Benzocarbapenems from indoles[1]

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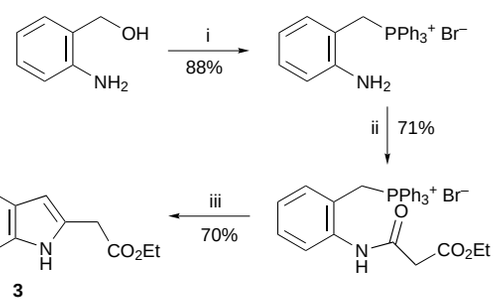
The 8,8a-dihydroazeto[1,2-*a*]indol-2(1*H*)-ones (benzocarbapenems) 1a, 16, 17, 22, 27, 35 and 36 have been prepared by cyclodehydration of the corresponding β-amino acids, these amino acids being obtained by reduction of the analogous 2-substituted or 2,7-disubstituted indoles. The hydroxy group of compound 36 is designed to mimic the carboxylic acid function of the carbapenems on the basis of molecular modelling. The azetidinones 1a and 27, which are unsubstituted at the methylene group of the four-membered ring, are unstable and highly susceptible to ring opening by nucleophiles but the compounds 22, 35 and 36 with two methyl substituents at this position are much more stable. The carbonyl stretching frequency in the IR is close to 1770 cm^{-1} for all the azetidinones except the phenol 36 for which the absorption is at 1735 cm^{-1}. An X-ray crystal structure of compound 36 is reported.

We have been investigating syntheses of bicyclic and tricyclic β-lactams in which aromatic heterocycles are used as the precursors. Because of the high stability and predictable chemistry of these heterocycles it should be possible to devise short routes to new or little known ring systems or to introduce new substitution patterns. The synthesis of carbapenams from pyrroles has been described in an earlier paper.[2] In this paper we give the results of an investigation of the synthesis of 8,8a-dihydroazeto[1,2-*a*]indol-2(1*H*)-ones (benzocarbapenems) **1** from indoles. A related route to benzocarbacephems from quinolines is described in the following paper.[3]

We chose as our initial target the parent unsubstituted benzocarbapenem **1a**, in order to establish a viable synthetic route to more biologically relevant molecules.† The starting point for the synthesis of **1a** is an indole-2-acetic acid and the route is, in principle, very simple (Scheme 1). The two steps are the reduction of the double bond in the five-membered ring and the cyclisation of the β-amino acid derivative to the β-lactam. The synthesis therefore required a route to indole-2-acetic acid or to one of its esters that could subsequently be used for the corresponding 7-hydroxyindole-2-acetic acid (for reasons given below), and reliable methods for carrying out the reduction and cyclisation steps.

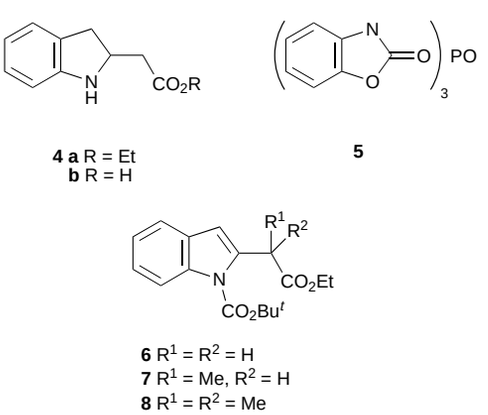
Scheme 1

There are two general routes to indole-2-acetic acid derivatives. The first requires the construction of the five-membered ring of the indole skeleton with the side chain already in place; in the second, the side chain is introduced at a late stage by alkylation of indole[6] or by modification of an existing 2-substituent.[7] After considerable experimentation with several of the literature procedures we chose to use a route of the first type involving an intramolecular Wittig reaction as the key step[5d] (Scheme 2) since it proved to be reliable when carried out on a large scale. Ethyl indole-2-acetate **3** was prepared from 2-aminobenzyl alcohol in three steps and in an overall yield of 44% by this method.



Scheme 2 *Reagents:* i, PPh_3·HBr; ii, EtO_2CCH_2COCl; iii, $KOBu^t$

The reduction of ethyl indole-2-acetate to the corresponding indoline ester **4a** was carried out (82%) by dissolving the ester in TFA then adding trimethylamine–borane complex to the solution at 0 °C over a period of five minutes. Similar reductions of indoles by pyridine–borane complex have been described.[8] The



† The parent compound **1a** had been synthesised once before but not fully characterised.[4]

ester was hydrolysed to the corresponding carboxylic acid **4b** in concentrated HCl, the product being isolated (60%) and characterised as its crystalline hydrochloride. As in the earlier work,[2] the cyclising agent used to produce the β-lactam **1a** from the carboxylic acid **4b** was tris(2-oxobenzoxazolin-3-yl)phosphine oxide **5**.[9] This proved to be more efficient than other cyclising agents [dicyclohexylcarbodiimide (DCCI) or dipyridyl disulfide with triphenylphosphine]. The β-lactam **1a** was isolated as a crystalline solid (37%) after purification by sublimation. It shows a carbonyl stretching absorption in the IR spectrum at 1773 cm^{-1} and its NMR spectrum is consistent with that reported earlier.[4]

The benzocarbapenem **1a** starts to decompose within a few hours when left in air at room temperature but it was stored for up to a month under nitrogen at −20 °C without significant decomposition. It is highly susceptible to ring opening by nucleophiles. An attempt to obtain a mass spectrum of a sample dissolved in methanol gave only a spectrum consistent with a product of ring opening, methyl 2,3-dihydro-1*H*-indole-2-acetate. An electron impact mass spectrum of the purified solid gave a molecular ion; the major breakdown pathway is its cleavage to indole and ketene.

The high reactivity of the compound should be moderated by substitution of the methylene group of the four membered ring since this is likely to lower the internal angle strain. In order to establish this the synthesis was applied to derivatives bearing one and two methyl substituents in the four membered ring. Two approaches were considered: (i) to incorporate the methyl substituents into the precursors for the intramolecular Wittig reaction and (ii) to alkylate the side chain methylene group of ethyl indole-2-acetate. Since the second approach appeared to be potentially more versatile this was the method adopted. The nitrogen atom of ethyl indole-2-acetate was protected by introduction of a *tert*-butoxycarbonyl (Boc) group and the protected ester **6** was methylated by reaction with potassium hexamethyldisilazide (KHMDS) and iodomethane to give the α-methyl ester **7** in 92% yield. By repeating the methylation procedure without isolation of the intermediate **7**, the dimethylated ester **8** was obtained in 83% yield from ethyl indole-2-acetate.

The ester **7** was deprotected by reaction with TFA (Scheme 3, route A). Reduction of the double bond of the product **9** with trimethylamine–borane complex was inefficient but reduction by sodium cyanoborohydride in TFA gave the corresponding dihydroindole esters **10** and **11** in a combined yield of 79%. As expected, the reduction was unselective and the isomers were obtained in a 1 : 1 ratio, as estimated from the NMR spectrum of the mixture. The components could not be separated by column chromatography.

The Boc protected ester **7** was also reduced directly to the corresponding dihydroindoles **12** and **13** by catalytic hydrogenation at 200 psi over rhodium in a mixture of ethanol and acetic acid[10] (route B in Scheme 3). The esters were isolated in a combined yield of 88% as a 5 : 1 mixture of diastereoisomers. The major isomer was subsequently shown to be **12**. The stereoselectivity of the reduction can be ascribed to reaction through a conformer (Fig. 1) that was found by molecular mechanics to be the lowest energy of those examined. The same stereoselectivity was observed in the catalytic hydrogenation of analogous pyrroles to pyrrolidines.[2] The Boc protecting group was removed by reaction with TFA to give the esters **10** and **11**.

The mixed esters obtained by each of the two reduction procedures were hydrolysed to the corresponding amino acids, which were characterised as the TFA salts **14** and **15**. The salts (as mixtures) were then cyclised (56–63% yield) by reaction with the phosphine oxide **5** and triethylamine. The mixtures of β-lactams **16** and **17** were obtained as low melting point crystalline solids and were characterised without being separated. The mixture obtained by the catalytic hydrogenation route proved to contain **16** as the predominant component and this established the isomer **12** as the major product in the hydrogenation step. The β-lactams **16** and **17** were distinguished by the signals for H-1 in the NMR spectrum. The signal for **16** appears at lower field than that for **17** (at δ 3.70 for **16**, close to δ 3.17 for **17**) and shows *cis* coupling to the bridgehead hydrogen H-8a (J 5.5 Hz; J 2.8 Hz for **17**). These β-lactams are somewhat more stable than the unsubstituted compound **1a**; they could be stored under nitrogen below 0 °C without decomposition.

The ester **8** was converted into the β-lactam **22** by an analogous route, shown in Scheme 4. The final cyclisation step proceeded in 73% yield and gave the product **22** as a crystalline solid that was significantly more stable than **1a**. The carbonyl

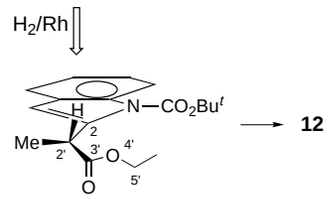
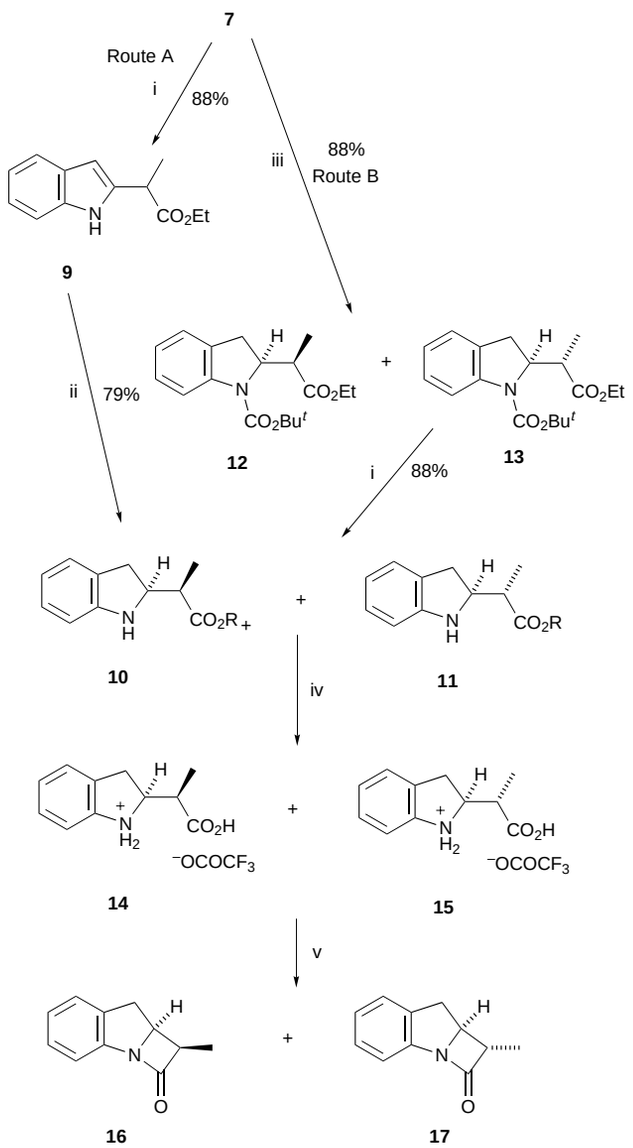


Fig. 1 Addition of hydrogen to the indole **7** in its lowest energy conformation



Scheme 3 *Reagents:* i, TFA; ii, $NaCNBH_3$, TFA; iii, H_2, Rh/C; iv, aq. KOH then TFA; v, **5**, Et_3N

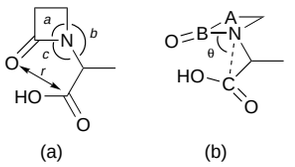
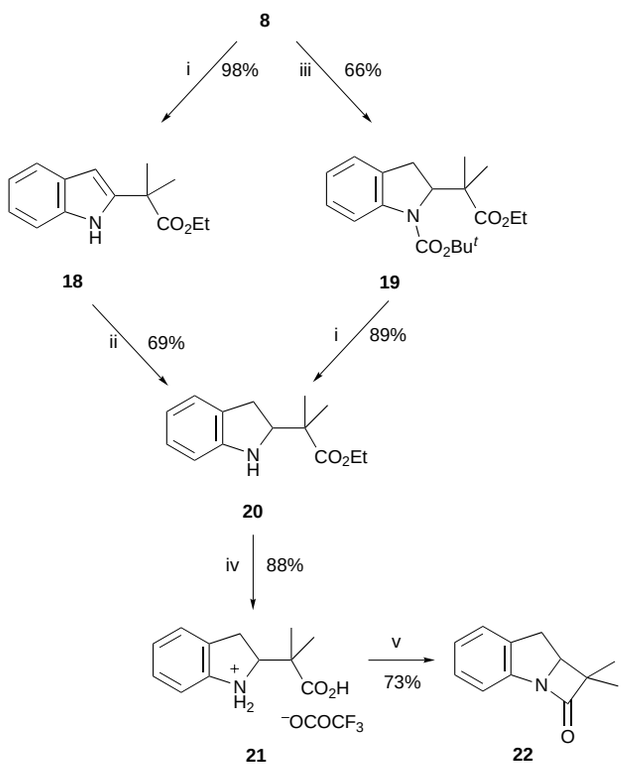


Fig. 2 (a) Pyramidality $360° - (a + b + c)°$; Cohen distance (Å) = r; (b) through space torsion angle between the ring plane ABN and carbon atom C = $\theta°$



Scheme 4 *Reagents:* i, TFA; ii, $NaCNBH_3$, TFA; iii, H_2, Rh/C; iv, aq. KOH then TFA; v, **5**, Et_3N

stretching frequency in the IR spectrum was at 1771 cm^{-1}, almost the same as that of **1a**.

It was perhaps no surprise that benzocarbapenems **1a**, **16**, **17** and **22** lacked any useful antibacterial and/or β-lactamase inhibitory activity. It is generally believed that the presence of an acidic functionality is essential for good antibacterial activity. The free carboxylate of β-lactam antibiotics anchors the nuclei electrostatically by binding to an unstabilised lysine or histidine residue in the basal cleft, while an oxyanion hole locates and activates the β-lactam carbonyl oxygen atom by way of two hydrogen bonds.[11] These primary anchorages present the carbonyl carbon atom to the active-site serine hydroxy group, prior to acylation.

We therefore proposed to introduce an appropriate acidic functionality into the C-7 position of the benzocarbapenem ring system. Preliminary comparison of the three-dimensional structure of the benzocarbapenem ring system with that of the carbapenem carboxylic acid **2a** identified the phenol derivative **1b** as an appropriate candidate. Further encouragement was provided by performing a more detailed conformational analysis of **1b**. Early work by Rao and Vasudevan and by Cohen identified that the degree of β-lactam nitrogen pyramidality and the position of the carboxylate group, particularly the Cohen distance, (Fig. 2) are pivotal features for penicillin binding protein (PBP) inhibition.[12] Cohen argued that when the 'Cohen' distance is greater than 3.95 Å, the β-lactam derivative is inactive, due to its inability to fit the catalytic triad of active-site residues: the unstabilised lysine, the oxyanion hole and the serine hydroxy group. The degree of β-lactam pyramidality is interpreted as increasing the reactivity towards nucleophilic attack, by perturbation of β-lactam amide resonance.

Table 1 Observed and calculated geometries of the azetidinones **2b**, **2a** and **1b**

Structure	**2b**[a]	**2a**[b]	**1b**[b]
Pyramidality (°)	35.8	45.0	44.6
Torsion angle, θ (°)	152.7	143.0	138.9
Cohen distance, r (Å)	3.61	3.67	3.71

[a] Observed. [b] Calculated.

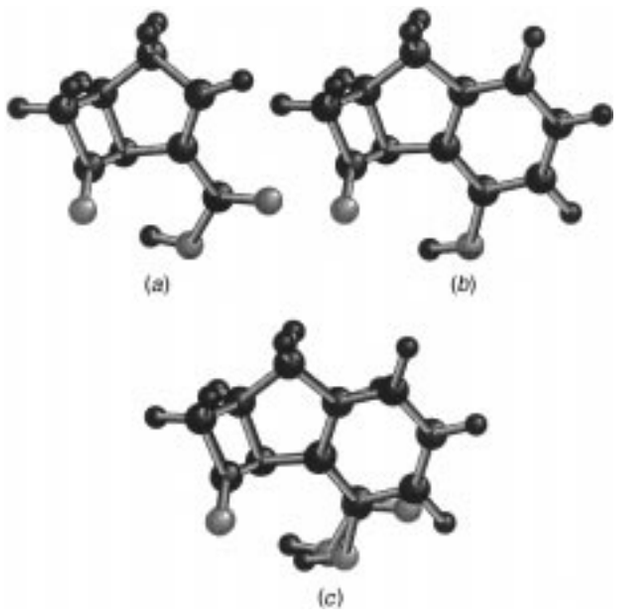
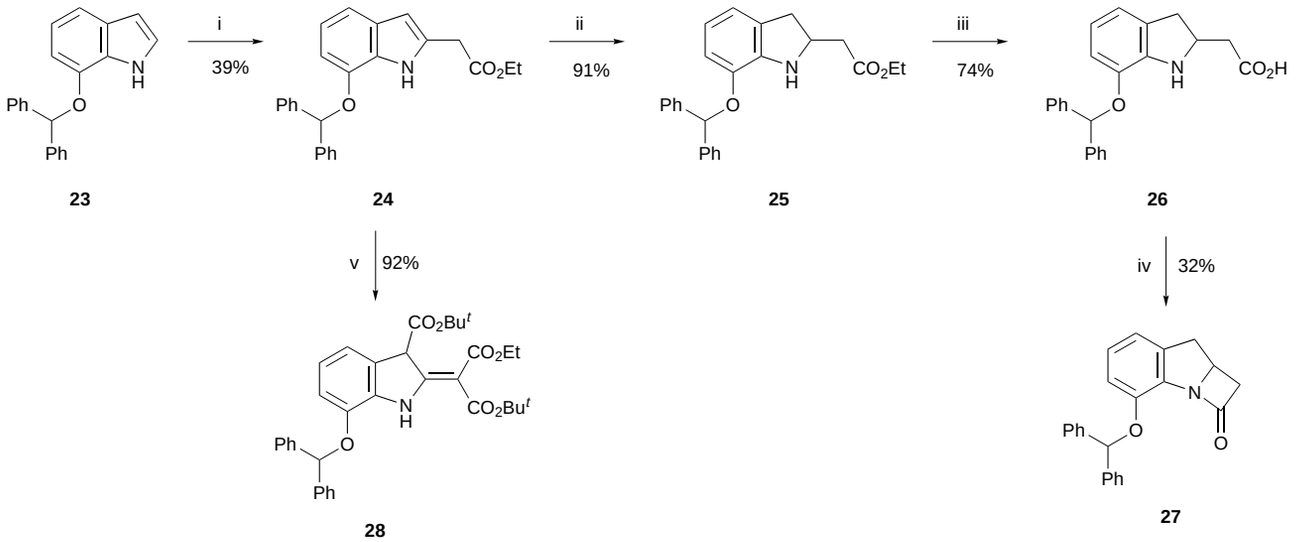


Fig. 3 Molecular modelling (*a*) of the carboxylic acid **2a**; (*b*) of the phenol **1b**; (*c*) superposition of the two structures

After construction and geometry optimisation using the molecular mechanics within SYBYL,[13] molecules **1b** and **2a** were submitted for full geometry optimisation within MOPAC[14] using AM1 Hamiltonians. The minimum energy conformations thus obtained were validated by comparison of the optimised structure for **2a** with the X-ray structure of the carbapenem ester **2b**, imported from the Cambridge Crystallographic Database (Table 1). The observed values for the pyramidality and the Cohen distance (the distance between the oxygen atom of the β-lactam and the carbon atom of the carboxylate or phenolic oxygen functionality) all lie in the range that is found in biologically active compounds.[12] Indeed, the fully optimised structures of **1b** and **2a** can be overlaid such that the functional groups in the two compounds are essentially superimposable (Fig. 3). This raised the possibility that the hydroxy function in the benzocarbapenem **1b** might mimic the role of the carboxy function in the carbapenems. Although β-lactams bearing phenolic hydroxy groups have been prepared before,[15] their structures have not been specifically matched to those of biologically active compounds.

The Bartoli indole synthesis provides an attractive route to 7-substituted indoles[16] and 7-(benzhydryloxy)indole **23** has been prepared in two steps from 2-nitrophenol by this route.[17] This preparation, in combination with the radical alkylation of indole introduced by Baciocchi *et al.*,[6] offered a short synthesis of ethyl 7-(benzhydryloxy)indole-2-acetate **24**, a suitably protected precursor to **1b**.

The indole **23** was prepared by a slight modification of the literature procedure in an overall yield of 38% from 2-nitrophenol. Radical alkylation of indole by ethyl iodoacetate as described by Baciocchi *et al.* is a synthetically valuable and



Scheme 5 *Reagents:* i, ICH_2CO_2Et, $FeSO_4$, DMSO, H_2SO_4, urea–H_2O_2; ii, $NaCNBH_3$, AcOH; iii, aq. KOH then citric acid; iv, **5**, Et_3N; v, $(Bu^tOCO)_2O$, DMAP

unusual reaction since it provides a rare example of preferential 2-substitution. We explored the reaction of the indole **23** and ethyl iodoacetate under a variety of conditions. The desired alkylation product **24** was obtained in acceptable yield only when the indole was used in three- or four-fold excess. The use of urea–hydrogen peroxide complex in place of aqueous hydrogen peroxide resulted in a slight improvement in the yield (Scheme 5). In our hands, the product was obtained in the highest yield (39%) when the reaction was carried out on a modest scale (5 mmol ethyl iodoacetate). The reaction mixture was relatively clean, most of the remainder being the precursor indole **23** which could be recovered by column chromatography and recycled.

The indole **24** was reduced to the dihydroindole **25** (91%) by sodium cyanoborohydride in acetic acid. This was hydrolysed to the acid **26** under basic conditions and the cyclisation of the acid gave the desired β-lactam **27** in 32% yield. IR and NMR spectra of the product were consistent with the proposed structure but the product was not fully characterised because it was extremely unstable. The analogous unsubstituted β-lactam **1a** was purified by vacuum sublimination but this technique failed with compound **27**.

Since methylation of the acetate side chain had produced more stable compounds **16**, **17** and **22** in the earlier series, the same procedure was attempted with the 7-substituted indole **24**. This required protection of the indole nitrogen atom of the ester **24** before alkylation. Unfortunately it proved impossible to introduce the Boc protecting group on to the nitrogen atom. Instead a disubstituted compound, to which the structure **28** has been assigned, was produced in high yield. Evidently the bulky substituent at C-7 prevents the normal substitution at nitrogen. Attempts to introduce other protecting groups (TBDMS, SEM) were also unsuccessful, and this approach was abandoned in favour of one based on the intramolecular Wittig reaction for the construction of the required indole.

The route is shown in Scheme 6. 2-Amino-3-methoxybenzyl alcohol **29** was prepared in two steps from commercially available 3-methoxy-2-nitrobenzoic acid. This amine was then converted into the indole ester **32** by way of the isolated intermediates **30** and **31**. The indole ester was reduced to the indoline **33** by sodium cyanoborohydride in acetic acid. The ester was hydrolysed to the acid **34** which was cyclised in good yield to the azetidinone **35**. This compound is a stable crystalline solid. It was purified by column chromatography and fully characterised. The final step, the cleavage of the methyl ether, was achieved with boron tribromide to give the phenol **36** as a crystalline solid. An X-ray crystal structure of the product was obtained (Fig. 4). Selected bond lengths and bond angles are listed in Table 2.‡

Table 2 Selected bond lengths and bond angles for **36**[a]

Bond lengths (Å)		Bond angles (°)	
N1–C2	1.379(4)	C2–N1–C3	93.1(2)
N1–C3	1.505(4)	N1–C2–C1	93.7(3)
N1–C6	1.426(4)	C2–C1–C3	85.1(2)
C1–C2	1.532(5)	N1–C3–C1	87.6(2)
C1–C3	1.567(5)	N1–C6–C7	127.8(3)
C6–C7	1.379(4)	C11–C1–C12	111.8(3)
O1–C7	1.369(4)	O1–C7–C6	118.8(3)
O2–C2	1.214(4)	N1–C2–O2	131.6(3)

[a] Atom numbering corresponds to that in Fig. 4.

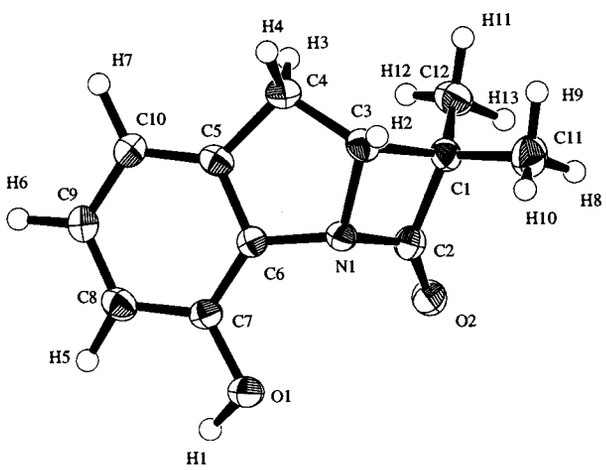
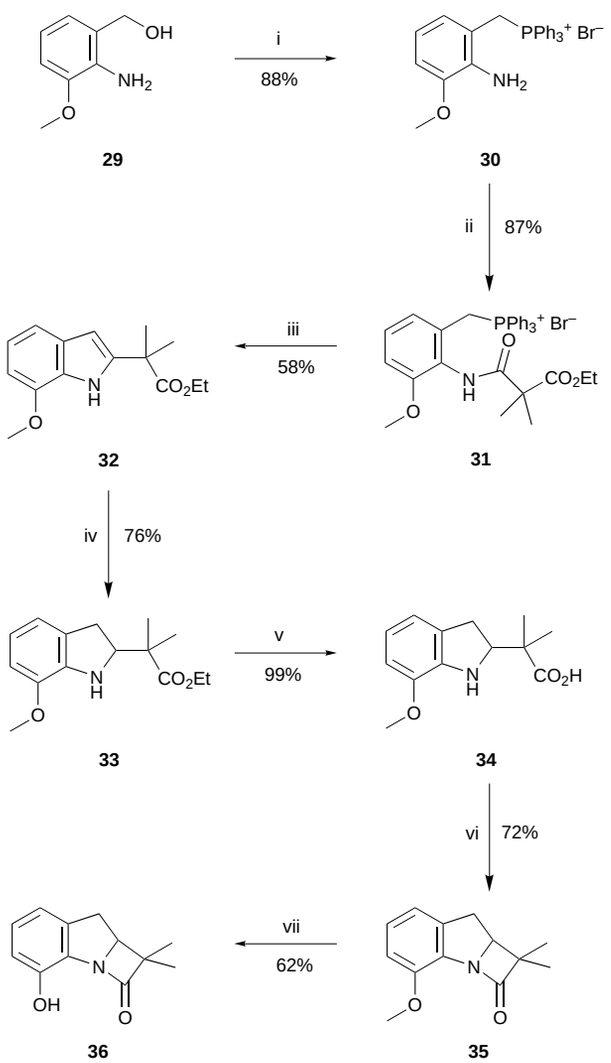


Fig. 4 Structure of compound **36**

The carbonyl stretching absorption in the IR spectrum of the phenol **36** is at 1735 cm^{-1} whereas that of the ether **35** is at 1774 cm^{-1}. This lowering of the frequency is also observed in other azetidinones bearing an adjacent phenolic substituent.[15] It can

‡ 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 207/194.



Scheme 6 *Reagents:* i, PPh_3·HBr; ii, EtO_2CCMe_2COCl; iii, KOBu^t; iv, $NaCNBH_3$, AcOH; v, aq. KOH then citric acid; vi, **5**, Et_3N; vii, BBr_3

be ascribed to intramolecular hydrogen bonding, although the X-ray structure of compound **36** shows no evidence for either intramolecular or intermolecular hydrogen bonding in the crystal.

In summary, routes to several azeto[1,2-*a*]indol-2(1*H*)-ones have been devised. Those derivatives lacking substitution at the C-1 position in the benzocarbapenem ring system are isolable but very unstable. Chemical stability is significantly increased by the presence of one or two methyl substituents at this position. These compounds, as well as the 7-hydroxy derivative **36**, are devoid of any useful biological activity. Introduction of an (*R*)-hydroxyethyl substituent at the C-1 position (as in thienamycin) may improve the possibility of achieving antibacterial activity in this novel series of tricyclic β-lactam derivatives and will be the focus of future chemistry.

Experimental

General

^{1}H NMR spectra were recorded on Bruker AC 200 (200 MHz), Varian Gemini 2000 (300 MHz) and Bruker AMX (400 MHz) spectrometers. Multiplicities are recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), quartets (q) and multiplets (m). *J* Values are in Hz. Infrared spectra were recorded either on a Perkin-Elmer 298 or on a Perkin-Elmer 1720-X FTIR spectrometer. Solid samples were run as Nujol mulls, and liquids as thin films. Mass spectra were recorded on a VG Micromass 7070E machine as electron impact spectra (70 eV). Microanalyses were performed in the University of Liverpool Microanalysis Laboratory. Melting points (mp) were determined on a Kofler block and are uncorrected. Flash chromatography was carried out using Kieselgel 60 and water pump vacuum. Thin layer chromatography (TLC) was carried out on Merck 10 × 2 cm aluminium-backed plates with a 0.2 mm layer of Kieselgel 60 F_{254}. Light petroleum refers to the fraction bp 60–80 °C and ether refers to diethyl ether.

2-Aminobenzyltriphenylphosphonium bromide[5d]

Triphenylphosphonium hydrogen bromide (37.48 g, 0.109 mol) was added to a stirred and boiling solution of 2-aminobenzyl alcohol (13.45 g, 0.109 mol) in acetonitrile (750 cm^3). The reaction mixture was heated under reflux for 7 h then allowed to cool. The solid precipitate was filtered off and the filtrate was reduced in volume to give a further crop; total 43.17 g (88%); δ_H(200 MHz; $CDCl_3$) 5.21 (2 H, d, *J* 12.2) and 7.26–7.76 (19 H, m).

[2-(Ethoxycarbonylacetamido)benzyl]triphenylphosphonium bromide[5d]

Ethyl malonyl chloride (7.43 g, 49 mmol) was added to a stirred solution of 2-aminobenzyltriphenylphosphonium bromide (22.1 g, 49.0 mmol) in dichloromethane (100 cm^3). After 3 h the solvent was distilled off and the residue was crystallised from hot ethanol (20 cm^3) to give the phosphonium bromide (19.64 g, 71%); ν_{max}(Nujol)/cm^{-1} 3481, 1765 and 1688; δ_H(200 MHz; $CDCl_3$) 1.24 (3 H, t, *J* 7.1), 3.49 (2 H, s), 4.14 (2 H, q, *J* 7.1), 5.52 (2 H, d, *J* 14.4), 7.24–7.77 (19 H, m) and 10.51 (1 H, br s, NH).

Ethyl 1*H*-indole-2-acetate 3[5d]

Freshly prepared potassium *tert*-butoxide (5.00 g) was slowly added to a stirred suspension of the phosphonium bromide (8.05 g, 14 mmol) in toluene (35 cm^3) under reflux. After 15 min the reaction mixture was filtered hot and the filtrate was evaporated to dryness. The residue was purified by flash chromatography which gave (with dichloromethane) ethyl 1*H*-indole-2-acetate **3** (2.07 g, 70%) as an oil; ν_{max}(film)/cm^{-1} 3395 and 1726; δ_H(200 MHz; $CDCl_3$) 1.28 (3 H, t, *J* 7.1), 3.81 (2 H, s), 4.22 (2 H, q, *J* 7.1), 6.34 (1 H, s), 7.03–7.56 (5 H, m) and 8.67 (1 H, br s).

Ethyl 2,3-dihydro-1*H*-indole-2-acetate 4a

To an ice-cooled solution of ethyl 1*H*-indole-2-acetate **3** (1.12 g, 5.5 mmol) in TFA (10 cm^3) was added trimethylamine–borane complex (3.00 g) in small amounts during 5 min. The mixture was stirred for a further 15 min then aq. sodium hydrogen carbonate (8 g in 50 cm^3 water) was added. The aqueous layer was washed with toluene. The toluene extract was washed with saturated aqueous sodium chloride and dried over Na_2SO_4. The solvent was distilled off and the residue was subjected to flash chromatography, which gave [with light petroleum–ethyl acetate (19 : 1)] *ethyl* 2,3-*dihydro*-1H-*indole*-2-*acetate* **4a** (0.93 g, 82%) (Found: C, 70.2; H, 7.4; N, 6.85. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.4; N, 6.8%); ν_{max}(film)/cm^{-1} 3374 and 1729; δ_H(200 MHz; $CDCl_3$) 1.28 (3 H, t, *J* 7.1), 2.62 (2 H, d, *J* 6.6, C$H_2$$CO_2$Et), 2.69 (1 H, dd, *J* 8.2 and 15.4, 3-H), 3.18 (1 H, dd, *J* 8.2 and 15.4, 3-H), 4.17 (2 H, q, *J* 7.1), 4.12–4.30 (1 H, m, 2-H), 6.59–6.73 (2 H, m) and 6.98–7.33 (2 H, m); *m*/*z* 205 (M$^+$, 17%) and 118 (100).

2,3-Dihydro-1*H*-indole-2-acetic acid 4b

Method A. To a stirred solution of the ester **4a** (0.422 g, 2 mmol) in dioxan (4 cm^3) was added potassium hydroxide (0.4 g) followed by water (1 cm^3). The progress of the reaction was followed by TLC until no starting material remained. The solvent was removed and the residue was acidified by the addition of 10% aq. citric acid (20 cm^3). The solution was extracted with dichloromethane (3 × 30 cm^3) and ether (2 × 30 cm^3), then

dried over $MgSO_4$. The solvent was removed *in vacuo* to give the acid **4b** as an oil; δ_H(200 MHz; $CDCl_3$) 2.72 (2 H, d, *J* 6.6, CH_2CO$_2$Et), 2.73 (1 H, dd, *J* 8.8 and 15.4, 3-H), 3.21 (1 H, dd, *J* 8.8 and 15.4, 3-H), 4.16–4.31 (1 H, m, 2-H), 6.23 (1 H, br s, N*H*), 6.65–6.79 (2 H, m) and 7.01–7.25 (2 H, m); *m*/*z* 177 (M^+, 13%), 130 (24), 118 (100) and 117 (38).

Method B. A solution of the ester **4a** (1.15 g, 5.6 mmol) in concentrated hydrochloric acid (30 cm^3) was stirred for 1 h at room temperature (RT). The solution was diluted with water (20 cm^3) and was stirred for a further 24 h. The solution was evaporated to dryness and the solid residue was crystallised to give the *hydrochloride* of compound **4b** (0.72 g, 60%), mp 139 °C (from ethanol–light petroleum) (Found: C, 56.1; H, 5.7; N, 6.5. $C_{10}H_{12}ClNO_2$ requires C, 56.2; H, 5.7; N, 6.6%); ν_{max}(Nujol)/cm^{-1} 2919 and 1714; δ_H(200 MHz; D_2O) 3.03 (2 H, d, *J* 8.8, CH_2CO$_2$Et), 3.06 (1 H, dd, *J* 8.2 and 16.5, 3-H), 3.48 (1 H, dd, *J* 8.2 and 16.5, 3-H), 4.50–4.57 (1 H, m, 2-H) and 7.36–7.44 (4 H, m); *m*/*z* 177 (M^+, 26%) and 118 (100).

8,8a-Dihydroazeto[1,2-*a*]indol-2(1*H*)-one 1a

To a stirred suspension of the hydrochloride of **4b** (0.21 g, 1.0 mmol) in dry acetonitrile (100 cm^3) was added tris(2-oxobenzoxazolin-3-yl)phosphine oxide **5** (0.45 g, 1.0 mmol) and dry triethylamine (0.41 g, 4.0 mmol). The reaction mixture was heated under reflux for 6 h. The solvent was removed under reduced pressure and the crude product was subjected to flash chromatography (dichloromethane) and sublimation (70 °C and 0.2 mmHg) to give 8,8a-dihydroazeto[1,2-*a*]indol-2(1*H*)-one **1a** (0.06 g, 37%), mp 77 °C (Found: C, 75.3; H, 5.7; N, 8.7. $C_{10}H_9NO$ requires C, 75.45; H, 5.7; N, 8.8%); ν_{max}(Nujol)/cm^{-1} 1773, 1645 and 1600; δ_H(200 MHz; $CDCl_3$) 2.98 (1 H, dd, *J* 3.3 and 16.5, 1-H), 3.15 (1 H, dd, *J* 7.8 and 16.8, 8-H), 3.37 (1 H, dd, *J* 8.8 and 16.8, 8-H), 3.53 (1 H, dd, *J* 5.2 and 16.5, 1-H), 4.32–4.44 (1 H, m, 8a-H) and 7.03–7.25 (4 H, m); *m*/*z* 159 (M^+, 33%) and 117 (100, $M^+ - CH_2CO$).

Ethyl 1-*tert*-butoxycarbonyl-1*H*-indole-2-acetate 6

To a stirred solution of ethyl 1*H*-indole-2-acetate **3** (0.51 g, 2.5 mmol) in dry dichloromethane (40 cm^3) was added 4-dimethylaminopyridine (0.31 g, 2.5 mmol) followed by di-*tert*-butyl dicarbonate (0.82 g, 3.8 mmol). The solution was stirred at room temperature for 3 h. Evaporation of the solvent followed by flash chromatography [dichloromethane–hexane (1 : 1)] gave the *ester* **6** as an oil (0.76 g, 100%) (Found: C, 67.7; H, 7.0; N, 4.6. $C_{17}H_{21}NO_4$ requires C, 67.3; H, 7.0; N, 4.6%); ν_{max}(film)/cm^{-1} 1734; δ_H(200 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7.1), 1.66 (9 H, s), 4.03 (2 H, s), 4.18 (2 H, q, *J* 7.1), 6.47 (1 H, s, 3-H), 7.19–7.28 (2 H, m), 7.47–7.52 (1 H, m) and 8.08 (1 H, d, *J* 8.8); *m*/*z* 303 (M^+, 16%) and 130 (100).

Ethyl 2-(1-*tert*-butoxycarbonyl-1*H*-indol-2-yl)propanoate 7

To a solution of the ester **6** (0.53 g, 1.7 mmol) in dry THF (5 cm^3) at −78 °C was added slowly dropwise KHMDS (3.4 cm^3, 0.5 M in toluene, 1.7 mmol). After 1 h iodomethane (0.30 g, 2 mmol) was added dropwise. The reaction mixture was stirred for 30 min then allowed to warm to RT. Saturated aq. ammonium chloride was added and the organic components were extracted with ether (3 × 30 cm^3). The ether extracts were washed with water (3 × 30 cm^3) and brine (30 cm^3) and dried over $MgSO_4$. The solvent was removed and the crude residue was subjected to flash chromatography [dichloromethane–hexane (1 : 1)] to give the *ester* **7** (0.51 g, 92%) as an oil (Found: C, 68.3; H, 7.3; N, 4.4. $C_{18}H_{23}NO_4$ requires C, 68.1; H, 7.3; N, 4.4%); ν_{max}(film)/cm^{-1} 3052, 1734 and 1453; δ_H(200 MHz; $CDCl_3$) 1.07 (3 H, t, *J* 7.1), 1.50 (3 H, d, *J* 7.1), 1.51 (9 H, s), 4.00 (2 H, q, *J* 7.1), 4.27 (1 H, q, *J* 7.1), 6.38 (1 H, s, 3-H), 6.99–7.14 (2 H, m), 7.34 (1 H, dd, *J* 2.2 and 6.0) and 7.89 (1 H, dd, *J* 2.2 and 7.1); *m*/*z* 317 (M^+, 7%) and 57 (100).

Ethyl 2-(1*H*-indol-2-yl)propanoate 9[18]

TFA (0.5 cm^3) was added to a stirred solution of the ester **8** (0.45 g, 1.4 mmol) in dichloromethane (4 cm^3) at RT. After 3 h the solution was poured into saturated aq. sodium hydrogen carbonate (30 cm^3). The mixture was extracted with dichloromethane (2 × 20 cm^3) and the extracts were combined, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography (dichloromethane) to give the ester **9** (0.27 g, 88%) as an oil; δ_H(200 MHz; $CDCl_3$) 1.27 (3 H, t, *J* 7.1), 1.60 (3 H, d, *J* 7.1), 3.93 (1 H, q, *J* 7.1), 4.19 (2 H, q, *J* 7.1), 6.35–6.37 (1 H, m, 3-H), 7.03–7.19 (1 H, m), 7.31–7.36 (1 H, m), 7.53–7.57 (1 H, m) and 8.56 (1 H, br s, NH).

Ethyl 2-(2,3-dihydro-1*H*-indol-2-yl)propanoates 10 and 11

(i) By route A. Sodium cyanoborohydride (0.55 g) was added slowly in small portions to TFA (10 cm^3) at 0 °C under N_2. After 15 min the ester **9** (0.35 g, 1.6 mmol) was added slowly. The mixture was allowed to warm to RT and, after 1 h, additional sodium cyanoborohydride (0.60 g) was added in portions. The mixture was stirred for a further 1 h before water (30 cm^3) was added. The resulting reaction mixture was added to saturated aq. sodium hydrogen carbonate and the mixture was extracted with dichloromethane (3 × 25 cm^3). The organic product was subjected to flash chromatography [dichloromethane–hexane (1 : 1)] to give the *esters* **10** and **11** (0.28 g, 79%) as an oil (Found: C, 71.5; H, 7.9; N, 6.5. $C_{18}H_{25}NO_4$ requires C, 71.2; H, 7.8; N, 6.4%); ν_{max}(film)/cm^{-1} 3373 and 1724; δ_H(200 MHz; $CDCl_3$) 1.22 (d, *J* 7.1, CHCH_3 of **11**), 1.23 (d, *J* 7.1, CHCH_3 of **10**), 1.26 (t, *J* 7.1, CH_2CH_3 of **10**), 1.28 (t, *J* 7.1, CH_2CH_3 of **11**) (these four signals together, 6 H; ratio **10** : **11** = 1 : 1), 2.54–2.88 (2 H, m, 3-H and C*H*CH$_3$), 3.14 (1 H, dd, *J* 8.6 and 14.8, 3-H of both isomers), 3.95–4.11 (1 H, m, 2-H), 4.08–4.23 (2 H, m, CH_2CH$_3$), 6.57–6.71 (2 H, m) and 6.96–7.10 (2 H, m); *m*/*z* 233 (M^+, 6%) and 118 (100).

(ii) By route B. TFA (7 cm^3) was added to a stirred solution of the mixture of esters **12** and **13** (0.38 g, 1.2 mmol) in dichloromethane (4 cm^3) at room temperature. After 3 h, the products were poured into saturated aqueous sodium hydrogen carbonate (50 cm^3). The organic products were extracted with dichloromethane (3 × 40 cm^3), and the extracts were combined, dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography gave (with dichloromethane) a mixture of the esters **10** and **11** (0.23 g, 88%) as an oil ν_{max}(film)/cm^{-1} 3373 and 1724. The NMR spectrum showed the same signals as those in the spectrum of the product from method (i) but in the ratio **10** : **11** = 5 : 1.

Ethyl 2-(1-*tert*-butoxycarbonyl-2,3-dihydro-1*H*-indol-2-yl)-propanoates 12 and 13

The ester **7** (0.17 g, 0.5 mmol) in ethanol (4 cm^3) and acetic acid (0.5 cm^3) was hydrogenated at 200 psi over rhodium (5% on alumina, 300 mg). Flash chromatography gave (with dichloromethane) a mixture of the esters **12** and **13** (0.15 g, 88%) as an oil (Found: C, 67.4; H, 7.9; N, 4.35. $C_{18}H_{25}NO_4$ requires C, 67.7; H, 7.9; N, 4.4%); δ_H(200 MHz; $CDCl_3$) 0.95 (3 H, t, *J* 7.2), 1.16 (3 H, d, *J* 7.2), 1.61 (9 H, s), 2.99 (1 H, dd, *J* 2.2 and 16.5, 3-H), 3.24 (1 H, dd, *J* 9.4 and 16.5, 3-H), 3.80 (2 H, q, *J* 7.2), 3.59–4.19 (2 H, m), 6.86–6.94 (2 H, m), 7.08–7.16 (2 H, m); *m*/*z* 319 (M^+, 2%), 219 (11) and 118 (100).

2-(2,3-Dihydro-1*H*-indolium-2-yl)propanoic acid trifluoroacetates 14 and 15

(i) By route A. Potassium hydroxide (150 mg) dissolved in the minimum amount of water was slowly added to a stirred solution of the 1 : 1 mixture of esters **10** and **11** (80 mg) in ethanol (2 cm^3). The reaction vessel was flushed with nitrogen and the solution was stirred until the starting material could no longer be detected by TLC. The ethanol was distilled off and the remaining aqueous solution was extracted with ethyl acetate (3 × 25 cm^3). The extracts were combined, dried over $MgSO_4$ and concentrated. The residue was then dissolved in TFA and the excess TFA was removed by rotary evaporation to leave the

trifluoroacetates **14** and **15** (90 mg, 81%) as a solid; ν_{max}(Nujol)/cm^{-1} 2950 and 1719; δ_H(200 MHz; TFA–C_6D_6) 1.24 and 1.27 (together 3 H, each d, *J* 7.1, CHCH_3), 2.98–3.14 (2 H, m, C*H*CH$_3$ and 3-H), 3.40 (1 H, dd, *J* 8.8 and 16.5, 3-H), 4.20–4.43 (1 H, m, 2-H) and 7.30–7.40 (4 H, m); *m*/*z* 191 (M^+, 9%) and 118 (100).

(ii) By route B. Potassium hydroxide (180 mg) dissolved in the minimum amount of water was added to a stirred solution of the esters **10** and **11** (140 mg) in ethanol (2 cm^3). The reaction vessel was flushed with nitrogen and the solution was stirred until the starting material could no longer be detected by TLC. The ethanol was removed *in vacuo* and the remaining aqueous solution was extracted with ethyl acetate (3 × 25 cm^3). The extracts were combined, dried over $MgSO_4$ and concentrated. The residue was then dissolved in TFA and the excess TFA was removed by rotary evaporation to give the trifluoroacetate salts **14** and **15** (180 mg, 92%) as a solid.

8,8a-Dihydro-1-methylazeto[1,2-*a*]indol-2(1*H*)-ones 16 and 17

(i) By route A. Tris(2-oxobenzoxazol-3-yl)phosphine oxide **5** (0.27 g, 0.6 mmol) and dry triethylamine (0.25 g, 2.4 mmol) were added to a stirred suspension of the TFA salt (0.19 g, 0.6 mmol) in dry acetonitrile (100 cm^3). The reaction mixture was heated under reflux for 6 h. The solvent was removed under reduced pressure and the crude product was subjected to flash chromatography (dichloromethane) and sublimation (70 °C, 0.2 mmHg) to give 8,8a-*dihydro*-1-*methylazeto*[1,2-a]*indol*-2(1H)-*ones* **16** and **17** (60 mg, 56%), mp 35–40 °C (Found: C, 76.0; H, 6.4; N, 8.05%; M^+, 173.084. $C_{11}H_{11}NO$ requires C, 76.3; H, 6.4; N, 8.1%; *M*, 173.084); ν_{max}(Nujol)/cm^{-1} 1778 and 1601; δ_H(200 MHz; $CDCl_3$) (ratio **16**:**17** = 1:1) 1.26 (d, *J* 7.7, 1-Me of **16**), 1.51 (d, *J* 7.7, 1-Me of **17**), 3.02–3.26 (m, 2 × 8-H of **16** and 8-H of **17**), 3.17 (dq, *J* 2.8 and 7.7, 1-H of **17**), 3.34 (dd, *J* 9.3 and 16.8, 8-H of **17**), 3.70 (dq, *J* 5.5 and 7.7, 1-H of **16**), 4.03 (ddd, *J* 2.8, 7.7 and 9.3, 8a-H of **17**), 4.46 (ddd, *J* 5.5, 8.2 and 9.4, 8a-H of **16**) and 7.01–7.25 (m, Ar-H); *m*/*z* 173 (M^+, 21%), 130 (20) and 117 (100, M^+ − MeCHCO).

(ii) By route B. The salts **14** and **15** (0.28 g, 0.9 mmol) were cyclised as in (a) to give the azetidinones **16** and **17** (100 mg, 63%), mp 40–68 °C (Found: C, 76.1; H, 6.4; N, 8.05. $C_{11}H_{11}NO$ requires C, 76.3; H, 6.4; N, 8.1%); the NMR spectrum showed the same signals as those in (a) in the ratio **16**:**17** = 5:1.

Ethyl 2-(1-*tert*-butoxycarbonyl-1*H*-indol-2-yl)-2-methylpropanoate 8

KHMDS (0.5 M in toluene, 7.20 cm^3, 3.6 mmol) was added at −78 °C to a solution of the ester **6** (0.74 g, 2.4 mmol) in dry THF (10 cm^3). After 30 min iodomethane (0.57 g, 4.0 mmol) in THF (5 cm^3) was added. The reaction mixture was allowed to warm to RT then, after 30 min, it was again cooled to −78 °C. KHMDS (9.00 cm^3, 4.5 mmol) was added then, after 30 min, iodomethane (0.85 g, 6 mmol) in THF (5 cm^3). The reaction mixture was quenched and the product was extracted as described for the ester **7**. Flash chromatography gave [with dichloromethane–hexane (1:1)] the *ester* **8** (0.67 g, 83%) as colourless crystals mp 92 °C (Found: C, 68.8; H, 7.6; N, 4.2. $C_{19}H_{25}NO_4$ requires C, 68.9; H, 7.6; N, 4.2%); ν_{max}(Nujol)/cm^{-1} 1735; δ_H(200 MHz; $CDCl_3$) 1.60 (3 H, t, *J* 7.1), 1.68 (15 H, s, Bu^t and CMe_2), 4.10 (2 H, q, *J* 7.1), 6.59 (1 H, s, 3-H), 7.20–7.28 (2 H, m), 7.48–7.53 (1 H, m) and 7.98 (1 H, d, *J* 7.2); *m*/*z* 331 (M^+, 6%), 231 (29) and 158 (100).

Ethyl 2-(1*H*-indol-2-yl)-2-methylpropanoate 18

TFA (1.5 cm^3) was added to a stirred solution of the ester **8** (1.88 g, 5.7 mmol) in dichloromethane (5 cm^3) at room temperature. Extraction of the product and flash chromatography gave the *ester* **18** (1.29 g, 98%), mp 111–114 °C (Found: C, 72.5; H, 7.5; N, 6.0. $C_{14}H_{17}NO_2$ requires C, 72.7; H, 7.4; N, 6.1%); ν_{max}(Nujol)/cm^{-1} 3359 and 1696; δ_H(200 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7.1), 1.66 (6 H, s), 4.17 (2 H, q, *J* 7.1), 6.31–6.35 (1 H, m), 7.03–7.19 (2 H, m), 7.32–7.36 (1 H, m), 7.53–7.57 (1 H, m) and 8.57 (1 H, br s); *m*/*z* 231 (M^+, 17%) and 158 (100).

Ethyl 2-(1-*tert*-butoxycarbonyl-2,3-dihydro-1*H*-indol-2-yl)-2-methylpropanoate 19

The ester **8** (0.09 g, 0.3 mmol) was hydrogenated by the same procedure as described for the preparation of the indolines **12** and **13**. The *ester* **19** was isolated (0.06 g, 66%) as an oil (Found: M^+, 333.194. $C_{19}H_{27}NO_4$ requires *M*, 333.194); ν_{max}(film)/cm^{-1} 2977, 1704 and 1603; δ_H(200 MHz; $CDCl_3$) 0.96 (3 H, s), 1.18 (3 H, t, *J* 7.1), 1.25 (3 H, s), 1.56 (9 H, s), 2.72 (1 H, dd, *J* 1.7 and 16.5, 3-H), 3.33 (1 H, dd, *J* 9.4 and 16.5, 3-H), 3.89–4.10 (2 H, m), 4.85 (1 H, dd, *J* 1.7 and 9.4, 2-H), 6.93–6.98 (1 H, m), 7.07–7.14 (2 H, m) and 7.50–7.56 (1 H, br m); *m*/*z* 333 (M^+, 3%) and 118 (100).

Ethyl 2-(2,3-dihydro-1*H*-indol-2-yl)-2-methylpropanoate 20

(i) From the ester 18. Sodium cyanoborohydride (0.30 g) was added slowly and in small portions to TFA (10 cm^3) at 0 °C under N_2. After 15 min the ester **18** (0.20 g, 0.9 mmol) was added slowly. The mixture was allowed to warm to RT and, after 1 h, additional sodium cyanoborohydride (0.30 g) was added in portions. The mixture was stirred for a further 1 h before water (30 cm^3) was added. The product was extracted and purified as described for compound **9**. Flash chromatography gave the *ester* 20 (0.14 g, 69%) as an oil (Found: C, 72.1; H, 8.2; N, 6.0. $C_{14}H_{19}NO_2$ requires C, 72.1; H, 8.2; N, 6.0%); ν_{max}(Nujol)/cm^{-1} 3374 and 1719; δ_H(200 MHz; $CDCl_3$) 1.18 (3 H, s), 1.22 (3 H, s), 1.26 (3 H, t, *J* 7.1), 2.84 (1 H, dd, *J* 9.3 and 15.9, 3-H), 3.02 (1 H, dd, *J* 9.4 and 15.9, 3-H), 4.14 (2 H, q, *J* 7.1), 4.18 (1 H, t, *J* 9.4, 2-H), 6.55–6.69 (2 H, m) and 6.96–7.07 (2 H, m); *m*/*z* 233 (M^+, 6%) and 118 (100).

(ii) From the ester 19. TFA (2 cm^3) was added to a stirred solution of the ester **19** (1.22 g, 3.7 mmol) in dichloromethane (5 cm^3) at RT. After 3 h, the products were poured into saturated aq. sodium hydrogen carbonate (50 cm^3). Extraction (dichloromethane) followed by flash chromatography gave the ester **20** (0.76 g, 89%) as an oil.

2-(2,3-Dihydro-1*H*-indolium-2-yl)-2-methylpropanoic acid trifluoroacetate 21

A solution of potassium hydroxide (250 mg) in the minimum amount of water was added to a stirred solution of the ester **20** (200 mg) in ethanol (2 cm^3). After the starting ester had been consumed (TLC) the ethanol was distilled off and the remaining aqueous solution was extracted with ethyl acetate (3 × 25 cm^3). The extracts were combined, dried and evaporated to dryness. The residue was dissolved in TFA and the excess TFA was removed by rotary evaporation to give the trifluoroacetate **21** (0.24 g, 88%) as a solid; ν_{max}(Nujol)/cm^{-1} 2924 and 1724; δ_H(200 MHz; TFA–C_6D_6) 2.05 (3 H, s), 2.18 (3 H, s), 3.81 (1 H, dd, *J* 9.4 and 15.9, 3-H), 4.00–4.12 (1 H, dd, *J* 8.2 and 16.5, 3-H), 4.88–5.02 (1 H, m, 2-H) and 7.97–8.07 (4 H, m); *m*/*z* 205 (M^+, 6%) and 118 (100).

8,8a-Dihydro-1,1-dimethylazeto[1,2-*a*]indol-2(1*H*)-one 22

The phosphine oxide **5** (0.41 g, 0.9 mmol) and dry triethylamine (0.32 g, 3.7 mmol) were added to a stirred suspension of the salt **21** (0.28 g, 0.9 mmol) in dry acetonitrile (100 cm^3). The reaction mixture was heated under reflux for 6 h. The solvent was removed under reduced pressure and the crude product was subjected to flash chromatography (dichloromethane) and sublimation (70 °C, 0.2 mmHg) to give the azetidinone **22** (0.12 g, 73%), mp 82–83 °C (Found: C, 77.1; H, 7.0; N, 7.5. $C_{12}H_{13}NO$ requires C, 77.0; H, 7.0; N, 7.5%); ν_{max}(Nujol)/cm^{-1} 1771, 1600 and 1585; δ_H(400 MHz; $CDCl_3$) 1.23 (3 H, s), 1.51 (3 H, s), 3.11 (1 H, dd, *J* 9.5 and 17.0, 8-H), 3.20 (1 H, dd, *J* 7.9 and 17.0, 8-H), 4.15 (1 H, dd, *J* 7.9 and 9.5, 8a-H), 7.03–7.07 (1 H, m) and

7.16–7.23 (3 H, m); δ_C(100 MHz, $CDCl_3$) 16.11 (1-Me), 23.46 (1-Me), 30.56 (8-C), 53.66 (1-C), 63.61 (8a-C), 116.73 (4-C), 124.90 (Ar-C), 125.56 (Ar-C), 127.61 (Ar-C), 136.93 (7a-C), 141.93 (3a-C) and 161.01 (2-C); *m*/*z* 187 (M^+, 59%), 144 (100), 118 (87) and 70 (71).

7-(Benzhydryloxy)-1*H*-indole 23[17]

2-(Benzhydryloxy)nitrobenzene was prepared (87%) from 2-nitrophenol and benzhydryl bromide with potassium carbonate in DMF, mp 97 °C (from dichloromethane–hexane); ν_{max}(Nujol)/cm^{-1} 1604; δ_H(200 MHz; $CDCl_3$) 6.36 (1 H, s), 6.96 (1 H, t, *J* 7.7, 3-H), 7.03 (1 H, d, *J* 8.2, 6-H), 7.20–7.40 (7 H, m), 7.47 (4 H, dd, *J* 1.7 and 8.2) and 7.83 (1 H, dd, *J* 1.6 and 8.2); *m*/*z* 305 (M^+, 3%) and 167 (100). Vinylmagnesium bromide (70 cm^3, 1 M in THF, 70 mmol) was added portionwise at −40 °C to a stirred solution of 2-(benzhydryloxy)nitrobenzene (6.10 g, 20 mmol) in dry THF (100 cm^3) under N_2. After 1 h the reaction mixture was quenched with saturated aq. ammonium chloride. Extraction and flash chromatography gave [with dichloromethane–hexane (1 : 1)] the indole **23** (2.62 g, 44%), mp 110–112 °C (from cyclohexane) (lit.,[17] 110–112 °C); ν_{max}(Nujol)/cm^{-1} 3436 and 3030; δ_H(200 MHz; $CDCl_3$) 6.33 (1 H, s), 6.47 (1 H, dd, *J* 2.5 and 3.3, 3-H), 6.53 (1 H, d, *J* 7.7, 6-H), 6.85 (1 H, t, *J* 7.8, 5-H), 7.00 (1 H, t, *J* 2.7, 2-H), 7.10–7.49 (11 H, m) and 8.32 (1 H, br s, NH); *m*/*z* 299 (M^+, 16%) and 167 (100).

Ethyl 7-(benzhydryloxy)-1*H*-indole-2-acetate 24

7-(Benzhydryloxy)-1*H*-indole (5.98 g, 20 mmol), ethyl iodoacetate (1.07 g, 5 mmol) and iron(II) sulfate heptahydrate (1.30 g, 4.5 mmol) were dissolved in DMSO (50 cm^3) with water (1 cm^3) and concentrated H_2SO_4 (1 cm^3) and the solution was stirred at RT. Urea–hydrogen peroxide (6.00 g) was added in portions over 2 h. The reaction mixture was diluted with brine (60 cm^3) then extracted with ether (3 × 50 cm^3). Flash chromatography gave [with dichloromethane–hexane(1 : 1)] the *ester* **24** (0.76 g, 39%), mp 108 °C (Found: C, 77.8; H, 6.1; N, 3.5. $C_{25}H_{23}NO_3$ requires C, 77.9; H, 6.0; N, 3.6%); ν_{max}(Nujol)/cm^{-1} 3307 and 1711; δ_H(250 MHz; $CDCl_3$) 1.29 (3 H, t, *J* 7.2), 3.82 (2 H, s), 4.21 (2 H, q, *J* 7.2), 6.85 (1 H, t, *J* 7.8, 5-H), 7.00 (1 H, t, *J* 2.7, 3-H), 7.10–7.49 (11 H, m) and 8.32 (1 H, br s, NH); *m*/*z* 385 (M^+, 9%) and 167 (100).

Ethyl 7-benzhydryloxy-2,3-dihydro-1*H*-indole-2-acetate 25

Sodium cyanoborohydride (1.00 g) was added in one portion to a stirred solution of ethyl 7-(benzhydryloxy)-1*H*-indole-2-acetate **24** (0.57 g, 1.5 mmol) in acetic acid (5 cm^3) at 15–17 °C under N_2. Water (15 cm^3) was added and the reaction mixture was neutralised with saturated aq. sodium hydrogen carbonate. Extraction with ether and flash chromatography gave (with dichloromethane) the *ester* **25** (0.52 g, 91%), mp 86–87 °C (Found: C, 77.8; H, 6.6; N, 3.45. $C_{25}H_{25}NO_3$ requires C, 77.5; H, 6.5; N, 3.6%); ν_{max}(Nujol)/cm^{-1} 3362 and 1721; δ_H(200 MHz; $CDCl_3$) 1.26 (3 H, t, *J* 7.1), 2.65 (2 H, d, *J* 7.7), 2.73 (1 H, dd, *J* 8.2 and 15.9, 3-H), 3.21 (1 H, dd, *J* 8.2 and 15.9, 3-H), 4.16 (2 H, q), 4.11–4.31 (1 H, m, 2-H), 6.17 (1 H, m), 6.48–6.72 (3 H, m) and 7.25–7.44 (10 H, m); *m*/*z* 387 (M^+, 5%), 300 (5), 220 (24) and 167 (100).

7-Benzhydryloxy-2,3-dihydro-1*H*-indole-2-acetic acid 26

Potassium hydroxide (0.54 g, 10 mmol) in water (1 cm^3) was added to a solution of ethyl 7-benzhydryloxy-2,3-dihydro-1*H*-indole-2-acetate **25** (0.48 g, 1.2 mmol) in ethanol (3 cm^3). The reaction mixture was stirred at RT for 12 h and evaporated to dryness. The residue was taken up in water (20 cm^3) and washed with ethyl acetate (20 cm^3). The aqueous layer was cooled in an ice bath and acidified with 10% aq. citric acid. Extraction with ethyl acetate (3 × 25 cm^3) gave the *acid* **26** (0.33 g, 74%) as an oil (Found: M^+, 359.152. $C_{23}H_{21}NO_3$ requires *M*, 359.152); ν_{max}(Nujol)/cm^{-1} 3381 and 1701; δ_H[200 MHz; $(CD_3)_2CO$)] 2.66 (2 H, d, *J* 6.6), 2.70 (1 H, dd, *J* 8.8 and 15.4, 3-H), 3.18 (1 H, dd, *J* 9.3 and 15.4, 3-H), 4.11–4.29 (1 H, m, 2-H), 6.42 (1 H, m), 6.64–6.70 (2 H, m), 7.21–7.37 (7 H, m) and 7.51–7.61 (4 H, m); *m*/*z* 359 (M^+, 1%) and 167 (100).

4-Benzhydryloxy-8,8a-dihydroazeto[1,2-*a*]indol-2(1*H*)-one 27

The acid **26** (0.23 g, 0.64 mmol) was cyclised by the method described for the preparation of the azetidinone **1a**. Flash chromatography gave [with dichloromethane–hexane (1 : 1)] the azetidinone **27** (70 mg, 32%) as an amorphous solid that was not fully characterised; ν_{max}(Nujol)/cm^{-1} 1773, 1610 and 1582; δ_H(200 MHz; $CDCl_3$) 2.99 (1 H, dd, *J* 2.7 and 16.5, *endo* 1-H), 3.13 (1 H, dd, *J* 8.2 and 16.5, 8-H), 3.30 (1 H, dd, *J* 8.8 and 16.5, 8-H), 3.54 (1 H, dd, *J* 5.5 and 16.5, *exo* 1-H), 4.31–4.44 (1 H, m, 8a-H), 6.38 (1 H, m) and 7.16–7.44 (13 H, m); *m*/*z* 341 (M^+, 0.3%), 167 (100, Ph_2CH^+) and 165 (24).

***tert*-Butyl ethyl 2-(7-benzhydryloxy-3-*tert*-butoxycarbonyl-2,3-dihydro-1*H*-indol-2-ylidene)malonate 28**

DMAP (0.16 g, 1.3 mmol) and di-*tert*-butyl dicarbonate (0.48 g, 2.2 mmol) were added to a stirred solution of the ester **24** (0.43 g, 1.1 mmol) in dichloromethane (10 cm^3). After 12 h the solvent was removed and the residue was subjected to flash chromatography which gave (with dichloromethane) the *ester* **28** (0.59 g, 92%), mp 106 °C (Found: C, 71.55; H, 6.75; N, 2.4%; M^+, 585.273. $C_{35}H_{39}NO_7$ requires C, 71.8; H, 6.7; N, 2.4%; *M*, 585.273); ν_{max}(film)/cm^{-1} 3431, 1741 and 1685; δ_H(200 MHz; $CDCl_3$) 1.28 (3 H, t, *J* 7.1), 1.47 (9 H, s), 1.63 (9 H, s), 4.15–4.35 (2 H, m), 6.11 (1 H, s), 6.38 (1 H, s), 6.62 (1 H, d, *J* 7.7), 6.98 (1 H, dd, *J* 7.7 and 8.2), 7.25–7.46 (10 H, m), 7.65 (1 H, d, *J* 8.2) and 9.71 (1 H, br s, NH); *m*/*z* 585 (M^+, 0.2%), 484 (0.4) and 167 (100).

2-Amino-3-methoxybenzyl alcohol 29

2-Amino-3-methoxybenzoic acid[19] (10.70 g, 64 mmol) was placed in the thimble of a Soxhlet extractor. Lithium aluminium hydride (10 g) in dry ether (500 cm^3) was placed in the attached reaction flask and the ether was heated under reflux until all the acid had been consumed. The excess of lithium aluminium hydride was decomposed by careful addition of water. To the reaction mixture was added 10% sodium hydroxide solution (250 cm^3). The ether layer was separated off and the aqueous layer was extracted with ether (2 × 100 cm^3). The ether extracts were combined, dried over $MgSO_4$ and concentrated under reduced pressure to give the *alcohol* **29** (8.69 g, 89%) as an oil (Found: M^+, 153.079. $C_8H_{11}NO_2$ requires *M*, 153.079); ν_{max}(film)/cm^{-1} 3372 and 1618; δ_H(200 MHz; $CDCl_3$) 3.85 (3 H, s), 4.66 (2 H, s) and 6.63–6.81 (3 H, m); *m*/*z* 153 (M^+, 59%) and 122 (100).

(2-Amino-3-methoxybenzyl)triphenylphosphonium bromide 30

To a stirred and boiling solution of 2-amino-3-methoxybenzyl alcohol **29** (8.69 g, 57 mmol) in acetonitrile (500 cm^3) was added triphenylphosphonium hydrogen bromide (19.50 g, 57 mmol). The reaction mixture was heated under reflux for 7 h then allowed to cool. The solvent was removed to leave the crude phosphonium salt **30** (23.89 g, 88%) as a solid; ν_{max}(Nujol)/cm^{-1} 3441, 3306 and 1627; δ_H(200 MHz; $CDCl_3$) 3.77 (3 H, s), 5.35 (2 H, d, *J* 13.7), 6.13–6.18 (1 H, m), 6.41 (1 H, t, *J* 8.0), 6.64–6.72 (1 H, m) and 7.55–7.78 (15 H, m).

[2-(2-Ethoxycarbonyl-2-methylpropanamido)-3-methoxybenzyl]triphenylphosphonium bromide 31

A solution of ethyl 3-chloro-2,2-dimethyl-3-oxopropanoate[20] (4.47 g, 25 mmol) in dichloromethane (30 cm^3) was slowly added to a stirred mixture of the phosphonium salt **30** (11.00 g, 23 mmol) in dichloromethane (150 cm^3). Pyridine (2.68 g, 2.75 cm^3, 34 mmol) was then added dropwise, and the mixture was heated under reflux for 30 min. After cooling to room temperature the reaction mixture was washed with 5% aq. phosphoric

acid and 15% aq. Na_2CO_3. The organic layer was washed with water (2 × 60 cm^3), dried over $MgSO_4$ and evaporated to leave the phosphonium salt **31** (12.43 g, 87%) as a solid; ν_{max}(Nujol)/cm^{-1} 3404, 1728 and 1671; δ_H(200 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7.1), 1.49 (6 H, s), 3.78 (3 H, s), 4.16 (2 H, q, *J* 7.1), 5.18 (2 H, d, *J* 14.1), 6.35–6.39 (1 H, m), 6.81–6.99 (2 H, m), 7.49–7.79 (15 H, m) and 8.58 (1 H, br s, NH).

Ethyl 2-(7-methoxy-1*H*-indol-2-yl)-2-methylpropanoate 32

Freshly prepared potassium *tert*-butoxide (2.50 g) was slowly added to a stirred suspension of the phosphonium bromide **31** (6.00 g, 10 mmol) in toluene (100 cm^3) under reflux. After 30 min the reaction mixture was concentrated to a volume of 20 cm^3 and ether (100 cm^3) was added to precipitate most of the triphenylphosphine oxide. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was purified by flash chromatography which gave (with dichloromethane) the *indole* **32** (1.47 g, 58%) as an oil (Found: M^+, 261.136. $C_{15}H_{19}NO_3$ requires *M*, 261.136); ν_{max}(film)/cm^{-1} 3377, 1727 and 1628; δ_H(200 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7.1), 1.66 (6 H, s), 3.95 (3 H, s), 4.17 (2 H, q, *J* 7.1), 6.35 (1 H, d, *J* 2.2, 3-H), 6.61 (1 H, d, *J* 7.7), 6.99 (1 H, d, *J* 7.7), 7.16 (1 H, d, *J* 8.2) and 8.67 (1 H, br s, NH); *m*/*z* 261 (M^+, 30%) and 188 (100).

Ethyl 2-(2,3-dihydro-7-methoxy-1*H*-indol-2-yl)-2-methylpropanoate 33

Sodium cyanoborohydride (0.70 g) was added in one portion to a stirred solution of the indole **32** (0.60 g, 2.3 mmol) in acetic acid (5 cm^3) at 15–17 °C under N_2. After 3 h, water (15 cm^3) was added and the reaction mixture was neutralised with saturated aq. sodium hydrogen carbonate. Extraction with ether and flash chromatography gave (with dichloromethane) the *indoline* **33** (0.46 g, 76%) as an oil (Found: M^+, 263.152. $C_{15}H_{21}NO_3$ requires *M*, 263.152); ν_{max}(film)/cm^{-1} 3395, 1719 and 1618; δ_H(200 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7.1), 1.19 (3 H, s), 1.25 (3 H, s), 2.87 (1 H, dd, *J* 10.5 and 15.9, 3-H), 3.02 (1 H, dd, *J* 9.4 and 15.9, 3-H), 3.80 (3 H, s), 4.14 (2 H, q, *J* 7.1), 4.12–4.27 (1 H, m, 2-H) and 6.59–6.75 (3 H, m); *m*/*z* 263 (M^+, 8%) and 148 (100).

2-(2,3-Dihydro-7-methoxy-1*H*-indol-2-yl)-2-methylpropanoic acid 34

The ester **33** (0.50 g, 1.9 mmol) in ethanol (3 cm^3) was hydrolysed with aq. potassium hydroxide as described for the ester **25**. This gave the *acid* **34** (0.45 g, 99%) as an oil (Found: M^+, 235.121. $C_{13}H_{17}NO_3$ requires *M*, 235.121); δ_H(200 MHz; CD_3COCD_3) 1.22 (3 H, s), 1.26 (3 H, s), 2.77 (1 H, dd, *J* 10.9 and 15.8, 3-H), 3.11 (1 H, dd, *J* 9.4 and 15.8, 3-H), 3.77 (3 H, s), 4.10 (1 H, dd, *J* 9.4 and 10.9, 2-H) and 6.67–6.74 (3 H, m); *m*/*z* 235 (M^+, 13%) and 148 (100).

8,8a-Dihydro-1,1-dimethyl-4-methoxyazeto[1,2-*a*]indol-2(1*H*)-one 35

The acid **34** (0.42 g, 1.8 mmol) was cyclised by the procedure described for the cyclisation of the salt **21**. Flash chromatography gave [with dichloromethane–hexane (1:1)] the *azetidinone* **35** (280 mg, 72%), mp 73–75 °C (Found: C, 71.8; H, 6.9; N, 6.5%; M^+, 217.110, $C_{13}H_{15}NO_2$ requires C, 71.9; H, 7.0; N, 6.45%; *M*, 217.110); ν_{max}(Nujol)/cm^{-1} 1774, 1609 and 1586; δ_H(300 MHz; $CDCl_3$) 1.26 (3 H, s, *endo* 1-Me), 1.53 (3 H, s, *exo* 1-Me), 3.09 (1 H, dd, *J* 9.3 and 16.8, 8-H), 3.20 (1 H, dd, *J* 8.2 and 16.8, 8-H), 3.92 (3 H, s), 4.16 (1 H, dd, *J* 8.2 and 9.3, 8a-H), 6.77–6.85 (2 H, m) and 6.99–7.07 (1 H, m); *m*/*z* 217 (M^+, 44%), 147 (34) and 118 (100).

8,8a-Dihydro-1,1-dimethyl-4-hydroxyazeto[1,2-*a*]indol-2-(1*H*)-one 36

Boron tribromide (0.50 cm^3, 1.0 M in dichloromethane, 0.5 mmol) was added dropwise to a stirred solution of the methyl ether **35** (72 mg, 0.40 mmol) in dry dichloromethane (10 cm^3) at −78 °C under N_2. After 24 h the reaction mixture was quenched by the addition of water (5 cm^3). Extraction with dichloromethane and evaporation gave a solid that was recrystallised to give the *azetidinone* **36** (42 mg, 62%), mp 125–126 °C (from ether) (Found: C, 70.8; H, 6.5; N, 6.9. $C_{12}H_{13}NO_2$ requires C, 70.9; H, 6.45; N, 6.9%); ν_{max}(Nujol)/cm^{-1} 3294, 1735, 1626 and 1588; δ_H(200 MHz; $CDCl_3$) 1.26 (3 H, s, *endo* 1-Me), 1.52 (3 H, s, *exo* 1-Me), 3.10–3.22 (2 H, m, 8-H), 4.18 (1 H, dd, *J* 7.7 and 8.8, 8a-H), 5.77 (1 H, br s, OH), 6.76–6.85 (2 H, m) and 6.91–7.06 (1 H, m); *m*/*z* 203 (M^+, 34%) and 133 (100).

Crystal data for 36

$C_{12}H_{13}NO_2$, $M = 203.24$. Monoclinic, $a = 9.832(9)$, $b = 8.687(5)$, $c = 12.932(6)$ Å, $\beta = 108.52(4)°$, $V = 1047(1)$ Å^3, $F(000)$ 432, $\lambda = 0.710\,69$ Å, $T = 153(2)$ K, space group $P2_1/c$ (no. 14), $Z = 4$, $D_c = 1.289$ g cm^{-3}, colourless prism, 0.15 × 0.10 × 0.25 mm.

Data collection and processing. Rigaku AF6S diffractometer, graphite-monochromated Mo-Kα radiation, $\omega - 2\theta$ scans to a maximum 2θ value of 50.1° with ω scan width (1.52 + 0.30 tan θ)°; 2108 reflections collected of which 1989 were unique ($R_{int} = 0.026$). The intensities of three representative reflections which were measured after every 150 reflections remained constant throughout data collection; no decay correction was applied.

Structure solution and refinement. Automatic direct methods[21] (all non-H atoms). Non-H atoms were refined either anisotropically or isotropically. The final cycle of full-matrix least-squares refinement was based on 1006 observed reflections [$I > 3.00\sigma(I)$] and 136 variable parameters and converged (largest parameter shift was 0.02 times its esd) with weighted and unweighted agreement factors of:

$$R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.045$$

$$R_w = [(\Sigma w(|F_o| - |F_c|)^2/\Sigma w F_o^2)]^{\frac{1}{2}} = 0.047$$

The standard deviation of an observation of unit weight was 1.48. The weighting scheme was based on counting statistics and included a factor ($\rho = 0.03$) to downweight the intense reflections. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.17 and −0.23 e Å^{-3}, respectively. All calculations were performed using the TEXSAN crystallographic structure package of the Molecular Structure Corporation.[22]

Molecular mechanics calculations

After building and geometry optimisation using the molecular mechanics within SYBYL[13] the molecule **7** was submitted for full geometry optimisation using the AM1 method in MOPAC.[14] The following conformational searches were then performed using the Tripos force field within SYBYL: (i) a random conformational search around 9 bonds, with 1000 conformations considered and using Gasteiger–Hückel charges; (ii) a gridsearch, rotating C_2–$C_{2'}$ through 360° in 15° intervals, without charges; (iii) as in (ii) and using Gasteifer–Hückel charges; (iv) a gridsearch with Gasteiger–Hückel charges, rotating bonds C_2–$C_{2'}$, $C_{2'}$–$C_{3'}$, $C_{3'}$–$O_{4'}$ and $O_{4'}$–$C_{5'}$ (numbering as in Fig. 1) through 360° in 60° intervals. In all searches the minimum energy conformation was similar to that depicted in Fig. 1, with the methyl group eclipsing the plane of the indole ring.

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