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Catalytic Effects in Baylis–Hillman Reactions of Chromone-3-carbaldehydes with Acrylonitrile and Methyl Acrylate

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Abstract: The effects of various catalysts, the solvent system, and the temperature on the efficiency and chemoselectivity of reactions of a series of chromone-3-carbaldehydes with acrylonitrile and methyl acrylate are discussed.

Keywords: Baylis–Hillman catalysts, chromone-3-carbaldehydes, solvent systems

The Baylis–Hillman reaction between activated alkenes and aldehydes in the presence of a tertiary amine catalyst often provides convenient access to polyfunctional products containing a new stereogenic center.[1–5] In our own laboratories, we have used this reaction to develop syntheses of various heterocyclic systems[6] and have been exploring their potential in the construction of medicinal compounds, including HIV-1 protease inhibitors.[7] We also have an ongoing interest in chromone chemistry and have reported Baylis–Hillman reactions between chromone-3-carbaldehydes and the activated alkenes, acrylonitrile,[1] methyl acrylate, and methyl vinyl ketone,[8] using 1,4-diazabicyclo[2.2.2]octane as catalyst. However, the choice of catalyst often has a significant effect on the efficiency and rate of Baylis–Hillman reactions. In this communication, we report the results of a comparative study of the relative efficacy of three catalysts, 1,4-diazabicyclo[2.2.2]octane (DABCO), 3-hydroxyquinuclidine

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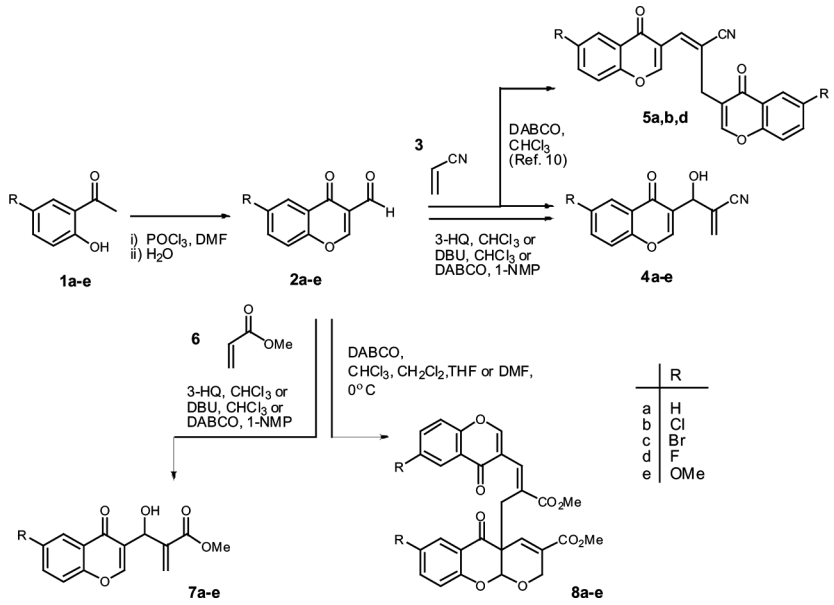


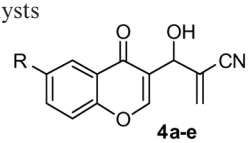
Scheme 1. Baylis–Hillman reactions of chromone-3-carbaldehydes.

(3-HQ), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), under various conditions.

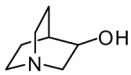
The series of chromone-3-carbaldehydes **2a–e**, prepared by "double" Vilsmeier–Haack formylation[9] of the corresponding 2-hydroxyacetophenones **1a–e**, were reacted with acrylonitrile **3** using 3-hydroxyquinuclidine as catalyst in a minimal volume of chloroform at 25°C for 24 h (Scheme 1). Purification of the crude products using flash chromatography afforded the desired Baylis–Hillman adducts **4a–e** in yields ranging from 57 to 73% (Table 1). The chromatographic separation was optimized by adding a few drops of dichloromethane (DCM) immediately after loading the sample onto the silica column. The yields are comparable to those obtained previously using 3-hydroxyquinuclidine (53–67%)[1] and significantly better than those obtained after several weeks using DABCO as catalyst (12–31%).[10]

Use of DBU as catalyst afforded the Baylis–Hillman adducts **4a–e** in yields ranging from 51 to 64% after 6 h, and 60 to 80% after 24 h (Table 1), indicating that DBU is, in fact, a very acceptable catalyst, in terms of both reaction rate and efficiency, when compared with the previously favored catalyst, 3-hydroxyquinuclidine.[11] As already indicated, the DABCO-catalyzed reactions have proved not only to be very slow but

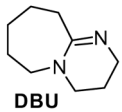
Table 1. Isolated yields (%) of Baylis–Hillman products **4a–e** using various catalysts



4a-e



3-HQ



DBU

DABCO

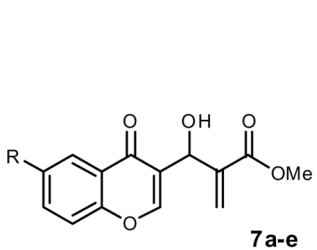
R	Compound	3-HQ in $CHCl_3$ (24 h)	DBU in $CHCl_3$ (6 h)	DBU in $CHCl_3$ (24 h)	DABCO in NMP (24 h)
H	**4a**	57	64	80	60
Cl	**4b**	66	57	71	50
Br	**4c**	73	52	64	50
F	**4d**	60	51	60	50
MeO	**4e**	71	55	77	45

also very inefficient.[10] However, both the rate and efficiency of the reaction were found to increase markedly when DABCO was used as the catalyst in the presence of the aprotic solvent 1-methyl-2-pyrrolidinone (NMP)[12]; the Baylis–Hillman adducts were isolated in yields ranging from 45 to 60% after 24 h (Table 1). Use of DABCO in the previous reactions also afforded, in some cases, the bis(chromone)-acrylonitrile adducts **5** in poor yield (5–24%), but these compounds were not isolated from reactions using the improved catalytic systems described above.

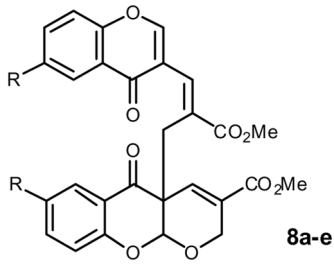
The chromone-3-carbaldehydes **2a–e** were also reacted with methyl acrylate **6** using 3-HQ, DBU, and DABCO in the presence of 1-methyl-2-pyrrolidinone. Thus, flash chromatography of the crude products obtained after 24 h from reactions using 3-hydroxyquinuclidine as the catalyst and chloroform as solvent (Scheme 1) gave the Baylis–Hillman adducts **7a–e** in moderate overall yields ranging from 52 to 63% (Table 2), improving considerably on the efficiencies obtained previously using DABCO (8–17%).[8] The corresponding Baylis–Hillman dimers **8a–e** were obtained as minor products in considerably lower yields (3–6%). When DBU was used as the catalyst, only the Baylis–Hillman adducts appeared to be formed (50–63% yield). Similar chemoselectivity appears to occur when DABCO is used in the presence of 1-methyl-2-pyrrolidinone as solvent, because under these conditions, the Baylis–Hillman adducts **7a–e** were again isolated as the sole products.

Good yields of Baylis–Hillman adducts have been reported when DABCO-catalyzed reactions were conducted at reduced temperature.[13] Consequently, the chromone-3-carbaldehydes **7a–e** were reacted with methyl acrylate at 0°C for 12 h, in the presence of DABCO using minimal

Table 2. Isolated yields (%) of the Baylis–Hillman products **7a**–**e** and Baylis–Hillman dimers **8a**–**e**[a] obtained using various catalysts after 24 h



7a-e



8a-e

R	B-H product	3-HQ[a] in $CHCl_3$	DBU in $CHCl_3$	DABCO in NMP
H	**7a**	52 (4)	62	50
Cl	**7b**	60 (5)	63	47
Br	**7c**	63 (3)	57	38
F	**7d**	63 (5)	50	30
MeO	**7e**	50 (6)	61	44

[a]Yields in parentheses.

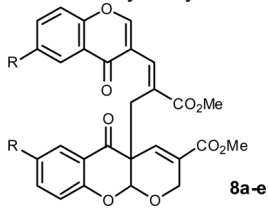
volumes of various solvents viz., $CHCl_3$, CH_2Cl_2, tetrahydrafuran (THF), and dimethylformamide (DMF). Purification of the crude products using flash chromatography appeared to afford the Baylis-Hillman dimers **8a**–**e** chemoselectively in yields ranging from 5 to 45% (Table 3). Neither the Baylis-Hillman adducts **7a**–**e** nor the expected[13] dioxanone derivatives were observed after 12 h, and although these reactions were not particularly efficient, the conditions employed clearly permit chemoselective formation of the Baylis–Hillman dimers **8**.

In summary, it is apparent that the reaction conditions can be controlled to permit efficient and selective formation of the primary Baylis–Hillman adducts **7**, but at low temperature the Baylis–Hillman dimers **8** were the only products to be isolated.

EXPERIMENTAL

NMR spectra were recorded on Bruker AMX400 or Avance 400-MHz spectrometers at 303 K in $CDCl_3$ and calibrated using solvent signals. Infrared (IR) spectra were recorded on a Perkin-Elmer Fourier transform–infrared (FT-IR) Spectrum 2000 spectrometer. Low-resolution mass spectra (LRMS) were obtained on Finnigan-Mat GCQ (EI) and

Table 3. Yields (%) of the Baylis–Hillman dimers **8a–c** isolated from DABCO-catalyzed reactions with methyl acrylate in different solvents at 0 °C



8a-e

R	Dimer	THF	CH_2Cl_2	$CHCl_3$	DMF
H	**8a**	5	22	45	15
Cl	**8b**	12	35	25	20
Br	**8c**	17	37	30	27

LCQ (ES) mass spectrometers, and high-resolution (EI) mass were determined spectra on a VG70-SEQ Micromass double-focusing magnetic sector spectrometer (Cape Technikon mass spectrometry unit). The chromone-3-carbaldehydes **2a–e** were prepared as described previously.[1]

3-(2-Cyano-1-hydroxy-2-propenyl)-4*H*-1-benzopyran-4-one 4a

Acrylonitrile (0.56 mL, 8.6 mmol) was added to a stirred solution of chromone-3-carbaldehyde **2a** (1.0 g, 5.7 mmol) and 3-hydroxyquinuclidine (3.7 g, 29 mmol) in $CHCl_3$ (7.0 mL). The resulting mixture was stirred vigorously at room temperature for 25 h. Evaporation of the solvent in vacuo gave a brown oily residue which was purified by flash chromatography [on silica; elution with hexane–EtOAc (2:3)] to afford 3-(2-cyano-1-hydroxy-2-propenyl)-4*H*-1-benzopyran-4-one **4a** as a yellow crystalline solid (0.65 g, 57%), mp 68–70°C (lit.[1] 69–71°C). Found $\mathbf{M}^+$: 227.0570. Calc. for $C_{13}H_9NO_3$, *M*: 227.0582. ν_{max} (KBr)/cm^{-1} 3430 (br, OH), 2225 (CN) and 1630 (C=O); δ_H (400 MHz; $CDCl_3$) 4.22 (1H, br s, 3′-OH), 5.29 (1H, s, 3′-H), 6.13 and 6.32 (2H, 2xs, 1′-CH_2), 7.44 (1H, t, $J = 7.6$ Hz, 6-H), 7.50 (1H, d, $J = 8.5$ Hz, 8-H), 7.72 (1H, t, $J = 7.8$ Hz, 7-H), 8.05 (1H, s, 2-H) and 8.18 (1H, d, $J = 8.0$ Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 69.3 (C-3′), 116.7 and 124.3 (C-2′ and CN), 118.3 (C-8), 121.3 (C-3), 123.8 (C-4a), 125.5 (C-5), 125.6 (C-6), 131.0 (C-1′), 134.4 (C-7), 153.8 (C-2), 156.4 (C-8a) and 177.6 (C=O); *m/z* 227 ($\mathbf{M}^+$, 46%) and 210 (100).

This reaction was repeated using DBU (2.2 mL, 15 mmol) as catalyst for 6 h and 24 h. The reaction was then quenched, in each case, by

diluting with diethyl ether (20 mL), and the resulting mixture was washed with aq. HCl (2 M, 20 mL) and then with water (20 mL) and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave a brown oily residue, which was purified by flash chromatography [on silica; elution with hexane–EtOAc (2:3)] to afford 3-(2-cyano-1-hydroxy-2-propenyl)-4*H*-1-benzopyran-4-one **4a** as a yellow crystalline solid (0.73 g, 64%, and 0.91 g, 80%).

The reaction was repeated for 24 h using DABCO (0.27 g, 2.4 mmol) as catalyst and 1-methyl-2-pyrrolidinone (4 mL) as solvent. The reaction was quenched by dilution with water (15 mL) followed by extraction with EtOAc (3×10 mL). Evaporation of the organic solvent in vacuo gave a brown oily residue, which was purified by flash chromatography [on silica; elution with hexane–EtOAc (1:2)] to afford 3-(2-cyano-1-hydroxy-2-propenyl)-4*H*-1-benzopyran-4-one **4a** as a yellow crystalline solid (0.68 g, 60%).

6-Chloro-3-(2-cyano-1-hydroxy-2-propenyl)-4*H*-1-benzopyran-4-one 4b

The experimental procedure employed for the synthesis of 3-(2-cyano-1-hydroxy-2-propenyl)-4*H*-1-benzopyran-4-one **4a** was followed, using 6-chlorochromone-3-carbaldehyde **2b** (0.50 g, 2.40 mmol), acrylonitrile (0.24 mL, 3.6 mmol), 3-hydroxyquinuclidine (1.53 g, 12.0 mmol), and $CHCl_3$ (7.0 mL). Workup afforded 6-chloro-3-(2-cyano-1-hydroxy-2-propenyl)-4*H*-1-benzopyran-4-one **4b** as a yellow crystalline solid (0.42 g, 66%), mp 132–133°C (lit.[1] 133–134°C). Found $\mathbf{M}^+$: 261.0196. Calc. for $C_{13}H_8O_3N^{35}Cl$, *M*: 261.0193. ν_{max} (KBr)/cm^{-1} 3440 (br, OH), 2300 (CN), and 1653 (C=O); δ_H (400 MHz; $CDCl_3$) 4.04 (1H, br s, 3′-OH), 5.34 (1H, s, 3′-H), 6.12 and 6.30 (2H, 2xs, 1′-CH_2), 7.45 (1H, dd, $J = 8.9$ and 2.1 Hz, 7-H), 7.64 (1H, d, $J = 8.9$ Hz, 8-H), 8.08 (1H, s, 2-H) and 8.12 (1H, d, $J = 2.1$ Hz, 5-H); δ_C(100 MHz; $CDCl_3$) 69.5 (C-3′), 104.3 (C-5), 116.8 (C-3), 119.8 (C-8), 120.2 (C-4a), 124.2 and 124.3 (C-2′ and CN), 124.7 (C-7), 131.0 (C-1′), 151.2 (C-8a), 153.4 (C-2), 157.4 (C-6) and 177.6 (C=O); *m/z* 261 ($\mathbf{M}^+$, 52%) and 209 (100).

When DBU (0.91 g, 6.2 mmol) was used as catalyst, workup after 6 h and 24 h afforded 6-chloro-3-(2-cyano-1-hydroxy-2-propenyl)-4*H*-1-benzopyran-4-one **4b** as a yellow crystalline solid (0.36 g, 57%, and 0.45 g, 71%).

When DABCO (0.14 g, 1.2 mmol) and 1-methyl-2-pyrrolidinone (2 mL) were used as catalyst and solvent, respectively, workup afforded 6-chloro-3-(2-cyano-1-hydroxy-2-propenyl)-4*H*-1-benzopyran-4-one **4b** as a yellow crystalline solid (0.32 g, 50%).

6-Bromo-3-(2-cyano-1-hydroxy-2-propenyl)-4*H*-1-benzopyran-4-one 4c

The experimental procedure employed for the synthesis of 3-(2-cyano-1-hydroxy-2-propenyl)-4*H*-1-benzopyran-4-one **4a** was followed, using 6-bromochromone-3-carbaldehyde **2c** (1.00 g, 3.95 mmol), acrylonitrile (0.39 mL, 5.9 mmol), 3-hydroxyquinuclidine (2.5 g, 20 mmol), and $CHCl_3$ (7.0 mL). Workup afforded 6-bromo-3-(2-cyano-1-hydroxy-2-propenyl)-4*H*-1-benzopyran-4-one **4c** as an orange-yellow crystalline solid (0.88 g, 73%), mp 124–125°C (lit.,[1] 123–125°C). Found $\mathbf{M}^+$: 304.9724. Calc. for $C_{13}H_8O_3N^{79}Br$, *M*: 304.9688. ν_{max} (KBr)/cm^{-1} 3420 (br, OH), 2225 (CN) and 1648 (C=O); δ_H (400 MHz; $CDCl_3$) 4.18 (1H, br s, 3′-OH), 5.33 (1H, s, 3′-H), 6.12 and 6.31 (2H, 2xs, 1′-CH_2), 7.40 (1H, d, $J = 8.9$ Hz, 8-H), 7.79 (1H, dd, $J = 8.9$ and 2.40 Hz, 7-H), 8.09 (1H, s, 2-H) and 8.28 (1H, d, $J = 2.4$ Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 69.0 (C-3′), 116.5 (CN), 119.3 (C-6), 120.3 (C-8), 121.6 (C-2′), 123.9 (C-3), 124.9 (C-4a), 128.2 (C-5), 131.5 (C-1′), 137.5 (C-7), 154.0 (C-2), 155.1 (C-8a) and 176.1 (C=O); *m*/*z* 305 ($\mathbf{M}^+$, 44%) and 253 (100).

When DBU (2.2 g, 15 mmol) was used as catalyst, workup after 6 h and 24 h afforded 6-bromo-3-(2-cyano-1-hydroxy-2-propenyl)-4*H*-1-benzopyran-4-one **4c** as a yellow crystalline solid (0.63 g, 52%, and 0.78 g, 64%, respectively).

When DABCO (0.14 g, 1.2 mmol) and 1-methyl-2-pyrrolidinone (2 mL) were used as catalyst and solvent, respectively, workup afforded 6-bromo-3-(2-cyano-1-hydroxy-2-propenyl)-4*H*-1-benzopyran-4-one **4c** as a yellow crystalline solid (0.60 g, 50%).

3-(2-Cyano-1-hydroxy-2-propenyl)-6-fluoro-4*H*-1-benzopyran-4-one 4d

The experimental procedure employed for the synthesis of 3-(2-cyano-1-hydroxy-2-propenyl)-4*H*-1-benzopyran-4-one **4a** was followed, using 6-fluorochromone-3-carbaldehyde **2d** (0.50 g, 2.6 mmol), acrylonitrile (0.26 mL, 3.9 mmol), 3-hydroxyquinuclidine (1.6 g, 13 mmol), and $CHCl_3$ (7.0 mL). Workup afforded 3-(2-cyano-1-hydroxy-2-propenyl)-6-fluoro-4*H*-1-benzopyran-4-one **4d** as a yellow crystalline solid (0.39 g, 60%), mp 59–60°C (lit.,[1] 60–62°C). Found: $\mathbf{M}^+$, 245.0490. $C_{13}H_8O_3NF$ requires *M*, 245.0488. ν_{max} (KBr)/cm^{-1} 3200 (br, OH), 2235 (CN) and 1640 (C=O); δ_H (400 MHz; $CDCl_3$) 4.08 (1H, br s, 3′-OH), 5.31 (1H, s, 3′-H), 6.15 and 6.33 (2H, 2xs, 1′-CH_2), 7.45 (1H, m, 7-H), 7.53 (1H, m, 8-H), 7.81 (1H, dd, $J = 8.1$ and 3.1 Hz, 5-H) and 8.08 (1H, s, 2-H); δ_C (100 MHz; $CDCl_3$) 69.1 (C-3′), 110.3 ($J_{CF} = 23$ Hz, C-5), 116.6 and 124.0 (C-2′ or CN), 120.5 ($J_{CF} = 8.1$ Hz, C-8), 120.7 (C-3), 122.9 ($J_{CF} = 25$ Hz, C-7), 124.9 ($J_{CF} = 7.6$ Hz, C-4a), 131.4 (C-1′), 152.5

(C-8a), 154.0 (C-2), 160.0 (C-6) and 176.5 (C=O); m/z 245 ($\mathbf{M}^+$, 57%) and 193 (100).

When DBU (1.0 g, 6.7 mmol) was used as catalyst, workup after 6 h and 24 h afforded 3-(2-cyano-1-hydroxy-2-propenyl)-6-fluoro-4*H*-1-benzopyran-4-one **4d** as a yellow crystalline solid (0.32 g, 51%, and 0.39 g, 60%, respectively).

When DABCO (0.14 g, 1.2 mmol) and 1-methyl-2-pyrrolidinone (2 mL) were used as catalyst and solvent, respectively, workup afforded 3-(2-cyano-1-hydroxy-2-propenyl)-6-fluoro-4*H*-1-benzopyran-4-one **4d** as a yellow crystalline solid (0.31 g, 50%).

3-(2-Cyano-1-hydroxy-2-propenyl)-6-methoxy-4*H*-1-benzopyran-4-one 4e

The experimental procedure employed for the synthesis of 3-(2-cyano-1-hydroxy-2-propenyl)-4*H*-1-benzopyran-4-one **4a** was followed, using 6-methoxychromone-3-carbaldehyde **2e** (1.0 g, 4.9 mmol), acrylonitrile (0.48 mL, 7.3 mmol), 3-hydroxyquinuclidine (3.1 g, 25 mmol), and $CHCl_3$ (10 mL). Workup afforded 3-(2-cyano-1-hydroxy-2-propenyl)-6-methoxy-4*H*-1-benzopyran-4-one **4e** as a yellow crystalline solid (0.89 g, 71%), mp 114–115°C (lit.,[1] 114–117°C). Found: $\mathbf{M}^+$: 257.0686. Calc. for $C_{14}H_{11}O_4N$, M: 257.0688. ν_{max} (KBr)/cm^{-1} 3400 (br, OH), 2225 (CN), and 1650 (C=O); δ_H (400 MHz; $CDCl_3$) 3.89 (3H, s, OCH_3), 4.41 (1H, br s, 3′-OH), 5.28 (1H, s, 3′-H), 6.14 and 6.34 (2H, 2xs, 1′-CH_2), 7.32 (1H, dd, $J = 9.2$ and 3.1 Hz, 7-H), 7.45 (1H, d, $J = 9.2$ Hz, 8-H), 7.52 (1H, d, $J = 3.1$ Hz, 5-H) and 8.08 (1H, s, 2-H); δ_C (100 MHz; $CDCl_3$) 55.9 (OCH_3), 69.1 (C-3′), 104.4 (C-5), 116.8 and 124.2 (C-2′ or CN), 119.8 (C-8), 120.3 (C-3), 124.3 (C-7), 124.8 (C-4a), 131.0 (C-1′), 151.3 (C-8a), 154.0 (C-2), 160.0 (C-6) and 176.5 (C=O); m/z 257 ($\mathbf{M}^+$, 46%) and 205 (100).

When DBU (1.85 g, 12.6 mmol) was used as catalyst, workup after 6 h and 24 h afforded 3-(2-cyano-1-hydroxy-2-propenyl)-6-methoxy-4*H*-1-benzopyran-4-one **4e** as a yellow crystalline solid (0.69 g, 55%, and 0.97 g, 77%, respectively).

When DABCO (0.14 g, 1.2 mmol) and 1-methyl-2-pyrrolidinone (2 mL) were used as catalyst and solvent, respectively, the workup afforded 3-(2-cyano-1-hydroxy-2-propenyl)-6-methoxy-4*H*-1-benzopyran-4-one **4e** as a yellow crystalline solid (0.57 g, 45%).

3-[1-Hydroxy-2-(methoxycarbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one 7a and the Corresponding Baylis–Hillman Dimer 8a

Methyl acrylate (0.56 mL, 8.6 mmol) was added to a stirred solution of chromone-3-carbaldehyde **2a** (1.0 g, 5.7 mmol) and 3-hydroxyquinuclidine

(3.7 g, 29 mmol) in $CHCl_3$ (7.0 mL). The resulting mixture was stirred vigorously at room temperature for 24 h. Evaporation of the solvent in vacuo gave a brown oily residue, which was purified by flash chromatography [on silica; elution with hexane–EtOAc (1:2)] and afforded two fractions:

3-[1-Hydroxy-2-(methoxycarbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one **7a** as a yellow solid (0.78 g, 52%), mp 109–110°C (lit.,[8] 109–112°C). Found $\mathbf{M}^+$: 260.0690. Calc. for $C_{14}H_{12}O_5$, *M*: 260.0685. ν_{max} (KBr)/cm^{-1} 3423 (br, OH), 1723 and 1655 (2x C=O); δ_H (400 MHz; $CDCl_3$) 3.74 (3H, s, OCH_3), 4.57 (1H, br s, 3′-OH), 5.59 (1H, s, 3′-H), 6.14 and 6.43 (2H, 2xs, 1′-CH_2), 7.41 (1H, m, 6-H), 7.45 (1H, d, $J = 8.0$ Hz, 8-H), 7.68 (1H, m, 7-H), 8.02 (1H, s, 2-H) and 8.18 (1H, dd, $J = 8.0$ and 1.4 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 52.0 (OCH_3), 67.6 (C-3′), 118.3 (C-8), 123.0 (C-3), 124.0 (C-4a), 125.4 (C-6), 125.6 (C-5), 126.8 (C-1′), 134.0 (C-7), 139.5 (C-2′), 154.3 (C-2), 156.3 (C-8a), 166.5 (CO.O) and 177.9 (C=O); *m/z* 260 ($\mathbf{M}^+$, 7%) and 200 (100).

The Baylis–Hillman dimer **8a** as a pale yellow solid (0.12 g, 4%), mp 193–195°C (lit.,[8] 192–195°C). Found: $\mathbf{M}^+$, 502.1250. Calc. for $C_{28}H_{22}O_9$, *M*: 502.1257. ν_{max} (KBr)/cm^{-1} 1712, 1707, 1653 and 1631 (4x C=O); δ_H (400 MHz; $CDCl_3$) 3.12 and 3.37 (2H, 2x d, $J = 14.7$ Hz, 13-CH_2), 3.61 and 3.65 (6H, 2xs, 12-and 16-CH_3), 4.50 (2H, dd, $J = 17$ and 1.6 Hz, 2-CH_2), 5.05 (1H, s, 9a-H), 6.90 (1H, t, $J = 7.8$ Hz, 6-H), 6.97 (1H, d, $J = 8.4$ Hz, 5-H), 7.30 (1H, s, 4-H), 7.35 (1H, t, $J = 8.4$ Hz, 7-H) 7.40 (2H, m, 7′-H and 8′-H), 7.50 (1H, s, 17-H), 7.69 (1H, t, $J = 7.2$ Hz, 6′-H), 7.72 (1H, dd, $J = 7.9$ and 1.5 Hz, 8-H), 7.90 (1H, s, 2′-H) and 8.16 (1H, d, $J = 7.2$ Hz, 5′-H); δ_C (100 MHz; $CDCl_3$) 28.4 (C-13), 50.3 (C-4a), 51.8 (C-12), 52.1 (C-16), 65.8 (C-2), 99.9 (C-9a), 117.7 (C-8), 117.9 (C-8′), 119.9 (C-10a), 120.5 (C-4a′), 122.7 (C-6), 123.9 (C-3′), 125.5 (C-6′), 126.2 (C-5), 127.7 (C-5′), 129.1 (C-3), 130.8 (C-14), 133.1 (C-17), 133.8 (C-4), 136.0 (C-7), 136.1 (C-7′), 154.9 (C-2′), 157.1 (C-8a), 155.8 (C-8a′), 163.8 (C-11), 167.3 (C-15), 174.9 (C-4′) and 191.4 (C-10); *m/z* 502 ($\mathbf{M}^+$, 24%) and 243 (100).

The reaction was repeated using DBU (2.19 mL, 15 mmol) as catalyst. After 24 h, the reaction was quenched by diluting it with diethyl ether (20 mL). The resulting solution was washed with aq. HCl (2 M; 20 mL), followed by water (20 mL), and then dried over Na_2SO_4. Evaporation of the solvent in vacuo gave a brown oily residue, which was purified by flash chromatography [on silica; elution with hexane–EtOAc (2:3)] to afford 3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one **7a** as a yellow solid (0.93 g, 62%).

The reaction was repeated using DABCO (0.27 g, 2.4 mmol) as catalyst and 1-methyl-2-pyrrolidinone (4 mL) as solvent. After 24 h, the reaction was quenched by dilution with water (15 mL), and the resulting mixture was extracted with EtOAc (3×10 mL). Evaporation of the

organic solvent in vacuo gave a brown oily residue, which was purified by flash chromatography [on silica gel and elution with hexane–EtOAc (1:2)] to afford 3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one **7a** as a yellow crystalline solid (0.75 g, 50%).

6-Chloro-3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one 7b and the Corresponding Baylis–Hillman Dimer 8b

The experimental procedure employed for the synthesis of 3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one **7a** and the corresponding Baylis–Hillman dimer **8a** was followed, using 6-chlorochromone-3-carbaldehyde **2b** (1.0 g, 4.8 mmol), methyl acrylate (0.48 mL, 7.2 mmol), 3-hydroxyquinuclidine (3.1 g, 24 mmol), and $CHCl_3$ (7.0 mL). Workup and flash chromatography afforded two fractions.

6-Chloro-3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one **7b** as yellow solid (0.85 g, 60%), mp 108–110°C (lit.,[8] 110–112°C). Found $\mathbf{MH}^+$: 295.0373. Calc. for $C_{14}H_{11}{}^{35}ClO_5$, $M+1$: 295.0373. ν_{max} (KBr)/cm^{-1} 3423 (br, OH), 1718 and 1650 (2 × C=O); δ_H (400 MHz; $CDCl_3$) 2.90 (1H, br s, 3′-OH), 3.74 (3H, s, OCH_3), 5.60 (1H, s, 3′-H), 6.14 and 6.44 (2H, 2xs, 1′-CH_2), 7.42 (1H, d, $J = 8.9$ Hz, 8-H), 7.61 (1H, dd, $J = 8.9$ and 2.5 Hz, 7-H), 8.04 (1H, s, 2-H) and 8.13 (1H, d, $J = 2.5$ Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 52.0 (OCH_3), 67.4 (C-3′), 120.0 (C-8), 123.2 (C-3), 124.8 (C-6), 125.1 (C-4a), 125.6 (C-5), 127.0 (C-1′), 131.4 (C-5), 134.2 (C-7), 154.5 (C-2), 154.6 (C-8a), 166.5 (CO.O), and 176.6 (C=O); m/z 294 ($\mathbf{M}^+$, 33%) and 234 (100).

The Baylis–Hillman dimer **8b** as yellow solid (0.13 g, 5%), mp 210–212°C (lit.,[8] 210–213°C). Found $\mathbf{M}^+$: 572.0636. Calc. for $C_{28}H_{20}O_9{}^{35}Cl_2$, M: 572.0641. ν_{max} (KBr)/cm^{-1}, 1715, 1710, 1650, and 1646 (4x C=O); δ_H (400 MHz; $CDCl_3$) 3.10 and 3.35 (2H, 2xd, $J = 14.7$ Hz, 13-CH_2), 3.67 and 3.69 (6H, 2xs, 12 and 16-OCH_3), 4.52 (2H, dd, $J = 17$ and 2.0 Hz, 2-CH_2), 5.04 (1H, s, 9a-H), 6.93 (1H, d, $J = 8.9$ Hz, 8-H), 7.27 (1H, m, 4-H), 7.29 (1H, m, 7-H) 7.42 (1H, d, $J = 9$ Hz, 8′-H), 7.48 (1H, s, 17-H), 7.61 (1H, m, 7′-H), 7.65 (1H, d, $J = 2.4$ Hz, 5-H), 8.00 (1H, s, 2′-H) and 8.10 (1H, d, $J = 2.5$ Hz, 5′-H); δ_C (100 MHz; $CDCl_3$) 28.4 (C-13), 50.3 (C-4a), 51.9 (C-12), 52.3 (C-16), 66.0 (C-2), 100.0 (C-9a), 119.5 (C-8), 119.8 (C-8′), 120.5 (C-4a), 120.8 (C-3′), 125.5 (C-5′), 127.0 (C-5), 128.5 (C-10a), 129.4 (C-3), 131.2 (C-14), 131.7 (C-6′), 132.3 (C-17), 134.4 (C-7′), 135.4 (C-7), 136.0 (C-4), 154.0 (C-8a), 155.1 (C-2′), 155.5 (C-8a′), 163.8 (C-6), 167.8 (C-11), 173.6 (C-15), 175.7 (C-4′) and 190.3 (C-10); m/z 571 ($\mathbf{M}^+$, 38%) and 277 (100).

When DBU (1.8 g, 12 mmol) was used as the catalyst, workup after 24 h afforded 6-chloro-3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-4-*H*-1-benzopyran-4-one **7b** as a yellow crystalline solid (0.89 g, 63%).

When DABCO (1.1 g, 9.6 mmol) was used as catalyst and 1-methyl-2-pyrrolidinone (5 mL) as solvent, workup after 24 h afforded 6-chloro-3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one **7b** as a yellow crystalline solid (0.66 g, 47%).

6-Bromo-3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one 7c and the Corresponding Baylis–Hillman Dimer 8c

The experimental procedure employed for the synthesis of 3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one **7a** and the corresponding Baylis–Hillman dimer **8a** was followed, using 6-bromochromone-3-carbaldehyde **2c** (1.1 g, 4.3 mmol), methyl acrylate (0.44 mL, 6.6 mmol), 3-hydroxyquinuclidine (2.8 g, 22 mmol), and $CHCl_3$ (7.0 mL). Workup and flash chromatography afforded two fractions.

6-Bromo-3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one **7c** as a yellow solid (0.93 g, 63%), mp 114–116°C (lit.,[8] 114–116°C). Found $\mathbf{M}^+$: 337.9790. Calc. for $C_{14}H_{11}{}^{79}BrO_5$, *M*: 337.9789. ν_{max} (KBr)/cm^{-1} 3440 (br, OH), 1716 and 1642 (2x C=O); δ_H (400 MHz; $CDCl_3$) 3.75 (3H, s, OCH_3), 4.38 (1H, d, $J = 8.0$ Hz, 3′-OH), 5.59 (1H, d, $J = 8.0$ Hz, 3′-H), 6.11 and 6.42 (2H, 2xs, 1′-CH_2), 7.37 (1H, d, $J = 8.9$ Hz, 8-H), 7.75 (1H, dd, $J = 9.0$ and 2.5 Hz, 7-H), 8.02 (1H, s, 2-H) and 8.28 (1H, d, $J = 2.5$ Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 52.0 (OCH_3), 67.5 (C-3′), 118.8 (C-8), 120.2 (C-6), 123.3 (C-3), 125.2 (C-4a), 125.6 (C-5), 127.0 (C-1′), 128.3 (C-5), 137.0 (C-7), 154.5 (C-2), 155.0 (C-8a), 166.5 (CO_2O), and 176.5 (C=O); *m/z* 338 ($\mathbf{M}^+$, 17%) and 280 (100).

The corresponding Baylis–Hillman dimer **8c** (50 mg, 3%), mp 223–225°C (lit.,[8] 223–225°C). Found $\mathbf{M}^+$: 657.9471. Calc. for $C_{28}H_{20}{}^{79}Br_2O_5$, *M*: 657.9474. ν_{max} (KBr)/cm^{-1} 1715, 1705, 1650, and 1646 (4x C=O); δ_H (400 MHz; $CDCl_3$) 3.11 and 3.33 (2H, 2xd, $J = 14.7$ Hz, 13-CH_2), 3.65 and 3.69 (3H, 2xs, 12 and 16-OCH_3), 4.51 (2H, dd, $J = 17.0$ and 2.0 Hz, 2-CH_2), 5.02 (1H, s, 9a-H), 6.88 (1H, d, $J = 8.8$ Hz, 8-H), 7.27 (1H, m, 4-H), 7.35 (1H, d, $J = 8.9$ Hz, 7′-H), 7.41 (1H, dd, $J = 9.0$ and 2.5 Hz, 7-H), 7.48 (1H, s, 17-H), 7.78 (1H, dd, $J = 9.0$ and 2.5 Hz, 8′-H), 7.81 (1H, d, $J = 2.5$ Hz, 5-H), 7.88 (1H, s, 2′-H) and 8.26 (1H, d, $J = 2.5$ Hz, 5′-H); δ_C (100 MHz; $CDCl_3$) 28.4 (C-13), 50.3 (C-4a), 52.0 (C-12), 52.3 (C-16), 66.0 (C-2), 100.0 (C-9a), 115.7 (C-8), 119.2 (C-4a′), 119.8 (C-8′), 120.1 (C-10a), 120.6 (C-6), 121.3 (C-6′), 125.0 (C-3′), 128.8 (C-5′), 129.3 (C-3), 130.1 (C-5), 131.2

(C-14), 132.8 (C-17), 135.4 (C-7′), 137.0 (C-7), 138.8 (C-4), 154.4 (C-2′), 155.0 (C-8a′), 156.0 (C-8a), 163.8 (C-11), 167.1 (C-15), 173.5 (C-4′), and 190.2 (C-10); m/z 658 ($\mathbf{M}^+$, 10%) and 323 (100).

When DBU (1.8 g, 12 mmol) was used as catalyst, workup after 24 h afforded 6-bromo-3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one **7c** as a yellow solid (0.86 g, 57%).

When DABCO (0.99 g, 8.8 mmol) was used as the catalyst and 1-methyl-2-pyrrolidinone (5 mL) as solvent, workup after 24 h afforded 6-bromo-3-[1-hydroxy-2-(methoxy-carbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one **7c** as a yellow solid (0.57 g, 38%).

6-Fluoro-3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one 7d and the Baylis–Hillman Dimer 8d

The experimental procedure employed for the synthesis of 3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one **7a** and the corresponding Baylis–Hillman dimer **8a** was followed, using 6-fluorochromone-3-carbaldehyde **2d** (0.50 g, 2.6 mmol), methyl acrylate (0.20 mL, 3.9 mmol), 3-hydroxyquinuclidine (1.7 g, 13 mmol), and $CHCl_3$ (7.0 mL). Workup and flash chromatography afforded two fractions.

6-Fluoro-3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one **7d** as a yellow solid (0.46 g, 63%), mp 139–141°C (lit.,[8] 140–142°C). Found $\mathbf{M}^+$: 278.0596. Calc. for $C_{14}H_{11}FO_5$, *M*: 278.0591. ν_{max} (KBr)/cm^{-1} 3423 (br, OH), 1716 and 1640 (2x C=O); δ_H (400 MHz; $CDCl_3$), 3.75 (3H, s, OCH_3), 4.43 (1H, d, $J = 7.8$ Hz, 3′-OH), 5.60 (1H, d, $J = 7.8$ Hz, 3′-H), 6.12 and 6.46 (2H, 2xs, 1′-CH_2), 7.40 (1H, m, 7-H), 7.48 (1H, dd, $J = 9.1$ and 4.2 Hz, 8-H), 7.81 (1H, dd, $J = 8.3$ and 3.0 Hz, 5-H), and 8.05 (1H, s, 2-H); δ_C (100 MHz; $CDCl_3$) 52.0 (OCH_3), 67.6 (C-3′), 110.5 (C-5), 120.4 (C-8), 122.3 (C-7), 122.5 (C-3), 125.8 (C-4a), 126.9 (C-1′), 139.2 (C-2′), 152.5 (C-8a), 154.6 (C-2), 159.6 (C-6), 166.5 (CO.O) and 177.1 (C=O); m/z 278 ($\mathbf{M}^+$, 34%) and 193 (100).

The Baylis–Hillman dimer **8d** as yellow solid (70 mg, 5%), mp 198–200°C (lit.,[8] 200–202°C). Found: $\mathbf{M}^+$: 538.1074. Calc. for $C_{28}H_{20}F_2O_5$, *M*: 538.1075. ν_{max} (KBr)/cm^{-1} 1727, 1713, 1650, and 1648 (4x C=O); δ_H (400 MHz; $CDCl_3$) 3.10 and 3.35 (2H, 2xd, $J = 14.7$ Hz, 13- CH_2), 3.64 and 3.70 (3H, 2xs, 12 and 16-OCH_3), 4.51 (2H, dd, $J = 17.0$ and 2.0 Hz, 2-CH_2), 5.01 (1H, s, 9a-H), 6.97 (1H, dd, $J = 9.0$ and 4.0 Hz, 5-H), 7.05 (1H, m, 7-H), 7.24 (1H, s, 4-H), 7.33 (1H, dd, $J = 8.3$ and 2.8 Hz, 8-H), 7.38–7.48 (2H, m, 5′-H and 7′-H), 7.50 (1H, s, 17-H), 7.78 (1H, dd, $J = 8.3$ and 2.8 Hz, 8′-H) and 7.90 (1H, s, 2′-H); δ_C (100 MHz; $CDCl_3$) 28.4 (C-13), 50.2 (C-4a), 51.9

(C-12), 52.2 (C-16), 65.9 (C-2), 100.1 (C-9a), 111.0 (C-8′), 112.7 (C-8), 119.5 (C-5), 119.8 (C-3′), 120.2 (C-5′), 120.6 (C-10a), 122.3 (C-7′), 123.6 (C-7), 124.9 (C-4a′), 129.4 (C-3), 131.1 (C-14), 132.8 (C-17), 135.4 (C-4), 151.9 (C-8a′), 153.3 and 157.8 (C-8a and C-6′), 155.1 (C-2′), 159.7 (C-6), 163.8 (C-11), 167.1 (C-15), 174.0 (C-14′) and 190.6 (C-10); *m/z* 538 ($\mathbf{M}^+$, 21%) and 261 (100).

When DBU (0.99 g, 6.7 mmol) was used as the catalyst, workup after 24 h afforded 6-fluoro-3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-4-*H*-1-benzopyran-4-one **7d** as a yellow solid (0.37 g, 50%).

When DABCO (0.585 g, 5.20 mmol) was used as the catalyst and 1-methyl-2-pyrrolidinone (5 mL) as solvent, workup after 24 h afforded 6-fluoro-3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one **7d** as a yellow solid (0.22 g, 30%).

3-[1-Hydroxy-2-(methoxycarbonyl)-2-propenyl]-6-methoxy-4*H*-1-benzopyran-4-one 7e and the Corresponding Baylis–Hillman Dimer 8e

The experimental procedure employed for the synthesis of 3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-4*H*-1-benzopyran-4-one **7a** and the corresponding Baylis–Hillman dimer **8a** was followed, using 6-methoxychromone-3-carbaldehyde **2e** (1.0 g, 4.9 mmol), methyl acrylate (0.49 mL, 7.3 mmol), 3-hydroxyquinuclidine (3.1 g, 25 mmol), and $CHCl_3$ (7.0 mL). Workup and flash chromatography afforded two fractions.

3-[1-Hydroxy-2-(methoxycarbonyl)-2-propenyl]-6-methoxy-4*H*-1-benzopyran-4-one **7e** as yellow oil (0.73 g, 50%). Found $\mathbf{M}^+$: 290.0780. Calc for $C_{15}H_{14}O_6$, *M*: 290.0790. ν_{max} (KBr)/cm^{-1} 3426 (br, OH), 1723 and 1643 (2x C=O); δ_H (400 MHz; $CDCl_3$) 3.70 (3H, s, CO.*OCH*$_3$), 3.81 (3H, s, 6-OCH_3), 4.68 (1H, d, $J = 4.5$ Hz, 3′-OH), 5.60 (1H, d, $J = 2.5$ Hz, 3′-H), 6.10 and 6.39 (2H, 2xs, 1′-H), 7.18 (1H, dd, $J = 9.1$ and 3.0 Hz, 7-H), 7.30 (1H, d, $J = 9.0$ Hz, 8-H), 7.44 (1H, d, $J = 3.0$ Hz, 5-H) and 7.98 (1H, s, 2-H); δ_C (100 MHz; $CDCl_3$) 51.7 (CO.O*C*H_3), 55.6 (6-OCH_3), 67.1 (C-3′), 104.3 (C-5), 119.4 (C-8), 122.2 (C-3), 123.9 (C-7), 124.3 (C-4a), 126.3 (C-1′), 139.7 (C-2′), 150.9 (C-8a), 154.0 (C-2), 156.8 (C-6), 166.3 (CO_2O), and 177.4 (C=O); m/z 290 ($\mathbf{M}^+$, 26%) and 151 (100).

The Baylis–Hillman dimer **8e** (0.15 g, 6%) as a yellow viscous oil. Found: $\mathbf{M}^+$, 562.1467. Calc. for $C_{30}H_{26}O_{11}$, *M*: 562.1475. ν_{max} (KBr)/cm^{-1}, and 1722, 1715, 1650, and 1646 (4x C=O); δ_H (400 MHz; $CDCl_3$) 3.10 and 3.35 (2H, 2xd, $J = 14.7$ Hz, 13-CH_2), 3.60 (3H, s, 12-H), 3.70 (3H, s, 6-OCH_3), 3.78 (3H, s, 16-H), 3.89 (3H, s, 6′-OCH_3), 4.39–4.53 (2H, dd, $J = 17$ and 2.0 Hz, 2-CH_2), 5.45 (1H, s, 9a-H), 6.70

(1H, s, 4-H), 6.73 (1H, d, $J = 9.0$ Hz, 9-H), 7.00 (1H, m, 7-H), 7.10 (1H, d, $J = 3.0$ Hz, 5-H), 7.26 (1H, dd, $J = 9.0$ and 3.0 Hz, 7′-H), 7.38 (1H, d, $J = 9.1$ Hz, 8′-H), 7.50 (1H, d, $J = 3.2$ Hz, 5′-H), 7.55 (1H, s, 17-H) and 7.91 (1H, s, 2′-H); δ_C (100 MHz; $CDCl_3$) 31.2 (C-13), 51.0 (C-4a), 51.7 (C-12), 52.2 (C-16), 55.7 (6-OCH_3), 55.9 (6′-OCH_3), 62.9 (C-2), 99.2 (C-9a), 105.3 (C-5′), 107.6 (C-5), 119.0 (C-10a), 119.2 (C-8), 119.4 (C-8′), 119.6 (C-3′), 123.9(C-7′), 124.5 (C-4a′), 125.6 (C-7), 129.9 (C-3), 130.6 (C-14), 133.3 (C-17), 135.0 (C-4), 150.7 (C-8a′), 151.8 (C-8a), 154.3 (C-2′), 154.7 (C-6), 157.1 (C-6′), 163.9 (C-11), 167.8 (C-15), 175.1 (C-4′) and 192.4 (C-10); m/z 562 ($\mathbf{M}^+$, 37%) and 289 (100).

When DBU (1.9 g, 13 mmol) was used as the catalyst, workup after 24 h afforded 3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-6-methoxy-4*H*-1-benzopyran-4-one **7e** as a yellow solid (0.86 g, 61%).

When DABCO (1.10 g, 9.78 mmol) was used as the catalyst and 1-methyl-2-pyrrolidinone (5 mL) as the solvent, workup after 24 h afforded 3-[1-hydroxy-2-(methoxycarbonyl)-2-propenyl]-6-methoxy-4*H*-1-benzopyran-4-one **7e** as a yellow solid (0.62 g, 44%).

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REFERENCES

1. Kaye, P. T.; Molefe, D. M.; Nchinda, A. T.; Sabbagh, L. V. Chromone studies, part 15: Formation and condensation of Baylis–Hillman adducts in DABCO-catalyzed reactions of chromone-3-carbaldehydes with acrylonitrile. *J. Chem. Res.* **2004**, *4*, 303–306.
2. Drewes, S. E.; Emslie, N. D.; Field, J. S.; Khan, A. A.; Ramesar, N. S. A novel tetrahydrofuran derivative via a tertiary ketol-type rearrangement. *Tetrahedron Lett.* **1993**, *34* (7), 1205–1208.
3. Kataoka, T.; Iwama, T.; Tsujiyama, S.; Iwamura, T.; Watanabe, S. The chalcogeno-Baylis–Hillman reaction: A new preparation of allylic alcohols from aldehydes and electron-deficient alkenes. *Tetrahedron* **1998**, *54* (39), 11813–11824.
4. Yu, C.; Liu, B.; Hu, L. Efficient Baylis–Hillman reaction using stoichiometric base catalyst and an aqueous medium. *J. Org. Chem.* **2001**, *66* (16), 5413–5418.
5. Luo, S.; Mi, X.; Xu, H.; Wang, P. G.; Cheng, J.-P. Efficient Baylis–Hillman reactions of cyclic enones in methanol as catalyzed by methoxide anion. *J. Org. Chem.* **2004**, *69* (24), 8413–8422.

6. (a) Familoni, O. B.; Klaas, P. J.; Lobb, K. A.; Pakade, V. E.; Kaye, P. T. The Baylis–Hillman approach to quinoline derivatives. *Org. Biomol. Chem.* **2006**, *4*, 3960–3965; (b) Kaye, P. T. The Baylis–Hillman entree to heterocyclic systems—The Rhodes contribution. *S. A. J. Science* **2004**, *100*, 545–548.
7. Kaye, P. T.; Musa, M. A.; Nchinda, A. T.; Nocanda, X. W. Novel heterocyclic analogues of the HIV-1 protease inhibitor, ritonavir. *Synth. Commun.* **2004**, *34* (14), 2575–2589.
8. (a) Kaye, P. T.; Nchinda, A. T.; Sabbagh, L. V.; Bacsa, J. Chromone studies, part 14: Unprecedented dimerization of chromone-3-carbaldehyde-derived Baylis–Hillman adducts. *J. Chem. Res. Synop. 2003*, *3*, 111–113; (b) *J. Chem. Res. Minipr.* **2003**, 0301.
9. Nohara, A.; Umetani, T.; Sanno, Y. Antianaphylactic agents, I: Facile synthesis of 4-oxo-4H-1-benzopyran-3-carboxaldehydes by Vilsmeier reagents. *Tetrahedron* **1974**, *30* (19), 3353–3361.
10. Sabbagh, L. V. Chemical studies of chromone derivatives. PhD thesis, Rhodes University, 2000.
11. Aggarwal, V. K.; Mereu, A. Superior amine catalysts for the Baylis–Hillman reaction: The use of DBU and its implications. *J. Chem Soc., Chem. Commun.* **1999**, *22*, 2311–2112.
12. (a) Krishna, P. R.; Manjuvani, A.; Sekhar, E. R. Novel aprotic polar solvents for facile Baylis–Hillman reaction. *Arkivoc* **2005**, *3*, 99–109; (b) *Chem. Abstr.* **2005**, 38955.
13. (a) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. The asymmetric Baylis–Hillman reaction as a template in organic synthesis. *Tetrahedron* **1997**, *53* (48), 16423–16434; (b) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. Chiral amine-catalyzed asymmetric Baylis–Hillman reaction: A reliable route to highly enantiomerically enriched (α-methylene-β-hydroxy)esters. *J. Am. Chem. Soc.* **1999**, *121* (43), 10219–10220.