A Convenient and Improved Baylis–Hillman Synthesis of 3-Substututed 2*H*-1-benzopyran-2-ones

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Abstract: Halogen acid-catalysed deprotection and cyclisation of Baylis–Hillman products obtained using *O*-benzylated salicylaldehyde precursors has been shown to afford 3-(halomethyl)coumarins (3-halomethyl-2*H*-1-benzopyran-2-ones) chemoselectively and in good yield.

Key words: heterocycles, synthesis, coumarins, 2*H*-1-benzopyran-2-ones, Baylis–Hillman reaction

The coumarin (2*H*-1-benzopyran-2-one) nucleus is present in many compounds that exhibit pharmacological activity.[1] These include antibiotics, such as novobiocin,[2] the anticoagulant, dicoumarol,[3] and the calanolides A and B, which act as *in vitro* inhibitors of HIV-1 replication.[4] 4-Hydroxycoumarin derivatives have also shown promise as HIV-1 integrase- and non-peptidic HIV-1 protease inhibitors.[5,6] Various methods for preparing coumarin derivatives have been developed, including the classic Pechmann,[7] Claisen,[8] Wittig[9] and Knoevenagel[10] reactions. There is, nevertheless, a continuing interest in the synthesis of these important systems. Bogdal,[11] for example, has recently reported a microwave-assisted Knoevenagel condensation that affords coumarins in yields of up to 94%, while Santana and co-workers[12] have applied Wittig and Reformatsky methodology in the synthesis of potential antipsychotic compounds containing the coumarin nucleus.

In our own research on applications of Baylis–Hillman methodology in the construction of benzannulated heterocycles, we have developed convenient syntheses of indolizines,[13] quinolines[14] and 2*H*-1-thiochromenes.[15] Earlier attempts to use this approach to access 2*H*-1-chromenes from salicylaldehyde precursors **1** afforded complex mixtures of chromene and coumarin derivatives[16,17] via, as we have suggested, cyclisation of putative Baylis–Hillman intermediates **3** (Figure 1). Attention was subsequently focussed on controlling the regioselectivity of cyclisation to afford *either* chromene *or* coumarin derivatives. Chemoselective access to 2*H*-1-chromenes has been achieved[18] using activated alkenes that preclude acyl substitution and, in a recent communication,[19] we have reported the use of Baylis–Hillman methodology to prepare 3-substituted coumarin derivatives (**7** and **8**, Scheme 1). The strategy adopted to inhibit the formation of chromene derivatives (Path I, Figure 1) followed an approach previously identified by Drewes et al.[20] and involved three phases: i) protection of the salicylaldehyde phenolic hydroxyl group as a benzyl ether; ii) nucleophilic interception of the electrophilic vinylic centre in the Baylis–Hillman product using benzylamine or piperidine; and iii) deprotection of the phenolic oxygen (via hydrogenolysis in the presence of 10% Pd/C catalyst) to permit cyclisation to coumarins via acyl substitution. We now report an extension of this approach that eliminates the need for a *separate* nucleophilic interception step.

The benzyl ethers **4a**–**f**, obtained in good yield by treating the salicylaldehyde precursors **1a**–**f** with benzyl bromide in the presence of K_2CO_3 and NaI, were reacted with methyl acrylate **2** in the presence of DABCO to afford the *O*-benzylated Baylis–Hillman products **5a**–**f** (Scheme 1).[19] Ethers are typically cleaved on heating with concentrated hydriodic acid or hydrobromic acid, and Santana and coworkers[12] have reported the use of hydriodic acid in the

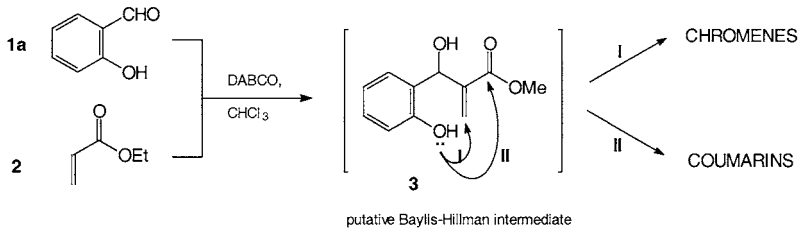

Figure 1 Cyclisation of putative Baylis–Hillman intermediates via conjugate addition (I) or acyl substitution (II) pathways

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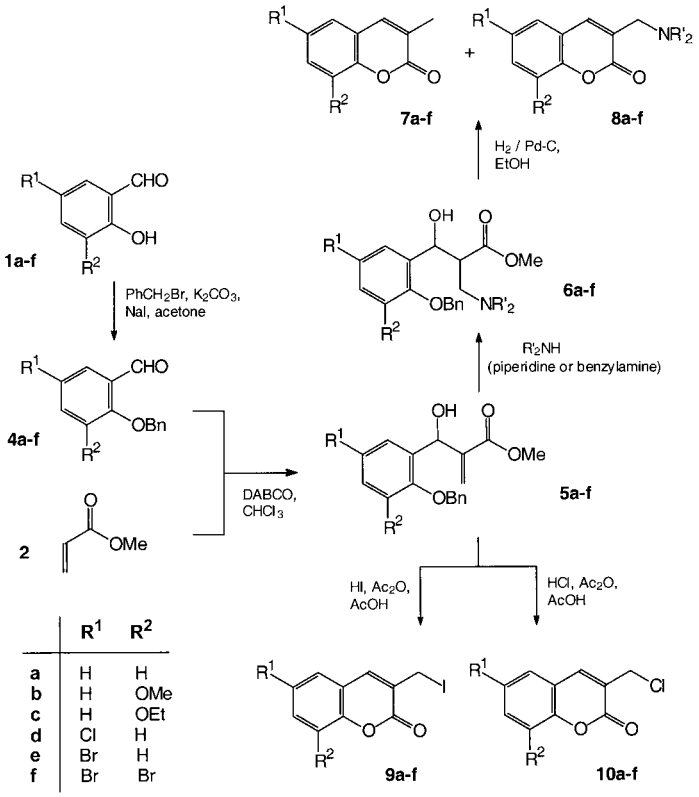
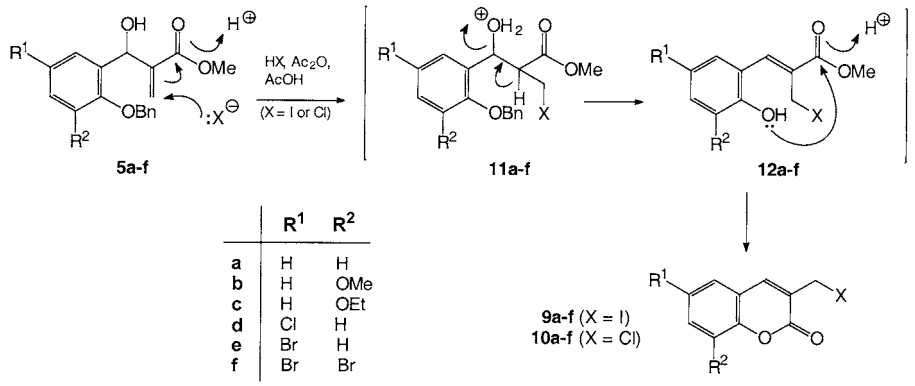


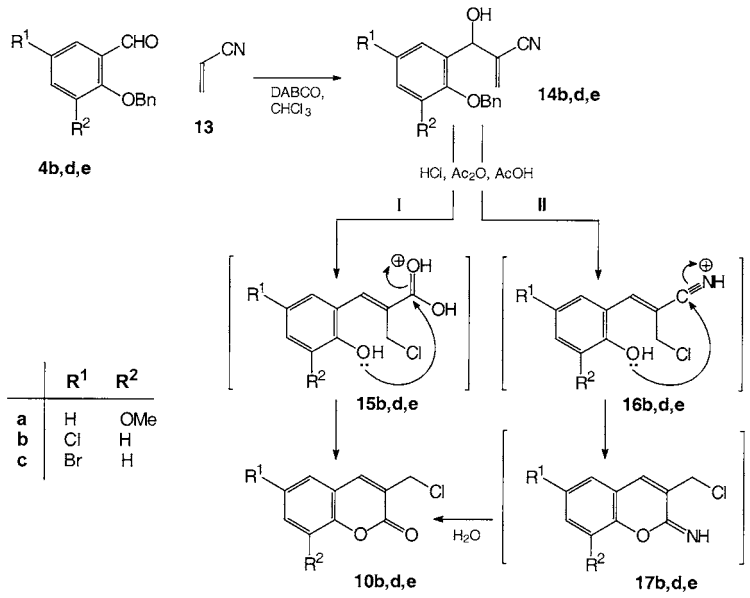
Scheme 1

demethylation and subsequent cyclisation of ethyl 3-cyclohexyl-3-hydroxy-3-(2,5-dimethoxyphenyl)prop-2-enoate to afford 4-cyclohexyl-6-methoxycoumarin in yields of up to 68%. The *O*-benzylated Baylis–Hillman products **5a**–**f** were therefore treated with hydriodic acid in a mixture of acetic acid and acetic anhydride at reflux temperature to afford, after workup, the 3-(iodomethyl)coumarins **9a**–**f** in yields ranging from 61 to 85% (Table 1). Hydriodic acid, however, is relatively expensive and unpleasant to handle and concentrated hydrochloric acid was investigated as an alternative reagent. When the *O*-benzylated Baylis–Hillman products **5a**–**f** were reacted with concentrated hydrochloric acid, the 3-chloromethyl analogues **10a**–**f** were obtained in even better yields (up to 94%)!

The formation of the novel 3-(halomethyl)coumarins **9** and **10** presumably involves: conjugate addition of the halogen acid to the α,β-unsaturated ester moiety and acid-catalysed dehydration (i.e. **5** → **11** → **12**);[21] cleavage of the benzyl ether; and, finally, cyclisation (Scheme 2). Addition of the halogen acid to the double bond appears to inhibit cyclisation of the intermediates **12** to the chromene analogues. This approach thus eliminates the need to use an amine to 'protect' the double bond, and permits deprotection of the *O*-benzyl ethers **5** and cyclisation in one-pot and in high yield.



Scheme 2



Scheme 3

Acrylonitrile (**13**) also serves as an activated alkene in Baylis–Hillman reactions and, consequently, was reacted with the *O*-benzylated salicylaldehydes **4b**,**d**,**e** to afford the corresponding adducts **14b**,**d**,**e** (Scheme 3). These adducts were then treated with concentrated hydrochloric acid in a reluxing mixture of acetic acid and acetic anhydride for 45 minutes to give the 3-(chloromethyl)coumarin derivatives **10b**,**d,e** in yields of up to 87% (Scheme 3, Table 1). Acidic hydrolysis of nitriles typically affords carboxylic acids (or the intermediate amides), and in situ hydrolysis of the nitrile function, followed by intramolecular acyl substitution, would account for the formation of the coumarins (Scheme 3, Path I). An alternative pathway (Path II) could be envisaged, however, in which cyclisation proceeds via acid-catalysed nucleophilc addition to an intermediate nitrile **16**, followed by hydrolysis of the resulting imine **17**.

In summary, one-pot, acid-catalysed deprotection and cyclisation of *O*-benzylated Baylis–Hillman adducts has been shown to provide a convenient, efficient and chemoselective access to a range of 3-halomethylcoumarins.

NMR spectra were recorded on Bruker AMX400 or Avance 400 MHz spectrometers at 303 K in $CDCl_3$ or DMSO-d_6, and calibrated using solvent signals. IR spectra were recorded on a Perkin Elmer FT-IR Spectrum 2000 spectrometer. Low-resolution (EI) mass spectra were obtained on a Finnigan GCQ mass spectrometer and high-resolution (EI) mass spectra on a VG70-SEQ Micromass double-focusing magnetic sector spectrometer (Cape Technikon Mass Spectrometry unit). The *O*-benzylated Baylis–Hillman adducts **5a**–**f** and their *O*-benzylated salicylaldehyde precursors **4a**–**f** were prepared as described previously.[19] The synthetic procedures for other compounds in this study are illustrated by the following examples of typical procedures.

Table 1 Coumarin Derivatives **9** and **10** Prepared[a]

No.	Substrate		Product		Yield (%)[b]
	R^1	R^2	No.	Y	
5a	H	H	**9a**	I	67
			10a	Cl	80
5b	H	OMe	**9b**	I	62
			10b	Cl	87
5c	H	OEt	**9c**	I	61
			10c	Cl	94
5d	Cl	H	**9d**	I	85
			10d	Cl	94
5e	Br	H	**9e**	I	61
			10e	Cl	79
5f	Br	Br	**9f**	I	61
			10f	Cl	90
14b	H	OMe	**10b**	Cl	69
14d	Cl	H	**10d**	Cl	87
14e	Br	H	**10e**	Cl	75

[a] See Schemes 1 and 3.
[b] Isolated product.

3-(Iodomethyl)coumarin (9a); Typical Procedure
Concd. HI (57%, 10 mL) was added to a solution of **5a** (0.31 g, 1.0 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 r.t. and then poured into ice-cold water (10 mL). Stirring for ca. 30 min gave a precipitate, which was filtered off and washed with hexane to afford **9a** as a grey solid (0.20 g, 67%); mp 150–152 °C.

IR (KBr): 1709 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$): δ = 4.34 (2 H, s, CH_2I), 7.22–7.52 (4 H, series of mutiplets, Ar-H), 7.81 (1 H, s, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –1.6 (CH_2I), 116.7, 119.1, 124.7, 127.2, 127.6, 131.9, 140.4, 153.5 (C=C and Ar-C), 159.7 (C=O).

MS (EI): *m*/*z* (%) = 287 (MH^+, 0.21), 159 (100).

HRMS: *m*/*z* calcd for $C_{10}H_8IO_2$, 286.9554; found, 286.9569.

3-(Iodomethyl)-8-methoxycoumarin (9b)
Light-yellow solid; yield: 0.20 g (61%); mp 184–186 °C.

IR (KBr): 1718 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$): δ = 3.96 (3 H, s, OCH_3), 4.37 (2 H, s, CH_2I), 7.05 (1 H, dd, *J* = 1.0, 8.0 Hz, Ar-H), 7.07 (1 H, d, *J* = 8.0 Hz, Ar-H), 7.20 (1 H, t, *J* = 8.0 Hz, Ar-H), 7.80 (1 H, s, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –1.7 (CH_2I), 56.3 (OCH_3), 113.8, 119.1, 119.8, 124.6, 127.6, 134.6, 140.6, 143.0 (C=C and Ar-C), 159.2 (C=O).

MS (EI): *m*/*z* (%) = 317 (MH^+, 62), 189 (100).

HRMS: *m*/*z* calcd for $C_{11}H_{10}IO_3$, 316.9675; found, 316.9666.

8-Ethoxy-3-(iodomethyl)coumarin (9c)
Brown solid; yield: 0.21 g (62%); mp 120–122 °C.

IR (KBr): 1714 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.49 (3 H, t, *J* = 7.0 Hz, CH_3), 4.20 (2 H, q, *J* = 7.0 Hz, OCH_2CH_3), 4.37 (2 H, s, CH_2I), 7.03 (1 H, dd, *J* = 1.0, 8.0 Hz, Ar-H), 7.06 (1 H, dd, *J* = 1.0, 8.0 Hz, Ar-H), 7.18 (1 H, t, *J* = 7.8 Hz, Ar-H), 7.80 (1 H, s, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –1.5 (CH_2I), 14.7 (OCH_2CH_3), 65.0 (OCH_2CH_3), 115.0, 119.1, 119.9, 124.6, 127.4, 140.7, 143.4, 146.3 (C=C and Ar-C), 159.4 (C=O).

MS (EI): *m*/*z* (%) = 330 (M^+, 1.2), 203 (100).

HRMS: *m*/*z* Found: 329.97490. $C_{12}H_{11}IO_3$ requires: 329.97530.

HRMS: *m*/*z* calcd for $C_{12}H_{11}IO_3$, 329.97530; found, 329.97490.

6-Chloro-3-(iodomethyl)coumarin (9d)
Yellow solid; yield: 0.28 g (85%); mp 188–190 °C.

IR (KBr): 1747 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$): δ = 4.35 (2 H, s, CH_2I), 7.29–7.48 (3 H, series of multiplets, Ar-H), 7.75 (1 H, s, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –2.3 (CH_2I), 118.2, 120.1, 126.9, 128.7, 130.0, 131.7, 140.0, 151.9, 159.1(Ar-C and C=O).

MS (EI): *m*/*z* (%) = 321 [MH^+(^{35}Cl), 62.8], 193 (100).

HRMS: *m*/*z* calcd for $C_{10}H_6{}^{35}ClINaO_2$, 342.8979; found, 342.8998.

6-Bromo-3-(iodomethyl)coumarin (9e)
Grey solid; yield: 0.23 g (64%); mp 148–150 °C.

IR (KBr): 1722 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$): δ = 4.35 (2 H, s, CH_2I), 7.20–7.61 (3 H, series of overlapping signals), 7.74 (1 H, s, 4-H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = –2.4 (CH_2I), 117.3, 118.5, 120.6, 128.6, 130.0, 134.6, 138.9, 152.3 (C = C and Ar-C), 159.1 (C=O).

MS (EI): *m*/*z* (%) = 365 [MH^+(^{35}Cl), 38.9], 239 (100).

HRMS: *m*/*z* calcd for $C_{10}H_7{}^{79}BrIO_2$, 364.86747; found, 364.86850.

6,8-Dibromo-3-(iodomethyl)coumarin (9f)
Pink solid; yield: 0.28 g (61%); mp 208–210 °C.

IR (KBr): 1747 (C=O) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.36 (2 H, s, CH_2I), 7.56 (1 H, d, *J* = 2.0 Hz, Ar-H), 7.70 (1 H, s, Ar-H), 7.87 (1 H, d, *J* = 2.0 Hz, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –3.1 (CH_2I), 111.3, 117.2, 121.4, 129.2, 129.5, 137.3, 138.5, 149.3 (C=C and Ar-C), 158.2 (C=O).

MS (EI): *m*/*z* (%) = 442 [M^+($^{79}Br_2$), 0.5], 317 (100).

HRMS: *m*/*z* calcd for $C_{10}H_5{}^{79}Br_2IO_2$, 441.77010; found, 441.77080.

3-(Chloromethyl)coumarin (10a)
Method 1: Conc. HCl (10 mL) was added to a solution of **5a** (0.31 g, 1.0 mmol) in AcOH (5 mL) and Ac_2O (5 mL). The mixture was boiled under refluxed for 2 h, allowed to cool to r.t. 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 **10a** as a purple solid (0.16 g, 79%); mp 108–110 °C.

IR (KBr): 1713 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$): δ = 4.55 (2 H, s, CH_2Cl), 7.27–7.56 (4 H, series of multiplets, Ar-H), 7.88 (1 H, s, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.0 (CH_2), 116.7, 118.8, 124.7, 125.0, 128.1, 132.0, 141.1, 153.5 (C=C and Ar-C), 160.1 (C=O).

MS (EI): *m*/*z* (%) = 194 (M^+, 31.4), 159 (100).

HRMS: *m*/*z* calcd for $C_{10}H_7{}^{35}ClO_2$, 194.01346; found, 194.01346.

3-(Chloromethyl)-8-ethoxycoumarin (10c)
Pale-pink solid; yield: 0.23 g (94%); mp 122–124 °C.

IR (KBr): 1709 (C=O) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.49 (3 H, t, *J* = 7.0 Hz, OCH_2CH_3), 4.18 (2 H, q, *J* = 7.0 Hz, OCH_2CH_3), 4.55 (2 H, d, *J* = 0.8 Hz, CH_2Cl), 7.07 (2 H, d, *J* = 7.6 Hz, Ar-H), 7.20 (1 H, t, *J* = 7.6 Hz, Ar-H), 7.85 (1 H, s, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7 (OCH_2CH_3), 41.0 (CH_2Cl), 55,1 (OCH_2CH_3), 115.2, 119.4, 119.6, 124.6, 125.1, 141.3, 143.4, 146.5 (C=C and Ar-C), 159.8 (C=O).

MS (EI): *m*/*z* (%) = 238 (M^+, 28.5), 175 (100).

HRMS: *m*/*z* calcd for $C_{12}H_{11}{}^{35}ClO_3$, 238.03967; found, 238.03987.

6-Chloro-3-(chloromethyl)coumarin (10d)
Pale-pink solid: yield: 0.33 g (94%); mp 112–114 °C.

IR (KBr): 1729 (C=O) cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.54 (2 H, s, CH_2Cl), 7.29 (1 H, d, *J* = 8.8 Hz, Ar-H), 7.47–7.51 (2 H, m, Ar-H), 7.81 (1 H, s, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.8 (CH_2), 118.1, 119.8, 126.3, 127.3, 130.0, 131.9, 139.7, 151.8 (C=C and Ar-C), 159.5 (C=O).

MS (EI): *m*/*z* (%) = 228 [M^+($^{35}Cl_2$), 23.2], 193 (100).

HRMS: *m*/*z* calcd for $C_{10}H_6{}^{35}Cl_2O_2$, 227.97448; found, 227.97476.

6-Bromo-3-(chloromethyl)coumarin (10e)
Pale-pink solid; yield: 0.22 g (78%); mp 116–118 °C.

IR (KBr): 1722 cm^{-1} (C=O).

^1H NMR (400 MHz, $CDCl_3$): δ = 4.53 (2 H, s, CH_2Cl), 7.23 (1 H, d, *J* = 8.8 Hz, Ar-H), 7.61, 7.63 (1 H, dd, *J* = 2.0, 8.8 Hz, Ar-H), 7.66 (1 H, d, *J* = 2.0 Hz, Ar-H), 7.80 (1 H, s, 4-H).

^{13}C NMR (100 MHz; $CDCl_3$): δ = 40.8 (CH_2), 117.3, 118.4, 120.3, 126.3, 130.3, 134.7, 139.6, 142.3 (C=C and Ar-C), 159.4 (C=O).

MS (EI): *m*/*z* (%) = 272 [M^+($^{35}Cl^{79}Br$), 60.7], 237(100).

HRMS: *m*/*z* calcd for $C_{10}H_6{}^{79}Br^{35}ClO_2$, 271.92397; found, 271.92412.

6,8-Dibromo-3-(chloromethyl)coumarin (10f)
Pink solid; yield: 0.32 g (88%); mp 166–168 °C.

IR (KBr): 1727 cm^{-1} (C=O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.54 (2 H, s, CH_2Cl), 7.58 (1 H, d, *J* = 2.2 Hz, Ar-H), 7.78 (1 H, s, 4-H), 7.88 (1 H, d, *J* = 2.2 Hz, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.5 (CH_2), 111.2, 117.3, 121.1, 127.1, 129.6, 137.5, 139.2, 149.3 (C=C and Ar-C), 158.48 (C=O).

MS (EI): *m*/*z* (%) = 350 [M^+ ($^{35}Cl^{79}Br_2$), 40.9], 317 (100).

HRMS: *m*/*z* calcd for $C_{10}H_5{}^{79}Br_2{}^{35}ClO_2$, 349.83448; found: 349.83490.

3-(Chloromethyl)-8-methoxycoumarin (10b)
Method 2: Concd HCl (10 mL) was added to a solution of **14b** (vide infra) (0.30 g, 1.0 mmol) in AcOH (5 mL) and Ac_2O (5 mL). The mixture was boiled under reflux for ca. 1 h, allowed to cool to r.t. and then poured into ice-cold water (10 mL). Stirring for ca. 30 min gave a precipitate, which was filtered off and washed with hexane to afford **10b** as a purple solid (0.16 g, 70%); mp 146–148 °C.

IR (KBr): 1720 cm^{-1} (C=O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.96 (3 H, s, OCH_3), 4.55 (2 H, s, CH_2Cl), 7.10 (2 H, d, *J* = 8.0 Hz, Ar-H), 7.23 (1 H, t, *J* = 8.0 Hz, Ar-H), 7.86 (1 H, s, 4-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.0 (CH_2), 56.3 (OCH_3), 113.8, 119.4, 119.43, 124.6, 125.2, 141.2, 143.2, 147.2 (C=C, Ar-C), 159.6 (C=O).

MS (EI): *m*/*z* (%) = 224 (M^+), 75.9], 189 (100).

HRMS: *m*/*z* calcd for $C_{11}H_9{}^{35}ClO_3$, 224.02402; found, 224.02470.

3-(2-Benzyloxy-3-methoxyphenyl)-3-hydroxy-2-methylenepropanenitrile (14b)
A mixture of **4b** (1.21 g, 5.0 mmol), acrylonitrile **13** (1.72 mL, 26.3 mmol) and DABCO (294 mg, 2.63 mmol) in $CDCl_3$ (0.25 mL) was stirred in a stoppered reaction flask for 21 d. The mixture was concentrated in vacuo to give a dark brown oil (1.67 g), which was chromatographed [flash chromatography on silica gel; elution with hexane–EtOAc (3:1)] to afford **14b** (0.90 g, 61%) as a pale yellow oil.

IR (KBr): 3432 (OH), 2227 cm^{-1} (C≡N).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.76 (1 H, d, *J* = 5.6 Hz, OH), 3.90 (3 H, s, OCH_3), 5.06, 5.14 (2 H, 2 d, *J* = 11.2 Hz, O*CH*$_2$Ph), 5.43 (1 H, d, *J* = 5.6 Hz, C*H*OH), 5.89, 5.92 (2 H, 2 d, *J* = 1.4 Hz, C=CH_2), 6.93–7.42 (8 H, series of overlapping signals, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.8 (OCH_3), 69.6 (CHOH) 74.9 (O*C*H$_2$Ph), 128.9 (C=*C*H$_2$), 113.0, 117.1, 119.4, 124.6, 125.8, 128.2, 128.3, 128.5, 133.0, 137.2, 145.2 (*C*=CH_2 and Ar-C), 152.5 (C≡N).

MS (EI): *m*/*z* (%) = 295 (M^+, 35.2), 187 (100).

HRMS: *m*/*z* calcd for $C_{18}H_{17}NO_3$, 295.12084; found, 295.12122.

3-(2-Benzyloxy-3-chlorophenyl)-3-hydroxy-2-methylenepropanenitrile (14d)
Pale-yellow oil; yield: 0.82 g (55%).

IR (KBr): 3397 (OH), 2227 cm^{-1} (C≡N).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.88 (1 H, d, *J* = 6.0 Hz, OH), 5.05, 5.08 (2 H, 2 d, *J* = 11.6Hz, O*CH*$_2$Ph), 5.54 (1 H, d, *J* = 6.0 Hz, C*H*OH), 5.94, 5.98 (2 H, 2 d, *J* = 1.6 Hz, C=CH_2), 6.89 (1 H, d, *J* = 8.8 Hz, Ar-H), 7.24–7.42 (7 H, series of multiplets, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.6 (CHOH), 70.9 (O*C*H$_2$Ph), 130.3 (C=*C*H$_2$), 113.5, 116.8, 125.2, 126.6, 127.6, 127.8, 128.5, 128.8, 129.2, 129.6, 135.8 (*C*=CH_2 and Ar-C), 154.3 (C≡N).

MS (EI): *m*/*z* = 299 [M^+(^{35}Cl), 18.1], 91 (100).

HRMS: *m*/*z* calcd for $C_{17}H_{14}{}^{35}ClNO_2$, 299.07131; found, 299.07235.

3-(2-Benzyloxy-5-bromophenyl)-3-hydroxy-2-methylenepropanenitrile (14e)
Pale-yellow crystals; yield: 0.88 g (51%); mp 80–82 °C.

IR (KBr): 3413 (OH), 2231 cm^{-1} (C≡N).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.83 (1 H, d, *J* = 5.4 Hz, OH), 5.05, 5.08 (2 H, 2 d, *J* = 11.6 Hz, O*CH*$_2$Ph), 5.54 (1 H, d, *J* = 5.4 Hz, C*H*OH), 5.94, 5.98 (2 H, 2 d, *J* = 1.4 Hz, C=CH_2), 6.85 (1 H, d, *J* = 8.8 Hz, Ar-H), 7.35–7.42 (6 H, series of overlapping signals, Ar-H), 7.52 (1 H, d, *J* = 2.4 Hz, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.5 (CHOH), 70.8 (O*C*H$_2$Ph), 130.3 (C=*C*H$_2$), 113.8, 113.9, 116.8, 125.2, 127.6, 128.5, 128.8, 129.6, 130.7, 132.6, 135.7 (*C*=CH_2 and Ar-C), 154.8 (C≡N).

MS (EI): *m*/*z* (%) = 343 [M^+(^{79}Br), 13.2), 92 (100).

HRMS: *m*/*z* calcd for $C_{17}H_{14}{}^{79}BrNO_2$, 343.02079; found, 343.02079.

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References

(1) Murray, R. D. H. In *Progress in the Chemistry of Natural Products*; Herz, W.; Grisebach, H.; Kirby, G. W., Eds.; Springer: New York, **1978**, 199–429.
(2) (a) Periers, A.-M.; Laurin, P.; Benedetti, Y.; Lachaud, S.; Ferroud, D.; Iltis, A.; Haesslein, J.-L.; Klich, M.; L'Hermite, G.; Musicki, B. *Tetrahedron Lett.* **2000**, *41*, 867.
(b) Peixoto, C.; Laurin, P.; Klich, M.; Dupuis-Hamelin, C.; Mauvais, P.; Lassaigne, P.; Bonnefoy, A.; Musicki, B. *Tetrahedron Lett.* **2000**, *41*, 1741.
(3) (a) Hermodson, M. A.; Barker, W. M.; Link, K. P. *J. Med. Chem.* **1971**, *14*, 167. (b) Conlin, G. M.; Gear, J. R. *J. Nat. Prod.* **1993**, *56*, 1402.
(4) Fuller, R. W.; Bokesch, H. R.; Gustafson, K. R.; McKee, T. C.; Cardellina, J. H. II.; McMahon, J. B.; Cragg, G. M.; Soejarto, D. D.; Boyd, M. R. *Bioinorg. Med. Chem. Lett.* **1994**, *4*, 1961.
(5) Zhao, H.; Neamati, N.; Hong, H.; Mazumder, A.; Wang, S.; Sunder, S.; Milne, G. W. A.; Pommier, Y.; Burke, T. R. Jr. *J. Med. Chem.* **1997**, *40*, 242.
(6) Hariprasad, V.; Talele, T. T.; Kulkarni, V. M. *Pharm. Pharmacol. Commun.* **1998**, *4*, 365.
(7) John, E. V. O.; Israelstam, S. S. *J. Org. Chem.* **1961**, *26*, 240.
(8) Panetta, J. A.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 946.
(9) Mali, R. S.; Yadav, V. J. *Synthesis* **1977**, 464.
(10) Hepworth, J. D. In *Comprehensive Heterocyclic Chemistry*, Vol. 3; Boulton, A. J.; McKillop, A., Eds.; Pergamon: Oxford, **1984**, 881.
(11) Bogdal, D. *J. Chem. Res., Synop* **1998**, 468.

(12) Fall, Y.; Teran, C.; Teijeira, M.; Santana, L.; Uriarte, E. *Synthesis* **2000**, 643.
(13) Bode, M. L.; Kaye, P. T. *J. Chem Soc., Perkin Trans 1* **1990**, 2612.
(14) Familoni, O. B.; Kaye, P. T.; Klaas, P. J. *Chem. Commun.* **1998**, 2563.
(15) Kaye, P. T.; Nocanda, X. W. *Synthesis* **2001**, 2389.
(16) Kaye, P. T.; Robinson, R. S. *Synth. Commun.* **1996**, *26*, 2085.
(17) (a) Bacsa, J.; Kaye, P. T.; Robinson, R. S. *S. Afr. J. Chem.* **1998**, *51*, 47. (b) Bode, M. L.; English, R. B.; Kaye, P. T. *S. Afr. J. Chem.* **1992**, *45*, 25.
(18) (a) Kaye, P. T.; Nocanda, X. W. *J. Chem. Soc., Perkin.Trans. 1* **2000**, 1331. (b) Kaye, P. T.; Nocanda, X. W. *J. Chem. Soc., Perkin.Trans. 1* **2002**, 1318.
(19) Kaye, P.T.; Musa, M.A. *Synth. Commun.*, in press (SC-2002-051).
(20) Drewes, S. E.; Njamela, O. L.; Emslie, N. D.; Ramesar, N.; Field, J. S. *Synth. Commun.* **1993**, *23*, 2807.
(21) Athough an allylic displacement (S_N') pathway cannot be excluded, there are some precedents for the addition-elimination sequence outlined in Scheme 2. See Ref.[15] for further comment.