Michael additions of 1,2-dihydro-3*H*-indol-3-ones and some reactions of Michael adducts with ammonium acetate

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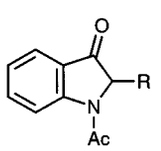
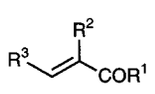
Reactions of 1-acetyl-1,2-dihydro-3*H*-indol-3-one and 1-acetyl-2-methoxy-1,2-dihydro-3*H*-indol-3-one with ethylenic and acetylenic carbonyl compounds took place with Michael addition to give 1,3-di- and/or 1,2,3-tri-acylpropane compounds, respectively, which were elaborated to provide several kinds of heterocyclic compounds: carbazoles, oxaspiroindoles, a pyrano[3,2-*b*]indole, pyrroles and pyrrolo[1,2-*a*]indoles.

1,2-Dihydro-3*H*-indol-3-ones are utilized as synthetic intermediates for alkaloids and biologically active compounds such as indomethacin,[1] serotonin,[2] ellipticine,[3] hyellazole,[4] carbazomycin,[5] flustramine C,[6] and others.[7] Michael reactions of 1,2-dihydro-3*H*-indol-3-ones with α,β-unsaturated carbonyl compounds are attractive in the provision of useful 1,3-dicarbonyl compounds for synthesis of heterocycles, *i.e.*, γ-carbolines,[8] pyrano[2,3-*b*]indoles,[9] pyrano[3,2-*b*]indoles,[10] and pyrrolo[1,2-*a*]-indoles.[10,11] However, 1,2-dihydro-3*H*-indol-3-ones react with α,β-unsaturated carbonyl compounds having no substituent at the β-position *via* double Michael addition to afford dialkylated products.[12] We previously reported a useful synthetic method for 2-monosubstituted 1,2-dihydro-3*H*-indol-3-ones using alkylation of 2-methoxy-1,2-dihydro-3*H*-indol-3-ones.[9] In connection with our studies on the chemistry of 1,2-dihydro-3*H*-indol-3-ones,[13] we now report the Michael additions of 1-acetyl-1,2-dihydro-3*H*-indol-3-one **1** and 1-acetyl-2-methoxy-1,2-dihydroindol-3-one **2** with ethylenic **3** and acetylenic carbonyl compounds **4** and transformation of the Michael adducts, namely 1,3-di- and 1,2,3-tri-acylpropane compounds, to heterocyclic compounds: carbazoles, oxaspiroindoles, a pyrano[3,2-*b*]indole, pyrroles and pyrrolo[1,2-*a*]indoles.



1; R = H
2; R = OMe



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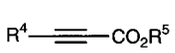
a; R^1= Me, R^2= R^3= H
b; R^1= R^2= R^3= Me
c; R^1= Ph, R^2 =H, R^3= COPh
d; R^1= Me, R^2 =H, R^3= COMe
e; R^1= OMe, R^2= R^3= H
f; R^1= OMe, R^2 =H, R^3= CO_2Me



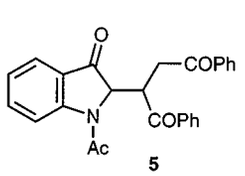
4

a; R^4= CO_2Me, R^5= Me
b; R^4= Me, R^5= Et

Michael additions of 1-acetyl-1,2-dihydro-3*H*-indol-3-one 1 and 1-acetyl-2-methoxy-1,2-dihydro-3*H*-indol-3-one 2

The 1,2-dihydro-3*H*-indol-3-ones **1** and **2** were readily available by our synthetic methods.[14] The reaction of compound **1** with methyl vinyl ketone **3a** in the presence of potassium hydroxide took place with double Michael addition followed by double intramolecular aldol condensation to give the carbazole product, while the reaction using triethylamine instead of potassium hydroxide provided mono- and di-alkylated products.[12] We first examined the reactions of 2-unsubstituted indol-3-one **1** with ethylenic **3c**, **3e**, **3f** and acetylenic carbonyl compounds **4a**. Thus, the reaction of compound **1** with *E*-1,2-dibenzoylethylene (DBE) **3c** was carried out under refluxing conditions and was complete in 0.5 h to give a diastereoisomeric mixture (1.4 : 1) of trione **5** in 96% yield without the formation of a double Michael adduct. When compound **1** was treated with *E*- and *Z*-**3c** in the presence of triethylamine in *tert*-butyl alcohol at 0 °C for 25 and 19 h, mixtures of diastereoisomers (2 : 1 and 2.4 : 1) of Michael adduct **5** were obtained in 91 and 86% yield, respectively. These results show that the electron-deficient 1,2-dicarbonyl compound **3c** is more reactive than mono carbonyl **3a** compound. In spite of the higher reactivity of dione **3c**, however, double Michael additions did not occur because of steric hindrance between the bulky substituent at the 2-site of the initial product **5** and second molecule of dione **3c**. Michael additions of compound **1** with ethylenic esters **3e** and **3f** on prolonged heating, however, did not occur at all. The reaction of compound **1** with dimethyl acetylenedicarboxylate (DMAD) **4a** in the presence of triethylamine at rt for 2 h took place smoothly with double Michael additions to produce the 1 : 2-adduct **6** in 78% yield. This formation of diadduct **6** can be explained in terms of the powerful electrophilicity of compound **4a** being superior to the steric hindrance at the reaction site of the intermediary monoadduct.

Next, we tried the reactions of the 2-methoxyindol-3-one **2** with ethylenic **3** and acetylenic carbonyl compounds **4** in order to produce the monoadducts. When compound **2** was treated with methyl vinyl ketone **3a** in the presence of triethylamine in refluxing *tert*-butyl alcohol, the reaction required prolonged heating; however, the desired mono adduct **7a** was obtained in 97% yield. In the case of a β-alkylated compound such as 3-methylpent-3-en-2-one **3b**, no desired Michael reaction under the same conditions took place owing to steric hindrance at the reaction site, but there was oxidative degradation of compound **2** to *N*-acetylanthranilic acid. 1,2-Dibenzoylethylene **3c**, however, reacted with substrate **2** under the same conditions to afford a mixture of diastereoisomers (1 : 1.3) of the Michael



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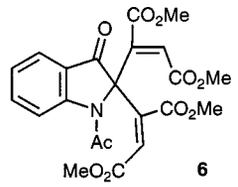

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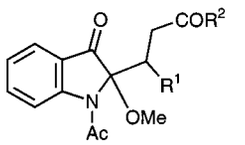
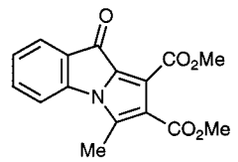


7a; R^1= H, R^2= Me
7b; R^1= COPh, R^2= Ph
7c; R^1= COMe, R^2= Me
7d; R^1= CO_2Me, R^2= OMe



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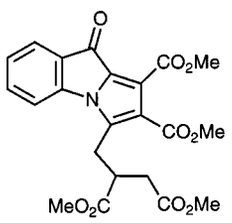

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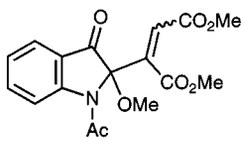

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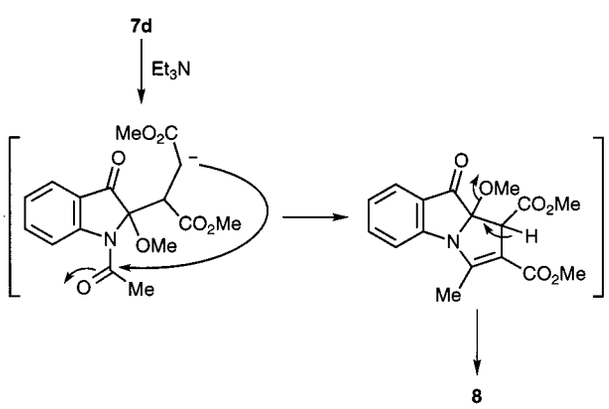
adduct **7b** in 85% yield. These results demonstrate that compound **3c** is much more electrophilic than analogues **3a** and **3b**, and that since the reaction site of compound **2** attached to the methoxy group is more bulky than that of compound **1**, the reaction of compound **2** with dione **3c** required prolonged heating (29 h) compared with that of compound **1** with dione **3c** (0.5 h). The similar reaction of compound **2** with 1,2-diacetylethylene **3d** gave the corresponding adduct **7c** (34%). Michael addition of compound **2** with less reactive methyl acrylate **3e** was not observed, although dimethyl fumarate **3f** reacted very slowly with compound **2** in the presence of triethylamine to provide the adduct **7d** in 38% yield together with pyrrolo[1,2-*a*]indoles **8** (16%) and **9** (3%). Heating of compound **7d** with triethylamine also produced compound **8** (45%). The formation of this product can be explained by the intramolecular aldol cyclization of compound **7d** taking place initially followed by elimination of methanol to result in aromatization to the pyrrole **8** (Scheme 1): further Michael addition of compound **8** to fumarate **3f** may generate tetraester **9**.



Scheme 1

When the indol-3-one **2** was allowed to react with acetylene dicarboxylate **4a** in the presence of triethylamine at rt for 4.5 h, the result was a mixture of the *E*- and *Z*-isomer (1 : 2) of the monoadduct **10** in 84% yield. Attempts to get butynoate **4b** to react with compound **2**, however, failed.

Transformation of Michael adducts 7a and 10 to monosubstituted indol-3-ones 18 and 20

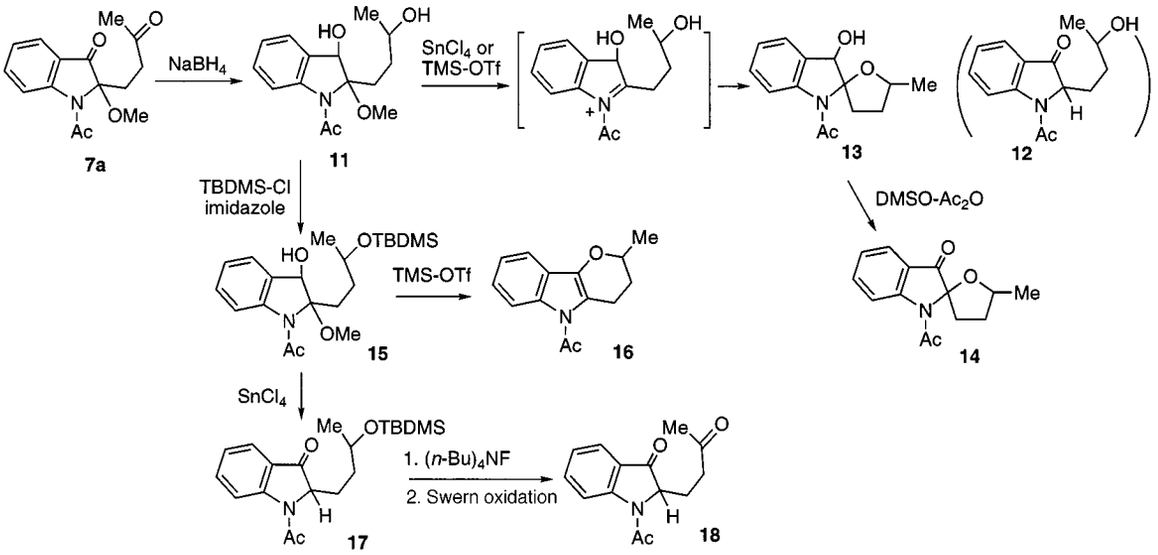
We next attempted to prepare monalkylated 1,2-dihydro-3*H*-indol-3-ones **18** and **20**, which could not be obtained in the reaction of compound **1** with substrates **3a** and **4a** owing to double Michael addition, by reduction of products **7a** and **10** followed by demethoxylation. Sodium borohydride reduction of compound **7a** gave a diol product **11** (85%), which when treated with tin(IV) chloride or TMS trifluoromethanesulfonate (triflate) (TMSOTF) did not proceed *via* the desired demethoxylation to monoalkylated 1,2-dihydro-3*H*-indol-3-one **12**, but instead underwent demethoxylation-substitution of intermediate **11** to give spiro compound **13** in 29 and 31% yield, respectively, whose structure was confirmed by its spectral data and chemical transformation of spiro ketone **14**. Therefore, we carried out the selective protection of the hydroxy group on the side chain of intermediate **11** with TBDMS chloride to give the silyl ether **15** (85%). Demethoxylation of the silyl ether **15** was carried out in the following manner. Treatment of compound **15** with TMS triflate unexpectedly provided the pyrano[3,2-*b*]-indole **16** in 63% yield; however, use of tin(IV) chloride instead of TMS triflate afforded the desired demethoxylation of compound **15**, giving product **17** (63%). Deprotection of compound **17** with TBAF followed by Swern oxidation provided the monoalkylated 1,2-dihydro-3*H*-indol-3-one **18** (90%) (Scheme 2).

When diester **10** was reduced with sodium borohydride, overreduction took place to give a complex mixture. Therefore, we performed sodium borohydride reduction of diester **10** in the presence of cerium(III) chloride which resulted in selective reduction of the keto group to afford the alcohol **19** in 80% yield. Demethoxylation of compound **19** with tin(IV) chloride gave the desired monosubstituted 1,2-dihydro-3*H*-indol-3-one **20** in 32% yield together with an isomeric product **21** (5%) (Scheme 3).

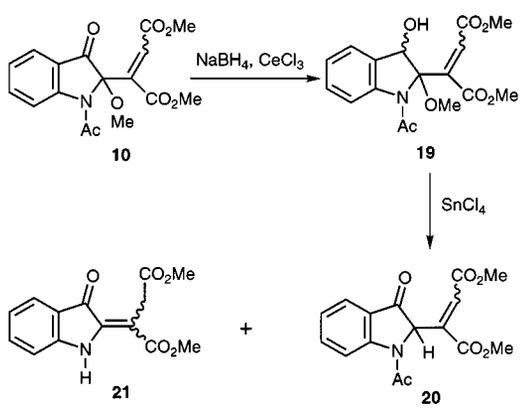
Cyclization reactions of Michael adducts to several heterocycles

The Michael adducts described above are regarded as 1,2-di-, 1,3-di- or 1,2,3-tri-acylpropane derivatives, which might be useful functionalities for synthesis of a variety of heterocyclic compounds. As shown above, the spontaneous intramolecular cyclization of the adduct **7d** to tricycle **8** and transformations of dione **7a** to O-heterocycles **13** and **16** proceeded readily. Furthermore, we attempted to achieve reaction of substrates **5**, **7a**–**c**, and **10** with ammonium acetate in order to synthesize heterocycles. Initially the adduct **7a** was treated with ammonium acetate in refluxing acetic acid for 1 h and the dicarbazolylamine **22** was obtained in 81% yield. When methanol containing acetic acid was used instead of acetic acid as a solvent, the reaction took place smoothly with intramolecular aldol cyclization to give the tetrahydrocarbazole **23** (72%), which was allowed to react with ammonium acetate under the previous conditions to obtain **22** in 65% yield. The formation of compound **22** can be explained in terms of imination of enone **23** followed by demethoxylation to aromatize to an intermediary 3-aminocarbazole, which condensed with another molecule of enone **23**, followed again by demethoxylation.

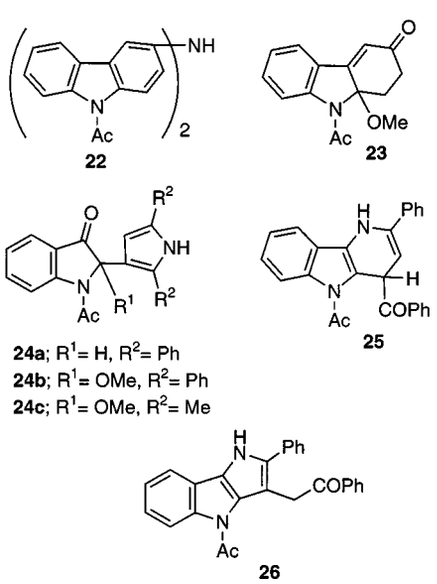
We next attempted the cyclization of dione **5** with ammonium acetate, which was assumed to proceed in three ways **A**–**C** as shown in Fig. 1. When dione **5** was heated with ammonium acetate in acetic acid for 0.5 h, it cyclized as a 1,2-diacyl ethane derivative smoothly along route **A** to afford pyrrole derivative **24a** in 40% yield. The structure was assigned on the basis of spectral data; the isomeric structures **25** and **26** formed *via* routes **B** and **C** were readily ruled out by the appearance of ^{1}H-NMR signals due to a methyne proton (singlet at δ 5.32)



Scheme 2



Scheme 3



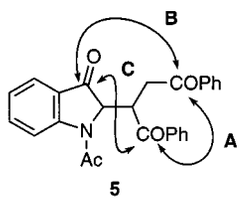
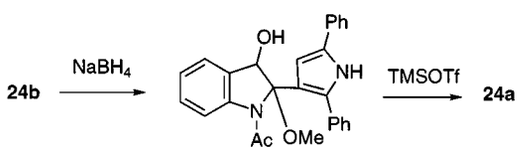


Fig. 1



Scheme 4

and a β-proton of a pyrrole ring (doublet at δ 6.15, J 2.6 Hz). The similar reaction of compounds **7b** and **7c** with ammonium acetate gave the corresponding pyrrole derivatives **24b** (69%) and **24c** (57%), respectively. Sodium borohydride reduction of compound **24b** followed by treatment with TMS triflate afforded the demethoxy derivative **24a** in 62% overall yield (Scheme 4). These 2-pyrrolyl-1,2-dihydro-3*H*-indol-3-ones **24** are of interest in connection with 2-aryl-1,2-dihydro-3*H*-indol-3-ones which possess biological activities.[7b]

Finally, we attempted the reaction of diester **10** with ammonium acetate. In a similar manner, compound **10** was allowed to react with ammonium acetate to form (unexpectedly) the pyrrole **28** in 33% yield, whose structure was confirmed by spectral data and X-ray crystallographic analysis (Fig. 2). The formation of compound **28** can be explained in terms of Michael addition of ammonia to diester **10** followed by cyclization to afford the intermediary pyrroloindole **27**, decomposition of which involves fission of the indole ring as shown in Scheme 5.

Experimental

All mps were measured on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded with a Hitachi 270-30 or a Shimadzu FTIR-8100 spectrophotometer. NMR spectra were determined with a JEOL JNM-GX 270 spectrometer with tetramethylsilane as internal standard. *J*-Values are given in Hz. Mass spectra were obtained with a JEOL JMS-DX302 instrument with a direct-inlet system operating at 70 eV. Elemental analyses were obtained using a Perkin-Elmer Model 240B elemental analyzer. Column chromatography was carried out on silica gel (Kanto Chemical Co. Inc., 100–200 mesh and Merck, 400 mesh). Preparative TLC (PLC) was performed on silica gel (Merck silica gel 60 F254). 1,2-Dihydro-3*H*-indol-3-ones **1** and **2** were prepared according to the reported procedures.[14]

The Michael addition of 1-acetyl-1,2-dihydro-3*H*-indol-3-one 1 with DBE 3c

Procedure A. A mixture of the indol-3-one **1** (25.5 mg, 0.14 mmol), *E*-DBE **3c** (52 mg, 0.22 mmol), and triethylamine (0.04

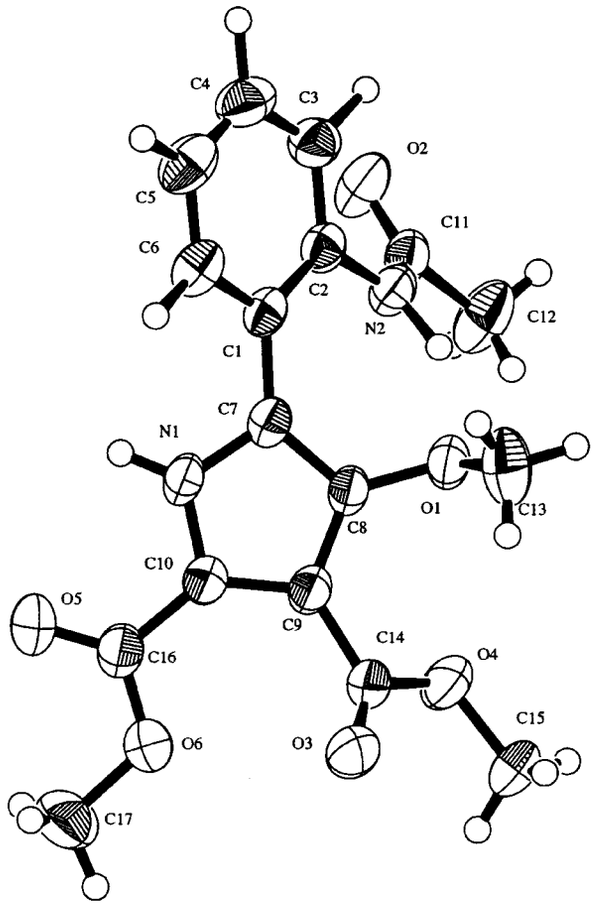
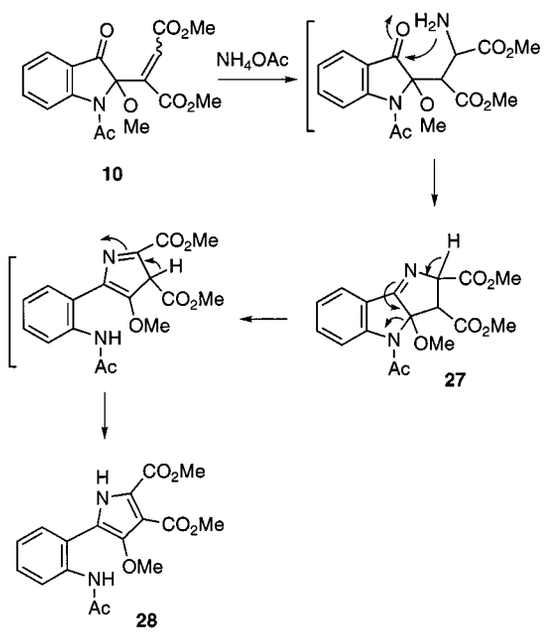


Fig. 2 X-Ray molecular structure of compound **28**.



Scheme 5

ml) in *tert*-butyl alcohol (0.8 ml) was stirred at 0 °C for 24 h. The reaction mixture was evaporated under reduced pressure to give an oily residue, which was chromatographed on silica gel. Elution with ethyl acetate–hexane (1:1) gave a mixture of diastereoisomers (2:1) of 1-acetyl-2-(1,2-dibenzoylethyl)-1,2-dihydro-3*H*-indol-3-one **5** (54 mg, 91%), mp 153–156 °C (Found: M^+, 411.1476. $C_{26}H_{21}NO_4$ requires *M*, 411.1469); $\nu_{max}(CHCl_3)/cm^{-1}$ 1723 and 1682; $\delta_H(CDCl_3)$ 2.40 (3H × 2/3, br s), 2.52 (3H × 1/3, s), 2.87 (1H × 1/3, dd, *J* 17.5 and 4.3), 3.65 (1H × 1/3, dd, *J* 17.5 and 8.9), 3.72 (1H × 2/3, br s), 3.85 (1H × 2/3, br s), 4.68 (1H × 2/3, br s), 5.01 (1H × 1/3, br s), 5.30 (1H × 1/3, br s), 5.26 (1H × 2/3, dd, *J* 11.2 and 6.6), 7.22 (1H, t, *J* 7.9), 7.26–7.84 (12H, m), 8.00 (1H × 2/3, br d, *J* 6.9) and 8.14 (1H × 1/3, br d, *J* 7.3); *m/z* 411 (M^+, 32%), 264 (61), 105 (100) and 77 (39).

Procedure B. A mixture of the indol-3-one **1** (15 mg, 0.85 mmol), *Z*-DBE **3c** (31 mg, 0.13 mmol), and triethylamine (0.02 ml) in methylene dichloride (0.5 ml) was stirred at 0 °C for 19 h. The reaction mixture was treated similarly to the procedure described above to give a mixture of diastereoisomers (2.4:1) of compound **5** (31 mg, 86%).

Procedure C. A mixture of the indol-3-one **1** (50 mg, 0.29 mmol), *E*-DBE **3c** (101 mg, 0.43 mmol), and triethylamine (0.08 ml) in *tert*-butyl alcohol (1.4 ml) was heated for 0.5 h. The reaction mixture was treated similarly to the above procedure to give a mixture of diastereoisomers (1.4:1) of compound **5** (112 mg, 96%).

The Michael addition of the indol-3-one 1 with DMAD 4a

A mixture of the indol-3-one **1** (12 mg, 0.07 mmol), DMAD **4a** (29 mg, 0.21 mmol), and triethylamine (0.02 ml) in methylene dichloride (0.4 ml) was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure to give an oily residue, which was chromatographed on silica gel with ethyl acetate–hexane (3:1) to give methyl 2-{1-acetyl-2-[1,2-bis-(methoxycarbonyl)vinyl]-3-oxoindolin-2-yl}but-2-enedioate **6** (25 mg, 78%) as a viscous oil (Found: M^+, 459.1173. $C_{22}H_{21}NO_{10}$ requires *M*, 459.1165); $\delta_H(CDCl_3)$ 2.42 (3H, br s), 3.63 (6H, s), 3.76 (6H, s), 6.59 (2H, s), 7.24 (1H, t, *J* 7.2), 7.29 (1H, d, *J* 7.2), 7.70 (1H, t, *J* 7.2) and 7.84 (1H, d, *J* 7.2); *m/z* 459 (M^+, 36%), 400 (98), 358 (100), 326 (49) and 398 (44).

General procedure for the Michael addition of 1-acetyl-2-methoxy-1,2-dihydro-3*H*-indol-3-one 2 with the ethylenic compounds 3a–f

A mixture of the 2-methoxyindol-3-one **2** (1 mmol), an ethylenic compound **3a**–**f** (3–5 mmol), and triethylamine (0.3 ml) in *tert*-butyl alcohol (5 ml) was heated under reflux for 30–114 h. The reaction mixture was concentrated under reduced pressure to give an oily residue, which was purified by column chromatography on silica gel with diethyl ether–hexane (2:3) for compound **7a**, ethyl acetate–hexane (1:2, 1:1, 1:3) for compounds **7b**, **7c**, **7d** as eluent, to give the corresponding Michael adducts **7a**–**d**.

1-Acetyl-2-methoxy-3-oxo-2-(3-oxobutyl)indoline 7a. This was prepared from compound **2** (1.8 g, 8.8 mmol) and methyl vinyl ketone **3a** (1.85 g, 26.4 mmol) in 97% yield (2.36 g), mp 113–115 °C (from hexane) (Found: C, 65.25; H, 6.25; N, 5.0. $C_{15}H_{17}NO_4$ requires C, 65.45; H, 6.20; N, 5.1%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1728 and 1679; $\delta_H(CDCl_3)$ 2.06 (3H, s), 2.40 (4H, m), 2.48 (3H, s), 3.15 (3H, s), 7.25 (1H, t, *J* 6.9), 7.94 (2H, m) and 8.63 (1H, d, *J* 8.3); $\delta_C(CDCl_3)$ 23.2, 29.3, 30.8, 35.8, 51.6, 94.2, 118.2, 121.6, 123.5, 124.3, 138.3, 153,0, 169.7, 196.9 and 205.9; *m/z* 275 (M^+, 7%), 232 (97), 162 (93) and 43 (100).

1-Acetyl-2-(1,2-dibenzoylethyl)-2-methoxy-3-oxoindoline 7b. This was prepared from compound **2** (0.25 g, 1.2 mmol) and DBE **3c** (0.85 g, 3.7 mmol) in 85% yield (0.45 g), mp 122–125 °C (from diethyl ether) (Found: C, 73.05; H, 5.45; N, 3.0. $C_{27}H_{23}NO_5$ requires C, 73.45; H, 5.25; N, 3.15%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1737 and 1683; $\delta_H(CDCl_3)$ 2.64 (3H, s), 3.04 (3H, s), 2.98 (1H, dd, *J* 17.8 and 2.9), 3.75 (1H, dd, *J* 17.8 and 10.6), 5.12 (1H, dd, *J* 10.5 and 2.9), 7.2–7.6 (7H, m), 7.65–7.8 (4H, m), 8.0–8.1 (2H, m) and 8.46 (1H, d, *J* 8.2); *m/z* 441 (M^+, 7%), 398 (37), 162 (41), 105 (100) and 77 (35).

1-Acetyl-2-(1,2-diacetylethyl)-2-methoxy-3-oxoindoline 7c. This was prepared from compound **2** (0.41 g, 2 mmol) and 2,5-dioxohex-3-ene **3d** (0.68 g, 6 mmol) in 34% yield (0.21 g), mp 231–234 °C (Found: M^+, 317.1266. $C_{17}H_{19}NO_5$ requires *M*, 317.1263); $\nu_{max}(CHCl_3)/cm^{-1}$ 1736, 1717, 1680 and 1608; $\delta_H(CDCl_3)$ 1.92 (1H, dd, *J* 17.5 and 2.6), 2.00 (3H, s), 2.52 (3H, s), 2.56 (3H, s), 2.79 (1H, dd, *J* 17.5 and 11.2), 3.22 (3H, s), 4.05 (1H, dd, *J* 11.2 and 2.6), 7.26 (1H, dd, *J* 8.9 and 7.3), 7.73 (1H, dd, *J* 7.6 and 7.3), 7.75 (1H, d, *J* 7.6) and 8.61 (1H, d, *J* 8.9); *m/z* 317 (M^+, 18%), 274 (55), 232 (38), 200 (100), 172 (31) and 162 (94).

Dimethyl 2-(1-acetyl-2-methoxy-3-oxoindolin-2-yl)butanedioate 7d. This was prepared from compound **2** (1.50 g, 5.1 mmol) and dimethyl fumarate **3f** (3.67 g, 25.5 mmol) in 38% yield (0.67 g), together with *dimethyl 3-methyl-9-oxo-9H-pyrrolo[1,2-a]indole-1,2-dicarboxylate* **8** (0.24 g, 16%) and *dimethyl 3-[2,3-bis(methoxycarbonyl)propyl]-9-oxo-9H-pyrrolo-[1,2-a]indole-1,2-dicarboxylate* **9** (0.06 g, 3%).

Compound **7d**; mp 75.5–78 °C (from diethyl ether–hexane) (Found: C, 58.5; H, 5.5; N, 4.0. $C_{17}H_{19}NO_7$ requires C, 58.45; H, 5.5; N, 4.0%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1744 and 1684; δ_H(60 MHz; $CDCl_3$) 2.55 (3H, s), 3.17 (3H, s), 3.30 (3H, s), 3.0–4.2 (3H, m), 3.67 (3H, s), 7.18 (1H, t, *J* 8), 7.45–7.85 (2H, m) and 8.58 (1H, d, *J* 8); *m/z* 349 (M^+, 18%), 307 (32), 246 (100), 216 (37), 188 (43), 162 (65) and 145 (35).

Compound **8**; mp 206–209 °C (from ethyl acetate) (Found: C, 64.15; H, 4.25; N, 4.65. $C_{16}H_{13}NO_5$ requires C, 64.2; H, 4.4; N, 4.7%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1738, 1708 and 1620; δ_H(400 MHz; $CDCl_3$) 2.80 (3H, s), 3.83 (3H, s), 3.95 (3H, s), 7.24 (1H, t, *J* 7.6), 7.36 (1H, d, *J* 8.0), 7.51 (1H, dd, *J* 8.0 and 7.6) and 7.64 (1H, d, *J* 7.6); δ_C(250 MHz; $CDCl_3$) 12.3, 51.7, 52.6, 112.9, 117.9, 120.1, 125.2, 126.7, 128.2, 130.1, 134.7, 143.1, 163.5, 163.6 and 177.5; *m/z* 299 (M^+, 57%) and 267 (100).

Compound **9**; mp 168–171 °C (from ethyl acetate) (Found: C, 59.35; H, 4.7; N, 3.1. $C_{22}H_{21}NO_9$ requires C, 59.6; H, 4.75; N, 3.15%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1736 and 1709; δ_H(400 MHz; $CDCl_3$) 2.68 (1H, dd, *J* 17.3 and 5.5), 2.87 (1H, dd, *J* 17.3 and 7.6), 3.30 (1H, br quintet), 3.55 (1H, dd, *J* 14.4 and 6.6), 3.59 (1H, dd, *J* 14.4 and 9.0), 3.66 (3H, s), 3.69 (3H, s), 3.83 (3H, s), 3.96 (3H, s), 7.29 (1H, t, *J* 7.3), 7.57 (1H, d, *J* 7.3), 7.60 (1H, d, *J* 7.3) and 7.71 (1H, d, *J* 7.3); *m/z* 443 (M^+, 100%), 411 (76), 351 (90), 348 (37) and 338 (57).

The Michael addition of the indol-3-one 2 with DMAD 4a

A mixture of the indol-3-one **1** (1.03 g, 5 mmol), DMAD **4a** (2.13 g, 15 mmol), and triethylamine (1.4 ml) in methylene dichloride (25 ml) was stirred at rt for 4.5 h. The reaction mixture was evaporated under reduced pressure to give a residue, which was chromatographed on silica gel with hexane–methylene dichloride as eluent to give a mixture of *E*- and *Z*-*isomers* (1 : 2) of *dimethyl 2-(1-acetyl-2-methoxy-3-oxoindolin-2-yl)but-2-enedioate* **10** (1.45 g, 84%) mp 146.5–148 °C (Found: C, 58.8; H, 4.95; N, 4.05. $C_{17}H_{17}NO_7$ requires C, 58.8; H, 4.85; N, 3.85%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1738 and 1685; $\delta_H(CDCl_3)$ 2.37 (3H, s), 3.17 (3H × 1/3, s), 3.25 (3H × 2/3, s), 3.52 (3H × 2/3, s), 3.56 (3H × 1/3, s), 3.76 (3H × 2/3, s), 3.86 (3H × 1/3, s), 6.66 (1H × 2/3, s), 7.19 (1H × 1/3, s), 7.23–7.28 (1H, m), 7.67–7.72 (1H, m), 7.79 (1H, d, *J* 7.2), 8.59 1H × 1/3, d, *J* 8.3) and 8.60 (1H × 2/3, d, *J* 8.3); *m/z* 347 (M^+, 45%), 304 (100), 288 (60), 246 (69), 218 (43), 214 (36), 186 (48) and 171 (69).

Reduction of the adduct 7a with sodium borohydride

Sodium borohydride (0.3 g, 7.9 mmol) was added to a stirred solution of dione **7a** (0.3 g, 1.1 mmol) in methanol (10 ml) at 0 °C. After 1 h, brine was added to the reaction mixture, which was then extracted with methylene dichloride. The extract was dried over magnesium sulfate and the solvent was evaporated off. The residue was chromatographed on silica gel with ethyl acetate as eluent to give *1-acetyl-3-hydroxy-2-(3-hydroxybutyl)-2-methoxyindoline* **11** (0.26 g, 85%) (Found: M^+, 279.1476. $C_{15}H_{21}NO_4$ requires *M*, 279.1481); $\nu_{max}(CHCl_3)/cm^{-1}$ 3400, 1663 and 1607; $\delta_H(CD_3CN)$ 1.08 (3H, d, *J* 6.3), 1.33 (2H, m), 2.13 (1H, m), 2.25 (1H, m), 2.37 (3H, s), 2.99 (1H, br), 3.16 (3H, s), 3.68 (1H, br), 4.30 (1H, br s), 5.04 (1H, d, *J* 5.6), 7.09 (1H, t, *J* 7.3), 7.23 (1H, d, *J* 7.3), 7.34 (1H, t, *J* 7.3) and 8.14 (1H, br); *m/z* 279 (M^+, 3%), 132 (22), 122 (27) and 115 (100).

Treatment of the indoline 11 with tin(IV) chloride or trimethylsilyl triflate

A catalytic amount of tin(IV) chloride or TMSOTf was added to a solution of compound **11** (100 mg, 0.36 mmol) in dry methylene dichloride (10 ml) at 0 °C under argon. The mixture was stirred for 5 min, quenched with brine, and extracted with methylene dichloride. The extract was dried over magnesium sulfate and the solvent was evaporated off. The residue was chromatographed on silica gel with ethyl acetate–hexane (1 : 1) as eluent to give a diastereoisomer mixture of the *alcohol* **13** (28 mg, 29% or 26 mg, 31%) (Found: M^+, 247.1219. $C_{14}H_{17}NO_3$ requires *M*, 247.1209); $\nu_{max}(CHCl_3)/cm^{-1}$ 3492, 3408 and 1752; $\delta_H(CDCl_3)$ 1.36 (3H, d, *J* 6.3), 1.73 (1H, m), 2.10–2.33 (2H, m), 2.45 (3H, s), 2.69 (1H, m), 3.23 (1H, d, *J* 5.9), 4.53 (1H, d, *J* 5.6), 4.71 (1H, m), 7.08 (1H, t, *J* 7.6), 7.26 (1H, t, *J* 7.6), 7.43 (1H, d, *J* 7.6) and 7.59 (1H, br); *m/z* 247 (M^+, 52%), 205 (33), 204 (100) and 122 (64).

Oxidation of the alcohol 13 to the ketone 14

A mixture of alcohol **13** (25 mg, 0.1 mmol) and acetic anhydride (3.7 ml) in DMSO (5.5 ml) was stirred at rt overnight. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by PLC on silica gel with ethyl acetate–hexane (2 : 1) as a developing solvent to give the *ketone* **14** (19.5 mg, 80%) (Found: M^+, 245.1060. $C_{14}H_{15}NO_3$ requires *M*, 245.1052); $\nu_{max}(CHCl_3)/cm^{-1}$ 1731 and 1680; $\delta_H(CDCl_3)$ 1.44 (3H, d, *J* 6.3), 2.2–2.6 (4H, m), 2.45 (3H, s), 2.75 (1H, m), 7.19 (1H, t, *J* 7.6), 7.64 (1H, t, *J* 7.6), 7.73 (1H, d, *J* 6.6) and 8.29 (1H br); *m/z* 245 (M^+, 46%), 202 (100) and 175 (75).

5-Acetyl-2-methyl-2,3,4,5-tetrahydropyrano[3,2-*b*]indole 16; silylation of the diol 11 followed by treatment with trimethylsilyl triflate

A mixture of diol **11** (308 mg, 1.1 mmol), imidazole (560 mg, 8.2 mmol), and TBDMS chloride (412 mg, 2.7 mmol) in DMF (2.2 ml) was stirred at rt overnight. The reaction mixture was diluted with diethyl ether, washed successively with saturated aq. sodium hydrogen bicarbonate and saturated aq. ammonium chloride. The organic layer was dried over magnesium sulfate and the solvent was evaporated off to give a residue, which was purified by column chromatography on silica gel with ethyl acetate–hexane (3 : 1) as eluent to give the TBDMS ether **15** (370 mg, 85%).

TMSOTf was gradually added to a solution of TBDMS ether **15** (15 mg, 0.04 mmol) in dry methylene dichloride (1 ml) at −10 °C under argon until the alcohol **15** had disappeared (checked by TLC; ethyl acetate–hexane 1 : 3). After 1 h, the reaction mixture was diluted with methylene dichloride and washed with brine. The organic layer was dried over magnesium sulfate and the solvent was evaporated to give a residue, which was purified by column chromatography on silica gel with ethyl acetate–hexane (1 : 3) as eluent to give the *pyranoindole* **16** (5.8 mg, 63%) (Found: M^+, 229.1105. $C_{14}H_{15}NO_2$ requires *M*, 229.1103); $\nu_{max}(CHCl_3)/cm^{-1}$ 1688; $\delta_H(CDCl_3)$ 1.41 (3H, d, *J* 6.3), 1.70 (1H, m), 1.95 (1H, m), 2.46 (3H, s), 2.85 (2H, m), 4.10 (1H, m), 7.17 (1H, t, *J* 7.3), 7.22 (1H, t, *J* 7.3), 7.44 (1H, d, 7.3) and 8.06 (1H, br); $\delta_C(CDCl_3)$ 20.3, 23.2, 26.2, 29.2, 72.5, 115.4, 115.5, 116.4, 122.7, 122.9, 124.4, 133.6, 140.1 and 169.0; *m/z* 229 (M^+, 51%), 187 (46) and 145 (100).

1-Acetyl-2-(3-oxobutyl)-1,2-dihydro-3*H*-indol-3-one 18; treatment of alcohol 15 with tin(IV) chloride, then desilylation followed by Swern oxidation

Tin(IV) chloride (1.64 g, 6.3 mmol) was gradually added to a solution of alcohol **15** (1.67 g, 4.2 mmol) in dry methylene dichloride (115 ml) at −78 °C under argon until substrate **15** had disappeared (checked by TLC; hexane–ethyl acetate 1:3). The reaction mixture was allowed to warm up to −10 °C, was diluted with methylene dichloride, and washed with brine. The organic layer was evaporated to give a residue, which was chromatographed on silica gel with hexane–diethyl ether (3:1) to give the TBDMS ether **17** (0.98 g, 63%).

TBAF (0.70 g, 2.7 mmol) was added to a solution of the TBDMS ether **17** (0.98 g, 2.7 mmol) in THF–water–ACOH (2:2:1, 5 ml) at 0 °C. The mixture was then stirred at rt overnight, diluted with ethyl acetate, and washed with saturated aq. sodium carbonate. The organic layer was dried over magnesium sulfate and the solvent was evaporated to give an alcohol, a part of which was used in the following reaction without purification. A solution of DMSO (7.5 μl) in methylene dichloride (0.02 ml) was added to a solution of oxalyl dichloride (7.0 μl) in methylene dichloride (0.02 ml) at −78 °C under argon. After 10 min, a solution of the alcohol (10 mg, 0.04 mmol) in methylene dichloride (0.5 ml) was added to the mixture at the same temperature. The reaction mixture was kept at the same temperature for 15 min and at −45 °C for 1 h. Triethylamine (0.01 ml) was added to the mixture at the same temperature. After being stirred at 0 °C for 1 h, the mixture was quenched with saturated aq. ammonium chloride and extracted with ethyl acetate. The extract was dried over magnesium sulfate and the solvent was evaporated off to give a residue, which was purified by column chromatography on silica gel with ethyl acetate–hexane (1:3) as eluent to give the *indol-3-one* **18** (8.8 mg, 90%) (Found: M^+, 245.1055. $C_{14}H_{15}NO_3$ requires *M*, 245.1052); $\nu_{max}(CHCl_3)/cm^{-1}$ 1720 and 1679; $\delta_H(CDCl_3)$ 2.10 (1H, br s), 2.12 (3H, s), 2.3–2.5 (2H, m), 2.46 (3H, s), 2.57 (1H, br), 4.35 (1H, br), 7.23 (1H, t, *J* 7.6), 7.67 (1H, t, *J* 7.3), 7.72 (1H, d, *J* 7.3) and 8.50 (1H, br); *m/z* 245 (M^+, 36%), 203 (65), 146 (45) and 145 (100).

Reduction of the adduct 10 with sodium borohydride–cerium(III) chloride

Sodium borohydride (81 mg, 2.1 mmol) was gradually added to a stirred solution of ketone **10** (347 mg, 1 mmol) and cerium(III) chloride·$7H_2O$ (373 mg, 1 mmol) in methanol (10 ml) at 0 °C. After 2 h, brine was added to the reaction mixture, and the mixture was extracted with methylene dichloride. The extract was dried over magnesium sulfate and the solvent was evaporated off. The residue was chromatographed on silica gel with methylene dichloride as eluent to give *dimethyl 2-(1-acetyl-3-hydroxy-2-methoxyindolin-2-yl)but-2-enedioate* **19** (280 mg, 80%), mp 150–151 °C (from diethyl ether) (Found: C, 58.4; H, 5.5; N, 4.0. $C_{17}H_{19}NO_7$ requires C, 58.45; H, 5.5; N, 4.0%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3492, 1732 and 1671; δ_H(60 MHz, $CDCl_3$) 2.27 (3H, s), 3.20 (3H, s), 3.70 (6H, s), 4.07 (1H, br), 5.40 (1H, s), 6.73 (1H, br), 7.0–7.5 (3H, m) and 8.17 (1H, br); *m/z* 349 (M^+, 9%), 274 (35), 243 (35), 186 (100) and 43 (38).

Treatment of the indoline 19 with tin(IV) chloride

Tin(IV) chloride (169 mg, 0.65 mmol) was added to a solution of compound **19** (175 mg, 0.5 mmol) in dry methylene dichloride (5 ml) at 0 °C under argon. The mixture was stirred for 1 h, quenched with brine, and extracted with methylene dichloride. The extract was dried over magnesium sulfate and the solvent was evaporated off. The residue was chromatographed on silica gel with ethyl acetate–hexane (1:1) as eluent to give a diastereoisomer mixture of dimethyl 2-(1-acetyl-3-oxoindolin-2-yl)but-2-enedioate **20** (51 mg, 32%) and dimethyl 2-(3-oxoindolin-2-ylidene)butanedioate **21** (7 mg, 5%).

Compound **20**; mp 154–158 °C (decomp., from ethyl acetate–diethyl ether); $\nu_{max}(CHCl_3)/cm^{-1}$ 1732 and 1685; δ_H(60 MHz; $CDCl_3$) 2.26 (3H, s), 3.56 (3H, s), 4.16 (3H, s), 6.60 (1H, s), 6.96 (1H, s), 7.16 (1H, t, *J* 6.7), 7.5–8.0 (2H, m) and 8.41 (1H, d, *J* 8.2); *m/z* 317 (M^+, 27%), 275 (35) and 243 (100).

Compound **21**; mp 207–214 °C (decomp., from methanol) (Found: C, 60.8; H, 4.6; N, 5.1. $C_{14}H_{13}NO_5$ requires C, 61.1; H, 4.75; N, 5.1%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3420, 1740, 1684 and 1606; δ_H(60 MHz; $CDCl_3$) 3.67 (3H, s), 3.78 (3H, s), 4.03 (2H, s), 6.68 (1H, t, *J* 7), 7.2–7.65 (2H, m) and 9.40 (1H, br s); *m/z* 275 (M^+, 58%), 243 (100), 216 (33), 211 (42), 184 (44) and 156 (51).

General procedure for the reaction of Michael adducts 5, 7a–c, and 10 with ammonium acetate

A mixture of a Michael adduct **5**, **7a**–**c**, or **10** (1 mmol) and ammonium acetate (10 mmol) in acetic acid (2 ml) was treated at 100 °C or 65 °C for 1–5 h. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by column chromatography to give the corresponding heterocyclic compounds **22**, **23**, **24a**–**c**, or **28**.

Bis(9-acetylcarbazol-3-yl)amine 22. *From 7a*. The reaction of compound **7a** (205 mg, 0.75 mmol) with ammonium acetate (770 mg, 10 mmol) was carried out in acetic acid (2 ml) at 100 °C for 1 h. Column chromatography was performed with methylene dichloride as eluent to give *title amine* **22** (131 mg, 81%), mp 227–233 °C (decomp., from chloroform–ethyl acetate) (Found: M^+, 431.1631. $C_{28}H_{21}N_3O_2$ requires *M*, 431.1634); ν_{max}(KBr)/cm^{-1} 3356, 1689 and 1674; δ_H(60 MHz; d_6-DMSO–$CDCl_3$) 2.37 (6H, s) and 7.15–8.5 (14H, m); *m/z* 431 (M^+, 100%), 389 (47) and 347 (77).

From 23. The reaction of **23** (128 mg, 0.5 mmol) was carried out at 100 °C for 1.5 h. Similar treatment gave **22** (70 mg, 65%).

9-Acetyl-9a-methoxy-3-oxo-2,3,9,9a-tetrahydro-4*H*-carbazole 23. The reaction of adduct **7a** (275 mg, 1 mmol) was carried out in acetic acid (1 ml)–methanol (10 ml) at 100 °C for 5 h. Column chromatography was performed with ethyl acetate–hexane (2:3) as eluent to give *title compound* **23** (149 mg, 72%), mp 147.5–148 °C (from diethyl ether) (Found: C, 70.05; H, 5.75; N, 5.35. $C_{15}H_{15}NO_3$ requires C, 70.05; H, 5.9; N, 5.45%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1661, 1636 and 1601; $\delta_H(CDCl_3)$ 2.26 (1H, ddd, *J* 18.3, 12.2, and 5.3), 2.52 (3H, s), 2.56 (1H, dd, *J* 17.8 and 5.3), 2.90 (1H, ddd, *J* 17.8, 12.3, and 5.6), 3.02 (3H, s), 3.07 (1H, dd, *J* 18.3 and 5.6), 6.37 (1H, s), 7.18 (1H, dd, *J* 7.6 and 7.0), 7.49 (1H dd, *J* 8.3 and 7.0), 7.58 (1H, dd, *J* 7.6) and 7.48 (1H, d, *J* 8.3); $\delta_C(CDCl_3)$ 24.4, 32.8, 33.9, 51.1, 92.5, 117.4, 117.9, 121.8, 123.4, 124.6, 134.1, 146.3, 155.6, 170.2 and 197.4; *m/z* 257 (M^+, 24%), 225 (24) and 183 (100).

1-Acetyl-2-(2,5-diphenylpyrrol-3-yl)-1,2-dihydro-3*H*-indol-3-one 24a. *From compound 5*. The reaction of adduct **5** (15 mg, 0.04 mmol) with ammonium acetate (54 mg, 0.8 mmol) was carried out in acetic acid (0.3 ml) at 100 °C for 0.5 h. Column chromatography was performed with ethyl acetate–hexane (2:3) as eluent to give *title compound* **24a** (5.7 mg, 40%), mp 127–130 °C (Found: M^+, 392.1523. $C_{26}H_{20}N_2O_2$ requires *M*, 392.1525); $\nu_{max}(CHCl_3)/cm^{-1}$ 3457, 1725, 1676 and 1607; $\delta_H(CDCl_3)$ 1.85 (3H, s), 5.32 (1H, s), 6.15 (1H, d, *J* 2.6), 7.1–7.6 (9H, m), 7.65–7.85 (4H, m), 8.62 (1H, br s) and 8.65 (1H, d, *J* 8.2); *m/z* 392 (M^+, 100%), 350 (84) and 321 (53).

From compound 24b. Sodium borohydride (45 mg, 1.2 mmol) was gradually added to a solution of the following 2-methoxyindol-3-one **24b** (50 mg, 0.12 mmol) in methanol (3.6 ml) at 0 °C. The reaction mixture was extracted with methylene dichloride. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue (49 mg). To a solution of the residue was slowly added TMSOTf (10 mg, 0.15 mmol) at 0 °C. After 0.5 h, the reaction mixture was extracted with methylene dichloride,

washed with brine, dried over magnesium sulfate, and evaporated to give a residue. The residue was purified by column chromatography with ethyl acetate–hexane (1:2) to give *title compound* **24a** (8.8 mg, 63%).

1-Acetyl-2-(2,5-diphenylpyrrol-3-yl)-2-methoxy-1,2-dihydro-3*H*-indol-3-one 24b. The reaction of adduct **7b** (1.09 g, 2.5 mmol) with ammonium acetate (3.37 g, 50 mmol) was carried out in acetic acid (5 ml) at 100 °C for 1 h. Column chromatography was performed with ethyl acetate–hexane (20:1) as eluent to give *title compound* **24b** (0.79 g, 69%), mp 216–219 °C (from ethyl acetate–hexane) (Found: C, 76.65; H, 5.15; N, 6.55. $C_{27}H_{22}N_2O_3$ requires C, 76.75; H, 5.25; N, 6.62%); ν_{max}(KBr)/cm^{-1} 3350, 1734, 1684, 1661 and 1608; δ_H(60 MHz; $CDCl_3$) 2.13 (3H, s), 3.17 (3H, s), 6.57 (1H, d, *J* 3), 7.1–7.9 (14H, m) and 8.22 (1H, d, *J* 8); *m*/*z* 422 (M^+, 100%), 379 (56), 351 (21) and 246 (70).

1-Acetyl-2-(2,5-dimethylpyrrol-3-yl)-2-methoxy-1,2-dihydro-3*H*-indol-3-one 24c. The reaction of adduct **7c** (15 mg, 0.05 mmol) with ammonium acetate (68 mg, 1 mmol) was carried out in acetic acid (1 ml) at 65 °C for 10 h. Column chromatography was performed with ethyl acetate–hexane (1:2) as eluent to give *title compound* **24c** (8.1 mg, 57%), mp 184–186 °C (from ethyl acetate) (Found: M^+, 298.1319. $C_{17}H_{18}N_2O_3$ requires *M*, 298.1317); ν_{max}(KBr)/cm^{-1} 3455, 1728, 1674 and 1609; δ_H($CDCl_3$) 2.11 (3H, s), 2.21 (3H, s), 2.23 (3H, s), 3.27 (3H, s), 5.62 (1H, d, *J* 3.0), 7.20 (1H, t, *J* 8.2), 7.60 (1H, br), 7.69 (1H t, *J* 7.6), 7.71 (1H, d, *J* 7.3) and 7.69 (1H, t, *J* 7.6); *m*/*z* 298 (M^+, 79%), 266 (34), 255 (100), 213 (57) and 122 (91).

Dimethyl 5-(2-acetamidophenyl)-4-methoxypyrrole-2,3-dicarboxylate 28. The reaction of adduct **10** (120 mg, 0.34 mmol) was carried out in acetic acid (1 ml) at 100 °C for 5 h. Column chromatography was performed with ethyl acetate–hexane (1:1) as eluent to give *title compound* **28** (40 mg, 33%), mp 197–199 °C (from ethyl acetate–hexane) (Found: C, 59.5; H, 5.2; N, 7.8. $C_{17}H_{18}N_2O_6$ requires C, 58.95; H, 5.25; N, 8.1%); ν_{max}($CDCl_3$)/cm^{-1} 3444 and 1701; δ_H($CDCl_3$) 2.11 (3H, s), 3.71 (3H, s), 387 (3H, s), 3.94 (3H, s), 7.11 (1H, d, *J* 7.2), 7.23–7.34 (2H, m), 7.98 (1H, d, *J* 8.2), 8.73 (1H, s) and 10.10 (1H, br s); δ_C($CDCl_3$) 24.4, 52.15, 52.25, 63.3, 113.4, 119.2, 121.2, 122.2, 124.2, 124.6, 128.9, 129.1, 134.9, 142.5, 160.3, 164.3 and 169.1; *m*/*z* 346 (M^+, 100%), 272 (65) and 257 (58).

X-Ray structure analysis of the pyrrole 28

Crystal data. $C_{17}H_{18}N_2O_6$, M = 346.34, T = 296 K, Triclinic, a = 9.628(3), b = 11.717(2), c = 8.213(3) Å, α = 98.35(2), β = 110.36(2), γ = 85.01(2)°, V = 858.7(4) Å^3 (from setting angles of 25 centred reflections with $35.09 < 2\theta < 44.42$; λ = 1.541 78 Å, T = 296 K), space group $P1$(#2), Z = 2, D_c = 1.34 g cm^{-3}. Prisms 0.25 × 0.20 × 0.13 mm^3, μ(Cu-Kα) = 8.66 cm^{-1}.

Data collection and processing. Rigaku AFC7R four-circle diffractometer with fine-focused 3.7 kW rotating anode generator, $\omega/2\theta$ scans with ω scan width (1.68 + 0.30 tan θ)°, graphite-monochromated Cu-Kα radiation; 3105 reflections measured to $2\theta_{max}$ = 130.2°, giving 2332 with $I > 3\sigma(I)$ which were retained in all calculations. No decay correction was observed and no corrections were applied for absorption.

Structure solution and refinement. The structure was solved by direct methods using SAPI91,[15] expanded using Fourier techniques DIRDIF94[16] and refined by the full-matrix least-squares method with all non-H-atoms anisotropic. All calculations were performed using the teXsan[17] crystallographic software package from Molecular Structure Corporation. The weighting scheme $w = 4F_o^2/\sigma^2(F_o^2)$ gave satisfactory agreement analyses. Final *R*-value was 0.051, R_w = 0.047, S = 1.80 and 227 refined parameters. The maximum and minimum peaks on the final ΔF map corresponded to 0.21 and −0.25 e Å^{-3}, respectively.

Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web page (http//www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/288.

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Paper 8/07895E