γ-Phosphono-γ-lactones. The use of allyl esters as easily removable phosphonate protecting groups

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During the synthesis of γ-lactones bearing a phosphonic acid group at the γ-position, difficulties were encountered generating the free phosphonic acids from corresponding esters. A protecting group used for carboxylic acids was adapted to phosphonic acids, making this transformation easy.

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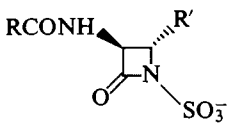
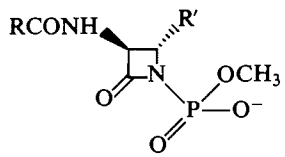
Lors d'une synthèse de γ-lactones ayant un acide phosphonique en position γ, nous avons éprouvé des difficultés à transformer des esters phosphoniques en acides libres. Cette transformation a été rendue facile par adaptation aux acides phosphoniques d'un groupe utilisé pour protéger les acides carboxyliques.

Introduction

Some years ago (1), we pointed out that the steric strain responsible for the chemical reactivity and hence biological activity of the classical β-lactam antibiotics could be replaced by a strain generated by electron-withdrawing groups attached to the nitrogen atom of the β-lactam moiety. This concept was borne out by the discovery of monobactams (2) **1**, which are monocyclic β-lactams substituted by a sulfonic acid at the amidic nitrogen, and the synthesis of analogous monophosphams (3) of type **2**, of which the monomethyl ester **2** seemed to be the most active (3).



1 R′ = H, CH_3



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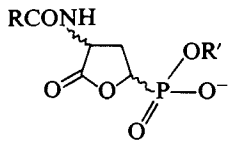

3*a* R′ = H, K[1]
b R′ = CH_3

It occurred to us that the activated β-lactam function, $\nu \geq 1765\ cm^{-1}$, which most probably acts as an acylating agent (4), could be replaced by a γ-lactone, $\nu \simeq 1780\ cm^{-1}$, which should have similar acylating properties. We therefore decided to prepare γ-lactones **3***a and* **3***b*, the latter because of its similarity with monophospham **2**.

Synthesis of phosphonolactone ***12***

Glycine was transformed in 80% yield to its allyl ester hydrochloride, mp 68–71°C, using the recently described method of Brooks and Chan (5), and acylated in 80% yield with di-*tert*-butydicarbonate to **4**. Rearrangement of the bis-silylated dianion of **4** according to the procedure developed by Bartlett and Barstow (6) gave **6***a*, which was transformed to methyl ester **6***b*, using ethereal diazomethane.

Because of relatively low yields in the rearrangement step, and the necessity to esterify the carboxyl function with diazomethane on a large scale, carbobenzyloxyglycine was subjected to a similar sequence. Ester formation with allyl alcohol – trimethylsilyl chloride (Me_3SiCl) gave **5**, mp 36–37°C, and rearrangement of the bis-trimethylsilyl ether of the dianion of **5** gave crude acid **7***a*. Methylation with methanol–Me_3SiCl (5) gave **7***b*, mp 40–41°C, in 85% overall yield, based on carbobenzyloxyglycine.

Whereas the ozonolysis of analogous rearranged compounds derived from crotyl esters of type **7** to the corresponding aldehyde was apparently not possible (6), **7***b* could be easily ozonized at −78°C, using methylene chloride as solvent. Reductive work-up using dimethyl sulfide gave **8**, contaminated with a side-product which was difficult to remove.

Treatment of the crude aldehyde **8** with dimethyl phosphite in methylene chloride containing some triethylamine at 20°C overnight gave a mixture of the aldehyde-phosphonate adduct **13** and the cyclic phosphono-lactone **12** as a mixture of diastereoisomers. Stirring of the mixture in methylene chloride – trifluoroacetic acid (5:1) resulted in the complete conversion of the adduct **13** to the highly strained lactone **12**, $\nu = 1800\ cm^{-1}$.

Alternatively, phosphonolactone **12** was obtained, albeit in very low yield, in the following manner. Olefinic acid **7***a* was ozonolyzed to **9**, mp 139–142°C. Mesylation of **9** gave a mixture of mesylate **10** and chloride **11**. The latter was also obtained by treating **9** with thionyl chloride. Arbusov reaction of **11** with trimethyl phosphite gave **12** in very low yield.

Attempts to hydrolyse, partially or completely, dimethyl phosphonate **12** to monomethyl ester or diacid **3** (R = OCH_2Ph) failed. These attempts included (a) reaction with Me_3SiCl/KI or NaBr in acetonitrile (7, 8), which resulted either in opening of the lactone ring, or very slow reaction giving ill-defined products; (b) reaction with HBr/acetic acid (9), which gave polar products that did not provide starting material upon remethylation; (c) treatment with LiI/2,4,6-collidine in DMF (10) (similar to b); (d) reaction with thiourea (11): this gave what appeared to be the desired acid or acids, since remethylation provided starting material. However, the purification proved to be extremely difficult, and no clean acid could be isolated; (e) sodium bromide/benzyl triethylammonium chloride (12): the reaction was very slow, and no desired acid could be isolated.

It was clear that no good method was at hand, and that we required a phosphonic acid protecting group which could be removed under mild conditions, and where the requisite dialkyl or alkyl methyl phosphonate could be prepared and handled with relative ease. Furthermore, the resulting phosphonic acid

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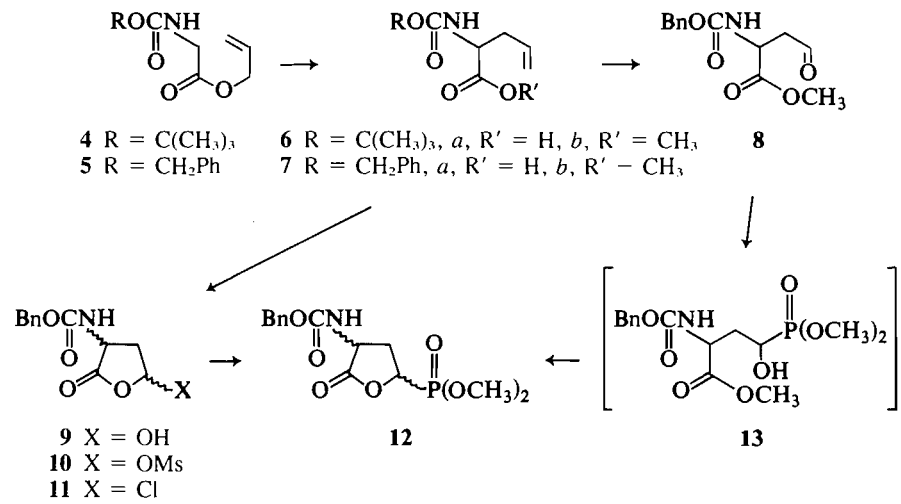
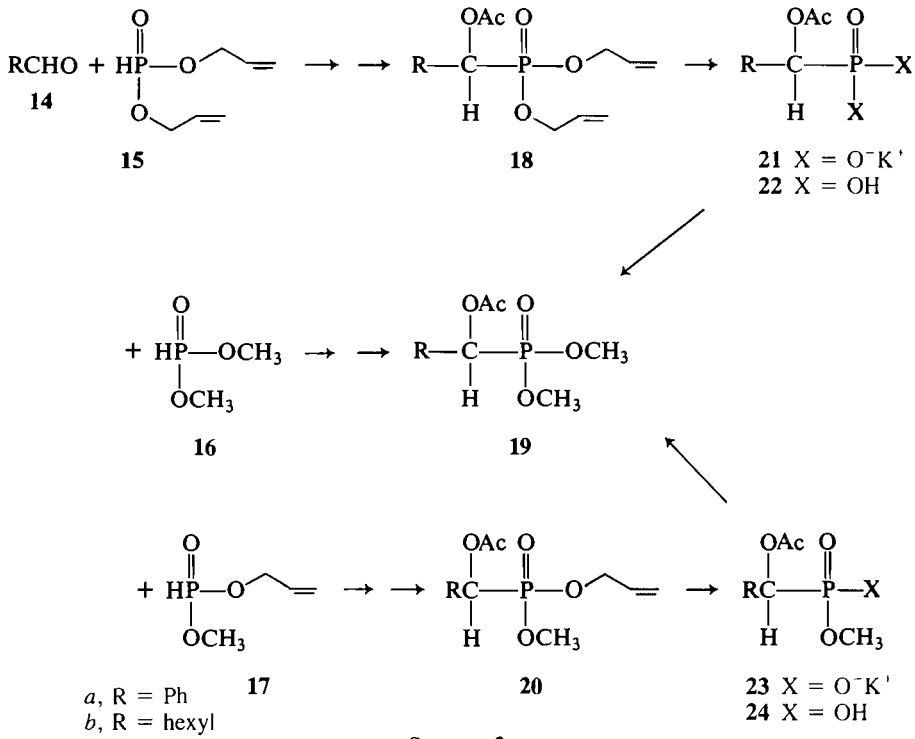


4 R = $C(CH_3)_3$
5 R = CH_2Ph
6 R = $C(CH_3)_3$, *a*, R′ = H, *b*, R′ = CH_3
7 R = CH_2Ph, *a*, R′ = H, *b*, R′ = CH_3
8
9 X = OH
10 X = OMs
11 X = Cl
12
13

SCHEME 1



14
15
18
21 X = O^-K^+
22 X = OH
16
19
17
20
23 X = O^-K^+
24 X = OH
a, R = Ph
b, R = hexyl

SCHEME 2

or salt should not require further purification beyond simple extraction or crystallization.

A variety of dialkyl phosphonates were investigated, and abandoned for the following reasons.

(a) Dibenzyl or benzyl methyl phosphonates are unstable compounds.

(b) Methyl trichloroethyl phosphonate is difficult to prepare, and trouble was anticipated in separating the free phosphonic acid from the zinc ions produced during Zn-mediated removal of the trichloroethyl group.

(c) Bis-trimethylsilylethyl phosphonate rearranges to trimethylsilyl phosphonate with extrusion of ethylene.

We then investigated the suitability of using diallyl and allyl methyl phosphonate as phosphonating agent. Diallyl phosphonate was prepared according to the general procedure described (13). After numerous trials (14, 15; also ref. 13, p. 28), allyl methyl phosphonate was prepared by reaction of allyl alcohol with phosphorus trichloride, and treating the resulting allyl phosphorodichloridite, bp 45–52°C (15 Torr; 1 Torr = 133.3 Pa), first with methanol–pyridine and then with water–pyridine.

For model studies, we prepared six α-acetoxyphosphonates **18***a*, *b*, **19***a*, *b*, and **20***a*, *b* by treating benzaldehyde or heptanal with the appropriate diallyl, dimethyl, and allyl methyl phosphonates **15**, **16**, and **17**, and acetylating the resulting dialkyl hydroxyphosphonates. Three systems were used to try to remove the allyl group.

(1) Catalytic transfer hydrogenation using ammonium formate in methanol and 10% Pd/C (16). The results were not very reproducible, and methanolysis of the acetate group was observed.

(2) 3% $Pd(PPh_3)_4$/4–5%PPh_3/potassium 2-ethylhexanoate

in ethyl acetate (17). This system removed the allyl group smoothly to give potassium salts **21***a, b* and **23***a, b*. Their structures were proven by remethylation to give the dimethyl α-acetoxyphosphonates **19***a, b*. In each case, no starting materials **18***a, b* or **20***a, b* could be detected, and **19***a, b* was obtained as the major product (>90%), as established by tlc, and 200-MHz ^{1}H nmr in the case of **21***a*.

The isolation of the potasium salt was achieved by crystallization (**21***a*, 83%), or required evaporation to dryness, and washing with ether (**21***b*, **23***a*, **23***b*, 5–10% potassium 2-ethylhexanoate contamination). Other, more polar, diallyl phosphonates (see following paper) gave less soluble potassium salts which precipitated and were obtained in high yield and purity.

(3) Wilkinson's catalyst ($(Ph_3P)_3RhCl$). Heating to reflux of phosphonates **18***a*, **18***b*, **20***a*, and **20***b* in 15% aqueous acetonitrile containing 2–3% Wilkinson's catalyst for 1–2 hours (18) resulted in the disappearance of the starting material (tlc) and formation of **22***a*, **22***b*, **24***a*, and **24***b* in 71, 69, 86, and 78%, respectively. The work-up required evaporation of the solvent, dissolving the phosphonic acids in water, and separation from the precipitated Wilkinson's catalyst by filtration. Freeze-drying then gave the products. Their structures were proven by remethylation with ethereal diazomethane (tlc and, in the case of **24***a*, 200-MHz ^{1}H nmr).

None of the yields were optimized. Dimethyl phosphonates **19***a, b* were stable to the reaction conditions outlined under (2) and (3).

The application of this methodology to phosphono lactones **3** will be reported in due course.

Experimental

Thin-layer chromatography (tlc) was performed on Merck Silica Gel 60 F_{254} aluminum-backed plates. Flash chromatography was done on Woelm Silica (32–63 μm). Melting points (mp) were measured on a Gallenkamp block and are uncorrected, unless specified otherwise. The nmr spectra were recorded on Varian T-60, T-60A, and, where noted, XL-200 and Bruker WH-90 spectrometers. Infrared (ir) spectra were recorded on a Perkin Elmer 257 spectrophotometer. Abbreviations: br = broad, s = strong, m = medium, w = weak.

Mass spectra (ms) were obtained on HP 5984A or LKB 9000 spectrometers, in the direct inlet mode unless indicated otherwise.

Carbobenzyloxy (Cbz) glycine allyl ester **5**

Cbz-glycine (6.3 g, 30 mmol) was dissolved in 35 mL allyl alcohol. Then Me_3SiCl (9.5 mL, 73 mmol) was added over a period of 5 min and the mixture left under a N_2 atmosphere at room temperature overnight (5). The solvent was evaporated and the product filtered through silica gel (short 3 × 5 cm column, methylene chloride). After crystallization from ether/petroleum ether, 7.20 g (28.9 mmol, 96%) of ester **5** was obtained, mp 36–37°C; ir ($CHCl_3$, cm^{-1}): 3860 m, 3620 m, 3450 m, 3020 s, 2990 m, 1745 s, 1725 s, 1515 m, 1420 m, 1210 s, 1050 m, 930 m, 750 s; ^{1}H nmr (60 MHz, $CDCl_3$) δ: 7.4 (s, 5H, C_6H_5), 6.2–5.6 (m, 2H, NH and =CH), 5.5–5.3 (m, 2H, H_2C=), 5.2 (s, 2H, Ar—CH_2—O), 4.7 (d, J = 6 Hz, 2H, O—CH_2—CH=CH_2), 4.1 (d, J = 6 Hz, 2H, CO—CH_2—N); ms (m/z, %): 249 (M^+, 6), 108 (41), 107 (31), 91 (100, 65 (11), 41 (17).

Rearranged acid **7***a (ref. 6)*

Hexamethyldisilazane (7 mL, 33 mmol) was dissolved in 100 mL dry tetrahydrofuran (THF) and cooled under N_2 to 0°C. Then n-butyllithium (20 mL, 1.55 *n* in hexane, 31 mmol) was added dropwise and after 10 min the solution was cooled to −78°C. The allyl ester **5** (3.75 g, 15.05 mmol, dissolved in 10 mL THF) was added over 5 min. After another 30 min, Me_3SiCl (4.2 mL, 33 mmol) was added, the mixture stirred for 15 min at −78°C, and then warmed up over 1 h to 20°C. The yellow solution was then warmed for 1–1.5 h to 55–60°C, cooled to 20°C, and diluted with 20 mL methanol. The solvents were evaporated to about 20% of their original volume, diluted with ether, and extracted 4 times with a 5% NaOH solution. Acidification of the combined water layers with cold 6 *N* HCl and extraction with methylene chloride (CH_2Cl_2) gave, after drying ($MgSO_4$) and evaporation, a quantitative yield of the crude acid **7***a* (7.5 g) as a yellowish oil. It was used without further purification; ir ($CHCl_3$, cm^{-1}): 3550–2500 br, m, 3440 m, 2950 m, 1720 s, 1500 m, 1340 m, 1050 m, 900 m; ^{1}H nmr (60 MHz, $CDCl_3$) δ: 10.5 (s, 1H, COOH), 7.3 (s, 5H, C_6H_5), 6.0–5.4 (m, 1H, =CH), 5.3–5.0 (m, approx. 3H, NH and H_2C=), 5.1 (s, 2H, Ar—CH_2—O), 4.4 (m, 1H, N—C*H*—COO), 2.6 (t, J = 6 Hz, 2H, CH_2—CH=CH_2); ms (m/z, %): 249 (M^+, 11), 208 (M^+ − 41, 2), 204 (M^+ − 45, 2), 108 (22), 107 (10), 91 (100), 79 (16), 65 (12), 41 (29).

Methyl ester 7b

Crude acid **7***a* (7.5 g) was dissolved in 30 mL methanol and Me_3SiCl (4.5 mL, 35.5 mmol) was added. Stirring overnight under N_2, evaporation to dryness, and recrystallization from ether/hexane gave the ester **7***b* as colourless crystals (3.47 g, 13.2 mmol, 88% from allylester **5**), mp 40–41°C; ir ($CHCl_3$, cm^{-1}): 3450 m, 2990 m, 1740 s, 1720 s, 1515 m, 1210 s, 1050 m, 920 m; ^{1}H nmr (60 MHz, $CDCl_3$) δ: 7.2 (s, 5H, C_6H_5), 5.9–5.3 (m, 2H, NH and =CH), 5.2–4.9 (m, 2H, H_2C=), 5.1 (s, 2H, Ar—CH_2—O), 4.4 (m, 1H, N—C*H*—COO), 3.7 (s, 3H, $COOCH_3$), 2.5 (t, J = 6 Hz, 2H, CH_2—CH=CH_2); ms (m/z, %): 263 (M^+, 17), 222 (M^+ − 41, 6) 204 (M^+ − 59, 4), 178 (4), 160 (4), 108 (8), 107 (3), 91 (100), 79 (4), 65 (8), 59 (2), 41 (5).

Aldehyde **8**

The ester **7***b* (1.78 g, 6.75 mmol) was dissolved in CH_2Cl_2 and cooled to −78°C. Then ozone was bubbled through the solution until it turned blue. Excess ozone was removed with a steam of dry N_2. Dimethylsulfide (5 mL) was added and the reaction left at ~20°C overnight. The solvent was evaporated and the crude yellow oil partitioned between ether and saturated $NaHCO_3$ solution, and the ether layer dried over $MgSO_4$ and evaporated to give crude aldehyde **8** (1.73 g, 6.53 mmol, 96%) as a yellowish oil. The aldehyde **8** could be used without further purification; ir ($CHCl_3$, cm^{-1}): 3430 m, 2950 m, 2940 m, 1720 br s, 1500 s, 1430 m, 1330 m, 1050 m; ^{1}H nmr (60 MHz, $CDCl_3$) δ: 9.7 (s, 1H, CHO), 7.3 (s, approx. 5H, C_6H_5), 5.6 (m, 1H, NH), 5.2 (s, approx. 2H, Ar—CH_2—O), 4.7 (m, 1H, N—C*H*—COO), 3.7 (s, 3H, $COOCH_3$), 3.1 (d, J = 6 Hz, 2H, —CH_2—CHO); ms (m/z, %): 265 (M^+, 6), 206 (M^+ − 59, 3), 162 (M^+ − 59–44, 3), 115 (3), 108 (22), 107 (9), 91 (100), 79 (6), 77 (5), 69 (9), 65 (12), 59 (2), 55 (6), 44 (4), 43 (8), 41 (5).

Lactone **12**

Crude aldehyde **8** (580 mg, 2.2 mmol) was dissolved in 1 mL CH_2Cl_2, dimethylphosphite (0.5 mL, 3.8 mmol) and triethylamine (0.1 mL) were added, and the mixture left overnight at ~20°C. The solvent was pumped off, 2.5 mL CH_2Cl_2 and 0.5 mL trifluoroacetic acid were added, and the mixture left for ~20 h. Flash chromatography (silica gel, ethyl acetate – hexane 5:1) gave 490 mg (1.43 mmol, 65%) of the lactone **12** as a mixture of 2 diastereoisomers; ir ($CHCl_3$, cm^{-1}): 3420 m, 2950 m, 2850 m, 1800 s, 1720 s, 1495 m, 1450 m, 1250 m, 1150 s, 1030 s; ^{1}H nmr (60 MHz, $CDCl_3$) δ: 7.3 (s, 5H, C_6H_5), 6.0–5.7 (m, 1H, NH), 5.1 (s, 2H, Ar—CH_2—O), 4.8–4.2 (m, 2H, P—CH and N—CH—COO), 3.8 (m, 6H, 2 P—O—CH_3), 2.9–2.1 (m, 2H, —CH_2—); ms (m/z, %): 343 (M^+, 19), 282 (3), 252 (17), 237 (7), 236 (76), 234 (2), 174 (4), 137 (13), 108 (10), 91 (100), 79 (11), 65 (11), 59 (4), 44 (6).

Allyl phosphorodichloridite

To 320 mmol PCl_3 at −75°C was added 320 mmol of freshly distilled allyl alcohol over a period of 5 h. The HCl formed was removed with a stream of dry N_2. The reaction mixture was warmed slowly to room temperature and kept stirring overnight (N_2 stream). Distillation was interrupted after 55 mmol (17%) allyl phosphorodichloridite, bp 35–40°C/10 Torr, was obtained because of

reported spontaneous polymerization resulting in explosion of the mixture distilled to less than half of its volume.

Allyl methyl phosphonate ***17***

Allyl phosphorodichloridite (23.6 mmol) was dissolved in 80 mL dry THF and cooled under N_2 to −78°C. Then 23.6 mmol methanol and 23.6 mmol pyridine in 10 mL THF were added dropwise over a period of 30 min. Stirring was continued for another 1.5 h at −78°C, and for 2 h at 20–25°C. The reaction mixture was cooled to 0°C and 10 mL THF containing 25 mmol water and 26 mmol pyridine were added dropwise. The mixture was stirred 0.5 h at 0°C and then 2 h at 20–25°C. After filtration and evaporation, the crude yellow oil was dissolved in 2 mL of CH_2Cl_2 and filtered over 5 g silica gel using CH_2Cl_2 as eluant. After evaporation to dryness, the methyl allyl phosphonate **17** could be obtained as a clear oil (2.51 g, 18.5 mmol, 78.5%); ir ($CHCl_3$, cm^{-1}): 2440 (P—H), 1270–1180 (P=O, C—O); ^1H nmr (60 MHz, $CDCl_3$) δ: 6.85 (d, J = 700 Hz, 1H, PH), 6.2–5.7 (m, 1H, =CH), 5.6–5.1 (m, 2H, H_2C=), 4.7–4.4 (m, 2H, H_2COP), 3.8 (d, J = 12 Hz, 3H, H_3COP); ms (m/z, %): 137 (M^+ + 1, 0.5), 97 (29), 95 (M^+ − 41, 7), 80 (29), 79 (M^+ − 57, 100), 58 (66), 47 (25), 41 (27).

Diallyl phosphonate ***15***

Diallyl phosphonate was prepared in 86% yield from 1 equiv. phosphorus trichloride, 3 equiv. allyl alcohol, and 2 equiv. pyridine using the general procedure described (13); ir ($CHCl_3$, cm^{-1}): 2430 (P—H), 1270–1200 (P=O, C—O); ^1H nmr (60 MHz, $CDCl_3$) δ: 6.8 (d, J = 700 Hz, 1H, PH), 6.2–5.6 (m, 2H, =CH), 5.5–5.1 (m, 4H, H_2C=), 4.7–4.3 (m, 4H, H_2COP); ms (m/z, %): 121 (M^+ − 41 (C_3H_5), 51), 105 (M^+ − 57, 4), 83 (12), 80 (10), 79 (17), 65 (14), 58 (11), 57 (CH_2=$CHCH_2O$, 100), 41 (80).

Diallyl, methyl allyl, and dimethyl acetoxyphosphonates ***18***, ***19***, *and* ***20***

All six compounds were prepared in an identical manner, and their spectra were very similar. A representative example is described. To a methylene chloride (5 mL) solution of benzaldehyde **14***a* (2 mmol) was added diallyl phosphonate **15** (2.16 mmol) and 3 drops of triethylamine. After tlc indicated completion of the reaction (16 h), acetic anhydride (2 mL) and triethylamine (1 mL) were added at 0°C. After 2 h, diethyl ether and ice-water were added. Stirring for 0.5 h and washing to neutrality gave after drying ($MgSO_4$), evaporation, and flash chromatography (silica gel, petroleum ether – acetone 10:1) diallyl phosphonate **18***a* (1.36 mmol, 68%) as a clear oil.

18*a*: ir (film, cm^{-1}): 1755 (C=O), 1260 (P=O), 1220 (O—C), 1020 (P—O); ^1H nmr (60 MHz, $CDCl_3$) δ: 7.3 (m, 5H, C_6H_5), 6.1 (d, J = 13 Hz, approx. 1H, HCP), 6.1–5.5 (m, 2H, =CH), 5.4–5.0 (m, 4H, H_2C=), 4.6–4.3 (m, 4H, H_2COP), 2.1 (s, 3H, H_3CCO); ms (m/z, %): 310 (M^+, 0.2), 267 (M^+ − 43, 4), 162 ($HPO(OCH_2CH$=$CH_2)_2$, 10), 121 (HPO_2OCH_2CH=CH_2, 20), 107 (C_6H_5CHOH, 17), 77 (C_6H_5, 10), 57 (H_2C=$CHCH_2O$, 9), 43 ($COCH_3$, 100), 41 (CH_2CH=CH_2, 66).

Spectral characteristics of ***18***, ***19***, *and* ***20***

Dimethyl phosphonate **19***a*: 3.6 and 3.7 ppm (two d, J = 10 Hz, 6H, 2 CH_3OP); **19***b*: 3.78 and 3.80 ppm (two d, J = 10.6 Hz, 6H, 2 CH_3OP); allyl methyl phosphonate **20***a*: 3.6 and 3.7 ppm (two d, J 10 Hz, 3H, CH_3OP); **20***b*: 3.7 ppm (d, J = 10 Hz, 3H, CH_3OP); **18***a*, **19***a*, **20***a*: Ph—C*H*—*P*: J = 13 Hz, d; **18***b*, **19***b*, **20***b*: $C_5H_{11}CH_2$—C*H*—*P*: $J_{AX} + J_{BX}$ = 15 Hz, J(d) = 9 Hz. All mass spectra showed m/z for $HPO(OR)_2$; $HOP(OMe)_2$: **19***a* 110 (100%), **19***b* (97%); HOP(OM) (OCH_2CH=CH_2): **20***a* 136 (20%); **20***b* (80%); $HOP(OCH_2CH$=$CH_2)_2$: **18***a* 162 (10%); **18***b* (7%).

All phosphonate esters showed negligible (<0.4%) M^+ or (M + 1)$^+$ peaks except for **19***a*: M^+ 258.0664 (27.5%; calcd. 258.0657).

Dipotassium salt ***21***a

To 86 mg (0.28 mmol) of **18***a*, 1.33 mL 0.5 *M* (2.4 equiv.) potassium 2-ethylhexanoate in ethyl acetate, 20 mg (6.3 mol%) tetrakis(triphenylphosphine)palladium(0), and 6 mg (8 mol%) triphenylphosphine were added. The reaction mixture was stirred at 20–25°C until all starting material had reacted (1.5 to 2 h). After addition of 2 mL acetone, the salt precipitated out as white crystals. Filtration gave 79 mg (83%) dipotassium salt **21***a*; ir (4% in KBr, cm^{-1}): 1705 (C=O), 1250 (P=O); ^1H nmr (60 MHz, CD_3OD) δ: 7.1 (m, 5H, C_6H_5), 5.5 (d, J = 13 Hz, 1H, HCP), 1.8 (s, 3H, H_3CCO), Dipotassium salt **21***a* was converted to its dimethyl ester **19***a* by dissolving it in methanol, and adding acidic ion-exchange resin (Amberlyte IR-120) and then ethereal diazomethane.

Potassium salt ***23***b

To 51 mg (0.17 mmol) **20***b*, 0.38 mL 0.5 *M* (1.12 equiv.) potassium 2-ethylhexanoate in ethyl acetate, 6 mg (3 mol%) tetrakis(triphenylphosphine)palladium(0), and 2 mg (4.5 mol%) triphenylphosphine were added and the mixture stirred at 20–25°C until all starting material had reacted (1.5 to 2 h). No crystals precipitated out, so the solvent was evaporated, and after the remaining yellowish oil was washed several times with ether, it solidified in the cold. Yield approximately 85–90%; ir ($CHCl_3$, cm^{-1}): 1725 (C=O), 1230 (P=O); ^1H nmr (60 MHz, $CDCl_3$) δ: 5.2 (m, 1H, HCP), 3.6 (d, J = 10 Hz, 3H, H_3COP), 2.2 (s, 3H, H_3CCO), 2.0–1.0 (br m, approx. 13H, alkyl) (^1H nmr spectrum shows approximately 5–8% impurities due to the remaining triphenylphosphine and 2-ethylhexanoate). The monopotassium salt **23***b* was converted to its dimethyl ester **19***b* as described earlier.

Phosphonic acid ***24***a

To a solution of 74 mg (0.26 mmol) **20***a* in 3 mL acetonitrile/ water (85:15), 5 mg (2 mol%) of Wilkinson's catalyst was added. After refluxing for 2 h all the starting material had reacted. The solvent was evaporated, and the residue stirred for 5 min in 5 mL of water. After filtration, the water layer was freeze-dried to give 65 mg (0.22 mmol, 86%) of the acid **24***a* as a yellow oil; ir ($CHCl_3$, cm^{-1}): 1740 (C=O), 1180 (P=O); ^1H nmr (60 MHz, $CDCl_3$) δ: 7.3 (br s, approx. 5H, C_6H_5), 6.1 (br s, 1H, HCP), 3.6 (br s, 3H, H_3COP), 2.2 (s, 3H, H_3CCO). The acid **24***a* was treated with ethereal diazomethane to give dimethyl ester **19***a*.

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