopic solid: yield 100 mg (77% based on the blocked nucleoside); mp indefinite; UV λ_{max} ($10^{-3}\epsilon$) unstable at pH 1, 267 nm at pH 7 (18.9), 268 at pH 13 (16.3); ^1H NMR δ 1.82 (m, 2 $H_{5'}$), 2.4 (m, 2 $H_{6'}$), 3.3–3.5 (br, H_2O, CH_3OH), 3.75 (d, $H_{3'}$ and $H_{4'}$), 4.05 (t, $H_{2'}$), 5.58 (s, H_5), 5.72 (d, $J_{1',2'}$ = 4 Hz, $H_{1'}$), 6.06 (s, $H_{8'}$), 7.55 (d, H_6); mass spectrum, (FD) *m/e* 311 [(MD + 1)$^+$].

Anal. Calcd for $C_{12}H_{14}N_4O_6 \cdot 0.4MeOH \cdot 0.4H_2O$: C, 45.15; H, 4.89; N, 16.88. Found: C, 45.19; H, 4.90; N, 17.04.

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Registry No. 1, 21090-30-2; 2, 5983-15-3; 2 dianilinoethane adduct, 75863-39-7; 3, 75863-40-0; 4, 75863-41-1; 5, 75863-42-2; 6, 75863-43-3; 11, 75863-44-4; 15, 75863-45-5; 16, 75863-46-6; 19, 75863-47-7; 19 chloro ketone, 75863-55-7; 31, 75863-53-5; 20, 75863-54-6; 21, 362-43-6; 23, 75917-52-1; 24, 75863-48-8; 25, 65926-38-7; 26, 75863-49-9; 27, 75863-50-2; 28, 75863-51-3; 29, 75863-52-4; 30 chloro ketone, 75863-56-8; (carboxymethylene)triphenylphosphorane, 15677-02-8; benzyl bromoacetate, 5437-45-6; triphenylphosphine, 603-35-0; [(carbobenzyloxy)methylene]triphenylphosphorane, 15097-38-8; 4-toluyl chloride, 874-60-2.