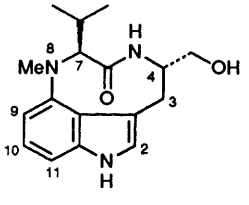
Synthesis of (−)-Indolactam V

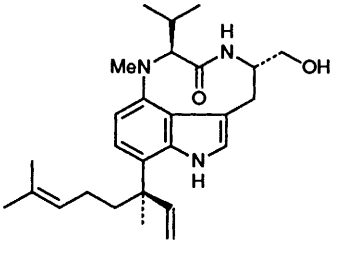
Mark Mascal, Christopher J. Moody,*† Alexandra M. Z. Slawin and David J. Williams
Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW7 2AY, UK

A stereospecific 7-step synthesis of (−)-indolactam V **1** from tryptophan methyl ester is described. The key steps are the photocyclisation of the dichloroamide **6** to give the isomeric 7-hydroxy-7-isopropylpyrrolo[4,3,2-*fg*][3]benzazocines **16** + **18** and the nitrene-mediated ring expansion of the derived azide **5** to give the 9-membered imine **4**. The synthesis is completed by stereoselective reduction of the imine bond and *N*-methylation.

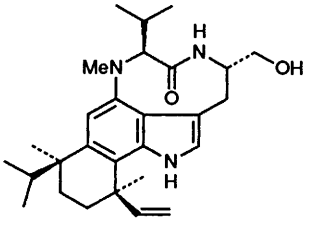
In 1960 a highly toxic skin irritant was isolated in Japan from certain strains of *Streptomyces*.[1] Named teleocidin because of its toxicity to the teleost fish, it was to be the first representative of a still growing family of indole alkaloids,[2] exemplified by indolactam V **1**, teleocidin A1 **2**, and teleocidin B1 **3**. These compounds became the focus of much attention after the discovery that they possessed similar biological activity to phorbol esters in their capacity to act as tumour promoters through activation of protein kinase C. The structure–activity relationships within this series of alkaloids and their simple derivatives have been reviewed.[3]



1



2

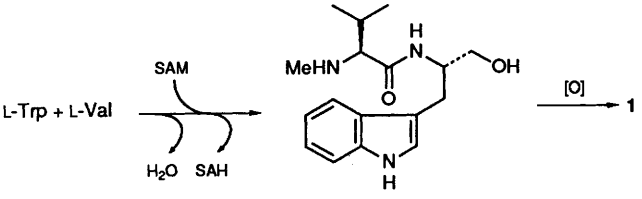


3

Indolactam V **1**, which contains the key structural unit (the indole bridged across its 3- and 4-position by a 9-membered lactam) of the teleocidin family of tumour promoters, is biosynthesized from tryptophan and valine, with the *N*-methyl group coming from methionine, by cyclisation of *N*-methyl-L-valyl-L-tryptophanol (Scheme 1).[4]

To date, attempts to emulate Nature and synthesize indolactam V **1** by cyclisation of a dipeptide to the indole 4-position have proved unsuccessful, and most routes have instead made use of precursors which have functionality in both the indole 3- and 4-position which is then used to build up the lactam ring by formation of the amide bond. Thus, the first synthesis by Endo *et al.* started from 4-nitrogramine and gave (±)-indolactam V in about 3% overall yield in 15 steps.[5]

† *Present address:* Department of Chemistry, Loughborough University of Technology, Loughborough, Leicestershire, LE11 3TU, UK.



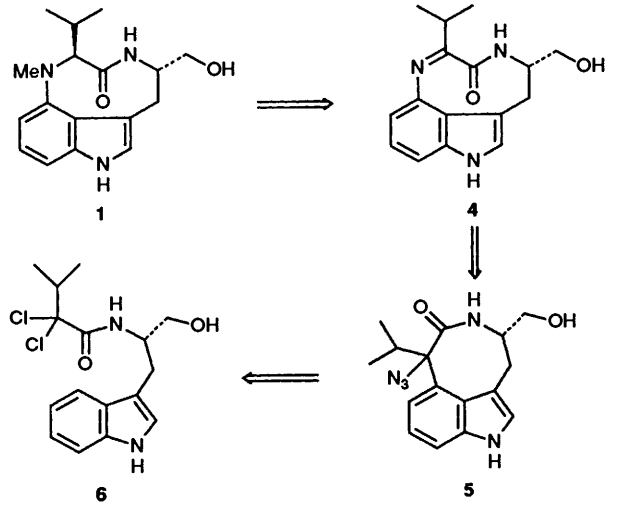
Scheme 1

The natural (−)-isomer was subsequently prepared by incorporating a classical resolution step. A more efficient synthesis of racemic indolactam V was reported by Ley and co-workers starting from 4-aminoindole.[6] The problems of starting from a 4-unsubstituted indole are illustrated by Nakatsuka's synthesis based on (−)-tryptophan.[7] Although one stereocentre is incorporated from the start, the introduction of a nitro group into the 4-position (40%) of a suitable derivative was complicated by competing attack at the 6-position (35%), and the method still lacked control at the second stereocentre. Recently, Kozikowski has reported the synthesis of (−)-5-*tert*-butylindolactam V by a route which involves formation of the indole ring by annulation to a pyrrole,[8] a strategy also used by Natsume in his elegant synthesis of the teleocidins.[9] Finally, Kogan has reported a regio- and stereo-controlled synthesis of the (−)-isomer in 10 steps from (−)-tryptophan methyl ester in 17% overall yield.[10] We now report the full details of a short 7-step synthesis of (−)-indolactam V which is fundamentally different and involves as key steps (Scheme 2) the photocyclisation of a simple tryptophan derivative followed by a nitrene-mediated ring expansion.[11]

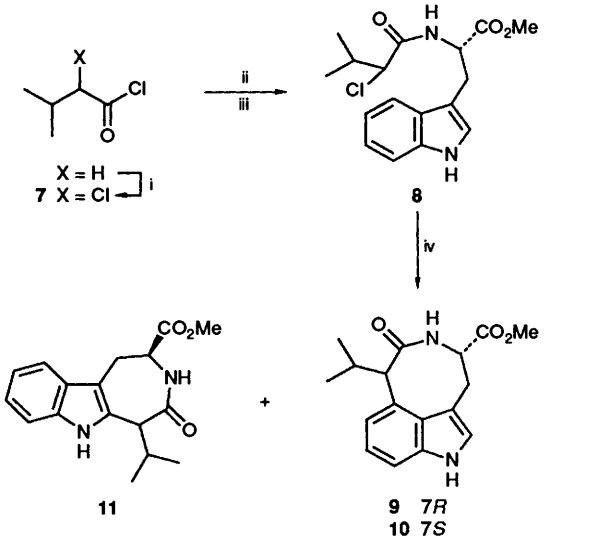
Results and Discussion

The retrosynthetic plan shown in Scheme 2 for (−)-indolactam V **1** is based on our previously described photocyclisation reactions of *N*-halogenoacetyltryptophan derivatives,[12] and requires as a starting material the α,α-dichloroisovaleryl amide of tryptophanol, compound **6**.

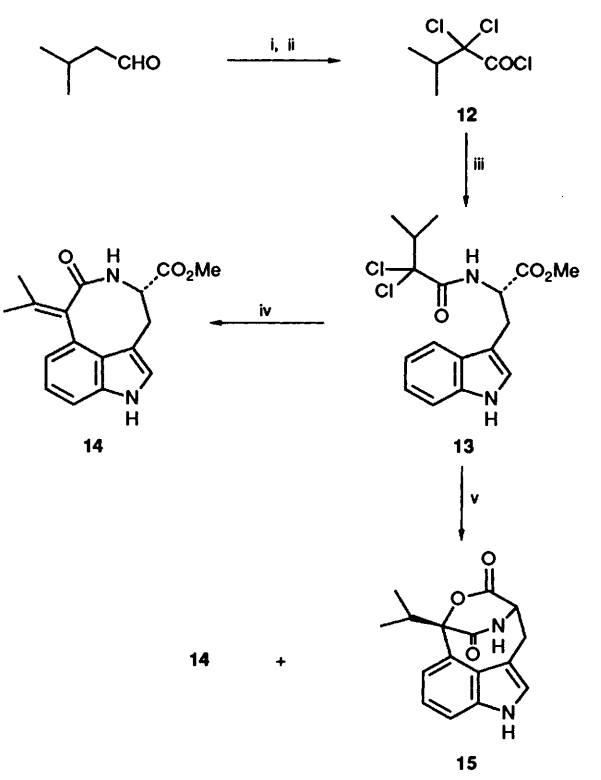
The above plan requires that a bulky isopropyl group be present at the cyclising centre, and as a test of whether this steric bulk would impede photocyclisation, a model reaction was carried out on the readily accessible *N*-(2-chloro-3-methylbutanoyl)tryptophan methyl ester **8** (Scheme 3). This was prepared as shown from isovaleryl chloride by chlorination (85%), reaction with tryptophan, and esterification (73%). On irradiation in acetonitrile, the chloroisovaleryl tryptophan **8** gave 3 products: the isomeric 7-isopropyl azocinoindoles **9** (42%) and **10** (10%), demonstrating that the isopropyl group did not prevent the desired cyclisation, and the 2-cyclised product **11** (17%). The *trans*-stereochemistry of the major



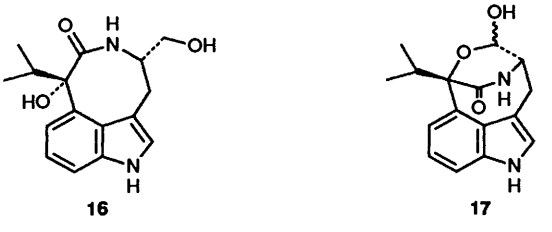
Scheme 2



Scheme 3 *Reagents and conditions:* i, *N*-chlorosuccinimide, $SOCl_2$, heat; ii, (L)-Trp, NaOH; iii, CH_2N_2; iv, *hν*, MeCN



Scheme 4 *Reagents and conditions:* i, SO_2Cl_2, heat; ii, *tert*-BuOCl, CH_2Cl_2; iii, (L)-Trp-OMe, aq. $NaHCO_3$, CH_2Cl_2; iv, *hν*, MeCN; v, *hν*, aq. MeCN



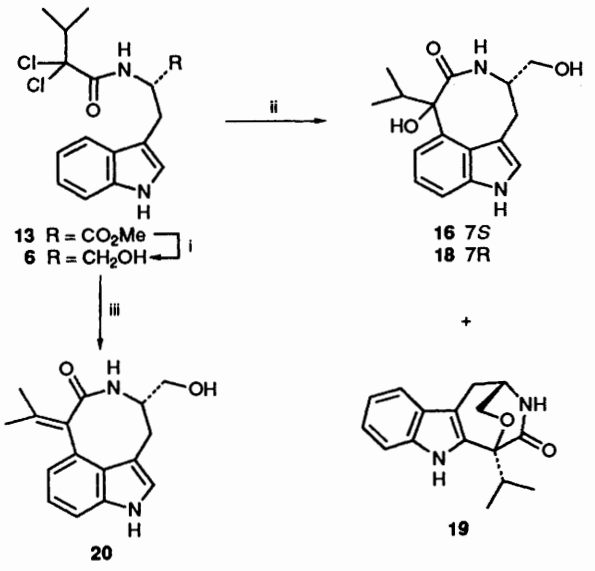
product **9** was assigned by comparison of its NMR spectrum with those of 7-substituted azocinoindoles of known stereochemistry.[12]

The reaction was then extended to the corresponding dichloroamide. The required starting material, 2,2-dichloro-3-methylbutanoyl chloride **12**, was prepared by halogenation of isovaleraldehyde followed by direct conversion into the acid chloride with *tert*-butyl hypochlorite, since, somewhat surprisingly, neither isovaleric acid nor its acid chloride could be cleanly dichlorinated. Subsequent reaction with tryptophan methyl ester gave the desired substrate **13** for the photocyclisation. On irradiation in dry acetonitrile, dichloroamide **13** underwent photocyclisation followed by elimination of HCl to give the isopropylidenelactam **14** in 43% yield (Scheme 4).

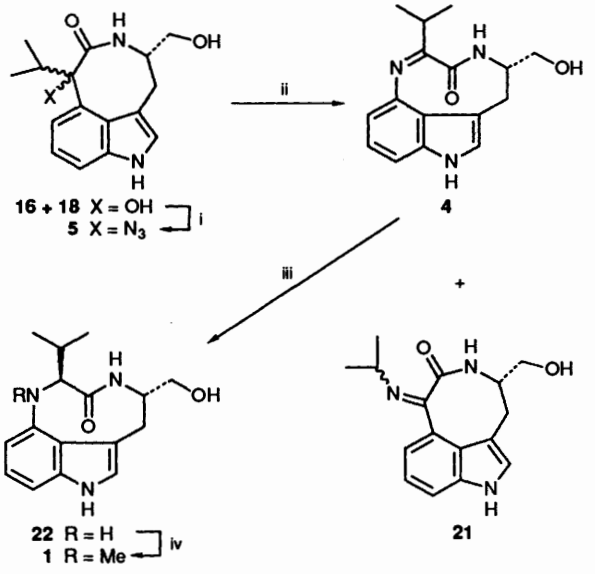
The formation of the alkene **14** caused a minor revision of the synthetic plan since it proved impossible to add HCl or HN_3 back across the double bond. The problem was solved initially by carrying out the irradiation in aqueous acetonitrile to intercept the (presumed) chloride-containing intermediate. Although compound **14** was still formed (16%), the major product (46%) was the bridged indole **15** apparently formed by spontaneous lactonisation of the intermediate 7-hydroxy azocinoindole. Although the lactone **15** proved resistant to attempts to open it with azide, it was readily reduced with sodium borohydride to give a mixture of the 7-hydroxy-7-isopropyl azocinoindole-4-methanol **16** (42%) and the diastereomeric lactols **17** (1:1 ratio; 35%).

The tertiary alcohol **16** proved to be the key intermediate in our synthesis, and was more conveniently prepared in quantity in just 3 steps from (−)-tryptophan methyl ester as follows: The commercially available ester was acylated with 2,2-dichloro-3-methylbutanoyl chloride **12** to give the aforementioned amide **13** (97%), reduction of which with sodium borohydride gave the corresponding tryptophanol **6** in 83% yield. Photocyclisation of compound **6** in aqueous acetonitrile gave the diastereoisomeric diols **16** and **18** (54%) in a *ca.* 4:1 ratio, together with the indole **19** (25%) formed by cyclisation to the 2-position followed by formation of the ether linkage. By contrast, irradiation of compound **6** in *dry* acetonitrile gave, as above, an alkene **20** in 42% yield (Scheme 5). The major stereoisomer of diol mixture **16**/**18** is the one with the isopropyl group *trans* to the hydroxymethyl substituent, *i.e.* the same compound **16** that was obtained previously. However, the (difficult) separation of these isomers is unnecessary as stereochemistry at this centre is subsequently destroyed before being reintroduced stereoselectively in the penultimate step of the synthesis.

In order to effect the required nitrene-mediated ring expansion, the tertiary hydroxy group had to be converted into the corresponding azide. Several methods were attempted, and the procedure which gave the most satisfactory results involved treatment of the **16** + **18** mixture with a chloroform solution of hydrazoic acid (~1.5 mol dm^{-3}) at room temperature. Easy dehydration of the tertiary alcohol and intramolecular cyclis-



Scheme 5 *Reagents and conditions:* i, $NaBH_4$; EtOH; ii, *hv*, aq. MeCN; iii, *hv*, MeCN



Scheme 6 *Reagents and conditions:* i, NaN_3, CF_3CO_2H, $CHCl_3$; ii, *hv*, MeCN; iii, $NaBH_3CN$, MeOH; iv, MeI, $NaHCO_3$, MeOH

ation involving the primary alcohol group limit the extent to which the azide introduction reaction could be driven by, for example, the addition of acid. The modest yields of azide **5** (*ca.* 35% based on conversion) are, however, compensated by the easy availability of its precursor.

Irradiation of the azide **5** in acetonitrile gave the required ring-expanded imine **4** in 23% yield, resulting from migration of the aryl group to the electron deficient centre, along with the exocyclic amine **21** (*E*/*Z*-mixture) (28%). This exocyclic imine, the structure of which (*Z*-isomer) was confined by X-ray crystallography (Fig. 1), arises from competing isopropyl-group migration, showing that in this case the relative migratory aptitudes of the aromatic ring residue and the alkyl group are finely balanced.[13] Although the azide **5** was a mixture of diastereoisomers, the fact that these were inseparable by chromatography precluded an investigation of the possibility that the individual isomers might behave differently upon irradiation. Treatment of the imine **4** with sodium cyanoborohydride in methanol resulted in stereoselective (≥95%) reduction to give demethylindolactam V **22** in 69% yield, methylation of which under standard conditions gave (−)-indolactam V **1** {$[\alpha]_D$ −136.0° (*c* 0.30, MeOH); lit.,[5c] −134.5 (*c* 0.70, MeOH)}, identical (TLC, IR, NMR) with a synthetic racemic sample[6] (Scheme 6).

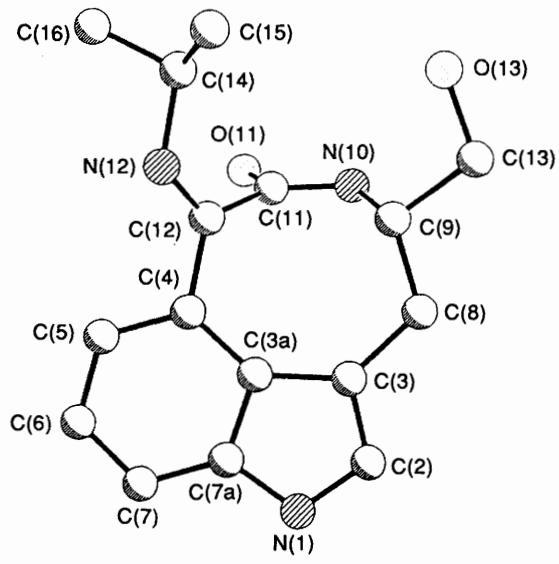
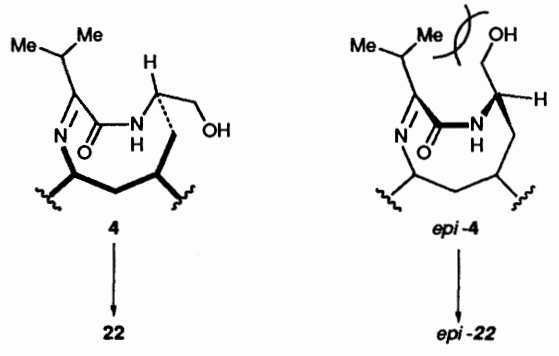


Fig. 1 X-Ray molecular structure of 1,3,4,5,6,7-hexahydro-4-hydroxymethyl-7-isopropylimino-6-oxopyrrolo[4,3,2-*fg*][3]benzazocine **21** showing crystallographic numbering



The stereoselectivity of the cyanoborohydride reduction is not thought to involve prior complexation of the reagent to the pendant CH_2OH group followed by internal delivery from the lower face of the imine double bond since the reaction is carried out in methanol. Rather, it would appear that the reduction is controlled by the conformation of the 9-membered ring.[14] Thus two distinct conformations in which the imine and amide are constrained to planarity emerge on examination of molecular models. Assuming *exo* attack of borohydride, conformation A will lead to (−)-demethylindolactam V **22**, whereas conformation B, which is effectively precluded by unfavourable steric interactions, would have given the isomer with unnatural stereochemistry at the crystallographic C-12.

In summary, we have completed a 7-step synthesis of (−)-indolactam V **1** starting from commercially available (−)-tryptophan methyl ester and proceeding through the amide **13** (97%), alcohol **6** (83%), azocinoindoles **16**/**18** (54%), azide **5** (35% based on conversion), imine **4** (23%), the demethyl compound **22** (69%) and thence to the natural product **1** (51%).

Experimental

For general experimental points, see ref. 12. ^1H NMR spectroscopic *J*-values are given in Hz.

2-Chloro-3-methylbutanoyl Chloride **7**.—3-Methylbutanoyl chloride was prepared by heating a mixture of 3-methylbutanoic

acid (2.16 cm^3, 2.00 g, 19.6 mmol) and thionyl chloride (5.7 cm^3, 9.3 g, 78 mmol) at 70 °C for 30 min. This was cooled to room temperature and *N*-chlorosuccinimide (7.8 g, 59 mmol), thionyl chloride (10 cm^3), and conc. hydrochloric acid (3 drops) were added. Heating was then resumed at 85 °C for 4 h, during which time the solution went from pale green to black. The excess of thionyl chloride was removed under reduced pressure and the residue was triturated with several portions of carbon tetrachloride. The washings were combined and evaporated giving the title compound **7** (2.58 g, 85%) as a pungent brown oil which was essentially pure by ^1H NMR spectroscopy, b.p. 146–149 °C (lit.,[15] 148–149 °C); δ_H(60 MHz; CCl_4) 1.06 (3 H, d, *J* 6.7, CH*Me*$_2$), 1.13 (3 H, d, *J* 7.0, CH*Me*$_2$), 2.61 (1 H, m, C*H*Me$_2$) and 4.43 (1 H, d, *J* 5.8, COCHCl).

N-(2-*Chloro*-3-*methylbutanoyl*)*tryptophan Methyl Ester* **8**.—Tryptophan (1.00 g, 4.90 mmol) was dissolved in 1.0 mol dm^{-3} sodium hydroxide (5.0 cm^3, 5.0 mmol) and the solution was cooled in an ice-bath. 2-Chloro-3-methylbutanoyl chloride **7** (0.95 g, 6.1 mmol) was added dropwise during 15 min to the stirred solution while the pH was kept constant at 10–11 by the simultaneous addition of 5 mol dm^{-3} sodium hydroxide (1.4 cm^3, 7.0 mmol). The mixture was stirred at bath temperature for 30 min then transferred to a separatory funnel, where it was covered by a layer of ethyl acetate and acidified to pH 3 (with indicator paper) with 6 mol dm^{-3} hydrochloric acid. The aqueous layer was extracted twice more and the combined organic extracts were dried over magnesium sulfate. Evaporation left a brown oil, which was taken up in methanol (15 cm^3) and treated with excess of diazomethane in ether. The solvent was evaporated off and the crude product was chromatographed (3% Et_2O–CH_2Cl_2) to give the *title compound* **8** (1:1 mixture of diastereoisomers) (1.21 g, 73%) as a pale yellow resin, a small portion of which was rechromatographed for analysis, providing a crystalline solid (Found: C, 60.5; H, 6.2; N, 8.3. $C_{17}H_{21}ClN_2O_3$ requires C, 60.6; H, 6.3; N, 8.3%); $[\alpha]_D$ −4.2 (*c* 2.00 in MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3479 (indole NH), 3408 (amide NH), 3028, 3010, 2970, 2876, 1743 (ester C=O), 1669 (amide C=O), 1519, 1458, 1440, 1420, 1359, 1182, 1119, 1093, 1012 and 837; λ_{max}(MeOH)/nm 218 (log δ 4.52) and 278 (3.78); δ_H(250 MHz; [$^2H_6$]acetone) (both isomers) 0.87–0.95 (12 H, m, CH*Me*$_2$), 2.28 (2 H, m, C*H*Me$_2$), 3.27–3.31 (4 H, m, ArC*H*$_2$), 3.65 (3 H, s, CO_2Me), 3.66 (3 H, s. CO_2Me), 4.25 (2 H, d, *J* 6.3, COCHCl), 4.78 (2 H, m, C*H*NHCO), 7.02 (2 H, t, *J* 7.3, 5-H), 7.09 (2 H, t, *J* 7.4, 6-H), 7.20 (1 H, s, 2-H), 7.21 (1 H, s, 2-H), 7.37 (2 H, d, *J* 8.0, 7-H), 7.56 (2 H, d, *J* 7.6, 4-H) and 10.16 (2 H, br s, 1-H); *m*/*z* 336 (M^+, 6%), 2.01 (26, M − H_2NCOCHClCHMe$_2$), 170 (3), 130 (100, $ArCH_2^{\bullet+}$), 103 (3), 77 (3) and 55 (3).

Irradiation of N-(2-*Chloro*-3-*methylbutanoyl*)*tryptophan Methyl Ester* **8**.—A solution of *N*-(2-chloro-3-methylbutanoyl)-tryptophan methyl ester **8** (212 mg, 0.63 mmol) in acetonitrile (100 cm^3) was irradiated for 1 h. The solvent was evaporated off and the residue was chromatographed (1% MeOH–Et_2O) to give, in the following elution order, *methyl* 1,2,3,4,5,6-*hexahydro*-5-*isopropyl*-4-*oxoazepino*[4,5-b]*indole*-2-*carboxylate* **11** (33 mg, 17%) as a solid, m.p. 95–100 °C (Found: M^+, 300.1473. $C_{17}H_{20}N_2O_3$ requires M, 300.1474); $[\alpha]_D$ −82.4 (*c* 0.575 in MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3469 (indole NH), 3374 (amide NH), 3009, 2966, 1744 (ester C=O), 1661 (amide C=O), 1462, 1434, 1392, 1318, 1280, 1163, 1103, 1006 and 893; λ_{max}(MeOH)/nm 219 (log ε 4.47) and 281 (3.89); δ_H(250 MHz; [$^2H_6$]acetone) 1.00 (3 H, d, *J* 7.0, CHMe*Me*), 1.11 (3 H, d, *J* 7.0, CH*Me*Me), 2.33 (1 H, m, C*H*Me$_2$), 2.96 (1 H, d, *J* 15.8, 1-H), 3.37 (1 H, d, *J* 11.1, 5-H), 3.44 (1 H, dd, *J* 2.7 and 15.8, 1-H), 3.86 (3 H, s, CO_2Me), 4.98 (1 H, m, 2-H), 6.58 (1 H, br s, 3-H), 7.00 (1 H, t, *J* 7.5, 9-H), 7.09 (1 H, t, *J* 7.4, 8-H), 7.31 (1 H, d, *J* 8.0, 7-H), 7.44 (1 H, d, *J* 7.9, 10-H) and 10.10 (1 H, br s, 6-H); *m*/*z* 300 (M^+, 100%), 285 (12, M − Me), 257 (16, M − CHMe$_2$), 241 (4, M − CO_2Me), 229 (20), 225 (14), 212 (82), 197 (16), 184 (34), 170 (90), 154 (11), 130 (8) and 115 (13, $Ar^{\bullet+}$); (7S)-*methyl*-1,3,4,5,6,7-*hexahydro*-7-*isopropyl*-6-*oxopyrrolo*[4,3,2-fg][3]*benzazocine*-4-*carboxylate* **10** (19 mg, 10%) as a solid, m.p. 255–256 °C (Found: C, 67.9; H, 6.8; N, 9.2. $C_{17}H_{20}N_2O_3$ requires C, 68.0; H, 6.7; N, 9.3%); $[\alpha]_D$ −95.1 (*c* 0.142 in MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3476 (indole NH), 3372 (amide NH), 3033, 3002, 2979, 2959, 2871, 1744 (ester C=O), 1659 (amide C=O), 1457, 1436, 1395, 1387, 1341, 1258, 1248, 1185, 1106, 1083, 1005, 932, 741 and 730; δ_H(250 MHz; [$^2H_6$]acetone) 1.10 (3 H, d, *J* 6.5, CHMe*Me*), 1.11 (3 H, d, *J* 6.6, CH*Me*Me), 2.77 (1 H, m, C*H*Me$_2$), 3.51 (1 H, dd, *J* 3.3 and 16.5, 3-H), 3.81 (3 H, s, CO_2Me), 4.12 (1 H, dd, *J* 9.2 and 16.5, 3-H), 4.26 (1 H, d, *J* 10.8, 7-H), 4.96 (1 H, m, 4-H), 5.97 (1 H, br s, 5-H), 6.94 (1 H, d, *J* 7.3, 8-H), 7.05 (1 H, t, *J* 7.7, 9-H), 7.09 (1 H, s, 2-H), 7.21 (1 H, d, *J* 8.2, 10-H) and 10.13 (1 H, br s, 1-H); *m*/*z* 300 (M^+, 100%), 285 (8, M − Me), 257 (7, M − CHMe$_2$), 241 (6, M − CO_2Me), 229 (9), 213 (15), 196 (10), 186 (69), 170 (52), 154 (23), 144 (12), 142 (10), 130 (11) and 115 (14, $Ar^{\bullet+}$); and (7R)-*methyl*-1,3,4,5,6,7-*hexahydro*-7-*isopropyl*-6-*oxopyrrolo*[4,3,2-fg][3]-*benzazocine*-4-*carboxylate* **9** (80 mg, 42%) as a solid, m.p. 222–223 °C (Found: C, 68.0; H, 6.7; N, 9.3%); $[\alpha]_D$ −66.3 (*c* 1.00 in MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3476 (indole NH), 3395 (amide NH), 3031, 3000, 2979, 2957, 2873, 1746 (ester C=O), 1661 (amide C=O), 1459, 1436, 1416, 1345, 1281, 1262, 1245, 1169, 1102, 1017, 803, 731 and 618; λ_{max}(MeOH)/nm 203 (log ε 4.37) and 288 (3.77); δ_H(250 MHz; [$^2H_6$]acetone) 1.06 (3 H, d, *J* 6.7, CHMe*Me*), 1.16 (3 H, d, *J* 6.6, CH*Me*Me), 2.81 (1 H, m, C*H*Me$_2$), 3.53 (1 H, dd, *J* 8.7 and 15.2, 3-H), 3.78 (3 H, s, CO_2Me), 3.85 (1 H, dd, *J* 11.4 and 15.2, 3-H), 4.20 (1 H, d, *J* 10.6, 7-H), 4.24 (1 H, m, 4-H), 6.47 (1 H, br d, 5-H), 6.92 (1 H, d, *J* 7.3, 8-H), 7.04 (1 H, t, *J* 7.7, 9-H), 7.20 (1 H, d, *J* 8.0, 10-H), 7.21 (1 H, s, 2-H) and 10.11 (1 H, br s, 1-H); *m*/*z* 300 (M^+, 70%), 285 (7, M − Me), 257 (8, M − CHMe$_2$), 241 (6, M − CO_2Me), 240 (6), 229 (14), 225 (5), 213 (18), 201 (9), 196 (13), 186 (100), 170 (69), 154 (33), 144 (23), 130 (62) and 115 (23, $Ar^{\bullet+}$).

2,2-*Dichloro*-3-*methylbutanal*.—3-Methylbutanal (12.5 cm^3, 10.0 g, 0.116 mol) was added down the top of a water-cooled condenser to sulfuryl dichloride (40 cm^3). After a brief induction period vigorous evolution of gas was observed, which subsided after about 15 min whereupon heat was applied to bring the mixture to reflux. The reaction was followed by NMR spectroscopy, which indicated complete conversion into the monochloro product after 2 h, a *ca.* 1:1 mixture of the mono- and di-chloro products after 6 h, and complete conversion into the dichloro product within 18 h. The excess of sulfuryl dichloride was removed and the residue was distilled, giving the *title compound* (11.4 g, 64%) as a liquid, b.p. 138–142 °C (Found: C, 39.0; H, 5.4; Cl, 45.6. $C_5H_8Cl_2O$ requires C, 38.7; H, 5.2; Cl, 45.7%); ν_{max}(film)/cm^{-1} 2980, 2943, 2882, 2841, 1752 (C=O), 1466, 1392, 1372, 1325, 1184, 1122, 1084, 1035, 992, 919, 864, 775, 730, 672, 627, 550, 525, 502 and 492; δ_H(250 MHz; [$^2H_6$]acetone) 1.12 (6 H, d, *J* 6.5, CH*Me*$_2$), 2.64 (1 H, m, C*H*Me$_2$) and 9.36 (1 H, s, CHO); *m*/*z* 155 (MH^+, 5%), 128 (58), 125 (45, M − CHO), 112 (30, M − MeCH=CH$_2$), 89 (34), 71 (100) and 43 (46, $CHMe_2^{\bullet+}$).

2,2-*Dichloro*-3-*methylbutanoyl Chloride* **12**.—To a solution of 2,2-dichloro-3-methylbutanal (10.0 g, 0.065 mol) in methylene dichloride (10 cm^3) was added *tert*-butyl hypochlorite (7.50 g, 0.069 mmol). After a brief induction period vigorous evolution of gas was observed, and the occasional application of an ice-bath was necessary to moderate the reaction. Spontaneous reflux ceased after *ca.* 15 min and the mixture was stirred at

room temperature for 1.5 h, then finally brought again to reflux for 15 min. The volatile components were evaporated off and the residue was distilled (short path) to give the title compound **12** (4.40 g, 30%, contaminated with small amounts of the starting material), as a liquid, b.p. 156–162 °C, which was used in the next step without delay; ν_{max}(film)/cm^{-1} 2982, 2941, 2882, 1802 (C=O), 1775, 1736, 1466, 1393, 1374, 1267, 1119, 1063, 1020, 958, 869, 821, 799, 733, 629, 549 and 500; δ_H(270 MHz; $CDCl_3$) 1.17 (6 H, d, *J* 6.5, CH*Me*$_2$) and 2.79 (1 H, septet, *J* 6.5, C*H*Me$_2$).

N-(2,2-*Dichloro*-3-*methylbutanoyl*)*tryptophan Methyl Ester* **13**.—A two-phase system of tryptophan methyl ester (2.06 g, 9.42 mmol) in methylene dichloride (20 cm^3) and sodium hydrogen carbonate (1.20 g, 14.3 mmol) in water (20 cm^3) was vigorously stirred at 0 °C while a solution of 2,2-dichloro-3-methylbutanoyl chloride **12** (1.96 g, 10.3 mmol) in methylene dichloride (10 cm^3) was added dropwise over a 15-min period. The reaction mixture was kept for an additional 1 h at 0 °C, then poured into water and extracted with methylene dichloride. The combined organic layer was dried over sodium sulfate and evaporated, to give a light brown oil which solidified on storage to a buff-coloured crystalline mass. Recrystallisation from benzene provided crystals of the *title compound* **13** (3.16 g), and chromatography of the mother liquor (40% light petroleum–diethyl ether) gave additional product **13** (0.23 g, total 3.39 g, 97%), m.p. 96–97 °C (Found: C, 55.0; H, 5.4; N, 7.5. $C_{17}H_{20}Cl_2N_2O_3$ requires C, 55.0; H, 5.4; N, 7.5%); $[\alpha]_D$ −25.9 (*c* 0.920 in MeOH); ν_{max}($CHCl_3$)/cm^{-1} 3476 (indole NH), 3405 (amide NH), 2981, 2954, 1742 (ester C=O), 1686 (amide C=O), 1513, 1457, 1439, 1358, 1281, 1254, 1181, 1110, 1092, 1011, 816, 772 and 755; λ_{max}(MeOH)/nm 218 (log ε 4.53) and 278 (3.75); δ_H(250 MHz; [$^2H_6$]acetone) 0.96 (3 H, d, *J* 6.6, CH*Me*Me), 0.99 (3 H, d, *J* 6.8, CHMe*Me*), 2.70 (1 H, septet, *J* 6.5, C*H*Me$_2$), 3.38 (2 H, d, ArC*H*$_2$), 3.69 (3 H, s, CO_2Me), 4.76 (1 H, m, C*H*NHCO), 7.03 (1 H, t, *J* 7.4, 5-H), 7.10 (1 H, t, *J* 7.6, 6-H), 7.25 (1 H, s, 2-H), 7.38 (1 H, d, *J* 8.1, 7-H), 7.59 (1 H, d, *J* 7.8, 4-H), 7.85 (1 H, br s, CHN*H*CO) and 10.19 (1 H, br s, 1-H); *m/z* 370 (M$^+$, 4%), 245 (3, M − Cl_2CCHMe$_2$), 201 (19, M − H_2NCOCCl$_2$CHMe$_2$), 170 (3), 156 (3), 143 (2), 130 (100, ArCH$_2^{\bullet+}$), 103 (3) and 77 (3).

Irradiation of N-(2,2-*Dichloro*-3-*methylbutanoyl*)*tryptophan Methyl Ester* **13**.—A. *In acetonitrile solution.* A solution of *N*-(2,2-dichloro-3-methylbutanoyl)tryptophan methyl ester **13** (300 mg, 0.81 mmol) in acetonitrile (120 cm^3) was irradiated for 1 h. The solvent was evaporated off and the residue was preadsorbed onto silica gel and chromatographed (35% EtOAc–Et_2O) giving a brown resin, which was triturated with ether to provide a tan, microcrystalline solid. This was identified as *methyl*-1,3,4,5,6,7-*hexahydro*-7-*isopropylidene*-6-*oxopyrrolo*-[4,3,2-fg][*benzozacine*-4-*carboxylate* **14** (103 mg, 43%), m.p. 211–213 °C (from $CHCl_3$) (Found: C, 68.2; H, 6.1; N, 9.3. $C_{17}H_{18}N_2O_3$ requires C, 68.4; H, 6.1; N, 9.4%); [α] −260.9 (*c* 0.368 in MeOH); ν_{max}($CHCl_3$)/cm^{-1} 3474 (indole NH), 3384 (amide NH), 3000, 1742 (ester C=O), 1650 (amide C=O), 1436, 1380, 1326, 1287, 1245, 1167, 1000 and 805; λ_{max}(MeOH)/nm 203 log ε 4.40), 224 (4.36) and 296 (3.91); δ_H(250 MHz; [$^2H_6$]acetone) (major conformer) 1.81 (3 H, s, C=CMe), 1.87 (3 H, s, C=CMe), 3.29 (1 H, dd, *J* 11.6 and 16.5, 3-H), 3.56 (1 H, dd, *J* 3.8 and 16.5, 3-H), 3.77 (3 H, s, CO_2Me), 5.08 (1 H, m, 4-H), 6.66 (1 H, br s, 5-H), 6.85 (1 H, d, *J* 7.1, 8-H), 7.06 (1 H, t, *J* 7.8, 9-H), 7.22 (1 H, s, 2-H), 7.32 (1 H, d, *J* 8.1, 10-H) and 10.41 (1 H, br s, 1-H); (minor conformer) 1.66 (3 H, s, C=CMe), 1.94 (3 H, s, C=CMe), 3.29 (1 H, dd, *J* 5.8 and 14.5, 3-H), 3.63 (1 H, t, *J* 14.1, 3-H), 3.75 (3 H, s, CO_2Me), 5.06 (1 H, m, 4-H) 6.76 (1 H, d, *J* 7.1, 8-H), 7.06 (1 H, t, *J* 7.8, 9-H), 7.25 (1 H, s, 2-H), 7.28 (1 H, d, *J* 8.4, 10-H), 7.45 (1 H, br d, 5-H) and 10.18 (1 H, br s, 1-H); *m/z* 298 (M$^+$, 100%), 239 (9, M − CO_2Me), 211 (76), 194 (30), 182 (31), 168 (78), 154 (20), 141 (11), 127 (7), 119 (6), 115 (12, Ar$^{\bullet+}$), 98 (12) and 84 (13).

B. *In aqueous solution.* A solution of *N*-(2,2-dichloro-3-methylbutanoyl)tryptophan methyl ester **13** (250 mg, 0.67 mmol) in 20% water–acetonitrile (120 cm^3) was irradiated for 1 h. The bright yellow solution was evaporated and the residue was chromatographed (6% MeOH–CH_2Cl_2) to give olefin **14** (32 mg, 16%), and 1,3,4,5,6,7-*hexahydro*-7-*isopropyl*-6,12-*dioxo*-7,4-(*epoxymethano*)*pyrrolo*[4,3,2-fg][3][*benzazocine* **15** (88 mg, 46%) as a sparingly soluble crystalline solid, m.p. >300 °C (Found: C, 67.3; H, 5.6; N, 9.8. $C_{16}H_{16}N_2O_3$ requires C, 67.6; H, 5.7; N, 9.9%); $[\alpha]_D$ +166.4 (*c* 0.500 in MeOH); ν_{max}(KBr)/cm^{-1} 3285br, 3138, 3111, 3050, 2997, 2933, 2912, 1723 (ester (C=O), 1672 (amide C=O), 1616, 1559, 1537, 1504, 1467, 1445, 1414, 1392, 1369, 1358, 1328, 1296, 1249, 1224, 1210, 1166, 1124, 1086, 1055, 1031, 1017, 974, 935, 909, 878, 849 and 833; λ_{max}(MeOH)/nm 202 (log ε 4.29), 226 (4.29) and 296 (3.79); δ_H(250 MHz; [$^2H_6$]acetone) 1.12 (3 H, d, *J* 6.6, CH*Me*Me), 1.21 (3 H, d, *J* 7.0, CHMe*Me*), 3.24 (1 H, septet, *J* 6.6, C*H*Me$_2$), 3.63 (1 H, dd, *J* 4.4 and 17.1, 3-H), 3.77 (1 H, dd, *J* 3.5 and 17.4, 3-H), 4.63 (1 H, m, 4-H), 7.11 (1 H, t, *J* 7.8, 9-H), 7.24 (1 H, d, *J* 7.6, 8-H), 7.34 (1 H, s, 2-H), 7.45 (1 H, dd, *J* 1.2 and 8.1, 10-H), 7.76 (1 H, br s, 5-H) and 10.68 (1 H, br s, 1-H); *m/z* 284 (M$^+$, 100%), 256 (2, M − CO), 255 (3), 240 (11, M − CO_2), 214 (29), 213 (25), 212 (23), 198 (17), 185 (45), 170 (40), 158 (24), 154 (19), 130 (22), 115 (20, Ar$^{\bullet+}$), 46 (29), 43 (23) and 28 (27).

Reduction of Compound **15**.—To a solution of lactone **15** (50 mg, 0.18 mmol) in ethanol (1 cm^3) was added sodium borohydride (33 mg, 0.87 mmol) and the mixture was stirred for 2 h, then diluted with water, saturated with salt, and extracted with ethyl acetate. After being dried over magnesium sulfate the organic layer was evaporated and the residue was chromatographed (68:30:2 ether–acetone–water) to give (7S)-1,3,4,5,6,7-*hexahydro*-7-*hydroxy*-4-*hydroxymethyl*-7-*isopropyl*-6-*oxopyrrolo*[4,3,2-fg][3]*benzazocine* **16** (21 mg, 42%) as a solid, m.p. 197–198 °C (from $CHCl_3$) (Found: C, 66.7; H, 7.0; N, 9.7. $C_{16}H_{20}N_2O_3$ requires C, 66.6; H, 7.0; N, 9.7%); $[\alpha]_D$ +15 (*c* 1.15 in MeOH); ν_{max}($CHCl_3$)/cm^{-1} 3478 (indole NH), 3364 (amide NH), 3010, 2967, 2938, 2877, 1675, 1636 (C=O), 1447, 1407, 1387, 1336, 1166, 1110, 1054 and 1019; ν_{max}(MeOH)/nm 203 (log ε 4.29), 224 (4.27) and 292 (3.76); δ_H(250 MHz; [$^2H_6$]acetone; −20 °C) 0.76 (3 H, d, *J* 6.4, CH*Me*Me), 1.15 (3 H, d, *J* 6.7, CHMe*Me*), 2.96 (1 H, dd, *J* 6.5 and 15.4, 3-H), 3.49 (1 H, dd, *J* 7.6 and 16.4, 3-H), 3.60 (1 H, m, C*H*HOH), 3.74 (1 H, dd, *J* 5.2 and 10.8, CH*H*OH), 3.85 (1 H, m, C*H*Me$_2$) 4.28 (1 H, m, 4-H), 6.82 (1 H, br s, 5-H), 7.05 (1 H, t, *J* 8.0, 9-H), 7.21 (1 H, s, 2-H), 7.32 (1 H, d, *J* 8.0, 10-H), 7.59 (1 H, d, *J* 7.6, 8-H) and 10.47 (1 H, br s, 1-H); *m/z* 288 (M$^+$, 69%), 270 (18, M − H_2O), 245 (43, M − CHMe$_2$), 239 (10), 227 (24), 217 (17), 214 (20), 201 (43), 184 (22), 170 (26), 158 (100), 155 (25), 144 (13), 130 (47), 115 (15, ArCH$^{\bullet+}$), 60 (36) and 43 (28); and an inseparable mixture of diastereoisomeric 1,3,4,5,6,7-*hexahydro*-2-*hydroxy*-7-*isopropyl*-6-*oxo*-7,4-*epoxymethanopyrrolo*[4,3,2-fg][3]*benzazocines* **17** (18 mg, 35%), one isomer of which predominated in the ratio 1.4:1 (Found: M$^+$, 286.1317. $C_{16}H_{18}N_2O_3$ requires M, 286.1317); ν_{max}($CHCl_3$)/cm^{-1} 3480 (indole NH), 1673 (C=O), 1603, 1442, 1413, 1337, 1123, 1023, 1008 and 954; δ_H(250 MHz; [$^2H_6$]acetone) (major isomer) 1.02 (3 H, d, *J* 6.6, CH*Me*Me), 1.20 (3 H, d, *J* 6.6, CHMe*Me*), 3.07–3.95 (uninterpretable collection of peaks comprising signals for 3-, 4- and 11-H), 5.41 (1 H, septet, C*H*Me$_2$) and 6.94–7.28 (uninterpretable collection of peaks comprising signals for 2-, 8-, 9- and 10-H); (minor isomer) 1.11 (3 H, d, *J* 6.7, CH*Me*Me), 1.16 (3 H, d, *J* 6.7, CHMe*Me*), 3.07–3.95 (uninterpretable collection of peaks comprising signals for 3-, 4-, and 11-H), 5.55 (1 H, s, C*H*Me$_2$)

and 6.94–7.28 (uninterpretable collection of peaks comprising signals for 2-, 8-, 9- and 10-H); *m/z* 286 (M^+, 100%), 268 (11, M − H_2O), 243 (6, M − $CHMe_2$), 214 (12), 212 (12), 200 (55), 197 (18), 184 (23), 182 (22), 172 (37), 170 (27), 158 (36), 154 (27), 144 (26), 130 (31), 115 (14, $Ar^{\bullet+}$) and 43 (47).

N-(2,2-*Dichloro*-3-*methylbutanoyl*)*tryptophanol* **6**.—To a solution of *N*-(2,2-dichloro-3-methylbutanoyl)tryptophan methyl ester **13** (2.00 g, 5.39 mmol) in ethanol (20 cm^3) was added a solution of sodium borohydride (0.41 g, 10.8 mmol) in water (2 cm^3). The reaction was followed by TLC and was complete within 8 h, after which time the mixture was diluted with water, saturated with salt, and extracted with ether. The combined extracts were dried over magnesium sulfate and evaporated to leave a crude product, which was purified by chromatography (3% MeOH–CH_2Cl_2) to yield the *title compound* **6** (1.54 g, 83%) as a clear resin (Found: C, 56.1; H, 5.8; N, 8.2. $C_{16}H_{20}Cl_2N_2O_2$ requires C, 56.0; H, 5.9; N, 8.2%); $[\alpha]_D$ −41.5 (*c* 0.465 in MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3479 (indole NH), 3416 (amide NH), 3011, 2978, 2942, 2881, 1681 (C=O), 1515, 1458, 1420, 1391, 1339, 1092, 1037, 945 and 814; λ_{max}(MeOH)/nm 219 (log ε 4.49) and 279 (3.71); δ_H(250 MHz; [$^2H_6$]acetone) 0.94 (3 H, d, *J* 6.5, CH*Me*Me), 1.03 (3 H, d, *J* 6.7, CHMe*Me*), 2.75 (1 H, septet, *J* 6.7, C*H*Me_2), 3.08 (2 H, m, ArCH_2), 3.61 (1 H, dd, *J* 5.2 and 11.2, C*H*HOH), 3.69 (1 H, dd, *J* 4.6 and 11.0, CH*H*OH), 4.21 (1 H, m, C*H*NHCO), 7.01 (1 H, t, *J* 7.6, 5-H), 7.09 (1 H, t, *J* 7.7, 6-H), 7.21 (1 H, s, 2-H), 7.36 (1 H, d, *J* 8.2, 7-H), 7.62 (1 H, br s, CHN*H*CO), 7.73 (1 H, d, *J* 7.6, 4-H) and 10.09 (1 H, br s, 1-H); *m/z* 342 (M^+, 4%), 308 (3), 290 (2), 276 (3), 270 (1), 254 (1), 217 (1, M − Cl_2CCHMe_2), 173 (38, M − $H_2NCOCCl_2CHMe_2$), 130 (100, $ArCH_2^{\bullet+}$), 117 (7), 84 (17), 74 (30), 59 (42), 49 (20), 45 (31) and 31 (73).

Irradiation of N-(2,2-*Dichloro*-3-*methylbutanoyl*)*tryptophanol* **6**.—A. *In aqueous solution.* A solution of *N*-(2,2-dichloro-3-methylbutanoyl)tryptophanol **6** (1.00 g, 2.91 mmol) in a 1:1 mixture of acetonitrile–0.05 mol dm^{-3} sulfuric acid (500 cm^3) was irradiated for 70 min. The bright yellow reaction mixture was neutralised by the addition of sodium hydrogen carbonate, evaporated to a minimum volume, saturated with salt, and extracted with methylene dichloride. The pooled extracts were dried over sodium sulfate and evaporated, and the residue was chromatographed (8% MeOH–CH_2Cl_2) to give, first, 1,2,3,4,5,6-*hexahydro*-5-*isopropyl*-4-*oxo*-5,2-(*epoxymethano*)-*azepino*[4,5-b]*indole* **19** (0.193 g, 25%) as crystals, m.p. 297–299 °C (Found: C, 71.2; H, 6.8; N, 10.4. $C_{16}H_{18}N_2O_2$ requires C, 71.1; H, 6.7; N, 10.4%); $[\alpha]_D$ −49.7 (*c* 1.00 in MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3480 (indole NH), 3407 (amide NH), 3009, 1683 (C=O), 1456, 1430, 1389, 1368, 1299, 1156, 1124, 1034, 1012 and 948; λ_{max}(MeOH)/nm 218 (log ε 4.46) and 287 (4.00); δ_H(250 MHz; [$^2H_6$]acetone) 1.16 (3 H, d, *J* 6.5, CH*Me*Me), 1.20 (3 H, d, *J* 6.6, CHMe*Me*), 2.89 (1 H, septet, *J* 6.8, C*H*Me_2), 3.09 (1 H, dd, *J* 2.4 and 16.8, 1-H), 3.21 (1 H, d with multiple fine splitting, *J* 16.8, 1-H), 4.08 (2 H, t, *J* 8.9, 12-H_2), 4.13 (1 H, m, 2-H), 6.99 (1 H, t, *J* 7.3, 9-H), 7.08 (1 H, t, *J* 7.5, 8-H), 7.20 (1 H, br s, 3-H), 7.34 (1 H, d, *J* 7.8, 7-H), 7.41 (1 H, d, *J* 7.7, 10-H) and 10.12 (1 H, br s, 6-H); *m/z* 270 (M^+, 100%), 227 (14, M − $CHMe_2$), 212 (76), 211 (98), 201 (30), 200 (37), 199 (24), 184 (45), 168 (19), 167 (19), 158 (39), 156 (47), 154 (25), 130 (66), 115 (12, $Ar^{\bullet+}$), 102 (11), 77 (21), 43 (50) and 41 (24).

Continued chromatography gave a *ca.* 4:1 mixture of isomeric diols **16** and **18**, respectively (0.454 g, 54%). (7*R*)-1,3,4,5,6,7-Hexahydro-7-hydroxy-4-hydroxymethyl-7-isopropyl-6-oxopyrrolo[4,3,2-*fg*][3]benzazocine **18** had $\nu_{max}(CHCl_3)/cm^{-1}$ 3477 (indole NH), 3389 (amide NH), 3012, 2970, 2939, 2880, 1710 (C=O), 1685, 1499, 1468, 1446, 1389, 1365, 1321, 1277, 1165, 1146, 1132, 1118, 1045, 990, 960, 902 and 819; δ_H(250 MHz; [$^2H_6$]acetone) 0.75–1.2 (6 H, br, CH*Me*$_2$), 2.5–4.5 (broad humps comprising signals for 3-H, 4-H, 12-H_2 and C*H*Me_2), 7.0–7.4 (broad humps comprising signals for 2-, 8-, 9- and 10-H) and 10.2 (1 H, br s, 1-H); *m/z* 288 (M^+, 61%), 270 (36, M − H_2O), 245 (54, M − $CHMe_2$), 239 (20), 227 (27), 217 (18), 214 (20), 211 (12), 201 (41), 184 (23), 182 (19), 169 (34), 158 (100), 155 (42), 130 (53), 115 (18, $Ar^{\bullet+}$), 103 (10), 60 (34) and 43 (26).

B. *In acetonitrile.* A solution of *N*-(2,2-dichloro-3-methylbutanoyl)tryptophanol **6** (305 mg, 0.89 mmol) in acetonitrile (120 cm^3) was irradiated for 1 h. The solvent was evaporated off and the residue was chromatographed (6% MeOH–CH_2Cl_2) to give 1,3,4,5,6,7-*hexahydro*-4-*hydroxymethyl*-7-*isopropylidene*-6-*oxopyrrolo*[4,3,2-fg][3]*benzazocine* **20** (100 mg, 42%) as a microcrystalline solid, m.p. 257–259 °C (Found: C, 71.1; H, 6.8; N, 10.2. $C_{16}H_{18}N_2O_2$ requires C, 71.1; H, 6.7; N, 10.4%); $[\alpha]_D$ −305 (*c* 1.00 in MeOH); $\nu_{max}(CHCl_3)/cm^{-1}$ 3479 (indole NH), 3382 (amide NH), 3016, 2933, 2873, 1641 (C=O), 1458, 1435, 1376, 1340, 1167, 1091, 1048 and 814; λ_{max}(MeOH)/nm 204 (log ε 4.37), 226 (4.36) and 297 (3.89); δ_H(250 MHz; [$^2H_6$]acetone) (major conformer) 1.78 (3 H, s, C*Me*Me), 1.87 (3 H, s, CMe*Me*), 2.99 (1 H, dd, *J* 10.6 and 16.3, 3-H), 3.25 (1 H, d with multiple fine splitting, *J* 16.3, 3-H), 3.68 (2 H, d, *J* 5.9, CH_2OH), 4.23 (1 H, m, 4-H), 6.42 (1 H, br s, 5-H), 6.82 (1 H, d, *J* 7.2, 8-H), 7.03 (1 H, t, *J* 7.8, 9-H), 7.16 (1 H, s, 2-H), 7.30 (1 H, d, *J* 8.3, 10-H) and 10.30 (1 H, br s, 1-H); (minor conformer) 1.64 (3 H, s, C*Me*Me), 1.90 (3 H, s, C*Me*), 6.73 (1 H, d, *J* 7.3, 8-H), 7.04 (1 H, t, *J* 7.9, 9-H) and 7.26 (1 H, d, *J* 8.3, 10-H) (note: signals for 2-, 3-, 4- and 5-H, and CH_2OH were obscured by those of the major conformer); *m/z* 270 (M^+, 71%), 252 (6, M − H_2O), 239 (8, M − CH_2OH), 211 (90), 196 (16), 194 (34), 182 (26), 170 (85), 168 (100), 154 (29), 149 (10), 141 (17), 115 (23, $Ar^{\bullet+}$) and 98 (23).

7-*Azido*-1,3,4,5,6,7-*hexahydro*-4-*hydroxymethyl*-7-*isopropyl*-6-*oxopyrrolo*[4,3,2-fg][3]*benzazocine* **5**.—A. *Small-scale reaction.* A solution of the above described mixture of diols **16** and **18** (67 mg, 0.23 mmol) in 20% methanol–chloroform (2 cm^3) was introduced into a mixture of sodium azide (5.0 g, 77 mmol), trifluoroacetic acid (TFA) (6.0 cm^3, 8.8 g, 77 mmol) and chloroform (50 cm^3) which had previously been agitated in a mechanical shaker for 30 min. The soupy reaction mixture was shaken for 18 h, then poured into saturated aq. sodium hydrogen carbonate and extracted with methylene dichloride. The combined extracts were dried over sodium sulfate and the solvent was evaporated off. Chromatography (8% MeOH–CH_2Cl_2) of the residue gave the *title compound* **5** (20 mg, 27%, or 40% based on consumed starting material) as an amorphous, tan-coloured solid (Found: M^+, 313.1539. $C_{16}H_{19}N_5O_2$ requires M, 313.1539); $\nu_{max}(CHCl_3)/cm^{-1}$ 3476 (indole NH), 3363 (amide NH), 3010, 2970, 2940, 2881, 2110 (N_3), 1692 (C=O), 1645, 1500, 1469, 1447, 1433, 1397, 1370, 1346, 1311, 1246, 1169, 1110, 1049, 1001, 954 and 898; λ_{max}(MeOH)/nm 202 (log ε 4.38), 224 (4.38) and 293 (3.77); δ_H(250 MHz; [$^2H_6$]acetone; −20 °C) 0.98 (3 H, d, *J* 7.2, CH*Me*Me), 1.10 (3 H, br d, CHMe*Me*), 2.52 (1 H, m, C*H*Me_2), 2.87 (1 H, br m, 3-H), 3.46 (1 H, br m, 3-H), 3.62 (1 H, br m, C*H*(HOH), 3.99 (1 H, br m, CH*H*OH), 4.16 (1 H, br m, 4-H), 6.71 (1 H, br d, 5-H), 7.20 (1 H, br t, 9-H), 7.28–7.38 (2 H, br m, 2- and 10-H), 7.48 (1 H, br d, 8-H) and 10.63 (1 H, br s, 1-H); evidence for a minor isomer was present in the methyl-group region: δ 0.89 (d, *J* 7.3 Hz) and 1.03 (br d); *m/z* 313 (M^+, 7%), 285 (45, M − N_2), 272 (18), 270 (50, M − $CHMe_2$), 268 (22), 254 (24), 242 (21), 240 (39), 225 (26), 212 (72), 197 (54), 184 (48), 181 (37), 169 (59), 155 (100), 130 (57), 115 (20, $Ar^{\bullet+}$) and 94 (48).

B. *Large-scale reaction.* In a typical trial, a solution of the diol mixture (**16** and **18**) (486 mg, 1.59 mmol) in methanol (4 cm^3) was introduced into a mixture of sodium azide (15.0 g, 231 mmol), TFA (17.9 cm^3, 26.5 g, 232 mmol) and chloroform

(150 cm^3) which had previously been agitated in a mechanical shaker for 30 min. The reaction mixture was stirred for 9 days and was worked up as described above. Chromatography gave the title compound **5** (67 mg, 13%, or 32% based on consumed starting material).

Irradiation of Azide **5**.—A solution of azide **5** (94 mg, 0.30 mmol) in acetonitrile (100 cm^3) was irradiated for 40 min. The solvent was evaporated off and the residue was chromatographed (8% MeOH–CH_2Cl_2) to give 7,8-*didehydro*-8-*norindolactam V* **4** (16.2 mg) as a yellow resin. A number of fractions crossed with minor amounts of olefin **20** were subsequently rechromatographed to provide an additional crop of compound **4** (3.3 mg), bringing the total yield to 19.5 mg (23%) (Found: M^+, 285.1483. $C_{16}H_{19}N_3O_2$ requires M, 285.1477); $\nu_{max}(CHCl_3)/cm^{-1}$ 3478 (indole NH), 3364 (amide NH), 3007, 2970, 2932, 2875, 1641 (C=O), 1577, 1555, 1498, 1454, 1384, 1338, 1278, 1234, 1089, 1053, 1018, 915, 867, 835 and 817; λ_{max}(MeOH)/nm 216 (log ε 4.39) and 296 (3.69); δ_H(250 MHz; [$^2H_6$]acetone) 1.31 (3 H, d, *J* 7.1, CH*Me*Me), 1.36 (3 H, d, *J* 6.8, CHMe*Me*), 2.76 (1 H, d, *J* 15.1, C*H*HOH), 2.93 (1 H, septet, *J* 6.9, C*H*Me_2), 3.36 (1 H, dd, *J* 7.3 and 15.4, CH*H*OH), 3.53 (1 H, dd, *J* 8.8 and 10.6, 3-H), 3.65 (1 H, dd, *J* 6.3 and 10.6, 3-H), 3.86 (1 H, m, 4-H), 6.03 (1 H, br s, 5-H), 6.45 (1 H, dd, *J* 1.5 and 7.3, 9-H), 6.98 (1 H, t, *J* 7.5, 10-H), 7.01 (1 H, s, 2-H), 7.05 (1 H, d, *J* 8.2, 11-H and 10.09 (1 H, br s, 1-H); *m/z* 285 (M^+, 89%), 270 (51, M – Me), 254 (8, M – CH_2OH), 242 (12, M – $CHMe_2$), 226 (12), 211 (56), 199 (29), 194 (14), 186 (15), 183 (24), 170 (48), 168 (42), 155 (100), 145 (14), 141 (8), 130 (22), 115 (16, $Ar^{\cdot+}$) and 102 (12).

Continued chromatography gave 1,3,4,5,6,7-*hexahydro*-4-*hydroxymethyl*-7-*isopropylimino*-6-*oxopyrrolo*[4,3,2-fg][3]*benzazocine* **21** (23.9 mg, 28%), the *Z*-isomer of which (see Fig. 1) was crystallised from methanol solution, m.p. 271–274 °C (Found: M^+, 285.1480. $C_{16}H_{19}N_3O_2$ requires M, 285.1477); ν_{max}(20% MeOH–$CHCl_3$)/cm^{-1} 1656 (C=O), 1450 and 1412; λ_{max}(MeOH)/nm 204 (log ε 4.34) and 318 (3.73; δ_H(270 MHz; [$^2H_6$]acetone) (*Z*-isomer) 1.20 (3 H, d, *J* 6.2, CH*Me*Me), 1.23 (3 H, d, *J* 6.2, CHMe*Me*), 3.11 (1 H, dd, *J* 11.7 and 16.7, 3-H), 3.25 (1 H, dd, *J* 2.7 and 16.7, 3-H), 3.81 (2 H, m, CH_2OH), 4.21 (1 H, m, 4-H), 6.97 (1 H, br d, 5-H), 7.10 (1 H, t, *J* 7.7, 9-H), 7.23 (1 H, dd, *J* 1.2 and 7.2, 8-H), 7.28 (1 H, s, 2-H), 7.47 (1 H, dd, *J* 1.2 and 8.2, 10-H) and 10.50 (1 H, br s, 1-H); δ_H(250 MHz; [$^2H_6$]acetone) (*E*-isomer, which exists as a *ca.* 1:1 mixture of conformers) 1.06 [3 H, d, *J* 7.1, CH*Me*(Me)], 1.11 [3 H, d, *J* 7.1, CH*Me*(Me)], 1.28 [3 H, d, *J* 6.5, CH*Me*(Me)], 1.30 [3 H, d, *J* 6.5, CH*Me*(Me)], 2.7–3.9 (uninterpretable collection of peaks comprising signals for 3-H, CH_2OH, and C*H*Me_2), 4.02 (1 H, br m, 4-H), 4.28 (1 H, br m, 4-H), 6.93 (1 H, d, *J* 7.2, 8-H), 6.95 (1 H, d, *J* 7.1, 8-H), 7.09 (2 H, t, *J* 7.7, 9-H), 7.11 (1 H, br s, 2-H), 7.20 (1 H, br s, 2-H), 7.38 (1 H, d, *J* 8.1, 10-H), 7.39 (1 H, d, *J* 8.1, 10-H) and 10.27 (2 H, br s, 1-H); *m/z* 285 (M^+, 39%), 267 (14, M – H_2O), 254 (5, M – CH_2OH), 242 (35, M – $CHMe_2$), 226 (15), 224 (12), 211 (16), 199 (14), 198 (14), 197 (14), 196 (18), 183 (18), 169 (40), 155 (100), 142 (10), 128 (9), 115 (16, $Ar^{\cdot+}$) and 31 (30).

(–)-8-*Norindolactam V* **22**.—To a solution of compound **4** (16.2 mg, 0.057 mmol) in methanol (2 cm^3) were added sodium cyanoborohydride (5.0 mg, 0.080 mmol) and acetic acid (1 drop). After 21 h, additional sodium cyanoborohydride (5.0 mg) and acetic acid (1 drop) were added and the mixture was stirred for a further 1.5 h before being neutralised with saturated aq. sodium hydrogen carbonate (2 drops) and evaporated. Chromatography (8% MeOH–CH_2Cl_2) of the residue gave the title compound **22** (11.3 mg, 69%) as a pale gold resin. The R_f-value of this material on TLC was identical with that of a synthetic racemic sample;[6] $[\alpha]_D$ –78.3 (*c* 0.30 in MeOH) [lit.,[5c] –76.0 (*c* 0.72 in MeOH)]; $\nu_{max}(CHCl_3)cm^{-1}$ 3478 (indole NH), 3378 (amide NH), 3006, 2963, 2931, 2873, 1653 (C=O), 1500, 1464, 1437, 1423, 1406, 1347, 1255, 1117, 1089, 1065, 1049 and 1015; δ_H(500 MHz; $CDCl_3$) (major conformer) 1.03 (d, *J* 6.5, CH*Me*Me), 1.16 (d, *J* 6.5, CHMe*Me*), 2.27 (br m, C*H*Me_2), 2.80 (m, 3-H), 3.03 (m, 3-H), 3.3–3.8 (uninterpretable collection of peaks comprising signals for 7-H and CH_2OH), 6.64 (br s, 9-H), and 6.8–7.1 (uninterpretable collection of peaks comprising signals for 2-H, 10-H, and 11-H); *m/z* 287 (M^+, 55%), 256 (4, M – CH_2OH), 242 (4), 213 (5), 201 (27), 200 (22), 199 (23), 187 (16), 183 (9), 171 (13), 157 (100), 145 (12) and 130 (19).

(–)-*Indolactam V* **1**.—To a solution of (–)-norindolactam V **22** (11.3 mg, 0.039 mmol) in 1:1 methanol–methyl iodide (10 cm^3) was added sodium hydrogen carbonate (84 mg, 1.0 mmol) and the mixture was heated at reflux for 72 h. The solvent was removed and the residue was chromatographed (8% MeOH–CH_2Cl_2) to give the title compound **1** (6.0 mg, 51%) as a yellow resin. The R_f-value of this material on TLC was identical with that of a synthetic racemic sample;[6] $[\alpha]_D$ –136 (*c* 0.30 in MeOH) [lit.,[5c] –134.5 (*c* 0.70 in MeOH)]; $\nu_{max}(CHCl_3)/cm^{-1}$ 3478 (indole NH), 3382 (amide NH), 3006, 2960, 2932, 2872, 1657 (C=O), 1607, 1569, 1549, 1502, 1482, 1470, 1450, 1408, 1373, 1352, 1297, 1275, 1252, 1090, 1068 and 1041; δ_H(250 MHz; $CDCl_3$) (major conformer) 0.61 (3 H, d, *J* 6.6, CH*Me*Me), 0.90 (3 H, d, *J* 6.3, CHMe*Me*), 2.57 (1 H, m, C*H*Me_2), 2.89 (3 H, s, NMe), 3.02 (1 H, dd, *J* 3.6 and 17.0, 3-H), 3.15 (1 H, d, *J* 17.0, 3-H), 3.53 (1 H, dd, *J* 8.5 and 11.2, CH*H*OH), 3.71 (1 H, dd, *J* 3.9 and 11.3, C*H*OH), 4.28 (1 H, m, 4-H), 4.37 (1 H, d, *J* 10.2, 7-H), 6.47 (1 H, d, *J* 7.7, 9-H), 6.87 (1 H, s, 2-H), 6.87 (1 H, d, *J* 7.9, 11-H), 7.03 (1 H, t, *J* 7.8, 10-H), 7.30 (1 H, br s, 5-H) and 8.03 (1 H, br s, 1-H); *m/z* 301 (M^+, 52%), 283 (17, M – H_2O), 278 (23), 270 (17, M – CH_2OH), 268 (24), 258 (16, M – $CHMe_2$), 256 (17), 240 (14), 215 (37), 213 (26), 212 (26), 199 (20), 197 (25), 184 (43), 171 (100), 159 (39), 157 (33), 155 (32), 149 (54), 143 (17), 130 (39), 121 (43), 115 (25, $Ar^{\cdot+}$), 105 (66), 91 (34), 77 (73) and 57 (63).

Crystal Data.—Single crystals of compound **21**, suitable for X-ray crystallography, were grown from methanol. $C_{16}H_{19}N_3O_2$, M = 285.3, monoclinic, a = 6.341(2), b = 16.502(5), c = 7.373(3) Å, β = 106.36(3)°, V = 740 $Å^3$, space group $P2_1$, Z = 2, D_c = 1.28 g cm^{-3}. Clear, air-stable plates, crystal

Table 1 Atomic co-ordinates (× 10^4) with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*
N(1)	4349(3)	5055	4133(3)
C(2)	5367(3)	4872(2)	2802(3)
C(3)	4935(3)	4108(1)	2131(3)
C(3a)	3459(3)	3771(1)	3140(3)
C(4)	2335(3)	3034(1)	3200(3)
C(5)	925(3)	2977(2)	4330(3)
C(6)	613(3)	3623(2)	5458(3)
C(7)	1716(4)	4336(2)	5484(3)
C(7a)	3121(3)	4397(2)	4358(3)
C(8)	5824(3)	3780(2)	584(3)
C(9)	5138(3)	2945(1)	–174(3)
N(10)	6055(2)	2328(1)	1255(2)
C(11)	5035(3)	2035(1)	2448(2)
O(11)	5897(2)	1583(1)	3781(2)
C(12)	2643(3)	2295(1)	2156(2)
N(12)	1014(2)	1870(1)	1269(2)
C(13)	5882(3)	2766(2)	–1931(3)
O(13)	5075(2)	1989(1)	–2638(2)
C(14)	1348(3)	1120(1)	328(3)
C(15)	253(4)	1212(2)	–1768(3)
C(16)	380(4)	430(2)	1181(4)

dimensions 0.25 × 0.40 × 0.50 mm, μ(Cu-Kα) = 6.6 cm^{-1}, $F(000)$ = 304. Data were collected on a Nicolet R3m diffractometer, ω-scan method, $0 \leq 2\theta \leq 116°$, graphite-monochromated Cu-Kα radiation (χ = 1.541 78 Å); 1026 independent reflections were measured, of which 1024 had $|F_o| > 3\sigma(|F_o|)$ and were considered observed. The data were corrected for Lorentz and polarisation factors. No absorption correction was applied. The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically. The positions of the hydrogen atoms on N(1), N(10) and O(13) were located from a ΔF map and allowed to refine isotropically, subject to a distant constraint (X–H 0.98 Å). All the other hydrogen atoms were idealised (C–H 0.96 Å), assigned isotropic thermal parameters, U(H) = 1.2 U_{eq}(C) and allowed to ride on their parent carbons. Refinement was by block-cascade full-matrix least squares to give R = 0.032, R_w = 0.037 [$w^{-1} = \sigma^2(F) + 0.002F^2$]. The maximum residual electron densities in the final ΔF map was 0.27 e $Å^{-3}$ and the mean and maximum shift/error in the final refinement cycle were 0.024 and 0.106, respectively. Computations were carried out on an Eclipse S140 using the SHELXTL program system.[16,*] Atomic co-ordinates are given in Table 1.

Acknowledgements

We thank Professor Steven V. Ley for synthetic samples and spectra of racemic indolactam V, its demethyl derivative, and their epimers, and the Royal Society of Chemistry for a Hickinbottom Fellowship (to C. J. M.).

* The bond lengths and bond angles are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by a full literature citation for this communication. For details of the desposition scheme see 'Instructions to Authors (1992)', Section 5.6.3, in the January issue.

References

1 M. Takashima and H. Sakai, *Bull. Agric. Chem. Soc. Jpn.*, 1960, **24**, 647 and 652.
2 For a recent addition to the family see: K. Irie, S.-I. Kajiyama, K. Koshimizu, H. Hiyashi and M. Arai, *Tetrahedron Lett.*, 1990, **31**, 7337.
3 K. Irie and K. Koshimizu, *Mem. Coll. Agric., Kyoto Univ.*, 1988, **132**, 1; A. P. Kozikowski, P. W. Shum, A. Basu and J. S. Lazo., *J. Med. Chem.*, 1991, **34**, 2420.
4 K. Irie, S.-I. Kajiyama, A. Funaki, K. Koshimizu, H. Hayashi and M. Arai, *Tetrahedron Lett.*, 1990, **31**, 101; *Tetrahedron*, 1990, **46**, 2773.
5 (*a*) Y. Endo, K. Shudo and T. Okamoto, *Chem. Pharm. Bull.*, 1982, **30**, 3457; (*b*) Y. Endo, K. Shudo, K. Furuhata, H. Ogura, S. Sakai, N. Aimi, Y. Hitotsuyanagi and Y. Koyama, *Chem. Pharm. Bull.*, 1984, **32**, 358; (*c*) Y. Endo, K. Shudo, A. Itai, M. Hasegawa and S. Sakai, *Tetrahedron*, 1986, **42**, 5905.
6 S. E. deLaszlo, S. V. Ley and R. A. Porter, *J. Chem. Soc., Chem. Commun.*, 1986, 344.
7 S. Nakatsuka, T. Masuda, K. Sakai and T. Goto, *Tetrahedron Lett.*, 1986, **27**, 5735.
8 A. P. Kozikowski, K. Sato, A. Basu and J. S. Lazu, *J. Am. Chem. Soc.*, 1989, 111, 6228.
9 H. Muratake and M. Natsume, *Tetrahedron*, 1991, **47**, 8535; H. Muratake, K. Okabe and M. Natsume, *Tetrahedron*, 1991, **47**, 8545; K. Okabe, H. Muratake and M. Natsume, *Tetrahedron*, 1991, **47**, 8559.
10 T. P. Kogan, T. C. Somers and M. C. Venuti, *Tetrahedron*, 1990, **46**, 6623.
11 Preliminary communication, M. Mascal and C. J. Moody, *J. Chem. Soc., Chem. Commun.*, 1988, 589.
12 A. L. Beck, M. Mascal, C. J. Moody, A. M. Z. Slawin, D. J. Williams and W. J. Coates, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1/05782K.
13 For a discussion of the relative migratory aptitudes of aryl and alkyl groups in the decomposition of aralkyl azides, see: F. D. Lewis and W. H. Saunders, in *Nitrenes*, ed. W. Lwowski, Interscience, New York, 1970, ch. 3.
14 W. C. Still and I. Galynker, *Tetrahedron*, 1981, **37**, 3981.
15 *Handbook of Chemistry and Physics*, ed. R. C. Weast, CRC Press, Boca Raton, Florida, 58th edn, p. C-224.
16 G. M. Sheldrick, SHELXTL, An Integrated System for Solving, Refining and Displaying Crystal Structures from Diffraction Data, University of Gottingen, Germany, Revision 4.1, 1983.

Paper 1/05752I
Received 13*th November* 1991
Accepted 6*th January* 1992