The coumarin→indole transformation—a method for preparing 4-halo-5-hydroxyindoles from coumarins†

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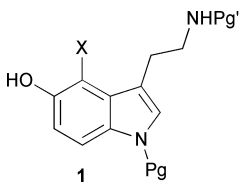
Readily accessible 3-alkoxycarbonyl-6-hydroxy-5-halocoumarins can be converted into 4-halo-5-hydroxyindoles by a sequence whose essential steps are conjugate reduction or conjugate addition, decarboxylation, lactone opening with ammonia, phenolic oxygen protection, Hofmann rearrangement to an *N*-Boc ethylamine, oxidation to a quinone and deprotection of the nitrogen. The resulting β-aminoethyl quinone cyclizes to a mixture of quinone imine and indole, and the imine tautomerizes to the indole spontaneously or on treatment with rhodium on alumina.

Introduction

During preliminary studies on the synthesis of an alkaloid containing a 5-oxyindole subunit, we needed to prepare a protected 4-haloserotonin (**1**), and became interested in routes to the parent 4-halo-5-hydroxyindoles (**2**) that have substituents only at C(4) and C(5). Although there is a very large literature on the preparation of indoles,[1] there are no reports of the 4-halo-5-hydroxyindoles **2**, apart from the 4-fluoro compound,[2] which was not relevant to our requirements. 4-Halo-5-oxyindole derivatives are not very easily accessed by current methodology. The patent literature describes the use of 4-mercuration, followed by replacement of mercury by halogen,[3] but a much more convenient method is the Snieckus lateral deprotonation procedure.[4] A few 5-alkoxy-4-haloindoles are known[3,5,6] and, in principle, *O*-dealkylation could afford the 5-hydroxy-4-haloindoles that were needed; however, we decided to develop a new synthetic route and report here an approach that is based on the conversion of readily available coumarins[7,8] into indoles. In this new procedure, many of the intermediates are easily crystallized so that chromatographic purification is usually not needed.



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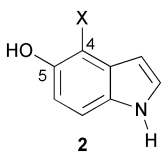

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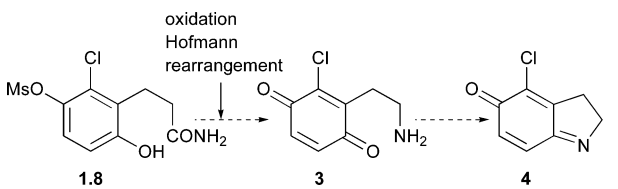
Results and discussion

The coumarin **1.2**, which served as a common starting material for the chloro-, bromo- and iodoindoles of type **2**, is readily made (79%) from aldehyde **1.1** by condensation with diethyl malonate according to a classical procedure (Scheme 1).[9] Chlorination with SO_2Cl_2[10] gave **1.4** which was also accessible from chloroaldehyde **1.3**[11] by the same general[9a] malonate condensation used with **1.1**. The phenolic hydroxyl was then protected by mesylation (**1.4**→**1.5**, 100%), and treatment with $LiBH_4$[12] served to generate (100%) the dihydrocoumarin **1.6**. The conversion of **1.5** into **1.6** is a key step, as the presence of halogen (especially in the subsequent examples with bromine and iodine) is expected to preclude the use of catalytic hydrogenation, which is a standard method[13] for making dihydrocoumarins from coumarins. Treatment with 20% aqueous hydrochloric acid at reflux for 3 h, followed by heating in PhMe in the presence of a catalytic amount of $TsOH{\cdot}H_2O$, served to effect overall decarboxylation of **1.6** to **1.7**. This two-step method was used because attempted Krapcho decarboxylation[14] of the methyl ester corresponding to **1.6** was unsuccessful. The lactone was then opened by passing NH_3 through a THF solution of **1.7**.[15] At that point, the phenolic hydroxyl was protected by silylation (**1.8**→**1.9**), and then Hofmann rearrangement, mediated by $Pb(OAc)_4$ in *t*-BuOH,[16] gave the protected amine **1.10** in 68% overall yield from **1.2**. We had initially wanted to avoid the protection step (**1.8**→**1.9**) by oxidizing **1.8** with $PhI(OAc)_2$ in the presence of water,[17] hoping to effect sequential oxidation to a quinone, Hofmann rearrangement,[18] and cyclization to a quinone imine **4**[19,20] (eqn (1))—all without isolation of intermediates—but experiments to this end were not successful.[21] When the silylated compound **1.10** was treated with a mixture of NaF and



1.8 **3** **4** (1)

$PhI(OAc)_2$ in aqueous MeCN it was converted (73–100%) into quinone **1.11**. Finally, treatment with $Me_3SiOSO_2CF_3$ in the presence of 2,6-lutidine gave a mixture of indoles **1.12a** and **1.12b**, which were separated by chromatography.[23] The silyl ether **1.12a** was transformed cleanly in aqueous MeOH-K_2CO_3 into the desired unprotected indole **1.12b**, the total yield of this substance being 78% from **1.11**.

During the sequence from the starting aldehyde **1.1**, filtration through a short pad of silica gel (or Florisil) was used to separate inorganic impurities in the steps using $LiBH_4$ and $Pb(OAc)_4$, but

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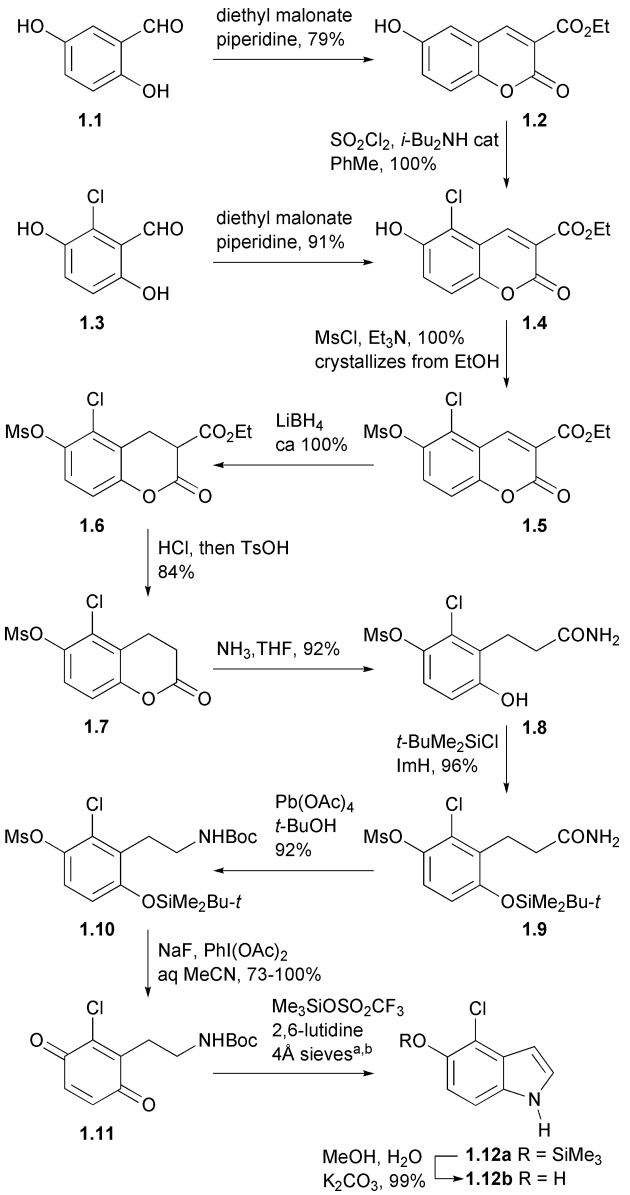
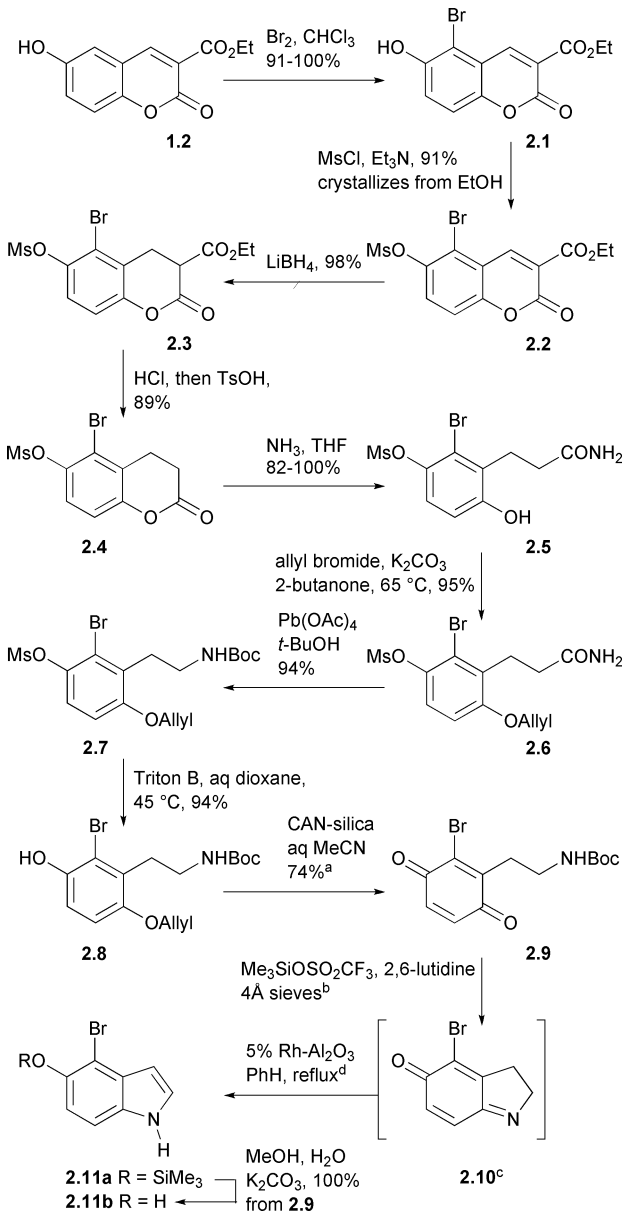


Scheme 1 Formation of 4-chloro-5-hydroxyindole. [a]The reaction gives **1.12a** (15%) and **1.12b** (63%). [b]Conversion of **1.11** into **1.12b** can also be done by treatment with $BF_3{\cdot}Et_2O$, followed by Pd–C (cat), PhH, reflux, 60% overall.



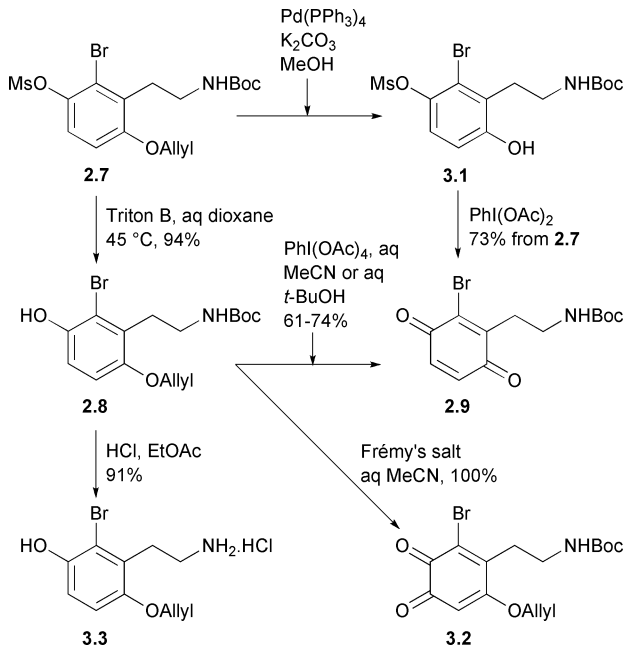
Scheme 2 Formation of 4-bromo-5-hydroxyindole. [a]With $PhI(OAc)_2$, the yield was 61–64%. [b]The quinone imine is the main product, but some **2.11a** and **2.11b** are also formed; the mixture was processed without separation. [c]Presumed intermediate, which is accompanied by silylated material. [d]**2.11a** isolated in 26% yield and **2.11b** in 74% yield from **2.9**.

flash chromatography was used only for isolation of **1.11** and the final indoles **1.12a** and **1.12b**; presumably, deliberate isolation of **1.12a** is unnecessary, but this modification has not been tried. The *N*-Boc group of **1.11** could also be removed with $BF_3{\cdot}Et_2O$ to afford a mixture of **1.12b** and the quinone imine **4** (eqn (1)); but the use of $Me_3SiOSO_2CF_3$ gave a better yield. The cyclization of amino quinones of type **3** is reminiscent of the Nenitzescu indole synthesis.[1]

4-Bromo-5-hydroxyindole (**2.11b**) was synthesized (Scheme 2) by a similar route beginning with bromination of **1.2**, which was then subjected to an identical series of steps as used in the chloro series, until phenolic amide **2.5** was reached. As shown in the Scheme, bromination (**1.2**→**2.1**), mesylation (**2.1**→**2.2**), conjugate reduction (**2.2**→**2.3**), decarboxylation (**2.3**→**2.4**) and lactone opening (**2.4**→**2.5**) all worked in high yield. Our attempt to silylate the phenolic hydroxyl of **2.5** did not give a satisfactory yield and partial reclosure back to lactone **2.4** was observed. However, the hydroxyl could be protected efficiently by allylation, after which Hofmann rearrangement [$Pb(OAc)_4$, *t*-BuOH] gave **2.7**, as expected. The presence of an allyl group instead of a silyl group (cf **1.9**) provided several possibilities for the deprotection–oxidation sequence leading to quinone **2.9**. The most effective procedure involved removal of the methanesulfonyl group by treatment of **2.7** with Triton B in aqueous dioxane at 45 °C,[24] followed by oxidation to quinone **2.9**, using $(NH_4)_2Ce(NO_2)_6$, which gave a higher yield than $PhI(OAc)_2$. Removal of the nitrogen protecting group then led to a mixture of quinone imine[20] **2.10** and the indoles **2.11a** and **2.11b**, with the quinone imine being the

major product. The mixture was heated in PhH with a catalytic amount of 5% Rh–Al_2O_3 (catalyst loading <1% of Rh)[20] and the two resulting indoles **2.11a** and **2.11b** were then separated. The former was hydrolyzed (MeOH, water, K_2CO_3) to afford **2.11b**, the overall yield of **2.11b** from **2.9** being 100%. The Rh-catalyzed isomerization was not necessary in the chloro series.

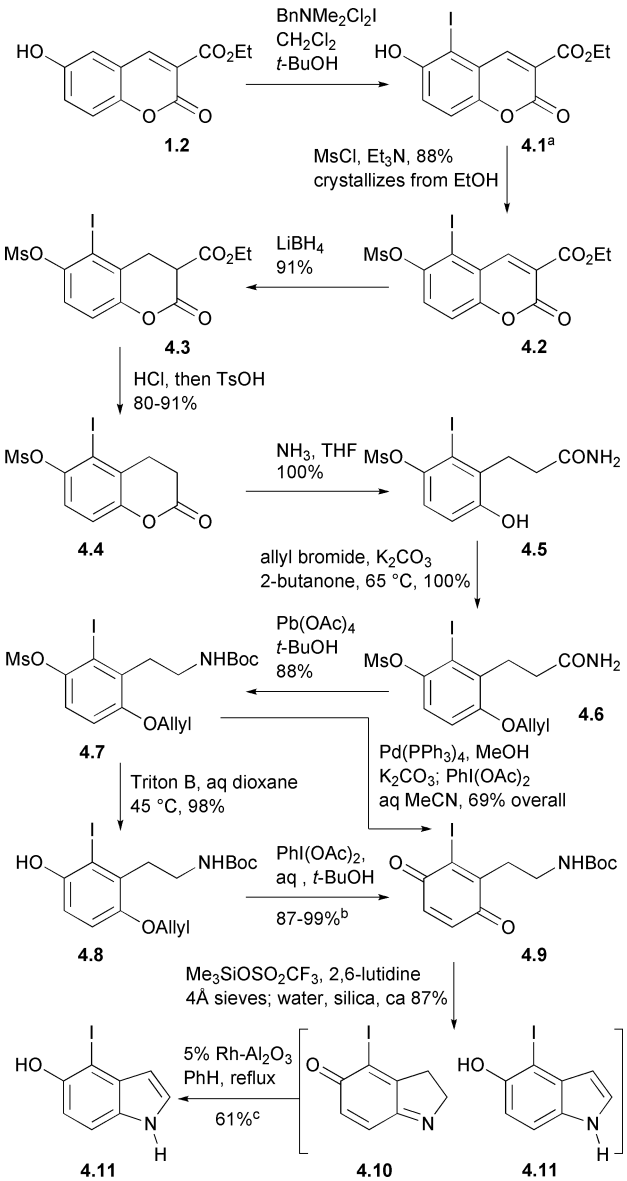
When the allyl group is removed first (Scheme 3, **2.7**→**3.1**), oxidation with $PhI(OAc)_2$ gave quinone **2.9**, but we prefer the route *via* **2.8** because this compound can be isolated pure by aqueous workup alone. The outcome of the oxidation of **2.8** is sensitive to the type of oxidant, as use of Frémy's salt led to the *ortho*-quinone **3.2**.[25] We made the incidental observation that the phenethylamine salt **3.3** could be obtained in high yield by treatment of **2.8** with HCl in EtOAc.



Scheme 3 Formation of bromoquinone 2.9.

Iodoindole **4.11** was also made (Scheme 4) along the lines used for the bromo compound. Iodination of coumarin **1.2** was best done with benzyltrimethylammonium dichloroiodate ($BnNMe_3Cl_2I$[26]) rather than with ICl. The product (**4.1**) partially loses iodine on isolation and should be mesylated *in situ* to afford **4.2** in high yield (87–100% from **1.2**). Fortunately, the mesylate shows no tendency to lose the iodine. The 3,4-double bond was reduced with $LiBH_4$ (**4.2**→**4.3**), and from that point, the sequence of reactions used in the bromo series was applied to afford the iodoindole **4.11**. Apart from the need to avoid isolation of iodophenol **4.1**, the sequence proceeded without incident in a manner exactly analogous to our observations in the bromo series, and with comparable yields.

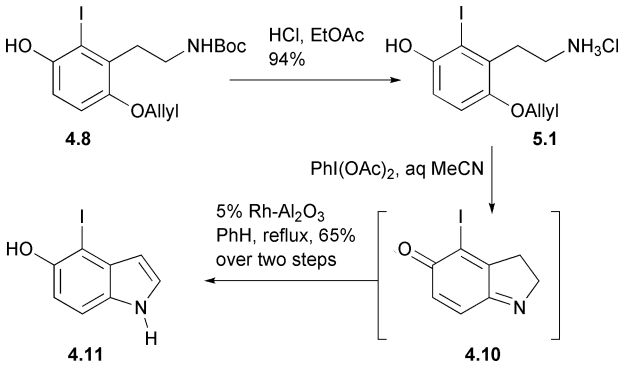
We also examined a minor modification, by removing the allyl group of **4.7** with $Pd(PPh_3)_4$ and then carrying out the oxidation to **4.9**. However, this sequence gave a lower overall yield than the route *via* **4.8**. In addition, an alternative route from phenol **4.8** was developed (Scheme 5). In this approach the nitrogen was deprotected, again with HCl in EtOAc, and the resulting hydrochloride salt **5.1** was oxidized in aqueous MeCN with $PhI(OAc)_2$. The crude quinone imine **4.10** was then treated



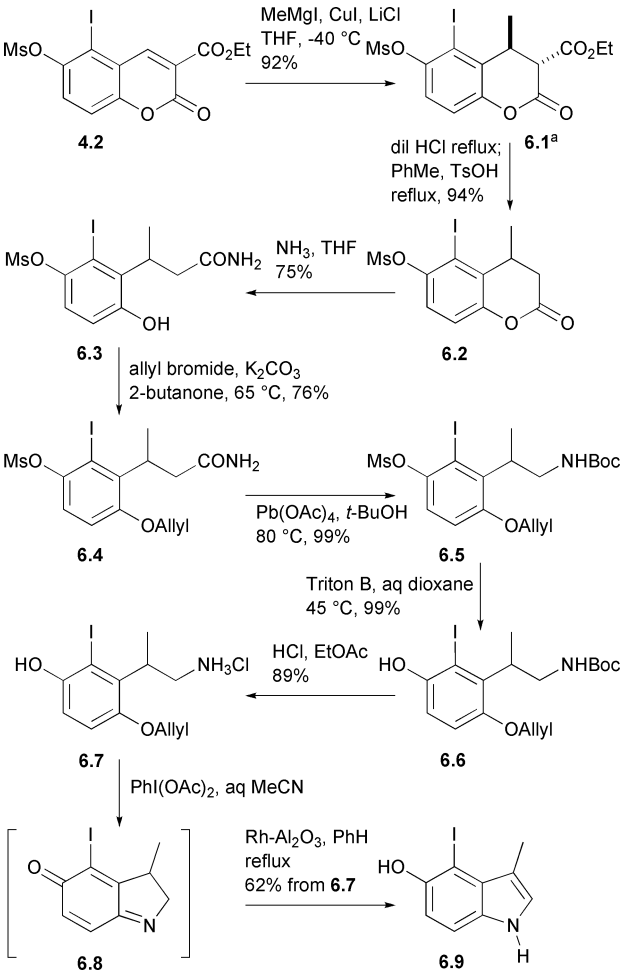
Scheme 4 Formation of 5-hydroxy-4-iodoindole. [a]The iodophenol is unstable and should be mesylated without any attempt at purification, the iodination–mesyaltion being best done in the same flask. [b]Inverse addition, *i.e.* the phenol is added to the reagents. [c]Some quinone imine (30%) was also recovered.

with catalytic 5% Rh–Al_2O_3 to afford the desired iodoindole **4.11**. The overall yield of this sequence was slightly higher than that of the first route, and it avoids use of the sensitive reagent $Me_3SiOSO_2CF_3$. Additionally, the method of Scheme 5 avoids the necessity of chromatographing the quinone **4.9** (Scheme 4), and the salt **5.1** is isolated simply by trituration.

The above approach to 4-haloindoles gives products lacking a substituent at C(3) because the α,β-unsaturated ester subunit in early coumarin intermediates is subjected to conjugate reduction. However, these same intermediates can also undergo conjugate addition of alkyl groups, so as to eventually give indoles bearing a substituent at C(3). To illustrate this versatility, the iodocoumarin **4.2** was subjected to the action of a methylcopper species[27] and was found to undergo efficient conjugate addition (Scheme 6,



Scheme 5 Formation of 5-hydroxy-4-iodoindole by second route.



Scheme 6 Formation of 5-hydroxy-4-iodo-3-methylindole. [a] *trans* stereochemistry established by X-ray analysis.

4.2→6.1). Acid hydrolysis of the lactone and ester groups was accompanied by spontaneous decarboxylation, and then acid catalyzed relactonization of the resulting crude phenolic acid, gave the dihydrocoumarin **6.2.**

Lactone opening with NH_3, *O*-allylation and Hofmann rearrangement (**6.2→6.3→6.4→6.5**)—using similar conditions to those already established in making **2.11b** and **4.11**—gave the protected amine **6.5**, as expected. Once again, the methanesulfonyl group and the nitrogen protecting group were removed with Triton B and HCl, respectively (**6.5→6.6→6.7**). Finally, oxidation [$PhI(OAc)_2$] and isomerization (5% $Rh–Al_2O_3$) produced 5-hydroxy-4-iodo-3-methylindole (**6.9**).

Conclusion

Our experiments show that 6-hydroxycoumarins can be converted into 4-halo-5-hydroxyindoles using a series of efficient reactions and with little dependence on the need for chromatography. Direct halogenation at C(4) of 5-oxyindoles is usually unsatisfactory,[28] because other positions such as C(3) and C(2) can react preferentially, if not blocked. In contrast, direct C(5) halogenation of 6-hydroxycoumarins (leading to 4-haloindoles) is easily accomplished, and forms the basis of the present method.[26a] This method is general for the three halogens examined and its ability to accommodate the introduction of a substituent at C(3) of the indole nucleus was demonstrated for the simple case of a methyl group.

Experimental

5-Iodo-6-[(methanesulfonyl)oxy]-2-oxo-2*H*-chromene-3-carboxylic acid ethyl ester (4.2)

Attempts to isolate the intermediate **4.1** resulted in formation of a mixture of **4.2** and **1.2**.

Benzyltrimethylammonium dichloroiodate[26] (8.80 g, 25.3 mmol) was added in one portion to a stirred suspension of **1.2** (5.39 g, 23.0 mol) in 1 : 1 *t*-BuOH-CH_2Cl_2 (100 mL) (N_2 atmosphere) and stirring was continued for 45 min. The mixture was then cooled in an ice bath and Et_3N (8.0 mL, 57 mmol) was added by syringe, resulting in a red solution. MsCl (2.0 mL, 26 mmol) was then added by syringe, the color being discharged by the end of the addition. After 30 min, the mixture was diluted with CH_2Cl_2 (150 mL) and then washed with water (2 × 100 mL) and dried ($MgSO_4$). The solution was filtered through a pad of flash chromatography silica gel (5 × 5 cm), using CH_2Cl_2 (300 mL). Evaporation of the filtrate gave a residue which was dissolved in boiling 95% EtOH (250 mL) and the solution was allowed to cool and stand overnight. The resulting platelets were collected to afford **4.2** (8.85 g, 88%): mp 156–158 °C; FTIR ν_{max} (microscope)/cm^{-1} 1767, 1713; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.45 (t, J = 7.1 Hz, 3 H), 3.40 (s, 3 H), 4.47 (q, J = 7.1 Hz, 2 H), 7.40 (d, J = 9.1 Hz, 1 H), 7.68 (d, J = 9.1 Hz, 1 H), 8.74 (s, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.4 (q), 39.9 (q), 62.7 (t), 96.1 (s), 118.5 (d), 120.9 (s), 122.3 (s), 127.8 (d), 147.0 (s), 151.5 (d), 153.6 (s), 155.8 (s), 162.6 (s); exact mass *m*/*z* calcd for $C_{13}H_{11}INaO_7S$ (M + Na) 460.9163, found 460.9164.

5-Iodo-6-[(methanesulfonyl)oxy]-2-oxochroman-3-carboxylic acid ethyl ester (4.3)

$LiBH_4$ (1 M in THF, 2.6 mL, 2.6 mmol) was added by syringe to a stirred and cooled (–15 °C, ice–acetone bath) solution of **4.2** (3.74 g, 8.54 mmol) in THF (50 mL). Stirring was continued for 20 min and then another aliquot of $LiBH_4$ (1 M in THF, 1.0 mL) was added by syringe. After a further 15 min, the reaction flask was transferred to an ice bath and aqueous tartaric acid (0.5 M, 36 mL) was added, followed by Et_2O (30 mL). The resulting

biphasic mixture was stirred for 3.5 h and then the organic phase was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4.5 × 4 cm), using CH_2Cl_2 (500 mL), gave **4.3** (3.40 g, 91%): mp 137–138 °C; FTIR ν_{max} (microscope)/cm^{-1} 1780, 1737; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.16–1.20 (m, 3 H), 3.24 (dd overlapping with a singlet, J = 6.2, 16.7 Hz, 1 H), 3.26 (s, 3 H), 3.50 (dd, J = 8.6, 16.7 Hz, 1 H), 3.71 (dd, J = 6.3, 8.6 Hz, 1 H), 4.15–4.20 (m, 2 H), 7.06 (d, J = 8.9 Hz, 1 H), 7.31 (dd, J = 0.6, 8.9 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.2 (q), 33.6 (t), 39.7 (q), 46.0 (d), 62.8 (t), 95.9 (s), 118.4 (d), 122.7 (d), 127.5 (s), 146.5 (s), 149.5 (s), 163.8 (s), 166.9 (s); exact mass m/z calcd for $C_{13}H_{13}INaO_7S$ (M + Na) 462.9319, found 462.9314.

In a larger scale experiment, using **4.2** (8.8 g), the product **4.3** was obtained in 89% yield.

Methanesulfonic acid 5-iodo-2-oxochroman-6-yl ester (4.4)

Dilute hydrochloric acid (20%, 100 mL) was added to a stirred solution of **4.3** (2.62 g, 5.95 mmol) in acetone (25 mL). The resulting white suspension was then refluxed for 5 h open to the atmosphere. The solution was cooled and extracted with EtOAc (2 × 30 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The crude residue was covered with PhMe (60 mL) and $TsOH{\cdot}H_2O$ (46.7 mg) was added with stirring and the mixture was then refluxed. After 3 h the nearly colorless solution was cooled to room temperature and extracted with EtOAc (30 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ and the aqueous layer was back-extracted once with EtOAc. The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave **4.4** (1.76 g, 80%): mp 125–128 °C; FTIR ν_{max} (microscope)/cm^{-1} 1777; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.82 (t, J = 7.7 Hz, 2 H), 3.15 (t, J = 7.7 Hz, 2 H), 3.34 (s, 3 H), 7.11 (d, J = 8.9 Hz, 1 H), 7.37 (d, J = 8.9 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.6 (t), 30.1 (t), 39.5 (q), 95.7 (s), 118.3 (d), 122.1 (d), 128.8 (s), 146.0 (s), 150.0 (s), 167.1 (s); exact mass m/z calcd for $C_{10}H_{10}IO_5S$ 368.9288, found 368.9290.

In a smaller scale experiment [**4.3** (0.39 g, 0.89 mmol)], a higher a yield of 91% was obtained.

Methanesulfonic acid 3-(2-carbamoylethyl)-4-hydroxy-2-iodophenyl ester (4.5)

A three-necked round bottomed flask was charged with **4.4** (1.76 g, 4.78 mmol) and THF (50 mL). The flask was fitted with a drying tube containing NaOH pellets, a stopper and an adapter carrying a Pasteur pipette extending *ca.* 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 30 min. Evaporation of the solvent, followed by trituration of the residue under $CHCl_3$ (3 mL) at room temperature, gave **4.5** (1.84 g, 100%) as a white solid: mp 145–147 °C; FTIR ν_{max} (microscope)/cm^{-1} 3455, 3356, 3199, 3030, 2937, 1662; ^{1}H-NMR (400 MHz, acetone-d_6): δ 2.72 (t, J = 6.2 Hz, 2 H), 3.10 (t, J = 6.2 Hz, 2 H), 3.35 (s, 3 H), 6.75 (br s, 1 H), 6.90 (d, J = 8.9 Hz, 1 H), 7.19 (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 30.7 (t), 34.5 (t), 39.2 (q), 98.9 (s), 118.8 (d), 122.0 (s), 134.2 (s), 144.1 (s), 155.2 (s), 177.1 (s); exact mass m/z calcd for $C_{10}H_{12}INNaO_5S$ (M + Na) 407.9373, found 407.9373.

Methanesulfonic acid 4-allyloxy-3-(2-carbamoylethyl)-2-iodophenyl ester (4.6)

K_2CO_3 (0.909 g, 6.58 mmol), followed by allyl bromide (0.45 mL, 5.2 mmol), were added to a stirred solution of **4.5** (1.84 g, 4.78 mmol) in 2-butanone. The reaction flask was fitted with a condenser and the mixture was heated at 70 °C overnight. At this stage the reaction was still incomplete (TLC control) and so an additional portion of allyl bromide (0.08 mL, 0.9 mmol) was added. More 2-butanone was added to replace that lost by evaporation and the mixture was heated at 70 °C until the starting material (**4.5**) had been consumed (*ca.* 3 h, TLC control). Surprisingly, the product **4.6** has a lower R_f than the starting material **4.5** (silica gel, 80% EtOAc–hexanes.) The mixture was diluted with EtOAc (*ca.* 50 mL) and then washed with water (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and evaporated to afford pure **4.6** (2.03 g, 100%): FTIR ν_{max} (film cast)/cm^{-1} 3349, 2539, 2481, 2385, 1633; ^{1}H-NMR (400 MHz, acetone-d_6): δ 2.34–2.38 (m, 2 H), 3.18–3.22 (m, 2 H), 3.37 (s, 3 H), 4.65 (ddd as an apparent dt, J = 4.9, 1.7, 1.7 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, 1.7, 1.7 Hz, 1 H), 6.08 (ddt, J = 17.3, 10.6, 4.9 Hz, 1 H), 6.18 (br s, 1 H), 6.73 (br s, 1 H), 7.05 (d, J = 9.0 Hz, 1 H), 7.28 (d, J = 8.9 Hz, 1 H); ^{1}H-NMR (400 MHz, CD_3OD): δ 2.38–2.42 (m, 2 H), 3.21–3.25 (m, 2 H), 4.61 (ddd as an apparent dt, J = 5.0, 1.6, 1.6 Hz, 2 H), 4.83 (s, 3 H), 5.26–5.26 (m, 1 H), 5.41–5.47 (m, 1 H), 6.08 (ddt, J = 17.2, 10.5, 4.9 Hz, 1 H), 7.00 (d, J = 9.0 Hz, 1 H), 7.27 (d, J = 8.9 Hz, 1 H); ^{13}C-NMR (100 MHz, acetone-d_6): δ 32.4 (t), 34.3 (t), 39.3 (q), 70.1 (t), 98.7 (s), 113.2 (d), 117.5 (t), 121.5 (d), 134.1 (d), 136.1 (s), 144.4 (s), 155.5 (s), 173.7 (s); ^{13}C-NMR (100 MHz, CD_3OD): δ 31.4, 33.5, 37.9, 69.5, 97.6, 112.2, 116.6, 120.8, 133.1, 134.8, 143.7, 154.8; exact mass m/z calcd for $C_{13}H_{16}INNaO_5S$ (M + Na) 447.9686, found 447.9683.

Methanesulfonic acid 4-Allyloxy-3-[(2-*tert*-butoxycarbonylamino)-ethyl]-2-iodo-phenyl ester (4.7)

$Pb(OAc)_4$ (2.49 g, 5.61 mmol) was added in one portion to a stirred and heated (80 °C) solution of **4.6** (2.03 g, 4.78 mmol) in dry *t*-BuOH (50 mL). Reaction was complete in less than 1 h (TLC control, silica, 80% EtOAc–hexane). The mixture was cooled and filtered through Florisil (2 × 2.5 cm), using CH_2Cl_2 (*ca.* 100 mL). The residue obtained by evaporation of the filtrate was filtered through flash chromatography silica gel (2 × 2.5 cm), using 25% EtOAc–hexanes, complete elution being monitored by TLC (silica, 80% EtOAc–hexane). These filtrations through Florisil and silica were necessary to remove lead residues. Evaporation of the filtrate gave pure **4.7** (2.14 g, 88%): mp 105.5–108.5 °C (silky, white needles from heptane); FTIR ν_{max} (film cast)/cm^{-1} 3424, 2977, 2933, 1707; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 9 H), 3.15 (t, J = 6.7 Hz, 2 H), 3.27 (s, 3 H), (dt as an apparent q, J = 6.0, 6.0 Hz, 2 H), 4.57 (ddd as an apparent dt, J = 5.1, 1.5, 1.5 Hz, 2 H), 4.70 (br s, 1 H), 5.32 (ddt as an apparent dq, J = 10.5, 1.3, 1.3 Hz, 1 H), 5.43 (ddt as an apparent dq, J = 17.3, 1.5, 1.5 Hz, 1 H), 6.05 (ddt, J = 17.3, 10.4, 5.1 Hz, 1 H), 6.85 (d, J = 9.0 Hz, 1 H), 7.30 (d, J = 9.0 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.7 (q), 35.8 (s), 39.3 (q), 39.6 (two t overlapping), 70.0 (t), 98.9 (s), 112.3 (d), 118.4

(t), 121.5 (d), 132.7 (d), 133.6 (s), 143.5 (s), 155.2 (s), 156.0 (s); exact mass m/z calcd for $C_{17}H_{24}INNaO_6S$ (M + Na) 520.0261, found 520.0210.

[2-(6-Allyloxy-3-hydroxy-2-iodophenyl)ethyl]carbamic acid *tert*-butyl ester (4.8)

Benzyltrimethylammonium hydroxide (Triton B, 40% w/w in MeOH, 4.8 mL, 11 mmol) was added to a stirred solution of **4.7** (1.00 g, 2.01 mmol) in 1,4-dioxane (24 mL) and water (9 mL). The mixture was heated at 45 °C for 5 h open to the atmosphere, cooled, acidified (litmus test) with dilute hydrochloric acid (5%), diluted with water (30 mL) and extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated to afford **4.8** (0.827 g, 98%) as an oil which solidified to a white amorphous solid on standing: mp 105–106 °C; FTIR ν_{max} (film cast)/cm^{-1} 3318, 2978, 2933, 1682; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 9 H), 3.08 (t, J = 6.7 Hz, 2 H), 3.34–3.36 (m, 2 H), 4.50 (ddd as an apparent dt, J = 5.1, 1.6, 1.6 Hz, 2 H), 4.82 (br s, 1 H), 5.27 (ddt as an apparent dq, J = 10.5, 1.4, 1.4 Hz, 1 H), 5.40 (apparent dd, J = 17.3, 1.6 Hz, 1 H), 5.64 (br s, 1 H), 6.03 (ddt, J = 17.3, 10.5, 5.2 Hz, 1 H), 6.76 (d, J = 8.9 Hz, 1 H), 6.85 (d, J = 8.7 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 28.5 (q), 35.4 (t), 39.8 (t), 70.0 (t), 79.0 (s), 94.8 (s), 112.8 (d), 113.5 (d), 117.6 (t), 131.4 (s), 133.2 (d), 149.5 (s), 150.2 (s), 156.0 (s); exact mass m/z calcd for $C_{16}H_{22}INNaO_4$ (M + Na) 442.0486, found 442.0484.

[2-(2-Iodo-3,6-dioxocyclohexa-1,4-dienyl)ethyl]carbamic acid *tert*-butyl ester (4.9)

A solution of **4.8** (0.142 g, 0.339 mmol) in *t*-BuOH (3 mL) and water (1 mL) was added dropwise by Pasteur pipette to a stirred mixture of $PhI(OAc)_2$ (0.120 g, 0.374 mmol), *t*-BuOH (2 mL) and water (2 ml) open to the atmosphere. Stirring was continued for *ca.* 30 min and then the mixture was diluted with water (15 mL) and extracted with Et_2O (3 × 7 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by filtration through a pad of flash chromatography silica gel (2 × 4 cm), using hexanes (25 mL) and then 20% EtOAc–hexanes (20 mL). The eluent was discarded and the pad was then eluted with 26% EtOAc–hexanes (*ca.* 50 mL). The canary yellow fraction was evaporated to afford **4.9** (0.111 g, 87%): mp 126–129 °C; FTIR ν_{max} (film cast)/cm^{-1} 3380, 2977, 2931, 1693, 1664; ^{1}H-NMR (400 MHz, C_6D_6): δ 1.33 (s, 9 H), 2.54 (t, J = 6.2 Hz, 2 H), 3.00 (dt as an apparent q, J = 6.3 Hz, 2 H), 3.99 (br s, 1 H), 6.00 (d, J = 9.8 Hz, 1 H), 6.13 (d, J = 9.9 Hz, 1 H); ^{1}H-NMR (498 MHz, $CDCl_3$): δ 1.41 (s, 9 H), 3.04 (t, J = 6.0 Hz, 2 H), 3.44 (m, 2 H), 4.70 (br s, 1 H), 6.86 (d, J = 10.0 Hz, 1 H), 7.01 (d, J = 9.5 Hz, 1 H); ^{13}C-NMR (100 MHz, C_6D_6): δ 28.4 (q), 37.7 (t), 39.3 (t), 78.8 (s), 122.6 (s), 133.8 (d), 135.9 (d), 153.2 (s), 155.9 (s), 180.1 (s), 181.8 (s); exact mass m/z calcd for $C_{13}H_{16}INNaO_4$ (M + Na) 400.0016, found 400.0017.

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

2,6-Lutidine (10% v/v in CH_2Cl_2, 0.23 mL, 0.20 mmol) and then $Me_3SiOSO_2CF_3$ (10% v/v in CH_2Cl_2, 0.30 mL, 0.17 mmol) were added dropwise by syringe to a stirred and cooled (0 °C) mixture of **4.9** (53.9 mg, 0.143 mmol) in CH_2Cl_2 (4.4 mL) and 4 Å molecular sieves (*ca.* 0.3 g, activated >200 °C). After the addition the ice bath was removed and the mixture was refluxed overnight, cooled to room temperature, washed with water (2 × 2 mL), dried ($MgSO_4$) and evaporated. The residue was passed through a Pasteur pipette containing flash chromatography silica gel (0.5 × 10 cm), using 40% EtOAc–hexanes, to give a mixture of quinone imine **4.10** and indole **4.11** (32.2 mg, 87% in all). This mixture was dissolved in PhH (3.6 mL) and Rh–Al_2O_3 (1.6 mg, 5% Rh, 0.00080 mmol) was added. The mixture was refluxed for 3 h, cooled and evaporated. Flash chromatography of the residue over silica gel (0.5 × 10 cm), using 25% EtOAc–hexanes, gave indole **4.11** (19.8 mg, 61%) as an oil and recovered quinone imine (9.5 mg, 30%). Indole **4.11** had: FTIR ν_{max} (microscope)/cm^{-1} 3416; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.12 (s, 1 H), 6.38–6.39 (m, 1 H), 6.93 (dd, J = 8.6, 0.5 Hz, 1 H), 7.24–7.26 (two overlapping m, 2 H), 8.25 (br s, 1 H);^{13}C-NMR (100 MHz, $CDCl_3$): δ 76.2 (s), 105.9 (d), 111.0 (d), 112.5 (d), 125.6 (d), 130.0 (s), 132.6 (s), 149.7 (s); exact mass m/z calcd for C_8H_6INO 258.9494, found 258.9487.

The quinone imine **4.10** had: ^{1}H-NMR (400 MHz, $CDCl_3$) (data taken from a spectrum of a mixture of the quinone imine **4.10** and indole **4.11**): δ 2.91–2.93 (m, 2 H), 4.42–4.44 (m, 2 H), 6.81 (dt, J = 9.8, 1.0 Hz, 1 H), 7.45 (d, J = 9.8 Hz, 1 H).

trans-5-Iodo-6-[(methanesulfonyl)oxy]-4-methyl-2-oxochroman-3-carboxylic acid ethyl ester (6.1)

LiCl (1.37 g, 32.3 mmol) was dried in a round-bottomed flask by heating (heat gun) under oil-pump vacuum for *ca.* 3 min. CuI (4.7 g, 25 mmol) was then added and the flask was flushed with Ar. THF (60 mL) was added and the mixture was stirred at room temperature until all solids dissolved (10 min). The stirred solution was cooled to –40 °C (dry ice–MeCN bath) and MeMgI (3 M in Et_2O, 7.50 mL, 22.5 mmol) was added by syringe. After 10 min a solution of **4.2** (4.91 g, 11.2 mmol) in THF (100 mL) was added by syringe over *ca.* 10 min. The mixture was stirred for 20 min and then quenched by addition of saturated aqueous NH_4Cl (30 mL). Acetone (20 mL) was then added to prevent the formation of copper-containing solids. The mixture was diluted with EtOAc (50 mL) and water (20 mL) and stirred open to the atmosphere at room temperature for 1 h. The dark blue aqueous layer was extracted with EtOAc (30 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. CH_2Cl_2 (*ca.* 15 mL) was added to the residue to produce a beige–orange suspension which was filtered through a pad of flash chromatography silica gel (4 × 4 cm), using 1 : 1 EtOAc–hexanes (300 mL). Some of the product crystallized from the eluent as square plates on standing overnight at room temperature. The supernatant liquid was decanted and evaporated to afford **6.1**. The original crystals were dried, and X-ray analysis showed that the material had *trans* stereochemistry. The total yield of product amounted to 4.69 g (92%): mp 112–115 °C; FTIR ν_{max} (film cast microscope)/cm^{-1} 1786, 1737; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.08 (t, J = 7.1 Hz, 3 H), 1.30 (d, J = 7.3 Hz, 3 H), 3.32 (s, 3 H), 3.77 (d, J = 1.9 Hz, 1 H), 3.90 (dq, J = 7.3, 1.9 Hz, 1 H), 4.08 (q, J = 7.1 Hz, 2 H), 7.13 (dd, J = 9.0, 0.4 Hz, 1 H), 7.37 (d, J = 8.9 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.1 (q), 18.1 (q), 39.4 (q), 40.1 (d), 53.0 (d), 62.5 (t), 95.0 (s), 118.4 (d), 122.4 (d), 131.2 (s), 146.3 (s), 148.4 (s), 163.1 (s), 166.0 (s); exact mass m/z calcd for $C_{14}H_{15}INaO_7S$ (M + Na) 476.9476, found 476.9475.

Methanesulfonic acid 5-iodo-4-methyl-2-oxochroman-6-yl ester (6.2)

Dilute hydrochloric acid (30%, 22 mL) was added to a stirred solution of **6.1** (2.18 g, 4.80 mmol) in acetone (6 mL), causing the material to precipitate. The resulting suspension was then refluxed open to the atmosphere for 3 h and then stirred at room temperature overnight. The mixture was extracted with EtOAc (3 × 20 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was covered with PhMe (12 mL), and $TsOH{\cdot}H_2O$ (50 mg, 0.26 mmol) was added with stirring. The mixture was then refluxed for 5 h, cooled, diluted with EtOAc (20 mL), and washed with saturated aqueous $NaHCO_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by filtration through flash chromatography silica gel (1.5 × 2 cm), using 1 : 1 EtOAc–hexanes, to afford **6.2** (1.73 g, 94%) as an oil. In some runs this filtration step was not necessary, while in others flash chromatography was done in order to obtain pure **6.2**, the choice of isolation procedure being made on the basis of TLC analysis. Compound **6.2** had: mp 86–88 °C; FTIR ν_{max} (film cast)/cm^{-1} 1779; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.26 (d, J = 7.3 Hz, 3 H), 2.82 (d, J = 2.6 Hz, 1 H), 2.83 (d, J = 5.4 Hz, 1 H), 3.34 (s, 3 H), 3.42–3.49 (m, 1 H), 7.11 (dd, J = 8.9, 0.4 Hz, 1 H), 7.35 (d, J = 8.9 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 18.8 (q), 35.9 (t), 36.3 (d), 39.7 (q), 95.2 (s), 118.8 (d), 122.3 (d), 133.4 (s), 146.2 (s), 149.3 (s), 167.2 (s); exact mass m/z calcd for $C_{11}H_{11}INaO_5S$ (M + Na) 404.9264, found 404.9267.

Methanesulfonic acid 3-(2-carbamoyl-1-methylethyl)-4-hydroxy-2-iodophenyl ester (6.3)

A three-necked round bottomed flask was charged with **6.2** (0.368 g, 0.962 mmol) and THF (8 mL). The flask was fitted with a drying tube containing NaOH pellets, a stopper and an adapter carrying a Pasteur pipette extending *ca.* 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. After NH_3 had been bubbled into the solution for 30 min, more THF (5 mL) was added and passage of NH_3 was continued for 1 h. The flask was completely stoppered and stirring was continued. When all the starting dihydrocoumarin had reacted (TLC control, *ca.* 3 h) the solvent was evaporated and the residue was purified by trituration under hot $CHCl_3$. Without separation, the two-phase mixture was allowed to cool and filtration afforded **6.3** (0.289 g, 75%): FTIR ν_{max} (microscope)/cm^{-1} 3460, 3366, 3198, 1776, 1661; ^{1}H-NMR (400 MHz, acetone-d_6): δ 1.32 (d, J = 7.0 Hz, 3 H), 2.67 (dd, J = 14.8, 5.3 Hz, 1 H), 2.85 (dd, J = 14.8, 8.1 Hz, 1 H), 3.32 (s, 3 H), 3.93–3.98 (m, 1 H), 6.13 (br s, 1 H), 6.73 (br s, 1 H), 6.87 (d, J = 8.7 Hz, 1 H), 7.12 (d, J = 8.8 Hz, 1 H), 9.22 (br s, 1 H); ^{1}H-NMR (500 MHz, CD_3OD): δ 1.33 (d, J = 7.0 Hz, 3 H), 2.75–2.84 (m, 2 H), 3.27 (s, 3 H), 3.89–3.96 (m, 1 H), 6.77 (d, J = 8.8 Hz, 1 H), 7.11 (d, J = 8.8 Hz, 1 H); ^{13}C-NMR (125 MHz, CD_3OD): δ 17.9 (q), 39.1 (d), 40.9 (t), 43.8 (q), 100.2 (s), 117.3 (d), 121.7 (d), 137.1 (s), 143.9 (s), 155.8 (s), 178.1 (s); exact mass m/z calcd for $C_{11}H_{14}INNaO_5S$ (M + Na) 421.9530, found 421.9533.

In a larger scale experiment, using **6.2** (5.55 g, 14.5 mmol), a yield of 82% was obtained over two steps after conversion of **6.3** to the allyl ether **6.4**.

Methanesulfonic acid 4-allyloxy-3-(2-carbamoyl-1-methylethyl)-2-iodophenyl ester (6.4)

K_2CO_3 (0.185 g, 1.34 mmol) was added to a stirred solution of **6.3** (0.243 g, 0.609 mmol) in 2-butanone (6.6 mL) and allyl bromide (0.07 mL, 0.8 mmol) was added by syringe (Ar atmosphere). The mixture was then heated at 55 °C overnight. A second portion of allyl bromide (0.03 mL, 0.3 mmol) was added, heating was continued for 2 h, and the mixture was cooled and partitioned between Et_2O (15 mL) and water (20 mL). The aqueous phase was extracted with Et_2O (10 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and evaporated. Trituration of the solid residue with two portions of cold (ice bath) 1 : 1 $CHCl_3$–hexane afforded **6.4** (0.204 g, 76%) as a white solid: mp 155 °C; FTIR ν_{max} (film cast)/cm^{-1} 3084, 2965, 2933, 2872, 2588, 2401, 1649; ^{1}H-NMR (500 MHz, acetone-d_6): δ 1.30 (d, J = 7.0 Hz, 3 H), 2.61 (ddt, J = 14.9, 5.6, 1.4 Hz, 1 H), 2.82 (dd, J = 14.8, 8.7 Hz, 1 H), 2.75 (d, J = 16.6 Hz, 1 H), 3.34 (s, 1 H), 3.98–4.05 (m, 1 H), 4.63–4.70 (m, 2 H), 5.28 (apparent dd, J = 10.6, 1.5 Hz, 1 H), 5.45 (ddt as an apparent dq, J = 17.3, 1.6, 1.6 Hz, 1 H), 5.98 (br s, 1 H), 6.14 (ddt, J = 17.3, 10.5, 5.1 Hz, 1 H), 6.58 (br s, 1 H), 7.05 (d, J = 9.1 Hz, 1 H), 7.24 (d, J = 9.0 Hz, 1 H); ^{13}C-NMR (125 MHz, acetone-d_6): δ 17.5, 38.6, 40.1, 42.5, 69.8, 99.6, 113.4, 117.4, 120.6, 133.6, 139.0, 143.8, 155.6, 173.1; exact mass m/z calcd for $C_{14}H_{18}INNaO_5S$ (M + Na) 461.9843, found 461.9843.

In a larger scale experiment, using the dihydrocoumarin **6.2** (5.55 g, 14.5 mmol), compound **6.4** was obtained in 82% yield over the two steps.

[2-[(6-Allyloxy-2-iodo-3-methanesulfonyl)phenyl]propyl]carbamic acid *tert*-butyl ester (6.5)

$Pb(OAc)_4$ (0.223 g, 0.504 mmol) was added in one portion to a stirred and heated (75 °C) suspension of **6.4** (0.195 g, 0.443 mmol) in dry *t*-BuOH and heating was continued for 20 min (Ar atmosphere). The mixture was cooled to room temperature and filtered through a pad of Florisil (1 × 2 cm), using 10 mL-aliquots of 30%, 40%, and 50% EtOAc–hexanes, to afford **6.5** (0.224 g, 99%) as an oil: FTIR ν_{max} (film cast)/cm^{-1} 3421, 2977, 2934, 1706; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.30 (d, J = 6.9 Hz, 3 H), 1.39 (s, 9 H), 3.28 (s, 3 H), 3.49–3.54 (m, 1 H), 3.56–3.62 (m, 1 H), 3.66–3.69 (m, 1 H), 4.47 (br s, 1 H), 4.53–4.60 (m, 2 H), 5.33 (apparent dd, J = 10.5, 1.2 Hz, 1 H), 5.41 (ddt as an apparent dq, J = 17.2, 1.6 Hz, 1 H), 6.07 (ddt, J = 17.2, 10.5, 5.3 Hz, 1 H), 6.85 (d, J = 9.0 Hz, 1 H), 7.28 (d, J = 9.0 Hz, 1 H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 15.9 (q), 28.4 (q), 39.2 (q), 44.1 (t), 46.7 (d), 69.7 (t), 79.0 (s), 100.7 (s), 112.7 (d), 118.4 (t), 121.0 (d), 132.4 (d), 136.7 (s), 143.2 (s), 155.3 (s), 155.8 (s); exact mass m/z calcd for $C_{18}H_{26}INNaO_6S$ (M + Na) 534.0418, found 534.0417.

In a larger scale experiment, using **6.4** (5.21 g, 11.9 mmol), removal of the methanesulfonyl group with Triton B (see below) gave compound **6.6** in 94% yield over two steps.

[2-(6-allyloxy-3-hydroxy-2-iodophenyl)propyl]carbamic acid *tert*-butyl ester (6.6)

Benzyltrimethylammonium hydroxide (Triton B, 40% w/w in MeOH, 0.76 mL, 1.7 mmol) was added to a stirred solution of **6.5** (0.224 g, 0.438 mmol) and the mixture was then kept at 45 °C

open to the atmosphere. Stirring was continued for 6.5 h and then the mixture was partitioned between water (15 mL) and Et_2O (15 mL). The organic extract was washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 20 cm), using 36% EtOAc–hexanes, gave **6.6** (0.189 g, 99%) as an oil: FTIR ν_{max} (film cast)/cm^{-1} 3312, 2977, 2930, 1682; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.29 (d, J = 5.8 Hz, 3 H), 1.40 (s, 9 H), 3.52–3.58 (m, 3 H), 4.44–4.50 (m, 2 H), 4.53 (br s, 1 H), 5.27 (ddt as an apparent dq, J = 10.6, 1.3, 1.3 Hz, 1 H), 5.38 (ddt as an apparent dq, J = 17.3, 1.6, 1.6 Hz, 1 H), 5.86 (br s, 1 H), 6.03 (ddt, J = 17.3, 10.6, 5.3 Hz, 1 H), 6.76 (d, J = 8.9 Hz, 1 H), 6.85 (d, J = 8.9 Hz, 1 H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 16.4, 28.7, 44.7, 46.9, 70.1, 79.3, 97.3, 112.9, 114.2, 117.9, 133.4, 134.9, 149.7, 150.7, 156.3; exact mass m/z calcd for $C_{17}H_{24}INNaO_4$ (M + Na) 456.0642, found 456.0646.

In a larger scale experiment, using **6.4** (5.21 g, 11.9 mmol), compound **6.6** was obtained in 94% yield over two steps.

4-Allyloxy-3-(2-amino-1-methylethyl)-2-iodophenol hydrochloride (6.7)

A solution of HCl in EtOAc (*ca.* 2.6 M, 25 mL, 65 mmol) was added by syringe to a stirred and cooled (0 °C) solution of **6.6** (4.99 g, 11.2 mmol) in EtOAc (25 mL) (Ar atmosphere). After the addition the ice bath was removed and, when the mixture reached room temperature, the Ar inlet was removed. Stirring was continued for 4 h and then a second aliquot of the solution of HCl in EtOAc (*ca.* 2.6 M, 8.0 mL, 21 mmol) was added. When deprotection was complete (*ca.* 3 h, TLC control, silica, 1 : 1 EtOAc–hexanes) the solvent was evaporated and the residue was triturated under $CHCl_3$ to afford **6.7** (3.67 g, 89%): FTIR ν_{max} (microscope)/cm^{-1} 2970, 2213, 1647, 1573; ^{1}H-NMR (400 MHz, CD_3OD): δ 1.35 (d, J = 7.0 Hz, 3 H), 3.33 (dd, J = 12.5, 7.4 Hz, 1 H), 3.48 (dd, J = 12.5, 7.5 Hz, 1 H), 3.82 (apparent sextet, J = 7.2 Hz, 1 H), 4.50–4.58 (m, 2 H), 5.33 (apparent dd, J = 10.5, 1.1 Hz, 1 H), 5.40 (apparent dd, J = 17.3, 1.5 Hz, 1 H), 6.10 (ddt, J = 17.2, 10.6, 5.3 Hz, 1 H), 6.77 (d, J = 8.9 Hz, 1 H), 6.90 (d, J = 8.9 Hz, 1 H); ^{13}C-NMR (100 MHz, CD_3OD): δ 16.6, 44.4, 44.9, 70.8, 94.8, 114.3, 115.0, 118.1, 133.4, 134.5, 151.0, 152.4; exact mass m/z calcd for $C_{12}H_{17}INO_2$ 334.0299, found 334.0298.

4-Iodo-3-methyl-1*H*-indol-5-ol (6.9)

The best yield was obtained on a small scale, as follows: $PhI(OAc)_2$ (20 mg, 0.06 mmol) was added in one portion to a stirred and cooled (0 °C) solution of **6.7** (21.7 mg, 0.0510 mmol) in MeCN (1.3 mL) and water (0.5 mL). Stirring was continued under air for 30 min and then the mixture was partitioned between EtOAc (10 mL) and water (10 mL). The organic phase was washed with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.5 × 10 cm) in a Pasteur pipette, using 30% EtOAc–hexanes (10 mL) and then 40% EtOAc–hexanes (10 mL), gave quinone imine intermediate **6.8** (12.9 mg, 93%). The freshly isolated material is a yellow crystalline solid: mp 80 °C. This material isomerizes partially to indole **6.9** in the solid state, the ratio of quinone imine to indole being 2 : 1 after 4.5 h (^{1}H-NMR).

The above quinone imine–indole mixture (10.9 mg, 0.0400 mmol) was dissolved in PhH (2.5 mL). Rh–Al_2O_3 (2.3 mg, 5% Rh, 0.0011 mmol) was added with stirring and the mixture was refluxed for 2 h (N_2 atmosphere). Evaporation of the solvent and flash chromatography of the residue over silica gel (0.5 × 10 cm) in a Pasteur pipette, using 20% EtOAc–hexanes, gave **6.9** (10.9 mg, 100%) as an oil, making the total yield 93% over the two steps from **6.7**. Indole **6.9** is sensitive to light.

Quinone imine **6.8** had: mp 80 °C; ^{1}H-NMR (300 MHz, C_6D_6): δ 0.76 (d, J = 7.3 Hz, 3 H), 2.28–2.38 (m, 1 H), 3.44 (d, J = 20.4 Hz, 1 H), 3.76 (dd, J = 20.5, 5.7 Hz, 1 H), 6.23 (apparent dt, J = 9.7, 0.9 Hz, 1 H), 6.75 (d, J = 9.7 Hz, 1 H).

Indole **6.9** had: FTIR ν_{max} (film cast)/cm^{-1} 3418; ^{1}H-NMR (300 MHz, C_6D_6): δ 2.47 (s, 3 H), 5.20 (s, 1 H), 6.28 (s and br s coincident, 2 H), 6.63 (d, J = 8.6 Hz, 1 H), 6.94 (d, J = 8.6 Hz, 1 H); ^{13}C-NMR (100 MHz, C_6D_6): δ 12.7, 75.6, 110.7, 112.6, 112.7, 124.7, 128.9, 131.8, 149.5; exact mass m/z calcd for C_9H_8INO 272.9651, found 272.9646.

The above procedure should be followed closely: In a subsequent experiment, using **6.7** (93.7 mg, 0.254 mmol), the intermediate quinone imine was simply filtered through a short pad of flash chromatography silica gel in a filter funnel and the final yield of the indole **6.9** was 62% over the two steps from **6.7**. A larger scale experiment, using **6.7** (1.78 g, 4.80 mmol), and the same simple filtration method, gave **6.9** (0.567 g, 43%) and recovered quinone imine **6.8** (0.187 g, 14%), corresponding to a corrected yield of 57% over two steps from **6.7**.

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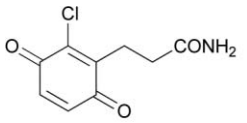
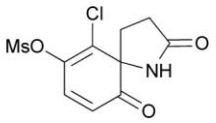
Notes and references

1 Indole synthesis: (*a*) G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875–2911.
2 (*a*) S. Huang, R. Li, P. J. Connolly, G. Xu, M. D. Gaul, S. L. Emanuel, K. R. LaMontagne and L. M. Greenberger, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 6063–6066; (*b*) L. F. A. Hennequin, WO 03/064413.
3 M. E. Flaugh, *US pat.* 6,022,980, 2000.
4 E. J. Griffen, D. G. Roe and V. Snieckus, *J. Org. Chem.*, 1995, **60**, 1484–1485.
5 (*a*) L. I. Kruse, R. C. Young and A. J. Kaumann, WO 93/00333; (*b*) M. A. Brown and M. A. Kerr, *Tetrahedron Lett.*, 2001, **42**, 983–985; (*c*) M. D. Meyer and L. I. Kruse, *J. Org. Chem.*, 1984, **49**, 3195–3199; (*d*) M. E. Flaugh, T. A. Crowell, J. A. Clemens and B. D. Sawyer, *J. Med. Chem.*, 1979, **22**, 63–69; (*e*) J. H. Tidwell and S. L. Buchwald, *J. Am. Chem. Soc.*, 1994, **116**, 11797–11810; (*f*) A. J. Peat and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 1028–1030; (*g*) C. J. Moody and E. Swan, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2561–2565.
6 For halogenation of indoles at C(4), see (*a*) reference 5*e*; (*b*) J. H. Tidwell, D. R. Senn and S. L. Buchwald, *J. Am. Chem. Soc.*, 1991, **113**, 4685–4686; (*c*) C. R. Hurt, R. Lin and H. Rapoport, *J. Org. Chem.*, 1999, **64**, 225–233.
7 Reviews on synthesis of coumarins: (*a*) F. Borges, F. Roleira, N. Milhazes, L. Santana and E. Uriarte, *Curr. Med. Chem.*, 2005, **12**, 887–916; (*b*) L. Bonsignore, F. Cottiglia, S. M. Lavagna, G. Loy and D. Secci, *Farmaco*, 1998, **53**, 693–697; (*c*) M. A. Musa, J. S. Cooperwood and M. O. F. Khan, *Curr. Med. Chem.*, 2008, **15**, 2664–2679; (*d*) Y.-L. Shi and M. Shi, *Org. Biomol. Chem.*, 2007, **5**, 1499–1504.
8 Recent examples of coumarin and dihydrocoumarin synthesis: (*a*) N. M. F. S. A. Cerqueira, A. M. F. Oliveira-Campos, P. J. Coelho, L. H. M. de Carvalho, A. Samat and R. Guglielmetti, *Helv. Chim. Acta*, 2002, **85**, 442–450; (*b*) E. Fillion, A. M. Dumas, B. A. Kuropatwa, N. R. Malhotra and T. Sitler, *J. Org. Chem.*, 2006, **71**, 409–412; (*c*) K. Zeitler and C. A. Rose, *J. Org. Chem.*, 2009, **74**, 1759–1762.

9 (*a*) W. H. Perkin, Jun and R. Robinson, *J. Chem. Soc. Trans.*, 1914, **105**, 2376–2392; (*b*) N. M. F. S. A. Cerqueira, L. M. Rodrigues, A. M. F. Oliveira-Campos, L. H. M. de Carvalho, P. J. Coelho, R. Dubest, J. Aubard, A. Samat and R. Guglielmetti, *Helv. Chim. Acta*, 2003, **86**, 3244–3253; (*c*) F. Cramer and H. Windel, *Chem. Ber.*, 1956, **89**, 354–365.
10 U. Wriede, M. Fernandez, K. F. West, D. Harcourt and H. W. Moore, *J. Org. Chem.*, 1987, **52**, 4485–4489.
11 J. A. Valderrama, C. Zamorano, M. F. González, E. Prina and A. Fournet, *Bioorg. Med. Chem.*, 2005, **13**, 4153–4159.
12 Use of $NaBH_4$: M. F. Simeonov, S. L. Spassov, A. Bojilova, C. Ivanov and R. Radeglia, *J. Mol. Struct.*, 1985, **127**, 127–133.
13 Many examples are known for the catalytic hydrogenation of coumarins: see for example: (*a*) P. Yates and T. S. Macas, *Can. J. Chem.*, 1988, **66**, 1–10; (*b*) R. O. Clinton and S. C. Laskowski, *J. Am. Chem. Soc.*, 1949, **71**, 3602–3606; (*c*) I. G. Collado, R. Hernández-Galán, G. M. Massanet, F. Rodríguez-Luis and J. Salvá, *Tetrahedron Lett.*, 1991, **32**, 3209–3212; (*d*) D. J. Collins, L. M. Downes, A. G. Jhingran, S. B. Rutschmann and G. J. Sharp, *Aust. J. Chem.*, 1989, **42**, 1235–1248; (*e*) L. I. Smith and P. F. Wiley, *J. Am. Chem. Soc.*, 1946, **68**, 887–893; (*f*) Preservation of Br during hydrogenation: G. Falsone, F. Cateni, M. M. De Nardo and M. M. Darai, *Z. Naturforsch., Teil B.*, 1993, **48**, 1391–1397.
14 A. P. Krapcho and G. A. J. Glynn, *Tetrahedron Lett.*, 1967, **8**, 215–217.
15 Cf. E. Fischer and O. Nouri, *Chem. Ber.*, 1917, **50**, 693–701.
16 (*a*) Cf. H. E. Baumgarten and A. Staklis, *J. Am. Chem. Soc.*, 1965, **87**, 1141–1142; (*b*) D. A. Evans, K. A. Scheidt and C. W. Downey, *Org. Lett.*, 2001, **3**, 3009–3012.
17 (*a*) Y. Tamura, T. Yakura, H. Tohma, K. Kikuchi and Y. Kita, *Synthesis*, 1989, 126–127; (*b*) N. Lewis and P. Wallbank, *Synthesis*, 1987, 1103–1105; (*c*) A. Pelter and S. Elgendy, *Tetrahedron Lett.*, 1988, **29**, 677–680.
18 (*a*) G. Stork and K. Zhao, *J. Am. Chem. Soc.*, 1990, **112**, 5875–5876; (*b*) R. M. Moriarty, C. J. Chany II, R. K. Vaid, O. Prakash and S. M. Tuladhar, *J. Org. Chem.*, 1993, **58**, 2478–2482; (*c*) D. E. DeMong and R. M. Williams, *J. Am. Chem. Soc.*, 2003, **125**, 8561–8565; (*d*) G. M. Loudon, A. S. Radhakrishna, M. R. Almond, J. K. Blodgett and R. H. Boutin, *J. Org. Chem.*, 1984, **49**, 4272–4276.
19 For examples of oxidative cyclization of phenethylamines to indoles, see: (*a*) J. Harley-Mason and A. H. Jackson, *J. Chem. Soc.*, 1954, 1165–1171; (*b*) R. I. T. Cromartie and J. Harley-Mason, *J. Chem. Soc.*, 1952, 2525–2527; (*c*) Y. Ozaki, Z.-S. Quan, K. Watabe (née Okamura) and S.-W. Kim, *Heterocycles*, 1999, **51**, 727–731.
20 Cf. Y. Kita, H. Tohma, M. Inagaki and K. Hatanaka, *Heterocycles*, 1992, **33**, 503–506.
21 These experiments led to phenol oxidation only, with the quinone **i** being the major product, and the spirocycle **ii** being a significant byproduct (*cf.* ref. 22).



i



ii

22 (*a*) S. Canesi, D. Bouchu and M. A. Ciufolini, *Org. Lett.*, 2005, **7**, 175–177; (*b*) S. Canesi, P. Belmont, D. Bouchu, L. Rousset and M. A. Ciufolini, *Tetrahedron Lett.*, 2002, **43**, 5193–5195.
23 Mechanistic study of the cyclization of quinone amines: T. E. Young and W. T. Beidler, *J. Org. Chem.*, 1984, **49**, 4833–4838.
24 *Cf.* T. Ohgiya and S. Nishiyama, *Tetrahedron Lett.*, 2004, **45**, 6317–6320.
25 M. J. Begley, P. V. Fish, G. Pattenden and S. T. Hodgson, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2263–2271.
26 (*a*) T. Harayama and Y. Nishita, *Chem. Pharm. Bull.*, 1996, **44**, 1986–1988; (*b*) V. D. Filiminov, N. I. Semenischeva, E. A. Krasnokutskaya, H. Y. Hwang and K.-W. Chi, *Synthesis*, 2008, 401–404.
27 *Cf.* B. H. Lipshutz, E. L. Ellsworth, S. H. Dimock and R. A. J. Smith, *J. Am. Chem. Soc.*, 1990, **112**, 4404–4410.
28 (*a*) M. Somei, Y. Fukui, M. Hasegawa, N. Oshikiri and T. Hayashi, *Heterocycles*, 2000, **53**, 1725–1736; (*b*) M. Mor, S. Rivara, C. Silva, F. Bordi, P. V. Plazzi, G. Spadoni, G. Diamantini, C. Balsamini, G. Tarzia, F. Fraschini, V. Lucini, R. Nonno and B. M. Stankov, *J. Med. Chem.*, 1998, **41**, 3831–3844; (*c*) M. S. Morales-Ríos, N. F. Santos-Sánchez, O. R. Suárez-Castillo and P. Joseph-Nathan, *J. Org. Chem.*, 2003, **68**, 305–311; (*d*) U. Schmidt and S. Weinbrenner, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1336–1338; (*e*) U. Schmidt and S. Weinbrenner, *Synthesis*, 1996, 28–30; (*f*) P. Zhang, R. Liu and J. M. Cook, *Tetrahedron Lett.*, 1995, **36**, 3103–3106; (*g*) L. I. Kruse and M. D. Meyer, *J. Org. Chem.*, 1984, **49**, 4761–4768; (*h*) G. C. Condie, M. F. Channon, A. J. Ivory, N. Kumar and D. StC. Black, *Tetrahedron*, 2005, **61**, 4989–5004; (*i*) M. Tani, H. Ikegami, M. Tashiro, T. Hiura, H. Tsukioka, C. Kaneko, T. Notoya, M. Shimizu, M. Uchida, Y. Aida, Y. Yokoyma and Y. Murakami, *Heterocycles*, 1992, **34**, 2349–2362.

