# Synthesis of nitrogen and sulfur analogues of the seco-CI alkylating agent

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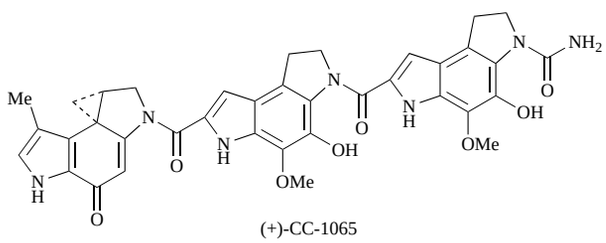
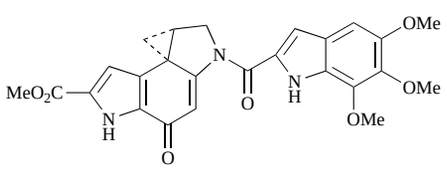
**Two complementary syntheses of amino seco-CI (CI = 1a,2,3,5-tetrahydro-1*H*-cycloprop[1,2-*c*]indol-5-one) alkylating agents starting from isomeric chloronitrobenzoic acids are reported. Further reactions of these compounds, including diazotisation to phenol and thiophenol derivatives, and alkylation and acylation reactions relevant to the preparation of pro-drug forms are also described.**

## Introduction

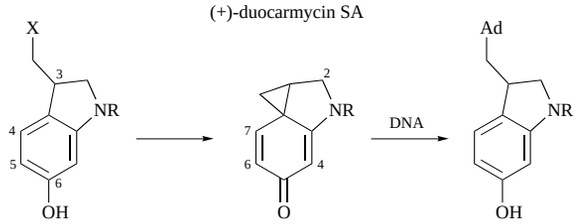
CC-1065 and the duocarmycins constitute a group of exceptionally potent antitumour antibiotics which bind to DNA in the minor groove and alkylate at N-3 of adenine in a sequence selective manner.[1] Extensive investigation of these natural products and related synthetic derivatives has identified structure **2** [1a,2,3,5-tetrahydro-1*H*-cycloprop[1,2-*c*]indol-5-one (IUPAC-numbering); CI] as the minimum potent pharmacophore, which can be formed by ring closure of a seco-CI parent **1**. Many synthetic variations on the CI theme have been



(+)-CC-1065



(+)-duocarmycin SA



seco-CI **1** CI **2**

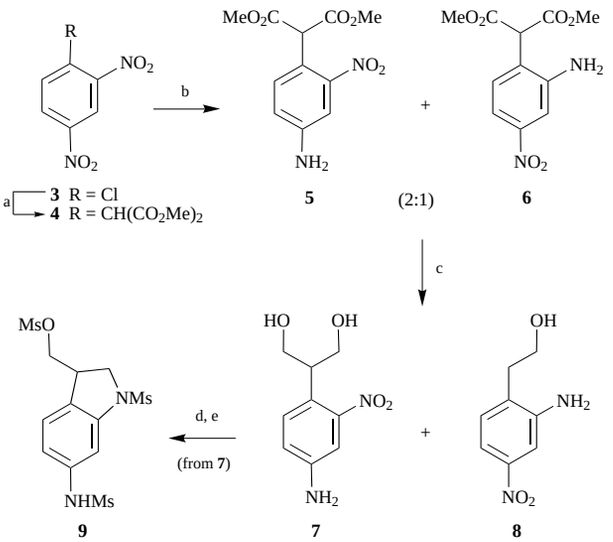
reported, including ring fusion at C-6,7[1,2] (CI-numbering) or other substitution at C-6,[3] alteration of the minor groove targeting unit R,[4] expansion[5] or deletion[6] of the N-containing ring, and variation of the leaving group X of the seco-CI precursor.[3,7] However, only restricted modifications of the seco-CI C-6 substituent have been described. In particular, the phenol has been protected in the form of ether,[7] ester,[8] carbamate[8] or glycoside[9] derivatives, or replaced entirely by either H[7,10] or CN.[10] These analogues have been used to demonstrate that a free phenol (*i.e.* the ability of a seco-CI to ring close to a cyclopropane) is *not* obligatory for DNA alkylation. Rather, for those agents incapable of ring closure, both alkylating ability and cytotoxicity appear related to the electron-donating ability of the C-6 substituent.[7]

Prompted by these interesting observations, we recently reported the first seco-CI derivatives in which the oxygen functionality at C-6 is replaced by a nitrogen or sulfur substituent.[11] These compounds are of interest for several reasons. Firstly, heteroatom substitution at this crucial position raises the question of whether such analogues also retain the ability to alkylate DNA, and if so, whether by the same mechanism and with the same or altered sequence selectivity. Secondly, we wished to examine the relationship between the properties of the C-6 substituent (*e.g.* electron-donating ability, acidity, level of alkylation) and the resulting cytotoxicity of these compounds. This is of particular interest in the formation of less toxic pro-drug forms of these alkylating agents. And finally, changing from an oxygen to a nitrogen C-6 substituent confers substantial synthetic versatility: new routes to seco-CI compounds and new pro-drug forms can be contemplated, while the C-6 substituent, especially if an amino group is considered, may be modified to introduce new functional groups at a late stage in the synthesis. These points are illustrated in the discussion below.

## Results and discussion

Our approach to amino seco-CI compounds was based on a route to related pyrrole-fused analogues.[12] In this synthesis the indoline ring is derived from a malonate substituent, which is introduced by nucleophilic displacement of a suitably substituted chloronitrobenzene. In place of the reported starting material, 4-chloro-3-nitrophenol, we initially explored reactions with chloro-2,4-dinitrobenzene (Scheme 1). Our intention was to differentiate the $NO_2$ groups at a later stage in the synthesis so that the 2-$NO_2$ group would provide the nitrogen of the indoline ring, while the other would eventually become the seco-CI C-6 substituent. As expected, the highly activated chlorine was displaced by dimethyl malonate anion in very good yield,[13] but difficulties were encountered in subsequent attempts to reduce either the ester or nitro functional groups. The most promising of the reactions investigated, namely selective nitro group reduction using sodium sulfide, gave a mixture of the two possible nitroanilines **5** and **6** in only moderate yield.† The isomers were not separable by chromatography, and recrystallisation only partially enriched the major isomer. The assignment of the major isomer as structure **5** was later confirmed by an unambiguous preparation as described below. Reduction of the isomeric mixture with diisobutylaluminium hydride (DIBALH) gave two readily separable products **7** and **8**. The major product **7** was identified as the 4-amino-2-nitro isomer as shown since it was found to cyclise to an indoline (**9**)

† A similar reduction using ammonium sulfide has been reported[13] to give two unidentified isomers in unspecified yield.



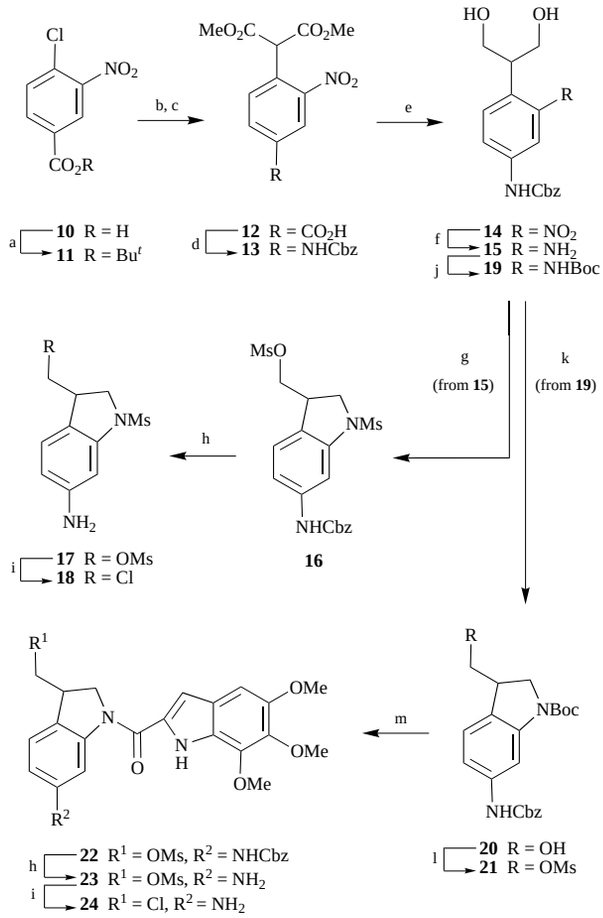

**Scheme 1** *Reagents and conditions*: a, $CH_2(CO_2Me)_2$, NaH (93%); b, $Na_2S$ (30–55%); c, DIBALH (60% **7**, 18% **8**); d, $H_2$, Pd/C; e, MsCl, pyridine (61%)

on treatment with methanesulfonyl chloride *only* if the nitro group was first reduced. The minor product **8** was tentatively identified as 2-(2-hydroxyethyl)-5-nitroaniline. When the DIBALH reduction was repeated using the recrystallised isomeric mixture this product was formed in only trace amounts. Thus it appears that the minor isomer **6**, the more synthetically useful of the two, undergoes fragmentation in the DIBALH reduction. These observations prompted a modification to the planned synthesis.

Two alternative starting materials can be considered by replacing either of the nitro groups of chloro-2,4-dinitrobenzene with a carboxylic acid. The electron withdrawing carboxy substituent should still assist nucleophilic displacement, and could be used to introduce the amino group regioselectively by Curtius rearrangement. In the event, two complementary syntheses of amino seco-CI compounds were developed along these lines, one starting from 4-chloro-3-nitrobenzoic acid[11a] (Scheme 2) and the other from 2-chloro-5-nitrobenzoic acid[11b] (Scheme 3).

Malonate displacement on the sodium salt of acid **10** was difficult to force to completion, and the product and starting materials were not easily separated. Instead, the acid was converted to its *tert*-butyl ester **11** (addition of potassium *tert*-butoxide to the acid chloride minimised competitive attack at the aromatic ring), then condensed with dimethyl malonate and the *tert*-butyl ester selectively hydrolysed. Curtius rearrangement of the acid **12** and trapping of the isocyanate with benzyl alcohol gave the carbamate **13** in which the required amine substituent is protected as its benzyloxycarbonyl (Cbz) derivative, suitable for the following steps in the synthesis. Trapping with 2-(trimethylsilyl)ethanol gave the corresponding 2-(trimethylsilyl)ethoxycarbonyl derivative also in good yield, but, aside from deprotection with tetrabuytlammonium fluoride (TBAF) to give an authentic sample of the nitroaniline **5**, this protecting group was not investigated further. Reduction of the esters and nitro group proceeded as expected,[12] without loss of the Cbz group, to give the key intermediate **15**. This compound underwent protection and *in situ* cyclisation in almost quantitative yield on treatment with methanesulfonyl chloride and pyridine.[12] Reductive removal of the Cbz group of indoline **16** and displacement of the relatively labile methanesulfonate with lithium chloride provided the aminoindoline **18**, the parent amino seco-CI in which the indoline nitrogen is protected with a methylsulfonyl substituent.

In order to incorporate minor groove targeting units the amino group of the aniline **15** was selectively protected as its

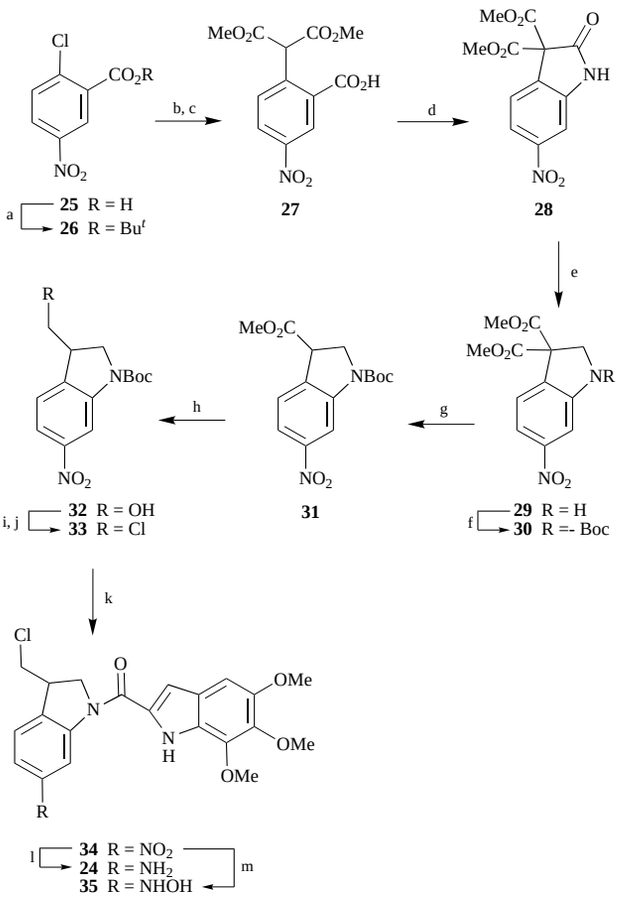



**Scheme 2** *Reagents and conditions*: a, $SOCl_2$ then KOBu′ (89%); b, $CH_2(CO_2Me)_2$, NaH; c, $HCO_2H$ (87%); d, $SOCl_2$ then $NaN_3$ then $PhCH_2OH$ (81–88%); e, DIBALH (61%); f, $H_2$, $PtO_2$ (86–94%); g, MsCl, pyridine (93%); h, $HCO_2NH_4$, Pd/C (89% **17**); i, LiCl (94% **18**, 61% **24**); j, $Boc_2O$ (85–91%); k, DEAD, $PPh_3$ (79%); l, MsCl, $Et_3N$ (97%); m, HCl then EDCI·HCl, TMI acid (59%)

*tert*-butyloxycarbonyl (Boc) derivative (di-*tert*-butyl dicarbonate, $Na_2CO_3$, tetrahydrofuran–water).‡ Cyclisation of the protected aniline **19** under Mitsunobu conditions provided the alcohol **20** which was converted to the methanesulfonate **21**. Removal of the Boc protecting group and coupling with 5,6,7-trimethoxyindole-2-carboxylic acid (TMI acid, to provide the TMI group common to the duocarmycins) using standard conditions[7] provided the amide **22**. Deprotection of the Cbz group and displacement with lithium chloride as described above gave the chloromethylindoline **24**, thus completing the first synthesis of an amino seco-CI compound bearing a minor groove targeting unit.

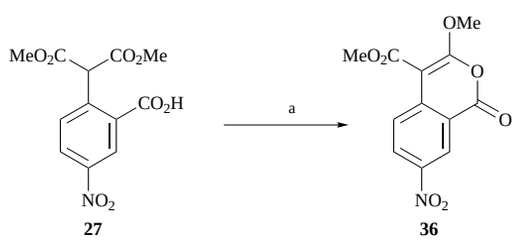
The alternative synthesis (Scheme 3) began with the isomeric 2-chloro-5-nitrobenzoic acid. Curtius rearrangement was expected to provide the nitrogen to be incorporated in the indoline ring, allowing the $NO_2$ group being carried intact through the synthesis up to the stage of a nitro seco-CI. Such a compound was of interest as a pro-drug form of an amino seco-CI that could be activated by reduction; given the strong electron-withdrawing nature of the $NO_2$ group a large cytotoxicity differential between the amino and nitro forms was anticipated. In the manner described above, the acid **25** was protected as the *tert*-butyl ester **26**, which was condensed with dimethyl malonate, and the *tert*-butyl ester hydrolysed. However, attempts to conduct the Curtius rearrangement under standard conditions gave the isochromene **36** as the major product

‡ Surprisingly, reaction of a similar substrate (OBn in place of NHCbz) using di-*tert*-butyl dicarbonate and 4-dimethylaminopyridine led to selective protection of the alcohols.



**Scheme 3** *Reagents and conditions*: a, $SOCl_2$ then $KOBu^t$ (81%); b, $CH_2(CO_2Me)_2$, NaH; c, $HCO_2H$ (88%); d, DPPA, $Et_3N$ (84%); e, $BH_3{\cdot}Me_2S$ (55%); f, $Boc_2O$ (99%); g, NaOMe then $CF_3CO_2H$; h, DIBALH (87% from **30**); i, MsCl, $Et_3N$; j, LiCl (92%); k, HCl then EDCI·HCl, TMI acid (78–82%); l, $H_2$, $PtO_2$, THF (93–100%); m, $H_2$, $PtO_2$, DMF (38%)

(Scheme 4), apparently through intramolecular attack on the intermediate acid chloride. Even mild methods of generating the acid chloride (*e.g.* oxalyl chloride with catalytic dimethylformamide) followed by trapping with methanol gave no better than a 1 : 1 mixture of the isochromene **36** and the Me ester of acid **27**. When the acid **27** was allowed to react with diphenyl-

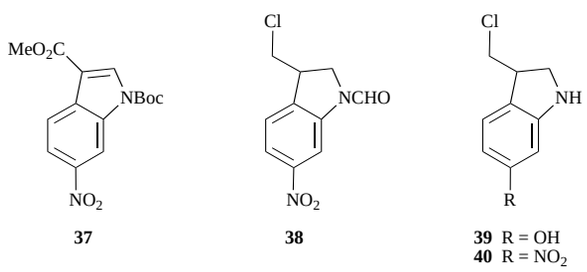


**Scheme 4** *Reagents and conditions*: a, $SOCl_2$, then $NaN_3$ (48%)

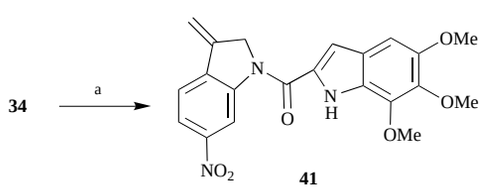
phosphoryl azide (DPPA)[14] and triethylamine at 20 °C the corresponding acyl azide was isolated in moderate yield. Heating of this in tetrahydrofuran without added base gave good conversion to the indolinone **28**. This reaction could be done in a single step without isolating the acyl azide—rearrangement and intramolecular trapping of the isocyanate occurred even in the presence of added alcohol (*tert*-butyl alcohol), and the poorly soluble indolinone **28** precipitated from the reaction mixture in good yield.

Reduction of the indolinone **28** with borane–dimethyl sulfide gave the indoline **29**, accompanied by a small amount of the indole **37** if the reaction was left to run for an extended period. The indoline nitrogen of **29** was protected as the Boc derivative and the product **30** demethoxycarbonylated. After some experimentation this was found to be easily achieved by treatment with a single equivalent of sodium methoxide. The deep purple nitronate solution that was immediately generated was quenched with trifluoroacetic acid to give the monoester **31** in practically quantitative yield. If more than stoichiometric amounts of base were used, increasing quantities of the indole **37** were again observed as a byproduct. Ester **31** showed signs of air oxidation on standing at room temperature, so was generally used directly in the next step. DIBALH reduction provided the alcohol **32** which was converted to the chloride **33**.

Coupling with TMI acid to give nitro seco-CI **34** proceeded in good yield considering the weakly nucleophilic nature of the intermediate aniline. Minor modifications to the Boc deprotection–coupling procedure[7] have been made: deprotection with hydrochloric acid in dioxane rather than ethyl acetate avoids the possibility of competitive reaction with acetic acid which may be formed by hydrolysis of the solvent. Also, a minor byproduct from some coupling reactions run in dimethylformamide proved to be the *N*-formyl derivative **38**; cleaner reactions and slightly higher yields were obtained using dimethylacetamide. It is also worth noting that whereas the hydroxyindoline **39** is reported to be unstable, even as the hydrochloride salt,[7] the nitroindoline **40** is a stable solid that



can be recrystallised from benzene without decomposition. However, nitroindoline **40** and its derivatives do readily undergo elimination in the presence of base (*e.g.* the formation of the alkene **41**, Scheme 5), a side reaction that has been observed in

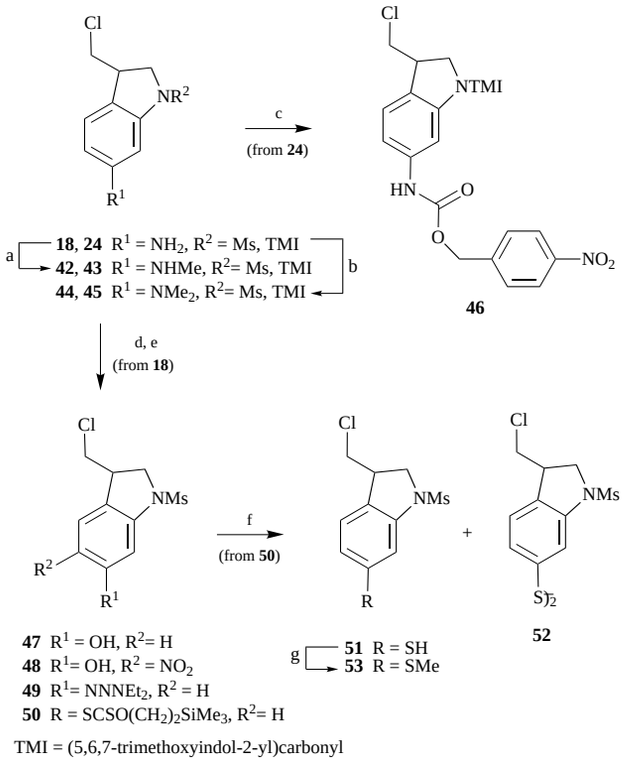


**Scheme 5** *Reagents and conditions*: a, NaOMe (64%)

some coupling reactions with acids other than TMI acid. To complete the alternative amino seco-CI synthesis the nitroindoline **34** was hydrogenated over platinum oxide in tetrahydrofuran to give the aminoindoline **24** in very good yield. Hydrogenation in dimethyl formamide was found to proceed more slowly and gave a moderate yield of the hydroxylamine **35**. This compound is another candidate cytotoxin which may be generated by reductive activation of the nitroindoline **34**.[11b]

Scheme 6 presents a summary of the chemistry of the amino seco-CI compounds investigated to date, including simple alkylation and acylation reactions (*i.e.* the preparation of derivatives **42**–**46**). We have previously noted that mono- and di-methylation of the amino group does not decrease cytotoxicity,[11a] in contrast to methylation of a phenol seco-CI,[7] while acylation does give significantly less potent compounds.[11b]

Diazonium ion chemistry with amino seco-CIs has also been briefly explored. Diazotisation of the aminoindoline **18** in sulfuric acid and heating of the diazonium solution gave the phenol **47** in 52% yield, thus providing an alternative (but low-




**Scheme 6** *Reagents and conditions*: a, AcOCHO, $BH_3$·$Me_2S$ (76% **42**, 62% **43**); b, HCHO, $NaBH_3CN$ (84% **44**, 64% **45**); c, 4-$NO_2$-$C_6H_4CH_2OCOCl$ (77%); d, $H^+$ then $NaNO_2$; e, for **47** toluene reflux (52%), for **48** $Cu(NO_3)_2$, $Cu_2O$ (29%), for **49** $Et_2NH$, $K_2CO_3$ (90%), for **50** $KSCSO(CH_2)_2SiMe_3$; f, TBAF (10% **51**, 14% **52**); g, MeI, $NaHCO_3$ (84%)

yielding) route to phenol seco-CI compounds. Other diazotisation routes to the phenol were not as successful: treatment of the diazonium solution with copper(I) oxide and copper(II) nitrate[15] gave a low yield of the nitrated phenol **48**, and while the triazene **49** was easily prepared, treatment of this with cation exchange resins[16] gave the phenol **47** in only trace amounts.

Diazotisation routes to thio seco-CI analogues were also investigated. Treatment of the diazonium solution with either sodium sulfide[17] or potassium thiocyanate and copper(I) thiocyanate[18] was unsuccessful. A more widely used diazotisation route to thiophenols relies on an *O*-ethyl dithiocarbonate intermediate, but requires a strongly basic hydrolysis step to give the free thiophenol. As a thio seco-CI was not expected to be stable under these conditions, other dithiocarbonate derivatives were considered. A model aniline [3-(methylsulfonylamino)-4-methylaniline] was diazotised and allowed to react with potassium ethyl, benzyl,[19] or (trimethylsilylethyl) dithiocarbonate to give the corresponding *O*-alkyl dithiocarbonates in 47%, 20% and 48% yield respectively. While the ethyl dithiocarbonate was cleaved almost quantitatively using potassium hydroxide in ethanol–water, treatment of the benzyl dithiocarbonate with mild acid gave none of the required thiophenol. The (trimethylsilylethyl) dithiocarbonate derivative was more promising, as reaction with TBAF and oxidative work-up (hydrogen peroxide) gave 59% of the corresponding disulfide. This diazotisation and trapping procedure was applied to the aminoindoline **18**, and the crude dithiocarbonate **50** treated with TBAF (without an oxidative work-up) to give the thiophenol **51** and the disulfide **52** in 10% and 14% yield respectively. The combined overall yield is thus comparable to that obtained with the model compound. Methylation of the thiophenol **51** with methyl iodide gave the methylthioindoline **53**.

Although this route to thiophenols proceeds in a disappointing overall yield, the (trimethylsilylethyl) dithiocarbonate reagent may be of use in the synthesis of other thiophenols which contain base sensitive functional groups.

In summary, two alternative syntheses of amino seco-CI compounds have been developed, each proceeding in 10 steps from an inexpensive starting material. The second route (Scheme 3) is favoured as it gives a higher overall yield (20% compared with 12%), is suitable for multigram scale synthesis, and provides access to nitro seco-CI compounds which have displayed considerable potential as reductively activated pro-drugs.[11b] Further studies on the preparation of amino analogues of other CI-type alkylation units, and their conversion to a range of less cytotoxic pro-drug forms is in progress.

## Experimental

Moisture- or air-sensitive reactions were conducted under nitrogen in distilled solvents. The standard reaction work-up involved drying the solution of crude product over $Na_2SO_4$, removing the solvent under reduced pressure, and purifying the residue by column chromatography on silica gel with the eluting solvent indicated. Routine NMR spectra were conducted at 400 MHz ($^1H$) or 100 MHz ($^{13}C$), with $Me_4Si$ as an internal standard, and *J* values are given in Hz. Carbon signals were assigned by a DEPT pulse sequence. Light petroleum refers to the fraction with bp 60–80 °C.

**Dimethyl (2,4-dinitrophenyl)malonate 4**

Chloro-2,4-dinitrobenzene **3** was converted to **4** essentially as described for the malonate displacement in the preparation of the acid **27**, although the reaction was run in tetrahydrofuran and was complete within 20 min at 20 °C. Recrystallisation gave the malonate **4** (93%) as a cream solid, mp 94–95 °C (from methanol) (lit.,[13] 95 °C).

**2-(4-Amino-2-nitrophenyl)propane-1,3-diol 7**

Powdered $Na_2S$·$xH_2O$ (60–62%; 3.43 g, 27 mmol) was added in portions over 10 min to a stirred solution of malonate **4** (2.00 g, 6.7 mmol) in methanol (50 ml) at reflux. After 20 min the mixture was cooled, diluted with water, extracted with ethyl acetate and the extracts were dried and evaporated. Chromatography (50% ethyl acetate–light petroleum) gave a mixture of the nitroanilines **5** and **6** (0.65 g, 36%) (*ca*. 2:1 by $^1H$ NMR) as an orange crystalline solid. Recrystallisation (benzene–light petroleum) enriched the major isomer (*ca*. 10:1). A solution of the nitroanilines **5** and **6** (*ca*. 2:1 mix of isomers; 0.65 g, 2.42 mmol) in tetrahydrofuran (50 ml) was added dropwise over 30 min to a solution of DIBALH (1 M solution in hexanes; 17.0 ml, 17.0 mmol) in tetrahydrofuran (20 ml) under nitrogen with cooling in an ice–salt bath. The mixture was allowed to warm to 20 °C over 1 h, poured into hydrochloric acid (3 M; 60 ml), basified with concentrated aqueous $NH_3$, and extracted with ethyl acetate. The extracts were dried, evaporated and separated by chromatography (50% ethyl acetate–light petroleum) to give 2-(2-hydroxyethyl)-5-nitroaniline **8** (80 mg, 18%) as a yellow–orange oil; $\delta_H(CDCl_3)$ 7.21 (1 H, d, *J* 2.5, 6-H), 7.16 (1 H, d, *J* 8.3, 3-H), 6.84 (1 H, dd, *J* 8.3 and 2.5, 4-H), 3.91 (2 H, s, $NH_2$), 3.87 (2 H, t, *J* 4.3, $CH_2OH$), 3.03 (2 H, t, *J* 4.3, $ArCH_2$), 1.75 (1 H, s, OH); $\delta_C(CDCl_3)$ 150.1, 145.9, 122.7 (1, 2, 5-C), 133.5, 119.6, 110.3 (3, 4, 6-C), 63.0 ($CH_2OH$), 35.4 ($ArCH_2$). (When the reaction was repeated using a 10:1 mix of isomers, this product was present in only trace amounts.)

Further elution (ethyl acetate) gave the *propanediol* **7** (307 mg, 60%) as an orange oil, mp 108–109 °C (from ethanol) (Found: C, 50.8; H, 5.8; N, 13.0; $C_9H_{12}N_2O_4$ requires C, 50.9; H, 5.7; N, 13.2%); $\delta_H([^2H_6]DMSO)$ 7.17 (1 H, d, *J* 8.5, 6-H), 6.89 (1 H, d, *J* 2.3, 3-H), 6.78 (1 H, dd, *J* 8.5 and 2.3, 5-H), 5.52 (2 H, s, $NH_2$), 4.57 (2 H, t, *J* 5.1, OH), 3.68–3.59 (2 H, m, $CH_2OH$), 3.58–3.49 (2 H, m, $CH_2OH$), 3.09–3.02 (1 H, m, ArCH); $\delta_C([^2H_6]DMSO)$ 151.5, 147.7, 121.3 (1, 2, 4-C), 129.6, 117.8, 107.4 (3, 5, 6-C), 62.1 ($CH_2OH$), 43.7 (ArCH).

**1-(Methylsulfonyl)-6-[(methylsulfonyl)amino]-3-[(methylsulfonyloxy)methyl]indoline 9**

A solution of the propanediol **7** (97 mg, 0.46 mmol) in ethanol (10 ml) with Pd/C (5%; 30 mg) was hydrogenated at 50 psi for 45 min. The catalyst was filtered off and the filtrate evaporated. The residue was dissolved in pyridine (4 ml) under nitrogen, the solution cooled to 0 °C and methanesulfonyl chloride (0.21 ml, 2.8 mmol) was added. After 30 min at 0 °C water was added and the mixture extracted with ethyl acetate. The extracts were washed with aq. hydrochloric acid (2 M), dried and evaporated. Chromatography (70% ethyl acetate–light petroleum) gave the *indoline* **9** (112 mg, 61%) as a cream solid, mp 175–176 °C (from ethyl acetate–light petroleum) (Found: C, 36.3; H, 4.3; N, 7.0; $C_{12}H_{18}N_2O_7S_3$ requires C, 36.2; H, 4.55; N, 7.0%); $\delta_H$([$^2H_6$]-DMSO) 9.79 (1 H, s, NH), 7.36 (1 H, d, *J* 8.2, 4-H), 7.25 (1 H, d, *J* 1.8, 7-H), 6.92 (1 H, dd, *J* 8.2 and 1.8, 5-H), 4.43 (1 H, dd, *J* 9.9 and 4.9, C*H*$_2$OSO$_2$Me), 4.34 (1 H, dd, *J* 9.9 and 6.5, C*H*$_2$OSO$_2$Me), 4.16–4.08 (1 H, m, CHCH$_2$N), 3.83–3.75 (2 H, m, CHCH$_2$N), 3.20 (3 H, s, SO$_2$Me), 3.03 (3 H, s, SO$_2$Me), 2.98 (3 H, s, SO$_2$Me); $\delta_C$([$^2H_6$]DMSO) 143.2, 139.2, 126.1, 125.6, 114.7, 105.1 (aromatic C and CH), 71.0 (*C*H$_2$OSO$_2$Me), 52.7 (2-C), 39.2, 38.6, 36.6, 34.5 (1-C, 3 × SO$_2$Me).

***tert*-Butyl 4-chloro-3-nitrobenzoate 11**

4-Chloro-3-nitrobenzoic acid **10** was converted to the ester **11** by the method described below for the preparation of ester **26**. Chromatography (3% ethyl acetate–light petroleum) and crystallisation gave the tert-*butyl ester* **11** (89%) as a white solid, mp 70–71 °C (from light petroleum) (Found: C, 51.6; H, 4.8; N, 5.4; Cl, 14.0; $C_{11}H_{12}ClNO_4$ requires C, 51.3; H, 4.7; N, 5.4; Cl, 13.8%); $\delta_H$(CDCl$_3$) 8.42 (1 H, d, *J* 2.0, 2-H), 8.11 (1 H, dd, *J* 8.4 and 2.0, 6-H), 7.61 (1 H, d, *J* 8.4, 5-H), 1.61 (9 H, s, Bu$^t$); $\delta_C$(CDCl$_3$) 163.1 (CO$_2$Bu$^t$), 148.0, 133.9, 132.4, 132.3, 131.4, 126.8 (aromatic C and CH), 83.4 (OCMe$_3$), 28.5 (Bu$^t$).

**Dimethyl (4-carboxy-2-nitrophenyl)malonate 12**

The ester **11** was converted to the acid **12** by the method described below for the preparation of **27**. Crystallisation gave the *acid* **12** (87%) as cream prisms, mp 147–149 °C (from benzene) (Found: C, 48.7; H, 3.5; N, 4.7; $C_{12}H_{11}NO_8$ requires C, 48.5; H, 3.7; N, 4.7%); $\delta_H$([$^2H_6$]DMSO) 13.77 (1 H, br s, CO$_2$H), 8.52 (1 H, d, *J* 1.7, 3-H), 8.28 (1 H, dd, *J* 8.1 and 1.7, 5-H), 7.70 (1 H, d, *J* 8.1, 6-H), 5.62 (1 H, s, ArCH), 3.71 (6 H, s, CO$_2$Me); $\delta_C$([$^2H_6$]DMSO) 166.9, 165.1 (CO$_2$H, CO$_2$Me), 148.2, 134.0, 133.1, 132.3, 132.1, 125.5 (aromatic C and CH), 54.3 (ArCH), 52.9 (CO$_2$*Me*).

**Dimethyl [4-(benzyloxycarbonyl)amino-2-nitrophenyl]malonate 13**

A solution of the acid **12** (4.05 g, 13.6 mmol), thionyl chloride (1.2 ml, 16.4 mmol) and dimethylformamide (4 drops) in 1,2-dichloroethane (60 ml) was stirred at reflux for 1 h, cooled and evaporated. The residue was dissolved in acetone (30 ml) and added dropwise over 10 min to a vigorously stirred solution of sodium azide (2.66 g, 41 mmol) in water (30 ml) and acetone (100 ml) at 0 °C. After a further 30 min at 0 °C ethyl acetate (100 ml) was added, most of the acetone evaporated, and the ethyl acetate layer was washed with water, dried and evaporated. The residue was dissolved in dry toluene (35 ml) and stirred at reflux for 40 min. Benzyl alcohol (2.8 ml, 27 mmol) was added to the cooled solution and the mixture stirred at 20 °C for 2 h [until a sample spotted on a TLC plate no longer showed the formation of yellow dimethyl (4-amino-2-nitrophenyl)malonate]. The mixture was evaporated and the residue Kugelrohr distilled (1 mmHg; 90 °C) to remove excess benzyl alcohol. Chromatography (25% ethyl acetate–light petroleum) gave the *carbamate* **13** (4.83 g, 88%) as a pale yellow foam; $\delta_H$(CDCl$_3$) 8.16 (1 H, d, *J* 2.3, 3-H), 7.59 (1 H, dd, *J* 8.5 and 2.3, 5-H), 7.42–7.33 (6 H, m, 6-H and Ph), 7.11 (1 H, s, NH), 5.25 (1 H, s, ArCH), 5.22 (2 H, s, OC*H*$_2$Ph), 3.78 (6 H, s, CO$_2$Me); $\delta_C$(CDCl$_3$) 167.9 (CO$_2$Me), 152.8 (NCO$_2$), 149.0, 139.1, 135.4, 131.9, 128.7, 128.6, 128.4, 122.7, 121.9, 114.6 (aromatic C and CH), 67.6 (OCH$_2$Ph), 53.5 (ArCH), 53.2 (CO$_2$*Me*); *m/z* (DEI) 402.1059 (2%, M$^+$. $C_{19}H_{18}N_2O_8$ requires 402.1063), 91 (100, $C_7H_7$).

**2-[4-(Benzyloxycarbonyl)amino-2-nitrophenyl]propane-1,3-diol 14**

A solution of the carbamate **13** (8.07 g, 20.1 mmol) in tetrahydrofuran (150 ml) was added dropwise over 30 min to a solution of DIBALH (1 M solution in hexanes; 200 ml, 200 mmol) in tetrahydrofuran (250 ml) under nitrogen, with cooling in an ice–salt bath (maintaining the internal temperature at −8 to −2 °C). The mixture was allowed to warm to 20 °C over 1 h, then poured into ice-cold aq. hydrochloric acid (3 M; 600 ml). The tetrahydrofuran was evaporated, the aqueous residue extracted with ethyl acetate, and the extracts were dried and evaporated. Chromatography (60% ethyl acetate–light petroleum) gave the *diol* **14** (4.26 g, 61%) as a pink foam, mp 119–121 °C (from chloroform) (Found; C, 58.9; H, 5.4; N, 8.3; $C_{17}H_{18}N_2O_6$ requires C, 59.0; H, 5.2; N, 8.1%); $\delta_H$([$^2H_6$]DMSO) 10.15 (1 H, s, NH), 7.97 (1 H, d, *J* 2.2, 3-H), 7.60 (1 H, dd, *J* 8.6 and 2.2, 5-H), 7.49 (1 H, d, *J* 8.6, 6-H), 7.45–7.33 (5 H, m, Ph), 5.18 (2 H, s, OC*H*$_2$Ph), 4.67 (2 H, t, *J* 5.3, OH), 3.73–3.66 (2 H, m, C*H*$_2$OH), 3.63–3.56 (2 H, m, C*H*$_2$OH), 3.23 (1 H, quintet, *J* 6.4, ArCH); $\delta_C$([$^2H_6$]DMSO) 153.3 (NCO$_2$), 150.9, 137.8, 136.2, 129.0 (aromatic C), 129.9, 128.4, 128.11, 128.09, 121.7, 112.3 (aromatic CH), 66.1 (OCH$_2$Ph), 61.8 (CH$_2$OH), 44.1 (ArCH).

**2-[2-Amino-4-(benzyloxycarbonyl)aminophenyl]propane-1,3-diol 15**

A solution of the diol **14** (1.02 g, 2.9 mmol) in ethanol (80 ml) with PtO$_2$ (0.12 g) was hydrogenated at 50 psi and 20 °C for 50 min, filtered through Celite and evaporated. Chromatography (5–10% methanol–ethyl acetate gradient) gave the *aminodiol* **15** (0.88 g, 94%) as a very pale yellow oil; $\delta_H$([$^2H_6$]DMSO) 9.36 (1 H, s, NH), 7.43–7.30 (5 H, m, Ph), 6.82 (1 H, d, *J* 2.1, 3-H), 6.81 (1 H, d, *J* 8.3, 6-H), 6.58 (1 H, dd, *J* 8.3 and 2.1, 5-H), 5.12 (2 H, s, OC*H*$_2$Ph), 4.82 (2 H, s, NH$_2$ or OH), 4.50 (2 H, s, NH$_2$ or OH), 3.69–3.62 (2 H, m, C*H*$_2$OH), 3.54–3.46 (2 H, m, C*H*$_2$-OH), 2.83 (1 H, quintet, *J* 6.2, ArCH); $\delta_C$([$^2H_6$]DMSO) 153.2 (NCO$_2$), 146.8, 137.2, 136.8, 120.4 (aromatic C), 128.3, 127.92, 127.86, 127.0, 107.2, 105.2 (aromatic CH), 65.3 (OCH$_2$Ph), 62.3 (CH$_2$OH), 43.2 (ArCH); *m/z* (DEI) 316.1418 (30%, M$^+$. $C_{17}H_{20}N_2O_4$ requires 316.1423), 285 (30, M − CH$_2$OH), 91 (100, $C_7H_7$).

**6-[(Benzyloxycarbonyl)amino]-1-(methylsulfonyl)-3-[(methylsulfonyloxy)methyl]indoline 16**

Methanesulfonyl chloride (4.44 ml, 57 mmol) was added dropwise over 25 min to a solution of the aminodiol **15** (2.27 g, 7.18 mmol) in pyridine (70 ml) under nitrogen at 0 °C. The mixture was stirred at this temperature for a further 35 min, diluted with ice-cold water (100 ml), and extracted with ethyl acetate. The extracts were washed with cold hydrochloric acid (2 M), then with aq. NaHCO$_3$ and dried. The solution was filtered through a short column of silica, eluting with ethyl acetate, to give the *indoline* **16** (3.02 g, 93%) as a pink solid, mp 171–172 °C (from ethyl acetate) (Found: C, 50.1; H, 4.75; N, 6.2; S, 14.3; $C_{19}H_{22}N_2O_7S_2$ requires C, 50.2; H, 4.9; N, 6.2; S, 14.15%); $\delta_H$([$^2H_6$]DMSO) 9.86 (1 H, s, NH), 7.63 (1 H, d, *J* 2.0, 7-H), 7.44–7.32 (5 H, m, Ph), 7.29 (1 H, d, *J* 8.2, 4-H), 7.13 (1 H, dd, *J* 8.2 and 2.0, 5-H), 5.14 (2 H, s, OCH$_2$Ph), 4.41 (1 H, dd, *J* 9.8 and 4.9, C*H*$_2$OSO$_2$Me), 4.31 (1 H, dd, *J* 9.8 and 6.6, C*H*$_2$-OSO$_2$Me), 4.14–4.07 (1 H, m, NCH$_2$CH), 3.81–3.72 (2 H, m, NCH$_2$CH), 3.19 (3 H, s, SO$_2$Me), 3.00 (3 H, s, SO$_2$Me); $\delta_C$([$^2H_6$]DMSO) 153.2 (NCO$_2$), 142.8, 139.8, 136.5, 123.9 (aromatic C), 128.4, 128.0, 125.5, 113.3, 103.7 (aromatic CH, one peak not observed), 71.1 (*C*H$_2$OSO$_2$Me), 65.7 (OCH$_2$Ph), 52.7 (2-C), 38.6, 36.5, 34.5 (3-C, 2 × SO$_2$Me).

**6-Amino-1-(methylsulfonyl)-3-[(methylsulfonyloxy)methyl]-indoline 17**

A solution of ammonium formate (1.46 g, 23 mmol) in water (15 ml) was added to the indoline **16** (1.05 g, 2.3 mmol) and Pd/C (10%; 0.42 g) in tetrahydrofuran (80 ml) and the mixture stirred at 20 °C for 20 min. The catalyst was filtered off and washed with ethyl acetate. The filtrate was diluted with water, extracted with ethyl acetate and the extracts were dried and evaporated. Chromatography (60% ethyl acetate–light petroleum) gave the *aminoindoline* **17** (0.66 g, 89%) as a cream foam. A sample decomposed on attempted crystallisation from diethyl ether–dichloromethane; $\delta_H([^2H_6]DMSO)$ *ca.* 10 (2 H, br s, $NH_2$), 7.46 (1 H, d, *J* 8.0, 4-H), 7.25 (1 H, d, *J* 1.7, 7-H), 7.01 (1 H, dd, *J* 8.0 and 1.7, 5-H), 4.47–4.35 (2 H, m, C*H*$_2$OSO$_2$Me), 4.22–4.12 (1 H, m, NCH$_2$CH), 3.90–3.80 (1 H, m, NCH$_2$CH), 3.20 (3 H, s, $SO_2Me$), 3.07 (3 H, s, $SO_2Me$); $\delta_C([^2H_6]DMSO)$ 143.2, 134.1, 128.8 (3a, 6, 7a-C), 126.4, 117.1, 107.3 (4, 5, 7-C), 70.8 (*C*H$_2$OSO$_2$Me), 52.6 (2-C), 38.6 (3-C), 36.5, 34.7 (2 × $SO_2Me$); *m*/*z* (DEI) 320.0500 (5%, $M^+$. $C_{11}H_{16}N_2O_5S_2$ requires 320.0501), 96 (95), 79 (100).

**6-Amino-3-(chloromethyl)-1-(methylsulfonyl)indoline 18**

The aminoindoline **17** (320 mg, 1.0 mmol) and lithium chloride (0.18 g, 4.2 mmol) were stirred in dimethylformamide (8 ml) at 90 °C under nitrogen for 45 min, and the dimethylformamide was evaporated. The residue was diluted with water, extracted with ethyl acetate and the organic extracts were dried and evaporated. Chromatography (50% ethyl acetate–light petroleum) gave the *chloride* **18** (244 mg, 94%) as a pale yellow foam, mp 83.5–85 °C (from diethyl ether–light petroleum) (Found: C, 46.1; H, 5.1; N, 10.8; $C_{10}H_{13}ClN_2O_2S$ requires C, 46.1; H, 5.0; N, 10.7%); $\delta_H(CDCl_3)$ 6.99 (1 H, d, *J* 8.0, 4-H), 6.78 (1 H, d, *J* 2.2, 7-H), 6.35 (1 H, dd, *J* 8.0 and 2.2, 5-H), 4.04 (1 H, dd, *J* 10.8 and 8.7, $CH_2N$), 3.93 (1 H, dd, *J* 10.8 and 4.7, $CH_2N$), 3.80 (2 H, br s, $NH_2$), 3.70 (1 H, dd, *J* 10.4 and 4.1, $CH_2Cl$), 3.67–3.60 (1 H, m, 3-H), 3.54 (1 H, dd, *J* 10.4 and 8.1, $CH_2Cl$), 2.90 (3 H, s, $SO_2Me$); $\delta_C(CDCl_3)$ 148.0, 143.2, 120.1 (3a, 6, 7a-C), 125.6, 110.2, 100.4 (4, 5, 7-C), 54.6 (2-C), 46.9 ($CH_2Cl$), 41.9 (3-C), 34.5 ($SO_2Me$).

**2-[4-(Benzyloxycarbonyl)amino-2-(*tert*-butoxycarbonyl)amino-phenyl]propane-1,3-diol 19**

A mixture of the aminodiol **15** (3.03 g, 9.6 mmol), di-*tert*-butyl dicarbonate (2.3 g, 10.5 mmol), $Na_2CO_3$ (1.12 g, 10.5 mmol), tetrahydrofuran (200 ml) and water (100 ml) was stirred at 20 °C. More di-*tert*-butyl dicarbonate (3 × 2.3 g) was added after 5, 9 and 12 days, with sufficient tetrahydrofuran and water to maintain a single phase. After 14 days the tetrahydrofuran was evaporated, the aqueous layer extracted with ethyl acetate and the organic extracts were dried and evaporated. Chromatography (70% ethyl acetate–light petroleum) gave the *carbamate* **19** (3.62 g, 91%) as a white foam; $\delta_H([^2H_6]DMSO)$ 9.67 (1 H, s, NH), 8.62 (1 H, s, NH), 7.60 (1 H, s, 3-H), 7.44–7.31 (5 H, m, Ph), 7.19 (1 H, dd, *J* 8.5 and 1.7, 5-H), 7.08 (1 H, d, *J* 8.5, 6-H), 5.14 (2 H, s, OC*H*$_2$Ph), 4.84 (2 H, t, *J* 4.7, OH), 3.78–3.70 (2 H, m, C*H*$_2$OH), 3.54–3.45 (2 H, m, C*H*$_2$OH), 2.98 (1 H, quintet, *J* 6.3, ArCH), 1.45 (9 H, s, Bu$^t$); $\delta_C([^2H_6]DMSO)$ 153.3 (resolves into two peaks on $D_2O$ exchange, 2 × $NCO_2$), 137.1, 137.0, 136.7, 129.4 (aromatic C), 128.4, 127.91, 127.87, 127.4, 114.6, 114.4 (aromatic CH), 78.8 ($OCMe_3$), 65.5 ($OCH_2Ph$), 62.8 ($CH_2OH$), 43.9 (ArCH), 28.1 (Bu$^t$); *m*/*z* (DEI) 416.1954 (2%, $M^+$. $C_{22}H_{28}N_2O_6$ requires 416.1947), 91 (100, $C_7H_7$).

**6-[(Benzyloxycarbonyl)amino]-1-(*tert*-butoxycarbonyl)-3-(hydroxymethyl)indoline 20**

Diethyl azodicarboxylate (DEAD) (2.32 ml, 14.8 mmol) was added dropwise over 5 min to a solution of the carbamate **19** (3.62 g, 8.69 mmol) and triphenylphosphine (4.10 g, 15.6 mmol) in tetrahydrofuran (100 ml) under nitrogen and the mixture was stirred at 20 °C. After 20 min the mixture was diluted with ethyl acetate, washed with aq. NaCl, and the organic phase was dried and evaporated. Some of the 1,2-bis(ethoxycarbonyl)hydrazine byproduct was precipitated by slow addition of light petroleum to an ethyl acetate solution of the crude product, the rest was removed by chromatography (50% ethyl acetate–light petroleum), to give the *indoline* **20** (2.73 g, 79%) as a white foam; $\delta_H([^2H_6]DMSO)$ 9.68 (1 H, s, NH), 7.97 (1 H, br s, 7-H), 7.44–7.31 (5 H, m, Ph), 7.11 (1 H, d, *J* 8.1, 4-H), 6.98 (1 H, br d, *J* *ca.* 8, 5-H), 5.13 (2 H, s, $OCH_2Ph$), 4.90 (1 H, t, *J* 5.0, OH), 3.94 (1 H, t, *J* 10.3, $NCH_2$), 3.75 (1 H, dd, *J* 11.3 and 5.1, $NCH_2$), 3.61–3.54 (1 H, m, C*H*$_2$OH), 3.41–3.28 (2 H, m, C*H*C*H*$_2$OH), 1.51 (9 H, s, Bu$^t$); $\delta_C([^2H_6]DMSO)$ 153.2, 151.6 (2 × $NCO_2$), 138.6, 136.7, 126.4 (aromatic C, one peak not observed), 128.3, 127.96, 127.90, 124.4, 112.1, 105.0 (aromatic CH), 79.7 ($OCMe_3$), 65.5 ($OCH_2Ph$), 63.9 ($CH_2OH$), 51.4 (2-C), 41.2 (3-C), 28.0 (Bu$^t$); *m*/*z* (DEI) 398.1840 (4%, $M^+$. $C_{22}H_{26}N_2O_5$ requires 398.1841).

**6-[(Benzyloxycarbonyl)amino]-1-(*tert*-butoxycarbonyl)-3-[(methylsulfonyloxy)methyl]indoline 21**

Methanesulfonyl chloride (0.69 ml, 8.9 mmol) was added to a solution of the indoline **20** (2.73 g, 6.85 mmol) and triethylamine (1.43 ml, 10.3 mmol) in dichloromethane (70 ml) at 0 °C, and the mixture stirred for 10 min. Aq. $NaHCO_3$ was added, the mixture was extracted with dichloromethane and the extracts were dried and evaporated. Chromatography (40% ethyl acetate–light petroleum) gave the *methanesulfonate* **21** (3.16 g, 97%) as a white foam; $\delta_H(CDCl_3)$ (NH not observed) 7.73 (1 H, s, 7-H), 7.41–7.31 (5 H, m, Ph), 7.12 (1 H, d, *J* 8.1, 4-H), 6.73 (1 H, s, 5-H), 5.19 (2 H, s, $OCH_2Ph$), 4.32 (1 H, dd, *J* 9.9 and 5.5, C*H*$_2$OSO$_2$Me), 4.18 (1 H, dd, *J* 9.9 and 8.1, C*H*$_2$OSO$_2$Me), 4.11–4.02 (1 H, m, $NCH_2$), 3.92–3.84 (1 H, m, $NCH_2$), 3.72–3.62 (1 H, m, 3-H), 2.96 (3 H, s, $SO_2Me$), 1.56 (9 H, s, Bu$^t$); $\delta_C(CDCl_3)$ 153.2, 152.1 (2 × $NCO_2$), 143.9, 138.7, 136.0, 123.6 (aromatic C), 128.6, 128.3, 124.9, 112.7, 105.9 (aromatic CH, one peak not observed), 81.2 ($OCMe_3$), 71.0 (*C*H$_2$OSO$_2$Me), 67.0 ($OCH_2Ph$), 51.1 (2-C), 39.1 (3-C), 37.5 ($OSO_2Me$), 28.4 (Bu$^t$); *m*/*z* (DEI) 476.1607 (5%, $M^+$. $C_{23}H_{28}N_2O_7S$ requires 476.1617), 91 (100, $C_7H_7$).

**6-[(Benzyloxycarbonyl)amino]-3-[(methylsulfonyloxy)methyl]-1-[(5,6,7-trimethoxyindol-2-yl)carbonyl]indoline 22**

The methanesulfonate **21** (3.16 g, 6.63 mmol) was stirred in HCl-saturated ethyl acetate (50 ml) at 20 °C for 2 h (until TLC indicated complete reaction) and the mixture was evaporated. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI·HCl) (2.54 g, 13.2 mmol) and 5,6,7-trimethoxyindole-2-carboxylic acid[20] (1.67 g, 6.63 mmol) in dimethylformamide (80 ml) were added and the mixture was stirred at 20 °C under nitrogen for 48 h. The dimethylformamide was evaporated, the residue was diluted with aq. $NaHCO_3$, extracted with ethyl acetate and the extracts were dried and evaporated. Chromatography (50% ethyl acetate–light petroleum) gave the *amide* **22** (2.40 g, 59%) as a cream crystalline solid, mp 153–154 °C (from ethyl acetate–light petroleum) (Found: C, 58.7; H, 5.3; N, 6.6; $C_{30}H_{31}N_3O_9S\cdot\frac{1}{2}EtOAc$ requires C, 58.8; H, 5.4; N, 6.4%); $\delta_H([^2H_6]DMSO)$ 11.44 (1 H, s, NH), 9.85 (1 H, s, NH), 8.38 (1 H, s, 7-H), 7.46–7.33 (5 H, m, Ph), 7.33 (1 H, d, *J* 8.2, 4-H), 7.25 (1 H, dd, *J* 8.2 and 1.8, 5-H), 7.03 (1 H, d, *J* 1.9, 3′-H), 6.95 (1 H, s, 4′-H), 5.15 (2 H, s, $OCH_2Ph$), 4.62 (1 H, t, *J* 10.0, $CH_2$), 4.45 (1 H, dd, *J* 9.8 and 5.1, $CH_2$), 4.35 (1 H, dd, *J* 9.8 and 7.2, 1 H, $CH_2$), 4.27 (1 H, dd, *J* 10.9 and 5.3, $CH_2$), 3.93 (3 H, s, OMe), 3.87–3.80 (1 H, m, 3-H), 3.81 (3 H, s, OMe), 3.80 (3 H, s, OMe), 3.18 (3 H, s, $OSO_2Me$); $\delta_C([^2H_6]DMSO)$ 160.1 (NCO), 153.3 ($NCO_2$), 149.1, 144.0, 139.8, 139.1, 139.0, 136.6, 130.8, 124.6, 123.1 (aromatic C, one peak not observed), 128.4, 128.0, 127.9, 125.3, 113.9, 107.7, 106.1, 98.0 (aromatic CH), 71.3 (*C*H$_2$OSO$_2$Me), 65.6 ($OCH_2Ph$), 61.0, 60.9, 55.9 (3 × OMe), 53.0 (2-C), 39.3 (3-C), 36.5 ($OSO_2Me$).

**6-Amino-3-(chloromethyl)-1-[(5,6,7-trimethoxyindol-2-yl)carbonyl]indoline 24 (prepared by the method of Scheme 2)**

A solution of ammonium formate (2.48 g, 39 mmol) in water (20 ml) was added to the carbamate **22** (2.40 g, 3.94 mmol) and Pd/C (5%; 0.25 g) in tetrahydrofuran (250 ml) and the mixture was stirred at 20 °C for 30 min. The catalyst was filtered off and washed with ethyl acetate, and the filtrate was dried and evaporated. Chromatography (70–90% ethyl acetate–light petroleum gradient) gave 6-amino-3-[(methylsulfonyloxy)methyl]-1-[(5,6,7-trimethoxyindol-2-yl)carbonyl]indoline **23** (*ca*. 1.70 g) as a pale yellow foam. This crude methanesulfonate and lithium chloride (0.86 g, 20 mmol) were stirred in dimethylformamide (50 ml) at 70 °C under nitrogen for 1 h, and the dimethylformamide was evaporated. The residue was diluted with water, extracted with ethyl acetate and the extracts were dried and evaporated. Chromatography (50% ethyl acetate–light petroleum) gave the *chloromethylindoline* **24** (1.00 g, 61% from **22**) as a pale yellow foam, mp 173–174 °C (from ethyl acetate–diethyl ether) (Found: C, 60.65; H, 5.3; N, 10.1; $C_{21}H_{22}ClN_3O_4$ requires C, 60.7; H, 5.4; N, 9.8%); $\delta_H([^2H_6]DMSO)$ 11.36 (1 H, d, *J* 1.6, NH), 7.44 (1 H, br s, 7-H), 7.05 (1 H, d, *J* 8.0, 4-H), 6.96 (1 H, d, *J* 2.1, 3′-H), 6.95 (1 H, s, 4′-H), 6.30 (1 H, dd, *J* 8.0 and 2.2, 5-H), 5.18 (2 H, s, $NH_2$), 4.54 (1 H, dd, *J* 10.8 and 8.7, $NCH_2$), 4.20 (1 H, dd, *J* 10.8 and 4.4, $NCH_2$), 3.93 (3 H, s, OMe), 3.91 (1 H, dd, *J* 9.9 and 3.5, $CH_2Cl$), 3.81 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.74–3.60 (2 H, m, $CHCH_2Cl$); $\delta_C([^2H_6]DMSO)$ 159.9 (NCO), 149.0, 144.2, 139.6, 139.0, 131.2, 125.1, 123.1, 118.8 (aromatic C, one peak not observed), 124.7, 109.5, 105.6, 102.9, 98.0 (aromatic CH), 61.0, 60.9, 55.9 (3 × OMe), 54.5 (2-C), 47.9 ($CH_2Cl$), 41.8 (3-C).

***tert*-Butyl 2-chloro-5-nitrobenzoate 26**

A suspension of 2-chloro-5-nitrobenzoic acid **25** (20.26 g, 101 mmol), thionyl chloride (9.6 ml, 111 mmol) and dimethylformamide (7 drops) in 1,2-dichloroethane (100 ml) was stirred at reflux for 14 h, cooled and evaporated. The acid chloride was dissolved in tetrahydrofuran (200 ml), cooled to 0 °C, and a solution of potassium *tert*-butoxide (11.3 g, 101 mmol) in tetrahydrofuran (300 ml) was added dropwise over 30 min under nitrogen. The mixture was stirred a further 30 min at 0 °C, diluted with aq. $NaHCO_3$, extracted with ethyl acetate, and the extracts were dried and evaporated. Recrystallisation gave the *ester* **26** (21.0 g, 81%) as a white solid, mp 91.5–92 °C (from light petroleum) (Found: C, 51.5; H, 4.5; N, 5.6; Cl, 14.0; $C_{11}H_{12}ClNO_4$ requires C, 51.3; H, 4.7; N, 5.4; Cl, 13.8%); $\delta_H(CDCl_3)$ 8.59 (1 H, d, *J* 2.8, 6-H), 8.24 (1 H, dd, *J* 8.8 and 2.8, 4-H), 7.63 (1 H, d, *J* 8.8, 5-H), 1.65 (9 H, s, $Bu^t$); $\delta_C(CDCl_3)$ 163.0 ($CO_2Bu^t$), 146.1, 140.0, 133.3, 132.0, 126.1, 126.0 (aromatic C and CH), 84.0 ($OCMe_3$), 28.1 ($Bu^t$).

**Dimethyl (2-carboxy-4-nitrophenyl)malonate 27**

Sodium hydride (60% dispersion in oil; 12.42 g, 310 mmol) was washed with light petroleum under nitrogen and suspended in dry dimethyl sulfoxide (250 ml). A solution of dimethyl malonate (37.3 ml, 330 mmol) in dimethyl sulfoxide (50 ml) was added dropwise over 35 min with water-bath cooling. The ester **26** (20.0 g, 78 mmol) was added and the mixture stirred at 70–80 °C under nitrogen for 4 h. The red–brown solution was cooled, poured into water (300 ml) and aq. hydrochloric acid (2 M; 60 ml) was added to disperse the red nitronate colour. The mixture was extracted with dichloromethane and the extracts were dried and evaporated. Formic acid (60 ml) was added to the residue and the mixture was stirred at 20 °C for 15 h then 50 °C for 7 h (when TLC analysis showed no remaining *tert*-butyl ester). The formic acid was evaporated and the residue was taken up in ethyl acetate and washed with aq. NaCl. The organic layer was extracted with aq. $NaHCO_3$, then the aqueous phase was acidified (conc. HCl) and extracted with dichloromethane. The organic phase was dried and evaporated and the residue was recrystallised to give the *acid* **27** (20.27 g, 88%) as cream needles, mp 163–164 °C (from benzene) (Found: C, 48.7; H, 3.7; N, 5.0; $C_{12}H_{11}NO_8$ requires C, 48.5; H, 3.7; N, 4.7%); $\delta_H(CDCl_3)$ 8.99 (1 H, d, *J* 2.5, 3-H), 8.44 (1 H, dd, *J* 8.6 and 2.5, 5-H), 8.4 (1 H, br s, $CO_2H$), 7.73 (1 H, d, *J* 8.6, 6-H), 5.94 (1 H, s, ArCH), 3.83 (6 H, s, $CO_2Me$); $\delta_C(CDCl_3)$ 169.6, 167.8 ($CO_2Me$, $CO_2H$), 147.4, 141.4, 132.2, 129.7, 127.6, 126.8 (aromatic C and CH), 54.4 (ArCH), 53.3 ($CO_2Me$).

**3,3-Bis(methoxycarbonyl)-6-nitroindolin-2-one 28**

Triethylamine (8.64 ml, 62 mmol) was added to a solution of the acid **27** (18.43 g, 62 mmol) and DPPA (13.4 ml, 62 mmol) in tetrahydrofuran (300 ml) and the mixture stirred at reflux for 15 h. The orange–brown solution was cooled and concentrated to a small volume. The solid that precipitated was filtered off and washed with hydrochloric acid (2 M) and water. The solid was dried and triturated with hot methanol (*ca*. 80 ml) to give the *indolinone* **28** (15.4 g, 84%) as a pale yellow powder, mp 234–239 °C (decomp.) (Found: C, 49.1; H, 3.4; N, 9.65; $C_{12}H_{10}N_2O_7$ requires C, 49.0; H, 3.4; N, 9.5%); $\delta_H([^2H_6]DMSO)$ 11.43 (1 H, br s, NH), 7.97 (1 H, dd, *J* 8.3 and 2.1, 5-H), 7.66 (1 H, d, *J* 8.3, 4-H), 7.62 (1 H, d, *J* 2.1, 7-H), 3.76 (6 H, s, $CO_2Me$); $\delta_C([^2H_6]DMSO)$ 167.4, 163.9 ($CO_2Me$, CONH), 148.4, 143.7, 130.4 (3a, 6, 7a-C), 126.7, 117.7, 104.6 (4, 5, 7-C), 65.7 (3-C), 54.0 ($CO_2Me$); *m*/*z* (DEI) 294.0485 (85%, $M^+$. $C_{12}H_{10}N_2O_7$ requires 294.0488), 250 (100, M − $CO_2$).

**3,3-Bis(methoxycarbonyl)-6-nitroindoline 29**

Borane–dimethyl sulfide (10.7 ml, 107 mmol) was added to a suspension of the indolinone **28** (17.56 g, 59.7 mmol) in tetrahydrofuran (350 ml) under nitrogen, and the mixture was stirred at reflux for 1 h. The pale yellow solution was cooled, then methanol (10 ml), water (10 ml) and aq. hydrochloric acid (2 M, 50 ml) were added sequentially, and the mixture was stirred at 20 °C for a few minutes. The tetrahydrofuran was evaporated and the residue extracted with ethyl acetate. The extracts were dried and evaporated, and the resulting orange solid was triturated with dichloromethane (2 × 100 ml) at 20 °C and filtered through Celite to remove most of the indole **37**. The dichloromethane solution was filtered through a short column of silica, eluting with more dichloromethane. The filtrate was evaporated, and the resulting solid recrystallised to give the *indoline* **29** (9.16 g, 55%) as a yellow crystalline solid, mp 139.5–140.5 °C (from methanol) (Found: C, 51.4; H, 4.4; N, 10.0; $C_{12}H_{12}N_2O_6$ requires C, 51.4; H, 4.3; N, 10.0%); $\delta_H(CDCl_3)$ 7.64 (1 H, dd, *J* 8.3 and 2.1, 5-H), 7.56 (1 H, d, *J* 8.3, 4-H), 7.41 (1 H, d, *J* 2.1, 7-H), 4.24 (2 H, d, *J* 1.9, $NCH_2$), 4.16 (1 H, br s, NH), 3.82 (6 H, s, $CO_2Me$); $\delta_C(CDCl_3)$ 168.7 ($CO_2Me$), 151.7, 149.8, 130.8 (3a, 6, 7a-C), 127.2, 114.2, 104.2 (4, 5, 7-C), 62.7 (3-C), 54.1 (2-C), 53.6 ($CO_2Me$).

**1-(*tert*-Butoxycarbonyl)-3,3-bis(methoxycarbonyl)-6-nitroindoline 30**

A solution of the indoline **29** (3.04 g, 10.8 mmol), di-*tert*-butyl dicarbonate (3.55 g, 16.3 mmol) and 4-dimethylaminopyridine (70 mg, 0.5 mmol) in tetrahydrofuran (100 ml) was stirred at 20 °C for 2 h then at reflux for 10 min. The tetrahydrofuran was evaporated and the residue purified by chromatography (20% ethyl acetate–light petroleum) to give the *carbamate* **30** (4.10 g, 99%) as a pale yellow foam, mp 131.5–132.5 °C (from methanol) (Found: C, 53.6; H, 5.4; N, 7.5; $C_{17}H_{20}N_2O_8$ requires C, 53.7; H, 5.3; N, 7.4%); $\delta_H(CDCl_3)$ 8.70, 8.34 (1 H, 2 br s, carbamate conformers, 7-H), 7.89 (1 H, dd, *J* 8.5 and 2.2, 5-H), 7.66 (1 H, d, *J* 8.5, 4-H), 4.59 (2 H, s, $NCH_2$), 3.83 (6 H, s, $CO_2Me$), 1.60 (9 H, s, $Bu^t$); $\delta_C(CDCl_3)$ 168.1 ($CO_2Me$), 151.2, 149.7 ($NCO_2$, 3a, 6, 7a-C, two peaks not observed), 127.4, 117.6, 110.0 (4, 5, 7-C), 82.5 ($OCMe_3$), 61.0 (br, 3-C), 54.6 (2-C), 53.9 ($CO_2Me$), 28.3 ($Bu^t$).

**1-(*tert*-Butoxycarbonyl)-3-(hydroxymethyl)-6-nitroindoline 32**

Sodium methoxide (1.36 M solution in methanol; 7.80 ml, 10.6

mmol) was added dropwise to a solution of the diester **30** (4.02 g, 10.6 mmol) in tetrahydrofuran (100 ml) under nitrogen at 20 °C, immediately giving an intense purple colour. After 1 min trifluoroacetic acid (1.03 ml, 11.6 mmol) was added in one portion, causing the nitronate colour to disperse. The tetrahydrofuran was evaporated, the residue was diluted with water and extracted with ethyl acetate. The extracts were dried and evaporated to give crude 1-(*tert*-butoxycarbonyl)-3-(methoxycarbonyl)-6-nitroindoline **31** as a yellow oil. This compound showed signs of air oxidation on standing at room temperature, and was not further purified; $\delta_H(CDCl_3)$ 8.67, 8.34 (1 H, 2 br s, carbamate conformers, 7-H), 7.85 (1 H, dd, *J* 8.2 and 2.1, 5-H), 7.49 (1 H, d, *J* 8.2, 4-H), 4.48 (1 H, dd, *J* 10.5 and 5.4, $NCH_2CH$), 4.28 (1 H, dd, *J* 10.5 and 5.3, $NCH_2CH$), 4.22 (1 H, t, *J* 10.6, $NCH_2CH$), 3.82 (3 H, s, $CO_2Me$), 1.60 (9 H, s, Bu$^t$); *m*/*z* (DEI) 322.1162 (6%, $M^+$. $C_{15}H_{18}N_2O_5$ requires 322.1164), 57 (100).

A solution of this crude monoester **31** in tetrahydrofuran (100 ml) was added dropwise over 35 min to a solution of DIBALH (1 M solution in toluene; 42.4 ml, 42.4 mmol) in tetrahydrofuran (150 ml) under nitrogen at 0 °C. The yellow–orange solution was stirred at this temperature for 10 min, then poured into ice-cold aq. hydrochloric acid (0.5 M; 200 ml). Most of the tetrahydrofuran was evaporated and the residue was extracted with ethyl acetate. The extracts were washed with aq. NaCl, dried, and concentrated to a small volume from which the *alcohol* **32** (2.19 g, 70%) crystallised as a yellow–orange solid, mp 168.5–169 °C (Found: C, 57.2; H, 6.2; N, 9.5; $C_{14}H_{18}N_2O_5$ requires C, 57.1; H, 6.2; N, 9.5%). The mother liquor was evaporated and purified by chromatography (50% ethyl acetate–light petroleum) to give more of the alcohol **32** (0.52 g, 17%); $\delta_H(CDCl_3)$ 8.64, 8.31 (1 H, 2 br s, carbamate conformers, 7-H), 7.83 (1 H, dd, *J* 8.2 and 2.3, 5-H), 7.34 (1 H, d, *J* 8.2, 4-H), 4.16 (1 H, dd, *J* 11.4 and 10.3, $NCH_2$), 3.96 (1 H, dd, *J* 11.4 and 5.4, $NCH_2$), 3.84 (2 H, d, *J* 6.2, $CH_2OH$), 3.62–3.54 (1 H, m, 3-H), 1.91 (1 H, br s, OH), 1.59 (9 H, s, Bu$^t$); $\delta_C(CDCl_3)$ 152.0, 148.6, 144 (br), 139 (br) ($NCO_2$, 3a, 6, 7a-C), 124.6, 117.7, 109.7 (4, 5, 7-C), 81.7 ($OCMe_3$), 64.8 ($CH_2OH$), 51.3 (2-C), 41.8 (3-C), 28.3 (Bu$^t$).

**1-(*tert*-Butoxycarbonyl)-3-(chloromethyl)-6-nitroindoline 33**

Methanesulfonyl chloride (1.04 ml, 13.4 mmol) was added dropwise to a solution of the alcohol **32** (2.19 g, 7.44 mmol) and triethylamine (2.07 ml, 14.9 mmol) in dichloromethane (60 ml) at 0 °C, and the pale yellow solution stirred for 5 min. The mixture was diluted with water, extracted with dichloromethane, and the extracts were dried and evaporated. The crude methanesulfonate was dissolved in dimethylformamide (15 ml) with lithium chloride (1.26 g, 30 mmol) and the mixture was stirred at 80 °C under nitrogen for 40 min. The dimethylformamide was evaporated and the residue diluted with water. The mixture was extracted with ethyl acetate and the extracts were dried and evaporated. Chromatography (10% ethyl acetate–light petroleum) gave the *chloromethylindoline* **33** (2.14 g, 92%) as pale yellow foam, mp 111–111.5 °C (from benzene–light petroleum) (Found: C, 54.0; H, 5.5; N, 9.1; Cl, 11.5; $C_{14}H_{17}ClN_2O_4$ requires C, 53.8; H, 5.5; N, 9.0; Cl, 11.3%); $\delta_H(CDCl_3)$ 8.67, 8.34 (1 H, 2 br s, carbamate conformers, 7-H), 7.86 (1 H, dd, *J* 8.2 and 2.2, 5-H), 7.35 (1 H, d, *J* 8.2, 4-H), 4.22 (1 H, dd, *J* 11.6 and 9.6, $NCH_2$), 4.04–3.97 (1 H, m, $NCH_2$), 3.82–3.74 (2 H, m, $CHCH_2Cl$), 3.68–3.62 (1 H, m, $CH_2Cl$), 1.60 (9 H, s, Bu$^t$); $\delta_C(CDCl_3)$ 151.8, 149.0, 144 (br), 138 (br) ($NCO_2$, 3a, 6, 7a-C), 124.6, 117.8, 110.0 (4, 5, 7-C), 82.0 ($OCMe_3$), 52.4 (2-C), 46.3 ($CH_2Cl$), 41.7 (3-C), 28.4 (Bu$^t$).

**3-(Chloromethyl)-6-nitro-1-[(5,6,7-trimethoxyindol-2-yl)-carbonyl]indoline 34**

The chloromethylindoline **33** (2.38 g, 7.61 mmol) was stirred in HCl-saturated 1,4-dioxane (80 ml) at 20 °C for 2 h (until TLC indicated complete reaction) and the mixture was evaporated. EDCI·HCl (2.92 g, 15.2 mmol), 5,6,7-trimethoxyindole-2-carboxylic acid[20] (2.01 g, 8.0 mmol), and dry dimethylacetamide (25 ml) were added and the mixture was stirred at 20 °C. After 12 h the mixture was poured into aq. $NaHCO_3$ and the solid was filtered off and dried. Recrystallisation gave the *amide* **34** (2.53 g, 75%) as yellow prisms, mp 187–188 °C (from ethyl acetate) (Found: C, 56.8; H, 4.5; N, 9.3; Cl, 8.1; $C_{21}H_{20}ClN_3O_6$ requires C, 56.6; H, 4.5; N, 9.4; Cl, 7.95%). The mother liquor was evaporated and purified by chromatography (50% ethyl acetate–light petroleum) to give more amide **34** (0.25 g, 7%); $\delta_H(CDCl_3)$ 9.48 (1 H, s, NH), 9.08 (1 H, d, *J* 2.2, 7-H), 7.92 (1 H, dd, *J* 8.4 and 2.2, 5-H), 7.38 (1 H, d, *J* 8.4, 4-H), 6.94 (1 H, d, *J* 2.4, 3′-H), 6.81 (1 H, s, 4′-H), 4.73 (1 H, dd, *J* 10.5 and 9.6, $NCH_3$), 4.52 (1 H, dd, *J* 10.5 and 5.2, $NCH_2$), 4.07 (3 H, s, OMe), 4.02–3.95 (1 H, m, 3-H), 3.95 (3 H, s, OMe), 3.89 (3 H, s, OMe), 3.87 (1 H, dd, *J* 11.2 and 4.7, $CH_2Cl$), 3.71 (1 H, dd, *J* 11.2, and 8.1, $CH_2Cl$); $\delta_C(CDCl_3)$ 160.4 (NCO), 150.3, 148.7, 144.7, 140.7, 138.8, 137.7, 128.8, 125.8, 123.5 (aromatic C), 124.2, 119.5, 112.9, 106.9, 97.5 (aromatic CH), 61.4, 61.1, 56.2 (3 × OMe), 54.3 (2-C), 46.1 ($CH_2Cl$), 43.2 (3-C).

**Indoline 24 (prepared by the method of Scheme 3)**

A solution of the nitroindoline **34** (0.52 g, 1.17 mmol) in tetrahydrofuran (80 ml) with $PtO_2$ (0.11 g) was hydrogenated at 50 psi for 25 min. The catalyst was filtered off and the filtrate evaporated to give the aminoindoline **24** as a cream foam in quantitative yield, suitable ($^1$H NMR) for further reactions. Crystallisation from ethyl acetate gave a cream solid (0.45 g, 93%) identical to that described above.

**3-(Chloromethyl)-6-(hydroxyamino)-1-[(5,6,7-trimethoxyindol-2-yl)carbonyl]indoline 35**

A solution of the nitroindoline **34** (431 mg, 0.97 mmol) in dimethylformamide (50 ml) with $PtO_2$ (45 mg) was hydrogenated at 50 psi for 25 min, filtered through Celite and the filtrate evaporated. Chromatography (1% ethanol–chloroform) followed by trituration with dichloromethane–ethyl acetate gave the *hydroxylamine* **35** (159 mg, 38%) as a cream powder, mp 173–174 °C (decomp.) (Found: C, 58.4; H, 4.7; N, 10.1; $C_{21}H_{22}ClN_3O_5$ requires C, 58.4; H, 5.1; N, 9.7%); $\delta_H([^2H_6]DMSO)$ 11.37 (1 H, d, *J* 1.6, NH), 8.34 (2 H, s, NHOH), 7.73 (1 H, s, 7-H), 7.20 (1 H, d, *J* 8.1, 4-H), 6.99 (1 H, d, *J* 2.1, 3′-H), 6.96 (1 H, s, 4′-H), 6.58 (1 H, dd, *J* 8.1 and 2.0, 5-H), 4.58 (1 H, dd, *J* 10.8 and 8.9, $NCH_2$), 4.25 (1 H, dd, *J* 10.8 and 4.2, $NCH_2$), 3.97–3.93 (1 H, m, $CHCH_2Cl$), 3.92 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.79 (3 H, s, OMe), 3.80–3.74 (2 H, m, $CHCH_2Cl$); $\delta_C([^2H_6]DMSO)$ 160.0 (NCO), 152.6, 149.1, 143.9, 139.7, 139.0, 131.0, 125.1, 123.1, 122.6 (aromatic C), 124.3, 108.5, 105.7, 102.3, 98.0 (aromatic CH), 61.0, 60.9, 55.9 (3 × OMe), 54.5 (2-C), 47.8 ($CH_2Cl$), 41.7 (3-C).

**Methyl 3-methoxy-7-nitro-1-oxoisochromene-4-carboxylate 36**

A solution of the acid **27** (257 mg, 0.86 mmol), thionyl chloride (0.08 ml, 1.04 mmol) and dimethylformamide (1 drop) in 1,2-dichloroethane (10 ml) was stirred at reflux for 3 h, cooled and evaporated. The residue was dissolved in acetone (30 ml) at 0 °C, and a solution of sodium azide (0.17 g, 2.6 mmol) in water (5 ml) was added. After 15 min the precipitated solid was filtered off and dried, to give the *isochromene* **36** (115 mg, 48%), mp 170.5–172.5 °C (from ethyl acetate) (Found: C, 51.5; H, 2.9; N, 5.0; $C_{12}H_9NO_7$ requires C, 51.6; H, 3.25; N, 5.0%); $\delta_H([^2H_6]DMSO)$ 8.73 (1 H, d, *J* 2.5, 8-H), 8.53 (1 H, dd, *J* 9.3 and 2.5, 5-H), 8.19 (1 H, d, *J* 9.3, 6-H), 4.12 (3 H, s, OMe), 3.85 (3 H, s, OMe); $\delta_C([^2H_6]DMSO)$ 164.2, 162.1, 157.5, 144.1, 142.9, 116.1, 88.3 ($CO_2Me$, 1, 3, 4, 4a, 7, 8a-C), 129.3, 125.2, 124.8 (5, 6, 8-C), 57.5, 52.3 (2 × OMe).

**3-(Chloromethyl)-6-nitroindoline 40**

The indoline **33** (116 mg, 0.37 mmol) was stirred in HCl-saturated ethyl acetate (8 ml) for 1.5 h. The solvent was evapor-

ated and the residue diluted with water. The mixture was extracted with ethyl acetate and the extracts were dried and evaporated. Chromatography (20% ethyl acetate–light petroleum) gave the *nitroindoline* **40** (68 mg, 86%) as an orange solid, mp 123.5–124 °C (from benzene) (Found: C, 51.0; H, 4.2; N, 12.9; Cl, 16.7; $C_9H_9ClN_2O_2$ requires C, 50.8; H, 4.3; N, 13.2; Cl, 16.7%); $\delta_H(CDCl_3)$ 7.59 (1 H, dd, *J* 8.2 and 2.1, 5-H), 7.38 (1 H, d, *J* 2.1, 7-H), 7.24 (1 H, d, *J* 8.2, 4-H), 4.05 (1 H, br s, NH), 3.90–3.83 (1 H, m, $CH_2CHCH_2Cl$), 3.77–3.61 (4 H, m, $CH_2CHCH_2Cl$); $\delta_C(CDCl_3)$ 152.4, 149.1, 135.7 (3a, 6, 7a-C), 124.6, 114.1, 103.5 (4, 5, 7-C), 51.5 (2-C), 45.8 ($CH_2Cl$), 44.2 (3-C).

**6-Nitro-3-methylene-1-[(5,6,7-trimethoxyindol-2-yl)carbonyl]-indoline 41**

Sodium methoxide (0.54 M solution in methanol; 1.32 ml, 0.71 mmol) was added to a solution of the nitroindoline **34** (107 mg, 0.24 mmol) in dry tetrahydrofuran (5 ml) under nitrogen at 20 °C. The solution was stirred for 5 min, then diluted with water and ethyl acetate, which caused a solid to precipitate. After a few minutes the solid was filtered off, washed with ethyl acetate and dried to give the *methyleneindoline* **41** (63 mg, 64%) as a yellow solid, mp 216–218 °C (Found: C, 61.8; H, 4.45; N, 10.3; $C_{21}H_{19}N_3O_6$ requires C, 61.6; H, 4.7; N, 10.3%); $\delta_H([^2H_6]DMSO)$ 11.51 (1 H, s, NH), 9.06 (1 H, d, *J* 2.9, 7-H), 8.00 (1 H, dd, *J* 8.4 and 2.0, 5-H), 7.91 (1 H, d, *J* 8.4, 4-H), 7.19 (1 H, d, *J* 1.7, 3′-H), 6.92 (1 H, s, 4′-H), 5.96 (1 H, s, C=$CH_2$), 5.48 (1 H, s, C=$CH_2$), 5.26 (2 H, s, $NCH_2$), 3.93 (3 H, s, OMe), 3.81 (3 H, s, OMe), 3.80 (3 H, s, OMe); $\delta_C([^2H_6]DMSO)$ 160.1 (NCO), 149.2, 147.9, 145.9, 140.2, 139.4, 139.0, 135.9, 129.6, 125.7, 123.2 (aromatic C), 121.3, 119.4, 111.9, 107.2, 97.9 (aromatic CH), 108.0 (C=*C*$H_2$), 61.0, 60.9, 55.8 (3 × OMe), 55.3 (2-C).

**3-(Chloromethyl)-1-(methylsulfonyl)-6-(methylamino)indoline 42**

Freshly prepared acetic formic anhydride (0.20 ml, *ca*. 1.4 mmol) was added to a solution of the aminoindoline **18** (77 mg, 0.30 mmol) in dry tetrahydrofuran (6 ml) under nitrogen at 0 °C and the mixture stirred at this temperature for 5 min (when TLC indicated complete formylation). The mixture was evaporated and the residue redissolved in dry tetrahydrofuran (10 ml) under nitrogen. Borane–dimethyl sulfide (2 M solution in tetrahydrofuran; 0.38 ml, 0.75 mmol) was added and the mixture stirred at reflux for 1 h, then cooled to 20 °C. Methanol (3 ml) then hydrochloric acid (2 M; 8 ml) were added slowly and the mixture stirred at reflux for a further 30 min, cooled and evaporated. The residue was diluted with aq. $NaHCO_3$ (until alkaline), extracted with ethyl acetate, and the extracts were dried and evaporated. Chromatography (30% ethyl acetate–light petroleum) gave the *methylaminoindoline* **42** (62 mg, 76%) as a colourless oil, mp 104.5–106 °C (from benzene–light petroleum) (Found: C, 47.9; H, 5.6; N, 10.35; S, 11.85; $C_{11}H_{15}ClN_2O_2S$ requires C, 48.05; H, 5.5; N, 10.2; S, 11.7%); $\delta_H(CDCl_3)$ 7.03 (1 H, d, *J* 8.2, 4-H), 6.70 (1 H, d, *J* 2.1, 7-H), 6.29 (1 H, dd, *J* 8.2 and 2.1, 5-H), 4.04 (1 H, dd, *J* 10.8 and 8.7, $CH_2N$), 3.94 (1 H, dd, *J* 10.8 and 4.6, $CH_2N$), 3.88 (1 H, br s, NH), 3.71 (1 H, dd, *J* 10.4 and 4.1, $CH_2Cl$), 3.67–3.61 (1 H, m, 3-H), 3.54 (1 H, dd, *J* 10.4 and 8.2, $CH_2Cl$), 2.90 (3 H, s, Me), 2.83 (3 H, s, Me); $\delta_C(CDCl_3)$ 150.8, 143.3, 118.8 (3a, 6, 7a-C), 125.5, 107.4, 97.9 (4, 5, 7-C), 54.7 (2-C), 47.0 ($CH_2Cl$), 42.0 (3-C), 34.5 ($SO_2Me$), 30.8 (NHMe).

**3-(Chloromethyl)-6-(methylamino)-1-[(5,6,7-trimethoxyindol-2-yl)carbonyl]indoline 43**

The aminoindoline **24** was converted to the *methylaminoindoline* **43** (62%) by the method described for the preparation of **42**. Crystallisation gave a pale yellow powder, mp 165–166 °C (decomp.) (from benzene–light petroleum) (Found: C, 61.3; H, 5.5; N, 9.9; $C_{22}H_{24}ClN_3O_4$ requires C, 61.5; H, 5.6; N, 9.8%); $\delta_H(CDCl_3)$ 9.48 (1 H, s, NH), 7.70 (1 H, d, *J* 2.2, 7-H), 7.05 (1 H, d, *J* 8.1, 4-H), 6.95 (1 H, d, *J* 2.4, 3′-H), 6.86 (1 H, s, 4′-H), 6.34 (1 H, dd, *J* 8.1 and 2.2, 5-H), 4.62–4.55 (1 H, m, $NCH_2$), 4.43 (1 H, dd, *J* 10.6 and 4.1, $NCH_2$), 4.06 (3 H, s, OMe), 3.94 (3 H, s, OMe), 3.91 (3 H, s, OMe), 3.80–3.70 (2 H, m, $CHCH_2Cl$), 3.53–3.45 (1 H, m, $CHCH_2Cl$), 2.86 (3 H, s, NH*Me*); $\delta_C(CDCl_3)$ 160.1 (NCO), 150.4, 150.1, 144.7, 140.4, 138.8, 130.1, 125.4, 123.6, 119.6 (aromatic C), 124.5, 108.2, 106.3, 102.3, 97.7 (aromatic CH), 61.5, 61.1, 56.2 (3 × OMe), 54.8 (2-C), 47.4 ($CH_2Cl$), 43.2 (2-C), 30.9 (NHMe).

**3-(Chloromethyl)-6-(dimethylamino)-1-(methylsulfonyl)indoline 44**

Sodium cyanoborohydride (44 mg, 0.70 mmol) then hydrochloric acid (2 M; 0.5 ml) were added to a solution of the aminoindoline **18** (70 mg, 0.27 mmol) and formaldehyde (40% w/w aq. solution; 0.20 ml, 2.7 mmol) in methanol (3 ml) and the pale yellow solution was stirred at 20 °C for 20 min. The mixture was diluted with water, extracted with dichloromethane and the extracts were dried and evaporated. Chromatography (30% ethyl acetate–light petroleum) gave the *dimethylaminoindoline* **44** (65 mg, 84%) as a colourless oil, mp 102–103 °C (from diethyl ether–light petroleum) (Found: C, 49.85; H, 6.0; N, 9.7; $C_{12}H_{17}ClN_2O_2S$ requires C, 49.9; H, 5.9; N, 9.70%); $\delta_H(CDCl_3)$ 7.07 (1 H, d, *J* 8.4, 4-H), 6.82 (1 H, d, *J* 2.4, 7-H), 6.40 (1 H, dd, *J* 8.4 and 2.4, 5-H), 4.04 (1 H, dd, *J* 10.9 and 8.8, $NCH_2$), 3.94 (1 H, dd, *J* 10.9 and 4.7, $NCH_2$), 3.72 (1 H, dd, *J* 10.4 and 4.1, $CH_2Cl$), 3.69–3.61 (1 H, m, 3-H), 3.54 (1 H, dd, *J* 10.4 and 8.2, $CH_2Cl$), 2.96 (6 H, s, $NMe_2$), 2.90 (3 H, s, $SO_2Me$); $\delta_C(CDCl_3)$ 151.8, 143.4, 118.0 (3a, 6, 7a-C), 125.2, 107.7, 97.8 (4, 5, 7-C), 54.8 (2-C), 47.0 ($CH_2Cl$), 41.9 (3-C), 40.7 ($NMe_2$), 34.4 ($SO_2Me$).

**3-(Chloromethyl)-6-(dimethylamino)-1-[(5,6,7-trimethoxyindol-2-yl)carbonyl]indoline 45**

The aminoindoline **24** was converted to the *dimethylaminoindoline* **45** (64%) by the method described for **44**. Crystallisation gave a cream powder, mp 169–171 °C (from diethyl ether–ethyl acetate) (Found: C, 62.3; H, 5.8; N, 9.3; Cl, 7.8; $C_{23}H_{26}ClN_3O_4$ requires C, 62.2; H, 5.9; N, 9.5; Cl, 8.0%); $\delta_C(CDCl_3)$ 9.46 (1 H, s, NH), 7.86 (1 H, d, *J* 2.2, 7-H), 7.10 (1 H, d, *J* 8.4, 4-H), 6.95 (1 H, d, *J* 2.2, 3′-H), 6.87 (1 H, s, 4′-H), 6.46 (1 H, dd, *J* 8.4 and 2.4, 5-H), 4.63–4.56 (1 H, m, $NCH_2$), 4.44 (1 H, dd, *J* 10.7 and 4.1, $NCH_2$), 4.06 (3 H, s, OMe), 3.94 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.81–3.72 (2 H, m, $CHCH_2Cl$), 3.53–3.46 (1 H, m, $CHCH_2Cl$), 2.99 (6 H, s, $NMe_2$); $\delta_C(CDCl_3)$ 160.1 (NCO), 151.5, 150.0, 144.8, 140.4, 138.8, 130.1, 125.4, 123.6, 118.8 (aromatic C), 124.3, 108.5, 106.3, 102.4, 97.7 (aromatic CH), 61.4, 61.1, 56.2 (3 × OMe), 54.8 (2-C), 47.4 ($CH_2Cl$), 43.1 (3-C), 40.8 ($NMe_2$).

**3-(Chloromethyl)-6-[(4-nitrobenzyloxycarbonyl)amino]-1-[(5,6,7-trimethoxyindol-2-yl)carbonyl]indoline 46**

4-Nitrobenzyl chloroformate (27 mg, 1.7 mmol) was added to a solution of the aminoindoline **24** (30 mg, 0.07 mmol) in tetrahydrofuran (4 ml) at 0 °C, and the mixture stirred at this temperature for 30 min. The mixture was diluted with water, extracted with ethyl acetate and the extracts were dried and evaporated. Chromatography (50% ethyl acetate–light petroleum) gave a pale yellow oil that was dissolved in chloroform (1 ml) and triturated with diethyl ether (6 ml) to give **46** (33 mg, 77%) as a pale yellow powder, mp 199–200 °C (Found: C, 58.4; H, 4.3; N, 9.3; $C_{29}H_{27}ClN_4O_8$ requires C, 58.5; H, 4.6; N, 9.4%); $\delta_H([^2H_6]DMSO)$ 11.43 (1 H, s, NH), 9.97 (1 H, s, NH), 8.35 (1 H, br s, 7-H), 8.28 (2 H, br d, *J* 8.8, 3″, 5″-H), 7.70 (2 H, br d, *J* 8.8, 2″, 6″-H), 7.34 (1 H, d, *J* 8.2, 4-H), 7.24 (1 H, dd, *J* 8.2 and 1.8, 5-H), 7.02 (1 H, d, *J* 2.0, 3′-H), 6.96 (1 H, s, 4′-H), 5.30 (2 H, s, $OCH_2Ar$), 4.63 (1 H, dd, *J* 10.8 and 8.7, $NCH_2$), 4.28 (1 H, dd, *J* 10.8 and 4.5, $NCH_2$), 4.02–3.95 (1 H, m, $CH_2Cl$), 3.92 (3 H, s, OMe), 3.86–3.76 (2 H, m, $CHCH_2Cl$), 3.81 (3 H, s, OMe), 3.79 (3 H, s, OMe).

**3-(Chloromethyl)-6-hydroxy-1-(methylsulfonyl)indoline 47**
The aminoindoline **18** (48 mg, 0.18 mmol) was stirred in warm sulfuric acid (33%; 2 ml) and the pale yellow solution cooled in an ice bath, giving a white precipitate. A solution of sodium nitrite (15 mg, 0.22 mmol) in water (1.5 ml) was added dropwise and the yellow solution stirred at 0 °C for 20 min. Urea (10 mg, 0.17 mmol) and toluene (4 ml) were added and the mixture was stirred at reflux for 15 min, cooled and diluted with water. The mixture was extracted with ethyl acetate, the extracts were dried and evaporated, and the residue was purified by chromatography (30% ethyl acetate–light petroleum ether) to give the phenol **47** (25 mg, 52%) as a colourless oil, mp 121.5–122.5 °C (from benzene–light petroleum) (Found: C, 46.0; H, 4.7; N, 5.35; Cl, 13.7; $C_{10}H_{12}ClNO_3S$ requires C, 45.9; H, 4.6; N, 5.35; Cl, 13.55%); $^1$H NMR spectrum identical to that reported.[3]

**3-(Chloromethyl)-6-hydroxy-1-(methylsulfonyl)-5-nitroindoline 48**
The aminoindoline **18** (50 mg, 0.19 mmol) was converted to a diazonium solution as described for the preparation of phenol **47**. A cold solution of copper(II) nitrate trihydrate (0.74 g, 3.1 mmol) in water (7 ml) was added, followed by copper(I) oxide (25 mg, 0.18 mmol). The mixture was stirred vigorously at 0 °C for 5 min then extracted with ethyl acetate. The extracts were dried and evaporated to give the nitrophenol **48** (17 mg, 29%) as a yellow solid, mp 159–160.5 °C (from benzene) [lit.,[3] mp 133–135 °C (from dichloromethane)]. $^1$H NMR spectrum identical to that reported.[3] As the mp did not match the reported value, the literature preparation of **48** by nitration of the phenol **47** was repeated, giving pale yellow needles, mp 160–161 °C (from dichloromethane), 159–162 °C (from benzene).

**1-[3-(Chloromethyl)-1-(methylsulfonyl)indolin-6-yl]-3,3-diethyltriazene 49**
The aminoindoline **18** (107 mg, 0.41 mmol) was stirred in warm hydrochloric acid (50%; 3 ml, 18 mmol) then cooled in an ice bath. A solution of sodium nitrite (31 mg, 0.45 mmol) in water (1 ml) was added dropwise and the yellow mixture stirred at 0 °C for 20 min. The mixture was added dropwise to a vigorously stirred ice-cold solution of potassium carbonate (1.2 g, 9 mmol) and diethylamine (1.0 ml, 9.7 mmol) in water (2 ml). Ethyl acetate was added, and after 10 min the ethyl acetate layer was separated, dried and evaporated. Chromatography (30% ethyl acetate–light petroleum) gave the *triazene* **49** (128 mg, 90%) as a pale yellow oil, mp 97–98 °C (from methanol) (Found: C, 48.6; H, 6.3; N, 16.2; S, 9.4; $C_{14}H_{21}ClN_4O_2S$ requires C, 48.8; H, 6.1; N, 16.25; S, 9.3%); $\delta_H(CDCl_3)$ 7.49 (1 H, d, *J* 1.7, 7-H), 7.17 (1 H, d, *J* 8.1, 4-H), 7.12 (1 H, dd, *J* 8.1 and 1.7, 5-H), 4.13–4.07 (1 H, m, 2-H), 3.98 (1 H, dd, *J* 10.8 and 4.8, 2-H), 3.80–3.69 (6 H, m, $NCH_2CH_3$ and 2 H of $CHCH_2Cl$), 3.64–3.58 (1 H, m, $CHCH_2Cl$), 2.93 (3 H, s, $NSO_2Me$), 1.26 (6 H, t, *J* 7.1, $NCH_2CH_3$); $\delta_C(CDCl_3)$ 152.9, 142.8, 126.9 (3a, 6, 7a-C), 125.0, 116.4, 105.6 (4, 5, 7-C), 54.5 (2-C), 48.7 ($NCH_2CH_3$), 46.6 ($CH_2Cl$), 42.2 (3-C), 34.6 ($SO_2Me$), 14.2 ($NCH_2CH_3$).

**Potassium *O*-[2-(trimethylsilyl)ethyl] dithiocarbonate**
2-(Trimethylsilyl)ethanol (10.6 ml, 74 mmol) and carbon disulfide (3.7 ml, 62 mmol) were added to a vigorously stirred suspension of powdered potassium hydroxide (3.46 g, 62 mmol) in light petroleum (150 ml), immediately giving a yellow precipitate. After 5 h the solid was filtered off, washed with light petroleum and dissolved in acetone (500 ml). The solution was dried, concentrated to *ca*. 40 ml and allowed to stand. The product precipitated as pale yellow flakes (6.73 g, 47%) (Found: C, 31.4; H, 5.4; $C_6H_{13}KOS_2Si$ requires C, 31.0; H, 5.65); $\delta_H([^2H_6]DMSO)$ 4.25–4.31 (2 H, m, $OCH_2$), 0.99–0.93 (2 H, m, $SiCH_2$), 0.02 (9 H, s, $SiMe_3$).

**3-(Chloromethyl)-6-mercapto-1-(methylsulfonyl)indoline 51 and bis[3-(chloromethyl)-1-(methylsulfonyl)indolin-6-yl] disulfide 52**
A mixture of the aminoindoline **18** (0.90 g, 3.45 mmol) and hydrochloric acid (2 M; 4.3 ml, 8.6 mmol) was stirred at 50 °C for 5 min then cooled in an ice bath. A solution of sodium nitrite (0.25 g, 3.6 mmol) in water (3 ml) was added dropwise to the resulting pale yellow paste, giving an orange–brown mixture that was stirred at 0 °C for 20 min. This diazonium salt preparation was added dropwise to a solution of potassium *O*-[2-(trimethylsilyl)ethyl] dithiocarbonate (1.61 g, 6.9 mmol) in water (40 ml) stirred vigorously with toluene (40 ml) at 50 °C. The mixture was stirred at this temperature for a further 15 min, cooled, diluted with aq. NaCl, and extracted with ethyl acetate. The extracts were washed with water, dried, and evaporated. Chromatography (20% ethyl acetate–light petroleum) gave crude *S*-[3-(chloromethyl)-1-(methylsulfonyl)indolin-6-yl] *O*-[(2-trimethylsilyl)ethyl] dithiocarbonate **50** that was used directly in the next step. TBAF (1 M solution in tetrahydrofuran; 2.47 ml, 2.47 mmol) was added to a solution of this crude dithiocarbonate in tetrahydrofuran (40 ml) under nitrogen, immediately giving a yellow–orange colour that became green within a few minutes and faded slowly. After 15 min hydrochloric acid (2 M; 2 ml) was added giving a colourless solution which was diluted with aq. NaCl and extracted with ethyl acetate. The extracts were dried and evaporated and the residue was separated by chromatography (20% ethyl acetate–light petroleum) giving the *indolinethiol* **51** (95 mg, 10%) as a colourless oil, mp 91–93 °C (from diethyl ether–light petroleum) (Found: C, 44.15; H, 4.45; N, 4.8; S, 22.7; $C_{10}H_{12}ClNO_2S_2 \cdot \frac{1}{8}Et_2O$ requires C, 43.9; H, 4.65; N, 4.9; S, 22.3%); $\delta_H(CDCl_3)$ 7.35 (1 H, d, *J* 1.6, 7-H), 7.10 (1 H, d, *J* 7.9, 4-H), 6.95 (1 H, dd, *J* 7.9 and 1.6, 5-H), 4.09 (1 H, dd, *J* 10.9 and 9.3, $NCH_2$), 3.96 (1 H, dd, *J* 10.9 and 4.9, $NCH_2$), 3.76–3.68 (2 H, m, $CHCH_2Cl$), 3.66–3.58 (1 H, m, $CHCH_2Cl$), 3.55 (1 H, s, SH), 2.93 (3 H, s, $SO_2Me$); $\delta_C(CDCl_3)$ 142.9, 132.9, 128.1 (3a, 6, 7a-C), 125.4, 124.1, 113.9 (4, 5, 7-C), 54.1 (2-C), 46.3 ($CH_2Cl$), 41.9 (3-C), 35.0 ($SO_2Me$); *m/z* (DEI, $^{35}$Cl) 276.9990 (40%, $M^+$. $C_{10}H_{12}ClNO_2S_2$ requires 276.9998), 228 (100, $M - CH_2Cl$).

Further elution (30% ethyl acetate–light petroleum) gave the *disulfide* **52** (137 mg, 14%) as a colourless oil, mp 180–182 °C (decomp.) (from ethyl acetate) (Found: C, 43.7; H, 3.9; N, 4.9; S, 23.25; $C_{20}H_{22}Cl_2N_2O_4S_4$ requires C, 43.4; H, 4.0; N, 5.1; S, 23.2%); $\delta_H(CDCl_3)$ 7.56 (1 H, d, *J* 1.5, 7-H), 7.21 (1 H, dd, *J* 7.9 and 1.5, 5-H), 7.18 (1 H, d, *J* 7.9, 4-H), 4.09 (1 H, dd, *J* 10.9 and 8.9, $NCH_2$), 3.95 (1 H, dd, *J* 10.9 and 4.9, $NCH_2$), 3.78–3.70 (2 H, m, $CHCH_2Cl$), 3.66–3.59 (1 H, m, $CHCH_2Cl$), 2.89 (3 H, s, $SO_2Me$); $\delta_C(CDCl_3)$ 143.1, 138.6, 130.2 (3a, 6, 7a-C), 125.4, 123.1, 112.6 (4, 5, 7-C), 54.1 (2-C), 46.2 ($CH_2Cl$), 42.0 (3-C), 35.1 ($SO_2Me$).

**3-(Chloromethyl)-1-(methylsulfonyl)-6-(methylthio)indoline 53**
A mixture of the indolinethiol **51** (77 mg, 0.28 mmol), methyl iodide (19 μl, 0.30 mmol) and $NaHCO_3$ (26 mg, 0.30 mmol) in ethyl acetate (2 ml) and methanol (2 ml) was stirred at 20 °C for 20 h. The methanol was evaporated, the residue was diluted with water, extracted with ethyl acetate and the extracts were dried and evaporated. Chromatography (10% ethyl acetate–light petroleum) gave the *methylthioindoline* **53** (68 mg, 84%) as a colourless oil, mp 93–94.5 °C (from diethyl ether–light petroleum) (Found: C, 45.3; H, 5.1; N, 4.5; $C_{11}H_{14}ClNO_2S_2$ requires C, 45.3; H, 4.8; N, 4.8%); $\delta_H(CDCl_3)$ 7.34 (1 H, d, *J* 1.6, 7-H), 7.15 (1 H, d, *J* 8.0, 4-H), 6.94 (1 H, dd, *J* 8.0 and 1.6, 5-H), 4.10 (1 H, dd, *J* 10.9 and 9.2, $NCH_2$), 3.97 (1 H, dd, *J* 10.9 and 4.9, $NCH_2$), 3.77–3.69 (2 H, m, $CHCH_2Cl$), 3.65–3.58 (1 H, m, $CHCH_2Cl$), 2.92 (3 H, s, $SO_2Me$), 2.49 (3 H, s, SMe); $\delta_C(CDCl_3)$ 142.8, 140.7, 127.4 (3a, 6, 7a-C), 125.1, 121.5, 111.1 (4, 5, 7-C), 54.2 (2-C), 46.4 ($CH_2Cl$), 42.0 (3-C), 34.9 ($SO_2Me$), 15.7 (SMe).

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