Stereoselective Addition of a Wittig Reagent To Give a Single Nucleoside Oxaphosphetane Diastereoisomer. Synthesis of 2′(and 3′)-Deoxy-2′(and 3′)-methyleneuridine (and cytidine) Derivatives from Uridine Ketonucleosides [1]

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Treatment of 3′,5′(or 2′,5′)-bis-*O*-silyl-protected 2′(or 3′)-ketouridine derivatives with methyltriphenylphosphonium bromide and sodium 2-methyl-2-butoxide in diethyl ether/benzene at 0–4 °C resulted in the slow formation of the corresponding 2′(or 3′)-deoxy-2′(or 3′)-methylene analogues. ^{1}H- and ^{31}P-NMR spectra were in harmony with formation of a single oxaphosphetane diastereoisomer during early stages of the Wittig reaction. Conversions of protected deoxymethyleneuridine to deoxymethylenecytidine derivatives were effected smoothly via 4-(1,2,4-triazol-1-yl) intermediates. Deprotection with tetrabutylammonium fluoride gave 2′(or 3′)-deoxy-2′(or 3′)-methyleneuridine and cytidine nucleosides.

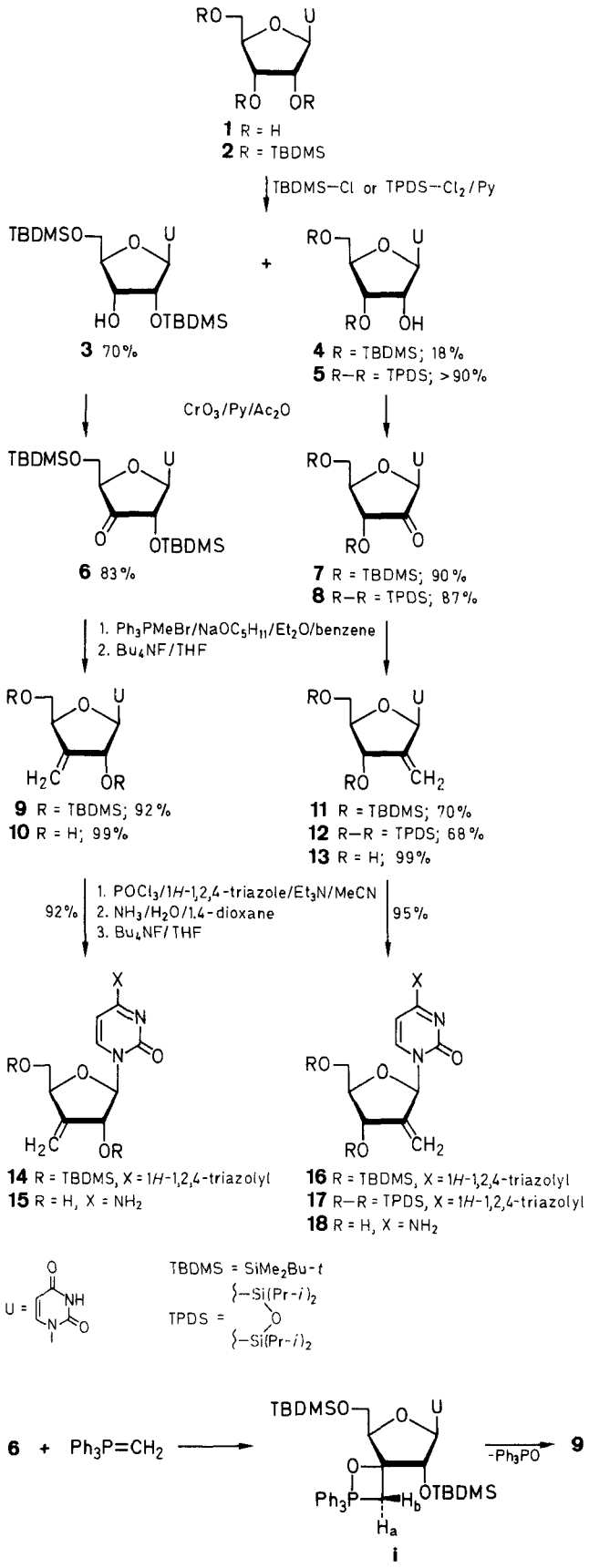
Many nucleoside analogues have been prepared and subjected to biological testing. Significant numbers of these compounds have potent inhibitory effects and several are used as clinical agents against viral diseases[2] and cancer.[3] Most biologically effective nucleoside analogues are "activated" by enzymatic 5′-phosphorylation to give nucleotide analogues that exert alternative substrate inhibition of specific enzymes and/or interfere with "genetic information processing" after incorporation into nucleic acids. The 2′(3′)-deoxy-2′(3′)-methylene analogues are a recently conceived class of nucleosides[4] that contain functionalities of interest to us in the study of "mechanism-based" inhibition of enzymes in the nucleic acid manifold. Ueda and co-workers prepared various alkyl- and alkylidenesugar nucleoside derivatives in their study of carbon-linked cyclonucleosides with fixed sugar-base conformations,[5–9] and recently reported potent anticancer activity of 2′-deoxy-2′-methylenecytidine.[8] We now describe methods for the mild and efficient conversion of uridine into the four possible *exo*-methylene allylic secondary alcohol analogues of 2′-deoxy and 3′-deoxyuridine and cytidine.

Uridine (**1**) was protected[10] with *tert*-butyldimethylsilyl chloride to give 2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)uridine (**3**, 70%), 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)uridine (**4**, 18%) and 2′,3′,5′-tris-*O*-(*tert*-butyldimethylsilyl)uridine (**2**, 5%). Treatment of **1** with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane[11] gave 3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)uridine[12,13] (**5**) for selective C-2′ manipulation.

Moffatt and co-workers first described oxidations of pyrimidine nucleosides to ketonucleosides with dimethyl sulfoxide/dicyclohexylcarbodiimide[14] and dimethyl sulfoxide/acetic anhydride.[15] However, these oxidants gave variable yields of the desired ketones and *O*′-methylthiomethyl byproducts.[16] Ueda and co-workers[5,7] have applied the Swern modification[17] (dimethyl sulfoxide/oxalyl chloride) of the Moffatt oxidation to nucleosides. We investigated that procedure,[17] but observed significant contamination by heterocyclic *N*- and *O*-methylthiomethyl derivatives with Swern oxidation of lactam-containing nucleosides (e.g. uridine and inosine).

We obtained higher yields (89–93%) of ketouridine derivatives **6**–**8**[16] with Garegg's chromium trioxide/pyridine/acetic anhydride reagent.[18,19] Recently we found that the Dess–Martin 12-I-5 periodinane reagent[20] effects smooth and efficient oxidation of protected nucleoside derivatives.[21] This methodology is the most general and convenient we have examined for the preparation of ketonucleosides.[22]

Treatment of 1-[2,5-bis-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuran-3-ulosyl]uracil (**6**)[16] with methylenetriphenylphosphorane (generated[23] under "salt-free" conditions[24] from methyltriphenylphosphonium bromide with the organic-soluble sodium 2-methyl-2-butoxide[25] in diethyl ether/benzene) at −78 to −10 °C resulted in the disappearance of **6** and formation of an intermediate that remained at the baseline on TLC plates. Upon standing at 0–4 °C, slow conversion of the "baseline intermediate" to rapidly migrating (TLC) 2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-3′-deoxy-3′-methyleneuridine (**9**) occurred to give **9** (92%) as a colorless glass after flash chromatography.[26] Analogous treatment of 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)- and 3′,5′-*O*-(1,1,3,3-tetraisopropyldisiloxan-1,3-diyl)-protected 2′-ketouridine derivatives **7**[16] and **8**[16] gave the corresponding 2′-deoxy-2′-methyleneuridine derivatives **11** and **12**[6] in 70 and 68% yields, respectively, via analogous "baseline intermediates" (TLC). Deprotection of **9** and **11** (or **12**) with



tetrabutylammonium fluoride in tetrahydrofuran and purification on Dowex 50 (H^+) resin columns gave quantitative yields of the amorphous 3'-deoxy-3'-methyleneuridine (**10**) and 2'-deoxy-2'-methyleneuridine (**13**), respectively (Table 1).

As noted, addition of **6** to methylenetriphenylphosphorane under "salt-free" conditions[24] at low temperature resulted in the formation of an intermediate that behaved as a highly polar compound. Such minimal TLC migration would be expected with a phosphonium salt (either the triphenylphosphonium oxide betaine produced by direct attack of the ylide on the ketone, or its protonated triphenylphosphonium alcohol product). However, it has been pointed out that tetravalent-phosphorus intermediates that would result from the direct nucleophilic attack of Wittig reagents on carbonyl compounds have never been observed under "salt-free" conditions.[24,27] Only the pentavalent oxaphosphetane intermediates have been characterized by NMR spectroscopy under such conditions.[24,27-29] Therefore, the initial Wittig intermediate from ketone **6** was examined by NMR spectroscopy.

Our spectra (^{1}H- and ^{31}P-NMR) of the intermediate formed by treatment of **6** with methylenetriphenylphosphorane in toluene-d_8 were in harmony with prior observations.[24,27-29] Signals for a single intermediate (presumed to be oxaphosphetane **i**) were observed within 1 h (at -78 to -10 °C) with concomitant disappearance of signals for **6**. The ^{31}P-NMR spectrum (202 MHz) of **i** had a strong peak at $\delta = -69.35$ (upfield from H_3PO_4) in harmony with a pentavalent oxaphosphetane.[24,27,30-32] The ^{1}H-NMR spectrum (200 MHz) of **i** had sharp signals for H-1' at $\delta = 6.06$ (d, $J_{1',2'} = 2.2$ Hz), H-2' at 3.93 (d), and H-4' at 4.38 (t, $J_{4'-5',5''} = 4.4$ Hz). The 1',2', and 4'-proton signals in ketone **6** were at $\delta = 6.38$ (d, $J_{1',2'} = 8$ Hz), 4.30 (d), and 3.60 (s), respectively. The methylene protons on the oxaphosphetane ring (H_a and H_b) were nonequivalent. Their signals appeared as "triplets" at $\delta = 4.66$ ($J_{a,b} \cong J_{a,P} \cong 15.5$ Hz) and 4.97 ($J_{b,a} \cong J_{b,P} \cong 15.5$ Hz). The geminal proton-phosphorus coupling ($^2J_{HC,P} \cong 15.5$ Hz) in **i** is the same as reported for the oxaphosphetane intermediate ($^2J_{HC,P} = 15.7$ Hz)[30] derived from methylenetriphenylphosphorane and cyclohexanone.

Spectra of our small scale Wittig reaction mixture (maintained at -5 to 0 °C) were obtained at intervals to monitor the progressive reaction. After 24 h, the ^{1}H-NMR signals for **i** had diminished to ~ 25% (integrated intensities) with the accompanying appearance of signals (~ 75%) corresponding to the 3'-methylene derivative **9** at $\delta = 6.45$ (*d*, $J_{1',2'} = 7.0$ Hz, 1, H-1'), 4.76 (d of m, 1, H-2'), 4.34 (m, 1, H-4'), 4.93 (br s, 1, CH_AH_B), and 5.33 (br s, 1, CH_AH_B). Intensities of the ^{31}P-NMR signals for **i** ($\delta = -69.35$) and a new peak at $\delta = 24.5$ were in a similar ratio of ~ 1:3, respectively. After 48 h at -5 to 0 °C, the ^{1}H-NMR spectrum had sharp signals for **9**, and hardly visible peaks for **i**. The ^{31}P-NMR peak at $\delta = -69.35$ was barely visible, and the strong peak at $\delta = 24.5$ was enhanced by addition of triphenylphosphine oxide to the NMR tube.

These observations are consistent with the complete reaction of methylenetriphenylphosphorane and **6** within 1 h (at -78 to -10 °C) to give a single diastereoisomeric oxaphosphetane intermediate. NOESY spectra of this intermediate had a weak cross-peak connecting the *trans*-

Table 1. Compounds **9–18** Prepared

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a] or Lit. mp (°C)	UV (MeOH) λ_{max}(nm)(ε)	^{1}H-NMR (solvent/TMS) δ, J (Hz)	MS[b] (*m/z*)
9	92	52–53 (hexane)	–[c]	262 (8900)	$CDCl_3$: 0.0–0.1 [4s, 3H each, 2 × $Si(CH_3)_2$], 0.90, 0.92 [2s, 9H each, 2 × $SiC(CH_3)_3$], 3.72 (dd, 1H, $J_{5',5''}$ = 11, $J_{5',4'}$ = 1.6, H-5'), 4.00 (dd, 1H, $J_{5'',4'}$ = 2, H-5''), 4.56 (d"q", 1H, $J_{2',1'}$ = 6.6, $J_{\text{..q''}}$ = 2, H-2'), 4.67 ("q", 1H, $J_{\text{..q''}}$ = 1.8, H-4'), 5.16 (dd, 1H, J = 2, 1.5, $C\underline{H}_A H_B$), 5.27 (t, 1H, J = 2, $CH_A\underline{H}_B$), 5.76 (dd, 1H, $J_{5,6}$ = 8, $J_{5,NH}$ = 2.2, H-5), 5.96 (d, 1H, $J_{1',2'}$ = 6.6, H-1'), 7.99 (d, 1H, $J_{6,5}$ = 8, H-6), 8.75 (br s, 1H, NH)	412 [MH^+–$C(CH_3)_3$, 60], 329 (MH^+–B–CHO)
10	99	colorless foam	$C_{10}H_{12}N_2O_5 \cdot 0.25H_2O$ (244.7)	260 (10200)[d]	DMSO-d_6: 3.5–3.7 (m, 2H, H-5', 5''), 4.47 (br t, $J_{2',1'} = J_{2',OH}$ = 6, H-2'), 4.53 (m, 1H, H-4'), 5.10 (br t, 1H, J = 5, 5'-OH), 5.14 (br s, 1H, $C\underline{H}_A H_B$), 5.18 (br s, 1H, $CH_A\underline{H}_B$), 5.65 (d, 1H, $J_{1',2'}$ = 6, H-1'), 5.69 (br d, 1H, $J_{5,6}$ = 8, H-5), 5.83 (d, 1H, $J_{OH,2'}$ = 6, 2'-OH), 7.86 (d, 1H, $J_{6,5}$ = 8, H-6), 11.40 (br s, 1H, NH)	240 (M^+, 6), 209 (M^+–CH_2OH, 60), 81 (100)
11	70	158–159 (hexane)	–[c]	260 (9200)	$CDCl_3$: 0.0–0.2 [4s, 3H each, 2 × $Si(CH_3)_2$], 0.90, 0.91 [2s, 9H each, 2 × $SiC(CH_3)_3$], 3.76 (dt, 1H, $J_{4',3'}$ = 7, $J_{4',5'} = J_{4',5''}$ = 2, H-4'), 3.82 (dd, 1H, $J_{5',5''}$ = 12, H-5'), 3.97 (dd, 1H, $J_{5'',5'}$ = 12, $J_{5'',4'}$ = 2, H-5''), 4.79 (d"q", 1H, $J_{\text{..q''}}$ = 1.6, H-3'), 5.36 (t, 1H, J = 2, $C\underline{H}_A H_B$), 5.38 (dd, 1H, J = 2.2, 2, $CH_A\underline{H}_B$), 5.68 (dd, 1H, $J_{5,6}$ = 8, $J_{5,NH}$ = 2.4, H-5), 6.65 ("q", 1H, J = 1.8, H-1'), 7.60 (d, 1H, $J_{6,5}$ = 8, H-6), 8.56 (br s, 1H, NH)	412 (MH^+–$C(CH_3)_3$, 100), 300 (M^+–B–$C(CH_3)_3$, 25)
12	68	colorless foam	–[c]	260	$CDCl_3$: 0.9–1.1 [m, 28H, 4 × $SiCH(CH_3)_2$], 3.66 (d, t, 1H, $J_{4',3'}$ = 8.8, $J_{4',5'} = J_{4',5''}$ = 2.6, H-4'), 4.01 (dd, 1H, $J_{5',5''}$ = 13, $J_{5',4'}$ = 2.6, H-5'), 4.12 (dd, 1H, $J_{5'',5'}$ = 13, $J_{5'',4'}$ = 2.6, H-5''), 4.79 (d"q", 1H, $J_{\text{..q''}}$ = 1.6, H-3'), 5.43 (t, 1H, J = 2.2, $C\underline{H}_A H_B$), 5.51 (dd, 1H, J = 2.8, 1, $CH_A\underline{H}_B$), 5.68 (dd, 1H, $J_{5,6}$ = 8 Hz, $J_{5,NH}$ = 2, H-5), 6.49 ("q", 1H, J = 1.5, H-1'), 7.42 (d, 1H, $J_{6,5}$ = 8, H-6), 9.16 (br s, 1H, NH)	439 [M^+–$CH(CH_3)_2$, 100], 371 (M^+–B, 50), 329 [MH^+–B–$CH(CH_3)_2$, 75]
13	99	165–166 (*i*-PrOH/ Et_2O)	$C_{10}H_{12}N_2O_5$ (240.2)	260 (9100)[d]	DMSO-d_6: 3.5–3.7 (m, 3H, H-4',5',5''), 4.50 (br t, 1H, $J_{3',4'} = J_{3',OH}$ = 6, H-3'), 4.95 (t, 1H, J = 5, 5'-OH), 5.25 (dd, 1H, J = 2.2, 1.8, $C\underline{H}_A H_B$), 5.39 (t, 1H, J = 2.2, $CH_A\underline{H}_B$), 5.54 (dd, 1H, $J_{5,6}$ = 8, $J_{5,NH}$ = 2.2, H-5), 5.60 (d, 1H, $J_{OH,3'}$ = 6, 3'-OH), 6.46 ("q", 1H, J = 1.8, H-1'), 7.49 (d, 1H, $J_{6,5}$ = 8, H-6), 11.28 (br s, 1H, NH)	210 (MH^+–CH_2OH, 6), 129 (M^+–B, 100)
14	99	yellowish foam	–[c]	316, 250	$CDCl_3$: 0.0–0.2 [4s, 3H each, 2 × $Si(CH_3)_2$], 0.88, 0.92 [2s, 9H each, $SiC(CH_3)_3$], 3.84 (dd, 1H, $J_{5',5''}$ = 11.6, $J_{5',4'}$ = 2, H-5'), 4.11 (dd, 1H, $J_{5'',5'}$ = 11.6, $J_{5'',4'}$ = 2, H-5''), 4.52 (d"q", 1H, $J_{2',1'}$ = 4.1, $J_{\text{..q''}}$ = 1.5, H-2'), 4.77 ("q", 1H, J = 2, H-4'), 5.13 (t, 1H, J = 1.8, $C\underline{H}_A H_B$), 5.25 (t, 1H, J = 1.8, $CH_A\underline{H}_B$), 6.06 (d, 1H, $J_{1',2'}$ = 4.1, H-1'), 6.94 (d, 1H, $J_{5,6}$ = 7.3, H-5), 8.10 (s, 1H, triazole), 8.70 (d, 1H, $J_{6,5}$ = 7.2, H-6), 9.27 (s, 1H, triazole)	462 [M^+–$C(CH_3)_3$, 100]
15	93	colorless foam	$C_{10}H_{13}N_3O_4 \cdot 0.25H_2O$ (243.7)	270 (8900)[d]	DMSO-d_6: 3.5–3.7(m, 2H, H-5',5''), 4.4–4.5 (m, 2H, H-2',4'), 5.00 (t, 1H, J = 5.2, 5'-OH), 5.11 (t, 1H, J = 1.5, $C\underline{H}_A H_B$), 5.16 (t, 1H, J = 1.5, $CH_A\underline{H}_B$), 5.70 (d, 1H, $J_{1',2'}$ = 7, H-1'), 5.72 (br s, 1H, 2'-OH), 5.74 (d, 1H, $J_{5,6}$ = 7.4, H-5), 7.20 (br s, 2H, NH_2), 7.75 (d, 1H, $J_{6,5}$ = 7.4, H-6)	208 (M^+–CH_2OH, 2), 140 (BCH_2O, 100)
16	99	yellowish foam	–[c]	314, 250	$CDCl_3$: 0.0–0.2 [2s, 6H each, 2 × $Si(CH_3)_2$], 0.88, 0.92 [2s, 9H each, 2 × $SiC(CH_3)_2$], 3.81 (br d, 1H, $J_{4',3'}$ = 7.6, H-4'), 3.83 (dd, 1H, $J_{5',5''}$ = 12, $J_{5',4'}$ = 1.6, H-5'), 4.06 (dd, 1H, $J_{5'',5'}$ = 12, $J_{5'',4'}$ = 2, H-5''), 4.77 (d"q", 1H, $J_{3',4'}$ = 7.6, $J_{\text{..q''}}$ = 1.3, H-3'), 5.35 (dd, 1H, J = 2.3, 1.8, $C\underline{H}_A H_B$), 5.76 (dd, 1H, J = 2.3, 1.4, $CH_A\underline{H}_B$), 6.77 ("q", 1H, J = 1.4, H-1'), 6.94 (d, 1H, $J_{5,6}$ = 7.2, H-5), 8.10 (s, 1H, triazole), 8.55 (d, 1H, $J_{6,5}$ = 7.2, H-6), 9.26 (s, 1H, triazole)	462 [M^+–$C(CH_3)_2$, 100], 357 (M^+–B, 40)

Table 1. (continued)

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a] or Lit. mp (°C)	UV (MeOH) λ_{max}(nm)(ε)	^{1}H-NMR (solvent/TMS) δ, J (Hz)	MS[b] (m/z)
17	99	yellowish foam	–[c]	314, 250	$CDCl_3$: 0.9–1.2 [m, 28H, 4 × $SiCH(CH_3)_2$], 3.76 (br d, 1H, $J_{4',3'}$ = 9.1, H-4'), 4.05 (dd, 1H, $J_{5',5''}$ = 13.5, $J_{5',4'}$ = 2.5, H-5'), 4.23 (d, 1H, $J_{5'',5'}$ = 13.5, H-5''), 4.80 (br d, 1H, $J_{3',4'}$ = 9.1, H-3'), 5.42 (br s, 1H, $C\underline{H}_A H_B$), 5.87 (d, 1H, J = 2.7, $CH_A\underline{H}_B$), 6.64 (s, 1H, H-1'), 6.98 (d, 1H, $J_{5,6}$ = 7.3, H-5), 8.10 (s, 1H, triazole), 8.34 (d, 1H, $J_{6,5}$ = 7.3, H-6), 9.23 (s, 1H, triazole)	533 (M^+, 2), 490 [M^+–$CH(CH_3)_2$, 100], 371 (M^+–B, 15)
18	96	89–90 (H_2O)	$C_{10}H_{13}N_3O_4 \cdot 0.75H_2O$ (252.7)	268 (8400)[d]	DMSO-d_6: 3.4–3.7 (m, 3H, H-4',5',5''), 4.42 (br t, 1H, J = 6, H-3'), 4.92 (t, 1H, J = 5, 5'-OH), 5.13 (br s, 1H, $C\underline{H}_A H_B$), 5.29 (br s, 1H, $CH_A\underline{H}_B$), 5.61 (d, 1H, $J_{OH,3'}$ = 6, 3'-OH), 5.69 (d, 1H, $J_{5,6}$ = 7.3, H-5), 6.50 (br s, 1H, H-1'), 7.21 (br s, 2H, NH_2), 7.47 (d, 1H, $J_{6,5}$ = 7.3, H-6)	239 (M^+, 8), 221 (M^+–H_2O, 10), 111 (BH, 100)

[a] Satisfactory microanalyses obtained: C ±0.30, H ±0.21, N ±

[b] B in MS fragments refers to the corresponding uracil substituent.

[c] Microanalysis not determined for these intermediates

[d] Solvent: H_2O (pH 7).

Table 2. ^{13}C-NMR Chemical Shift Data, δ[a]

Compound	C-2	C-4	C-5	C-6	CH_2	C-1'	C-2'	C-3'	C-4'	C-5'
9	151.11	163.86	103.26	140.82	108.85	87.95	76.98	147.56	81.53	66.42
10	151.15	163.37	102.46	141.14	108.17	87.36	73.83	148.18	80.85	63.95
11	151.00	163.26	102.99	141.23	113.74	85.11	149.33	70.02	84.38	61.09
12	150.93	163.66	102.94	140.13	112.41	84.14	147.08	70.02	83.28	60.59
13	151.03	163.48	102.48	141.94	112.36	84.76	149.94	69.86	83.74	60.52
14[b]	155.19	159.69	94.70	147.98	110.49	90.71	79.36	146.02	81.97	64.50
15	156.06	165.74	94.73	142.13	108.11	88.69	74.20	148.73	80.57	63.90
16[b]	155.50	159.70	94.94	147.51	114.44	86.15	148.78	69.07	85.55	60.87
17[b]	155.15	159.75	94.92	146.52	113.15	85.97	146.08	68.48	84.05	60.20
18	155.87	165.82	94.85	142.45	111.30	84.33	151.13	69.86	84.33	60.49

[a] Internal standard: TMS; solvent: $CDCl_3$for **9, 11, 12, 14, 16, 17** and DMSO-d_6 for **10, 13, 15, 18**.

[b] Triazole peaks at δ = ~154 and ~156.

oriented H-1' and H-2' protons. A weaker interaction linking H-2' with H_b also was observed, but no interactions linking H_a or H_b with H-4', H-5', or H-5'' were detected. Inspection of Dreiding models suggested that the expected distance between H-2' and H-1' should be approximately the same as between H-2' and H_b in intermediate **i**. However, the distance between H_a and H-4' in **i** would be expected to be shorter. The other possible oxaphosphetane intermediate (attack of the Wittig reagent from the β face) would be expected to have H_a in close proximity to H-5' or H-5''. However, the absence of NOE interactions is not a valid criterion for the assignment of stereochemistry and therefore the NOESY results are inconclusive.

The Wittig reagent is presumed to have added from the less hindered α-face to give **i** analogously to our recent results involving α-face diastereoselection by a bulky reducing agent with an identically protected 3'-ketonucleoside.[21] ^{1}H- and ^{31}P-NMR spectra are consistent with formation of a single diastereoisomer and its collapse to **9** plus triphenylphosphine oxide. TLC also showed disappearance of **6** (within 1 h) with formation of a highly polar intermediate that disappeared progressively (over 48 h) with formation of rapidly migrating **9** and triphenylphosphine oxide. Thus, the protected nucleoside ketones apparently react with methylenetriphenylphosphorane at low temperatures to give oxaphosphetanes, which slowly collapse to the methylene nucleosides plus triphenylphosphine oxide. Acidic silica gel TLC plates would be expected to catalyze ring opening of the oxaphosphetane intermediates to give phosphonium species that would not migrate from the baseline.[24,27]

Treatment of **9** with phosphoryl chloride/1,2,4-triazole/triethylamine[33] in acetonitrile at ambient temperature gave quantitative conversion to the 4-(1,2,4-triazol-1-yl) derivative **14**. Intermediate **14** was treated sequentially at ambient temperature with aqueous ammonia/1,4-dioxane and tetrabutylammonium fluoride/tetrahydrofuran. Purification on a column of Dowex 1X2 (OH^-) resin gave 3'-deoxy-3'-methylenecytidine (**15**, 93% as a colorless glass). Analogous treatment of **11** or **12** gave 2'-deoxy-2'-methylenecytidine[8,9] (**18**, 96% as a colorless glass). Crystallization of **18** occurred, but **15** was converted to its crystalline hydrochloride salt.

As also observed by others,[5-9,34,35] silyl-protected ketouridine nucleosides are sufficiently stable to undergo reactions with Wittig (and organometallic) reagents under mild conditions. Our use of sodium 2-methyl-2-butoxide[23] allows formation of clear solutions of "salt-free" Wittig reactions[24] in diethyl ether/benzene that provide good to high yields of the methylene-uridine analogues. Methylenetriphenylphosphorane reacts with a protected ketonucleoside within 1 h at −78 to −10 °C to give a single oxaphosphetane diastereoisomer (^{1}H- and ^{31}P-NMR). This intermediate, which is converted on TLC plates into polar species that do not migrate from the baseline, slowly collapses to give the methylene-nucleoside and triphenylphosphine oxide at −5 to 0 °C.

Quantitative conversions of the protected methylene-uridine analogues to their methylene-cytidine counterparts can be effected via 4-(1,2,4-triazol-1-yl)pyrimidin-2(1*H*)-one intermediates.[33] These reactions, performed at ambient or lower temperatures, utilize routine bench top methodology and equipment.

Melting points were determined with a Hoover apparatus and are uncorrected. UV spectra were measured in MeOH (unless otherwise specified) using a Hewlett-Packard 8451 A spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded at 200 and 50 MHz, respectively, on a Varian Gemini-200 spectrometer. ^{31}P-NMR spectra were obtained at 202.33 MHz under broad-band proton decoupling with 85% H_3PO_4 as external reference on a Varian VXR-500S spectrometer. Low resolution electron impact MS were obtained at 20 eV with direct probe sample introduction on a Finnigan MAT 8430 spectrometer. Evaporations were effected with a Büchi rotary evaporator under water aspirator or mechanical oil pump vacuum at < 35 °C. HPLC was performed on a Waters Prep LC/System 500 A with PrepPAK-500/silica cartridges. TLC was performed on E. Merck 60-F_{254} sheets. E. Merck Kieselgel 60, (230–400 mesh) was used for flash chromatography. Unless specified, the solvent system for all chromatography was EtOAc/hexane (3:7, v/v). Reagent grade solvents and reagents were redistilled prior to use. Pyridine, Et_3N, and benzene were dried by heating at reflux with CaH_2, and then distilled. Et_2O was distilled from sodium benzophenone ketyl. MeCN was distilled from P_2O_5. *tert*-Butyldimethylsilyl chloride (TBDMS-Cl) and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (TPDS-Cl_2) were purchased from Aldrich Chemical Co.

A ~1.1 M solution of sodium 2-methyl-2-butoxide in benzene, which can be stored under N_2 at r.t. for several months, was prepared as reported.[25]

Silylation of Uridine (1):
TBDMS-Cl (11.1 g, 73.8 mmol) is added to a solution of uridine (**1**; 6.0 g, 24.6 mmol) in pyridine (50 mL). The mixture is stirred at r.t. for 48 h, evaporated, and the residue partitioned between CH_2Cl_2 (500 mL) and ice-cold 5% aq HCl (200 mL). The organic phase is washed with sat. $NaHCO_3$ (200 mL), brine (200 mL), dried (Na_2SO_4), concentrated, and purified by preparative HPLC to give colorless foams of 2′,3′,5′-tris-*O*-(*tert*-butyldimethylsilyl)uridine (**2**); yield: 0.72 g (5%) (R_f ~ 0.6); 2′,5′-bis-*O*-(*tert*-butyldimethylsilyl)uridine (**3**); yield: 8.13 g (70%) (R_f ~ 0.44); and 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)uridine (**4**); yield: 2.11 g (18%) (R_f ~ 0.16) with spectra data as reported.[10]

Oxidation of Uracils 3–5; General Procedure:
Acetic anhydride (2.1 mL, 21.7 mmol) and pyridine (3.5 mL, 43.3 mmol) are added to an ice-cooled suspension of CrO_3 (2.16 g, 21.7 mmol) in CH_2Cl_2 (150 mL) and the mixture is stirred at r.t. until homogeneous (~ 15 min). A concentrated solution of **3**, **4** or **5** (7.3 mmol) in CH_2Cl_2 is added, the mixture stirred r.t. for 1 h, poured into cold EtOAc (1 L), and filtered through a glass microfibre filter GF/A. The filtrate is concentrated (< 25 °C) and subjected to flash chromatography[26] (EtOAc).

6: colorless powder; yield: 83%; **7:** colorless powder; yield: 90%; **8:** yellowish powder; yield: 87%. The spectral data of **6–8** are identical with the reported[16] values.

1-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-methylene-β-D-*erythro*-pentofuranosyl]uracil (9); Typical Procedure:
To a stirred suspension of methyltriphenylphosphonium bromide (1.55 g, 4.35 mmol) in anhydrous Et_2O (125 mL) is added a ~ 1.1 M soln of sodium 2-methyl-2-butoxide (3.95 mL, 4.35 mmol) in benzene, and the bright-yellow mixture stirred under N_2 for 2 h and cooled to −78 °C. To this suspension is added the appropriate ketouridine **6** (1.0 g, 2.12 mmol) in one portion and the mixture allowed to warm to −10 °C over 1 h and stored at 0–4 °C for 48 h. The mixture is quenched with sat. aq NH_4Cl (50 mL) and the aqueous phase is extracted with Et_2O (2 × 50 mL). The combined organic phases are washed with brine (50 mL), dried (Na_2SO_4), evaporated, and the crude residue purified by flash chromatography; yield: 0.92 g (92%) (Tables 1 and 2).

1-(3-Deoxy-3-methylene-β-D-*erythro*-pentofuranosyl)uracil (3′-deoxy-3′-methyleneuridine) (10); Typical Procedure:
To a magnetically stirred solution of **9** (0.89 g, 1.9 mmol) in THF (12 mL) is added 1 M THF solution of Bu_4NF (3.9 mL, 3.9 mmol). After 2 h, the solvent is evaporated and the residue partitioned between H_2O (15 mL) and Et_2O (10 mL). The aqueous phase is washed with Et_2O (10 mL), concentrated (< 35 °C), and applied to a column of Dowex 50 (H^+) resin packed in H_2O. Elution of the product with H_2O and evaporation of appropriate fractions affords **10** as a colorless foam; yield: 0.46 g (99%) (Tables 1 and 2).

1-[2,5-Bis-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-3-methylene-β-D-*erythro*-pentofuranosyl]-4-(1,2,4-triazol-1-yl)pyrimidin-2(1*H*)-one (14); Typical Procedure:
To a stirred mixture of 1,2,4-triazole (0.93 g, 13.4 mmol), $POCl_3$ (0.42 g, 0.26 mL, 2.85 mmol) and MeCN (8 mL) cooled to 0 °C, is added dropwise Et_3N (1.3 g, 1.78 mL, 12.8 mmol). To this mixture is added a solution of **9** (0.6 g, 1.28 mmol) in MeCN (5 mL) and stirring is continued at r.t. for 2 h. Et_3N (1.24 mL, 8.96 mmol) and H_2O (0.5 mL) are added, and after 10 min the mixture is evaporated. The residue is partitioned between CH_2Cl_2 (30 mL) and ice-cold sat. aq $NaHCO_3$ (30 mL). The aqueous phase is extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts are washed with brine (50 mL), dried (Na_2SO_4), and evaporated to give **14** as a yellowish foam; yield: 0.66 g (99%) (Tables 1 and 2).

1-(3-Deoxy-3-methylene-β-D-*erythro*-pentofuranosyl)cytosine (3′-deoxy-3′-methylenecytidine) (15); Typical Procedure:
To a solution of **14** (0.66 g, 1.27 mmol) in 1,4-dioxane (6 mL) is added 30% aq NH_3 (2 mL). After stirring at r.t. for 12 h, the solvent is evaporated and the residue dissolved in THF (10 mL). To this mixture is added 1 M THF solution of Bu_4NF (3 mL, 3 mmol) and stirring continued for 2 h. Solvent is evaporated and the residue partitioned between Et_2O (10 mL) and H_2O (15 mL). The aqueous phase is concentrated and applied to a column of Dowex 1 × 2 (OH^-) resin (packed in H_2O). Elution with H_2O and evaporation affords **15** as a colorless foam; yield: 0.28 (93%) (Tables 1 and 2).

15 · HCl: Compound **15** is isolated as a crystalline hydrochloride salt by treating a suspension of 15 in MeOH with 5% aq HCl. The solution is filtered, the filtrate concentrated, and excess HCl removed by repetitive addition and evaporation of MeOH/H_2O. The resulting yellowish oil is crystallized from MeOH to give **15 · HCl** as yellowish prisms; mp 190–192 °C (dec).

$C_{10}H_{13}N_3O_4 \cdot HCl$	calc.	C 43.57	H 5.12	N 15.24	Cl 12.86
(275.7)	found	43.57	5.33	15.03	13.03

UV (H_2O, pH 7): λ_{max} = 270 nm (ε = 8900).

^{1}H-NMR (DMSO-d_6/TMS): δ = 3.57 (dd, 1H, $J_{5',5''}$ = 12, $J_{5',4'}$ = 3.5 Hz, H-5′), 3.6 (br m, 3H, OH + NH), 3.67 (dd, 1H, $J_{5'',4'}$ = 3 Hz, H-5″), 4.47 (d"q", 1H, $J_{2',1'}$ = 6 Hz, J''_q = 1.5 Hz,

H-2'), 4.61 (m, 1 H, H-4'), 5.17 (t, 1 H, J = 1.8 Hz, CH_AH_B), 5.22 (t, 1 H, J = 1.8 Hz, CH_AH_B), 5.70 (d, 1 H, H-1'), 6.20 (d, 1 H, $J_{5,6}$ = 7.7 Hz, H-5), 8.21 (d, 1 H, H-6), 8.72, 9.84 (2 br s, 2 H, NH_2^+).

Low-Temperature ^{1}H- and ^{31}P-NMR Experiments:
A two-necked 15 mL round-bottom flask is flame-dried, purged with N_2, and charged with methyltriphenylphosphonium bromide (28 mg, 77 μmol) and anhydrous Et_2O (2.5 mL). A 1.9 M solution of sodium 2-methyl-2-butoxide/benzene (40 μL, 76 μmol) is added and the resulting bright-yellow mixture stirred under N_2 for 2 h at r.t. The fine suspension is allowed to settle and the supernatent transferred (double-tipped needle) to a second two-necked 15-mL round-bottom flask. This solution is cooled to −78 °C and **6** (13 mg, 30 μmol) added in one portion. The mixture is allowed to warm to −10 °C over 1 h. TLC shows a new spot at the baseline and no starting **6**. Solvents are evaporated *in vacuo* (< −10 °C) and the orange residue is cooled to −15 °C, dissolved in toluene-d_8 (0.6 mL), transferred by syringe to a 5-mm NMR tube, and stored at 0 to −5 °C. ^{1}H- and ^{31}P-NMR spectra are obtained at −10 °C every 8 h for 2 d. After 24 h a fine precipitate of Ph_3PO appears. The characteristic chemical shifts of the oxaphosphetane **i** in NMR are:

^{1}H-NMR (toluene-d_8): δ = 3.70 (dd, 1 H, $J_{5',5''}$ = 11.0 Hz, $J_{5',4'}$ = 4.4 Hz, H-5'), 3.90 (dd, 1 H, $J_{5'',4'}$ = 4.4 Hz, H-5''), 3.93 (d, 1 H, $J_{2',1'}$ = 2.2 Hz, H-2'), 4.38 (t, 1 H, H-4'), 4.66 ("t", 1 H, $J_{a,b} = J_{a,P}$ = 15.5 Hz, CH_aH_b), 4.97 ("t", 1 H, $J_{b,a} = J_{b,P}$ = 15.5 Hz, CH_aH_b), 5.88 (d, 1 H, $J_{5,6}$ = 8.0 Hz, H-5), 6.06 (d, 1 H, H-1'), 7.0–8.0 (m, 15 H_{arom}).

^{31}P-NMR (toluene-d_8): δ = −69.35 (s, major), [22.75 (s, minor), 25.35 (s, minor)].

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