SUPPLEMENATARY MATERIAL

The Coumarin→Indole Transformation — a Method for Preparing 4-Halo-5-hydroxyindoles from Coumarins

Elia J. L. Stoffman and Derrick. L. J. Clive*

Chemistry Department, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

e-mail: derrick.clive@ualberta.ca

Experimental procedures

Column sizes are quoted in the form diameter x length. Evaporations were done under water-pump vacuum using a rotary evaporator and the residue was then kept unde oil pump vacuum.

Ar and N_2 were purified by passage through a column (3.5 x 42 cm) of BASF R-311 catalyst and then through a similar column of Drierite. Glassware was dried in an oven (120 °C) for at least 3 h before use and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of argon. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

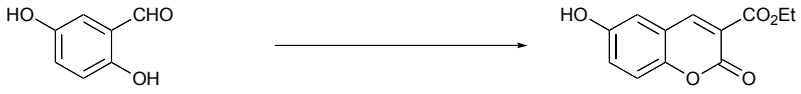
Solvents for chromatography or extractions were distilled before use.

Melting points were determined on a Kofler block melting point apparatus. Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F–254) were used. Compounds were detected by examination under UV light or by dipping the plate into a solution of phosphomolybdic acid,[29] followed by charring with a heat gun. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by oven-dried syringes. Dry THF was distilled from Na and benzophenone ketyl. Dry PhH and PhMe were distilled from Na. Dry Et_3N, CH_2Cl_2, MeOH, pyridine, and DMF were distilled from CaH_2, the last two solvents being distilled under water pump vacuum.

The symbols s, d, t, and q used for ^{13}C-NMR spectra (ATP) indicate 0, 1, 2, or 3 attached hydrogens.

6-Hydroxy-2-oxo-*2H*-chromene-3-carboxylic Acid Ethyl Ester (1.2).



1.1 **1.2**

Diethyl malonate (18.6 mL, 0.123 mol), followed by piperidine (0.7 mL, 7 mmol), were added to a stirred solution of **1.1** (13.1 g, 94.6 mmol) in absolute EtOH (130 mL). The flask was stoppered and the mixture was stirred under air for 3 days, during which time the product precipitated. Filtration gave a first crop of **1.2** (17.0 g). After being allowed to stand for several h, the mother liquor afforded a second crop (0.588 g). The total yield of **1.2**[9] amounted to 79%.

5-Chloro-6-hydroxy-2-oxo-2*H*-chromene-3-carboxylic Acid Ethyl Ester (1.4).

1.3 **1.4**

Diethyl malonate (15 mL, 98 mmol), followed by piperidine (1.3 mL, 13 mmol), were added to a stirred solution of **1.3** (22.1 g, 83.5 mmol) in EtOH (200 mL) (without protection from air). Stirring was continued overnight during which time the product precipitated as a yellow solid. The mixture was cooled to 5 °C and the product (24.8 g, 82%) was filtered off. Two more crops were then obtained from the mother liquor on standing to yield **1.4** (27.3 g in all, 91%): mp 193.5-195 °C; FTIR ν_{max} (microscope)/cm^{-1} 3343, 1749; ^{1}H-NMR (400 MHz, acetone-d_6): δ 1.34 (t, J = 7.1 Hz, 3 H), 4.34 (q, J = 7.1 Hz, 2 H), 7.22 (dd, J = 9.1, 0.7 Hz, 1 H), 7.39 (d, J = 9.1 Hz, 1 H), 8.71 (d, J = 0.7 Hz, 1 H), 9.24 (br s, 1 H); ^{13}C-NMR (100 MHz, acetone-d_6): δ 14.4 (q), 62.3 (t), 116.6 (d), 117.7 (s), 118.2 (s), 120.5 (s), 123.4 (d), 144.1 (d), 150.2 (s), 150.9 (s), 156.1 (s), 163.5 (s); exact mass m/z calcd for $C_{12}H_9ClNaO_5$ (M + Na) 291.0031, found 291.0030.

5-Chloro-6-hydroxy-2-oxo-2*H*-chromene-3-carboxylic Acid Ethyl Ester (1.4).

1.2 **1.4**

SO_2Cl_2 (0.26 mL, 3.2 mmol) was added over 6 min to a stirred and heated (70 °C) solution of **1.2** (0.666 g, 3.00 mmol) and *i*-Bu_2NH (0.06 mL, 0.3 mmol) in PhMe (13 mL) (Ar atmosphere). Stirring at 70 °C was continued for 2.5 h, and the mixture was cooled and partitioned between EtOAc (60 mL) and water (60 mL). The organic extract was washed once with water and once with brine, dried ($MgSO_4$) and evaporated to afford **1.4** (0.77 g, 100%).

5-Chloro-6-[(methanesulfonyl)oxy]-2-oxo-2*H*-chromene-3-carboxylic Acid Ethyl Ester (1.5).

1.4 **1.5**

Et_3N (1.3 mL, 9.3 mmol), followed by MsCl (0.60 mL, 7.8 mmol), were added by syringe to a stirred and cooled (0 °C) solution of **1.4** (2.36 g, 6.56 mmol) in CH_2Cl_2 (20 mL). The ice bath was left in place but not recharged. After 3 h, the reaction was still incomplete (TLC control) and so additional portions of Et_3N (0.6 mL, 4.3 mmol), followed by MsCl (0.30 mL, 3.9 mmol), were added. Stirring was continued for 5 min. The mixture was washed with water (20 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with water (1 x 40 mL), dried ($MgSO_4$) and evaporated. The residue was dissolved in boiling EtOH and the product (**1.5**) crystallized as light, dull-yellow crystals (3.00 g, 100%) when the solution cooled: mp 124 °C; FTIR ν_{max} (microscope)/cm^{-1} 3088, 2986, 2940, 1765, 1714; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.42 (t, J = 7.1 Hz, 3 H), 3.32 (s,

3 H), 4.44 (q, J = 7.1 Hz, 2 H), 7.33 (d, J = 9.2, 1 H), 7.69 (d, J = 9.2, 1 H), 8.81 (s, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.2 (q), 39.0 (q), 62.5 (t), 116.4 (d), 117.6 (s), 120.12 (s), 126.6 (s), 129.1 (d), 141.9 (s), 143.8 (d), 153.8 (s), 155.1 (s), 162.3 (s); exact mass m/z calcd for $C_{13}H_{11}ClNaO_7S$ (M + Na) 368.9806, found 368.9803.

5-Chloro-6-[(methanesulfonyl)oxy]-2-oxochroman-3-carboxylic Acid Ethyl Ester (1.6).

1.5 **1.6**

DIBAL-H (1 M in hexane, 0.09 mL, 0.09 mmol) was added to a stirred and cooled (–78 °C) solution of **1.5** (35.9 mg, 0.0819 mmol) in THF (2 mL). After 1 h, the reaction was still incomplete (TLC control), and so an additional aliquot of DIBAL-H (1 M in hexanes, 0.08 mL, 0.08 mmol) was added. Stirring was continued at –78 °C for an additional 30 min, the mixture was quenched with dilute hydrochloric acid (5%, 1 mL) and the cooling bath was removed. Water (1 mL) and EtOAc (1 mL) were added and the mixture was allowed to warm and kept at room temperature for 1 h. Aluminum-containing solids were filtered off with the aid of Celite, and the organic phase was dried ($MgSO_4$) and evaporated to afford pure **1.6** (44.7 mg, 100%): mp 95-96 °C.

The above procedure did not give a pure product on a larger scale and the following procedure, using $LiBH_4$, and tartaric acid in the work-up, should be followed: A suspension of

$LiBH_4$ (1.2 M in THF, 0.71 mL, 0.85 mmol) was added by syringe to a stirred and cooled (0 °C) solution of **1.5** (0.835 g, 2.41 mmol) in THF (Ar atmosphere). After 30 min at 0 °C the mixture was quenched with aqueous tartaric acid (0.5 M, 3 mL). Stirring was continued for 1 min, the ice bath was removed and water (15 mL) was added, followed by Et_2O (10 mL). The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated to afford **1.6** (0.882 g, 108%), which was pure enough for use in the next step. The material had: mp 95-96 °C; FTIR ν_{max} (microscope)/cm^{-1} 1782, 1740; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.21 (t, *J* = 7.1 Hz, 3 H), 3.24 (s, 3 H), 3.31 (dd, *J* = 16.9, 6.3 Hz, 1 H), 3.52 (dd, *J* = 16.8, 8.5 Hz, 1 H), 3.77 (dd, *J* = 8.5, 6.4 Hz, 1 H), 4.20 (dq, *J* = 7.1, 1.2 Hz, 2 H), 7.02 (d, *J* = 9.0 Hz, 1 H), 7.35 (d, *J* = 9.0 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.0 (q), 25.3 (t), 38.7 (q), 45.0 (d), 62.5 (t), 116.1 (d), 121.8 (s), 123.8 (d), 126.6 (s), 142.0 (s), 150.1 (s), 163.2 (s), 166.7 (s); exact mass *m*/*z* calcd for $C_{13}H_{13}ClNaO_7S$ (M + Na) 370.9963, found 370.9967.

Methanesulfonic Acid 5-Chloro-2-oxochroman-6-yl Ester (1.7).

1.6 **1.7**

The following procedure, using acid hydrolysis, is more reliable than base (LiOH) hydrolysis:

Aqueous HCl (20%, 35 mL) was added to a stirred solution of **1.6** (0.882 g, 2.53 mmol) in acetone (6 mL) and the resulting suspension was refluxed open to the atmosphere for 3 h, cooled to room temperature and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. The residue was suspended in PhMe (18 mL) and 4 Å molecular sieves (1.5 g) were added, followed by TsOH (39.3 mg, 0.207 mmol). The mixture was then refluxed for 3 h and then cooled to room temperature in a water bath. Et_2O (30 mL) was added and the mixture was poured into saturated aqueous $NaHCO_3$ (20 mL) and shaken carefully. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated. The residue was filtered through a short column of flash chromatography silica gel (2 x 4 cm) in a filter funnel, using CH_2Cl_2 to apply the material to the column, which was then washed with hexanes (5 mL) and 10% EtOAc-hexanes (10 mL). The eluent was discarded and the product (**1.7**) was then washed out using CH_2Cl_2 to give **1.7** (0.586 g, 84%): mp 118-120 °C (amorphous solid), or 123-124 °C (after crystallization from MeOH); FTIR ν_{max} (microscope)/cm^{-1} 3094, 3034, 2940, 1779; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.79 (apparent t as part of a higher order multiplet, 2 H), 3.13 (apparent t as part of a higher order multiplet, 2 H), 3.25 (s, 3 H), 6.99 (d, J = 9.0 Hz, 1 H), 7.33 (d, J = 9.0 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.9 (t), 27.7 (t), 38.7 (q), 116.2 (d), 123.3 (s), 123.4 (d), 126.4 (s), 141.7 (s), 150.9 (s), 166.7 (s); exact mass m/z calcd for $C_{10}H_9ClNaO_5S$ 275.9859, found 275.9857.

Methanesulfonic Acid 3-(2-carbamoylethyl)-2-chloro-4-hydroxyphenyl Ester (1.8).

1.7 **1.8**

A three-necked round-bottomed flask was charged with **1.7** (0.602 g, 2.17 mmol) and THF (22 mL). The flask was fitted with a drying tube containing NaOH pellets, a stopper and an adapter carrying a Pasteur pipette that extended 1 cm below the surface of the solution. The pipette was connected by Tygon tubing to another flask containing liquid NH_3 as a source of gaseous NH_3, which was bubbled through the THF solution for 1 h. Evaporation of the solvent gave **1.8** (0.591 g, 93%) as a white solid: mp 156-160 °C (from EtOH); FTIR ν_{max} (microscope)/cm^{-1} 3461, 3323, 3284, 3226, 3077, 3049, 3022, 2965, 2944, 1668; ^{1}H-NMR (400 MHz, acetone-d_6): δ 2.74 (t, *J* = 5.9 Hz, 2 H), 3.02 (t, *J* = 6.0 Hz, 2 H), 3.31 (s, 3 H), 6.72 (br s, 1 H), 6.84 (d, *J* = 8.9 Hz, 1 H), 7.22 (br s and d overlapping, *J* = 8.9 Hz, 2 H), 10.06 (br s, 1 H); ^{13}C-NMR (100 MHz, acetone-d_6): δ 23.2 (t), 34.2 (t), 38.5 (q), 117.1 (d), 123.3 (d), 128.4 (s), 129.3 (s), 139.8 (s), 156.1 (s), 177.0 (s); exact mass *m*/*z* calcd for $C_{10}H_{12}ClNNaO_5S$ (M + Na) 316.0017, found 316.0017.

Methanesulfonic Acid 4-[(*tert*-Butyldimethylsilyl)oxy]-3-(2-carbamoylethyl)-2-chlorophenyl Ester (1.9).

1.8 **1.9**

Imidazole (81.5 mg, 1.20 mmol) was added in one portion to a stirred solution of **1.8** (0.249 g, 0.849 mmol) in DMF (6 mL), followed by *t*-$BuMe_2SiCl$ (150 mg, 0.995 mmol), which was also added in one portion. The mixture was heated at 70 °C for 18 h and then cooled to room temperature. Et_2O (40 mL) was added and the mixture was washed with water (1 x 10 mL) and brine (1 x 10 mL), dried ($MgSO_4$) and evaporated. At this point a portion of **1.9** crystallized from the aqueous layer as small silky needles, which were filtered off. The residue from the organic extract was redissolved in DMF (10 mL) and this solution was poured into ice-water (45 mL). The mixture became cloudy, but no crystals formed. Et_2O (20 mL) was added and the mixture was shaken in a separatory funnel and then drained into a beaker. The upper ether layer was allowed to evaporate to leave a crystalline white solid on the water surface. Filtration gave **1.9** (0.283 g, 82%, including the above small amount that crystallized from the initial aqueous DMF solution): mp 120-122 °C; FTIR ν_{max} (microscope)/cm^{-1} 3459, 3383, 3201, 1672; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.25 (s, 6 H), 1.00 (s, 9 H), 2.40 (t, J = 7.8 Hz, 2 H), 3.10 (t, J = 8.1 Hz, 2 H), 3.20 (s, 3 H), 5.59 (br s, 1 H), 5.97 (br s, 1 H), 6.72 (d, J = 8.9 Hz, 1 H), 7.17 (d, J = 8.9 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ -4.3 (q), 18.1 (s), 23.9 (t), 25.6 (q), 33.8 (t), 38.3 (q), 116.7 (d), 122.0 (d), 127.6 (s), 131.6 (s), 139.2 (s), 153.0 (s), 174.1 (s); exact mass *m*/*z* calcd for $C_{16}H_{26}ClNNaO_5SSi$ (M + Na) 430.0882, found 430.0883.

In a larger scale experiment a slightly better yield was obtained: Imidazole (0.188 g, 2.77 mmol), followed by *t*-$BuMe_2SiCl$ (0.368 g, 2.44 mmol), were added to a stirred solution of **1.8** (0.591 g, 2.01 mmol) in DMF (6.6 mL) and the mixture was heated at 65 °C (Ar atmosphere). After 1.5 days the mixture was cooled and partitioned between Et_2O (40 mL) and water (40 mL). The aqueous phase was extracted Et_2O and the combined organic extracts were washed with water and brine, and dried (Na_2SO_4). Upon standing overnight a small portion of **1.9** crystallized

from the aqueous layer and was collected. A further portion of **1.9** also crystallized from the ether extract as silky fine needles and these were separated from the Na_2SO_4 drying agent by filtering the mixture and washing **1.9** out of the drying agent with dry acetone. The initial ether filtrate was set aside and the acetone filtrate was evaporated to give a batch of **1.9**. The ether filtrate was poured into a beaker containing water (40 mL) and the ether was allowed to evaporate, leaving a crust of **1.9** on the surface of the water. This material was collected and the combined batches of **1.9** weighed 0.792 g (96%).

Methanesulfonic Acid 3-[(2-*tert*-Butoxycarbonylamino)ethyl]-4-[(*tert*-butyldimethyl-silyl)oxy]-2-chlorophenyl Ester (1.10).

1.9 **1.10**

$Pb(OAc)_4$ (0.176 g, 0.397 mmol) was added in one portion to a stirred and heated (60 °C) solution of **1.9** (70.4 mg, 0.173 mmol) in freshly distilled dry *t*-BuOH (3 mL) and heating was continued for 4 h (Ar atmosphere). The mixture was cooled to room temperature and filtered through a pad of Florisil (1 x 1.5 cm), using CH_2Cl_2 (20 mL). The filtrate was evaporated and the residue was dissolved in CH_2Cl_2 and applied to a short column of flash chromatography silica gel (2 x 3 cm), which was washed with 18% EtOAc-hexanes (30 mL) to remove remaining lead residues (these remained on the silica). Evaporation of the filtrate gave **1.10** (76.4 mg, 92%): FTIR ν_{max} (microscope)/cm^{-1} 3422, 1710; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.28 (s, 6 H),

1.02 (s, 9 H), 1.38 (s, 9 H), 3.00 (t, J = 6.8, 2 H), 3.20 (s, 3 H), 3.35-3.37 (m, 2 H), 4.66 (br s, 1 H), 6.74 (d, J = 8.9 Hz, 1 H), 7.22 (d, J = 8.9 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 0.0 (q), 22.4 (t), 26.3 (s), 29.9 (q), 32.5 (q), 42.5 (q), 43.6 (t), 83.2 (s), 120.9 (d), 126.6 (d), 132.3 (s), 134.3 (s), 143.7 (s), 157.5 (s), 159.9 (s); exact mass m/z calcd for $C_{20}H_{34}ClNNaO_6SSi$ (M + Na) 502.1457, found 502.1457.

In another experiment, a slightly different workup was used: $Pb(OAc)_4$ (1.01 g, 2.28 mmol) was added in one portion to a stirred and heated (60 °C) solution of **1.9** (0.792 g, 1.94 mmol) in dry *t*-BuOH (18 mL) and heating was continued at 75 °C for 30 min (Ar atmosphere). The mixture was cooled to room temperature and filtered by gravity through a fluted filter paper. The filtrate was evaporated and the residue was filtered through Florisil (4 x 4 cm) by suction, using 20% EtOAc-hexanes (200 mL) and then 30% EtOAc-hexanes (100 mL). Evaporation of the filtrate gave **1.10** (0.835 g, 90%) which eventually solidified under oil-pump vacuum to a crystalline solid: mp 84-86 °C.

[2-(2-Chloro-3,6-dioxocyclohexa-1,4-dienyl)ethyl]carbamic Acid *tert*-Butyl Ester (1.11).

1.10 **1.11**

NaF (0.560 g, 14.3 mmol), followed by $PhI(OAc)_2$ (0.831 g, 2.58 mmol), were each added in single portions to a stirred solution of **1.10** (1.13 g, 2.35 mmol) in MeCN (13 mL) and

water (8 mL). After 1.5 h, Et_2O (ca 30 mL) was added and the mixture was washed with water (2 x 10 mL) and brine (1 x 10 mL), dried ($MgSO_4$) and evaporated. Filtration of the residue through a pad of flash chromatography silica gel (2.5 x 1 cm), using CH_2Cl_2, gave **1.11** (0.468 g, 73%) as orange crystals: mp 118-120 °C; ; FTIR ν_{max} (microscope)/cm^{-1} 3377, 2979, 2935, 1674; ^{1}H-NMR (400 MHz, C_6D_6): δ 1.33 (s, 9 H), 2.39 (t, J = 6.4 Hz, 2 H), 2.97 (dt as apparent q, J = 6.4, 12.6 Hz, 2 H), 3.92 (br s, 1 H), 6.02 (apparent s, 2 H); exact mass m/z calcd for $C_{13}H_{16}ClNNaO_4$ (M + Na) 308.0660, found 308.0662. The material is unstable and was used immediately without full characterization.

In a smaller scale experiment, using **1.10** (74 mg), a quantitative yield was obtained.

4-Chloro-1*H*-indol-5-ol (1.12b).

1.11 **1.12b**

2,6-Lutidine (0.15 mL, 1.3 mmol), followed by $Me_3SiOSO_2CF_3$ (0.21 mL, 1.2 mmol), were added dropwise by syringe to a stirred and cooled (0 °C) solution of **1.11** (0.268 g, 0.937 mmol) in CH_2Cl_2 (10 mL) containing 4 Å molecular sieves (ca 1 g). After the addition the mixture was refluxed overnight (Ar atmosphere), cooled and partitioned between Et_2O (25 mL) and water (15 mL). The organic phase was washed once with water and once with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 x 30 cm), using 10% EtOAc-hexanes (50 mL) and then 25% EtOAc-hexane (50 mL), gave **1.12b** (99.7 mg, 63%)

and the corresponding trimethylsilyl ether (**1.12a**) (33.3 mg, 15%) as oils. The quinone imine **4**, which was initially observed by TLC, did not come off the column, even after elution with 60% EtOAc-hexanes (50 mL).

The trimethylsilyl ether **1.12a** had: FTIR ν_{max} (film microscope)/cm^{-1} 3422, 2959; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.30 (s, 9 H), 6.61 (ddd, *J* = 1.0, 2.2, 3.2 Hz, 1 H), 6.82 (dd, *J* = 0.4, 8.6 Hz, 1 H), 7.16 (dd, *J* = 1.0, 8.6 Hz, 1 H), 7.21 (ddd, *J* = 0.4, 2.5, 3.0 Hz, 1 H), 8.15 (br s, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 0.4 (q), 101.4 (d), 109.6 (d), 115.7 (s), 116.8 (d), 125.3 (d), 127.8 (s), 131.6 (s), 144.7 (s); exact mass *m*/*z* calcd for $C_{11}H_{14}ClNNaOSi$ (M + Na) 262.0425, found 262.0425.

The trimethylsilyl ether **1.12a** was desilylated as follows: K_2CO_3 (56.7 mg, 0.410 mmol) was added in one portion to a stirred solution of the above trimethylsilyl ether **1.12a** (33.0 mg, 0.138 mmol) in 80% MeOH (2 mL). The flask was stoppered and stirring was continued under air for 30 min. The mixture was then neutralized with dilute hydrochloric acid (5%). Water (10 mL) was added and the mixture was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated to afford **1.12b** (23.0 mg, 99%): FTIR ν_{max} (microscope)/cm^{-1} 3421, 3132; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.29 (s, 1 H), 6.56 (ddd, *J* = 1.0, 2.2, 3.2 Hz, 1 H), 6.94 (dd, *J* = 0.4, 8.6 Hz, 1 H), 7.21 (dd, *J* = 0.8, 8.6 Hz, 1 H), 7.23-7.24 (m overlapping with a signal centered at δ 7.21, 1 H), 8.16 (br s, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 100.8 (d), 109.6 (s), 110.5 (d), 111.8 (d), 125.5 (d), 126.7 (s), 131.0 (s), 145.3 (s); exact mass *m*/*z* calcd for C_8H_6ClNO 167.0138, found 167.0137.

An alternative procedure is as follows:

$BF_3{\cdot}OEt_2$ (10% v/v in CH_2Cl_2, 0.84 mL, 0.66 mmol) was added dropwise by syringe to a stirred and cooled (0 °C) solution of **1.11** (47.2 mg, 0.221 mmol) in CH_2Cl_2 (3 mL) containing

4Å molecular sieves (ca 0.5 g, activated at >200 °C under oil pump vacuum overnight). The cooling bath was left in place but not recharged and stirring was continued overnight. The supernatant liquid was rinsed into a separatory funnel containing saturated aqueous $NaHCO_3$ (ca 5 mL), using CH_2Cl_2 (ca 5 mL). The mixture was shaken and the organic layer was dried ($MgSO_4$) and evaporated. The residue was passed through a Pasteur pipette containing flash chromatography silica gel, using 40% EtOAc-hexanes, to give a mixture of indole **1.12b** and quinone imine **4**. This mixture was dissolved in PhH (3.6 mL), and Pd-C (10% Pd, 5.5 mg) was added in one portion. The resulting heterogeneous mixture was refluxed for 3 h, cooled and evaporated. Flash chromatography of the residue over silica gel (0.5 x 10 cm), using 25% EtOAc-hexanes, gave **1.12b** (22.3 mg, 60% over two steps) as a brownish oil.

In another experiment, a slightly impure sample of qunione imine **4** was isolated: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.00-3.03 (m, 2 H), 4.48-4.50 (m, 2 H), 6.79 (dt, J = 0.9, 9.8 Hz, 1 H), 7.49 (d, J = 9.7 Hz, 1 H).

5-Bromo-6-hydroxy-2-oxo-2*H*-chromene-3-carboxylic Acid Ethyl Ester (2.1).

1.2 **2.1**

A solution of Br_2 (0.14 mL, 2.7 mmol) in $CHCl_3$ (5 mL) was added dropwise to a stirred suspension of **1.2** (0.552 g, 2.36 mmol) in $CHCl_3$ (13 mL) (N_2 atmosphere). Stirring was continued for 12 h after the addition, and the mixture was then transferred to a separatory funnel

and washed with dilute aqueous $Na_2S_2O_3$ (5 mL saturated solution in 10 mL water). The aqueous layer was extracted with CH_2Cl_2 until the organic layer was colorless. Solid product was present in the organic phase. Acetone was added to the combined organic extracts until all the solid dissolved, and the solution was dried ($MgSO_4$) and evaporated to give pure **2.1** (0.770 g, 100%): mp 201-203 °C (from EtOH); FTIR ν_{max} (microscope)/cm^{-1} 3368, 1757; ^{1}H-NMR (400 MHz, acetone-d_6): δ 1.35 (t, *J* = 7.1 Hz, 3 H), 4.34 (q, *J* = 7.1 Hz, 2 H), 7.26 (dd, *J* = 9.1, 0.7 Hz, 1 H), 7.38 (d, *J* = 9.0 Hz, 1 H), 8.72 (d, *J* = 0.7 Hz, 1 H), 9.35 (br s, 1 H); ^{13}C-NMR (100 MHz, acetone-d_6): δ 13.8 (q), 61.6 (t), 108.6 (s), 116.7 (d), 118.5 (s), 120.1 (s), 122.4 (d), 146.1 (d), 149.7 (s), 151.6 (s), 155.6 (s), 162.9 (s); exact mass *m*/*z* calcd for $C_{12}H_9{}^{79}BrNaO_5$ (M + Na) 334.9526, found 334.9530.

A larger scale experiment, using **1.2** (3.80 g), gave **2.1** (4.60 g, 91%).

5-Bromo-6-[(methanesulfonyl)oxy]-2-oxo-2*H*-chromene-3-carboxylic Acid Ethyl Ester (2.2).

2.1 **2.2**

Et_3N (0.41 mL, 2.9 mmol) was added to a stirred and cooled (0 °C) suspension of **2.1** (0.699 g, 2.23 mmol) in CH_2Cl_2 (20 mL) to produce a red solution. MsCl (0.19 mL, 2.5 mmol) was added dropwise by syringe over ca 5 min. Near the end of the addition the red color was discharged. Stirring was then continued for 30 min at 0 °C and the mixture was washed with

water (2 x 10 mL), dried ($MgSO_4$) and evaporated. The residue was dissolved in boiling 95% EtOH (20 mL) and the solution was allowed to cool and then refrigerated at 5 °C for 12 h to give **2.2** as very light-amber platelets (0.797 g, 91%): mp 125-126 °C; FTIR ν_{max} (microscope)/cm^{-1} 3086, 2986, 2939, 1770, 1713; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.42 (t, J = 7.2 Hz, 3 H), 3.34 (s, 3 H), 4.43 (q, J = 7.1 Hz, 2 H), 7.36 (dd, J = 0.7, 9.2 Hz, 1 H), 7.69 (d, J = 9.2 Hz, 1 H), 8.80 (d, J = 0.7 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.2 (q), 39.2 (q), 62.5 (t), 117.2 (d), 117.7 (s), 119.1 (s), 120.3 (s), 128.8 (d), 143.4 (s), 146.4 (d), 153.8 (s), 155.2 (s), 162.3 (s); exact mass *m*/*z* calcd for $C_{13}H_{11}{}^{79}BrNaO_7S$ (M + Na) 412.9301, found 412.9303.

5-Bromo-6-[(methanesulfonyl)oxy]-2-oxochroman-3-carboxylic Acid Ethyl Ester (2.3).

2.2 **2.3**

$LiBH_4$ in THF (1.2 M, 2.2 mL, 2.6 mmol) was added by syringe to a stirred and cooled (0 °C) solution of **2.2** (2.65 g, 6.78 mmol) in THF (42 mL) (Ar atmosphere). The mixture was stirred for 15 min and then a second aliquot of $LiBH_4$ in THF (1.2 M, 0.30 mL, 0.36 mmol) was added. Stirring at 0 °C was continued for 20 min and the mixture was then quenched by addition of aqueous tartaric acid (0.5 M, 13 mL, 6.5 mmol) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated to afford pure **2.3** (2.62 g, 98%): mp 122-125 °C; FTIR ν_{max} (microscope)/cm^{-1} 3112, 3084, 3032,

2995, 2936, 1768, 1731; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.25 (t, *J* = 7.2 Hz, 3 H), 3.29 (s, 3 H), 3.34 (dd, *J* = 6.3, 16.9 Hz, 1 H), 3.58 (dd, *J* = 8.5, 16.8 Hz, 1 H), 3.78 (dd, *J* = 6.3, 8.5 Hz, 1 H), 4.22-4.26 (m, 2 H), 7.10 (d, *J* = 9.0 Hz, 1 H), 7.40 (d, *J* = 9.0 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.2 (q), 28.4 (t), 39.3 (q), 45.6 (d), 62.9 (t), 117.2 (d), 117.8 (s), 123.9 (d), 123.9 (s), 143.6 (s), 150.3 (s), 163.5 (s), 166.9 (s); exact mass *m*/*z* calcd for $C_{13}H_{13}{}^{79}BrO_7S$ 393.9545, found 393.9562.

Methanesulfonic Acid 5-Bromo-2-oxochroman-6-yl Ester (2.4).

2.3 **2.4**

Dilute hydrochloric acid (20%, 52 mL) was added to a stirred solution of **2.3** (1.39 g, 3.53 mmol) in acetone (8 mL), causing a white precipitate to form. The mixture was refluxed open to the atmosphere for ca 2 h and then cooled and extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. The resulting colorless oil was covered with PhMe (54 mL), and $TsOH{\cdot}H_2O$ (55.3 mg, 0.291 mmol) was added. The mixture was refluxed for ca 5 h, and then evaporated. The residue was filtered through a small column of flash chromatography silica gel (3 x 4 cm), using 20% EtOAc-hexanes to remove a faster-eluting impurity (TLC control), and then **2.4** (1.01 g, 89%) was eluted, using 50% EtOAc-hexanes: mp 123-125 °C (from MeOH); FTIR ν_{max} (microscope)/cm^{-1} 3084, 3021, 2936, 1755; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.83 (t, *J* = 7.8 Hz, 2

H), 3.17 (t, *J* = 7.8 Hz, 2 H), 3.30 (s, 3 H), 7.08 (d, *J* = 8.9 Hz, 1 H), 7.38 (d, *J* = 9.0 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 25.0 (t), 28.3 (t), 39.2 (q), 117.3 (d), 117.7 (s), 123.5 (d), 125.5 (s), 143.2 (s), 151.0 (s), 167.0 (s); exact mass *m*/*z* calcd for $C_{10}H_9{}^{79}BrO_5S$ 321.9334, found 321.9334.

Methanesulfonic Acid 2-Bromo-3-(2-carbamoylethyl)-4-hydroxyphenyl Ester (2.5).

2.4 **2.5**

NH_3 was bubbled through a solution of **2.4** (0.172 g, 0.537 mmol) in THF (9 mL) for 35 min (without protection from air). Evaporation of the solvent gave **2.5** as a white solid (0.180 g, 100%): mp 136-139 °C; FTIR ν_{max} (microscope)/cm^{-1} 3445, 3367, 3199, 2938, 1661, 1592; ^{1}H-NMR (400 MHz, acetone-d_6): δ 2.74 (t, *J* = 6.7 Hz, 2 H), 3.06 (t, *J* = 6.7 Hz, 2 H), 3.32 (s, 3 H), 6.75 (br s, 1 H), 6.89 (d, *J* = 8.9 Hz, 1 H), 7.23 (d, *J* = 8.9 Hz, 1 H), 7.26 (br s, 1 H), 10.10 (br s, 1 H); ^{13}C-NMR (100 MHz, acetone-d_6): δ 25.6 (t), 34.1 (t), 38.5 (q), 117.6 (d), 119.6 (s), 122.9 (d), 130.8 (s), 140.8 (s), 155.9 (s), 177.0 (s); exact mass *m*/*z* calcd for $C_{10}H_{12}{}^{79}BrNNaO_5S$ (M + Na) 359.9512, found 359.9515.

In a larger scale experiment, using **2.4** (1.32 g, 4.17 mmol), a yield of 82% was obtained.

Compound **2.5** can be purified by trituration under hot $CHCl_3$, followed by cooling of the supernatant solution. Alternatively, it can be crystallized from 2-butanone-$CHCl_3$.

Methanesulfonic Acid 4-Allyloxy-2-bromo-3-(2-carbamoylethyl)phenyl Ester (2.6).

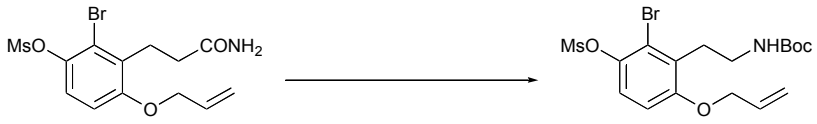
2.5 **2.6**

K_2CO_3 (0.112 g, 0.813 mmol) was added to a stirred solution of **2.5** (0.184 g, 0.545 mmol) in 2-butanone (5 mL) (N_2 atmosphere), and allyl bromide (0.05 mL, 0.58 mmol) was added by syringe. The flask was equipped with a condenser and the stirred mixture was kept at 45 °C overnight. At this point the reaction was still incomplete (TLC control) and so more allyl bromide (0.02 mL, 0.23 mmol) was added and the mixture was heated at 65 °C for 1 h. More K_2CO_3 (0.1 g, 0.7 mmol) was added, followed by another portion of allyl bromide (0.03 mL, 0.35 mmol), and stirring at 65 °C was continued for 1.5 h. The mixture was cooled to room temperature, diluted with EtOAc (15 mL) and washed with water (2 x 10 mL) and brine (10 mL). The organic extract was dried ($MgSO_4$) and evaporated to give **2.6** as a white, amorphous solid (0.189 g, 92%): mp 139-141 °C; FTIR ν_{max} (microscope)/cm^{-1} 3360, 3203, 2942, 1643; ^{1}H-NMR (400 MHz, acetone-d_6): δ 2.36-2.40 (m, 2 H), 3.14-3.18 (m, 2 H), 3.33 (s, 3 H), 4.66 (ddd as an apparent dt, J = 4.9, 1.6, 1.6 Hz, 2 H), 5.25 (ddt as an apparent dq, J = 10.6, 1.5, 1.5 Hz, 1 H), 5.46 (ddt as an apparent dq, J = 17.3, 1.8, 1.8 Hz, 1 H), 6.08 (ddt, J = 17.3, 10.7, 4.9 Hz, 1 H), 6.19 (br s, 1 H) 6.73 (br s, 1 H), 7.04 (dd, J = 0.2, 9.0 Hz, 1 H), 7.31 (d, J = 9.0 Hz, 1 H); ^{13}C-NMR (100 MHz, acetone-d_6): δ 26.6 (t), 33.6 (t), 38.2 (q), 69.5 (t), 111.7 (d), 116.9 (t), 119.1 (s), 121.9 (d), 132.1 (s), 133.4 (d), 140.8 (s), 155.8 (s), 173.2 (s); exact mass m/z calcd for $C_{13}H_{16}{}^{79}BrNNaO_5S$ (M + Na) 399.9825, found 399.9823.

A larger scale experiment was done as follows:

K_2CO_3 (1.3 g, 9.4 mmol) was added to a stirred solution of **2.5** (1.16 g, 3.43 mmol) in 2-butanone (26 mL) (N_2 atmosphere), and allyl bromide (0.41 mL, 4.7 mmol) was added by syringe. The flask was equipped with a condenser and the stirred mixture was kept at 65 °C for 6 h. At this point the reaction was still incomplete (TLC control) and so more allyl bromide (0.36 mL, 4.2 mmol) was added and the mixture was kept at 45 °C overnight. The mixture was cooled to room temperature, and the solvent was evaporated. The solid residue was partitioned between EtOAc (50 mL) and water (50 mL). The organic extract was washed with water and brine, dried ($MgSO_4$) and evaporated to give **2.6** as a white, amorphous solid (1.2286 g, 95%).

Methanesulfonic Acid 4-Allyloxy-2-bromo-3-[(2-*tert*-butoxycarbonylamino)ethyl]-phenyl Ester (2.7).

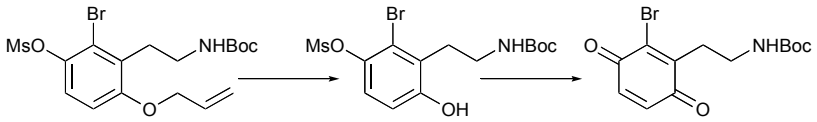


2.6 **2.7**

$Pb(OAc)_4$ (1.62 g, 3.66 mmol) was added in one portion to a stirred and heated (70 °C) suspension of **2.6** (1.23 g, 3.25 mmol) in dry *t*-BuOH (24 mL) and heating at 70 °C was continued for 30 min. The mixture was cooled and the inorganic solids were removed by gravity filtration through a fluted filter paper, using Et_2O (30 mL total) as a rinse. The filtrate was evaporated and the residue was filtered through a pad of flash chromatography silica gel (3.5 x 3.5 cm), using 20% EtOAc-hexanes (300 mL), to afford **2.7** (1.37 g, 94%): mp 96-98 °C; FTIR

ν_{max} (microscope)/cm^{-1} 1708; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.39 (s, 9 H), 3.10 (t, *J* = 6.7 Hz, 2 H), 3.23 (s, 3 H), 3.37 (m, 2 H), 4.58 (ddd as an apparent dt, *J* = 5.1, 1.5, 1.5 Hz, 2 H), 4.69 (br s, 1 H), 5.32 (ddt as an apparent dq, *J* = 10.5, 1.4, 1.4 Hz, 1 H), 5.43 (ddt as an apparent dq, *J* = 17.2, 1.4, 1.4 Hz, 1 H), 6.04 (ddt, *J* = 17.3, 10.5, 5.1 Hz, 1 H), 6.83 (d, *J* = 9.1 Hz, 1 H), 7.30 (d, *J* = 9.0 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$) (two signals overlap): δ 28.4 (q), 30.6 (t), 38.5 (q), 39.2 (t), 69.6 (t), 79.0 (s), 111.0 (d), 118.1 (t), 119.6 (s), 122.2 (d), 130.0 (s), 132.4 (d), 140.3 (s), 155.8 (s); exact mass *m*/*z* calcd for $C_{17}H_{24}{}^{79}BrNNaO_6S$ (M + Na) 472.0400, found 472.0404.

[2-(2-Bromo-3,6-dioxocyclohexa-1,4-dienyl)ethyl]carbamic Acid *tert*-Butyl Ester (2.9).



2.7 **3.1** **2.9**

K_2CO_3 (28.4 mg, 0.205 mmol), followed by $Pd(PPh_3)_4$ (1.9 mg, 0.0016 mmol), were added to a stirred solution of **2.7** (25.2 mg, 0.560 mmol) in MeOH (3 mL) and stirring was continued for 4 h (Ar atmosphere). The mixture was then acidified (litmus test) with dilute hydrochloric acid (5%), diluted with water and extracted with Et_2O (10 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. The crude residue (**3.1**) was dissolved in a stirred mixture of *t*-BuOH (1.8 mL) and water (0.5 mL). The mixture was cooled to 0 °C and $PhI(OAc)_2$ (24 mg, 0.075 mmol) was added in one portion. The ice bath was removed after 10 min and stirring was continued for ca 1 h. The mixture was

extracted with Et_2O (10 mL) and the organic extract was washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was filtered through Al_2O_3 (grade 1, neutral, 1 x 1 cm), using 40% EtOAc-hexanes, to afford **2.9** (13.4 mg, 73% from **2.7**): mp 112-114 °C; FTIR ν_{max} (film cast)/cm^{-1} 3363, 2978, 2932, 1693; ^{1}H-NMR (400 MHz, C_6D_6): δ 1.36 (s, 9 H), 2.93 (t, J = 6.3 Hz, 2 H), 3.38 (dt as an apparent q, J = 6.3, 6.3 Hz, 2 H), 4.67 (br s, 1 H), 6.84 (d, J = 10.0 Hz, 1 H), 6.92 (d, J = 10.0 Hz, 1 H); ^{13}C-NMR (100 MHz, C_6D_6): δ 28.2, 32.4, 38.9, 78.7, 134.8, 136.0, 136.3, 147.0, 155.8, 178.8, 183.2; exact mass m/z calcd for $C_{13}H_{16}{}^{79}BrNNaO_4$ (M + Na) 352.0155, found 352.0152.

[2-(6-Allyloxy-2-bromo-3-hydroxyphenyl)ethyl]carbamic Acid *tert*-Butyl Ester (2.8).

2.7 **2.8**

Benzyltrimethylammonium hydroxide (Triton B, 40% w/w in MeOH, 0.23 mL, 0.51 mmol) was added to a stirred solution of **2.7** (62.4 mg, 0.139 mmol) in dioxane (1.3 mL) and water (0.5 mL). The mixture was heated at 50-60 °C open to the atmosphere for 6 h, cooled, neutralized with dilute hydrochloric acid (5%), and extracted with EtOAc (10 mL). The organic extract was washed with water and brine, dried (Na_2SO_4) and evaporated to afford **2.8** (48.7 mg, 94%): FTIR ν_{max} (film cast)/cm^{-1} 3332, 2978, 2933, 1683; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 9 H), 3.05 (t, J = 6.6 Hz, 2 H), 3.35-3.38 (m, 2 H), 4.52 (ddd as an apparent dt, J = 5.2, 1.6, 1.6 Hz, 2 H), 4.76 (br s, 1 H), 5.29 (ddt as an apparent dq, J = 10.6, 1.5, 1.5 Hz, 1 H), 5.38 (s, 1

H), 5.41 (ddt as an apparent dq, J = 17.2, 1.5, 1.5 Hz, 1 H), 6.04 (ddt, J = 17.2, 10.5, 5.2 Hz, 1 H), 6.77 (d, J = 8.9 Hz, 1 H), 6.88 (d, J = 8.9 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.4 (q), 30.6 (t), 39.7 (t), 69.9 (t), 78.9 (s), 112.5 (d), 113.4 (d), 114.3 (s), 117.5 (t), 128.2 (s), 133.1 (d), 146.7 (s), 150.8 (s), 155.9 (s); exact mass m/z calcd for $C_{16}H_{22}{}^{79}BrNNaO_4$ (M + Na) 394.0624, found 394.0624.

[2-(2-Bromo-3,6-dioxocyclohexa-1,4-dienyl)ethyl]carbamic Acid *tert*-Butyl Ester (2.9).

2.8 **2.9**

Procedure A.

$(NH_4)_6Ce(NO_2)_4$ on flash chromatography silica gel (18% w/w, 0.373 g, 0.122 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **2.8** (22.8 mg, 0.0613 mmol) in MeCN (1.2 mL) containing water (0.1 mL). The mixture was stirred open to the atmosphere for 30 min and then evaporated. The residual solid was washed with CH_2Cl_2 and the organic extract was evaporated and filtered through Al_2O_3 (grade 1, neutral, 1 x 2 cm), using 30% EtOAc-hexanes (10 mL), to afford **2.9** (14.9 mg, 74%).

Procedure B.

$PhI(OAc)_2$ (0.287 g, 0.892 mmol) was added in one portion to a stirred solution of **2.8** (0.286 g, 0.768 mmol) in *t*-BuOH (6 mL) and water (3 mL). The flask was stoppered and stirring was continued under air for 40 min. The mixture was then extracted with EtOAc (25 mL) and the organic extract was washed with water and brine, dried (Na_2SO_4) and evaporated. The residue was purified by filtration through Al_2O_3 (grade 1, neutral, 2 x 3 cm), using first hexanes (30 mL) and then 10% EtOAc-hexanes (20 mL). The product was then eluted, using 30% EtOAc-hexanes (30 mL), and the yellow fraction was evaporated to afford **2.9** (0.154 g, 61%).

A slightly higher yield (67%) was obtained in a smaller scale experiment, using **2.8** (27.7 mg, 0.0744 mmol).

4-Bromo-1*H*-indol-5-ol (2.11b).

2.9 **2.11b**

A flask was charged with **2.9** (0.131 g, 0.396 mmol) and 4 Å molecular sieves (0.5 g, activated), and CH_2Cl_2 (3.6 mL) was injected with stirring (Ar atmosphere). The mixture was cooled to 0 °C and 2,6-lutidine (0.06 mL, 0.5 mmol) was added by syringe. $Me_3SiOSO_2CF_3$ (10% v/v in CH_2Cl_2, 0.85 mL, 0.47 mmol) was then added dropwise by syringe. After the addition the ice bath was removed, the flask was equipped with a reflux condenser and the mixture was heated at 40 °C overnight. The mixture was then cooled and partitioned between

Et_2O (20 mL) and water (20 mL). The organic extract was washed with water, dilute aqueous $NaHCO_3$ [from saturated aqueous $NaHCO_3$ (2 mL) and water (10 mL)] and brine, dried (Na_2SO_4) and evaporated. The residue was dissolved in PhMe (5 mL) and Rh-Al_2O_3 (5% w/w Rh, 9.9 mg, 0.0050 mmol) was added. The mixture was then heated at 80 °C for 5 h and then cooled. Evaporation of the solvent and flash chromatography of the residue over silica gel (0.5 x 30 cm), using 10% EtOAc-hexanes (10 mL), 20% EtOAc-hexanes (50 mL) and then 30% EtOAc-hexanes (40 mL), gave two products. The faster eluting product (R_f = 0.60, 1:1 EtOAc-hexanes, TLC silica) was **2.11a** (29.3 mg, 26%), which was obtained as an oil: FTIR ν_{max} (film cast)/cm^{-1} 3421, 2959; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.32 (s, 9 H), 6.55-6.57 (m, 1 H), 6.79-6.82 (m, 1 H), 7.19-7.21 (m, 1 H), 7.22-7.24 (m, 1 H), 8.17 (br s, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 0.0, 102.8, 105.3, 109.8, 115.9, 124.8, 129.3, 130.8, 145.6; exact mass *m*/*z* calcd for $C_{11}H_{15}{}^{79}BrNOSi$ 284.0101, found 284.0101.

The slower eluting product (R_f = 0.45, 1:1 EtOAc-hexanes) was **2.11b** (62.1 mg, 74%), which was obtained as an oil: FTIR ν_{max} (microscope)/cm^{-1} 3421; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.31 (br s, 1 H), 6.52 (ddd, *J* = 3.1, 2.2, 0.9 Hz, 1 H), 6.97 (dd, *J* = 8.7, 0.4 Hz, 1 H), 7.25 (ddd, *J* = 3.1, 2.6, 0.4 Hz, 1 H), 7.26 (dd, *J* = 8.6, 0.9 Hz, 1 H), 8.20 (br s, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 100.4 (s), 102.7 (d), 11.5 (d), 111.9 (d), 125.8 (d), 128.6 (s), 130.9 (s), 146.7 (s); exact mass *m*/*z* calcd for $C_8H_6{}^{79}BrNO$ 212.9621, found 212.9616.

A slightly larger scale experiment, using **2.9** (0.216 g, 0.654 mmol) and $Me_3SiOSO_2CF_3$ (0.190 mL, 1.05 mmol), gave **2.11a** (34%) and **2.11b** (33%) after Rh catalyzed isomerization, corresponding to a total yield of 67% from **2.9** to a mixture of **2.11a** and **2.11b**. Conversion of **2.11a** to **2.11b** is quantitative (see below).

4-Bromo-1*H*-indol-5-ol (2.11b).

2.11a **2.11b**

K_2CO_3 (48 mg, 0.35 mmol) was added in one portion to a stirred solution of **2.11a** (23.3 mg, 0.0820 mmol) in 80% MeOH (2 mL). The flask was stoppered, stirring was continued under air for 1 h and then the mixture was neutralized with dilute hydrochloric acid (5%). Water (8 mL) was added and the mixture was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5 x 10 cm) in a Pasteur pipette, using 18% EtOAc-hexanes (to remove a faster eluting by-product), gave **2.11b** (17.4 mg, 100%).

[2-(6-Allyloxy-2-bromo-3,4-dioxocyclohexa-1,5-dienyl)ethyl]carbamic Acid *tert*-Butyl Ester (3.2).

2.8 **3.2**

Frémy's salt (61.4 mg, 0.229 mmol) was added to a stirred and cooled (0 °C) solution of **2.8** (15.1 mg, 0.0406 mmol) in MeCN (1 mL) and water (0.3 mL). After the addition more water (0.6 mL) was added to dissolve the Frémy's salt. The ice bath was removed after 15 min and

stirring was continued for ca 30 min. The mixture was extracted with EtOAc (10 mL) and the organic extract was washed with water and brine, dried ($MgSO_4$) and evaporated. The residue was filtered through flash chromatography silica gel (1 x 1 cm), using 36% EtOAc-hexanes, and the orange fraction was evaporated to afford **3.2** (15.7 mg, 100%) as an oil: FTIR ν_{max} (film cast)/cm^{-1} 3374, 3080, 2977, 2933, 1698, 1662; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 9 H), 3.01 (t, *J* = 6.4 Hz, 2 H), 3.46 (dt as an apparent q, *J* = 6.4, 6.4 Hz, 2 H), 4.61 (ddd as an apparent dt, *J* = 5.5, 1.2, 1.2 Hz, 2 H), 4.68 (br s, 1 H), 5.41-5.45 (m, 1 H), 5.50-5.51 (m, 1 H), 5.79 (s, 1 H), 6.03 (ddt, *J* = 17.2, 10.6, 5.6 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.6, 33.7, 39.2, 71.4, 79.9, 102.8, 120.6, 128.3, 130.2, 148.8, 156.1, 167.3, 173.2, 176.8; exact mass *m*/*z* calcd for $C_{16}H_{20}{}^{79}BrNNaO_5$ (M + Na) 408.0417, found 408.0414.

4-Allyloxy-3-(2-aminoethyl)-2-bromophenol Hydrochloride (3.3).

2.8 **3.3**

A flask was charged with **2.8** (22.1 mg, 0.0594 mmol) and then flushed with N_2. A solution of HCl in EtOAc (ca 1.6 M, 1.1 mL, 1.8 mmol) was then added by syringe with stirring. After 5 h, the reaction was still incomplete (TLC control) and so a second aliquot of HCl in EtOAc (ca 1.6 M, 1 mL, 1.6 mmol) was added. Stirring was continued for 1 h and the solvent was then evaporated. The solid residue was washed with Et_2O to afford **3.3** (16.6 mg, 91%): FTIR ν_{max} (microscope)/cm^{-1} 2979; ^{1}H-NMR (400 MHz, D_2O): δ 3.18-3.19 (m, 4 H), 4.56 (d, *J* =

5.5 Hz, 2 H), 4.75 (br s, 1 H), 5.31 (dd, *J* = 10.5, 1.1 Hz, 1 H), 5.40 (dd, *J* = 17.4, 1.4 Hz, 1 H), 6.09 (ddt, *J* = 16.1, 10.6, 5.5 Hz, 1 H), 6.90-6.96 (m, 2 H); ^{13}C-NMR (100 MHz, D_2O): δ 27.9 (t), 38.8 (t), 70.7 (t), 113.5 (s), 113.9 (d), 115.5 (d), 118.5 (t), 126.5 (s), 133.5 (d), 147.4 (s), 150.8 (s); exact mass *m*/*z* calcd for $C_{11}H_{15}{}^{79}BrNO_2$ 272.0281, found 272.0282.

Methanesulfonic Acid 3-[(2-*tert*-Butoxycarbonylamino)ethyl]-4-hydroxy-2-iodo-phenyl Ester (A-1).

4.7 **A-1**

K_2CO_3 (0.424 g, 3.07 mmol), followed by $Pd(PPh_3)_4$ (38.8 mg, 0.0336 mmol), were added in single portions to a stirred solution of **4.7** (0.495 g, 0.980 mmol) in MeOH (8 mL). After 2 h, the mixture was diluted with water (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with water (2 x 120 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. The crude residue was loaded onto a pad of flash chromatography silica gel (2 x 3 cm), using CH_2Cl_2, and the pad was washed with CH_2Cl_2 (30 mL) which was discarded. The product was then eluted, using 54% EtOAc-hexanes (40 mL) and evaporation of the filtrate gave crude **A-1** (0.47 g, 105%) which was used without further purification. (Compound labelled here as **A-1** is not numbered in the manuscript.)

[2-(2-Iodo-3,6-dioxocyclohexa-1,4-dienyl)ethyl]carbamic Acid *tert*-Butyl Ester (4.9).

A-1 **4.9**

$PhI(OAc)_2$ (0.224 g, 0.694 mmol) was added in one portion to a stirred and cooled (0 °C) solution of the crude **A-1** (0.285 g, 0.623 mmol) in MeCN (6 mL) and water (2 mL). Stirring was continued for 30 min without protection from air. Water (25 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with water (10 mL), dried ($MgSO_4$) and evaporated. The crude residue was purified by filtration through a pad of flash chromatography silica gel (2.5 x 4 cm), using CH_2Cl_2 to apply the material and 18% EtOAc-hexanes for elution. Evaporation of the yellow fractions gave **4.9** (0.168 g, 69% over two steps).

In a separate experiment on a similar scale, but using *t*-BuOH-water as solvent, the product **4.9** was obtained in 61% yield.

4-Allyloxy-3-(2-aminoethyl)-2-iodophenol Hydrochloride (5.1).

4.8 **5.1**

A solution of HCl in EtOAc (ca 1.6 M, 25 mL, 40 mmol) was added with stirring and cooled (0 °C) to **4.8** (0.629 g, 1.50 mmol). After 45 min the ice bath was removed and stirring

was continued for 1 h, at which time deprotection was complete (TLC). The solvent was evaporated and the residue was triturated under CH_2Cl_2 to afford **5.1** (0.500 g, 94%) as an off-white solid: mp 180 °C; FTIR ν_{max} (microscope)/cm^{-1} 3304, 2915, 2749, 2652, 2542, 2464; ^{1}H-NMR (400 MHz, CD_3OD): δ 3.04 (t, *J* = 7.3 Hz, 2 H), 3.23-3.30 (m, 2 H), 4.53 (dt, *J* = 5.3, 1.4 Hz, 2 H), 5.25 (ddt as an apparent dq, *J* = 10.5, 1.5, 1.5 Hz, 1 H), 5.38 (ddt as an apparent dq, *J* = 17.3, 1.5, 1.5 Hz, 1 H), 6.08 (ddt, *J* = 17.3, 10.6, 5.3 Hz, 1 H), 6.78 (d, *J* = 8.9 Hz, 1 H), 6.86 (d, *J* = 8.9 Hz, 1 H); ^{13}C-NMR (100 MHz, CD_3OD): δ 34.2, 39.5, 49.8, 71.1, 93.1, 114.6, 117.9, 130.0, 134.9, 150.9, 152.4; exact mass *m*/*z* calcd for $C_{11}H_{15}INO_2$ 320.0142, found 320.0142.

4-Iodo-1*H*-indol-5-ol (4.11).

5.1 **4.11**

$PhI(OAc)_2$ (0.233 g, 0.723 mmol) was added in one portion to a stirred and cooled (0 °C solution of **5.1** (0.235 g, 0.660 mmol) in MeCN (4 mL) and water (2 mL). The mixture was stirred open to the atmosphere for ca 30 min, poured into brine (ca 10 mL) and neutralized with saturated aqueous $NaHCO_3$. The intermediate quinone imine **4.10** was extracted into EtOAc (ca 20 mL) and the organic extract was dried ($MgSO_4$) and evaporated. The residue was filtered through a short column of flash chromatography silica gel (2 x 4 cm), using 50% EtOAc-hexanes. The solvent was evaporated and replaced with PhH (5 mL). Rh-Al_2O_3 (10 mg, 5% Rh, 0.0049 mmol) was added and the mixture was refluxed for ca 4 h (Ar atmosphere). The

mixture was cooled, concentrated to ca 1 mL and filtered through a pad of flash chromatography silica gel (2 x 3 cm), using 40% EtOAc-hexanes (80 mL), to afford **4.11** (0.1105 g, 65% from **4.8**) as an oil.

Reference

(29) Phosphomolybdic acid (15 g) and $(NH_4)_2Ce(NO_3)_6$ (2.5 g) dissolved in a mixture of water (485 mL) and concentrated H_2SO_4 (15 mL).