Tandem Michael Addition–[3,3]Sigmatropic Rearrangement Processes. Part 2.[1] Construction of Cyclopropa[3,4]pyrrolo[3,2-*e*]indol-4-one (CPI) Unit of Antitumour Antibiotic CC-1065

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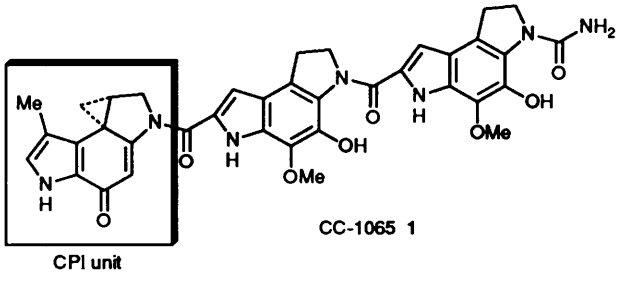
Development of an alternative strategy for preparing 3-acetoxymethyl-2,3-dihydro-1-methylsulfonyl-6-methoxyindole **25** has been completed. Since **25** was an intermediate in a previous synthesis of the CPI unit **5** of the antitumour antibiotic CC-1065 **1**, this achievement constitutes a formal synthesis of the racemic compound **5**. The key strategic element of the approach involves the tandem Michael addition–[3,3]sigmatropic rearrangement process of methyl propiolate **10** and benzyl *N*-hydroxy-*N*-(3-methoxyphenyl)carbamate **9**, prepared from *m*-nitroanisole **19**, to furnish indole **8** as the sole product. Subsequent elaboration of compound **8** into indoline **25** was then achieved by applying Cava's technique. The conversion of **25** into **5** was also demonstrated on the basis of the well-established Wierenga's procedure.

CC-1065 **1** is an antitumour antibiotic agent that was isolated in trace quantities from culture of *Streptomyces zelensis* in 1978 by workers at The Upjohn Company.[2a,†] The unique structure of **1**, determined by single-crystal X-ray analysis,[3] was shown to consist of two identical substituted 1,2-dihydropyrrolo[3,2-*e*]indole central and right-hand segments and the third similar pyrrolo[3,2-*e*]indole left-hand unit bearing the unusual spirobicyclo[5.2.0]octa-2,5-dien-4-one moiety (Scheme 1).



Scheme 1

Naturally occurring **1** possesses exceptionally potent *in vitro* cytotoxic activity,[4] broad spectrum antimicrobial activity,[2] and potent *in vivo* antitumour activity against a variety of implanted murine tumours.[5] As compared to other antineoplastic agents, **1** is about 400 times more potent than adriamycin,[6] 80 times more potent than actinomycin D and about twice as potent as maytansine[7] against L1210 leukemia cells *in vitro*.

The molecular mechanism of action of **1** has been shown to proceed with minor groove adenine alkylation by the electrophilic cyclopropa[3,4]pyrrolo[3,2-*e*]indol-4-one present in the left-hand segment (CPI) of **1** and this fact indicates that CC-1065 serves to covalently anchor the agent to DNA (Scheme 2).

Given its intricate architecture coupled with its strong antitumour activity, it is not surprising that **1** and its CPI unit have been subject to a number of synthetic investigations.[8] Since the cyclopropa[3,4]pyrrolo[3,2-*e*]indol-4-one (CPI) unit of natural **1** is essential for antitumour activity, our current goal was to synthesize the CPI unit **5** of CC-1065 **1**.

† The antibiotic rachelmycin, isolated from *Streptomyces* strain C-329, has been shown to be identical with CC-1065.[2b]

Results and Discussion

Our synthetic strategy based upon the synthetic analysis is shown below. Namely, reduction of the indole **8**, obtained *via* a novel tandem Michael addition–[3,3]sigmatropic rearrangement of the phenylhydroxylamine **9** and methyl propiolate **10**, followed by regioselective introduction of an amino group would give the indole **7**, which could be transformed into the bromide **6**, convertible into the desired mesylate **5** (Scheme 3).

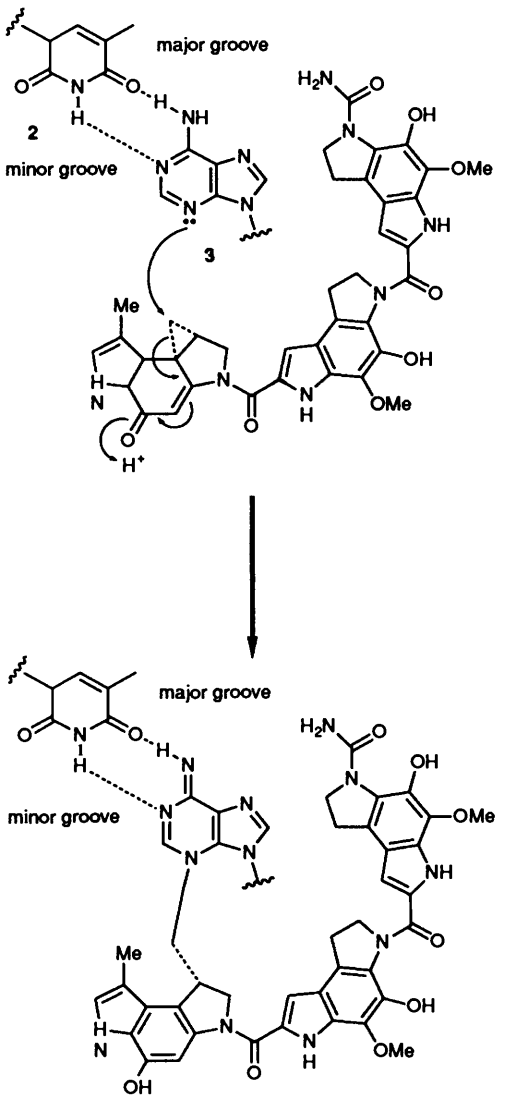
In order to explore the feasibility of the designed synthetic strategy, the novel tandem Michael addition–[3,3]sigmatropic rearrangement of the phenylhydroxylanime **11**, the model compound of **9**, was first examined. The requisite compound **11** could be readily prepared using an established method.[9] With compound **11** in hand, the crucial tandem Michael addition–[3,3]sigmatropic rearrangement reaction was attempted under a variety of conditions. Some of the conditions and yields examined for cyclization of **11** and **10** are listed in Table 1 (Scheme 4). The best result, 89% yield, was obtained for the reaction using nitromethane as solvent in the presence of Hünig's base.

Being encouraged by this result, the tandem Michael addition–[3,3]sigmatropic rearrangement reaction was next examined employing **9** which bears a methoxy group at the *meta* position, to explore the regioselectivity of the [3,3]sigmatropic shifts.

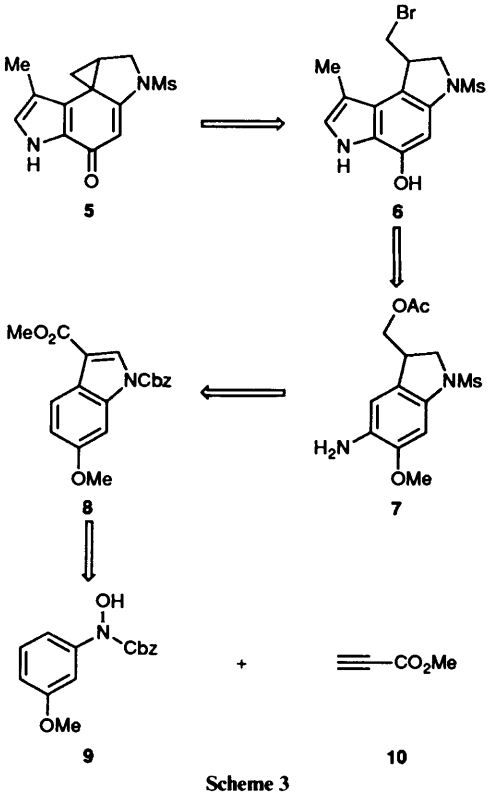
As summarized in Table 1, the reaction was found to proceed in a highly regioselective manner, affording the indole **8** in 66% yield. The structure of **12** and **8** could be readily determined by their spectral data.

As the most plausible mechanism[9] that accounts for the observation, we propose the tandem Michael addition–[3.3]-sigmatropic rearrangement shown in Fig. 1. The first step of the novel reaction can be rationalized in term of [3,3]sigmatropic shifts of the Michael adduct **13**. The resulting rearranged intermediate **14** is transformed into **15** by intramolecular addition of the nitrogen atom of imino group to the formyl group. The unstable α-hydroxylamine **15** is smoothly converted into the indole **12** or **8** by dehydroxylation followed by migration of hydrogen (Fig. 1).

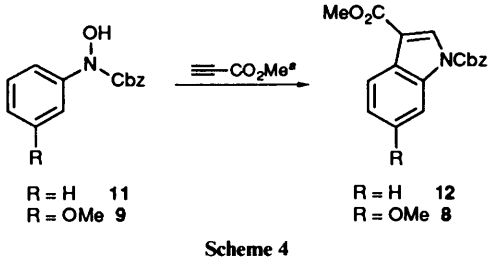
The regioselectivity of the [3,3]sigmatropic process in the intermediate **13** can be rationalized by considering the transition states **17** and **18**. The steric congestion in the transition state **18** makes it less favourable than the alternative



Scheme 2



Scheme 3



Scheme 4

transition state **17** which gives rise to the desired product **8** (Scheme 5).

Since the novel tandem Michael addition–[3.3]sigmatropic rearrangement of the phenylhydroxylamine **9** and methyl propiolate **10** with a reasonable degree of efficiency and regioselectivity has been developed, the elaboration of **8** into the intermediate **25** emerged as an attractive option.

Removal of the protecting group of compound **8** in the presence of 10% palladium–charcoal led quantitatively to the indole **20**. All attempts to reduce the 2,3-double bond in **20** were unsuccessful; * only starting material was recovered unchanged.

We then decided to attempt the transformation of the functional group at the C-3 position of **20** into a cyanomethyl moiety prior to reducing the pyrrole part of the indole nucleus, since conversion of the indole derivative with a cyanomethyl moiety at the C-3 position such as **22** into an indoline derivative has been well investigated in previous synthetic studies on CC-1065 1.[10] Reduction of the ester **20** with diisobutylaluminium hydride (DIBAL) in tetrahydrofuran (THF) gave the alcohol **21**, which was treated with sodium cyanide in refluxing ethanol to afford the nitrile **22** in 96% yield from **20**. Hydrolysis of the cyano group in **22** with potassium hydroxide in hot ethanol followed by acidic treatment (absolute methanol–camphor-10-sulfonic acid) gave rise to the indoleacetate **23** in 98% yield. The indole **23** was smoothly reduced with sodium cyanoborohydride in acetic acid,[11] followed by immediate protection with methanesulfonyl chloride to give the 1-mesylindoline **24** in 98% yield from **23**. The ester **24** was hydrolysed (5% sodium hydroxide–methanol, 55 °C) to the free acid, which was

Table 1 Conditions and yields of formation of the indole derivatives[b]

Entry	R	Base	Solvent	Yield (%)
1	H	Et_3N	C_6H_6	25
2	H	NMM[c]	C_6H_6	31
3	H	Pr^i_2NEt	C_6H_6	65
4	H	Pr^i_2NEt	CH_2Cl_2	66
5	H	Pr^i_2NEt	MeCN	78
6	H	Pr^i_2NEt	$MeNO_2$	89
7	OMe	Pr^i_2NEt	MeCN	trace
8	OMe	Pr^i_2NEt	$MeNO_2$	2
9	OMe	Et_3N	C_6H_6	31
10	OMe	NMM	C_6H_6	46
11	OMe	NMM	$CHCl_3$	60
12	OMe	NMM	CH_2Cl_2	66[d]

[a] 2.0 Equiv. of methyl propiolate was used. [b] All reactions were carried out under an atmosphere of argon. [c] *N*-Methylmorpholine. [d] Not optimized.

* Indole **9** was inert to $NaBH_4$ AcOH, $NaBCNH_3$ AcOH, Zn AcOH and $Et_3SiH \cdot CF_3CO_2H$.

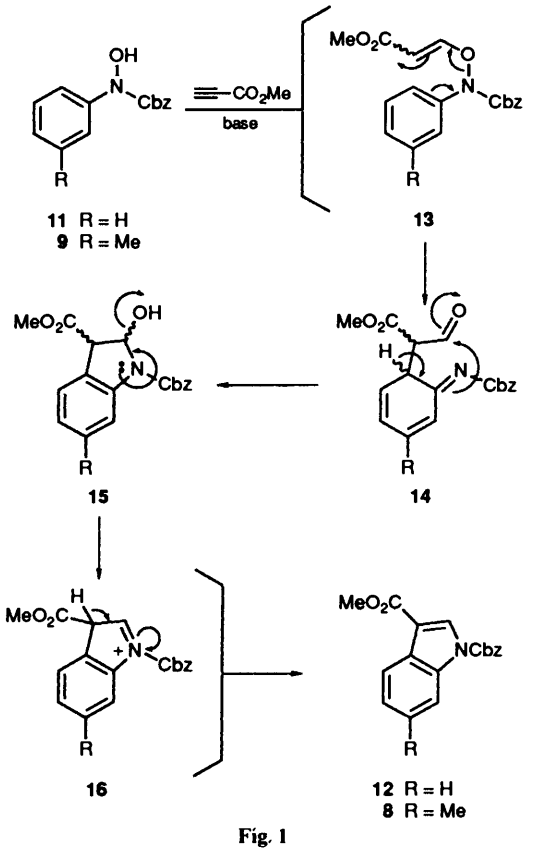
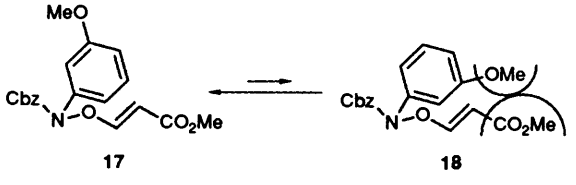


Fig. 1

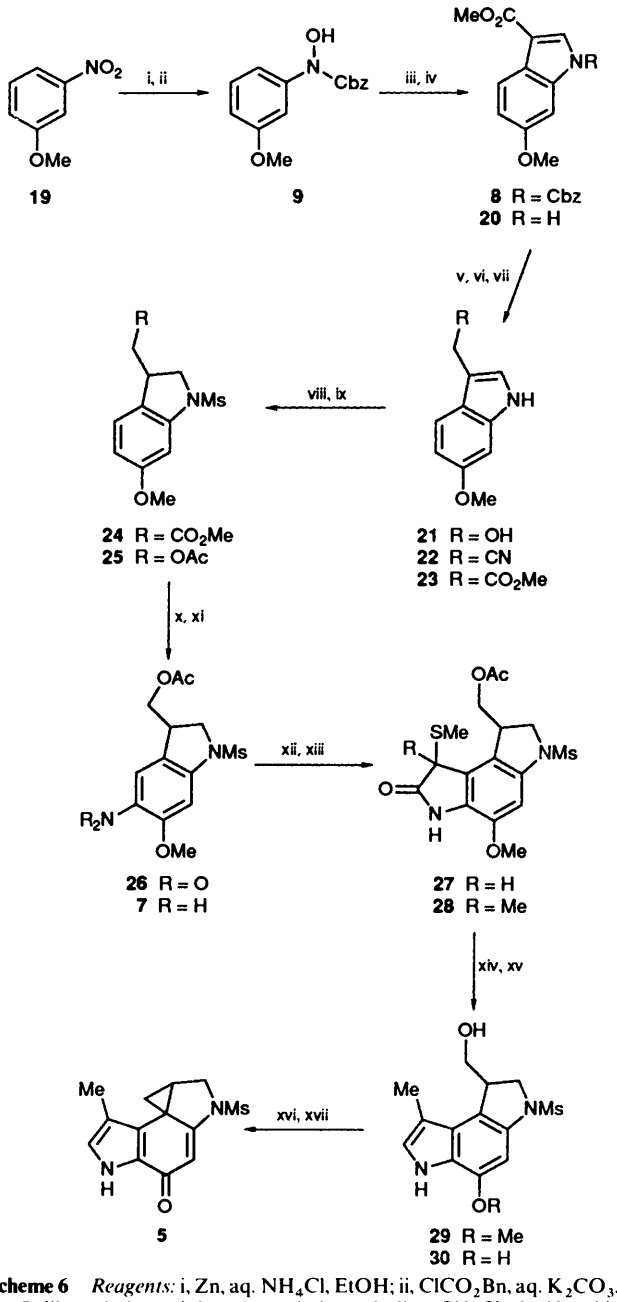


Scheme 5

converted into the corresponding acid chloride (oxalyl chloride–benzene–dimethylformamide, room temp.), and then subjected to a Barton reaction carried out using the sodium salt of 2-mercaptopyridine *N*-oxide, 4-dimethylaminopyridine (DMAP), and carbon tetrabromide. After treatment of the resulted bromide with mercuric acetate in acetic acid, the acetate **25** was obtained in 82% yield from **24**. Nitration of **25** with fuming nitric acid occurred at the C-5 position to afford the nitro compound **26**, which was reduced to the aminoindole **7**.

A modification of the oxindole synthesis of Gassman[12] was employed to introduce the third ring. Addition of **7** to the chloride complex of ethyl methylthioacetate at −78 °C in the presence of Proton Sponge® followed by a triethylamine catalysed Sommelet–Hauser type [2.3]sigmatropic rearrangement and an acid-induced cyclization gave the tricyclic compound **27** in 87% yield as a 5:1 diastereoisomeric mixture. Methylation of **27** with methyl iodide in the presence of potassium carbonate at room temperature afforded, in 87% yield, a diastereoisomeric mixture (2:1) of the methylated tricyclic compound **28** which could be separated by silica gel column chromatography.

Our synthetic efforts were next focused on the reductive pyrrole ring formation and subsequent Winstein cyclization reaction. Treatment of **28** with an excess of borane-dimethyl sulfide complex[13] gave, in 89% yield, the crude alcohol **29**, which was subjected to cleavage of the methoxy group with



Scheme 6 *Reagents:* i, Zn, aq. NH_4Cl, EtOH; ii, $ClCO_2Bn$, aq. K_2CO_3, Et_2O; iii, methyl propiolate, *N*-methylmorpholine, CH_2Cl_2; iv, H_2, 10% Pd–C, EtOAc; v, DIBAL, THF; vi, NaCN, EtOH; vii, KOH, aq. EtOH then MeOH, CSA; viii, $NaBH_3CN$, AcOH then MsCl, Py; ix, KOH, aq. EtOH; $(COCl)_2$, C_6H_6, DMF; CBr_4, 2-mercaptopyridine *N*-oxide sodium salt, C_6H_6, $Hg(OAc)_2$, AcOH; x, HNO_3, MeCN; xi, H_2, PtO_2, EtOAc; xii, ethyl methylthioacetate, SO_2Cl_2, CH_2Cl_2; Proton Sponge®, **7**, CH_2Cl_2; Et_3N; AcOH; xiii, MeI, K_2CO_3, Me_2CO, DMF; xiv, $BH_3{\cdot}SMe_2$, THF; xv, BuSLi, HMPA; xvi, CBr_4, PPh_3, MeCN; xvii Pr^i_2NEt, CH_2Cl_2

mercaptide anion[14] in hexamethylphosphoramide to afford in 88% yield the phenolic alcohol **30**. Bromination of this alcohol **30** with carbon tetrabromide and triphenylphosphine furnished the crude bromide in 78% yield. Finally, formation of the cyclopropadienone system was achieved by treatment of the crude bromide with Hünig's base to give rise to the CPI unit **5** of CC-1065 **1** in 73% yield.

The NMR, IR and mass spectra of the synthetic material matched precisely those available from the literature[13] (Scheme 6).

In summary, the novel synthesis of the CPI unit **5** of the antitumour antibiotic CC-1065 **1** using a tandem Michael

addition–[3.3]sigmatropic rearrangement as a key step has been accomplished. The synthesis is achieved by modifying various literature procedures and allows preparation of the CPI unit **5** starting from commercially available *m*-nitroanisole **19**.

Experimental

General Method.—M.p.s are uncorrected and were measured on Yanako micromelting point apparatus. IR spectra were recorded on a JASCO IR-Report-100 spectrophotometer. All NMR spectra were measured on a JEOL-JNM-GX-500 spectrometer in $CDCl_3$ unless stated otherwise. The chemical shifts are referenced against TMS as an internal standard ($\delta = 0$), and J values are given in Hz. Mass spectra were taken on a JEOL-01SG-2, JEOL-DX-300 or JEOL-DX-303 spectrometer. All reactions involving air- and/or moisture-sensitive reagents were conducted under an atmosphere of argon, and the glassware was oven-dried under a steam of dry argon prior to use. Solvents were freshly distilled immediately prior to use: THF was distilled under argon from sodium–benzophenone ketyl. Dichloromethane (CH_2Cl_2), acetonitrile (MeCN), triethylamine (Et_3N), methyl iodide (MeI), hexamethylphosphoramide (HMPA), and Hünig's base (Pr^i_2NEt) were distilled under argon from calcium hydride, whereas benzene was distilled under argon from sodium. Unless otherwise noted, all reaction mixtures were dried, after work-up, over anhydrous $MgSO_4$. Flash column chromatography was performed on Merck Kieselgel 60 (230–400 mesh). TLC was carried out on Merck Kieselgel 60 F_{254} (0.25 mm).

Benzyl N-*Hydroxy*-N-(3-*methoxyphenyl*)*carbamate* **9**.—To a stirred suspension of *m*-nitroanisole **19** (5.80 g, 37.9 mmol) and 85% zinc (5.83 g, 75.8 mmol) in ethanol (15 cm^3) and water (15 cm^3) was added dropwise saturated aqueous ammonium chloride (total 30 cm^3). After a few minutes an exothermic reaction ensued, which subsided after several minutes of vigorous boiling. After having been cooled to room temperature, the resulting mixture was filtered through Celite and the filtrate was extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated to give the crude hydroxylamine (5.99 g) as an oil.

To a stirred solution of the above hydroxylamine and potassium carbonate (3.0 g, 21.71 mmol) in diethyl ether (60 cm^3) and water (15 cm^3) was added dropwise benzyl chloroformate (6.50 cm^3, 45.53 mmol) at 0 °C, and the mixture was then stirred for 1 h. After addition of brine, the resulting mixture was extracted with ethyl acetate. The extract was dried and evaporated to give an oil, which was purified by flash silica gel chromatography. Elution with CH_2Cl_2–acetone (100:5 v/v) afforded *compound* **9** (10.34 g, 100%) as an oil (Found: M^+, 273.0973. $C_{15}H_{15}NO_4$ requires M, 273.1001); ν_{max}(neat)/cm^{-1} 3300 (OH) and 1700 (C=O); δ_H 3.75 (3 H, s, OMe), 5.25 (2 H, s, CH_2Ar), 6.73 (1 H, br dd, J 2.0 and 8.0, 4-H), 7.06 (1 H, t, J 8.0, 2-H), 7.08 (1 H, br dt, J 2.0 and 8.0, 6-H), 7.23 (1 H, t, J 8.0, 5-H) and 7.39 (1 H, br s, OH).

1-*Benzyl* 3-*Methyl* 6-*Methoxyindole*-1,3-*dicarboxylate* **8**.—To a stirred solution of the phenylhydroxylamine **9** (1.84 g, 6.74 mmol) and methyl propiolate **10** (1.20 cm^3, 13.50 mmol) in dry CH_2Cl_2 (20 cm^3) was added *N*-methylmorpholine (0.74 cm^3, 6.73 mmol) at room temperature. As the reaction proceeded, the temperature rose to 40 °C. After the mixture had been stirred for 1 h, the solvent was evaporated off. Flash silica gel chromatography (CH_2Cl_2–hexane 1:1 v/v) on the residual yellow oil gave rise to a solid, which was recrystallized from methanol to afford *compound* **8** (1.51 g, 66%) as needles, m.p. 117.0 °C (Found: C, 67.35; H, 5.15; N, 4.1. $C_{19}H_{17}NO_5$ requires C, 67.25; H, 5.05; N, 4.15%); ν_{max}($CHCl_3$)/cm^{-1} 1745 and 1705 (C=O); δ_H 3.83 (3 H, s, ArO*Me*), 3.93 (3 H, s, CO_2Me), 5.50 (2 H, s, CH_2Ar), 6.96 (1 H, dd, J 2.2 and 8.8, 5-H), 7.37–7.51 (5 H, m, ArH), 7.74 (1 H, br s, 7-H), 8.00 (1 H, d, J 8.8, 4-H) and 8.19 (1 H, s, 2-H).

Methyl 6-*Methoxyindole*-3-*carboxylate* **20**.—A mixture of the indole **8** (270 mg, 0.80 mmol) and 10% palladium–charcoal (5 mg) in ethyl acetate (10 cm^3) was stirred under an atmosphere of hydrogen until absorption of hydrogen had ceased. After filtration, the filtrate was evaporated and the residue was chromatographed on silica gel. Elution with CH_2Cl_2–hexane (2:1 v/v) yielded a solid, which was recrystallized from methanol to give *compound* **20** (163 mg, 100%) as needles, m.p. 147–148 °C (Found: C, 64.35; H, 5.3; N, 6.8. $C_{11}H_{11}NO_3$ requires C, 64.4; H, 5.4; N, 6.85%); ν_{max}($CHCl_3$)/cm^{-1} 1695 (C=O); δ_H 3.82 (3 H, s, ArOMe), 3.92 (3 H, s, CO_2Me), 6.86 (1 H, d, J 2.2, 7-H), 6.93 (1 H, dd, J 2.2 and 8.8, 5-H), 7.79 (1 H, d, J 8.8, 4-H), 8.04 (1 H, d, J 8.8, 4-H) and 8.71 (1 H, br s, 1-H).

(6-*Methyoxyindol*-3-*yl*)*methanol* **21**.—To a stirred solution of the ester **20** (501 mg, 2.44 mmol) in dry THF (40 cm^3) at −78 °C under argon was added DIBAL (2.13 g, 15.00 mmol) and the mixture was then stirred for 0.5 h. After dropwise addition of water (19.5 cm^3) to the stirred mixture at the same temperature, the resulting mixture was allowed to warm to room temperature over a period of 1 h with stirring. The mixture was stirred for a further 0.5 h at room temp. and then filtered through Celite. Evaporation of the filtrate gave crude compound **21**. Partial purification was accomplished by chromatography on neutral alumina (benzene–acetone 10:3 v/v) to afford crystals (434 mg), which were used in the next step without further purification (Found: M^+, 177.0772. $C_{10}H_{11}NO_2$ requires M, 177.0790); δ_H 3.80 (3 H, s, OMe), 4.85 (2 H, s, CH_2OH), 6.84 (1 H, dd, J 2.5 and 8.5, 5-H), 6.87 (1 H, d, J 2.0, 2-H), 7.10 (1 H, d, J 2.5, 7-H), 7.61 (1 H, d, J 8.5, 4-H) and 7.95 (1 H, br s, NH).

2-(6-*Methoxyindol*-3-*yl*)*ethanenitrile* **22**.—To a stirred solution of the crude **21** (434 mg, 2.45 mmol) in ethanol (20 cm^3) was added sodium cyanide (1.20 g, 24.48 mmol) at room temperature, and the mixture was refluxed for 2 h. After having been cooled to room temperature, the resulting mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The crude product was purified by chromatography on neutral alumina to afford a solid, which was recrystallized from ethanol to give the *title compound* **22** (436 g, 96% from **20**) as needles, m.p. 113–114 °C (lit.,[10] 105 °C) (Found: M^+, 186.0789. $C_{11}H_{10}N_2O$ requires M, 186.0793); ν_{max}($CHCl_3$)/cm^{-1} 2250 (C≡N); δ_H 3.80 (2 H, d, J 1.0, CH_2CN), 3.85 (3 H, s, OMe), 6.85 (1 H, dd, J 2.3 and 8.5, 5-H), 6.87 (1 H, d, J 2.3, 7-H), 7.11 (1 H, br dt, J 1.0 and 2.5, 2-H), 7.45 (1 H, d, J 8.5, 4-H) and 8.05 (1 H, br s, NH).

Methyl (6-*Methoxylindol*-3-*yl*)*acetate* **23**.—A mixture of the nitrile **22** (131 mg, 0.70 mmol) and 85% potassium hydroxide (395 mg, 7.04 mmol) in ethanol (10 cm^3) and water (2 cm^3) was refluxed for 10 h. The mixture was cooled and to it was added 15% aqueous sodium hydroxide (10 cm^3) and the resulting mixture was washed twice with diethyl ether, and acidified with 10% aqueous sulfuric acid under ice cooling. The resulting acidic solution was extracted with ethyl acetate (3 × 30 cm^3). The extract was washed with brine, dried and evaporated to give crystals, which without further purification were used in the following reaction.

To a stirred solution of the crude acid (143 mg) in dry methanol (5 cm^3) was added camphor-10-sulfonic acid (5 mg, 0.02 mmol) at ambient temperature, then the mixture was stirred for 12 h. After evaporation of the solvent, followed by addition of saturated aqeuous sodium hydrogen carbonate, the mixture was extracted with ethyl acetate. The extract was dried

and evaporated to give a solid, which was recrystallized from benzene–hexane to yield the *ester* **23** (151 mg, 98%) as needles, m.p. 101–102 °C (lit.,[10] 92 °C) (Found: C, 65.75; H, 5.9; N, 6.35. $C_{12}H_{13}NO_3$ requires C, 65.75; H, 6.0; N, 6.4%); δ_H 3.75 (3 H, s, CO_2Me), 3.78 (2 H, s, CH_2CO_2Me), 3.82 (3 H, s, OMe), 6.81 (1 H, dd, *J* 2.5 and 8.5, 5-H), 6.82 (1 H, br s, 7-H), 7.01–7.03 (1 H, m, 2-H), 7.47 (1 H, d, *J* 8.5, 4-H) and 7.98 (1 H, br s, NH).

Methyl (2,3-Dihydro-1-methylsulfonyl-6-methoxyindol-3-yl)acetate **24**.—To a stirred solution of the indole **23** (31 mg, 0.14 mmol) in glacial acetic acid (5 cm^3) was added sodium cyanoborohydride (total *ca.* 500 mg, 7.96 mmol) in *ca.* 50 mg portions at ambient temperature over a period of 1 h. The mixture was poured into water and basified to pH 8 with saturated aqueous potassium carbonate under ice cooling. The resulting basic solution was extracted with ethyl acetate (3 × 20 cm^3). The extract was washed with brine, dried and evaporated to give an oil, which was used directly in the next step without purification.

To a stirred solution of the crude indoline in dry pyridine (1.5 cm^3) was added methanesulfonyl chloride (0.02 cm^3, 0.26 mmol) at 0 °C. After 1 h, the mixture was poured into saturated aqueous potassium hydrogen sulfate (30 cm^3) at 0 °C with stirring, then the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated to give rise to a residue, which was purified by silica gel column chromatography. Elution with benzene–acetone (10:1 v/v) afforded the *title compound* **24** (41 mg, 98%) (Found: M^+, 299.0825. $C_{13}H_{17}NO_5S$ requires *M*, 299.0828); δ_H 2.82 (3 H, s, SO_2Me), 2.45–2.80 (2 H, m, CH_2CO_2Me), 3.75 (3 H, s, CO_2Me), 3.85 (3 H, s, ArO*Me*), 4.15–4.23 (1 H, m, CH), 6.49 (1 H, dd, *J* 2.0 and 8.5, 5-H), 7.04 (1 H, d, *J* 2.0, 7-H) and 7.27 (1 H, d, *J* 8.5, 4-H).

3-Acetoxymethyl-2,3-dihydro-1-methylsulfonyl-6-methoxyindole **25**.—A mixture of the ester **24** (135 mg, 0.45 mmol) and 1 mol dm^{-3} sodium hydroxide solution (2 cm^3) in methanol (5 cm^3) was heated at 55 °C for 2 h. Water (10 cm^3) was added to the above mixture, and then the resulting mixture was acidified to pH 2 with 10% aqueous sulfuric acid at 0 °C. The acidic solution was extracted with ethyl acetate (3 × 30 cm^3). The extract was washed with brine, dried and evaporated to give a residue, which was dissolved in dry benzene (5 cm^3). To this solution were added dimethylformamide (3 drops) and oxalyl chloride (0.40 cm^3, 4.60 mmol) at ambient temperature. After 1 h, the solvent was evaporated off. To a dry benzene solution (5 cm^3) of the crude acid chloride were added 4-dimethylaminopyridine (5 mg, 0.04 mmol), carbon tetrabromide (225 mg, 0.68 mmol) and 2-mercaptopyridine *N*-oxide sodium salt (101 mg, 0.68 mmol), then the resulting mixture was refluxed for 4 h. After having been cooled to room temperature, the mixture was filtered through Celite and the residue was washed with benzene. The combined filtrate and washings were concentrated to yield an oil, to which was added mercuric acetate (210 mg, 0.66 mmol) in acetic acid (5 cm^3) at 110 °C. The mixture was stirred at the same temperature for 4 h before removal of the solvent under reduced pressure. The residue was partitioned between brine and ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate, dried and evaporated to give the crude product, which was purified by column chromatography on neutral alumina (benzene–acetone 100:2 v/v) to afford the *acetate* **25** (110 mg, 82%) (Found: M^+, 299.0835. $C_{13}H_{17}NO_5S$ requires *M*, 299.0828); ν_{max}(neat)/cm^{-1} 1740 (C=O), 1360 and 1160 (SO_2); δ_H 2.05 (3 H, s, OAc), 2.92 (3 H, s, SO_2Me), 3.80 (3 H, s, OMe), 3.50–3.60 (1 H, m, $CHCH_2$), 4.00–4.12 (2 H, m, NCH_2), 4.20 (2 H, dd, *J* 6.0 and 11.0, CH_2OAc), 6.50 (1 H, dd, *J* 2.0 and 8.5, 5-H), 7.03 (1 H, d, *J* 2.0, 7-H) and 7.18 (1 H, d, *J* 8.5, 4-H).

3-Acetoxymethyl-2,3-dihydro-1-methylsulfonyl-6-methoxy-5-nitroindole **26**.—Fuming nitric acid (0.07 cm^3, 1.56 mmol) was added slowly to a solution of **25** (300 mg, 1.00 mmol) in dry MeCN (5 cm^3) at 0 °C. After being stirred for 1 h, the reaction mixture was diluted with ethyl acetate (30 cm^3) and then washed with saturated aqueous sodium hydrogen carbonate and brine. The organic layer was dried and evaporated to yield a residue, which was purified by silica gel flash column chromatography. Elution with benzene–acetone (10:1 v/v) gave the *title compound* **26** (314 mg, 91%) as powders (Found: M^+, 344.0677. $C_{13}H_{16}N_2O_7S$ requires *M*, 344.0678); δ_H 2.10 (3 H, s, OAc), 3.01 (3 H, s, SO_2Me), 3.66–3.74 (1 H, m, 3-H), 3.93 (1 H, dd, *J* 4.9 and 11.0), 3.98 (3 H, s, OMe), 4.17 (1 H, dd, *J* 1.0 and 11.0), 4.18 (1 H, dd, *J* 7.9 and 11.6), 4.24 (1 H, dd, *J* 6.1 and 11.0), 7.18 (1 H, s, 7-H) and 7.87 (1 H, d, *J* 1.2, 4-H).

3-Acetoxymethyl-2,3-dihydro-1-methylsulfonyl-6-methoxyindol-5-amine **7**.—A mixture of the nitro compound **26** (240 mg, 0.70 mmol) and platinum oxide (10 mg) in ethyl acetate (15 cm^3) was stirred for 3 h at room temperature under hydrogen. The catalyst was filtered off and washed with CH_2Cl_2. Concentration of the combined filtrates afforded a residue, which was chromatographed on silica gel. Elution with benzene–acetone (10:1 v/v) yielded the *amine* **7** (210 mg, 96%) as an oil, which crystallized upon storage in a refrigerator (Found: M^+, 314.0937. $C_{13}H_{18}N_2O_5S$ requires *M*, 314.0937); δ_H 2.07 (3 H, s, OAc), 2.83 (3 H, s, SO_2Me), 3.55–3.63 (1 H, m, 3-H), 3.79 (1 H, dd, *J* 6.1 and 11.6), 3.86 (3 H, s, OMe), 4.03 (1 H, dd, *J* 9.2 and 11.6), 4.06 (1 H, dd, *J* 8.6 and 11.0), 4.25 (1 H, dd, *J* 5.5 and 11.0), 6.61 (1 H, s, 4-H) and 7.00 (1 H, s, 7-H).

8-Acetoxymethyl-3,6,7,8-tetrahydro-6-methylsulfonyl-4-methoxy-1-methylthiobenzo[1,2-b:4,3-b′]dipyrrol-2(1H)-one **27**.—To a stirred solution of ethyl methylthioacetate (0.19 cm^3, 1.48 mmol) in dry CH_2Cl_2 (5 cm^3) was added sulfuryl chloride (0.11 cm^3, 1.37 mmol) at −78 °C, then the resulting mixture was stirred at the same temperature for 20 min. To the mixture was added, over 15 min, a solution of the amine **7** (377 mg, 1.20 mmol) and Proton Sponge® (308 mg, 1.44 mmol) in dry CH_2Cl_2 (3 cm^3). After an additional 2 h, Et_3N (0.20 cm^3, 1.43 mmol) was added, the mixture was stirred for 1 h at the same temperature before being allowed to warm to room temperature. The mixture was diluted with CH_2Cl_2, washed with brine, dried and evaporated to yield a residue which, without purification, was used in the next step.

The crude product was treated with glacial acetic acid (5 cm^3) at room temperature for 1 h. After evaporation of acetic acid, the residue was extracted with ethyl acetate, the extract was washed with saturated aqueous potassium hydrogen carbonate and brine, dried and evaporated to give the crude title compound, which was purified by flash silica gel chromatography (benzene–acetone 10:2 v/v) to afford the *amide* **27** (415 mg, 87%) as a *ca.* 5:1 mixture of diastereoisomers (Found: M^+, 400.0725. $C_{16}H_{20}N_2O_6S_2$ requires *M*, 400.0763); ν_{max}($CHCl_3$)/cm^{-1} 3450 (N–H), 1740 (C=O), 1735 (NHC=O), 1360 and 1160 (SO_2); δ_H(diastereochemical shift when different is given in brackets) 2.05 (3 H, s), 2.07 (3 H, s), 2.90 [2.93] (3 H, s, SO_2Me), 3.88 [3.89] (3 H, s, OMe), 3.83–4.35 (5 H, m), 4.35 (1 H, s, 1-H), 7.06 (1 H, s, 5-H) and 7.52 (1 H, br s, NH).

8-Acetoxymethyl-3,6,7,8-tetrahydro-6-methylsulfonyl-4-methoxy-1-methyl-1-methylthiobenzo[1,2-b:4,3-b′]dipyrrol-2(1H)-one **28**.—To a mixture of the amide **27** (405 mg, 1.01 mmol) and sodium carbonate (1.72 g, 16.23 mmol) in dimethylformamide (10 cm^3) and acetone (10 cm^3) was added MeI (0.61 cm^3, 9.80 mmol) at ambient temperature. After 4 h, the mixture was concentrated and the residue was dissolved in CH_2Cl_2. The organic layer was washed with brine, dried and

evaporated to give the crude product, which was subjected to silica gel column chromatography. Elution with benzene–acetone (10:2 v/v) afforded the *title compound* **28** (234 mg, 56%) as an oil, which crystallized upon storage in a refrigerator (Found: M^+, 414.0911. $C_{17}H_{22}N_2O_6S_2$ requires *M*, 414.0919); δ_H 1.81 (3 H, s, 1-Me), 1.94 (3 H, s, SMe), 2.10 (3 H, s, OAc), 2.94 (3 H, s, SO_2Me), 3.79–3.97 (3 H, m), 3.89 (3 H, s, OMe), 4.06–4.16 (1 H, m), 4.32–4.40 (1 H, m), 7.07 (1 H, s, 5-H) and 7.60 (1 H, br s, NH).

Further elution gave the *diastereoisomer* (123 mg, 29%) as an oil, which crystallized upon storage in a refrigerator (Found: M^+, 414.0897. $C_{17}H_{22}N_2O_6S_2$ requires *M*, 414.0919); δ_H 1.75 (3 H, s, 1-Me), 1.97 (3 H, s, SMe), 2.09 (3 H, s, OAc), 2.94 (3 H, s, SO_2Me), 3.65–3.73 (1 H, m), 3.80–3.96 (2 H, m), 3.89 (3 H, s, OMe), 4.06–4.13 (1 H, m), 4.94 (1 H, dd, *J* 3.7 and 11.0), 7.09 (1 H, s, 5-H) and 7.46 (1 H, br s, NH).

(1,2,3,6-*Tetrahydro*-3-*methylsulfonyl*-5-*methoxy*-8-*methylbenzo*[1,2-b:4,3-b′]*dipyrrol*-1-*yl*)*methanol* **29**.—To a stirred solution of a mixture of the two diastereoisomers **28** (15 mg, 0.036 mmol) in dry THF (5 cm^3) was added borane-dimethyl sulfide complex (28 mg, 0.369 mmol) at room temperature. The mixture was refluxed for 3 h. After having been cooled to room temperature, to the mixture was added 5% aqueous hydrogen chloride solution (5 cm^3), then the resulting mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, dried and evaporated to give a residue, which was purified by flash column chromatography on silica gel with benzene–acetone (10:2 v/v) to afford the *alcohol* **29** (10 mg, 89%) as an oil (Found: M^+, 310.0985. $C_{14}H_{18}N_2O_4S$ requires *M*, 310.0988); ν_{max}($CHCl_3$)/cm^{-1} 3700–3150 (OH), 3475 (NH), 1360 and 1160 (SO_2); δ_H 2.39 (3 H, s, ArMe), 2.88 (3 H, s, SO_2Me), 3.70–4.04 (4 H, m), 3.95 (3 H, s, OMe), 4.25 (1 H, dd, *J* 1.8 and 11.0), 6.97 (1 H, br s, 7-H), 6.98 (1 H, s, 4-H) and 8.14 (1 H, br s, NH).

1,2,3,6-*Tetrahydro*-1-*hydroxymethyl*-3-*methylsulfonyl*-8-*methylbenzo*[1,2-b:4,3-b′]*dipyrrol*-5-*ol* **30**.—A mixture of the ether **29** (55 mg, 0.18 mmol) and lithium butanethiolate (187 mg, 1.95 mmol) in dry HMPA (4 cm^3) was heated at 110 °C for 1 h. The mixture was poured into brine, and then the resulting mixture was extracted with ethyl acetate. The extract was dried and evaporated to yield a residue, which was subjected to flash column chromatography on silica gel. Elution with benzene–acetone (10:3 v/v) gave the *phenol* **30** (46 mg, 88%) as an oil, which crystallized upon storage in a refrigerator (Found: M^+, 296.0867, $C_{13}H_{16}N_2O_4S$ requires *M*, 296.0831); ν_{max}($CHCl_3$)/cm^{-1} 3700–3150 (OH), 3450 (NH) 1360 and 1160 (SO_2); δ_H[$(CD_3)_2CO$] 2.37 (3 H, s, Ar*Me*), 2.86 (3 H, s, SO_2Me), 3.41–4.25 (5 H, m), 6.86 (1 H, br s), 7.06 (1 H, s), 8.57 (1 H, s) and 9.83 (1 H, br s).

1,2,8,8a-*Tetrahydro*-2-*methylsulfonyl*-7-*methylcyclopropa*[3,4]*pyrrolo*[3,2-e]*indol*-4-*one* **5**.—A mixture of carbon tetrabromide (74 mg, 0.223 mmol), triphenylphosphine (68 mg, 0.259 mmol) and the alcohol **30** (22 mg, 0.074 mmol) in dry MeCN (3 cm^3) was stirred at room temperature for 1.5 h and then heated at 55 °C for 10 min. After having been cooled, to this was added saturated aqueous sodium thiosulfate, then the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated to give the crude bromide. Partial purification was accomplished by chromatography on silica gel (benzene–acetone 10:3 v/v) to afford solids (21 mg, 78%), which were used in the next step without further purification (Found: M^+, 357.9959. $C_{13}H_{15}BrN_2O_3S$ requires *M*, 357.9987).

To a stirred solution of the bromide (16 mg, 0.045 mmol) in dry CH_2Cl_2 (3 cm^3) was added dropwise Pr^i_2NEt (0.05 cm^3, 0.29 mmol) at room temperature. After 1 h, the solvent was removed under reduced pressure. The residue was subjected to chromatography on silica gel. Elution with benzene–acetone (10:3 v/v) afforded the *title compound* **5** (9 mg, 73%) as a powder (Found: M^+, 278.0750. $C_{13}H_{14}N_2O_3S$ requires *M*, 278.0725); ν_{max}($CHCl_3$)/cm^{-1} 3450 (NH), 3440–3100 (OH), 1620 (C=O), 1360 and 1160 (SO_2); δ_H 1.41 (1 H, dd, *J* 4.3 and 4.9, 8-H), 1.98 (1 H, dd, *J* 4.3 and 7.3, 8-H), 2.02 (3 H, s, 7-Me), 2.94–2.99 (1 H, m, 8a-H), 3.05 (3 H, s, SO_2Me), 3.98 (1 H, dd, *J* 4.9 and 10.4, 1-H), 4.14 (1 H, d, *J* 10.4, 1-H), 6.33 (1 H, s, 3-H), 6.83 (1 H, br d, *J* 1.8, 6-H) and 9.49 (1 H, br s, NH).

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