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PAPER

A novel approach to isoindolo[2,1-*a*]indol-6-ones†

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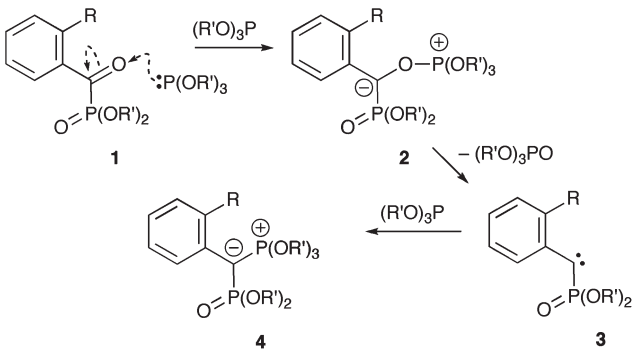
A convenient route to isoindolo[2,1-*a*]indol-6-ones has been developed starting from the appropriate 2-(*N*-phthaloyl)benzoic acids. Formation of the acid chlorides with thionyl chloride followed by heating with triethyl phosphite in a suitable solvent resulted in a multistep reaction giving tetracyclic β-ketophosphonates that on reduction with sodium borohydride gave the required indolones in good overall yields. Analogous β-ketophosphonates were also prepared starting with *N*,*N*-(1,8-naphthaloyl)-2-aminobenzoic acid and 2-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)benzoic acids although of these only the naphthaloyl product could be reduced with sodium borohydride without cleaving the amide bond in the ring system.

Introduction

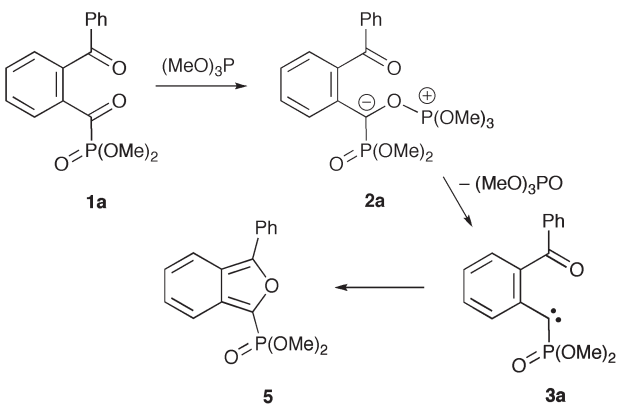
We have previously shown that trialkyl phosphites react with benzoylphosphonates **1** to initially give the anionic intermediates **2** which, in the absence of electrophiles, undergo α(C–O) bond cleavage to give reactive carbene intermediates **3** (Scheme 1).[1] For the unsubstituted benzoylphosphonate **1** (R = H) the carbene intermediate then reacts intermolecularly with the trialkyl phosphite in the reaction mixture to give an ylidic phosphonate **4** (R = H).

However, if a suitable *ortho* substituent is present on the phenyl ring an intramolecular trapping reaction may occur involving the substituent, either *via* the initially formed anionic centre in **2** or the subsequently formed carbene centre in **3**. Both these alternative pathways have been observed in the case of *ortho*-substituted benzoylphosphonates **1** where the substituent contains a carbonyl group.

Thus, for example, in the case of the 2-benzoylbenzoylphosphonate system **1a** (R = PhCO, R′ = Me) the carbonyl group cannot adopt a position that facilitates its attack by the anionic centre in **2a**. As a consequence the carbene intermediate **3a** forms which then inserts into the carbonyl group to give the isobenzofuran system **5** (Scheme 2).[3]



Scheme 1[2]



Scheme 2

In contrast, with the 2-benzoyloxybenzoylphosphonate system **1b** (R = $PhCO_2$, R′ = Me) the carbonyl group is accessible to the anionic centre in **2b** leading to the initial formation of the dioxaphospholane **6** (Scheme 3).[4]

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†Electronic supplementary information (ESI) available: A. Preparation, isolation and characterisation information for benzoic acids **13a–d**, **24**, **31a** and **31c**, and benzoyl chlorides **14a–d**, **25**, **32a**, **32c** and **41**. B. X-ray crystallographic data for **15a**, **28**, **35c** and **37c**. C. Selected NMR spectra for **13a,b**, **15a–d**, **16a**, **20a–d**, **23a–d**, **26–29**, **35a,c**, **38c**, **40**, **44**, **50** and **52**. CCDC 865150 (**15a**), 865151 (**28**), 865152 (**35c**) and 865153 (**37c**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25314c

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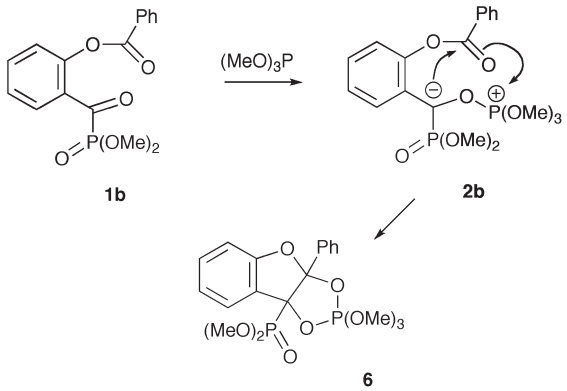
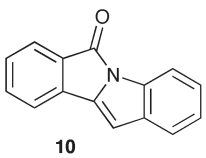


Scheme 3

This particular cyclisation is of interest since the resulting dioxaphospholane **6** then undergoes further reaction, the outcome of which depends on whether excess trialkyl phosphite is still present. In the presence of trialkyl phosphite the reaction is faster leading to the formation of the benzofuran **7** by a pathway thought to be that shown in Scheme 4.[4]

However, in the absence of excess phosphite, the dioxaphospholane **6** undergoes a novel rearrangement in which trimethyl phosphate is lost and the phosphonate group migrates to give the β-ketophosphonate **8**.[4] Moreover, the subsequent reduction of this β-ketophosphonate with sodium borohydride led smoothly to 2-phenylbenzofuran **9** in good yields (Scheme 5).

We have recently been investigating whether we could exploit these interesting pathways to provide routes to some synthetically useful products. As part of these studies we have developed a novel, convenient route to the isoindolo[2,1-*a*]indol-6-one ring system **10**. Compounds of this type have attracted interest because of their biomedical applications. Their anticancer activity[5] and ability to bind to the nNK1 receptor[6] have been investigated, as has their use as high affinity ligands for the melatonin MT3 binding site.[7] They can also be used as synthetic precursors for other bioactive molecules.[8] It would therefore be useful to develop a convenient route to such systems that would offer the flexibility of introducing substituents at a wide range of positions on the ring system.



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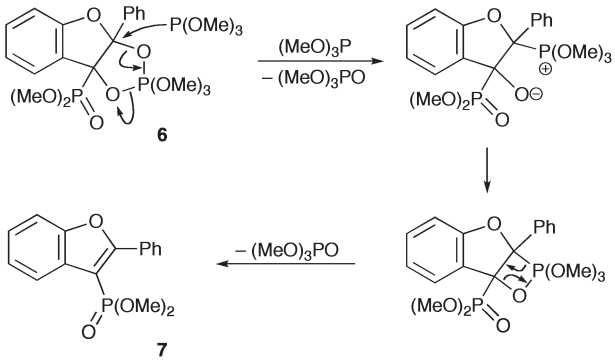
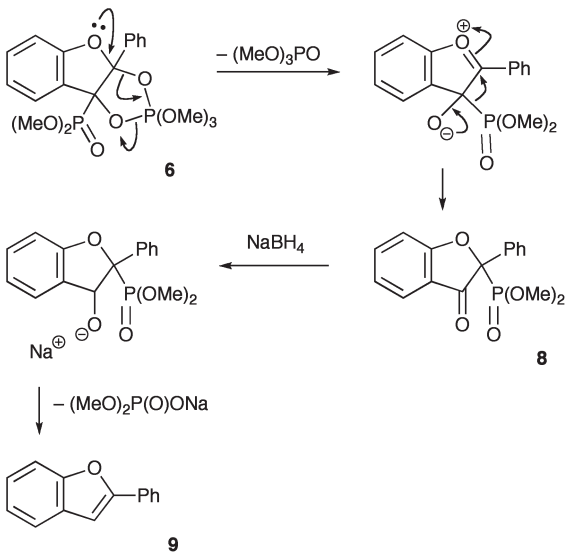
Results and discussion

Syntheses based on the 2-(phthalimido)benzoic acids 13a–d

Our strategy for the preparation of the isoindolo[2,1-*a*]indol-6-one involved the initial preparation of the 2-(*N*-phthaloyl) benzoic acids **13a–d** from the reaction of the appropriate 2-aminobenzoic acids **12** and phthalic anhydrides **11** (Scheme 6), which generally proceeded in good yield. The resulting acids were then converted into the corresponding acid chlorides **14a–d**



Scheme 4



Scheme 5

in essentially quantitative yield by the action of thionyl chloride and then onto the corresponding β-ketophosphonates **15a–d** by their reaction with triethyl phosphite in effectively a one pot reaction (Scheme 6).

The reaction pathway by which the acid chlorides **14** are converted to the corresponding β-ketophosphonates **15** by the action of triethyl phosphite was determined for the parent system **15a** by monitoring the various steps in the pathway using NMR and is shown in Scheme 7. This showed that the reaction of the acid chloride **14a** with triethyl phosphite initially proceeded cleanly to give the corresponding aroylphosphonate **16a** which exhibited a characteristic ^{31}P NMR resonance around δ_P −2 ppm and a large low-field doublet in the ^{13}C NMR spectrum (δ_C 200 ppm, J_{PC} 178.5 Hz) for the α-carbonyl resonance. Although this material could be isolated in an analytically pure state by column chromatography on silica and fully characterized, significant losses occurred during this process due to decomposition on the column. For this reason, it was generally found preferable to prepare the aroylphosphonates **16a–d** *in situ* and to react them further with triethyl phosphite without attempting to isolate them.

The outcome of the reaction of the aroylphosphonate **16a** with further triethyl phosphite was found to depend on the conditions

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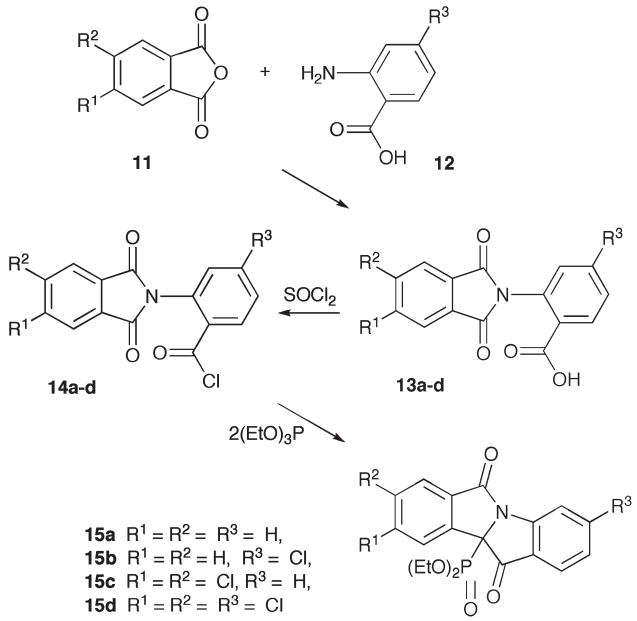
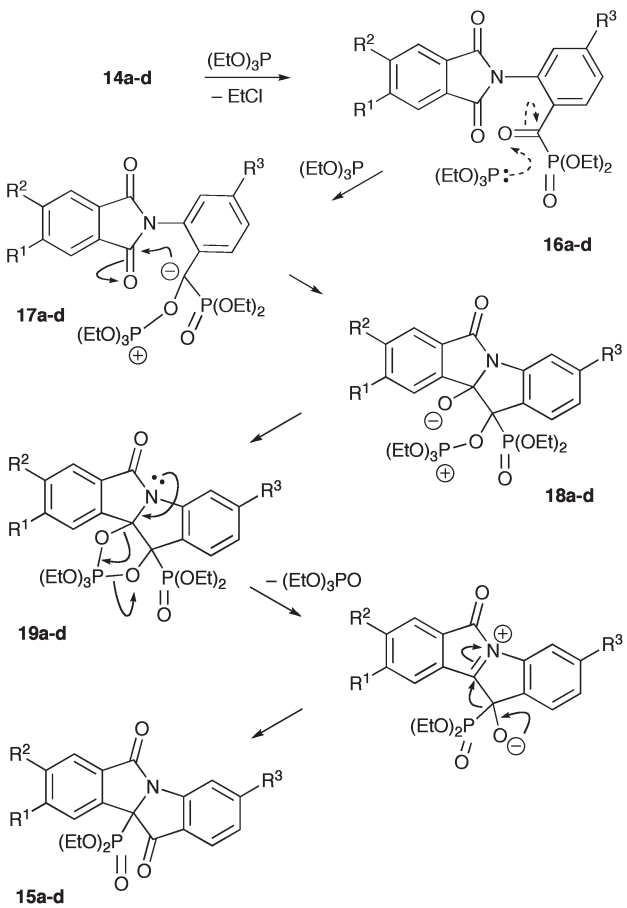


Scheme 6



Scheme 7[2]

used. If the reaction was carried out at room temperature the dioxaphospholane **19a** formed giving a characteristically high field doublet in the ^{31}P NMR spectrum at δ_P −51.8 ppm for the

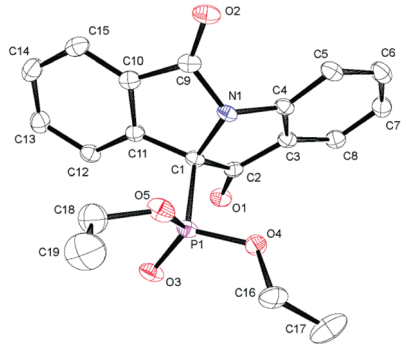
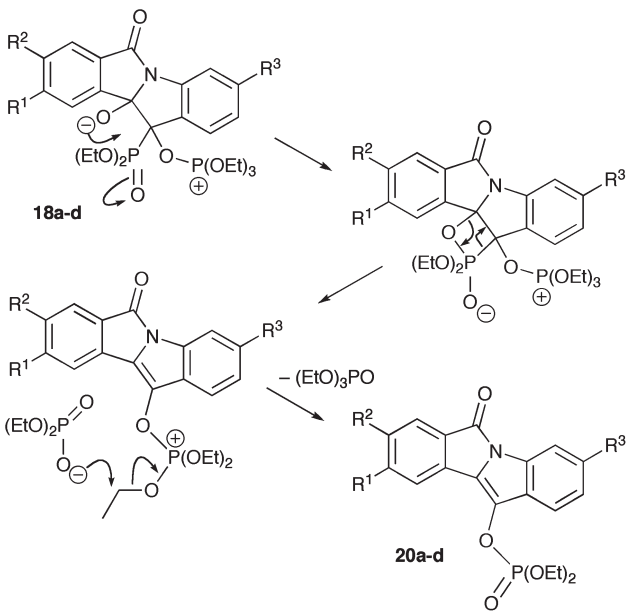


Fig. 1 X-ray crystal structure of the β-ketophosphonate **15a**.[9]



Scheme 8

5-coordinated ring phosphorus atom with coupling (J_{PP} 51.5 Hz) to the phosphonate group at δ_P 15.0 ppm. However, if the aroylphosphonate **16a** was heated with triethyl phosphite in toluene the reaction proceeded smoothly to give the β-ketophosphonates **15a** in excellent yield (*ca.* 95% by NMR). The X-ray crystal structure of **15a** is shown in Fig. 1.

This formation of **15a** from **19a** (Scheme 7) is analogous to the decomposition of the dioxaphospholane **6** previously discussed (Scheme 5) with both processes involving loss of phosphate, migration of the phosphonate group and formation of a β-ketophosphonate. However, it is interesting to note that while the decomposition of **6** to give **8** only occurred in the absence of trimethyl phosphite, the formation of **15a** occurred even in the presence of triethyl phosphite. An analogous decomposition pathway to that shown in Scheme 4 was not observed in the case of the dioxaphospholane **19a**.

The formation of the β-ketophosphonate **15a** was also observed when the reaction of the aroylphosphonate **16a** with triethyl phosphite was carried out in boiling DCM although with this solvent an additional product, the phosphate **20a** was also formed (**15a** : **20a** = 80 : 15). This phosphate can be seen to arise

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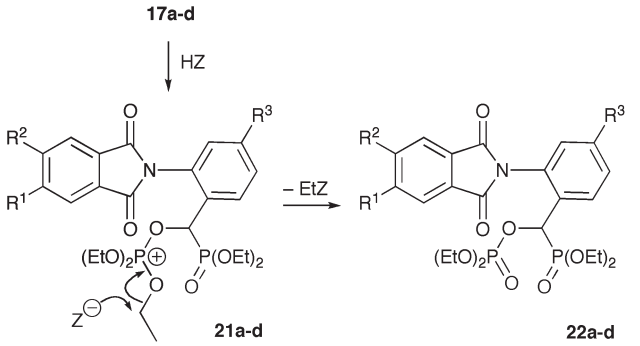


Scheme 9

Table 1 Effect of reaction solvent on product ratio when the acid chlorides **14a–d** react with excess triethyl phosphite

Acid chloride	With toluene as the reaction solvent	With DCM as the reaction solvent
14a	**15a** (96%), **20a** (1.5%), **22a** (2.5%)[a]	**15a** (80%), **20a** (15%), **22a** (5%)[a]
14b	**15b** (92%), **20b** (2.5%), **22b** (5.5%)[a]	**15b** (45%), **20b** (39%), **22b** (16%)[a]
14c	**15c** (85%), **20c** (<1%), **22c** (~14%)[a]	**15c** (78%), **20c** (11%), **22c** (11%)[a]
14d	**15d** (93%), **20d** (~1%), **22d** (6%)[a]	**15d** (86%), **20d** (10%), **22d** (4%)[a]

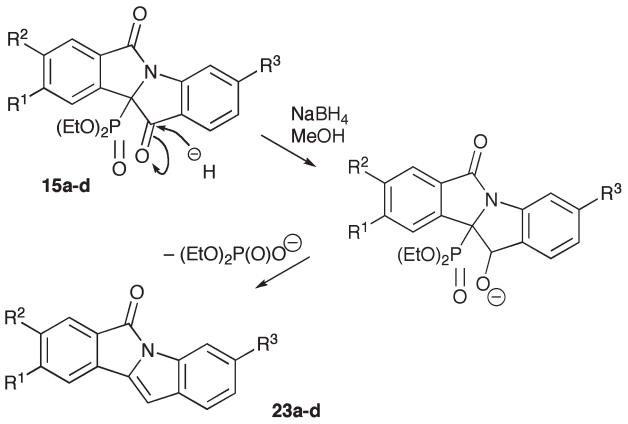
[a] No **22a–d** could form if further steps were taken to rigorously exclude proton donors from the reaction mixture.

via an alternative decomposition pathway for the intermediate **18a** (Scheme 8).

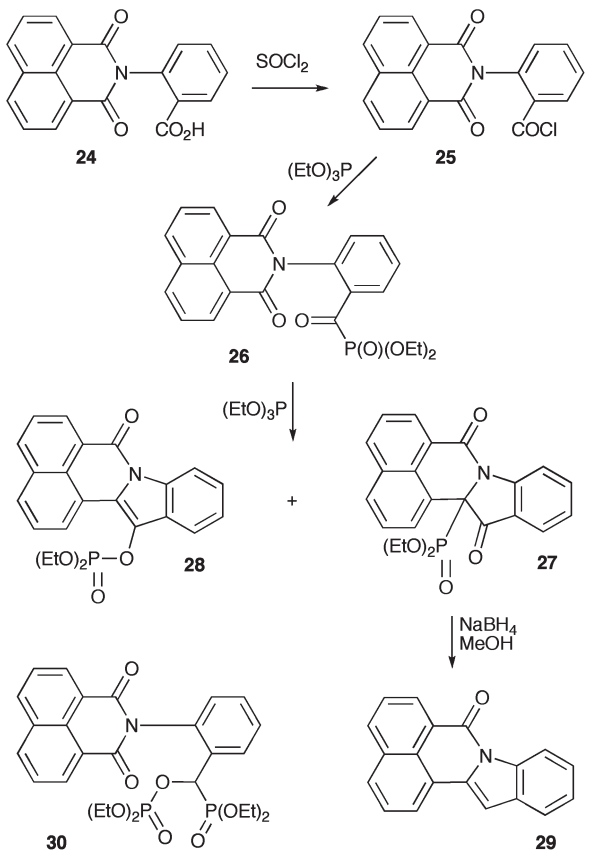
As anticipated, small quantities of the phosphate–phosphonate **22a** were also seen in those reactions where there was either ingress of moisture or incomplete formation of the acid chloride **14a** from the acid **13a** prior to addition of the triethyl phosphite. The presence of a proton donor in the reaction mixture results in protonation of the initially formed intermediate **17a**, and subsequent dealkylation of the resulting quasiphosphonium salt **21a** gives the observed phosphate–phosphonate **22a** (Scheme 9).

The reactions of the substituted acid chlorides **14b–d** with triethyl phosphite were also investigated to demonstrate that this approach could be also be used to prepare the tetracyclic phosphonates **15b–d** in which the ring system contains substituents on either or both of the phenyl rings. As with the parent system **14a**, these reactions too proceeded cleanly in boiling toluene to give the required β-ketophosphonates **15b–d** in good yields. They also led to the formation of some of the phosphates **20b–d** with DCM as the reaction solvent (Table 1).

The conversion of the β-ketophosphonates **15a–d** to the corresponding isoindolo[2,1-*a*]indol-6-ones **23a–d** was then investigated using sodium borohydride as previously used for the conversion of the β-ketophosphonates **8** to the benzofuran **9** (Scheme 5). These reactions (Scheme 10) proceeded cleanly to give the desired isoindolo[2,1-*a*]indol-6-ones **23a–d** which usually precipitated from the reaction mixture in good yield.



Scheme 10



Scheme 11

Syntheses based on *N*,*N*-(1,8-naphthaloyl)-2-aminobenzoic acid 24

We have also shown that further variations in the structure of the final polycyclic ring system are possible using modifications of this same basic approach. So, for example, the benzoylphosphonate **26** (Scheme 11) reacted with triethyl phosphite in boiling toluene to give largely the corresponding β-ketophosphonate **27** which on reduction with sodium borohydride gave the pentacyclic system **29** in good yield (75%).

However, this system once again illustrated the impact of changing the reaction solvent and temperature. Thus, while the

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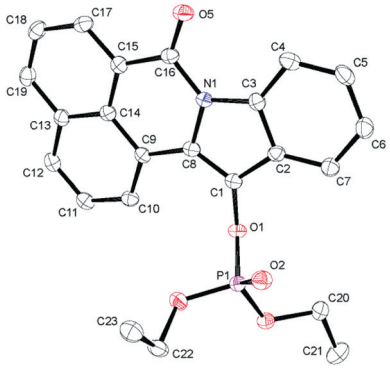
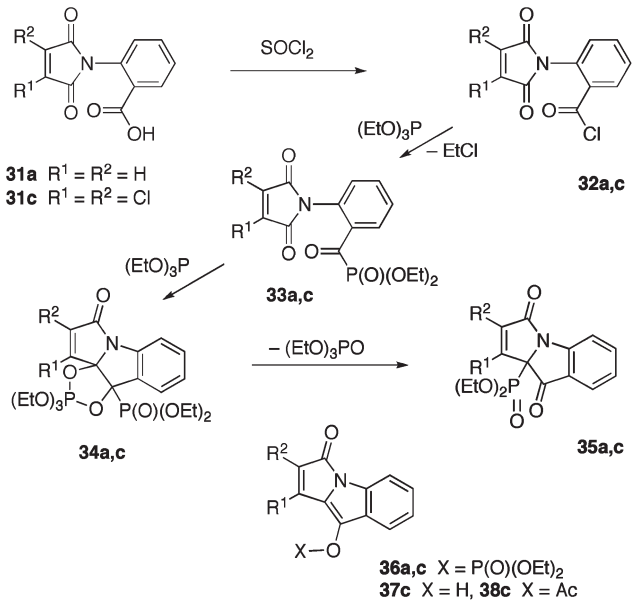


Fig. 2 X-ray crystal structure of the enolphosphate **28**.[9]



Scheme 12

reaction of the benzoylphosphonate **26** with triethyl phosphite in boiling toluene gave mainly the β-ketophosphonate **27** and only a little of the enolphosphate **28** (see X-ray structure in Fig. 2) [**27** : **28** = 92 : 8] this product ratio changed to 52 : 48 when the reaction was carried out in DCM at room temperature. As usual in these types of reaction, some of the corresponding phosphate–phosphonate **30** was also formed due to the incomplete exclusion of proton donors, such as moisture, from the reaction mixture.

Syntheses based on 2-(*N*-maleimido)benzoic acids 31a and 31c

The possible use of the maleimido-substituted benzoic acids **31a** and **31c** (Scheme 12) as the starting materials for the preparation of the analogous β-ketophosphonate **35a** and **35c** was also investigated.

With the dichloro-substituted system **31c** the synthesis of **35c** proceeded satisfactorily. Thus, when the initially formed acid chloride **32c** was heated with two molar equivalents of triethyl phosphite in either DCM or toluene under reflux, the reaction proceeded cleanly to give the β-ketophosphonate **35c** as the

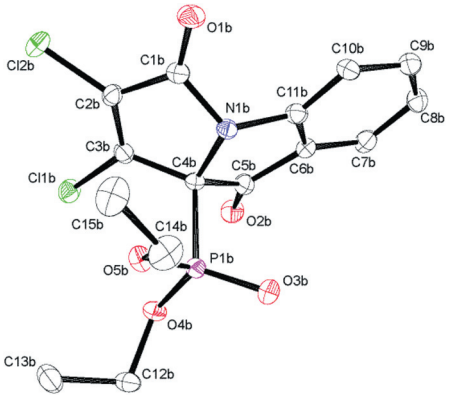
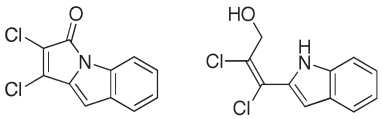


Fig. 3 X-ray crystal structure of one of the two arrangements adopted by the β-ketophosphonate **35c** in the solid state.[9,10]

dominant product (Scheme 12). Moreover, as expected, when excess triethyl phosphite was added to a cooled solution of the acid chloride **32c**, the formation of the intermediate dioxaphospholane **34c** was observed. This dioxaphospholane subsequently decomposed at room temperature over a period of time with the loss of triethyl phosphate to give the β-ketophosphonate **35c**. The X-ray crystal structure of one of the two[10] arrangements adopted by the β-ketophosphonate **35c** in the solid phase is shown in Fig. 3. Unsurprisingly, this ring structure is very similar to that of the corresponding portion of the β-ketophosphonate structure displayed for **15a** in Fig. 1.[10]

A number of additional compounds were also formed during this extended period of reaction most of which are thought to arise from reaction of the chlorinated ring with the excess triethyl phosphite present in the reaction mixture. We have previously observed that chlorinated maleimide type-systems will undergo reaction with trialkyl phosphites under appropriate conditions.[11] A small quantity of the hydroxy compound **37c** was also isolated from this reaction mixture and converted into the corresponding acetylated derivative **38c** for characterisation purposes. The presence of the enol group in **37c** was confirmed by its X-ray crystal structure (Fig. 4), which shows the enol C(5)–O(2) bond length (1.325 Å) to be significantly longer than that of the carbonyl C(1)–O(1) double bond (1.231 Å) and the C(5)–C(4) bond length (1.358 Å) of comparable length to the C(3)–C(2) carbon–carbon double bond (1.349 Å).[10] It seems likely that this compound arises from hydrolysis of an initially formed enolphosphate **36c** during its isolation by column chromatography. Such an enolphosphate could form by a pathway analogous to that used to explain the formation of the enolphosphates **20a–d** (Scheme 8) although it is interesting to note that none of the intact enolphosphate **36c** was isolated from the reaction mixture.

An attempt to reduce the β-ketophosphonate **35c** with sodium borohydride to give **39** was unsuccessful since reduction of the amide bond also occurred to give the ring-opened system **40**.



39 **40**

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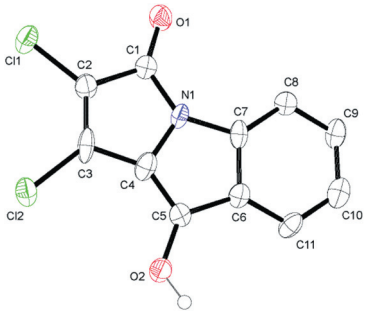
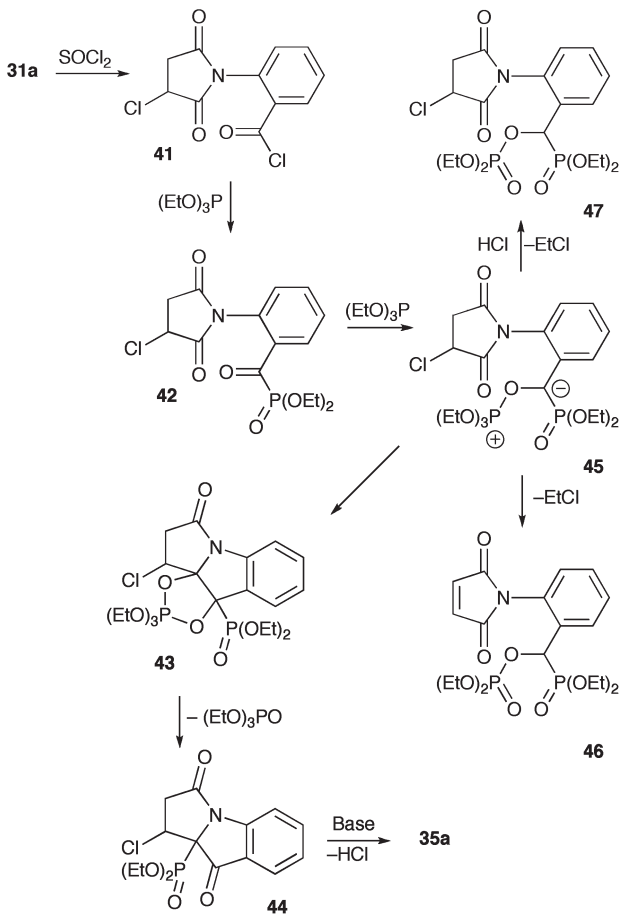
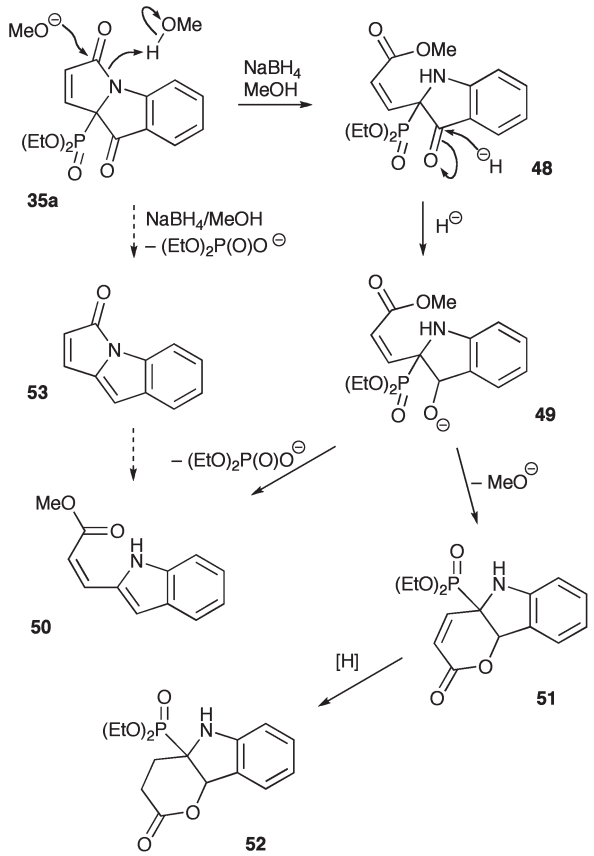


Fig. 4 X-ray crystal structure of the hydroxy compound **37c**.[9]



Scheme 13

With the corresponding non-chlorinated acid **31a** further complications arose. In particular, attempts to prepare the acid chloride **32a** using oxalyl chloride led also to the formation of the chlorinated ring system **41**. These two systems proved difficult to separate and so a preliminary investigation of the reaction of triethyl phosphite with this mixture was carried out using NMR to monitor the progress of the reaction. This showed the formation of intermediates that were consistent with the reaction pathways shown in Schemes 12 and 13. Thus resonances characteristic of the dioxaphospholanes **34a** and **43** were initially observed which were then replaced by signals for triethyl phosphate and β-ketophosphonates **35a** and **44**. Samples of both



Scheme 14

these β-ketophosphonates were isolated by chromatography although it is interesting to note that the quantity of the unsaturated β-ketophosphonate **35a** isolated exceeded the quantity of the unsaturated acid chloride **32a** initially present in the reaction mixture. This clearly indicated that some of the unsaturated β-ketophosphonate **35a** was being derived from the chlorinated acid chloride **41**. The formation of some of the phosphate–phosphonates **46** and **47** during the reaction suggests that the anionic intermediate **45** may be the base causing this elimination of HCl. We were also able to show that a further quantity of the β-ketophosphonate **35a** could be obtained from the β-ketophosphonate **44** we had isolated by the action of a base such as triethylamine.

Interestingly, reduction of the β-ketophosphonate **35a** with sodium borohydride in methanol gave the indolylacrylate **50** and the lactone **52** (Scheme 14) rather than formation of the expected ring system **53**. While the formation of the acrylate **50** might be viewed as the product arising from the methanolysis of the amide bond in **53** we isolated none of this latter compound from the reaction mixture. An alternative pathway that would account for the formation of both **50** and **52** is shown in Scheme 14 and involves cleavage of the amide bond in the β-ketophosphonate **35a** prior to reduction of the 'keto' group. Reduction of the 'keto' group in the resulting methyl ester **48** then gives the intermediate **49** which can then either lose phosphate to give the acrylate **50** or lose methoxide to give the lactone **51** which clearly then undergoes further reduction to give the observed product **52**. An analogous reduction of an α,β-unsaturated

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δ-lactone with sodium borohydride in the presence of triethylamine has been previously reported.[12]

Conclusions

We have developed a simple and convenient procedure for the preparation of a range of substituted isoindolo[2,1-*a*]indol-6-ones **23** and related compounds from readily prepared 2-(phthalimido)benzoic acids **13**. Reaction of the corresponding benzoyl chlorides **14** with trialkyl phosphites in boiling toluene (we found triethyl phosphite to be the most convenient) proceeds cleanly to give the β-ketophosphonates **15**, the immediate precursors of the required heterocyclic systems, in good yield (typically >80%). This reaction was shown to proceed *via* a multistep reaction pathway (see Scheme 7) involving initial formation of the benzoylphosphonates **16** which then react further with the phosphite to give the 1,3,2-dioxaphospholanes **19**. These dioxaphospholanes then decompose under the reaction conditions with loss of trialkyl phosphate and migration of a phosphonate group to give the required β-ketophosphonates **15**. Analogous reactions occur with some other 2-'imido'-benzoic acids (see Schemes 11–13).

It is worth noting that the choice of reaction solvent in the reactions of the acid chlorides **14** with triethyl phosphite is important since if they are carried out in DCM rather than toluene an alternative reaction pathway giving the enolphosphates **20** (see Scheme 8) becomes significant (see Table 1).

Subsequent reaction of the β-ketophosphonates **15** with sodium borohydride results in reduction of the 'keto' group and loss of diethyl phosphate (Scheme 10), usually resulting in the precipitation of the required isoindolo[2,1-*a*]indol-6-ones **23** in good yields (typically *ca.* 70%) and requiring minimal further purification. A similar reduction/elimination reaction occurs with the β-ketophosphonate **27** derived from *N*,*N*-(1,8-naphthaloyl)-2-aminobenzoic acid **24**, but with the β-ketophosphonate **35a** and **35c** from 2-(*N*-maleimido)benzoic acids **31a** and **31c** the reduction products showed additional cleavage of the amide bond.

Experimental

General details[10]

NMR (^{1}H, ^{13}C, ^{31}P, COSY and HSQC correlated) spectra were recorded on JEOL EX-270 and Bruker AMX400, AV400 and AV600 spectrometers. ^{1}H NMR spectra in $CDCl_3$ are referenced to TMS and those in d_6-DMSO to the residual CD_2H signal at δ_H 2.50 ppm unless otherwise indicated. ^{13}C NMR spectra are referenced to the solvent resonance, *i.e.* $CDCl_3$ at δ_C 77.23 ppm or d_6-DMSO at δ_C 39.51 ppm unless otherwise indicated. *J* values are given in Hz. '*J*' indicates an apparent coupling constant in a second order spin system or in a resonance showing substantial line broadening, q indicates an unassigned quaternary carbon resonance.

Details of the preparation and characterisation of the acids **13a–d**, **24**, **31a** and **31c** and the acid chlorides **14a–d**, **25**, **32a**, **32c** and **41** are provided in the ESI.†

All reactions involving the acid chlorides **14**, **25** and **32** and benzoylphosphonates **16**, **26** and **33** should be carried out with the rigorous exclusion of moisture.

The reaction of the benzoyl chloride 14a with triethyl phosphite

The preparation of the benzoylphosphonate 16a. To a solution of the benzoyl chloride **14a** (570 mg, 2 mmol) in DCM (15 cm^3) was added dropwise triethyl phosphite (335 mg, 2 mmol). After stirring this solution for 15 min at room temperature volatile components were removed under reduced pressure (30 °C at 15 mmHg) and the residue analysed by ^{31}P NMR spectroscopy. This showed the major product to be the benzoylphosphonate **16a** (70%) although a quantity of the tetracyclic phosphonate **15a** (22%) and a little enolphosphate **20a** (2%) and phosphate–phosphonate **22a** (6%) were also present. A pure sample of the benzoylphosphonate **16a** (150 mg, 20%), mp 126–127 °C, isolated by column chromatography on silica gel using ethyl acetate as the eluant; δ_P(109.3 MHz, $CDCl_3$) −2.3; δ_H(270 MHz, $CDCl_3$) 1.23 (6 H, t, J_{HH} 7, Me), 4.13 (4 H, m, $POCH_2$), 7.36 (1 H, ddd, J_{HH} 7.7 and 1.5, J_{PH} 1.5, 3-H), 7.54 (1 H, td, J_{HH} 7.7 and 1.5, 5-H), 7.67 (1 H, td, J_{HH} 7.7 and 1.5, 4-H), 7.68–7.73 (2 H, m, 4′/7′-H), 7.80–7.85 (2 H, m, 5′/6′-H), 8.50 (1 H, dd, J_{HH} 7.7 and 1.5, 6-H); δ_C(67.9 MHz, $CDCl_3$) 16.3 (×2)(d, J_{PC} 5, Me), 64.3 (×2)(t, J_{PC} 7, $POCH_2$), 123.8 (×2) (C-4′/7′), 129.0 (C-5), 129.9 (d, J_{PC} 6, C-2), 130.3 (d, J_{PC} 2, C-3), 132.0 (×2)(C-3a′/7a′), 132.4 (C-6), 133.2 (d, J_{PC} 64, C-1), 134.3 (C-4), 134.4 (×2)(C-5′/6′), 167.1 (×2)(C-1′/3′), 200.0 (d, J_{PC} 179, C═O); ν_{max}/cm^{-1} (ATM) 2973, 1715, 1655, 1596, 1486, 1465, 1451, 1366, 1281, 1253, 1222, 1162, 1132, 1104, 1067, 1012, 980, 963, 925, 885, 795, 724; *m*/*z* (ESI) 387.0812 (M^+. $C_{19}H_{18}NO_6P$ requires 387.0872).

Reaction of the benzoylphosphonate 16a with further triethyl phosphite

1. In DCM at room temperature. Triethyl phosphite (600 mg, 3.6 mmol) was added in one portion to a solution of the benzoylphosphonate **16a** (150 mg, 0.39 mmol) in dry dichloromethane (2 cm^3) and the mixture stirred at room temperature and monitored by ^{31}P NMR to optimise formation of the initially formed dioxaphospholane **19a**. Volatile components were then removed *in vacuo* (20 °C at 0.01 mmHg) to leave a viscous yellow oil which was shown to contain >80% of the dioxaphospholane **19a** together with a little triethyl phosphate. NMR analysis was carried out on this product since attempts to remove the remaining triethyl phosphate *in vacuo*, by increasing the temperature, caused some decomposition of the dioxaphospholane. The diethyl (2,2,2-triethoxy-9-oxo-3a*H*,9*H*-2λ^5-[1,3,2]dioxaphospholo[4,5-*b*]isoindolo[2,1-*a*]indol-3a-yl)phosphonate **19a** gave δ_P(109.3 MHz, $CDCl_3$) −51.8 [d, J_{PP} 51.5, $P(OEt)_3$], 15.0 [d, J_{PP} 51.5, $P(O)(OEt)_2$]; δ_H(270 MHz, $CDCl_3$)[13] 7.11 (1 H, t, J_{HH} 7.5, 2-H), 7.37 (1 H, t, J_{HH} 7.5, 8-H), 7.44 (1 H, t, J_{HH} 7.5, 3-H), 7.49–7.55 (1 H, m, 1-H), 7.57 (1 H, d, J_{HH} 7.5, 4-H), 7.69 (1 H, d, J_{HH} 7.5, 10-H), 7.73 (1 H, d, J_{HH} 7.5, 7-H), 7.76–7.9 (1 H, m, 9-H); δ_C(67.9 MHz, $CDCl_3$)[13] 81.0 (dd, J_{PC} 187 and 5, C-12), 98.7 (t, J_{PC} 7.5, C-11), 117.1 (C-7), 123.4 (C-9), 125.1 (CH), 126.6 (CH), 127.4 (CH), 129.4 (C-6a), 130.3

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(CH), 130.9 (CH), 132.6 (CH), 133.8 (d, J_{PC} 4, C-12a), 139.4 (d, J_{PC} 7, C-4a), 143.6 (C-10a), 167.4 (C-6).

2. In DCM with heating. Triethyl phosphite (2.3 g, 13.8 mmol) was added dropwise to a stirred solution of the benzoyl chloride **14a** (1.6 g, 5.6 mmol) in dry DCM (15 cm^3) at room temperature to generate the benzoylphosphonate **16a** *in situ*. The solution was then heated at 40 °C for 20 h, cooled and volatile components removed under reduced pressure (70 °C at 0.015 mmHg) to leave a yellow oil which solidified on standing. This solid was triturated with a hexane–DCM (98 : 2) mixture and then dried. ^{31}P NMR analysis showed the resulting solid to consist largely of a phosphonate component **15a** (δ_P 12.6 ppm)(*ca.* 80%), a phosphate **20a** (δ_P −4.4 ppm)(*ca.* 15%) and a small quantity of the phosphate–phosphonate **22a** (δ_P = −1.0 [d, J_{PP} 28, $P(OEt)_3$], 16.8 [d, J_{PP} 28, $P(O)(OEt)_2$]) The major components were isolated by chromatography on silica gel eluting with DCM–EtOAc mixtures.

Diethyl 6-oxo-6H-isoindolo[2,1-a]indol-11-yl phosphate **20a** (100 mg, 9%) [r_f = 0.6 DCM–EtOAc (9 : 1)] was isolated as yellow needle shaped crystals, mp 142–143 °C, following its crystallisation by the slow evaporation of a hexane–DCM solution; δ_P(109.3 MHz, $CDCl_3$) −4.4; δ_H(400 MHz, $CDCl_3$) 1.27 (6 H, td, J_{HH} 7, J_{PH} 1, Me), 4.11–4.26 (4 H, m, $POCH_2$), 7.08 (1 H, t, J_{HH} 7.5, 2-H), 7.21 (1 H, t, J_{HH} 8, 3-H), 7.22 (1 H, t, J_{HH} 7.5, 8-H), 7.42 (1 H, t, J_{HH} 7.5, 9-H), 7.45 (1 H, d, J_{HH} 8, 1-H), 7.64 (1 H, d, J_{HH} 7.5, 7-H), 7.70 (1 H, d, J_{HH} 7.5, 10-H), 7.77 (1 H, d, J_{HH} 8, 4-H); δ_C(100.6 MHz, $CDCl_3$) 16.3 (×2)(d, J_{PC} 6, Me), 65.5 (×2)(d, J_{PC} 7, $POCH_2$), 113.6 (C-4), 119.9 (C-1), 123.1 (C-10), 124.1 (C-2), 125.4 (C-7), 126.2 (d, J_{PC} 6, C-10b), 127.5 (C-3), 128.4 (d, J_{PC} 2, C-11a), 128.8 (C-8), 129.4 (d, J_{PC} 9, C-11), 131.9 (C-6a), 133.3 (d, J_{PC} 2, C-10a), 133.4 (C-4a), 134.0 (C-9), 162.4 (C-6); ν_{max}/cm^{-1} (ATM) 2992, 1721, 1612, 1448, 1391, 1365, 1312, 1243, 1152, 1020, 975, 914, 891, 884, 819, 748, 690; *m/z* (ESI) 371.0866 (M^+. $C_{19}H_{18}NO_5P$ requires 371.0917).

Diethyl (6,11-dioxo-6H-isoindolo[2,1-a]indol-10b(11H)-yl)-phosphonate **15a** (800 mg, 72%) [r_f = 0.4, DCM–EtOAc (9 : 1)] was isolated as a yellow solid. Crystallisation of this material by the slow evaporation of a hexane–DCM solution yielded crystals suitable for X-ray diffraction studies, mp 159–160 °C; δ_P(109.3 MHz, $CDCl_3$) 12.6; δ_H(400 MHz, $CDCl_3$) 1.06 (3 H, q, *J* 7, Me), 1.07 (3 H, q, J_{HH} 7, Me), 3.88 (1 H, ddq, J_{AB} 10.3, J_{PH} 8.7, J_{HH} 7, POCH), 4.01 (2 H, dq, J_{PH} 8.2, J_{HH} 7, POCH), 4.03 (1 H, m, POCH), 7.20 (1 H, td, J_{HH} 7.5, J_{HH} 1, 2-H), 7.49 (1 H, tdd, J_{HH} 7.5 and 1, J_{PH} 2, 8-H), 7.65 (2 H, td, J_{HH} 7.5 and 1, 3/9-H), 7.69 (1 H, ddd, J_{HH} 7.5 and 1, J_{PH} 1.5, 1-H), 7.80 (1 H, dm, J_{HH} 7.5, 7-H), 7.93 (1 H, dt, J_{HH} 7.5 and 1, 4-H), 7.99 (1 H, ddt, J_{HH} 7.5 and 1, J_{PH} 2, 10-H); δ_C(67.9 MHz, $CDCl_3$) 16.3 (×2)(d, J_{PC} 6, Me), 65.0 (d, J_{PC} 7, $POCH_2$), 65.3 (d, J_{PC} 7, $POCH_2$), 76.6 (d, J_{PC} 148, C-10b), 118.2 (C-4), 124.5 (d, J_{PC} 3, C-10), 125.3 (C-1), 125.5 (C-7), 125.6 (C-2), 129.1 (C-11a), 130.2 (C-8), 132.1 (d, J_{PC} 4, C-6a), 134.5 (d, J_{PC} 3, C-9), 137.5 (C-3), 139.4 (d, J_{PC} 5, C-10a), 152.4 (d, J_{PC} 2, C-4a), 169.5 (d, J_{PC} 2, C-6), 190.8 (C-11); ν_{max}/cm^{-1} (ATM) 2985, 1716, 1601, 1464, 1332, 1298, 1258, 1233, 1200, 1154, 1087, 1044, 1010, 969, 800, 776, 762, 740; *m/z* (ESI) 371.0963 (M^+. $C_{19}H_{18}NO_5P$ requires 371.0917).

3. In toluene with heating (*via* preparation of the benzoylphosphonate 16a *in situ*). The benzoyl chloride **14a** (5.7 g, 20 mmol) was heated with toluene (25 cm^3) at 80 °C until it dissolved and then triethyl phosphite (8.7 g, 52.4 mmol) was added over a period of about 5 min. The mixture was then heated at 100 °C for 16 h. Volatile components were removed under reduced pressure and the resulting oil then warmed *in vacuo* (75 °C at 0.01 mmHg) to give a yellow solid that was shown to be the phosphonate **15a** in a good state of purity (see Table 1). Slow evaporation of a solution of the solid in MeOH–DCM 95 : 5 gave crystals of the pure phosphonate **15a** (6.2 g, 82%).

The reaction of the benzoyl chloride 14b with excess triethyl phosphite

1. In DCM with heating. To a solution of the benzoyl chloride **14b** (1.05 g, 3.3 mmol) in dry DCM (20 cm^3) was added dropwise, over a period of 5 min, triethyl phosphite (1.3 g, 7.8 mmol). The solution was then stirred at room temperature and monitored by ^{31}P NMR. After initial formation of the benzoylphosphonate **16b** (δ_P = −3.0 ppm) further reaction occurred leading after 1 h to the formation of the dioxaphospholane **19b** (δ_P = −51.9 [d, J_{PP} 51.6, $P(OEt)_3$], 14.4 [d, J_{PP} 51.6, $P(O)(OEt)_2$]) (32.5%) together with some of the phosphate **20b** (δ_P = −4.5 ppm) (38.5%), the phosphonate **15b** (δ_P = 12.1 ppm) (13%) and the phosphate–phosphonate **22b** (δ_P = −1.2 [d, J_{PP} 28, $P(OEt)_3$], 16.0 [d, J_{PP} 28, $P(O)(OEt)_2$]) (16%). The reaction mixture was then heated under reflux for 16 h. This resulted in loss of the signals for the dioxaphospholane **19b** and the formation of a mixture containing the phosphate **20b** (39%), the phosphonate **15b** (45%) and the phosphonate phosphate (16%). Volatile components were removed under reduced pressure (75 °C at 0.01 mmHg) and samples of the two major components isolated by chromatography on silica gel eluting with DCM–EtOAc mixtures.

Diethyl 3-chloro-6-oxo-6H-isoindolo[2,1-a]indol-11-yl phosphate **20b** [r_f = 0.8 DCM–EtOAc (9 : 1)] was isolated as a yellow solid, mp 105–106 °C; δ_P(109.3 MHz, $CDCl_3$) −4.3; δ_H(400 MHz, $CDCl_3$) 1.27 (6 H, td, J_{HH} 7, J_{PH} 1, Me), 4.11–4.26 (4 H, m, $POCH_2$), 7.04 (1 H, dd, J_{HH} 8 and 2, 2-H), 7.24 (1 H, t, J_{HH} 7.5, 8-H), 7.35 (1 H, d, J_{HH} 8, 1-H), 7.44 (1 H, t, J_{HH} 7.5, 9-H), 7.64 (1 H, d, J_{HH} 7.5, 7-H), 7.66 (1 H, d, J_{HH} 7.5, 10-H), 7.75 (1 H, d, J_{HH} 2, 4-H); δ_C(100.6 MHz, $CDCl_3$) 16.3 (×2)(d, J_{PC} 6, Me), 65.6 (×2)(d, J_{PC} 7, $POCH_2$), 113.8 (C-4), 120.7 (C-1), 123.1 (C-10), 124.6 (C-2), 125.5 (C-7), 126.5 (d, J_{PC} 6, C-10b), 126.7 (d, J_{PC} 3, C-11a), 128.8 (d, J_{PC} 9, C-11), 129.0 (C-8), 132.0 (C-6a), 132.8 (C-10a), 133.0 (C-3), 133.5 (C-4a), 134.2 (C-9), 162.2 (C-6); ν_{max}/cm^{-1} (ATM) 3098, 2978, 1728, 1605, 1442, 1384, 1352, 1278, 1224, 1173, 780, 763, 755, 729, 658; *m/z* (ESI)[14] 405.0538 (M^+. $C_{19}H_{17}ClNO_5P$ requires 405.0527).

Diethyl (3-chloro-6,11-dioxo-6H-isoindolo[2,1-a]indol-10b(11H)-yl)phosphonate **15b** [r_f = 0.45 DCM–EtOAc (9 : 1)] was isolated as a yellow solid, mp 164–165 °C; δ_P(109.3 MHz, $CDCl_3$) 12.3; δ_H(400 MHz, $CDCl_3$) 1.08 (3 H, t, J_{HH} 7, Me), 1.09 (3 H, t, J_{HH} 7, Me), 3.85–3.95 (1 H, m, $POCH_2$), 3.97–4.06 (3 H, m, $POCH_2$), 7.17 (1 H, dd, J_{HH} 8 and 2, 2-H), 7.50 (1 H, t, J_{HH} 7.5, 8-H), 7.61 (1 H, d, J_{HH} 8, 1-H) 7.67 (1 H, t, J_{HH} 7.5,

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9-H), 7.80 (1 H, d, J_{HH} 7.5, 7-H), 7.93 (1 H, d, J_{HH} 2, 4-H), 7.95 (1 H, dd, J_{HH} 7.5, J_{PH} 1, 10-H); δ_C(100.6 MHz, $CDCl_3$) 16.3 (×2)(d, J_{PC} 5, Me), 65.0 (d, J_{PC} 7, $POCH_2$), 65.3 (d, J_{PC} 7, $POCH_2$), 76.8 (d, J_{PC} 146.5, C-10b), 118.5 (C-4), 124.4 (d, J_{PC} 3, C-10), 125.6 (C-7), 125.95 (C-2), 126.02 (C-1), 127.5 (C-11a), 130.2 (d, J_{PC} 2, C-8), 131.6 (d, J_{PC} 4, C-6a), 134.6 (d, J_{PC} 3, C-9), 139.2 (d, J_{PC} 6, C-10a), 143.9 (C-3), 152.8 (d, J_{PC} 3, C-4a), 169.1 (d, J_{PC} 2, C-6), 189.5 (C-11); ν_{max}/cm^{-1} (ATM) 2982, 1724, 1600, 1470, 1431, 1301, 1258, 1203, 1011, 957, 906, 833, 802, 762, 684; *m/z* (ESI)[14] 406.0600 ($M + H^+$. $C_{19}H_{18}ClNO_5P$ requires 406.0606).

2. In toluene with heating. The benzoyl chloride **14b** (4.8 g, 15 mmol) was warmed at 70 °C with toluene (25 cm^3) until it had dissolved and triethyl phosphite (5 cm^3, 30 mmol) was then added and the mixture stirred and heated at 100 °C for 6 h. The solvent was removed by evaporation and the residue warmed *in vacuo* (75 °C at 0.01 mmHg) to give a solid that was shown to be the phosphonate **15b** (92%) (Table 1). Crystallisation of this solid from MeOH–DCM 95 : 5 gave the pure phosphonate **15b** (4.0 g, 66%).

The reaction of the benzoyl chloride 14c with excess triethyl phosphite

1. In DCM with heating. Triethyl phosphite (1.6 g, 9.6 mmol) was added dropwise to a solution of the benzoyl chloride **14c** (1.06 g, 4.5 mmol) in dry DCM (15 cm^3) and the mixture warmed at 40 °C for 16 h. The solvent was then removed by evaporation and the residue warmed *in vacuo* (75 °C at 0.01 mmHg) to give a viscous yellow residue that was shown to be largely the phosphonate **15c** (78%) together with a little of the phosphate **20c** (11%). Some of the phosphate–phosphonate **22c** (δ_P = −0.8 [d, J_{PP} 28, $P(OEt)_3$], 16.6 [d, J_{PP} 28, $P(O)(OEt)_2$]) (11%) was also present. Pure samples of the phosphonate **15c** and the phosphate **20c** were isolated by chromatography on silica gel eluting with DCM–EtOAc mixtures.

Diethyl 8,9-dichloro-6-oxo-6H-isoindolo[2,1-a]indol-11-yl-phosphate **20c** (80 mg, 6%) [r_f = 0.62 DCM–EtOAc (19 : 1)] was isolated, after recrystallisation from a hexane–DCM mixture, as pale yellow crystals, mp 142–143 °C; δ_P(109.3 MHz, $CDCl_3$) −4.5; δ_H(400 MHz, $CDCl_3$) 1.29 (6 H, td, J_{HH} 7, J_{PH} 1, Me), 4.13–4.27 (4 H, m, $POCH_2$), 7.09 (1 H, t, J_{HH} 7.5, 2-H), 7.22 (1 H, t, J_{HH} 7.5, 3-H), 7.40 (1 H, d, J_{HH} 7.5, 1-H), 7.63 (1 H, s, 7-H), 7.70 (1 H, d, J_{HH} 7.5, 4-H), 7.76 (1 H, s, 10-H); δ_C(100.6 MHz, $CDCl_3$) 16.3 (×2)(d, J_{PC} 6, Me), 65.6 (×2)-(d, J_{PC} 7, $POCH_2$), 113.5 (C-4), 120.0 (C-1), 124.0 (d, J_{PC} 6, C-11), 124.6 (C-2), 124.8 (C-10), 126.9 (C-7), 127.6 (d, J_{PC} 13, C-10b), 128.1 (C-3), 130.3 (d, J_{PC} 9, C-11a), 131.9 (C-6a), 132.2 (d, J_{PC} 2, C-10a), 132.6 (C-8), 133.1 (C-9), 138.4 (C-4a), 160.1 (C-6); ν_{max}/cm^{-1} (ATM) 2975, 1742, 1612, 1456, 1438, 1387, 1347, 1310, 1278, 1243, 1231, 1163, 1152, 1053, 1024, 993, 972, 911, 830, 769, 759, 700; *m/z* (ESI)[14] 439.0133 (M^+. $C_{19}H_{16}Cl_2NO_5P$ requires 439.0143).

Diethyl (8,9-dichloro-6,11-dioxo-6H-isoindolo[2,1-a]indol-10b(11H)-yl)phosphonate **15c** (650 mg, 50%) [r_f = 0.43 DCM–EtOAc (9 : 1)] was isolated as a yellow solid, mp 122–123 °C; δ_P(109.3 MHz, $CDCl_3$) 11.8; δ_H(400 MHz, $CDCl_3$) 1.17 (3 H, t, J_{HH} 7, Me), 1.19 (3 H, t, J_{HH} 7, Me), 3.95–4.08 (1 H, m, $POCH_2$), 4.08–4.18 (3 H, m, $POCH_2$), 7.30 (1 H, t, J_{HH} 7.5, 2-H), 7.74 (1 H, t, J_{HH} 7.5, 3-H), 7.76 (1 H, d, J_{HH} 7.5, 1-H), 7.92 (1 H, s, 7-H), 7.96 (1 H, d, J_{HH} 7.5, 4-H), 8.11 (1 H, d, J_{PH} 2, 10-H); δ_C(100.6 MHz, $CDCl_3$) 16.3 (d, J_{PC} 6, Me), 16.4 (d, J_{PC} 6, Me), 65.3 (d, J_{PC} 7, $POCH_2$), 65.6 (d, J_{PC} 7, $POCH_2$), 75.8 (d, J_{PC} 145.6, C-10b), 118.3 (C-4), 125.5 (C-1), 126.0 (C-2), 126.4 (d, J_{PC} 3, C-10), 127.0 (d, J_{PC} 2, C-7), 128.9 (C-11a), 131.7 (d, J_{PC} 4, C-8), 135.4 (d, J_{PC} 3, C-9), 137.8 (C-3), 138.4 (d, J_{PC} 6, C-10a), 139.4 (C-6a), 152.0 (d, J_{PC} 2, C-4a), 167.4 (d, J_{PC} 6, C-6), 189.9 (C-11); ν_{max}/cm^{-1} (ATM) 2985, 1721, 1601, 1464, 1389, 1289, 1258, 1200, 1162, 1097, 1044, 1009, 956, 789, 762; *m/z* (ESI)[14] 439.0184 (M^+. $C_{19}H_{16}Cl_2NO_5P$ requires 439.0143).

2. In toluene with heating. The benzoyl chloride **14c** (1.06 g, 3 mmol) was warmed at 100 °C with toluene (15 cm^3) until it had dissolved and triethyl phosphite (1.1 g, 6.6 mmol) was then added dropwise over a period of about 5 min. The mixture was stirred and heated at 100 °C for 3 h and the solvent then removed by evaporation. The residue was then heated *in vacuo* (80 °C at 0.01 mmHg) to give a viscous oil that was shown to contain only two significant products, the phosphonate **15c** (*ca.* 85%) and the phosphate–phosphonate **22c** (*ca.* 14%), there was no evidence for the formation of the phosphate **20c**. A quantity of the pure phosphonate **15c** (650 mg, 50%) was obtained by chromatography on silica gel eluting with DCM–EtOAc mixtures.

The reaction of the benzoyl chloride 14d with excess triethyl phosphite

1. In DCM with heating. Triethyl phosphite (1.1 g, 6.6 mmol) was added dropwise to a solution of the benzoyl chloride **14d** (1.25 g, 3.2 mmol) in dry DCM (15 cm^3) and the mixture heated under reflux for 24 h. Volatile components were then removed under reduced pressure to give a yellow oil. Analysis of this residue by NMR spectroscopy indicated that the major product was the tetracyclic phosphonate **15d** (δ_P 11.4 ppm) (75%) although a little of the enolphosphate **20d** (δ_P −4.4 ppm) (8%) was also present together with some of the initially formed benzoylphosphonate **16d** (δ_P −2.7 ppm)(15%). Pure samples of **15d** and **20d** were isolated by chromatography on silica gel eluting with DCM–EtOAc mixtures.

Diethyl 3,8,9-trichloro-6-oxo-6H-isoindolo[2,1-a]indol-11-yl-phosphate **20d** [r_f = 0.75 DCM–EtOAc (19 : 1)] was isolated, after recrystallisation from a hexane–DCM (95 : 5) mixture, as yellow crystals, mp 191–192 °C; δ_P(109.3 MHz, $CDCl_3$) −4.4; δ_H(400 MHz, $CDCl_3$) 1.39 (6 H, td, J_{HH} 7, J_{PH} 1, Me), 4.15–4.17 (4 H, m, $POCH_2$), 7.20 (1 H, dd, J_{HH} 8 and 1.5, 2-H), 7.47 (1 H, d, J_{HH} 8, 1-H), 7.82 (1 H, s, 7-H), 7.89 (1 H, d, J_{HH} 1.5, 4-H), 7.91 (1 H, s, 10-H); δ_C(100.6 MHz, $CDCl_3$) 16.4 (×2) (d, J_{PC} 6, Me), 65.9 (×2)(d, J_{PC} 7, $POCH_2$), 114.2 (C-4), 121.1 (C-1), 124.6 (d, J_{PC} 6, C-11), 125.1 (C-10), 125.3 (C-2), 126.8 (d, J_{PC} 4, C-11a), 127.3 (C-8), 127.4 (C-7), 130.1 (d, J_{PC} 9, C-11), 132.2 (C-6a). 132.4 (C-10b), 133.6 (C-4a), 134.5 (C3), 139.0 (C-9), 160.2 (C-6); ν_{max}/cm^{-1} (ATM) 2978, 1743, 1613, 1458, 1440, 1390, 1349, 1312, 1279, 1245, 1164, 1154, 1054, 1020, 995, 974, 912, 832, 771, 761, 751; *m/z* (ESI)[14] 473 (M^+. $C_{19}H_{15}Cl_3NO_5P$ requires 473).

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Diethyl (3,8,9-trichloro-6,11-dioxo-6H-isoindolo[2,1-a]indol-10b(11H)-yl)phosphonate **15d** [r_f = 0.45 DCM–EtOAc (19 : 1)] was isolated, after recrystallisation from hexane–DCM, as a yellow solid, mp 134–135 °C; δ_P(109.3 MHz, $CDCl_3$) 11.5; δ_H(400 MHz, $CDCl_3$) 1.13 (3 H, t, J_{HH} 7, Me), 1.15 (3 H, t, J_{HH} 7, Me), 3.96–4.17 (4 H, m, $POCH_2$), 7.20 (1 H, dd, J_{HH} 8 and 1.5, 2-H), 7.61 (1 H, d, J_{HH} 8, 4-H), 7.86 (1 H, s, 7-H), 7.90 (1 H, d, J_{HH} 1.5, 1-H), 8.02 (1 H, d, J_{PH} 2, 10-H); δ_C(100.6 MHz, $CDCl_3$) 16.2 (d, J_{PC} 6, Me), 16.2 (d, J_{PC} 6, Me), 65.3 (d, J_{PC} 7, $POCH_2$), 65.6 (d, J_{PC} 7, $POCH_2$), 76.1 (d, J_{PC} 144.5, C-10b), 118.6 (C-11), 126.3 (C-1), 126.4 (d, J_{PC} 3, C-10), 126.6 (C-2), 127.1 (d, J_{PC} 2, C-7), 127.2 (C-11a), 131.3 (d, J_{PC} 4, C-8), 135.2 (d, J_{PC} 4, C-6a), 138.3 (d, J_{PC} 6, C-10a), 139.7 (d, J_{PC} 4, C-9), 144.4 (C-3), 152.5 (d, J_{PC} 1, C-4a), 167.1 (C-6), 188.6 (C-11); ν_{max}/cm^{-1} (ATM) 3106, 2989, 1718, 1596, 1427, 1388, 1281, 1200, 1171, 1142, 1065, 1009, 983, 922, 832, 799, 768, 738; *m/z* (ESI)[14] 472.9742 (M^+. $C_{19}H_{15}ClNO_5P$ requires 472.9753).

2. In toluene with heating. The benzoyl chloride **14d** (1.24 g, 3.2 mmol) was warmed at 100 °C with toluene (15 cm^3) until it had dissolved and triethyl phosphite (1.08 g, 6.5 mmol) was then added dropwise over a period of about 2 min and the mixture then stirred and heated at 100 °C. After 3 h NMR indicated the formation of only one major product in addition to triethyl phosphate, the phosphonate **15d** (93%). Small quantities of the phosphate–phosphonate **22d** (6%) and the phosphate **20d** (~1%) were also present. Volatile components were removed *in vacuo* (80 °C at 0.01 mmHg) and the pure phosphonate **15d** isolated by chromatography on silica gel eluting with DCM–EtOAc mixtures.

The reaction of 25 with triethyl phosphite in toluene.

The preparation of the benzoylphosphonate 26. Triethyl phosphite (600 mg, 3.6 mmol) was added dropwise with stirring to a solution of the freshly prepared benzoyl chloride **25** (1.0 g, 3.3 mmol) dissolved in dry toluene (25 cm^3) warmed at 70 °C. The resulting yellow solution was stirred at this temperature for 30 min and volatile components were then removed *in vacuo* to leave an essentially quantitative recovery of the phosphonate **26** as a yellow solid. Recrystallisation of this material from a hexane–DCM mixture gave diethyl {2-(1,3-dioxo-1*H*-benzo[*de*]-isoquinolin-2(3*H*)-yl}benzoylphosphonate **26** as a yellow powder (1.1 g, 76%); mp 150–151 °C; δ_P(109.3 MHz, $CDCl_3$) −1.9; δ_H(270 MHz, $CDCl_3$) 1.28 (6 H, t, J_{HH} 7, Me), 4.11 (2 H, qd, J_{HH} 7, J_{PH} 3, $POCH_2$), 4.14 (2 H, qd, J_{HH} 7, J_{PH} 3, $POCH_2$), 7.39 (1 H, d, J_{HH} 7.5, 3-H), 7.65 (1 H, t, J_{HH} 7.5, 5-H), 7.74 (2 H, t, J_{HH} 8, 5′/8′-H), 7.79 (1 H, t, J_{HH} 7.5, 4-H), 8.21 (2 H, d, J_{HH} 8, 6′/7′-H), 8.54 (2 H, d, J_{HH} 8, 4′/9′-H), 8.76 (1 H, d, J_{HH} 7.5, 6-H); δ_C(100.6 MHz, $CDCl_3$) 16.4(×2)(d, J_{PC} 5, Me), 64.3 (×2)(d, J_{PC} 7, $POCH_2$), 123.0 (×2)(C-3a′/9a′), 127.0 (×2)(C-5′/8′), 128.9 (C-9b′), 129.3 (C-5), 131.2 (d, J_{PC} 3, C-3), 131.6 (×2)(C-4′/9′), 132.0 (C-6a′), 133.0 (d, J_{PC} 65, C-1), 133.6 (C-6), 134.5 (×2)(C-6′/7′), 134.7 (d, J_{PC} 7.5, C-2), 134.9 (C-4), 164.5 (×2)(C-1′/3′), 199.4 (d, J_{PC} 176.5, PC=O); ν_{max}/cm^{-1} (ATM) 2989, 1703, 1661, 1588, 1375, 1357, 1262, 1240, 1198, 1046, 1016, 984, 930, 903, 777, 691; *m/z* (ESI) 438.1101 ($M + H^+$. $C_{23}H_{21}NO_6P$ requires 438.1107).

If necessary, the remaining ketophosphate **26** can be recovered from the filtrate and purified by chromatography on silica gel using DCM–EtOAc mixtures as the eluant (r_f = 0.5, DCM–EtOAc 1 : 1).

Reaction of the benzoylphosphonate 26 with further triethyl phosphite

1. In toluene. The benzoylphosphonate **26** (1.4 g, 3.2 mmol) was heated (*ca.* 100 °C) with toluene (10 cm^3) until it dissolved and triethyl phosphite (1.1 cm^3, 6.5 mmol) was then added and the mixture heated at 115 °C for 17 h. ^{31}P NMR of the resulting mixture showed that, in addition to triethyl phosphate, the major product was the phosphonate **27** (83%). A little of the phosphate **28** (7%) and a small quantity of the phosphate–phosphonate **30** (10%) (δ_P = −0.5 [d, J_{PP} 21, $P(OEt)_3$], 16.9 [d, J_{PP} 21, $P(O)(OEt)_2$]) were also present. Samples of the phosphonate **27** and the phosphate **28** were isolated by chromatography on silica gel eluting with DCM–EtOAc mixtures.

Diethyl 7-oxo-7H-benzo[de]indolo[2,1-a]isoquinolin-13-yl phosphate **28** (60 mg, 5%) [r_f = 0.9 DCM–EtOAc (9 : 1)] was isolated, after recrystallisation from hexane–DCM, as yellow crystals suitable for X-ray diffraction studies, mp 100–101 °C; δ_P(109.3 MHz, $CDCl_3$) −4.2; δ_H(400 MHz, $CDCl_3$) 1.18 (6 H, td, J_{HH} 7, J_{PH} 1, Me), 4.06–4.18 (4 H, m, $POCH_2$), 7.20 (1 H, td, J_{HH} 7.5 and 1, 11-H), 7.25 (1 H, td, J_{HH} 7.5 and 1, 10-H), 7.33 (1 H, t, J_{HH} 8, 2-H), 7.35 (1 H, t, *J* 8, 5-H), 7.49 (1 H, d, J_{HH} 8, 3-H), 7.72 (2 H, br d, J_{HH} 7.5, 4/12-H), 8.22 (1 H, d, J_{HH} 8, 1-H), 8.29 (1 H, d, J_{HH} 8, 5-H), 8.57 (1 H, d, J_{HH} 7.5, 9-H); δ_C(100.6 MHz, $CDCl_3$) 16.2 (×2)(d, J_{PC} 6, Me), 65.2 (×2)(d, J_{PC} 6, $POCH_2$), 116.9 (C-9), 118.8 (C-12), 121.0 (d, J_{PC} 2, C-13b), 122.2 (d, J_{PC} 8, C13), 123.7 (q), 123.7 (d, J_{PC} 2, C-12a), 124.4 (C-11), 124.5 (C-1), 126.0 (q), 126.1 (C-10), 126.4 (C-5), 126.8 (C-2), 127.8 (C-3), 129.2 (C-6), 131.2 (d, J_{PC} 2, C-13a), 132.0 (q), 132.5 (C-8a), 133.8 (C-4), 160.5 (C-7); ν_{max}/cm^{-1} (ATM) 3055, 2963, 1688, 1598, 1508, 1451, 1363, 1319, 1263, 1229, 1216, 1193, 1093, 1008, 984, 953, 917, 797, 771, 740, 705, 686; *m/z* (ESI) 422.1146 ($M + H^+$. $C_{23}H_{21}NO_5P$ requires 422.1152).

Diethyl (7,13-dioxo-13,13a-dihydro-7H-benzo[de]indolo[2,1-a]-isoquinolin-13a-yl)phosphonate **27** (950 mg, 75%) [r_f = 0.55 DCM–EtOAc (9 : 1)] was isolated, after recrystallisation from hexane–DCM, as a yellow powder, mp 175–176 °C; δ_P(109.3 MHz, $CDCl_3$) 13.0; δ_H(400 MHz, $CDCl_3$) 0.67 (3 H, t, J_{HH} 7, Me), 0.84 (3 H, t, J_{HH} 7, Me), 3.26–3.32 (1 H, m, $POCH_2$), 3.61–3.73 (3 H, m, $POCH_2$), 7.19 (1 H, t, J_{HH} 8, 11-H), 7.49 (1 H, t, J_{HH} 8, 2-H), 7.51 (1 H, t, J_{HH} 8, 5-H), 7.64 (1 H, t, *J* 8, 10-H), 7.73 (1 H, dd, J_{HH} 8, J_{PH} 2.5, 1-H), 7.78 (1 H, d, J_{HH} 8, 12-H), 7.86 (1 H, d, J_{HH} 8, 4-H), 8.37 (1 H. d, J_{HH} 8, 6-H), 8.57–8.59 (1 H, m, 3-H), 8.61 (1 H, d, J_{HH} 8, 9-H); δ_C(100.6 MHz, $CDCl_3$) 15.87 (d, J_{PC} 6, Me), 15.99 (d, J_{PC} 6, Me), 64.91 (d, J_{PC} 7.5, $POCH_2$), 65.04 (d, J_{PC} 7.5, $POCH_2$), 72.2 (d, J_{PC} 135.5, C-13a), 117.9 (C-9), 122.8 (d, J_{PC} 7.5, C-13b), 124.23 (C-12a), 124.26 (C-12), 124.5 (d, J_{PC} 5, C-2), 127.8 (d, J_{PC} 2, C-6), 128.3 (d, J_{PC} 4.5, C-1), 129.3 (d, J_{PC} 4, C-13c), 132.4 (d, J_{PC} 3, C-3a), 133.0 (d, J_{PC} 1, C-4), 137.5 (C-10), 152.3 (d, J_{PC} 1.5, C-8a), 161.5 (C-7), 191.6 (d, J_{PC} 2, C-13); ν_{max}/cm^{-1} (ATM) 2982, 1706, 1672, 1601, 1460, 1363,

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1337, 1298, 1251, 1161, 1122, 1042, 1014, 965, 832, 780, 769; *m/z* (ESI) 422.1148 ($M + H^+$. $C_{23}H_{21}NO_5P$ requires 422.1152).

2. In DCM after preparation of the aroylphosphonate 26 *in situ*. The benzoyl chloride **25** (1.1 g, 3.6 mmol) was dissolved in dry DCM (20 cm^3) and the solution cooled to 5 °C. Triethyl phosphite (1.5 g, 9 mmol) was then added dropwise keeping the reaction mixture below 5 °C. The mixture was then stirred at 5 °C for 1 h and then at room temperature for 16 h. ^{31}P NMR showed the major products to be the benzoylphosphonate **26** (30%), the pentacyclic phosphonate **27** (23%), the phosphate **28** (21%) and some phosphate–phosphonate **30** (21%).

The reaction of the benzoyl chloride 32c with triethyl phosphite

1. With excess trimethyl phosphite in DCM with initial cooling. Triethyl phosphite (2.9 cm^3, 17 mmol) was added dropwise to a solution of the freshly prepared benzoyl chloride **32c** (1.28 g, 4.2 mmol) in dry DCM (25 cm^3) cooled in an ice bath at such a rate that the temperature did not exceed 5 °C. Stirring was continued at 0–5 °C for 1 h and the cooling bath was then removed and the reaction continued at room temperature whilst being monitored by ^{31}P NMR. After 1 h the major product was the dioxaphospholane **34c**, δ_P(109.3 MHz, $CDCl_3$) −51.5 [d, J_{PP} 55, $P(OEt)_3$], 13.7 [d, J_{PP} 55, $P(O)(OEt)_2$], but after 16 h this had decomposed to give the phosphonate **35c** together with other components apparently arising from further reactions involving the chlorinated ring. Excess solvent was removed under reduced pressure (50 °C at 15 mmHg) and the remaining volatile components evaporated *in vacuo* (70 °C at 0.01 mmHg) to leave a viscous oil which was subjected to column chromatography on silica gel eluting initially with a DCM–EtOAc 1 : 1 mixture followed by EtOAc and finally an EtOAc–MeOH mixture. This enabled a quantity of the phosphonate **35c** and a small sample of the indolone **37c** to be isolated.

The *diethyl 1,2-dichloro-3,9-dioxo-9,9a-dihydro-3H-pyrrolo[1,2-a]indol-9a-ylphosphonate* **35c** (r_f = 0.85 EtOAc–DCM 1 : 1) initially isolated was crystallised by the slow evaporation of a solution in a DCM–hexane (5 : 95) mixture. This gave crystals of the phosphonate **35c** (360 mg, 22%) suitable for X-ray diffraction studies, mp 116–117 °C, δ_P(109.3 MHz, $CDCl_3$) 9.0; δ_H(270 MHz, $CDCl_3$) 1.16 (3 H, t, J_{HH} 7, Me), 1.22 (3 H, t, J_{HH} 7, Me), 4.06–4.22 (4 H, m, $POCH_2$), 7.27 (1 H, t, J_{HH} 8, 7-H), 7.71 (1 H, t, J_{HH} 8, 6-H), 7.72 (1 H, d, J_{HH} 8, 5-H), 7.81 (1 H, d, J_{HH} 8, 8-H); δ_C(67.9 MHz, $CDCl_3$) 16.32 (d, J_{PC} 6, Me), 16.41 (d, J_{PC} 6, Me), 65.8 (d, J_{PC}, $POCH_2$), 66.0 (d, J_{PC} 7, $POCH_2$), 76.9 (d, J_{PC} 147.5, C-9a), 118.6 (C-5), 125.7 (C-7), 126.5 (C-8), 127.5 (d, J_{PC} 8.5, C-2), 129.0 (C-8a), 138.1 (C-6), 144.4 (d, J_{PC} 8, C-1), 151.5 (C-4a), 165.4 (C-3), 186.1 (C-9); ν_{max}/cm^{-1} (ATM) 2998, 1740, 1722, 1601, 1470, 1392, 1293, 1261, 1236, 1155, 1132, 1099, 1043, 1002, 959, 811, 798, 787, 777, 764; *m/z* (ESI)[14] 390.0064 (M^+. $C_{15}H_{15}Cl_2O_5P$ requires 390.0065).

1,2-Dichloro-9-hydroxy-3H-pyrrolo[1,2-a]indol-3-one **37c** (r_f = 0.2, EtOAc) was eluted with ethyl acetate and isolated as a red solid. Slow evaporation of an acetonitrile solution of this material gave crystals of pure 1,2-dichloro-9-hydroxy-3*H*-pyrrolo[1,2-*a*]indol-3-one (90 mg, 9%) suitable for X-ray diffraction studies, mp 215–216 °C (dec.); δ_H(270 MHz, d_6-DMSO) 7.16 (1 H, t, *J* 8, 7-H), 7.39 (1 H, t, *J* 8, 6-H), 7.50 (1 H, d, *J* 8, 8-H), 7.75 (1 H, d, *J* 8, 5-H); δ_C(100.6 MHz, d_6-DMSO) 112.1 (C-5), 114.7 (C-9), 118.2 (C-9a), 122.2 (C-7), 123.6 (C-8), 126.6 (C-2), 130.1 (C-6), 132.3 (C-4a), 133.9 (C-8a), 144.1 (C-1), 156.2 (C-3); ν_{max}/cm^{-1} (ATM) 3386, 1710, 1672, 1636, 1521, 1463, 1430, 1346, 1297, 1204, 1107, 1014, 895, 845, 737, 674, 654.

The acetate **38c** was formed by heating the hydroxy compound **37c** (35 mg, 0.14 mmol) with acetic anhydride (2 cm^3) at 100 °C for 16 h followed by removal of the volatile components *in vacuo*. Slow evaporation of a DCM–hexane solution of the residue gave *1,2-dichloro-3-oxo-3H-pyrrolo[1,2-a]indol-9-yl acetate* **38c** (35 mg, 86%) as a brown solid, mp 163–164 °C; δ_H(400 MHz, $CDCl_3$) 2.43 (3 H, s, CH_3), 7.16 (1 H, t, *J* 8, 7-H), 7.30 (1 H, t, *J* 8, 8-H), 7.37 (1 H, t, *J* 8, 6-H), 7.68 (1 H, t, *J* 8, 5-H); δ_C(100.6 MHz, $CDCl_3$) 20.6 (Me), 113.3 (C-5), 120.9 (C-8), 124.3 (C-8a), 124.4 (C-7), 125.3 (C-9a), 127.0 (C-2), 129.6 (C-6), 132.9 (C-4a), 133.4 (C-1), 133.8 (C-9), 157.3 (C-3), 167.4 (C═O); ν_{max}/cm^{-1} (ATM) 1765, 1744, 1633, 1609, 1550, 1450, 1394, 1367, 1339, 1315, 1256, 1205, 1148, 1124, 1032, 1007, 893, 779, 760, 744, 728; *m/z* (ESI)[14] 295.9875 ($M + H^+$. $C_{13}H_8Cl_2NO_3$ requires 295.9881).

2. In DCM with heating under reflux. Triethyl phosphite (1.7 cm^3, 10.1 mmol) was added dropwise to a freshly prepared solution of 2-(3,4-dichloro-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)benzoyl chloride **32c** (1.58 g, 5.2 mmol) in dry DCM (20 cm^3) and the mixture heated under reflux for 16 h. ^{31}P NMR spectroscopy indicated the formation of only one main product [δ_P *ca.* 8.6 ppm] together with an equimolar quantity of triethyl phosphate. Volatile components, including the triethyl phosphate, were then removed under reduced pressure (initially at 30 °C at 15 mmHg and then at 75 °C at 0.01 mmHg) to give diethyl (1,2-dichloro-3,9-dioxo-9,9a-dihydro-3*H*-pyrrolo[1,2-*a*]-indol-9a-yl)phosphonate **35c** as a yellow solid (>95% purity) [$\delta_P(CDCl_3)$ 8.9 ppm]. This product was sufficiently pure to be used without further purification. An analytically pure sample of this material was obtained by chromatography on silica gel eluting with DCM–EtOAc mixtures and characterised by comparison with the authentic sample of **35c** isolated earlier.

3. In toluene with heating. With the exclusion of moisture, triethyl phosphite (0.75 cm^3, 4.5 mmol) was added dropwise over 2 min to a solution of the freshly prepared benzoyl chloride **32c** (0.55 g, 1.8 mmol) in dry toluene (5 cm^3) at 70 °C. The temperature of the reaction mixture was then increased to 100 °C for 30 min. Volatile components were then removed *in vacuo* (100 °C at 0.01 mmHg) to leave a brown viscous residue which was shown by NMR to contain about 50% of the 1,3,2-dioxaphospholane, *diethyl (4,5-dichloro-2,2,2-triethoxy-6-oxo-6H,11bH-2λ⁵-[1,3,2]dioxaphospholo[4,5-b]pyrrolo[1,2-a]indol-11b-yl)phosphonate*, **34c**, δ_P(109.3 MHz, $CDCl_3$) −51.5 [d, J_{PP} 55, $P(OEt)_3$], 13.7 [d, J_{PP} 55, $P(O)(OEt)_2$]; δ_C(67.9 MHz, $CDCl_3$)[13] 80.4 (dd, J_{PC} 186 and 6, O–C–P), 97.6 (dd, J_{PC} 10 and 5, O–C–N), 116.6 (C–H), 125.2 (C–H), 127.1 (C–H), 130.6 (C–H), 145.7 (═C–Cl), 153.7 (C–N), 162.3 (C═O). Heating a solution of the residue in acetonitrile (20 cm^3) under reflux for 90 min converted the dioxaphospholane **34c** into the

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β-ketophosphonate **35c** which was isolated using the procedure described above.

The reaction of a mixture of the benzoyl chlorides 32a and 41 with excess triethyl phosphite in DCM

A quantity of the acid chloride mixture containing **41** (1.9 mmol) and **32a** (0.6 mmol), prepared as previously described, was dissolved in dry DCM (15 cm^3) and triethyl phosphite (830 mg, 5 mmol) was added. The mixture was then heated at 40 °C for 2 h and then analysed by NMR spectroscopy. This showed the formation of two major components, the 1,3,2-dioxaphospholanes **43**, $\delta_P(CDCl_3)$ −53.4 [d, J_{PP} 49, $P(OEt)_3$], 15.2 [d, J_{PP} 49, $P(O)(OEt)_2$], and **34a**, $\delta_P(CDCl_3)$ −51.8 [d, J_{PP} 47, $P(OEt)_3$], 14.7 [d, J_{PP} 47, $P(O)(OEt)_2$], in the ratio of 6 : 4. Some decomposition of these dioxaphospholanes to give triethyl phosphate and the β-ketophosphonates **44** [$\delta_P(CDCl_3)$ 12.9] and **35a** [$\delta_P(CDCl_3)$ 11.7] (in the ratio 4 : 1) was also observed. A little of the phosphate–phosphonate components later identified as **46** and **47** were also present in the product mixture.

After heating this mixture under reflux for 2 h in MeCN the dioxaphospholanes had decomposed to the corresponding β-ketophosphonates **44** and **35a**. Samples of these two β-ketophosphonates (combined yield 77%) together with a small sample of the phosphate–phosphonate **46**, some of which was derived from **47**, were isolated by chromatography on silica gel eluting with DCM–EtOAc–MeOH mixtures. A very small impure sample of the phosphate–phosphonate **47** [δ_P(162.0 MHz, $CDCl_3$) 16.2 (s, –P(O)OEt_2), −4.0 (s, –OP(O)-OEt_2); δ_H(270 MHz, $CDCl_3$) 4.09 (1 H, dd, J_{HH} 8.4 and 4.2, 1-H), 5.31 (1 H, dd, J_{PH} 11.73 and 7.8, α-CH)] was also obtained.

Diethyl (1-chloro-3,9-dioxo-2,3-dihydro-1H-pyrrolo[1,2-a]-indol-9a(9H)-yl)phosphonate **44** (429 mg, 1.19 mmol) [r_f = 0.15, (DCM–EtOAc 19 : 1)] was isolated as a pale yellow waxy solid, δ_P(109.3 MHz, $CDCl_3$) 13.2; δ_H(400 MHz, $CDCl_3$) 1.09 (3 H, t, J_{HH} 7, Me), 1.38(3 H, t, J_{HH} 7, Me), 2.86 (1 H, d, J_{HH} 17.5, 2-H), 3.98 (1 H, dd, J_{HH} 17.5 and 5, 2-H), 4.01–4.29 (4 H, m, $POCH_2$), 5.05 (1 H, dd, J_{PH} 7 and J_{HH} 5, 1-H), 7.30 (1 H, t, J_{HH} 7.5, 7-H), 7.71 (1 H, t, J_{HH} 7.5, 6-H), 7.76 (1 H, d, J_{HH} 7.5, 8-H), 7.96 (1 H, d, J_{HH} 7.5, 5-H); δ_C(100.6 MHz, $CDCl_3$) 16.3 (d, J_{PC} 5, Me), 16.6 (d, J_{PC} 5, Me), 47.1 (C-2), 54.5 (d, J_{PC} 10.5, C-1), 65.1 (d, J_{PC} 7, $POCH_2$), 65.6 (d, J_{PC} 7, $POCH_2$), 78.2 (d, J_{PC} 146, C-9a), 117.0 (C-5), 125.3 (C-8), 125.7 (C-7), 126.3 (C-8a), 137.3 (C-6), 151.6 (d, J_{PC} 2, C-4a), 171.0 (C-3), 191.0 (C-9); ν_{max}/cm^{-1} (ATM) 2988, 1742, 1721, 1602, 1463, 1339, 1249, 1209, 1161, 1082, 1044, 1011, 983, 776, 757, 695; *m/z* (ESI)[14] 357.0531 (M^+. $C_{15}H_{17}ClNO_5P$ requires 357.0533).

Diethyl 3,9-dioxo-9,9a-dihydro-3H-pyrrolo[1,2-a]indol-9a-ylphosphonate **35a** (240 mg, 0.74 mmol) [r_f = 0.20, (DCM–EtOAc 9 : 1)] was isolated as a pale yellow waxy solid, δ_P(109.3 MHz, $CDCl_3$) 11.9; δ_H(270 MHz, $CDCl_3$) 1.22 (3 H, t, J_{HH} 7, Me), 1.25 (3 H, t, J_{HH} 7, Me), 4.09–4.25 (4 H, m, $POCH_2$), 6.27 (1 H, dd, J_{HH} 5.5, J_{PH} 4.5, 1-H), 7.27 (1 H, td, J_{HH} 7.5 and 1, 7-H), 7.46 (1 H, dd, J_{HH} 5.5, J_{PH} 3, 2-H), 7.71 (1 H, td, J_{HH} 7.5 and 1, 6-H), 7.73 (1 H, d, J_{HH} 7.5, 8-H), 7.83 (1 H, d, J_{HH} 7.5, 5-H); δ_C(67.9 MHz, $CDCl_3$) 16.5 (d, J_{PC} 5, Me), 16.5 (d, J_{PC} 5, Me), 65.27 (d, J_{PC} 7, $POCH_2$), 65.35 (d, J_{PC} 7, $POCH_2$), 81.2 (d, J_{PC} 146.5, C-9a), 118.5 (C-5), 125.6 (C-8), 125.8 (C-7), 129.4 (C-8a), 129.9 (d, J_{PC} 8.5, C-2), 137.8 (C-6), 146.0 (d, J_{PC} 6.5, C-1), 152.0 (d, J_{PC} 2, C-4a), 172.2 (C-3), 189.3 (C-9); ν_{max}/cm^{-1} (ATM) 2986, 1714, 1601, 1464, 1297, 1259, 1204, 1161, 1041, 1011, 962, 896, 818, 772, 694; *m/z* (ESI) 321.0798 (M^+. $C_{15}H_{16}NO_5P$ requires 321.0766).

Diethyl (diethoxyphosphoryloxy)[2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)phenyl]methylphosphonate **46** was isolated as a viscous brown oil (r_f 0.45 EtOAc–MeOH 19 : 1); δ_P(162.0 MHz, $CDCl_3$) 16.1 (d, J_{PP} 28.5 –P(O)OEt_2), −1.4 (d, J_{PP} 28.5, –OP(O)-OEt_2); δ_H(400 MHz, $CDCl_3$) 1.09 (3 H, td, J_{HH} 7, J_{PH} 1, Me), 1.19 (3 H, t, J_{HH} 7, Me), 1.21 (3 H, t, J_{HH} 7, Me), 1.26 (3 H, td, J_{HH} 7, J_{PH} 1, Me), 3.77–4.14 (8 H, m, $POCH_2$), 5.58 (1 H, dd, J_{PH} 13.7 and 11.0, α-CH), 6.84 (1 H, J_{AB} 6, 3′-H), 6.85 (1 H, J_{AB} 6, 4′-H), 7.12 (1 H, ddd, J_{HH} 7.5 and 1.5, J_{PH} 1.5, 3-H), 7.46 (1 H, tdd, J_{HH} 7.5 and 2, J_{PH} 2, 4-H), 7.48 (1 H, td, J_{HH} 7.5 and 1.5, 5-H), 7.94 (1 H, ddd, J_{HH} 7.5 and 2, J_{PH} 2, 6-H); δ_C(100.6 MHz, $CDCl_3$) 15.8 (d, J_{PC} 7, Me), 16.0 (d, J_{PC} 7, Me), 16.35 (d, J_{PC} 5, Me), 16.40 (d, J_{PC} 5, Me), 63.7 (d, J_{PC} 7, $POCH_2$), 63.8 (d, J_{PC} 7, $POCH_2$), 64.2 (d, J_{PC} 7, $POCH_2$), 64.3 (d, J_{PC} 7, $POCH_2$), 70.2 (dd, J_{PC} 173.5 and 7, α-CH), 129.5 (d, J_{PC} 2.4, C-3), 129.6 (d, J_{PC} 1, C-5), 129.9–130.1 (m, C-1/4/6), 133.0 (d, J_{PC} 2, C-2), 134.64 (C-3′), 134.67 (C-4′), 169.2 (C-2′), 169.8 (C-5′); ν_{max}/cm^{-1} (ATM) 2986, 1715, 1495, 1454, 1390, 1255, 1147, 1013, 952, 861, 827; *m/z* (ESI) 476.1235 (M + H^+. $C_{19}H_{28}NO_9P_2$ requires 476.1239).

Diethyl (3,9-dioxo-9,9a-dihydro-3*H*-pyrrolo[1,2-*a*]indol-9a-yl)phosphonate 35a from diethyl (1-chloro-3,9-dioxo-2,3,9,9a-tetrahydro-1*H*-pyrrolo[1,2-*a*]indol-9a-yl)phosphonate 44

Triethylamine (0.2 cm^3, 2.0 mmol) was added dropwise to a solution of the phosphonate **44** (100 mg, 0.28 mmol) in DCM (15 cm^3) and the mixture stirred at room temperature for 1 h. The resulting solution was then washed with water (15 cm^3), dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure (20 °C at 0.01 mmHg) to give the elimination product **35a** in a good state of purity. This product was purified by column chromatography on silica gel eluting with a DCM–EtOAc 9 : 1 mixture to give the pure diethyl (3,9-dioxo-9,9a-dihydro-3*H*-pyrrolo[1,2-*a*]indol-9a-yl)phosphonate **35a** (71 mg, 78%) as a yellow solid. It was characterised by comparison with the authentic sample isolated above.

Reduction of the β-ketophosphonates 15a–d, 27, 35a and 35c with sodium borohydride

Reduction of the β-ketophosphonate 15a. Sodium borohydride (250 mg, 7 mmol) was added in small portions to a stirred solution of the β-ketophosphonate **15a** (2.5 g, 6.75 mmol) in dry methanol (50 cm^3) and the mixture stirred at room temperature for 2 h. The precipitated solid was filtered off, washed with petroleum ether (bp 40–60 °C), and then dried to give the indolone **23a** (860 mg, 58%). A further crop of this product (160 mg, 11%) was isolated from the filtrate by chromatography on silica gel (r_f = 0.9, DCM) using DCM–EtOAc mixtures as the eluent. *6H-Isoindolo[2,1-a]indol-6-one* **23a** (1.02 g, 69%) was isolated as a yellow solid, mp 153–154 °C (lit.,[15] 153–154 °C);

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δ_H(270 MHz, $CDCl_3$)[15] 6.52 (1 H, d, *J* 1.3, 11-H), 7.11 (1 H, td, *J* 8 and 1, 2-H), 7.28–7.31 (2 H, m, 8-H, 3-H), 7.42 (1 H, d, *J* 8, 1-H), 7.46–7.50 (2 H, m, 9-H, 10-H), 7.69 (1 H, d, *J* 8, 7-H), 7.84 (1 H, dd, *J* 8 and 1, 4-H); δ_C(67.9 MHz, $CDCl_3$)[15] 103.7 (C-11), 113.5 (C-4), 121.4 (C-10), 122.5 (C-1), 124.1 (C-2), 125.4 (C-7), 126.5 (C-3), 129.0 (C-8), 133.8 (C-4a), 133.9 (C-9), 134.0 (C-6a), 134.7 (C-11a), 134.9 (C-10b), 139.0 (10a), 162.8 (C-6); ν_{max}/cm^{-1} (ATM) 1720, 1609, 1442, 1375, 1299, 1140, 913, 817, 802, 738, 689.

Reduction of the β-ketophosphonate 15b. Sodium borohydride (35 mg, 0.92 mmol) was added to a stirred solution of the β-ketophosphonate **15b** (300 mg, 0.74 mmol) in MeOH (15 cm^3). After 5 min a yellow solid precipitated and the mixture stirred for a further 2 h. The yellow solid was filtered off and crystallised by the slow evaporation of a chloroform solution to give the 3-chloro-6*H*-isoindolo[2,1-*a*]indol-6-one **23b** as yellow crystals (105 mg, 56%), mp 208–209 °C; δ_H(400 MHz, $CDCl_3$) 6.50 (1 H, s, 11-H), 7.14 (1 H, dd, *J* 8 and 2, 3-H), 7.36 (1 H, d, *J* 8, 4-H), 7.36–7.42 (1 H, m, 8-H), 7.53–7.57 (2 H, m, 9/10-H), 7.77 (1 H, d, *J* 7.5, 7-H), 7.91 (1 H, d, *J* 2, 1-H); δ_C(100.6 MHz, $CDCl_3$) 103.2 (C-11), 113.9 (C-4), 121.6 (C-10), 123.1 (C-1), 124.6 (C-2), 125.7 (C-7), 129.3 (C-8), 132.5 (C-10b), 133.2 (C-11a), 133.7 (C-3), 134.1 (C-4a), 134.2 (C-9), 134.7 (C-6a), 139.5 (C-10a), 162.6 (C-6); ν_{max}/cm^{-1} (ATM) 3114, 1720, 1619, 1471, 1340, 1355, 1332, 1310, 1263, 1225, 1181, 1144, 1114, 1092, 1078, 1051, 926, 893, 846, 832, 794, 758, 734, 693, 672, 645; *m*/*z* (ESI)[14] 254.0386 ($M + H^+$. $C_{15}H_9ClNO$ requires 254.0373).

Reduction of the β-ketophosphonate 15c. Sodium borohydride (110 mg, 3.1 mmol) was added in small portions to a stirred solution of the β-ketophosphonate **15c** (1.1 g, 2.5 mmol) in dry methanol (10 cm^3) and the mixture was stirred at room temperature for 2 h. The precipitated solid was then filtered off, washed with petroleum ether (20 cm^3, bp 40–60 °C), and dried to give the 8,9-dichloro-6*H*-isoindolo[2,1-*a*]indol-6-one **23c** (225 mg, 78%) as a yellow solid, mp >260 °C; δ_H(270 MHz, CCl_4, 50 °C)[16] 6.56 (1 H, s, 11-H), 7.11 (1 H, t, J_{HH} 8, 2-H), 7.27 (1 H, t, J_{HH} 8, 3-H), 7.39 (1 H, t, J_{HH} 8, 1-H), 7.57 (1 H, s, 10-H), 7.82 (1 H, s, 7-H), 7.86 (1 H, d, J_{HH} 8, 4-H); ν_{max}/cm^{-1} (ATM) 3116, 3084, 1713, 1612, 1428, 1392, 1377, 1318, 1226, 1187, 1163, 1140, 1127, 1077, 966, 896, 826, 771, 725, 664, 649; *m*/*z* (ESI)[14] 286.9978 (M^+. $C_{15}H_7Cl_2NO$ requires 286.9905).

Reduction of the β-ketophosphonate 15d. Sodium borohydride (35 mg, 1 mmol) was added in small portions to a stirred solution of the β-ketophosphonate **15d** (290 mg, 0.61 mmol) in dry methanol (10 cm^3). A brisk effervescence was observed and the indolone **23d** began to precipitate. The mixture was stirred at room temperature for 3 h and the precipitate was then filtered off and heated in MeCN (30 cm^3). After cooling the solid was then recovered, washed with petroleum ether (20 cm^3, bp 40–60 °C) and dried to give the pure 3,8,9-trichloro-6*H*-isoindolo[2,1-*a*]-indol-6-one **23d** as a yellow powder (229 mg, 71%); mp >260 °C; δ_H(270 MHz, d_6-DMSO, 60 °C[16]) 7.07 (1 H, s, 11-H), 7.28 (1 H, dd, *J* 8.5 and 1.8, 2-H), 7.66 (1 H, d, *J* 8.5, 1-H), 7.75 (1 H, d, *J* 1.8, 4-H), 8.00 (1 H, s, 10-H), 8.20 (1 H, s, 7-H); ν_{max}/cm^{-1} (ATM) 3114, 3085, 1719, 1617, 1603, 1430, 1393, 1359, 1339, 1317, 1269, 1225, 1182, 1110, 1086, 1052, 972, 927, 895, 834, 805, 780, 772, 737, 699; *m*/*z* (ESI)[14] 321.9585 ($M + H^+$. $C_{15}H_7Cl_3NO$ requires 321.9588).

Reduction of the β-ketophosphonate 27. Sodium borohydride (40 mg, 1.05 mmol) was added in small portions to a stirred solution of the β-ketophosphonate **27** (250 mg, 0.59 mmol) in dry methanol (15 cm^3). The mixture was then stirred at room temperature for 16 h during which time an orange precipitate formed. This precipitate was then filtered off and recrystallised from chloroform to give the pure 7*H*-benzo[*de*]indolo[2,1-*a*]isoquinolin-7-one **29** as an orange solid (202 mg, 75%), mp 223–224 °C; δ_H(400 MHz, $CDCl_3$) 7.23 (1 H, s, 13-H), 7.35 (1 H, td, J_{HH} 7.5 and 1, 11-H), 7.42 (1 H, td, J_{HH} 7.5 and 1, 10-H), 7.61 (1 H, d, J_{HH} 8, 2-H), 7.65 (1 H, d, J_{HH} 7.5, 12-H), 7.71 (1 H, t, J_{HH} 7.5, 5-H), 7.88 (1 H, d, J_{HH} 8, 3-H), 8.11 (1 H, d, J_{HH} 7.5, 4-H), 8.13 (1 H, d, J_{HH} 7.5, 1-H), 8.67 (1 H, dd, J_{HH} 7.5 and 1, 6-H), 8.77 (1 H, d, J_{HH} 7.5, 9-H); δ_C(100.6 MHz, $CDCl_3$) 103.9 (C-13), 117.2 (C-9), 121.0 (C-12), 123.0 (C-1), 123.2 (q), 124.7 (C-11), 124.8 (q), 125.4 (C-10), 126.7 (q), 126.9 (C-5), 127.1 (C-2), 128.4 (C-3), 130.0 (C-6), 130.4 (q), 132.7 (q), 134.1 (C-4), 135.7 (q), 136.1 (q), 161.3 (C-7); ν_{max}/cm^{-1} (ATM) 3098, 1690, 1569, 1506, 1453, 1382, 1358, 1323, 1237, 1215, 1186, 1156, 1105, 931, 903, 880, 859, 827, 774, 744, 670; *m*/*z* (ESI) 270.0910 ($M + H^+$. $C_{19}H_{12}NO$ requires 270.0913).

Reduction of the β-ketophosphonate 35c. Sodium borohydride (62 mg, 1.6 mmol) was added in small portions to a stirred solution of the β-ketophosphonate **35c** (160 mg, 0.41 mmol) in dry methanol (3 cm^3). The mixture was then stirred at room temperature for 1 h after which time no starting material remained. Volatile components were removed under reduced pressure (50 °C at 15 mmHg) and water (20 cm^3) added to the residue. This mixture was then extracted with DCM (3 × 20 cm^3) and the combined extracts dried ($MgSO_4$), filtered and volatile components then removed under reduced pressure (35 °C at 15 mmHg). This mixture was subjected to chromatography on silica gel eluting with DCM followed by a DCM–EtOAc mixture (8 : 2). This enabled a sample of (*Z*)-*2,3-dichloro-3-(1H-indol-2-yl)prop-2-en-ol* **40** (65 mg, 65%) (r_f = 0.15, DCM) to be isolated as a dark brown solid, mp 86–88 °C; δ_H(400 MHz, $CDCl_3$) 2.75 (1 H, br s, OH), 4.56 (2 H, s, 1-H), 6.79 (1 H, s, 3′-H), 7.14 (1 H, t, *J* 8, 5′-H), 7.26 (1 H, t, *J* 8, 6′-H), 7.35 (1 H, d, *J* 8, 4′-H), 7.63 (1 H, d, *J* 8, 7′-H), 8.92 (1 H, br s, NH); δ_C(100.6 MHz, $CDCl_3$) 65.0 (C-1), 106.5 (C-3′), 111.5 (C-7′), 120.9 (C-5′), 121.5 (C-4′), 124.1 (C-6′), 126.3 (C-2′), 127.8 (C-3a′), 131.2 (C-3), 132.0 (C-2), 136.7 (C-7a); ν_{max}/cm^{-1} (ATM) 3386, 1716, 1604, 1519, 1403, 1348, 1299, 1233, 1175, 1104, 1018, 971, 935, 813, 795, 745, 720, 675; *m*/*z* (ESI)[14] 242.0129 ($M + H^+$. $C_{11}H_{10}Cl_2NO$ requires 242.0134).

Reduction of the β-ketophosphonate 35a. Sodium borohydride (11 mg, 0.29 mmol) was added to a stirred solution of the β-ketophosphonate **35a** (90 mg, 0.28 mmol) in dry methanol (5 cm^3) and the mixture stirred at room temperature for 4 h. Volatile components were removed under reduced pressure (50 °C at 15 mmHg) and the residue dissolved in DCM (20 cm^3). This solution was then washed with water (2 × 15 cm^3), dried ($MgSO_4$), filtered and volatile components then removed under reduced pressure (35 °C at 15 mmHg). NMR of the residue indicated the

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presence of two main compounds, the acrylate **50** and the lactone **52**. These components were isolated by chromatography on silica gel with DCM–EtOAc–MeOH mixtures as the eluant.

Z-Methyl 3-(1H-indol-2-yl)acrylate **50** (30 mg, 54%) (r_f = 0.9 DCM) was isolated as a yellow solid, δ_H(400 MHz, $CDCl_3$)[17] 3.83 (3 H, s, OMe), 5.79 (1 H, d, *J* 12.5, 2-H), 6.77 (1 H, s, 3′-H), 6.94 (1 H, d, *J* 12.5, 3-H), 7.10 (1 H, t, *J* 7.5 6′-H), 7.44 (1 H, d, *J* 7.5, 4′-H), 7.62 (1 H, d, *J* 7.5, 7′-H), 11.80 (1 H, br s, N–H); δ_C(67.9 MHz, $CDCl_3$) 52.1 (OMe), 112.1 (C-3′), 112.2 (C-7′), 112.6 (C-5′), 120.4 (C-4′), 121.7 (C-2), 125.0 (C-6′), 127.7 (C-2′), 133.9 C-3a′), 135.5 (C-3), 137.9 (C-7a′), 169.1 (C-1).

Diethyl 2-oxo-2,3,4,4a,5,9b-hexahydropyrano[3,2-b]indol-4a-ylphosphonate **52** (10 mg, 11%) (r_f = 0.4 EtOAc–MeOH 9 : 1) was isolated as a waxy solid, δ_P(109.3 MHz, $CDCl_3$) 24.3; δ_H(400 MHz, $CDCl_3$) 1.07 (3 H, t, J_{HH} 7, Me), 1.12 (3 H, t, J_{HH} 7, Me), 2.22–2.32 (2 H, m, 3-H, 4-H), 2.65–2.81 (1 H, m, 4-H), 3.03–2.12 (1 H, m, 3-H), 3.78–4.02 (4 H, m, $POCH_2$), 5.05 (1 H, d, J_{PH} 8.5, 9b-H), 7.15 (1 H, t, J_{HH} 7.5, 8-H), 7.35 (1 H, t, J_{HH} 7.5, 7-H), 7.47 (1 H, d, J_{HH} 7.5, 9-H), 7.61 (1 H, d, J_{HH} 7.5, 6-H); δ_C(100.6 MHz, $CDCl_3$) 16.37 (d, J_{PC} 6, Me), 16.43 (d, J_{PC} 6, Me), 21.8 (C-4), 35.4 (C-3), 63.36 (d, J_{PC} 7, $POCH_2$), 63.57 (d, J_{PC} 7, $POCH_2$), 71.5 (d, J_{PC} 14 C-9b), 73.0 (d, J_{PC} 160, C-4a), 115.9 (C-6), 125.3 (C-8), 126.3 (C-9), 130.2(C-7), 135.6 (C-9a), 139.5 (C-5a), 174.7 (C-2); ν_{max}/cm^{-1} (ATM) 3286, 2966, 1705, 1607, 1479, 1367, 1261, 1230, 1013, 982, 799, 657; *m*/*z* (ESI) 326.1154 ($M + H^+$. $C_{15}H_{21}NO_5P$ requires 326.1157).

X-ray crystallography

Further details of the structure determination of compounds **15a**, **28**, **35c** and **37c** together with selected bond lengths and angles are provided within the ESI.†

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Notes and references

1 D. V. Griffiths, P. A. Griffiths, B. J. Whitehead and J. C. Tebby, *J. Chem. Soc., Perkin Trans. 1*, 1992, 479–484.
2 Although the formation of the intermediate **2** can be represented by the mechanistic arrows shown, they are 'dashed' to indicate that this is likely to be an oversimplification of the process involved.
3 D. V. Griffiths, K. Karim and B. J. Whitehead, *Zh. Obshch. Khim.*, 1993, **63**, 2245–2251.
4 Y.-K. Cheong, P. Duncanson and D. V. Griffiths, *Tetrahedron*, 2008, **64**, 2329–2338.
5 J. Guillaumel, S. Léonce, A. Pierré, P. Renaud, B. Pfeiffer, P. B. Arimondo and C. Monneret, *Eur. J. Med. Chem.*, 2006, **41**, 379–386.
6 K. Dinnell, G. G. Chicchi, M. J. Dhar, J. M. Elliot, G. J. Hollingsworth, M. M. Kurtz, M. P. Ridgill, W. Rycroft, K.-L. Tsao, A. R. Williams and C. J. Swain, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1237–1240.
7 M.-F. Boussard, S. Truche, A. Rousseau-Rojas, S. Briss, S. Desamps, M. Droual, M. Wierzbicki, G. Ferry, V. Audinot, P. Delagrange and J. A. Boutin, *Eur. J. Med. Chem.*, 2006, **41**, 306–320.
8 S. Samorson, J. B. Bremner, A. Ball and K. Lewis, *Bioorg. Med. Chem.*, 2006, **14**, 857–865.
9 Data have been deposited with the Cambridge Crystallographic Data Centre. For **15a** as CCDC 865150, **28** as CCDC 865151, **35c** as CCDC 865152, and for **37c** as CCDC 865153.
10 Further relevant information is available in the ESI.†.
11 Y-K. Cheong, P. Duncanson and D. V. Griffiths, 'The Reaction of Trivalent Phosphorus Compounds with Halogenated Pyrrole- and Furan-2,5-diones', Abstracts from XV International Conference on Chemistry of Phosphorus Compounds, May 2008, p. 124, St. Petersburg, Russia ISBN5-88851-065-3.
12 M. Bidar, G. Tokmajyan, F. Nasiri and A. Avetisyan, *Arkivoc*, 2011, **ix**, 422–428.
13 NMR resonances for the ethoxy groups in the main product were partly obscured by other minor components present.
14 The molecular ions showed the expected isotopic ratio pattern.
15 L. A. Crawford, N. C. Clemence, H. McNab and R. G. Tyas, *Org. Biomol. Chem.*, 2008, **6**, 2334–2339.
16 Very limited solubility in organic solvents at lower temperatures.
17 M. Eitel and U. Pindur, *Synthesis*, 1989, 364–367.

Published on 03 April 2012 on http://pubs.rsc.org | doi:10.1039/C2OB25314C
Downloaded by Universidade Federal do Acre on 16 June 2012