Inter- and Intra-molecular Reactions of Indol-2-yl Carbenes and Related Species. Preparation of 1,1a,2,8b-Tetrahydroazirino[2',3':3,4]pyrrolo[1,2-*a*]indoles

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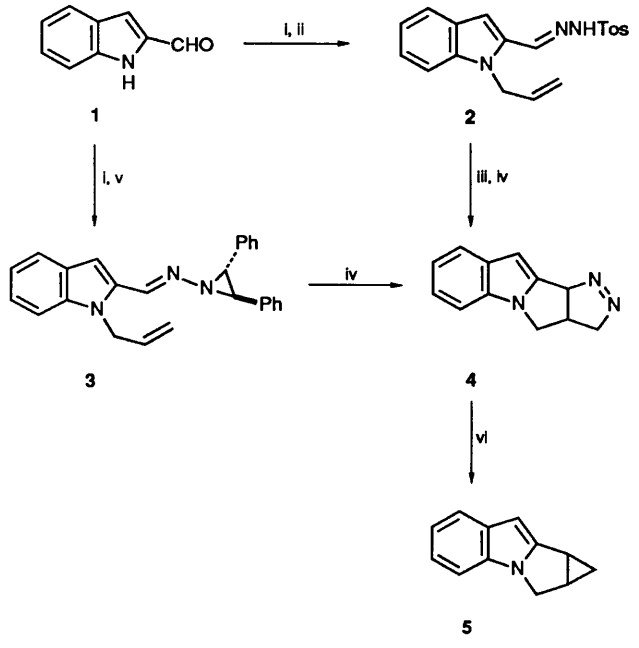
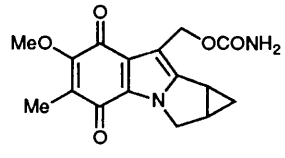
The intramolecular cycloaddition of 2-indolylcarbenes, or their precursors, has been successfully extended to the C=N bond of *O*-methyl oximes. Thus the sodium salts of the tosylhydrazones **10**, prepared from the corresponding indole-2-carbaldehydes, decomposed to the azirinopyrroloindoles **11**. The *N*-methoxyaziridine **11a** exists as a single invertomer at nitrogen. Several 1-(2-alkynyl)indole-2-carbaldehydes were converted into the corresponding Eschenmoser hydrazones by reaction with *trans*-1-amino-2,3-diphenylaziridine. No addition of the resulting carbene onto the triple bond occurred upon thermolysis. The only products that were isolated corresponded to attack of the carbene on the solvent. In one case the carbene could be trapped bimolecularly to give an indolyl substituted cyclopropane derivative.

The development of new methods for the construction of mono- and poly-cyclic heterocyclic rings continues to be of paramount importance to organic chemists, and in recent years cycloaddition reactions, both inter- and intra-molecular, have played a key role in this area.[1] Within the family of cycloaddition reactions, the reactions of diazo compounds, or their precursors, have been studied under thermal, photochemical and transition-metal catalysed conditions, such that the intramolecular cyclisation of the resulting carbenes or carbenoids by addition to a C=C bond have become useful reactions.[2] In contrast, the corresponding reactions with C=N,[3] C=O[4] and C≡C bonds[5] have been less widely studied, until the recent investigation by one of us.[3–5]

In connection with the development of new methods for the synthesis of pyrrolo[1,2-*a*]indoles,[6] compounds related to the antitumour mitomycins and mitosenes,[7] we have recently described the preparation of novel cyclopropapyrrolo[1,2-*a*]indoles by intramolecular cycloaddition.[8] Thus, thermal decomposition of the sodium salt of the tosylhydrazone **2**, readily prepared from indole-2-carbaldehyde **1**, results in intramolecular cycloaddition to give, after loss of nitrogen, the desired cyclopropapyrroloindole **5** (Scheme 1). At lower temperatures, the intermediate cycloadduct, the pyrazoline **4** could be isolated,[9] although this was best obtained from the hydrazone **3** derived from *trans*-1-amino-2,3-diphenylaziridine.[10] Eschenmoser and his co-workers have used aziridinylimines as masked diazo compounds; these have the advantage over other diazoalkane precursors, such as tosylhydrazones, that they are cleaved thermally without the introduction of an external base, and being soluble in organic solvents, they allow homogeneous reactions to occur. The overall reaction (Scheme 1) has been extended to substituted allyl groups,[8] and has been used in preparation of a fully functionalised cyclopropamitosene **6**.[11]



Scheme 1 *Reagents and conditions:* i, NaH, DMF, $H_2C{=}CHCH_2Br$; ii, $TosNHNH_2$, MeOH; iii, NaH, THF; heat, benzene; iv, benzene, reflux; v, *trans*-1-amino-2,3-diphenylaziridine, ether; vi, xylene, reflux



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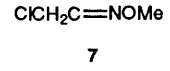

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We have now studied the corresponding reactions of 1-substituted $CH_2CH{=}NR$ and $CH_2C{\equiv}CR$ indoles in order to learn more about cycloaddition to other π-bonds, and also as a route to mitomycin related pyrroloindoles, and we report herein our results in full.[12]

Results and Discussion

Addition to C=N *Bonds.*—The 1,3-dipolar cycloaddition of dipoles to various hetero-substituted pi-bonds has been studied extensively over the past three decennia.[2] Single step, concerted reactions occur with a wide variety of dipolarophiles such as carbonyl compounds and nitriles. Therefore, it is somewhat surprising that oxime ethers have received only scarce attention as dipolarophiles and that the synthetic usefulness of the reaction has not been evaluated at all. As part of our research in this area,[6,8] we thought that the intramolecular addition of diazoalkanes to oxime ethers would represent a general approach toward the synthesis of bicyclic aziridines. By analogy with our previous work (Scheme 1),[8] the required indole

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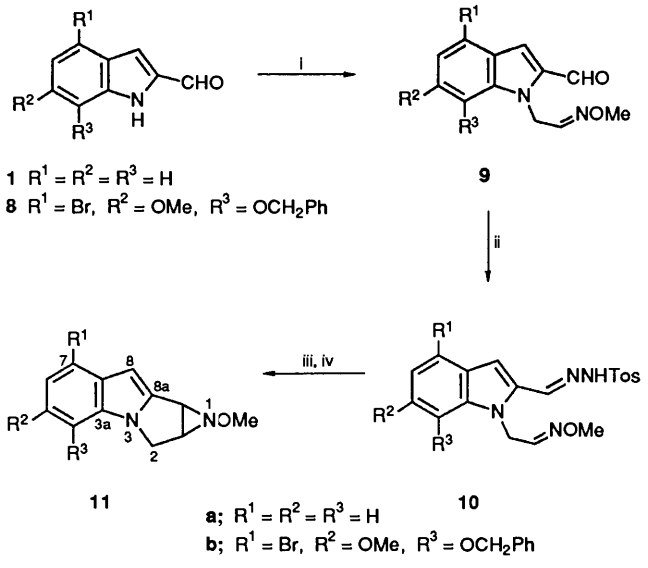
1-substituent should be introduced from a halide of the type, $XCH_2CH{=}NR$. However, few such species are readily available, and therefore the *O*-methyl oxime, $ClCH_2CH{=}NOMe$ **7** was chosen. This was prepared, following a patent procedure,[13] as a 7:3 mixture of geometric isomers by the reaction of aqueous chloroacetaldehyde with methoxylamine hydrochloride. Attempts to condense other nitrogen reagents with chloroacetaldehyde were largely unsuccessful, except for *O*-benzylhydroxylamine and 2,4-dinitrophenylhydrazine.[14] Addition of the chlorooxime **7** to the sodium salt of indole-2-carbaldehyde **1** in DMF resulted in recovery of the indole aldehyde. However, adding sodium hydride in portions during 30 min to a mixture of aldehyde **1** and chlorooxime **7** gave the required indole **9a** in 79% yield. Reaction of **9a** with $TosNHNH_2$ gave the tosylhydrazone **10a**; decomposition of the latter under the usual conditions gave the desired aziridinopyrrolo[1,2-*a*]indole **11a** in 61% yield (Scheme 2), with no evidence for any intermediate [3 + 2] cycloadduct. Thus, it is possible to form fused aziridines by intramolecular cycloaddition of a carbene, or its precursor, to a C=N bond. Although such a process has been previously suggested as a mechanistic possibility,[15] it had not been firmly established. Indeed, the formation of aziridines, either directly or indirectly *via* 1,2,3-triazolines, by *intermolecular* cycloaddition of neutral C=N bonds to carbenes or diazo compounds is rare.[16–18] This is in direct contrast to the preparation of aziridines by inter- and intra-molecular addition of nitrenes, or related species, to alkene C=C bonds.[19]

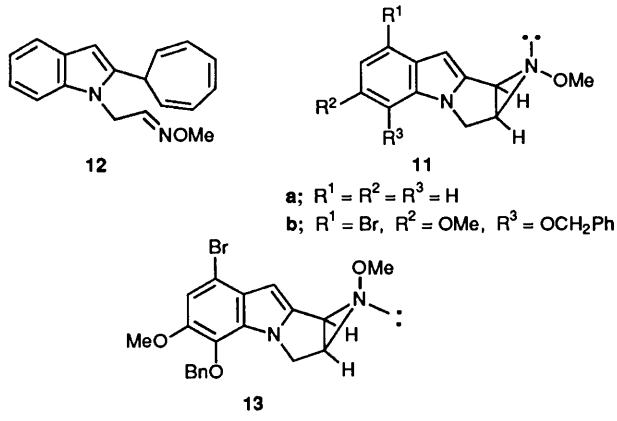


Scheme 2 *Reagents and conditions:* i, $MeON{=}CHCH_2Cl$, 7, DMF, NaH; ii, $TosNHNH_2$, MeOH; iii, NaH, THF; iv, benzene, heat

The desired cycloadduct **11a** was accompanied by a minor product (12%) identified as the cycloheptatriene **12**, the result of a net addition of the indolylcarbene to the solvent, benzene. When the sodium salt of the tosylhydrazone **10a** was decomposed in boiling chlorobenzene, the yield of **11a** was increased to 73% with no solvent adduct being formed.

Similarly, the more highly substituted indole aldehyde **8**[20] was converted into the corresponding azirinopyrrolo[1,2-*a*]indole **11b** *via* the aldehyde **9b** (65%) and tosylhydrazone **10b** (93%), the yield in the key cycloaddition step being 86%.

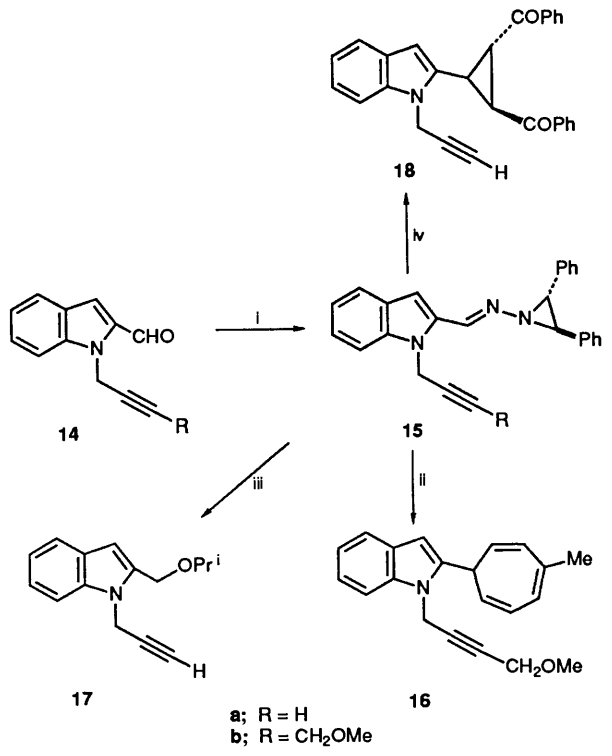
The structure of the azirinopyrroloindole **11a** was confirmed by X-ray crystallography which showed that, in the crystalline state at least, the aziridine **11a** existed as a single invertomer with the methoxy group *cis* to the ring-junction protons. It is well known that oxygen substituents raise the inversion barrier at nitrogen, and the synthesis and resolution of simple *N*-alkoxyaziridines has been studied previously.[16,21] In the case of



the fused aziridine **11b** we were able to isolate both invertomers of the aziridine, and separate them by chromatography. The major isomer (64%) is, by analogy with **11a**, assigned the *exo* structure **11b**, with the minor isomer (19%) the *endo* structure **13**. Since the invertomers **11b** and **13** exhibit significant differences in their NMR spectra, we were able to take a pure sample of the minor isomer **13** (N–OMe at δ 3.38, benzyl CH_2,AB at δ 5.13) and heat it in [$^2H_6$]DMSO in the probe of an NMR spectrometer. At about 70 °C, the peaks due to the other invertomer **11b** (N–OMe at δ 3.49, benzyl CH_2, singlet at δ 5.09) became clearly visible, and by about 110 °C, an equilibrium ratio of **11b**–**13** 5.5:1 was attained.

Attempted Addition to C≡C *Bonds.*—One of the more important pathways for assembling complex carbocyclic systems involves the intramolecular cyclopropanylation of olefins.[22] Since the pioneering observation by Stork and Ficini in 1961,[23] intramolecular reactions of unsaturated diazo compounds have attracted considerable interest. The mechanistic as well as the stereochemical aspects of carbon–carbon bond formation by this method have been studied in detail,[24] and a vast array of experimental conditions for the generation of carbenes and carbenoids is offered through excellent reviews.[25–27] By comparison, the intramolecular addition of diazo compounds to acetylenes is far less common. With the exception of an earlier report by Jones and Mykytka,[28] the internal cyclopropenylation reaction of diazo alkynes is essentially unexplored.[5] In order to investigate the intramolecular addition of indol-2-yl carbenes to C≡C bonds, the indole aldehydes **14a** and **14b** were prepared by reaction of indole-2-carbaldehyde **1** with prop-2-ynyl bromide and 1-bromo-4-methoxybut-2-yne, respectively, in the presence of sodium hydride in DMF. The aldehydes **14** were converted into the corresponding 'Eschenmoser hydrazones' **15** by reaction with *trans*-1-amino-2,3-diphenylaziridine. The hydrazones **15** were not purified, but were heated directly to generate the corresponding carbenes. When hydrazone **15b** was heated in toluene, no addition to the triple bond occurred, the only identifiable product being the solvent–adduct, the cycloheptatriene **16** (78% yield). Likewise, when the hydrazone **15a** was heated in propan-2-ol, only the solvent O–H insertion product **17** was formed in 82% yield. We also examined the reaction of hydrazone **15a** with an external trapping agent. Heating a sample of **15b** in the presence of *trans*-1,2-dibenzoylethene in dichloromethane in a sealed tube afforded the carbene derived cyclopropane **18**.

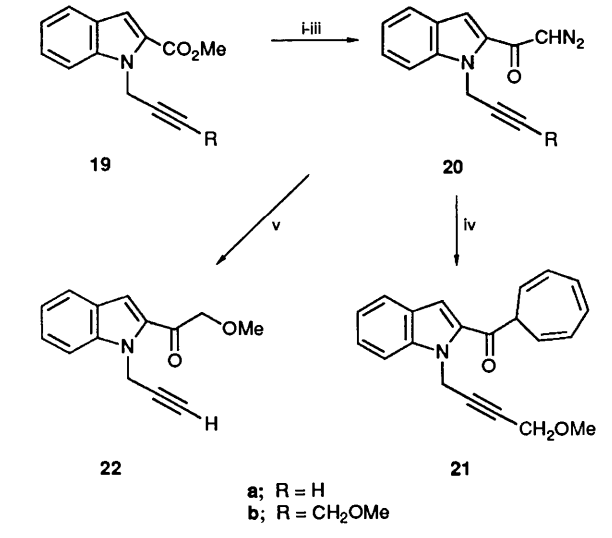
With the failure to observe any C≡C addition in the above reactions, and since the rhodium(II)-catalysed intramolecular addition of diazoketones to acetylenic π-bonds had previously been successful,[5] the corresponding diazoketones in the indole series were prepared. Thus, methyl indole-2-carboxylate was alkylated with prop-2-ynyl bromide or 1-bromo-4-methoxybut-



Scheme 3 *Reagents and conditions:* i, *trans*-1-amino-2,3-diphenylaziridine; ii, heat, toluene; iii, heat, propan-2-ol; iv, *trans*-1,2-dibenzoylethene, CH_2Cl_2, 120 °C

2-yne to give the esters **19a** (68%) and **19b**) (62%), respectively. Hydrolysis of the esters using potassium trimethylsilanolate,[29] followed by mixed anhydride formation, and reaction with diazomethane gave the diazoketones **20** as yellow solids. However, on rhodium(II) catalysed decomposition, the diazoketones only gave solvent addition products with no evidence for interaction of the rhodium carbenoid with the triple bond. Thus, treatment of **20b** with rhodium(II) mandelate in benzene gave the cycloheptatriene **21** (72%). Reaction of **20a** with rhodium(II) mandelate in methanol gave the methoxymethyl ketone **22** (74%) by O–H insertion.

The failure of the rhodium carbenoid to react with the triple bond may well be related to geometric factors. Further studies are planned in order to probe this point.



Scheme 4 *Reagents:* i, Me_3SiOK, ether; ii, $ClCO_2Me$; iii, CH_2N_2, ether; iv, cat. rhodium(II) mandelate, benzene; v, cat. rhodium(II) mandelate, methanol

Conclusions

The intramolecular cycloaddition of indol-2-ylcarbenes, or their precursors, has been successfully extended to the C=N bond of *O*-methyl oximes. The resulting azirinopyrroloindoles are closely related to the mitomycin–mitosene antitumour antibiotics, and the application of this cycloaddition process in this area is continuing.[30] The corresponding addition reactions to C≡C bonds were not observed, however, and only intermolecular solvent derived products were isolated.

Experimental

For general experimental procedures, see references 6 and 8. All *J* values are in Hz.

1-*Chloro*-2-*methoxyiminoethane* **7**.—Methoxylamine hydrochloride (13.9 g, 166 mmol) and chloroacetaldehyde solution (45% v/v water, 10.0 g, 125 mmol) were stirred vigorously for 12 h in a stoppered round bottom flask (100 cm^3). The mixture was extracted with ether (5 × 50 cm^3), the combined extracts were washed with water (2 × 100 cm^3) then dried ($MgSO_4$). The ethereal solution was condensed to a volume of 25 cm^3 using a rotary evaporator while keeping a supply of ice in the water bath. The residual volume was transferred to a distillation apparatus, the remaining ether carefully distilled and then the remaining residue distilled cleanly at 105 °C, giving the *title compound* **7** as a 7:3 mixture of geometric isomers (2.7 g, 20%) as a colourless oil, b.p. 105 °C (lit.,[13] 106–108 °C); ν_{max}(film)/cm^{-1} 1625, 1255, 1104, 1039, 852 and 471; δ_H(250 MHz; $CDCl_3$) 7.40 (0.7 H, t, *J* 6, CH_2CH), 6.79 (0.3 H, t, *J* 4, CH_2C*H*), 4.20 (0.6 H, d, *J* 4, CH_2), 4.07 (1.4 H, t, *J* 6, CH_2), 3.89 (0.9 H, s, MeO) and 3.84 (2.1 H, s, MeO).

1-(2-*Methoxyiminoethyl*)*indole*-2-*carbaldehyde* **9a**.—Sodium hydride (50%; 0.292 g, 6.10 mmol) was added in portions to a stirred solution of indole-2-carbaldehyde **1** (0.885 g, 6.10 mmol) and 1-chloro-2-methoxyiminoethane (0.903 g, 7.324 mmol) in dry DMF (60 cm^3). On completion of the addition of all the base (approx. 30 min), water (2 cm^3) was added, and the mixture extracted with ethyl acetate (250 cm^3). The combined extracts were washed with water (2 × 100 cm^3), brine (1 × 50 cm^3) and then dried ($MgSO_4$). Removal of the solvent under reduced pressure, followed by chromatography of the residue gave the *title compound* **9a** (1.04 g, 79%) as a colourless oil (Found: C, 66.5; H, 5.7; N, 12.7. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6; N, 13.0%); ν_{max}(film)/cm^{-1} 1671, 1615, 1462, 1116, 753 and 738; δ_H(250 MHz; $CDCl_3$) (2.5:1 mixture of *Z*–*E*) 9.90 (1 H, s, CHO), 7.78–7.19 (5 H, m, ArH + 3-H), [6.68 (t, *J* 4) and 7.78–7.19 (t, hidden) 1 H, CH=NOMe], [5.49 (d, *J* 4) and 5.32 (d, *J* 6), 2 H, CH_2CH=N], 4.01 and 3.85 (3 H, s, MeO); *m*/*z* 216 (M^+, 44%), 215 (44), 199 (100), 185 (74) and 168 (97).

1-(2-*Methoxyiminoethyl*)*indole*-2-*carbaldehyde Tosylhydrazone* **10a**.—Tosylhydrazide (0.493 g, 2.648 mmol) and 1-(2-methoxyiminoethyl)indole-2-carbaldehyde **9a** (0.520 g, 2.4074 mmol) were stirred in methanol (10 cm^3) for 30 min. The resulting precipitate was collected, and recrystallised from methanol–water to give the *title compound* **10a** (0.831 g, 97%) as a colourless crystalline solid, m.p. 129–131 °C (Found: C, 59.2; H, 5.2; N, 14.5. $C_{19}H_{20}N_4O_3S$ requires C, 59.4; H, 5.2; N, 14.6%); ν_{max}(Nujol)/cm^{-1} 3187, 1600, 1370, 1165 and 1043; δ_H(250 MHz; $CDCl_3$) (1:1 mixture of *E*–*Z*) 8.22 and 8.14 (1 H, s, NH), 7.80 (1 H, s, HC=NTos), 7.78 (2 H, d, *J* 8, Tos AB), 7.22 (2 H, d, *J* 8, Tos AB), 7.52–7.00 (4 H, m, ArH), 6.63 and 6.62 (1 H, s, 3-H), 6.49 (and 7.52–7.00 (hidden) (1 H, t, *J* 4, CH_2CH=NOMe), 5.42 and 5.18 (2 H, d, *J* 4 and 5, CH_2-CH=NOMe), 4.10 and 3.89 (3 H, s, MeO) and 2.43 (3 H, s, Tos Me); *m*/*z* 356 (M^+ −28, 11%), 201 (100), 170 (76) and 91 (88).

N-*Methoxy*-1,1a,2,8b-*tetrahydroaziridino*[2′,3′:3,4]*pyrrolo*-[1,2-a]*indole* **11a**.—Sodium hydride (50%; 0.060 g, 1.25 mmol) was added to a solution of 1-(2-methoxyiminoethyl)indole-2-carbaldehyde tosylhydrazone **10a** (0.480 g, 1.25 mmol) in dry THF (10 cm^3). The mixture was stirred at room temperature for 10 min, and a solid precipitated from the solution, which was collected by filtration, washed with THF (*ca.* 15 cm^3), and dried using a vacuum pump. The dry solid was then dissolved in dry benzene (80 cm^3), and the solution was refluxed for 2 h. The solution was then concentrated under reduced pressure, and the residual oil purified by column chromatography to give the *title compound* **11a** (0.1525 g, 61%) as a colourless crystalline solid, m.p. 95–96 °C. (Found: C, 71.7; H, 6.0; N, 14.0. $C_{12}H_{12}N_2O$ requires C, 72.0; H, 6.0; N, 14.0%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1600, 1450, 1170, 1100 and 890; δ_H(250 MHz; $CDCl_3$) 7.57 (1 H, d, *J* 9, ArH), 7.18–7.03 (3 H, m, ArH), 6.46 (1 H, s, 8-H), 4.28 (1 H, d, *J* 12, 2-HH), 4.16 (1 H, dd, *J* 12, 4, 4, 2-HH), 3.64 (3 H, s, MeO) and 3.56 (2 H, m, 1a H + 8b H); *m/z* 200 (M^+, 74%), 169 (100), 155 (89) and 154 (570).

Also isolated was 1-(2-*methoxyiminoethyl*)-2-*cyclohepta*-2,4,6-*trienylindole* **12** (0.042 g, 12%), as a colourless oil (Found: M^+, 278.1414. $C_{18}H_{18}N_2O$ requires *M*, 278.1419); $\nu_{max}(CDCl_3)/cm^3$ 1620, 1460, 1370, 1180, 1060 and 880; δ_H(250 MHz; $CDCl_3$) (3:2 mixture of *E*–*Z*) 7.68–7.12 (4 H, m, ArH), 6.83 (2 H, m, triene 4-, 5-H), 6.65 (1 H, s, 3-H), 6.60 (and 7.68–7.12, hidden) (1 H, t, *J* 4, CH_2CH=NOMe), 6.38 (2 H, m, triene 3-, 6-H), 5.52 (2 H, m, triene 2-, 7-H), 4.92 and 4.78 (2 H, d, *J* 4, *J* 5, CH_2CH=NOMe), 3.98 and 3.85 (3 H, s, MeO) and 2.90 (1 H, m, triene 1-H); *m/z* 278 (M^+, 100%), 264 (35), 247 (63), 220 (71), 281 (95) and 206 (94).

Thermolysis of the Sodium Salt of Compound **10a** *using Chlorobenzene*.—In one experiment, the procedure was used exactly as above, except chlorobenzene was used as the thermolysis solvent. Thus, **10a** (0.022 g, 0.0572 mmol) and sodium hydride (0.003 g, 0.0572 mmol) were thermolysed in chlorobenzene (5 cm^3) at 80 °C for 30 min, which gave aziridine **11a** (0.0084 g, 73%) identical with previous sample. No trace of the chloro version of **12** was detected. Attempts to carry out this reaction on a much larger scale with chlorobenzene as the thermolysis solvent resulted in significantly lower yields of **11a**, and streaking was noted on TLC.

7-*Benzyloxy*-4-*bromo*-6-*methoxy*-1-(2-*methoxyiminoethyl*)-*indole*-2-*carbaldehyde* **9b**.—Sodium hydride (50%; 0.160 g, 3.32 mmol) was added in portions to a stirred solution of 7-benzyloxy-4-bromo-6-methoxyindole-2-carbaldehyde **8** (1.00 g, 2.76 mmol) and 1-chloro-2-methoxyiminoethane **7** (0.412 g, 3.32 mmol) in dry DMF (60 cm^3). On completion of the addition of all the base (approx. 30 min) the mixture was warmed to 60 °C for 2 h, then water (5 cm^3) added, and the mixture was extracted with ethyl acetate (250 cm^3). The combined extracts were washed with water (2 × 100 cm^3), brine (1 × 50 cm^3) and then dried ($MgSO_4$). Removal of solvent under reduced pressure, followed by chromatography of the residue gave the *title compound* **9b** (0.770 g, 65%) as a colourless solid, m.p. 94–104 °C (Found: C, 55.8; H, 4.3; N, 6.4. $C_{20}H_{19}BrN_2O_4$ requires C, 55.7; H, 4.4; N, 6.5%); ν_{max}(Nujol)/cm^{-1} 1663, 1610, 1446, 1249, 1138 and 1044; δ_H(270 MHz; $CDCl_3$) (3:2 mixture of *Z*:*E*) 9.44 and 9.43 (1 H, s, CHO), 7.18–7.0 (5 H, m, ArH), 6.89 (1 H, s, 3-H), 6.79 (1 H, s, 5-H), 6.25 (and 7.18–7.0 hidden) (1 H, t, *J* 4, CH_2CH=N), 5.31 and 5.15 (2 H, d, *J* 4, 5, CH_2CH=N), 4.80 and 4.72 (2 H, s, OCH_2), 3.62 (3 H, s, 5-MeO) and 3.45 with 3.38 (3 H, s, NOMe); *m/z* 432/430 (M^+, 15%), 341/339 (30) and 91 (100).

7-*Benzyloxy*-4-*bromo*-6-*methoxy*-1-(2-*methoxyiminoethyl*)-*indole*-2-*carbaldehyde Tosylhydrazone* **10b**.—Tosylhydrazide (0.173 g, 0.9314 mmol) and 7-benzyloxy-4-bromo-6-methoxy-1-(2-methoxyiminoethyl)indole-2-carbaldehyde **9b** (0.365 g, 0.8468 mmol) were stirred in methanol (15 cm^3) for 30 min at 40 °C. The resulting precipitate was collected, and recrystallised from methanol–water to give the *title compound* **10b** (0.473 g, 93%) as a colourless crystalline solid, m.p. 174–175 °C (decomp.) (Found: C, 53.8; H, 4.4; N, 9.1. $C_{27}H_{27}BrN_4O_5S$ requires C, 54.1; H, 4.5; N, 9.3%); ν_{max}(Nujol)/cm^{-1} 3200, 1620, 1160 and 900; δ_H [250 MHz; $(CD_3)_2CO$] (3:2, *E*–*Z*) major, 10.16 (1 H, s, NH), 8.04 (1 H, s, CH=NNHTos), 7.83–7.33 [9 H, m, ArH + 1 H (hidden) CH_2CH], 7.18 (1 H, s, 3-H), 6.69 (1 H, s, 6-H), 5.62 (2 H, d, *J* 4, CH_2CH=N), 5.10 (2 H, s, CH_2OBn), 3.96 (3 H, s, 6-MeO), 3.85 (3 H, s, MeON) and 2.40 (3 H, s, TosMe); minor, 10.24 (1 H, s, NH), 8.03 (1 H, s, CH=NNHTos), 7.83–7.33 (9 H, m, ArH), 7.27 (1 H, t, *J* 4.6, CH_2CH), 7.17 (1 H, s, 3-H), 6.69 (1 H, s, 5-H), 5.48 (2 H, d, *J* 4.6, CH_2CH), 5.18 (2 H, s, CH_2OBn), 3.96 (3 H, s, 5-MeO), 3.62 (3 H, s, MeO) and 2.40 (3 H, s, TosMe); *m/z* 572/570 (M^+ − 28, 6%), 481/479 (18), 417/415 (20), 293 (61) and 91 (100).

4-*Benzyloxy*-7-*bromo*-1,5-*dimethoxy*-1,1a,2,8b-*tetrahydro*-*azirino*[2′,3′:3,4]*pyrrolo*[1,2-a]*indoles* **11b**, **13**.—Sodium hydride (50%; 0.020 g, 0.408 mmol) was added to a solution of 7-benzyloxy-4-bromo-6-methoxy-1-(2-methoxyiminoethyl)-indole-2-carbaldehyde tosylhydrazone **10b** (0.245 g, 0.408 mmol) in dry THF (5 cm^3). After being stirred at room temperature for 10 min, the mixture was filtered and the filtrate evaporated under reduced pressure to give a white foamy residue, which was then dried using a vacuum pump. The dry solid was then dissolved in dry benzene (130 cm^3), and the solution refluxed for 30 min. The solution was then concentrated under reduced pressure, and the residue purified by column chromatography to give the *title compound*, as a mixture of invertomers *exo*-**11b** (0.108 g, 67%) as a pale yellow crystalline solid, m.p. 112 °C, and *endo*-**13** (0.032 g, 19%) as a yellow solid, m.p. 107–109 °C.

Compound **11b** (Found: C, 57.8; H, 4.6; N, 6.7. $C_{20}H_{19}BrN_2O_3$ requires C, 57.8; H, 4.6; N, 6.7%); ν_{max}(Nujol)/cm^{-1} 1500, 1260, 1180, 1120 and 720; δ_H(250 MHz; $CDCl_3$) 7.46–7.34 (5 H, m, ArH), 6.95 (1 H, s, 8-H), 6.35 (1 H, s, 6-H), 5.10 (2 H, s, *J* 11 Hz, CH_2OBn), 4.25 (1 H, d, *J* 12.5, 2-CHH), 4.06 (1 H, dd, *J* 12.5, 5, 2-CHH), 3.89 (3 H, s, 5-MeO), 3.70 (2 H, m, 1a-, 8b-H) and 3.49 (3 H, s, N–OMe); *m/z* 416/414 (M^+, 36%), 385/383 (24), 325/323 (79), 280/278 (100) and 91 (74).

Compound **13** (Found: C, 57.85; H, 4.4; N, 6.4. $C_{20}H_{19}BrN_2O_3$ requires C, 57.8; H, 4.6; N, 6.7%); ν_{max}(Nujol)/cm^{-1} 1520, 1280, 1270, 1180, 1120 and 720; δ_H(250 MHz; $CDCl_3$) 7.47–7.55 (5 H, m, Ar), 6.96 (1 H, s, 8-H), 6.37 (1 H, s, 6-H), 5.13 (2 H, ABq, CH_2OBn), 4.30 (1 H, d, *J* 13, 2-CHH), 4.10 (1 H, dd, *J* 13, 5, 2-CHH), 3.91 (3 H, s, 5-MeO), 3.605–3.40 (2 H, m, 1a-, 8b-H) and 3.38 (3 H, s, N–OMe); *m/z* 416/414 (M^+, 25%), 385/383 (14), 325/323 (43), 280/278 (44) and 57 (100).

1-(*Prop*-2-*ynyl*)*indole*-2-*carbaldehyde* **14a**.—To a solution containing indole-2-carbaldehyde **1** (1.5 g, 10.3 mmol) in DMF (35 cm^3) was added sodium hydride (60% dispersion; 0.41 g). The mixture was stirred under a nitrogen atmosphere for 30 min at 0 °C and then prop-2-ynyl bromide (1.8 g, 1.5 equiv.) was added dropwise. When the addition was complete, stirring was continued for an additional 2 h. The mixture was washed with water, extracted with ether and the ether layer was dried over magnesium sulphate. Concentration of the solution under reduced pressure left a residue which was recrystallised from ether–hexane to give the *title aldehyde* **14a** (1.23 g, 65%), m.p. 137–138 °C (Found: C, 78.5; H, 4.8; N, 7.5. $C_{12}H_9NO$ requires C, 78.6; H, 4.9; N, 7.6%); ν_{max}(KBr)/cm^{-1} 3250, 2880, 1680, 1370, 1180 and 1025; δ_H(90 MHz; $CDCl_3$) 2.21 (1 H, t, *J* 3.2), 5.42 (2 H, d, *J* 3.2), 7.20–7.85 (5 H, m) and 9.86 (1 H, s); δ_C(20

MHz; $CDCl_3$) 34.3, 72.5, 78.6, 111.3, 118.8, 122.3, 123.8, 128.1, 134.7, 140.1 and 182.6.

2-Isopropoxymethyl-1-(prop-2-ynyl)indole **17**.—To a solution containing the aldehyde **14** (1.2 g) in dry benzene (25 cm^3) was added *trans*-1-amino-2,3-diphenylaziridine (1.64 g, 1.2 equiv.).[10] The reaction mixture was stirred for 1 h at room temperature and the solvent was removed under reduced pressure at a temperature below 30 °C. The resulting crude hydrazone **15a** was used in the next step without further purification; $\nu_{max}(CHCl_3)/cm^{-1}$ 3300, 3085, 2110, 1645, 1495, 1350 and 1025; δ_H(90 MHz; $CDCl_3$) 2.23 (1 H t, *J* 3.2), 3.76 (2 H, s), 5.10 (2 H, d, *J* 3.2), 6.60 (1 H, s), 7.12–7.65 (4 H, m) and 8.33 (1 H, s).

The crude hydrazone **15a** was dissolved in propan-2-ol (25 cm^3) and the mixture was heated at reflux for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column using a 3:1 mixture of hexane–ethyl acetate as the eluent. The major fraction isolated (82%) was identified as the *indole* **17** (Found: C, 79.1; H, 7.4; N, 6.0. $C_{15}H_{17}NO$ requires C, 79.2; H, 7.5; N, 6.0%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3300, 3080, 2110, 1620, 1470, 1180 and 750; δ_H(300 MHz; $CDCl_3$) 1.18 (d, 6 H, *J* 2.4), 2.25 (1 H, t, *J* 3.2), 3.70 (1 H, q, *J* 2.4), 4.70 (2 H, s), 5.01 (2 H, d, *J* 3.2) and 7.08–7.50 (5 H, m); δ_C(20 MHz; $CDCl_3$) 21.3, 34.7, 67.5, 69.6, 72.6, 78.8, 111.5, 118.9, 122.5, 123.9, 127.7, 128.3, 134.9 and 140.3.

1-Bromo-4-methoxybut-2-yne.—To an ether solution of ethylmagnesium bromide (100 mmol) was added methyl prop-2-ynyl ether (5.0 g) diluted with diethyl ether (10 cm^3) dropwise at 0 °C. The mixture was stirred at 0 °C for 2 h and paraformaldehyde (2 equiv.) was added in one portion. The mixture was stirred at room temperature for 2 h and was then washed with saturated aqueous ammonium chloride. Extraction with ether was followed by drying over magnesium sulphate. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column using a 5:1 hexane–ethyl acetate mixture as the eluent. The major product isolated in 72% yield was identified as 4-methoxybut-2-yn-1-ol on the basis of its spectral data: ν_{max}(neat)/cm^{-1} 3600–3200, 2980, 1455, 1370, 1240, 1140 and 920; δ_H(90 MHz; $CDCl_3$) 2.92 (1 H, t, *J* 6), 3.40 (3 H, s), 4.18 (2 H, d, *J* 6) and 4.32 (2 H, d, *J* 1).

To a solution of the above alcohol (3.0 g) in dry dichloromethane (75 cm^3) was added carbon tetrabromide (12.4 g, 38 mmol) in one portion under a nitrogen atmosphere at −78 °C. After the addition was complete, triphenylphosphine (9.70 g, 38 mmol) was introduced into the reaction mixture in five portions during 30 min. The temperature was slowly allowed to reach −20 °C over a period of 2–3 h. When the reaction was complete, the solution was concentrated and the crude residue was chromatographed on a silica gel column using a 10:1 mixture of hexane–ethyl acetate as the eluent. The major fraction isolated (74% yield) was identified as 1-bromo-4-methoxybut-2-yne; ν_{max}(neat)/cm^{-1} 2980, 1450, 1375, 1220, 1100, 1010 and 915; δ_H(90 MHz; $CDCl_3$) 3.40 (3 H, s), 4.00 (2 H, t, *J* 3) and 4.16 (2 H, t, *J* 3).

1-(4-Methoxybut-2-ynyl)indole-2-carbaldehyde **14b**.—To a solution containing indole-2-carbaldehyde **1** (1.5 g, 10.3 mmol) in DMF (25 cm^3) was added sodium hydride (60% dispersion; 0.41 g). The mixture was stirred under a nitrogen atmosphere for 30 min at 0 °C and then 1-bromo-4-methoxybut-2-yne (2.01 g, 1.5 equiv.) was added dropwise. When the addition was complete, stirring was continued for an additional 2 h. The mixture was washed with water, extracted with ether and the ether layer was dried over magnesium sulphate. The solution was concentrated under reduced pressure and the crude residue was recrystallised from ether–hexane to give *1-(4-methoxybut-2-ynyl)indole-2-carbaldehyde* **14b** (1.47 g, 63%) (Found: C, 73.6; H, 5.9; N, 6.3. $C_{14}H_{13}NO_2$ requires C, 73.9; H, 5.8; N, 6.2%); ν_{max}(neat)/cm^{-1} 3085, 2820, 1730, 1670, 1445, 1260 and 1090; δ_H(90 MHz; $CDCl_3$) 3.25 (3 H, s), 3.98 (2 H, d, *J* 1), 5.51 (2 H, d, *J* 1), 7.25–7.80 (5 H, m) and 9.91 (1 H, s); δ_C(20 MHz; $CDCl_3$) 33.6, 59.2, 76.5, 79.1, 80.6, 111.3, 119.7, 122.8, 132.7, 127.6, 128.8, 134.9, 141.0 and 182.3.

Reaction of 1-(4-Methoxybut-2-ynyl)indole-2-carbaldehyde **14b** *with 1-Amino-2,3-Diphenylaziridine and Thermolysis of the Resulting Hydrazone*.—To a solution containing the aldehyde **14b** (600 mg) in dry benzene (15 cm^3) was added *trans*-1-amino-2,3-diphenylaziridine (665 mg, 1.2 equiv.).[10] The reaction mixture was stirred for 1 h at room temperature and then the solvent was removed under reduced pressure. The crude hydrazone **15b** was used in the next step without further purification; ν_{max}(neat)/cm^{-1} 3085, 3020, 2110, 1605, 1355, 975 and 915; δ_H(90 MHz; $CDCl_3$) 3.25 (3 H, s), 3.75 (2 H, d, *J* 2), 5.15 (2 H, *J* 2), 6.65 (1 H, s), 7.20–7.23 (14 H, m) and 8.32 (1 H, s).

The crude hydrazone **15b** was heated in dry toluene (25 cm^3) at reflux for 1 h. The solvent was removed under reduced pressure. The resulting oil was assigned as *cycloheptatriene* **16** (78%) on the basis of its spectral data (Found: C, 83.3; H, 6.9; N, 4.5. $C_{21}H_{21}NO$ requires C, 83.1; H, 6.9; N, 4.6%); ν_{max}(neat)/cm^{-1} 3090, 2110, 1610, 1340, 1100 and 775; δ_H(300 MHz; $CDCl_3$), 2.17 (3 H, s), 3.07 (1 H, m), 3.28 (3 H, s), 4.01 (2 H, br s), 4.80 (2 H, br s), 5.54 (2 H, m), 5.58 (1 H, m), 6.57 (1 H, m), 6.67 (1 H, m) and 7.13–7.59 (5 H, m).

2-(trans-2,3-Dibenzoylcyclopropyl)-1-(prop-2-ynyl)indole **18**.—To a solution containing the hydrazone **15a** (650 mg) in dichloromethane (40 cm^3) was added 1,2-dibenzoylethene (1.7 g). The mixture was placed into a sealed tube and heated at 120 °C for 2 h. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column using a 5:1 mixture of hexane–ethyl acetate mixture as the eluent. The major fraction contained a yellow solid (470 mg), m.p. 145–146 °C, which was identified as *indole* **18** on the basis of its spectral data (Found: 403.1569. $C_{28}H_{21}NO_2$ requires 403.1572); ν_{max}(KBr)/cm^{-1} 3010, 2120, 1680, 1610 and 1465; δ_H(300 MHz; $CDCl_3$) 2.04 (1 H, t, *J* 2.1), 3.59 (1 H, m), 3.85 (1 H, m), 4.27 (1 H, m), 4.77 (2 H, d, *J* 2.1), 6.39 (1 H, s), 7.05–7.63 (12 H, m) and 8.03 (2 H, m); δ_C(20 MHz; $CDCl_3$) 28.5, 29.5, 32.0, 35.4, 72.1, 77.2, 119.5, 120.2, 121.3, 126.9, 127.9, 128.0, 128.1, 128.4, 131.9, 132.9, 133.2, 136.1, 136.4, 191.4 and 196.0.

Preparation and Rhodium Catalysed Reaction of 2-(Diazoacetyl)-1-(prop-2-ynyl)indole **20a**.—To a solution containing methyl indole-2-carboxylate (2.0 g, 11.4 mmol) in dry DMF (30 cm^3) was added sodium hydride (60% dispersion; 0.45 g, 11.4 mmol). The mixture was stirred under nitrogen for 30 min at 0 °C, and then prop-2-ynyl bromide (17 mmol) was added dropwise. Stirring was continued for an additional 2 h at room temperature. The mixture was washed with water and extracted with ether. The ether layer was dried over magnesium sulphate and then concentrated under reduced pressure. The crude residue obtained was recrystallised from ether–hexane to give *methyl 1-(prop-2-ynyl)indole-2-carboxylate* **19a**, (1.65 g, 68%), m.p. 88–89 °C (Found: C, 73.0; H, 5.1; N, 6.7. $C_{13}H_{11}NO_2$ requires C, 73.2; H, 5.2; N, 6.6%); ν_{max}(KBr)/cm^{-1} 3330, 2985, 1720, 1530, 1205, 1010 and 955; δ_H(90 MHz; $CDCl_3$) 2.25 (1 H, t, *J* 3.2), 3.92 (3 H, s), 5.50 (2 H, d, *J* 3.2) and 7.25–7.80 (5 H, m).

To a solution containing the ester **10a** (1.5 g, 7.4 mmol) in dry ether (50 cm^3) was added potassium trimethylsilanolate (0.9 g).[29] The reaction mixture was stirred at room temperature

for 2 h and then methyl chloroformate (15 mmol) was added dropwise. The solution was stirred for an additional 1 h and the solid that formed was filtered off. To the resulting solution was added ethereal diazomethane (15 mmol) and the mixture was stirred for 2 h at 25 °C. The solvent was removed under reduced pressure and the crude residue was chromatographed on a silica gel column using a 3:1 hexane–ethyl acetate mixture as the eluent. The major fraction contained 0.88 g (60%) of a yellow solid, m.p. 99–100 °C, which was identified as the *title indole* **20a** on the basis of its spectral properties (Found: C, 69.7; H, 4.2; N, 18.7. $C_{13}H_9N_3O$ requires C, 69.9; H, 4.1; N, 18.8%); ν_{max}(KBr)/cm^{-1} 3220, 2110, 1610, 1455, 1360, 1180 and 745; δ_H(90 MHz; $CDCl_3$) 2.25 (1 H, t, *J* 3.2), 5.50 (2 H, d, *J* 3.2), 5.90 (1 H, s), 6.95 (1 H, s) and 7.25–7.65 (4 H, m).

The α-diazoketone **20a** (250 mg) was dissolved in dry methanol (15 cm^3) and was treated with rhodium(II) mandelate (5 mg). The mixture was stirred for 30 min at room temperature. The excess of methanol was removed under reduced pressure and the crude residue was recrystallised from dichloromethane to give the *methoxy ketone* **22** (178 mg, 74%), m.p. 131–132 °C (Found: C, 73.6; H, 5.7; N, 6.1. $C_{14}H_{13}NO_2$ requires C, 74.0; H, 5.8; N, 6.2%); ν_{max}($CHCl_3$)/cm^{-1} 3250, 1675, 1515, 1455, 1175, 1120 and 1030; δ_H(300 MHz; $CDCl_3$) 2.25 (1 H, t, *J* 3), 3.52 (3 H, s), 4.63 (2 H, s), 5.45 (2 H, d, *J* 3) and 7.16–7.70 (5 H, m); δ_C(20 MHz; $CDCl_3$) 34.5, 59.6, 72.8, 88.7, 111.4, 112.7, 121.3, 122.2, 125.9, 126.1, 130.4, 139.6 and 190.8.

Preparation and Rhodium Catalysed Reaction of 2-Diazoacetyl-1-(4-methoxybut-2-ynyl)indole **20b**.—To a solution containing methyl indole-2-carboxylate (2.50 g, 14 mmol) in DMF (40 cm^3) was added sodium hydride (60% dispersion; 0.56 g). The mixture was stirred under a nitrogen atmosphere for 30 min at 0 °C and then 1-bromo-4-methoxybut-2-yne (2.73 g, 16.8 mmol) was added dropwise. After the addition was complete, stirring was continued for 4 h. The mixture was washed with water, extracted with ether and the ether layer was dried over magnesium sulphate. The solvent was removed under reduced pressure and the residue was recrystallised from ether–hexane to give *methyl 1-(4-methoxybut-2-ynyl)indole-2-carboxylate* **19b** (2.23 g, 62%) (Found: C, 69.9; H, 5.6; N, 5.2. $C_{15}H_{15}NO_3$ requires C, 70.0; H, 5.9; N, 5.4%); ν_{max}(KBr)/cm^{-1} 3085, 2110, 1720, 1515, 1345 and 810; δ_H(90 MHz; $CDCl_3$) 3.25 (3 H, s), 3.80 (3 H, s), 3.93 (2 H, t, *J* 3), 5.36 (2 H, t, *J* 3) and 7.10–7.70 (5 H, m).

The ester **19b** (2.0 g) was added in one portion to a stirred solution containing potassium trimethylsilanolate (1.0 g, 8.5 mmol) in ether (50 cm^3) at room temperature under a nitrogen atmosphere.[29] The reaction mixture was stirred for 3 h and then methyl chloroformate (16 mmol) was added dropwise. The solution was stirred for an additional 2 h and the solid that formed was filtered. To the resulting solution was added ethereal diazomethane (20 mmol) and the mixture was stirred for an additional 2 h at room temperature. The solvent was removed under reduced pressure and the crude residue was chromatographed on a silica gel column using a 5:1 hexane–ethyl acetate mixture as the eluent. The major fraction contained a yellow solid (1.18 g, 55%), m.p. 116–117 °C, which was identified as the *title indole* **20b** on the basis of its spectral data (Found: C, 67.5; H, 4.7; N, 15.5. $C_{15}H_{13}N_3O_2$ requires C, 67.4; H, 4.9; N, 15.7%); ν_{max}($CHCl_3$)/cm^{-1} 3095, 2105, 1625, 1395, 1175 and 810; δ_H(90 MHz; $CDCl_3$) 3.21 (3 H, s), 3.95 (2 H, d, *J* 2), 5.52 (2 H, d, *J* 2), 5.80 (1 H, s), 6.87 (1 H, s) and 7.15–7.75 (4 H, m).

A solution containing the diazoketone **20b** (300 mg) in dry benzene (15 cm^2) was treated with rhodium(II) mandelate (5 mg). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column using a 3:1 mixture of hexane–ethyl acetate as the eluent. The major product isolated (72%) was identifed as 2-(*cyclohepta-2,4,6-trienylcarbonyl*)-1-(*4-methoxybut-2-ynyl*)*indole* **21** on the basis of its spectral properties (Found: C, 79.3; H, 5.9; N, 4.1. $C_{21}H_{19}NO_2$ requires C, 79.5; H, 6.0; N, 4.4%); ν_{max}(neat)/cm^{-1} 3010, 1660, 1455, 1190, 1150 and 950; δ_H(300 MHz; $CDCl_3$) 3.06 (1 H, t, *J* 5.4), 3.29 (3 H, s), 4.04 (2 H, s), 5.24 (2 H, dd), 5.55 (2 H, s), 6.34 (2 H, m), 6.68 (2 H, t, *J* 3) and 7.15–7.67 (5 H, m); δ_C(20 MHz; $CDCl_3$) 33.6, 51.8, 56.9, 59.2, 60.1, 76.5, 76.6, 79.1, 80.6, 110.7, 111.9, 111.95, 120.7, 122.4, 124.9, 125.3, 125.6, 138.7, 160.4 and 167.7.

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