O-Alkyl Diol *O*-, *S*- and *Se*-Phosphoroamidates of DL-α-Tocopherol and Their Dimethylaminoalkyl Derivatives as Diester and Triester Models of Phospholipids

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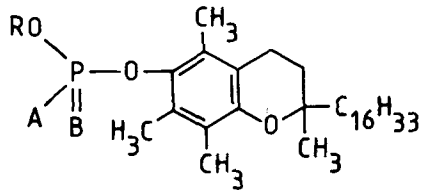
Hexamethyltriamide of phosphorous acid, activated by addition of iodine at an optimal molar ratio of 1.05:0.05, was used as a phosphorylating reagent to synthesize 1-hexadecyloxyethyl-2-*O*-, 1-hexadecyloxypropyl-3-*O*-, and 1-hexadecyloxybutyl-4-*O*-(DL-α-tocopheryl-6-*O*)-(*N*,*N*-dimethylamido)selenophosphate, -thiophosphate and -phosphate derivatives, and some of their 2-dimethyl-aminoethyl-1-*O*-, and 3-dimethylaminopropyl-1-*O*-triester analogues in a "one-pot procedure" in overall yields of 69–87%. Activation of the reaction with an equimolar mixture of imidazole and carbon disulfide at the triester formation step permits selective phosphorylation at room temperature. The compounds synthesized represent new diester and triester models containing alkyl ether diolphospholipid structures. *Lipids 28,* 351–354 (1993).



1ad0; 1bdS; 1cdSe; 1adeS; 1cdgSe

FIG. 1. For 1adO: R = 1-Hexadecyloxyethyl-; A = $N(CH_3)_2$; B = O; 1bdS: R = 1-hexadecyloxypropyl-; A = $N(CH_3)_2$; B = S; 1cdSe: R = 1-hexadecyloxybutyl-; A = $N(CH_3)_2$; B = Se; 1adeS: R = 1-hexadecyloxyethyl-; A = 2-dimethylaminoethyl-*O*-; B = S; 1cdgSe: R = 1-hexadecyloxybutyl-; A = 3-dimethylamino-1-propyl-*O*-; B = Se.

O-Alkyl diolphospholipids and polar lipids containing phosphate triester linkages are important mediators of a variety of biological activities (1–4). Diester types of naturally occurring and of model alkyl ether diolphospholipids have been obtained synthetically to elucidate their chemical and pharmacological properties (4–7). Triester derivatives, or thio- and selenophosphate analogues of alkyl ether diolphospholipids have not been reported to date. Thiophosphate model analogues of other naturally occurring phospholipids, however, are now well recognized as advantageous probes in biochemical and membrane studies (8,9).

Further developments in diolphospholipid research will be stimulated by the design of novel chemical structures that include (in addition to a diol moiety) a membrane active lipid (steroid, tocopherol, etc.) joined *via* a phosphate bridge. This new and challenging approach is expected to contribute to progress in biochemistry, pharmacology and membrane science (10,11).

In the present paper we describe the synthesis of alkyl esters of diol *O*-, *S*- and *Se*-phosphoroamidates of DL-α-tocopherol and some of their dimethylaminoalkyl triester analogues (Fig. 1). These compounds represent model types of ether diolphospholipids that have not been reported previously.

MATERIALS AND METHODS

The tris(*N*,*N*-dimethyl)amide of phosphorous acid (1) was prepared as described by Burg and Slota (12). 1-Hexadecyloxyethan-2-ol (a), 1-hexadecyloxy-propan-3-ol (b) and 1-hexadecyloxybutan-4-ol (c) were synthesized as described by Tsushima *et al.* (4). DL-α-Tocopherol (d), 2-dimethylaminoethanol (e), 1-dimethylamino-2-propanol (f) and 3-dimethylamino-1-propanol (g) (Fluka, Buchs, Switzerland; and Merck, Darmstadt, Germany) had a purity of more than 98%. All other reagents were purchased from Janssen (Stockholm, Sweden) and were better than 98% pure. Benzene (Merck) was dried over sodium and freshly distilled prior to use. Reaction conditions were kept strictly anhydrous.

Analytical thin-layer chromatography (TLC) on precoated aluminum sheets of Silica Gel 60 F_{254} (Merck) was routinely used for monitoring reactions. High-performance liquid chromatography (HPLC) was done (Gilson 305 System, equipped with a Gilson 131 refractive index detector; Medical Electronics, Middleton, WI) using a Polygosil 60-7 silica gel column (Scandinaviska Genetik AB, Sweden; 250 × 10 mm). Chloroform (System A), *n*-hexane/diethyl ether (20:80, vol/vol; System B), *n*-heptane/ethyl acetate (80:20, vol/vol; System C) and chloroform/methanol (90:10, vol/vol; System D) were used as mobile phases.

^{13}C Nuclear magnetic resonance (NMR) spectra were recorded on a Varian (Palo Alto, CA) XL-300 spectrometer at 75.43 MHz. ^{13}C Chemical shifts are reported in ppm relative to tetramethylsilane (TMS). ^{31}P NMR spectra were recorded on the same instrument at 121.42 MHz. ^{31}P Chemical shifts are reported in ppm relative to 85% phosphoric acid (external) where a positive sign is downfield from the standard. All ^{13}C and ^{31}P NMR data given refer to proton decoupled spectra. Infrared (IR) spectra were recorded on a Perkin-Elmer (Beaconsfield, England) FT-IR 1750 spectrometer. Peak positions are reported in cm^{-1}. Satisfactory microanalyses were obtained for **1adO, 1bdS, 1cdSe, 1adeS,** and **1cdgSe:** C, ±0.21; H, ±0.11; N, ±0.08; P, ±0.10; S, ±0.10.

1-Hexadecyloxyethyl-2-O-(DL-α-tocopheryl-6-O)-(N,N-dimethylamido)phosphate, ***1adO.*** *Representative proce-*

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Abbreviations: HPLC, high-performance liquid chromatography; IR, infrared; NMR, nuclear magnetic resonance; TLC, thin-layer chromatography; TMS, tetramethylsilane.

dure. A mixture of iodine (0.025 g, 0.1 mmol) and the *tris* (*N,N*-dimethyl)amide of phosphorous acid (**1**; 0.343 g, 2.1 mmol) in benzene (50 mL) was heated at 70°C in a stream of argon for about 15 min until the precipitate dissolved. 1-Hexadecyloxyethan-2-ol (**a**; 0.576 g, 2.0 mmol) was added and the mixture was kept under these conditions for 5 min. Then DL-α-tocopherol (**d**; 0.861 g, 2.0 mmol) was added and the reaction mixture was heated at 70°C for 2 h. The resultant diester phosphite **1ad** was transformed to the phosphate **1adO** by reaction with benzoyl peroxide (with 20% water) (0.636 g, 2.1 mmol) at room temperature (20–25°C) for 10 min. The solvent was removed under vacuum, and the compounds was isolated by HPLC (System C) in pure form. Yield of **1adO**: 1.40 g (87%); $n_D^{40} = 1.4787$; R_f (System A), 0.11; Anal. Calcd. for $C_{49}H_{92}NO_5P$ (806.4): C, 72.98; H, 11.52; N, 1.74; P, 3.84. Found: C, 72.77; H, 11.60; N, 1.80; P, 3.90. ^{13}C NMR ($CDCl_3$) 1-hexadecyloxyethyl-2-*O*-fragment: δ 11.9 ppm (C-16); 23.9 (C-15); 26.1 (C-2); 29.4–29.7 (*m*, C-5 to C-13); 31.9 (C-14); 65.4 (*d*, $CH_2\underline{C}H_2OP$, $J = 6$ Hz); 69.7 (*d*, $\underline{C}H_2CH_2OP$, $J = 8$ Hz); 71.4 (C-1); DL-α-tocopheryl-6-*O*-fragment: 13.0 (5-CH_3); 13.9 (7-CH_3); 14.1 (8-CH_3); 20.8 (C-4); 21.0 (C-3); 23.8 (2-CH_3); 74.8 (C-2); 140.9 (*d*, C-6, $J = 9$ Hz); 148.4 (C-9) (nucleus); 19.6 (C-13, 12-CH_3); 22.6, 22.7 (4-CH_3, 8-CH_3) (chain); 36.9 (*m*, CH_3N). ^{31}P NMR ($CDCL_3$) δ 7.9 ppm (*s*). IR (KBr, film) ν 1245, 836 (PO-C, P-OC_{aryl}); 1191 (P = O); 1050, 791 (PO-C, P-OC); 735 cm^{-1} (P-N).

1-Hexadecyloxypropyl-3-O-(DL-α-tocopheryl-6-O)-(N,N-dimethylamido)thiophosphate ***1bdS.*** The intermediate **1bd** was prepared using 1-hexadecyloxypropan-3-ol (**b**, 0.601 g, 2.0 mmol) and DL-α-tocopherol (**d**, 0.861 g, 2.0 mmol) as described for **1adO.** Transformation to the thiophosphate **1bdS** was accomplished by reaction with sulfur (0.067 g, 2.1 mmol) at 70°C for 3 min. The derivative was isolated by HPLC (System C) as described for **1adO.** Yield of **1bdS**: 1.41 g (84%); $n_D^{40} = 1.4909$; R_f (System A), 0.66; Anal. Calcd. for $C_{50}H_{94}NO_4PS$ (836.5): C, 71.78; H, 11.35; N, 1.67; P, 3.71; S, 3.83. Found: C, 71.85; H, 11.24; N, 1.67; P, 3.66; S, 3.93. ^{13}C NMR ($CDCl_3$) 1-hexadecyloxypropyl-3-*O*- fragment: δ 12.0 ppm (C-16); 23.9 (C-15); 26.3 (C-2); 29.5–29.8 (*m*, C-5 to C-13); 30.6 (*d*, $CH_2\underline{C}H_2CH_2OP$, $J = 9$ Hz); 32.0 (C-14); 63.7 (*d*, $CH_2CH_2\underline{C}H_2OP$, $J = 6$ Hz); 66.9 ($\underline{C}H_2CH_2CH_2OP$); 71.2 (C-1); DL-α-tocopheryl-6-*O*- fragment: 13.4 (5-CH_3); 14.2 (7-CH_3); 14.3 (8-CH_3); 20.8 (C-4); 21.1 (C-3); 23.8 (2-CH_3); 74.7 (C-2); 142.0 (*d*, C-6, $J = 9$ Hz); 148.4 (C-9) (nucleus); 19.7 (C-13, 12-CH_3); 22.7 (4-CH_3, 8-CH_3) (chain); 37.4 (*m*, CH_3N). ^{31}P NMR ($CDCl_3$) δ 74.8 ppm (*s*). IR (KBr, film) ν 1246, 834 (PO-C, P-OC_{aryl}); 1050, 792 (PO-C, P-OC); 747 (P-N); 719 cm^{-1}(P = S).

1-Hexadecyloxybutyl-4-O-(DL-α-tocopheryl-6-O)-(N,N-dimethylamido)selenophosphate ***1cdSe.*** The phosphite **1cd** was prepared using 1-hexadecyloxybutan-4-ol (**c**, 0.629 g, 2.0 mmol) and DL-α-tocopherol (**d**, 0.861 g, 2.0 mmol) following the procedure described for **1adO.** Then selenium powder (0.166 g, 2.1 mmol) was added and the mixture was stirred at 70°C for 4 h. The selenophosphate **1cdSe** was isolated as described for **1adO.** Yield of **1cdSe**: 1.43 g (80%); $n_D^{40} = 1.4942$; R_f (System A), 0.67; Anal. Calcd. for $C_{51}H_{96}NO_4PSe$ (897.4): C, 68.25; H, 10.80; N, 1.56; P, 3.45. Found: C, 68.22; H, 10.83; N, 1.53; P, 3.35. ^{13}C NMR ($CDCl_3$) 1-hexadecyloxybutyl-4-*O*- fragment: δ 12.0 ppm (C-16); 23.8 (C-15); 26.2 ($CH_2\underline{C}H_2CH_2CH_2OP$); 26.3 (C-2); 26.9 (*d*, $CH_2CH_2\underline{C}H_2CH_2OP$, $J = 9$ Hz); 29.5–29.8 (*m*, C-5 to C-13); 32.0 (C-14); 67.0 (*d*, $CH_2\underline{C}H_2OP$, $J = 5$ Hz); 70.1 ($\underline{C}H_2CH_2CH_2CH_2OP$); 71.0 (C-1); DL-α-tocopheryl-6-*O*-fragment: 13.6 (5-CH_3); 14.2 (7-CH_3); 14.4 (8-CH_3); 20.8 (C-4); 21.0 (C-3); 23.8 (2-CH_3); 74.8 (C-2); 142.3 (*d*, C-6, $J = 9$ Hz); 148.5 (C-9) (nucleus); 19.7 (*m*, C-13, 12-CH_3); 22.7 (*m*, 4-CH_3, 8-CH_3) (chain); 37.4 (*m*, CH_3N). ^{31}P NMR ($CDCl_3$) δ 79.7 ppm (*t*, $J_{P-Se} = 457$ Hz). IR (KBr, film) ν 1245, 832 (PO-C, P-OC_{aryl}); 1041, 784 (PO-C, P-OC); 752 (P-N); 720 cm^{-1} (P = Se).

1-Hexadecyloxyethyl-2-O-(DL-α-tocopheryl-6-O)-(2-dimethylaminoethyl-1-O-)thiophosphate ***1adeS.*** *Representative procedure.* The diester **1ad** was prepared using 1-hexadecyloxyethan-2-ol (**a**, 0.576 g, 2.0 mmol) and DL-α-tocopherol (**d**, 0.861 g, 2.0 mmol) as described for **1adO.** The solution was cooled to room temperature (20–25°C) and added to a mixture of 2-dimethylaminoethanol (**e**, 0.178 g, 2.0 mmol), imidazole (0.136 g, 2.0 mmol) and carbon disulfide (0.152 g, 2.0 mmol) in benzene (50 mL). After 7 h at 20–25°C, the resultant triester phosphite **1ade** was transformed to the thiophosphate **1adeS** by reacting with sulfur (0.067 g, 2.1 mmol) for 30 min at the temperature indicated. The solvent was removed under vacuum, and the derivative was isolated by HPLC (System D) in pure form. Yield of **1adeS**: 1.23 g (71%); $n_D^{40} = 1.4859$; R_f (System B), 0.23; Anal. Calcd. for $C_{51}H_{96}NO_5PS$ (866.5): C, 70.68; H, 11.19; N, 1.62; P, 3.58; S, 3.70. Found: C, 70.62; H, 11.22; N, 1.65; P, 3.48; S, 3.75. ^{13}C NMR ($CDCl_3$) 1-hexadecyloxyethyl-2-*O*- fragment: δ 11.9 ppm (C-16); 23.9 (C-15); 26.1 (C-2); 29.4–29.7 (*m*, C-5 to C-13); 31.9 (C-14); 66.1 (*d*, $CH_2\underline{C}H_2OP$, $J = 6$ Hz); 69.4 (*d*, $\underline{C}H_2CH_2OP$, $J = 8$ Hz); 71.5 (C-1); DL-α-tocopheryl-6-*O*- fragment: 13.5 (5-CH_3); 14.1 (7-CH_3); 14.4 (8-CH_3); 20.8 (C-4); 21.0 (C-3); 23.8 (2-CH_3); 74.9 (C-2); 141.6 (*d*, C-6, $J = 9$ Hz); 148.7 (C-9) (nucleus); 19.7 (*m*, C-13, 12-CH_3); 22.7 (*m*, 4-CH_3, 8-CH_3) (chain); 2-dimethylaminoethyl-1-*O*- fragment: 45.5 (CH_3N); 58.5 (CH_2N); 67.6 (*d*, CH_2OP, $J = 6$ Hz). ^{31}P NMR ($CDCl_3$) δ 65.3 ppm (*s*). IR(KBr, film) ν 1246, 837 (PO-C, P-OC_{aryl}); 1040; 818 (PO-C, P-OC); 722 cm^{-1} (P = S).

1-Hexadecyloxybutyl-4-O-(DL-α-tocopheryl-6-O)-(3-dimethylaminopropyl-1-O-)selenophosphate ***1cdgSe.*** The phosphite **1cdg** was prepared using 1-hexadecyloxybutan-4-ol (**c**, 0.629 g, 2.0 mmol), DL-α-tocopherol (**d**, 0.861 g, 2.0 mmol) and 3-dimethylamino-1-propanol (**g**, 0.206 g, 2.0 mmol) following the procedure described for **1adeS.** Transformation to the selenophosphate **1cdgSe** was accomplished by reaction with selenium (0.166 g, 2.1 mmol) at 70°C for 5 h. The crude derivative was purified by HPLC (System D). Yield of **1cdgSe**: 1.32 g (69%); $n_D^{40} = 1.4873$; R_f (System B), 0.28; Anal. Calcd. for $C_{54}H_{102}NO_5PSe$ (955.5): C, 67.87; H, 10.78; N, 1.47; P, 3.24. Found: C, 67.83; H, 10.75; N, 1.48; P, 3.24. ^{13}C NMR ($CDCl_3$) (Fig. 2) 1-hexadecyloxybutyl-4-*O*- fragment: δ 11.9 ppm (C-16); 23.8 (C-15); 25.9 ($CH_2\underline{C}H_2CH_2CH_2OP$); 26.3 (C-2); 27.0 (*d*, $CH_2CH_2\underline{C}H_2CH_2OP$, $J = 8$ Hz); 29.4–29.7 (*m*, C-5 to C-13); 31.9 (C-14); 67.4 (*d*, $CH_2\underline{C}H_2OP$, $J = 5$ Hz); 70.0 ($\underline{C}H_2CH_2CH_2CH_2OP$); 71.0 (c-1); DL-α-tocopheryl-6-*O*- fragment: 13.8 (5-CH_3); 14.1 (7-CH_3); 14.6 (8-CH_3); 20.8 (C-4); 21.0 (C-3); 23.8 (2-CH_3); 74.8 (C-2); 141.9 (*d*, C-6, $J = 9$ Hz); 148.7 (C-9) (nucleus); 19.7 (*m*, C-13, 12-CH_3); 22.7 (*m*, 4-CH_3, 8-CH_3) (chain); 3-dimethylaminopropyl-1-*O*- fragment: 28.3 (*d*, $\underline{C}H_2CH_2OP$, $J = 8$ Hz); 45.4 (CH_3N); 55.8 (CH_2N); 69.0 (*d*, $\underline{C}H_2OP$, $J = 5$ Hz). ^{31}P NMR ($CDCl_3$) δ 68.8 ppm (*t*,

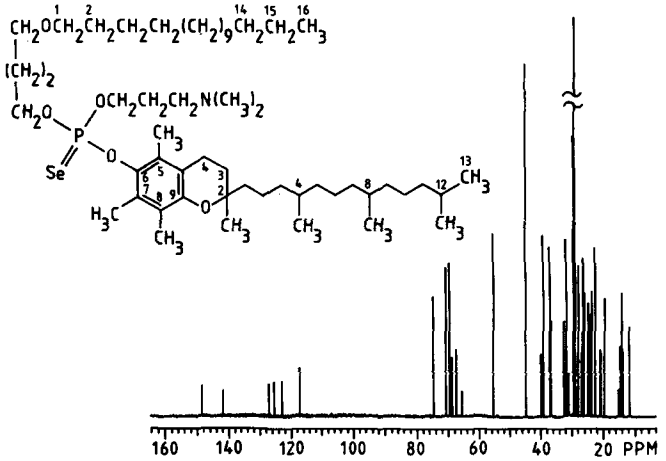

FIG. 2. Proton-decoupled 75.43 MHz ^{13}C nuclear magnetic resonance spectrum of 1-hexadecyloxybutyl-4-*O*-(DL-α-tocopherol-6-*O*)-(3-dimethylaminopropyl-1-*O*)selenophosphate, 1cdgSe.

J_{P-Se} = 453 Hz). IR (KBr, film) ν 1245, 834 (PO-C, P-OC_{aryl}); 1039, 789 (PO-C, P-OC); 735 cm^{-1} (P = Se).

RESULTS AND DISCUSSION

As it has been shown, the acyclic triamides of phosphorous acid offer a number of advantages over conventional phosphorylating reagents (10,11). Moreover, these phosphamides, after appropriate activation, can also be subjected to stoichiometric alcoholysis under mild conditions to give mono-, di- and triester phosphites in high yields (13–15).

The *tris*(*N,N*-dimethyl)amide of phosphorous acid with iodine at the optimum molar ratio of 1.05:0.05 was used as base reagent, **1**. 1-Hexadecyloxyethan-2-ol **a**, 1-hexadecyloxypropan-3-ol **b**, 1-hexadecyloxybutan-4-ol **c**, DL-α-tocopherol **d**, 2-dimethylaminoethanol **e**, 1-dimethylamino-2-propanol **f** and 3-dimethylamino-1-propanol **g** were selected as substrates for phosphorylation. The synthesis was performed according to the method we recently proposed (13,14).

The diesters **1ad, 1bd, 1cd** were obtained in a "one-pot" procedure (Fig. 3) by consecutive treatment of the reagent **1** with equivalent quantities of the ether diols **a, b, c** and DL-α-tocopherol **d** at 70°C in high yields. This was proven by transformation of the phosphites to the corresponding phosphate **1adO**, thiophosphate **1bdS**, and selenophosphate **1cdSe** derivatives. The reverse phosphorylation sequence (DL-α-tocopherol first, and then an ether diol) led to transesterification, probably for both steric and chemical reasons. The reaction sequence established earlier for the synthesis of diol S- and O-phosphoroamidates of some sterols supports this explanation. The molecular masses of the diols chosen had no effect on the rates of phosphorylation.

The high selectivity of diester formation permits the direct synthesis of unsymmetrical triesters. Thus, an equimolar mixture of the third substrate, *e.g.*, imidazole and carbon disulfide, was treated in stoichiometric proportions with the crude diester intermediates **1ad, 1cd** at room temperature for 7 h (Fig. 4). Treating the reaction

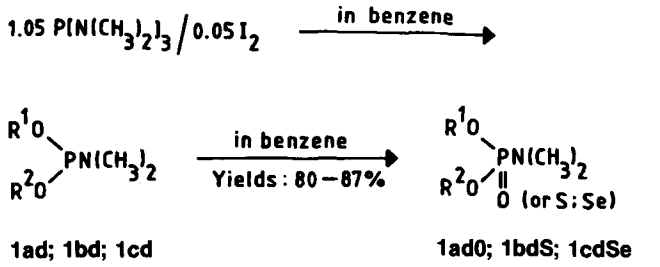

FIG. 3. For the synthesis of 1ad, 1bd, 1cd: 1.) R^1OH = a, b, or c (70°C/5 min); 2.) R^2OH = d (70°C/2 h); for the synthesis of 1adO: 3.) $(C_6H_5CO)_2O_2$ (20–25°C/10 min); or 1bdS: S_8 (70°C/3 min); or 1cdSe: Se (70°C/4 h). For a, 1ad, 1adO: R^1 = 1-hexadecyloxyethyl-; b, 1bd, 1bdS: R^1 = 1-hexadecyloxypropyl-; c, 1cd, 1cdSe: R^1 = 1-hexadecyloxybutyl-; d, 1ad, 1bd, 1cd, 1adO, 1bdS, 1cdSe: R^2 = DL-α-tocopheryl-.

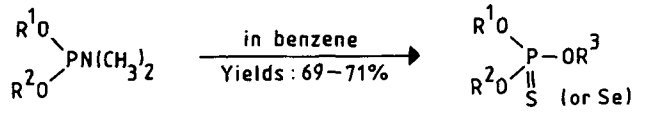

FIG. 4. For the synthesis of 1adeS, 1cdgSe: 1.) R^3OH = e, g/Im/CS_2 (20–25°C/7 h); 2.) S_8 (20–25°C/30 min); or Se (70°C/5 h). For 1ad, 1adeS: R^1 = 1-hexadecyloxyethyl-; R^2 = DL-α-tocopheryl-; 1cd, 1cdgSe: R^1 = 1-hexadecyloxybutyl-; R^2 = DL-α-tocopheryl-; e, 1adeS: R^3 = 2-dimethylaminoethyl-; g, 1cdgSe: R^3 = 3-dimethylamino-1-propyl-; Im = imidazole.

product then with sulfur, or selenium, generated the triester thiophosphate **1adeS**, or the selenophosphate **1cdgSe** (Fig. 2), in good overall yields.

Our attempts to obtain the 1-hexadecyloxypropyl-3-*O*-(1-dimethylaminopropyl-2-*O*) triester derivative of DL-α-tocopherol failed. Despite extended reaction times (up to one week), at the last synthetic step the third substrate **f** was not coupled with the activated diester intermediate **1bd**. The 1-dimethylamino-2-propanol **f** was not reactive either toward the other diester phosphites **1ad, 1cd**. This is probably due to the steric hindrance at the methyl substituted secondary hydroxyl function of **f**.

As a rule, reaction with selenium required relatively longer reaction times than oxidation or reaction with sulfur. No attempts were made to optimize this process.

Conclusions on the structures of the compounds synthesized were drawn on the basis of spectral and microanalytical data. ^{13}C NMR indicated that all characteristic signals present in the spectra of the starting substrates were also seen in the spectra of the corresponding target *O-*, *S-* and *Se*-phosphate derivatives. No chemical alterations in the alkyl ether diol (**a, b, c**), tocopheryl (**d**) and dimethylaminoalkyl (**e, g**) moieties were detected after oxidation, sulfurization or selenization. The ^{31}P NMR spectral analysis provided compelling evidence that the latter processes concerned the P^{III} atom, exclusively, under the specific experimental conditions selected. These results are in agreement with those reported in the literature for analogous systems (7,11,15).

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