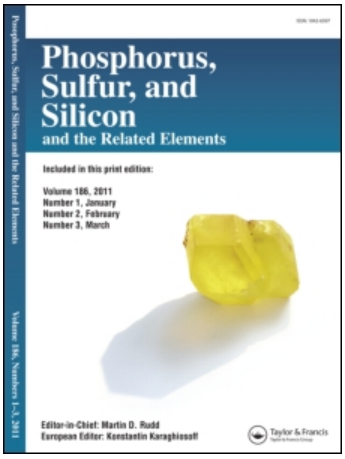

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EFFECTS OF METHYL IODIDE, BROMINE AND IODINE ADDITIVES ON PHOSPHORYLATING CHARACTERISTICS OF THE HEXAETHYLTRIAMIDE OF PHOSPHOROUS ACID. GLYCEROAMIDOTHIOPHOSPHATES OF THE VITAMINS D_2, D_3, AND E

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EFFECTS OF METHYL IODIDE, BROMINE AND IODINE ADDITIVES ON PHOSPHORYLATING CHARACTERISTICS OF THE HEXAETHYLTRIAMIDE OF PHOSPHOROUS ACID. SYNTHESIS OF DIOL- AND GLYCEROAMIDOTHIOPHOSPHATES OF THE VITAMINS D_2, D_3, AND E

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The effects of methyl iodide, bromine and iodine additives on the reacting ability and selectivity of phosphorylation by means of tris(diethylamido)-phosphite are investigated. The one-pot synthesis of diester diol- and glyceroamidothiophosphates of the vitamins D_2, D_3, and E is described.

Key words: Phosphorylation; tris(diethylamido)-phosphite; methyl iodide; bromine; iodine additives; amidothiophosphates; lipid-soluable vitamins.

The acyclic triamides of phosphorous acid in itself demonstrate unsatisfactory reacting ability and low selectivity as phosphorylating reagents.[1-3] The latter types of compounds cannot be subjected to stoichiometrical alcoholysis (or phenolysis) if monoester derivatives are desired, which excludes the possibility of direct synthesis of unsymmetrical diesters. Using catalytic amounts of some halogen additives, however, these preparative disadvantages can be avoided. The effect of iodine on the phosphorylating characteristics of tris(N,N-dialkyl)-amides of phosphorous acid was reported in a previous work.[4] The synthesis of some unusual mono- and diester phospholipids was accomplished selectively by means of activated phosphamides under mild conditions and in high overall yields.[4-7]

We now describe, in principle, the effects of two new additives (methyl iodide and bromine) in comparison with the effect of iodine, on the phosphorylating ability and reaction selectivity of tris(N,N-diethylamido)-phosphite as a reagent for the synthesis of monoester and unsymmetrical diester model phospholipids.

RESULTS AND DISCUSSION

By preliminary model studies we have established that minor amounts of methyl iodide, bromine, or iodine, dramatically increase the rate and selectivity of the

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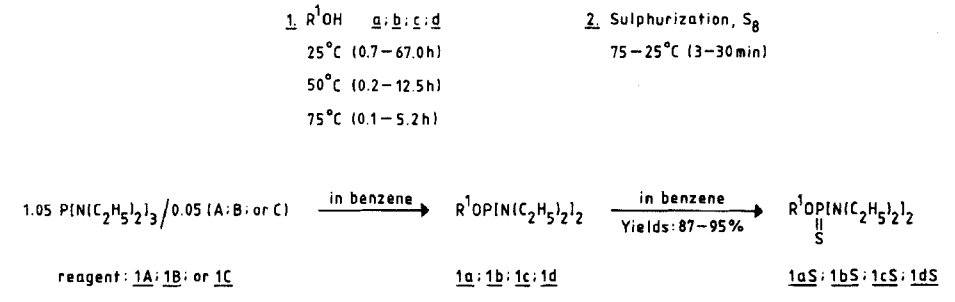
phosphorylation with acyclic triamides of phosphorous acid. The effect approaches an optimum at a molar concentration of about 5%. In this case, the tris(N,N-diethylamido)-phosphite, **1**, was activated by the addition of methyl iodide, **A**, bromine, **B**, and iodine, **C**, at the fixed molar ratio of 1.05:0.05, to give the reagents, **1A**, **1B**, and **1C**, respectively.

1-Oleoyloxyethane-2-ol, **a**, ergocalciferol, **b**, cholecalciferol, **c**, DL-α-tocopherol, **d**, and 1,2-dioleoyl-rac-glycerol, **e**, were selected as substrates containing primary and secondary hydroxyl- and sterically hindered phenolic hydroxyl functions.

The monoester formation stage was studied first (Scheme I). The phosphorylation of the representative substrates, **a**; **b**; **c**; **d**, (primary and secondary alcohol; and sterically hindered phenolic systems) was carried out at three defined temperatures: 25°C; 50°C; and 75°C. The activated phosphamide (**1A**; **1B**; or **1C**) was then reacted with the substrate given (**a**; **b**; **c**; or **d**) in stoichiometric amounts at these temperatures. In all cases, the resultant monoester phosphite (**1a**; **1b**; **1c**; or **1d**) was transformed to the corresponding thiophosphate (**1aS**; **1bS**; **1cS**; or **1dS**). The final yields in the range of 87 – 97% were accepted as a limiting factor of the phosphorylation.

The experimental data summarized in Table I indicate that the effect of the additives on the reacting ability of the tris(diethylamido)-phosphite, **1**, is expressed most strongly in iodine, decreasing progressively from bromine toward methyl iodide. Thus, the bromine, **1B**, and methyl iodide, **1A**, activated reagents exert from four to six times, respectively, lower phosphorylating ability compared to that of iodine, **1C**. As would be expected, the reactivity (under equal other conditions) decreases from the primary- toward the secondary and sterically hindered hydroxyl functions. Regardless of the activator and the thermal conditions used, selectivity of the phosphorylation remain extremely high. The latter circumstance permits the synthesis of unsymmetrical diesters to be performed as a one-pot procedure. In order to avoid the extended reaction times at lower temperatures, introduction of the second P-O bond was studied at 75°C.

According to Scheme II, the consecutive treatment of the crude intermediate (**1a**; **1b**; **1c**; or **1d**) (prepared on the basis of **1A**; **1B**; or **1C**) with an equivalent quantity of the second substrate (**a**; **d**; or **e**) and sulfur at 75°C for 1 – 18 h and 3 min, respectively, afforded the diester thiophosphates (**1abS**; **1acS**; **1adS**; **1beS**;

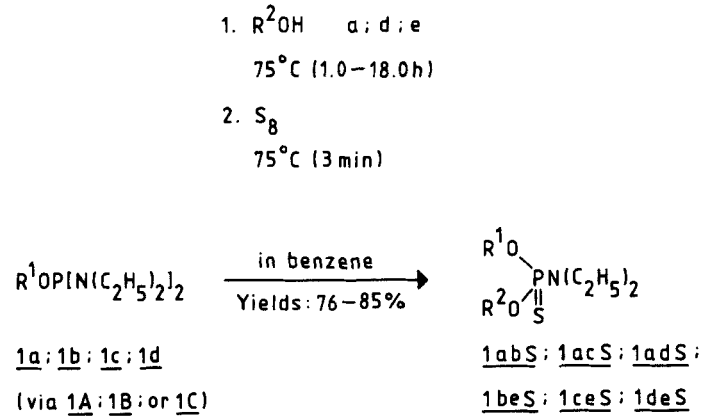


SCHEME I For **A** = CH_3I; **B** = Br_2; **C** = I_2; **a**; **1a**; **1aS**: R^1 = 1-Oleoyloxyethyl-; **b**; **1b**; **1bS**: R^1 = Ergocalciferyl-; **c**; **1c**; **1cS**: R^1 = Cholecalciferyl-; **d**; **1d**; **1dS**: R^1 = DL-α-Tocopheryl-.

TABLE I

Synthesis of monoester amidothiophosphates (**1aS**; **1bS**; **1cS**; **1dS**) at the molar ratio of hexaethyltriamide of phosphorous acid (**1**) / activator (**A**; **B**; **C**) / substrate (**a**; **b**; **c**; **d**) = 1.05 / 0.05 / 1.00

Reagent used	Reaction temperature, °C	Reaction time, h				Yield, %			
		a	b	c	d	1aS	1bS	1cS	1dS
	25	4.6	25.0	26.0	67.0	89	90	92	88
1A ($P(NEt_2)_3/CH_3I$)	50	1.3	3.0	3.1	12.5	90	91	92	87
	75	0.4	0.8	0.9	5.2	91	93	91	92
	25	2.9	15.0	15.5	45.0	90	93	90	91
1B ($P(NEt_2)_3/Br_2$)	50	0.5	1.8	2.0	8.5	92	93	91	90
	75	0.1	0.2	0.2	3.5	92	92	93	93
	25	0.7	4.2	4.1	10.0	91	94	93	89
1C ($P(NEt_2)_3/I_2$)	50	0.2	0.5	0.5	2.0	92	92	95	93
	75	< 0.1	0.1	0.1	0.8	93	94	95	95



SCHEME II For **1a**; **1adS** (as R^1) and **a**; **1abS**; **1acS** (as R^2): 1-Oleoyloxyethyl-; **1b**; **1abS**; **1beS** (as R^1): Ergocalciferyl-; **1c**; **1acS**; **1ceS** (as R^1): Cholecalciferyl-; **1d**; **1deS** (as R^1) and **d**; **1adS** (as R^2): DL-α-Tocopheryl-; **e**; **1beS**; **1ceS**; **1deS** (as R^2): 1,2-Dioleoyl-rac-glyceryl-.

1ceS; or **1deS**). Overall yields within the range of 75 – 85% were postulated as the limiting factor of the diester formation.

An approach using bis(N,N-diethylamido)-phosphites, **1a** and **1e**, as the initial key intermediates for the synthesis of (**1abS**; **1acS**) and (**1beS**; **1ceS**; **1deS**), respectively, was not effective because of transesterification processes taking place under the experimental conditions stated.

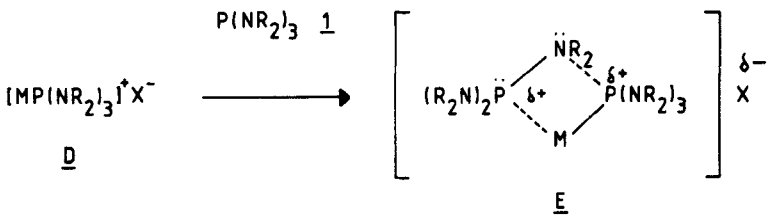
A comparison with the results shown in Table I indicates that the activating ability of the additives, **A**; **B**; **C**, is considerably depressed at the diester formation stage (Table II). Thus, the activities of iodine, **1C**, and bromine, **1B**, reagents are almost equalized but, as a whole, they exceed double the reactivity of the methyl iodide reagent, **1A**.

As has previously been assumed,[4] the high selectivity of the reagents: **1A**; **1B**; **1C**, is probably due to the action of an initial quasiphosphonium compound, **D**, which forms an activated complex, **E**, with the triamide of phosphorous acid, **1**, by electrophilic orientation on nitrogen (Scheme III). As a result, one of the amido groups in the triamide, **1**, is converted to a good leaving group and could then easily be substituted by nucleophilic attack on phosphorus. In this context, it could be expected that some electronic changes induced at phosphorus (size of the resultant charge; presence of P-O bond; etc.) should lead to alterations in phosphorylating ability of the reagent (**1A**; **1B**; or **1C**). The experimental data obtained herein are in agreement with such a suggestion. This hypothesis, however, needs further, model investigations which are beyond the goal of the present paper.

TABLE II

Synthesis of diester amidothiophosphates (**1abS**; **1acS**; **1adS**; **1beS**; **1ceS**; **1deS**) at the molar ratio of the monoester phosphite (**1a**; **1b**; **1c**; **1d**) / second substrate (**a**; **d**; **e**) = 1.00 / 1.00

Base reagent	Monoester phosphite used	Reaction time, h a	d	e	Yield, % 1abS	1acS	1adS	1beS	1ceS	1deS
1A	1a		8.5				78			
	1b	2.3		4.2	81			80		
	1c	2.5		4.5		79			78	
	1d			18.0						76
1B	1a		5.3				79			
	1b	1.3		2.6	80			81		
	1c	1.2		2.8		82			82	
	1d			11.0						80
1C	1a		4.0				85			
	1b	1.0		2.2	84			83		
	1c	1.0		2.0		85			83	
	1d			8.0						81



SCHEME III For reagent **1A**: **M** = CH_3; **X** = I; **1B**: **M** = **X** = Br; **1C**: **M** = **X** = I; **R** = ethyl.

EXPERIMENTAL

The tris(N,N-diethylamido)-phosphite, **1**, was prepared according to Reference 8. 1-Oleoyloxyethane-2-ol, **a**, and 1,2-dioleoyl-rac-glycerol, **e**, were prepared as described in References 9 and 10. Ergocalciferol, **b**, cholecalciferol, **c**, and DL-α-tocopherol, **d**, (all Merck) had a purity of greater than 98%. All other reagents were also of a purity better than 98% (Janssen). Benzene (Merck) was dried over sodium and freshly distilled. Reaction conditions were kept strictly anhydrous.

All processes were monitored by analytical thin-layer chromatography (TLC) on pre-coated aluminum sheets of silica gel 60 F_{254} (Merck). High performance liquid chromatography (HPLC) was carried out (Gilson 305 system, equipped with Gilson 131 Refractive Index Detector) using POLYGOSIL 60-7 silica gel column (250 × 10 mm). Chloroform (system A) and *n*-heptane/ethyl acetate 80/20, *v/v* (system B) were used as the mobile phases.

^{13}C NMR spectra were recorded on a Varian 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 in 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. IR spectra were recorded on a Perkin-Elmer FT-IR 1750 spectrometer. Peak positions are reported in cm^{-1}. For **1abS**, **1acS**, **1adS**, **1beS**, **1ceS**, and **1deS** satisfactory microanalyses were obtained: C, ±0.23; H, ±0.12; N, ±0.10; P, ±0.10; S, ±0.11. The yields were determined gravimetrically and are the average of three parallel measurements.

1-Oleoyloxyethyl-2-0-bis(N,N-diethylamido)-thiophosphate, **1aS**. *Representative procedure.* A mixture of iodine (0.025 g, 0.1 mmol) and tris(N,N-diethylamido)-phosphite (**1**; 0.519 g, 2.1 mmol) in benzene (50 ml) was heated at 75°C in a stream of argon for about 15 min until the precipitate dissolved (reagent **1C**). The solution was cooled to 25°C, 1-oleoyloxyethane-2-ol (**a**; 0.653 g, 2.0 mmol) was added, and the reaction system was kept under these conditions for 40 min to give, **1a**. Sulfur (0.067 g, 2.1 mmol) was then added and the mixture was stirred for 30 min. The solvent was removed under vacuum and the thiophosphate, **1aS**, was isolated by HPLC (system B) in analytically pure form.
Yield of **1aS**: 0.97 g (91%); n_D^{20} = 1.4810; Rf(system A): 0.65; ^{31}P NMR-{H} ($CDCl_3$) δ 77.8 ppm (*s*); Reference 5: n_D^{20} = 1.4805; ^{31}P NMR-{H} (C_6D_6) δ 77.9 ppm (*s*).

Ergocalciferyl-3-0-bis(N,N-diethylamido)-thiophosphate, **1bS**. Using reagent **1A** (activated by methyl iodide: 0.014 g, 0.1 mmol) and ergocalciferol (**b**; 0.793 g, 2.0 mmol), the derivative, **1b**, was synthesized at 25°C for 28 h, then transformed to the thiophosphate, **1bS**, and purified in the same way as described for, **1aS**.
Yield of **1bS**: 1.09 g (90%); n_D^{40} = 1.5230; Rf(system A): 0.82; ^{31}P NMR-{H} ($CDCl_3$) δ 77.2, 77.4 ppm (each *s*); Reference 11: n_D^{40} = 1.5220; ^{31}P NMR-{H} ($CDCl_3$) δ 77.2, 77.4 ppm (each *s*).

Cholecalciferyl-3-0-bis(N,N-diethylamido)-thiophosphate, **1cS**. Using reagent **1B** (activated by bromine: 0.016 g, 0.1 mmol) and cholecalciferol (**c**; 0.769 g, 2.0 mmol), the phosphite, **1c**, was prepared at 50°C for 2 h. The compound, **1cS**, was obtained following the procedures described for, **1aS**.
Yield of **1cS**: 1.07 g (91%); n_D^{40} = 1.5180; Rf(system A): 0.80; ^{31}P NMR-{H} ($CDCl_3$) δ 75.6, 75.7 ppm (each *s*); Reference 11: n_D^{40} = 1.5189; ^{31}P NMR-{H} ($CDCl_3$) δ 75.6, 75.8 ppm (each *s*).

DL-α-Tocopheryl-6-0-bis(N,N-diethylamido)-thiophosphate, **1dS**. Using reagent **1C** and DL-α-tocopherol (**d**; 0.861 g, 2.0 mmol), the phosphite, **1d**, was synthesized at 75°C for 45 min, transformed to the thiophosphate, **1dS**, (75°C; about 3 min), and then purified as described for, **1aS**.
Yield of **1dS**: 1.21 g (95%); n_D^{20} = 1.5144; Rf(system A): 0.92; ^{31}P NMR-{H} ($CDCl_3$) δ 72.5 ppm (*s*); Reference 4: n_D^{20} = 1.5137; ^{31}P NMR-{H} (C_6D_6) δ 72.6 ppm (*s*).

1-Oleoyloxyethyl-2-0-(ergocalciferyl-3-0-)-(N,N-diethylamido)-thiophosphate, **1abS**. *Representative procedure.* Using reagent **1A** and ergocalciferol (**b**; 0.793 g, 2.0 mmol), the key intermediate, **1b**, was prepared as described for, **1bS**. 1-Oleoyloxyethane-2-ol (**a**; 0.653 g, 2.0 mmol) was then added and the mixture was heated at 75°C for 2.3 h. Transformation to the thiophosphate, **1abS**, was accomplished by reaction with sulfur (0.067 g, 2.1 mmol) at 75°C for 3 min. The solvent was removed under vacuum, and the compound was isolated by HPLC (system B) in pure form.
Yield of **1abS**: 1.39 g (81%); n_D^{40} = 1.5095; Rf(system A): 0.88; $C_{52}H_{90}NO_4PS$ (856.5). ^{13}C NMR-{H} ($CDCl_3$) δ 12.5 ppm (*s*, C-18); 130.1, 130.2 (each *s*, C-9, C-10); 172.7 (*s*, C-1): oleoyl-fragment; 63.0 (*m*, CH_2CH_2OP); 64.4 (*s*, CH_2CH_2OP): diol-fragment; 12.4 (*s*, C-18); 18.0 (*s*, C-28); 19.9 (*s*, C-26); 20.2 (*s*, C-27); 74.2 (*m*, C-3); 108.5, 112.7 (each *s*, C-19); 116.7, 118.3 (each *s*, C-7); 122.9, 123.0 (each *s*, C-6); 132.2 (*s*, C-23); 135.3 (*m*, C-8); 136.1 (*s*, C-22); 141.9, 144.1 (each *s*, C-5); 145.9, 149.9 (each *s*, C-10): ergocalciferyl-3-0-fragment; 14.3 (*m*, CH_3CH_2N); 40.4 (*m*, CH_2N). ^{31}P NMR-{H} ($CDCl_3$) δ 73.4 ppm (*s*). IR (KBr, film) ν 3020 (CH=); 1745 (C=O); 1645 (C=C); 1025, 816 (PO—C, P—OC); 730 (P—N); 695 cm^{-1} (P=S).

1,2-Dioleoyl-rac-glycero-3-0-(ergocalciferyl-3-0-)-(N,N-diethylamido)-thiophosphate, **1beS**. Using reagent **1A**, ergocalciferol (**b**; 0.793 g, 2.0 mmol) and 1,2-dioleoyl-rac-glycerol (**e**; 1.242 g, 2.0 mmol), the compound, **1beS**, (diester formation time: 4.2 h) was synthesized and purified as described for, **1abS**.
Yield of **1beS**: 1.84 g (80%); n_D^{40} = 1.5010; Rf(system A): 0.89; $C_{71}H_{124}NO_6PS$ (1151.0). ^{13}C NMR-{H} ($CDCl_3$) δ 12.6 ppm (*s*, C-18); 130.1, 130.2 (each *s*, C-9, C-10); 172.6 (*s*, C-1): oleoyl-fragment; 62.9 (*m*, $OCH_2CH(O)CH_2OP$); 64.7 (*m*, CH_2OP); 70.1 (*m*, $OCH_2CH(O)CH_2OP$): glycerol-fragment; 12.5 (*s*, C-18); 18.0 (*s*, C-28); 19.9 (*s*, C-26); 20.2 (*s*, C-27); 73.8 (*m*, C-3); 108.6, 112.9 (each *s*, C-19); 116.9, 118.4 (each *s*, C-7); 122.3, 123.1 (each *s*, C-6); 132.2 (*s*, C-23); 135.2 (*m*, C-8); 136.1 (*s*, C-22); 141.8, 144.0 (each *s*, C-5); 145.8, 149.9 (each *s*, C-10): ergocalciferyl-3-0-fragment; 14.3 (*m*, CH_3CH_2N); 40.4 (*m*, CH_2N). ^{31}P NMR-{H} ($CDCl_3$) δ 73.5 ppm (*m*).
IR (KBr, film) ν 3030 (CH=); 1740 (C=O); 1640 (C=C); 1010, 818 (PO—C, P—OC); 745 (P—N); 715 cm^{-1} (P=S).

1-Oleoyloxyethyl-2-0-(cholecalciferyl-3-0-)-(N,N-diethylamido)-thiophosphate, **1acS**. Using reagent **1B**, cholecalciferol (**c**; 0.769 g, 2.0 mmol) and 1-oleoyloxyethane-2-ol (**a**; 0.653 g, 2.0 mmol), the derivative, **1acS**, (diester formation time: 1.2 h) was synthesized and purified as described for, **1cS** and **1abS**.
Yield of **1acS**: 1.38 g (82%); n_D^{40} = 1.5064; Rf(system A): 0.87; $C_{51}H_{90}NO_4PS$ (844.5). ^{13}C NMR-{H} ($CDCl_3$) δ 12.3 ppm (*s*, C-18); 130.1, 130.2 (each *s*, C-9, C-10); 172.7 (*s*, C-1): oleoyl-fragment; 63.0 (*m*, CH_2CH_2OP); 64.4 (*s*, CH_2CH_2OP): diol-fragment; 12.2 (*s*, C-18); 22.8 (*s*, C-26); 23.0 (*s*, C-27); 74.3 (*m*, C-3); 108.4, 112.7 (each *s*, C-19); 116.7, 118.3 (each *s*, C-7); 121.7, 123.0 (each *s*, C-6); 134.8 (*m*, C-8); 142.0, 144.2 (each *s*, C-5); 145.4, 149.4 (each *s*, C-10): cholecalciferyl-3-0-fragment; 14.3 (*m*, CH_3CH_2N); 40.8 (*m*, CH_2N). ^{31}P NMR-{H} ($CDCl_3$) δ 73.4 ppm (*s*).
IR (KBr, film) ν 3025 (CH=); 1750 (=O); 1643 (C=C); 1030, 820 (PO—C, P—OC); 733 (P—N); 695 cm^{-1}(P=S).

1,2-Dioleoyl-rac-glycero-3-0-(cholecalciferyl-3-0-)-(N,N-diethylamido)-thiophosphate, **1ceS**. Using reagent **1B**, cholecalciferol (**c**; 0.769 g, 2.0 mmol), and 1,2-dioleoyl-rac-glycerol (**e**; 1.242 g, 2.0 mmol), the compound, **1ceS**, (diester formation time: 2.8 h) was prepared and purified in the same way as described for, **1cS** and **1abS**.
Yield of **1ceS**: 1.86 g (82%); n_D^{40} = 1.4898; Rf(system A): 0.89; $C_{70}H_{124}NO_6PS$ (1139.0). ^{13}C NMR-{H} ($CDCl_3$) δ 12.3 ppm (*s*, C-18); 130.1, 130.2 (each *s*, C-9, C-10); 172.5 (*s*, C-1): oleoyl-fragment; 62.9 (*m*, $OCH_2CH(O)CH_2OP$); 64.5 (*m*, CH_2OP); 70.3 (*m*, $OCH_2CH(O)CH_2OP$): glycerol-fragment; 12.2 (*s*, C-18); 22.8 (*s*, C-26); 23.0 (*s*, C-27); 74.2 (*m*, C-3); 108.3, 112.9 (each *s*, C-19); 116.8, 118.5 (each *s*, C-7); 121.9, 123.2 (each *s*, C-6); 135.0 (*m*, C-8); 142.2, 144.5 (each *s*, C-5);.145.5, 149.5 (each *s*, C-10): cholecalciferyl-3-0-fragment; 14.3 (*m*, CH_3CH_2N); 40.3 (*m*, CH_2N). ^{31}P NMR-{H} ($CDCl_3$) δ 73.3 ppm (*m*).
IR (KBr, film) ν 3030 (CH=); 1750 (C=O); 1644 (C=C); 1020, 820 (PO—C, P—OC); 754 (P—N); 720 cm^{-1} (P=S).

1-Oleoyloxyethyl-2-0-(DL-α-tocopheryl-6-0-)-(N,N-diethylamido)-thiophosphate, **1adS**. Using reagent **1C** and 1-oleoyloxyethane-2-ol (**a**; 0.653 g, 2.0 mmol), the monoester, **1a**, was synthesized as described for, **1aS**. DL-α-Tocopherol (**d**; 0.861 g, 2.0 mmol) was then added and the reaction system was treated at 75°C for 4 h. The procedures for transformation to thiophosphate and isolation of the compound, **1adS**, were identical with those described for, **1abS**.
Yield of **1adS**: 1.51 g (85%); n_D^{40} = 1.4930; Rf(system A): 0.90; $C_{53}H_{96}NO_5PS$ (890.6). ^{13}C NMR-{H} ($CDCl_3$) δ 12.5 ppm (*s*, C-18); 129.6, 129.7 (each *s*, C-9, C-10); 173.1 (*s*, C-1): oleoyl-fragment; 63.6 (*d*, CH_2CH_2OP, J = 11 Hz); 64.6 (*s*, CH_2CH_2OP): diol-fragment; 14.2 (*m*, CH_3-5, CH_3-7, CH_3-8);

20.8 (*s*, C-4); 21.1 (*s*, C-3); 23.8 (*s*, CH_3-2); 74.9 (*s*, C-2); 141.7 (*m*, C-6); 148.5 (*s*, C-9): nucleus; 19.7 (*m*, C-13, CH_3-12); 22.7 (*m*, CH_3-4, CH_3-8): chain, DL-tocopheryl-6-0-fragment; 14.2 (*m*, CH_3CH_2N); 40.6 (*m*, CH_2N). ^{31}P NMR-{H} ($CDCl_3$) δ 72.1 ppm (*s*).
IR (KBr, film) ν 3010 (CH=); 1750 (C=O); 1650 (C=C); 1245, 835 (PO—C, P—OC_{aryl}); 1030, 795 (PO—C, P—OC); 725 (P—N); 694 cm^{-1} (P=S).

1,2-Dioleoyl-rac-glycero-3-0-(DL-α-tocopheryl-6-0-)-(N,N-diethylamido)-thiophosphate, **1deS**. Using reagent **1C** and DL-α-tocopherol (**d**; 0.861 g, 2.0 mmol), the monoester, **1d**, was prepared first, according to the procedure described for, **1dS**. The reaction system was then treated with the 1,2-dioleoyl-rac-glycerol (**e**; 1.242 g, 2.0 mmol) at 75°C for 8 h. The resultant diester phosphite, **1de**, was transformed to the thiophosphate, **1deS**, and purified in a synonymous way with the procedures described for, **1abS**. Yield of **1deS**: 1.92 g (81%); n_D^{40} = 1.4823; Rf(system A): 0.92; $C_{72}H_{130}NO_7PS$ (1185.1). ^{13}C NMR-{H} ($CDCl_3$) δ 11.9 ppm (*s*, C-18); 129.6, 129.8 (each *s*, C-9, C-10); 173.0 (*m*, C-1): oleoyl-fragment; 62.5 (*m*, $OCH_2CH(O)CH_2OP$); 64.0 (*m*, CH_2OP); 69.7 (*m*, $OCH_2CH(O)CH_2OP$): glycerol-fragment; 14.2 (*m*, CH_3-5, CH_3-7, CH_3-8); 20.8 (*s*, C-4); 21.1 (*s*, C-3); 23.8 (*s*, CH_3-2); 74.8 (*s*, C-2); 141.7 (*m*, C-6); 148.4 (*s*, C-9): nucleus; 19.6 (*m*, C-13, CH_3-12); 22.7 (*m*, CH_3-4, CH_3-8): chain, DL-α-tocopheryl-6-0-fragment; 14.2 (*m*, CH_3CH_2N); 40.6 (*m*, CH_2N). ^{31}P NMR-{H} ($CDCl_3$) δ 74.3 ppm (*m*).
IR (KBr, film) ν 3010 (CH=); 1740 (C=O); 1654 (C=C); 1240, 835 (PO—C, P—OC_{aryl}); 1030, 795 (PO—C, P—OC); 725 (P—N); 670 cm^{-1} (P=S).

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