Pergamon

Tetrahedron, Vol. 52, No. 36, pp. 11695-11704, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00684-9

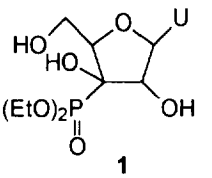
Synthesis of Nucleoside Epoxyphosphonates

Wenkui Lan McEldoon and David F. Wiemer*†

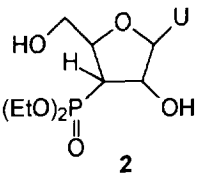
Department of Chemistry
University of Iowa
Iowa City, Iowa 52245

Abstract: Reaction of two regioisomeric uridine derivatives, 1-[3-(diethoxyphosphinyl)-5-O-trityl-β-D-xylofuranosyl]uracil (**4**) and 1-[2-(diethoxyphosphinyl)-5-O-trityl-β-D-arabinofuranosyl]uracil (**13**), with triflyl chloride and 4-pyrrolidinopyridine (4-PDP) results in formation of the corresponding nucleoside epoxyphosphonates. This transformation is immediately useful for confirming the trans relationship of the 2'- and 3'-hydroxyl groups in the *geminal* hydroxyphosphonates **3** and **12**, and provides access to two new families of nucleoside derivatives that may be of interest for their synthetic utility and biological properties. Copyright © 1996 Elsevier Science Ltd

The quest for new and effective anti-viral agents has spurred preparation of many new families of nucleoside and nucleotide analogues.[1] Widespread interest in carbohydrate modifications of intact nucleosides,[2] together with our own interests in studies of C-P bond formation,[3] have led to procedures for preparation of *geminal*-hydroxyphosphonates (e.g. **1**)[4,5] and for their deoxygenation to the parent phosphonic acids (e.g. **2**).[5] The many functional groups present within these compounds should allow their elaboration into a variety of related nucleoside derivatives. However, while phosphonates such as compound **1** now are readily accessible via phosphite addition to a 3' ketone, it is still problematic to identify the resulting stereoisomer unless the product is amenable to diffraction analysis.[6] In this report we present a procedure for preparation of nucleoside epoxyphosphonates, an array of functionality apparently new to nucleoside systems[7] despite its strong similarity to well-known nucleoside phosphates. In addition to potential interest in epoxyphosphonates themselves, this methodology can be used to establish the stereochemistry of ribose-derived *geminal* hydroxyphosphonates.



1

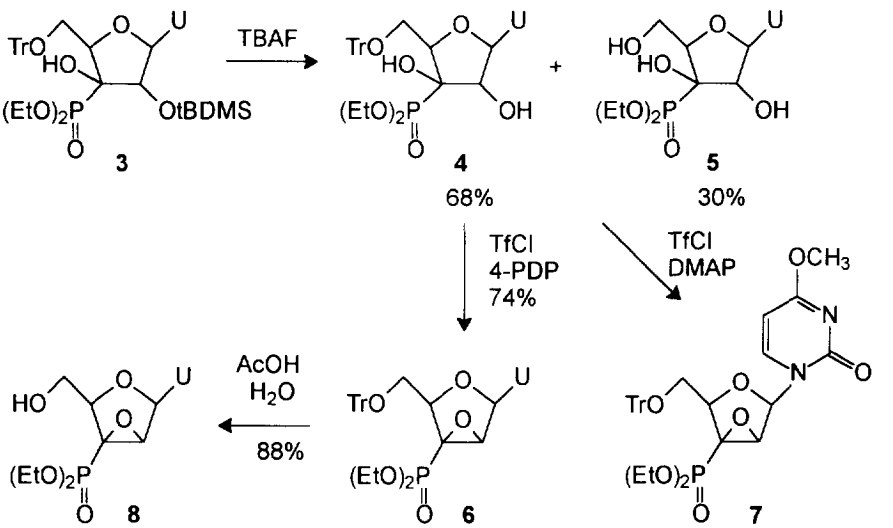


2

† Dedicated to Prof. Nelson J. Leonard on the occasion of his 80th birthday.

Several procedures are available for preparation of nucleoside epoxides, including displacement of 2,2'-anhydro derivatives of uridine,[8] cyclization of arabinosides by treatment with triphenylphosphine/diethyl azodicarboxylate,[9] and displacements of mesylates.[10] Preparations of epoxyphosphonates may be more numerous,[11] but often involve Darzens-like condensations of ketones with α-haloalkylphosphonates,[11] or epoxidation of vinyl phosphonates.[12,7] Direct conversion of α-halo[13] or α-tosyloxy[7,11] ketones to epoxyphosphonates through reaction with phosphite anions also has been reported, but sometimes, especially with cyclic ketones,[14] these conditions afford vinyl phosphates instead.

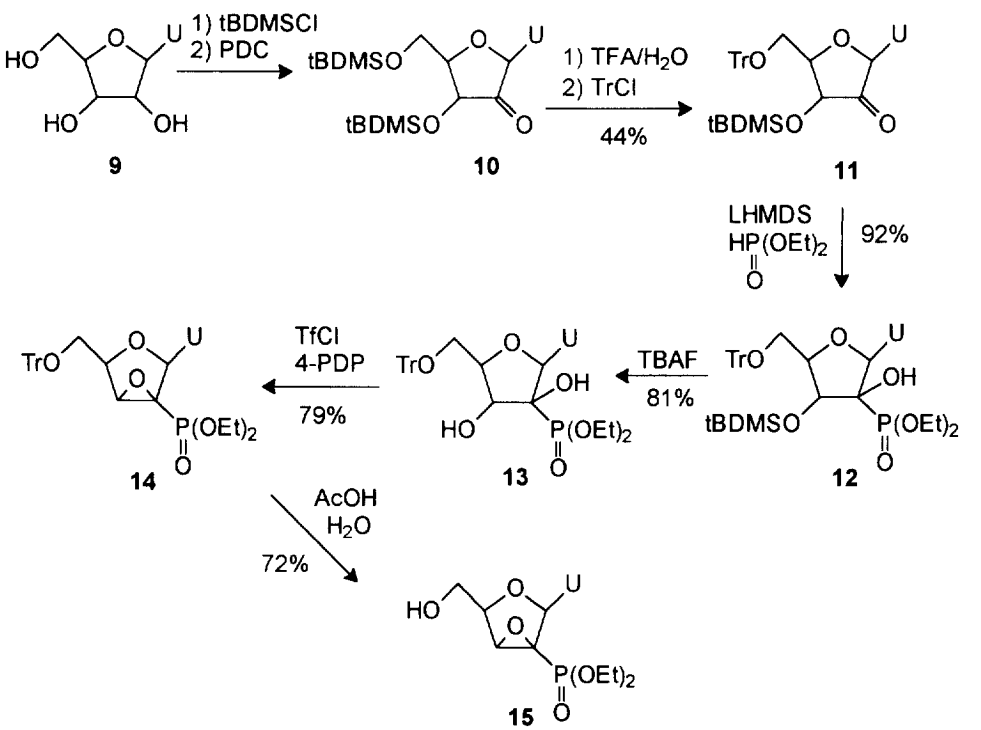
The first attempt at preparation of a nucleoside epoxyphosphonate began with the protected uracil derivative **3**.[5] To obtain the desired *lyxo* epoxide, it was necessary to replace the 2' protecting group with a suitable leaving group at this position. Removal of the 2'-silyl group by treatment with tetrabutylammonium fluoride (TBAF) gave the expected diol **4** in 68% yield, accompanied by a significant amount (30%) of the detritylated product **5**. While a 5'-trityl group is normally stable to these conditions, this hydrolysis was not problematic because the by-product was easily separated and could be readily recycled to compound **4** by reaction with trityl chloride.



To convert the 2' hydroxyl group of compound **4** into a suitable leaving group, preparation of the corresponding triflate was attempted.[15] In fact, treatment of diol **4** with triflyl chloride (TfCl) and 4-dimethylaminopyridine (DMAP) directly affords the desired epoxide **6** in modest yield (31%), presumably via displacement of an intermediate 2'-triflate. Use of a larger excess of DMAP gave little improvement in the yield (35%), but instead resulted in formation of a significant by-product. This by-product ultimately was identified as a methylated uracil derivative and assigned structure **7**.[16] Based on the premise that methylation

followed activation of the DMAP by formation of an N-triflyl intermediate, we turned to use of a DMAP analogue less able to serve as an alkylating agent. When the hydroxyphosphonate **4** was treated with triflyl chloride and 4-pyrrolidinopyridine (4-PDP) in methylene chloride at 0° C, the desired product **6** was obtained in 74% yield, and no alkylated by-products were detected. Methylation also could be suppressed through use of DMAP and triflic anhydride rather than triflyl chloride, but these reagents also gave a lower yield of the desired epoxide. Once the epoxide was formed, removal of the 5'-trityl group from phosphonate **6** was straightforward, affording 1-[2,3-anhydro-3-(diethoxyphosphinyl)-β-D-lyxofuranosyl]uracil (**8**) in 88% yield.

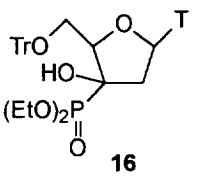
To establish if this strategy also could be used to prepare the isomeric 2',3'-epoxy-2'-phosphono compounds, a second uracil derivative was examined. Selective protection of the 5'- and 3'-hydroxy groups of uridine (**9**),[17] and subsequent oxidation of the 2' hydroxyl group with PDC, gave the 2'-keto uridine derivative **10**. After selectively removing the *tert*-butyldimethylsilyl group at the 5'-position by treatment of compound **10** with trifluoroacetic acid in water, the 5'-hydroxy group was protected with trityl chloride to give the 2'-ketone **11** in 44% overall yield from uridine. The *geminal* hydroxyphosphonate **12** was prepared from the 2'-ketone **11** in good yield by reaction with diethyl phosphite under standard conditions.[4,5]



Treatment of compound **12** with TBAF to remove the *tert*-butyldimethylsilyl group at the 3'-position, gave diol **13** in 81% yield. In this case, the trityl group of compound **12** was more stable under the reaction conditions relative to its regioisomer **3**, and the 5' deprotected product was not observed. This difference in reactivity may originate in strain derived from interaction between the sterically demanding trityl and diethyl-phosphono groups in compound **3**, making it more sensitive to hydrolysis than the isomeric compound **12**.

The epoxide ring was formed by treatment of compound **13** with triflyl chloride and 4-PDP in a manner similar to that described for synthesis of epoxyphosphonate **6**, to give compound **14** in 79% yield. The trityl group was removed by treatment of compound **14** with acetic acid in water, providing the final target, 1-[2,3-anhydro-2-(diethoxyphosphinyl)-β-D-lyxofuranosyl]uracil (**15**), in good yield.

In our previous reports,[4,5] the stereochemistry of a series of *geminal* hydroxyphosphonates was assigned based on a diffraction analysis of one, compound **16**,[6] and the assumption that the phosphorus anion adds from the less hindered α face in all cases to provide β-hydroxy-α-phosphono nucleosides. While this was a reasonable assumption, the stereochemistry of phosphite addition to ketones derived from ribosides could differ from that found in the 2'-deoxy nucleoside **16**. However, the stereochemistry assigned to the *geminal* hydroxyphosphonates **3** and **12** is confirmed by formation of the epoxyphosphonates **6** and **14**. In these series, the α stereochemistry of the original 2' and 3' hydroxyl groups was determined by choice of uridine as the starting material. Because a trans relationship of the 2' and 3' hydroxyl groups in the phosphonates **4** and **13** is required for facile epoxide formation, it is reasonable to conclude that the phosphite additions leading to compounds **3** and **12** occur from the less hindered α face of the ribose and generate trans diols.



16

Both compounds **8** and **15** have been submitted to the National Cancer Institute and evaluated for *in vitro* anti-HIV and anti-cancer activity, but both compounds were judged inactive in these assays. Even though these particular bioassays showed little activity, the new epoxyphosphonates may still be useful as synthons for preparation of a variety of other modified nucleosides, and may express activity in other types of bioassays.

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled from sodium/benzophenone, while pyridine 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 62 silica

gel (230-400 mesh), while radial chromatography was performed on Merck PF254 silica gel with $CaSO_4 \cdot 0.5$ H_2O. NMR spectra (^1H at 300 MHz and ^{13}C at 75 MHz) were recorded with $CDCl_3$ as solvent and $(CH_3)_4Si$ (^1H) or $CDCl_3$ (^{13}C, 77.0 ppm) as internal standards. ^{31}P NMR shifts are reported in ppm relative to 85% H_3PO_4 (external standard). High-resolution and FAB mass spectra were obtained on a ZAB-HF reversed geometry mass spectrometer at the University of Iowa Mass Spectrometry facility. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA) or in the University of Iowa Chemistry Department.

1-[3-(Diethoxyphosphinyl)-5-O-trityl-β-D-xylofuranosyl]uracil (4).

To an ice-cold solution of compound **3**[5] (1.3 g, 1.75 mmol) in THF (35 mL) was added dropwise a solution of TBAF (1.75 mL, 1.0 M in THF). The reaction mixture was stirred at 0 °C for 2 h, then the ice bath was removed and the reaction was allowed to stir at rt for another hour. The solvent was removed in vacuo and the residue was partitioned between $CHCl_3$ (50 mL) and water (30 mL). After separation of the layers, the organic phase was washed with saturated $NaHCO_3$ (65 mL) and water (50 mL), and then dried over Na_2SO_4. The solvent was removed in vacuo and the residue was purified by radial chromatography ($CHCl_3$:MeOH, 90:10) to afford compound **4** (745 mg, 68%) as a white solid. ^1H NMR ($CDCl_3$) δ 10.86 (br s, 1H), 7.68 (d, 1H, $J_{6,5}$ = 8.2 Hz), 7.50-7.23 (m, 15H), 5.85 (s, 1H), 5.54 (br s, 1H, OH), 5.43 (br s, 1H, OH), 5.42 (d, 1H, $J_{5,6}$ = 8.2 Hz), 4.80 (br d, 1H, J_{HP} = 6.4 Hz), 4.61 (br d, 1H, J = 4.7 Hz), 4.08-3.90 (m, 4H), 3.70-3.57 (m, 2H), 1.19 (t, 3H, J = 7.1 Hz), 1.04 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 164.3, 151.5, 143.4 (3C), 140.7, 128.8 (6C), 127.9 (6C), 127.1 (3C), 100.9, 93.0 (d, J_{CP} = 12.8 Hz), 87.4, 84.0 (d, J_{CP} = 17.2 Hz), 81.9, 80.6 (d, J_{CP} = 175.1 Hz), 63.4 (t, J_{CP} = 6.3 Hz), 62.6, 16.3 (d, J_{CP} = 5.5 Hz), 16.2 (d, J_{CP} = 5.5 Hz); ^{31}P NMR + 19.1. Anal. calcd for $C_{32}H_{35}O_9N_2P \cdot 1.5\ H_2O$: C, 59.16; H, 5.90; N, 4.31. Found: C, 59.18; H, 5.58; N, 4.22.

1-[2,3-Anhydro-3-(diethoxyphosphinyl)-5-O-trityl-β-D-lyxofuranosyl]uracil (6).

Method A: A mixture of diol **4** (213 mg, 0.34 mmol) and DMAP (250 mg, 2.05 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL), and the solution was cooled to 0 °C under N_2. To the ice-cold solution triflyl chloride (43.6 μL, 0.41 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min, the ice bath was removed and the reaction was allowed to stir at rt for another hour, and the resulting mixture was poured into water (30 mL). After separation of the layers, the aqueous phase was extracted with CH_2Cl_2 (20 mL x 2). The combined organic extracts were washed with brine (35 mL x 2) and water (30 mL x 2), and then dried over Na_2SO_4. Removal of the solvent in vacuo and purification of the residue by

radial chromatography ($CHCl_3$:MeOH, 95:5) gave phosphonate **6** (72 mg, 35%) and byproduct **7** (41 mg, 20%). Both compounds were obtained as white foams.

For compound **6**: ^{1}H NMR ($CDCl_3$) δ 9.24 (br s, 1H), 7.66 (d, 1H, $J_{6,5}$ = 8.2 Hz), 7.48-7.22 (m, 15H), 6.31 (s, 1H), 5.60 (d, 1H, $J_{5,6}$ = 8.2 Hz), 4.52-4.49 (m, 1H), 4.14 (d, 1H, J_{HP} = 3.1 Hz), 4.11-4.01 (m, 4H), 3.54-3.50 (m, 2H), 1.22 (t, 3H, J = 6.9 Hz), 1.22 (t, 3H, J = 6.9 Hz); ^{13}C NMR δ 163.0, 150.3, 143.3 (3C), 141.1, 128.7 (6C), 127.9 (6C), 127.2 (3C), 102.6, 87.2, 80.9, 76.9 (d, J_{CP} = 20.3 Hz), 63.9 (d, J_{CP} = 6.3 Hz), 63.6 (d, J_{CP} = 7.1 Hz), 62.4, 61.0, 59.8 (d, J_{CP} = 212.4 Hz), 16.3 (d, 2C, J_{CP} = 5.7 Hz); ^{31}P NMR +11.8. Anal. calcd for $C_{32}H_{33}O_8N_2P{\cdot}0.5\ H_2O$: C, 62.64; H, 5.58; N, 4.57. Found: C, 62.86; H, 5.51; N, 4.41.

For compound **7**: ^{1}H NMR ($CDCl_3$) δ 7.80 (d, 1H, $J_{6,5}$ = 7.5 Hz), 7.49-7.22 (m, 15H), 6.38 (s, 1H), 5.77 (d, 1H, $J_{5,6}$ = 7.5 Hz), 4.54 (t, 1H, $J_{4',5'}$ = 4.5 Hz), 4.24 (d, 1H, J_{HP} = 3.2 Hz), 4.09-4.00 (m, 4H), 3.97 (s, 3H), 3.54 (d, 2H, $J_{5',4'}$ = 4.7 Hz), 1.23 (t, 3H, J = 7.1 Hz), 1.22 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 172.0, 155.8, 143.7, 143.4 (3C), 128.7 (6C), 127.8 (6C), 127.1 (3C), 95.7, 87.1, 82.5, 77.2 (d, J_{CP} = 21.2 Hz), 63.7 (d, J_{CP} = 6.4 Hz), 63.6 (d, J_{CP} = 9.5 Hz), 62.5, 61.0, 60.1 (d, J_{CP} = 213.3 Hz), 54.5, 16.3 (d, 2C, J_{CP} = 5.7 Hz); ^{31}P NMR + 11.9; HRFAB calcd for $C_{33}H_{36}O_8N_2P$ 619.2209 $(M+H)^+$, found 619.2194.

Method B: To an ice cold solution of compound **4** (146 mg, 0.23 mmol) and 4-pyrrolidinopyridine (4-PDP, 210 mg, 1.42 mmol) in CH_2Cl_2 (4 mL) was added dropwise triflyl chloride (30 μL, 0.28 mmol) under N_2. The reaction mixture was allowed to warm to rt over 1 h with stirring, and then poured into water (20 mL). After separation of the layers, the water phase was extracted with CH_2Cl_2 (15 mL x 3), and the combined organic phase was washed with brine (20 mL x 2), and water (20 mL x 2) and then dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by radial chromatography ($CHCl_3$:MeOH, 95:5) to give phosphonate **6** (105 mg, 74%).

1-[2,3-Anhydro-3-(diethoxyphosphinyl)-β-D-lyxofuranosyl]uracil (8).

Compound **6** (77 mg, 0.13 mmol) was dissolved in aqueous acetic acid (3 mL, 80% acetic acid in water), and the solution was stirred at rt overnight. After concentration in vacuo, the residue was purified by radial chromatography ($CHCl_3$:MeOH, 95:5) to give epoxyphosphonate **8** (41 mg, 88%). ^{1}H NMR ($CDCl_3$) δ 7.59 (d, 1H, $J_{6,5}$ = 8.2 Hz), 6.24 (s, 1H), 5.77 (d, 1H, $J_{5,6}$ = 8.2 Hz), 4.36 (t, 1H, J = 5.5 Hz), 4.30-4.19 (m, 4H), 4.16 (d, 1H, J_{HP} = 3.2 Hz), 3.98 (dd, 1H, $J_{5'a,5'b}$ = 12.0 Hz, $J_{5'a,4'}$ = 6.0 Hz), 3.87 (dd, 1H, $J_{5'b,5'a}$ = 12.0 Hz, $J_{5'b,4'}$ = 5.1 Hz), 1.39 (t, 3H, J = 7.1 Hz), 1.36 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 163.5, 150.5, 140.5, 102.9, 80.5, 77.7, 64.7 (d, J_{CP} = 6.8 Hz), 64.1 (d, J_{CP} = 6.8 Hz), 61.4, 60.3, 59.7 (d, J_{CP} =

214.0 Hz), 16.4, 16.3; ^{31}P NMR + 13.2; HRFAB calcd for $C_{13}H_{19}O_8N_2P$ 363.0957 $(M+H)^+$, found 363.0957.

3'-O-(*tert*-Butyldimethylsilyl)-2'-keto-5'-O-trityluridine (11).

Commercial uridine **9** was converted to the 3',5'-bis-TBDMS derivative,[17] oxidized to the 2'-keto compound **10**, and then selectively deprotected at the 5' position, by minor variations of literature procedures.[5] To a solution of the 5' alcohol (1.65 g, 4.63 mmol) in THF (110 mL) was added anhydrous pyridine (1.87 mL, 23.15 mmol) and $AgNO_3$ at rt. After stirring at rt for 20 min, trityl chloride was added, and the reaction mixture was stirred at rt overnight. The resulting mixture was filtered, the filtrate was concentrated in vacuo, and the residue was partitioned between water (100 mL) and CH_2Cl_2 (100 mL). After separation of the layers, the aqueous phase was extracted with CH_2Cl_2 (100 mL x 2), the combined organic phase was washed with saturated $NaHCO_3$ (100 mL x 2) and water (100 mL), and the solvent was removed under reduced pressure. The residue was purified by radial chromatography (EtOAc:hexanes, 1:3) to give the ketone **11** (2.46 g, 89%) as a white foam. ^{1}H NMR ($CDCl_3$) δ 8.97 (br s, 1H), 7.64 (d, 1H, $J_{6,5}$ = 8.2 Hz), 7.31-7.25 (m, 15H), 6.25 (d, 1H, J = 8.0 Hz), 5.40 (dd, 1H, $J_{5,6}$ = 8.2 Hz, J = 1.9 Hz), 4.55 (d, 1H, J = 8.0 Hz), 4.24 (br s, 1H), 3.65 (dd, 1H, $J_{5'a,5'b}$ = 10.6 Hz, $J_{5'b,5'a}$ = 2.3 Hz), 3.40 (dd, 1H, $J_{5'b,5'a}$ = 10.5 Hz, $J_{5'b,4'}$ = 2.3 Hz), 0.91 (s, 9H), 0.18 (s, 3H), 0.10 (s, 3H); HRFAB calcd for $C_{34}H_{38}O_6N_2Si$ 621.2397 $(M+Na)^+$, found 621.2402.

1-[3-O-(*tert*-Butyldimethylsilyl)-2-(diethoxyphosphinyl)-5-O-trityl-β-D-arabinofuranosyl]uracil (12).

To a solution of diethyl phosphite (0.13 mL, 1.0 mmol) in THF (1 mL) at -78 °C was added dropwise via syringe LHMDS (1.0 mL, 1.0 M in THF) under an N_2 atmosphere. After 10 to 15 min, a solution of ketone **11** (299 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 then 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 the desired product **12** as a single diastereomer (337 mg, 92%). ^{1}H NMR ($CDCl_3$) δ 11.81 (br s, 1H), 7.49-7.20 (m, 16H, arom and H6), 6.55 (d, 1H, J_{HP} = 1.7 Hz), 5.62 (d, 1H, J_{HP} = 4.6 Hz, OH), 5.44 (dd, 1H, $J_{5,6}$ = 8.1 Hz, J = 2.0 Hz), 4.42-4.12 (m, 6H), 3.52-3.40 (m, 2H), 1.36 (t, 3H, J = 7.1 Hz), 1.32 (t, 3H, J = 7.1 Hz), 0.91(s, 9H), 0.10 (s, 3H), 0.04 (s, 3H); ^{13}C NMR δ 165.2, 149.3, 143.6 (3C), 143.2, 128.6 (6C), 127.7 (6C), 127.0 (3C), 100.7, 86.8, 86.6 (d, J_{CP} = 21.9 Hz), 86.1 (d, J_{CP} = 9.8 Hz), 81.0, 80.5 (d, J_{CP} = 173.5 Hz), 64.2 (d, J_{CP} = 8.1 Hz), 64.0, 63.5 (d, J_{CP} = 6.5 Hz), 25.6 (3C), 17.7, 16.5 (d, J_{CP} = 5.6 Hz), 16.3 (d, J_{CP} = 6.2 Hz), -4.4, -5.1; ^{31}P NMR + 19.7. Anal. calcd for $C_{38}H_{49}O_9N_2PSi{\cdot}H_2O$: C, 60.46; H, 6.81; N, 3.71. Found: C, 60.50; H, 6.71; N, 3.77.

1-[2-(Diethoxyphosphinyl)-5-O-trityl-β-D-arabinofuranosyl]uracil (13).

Compound **12** (104 mg, 0.14 mmol) was desilylated in the same manner as described for compound **4**, to give diol **13** (71 mg, 81%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 10.38 (br s, 1H), 7.85 (d, 1H, $J_{6,5}$ = 8.2 Hz), 7.44-7.23 (m, 15H), 6.58 (d, 1H, J_{HP} = 9.8 Hz), 6.05 (s, 1H, OH), 5.37 (d, 1H, $J_{5,6}$ = 8.1 Hz), 4.77 (br s, 1H, OH), 4.71-4.61 (m, 1H), 4.32-4.19 (m, 4H), 4.14-4.11 (m, 1H), 3.50 (br d, 2H, J = 2.1 Hz), 1.34 (t, 3H, J = 7.1 Hz), 1.33 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 164.1, 150.6, 143.3 (3C), 142.2, 128.7 (6C), 127.9 (6C), 127.3 (3C), 101.4, 87.3, 84.8 (d, J_{CP} = 12.1 Hz), 81.1 (d, J_{CP} = 168.6 Hz), 80.5, 77.9, 65.4 (d, J_{CP} = 7.1 Hz), 65.7 (d, J_{CP} = 7.8 Hz), 61.6, 16.3,16.2; ^{31}P NMR + 20.2. Anal. calcd for $C_{32}H_{35}O_9N_2P{\cdot}H_2O$: C, 60.00; H, 5.82; N, 4.38. Found: C, 60.25; H, 5.70; N, 4.38.

1-[2,3-Anhydro-2-(diethoxyphosphinyl)-5-O-trityl-β-D-lyxofuranosyl]uracil (14).

According to the procedure described for synthesis of compound **6** (Method B), the diol **13** (378 mg, 0.61 mmol) was treated with 4-PDP (543 mg, 3.66 mmol) and trifloromethanesulfonyl chloride (77.7 μL, 0.73 mmol) to afford compound **14** (290 mg, 79%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.61 (d, 1H, $J_{6,5}$ = 8.2 Hz), 7.45-7.23 (m, 15H), 6.43 (s, 1H), 5.68 (d, 1H, $J_{5,6}$ = 8.2 Hz), 4.27-4.11 (m, 6H), 3.46 (dd, 1H, $J_{5'a,5'b}$ = 9.8 Hz, $J_{5'b,5'a}$ = 5.5 Hz), 3.35 (dd, 1H, $J_{5'b,5'a}$ = 9.6 Hz, $J_{5'b,4'}$ = 6.2 Hz), 1.37 (t, 3H, J = 7.1 Hz) , 1.29 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 162.7, 149.9, 143.3 (3C), 141.2, 128.6 (6C), 128.0 (6C), 127.3 (3C), 102.7, 87.3, 80.3 (d, J_{CP} = 20.3 Hz), 75.6, 64.2 (d, J_{CP} = 6.1 Hz), 63.9 (d, J_{CP} = 6.9 Hz), 61.7, 61.2, 59.4 (d, J_{CP} = 217.3 Hz), 16.5, 16.3; ^{31}P NMR + 11.4. Anal. calcd for $C_{32}H_{33}O_8N_2P{\cdot}0.5\ H_2O$: C, 62.64; H, 5.58; N, 4.57. Found: C, 62.66; H, 5.47; N, 4.56.

1-[2,3-Anhydro-2-(diethoxyphosphinyl)-β-D-lyxofuranosyl]uracil (15).

Compound **14** (367 mg, 0.06 mmol) was treated with aqueous acetic acid (2 mL, 80% acetic acid in water), and the reaction was stirred at rt overnight. After removal of the solvent in vacuo and purification of the residue by radial chromatography ($CHCl_3$:MeOH, 90:10), the epoxide **15** (16 mg, 72%) was obtained. ^{1}H NMR ($CDCl_3$) δ 7.66 (d, 1H, $J_{6,5}$ = 8.2 Hz), 6.45 (s, 1H), 5.76 (d, 1H, $J_{5,6}$ = 8.2 Hz), 4.27-4.13 (m, 6H, OCH_2CH_3, H3' and H4'), 3.88 (d, 2H, $J_{5',4'}$ = 5.8 Hz), 1.35 (t, 3H, J = 7.1 Hz), 1.30 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 163.1, 150.1, 141.0, 103.0, 80.2 (d, J_{CP} = 20.5 Hz), 76.8 (d, J_{CP} = 1.5 Hz), 64.4 (d, J_{CP} = 6.4 Hz), 64.5 (d, J_{CP} = 6.4 Hz), 60.8, 60.7, 59.1 (d, J_{CP} = 217.3 Hz), 16.4 (d, J_{CP} = 4.6 Hz), 16.3 (d, J_{CP} = 4.6 Hz); ^{31}P NMR + 11.2; HRFAB calcd for $C_{13}H_{19}O_8N_2P$ 363.0957 $(M+H)^+$, found 363.0959.

ACKNOWLEDGMENTS

We thank Ms. Tracy J. Roper for conducting the epoxidation of compound **4** with triflic anhydride. Financial support from the National Institutes of Health (GM-44986) is gratefully acknowledged.

REFERENCES AND NOTES

1. De Clercq, E. *AIDS Res. Human Retroviruses*, **1992**, *8*, 119-137.
2. Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745-1768.
3. a) An, J.; Wilson, J. M.; An, Y. Z.; Wiemer, D. F. *J. Org. Chem.* **1996**, *61*, 4040-4045. b) An, Y. Z.; An, J.; Wiemer, D. F. *J. Org. Chem.* **1994**, *59*, 8197-8202, and references cited therein; c) Lee, K.; Wiemer, D. F. *J. Org. Chem.*, **1991** *56*, 5556-5560.
4. McEldoon, W. L.; Lee, K.; Wiemer, D. F. *Tetrahedron Lett.*, **1993**, *34*, 5843-5846.
5. McEldoon, W. L.; Wiemer, D. F. *Tetrahedron*, **1995**, *51*, 7131-7148.
6. Capron, M. A.; McEldoon, W.. L.; Baenziger, N. C.; Wiemer, D. F. *Acta Crys. Ser. C*, **1994**, *C50*, 291-294.
7. Following completion of this research, an example of an acyclic carbohydrate epoxyphosphonate was discovered: Glebova, Z. I.; Eryuzheva, O. V.; Zhdanov, Y. A. *Zh. Obshch. Khim.* **1993**, *63*, 1677-1678.
8. a) Codington, J. F.; Fecher, R.; Fox, J. J. *J. Org. Chem.* **1962**, *27*, 163-167. b) Brokes, J., Beranek, J. *Coll. Czech. Chem. Commun.* **1975**, *40*, 3061-3067. c) Horwitz, J. P.; Chua, J.; Darooge, M. A; Noel, M.; Klundt, I. L. *J. Org. Chem.* **1966**, *31*, 205-211. d) Sasaki, T.; Minamoto, K.; Suzuki, H. *J. Org. Chem.* **1973**, *38*, 598-607.
9. a) Mengel, R.; Bartke, M. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 679-680; b) Chen, Y-C, J.; Hansske, F.; Janda, K. D.; Robins, M. J. *J. Org. Chem.* **1991**, *56*, 3410-3413.
10. Maruyama, T.; Utzumi, K.; Sato, Y.; Richman, D. D. *Nucleosides & Nucleotides* **1994**, *13*, 527-537.
11. Redmore, D. *Chem. Rev.* **1971**, *71*, 315-337.
12. Ohler, E.; Zbiral., E. *Synthesis* **1991**, 357-361.
13. a) Springs, B.; Haake, P. *Org. Chem.* **1976**, *41*, 1165-1168; b) Kossev, K.; Troev, K.; Roundhill, D. M. *Phosphorus, Sulfur, and Silicon* **1993**, *83*, 1-7.
14. Arbuzov, B. A.; Vinogradova, V. S.; Zvereva, M. A. *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1960**, 1772-1778; *Chem. Abstr.* **1961**, *55*, 16398.

15. a) Krawczyk, S. H.; Bernier-Rodriguez, M.; Nassiri, M. R.; Kern, E. R.; Wotring, L. L.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **1990**, *33*, 3160-3169. b) Robins, M. J.; Hawrelak, S. D.; Hernandez, A. E.; Wnuk, S. F. *Nucleosides & Nucleotides* **1992**, *11*, 821-834.

16. This assignment was based on comparison with published NMR data for O^2-, N^3-, and O^4-methyluridines. Both the ^1H and ^{13}C shifts observed for the methyl resonance indicate an O-methyl rather than an N-methyl substituent. Comparison of the observed carbon resonance for C-5 (δ 95.7) with those reported for O^4-methyluridine (δ 98.5) and O^2-methyluridine (δ 108.3) strongly supports assignment of compound 7 as the 4-methyl isomer, cf: Hruska, F. E.; Blonski, W. J. P. *Can. J. Chem.*, **1982**, *60*, 3026-3032.

17. a) Hakimelahi, G. H.; Proba, Z. A.; Ogilvie, K. K. *Can. J. Chem.* **1982**, *60*, 1106-1113. b) Ogilvie, K. K.; Beaucage, S. L.; Schifman, A. L.; Theriault, N. Y. *Can. J. Chem.* **1978**, *56*, 2768-2780.

(*Received in USA* 18 *April* 1996; *accepted* 15 *July* 1996)