Tetrahedron 66 (2010) 4452–4461

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 4-haloserotonin derivatives and synthesis of the toad alkaloid dehydrobufotenine

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

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

ARTICLE INFO

Article history:
Received 20 March 2010
Received in revised form 19 April 2010
Accepted 19 April 2010
Available online 24 April 2010

Keywords:
4-Haloserotonins
Dehydrobufotenine
Coumarins
Haloindoles

ABSTRACT

4-Chloro-, 4-bromo- and 4-iodoserotonin derivatives were synthesized from 4-halo-5-oxyindoles, themselves derived from coumarins. Synthesis of the 4-iodoserotonins involved conjugate addition of an allyl group to a 5-iodocoumarin, followed by conversion of the allyl group into an aminoethyl unit. One of the iodoserotonin derivatives was converted into the toad alkaloid dehydrobufotenine, which was isolated as its hydroiodide.

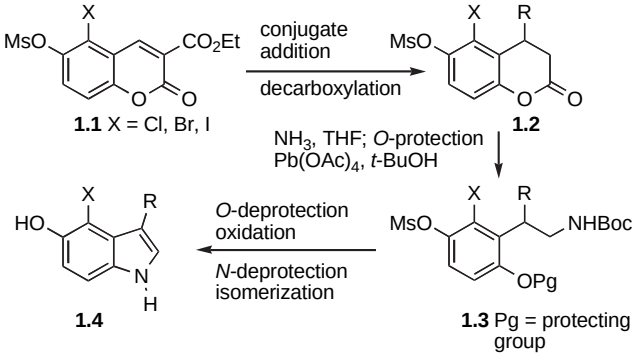
1. Introduction

5-Hydroxytryptamine (serotonin) and some of its derivatives have a wide range of important biological properties.[1,2] A potentially useful synthetic route to analogues of 5-hydroxytryptamine would involve palladium-mediated coupling reactions of various halo tryptamine derivatives.[3] Among these derivatives, one subgroup—those with a halogen at C(4) of the indole nucleus—is not easily accessed by current methodology.[4] Such compounds may be useful in routes to complex indoles[4c] and could also be medically important because some 4-haloserotonins are reported in patent literature[4b] that deals with the development of drugs to treat migraine and portal hypertension.

2. Results and discussion

We have recently developed a method for making 5-hydroxy-4-haloindoles[5] from readily accessible coumarins, and we now describe the application of this method to the preparation of a number of 4-haloserotonin derivatives and to the synthesis of the toad alkaloid[6] dehydrobufotenine.

The general principle of our approach[5] to 5-hydroxy-4-haloindoles (Scheme 1) involves ring opening of dihydrocoumarins with ammonia, followed by Hofmann rearrangement of the resulting amide to an *N*-Boc amine, and oxidation of the aromatic ring to a quinone. The *N*-protecting group is then removed and cyclization occurs to form a quinone imine, which isomerizes to the indole, either spontaneously or on treatment with a catalytic amount of Rh–Al_2O_3[5] or Rh–C. The nitrogen protecting group (Boc) can also be removed prior to oxidizing the benzene ring.



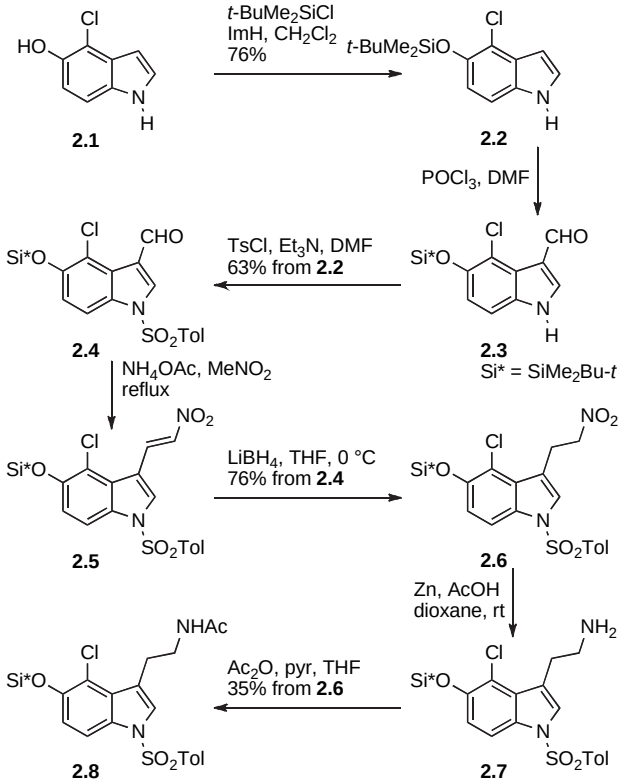
Scheme 1. General route for conversion of 5-halocoumarins into indoles.

The two simplest routes to the serotonins we have made are those leading to the chloro compound **2.8** (Scheme 2) and the bromo analogue **3.8** (Scheme 3). The chloro series begins with silylation of indole **2.1**, which was made by the method we have developed,[5] followed by Vilsmeier–Haack formylation, to produce aldehyde **2.3** (**2.1**→**2.2**→**2.3**). The nitrogen was then protected by sulfonylation, and base catalyzed condensation with $MeNO_2$ gave the unsaturated nitro compound **2.5**. At this stage the pendant double bond was saturated by treatment with $LiBH_4$ (76%)[7] and the nitro

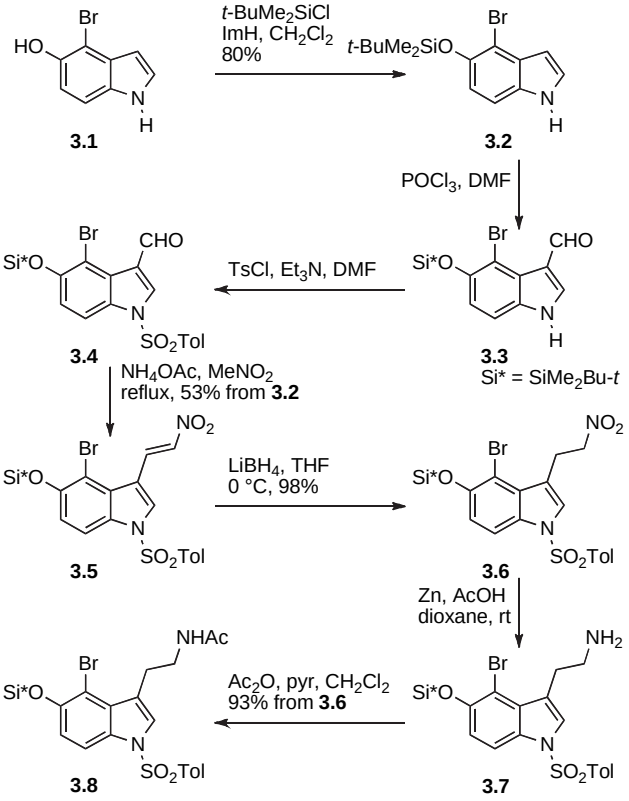
* Corresponding author. Tel.: +1 780 492 3251; fax: +1 780 492 8231; e-mail address: derrick.clive@ualberta.ca (D.L.J. Clive).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.04.081

group was reduced with Zn–AcOH. Finally, N-acetylation yielded the chloroserotonin derivative **2.8**. The corresponding bromoserotonin derivative **3.8** was made in exactly the same way (Scheme 3).

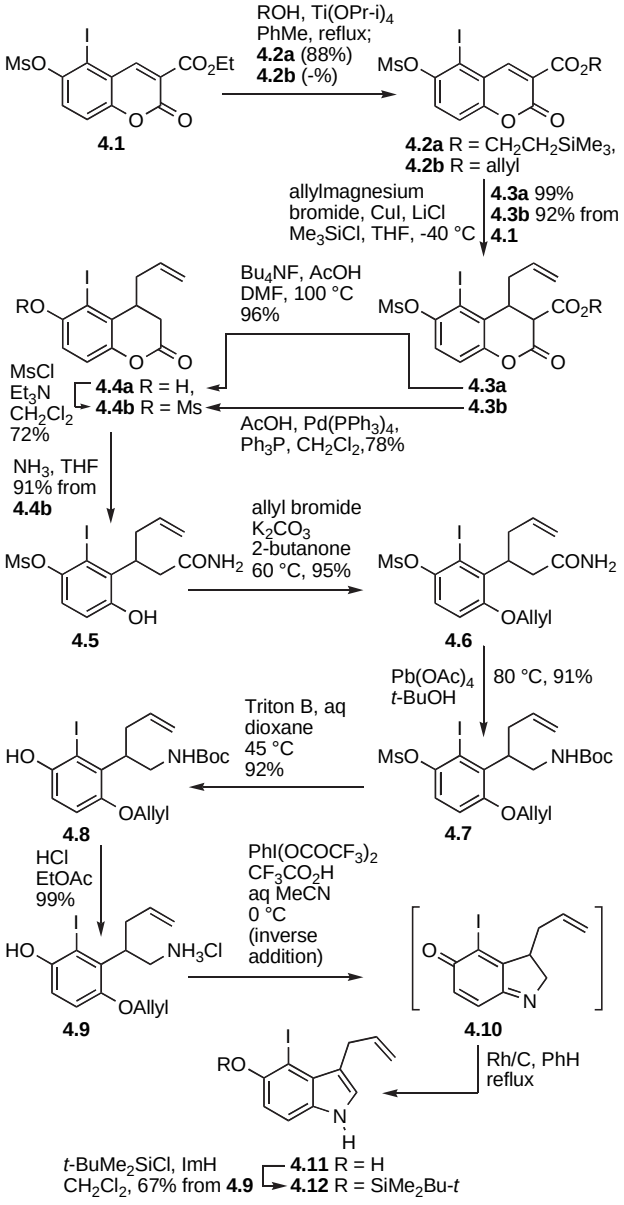


Scheme 2. Synthesis of a chloroserotonin derivative.



Scheme 3. Synthesis of a bromoserotonin derivative.

In both the above routes the zinc reduction (i.e., **2.6**→**2.7** and **3.6**→**3.7**) was completely selective for the aliphatic nitro group over the aromatic halogen; however, this method cannot be applied to the iodo series because the iodine is lost during the Zn reduction step. Consequently, the route described below (Scheme 4) was developed in order to gain access to 4-iodoserotonins, which we expected to be more useful for subsequent transition metal-mediated coupling reactions.[8]



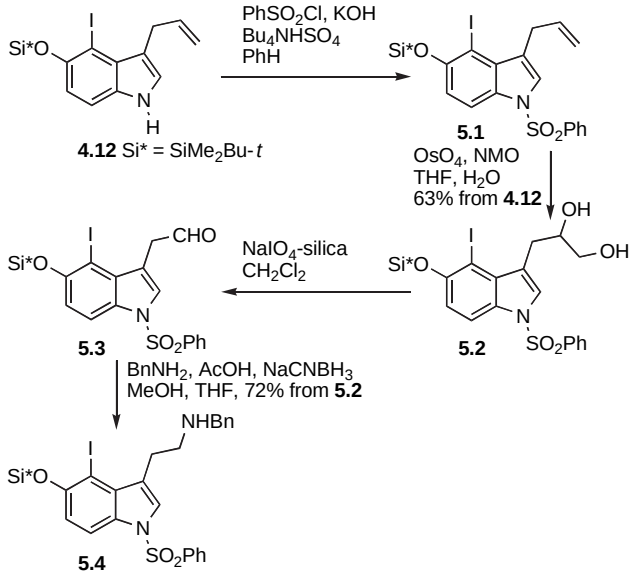
Scheme 4. Synthesis of 3-allyl-5-hydroxy-4-iodoindole.

The method, which we used to prepare the starting materials **2.1**[5] and **3.1**[5] for the present work can be easily modified[5] so that it affords indoles carrying a substituent at C(3), and we now took advantage of this useful feature to make 4-iodoserotonin derivatives. We chose an allyl group as the C(3) substituent so that oxidative cleavage of the double bond would give an aldehyde that could undergo reductive amination, using conditions that are compatible with the presence of an aromatic iodide.

Coumarin **4.1**[5] was subjected to ester exchange with 2-(trimethylsilyl)ethanol and also with allyl alcohol (Scheme 4). This exchange process was necessary because use of the ethyl ester did not

allow reproducible or efficient hydrolysis and decarboxylation at a later stage (see **4.3a**,**b**→**4.4a**,**b**). Conjugate addition to the new esters, using allylmagnesium bromide and CuI in the presence of LiCl and Me_3SiCl,[9] afforded the dihydrocoumarins **4.3a** (99%) and **4.3b** (92% from **4.1**), respectively. The next step was a decarboxylation for which the method used depended on the nature of the ester. In the case of **4.3a**, Bu_4NF–AcOH in hot DMF (100 °C) was satisfactory, but the methanesulfonyl group was lost at the same time and had to be replaced (**4.3a**→**4.4a**→**4.4b**). The high cost of 2-(trimethylsilyl)ethanol and the need to replace the methanesulfonyl group (subsequent reaction with NH_3 did not work with a free hydroxyl) made us examine the allyl ester series. Decarboxylation of allyl ester **4.3b** was first effected with $Pd(PPh_3)_4$ in the presence of an excess of dimedone (**4.3b**→**4.4b**, 61%), but we later found that AcOH and catalytic amounts of Ph_3P and $Pd(Ph_3P)_4$ in refluxing CH_2Cl_2 was much superior, since with this reagent system[10] all byproducts are volatile and the yield was higher (78%). The mesylate **4.4b** was then subjected to the following sequence: lactone opening with NH_3, O-allylation and Hofmann rearrangement (**4.4b**→**4.5**→**4.6**→**4.7**). At this point, Triton B and HCl were used to remove the methanesulfonyl group and the nitrogen protecting group, respectively (**4.7**→**4.8**→**4.9**). Oxidation [$PhI(OCOCF_3)_2$] and isomerization of the resulting quinone imine (**4.10**), using a catalytic amount of 5% Rh–Al_2O_3, then gave the 3-allylindole **4.11**. The oxidation step required some optimization to avoid formation of a purple byproduct. Use of $PhI(OCOCF_3)_2$ in the presence of CF_3CO_2H[11] was superior to $PhI(OAc)_2$ alone[11] and, to suppress formation of the purple byproduct, the quinone imine **4.10** and the final indole (**4.11**) were protected from light, and a trace of 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to their solutions. Evaporation of solutions of these compounds to dryness was only done immediately before changing the solvent and further processing (see Experimental section). We found it best to prepare **4.10** and **4.11** the same day as they were to be used. O-Silylation of **4.11** (**4.11**→**4.12**) made the compound much more stable.

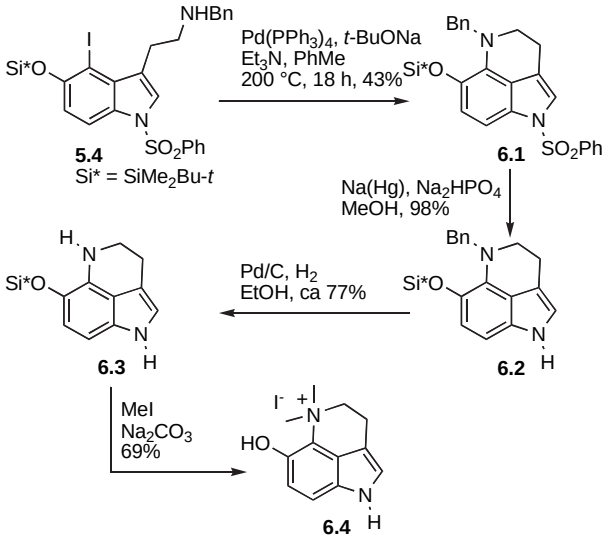
The allylindole **4.12** was then converted (Scheme 5) into the iodoserotonin derivative **5.4**. To this end, the nitrogen of **4.12** was protected by sulfonylation[12] (**4.12**→**5.1**). Cleavage of the pendant double bond[12] by dihydroxylation (OsO_4) and treatment with $NaIO_4$ on silica gel[13] gave aldehyde **5.3**, which we expect will be a versatile intermediate for the preparation of serotonin derivatives since it should undergo reductive amination with a wide range of amines.



Scheme 5. Synthesis of a 4-iodoserotonin derivative.

In the present case it was treated with $BnNH_2$ and $NaBH_3CN$[14] to produce the iodoserotonin derivative **5.4**.

As a simple example to demonstrate the use of the iodoserotonin **5.4** in synthesis, we converted the compound into the hydroiodide of the toad alkaloid dehydrobufotenine (**6.4**).[6,15] This was done (Scheme 6) by palladium-mediated intramolecular amination (**5.4**→**6.1**), along the lines of a reported[15b,16] method. The use of *t*-BuONa[16] rather than K_2CO_3[15b] was essential for our particular substrate, in contrast to a related[15b] cyclization where K_2CO_3 was the required base. Removal of the sulfonyl group with Na(Hg) in dry MeOH buffered with Na_2HPO_4[17] (**6.1**→**6.2**), followed by hydrogenolysis of the benzyl group (**6.2**→**6.3**) and dimethylation with MeI, gave dehydrobufotenine hydroiodide (**6.4**) directly, since the silicon protecting group was conveniently lost during the methylation. In preliminary experiments, we had removed the silicon protecting group from **6.2**, with the intention of then removing the benzyl group; however, the phenol resulting from desilylation of **6.2** was unstable and decomposed rapidly—a property that dictated the order of the last few steps that led to the alkaloid (Scheme 6).



Scheme 6. Synthesis of dehydro bufotenine.

3. Conclusion

The method reported here for the synthesis of 4-haloserotonins, especially the iodo compound, should be useful for a variety of coupling reactions that would give access to a large range of serotonin derivatives. The ability to incorporate an allyl group at C(3) of the indole nucleus gives easy access to iodoserotonin derivatives because it allows introduction of an amino group under reductive conditions that are fully compatible with the presence of the iodine atom; this reductive amination should be general for numerous primary and secondary amines.

4. Experimental section

4.1. General

Column sizes are quoted in the form diameter×length. Evaporations were done under water-pump vacuum using a rotary evaporator and the residue was then kept under oil-pump vacuum. Ar and N_2 were purified by passage through a column (3.5×42 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 Ar or N. 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 (Ref. 18 in Supplementary data), 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. ^1H NMR spectra were recorded with Varian INOVA-300 (at 300 MHz), Varian INOVA-400 (at 400 MHz) and Varian INOVA-500 (at 500 MHz) spectrometers in the specified deuterated solvent. ^{13}C spectra were recorded with Varian INOVA-400 (at 100 MHz) and Varian INOVA-500 (at 125 MHz). Mass spectra were recorded with Agilent Technologies 6220 Accurate-Mass TOF LC/MS, Perseptive Biosystems Mariner Biospectrometry Workstation, Kratos MS50 or Micromass ZabSpec Hybrid Sector-TOF mass spectrometers.

4.2. 4-Bromo-5-[(*tert*-butyldimethylsilyl)oxy]-1*H*-indole (3.2)

Imidazole (26.2 mg, 0.385 mmol) followed by *t*-$BuMe_2SiCl$ (47.0 mg, 0.312 mmol) were added in single portions to a stirred solution of **3.1** in CH_2Cl_2 (3 mL). Stirring was continued overnight and the mixture was diluted with CH_2Cl_2 (10 mL), washed once with water, dried ($MgSO_4$) and evaporated. The residue was then filtered through flash chromatography silica gel (1×1 cm), using 20% EtOAc–hexanes (10 mL), to afford **3.2** (76.4 mg, 80%) as an oil: FTIR (film cast) 3423, 2956, 2930, 2886, 2858, 1567, 1471, 1438, 1411, 1278, 1242, 1185, 1076, 1003, 885, 834, 781, 761, 723 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.25 (s, 6H), 1.08 (s, 9H), 6.56 (ddd, *J*=3.1, 2.3, 0.8 Hz, 1H), 6.81 (d, *J*=8.7 Hz, 1H), 7.19 (dd, *J*=8.7, 0.8 Hz, 1H), 7.22–7.23 (m, 1H), 8.14 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −3.9 (q), 18.7 (s), 26.2 (q), 103.5 (d), 105.8 (s), 110.4 (d), 116.4 (d), 125.5 (d), 130.1 (s), 131.3 (s), 146.5 (s); exact mass (EI) *m*/*z* calcd for $C_{14}H_{20}{}^{79}BrNOSi$ 327.0477, found 327.0476.

4.3. 4-Bromo-5-[(*tert*-butyldimethylsilyl)oxy]-1*H*-indole-3-carbaldehyde (3.3)

$POCl_3$ (10% v/v in DMF solution prepared 5 min before needed, 0.13 mL, 0.139 mmol) was added by syringe to stirred DMF (1.3 mL) (Ar atmosphere). After 20 min, a solution of **3.2** (25.9 mg, 0.0794 mmol) in DMF (0.8 mL plus 0.4 mL as a rinse) was added by syringe, and stirring was continued for 1 h. Saturated aqueous $NaHCO_3$ was then added dropwise by Pasteur pipette until the mixture was ca. pH 9 (litmus paper). A slight exotherm was detected during this quenching. The basic mixture was stirred for 30 min, diluted with water (ca. 10 mL) and extracted with Et_2O (2×10 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and evaporated. The crude oily product was used immediately. The material was of satisfactory quality and the yield of the 3-nitrovinyl indole **3.5** (see later) subsequently obtained from it was 53% over the three steps from **3.2**.

In another experiment, using **3.2** (76.4 mg), flash chromatography of the crude product over silica gel (1×30 cm), using 20% EtOAc–hexanes (50 mL), 40% EtOAc/hexanes (50 mL) and then 50% EtOAc–hexanes (30 mL), gave **3.3** [24.1 mg, 44% after correction for recovered **3.2** (25.9 mg)] as an analytically pure sample. Aldehyde **3.3** had: FTIR (film cast) 3108, 2928, 2894, 2856, 1626, 1570, 1504, 1463, 1429, 1386, 1334, 1268, 1252, 1232, 1080, 983, 920, 838, 799, 781, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (one H not visible in spectrum) δ 0.27 (s, 6H), 1.08 (s, 9H), 6.70 (d, *J*=8.6 Hz, 1H), 7.30 (d, *J*=8.6 Hz, 1H), 8.05 (d, *J*=2.9 Hz, 1H), 9.08 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.0 (q), 22.5 (s), 29.9 (q), 109.8 (s), 115.7 (d), 120.9 (d), 124.1 (s), 130.8 (s), 135.3 (d), 136.4 (s), 153.0 (s), 191.1 (d); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{20}{}^{79}BrNNaO_2Si$ (M+Na) 376.0339, found 376.0337.

4.4. 4-Bromo-5-[(*tert*-butyldimethylsilyl)oxy]-1-(toluene-4-sulfonyl)-1*H*-indole-3-carbaldehyde (3.4)

TsCl (18.4 mg, 0.0965 mmol) was added in one portion to a stirred solution of crude **3.3** (from above experiment and assumed to represent 0.0794 mmol) and Et_3N (0.03 mL, 0.2 mmol) in DMF (2 mL), and stirring was continued for 4 h (Ar atmosphere). The mixture was extracted with Et_2O (10 mL) and the organic extract was washed with water and saturated aqueous Na_2CO_3, dried (Na_2SO_4) and evaporated. The oily residue was pure enough for the next step and its use led to the nitrovinyl indole **3.5** in 53% over three steps from **3.2**. Compound **3.4** had: FTIR (film cast) 3391, 2956, 2930, 2886, 2859, 1598, 1554, 1458, 1423, 1373, 1263, 1189, 1174, 1111, 1088, 1013, 960, 840, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.26 (s, 6H), 1.06 (s, 9H), 2.39 (s, 3H), 6.95 (apparent dt, *J*=0.4, 8.9 Hz, 1H), 7.29–7.31 (m, 1H), 7.80–7.83 (m, 1H), 7.85 (apparent dd, *J*=0.4, 8.9 Hz, 1H), 8.35 (apparent q, *J*=0.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.1 (q), 21.7 (s), 25.7 (overlapping signals, both q), 106.1 (s), 113.3 (d), 118.0 (d), 122.3 (s), 127.3 (d), 128.6 (s), 130.3 (d), 130.6 (s), 132.2 (d), 134.2 (s), 146.2 (s), 150.3 (s), 186.6 (d); exact mass (electrospray) *m*/*z* calcd for $C_{22}H_{26}{}^{79}BrNNaO_4SSi$ (M+Na) 530.0427, found 530.0427.

4.5. 4-Bromo-5-[(*tert*-butyldimethylsilyl)oxy]-3-(2-nitrovinyl)-1-(toluene-4-sulfonyl)-1*H*-indole (3.5)

NH_4OAc (6.2 mg, 0.080 mmol) was added to a stirred solution of **3.4** (from above experiment and assumed to correspond to 0.0794 mmol) in $MeNO_2$ (3.6 mL) and the mixture was heated at 100 °C for 3 h (Ar atmosphere). Evaporation of the solvent and filtration of the residue through a pad of flash chromatography silica gel (1×3 cm), using 10% EtOAc–hexanes (10 mL), gave **3.5** (23.1 mg, 53% over the three steps from **3.2**) as a light orange oil. The material was unstable and was fully characterized after reduction (see below).

In another experiment, using **3.3** (19.8 mg), the nitrovinyl indole **3.5** was obtained in 94% yield over the two steps from **3.3**.

4.6. 4-Bromo-5-[(*tert*-butyldimethylsilyl)oxy]-3-(2-nitroethyl)-1-(toluene-4-sulfonyl)-1*H*-indole (3.6)

$LiBH_4$ (1 M in THF, 0.07 mL, 0.07 mmol) was added by syringe to a stirred and cooled (0 °C) solution of **3.5** (29.1 mg, 0.0526 mmol) in THF (2.2 mL) (Ar atmosphere). The mixture was stirred for 30 min and then quenched by addition of 13 drops (Pasteur pipette) of aqueous tartaric acid (1 M), followed by water (2 mL). The mixture was extracted with Et_2O (15 mL) and the organic extract was washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (0.5×10 cm) in a Pasteur pipette, using 10% EtOAc–hexanes, gave **3.6** (28.8 mg, 99%) as an oil: FTIR (film cast) 3108, 2956, 2930, 2896, 2858, 1597, 1533, 1455, 1421, 1375, 1264, 1189, 1174, 1131, 1113, 1088, 1013, 990, 966, 929, 836, 812, 783, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.25 (s, 6H), 1.05 (s, 9H), 2.36 (s, 3H), 3.64 (dt, *J*=6.9, 0.7 Hz, 2H), 4.71 (t, *J*=6.9 Hz, 2H), 6.88 (d, *J*=8.9 Hz, 1H), 7.24 (apparent dd as part of a higher order multiplet, *J*=8.6, 0.7 Hz, 2H), 7.45 (s, 1H), 7.68

(apparent d as part of a higher order multiplet, J=8.4 Hz, 2H), 7.80 (d, J=8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.1, 18.3, 21.6, 24.4, 25.7, 76.0, 106.0, 113.3, 117.2, 117.6, 126.8, 127.3, 129.3, 130.0, 131.0, 134.6, 145.3, 149.2; exact mass (electrospray) m/z calcd for $C_{23}H_{29}{}^{79}BrN_2NaO_5SSi$ (M+Na) 575.0642, found 575.0647.

In another experiment, using **3.5** (23.1 mg), a yield of 98% was obtained.

4.7. *N*-[2-[4-Bromo-5-[(*tert*-butyldimethylsilyl)oxy]-1-(toluene-4-sulfonyl)-1*H*-indol-3-yl]ethyl]acetamide (3.8)

Zn powder (25 mg, 0.382 mmol) was added to a stirred solution of **3.6** (9.1 mg, 0.0164 mmol) in 1,4-dioxane (1.3 mL), and AcOH (0.03 mL, 0.524 mmol) was added by syringe (Ar atmosphere). Stirring was continued for 4 h and the mixture was filtered through Celite using MeOH (15 mL). Evaporation of the filtrate gave **3.7** as a white solid. The ^{1}H NMR spectrum was of poor quality, but it was not clear if this was due to the presence of impurities, and so the material was acetylated for characterization.

Pyridine (10% v/v in Et_2O, 0.08 mL, 0.10 mmol) followed by Ac_2O (5% v/v in Et_2O, 0.04 mL, 0.02 mmol) were added by syringe to a stirred and cooled (0 °C) white suspension of the crude amine (from the above step and assumed to be 0.0164 mmol) in Et_2O (1.3 mL). After 10 min the ice bath was removed and the mixture was poured into a separatory funnel containing saturated aqueous $NaHCO_3$ (10 mL). More Et_2O (10 mL) was added, the mixture was shaken for 1 min and the organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (0.5×10 cm) in a Pasteur pipette, using 80% EtOAc–hexanes, gave **3.8** (8.6 mg, 93% from **3.6**) as an oil: FTIR (film cast) 3291, 3097, 2956, 2930, 2858, 1650, 1554, 1451, 1419, 1372, 1261, 1174, 965, 836, 670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.24 (s, 6H), 1.05 (s, 9H), 1.97 (s, 3H), 2.36 (s, 3H), 3.15 (apparent dt, J=0.9, 7.0 Hz, 2H), 3.56–3.61 (m, 2H), 5.50 (br s, 1H), 6.90 (dd, J=0.4, 8.9 Hz, 1H), 7.23 (apparent dd as part of a higher order multiplet, J=0.7, 8.7 Hz, 2H), 7.37 (d, J=0.4 Hz, 1H), 7.71 (apparent d as part of a higher order multiplet, J=8.4 Hz, 2H), 7.83 (d, J=8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −3.9, 18.6, 21.7, 23.5, 25.9, 26.6, 40.1, 106.6, 113.1, 117.4, 120.4, 125.9, 126.8, 129.9, 130.0, 131.1, 134.9, 145.1, 149.1, 169.9; exact mass (electrospray) m/z calcd for $C_{25}H_{33}{}^{79}BrN_2NaO_4SSi$ (M+Na) 587.1006, found 587.1002.

4.8. 5-Iodo-6-[(methanesulfonyl)oxy]-2-oxo-2*H*-chromene-3-carboxylic acid 2-(trimethylsilyl)ethyl ester (4.2a)

$Me_3SiCH_2CH_2OH$ (6 mL, 41.86 mmol) followed by Ti(OPr-*i*)$_4$ (0.15 mL, 0.50 mmol) were added by syringe to a stirred solution of **4.1** (2.2631 g, 5.165 mmol) in PhMe (18 mL) and the mixture was refluxed for 1.5 h (Ar atmosphere). The mixture was evaporated and the residue was filtered through Florisil (2.5×3.5 cm), using CH_2Cl_2. Evaporation of the solvent gave a residue, which was dissolved in hot EtOAc (10 mL) and hexanes (30 mL). The mixture was boiled and more hexanes were added until the boiling mixture remained cloudy. Enough EtOAc to just clarify the solution (3 mL) was added and the solution was allowed to cool to room temperature to give **4.2a** (2.3091 g, 88%) as white crystals: mp 124–126 °C; FTIR (film cast) 3084, 3032, 2954, 2898, 1767, 1714, 1612, 1591, 1561, 1458, 1413, 1374, 1359, 1334, 1280, 1248, 1232, 1205, 1174, 986, 967, 934, 841, 798 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 9H), 1.17–1.21 (m, 2H), 3.38 (s, 3H), 4.47–4.51 (m, 2H), 7.39 (dd, J=9.1, 0.7 Hz, 1H), 7.67 (d, J=9.2 Hz, 1H), 8.72 (d, J=0.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.4 (q), 17.5 (t), 39.7 (q), 65.0 (t), 95.8 (s), 118.3 (d), 120.8 (s), 122.1 (s), 127.5 (d), 146.7 (s), 151.1 (d), 153.3 (s), 155.5 (s), 162.5 (s); exact mass (electrospray) m/z calcd for $C_{16}H_{19}INaO_7SSi$ (M+Na) 532.9558, found 532.9558.

4.9. 5-Iodo-6-[(methanesulfonyl)oxy]-2-oxo-2*H*-chromene-3-carboxylic acid allyl ester (4.2b)

Allyl alcohol (1.0 mL, 15 mmol) followed by Ti(OPr-*i*)$_4$ (0.02 mL, 0.07 mmol) were added by syringe to a stirred solution of **4.1** (0.50 g, 1.14 mmol) in PhMe and the mixture was refluxed for 4 h (N_2 atmosphere) and then evaporated. Slow crystallization of the residue from allyl alcohol (ca. 6 mL), and washing of the crystals with EtOH (95%) gave **4.2b** (0.3391 g, 66%) in one crop. The compound was judged to be pure by ^{1}H NMR, but full characterization data were not obtained; the structure of **4.2b** is established by conversion into the fully characterized **4.4b** (see below): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38 (s, 3H), 4.89 (ddd as an apparent dt, J=4.7, 1.5, 1.5 Hz, 2H), 5.35 (ddt as an apparent dq, J=10.6, 1.3 Hz, 1H), 5.50 (ddt as an apparent dq, J=17.1, 1.5 Hz, 1H), 6.05 (ddt, J=17.2, 10.6, 5.7 Hz, 1H), 7.40 (dd, J=9.1, 0.6 Hz, 1H), 7.68 (d, J=9.1 Hz, 1H), 8.78 (d, J=0.6 Hz, 1H).

In a larger scale experiment, allyl alcohol (69 mL, 1.0 mol) followed by Ti(OPr-*i*)$_4$ (0.64 mL, 2.2 mmol) were added to a stirred solution of **4.1** (26.06 g, 59.47 mmol) in PhMe (180 mL). The mixture was stirred and heated at 80 °C for 24 h (Ar atmosphere), at which time ca. 50% conversion had taken place (^{1}H NMR). A second portion of Ti(OPr-*i*)$_4$ (0.66 mL, 2.2 mmol) was added by syringe and stirring was continued overnight (ca. 12 h) at which time the observed conversion was ca. 80% (^{1}H NMR). Further portions of allyl alcohol (18 mL, 0.26 mol), followed by Ti(OPr-*i*)$_4$ (0.60 mL, 2.0 mmol), were added and stirring was continued for ca. 12 h, at which point the conversion was observed to be >95% (^{1}H NMR). Volatile material was then removed in vacuo and the crude residue was used for the conjugate addition to prepare **4.3b** (see below), which was obtained in a yield of 92% over the two steps from **4.1**.

4.10. 4-Allyl-5-iodo-6-[(methanesulfonyl)oxy]-2-oxochroman-3-carboxylic acid 2-(trimethylsilyl)ethyl ester (4.3a)

LiCl (0.45 g, 11 mmol) was dried in a round-bottomed flask by heating (heat gun) under oil-pump vacuum for ca. 3 min. CuI (1.8378 g, 9.650 mmol) was then added and the flask was flushed with Ar. THF (15 mL) was injected and the mixture was stirred at room temperature until all solids had dissolved (10 min). The stirred solution was cooled to −78 °C and allylmagnesium bromide (1 M in Et_2O, 9 mL, 9 mmol) was added at a fast dropwise rate by syringe, followed by Me_3SiCl (1.2 mL, 9.4 mmol), which was also added at a fast dropwise rate. A solution of **4.2a** (2.3091 g, 4.524 mmol) in THF (10 mL) was then added at a fast dropwise rate by syringe. The mixture was stirred for 15 min and then quenched by addition of saturated aqueous NH_4Cl (20 mL). The resulting biphasic mixture was stirred at room temperature open to the atmosphere for 1 h and then filtered through Celite to remove copper-containing solids. The filtrate was diluted with EtOAc, washed with brine, dried ($MgSO_4$) and evaporated. The residue was filtered through flash chromatography silica gel (2×4 cm), using 20% EtOAc–hexanes, to give **4.3a** (2.4887 g, 99%) as an oil: FTIR (film cast) 3082, 3032, 2955, 2900, 1787, 1736, 1641, 1596, 1575, 1454, 1414, 1375, 1333, 1251, 1162, 972, 954, 925, 860, 836 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.01 (s, 9H), 0.78–0.87 (m, 2H), 2.06–2.12 (m, 1H), 2.51–2.56 (m, 1H), 3.33 (s, 3H), 3.81 (ddd, J=10.9, 4.3, 1.8 Hz, 1H), 3.94 (d, J=1.8 Hz, 1H), 4.06–4.16 (m, 2H), 5.18 (dd, J=17.0, 1.0 Hz, 1H), 5.24 (d, J=10.1 Hz, 1H), 5.81 (dddd, J=17.0, 10.3, 8.6, 5.8 Hz, 1H), 7.13 (d, J=9.0 Hz, 1H), 7.38 (d, J=8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.3 (q), 17.6 (t), 36.7 (t), 39.8 (q), 44.7 (d), 50.1 (d), 65.5 (t), 95.8 (s), 118.6 (d), 120.6 (s), 122.7 (d), 130.0 (t), 132.6 (d), 146.5 (s), 148.8 (s), 163.0 (s), 166.7 (s); exact mass (electrospray) m/z calcd for $C_{19}H_{25}INaO_7SSi$ (M+Na) 575.0027, found 575.0024.

4.11. 4-Allyl-5-iodo-6-[(methanesulfonyl)oxy]-2-oxochroman-3-carboxylic acid allyl ester (4.3b)

LiCl (6.7 g, 158.1 mmol) was dried in a round-bottomed flask by heating (heat gun) under oil-pump vacuum for ca. 7 min. CuI (25.1 g, 131.8 mmol) was then added and the flask was flushed with Ar. THF (400 mL) was injected and the mixture was stirred at room temperature until all solids had dissolved (10 min). The solution was then cooled to −78 °C and allylmagnesium chloride (2 M in THF, 60 mL, 120 mmol) was added at a fast dropwise rate by syringe, followed by Me_3SiCl (15 mL, 138.1 mmol), which was also added at a fast dropwise rate. A solution of **4.2b** [all the material obtained from **4.1** (26.06 g), assumed to comprise 59.47 mmol, see above] in THF (100 mL) was then added at a fast dropwise rate by syringe. The mixture was stirred for 15 min and then quenched by addition of saturated aqueous NH_4Cl (200 mL). The resulting biphasic mixture was stirred at room temperature open to the atmosphere for 1 h and then filtered through Celite to remove copper-containing solids. The filtrate was diluted with EtOAc, washed with brine, dried ($MgSO_4$) and evaporated. The residue was filtered through flash chromatography silica gel (5×10 cm), using 40% EtOAc–hexanes, to give **4.3b** (26.25 g, 92% from **4.1**) as an oil. The compound was sufficiently pure for the next step (^{1}H NMR) but full characterization data were not obtained; the structure of **4.3b** is established by conversion into the fully characterized **4.4b** (see below).

4.12. 4-Allyl-6-hydroxy-5-iodochroman-2-one (4.4a)

AcOH (0.5 mL, 9 mmol) followed by Bu_4NF (1 M in THF, 16 mL, 16 mmol) were added by syringe to a stirred solution of **4.3a** (2.4811 g, 4.491 mmol) in DMF (30 mL) and the mixture was then heated at 100 °C for 4 h, cooled, diluted with EtOAc (60 mL), washed four times with water and once with brine. The organic extract was dried (Na_2SO_4) and evaporated. Filtration of the residue through flash chromatography silica gel (2×4 cm), using CH_2Cl_2, gave **4.4a** (1.3322 g, 96%). The compound was judged to be pure by ^{1}H NMR but full characterization data were not obtained; the structure of **4.4a** is established by conversion into the fully characterized **4.4b** (see below). Compound **4.4a** had: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09–2.18 (m, 1H), 2.41–2.47 (m, 1H), 2.71 (ddd, J=1.0, 6.3, 16.2 Hz, 1H), 2.95 (dd, J=1.8, 16.2 Hz, 1H), 3.23 (dddd, J=1.8, 4.1, 6.1, 6.1 Hz, 1H), 5.14–5.17 (m, 1H), 5.186–5.191 (m, 1H), 5.33 (s, 1H), 5.73–5.83 (m, 1H), 6.93 (d, J=8.9 Hz, 1H), 7.00 (d, J=8.9 Hz, 1H).

4.13. Methanesulfonic acid 4-allyl-5-iodo-2-oxochroman-6-yl ester (4.4b)

Et_3N (0.78 mL, 5.60 mmol) followed by MsCl (0.36 mL, 4.7 mmol) were added dropwise by syringe to a stirred and cooled (0 °C) solution of **4.4a** (1.3322 g, 4.2960 mmol) in CH_2Cl_2 (18 mL). After the addition the ice bath was removed and stirring was continued for 30 min. The mixture was washed with water, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5×35 cm), using 25–30% EtOAc–hexanes, gave **4.4b** (1.2672 g, 72%): mp 110 °C; FTIR (film cast) 3080, 3027, 2980, 2917, 2849, 1778, 1640, 1595, 1573, 1453, 1412, 1370, 1239, 1219, 1174, 1150, 1054, 953, 919, 829, 799, 728 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.10–2.16 (m, 1H), 2.44–2.49 (m, 1H), 2.73 (ddd, J=16.3, 6.3, 1.1 Hz, 1H), 2.99 (dd, J=16.2, 1.7 Hz, 1H), 3.34 (s, 3H), 3.36 (dddd partially overlapping with s at δ 3.34 ppm, J=6.0, 4.1, 4.1, 1.7 Hz, 1H), 5.16 (dddd as an apparent dq, J=16.9, 1.3, 1.3, 1.3 Hz, 1H), 5.18–5.20 (m overlapping with signal at δ 5.16 ppm, 1H), 5.78 (dddd, J=16.7, 10.2, 8.2, 6.2 Hz, 1H), 7.11 (d, J=8.9 Hz, 1H), 7.36 (d, J=9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.3 (t), 37.0 (t), 39.5 (q), 40.4 (d), 95. 5 (s), 118.5 (d), 119.8 (t), 122.2 (d), 131.6 (s), 132.9 (d), 146.1 (s), 149.4 (s), 166.8 (s); exact mass (EI) m/z calcd for $C_{13}H_{13}IO_5S$ 407.9529, found 407.9525.

4.14. Methanesulfonic acid 4-allyl-5-iodo-2-oxochroman-6-yl ester (4.4b)

AcOH (1.8 mL, 31 mmol) was added by syringe to a stirred solution of **4.3b** (6.76 g, 14.1 mmol) in CH_2Cl_2 (54 mL). Ph_3P (0.1830 g, 0.6977 mmol) followed by $Pd(PPh_3)_4$ (0.5361 g, 0.4640 mmol) were then added in single portions and the mixture was refluxed for 7 h (Ar atmosphere), at which point the ^{1}H NMR spectrum of an aliquot (after evaporation of the solvent) indicated 97% conversion. The reaction mixture was evaporated and an attempt was made to isolate **4.4b** by flash chromatography using EtOAc–hexanes. However, this was not effective, as the material precipitated on the column, and use of CH_2Cl_2 as eluent gave impure product. The material recovered from the chromatography was then crystallized by dissolving it in a small volume of boiling EtOAc, adding *n*-heptane until permanent cloudiness developed, and then adding the minimum amount of EtOAc to produce a clear solution. Some red oil separated out on heating and this was removed by decanting the supernatant solution, which was then allowed to cool slowly to give **4.4b** (4.48 g, 78%) as white needles.

In a subsequent larger scale experiment we found that the red oil contains a significant amount of **4.4b** and that the crude material can be filtered through Florisil and then crystallized from *i*-Pr_2O. Compound **4.4b** also crystallizes from isooctane, but a large volume is required to dissolve the molten crude material. Alternatively, pure product can be obtained by flash chromatography over silica gel using 5–10% EtOAc–benzene.

4.15. Methanesulfonic acid 3-[(1-carbamoylmethyl)but-3-enyl]-4-hydroxy-2-iodophenyl ester (4.5)

A three-necked round-bottomed flask was charged with **4.4b** (0.6112 g, 1.500 mmol) and THF (24 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 2 h. The reaction flask was then stoppered and stirring was continued until reaction was complete (TLC control, ca. 4 h). The mixture was evaporated and the residue was loaded directly onto a pad of flash chromatography silica gel (1.5×4 cm), using CH_2Cl_2. A faster-eluting impurity was removed by washing the pad with 50% EtOAc/hexanes (TLC control), and elution with 8% MeOH in CH_2Cl_2 then gave **4.5** (0.5802 g, 91%): FTIR (film cast) 3462, 3371, 3198, 3078, 3031, 2935, 1662, 1606, 1581, 1419, 1359, 1280, 1254, 1214, 1172, 1129, 969, 918, 853, 823, 792, 698 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 2.47–2.54 (m, 1H), 2.73–2.81 (m, 1H), 2.78 (dd overlapping with previous signal, J=7.2, 2.5 Hz, 2H), 3.29 (s, 3H), 4.00 (dddd, J=9.1, 6.9, 6.9, 6.9 Hz, 1H), 4.80 (ddt, J=10.1, 2.2, 1.0 Hz, 1H), 4.91 (ddt, J=17.1, 2.3, 1.4 Hz, 1H), 5.72 (dddd, J=17.3, 10.2, 7.3, 7.3 Hz, 1H), 6.22 (br s, 1H), 6.78 (br s, 1H), 6.85 (d, J=8.8 Hz, 1H), 7.12 (d, J=8.9 Hz, 1H), 9.37 (br s, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 37.4 (t), 39.0 (d and t coincident), 47.6 (d), 101.7 (s), 116.1 (t), 117.5 (d), 121.5 (d), 135.3 (s), 137.9 (d), 143.7 (s), 155.0 (s), 174.6 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{16}INNaO_5S$ (M+Na) 447.9686, found 447.9687.

4.16. Methanesulfonic acid 4-allyloxy-3-[(1-carbamoylmethyl)but-3-enyl]-2-iodophenyl ester (4.6)

K_2CO_3 (2.26 g, 16.4 mmol) was added to a stirred solution of **4.5** (1.2927 g, 3.040 mmol) in 2-butanone (18 mL). Allyl bromide (0.47 mL, 5.4 mmol) was injected and the mixture was then heated

at 65 °C for 4.5 h, and a second portion of allyl bromide (0.47 mL, 5.4 mmol) was added (Ar atmosphere). After a further 2 h, a third portion of allyl bromide (0.18 ml, 2.1 mmol) was added and stirring at 65 °C was continued for 1 h. The mixture was cooled and partitioned between Et_2O (50 mL) and water (50 mL). The aqueous phase was extracted with Et_2O (20 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and dried (Na_2SO_4). Evaporation of the solvent gave **4.6** (1.3505 g, 95%) as a white solid: mp 110–111 °C; FTIR (film cast) 3461, 3377, 3192, 3078, 2978, 2934, 1672, 1611, 1582, 1451, 1424, 1365, 1265, 1216, 1173, 1141, 1016, 997, 969, 918, 846, 827, 794, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.47–2.54 (m, 1H), 2.62–2.67 (m, 1H), 2.69 (dd, J=14.8, 7.0 Hz, 1H), 2.83 (dd, J=14.7, 7.8 Hz, 1H), 3.25 (s, 3H), 3.97–4.05 (m, 1H), 4.57–4.60 (m, 2H), 4.88–4.96 (two overlapping m, 2H), 5.32–5.33 (two overlapping br s, 2H), 5.36 (ddt as an apparent dq, J=10.6, 1.3, 1.3 Hz, 1H), 5.44 (ddt as an apparent dq, J=17.2, 1.6, 1.6, 1.6 Hz, 1H), 5.72 (dddd, J=17.2, 10.0, 7.2, 7.2 Hz, 1H), 6.08 (ddt, J=17.3, 10.6, 5.4 Hz, 1H), 6.85 (d, J=9.0 Hz, 1H), 7.28 (d, J=9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.4 (t), 39.1 (t), 39.1 (q), 47.2 (d), 69.8 (t), 101.2 (s), 112.8 (d), 116.6 (t), 118.6 (t), 121.2 (d), 132.4 (d), 136.0 (s), 136.2 (d), 143.3 (s), 155.1 (s), 174.0 (s); exact mass (electrospray) m/z calcd for $C_{16}H_{20}INNaO_5S$ (M+Na) 487.9999, found 488.0002.

4.17. Methanesulfonic acid 4-allyloxy-3-[[1-[(*tert*-butoxycarbonyl)amino]methyl]but-3-enyl]-2-iodophenyl ester (4.7)

$Pb(OAc)_4$ (10.27 g, 23.16 mmol) was added in one portion to a stirred and heated solution of **4.6** (10.67 g, 22.93 mmol) in boiling *t*-BuOH (120 mL) (bath temperature 125 °C) and stirring was continued for 30 min (Ar atmosphere). The mixture was cooled to room temperature and then Celite (ca. 10 g) was added and the solids were filtered off, using CH_2Cl_2 as a rinse. The filtrate was evaporated and the residue was filtered through flash chromatography silica gel (5×10 cm), using 20% EtOAc–hexanes. The second filtration was necessary to remove lead residues. Evaporation of the solvent gave **4.7** (11.21 g, 91%) as an oil: FTIR (film cast) 3421, 3078, 2977, 2933, 1706, 1509, 1451, 1366, 1250, 1225, 1174, 996, 969, 915, 845, 826, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9H), 2.50 (apparent dtt, J=13.9, 6.9, 1.3 Hz, 1H), 2.62–2.70 (m, 1H), 3.26 (s, 3H), 3.56–3.59 (m, 2H), 3.71–3.78 (m, 1H), 4.46 (br s, 1H), 4.53–4.62 (m, 2H), 4.89 (apparent d, J=9.8 Hz, 1H), 4.95 (apparent dd, J=17.0, 7.0 Hz, 1H), 5.34 (ddt as an apparent dq, J=10.6, 1.4, 1.4 Hz, 1H), 5.43 (ddt as an apparent dq, J=17.3, 1.6, 1.6 Hz, 1H), 5.71 (dddd, J=17.2, 10.1, 7.1, 7.1 Hz, 1H), 6.06 (ddt, J=17.2, 10.6, 5.4 Hz, 1H), 6.85 (d, J=9.1 Hz, 1H), 7.30 (d, J=9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6 (q), 35.5 (t), 39.1 (q), 42.9 (t), 51.6 (d), 69.8 (t), 79.1 (s), 101.9 (s), 112.6 (d), 116.2 (t), 118.5 (t), 121.2 (d), 132.3 (d), 135.0 (s), 136.2 (d), 143.2 (s), 155.1 (s), 155.7 (s); exact mass (electrospray) m/z calcd for $C_{20}H_{28}INNaO_6S$ (M+Na) 560.0574, found 560.0574.

4.18. [2-(6-Allyloxy-3-hydroxy-2-iodophenyl)pent-4-enyl] carbamic acid *tert*-butyl ester (4.8)

Benzyltrimethylammonium hydroxide (Triton B, 40% w/w in MeOH, 3.3 mL, 7.2 mmol) was added to a stirred solution of **4.7** (1.0924 g, 2.0330 mmol) and stirring was continued overnight open to the atmosphere. The mixture was warmed to 45 °C and stirring at this temperature was continued for 3 h. The mixture was cooled and partitioned between water (15 mL) and Et_2O (15 mL). The organic phase was washed with water and brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5×30 cm), using 20% EtOAc–hexanes, gave **4.8** (0.8544 g, 92%) as an oil: FTIR (film cast) 3312, 3078, 2978, 2931, 2868, 1682, 1641, 1572, 1515, 1480, 1454, 1423, 1393, 1367, 1278, 1256, 1169, 1020, 996, 914, 818, 805, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.45–2.52 (m, 1H), 2.64–2.70 (m, 1H), 3.56 (apparent br s, 3H), 4.45–4.57 (m overlapping with br s, 3H), 4.89 (apparent d, J=9.9 Hz, 1H), 4.97 (apparent d, J=17.0 Hz, 1H), 5.28 (br s, <1H due to exchange), 5.30 (apparent dt, J=10.5, 1.4 Hz, 1H), 5.40 (apparent dt, J=17.3, 1.5 Hz, 1H), 5.71 (dddd, J=17.1, 9.8, 7.1, 7.1 Hz, 1H), 6.05 (ddt, J=17.2, 10.5, 5.3 Hz, 1H), 6.79 (d, J=8.9 Hz, 1H), 6.88 (d, J=8.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.5 (q), 35.6 (t), 43.1 (t), 51.8 (d), 69.8 (t), 79.0 (s), 98.5 (s), 112.8 (d), 113.8 (d), 116.1 (t), 117.8 (t), 132.7 (s), 133.1 (d), 136.5 (d), 149.1 (s), 150.5 (s), 155.9 (s); exact mass (electrospray) m/z calcd for $C_{19}H_{26}INNaO_4$ (M+Na) 482.0799, found 482.0797.

4.19. 4-Allyloxy-3-[(1-aminomethyl)but-3-enyl]-2-iodophenol hydrochloride (4.9)

A solution of HCl in EtOAc (ca. 2.6 M, 8 mL, 20.8 mmol) was added to a stirred and cooled (0 °C) solution of **4.8** (0.8351 g, 1.8180 mmol) (N_2 atmosphere). After the addition the ice bath was left in place for 5 min and then removed. Stirring was continued for 2 h and the mixture was evaporated. The residue was triturated under Et_2O to give **4.9** (0.7182 g, 99%) as an extremely hygroscopic solid: FTIR (microscope) 2978, 1641, 1598, 1573, 1480, 1460, 1423, 1365, 1258, 1231, 1189, 1157, 1089, 1019, 996, 919, 810, 736 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 2.50–2.57 (m, 1H), 2.67–2.74 (m, 1H), 3.29–3.33 (m, 1H), 3.55 (dd, J=12.8, 8.6 Hz, 1H), 3.90 (dddd, J=8.5, 8.5, 6.5, 6.5 Hz, 1H), 4.49–4.61 (m, 2H), 4.84 (br s, 1H), 4.91 (apparent dd, J=10.1, 1.8 Hz, 1H), 4.96–5.02 (m, 1H), 5.28–5.31 (m, 1H), 5.41 (ddt as an apparent dq, J=17.3, 1.6, 1.6 Hz, 1H), 5.72 (dddd, J=17.2, 10.1, 7.1, 7.1 Hz, 1H), 6.11 (ddt, J=17.2, 10.6, 5.4 Hz, 1H), 6.83 (d, J=8.9 Hz, 1H), 6.91 (d, J=8.9 Hz, 1H) (the spectrum showed the presence of an impurity (signals at ca. 1.2 ppm)); ^{13}C NMR (125 MHz, CD_3OD) δ 36.8, 43.3, 49.7, 71.0, 96.7, 114.9, 115.1, 117.6, 118.4, 131.5, 134.7, 136.7, 151.4, 152.6; exact mass (electrospray) m/z calcd for $C_{14}H_{19}INO_2$ (amine+H) 360.0455, found 360.0456.

4.20. 3-Allyl-5-[(*tert*-butyldimethylsilyl)oxy]-4-iodo-1*H*-indole (4.12)

CF_3CO_2H (0.11 mL, 1.5 mmol) was added to a stirred solution of $PhI(OCOCF_3)_2$ (0.6806 g, 1.583 mmol) in 1:1 MeCN–H_2O (26 mL) and the mixture was then cooled in an ice bath. A solution of **4.9** (0.5942 g, 1.438 mmol) in 1:1 MeCN–H_2O (10 mL) was then added at a fast dropwise rate (over ca. 5 min) (exposure to the atmosphere). After the addition stirring was continued for 15 min, $NaHCO_3$ (0.43 g, 5.1 mmol) was added and MeCN was evaporated (water pump, room temperature), leaving an aqueous mixture. The mixture was extracted with CH_2Cl_2 (3×20 mL) and the combined organic extracts were dried (Na_2SO_4). The solution (without evaporation) was directly filtered through flash chromatography silica gel (1.5×4 cm), using 35% EtOAc–hexanes (80 mL). 2,6-Di-*tert*-butyl-4-methylphenol (ca. 3 mg) was added to the filtrate, which was then evaporated to give crude quinone imine **4.10** (0.3929 g). This was covered in PhH (8 mL) and Rh–C (5% Rh, 26 mg, 0.013 mmol) was added. The mixture was refluxed for 2 h with vigorous stirring to avoid uneven heating (Ar atmosphere). It should be noted that the reaction was still incomplete (TLC control) at this point, but exceeding this reaction time results in decomposition and a poorer yield. The isomerization proceeds to completion in the following protection step. The mixture was cooled to room temperature and, without evaporation, filtered through flash chromatography silica gel (1.5×2 cm), using 40% EtOAc–hexanes (50 mL). The filtrate was evaporated and the residue was dissolved in CH_2Cl_2 (8 mL). Imidazole (95 mg, 1.4 mmol) followed by *t*-$BuMe_2SiCl$ (168 mg, 1.12 mmol) were added in single portions and stirring was continued overnight (stoppered flask but no protection from air). The mixture was washed once with water, dried ($MgSO_4$) and evaporated. Flash chromatography of the

residue over silica gel (1×35 cm), using 20% EtOAc–hexanes, gave **4.12** (0.3954 g, 67% overall) as an oil: FTIR (film cast) 3421, 3075, 2956, 2929, 2895, 2857, 1640, 1614, 1559, 1471, 1451, 1435, 1413, 1362, 1323, 1280, 1255, 1210, 985, 899, 835, 780 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.29 (s, 6H), 1.09 (s, 9H), 3.87 (dddd as an apparent dq, J=6.4, 1.4, 1.4, 1.4 Hz, 2H), 5.06 (ddt as an apparent dq, J=6.3, 1.8, 1.8 Hz, 1H), 5.10 (apparent t, J=1.5 Hz, 1H), 6.11–6.24 (m, 1H), 6.76 (d, J=8.6 Hz, 1H), 7.00–7.02 (m, 1H), 7.16 (d, J=8.6 Hz, 1H), 7.86 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −3.7, 18.6, 26.2, 30.8, 80.2, 111.4, 114.1, 115.4, 116.6, 124.6, 129.0, 132.3, 138.1, 149.0; exact mass (electrospray) m/z calcd for $C_{17}H_{25}INOSi$ (M+H) 414.0745, found 414.0746.

In an earlier experiment the indole **4.11** was isolated as an oil and characterized: FTIR (film cast) 3419, 3074, 3000, 2975, 2917, 2849, 1637, 1616, 1563, 1468, 1437, 1413, 1349, 1187, 946, 911, 873, 793, 753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.81 (dddd as an apparent dq, J=6.2, 1.4, 1.4, 1.4 Hz, 2H), 5.06 (ddt as an apparent dq, J=17.0, 1.7, 1.7 Hz, 1H), 5.11 (ddt as an apparent dq, J=10.1, 1.6, 1.6 Hz, 1H), 5.30 (s, 1H), 6.16 (ddt, J=16.4, 10.1, 6.1 Hz, 1H), 6.93 (d, J=8.6 Hz, 1H), 7.03 (t, J=1.3 Hz, 1H), 7.21 (d, J=8.6 Hz, 1H), 7.94 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.1, 75.0, 110.5, 112.5, 115.6 (two overlapping signals), 124.7, 127.6, 131.8, 137.8, 148.9; exact mass (electrospray) m/z calcd for $C_{11}H_{11}INO$ (M+H) 299.9880, found 299.9882.

4.21. 3-Allyl-5-[(*tert*-butyldimethylsilyl)oxy]-4-iodo-1*H*-indole (4.12)

Imidazole (84.8 mg, 1.246 mmol) followed by *t*-$BuMe_2SiCl$ (0.1049 g, 0.696 mmol) were added in single portions to a stirred solution of freshly prepared **4.11** (0.1891 g, 0.6323 mmol) in CH_2Cl_2. The flask was stoppered and stirring was continued for ca. 5 h. The mixture was washed once with water, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5×30 cm), using 18% EtOAc–hexanes, gave **4.12** (0.2074 g, 79%) as an oil. The spectral data for this indole are given above.

4.22. 3-Allyl-1-benzenesulfonyl-5-[(*tert*-butyldimethylsilyl)-oxy]-4-iodo-1*H*-indole (5.1)

$Bu_4N\cdot HSO_4$ (ca. 3 mg), $PhSO_2Cl$ (0.08 mL, 0.6 mmol) and aqueous KOH (50% w/v, 0.1 mL, 0.9 mmol) were added in that order to a stirred solution of **4.12** (0.2074 g, 0.5018 mmol) in PhH (5 mL). The flask was stoppered and the mixture was stirred for 1.5 h under air, diluted with EtOAc (10 mL) and washed with water and brine. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5×25 cm), using 6% EtOAc–hexanes, gave material (**5.1**) containing a slower-running impurity. The crude sample weighed 0.2980 g and was processed as described below. The material had: mp 75–79 °C.

4.23. 3-[1-Benzenesulfonyl-5-[(*tert*-butyldimethylsilyl)oxy]-4-iodo-1*H*-indol-3-yl]propane-1,2-diol (5.2)

N-Methylmorpholine-*N*-oxide (0.2 g, 2 mmol) followed by OsO_4 (tiny crystal, catalytic) were added to a stirred solution of **5.1** (assumed to be 0.5018 mmol from the above experiment) in THF (3 mL) and water (3 mL). The flask was stoppered and covered with Al foil and the mixture was stirred for 5 h, diluted with EtOAc (ca. 10 mL) and washed with water and brine. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.5×20 cm), using 1:1 EtOAc–hexanes, gave **5.2** (0.1861 g, 63% over the two steps from **4.12**) as an oil: FTIR (film cast) 3386, 2955, 2930, 2886, 2858, 1584, 1552, 1472, 1463, 1440, 1413, 1371, 1259, 1223, 1175, 1128, 1089, 1004, 960, 909, 832, 816, 726, 685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 6H), 1.06 (s, 9H), 2.14 (br s, 2H), 2.93 (dd, J=14.7, 8.0 Hz, 1H), 3.30 (dd, J=14.7, 4.7 Hz, 1H), 3.56 (dd, J=11.2, 6.7 Hz, 1H), 3.77 (dd, J=11.2, 2.7 Hz, 1H), 4.10–4.18 (m, 1H), 6.84 (d, J=8.9 Hz, 1H), 7.41–7.47 (m, 2H), 7.51–7.57 (m, 2H), 7.82–7.85 (overlapping m and s, 2H), 7.87 (d, J=8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −3.6, 18.7, 26.2, 29.9, 65.9, 71.8, 81.5, 114.4, 115.7, 120.3, 127.0, 127.6, 129.5, 131.1, 133.0, 134.2, 138.0, 152.1; exact mass (electrospray) m/z calcd for $C_{23}H_{30}INNaO_5SSi$ (M+Na) 610.0551, found 610.0548.

4.24. [1-Benzenesulfonyl-5-[(*tert*-butyldimethylsilyl)oxy]-4-iodo-1*H*-indol-3-yl]-acetaldehyde (5.3)

$NaIO_4$–SiO_2 (18% w/w, 1.35 g, 1.14 mmol) was added in one portion to a stirred solution of **5.2** (0.1861 g, 0.3168 mmol) in CH_2Cl_2 (5 mL). Stirring was continued for 30 min by which time complete and clean conversion to **5.3** was observed by TLC. The solid was filtered off to afford the crude oily product, which, without characterization, was subjected to the reductive amination described below.

4.25. [2-[1-Benzenesulfonyl-5-[(*tert*-butyldimethylsilyl)oxy]-4-iodo-1*H*-indol-3-yl]ethyl]benzylamine (5.4)

AcOH (0.06 mL, 1 mmol) followed by $BnNH_2$ (0.04 mL, 0.4 mmol) were added to a stirred solution of **5.3** (assumed to be 0.3168 mmol from above experiment) in 2:1 MeOH–THF (7.5 mL). $NaBH_3CN$ (26 mg, 0.41 mmol) was then added and stirring was continued overnight (Ar atmosphere). The solvent was evaporated and the residue was dissolved in EtOAc (ca. 10 mL) and washed with saturated aqueous $NaHCO_3$ and brine. The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5×25 cm), using 5% MeOH–1% Et_3N in CH_2Cl_2, gave **5.4** (0.1483 g, 72%) as an oil. The oily tertiary amine resulting from reductive amination between **5.3** and the secondary amine **5.4** was also isolated (58.9 mg). Compound **5.4** had: FTIR (film cast) 3063, 3028, 2957, 2927, 2856, 1584, 1551, 1447, 1441, 1413, 1372, 1259, 1175, 1157, 1127, 1109, 1089, 1003, 959, 927, 832, 782, 724, 686 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 0.10 (s, 6H), 0.99 (s, 9H), 2.43–2.48 (m, 2H), 2.56–2.61 (m, 2H), 3.48 (s, 2H), 6.59–6.71 (m, 3H), 6.86 (dd, J=8.9, 2.4 Hz, 1H), 7.01 (d, J=2.4 Hz, 1H), 7.09 (apparent tt, J=5.9, 1.7 Hz, 1H), 7.17–7.25 (m, 3H), 7.39 (s, 1H), 7.68–7.72 (m, 2H), 8.13 (d, J=8.9 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ −4.4, 18.3, 25.8, 25.9 (overlaps with signal at δ 25.8 ppm), 48.4, 53.9, 110.0, 115.1, 118.3, 121.7, 124.8, 126.7, 127.1, 128.3 (overlaps with solvent signal), 128.5, 128.9, 131.2, 132.9, 133.1, 139.0, 141.1, 152.5; exact mass (electrospray) m/z calcd for $C_{29}H_{36}IN_2O_3SSi$ (M+H) 647.1255, found 647.1266.

The HCl salt of **5.4**, prepared by dissolving a sample in 2 M HCl in EtOAc and then removing the solvent in vacuo, was obtained as a glass and had: FTIR (film cast) 3403, 2955, 2931, 2896, 2858, 2763, 2615, 1584, 1551, 1471, 1447, 1414, 1373, 1260, 1176, 1159, 1129, 1113, 1089, 1005, 957, 910, 832, 782, 725, 699, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.23 (s, 6H), 1.03 (s, 9H), 3.13 (apparent br s, 2H), 3.50 (t, J=7.9 Hz, 2H), 4.11 (s, 2H), 6.80 (d, J=8.9 Hz, 1H), 7.22–7.26 (m, 1H), 7.31–7.35 (m, 2H), 7.39–7.43 (m, 2H), 7.49–7.54 (overlapping m and s, 2H), 7.59 (apparent d, J=7.2 Hz, 2H), 7.81 (d, J=8.9 Hz, 1H), 7.83–7.86 (m, 2H), 10.24 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −3.9, 18.4, 22.8, 25.9, 47.3, 51.0, 81.3, 113.9, 115.6, 118.7, 126.9, 127.4, 129.1, 129.3, 129.4, 130.0, 130.4, 130.5, 132.2, 134.0, 137.8, 151.7; exact mass (electrospray) m/z calcd for $C_{29}H_{36}IN_2O_3SSi$ (M+H) 647.1255, found 647.1252.

4.26. 1-Benzenesulfonyl-5-benzyl-6-[(*tert*-butyldimethylsilyl)-oxy]-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (6.1)

A microwave flask was charged with $Pd(PPh_3)_4$ (8.0 mg, 0.0069 mmol) and then *t*-BuONa (10 mg, 0.10 mmol) was weighed into it in a dry box. The flask was capped with a septum and

a solution of **5.4** (56.3 mg, 0.0870 mmol) in PhMe (1.5 mL) and Et_3N (0.5 mL) was injected (Ar atmosphere). The mixture was stirred at 200 °C for 18 h, cooled and filtered through Celite (1×2 cm), using CH_2Cl_2. Evaporation of the solvent and flash chromatography of the residue over silica gel (1×30 cm), using 6% EtOAc–hexanes, gave **6.1** (19.2 mg, 43%) as an oil: FTIR (film cast) 3063, 3029, 2955, 2930, 2857, 1613, 1573, 1495, 1472, 1448, 1438, 1368, 1350, 1251, 1174, 1122, 1090, 1000, 964, 839, 781, 724, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.21 (s, 6H), 0.93 (s, 9H), 2.50 (dt, J=5.7, 1.3 Hz, 2H), 3.18 (t, J=5.7 Hz, 2H), 4.63 (s, 2H), 6.80 (d, J=8.6 Hz, 1H), 6.97 (s, 1H), 7.20–7.24 (m, 5H), 7.28 (d overlapping with solvent signal, J=8.6 Hz, 1H), 7.41–7.45 (m, 2H), 7.51–7.55 (m, 1H), 7.84–7.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, −60 °C) δ −4.2 (q), 18.2 (t), 20.0 (s), 25.7 (q), 47.3 (t), 55.6 (t), 104.4 (d), 117.6 (d), 118.2 (s), 119.0 (d), 124.2 (s), 126.6 (d), 126.8 (d), 128.0 (d), 128.2 (d), 128.5 (s), 129.1 (d), 131.4 (s), 133.6 (d), 137.2 (s), 139.3 (s), 139.4 (s); exact mass (electrospray) m/z calcd for $C_{29}H_{35}N_2O_3SSi$ (M+H) 519.2132, found 519.2131.

4.27. 5-Benzyl-6-[(*tert*-butyldimethylsilyl)oxy]-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]-quinoline (6.2)

Na_2HPO_4 (0.2083 g, 1.467 mmol) followed by Na(Hg) (10% Na, 0.26 g, 1.1 mmol) were added in single portions to a stirred solution of **6.1** (42.2 mg, 0.0814 mmol) in dry MeOH (3.6 mL) and stirring was continued for 1.5 h (Ar atmosphere). The mixture was then poured into water (15 ml) and extracted with Et_2O (2×8 mL). The combined organic extracts were washed once with brine, dried ($MgSO_4$) and evaporated to afford pure **6.2** (28.9 mg, 98%) as an oil: FTIR (film cast) 3409, 3062, 3027, 2955, 2929, 2896, 2857, 1604, 1503, 1452, 1443, 1360, 1340, 1274, 1253, 1232, 1166, 1067, 990, 839, 779, 700 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.28 (s, 6H), 1.05 (s, 9H), 2.50 (dt, J=5.5, 1.1 Hz, 2H), 3.20 (t, J=5.5 Hz, 2H), 4.77 (s, 2H), 6.18 (apparent d, J=1.9 Hz, 1H), 6.45 (br s, 1H), 6.62 (d, J=8.4 Hz, 1H), 6.99 (d, J=8.4 Hz, 1H), 7.02–7.10 (m, 3H), 7.31–7.33 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) (a high quality ^{13}C NMR spectrum could not be obtained) δ −3.9 (q), 18.5 (s), 21.1 (t), 26.2 (q), 49.1 (t), 56.8 (t), 102.5 (d), 111.0 (s), 116.4 (d), 118.5 (d), 122.7 (s), 126.8 (d), 128.3 (d), 128.4 (d), 130.9 (s), 131.3 (s), 136.0 (s), 140.8 (s); exact mass (electrospray) m/z calcd for $C_{23}H_{31}N_2OSi$ (M+H) 379.2200, found 379.2201.

4.28. 6-[(*tert*-Butyldimethylsilyl)oxy]-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (6.3)

Pd–C (10% Pd, 10 mg, 0.0094 mmol) was added to a stirred solution of **6.2** (28.9 mg, 0.0797 mmol) in EtOH (2.2 mL). The mixture was degassed by applying house vacuum and filling the flask with H_2. This process was repeated twice more and the flask was fitted with a balloon filled with H_2. The mixture was stirred and warmed at 45 °C for 15 h and then filtered through Celite (1×1 cm), using CH_2Cl_2. Evaporation of the filtrate gave crude **6.3** (17.7 mg, 77%) as an oil, which was used directly in the final step. The crude material had: ^1H NMR (300 MHz, C_6D_6) δ 0.22 (s, 6H), 1.08 (s, 9H), 2.81 (dt, J=5.7, 0.8 Hz, 2H), 3.10 (t, J=5.7 Hz, 2H), 3.97 (br s, 1H), 6.20 (s, 1H), 6.49 (br s, 1H), 6.49 (d, J=8.5 Hz, 1H), 6.91 (d, J=8.5 Hz, 1H).

4.29. 1,3,4,5-Tetrahydro-6-hydroxy-5,5-dimethylpyrrolo-[4,3,2-*de*]quinolinium iodide (6.4)

$NaHCO_3$ (12 mg, 0.14 mmol) was added to a stirred solution of **6.3** (17.7 mg, 0.0614 mmol) in dry MeOH (1.8 mL). MeI (10% v/v in MeOH, 0.13 mL, 0.21 mmol) was then added by syringe and stirring was continued for 1 h. At this point very little reaction had occurred (TLC control) and so a second aliquot of MeI (10% v/v in MeOH, 0.10 mL, 0.16 mmol) was added. The flask was then capped with a glass stopper under Ar and stirring was continued overnight (13 h). A third aliquot of MeI (10% v/v in MeOH, freshly prepared, 0.06 mL, 0.1 mmol) was added and stirring was continued for 4 h. The mixture was evaporated and the residue was washed with hexanes to remove non-polar impurities. Attempted extraction of the product into CH_2Cl_2 was not successful as the product was not soluble enough. The residue was therefore combined with the small amount of material recovered by evaporating the CH_2Cl_2 extract, and dissolved in MeOH (ca. 1 mL) with warming. The flask was stoppered and placed in the freezer (ca. −10 °C) overnight, during which time a small amount of **6.4** (5.7 mg, 28%) crystallized. The mother liquor was evaporated, and the residue 'A' was washed with hexanes at room temperature, with three portions of boiling CH_2Cl_2, and then with one portion of boiling $CHCl_3$. The content of the CH_2Cl_2 and $CHCl_3$ extracts was analyzed separately by ^1H NMR. The salt **6.4** was found to be insoluble in CH_2Cl_2 and $CHCl_3$, and these fractions contained only a trace amount of impure product. The CH_2Cl_2 and $CHCl_3$ extracts were combined and added to residue 'A'. The original crystals from MeOH (5.7 mg) were also added and all the material was suspended in 95% EtOH. One drop (Pasteur pipette) of HI was added to ensure that the iodide was obtained, and the solvent was removed in vacuo. The residue was then dissolved, with warming, in 95% EtOH (ca. 0.5 mL), and the solution was placed in a freezer (ca. −10 °C) for 3 days. The salt **6.4** (8.6 mg, 43%) crystallized as a grey solid. The mother liquor was concentrated in a Craig tube to ca. 0.3 mL and a further crop of (5.2 mg, 26%) of **6.4** was formed after storage in a freezer, bringing the total yield to 69%: darkens at 229–233 °C, but does not melt; FTIR (film cast) 3436, 3214, 2553, 1622, 1478, 1424, 1355, 1256, 1229, 1191, 1120, 1103, 1086, 986, 824, 801 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 3.26 (t, J=5.7 Hz, 2H), 3.71 (s, 6H), 3.93 (t, J=5.7 Hz, 2H), 6.70 (d, J=8.7 Hz, 1H), 6.99 (s, 1H), 7.17 (d, J=8.7 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 20.0, 54.0, 69.6, 104.6, 115.0, 118.9, 120.6, 121.1, 122.5, 128.9, 149.0; exact mass (electrospray) m/z calcd for $C_{12}H_{14}N_2NaO$ (M+Na) 225.0998, found 225.1002.

Acknowledgements

We thank the Natural Sciences and Engineering Research Council of Canada for financial support.

Supplementary data

Experimental procedures and copies of NMR spectra. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.04.081.

References and notes

1. (a) Sanders-Bush, E.; Mayer, S. E. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th ed.; Hardman, J. G., Limbird, L. E., Eds.; McGraw-Hill: New York, NY, 2001; p 269; (b) Glennon, R. A. *J. Med. Chem.* **1987**, *30*, 1–12.
2. Hugel, H. M.; Kennaway, D. J. *Org. Prep. Proced. Int.* **1995**, *27*, 3–31.
3. cf. (a) Spadoni, G.; Balsamini, C.; Diamantini, G.; Di Giacomo, B.; Tarzia, G.; Mor, M.; Plazzi, P. V.; Rivara, S.; Lucini, V.; Nonno, R.; Pannacci, M.; Fraschini, F.; Stankov, B. M. *J. Med. Chem.* **1997**, *40*, 1990–2002; (b) Kruse, L. I.; Meyer, M. D. *J. Org. Chem.* **1984**, *49*, 4761–4768; (c) Chang, K.-J.; Kang, B.-N.; Lee, M.-H.; Jeong, K.-S. *J. Am. Chem. Soc.* **2005**, *127*, 12214–12215.
4. cf. (a) Flaugh, M. E. U.S. Patent 6,022,980, 2000. (b) Kruse, L. I.; Young, R. C.; Kaumann, A. J. WO 93/00333, 1993. (c) Brown, M. A.; Kerr, M. A. *Tetrahedron Lett.* **2001**, *42*, 983–985; (d) Flaugh, M. E.; Crowell, T. A.; Clemens, J. A.; Sawyer, B. D. *J. Med. Chem.* **1979**, *22*, 63–69; (e) For an example based on a zirconocene-stabilized benzyne, see: Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797–11810.
5. Clive, D. L. J.; Stoffman, E. J. L. *Org. Biomol. Chem.* **2009**, *7*, 4862–4870.
6. (a) Wieland, H.; Wieland, T. *Liebigs Ann. Chem.* **1937**, *528*, 234–246; (b) Märki, F.; Robertson, A. V.; Witkop, B. *J. Am. Chem. Soc.* **1961**, *83*, 3341–3342; (c) Robinson, B.; Smith, G. F.; Jackson, A. H.; Shaw, D.; Frydman, B.; Deulofeu, V. *Proc. Chem. Soc.* **1961**, 310–311; (d) Ghosal, S.; Dutta, S. K.; Sanyal, A. K.; Bhattacharya, S. K. *J. Med. Chem.* **1969**, *12*, 480–483.
7. (a) Use of $NaBH_4$: Simeonov, M. F.; Spassov, S. L.; Bojilova, A.; Ivanov, C.; Radeglia, R. *J. Mol. Struct.* **1985**, *127*, 127–134; (b) Use of $NaBH_4$–silica–$CHCl_3$–*i*-PrOH, see: Sinhababu, A. K.; Borchardt, R. T. *Tetrahedron Lett.* **1983**, *24*, 227–230.

8. For one of the few references to the preparation of 4-iodo-5-oxyindoles, see: Moody, C. J.; Swann, E. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2561–2565.
9. Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1990**, *112*, 4404–4410.
10. cf. (a) Jeffrey, P. D.; McCombie, S. W. *J. Org. Chem.* **1982**, *47*, 587–590; (b) Kunz, H.; Unverzagt, C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 436–437.
11. (a) $PhI(OCOCF_3)_2$ alone gave the same unsatisfactory result as $PhI(OAc)_2$; we did not test the later in the present of CF_3CO_2H. (b) We did not establish if the role of the acid is simply to protonate the nitrogen. (c) The presence of CF_3CO_2H can influence the course of $PhI(OAc)_2$ oxidations: Liang, H.; Ciufolini, M.A. *J. Org. Chem.* **2008**, *73*, 4299–4301.
12. Mann, J.; Barbey, S. *Tetrahedron* **1995**, *51*, 12763–12774.
13. cf. Daumas, M.; Vo-Quang, Y.; Vo-Quang, L.; Le Goffic, F. *Synthesis* **1989**, 64–65.
14. (a) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904; (b) Cf Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.
15. (a) Gannon, W. F.; Benigni, J. D.; Suzuki, J.; Daly, J. W. *Tetrahedron Lett.* **1967**, *8*, 1531–1533; (b) Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1028–1030; (c) We isolated the alkaloid as its iodide; normally it is isolated from natural sources as the chloride.
16. Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348–1350.
17. Sundberg, R. J.; Cherney, R. J. *J. Org. Chem.* **1990**, *55*, 6028–6037.