4 H); ^{13}C NMR ($CDCl_3$) δ 129.61 (d), 106.34 (s), 77.69 (s), 76.76 (s), 52.56 (d), 51.56 (q), 51.09 (q), 49.33 (d), and 36.50 (d); MS, *m/e* (relative intensity) 370 (9), 368 (16), 366 (15) [M^+], 337 (21), 335 (38), 333 (94), 331 (100).

Anal. Calcd for $C_{15}H_{14}Cl_4O_2$: C, 48.92; H, 3.83; Cl, 38.54. Found: C, 48.84; H, 3.84; Cl, 38.37.

5,5-Dimethoxyhexacyclo[5.5.1.0^{2,6}.0^{3,10}.0^{4,8}.0^{9,13}]tridec-11-ene (6). Into a 100-mL reaction flask were placed, in order, compound **5** (3.0 g, 0.008 mol), dry tetrahydrofuran (60 mL), *tert*-butyl alcohol (6.0 g, 0.008 mol), and sodium (5.4 g, 0.235 g-atom) chopped into 5-mm cubes. The mixture was vigorously stirred and refluxed under a nitrogen atmosphere for 36 h, then cooled to room temperature, and filtered to remove unreacted sodium. The filtrate was poured into ice water (20 mL) and extracted with ether (2 × 30 mL). The organic phase was washed with brine (30 mL), dried, and concentrated. The resulting pale brown residue was purified via flash chromatography on silica gel (1:20 ethyl acetate–hexane eluent) and recrystallization from the same system of solvents to furnish pure **6** (1.4 g, 74%) as a colorless crystalline solid: mp 74–75 °C; IR (KBr) 3015 (w), 1615 (w), 1060 cm^{-1} (s); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.22 (center of an ABX-like system, J = 4.9 and 3.1 Hz, 2 H), 3.30 (s, 3 H), 3.23 (s, 3 H), 2.84 (m, 2 H), 2.64 (m, 2 H), 2.30 (m, 2 H), 2.26 (m, 2 H), and 2.20 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 130.53 (d), 117.77 (s), 50.89 (q), 50.79 (q), 46.54 (d), 45.94 (d), 40.66 (d), 40.49 (d), and 40.39 (d); MS, *m/e* (relative intensity) 230 (100) [M^+], 199 (37) [$M^+ - OCH_3$], 152 (32), 121 (26), 74 (31).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.22; H, 7.88. Found: C, 78.33; H, 7.87.

Hexacyclo[5.5.1.0^{2,6}.0^{3,10}.0^{4,8}.0^{9,13}]tridec-11-en-5-one (7). To a solution of acetal **6** (1.0 g, 0.0043 mol) in tetrahydrofuran (30 mL) containing water (20 mL) was added a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was refluxed overnight and then extracted with ether (2 × 25 mL). The extracts were washed with water (20 mL) and brine (20 mL) prior to drying and filtration. Concentration and flash chromatography on silica gel (1:8 ethyl acetate–hexane eluent) of the resulting residue afforded pure ketone **7** (0.74 g, 92%), which was crystallized from ethyl acetate–hexane as a colorless crystalline solid: mp 103–104 °C; IR (KBr) 3015 (w), 1760 (s), 1735 cm^{-1} (sh); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.29 (center of an ABX-like system, J = 4.9 and 3.2 Hz, 2 H), 3.09 (m, 2 H), 2.78 (m, 2 H), 2.46 (m, 2 H), 2.31 (m, 2 H), and 2.11 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 215.06 (s), 129.97 (d), 46.47 (d), 42.78 (d), 42.25 (d), 41.39 (d), and 36.84 (d); MS, *m/e* (relative intensity) 184 (100) [M^+], 156 (18) [$M^+ - CO$], 141 (4), 106 (6), 91 (7), 78 (74).

Anal. Calcd for $C_{13}H_{12}O$: C, 84.74; H, 6.57. Found: C, 84.83; H, 6.61.

Hexacyclo[6.5.1.0^{2,7}.0^{3,11}.0^{4,9}.0^{10,14}]tetradec-12-en-5-one (8). An ethereal solution (30 mL) of ketone **7** (670 mg, 3.6 mmol) was saturated with freshly generated diazomethane at 0 °C. The mixture was then allowed to stand in the dark in a refrigerator (ca. 4 °C) for 2 days. The pale yellow color of the solution disappeared almost completely at this point. The solution was concentrated to leave an off-white solid, which was purified via flash chromatography on silica gel (1:8 ethyl acetate–hexane eluent) to afford pure enone **8** (690 mg, 96%). Recrystallization from ethyl acetate–hexane gave an analytical sample as a colorless crystalline solid: mp 90–91 °C; IR (KBr) 3035 (w), 1735 (s), 1625 cm^{-1} (w); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.26 (m, 2 H), 2.93 (m, 1 H), 2.69 (m, 2 H), 2.62 (m, 1 H), 2.45 (m, 1 H), 2.36 (m, 2 H), 2.22 (m, 2 H), 2.12 (m, 2 H), and 1.92 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 216.89 (s), 131.44 (d), 129.48 (d), 50.71 (d), 42.54 (d), 40.82 (d), 40.54 (d), 40.34 (d), 39.89 (d), 39.62 (d), 38.73 (d), 37.34 (t), 36.78 (d), and 35.92 (d); MS, *m/e* (relative intensity) 198 (100) [M^+], 156 (31) [$M^+ - H_2C{=}C{=}O$], 154 (69), 131 (30), 118 (14), 78 (30).

Anal. Calcd for $C_{14}H_{14}O$: C, 84.80; H, 7.12. Found: C, 84.65; H, 7.18.

Hexacyclo[6.5.1.0^{2,7}.0^{3,11}.0^{4,9}.0^{10,14}]tetradec-12-en-5-ol (9). To a stirred solution of **8** (500 mg, 2.5 mmol) in methanol (25 mL) was added sodium borohydride (500 mg, 12.5 mmol) in three portions in a period of 3 min. The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC analysis. When ketone **8** had disappeared (ca. 10 min), a solution of 10% HCl (10 mL) was added. The bulk of the methanol was removed under reduced pressure, and the product was extracted into ether. The ethereal solution was washed with 5% sodium bicarbonate solution and brine, dried, and evaporated to leave crude **9** (510 mg) as a colorless solid. Flash chromatography on silica gel (1:10 ethyl acetate–hexane as eluent) furnished a 1:1 mixture of epimeric alcohols **9** (490 mg, 97%), which was recrystallized from the same system of solvents to give an analytical sample as a colorless crystalline solid: mp 80–82 °C; IR (KBr) 3270 (s, br), 3020 (w), 1625 (w), 1100 (s), 1050 cm^{-1} (s); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.26 (m, 4 H, olefinic protons), 4.22 (m, 1 H, HCO), 3.95 (m, 1 H, HCO), 2.79 (m, 1 H), 2.52 (m, 6 H), 2.45 (m, 1 H), 2.24 (m, 4 H), 1.96 (m, 2 H), and 1.82–1.28 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 131.21 (d), 130.94 (d), 130.63 (d), 130.44 (d), 65.59 (d), 65.37 (d), 41.47 (d), 41.27 (d), 41.21 (d), 40.96 (d), 40.77 (d), 40.58 (d, 2 C), 40.34 (d), 40.32 (d), 39.93 (d), 39.79 (d), 39.70 (d), 39.18 (d), 37.40 (d), 36.92 (d), 36.71 (d), 35.56 (d), 33.54 (d), 33.24 (d), 32.32 (d), 31.17 (t), 30.73 (t); MS, *m/e* (relative intensity) 200 (100) [M^+], 182 (33) [$M^+ - H_2O$], 167 (8), 156 (19), 141 (9), 133 (7), 104 (11), 91 (15), 80 (23), 78 (12).

Anal. Calcd for $C_{14}H_{16}O$: C, 83.95; H, 8.06. Found: C, 83.85; H, 8.17.

Hexacyclo[6.5.1.0^{2,7}.0^{3,11}.0^{4,9}.0^{10,14}]tetradeca-5,12-diene (1). A catalytic amount of *p*-toluenesulfonic acid was added to a solution of **9** (100 mg, 0.5 mmol) in dry benzene (30 mL), and the reaction mixture was heated at reflux temperature in an atmosphere of nitrogen for 3 days under a Dean–Stark trap. Most of the benzene was then removed in vacuo, and the residue was purified via flash chromatography on silica gel (hexane eluent) to afford diene **1** (73 mg, 80%) as a colorless liquid: IR (film) 3030 (m), 1620 (m), 1380 (m), 1320 (m), 830 (m), 685 cm^{-1} (m); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.27 (center of an ABX-like system, J = 4.8 and 3.2 Hz, 4 H, olefinic protons), 2.53 (br s, 4 H, allylic bridgehead protons), 2.28 (m, 4 H, cyclobutane methine protons), and 1.60 (m, 2 H, bridgehead methine protons); ^{13}C NMR ($CDCl_3$) δ 131.72 (d), 44.10 (d), 39.22 (d), and 38.79 (d); MS, *m/e* (relative intensity) 182 (100) [M^+], 167 (11), 154 (4), 141 (5), 104 (60), 91 (30).

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Synthesis of 2′,3′-Dideoxyuridine via Deoxygenation of 2′,3′-*O*-(Methoxymethylene)uridine

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Reductive deoxygenation of a vicinal diols moiety of a nucleoside is an attractive synthetic route to 2′,3′-dideoxynucleosides, which are physiologically important[1] and play an important role in protecting cells against the cytopathic effect of HIV.[2] In fact, the syntheses of dideoxynucleosides from ribonucleosides have been studied extensively. For example, 2′-*O*-acetyl-3′-bromo-3′-deoxynucleoside derivatives have been used as precursors of

(1) Recently, 2′,3′-dideoxynucleosides, such as 2′,3′-dideoxycytidine, 2′,3′-dideoxyadenosine, and 2′,3′-dideoxyinosine, were found to be effective against AIDS (acquired immune deficiency syndrome). (a) Mitsuya, H.; Weinhold, K. J.; Ufrmann, P. A.; St. Clair, M. H.; Lehrman, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096. (b) Mitsuya, H.; Broder, S. *Ibid.* **1986**, *83*, 1911. (c) Kim, C.; Marquez, V. E.; Broder, S.; Mitsuya, H.; Driscoll, J. S. *J. Med. Chem.* **1987**, *30*, 862. (d) Herdewijn, P.; Balzarini, J.; Clercq, E. D.; Pawels, R.; Baba, M.; Broder, S. *Ibid.* **1987**, *30*, 1270.

(2) Human immunodeficiency virus, which causes AIDS. For instnace: (a) Provic, M.; Sarngadharan, M. G.; Read, E.; Gallo, R. C. *Science (Washington, D.C.)* **1984**, *224*, 497. (b) Broder, S.; Gallo, R. C. *Annu. Rev. Immunol.* **1985**, *3*, 321. (c) Wong-Staal, F.; Gallo, R. C. *Nature (London)* **1985**, *317*, 395.

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Table I. Transformation of 2',3'-*O*-(Methoxymethylene)uridine into Olefins

starting nucleoside	solvent[a]	cat. (equiv)	reaction condition: temp, °C	reaction condition: time, h[b]	product	% yield[c]
2	Ac_2O		132–128	3	**4a**	53
2	Ac_2O		100	1	**3**	99
3	Ac_2O		132	4	**4a**	46
2	Ac_2O	Py (0.1)	132	3	**4a**	50
2	Ac_2O	BH_3NEt_3 (0.1)	132–125	1	**4a**	56
2	Ac_2O	BH_3NEt_3 (0.1) Py	132	1.5	**4a**	56
3	Ac_2O	PhCOOH (1.0)	132	3	**4a**	47
3	Ac_2O	BH_3NEt_3 (0.1)	132	1.5	**4a**	49

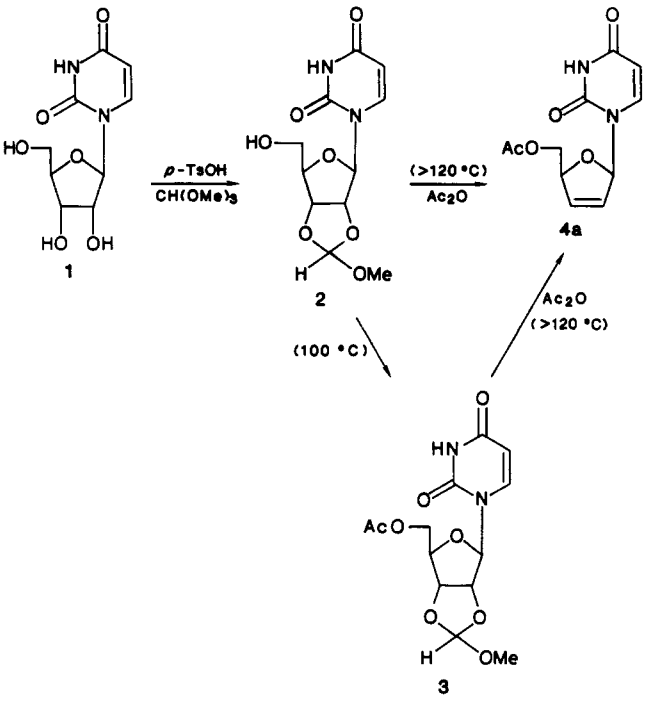
[a] Concentration of reaction mixture are 10 g/dL (starting nucleoside/Ac_2O). [b] The indicated reaction times are those at the maximum yields. [c] Yields are determined by HPLC analysis of reaction mixture.

deoxy- or dideoxynucleosides by hydrogenation with palladium catalyst[3a,c] or zinc.[3b] In addition, tributyltin radical initiated reduction of thiocarbonates in the synthesis of deoxy- or dideoxycytidine[4,1c] and the selective photosensitized deoxygenation of adenosine via a tribenzoate[5] are also known. Recently, an elegant method for the preparation of 2',3'-dideoxynucleoside from L-glutamic acid has been reported.[6] However, many difficulties are envisioned in adapting these methods for large-scale production of 2',3'-dideoxynucleosides, because they require many steps, need expensive reagents, or have the problem of stereospecificity.

Thus we turned our attention to an alternative indirect route for reductive deoxygenation, which consists of transformation of the vicinal diols into the olefin followed by hydrogenation of the resulting olefin.[7] Several methods are known for the conversion of vicinal diols into olefins.[8] Corey–Winter reaction[9] of 5'-trityluridine 2',3'-*O*-thionocarbonate was attempted for preparation of 2',3'-didehydro-2',3'-dideoxy-5'-*O*-trityluridine, but resulted in a very low yield of the desired olefin because of the concomitant methylation at N^3 by trimethyl phosphite.[8a] Here we report a simple and convenient route to 1-(2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (**4**), from uridine (**1**) by using the Eastwood olefination reaction[10] of vicinal diols (Scheme I). 2',3'-Dideoxyuridine (**5**) could then be easily obtained from **4** by a known method.[11]

Uridine (**1**) was converted into 2',3'-*O*-methoxymethyleneuridine (**2**) almost quantitatively upon treatment with trimethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid monohydrate.[12] A solution of **2** in acetic anhydride was heated at 130 °C for 3 h to give 1-(5-*O*-acetyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (**4a**). However, the reaction at 100 °C for 1 h gave only **3**.

Scheme I



Scheme II

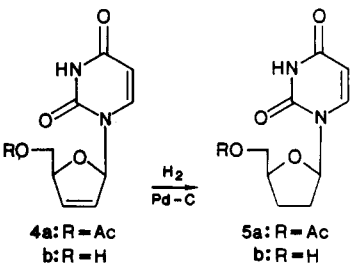


Table I shows the results of the transformation of **2** or **3** into **4a** under various conditions. In the reaction of **2**, acetic acid was produced first by acetylation of 5'-alcohol of **2** to give **3**. The formation of **4a** from **3** was catalyzed by this acetic acid according to the mechanism assumed by Eastwood.[10] Meanwhile, it was reported that heating a solution of 2-methoxy-1,3-dioxolanes in refluxing acetic anhydride without acetic acid produced the corresponding olefins in high yields.[13] As expected, **3** formed in the

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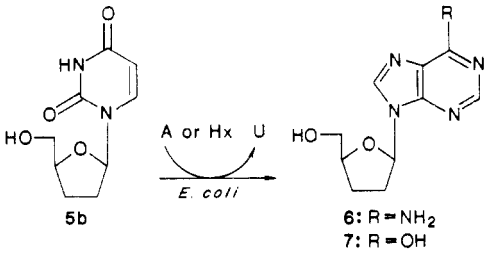
Scheme III



reaction with acetic anhydride at 100 °C gave **4a**, but the rate was slower and the yield was slightly lower than that of the reaction of **2** under the same conditions.

These results suggest that acetic acid promotes the reaction, but produced **4a** was unstable under acidic conditions and a considerable amount of *N*-acetyluracil was produced as a major byproduct (37% yield). Use of another acid catalyst such as PhCOOH or a base such as pyridine in order to improve the yield was not successful. Addition of Et_3N and Na_2CO_3 inhibited the reaction. Among other catalysts, the highest yield of **4a** was produced within 1.5 h in the presence of a catalytic amount of BH_3NEt_3 while a stoichiometric amount of BH_3NEt_3 reduced the yield of **4a** remarkably, although **5a**, which is assumed to be derived from hydroboration of **4a**, was detected in low yield. The use of $B(OEt)_3$ or BH_3Py did not give satisfactory results.

Hydrogenation of **4** easily provided 2′,3′-dideoxyuridines (**5**) in high yields.[10] Compounds **4a** and **5a** were deacylated quantitatively with aqueous sodium hydroxide or ammonia to yield **4b** and **5b**, respectively (Scheme II). Combining the two reactions, olefination of vicinal diols (Scheme I) and hydrogenation of resulting olefin (Scheme II), provides a simple route to **5b** from **1**.

Attempts to prepare other dideoxynucleosides such as 2′,3′-dideoxycytidine and 2′,3′-dideoxyadenosine by the same procedure did not succeed. Purine nucleosides were unstable under the acidic conditions to provide free purine.

Base modification by chemical conversion of **5b** to 2′,3′-dideoxycytidine has also been reported.[14] However, we had already developed a method for transglycosylation[15] by which we were able to synthesize various kind of nucleosides. Whether an enzyme to catalyze transdideoxyribosylation exists has been of great interest, and indeed we have found that **5b** was a suitable substrate for transdideoxyribosylation, and 2′,3′-dideoxyadenosine (**6**) or 2′,3′-dideoxyinosine (**7**) was efficiently obtained from **5b** and adenine or, hypoxanthine, respectively, by catalytic action of *Escherichia coli* AJ 2595 (Scheme III).[16]

In conclusion, a method using a combination of chemical and enzymatic reactions offers a preferable route for large-scale preparation of 2′,3′-dideoxynucleoside analogues.

Experimental Section

Melting points were measured with a Yamato melting point apparatus and are uncorrected. UV spectra were recorded on a Hitachi U-3200 spectrometer. ^1H NMR spectra were obtained on a Varian XL-300 or JEOL JNM-GX400 spectrometers and are reported as ppm values downfield from Me_4Si. Fast atom bombardment mass spectra were obtained on a JEOL D-300 instrument. HPLC was carried out on a 15 cm YMC A-312 column with a Hitachi 655 system equipped with a Shimadzu C-R4A integrator and a Hitachi variable wavelength UV monitor set at 260 nm. The mobile phase was 10% CH_3CN/0.1 N NaH_2PO_4.

2′,3′-*O*-(Methoxymethylene)uridine (2). To a solution of uridine (**1**) (100 g, 410 mmol) in trimethyl orthoformate (250 mL) was added *p*-toluenesulfonic acid monohydrate (3.0 g, 15.8 mmol). The solution was stirred at room temperature for 16 h and then cooled to 10 °C. Sodium methoxide in methanol (28%, 3.39 g, 17.6 mmol) and toluene (100 ml) was added, and the resulting mixture was stirred for 1 h at 10 °C. The reaction mixture was filtered, and the separated crystal was washed with toluene (100 mL) and dried to yield **2** (113.6 g, 96% yield) as a white crystal (single diastereomer): TLC R_f ($CHCl_3$/MeOH, 10/1) 0.34; λ_{max} (MeOH) 259 nm (ϵ 10950), λ_{min} (MeOH) 232 nm (ϵ 4950); ^1H NMR (Me_2SO-d_6) δ 3.21 (s, 3 H), 3.60 (dd, 2 H, J = 5.49, 8.79 Hz), 4.06 (dt, 1 H, J = 8.79, 3.60 Hz), 4.86 (dd, 1 H, J = 3.60, 6.40 Hz), 5.02 (dd, 1 H, J = 2.57, 6.40 Hz), 5.12 (t, 1 H, J = 5.49 Hz), 5.65 (d, 1 H, J = 8.06 Hz), 5.80 (d, 1 H, J = 2.57 Hz), 6.10 (s, 1 H), 7.77 (d, 1 H, J = 8.06 Hz), 11.40 (br s, 1 H); fast atom bombardment mass spectrum, m/z 287 (MH^+).

5′-*O*-Acetyl-2′,3′-*O*-(methoxymethylene)uridine (3). A solution of **2** (10 g, 35.0 mmol) in acetic anhydride (100 mL) was heated at 100 °C for 1 h. After disappearance of starting material, the reaction mixture was evaporated. Addition of methanol (50 mL) followed by concentration (three times) afforded **3** as a white crystal (11.4 g, 99% yield): TLC R_f ($CHCl_3$/MeOH, 10/1) 0.50; λ_{max} (MeOH) 257 nm (ϵ 9920), λ_{min} (MeOH) 232 nm (ϵ 4920); ^1H NMR (Me_2SO-d_6) δ 2.05 (s, 3 H), 3.21 (s, 3 H), 4.10–4.40 (m, 3 H), 4.90 (m, 1 H), 5.12 (m, 1 H), 5.67 (d, 1 H, J = 8.06 Hz), 5.80 (m, 1 H), 6.14 (s, 1 H), 7.70 (d, 1 H, J = 8.06 Hz), 11.43 (br s, 1 H); fast atom bombardment mass spectrum, m/z 329 (MH^+).

Olefination of 2 into 1-(5-*O*-Acetyl-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (4a). A solution of **2** (5.0 g, 17.5 mmol) in acetic anhydride (50 mL) was stirred for 3 h at 132 °C. The reaction mixture was cooled to room temperature and evaporated. Chloroform (50 mL) was added, and the mixture was washed with aqueous $NaHCO_3$ (50 mL). Aqueous layer was extracted with $CHCl_3$ (50 mL), and the combined organic layers were dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography ($CHCl_3$/MeOH, 10/1) to give **4a** (1.87 g, 7.4 mmol, 42% yield). By recrystallization from EtOH, an analytical sample was obtained: mp 128–128.5 °C; λ_{max} (MeOH) 259 nm (ϵ 9670), λ_{min} (MeOH) 232 nm (ϵ 4200); ^1H NMR ($CDCl_3$) δ 2.08 (s, 3 H), 4.25 (dd, 1 H, J = 3.29, 12.45 Hz), 4.37 (dd, 1 H, J = 3.66, 12.45 Hz), 5.07 (m, 1 H), 5.72 (d, 1 H, J = 8.06 Hz), 5.92 (m, 1 H), 6.30 (d, 1 H, J = 5.86 Hz), 7.01 (d, 1 H, J = 5.86 Hz), 7.47 (d, 1 H, J = 8.06 Hz), 8.83 (br s, 1 H); fast atom bombardment mass spectrum, m/z 253 (MH^+). Anal. Calcd for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.32; H, 4.87; N, 10.73. *N*-Acetyluracil (1.0 g, 6.5 mmol, 37% yield), *N*,*N*′-diacetyluracil (93 mg, 0.5 mmol, 3%), and N-acetylated compound **4a** (95 mg, 0.3 mmol, 2%) were also obtained as byproducts whose structures were confirmed by ^1H NMR spectroscopy.

1-(2,3-Dideoxy-β-D-*glycero*-pent-2-enofuranosyl)uracil (4b). The crude concentrated product from the reaction of **2** as described above was treated with 29% NH_4OH (20 mL) and MeOH (20 mL) for 12 h at room temperature. The reaction mixture was evaporated, and the resulting residue was chromatographed on silica gel ($CHCl_3$/MeOH, 10/1) to give **4b** (1.58 g, 7.5 mmol, 43% yield): mp 150.0–151.0 °C; λ_{max} (MeOH) 260 nm (ϵ 9980), λ_{min} (MeOH) 231 nm (ϵ 3980); ^1H NMR (Me_2SO-d_6) δ 3.58 (d, 1 H, J = 5.13 Hz), 3.59 (d, 1 H, J = 5.13 Hz), 4.78 (m, 1 H), 4.98 (t, 1 H, J = 5.13 Hz), 5.59 (d, 1 H, J = 8.05 Hz), 5.92 (d, 1 H, J = 5.86 Hz), 6.40 (d, 1 H, J = 5.86 Hz), 6.82 (m, 1 H), 7.75 (d, 1 H, J = 8.05 Hz), 11.31 (br s, 1 H); fast atom bombardment mass spectrum, m/z 211 (MH^+). Anal. Calcd for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.32; H, 4.81; N, 13.31. Uracil (0.77 g, 6.9 mmol, 34% yield) was obtained as a byproduct.

2′,3′-Dideoxyuridine (5b). A solution of **4b** (1.0 g, 4.8 mmol) in methanol (10 mL) containing a catalyst (wet 5% palladium on carbon) (400 mg) was stirred in an atmosphere of hydrogen

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for 1 h. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was chromatographed on silica gel ($CHCl_3$/MeOH, 5/1) to give **5b** (0.99 g, 97% yield): mp 121.2–121.7 °C; λ_{max} (MeOH) 262 nm (ϵ 10560), λ_{min} (MeOH) 232 nm (ϵ 3810); ^{1}H NMR (Me_2SO-d_6) δ 1.74–2.00 (m, 3 H), 2.20–2.35 (m, 1 H), 3.49–3.55 (m, 1 H), 3.64–3.69 (m, 1 H), 4.00–4.03 (br s, 1 H), 5.03 (s, 1 H), 5.58 (d, 1 H, J = 8.06 Hz), 5.95 (m, 1 H), 7.94 (d, 1 H, J = 8.06 Hz), 11.25 (br s, 1 H); fast atom bombardment mass spectrum, m/z 213 (MH^+). Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.95; H, 5.71; N, 13.20.

5′-*O*-Acetyl-2′,3′-dideoxyuridine (5a). The compound **4a** was hydrogenated into **5a** in the same way: mp 80.1–80.6 °C; λ_{max} (MeOH) 262 nm (ϵ 10290), λ_{min} (MeOH) 232 nm (ϵ 3850); ^{1}H NMR (Me_2SO-d_6) δ 1.75–1.87 (m, 1 H), 1.92–2.06 (m, 2 H), 2.05 (s, 3 H), 2.20–2.38 (m, 1 H), 4.14–4.26 (m, 3 H), 5.63 (d, 1 H, J = 8.06 Hz), 5.99 (m, 1 H), 7.66 (d, 1 H, J = 8.06 Hz); fast atom bombardment mass spectrum, m/z 255 (MH^+). Anal. Calcd for $C_{11}H_{14}N_2O_5$: C, 51.97; H, 5.55; N, 11.02. Found: C, 52.02; H, 5.59; N, 10.97.

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General Approach to the Synthesis of Polyquinenes. 9. The Monofunctionalization and Alteration of the Symmetry of the *cis*-Bicyclo[3.3.0]octane-3,7-dione Unit[1]

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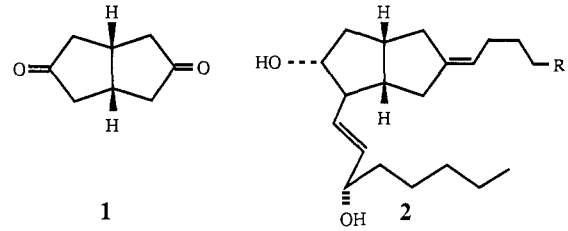
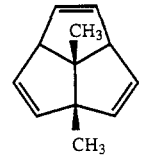
Interest in the synthesis of polyquinanes has gained momentum in recent years due, in part, to the isolation of natural products whose molecular architecture is comprised of polyfused five-membered rings (e.g. capnallane, corriolin, cripnallane).[2] Moreover, interest in the synthesis of nonnatural products such as triquinacene,[3] peristylane,[4] pagodane,[5a] and dodecahedrane[5b] has been stimulated due to the unique topology of such systems,[2] as well as their chemical behavior.[4,5] Retrosynthetic analysis of the molecules mentioned above, via at least one pathway, will ultimately terminate in the structure of a *cis*-bicyclo[3.3.0]octane unit. This versatile building block, represented in the present paper as *cis*-bicyclo[3.3.0]octane-3,7-dione (**1**), is available on large scale from the Weiss reaction.[6,7] Numerous attempts to differentiate between the two five-membered rings of **1** have been reported[8] due to the activity of carboprostacyclines **2**[9] and to the use of **1** in the synthesis of other polyquinanes.[10,11] Previous





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attempts to monofunctionalize the symmetrical bicyclooctanedione unit **1** have employed multistep synthesis,[2] protection–deprotection sequences accompanied by several recycle passes,[9,12] or alkylation reactions, the yields of which have been only moderate.[13,14] In order to surmount this problem we have recently developed a new approach to the monoalkylation of **1**, which ultimately resulted in the synthesis of centrosubstituted triquinacenes such as **3**.

Initially, a number of obvious methods to monoalkylate **1** were attempted but met with little success.[14] However, the versatility of the Weiss reaction could be exploited at this juncture. When glyoxal **5a** was stirred with di-*tert*-butyl β-ketoglutarate **4b** in alkaline solution, a 93% yield of tetra-*tert*-butyl-3,7-dihydroxy-*cis*-bicyclo[3.3.0]octanetetracarboxylate (**6b**) was realized. This tetraester was converted into the requisite bisenol ether **7b** on stirring with diazomethane (Scheme I). Although various reaction conditions were studied, it was found that monoalkylation of the glyoxal-derived tetra-*tert*-butyl ester **7b** could best be achieved at low temperatures (−30 to −60 °C), as illustrated in Table I. When the temperature rose above this, dialkylation began to compete in the process. Hydrolysis and decarboxylation of the monoalkylated tetraesters represented by **8** gave the corresponding monoalkylated *cis*-bicyclo[3.3.0]octane-3,7-diones **9**. Conditions for this alkylation reaction were developed earlier during

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