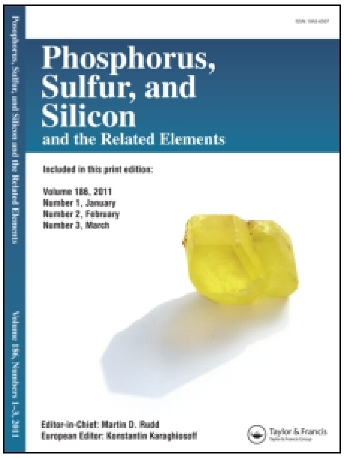

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PHOSPHONIC SYSTEMS. PART 10. SYNTHESIS OF 2-HYDROXYALKYLPHOSPHONIC DIAMIDES *VIA* OPENING OF EPOXIDES WITH DIAMIDOPHOSPHITE ANIONS

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PHOSPHONIC SYSTEMS. PART 10. SYNTHESIS OF 2-HYDROXYALKYLPHOSPHONIC DIAMIDES *VIA* OPENING OF EPOXIDES WITH DIAMIDOPHOSPHITE ANIONS

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Lithiated bis-dialkylamidophosphites react with mono- and 1,2-disubstituted epoxides yielding 2-hydroxyalkylphosphonic diamides. Conformational analysis of the products revealed strong intramolecular attraction between the 2-hydroxy group and the $P(O)(NR_2)_2$ function. Reaction of a lithiated optically active bis-dialkylamidophosphite with 1,2-epoxybutane gave the corresponding product with poor (2:1) diastereoselectivity, but opened a potential route to the optically active 2-substituted alkylphosphonic acids.

Key words: Bis-dialkylamidophosphites as nucleophiles; 2-hydroxyalkylphosphonic diamides; asymmetric induction in opening of epoxides.

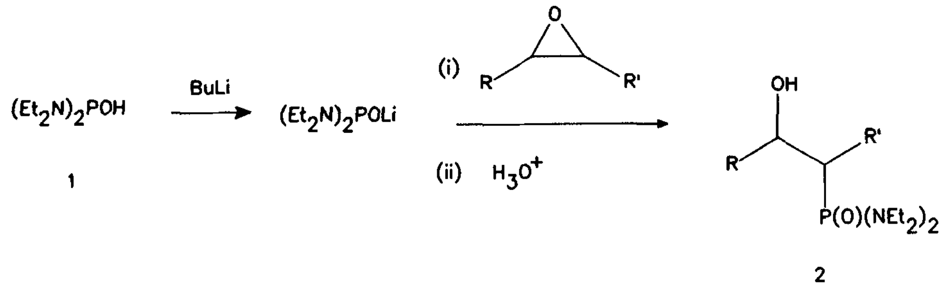
INTRODUCTION

The ability of phosphines to open an epoxide ring was employed in early work on the mechanism of the Wittig reaction,[1] and used in the *cis/trans* isomerization of alkenes.[2] The opening by sodium salts of dialkylphosphites, leading to the 2-hydroxyalkylphosphonic esters, was reported to be a slow reaction.[3] Corey and Cane[4] reported that anions derived from bis-dialkylamidophosphorous acid (bis-dialkylamidophosphite anions) react with epoxides affording (albeit in poor yields) the corresponding 2-hydroxyalkylphosphonic diamides, used as precursors for alkenes. We have found that the same type of nucleophile, lithium bis-diethylamidophosphite, $(Et_2N)_2POLi$ (**1**) reacts easily with haloalkanes, offering a general route to alkylphosphonic diamides.[5] Recently, Spilling *et al.* extended the application of reagents of the type **1** by studying their reaction with aldehydes which leads to 1-hydroxyalkylphosphonic products.[6]

In continuation of our interest in the preparation and reactivity of phosphonic systems, we report here our results of the reaction between lithiated bis-dialkylamidophosphites and mono- or 1,2-disubstituted epoxides.

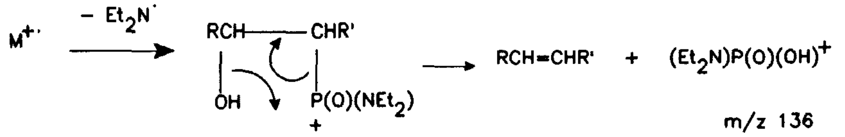
RESULTS AND DISCUSSION

Reaction of **1** with a series of epoxides led, as expected, to the formation of the corresponding 2-hydroxyalkylphosphonic diamides **2** (Equation 1).



(1)

For the monosubstituted epoxides ($R' = H$) reaction occurred with full regioselectivity; the phosphorus nucleophile always attacking the less hindered carbon, in accord with the known[7] S_N2 reactivity of epoxides. The high nucleophilicity of the anion of **1** was demonstrated by the mild conditions (about two hours at room temperature) required for the full conversion of the monosubstituted epoxides into products **2**. 1,2-Disubstituted substrates ($R' \neq H$) were much less reactive, and heating the reaction mixture in THF under reflux was necessary in order to achieve satisfactory conversions. With exo-2,3-epoxynorbornane as a substrate, no reaction was observed after heating under reflux for 24 hours; this result obviously reflects the high steric requirements of the bulky nucleophile **1**. Trans-stereoselectivity of the opening of the disubstituted epoxides was complete, and NMR spectroscopy (^{31}P, ^{1}H) demonstrated that only a single diastereoisomeric pair of enantiomers was formed in each case. Because of the known[8] thermal instability of 2-hydroxyalkylphosphonic amides, some of the products could not be purified by distillation. Since in products **2d** and **2e** *syn* orientation of the $P(O)(NEt_2)_2$ and OH groups, necessary for the thermal fragmentation, is not possible, these compounds should be thermally stable. **2d** and **2e** were, indeed distilled (bulb-to-bulb) without any decomposition; their purity was not, however, significantly higher than that of the undistilled products. Structure of products **2** was confirmed by NMR spectroscopy (^{31}P, ^{1}H, ^{13}C) and mass spectrometry. Although not all products gave molecular ion peaks in the mass spectra, the peak corresponding to the $[M^{+\cdot} - Et_2N^{\cdot}]$ fragment was always present. All products gave common fragments, such as $(Et_2N)_2PO^+$ (m/z 191), Et_2N^+ (m/z 72), $(Et_2N)P(O)H^+$ (m/z 120), and $(Et_2N)P(O)(OH)^+$ (m/z 136). The latter ion results from an interesting fragmentation involving 1,2-elimination of the amidophosphoric acid-derived species, reminiscent of the alkene-forming step in the Horner-Wittig reaction[9] (Equation 2).



(2)

The chirality of C-2 (and, in **2d**–**2g**, of C-1) in products **2** introduced diastereotopicity of several nuclei of the phosphonate skeleton and the NEt_2 groups, and that non-equivalence was clearly demonstrated in the ^{1}H and ^{13}C NMR spectra of all products. The results of the reaction represented by Equation 1 are given in Table I.

In our recent conformational analysis of 2-substituted alkylphosphonic esters,[10] we demonstrated that strong, intramolecular attractive interactions between the $P(O)(OR)_2$ and the OH (or OMe) groups play an important role in determining the distribution of individual conformers in solution. We have now carried out similar analysis for compounds **2**, in order to compare intramolecular interactions operating in the phosphonic amide and ester systems. In compounds **2a**–**2c** each of the diastereotopic protons of the α-methylene group forms an ABX system, and gives rise to a *ddd* pattern with ${}^{2}J_{HP}$, ${}^{2}J_{HH}$, and ${}^{3}J_{HH}$ coupling constants. The latter (vicinal) coupling constants were used in the conformational analysis carried out with respect to the rotation about the C_α—C_β bond. The three staggered confor-

TABLE I

N,N,N′,N′-Tetraethyl 2-hydroxyalkylphosphonodiamidates **2**

2	R	R′	Yield (%)	$\delta_P{}^a$	$\delta_H{}^a$ (J, Hz)	$\delta_C{}^a$ (J, Hz)	MS (m/z, %)
a	$PhCH_2$	H	79[b]	38.3	0.78(t,7.1)	13.5, 13.9	326(M^+,4)
					0.94(t,7.1)	31.5(d,114)	254(20)
					1.68(ddd,	38.1(d,4.6)	235(49)
					J_{gem} 14.9,	44.2(d,17.1)	191(100)
					J_{HP} 12.9,	67.7(d,3.7)	120(14)
					J_{BC} 2.0, H_B)	126.0,127.9	91(13)
					1.78(ddd,	129.0,137.6	72(23)
					J_{gem} 14.8,		
					J_{HP} 12.0,		
					J_{AC} 10.0, H_A)		
					2.48-2.97(m)		
					4.00(m, H_C)		
					5.31(br s)		
					7.01-7.25(m)		
b	Ph	H	99[c]	37.5	1.05(t,7.1)	14.2	240(5)
					1.14(t,7.1)	36.0(d,111)	191(15)
					1.91(ddd,	38.4(d,3.7)	136(34)
					J_{gem} 14.5,	38.6(d,4.4)	120(28)
					J_{HP} 12.3,	68.8(d,3.5)	105(53)
					J_{BC} 1.8, H_B)	125.3,127.2	72(100)
					2.13(ddd,	128.3,144.4	

TABLE I (*Continued*)

					J_{gem} 14.9,		
					J_{HP} 11.1,		
					J_{AC} 11.0, H_A)		
					2.90-3.17(m)		
					4.98(m, H_C)		
					5.68(br s)		
					7.20-7.37(m)		
c	Et	H	65[d]	38.6	0.83(t,7.4)	9.6, 14.1	264(M^+,5)
					0.99(t,7.1)	31.1(d,17.4)	235(21)
					1.00(t,7.0)	32.2(d,114)	192(86)
					1.25-1.80(m)	38.4	191(88)
					2.75-3.10(m)	67.6(d,4.6)	136(100)
					3.73(m)		120(55)
					5.03(br s)		72(95)
d	$(CH_2)_4$		76[e]	42.6	1.07(t,7.1)	13.3(d,3.6)	218(26)
					1.09(t,7.1)	13.8(d,1.1)	191(70)
					1.00-2.1(m)	24.1	136(67)
					2.90-3.10(m)	25.1(d,4.0)	120(100)
					3.65(m)	25.5(d,13.8)	72(70)
					6.19(br s)	34.9(d,14.0)	
						37.5(d,1.7)	
						38.7(d,3.3)	
						43.6(d,114)	
						68.7(d,4.7)	
e	$(CH_2)_3$		62[f]	40.6	1.04(t,7.0)	13.9(d,2.7)	204(10)
					1.07(t,7.0)	14.1	191(28)
					1.50-2.20(m)	22.2(d,10.6)	136(25)
					2.90-3.20(m)	25.2	120(51)
					4.20(m)	34.4(d,12.8)	72(100)
					5.41(br s)	38.0(d,3.9)	
						38.6(d,3.7)	
						44.9(d,119)	
						74.1	

TABLE I (*Continued*)

f	Me (RR/SS)	Me	50[g]	44.2	1.00(dd,16.6, 7.4) 1.10(t,7.8) 1.13(t,7.8) 1.21(d,6.1) 2.03(ddq,12.1, 9.1,7.4) 2.96-3.20(m) 3.87(m) 6.00(br s)	11.7(d,4.7) 13.6(d,4.1) 14.2(d,1.9) 21.4(d,15.2) 37.9(d,2.8) 39.1(d,4.1) 39.3(d,114) 67.7(d,4.0)	192(12) 191(35) 136(30) 120(42) 72(100)
g	Me (RS/SR)	Me	56[h]	42.2	1.00-1.08(m) 1.12(d,6.3) 1.82(ddq,12.4, 7.2,1.0) 2.84-3.08(m) 4.18(m) 4.63(br s)	5.6(d,1.4) 14.0, 14.2 20.2(d,15.4) 34.5(d,112) 38.6(d,3.3) 38.8(d,4.0) 64.9(d,3.4)	192(44) 191(65) 136(100) 120(91) 72(99)

[a] In $CDCl_3$; [b] oil, n_D^{25} 1.5072; [c] oil, n_D^{22} 1.5133; [d] oil, n_D^{27} 1.4658; [e] oil, distilled bulb-to bulb (oven temp 232-233°C/0.5 mm Hg), n_D^{17} 1.4923; [f] oil, distilled bulb-to-bulb (oven temp 200-210°C/0.5 mm Hg), n_D^{17} 1.4901; [g] white solid, mp 75-77°C; [h] oil, n_D^{17} 1.4769.

mations of phosphonoamidates **2** are shown in Figure 1. The observed $^3J_{HH}$ (H_A/H_C and H_B/H_C) coupling constants are related to the populations (x_1, x_2, x_3) and the calculated vicinal coupling constants of the individual rotamers according to Equation 3.

$$\begin{aligned} ^3J_{(AC)} &= x_1{}^3J_{AC}(X_1) + x_2{}^3J_{AC}(X_2) + x_3{}^3J_{AC}(X_3) \\ ^3J_{(BC)} &= x_1{}^3J_{BC}(X_1) + x_2{}^3J_{BC}(X_2) + x_3{}^3J_{BC}(X_3) \end{aligned} \tag{3}$$

In Equation 3 terms $^3J_{AC}(X_i)$ and $^3J_{BC}(X_i)$ refer to the vicinal coupling constants between protons A/C (and B/C) in a given rotamer X_i. Calculation of the individual vicinal coupling constants according to the approach of Haasnoot *et al.*[11] and using the available group electronegativities[12] allowed us to estimate the population of the conformations of compounds **2a** and **2b** in solution. In **2c** strong overlap of the signals of protons A, B, and C with other signals precluded accurate determination of coupling constants. The populations of three rotamers calculated for **2a** and **2b**,

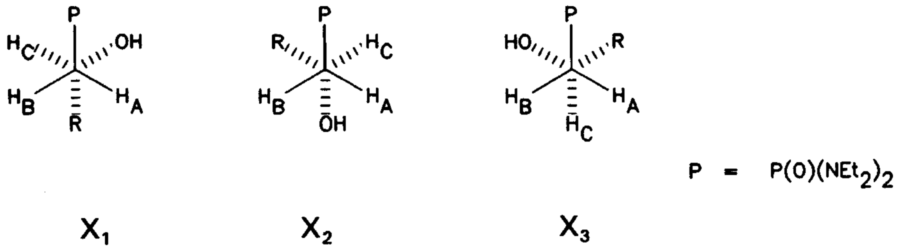


FIGURE 1 Staggered conformations of **2a–2c**.

TABLE II

Populations of rotamers (%) of 2-hydroxyalkylphosphonic diamides **2** and diesters, R—CH$_c$(OH)—CH$_A$H$_B$—P(O)X$_2$ (X = NEt$_2$ or OMe) in CDCl$_3$ at 30°C

R	P(O)X$_2$	X_1	X_2	X_3
PhCH$_2$	P(O)(NEt$_2$)$_2$	82	0	18
	P(O)(OMe)$_2$	54	24	22
Ph	P(O)(NEt$_2$)$_2$	93	0	7
	P(O)(OMe)$_2$	83	5	12

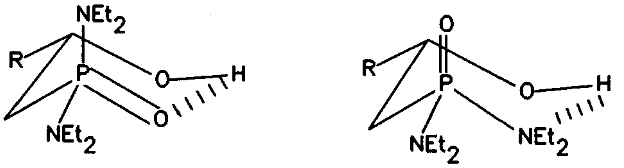
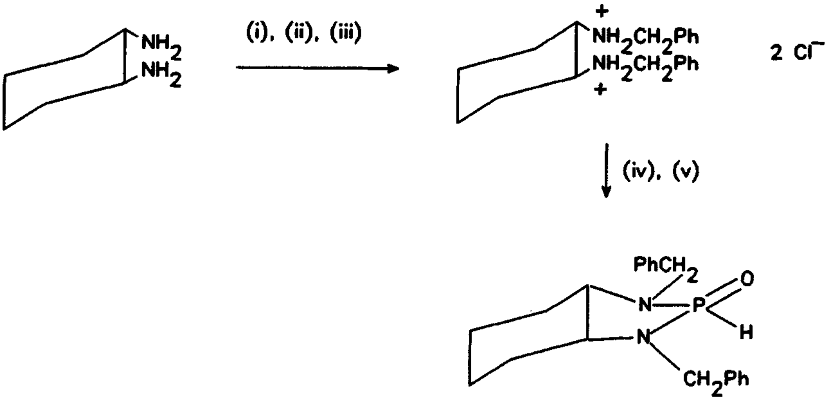


FIGURE 2 Intramolecular hydrogen bonding in phosphonodiamidates **2**.

together with the corresponding values obtained earlier for the dimethyl esters of the same phosphonic acids,[10] are given in Table II. It is obvious that the conformational preferences are much stronger for the diamidates **2** than for the analogous esters. For system **2** the population of the rotamer X_1 is greatly increased, and the rotamer involving the *trans* orientation of the P(O)(NEt$_2$)$_2$ and the OH groups (X_2) is virtually non-populated. The result can be best interpreted in terms of strong intramolecular hydrogen bonding between these two groups; stronger than the corresponding interactions involving the ester function, P(O)(OMe)$_2$. The IR spectrum of **2a** recorded as a dilute solution in CCl$_4$, revealed the OH stretching band at 3363 cm^{-1}, typical of a hydrogen-bonded hydroxyl group.[13] Intramolecular attraction in compounds **2** can involve both, the phosphoryl group, and the nitrogen atom of the NEt$_2$ group as hydrogen bond acceptor centres; these two possibilities are presented for the rotamer X_1 in Figure 2. The obvious consequence of the hydrogen bonding represented in Figure 2 is the large difference of the chemical shifts of the signals of the diastereotopic NEt_2 groups in the molecule of **2** observed in the respective ^1H NMR spectra.

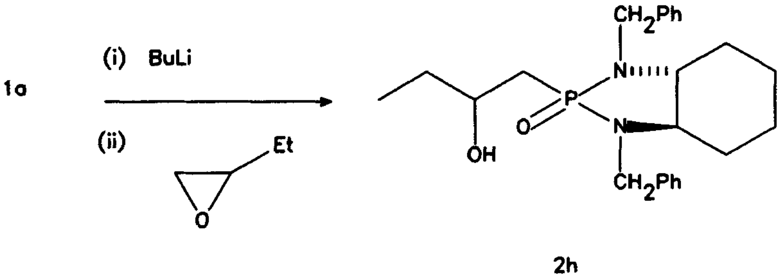
Changing the bis-diethylamidophosphite **1** to a substrate derived from a chiral diamine should produce a chiral auxiliary that would be expected to introduce stereoselectivity into the epoxide ring opening (Equation 1). Koeller and Spilling prepared this type of amidophosphites,[14] and showed that the reactions of the corresponding anions with aldehydes proceeds with modest diastereoselectivity.[6] We have prepared the reagent **1a**, derived from the S,S stereoisomer of *trans*-diaminocyclohexane following Spilling's procedure[14] (Equation 4), and, after lithiation, reacted the corresponding anion with 1,2-epoxybutane (Equation 5).



1a

(4)

(i) PhCHO; (ii) NaBH$_4$; (iii) HCl; (iv) Et$_3$N/PCl$_3$; (v) H$_2$O



2h

(5)

Product **2h** was formed as a mixture of two diastereomers (δ_P 44.1; 43.2), but their ratio was only 2:1, indicating rather poor asymmetric induction of the chiral auxiliary in the approach of the nucleophile to the epoxide ring. The diastereomeric mixture was then hydrolyzed (dil. aq. HCl) to the corresponding free 2-hydroxybutylphosphonic acid, $CH_3CH_2CH(OH)CH_2PO_3H_2$. As expected, the product showed only a single signal in the ^{31}P NMR spectrum, and its spectral characteristics were identical to that obtained for the same phosphonic acid prepared by the hydrolysis

of the analogous bis-diethyldiamide 2c. The reaction of epoxides with chiral anions of diamidophosphites can therefore serve in principle as a route to optically active 2-hydroxyalkylphosphonic acids.

EXPERIMENTAL

Solvents and commercially available substrates were purified and dried by standard methods immediately before use. All reactions that required inert atmosphere were carried out under dry nitrogen. n-Butyl lithium was used as 1.6 M solution in hexane. Bulb to bulb distillation was carried out using a Buchi GKR-50 apparatus. NMR spectra were recorded on a Bruker AC 300 MHz spectrometer for solutions in $CDCl_3$, and the chemical shift values are given relative to $SiMe_4$ (^1H, ^{13}C) and 85% phosphoric acid (^{31}P). Mass spectra were recorded on a Varian MAT-212 double-focusing direct-inlet spectrometer at a ionization potential of 70 eV. Only the values for selected ions (and their relative abundances), most relevant to structural determinations, are given. 1,2-Epoxy-3-phenylpropane was prepared by oxidation of allylbenzene with MCPBA in benzene. 64%; bp 50–54°C/0.6 mm Hg; n_D^{22} 1.5257 (lit.[15] n_D 1.5262). (S,S) Trans-1,2-diaminocyclohexane was obtained by resolution of a racemic material with (+)-tartaric acid, following the literature procedure.[16] [(−)$C_6H_{16}N_2$(+)tart]; dec > 230°C; $[\alpha]_D^{21}$ + 11.0 (1% aq. solution). (1S,2S)-*N*,*N'*-dibenzylcyclohexyl-1,2-diammoniumdichloride was prepared from the tartrate salt, benzaldehyde and sodium borohydride.[17] 48%; mp 209–212°C; $[\alpha]_D^{25}$ +48 (1% aq. solution). $\delta_H(D_2O)$ 1.32–1.48 (2H, m), 1.55–1.88 (4H, m), 2.25–2.40 (2H, m), 3.40–3.52 (2H, m), 4.13 (2H, d, J 13.0 Hz, CH_2 of CH_2Ph), 4.35 (2H, d, J 13.0 Hz, CH_2 of CH_2Ph), 7.36–7.53 (10H, m, 2 × Ph).

The product was then converted into **1a** by reaction with PCl_3 in the presence of triethylamine, followed by hydrolysis.[17] Yellow powder (72%). δ_P 20.8. δ_H 1.04–1.24 (4H, m), 1.59–1.91 (4H, m), 2.91–3.09 (2H, m), 4.01–4.23 (4H, m, 2 × CH_2 of CH_2Ph), 7.50 (1H, d, J_{HP} 600 Hz, P-H), 7.20–7.46 (10H, m, 2 × Ph).

Bis-diethyldiamidophosphite **1** *was prepared as described before.*[18]

Reaction of **1** *with monosubstituted epoxides. General procedure.* A solution of **1** in THF (0.5 mL/mmol) was cooled to −94°C and a solution of butyl lithium (1 mol equiv.) was added dropwise and the stirring was continued at −94°C for 20 min. The required epoxide (0.95 mol equiv.) was added and the mixture was allowed to warm up to ambient temperature over the period of 2 h. A diluted aqueous solution of ammonium chloride was added, and the mixture was extracted several times with ether. After drying ($MgSO_4$), filtration and evaporation, crude products **2** were obtained as pale-yellow oils.

Reaction of **1** *with 1,2-disubstituted epoxides. General procedure.* The reaction was carried out as above, but after warming up the mixture to ambient temperature, the solution was heated under reflux before the aqueous work-up. The duration of the heating was: **2d** (2h); **2e** (6h); **2f** (6h); **2g** (22h).

Reaction of **1a** *with 1,2-epoxybutane.* A solution of **1a** (1.0 g, 2.9 mmol) in THF (10 mL) was cooled to −94°C and BuLi (1.9 mL, 3.0 mmol) was added. Stirring was continued for 20 min and 1,2-epoxybutane (0.76 mL, 8.8 mmol) was added. After 10 min the cooling bath was removed, and after a further 20 min the mixture was heated under reflux for 1 h. After the usual aqueous work-up and extraction, **2h** was obtained as a yellow oil (71%). δ_P 44.1, 43.2 (2:1). δ_H 0.80 (3H, m, ω-Me), 1.05–1.25 (4H, m), 1.30–1.90 (6H, m), 2.13 (1H, m) and 2.33 (1H, m) (P-CH_2), 2.86 (1H, br s, OH), 2.95–3.12 (2H, m), 3.60–4.05 (4H, m, 2 × CH_2 of CH_2Ph), 4.40 (1H, m, β-CH), 7.10–7.30 (10H, m, 2 × Ph).

Sodium 2-hydroxybutylphosphonate. Diamide **2c** (0.5 g, 1.9 mmol) was incubated in water (10 mL) containing conc. HCl (2 mL) at room temperature for 16 h. The pH of the solution was adjusted to 7 with Na_2CO_3 and water was removed under reduced pressure. The solid residue was heated under reflux in ethanol, filtered hot, and the filtrate was poured into a large volume of ether. Pure product was obtained as white powder (9%). δ_P (D_2O) 22.7. δ_H 0.88 (3H, t, J 7.4 Hz, ω-Me), 1.38–1.90 (4H, overlapping m, α-CH_2 and γ-CH_2), 3.76–3.91 (1H, m, β-CH).

Hydrolysis of **2h**. **2h** was hydrolyzed in the same manner as above, yielding the sodium salt which gave the NMR (^{31}P and ^1H) spectra identical to those obtained for the product prepared from **2c**.

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