Silyl Phosphites. Part 20. A Facile Synthesis of Phosphoenolpyruvate and Its Analogue Utilizing *in situ* Generated Trimethylsilyl Bromide

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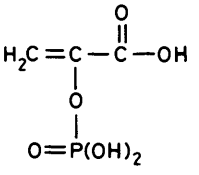
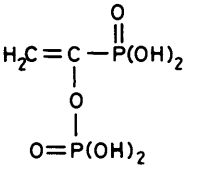
Phosphoenolpyruvate (PEP) has been synthesized from pyruvic acid and dimethyl trimethylsilyl phosphite in high yield by a new route which involves, successively, trimethylsilylation, bromination, and a Perkow reaction. A PEP analogue of 1-(dihydroxyphosphinyl)vinyl phosphate (1) has also been prepared.

PHOSPHOENOLPYRUVATE (PEP), a so-called high-energy phosphate compound, plays a vital role in enzymatic phosphate-transfer reactions involved in ATP synthesis. A number of preparative methods for PEP [2-10] and its homologues [11-14] have been reported. Here, we report a convenient method for the synthesis of PEP and its analogue (1).



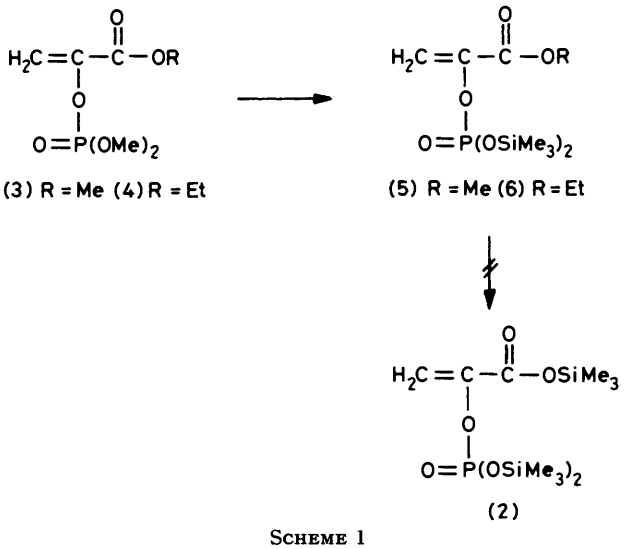
PEP



(1)

RESULTS AND DISCUSSION

The trimethylsilyl esters of carboxylic acids or phosphorus acids are hydrolysed by water or alcohols to give the corresponding free acids.[15-18] Further trimethylsilyl halides (Me_3SiX) have recently proved to be useful for the dealkylation of the alkyl esters of carboxylic acids,[19-23] phosphorus acids,[24-30] and related compounds.[31] We first attempted, therefore, the preparation of the tris(trimethylsilyl) ester (2) of PEP from trimethyl phosphoenolpyruvate (3) or dimethyl ethyl phosphoenolpyruvate (4). The dealkylations of compounds (3) and (4) with Me_3SiBr,[30] Me_3SiI,[28], Me_3SiCl–NaI,[32] or Me_3SiCl–LiI [33] however gave polymerized products or the disilyl esters (5) and (6) (Scheme 1).



(3) R = Me (4) R = Et

(5) R = Me (6) R = Et

(2)

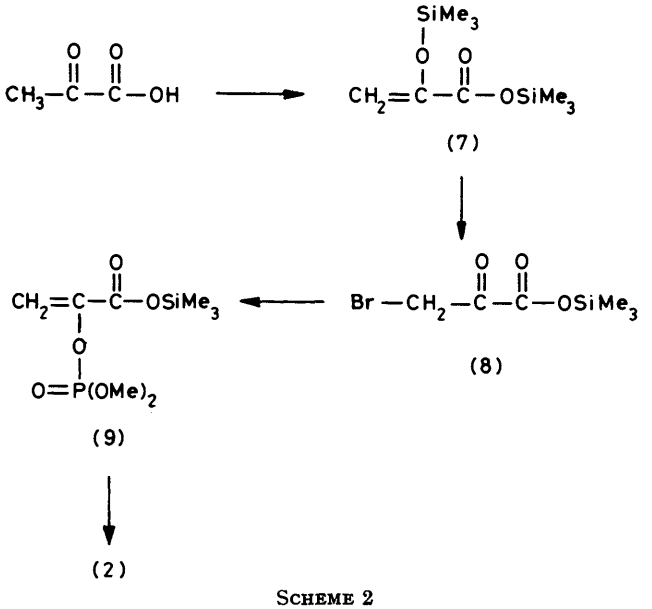
SCHEME 1

Therefore, we chose an alternative route (see Scheme 2) starting from pyruvic acid.

Initial attempts to convert pyruvic acid into trimethylsilyl 2-(trimethylsilyloxy)propenoate (7) by treatment with trimethylsilyl chloride and triethylamine under a variety of conditions resulted in a mixture of compound (7) and trimethylsilyl pyruvate, $MeCO{\cdot}CO{\cdot}OSiMe_3$ (10). 4-(Dimethylamino)pyridine (DMAP) as a catalyst was found, however, to be remarkably effective for the reaction and gave compound (7) in 80% yield.

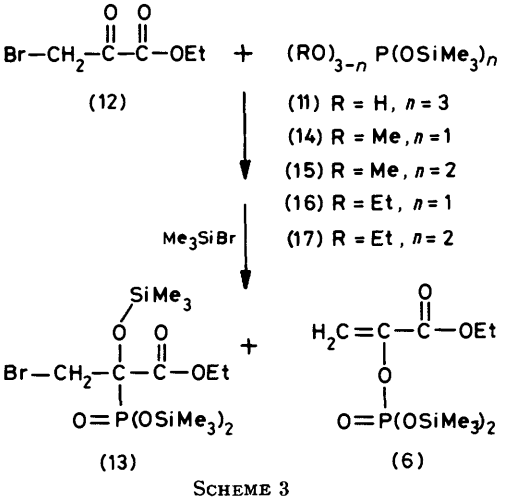
Bromination of compound (7) proceeded smoothly in methylene dichloride to give trimethylsilyl bromopyruvate (8) in 88% yield.[34] The latter reacted with trimethyl phosphite at room temperature, to give dimethyl trimethylsilyl phosphoenolpyruvate (9) in 90% yield. The conversion of compound (9) into (2) was achieved in 85% yield by the use of 2 equiv. of trimethylsilyl bromide at room temperature for 30 min.

In the Perkow reaction between compound (8) and trimethyl phosphite, 1 molar equiv. methyl bromide was eliminated; replacement of trimethyl phosphite in the reaction by a silyl phosphite having at least one trimethylsilyloxy-group gave, correspondingly, an equivalent of trimethylsilyl bromide. Since in the synthesis of compound (8) from compound (7) and bromine, 1 molar equiv. of trimethylsilyl bromide was also formed, we sought a more convenient synthesis of compound (2) not necessitating the external addition of trimethylsilyl bromide, *i.e.*, by utilising 2 molar equiv. of trimethylsilyl bromide, generated *in situ* from the bromination and the Perkow reaction. Tris(trimethylsilyl) phosphite (11) could not be used for our purpose since ethyl bromopyruvate (12) reacts with compound (11) to give a 1 : 1 carbonyl adduct (13) along with compound (6) [16c]. We therefore examined the reactions of other silyl phosphites (14)—(17) with compound (12). If the Perkow reaction gave only 1 equiv. of trimethylsilyl bromide, the alkyl esters of the initial Perkow reaction products would be converted into bis(trimethylsilyl) esters. The transesterifications, however, proceeded incompletely so that identification of the products was difficult. The reaction mixtures were, therefore, treated



SCHEME 2

with 2 molar equiv. of trimethylsilyl bromide and all the products were distilled and characterised as bis-(trimethylsilyl) esters (Scheme 3).



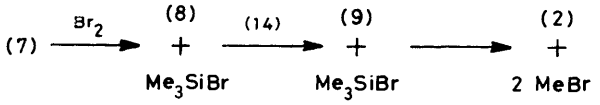
SCHEME 3

Reactions of compound (12) with $(RO)_{3-n}P(OSiMe_3)_n$ [a]

Phosphite	Yield (%) (6)	(13)
$P(OSiMe_3)_3$ [b]	36	31
$P(OSiMe_3)_2(OMe)$	61	8
$P(OSiMe_3)_2(OEt)$	57	20
$P(OSiMe_3)(OMe)_2$	71	0
$P(OSiMe_3)(OEt)_2$	75	0
$P(OMe)_3$	81	0
$P(OEt)_3$	91	0

[a] For the details of the reaction conditions see the Experimental section. [b] See ref. 16c.

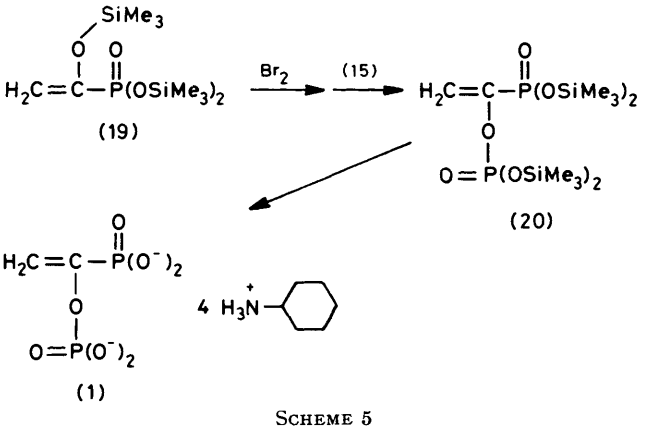
As shown in the Table, the reaction of compound (14) or (16) gave exclusively the desired enophosphate (6). Dimethyl trimethylsilyl phosphite (14) was the silyl phosphite of choice since the methyl group is more readily transesterified by the silyl bromide than the ethyl group. Consequently, the addition of compound (14) into the reaction mixture of (7) with bromine gave compound (2) in 90% yield (Scheme 4).



SCHEME 4

In view of the accessibility of alkaline metal salts as biological substrates, compound (2) was treated with 3 equiv. of sodium ethoxide in dry ethanol–diethyl ether to give the trisodium salt (18) of PEP as a white powder in almost quantitative yield.

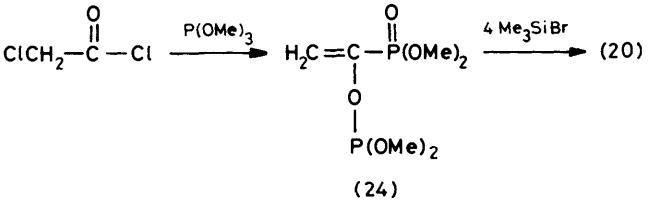
Synthesis of a PEP Analogue.—In a similar manner, an analogue (1) of PEP was synthesised as shown in Scheme 5. Three methods have been explored for the



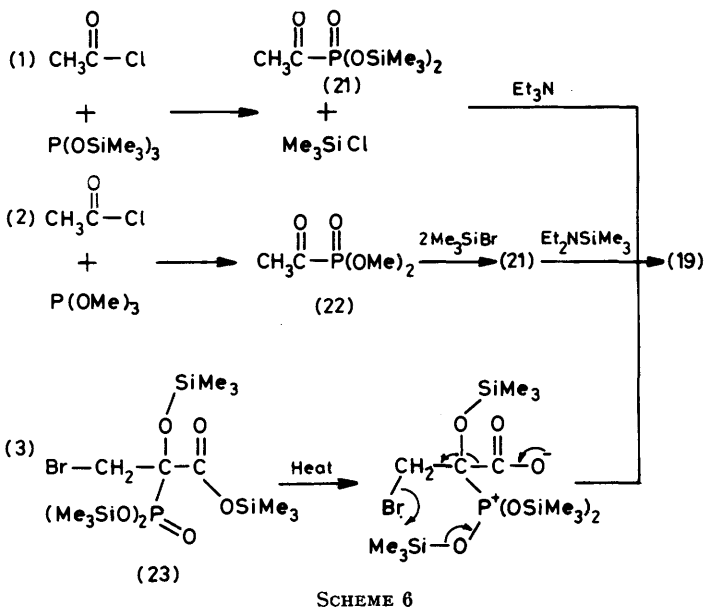
SCHEME 5

preparation of the key intermediate (19). They are illustrated in Scheme 6. In the first method, trimethylsilyl chloride, *in situ* generated from the Arbuzov reaction,[35] could be effectively utilised. The second method gave an excellent yield (89%) of compound (19). The third method involves a new type of decarboxylation, where a 1 : 1 carbonyl adduct (23) of compound (11) with compound (8) was used as the starting material.[36]

It was known that the tetraethyl ester of compound (1) was prepared by the reaction of chloroacetyl chloride with triethyl phosphite.[37] Therefore, the tetramethyl ester (24) of compound (1) was similarly prepared and



further converted by treatment with trimethylsilyl bromide into compound (20) in 88% yield. If the silyl



SCHEME 6

bromide became an accessible reagent, the latter method would be a more attractive route to (20) than the former methods.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded at 60 MHz on a Hitachi R-24B spectrometer with tetramethylsilane as internal reference. In the case of compounds having trimethylsilyl groups, a small amount of benzene was added to a sample tube and used as internal reference (δ 7.24). ^{31}P N.m.r. spectra were recorded on a JEOL PS-100 spectrometer at 40.50 Hz and referenced to 85% H_3PO_4. I.r. spectra were measured on a Hitachi 260-50 spectrophotometer.

Melting points and boiling points are uncorrected. Tetrahydrofuran (THF) was distilled over sodium hydroxide after being refluxed for 6 h, redistilled over sodium wire after being refluxed for 6 h, and finally purified by redistillation from sodium benzophenone ketyl. Benzene and hexane were distilled and stored over sodium wire. Trimethylsilyl chloride, a gift from the Chisso Co. Ltd., was purified by distillation from calcium hydride before use.

The following compounds were prepared by the literature procedure: ethyl bromopyruvate (42%), b.p. 80—85 °C/5 mmHg (lit.,[38] b.p. 83—88/8 mmHg); methyl bromopyruvate (43%), 55—69 °C/2 mmHg (lit.,[39] b.p. 82—84 °C/10 mmHg); compound (3) (80%), b.p. 101—104 °C/3 mmHg (lit.,[41] b.p. 60—64 °C/0.02 mmHg; compound (4) [40] (66%), 89—99 °C/0.2 mmHg); trimethylsilyl bromide (95%), b.p. 74—75 °C (lit.,[41] b.p. 77.3 °C/735 mmHg).

Trimethylsilyl 2-Trimethylsiloxypropenoate (7).—To a solution of pyruvic acid (purity 91%) (125.3 g, 1.42 mol) in dry benzene (1 l) were added DMAP (0.3 g, 2.5 mmol) and trimethylsilyl chloride (398 ml, 2.48 mol). Triethylamine (437 ml, 2.84 mol) was then added dropwise to the mixture, which was kept under gentle reflux by controlling the dropping rate. After the addition was complete, the mixture was refluxed for an additional 2 h. After cooling of the mixture, a white precipitate of triethylamine hydrochloride was filtered off *via* a glass filter under a stream of argon. The solvent was removed under reduced pressure, and the residue was distilled to afford compound (7) (240 g, 91%), b.p. 88—92 °C/26 mmHg (Found: C, 46.5; H, 8.5. $C_9H_{20}O_3Si_3$ requires C, 46.51; H, 8.65%); δ($CDCl_3$) 0.02 (9 H, s, Me_3Si), 0.29 (9 H, Me_3Si), 4.82 (1 H, s, CH_2=C), and 5.45 (1 H, s, CH_b=C); $\nu_{max.}$ (NaCl) 1 190, 1 258, 1 340, 1 620, 1 708, 2 900, and 2 960 cm^{-1}.

Trimethylsilyl Bromopyruvate (8).—To a solution of compound (7) (14.7 g, 63.1 mmol) in dry CH_2Cl_2 (15 ml) at −78 °C was added dropwise bromine (3.23 ml, 63.1 mmol) during a period of 10 min. After the addition was complete, the mixture was warmed to room temperature. The solvent was removed under reduced pressure and the residue was distilled to give compound (8) (13.3 g, 88%), b.p. 54—59 °C/2 mmHg (Found: C, 29.95; H, 4.6. $C_6H_{11}BrO_3Si$ requires C, 30.15; H, 4.65%), δ($CDCl_3$) 0.43 (9 H, s, Me_3Si) and 4.24 (2 H, s, CH_2).

Dimethyl Trimethylsilyl Phosphite (14).—Dimethyl phosphonate (29 g, 0.26 mmol) was mixed with hexamethyldisilazane (33.1 ml, 016 mol) and the mixture was heated to *ca.* 90 °C whereupon ammonia gas was evolved. After the mixture had been heated for 2 h, the evolution of ammonia gas ceased. The mixture was then distilled to afford compound (14) (42.8 g, 89%), b.p. 40—43 °C/15 mmHg (lit.,[42] b.p. 38 °C/10 mmHg); δ($CDCl_3$) 0.17 (9 H, s, Me_3Si) and 3.35 (6 H, d, *J* 10.4 Hz, CH_3O); ^{31}P n.m.r. δ −127.59 p.p.m. (lit.,[42] −126.2 p.p.m.).

Bis(trimethylsilyl) Methyl Phosphite (15).—To dimethyl phosphonate (20 ml, 0.20 mol) was added concentrated ammonium hydroxide (30 ml); an exothermic hydrolysis took place. The mixture was stirred at room temperature for 1 h and then concentrated to dryness. After repeated co-evaporation with dry pyridine (3 × 10 ml) and dry benzene (3 % 10 ml), the white residue was treated with hexamethyldisilazane (60 ml, 0.28 mol) under reflux for 4 h. Distillation of the reaction mixture gave compound (15) (27.8 g, 58%), b.p. 74—76 °C/20 mmHg; δ($CDCl_3$) 0.13 (18 H, s, Me_3Si), 3.30 (3 H, d, J_{PH} 8 Hz, CH_3O); ^{31}P n.m.r. δ −117 p.p.m. The elemental analysis of this compound was somewhat poor, indicating the presence of impurities. It was however used without further purification since its ^{31}N n.m.r. showed only a single peak.

General Procedure for the Reactions of Compound (12) *with* $(RO)_{3-n}P(OSiMe_3)_n$.—To a solution of compound (12) (3.87 g, 20 mmol) in dry benzene (40 ml) was added an appropriate phosphite (22 mmol). The solution was stirred at room temperature for 5 h. When compound (14) or (16) was used as the silyl phosphite, the mixture was further treated with trimethylsilyl bromide (6.12 g, 40 mmol) at room temperature for 3 h. In the case of compound (15) or (17), trimethylsilyl bromide (3.06 g, 20 mmol) was used. After removal of the solvent, distillation of the residue gave the product (see the Table).

Bis(trimethylsilyl) 1-(ethoxycarbonyl)vinyl phosphate (6). This had b.p. 112—120 °C/0.8 mmHg, δ(CCl_4) 0.33 (18 H, s, Me_3Si), 1.30 (3 H, t, *J* 8 Hz, CH_3C), 4.20 (2 H, q, *J* 8 Hz, CH_2O), 5.53 (1 H, m, CH_a=C), and 5.77 (1 H, m, CH_b=C).

Bis(trimethylsilyl) 1-ethoxycarbonyl-1-trimethylsilyloxy-2-bromoethylphosphonate (13). This had δ(CCl_4) 0.23 (9 H, s, Me_3Si), 0.30 (18 H, s, Me_3Si), 1.31 (3 H, t, *J* 7 Hz, CH_3C), 3.36 (2 H, d, *J* 5.5 Hz, CH_aCBr), 3.54 (2 H, d, *J* 5.5 Hz, CH_bCBr), 4.10 (2 H, m, CH_2O).

Bis(trimethylsilyl) 1-[(Trimethylsilyloxy)carbonyl]vinyl Phosphate (2).—Dry CH_2Cl_2 (20 ml) was placed in a 100-ml two-necked flask equipped with a dropping funnel and a serum cap, and compound (17) (12.2 g, 52.5 mmol) was added by a syringe at room temperature. To the solution was added dropwise bromine (2.7 ml, 52.5 mmol) in CH_2Cl_2 (10 ml) at −78 °C during a period of 70 min. After the addition was complete, the solution was warmed to 0 °C and compound (14) (8.45 g, 46.4 mmol) was added at 0 °C. After the exothermic reaction was over, the solvent was removed and the residue distilled to afford compound (2) (16.1 g, 90%), b.p. 112—116 °C/2.2 mmHg (Found: C, 37.25; H, 7.35. $C_3H_{29}O_6PSi_3$ requires C, 37.5; H, 7.6%); δ($CDCl_3$) 0.34 (18 H, s, Me_3Si), 0.37 (9 H, s, Me_3Si), 5.56 (1 H, dd, *J* 1.8 Hz, J_{P-H} 2.2 Hz, CH_a=C), 5.82 (1 H, dd, *J* 1.8 Hz, J_{P-H} 2.2 Hz, CH_b=C); ^{31}P n.m.r. δ +23.59 p.p.m.; $\nu_{max.}$ (NaCl) 1 265 ($\nu_{P=O}$), 1 640 ($\nu_{C=C}$), 1 733 ($\nu_{C=O}$), 2 900, and 2 970 cm^{-1}.

Dimethyl 1-[(Trimethylsilyloxy)carbonyl]vinyl Phosphate (9).—To a solution of compound (8) (4.42 g, 18.5 mmol) in dry benzene (37 ml) was added dropwise trimethyl phosphite (2.2 ml, 18.5 mmol) by a syringe at 0 °C. After being kept overnight at room temperature solvent was removed under reduced pressure from the mixture and the residue was distilled to afford compound (9) (3.98 g, 80%), b.p. 86—94 °C/0.4 mmHg (Found: C, 33.7; H, 6.05. $C_8H_{17}O_6PSi$ requires C, 35.82; H, 6.39%), δ($CDCl_3$) 0.40 (9 H, s, Me_3Si), 3.82 (6 H, d, *J* 11.4 Hz, CH_3O), and 5.57 (1 H, m, CH_b=C).

Preparation of Compound (2) *from Compound* (9).—Trimethylsilyl bromide (3.2 ml, 24.5 mmol) was added by a pipette at room temperature to compound (9) (3.29 g, 12.3 mmol); an immediate exothermic reaction occurred with evolution of methyl bromide. After 30 min, the mixture was distilled to afford compound (2) (4.0 g, 85%), 106—110 °C/0.7 mmHg.

Preparation of the Trisodium Salt of PEP.—To a solution of compound (2) (8.51 g, 22.1 mmol) in ether (200 ml) was added 2.3M-sodium ethoxide (28.8 ml) in ethanol. The precipitate was filtered off, washed with diethyl ether (3 × 10 ml), and dried *in vacuo* over P_4O_{10} to give the trisodium salt of PEP (5.02 g, 97%) which contained traces of ethanol and ether. The crude product (284 mg) was dissolved in water (10 ml) and the solution was rapidly evaporated under reduced pressure to afford an analytically pure sample of PEP·Na_3 (346 mg, 96%) (Found: C, 12.2; H, 2.8. $C_3H_2Na_3O_6P{\cdot}3H_2O$ requires C, 12.51; H, 2.80%); δ(D_2O/DSS) 5.13 (1 H, dd, *J* 0.8 Hz, J_{PH} 0.8 Hz, CH_a=C), and 5.32 (1 H, dd, *J* 0.8 Hz, J_{PH} 0.8 Hz, CH_b=C).

Bis(trimethylsilyl) 1-(Trimethylsilyloxy)vinyl Phosphonate (19).—*Method A.* To a solution of acetyl chloride (4.6 ml, 64.5 mmol) in CH_2Cl_2 (150 ml) at 0 °C was added compound (11) (18.5 g, 62 mmol). After the mixture had been stirred at room temperature for 1 h, triethylamine (9 ml, 64.5 mmol) was added; the solution immediately turned yellow. After the mixture had been stirred for 30 min, the precipitate was filtered off and the filtrate was concentrated. The residue was distilled to give compound (19) (13.2 g, 63%), b.p. 73—79 °C/0.8—0.9 mmHg.

Method B. To a solution of dimethyl acetylphosphonate (0.94 g, 6.17 mmol) in CH_2Cl_2 (5 ml) was added trimethylsilyl bromide (1.9 ml, 12.35 mmol); an exothermic reaction took place. After 2 h, the ^1H n.m.r. spectrum of the mixture showed that the dealkylation was complete. The solvent and the excess of reagent were removed under reduced pressure and the residue was allowed to react with diethyl(trimethylsilyl)amine (1.6 ml, 8.39 mmol) at room temperature overnight; after this it was heated under reflux for 30 min. The resulting solution was evaporated under reduced pressure at 50 °C for 1 h to afford compound (19) (1.86 g, 89%).

Method C. Compound (11) (16.5 g, 55.2 mmol) was added to compound (8) (13.2 g, 55.2 mmol) at 0 °C. The resulting mixture was warmed to room temperature and stirred at 50 °C for 1 h. The ^1H n.m.r. spectrum of the mixture showed that a mixture of compounds (23) and (2) was formed in the ratio of *ca.* 3 : 1. The mixture was heated at 150 °C for 1 h after which the ^1H n.m.r. spectrum of the mixture indicated the absence of compound (23) and the formation of compound (8). Distillation of the reaction mixture gave the latter (13.3 g, 71%), b.p. 74 °C/0.14 mmHg (Found: C, 33.65; H, 7.6. $C_{14}H_{38}O_7P_2Si_4$ requires C, 34.13; H, 7.77%); δ($CDCl_3$) 0.28 (9 H, s, Me_3Si), 0.32 (18 H, s, Me_3Si), 4.79 (1 H, dd, *J* 1.7 Hz, J_{PH} 37.8 Hz, CH_a=C), and 5.15 (1 H, dd, *J* 1.7 Hz, J_{PH} 10.8 Hz, CH_b=C); $\nu_{max.}$ (NaCl) 1 065, 1 290, 1 375, 1 440, 1 640, 1 740, 2 900, and 2 960 cm^{-1}.

Bis(trimethylsilyl) 1-[Bis(trimethylsilyloxy)phosphinyl]-vinyl Phosphate (20).—*Method A.* To a solution of compound (19) (9.32 g, 27.4 mmol) in CH_2Cl_2 (30 ml) at 0 °C was added dropwise bromine (1.4 ml, 27.4 mmol) in CH_2Cl_2 (5 ml) during a period of 15 min; the solution turned light yellow. After the solution had been stirred at room temperature for 1 h compound (14) (4.66 g, 25.6 mmol) was added and the mixture was continuously stirred for 5 h. The solvent was removed under reduced pressure and the residual oil was distilled to afford compound (20) (7.84 g, 62%), b.p. 130—131 °C/0.5—0.6 mmHg.

Method B. Trimethyl phosphite (46 ml, 0.39 mol) was slowly added to chloroacetyl chloride (22.14 g, 0.20 mol) in an ice-bath. After the addition was complete, the mixture was heated at 90 °C for 30 min. The resulting methyl chloride was removed under reduced pressure to give crude compound (20) (49.28 g, 97%). The latter (15.34 g, 59 mmol) was treated with trimethylsilyl bromide (32.3 ml, 0.24 mol) at 0 °C, after which the mixture was stirred at room temperature overnight. After the volatile compounds had been removed under reduced pressure, the residue was distilled to afford compound (24) (25.8 g, 89%), b.p. 118 °C/0.007 mmHg (Found: C, 33.65; H, 7.6. $C_{14}H_{38}O_7P_2Si_4$ requires C, 34.13; H, 7.77%); δ($CDCl_3$) 0.32 (36 H,

s, Me_3Si), 5.54 (1 H, ddd, J 2.4 Hz, J_{POCCH} 2.0 Hz, J_{PCCH} 11.6 Hz, CH_a=C), and 5.61 (1 H, dd, J 2.4 Hz, J_{PCCH} 36.2 Hz, CH_b=C); ^{31}P n.m.r. δ +10.98 (d, J_{PCOP} 37.9 Hz) and +24.05 (d, J_{PCOP} 37.9 Hz).

Preparation of Compound (1).—Compound (24) (1.866 g, 3.8 mmol) was added to a mixture of methanol (12 ml) and ether (50 ml). After 5 min, cyclohexylamine (1.74 ml, 15 mmol) was added to the solution to give a white precipitate which was filtered off, washed with ether (3 × 10 ml), and dried over NaOH to give the tetracyclohexylammonium salt of compound (1) (1.85 g, 81%), m.p. 174 °C (decomp.) (Found: C, 48.15; H, 8.3; N, 8.5. $C_{26}H_{58}N_4O_7P_2 \cdot 3H_2O$ requires C, 47.70; H, 9.85; N, 8.56%); δ(D_2O/DSS) 0.90—2.10 [40 H, m, $(CH_2)_5$], 3.00 (4 H, m, NCH), 4.76 (1 H, d, J 8 Hz, CH_a=C), and 5.01 (1 H, dd, J 16 Hz, J 26 Hz, CH_b=C).

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