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Synthesis of New Unexpected Stable Mixed Alkanoic, Phosphonic and Sulphonic (Dichloromethylene)bisphosphonic Anhydride Esters

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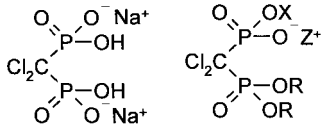
Abstract—New mixed alkanoic, phosphonic and sulphonic (dichloromethylene)bisphosphonic anhydride esters [$(RO)_2P(O)CCl_2$-$P(O)(OX)(O^-Z^+)$, $(RO)_2P(O)CCl_2P(O)(OX)(OR)$ and $(Z^+O^-)(RO)P(O)CCl_2P(O)(OX)(O^-Z^+)$; X=C(O)R, $P(O)(OR)_2$, SO_2Me; R=CH_3, C_6H_5, $CH(CH_3)_2$, $(CH_2)_5CH_3$; Z=ammonium, Na^+, K^+)] were selectively synthesised, and characterised by NMR spectroscopy. These new compounds are stable and bear potential bioreversible bisphosphonate protecting groups.

Clodronate (Cl_2MBP) **1** and other methylenebisphosphonates (MBP) are analogues of pyrophosphate, but resistant to chemical and enzymatic hydrolysis.[1] These compounds are used in the treatment of diseases related to enhanced bone resorption such as osteoporosis, Paget's disease and tumor-induced hypercalcaemia.[2–5] Due to their high polarity and ionisation at physiological pH, MBPs possess limited oral bioavailability (1–5%),[2,6] which is likely attributed to their poor lipophilicity and charge, which in addition prevents the cellular uptake.[2,7] Furthermore, complexation of MBPs with divalent metal cations may reduce the absorption to zero.[6–8] This and the low bioavailability could be avoided by masking one or more ionisable groups by using the prodrug approach: a promoiety is linked to the functional group of a drug to form a prodrug, which should undergo chemical or enzymatic hydrolysis or both to regenerate the parent compound after absorption.[9,10] In many cases, neutral esters, simple esters or acyloxyalkyl esters, have been used as bioreversible promoities for polar compounds.[10–13]



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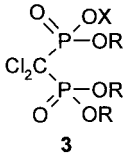

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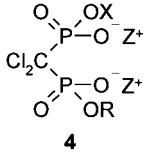

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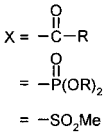

X = –C(=O)–R

= –P(=O)(OR)$_2$

= –SO_2Me

Earlier, the selective synthesis of tetraalkyl,[14,15] partial alkyl[16] and amide esters[17] of clodronate have been reported. From these, simple esters were shown to be ineffective as prodrugs due to their stability towards aqueous and enzymatic hydrolysis.[18] It has been proposed that esters bearing a negative charge in close proximity to the site of action of esterases are poor prodrugs.[19,20] This could probably be avoided by using acyloxyalkyl esters, where the site of action of the esterase is separated from the charge or by using anhydrides, which were shown to be bioreversible despite of the presence of negative charge in close proximity.[21] However, the method described in a patent[22] for preparing tetra(acyloxyalkyl) esters was not successful in our hands.

Based on the bioreversibility of anhydrides[21] and difficulties in preparing acyloxyalkyl derivatives, we decided to study the synthesis of mixed anhydride esters **2–4** [X=C(O)R, $P(O)(OR)_2$, SO_2Me; R=CH_3, C_6H_5, $CH(CH_3)_2$, $(CH_2)_5CH_3$] using simple esters as models for acyloxyalkyl esters. In such compounds, potential bioreversible anhydride structures are present and it is possible to mask three or even four chargeable groups of Cl_2MBP.

Results and Discussion

We have recently described the synthesis and in vitro evaluation of P,P′-dianhydrides of Cl_2MBP **5** (R=CH_3; $(CH_2)_2CH_3$; $C(CH_3)_3$; C_6H_5), which were obtained selectively from tetrasodium clodronate **6** and acid anhydrides (Scheme 1).[21] Although anhydrides of etidronate $[(H_3C)(HO)C[P(O)(OH)(O^-Na^+)]_2]$ were unstable under isolation, the dianhydrides of clodronate are stable and bioreversible. The obvious reason for the stability in water

Keywords: bisphosphonates; synthesis; mixed anhydrides.

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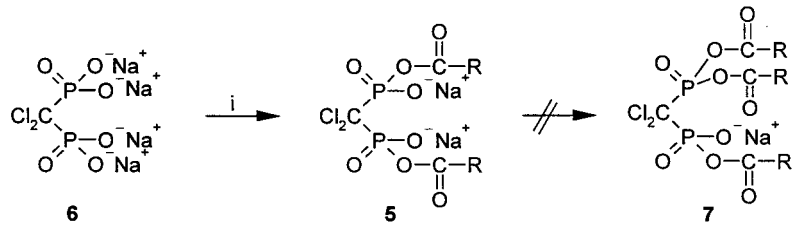
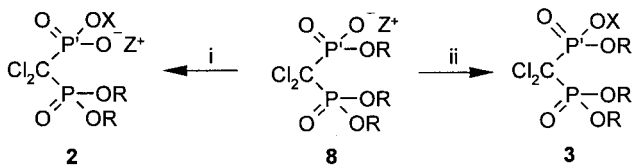


Scheme 1. (i) $(RCO)_2O$.

(half-lives from 15 to 790 h, pH 7.4) is the electronegative chlorine atoms in the bridging carbon. However, this synthesis strategy suffers from limitations: only dianhydrides of clodronate were formed selectively; tri (**7**) or tetra anhydrides were not detected in the reaction mixture. Thus, in order to mask more than two charges we used partial esters of Cl_2MBP to produce selectively mixed anhydride esters of Cl_2MBP.

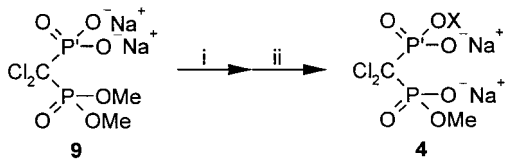
The strategy to prepare mixed anhydride esters of Cl_2MBP is based on our previous studies[23] to prepare P,P-diesters in which sulphonic-anhydride structure was an intermediate. Following this approach we prepared compounds **2** and **3** depending on the counterion Z^+, which promotes the reaction on P′. In Scheme 2, the reaction between **8a**–**b** and the reagent yielded selectively alkanoic, sulphonic and phosphonic anhydride esters of Cl_2MBP (**2a**–**f** and **2h**–**j**). For **8a** (R=Me, Z=Me^+NBu_3) 1-1.5 equiv. of the reagent was needed to complete the reaction, acylation and sulphonation were then easily achieved. These reactions occurred at room temperature, but when the mixture was heated at 60°C or under reflux, the reaction was complete in 1–2 h. After vacuum evaporation, the product was obtained quantitatively without need for purification, except in the case of **2c**. The phosphorylation of **8a** required 1 equiv. of freshly distilled phosphorochloridic acid dialkyl ester (R=Me, ^{i}Pr or Hex) under anhydrous reaction conditions, leading typically to a mixture of **8a**, the reagent, by-products and **2d**–**f** with about 80–85% selectivity. These products are stable in cold water thus the synthesis impurities were removed by washing with cold water, lowering the yields of desired products. The same approach was used for **8b** (R=^{i}Pr), but in this case increasing the amount of the reagents (1.5–2.0 equiv.) and heating the solvents under reflux for 2 h. After purification, the products (**2h**–**j**) were obtained with 60, 98 and 54% of the theoretical yield, respectively; **2i** and **2j** still containing impurities. If **8b** is not the main impurity, the crude products can be extracted to the aqueous layer to gain higher purity. For example, **2i** was extracted to the aqueous layer from the toluene layer and isolated with 97% yield and 96% purity.



Scheme 2. (i) ClC(O)R or $ClP''(O)(OR)_2$ or $ClSO_2Me$; (ii) NEt_3 and ClC(O)R or $ClP''(O)(OR)_2$.

Using the same method as above but adding a base in the reaction mixture, we found a remarkable change in the reaction for **8b**. In this way uncharged anhydride esters were selectively observed if the counterion was $^iPr^+$Pyridine. In Scheme 2, **3a**–**c** were obtained after **8b** was treated with triethylamine and benzoyl chloride or phosphorochloridic acid dialkyl ester at room temperature after 6 h stirring; **3a**–**c** are difficult to obtain otherwise, although $(HO)(^iPrO)P(O)CCl_2P(O)(O^iPr)_2$ reacted with phosphorochloridic acid dialkyl esters in the presence of K_2CO_3 yielding **3d**–**e**. The same method for $(MeO)_2P(O)CCl_2P(O)(OMe)(OH)$ yielded **2** and traces of **3**, and compound **2g** was synthesised in this manner. Without base no acylation or phosphorylation was observed for $(MeO)_2P(O)CCl_2P(O)(OMe)(OH)$, but in the case of $(HO)(^iPrO)P(O)CCl_2P(O)(O^iPr)_2$ the reaction succeeded in some extent with phosphorochloridic acid dialkyl esters. Efforts to synthesise **3**, where R=Me, using **8a** as starting material and the procedure used for **8b**, failed resulting in $(MeO)_2P(O)Cl_2CP(O)(O^-Z^+)(OX)$. The difference in reaction between **8a** and **8b** is probably caused by the catalytic effect from the formation of 1-propene. Indeed, in the case of **8b** the ^{1}H NMR spectra (at low temperature) confirmed the production of propene during the reaction. Efforts to synthesise mixed dianhydride esters of Cl_2MBP failed. We used $(Z^+O^-)(MeO)P(O)CCl_2P(O)(OMe)(O^-Z^+)$ (Z=H or ammonium) as a starting material and acetyl chloride or acetic anhydride as a reagent, but no desired product was obtained under any conditions from room temperature to heating under reflux.

Earlier we described the use of piperidine as a dealkylating agent for diester **9** to selectively form monoester derivative.[24] We used this derivative and acetic anhydride to selectively form mixed anhydride ester **4**. In Scheme 3, the P,P-diester **9** was first treated with an excess of piperidine in the presence of water to remove[24] selectively one of the methyl groups. After evaporation in vacuo, the residue was treated with a large excess of acetic anhydride. Due to the piperidinium exchange between P and P′, the diester **9** was P′ acylated. This was verified from the ^{1}H and ^{31}P NMR spectra: the ^{1}H spectrum showed a doublet at 2.22 ppm with 1 Hz coupling constant and the ^{1}H coupled ^{31}P spectrum



Scheme 3. (i) Water/piperidine; (ii) $(CH_3CO)_2O$.

Table 1. The yields, ^{31}P NMR shifts and $^{2}J_{PP}$ constants for mixed anhydride esters of Cl_2MBP

Compound	R	X	Z	δ_P	$\delta_{P'}$	$\delta_{P''}$	$^{2}J_{PP'}$	$^{2}J_{P'P''}$	Yield (%)
8a	Me	–	Me^+NBu_3	15.3	4.3	–	16.6	–	–
8b	^{i}Pr	–	^{i}Pr$^+$Pyridine	11.1	3.3	–	19.9	–	–
2a	Me	C(O)CH_3	Me^+NBu_3	14.15	−2.64	–	18.2	–	100
2b	Me	SO_2Me	Me^+NBu_3	12.37	−3.29	–	21.1	–	100
2c	Me	C(O)C_6H_5	Me^+NBu_3	14.71	−1.06	–	18.3	–	81
2d	Me	P(O)$(OMe)_2$	Me^+NBu_3	14.17	−4.61	−10.04	20.1	27.7	43
2e	Me	P(O)$(O^iPr)_2$	Me^+NBu_3	14.36	−4.90	−13.96	21.2	26.3	77
2f	Me	P(O)$(OHex)_2$	Me^+NBu_3	14.44	−4.43	−12.10	21.2	26.7	37
2g	Me	P(O)$(OHex)_2$	K^+	14.04	−3.27	−11.3	24.3	26.8	12
2h	^{i}Pr	SO_2Me	^{i}Pr$^+$Pyridine	8.27	−1.37	–	22.9	–	60
2i	^{i}Pr	P(O)$(O^iPr)_2$	^{i}Pr$^+$Pyridine	9.09	−3.91	−13.76	25.0	26.6	98
2j	^{i}Pr	P(O)$(OHex)_2$	^{i}Pr$^+$Pyridine	9.35	−3.52	−11.79	25.5	26.3	54
3a	^{i}Pr	C(O)C_6H_5	–	6.37	3.67	–	25.3	–	96
3b	^{i}Pr	P(O)$(O^iPr)_2$	–	6.32	−0.93	−14.55	25.7	28.9	100
3c	^{i}Pr	P(O)$(OHex)_2$	–	6.23	−0.84	−12.78	25.7	30.2	81
3d	^{i}Pr	P(O)$(OMe)_2$	–	6.10	−0.59	−10.78	25.6	29.7	48
3e	^{i}Pr	SO_2Me	–	5.61	0.66	–	25.1	–	32
4	–	C(O)CH_3	–	9.08	4.06	–	16.1	–	76

showed two patterns: a doublet of quartets at 9.08 ppm with a $^{3}J_{HP}$ constant of 10.4 Hz; a doublet at 4.06 ppm, but when resolution enhancement was used, a quartet was obtained with a $^{4}J_{PH}$ constant of 1 Hz. After 24 h of stirring of the mixture at room temperature, the acid-insoluble product **4** was easily collected as white solids from the solution. Other acid anhydrides, butyric or hexanoic anhydrides, formed a gel under the reaction conditions and no desired product was obtained.

Products were characterised by ^1H, ^{31}P and ^{13}C NMR spectroscopy, and ES–MS. NMR data is listed in the Experimental section and the ^{31}P chemical shifts are listed in Table 1. Some of the characteristic NMR features of these compounds are discussed below. Typically, the $^{31}P'$ signal for mixed anhydride esters migrates significantly upfield with respect to the starting material: the upfield shift is generally 4–9 ppm higher for the phosphorylated compounds. Also the $^{2}J_{PP}$ constants were informative: the increase for the products in $^{2}J_{PP'}$ was generally 1.6–5.8 Hz being higher for the phosphorylated compounds, for which the ^1H decoupled ^{31}P NMR spectra showed a triplet or doublet of doublets corresponding to P′. In addition, the formation of mixed sulphonic anhydrides was confirmed by the ^1H coupled ^{31}P NMR spectra: a $^{31}P'$ doublet of doublets was detected for uncharged **3e** at 0.66; a $^{31}P'$ doublet was detected at −3.29 or −1.37 for charged **2b** and **2h**, respectively. Strong evidence for the formation of alkanoic anhydrides was provided by ^1H decoupled ^{13}C NMR spectra, where the P–O–C^{α} shift for the carbonyl carbon appeared as a doublet with a $^{2}J_{CP}$ constant between 8.8 and 10.4 Hz in the region 167–160 ppm.

Conclusions

A selective and general method for the synthesis of mixed anhydride esters of Cl_2MBP has been developed. Starting the synthesis from triester **8** either P,P-diester-P′-anhydrides or P,P,P′-triester-P′-anhydride is obtained with good yields. The present mixed alkanoic, phosphonic and sulphonic (dichloromethylene)bisphosphonic anhydride esters are new compounds bearing potential enzyme-labile anhydride groups. Since simple esters of clodronate are not regenerated[18] to the parent drug, they are used here as models for acyloxyalkyl derivatives, which are potential enzyme-labile groups.[20] Thus, it is expected that mixed anhydride esters have a broad application in the prodrug approach.

Experimental

General

All solvents and reagents were high-purity-grade materials and used without further purification except acetic anhydride, acetyl chloride, methanesulphonyl chloride and phosphorochloridic acid dialkyl esters reagents, which were distilled before use. NMR spectra were recorded on a Bruker AM 400 spectrometer using TMS or TSP as an internal standard for ^1H and ^{13}C measurements and 85% H_3PO_4 as an external standard for ^{31}P measurements. The letter 'J' indicates normal 3JHH couplings and all *J* values are given in Hz. ES mass spectra was recorded using a Finnigan quadrupole ion trap mass spectrometer. HRMS spectra were recorded using Micromass LCT equipment and Bruker BioAPEX 47e FTICR mass spectrometer. The purity of products was >95% unless stated otherwise. Phosphorochloridic acid dialkyl esters were prepared from phosphorus trichloride.[24] Synthesis and characterisation of bisphosphonate starting materials **8a**–**b** and **9** have been reported earlier.[16,23]

General procedure for the synthesis of Cl_2MBP anhydride esters (2a–f)

Acetonitrile (3.0 ml), **8a** and acetyl chloride (1.5 equiv.), benzoyl chloride (1.05 equiv.), methanesulphonyl chloride (1.25 equiv.) or phosphorochloridic acid dialkyl ester (1.0 equiv.) were mixed and heated at 60°C (**2a**) for 1 h or under reflux for 45 min (**2d**–**e**), 1 h (**2b**), 2 h (**2c**) or 4 h (**2f**), and then evaporated to dryness in vacuo. The residue of **2c**–**f** was redissolved in 4.0 ml cold CH_2Cl_2 and washed once (twice for **2d**) with 0.5 ml cold saturated aq. NaCl (**2c**–**e**) or 0.5 ml cold saturated aq. $NaHCO_3$ (**2f**). A

centrifuge was used to facilitate the decantation. The organic phase was evaporated to dryness in vacuo.

Tributyl(methyl)ammonium *O*-acetyl[(dimethoxyphosphoryl)dichloromethyl]phosphonate (2a). Prepared from **8a** (200 mg) to give **2a** (213 mg, 100%) as yellowish oil; ν(KBr) 3417, 2964, 2291, 1751, 1465, 1266; δ_H (400.1 MHz, $CDCl_3$) 3.99 (6H, d, $^3J_{HP}$=9.0 Hz, OMe), 3.36 (6H, m, $^+NCH_2$), 3.20 (3H, s, $^+NCH_3$), 2.07 (3H, s, O_2CCH_3), 1.68 (6H, m, $^+NCH_2CH_2$), 1.43 (6H, m, CH_2CH_3), 0.99 (9H, t, J=7.2 Hz, CH_2CH_3); δ_P (162.0 MHz, $CDCl_3$) 14.15 (d, $^2J_{PP'}$=18.2 Hz), −2.64 (d); δ_C (100.6 MHz, $CDCl_3$) 166.97 (d, $^2J_{CP}$=9.4 Hz), 75.00 (dd, $^1J_{CP}$=149.9 Hz, $^1J_{CP}$=132.7 Hz), 61.26 (CH_2), 55.96 (qd, $^2J_{CP}$=6.8 Hz, CH_3), 48.74 (CH_3), 24.25 (CH_2), 19.65 (CH_2), 13.70 (CH_3); ES–MS ($C_5H_9Cl_2O_7P_2$) *m/z* 312.9 $[M-MeNBu_3]^-$; HRMS: $[MH-MeNBu_3+NH_4]^+$, found 331.9636. $C_5H_{14}NO_7P_2Cl_2$ required 331.9623.

Tributyl(methyl)ammonium *O*-methylsulphonyl[(dimethoxyphosphoryl)dichloromethyl]phosphonate (2b). Prepared from **8a** (240 mg) to give **2b** (272 mg, 100%) as yellowish oil; ν(KBr) 3427, 2965, 2253, 1464, 1263, 1180; δ_H (400.1 MHz, $CDCl_3$) 4.00 (6H, d, $^3J_{HP}$=10.7 Hz, OMe), 3.36 (3H, s, MeS), 3.31 (6H, m, $^+NCH_2$), 3.14 (3H, s, $^+NCH_3$), 1.68 (6H, m, $^+NCH_2CH_2$), 1.43 (6H, m, CH_2CH_3), 1.00 (9H, t, J=7.3 Hz, CH_2CH_3); δ_P (162.0 MHz, $CDCl_3$) 12.37 (d, $^2J_{PP'}$=21.1 Hz), −3.29 (d); δ_C (100.6 MHz, $CDCl_3$) 73.62 (dd, $^1J_{CP}$=151.54 Hz, $^1J_{CP}$=142.7 Hz), 61.39 (CH_2), 56.34 (d, $^2J_{CP}$=7.0 Hz, CH_3), 48.75 (CH_3), 39.72 (CH_3), 24.21 (CH_2), 19.63 (CH_2), 13.68 (CH_3); ES–MS ($C_4H_9Cl_2O_8P_2S$) 348.8 *m/z* $[M-MeNBu_3]^-$; HRMS: $[MH-MeNBu_3+NH_4]^+$, found 367.9314. $C_4H_{14}NO_8P_2SCl_2$ required 367.9292.

Tributyl(methyl)ammonium *O*-benzoylyl[(dimethoxyphosphoryl)dichloromethyl]phosphonate (2c). Prepared from **8a** (100 mg) to give **2c** (96 mg, 81%) as yellowish oil; ν(KBr) 3419, 2961, 1717, 1452, 1266; δ_H (400.1 MHz, $CDCl_3$) 8.18 (2H, m, Ph), 7.53 (1H, m, Ph), 7.42 (2H, m, Ph), 3.99 (6H, d, $^3J_{HP}$=10.7 Hz, OMe), 3.41 (6H, bs, $^+NCH_2$), 3.32 (3H, s, $^+NCH_3$), 1.67 (6H, bs, $^+NCH_2CH_2$), 1.42 (6H, m, CH_2CH_3), 0.98 (9H, t, J=7.1 Hz, CH_2CH_3); δ_P (162.0 MHz, $CDCl_3$) 14.71 (d, $^2J_{PP'}$=18.3 Hz), −1.06 (d); δ_C (100.6 MHz, $CDCl_3$) 162.86 (d, $^2J_{CP}$=8.8 Hz), 132.96 (CH), 130.94 (d, $^3J_{CP}$= 5.4 Hz, C), 130.59 (CH), 128.24 (CH), 74.72 (dd, $^1J_{CP}$= 150.8 Hz, $^1J_{CP}$=135.3 Hz), 61.22 (CH_2), 55.96 (d, $^2J_{CP}$= 3.2 Hz, CH_3), 48.98 (CH_3), 24.34 (CH_2), 19.69 (CH_2), 13.72 (CH_3); ES–MS ($C_{10}H_{11}Cl_2O_7P_2$) 375.0 *m/z* $[M-MeNBu_3]^-$; HRMS: $[MH-MeNBu_3+NH_4]^+$, found 393.9789. $C_{10}H_{16}NO_7P_2Cl_2$ required 393.9779.

Tributyl(methyl)ammonium *O*-dimethoxyphosphoryl-[(dimethoxyphosphoryl)dichloromethyl]phosphonate (2d). Prepared from **8a** (100 mg) to give **2d** (52 mg, 43%) as yellowish oil with 94% purity; ν(KBr) 3427, 2963, 2185, 1464, 1269; δ_H (400.1 MHz, $CDCl_3$) 4.00 (6H, d, $^3J_{HP}$= 10.6 Hz, OMe), 3.87 (6H, d, $^3J_{HP}$=11.6 Hz, OMe), 3.36 (6H, m, $^+NCH_2$), 3.24 (3H, s, $^+NCH_3$), 1.67 (6H, m, $^+NCH_2CH_2$), 1.44 (6H, m, CH_2CH_3), 1.00 (9H, t, J= 7.2 Hz, CH_2CH_3); δ_P (162.0 MHz, $CDCl_3$) 14.17 (d, $^2J_{PP'}$=20.1 Hz), −4.61 (dd), −10.04 (d, $^2J_{P'P''}$=27.7 Hz); δ_C (100.6 MHz, $CDCl_3$) 74.60 (ddd, $^1J_{CP}$=150.2 Hz, $^1J_{CP}$=137.5 Hz, $^3J_{CP}$=6.2 Hz), 61.26 (CH_2), 56.04 (d, $^2J_{CP}$=6.7 Hz, CH_3), 54.69 (d, $^2J_{CP}$=6.0 Hz, CH_3), 48.97 (CH_3), 24.30 (CH_2), 19.69 (CH_2), 13.73 (CH_3); ES–MS ($C_5H_{12}Cl_2O_9P_3$) 379.2 *m/z* $[M-MeNBu_3]^-$; HRMS: $[MH-MeNBu_3+NH_4]^+$, found 397.9509. $C_5H_{17}NO_9P_3Cl_2$ required 397.9493.

Tributyl(methyl)ammonium *O*-di(1-methylethoxy)phosphoryl[(dimethoxyphosphoryl)dichloromethyl]phosphonate (2e). Prepared from **8a** (100 mg) to give **2e** (101 mg, 77%) as yellowish oil with 94% purity; ν(KBr) 3419, 2966, 2253, 1466, 1286; δ_H (400.1 MHz, $CDCl_3$) 4.83 (2H, m, CH), 4.00 (6H, d, $^3J_{HP}$=10.7 Hz, OMe), 3.41 (6H, m, $^+NCH_2$), 3.29 (3H, s, $^+NCH_3$), 1.68 (6H, m, $^+NCH_2CH_2$), 1.44 (6H, m, CH_2CH_3), 1.35 (12H, d, J=6.1 Hz, CH_3), 1.00 (9H, t, J=7.27 Hz, CH_2CH_3); δ_P (162.0 MHz, $CDCl_3$) 14.36 (d, $^2J_{PP'}$=21.2 Hz), −4.90 (dd), −13.96 (d, $^2J_{P'P''}$=26.3 Hz); δ_C (100.6 MHz, $CDCl_3$) 74.72 (dd, $^1J_{CP}$=150.6 Hz, $^1J_{CP}$=137.2 Hz), 72.53 (d, $^2J_{CP}$=5.9 Hz, CH), 61.26 (CH_2), 56.03 (d, $^2J_{CP}$=5.4 Hz, CH_3), 48.98 (CH_3), 24.35 (CH_2), 23.81 (d, $^3J_{CP}$=3.8 Hz, CH_3), 23.60 (d, $^3J_{CP}$=5.0 Hz, CH_3), 19.71 (CH_2), 13.73 (CH_3); ES–MS ($C_9H_{20}Cl_2O_9P_3$) 435.0 *m/z* $[M-MeNBu_3]^-$; HRMS: $[MH_2-MeNBu_3]^+$, found 436.9883. $C_9H_{22}O_9P_3Cl_2$ required 436.9854.

Tributyl(methyl)ammonium *O*-dihexyloxyphosphoryl-[(dimethoxyphosphoryl)dichloromethyl]phosphonate (2f). Prepared from **8a** (50 mg) to give **2f** (27 mg, 37%) as yellowish oil; [Found: C, 42.94; H, 8.10; N 1.74. $C_{28}H_{62}Cl_2NO_9P_3\times4H_2O$ requires C, 42.43; H, 8.90; N 1.77%]; ν(KBr) 3423, 2962, 2331, 1466, 1289; δ_H (400.1 MHz, $CDCl_3$) 4.18 (4H, m, OCH_2), 4.00 (6H, d, $^3J_{HP}$=10.8 Hz, OMe), 3.35 (6H, m, $^+NCH_2$), 3.25 (3H, s, $^+NCH_3$), 1.60–1.70 (10H, m, $^+NCH_2CH_2$, OCH_2CH_2), 1.44 (6H, m, $^+N(CH_2)_2CH_2$), 1.36 (4H, m, $O(CH_2)_2CH_2$), 1.20–1.30 (8H, m, $O(CH_2)_3CH_2CH_2$), 1.00 (9H, t, J=7.2 Hz, $^+N(CH_2)_3CH_3$), 0.87 (6H, t, J=6.4 Hz, $O(CH_2)_5CH_3$); δ_P (162.0 MHz, $CDCl_3$) 14.44 (d, $^2J_{PP'}$=21.2 Hz), −4.43 (dd), −12.10 (d,$^2J_{P'P''}$=26.7 Hz); δ_C (100.6 MHz, $CDCl_3$) 74.51 (dd, $^1J_{CP}$=151.1 Hz, $^1J_{CP}$=136.4 Hz), 68.15 (d, $^2J_{CP}$=6.4 Hz, CH_2), 61.22 (CH_2), 56.04 (d, $^2J_{CP}$=7.3 Hz, CH_3), 49.21 (CH_2), 31.46 (CH_2), 30.25 (d, $^3J_{CP}$=7.8 Hz, CH_2), 25.21 (CH_2), 24.33 (CH_2), 22.58 (CH_2), 19.71 (CH_2), 14.03 (CH_3), 13.74 (CH_3); ES–MS ($C_{15}H_{32}Cl_2O_9P_3$) 519.3 *m/z* $[M-MeNBu_3]^-$; HRMS: $[MH_2-MeNBu_3]^+$, found 521.0758. $C_{15}H_{34}O_9P_3Cl_2$ required 521.0793.

General procedure for the synthesis of Cl_2MBP anhydride esters (2h–j)

Acetonitrile (3.0 ml), **8b** and sulphonyl chloride (1.5 equiv.) or phosphorochloridic acid dialkyl ester (2.0 equiv.) were mixed and heated under reflux for 2 h, and then evaporated to dryness in vacuo. The residue was redissolved in 10 ml (**2h**) or 4.0 ml (**2i**) cold CH_2Cl_2 or 2.0 ml cold toluene (**2j**), and washed once with 1.0 ml cold water (**2h**) or twice with 2.0 ml cold water (**2j**) or once with 0.5 ml cold saturated aq. NaCl (**2i**). A centrifuge was used to facilitate the decantation. The organic phase was evaporated to dryness in vacuo.

***N*-(1-Methylethyl)pyridinium *O*-methylsulphonyl[(di-1-methylethoxyphosphoryl)dichloromethyl]phosphonate (2h).** Prepared from **8b** (200 mg) to give **2h** (128 mg, 60%) as yellowish oil; ν(KBr) 3434, 2983, 1630, 1484; δ_H (400.1 MHz, $CDCl_3$) 9.33 (2H, bs, pyridinium), 8.44 (1H, bs, pyridinium) 8.21 (2H, bs, pyridinium), 5.28 (1H, m, $^+$NCH), 4.97 (2H, m, OCH), 3.36 (3H, s, SCH_3), 1.70 (6H, d, J=6.3 Hz, $^+$NCH(CH_3)$_2$), 1.41 (12H, d, J=6.2 Hz, OCH(CH_3)$_2$); δ_P (162.0 MHz, $CDCl_3$) 8.27 (d, $^2J_{PP'}$=22.9 Hz), −1.37 (d); δ_C (100.6 MHz, $CDCl_3$) 145.21 (CH), 143.55 (CH), 129.04 (CH), 75.10 (d, $^2J_{CP}$=7.5 Hz, CH), 74.37 (dd, $^1J_{CP}$=152.0 Hz, $^1J_{CP}$=138.8 Hz), 64.90 (CH), 39.65 (CH_3), 23.62 (d, $^3J_{CP}$=3.0 Hz, CH_3), 23.18 (CH_3); HRMS: [MH_2–^{i}Pr$^+$Pyridine]$^+$, found 406.9693. $C_8H_{19}O_8P_2SCl_2$ required 406.9653.

***N*-(1-Methylethyl)pyridinium *O*-di(1-methylethoxy)phosphoryl[(di-1-methylethoxyphosphoryl)dichloromethyl]-phosphonate (2i).** Prepared from **8b** (100 mg) to give **2i** (123 mg, 98%) as yellowish oil with 92% purity; ν(KBr) 3431, 2982, 2235, 1631, 1484; δ_H (400.1 MHz, $CDCl_3$) 9.61 (2H, m, pyridinium), 8.42 (1H, m, pyridinium), 8.22 (2H, m, pyridinium), 5.47 (1H, m, CH), 4.99 (2H, m, CH), 4.84 (2H, m, CH), 1.73 (6H, d, J=6.6 Hz, CH_3), 1.40 (12H, d, J=6.1 Hz, CH_3), 1.34 (12H, d, J=6.1 Hz, CH_3); δ_P (162.0 MHz, $CDCl_3$) 9.09 (d, $^2J_{PP'}$=25.0 Hz), −3.91 (t), −13.76 (d, $^2J_{P'P''}$ 26.6 Hz); δ_C (100.6 MHz, $CDCl_3$) 145.20 (CH), 143.83 (CH), 129.11 (CH), 74.99 (ddd, $^1J_{CP}$=151.7 Hz, $^1J_{CP}$=139.9 Hz, $^3J_{CP}$=5.7 Hz), 74.60 (d, $^2J_{CP}$=7.4 Hz, CH), 72.84 (d, $^2J_{CP}$=6.2 Hz, CH), 64.63 (CH), 24.26 (d, $^3J_{CP}$=2.8 Hz, CH_3), 23.74 (d, $^3J_{CP}$=4.7 Hz, CH_3), 23.62 (d, $^3J_{CP}$=4.4 Hz, CH_3), 23.57 (d, $^3J_{CP}$=3.6 Hz, CH_3), 23.10 (CH_3); ES–MS ($C_{13}H_{28}Cl_2O_9P_3$) 491.4 *m/z* [M−^{i}Pr$^+$Pyridine]$^-$; HRMS: [MH_2−^{i}Pr$^+$Pyridine]$^+$, found 493.0450. $C_{13}H_{30}O_9P_3Cl_2$ required 493.0480.

***N*-(1-Methylethyl)pyridinium *O*-dihexyloxyphosphoryl-[(di-1-methylethoxyphosphoryl)dichloromethyl]phosphonate (2j).** Prepared from **8b** (250 mg) to give **2j** (190 mg, 54%) as yellowish oil with 92% purity; ν(KBr) 3435, 2959, 2253, 1483, 1386, 1291; δ_H (400.1 MHz, $CDCl_3$) 9.48 (2H, m, pyridium), 8.37 (1H, m, pyridium), 8.23 (2H, m, pyridium), 5.43 (1H, bs, CH), 4.97 (2H, m, CH), 4.17 (4H, m), 1.69 (6H, d, J=6.1 Hz), 1.60–1.70 (4H, covered), 1.40 (6H, d, J=5.8 Hz), 1.39 (6H, d, J=6.1 Hz), 1.20–1.30 (8H, m), 1.3–1.4 (4H, covered), 0.87 (6H, t, J=6.7 Hz); δ_P (162.0 MHz, $CDCl_3$) 9.35 (d, $^2J_{PP'}$=25.5 Hz), −3.52 (t), −11.79 (d, $^2J_{P'P''}$=26.3 Hz); δ_C (100.6 MHz, $CDCl_3$) 144.69 (CH), 143.93 (CH), 128.99 (CH), 73.96 (ddd, $^1J_{CP}$=153.9 Hz, $^1J_{CP}$=148.8 Hz, $^3J_{CP}$=5.2 Hz), 74.64 (d, $^2J_{CP}$=7.3 Hz, CH), 68.21 (d, $^2J_{CP}$=6.4 Hz, CH_2), 64.60 (CH_2), 31.42 (CH_2), 30.20 (d, $^3J_{CP}$=7.8 Hz, CH_2), 25.19 (CH_2), 23.63 (d, $^3J_{CP}$=6.4 Hz, (CH_3), 23.27 (CH_3), 22.56 (CH_2), 14.01 (CH_3); ES–MS ($C_{19}H_{40}Cl_2O_9P_3$) 575.7 *m/z* [M−^{i}Pr$^+$Pyridine]$^-$; HRMS: [MH_2−^{i}Pr$^+$Pyridine]$^+$, found 577.1409. $C_{19}H_{42}O_9P_3Cl_2$ required 577.1419.

General procedure for the synthesis of Cl_2MBP anhydride esters (3a–c)

Triethyl amine (1.5 equiv.) and bentzoyl chloride (1.5 equiv.), or phosphorochloridic acid dialkyl ester (1.2 equiv.) were diluted in acetonitrile (2.0 ml). Compound **8b**, diluted in acetonitrile (3.0 ml), was added dropwise to the solution and stirred at room temperature for 6 h under argon atmosphere. After evaporation of the mixture to dryness in vacuo, the residue was diluted in 10 ml (**3a**) or 4.0 ml (**3c**) cold toluene or 4.0 ml cold CH_2Cl_2 (**3b**) and filtered if necessary. The filtrate was washed once with 1.0 ml cold water (**3a**) or 0.5 ml cold saturated aq. NaCl (**3b**) or 0.5 ml cold saturated aq. $NaHCO_3$ (**3c**). A centrifuge was used to facilitate decantation. The organic phase was evaporated to dryness in vacuo.

1-Methylethyl *O*-benzoyl[(di-1-methylethoxyphosphoryl)-dichloromethyl]phosphonate (3a). Prepared from **8b** (100 mg) to give **3a** (93 mg, 96%) as orange oil; ν(KBr) 2985, 2251, 1755, 1466, 1388, 1241; δ_H (400.1 MHz, $CDCl_3$) 8.21 (2H, m, Ph), 7.65 (1H, m, Ph), 7.50 (2H, m, Ph), 5.32 (1H, m, CH), 5.02 (1H, m, CH), 5.01 (1H, m, CH), 1.52 (6H, d, J=6.2 Hz, CH_3), 1.43 (12H, dd, CH_3); δ_P (162.0 MHz, $CDCl_3$) 6.37 (d, $^2J_{PP'}$=25.3 Hz), 3.67 (d); δ_C (100.6 MHz, $CDCl_3$) 160.31 (d, $^2J_{CP}$=10.4 Hz), 134.75 (CH), 131.27 (CH), 128.34 (CH), 127.77 (d, $^3J_{CP}$=6.3 Hz, CH), 78.00 (d, $^2J_{CP}$=7.6 Hz, CH), 75.70 (d, $^2J_{CP}$=7.6 Hz, CH), 75.60 (d, $^2J_{CP}$=7.5 Hz, CH), 71.44 (dd, $^1J_{CP}$=162.3 Hz, $^1J_{CP}$=155.3 Hz), 24.32 (bs), 23.84 (d, $^3J_{CP}$=3.6 Hz, CH_3), 23.52 (bs); HRMS: [M+Na]$^+$, found 497.0431. $C_{17}H_{26}O_7P_2Cl_2Na$ required 497.0423.

1-Methylethyl *O*-di(1-methylethoxy)phosphoryl[(di-1-methylethoxyphosphoryl)dichloromethyl]phosphonate (3b). Prepared from **8b** (100 mg) to give **3b** (109 mg, 100%) as yellowish oil; [Found: C, 36.60; H, 6.87. $C_{16}H_{35}Cl_2O_9P_3$ requires C, 35.90; H, 6.59%]; ν (KBr) 3010, 2270, 1468, 1395, 1290; δ_H (400.1 MHz, $CDCl_3$) 5.17 (1H, m, CH), 4.99 (1H, m, CH), 4.98 (1H, m, CH), 4.92 (1H, m, CH), 4.82 (1H, m, CH), 1.50 (3H, d, J=6.2 Hz, CH_3), 1.47 (3H, d, J=6.3 Hz, CH_3), 1.43 (12H, d, J=6.3 Hz, CH_3), 1.40 (12H, d, J=6.4 Hz, CH_3); δ_P (162.0 MHz, $CDCl_3$) 6.32 (d, $^2J_{PP'}$=25.7 Hz), −0.93 (t), −14.55 (d, $^2J_{P'P''}$=28.9 Hz); δ_C (100.6 MHz, $CDCl_3$) 77.87 (d, $^2J_{CP}$=7.4 Hz, CH), 75.74 (d, $^2J_{CP}$=7.4 Hz, CH), 75.65 (d, $^2J_{CP}$=7.5 Hz, CH), 74.80 (d, $^2J_{CP}$=6.0 Hz, CH), 74.65 (d, $^2J_{CP}$=6.2 Hz, CH), 71.46 (ddd, $^1J_{CP}$=165.9 Hz, $^1J_{CP}$=156.2 Hz, $^3J_{CP}$=4.7 Hz), 24.38 (d, $^3J_{CP}$=1.5 Hz, CH_3), 24.32 (d, $^3J_{CP}$=2.7 Hz, CH_3), 24.12 (d, $^3J_{CP}$=3.4 Hz, CH_3) 23.69 (d, $^3J_{CP}$=5.1 Hz, CH_3), 23.63 (d, $^3J_{CP}$=5.2 Hz, CH_3), 23.47 (bs); HRMS: [M+Na]$^+$, found 557.0760. $C_{16}H_{35}O_9P_3Cl_2Na$ required 557.0763.

1-Methylethyl *O*-dihexyloxyphosphoryl[(di-1-methyl-ethoxyphosphoryl)dichloromethyl]phosphonate (3c). Prepared from **8b** (100 mg) to give **3c** (102 mg, 81%) as yellowish oil with 94% purity; [Found: C, 43.52; H, 7.58. $C_{22}H_{47}Cl_2O_9P_3$ requires C, 42.66; H, 7.65%]; ν (KBr) 2960, 2252, 1467, 1387, 1288; δ_H (400.1 MHz, $CDCl_3$) 5.16 (1H, m, CH), 4.99 (1H, m, CH), 4.98 (1H, m, CH), 4.31–4.15 (4H, m, CH_2), 1.72 (4H, m, CH_2), 1.50 (3H, d, J=6.2 Hz, CH_3), 1.47 (3H, d, J=6.2 Hz, CH_3), 1.43 (12H, d, J=6.1 Hz, CH_3), 1.50–1.35 (4H, covered, CH_2), 1.30 (8H, m, CH_2), 0.89 (6H, m, CH_3); δ_P (162.0 MHz, $CDCl_3$) 6.23 (d, $^2J_{PP'}$=25.7 Hz), −0.84 (dd), −12.78 (d, $^2J_{P'P''}$=30.2 Hz); δ_C (100.6 MHz, $CDCl_3$) 77.96 (d, $^2J_{CP}$=7.5 Hz, CH), 75.78 (d, $^2J_{CP}$=7.2 Hz, CH), 75.69 (d, $^2J_{CP}$=7.3 Hz, CH), 71.40 (ddd, $^1J_{CP}$=165.6 Hz, $^1J_{CP}$=155.5 Hz, $^3J_{CP}$=4.6 Hz),

69.45 (d, $^2J_{CP}$=6.4 Hz, CH_2), 69.35 (d, $^2J_{CP}$=6.7 Hz, CH_2), 31.30 (CH_2), 30.05 (d, $^3J_{CP}$=7.6 Hz, CH_2), 25.03 (CH_2), 24.34 (bs), 24.13 (d, $^3J_{CP}$=2.6 Hz, CH_3), 23.45 (bs), 22.52 (CH_2), 13.98 (CH_3); ES–MS ($C_{22}H_{48}Cl_2O_9P_3$) 619.0 *m/z* $[MH]^+$; HRMS: $[M+Na]^+$, found 641.1711. $C_{22}H_{47}O_9P_3Cl_2Na$ required 641.1702.

General procedure for the synthesis of Cl_2MBP anhydride esters (2g and 3d–e)

Anhydrous K_2CO_3 [1.0 equiv. (**2g**), 2.5 equiv. (**3d**) or 1.5 equiv. (**3e**)], methane sulphonyl chloride (1.2 equiv.) or phosphorochloridic acid dialkyl ester [(1.0 equiv. (**2g**) or 2.0 equiv. (**3d**)] and $(HO)(^iPrO)P(O)CCl_2P(O)(O^iPr)_2$ or $(MeO)_2P(O)CCl_2P(O)(OMe)(OH)$ were mixed in acetonitrile (3.0 ml). The mixture was stirred at room temperature for 21 h (**3e**) or heated at 50°C for 8 h (**2g**) or heated at 60°C for 15 h (**3d**). The mixture was filtered and the filtrate was evaporated to dryness in vacuo. After evaporation **2g** was washed 6×20 ml hexane. The residue was diluted in 4.0 ml cold CH_2Cl_2 and washed once with 1.0 ml cold saturated aq. NaCl (**2g**) or 1.0 ml cold saturated aq. $NaHCO_3$ (**3d**–**e**). A centrifuge was used to facilitate decantation. The organic phase was evaporated to dryness in vacuo. Compound **3d** was further purified: **3d** was dissolved in hexane by washing the residue several times with hexane (22 ml). The hexane phase was evaporated to dryness in vacuo.

Potassium *O*-dihexyloxyphosphoryl[(dimethoxyphosphoryl)dichloromethyl]phosphonate (2g). Prepared from $(MeO)_2P(O)CCl_2P(O)(OMe)(OH)$ (147 mg) to give **2g** (35 mg, 12%) as a white solid; ν (KBr) 3367, 2945, 2499, 2239, 2072, 1031; δ_H (400.1 MHz, CD_3OD) 4.18 (4H, m, CH_2), 4.01 (6H, d, $^3J_{HP}$=10.8 Hz, OCH_3), 1.72 (4H, m, CH_2), 1.42 (4H, m, CH_2), 1.30–1.35 (8H, m, CH_2), 0.91 (6H, t, *J*=6.9 Hz, CH_3); δ_P (162.0 MHz, CD_3OD) 14.04 (d, $^2J_{PP'}$=24.3 Hz), −3.27 (t), −11.3 (d, $^2J_{P'P''}$=26.8 Hz); δ_C (100.6 MHz, CD_3OD) 75.27 (dd, $^1J_{CP}$=149.8 Hz, $^1J_{CP}$=145.1 Hz), 69.50 (d, $^2J_{CP}$=6.4 Hz, CH_2), 56.86 (d, $^2J_{CP}$=7.4 Hz, CH_3), 32.08 (CH_2), 30.81 (d, $^3J_{CP}$=7.5 Hz, CH_2), 25.86 (CH_2), 23.23 (CH_2), 14.21 (CH_3); ES–MS ($C_{15}H_{32}Cl_2O_9P_3$) 519.5 *m/z* $[M]^-$; HRMS: $[MH_2-K]^+$, found 521.0821. $C_{15}H_{34}O_9P_3Cl_2$ required 521.0793.

1-Methylethyl *O*-dimethoxyphosphoryl[(di-1-methylethoxyphosphoryl)dichloromethyl]phosphonate (3d). Prepared from $(HO)(^iPrO)P(O)CCl_2P(O)(O^iPr)_2$ (65 mg) to give **3d** (40 mg, 48%) as yellowish oil; [Found: C, 28.34; H, 5.63. $C_{12}H_{27}Cl_2O_9P_3{\times}H_2O$ requires C, 28.99; H, 5.88%]; ν(KBr); δ_H (400.1 MHz, $CDCl_3$) 5.16 (1H, m, CH), 4.98 (2H, m, CH), 3.96 (3H, d, $^3J_{HP}$=12.1 Hz, CH_3), 3.93 (3H, d, $^3J_{HP}$=12.0 Hz, CH_3), 1.50 (3H, d, *J*=6.2 Hz, CH_3), 1.48 (3H, d, *J*=6.2 Hz, CH_3), 1.43 (6H, d, *J*=6.1 Hz, CH_3), 1.42 (6H, d, *J*=5.9 Hz, CH_3); δ_P (162.0 MHz, $CDCl_3$) 6.10 (d, $^2J_{PP'}$=25.6 Hz), −0.59 (dd), −10.78 (d, $^2J_{P'P''}$=29.7 Hz); δ_C (100.6 MHz, $CDCl_3$) 78.22 (d, $^2J_{CP}$=7.4 Hz, CH), 75.80 (d, $^2J_{CP}$=7.5 Hz, CH), 75.76 (d, $^2J_{CP}$=7.4 Hz, CH), 71.32 (dd, $^1J_{CP}$=166.6 Hz, $^1J_{CP}$=151.8 Hz), 55.60 (d, $^2J_{CP}$=7.5 Hz, CH_3), 55.49 (d, $^2J_{CP}$=7.4 Hz, CH_3), 24.33 (bs), 24.09 (d, $^3J_{CP}$=2.7 Hz, CH_3), 23.49 (bs); ES–MS ($C_{12}H_{28}Cl_2O_9P_3$) 478.7 *m/z* $[MH]^+$; HRMS: $[M+Na]^+$, found 501.0139. $C_{12}H_{27}O_9P_3Cl_2Na$ required 501.0137.

1-Methylethyl *O*-methylsulphonyl[(di-1-methylethoxyphosphoryl)dichloromethyl]phosphonate (3e). Prepared from $(HO)(^iPrO)P(O)CCl_2P(O)(O^iPr)_2$ (119 mg) to give **3e** (45 mg, 32%) as yellowish oil; ν(KBr) 2986, 2248, 1379, 1284, 1193; δ_H (400.1 MHz, $CDCl_3$) 5.20 (1H, m, CH), 4.98 (2H, m, CH), 3.45 (3H, s, SCH_3), 1.51 (3H, d, *J*=6.2 Hz, CH_3), 1.50 (3H, d, *J*=6.0 Hz, CH_3), 1.43 (12H, d, *J*=6.0 Hz, CH_3); δ_P (162.0 MHz, $CDCl_3$) 5.61 (d, $^2J_{PP'}$=25.10), 0.66 (d); δ_C (100.6 MHz, $CDCl_3$) 79.39 (d, $^2J_{CP}$=8.3 Hz, CH), 76.19 (d, $^2J_{CP}$=7.5 Hz, CH), 70.80 (dd, $^1J_{CP}$=164.3 Hz, $^1J_{CP}$=155.5 Hz), 40.97 (CH_3), 24.36 (bs), 23.78 (d, $^3J_{CP}$=3.7 Hz, CH_3), 23.44 (bs); ES–MS ($C_{11}H_{24}Cl_2O_8P_2S$) 412.9 *m/z* $[MH-Cl]^+$.

Disodium (*O*(P′)-acetyl-*O*(P)-methyl)dichloromethylenebisphosphonate (4). The dealkylation of **9** was performed following the procedure described earlier[25] using 200 mg of **9**, 300 μl water and 4.0 ml piperidine. After reaction, water and the excess of piperidine were evaporated to dryness in vacuo and acetic anhydride (3.0 ml) was added to the residue. The mixture was stirred at room temperature for 48 h and then kept in cold (+5°C) overnight. The solids were collected and washed several times with cold acetone (14.0 ml), and dried in vacuo to give **4** (166 mg, 76%) as a white solid; ν(KBr) 3540, 2970, 1725, 1638; δ_H (400.1 MHz, D_2O) 3.78 (3H, d, $^3J_{HP}$=10.4 Hz, CH_3), 2.22 (3H, d, $^4J_{HP}$=1.0 Hz, CH_3); δ_P (162.0 MHz, D_2O) 9.08 (d, $^2J_{PP'}$=16.1 Hz), 4.06 (d); δ_C (100.6 MHz, D_2O) 172.66 (d, $^2J_{CP}$=10.2 Hz), 78.25 (dd, $^1J_{CP}$=146.6 Hz, $^1J_{CP}$=138.4 Hz), 57.91 (d, $^2J_{CP}$=4.2 Hz, CH_3), 24.86 (d, $^3J_{CP}$=1.5 Hz, CH_3); ES–MS ($C_4H_7Cl_2O_7P_2$) 299.1 *m/z* $[MH]^+$.

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