Regio-controlled Michaelis–Arbuzov reactions of 3-(halomethyl)-coumarins

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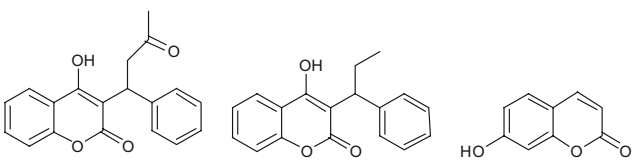
3-(Iodomethyl)coumarins and 3-(chloromethyl)coumarins, obtained chemoselectively *via* Baylis–Hillman reactions of salicylaldehyde derivatives with *t*-butyl acrylate, can be reacted with triethyl phosphite to afford regioisomeric Michaelis–Arbuzov products. Under nitrogen, the 3-(iodomethyl)coumarins undergo direct displacement of iodide to afford the expected 1'-phosphonated derivatives. The reactions with 3-(chloromethyl)coumarins in air, however, proceed with overall allylic rearrangement to afford the regioisomeric 3-methyl-4-phosphonated derivatives.

Keywords: 3-(chloromethyl)coumarins, 3-(iodomethyl)coumarins, Michaelis–Arbuzov reaction, allylic rearrangement

Many compounds containing the coumarin moiety (2*H*-1-benzopyran-2-one), both naturally-occurring and synthetic, have been shown to exhibit interesting medicinal properties, including anti-inflammatory,[1,2] antifungal[3] and anti-HIV properties.[4] Warfarin **1**, for example, is used as an anti-coagulant and has been shown to be weakly active against HIV-1 protease enzyme.[5] Another 4-hydroxycoumarin derivative, phenprocoumon **2,** acts as a competitive HIV-1 protease inhibitor and was identified as a lead structure in the design of non-peptidic inhibitors.[6] The hydroxycoumarin, umbelliferone **3**, is found in a variety of plants, and has been used as a sunscreen and as a fluorescence indicator.[7-9]

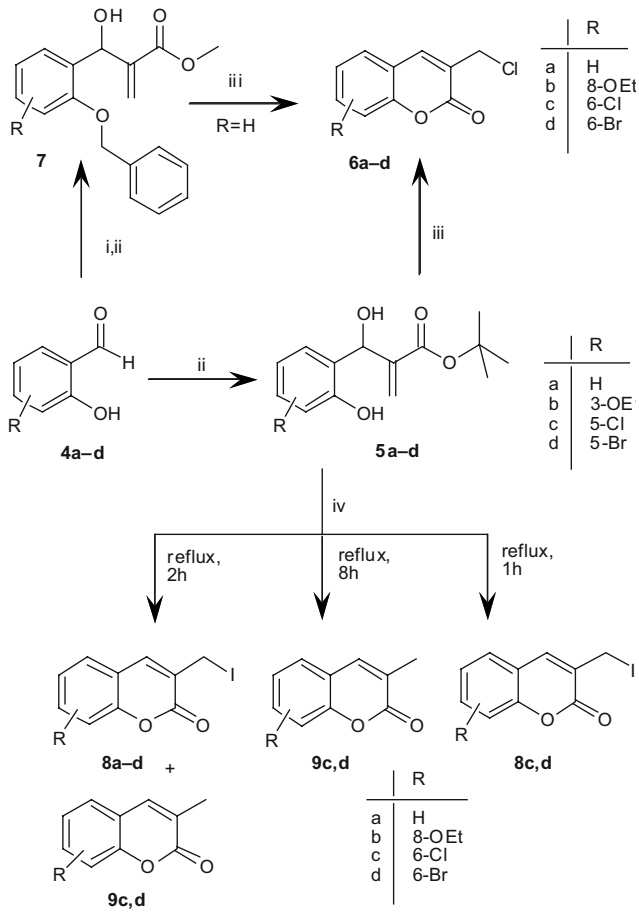


1 **2** **3**

Numerous methods have been developed for the the synthesis of coumarins, including the Pechmann condensation,[10,11] the Perkin reaction,[11] the Knoevenagel condensation[12] and the Wittig reaction.[13] In our own group, particular attention has been given to applications of the Baylis–Hillman reaction in the construction of benzannulated heterocyclic systems,[14,15] including coumarins.[16-18] We have found that reaction of salicylaldehyde derivatives **4** with *t*-butyl acrylate using 1,4-diazabicyclo[2.2.2]octane (DABCO) as catalyst affords the *isolable* Baylis–Hillman adducts **5** (Scheme 1), which cyclise on treatment with HCl to form the 3-(chloromethyl)coumarin derivatives **6** in good yields (86–90%).[18] This approach obviated the need to protect the nucleophilic phenolic group (*via* benzylation, as in **7**) and thus prevent the formation of complex mixtures of chromene and coumarin deivatives (Scheme 1).[16,17]

As part of an ongoing programme directed at the development of novel HIV-1 protease inhibitors,[19] we have begun to explore the synthesis of various coumarin derivatives as potential inhibitors. In this paper, we discuss the formation of phosphonated coumarin derivatives *via* Arbuzov reactions of series of specially prepared 3-(chloromethyl)- and 3-(iodomethyl)coumarins.

Following our earlier procedure,[18] the Baylis–Hillman adducts **5a–d** were reacted with hydrochloric acid in a mixture of acetic acid and acetic anhydride, under reflux for 2 hours, to give the 3-(chloromethyl)coumarin derivatives **6a–d** in yields of up to 94%. The Baylis–Hillman adducts **5a–d** were similarly reacted with hydriodic acid to give 3-(iodomethyl)coumarins **8a–d**, previously obtained



Scheme 1 *Reagents and conditions:* (i) $PhCH_2Br$, K_2CO_3, NaI, acetone; (ii) Methyl acrylate or *t*-butyl acrylate, DABCO, $CHCl_3$; (iii) HCl, Ac_2O, AcOH, reflux; (iv) HI, Ac_2O, AcOH, reflux.

using protection strategies.[16,17] However, in the cases of the 5-chloro- and 5-bromo substrates (**5c,d**), the 3-methyl analogues **9c,d** were isolated together with the corresponding 3-(iodomethyl)coumarins **8c,d**. When the reaction mixtures containing the adducts **5c** and **5d** were refluxed for 8 hours, the 3-methyl analogues **9c,d** were obtained as the sole products − a result attributed to HI-mediated reduction of the initially formed 3-(iodomethyl)coumarins **8c,d**. In view of this complication, the reaction time for these two substrates (**9c**,**d**) was reduced to 1 h and the required 3-(iodomethyl)coumarins **8c** and **8d** were obtained as the sole products (see Table 1).

The 3-(halomethyl)coumarins (**6a–d** and **8a–d**) may be expected, in principle, to be susceptible to nucleophilic attack at one or more of three electrophilic centres (C-2, C-4 or C-1'; Fig. 1).

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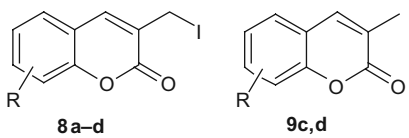
Table 1 Yields obtained for the synthesis of the coumarin derivatives **8a–d** and **9c,d** using HI (Scheme 1)



8a–d **9c,d**

Substrate	R	Reflux period/h	Yield of 8/%	Yield of 9/%
5a	H	2	60	–
5b	8-OEt	2	62	–
5c	6-Cl	1	61	–
		2	52	45
		8	–	91
5d	6-Br	1	58	–
		2	52	43
		8	–	80

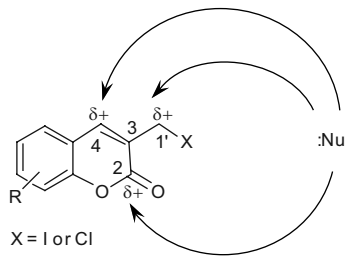
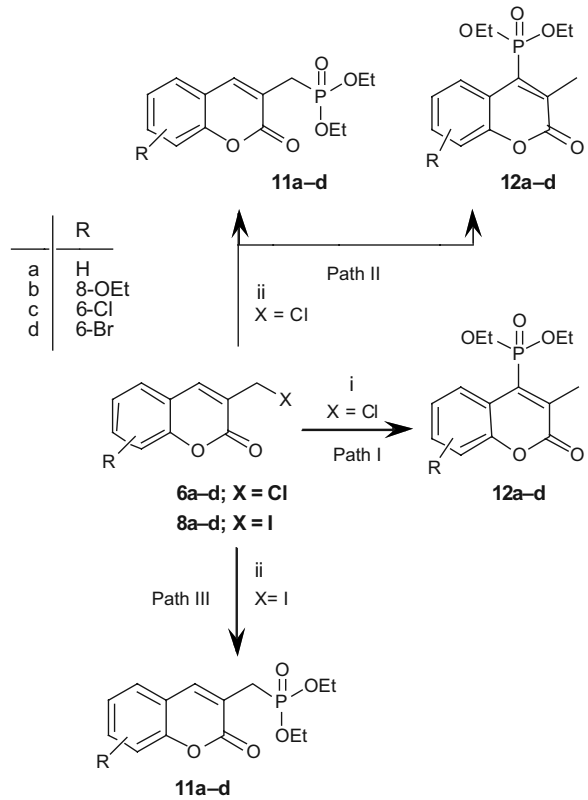


Fig. 1 Possible modes of nucleophilic attack on the 3-(halomethyl)coumarin derivatives **8** and **9**.

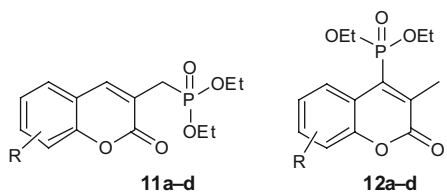
The Michaelis–Arbuzov reaction, which involves heating alkyl halides with triethyl phosphite, provides convenient access to alkylphosphonate derivatives, the mechanism typically involving direct (S_N) displacement of halide.[20] However, when the 3-(chloromethyl)coumarin derivatives **6a–d** were boiled under reflux with two equivalents of triethyl phosphite under solvent-free conditions in air (pathway I, Scheme 2), the 4-phosphonated (S_N') products **12a–d** were obtained in yields of up to 68% (Table 2), but none of the expected 1'-phosphonated products **11a–d**. [Interestingly, reactions of 3-substituted coumarins with nitrogen and carbon nucleophiles, examined in an earlier study,[21] appeared to proceed with exclusive, direct (S_N) substitution at the exocyclic C-1' electrophilic centre!] The 3-(chloromethyl)coumarin derivatives **6a–d** were then treated with 2 equivalents of triethylphosphite under the same conditions, except that the reaction was conducted under nitrogen (pathway II;). Flash chromatography of the isolated material afforded both the 1'-phosphonated (S_N) products **11a–d** (in yields of up to 67%) together with the 4-phosphonated (S_N') products **12a–d** (in yields of up to 16%). Remarkably, when the 3-(iodomethyl)coumarins **8a–d** were treated with 2 equivalents of triethyl phosphite under nitrogen, the 1'-phosphonated (S_N) products **11a–d** were isolated with no trace of the 4-phosphorylated analogues **12a–d** (pathway III, Scheme 2)! The role of nitrogen in these reactions, however, is not, as yet, understood.

Formation of the 1'-phosphonated products **11a–d** presumably proceeds by direct (S_N) displacement of the halide anion (chloride or iodide), whereas displacement of chloride in formation of the 4-phosphonated analogues **12a–d** could involve either an S_N' pathway or a conjugate addition-elimination sequence. The observed halide-specific regioselectivities may be tentatively rationalised in terms of the relative electronegativities of the halogen atoms and the leaving-group potential of the corresponding halide anions. Since iodide is a very good leaving group, the Michaelis–



Scheme 2 *Reagents and conditions:* (i) 2 equiv. $P(OEt)_3$, reflux, 4 h; (ii) 2 equiv. $P(OEt)_3$, N_2, reflux, 4 h.

Table 2 Yields obtained for the synthesis of 1'-phosphorylated products **11a–d** and 4-phosphorylated products **12a–d** (Scheme 2)

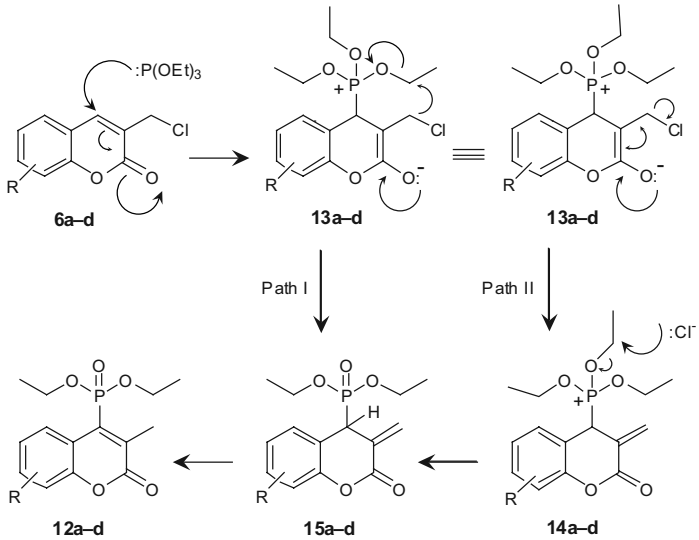


11a–d **12a–d**

Substrate	X	R	Method[a]	Yield of 11/%	Yield of 12/%
6a	Cl	H	A	–	60
6b	Cl	8-OEt	A	–	52
6c	Cl	6-Cl	A	–	68
6d	Cl	6-Br	A	–	65
6a	Cl	H	B	43	16
6b	Cl	8-OEt	B	67	14
6c	Cl	6-Cl	B	53	10
6d	Cl	6-Br	B	53	8
8a	I	H	B	61	–
8b	I	8-OEt	B	40	–
8c	I	6-Cl	B	54	–
8d	I	6-Br	B	40	–

[a]Method A: Reflux in air. Method B: reflux under nitrogen.

Arbuzov reaction may well favour attack of phosphorus at the less hindered 1'-centre of an intermediate, delocalised allylic carbocation *via* a direct (S_N1) pathway. Chloride, on the other hand, is a somewhat poorer leaving group, and its bimolecular displacement by phosphorus could occur at *either* the sp^3 allylic centre (C-1') *via* an S_N2 pathway *or*, preferentially, at the less-hindered sp^2 vinylic centre (C-4) *via* an S_N2' pathway, the electrophilicity of the latter centre being enhanced by the electron-withdrawing inductive effect of the more



Scheme 3 Mechanistic possibilities for the conjugate addition–elimination pathway.

electronegative chlorine. Alternatively, the mechanism for the formation of the 4-phosphonated analogues **12a–d** from the 3-(chloromethyl)coumarins derivatives **6a–d** could involve initial conjugate addition of $P(OEt)_3$ to the α,β-unsaturated carbonyl system to afford the intermediates **13a–d**. Concerted (Path I; Scheme 3) or step-wise (*via* intermediates **14**; Path II) routes, involving halide displacement and attack at one of the *O*-ethyl groups would both be expected to afford the common intermediates **15**. Rearrangement of the double bond would then afford the aromatic 4-phosphonated derivatives **12a–d**. Whatever the mechanism, the net result is, effectively, a Michaelis–Arbuzov reaction with allylic rearrangement – a process, which to our knowledge, is unprecedented!

All new products were fully characterised by elemental (HRMS) and spectroscopic (IR and 1- and 2-D NMR) analysis. In the ^{1}H NMR spectra of the 1'-phosphonate derivatives **11a–d**, the P-*O*-methylene protons typically resonate as a quartet at *ca.* 4.1 ppm, while the ^{13}C NMR data are consistent with magnetic equivalence of both *O*-methylene carbons. The P-*O*-methylene protons in the 4-phosphonate derivatives **12a–d**, on the other hand, resonate as a *pair* of discrete or overlapping multiplets in the region 4.1–4.3 ppm. The DEPT-135, HSQC and proton noise decoupled ^{13}C NMR spectra of each of the 4-phosphonate derivatives **12a–d**, however, indicate the presence of a *single*, P-*O*-methylene carbon doublet [*e.g.*, for **12c**: $\delta_C = 63.0$ (d, $^3J_{P,C} = 5.6$ Hz)] corresponding to the *pair* of methylene proton multiplets at *ca* 4.2 and 4.3 ppm. These observations are attributed to the diastereotopicity and, hence, magnetic non-equivalence of the geminal *O*-methylene protons on the magnetically equivalent *O*-methylene carbons.

Experimental

NMR spectra were recorded on Bruker AMX 400 and Biospin 600 spectrometers at 303K 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 (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 Kofler hot stage apparatus and are uncorrected. Flash column 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). IR 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-focusing magnetic sector spectrometer (Potchefstroom University Mass Spectrometry Unit). The reagents used in the present study were supplied by Aldrich and used without further purification.

Compounds **5a–d**, **6a–d**, **7** and **9c**,**d** are known.[16,17] The 3-(iodomethyl)coumarins **8a–d** are also known,[16,17] but their synthesis *via* the *tert*-butyl acrylate esters **5a–d** has not been published previously. The procedures used in this study are illustrated by the following examples.

3-(Iodomethyl)coumarin (**8a**): Conc. HI (10 mL) was added to a solution of *tert*-butyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylenepropanoate **5a** (0.50 g, 2.0 mmol) in a mixture of AcOH (5 mL) and Ac_2O (5 mL). The mixture was boiled under reflux for 2 h, allowed to cool to room temperature and then poured into ice-cooled water (10 mL). Stirring for *ca* 30 min gave a precipitate, which was filtered off and washed with hexane to afford 3-(iodomethyl)coumarin **8a** as a grey solid (0.35 g, 60%), m.p. 148–151 °C (lit.,[16] 150–152 °C).

6-Chloro-3-(iodomethyl)coumarin **8c** and *6-chloro-3-methyl-coumarin* (**9c**): The procedure described for the synthesis of 3-(iodomethyl)coumarin **8a** was followed, using conc. HI (10 mL) and *tert*-butyl 3-(5-chloro-2-hydroxyphenyl)-3-hydroxy-2-methyl-enepropanoate **5c** (0.52 g, 2 mmol) in a mixture of AcOH (5 mL) and Ac_2O (5 mL). Work-up and chromatography [on silica gel; elution with ethyl acetate-chloroform-hexane (1 : 1 : 3)] afforded two fractions. *Fraction 1*: 6-Chloro-3-(iodomethyl)coumarin **8c** as a yellow solid (0.308 g, 52%), m.p. 186–189 °C (lit.,[16] 188–190 °C). *Fraction 2*: 6-Chloro-3-methylcoumarin **9c** as pale yellow solid (0.162 g, 45%), m.p. 128–132 °C (lit.,[22] 158–160 °C).

Michaelis-Arbuzov phosphonation: Method A

*Diethyl (3-methyl-2-oxo-2*H*-chromen-4-yl)phosphonate* (**12a**): To 3-(chloromethyl)coumarin **6a** (0.35 g, 1.3 mmol) was added triethyl phosphite (0.42 mL) and the mixture was boiled under reflux for 4 h. Upon completion of the reaction, as monitored by TLC, the mixture was separated by flash column chromatography [on silica gel; elution with ethyl acetate–hexane (3 : 1)] to afford *diethyl (3-methyl-2-oxo-2*H*-chromen-4-yl)phosphonate* **12a** as a yellow solid (0.318 g, 60%), m.p. 47–49 °C; (Found M^+: 296.082484. $C_{14}H_{17}O_5P$ requires *M*: 296.081362); ν_{max} (nujol)/cm^{-1} 1734 (C=O) and 1240 (P = O); δ_H (400 MHz; $CDCl_3$) 1.34 (6H, t, $J = 7$ Hz, 2 × CH_2CH_3), 2.61 (3H, d, $J = 3.2$ Hz, 3-CH_3), 4.16 and 4.26 (4H, 2 × m, 2 × CH_2OP), 7.25-7.30 (2H, m, ArH), 7.46 (1H, m, ArH) and 8.49 (1H, dd, $J = 8.2$ and 1 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 16.26 (d, $J_{P,C} = 6.1$ Hz, 2 × CH_2CH_3), 16.3 (3-CH_3), 62.8 (d, $J_{P,C} = 5.5$ Hz, 2 × CH_2OP), 116.7 (d, $J_{P,C} = 2.6$ Hz), 118.1 (d, $J_{P,C} = 11.2$ Hz), 124.2, 128.0 (d, $J_{P,C} = 1.5$ Hz), 130.6, 135.5 (d, $J_{P,C} = 23$ Hz), 137.4 and 152.0 (d, $J_{P,C} = 13.2$ Hz) (ArC), and 161.1 (d, $J_{P,C} = 13.2$ Hz, C=O); *m/z* 296 (M^+, 100%).

Michaelis-Arbuzov phosphonation: Method B

*Diethyl [(2-oxo-2*H*-chromen-3-yl)methyl]phosphonate* **11a** and *diethyl (3-methyl-2-oxo-2*H*-chromen-4-yl)phosphonate* (**12a**): To 3-(chloromethyl)coumarin **6a** (0.823 g, 4.3 mmol) was added triethyl phosphite (1.4 mL) and the mixture was refluxed under nitrogen for 4 h. Upon completion of the reaction, as monitored by TLC, the mixture was separated by flash column chromatography [on silica gel; elution with ethyl acetate-hexane (3:1)] to afford two fractions.

Fraction 1: *Diethyl (3-methyl-2-oxo-2*H*-chromen-4-yl)phosphonate* (**12a**): Pale yellow solid (0.236 g, 16%).
Fraction 2: *Diethyl [(2-oxo-2*H*-chromen-3-yl)methyl]phosphonate* (**11a**): Pale brown oil (0.401 g, 43%); (Found M^+: 296.079819. $C_{14}H_{17}O_5P$ requires *M*: 296.081362); ν_{max} (nujol)/cm^{-1} 1734 (C=O) and 1240 (P = O); δ_H (400 MHz; $CDCl_3$) 1.31 (6H, t, *J* = 7 Hz, $2\times OCH_2CH_3$), 3.18 (2H, d, $J_{P,H}$ = 22 Hz, CH_2P), 4.14 (4H, m, $2\times CH_2OP$), 7.25–7.52 (4H, series of multiplets, ArH) and 7.83 (1H, d, $J_{P,C}$ = 4.4 Hz, 4-H); δ_C (100 MHz; $CDCl_3$) 16.3 (d, $J_{P,C}$ = 6.1 Hz, $2\times OCH_2CH_3$), 26.7 (d, $J_{P,C}$ = 139 Hz, CH_2P), 62.4 (d, $J_{P,C}$ = 6.6 Hz, $2\times CH_2OP$), 116.4, 119.1 (d, $J_{P,C}$ = 3.5 Hz), 120.5 (d, $J_{P,C}$ = 9.4 Hz), 124.4, 127.6 (d, $J_{P,C}$ = 1.3 Hz), 131.3, 141.7 (d, $J_{P,C}$ = 7.9 Hz) and 153.2 (d, $J_{P,C}$ = 1.8 Hz) (ArC) and 161.2 (d, $J_{P,C}$ = 6.6 Hz, C=O); *m/z* 296 (M^+, 90%) and 160 (100%).

Analytical data for other new compounds isolated in this study are as follows.
*Diethyl [(8-ethoxy-2-oxo-2*H*-chromen-3-yl)methyl]phosphonate* (**11b**): Yellow solid (0.83 g, 67%), m.p. 53–56 °C; (Found M^+: 340.107526. $C_{16}H_{21}O_6P$ requires *M*: 340.107577); ν_{max} (nujol)/cm^{-1} 1724 (C=O) and 1258 (P = O); δ_H (400 MHz; $CDCl_3$) 1.26 (6H, m, $2\times POCH_2CH_3$), 1.45 (3H, t, *J* = 6.8 Hz, Ar-OCH_2CH_3), 3.14 (2H, d, $J_{P,H}$ = 22 Hz, CH_2P), 4.11 (6H, m, $2\times CH_2OP$ and Ar-OCH_2CH_3), 7.00 (2H, dd, *J* = 7.8 and 4.6 Hz, ArH), 7.13 (1H, t, *J* = 7.8 Hz, ArH) and 7.77 (1H, d, $J_{P,C}$ = 4.4 Hz, 4-H); δ_C (100 MHz; $CDCl_3$) 14.6 (Ar-OCH_2CH_3), 16.3 (d, $J_{P,C}$ = 6.1 Hz, $2\times OCH_2CH_3$), 26.6 (d, $J_{P,C}$ = 139 Hz, CH_2P), 62.4 (d, $J_{P,C}$ = 6.5 Hz, $2\times CH_2OP$), 64.9 (Ar-OCH_2CH_3), 114.5, 119.0, 119.9, 120.3, 124.3, 142.0 (d, $J_{P,C}$ = 7.8 Hz), 143.1, 146.3 and 147..0 (ArC) and 160.8 (d, $J_{P,C}$ = 6.6 Hz, C=O); *m/z* 340 (M^+, 100%).
*Diethyl [(6-chloro-2-oxo-2*H*-chromen-3-yl)methyl]phosphonate* (**11c**): Yellow solid (0.61 g, 53%), m.p. 72–74 °C; (Found M^+: 330.042081. $C_{14}H_{16}{}^{35}ClO_5P$ requires *M*: 330.042389); ν_{max} (nujol)/cm^{-1} 1725 (C=O) and 1260 (P = O); δ_H (400 MHz; $CDCl_3$) 1.31 (6H, t, *J* = 7.2 Hz, $2\times OCH_2CH_3$), 3.18 (2H, d, $J_{P,H}$ = 22 Hz, CH_2P), 4.13 (4H, m, $2\times CH_2OP$), 7.27 (1H, s, ArH), 7.44–7.46 (2H, s and overlapping d, ArH) and 7.75 (1H, d, $J_{P,C}$ = 4 Hz, 4-H); δ_C (100 MHz; $CDCl_3$) 16.4 (d, $J_{P,C}$ = 6.1 Hz, $2\times CH_2CH_3$), 26.8 (d, $J_{P,C}$ = 139 Hz, CH_2P), 62.5 (d, $J_{P,C}$ = 6.4 Hz, $2\times CH_2OP$), 117.9, 120.1 (d, $J_{P,C}$ = 3.6 Hz), 121.6 (d, $J_{P,C}$ = 6.6 Hz), 126.8, 129.7, 131.2, 140.4 (d, $J_{P,C}$ = 7.9 Hz) and 151.5 (d, $J_{P,C}$ = 1.9 Hz) (ArC) and 161.3 (d, $J_{P,C}$ = 6.4 Hz, C=O); *m/z* 330 [M^+ (^{35}Cl), 80%] and 109 (100%).
*Diethyl [(6-bromo-2-oxo-2*H*-chromen-3-yl)methyl]phosphonate* (**11d**): Pale brown oil (0.761 g, 53%); (Found M^+: 375.849564. $C_{14}H_{16}{}^{81}BrO_5P$ requires *M*: 375.850947); ν_{max} (nujol)/cm^{-1} 1725 (C=O) and 1260 (P = O); δ_H (400 MHz; $CDCl_3$) 1.28 (6H, t, *J* = 7.2 Hz, $2\times CH_2CH_3$), 3.15 (2H, d, $J_{P,H}$ = 22 Hz, CH_2P), 4.10 (4H, q, *J* = 6.8 Hz, 2x CH_2OP), 7.27–7.45 (3H, series of multiplets, ArH) and 7.74 (1H, d, $J_{P,C}$ = 6.1 Hz, 4-H); *m/z* 376 [M + 1 (^{81}Br), 70%] and 109 (100%).
*Diethyl (8-ethoxy-3-methyl-2-oxo-2*H*-chromen-4-yl)phosphonate* (**12b**): Pale Yellow solid (0.186 g, 52%), m.p. 42–45 °C; (Found M^+: 340.106262. $C_{16}H_{21}O_6P$ requires *M*: 340.107577); ν_{max} (nujol)/cm^{-1} 1709 (C=O) and 1260 (P = O); δ_H (400 MHz; $CDCl_3$) 1.32 (6H, t, *J* = 7.2 Hz, $2\times POCH_2CH_3$), 1.46 (3H, t, *J* = 7 Hz, Ar-OCH_2CH_3), 2.60 (3H, d, $J_{P,H}$ = 3.2 Hz, 3-CH_3), 4.10–4.27 (6H, m, $2\times CH_2OP$ and $1\times$ Ar-OCH_2CH_3), 7.01 (1H, d, *J* = 8 Hz, ArH), 7.15 (1H, t, *J* = 8.2 Hz, ArH) and 8.03 (1H, d, *J* = 8.4 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 14.7 (Ar-OCH_2CH_3), 16.2 (3-CH_3), 16.3 (d, $J_{P,C}$ = 6.2 Hz, $2\times POCH_2CH_3$), 62.7 (d, $J_{P,C}$ = 5.5 Hz, $2\times CH_2OP$), 65.0 (Ar-OCH_2CH_3), 114.0, 118.8 (d, $J_{P,C}$ = 11.7 Hz), 119.3 (d, $J_{P,C}$ = 1.7 Hz), 123.7, 135.7, 135.8 (d, $J_{P,C}$ = 1.6 Hz), 137.5, 142.2 (d, $J_{P,C}$ = 1.9 Hz) and 146.3 (d, $J_{P,C}$ = 3.7 Hz) (ArC) and 160.6 (d, $J_{P,C}$ = 24 Hz, C=O).
*Diethyl (6-chloro-3-methyl-2-oxo-2*H*-chromen-4-yl)phosphonate* (**12c**): Pale yellow solid (0.26 g, 68%), m.p. 76–78 °C; (Found M^+: 330.042192. $C_{14}H_{16}{}^{35}Cl\ O_5P$ requires *M*: 330.042390); ν_{max} (nujol)/cm^{-1} 1730 (C=O) and 1255 (P = O); δ_H (400 MHz; $CDCl_3$) 1.34 (6H, t, *J* = 7 Hz, $2\times CH_2CH_3$), 2.57 (3H, d, $J_{P,H}$ = 3.2 Hz, 3-CH_3), 4.16 and 4.26 (4H, 2 × m, $2\times CH_2OP$), 7.19 (1H, d, *J* = 8.8 Hz, ArH), 7.40 (1H, dd, *J* = 8.8 and 2.4 Hz, ArH) and 8.52 (1H, d, *J* = 2.4 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 16.3 (d, $J_{P,C}$ = 6.2 Hz, $2\times OCH_2CH_3$), 16.5 ($J_{P,C}$ = 4.1 Hz, 3-CH_3), 63.0 (d, $J_{P,C}$ = 5.6 Hz, $2\times CH_2OP$), 117.9 (d, $J_{P,C}$ = 2.4 Hz), 119.1 (d, $J_{P,C}$ = 11 Hz), 127.5, 129.7, 130.7, 134.8, 136.5 (d, $J_{P,C}$ = 9 Hz) and 150.4 (d, $J_{P,C}$ = 13 Hz) (ArC) and 160.4 (d, $J_{P,C}$ = 23 Hz, C=O); *m/z* 330 [M^+ (^{35}Cl), 100%].
*Diethyl (6-bromo-3-methyl-2-oxo-2*H*-chromen-4-yl)phosphonate* (**12d**): Yellow solid (0.31 g, 65%), m.p. 77–79 °C; (Found M^+: 373.989683. $C_{14}H_{16}{}^{79}BrO_5P$ requires *M*: 373.991873); ν_{max} (nujol)/cm^{-1} 1734 (C=O) and 1240 (P = O); δ_H (400 MHz; $CDCl_3$) 1.36 (6H, t, *J* = 7.2 Hz, $2\times CH_2CH_3$), 2.59 (3H, d, $J_{P,H}$ = 3.2 Hz, 3-CH_3), 4.18 and 4.27 (4H, 2 × m, $2\times CH_2OP$), 7.16 (1H, d, *J* = 8.8 Hz, ArH), 7.55 (1H, dd, *J* = 8.8 and 1.8 Hz, ArH) and 8.69 (1H, d, $J_{P,H}$ = 2 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 16.3 (d, $J_{P,C}$ = 6.1 Hz, $2\times OCH_2CH_3$), 16.5 (d, $J_{P,C}$ = 4.1 Hz, 3-CH_3), 63.0 (d, $J_{P,C}$ = 5.6 Hz, $2\times CH_2OP$), 117.2, 118.3 (d, $J_{P,C}$ = 2.4 Hz), 119.6, 130.6, 133.5, 134.8, 136.6 (d, $J_{P,C}$ = 9 Hz) and 150.8 (d, $J_{P,C}$ = 13 Hz) (ArC), and 160.3 (d, $J_{P,C}$ = 23 Hz, C=O).

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