Pergamon

Tetrahedron 56 (2000) 4063–4070

TETRAHEDRON

Sequential 1,3-Dipolar Cycloaddition-Pictet–Spengler Reactions. A Versatile Tactical Combination

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Received 28 January 2000; revised 28 March 2000; accepted 13 April 2000

Abstract—The combination of thermal or Ag(I) catalysed imine→azomethine ylide→cycloaddition cascades with a subsequent Pictet–Spengler reaction allows the assembly of polyfunctional *N*-heterocycles, via formation of 4 bonds and 2 rings, in good yield.

The generation of azomethine ylides from imines by formal 1,2-prototropy,[1] metal salt-tertiary amine combinations[2] or decarboxylative processes[3] has provided a wealth of simple, effective, regio- and stereo-specific processes for the construction of polysubstituted pyrrolidines and their fused- and bridged-ring and spirocyclic analogues.

The Pictet–Spengler reaction,[4] involving an intramolecular Mannich reaction, is an important process for the construction of nitrogen heterocycles and has been widely applied for the synthesis of both indole and isoquinoline alkaloids. In a recent paper,[5] we reported examples of sequential 1,3-dipolar cycloaddition-Pictet–Spengler spirocyclisation reactions involving metallo-azomethine ylides derived from 1,5-dicarbonyl compounds. In this paper, we report alternative combinations of these two powerful ring forming processes.

Imines **1a–c** were treated with methyl acrylate (1.5 mol equiv.), AgOAc (1.2 mol equiv.) and DBU (1 mol equiv.) in MeCN (room temperature, 2–16 h) to afford cycloadducts **3a–c** via metallo-azomethine ylides **2** (Scheme 1). In all cases the endo-cycloadduct was obtained regio- and stereo-specifically in good yield.

Pictet–Spengler reaction of **3a–c** with various aldehydes (Table 1) proceeded smoothly to give **4a–f** in good to excellent yields. These reactions were carried out in benzene, in the presence of a catalytic amount of *p*-toluenesulfonic acid, using a Dean–Stark apparatus.

The stereochemistry of the Pictet–Spengler products **4a–f** was established by NOE studies. The stereochemical outcome of these reactions is dependent on the nature of the aldehyde and amine reactants (Table 1). Complete *cis*-selectivity was found in the reaction of **3a** with 2-furaldehyde.

Next, we briefly studied one example of the benzaldimine of DOPA dimethyl ether methyl ester **5** in the 1,3-dipolar cycloaddition-Pictet–Spengler reaction sequence (Scheme 2). Thus, imine **5** and methyl acrylate (1.5 mol equiv.) reacted (room temperature, 3 h) in the presence of AgOAc (1.5 mol equiv.) and DBU (1 mol equiv.) in MeCN to give the endo-cycloadduct **6** in 72% yield. Pictet–Spengler reaction of **6** and benzaldehyde gave **7** as a 3:1 mixture of *cis* and *trans* isomers in 78% yield (Table 1).

Finally, we studied an example of the thermal 1,2-prototropic generation of an azomethine ylide combined with a series of aldehydes in subsequent Pictet–Spengler reactions (Scheme 3). Thus, salicylaldimine **1d** and *N*-methylmaleimide react in xylene (140°C, 2 days) to afford the endo-cycloadduct **8** in excellent yield. Pictet–Spengler reaction (toluene, 110°C, 10 mol% TsOH) of the cycloadduct **8** with various aldehydes proceeded smoothly to give **9a–d** in 62–84% yield.

Much greater stereoselectivity was observed in the Pictet–Spengler reaction in these cases with **9a–c** being obtained as single stereoisomers and **9d** exhibiting the lowest

Keywords: metallo-azomethine ylides; Ag catalysis; cycloaddition; Pictet–Spengler reactions.

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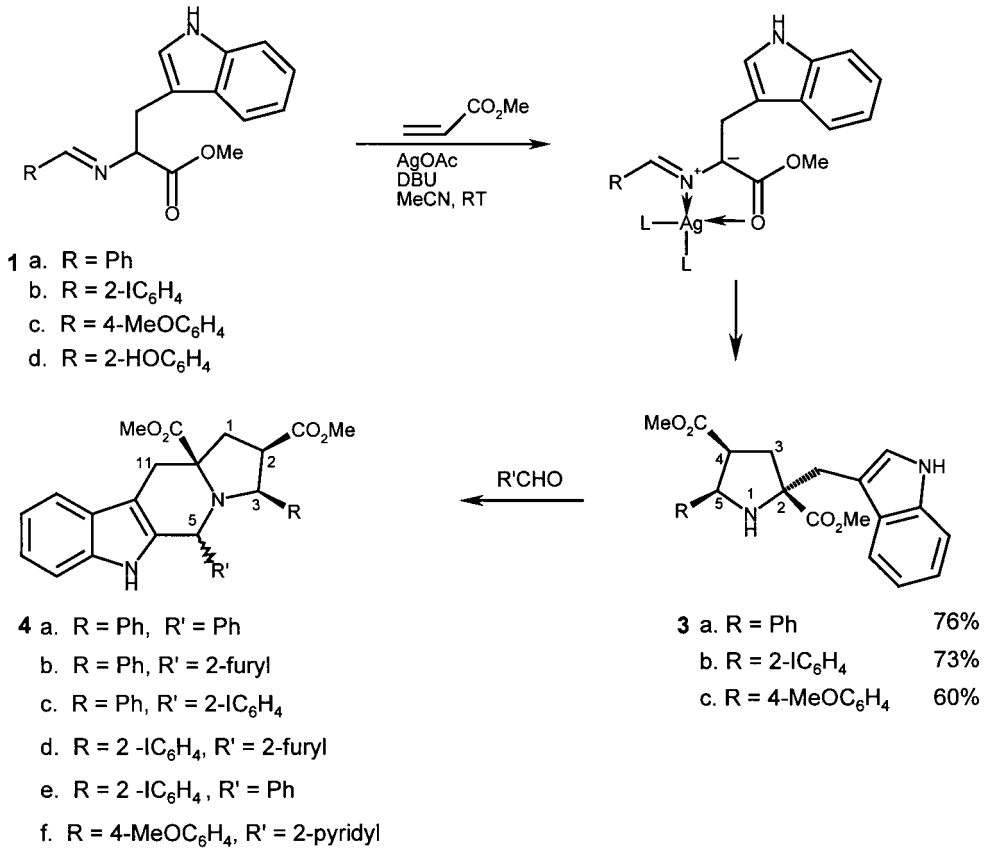
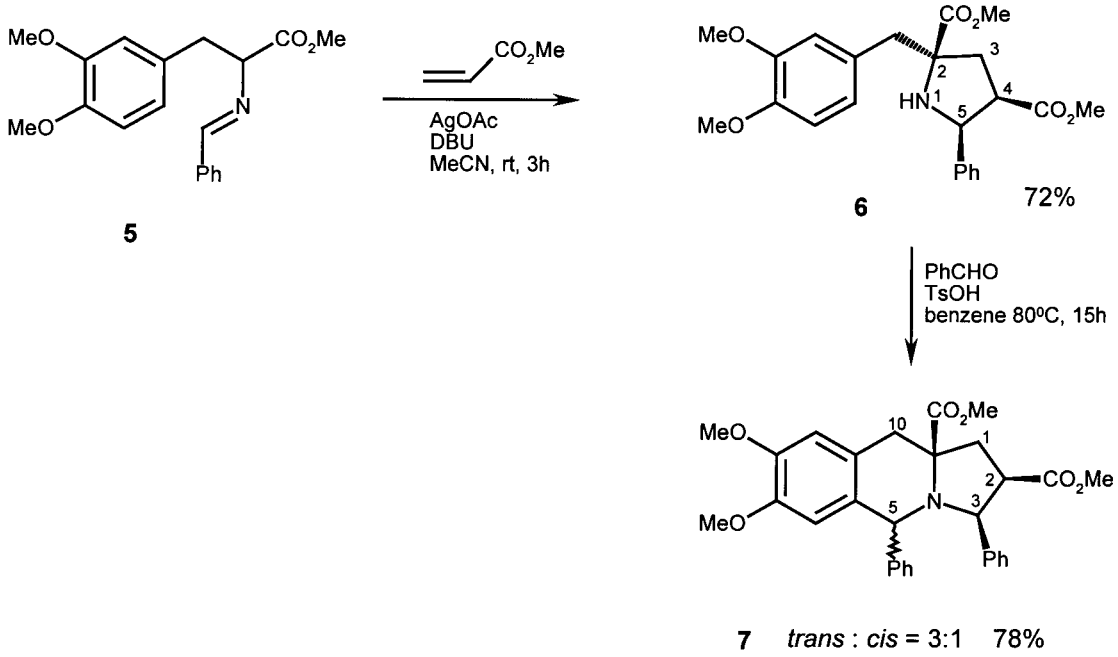


Scheme 1.

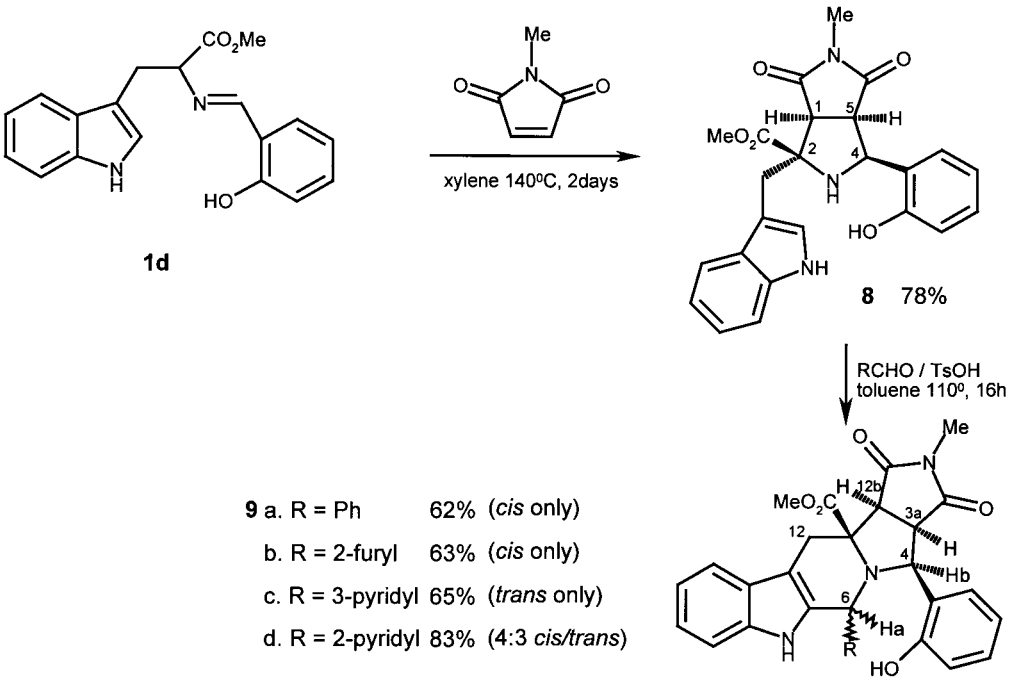
stereoselectivity. The stereochemistry of **9a** was established by X-ray crystallography (Fig. 1) whilst that of **9b–d** rests on both NOE and chemical shift data. Thus, in the *cis*-isomers Ha gives rise to a singlet at δ 5.1–5.2 ($CDCl_3$) whilst in the *trans*-isomers Ha appears as a singlet at δ 6.05 ($CDCl_3$). There is a positive NOE between the protons Ha and Hb of 5–12% in the *cis*-isomers whilst no NOE is observed between Ha and Hb in the *trans*-isomers.



Scheme 2.

Table 1. Pictet–Spengler reactions of pyrrolidines **3a–c** and **6** (All reactions were carried out in boiling benzene and employed 10 mol% TsOH at catalyst)

Substrate	Aldehyde	Time (h)	Product	*cis*/*trans* Ratio	Yield (%)
3a	PhCHO	24	4a	1:5	87
3a	(2-furyl)CHO	10	4b	*cis*	92
3a	2-IC_6H_4CHO	96	4c	1:2	66
3b	(2-furyl)CHO	10	4d	5:1	65
3b	PhCHO	36	4e	5:2	87
3c	2-pyridyl	9	4f	4:1	79
6	PhCHO	15	7	1:3	78



Scheme 3.

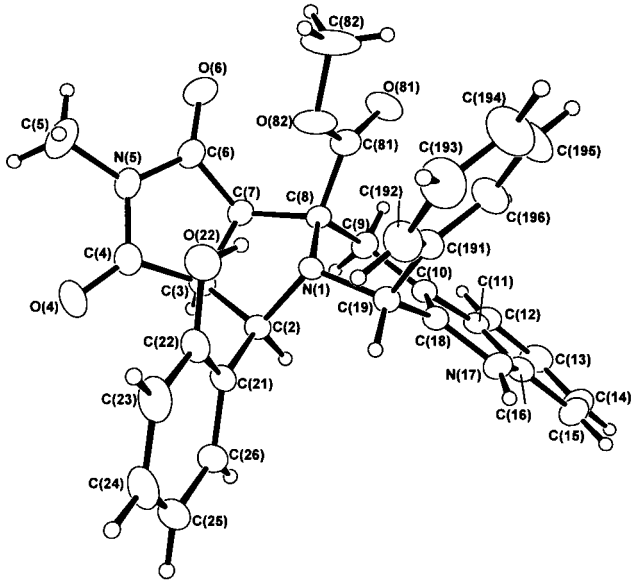


Figure 1. ORTEP[10] representation of the molecular structure of **9a**. Thermal ellipsoids are shown at the 30% probability level.

In summary, the combination of imine→azomethine ylide →cycloaddition cascades with the Pictet–Spengler reaction provides ready access to a range of novel nitrogen heterocycles.

Experimental

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. ^{1}H Nuclear magnetic resonance spectra were recorded at 300 MHz on a Bruker DPX 300 instrument or at 400 MHz on a Bruker WP 400 instrument. Deuterochloroform was used as solvent unless stated otherwise, and chemical shifts (δ) are given in parts per million. ^{1}H Spectra are referenced to tetramethylsilane or residual protonated solvent. Assignments of ^{1}H signals were made with the aid of 2D COSY spectra where necessary. Microanalyses were obtained using a Carlo Erba Elemental Analyser MOD 1106 instrument. Mass spectra were recorded on a VG-AutoSpec spectrometer using electron impact (EI) operating at 70 eV or by fast atom bombardment (FAB), as specified. Flash column chromatography employed silica gel 60 (Merk 230–400 mesh). Ether refers to diethyl ether and petroleum ether refers to the fraction

with boiling point 40–60°C. All reagents and solvents were purified according to literature procedures.[6] Imine **1a** was prepared by the literature method.[7]

General method for the preparation of imines

Tryptophan methyl ester (1 mol equiv.) and aldehyde (1 mol equiv.) were dissolved in dry dichloromethane and stirred with 4 Å molecular sieves at 25°C. After imine formation was complete (by NMR) dichloromethane was removed under reduced pressure to give the crude imine which was either purified by crystallisation (in the case of solids) or used in cycloaddition reactions without further purification (in the case of oils).

Methyl *N*-(2-iodobenzylidene)-tryptophanate 1b. Prepared by reacting tryptophan methyl ester (5 g, 22.9 mmol) with 2-iodobenzaldehyde (5.32 g, 22.9 mmol) for 5 h. The residue obtained after solvent removal was triturated with ether–petroleum ether to give the imine as a colourless solid (8.42 g, 85%) which crystallised from ether–petroleum ether as colourless prisms, mp 87–88°C. (Found: C, 53.0, H, 3.95, N, 6.35, I, 29.55. $C_{19}H_{17}IN_2O_2$ requires: C, 52.8, H, 3.95, N, 6.5, I, 29.4%); δ 8.06 (bs, 1H, indole NH), 7.96 (s, 1H, CH═N), 7.95 (d, 1H, J=9 Hz, ArH), 7.7 (d, 1H, J=8 Hz, ArH), 7.63 (d, 1H, J=7.6 Hz, ArH), 7.3 (d, 2H, J=7.6 Hz, ArH), 7.03 (m, 3H, ArH), 6.9 (d, 1H, J=2.1 Hz, 2-indole-H), 4.36 (dd, 1H, J=8.8 and 5 Hz, NC*H*CO_2Me), 3.74 (s, 3H, OMe), 3.53 (dd, 1H, J=14.5 and 5 Hz, indolyl-C*H*H) and 3.22 (dd, 1H, J=14.5 and 8.8 Hz, indolyl-CH*H*); *m*/*z* (%) 432 (M^+, 8), 232 (10) and 130 (100).

Methyl *N*-(4-methoxybenzylidene)-tryptophanate 1c. Prepared by reacting tryptophan methyl ester (5 g, 22.9 mmol) with 4-methoxybenzaldehyde (3.12 g, 22.9 mmol) for 7 h. Solvent removal gave the imine as a pale yellow thick oil (84%) which was used for the next stage without further purification. δ 8.8 (bs, 1H, indole NH), 7.81–6.64 (m, 10H, ArH and CH═N), 4.21 (m, NC*H*CO_2Me), 3.81 and 3.75 (2×s, 6H, OMe) and 3.45 and 3.24 (2×m, 2H, CH_2); *m*/*z* (%) 336 (M^+, 4), 207 (18), 135 (100), 107 (25), 84 (21) and 77 (39).

Methyl *N*-(2-hydroxybenzylidene)-tryptophanate 1d. Prepared by reacting tryptophan methyl ester (0.5 g, 2.29 mmol) with salicylaldehyde (0.28 g, 2.29 mmol) for 5 h. The residual oil obtained after solvent removal was triturated with ether–petroleum ether to give the imine **1d** (89%) as a pale yellow amorphous solid mp 111–113°C. (Found: C, 70.7, H, 5.6, N, 8.7. $C_{19}H_{18}N_2O_3$ requires: C, 70.8, H, 5.6, N, 8.7%); δ 13.4 (bs, 1H, ArOH), 8.37 (bs, 1H, indole NH), 7.63 (s, 1H, CH═N), 6.63–7.55 (m, 9H, ArH), 4.14 (m, 1H, NC*H*CO_2Me), 3.6 (s, 3H, OMe) and 3.56 and 3.12 (m, 2H, CH_2N); *m*/*z* (%) 322 (M^+, 42), 261 (23), 234 (13), 193 (44), 103 (26), 130 (100), 77 (44) and 51 (54).

Methyl *N*-(benzylidene)-3,4-dimethoxyphenylalaninate 5. A mixture of 3,4-dimethoxyphenylalanine methyl ester hydrochloride (1.5 g, 5.4 mmol), triethylamine (0.6 g, 5.9 mmol) and anhydrous magnesium sulphate in dry dichloromethane (40 ml) was stirred for 15 min before addition of benzaldehyde (0.52 g, 4.9 mmol). The resulting mixture was stirred at room temperature for 12 h, filtered, the filtrate washed with water, dried ($MgSO_4$) and evaporated. The residual crude imine (1.4 g, 86%), which was a pale yellow oil, was used directly for the next stage without further purification. δ 7.92 (s, 1H, CH═N), 7.7 (dd, 1H, J=6.8 and 2.0 Hz, ArH), 7.41 (m, 3H, ArH), 6.75 (m, 2H, ArH), 6.68 (s, 1H, ArH), 4.18 (dd, 1H, J=8.7 and 4.6 Hz, NC*H*CO_2Me), 3.82, 3.77 and 3.61 (3×s, 9H, 3×OMe), 3.3 (dd, 1H, J=13.4 and 4.6 Hz, C*H*HPh) and 3.12 (dd, 1H, J=13.4 and 8.7 Hz, CH*H*Ph); *m*/*z* (%): 327 (M^+, 4), 296 (26), 268 (100) and 91(63).

General method for silver(I) catalysed cycloaddition

Imine (1 mol. equiv.) was dissolved in dry acetonitrile and methyl acrylate (1.5 mol equiv.), AgOAc (1.2 mol equiv.) and DBU (1.2 mol equiv.) were added successively. The resulting mixture was stirred at 25°C in the dark for 5 h, filtered, the solvent removed under reduced pressure, the residue dissolved in dichloromethane and washed with saturated NH_4Cl solution. After drying ($MgSO_4$) the dichloromethane solution was evaporated under reduced pressure to give the product which was purified either by crystallisation or by flash chromatography.

Dimethyl 2-(3′-indolylmethyl)-c-5-phenylpyrrolidine-r-2-,c-4-dicarboxylate 3a. The solid residue obtained after workup was triturated with ether to give the cycloadduct (75%) which crystallised from ethyl acetate–ether as colourless rods, mp 158–159°C. (Found: C, 70.55, H, 6.2, N, 7.2. $C_{23}H_{24}N_2O_4$ requires: C, 70.4, H, 6.1, N, 7.2%); δ 8.19 (bs, 1H, indole NH), 7.6 (d, 1H, J=7.5 Hz, ArH), 7.15 (m, 9H, ArH), 4.56 (d, 1H, J=7.5 Hz, 5-H), 3.65 (s, 3H, OMe), 3.3 (d, 1H, J=14.2 Hz, indolyl-CH*H*), 3.2 (m, 1H, 4H), 3.16 (s, 3H, OMe), 3.12 (d, 1H, J=14.2 Hz, indolyl-C*H*H), 3.08 (bs, 1H, NH), 2.76 (dd, 1H, J=13.7 and 4.8 Hz, 3-H) and 2.24 (dd, 1H, J=13.7 and 7.5 Hz, 3-H); *m*/*z* (%) 392 (M^+, 4), 333 (12), 262 (100), 202 (44) and 130 (92).

Dimethyl 2-(3′-indolylmethyl)-c-5-(2′-iodophenyl)pyrrolidine-r-2-,c-4-dicarboxylate 3b. The residual oil obtained after workup was chromatographed on silica (gradient elution, petroleum ether: ether 4:1 to 1:1) to give the product as a colourless solid (73%) which crystallised from petroleum ether–ether as colourless prisms, mp 145–147°C. (Found: C, 53.3, H, 4.4, N, 5.4, I, 24.4. $C_{23}H_{23}IN_2O_4$ requires: C, 53.3, H, 4.45, N, 5.4, I, 24.5%); δ 8.2 (bs, 1H, indole NH), 7.8 (dd, 1H, J=7.9 and 1.1 Hz, ArH), 7.6 (d, 1H, J=7.5 Hz, ArH), 7.5 (dd, 1H, J=7.8 and 1.6 Hz, ArH), 7.15 (m, 5H, ArH), 6.9 (dt, 1H, J=7.7 and 1.6 Hz, ArH), 4.84 (d, 1H, J=7.6 Hz, 5-H), 3.68 (s, 3H, OMe), 3.57 (m, 1H, 4H), 3.39 and 3.2 (2×d, 2H, J=14.2 Hz, indolyl-CH_2), 3.1 (s, 3H, OMe), 2.86 (dd, 1H, J=13.6 and 3.7 Hz, 3-H) and 2.3 (dd, 1H, J=13.6 and 7.9 Hz, 3-H); *m*/*z* (%) 518 (M^+, 3), 459 (9), 388 (100), 131 (74) and 130 (57).

Dimethyl 2-(3′-indolylmethyl)-*c*-5-(4′-methoxyphenyl)-pyrrolidine-r-2-,c-4-dicarboxylate 3c. The solid residue obtained after workup was chromatographed on silica eluting with 9:1 v/v ether:petroleum ether to give the cycloadduct (81%) as colourless prisms, mp 153–155°C. (Found: C, 68.1, H, 6.3, N, 6.6. $C_{24}H_{26}N_2O_5$ requires: C, 68.2, H, 6.2, N, 6.65%); δ 8.29 (bs, 1H, indole NH), 7.62

(d, 1H, *J*=7.1 Hz, ArH), 7.0–7.25 (m, 6H, ArH), 6.78 (d, 2H, *J*=8.7 Hz, ArH), 4.54 (d, 1H, *J*=7.4 Hz, 5-H), 3.72, 3.7 and 3.21 (3×s, 3×3H, 3×OMe), 3.12 and 3.3 (d, 1H, *J*=14.2 Hz, indolyl-CH_2), 3.2 (m, 1H, 4H), 2.75 (dd, 1H, *J*=13.7 and 5.6 Hz, 3-H) and 2.24 (dd, 1H, *J*=13.7 and 7.5 Hz, 3-H); *m/z* (%) 423 (M^++1, 53), 363 (10), 292 (100), 232 (19) and 130 (91).

Dimethyl 2-(3′,4′-dimethoxybenzyl)-c-5-phenylpyrrolidine-*r*-2-,*c*-4-dicarboxylate 6. The residual oil obtained after workup and solvent removal was chromatographed on silica eluting with 2:1 v/v ether-hexane to give the cycloadduct (72%) as colourless prisms, mp 108–109°C. (Found: C, 66.65, H, 6.7, N, 3.35. $C_{23}H_{27}NO_6$ requires: C, 66.8, H, 6.6, N, 3.4%); δ, 7.25 (m, 5H, ArH), 6.91 (s, 1H, ArH), 6.88 (m, 2H, ArH), 4.45 (d, 1H, *J*=7.2 Hz, 5-H), 3.84, 3.82, 3.77 and 3.2 (4×s, 4×3H, 4×OMe), 3.18 (m, 1H, 4H), 3.14 and 2.9 (2×d, 2×1H, *J*=13.2 Hz, CH_2Ph), 2.76 (dd, 1H, *J*=13.4 and 4.1 Hz, 3-H), and 2.19 (dd, 1H, *J*=13.4 and 8.2 Hz, 3-H); *m/z* (%) 413 (M^+, 1), 382 (5), 354 (15), 262 (100) and 91 (12).

Methyl 4-(2′-hydroxyphenyl)-2-(3′-indolylmethyl)-7-methyl-6,8-dioxo-3,7-diazabicyclo(3.3.0)octane-2-carboxylate 8. A mixture of imine (**1d**) (0.2 g, 0.62 mmol) and NMM (0.07 g, 0.62 mmol) in degassed dry xylene (20 ml) was boiled under reflux for 2 days under a nitrogen atmosphere. Xylene was removed under reduced pressure and the residual oil chromatographed on silica eluting with 3:2 v/v ether–ethyl acetate to give the cycloadduct (0.21 g, 78%) as colourless prisms, mp 245–247°C. (Found: C, 66.75, H, 5.1, N, 9.4. $C_{24}H_{23}N_3O_5$ requires: C, 66.5, H, 5.35, N, 9.7%); δ, 10.35 (br, 1H, OH), 8.2 (bs, 1H, indole NH), 7.59–6.72 (m, 9H, ArH), 5.0 (d, 1H, *J*=9.5 Hz, 4-H), 3.83 (s, 3H, OMe), 3.82 (d, 1H, *J*=14.6 Hz, indolyl-CH*H*), 3.67 (t, 1H, *J*=8 Hz, 5H), 3.53 (d, 1H, *J*=7.9 Hz, 1H), 3.22 (d, 1H, *J*=14.6 Hz, indolyl-CH*H*) and 2.89 (s, 3H, NMe); *m/z* (%) 434 (M^+ +1, 100), 374 (7), 303 (66) and 130 (57).

General method for the Pictet–Spengler cyclisation

A mixture of the cycloadduct (1 mol equiv.), the aldehyde (1 mol equiv.) and TsOH (0.1 mol equiv.) in either dry benzene or dry toluene was boiled under reflux using a Dean–Stark apparatus. After the appropriate time the solvent was removed under vacuum and the crude product purified by flash chromatography.

Dimethyl 3,5-diphenyl-2,3,6,11-tetrahydro-1H-indolizino-[6,7-b]indole-2,11a(5H)-dicarboxylate 4a. Benzaldehyde (0.085 g, 0.8 mmol) and (**3a**) (0.3 , 0.76 mmol) were reacted in benzene (20 ml) for 24 h. The crude product was chromatographed on silica (gradient elution, petroleum ether—1:1 v/v petroleum ether:ether) to give **4a** (0.32 87%) as a 1:5 mixture of *cis* and *trans* isomers. The isomers were separated by fractional crystallisation from ether–petroleum ether.

Trans 4a. Colourless prisms, mp 228–229°C. (Found: C, 74.85, H, 5.8, N, 5.65. $C_{30}H_{28}N_2O_4$ requires: C, 75.0, H, 5.85, N, 5.85%); δ 7.5 (d, 1H, *J*=7.6 Hz, ArH), 6.7–7.2 (m, 14H, ArH), 5.7 (s, 1H, 5-H), 4.4 (d, 1H, *J*=8.9 Hz, 3-H), 3.6 (dd, 1H, *J*=14.7 and 1.4 Hz, 11-H), 3.3 (s, 3H, OMe), 3.28 (m, 1H, 2-H), 3.06 (dd, 1H, *J*=13.0 and 8.3 Hz, 1-H), 2.9 (s, 3H, OMe) 2.85 (dd, 1H, *J*=14.7 and 1.8 Hz, 11-H) and 2.17 (dd, 1H, *J*=13.0 and 7.95 Hz, 1-H); ^{1}H (NOEDS) (%) irradiation of 5-H caused no enhancement on the proton signal for 3-H and vice versa; *m/z* (%) 480 (M^+, 6), 421 (100), 259 (13) and 219 (59).

***cis* 4a**: Colourless solid, contaminated with a trace amount of *trans* isomer. δ (C_6D_6) 7.75 (m, 1H, ArH), 7.63 (d, 1H, *J*=7.1 Hz, ArH), 6.83–7.35 (m, 12H, ArH), 6.2 (s, 1H, indole NH), 4.67 (s, 1H, 5-H), 4.15 (d, 1H, *J*=10.5 Hz, 3-H), 3.9 (d, 1H, *J*=16.5 Hz, 11-H), 3.25 (m, 2H, 1-H and 2-H), 2.88 and 2.79 (2×s, 2×3H, 2×OMe), 2.49 (d, 1H, *J*=16.5 Hz, 11-H), and 1.83 (m, 1H, 1-H); *m/z* (%) 480 (M^+, 4), 421 (100), 218 (52), 91 (9) and 77 (5).

Dimethyl 5-(2′-furyl)-3-phenyl-2,3,6,11-tetrahydro-1H-indolizino[6,7-b]indole-2,11a(5H)-dicarboxylate 4b. 2-Furaldehyde (0.025 g, 0.26 mmol) and (**3a**) (0.1 g, 0.25 mmol) were reacted in benzene (10 ml) for 12 h. The crude product was chromatographed on silica (gradient elution, petroleum ether—1:1 v/v petroleum ether:ether) to give **4b** (0.11 g, 92%) as colourless needles, mp 185–186°C. (Found: C, 71.2, H, 5.3, N, 5.95. $C_{28}H_{26}N_2O_5$ requires: C, 71.5, H, 5.5, N, 5.95%); δ 7.73 (brs, 1H, indole NH), 7.6, 7.37, 7.28 and 7.17 (4×m, 4×1H, ArH), 6.15 (dd, 1H, *J*=3.2 and 1.8 Hz, furyl-H), 5.65 (d, 1H, *J*=3.2 Hz, furyl-H), 4.9 (s, 1H, 5-H), 4.4(d, 1H, *J*=10.6 Hz, 3-H), 3.6 (d, 1H, *J*=16.2 Hz, 11-H), 3.54 (m, 1H, 2-H), 3.3 and 3.06 (2×s, 2×3H, 2×OMe). 2.98 (dd, 1H, *J*=12.1 and 10.2 Hz, 1-H), 2.8 (d, 1H, *J*=16.2 Hz, 11-H) and 2.13 (dd, 1H, *J*=12.1 and 8.3 Hz, 1-H), ^{1}H (NOEDS) (%) irradiation of 5-H caused enhancement on the proton signal for 3-H (6.2) and irradiation of 3-H caused enhancement on the proton signal for 5-H (10.6); *m/z* (%) 470 (M^+, 6), 411 (48), 209 (100) and 180 (58).

Dimethyl 5-(2′-iodophenyl)-3-phenyl-2,3,6,11-tetrahydro-1H-indolizino[6,7-b]indole-2,11a(5H)-dicarboxylate 4c. 2-Iodobenzaldehyde (0.31 g, 1.34 mmol) and (**3a**) (0.5 g, 1.27 mmol) were reacted in benzene for 4 days. The crude product was chromatographed on silica (gradient elution, petroleum ether—4:1 v/v petroleum ether: ether) to give **4c**, (0.51 g, 66%) as a 1: 2 mixture of *cis* and *trans* isomers. The minor *cis* isomer was separated by fractional crystallisation from DCM-petroleum ether.

***cis* 4c**: Colourless prisms, mp 229–230°C. (Found: C, 59.2, H, 4.6, N, 4.55, I, 20.95. $C_{30}H_{27}IN_2O_4$ requires: C, 59.4, H, 4.45, N, 4.62, I, 20.95%); δ 7.6 (m, 3H, ArH), 7.4 (bs, 1H, indole NH), 7.19 (m, 10H, ArH), 6.92 (dt, 1H, *J*=7.6 and 1.76 Hz, ArH), 5.4 (s, 1H, 5-H), 4.6 (d, 1H, *J*=9.4 Hz, 3-H), 3.9 (d, 1H, *J*=15.3 Hz, 11-H), 3.63 (m, 1H, 2-H), 3.5 and 3.2 (2×s, 2×3H, 2×OMe), 2.91 (m, 2H, 1-H and 11-H) and 2.3 (dd, 1H, *J*=7.1 and 5.7 Hz, 1-H); ^{1}H (NOEDS) (%) irradiation of 5-H caused enhancement on the proton signal for 3-H (14.3) and irradiation of 3-H caused enhancement on the proton signal for 5-H (23.0); *m/z* (%) 606 (M^+, 16), 547 (100), 429 (6), 345 (8) and 218 (20).

***trans* 4c**: Colourless solid, contaminated with a trace amount of *cis* isomer (Found: C, 59.35, H, 4.4, N, 4.5, I, 21.1. $C_{30}H_{27}IN_2O_4$ requires: C, 59.4, H, 4.45, N, 4.62, I,

20.95%); δ ($CDCl_3$/C_6D_6) 7.5 (d, 2H, *J*=7.7 Hz, ArH), 7.3 (bs, 1H, indole NH), 7.0 (m, 10H, ArH), 6.79 (m, 1H, ArH), 6.05 (s, 1H, 5-H), 4.43 (d, 1H, *J*=9.3 Hz, 3-H), 3.6 (d, 1H, *J*=15.5 Hz, 11-H), 3.5 (s, 3H, OMe), 3.43 and 3.1 (2×m, 2×1H, 2-H and 1-H), 3.0 (s, 3H, OMe), 2.93 (d, 1H, *J*=15.5 Hz, 11-H) and 2.28 (m, 1H, 1-H); ^{1}H (NOEDS) (%) irradiation of 5-H caused enhancement on the proton signal for 3-H (1.3) and irradiation of 3-H caused enhancement on the proton signal for 5-H (3.0); *m/z* (%) 606 (M^+, 10), 547 (100), 429 (14), 345 (31) and 218 (46).

Dimethyl 5-(2′-furyl)-3-(2′-iodophenyl-2,3,6,11-tetrahydro-1H-indolizino[6,7-b]indole-2,11a(5H)-dicarboxylate 4d. 2-Furaldehyde (0.097 g, 1.0 mmol) and (**3b**) (0.5 g, 0.96 mmol) were reacted in benzene (30 ml) for 12 h. The crude product (*cis*:*trans* 5:1) was chromatographed on silica (gradient elution, petroleum ether—1:1 v/v petroleum ether:ether) to give **4d** (0.37 g, 66%) [major *cis*–isomer (50%), and mixture of isomers (16%)].

***cis* 4d**: Colourless prisms, mp 237–238°C. (Found: C, 56.35, H, 3.9, N, 4.4, I, 21.45. $C_{28}H_{25}IN_2O_5$ requires: C, 56.4, H, 4.2, N, 4.7, I, 21.3%); δ ($CDCl_3$/C_6D_6) 8.32 (dd, 1H, *J*=7.8 and 1.7 Hz, ArH), 7.63 (dd, 1H, *J*=7.8 and 1.15 Hz, ArH), 7.58 (dd, 1H, *J*=6.5 and 3.5 Hz, ArH), 7.3 (dt, 1H, *J*=7.7 and 1.15 Hz, ArH), 7.12 (m, 2H, ArH), 7.07 (d, 1H, *J*=0.8 Hz, ArH), 6.92 (m, 1H, ArH), 6.7 (dt, 1H, *J*=7.6 and 1.75 Hz, ArH), 5.83 (dd, 1H, *J*=3.2 and 1.75 Hz, ArH), 5.3(m, 1H, ArH), 4.68 (d, 1H, *J*=10.6 Hz, 3-H), 4.54 (s, 1H, 5-H),, 3.69 (d, 1H, *J*=16.3 Hz, 11-H), 3.43 (q, 1H, *J*=9.7 Hz, 2-H), 3.06 and 3.4 (2×s, 2×3H, 2×OMe). 3.03 (dd, 1H, *J*=12.0 and 9.7 Hz, 1-H), 2.55(dd, 1H, *J*=16.3 and 1.55 Hz, 11-H) and 1.85 (dd, 1H, *J*=12.0 and 8.5 Hz, 1-H); ^{1}H (NOEDS) (%) irradiation of 5-H caused enhancement on the proton signal for 3-H (5.0) and irradiation of 3-H caused enhancement on the proton signal for 5-H (5.5); *m/z* (%) 596 (M^+, 7), 409 (13), 209 (100) and 180 (35).

Dimethyl 5-phenyl-3-(2′-iodophenyl)-2,3,6,11-tetrahydro-1H-indolizino[6,7-b]indole-2,11a(5H)-dicarboxylate 4e. Benzaldehyde (0.11 g, 1.0 mmol) and (**3b**) (0.5 g, 0.96 mmol) were reacted in benzene (30 ml) for 36 h. The crude product (*cis*:*trans* 5:2) was chromatographed on silica (gradient elution, v/v petroleum ether:ether—4:1 to 3:2) to give **4e** (0.51 g, 87%) [major *cis*–isomer (50%), and mixture of isomers (37%)].

***cis* 4e**: Colourless prisms, mp 236–237°C. (Found: C, 59.6, H, 4.45, N, 4.85. $C_{30}H_{27}IN_2O_4$ requires: C, 59.4, H, 4.45, N, 4.62, I, 20.95%); δ (C_6D_6) 8.23 (dd, 1H, *J*=7.8 and 1.65 Hz, ArH), 7.75 (m, 1H, ArH), 7.6 (dd, 1H, *J*=7.8 and 1.06 Hz, ArH), 7.27 (m, 2H, ArH), 7.1 (t, 1H, *J*=7.6 Hz, ArH), 7.06 (m, 1H, ArH), 6.96 (m, 3H, ArH), 6.8 (d, 1H, *J*=6.6 Hz, ArH), 6.58 (dt, 1H, *J*=7.45 and 1.7 Hz, ArH), 6.42 (bs, 1H, indoleNH), 4.9 (d, 1H, *J*=10.8 Hz, 3-H), 4.7 (s, 1H, 5-H), 3.9(d, 1H, *J*=16.3 Hz, 11-H), 3.42 (m, 1H, 2-H), 3.24 (t, 1H, 11.5 Hz, 1-H), 2.78 and 3.0 (2×s, 2×3H, 2×OMe), 2.57 (d, 1H, *J*=16.3 Hz, 11-H) and 1.8 (dd, 1H, *J*=11.5 and 8.06 Hz, 1-H); ^{1}H (NOEDS) (%) irradiation of 5-H caused enhancement on the proton signal for 3-H (8.7) and irradiation of 3-H caused enhancement on the proton signal for 5-H (11.5); *m/z* (%) 606 (M^+, 1), 547 (8) and 219 (100).

***trans* 4e**: Colourless solid, contaminated with a trace amount of *cis* isomer δ 7.94 (dd, 1H, *J*=7.7 and 1.6 Hz, ArH), 7.5 (m, 2H, ArH), 7.48 (bs, 1H, indoleNH), 7.34 (t, 1H, *J*=7.4 Hz, ArH), 7.1 (m, 6H, ArH), 6.7 (m, 3H, ArH), 5.6 (s, 1H, 5-H), 4.77 (d, 1H, *J*=9.1 Hz, 3-H), 3.72 (d, 1H, *J*=16.2 Hz, 11-H), 3.7 (s, 3H, OMe), 3.6 (m, 1H, 2-H), 3.04 (s, 3H, OMe), 3.02 (m, 11-H and 1-H) and 2.4 (dd, 1H, *J*=13.0 and 7.9 Hz, 1-H); ^{1}H (NOEDS) (%) irradiation of 5-H caused no enhancement on the proton signal for 3-H and vice versa; *m/z* (%) 606 (M^+, 3), 547 (22) and 219 (100).

Dimethyl 5-(2′-pyridyl)-3-(4′-methoxyphenyl)-2,3,6,11-tetrahydro-1H-indolizino[6,7-b]indole-2,11a(5H)-dicarboxylate 4f. Pyridine-2-carboxaldehyde (0.175 g, 1.6 mmol) and (**3c**) (0.35 g, 0.85 mmol) were reacted in toluene (20 ml) for 9 h. The crude product was chromatographed on silica (gradient elution, petroleum ether—1:1 v/v petroleum ether:ether) to give **4f** (0.33 g, 79%) as a 4:1 mixture of *cis* and *trans* isomers. The isomers were separated by fractional crystallisation.

***cis* 4f**: Colourless plates, mp 203–205°C. (Found: C, 70.25, H, 5.6, N, 8.0. $C_{30}H_{29}N_3O_5$ requires: C, 70.45, H, 5.7, N, 8.2%); δ 9.3 (br, 1H, NH), 8.35 (d, 1H, *J*=6.8 Hz, ArH), 7.88–6.8 (m, 11H, ArH), 5.1 (s, 1H, 5-H), 4.48 (d, 1H, *J*=11.5 Hz, 3-H), 3.73 (s, 3H, OMe), 3.55 (m, 2H, 2-H and 11-H), 3.26 (s, 3H, OMe), 3.21 (d, 1H, 13.2 Hz, 11-H), 3.17 (s, 3H, OMe), 2.94 (d, 1H, *J*=12.5 Hz, 1-H) and 2.2 (dd, 1H, *J*=12.5 and 8.1 Hz, 1-H); *m/z* (%): 512 (M^++1, 65), 452 (10), 373 (20), 221 (100) and 69 (16).

***trans* 4f**: Colourless prisms. mp 179–181°C. (Found: C, 70.3, H, 5.65, N, 8.2. $C_{30}H_{29}N_3O_5$ requires: C, 70.45, H, 5.7, N, 8.2%); δ 9.3 (br, 1H, NH), 8.35 (d, 1H, *J*=6.8 Hz, ArH), 7.78–6.6 (m, 11H, ArH), 5.95 (s, 1H, 5-H), 4.56 (d, 1H, *J*=8.7 Hz, 3-H), 3.65 (d, 1H, *J*=14.6 Hz, 11-H), 3.6 (m, 1H, 2-H), 3.69, 3.52 and 3.18 (3×s, 3×3H, 3×OMe), 3.05 (m, 2H, 11-H and 1-H) and 2.6 (m, 1H, 1-H); ^{1}H (NOEDS) (%) irradiation of 5-H caused no enhancement on the proton signal for 3-H; *m/z* (%): 512 (M^++1, 24), 452 (11), 373 (23), 341 (10) and 221 (100).

Dimethyl 7,8-dimethoxy-3,5-diphenyl-2,3,5,10-tetrahydropyrrolo[1,2-b]isoquinoline-2,10a(1H)-dicarboxylate 7. Benzaldehyde (0.061 g, 0.58 mmol) and (**6**) (0.24 g, 0.58 mmol) were reacted in benzene (20 ml) for 15 h. The crude product was chromatographed on silica eluting with 3:1 v/v ether–hexane to give **7** (0.22 g, 78%) as a 1:3 mixture of *cis* and *trans* isomers as a colourless solid. The NMR data was obtained on this mixture which proved impossible to separate. (Found: C, 71.7, H, 6.3, N, 2.75. $C_{30}H_{31}NO_6$ requires: C, 71.85, H, 6.25, N, 2.8%).

***trans* 7**: δ 7.57 (d, 1H, *J*=6.9 Hz, ArH), 7.34–6.84 (m, 9H, ArH), 6.21 and 6.55 (2×s, 2×1H, ArH), 5.33 (s, 1H, 5-H), 4.38 (d, 1H, *J*=8.2 Hz, 3-H), 3.81, 3.6, 3.58 and 3.06 (4×s, 4×3H, 4×OMe), 3.39 and 3.15 (2×d, 2×1H, 13.5 Hz, 10-H), 3.12 (m, 1H, 2-H), 3.02 (dd, 1H, *J*=13.3 and 4.2 Hz, 1-H) and 2.26 (dd, 1H, *J*=13.3 and 7.8 Hz, 1-H); ^{1}H (NOEDS) (%) irradiation of 5-H caused no enhancement on the proton signal for 3-H.

***cis* 7**: δ 7.3–6.8(m, 10H, ArH), 6.79 and 6.46 (2×s, 2×1H, ArH), 4.78 (s, 1H, 5-H), 4.29 (d, 1H, *J*=8.5 Hz, 3-H), 3.9, 3.72, 3.34 and 3.12 (4×s, 4×3H, 4×OMe), 3.25 (m, 1H, 2-H), 3.13 and 2.79 (2×d, 2×1H, 13.8 Hz, 10-H), 2.88 (dd, 1H, *J*=13.1 and 6.8 Hz, 1-H) and 1.93 (dd, 1H, *J*= 13.1 and 8.3 Hz, 1-H); ^{1}H (NOEDS) (%) irradiation of 5-H caused enhancement on the proton signal for 3-H (8.0); *m/z* (%) 501 (M^+, 1), 470 (3), 442 (100), 262 (46) and 91 (24).

Methyl 4-(2-hydroxyphenyl)-2-methyl-1,3-dioxo-6-phenyl-1,2,3,3a,4,7,12,12b-octahydropyrrolo[3′,4′:1,2]indolizino-[6,7-b]indole-12a(6H)-carboxylate 9a. Benzaldehyde (0.025 g, 0.23 mmol) and (**8**) (0.1 g, 0.23 mmol) were reacted in toluene (10 ml) for 16 h. The crude product was chromatographed on silica eluting with 9:1 v/v ether–petroleum ether to give **9a** (0.075 g, 62%) as a colourless solid which crystallised from dichloromethane as colourless prisms, mp 289–291°C. (Found: C, 63.35, H, 4.6, N, 6.8. $C_{31}H_{27}N_3O_5.CH_2Cl_2$ requires: C, 63.35, H, 4.75, N, 6.9%); δ 9.67 (br, 1H, OH), 7.61 (brs, 1H, indole NH), 7.66–6.65 (m, 13H, ArH), 5.15 (s, 1H, 6-H), 4.62 (d, 1H, *J*=9.9 Hz, 4-H), 4.29 (d, 1H, *J*=16.4 Hz, 12-H), 3.64 (t, 1H, *J*=9.3 Hz, 3a-H), 3.42 (d, 1H, *J*=8.7 Hz, 12b-H), 3.0 (d, 1H, *J*=16.4 Hz, 12-H), 2.99 (s, 3H, OMe) and 2.90 (s, 3H, NMe); *m/z* (%) 522 (M^++1, 70), 462 (28), 303 (52), 219 (100) and 130 (3).

Methyl 4-(2-hydroxyphenyl)-2-methyl-1,3-dioxo-6-(2′-furyl)-1,2,3,3a,4,7,12,12b-octahydropyrrolo[3′,4′:1,2]-indolizino-[6,7-b]indole-12a(6H)-carboxylate 9b. 2-Furaldehyde (0.046 g, 0.46 mmol) and (**8**) (0.1 g, 0.23 mmol) were reacted in toluene (10 ml) for 8 h. The crude product was chromatographed on silica eluting with 9:1 v/v ether–petroleum ether to give **9b** (0.074 g, 63%) as colourless prisms, mp 280–282°C. (Found: C, 67.85, H, 5.1, N, 8.05. $C_{29}H_{25}N_3O_6$ requires: C, 68.1, H, 4.95, N, 8.2%); δ 9.47 (br, 1H, OH), 7.7 (brs, 1H, indole NH), 7.61–6.85 (m, 9H, ArH), 6.2 and 5.72 (2×m, 2H, furyl-H), 5.21 (s, 1H, 6-H), 4.52 (d, 1H, *J*=9.7 Hz, 4-H), 4.2 (d, 1H, *J*=16.5 Hz, 12-H), 3.61 (t, 1H, *J*=9.0 Hz, 3a-H), 3.42 (d, 1H, *J*=8.6 Hz, 12b-H), 2.29 (s, 3H, OMe), 3.0 (d, 1H, *J*=16.5 Hz, 12-H) and 2.95 (s, 3H, NMe); *m/z* (%) 512 (M^++1, 57), 452 (25), 303 (39), 209 (100) and 69 (8).

Methyl 4-(2-hydroxyphenyl)-2-methyl-1,3-dioxo-6-(3′-pyridyl)-1,2,3,3a,4,7,12,12b-octahydropyrrolo[3′,4′:1,2]-indolizino-[6,7-b]indole-12a(6H)-carboxylate 9c. Pyridine-3-carboxaldehyde (0.5 g, 4.6 mmol) and (**8**) (0.5 g, 1.15 mmol) were reacted in toluene (50 ml) for 36 h. The crude product was chromatographed on silica eluting with 3:1 v/v ethyl acetate–hexane to give **9c** (0.39 g, 65%) as colourless prisms, mp 296–298°C. (Found: C, 67.9, H, 4.9, N, 10.45. $C_{30}H_{26}N_4O_5$. 0.5 H_2O requires: C, 67.8, H, 5.0, N, 10.5%); δ 10.1 (br, 1H, OH), 8.1 (brs, 1H, indole NH), 7.62–6.8 (m, 12H, ArH), 6.4–6.3 (m, 3H, ArH), 6.05 (s, 1H, 6-H), 4.63 (d, 1H, *J*=10.6 Hz, 4-H), 3.88 (s, 3H, OMe), 3.85 (d, 1H, *J*=16.3 Hz, 12-H), 3.6 (t, 1H, *J*=9.3 Hz, 3a-H), 3.32 (d, 1H, *J*=8.7 Hz, 12b-H), 3.15 (d, 1H, *J*=16.3 Hz, 12-H) and 2.88 (s, 3H, NMe); *m/z* (%) 522 (M^+, 15), 463 (65), 304 (40), 219 (100) and 77 (13).

Methyl 4-(2-hydroxyphenyl)-2-methyl-1,3-dioxo-6-(2′-pyridyl)-1,2,3,3a,4,7,12,12b-octahydropyrrolo[3′,4′:1,2]-indolizino-[6,7-b]indole-12a(6H)-carboxylate 9d. Pyridine-2-carboxaldehyde (0.5 g, 4.6 mmol) and (**8**) (0.5 g, 1.15 mmol) were reacted in toluene (50 ml) for 24 h. The crude product was chromatographed on silica eluting with 3:1 v/v ethyl acetate–hexane to give **9d** (0.51 g, 84%) as a 4:3 mixture of *cis* and *trans* isomers. The isomers were separated by fractional crystallisation from dichloromethane.

***cis* 9d**: Colourless amorphous solid, mp 266–268°C. (Found: C, 61.7, H, 4.5, N, 9.25. $C_{30}H_{26}N_4O_5.CH_2Cl_2$ requires: C, 61.3, H, 4.65, N, 9.2%); δ 9.31 (br, 1H, OH), 8.51 (d, 1H, *J*=6.7 Hz, ArH), 7.37–6.75 (m, 12H, ArH), 5.2 (s, 1H, 6-H), 4.56 (d, 1H, *J*=9.7 Hz, 4-H), 4.2 (d, 1H, *J*=16.5 Hz, 12-H), 3.59 (t, 1H, *J*=9.3 Hz, 3a-H), 3.47 (d, 1H, *J*=7.0 Hz, 12b-H), 3.04 (s, 3H, OMe), 3.01 (d, 1H, *J*=16.4 Hz, 12-H) and 2.9 (s, 3H, NMe); *m/z* (%): 523 (M^++1, 66), 463 (21), 384 (10), 304 (25), 221 (100) and 73 (60).

***trans* 9d**: Colourless prisms, mp 271–273°C. (Found: C, 68.65, H, 5.1, N, 10.4. $C_{30}H_{26}N_4O_5$ requires: C, 68.95, H, 5.0, N, 10.7%); δ 10.2 (br, 1H, OH), 8.51–6.75 (m, 13H, ArH), 6.05 (s, 1H, 6-H), 4.81 (d, 1H, *J*=10.6 Hz, 4-H), 3.8 (d, 1H, *J*=16.5 Hz, 12-H), 3.79 (s, 3H, OMe), 3.64 (dd, 1H, *J*=8.1 and 10.6 Hz, 3a-H), 3.48 (d, 1H, *J*=8.0 Hz, 12b-H), 3.1 (d, 1H, *J*=16.4 Hz, 12-H) and 2.71 (s, 3H, NMe); *m/z* (%): 523 (M^++1, 17), 463 (6), 384 (7), 304 (6), 221 (100) and 73 (10).

Single crystal X-ray diffraction analysis of 9a—Crystallographic data for **9a** were measured on a Stoe STADI 4-circle diffractometer using ω–θ scans and graphite monochromated Cu-Kα radiation (λ=1.54184 Å). The structure was solved by direct methods using SHELXS-86[8] and was refined by full-matrix least-squares (based on F^2) using SHELXL-93.[9] The weighting scheme used was $w=[\sigma^2(F_o^2)+(0.0586P)^2+5.1475P]^{-1}$ where $P=(F_o^2+2F_c^2)/3$. All non-hydrogen atoms were refined with anisotropic displacement parameters (including those of a CH_2Cl_2 solvent molecule) whilst hydrogen atoms were constrained to predicted positions using a riding model. Refinement included an isotropic extinction parameter, *x*, so that $F'_c=kF_c[1+0.001*x*F_c^2*\lambda^3]^{-1/4}$ where *k*is the overall scale factor. The residuals wR_2 and R_1, given below, are defined as $wR_2=(\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[wF_o^2]^2)^{1/2}$ and $R_1=\Sigma||F_o|-|F_c||/\Sigma|F_o|$.

Crystal data for 9a—$C_{32}H_{29}N_3O_5.CH_2Cl_2$, 0.38×0.29×0.19 mm^3, *M*=606.48, monoclinic, space group $P2_1/n$, *a*=13.6086(3), *b*=11.2354(3), *c*=19.7018(4) Å, β=92.260(2)°, *U*=3010.02(11) Å^3, *Z*=4, D_c=1.34 mg m^{-3}, μ=2.31 mm^{-1}, *F*(000)=1264, *T*=298 K. Supplementary data, which include hydrogen co-ordinates, thermal parameters and complete bond lengths and angles, have been deposited at the Cambridge Crystallographic Data Centre and are available on request.

Acknowledgements

We thank SmithKline Beecham Pharmaceuticals and Leeds University for support.

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