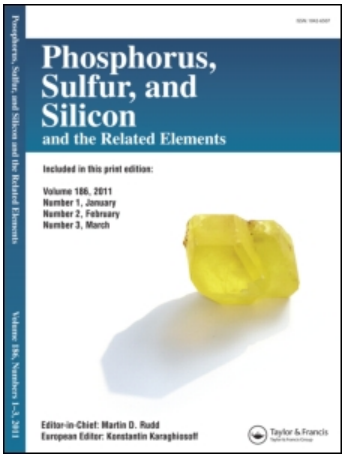

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PHOSPHONIC SYSTEMS. 7. REACTIONS OF 2,3-EPOXYPHOSPHONATES WITH NUCLEOPHILES: PREPARATION OF 2,3-DISUBSTITUTED ALKYLPHOSPHONIC ESTERS AND RELATED SYSTEMS

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PHOSPHONIC SYSTEMS. 7. REACTIONS OF 2,3-EPOXYPHOSPHONATES WITH NUCLEOPHILES: PREPARATION OF 2,3-DISUBSTITUTED ALKYLPHOSPHONIC ESTERS AND RELATED SYSTEMS

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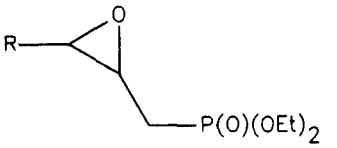
Diethyl 2,3-epoxyalkylphosphonates react regioselectively with various nucleophilic reagents yielding 2-hydroxy-3-substituted alkylphosphonic esters. The 2-hydroxy functionality can be easily converted into an ester or ether derivative. The reaction of diethyl 2,3-epoxypropylphosphonate with ketone enamines does not lead to hydroxyketophosphonates, but results in the incorporation of the 3-phosphonopropylidene group (CH—CH_2—CH_2—PO_3Et_2) into the position 2 of the parent ketone.

Key words: 2,3-Epoxyphosphonates; nucleophilic opening of epoxides; reaction of epoxides with enamines; 2-(3′-diethoxyphosphonyl)propylidenecycloalkanones.

INTRODUCTION

The importance of epoxides as substrates for a great variety of vicinally difunctionalised compounds is well established.[1] In the continuation of our interest in the reactivity of α, β and γ carbon atoms in dialkyl alkenylphosphonates,[2] we now turned our attention to the chemistry of the 2,3-epoxyalkylphosphonates (**1**) as direct precursors for the 2,3-difunctionalised phosphonic derivatives.



1

If the nucleophilic reaction of **1** occurred selectively at carbon **3**, the ring opening should yield a substituted 2-hydroxyphosphonate, an important intermediate in the olefination reaction via the phosphonate-stabilised carbanions.[3] In addition, we are particularly interested in 2-substituted alkylphosphonic derivatives as excellent models for the studies on the medium and ion effects on the conformations of organophosphorus compounds.[4]

The first report on the opening of the epoxide ring in diethyl 2,3-epoxypropylphosphonate (**1a**, R=H) was concerned with hydrolysis leading to the corresponding 2,3-diol.[5] Later, Griffin and Kundu reported that the alcoholysis and aminolysis

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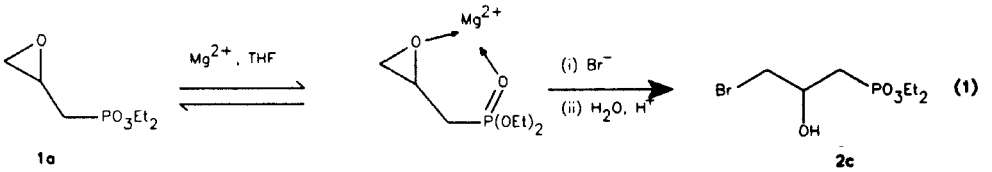
of 1,2-epoxyethyl- and 2,3-epoxypropylphosphonates always involve the attack at the terminal carbon atom;[6] the same regioselectivity was confirmed for the reaction of epoxides **1** with HCl.[7] Although the initial attempts of opening the epoxide ring in **1** with Grignard reagents failed,[6] Inamoto *et al.* showed that the carbon skeleton of a phosphonate can be modified at position 3 by reaction of **1** with Grignard reagents in the presence of CuI.[8] In this work we report on further ring-opening of two epoxyphosphonates **1** (**1a**, R=H; **1b**, R=Et) with nucleophiles, and on the derivatisation of the 2-hydroxyalkylphosphonates formed.

RESULTS AND DISCUSSION

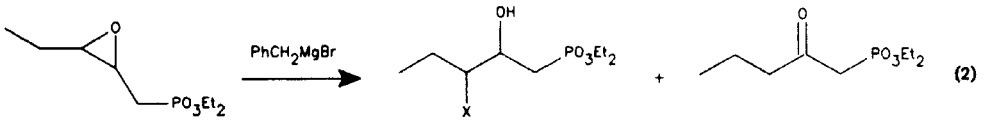
In the full agreement with earlier reports,[6–8] we have confirmed the rigorous regioselectivity of the epoxide ring opening in both, unsubstituted (**1a**), and substituted (**1b**) substrates. In agreement with earlier reports, **1a** reacts with aq. sulfuric acid[5] and with dry HCl[7] yielding diethyl 2,3-dihydroxypropyl, and 2-hydroxy-3-chloropropylphosphonates, respectively. Reaction with gaseous HBr did not lead, however, to the complete conversion, and always yielded the mixtures of the expected product and starting material; the latter being formed in the reversal of the ring opening step. Pure diethyl 2-hydroxy-3-bromopropylphosphonate (**2c**) could be, however, prepared in high yield by treating **1a** with dry magnesium bromide, followed by the aqueous work-up. We have recently observed chelating properties of the 2-hydroxy- (or 2-methoxy-) substituted alkylphosphonates with respect to Mg^{2+} in organic solvents;[9] this property should result in the electrophilic catalysis of the ring-opening reaction (Equation 1).



(1)

1a **2c**

Reactions with carbon nucleophiles. Griffin and Kundu[6] reported that **1a**, upon treatment with alkylmagnesium bromides did not yield any extension of the carbon skeleton, but produced the corresponding 2,3-diols in moderate yields. We have caused to react the epoxyphosphonate **1b** with benzylmagnesium bromide and also failed to observe any incorporation of the benzyl group into the molecule of **1b**. The substrate was however converted quantitatively into the mixture of three products, which, after separation, yielded the corresponding diethyl 2,3-dihydroxypentyl- (**2a**), 2-hydroxy-3-bromopentyl- (**2b**), and 2-oxopentylphosphonate (**3**) in a ratio 2.3:1:1.3, respectively (Equation 2).



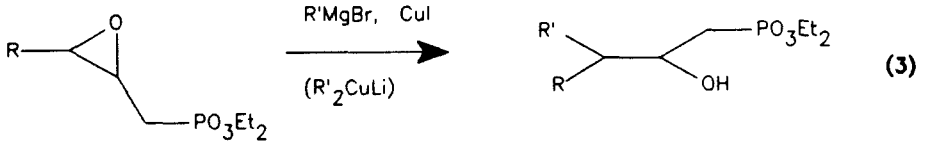
(2)

1b **2a** (X = OH) **3**

2b (X = Br)

All products shown in Equation 2 result from the reaction of **1b** with magnesium bromide (present in equilibrium with the Grignard reagent).[10] Product **2b** is formed according to Equation 1, while **2a** results from the hydrolysis of **1b**, either left in the reaction mixture, or formed from **2b** under the basic conditions of the reaction. Ketone **3** is the product of the known[11] $MgBr_2$-catalysed rearrangement of the epoxide; chelation of the Mg^{2+} ion (Equation 1) again playing the important role in the reaction. When **1b** was treated in an independent experiment with dry $MgBr_2$, similar mixture of **2a**, **2b**, and **3** was obtained in a ratio of ca 2:1:1 (as determined by ^{31}P NMR spectroscopy).

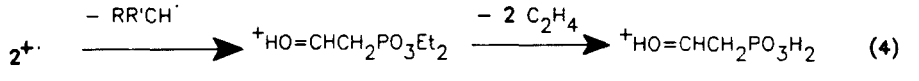
Formation of a new carbon-carbon bond could be, however, in agreement with the earlier report,[8] easily achieved in reactions of substrates **1** either with Grignard reagents in the presence of cuprous iodide, or with organocuprates (Equation 3).



(3)

1 **2**

Structure of products **2** was unequivocally determined by NMR (^1H, ^{13}C, ^{31}P) spectroscopy and mass spectrometry. In all cases the attack of a carbon nucleophile took place exclusively at carbon 3, and all products **2** (including the 2-hydroxy-3-haloderivatives described earlier) were formed as single diastereoisomers. The rigorous regioselectivity of the ring opening in **1** was demonstrated clearly by mass spectrometry of the reaction products. For compounds **2**, as for all secondary alcohols, radical site initiation[12] can lead to two pairs or products, each containing a different oxocarbonium ion and a radical. All compounds **2** prepared in this work gave in their mass spectra the base peak either at m/z 181, or m/z 125, corresponding to the oxocarbonium ion, $^+HO{=}CH{-}CH_2PO_3Et_2$, formed by the C(2)—C(3) α-cleavage, or to the product of the loss of two molecules of ethene from the latter ion via McLafferty rearrangement (Equation 4).[13]



(4)

m/z 181 m/z 125

Table I lists the products obtained in reactions of epoxides **1** with carbon, as well as other, nucleophiles.

Alcohols **2** could be then easily converted to the O-methyl, O-acetyl, and O-trifluoroacetyl derivatives **4** by standard procedures (Table II). Both, the parent alcohols, and their O-functionalised derivatives, show some interesting structural and reactivity properties. For the solutions of alcohols and ethers in organic solvents, we demonstrated intramolecular attraction between the OH (OMe) and the PO_3Et_2 groups, leading to a severe restriction of the free rotation about the C(1)—C(2) bond.[9] Trifluoroacetate esters of the type of **4j** show a new type of thermal frag-

TABLE I

Diethyl 2,3-disubstituted propyl- and pentylphosphonates **2**

2	R	R′	Reagent	Yield[a] (%)	δ_P[b]	δ_H[b] (J, Hz)	δ_C[b] (J, Hz)	MS (m/z, %)
a	H	OH	H_2O/H^+	50	25.8	c		213(5), 181(41), 153(17), 125(100), 107(33)
b	H	Cl	$HCl/CHCl_3$	84	d	d		231(1), 181(48), 153(19), 125(100), 29(59)
c	H	Br	$MgBr_2$ THF	90	24.1	1.28(t,7.0), 2.05 (ddd,15.4,11.5,4.1), 3.43 (2H,d,5.2), 4.02-4.10(m)		277(0.2), 181(53) 125(100), 107(29), 29(44)
d	H	Me	Me_2CuLi Et_2O	55	26.2	0.92(t,7.5),1.30, 1.31(2t,7.10), 1.52 (m), 1.88(m), 3.44 (br s), 3.89(m), 4.09(m)	9.5(d,2.2), 16.2(d,2.8) 30.9(d,16.7), 32.9(d, 139), 61.6(d,7.0), 67.6(d,5.6)	181(100), 153(38) 138(16), 125(91), 97(19), 55(12)
e	H	Et	EtMgBr CuI	70	26.3	1.02(t,7.1), 1.45(t, 7.1), 1.55(m), 3.56 (d,3.0), 4.11(m), 4.25(m)		225(1), 181(100), 153(30), 125(69), 107(9)
f	H	i-Pr	i-PrMgBr CuI	61	26.2	0.98(d,7.9), 1.32(m) 1.41(t,7.1), 1.76(m) 3.47(2t,7.1,5.4), 3.75(br s), 4.18(m)		181(53), 153(20), 125(100), 29(77)
g	H	n-Bu	$n\text{-}Bu_2CuLi$ THF	60[e]	26.2	0.79(t,6.0), 1.27(t, 7.1), 1.30(m), 1.80 (m), 3.50(br s), 3.90 (m), 3.99(m)	13.8, 16.2(d,5.5), 22.4 24.9, 31.5, 33.4(d, 138), 38.1(d,18.1), 61.6(d,7.2), 66.3 (d,5.7)	181(100), 153(38), 138(16), 125(91), 97(19), 55(12)
h	H	Ph	PhMgBr/ CuI Ph_2CuLi	81[e] 65	25.8	1.25(t,7.1), 1.88(m), 2.81(ddd,18.0,13.6, 6.8), 3.55(br s), 4.02(m), 4.19(m), 7.21(m)	16.4(d,6.6), 32.8(d, 139), 44.5(d,16.6), 61.8(d,9.1), 67.6(d, 5.5), 126.6, 128.5, 129.5, 137.7	254(8), 181(100), 153(39), 125(98), 91(30), 55(12)
i	Et	Me	Me_2CuLi THF	37	27.7	0.83(t,6.7), 0.84(d, 7.4), 1.29(t,7.1), 1.43(m), 1.80(m), 3.45(br s), 3.82(m), 4.02(m), 4.08(m)	11.4, 14.0, 16.3, 24.8, 29.5(d,149), 40.6(d, 15.8), 61.8(d,6.3), 69.7(d,6.5)	181(3), 153(31), 138(20), 125(83), 111(62), 97(45), 43(100)
j	Et	n-Bu	$n\text{-}Bu_2CuLi$ THF	55	27.7	0.88(m), 1.30(t,7.0), 1.31(m), 1.84(dd, 17.7,6.3), 3.01(br s) 4.00(m), 4.10(m)	11.6, 14.0, 16.4(d,3.3) 21.9, 23.1, 28.8, 29.4, 30.1(d,139), 45.5 (d,15.4), 61.9(d,3.0), 67.7(d,6.4)	267(1), 181(100), 153(10), 125(33), 107(5), 81(4)
k	Et	Ph	Ph_2CuLi THF	40	25.5	0.69(t,7.4), 1.23(t, 6.4), 1.59(m), 2.45 (m), 3.70(br s), 4.00 (m), 7.17(m)	11.9, 16.3(d,5.6), 24.5 31.5(d,137), 55.1(d, 16.6), 61.7(d,6.9), 70.2(d,5.9), 126.5, 126.6, 128.4, 139.9	284(3), 202(21), 181(100), 153(26), 125(44), 91(18)

[a] After bulb to bulb distillation or column chromatography; [b] in $CDCl_3$; [c] in agreement with the data given in the lit.[6] [d] in agreement with the data given in the lit.[7] [e] Lit.[8] yield 83%; no spectroscopic data given

mentation involving the P—C bond cleavage and the ethyl group migration from the phosphonate to the acetate oxygen.[14]

Reactions of **1a** *with enamines.* The reaction between ketone enamine and epoxide can serve as a route to γ-hydroxyketones,[15] hence (after oxidation) to 1,4-diketones. Application of this reaction to epoxides of the type **1** could lead to the synthesis of 2,5-diketophosphonates, useful substrates for the intramolecular Horner-Em-

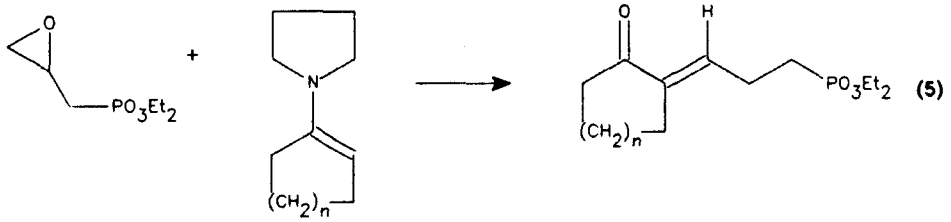
TABLE II

O-Derivatives of diethyl 2-hydroxy-3-substituted propylphosphonates, $RCH_2—CH(OY)CH_2PO_3Et_2$ (4)

4	R	Y	Yield[a] (%)	δ_P [b]	δ_H of Y[b]	MS m/z (%)
a	Cl	CF_3CO	94	19.1		291 (7), 213 (12), 177 (22), 69 (52), 29 (100)
b	Cl	Ac	60	20.8	1.95	291 (67), 181 (43), 153 (12), 125 (100), 107 (35)
c	Br	CF_3CO	98	19.2		291 (5), 257 (7), 177 (46), 121 (77), 81 (64), 41 (100)
d	Br	Ac	79	20.2	2.06	181 (100), 153 (31), 125 (84)
e	Et	CF_3CO	72	25.3		223 (17), 206 (100), 181 (79), 125 (67), 97 (27)
f	Et	Ac	70	25.2	2.11	206 (19), 192 (100), 181 (21), 138 (85), 124 (37), 111 (82), 97 (37)
g	Et	Me	50	30.0	3.41	223 (23), 195 (100), 181 (31), 125 (44), 138 (27), 109 (32)
h	i-Pr	CF_3CO	95	21.0		221 (10), 181 (69), 125 (100), 97 (25), 81 (42)
i	i-Pr	Ac	72	22.4	2.02	237 (53), 220 (75), 181 (100), 165 (24), 152 (49), 125 (44)
j	Ph	CF_3CO	92	20.3		181 (56), 125 (100), 91 (78), 65 (57)
k	Ph	Ac	75	22.2	1.99	254 (76), 226 (11), 181 (33), 153 (13), 117 (80), 91 (47), 43 (100)
l	Ph	Me	58	29.7	3.33	254 (82), 226 (5), 195 (100), 181 (3), 167 (14), 139 (25), 117 (42), 91 (26), 65 (10)

[a] After bulb to bulb distillation

mons reaction.[16] In order to test the reactivity of substrates **1** towards enamines, **1a** was reacted with enamines derived from pyrrolidine and cyclopentanone, or cyclohexanone, under conditions given in the literature.[15] In each case a single (according to ^{31}P NMR spectroscopy) phosphorus-containing product was formed which was isolated in pure state, but in low yield (ca. 35%) by column chromatography. The products of both reactions were unambigously identified by NMR (^{31}P, ^{1}H, ^{13}C) spectroscopy and mass spectrometry as the corresponding (E)-2-(3-diethoxyphosphonyl)propylidenecyclohexanone (or -cyclopentanone), **5a** and **5b** (Equation 5).

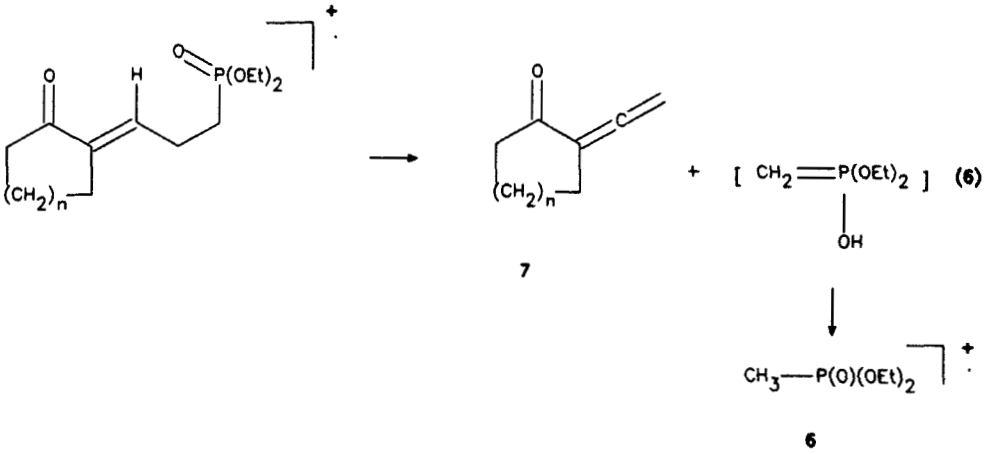


1a

5a, n = 2

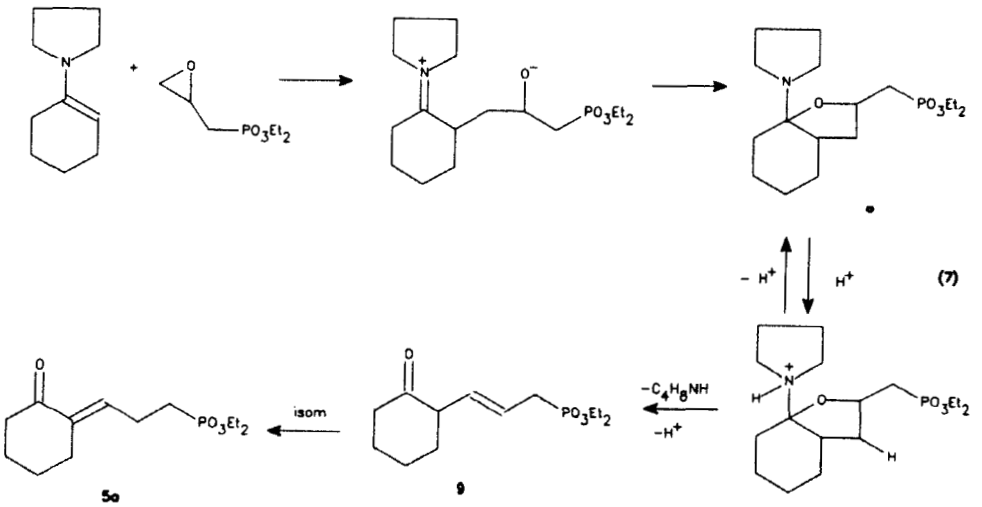
5b, n = 1

In the mass spectra of both products **5**, diethyl methylphosphonate (**6**) (m/z = 152) was observed as a base peak. Its formation can be envisaged as a result of a common McLafferty rearrangement yielding a molecule of an allene **7** as a side product (Equation 6).



The ^{13}C NMR spectrum demonstrated the absence of any hydroxyl-containing carbon atom, and the combination of the ^{1}H-coupled ^{13}C NMR, and the ^{1}H NMR spectra were in full agreement with the structure **5**. Since the geometry of the olefinic function could not be determined from the proton spin-spin coupling across the olefinic bond, the (E) configuration of **5a** and **5b** was assigned on the basis of the chemical shift value of the single olefinic proton (δ_H = 6.51 and 6.42, respectively). Considering the additivity of the substituent effects on the chemical shift of an olefinic proton in trisubstituted alkenes,[17] the calculated δ_H value for the *cis* relation of the olefinic proton and the carbonyl group in **5** is 6.54 ppm, as opposed to the value of 6.20 ppm for the *trans* relation.[17a]

Reaction of **1a** with enamines obviously does not involve simple epoxide ring opening leading, after aqueous work-up, to the expected hydroxyketophosphonate. The nucleophilic attack does occur at the position 3 (less hindered) in **1a**, but the initial adduct undergoes further transformations. The proposed mechanism for the formation of products **5** is presented (using the enamine derived from cyclohexanone) in Equation 7.



The first two steps of the reaction (formation of the furan derivative **8**) have been observed before in the reactions of enamines with epoxides.[15,18] In our case, the intermediate **8** underwent elimination to the ketophosphonate **9**, which isomerised under the reaction conditions[19] to the conjugated product **5**. When the reaction was repeated using the enamine derived from acetophenone, the product, although not isolated and purified, had, according to the NMR spectroscopy, the analogous structure of the type **5**. It seems therefore that the reaction of epoxides **1** with enamines can serve as a route to the δ-phosphonosubstituted α, β-unsaturated ketones, and the scope and utility of this reaction is being currently studied in our laboratory.

EXPERIMENTAL

Solvents and commercially available substrates were purified and dried by standard methods immediately before use. All reactions that required an inert atmosphere were carried out under dry nitrogen. The concentration of the organolithium reagents was determined by the reported method.[20] Sodium hydride (Fluka, 55–60% dispersion in oil) was used after removing the oil and washing several times with light petroleum. Bulb to bulb distillation was carried out using a Büchi GKR-50 apparatus. Precoated Kieselgel 60F 254 aluminum plates were used for TLC; for column chromatography Merck Kieselgel 60 (0.063–0.200 mm) was used as a stationary phase. NMR spectra were recorded on a Bruker AC 300 MHz spectrometer for solutions in $CDCl_3$, and the chemical shifts values are given relative to $SiMe_4$ (^1H, ^{13}C) and 85% phosphoric acid (^{31}P). Both ^1H-decoupled and ^1H-coupled ^{13}C NMR spectra were obtained for structural assignments. Diastereomeric nuclei are denoted by superscripts *a* and *b*. Mass spectra were recorded on a Varian MAT-212 double-focusing direct-inlet spectrometer at a ionization potential of 70 eV. Only the values for selected ions (and their relative abundances), most relevant to structural determinations, are given. IR spectra were recorded in chloroform solutions on a Bomem Michelson-100 FT spectrometer.

Diethyl 2,3-epoxypropylphosphonate **1a**.[6] A mixture of epibromohydrin (25.0 g, 0.18 mol) and triethyl phosphite (30.3 g, 0.18 mol) was heated to 130°C under nitrogen, in a flask equipped with Vigreux column and a condensor. At this temperature bromoethane distilled off; the mixture was then heated at 130°C for 4 h, and at 150°C for 1 h. The crude product was purified by distillation, bp 85—88°C/0.4 mm Hg (28.0 g, 80%). δ_H 1.32 (6H, t, J 7.1 Hz, 2 × Me of POEt), 1.81 (1H, ddd, J 19.9, 15.1, 6.4 Hz, α-CH^a), 2.16 (1H, ddd, J 18.2, 15.1, 5.6 Hz, α-CH^b), 2.54 (1H, dd, J 4.6, 2.5 Hz, γ-CH^a), 2.79 (1H, d, J 4.6 Hz, γ-CH^b), 3.13 (1H, m, β-CH), 4.09 (4H, m, 2 × CH_2 of POEt). δ_C 16.4 (d, J 6.7 Hz, 2 × Me of POEt), 30.2 (d, J 139 Hz, α-CH_2), 46.7 (d, J 2.5 Hz, β-CH), 47.2 (d, J 7.2 Hz, γ-CH_2) 61.9 (d, J 7.0 Hz, 2 × CH_2 of POEt). δ_P 21.7. MS m/z(%) 194 (M^+; 10), 181 (100), 139 (62), 125 (53), 111 (27), 81 (11).

Diethyl 2,3-epoxypentylphosphonate **1b**. Diethyl 2-pentenylphosphonate[21] (10.3 g, 0.05 mol), m-chloroperbenzoic acid (85% w/w, 12.1 g, 0.06 mol) and sodium carbonate (6.4 g, 0.06 mol) were stirred in dry dichloromethane (50 mL) at room temperature under dry nitrogen for 3 days. The mixture was filtered, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography (ethyl acetate/hexane, 7:3). Oil (56%). δ_H 0.95 (3H, t, J 7.6 Hz, ω-Me), 1.32 (6H, t, J 7.1 Hz, 2 × Me of POEt), 1.56 (2H, m, δ-CH_2), 1.82 (1H, qd, J 15.1, 6.6 Hz, α-CH^a), 2.13 (1H, qd, J 15.1, 5.6 Hz, α-CH^b), 2.73 (1H, dt, J 5.7, 2.0 Hz, γ-CH), 2.92 (1H, m, β-CH), 4.10 (4H, m, 2 × CH_2 of POEt). δ_C 9.6, 16.4 (d, J 6.0 Hz), 24.8, 29.9 (d, J 139 Hz), 52.4 (d, J 2.7 Hz), 60.2 (d, J 6.6 Hz), 61.8 (two d, J 1.8 Hz). δ_P 22.4. MS m/z(%) 222 (M^+; 0.2), 181 (73), 153 (39), 125 (100), 81 (19), 43 (22).

Diethyl 2,3-dihydroxypropylphosphonate **2a**. **1a** (2.0 g, 0.01 mol) in water (25 mL) containing a few drops of conc. H_2SO_4 was heated under reflux for 2.5 h. After neutralisation (Na_2CO_3), evaporation, extraction with chloroform (25 mL), filtration and evaporation of solvent under reduced pressure, crude **2a** was purified by bulb to bulb distillation (oven temp. 140–150°C/1 mm Hg).

Diethyl 2-hydroxy-3-chloropropylphosphonate **2b**.[7] Dry HCl was passed through the solution of **1a** (3.0 g, 0.015 mol) in chloroform (10 mL) for 1.5 h. After neutralisation with Na_2CO_3, extraction with chloroform (3 × 20 mL), drying and evaporation of the solvent, crude **2b** was purified by bulb to bulb distillation (oven temp. 120–122°C/1 mm Hg).

Diethyl 2-hydroxy-3-bromopropylphosphonate **2c**. A solution of **1a** (1.07 g, 0.0055 mol) in dry THF (1 mL) was added at 0°C to a stirred solution of $MgBr_2$ (3.2 g, 0.011 mol) in THF (20 mL) and the solution was stirred at 0–5°C for 2 h. Saturated aq. ammonium chloride (20 mL) was added, the mixture was stirred for 1 h, separated, and the aqueous layer was extracted with ether. After the combined organic phases were dried and evaporated under reduced pressure, crude **2c** was purified by bulb to bulb distillation (oven temp 120°C/0.5 mm Hg).

Reaction of **1b** *with benzylmagnesium bromide.* The solution of **1b** (1 mole equiv.) in ether (0.5 mL/5 mmol) was added dropwise to a cooled (−30°C) solution of the Grignard reagent (1 mol equiv.) in ether (1 mL/5 mmol). The solution was kept at −30°C for 15 min, allowed to warm up to 0°C, kept at this temperature for 2 h, and then warmed up to the room temperature. 15% Aq. ammonium chloride was added, the organic layer was separated, and the aqueous layer was extracted with ether. After drying the combined organic solutions the solvent was removed under reduced pressure, yielding crude product as an oil (72%), which was separated by column chromatography (chloroform/acetone, 8.5:1.5).

Fraction 1: Diethyl 2,3-dihydroxypentylphosphonate (48%). δ_H 1.00 (3H, t, J 7.2 Hz, ω-Me), 1.26 (6H, t, J 7.1 Hz, 2 × Me of POEt), 1.72 (2H, m, δ-CH_2), 2.03 (2H, m, α-CH_2), 3.95 (2H, m, β- and γ-CH), 4.01 (4H, m, 2 × CH_2 of POEt). δ_P 27.6.

Fraction 2: Diethyl 2-hydroxy-3-bromopentylphosphonate (21%). δ_H 1.02 (3H, t, J 7.3 Hz, ω-Me), 1.27 (6H, t, J 7.1 Hz, 2 × Me of POEt), 1.65 (2H, m, δ-CH_2), 2.08 (2H, m, α-CH_2), 3.51 (1H, m, γ-CH), 3.90 (1H, m, β-CH), 4.03 (4H, m, 2 × CH_2 of POEt). δ_P 23.8.

Fraction 3: 2-oxopentylphosphonate (28%). δ_H 0.88 (3H, t, J 7.5 Hz, ω-Me), 1.30 (6H, t, J 7.1 Hz, 2 × Me of POEt), 1.58 (2H, m, δ-CH_2), 2.56 (2H, t, J 7.2 Hz, γ-CH_2), 3.02 (2H, d, J 22.7 Hz, α-CH_2), 4.08 (4H, m, 2 × CH_2 of POEt). δ_P 17.8. IR: 1713 (C=O).

Reaction of **1a** *with Grignard reagents. General procedure.* A solution of Grignard reagant (ca. 0.1 mol) was transferred by means of a syringe into a three-necked flask equipped with a thermometer, nitrogen-filled balloon, and a rubber septum, and containing the suspension of copper(I) iodide (0.1 mol) in THF (30 mL) cooled to −30°C. The mixture was stirred for 10 min, warmed up to −15°C, and a solution of **1a** (12.7 g, 0.066 mol) in THF (20 mL) was added dropwise by means of a syringe. The mixture was allowed to warm up to 0°C and was stirred at this temperature for 2 h. Saturated aq. NH_4Cl (100 mL) was added, the mixture was stirred for 1 h, separated, and the aqueous layer was extracted with ether (4 × 100 mL). After the usual work-up, crude **2** was purified in the following manner.
2e: bulb to bulb distillation (oven temp. 120–125°C/3.5 mm Hg).
2f: bulb to bulb distillation (oven temp. 120–125°C/2 mm Hg).
2h: column chromatography (chloroform/acetone, 4:1). Mp 78–80°C.

Reaction of **1** *with organocuprates. General procedure.* An organolithium reagent (4 mol equiv.; solution in hexane) was added to a stirred suspension of copper(I) iodide (2 mol equiv.) in dry ether (10 mL/mmol) at −20°C under nitrogen. The mixture was stirred until all CuI had dissolved, and epoxide **1** (1 mol equiv.) was added dropwise. The temperature was raised to 0°C and the solution was stirred for 3 h. Saturated aq. NH_4Cl was added, the aqueous layer was separated and extracted with ether. After removal of the solvent, crude product **2** was purified by column chromatography (chloroform/acetone, 4:1).

Preparation of trifluoroacetates **4** *(Y = CF_3CO). General procedure.* Trifluoroacetic anhydride (1.6 mol equiv.) was added dropwise to a stirred solution of **2** (1 mol equiv.) in dry THF (10 mL/mmol) at room temperature. The mixture was then stirred for 15 min, evaporated under reduced pressure, and the residue was purified by bulb to bulb distillation (oven temp. °C/mm Hg): **4a**, 120–125/1; **4c**, 130/1; **4e**, 95–100/3.5; **4h**, 140–145/2; **4j**, 135–140/2.5

Preparation of acetates **4** *(Y = Ac). General procedure.* Hydroxyphosphonate **2** (ca. 6×10^{-4} mol) was dissolved in acetic anhydride (5 mL) and the solution was heated under reflux for 2.5 h. Excess of acetic anhydride was removed under reduced pressure, saturated aq. Na_2CO_3 was added until pH was 7, water was evaporated, and the residue was extracted with chloroform. After removal of the solvent the crude product was purified by bulb to bulb distillation (oven temp. °C/mm Hg): **4b**, 120–130/0.5; **4f**, 115/2; **4i**, 115–120/2.5; **4k**, 150–155/0.15.
4d was prepared by adding dropwise a solution of acetyl chloride (0.44 g, 0.0056 mol) to a stirred solution of **2c** (0.77 g, 0.0028 mol) in dry chloroform (10 mL) at room temperature. The mixture was stirred for 4 h, water was added, the mixture was neutralised with Na_2CO_3, evaporated and extracted with chloroform (25 mL). After removal of the solvent **4d** was purified by bulb to bulb distillation (oven temp. 140°C/2 mm Hg).

Preparation of methyl ethers **4** *(Y = Me). General procedure.* To a stirred and warmed (45–50°C) suspension of NaH (0.24 g, 0.01 mol) in THF (15 mL) a solution of **2** (0.005 mol) and iodomethane (1.42 g, 0.01 mol) in THF (15 mL) was added dropwise under nitrogen. The mixture was stirred at 45–50° for 40 min, cooled, and water (5 mL) was added dropwise to the solution. The product was extracted with ether (5 × 10 mL), the combined organic extract was washed with saturated aq. NaCl (5 mL), dried and evaporated under reduced pressure. The crude product was purified by bulb to bulb distillation (oven temp. °C/mm Hg): **4g**, 95–100/2; **4l**, 150–155/2.

Reaction of **1a** *with enamines.* A solution of an enamine (0.01 mol) and **1a** (0.01 mol) in DMF (60 mL) was heated under reflux for 4 h. Water (10 mL) was added, and the heating was continued for a further 30 min. The solution was cooled, diluted with water and extracted with ether (3 × 20 mL). The combined etheral extract was washed with 1M hydrochloric acid until all basic material was removed, then with diluted aq. Na_2CO_3, and dried. After removal of the solvent, the crude product was purified by column chromotography (chloroform/acetone, 4:1).

(E)-2-(3'-Diethoxyphosphonyl)propylidenecyclohexanone **5a**. δ_H 1.29 (6H, t, J 6.0 Hz, 2 × Me of POEt), 1.68–1.88 (6H, m, 2 × H-4, 2 × H-5, 2 × H-2'), 2.30–2.48 (6H, m, 2 × H-3, 2 × H-6, 2 × H-3'), 4.06 (4H, m, 2 × CH_2 of POEt), 6.51 (1H, m, H-1'). δ_C 16.4 (d, J_{CP} 5.8, J_{CH} 128 Hz, 2 × Me of POEt), 21.0 (d, J_{CP} 5.4, J_{CH} 129 Hz, C-2'), 23.2, 23.4 (two s, C-4, C-5), 24.7 (d, J_{CP} 141 Hz, C-3'), 26.7 (J_{CH} 136 Hz, C-3), 40.1 (J_{CH} 128 Hz, C-6), 61.6 (d, J_{CP} 6.9, J_{CH} 149 Hz, 2 × CH_2 of POEt), 136.9 (d, J_{CP} 17.3, J_{CH} 159 Hz, C-1'), 140.1 (C-2), 200.8 (CO). δ_P 26.3. IR: 1690 (C=O), 1613 (C=C). MS m/z(%) 292 (M^+, 0.2), 152 (100), 138 (28), 125 (71), 97 (26), 55 (14), 41 (23).

(E)-2-(3'-Diethoxyphosphonyl)propylidenecyclopentanone **5b**. δ_H 1.30 (6H, t, J 7.1 Hz, 2 × Me of POEt), 1.66–1.91 (4H, m, 2 × H-4, 2 × H-2'), 2.29–2.56 (4H, m, 2 × H-3, 2 × H-3'), 2.85 (2H, m, 2 × H-5), 4.06 (4H, m, 2 × CH_2 of POEt), 6.42 (1H, m, H-1'). δ_C 16.4 (d, J_{CP} 6.6, J_{CH} 132 Hz, 2 × Me of POEt), 22.5 (d, J_{CP} 4.3 Hz, C-2'), 23.3 (C-4), 26.1 (d, J_{CP} 129, J_{CH} 133 Hz, C-3'), 32.7, 34.2 (J_{CH} 132, 133 Hz, C-3, C-5), 61.6 (d, J_{CP} 6.7, J_{CH} 142 Hz, 2 × CH_2 of POEt), 132.7 (d, J_{CP} 17.6, J_{CH} 151 Hz, C-1'), 208.7 (CO). δ_P 25.7. MS m/z(%) 152 (100), 138 (72), 125 (81), 109 (61), 97 (45), 81 (50), 67 (49).

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