

Preparation and Identification of Tetraamide Esters of Methylene- and (Dichloromethylene)bisphosphonates

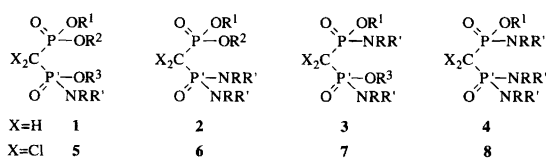
Jouko Vepsäläinen,^{a,*} Pirjo Vainiotalo,^b Heikki Nupponen^c and Esko Pohjala^c

^aUniversity of Kuopio, Department of Chemistry, P.O. Box 1627, SF-70211 Kuopio, Finland, ^bUniversity of Joensuu, Department of Chemistry, P.O. Box 111, SF-80101 Joensuu, Finland and ^cLeiras Oy, P.O. Box 33, SF-33721 Tampere, Finland

Vepsäläinen, J., Vainiotalo, P., Nupponen, H. and Pohjala, E., 1997. Preparation and Identification of Tetraamide Esters of Methylene- and (Dichloromethylene)bisphosphonates. – Acta Chem. Scand. 51: 932–937. © Acta Chemica Scandinavica 1997.

The preparation and identification of tetraamide esters of methylenebisphosphonates, $(Z^1)(Z^2)P(O)CX_2P(O)(Z^3)(Z^4)$, where $Z^1 = OMe$ or OEt , $Z^2 = OMe$, OPr^i or NEt_2 , $Z^3 = OMe$, OEt , OPr^i or NEt_2 , $Z^4 = NEt_2$, NBu_2 , $NOct_2$ and $X = H$ or Cl have been studied. Compounds were prepared from $Z_2P(O)CH_3$ and $ClP(O)Z_2$ species using LDA as the condensation reagent. 1H , ^{13}C , ^{31}P NMR data are reported including $^1J_{CP}$, $^2J_{CP}$ and $^2J_{PP}$ coupling constants. The fragmentation of some representative compounds was studied in the gas phase.

Methylenebisphosphonates (MBP), containing a stable P–C–P bridge against enzymatic hydrolysis, are commonly used to inhibit mineralization of soft tissues as well as in bone formation and resorption disorders, although their precise mechanism of action is still largely unknown.¹ MBP tetraesters, acids and their salts have been extensively studied in order to vary their biological properties by modifying the substituents at the bridging carbon.¹ Clodronate, Cl_2MBP , is one of the best documented MBP derivatives and, like other MBP compounds, its therapeutic index is narrow and bioavailability low due to very polar structure which, on the other hand, leads to compact binding of the drug to the bone surface.² Several less polar tetraalkyl^{3–7} and partial ester derivatives^{8–10} of MBP and Cl_2MBP have been prepared, but only little interest has been given to corresponding amide ester derivatives.^{6,11–13} These amido derivatives could also act as prodrugs for Cl_2MBP and partially esterified Cl_2MBP compounds. This work describes the synthesis, solution structure and mass spectrometric properties of tetraamide esters of methylene- and (dichloromethylene)bisphosphonates, **1–4** and **5–8**, respectively.

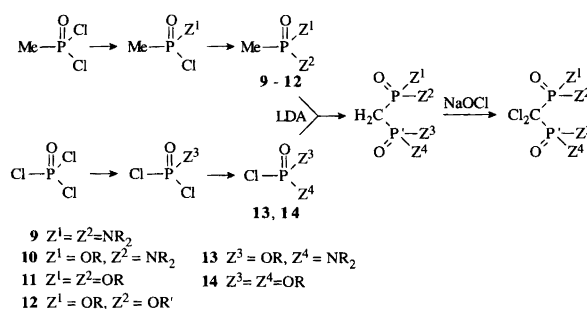


Scheme 1.

* To whom correspondence should be addressed.

Results and discussion

Preparation of monophosphorus starting materials. Methylphosphonic acid derivatives were prepared by known methods^{14,15} starting the synthesis from methylphosphonic dichloride and the corresponding amines or alcohols (see Scheme 2). The counter species in the LDA reaction, were prepared under dry conditions from phosphorus oxychloride via dichlorido esters, which were distilled before adding the second Z group.



Scheme 2.

Preparation of methylenebisphosphonates. MBP compounds were prepared from the above-mentioned MP species using the carbanion method as outlined in Scheme 2. In most cases the alkoxy group bound to phosphorus was methoxy, since these compounds were expected to be suitable starting materials for the synthesis of partial amide or amide ester Cl_2MBP compounds.^{8–10} Bisphosphonates **1–4**, e.g., **1a**, can be prepared in two different ways: starting from either **10a** and **14** or **11** and

13a, using LDA as the condensation reagent under dry conditions. The route selected depends mostly on the purity of the prepared MP species and the stability of the methylphosphonate anion. The yields of bisphosphonates were noticeably better when hindered and/or amide containing methylphosphonates were selected as the starting material, because the stability of anion is increased when more bulky groups are bound to phosphorus⁶ and, on the other hand, because the less bulky chlorine derivative reacts more readily than bulky ones. When **9** or **10** were used as the other starting material, the yields of MPB amides **1–4** were notably better compared with the yields when starting from **11** or **12** or with the yields of previously reported mixed MBP tetraesters.⁵ The purity of the products was 95% or more for all the compounds except for **1d**, which was isolated using chromatographic methods.

Preparation of (dichloromethylene)bisphosphonates. The main problem in the chlorination is to avoid decomposition of the product Cl_2MBP , by cleavage of either P–C–P or P–N bond during the reaction. Less bulky MBP compounds, e.g., **1a**, are chlorinated fast at neutral pH, but cleavage of the P–C–P backbone is observed under more basic conditions, ca. pH 10. On the other hand, sterically hindered compounds like **1d** required higher pH and temperature. Compounds containing both types of the group are most tricky to chlorinate and this is the reason why **5b** was obtained with only 94% purity although several conditions were tested. Moreover, with the octyl derivative **1c** only a trace amount of chlorinated compound **5c** was observed. The reason for the low yields in some cases (like **5d**) was the hydrolysis of P–N bond during the reaction. Obviously, the rate-limiting step in the halogenation is the substitution of the first hydrogen from P–CH₂–P' system, since in all cases the product contained either starting material or dichloride derivative, but monochloride was totally absent.

Identification of the compounds. ³¹P NMR spectroscopy is the easiest method for following the progress of the reactions and analysing the purity of the compounds. The ³¹P NMR shifts were sensitive to the number of amino groups bound to the phosphorus atoms and to the substituents on the bridging carbon. Compounds containing phosphorus with no nitrogen atom attached behaved like previously studied mixed MBP ester compounds.⁵ For molecules, e.g., **1d**, with two chiral phosphorus atoms four doublets are observed. The substituents on the nitrogen atoms had only a small influence on the ³¹P shifts and the shielding effects of the different alkoxy groups and the behavior of the ²J_{PP} coupling constants were similar to the corresponding mixed tetraesters.⁵

However, when electronegative halogen atoms were added to carbon bridged molecules containing only one nitrogen atom attached to either or both phosphorus atoms, the ³¹P shifts were observed significantly (ca.

8 ppm) upfield, but only a slight shielding effect was observed in the case of two nitrogens bound to the same phosphorus atom. This upfield shift can be explained by increased electron density coming from α -carbons (see Table 1); the ¹³C NMR shifts for the P–O–C α and P–N–C α subsystems are deshielded by ca. 3 and 1 ppm, respectively.

The ¹J_{CP} couplings for the middle carbon were sensitive to the number of amino groups on the phosphorus to which it was coupled, being approximately 150 Hz for P(O)(OR)₂, 123 Hz for P(O)(OR)(NR₂) and 105 Hz for P(O)(NR₂)₂ fragments. When chlorine atoms were added to the bridging carbon the values of the ¹J_{CP} couplings increased ca. 15 Hz in the first and ca. 8 Hz in the second case, but decreased slightly for the last P(O)(NR₂)₂ system.

The multiplets in the proton spectra were complex in appearance, but characteristic for the systems. Protons at the bridging carbon did not give rise to triplets as in the case of mixed MBP tetraesters, but four, eight or sixteen lines depending on the substituents on the phosphorus atoms. Another characteristic feature was found in the proton spectra, namely, the unequal chemical shifts of P–N–CH₂R and P–O–CH₂R (R \neq H) protons give rise to a complex splitting pattern classified as an ABX₃Y system. This behavior is because of the asymmetric or prochiral phosphorus center these groups are bound to.

The mass spectra were recorded for compounds **1–4**, **5a,b** and **6–8**. Although certain fragmentation routes were similar to those of molecules studied in the previous parts of this series, some new quite unexpected features were also found.^{4,5} The relative intensities, RI, of the ions formed in the fragmentation process are shown in Table 2 for the compounds studied. Typical fragmentation pathways for MBP and Cl₂MBP amide ester compounds are shown in Scheme 3. The molecular ion peak was clearly detected only for non-chlorinated derivatives; self-chemical ionization tended to form $[M + H]^+$ ions for the chlorinated species, which was observed in accurate mass measurement.

The fragmentation of nitrogen-containing H₂MBP and Cl₂MBP molecules was dominated by cleavage of the NR₂ \cdot fragment leading to the base peak $[M - \text{NR}_2]^+$ or NR₂⁺ with the exception of compounds **1b** and **5a**. Also the loss of ethyl as ethene after NR₂ \cdot unit from OEt-containing H₂MBP molecules was quite a favorable process. Compound **1b** even gave rise to the base peak via related process: consecutive loss of NR₂ \cdot and propene units. The loss of alkene from the P–NR₂ part was observed only for molecules containing two NR₂ units on the same phosphorus atom. With compound **5a** the base peak, $[\text{C}_5\text{H}_{13}\text{NO}_2\text{P}]^+$ ion at m/z 150, was formed through a radical-site-initiated cleavage with respect to the nitrogen atom leading to the cleavage of the P–C–P backbone. This fragment was relatively important for all chlorine-containing compounds but it was totally absent from spectra of H₂MBP compounds.

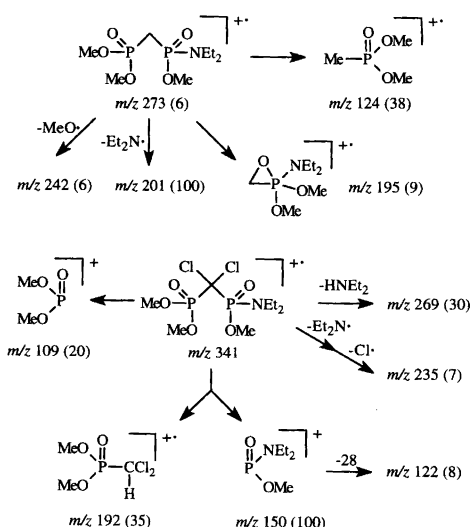
Table 1. ¹³C NMR chemical shifts in ppm and ¹J_{CP} and ²J_{CP} coupling constants in Hz for the compounds studied.

Compd.	X ₂ C	Z ¹		Z ²		Z ³		Z ⁴		X ₂ C		² J _{CP}		Z ³	Z ⁴	
		α	β	α	β	α	β	α	β	γ	δ	¹ J _{CP}	² J _{CP}			
1a	25.27	53.02	—	53.02	—	50.39	—	39.14	14.33	—	—	124.0	6.4	6.4	6.3	4.9
1b	25.88	52.79	—	52.69	24.16 ^a	68.90	—	38.74	14.02	—	—	123.4	6.3	6.2	6.4	4.9
1c	25.53	52.97	—	52.92	—	59.98	—	45.43	28.97	27.06	29.42 ^b	123.0	6.3	6.5	6.4	4.4
1d	26.10	52.94	—	71.43	24.11 ^c	50.49	—	45.18	31.13	20.21	13.90	123.6	6.3	6.6	6.4	4.6
2	25.20	53.08	—	71.49	24.20 ^d	50.55	—	45.13	31.08	20.21	13.90	123.7	6.6	6.5	6.5	4.8
3	25.17	52.99	—	52.99	—	39.00	—	39.00	14.24	—	—	106.6	6.5	6.5	4.4	4.4
4	27.60	50.06	—	39.16 ^e	14.44 [†]	59.57	—	39.11 [*]	14.42 [†]	—	—	122.7	6.6	4.8	6.4	4.8
5a	26.60	49.90	—	39.32 [*]	14.53 [†]	59.35	—	39.28 [*]	14.51 [†]	—	—	123.7	6.3	4.8	6.3	4.8
5b	26.73	59.29	16.28	39.42	14.58	39.09	—	39.03	14.35	—	—	106.0	6.3	4.9	4.5	4.4
5d	74.50	56.35	—	56.31	—	53.53	—	40.39	13.97	—	—	133.4	6.9	7.2	6.5	3.4
6	74.70	56.05	—	55.94	—	73.13	—	40.11	13.71	—	—	132.6	6.9	7.1	6.7	3.4
7	73.35	56.00	—	75.33	24.33 ^f	53.51	—	46.42	30.59	20.11	13.90	132.1	7.2	7.4	6.5	3.3
8	76.65	56.02	—	75.18	24.27 ^h	53.65	—	46.38	30.59	20.11	13.90	132.1	6.9	7.4	6.7	3.5
9	77.47	52.87	—	56.33	—	39.71	—	39.71	13.60	—	—	104.6	7.0	7.0	3.4	3.4
10	78.13	53.15	—	40.20	16.33	63.07	—	40.20	16.33	—	—	129.7	6.8	—	6.6	—
11	80.56	63.04	16.37	40.20	16.33	63.30	—	40.20	16.33	—	—	130.6	6.6	—	6.6	—
12	80.56	63.04	16.37	40.44	13.84	39.86	—	39.50	13.50	—	—	101.9	6.6	3.3	3.4	3.3

^aβ' 23.52. ^bRest of the chemical shifts 29.30, 31.83, 22.66 and 14.09. ^cβ' 23.96. ^dβ' 23.87. ^eβ' 23.60. ^fβ' 23.47. ^gNot observed owing to low intensity. ^hβ' 23.54. [†]Not resolved owing to complicated structure. ^{*}†Signals may be reversed.

Table 2 The 70 eV mass spectra of the compounds. Peaks with relative intensities (RI) greater than 5% of the intensity of the base peak are included unless not due to a molecular ion. The spectra are uncorrected for isotopic contributions.

Compd.	m/z (RI %)
1a	273 (M^{++} , 6), 242 (6), 202 (13), 201 (100), 195 (9), 124 (38), 94 (6), 93 (7), 72 (53).
1b	301 (M^{++} , 10), 242 (22), 230 (8), 205 (15), 195 (15), 187 (100), 173 (13), 124 (31), 93 (9), 79 (9), 72 (73), 58 (8).
1c	241 (19), 240 (100), 216 (10), 215 (85), 187 (58), 142 (47), 124 (19), 57 (10), 55 (10).
1d	298 (5), 230 (6), 229 (9), 201 (11), 188 (5), 187 (69), 152 (14), 129 (14), 128 (100), 127 (5), 111 (13), 110 (10), 86 (49), 84 (8), 72 (18), 57 (13).
2	314 (M^{++} , 8), 243 (16), 242 (60), 214 (6), 201 (6), 195 (21), 191 (5), 171 (15), 170 (7), 139 (7), 124 (68), 120 (7), 107 (6), 94 (7), 93 (8), 72 (100), 56 (6).
3	328 (M^{++} , 6), 257 (7), 256 (18), 228 (14), 184 (5), 179 (9), 166 (7), 165 (10), 150 (5), 138 (6), 136 (7), 135 (5), 93 (5), 73 (9), 72 (100), 71 (5), 58 (12) 56 (9).
4	369 (M^{++} , 13), 298 (22), 297 (28), 269 (12), 267 (6), 250 (15), 226 (9), 225 (19), 191 (7), 180 (6), 179 (19), 178 (12), 150 (10), 136 (7), 120 (6), 86 (7), 73 (8), 72 (100), 58 (13), 56 (9).
5a	272 (5), 271 (19), 270 (8), 269 (30), 235 (7), 194 (21), 192 (35), 151 (5), 150 (100), 149 (11), 122 (8), 109 (20), 97 (12), 94 (6), 93 (28), 79 (18), 72 (97), 71 (17), 56 (10).
5b	255 (10), 194 (17), 192 (27), 178 (21), 136 (14), 93 (6), 79 (12), 72 (100), 58 (18).
6	385 (5), 383 ($[M+H]^+$, 6), 313 (5), 311 (6), 194 (5), 192 (9), 191 (15), 120 (10), 73 (5), 72 (100), 56 (5).
7	324 (9), 296 (7), 249 (10), 247 (15), 235 (9), 233 (15), 218 (5), 164 (20), 150 (21), 136 (16), 134 (6), 120 (6), 79 (8), 73 (5), 72 (100), 71 (8), 70 (6), 58 (7), 56 (14).
8	368 (5), 366 (9), 249 (17), 247 (29), 191 (35), 166 (11), 164 (24), 162 (21), 138 (18), 136 (21), 134 (30), 120 (32), 118 (13), 72 (100), 58 (16).



Scheme 3.

Two other primary fragmentations observed from M^{++} were predictable,^{4,5} namely the loss of $RO\cdot$ and the cleavage of the P-C-P backbone with simultaneous rearrangement of a hydrogen leading to a C-P fragment containing the maximum number of oxygens available. Instead, the formation of the $[C_7H_{18}NO_3P]^+$ ion at m/z 195 for molecules **1a**, **1b** and **2** was quite unexpected. According to *B/E* results this ion was formed directly from M^{++} by loss of an O=P-OR group. The structure of the m/z 195 ion is either that displayed in Scheme 3 or $Et_2NCH_2P(O)(OMe)_2$, but further fragmentation to ions at m/z 124, 93 and 77 is more consistent with the first structure.

Experimental

Solvents for the butyllithium reaction were distilled over calcium hydride and solvents for other reactions were reagent grade. The apparatus used in the butyllithium reaction was as described before.⁹ Chlorine-containing MP species were distilled shortly before they were used.

WARNING. Methylphosphonic dichloride and its intermediates to compounds **9** and **10** are very toxic and must be handled in closed systems.

NMR spectroscopy. The 1H and ^{13}C spectra were recorded on a Bruker AM 400 WB operating at 400.1 and 100.6 MHz, respectively, and the ^{31}P NMR spectra were recorded on a Bruker AC 250 spectrometer operating at 101.3 MHz. The sample solutions were prepared in $CDCl_3$ using TMS as a reference for 1H and ^{13}C measurements and 85% H_3PO_4 as an external standard for ^{31}P measurements. In the experimental part, the order for ^{31}P chemical shifts is: P followed by P'. Coupling constant values J are given in Hz.

Mass spectrometry. The mass spectra were recorded on a VG 70-250SE or a Jeol JMS-300 mass spectrometer equipped with a combined electron ionization/chemical ionization source. The source conditions were: temperature 443 K, 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 done with the VG instrument at resolution 10 000 using a direct insertion probe. Fragmentation pathways were verified with accurate mass measurements and/or with metastable transitions.

Compounds. Symmetrical **11** was purchased from Aldrich-Chemie, **12** was prepared by known method,¹⁵ **9** was prepared from $MeP(O)Cl_2$ and **10** via $MeP(O)(OR)Cl$ ($R = Me, Et$).¹⁴ Chlorine-containing **14** was prepared directly from $Cl_3P(O)$ and mixed ester amides **13** via $Cl_2P(O)(OMe)$ or $Cl_2P(O)(OEt)$.¹⁴ Compounds **1-4** were synthesised from methylphosphonates and chlorophosphonates using LDA as the condensation agent.^{5,11} The halogenations of **1-4** were carried out using NaOCl solution under various

conditions. The purity of the compounds was 95% for all compounds, unless stated otherwise.

Methylphosphonate bis(diethylamide) (9). Prepared from MeP(O)Cl₂ (19.0 g, 0.143 mol) and diethylamine (44.0 g, 0.6 mol), to give **9** (15.9 g, 54%), b.p. 99–100 °C/1 mmHg; δ_p 34.63.

Methyl methylphosphonate diethylamide (10a). Prepared from MeP(O)Cl₂ (45.8 g, 0.3446 mol), MeOH (11.0 g, 0.3446 mol) and triethylamine (TEA, 34.8 g, 0.34 mol) followed by diethylamine (50.4 g, 0.69 mol) to give **10a** (23.8 g, 42%), b.p. 68 °C/0.5 mmHg; δ_p 34.56.

(1-Methylethyl) methylphosphonate diethylamide (10b). Prepared from MeP(O)Cl₂ (39.9 g, 0.30 mol), 2-propanol (18.0 g, 0.3 mol) and TEA (30.2 g, 0.3 mol) followed by HNEt₂ (43.9 g, 0.6 mol), to give **10b** (23.2 g, 40%, purity 93%), b.p. 113–117 °C/1 mmHg; δ_p 31.67.

Ethyl chlorophosphonate diethylamide (13a). Prepared from Cl₂P(O)(OEt) (81.5 g, 0.5 mol) and diethylamine (73.2 g, 1.0 mol), to give **13a** (75.9 g, 76%), b.p. 72 °C/1 mmHg; δ_p 16.51.

Methyl chlorophosphonate dibutylamide (13b). Prepared from Cl₂P(O)(OMe) (32.3 g, 0.22 mol) and HNBu₂ (55.57 g, 0.43 mol), to give **13b** (52.1 g, 98%, purity 87%); δ_p 19.19.

Ethyl chlorophosphonate dioctylamide (13c). Prepared from Cl₂P(O)(OEt) (5.0 g, 31 mmol), dioctylamine (7.4 g, 30.6 mmol) and TEA (3.14 g, 31 mmol), to give **13c** (10.3 g, 90%); δ_p 17.23.

P,P'-Trimethyl methylenebisphosphonate P'-diethylamide (1a). Prepared from **10a** (12.4 g, 75 mmol) and **14** (10.84 g, 75 mmol) by a known method⁶ to give **1a** (20.3 g, 99%). δ_H 3.811 (3 H, d, ³J_{PH} = 11.3), 3.806 (3 H, d, ³J_{PH} = 11.3), 3.64 (3 H, d, ³J_{PH} = 11.6 Hz), 3.12 (4 H, m), 2.42 (1 H, ddd, ²J_{PH} = 21.1, 19.8, ²J_{HH} = -15.4), 2.35 (1 H, ddd, ²J_{PH} = 21.2, 18.7), 1.14 (6 H, t, J = 7.1 Hz). δ_p 23.89 (²J_{PP} = 5.4), 25.11. (Found: M⁺, 273.0892. Calcd. for C₈H₂₁NO₅P₂: M⁺, 273.0895).

P,P'-Dimethyl P'-(1-methylethyl) methylenebisphosphonate P'-diethylamide (1b). Prepared as for **1a** from **10b** and **14**, yield 97%, purity 92%. δ_H 4.52 (1 H, dsept, ³J_{PH} = 8.6, J = 6.2), 3.69 (3 H, ³J_{PH} = 11.2), 3.68 (3 H, ³J_{PH} = 11.2), 3.00 (4 H, m), 2.28 (1 H, ddd, ²J_{PH} = 21.1, 19.7, ²J_{HH} = -15.4), 2.18 (1 H, d + d + d, ²J_{PH} = 21.1, 18.5), 1.24 (3 H, d, J = 6.2), 1.16 (3 H, d), 1.01 (6 H, t, J = 7.1). δ_p 22.10 (²J_{PP} = 5.8), 24.38. (Found: M⁺, 301.1209. Calcd. for C₁₀H₂₅NO₅P₂: M⁺, 301.1208).

P,P'-Dimethyl P'-ethyl methylenebisphosphonate P'-dioctylamide (1c). Prepared as for **1a** from **11** and **13c**, yield 81%, purity 85%. δ_H 4.02 (1 H, ddq, ²J_{HH} = -10.1,

³J_{HP} = 7.5, J = 7.1), 3.92 (1 H, ddq, ³J_{HP} = 8.1, J = 7.1), 3.810 (3 H, d, ³J_{PH} = 11.2), 3.807 (3 H, d, ³J_{PH} = 11.2), 3.74 (3 H, d, ³J_{PH} = 11.0), 3.08–2.91 (4 H, m), 2.41 (1 H, ddd, ²J_{PH} = 21.1, 19.5, ²J_{HH} = -15.3), 2.32 (1 H, ddd, ²J_{PH} = 21.1, 18.4), 1.51 (4 H, m), 1.30–1.20 (20 H, m), 0.88 (6 H, m). δ_p 23.70 (²J_{PP} = 6.4), 24.39. (Found: M⁺, 455.2967. Calcd. for C₂₁H₄₇NO₅P₂: M⁺, 455.2929).

P,P'-Dimethyl P'-(1-methylethyl) methylenebisphosphonate P'-dibutylamide (1d). Prepared as for **1a** from **12** and **13b**, yield of raw material 79%. This material was purified on silica gel (60, Merck) using CH₂Cl₂-CH₃OH (97:3) as the eluant to afford 55% of **1d**. δ_H 4.84–4.72 (1 H, m), 3.84–3.78 (3 H, d, ³J_{PH} = 11.3), 3.68–3.62 (3 H, d, ³J_{PH} = 11.5), 3.10–2.90 (4 H, m), 2.51–2.22 (2 H, m), 1.55–1.46 (4 H, m), 1.38–1.26 (10 H, m), 0.98 (6 H, t, J = 7.3). δ_p 21.82, 21.60 (²J_{PP} = 6.4, 5.9) 25.82, 25.65. (Found: M⁺, 357.18340. Calcd. for C₁₄H₃₃NO₅P₂: M⁺, 357.18338).

P,P'-Dimethyl methylenebisphosphonate P',P'-bis(diethylamide) (2). Prepared as for **1a** from **9** and **14**, yield 99%. δ_H 3.82 (6 H, d, ³J_{HP} = 11.2), 3.08 (8 H, m), 2.41 (2 H, ²J_{HP} = 22.0, 16.1), 1.13 (12 H, t, J = 7.1). δ_p 25.43 (²J_{PP} = 4.5), 25.51. (Found: M⁺, 314.1526. Calcd. for C₁₁H₂₈N₂O₄P₂: M⁺, 314.1524).

P-Ethyl P'-methyl methylenebisphosphonate P',P'-bis(diethylamide) (3). Prepared as for **1a** from **10a** and **13a**, yield 95%, purity 89%. δ_H 4.08 (1 H, m), 3.89 (1 H, m), 3.62 (1.5 H, d, ³J_{HP} = 11.53), 3.60 (1.5 H, d, ³J_{HP} = 11.5), 3.24–3.02 (8 H, m), 2.44–2.22 (2 H, m), 1.31 (1.5 H, td, J = 7.1, ⁴J_{HP} = 0.3), 1.30 (1.5 H, td, J = 7.1, ⁴J_{HP} = 0.3), 1.18–1.10 (12 H, m). δ_p 26.69, 26.66 (²J_{PP} = 7.7, 1.9), 24.78, 24.91. The ratio of diastereomers according to the ³¹P spectrum was 60:40. (Found: M⁺, 328.1690. Calcd. for C₁₂H₃₀N₂O₄P₂: M⁺, 328.1681).

P-Ethyl methylenebisphosphonate P',P',P'-tris(diethylamide) (4). Prepared as **1a** from **9** and **13a**, yield 98%. δ_H 4.07 (1 H, dqv, ²J_{HH} = -10.2, J = 7.2, ³J_{HP} = 7.1), 3.89 (1 H, ddq, J = 7.0, ³J_{HP} = 8.0), 3.3–3.0 (12 H, m), 2.32 (1 H, dd, ²J_{HP} = 20.2, 16.3), 2.31 (1 H, dd), 1.31 (3 H, t, J = 7.1), 1.132 (3 H, t, J = 7.1), 1.128 (3 H, t, J = 7.1), 1.116 (3 H, t, J = 7.1). δ_p 27.35 (²J_{PP} = 3.9), 27.13. (Found: M⁺, 369.2314. Calcd. for C₁₅H₃₇N₃O₃P₂: M⁺, 369.2310).

P,P',P'-Trimethyl (dichloromethylene)bisphosphonate P'-dioctylamide (5a). NaHCO₃ (80.6 g) was suspended in cold aqueous 10% NaOCl (211 ml, 0.10 mol) solution and 100 g of ice were added followed by **1a** (17.0 g, 62 mmol) with efficient stirring. The mixture was allowed to react 20 min at 0 °C and 1 h without cooling. The insoluble material was filtered off and filtrate was extracted twice with CH₂Cl₂ (ca. 100 ml). The organic layer was washed with saturated NaCl solution (30 ml), dried (MgSO₄) and evaporated to dryness to give **5a**

(17.5 g, 83%). δ_{H} 4.01 (6 H, d, $^3J_{\text{PH}}=10.7$), 3.90 (3 H, d, $^3J_{\text{PH}}=11.0$), 3.34 (4 H, m), 1.20 (6 H, $J=7.1$). δ_{P} 12.02 ($^2J_{\text{PP}}=21.4$), 17.09. (Found: $[M+H]^+$, 342.0177. Calcd. for $\text{C}_8\text{H}_{19}\text{Cl}_2\text{NO}_5\text{P}_2$: $[M+H]^+$, 342.0194).

P,P-Dimethyl *P'*-(1-methylethyl) (dichloromethylene) bisphosphonate *P'*-diethylamide (**5b**). Prepared as for **5a**, but the reaction time was 1 h at 0 °C and 17 h without cooling, yield 77%. δ_{H} 4.90 (1 H, dsept, $^3J_{\text{PH}}=6.7$, $J=6.2$), 4.00 (3 H, $^3J_{\text{PH}}=10.8$), 3.99 (3 H, $^3J_{\text{PH}}=10.8$), 3.43 (2 H, m), 3.26 (2 H, m), 1.44 (3 H, dm, $J=6.2$), 1.40 (3 H, d, $J=6.2$), 1.18 (6 H, t, $J=7.2$). δ_{P} 12.13 ($^2J_{\text{PP}}=22.8$), 13.50. (Found: $[M-\text{C}_3\text{H}_7\text{O}]^+$, 309.9932. Calcd. for $\text{C}_7\text{H}_{16}\text{Cl}_2\text{NOP}_2$: $[M-\text{C}_3\text{H}_7\text{O}]^+$, 309.9939).

P,P'-Dimethyl *P'*-(1-methylethyl) (dichloromethylene) bisphosphonate *P'*-dibutylamide (**5d**). **1d** (500 mg, 1.4 mmol), CCl_4 (10 ml), benzyltriethylammonium chloride (0.2 g) and 10% NaOCl solution (10 ml) were added to a flask in this order with efficient stirring. After 4.5 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 **5d** (360 mg, 61%). δ_{H} 4.98 (1 H, m), 3.983 (1.5 H, d, $^3J_{\text{PH}}=11.0$), 3.979 (1.5 H, d, $^3J_{\text{PH}}=10.9$), 3.893 (1.5 H, d, $^3J_{\text{PH}}=10.9$), 3.877 (1.5 H, d, $^3J_{\text{PH}}=10.9$), 3.33–3.10 (4 H, m), 1.58 (4 H, m), 1.42 (6 H, d, $J=6.2$), 1.32 (4 H, m), 0.94 (6 H, t, $J=7.3$). δ_{P} 10.14, 10.00 ($^2J_{\text{PP}}=21.6$, 21.0), 17.16, 17.02. (Found: M^+ , 425.1079. Calcd. for $\text{C}_{14}\text{H}_{31}\text{Cl}_2\text{NO}_5\text{P}_2$: M^+ , 425.1055).

P,P-Dimethyl (dichloromethylene) bisphosphonate *P',P'*-bis(diethylamide) (**6**). Prepared similarly to **5a**, but the reaction time was 30 min at 20 °C, yield 82%. δ_{H} 4.00 (6 H, d, $^3J_{\text{HP}}=10.9$), 3.40 (4 H, m), 3.23 (4 H, m), 1.19 (12 H, t, $J=7.1$). δ_{P} 12.91 ($^2J_{\text{PP}}=22.7$), 25.31. (Found: $[M+H]^+$, 383.0800. Calcd. for $\text{C}_{11}\text{H}_{27}\text{Cl}_2\text{N}_2\text{O}_4\text{P}_2$: $[M+H]^+$, 383.0823. Found: $[M+H]^+$, 383.0800).

P-Ethyl *P'*-methyl (dichloromethylene) bisphosphonate *P',P'*-bis(diethylamide) (**7**). Prepared as for **5d**, but the reaction time was 26 h at 25 °C, yield 71%. δ_{H} 4.36–4.06 (3 H, m), 3.81 and 3.80 (3 H, d, $^3J_{\text{HP}}=10.8$ and 11.0), 3.42–3.15 (8 H, m), 1.35 (3 H, tm, $J=7.1$), 1.13 (6 H, t, $J=7.1$), 1.12 (6 H, t, $J=7.1$). δ_{P} 18.60, 18.36 ($^2J_{\text{PP}}=20.5$, 17.9), 16.39, 16.48. (Found: $[M+H]^+$, 396.0956. Calcd. for $\text{C}_{12}\text{H}_{28}\text{Cl}_2\text{N}_2\text{O}_4\text{P}_2$: M^+ , 396.0901).

P-Ethyl (dichloromethylene) bisphosphonate *P',P',P'*-tris(diethylamide) (**8**). Prepared as for **5d**, but the reaction time was 91 h at 25 °C, yield 70%. δ_{H} 4.31 (1 H, ddq, $^2J_{\text{HH}}=-10.2$, $^3J_{\text{HP}}=8.7$, $J=7.1$), 4.21 (1 H, ddq, $^3J_{\text{HP}}=7.9$), 3.50–3.14 (12 H, m), 1.39 (3 H, td, $J=7.1$, $^4J_{\text{HP}}=0.6$), 1.172 (3 H, t, $J=7.1$), 1.166 (3 H, t, $J=7.1$), 1.163 (3 H, t, $J=7.1$). δ_{P} 17.66 ($^2J_{\text{PP}}=20.7$), 26.54. (Found: $[M+H]^+$, 438.15904. Calcd. for $\text{C}_{15}\text{H}_{36}\text{Cl}_2\text{N}_3\text{O}_3\text{P}_2$: $[M+H]^+$, 438.16088).

Acknowledgements. We would like to thank Mr. Jukka Knuutinen (Research Center Neulanen) for obtaining accurate mass measurements, Ritva Romppanen (University of Joensuu) for obtaining *B/E* measurements, Mrs. Maritta Salminkoski for technical assistance and the Academy of Finland for financial support to J.V.

References

- Bijvoet, O. L. M., Fleisch, H. A., Canfield, R. E. and Russell, R. G. G., Eds., *Bisphosphonate on Bones*, Elsevier, Amsterdam 1995.
- Hannuniemi, R., Laurén, L. and Puolijoki, H. *Drugs Tod.* 27 (1991) 375.
- McKenna, C. E., Khawli, L. A., Ahmad, W.-Y., Pham, P. and Bongartz, J.-P. *Phosphorus Sulfur* 37 (1988) 1.
- Vepsäläinen, J., Nupponen, H., Pohjala, E., Ahlgren, M. and Vainiotalo, P. *J. Chem. Soc., Perkin Trans. 2* (1992) 835.
- Vepsäläinen, J., Pohjala, E., Nupponen, H., Vainiotalo, P. and Ahlgren, M. *Phosphorus Sulfur* 70 (1992) 183.
- Teulade, M.-P., Savignac, P., Aboujaoude, E. E., Liétge, S. and Collignon, N. *J. Organomet. Chem.* 304 (1986) 283.
- Vaghefi, M. M., Bernacki, R. J., Hennen, W. J. and Robins, R. K. *J. Med. Chem.* 30 (1987) 1391.
- Vepsäläinen, J., Nupponen, H. and Pohjala, E. *Tetrahedron Lett.* 34 (1993) 4551.
- Vepsäläinen, J., Kivikoski, J., Ahlgren, M., Nupponen, H. and Pohjala, E. *Tetrahedron* 51 (1995) 6805.
- Vepsäläinen, J., Nupponen, H. and Pohjala, E. *Tetrahedron Lett.* 37 (1996) 3533.
- Aboujaoude, E.E., Liétge, S., Collignon, N., Teulade, M.-P. and Savignac, P. *Tetrahedron Lett.* 26 (1985) 4435.
- Novikova, Z. S., Prishchenko, A. A., Skorobogatova, S. Ya, Martynov, V. L. and Lutsenko, I. F. *Zh. Obshch. Khim.* 50 (1980) 989.
- Grison, C., Charbonnier, F. and Coutrot, Ph. *Tetrahedron Lett.* 35 (1994) 5425.
- Müller, E. *Methoden Der Organischen Chemie (Houben-Weyl)*, Thieme, Stuttgart, Germany, 1964, Vol. 12/1, pp. 529–538, Vol. 12/2, pp. 274–292 and 405–407.
- Vepsäläinen, J., Nupponen, H. and Pohjala, E. *Synth. Commun.* 22 (1992) 271.

Received November 4, 1996.