

Cyclisation reactions of 2-substituted benzoylphosphonates with trialkyl phosphites via nucleophilic attack on a carbonyl-containing *ortho* substituent

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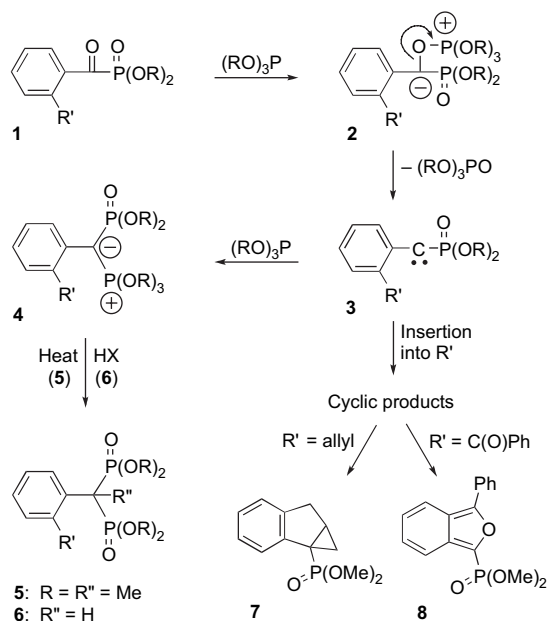
Abstract

Dimethyl 2-acetoxy- and dimethyl 2-benzoyloxy-benzoylphosphonate undergo cyclisation and deoxygenation in the presence of excess trimethyl phosphite to give dimethyl (3-methyl-1-benzofuran-2-yl)phosphonate and dimethyl (3-phenyl-1-benzofuran-2-yl)phosphonate, respectively. The reaction pathway has been shown to involve phosphite attack on initially formed tricyclic dioxaphospholane intermediates with the subsequent loss of two molecules of trimethyl phosphate. In the absence of additional trimethyl phosphite the initially formed tricyclic dioxaphospholane intermediates lose one molecule of trimethyl phosphate and then undergo a novel rearrangement to give β -ketophosphonates. The mechanism for this reaction helps explain some previously reported epoxide rearrangements. In contrast, the initially formed anionic intermediate from the reaction of dimethyl 2-benzoyloxymethylbenzoylphosphonate with trimethyl phosphite undergoes decomposition to give a carbene intermediate which is trapped by the trimethyl phosphite to give an ylidic phosphonate.

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1. Introduction

We have previously shown that the reactions of dialkyl benzoylphosphonates **1** with trialkyl phosphites ($R = \text{Me, Et, } ^i\text{Pr}$) usually proceed via the initial formation of anionic intermediates **2** which, in the absence of electrophiles, undergo $\alpha\text{C}=\text{O}$ bond cleavage to give carbene intermediates **3** (Scheme 1).¹ Moreover, if there is a substituent 'R' on the benzene ring capable of reacting with this carbene centre, intramolecular insertion reactions can occur leading to the formation of novel cyclisation products via some interesting reaction pathways.^{2–5} Thus, for example, the 2-allyl-substituted system **1** ($R = \text{Me}$, $R' = \text{CH}_2\text{CH}=\text{CH}_2$) reacts with trimethyl phosphite to give the cyclopropane-containing system **7**.² Intermolecular trapping of the carbene intermediates **3** by the trialkyl phosphite present can also occur to give the ylidic phosphonate **4** which can be used to prepare the analogous bisphosphonates **5** or **6**.



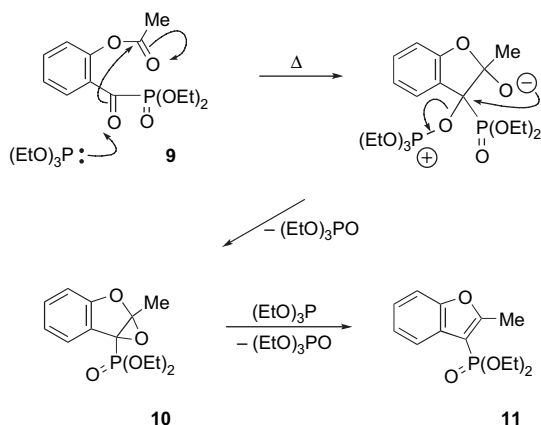
Scheme 1.

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More recently we have been investigating the reactions of some dialkyl benzoylphosphonates where the substituent contains an electrophilic centre such as a carbonyl-containing functional group. In particular, we were interested to see if such substituted benzoylphosphonates would preferentially undergo cyclisation in the presence of trialkyl phosphites via the initially formed anionic intermediates **2** rather than their immediate decomposition products, the carbene intermediates **3**.

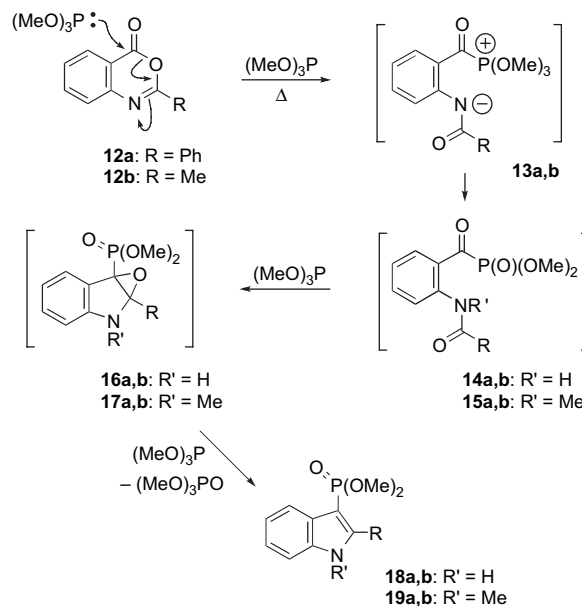
It has been speculated that the cyclisation of diethyl 2-acetoxybenzoylphosphonate **9** in triethyl phosphite to give diethyl 2-methyl-benzofuran-3-ylphosphonate **11** (Scheme 2)⁶ might involve such a mechanism although this has not been established.



Scheme 2.

An analogous pathway involving the epoxides **16a**, **16b**, **17a** and **17b** has also been proposed to explain the reported formation of the indole systems **18a**, **18b**, **19a** and **19b** when the benzoxazinones **12a** and **12b** were heated with trialkyl phosphites such as trimethyl phosphite (Scheme 3).⁷ However, no evidence for the intermediates on this pathway including the aroylphosphonates **14a**, **14b**, **15a** and **15b** could be obtained and the formation of the aroylphosphonates **14a** and **14b** clearly involves an additional source of protons.

We had concerns over the mechanism shown in Scheme 2 following our observation that the formation of the benzofuran-3-ylphosphonate **11** from the aroylphosphonate **9** proceeds even at room temperature. This would mean that the proposed epoxide **10** would have to undergo deoxygenation at a much lower temperature than has been reported for such deoxygenations. For example, the deoxygenation of ethylene oxide by triethyl phosphite⁸ is reported to require in excess of 1 h at 175 °C while the more sterically hindered 2-butene oxide could only be converted to butene in small yields even after prolonged heating with triethyl phosphite at 200 °C.⁹ It is also worth noting that some time ago we showed that the 2-benzoyl-substituted system **1** [$\text{R}=\text{Me}$, $\text{R}'=\text{C}(\text{O})\text{Ph}$] gave the benzofuran **8** via the interaction of the carbene centre in **3** [$\text{R}=\text{Me}$, $\text{R}'=\text{C}(\text{O})\text{Ph}$] with the carbonyl group,⁴ so that even if an epoxide such as **10** is involved it could, in principle, be produced by the interaction of the carbene centre in **3** ($\text{R}=\text{Et}$, $\text{R}'=\text{OAc}$) with the adjacent carbonyl group. A similar



Scheme 3.

rationale could be applied to the formation of the proposed epoxides **16a**, **16b**, **17a** and **17b**.

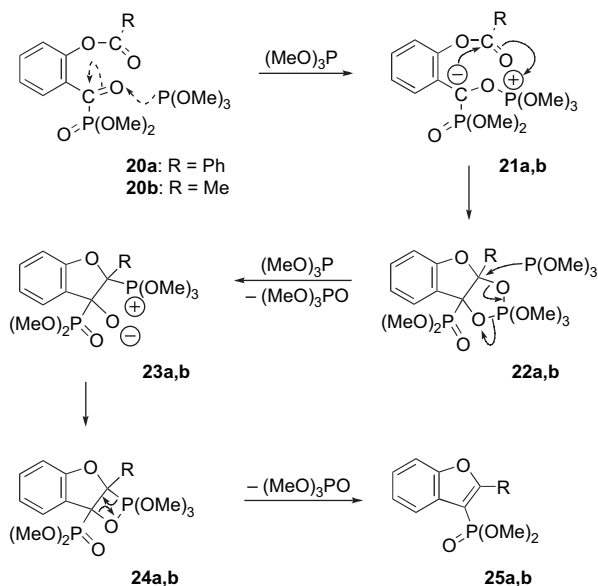
In the case of the 2-benzoyl-substituted system **1** [$\text{R}=\text{Me}$, $\text{R}'=\text{C}(\text{O})\text{Ph}$],⁴ the anionic centre in the intermediate **2** [$\text{R}=\text{Me}$, $\text{R}'=\text{C}(\text{O})\text{Ph}$] was not appropriately positioned to be able to attack the adjacent carbonyl group and the reaction therefore had no option other than to proceed via a carbene mechanism. We have therefore now investigated the reaction of systems such as the 2-benzoyloxy- and 2-benzoyloxy-methyl-substituted systems **1** [$\text{R}=\text{Me}$, $\text{R}'=\text{OC}(\text{O})\text{Ph}$ and $\text{CH}_2\text{OC}(\text{O})\text{Ph}$] to see if a suitable spacer between the disubstituted benzene ring and the carbonyl group in the substituent might facilitate the direct interaction of the carbanionic centre with the carbonyl carbon.¹⁰ These studies have enabled us to establish that the reaction pathway to diethyl 2-methyl-benzofuran-3-ylphosphonate **11** is not the one originally proposed.

2. Results and discussion

The reaction of the 2-benzoyloxy-substituted system **20a** with trimethyl phosphite proceeded to give the cyclic product, dimethyl 2-phenylbenzofuran-3-ylphosphonate **25a**, in good yield in an analogous reaction to that observed for the corresponding acetoxy-substituted system **9**.

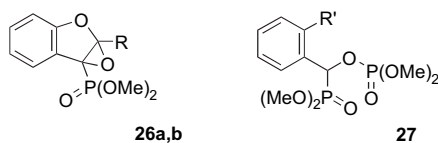
By using NMR spectroscopy to monitor the reaction of 2-benzoyloxybenzoylphosphonate **20a** with trimethyl phosphite, we have been able to show that the initially formed product is the dioxaphospholane **22a** [δ_{P} −48 (d) and +17 (d), J_{PP} 33 Hz], which can be seen to result from attack by the anionic centre in the intermediate **21a** on the carbonyl carbon in the *ortho* substituent (see Scheme 4).^{11,12}

We have also established that the mode of decomposition of this initial product depends on whether further trimethyl phosphite is present.



Scheme 4.

If additional phosphite is first removed from the reaction mixture, either by evaporation in vacuo or by prior reaction with sulfur, then thermal decomposition of **22a** occurs over several hours at room temperature with the loss of trimethyl phosphate to give a compound of formula $C_{16}H_{15}O_5P$ [$M+H^+$ 319, δ_P 14.5] that is unreactive towards trimethyl phosphite. In contrast, in the presence of trimethyl phosphite, the dioxaphospholane **22a** reacts more quickly to give two molecules of trimethyl phosphate and the benzofuran-3-ylphosphonate **25a** [δ_P 17.8] in an overall reaction analogous to that observed by Chiusoli et al.⁶ for the related ‘acetoxy’ system **9**.

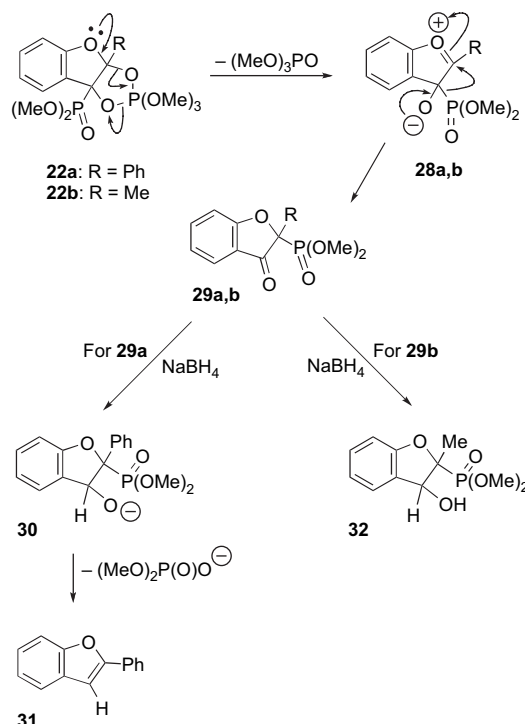


To explain the more rapid decomposition of the dioxaphospholane **22a** in the presence of trimethyl phosphite we propose that the phosphite attacks the dioxaphospholane **22a** (as shown in Scheme 4) leading to ring-opening and loss of trimethyl phosphate. The subsequent loss of a second molecule of trimethyl phosphate from the intermediate **24a** thus leads to the formation of the benzofuran-3-ylphosphonate **25a** without passing through an epoxide of the type that was proposed by Chiusoli et al.⁶ as a key intermediate on the reaction pathway for the corresponding ‘acetoxy’ system.

In contrast, the decomposition pathway for the dioxaphospholane in the absence of trialkyl phosphite was initially much less obvious due to difficulties identifying the final product. As previously noted, this phosphonate product was resistant to further reaction with trimethyl phosphite and was clearly not the epoxide **26a** since its ^{13}C NMR spectrum showed the

presence of a ketone carbonyl carbon [δ_C 194.6]. Interestingly, oxidation of the benzofuran-3-ylphosphonate **25a** with *meta*-chloroperbenzoic acid gave this same carbonyl compound, while reduction of this ketophosphonate oxidation product with sodium borohydride gave 2-phenylbenzofuran **31**.

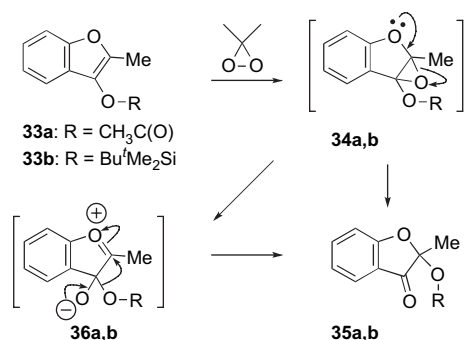
The solution to this problem was provided by a detailed study of the reaction of the corresponding 2-acetoxybenzoylphosphonate **20b** with trimethyl phosphite. This system proved to be a little more difficult to study than the corresponding ‘benzoyloxy’ system since the intermediate dioxaphospholane **22b** [δ_P –49.5 (d) and +18.3 (d), J_{PP} 32 Hz] decomposed more quickly but our NMR studies clearly showed that this system followed the same reaction pathway. However, with the ‘acetoxy’ system the sodium borohydride reduction of the ketophosphonate, from the decomposition of the dioxaphospholane **22b** in the absence of trimethyl phosphite, did not undergo elimination to give 2-methylbenzofuran but instead remained as a hydroxyphosphonate. This hydroxyphosphonate was readily identified as the β -hydroxyphosphonate **32**, which showed that its precursor was the β -ketophosphonate **29b**. The formation of the corresponding β -ketophosphonate **29a** in the phenyl-substituted system can also account for the formation 2-phenylbenzofuran **31** on its reduction with sodium borohydride (Scheme 5).¹³ This clearly shows that the decomposition of the intermediates **28a** and **28b** in the absence of trimethyl phosphite proceeds with the unexpected migration of the phosphonate groups from their original positions on the carbon skeleton to an adjacent carbon atom. We have therefore established that the decomposition of the initially formed dioxaphospholane in these systems in the absence of trimethyl phosphite proceeds as shown in Scheme 5



Scheme 5.

and that this too does not involve the epoxide intermediate proposed originally by Chiusoli et al.⁶

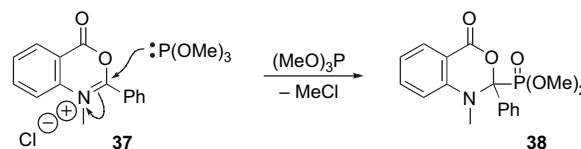
It is interesting to note that although considerable efforts were made to prepare the epoxides **26a** and **26b** by the oxidation of the analogous benzofuran-3-ylphosphonates **25a** and **25b**, using reagents such as dimethyldioxirane and *meta*-chloroperoxybenzoic acid, these were not successful. The latter reagent with the benzofuran-3-ylphosphonate **25b** did bring about oxidation of the C2–C3 carbon–carbon double bond but the product isolated was the β -ketophosphonate **29b**. In this context it is interesting to note that Adam et al.¹⁴ have observed similar behaviour in some of the benzofurans they have studied. Thus, for example, attempts to convert the acetoxy-substituted system **33a** and the silyloxy-substituted system **33b** into the corresponding epoxides led to the formation of the corresponding carbonyl systems **35a** and **35b** possibly via the initial formation of the epoxides **34a** and **34b**. These rearrangements were rationalised as involving the migration of the R group to the epoxide oxygen, although such a mechanism would not account for the formation of the β -ketophosphonate **29b** from the oxidation of the benzofuranylphosphonate **25b**. A more satisfactory mechanism might therefore be that in Scheme 6, which involves the intermediates **36a** and **36b** that are analogous to the intermediates **28a** and **28b** used to explain the formation of the β -ketophosphonates **29a** and **29b**.



Scheme 6.

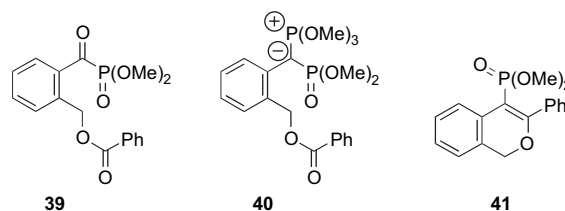
We have also attempted to prepare the nitrogen-containing aroylphosphonate **15a** under mild conditions so that its subsequent reaction with trimethyl phosphite might be examined under more controlled conditions. However, the reaction of the *N*-methylated salt **37** with trimethyl phosphite at room temperature resulted in attack at the iminium carbon to give the monophosphonate **38** (Scheme 7) rather than attack at the carbonyl group and ring-opening to give the benzoylphosphonate **15a** as proposed in Scheme 3.⁷ It would also appear that the conditions needed to bring about the conversion of the benzoxazinones **12a** and **12b** to the indole systems **18a**, **18b**, **19a** and **19b** are rather critical since we have not yet been able to successfully repeat these reactions under the conditions reported, although work is continuing.

As noted earlier, we also studied the reaction of dimethyl 2-(benzoyloxymethyl)benzoylphosphonate **39** with trimethyl phosphite to see whether the introduction of a slightly longer



Scheme 7.

spacer between the carbonyl group in the substituent and the phenyl ring of the dialkyl benzoylphosphonate could result in the formation of a larger ring system via a non-carbenoid pathway. However, this resulted in the formation of the ylidic phosphonate **40** [δ_P 29.4 (d) and 50.5 (d), J_{PP} 95 Hz] which was isolated as its decomposition product, the bisphosphonate **6** [R=Me, R'=CH₂OC(O)Ph], confirming that the initially formed anionic intermediate **2** [R=Me, R'=CH₂OC(O)Ph] had undergone decomposition to the corresponding carbene intermediate rather than directly undergoing reaction with the carbonyl group. There were no signs of the formation of a cyclisation product such as **41**.



3. Conclusions

We have shown that the benzoylphosphonates **20a** and **20b** react with trimethyl phosphite to give the benzofurans **25a** and **25b** by a reaction pathway that involves attack by the carbanionic centre in the initially formed anionic intermediates **21a** and **21b** on the adjacent carbonyl group rather than via the corresponding carbene intermediates **3**. This results in the subsequent formation of the dioxaphospholanes **22a** and **22b** (Scheme 4), which then react further with trimethyl phosphite to give the observed products. However, if the dioxaphospholanes **22a** and **22b** are allowed to decompose in the absence of trimethyl phosphite they undergo loss of trimethyl phosphate and a subsequent rearrangement to give the β -ketophosphonates **29a** and **29b**, which are unreactive towards trialkyl phosphites. The mechanism by which this rearrangement occurs (Scheme 5) may also help explain the observed rearrangements of some other related epoxides (Scheme 6).¹⁴

We also now know that this does not occur when a shorter or longer spacer between the carbonyl group and the phenyl ring of the benzoylphosphonate is used, as in the case of the benzoyl-substituted system **1** [R=Me, R'=C(O)Ph]⁴ and the benzoyloxymethyl-substituted system **39**. In these circumstances the initially formed anionic intermediates undergo cleavage to give the corresponding carbene intermediates **3** before reacting further. In the case of the benzoyl-substituted system **1** [R=Me, R'=C(O)Ph] the dominant pathway is an intramolecular cyclisation of the carbene intermediate involving

the *ortho* substituent to give the benzofuran **8**. However, with the 2-benzoyloxymethyl-substituted system **39** intermolecular trapping of the carbene by the trimethyl phosphite present in the reaction mixture occurs to give the corresponding ylidic phosphonate **40**.

We must therefore conclude that those reactions which involve nucleophilic attack on an *ortho* substituent will be restricted to those cases where the anionic centre in the initially formed intermediate **2** can react quickly with the adjacent substituent. In other cases the anionic intermediates **2** will undergo decomposition to give carbene intermediates **3** which will react further by alternative pathways.

4. Experimental

4.1. General details

Melting points were obtained on a Buchi SMP-20 capillary melting point apparatus and are uncorrected. NMR spectra were recorded on JEOL EX-270, Bruker AMX400 and Bruker AV600 spectrometers. ^{31}P NMR spectra are referenced to 85% phosphoric acid, ^1H NMR spectra to TMS and ^{13}C NMR spectra to CDCl_3 at 77.23 ppm. J values are given in hertz, ' J ' indicates an apparent coupling in a second order spectrum. IR spectra were taken on a Shimadzu FTIR-8300 instrument. Low resolution mass spectra were recorded on a ES Bruker Esquire 300 Plus Daltronics instrument with ES ionisation whilst high resolution spectra were obtained from the mass spectrometry facility at Kings College, London. TLC was performed with aluminium backed silica gel 60 F $_{254}$ plates eluting with the solvent system used for the column chromatography unless otherwise stated. The plates were visualised under UV light or developed in an iodine tank. Column chromatography was carried out using silica gel with particle size 33–50 μm , purchased from BDH. All other materials were purchased from Sigma–Aldrich Ltd and used as received unless indicated otherwise.

4.2. Dimethyl 2-acetoxybenzoylphosphonate **20b**

A solution of oxalyl chloride (2.54 g, 22 mmol) and 2-acetoxybenzoic acid (1 g, 5.5 mmol) in dichloromethane (10 mL) was stirred at room temperature overnight. Dry toluene (20 mL) was added to the reaction mixture and the excess oxalyl chloride and other volatile components were then removed under reduced pressure (75 °C at 10 mmHg). Ensuring the exclusion of moisture from the reaction flask by means of a rubber septum, the residue was cooled in an ice-bath (5 °C) and trimethyl phosphite (0.62 g, 5.5 mmol) was added dropwise, using a syringe. The reaction mixture was then allowed to warm to room temperature and stirred for 30 min. Volatile components were removed under reduced pressure (30 °C at 0.005 mmHg) to give dimethyl 2-acetoxybenzoylphosphonate **20b** as a pale yellow oil in essentially quantitative yield. If necessary, this product can be purified for analytical purposes by vacuum distillation (147 °C at 0.4 mmHg), but in most cases, the material is sufficiently pure to be used without

further purification. Found: C, 48.82; H, 4.93. $\text{C}_{11}\text{H}_{13}\text{O}_6\text{P}$ requires C, 48.54; H, 4.81%; δ_{H} (270 MHz, CDCl_3) 2.33 (3H, s, CH_3), 3.85 (6H, d, J_{PH} 11, POCH_3), 7.14 (1H, ddd, J_{HH} 8 and 1, J_{PH} 1.5, 3-H), 7.37 (1H, td, J_{HH} 8 and 1, 5-H), 7.60 (1H, td, J_{HH} 8 and 1.5, 4-H), 8.35 (1H, dd, J_{HH} 8 and 1.5, 6-H); δ_{C} (67.9 MHz, CDCl_3) 21.0 (CH_3), 54.3 ($\times 2$) (d, J_{PC} 7, POMe), 124.1 (d, J_{PC} 3, C-3), 126.3 (C-5), 128.7 (d, J_{PC} 65, C-1), 132.5 (C-6), 135.4 (C-4), 149.5 (d, J_{PC} 6, C-2), 169.3 (MeC=O), 198.1 (d, J_{PC} 181, P-C=O); δ_{P} (109.3 MHz, CDCl_3) 0.1; ν_{max} (film)/ cm^{-1} 3009, 2963, 2855, 1767, 1666, 1605, 1450, 1373, 1258, 1196, 1042, 910.

4.3. Dimethyl 2-benzoyloxybenzoylphosphonate **20a**

4.3.1. 2-Benzoyloxybenzoic acid

To a cooled, stirred solution of 2-hydroxybenzoic acid (10.0 g, 72 mmol) in a mixture of dry diethyl ether (50 mL) and pyridine (15.0 g, 190 mmol) was added a solution of benzoyl chloride (10.0 g, 71 mmol) in diethyl ether (50 mL) at such a rate that the reaction temperature did not exceed 5 °C. The reaction mixture was then stirred at room temperature for 1 h and then poured onto water. The mixture was made acid to litmus with hydrochloric acid (ca. 15 mL, 2 M) and the resulting solution was then extracted with chloroform (3 $\times$ 25 mL). The combined chloroform extracts were dried over magnesium sulfate and the solvent removed under reduced pressure to give a colourless solid, which was recrystallised from hexane. 2-Benzoyloxybenzoic acid (16.0 g, 93%) was obtained as colourless needles, mp 131 °C (lit.,¹⁵ 132 °C); δ_{H} (270 MHz, CDCl_3) 7.23 (1H, dd, J_{HH} 8 and 1, 3-H), 7.36 (1H, td, J_{HH} 8 and 1, 5-H), 7.50 (2H, t, J_{HH} 8, 3'/5'-H), 7.61 (2H, m, 4'-H and 4-H), 8.06 (1H, dd, J_{HH} 8 and 1, 6-H), 8.17 (2H, d, J_{HH} 8, 2'/6'-H), 9.1 (1H, br s, OH); δ_{C} (CDCl_3) 122.6 (C-1), 124.1 (C-3), 126.1 (C-5), 128.4 (C-3'), 129.4 (C-1'), 130.2 (C-2'), 132.5 (C-6), 133.5 (C-4'), 134.65 (C-4), 151.2 (C-2), 165.3 (C=O), 169.8 (C=O); ν_{max} (KBr)/ cm^{-1} 3500–2500 (br), 1740, 1685, 1684, 1650, 1609, 1489, 1452, 1420, 1312, 1263, 1204, 1180, 1088, 1078, 1065, 1022; m/z (EI) 242.0581 (M^+ , $\text{C}_{14}\text{H}_{10}\text{O}_4$ requires 242.0579).

4.3.2. Dimethyl 2-benzoyloxybenzoylphosphonate **20a**

This material was prepared in essentially quantitative yield from 2-benzoyloxybenzoic acid using the same procedure as that used for the preparation of dimethyl 2-acetoxybenzoylphosphonate **20b**. The benzoylphosphonate **20a** was isolated as a yellow oil; δ_{H} (270 MHz, CDCl_3) 3.80 (6H, d, J_{PH} 11, POMe), 7.25 (1H, d, J_{HH} 8, 3-H), 7.40 (1H, td, J_{HH} 8 and 1, 5-H), 7.47 (2H, tm, J_{HH} 8, 3'/5'-H), 7.60 (1H, tm, J_{HH} 8, 4-H), 7.64 (1H, tm, J_{HH} 8, 4'-H), 8.17 (2H, dm, J_{HH} 8, 2'/6'-H), 8.45 (1H, dd, J_{HH} 8 and 1.5, 6-H); δ_{C} (67.9 MHz, CDCl_3) 54.4 ($\times 2$) (d, J_{PC} 8, POMe), 124.3 (d, J_{PC} 3, C-3), 126.4 (C-5), 128.7 (C-3'/5'), 128.9 (d, J_{PC} 64, C-1), 129.3 (C-1'), 130.3 (C-2'/6'), 132.7 (C-6), 133.8 (C-4'), 135.4 (C-4), 149.6 (d, J_{PC} 7, C-2), 165.1 (CO_2), 197.8 (d, J_{PC} 179, PC=O); δ_{P} (CDCl_3) 0.0; ν_{max} (film)/ cm^{-1} 2959, 1740, 1659, 1601, 1450, 1261, 1204, 1192, 1075, 1026, 944; m/z (ESI) 357.0470 ($\text{M}+\text{Na}^+$, $\text{C}_{16}\text{H}_{15}\text{NaO}_6\text{P}$ requires 357.0499).

4.4. Dimethyl 2-methylbenzofuran-3-ylphosphonate **25b**

Trimethyl phosphite (1.24 g, 11 mmol) was allowed to react with dimethyl 2-acetoxybenzoylphosphonate **20b** (1.50 g, 5.5 mmol) with the exclusion of moisture. After a period of 2 h, volatile compounds were removed under reduced pressure (65 °C at 0.01 mmHg) and the residue was purified by chromatotron chromatography on silica using mixtures of ethyl acetate and petroleum ether (bp 40–60 °C) as the eluent. Dimethyl 2-methylbenzofuran-3-ylphosphonate **25b** (1.1 g, 85%) was obtained as a colourless oil; δ_{H} (270 MHz, CDCl_3) 2.74 (3H, d, J_{PH} 2, CH_3), 3.78 (6H, d, J_{PH} 11.5, POCH_3), 7.23–7.33 (2H, m, 5-H and 7-H), 7.46 (1H, dt, J 8 and 2, 6-H), 7.67 (1H, m, 4-H); δ_{C} (67.9 MHz, CDCl_3) 14.2 (Me), 52.7 ($\times 2$) (d, J_{PC} 5, $\text{P}(\text{OMe})_2$), 101.6 (d, J_{PC} 216, C-3), 111.1 (C-7), 121.0 (C-4), 123.9 (C-5), 124.8 (C-6), 128.0 (d, J_{PC} 11, C-3a), 154.3 (d, J_{PC} 15, C-7a), 165.4 (d, J_{PC} 29, C-2); δ_{P} (109.3 MHz, CDCl_3) 18.0; ν_{max} (film)/ cm^{-1} 2950, 2850, 1600, 1576, 1475, 1455, 1320, 1281, 1249, 1176, 1026; m/z (EI) 240.0551 (M^+ , $\text{C}_{11}\text{H}_{13}\text{O}_4\text{P}$ requires 240.0551).

4.5. Dimethyl 2-phenyl-1-benzofuran-3-ylphosphonate **25a**

This material was prepared and purified using the procedure previously described for the corresponding methyl-substituted system **25b** except that a 5 h reaction time was used in this case. Dimethyl 2-phenyl-1-benzofuran-3-ylphosphonate **25a** (0.9 g, 75%) was obtained as a pale yellow oil; δ_{H} (270 MHz, CDCl_3) 3.70 (6H, d, J_{PH} 11, $\text{P}(\text{OMe})_2$), 7.25–7.37 (2H, m, 5-H and 7-H), 7.42–7.47 (3H, m, 4-H and 3'/5'-H), 7.50 (1H, tm, J_{HH} 7.5, 6-H), 7.94 (1H, dm, J_{HH} 7, 4-H), 8.03 (1H, dm, J_{HH} 7, 2'/6'-H); δ_{C} (100.6 MHz, CDCl_3) 52.5 ($\times 2$) (d, J_{PC} 6, $\text{P}(\text{OMe})_2$), 101.6 (d, J_{PC} 213, C-3), 111.1 (C-7), 122.3 (C-4), 124.0 (C-5), 125.4 (C-6), 128.3 ($\times 2$) (C-2'/6'), 129.1 ($\times 2$) (C-3'/5'), 129.3 (C-1'), 129.4 (d, J_{PC} 12, C-3a), 130.3 (C-4'), 154.1 (d, J_{PC} 15, C-7a), 162.2 (d, J_{PC} 26, C-2); δ_{P} (109.3 MHz, CDCl_3) 17.2; ν_{max} (film)/ cm^{-1} 2952, 2849, 1550, 1490, 1444, 1255, 1184, 1026; m/z (EI) 302.0708 (M^+ , $\text{C}_{16}\text{H}_{15}\text{O}_4\text{P}$ requires 302.0708).

4.6. NMR studies of the reaction of the 2-substituted dimethyl benzoylphosphonates **20a** and **20b** with trimethyl phosphite in the presence of excess trimethyl phosphite

The dimethyl benzoylphosphonates **20a** and **20b** (5.5 mmol) were placed in a 50 mL round-bottomed Schlenk flask containing a magnetic stirrer bar. The flask was evacuated and then filled with dry nitrogen. Trimethyl phosphite (1.24 g, 11 mmol) was then added slowly via a rubber septum while the contents of the flask were stirred. When the addition was complete, a sample of the reaction mixture was transferred to an NMR tube and the progress of the reaction was monitored by NMR spectroscopy. This showed the initial formation of the corresponding dioxaphospholanes **14a** and **14b**. At this point deuteriochloroform was added to the sample so that accurate NMR chemical shift data could be obtained.

Neither of these compounds was stable under the reaction conditions and both decomposed over a period of time to give trimethyl phosphate and the corresponding 2-substituted dimethyl benzofuran-3-ylphosphonates **25a** and **25b**.

4.6.1. Dimethyl 2,2,2-trimethoxy-3a-phenyl-2 λ^5 -[1,3,2]-dioxaphos-pholo[4,5-b][1]benzofuran-8b(3aH)-ylphosphonate **22a**

δ_{C} (100.6 MHz, CDCl_3) 52.4 (d, J_{PC} 6, POCH_3), 53.1 (d, J_{PC} 6, POCH_3), 54.7 ($\times 3$) (d, J_{PC} 11, POCH_3), 83.9 (d, J_{PC} 192, C-8b), 109.4 (dd, $^2J_{\text{PC}} + ^2J_{\text{PC}}$ 16, ^{16}C -3a), 109.4 (C-5), 121.1 (C-7), 126.7 ($\times 2$) (C-2'/6'), 126.8 (C-6), 127.5 ($\times 2$) (C-3'/5'), 128.7 (d, J_{PC} 3, C-8a), 129.7 (C-4'), 131.5 (C-8), 136.7 (d, J_{PC} 9, C-1'), 158.7 (d, J_{PC} 10, C-4a); δ_{P} (162 MHz, CDCl_3) -48.2 [d, J_{PP} 33, $\text{O}_2\text{P}(\text{OMe})_3$] and 17.1 [d, J_{PP} 33, $\text{P}(\text{O})(\text{OMe})_2$].

4.6.2. Dimethyl 2,2,2-trimethoxy-3a-methyl-2 λ^5 -[1,3,2]-dioxaphos-pholo[4,5-b][1]benzofuran-8b-(3aH)-ylphosphonate **22b**

δ_{C} (100.6 MHz, CDCl_3) 22.0 (d, J_{PC} 9, CH_3), 53.3 (d, J_{PC} 7, POCH_3), 54.1 (d, J_{PC} 7, POCH_3), 55.1 ($\times 3$) (d, J_{PC} 10, POCH_3), 82.0 (d, J_{PC} 189, C-8a), 109.2 (dd, J_{PC} 11 and 3, C-3a), 110.1 (C-5), 121.0 (C-7), 126.9 (C-6), 128.9 (d, J_{PC} 4, C-8a), 131.7 (C-8), 158.2 (d, J_{PC} 10, C-4a); δ_{P} (162 MHz, CDCl_3) -49.3 [d, J_{PP} 30, $\text{O}_2\text{P}(\text{OMe})_3$] and 18.1 [d, J_{PP} 30, $\text{P}(\text{O})(\text{OMe})_2$].

4.7. An investigation into the decomposition of the initially formed tricyclic phosphorane **22a** in the absence of trimethyl phosphite: formation of dimethyl 3-oxo-2-phenyl-2,3-dihydro-1-benzofuran-2-ylphosphonate **29a**

A quantity of the tricyclic phosphorane intermediate **22a** was generated in toluene solution as described previously. Sulfur was then added to decompose any excess phosphite and the subsequent decomposition of intermediate **22a** was then monitored by ^{31}P NMR spectroscopy. This showed the formation of dimethyl 3-oxo-2-phenyl-2,3-dihydro-1-benzofuran-2-ylphosphonate **29a**, which was isolated as a colourless oil by preparative reverse phase HPLC on a Dynamax C-18 column using 80% aqueous methanol as the eluent; δ_{H} (600 MHz, CDCl_3) 3.71 (3H, d, J_{PH} 10, POCH_3), 3.73 (3H, d, J_{PH} 10, POCH_3), 7.14 (1H, t, J_{HH} 8, 4'-H), 7.32 (1H, d, J_{HH} 8, 4-H), 7.34 (1H, t, J_{HH} 8, 5-H), 7.40 (2H, t, J_{HH} 8, 3'/5'-H), 7.66 (1H, t, J_{HH} 8, 6-H), 7.70 (1H, d, J_{HH} 8, 7-H), 7.92 (2H, d, J_{HH} 8, 2'/6'-H); δ_{C} (150 MHz, CDCl_3) 54.7 (d, J_{PC} 6, POCH_3), 55.1 (d, J_{PC} 6, POCH_3), 89.2 (d, J_{PC} 160, C-2), 113.6 (C-7), 120.4 (C-3a), 122.9 (C-5), 125.2 (C-4), 125.5 ($\times 2$) (d, C-2'/6'), 128.5 ($\times 2$) (d, C-3'/5'), 128.9 (d, J_{PC} 3, C-4'), 131.4 (d, J_{PC} 1.5, C-1'), 138.2 (C-6), 171.3 (d, J_{PC} 4.5, C-7a), 194.6 (C=O); δ_{P} (CDCl_3) 14.5; ν_{max} (film)/ cm^{-1} 2958, 2854, 1718, 1625, 1608, 1475, 1464, 1448, 1325, 1297, 1264, 1240, 1182, 1147, 1030, 999, 943, 878, 839, 821, 748, 697, 668, 630; m/z (ESI) 341.0549 ($\text{M} + \text{Na}^+$, $\text{C}_{16}\text{H}_{15}\text{NaO}_5\text{P}$ requires 341.0549).

An alternative, equally successful, strategy for preventing the excess trimethyl phosphite from reacting with the tricyclic phosphorane intermediate **22a** involved removing the excess trimethyl phosphite in vacuo as described for **22b**.

*4.8. Investigation of the decomposition of dimethyl (2,2,2-trimethoxy-3a-methyl-2λ⁵-[1,3,2]dioxaphospholo[4,5-b][1]-benzofuran-8b(3aH)-yl)phosphonate **22b** in the absence of trimethyl phosphite: formation of dimethyl 2-methyl-3-oxo-2,3-dihydro-1-benzofuran-2-ylphosphonate **29b***

A quantity of the tricyclic phosphorane intermediate **22b** was generated in solution as previously described. Volatile components were then removed from the reaction mixture at room temperature in vacuo (0.005 mmHg) to ensure complete removal of any unreacted trimethyl phosphite. The residue was then taken up into deuteriochloroform and the decomposition of the tricyclic phosphorane **22b** monitored by NMR. This showed the formation of dimethyl 2-methyl-3-oxo-2,3-dihydro-1-benzofuran-2-ylphosphonate **29b** which was isolated in a pure state as a pale yellow oil by preparative reverse phase HPLC on a Dynamax C-18 column using 80% aqueous methanol as the eluent; δ_{H} (270 MHz, CDCl₃) 1.76 (3H, d, J_{PH} 16, CH₃), 3.81 (3H, d, J_{PH} 10, POCH₃), 3.86 (3H, d, J_{PH} 10, POCH₃), 7.15 (1H, tm, J_{HH} 8, 5-H), 7.21 (1H, dm, J_{HH} 8, 7-H), 7.67 (1H, t, J_{HH} 8, 6-H), 7.71 (1H, d, J_{HH} 8, 4-H); δ_{C} (100.6 MHz, CDCl₃) 18.7 (CH₃), 54.3 (d, J_{PC} 6, POCH₃), 54.7 (d, J_{PC} 6, POCH₃), 87.4 (d, J_{PC} 160, C-2), 113.7 (C-7), 120.3 (C-3a), 122.8 (C-5), 124.9 (C-4), 138.3 (C-6), 171.3 (d, J_{PC} 5, C-7a), 197.8 (d, J_{PC} 1, C=O); δ_{P} (162.0 MHz, CDCl₃) 16.8; ν_{max} (film)/cm⁻¹ 2958, 2854, 1717, 1612, 1470, 1462, 1300, 1261, 1030; m/z (ESI) 257.0573 (M+H⁺, C₁₁H₁₄O₅P requires 257.0578).

An alternative, equally successful, strategy for preventing the excess trimethyl phosphite from reacting with the tricyclic phosphorane intermediate **22b** involved adding excess sulfur to the solution, as described for **22a**. This converted the excess trimethyl phosphite to unreactive trimethyl thiophosphate.

*4.9. Oxidation of dimethyl 2-methylbenzofuran-3-ylphosphonate **25b** with *m*-CPBA*

A solution of the phosphonate **25b** (0.1 g, 0.4 mmol) and *meta*-chloroperoxybenzoic acid (0.35 g, 2 mmol) in chloroform (10 mL) was heated at 35 °C. After 24 h, NMR spectroscopy showed that ca. 30% of the starting material had been converted to dimethyl 2-methyl-3-oxo-2,3-dihydro-1-benzofuran-2-ylphosphonate **29b**. This component was isolated by column chromatography on silica using mixtures of ethyl acetate and hexane as the eluent and shown to have identical spectroscopic properties to those of the sample of **29b** (R=Me) prepared earlier from the decomposition of dimethyl (2,2,2-trimethoxy-3a-methyl-2λ⁵-[1,3,2]dioxaphospholo[4,5-b][1]benzofuran-8b(3aH)-yl)phosphonate **22b** in the absence of trimethyl phosphite.

*4.10. Reduction of **29a** with sodium borohydride*

A solution of dimethyl 3-oxo-2-phenyl-2,3-dihydro-1-benzofuran-2-ylphosphonate **29a** (0.1 g, 0.3 mmol) and sodium borohydride (0.02 g, 0.6 mmol) in methanol (5 mL) was stirred at room temperature overnight. Volatile components were then removed under reduced pressure (60 °C at 10 mmHg) and the organic residue was partitioned between water (10 mL) and methylene chloride (20 mL). The methylene chloride layer was separated and washed with water (3×5 mL), dried (magnesium sulfate) and filtered. The solvent was then removed under reduced pressure (40 °C at 10 mmHg) to give a colourless solid, subsequently identified as 2-phenylbenzofuran **31** (55 mg, 95%); δ_{H} (600 MHz, CDCl₃) 7.03 (1H, d, J 1, 3-H), 7.23 (1H, td, J 7.5 and 1, 5-H), 7.28 (1H, ddd, J 8, 7.5 and 1.5, 6-H), 7.35 (1H, tt, J 8 and 1, 4'-H), 7.44 (2H, tm, J 8, 3'/5'-H), 7.52 (1H, dd, J 8 and 1, 7-H), 7.58 (1H, ddd, J 7.5, 1.5 and 1, 4-H), 7.87 (2H, dm, J 8, 2'/6'-H); δ_{C} (100.6 MHz, CDCl₃) 101.3 (C-3), 111.2 (C-7), 120.9 (C-4), 122.9 (C-5), 124.3 (C-6), 124.9 (×2) (C-2'/6'), 128.6 (C-4'), 128.8 (×2) (C-3'/5'), 129.2 (C-3a), 130.5 (C-1'), 154.9 (C-7a), 155.9 (C-2) (lit.,¹⁷ 101.3, 111.2, 120.9, 122.9, 124.2, 124.9, 128.5, 128.7, 129.2, 130.5, 154.9, 155.9); ν_{max} (film)/cm⁻¹ 2923, 2854, 1562, 1456, 1377, 1039, 1020; m/z (ESI) 195.0804 (M+H⁺, C₁₄H₁₁O requires 195.0809).

*4.11. Reduction of **29b** with sodium borohydride*

Dimethyl 2-methyl-3-oxo-2,3-dihydro-1-benzofuran-2-ylphosphonate **29b** (0.1 g, 0.4 mmol) was reduced with sodium borohydride using the procedure previously described for the reduction of the analogous methyl system **29a**. Dimethyl 3-hydroxy-2-methyl-2,3-dihydro-1-benzofuran-2-ylphosphonate **32** was isolated as a colourless oil in essentially quantitative yield; δ_{H} (270 MHz, CDCl₃) 1.60 (3H, d, J_{PH} 15, CH₃), 3.63 (1H, d, J_{HH} 9.5, OH), 3.87 (3H, d, J_{PH} 11, POCH₃), 3.88 (3H, d, J_{PH} 11, POCH₃), 5.18 (1H, t, J_{PH} 9.5, J_{HH} 9.5, 3-H), 6.88 (1H, d, J_{HH} 8, 7-H), 6.99 (1H, td, J_{HH} 8 and 1, 5-H), 7.28 (1H, td, J_{HH} 8 and 1, 6-H), 7.43 (1H, d, J_{HH} 8, 4-H); δ_{C} (100.6 MHz, CDCl₃) 22.1 (d, J_{PC} 2, CH₃), 53.5 (d, J_{PC} 7, POCH₃), 54.5 (d, J_{PC} 7, POCH₃), 80.7 (d, J_{PC} 1, C-3), 89.2 (d, J_{PC} 170, PC-2), 111.2 (C-7), 122.0 (C-5), 126.3 (d, J_{PC} 0.7, C-6), 127.3 (d, J_{PC} 4, C-3a), 131.0 (C-4), 158.7 (d, J_{PC} 8, C-7a); δ_{P} (109.3 MHz, CDCl₃) 23.5; ν_{max} (film)/cm⁻¹ 3330 (br), 2957, 2928, 2854, 1601, 1478, 1464, 1372, 1241, 1188, 1060, 1031; m/z (ESI) 281.0547 (M+Na⁺, C₁₁H₁₅NaO₅P requires 281.0555).

*4.12. 2-(*N*-Benzoyl-*N*-methylamino)benzoic acid*

2-Methylaminobenzoic acid (5 g, 33 mmol) was dissolved in dry toluene (50 mL) containing triethylamine (4 g, 40 mmol) under an atmosphere of dry nitrogen gas and the resulting solution then cooled in an ice-bath (−5 °C). This mixture was then vigorously stirred under dry nitrogen and a solution of benzoyl chloride (4.6 g, 33 mmol) in dry toluene (5 mL) added dropwise over a period of 60 min. The temperature

of the reaction mixture was kept cool throughout the addition, but it was then allowed to warm to room temperature and stirred for a further 3 h. The reaction mixture was then filtered and the filtrate washed with hydrochloric acid (4×15 mL, 2 M). The organic layer was then dried (MgSO₄), filtered and the volatile components removed under reduced pressure (75 °C at 10 mmHg). The residue was purified by chromatography on silica using mixtures of chloroform and methanol. The 2-(*N*-benzoyl-*N*-methylamino)benzoic acid obtained in this way was recrystallised from a mixture of methylene chloride and toluene to give the product (2.36 g, 28%) as needle-like crystals, mp 166–170 °C (lit.,¹⁸ 164–165.5 °C); δ_{H} (400 MHz, CDCl₃) 3.46 (1H, s, NCH₃), 7.09 (2H, t, *J* 8, 3'/5'-H), 7.16 (1H, t, *J* 8, 4'-H), 7.19 (1H, d, *J* 8, 3-H), 7.24 (1H, t, *J* 8, 5-H), 7.29 (2H, d, *J* 8, 2'/6'-H), 7.42 (1H, t, *J* 8, 4-H), 7.88 (1H, d, *J* 8, 6-H), 11.1 (1H, br s, CO₂H); δ_{C} (100.6 MHz, CDCl₃) 38.7 (NCH₃), 127.7 (C-1), 127.8 (×2) (C-3'/5'), 127.9 (C-5), 128.5 (×2) (C-2'/6'), 129.8 (C-3), 130.2 (C-4'), 132.4 (C-6), 133.7 (C-4), 135.7 (C-1'), 145.0 (C-2), 168.9 (C=O), 171.5 (CO₂H); ν_{max} (KBr)/cm⁻¹ 3500–2250 (br), 1925, 1717, 1589, 1566, 1497, 1435, 1389, 1254, 1188, 1142, 1076, 1030, 976, 930, 883, 795.

4.13. Dimethyl 1-methyl-4-oxo-2-phenyl-1,4-dihydro-2H-3,1-benzoxazin-2-ylphosphonate **38**

2-(*N*-Benzoyl-*N*-methylamino)benzoic acid (1 g, 3.91 mmol) was dissolved in boiling thionyl chloride (10 mL, 0.14 mol) and the mixture stirred for 1 h at room temperature. NMR analysis of the reaction mixture indicated that cyclisation had occurred to give 1-methyl-4-oxo-2-phenyl-4H-3,1-benzoxazin-1-ium chloride **37** [δ_{C} (67.9 MHz, SOCl₂) 42.6 (NCH₃), 115.4 (C-2), 120.6 (C-8), 125.3 (C-1'), 130.3 (×2) (C-2'/6'), 131.1 (C-4'), 132.0 (×2) (C-3'/5'), 132.7 (C-4), 136.8 (C-6), 139.2 (C-8a), 139.8 (C-5), 162.8 (C-4a), 170.1 (C=O)]. Dry toluene (10 mL) was added and then removed under reduced pressure (75 °C at 10 mmHg), to ensure the complete removal of unreacted thionyl chloride, and a solution of trimethyl phosphite (2 mL, 17 mmol) in dry toluene was then slowly added. The reaction mixture was then stirred at room temperature overnight. Volatile components were removed under reduced pressure (65–70 °C at 0.005 mmHg) and the product purified by chromatography on silica using acetonitrile as the eluent. Dimethyl 1-methyl-4-oxo-2-phenyl-1,4-dihydro-2H-3,1-benzoxazin-2-ylphosphonate **38** (0.98 g, 72%) was isolated as a pale yellow oil; δ_{H} (400 MHz, CDCl₃) 2.99 (3H, s, N-CH₃), 3.40 (3H, d, *J* 10, POCH₃), 3.45 (3H, d, *J* 10, POCH₃), 6.67 (1H, t, *J* 8, 6-H), 6.73 (1H, d, *J* 8, 8-H), 7.14 (3H, m, 3'/5'-H and 4'-H), 7.27 (1H, t, *J* 8, 7-H), 7.54 (2H, d, *J* 7, 2'/6'-H), 7.66 (1H, d, *J* 8, 5-H); δ_{C} (100 MHz, CDCl₃) 52.6 (d, *J*_{PC} 7, POCH₃), 52.8 (d, *J*_{PC} 7, POCH₃), 93.7 (d, *J*_{PC} 186, PC-2), 114.2 (C-4a), 114.8 (C-8), 119.7 (C-6), 127.6 (C-2'), 127.7 (C-6'), 127.9 (C-3' and C-5'), 129.1 (C-4'), 129.4 (C-5), 135.5 (C-7), 136.4 (d, *J*_{PC} 7, C-1'), 147.4 (d, *J*_{PC} 6, C-8a), 161.4 (d, *J*_{PC} 6, C=O); δ_{P} (109.3 MHz, CDCl₃)

14.9; ν_{max} (film)/cm⁻¹ 3020, 2959, 2909, 2855, 2341, 2245, 1732, 1605, 1578, 1489, 1450, 1350, 1238, 1180, 1119, 1034, 918, 837; *m/z* (ESI) 348.1001 (M+H⁺, C₁₇H₁₉NO₅P requires 348.1001) and 370.0822 (M+Na⁺, C₁₇H₁₈NO₅PNa requires 370.0820).

4.14. Dimethyl 2-(benzoyloxymethyl)benzoylphosphonate **39**

4.14.1. 2-(Benzoyloxymethyl)benzoic acid

This material was prepared using a modification of the method of Cain.¹⁹

A mixture of phthalide (2.01 g, 15 mmol) and aqueous NaOH (12 mL, 20%) was warmed at 35 °C for ca. 30 min until the phthalide had completely dissolved. The solution was then cooled in an ice-bath (–5 °C) and cold benzoyl chloride (2.5 g, 18 mmol) added quickly with vigorous stirring. Sodium 2-(benzoyloxymethyl)benzoate precipitated from the aqueous solution almost immediately. This sodium salt was filtered off and washed with cold water, then ether and finally chloroform. Dilute hydrochloric acid (ca. 20 mL, 0.5 M) was then added until the resulting solution was acidic (ca. pH 3). The crude 2-(benzoyloxymethyl)benzoic acid was then filtered off and recrystallised from a mixture of chloroform and hexane to give the pure acid (1.2 g, 30%) as colourless crystals, mp 132–136 °C (lit.,¹⁹ 128–129 °C); δ_{H} (270 MHz, acetone-*d*₆) 5.80 (2H, s, CH₂), 7.42–7.52 (3H, m, 3'/5'-H and 3-H), 7.60–7.69 (3H, m, 4-H, 4'-H and 5-H), 8.07–8.10 (3H, m, 2'/6'-H and 6-H); δ_{C} (67.9 MHz, acetone-*d*₆) 65.6 (CH₂), 128.6 (C-5), 128.8 (C-4), 129.4 (×2) (C-3'/5'), 130.0 (C-1'), 130.3 (×2) (C-2'/6'), 131.0 (C-1), 131.8 (C-3), 133.3 (C-4'), 134.0 (C-6), 139.0 (C-2), 166.5 (C=O), 168.4 (CO₂H); ν_{max} (KBr, cm⁻¹) 3050–2525 (br), 1720, 1680, 1600, 1575, 1492, 1450, 1409, 1368, 1321, 1270, 1151, 1124, 1028, 998; *m/z* (ESI) 255 (M–H⁺, C₁₅H₁₁O₄[–] requires 255).

4.14.2. Dimethyl 2-(benzoyloxymethyl)benzoylphosphonate **39**

A mixture of 2-(benzoyloxymethyl)benzoic acid (1 g, 3.9 mmol) and oxalyl chloride (2.0 g, 15.6 mmol) in dichloromethane (10 mL) was stirred overnight under an atmosphere of dry nitrogen. Dry toluene (15 mL) was added to the mixture and then removed under reduced pressure (70 °C at 10 mmHg) to ensure removal of all the excess oxalyl chloride. While excluding moisture, the resulting 2-(benzoyloxymethyl)benzoyl chloride was cooled in an ice-bath (ca. 5 °C) and trimethyl phosphite (0.5 g, 4 mmol) was then added dropwise, with stirring. The reaction mixture was then allowed to warm to room temperature and stirred for 30 min. Volatile components were removed under reduced pressure (30 °C at 0.005 mmHg) to yield the benzoylphosphonate **39** in essentially quantitative yield and in a good state of purity; δ_{H} (270 MHz, CDCl₃) 3.75 (6H, d, *J*_{PH} 11, POCH₃), 5.52 (2H, s, CH₂), 7.27 (2H, t, *J*_{HH} 7, 3'/5'-H), 7.37 (1H, t, *J*_{HH} 7, 4'-H), 8.39 (1H, d, *J*_{HH} 8, 6-H), 7.49–7.53 (2H, m, 4-H and 5-H), 7.93 (2H, d, *J*_{HH} 7, 2'/6'-H), 8.43 (1H, d, *J*_{HH} 8, 3-H); δ_{C} (67.9 MHz, CDCl₃) 54.0 (2C, d, *J*_{PC} 7, POCH₃), 64.2 (CH₂), 127.7 (C-5), 128.0 (d, *J*_{PC} 3, C-3), 128.2 (×2) (C-3'/5'), 129.4 (×2) (C-2'/6'), 129.6 (C-1'), 132.8 (d, *J*_{PC} 2, C-6), 132.9 (C-4'), 133.3 (d,

J_{PC} 64, C-1), 133.9 (C-4), 137.8 (d, J_{PC} 9, C-2), 165.6 (C=O), 200.3 (d, J_{PC} 174, C=O); δ_{P} (109.3 MHz, CDCl_3) 0.8; ν_{max} (film)/ cm^{-1} 2958, 2854, 1721, 1653, 1601, 1573, 1489, 1452, 1375, 1315, 1271, 1226, 1179, 1110, 1029, 945; m/z (ESI) 371.0650 ($\text{M}+\text{Na}^+$, $\text{C}_{17}\text{H}_{17}\text{NaO}_6\text{P}$ requires 371.0660). To minimise side reactions, the benzoylphosphonate **39** was used immediately in its subsequent reaction with trimethyl phosphite without further purification.

4.15. The reaction of dimethyl 2-(benzoyloxymethyl)-benzoylphosphonate **39** with trimethyl phosphite

Taking steps to exclude moisture, trimethyl phosphite (0.96 mL, 8 mmol) was added to the dimethyl 2-(benzoyloxymethyl)benzoylphosphonate **39**, prepared as described above, and the mixture heated at 100 °C. After ca. 6 h NMR analysis of the reaction mixture showed that the major product was the ylidic phosphonate **40**; δ_{P} (109.3 MHz, CDCl_3) 29.4 [d, J_{PP} 95, $\text{P}(\text{O})(\text{OMe})_2$] and 50.5 [d, J_{PP} 95, $\text{P}(\text{OMe})_3$]; δ_{C} (100.6 MHz, CDCl_3) 25.2 (dd, J_{PC} 226 and 214, $\text{P}=\text{C}-\text{P}$). Heating was continued until the reaction was complete (ca. 12 h). At this point NMR showed that, in addition to trimethyl phosphate, three other components were present in the molar ratio of ca. 2:3:1. These were the phosphate-phosphonate **27** [$\text{R}'=\text{CH}_2\text{OC}(\text{O})\text{Ph}$], the ylidic phosphonate **40**, its decomposition product the bisphosphonate **6** [$\text{R}=\text{Me}$, $\text{R}'=\text{CH}_2\text{OC}(\text{O})\text{Ph}$]. Volatile components were then removed under reduced pressure (70 °C at 0.005 mmHg) and the components isolated by chromatography on silica using ethyl acetate as the eluent.

4.15.1. Tetramethyl [2-(benzoyloxymethyl)phenyl]methane-1,1-bisphosphonate **6** [$\text{R}=\text{Me}$, $\text{R}'=\text{CH}_2\text{OC}(\text{O})\text{Ph}$]

The ylidic phosphonate **40** was isolated as its hydrolysis product the bisphosphonate **6** [$\text{R}=\text{Me}$, $\text{R}'=\text{CH}_2\text{OC}(\text{O})\text{Ph}$] as a colourless oil; δ_{H} (400 MHz, CDCl_3) 3.57 (6H, d, J_{PH} 11, POCH_3), 3.74 (6H, d, J_{PH} 11, POCH_3), 4.39 (1H, t, J_{PH} 26, 1-H), 5.41 (2H, s, CH_2), 7.34 (1H, t, J_{HH} 8, 4-H), 7.40 (1H, d, J_{HH} 8, 5-H), 7.42 (2H, t, J_{HH} 8, 3'/5'-H), 7.52 (1H, d, J_{HH} 8, 3-H), 7.55 (1H, m, 4'-H), 7.94 (1H, dd, J_{HH} 8 and 1, 6-H), 8.08 (2H, dd, J_{HH} 8 and 1, 2'/6'-H); δ_{C} (100.6 MHz, CDCl_3) 40.3 (t, J_{PC} 133, $\alpha\text{-C}$), 53.7 (m, POCH_3), 54.3 (m, POCH_3), 65.3 (CH_2), 128.3 (t, J_{PC} 3, C-5), 128.5 (C-3'/5'), 129.2 (t, J_{PC} 3, C-3), 129.4 (t, J_{PC} 8, C-1), 123.0 (C-2'/6'), 130.05 (C-1'), 131.1 (t, J_{PC} 4.5, C-6), 131.5 (t, J_{PC} 1.6, C-4), 133.3 (C-4'), 134.9 (t, J_{PC} 8, C-2), 166.5 (C=O); δ_{P} (109.3 MHz, CDCl_3) 21.7; ν_{max} (film)/ cm^{-1} 2955, 1717, 1450, 1269, 1180, 1107, 1026, 860, 833; m/z (ESI) 465.0831 ($\text{M}+\text{Na}^+$, $\text{C}_{19}\text{H}_{24}\text{NaO}_8\text{P}_2$ requires 465.0844).

4.15.2. Dimethyl [1-(dimethoxyphosphoryloxy)-1-[2-(benzoyloxymethyl)phenyl]methyl]phosphonate **27** [$\text{R}=\text{CH}_2\text{OC}(\text{O})\text{Ph}$]

This component was isolated as a pale yellow viscous oil using ethyl acetate as the eluent; δ_{H} (400 MHz, CDCl_3) 3.5 (3H, d, J_{PH} 11.3, POCH_3), 3.59 (3H, d, J_{PH} 10.6, POCH_3), 3.68 (3H, d, J_{PH} 11.3, POCH_3), 3.76 (3H, d, J_{PH} 10.6, POCH_3), 5.58 (2H, d, J_{PH} 3, CH_2), 6.05 (1H, dd, J_{PH} 14 and

10, $\alpha\text{-CH}$), 7.38–7.46 (4H, m, 3'/5'-H, 4-H and 5-H), 7.54–7.58 (2H, m, 5-H and 6-H), 7.79 (1H, td, J_{HH} 2 and 8, 3-H), 8.12 (2H, dd, J_{HH} 1 and 8, 2'/6'-H); δ_{C} (100.6 MHz, CDCl_3) 54.1 (d, J_{PC} 7, POCH_3), 54.3 (d, J_{PC} 7, POCH_3), 54.5 (d, J_{PC} 6, POCH_3), 54.7 (d, J_{PC} 6, POCH_3), 64.4 (CH_2), 70.8 (dd, J_{PC} 6, 145 Hz, $\alpha\text{-C}$), 128.5 ($\times 2$) (C-3'/5'), 129.07 (C-4'), 129.1 (C-6), 129.6 (d, J_{PC} 2, C-5), 130.04 ($\times 2$) (C-2'/6'), 130.12 (C-1'), 130.5 (d, J_{PC} 2, C-3), 132.7 (C-1), 133.3 (C-4'), 134.5 (d, J_{PC} 7, C-2), 166.4 (C=O); δ_{P} (109.3 MHz, CDCl_3) 2.0 [d, J_{PP} 35, $\text{OP}(\text{O})(\text{OMe})_2$] and 19.7 [d, J_{PP} 35, $\text{P}(\text{O})(\text{OMe})_2$]; ν_{max} (film)/ cm^{-1} 2958, 2855, 1719, 1492, 1452, 1377, 1315, 1270, 1182, 1110, 1029, 950; m/z (ESI) 481.0785 ($\text{M}+\text{Na}^+$, $\text{C}_{19}\text{H}_{24}\text{NaO}_9\text{P}_2$ requires 481.0793).

4.15.3. Dimethyl 2-(benzoyloxymethyl)benzylphosphonate

When aqueous methanol (70%) was added to the reaction mixture prior to the chromatographic separation a further compound, dimethyl 2-(benzoyloxymethyl)benzylphosphonate, was formed from the hydrolysis²⁰ of the ylidic phosphonate **4** [$\text{R}=\text{Me}$, $\text{R}'=\text{CH}_2\text{OC}(\text{O})\text{Ph}$]. Dimethyl 2-(benzoyloxymethyl)benzylphosphonate was purified by chromatography on silica using a mixture of ethyl acetate and methanol (90:10) as the eluent and isolated as pale yellow oil; δ_{H} (CDCl_3 , 400 MHz) 3.38 (2H, d, J_{PH} 22, PCH_2), 3.66 (6H, d, J_{PH} 11, POCH_3), 5.49 (2H, s, CH_2), 7.29–7.35 (2H, m, 4-H and 5-H), 7.37 (1H, dt, J_{HH} 7 and 1, 6-H), 7.44 (2H, t, J_{HH} 8, 3'/5'-H), 7.49 (1H, d, J_{HH} 7, 3-H), 7.56 (1H, tt, J_{HH} 8 and 1, 4'-H), 8.06 (2H, dd, J_{HH} 8 and 1, 2'/6'-H); δ_{C} (CDCl_3 , 100.6 MHz) 30.0 (d, J_{PC} 139, PCH_2), 53.2 ($\times 2$) (d, J_{PC} 6, POCH_3), 64.9 (CH_2), 127.7 (d, J_{PC} 4, C-4), 128.6 ($\times 2$) (C-3'/5'), 128.9 (d, J_{PC} 3, C-3), 129.9 ($\times 2$) (C-2'/6'), 130.2 (C-1'), 130.5 (d, J_{PC} 3, C-5), 130.6 (d, J_{PC} 9, C-1), 131.4 (d, J_{PC} 5, C-6), 133.3 (C-4'), 135.0 (d, J_{PC} 7, C-2), 166.5 (C=O); δ_{P} (CDCl_3 , 109.3 MHz) 29.3; ν_{max} (film)/ cm^{-1} 2955, 1720, 1450, 1273, 1180, 1111, 1035, 1026; m/z (ESI) 357.0862 ($\text{M}+\text{Na}^+$, $\text{C}_{17}\text{H}_{19}\text{NaO}_5\text{P}$ requires 357.0862).

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10. Attempts to prepare the benzoylphosphonates **1** [$R=Me$, $R'=CH_2C(O)Ph$] were unsuccessful, efforts to prepare its precursor, 2-(2-oxo-2-phenylethyl)benzoyl chloride, from the corresponding carboxylic acid led to the formation of 3-phenyl-4a,8a-dihydroisochromen-1-one which is unreactive towards trimethyl phosphite.
11. The anionic intermediate **21a** can also become protonated if a proton donor, e.g., moisture, is present, leading to the formation of the phosphate-phosphonate **27** [$R'=OC(O)Ph$]; δ_P (CDCl₃) 1.9 [d, J_{PP} 32, $OP(O)(OMe)_2$] and 19.1 [d, J_{PP} 32, $P(O)(OMe)_2$]. Small quantities of this type of component are therefore invariably present following the reaction of the benzoylphosphonates **1** with trimethyl phosphite.
12. Although the overall conversion of **20a** into **21a** can be represented by the mechanistic arrows shown, these are 'dashed' to indicate that this is likely to be an oversimplification of the process involved.
13. The observed elimination of phosphonate from **30** is likely to be facilitated by the formation of a fully conjugated system.
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