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Synthesis of Nucleoside 3'-Phosphonates via 3'-Keto Nucleosides

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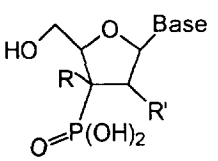
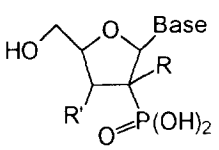
Abstract: Nucleophilic addition of diethyl phosphite anion to several 2'- or 3'-keto nucleosides results in an efficient synthesis of 2'-hydroxy-2'-phosphono- or 3'-hydroxy-3'-phosphononucleosides. The stereochemistry of one such adduct, 3'α-diethylphosphono-3'β-hydroxy-5'-O-tritylthymidine, was determined by single crystal diffraction analysis. When the 5'-hydroxyl group is protected with groups that are not sterically demanding, the 3' geminal hydroxy phosphonates undergo radical deoxygenation under modified Barton conditions to afford the reduced compounds in good yields. Removal of the remaining hydroxyl protecting groups, and hydrolysis of the phosphonate acid esters, then gives the parent nucleoside 3'-phosphonic acids.

The number of modified nucleosides has grown almost exponentially in recent years, at least in part in response to the pressing need for new anti-viral agents.[1] While several modified nucleosides have clinically verified utility in treatment of HIV infections,[2] both the demonstration of toxic side effects and the evolution of resistant viral strains stimulate further studies on the synthesis and biological activities of modified nucleosides. These observations, together with a longstanding interest in methods for C-P bond formation,[3,4] have led us to attempt synthesis of a variety of modified nucleosides containing phosphonate groups.[4c] While methylenephosphonate analogues of both nucleoside 5'- and 3'-phosphates have been known for many years,[5] direct attachment of a phosphono group at the 3'- (e.g. **1**) and 2'-positions (e.g. **2**) has not been described prior to this work.[6] Given the similarity of these phosphonates to the 3'-phosphates (**3**), the potential for biological activity in these new analogues appeared reasonable.



1



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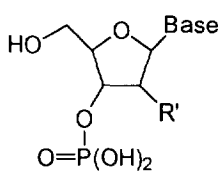


3

R = H or OH
R' = H or OH

In considering approaches to nucleoside phosphonates of the general structures **1** and **2**, a fundamental choice must be made between sequences involving glycosylation and those that begin with intact nucleosides. While glycosylation sequences might offer access to a greater variety of nucleosides, including those with

unnatural bases, standard glycosylation procedures might not be readily adaptable to use with highly modified carbohydrates. By approaching the target phosphonates from intact nucleosides, one could hope to accomplish an efficient synthesis while avoiding the issues of yield and stereocontrol that often plague formation of the glycosidic bond.[7] In this paper, we report the details of an exploration of this later strategy, including preparation of several nucleoside geminal hydroxy phosphonates and their conversion into the corresponding phosphonic acids via radical deoxygenation and simple hydrolysis of the requisite protecting groups.

Nucleophilic addition of a dialkyl phosphite anion to a carbonyl group is a well-known method for preparation of geminal hydroxy phosphonates.[8] However, phosphite additions can be complicated by an alkyl transfer that generates alkyl phosphonates,[9] and at least the 3'-keto nucleosides have a certain notoriety for the ease with which they undergo elimination of the base moiety under basic conditions.[10a] Nonetheless, these unstable ketones have been prepared and shown to undergo some carbonyl addition reactions,[10] encouraging exploration of their reactivity with phosphite anions.

Upon treatment with the lithium salt of diethyl phosphite, both 2'- and 3'-keto nucleosides have been found to undergo phosphite addition in very good yields (Table 1). At low temperature (-78° C), only a single diastereomer is generally observed from addition to either the 2'-ketones **4** and **6,** or the 3'-ketones **8**, **10**, **12,** and **14**, but at higher temperatures mixtures of diastereomers were sometimes found. While it may be reasonable to expect nucleophilic addition to predominate from the less hindered α-face, both on the basis of steric arguments and the limited literature precedent, it appears that previous stereochemical assignments have been justified primarily by NMR data.[11-13] To determine the stereochemistry of at least one phosphonate product unambiguously, a crystalline sample of compound **15** was subjected to single crystal diffraction analysis.[14] As shown in Figure 1, the X-ray analysis clearly indicates that phosphite anion has added to the carbonyl group from the sterically less hindered α-face of the nucleoside, to afford the α phosphonate **15**.

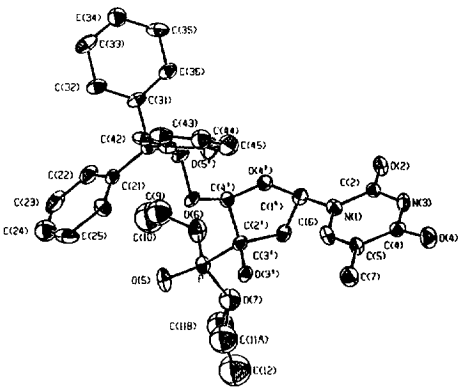
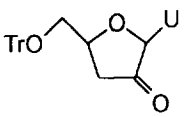
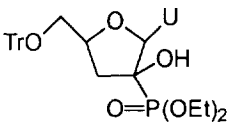
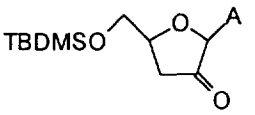
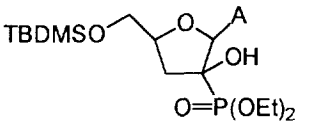
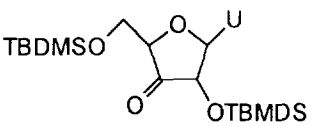
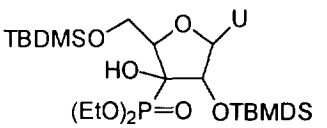
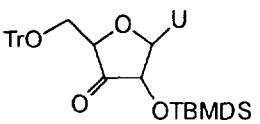
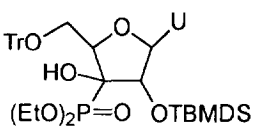
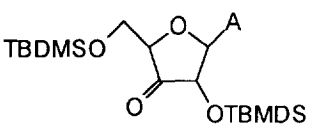
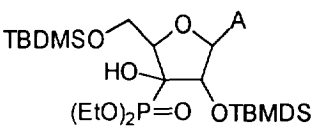
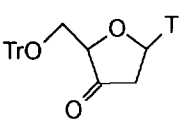
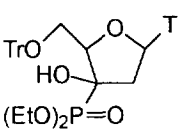


Figure 1. ORTEP drawing of Compound **15**

Conversion of geminal hydroxy phosphonates to the corresponding phosphonates theoretically requires only removal of the hydroxyl group. While the radical deoxygenation strategy described by Barton[15] is often employed for such reductions in nucleosides and carbohydrates in general, the original procedures are often problematic with tertiary alcohols due to competing eliminations. A variation employing methyl oxalyl chloride to generate a mixed oxalate ester followed by reaction with Bu_3SnH, has been reported to excel with tertiary

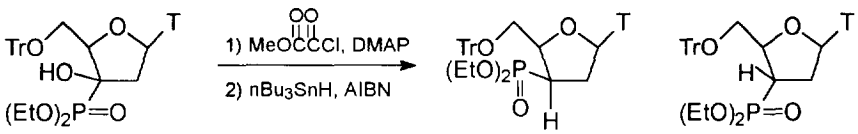
alcohols.[16] Accordingly, this strategy was explored with representative examples of these nucleoside geminal hydroxy phosphonates.

Table 1. Synthesis of Nucleoside *gem*-Hydroxy Phosphonates

keto nucleoside	product	yield %
 **4**	 **5**	80
 **6**	 **7**	82
 **8**	 **9**	91
 **10**	 **11**	91
 **12**	 **13**	93
 **14**	 **15**	76

Treatment of the thymidine derivative **15** with methyl oxalyl chloride and DMAP in anhydrous acetonitrile gave the desired ester in virtually quantitative yield. Given past observations that tertiary oxalate esters are often unstable,[16] this intermediate was treated in situ with Bu_3SnH and AIBN. The desired phosphonates were obtained in very good yield, as a 2.2:1 mixture of the diastereomers **16** and **17**. While a

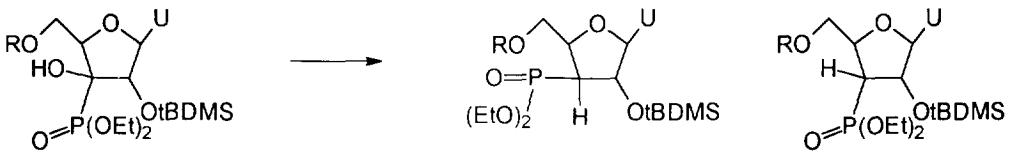
definitive proof is not yet available, it is likely that the major diastereomer is the ß-phosphono isomer **16**, since this would result through approach of the H-atom donor from the less hindered α-face of the ring.



15 **16** **17**

(2.2:1)

Extension of this deoxygenation protocol to the corresponding ribose derivatives was not completely straightforward. When hydroxy phosphonate **11** was treated under the same conditions, the deoxygenation was accomplished in only 26% yield, affording a 2.6:1 ratio of phosphonates **18** and **19**. The bis *t*BDMS compound **9** proved only slightly better, providing phosphonates **20** and **21** in about 30% yield. Based on the assumption that a sterically demanding substituent at the 5' position amplifies the steric hindrance of the tertiary alcohol, it would be desirable to employ smaller 5' protecting groups. Accordingly, the bis-silyl compound **9** was treated with aqueous TFA, to accomplish selective deprotection of the 5'-hydroxyl group.[17] When the resulting alcohol (**22**) was first treated with benzoyl chloride to obtain benzoate **23**, and this benzoate was then subjected to the modified Barton protocol, the desired deoxygenation products **24** and **25** were obtained in a much improved yield (92%), albeit still as a mixture of diastereomers (1.8:1). In a parallel sequence, the alcohol **22** was treated



11 R = Tr	**18** R = Tr	(2.6:1)	**19** R = Tr
9 R = tBDMS	**20** R = tBDMS	(1.9:1)	**21** R = tBDMS
22 R = H			
23 R = Bz	**24** R = Bz	(1.8:1)	**25** R = Bz
26 R = Ac	**27** R = Ac	(1.8:1)	**28** R = Ac

with acetic anhydride under standard conditions, and the resulting 5'-acetate (**26**) was subjected to the deoxygenation sequence. Again the reduced phosphonates (**27** and **28**) were obtained in good yield (89%), but again a 1.8:1 mixture of diastereomers was observed. These results suggest that smaller protecting groups at the 5'-position allow efficient formation of a radical intermediate at the 3'-position, but they also suggest that the radical is quenched primarily from the alpha face regardless of the size of the 5' protecting group.

While the diastereomeric ratios of these deoxygenation products can be readily determined by ^{31}P NMR, assignment of the specific 3' stereochemistry by NMR is a non-trivial task. Fortunately a sample of the major diastereomer (**24**) resulting from deoxygenation of the benzoyl compound **23** was obtained in crystalline form and could be subjected to a diffraction analysis.[18] As shown in Figure 2, this compound was found to embody the 3'ß-stereochemistry, as might be predicted from steric considerations. Once the stereochemistry was established in this pair, it could be assigned with some confidence in the other series based on ^{1}H and ^{31}P NMR data.

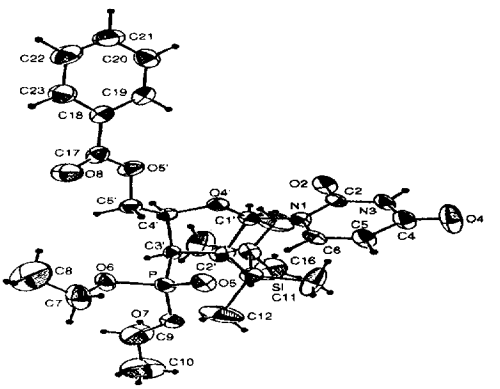
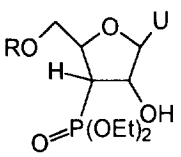
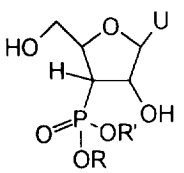


Figure 2. ORTEP drawing of compound **24**

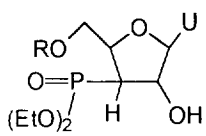
To more closely approximate nucleoside 3'-phosphates, it was necessary to remove the various protecting groups and cleave the phosphonate esters. After removal of the *t*BDMS group of compound **25** by reaction with fluoride ion, treatment of the α phosphonate **29** with Et_3N in $MeOH/H_2O$ resulted in formation of the 5' deprotected phosphonate diester **30**. Subsequent reaction of compound **30** with TMSBr in pyridine gave primarily the mono ester **31.** However, treatment of compound **29** with NaOH/EtOH resulted in complete loss of the benzoate and partial phosphonate hydrolysis, yielding a mixture of diester **30,** mono ester **31**, and phosphonic acid **32** after 3 days at room temperature.



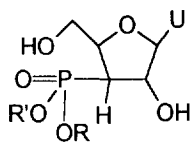
29 R = Bz



30 R = R' = Et
31 R = H; R' = Et
32 R = R' = H

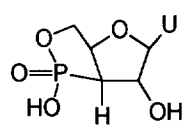


33 R = Bz



34 R = R' = Et
35 R = H; R' = Et
36 R = R' = H

The silyl group of the ß phosphonate **24** also was readily cleaved with fluoride ion, yielding compound **33**. When compound **33** was treated with Et_3N in $MeOH/H_2O$, the mono ester **35** was the predominant product (86%) instead of the diester **34**. Treatment of compound **33** with NaOH/EtOH at rt gave the parent phosphonic acid **36** in good yield. When compound **24** itself was treated with NaOH, followed by cleavage of the silyl group, the cyclic phosphonate **37** was the major product. It is somewhat surprising that no



37

isomerization of the C-3' stereochemistry was observed under these conditions, even though calculations suggest that the α-isomer is more stable by about 2.7 kcal/mol[19] and there is precedent for isomerization in similar systems.[7,20] However, it is still possible that isomerization could be observed under more forceful conditions.

In conclusion, we have shown that both nucleoside 2'- and 3'-ketones undergo efficient addition of diethyl phosphite under basic conditions to afford geminal hydroxy phosphonates. Furthermore, these geminal hydroxy phosphonates can be efficiently converted to the parent phosphonic acids through radical deoxygenation, provided they are not sterically hindered by large protecting groups at the 5'-position. While the phosphite addition proceeds cleanly from the less hindered α-face of the ribose, deoxygenation of the 3'-hydroxy 3'-phosphono compounds results in formation of a mixture of diastereomers in which the ß-isomer is the major product. Nevertheless, the most efficient route from commercial uridine to β phosphonate **36** requires only 9 steps and proceeds in 26% overall yield, while the isomeric α phosphonate **32** was obtained in about 9% yield. Because of the diminished need for protecting groups, the 2'-deoxy compounds are even more readily accessible. Thus these nucleotide analogues are now available in quantities sufficient to permit their incorporation into oligonucleotide analogues as well as their biological evaluation. Our further studies along these lines will be reported in due course.

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled from sodium/benzophenone; pyridine, acetonitrile, toluene, benzene, and dichloromethane were distilled from calcium hydride immediately prior to use. All reactions in these solvents were conducted under a positive pressure of an inert gas. Flash column chromatography was done on Merck grade 62Å silica gel (40 μm), while radial chromatography was performed with a Chromatotron apparatus and Merck PF254 silica gel with $CaSO_4 \cdot 0.5H_2O$. Preparative layer chromatography was performed on plates of silica gel 60 F_{254} (Merck). HPLC separations were conducted with a Spectra Physics SP 8800/8810 HPLC system equipped with a Rainin Dynamax column (RP C18, 1 x 25 cm, 8 μm particle size). NMR spectra (^1H, ^{13}C and ^{31}P) were recorded on either a Brucker WM-300 or a Brucker WM-360 spectrometer. ^{31}P chemical shifts are reported in ppm relative to 85% H_3PO_4 (external standard). Low-resolution electron impact (EI) mass spectra were obtained from a VG mass spectrometer (TRIO-1) operating at 70 ev in the electron impact mode; only selected ions are reported here. High-resolution and FAB mass spectra were obtained on a ZAB-HF reversed geometry mass spectrometer at the University of Iowa Mass Spectrometry facility. Samples were bombarded with 8KeV Xe atoms at an atom gun current of 1.5 mA. Saturated solutions of either CsI or NaI were used as calibrants, with 3-nitrobenzyl alcohol, thioglycerol, or dithiothreitol/dithioerythreitol as the matrices. For negative ion FAB experiments, triethanol amine was used

for the matrix. Elemental analyses were performed by Atlantic Microlab, Inc., or on a PE 2400 Series II CHNS/O Analyzer. X-ray crystallographic analyses were performed at the University of Iowa X-ray Laboratories.

3'-Deoxy-2'-keto -5'-O-trityluridine (4).

To a slurry of PDC (24.4 g, 64.8 mmol) and 3Å molecular sieve powder (25 g) in CH_2Cl_2 (80 mL) was added a solution of 3'-deoxy-5'-O-trityluridine[10c] (7.61 g, 16.2 mmol) in CH_2Cl_2 (45 mL) via a cannula, and the cannula was rinsed into the reaction mixture with 10 mL CH_2Cl_2. The mixture was stirred at room temperature overnight, and filtered through Celite. The filtrate was concentrated in vacuo, suspended in EtOAc, and filtered through a short silica gel column using EtOAc as eluent. After concentration of the filtrate, the light brown residue was purified by flash column (CH_2Cl_2:EtOAc, 1:1) to obtain compound **4** (6.44 g, 85%) as a white foam. ^{1}H NMR ($CDCl_3$) δ 8.99 (br s, 1H), 7.43-7.21 (m, 16H, arom and H_6), 5.61 (dd, 1H, $J_{5,6}$ = 8.0 Hz, J = 2.2 Hz), 5.35 (s, 1H), 4.58-4.55 (m, 1H), 3.53 (dd, 1H, $J_{5'a,5'b}$ = 10.4 Hz, $J_{5'a,4'}$ = 5.7 Hz), 3.39 (dd, 1H, $J_{5'b,5'a}$ = 10.4 Hz, $J_{5'b,4'}$ = 3.4 Hz), 2.85 (dd, 1H, $J_{3'a,3'b}$ = 18.9 Hz, $J_{3'a,4'}$ = 8.1 Hz), 2.61 (dd, 1H, $J_{3'b,3'a}$= 18.8 Hz, $J_{3'b,4'}$ = 7.7 Hz). EIMS *m/z* (relative intensity) 391 (M^+-C_6H_5, 0.9), 279 (2), 259 (7), 244 (34), 243 (100), 226 (3), 209 (11), 165 (68), 105 (62). HRFAB calcd for $C_{28}H_{24}N_2O_5$ 469.1763 $(M+H)^+$, found 469.1754.

3'-Deoxy-2'-α-diethylphosphono-2'-β-hydroxy-5'-O-trityluridine (5).

To a solution of diethyl phosphite (0.13 mL, 1.0 mmol) in THF (1 mL) at -78 °C was added dropwise via syringe lithium bis(trimethylsilyl)amide (LHMDS, 1.1 mL, 1.1 mmol, 1.0M in THF) under a nitrogen atmosphere. After 10 to 15 min, a solution of ketone **4** (234 mg, 0.5 mmol) in 3 mL THF was added, and the reaction mixture was allowed to warm to about 0 °C over 2 h. The reaction was quenched by slow addition of acetic acid in ether, and the resulting mixture was filtered through Celite. After concentration in vacuo, the residue was purified by radial chromatography ($CHCl_3$:MeOH, 95:5) to afford compound **5** (236 mg, 78%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.79 (br s, 1H), 7.53 (d, 1H, $J_{6,5}$ = 8.1 Hz), 7.49-7.21 (m, 15H), 6.35 (d, 1H, J_{HP} = 2.4 Hz), 5.65 (br d, 1H, J_{HP} = 2.8 Hz, OH), 5.49 (dd, 1H, $J_{5,6}$ = 8.1 Hz, J_{HP} = 2.0 Hz), 4.47-4.16 (m, 5H, $OC\underline{H}_2CH_3$, and $H_{4'}$), 3.49 (dd, 1H, $J_{5'a,5'b}$ = 10.0 Hz, $J_{5'a,4'}$ = 7.0 Hz), 3.20 (dd, 1H, $J_{5'b,5'a}$ = 10.1 Hz, $J_{5'b,4'}$ = 3.6 Hz), 2.69-2.65 (m, 1H), 2.06-2.00 (m, 1H), 1.39 (t, 3H, J = 7.1 Hz), 1.31 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 165.2, 149.3, 143.8 (3C), 143.5, 128.7 (6C), 127.9 (6C), 127.1 (3C), 100.6, 86.7, 86.3 (d, J_{CP} = 21.0 Hz), 76.5 (d, J_{CP} = 171.9 Hz), 75.8 (d, J_{CP} = 11.8 Hz), 66.8, 64.3 (t, J_{CP} = 6.0 Hz), 38.4, 16.5, 16.4; ^{31}P NMR + 19.9. HRFAB calcd for $C_{32}H_{35}N_2O_8P$ 629.2029 $(M+Na)^+$, found 629.2016.

Phosphonate 7.

According to the procedure described for compound **5**, ketone **6**[10b,c] (74 mg, 0.2 mmol in THF 1 mL) was added to a solution of diethyl phosphite (0.4 mmol) in THF (2 mL) at -78 °C and LHMDS (2 equiv,

1.0M) in THF. Standard workup and purification by radial chromatography (39:1, $CHCl_3$:MeOH) gave hydroxy phosphonate **7** (83 mg, 82%). ^{1}H NMR ($CDCl_3$) δ 8.22 (s, 1H), 8.21 (s, 1H), 6.51 (d, 1H, $J_{1',2'}$= 3.4 Hz), 6.41 (br s, 2H), 4.37 - 4.32 (m, 1H), 4.23 - 4.09 (m, 4H), 3.94 (dd, 1H, $J_{5'a,5'b}$ = 10.9 Hz, $J_{5'a,\,4'}$ = 3.3 Hz), 3.77 (dd, 1H, $J_{5'a,5'b}$ = 10.9 Hz, $J_{5'b,\,4'}$ = 3.5 Hz), 2.90 (ddd, 1H, J_{HP}= 14.1, J = 10.6, 8.8 Hz), 2.37 (ddd, 1H, J_{HP} = 14.1, J = 5.9, 5.5 Hz), 1.25 (t, 3H, J = 7.1 Hz), 1.21 (t, 3H, J = 7.1 Hz), 0.95 (s, 9H), 0.15 (2s, 6H); ^{13}C NMR δ 155.2, 152.6, 149.7, 140.7, 118.1, 85.6 (d, J_{CP} = 16.4 Hz), 76.5 (d, J_{CP} = 179.4 Hz), 76.4 (d, J_{CP} = 11.5 Hz), 64.9, 63.7 (d, J_{CP} = 7.2 Hz), 63.4 (d, J_{CP} = 7.2 Hz), 37.8, 25.9 (3C), 18,4, 16.2 (d, J_{CP} = 4.2 Hz), 16.1 (d, J_{CP} = 5.9 Hz), -5.4, -5.5; ^{31}P NMR +22.0. Anal Calcd for $C_{20}H_{36}N_5O_6PSi$: C, 47.88; H, 7.23; N, 13.96. Found: C, 48.13; H, 7.22; N, 14.65.

3'-α-Diethylphosphono-3'-β-hydroxy-2',5'-bis-O-*tert*-butyldimethylsilyluridine (9).

Ketone **8**[10a] (117 mg, 0.25 mmol) was treated with diethyl phosphite as described for the synthesis of compound **5**, to give geminal hydroxy phosphonate **9** (138 mg, 91%) as a single diastereomer after radial chromatography ($CHCl_3$:CH_3OH, 98:2). ^{1}H NMR ($CDCl_3$) δ 9.98 (br s, 1H), 7.99 (d, 1H, $J_{6,5}$ = 8.2 Hz), 5.78 (s, 1H), 5.63 (dd, 1H, $J_{5,6}$ = 8.2 Hz, J = 1.7 Hz), 5.28 (br s, 1H, OH), 4.45 (d, 1H, J_{HP} = 1.8 Hz), 4.36 (br s, 1H), 4.28-4.25 (m, 6H), 1.34 (t, 3H, J = 7.0 Hz), 1.34 (t, 3H, J = 7.0 Hz), 0.93 (s, 18H), 0.23, 0.19, 0.17 and 0.15 (4s, 12H); ^{13}C NMR δ 163.9, 150.5, 141.1, 101.0, 91.5 (d, J_{CP} = 12.3 Hz), 83.3, 82.0 (d, J_{CP} = 163.2 Hz), 80.7, 63.5 (d, J_{CP} = 7.3 Hz), 62.8, 62.3 (d, J_{CP} = 7.4 Hz), 25.7 (3C), 25.6 (3C), 18.0, 17.9, 16.6 (d, J_{CP} = 5.7 Hz), 16.3 (d, J_{CP} = 6.1 Hz), - 4.4, - 5.4, - 5.7, -5.8; ^{31}P NMR + 18.9. Anal. calcd for $C_{25}H_{49}N_2O_9Si_2P$: C, 49.30; H, 8.10; N, 4.60. Found: C, 49.65; H, 8.22; N, 4.27.

3'-Keto-2'-O-*tert*-butyldimethylsilyl-5'-O-trityluridine (10).

2'-O-*tert*-Butyldimethylsilyl-5'-O-trityluridine[21] (4.86 g, 8.1 mmol) was treated with PDC (12.19 g, 32.4 mmol) and 3Å molecular sieve (12.2 g) as described for the synthesis of compound **4** to give the ketone (3.92 g, 81%) as a light yellow foam. ^{1}H NMR ($CDCl_3$) δ 9.21 (br s, 1H), 7.64 (d, 1H, $J_{6,5}$ = 8.5 Hz), 7.31-7.25 (m, 15H), 6.26 (d, 1H, $J_{1',2'}$ = 7.9 Hz), 5.41 (d, 1H, $J_{5,6}$ = 8.1 Hz), 4.55 (d, 1H, $J_{2',1'}$ = 7.9 Hz), 4.25 (br s, 1H), 3.66 (d, 1H, $J_{5'a,5'b}$ = 9.0 Hz), 3.40 (d, 1H, $J_{5'b,5'a}$ = 9.0 Hz), 0.91 (s, 9H), 0.19 (s, 3H), 0.11 (s, 3H). HRFAB calcd for $C_{34}H_{38}N_2O_6Si$ 621.2397 $(M+Na)^+$, found 621.2384.

3'-α-Diethylphosphono-3'-β-hydroxy-2'-O-*tert*-butyldimethylsilyl-5'-O-trityluridine (11).

Ketone **10** (894 mg, 1.5 mmol) was treated with a solution containing LHMDS (3 mL, 1.0M in THF) and diethyl phosphite (0.39 mL, 2 mmol) as described for the synthesis of compound **5** to obtain compound **11** (1.0 g, 91%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 10.17 (br s, 1H), 7.90 (d, 1H, $J_{6,5}$ = 8.2 Hz), 7.47-7.26 (m, 15H), 5.77 (s, 1H), 5.43 (dd, 1H, $J_{5,6}$ = 8.2 Hz, J = 1.7 Hz), 4.90 (br s, 1H), 4.70-4.68 (m, 1H), 4.39 (br s,

1H), 4.14-3.94 (m, 4H), 3.73-3.69 (m, 2H), 1.21 (t, 3H, J = 7.1 Hz), 1.16 (t, 3H, J = 7.1 Hz), 0.92 (s, 9H), 0.24 (s, 3H), 0.18 (s, 3H); ^{13}C NMR δ 164.2, 150.3, 143.0 (3C), 141.3, 128.6 (6C), 127.9 (6C), 127.3 (3C), 100.5, 91.9, (d, J_{CP} = 12.0 Hz), 88.1, 82.8 (d, J_{CP} = 18.0 Hz), 82.6 (d, J_{CP} = 36.1 Hz), 81.0 (d, J_{CP} = 175.9 Hz), 63.5 (d, J_{CP} = 7.4 Hz), 62.6, 62.5 (d, J_{CP} = 7.6 Hz), 25.7 (3C), 17.9, 16.3 (d, J_{CP} = 5.9 Hz), 16.2 (d, J_{CP} = 5.9 Hz), -4.2, -5.6; ^{31}P NMR +19.2. Anal. calcd for $C_{38}H_{49}N_2O_9SiP$: C, 61.96; H, 6.66; N, 3.80. Found: C, 61.97; H, 6.75; N, 3.75.

Phosphonate 13.

In the same manner described above for compound **5**, the 3'-ketone **12**[10d,e] (99 mg, 0.2 mmol) was treated with diethyl phosphite and LHMDS in THF. Standard workup and final purification by radial chromatography (19:1, $CHCl_3$:MeOH) gave the desired hydroxy phosphonate **13** (117 mg, 93%): ^{1}H NMR ($CDCl_3$) δ 8.27 (s, 1H), 8.06 (s, 1H), 7.67 (d, 1H, J_{HP} = 4.2 Hz), 6.77 (br s, 2H), 6.02 (s, 1H), 4.55 (s, 1H), 4.52 (m, 1H), 4.32 - 4.08 (m, 6H), 1.31 (t, 3H, J = 7.1 Hz), 1.31 (t, 3H, J = 7.1 Hz), 0.91 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H), and 0.05 (s, 3H); ^{13}C NMR δ155.4, 152.7, 148.9, 140.7, 118.4, 90.7 (d, J_{CP} = 12.3 Hz), 84.3 (d, J_{CP} = 3.3 Hz), 84.1 (d, J_{CP} = 15.4 Hz), 81.5 (d, J_{CP} = 178.2 Hz), 64.4 (d, J_{CP} = 7.2 Hz), 62.7, 62.1 (d, J_{CP} = 7.5 Hz), 25.9 (3C), 25.7 (3C), 18,4, 17.8, 16.5 (d, J_{CP} = 5.8 Hz), 16.2 (d, J_{CP} = 6.4 Hz), -4.5, -5.0, -5.2, -5.4; ^{31}P NMR +20.0. Anal. calcd for $C_{26}H_{51}N_5O_7PSi_2$: C, 49.35; H, 8.12; N, 11.07. Found: C, 49.29; H, 7.97; N, 11.09.

3'-α-Diethylphosphono-3'-β-hydroxy-5'-O-tritylthymidine (15).

To a solution of diethyl phosphite (0.13 mL, 1 mmol) in THF (1 mL) at -78 °C was added dropwise via syringe LHMDS (1.0 mL, 1.0M in THF) under a nitrogen atmosphere. After 10 to 15 min, a solution of ketone **14**[10b] (241 mg, 0.5 mmol) in 6 mL THF was added, and the reaction mixture was allowed to warm to about 0 °C over 2 h. The reaction was quenched by slow addition of acetic acid in diethyl ether and the resulting mixture was filtered through Celite. After concentration in vacuo, the residue was purified by radial chromatography ($CHCl_3$:MeOH, 95:5) to afford compound **15** (236 mg, 76%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.17 (br s, 1H), 7.72 (s, 1H), 7.49-7.20 (m, 15H), 6.25 (dd, 1H, $J_{1',2'a}$ = 6.2 Hz, $J_{1',2'b}$ = 1.7 Hz), 5.45 (s, 1H, OH), 4.39-4.37 (m, 1H), 4.08-3.85 (m, 4H), 3.69-3.57 (m, 2H), 2.88-2.84 (m, 1H), 2.41-2.36 (m, 1H), 1.74 (s, 3H), 1.23 (t, 3H, J = 7.1 Hz), 1.07 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 164.7, 150.8, 143.4 (3C), 136.9, 128.7 (6C), 127.9 (6C), 127.2 (3C), 109.8, 87.4, 84.5 (d, J_{CP} = 16.2 Hz), 83.8 (d, J_{CP} = 14.2 Hz), 76.9 (d, J_{CP} = 177.9 Hz), 63.9 (d, J_{CP} = 7.2 Hz), 63.1 (d, J_{CP} = 12.8 Hz), 63.1, 43.0 (d, J_{CP} = 7.7 Hz), 16.4 (d, J_{CP} = 5.6 Hz), 16.3 (d, J_{CP} = 5.6 Hz), 12.5; ^{31}P NMR +20.8. Anal. calcd for $C_{33}H_{37}N_2O_8P \cdot H_2O$: C, 62.06; H, 6.15; N, 4.39. Found: C, 62.00; H, 5.86; N, 4.19.

3'β- and 3'α-Diethylphosphono-3'-deoxy-5'-O-tritylthymidine (16 and 17).

A mixture of hydroxyphosphonate **15** (124 mg, 0.2 mmol) and DMAP (122 mg, 1 mmol) was dissolved in anhydrous CH_3CN (1.3 mL), and the solution was cooled to about 6 °C. Methyl oxalyl chloride (92 μL, 1 mmol) was added dropwise. The mixture was stirred at 6-10 °C for 1 h, and poured into water (2 mL). The organic phase was separated, and the water layer was extracted with ethyl acetate (5 mL x 3). The combined organic phase was washed with saturated $NaHCO_3$ (10 mL x 2) and water (10 mL x 2), and then dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure, and the residue was dried under high vacuum. Without further purification, the residue was dissolved in anhydrous toluene (1 mL), and a solution of a mixture of 2,2'-azobisisobutyronitrile (AIBN, 9 mg, 0.05 mmol) and Bu_3SnH (81 μL, 0.3 mmol) in toluene (0.5 mL) was added via a cannula at room temperature. The mixture then was heated at 100 to 105 °C for 2 h under a nitrogen atmosphere. After concentration in vacuo, the residue was purified by radial chromatography (95:5, $CHCl_3$:CH_3OH) to obtain compounds **16** and **17** (98 mg, 81%) as a mixture of diastereomers in a ratio of 2.6:1 as measured by ^{31}P NMR. ^1H NMR ($CDCl_3$) of the major diastereomer δ 7.62 (s, 1H), 6.14 (dd, 1H, $J_{1',2'a}$ = 7.7 Hz, $J_{1',2'b}$ = 5.8 Hz), 4.56-4.47 (m, 1H), 1.73 (s, 3H); ^{31}P NMR +26.6. ^1H NMR ($CDCl_3$) of the minor diastereomer δ 7.67 (s, 1H), 6.20 (dd, $J_{1',2'a}$ = 6.8 Hz, $J_{1',2'b}$ = 4.0 Hz), 4.41-4.34 (m, 1H), 1.37 (s, 1H); ^{31}P NMR + 27.9. ^1H NMR ($CDCl_3$) of the mixture δ 4.10-3.69 (m, 4H), 3.56-3.34 (m, 2H), 2.97-2.61 (m, 2H), 2.44-1.98 (m, 1H), 1.24-1.07 (m, 6H). HRFAB calcd for $C_{33}H_{37}N_2O_7P$ 627.2236 $(M+Na)^+$, found 627.2230.

3'-Deoxy-3'β-diethylphosphono- and 3'-Deoxy-3'α-diethylphosphono-2'-O-*tert*-butyldimethylsilyl-5'-O-trityluridine (18 and 19).

Compound **11** (73 mg, 0.1 mmol) was deoxygenated in the same manner as compound **15** to yield the two diastereomers **18** (14 mg, 19%) and **19** (5 mg, 7%) after separation by radial chromatography.

For compound **18**: ^1H NMR ($CDCl_3$) δ 8.71 (br s, 1H), 7.74 (d, 1H, $J_{6,5}$ = 8.2 Hz), 7.49-7.22 (m, 15H), 5.75 (s, 1H), 5.53 (d, 1H, $J_{5,6}$ = 8.2 Hz), 4.71-4.52 (m, 2H), 4.20-3.67 (m, 5H, -OC$\underline{H}_2$CH$_3$ and one $H_{5'}$), 3.48 (br d, 1H, $J_{5'b,5'a}$ = 8.9 Hz), 2.42 (ddd, 1H, J_{HP} = 19.8 Hz, J = 7.3, 3.0 Hz), 1.24-1.15 (m, 6H), 0.89 (s, 9H), 0.25 (s, 3H), 0.19 (s, 3H); ^{31}P NMR + 24.9. HRFAB calcd for $C_{38}H_{49}N_2O_8PSi$ 743.2894 $(M+Na)^+$, found 743.2886.

For compound **19**: ^1H NMR ($CDCl_3$) δ 8.16 (br s, 1H), 8.12 (d, 1H, $J_{6,5}$ = 8.2 Hz), 7.43-7.26 (m, 15H), 5.77 (s, 1H), 4.94 (dd, 1H, $J_{5,6}$ = 8.1 Hz, J = 1.8 Hz), 4.75-4.69 (m, 1H), 4.62-4.60 (m, 1H), 4.16-4.00 (m, 4H), 3.92-3.80 (m, 1H), 3.58 (dd, 1H, $J_{5'b,5'a}$ = 11.2 Hz, $J_{5'b,4'}$ = 2.6 Hz), 2.73 (ddd, 1H, J_{HP} = 19.0 Hz, J = 10.5, 4.2 Hz), 1.24 (t, 3H, J = 7.0 Hz), 1.20 (t, 3H, J = 7.0 Hz), 0.92 (s, 9H), 0.25 (s, 3H), 0.22 (s, 3H); ^{31}P NMR + 22.6. HRFAB calcd for $C_{38}H_{49}N_2O_8PSi$ 743.2894 $(M+Na)^+$, found 743.2876.

3'-α-Diethylphosphono-3'-β-hydroxy-2'-O-*tert*-butyldimethylsilyluridine (22).

Compound **9** (1.93 g, 3.17 mmol) was added in one portion to an ice-cold mixture of trifluoroacetic acid and water (30 mL, 9:1). The mixture was stirred at 0 °C for 40 min, and the solvent was evaporated under reduced pressure. The residue was purified by radial chromatography (90:10, $CHCl_3$:CH_3OH) to afford compound **22** (1.50 g, 96%) as a colorless solid. ^{1}H NMR (DMSO-d_6) δ 11.29 (br s, 1H), 7.72 (d, 1H, $J_{6,5}$ = 8.2 Hz), 5.97 (br s, 1H), 5.58 (d, 1H, $J_{5,6}$ = 8.3 Hz), 5.55 (s, 1H), 5.05 (br s, 1H, OH), 4.38-4.35 (m, 2H), 4.10-4.00 (m, 4H), 3.79-3.75 (m, 2H), 1.23 (t, 6H, J = 7.0 Hz), 0.88 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H); ^{13}C NMR δ 163.3, 150.6, 140.7, 100.3, 90.7 (d, J_{CP} = 11.1 Hz), 84.4 (d, J_{CP} = 16.9 Hz), 82.4, 79.8 (d, J_{CP} = 175.1 Hz), 62.7 (d, J_{CP} = 7.2 Hz), 61.7 (d, J_{CP} = 7.6 Hz), 59.7, 25.7 (3C), 17.7, 16.3 (d, J_{CP} = 5.5 Hz), 16.2 (d, J_{CP} = 6.0 Hz), - 4.4, - 5.3; ^{31}P NMR +21.7. HRFAB calcd for $C_{19}H_{35}N_2O_9PSi$ 495.1928 $(M+H)^+$, found 495.1937.

5'-O-Benzoyl-3'-α-diethylphosphono-3'-β-hydroxy-2'-O-*tert*-butyldimethylsilyluridine (23).

A mixture of compound **22** (493 mg, 1 mmol) and DMAP (24 mg, 0.2 mmol) was dissolved in 5 mL anhydrous pyridine. After the solution was cooled to about 0 °C, benzoyl chloride (139 μL, 1.2 mmol) was added dropwise via syringe. The ice bath was then removed, and the reaction mixture was stirred at room temperature overnight. The resulting mixture was partitioned between water (10 mL) and $CHCl_3$ (10 mL). The organic phase was separated and the water phase was extracted with $CHCl_3$ (15 mL x 2). The combined organic phase was washed with saturated $NaHCO_3$ (15 mL x 2), water (15 mL x 2) and dried over Na_2SO_4. After concentration under reduced pressure, purification by radial chromatography ($CHCl_3$:MeOH, 95:5) gave compound **23** (593 mg, 99%) as a white foam. ^{1}H NMR ($CDCl_3$) δ 10.35 (br s, 1H), 8.08 (d, 2H, J = 7.3 Hz), 7.87 (d, 1H, $J_{6,5}$ = 8.2 Hz), 7.57 (t, 1H, J = 7.4 Hz), 7.44 (t, 2H, J = 7.6 Hz), 5.47 (s, 1H), 5.65 (dd, 1H, $J_{5,6}$ = 8.2 Hz, J = 1.9 Hz), 5.61 (br s, 1H, OH), 4.88-4.76 (m, 3H), 4.44 (s, 1H), 4.27-4.14 (m, 4H), 1.32 (t, 3H, J = 6.9 Hz), 1.32 (t, 3H, J = 6.9 Hz), 0.93 (s, 9H), 0.24 (s, 3H), 0.17 (s, 3H); ^{13}C NMR δ 166.2, 164.3, 150.6, 141.5, 133.2, 129.7 (2C), 129.6 (2C), 128.3, 100.8, 92.3 (d, J_{CP} = 12.2 Hz), 83.1, 82.1 (d, J_{CP} = 18.3 Hz), 80.1 (d, J_{CP} = 175.4 Hz), 64.1 (d, J_{CP} = 7.5 Hz), 63.2 (d, J_{CP} = 7.5 Hz), 62.5, 25.7 (3C), 17.9, 16.3 (d, 2C, J_{CP} = 6.0 Hz), -4.3. -5.4; ^{31}P NMR +19.5. Anal. calcd for $C_{26}H_{39}N_2O_{10}PSi$: C, 52.17; H, 6.57; N, 4.68. Found: C, 51.93; H, 6.48; N, 4.78.DFW

5'-O-Benzoyl-3'β- and 5'-O-Benzoyl-3'α-diethylphosphono-2'-O-*tert*-butyldimethylsilyluridine (24 and 25).

To a solution of compound **23** (454 mg, 0.76 mmol) and DMAP (463 mg, 3.8 mmol) in anhydrous CH_3CN (7 mL) was added dropwise methyl oxalyl chloride (0.35 mL, 3.8 mmol) at room temperature. The mixture was stirred at room temperature for 1 h under N_2, and then another 5 equivalents of DMAP and methyl oxalyl chloride were added and the reaction mixture was stirred for one more hour. The resulting mixture was diluted with EtOAc (30 mL) and washed successively with a saturated aqueous $NaHCO_3$ solution and H_2O

several times. The organic phase was dried over Na_2SO_4, the solvent was removed under reduced pressure (aspirator), and the resulting residue was dried under high vacuum. Without further purification, the residue was dissolved in anhydrous toluene (5 mL), and a solution containing AIBN (60 mg, 0.36 mmol) and Bu_3SnH (0.51 mL, 1.90 mmol) in toluene (7 mL) was added via a cannula at room temperature. The mixture then was heated at 100 to 105 °C for 2 h under N_2, allowed to cool to room temperature, and the solvent was evaporated in vacuo. The residue was purified by radial chromatography ($CHCl_3$:CH_3OH, 97.5:2.5) to obtain the two diastereomers **24** (209 mg, 59%) and **25** (117 mg, 33%) in a ratio of 1.8:1. Both compounds were obtained as white solids.

For compound **24**: ^{1}H NMR ($CDCl_3$) δ 9.50 (br s, 1H), 8.08 (dd, 2H, J = 7.8, 1.4 Hz), 7.88 (d, 1H, $J_{6,5}$ = 8.2 Hz), 7.58 (tt, 1H, J = 7.4, 1.4 Hz), 7.45 (t, 2H, J = 7.4 Hz), 5.91 (d, 1H, $J_{1',2'}$ = 3.4 Hz), 5.73 (d, 1H, $J_{5,6}$ = 8.1 Hz), 4.86-4.60 (m, 4H), 4.26-4.12 (m, 4H), 2.64 (ddd, 1H, J_{HP} = 19.6 Hz, $J_{3',2'}$ = 6.8 Hz, $J_{3',4'}$ = 3.1 Hz), 1.39 (t, 3H, J = 7.1 Hz), 1.33 (t, 3H, J = 7.1 Hz), 0.89 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR δ 166.2, 163.3, 150.4, 140.9, 133.2, 129.7 (2C), 129.7, 128.4 (2C), 102.5, 91.5 (d, J_{CP} = 6.7 Hz), 77.7, 64.2 (d, J_{CP} = 4.8 Hz), 62.6 (d, J_{CP} = 6.4 Hz), 62.5, 62.5 (d, J_{CP} = 6.3 Hz), 47.0 (d, J_{CP} = 144.8 Hz), 25.5 (3C), 17.7, 16.3 (d, J_{CP} = 4.8 Hz), 16.2 (d, J_{CP} = 4.8 Hz), -5.0, -5.1; ^{31}P NMR + 24.9. Anal. calcd for $C_{26}H_{39}N_2O_9PSi \cdot 0.5H_2O$: C, 52.79; H, 6.77; N, 4.74. Found: C, 52.41; H, 6.83; N, 4.73.

For compound **25**: ^{1}H NMR ($CDCl_3$) δ 9.49 (br s, 1H), 7.99 (dd, 2H, J = 7.8, 1.4 Hz), 7.75 (d, 1H, $J_{6,5}$ = 8.2 Hz), 7.63 (tt, 1H, J = 7.4, 1.3 Hz), 7.48 (t, 2H, J = 7.4 Hz), 5.67 (s, 1H), 5.47 (d, 1H, $J_{5,6}$ = 8.2 Hz), 4.99-4.93 (m, 1H), 4.86 (d, 1H, $J_{5'a,5'b}$ = 13.1 Hz), 4.76 (m, 1H), 4.61 (dd, 1H, $J_{5'b,5'a}$ = 13.0 Hz, $J_{5'a,4'}$ = 3.3 Hz), 4.20-4.01 (m, 4H), 2.60 (ddd, 1H, J_{HP} = 19.4 Hz, $J_{3',4'}$ = 10.8 Hz, $J_{3',2'}$ = 4.1 Hz), 1.31 (t, 3H, J = 7.1 Hz), 1.23 (t, 3H, J = 7.1 Hz), 0.96 (s, 9H), 0.27 (s, 3H), 0.23 (s, 3H); ^{13}C NMR δ 165.9, 163.5, 150.1, 139.2, 133.7, 129.4 (2C), 129.3, 128.7 (2C), 101.7, 92.3 (d, J_{CP} = 12.5 Hz), 79.7 (d, J_{CP} = 6.0 Hz), 78.0 (d, J_{CP} = 5.1 Hz), 63.2, 62.2 (d, J_{CP} = 6.8 Hz), 61.9 (d, J_{CP} = 7.1 Hz), 41.3 (d, J_{CP} = 155.4 Hz), 25.7 (3C), 18.0, 16.4 (d, J_{CP} = 5.4 Hz), 16.3 (d, J_{CP} = 5.4 Hz), -4.3, -5.4; ^{31}P NMR + 21.5. Anal. calcd for $C_{26}H_{39}N_2O_9PSi \cdot 0.5H_2O$: C, 52.79; H, 6.81; N, 4.74. Found: C, 52.74; H, 7.05; N, 4.59.

5'-O-Acetyl-3'-α-diethylphosphono-3'-β-hydroxy-2'-O-*tert*-butyldimethylsilyluridine (26).

To a suspension of compound **22** (314 mg, 0.63 mmol), Et_3N (106 mL, 0.76 mmol) and DMAP (16 mg, 0.13 mmol) in anhydrous CH_3CN (7 mL) was added dropwise Ac_2O (72 μL, 0.76 mmol) at room temperature. The suspension became a clear solution after stirring for 2 min, but stirring was continued for 30 min. Ethanol (0.7 mL) was then added, and the reaction mixture was concentrated under reduced pressure. The residue was purified by radial chromatography ($CHCl_3$:CH_3OH, 95:5) to yield compound **26** (330 mg, 98%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 10.62 (br s, 1H), 7.81 (d, 1H, $J_{6,5}$ = 8.2 Hz), 5.74 (s ,1H), 5.66 (d, 1H, $J_{5,6}$ = 8.2 Hz), 4.71-4.45 (m, 3H), 4.39 (s, 1H), 4.28-4.14 (m, 4H), 2.21 (s, 3H), 1.37-1.28 (m, 6H), 0.92 (s, 9H), 0.22

(s, 3H), 0.15 (s, 3H); ^{13}C NMR δ 170.4, 164.2, 150.6, 141.2, 100.8, 92.1 (d, J_{CP} = 12.2 Hz), 83.1, 81.8 (d, J_{CP} = 18.5 Hz), 81.1, 77.7 (d, J_{CP} = 164.2 Hz), 63.9 (d, J_{CP} = 7.4 Hz), 63.0 (d, J_{CP} = 7.6 Hz), 62.1, 25.6 (3C), 20.6, 17.8, 16.2 (d, 2C, J_{CP} = 5.1 Hz), 4.5, -5.5; ^{31}P NMR + 19.6. HRFAB calcd for $C_{21}H_{37}N_2O_{10}PSi$ 537.2033 $(M+H)^+$, found 537.2022.

5'-O-Acetyl-3'β- and 5'-O-Acetyl-3'α-diethylphosphono-3'-deoxy-2'-O-*tert*-butyldimethylsilyluridine (27 and 28).

Compound **26** (107 mg, 0.2 mmol) was treated with DMAP (244 mg, 2 mmol) and methyl oxalyl chloride (184 μL, 2 mmol), followed by reaction with Bu_3SnH (82 μL, 3 mmol) and a catalytic amount of AIBN (7 mg) as described for the synthesis of compounds **24** and **25** to give the two diastereomers **27** (59 mg, 57%) and **28** (33 mg, 32%).

For compound **27**: ^{1}H NMR ($CDCl_3$) δ 9.37 (br s, 1H), 7.87 (d, 1H, $J_{6,5}$ = 8.2 Hz), 5.88 (d, 1H, $J_{1',2'}$ = 3.3 Hz), 5.79 (d, 1H, $J_{5,6}$ = 8.2 Hz), 4.68-4.43 (m, 4H), 4.24-4.10 (m, 4H), 2.54 (ddd, 1H, J_{HP} = 19.5 Hz, $J_{3',2'}$ = 7.0 Hz, $J_{3',4'}$ = 2.7 Hz), 2.12 (s, 3H), 1.38 (t, 3H, J = 7.2 Hz), 1.38 (t, 3H, J = 7.2 Hz), 0.92 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR δ 170.5, 163.2, 150.4, 140.9, 102.5, 91.6 (d, J_{CP} = 6.0 Hz), 77.7, 63.7 (d, J_{CP} = 5.0 Hz), 62.6 (d, J_{CP} = 3.6 Hz), 62.5 (d, J_{CP} = 3.3 Hz), 47.0 (d, J_{CP} = 144.7 Hz), 25.5 (3C), 20.8, 17.7, 16.4 (d, J_{CP} = 5.9 Hz), 16.3 (d, J_{CP} = 5.9 Hz), -5.0, -5.1; ^{31}P NMR + 24.9. HRFAB calcd for $C_{21}H_{37}N_2O_9PSi$ 521.2084 $(M+H)^+$, found 521.2072.

For compound **28**: ^{1}H NMR ($CDCl_3$) δ 10.10 (br s, 1H), 7.77 (d, 1H, $J_{6,5}$ = 8.2 Hz), 5.70 (d, 1H, $J_{5,6}$ = 8.2 Hz), 5.63 (br s, 1H), 4.86-4.82 (m, 1H), 4.73-4.72 (m, 1H), 4.51 (br d, 1H, $J_{5'a,5'b}$ = 12.9 Hz), 4.43 (dd, 1H, $J_{5'b,5'a}$ = 12.9 Hz, $J_{5'b,4'}$ = 3.8 Hz), 4.20-4.08 (m, 4H), 2.43 (ddd, 1H, J_{HP} = 19.4 Hz, $J_{3',4'}$ = 10.9 Hz, $J_{3',2'}$ = 4.0 Hz), 2.13 (s, 3H), 1.32 (t, 3H, J = 7.1 Hz), 1.32 (t, 3H, J = 7.1 Hz), 0.95 (s, 9H), 0.26 (s, 3H), 0.21 (s, 3H); ^{13}C NMR δ 169.8, 163.8, 150.2, 139.3, 101.3, 92.4 (d, J_{CP} = 12.6 Hz), 79.4 (d, J_{CP} = 6.2 Hz), 77.8 (d, J_{CP} = 5.6 Hz), 63.0, 62.1 (d, J_{CP} = 6.3 Hz), 61.9 (d, J_{CP} = 7.0 Hz), 41.3 (d, J_{CP} = 155.2 Hz), 25.6 (3C), 20.6, 17.9, 16.3 (d, J_{CP} = 6.9 Hz), 16.2 (d, J_{CP} = 6.9 Hz), -4.4, -5.5; ^{31}P NMR + 21.8. HRFAB calcd for $C_{21}H_{37}N_2O_9PSi$ 521.2084, found 521.2070.

5'-O-Benzoyl-3'-α-diethylphosphono-3'-deoxyuridine (29).

To a solution of compound **25** (111 mg, 0.22 mmol) in THF (4 mL) was added dropwise a solution of tetrabutylammonium fluoride (TBAF, 0.25 mL, 1.0M in THF) at room temperature. The resulting solution was stirred at room temperature for 3 h, and then the solvent was removed under reduced pressure. The residue was partitioned between $CHCl_3$ (15 mL) and water (15 mL), the organic phase was separated, and the water phase was extracted with $CHCl_3$ (15 mL x 2). The combined organic phase was washed with saturated $NaHCO_3$ (25 mL) and water (20 mL) and then dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by radial chromatography ($CHCl_3$:CH_3OH, 95:5) to give phosphonate **29** (82 mg, 92%) as

a white solid. ^{1}H NMR ($CDCl_3$) δ 8.79 (dd, 2H, J = 7.8, 1.4 Hz), 7.73 (d, 1H, $J_{6,5}$ = 8.1 Hz), 7.63-7.58 (m, 1H), 7.46 (t, 2H, J = 7.6 Hz), 5.77 (s, 1H), 5.50 (d, 1H, $J_{5,6}$ = 8.1 Hz), 4.96-4.91 (m, 1H), 4.82 (br d, 1H, $J_{5'a,5'b}$ = 12.8 Hz), 4.71 (d, 1H, $J_{2',3'}$ = 4.6 Hz), 4.64 (dd, 1H, $J_{5'b,5'a}$ = 12.9 Hz, $J_{5'b,4'}$ = 3.2 Hz), 4.31-4.06 (m, 4H), 2.71 (ddd, 1H, J_{HP} = 18.4 Hz, $J_{3',4'}$ = 11.3 Hz, $J_{3',2'}$ = 4.7 Hz), 1.34 (t, 3H, J = 7.1 Hz), 1.22 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 165.9, 163.2, 151.3, 138.2, 129.4 (4C), 128.7, 102.2, 93.6 (d, J_{CP} = 13.1 Hz), 80.4 (d, J_{CP} = 5.9 Hz), 77.5, 63.4 (d, J_{CP} = 6.2 Hz), 63.0, 61.9 (d, J_{CP} = 6.3 Hz), 41.4 (d, J_{CP} = 153.8 Hz), 16.3 (d, J_{CP} = 6.1 Hz), 16.1 (d, J_{CP} = 6.3 Hz); 16.2 (d, J_{CP} = 6.3 Hz); ^{31}P NMR + 21.9. HRFAB calcd for $C_{20}H_{25}N_2O_9P$ 469.1376 $(M+H)^+$, found 469.1355.

3'-Deoxy-3'-α -diethylphosphonouridine (30).

Compound **29** (20 mg, 0.044 mmol) was treated with MeOH:H_2O (1:1, 1 mL) and Et_3N (44 μL), and the mixture was stirred at room temperature for 24 h. After concentration in vacuo, the residue was purified by radial chromatography ($CHCl_3$:MeOH, 90:10) to give phosphonate **30** (15 mg, 93%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 10.69 (br s, 1H), 8.05 (d, 1H, $J_{6,5}$ = 8.0 Hz), 5.72 (s, 1H), 5.67 (d, 1H, $J_{5,6}$ = 8.0 Hz), 5.48 (br s, 1H, OH), 4.70 (br s, 1H), 4.61 (t, 1H, J = 9.3 Hz), 4.24-4.10 (m, 5H, $OC\underline{H}_2CH_3$ and $H_{5'a}$), 3.82 (d, 1H, $J_{5'b,5'a}$ = 11.2 Hz), 2.88-2.78 (m, 1H), 1.32 (t, 6H, J = 7.0 Hz); ^{13}C NMR δ 164.3, 150.9, 140.7, 101.5, 93.1 (d, J_{CP} = 12.3 Hz), 82.6, 62.8 (d, J_{CP} = 6.1 Hz), 62.1 (d, J_{CP} = 6.3 Hz), 60.9, 39.8 (d, J_{CP} = 151.5 Hz), 16.3 (d, 2C, J_{CP} = 6.9Hz); ^{31}P NMR + 24.7. HRFAB calcd for $C_{13}H_{21}N_2O_8P$ 365.1114 $(M+H)^+$, found 365.1122.

3'-Deoxy-3'-α-ethylphosphonouridine (31).

To a suspension of compound **30** (8 mg, 0.02 mmol) in anhydrous CH_3CN (0.5 mL) was added a catalytic amount of anhydrous pyridine (6 μL). After stirring at room temperature for 10 min, bromotrimethylsilane (28 μL, 0.2 mmol) was added dropwise at room temperature under N_2. The suspension was stirred at room temperature overnight, and then pyridine (0.1 mL) and water (0.2 mL) were added. The resulting mixture was allowed to stir for two more hours, and then poured into water (1 mL). After washing with Et_2O (5 mL x 2) and concentration in vacuo, the residue was purified by preparative TLC (isopropyl alcohol:NH_4OH:H_2O, 8:1:1) to yield compound **31** (3 mg, 47%) as a colorless solid. ^{1}H NMR (D_2O) δ 7.89 (d, 1H, $J_{6,5}$ = 8.0 Hz), 5.70 (d, 1H, $J_{5,6}$ = 8.0 Hz), 5.64 (s, 1H), 4.45 (br s, 2H), 3.96 (d, 1H, $J_{5'a,5'b}$ = 13.2 Hz), 3.87-3.79 (m, 2H), 3.72 (dd, 1H, $J_{5'b,5'a}$ = 13.2 Hz, $J_{5'b,4'}$ = 3.9 Hz), 2.32-2.21 (m, 1H), 1.11 (t, 3H, J = 6.8 Hz); ^{31}P NMR + 17.4. HRFAB calcd for $C_{11}H_{17}N_2O_8P$ 359.0620 $(M+Na)^+$, found 359.0617.

Phosphonic Acid 32.

Compound **29** (9 mg, 0.02 mmol) was treated with 1N NaOH in EtOH (1 mL) as described for the synthesis of compound **36,** to afford a mixture of compound **30** (1 mg, 17%), compound **31** (2 mg, 23%), and the desired product **32** (3 mg, 55%): ^{1}H NMR (D_2O) δ 7.92 (d, 1H, $J_{6,5}$ = 8.0 Hz), 5.72 (d, 1H, $J_{5,6}$ = 8.1Hz), 5.66 (s, 1H), 4.49-4.47 (m, 2H), 3.99 (d, 1H, $J_{5'a,5'b}$ = 13.1 Hz), 3.79-3.72 (m, 1H), 2.32-2.21 (m, 1H); ^{31}P

NMR + 15.3. Negative ion FAB *m/z* (relative intensity) 307 $(M-H)^-$ (100), 295 (10), 251 (23), 237 (97), 223 (73).

5'-O-Benzoyl-3'-β-diethylphosphono-3'-deoxyuridine (33).

To a solution of compound **24** (136 mg, 0.23 mmol) in THF (4 mL) was added dropwise a solution of TBAF (0.25 mL, 1.0 M in THF) at room temperature. The solution was stirred at room temperature for 3 h, and the solvent was removed under reduced pressure. The residue was partitioned between $CHCl_3$ (15 mL) and water (15 mL), the organic phase was separated, and the water phase was extracted with $CHCl_3$ (15 mL x 2). The combined organic phase was washed with saturated $NaHCO_3$ (25 mL) and water (20 mL) and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by radial chromatography ($CHCl_3$:CH_3OH, 95:5) to obtain phosphonate **33** (101 mg, 93%) as a white solid. ^1H NMR ($CDCl_3$) δ 8.03 (dd, 2H, J = 7.8, 1.4 Hz), 7.73 (d, 1H, $J_{6,5}$ = 8.2 Hz), 7.58-7.53 (m, 1H), 7.43 (t, 2H, J = 7.6 Hz), 5.82 (d, 1H, $J_{1',2'}$ = 4.3 Hz), 5.66 (d, 1H, $J_{5,6}$ = 8.1 Hz), 4.92-4.63 (m, 4H), 4.25-4.13 (m, 4H), 2.94 (ddd, 1H, J_{HP} = 19.0 Hz, $J_{3',2'}$ = 7.9 Hz, $J_{3',4'}$ = 6.3 Hz), 1.35 (t, 3H, J = 7.1 Hz), 1.31 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 166.1, 163.7, 151.5, 140.1, 133.3, 129.6 (4C), 128.4, 102.2, 92.3 (d, J_{CP} = 11.7 Hz), 77.4, 76.9, 64.5, 63.0 (d, J_{CP} = 6.5 Hz), 62.5 (d, J_{CP} = 7.0 Hz), 44.9 (d, J_{CP} = 147.0 Hz), 16.4 (d, J_{CP} = 4.0 Hz), 16.3 (d, J_{CP} = 4.0 Hz); ^{31}P NMR + 24.6. HRFAB calcd for $C_{20}H_{25}N_2O_9P$ 469.1376 $(M+H)^+$, found 469.1360.

3'-Deoxy-3'-β-ethylphosphonouridine (35).

To a solution of compound **33** (11 mg, 0.23 mmol) in MeOH:H_2O (1:1, 0.5 mL) was added dropwise Et_3N (22 μL) at room temperature. The reaction mixture was stirred at room temperature for 24 h, and then the solvent was removed under reduced pressure. The resulting residue was purified by preparative TLC (isopropyl alcohol:NH_4OH:H_2O, 8:1:1) to afford compound **35** (7 mg, 89%) as a colorless solid. ^1H NMR (D_2O) δ 7.91 (d, 1H, $J_{6,5}$ = 7.9 Hz), 5.79 (d, 1H, $J_{5,6}$ = 7.8 Hz), 5.77 (d, 1H, $J_{1',2'}$ = 5.2 Hz), 4.45-4.35 (m, 2H), 3.87-3.78 (m, 3H, $OC\underline{H}_2CH_3$ and $H_{5'a}$), 3.72 (dd, 1H, $J_{5'b,5'a}$ = 10.2 Hz, $J_{5'b,4'}$ = 2.6 Hz), 2.73-2.62 (m, 1H), 1.12 (t, 3H, J = 7.0 Hz); ^{31}P NMR + 19.5. HRFAB calcd for $C_{11}H_{17}N_2O_8P$ 381.0440 $(M+2Na-H)^+$, found 381.0450.

Phosphonic Acid 36.

Compound **33** (12 mg, 0.026 mmol) was dissolved in 1N NaOH in EtOH (1 mL), and the mixture was stirred at room temperature for 3 days. The resulting suspension was diluted with water (0.5 mL) and neutralized by addition of 1N HCl in EtOH. After concentration in vacuo, the residue was purified by HPLC (H_2O, 100%) to give compound **36** (18 mg, 98%). ^1H NMR (D_2O) δ 7.93 (d, 1H, $J_{6,5}$ = 7.8 Hz), 5.82 (d, 1H, $J_{1',2'}$ = 7.0 Hz), 5.75 (d, 1H, $J_{5,6}$ = 7.9 Hz), 4.39-4.33 (m, 2H), 3.87 (d, 1H, $J_{5'a,5'b}$ = 13.0 Hz), 3.62-3.53 (m,

1H), 2.55-2.42 (m, 1H); ^{31}P NMR + 15.9. Negative ion FAB *m/z* (relative intensity) 329 $(M-2H+Na)^-$ (0.93), 307 $(M-H)^-$ (1), 249 (1), 237 (2), 215 (4), 165 (8), 143 (9), 139 (5), 107 (100).

Cyclic phosphonate 37.

To a solution of compound **24** (25 mg, 0.043 mmol) in MeOH (1.5 mL) was added a solution of 1N NaOH in MeOH until the pH of the solution was about 9. The mixture was heated at reflux for 5 h, neutralized with 1N HCl in MeOH, and then concentrated in vacuo. Without further purification, the residue was suspended in THF (1.5 mL), and a solution of TBAF (52 μL, 0.052 mmol, 1.0M in THF) was added dropwise at room temperature. After stirring for 3 h, the solvent was removed under reduced pressure. The residue was purified by preparative TLC (isopropyl alcohol:NH_4OH:H_2O, 8:1:1) to obtain phosphonate **35** (7 mg, 56%) as a white solid. ^{1}H NMR (D_2O) δ 7.69 (d, 1H, $J_{6,5}$ = 8.1 Hz), 5.75 (d, 1H, J = 4.3 Hz), 5.74 (d, 1H, $J_{5,6}$ = 8.0 Hz), 5.04 (ddd, 1H, J_{HP} = 20.7 Hz, $J_{4',3'}$ = 7.0 Hz, $J_{4',5'a}$ = 2.9 Hz), 4.51 (dt, 1H, J_{HP} = 13.9 Hz, J = 3.3 Hz), 4.12 (dd, 1H, J_{HP} = 25.8 Hz, $J_{5'a,5'b}$ = 11.9 Hz), 3.9 (dd, 1H, $J_{5'b,5'a}$ = 11.8 Hz, $J_{5'b,4'}$ = 3.0 Hz), 2.36 (ddd, 1H, J_{HP} = 13.4 Hz, $J_{3',2'}$ = 7.1 Hz, $J_{3',4'}$ = 2.8 Hz); ^{31}P NMR + 38.0. HRFAB calcd for $C_9H_{11}N_2O_7P$ 313.0202 $(M+Na)^+$, found 313.0221.

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