Protection of Phosphonate Function by Means of Ethoxycarbonyl Group. A New Method for Generation of Reactive Silyl Phosphite Intermediates

Mitsuo SEKINE, Hiroyuki MORI, and Tsujiaki HATA*

Department of Life Chemistry, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 227

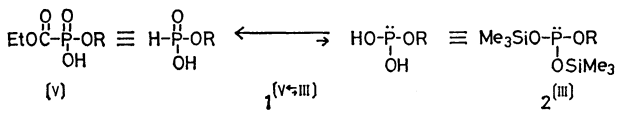
(Received June 12, 1981)

Nucleoside ethoxycarbonylphosphonates were prepared by condensation of appropriately protected nucleosides with ethoxycarbonylphosphonic acid. They were easily converted by treatment with 1 M NaOH followed by trimethylsilylation to highly reactive bis(trimethylsilyl) nucleoside phosphite intermediates which were allowed *in situ* to react with water, diphenyl disulfide, 2,2′-dipyridyl disulfide, and aldehydes to afford the corresponding nucleoside phosphonates, nucleoside *S*-phenyl phosphorothioates, nucleoside phosphates, and nucleoside α-hydroxy phosphonates in good yields, respectively. The nucleoside phosphonates were further converted to nucleosides under mild acidic conditions. Thus, the ethoxycarbonyl group proved to serve as a versatile protecting group for not only H–P(O) but also HO–P(O) and hydroxyl groups of sugars.

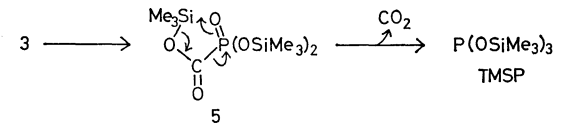
Nucleoside phosphonates (**1**) have been shown as versatile synthetic intermediates in nucleotide chemistry. For example, **1** could be converted to highly reactive "nucleoside bis(trimethylsilyl) phosphites (**2**)" having tervalent form by simple trimethylsilylation. Fixation of phosphonates in the tervalent form has proved to be quite useful for the synthesis of various phosphate and phosphonate derivatives.[2-11] The trimethylsilyl group of the silylated products was readily removed by addition of water or alcohols. The above feature enhances the synthetic value of **2**. Thus, the preparation of **1** as the starting materials for the synthesis of **2** has become of more importance in nucleotide chemistry. However, the preparative method of **1**, *i.e.*, the introduction of a hydroxyphosphinyl group [H(HO)P(O)–] into nucleoside hydroxyl groups has been extremely limited,[12-17] because **1** is unstable under weakly acidic conditions (for example, 80% acetic acid[12]) though it is quite stable under alkaline conditions. The H–P(O) group of **1** is also sensitive to oxidizing agents,[12,17,18] halogenating agents,[19-23] and condensing agents.[24]

In order to overcome the problems owing to the instability of the hydroxyphosphinyl group, an appropriate masking group is required. We feel that, in this case, the protection of the H–P(O) function should be designed not in reactive phosphite form but in nonreactive phosphonate form.

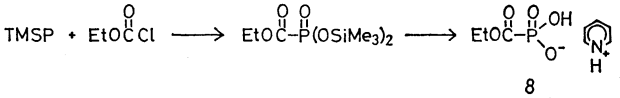
Warren[25] described an interesting study on decarboxylation of carboxyphosphonic acid (**3**) to give phosphonic acid (**4**) under relatively drastic conditions using strong acids. This fact suggests that the H–P(O) group of **1** can be protected by alkoxycarbonyl groups such as ethoxycarbonyl group. Therefore, our attention has been paid to the P–C bond cleavage of **3** with elimination of carbon dioxide under milder conditions than those reported by Warren.



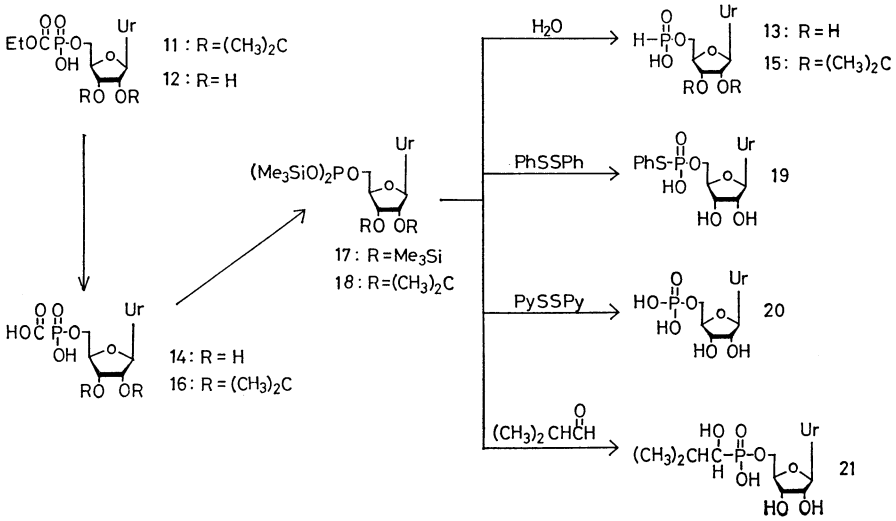
Consequently, we found a unique method for the decarboxylation of **3** *via* trimethylsilylation. When the pyridinium salt of **3** was treated with trimethylsilyl chloride and triethylamine (3.3 equiv. each) in tetrahydrofuran at room temperature for 30 min and then water was added, phosphonic acid was isolated as barium salt in 96% yield. When the reaction mixture was distilled without addition of water, tris(trimethylsilyl) phosphite (TMSP) was obtained in 81% yield. The mechanism of formation of TMSP might involve intramolecular rearrangement of one trimethylsilyl group *via* a five-membered ring transition state from a fully trimethylsilylated intermediate (**5**). Furthermore, the formation of TMSP was supported by the fact that treatment of the reaction mixture with diphenyl disulfide and benzaldehyde gave *S*-phenyl phosphorothioate (**6**) and α-hydroxybenzylphosphonic acid (**7**)



in 95 and 35% (quant. on TLC) yields, respectively. These results led us to study the protection of the H–P(O) group of **1** with ethoxycarbonyl group. Pyridinium ethoxycarbonylphosphonate (**8**) was prepared starting from TMSP and ethyl chloroformate according to the following equation. When compound **8** was condensed with 2′,3′-*O*-isopropylideneuridine (**10**) in the presence of 1-(*p*-toluenesulfonyl)-1*H*-1,2,4-triazole[26] at r.t. overnight, 2′,3′-*O*-isopropylideneuridine 5′-(ethoxycarbonyl)phosphonate (**11**) was obtained in 84% yield by paper chromatography. It was found that the ethoxycarbonyl group of **11** was quite stable under acidic conditions required for removal of the isopropylidene group. Accordingly, treatment of **11** with 60% formic acid at r.t. for 2 h gave **12** in 93% yield. The ethoxycarbonyl group was found to be stable toward agents such as iodine, *N*-bromosuccimide,[27] and 2,4,6-triisopropylbenzenesulfonyl chloride.[24,28]

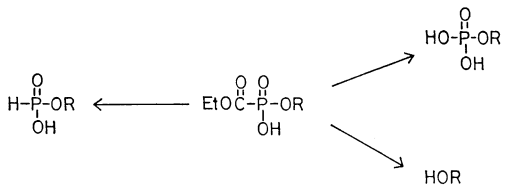


Compound **12** was treated with 1 M NaOH at r.t. for 5 min followed by neutralization with DIAION



SK 1B (pyridinium form). After the mixture was evaporated to dryness, the residual syrup was successively treated with *N,O*-bis(trimethylsilyl)acetamide (BSA) in pyridine at r.t. for 3 h. By treatment of the mixture with water, uridine 5′-phosphonate (**13**) was obtained in 92% yield. In this reaction, the first intermediate **14** was clearly detected as a single spot on TLC and electrophoresis. The intermediate **14** was characterized by its NMR spectrum. However, attempts to purify **14** by chromatographical methods were unsuccessful because **14** decomposed to **13** and uridine during the chromatography. In a similar manner, **11** was converted to 2′,3′-*O*-isopropylidene 5′-phosphonate (**15**) in 86% yield *via* intermediate **16**. It should be emphasized that the "*in situ*" treatment of **14** with BSA gave rapid and simultaneous generation of a silyl phosphite intermediate (**17**). The presence of **17** was confirmed by the subsequent reaction with diphenyl disulfide, which gave *S*-phenyl uridine 5′-phosphorothioate (**19**)[2] in 94% yield. Furthermore, the use of 2,2′-dipyridyl disulfide[3] in place of diphenyl disulfide gave uridine 5′-phosphate (**20**) in 95% yield. In addition, a new type of nucleotide derivative, uridine 5′-(1-hydroxy-2-methylpropyl)phosphonate (**21**), could be obtained in 84% yield through the reaction of the intermediate **19** with isobutyraldehyde at r.t. for 3 h. Moreover, it was found that the phosphonate group was removed from **13** by treatment with 80% acetic acid at 100 °C for 2 h[12] to give uridine in 90% yield.

Conclusion. In contrast with the fixation of **1** in the tervalent form **2** by the silylation described previously,[2] nucleoside ethoxycarbonylphosphonates can serve as the synthetic equivalents of **1** fixed perfectly in the phosphonate form **3**. It is significant that H–P(O) group can be fixed rigidly in the phosphonate form by the introduction of the (ethoxycarbonyl)hydroxyphosphinyl group. No study has appeared on protection of the H–P(O) group. From this point of view, the present work is the first example in phosphorus chemistry. It is also noteworthy that nucleoside derivatives having the (ethoxycarbonyl)hydroxyphosphinyl group can be converted under the varied conditions to nucleoside bis(trimethylsilyl) phosphites, nucleoside phosphonates, nucleoside phosphates, and nucleosides. From the different point of view, it can be said that the ethoxycarbonyl or (ethoxycarbonyl)hydroxyphosphinyl group can serve as a versatile protecting group for H–P(O), HO–P(O), or HO–R.



Experimental

Melting points and boiling points are uncorrected. ^{1}H NMR spectra were recorded at 60 MHz on a Hitachi R 24-B spectrometer using DSS and benzene (δ 7.24) as internal standards in D_2O and $CDCl_3$, respectively. IR spectra were measured on a Hitachi Model EPI-G3 spectrometer. ^{31}P NMR spectra were obtained on a JEOL PS-100 FT spectrometer at 40.50 MHz using 85% H_3PO_4 as an external standard. UV spectra were recorded with a Hitachi 124 spectrophotometer.

Paper chromatography was performed by descending technique with Toyo Roshi No. 51 and Whatman 3 MM papers. The solvent systems used were Solvent I: ethanol–1 M ammonium acetate (pH 7.5) (7:3, v/v); Solvent II: 1-butanol–water (84:16, v/v); Solvent III: 2-propanol–concentrated aqueous ammonia–water (6:1:3, v/v/v). Solvent IV: 2-propanol–concentrated aqueous ammonia–water (7:1:2, v/v/v). Paper electrophoresis was carried out by using Buffer I (0.05 M phosphate, pH 8.0) at 1200 V for 1.5 h. The Rm values relative to **13** were described. Estimation of the yields of products was carried out spectrophotometrically by using the ε value (10.1×10^3) of uridine at pH 7.0 after elution of the spots from paper chromatograms.

Phosphorus-containing spots were detected on TLC or paper by spraying Hanes-Isherwood reagent[29] followed by irradiation of UV.

Pyridine was distilled over *p*-toluenesulfonyl chloride and stored over calcium hydride. Tetrahydrofuran (THF) was distilled over $LiAlH_4$ and stored over sodium wire. Trimethylsilyl chloride was purchased from Nihon Silicon

Shokai Ltd. and distilled over calcium hydride before use. *N,O*-Bis(trimethylsilyl)acetamide (BSA) was purchased from Tokyo Kasai Ltd. and distilled before use.

Preparation of Tris(trimethylsilyl) Phosphite. An aqueous solution (100 ml) of trisodium carboxyphosphonate (2.83 g, 9.43 mmol) was passed through a column of DIAION SK 1B (pyridinium salt) (3×20 cm). The column was washed with 500 ml of pyridine–water (1:4, v/v). The eluents were combined, evaporated *in vacuo*, coevaporated with dry pyridine several times, and dissolved in dry THF (30 ml). Triethylamine (4.4 ml, 31.1 mmol) and trimethylsilyl chloride (3.9 ml, 31.1 mmol) were added and the mixture was vigorously stirred at room temperature. After 2 h, dry ether (15 ml) was added. The resulting precipitate was removed by filtration and washed with dry ether (10 ml). The filtrate and washings were combined, evaporated *in vacuo*, and the residue was distilled to give TMSP (2.27 g, 81%): Bp 76—77 °C/10 mmHg (lit,[30] 90—92/20 mmHg); ^{31}P NMR ($CDCl_3$) −113.2 ppm.

The same experiment was performed until washing with dry ether had been done. The residual liquid was treated with methanol (50 ml) and the solution was evaporated to dryness. The residue was dissolved in water (50 ml) and 9.5 ml of 1 M barium acetate aqueous solution was added. To the resulting solution was added with stirring ethanol (250 ml). The resulting precipitate was collected by filtration, washed with ethanol (50 ml) and ether (30 ml) and dried *in vacuo* over P_4O_{10} at 100 °C to give barium phosphonate **5** (1.98 g, 96%). This product was identified with the authentic sample by its IR spectra and paper chromatography (Solvent II).

*S-Phenyl Phosphorothioate (**6**).*[2] Trisodium carboxyphosphonate (90 mg, 0.3 mmol) was converted to the pyridinium salt as described in the above experiment. The salt was rendered anhydrous by repeated coevaporation with dry pyridine and dissolved in dry THF (5 ml). Diphenyl disulfide (71.9 mg, 0.33 mmol) was added and the mixture was treated with trimethylsilyl chloride (0.23 ml, 2 mmol) and triethylamine (0.25 ml, 2 mmol) at room temperature for 1 h. The reaction mixture was diluted with pyridine by using a measuring flask to 10.0 ml. A one-tenth of the solution was chromatographed on Whatman 3 MM paper (Solvent III) to give **6** (95%): R_f 0.42; $UV_{max}^{pH\ 7.0}$ 248 nm (ε=6560), $UV_{min}^{pH\ 7.0}$ 235 nm.

*α-Hydroxybenzylphosphonic Acid (**7**).* Trisodium carboxyphosphonate (900 mg, 3 mmol) was converted to the pyridinium salt as described before. The salt was rendered anhydrous by repeated coevaporation with dry pyridine and dissolved in dry THF (3 ml). To the solution was added successively benzaldehyde (318 mg, 3 mmol), triethylamine (2.52 ml, 18 mmol), and trimethylsilyl chloride (2.27 ml, 18 mmol). After the mixture was stirred at room temperature for 1 h, a white precipitate of triethylamine hydrochloride was removed by filtration. Ethanol (10 ml) was added to the filtrate. The resulting solution was concentrated to a small volume and hexane (100 ml) was added to the concentrated solution. A precipitate was collected by filtration, washed with hexane (20 ml), and dried over P_4O_{10} *in vacuo* to afford **7** (197 mg, 38%): Mp 171—174 °C (lit,[9] 179—180 °C). Found: C, 44.65; H, 4.84%. Calcd for $C_7H_9O_4P$: C, 44.69; H, 4.83%.

*2′,3′-O-Isopropylideneuridine 5′-(Ethoxycarbonyl)phosphonate (**11**).* An aqueous solution (100 ml) of anilinium ethoxycarbonylphosphonate[11] (296.6 mg, 1.2 mmol) was passed through a column (1×5 cm) of DIAION SK 1B (pyridinium salt). The column was washed with pyridine–water (1:5, v/v, 200 ml). The combined eluents were concentrated to a small volume and diluted with pyridine by using a measuring flask to 20 ml. From the measuring flask, 6.67 ml (0.75 mmol) of the standard solution was taken and 2′,3′-*O*-isopropylideneuridine (142 mg, 0.5 mmol) was added. The mixture was rendered anhydrous by repeated coevaporation with dry pyridine and dissolved in dry pyridine (2.5 ml). 1-(*p*-Toluenesulfonyl)-1*H*-1,2,4-triazole (227 mg, 1 mmol) was added. After being stirred at room temperature for 16 h, the mixture was quenched by addition of water and chromatographed on Whatman 3 MM papers (Solvent I). A band of R_f 0.90 was cut and eluted with water (1 l). The eluent was concentrated and applied to Whatman 3 MM papers. Rechromatography was performed by using Solvent II. A band of R_f 0.37 was cut and eluted with water (500 ml) to give the ammonium salt of **11** (4240 OD, 84%): R_m 0.92 (Buffer I); $UV_{max}^{pH\ 7.0}$ 262 nm, $UV_{min}^{pH\ 7.0}$ 232 nm; NMR (D_2O) δ 1.10 (t, 3H, J=7 Hz, CH_2CH_3), 1.18 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 3.53 (m, 2H, 5′-H), 4.04 (t, 2H, J=7 Hz, CH_2–CH_3), 4.47 (m, 1H, 4′-H), 4.85 (m, 2H, 2′- and 3′-H), 5.66 (d, 1H, J=8.2 Hz, 6-H), 5.72 (s, 1H, 1′-H), 7.61 (d, 1H, J=8.2 Hz, 5-H).

*Uridine 5′-(Ethoxycarbonyl)phosphonate (**12**).* The ammonium salt of **11** (0.062 mmol) was dissolved in 60% formic acid (30 ml). The solution was kept at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was chromatographed on Whatman 3 MM paper (Solvent II). A band of R_f 0.11 was cut and eluted with water (200 ml) and water–ethanol (3:1, v/v, 300 ml) to give the ammonium salt of **12** (576 OD, 93%): $UV_{max}^{pH\ 7.0}$ 262 nm, $UV_{min}^{pH\ 7.0}$ 230 nm; NMR (D_2O) δ 1.11 (t, 3H, J_{H-H}=7 Hz, CH_3), 3.90—4.38 (m, 5H, 2′, 3′, 4′, 5′-H), 5.72 (d, 1H, J_{H-H}=8.2 Hz, 6-H), 5.80 (s, 1H, 1′-H), 7.70 (d, 1H, J=8.2 Hz, 5-H).

*Alkaline Hydrolysis of **12**.* The ammonium salt of **12** (0.05 mmol) was treated with 1 M NaOH (0.8 ml) at room temperature. After being kept for 5 min, the solution was neutralized with DIAION SK 1B (NH_4^+ form). The resin was filtered and washed with water (20 ml). The filtrate and washings were combined and evaporated *in vacuo* to give the diammonium salt of **14**. Its analyses using paper electrophoresis and TLC showed a homogeneous spot: R_f 0.12 (Solvent I), 0.01 (Solvent II); R_m 1.40 (Buffer I); NMR (D_2O) δ 3.85—4.32 (m, 5H, 2′,3′,4′-H and 5′-H), 5.74 (d, 1H, J_{H-H}=8.2 Hz, 6-H), 5.78 (d, 1H, J_{H-H}=3.8 Hz, 1′-H), 7.84 (d, 1H, J_{H-H}=8.2 Hz, 5-H).

*Uridine 5′-Phosphonate (**13**).* The diammonium salt of **14** (0.01 mmol) was rendered anhydrous by repeated coevaporation with dry pyridine and dissolved in dry pyridine (0.5 ml). BSA (0.2 ml) was added and the mixture was stirred at room temperature for 30 min. Water (0.5 ml) was added and the resulting solution was kept for 1 h. The solution was applied to Whatman 3 MM papers. Chromatography using Solvent IV was performed. A band of R_f 0.36 was cut and eluted with water (200 ml) to give the ammonium salt of **13** (93 OD, 92%): This product was identified with the authentic sample by comparison with its R_f and R_m values and UV spectrum.

*S-Phenyl Uridine 5′-Phosphorothioate (**19**).* The diammonium salt of **14** (0.01 mmol) was rendered anhydrous as described in the above experiment. The dried material was mixed with diphenyl disulfide (2.6 mg, 0.012 mmol) and dissolved in dry pyridine (0.5 ml). BSA (0.2 ml) was added and the solution was kept at room temperature for 30 min. Water (0.5 ml) was added and the mixture was kept at room temperature for 1 h. Paper chromatography on Whatman 3 MM papers using Solvent IV gave a band of **19** (R_f 0.52, 100 OD, 94%): R_m (Buffer I); $UV_{max}^{pH\ 7.0}$ 244,

260 nm, $UV_{min}^{pH\ 7.0}$ 231, 251 nm. This compound was identified with the authentic sample obtained by the reaction of **15** with diphenyl disulfide in the presence of triethylamine and trimethylsilyl chloride in pyridine followed by treatment with 80% acetic acid.

*Uridine 5'-Phosphate (**20**).* The above mentioned reaction was done by using 2,2'-dipyridyl disulfide (2.7 mg, 0.012 mmol) in place of diphenyl disulfide. The usual work-up gave **20** (96 OD, 95%): R_f 0.10 (Solvent IV). $UV_{max}^{pH\ 7.0}$ 261 nm, $UV_{min}^{pH\ 7.0}$ 230 nm. The compound was identified with the authentic sample.

*Uridine 5'-(1-Hydroxy-2-methylpropyl)phosphonate (**21**).* The ammonium salt of **12** (0.038 mmol) was converted to **14** according to the method described before. Compound **14** was rendered anhydrous by repeated coevaporation with dry pyridine and dissolved in dry THF (1 ml). BSA (0.114 ml) was added and the mixture was kept at room temperature for 20 min. Then, isobutyraldehyde (0.066 ml) was added and the mixture was stirred for 3 h. The solution was applied to Whatman 3 MM papers and chromatographed using Solvent IV. A band of R_f 0.39 was cut and eluted with water (100 ml) to give the ammonium salt of **21** (323 OD, 84%): $UV_{max}^{pH\ 7.0}$ 262 nm, $UV_{min}^{pH\ 7.0}$ 231 nm; NMR (D_2O) δ 0.84 (d, 6H, J_{H-H}=6.4 Hz, $(CH_3)_2C$), 1.88 (m, 1H, CHCP), 3.42 (dd, 1H, J_{H-H}=5.4 Hz, J_{P-H}=8.9 Hz, CHP), 3.73—4.29 (m, 6H, 2',3',4'-H and 5'-H), 5.72 (d, 1H, J_{H-H}=8.4 Hz, 6-H), 5.76 (s, 1H, 1'-H), 7.80 (d, 1H, J_{H-H}=8.4 Hz, 5-H).

*2',3'-O-Isopropylideneuridine 5'-Phosphonate (**15**).* The ammonium salt of **11** (0.1 mmol) was dissolved in 1 M NaOH (1 ml). After being kept at room temperature for 5 min, the solution was neutralized with DIAION SK 1B (pyridinium salt). The resin was washed with water (20 ml). The eluent was concentrated and diluted with pyridine–H_2O (2:1, v/v) to 10 ml. The analysis by paper electrophoresis and TLC showed that **16** [R_m 1.44 (Buffer I); R_f 0.36 (Solvent I)] was obtained. The solution was evaporated and rendered anhydrous by repeated coevaporation with dry pyridine. The residue was dissolved in dry THF (1 ml) and triethylamine (0.084 ml, 0.6 mmol) and trimethylsilyl chloride (0.076 ml, 0.6 mmol) were added. After being kept at room temperature for 5 min, the solution was analyzed by paper electrophoresis, which showed that **15** [R_f 0.76 (Solvent III): R_m 0.95 (Buffer I); $UV_{max}^{pH\ 7.0}$ 262 nm, $UV_{min}^{pH\ 7.0}$ 231 nm] was obtained in 86% yield.

*Removal of Phosphonate Group from **13**.* Compound **13** (0.05 mmol) was dissolved in 80% acetic acid (100 ml). The solution was heated at 100 °C for 2 h and then cooled to room temperature. After the solvent was removed *in vacuo*, the residue was chromatographed on Whatman 3 MM paper (Solvent IV) to give a band of R_f 0.75 which was eluted with water and identified with the authentic sample of uridine. The yield was spectrophotometrically estimated to be 90%.

References

1) This paper participates as Part XIX in the series of silyl phosphites. Part XVIII: M. Sekine, M. Nakajima, A. Kume, A. Hashizume, and T. Hata, *Bull. Chem. Soc. Jpn.*, **55**, 224 (1982).
2) T. Hata and M. Sekine, *J. Am. Chem. Soc.*, **96**, 7363 (1974).
3) T. Hata and M. Sekine, *Tetrahedron Lett.*, **1974**, 3943.
4) M. Sekine and T. Hata, *Tetrahedron Lett.*, **1975**, 1711.
5) T. Hata, M. Sekine, and N. Kagawa, *Chem. Lett.*, **1975**, 635.
6) A. F. Rosenthal, L. A. Vogas, Y. A. Isaacson, and R. Bittman, *Tetrahedron Lett.*, **1975**, 977.
7) T. Hata, I. Yamamoto, and M. Sekine, *Chem. Lett.*, **1976**, 601.
8) D. E. Gibbs, *Tetrahedron Lett.*, **1977**, 679.
9) M. Sekine, I. Yamamoto, A. Hashizume, and T. Hata, *Chem. Lett.*, **1977**, 485.
10) M. Sekine, K. Okimoto, and T. Hata, *J. Am. Chem. Soc.*, **100**, 1001 (1978).
11) M. Sekine and T. Hata, *Chem. Commun.*, **1978**, 285.
12) J. A. Schofield and A. R. Todd., *J. Chem. Soc.*, **1961**, 2316.
13) A. M. Michelson, "The Chemistry of Nucleosides and Nucleotides" Academic Press, London (1963).
14) A. Holy and F. Sorm, *Collect. Czech. Chem. Commun.*, **31**, 1544 (1966).
15) A. Holy and F. Sorm, *Collect. Czech. Chem. Commun.*, **31**, 1562 (1966).
16) H. Pischel and A. Holy, *Collect. Czech. Chem. Commun.*, **35**, 3584 (1970), and references therein.
17) M. Yoshikawa, M. Sakuraba, and K. Kusashio, *Bull. Chem. Soc. Jpn.*, **43**, 456 (1970).
18) D. M. Brown and P. R. Hammond., *J. Chem. Soc.*, **1960**, 4229, 4232.
19) A. J. Kirby, *Chem. Ind.*, **1963**, 1877.
20) N. S. Corby, G. W. Kenner, and A. R. Todd., *J. Chem. Soc., C*, **1952**, 3669.
21) G. W. Kenner, A. R. Todd, and F. J. Weymouth, *J. Chem. Soc.*, **1952**, 3675.
22) T. Mukaiyama, H. Koba, and K. Kodera, *Bull. Chem. Soc. Jpn.*, **39**, 2721 (1966).
23) G. M. Blackburn, J. S. Cohen, and A. R. Todd., *J. Chem. Soc., (C)*, **1966**, 240.
24) M. Sekine, H. Mori, and T. Hata, *Tetrahedron Lett.*, **1979**, 1145.
25) S. Warren and M. R. Williams, *J. Chem. Soc., B*, **1971**, 618.
26) N. Katagiri, K. Itakura, and S. A. Narang, *J. Am. Chem. Soc.*, **97**, 7332 (1971).
27) In this case, 5-bromination of the uracil part occurred but the ethoxycarbonyl group itself remained intact.
28) R. Lohrmann and H. G. Khorana, *J. Am. Chem. Soc.*, **88**, 829 (1966).
29) C. A. Hanes and F. A. Isherwood, *Nature*, **164**, 1107 (1949).
30) M. Sekine, K. Okimoto, K. Yamada, and T. Hata, *J. Org. Chem.*, **46**, 2097 (1981).