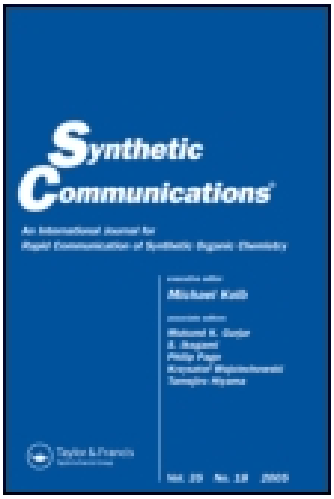

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SYNTHESIS OF BAYLIS–HILLMAN-DERIVED PHOSPHONATED 3-(BENZYLAMINOMETHYL)-COUMARINS

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Treatment of Baylis–Hillman-derived 3-(chloromethyl)coumarins with benzylamine has afforded benzylamino derivatives, sequential chloroacetylation and Michaelis–Arbuzov phosphonation of which have provided access to a series of phosphonate esters as potential HIV-1 protease inhibitors.

Keywords: Amides; Baylis–Hillman; coumarins; Michaelis–Arbuzov phosphonation

Coumarin (2*H*-1-benzopyran-2-one) **1** was first isolated, in 1822, from the tonka bean,[1] and many of its naturally occurring derivatives have been found to exhibit interesting and useful biological activity. Warfarin **2**,[2] for example, is not only used medicinally as a blood anti-coagulant but also as a rodenticide; dicoumarol **3**, found in sweet clover hay, acts as an anti-coagulant but is also responsible for sweet clover disease in cattle,[3,4] Warfarin **2** and its ''deacetylated'' analogue, phenprocoumon **4** both exhibit activity against HIV-1 protease,[5] the latter with an inhibition potential of 1 μM. Binding of these compounds in the HIV-1 protease receptor cavity is considered to involve hydrogen-bonding interactions between the 4-hydroxy group and the catalytic aspartic residues, and between the coumarin carbonyl group and an Ile-50 residue.[6] Kostova et al.[7] have reported the anti-HIV activity of various synthetic coumarins, and our own research on the development of novel HIV-1 protease inhibitors[8,9] has led us to explore the potential of coumarin derivatives as scaffolds for the construction of truncated analogues of the hydroxyethylene dipeptide isosteres currently in clinical use as HIV-1 protease inhibitors. In this paper, we discuss the preparation of a series phosphonated 3-(benzylaminomethyl)-coumarin derivatives as potential protease inhibitors.

We have previously reported the application of Baylis-Hillman methodology in the construction of 3-(chloromethyl)coumarin derivatives **7** *via* the DABCO-catalysed reaction of salicylaldehyde derivatives **5** with *t*-butyl acrylate (Scheme 1).[10] This

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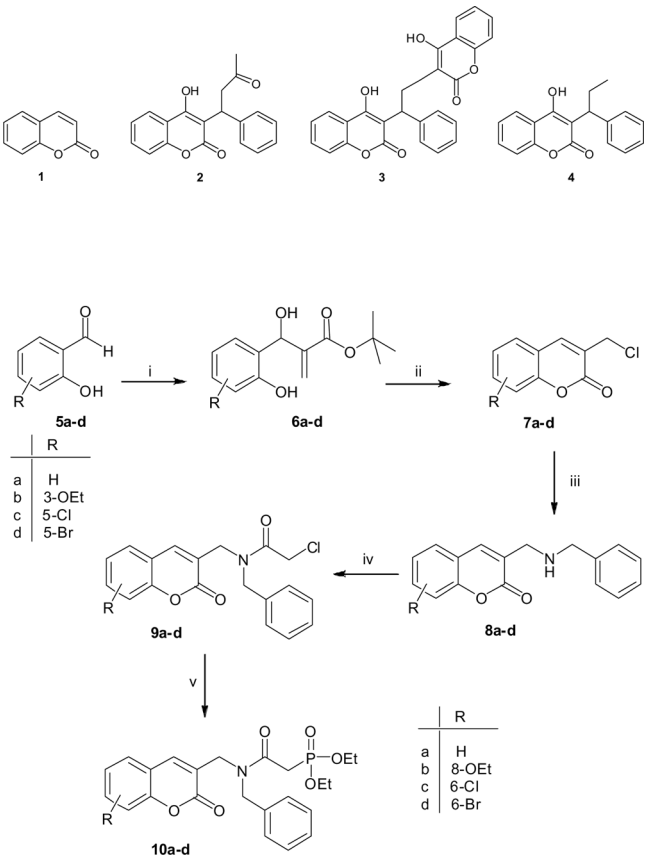

Scheme 1. Reagents and conditions: i) *t*-Butyl acrylate, DABCO, $CHCl_3$; ii) HCl, Ac_2O, AcOH, reflux; iii) $PhCH_2NH_2$, THF; iv) $ClCH_2COCl$, THF, reflux; v) $P(OEt)_3$, N_2, reflux.

approach permits isolation of the Baylis–Hillman adducts **6**, acid-catalysed cyclisation of which affords the 3-(chloromethyl)coumarin derivatives **7** in good yields (86% to 90%) and without the concomitant formation of isomeric chromenes.

The 3-(chloromethyl)coumarin derivatives **7** were reacted with benzylamine using THF as solvent (Scheme 1) and, following evaporation of the solvent *in vacuo*, the 3-(benzylaminomethyl)coumarin derivatives **8a–d** were isolated by flash chromatography in yields of up to 74% (Table 1). The ^{1}H-NMR spectra of the benzylamino derivatives **8a–d** are characterised by the presence of two, methylene proton singlets

Table 1. Isolated yields (%) of compounds **8a–d**, **9a–d**, and **10a–d** (Scheme 1)

	R	8	9	10
a	H	74	64	60
b	8-OEt	61	72	77
c	6-Cl	64	70	77
d	6-Br	35	56	86

at *ca*. 3.7 and 3.8 ppm, and the ^{13}C-NMR spectra by the corresponding methylene carbon signals at *ca*. 53 and 48 ppm.

The 3-(benzylaminomethyl)coumarin derivatives **8a-d** were then heated under nitrogen with chloroacetyl chloride in THF for 45 minutes to afford the chloroacetamide derivatives **9a–d** in yields of up to 72% (Table 1). The ^{1}H- and ^{13}C-NMR spectra were complicated by the presence of additional signals, which are attributed to the presence of rotamers arising from hindered rotation about the N-CO amide bond—a conclusion supported by the fact that when samples were run at higher temperature, the signals began to broaden and then coalesce (see Figure 1). Although complicated by the presence of signals corresponding to both rotamers, the COSY, HSQC and HMBC spectra were consistent with the assigned structures and the molecular formulae are supported by the HRMS data.

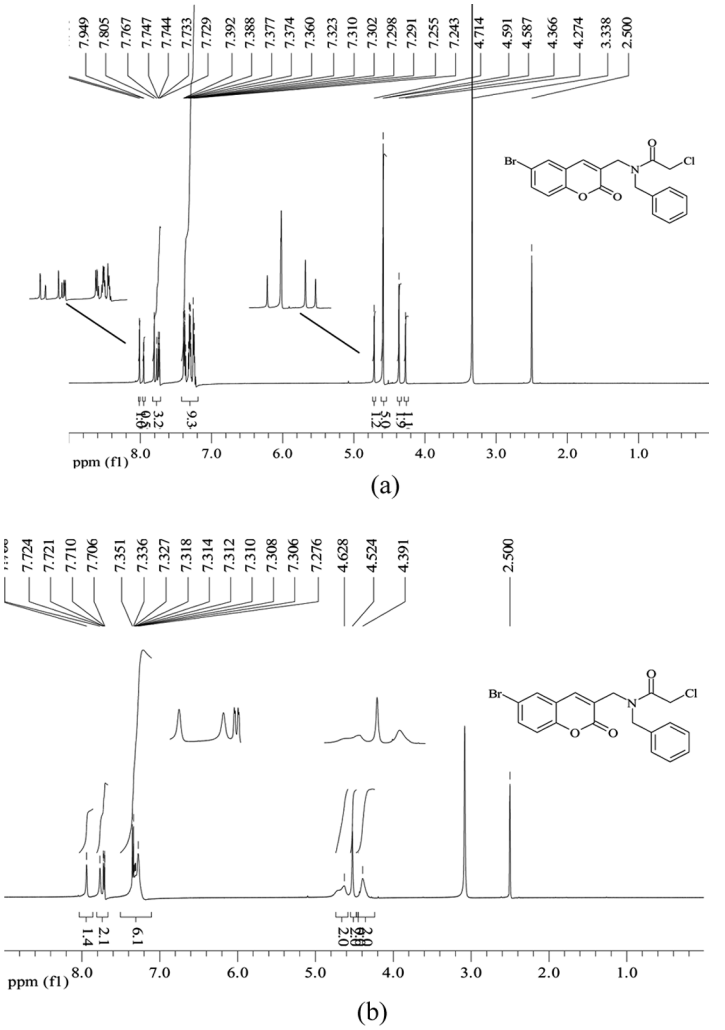

Figure 1. 400 MHz ^{1}H NMR spectra of compound **9d** in DMSO-d_6 at: a) 30 °C; and b) 100 °C.

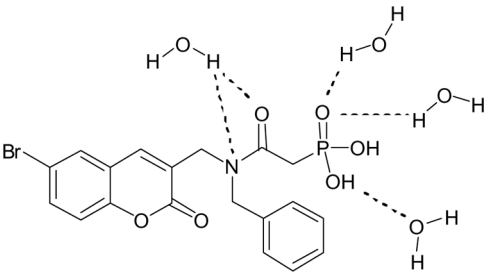

Figure 2. A schematic diagram of potential hydrogen-bonding interactions between the hydrolysed analogue of ligand **10d** and structural water molecules in the active site of the HIV-1 PR enzyme.[12]

In an earlier study,[11] we reported Michaelis–Arbuzov reactions of 3-(iodomethyl)- and 3-(chloromethyl)coumarins, the regiosectivity of which is determined by various factors; in the present study, however, direct (S_N) displacement of chloride by phosphite is the only option. Thus, when the chloroacetamide derivatives **9a–d** were heated under nitrogen with two equivalents of triethyl phosphite at 120–130 °C, flash chromatography afforded the phosphonated derivatives **10a–d** in good yields of up to 86% (Table 1). The ^{1}H– and ^{13}C–NMR spectra of the phosphonate esters were also complicated – not only by the presence of amide rotamers, but also by the expected ^{1}H–^{31}P and ^{13}C–^{31}P spin-spin coupling of proximate nuclei. Nevertheless, the 1- and 2-D NMR and HRMS data permitted unambiguous characterization of the products.

In vivo metabolism may be expected to effect hydrolysis of the phosphonate diester moiety, and preliminary *in silico* modelling of the hydrolysed analogue of ligand **10d** revealed several potential hydrogen-bonding interactions with structural water molecules in the active site of the HIV-1 PR enzyme (Figure 2).

Baylis–Hillman methodology has thus been used to provide access to precursors, which have been subjected, successfully, to tandem amination, chloroacetylation and Michaelis–Arbuzov phosphonation reactions to afford a series of phosphonated coumarin derivatives. Enzyme-binding, enzyme-inhibition and *in silico* enzyme receptor-site docking studies of these compounds are expected to elucidate their potential as readily accessible HIV-1 protease inhibitors. The 2-chloroacetamides **9** are also expected to serve as useful precursors for the construction of more complex derivatives.

EXPERIMENTAL

NMR spectra were recorded on Bruker AMX 400 and Biospin 600 spectrometers at 303 K in DMSO-d_6 or $CDCl_3$ and calibrated using solvent signals [7.25 ($CHCl_3$) and 2.50 ppm (DMSO-d_6) for ^{1}H NMR; 77.0 ($CDCl_3$) and 34.5 ppm (DMSO-d_6) for ^{13}C NMR]. ^{31}P NMR spectra were recorded using phosphoric acid (H_3PO_4) as an internal reference. Melting points were measured using a hot-stage apparatus and are uncorrected. Flash chromatography was performed using Merck Silica gel 60 [particle size 0.040–0.063 mm (230–400 mesh)] and MN Kieselgel 60 (particle size 0.063–0.200 mm). Infrared spectra were obtained on a Perkin Elmer

FT-IR Spectrum 2000 spectrometer using nujol mulls. Low-resolution (EI) mass spectra were obtained on a Finnigan-Mat GCQ mass spectrometer and high-resolution (EI) mass spectra on a VG70-SEQ Micromass double-focussing magnetic sector spectrometer (University of the North-West Mass Spectrometry Unit). The reagents used in the present study were supplied by Aldrich and used without further purification.

Docking of the hydrolysed derivative of ligand **10d** into the receptor cavity of an HIV-1 protease X-ray diffraction structure[11] was explored using the Ligandfit module in the Accelrys Cerius^2 platform on an SG-O^2 computer.

Compounds **6a–d**, **7a–d**, and **8a–d** are known and were prepared following reported methods.[10,11,13] The procedures used for the preparation of the compounds reported in this study are illustrated by the following examples.

N-Benzyl-2-chloro-*N*-[(6-bromo-2-oxo-2*H*-chromen-3-yl)-methyl]acetamide 9d

Chloroacetyl chloride (0.32 ml, 2 mmol) was added to 3-(benzylaminomethyl)-6-bromocoumarin **8d** (0.49 g, 1.4 mmol) in THF (6 ml) under nitrogen, and the mixture was boiled under reflux for 45 minutes. After cooling, the solvent was removed *in vacuo* and the residue crystallized from EtOH to afford N-*benzyl-2-chloro*-N-[(-*6-bromo-2-oxo-2H-chromen-3-yl)methyl*]*acetamide* **9d** as a white solid (0.34 g, 56%), m.p. 109–111 °C (Found M^+: 418.990988. $C_{19}H_{15}BrClNO_3$ requires *M*: 418.992382); ν_{max}(nujol)/cm^{-1} O–C=O (1721) and N–C=O (1658); δ_H (400 MHz; DMSO-d_6) 4.27–4.71 (6H, series of signals, 3 × CH_2), 7.23–7.80 (8H, overlapping multiplets, Ar-H) and 7.99 (1H, s, 4-H); *m/z* 421 (M + 1, 18%) and 182 (100%).[14]

Diethyl *N*-Benzyl-*N*-[(6-bromo-2-oxo-2*H*-chromen-3-yl)-methyl]carbamoylmethylphosphonate 10d

Triethyl phosphite (0.2 ml, 0.8 mmol) was added to *N*-benzyl-2-chloro-*N*-[(6-bromo-2-oxo-2*H*-chromen-3-yl)methyl]acetamide **9d** (0.157 g, 0.4 mmol), and the mixture was boiled under reflux, under nitrogen, for 4 hours. After cooling to room temperature, the crude mixture was flash chromatographed [on silica; elution with ethyl acetate-hexane (1:2)] to afford *diethyl* N-*benzyl*-N-[(*6-bromo-2-oxo-2*H-*chromen-3-yl)methyl*]*carbamoylmethylphosphonate* **10d** as a pale yellow solid (0.168 g, 86%), m.p. 137–139 °C (Found M^+: 521.058999. $C_{23}H_{25}BrNO_6P$ requires *M*: 521.060287); ν_{max} (nujol)/cm^{-1} O–C=O (1721), N–C=O (1658) and 1244 (P=O); (400 MHz; $CDCl_3$) 1.32 (6H, overlapping triplets, $J = 7$ Hz, 2 × OCH_2CH_3), 3.10 (2H, d, $J_{P,H} = 22$ Hz, CH_2P), 4.17 (2H, overlapping multiplets, 2 × CH_2OP), 4.50 and 4.83 (4H, 2 × s, 2 × CH_2N), 7.19–7.60 (7H, m, Ar-H), 7.67 (1H, s, 5-H), and 7.93 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$)[15] 16.3 (d, $J_{P,C} = 6.2$ Hz, 2 × OCH_2CH_3), 33.6 (d, $J_{P,C} = 140$ Hz, CH_2P), 45.9 and 52.8 (2 × CH_2N), 62.9 (d, $J_{P,C} = 6.4$ Hz, 2 × CH_2OP), 117.0, 118.0, 120.9, 124.2, 126.2, 127.9, 129.1, 130.2, 133.9, 135.7, 138.0, and 151.9 (Ar-C), 160.5 and 166.2 (C=O); *m/z* 523 (M + 1, 16%) and 106 (100%).

Analytical data for other compounds isolated in this study are as follows.

N-Benzyl-2-chloro-*N*-[(2-oxo-2*H*-chromen-3-yl)methyl]acetamide 9a

The procedure described for the synthesis of compound **9d** was followed using 3-[(benzylamino)methyl]coumarin **8a** (0.35 g, 1.3 mmol) and chloroacetyl chloride (0.30 ml, 2.6 mmol) in THF (6 ml). Crystallization from ethanol afforded N-*benzyl-2-chloro*-N-[(*2-oxo-2*H-*chromen-3-yl*)*methyl*]*acetamide* **9a** as a white solid (0.29 g, 64%), m.p. 98–100 °C (Found M^+: 341.083861. $C_{19}H_{16}ClNO_3$ requires *M*: 341.081871); ν_{max}(nujol)/cm^{-1} O−C=O (1721) and N−C=O (1658); δ_H (400 MHz; $CDCl_3$) 4.15–4.45 (6H, series of signals, $3 \times CH_2$), 7.23–7.57 (9H, overlapping multiplets, Ar-H) and 7.84 (1H, s, 4-H);[14] *m*/*z* 341 (M + 1, 22%) and 182 (100%).

N-Benzyl-2-chloro-*N*-[(8-ethoxy-2-oxo-2*H*-chromen-3-yl)-methyl]acetamide 9b

The procedure described for the synthesis of compound **9d** was followed using 3-[(benzylamino)methyl]-8-ethoxycoumarin **8b** (0.54 g, 1.7 mmol) and chloroacetyl chloride (0.4 ml, 4 mmol) in THF (8 ml). Chromatography [elution with ethyl acetate-hexane (1:4)] afforded N-*benzyl-2-chloro*-N-[(*8-ethoxy-2-oxo-2*H-*chromen-3-yl*)*methyl*]*acetamide* **55b** as a brown oil (0.48 g, 72%) (Found M^+: 385.108324. $C_{21}H_{20}ClNO_4$ requires *M*: 385.980888); ν_{max}(nujol)/cm^{-1} O−C=O (1721) and N−C=O (1658); δ_H (400 MHz; DMSO-d_6): 1.38 (3H, t, $J = 6.6$ Hz, OCH_2CH_3), 4.17 (2H, q, $J = 6.8$ Hz, OCH_2CH_3), 4.17–4.59 (6H, series of signals, $3 \times CH_2$), 7.26–7.38 (8H, overlapping multiplets, Ar-H) and 7.78 (1H, s, 4-H);[14] *m*/*z* 385 (M + 1, 25%) and 182 (100%).

N-Benzyl-2-chloro-*N*-[(6-chloro-2-oxo-2*H*-chromen-3-yl)-methyl]acetamide 9c

The procedure described for the synthesis of compound **9d** was followed using 3-[(benzylamino)methyl]-6-chlorocoumarin **8c** (0.18 g, 0.6 mmol) and chloroacetyl chloride (0.13 ml, 1.2 mmol) in THF (4 ml). Crystallization from ethanol afforded N-*benzyl-2-chloro*-N-[(*6-chloro-2-oxo-2*H-*chromen-3-yl*)*methyl*]*acetamide* **9c** as a white solid (0.156 g, 70%), m.p. 120–122 °C (Found M^+: 377.040222. $C_{19}H_{15}Cl_2NO_3$ requires *M*: 377.039949); ν_{max}(nujol)/cm^{-1} O−C=O (1721) and N−C=O (1658); δ_H (400 MHz; $CDCl_3$) 4.17–4.45 (6H, series of signals, $3 \times CH_2$), 7.27–7.48 (8H, overlapping multiplets, Ar-H), 7.74 (1H, s, 4-H);[14] *m*/*z* 377 (M + 1, 13%) and 91 (100%).

Diethyl *N*-Benzyl-*N*-[(2-oxo-2*H*-chromen-3-yl)-methyl]carbamoylmethylphosphonate 10a

The procedure described for the synthesis of compound **10d** was followed using *N*-benzyl-2-chloro-*N*-[(2-oxo-2*H*-chromen-3-yl)methyl]acetamide **9a** (0.16 g, 0.5 mmol) and triethyl phosphite (0.2 ml, 0.9 mmol). Chromatography afforded *diethyl* N-*benzyl*-N-[(*2-oxo-2*H-*chromen-3-yl*)*methyl*]*carbamoylmethylphosphonate* **10a** as a yellow solid (0.134 g, 60%), m.p. 138–140 °C (Found M^+: 443.152637. $C_{23}H_{26}NO_6P$ requires *M*: 443.149776); ν_{max}(nujol)/cm^{-1}: O−C=O (1721), N−C=O

(1658) and 1244 (P=O); (400 MHz; $CDCl_3$) 1.31 (6H, overlapping triplets, $2 \times OCH_2CH_3$), 3.10 (2H, d, $J_{P,H} = 22$ Hz, CH_2P), 4.09 (2H, overlapping signals, $2 \times CH_2OP$), 4.51 and 4.85 (4H, $2 \times$ s, $2 \times CH_2N$), 7.22–7.67 (9H, overlapping multiplets, Ar-H) and 7.98 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$)[15] 16.3 (d, $J_{P,C} = 6.3$ Hz, $2 \times OCH_2CH_3$), 33.6 (d, $J_{P,C} = 130$ Hz, CH_2P), 45.8 and 52.7 ($2 \times CH_2N$), 62.9 (d, $J_{P,C} = 6.6$ Hz, $2 \times CH_2OP$), 116.3, 119.3, 123.5 124.4, 126.2, 128.0, 128.7, 129.1, 131.2, 135.9, 139.6 and 153.1 (Ar-C), 161.3 and 166.1 (C=O); m/z 443 (M + 1, 10%) and 106 (100%).

Diethyl *N*-Benzyl-*N*-[(8-ethoxy-2-oxo-2*H*-chromen-3-yl)-methyl]carbamoylmethylphosphonate 10b

The procedure described for the synthesis of compound **10d** was followed using *N*-benzyl-2-chloro-*N*-[(8-ethoxy-2-oxo-2*H*-chromen-3-yl)methyl]acetamide **9b** (0.30 g, 0.8 mmol) and triethyl phosphite (0.26 ml, 2 mmol). Chromatography afforded *diethyl* N-*benzyl*-N-[(*8-ethoxy-2-oxo-2*H-*chromen-3-yl*)*methyl*]*carbamoyl-methylphosphonate* **10b** as a brown oil (0.19 g, 77%) (Found M^+: 487.174816. $C_{25}H_{30}NO_7P$ requires *M*, 487.175991); ν_{max} (nujol)/cm^{-1} O−C=O (1721), N−C=O (1658) and 1244 (P=O); (400 MHz; $CDCl_3$) 1.28 (6H, overlapping triplets, $2 \times OCH_2CH_3$), 1.46 (3H, t, $J = 7$ Hz, Ar-OCH_2CH_3), 3.1 (2H, d, $J_{P,H} = 22$ Hz, CH_2P), 4.17 (6H, overlapping multiplets, $2 \times CH_2OP$ and Ar-OCH_2CH_3), 4.50 and 4.82 (4H, $2 \times$ s, $2 \times CH_2N$), 7.10–7.43 (8H, overlapping multiplets, Ar-H), 7.92 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$)[15] 14.7 (Ar-OCH_2CH_3), 16.3 (d, $J_{P,C} = 4.2$ Hz, $2 \times OCH_2CH_3$), 27.4 (d, $J_{P,C} = 298$ Hz, CH_2P), 45.8 and 52.7 ($2 \times CH_2N$), 62.8 (d, $J_{P,C} = 4.3$ Hz, $2 \times CH_2OP$), 65.0 (Ar-OCH_2CH_3), 119.5, 120.1, 124.2, 124.6, 126.3; 127.9, 128.0, 128.7, 129.1, 136.0, 139.8 and 146.3 (Ar-C), 160.9 and 166.1 (C=O); m/z 487 (M + 1, 24%) and 106 (100%).

Diethyl *N*-Benzyl-*N*-[(6-chloro-2-oxo-2*H*-chromen-3-yl)-methyl]carbamoylmethylphosphonate 10c

The procedure described for the synthesis of compound **10d** was followed using *N*-benzyl-2-chloro-*N*-[(6-chloro-2-oxo-2*H*-chromen-3-yl)methyl]acetamide **9c** (0.46 g, 1.2 mmol) and triethyl phosphite (0.40 ml, 2 mmol). Chromatography afforded *diethyl* N-*benzyl*-N-[(*6-chloro-2-oxo-2*H-*chromen-3-yl*)*methyl*]*carbamoylmethylphos-phonate* **10c** as a yellow solid (0.455 g, 77%), m.p. 165–167 °C (Found M^+: 477.111852. $C_{23}H_{25}ClNO_6P$ requires *M*: 477.110804); ν_{max} (nujol)/cm^{-1} O−C=O (1721), N−C=O (1658) and 1244 (P=O); (400 MHz; $CDCl_3$) 1.35 (6H, overlapping triplets, $2 \times OCH_2CH_3$), 3.14 (2H, d, $J_{P,H} = 22$ Hz, CH_2P), 4.09 (4H, overlapping multiplets, $2 \times CH_2OP$), 4.55 and 4.87 (4H, $2 \times$ s, $2 \times CH_2N$), 7.27–7.49 (7H, m, Ar-H), 7.56 (1H, s, 5-H) and 7.93 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$)[15] 16.3 (d, $J_{P,C} = 6.2$ Hz, $2 \times OCH_2CH_3$), 33.6 (d, $J_{P,C} = 130$ Hz, CH_2P), 45.9 and 52.8 ($2 \times CH_2N$), 62.9 (d, $J_{P,C} = 6.5$ Hz, $2 \times CH_2OP$) 117.8, 120.4, 124.9, 127.2, 127.9, 128.7, 129.1, 129.7, 131.1, 135.8, 138.1 and 151.4 (Ar-C), 160.6 and 166.2 (C=O); m/z 477 (M + 1, 10%) and 106 (100%).

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14. ^{13}C data not cited due to multiplicity of signals arising from rotamers at 30 °C.
15. ^{13}C data cited for major rotamer.