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Strategies for the Selective Synthesis of Monosubstituted (Dichloromethylene)bisphosphonate Esters

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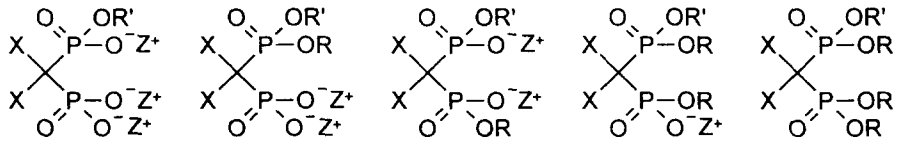
Abstract: Strategies for the selective synthesis of monosubstituted (dichloromethylene)bisphosphonate esters {$Cl_2C[P(O)(OR)(O^-Na^+)][P(O)(O^-Na^+)_2]$, where R = Pr, Pr^i, Hex, Ph} starting from monophosphorus species or from symmetric/unsymmetric H_2MBP or Cl_2MBP tetraester compounds, including the preparation of mixed tetraesters, are described and compared. © 1997 Elsevier Science Ltd.

Methylenebisphosphonate (MBP) compounds, which are characterised by a P-C-P bond, are a class of drugs used to treat various diseases of bone. These bisphosphonates bind strongly to hydroxyapatite crystals and inhibit their formation and dissolution. The physicochemical effect leads *in vivo* to the prevention of soft tissue calcification and, in some instances, to inhibition of normal calcification. The main effect is to inhibit bone resorption.[1] Recently these drugs have also been accepted as a treatment for osteoporosis.[2] Etidronate, pamidronate and clodronate are examples of commercially available drugs for these tumour-induced bone diseases.[1]

Clodronate (Cl_2MBP), which is one of the best documented and tolerated MBP derivatives, is similar to other tetraacidic MBP compounds in being highly polar, and bioavailability is only 1% to 2% of the drug dose. The efficiency of absorption increases with the concentration of the compound but diminishes when the drug is given in food and in the presence of calcium.[1] The preparation of Cl_2MBP partial esters (PE) offers a way to decrease the polarity and increase the absorption.



1 **2** **3** **4** **5**

Selective methods for all other but X_2MBP mono PEs have been described earlier.[3,4,5] Those strategies, and the processes reported here are based on selective hydrolysis of mixed (**5**) or symmetric (**10**) X_2MBP tetraester to produce Cl_2MBP PEs of type **1**, **2**, **3** and **4**.

The preparation of mixed tetraesters **5** and mono PEs **1** with published strategies and largely modified ones are described, and compared in the following.

RESULTS AND DISCUSSION

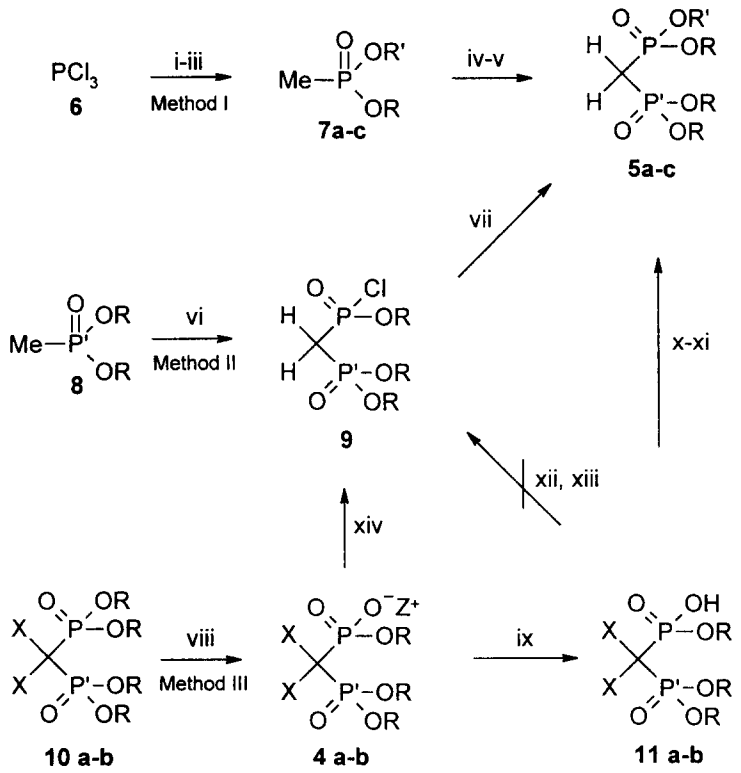
The progress of the reactions was followed by ^{31}P NMR spectroscopy and the purity of the products was determined by ^{31}P and ^{1}H NMR spectrometry. The most important chemical shifts and yields are listed in Table I. For identification of compounds see experimental.

Compound	X	R, Z	R'	δ_P	$\delta_{P'}$	Scheme/Method	Yield
1a	Cl	Na^+	Pr	11,63	9,37	II/A	60%
1b	Cl	Na^+	Hex	11,53	9,43	II/A	46%
1c	Cl	Na^+	Ph	9,54	8,94	II/A	39%
1d	Cl	Na^+	Pr	11,63	9,37	II/B	31%
1e	Cl	Na^+	Pr^i	11,00	9,50	III	75%
1f	Cl	Na^+	Hex	11,53	9,43	III	44%
2	Cl	Me, Na^+	Pr	11,43	9,22	II/B	72%
5a	H	Me	Pr	22,55	20,98	I/I	59%
5b	H	Me	Hex	22,66	21,10	I/I	90%
5b	H	Me	Hex	22,66	21,10	I/II	64%
5b	H	Me	Hex	22,66	21,10	I/III	53%
5c	H	Me	Ph	21,43	18,02	I/I	94%
5d	Cl	Me	Pr	11,21	9,83	II	55%
5e	Cl	Me	Hex	11,03	9,66	II	55%
5f	Cl	Me	Ph	10,77	6,16	II	76%
4a	H	Me, Me^+NEt_3	-	30,17	9,07	I/C	95%

Table 1. (Details in experimental). Method I: PCl_3 and ROH; MeOH/Base; MeI; LDA; $ClP(O)(OMe)_2$. Method II: $H_3CP(O)(OR)_2$ and $Cl_2P(O)OMe$; ROH. Method III: $H_2C[P(O)(OR)_2]_2$ and Et_3N; Ion exchange; $AgNO_3$; RI. Method A: $H_2C[P(O)(OR)_2][P(O)(OR)(OR')]$ and NaOCl; $ClSi(CH_3)_3$; NaOH. Method B: $H_2C[P(O)(OR)_2][P(O)(OR)(OR')]$ and NaOCl; NBu_3; $MeSO_2Cl$; NaOH; Piperidine /acetone; NaOH. Scheme III: $Cl_2C[P(O)(OR)_2][P(O)(O^-Na^+)_2]$ and piperidine /water

Mixed tetraesters **5a-c** were synthesised by three different methods (Scheme I) (Method I: condensation of dialkyl methylphosphonate and chlorophosphonic acid dialkylester by LDA; Method II: nucleophilic attack on methylenebisphosphonate by alcohol; Method III: alkylation of methylenebisphosphonic acid

monosilversalt triester by alkyl iodide). Compounds **5a-c** were prepared by method I, and compound **5b** was prepared in addition by methods II and III.

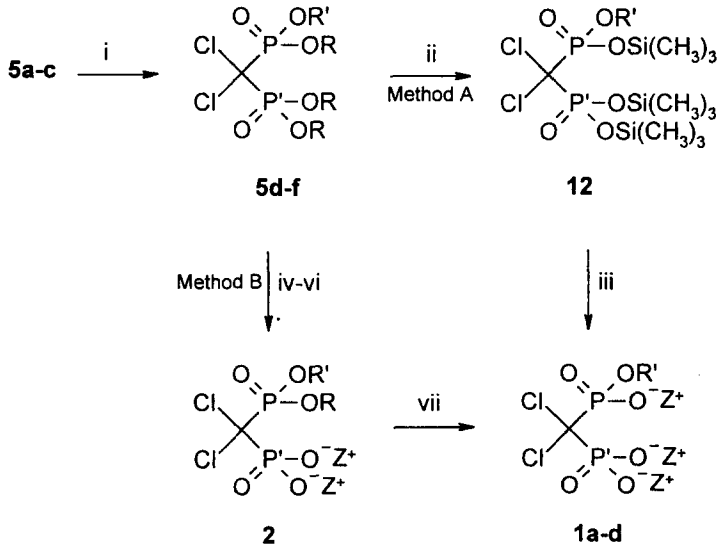


Scheme I. i) ROH; ii) MeOH/Base; iii) MeI; iv) LDA; v) $ClP(O)(OMe)_2$; vi) BuLi /$Cl_2P(O)OMe$; vii) ROH; viii) Et_3N, a=H, b=Cl; ix) Ion exchange; x) $AgNO_3$; xi) RI; xii) ClOCCOCl; xiii) $ClSi(CH_3)_3$ /PCl_5; xiv) $(ClCO)_2$

Method I can be used to prepare several different mixed tetraesters, including compound **5c**, something which is difficult to obtain by other methods. However, all steps are sensitive to water, and toxic monophosphate materials are present. The incomplete reactions result in lower overall yields. A yield of 90% was achieved for **5b** in the final step. Method II involves the reaction of a nucleophile (alcohols, thiols and amines) with compound **9**. However, because some of the steps are carried out *in situ,* by-products and unreacted toxic materials are present in the final product. Basic pH and column chromatography are required to reduce the amount of impurities to less than 5%.[6] In our work the addition of n-hexyl alcohol to **9** gave **5b** in 64% yield in the final step. Compound **5b** was also synthesised by method III, by adding hexyl iodide to methylenebisphosphonate acid monosilver salt trimethyl ester. The first step from **10a** to **4a** was previously[3] achieved for Cl_2MBP esters (**10b,** see also scheme II) with NBu_3, but unchlorinated MBP compounds (**10a**) required

harsher conditions and a less bulky tertiary amine (NEt_3) to complete the removal of the methyl group selectively (over 95% selectivity) with 95% yield and 98% purity. For the following step it was necessary to convert the mono N,N,N-triethyl-N-methyl ammonium salt **4a** to its acid form **11a**; for otherwise, during the final step, the methyl group of the ammonium salt would react with alkyl iodide to produce a mixture of products. The same strategy was applied to **4b**, but the experiment failed and a bright yellow precipitate, a mixture of silver salts, was produced. The final step gave the target **5b** in 53% yield and 86% purity, with P,P'-dihexyl P,P'-dimethyl tetraester of methylene bisphosphonic acid present as an impurity.

An attempt was made to prepare compound **9** from **11a** using oxalyl chloride[7], but the experiment failed and several products that could not be separated were obtained. Similar attempts to prepare **9** from **11a** using PCl_5[8] and $ClSi(CH_3)_3$ also failed and the desired product was not detected. The synthesis was successful when **4a** was diluted in a mixture of ether and acetonitrile and reacted with 2 equivalents of oxalyl chloride at 0 °C for 30 minutes. The purification for this reaction nevertheless caused problems, since the product was susceptible to react forward, and **9** was not detected in as high yields as reported by Saady et al.[7] for their compounds. These authors also described the selective hydrolysis of the benzyl group in the P,P-benzyl methyl P,P-diethyl difluorobisphosphonate tetraester, though it seems more likely that the methyl group would be more rapidly removed and hydrolysed than the benzyl group.[7]



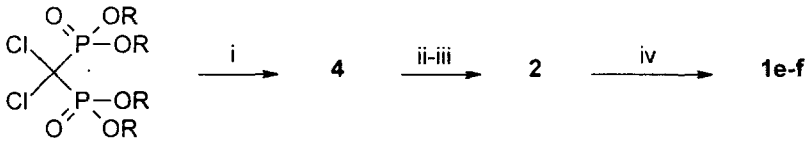
Scheme II. i) NaOCl; ii) $ClSi(CH_3)_3$; iii) NaOH; iv) NBu_3; v) $ClSO_2Me$; vi) NaOH; vii) Piperidine/acetone

The synthesis of PEs **1a-d** from the mixed tetraesters **5a-c** is described in Scheme II. Compounds **5a-c** were halogenated at the central carbon by applying NaOCl as described earlier[9]. Halogenation required control

over reaction time, temperature and pH[9] as the compounds tended to decompose during the procedure. The halogenation was achieved with less than 2% degration and the yields was 55-75%.

PEs **1a-d** were synthesised from the halogenated compounds **5d-f** by two different methods. Method A is based on silylation of the methyl groups, which was achieved in 10 to 15 minutes time for all compounds. Method A was more successful for **1c** than **1a** and **1b**, since no removal of the phenyl group occurred. The final products (**1a-c**) were crystallised from MeOH/NaOH(aq.) by adding acetone. Method B proceeded via removal of the P'P'-dimethyl ester groups by using NBu_3 and $ClSO_2Me$. From the P,P-dialkyl PEs that formed, only the **2** was isolated up to 72% yield. When this crude product was crystallised from water-alcohol mixture, up to 100% purity was obtained. Other methods do not give P,P-dialkyl PEs in such high purity. The presence of some by-products tended to decrease the yield, since in the first step ca. 25% of NBu_3 also reacted with the methyl group of P', giving a mixture of $(MeO)(RO)P(O)CCl_2P(O)(OMe)(O^-MeN^+R_3)$ and $(MeO)_2P(O)CCl_2P(O)(OR)(O^-MeN^+R_3)$. The selectivity of NBu_3 is increased with larger R-groups.

Of PEs **1** starting from symmetric tetraester **10b**, an alternative method for the synthesis is described in scheme III. The yields of PEs **1** were highly dependent on the first step. With methyl tetraesters tertiary amines reacted rapidly giving ca. 100% yield[5], but for other esters the yield was ca. 80%. As the lengths of the ester chains increased, the amount of P,P'-dialkyl esters also increased, even though some starting material was still available. The final product **1** was achieved in high yield for mono methyl ester[3] and up to 75% yield for long and branched esters.



10b

Scheme III. i) NR_3; ii) $ClSO_2Me$; iii) MeOH/NaOH; iv) Piperidine/water

CONCLUSION

Mono partial esters **1a-f** were prepared by different methods. All three methods for the synthesis of mixed tetraesters proved useful. Mixed phenyl ester (**5c**) was merely obtained by with method I through BuLi work. The silver salt method (III) gave good results for the long mixed tetraester **5b**. Short mono PEs were easily achieved via P,P-dialkyl PEs through selective removal of the methyl group from P'. This method (B) is also the only way to obtain unsymmetric P,P-diesters of **2** in high purity. Scheme III shows an easy way to obtain short and branched mono PEs.

EXPERIMENTAL

General: The apparatus used for the LDA reaction was dried for 2 hours at 120 °C and solvents and reagents were distilled before use. All other solvents and reagents were high-purity reagent-grade materials and used without further purification. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker AM 400 spectrometer operating at 400.1, 100.6 and 162.0 MHz, respectively; TMS or TSP (for D_2O solutions) was used as an internal standard for ^{1}H and ^{13}C measurements and 85% H_3PO_4 as an external standard for ^{31}P measurements. Normal $^{3}J_{HH}$ couplings are indicated by the letter "J" and all J values are given in Hz. The purity of products was >95% unless stated otherwise. Yields were not optimised. $H_2C[P(O)(OMe)_2]_2$ (**10a**) was purchased from Lancaster Synthesis. Synthesis and characterisation of the bisphosphonate starting materials have been reported earlier.[9,10]

Methyl propyl methylphosphonate (**7a**): Prepared following the procedure of Vepsäläinen *et al.*[9] from PCl_3 (50 g, 365 mmol), 1-propanol (14.8 g, 243 mmol), methanol (12.4 ml, 310 mmol), pyridine (25 ml, 310 mmol) and methyl iodide (8.0 ml, 128 mmol). Yield 12.31 g (26%), bp. 28-30 °C (p= 0.4-0.5 mbar); NMR ($CDCl_3$): δ_P 32.14

Hexyl methyl methylphosphonate (**7b**): Prepared similarly to **7a**. Yield 26%, bp. 54-56 °C (p= 0.2-0.3 mbar); NMR: ($CDCl_3$): δ_P 32.11.

Methyl phenyl methylphosphonate (**7c**): Prepared similarly to **7a**. Yield 10% bp. 72-76 °C (p= 0.3 mbar); ($CDCl_3$): δ_P 29.42.

[(Dimethoxyphosphino)methyl]phosphonic acid monomethyl ester N,N,N-triethyl-N-methyl ammonium salt (**4a**): Prepared following the procedure of Vepsäläinen *et al.*[3] from **10a** (5.0 g, 21.5 mmol) and triethylamine (25 ml) (refluxed for 3 hours and 35 minutes). Yield 6.82 g (95%). NMR: ($CDCl_3$): δ_H 3.78 (3H, d, $^{3}J_{PH}$=11.0), 3.76 (6H, d, $^{3}J_{PH}$=11.0), 3.55 (6H, q), 3.19 (3H, s), 2.28 (2H, t, J=18.3), 1.37 (9H, t, J=7.1). δ_P 30.17 d ($^{2}J_{pp}$= 7.2), 9.07 d. δ_C 55.56 t, 52.50 q+d ($^{2}J_{CP}$=6.4), 51.81 q+d ($^{2}J_{CP}$=6.0), 46.95 q, 24.41 t+t ($^{1}J_{CP}$=117), 7.98 q.

[(Dimethoxyphosphino)methyl]phosphonic acid monomethyl ester (**11a**): Prepared from **4a** using H^+-form Dowex resin. Yield 100%.

[(Dimethoxyphosphino)methyl]phosphonic acid methyl propyl ester (**5a**): Prepared following the procedure of Vepsäläinen *et al.*[9] from butyllithium (1.6 M in hexane, 22.2 ml, 35.5 mmol), di-isopropylamine (5.0 ml, 35.5 mmol), **7a** (3.0 g, 19.7 mmol) and dimethyl chlorophosphate (3.1 g, 19.7 mmol). Yield 2.95 g (59%); NMR: ($CDCl_3$): δ_H 4.08 (2H, m), 3.83 (3H, d, $^{3}J_{PH}$=11.3), 3.82 (6H, d, $^{3}J_{PH}$=11.3), 2.50 (2H, t, $^{2}J_{PH}$=21.1), 1.73 (2H, m), 0.98 (3H, t, J=7.4). δ_P 22.55 d ($^{2}J_{pp}$=5.7), 20.98 d. δ_C 68.26 t+d ($^{2}J_{CP}$=6.6), 53.16 q (3C), 24.05 t+t ($^{1}J_{CP}$=137.2), 23.83 t+d ($^{3}J_{CP}$=6.4), 10.00 q.

[(Dimethoxyphosphino)methyl]phosphonic acid hexyl methyl ester (**5b**): Method I: Prepared similarly to **5a.** Yield 90%. Method II: Prepared following the procedure of Grison *et al.*[6] from butyllithium (1.6 M in hexane, 5.75 ml, 9.2 mmol), **8** (1.1 g, 9.2 mmol), methyl dichlorophosphate (0.7 g, 4.6 mmol) and hexanol (0.6 ml, 4.6 mmol). Yield 0.88 g (64%). Method III: Prepared by mixing **11** (480 mg, 2.2 mmol), silver nitrate (380 mg, 2.2 mmol) and dry toluene (6 ml) in a flask. n-Hexyl iodide (340 ml, 2.2 mmol) in dry toluene (3 ml) was added to the mixture in dark, the mixture was refluxed for 90 minutes and filtered. The filtrate was evaporated to dryness and CH_2Cl_2 (10 ml) was added. The organic phase was washed twice with water (2 x 2 ml), dried ($MgSO_4$) and evaporated to dryness. Yield 360 mg (53%). NMR: ($CDCl_3$): δ_H 4.10 (2H, m), 3.84 (3H, d, $^{3}J_{PH}$=11.3) 3.81 (6H, d, $^{3}J_{PH}$=11.3), 2.48 (2H, t, $^{2}J_{PH}$=21.1), 1.70 (2H, m), 1.39 (2H, m), 1.31 (4H, m), 0.89 (3H, t, J=7.0). δ_P 22.66 d ($^{2}J_{pp}$=5.5), 21.10 d. δ_C 66.82 t+d ($^{2}J_{CP}$=6.5), 53.10 q (3C), 31.34 t, 30.43 t+d ($^{3}J_{CP}$=6.3), 25.47 t, 24.10 t+t ($^{1}J_{CP}$=137.7), 22.54 t, 13.99 q.

[(Dimethoxyphosphino)methyl]phosphonic acid methyl phenyl ester (**5c**): Prepared similarly to **5a.** Yield 94%. NMR: ($CDCl_3$): δ_H 7.38-7.31 (2H, m), 7.26-7.14 (3H, m), 3.89 (3H, d, $^3J_{HP}$=11.5), 3.84 (3H, d, $^3J_{HP}$=11.3), 3.81 (3H, d, $^3J_{HP}$=11.4), 2.62 (2H, t, $^2J_{HP}$=21.2). δ_P 21.43 d ($^2J_{pp}$=6.4) 18.02 d. δ_C 150.12 d ($^2J_{CP}$=8.2), 129.88 d (2C), 125.36 d, 120.52 d+d ($^3J_{CP}$=4.4), 53.99 q+d ($^2J_{CP}$=6.5), 53.42 q+d ($^2J_{CP}$=6.3), 53.16 q+d ($^2J_{CP}$=6.5), 24.24 t+t ($^1J_{CP}$=138.2).

[(Dimethoxyphosphino)dichloromethyl]phosphonic acid methyl propyl ester (**5d**): Prepared following the procedure of Vepsäläinen *et al.*[10] from NaOCl (8% solution, 18 ml) and **5a** (1.5 g, 5.8 mmol). Yield 1.04 g (55%). NMR: ($CDCl_3$): δ_H 4.29 (2H, m), 4.04 (3H, d, $^3J_{PH}$=10.9), 4.01 (6H, d, $^3J_{PH}$=10.9), 1.79 (2H, m), 1.01 (3H, t, J=7.4). δ_P 11.21 d ($^2J_{pp}$=23.4), 9.83 d. δ_C 71.80 t+d ($^2J_{CP}$=7.4), 71.62 t+t ($^1J_{CP}$=155.0), 56.52 q+d ($^2J_{CP}$=6.8), 56.48 q+d ($^2J_{CP}$=6.9), 23.90 t+d ($^3J_{CP}$=5.6), 9.93 q.

[(Dimethoxyphosphino)dichloromethyl]phosphonic acid hexyl methyl ester (**5e**): Prepared similarly to **5d**. Yield 55%. NMR: ($CDCl_3$): δ_H 4.32 (2H, m), 4.02 (3H, d, $^3J_{PH}$=10.9), 4.01 (6H, d, $^3J_{PH}$=10.9), 1.75 (2H, m), 1.41 (2H, m), 1.32 (4H, m), 0.90 (3H, t, J=7.0). δ_P 11.03 d ($^2J_{pp}$ =23.7), 9.66 d. δ_C 71.61 t+t ($^1J_{CP}$=155.0), 70.42 t+d ($^2J_{CP}$=7.3), 56.49 q (3C), 31.27 t, 30.47 t+d ($^3J_{CP}$=8.7), 24.99 t, 22.52 t, 13.98 q.

[(Dimethoxyphosphino)methyl]phosphonic acid methyl phenyl ester (**5f**): Prepared similarly to **5d**. Yield 76%. NMR: ($CDCl_3$): δ_H 7.32-7.18 (5H, m), 4.04 (3H, d, $^3J_{PH}$=12.2), 4.01 (6H, d, $^3J_{PH}$=12.0). δ_P 10.77 d ($^2J_{pp}$=24.0), 6.16 d. δ_C 150.63 d ($^2J_{CP}$=9.3), 129.84 d (2C), 125.69 d, 120.36 d+d (2C, $^3J_{CP}$=7.9), 71.30 t+t ($^1J_{CP}$=157.7), 57.18 q+d ($^2J_{CP}$=7.0), 56.58 q+d ($^2J_{CP}$=7.0).

{[(Methoxy(1-propyloxy)phosphino]dichloromethyl}phosphonic acid disodium salt (**2**). **5d** (400 mg, 1.3 mmol) and NBu_3 (380 mL, 1.6 mmol) were refluxed in acetonitrile (3 ml) for 70 minutes. Then $ClSO_2Me$ (168 mL, 1.3 mmol) was added to the mixture. After refluxing for 60 minutes, the solution was evaporated to dryness and the residue was diluted in methanol (5 ml). The mixture was cooled to 0 °C and 2 N NaOH (ca. 1.6 ml) was added until pH ~ 8-10. The mixture was evaporated to dryness and acetone (2 ml) was added. The precipitate was washed three times with a small amount of acetone. Yield 310 mg (72%). NMR: (D_2O): δ_H 4.26 (t+d, 2H, J=6.7, $^3J_{HP}$=8.3), 3.95 (d, 3H, $^3J_{HP}$=10.7), 1.75 (t+t, 2H, J=7.5), 0.97 (t, 3H). δ_P 11.43 d ($^2J_{pp}$=15.3), 9.22 d.

{[Hydroxy(1-propyloxy)phosphino]dichloromethyl}phosphonic acid trisodium salt (**1a**): Prepared following the procedure of Vepsäläinen *et al.*[4] from **5d** (500 mg, 1.52 mmol), NaI (750 mg, 5.01 mmol) and $ClSi(CH_3)_3$ (550 mg, 5.01 mmol). Yield 310 mg (60%). NMR: (D_2O): δ_H 4.06 (2H, m), 1.65 (2H, m), 0.93 (3H, t, J=7.4). δ_P 11.63 d ($^2J_{pp}$=15.7), 9.37 d. δ_C 83.33 d+d ($^1J_{CP}$=135.6, $^1J_{CP}$=117.5), 72.76 t+d ($^2J_{CP}$=7.3), 26.83 t+d ($^3J_{CP}$=4.7), 12.35 q.

{[Hydroxy(1-hexyloxy)phosphino]dichloromethyl}phosphonic acid trisodium salt (**1b**)**:** Prepared similarly to **1a.** Yield 46%. NMR: (D_2O): δ_H 4.11 (2H, m), 1.64 (2H, m), 1.40-1.30 (6H, m), 0.88 (3H, t, J=6.8). δ_P 11.53 d ($^2J_{pp}$=15.9), 9.43 d. δ_C 71.38 t+d ($^2J_{CP}$=11.3), 33.69 t, 33.45 t+d ($^3J_{CP}$=7.4), 27.45 t, 24.78 t, 16.19 q. The signal from central carbon (CCl_2, $t \geq 60$ s, no noe) was not observed owing to low solubility of the sample.

{[Hydroxy(phenyloxy)phosphino]dichloromethyl}phosphonic acid trisodium salt (**1c**): Prepared similarly to **1a**. Yield 39%. NMR: (D_2O): δ_H 7.38-7.20 (5H, m). δ_P 9.54 ($^2J_{pp}$=14.9), 8.94 d. δ_C 155.06 d ($^2J_{CP}$=8.7), 132.26 d, 126.92 d, 124.39 t+d ($^3J_{CP}$=3.7), 82.50 d+d ($^1J_{CP}$=141.0, $^1J_{CP}$=116.2).

{[Hydroxy(1-propyloxy)phosphino]dichloromethyl}phosphonic acid disodium N-methyl piperidinium salt (**1d**): **5d** (500 mg, 1.5 mmol) and NBu_3 (280 mg, 1.5 mmol) were refluxed in acetonitrile (5 ml) for 30 minutes. Then $ClSO_2Me$ (230 mg, 2.0 mmol) was added. After refluxing for 30 minutes, the solution was evaporated to dryness and the residue was

diluted in methanol (5 ml) and cooled to 0 °C for addition of 2 N NaOH (1.0 ml). The mixture was stirred for 1 hour and cooled to + 5 °C over night. Evaporation to dryness and addition of acetone (5 ml) followed. The precipitate was then collected and washed with a small amount of acetone and diluted in piperidine (2 ml) and heated with an oil bath at 100 °C for one hour. The excess of piperidine was evaporated. The residue was suspended in ether and evaporated to dryness. Yield 200 mg (31%). After ion-exchange (Na^+-form, 3 eq.), the ^1H and ^{31}P NMR chemical shifts were identical to those of **1a**.

Dealkylation of long chain and branched XYMBD P,P-dialkyl partial esters to monoesters 1e-f. General procedure. The preparation of compound **2** from **10b** with NBu_3 and $MeSO_2Cl$ has been described earlier.[3,5] Compound **2** and ten-fold excess of piperidine and water were refluxed until no more P,P-dialkyl PEs was detected by ^{31}P NMR. The reaction mixture was evaporated to dryness and treated with Dowex resin (H^+-form). NaOH was added until pH 10 was reached.

{[Hydroxy(1-methylethoxy)phosphino]dichloromethyl}phosphonic acid trisodium salt (**1e**): Yield 75% after crystallisation from water/acetone, white powder identical with the sample prepared in reference 4.

{[Hydroxy(1-hexyloxy)phosphino]dichloromethyl}phosphonic acid trisodium salt (**1f**): Yield 44% after crystallisation from water/ethanol, light brown solids identical with the sample **1b**.

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