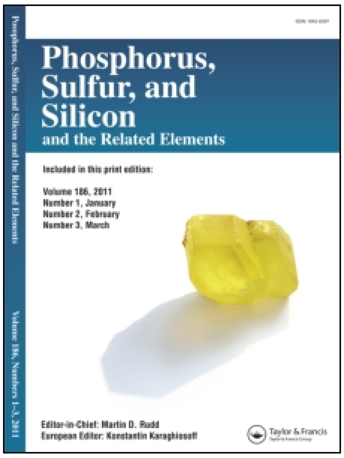

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BISPHOSPHONIC COMPOUNDS. IV.[1] PREPARATION AND IDENTIFICATION OF MIXED TETRAALKYL METHYLENE- AND (DICHLOROMETHYLENE)-BISPHOSPHONATES BY NMR SPECTROSCOPIC, MASS SPECTROMETRIC AND X-RAY CRYSTALLOGRAPHIC STUDIES

Jouko Vepsäläinen[a]; Esko Pohjala[b]; Heikki Nupponen[b]; Pirjo Vainiotalo[c]; Markku Ahlgren[c]
[a] Univ. Kuopio, Dept. Chem., Kuopio, Finland [b] Leiras Oy, Tampere, Finland [c] Dept. Chem., Univ. Joensuu, Joensuu, Finland

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BISPHOSPHONIC COMPOUNDS. IV.[1] PREPARATION AND IDENTIFICATION OF MIXED TETRAALKYL METHYLENE- AND (DICHLOROMETHYLENE)-BISPHOSPHONATES BY NMR SPECTROSCOPIC, MASS SPECTROMETRIC AND X-RAY CRYSTALLOGRAPHIC STUDIES

JOUKO VEPSÄLÄINEN†
Univ. Kuopio, Dept. Chem., P.O. Box 1627 SF-70211, Kuopio, Finland

and

ESKO POHJALA and HEIKKI NUPPONEN
Leiras Oy, P.O. Box 33, SF-33721 Tampere, Finland

and

PIRJO VAINIOTALO and MARKKU AHLGREN
Univ. Joensuu, Dept. Chem. P.O. Box 111, SF-80101 Joensuu, Finland

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The chemistry of 28 mixed tetraalkyl methylene- and (dichloromethylene)bisphosphonates, $(R^1O)(R^2O)P(O)CX_2P(O)(OR^3)(OR^4)$, where R^1=Et, Allyl, CH=CHMe, Pr^i, Bu, Bu^t, Hex, Ph, Bn or octadecyl, R^2=Me, Et, Pr^i, Bu, Bu^t, Hex, Ph or Bn, R^3=R^4=Me, Et, Pr^i or Ph and X=H or Cl, have been studied. ^1H, ^{13}C, ^{31}P NMR data are reported, including $^1J_{CH}$, $^2J_{CP}$, $^3J_{CP}$ and $^2J_{PP}$ coupling constants. The fragmentation of some representative compounds were studied in the gas phase. The solid state structure is given for $(PhO)_2P(O)CH_2P(O)(OMe)_2$.

Key words: Mixed methylenebisphosphonate esters; synthesis; NMR; MS; X-ray.

INTRODUCTION

Bisphosphonates, previously called diphosphonates, are widely used for the treatment of diseases in the skeletal system, bone formation and resorption disorders, as well as for the treatment of diseases in soft tissues.[2] Over the past few decades several methylenebisphosphonic acids (MDP), their salts and tetraesters, have been prepared in order to modify their biological properties by varying the substituents at the middle carbon.[3] Clodronate,[4] (Cl_2MDP), is one of the best documented bisphosphonates used in the treatment of these diseases.[5] Several tetraalkyl esters of clodronate have been made,[6] some interest has been direct towards mixed tetraalkyl esters of MDP[7] without systematic examination and only a few corresponding halogenated mixed tetraesters have been reported. In this work we ex-

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†Author to whom correspondence should be addressed.

amined the synthesis, solution structure, solid-state and mass spectrometric properties of mixed tetraesters of the methylene- and (halomethylene)bisphosphonic acids, while keeping in mind the possibility of increasing production to the multikilo scale. Also, preparation of different monophosphonic starting materials and methylenebisphosphonates using several routes have been discussed.

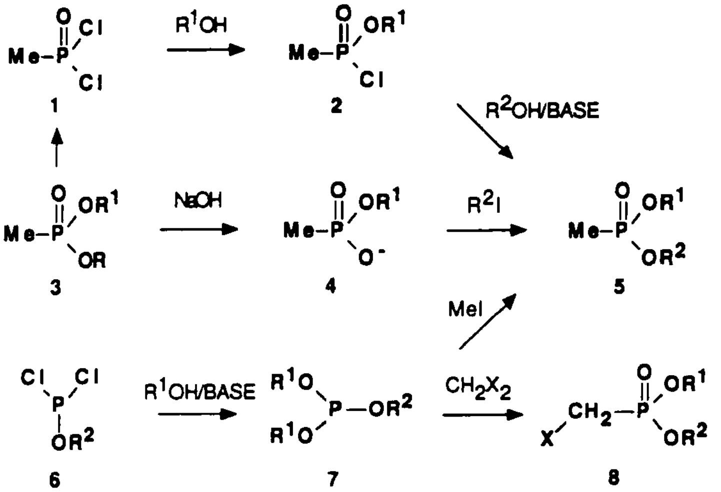
There are three main routes in the preparation of mixed tetraesters of MDP: the Michaelis-Becker reaction, the Arbuzov reaction or carbanion method (e.g. LDA, lithium diisopropylamine). An early synthesis of **16** by the Michaelis-Becker reaction encountered problems with the yield, which was only 10–55%.[7a,b] More recently, Lang has reported the preparation of **16** (R^1=Ph, R^2—R^4=Ph or Et) by the Michaelis-Arbuzov reaction with variable yields, 15–74%.[7c] A more convenient route is possible for **16**, commencing with the condensation of dialkyl methylphosphonate (**3**) and chlorophosphonic acid dialkyl ester (**13**) by LDA,[7d–g] although this method requires dry and oxygen free conditions to work well. The chlorination of **16** to **17** with NaOCl required carefully controlled conditions, because the speed of the reaction depended on the alkyl substituents. Unwanted degradation of **17** could be avoided by proper control of reaction time, temperature and pH.

Some of the dialkyl methylphosphonates, $MeP(O)(OR^1)(OR^2)$ (**3**, R^1=R^2), are commercially available or easily synthesized; but especially the mixed ones (**5**, $R^1 \neq R^2$) must be synthesized. We should point out that some of the monophosphonates (MP), or intermediates to these, are very toxic and must be handled in closed systems. Moreover, heating of allyl derivatives should be avoided, particularly MP or MDP with two or more allyl groups, since these compounds tend to react extremely fast. The counter species in the LDA reaction, $Cl—P(O)(OR^3)(OR^4)$, must be freshly prepared, since they are sensitive to moisture and some tend to decompose under light or heat while some others are polymerized.

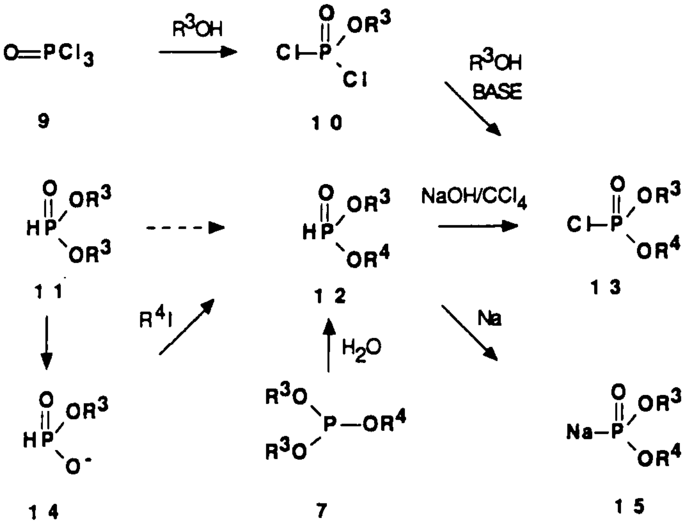
RESULTS AND DISCUSSION

Preparation of Starting Materials

The quality of starting materials always had a dramatic influence on the purity and yield of mixed tetraalkyl bisphosphonates when using the carbanion method. The synthesis of starting materials are described in Scheme I and II. Symmetric methylphosphonates **3** and **8** (X = halogen) are easily prepared from PCl_3 and the desired alcohol, using tertiary amine as an HCl binder,[8a] followed by the Michaelis-Arbuzov reaction with methyliodide or dihalomethane.[8b] The synthesis of mixed methylphosphonates **5** is more complicated and dependent on the ester part. Several routes to **5** have been described, but only some of them were useful in our hands. Mixed derivatives of **5** containing only *n*-alkyl esters were achieved using known methods, but for branched ones there was no generally applicable method existing in the literature. The route from **3a** to the dichloride **1**,[8c,9] via the esterchloride **2**[10,11a] to mixed diester **5**, was unsatisfactory since the esterification of **1** was difficult to control and purification by distillation was not efficient enough. Attempts to produce **5b** (R^1=Pr^i, R^2=Me) using the route mentioned above led to a mixture of **5b** (60%), **3a** (20%, R^1=Me) and **3c** (20%, R^1=Pr^i). Similar results were also obtained for the hexyl derivative **5c** (R^1=Me, R^2=Hex) and more hindered systems



SCHEME I. Preparation of mixed dialkyl methylphosphonates.



SCHEME II. Preparation of mixed dialkyl chlorophosphites.

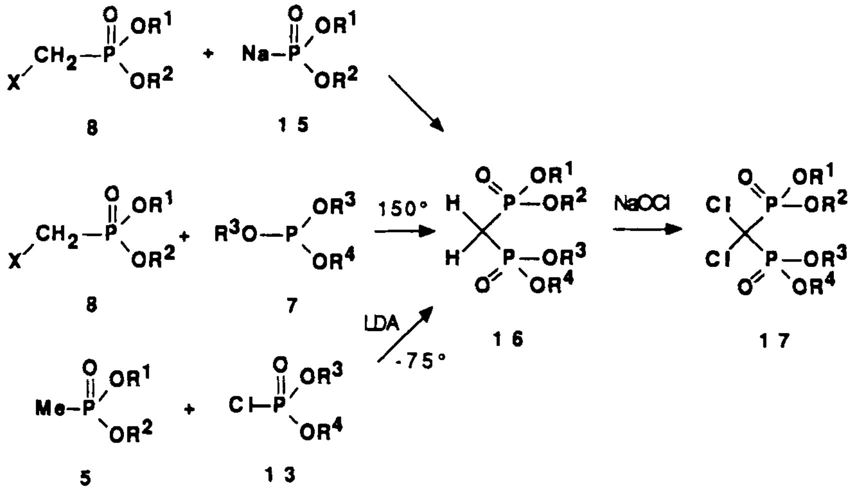
gives even poorer results e.g. for **5d** (R^2=Hex, R^2=Pr^i) of which the purity was only 50% (by ^{31}P NMR). Moreover, **1** and **2** are very toxic and must be handled with extreme care in closed systems.

A preferable path to **5** was realized via the monoester salt **4**,[11] prepared from **3a** with NaOH followed by replacing the Na^+ by a tetraalkyl ammonium salt. In the final step **4** was alkylated by the appropriate alkyl halide. This route was feasible to produce **5a** (R^1=Me, R^2=2-propenyl) and **5c**, but problems were encountered with the reactivity of branched and short alkyls. A convenient method to **5b** was made from PCl_3 via dichlorophosphite **6** and mixed trialkyl phoshite **7**, followed by the Arbuzov reaction to **5b**.[12]

Symmetric chlorophosphites **13** (R^3=R^4) were prepared either from phosphorus trichloride,[8d] phosphorus oxychloride **9**[13] or dialkylphosphite **11**[14]; and sodium phosphites **15** were prepared from the corresponding dialkylphosphites **12**. It was more demanding to produce enough pure mixed chlorophosphates than mixed methylphosphonates. Starting from **9**, via **10** to **13**[8e] (e.g. R^3=Me, R^4=Pr^i), led to a mixture of products, which could not be separated by distillation. The other route, from symmetric dialkylphosphite **11** to monoalkyl-phosphite **14**[15] or directly from **11** to mixed dialkylphosphite **12**,[16] proved successful for only some *tert*-butyl derivatives, since the chlorination of less hindered derivatives of **12** (e.g. Pr^i) led to a mixture of products.

Preparation of Mixed Methylenebisphosphonates

In our early experiments we tried to avoid reactions using LDA, which requires absolutely dry conditions and an oxygen free atmosphere. But after some attempts with two alternative methods, the Michaelis-Becker and the Michaelis-Arbuzov reactions, we conclude that the LDA method was the appropriate technique to produce mixed tetraesters of **16**. We synthesized **16a** using three methods (see Scheme III). The Michaelis-Becker reaction was initiated by the reaction of **11a** (R^3=Me) with sodium to give **15**, followed by the addition of **8b** (X=I and R^1=R^2=Et) to the mixture which gave **16a** in only 20% yield. Other bases, e.g. NaH, $KOBu^t$, BuLi and LDA, were also tested without success.[7a,b] Even lower yield was achieved from the Michaelis-Arbuzov reaction by allowing **8b** and **7a** (R^3=R^4=Me) to react with each other. After some experience with LDA, **16a** was obtained from **3b** (R^1=Et) and **13a** (R^3=R^4=Me) by following the procedure of Teulade *et al.*[7d] with 86% yield.



SCHEME III. Preparation of mixed tetraalkyl methylene- and (dichloromethyle)bisphosponates.

Other derivatives of **16** were prepared in a similar manner to **16a** with good yield and purity, when an excess (1.4–2 eq) of LDA was used. Normally only one product was achieved, except with the allyl (—CH_2—CH=CH_2) group, which tended to partially rearrange to a 1-propenyl (—CH=CH—CH_3) group. The LDA method was also useful for *tert*-butyl derivatives, but longer reaction times and a higher temperature were needed to complete the reaction, although some side reactions were observed. If both of the starting materials contained branched groups, only partial conversion to the final (**16j** and **16n**) product was observed due to dissolution of the lithium complex at higher temperature. More over, molecules with a long alkyl chain were wax like and awkward to handle.

Preparation of Mixed (Dichloromethylene) Bisphosphonates

The difficulty in the synthesis of mixed tetra(*n*-alkyl) (dihalomethylene)-bisphosphonates was cleavage of the P—C bond during halogenation with hypohalites.[6a] This problem was solved by carefully controlling the temperature, pH and reaction time during synthesis. Commercially available hypohalite solutions were normally too basic for the halogenation of *n*-alkyl derivatives of **16**, but after adjusting the pH to 9 with $NaHCO_3$ the reaction occurred rapidly with shorter *n*-alkyls, and in a reasonable time with longer chains, without breaking any P—C bonds. Moreover, in the isolation steps $NaHCO_3$ prevented the compounds containing three methyl groups to dissolve into the water phase. On the other hand, for **16** containing only branched alkyls or/and long alkyls a higher pH ($\geqslant 10$) was required for the halogenation reaction and they were not sensitive to temperature. Some of the branched methylenebisphosphonates, e.g. **16m**, required phase transfer conditions without adjusting pH, at low temperature (0°) and controlled reaction time, and chlorinated perfectly. Also for the other derivatives of **16**, the phase transfer conditions were suitable since chlorination was achieved during remarkably shortened reaction times.

More challenging was to chlorinate compounds having both branched alkyls and methyl or ethyl groups in same molecule. The chlorination of molecules containing only one long *n*-alkyl or branched group demanded pH and temperature maintenance with little longer reaction times than *n*-alkyls.[1] Molecules with before mentioned groups were sensitive to temperature and to some extent pH and reaction time. An additional complication was observed with *tert*-butyl esters, because of their tendency to decompose into water soluble partial esters by loss of one or more ester groups, which lowered yields.

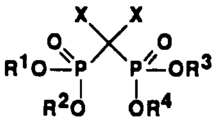
NMR Spectroscopy

NMR spectroscopy was the easiest way to follow the progress of reactions and to analyse the purity of the products. The ^{31}P chemical shifts are listed in Table I with $^2J_{PP}$ coupling constants. The ^{13}C chemical shifts are given in Table II and the coupling constants to proton and phosphorus in Table III and IV, respectively. The most significant impurities were well separated in the spectra and easily assigned by the main signal(s).

The phosphorus spectra of the compounds studied were sensitive to the ester group and substituents at the middle carbon. An increase in the chain length from methyl to hexyl led to an upfield shift of 3 ppm. Similar upfield shifts were also observed using branched substituents instead of *n*-alkyls. Pr^i group gave rise to an upfield shift of 5 ppm, and Bu^t and Ph groups of 10 ppm upfield compared to their methyl esters. More specific (about 11 ppm) upfield shifts were induced by intro-

TABLE I

List of studied compounds, ^{31}P NMR shifts and $^2J_{PP}$ constants



Comp.	X	R^1	R^2	R^3, R^4	P	P'	$^2J_{PP}$
16a	H	Et	Et	Me	19.55	22.65	6.0
16b	H	CH_2CHCH_2	Me	Me	21.67	22.53	6.0
16b'	H	CH_3CHCH	Me	Me	19.28	21.79	6.6
16c	H	Pr^i	Me	Me	17.64	22.82	6.3
16d	H	Pr^i	Pr^i	Me	17.43	23.00	7.1
16e	H	Pr^i	Pr^i	Et	17.77	20.20	7.4
16f	H	Pr^i	Me	Pr^i	17.77	20.58	7.4
16g	H	Bu	Bu	Pr^i	20.22	17.90	7.9
16h	H	Bu^t	Bu^t	Et	10.68	20.88	13.3
16i	H	Hex	Me	Me	21.15	22.78	6.1
16j	H	Hex	Bu^t	Pr^i	15.75	18.35	9.2
16k	H	Hex	Hex	Pr^i	20.13	17.84	7.6
16l	H	Ph	Ph	Me	12.84	20.95	8.0
16m	H	Bn	Bn	Ph	19.27	12.77	9.0
16n	H	Octadec	Bu^t	Pr^i	15.76	18.35	9.1
17a	Cl	Et	Et	Me	8.45	11.17	23.1
17b	Cl	CH_2CHCH_2	Me	Me	11.03	10.11	23.9
17b'	Cl	CH_3CHCH	Me	Me	10.74	6.88	23.9
17c	Cl	Pr^i	Me	Me	8.95	11.29	23.3
17d	Cl	Pr^i	Pr^i	Me	6.79	11.56	22.8
17e	Cl	Pr^i	Pr^i	Et	7.16	9.16	22.8
17f	Cl	Pr^i	Me	Pr^i	9.58	7.15	23.2
17g	Cl	Bu	Bu	Pr^i	9.02	7.17	23.0
17h	Cl	Bu^t	Bu^t	Et	-0.37	10.38	19.0
17i	Cl	Hex	Me	Me	9.60	11.10	23.6
17k	Cl	Hex	Hex	Pr^i	8.98	4.72	22.9
17l	Cl	Ph	Ph	Me	0.17	10.37	23.2
17m	Cl	Bn	Bn	Ph	8.87	0.43	22.9

ducing chlorine atoms on the middle carbon, as expected by the increased electronegativity.[17] Also the $^2J_{PP}$ coupling constants were sensitive to the size of the ester group and substituents at the middle carbon, ranging from 6 to 13 Hz with methylenephosphonates and from 19 to 24 Hz with dihalo compounds.

The proton and carbon chemical shifts, and $^1J_{CH}$ coupling constants were similar to their corresponding symmetric tetraalkyl derivatives of **16** and **17**.[1] The carbon

TABLE II

The ^{13}C NMR chemical shifts in ppm for the compounds studied

		R^1						R^2	R^3 and R^4			
Comp.	X_2C	α	β	χ (β')	δ	ε	ϕ	α	α	$\beta(\alpha')$	$\chi(\beta')$	δ
16a	24.70	62.70	16.35	-	-	-	-	*	53.10	-	-	-
16b	24.36	67.12	132.73	118.38	-	-	-	53.2	53.2	-	-	-
16b'	24.07	134.69	110.89	9.31	-	-	-	53.2	53.2	-	-	-
16c	24.78	71.88	24.09	(23.82)	-	-	-	52.94	53.14	(53.06)	-	-
16d	25.86	71.50	24.11	(23.85)	-	-	-	*	52.99	-	-	-
16e	26.66	71.38	24.11	(23.88)	-	-	-	*	62.47	16.37	-	-
16f	26.82	71.51	24.12	(23.93)	-	-	-	52.81	71.34	24.12	(23.93)	-
16g	26.57	66.21	32.56	18.75	13.61	-	-	*	71.37	24.10	(23.90)	-
16i	24.09	66.82	30.36	25.04	31.27	22.46	13.90	53.09	53.09	-	-	-
16k	26.49	66.51	30.48	25.14	31.39	22.56	14.00	*	71.36	24.10	(23.90)	-
16l	24.66	150.07	120.64	129.85	125.53	-	-	*	53.37	-	-	-
16m	25.89	68.40	135.76	128.24	128.60	128.57	-	*	150.05	120.69	129.79	125.45
17a	71.61	66.41	16.42	-	-	-	-	*	56.47	-	-	-
17b	71.41	70.32	132.15	118.92	-	-	-	56.3	56.3	-	-	-
17b'	71.19	135.83	111.10	9.29	-	-	-	56.3	56.3	-	-	-
17c	71.57	75.93	24.25	(23.45)	-	-	-	56.27	56.48	-	-	-
17d	71.86	75.67	24.33	(23.44)	-	-	-	*	56.37	-	-	-
17e	72.10	75.26	24.35	(23.48)	-	-	-	*	66.08	16.45	-	-
17f	72.07	75.46	24.29	(23.47)	-	-	-	55.97	75.35	24.35	(23.52)	-
17g	72.70	69.77	32.63	18.64	13.58	-	-	*	75.37	24.34	(23.51)	-
17i	71.65	70.47	30.47	24.98	31.27	22.51	13.95	56.5	56.5	-	-	-
17k	72.14	70.05	30.60	25.08	31.34	22.54	13.97	*	75.31	24.36	(23.51)	-
17l	71.08	150.66	120.44	129.837	125.84	-	-	*	56.74	-	-	-
17m	71.33	71.47	135.22	128.19	128.56	128.69	-	*	150.62	120.43	129.72	125.72

* shifts identical to R^1

TABLE III

The $^1J_{CH}$ coupling constants in Hz for the compounds studied

		R^1						R^2	R^3 and R^4			
Comp.	X_2C	α	β	χ (β')	δ	ε	ϕ	α	α	$\beta(\alpha')$	$\chi(\beta')$	δ
16a	124.9	148.0	127.3	-	-	-	-	*	148.2	-	-	-
16b	125.2	148.4	157.1	156.0	-	-	-	149	149			
16b'	125.3	194.6	157.7	127.8	-	-	-	149	149			
16c	124.8	147.8	126.8	(126.8)	-	-	-	148.0	148.2	(148.2)	-	-
16d	124.7	147.4	126.5	(126.8)	-	-	-	*	148.1	-	-	-
16e	124.3	147.3	126.7	(126.6)	-	-	-	*	147.9	127.1	-	-
16f	124.3	147.3	126.8	(126.8)	-	-	-	147.7	147.3	126.8	(126.8)	-
16g	124.3	146.9	126.9	124.1	124.8	-	-	*	147.3	126.7	(126.7)	-
16i	124.3	147.2	125.9	125	126.5	125.1	124.4	148.0	148.0	-	-	-
16k	124.3	147.0	126.2	126	126.1	125.5	124.2	*	147.3	126.7	(126.7)	-
16l	125.6	-	163.9	162.5	162.7	-	-	*	148.5	-	-	-
16m	125.9	149.0	-	161	162	161	-	*	-	163.9	162.3	162.1
17a	-	150.1	127.5	-	-	-	-	*	149.7	-	-	-
17b	-	150.4	158.7	156.2	-	-	-	150	150	-	-	-
17b'	-	198.4	157.9	127.8	-	-	-	150	150	-	-	-
17c	-	149.9	127.0	(127.3)	-	-	-	149.5	149.7	-	-	-
17d	-	149.6	127.0	(127.1)	-	-	-	*	149.6	-	-	-
17e	-	149.5	126.9	(127.1)	-	-	-	*	149.6	127.4	-	-
17f	-	149.6	127.0	(127.2)	-	-	-	149.2	149.6	127.0	(127.2)	-
17g	-	148.5	126.5	124.8	125.0	-	-	*	149.5	126.8	(127.1)	-
17i	-	149.2	126.2	125.1	126.1	125.3	124.5	149.6	149.8	(149.8)	-	-
17k	-	148.6	125.1	126	125.9	125.1	124.3	*	149.3	127.0	(127.2)	-
17l	-	-	164.5	162.3	162.4	-	-	*	150.0	-	-	-
17m	-	150.0	-	160.9	161.5	160.0	-	*	-	164.5	162.6	162.7

* couplings identical to R^1

TABLE IV

The $^1J_{CP}$, $^2J_{CP}$, $^3J_{CP}$ and $^4J_{CP}$ coupling constants for the compounds studied

			R^1			R^2	R^3 and R^4		
Comp.	$^1J_{CP}$	$^1J_{CP'}$	$^2J_{CP}$	$^3J_{CP}$	$^4J_{CP}$ ($^3J_{CP}$)	$^2J_{CP}$	$^2J_{CP}$	$^3J_{CP}$($^2J_{CP}$)	$^4J_{CP}$ ($^3J_{C'P}$)
16a	137.2	137.2	6.3	6.3	-	*	6.3	-	-
16b	137.4	137.4	6.1	6.3	-	#	#	-	-
16b'	137.7	137.7	6.1	9.8	1.0	#	#	-	-
16c	137.7	137.7	6.6	3.7	(5.5)	6.4	6.4	(6.4)	-
16d	138.3	137.1	6.5	3.8	(5.3)	*	6.4	-	-
16e	138.4	136.8	6.5	3.8	(5.3)	*	6.4	6.4	
16f	138.0	138.0	6.5	3.7	(5.3)	6.3	6.5	3.8	(5.3)
16g	136.8	138.5	6.5	6.2	-	*	6.5	3.9	(5.4)
16i	137.6	137.6	6.6	6.2	-	#	#	-	-
16k	136.8	138.4	6.6	6.3	-	*	6.5	3.8	(5.2)
16l	140.2	137.7	8.7	4.5	1.2^1	*	6.4	-	-
16m	137.4	139.8	6.3	6.1	-	*	8.8	4.5	1.0^1
17a	154.3	154.3	7.1	5.9	-	*	6.9	-	-
17b	155.3	155.3	6.8	6.0	-	#	#	-	-
17b'	156.3	156.3	6.6	9.8	-	#	#	-	-
17c	155.6	155.6	7.4	3.0	(6.5)	7.0	7.0	-	-
17d	155.7	155.1	7.4	2.7	(6.6)	*	6.9	-	-
17e	155.6	153.6	7.4	2.8	(6.6)	*	7.0	5.8	-
17f	155.3	155.3	7.4	3.0	(6.7)	7.0	7.3	2.8	(6.5)
17g	153.7	155.6	7.4	5.6	-	*	7.3	2.8	(6.5)
17i	154.9	154.9	7.4	5.7	-	#	#	-	-
17k	153.4	155.5	7.4	5.5	-	*	7.4	2.8	(6.6)
17l	163.3	156.1	9.5	4.6	0.8^2	*	6.9	-	-
17m	155.4	163.8	7.1	5.8	-	*	9.5	4.5	-

1 $^5J_{CP}$=1.4 Hz. 2 $^5J_{CP}$=1.2 Hz. * couplings identical to R^1.# not resolved due to complicate structure

spectra of halogenated methylenebisphosphonates **17** suffered from long relaxation times, and lacked nuclear Overhauser enhancement from the middle carbon. The $^1J_{CP}$ couplings were sensitive to charge density variation,[18] being approximately 137 Hz for methylene and 154 Hz for dihalomethylene compounds. Also small, but clear, a difference (from 1 Hz to 8 Hz) was observed between *n*-alkyl, branched and aromatic derivatives when comparing $^1J_{CP}$ couplings. By contrast, the $^2J_{CP}$ couplings were insensitive (~7 Hz) to the structure of the molecules studied. For Pr^i derivatives of **16** and **17** the proton decoupled carbon spectra showed two signals due to different electronic environments of the two symmetric β methyl carbons. The $^3J_{CP}$ couplings are dependent on the dihedral angles in the P—O—C—C system. A good starting point to predict the conformations in solution was the crystal structure for tetrakis(1-methylethyl) (dichloromethylene)bisphosphonate, giving 95° and 140° angles for the methyl carbons in Pr^i groups.[1] The conformation can be considered as a twisted form from the one where P and H are *gauche* to each other, showing a strong repulsion between the methyl groups and the O—P=O moiety. Using the formula given by Thiem[19] for $^3J_{CP}$ couplings the calculated constants for the crystal structure should be 0 Hz and 10.2 Hz. Comparing these values with observed, 2.8 Hz and 6.6 Hz (e.g. **17e**), indicated that at least two conformations existed in solution. By fitting these values to the crystal structure we may imagine that the Pr^i group is flipping between two conformations, one with the P—O—C—C dihedral angles of 95° and 140° (X-ray structure) and the other with 140° and 95°. Calculation of the rotamer populations for these two conformations results in 75% (the X-ray conformation) and 25%. For the corresponding Pr^i derivatives of **16**, $^3J_{CP}$ couplings of about 3.8 Hz and 5.3 Hz were observed, which means that both of the above mentioned conformations are equally populated. Rather similar dihedral angles were obtained before for other branched tetraalkyl derivatives.[1]

Mass Spectrometry

The electron ionization (EI at 70 eV) and chemical ionization (CI) mass spectrometric studies were done only for a few molecules (**16/17a**, **c**, **d**, **f**, **k**, **l**), since fragmentation resembled those presented in the preceding part of the series,[1] but some new features were found. Fragmentation pathways were verified by metastable ion analysis using linked scans at constant B/E. Elemental compositions of the ions were confirmed by accurate mass measurements. The relative intensities, RI, of the ions formed in the fragmentation process are shown in Table V for derivatives of **16** and in Table VI for derivatives of **17**. The molecular ion peak was clearly detected only for derivatives of **16** absent of two branched ester groups at the same phosphorus. Self-chemical ionization, tending to form $[M + H]^+$ ions, was a favorable process for both **16** and **17**, which was at the head observed in accurate mass measurement.

TABLE V

The 70 eV mass spectra of mixed esters of methylenebisposphonates for some representative compounds. Peaks with relative intensities (RI) greater than 5% (RI ≥ 10% marked with *) of the intensity of the base peak above m/z 50 are included unless they are not due to a molecular ion. The spectra are uncorrected for isotopic contributions

Comp.	m/z (relative intensity)
16a	261 (9), 260 (14), 233 (81), 215 (14), 205 (63), 187 (64), 173 (26), 155 (5), 152 (7), 126 (6), 125 (11), 124 (100), 109 (18), 96 (15), 95 (6), 94 (23), 93 (17), 79 (21), 65 (6).
16c	261 (35), 260 (28), 220 (7), 219 (100), 218 (32), 204 (11), 202 (10), 201 (98), 188 (6), 187 (54), 173 (6), 169 (7), 125 (79, 124 (62), 110 (28), 109 (6), 107 (10), 94 (13), 93 (27), 79 (19).
16d	247 (7), 231 (5), 229 (9), 205 (100), 204 (16), 188 (8), 187 (84), 173 (17), 126 (6), 125 (6), 124 (27), 96 (10), 94 (7), 93 (12), 79 (13).
16f*	317 (51), 275 (28), 259 (10), 233 (67), 232 (13), 217 (43), 215 (29), 205 (27), 191 (100), 190 (40),187 (22), 174 (31), 173 (100), 159 (34), 155 (11), 142 (13), 110 (39), 99 (13), 96 (30), 93 (14) 80 (10), 79 (26), 65 (14).
16k	345 (14), 303 (8), 261 (35), 176 (100), 158 (47), 125 (6), 98 (58), 97 (10), 96 (6), 56 (7), 55 (10).
16l	356 (11), 265 (5), 264 (39), 263 (100), 231 (42), 189 (7), 137 (9), 94 (5), 93 (10), 91 (9), 77 (30), 65 (9), 51 (7).

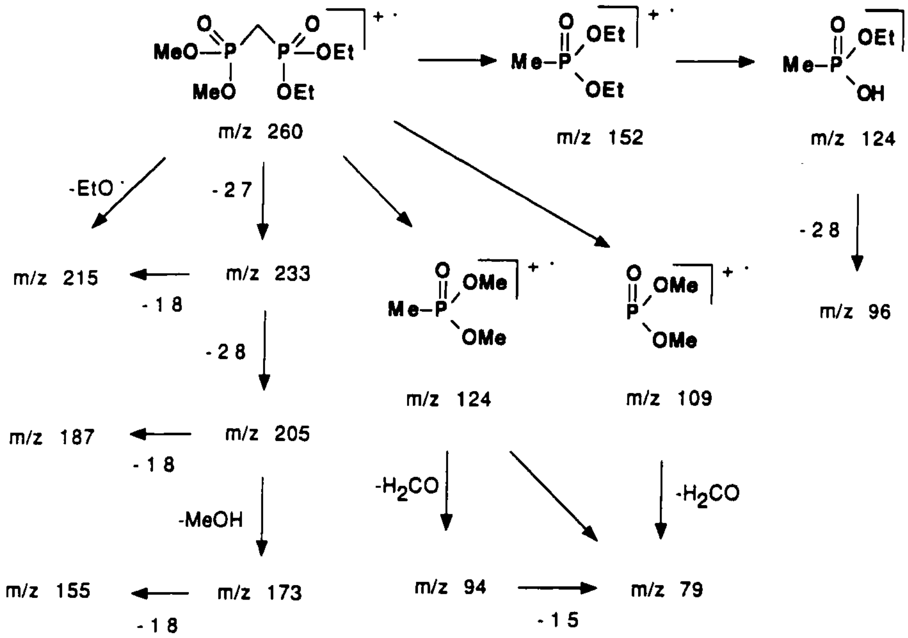
TABLE VI

The 70 eV mass spectra for derivatives of **17**. Marking as in Table V

17a*	330 (18), 328 (28), 302 (13), 300 (20), 284 (15), 274 (39), 273 (11), 272 (64), 256 (13), 195 (11), 194 (65), 193 (18), 192 (100), 159 (28), 109 (58), 95 (13), 93 (33), 81 (19), 79 (62), 65 (22).
17c*	290 (11), 288 (65), 287 (10), 286 (100), 271 (14), 269 (21), 205 (11), 194 (56), 192 (87), 187 (13), 178 (12), 173 (34), 137 (18), 127 (11), 111 (17), 109 (32), 97 (14), 95 (13), 93 (43), 79 (47).
17d*	275 (11), 274 (66), 273 (15), 272 (100), 257 (19), 255 (29), 219 (11), 194 (43), 193 (11), 192 (66), 173 (11), 159 (15), 127 (20), 123 (38), 109 (30), 97 (13), 95 (12), 93 (33), 79 (55), 65 (15), 63 (10).
17f	287 (7), 285 (10), 283 (6), 262 (13), 261 (7), 260 (90), 259 (12), 258 (100), 243 (17), 241 (28), 224 (7), 220 (5), 206 (6), 180 (26), 178 (42), 166 (9), 164 (15), 159 (8), 113 (9), 95 (14), 81 (6), 79 (22), 65 (15).
17k	412 (7), 331 (13), 330 (18), 329 (20), 328 (28), 248 (9), 247 (31), 246 (64), 245 (50), 244 (100), 229 (10), 227 (15), 211 (13), 210 (11), 193 (6), 192 (11), 166 (16), 165 (7), 164 (26),145 (7), 123 (9), 99 (12), 85 (11), 65 (8), 56 (7), 55 (20)
17l	335 (6), 333 (33), 332 (5), 331 (50), 318 (14), 317 (6), 316 (21), 297 (8), 264 (9), 263 (6), 233 (24), 217 (11), 215 (22), 171 (10), 170 (8), 168 (5), 161 (14), 159 (22), 141 (6), 140 (6), 139 (5), 109 (100), 105 (5), 97 (6), 96 (6), 95 (8), 94 (15), 93 (33), 79 (17), 78 (6), 77 (65), 65 (17), 63 (7), 51 (18).

The fragmentation of **16** depended mainly on the length and shape of the alkylester groups and took place via loss of four different groups (for **16a**, see Scheme IV); by elimination of $[P(O)(OR)_2—H]^{\bullet}$, $C_nH_{2n-1}^{\bullet}$ or C_nH_{2n}, $RO^{\bullet}$ or ROH, and H_2O units. The formation of the $[CH_3P(O)(OR)_2]^{+\bullet}$ ion gave rise to the base peak only for **16a** at m/z 124, but for derivatives including at least one branched ester group (not phenyl) the base peak was achieved after loss of all branched units. The elimination of the ROH group was characteristic only for methyl groups while loss of water was typical for branched substituents after loss of at least two branched units. A special case was **16l**, which tended to form the base peak by loss of one $PhO^{\bullet}$ unit.

The fragmentation of **16a** began via several routes; by elimination of $C_2H_3^{\bullet}$ (27), $EtO^{\bullet}$ (45) and P—C bond cleavage of either side (loss of 109 and 137) units producing ions at m/z 233, 215, 152 and 124, respectively. The loss of $C_2H_3^{\bullet}$ required



SCHEME IV. The fragmentation of **16a**.

the migration of two hydrogen atoms, one to the P=O oxygen and the other to the ester oxygen.[20] After this step the fragmentation continued by loss of the remaining ethyl group as ethylene (m/z 205), followed by loss of water (m/z 187) or MeOH (m/z 173), and finally cleavage of the P—C bond. Loss of ethylene from the ions at m/z 152 gave rise to the same peak, but different ion structure as before from direct P—C bond fragmentation at m/z 124. Further fragmentation of the ion at m/z 124 produced ions at m/z 96, 94 and 79 by elimination of C_2H_4, $H_2C{=}O$ and Me˙ from ions at m/z 94, respectively. The other route to the peak at m/z 79 resulted from the ion $[P(O)(OMe)_2]^{+\cdot}$ at m/z 109 by cleavage of $H_2C{=}O$ group. Other fragments below m/z 100 were almost identical to those formed from monophosphonates and have been studied in detail by other authors.[20a,b] Comparing these ions with fragmentation of tetramethyl and tetraethyl methylenebisphosphonates, the main differences were the absence of cleavage of the $H_2C{=}O$ group from the bisphosphonate skeleton and low intensity of the peak at m/z 152 compared to ions at m/z 124.

In general fragmentation of **16c**,**d**,**f** and **k** resembled that of **16a**. The dominating features of fragmentation for molecules with higher or/and branched ester groups was consecutive losses of the $R—C_2H_2^{\cdot}$ unit followed by $R—CH{=}CH_2$, water and methanol in the presence of methyl group. The loss of an RO˙ (R ≠ ME) radical was not very favorable although some signals can be rationalized to result from the elimination of these units. For **16l** the only primary fragmentation pathway was elimination of a PhO˙ (93) radical leading to ions at m/z 263 followed by the loss of a MeOH unit which produced ions at m/z 231. However, for **16l** the most remarkable difference was the absence of the $[Me—P(O)(OR)_2]^{+\cdot}$ and $[Me—P(O)(OH)(OR)]^{+\cdot}$ ions, since a phenyl group is a worse hydrogen donor than alkyl groups.

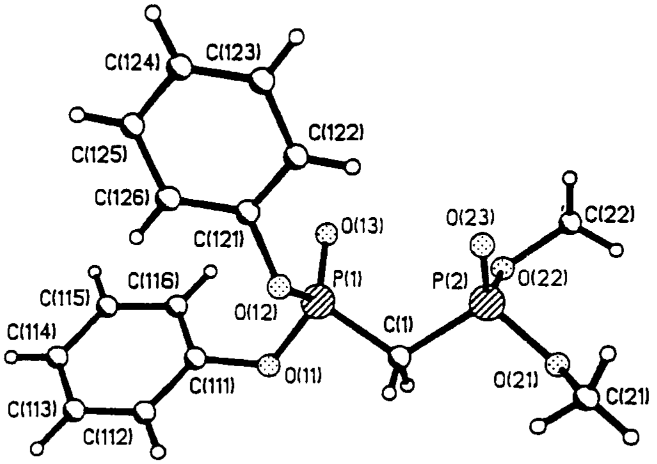


FIGURE 1 The molecular structure of $CH_2[P(O)(OMe)_2][P(O)(OPh)_2]$ (molecule A).

TABLE VII

Bond lengths (Å) for $CH_2[PO(OMe)_2][PO(OPh)_2]$ (**16l**)

Molecule A		Molecule B	
P(1)-O(11)	1.590(2)	P(3)-O(31)	1.585(2)
P(1)-O(12)	1.583(2)	P(3)-O(32)	1.587(3)
P(1)-O(13)	1.459(2)	P(3)-O(33)	1.457(2)
P(1)-C(1)	1.778(3)	P(3)-C(2)	1.776(3)
P(2)-O(21)	1.573(2)	P(4)-O(41)	1.577(2)
P(2)-O(22)	1.565(2)	P(4)-O(42)	1.566(2)
P(2)-O(23)	1.462(2)	P(4)-O(43)	1.466(2)
P(2)-C(1)	1.787(3)	P(4)-C(2)	1.786(2)
O(11)-C(111)	1.402(4)	O(31)-C(311)	1.403(3)
O(12)-C(121)	1.404(3)	O(32)-C(321)	1.407(4)
O(21)-C(21)	1.436(4)	O(41)-C(41)	1.436(4)
O(22)-C(22)	1.440(4)	O(42)-C(42)	1.437(4)
C(111)-C(112)	1.375(5)	C(311)-C(312)	1.362(5)
C(111)-C(116)	1.370(4)	C(311)-C(316)	1.374(5)
C(112)-C(113)	1.386(5)	C(312)-C(313)	1.385(5)
C(113)-C(114)	1.365(6)	C(313)-C(314)	1.349(7)
C(114)-C(115)	1.370(6)	C(314)-C(315)	1.366(7)
C(115)-C(116)	1.389(5)	C(315)-C(316)	1.388(5)
C(121)-C(122)	1.353(5)	C(321)-C(322)	1.368(5)
C(121)-C(126)	1.373(5)	C(321)-C(326)	1.370(4)
C(122)-C(123)	1.385(5)	C(322)-C(323)	1.381(6)
C(123)-C(124)	1.361(6)	C(323)-C(324)	1.362(5)
C(124)-C(125)	1.371(7)	C(324)-C(325)	1.364(6)
C(125)-C(126)	1.389(5)	C(325)-C(326)	1.390(6)

TABLE VIII
Bond angles (°) for $CH_2[PO(OMe)_2][PO(OPh)_2]$ (**16l**)

Molecule A		Molecule B	
O(11)-P(1)-O(12)	104.1(1)	O(31)-P(3)-O(32)	103.7(1)
O(11)-P(1)-O(13)	115.7(1)	O(31)-P(3)-O(33)	115.9(1)
O(12)-P(1)-O(13)	113.8(1)	O(32)-P(3)-O(33)	114.0(1)
O(11)-P(1)-C(1)	97.8(1)	O(31)-P(3)-C(2)	98.2(1)
O(12)-P(1)-C(1)	104.7(1)	O(32)-P(3)-C(2)	105.1(1)
O(13)-P(1)-C(1)	118.5(1)	O(33)-P(3)-C(2)	117.8(1)
O(21)-P(2)-O(22)	102.1(1)	O(41)-P(4)-O(42)	101.9(1)
O(21)-P(2)-O(23)	114.2(1)	O(41)-P(4)-O(43)	114.1(1)
O(22)-P(2)-O(23)	116.7(1)	O(42)-P(4)-O(43)	116.9(1)
O(21)-P(2)-C(1)	106.1(1)	O(41)-P(4)-C(2)	106.4(1)
O(22)-P(2)-C(1)	102.6(1)	O(42)-P(4)-C(2)	102.3(1)
O(23)-P(2)-C(1)	113.7(1)	O(43)-P(4)-C(2)	113.8(1)
P(1)-O(11)-C(111)	125.0(2)	P(3)-O(31)-C(311)	124.1(2)
P(1)-O(12)-C(121)	124.9(2)	P(3)-O(32)-C(321)	124.5(2)
P(2)-O(21)-C(21)	120.4(2)	P(4)-O(41)-C(41)	120.7(2)
P(2)-O(22)-C(22)	120.7(2)	P(4)-O(42)-C(42)	120.6(2)
P(1)-C(1)-P(2)	115.1(1)	P(3)-C(2)-P(4)	115.2(1)
O(11)-C(111)-C(112)	116.4(3)	O(31)-C(311)-C(312)	120.9(3)
O(11)-C(111)-C(116)	120.6(3)	O(31)-C(311)-C(316)	116.8(3)
C(112)-C(111)-C(116)	122.8(3)	C(312)-C(311)-C(316)	122.3(3)
C(111)-C(112)-C(113)	117.6(3)	C(311)-C(312)-C(313)	118.3(3)
C(112)-C(113)-C(114)	121.2(4)	C(312)-C(313)-C(314)	121.3(4)
C(113)-C(114)-C(115)	119.8(4)	C(313)-C(314)-C(315)	119.4)4)
C(114)-C(115)-C(116)	120.9(3)	C(314)-C(315)-C(316)	121.5(4)
C(111)-C(116)-C(115)	117.7(3)	C(311)-C(316)-C(315)	117.3(4)
O(12)-C(121)-C(122)	119.5(3)	O(32)-C(321)-C(322)	118.7(3)
O(12)-C(121)-C(126)	118.4(3)	O(32)-C(321)-C(326)	119.0(3)
C(122)-C(121)-C(126)	121.8(3)	C(322)-C(321)-C(326)	122.1(3)
C(121)-C(122)-C(123)	119.6(3)	C(321)-C(322)-C(323)	118.0(3)
C(122)-C(123)-C(124)	119.4(4)	C(322)-C(323)-C(324)	121.1(4)
C(123)-C(124)-C(125)	121.2(4)	C(323)-C(324)-C(325)	120.2(4)
C(124)-C(125)-C(126)	119.6(4)	C(324)-C(325)-C(326)	120.0(3)
C(121)-C(126)-C(125)	118.5(4)	C(321)-C(326)-C(325)	118.6(3)

The fragmentation of mixed tetraalkyl (dichloromethylene)bisphosphonates (**17**) was much like that presented above, but cleavage of a P—C bond was accelerated by chlorine atoms at the middle carbon for methyl containing compounds (see Table VI). For **17a,c** and **d** this fragmentation led to a strong signal at m/z 192, $[Cl_2HCP(=O)(OMe)_2]^{+\cdot}$, but for **17l** this peak was missing even though several ions due to P—C bond cleavage were observed: $[Cl_2HCP(=O)(OPh)_2]^{+\cdot}$ (m/z 316), $[P(=O)(OPh)_2]^{+\cdot}$ (m/z 233) and $[P(=O)(OMe)_2]^{+\cdot}$ (m/z 109). By contrast, for **17k** P—C fragmentation was less favorable and tended to eliminate first all alkyls, leading to the base peak at m/z 244. Another difference, comparing also symmetric tetra-*n*-alkyl derivatives, was at the beginning of the fragmentation process by elimination of $R—CH_2=CH_2$ unit, not $R—C_2H_2^{\cdot}$. Also the elimination of water molecules was less frequent than for derivatives of **16**.

X-Ray Crystallography

One of the studied compounds was a crystalline solid at room temperature, **16l** (82°C), thus being stable enough for X-ray structure analysis. The structural determination revealed that the asymmetric unit contained two independent molecules A and B the conformation of which, bond lengths and angles are quite similar. In Figure 1 the structure of molecule A is shown with the numbering scheme. Bond lengths and angles are presented in Tables VII and VIII.

The P—C bond lengths of 1.776(3)–1.787(3) Å were somewhat shorter than the corresponding distances in $Br_2C[PO(OMe)_2]_2$ (1.822(8) and 1.846(10) Å) and in $Cl_2C[PO(OPr^i)_2]_2$ (1.854(3) Å).[1] Moreover in the present compound the P(1)—C(1) and P(3)—C(2) bond lengths were 0.01 Å shorter than the P(2)—C(1) and P(4)—C(2) distances due to different substituents on the P atoms. In contrast the P—C—P angles in the present compound and in $Br_2C[PO(Me)_2]_2$ and $Cl_2C[PO(OPr^i)_2]_2$ seem to be equal (~115°) within experimental error, and independent of the substituents on the central methylene carbon atom. This asymmetry between the P atoms of the methylenebisphosphonate skeleton were also clearly seen in the ^{31}P NMR data by the phenoxy substituents containing P atoms which gave a signal at 12.84 ppm and 20.95 ppm for the other atom.

CONCLUSIONS

The products studied were easily prepared with good purity and yield using the approach developed. The structures and purity of these compounds were identified using either NMR spectroscopy or mass spectrometry.

In NMR studies the chemical shifts, multiplicities of the signals and $^2J_{PP}$ coupling constant offered a possibility to assign the amounts and type of alkyls in each phosphorus atom, and substituents at the middle carbon. For branched alkyl ester derivatives the dihedral angles of β-carbons were calculated by using the value of $^3J_{CP}$ constant.

In the mass spectrometric studies of unhalogenated methyl containing esters the characteristic features were the loss of the P—C-bond and for longer esters the consecutive losses of the $R—C_2H_2^{\cdot}$ unit followed by $R—CH=CH_2$ units. For halogenated methyl esters cleavage of the P—C-bond, and for longer esters the consecutive losses of the ester groups were typical.

EXPERIMENTAL

The apparatus used in the butyllithium reaction (three necked flask, dropping funnel pressure-equalization arm and adapter for thermometer) was dried for 2h at 120°C, cooled in a desiccator under dry nitrogen, collected quickly and the two open ends were closed with rubber septa. The apparatus was rinsed 20 min with dry nitrogen and two nitrogen balloons were placed to stabilize pressure changes. Solvents for this reaction were distilled over calcium hydride. Melting points were determined with a Gallenkamp melting-point apparatus and were uncorrected.

NMR Spectroscopy

^{31}P NMR spectra were recorded on a Bruker AC 250 spectrometer operating at 101.3 MHz. ^{13}C and ^{1}H spectra were recorded on a Bruker AM 400 WB operating at 100.6 MHz and 400.1 MHz, respectively. The sample solutions were prepared in 5 mm tubes (CD_3Cl) using $(HO)_4P^+ClO_4^-$ (-0.07 ppm) as an external standard for ^{31}P measurements and TMS as a reference for ^{13}C and ^{1}H measurements. The ^{1}H, ^{13}C and ^{31}P spectra were acquired using 32 kW data points with resolution enhancement and zero filling to point resolution better than 0.1 Hz.

Mass Spectrometry

The mass spectra were recorded on a JEOL JMS-D300 mass spectrometer equipped with a combined electron ionization/chemical ionization source. The system was controlled by a JEOL JMA-2000H data

TABLE IX

Crystal data and details of the crystallographic analyses

Formula	$C_{15}H_{18}O_6P_2$
M_r	356.25
Space group	P-1
a/Å	10.301(1)
b/Å	10.848(1)
c/Å	15.810(2)
α/°	79.44(1)
β/°	84.55(1)
γ/°	89.86(1)
V/Å^3	1728.8(4)
Z	4
D_c/g cm^{-3}	1.37
F(000)	744
Crystal dimensions/mm	0.40 x 0.40 x 0.45
Radiation	Mo-Kα
μ/mm^{-1}	0.27
Scan range/°	$5 \leq 2\theta \leq 55$
Scan type	ω
Number of unique data	7999
Number $F_{obs} \geq 5\,\sigma(F)$	5143
Number of variables	415
Residual density:	
Maximum (e cm^{-3})	0.33
Minimum (e cm^{-3})	-.28
R	0.045
R_w	0.048
g	0.0009
Goodness of fit	1.30

system. The source conditions were: temperature 170°C, electron energy 70 eV, acceleration voltage 3 kV and ionization current 300 μA. Samples were introduced through a direct inlet system. Accurate mass measurements were determined on a VG 70-250SE mass spectrometer at resolution 10 000 using a direct insertion probe. Fragmentation pathways were verified with metastable-ion transitions and/or CID spectra using linked scans at constant B/E.

TABLE X

Non-hydrogen atomic co-ordinates (× 10^4) for $CH_2[PO(OMe)_2][PO(OPh)_2]$ (**16l**)

	x	y	z
P(1)	2000(1)	1862(1)	1603(1)
P(2)	2568(1)	1209(1)	-163(1)
P(3)	3014(1)	7720(1)	-1647(1)
P(4)	2445(1)	6153(1)	127(1)
O(11)	2341(2)	3113(2)	1931(1)
O(12)	2797(2)	814(2)	2159(1)
O(13)	614(2)	1562(2)	1637(1)
O(21)	3482(2)	1681(2)	-1016(1)
O(22)	1202(2)	1678(2)	-432(1)
O(23)	2671(2)	-129(2)	185(1)
O(31)	2676(2)	9138(2)	-1993(1)
O(32)	2215(2)	6963(2)	-2201(1)
O(33)	4396(2)	7427(2)	-1671(1)
O(41)	1529(2)	6181(2)	981(1)
O(42)	3809(2)	6483(2)	394(1)
O(43)	2343(2)	4991(2)	-213(1)
C(1)	2921(3)	2199(2)	576(2)
C(2)	2099(3)	7531(2)	-621(2)
C(21)	4736(3)	1129(3)	-1152(2)
C(22)	568(3)	1136(3)	-1054(2)
C(41)	278(3)	5559(3)	1127(2)
C(42)	4440(3)	5617(3)	1021(2)
C(111)	2025(3)	3331(3)	2772(2)
C(112)	3043(3)	3658(3)	3194(2)
C(113)	2745(4)	3985(4)	3996(2)
C(114)	1488(4)	3966(3)	4360(2)
C(115)	497(4)	3619(4)	3929(2)
C(116)	752(3)	3305(3)	3117(2)
C(121)	2246(3)	-262(3)	2706(2)
C(122)	2117(3)	-1329(3)	2390(2)
C(123)	1683(4)	-2420(4)	2946(3)
C(124)	1392(5)	-2400(4)	3801(3)
C(125)	1509(5)	-1317(4)	4121(2)
C(126)	1951(4)	-224(3)	3566(2)
C(311)	2976(3)	9759(3)	-2849(2)
C(312)	4238(4)	9942(3)	-3197(2)
C(313)	4477(5)	10627(4)	-4027(3)
C(314)	3492(5)	11097(4)	-4487(3)
C(315)	2234(5)	10877(4)	-4133(3)
C(316)	1945(4)	10206(4)	-3301(2)
C(321)	2776(3)	6163(3)	-2737(2)
C(322)	2894(3)	4920(3)	-2395(2)
C(323)	3352(4)	4130(4)	-2945(3)
C(324)	3664(4)	4571(4)	-3804(3)
C(325)	3542(4)	5813(4)	-4135(2)
C(326)	3090(4)	6632(4)	-3597(2)

Crystallography
Details of X-ray crystal parameters, data-collection parameters and refined data for **16l** are summarized in Table IX. Intensity measurements were made on a Nicolet R3m diffractometer using graphite-monochromatized Mo-Kα radiation (ω scan mode with scan width 0.7° from K$\alpha_{1,2}$ and scan speed 2.44–29.3° min^{-1}). Monitoring of two intensity check reflections showed no crystal decay during the data collection. The data were corrected for Lorentz and polarization factors but not for absorption.

Structure analysis and refinement
The crystal structure was determined by direct methods and subsequent Fourier synthesis using the SHELXTL program package.[21] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed at calculated positions with fixed isotropic thermal parameters (C—H 0.96 Å and U 0.08 Å^2). The final atomic coordinates are presented in Table X.

Compounds
Dimethyl methylphosphonate (**3a**), trimethyl phosphite (**7a**) and diphenyl chlorophosphate (**13f**) were purchased from Aldrich-Chemie. Symmetric diethyl (**3b**), bis(1-ethylmethyl) (**3c**), dibutyl (**3d**) and dihexyl methylphosphonate (**3e**) were prepared from trialkylphosphite and methyliodide,[22] and dibenzyl methylphosphonate (**3f**) from dibenzyl sodiumphosphite and methyliodide by a known method.[8f] Mixed *n*-alkyl methylphosphonates (**5a** and **5c**) were prepared using the method developed by Thuong *et al.*[11a] and methyl (1-methylethyl) derivative **5b** according to Vepsäläinen *et al.*[12] Symmetric dimethyl (**13a**) and bis(1-methylethyl) chlorophosphates (**13b**) were prepared from phosphorus trichloride[8d] and bis(1,1-dimethylethyl) chlorophosphate (**13c**) from bis(1,1-dimethylethyl) phosphite following the procedure of Gajda *et al.*[14] Mixed chlorophosphates **13d** and **13e** were prepared from corresponding dialkyl phosphites as **13c**. Mixed methylenebisphosphonates **16** were synthesised based on the procedure by Teulade *et al.*[7d] with required modifications depending on the ester groups. The halogenations of **16** were carried out using NaOCl solution in various conditions.

*Methyl (2-propenyl) methylphosphonate (**5a**):* Prepared from **4a** (R^1=ME) and $BrCH_2CH{=}CH_2$ according to the procedure of Thuong *et al.*[11a] to give 66% of **5a** (b.p. 56–60°C/1mmHg); NMR: δ_P 30.4; δ_H 5.95 (1H, d + d + t, $^3J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 5.5 Hz), 5.37 (1H, d + m, $^3J_{HH}$ = 17.1 Hz), 5.25 (1H, d + m, $^3J_{HH}$ = 10.4 Hz), 4.54 (2H, m), 3.73 (3H, d, $^3J_{PH}$ = 11.1 Hz), 1.50 (3H, d, $^2J_{PH}$ = 17.6 Hz); δ_C 133.12 (d + d, $^1J_{CH}$ = 157.6 Hz, $^3J_{CP}$ = 5.9 Hz), 117.90 (t, $^1J_{CH}$ = 157.8 Hz), 66.05 (t + d, $^1J_{CH}$ = 147.3 Hz, $^2J_{CP}$ = 6.1 Hz), 52.07 (q + d, $^1J_{CH}$ = 147.4 Hz, $^2J_{CP}$ = 6.4 Hz), 10.72 (d + q, $^1J_{CP}$ = 144.7 Hz, $^1J_{CH}$ = 128.5 Hz).

*Methyl (1-methylethyl) methylphosphonate (**5b**):* According to Vepsäläinen *et al.*[12] to give 79% of **5b**; NMR: δ_P 31.3.

*Hexyl methyl methylphosphonate (**5c**):* Prepared from **4a** and 1-iodohexane as **5a** to give 71% of **5c**; NMR: δ_P 32.3; δ_H 4.02 (2H, m), 3.72 (3H, d, $^3J_{PH}$ = 11.0 Hz), 1.67 (2H, m), 1.47 (2H, d, $^2J_{PH}$ = 17.5 Hz), 1.4–1.3 (6H, m), 0.90 (3H, m); δ_C 65.84 (t + d, $^1J_{CH}$ = 146.3 Hz, $^2J_{CP}$ = 6.4 Hz), 52.07 (q + d, $^1J_{CH}$ = 147.2 Hz, $^2J_{CP}$ = 6.3 Hz), 31.37 (t, $^1J_{CH}$ = 127.0 Hz), 30.51 (t + d, $^1J_{CH}$ = 125 Hz, $^3J_{CP}$ = 6.1 Hz), 25.21 (t, $^1J_{CH}$ = 125 Hz), 22.55 (t, $^1J_{CH}$ = 125 Hz), 13.99 (q, $^1J_{CH}$ = 124.3 Hz), 10.41 (q + d, $^1J_{CH}$ = 128.2 Hz, $^1J_{CP}$ = 144.6 Hz).

*Hexyl (1,1-dimethylethyl) phosphite (**12d**):* Following the procedure of Kluba *et al.*[15b] from tetra-n-butylammonium (1,1-dimethylethyl) hydrogen phosphite **14d** (37.9 g, 0.1 mol) and hexyl iodide (21.2 g, 0.1 mol) to give 18.5 g (83%) of **12d**; NMR: δ_P 3.05.

*Octadecyl (1,1-dimethylethyl) phosphite (**12e**):* Prepared as **12d** from **14d** (3.8 g, 10 mmol) and $CH_3(CH_2)_{17}I$ (4.1 g, 10 mmol) to give 3.7 g (95%) of **12e**; NMR: δ_P 3.0.

*Hexyl (1,1-dimethylethyl) chlorophosphate (**13d**):* Prepared from **12d** according to the procedure of Gajda *et al.*[14] to give 93% of **13d**; NMR: δ_P −0.2; δ_H 4.07 (2H, m), 1.67 (2H, m), 1.53 (9H, s), 1.34 (2H, m), 1.26 (4H, m), 0.84 (3H, t); δ_C 88.26 (d, $^2J_{CP}$ = 8.7 Hz), 69.06 (t + d, $^1J_{CH}$ = 148.1 Hz, $^2J_{CP}$ = 7.5 Hz), 31.08 (t, $^1J_{CH}$ = 126 Hz), 29.72 (q + d, $^1J_{CH}$ = 127.3 Hz, $^3J_{CP}$ = 4.6 Hz), 29.61 (t + d, $^1J_{CH}$ = 125 Hz, $^3J_{CP}$ = 7.8 Hz), 24.92 (t, $^1J_{CH}$ = 125.9 Hz), 22.33 (t, $^1J_{CH}$ = 125.0 Hz), 13.80 (q, $^1J_{CH}$ = 124.2 Hz).

*Octadecyl (1,1-dimethylethyl) chlorophosphate (**13e**):* Prepared from **12e** as **13d** to give 95% of **13e**; NMR: δ_P δ −0.1 (t, $^3J_{PH}$ = 8.1 Hz); δ_H 4.08 (2H, m), 1.68 (2H, m), 1.55 (9H, s), 1.22 (30H, m), 0.84 (3H, t); δ_C 88.17 (d, $^2J_{CP}$ = 8.7 Hz), 69.06 (t + d, $^1J_{CH}$ = 148.3 Hz, $^2J_{CP}$ = 7.4 Hz), 31.84 (t, $^1J_{CH}$ = 126 Hz), 29.8–29.0 (13C, m), 25.30 (t, $^1J_{CH}$ = 125 Hz), 22.59 (t, $^1J_{CH}$ = 124.8 Hz), 14.00 (q, $^1J_{CH}$ = 124.2 Hz).

*P,P-Diethyl P',P'-dimethyl methylenebisphosphonate (**16a**):* Based on the procedure by Teulade *et al.*[7d] Butyllithium (2.5 M in hexane, 30 ml, 75 mmol) and bis(1-methylethyl)amine (8.1 g, 80 mmol) were added to dry tetrahydrofuran (THF, 60 ml) at −15°C and the mixture stirred at this temperature for 30 min. The solution was cooled to −75°C and **3b** (6.2 g, 41 mmol) in THF (10 ml) added at −74°C. The mixture was allowed to react at −65°C for 15 min followed by addition of **13a** (6.1 g, 42 mmol) in THF (10 ml) at −74°C. After 15 min the mixture was warmed to −20°C over 70 min. 5 N HCl was added to the vigorously stirred solution to pH 5–6, at −50°C. THF was evaporated and water (75 ml) was added. The mixture was extracted three times with $CHCl_3$ (á 50 ml), and the combined $CHCl_3$ layers were washed with cold 0.5 N NaOH (30 ml) and saturated NaCl (30 ml) solutions. The residue after drying and evaporation was dissolved in ether and allowed to stand overnight, the solids filtered and the filtrate evaporated under reduced pressure to constant weight to give 10.1 g (86%) of **16a**; NMR: δ_H 4.19 (4H, m), 3.82 (6H, d, $^3J_{PH}$ = 11.3 Hz), 2.46 (2H, t, $^2J_{PH}$ = 21.1 Hz), 1.36 (6H, t).

(1- and 2-Propenyl) trimethyl methylenebisphosphonate (**16b/16b'**): Similarly from **5a** (8.0 g, 53 mmol) and **13a** (7.9 g, 55 mmol) to give 10.3 g (72%) mixture of **16b** (60%) and **16b'** (40%). **16b**; NMR: δ_H 5.97 (1H, m), 5.40 (1H, m), 5.27 (1H, m), 4.63 (2H, m), 3.88–3.80 (9H, m), 2.50 (2H, t, $^2J_{PH}$ = 21.2). **16b'**: δ_H 6.48 (1H, m), 4.98 (1H, m), 3.88–3.80 (9H, m), 2.55 (2H, t, $^2J_{PH}$ = 21.3 Hz), 1.67 (3H, m); Calcd for $C_7H_{16}O_6P_2$:$M^{+\cdot}$ 258.0422. Found: $M^{+\cdot}$258.0394.

(1-Methylethyl) trimethyl methylenebisphosphonate (**16c**): Prepared from **5b** (9.1 g, 60 mmol) and **13a** (8.8 g, 61 mmol) as **16a** to give 13.4 g (86%) of **16c**; NMR: δ_H 4.79 (1H, d + m, $^3J_{PH}$ = 7.7 Hz), 3.82 (3H, d, $^3J_{PH}$ = 11.3 Hz), 3.81 (3H, d, $^3J_{PH}$ = 11.3 Hz), 3.80 (3H, d, $^3J_{PH}$ = 11.4 Hz), 2.44 (2H, t, $^2J_{PH}$ = 21.1), 1.37 (6H, d), 1.36 (6H, d, $^3J_{HH}$ = 6.2 Hz); Calcd for $C_7H_{19}O_6P_2$: $[M + H]^+$ 261.0657. Found: $[M + H]^+$ 261.0648.

P,P-Bis(1-methylethyl) P',P'-dimethyl methylenebisphosphonate (**16d**): From **3a** (7.7 g, 62 mmol) and **13b** (13.0 g, 65 mmol) as **16a** to give 16.7 g (94%) of **16d**; NMR: δ_H 4.78 (2H, d + m, $^3J_{PH}$ = 7.9 Hz), 3.81 (6H, d, $^3J_{PH}$ = 11.3 Hz), 2.42 (2H, t, $^2J_{PH}$ = 21.1 Hz), 1.37 (6H, d), 1.36 (6H, d).

P,P-Bis(1-methylethyl) P',P'-diethyl methylenebisphosphonate (**16e**): Prepared from **3b** (8.2 g, 54 mmol) and **13b** (11.0 Hg, 55 mmol) as **16a**, but after completed addition of **13b** the mixture was allowed to react at 0°C for 1 h to give 14.5 g (85%) of **16e**; NMR: δ_H 4.77 (2H, d + sept, $^3J_{PH}$ = 7.9 Hz, $^3J_{HH}$ = 6.2 Hz), 4.18 (4H, m), 2.41 (2H, t, $^2J_{PH}$ = 21.1 Hz), 1.36 (12H, m), 1.35 (6H, t + d, $^3J_{HH}$ = 7.1 Hz, $^4J_{PH}$ = 0.6 Hz).

Tris(1-methylethyl) methyl methylenebisphosphonate (**16f**): Prepared from **5b** (8.2 g, 54 mmol) and **13b** (11.0 g, 55 mmol) as **16e** to give 14.0 g (82%) of **16f**; NMR: δ_H 4.78 (3H, m), 3.79 (3H, d, $^3J_{PH}$ = 11.4 Hz), 2.39 (2H, t, $^2J_{PH}$ = 21.1 Hz), 1.35 (18H, m); Calcd for $C_{11}H_{27}O_6P_2$: $[M + H]^+$ 317.1283. Found: $[M + H]^+$ 317.1268.

P,P-Dibutyl P',P'-bis(1-methylethyl) methylenebisphosphonate (**16g**): Prepared from **3d** (3.3 g, 16 mmol) and **13b** (3.4 g, 17 mmol) as **16e** to give 5.08 g (85%) of **16g**; NMR: δ_H 4.77 (2H, d + m, $^3J_{PH}$ = 8.0 Hz), 4.11 (4H, d + t, $^3J_{PH}$ = 7.6 Hz, $^3J_{HH}$ = 6.7 Hz), 2.41 (2H, t, $^2J_{PH}$ = 21.1 Hz), 1.67 (4H, m), 1.42 (4H, m), 1.35 (12H, m), 0.94 (6H, t); Calcd for $C_{15}H_{35}O_6P_2$: $[M + H]^+$ 373.1909. Found: $[M + H]^+$ 373.1875.

P,P-Bis(1,1-dimethylethyl) P',P'-diethyl methylenebisphosphonate (**16h**): Prepared from **3b** (3.0 g, 20 mmol) and **13c** (4.8 g, 21 mmol) as **16a**. After completed addition of **13c** the mixture was allowed to react at 20°C for 3 h to give 5.1 g (75%) **16h**.[23,24]

Hexyl trimethyl methylenebisphosphonate (**16i**): Prepared from **5c** (11.7 g, 60 mmol) and **13a** (8.8 g, 61 mmol) as **16a** to give 17.5 g (97%) of **16i**; NMR: δ_H 4.10 (2H, m), 3.81 (3H, d, $^3J_{PH}$ = 11.3 Hz), 3.80 (6H, d, $^3J_{PH}$ = 11.3 Hz), 2.45 (2H, t, $^2J_{PH}$ = 21.1 Hz), 1.68 (2H, m), 1.38 (2H, m), 1.31 (4H, m), 0.89 (3H, t, $^3J_{HH}$ = 7.1 Hz).

P-Hexyl P-(1,1-dimethylethyl) P',P'-bis(1-methylethyl) methylenebisphosphonate (**16j**): Prepared from **3c** (5.4 g, 30 mmol) and **13d** (7.7 g 30 mmol) as **16h**, leaving 12.5 g of recidue, which contained about 75% of **16j**.[23,24]

P,P-Dihexyl P',P'-bis(1-methylethyl) methylenebisphosphonate (**16k**): Prepared from **3e** (4.8 g, 17 mol) and **13b** (3.6 g, 18 mmol) as **16e** to give 6.3 g (90%) of **16k**; NMR: δ_H 4.78 (2H, d + sept, $^3J_{PH}$ = 8.0 Hz, $^3J_{HH}$ = 6.2 Hz), 4.10 (4H, d + t, $^3J_{PH}$ = 7.6 Hz, $^3J_{HH}$ = 6.7 Hz), 2.41 (2H, t, $^2J_{PH}$ = 21.1 Hz), 1.68 (4H, m), 1.40–1.28 (24H, m), 0.89 (6H, m); Calcd for $C_{19}H_{43}O_6P_2$: $[M + H]^+$ 429.2535. Found: $[M + H]^+$ 429.2498.

P,P-Diphenyl P',P'-dimethyl methylenebisphosphonate (**16l**): Prepared from **3a** (4.2 g, 34 mmol) and **13f** (9.5 g, 36 mmol) as **16a**. The solid raw material (7.0 g) was recrystallized from CH_2Cl_2/hexane to give 5.7 g (47%) of **16l** (m.p. 89°C); NMR: δ_H 7.35–7.16 (10H, m), 3.83 (6H, d, $^3J_{PH}$ = 11.4 Hz), 2.78 (2H, t, $^2J_{PH}$ = 21.1 Hz); Calcd for $C_{15}H_{18}O_6P_2$: $M^{+\cdot}$356.0579. Found: $M^{+\cdot}$356.0565.

P,P-Dibenzyl P′,P′-diphenyl methylenebisphosphonate (**16m**): Prepared from **3f** (6.3 g, 23 mmol) and **13f** (6.45 g, 0.024 mol) as **16a**, but the lithium complex of **16l** was treated with hexamethylphosphoric triamide (HMPT, 4.1 g, 23 mmol) before acid handling[34] and separation. The raw material (12.6 g) was separated by flash chromatography using CH_2Cl_2: EtOAc (4:3) as eluent to give 5.0 g (Rf = 0.76, yield 43%) of **16m**; NMR: δ_H 7.35–7.12 (20H, m), 5.10 (4H, m), 2.76 (2H, t, $^2J_{PH}$ = 21.2 Hz); Calcd for $C_{27}H_{27}O_6P_2$: $[M + H]^+$ 509.1283. Found: $[M + H]^+$ 509.1230.

P-Octadecyl P-(1,1-dimethylethyl) P′,P′-bis(1-methylethyl) methylenebisphosphonate (**16n**): Prepared from **3c** (5.9 g, 33 mmol) and **13e** (14.0 g, 33 mmol) as **16h**, leaving 15.4 g of recidue, which contained about 60% of **16n**.[23,24]

P,P-Diethyl P′,P′-dimethyl (dichloromethylene)bisphosphonate (**17a**): $NaHCO_3$ (17 g) was suspended in aqueous 10% NaOCl (85 ml, 0.11 mol), the solution was cooled to 0°C and kept at 0°C during reaction. **16a** (8.5 g, 29 mmol) in CCl_4 (80 ml) was added with efficient stirring. After an additional 20 min of stirring at 0°C, the CCl_4 layer was separated and washed with a saturated NaCl solution (30 ml), dried and evaporated to dryness to give 9.1 g (88%) of **17a**; NMR: δ_H 4.41 (4H, m), 4.02 (6H, d, $^3J_{PH}$ = 10.9 Hz), 1.42 (6H, t, $^3J_{HH}$ = 7.1 Hz); Calcd for $C_7H_{16}Cl_2O_6P_2$: $M^{+\cdot}$ 327.9799. Found: $M^{+\cdot}$ 327.9767.

(1- and 2-Propenyl) trimethyl (dichloromethylene)bisphosphonate (**17b/17b′**): As above, yield 95% mixture of **17b** (60%) and **17b′** (40%). **17b**; NMR: δ_H 6.00 (1H, t + d + d + d, $^3J_{HH}$ = 17.1 Hz, $^3J_{HH}$ = 10.4 Hz, $^3J_{HH}$ = 5.7 Hz, $^4J_{PH}$ = 0.6 Hz), 5.44 (1H, d + m, $^3J_{HH}$ = 17.1 Hz), 5.31 (1 H, d + m, $^3J_{HH}$ = 10.4 Hz), 4.81 (2H, m), 4.08–4.00 (9H, m). **17b′**: δ_H 6.56 (1H, m), 5.03 (1H, q + d + d, $^3J_{HH}$ = 6.9 Hz, $^3J_{HH}$ = 5.7 Hz, $^4J_{PH}$ = 2.4 Hz), 4.08–4.00 (9H, m), 1.70 (3H, d + d + d, $^3J_{HH}$ = 6.9 Hz, $^4J_{HH}$ = 1.8 Hz, $^5J_{PH}$ = 1.0 Hz); Calcd for $C_7H_{14}Cl_2O_6P_2$: $M^{+\cdot}$ 325.9643. Found: $M^{+\cdot}$ 325.9699.

(1-Methylethyl) trimethyl (dichloromethylene)bisphosphonate(**17c**): Prepared similarly to **17a**, yield 93%; NMR: δ_H 4.98 (1H, m), 4.02 (3H, d, $^3J_{PH}$ = 10.9 Hz), 4.01 (3H, d, $^3J_{PH}$ = 10.9 Hz), 4.00 (3H, d, $^3J_{PH}$ = 10.9 Hz), 1.44 (6H, d + m, $^3J_{HH}$ = 6.2 Hz), 1.36 (6H, d); Calcd for $C_7H_{16}Cl_2O_6P_2$: $M^{+\cdot}$ 327.9799. Found: $M^{+\cdot}$ 327.9794.

P,P-Bis(1-methylethyl) P′,P′-dimethyl (dichloromethylene)bisphosphonate (**17d**): Prepared similarly to **17a**, but reaction time was 30 min at 10°C, yield 93%; NMR: δ_H 4.98 (2H, m), 4.01 (6H, d, $^3J_{PH}$ = 10.9 Hz), 1.43 (12H, m, $^3J_{HH}$ = 6.2 Hz); Calcd for $C_9H_{20}Cl_2O_6P_2$: $M^{+\cdot}$ 356.0112. Found: $M^{+\cdot}$ 356.0052.

P,P-Bis(1-methylethyl) P′,P′-diethyl (dichloromethylene)bisphosphonate (**17e**): Prepared similarly to **17d**, but reaction time was 3 h at 20°C, yield 96%; NMR: δ_H 4.97 (2H, m), 4.39 (4H, m), 1.42 (12H, m, $^3J_{HH}$ = 6.2 Hz), 1.40 (6H, t, $^3J_{HH}$ = 7.1); Calcd for $C_{11}H_{25}Cl_2O_6P_2$: $[M + H]^+$ 385.0503. Found: $[M + H]^+$ 385.0501.

Tris(1-methylethyl) methyl (dichloromethylene)bisphosphonate (**17f**): **16f** (0.32 g, 1 mmol) and CCl_4 (10 ml) were cooled to 0°C, and a 10% NaOCl (5 ml, 6 mmol) solution was added with efficient stirring. After 1.5 h of stirring at 0°C, the CCl_4 layer was separated and washed with a saturated NaCl solution (10 ml), dried and evaporated to dryness to give 0.36 g (95%) of **17f**; NMR: δ_H 4.97 (3H, m), 3.98 (3H, d, $^3J_{PH}$ = 10.9 Hz), 1.43 (18H, m); Calcd for $C_{11}H_{25}Cl_2O_6P_2$: $[M + H]^+$ 385.0503. Found: 385.0491.

P,P-Dibutyl P′,P′-bis(1-methylethyl) (dichloromethylene)bisphosphonate (**17g**): **16g** (2.0 g, 5.4 mmol), CCl_4 (10 ml), benzyltriethylammonium chloride (TEBAC, 0.6 g) and 10% NaOCl solution (20 ml) were added to a flask in this order with efficient stirring. After 17 h the layers were separated and the water layer extracted with CCl_4 (20 ml). The combined CCl_4 layers were washed twice with water (30 ml), dried ($MgSO_4$) and evaporated to give 1.9 g (80%) of **17g**; NMR: δ_H 4.97 (2H, m), 4.31 (4H, m), 1.73 (4H, m), 1.44 (4H, m), 1.42 (12H, d, $^3J_{HH}$ = 6.2 Hz), 0.95 (6H, t, $^3J_{HH}$ = 7.4 Hz); Calcd for $C_{15}H_{33}Cl_2O_6P_2$: $[M + H]^+$ 441.1129). Found: $[M + H]^+$ 441.1229.

P,P-Bis(1,1-dimethylethyl) P′,P′-diethyl (dichloromethylene)bisphosphonate (**17h**): Water (10 ml) and 10% NaOCl solution (10 ml, mmol) were cooled to 0°C and **16h** (1.0 g, mmol) in ethanol (3 ml) was added. The mixture was stirred at 0°C for 3 days, extracted three times with cold (0°C) CH_2Cl_2 (100 ml), washed with cold saturated NaCl solution (10 ml), dried ($MgSO_4$) and evaporated to dryness to give 0.2 g (20%) residue, which contained about 80% of **17h**.[23,24]

Hexyl trimethyl (dichloromethylene)bisphosphonate (**17i**): Prepared similarly to **17b**, yield 95%; NMR: δ_H 4.33 (2H, m), 4.01 (3H, d, $^3J_{PH}$ = 10.4 Hz), 4.00 (6H, d, $^3J_{PH}$ = 10.8 Hz), 1.74 (2H, m), 1.41 (2H, m), 1.32 (4H, m), 0.90 (3H, t, $^3J_{HH}$ = 7.1 Hz); Calcd for $C_{10}H_{22}Cl_2O_6P_2$: $[M + H]^+$ 370.0269). Found: $[M + H]^+$ 370.0237.

P,P-Dihexyl P′,P′-bis(1-methylethyl) (dichloromethylene)bisphosphonate (**17k**): Prepared similarly to **17g**, yield 85%; NMR: δ_H 4.97 (2H, m), 4.30 (4H, m), 1.73 (4H, m), 1.42 (12H, d + m, $^3J_{HH}$ = 6.2

Hz), 1.40–1.38 (12H, m), 0.89 (6H, m); Calcd for $C_{19}H_{41}Cl_2O_6P_2$: $[M + H]^+$ 497.1755. Found: $[M + H]^+$ 497.1732.

P,P-Diphenyl P′,P′-dimethyl (dichloromethylene)bisphosphonate (**17l**): Prepared similarly to **17b**, yield 88%; NMR: δ_H 7.37 (10H, m), 4.03 (6H, $^3J_{PH}$ = 11.0 Hz); Calcd for $C_{15}H_{16}Cl_2O_6P_2$: $M^{+\cdot}$ 423.9799. Found: $M^{+\cdot}$ 423.9784.

P,P-Dibenzyl P′,P′-diphenyl (dichloromethylene)bisphosphonate (**17m**): Prepared similarly to **17f**, but reaction time was 3 h at 0°C, yield 93%; NMR: δ_H 7.32–7.13 (20H, m), 5.28 (4H, m).

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