# 53. First Use of Benzyl Phosphites in the *Michaelis-Arbuzov* Reaction

## Synthesis of Mono-, Di-, and Triphosphate Analogs

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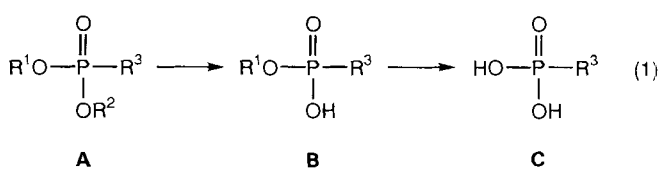
(30.XI.94)

Benzyl phosphites were used in the *Michaelis-Arbuzov* reaction. Special experimental conditions allowed preparation of a set of phosphonate analogs of mono-, di-, and triphosphate. Furthermore, regioselective monodeprotection makes these molecules useful building blocks for the synthesis of analogs of polyphosphorylated compounds of biological interest (*e.g.* nucleotides), after removal of all phosphonate benzyl ester groups under very mild conditions and high yields.

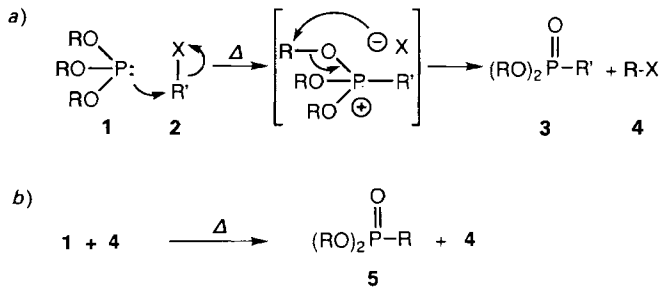
**Introduction.** – Drastic and non-selective reaction conditions are generally necessary for the hydrolysis of phosphonic diesters **A** to acids **C** (*via* monoesters **B**). Depending on the nature of $R^1$ and $R^2$, the hydrolysis can be achieved using acidic, basic, or nucleophilic conditions that do not always fully respect the integrity of the $R^3$ group [1–3]. In addition, it is often problematic to perform monodeprotection (→ **B**) of phosphonates **A** due to the lack of selectivity during the hydrolyses. To overcome these difficulties, we have tried to take advantage of the benzyl moiety as protective group and planned to prepare benzyl phosphonates using the *Arbuzov* reaction.




(1)

The *Michaelis-Arbuzov* rearrangement is one of the most extensively investigated reaction in organophosphorus chemistry and is widely used to prepare phosphonates, phosphinates, and phosphine oxides [4–11]. In the case of the reaction of trialkyl phosphites **1** with halides **2** (*Scheme 1a*), the rearrangement to phosphonates **3** with the formation of alkyl halides **4** proceeds especially easily when the alkyl group R of **1** is a good electron-donating group and increases the nucleophilicity of the trivalent P-atom. In the reaction with MeI the reactivity of **1** increases with the sequence R = Me < Et < i-Pr [12]. Besides, the yield of the reaction will depend on the nature of the generated halide **4** since it can also be a target for nucleophilic attack by phosphite **1** (→ **5**) and thus compete with halide **2** (*Scheme 1b*).

*Scheme 1*



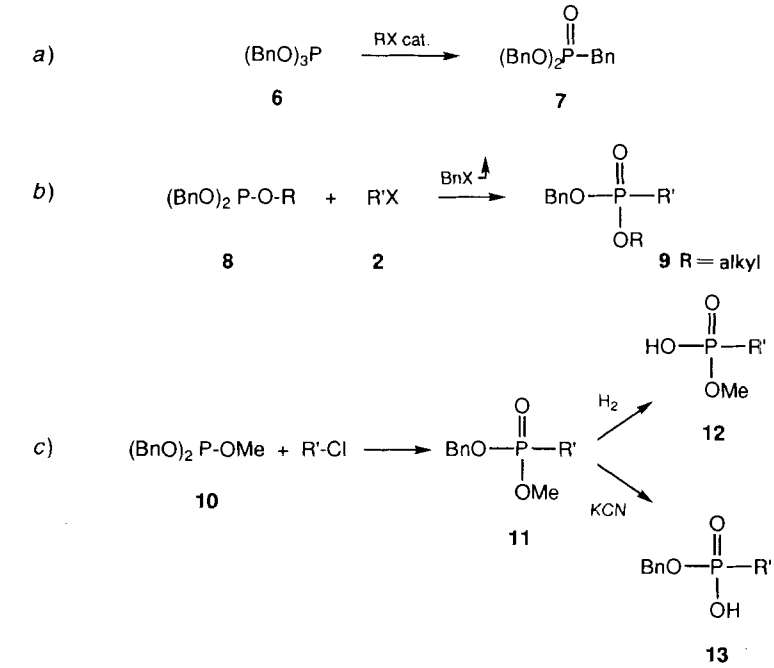

So it is essential that halide **4** is efficiently removed from the reaction medium or alternatively that it is less reactive than halide **2** to avoid formation of **5** in high yield. For these reasons, the *Michaelis-Arbuzov* reaction was essentially worked out with low molecular weight phosphites (*e.g.* $(MeO)_3P$, $(EtO)_3P$, $(i\text{-}PrO)_3P$, $(BuO)_3P$). In these cases, the volatile by-product **4** can be removed from the reaction mixture by distillation as it forms.

**Results and Discussion.** – *Monophosphate Analogs.* Up to now, the only reported examples of the *Michaelis-Arbuzov* reaction using benzyl phosphites in the literature refer to the intramolecular photo-*Arbuzov* rearrangement [13]. Tribenzyl phosphite (**6**) in the presence even of a catalytic amount of alkyl halide is rapidly and totally converted into the corresponding benzylphosphonate **7** (*Scheme 2a*), *i.e.*, the use of benzyl phosphites in the *Michaelis-Arbuzov* reaction requires an efficient removal of the benzyl halide (preferentially chloride) generated during the reaction. This can be satisfactorily achieved at high temperature (140°) and reduced pressure (4–20 Torr). Such reaction conditions give access to dibenzyl alkylphosphonates provided, however, that reagent halide **2** is not volatile under the conditions used. This synthetic pathway readily allows the preparation of alkyl benzyl phosphonates **9** from mixed alkyl benzyl phosphites **8** (*Scheme 2b*).

As a matter of fact, a benzyl group is more sensitive than an alkyl group R to the nucleophilic attack by the halide anion (*Scheme 1a*), resulting in the formation of BnX instead of RX. From dibenzyl methyl phosphite (**10**), mixed benzyl methyl phosphonates **11** are obtained that can be selectively monodeprotected either at the benzyl group (→ **12**) by hydrogenolysis or at the methyl group (→ **13**) using potassium cyanide [3e] (*Scheme 2c*). That sequence is especially useful for the synthesis of building blocks including one or more methylene bis(phosphonate) moieties.

*Diphosphate and Triphosphate Analogs.* Di- and triphosphates **D** are widespread chemical species in nature (nucleosides, isoprenoids, and thiamin polyphosphates, NADP *etc.*). However, the poor stability of pyrophosphates drastically reduces the fields of investigations related to these compounds. There is, consequently, a real need for non-hydrolyzable analogs of such biological species. A way to stabilize a di- or triphosphate sequence **D** is to replace the O-atom of pyrophosphate with a methylene group (see **E**; *Scheme 3a*) [14]. The synthesis of that kind of structures can be realized using a sequence involving one or two successive *Michaelis-Arbuzov* rearrangements starting from (chloromethyl)phosphonic or bis(chloromethyl)phosphinic esters **F** and **G**, respectively [15]. These compounds are readily prepared starting from sodium hypophosphite [16], *e.g.* the benzyl esters **16** and **17** *via* **14** and **15**, respectively (*Scheme 3b*).

*Scheme 2*



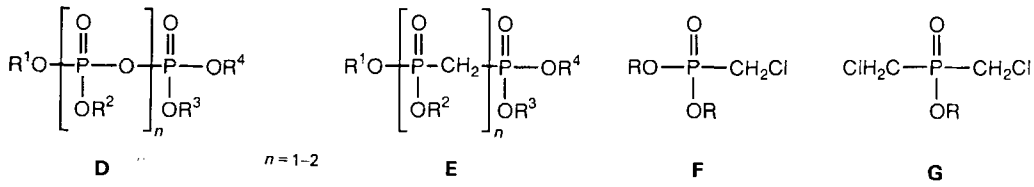

(Chloromethyl)phosphonate **16** and bis(chloromethyl)phosphinate **17** react with tribenzyl phosphite (**6**) to yield the perbenzyl esters of diphosphate analog **18** and triphosphate analog **20** (*Scheme 3c*). It is noteworthy that during the double *Arbuzov* reaction with **17** *via* **19**, benzyl ester **17** is partially dragged off the reaction mixture by distillation. However, the overall yield of **20** is 71%.

To increase the yield of the double *Arbuzov* reaction, different benzyl esters with higher boiling points were prepared from **15**, *i.e.* **21**–**23** (*Scheme 4a*). These three phosphinates react with tribenzyl phosphite (**6**) under the same experimental conditions as described for **17**. The results obtained are specified in the *Table*. Surprisingly, with phosphinates **21** and **22**, compound **20** is obtained revealing a transesterification at the central P-atom. However, there is no benzyl alcohol in the reaction mixture, thus classical transesterification mechanism cannot be invoked. It seems likely that the benzylic position is very sensitive to a nucleophilic attack by $Cl^-$ anions. Therefore, the reaction product accounts for an 'abnormal' *Arbuzov* rearrangement resulting from an intramolecular attack by $Cl^-$ at the benzylic position on the phosphinate (*Path A*) instead of one on the phosphite (*Path B*; *Scheme 4b*).

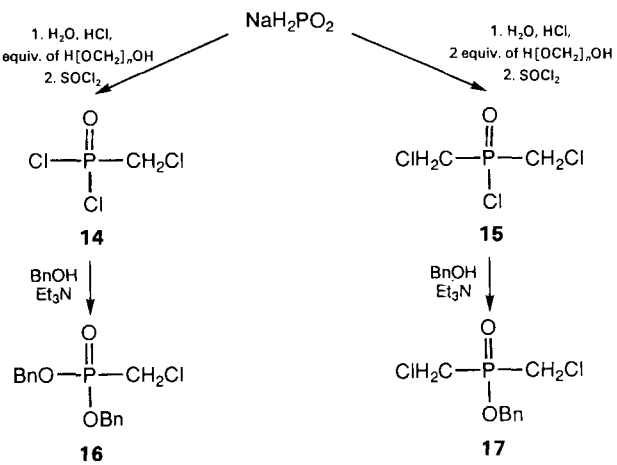
The same mechanism (*Path A*) could be invoked for the reaction of **17** with tribenzyl phosphite (**6**), but it results in the same product as in the classical *Arbuzov* reaction. However, when steric hindrance at the benzylic position is enhanced with a *tert*-butyl group (see **23**), there is no more intramolecular attack by $Cl^-$, and the *Arbuzov* reaction proceeds normally to give **24** (see *Table*). As phosphinate **23** is less volatile than **17**, the overall yield of the double *Michaelis-Arbuzov* reaction can be increased to 83%.

*Scheme 3*

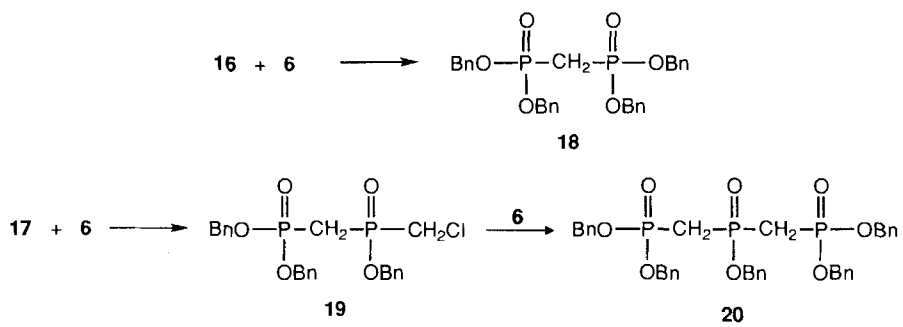
*a)*




*b)*




*c)*




Due to the use of a large excess of tribenzyl phosphite (**6**; *i.e.*, 4–5 equiv.) in the reaction with the phosphinates, the formation of (chloro)diphenylmethane (**25**) or 1-(chloromethyl)naphthalene (from **21**) further reacting with 1 equiv. of phosphite cannot account for the lower yield obtained with **21** and **22** in this reaction. This should be more likely attributed to thermal degradation of the phosphinate during the course of the reaction.

Furthermore, the scope of this new approach is enlarged by introducing on the protected di- or triphosphate analog a methyl-ester group easily removable under conditions respecting the integrity of benzyl esters [3e]. Thus, the synthesis of methylenebis-

*Scheme 4*

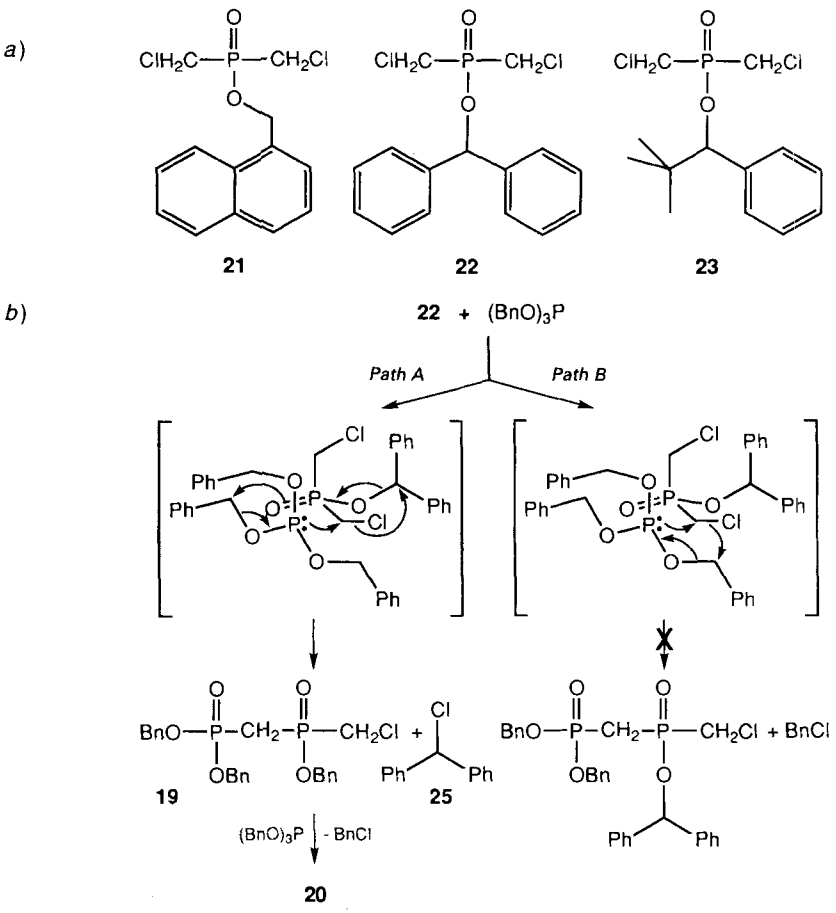


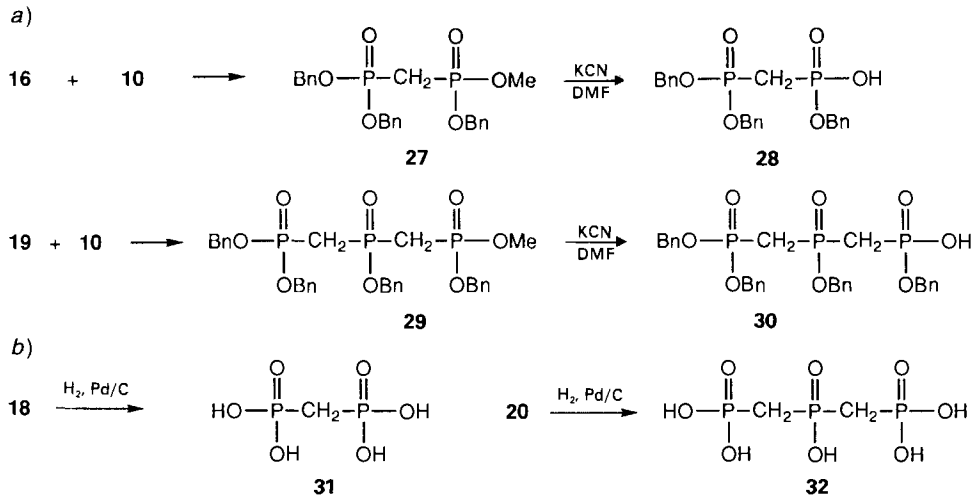

Table. *Results of the Double* Arbuzov *Reaction with* **17** *and* **21–23**

$RO(O)P[CH_2Cl]_2 + (BnO)_3P \rightarrow R'O(O)P[CH_2P(O)(OBn)_2]_2$

| Reagent | R | Product | R′ | Yield [%] |
|---|---|---|---|---|
| **17** | $PhCH_2$ | **20** | $PhCH_2$ | 71 |
| **21** | (Naphth-1-yl)$CH_2$ | **20** | $PhCH_2$ | 30 |
| **22** | $Ph_2CH$ | **20** | $PhCH_2$ | 41 |
| **23** | (*t*-Bu)PhCH | **24** | (*t*-Bu)PhCH | 83 |

(phosphonate) monomethyl esters is achieved using mixed dibenzyl methyl phosphite (**10**) and **16** or **19** (*Scheme 5a*); benzyl methyl esters **27** and **29**, respectively, are obtained in 65 and 85% yield, and no trace of perbenzyl esters **18** and **20**, respectively, can be detected. Selective deprotection of the methyl esters is achieved using KCN in DMF, and monoacids **28** and **30** are quantitatively obtained.

*Scheme 5*

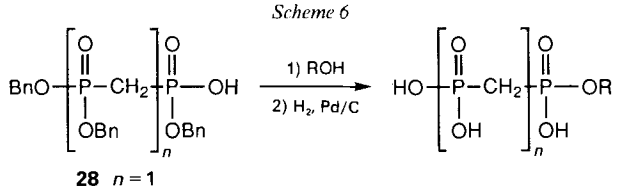


On the other hand, fully deprotected di- and triphosphate analogs **31** and **32** are quantitatively obtained from perbenzyl esters **18** and **20** *via* hydrogenolysis using Pd/C (*Scheme 5b*). Compounds **31** and **32** can then be specifically esterified following well established procedures [17–26].

**Conclusion.** – The use of benzyl phosphites in the *Michaelis-Arbuzov* reaction requires the efficient removal of benzyl chloride generated *in situ*. This is achieved performing the reaction at high temperature under vacuum.

The use of mixed alkyl benzyl phosphites provides a convenient synthetic route to monodeprotected phosphonic acid esters that can be further esterified. Consequently, building blocks such as **28** and **30** allow the straightforward preparation of di- and triphosphate analogs of various alcohols of interest (nucleosides, vitamins, *etc.*) *via* a coupling reaction prior to selective removal of all benzyl groups by hydrogenolysis (*Scheme 6*).

*Scheme 6*



The authors are thankful to *A. Valleix* for running mass spectra. This work was supported in part by a grant from the *Association pour la Recherche sur le Cancer*.

## Experimental Part

*General.* THF and $Et_2O$ were distilled over Na/benzophenone and $CH_2Cl_2$ over $CaH_2$, just before use. Reactions were monitored by TLC (*Merck* precoated plates 0.25 mm, silica gel *60* $F_{254}$, 0.040–0.060 mm, 230–400 mesh ASTM). Liquid chromatography: silica gel *60* (*Merck*, 0.040–0.060 mm, 230–400 mesh ASTM). IR Spectra:

*Perkin-Elmer-1600-FT* spectrometer; absorption values in $cm^{-1}$. $^1H$-, $^{13}C$-, and $^{31}P$-NMR Spectra: *Bruker-WP-200-Sy* spectrometer; chemical shifts $\delta$ in ppm rel. to an internal reference ($^1H$: $CHCl_3$ at 7.27 ppm or $CD_2HOD$ at 3.31 ppm; $^{13}C$: $CDCl_3$ at 77.0 ppm or $CD_3OD$ at 49.0 ppm; $^{31}P$: $H_3PO_4$ at 0.00 ppm), $J$ in Hz. Mass spectra: *Finnigan-4600* quadrupole instrument; for compound **32**, *VG-ZAB-HF* double-focussing instrument fitted with a Xe-atom gun (negative-ion mode, nitrilotris(ethanol) matrix); CI = chemical ionization, FAB = fast-atom-bombardment ionization.

*Tribenzyl Phosphite* (**6**). Anh. $Et_3N$ (123.8 ml, 888.3 mmol, 3.1 equiv.) is added dropwise to $PCl_3$ (25.0 ml, 286.5 mmol, 1.0 equiv.) in anh. $Et_2O$ (1.5 l) at −78° under Ar. The mixture is treated dropwise with benzyl alcohol (89.0 ml, 859.6 mmol, 3.0 equiv.) in $Et_2O$ (300 ml) and stirred for 2 h at −78° and then for 8 h at r.t. The precipitate is removed by filtration and the filtrate evaporated. The residue is chromatographed ($Et_2O$/hexane/$Et_3N$ 40:60:1): **6** (90.0 g, 89%). Colourless liquid. TLC ($Et_2O$/hexane/$Et_3N$ 50:50:1): $R_f$ 0.5. IR (liq.): 3088, 3063, 3031, 2940, 2874, 1606, 1497, 1454, 1375, 1211, 994, 787. $^1H$-NMR ($CDCl_3$, 200 MHz): 7.37 (*m*, 15 H); 4.94 (*d*, $J$ = 8.0, 6 H). $^{13}C$-NMR ($CDCl_3$, 50 MHz): 138.21; 128.37; 127.67; 127.49; 64.47 (*d*, $J$ = 11.1). $^{31}P$-NMR ($CDCl_3$, 81.015 MHz): 20.17.

*Dibenzyl Benzylphosphonate* (**7**). Ester **6** (10.0 g, 28.4 mmol, 1.0 equiv.) and benzyl chloride (0.4 g, 2.8 mmol, 0.1 equiv.) are stirred for 10 h at 140°. The crude mixture is chromatographed ($Et_2O$/hexane 7:3→10:0): **7** (8.8 g, 88%). Colourless oil that crystallizes on standing. TLC ($Et_2O$): $R_f$ 0.5. IR (liq.): 3089, 3032, 2893, 1603, 1496, 1455, 1378, 1249, 1217, 997. $^1H$-NMR ($CDCl_3$, 200 MHz): 7.32–7.27 (*m*, 15 H); 4.93 (*d*, $J$ = 8.3, 4 H); 3.20 (*d*, $J$ = 21.5, 2 H). $^{13}C$-NMR ($CDCl_3$, 50 MHz): 136.30 (*d*, $J$ = 5.6); 131.17 (*d*, $J$ = 9.1): 129.81; 129.68; 128.35; 128.14; 127.74; 126.81; 126.74; 67.48 (*d*, $J$ = 6.6); 33.99 (*d*, $J$ = 137.1). $^{31}P$-NMR ($CDCl_3$, 81.015 MHz): 28.11.

*Dibenzyl Methyl Phosphite* (**10**). Anh. $Et_3N$ (123.8 ml, 888.3 mmol, 3.1 equiv.) is added dropwise to $PCl_3$ (25.0 ml, 286.5 mmol, 1.0 equiv.) in anh. $Et_2O$ (1.5 l) at −78° under Ar. The mixture is treated dropwise with benzyl alcohol (59.6 ml, 573.0 mmol, 2.0 equiv.) in $Et_2O$ (300 ml) and stirred for 5 h at −78° before anh. MeOH (11.6 ml, 286.5 mmol, 1.0 equiv.) in $Et_2O$ (200 ml) is slowly added. The mixture is warmed to r.t. and stirred for 4 h prior to filtration. The filtrate is evaporated and chromatographed ($Et_2O$/hexane/$Et_3N$ 50:50:1): **10** (47.5 g, 60%). Colourless liquid. TLC ($Et_2O$/hexane/$Et_3N$ 60:40:1): $R_f$ 0.5. IR (liq.): 3080, 3067, 3031, 2940, 2876, 1604, 1497, 1454, 1375, 1211, 994, 787. $^1H$-NMR ($CDCl_3$, 200 MHz): 7.38–7.36 (*m*, 10 H); 5.01 (*d*, $J$ = 7.7, 4 H); 3.65 (*d*, $J$ = 11.0, 3 H). $^{13}C$-NMR ($CDCl_3$, 50 MHz): 137.93 (*d*, $J$ = 6.2); 128.10; 126.95; 126.86; 63.62 (*d*, $J$ = 11.1); 48.76 (*d*, $J$ = 10.1). $^{31}P$-NMR ($CDCl_3$, 81.015 MHz): 20.17.

*Dibenzyl (Chloromethyl)phosphonate* (**16**). Anh. $Et_3N$ (10.3 ml, 73.9 mmol, 3.0 equiv.) is added dropwise to (chloromethyl)phosphonic dichloride (**14**) [17] (4.1 g, 24.5 mmol, 1.0 equiv.) in THF (300 ml) at 0°. Benzyl alcohol (5.6 ml, 53.9 mmol, 2.2 equiv.) in THF (50 ml) is added dropwise and the mixture stirred at 0° for 1 h and then at r.t. for 4 h. The precipitate is filtered, the filtrate evaporated, and its residue chromatographed ($Et_2O$/hexane 1:1→1:0): **16** (6.3 g, 83%). Colourless oil. TLC ($Et_2O$/hexane 1:1): $R_f$ 0.3. $^1H$-NMR ($CDCl_3$, 200 MHz): 7.37–7.35 (*m*, 10 H); 5.07 (*AB* of *ABX*, $J_{AB}$ = 13.8, $J_{AX}$ = 8.8, $J_{BX}$ = 7.8, $\upsilon_A$ = 5.16, $\upsilon_B$ = 5.06, 4 H); 3.49 (*d*, $J$ = 10.5, 3 H). $^{13}C$-NMR ($CDCl_3$, 50 MHz): 135.80; 128.02; 127.89; 68.76 (*d*, $J$ = 6.8); 31.19 (*d*, $J$ = 91.7). CI-MS ($NH_3$): 328.4 ($[M + NH_4]^+$).

*Benzyl Bis(chloromethyl)phosphinate* (**17**). Anh. $Et_3N$ (16.9 ml, 121.3 mmnol, 1.1 equiv.) is added dropwise to bis(chloromethyl)phosphinic chloride (**15**) [17] (20.0 g, 110.3 mmol, 1.0 equiv.) in $Et_2O$ (400 ml) at 0°. Benzyl alcohol (12.6 ml, 121.3 mmol, 1.1 equiv.) in $Et_2O$ (50 ml) is added dropwise. The mixture is stirred at 0° for 1 h, then at r.t. for 2 h. The precipitate is filtered the filtrate evaporated, and its residue chromatographed ($Et_2O$/hexane 6:4→10:0): **17** (24.6 g, 88%). Colourless oil. TLC ($Et_2O$): $R_f$ 0.5. IR (liq.): 3091, 3050, 3000, 2950, 2895, 1498, 1456, 1393, 1262, 1200, 1110, 1007, 847. $^1H$-NMR ($CDCl_3$, 200 MHz): 7.45–7.37 (*m*, 5 H); 5.19 (*d*, $J$ = 9.3, 2 H); 3.66 (*AB* of *ABX*, $J_{AB}$ = 12.5, $J_{AX}$ = 7.5, $J_{BX}$ = 8.1, $\upsilon_A$ = 3.72, $\upsilon_B$ = 3.60, 4 H). $^{13}C$-NMR ($CDCl_3$, 50 MHz): 134.93 (*d*, $J$ = 5.1); 128.63; 128.40; 127.97; 67.73 (*d*, $J$ = 6.5); 32.63 (*d*, $J$ = 104.7). $^{31}P$-NMR ($CDCl_3$, 81.015 MHz): 41.25. CI-MS ($NH_3$): 270.6 ($[M + NH_4]^+$).

*Tetrabenzyl Methylenebis(phosphonate)* (**18**). Phosphite **6** (8.0 g, 22.7 mmol, 2.0 equiv.) and **16** (3.5 g, 11.3 mmol, 1.0 equiv.) are stirred for 8 h at 140°/6–10 Torr. The crude mixture is chromatographed (AcOEt/hexane 8:2→10:0): **18** (5.6 g, 92%). Colourless oil. TLC (AcOEt): $R_f$ 0.45. IR (liq.): 3070, 3063, 3033, 2953, 2898, 1497, 1468, 1380, 1250, 1182, 998. $^1H$-NMR ($CDCl_3$, 200 MHz): 7.32–7.29 (*m*, 20 H); 5.02 (*d*, $J$ = 7.5, 8 H); 2.52 (*t*, $J$ = 21.1, 2 H). $^{13}C$-NMR ($CDCl_3$, 50 MHz): 135.84 (*d*, $J$ = 6.4); 128.30, 128.17; 127.80; 67.84 (*d*, $J$ = 5.9); 26.40 (*t*, $J$ = 135.0). $^{31}P$-NMR ($CDCl_3$, 81.015 MHz): 20.79. CI-MS ($NH_3$): 554.0 ($[M + NH_4]^+$).

*Dibenzyl {[(Benzyloxy)(chloromethyl)phosphinoyl]methyl}phosphonate* (**19**). Phosphite **6** (15.0 g, 42.5 mmol, 2.0 equiv.) and **17** (5.4 g, 21.3 mmol, 1.0 equiv.) are stirred for 8 h at 140°/6–10 Torr. The crude mixture is chromatographed (AcOEt/hexane 6:4 to 10:0): **19** (4.5 g, 44%). Colourless oil. TLC (AcOEt): $R_f$ 0.6. IR (liq.): 3034, 2955, 2893, 1498, 1456, 1379, 1255, 1213, 1176, 998, 836, 734. $^1H$-NMR ($CDCl_3$, 200 MHz): 7.40–7.32 (*m*, 15 H); 5.19–4.94 (*m*, 6 H); 3.66 (*AB* of *ABX*, $J_{AB}$ = 14.0, $J_{AX}$ = 7.4, $J_{BX}$ = 9.4, $\upsilon_A$ = 3.74, $\upsilon_B$ = 3.59, 2 H); 2.62 (*m*,

2 H). $^{13}$C-NMR ($CDCl_3$, 50 MHz): 135.52 (*d*, $J$ = 9.1); 135.36 (*d*, $J$ = 6.9); 128.52; 128.04; 127.97; 68.25 (*d*, $J$ = 6.2); 67.97 (*d*, $J$ = 6.3); 67.39 (*d*, $J$ = 6.4); 36.05 (*d*, $J$ = 102.6); 25.55 (*dd*, $J$ = 134.4, 88.5). $^{31}$P-NMR ($CDCl_3$, 81.015 MHz): 39.88; 20.04. CI-MS ($NH_3$): 496.1 ($[M + NH_4]^+$).

*Tetrabenzyl {[(Benzyloxy)phosphoryl]bis(methylene)}bis(phosphonate)* (**20**). Phosphite **6** (44.5 g, 126.4 mmol, 4.0 equiv.) and **17** (8.0 g, 31.6 mmol, 1.0 equiv.) are stirred for 10 h at 140°/6–10 Torr. The crude mixture is chromatographed ($Et_2O$/AcOEt/EtOH 10:0:0→0:8:2): **20** (15.8 g, 71%). Colourless oil. TLC (AcOEt): $R_f$ 0.4. IR (liq.): 3088, 3033, 2954, 2894, 1497, 1468, 1380, 1250, 1182, 998. $^1$H-NMR ($CDCl_3$, 200 MHz): 7.32–7.28 (*m*, 25 H); 5.13–4.95 (*m*, 10 H); 2.84 (*dd*, $J$ = 20.3, 18.2, 4 H). $^{13}$C-NMR ($CDCl_3$, 50 MHz): 135.77–135.57 (*m*); 128.75–127.85 (*m*); 67.79 (*dd*, $J$ = 6.2, 10.8); 66.79 (*d*, $J$ = 6.5); 28.65 (*dd*, $J$ = 130.0, 87.5). $^{31}$P-NMR ($CDCl_3$, 81.015 MHz): 38.47 (*t*, $J$ = 4.5, 1 P); 20.90 (*d*, $J$ = 4.5, 2 P). CI-MS ($NH_3$): 721.8 ($[M + NH_4]^+$).

*(Naphthalen-1-yl)methyl Bis(chloromethyl)phosphinate* (**21**). As described for **17**, from **15** (1.30 g, 7.1 mmol, 1.0 equiv.) and naphthalene-1-methanol (1.25 g, 7.9 mmol, 1.1 equiv.): **21** (1.75 g, 81%). TLC ($Et_2O$): $R_f$ 0.5. IR ($CH_2Cl_2$): 3097, 3040, 2955, 2891, 1496, 1465, 1380, 1250, 1180, 1110, 1001, 980. $^1$H-NMR ($CDCl_3$, 200 MHz): 8.16–7.44 (*m*, 7 H); 5.67 (*d*, $J$ = 9.2, 2 H); 3.62 (*d*, $J$ = 8.6, 4 H). $^{13}$C-NMR ($CDCl_3$, 50 MHz): 133.57; 130.65; 130.56; 130.13; 128.63; 127.88; 126.81; 126.14; 125.08; 123.32; 66.41 (*d*, $J$ = 7.2); 32.72 (*d*, $J$ = 105.4). $^{31}$P-NMR ($CDCl_3$, 81.015 MHz): 41.65. CI-MS ($NH_3$): 302.7 ($[M + NH_4]^+$).

*Diphenylmethyl Bis(chloromethyl)phosphinate* (**22**). As described for **17**, from **15** (1.00 g, 5.5 mmol, 1.0 equiv.) and diphenylmethanol (= benzhydrol; 1.10 g, 6.0 mmol, 1.1 equiv.): **22** (1.56 g, 86%). TLC ($Et_2O$/hexane 95:5): $R_f$ 0.5. IR ($CH_2Cl_2$): 3097, 3040, 3005, 2967, 2891, 1496, 1458, 1391, 1262, 1190, 1110, 1007, 985. $^1$H-NMR ($CDCl_3$, 200 MHz): 7.44–7.28 (*m*, 10 H); 6.65 (*d*, $J$ = 8.0, 1 H); 3.52 (*AB* of *ABX*, $J_{AB}$ = 14.0, $J_{AX}$ = 8.3, $J_{BX}$ = 8.9, $\upsilon_A$ = 3.58, $\upsilon_B$ = 3.47, 4 H). $^{13}$C-NMR ($CDCl_3$, 50 MHz): 139.40 (*d*, $J$ = 4.3); 134.08; 133.99; 132.45; 79.49 (*d*, $J$ = 6.1); 32.40 (*d*, $J$ = 105.2). $^{31}$P-NMR ($CDCl_3$, 81.015 MHz): 39.74. CI-MS ($NH_3$): 346.8 ($[M + NH_4]^+$).

*(±)-2,2-Dimethyl-1-phenylpropyl Bis(chloromethyl)phosphinate* (**23**). As described for **17**, from **15** (5.3 g, 29.2 mmol, 1.0 equiv.) and (±)-2,2-dimethyl-1-phenylpropan-1-ol (5.3 g, 32.1 mmol, 1.1 equiv.): **23** (5.5 g, 61%). TLC ($Et_2O$/hexane 7:3): $R_f$ 0.5. IR ($CH_2Cl_2$): 3094, 3038, 3001, 2972, 2889, 1496, 1458, 1391, 1262, 1203, 1110, 998. $^1$H-NMR ($CDCl_3$, 200 MHz): 7.29 (*m*, 5 H); 5.18 (*d*, $J$ = 9.0, 1 H); 3.75 (*d*, $J$ = 8.7, 2 H); 3.20 (*AB* of *ABX*, $J_{AB}$ = 14.2, $J_{AX}$ = 8.4, $J_{BX}$ = 9.2, $\upsilon_A$ = 3.27, $\upsilon_B$ = 3.13, 2 H); 0.94 (*s*, 9 H). $^{13}$C-NMR ($CDCl_3$, 50 MHz): 137.30; 128.37; 127.77; 127.69; 86.26 (*d*, $J$ = 7.4); 35.84 (*d*, $J$ = 6.1); 33.02 (*d*, $J$ = 101.0); 32.80 (*d*, $J$ = 110.6); 25.66. CI-MS ($NH_3$): 326.7 ($[M + NH_4]^+$).

*Tetrabenzyl {[(2,2-Dimethyl-1-phenylpropyloxy)phosphoryl]bis(methylene)}bis(phosphonate)* (**24**). As described for **20**, from **6** (10.0 g, 28.4 mmol, 4.0 equiv.) and **23** (2.2 g, 7.1 mmol, 1.0 equiv.): **24** (4.5 g, 84%). TLC (AcOEt): $R_f$ 0.5. $^1$H-NMR ($CDCl_3$, 200 MHz): 7.37–7.20 (*m*, 25 H); 5.17 (*d*, $J$ = 10.8, 1 H); 5.09 (*d*, $J$ = 8.8, 2 H); 5.06 (*d*, $J$ = 8.5, 4 H); 4.90 (*dd*, $J$ = 2.2, 8.7, 2 H); 3.17 (*ddd*, $J$ = 15.4, 16.6, 20.7, 1 H); 2.88–2.55 (*m*, 2 H); 2.03 (*ddd*, $J$ = 16.2, 20.6, 21.5, 1 H); 0.89 (*s*, 9 H). $^{31}$P-NMR ($CDCl_3$, 121.44 MHz): 37.79 (*d*, $J$ = 8.3); 21.61 (*s*); 21.11 (*d*, $J$ = 8.3). CI-MS ($NH_3$): 778 ($[M + NH_4]^+$), 761 ($MH^+$).

*Tribenzyl Methyl Methylenebis(phosphonate)* (**27**). Phosphite **10** (9.3 g, 33.6 mmol, 4.0 equiv.) and **16** (2.6 g, 8.4 mmol, 1.0 equiv.) are heated at 140°/10–15 Torr for 8 h. The crude mixture is purified by chromatography (AcOEt/hexane 7:3): **27** (2.5 g, 65%). Colourless oil. TLC: (AcOEt) $R_f$ 0.3. IR (liq.): 3090, 3030, 2955, 2890, 1497, 1465, 1380, 1250, 1180, 1010. $^1$H-NMR ($CDCl_3$, 200 MHz): 7.35–7.27 (*m*, 15 H); 5.19–4.96 (*m*, 6 H); 3.68 (*d*, $J$ = 11.4, 3 H); 2.50 (*t*, $J$ = 21.1, 2 H). $^{13}$C-NMR ($CDCl_3$, 50 MHz): 136.20; 136.14; 136.00; 128.59; 128.48; 128.09; 68.21 (*d*, $J$ = 5.5); 68.16 (*d*, $J$ = 6.6); 52.98 (*d*, $J$ = 6.5); 25.82 (*t*, $J$ = 136.0). $^{31}$P-NMR ($CDCl_3$, 81.015 MHz): 21.43; 20.19. CI-MS ($CH_4$): 461 ($MH^+$).

*Tribenzyl Hydrogen Methylenebis(phosphonate)* (**28**). KCN (778 mg, 11.9 mmol, 1.1 equiv.) and **27** (5.0 g, 10.9 mmol, 1.0 equiv.) in anh. DMF (70 ml) are stirred for 4 h at 70°. The solvent is evaporated, the residue dissolved in 5% HCl soln. (50 ml), and the aq. phase extracted with AcOEt. The org. layer is dried ($Na_2SO_4$) and evaporated: **28** (4.6 g, 95%; no further purification). Slightly yellow oil. TLC ($CH_2Cl$/MeOH 8:2): $R_f$ 0.3. IR (liq.): 3400, 3065, 2956, 2894, 2662, 2238, 1607, 1497, 1455, 1380, 1254, 1016. $^1$H-NMR ($CDCl_3$, 200 MHz): 7.36–7.28 (*m*, 15 H); 5.10 (*d*, $J$ = 11.9, 2 H); 5.02 (*d*, $J$ = 12.0, 4 H); 2.57 (*t*, $J$ = 21.1, 2 H). $^{13}$C-NMR ($CDCl_3$, 50 MHz): 136.21 (*d*, $J$ = 7.0); 135.86 (*d*, $J$ = 6.5); 128.36; 128.31; 128.23; 128.02; 127.87; 127.46; 68.11 (*d*, $J$ = 6.5); 67.30 (*d*, $J$ = 6.0); 26.06 (*t*, $J$ = 134.5). $^{31}$P-NMR ($CDCl_3$, 81.015 MHz): 22.06 (*d*, $J$ = 6.2); 19.79 (*d*, $J$ = 6.2). CI-MS ($NH_3$): 446.1 ($MH^+$).

*Tribenzyl Methyl {[(Benzyloxy)phosphoryl]bis(methylene)}bis(phosphonate)* (**29**). Phosphite **10** (18.5 g, 66.8 mmol, 4.0 equiv.) and **19** (8.0 g, 16.7 mmol, 1.0 equiv.) are heated at 140°/4–10 Torr for 10 h. The crude mixture is purified by chromatography (silica gel, $Et_2O$/AcOEt/EtOH 10:0:0→0:7:3): **29** (9.0 g, 85%) as a mixture of 2 diastereoisomers. TLC (AcOEt/EtOH 9:1): $R_f$ 0.4. $^1$H-NMR (CDCl, 200 MHz): 7.38–7.29 (*m*, 20 H); 5.16–4.94 (*m*, 8 H); 3.69, 3.63 (2*d*, $J$ = 11.5, 3 H); 2.87–2.72 (*m*, 4 H). $^{13}$C-NMR (CDCl, 50 MHz): 135.85 (*m*); 128.42–127.87 (*m*); 68.13–67.77 (*m*); 66.95 (*d*, $J$ = 6.2); 52.75, 52.60 (2*d*, $J$ = 6.2); 28.87, 28.58 (2*dd*, $J$ = 87.3, 132.5). $^{31}$P-NMR ($CDCl_3$, 81.015 MHz): 38.52 (*s*, 1 P); 21.75 (*s*, 1 P); 20.89 (*s*, 1 P). CI-MS ($NH_3$): 646.0 ($[M + NH_4]^+$).

*Tribenzyl Hydrogen {[(Benzyloxy)phosphoryl]bis(methylene)}bis(phosphonate)* (**30**). KCN (242 mg, 3.67 mmol, 1.1 equiv.) and **29** (2.10 g, 3.34 mmol, 1.0 equiv.) in anh. DMF (50 ml) are stirred for 4 h at 70°. The solvent is evaporated and the residue dissolved in $H_2O$/MeOH 3:7 (50 ml) and applied on a cation-exchange resin (*Dowex 50X8*, $H^+$ form) for 2 h. The polymer is removed by filtration and the filtrate evaporated several times with toluene: **30** (1.93 g, 94%; not further purified). Slightly yellow syrup. IR (liq.): 3064, 3033, 2953, 2897, 2635, 2306, 1668, 1498, 1455, 1382, 1216, 997. $^1$H-NMR ((D)$_6$DMSO, 200 MHz): 7.37–7.31 (*m*, 20 H); 5.07 (*d*, *J* = 7.2, 2 H); 4.97 (*d*, *J* = 7.4, 6 H); 2.77 (*t*, *J* = 20.1, 4 H). $^{13}$C-NMR ($CD_3OD$, 50 MHz): 137.82–137.38 (*m*); 129.60–128.85 (*m*); 69.38 (*d*, *J* = 5.7); 68.63 (*d*, *J* = 5.7); 68.34 (*d*, *J* = 6.3); 29.61 (*dd*, *J* = 87.1, 130.6). $^{31}$P-NMR ($CDCl_3$, 81.015 MHz): 41.21 (*t*, *J* = 4.7, 1 P); 18.59 (*d*, *J* = 5.1, 2 P). CI-MS ($NH_3$): 631.9 ($[M + NH_4]^+$), 524.2.

*Methylenebis(phosphonic Acid)* (**31**). Ester **18** (256 mg, 0.48 mmol, 1.0 equiv.), 10% Pd/C (26 mg), and ammonium formate (1.50 g, 23.80 mmol, 50.0 equiv.) are refluxed in $H_2O$/MeOH 8:2 (10 ml) for 1.5 h. The mixture is filtered the filtrate evaporated, and the residue dissolved in MeOH (20 ml). Acetone (10 ml) is added and the precipitate collected by centrifugation and dried under vacuum: **31** (79 mg, 94%). White hygroscopic powder. $^1$H-, $^{13}$C-, and $^{31}$P-NMR: identical to that of an authentic sample.

*Phosphorylbis(methylene)]bis(phosphonic Acid)* (**32**). As described for **31**, from **20**: **32** (103 mg, 95%). Very hygroscopic white powder. $^1$H-NMR ($D_2O$, 200 MHz): 2.15 (*dd*, *J* = 20.3, 18.2). $^{31}$P-NMR ($D_2O$, 81.015 MHz): 37.3 (*s*, 1 P); 17.5 (*s*, 2 P). FAB-MS: 252.9 ($[M - H]^-$).

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