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ATTEMPTED SYNTHESIS OF 5′ – DEOXY – 5′ – PHOSPHONO – ISOCYTIDINE. SYNTHESIS OF PHOSPHONIC ACID DERIVATIVES OF ACYCLO – NUCLEOSIDES. PREPARATION OF 1– ß– D- ARABINOFURANOSYL PYRIMIDINES.

G. H. Hakimelahi* and A. Khalafi - Nezhad

Department of Chemistry, Faculty of Science University of Shiraz, Shiraz, Islamic Republic of Iran

Abstract

The synthesis of 5′ - deoxynucleoside 5′ - phosphonates which contains a 5′ - CP bond in place of the 5′ - COP bond of the naturally occuring nucleotides is described. The preparation of phosphonate derivatives of acyclo - nucleosides and a simple method for the conversion of 1-ß -D-ribofuranosyl pyrimidines to the corresponding 1-ß -D-arabinofuranosyl pyrimidines are also explained.

Introduction

Certain viruses produce an enzyme called thymidine/ deoxycytidine kinase, which is responsible for adding a phosphate group to nucleosides. This is the first step in the conversion of nucleosides into a building block unit of the genes. In the next step enzymes native to the infected cell add two more phosphate groups to make nucleside triphosphoates (dGTP, dATP, dTTP, and dCTP), the direct precursors of the four nucleotide building blocks that are linked together in precise sequences to make DNA [1]. Nucleoside analogues [2] similarly form triphosphates to bind to the enzyme, called DNA polymerase, that links the nucleotides together during the replication of viral DNA. This somehow inhibits copies of viral DNA from being made, and is the basis of antiviral activiy of certain nucleoside analogues [3]. However, viruses are not able to produce thymidine / deoxycytidine kinase after long term stimulation by the antiviral agents of the acyclo - nucleoside or cyclo - nucleoside analogues. This makes them become resistant to the drugs. Therefore, the preparation of 5′ - deoxynucleoside 5′ - phosphonates which contains 5′ - CP bound in place of the 5′ - COP bond of the naturally occuring nucleotides might be of some biochemical interest because of their structural resemblance to nucleotides on the one hand and their possible resistance to the action of the nucleolytic enzymes on the other [4]. Furthermore, this type of compound might be active against thymidine / deoxycytidine kinase deficient viruses. The above might well have some value in the case of antitumor drugs [5]. Since isocytidine exhibits excellent antitumor activity *in vitro,* it was decided to prepare the 5′ - deoxynucleoside 5′ - phosphonate analogue of isocytidine which might have interesting anticancer activity.

Key words: Arabinonucleosides, Acyclonucleosides

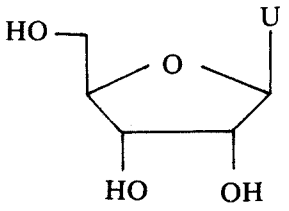
Results and Discussion

The general scheme for the synthesis of 5′ - deoxy - 5′ - phosphono - isocytidine (9) consists in the transformation of 1 → 2 → 3 → 7. Uridine (1) was converted to 2′, 3′ - O- isopropylideneuridine (2) in acetone in the presence of $CuSO_4$ / H_2SO_4 [6]. Reaction of **2** with methyltriphenoxyphosphonium iodide in DMF gave the corresponding 5′ - deoxy - 5′ - iodonucleoside **3** [6]. Compound **3** was treated with trimethyl phosphite at 140° to afford a mixture of 5′ - dimethyl (5′ - deoxy - 2′, 3′ - O - isopropylideneuridine) phosphonate (4) and 5′ - methyl (5′ - deoxy - 2′, 3′ - O - isopropylidene - 2 -

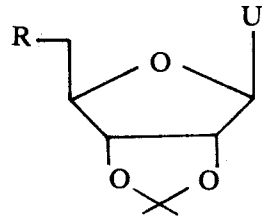
methoxy - uridine) phosphonate (6) in 1:1 ratio (85%). It should be noted that compound **3** at 25° was spontaneously transformed to 2,5′ - anhydro - 2′,3′ - O - isopropylideneuridine (5) after 68 h. However, **3** is stable for months at - 5°. Heating the mixture of **4** and **6** at 200- 210° afforded exlusively **6** after 20 h. Reaction of **3** with trimethyl phosphite at the same temperature also afforded **6** (90%) after 20 h. All attempts to remove the methyl groups from **6** (NaI / THF / reflux [7], CF_3COOH / $CHCl_3$ [8], t - $BuNH_2$ / THF [9], t - $Bu(Me)_2$ SiI / CH_3CN [10], Et_3NSH / CH_2Cl_2, KOH / MeOH) failed and resulted in the destruction or recovery of the starting material. Next, it was decided to remove the isopropyledene protecting group. Treatment of **6** with 80% aq. CH_3COOH at 25° gave 5′ methyl (5′ - deoxy - 2- methoxyuridine) phosphonate (7) after 2 h in excellent yield. But, deprotection of the isopropyledene function, in the same manner, did not work in the case of compound **4**, even after 10 h. Therefore, the ease of deprotection of the isopropyledene group in **6** must be due to an internal acid catalyzed reaction by the OH function of the monomethoxy phosphonate group.

In an attempt to prepare 5′ - deoxy - 5′ - phosphono - isocytidine **9**, compound **7** was treated with NH_3 / MeOH in a pressure bottle at 100° for 24 h. 5′ - Deoxy - 5′ - phosphono - 2 - methoxyuridine (8) was the only formed product (60%).

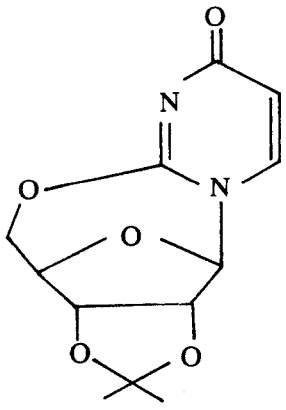
At this point it was decide to carry out the above methodology on acyclonucleoside **10**. Reaction of 1-(2- bromoethoxymethyl) uracil (10) [11] with trimethyl phosphite at 200- 210° gave a mixture of compounds **11** and **12** (1:1) in high yield. Separate treatment of **11** and **12** with NH_3 / MeOH, as described above, afforded the respective products **13** and **14** in good yield. The exclusive replacement of the methoxy group by the NH_2 function from C - (4) clearly indicates the significant differences in the chemical reactivity of the 2- and 4- positions of pyrimidines. It should be noted that the reaction of **10** with trimethyl phosphite at 140° afforded **15** (88%) after 15 h. When compound **15** was heated at 200- 210°, **16** was the exclusively formed product. Therefore, the alkylation of the carbonyl function in **11** and **12** was occured by means of the resulting CH_3Br, from the respective Arbuzov reac-



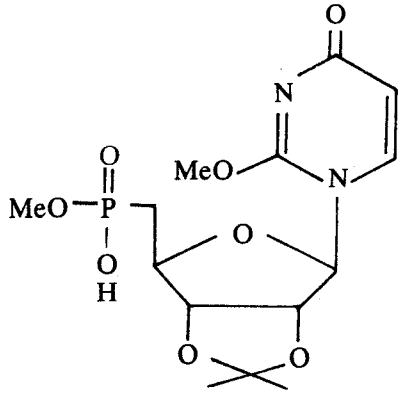
1 U = uracil



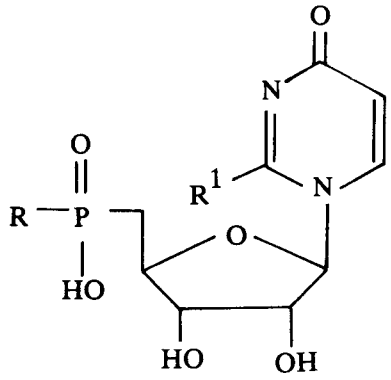
2 R = OH, U = uracil
3 R = I, U = uracil
4 R = $PO(OMe)_2$, U = uracil



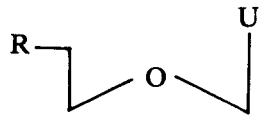
5



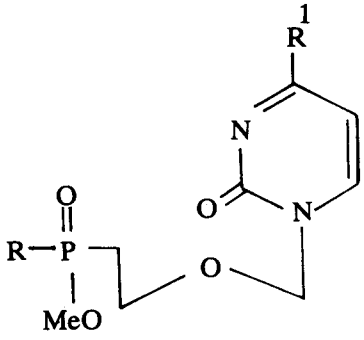
6



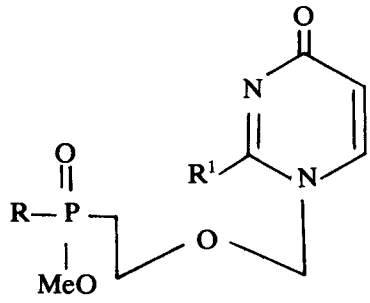
7 R = OMe, R^1 = OMe
8 R = $O^-NH_4^+$, R^1 = OMe
9 R = $O^-NH_4^+$, R^1 = NH_2



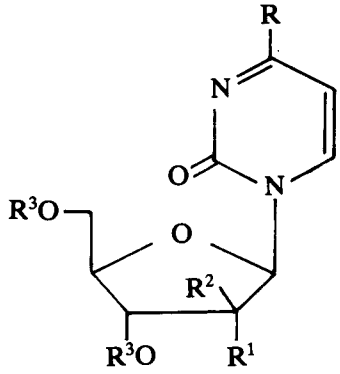
10 R = Br, U = uracil
15 R = $PO(OMe)_2$, U = uracil



11 R^1 = OMe, R = OMe
13 R^1 = NH_2, R = $O^-NH_4^+$



12 R^1 = OMe, R = OMe
14 R^1 = OMe, R = $O^-NH_4^+$
16 R^1 = OMe, R = OH



17a R = OH, R^1 = OH, R^2 = H, R^3 = H
17b R = NH_2, R^1 = OH, R^2 = H, R^3 = H

18a R = OH, R^1 = OH, R^2 = H, R^3 = $[(CH_3)_2CH]_3Si$
18b R = NH_2, R^1 = OH, R^2 = H, R^3 = $[(CH_3)_2CH]_3Si$

19a R = OH, R^1 = H, R^2 = OH, R^3 = $[(CH_3)_2CH]_3Si$
19b R = NH_2, R^1 = H, R^2 = OH, R^3 = $[(CH_3)_2CH]_3Si$

20a R = OH, R^1 = H, R^2 = OH, R^3 = H
20b R = NH_2, R^1 = H, R^2 = OH, R^3 = H

tions [12]. However, the preparation of **6** and **16** was achieved by an internal methyl migration from the phosphonate function.

With respect to the ease of the preparation of **5**, it was decided to take advantage of it for the one pot conversion of ribonucleosides to the corresponding arabinonucleosides. Thus, the 3', 5' - OH funtions in **17a-b** were silylated with tri-(isopropyl) silyl chloride in the presence of 1,4- diazabicyclo [2, 2, 2] octane (DABCO) and Ag No_3 to afford **18a-b** ($\sim$ 90%) [15]. Separate reactions of **18a-b** with methyltriphenoxyphosphonium iodide and subsequent hydrolysis of the resulting anhydronucleosides with KOH / EtOH gave the corresponding compounds **19a-b**. Treatments with Bu_4NF in THF [16] afforded the respective 1-ß -D-arabinofuranosyl pyrimidine nucleosides **20a-b**, in 60 and 40% yields, which were found to be identical with the authentic samples.

Experimental Section

General Remarks. See [13].

2', 3'-O-Isopropylideneuridine (2). Dry, finely powdered uridine (1) (5 g, 0.02 mol) is suspended in acetone (200 ml), and then 10 g of anhydrous $CuSO_4$ and 0.1 ml of conc. H_2SO_4 are added. The bottle is tightly corked, and the suspension is shaken at 35° for 48 h. The mixture is filtered and the clear filtrate transferred to a 250 ml bottle containing 10 g of dry $Ca(OH)_2$ powder, the bottle is tightly corked, and the suspension is shaken at 25° for 1 h. The mixture is filtered and evaporated to dryness under diminished pressure. Crystallization from methanol gave **2** (100%), m.p. 162°. Lit. [6] m.p. 159-160°. $[\alpha]_D^{27}$ -15.8° (c 1.01, MeOH). R_f (ether/MeOH 10:1) 0.6. ^{1}H-NMR (DMSO-d6 / Acetone): 1.20, 1.40 (2s, 6H, $2CH_3$); 3.46 (d, 2H, CH_2O); 3.96 (m, 1H, CHO); 4.71 (m, 2H, CHCH); 5.51 (d, 1H, J = 8 Hz, H-C(5)); 5.60 (br., 1H, OH); 5.71 (d, 1H, J = 1Hz, OCHN); 7.70 (d, 1H, J = 8 hz, H-C (6)); 10.61 (br., 1H, NH). UV (EtOH): 263 nm.

5' - Deoxy - 5' - iodo - 2', 3' - O - isopropylideneuridine (3). Triphenyl phosphite (15 g, 0.05 mol) and CH_3I (10.5 g, 0.075 mol) are refluxed together for 36 h, during which time the temperature of the liquid rises to 115°. The solution is cooled, and anhydrous ether (100 ml) is gradually added, causing the separation of palebrown crystals of methyltriphenoxyphosphonium iodide; this is repeatedly washed by decantation with anhydrous ether until the washings are essentially colorless (8 times). The crystalline product is then dried, and used in the following manner.

A solution of **2** (1.80 g, 6.3 mmol) and methyltriphenoxyphosphonium iodide (5.70 g, 12.6 mmol) in dry DMF (20 ml) is kept at 25° for 3 h. AcOEt (300 ml) was added to the reaction mixture and then washed with H_2O (5 × 120 ml). The organic layer was dried (Na_2SO_4), filtered and evaporated to 3 ml. Dropwise addition of hexane at 80° afforded **3** (95%) as colorless crystals, m.p. 162°. Lit. [6] m.p. 164°. R_f (ether / MeOH 10:1) 0.98. ^{1}H-NMR ($CDCl_3$): 1.30, 1.50 (2s, 6H, $2CH_3$); 3.40 (q. 2H, J_1 = 3Hz, J_2 = 6Hz, CH_2I); 4.21 (m, 1H, CHO); 4.89 (m, 2H, CHCH); 5.61 (d, 1H, J = 1Hz, OCHN); 5.71 (d, 1H, J = 8Hz, H-C(5)); 7.34 (d, 1H, J = 8Hz, H-C(6)); 9.83 (br., 1H, NH). UV (EtOH): 262 nm.

2, 5' - Anhydro - 2' - 3' - O - isopropylideneuridine (5). Compound **3** (1 mmol) in MeOH (3 ml) was left at 25° for 68 h to afford **5** (78%), sinter at 190° and darken without melting. R_f (ether / MeOH 10:1) 0.53. UV (EtOH) 249 nm (ε 14100); identical with the authentic sample [14].

5' – Dimethyl (5' – deoxy – 2', 3' – 0 – isopropylideneuridine) phosphonate (4) and 5' -methyl (5' - deoxy – 2' – 3' – 0 – isoprophylidene – 2 - methoxyuridine) phosphite (6). Compound 3 (0.01 mol) and trimethyl (0.2 mol) were heated together at 140°. After 20 h, the residue was dissolved in MeOH (7 ml) and poured into a stirred solution of ether (300 ml) to afford a precipitate. Chromatography on silica gel and elution with AcOEt and AcOEt / acetone 1:1 afforded compounds **4** (42.5%), R_f (ether / MeOH 10:1) 0.78, and **6** (42.5%), R_f (ether / MeOH 10:1) 0.38 respectively. **4**: M.p. 160°. ^{1}H-NMR ($CDCl_3$): 1.32, 1.53 (2s, 6H, $2CH_3$, dist., 12 Hz); 2.00 - 2.70 (m, 2H, CH_2P); 3.85 (d, 6H, J = 11 Hz, $2CH_3OP$); 4.40 (br., m, 1H, CHO); 5.05 (br. m, 2H, CHCH); 5.65 (d, 1H, J = 1 Hz, OCHN); 5.76 (d, 1H, J = 8 Hz, H-C(5)); 7.35 (d, 1H, J = 8 Hz, H-C(6)); 10.20 (br., 1H, NH). UV (EtOH): 262.5 nm.

6: M.p. 200 - 203°. ^{1}H-NMR ($CDCl_3$): 1.32, 1.53 (2s, 6H, $2CH_3$, dis. 12 Hz); 1.90 - 2.60 (m, 2H, CH_2P); 3.30 (s, 3H, OMe); 3.58 (d, 3H, J = 11 Hz, CH_3OP); 4.40 (br. m, 1H, CHO); 4.91 (br. m, 2H, CHCH); 5.62 (d, 1H, J = 1 Hz, OCHN); 5.75 (d, 1H, J = 8 Hz, H-C(5)); 7.40 (m, 2H, H-C(6) and HOP); 10.20 (br. 1H, NH). UV (EtOH): 253 nm.

Compound **6** was also prepared either by heating the mixture of **4** and **6** at 200 - 210° after 20 h or by refluxing

3 in trimethyl phosphite at 200 - 210° (oil bath) after 20 h.

5′ -Methyl (5′ -deoxy -2 -methoxyuridine) phosphonate (7). A solution of compound **6** (1.3 mmol) in 80% acetic acid (12 ml) is heated at 100° for 2 h. The solvent are removed by coevapotation with MeOH. The residue is purified on silica gel using AcOEt / acetone 1.5:1 (87%), m.p. 239°. R_f (ether / MeOH 10:1) 0.11. ^{1}H-NMR (Acetone - d6/D_2O): 1.61 (d, 2H, J = 18 Hz, CH_2P); 3.21 (s, 3H, CH_3); 3.71 (d, 3H, J = 11 Hz, CH_3OP); 4.30 (br. m, 1H, CHO); 4.81 (m, 2H, CHCH); 5.72 (d, 1 H, J = 8 Hz, H-C(5)); 5.91 (d, 1 H, J = 1 Hz, OCHN); 7.75 (d, 1 H, J = 8 Hz, H-C (6)). UV (EtOH): 255 nm. IR (nujol): 3120 - 3630 (3 OH), 1710 (C = O), 1661 (C = N), 1350 - 1461 (phosphonate), 1040, 1110 (ether).

5′- Deoxy- 5′- phosphono- 2- methoxyuridine (8). Compound **7** (0.01 mol) was dissolved in MeOH (400 ml). The solution was saturated with NH_3 gas in a pressure bottle, and heated at 100° for 24 h. After cooling at 25°, the solvent was evaporated to dryness and the residue was purified by tick - layer chromatography using MeOH / ether 3:2 as solvent to give **8** (60%), m.p. 180° (sof.) and 287° (dec.). R_f (ether / MeOH 10:1): 0.02. ^{1}H-NMR (D_2O): 1.35 (d, 2 H, J = 18 Hz, CH_2P); 3.30 (s, 3 H, CH_3); 4.00 - 4.40 (m, 3 H, CHCHCH); 5.90 (br. s, 1 H, OCHN); 6.01 (d, 1 H, J = 7.5 Hz, H-C (5)); 7.95 (d, 1 H, J = 7.5 Hz, H-C (6)). UV (EtOH): 255 nm.

2- Dimethyl [1- (ethoxymethyl)- 4- methoxyuracil] phosphonate (11), 2- Dimethyl [1- (ethoxymethyl)- 2- methoxyuracil] phosphonate (12), and 2- Dimethyl [1- (ethoxymethyl) uracil] phosphonate (15). Compound **10** (0.005 mol) and trimethyl phosphite (0.05 mol) were heated together at 200 - 210°. After 28 h, the mixture was poured into ether (200 ml) to give an oil. The ether was decanted and the oily product was chromatographed on silica gel. Compound **11** (38%) was eluted with CH_2Cl_2 and **12** (40%) was eluted with $CHCl_3$. The above reaction at 140° gave **15** (88%) after 15 h. Compound **15** at 200 - 210° gave **16**, after 6 h, in quantitative yield.

11: Oil. R_f (MeOH / AcOEt 0.5:2) 0.4. ^{1}H-NMR ($CDCl_3$): 2.09 (sixth., 2 H, J_1 = 7 Hz, J_2 = 14 Hz, J_3 = 18 Hz, CH_2P); 3.20 (s, 3 H, CH_3); 3.40 - 4.00, 3.68 (m, 2 H, CH_2O, and d, 6 H, J = 11 Hz, $2CH_3OP$); 5.20 (s, 2 H, OCH_2N); 5.73 (d, 1 H, J = 8 Hz, H-C (5)); 7.54 (s, 1 H, J = 8 Hz, H-C (6)). UV (EtOH): 259 nm.

12: Oil. R_f (MeOH / AcOEt 0.5:2) 0.36. ^{1}H-NMR spectrum similar to that of **11**. UV (EtOH): 253.

15: Foma. R_f (MeOH / AcOEt 0.5:2) 0.17. ^{1}H-NMR ($CDCl_3$): 2.00 (m, 2 H, CH_2P); 3.41 - 4.00, 3.65 (m, 2 H, CH_2O, and d, 6 H, J = 11 Hz, $2CH_3OP$); 5.50 (s, 2 H, OCH_2N); 5.70 (d, 1 H, J = 8 Hz, H-C (5)); 7.31 (d, 1 H, J = 8 Hz. H-C (6)); 10.20 (br., 1 H, NH). UV (EtOH): 265 nm.

16: M. P. 140°. R_f (MeOH): 0.90. ^{1}H-NMR spectrum similar to that of **11** and **14**. UV (EtOH): 254 nm.

2 – Ammonium 2 – methyl [1 – (ethoxymethyl) cytosine] phosphonate (13) and 2-Ammonium – 2 – methyl [1- (ethoxymethyl) -2 -methoxyuracil] phosphonate (14). Both compounds were prepared in an identical manner. Representative procedure: Compound **11** (1 mmol) was dissolved in 100 ml of saturated NH_3/MeOH in a pressure bottle. The solution was sealed and maintained at 100° for 48 h. The mixture was concentrated to 10 ml, and ether (50 ml) was added to afford a precipitate. Filteration gave **13** (70%), m.p. 270° (dec.). R_f (MeOH) 0.38. ^{1}H-NMR (Acetone-d6): 2.21 (m, 2H, CH_2PO; 3.18 - 4.01 (m, 5H, CH_3OP, J = 11 Hz, and CH_2O); 5.21 (br. s, 2H, OCH_2N); 5.70 (d, 1H, J = 8 Hz, H-C(5)); 7.75 (br., 7H, NH_4, NH_2, H-C(6), after D_2O exchange: 1H, J = 8 Hz, H-C(6). UV (EtOH): 241, 274 nm.

14: M.P. 210°. R_f (MeOH) 0.68. ^{1}H-NMR (DMSO-d6): 1.89 (m, 2H, CH_2P); 3.20 (s, 3H, CH_3); 3.45 (d, 3H, CH_3OP); 3.21 - 3.90 (m, 2H, CH_2O); 5.15 (s, 2H, OCH_2N); 5.74 (d, 1H, J = 8 Hz, H-C(5)); 6.20 - 8.50, 7.76 (br. 4H, NH_4, exchanged with D_2O, and d, 1H, J = 8 Hz, H-C(6)). UV (EtOH): 253 nm.

Silylation of Uridine (17a) and Cytidine (17b). Representative procedure: Uridine (**17a**, 1 mmol) was dissolved in THF (30 ml). DABCO (6 mmol) and $AgNO_3$ (2.20 mmol) were added and stirring was continued for 5 min. Triisopropylsilyl chloride (2.20 mmol) was added and the mixture was stirred for 2 h. The solution was collected by filtration and the solvent was evaporated. Compound **18a** (90%) was isolated by short column chromatography on silica gel using $CHCl_3$ as solvent, m.p. 100 - 101°. R_f (hexane / ether 1:3) 0.10. ^{1}H-NMR ($CDCl_3$): 0.1 (m, 6H, 6CHSi); 1.10 (s, 36H, $12CH_3$); 2.75 (br., 1H, OH); 4.10 (m, 3H, CH_2OSi and CHOSi); 4.51 (m, 2H, 2CHO); 5.73 (d, 1H, J = 8 Hz, H-C(5)); 6.02 (d, 1H, J = 5 Hz, OCHN); 7.81 (d, 1H, J = 8 Hz, H-C(6)); 10.30 (br., 1H, NH). UV (EtOH): 263.

18b: (80%), m.p. 250°. R_f (hexane / ether 1:3) 0.03.

^{1}H-NMR similar to that of **18a**. UV (EtOH): 241, 274 nm.

One Pot Synthesis of 1-ß-D-Arabinofuranosyl uracil (20a) and 1-ß-D-Arabinofuranosy cytosine (20b). Both compounds were prepared (**18a-b** ——→ **20a-b**) in the same manner. Representative prodedure: A solution of **18a** (5 mmol) and methyltriphenoxyphosphonium iodide (7 mmol) in dry DMF (20 ml) was stirred at 25° for 4 h. The solvent was evaporated to a thick syrup to which was added 60 ml of 0.10 molar KOH/EtOH. The reaction was stirred overnight at 25° and then was refluxed at 25° for 5 h. The mixture was then neutralized (pH 7), using 3.0 normal HCl/EtOH and evaporated to an oil. The oil was taken up in $CHCl_3$ (80 ml), washed with H_2O, dried (Na_2SO_4), and filtered. Evaporation afforded **19a** which was dissolved in THF and treated with Bu_4NF (10 mmol) to afford **20a** (60%), m.p. 228°. Lit. [17] m.p. 225 - 227.5°.

20b: (40%), m.p. 211°. Lit. [18] m.p. 212 - 213°.

Acknowledge ment

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