Regioselectivity in the Reaction of Ethyl Diethoxyphosphorylacetate with 1-Aryl-2-haloalkan-1-ones: Effective Synthesis of 4-Aryl-2-diethoxyphosphoryl-4-oxobutanoates

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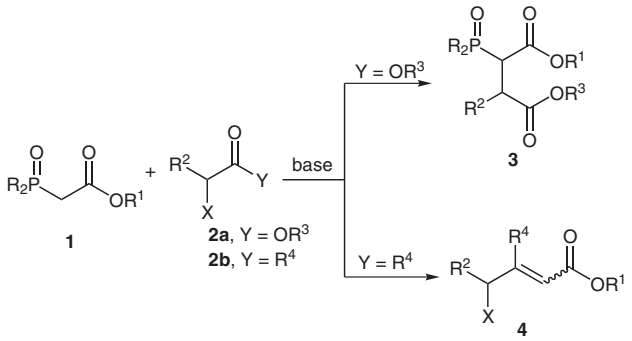
Abstract: The regioselectivity of the reaction of ethyl diethoxyphosphorylacetate with 1-aryl-2-haloalkan-1-ones has been investigated. It has been found that, depending on the nature of the halogen atom in 1-aryl-2-haloalkan-1-ones and the reaction conditions, alkylation or olefination products can be obtained with excellent or even full selectivity.

Key words: alkylations, Horner–Wadsworth–Emmons olefination, regioselectivity, ethyl diethoxyphosphorylacetate, α-haloketones

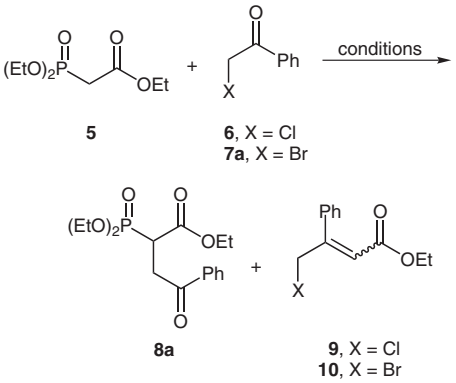
Alkylations of double-activated methylene compounds with α-halo ketones and α-halo esters are frequently employed in order to obtain highly functionalized structures containing carbonyl or alkoxycarbonyl groups. Accordingly, phosphorylacetates **1** are effectively alkylated with α-halo esters **2a**, producing phosphorylated succinates **3**, which are valuable intermediates in organic synthesis.[1] However, in the reactions of **1** with α-halo ketones **2b** the Horner–Wadsworth–Emmons olefination competes effectively with the alkylation and 4-halo-2-alkenoates **4** are usually formed (Scheme 1).



Scheme 1

Thus, the olefination products were obtained in the reactions of alkyl diethoxyphosphorylacetate with α-fluoro[2] as well as α-chloro[3] and α-bromo[4] ketones. However, Fujiwara described the alkylation of ethyl diethoxyphosphorylacetate with α-bromoacetophenone.[5] Unfortunately, no details for this reaction were given. In the same paper it was reported that the reaction of ethyl diethoxyphosphorylacetate with chloro or bromoacetone and α-chloroacetophenone yielded the olefination products. Additionally, a very recent study by Warren reports the successful alkylation of diphenyl(2-phenyl-2-oxoethyl)phosphine oxide with α-bromoacetophenone using sodium methoxide in tetrahydrofuran (THF).[6] Despite the lack of detail, this latter information implied that careful selection of the reactants and the reaction conditions may enable control of regioselectivity and consequently the effective alkylation of **1** with α-halo ketones. Therefore, we have undertaken more systematic studies focused on this problem.

In the initial experiments we performed the reaction of ethyl 2-diethoxyphosphorylacetate (**5**) with chloro- and bromoacetophenone **6** and **7a** in THF using sodium ethoxide (EtONa) or sodium hydride (NaH) as base (Scheme 2, Table 1). Combined yields and the alkylation to olefination product ratios were determined by analysis of the ^{31}P NMR spectra of the reaction mixtures. For this purpose, integration of the signals of the alkylation product **8a** and the signal arising from diethyl hydrogen phosphate, which is one of the products of the olefination reaction, were compared with the integration of all the remaining signals in ^{31}P NMR spectrum and to each other. It was assumed that the intensity of the diethyl hydrogen phosphate signal was indicative of the amount of the olefination product **9** or **10**. As can be seen from Table 1, the regiochemistry of this reaction can be easily controlled simply by choosing chloro- or bromoacetophenone as substrate, with the former favoring olefination and the latter the alkylation reaction. Furthermore, the use of NaH as a base gave excellent or even full selectivity of the alkylation or olefination reaction, respectively.



Scheme 2

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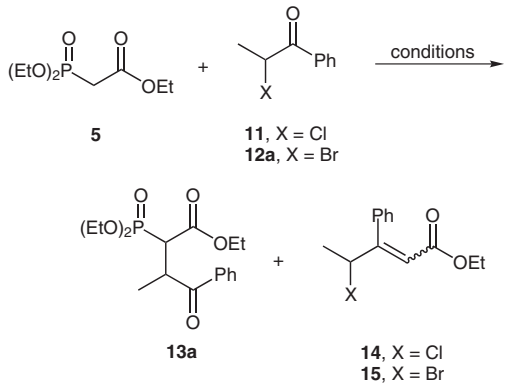
Table 1 Initial Reactions of Ethyl 2-Diethoxyphosphorylacetate (**5**) with Chloro- and Bromoacetophenones

Entry	Base[a]	Chloroacetophenone (**6**)		Bromoacetophenone (**7a**)	
		Yield (%)[b]	Selectivity (alkylation/olefination)[b]	Yield (%)[b]	Selectivity (alkylation/olefination)[b]
1	EtONa	83	5:95	60	60:40
2	NaH	77	0:100	88	95:5

[a] Reaction conditions: THF, 0 °C→r.t., 20 h.
[b] Determined by the analysis of the ^{31}P NMR spectra of the reaction mixture.

We then turned our attention to the reaction of **5** with 1-aryl-2-halopropan-1-ones. Reaction with chloropropiophenone (**11**), using the THF/NaH system described above, gave exclusively the olefination product **14** with excellent yield (Scheme 3, Table 2, entry 1). Disappointingly, bromopropiophenone (**12a**), under the same conditions, yielded a mixture of alkylation and olefination products **13a** and **15**, respectively, in a 50:50 ratio and in moderate yield (54%). Addition of 10 mol% tetrabutylammonium iodide (TBAI) improved the yield significantly but did not change the selectivity, whereas performing this reaction in a mixture of THF and DMSO (1:1 ratio) led to improvements in both the yield and selectivity (entries 3 and 4, respectively). Finally, a combination of these improvements gave an excellent 93% yield and satisfactory 90:10 selectivity (entry 4).

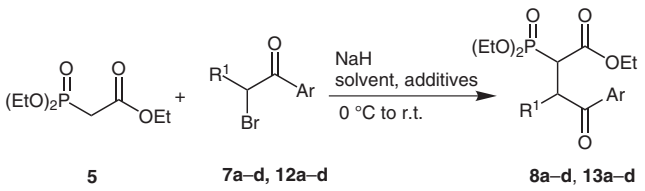


Scheme 3

With these results in hand, we decided to examine the effectiveness of the THF/NaH system in the reaction of ethyl 2-diethoxyphosphorylacetate (**5**) with various 1-aryl-2-bromoethanones **7a–d** (Scheme 4). All reactions proceeded well and, after standard work-up, crude products were purified by column chromatography to give 4-aryl-2-diethoxyphosphoryl-4-oxobutanoates **8a–d** in good to excellent yields (Table 3).

Applying optimized conditions to the reaction of **5** with 1-aryl-2-bromopropan-1-ones **12a–d** gave, after standard work up and column chromatography, pure 4-aryl-2-diethoxyphosphoryl-3-methyl-4-oxobutanoates **13a–c** in excellent yields (Table 3). Disappointingly, the alkylation of phosphonoacetate **5** with 2-bromo-1-(naphthalen-1-yl)propan-1-one **12d** gave a complex mixture of products which were difficult to isolate. Pleasingly, the same reaction performed in THF alone provided, after standard work-up procedure and column chromatography, the expected butanoate **13d** in moderate yield.

Butanoates **13a–d** were formed as mixtures of diastereomers in the ratios shown in Table 3. Diastereomers of butanoate **13b** were successfully separated using column



Scheme 4

Table 2 Reactions of Ethyl 2-Diethoxyphosphorylacetate (**5**) with Chloro- and Bromopropiophenone

Entry	Conditions[a]	Chloropropiophenone (**11**)		Bromopropiophenone (**12a**)	
		Yield (%)[b]	Selectivity (alkylation/olefination)[b]	Yield (%)[b]	Selectivity (alkylation/olefination)[b]
1	THF, NaH	95	0:100	54	50:50
2	THF, NaH, TBAI (10 mol%)	–	–	80	50:50
3	THF–DMSO 1:1, NaH	–	–	63	75:25
4	THF–DMSO 1:1, NaH, TBAI (10 mol%)	–	–	93	90:10

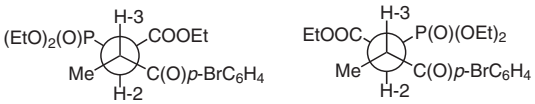
[a] Reaction conditions: THF, 0 °C→r.t., 20 h.
[b] Determined by the analysis of the ^{31}P NMR spectra of the reaction mixture.

Table 3 Synthesis of 2-Diethoxyphosphoryl-4-oxo-4-arylbutanoates **8a–d** and **13a–d**

Compound	R^1	Ar	Solvent/additives	*syn/anti*	Yield (%)[a]
8a	H	Ph	THF		75
8b	H	*p*-BrC_6H_4	THF		70
8c	H	*p*-$MeOC_6H_4$	THF		80
8d	H	1-naphthyl	THF		85
13a	Me	Ph	THF–DMSO 1:1, TBAI (10 mol%)	65:35	79
13b	Me	*p*-BrC_6H_4	THF–DMSO 1:1, TBAI (10 mol%)	60:40	71
13c	Me	*p*-$MeOC_6H_4$	THF–DMSO 1:1, TBAI (10 mol%)	65:35	84
13d	Me	1-naphthyl	THF, TBAI (10 mol%)	65:35	40

[a] Yield of isolated product after column chromatography.

chromatography. The assignment of the relative configuration for the major *syn*-**13b** and minor *anti*-**13b** diastereomers was possible by careful analysis of the ^1H and ^{13}C NMR spectra (Figure 1 and Table 4).



syn-**13b** *anti*-**13b**

Figure 1

Table 4 Selected ^1H and ^{13}C NMR Data for the Major and Minor Diastereomers of **13b**[a]

NMR	Assignment	Major diastereomer *syn*-**13b**	Minor diastereomer *anti*-**13b**
^1H	H-2	3.49 (dd, J = 21.7, 10.9 Hz)	3.66 (dd, J = 21.2, 10.2 Hz)
^{13}C	Me	16.3 (s)	16.5 (d, J = 14.1 Hz)
	C-4	200.5 (d, J = 16.9 Hz)	199.5 (d, J = 3.2 Hz)

[a] Data taken from the spectra of the separated isomers.

The ^1H NMR spectra of both isomers showed well-resolved signals arising from the H-2 protons with $J_{H\text{-}2/H\text{-}3}$ = 0.9 and 10.2 Hz for the major and minor diastereomer, respectively. According to the Carplus equation, these values indicate an antiperiplanar alignment of the H-2 and H-3 protons in both *syn*-**13b** and *anti*-**13b**. On the other hand, the ^{13}C NMR spectra of *syn*-**13b** and *anti*-**13b** showed characteristic signals for the methyl group and C-4. Large $J_{P/C\text{-}4}$ coupling and the absence of significant $J_{P/Me}$ coupling in the spectrum of *syn*-**13b** suggest an antiperiplanar alignment of the phosphoryl and carbonyl groups and a *gauche* alignment of the phosphoryl and methyl groups, respectively. In the spectrum of *anti*-**13b**, a large $J_{P/Me}$ and a small $J_{P/C\text{-}4}$ indicated an antiperiplanar positioning of the phosphoryl and methyl groups and a *gauche* alignment of the phosphoryl and carbonyl groups. These data allowed for the assignment of the relative configuration for the major diastereomer as *syn*-**13b** and for the minor diastereomer as *anti*-**13b**. We believe that similar spectroscopic characteristics present in the NMR spectra of diastereomeric **13a**, **13c** and **13d** permit the assignment of the *syn* configuration for all major diastereomers and the *anti* configuration for all minor diastereomers.

In conclusion, excellent control of regioselectivity was achieved in the reaction of ethyl diethoxyphosphorylacetate with 1-aryl-2-haloalkan-1-ones. Appropriate choice of halogen, solvent, base and additives enable substantial suppression of the olefination reaction and effective synthesis of 2-diethoxyphosphoryl-4-oxo-4-arylbutanoates **8** and **13**. It is worth stressing that, according to the literature data, the availability of butanoates of this structure have been so far limited to ethyl 2-diethoxyphosphoryl-4-oxo-4-phenylbutanoate (**8a**), prepared in 67% yield by the reaction of diethyl hydrogen phosphite with ethyl 4-oxo-4-phenyl-2-butenoate.[7] We believe that the highly functionalized butanoates **8** and **13** will prove valuable intermediates in organic synthesis and will find various synthetic applications. For example, they can be transformed into biologically important α-alkylidene-γ-lactones and lactams such as 3-alkylidenedihydrofuran-2(3*H*)-ones or 4-alkylpyridazin-3(2*H*)-ones, using methodology which has been recently developed in our laboratory.[8] Further studies in this area are currently under investigation.

Organic solvents and reagents were purified by the appropriate standard procedures. Column chromatography was performed using Fluka silica gel 60 (230–400 mesh). IR spectra were recorded on Specord M-80 spectrometer. ^1H NMR (250 MHz), ^{13}C NMR (62.9 MHz), and ^{31}P NMR (101 MHz) spectra were recorded on a Bruker DPX-250 spectrometer with TMS as an internal standard for ^1H NMR and ^{13}C NMR, and 85% H_3PO_4 as an external standard for ^{31}P NMR. ^{31}P NMR spectra were recorded using broad-band proton decoupling. In the optimization experiments, in which the yield was determined by ^{31}P NMR spectroscopy, two methods of ^{31}P decou-

pling were examined: (i) the inverse-gated decoupling with 90° pulse and $5T_1$ repetition time, as well as the regular broad-band proton decoupling. Both methods gave the same integrations ratio, within an accuracy of 1%. Therefore, further NMR measurements were performed using less time-consuming, routine broad-band proton decoupling. Elemental analyses were performed on a Perkin–Elmer PE-2400 analyzer.

1-Aryl-2-bromoethanones **7b**,**d** and 1-aryl-2-bromopropan-1-ones **12b**,**d** were prepared by bromination of the corresponding methyl or ethyl aryl ketones applying a previously described literature procedure.[9] 1-(Naphthalen-1-yl)propan-1-one was prepared as described in the literature.[10] Other methyl or ethyl aryl ketones and ethyl 2-diethoxyphosphorylacetate were purchased from Fluka and used without further purification.

Reaction of Ethyl 2-Diethoxyphosphorylacetate (5) with Chloro- and Bromoacetophenone 6 and 7a; General Procedure

To a mixture of EtONa (76 mg, 1.1 mmol) or NaH (26 mg, 1.1 mmol) in THF (2 mL) a solution of ethyl 2-diethoxyphosphorylacetate (**5**; 225 mg, 1.0 mmol) in THF (0.5 mL) was added. The mixture was stirred at r.t. for 30 min then cooled to 0 °C and a solution of chloro- or bromoacetophenone **6** or **7a** (1.0 mmol) in THF (1.0 mL) was added dropwise. Stirring was continued at r.t. for an additional 20 h. After this time, a sample from the reaction mixture (300 μL) was placed in an NMR tube, AcOH (30 μL) was added and a ^{31}P NMR spectrum was recorded. Integrations of the signals of **8a** (δ = 23.07 ppm), diethyl hydrogen phosphate (δ = 1.03 ppm) and other signals present in the spectrum were compared in order to determine yield.

Reaction of Ethyl 2-Diethoxyphosphorylacetate (5) with Chloro- and Bromopropiophenone 11 and 12a; General Procedure

To a mixture of NaH (26 mg, 1.1 mmol) in THF (2 mL) or a mixture of DMSO (2.0 mL) and THF (0.5 mL) a solution of ethyl 2-diethoxyphosphorylacetate (**5**; 225 mg, 1.0 mmol) in THF (0.5 mL) was added. The mixture was stirred at r.t. for 30 min, cooled to 0 °C, then a solution of chloro- or bromopropiophenone **11** or **12a** (1.0 mmol), either with or without TBAI (Table 2; 37 mg, 0.1 mmol), in THF (1.0 mL) was added dropwise. Stirring was continued at r.t. for an additional 20 h. After this time a sample from the reaction mixture (300 μL) was placed in an NMR tube, AcOH (30 μL) was added and a ^{31}P NMR spectrum was recorded. Integrations of the signals of *syn*- and *anti*-**13a** (δ = 22.58 and 21.71 ppm), diethyl hydrogen phosphate (δ = 1.03 ppm) and other signals present in the spectrum were compared in order to determine yield.

Ethyl 4-Aryl-2-diethoxyphosphoryl-4-oxobutanoates 8a–d; General Procedure

To a suspension of NaH (0.45 g, 18.7 mmol) in THF (40 mL), a solution of ethyl 2-diethoxyphosphorylacetate (**5**; 4.0 g, 17.8 mmol) in THF (5 mL) was added. The mixture was stirred at r.t. for 30 min, cooled to 0 °C, then a solution of the appropriate 1-aryl-2-bromoethanone **7a–d** (17.8 mmol) in THF (5 mL) was added dropwise. Stirring was continued at r.t. for an additional 20 h then the reaction was quenched with H_2O (20 mL) and the solvent was evaporated. The residue was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated to afford the crude products which were purified by column chromatography (silica gel; $CHCl_3$–acetone, 99:1).

Ethyl 2-(Diethoxyphosphoryl)-4-oxo-4-phenylbutanoate (8a)

Yield: 4.6 g (75%); yellow oil; R_f = 0.20 ($CHCl_3$–acetone, 99:1).

IR (film): 1736, 1688, 1256 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.25–1.37 [m, 9 H, P(O)(OCH$_2$CH_3)$_2$ and C(O)OCH$_2$CH_3], 3.46 (ddd, *J* = 2.5, 7.7, 17.7 Hz, 1 H, H-2), 3.55–3.93 (m, 2 H, H-3), 4.13–4.28 [m, 6 H, P(O)(OCH_2CH$_3$)$_2$, C(O)OCH_2CH$_3$], 7.08–7.28 (m, 5 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 13.9 [s, C(O)OCH$_2$*C*H$_3$], 16.2 [d, *J* = 2.5 Hz, P(O)(OCH$_2$*C*H$_3$)$_2$], 35.9 (d, *J* = 1.9 Hz, C-3), 40.1 (d, *J* = 131.6 Hz, C-2), 61.5 [s, C(O)O*C*H$_2$CH$_3$], 62.8 [d, *J* = 6.9 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$], 128.0 (s, 2 × Ar-C), 128.5 (s, Ar-C), 133.4 (s, 2 × Ar-C), 135.9 (s, Ar-C), 168.3 (d, *J* = 4.5 Hz, C-1), 196.4 (d, *J* = 18.9 Hz, C-4).

^{31}P NMR ($CDCl_3$): δ = 23.07.

Anal. Calcd for $C_{16}H_{23}O_6P$: C, 56.14; H, 6.77. Found: C, 56.25; H, 6.80.

Ethyl 4-(4-Bromophenyl)-2-(diethoxyphosphoryl)-4-oxobutanoate (8b)

Yield: 5.25 g (70%); yellow oil; R_f = 0.20 ($CHCl_3$–acetone, 99:1).

IR (film): 1732, 1688, 1256 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.23–1.40 [m, 9 H, P(O)(OCH$_2$CH_3)$_2$ and C(O)OCH$_2$CH_3], 3.34 (ddd, *J* = 2.5, 9.0, 18.2 Hz, 1 H, H-2), 3.59–3.85 (m, 2 H, H-3), 4.12–4.27 [m, 6 H, P(O)(OCH_2CH$_3$)$_2$ and C(O)OCH_2CH$_3$], 7.59–7.86 (m, 4 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 13.7 [s, C(O)OCH$_2$*C*H$_3$], 16.0 [d, *J* = 2.5 Hz, P(O)(OCH$_2$*C*H$_3$)$_2$], 35.6 (s, C-3), 39.9 (d, *J* = 131.6 Hz, C-2), 61.4 [s, C(O)O*C*H$_2$CH$_3$], 62.7 [d, *J* = 5.6 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$], 128.4 (s, Ar-C), 129.3 (s, 2 × Ar-C), 131.6 (s, 2 × Ar-C), 134.4 (s, Ar-C), 168.0 (d, *J* = 5.6 Hz, C-1), 195.2 (d, *J* = 15.2 Hz, C-4).

^{31}P NMR ($CDCl_3$): δ = 23.15.

Anal. Calcd for $C_{16}H_{22}BrO_6P$: C, 45.62; H, 5.26. Found: C, 45.67; H, 5.34.

Ethyl 2-(Diethoxyphosphoryl)-4-(4-methoxyphenyl)-4-oxobutanoate (8c)

Yield: 5.3 g (80%); yellow oil; R_f = 0.25 ($CHCl_3$–acetone, 99:1).

IR (film): 1736, 1680, 1260 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.26–1.40 [m, 9 H, P(O)(OCH$_2$CH_3)$_2$ and C(O)OCH$_2$CH_3], 3.30–3.47 (m, 1 H, H-2), 3.55–3.80 (m, 2 H, H-3), 3.87 (s, 3 H, OCH$_3$), 4.16–4.25 [m, 6 H, P(O)(OCH_2CH$_3$)$_2$ and C(O)OCH_2CH$_3$], 6.89–7.99 (m, 4 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 13.7 [s, C(O)OCH$_2$*C*H$_3$], 15.9 [d, *J* = 3.1 Hz, P(O)(OCH$_2$*C*H$_3$)$_2$], 35.2 (s, C-3), 39.9 (d, *J* = 131.6 Hz, C-2), 55.1 (s, OCH$_3$), 61.2 [s, C(O)O*C*H$_2$CH$_3$], 62.5 (d, *J* = 5.6 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$], 62.5 [d, *J* = 6.1 Hz, P(O)O*C*H$_2$CH$_3$], 114.4 (s, 2 × Ar-C), 128.7 (s, Ar-C), 130.0 (s, 2 × Ar-C), 163.4 (s, Ar-C), 168.1 (d, *J* = 5.3 Hz, C-1), 194.4 (d, *J* = 15.7 Hz, C-4).

^{31}P NMR ($CDCl_3$): δ = 23.33.

Anal. Calcd for $C_{17}H_{25}O_7P$: C, 54.84; H, 6.77. Found: C, 54.97; H, 6.84.

Ethyl 2-(Diethoxyphosphoryl)-4-(naphthalen-1-yl)-4-oxobutanoate (8d)

Yield: 5.95 g (85%); yellow oil; R_f = 0.15 ($CHCl_3$–acetone, 99:1).

IR (film): 1732, 1684, 1256 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.23–1.46 [m, 9 H, P(O)(OCH$_2$CH_3)$_2$ and C(O)OCH$_2$CH_3], 3.51 (ddd, *J* = 2.5, 7.7, 17.7 Hz, 1 H, H-2), 3.60–3.93 (m, 2 H, H-3), 4.16–4.29 [m, 6 H, P(O)(OCH_2CH$_3$)$_2$ and C(O)OCH_2CH$_3$], 7.48–8.60 (m, 7 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 13.8 [s, C(O)OCH$_2$*C*H$_3$], 16.1 [d, *J* = 2.5 Hz, P(O)(OCH$_2$*C*H$_3$)$_2$], 38.7 (s, C-3), 40.4 (d, *J* = 131.7 Hz, C-2), 61.5 [s, C(O)O*C*H$_2$CH$_3$], 62.7 [d, *J* = 5.6 Hz, P(O)(O*C*H$_2$CH$_3$)$_2$], 124.1 (s, Ar-C), 125.4 (s, Ar-C), 126.3 (s, Ar-C), 127.8 (s, 2 × Ar-C), 128.2 (s, Ar-C), 129.8 (s, Ar-C), 132.9 (s, Ar-C), 133.6 (s, Ar-

C), 134.4 (s, Ar-C), 168.3 (d, J = 5.6 Hz, C-1), 200.1 (d, J = 15.7 Hz, C-4).

^{31}P NMR ($CDCl_3$): δ = 23.02.

Anal. Calcd for $C_{20}H_{25}O_6P$: C, 61.22; H, 6.42. Found: C, 61.39; H, 6.28.

Ethyl 4-Aryl-2-diethoxyphosphoryl-3-methyl-4-oxobutanoates 13a–c; General Procedure

To a suspension of NaH (0.45 g, 18.7 mmol) in DMSO (30 mL) and THF (5 mL), a solution of ethyl 2-diethoxyphosphorylacetate (**5**; 4.0 g, 17.8 mmol) in THF (5 mL) was added. The mixture was stirred r.t. for 0.5 h, cooled to 0 °C and a solution of the appropriate 1-aryl-2-bromopropan-1-one **12a–c** (17.8 mmol) and TBAI (0.69 g, 10 mol%) in THF (20 mL) was added dropwise. After stirring for 20 h at this temperature, the reaction mixture was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with H_2O (20 mL) and dried ($MgSO_4$). The solvent was evaporated and the crude product was purified by column chromatography (silica gel, EtOAc–hexane, 4:1).

Ethyl 2-(Diethoxyphosphoryl)-3-methyl-4-oxo-4-phenylbutanoate (13a)

Yield: 5.0 g (79%); yellow oil; mixture of diastereoisomers in a 65:35 ratio; R_f = 0.36, 0.38 (EtOAc–hexane, 4:1).

IR (film): 1732, 1684, 1252 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ [major diastereomer (*syn*)][11] = 1.15–1.41 [m, 12 H, P(O)(OCH$_2$CH_3)$_2$, C(O)OCH$_2$CH_3, CH_3], 3.50 (dd, J = 21.6, 11.0 Hz, 1 H, H-2), 4.00–4.30 [m, 7 H, P(O)(OCH_2CH$_3$)$_2$, C(O)OCH_2CH$_3$, H-3], 7.40–7.60 (m, 5 H, Ar-H).

^{1}H NMR ($CDCl_3$): δ [minor diastereomer (*anti*)][11] = 1.15–1.41 [m, 12 H, P(O)(OCH$_2$CH_3)$_2$, C(O)OCH$_2$CH_3, CH_3], 3.69 (dd, J = 21.2, 10.0 Hz, 1 H, H-2), 4.00–4.30 [m, 7 H, P(O)(OCH_2CH$_3$)$_2$, C(O)OCH_2CH$_3$, H-3], 7.40–7.60 (m, 5 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ [major diastereomer (*syn*)][11] = 13.3 [s, C(O)OCH$_2$CH_3)], 15.5 (d, J = 5.2 Hz, P(O)(OCH$_2$CH_3)$_2$], 16.2 (d, J = 6.5 Hz, CH_3C-3), 39.7 (s, C-3), 47.2 (d, J = 129.4 Hz, C-2), 60.6 [s, C(O)OCH_2CH$_3$], 61.9 [d, J = 15.5 Hz, P(O)(OCH_2CH$_3$)$_2$], 127.5 (s, 2 × Ar-C), 127.8 (s, 2 × Ar-C), 132.4 (s, Ar-C), 134.4 (s, Ar-C), 167.3 (s, C-1), 199.9 (s, C-4).

^{13}C NMR ($CDCl_3$): δ [minor diastereomer (*anti*)][11] = 13.1 [s, C(O)OCH$_2$CH_3], 15.3 (d, J = 3.4 Hz, P(O)(OCH$_2$CH_3)$_2$], 16.1 (d, J = 5.3 Hz, CH_3C-3), 38.5 (s, C-3), 47.7 (d, J = 130.6 Hz, C-2), 60.5 [s, C(O)OCH_2CH$_3$], 61.8 [d, J = 9.3 Hz, P(O)(OCH_2CH$_3$)$_2$], 127.5 (s, 2 × Ar-C), 127.8 (s, 2 × Ar-C), 132.4 (s, Ar-C), 134.8 (s, Ar-C), 168.0 (s, C-1), 201.5 (d, J = 16.5 Hz, C-4).

^{31}P NMR ($CDCl_3$): δ = 22.58 (major); 21.71 (minor).[11]

Anal. Calcd for $C_{17}H_{25}O_6P$: C, 57.30; H, 7.07. Found: C, 57.41; H, 7.21.

Ethyl 4-(4-Bromophenyl)-2-(diethoxyphosphoryl)-3-methyl-4-oxobutanoate (13b)

Yield: 5.5 g (71%); yellow oil; mixture of diastereoisomers in a 60:40 ratio; R_f = 0.42, 0.53 (EtOAc–hexane, 4:1).

IR (film): 1732, 1688, 1256 cm^{-1}.

Anal. Calcd for $C_{17}H_{24}BrO_6P$: C, 46.91; H, 5.56. Found: C, 46.85; H, 5.69.

Ethyl *syn*-4-(4-Bromophenyl)-2-(diethoxyphosphoryl)-3-methyl-4-oxobutanoate (*syn*-13b)

^{1}H NMR ($CDCl_3$): δ = 1.18 [t, J = 7.1 Hz, 3 H, C(O)OCH$_2$CH_3], 1.33–1.41 [m, 9 H, P(O)(OCH$_2$CH_3)$_2$, CH_3], 3.49 (dd, J = 21.7, 10.9 Hz, 1 H, H-2), 4.10 [q, J = 7.1 Hz, 2 H, C(O)OCH_2CH$_3$], 4.13–4.29 [m, 5 H, P(O)(OCH_2CH$_3$)$_2$, H-3], 7.60–7.90 (m, 4 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 13.4 [s, C(O)OCH$_2$CH_3], 15.8 [d, J = 5.8 Hz, P(O)(OCH$_2$CH_3)$_2$], 16.3 (s, CH_3C-3), 39.9 (s, C-3), 47.8 (d, J = 130.7 Hz, C-2), 60.9 [s, C(O)OCH_2CH$_3$], 62.3 [d, J = 7.1 Hz, P(O)(OCH_2CH$_3$)$_2$], 62.4 [d, J = 8.1 Hz, P(O)(OCH_2CH$_3$)$_2$], 127.8 (s, Ar-C), 129.5 (s, 2 × Ar-C), 131.5 (s, 2 × Ar-C), 133.6 (s, Ar-C), 168.1 (d, J = 5.2 Hz,C-1), 200.5 (d, J = 16.9 Hz, C-4).

^{31}P NMR ($CDCl_3$): δ = 22.27.

Ethyl *anti*-4-(4-Bromophenyl)-2-(diethoxyphosphoryl)-3-methyl-4-oxobutanoate (*anti*-13b)

^{1}H NMR ($CDCl_3$): δ = 1.18–1.28 [m, 9 H, P(O)(OCH$_2$CH_3)$_2$, CH_3], 1.33 [t, J = 7.1 Hz, 3 H, C(O)OCH$_2$CH_3], 3.66 (dd, J = 21.2, 10.2 Hz, 1 H, H-2), 3.96–4.21 [m, 5 H, P(O)(OCH_2CH$_3$)$_2$, H-3], 4.27 [q, J = 7.1 Hz, 2 H, C(O)OCH_2CH$_3$], 7.59–7.89 (m, 4 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ = 13.7 [s, C(O)OCH$_2$CH_3], 15.7 [d, J = 5.9 Hz, P(O)(OCH$_2$CH_3)$_2$], 15.8 [d, J = 5.7 Hz, P(O)(OCH$_2$CH_3)$_2$], 16.5 (d, J = 14.1 Hz, CH_3C-3), 38.9 (d, J = 3.6 Hz, C-3), 47.6 (d, J = 129.5 Hz, C-2), 61.1 [s, C(O)OCH_2CH$_3$], 62.3 [d, J = 7.2 Hz, P(O)(OCH_2CH$_3$)$_2$], 62.5 [d, J = 7.4 Hz, P(O)(OCH_2CH$_3$)$_2$], 127.9 (s, Ar-C), 129.7 (s, 2 × Ar-C), 131.6 (s, 2 × Ar-C), 134.2 (s, Ar-C), 167.5 (d, J = 4.8 Hz, C-1), 199.5 (d, J = 3.2 Hz, C-4).

^{31}P NMR ($CDCl_3$): δ = 21.55.

Ethyl 2-(Diethoxyphosphoryl)-4-(4-methoxyphenyl)-4-methyl-4-oxobutanoate (13c)

Yield: 5.8 g (84%); yellow oil; mixture of diastereoisomers in a 65:35 ratio; R_f = 0.38, 0.42 (EtOAc–hexane, 4:1).

IR (film): 1732, 1676, 1256 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ [major diastereomer (*syn*)][11] = 1.15–1.42 [m, 12 H, P(O)(OCH$_2$CH_3)$_2$, C(O)OCH$_2$CH_3, CH_3], 3.51 (dd, J = 21.4, 11.0 Hz, 1 H, H-2), 3.80 (s, 3 H, OCH$_3$), 3.96–4.33 [m, 7 H, P(O)(OCH_2CH$_3$)$_2$, C(O)OCH_2CH$_3$, H-3], 6.94–8.04 (m, 4 H, Ar-H).

^{1}H NMR ($CDCl_3$): δ [minor diastereomer (*anti*)][11] = 1.15–1.42 [m, 12 H, P(O)(OCH$_2$CH_3)$_2$, C(O)OCH$_2$CH_3, CH$_3$], 3.69 (dd, J = 21.0, 10.1 Hz, 1 H, H-2), 3.91 (s, 3 H, OCH$_3$), 3.96–4.33 [m, 7 H, P(O)(OCH_2CH$_3$)$_2$, C(O)OCH_2CH$_3$, H-3], 6.94–8.04 (m, 4 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ [major diastereomer (*syn*)][11] = 13.2 [s, C(O)OCH$_2$CH_3], 15.6 [d, J = 5.9 Hz, P(O)(OCH$_2$CH_3)$_2$], 16.5 (s, CH_3C-3), 39.4 (s, C-3), 47.8 (d, J = 130.3 Hz, C-2), 54.8 (s, CH$_3$O), 60.6 [s, C(O)OCH_2CH$_3$], 62.1 [d, J = 7.8 Hz, P(O)(OCH_2CH$_3$)$_2$], 62.2 [d, J = 7.7 Hz, P(O)(OCH_2CH$_3$)$_2$], 113.2 (s, 2 × Ar-C), 127.4 (s, Ar-C), 130.1 (s, 2 × Ar-C), 163.1 (s, Ar-C), 168.1 (d, J = 5.3 Hz, C-1), 199.7 (d, J = 16.9 Hz, C-4).

^{13}C NMR ($CDCl_3$): δ [minor diastereomer (*anti*)][11] = 13.4 [s, C(O)OCH$_2$CH_3], 15.5 [d, J = 5.6 Hz, P(O)(OCH$_2$CH_3)$_2$], 15.4 [d, J = 5.6 Hz, P(O)(OCH$_2$CH_3)$_2$], 16.4 (s, CH_3C-3), 38.1 (d, J = 3.5 Hz, C-3), 47.3 (d, J = 129.7 Hz, C-2), 54.8 (s, CH_3O), 60.7 [s, C(O)OCH_2CH$_3$], 61.9 [d, J = 8.8 Hz, P(O)(OCH_2CH$_3$)$_2$], 62.1 [d, J = 7.9 Hz, P(O)(OCH_2CH$_3$)$_2$], 113.2 (s, 2 × Ar-C), 127.9 (s, Ar-C), 130.1 (s, 2 × Ar-C), 163.1 (s, Ar-C), 167.5 (d, J = 4.6 Hz, C-1), 198.4 (d, J = 3.2 Hz, C-4).

^{31}P NMR ($CDCl_3$): δ = 22.81 (major), 21.78 (minor).[11]

Anal. Calcd for $C_{18}H_{27}O_7P$: C, 55.95; H, 7.04. Found: C, 56.15; H, 7.21.

Ethyl 2-(Diethoxyphosphoryl)-3-methyl-4-(naphthalen-1-yl)-4-oxobutanoate (13d)

To a suspension of NaH (0.45 g, 18.7 mmol) in THF (30 mL), a solution of ethyl 2-diethoxyphosphorylacetate (**5**; 4.0 g, 17.8 mmol) in THF (5 mL) was added. The mixture was stirred at r.t. for 30 min, cooled to 0 °C and a solution of 2-bromo-1-(naphthalen-1-yl)pro-

pan-1-one (**12d**; 4.7 g, 17.8 mmol) and TBAI (0.69 g, 10 mol%) in THF (15mL) was added dropwise. Stirring was continued at r.t. for an additional 20 h then the reaction was quenched with H_2O (20 mL). The THF was evaporated and the residue was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to afford the crude products, which were purified by column chromatography (silica gel; $CHCl_3$–acetone, 99:1).

Yield: 2.9 g (40%); yellow oil; mixture of diastereoisomers in a 65:35 ratio; R_f = 0.40, 0.42 (EtOAc–hexane, 4:1).

IR (film): 1728, 1688, 1256 cm^{-1}.

^1H NMR ($CDCl_3$): δ (major and minor diastereomers)[11] = 1.20–1.42 [m, 12 H, P(O)(OCH_2CH_3)$_2$, C(O)OCH_2CH_3, CH_3], 3.50 (dd, J = 21.5, 11.1 Hz, 1 H, H-2 major), 3.60 (dd, J = 20.5, 10.1 Hz, 1 H, H-2 minor), 4.06–4.32 [m, 7 H, P(O)(OCH_2CH_3)$_2$, C(O)OCH_2CH_3, H-3], 7.45–8.42 (m, 7 H, Ar-H).

^{13}C NMR ($CDCl_3$): δ [major diastereomer (*syn*)][11] = 14.0 [s, C(O)OCH_2CH_3], 15.7 [d, J = 5.2 Hz, P(O)(OCH_2CH_3)$_2$], 16.05 (d, J = 5.1 Hz, CH_3C-3), 36.8 (s, C-3), 48.0 (d, J = 130.1 Hz, C-2), 60.4 [s, C(O)OCH_2CH_3], 62.6 [d, J = 6.0 Hz, P(O)(OCH_2CH_3)$_2$], 124.2 (s, Ar-C), 125.2 (s, Ar-C), 126.2 (s, Ar-C), 127.5 (s, Ar-C), 127.8 (s, Ar-C), 130.4 (s, Ar-C), 132.2 (s, Ar-C), 133.2 (s, Ar-C), 135.0 (s, Ar-C), 139.6 (s, Ar-C), 167.8 (s, C-1), 205.4 (d, J = 17.0 Hz, C-4).
^{13}C NMR ($CDCl_3$): δ [minor diastereomer (*anti*)][11] = 13.8 [s, C(O)OCH_2CH_3], 15.5 [d, J = 3.2 Hz, P(O)(OCH_2CH_3)$_2$], 15.5 (d, J = 4.9 Hz, CH_3C-3), 36.7 (s, C-3), 47.2 (d, J = 131.1 Hz, C-2), 60.4 [s, C(O)OCH_2CH_3], 62.6 [d, J = 6.0 Hz, P(O)(OCH_2CH_3)$_2$], 124.2 (s, Ar-C), 125.2 (s, Ar-C), 126.2 (s, Ar-C), 127.5 (s, Ar-C), 127.8 (s, Ar-C), 130.3 (s, Ar-C), 132.2 (s, Ar-C), 133.2 (s, Ar-C), 134.9 (s, Ar-C), 139.8 (s, Ar-C), 167.9 (s, C-1), 203.6 (d, J = 6.0 Hz, C-4).

^{31}P NMR ($CDCl_3$): δ = 22.44 (major), 21.17 (minor).[11]

Anal. Calcd for $C_{21}H_{27}O_6P$: C, 62.06; H, 6.70. Found: C, 62.21; H, 6.83.

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