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Sonogashira/*N*-acyliminium ion aromatic π-cyclisation processes: access to tetra- and pentacyclic lactams

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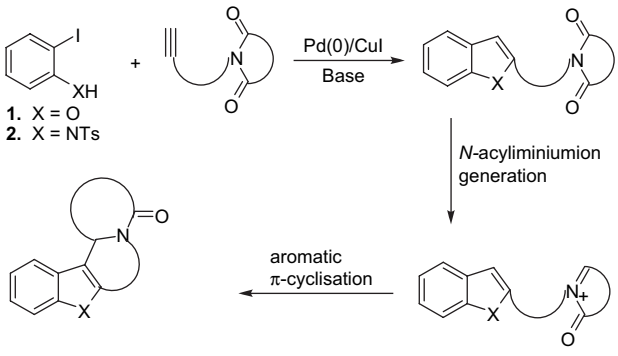
ABSTRACT

Application of the Sonogashira reaction of *N*-alkynylimides with 2-iodophenol or 2-iodo-*N*-tosylaniline affords 2-(*N*-alkylimino)-benzofurans and indoles in good yield. Selective partial reduction of the latter followed by treatment with TsOH generates *N*-acyliminium ions, which cyclise to afford tetra- and pentacyclic lactams in good yield. The latter are reduced to the analogous cyclic amines by BH_3.

1. Introduction

We have developed a number of one pot sequential or cascade protocols, which employ several types of core organic reactions (1,3-dipolar cycloaddition, Diels–Alder, retro-Diels–Alder, Michael addition, Knoevenagel condensations) and palladium catalysed cascade processes.[1–7] These combinations result in products possessing a high degree of complexity, which would otherwise require tedious and/or technically demanding multistep syntheses. Tactical combinations of this general type can adopt two broad strategies in which palladium catalysed cascade either precedes or follows the core reaction.

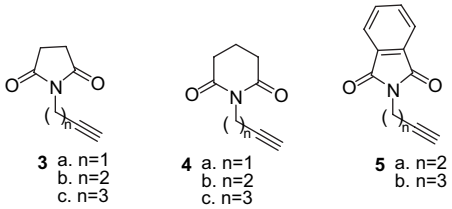
As part of our interest in developing palladium catalysed cascade reactions in a tactical combination with core reactions, we have explored combinations of Pd(0)/CuI catalysed construction of benzofurans and indoles, bearing a tethered imide, followed by *N*-acyliminium ion formation and electrophilic attack (intramolecular Mannich reaction) on the furan/pyrrole moiety furnishing tetracyclic products. *N*-Acyliminium ion chemistry has played an important role in the construction of cyclic nitrogen compounds. The use of electron rich-aromatic rings as nucleophilic partners for *N*-acyliminium ions has emerged as a powerful tool for the synthesis of heterocycles and natural products.[8,9] The combination of the above process with palladium/copper catalysed Sonogashira coupling of terminal alkynes[10] (containing an imide as the *N*-acyliminium ion precursor) with 2-iodophenol **1** or 2-iodo-*N*-tosylaniline **2** would produce novel polycyclic heterocycles (Scheme 1). Our studies on this combination form the basis of this paper.



Scheme 1.

2. Results and discussion

The *N*-alkynylimides are easily synthesised from commercially available starting materials.[11–14] Thus a series of succinic **3a–c**, glutaric **4a–c** and phthalic **5a,b** alkynylimides were readily prepared in good to excellent yield.



The terminal alkynes **3–5** (2 mmol) were then reacted with either 2-iodophenol **1** (1 mmol) or 2-iodo-*N*-tosylaniline **2** (1 mmol) in the presence of $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (13 mol %) and Et_3N (2 mol equiv) in DMF at 60 °C for 18–24 h to give a series

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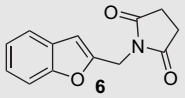
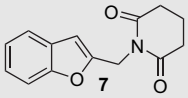
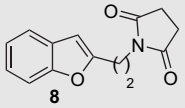
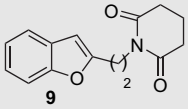
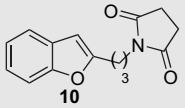
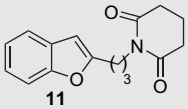
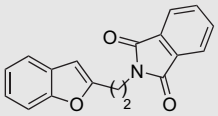
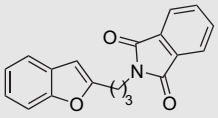
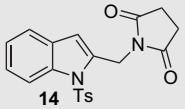
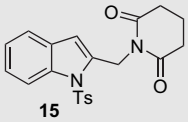
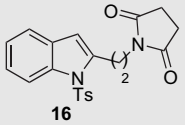
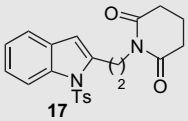
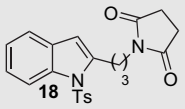
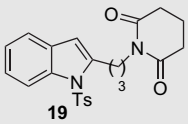
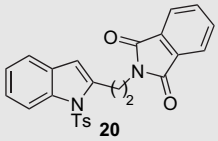
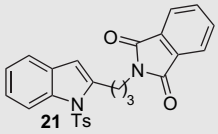
Table 1
Pd/Cu catalysed coupling of aryl iodides and alkynes[a]

Entry	Alkyne	Aryl iodide	Product	Yield[b] (%)
1	**3a**	**1**	 **6**	73
2	**4a**	**1**	 **7**	72
3	**3b**	**1**	 **8**	85
4	**4b**	**1**	 **9**	81
5	**3c**	**1**	 **10**	82
6	**4c**	**1**	 **11**	65
7	**5a**	**1**	 **12**	75
8	**5b**	**1**	 **13**	73
9	**3a**	**2**	 **14**	88
10	**4a**	**2**	 **15**	85
11	**3b**	**2**	 **16**	83
12	**4b**	**2**	 **17**	89
13	**3c**	**2**	 **18**	74
14	**4c**	**2**	 **19**	65
15	**5a**	**2**	 **20**	80
16	**5b**	**2**	 **21**	81

[a] All reactions were carried out in DMF at 60 °C using either 2-iodophenol **1** (1 mmol) or 2-iodo-*N*-tosylaniline **2** (1 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol %), CuI (13 mol %) and Et_3N (2 mol equiv).
[b] Isolated yield.

of novel 2-substituted benzofurans and *N*-tosyl protected indoles **6**–**21** (Table 1).Indoles were formed in slightly higher yields than the corresponding benzofurans (Table 1) under the conditions we employed. Others have also reported related palladium catalysed processes to synthesise 2-substituted benzofurans and indoles.[15]

Next we explored the *N*-acyliminium ion aromatic π-cyclisation processes. *N*-Acyliminium ions can be generated in situ from a cyclic imide in two distinct steps, the first of which is half-reduction of the imide to give the intermediate hydroxy lactam, which upon treatment with acid affords the reactive acyliminium species. Reduction of imides **6**–**21** with lithium triethylborohydride[16] (1.7 mol equiv, THF, −78 °C, 20 min) proved to be a convenient method for the preparation of the α-hydroxy lactams and furnished the masked *N*-acyliminium ions in excellent yield (∼90%). Purification of α-hydroxy lactams has been reported to be problematic, consequently it was deemed more practical to use the crude α-hydroxy lactams directly. Thus boiling the crude α-hydroxy lactam derivatives in toluene with 1 mol equiv of *p*-TsOH·H_2O using a Dean–Stark trap afforded the desired π-cyclisation products **22**–**34** in 56–77% yields (Table 2). In general, 6-*endo-trig* cyclisations were faster and higher yielding than the corresponding 7-*endo-trig* cyclisations, as would be expected from typical relative rates of ring closure (Table 2, entries 3, 4 and 6), whilst 5-*endo-trig* cyclisations failed to proceed (Table 2, entries 1, 2, 9 and 10). Attempted reduction/cyclisation of **6**, **7**, **14** and **15** failed to show any lactam formation after treatment with 1 mol equiv of *p*-TsOH·H_2O and boiling in toluene for 1 week. Baldwin's rules of ring closure suggest that the 5-*endo-trig* mode of ring closure is unfavourable.[17] Generally, tosyl protected indoles (Table 2) cyclised in a higher yield than the corresponding benzofurans (Table 2), suggesting that the former are better π-nucleophiles. The ^{1}H NMR spectra of lactams **22**–**33** showed two characteristic peaks arising from the NCH_βC (δ 4.75–5.91) and CH_βNCH_{eq} (δ 4.15–5.14) (Fig. 1), which are both deshielded, the former because it is adjacent to both an aromatic ring and nitrogen (bridgehead hydrogen) whilst the latter is adjacent to nitrogen and within the nodal plane (deshielding region) of the carbonyl group.

Finally selected lactams **22**, **25**, **29** and **31** were reduced, using borane/THF complex, to the corresponding amines **34**–**37** in 61–81% yields.

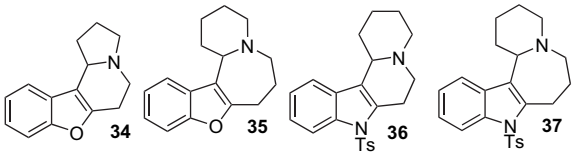
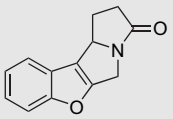
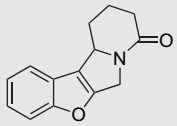
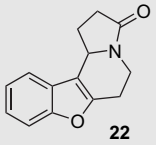
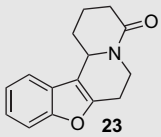
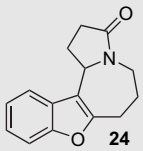
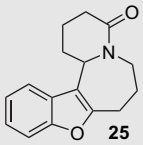
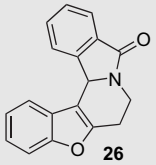
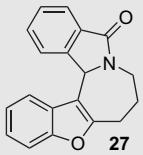
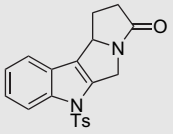
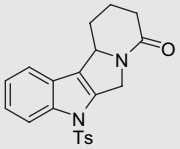
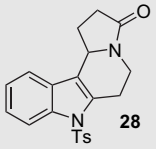
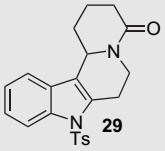
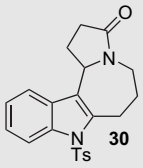
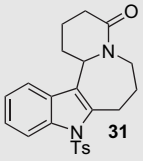
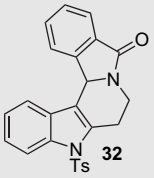
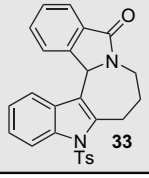


Table 2
N-Acyliminium ion aromatic π-cyclisation[a]

Entry	Imide	Product	Time (h)	Yield (%)[b]
1	**6**		168	—[c]
2	**7**		168	—[c]
3	**8**	 **22**	0.5	64
4	**9**	 **23**	0.5	61
5	**10**	 **24**	4	57
6	**11**	 **25**	4	63
7	**12**	 **26**	1	73
8	**13**	 **27**	3	69
9	**14**		168	—[c]
10	**15**		168	—[c]
11	**16**	 **28**	0.5	69
12	**17**	 **29**	0.5	74
13	**18**	 **30**	3	63
14	**19**	 **31**	3	67
15	**20**	 **32**	1.1	77
16	**21**	 **33**	2.1	61

[a] All reactions were carried out in boiling toluene using a Dean–Stark trap, α-hydroxy lactam (1 mmol) and *p*-TsOH·H_2O (1 mol equiv).
[b] Isolated yield.
[c] Reactions failed to proceed.

3. Conclusions

We have successfully carried out consecutive Sonogashira/*N*-acyliminium ion aromatic π-cyclisation processes to synthesise a series of novel tetracyclic and pentacyclic lactams in good to excellent yields. The overall process leads to the formation of three new bonds and two new fused rings.

4. Experimental

4.1. General

All reagents and solvents were purified according to literature procedures. The term ether refers to diethyl ether and petroleum ether refers to the fraction with boiling point 40–60 °C. Melting

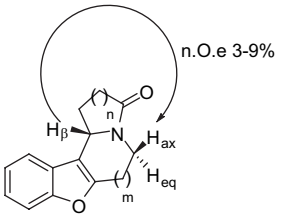


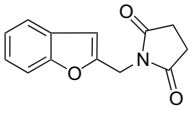
Figure 1.

points were obtained on a Reichert hot-stage apparatus and are uncorrected. Microanalyses were determined using a Carlo Erba MOD 1106 instrument. Mass spectrometric data were recorded on a V.G.Autospec instrument operating at 70 eV and accurate molecular weights were determined using perfluorokerosine as an internal standard. Infrared spectra were recorded on a Nicolet FTIR spectrophotometer. Nuclear magnetic resonance spectra were recorded on QE300, AM400 and DRX500 Bruker instruments operating at 300, 400 and 500 MHz, respectively. Deuterochloroform was used as the NMR solvent with tetramethylsilane as the internal standard unless otherwise stated. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane and coupling constants are given in hertz. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, dd=double doublet, dt=double triplet, m=multiplet. Flash column chromatography was performed using silica gel 60 (230–400 mesh) or Kieselgel GF_{254} (Merck 7730).

4.2. General method for the preparation of 2-substituted benzofurans/*n*-protected indoles from aryl halides and alkynylimides

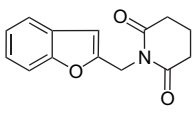
Aryl halide (2 mmol), bistriphenylphosphine palladium(II) chloride (0.049 g, 0.07 mmol), copper(I) iodide (0.048 g, 0.25 mmol) and triethylamine (0.410 g, 4 mmol) were dissolved in dry DMF (5 mL) and stirred at ambient temperature for 1 h under an atmosphere of dry nitrogen. The alkynyl imide (3 mmol) was then added, and the mixture stirred and heated at 60 °C until TLC analysis indicated that the reaction had gone to completion. The DMF was removed under reduced pressure, dichloromethane (50 mL) added and the mixture washed with 5 M NaOH (3×50 mL), water, dried ($MgSO_4$), filtered and filtrate evaporated under reduced pressure to afford the crude product, which was purified by flash chromatography.

4.2.1. 1-Benzofuran-2-yl-methyl-pyrrolidine-2,5-dione (**6**)



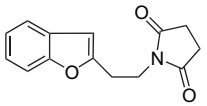
Prepared from 2-iodophenol (2.20 g, 10 mmol) and 1-prop-2-ynyl-pyrrolidine-2,5-dione (2.06 g, 15 mmol) by the general procedure. After 18 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 6:1 v/v ether/petroleum ether gave the product (**6**) (1.68 g, 73%) as a colourless solid, which crystallised from ether as colourless needles, mp 121–122 °C. (Found: C, 67.90; H, 4.90; N, 6.00. $C_{13}H_{11}NO_3$ requires C, 68.10; H, 4.85; N, 6.10%.) δ 2.75 (s, 4H, 2×CH_2), 4.82 (s, 2H, NCH_2), 6.71 (s, 1H, ArH), 7.19–7.26 (m, 2×1H, ArH) and (2×d, 2×1H, J 7 Hz, ArH); m/z (%) 229 (M^+, 100), 201 (23), 200 (50), 184 (34), 172 (23), 157 (28), 146 (26), 145 (25), 131 (73), 118 (25), 102 (21), 89 (17), 77 (32) and 63 (16); ν_{max}(DCM) 3020, 2950, 1775, 1705, 1165 and 750 cm^{-1}.

4.2.2. 1-Benzofuran-2-yl-methyl-piperidine-2,6-dione (**7**)



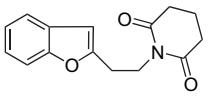
Prepared from 2-iodophenol (2.20 g, 10 mmol) and 1-prop-2-ynyl-piperidine-2,6-dione (2.26 g, 15 mmol) by the general procedure. After 18 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with ether gave the product (**7**) (1.75 g, 72%) as a colourless solid, which crystallised from ether as colourless prisms, mp 81–83 °C. (Found: C, 68.95; H, 5.40; N, 5.70. $C_{14}H_{13}NO_3$ requires C, 69.10; H, 5.40; N, 5.75%.) δ 1.94–1.98 (m, 2×1H, J 6 Hz, CH_2), 2.67 (t, 4×1H, J 6 Hz, 2×CH_2), 5.11 (s, 2H, NCH_2), 6.63 (s, 1H, ArH), 7.20 (2×t, 2×1H, J 8 Hz, ArH) and 7.45 (2×d, 2×1H, J 8 Hz, ArH); m/z (%) 243 (M^+, 100), 214 (21), 198 (21), 187 (38), 186 (29), 172 (15), 159 (23), 145 (48), 144 (43), 131 (79), 118 (10), 102 (11), 89 (13), 77 (26) and 55 (17) cm^{-1}.

4.2.3. 1-(2-Benzofuran-2-yl-ethyl)-pyrrolidine-2,5-dione (**8**)



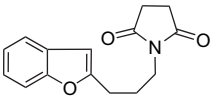
Prepared from 2-iodophenol (2.20 g, 10 mmol) and 1-but-3-ynyl-pyrrolidine-2,5-dione (2.26 g, 15 mmol) by the general procedure. After 18 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with ether gave the product (**8**) (2.07 g, 85%) as a colourless solid, which crystallised from ether as colourless prisms, mp 144–146 °C. (Found: C, 69.00; H, 5.60; N, 5.95. $C_{14}H_{13}NO_3$ requires C, 69.10; H, 5.40; N, 5.75%.) δ 2.68 (s, 4×1H, 2×CH_2), 3.10 (t, 2H, J 7 Hz, CCH_2), 3.92 (t, 2H, J 7 Hz, NCH_2), 6.48 (s, 1H, ArH), 7.20 (2×t, 2×1H, J 7 Hz, 2×ArH), 7.45 (2×d, 2×1H, J 7 Hz, ArH); m/z (%) 243 (M^+, 9), 145 (13), 144 (100), 131 (25), 115 (8), 77 (10) and 55 (8).

4.2.4. 1-(2-Benzofuran-2-yl-ethyl)-piperidine-2,6-dione (**9**)



Prepared from 2-iodophenol (2.20 g, 10 mmol) and 1-but-3-ynyl-piperidine-2,6-dione (2.48 g, 15 mmol) by the general procedure. After 18 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with ether gave the product (**9**) (2.08 g, 81%) as a colourless solid, which crystallised from ether as colourless rods, mp 102–103 °C. (Found: C, 69.90; H, 5.90; N, 5.55. $C_{15}H_{15}NO_3$ requires C, 70.00; H, 5.90; N, 5.45%.) δ 1.89–1.95 (m, 2H, J 6 Hz, $CH_2CH_2CH_2$), 2.60–2.66 (m, 2×2H, J 6 Hz, 2×CH_2), 3.02 (t, 2H, J 7 Hz, CCH_2), 4.16 (t, 2H, J 7 Hz, NCH_2), 6.45 (s, 1H, ArH), 7.14–7.26 (2×t, 2×1H, J 6 Hz, 2×ArH), 7.45 (2×d, 2×1H, J 7 Hz, ArH); m/z (%) 257 (M^+, 7), 144 (100), 131 (14), 115 (7), 77 (8) and 55 (11); ν_{max} (DCM) 3020, 2970, 1725, 1680, 1180 and 765 cm^{-1}.

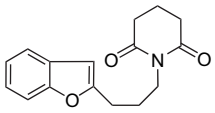
4.2.5. 1-(3-Benzofuran-2-yl-propyl)-pyrrolidine-2,5-dione (**10**)



Prepared from 2-iodophenol (2.20 g, 10 mmol) and 1-pent-4-ynyl-pyrrolidine-2,5-dione (2.48 g, 15 mmol) by the general procedure. After 18 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with ether gave the product (**10**) (2.10 g, 82%) as a colourless solid, which crystallised from ether as colourless needles, mp 97–99 °C. (Found: C, 69.95; H, 6.00; N, 5.45. $C_{15}H_{15}NO_3$ requires C, 70.00; H, 5.90; N, 5.45%.) δ 2.05–2.10 (m, 2H, J 7 Hz, NCH_2CH_2), 2.56 (s, 4H, 2×CH_2), 2.81 (t, 2H, J 7 Hz, ArCH_2), 3.63 (t, 2H, J 7 Hz, NCH_2), 6.43 (s, 1H, ArH), 7.17–

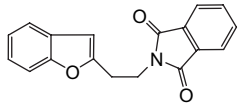
7.26 (m, 2H, *J* 8 Hz, 2×Ar*H*), 7.44 (2×d, 2×1H, *J* 8 Hz, Ar*H*); *m*/*z* (%) 257(M^+, 45), 158 (100), 145 (41), 131 (83), 117 (14), 115 (14), 103 (6) and 77 (19); ν_{max} (DCM) 3070, 2950, 1785, 1705, 1155 and 760 cm^{-1}.

*4.2.6. 1-(3-Benzofuran-2-yl-propyl)-piperidine-2,6-dione (**11**)*



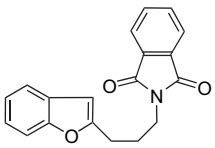
Prepared from 2-iodophenol (2.20 g, 10 mmol) and 1-pent-4-ynyl-piperidine-2,6-dione (2.69 g, 15 mmol) by the general procedure. After 24 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with ether gave the product (**11**) (1.76 g, 65%) as a thick colourless oil. (Found: C, 70.55; H, 6.60; N, 5.30. $C_{16}H_{17}NO_3$ requires C, 70.85; H, 6.30; N, 5.15%.) δ 1.79–1.87 (m, 2H, CH_2), 2.58 (t, 2×2H, *J* 7 Hz, 2×CH_2), 2.80 (t, 2H, *J* 7 Hz, CCH_2), 3.90 (t, 2H, *J* 7 Hz, NCH_2), 6.44 (s, 1H, Ar*H*), 7.16–7.20 (2×t, 2×1H, 2×Ar*H*), 7.44 (2×d, 2×1H, *J* 7 Hz, Ar*H*); *m*/*z* (%) 271 (M^+, 36), 158 (100), 157 (27), 131 (55), 114 (19), 77 (19) and 55 (15).

*4.2.7. 2-(2-Benzofuran-2-yl-ethyl)-isoindole-1,3-dione (**12**)*



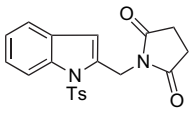
Prepared from 2-iodophenol (1.32 g, 6.0 mmol) and 2-but-3-ynyl-isoindole-1,3-dione (1.79 g, 9.0 mmol) by the general procedure. After 18 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 1:1 v/v ether/petroleum ether gave the product (**12**) (1.30 g, 75%) as a pale yellow solid, which crystallised from ether as colourless needles, mp 135–136 °C. (Found: C, 74.00; H, 4.50; N, 4.85. $C_{18}H_{13}NO_3$requires C, 74.20; H, 4.50; N, 4.80%.) δ 3.19 (t, 2H, *J* 7 Hz, CCH_2), 4.09(t, 2H, *J* 7 Hz, NCH_2), 6.49 (s, 1H, Ar*H*), 7.13–7.26 (m, 2H, Ar*H*), 7.37 (d, 1H, *J* 7.0 Hz, Ar*H*), 7.45 (d, 2H, *J* 7.0 Hz, Ar*H*), 7.67–7.73 (m, 2H, Ar*H*) and 7.80–7.86 (m, 1H, Ar*H*); *m*/*z* (%) 291 (M^+, 11), 160 (30), 144 (100), 131 (22), 115 (9), 114 (7), 77 (25) and 76 (11); ν_{max} (DCM) 3070, 2950, 1775, 1710, 1400, 1170 and 790 cm^{-1}.

*4.2.8. 2-(3-Benzofuran-2-yl-propyl)-isoindole-1,3-dione (**13**)*



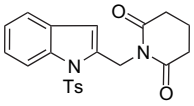
Prepared from 2-iodophenol (2.20 g, 10.0 mmol) and 2-pent-4-ynyl-isoindole-1,3-dione (3.20 g, 15.0 mmol) by the general procedure. After 18 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 1:2 v/v ether/petroleum ether gave the product (**13**) (2.23 g, 73%) as a colourless solid, which crystallised from ether as colourless plates, mp 104–106 °C. (Found: C, 74.45; H, 5.00; N, 4.45. $C_{19}H_{15}NO_3$ requires C, 74.75; H, 4.95; N, 4.60%.) δ 2.16 (q, 2H, *J* 7 Hz, NCH$_2$CH_2), 2.84 (t, 2H, *J* 7 Hz, CCH_2), 3.81 (t, 2H, *J* 7 Hz, NCH_2), 6.44 (s, 1H, Ar*H*), 7.10–7.20 (m, 2H, Ar*H*), 7.34 (d, 1H, *J* 7.5 Hz, Ar*H*), 7.42 (d, 1H, *J* 7.9 Hz, Ar*H*), 7.64–7.71 (m, 2H, Ar*H*) and 7.77–7.84 (m, 2H, Ar*H*); *m*/*z* (%) 305 (M^+, 72), 161 (51), 160 (24), 158 (91), 145 (100), 132 (61), 117 (38), 115 (24) and 77 (53); ν_{max} (DCM) 3050, 2940, 1775, 1710, 1400, 1170 and 730 cm^{-1}.

*4.2.9. 1-[1-(Toluene-4-sulphonyl)-1H-indol-2-yl-methyl]-pyrrolidine-2,5-dione (**14**)*



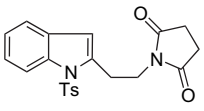
Prepared from *N*-(2-iodophenyl)-4-methyl-benzenesulphonamide (3.00 g, 8.04 mmol) and 1-prop-2-ynyl-pyrrolidine-2,5-dione (1.65 g, 12.06 mmol) by the general procedure. After 18 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 10:1 v/v ether/ethyl acetate gave the product (**14**) (2.72 g, 88%) as a pale yellow solid, which crystallised from DCM/petroleum ether as colourless prisms, mp 185–187 °C. (Found: C, 62.60; H, 5.00; N, 7.10; S, 8.30. $C_{20}H_{18}N_2O_4S$ requires C, 62.80; H, 4.75; N, 7.30; S, 8.40%.) δ 2.31 (s, 3H, CH_3), 2.46 (s, 4H, 2×CH_2), 5.19 (s, 2H, NCH_2), 6.18 (s, 1H, Ar*H*), 7.16–7.27 (m, 4H, Ar*H*), 7.33 (d, 1H, *J* 7.7 Hz, Ar*H*), 7.77 (d, 2H, *J* 8.1 Hz, Ar*H*) and 8.05 (d, 1H, *J* 8.4 Hz, Ar*H*); *m*/*z* (%) 382 (M^+, 7), 268 (14), 228 (18), 227 (100), 182 (11), 145 (27), 144 (16), 128 (13), 117 (30), 91 (81), 77 (10), 65 (33) and 55 (50); ν_{max} (DCM) 3060, 2940, 1780, 1710, 1360, 1180 and 760 cm^{-1}.

*4.2.10. 1-[1-(Toluene-4-sulphonyl)-1H-indol-2-yl-methyl]-piperidine-2,6-dione (**15**)*



Prepared from *N*-(2-iodophenyl)-4-methyl-benzenesulphonamide (3.00 g, 8.04 mmol) and 1-prop-2-ynyl-pyrrolidine-2,5-dione (1.65 g, 12.06 mmol) by the general procedure. After 18 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 10:1 v/v ether/ethyl acetate gave the product (**15**) (2.72 g, 88%) as a pale yellow solid, which crystallised from DCM/petroleum ether as colourless prisms, mp 136–138 °C. (Found: C, 63.70; H, 5.15; N, 7.15; S, 8.05. $C_{21}H_{20}N_2O_4S$ requires C, 63.60; H, 5.10; N, 7.05; S, 8.10%.) δ 2.06–2.10 (m, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.80 (t, 2×2H, *J* 7 Hz, 2×CH_2), 5.45 (s, 2H, N–CH_2), 6.08 (s, 1H, Ar*H*), 7.12–7.26 (m, 4H, Ar*H*), 7.32 (d, 1H, *J* 7.6 Hz, Ar*H*), 7.82 (d, 2H, *J* 8.3 Hz, Ar*H*) and 8.03 (d, 1H, *J* 8.4 Hz, Ar*H*); *m*/*z* (%) 396 (M^+, 3), 242 (23), 241 (100), 182 (6), 146 (11), 145 (43), 144 (22), 130 (10), 118 (14), 91 (31), 65 (12) and 55 (28) cm^{-1}.

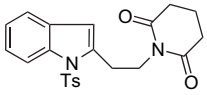
*4.2.11. 1-{2-[1-(Toluene-4-sulphonyl)-1H-indol-2-yl]-ethyl}-pyrrolidine-2,5-dione (**16**)*



Prepared from *N*-(2-iodophenyl)-4-methyl-benzenesulphonamide (2.20 g, 5.9 mmol) and 1-but-3-ynyl-pyrrolidine-2,5-dione (1.34 g, 8.85 mmol) by the general procedure. After 18 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with ether gave the product (**16**) (1.95 g, 85%) as a pale yellow solid, which crystallised from DCM/petroleum ether as colourless plates, mp 138–14 °C. (Found: C, 63.70; H, 5.15; N, 7.0; S, 8.00. $C_{21}H_{20}N_2O_4S$ requires C, 63.60; H, 5.10; N, 7.05; S, 8.10%.) δ 2.32 (s, 3H, CH_3), 3.35 (s, 4H, 2×CH_2), 3.35 (t, 2H, *J* 7 Hz, ArCH_2), 3.95 (t, 2H, *J* 7 Hz, NCH_2), 6.43 (s, 1H, Ar*H*), 7.16–7.29 (m, 4H,

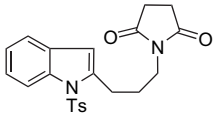
ArH), 7.40 (d, 1H, J 7.5 Hz, ArH), 7.63 (d, 2H, J 8.3 Hz, ArH) and 8.13 (d, 1H, J 8.1 Hz, ArH); m/z (%) 396 (M^+, 6), 297 (20), 242 (42), 241 (100), 233 (17), 220 (22), 155 (17), 143 (26), 142 (47), 130 (28), 129 (24), 115 (19), 91 (65), 65 (28) and 55 (39); ν_{max} (DCM) 3070, 2950, 1775, 1710, 1360, 1170 and 750 cm^{-1}.

*4.2.12. 1-{2-[1-(Toluene-4-sulphonyl)-1H-indol-2-yl]-ethyl}-piperidine-2,6-dione (**17**)*



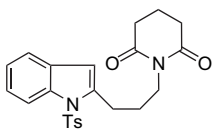
Prepared from *N*-(2-iodophenyl)-4-methyl-benzenesulphonamide (2.20 g, 5.9 mmol) and 1-but-3-ynyl-piperidine-2,6-dione (1.46 g, 8.85 mmol) by the general procedure. After 18 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with ether gave the product (**17**) (2.17 g, 89%) as a colourless solid, which crystallised from ether as colourless prisms, mp 146–148 °C. (Found: C, 64.05; H, 5.40; N, 6.80; S, 7.90. $C_{22}H_{22}N_2O_4S$ requires C, 64.35; H, 5.45; N, 6.80; S, 7.80%.) δ 1.91–1.95 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.64 (t, 4H, J 6 Hz, 2×CH_2), 3.29 (t, 2H, J 7 Hz, ArCH_2), 4.21 (t, 2H, J 7 Hz, NCH_2), 6.40 (s, 1H, ArH), 7.162–7.26 (m, 4H, ArH), 7.39 (d, 1H, J 7.5 Hz, ArH), 7.64 (d, 2H, J 8.0 Hz, ArH) and 8.13 (d, 1H, J 8.3 Hz, ArH); m/z (%) 410 (M^+, 3), 297 (23), 256 (22), 255 (100), 233 (23), 228 (12), 143 (31), 142 (32), 130 (15), 91 (30) and 55 (25); ν_{max} (DCM) 3050, 2960, 1730, 1680, 1350, 1180 and 750 cm^{-1}.

*4.2.13. 1-{3-[1-(Toluene-4-sulphonyl)-1H-indol-2-yl]-propyl}-pyrrolidine-2,5-dione (**18**)*



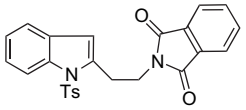
Prepared from *N*-(2-iodophenyl)-4-methyl-benzenesulphonamide (2.20 g, 5.9 mmol) and 1-pent-4-ynyl-pyrrolidine-2,5-dione (1.46 g, 8.85 mmol) by the general procedure. After 18 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with ether gave the product (**18**) (1.78 g, 79%) as a pale yellow solid, which crystallised from DCM/petroleum ether as colourless prisms, mp 132–133 °C. (Found: C, 64.35; H, 5.40; N, 6.75; S, 7.70. $C_{22}H_{22}N_2O_4S$ requires C, 64.40; H, 5.40; N, 6.80; S, 7.80%.) δ 2.02–2.10 (m, 2H, NCH$_2$CH_2), 2.34 (s, 3H, CH_3), 2.72 (s, 4H, 2×CH_2), 3.02 (t, 2H, J 7 Hz, ArCH_2), 3.66 (t, 2H, J 7 Hz, NCH_2), 6.44 (s, 1H, ArH), 7.17–7.26 (m, 4H, ArH), 7.40 (d, 1H, J 7.0 Hz, ArH), 7.59 (d, 2H, J 8.2 Hz, ArH) and 8.13 (d, 1H, J 7.9 Hz, ArH); m/z (%) 410 (M^+, 8), 256 (26), 255 (83), 157 (33), 156 (100), 155 (30), 143 (34), 130 (36), 91 (55), 77 (8), 65 (20) and 55 (24); ν_{max} (DCM) 3070, 2950, 1785, 1710, 1360, 1180 and 750 cm^{-1}.

*4.2.14. 1-{3-[1-(Toluene-4-sulphonyl)-1H-indol-2-yl]-propyl}-piperidine-2,6-dione (**19**)*



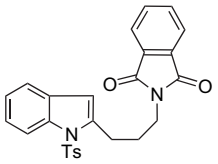
Prepared from *N*-(2-iodophenyl)-4-methyl-benzenesulphonamide (2.20 g, 5.9 mmol) and 1-pent-4-ynyl-piperidine-2,6-dione (1.59 g, 8.85 mmol) by the general procedure. After 18 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 10:1 v/v ether/hexane gave the product (**19**) (1.63 g, 65%) as a pale yellow solid, which crystallised from DCM/petroleum ether as colourless needles, mp 105–107 °C. (Found: C, 65.00; H, 5.90; N, 6.35; S, 7.60. $C_{23}H_{24}N_2O_4S$ requires C, 65.10; H, 5.70; N, 6.60; S, 7.55%.) δ 1.91–2.00 (m, 4H, 2×CH_2), 2.30 (s, 3H, CH_3), 2.65 (t, 4H, J 7 Hz, 2×CH_2), 3.01 (t, 2H, J 7 Hz, ArCH_2), 3.90 (t, 2H, J 7 Hz, NCH_2), 6.45 (s, 1H, ArH), 7.15–7.25 (m, 4H, ArH), 7.39 (d, 1H, J 7.4 Hz, ArH), 7.59 (d, 2H, J 8.0 Hz, ArH) and 8.12 (d, 1H, J 8.1 Hz, ArH); m/z (%) 424 (M^+, 3), 298 (2), 270 (19), 269 (71), 157 (29), 156 (100), 155 (18), 143 (21), 130 (25), 91 (34) and 55 (24); ν_{max} (DCM) 3070, 2950, 1735, 1680, 1360, 1175 and 780 cm^{-1}.

*4.2.15. 2-{2-[1-(Toluene-4-sulphonyl)-1H-indol-2-yl]-ethyl}-isoindole-1,3-dione (**20**)*



Prepared from *N*-(2-iodophenyl)-4-methyl-benzenesulphonamide (2.61 g, 7.0 mmol) and 2-but-3-ynyl-isoindole-1,3-dione (2.24 g, 10.5 mmol) by the general procedure. After 18 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 1:1 v/v ether/petroleum ether gave the product (**20**) (2.49 g, 80%) as a pale orange solid that precipitated from DCM/petroleum ether as a colourless amorphous solid, mp 163–165 °C. (Found: C, 67.75; H, 4.75; N, 6.10; S, 7.20. $C_{25}H_{20}N_2O_4S$ requires C, 67.55; H, 4.55; N, 6.30; S, 7.20%.) δ 3.46 (t, 2H, J 7 Hz, CCH_2), 4.13 (t, 2H, J 7 Hz, NCH_2), 6.45 (s, 1H, ArH), 7.10–7.20 (m, 4H, ArH), 7.37 (d, 1H, J 7.6 Hz, ArH), 7.64–7.72 (m, 4H, ArH), 7.83 (d, 2H, J 8.5 Hz, ArH) and 8.14 (d, 1H, J 8.5 Hz, ArH); m/z (%) 444 (M^+, 2), 289 (100), 271 (12), 220 (17), 160 (41), 142 (18), 129 (13), 91 (32) and 77 (16); ν_{max} (DCM) 3050, 2930, 1780, 1720, 1360, 1170 and 730 cm^{-1}.

*4.2.16. 2-{3-[1-(Toluene-4-sulphonyl)-1H-indol-2-yl]-propyl}-isoindole-1,3-dione (**21**)*



Prepared from *N*-(2-iodophenyl)-4-methyl-benzenesulphonamide (2.98 g, 8.0 mmol) and 2-pent-4-ynyl-isoindole-1,3-dione (2.56 g, 12.00 mmol) by the general procedure. After 18 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 1:1 v/v ether/hexane gave the product (**21**) (2.97 g, 81%) as a pale orange solid, which crystallised from DCM/petroleum ether as colourless prisms, mp 138–139 °C. (Found: C, 67.85; H, 4.85; N, 5.95; S, 7.00. $C_{26}H_{22}N_2O_4S$ requires C, 68.10; H, 4.850; N, 6.10; S, 7.00%.) δ 2.15 (q, 2H, J 7 Hz, NCH$_2$CH_2) 3.05 (t, 2H, J 7 Hz, CCH_2), 3.80 (t, 2H, J 7 Hz, NCH_2), 6.46 (s, 1H, ArH), 7.15 (d, 2H, J 8.0 Hz, ArH), 7.18–7.22 (m, 2H, ArH), 7.40 (d, 1H, J 7.7 Hz, ArH), 7.58 (d, 2H, J 8.4 Hz, ArH), 7.71–7.74 (m, 2H, ArH), 7.84–7.88 (m, 2H, ArH), 8.15 (d, 1H, J 8.3 Hz, ArH); m/z (%) 458 (3), 303 (68), 186 (12), 160 (44), 156 (100), 143 (15), 130 (28), 91 (28) and 77 (13); ν_{max} (DCM) 3070, 2950, 1775, 1715, 1400, 1175 and 725 cm^{-1}.

4.3. General procedure for the reduction of imides to α-hydroxy lactams

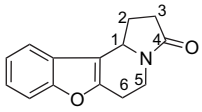
A THF solution (1 M) of lithium triethylborohydride (1.7 mol equiv) was added in one portion to a cooled (−78 °C)

solution of the appropriate imide (1 mmol) in THF (4 mL). The resulting solution was stirred for 20 min at −78 °C and then quenched by the addition of saturated aqueous $NaHCO_3$ (5–10 mL) and 30% hydrogen peroxide (1–2 mL). The resulting mixture was stirred for 20 min at 0 °C, the THF removed in vacuo and the aqueous residue extracted with DCM (3×50 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure to afford the crude α-hydroxy lactam, which was used without further purification.

4.4. *N*-Acyliminium ion aromatic π-cyclisation: general procedure for the intramolecular Mannich reaction

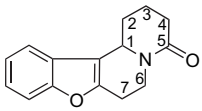
p-Toluene sulphonic acid monohydrate (1 mmol) was added to a stirred solution of the crude α-hydroxy lactam (1 mmol) in toluene (20 mL). A Dean–Stark trap and condenser were attached to the flask. The reaction was heated at reflux under nitrogen until completion was indicated by ^1H NMR monitoring. The solvent was removed in vacuo, the residue dissolved in DCM (50 mL) and washed with saturated aqueous $NaHCO_3$ (2×10 mL), saturated aqueous NaCl (10 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure to afford the crude product. The residue was purified by flash chromatography.

*4.4.1. 1,5,6,11c-Tetrahydro[1]benzofuro[2,3-g]indolizin-3(2H)-one (**22**)*



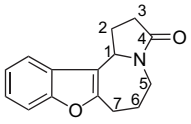
Initial treatment of (**8**) (0.871 g, 3.58 mmol) with a 1 M lithium triethylborohydride THF solution (6.10 mL) followed by workup according to the general procedure gave the crude hydroxy lactam, which was reacted with *p*-toluene sulphonic acid monohydrate (0.680 g, 3.58 mmol) by the general procedure. After 0.5 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 9:1 v/v ether/acetone gave the product (**22**) (0.521 g, 64%) as a colourless solid, which crystallised from DCM/ether as colourless prisms, mp 210–212 °C. (Found: C, 73.95; H, 5.80; N, 6.05. $C_{14}H_{13}NO_2$ requires C, 74.00; H, 5.75; N, 6.15%.) δ (400 MHz) 1.87–1.99 (m, 1H, $NCH_\beta CH_\alpha CH_2$), 2.44–2.53 (m, 1H, $NCH_\beta CH_2CH$), 2.58–2.72 (m, 2×1H, $NCH_\beta CH_\beta CH_2$ and $NCH_\beta CH_2CH$), 2.78–2.83 (m, 1H, NCH_2CH_β), 2.92–2.97 (m, 1H, NCH_2CH_α), 3.03–3.10 (m, 1H, $NCH_\beta CH_2C$), 4.57 (dd, 1H, *J* 12.7, 5.8 Hz, $NCH_\alpha CH_2C$), 4.87–4.92 (m, 1H, $NCH_\beta C$), 7.20–7.29 (2×t, 2×1H, 2×Ar*H*), 7.36–7.46 (2×d, 2×1H, *J* 7 Hz, 2×Ar*H*); *m*/*z* (%) 227 (M^+, 100), 226 (86), 172 (20), 171 (34), 170 (63), 157 (11), 144 (19), 139 (5), 128 (28), 115 (66), 102 (13), 89 (17), 77 (18) and 55 (29); ν_{max} (DCM) 3030, 2940, 1680, 1420, 1040 and 765 cm^{-1}.

*4.4.2. 1,2,3,6,7,12c-Hexahydro-4H-[1]benzofuro[3,2-a]quinolizin-4-one (**23**)*



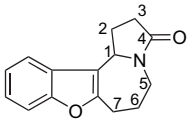
Initial treatment of (**9**) (0.798 g, 3.10 mmol) with a 1 M lithium triethylborohydride THF solution (5.3 mL) followed by workup according to the general procedure gave the crude hydroxy lactam, which was reacted with *p*-toluene sulphonic acid monohydrate (0.590 g, 3.10 mmol) by the general procedure. After 0.5 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 9:1 v/v ether/acetone gave the product (**23**) (0.453 g, 61%) as a yellow solid, which crystallised from DCM/ether as pale yellow prisms, mp 151–152 °C. (Found: C, 74.45; H, 6.00; N, 6.00. $C_{15}H_{15}NO_2$ requires C, 74.65; H, 6.25; N, 5.80%.) δ (400 MHz) 1.64–1.74 (m, 1H, $NCH_\beta CH_\alpha CH_2$), 1.81–1.91 (m, 2×1H, $NCH_\beta CH_2CH_2$), 2.33–2.42 (m, 1H, O=CCH_α), 2.55–2.61 (m, 1H, O=CCH_β), 2.71–2.75 (m, 2×1H, NCH_2CH_α and $NCH_\beta CH_\beta CH_2$), 2.79–2.86 (m, 1H, NCH_2CH_β), 2.92–3.01 (m, 1H, $NCH_\beta CH_2C$), 4.72 (br d, 1H, *J* 10.7 Hz, $NCH_\beta C$), 5.19 (dd, 1H, *J* 12.5, 5.3 Hz, $NCH_\alpha CH_2C$), 7.18–7.25 (2×t, 2×1H, *J* 7 Hz, 2×Ar*H*) and 7.42–7.46 (2×d, 2×1H, *J* 7 Hz, 2xAr*H*); *m*/*z* (%) 241 (M^+, 100), 224 (827), 212 (16), 186 (12), 171 (57), 170 (50), 157 (10), 148 (13), 144 (11), 135 (10), 128 (15), 115 (22) and 77 (6); ν_{max} (DCM) 3070, 2940, 1675, 1365, 1170 and 750 cm^{-1}.

*4.4.3. 1,2,5,6,7,12c-Hexahydro-3H-[1]benzofuro[3,2-c]pyrrolo[1,2-a]azepin-3-one (**24**)*



Initial treatment of (**10**) (0.517 g, 2.01 mmol) with a 1 M lithium triethylborohydride THF solution (3.4 mL) followed by workup according to the general procedure gave the crude hydroxy lactam, which was reacted with *p*-toluene sulphonic acid monohydrate (0.382 g, 2.01 mmol) by the general procedure. After 4 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 9:1 v/v ether/acetone gave the product (**24**) (0.275 g, 57%) as a pale brown solid, which crystallised from DCM/ether as pale yellow prisms, mp 136–138 °C. (Found: C, 74.85; H, 6.15; N, 5.60. $C_{15}H_{15}NO_2$ requires C, 74.65; H, 6.25; N, 5.80%.) δ (400 MHz) 2.01–2.08 (m, 2×1H, NCH_2CH and NCH_2CH_2CH), 2.16–2.22 (m, 1H, $NCH_\beta CH_\alpha CH_2C$=O), 2.49–2.54 (m, 2×1H, O=CCH_2), 2.68–2.77 (m, 1H, $NCH_\beta CH_\beta CH_2C$=O), 2.90–2.98 (m, 2×1H, $NCH_\beta CH_2CH_2C$ and NCH_2CH_2CH), 3.06 (dtd, 1H, *J* 17.2, 5.8, 1.2 Hz, NCH_2CH), 4.36 (dt, 1H, *J* 14.0, 5.1 Hz, $NCH_\alpha CH_2CH_2$), 4.91–4.94 (m, 1H, $NCH_\beta C$), 7.22 (2×t, 2×1H, 2×Ar*H*) and 7.42 (2×d, 2×1H, 2×Ar*H*); *m*/*z* (%) 241 (M^+, 82), 240 (100), 224 (51), 184 (22), 170 (19), 157 (16), 128 (14), 115 (12), 102 (6) and 77 (8); ν_{max} (DCM) 3050, 2970, 1685, 1330 and 760 cm^{-1}.

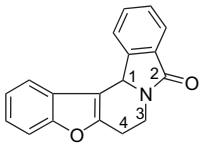
*4.4.4. 2,3,6,7,8,13c-Hexahydro[1]benzofuro[3,2-c]pyrido[1,2-a]azepin-4(1H)-one (**25**)*



Initial treatment of (**11**) (0.684 g, 2.52 mmol) with a 1 M lithium triethylborohydride THF solution (4.3 mL) followed by workup according to the general procedure gave the crude hydroxy lactam, which was reacted with *p*-toluene sulphonic acid monohydrate (0.479 g, 2.52 mmol) by the general procedure. After 4 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 9:1 v/v ether/acetone gave the product (**25**) (0.361 g, 56%) as a yellow solid, which precipitated from DCM/ether as an amorphous pale yellow solid, mp 92–94 °C. (Found: C, 75.20; H, 6.85; N, 5.40. $C_{16}H_{17}NO_2$ requires C, 75.25; H,

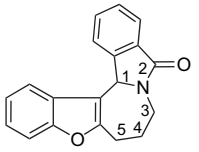
6.70; N, 5.50%.) δ (500 MHz) 1.71–1.79 (m, 2H, $CHCH_2CH_2$), 1.80–1.86 (m, 1H, NCH_2CH), 1.98–2.05 (m, 1H, NCHCH), 2.26–2.33 (m, 1H, NCHCH), 2.36–2.48 (m, 3H, NCH_2CH and $O{=}CCH_2$), 2.74–2.81 (m, 2H, CHNCH and NCH_2CH_2CH), 2.87–2.91 (dddd, 1H, *J* 15.7, 11.7, 7.3, 1.6 Hz, NCH_2CH_2CH), 4.36 (dd, 1H, *J* 13.7, 6.7 Hz, CHNCH), 4.75 (t, 1H, *J* 6.7 Hz, NCHC), 7.18–7.24 (m, 2H, ArH) and 7.37–7.42 (m, 2H, ArH); *m*/*z* (%) 255 (M^+, 100), 238 (17), 227 (11), 199 (12), 185 (95), 184 (49), 170 (27), 158 (33), 157 (26), 128 (18), 115 (15) and 77 (8); ν_{max} (DCM) 3070, 2960, 1650, 1460, 1095 and 750 cm^{-1}.

4.4.5. 6,13b-Dihydro[1]benzofuro[3′,2′:3,4]pyrido[2,1-a]isoindol-9(7H)-one (**26**)



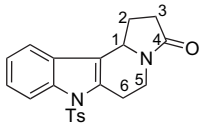
Initial treatment of (**12**) (0.378 g, 1.30 mmol) with a 1 M lithium triethylborohydride in THF solution (2.2 mL) followed by workup according to the general procedure gave the crude hydroxy lactam, which was reacted with *p*-toluene sulphonic acid monohydrate (0.247 g, 1.30 mmol) by the general procedure. After 1 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 8:1 v/v ether/petroleum ether gave the product (**26**) (0.262 g, 73%) as a pale yellow solid, which crystallised from ether/acetone as pale yellow prisms, mp 183–185 °C. (Found: C, 78.35; H, 4.90; N, 4.90. $C_{18}H_{13}NO_2$ requires C, 78.55; H, 4.75; N, 5.10%.) δ (400 MHz) 2.82 (dd, 1H, *J* 16.5, 4.6 Hz, NCH_2CH_β), 2.99–3.09 (m, 1H, NCH_2CH_α), 3.31–3.38 (m, 1H, $NCH_\beta CH_2$), 4.88 (dd, 1H, *J* 13.2, 6.3 Hz, $NCH_\alpha CH_2$), 5.84 (s, 1H, $NCH_\beta C$) and 7.26–7.98 (m, 8H, ArH); *m*/*z* (%) 275 (M^+, 100), 274(M−1, 95), 257 (11), 246 (32), 218 (15), 189 (22), 182 (24), 169 (12) and 95 (13); ν_{max} (DCM) 3060, 2940, 1690, 1400, 1120 and 740 cm^{-1}.

4.4.6. 6,7,8,14b-Tetrahydro-10H-[1]benzofuro[3′,2′:3,4]azepino[2,1-a]isoindol-10-one (**27**)



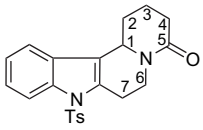
Initial treatment of (**13**) (0.977 g, 3.20 mmol) with a 1 M lithium triethylborohydride THF solution (5.4 mL) followed by workup according to the general procedure gave the crude hydroxy lactam, which was reacted with *p*-toluene sulphonic acid monohydrate (0.608 g, 3.20 mmol) by the general procedure. After 3 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 8:1 v/v ether/petroleum ether gave the product (**27**) (0.637 g, 69%) as a pale yellow solid, which crystallised from ether/acetone as colourless needles, mp 212–213 °C. (Found: C, 78.75; H, 5.20; N, 4.85. $C_{19}H_{15}NO_2$ requires C, 78.85; H, 5.25; N, 4.85%.) δ (400 MHz) 1.94–2.03 (m, 1H, NCH_2CH_β), 2.47–2.53 (m, 1H, NCH_2CH_α), 2.77–2.89 (m, 2×1H, $NCH_2CH_2CH_2$), 3.32–3.40 (m, 1H, $NCH_\beta CH_2$), 4.42–4.51 (m, 1H, $NCH_\alpha CH_2$), 5.84 (s, 1H, $NCH_\beta C$) and 7.29–7.91 (m, 8H, ArH); *m*/*z* (%) 289 (M^+, 100), 288 (M−1, 77), 272 (23), 260 (41), 231 (16), 202 (14), 189 (13), 176 (13), 130 (20), 115 (14) and 77 (23); ν_{max} (DCM) 3070, 2940, 1695, 1210 and 730 cm^{-1}.

4.4.7. 7-[(4-Methylphenyl)sulfonyl]-1,2,5,6,7,11c-hexahydro-3H-indolizino[7,8-b]indol-3-one (**28**)



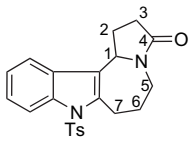
Initial treatment of (**16**) (0.527 g, 1.33 mmol) with a 1 M lithium triethylborohydride THF solution (2.3 mL) followed by workup according to the general procedure gave the crude hydroxy lactam, which was reacted with *p*-toluene sulphonic acid monohydrate (0.253 g, 1.33 mmol) by the general procedure. After 0.5 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 17:3 v/v ether/acetone gave the product (**28**) (0.348 g, 69%) as a yellow solid that crystallised from DCM/petroleum ether as colourless prisms, mp 178–180 °C. (Found: C, 66.20; H, 5.30; N, 7.15; S, 8.50. $C_{21}H_{20}N_2O_3S$ requires C, 66.30; H, 5.30; N, 7.35; S, 8.45%.) δ (500 MHz) 1.76–1.84 (m, 1H, $NCH_\beta CH_\alpha$), 2.36 (s, 3H, CH_3), 2.44 (ddd, 1H, *J* 16.6, 9.5, 1.5 Hz, $O{=}CCH_\alpha$), 2.56–2.64 (m, 1H, $O{=}CCH_\beta$), 2.67–2.73 (m, 1H, $NCH_\beta CH_\beta$), 2.96–3.01 (m, 2×1H, $NCH_\alpha CH_2C$ and $NCH_2CH_\beta C$), 3.31–3.35 (m, 1H, $NCH_2CH_\alpha C$), 4.49–4.54 (m, 1H, $NCH_\beta CH_2C$), 4.83–4.87 (m, 1H, $NCH_\beta C$), 7.21–7.26 (m, 3H, ArH), 7.33 (t, 2H, *J* 8.1 Hz, ArH), 7.65 (d, 2H, *J* 8.3 Hz, ArH) and 8.20 (d, 2H, *J* 8.3 Hz, ArH); *m*/*z* (%) 298 (M^+, 22), 379 (12), 226 (17), 225 (100), 224 (13), 169 (17), 168 (13), 115 (7), 91 (33) and 65 (13); ν_{max} (DCM) 3070, 2930, 1690, 1370, 1170 and 750 cm^{-1}.

4.4.8. 8-[(4-Methylphenyl)sulfonyl]-2,3,6,7,8,12c-hexahydro-indolo[3,2-a]quinolizin-4(1H)-one (**29**)



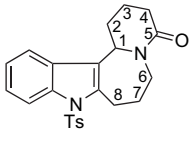
Initial treatment of (**17**) (0.866 g, 2.11 mmol) with a 1 M lithium triethylborohydride THF solution (3.6 mL) followed by workup according to the general procedure gave the crude hydroxy lactam, which was reacted with *p*-toluene sulphonic acid monohydrate (0.401 g, 2.11 mmol) by the general procedure. After 0.5 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 17:3 v/v ether/acetone gave the product (**29**) (0.612 g, 74%) as a yellow solid, which crystallised from DCM/petroleum ether as colourless plates, mp 192–193 °C. (Found: C, 66.70; H, 5.70; N, 7.05; S, 8.00. $C_{22}H_{22}N_2O_3S$ requires C, 67.00; H, 5.60; N, 7.10; S, 8.15%.) δ 1.49 (dddd, 1H, *J* 16.6, 11.3, 9.7, 3.4 Hz, $NCH_\beta CH_\alpha CH_2$), 1.83–1.90 (m, 1H, $NCH_\beta CH_2CH_\beta$), 1.92–1.96 (m, 1H, $NCH_\beta CH_2CH_\alpha$), 2.35 (s, 3H, CH_3), 2.37 (ddd, 1H, *J* 18.0, 12.3, 6.7 Hz, $O{=}CCH_\alpha$), 2.58 (dd, 1H, *J* 17.8,5.4 Hz, $O{=}CCH_\beta$), 2.69 (td, 1H, *J* 12.4, 3.8 Hz, $NCH_\beta CH_2C$), 2.97–3.05 (m, 1H, $NCH_2CH_\alpha C$), 3.25 (ddd, 1H, *J* 15.7, 3.8, 1.7 Hz, NCH_2CH_β), 4.72–4.75 (m, 1H, $NCH_\beta C$), 5.14 (ddd, 1H, *J* 12.9, 5.3, 1.2 Hz, $NCH_\alpha CH_2C$), 7.21–7.26 (m, 3H, ArH), 7.31 (td, 1H, *J* 7.8, 1.1 Hz, ArH), 7.43 (d, 1H, *J* 7.8 Hz, ArH), 7.66 (d, 2H, *J* 8.4 Hz, ArH) and 8.20 (d, 1H, *J* 8.4 Hz, ArH), *m*/*z* (%) 394 (M^+, 18), 324 (7), 240 (19), 239 (100), 183 (11), 169 (42), 155 (22), 144 (12), 115 (14), 91 (78), 77 (6), 65 (33) and 55 (20); ν_{max} (DCM) 3070, 2930, 1640, 1370, 1175 and 750 cm^{-1}.

*4.4.9. 8-[(4-Methylphenyl)sulfonyl]-1,5,6,7,8,12c-hexahydro-pyrrolo[1′,2′:1,2]azepino[4,3-b]indol-3(2H)-one (**30**)*



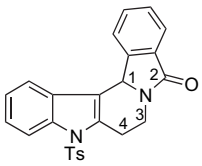
Initial treatment of (**18**) (0.599 g, 1.46 mmol) with a 1 M lithium triethylborohydride THF solution (2.5 mL) followed by workup according to the general procedure gave the crude hydroxy lactam, which was reacted with *p*-toluene sulphonic acid monohydrate (0.278 g, 1.46 mmol) by the general procedure. After 3 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 9:1 v/v ether/acetone gave the product (**30**) (0.364 g, 63%) as a yellow solid, which crystallised from DCM/petroleum ether as pale yellow prisms, mp 159–161 °C. (Found: C, 67.20; H, 5.70; N, 7.30; S, 8.20. $C_{22}H_{22}N_2O_3S$ requires C, 67.00; H, 5.60; N, 7.10; S, 8.15%.) δ (400 MHz) 1.61–1.70 (m, 1H, NCH_2CH), 1.95–2.03 (m, 1H, NCHC*H*), 2.11–2.20 (m, 1H, NCH_2CH), 2.24–2.32 (m, 1H, O=CC*H*), 2.34 (s, 3H, CH_3), 2.39–2.50 (m, 1H, O=CC*H*), 2.51–2.57 (m, 1H, NCHC*H*), 2.72–2.81 (m, 1H, NCH_2CH_2CH), 2.84–2.91 (m, 1H, $NCH_\alpha CH_2CH_2C$) 3.62 (dt, 1H, *J* 16.2, 4.1 Hz, NCH_2CH_2CH), 4.15 (ddd, 1H, *J* 14.0, 8.2, 5.3 Hz, $NCH_\beta CH_2CH_2$), 4.93 (td, 1H, *J* 7.4, 1.3 Hz, $NCH_\beta C$), 7.18 (d, 2H, *J* 8.5 Hz, Ar*H*), 7.22–7.34 (m, 3H, Ar*H*), 7.56 (d, 2H, *J* 8.5 Hz, Ar*H*) and 8.25 (d, 1H, *J* 8.2 Hz, Ar*H*); *m*/*z* (%) 394 (M^+, 22), 240 (21), 239 (100), 183 (16), 156 (9), 130 (5), 91 (17) and 65 (63); ν_{max} (DCM) 3070, 2955, 1640, 1450, 1200 and 750 cm^{-1}.

*4.4.10. 9-[(4-Methylphenyl)sulfonyl]-1,2,3,6,7,8,9,13c-octahydro-4H-pyrido[1′,2′:1,2]azepino[4,3-b]indol-4-one (**31**)*



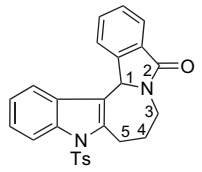
Initial treatment of (**19**) (0.429 g, 1.01 mmol) with a 1 M lithium triethylborohydride THF solution (1.7 mL) followed by workup according to the general procedure gave the crude hydroxy lactam, which was reacted with *p*-toluene sulphonic acid monohydrate (0.192 g, 1.01 mmol) by the general procedure. After 3 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 9:1 v/v ether/acetone gave the product (0.278 g, 67%) as a colourless solid, which crystallised from DCM/petroleum ether as colourless prisms, mp 140–142 °C. (Found: C, 67.03; H, 5.85; N, 6.70; S, 7.95. $C_{23}H_{24}N_2O_3S$ requires C, 67.60; H, 5.90; N, 6.85; S, 7.85%.) δ(500) 1.40 (ddd, 1H, *J* 20.7, 13.0, 6.1 Hz, NCH_2CH_β), 1.70–1.81 (m, 3H, $NCH_\beta CH_\beta CH_2CH_2$ and $NCH_\beta CH_2CH_2CH_2$), 2.24–2.33 (m, 2H, $NCH_\beta CH_\alpha CH_2CH_2$ and NCH_2CH_α), 2.37 (s, 3H, CH_3), 2.39–2.46 (m, 1H, O=CC*H*), 2.48–2.54 (m, 1H, O=CC*H*), 2.65 (ddd, 1H, *J* 13.6, 11.0, 7.0 Hz, $CH_\beta NCH_\beta$), 2.74 (ddd, 1H, *J* 15.4, 13.4, 6.1 Hz, $NCH_2CH_2CH_\alpha$), 3.63 (ddd, 1H, *J* 15.4, 5.5, 1.8 Hz, $NCH_2CH_2CH_\beta$), 4.25 (dd, 1H, *J* 13.6, 7.6 Hz, $CH_\beta NCH_\alpha$), 4.85 (m, 1H, $NCH_\beta C$), 7.22 (d, 2H, *J* 8.2 Hz, Ar*H*), 7.25–7.28 (m, 3H, Ar*H*), 7.32 (t, 2×1H, *J* 7.7 Hz, Ar*H*), 7.61 (d, 2H, *J* 8.4 Hz, Ar*H*) and 8.29 (dd, 1H, *J* 7.7, 1.8 Hz, Ar*H*); *m*/*z* (%) 408 (M^+, 7), 253 (100), 183 (80), 168 (15), 156 (25), 130 (8) and 91 (17); ν_{max} (DCM) 3025, 2950, 1640, 1365, 1170 and 750 cm^{-1}.

*4.4.11. 5-[(4-Methylphenyl)sulfonyl]-5,6,7,13b-tetrahydro-9H-benzo[1,2]indolizino[7,8-b] indol-9-one (**32**)*



Initial treatment of (**20**) (0.889 g, 2.00 mmol) with a 1 M lithium triethylborohydride THF solution (3.4 mL) followed by workup according to the general procedure gave the crude hydroxy lactam, which was reacted with *p*-toluene sulphonic acid monohydrate (0.380 g, 2.00 mmol) by the general procedure. After 1 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 4:1 v/v ether/petroleum ether gave the product (**33**) (0.657 g, 77%) as a pale yellow solid, which crystallised from DCM/petroleum ether as colourless plates, mp 197–198 °C. (Found: C, 70.10; H, 5.00; N, 6.30; S, 7.35. $C_{25}H_{20}N_2O_3S$ requires C, 70.10; H, 4.70; N, 6.55; S, 7.50%.) δ (400 MHz) 2.27 (s, 3H, CH_3), 2.98–3.07 (m, 1H, NCH_2CH_α), 3.20 (ddd, 1H, *J* 13.3, 11.4, 4.0 Hz, $NCH_\beta CH_2$), 3.41 (dd, 1H, *J* 17.0, 4.0 Hz, NCH_2CH_β), 4.81 (dd, 1H, *J* 13.3, 5.4 Hz, $NCH_\alpha CH_2$), 5.87 (s, 1H, $NCH_\beta C$), 7.13 (d, 2H, *J* 8.1 Hz, Ar*H*), 7.33–7.46 (m, 2H, Ar*H*), 7.44 (t, 1H, *J* 7.4 Hz, Ar*H*), 7.52 (t, 1H, *J* 7.4 Hz, Ar*H*), 7.61 (d, 2H, *J* 8.4 Hz, Ar*H*), 7.86–7.95 (m, 3H, Ar*H*) and 8.22 (d, 1H, *J* 8.0 Hz, Ar*H*); *m*/*z* (%) 428 (M^+, 35), 274 (22), 273 (100), 272 (42), 271 (42), 270 (37), 243 (10), 216 (9), 189 (6), 130 (15), 91 (32) and 77 (7); ν_{max} (DCM) 3070, 2940, 1705, 1380, 1180 and 740 cm^{-1}.

*4.4.12. 5-[(4-Methylphenyl)sulfonyl]-6,7,8,14b-tetrahydro-isoindolo[2′,1′:1,2]azepino[4,3-b]indol-10(5H)-one (**33**)*

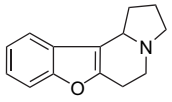


Initial treatment of (**21**) (0.926 g, 2.02 mmol) with a 1 M lithium triethylborohydride THF solution (3.4 mL) followed by workup according to the general procedure gave the crude hydroxy lactam, which was reacted with *p*-toluene sulphonic acid monohydrate (0.380 g, 2.02 mmol) by the general procedure. After 1 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 8:1 v/v ether/petroleum ether gave the product (**33**) (0.542 g, 61%) as a pale yellow solid, which precipitated from DCM/petroleum ether a colourless amorphous solid, mp 108–110 °C. (Found: C, 70.55; H, 5.30; N, 6.10; S, 7.20. $C_{26}H_{22}N_2O_3S$ requires C, 70.55; H, 5.00; N, 6.35; S, 7.25%.) δ (400 MHz) 1.54–1.63 (m, 1H, NCH_2CH_β), 2.33 (s, 3H, CH_3), 2.35–2.41 (m, 1H, NCH_2CH_α), 2.41–2.52 (m, 1H, NCH_2CH_2CH), 3.14–3.22 (m, 1H, $NCH_\beta CH_2$), 3.50–3.55 (m, 1H, NCH_2CH_2CH), 4.31 (dd, 1H, *J* 14.6, 7.9 Hz, $NCH_\alpha CH_2$), 5.91 (s, 1H, $NCH_\beta C$), 7.17 (d, 2H, *J* 8.6 Hz, Ar*H*), 7.37–7.48 (m, 5H, Ar*H*), 7.59 (d, 2H, *J* 8.6 Hz, Ar*H*), 7.74 (d, 1H, *J* 7.9 Hz, Ar*H*), 7.86 (d, 1H, *J* 8.6 Hz, Ar*H*) and 8.31 (d, 1H, *J* 8.1 Hz, Ar*H*); *m*/*z* (%) 442 (M^+, 34), 288 (31), 287 (100), 286 (31), 285 (20), 271 (10), 258 (14), 230 (10), 156 (12), 130 (13), 91 (27) and 77 (6); ν_{max} (DCM) 3070, 2940, 1700, 1370, 1120 and 740 cm^{-1}.

4.5. General procedure for reduction of lactams to cyclic tertiary amines

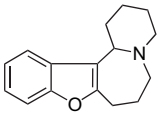
A solution of the lactam (1 mmol) in dry THF (5 mL) was added dropwise over 15 min to a stirred solution of BH_3/THF complex (10 mol equiv, 1 M) at 0 °C under nitrogen. The reaction was allowed to warm to ambient temperature and stirred for 3 h, then cooled to 0 °C and 6 N HCl carefully added until hydrogen evolution had subsided. The mixture was then boiled under reflux for 1 h, and the bulk THF distilled off. After cooling, the reaction mixture was basified with NaOH pellets, and the product extracted with DCM (2×25 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and the solvent removed under reduced pressure to afford the crude product.

4.5.1. 1,2,3,5,6,11c-Hexahydro[1]benzofuro[2,3-g]indolizine (**34**)



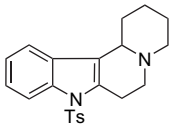
Prepared from (**22**) (0.798 g, 3.48 mmol) and BH_3/THF (34.8 mL, 34.8 mmol) by the general procedure. After 3 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 98:2 v/v ether/triethylamine gave the product (**34**) (0.428 g, 58%) as a pale yellow oil, which darkened on standing. (Found: C, 78.75; H, 7.35; N, 6.60. $C_{14}H_{15}NO$ requires C, 78.85; H, 7.10; N, 6.55%.) δ (500 MHz) 1.81–1.98 (m, 3H, NCHC*H* and NCHCH$_2$C*H*$_2$), 2.27–2.43 (m, 1H, NCH$_2$C*H*), 2.63–2.69 (m, 1H, CHNC*H*CH$_2$C), 2.78–2.83 (m, 1H, NCHCH$_2$CH$_2$C*H*), 2.87–2.92 (m, 1H, NCHCH$_2$CH$_2$C*H*), 2.99–3.09 (m, 2H, CHNC*H*CH$_2$C and CHNCH$_2$*H*C), 3.37–3.42 (m, 1H, CHNCH$_2$C*H*C), 4.07–4.11 (m, 1H, NC*H*C), 7.17–7.26 (m, 2H, Ar*H*) and 7.40–7.44 (m, 2H, Ar*H*); *m*/*z* (%) 213 (M^+, 61), 212 (100), 185 (39), 170 (15), 157 (16), 128 (14), 120 (13), 115 (13), 107 (9), 92 (6) and 77 (6).

4.5.2. 1,2,3,4,6,7,8,13c-Octahydro[1]benzofuro[3,2-c]pyrido[1,2-a]azepine (**35**)



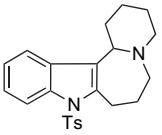
Prepared from (**25**) (0.162 g, 0.63 mmol) and BH_3/THF (6.3 mL, 6.3 mmol) by the general procedure. After 3 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 99:99:2 v/v/v ether/petroleum ether/triethylamine gave the product (**35**) (0.124 g, 81%) as colourless needles, mp 67–69 °C. (Found: C, 79.40; H, 7.70; N, 6.00. $C_{16}H_{19}NO$ requires C, 79.65; H, 7.95; N, 5.80%.) δ(500 MHz) 1.43–1.67 (m, 4H, NCHCH$_2$C*H*, NCHC*H*$_{ax}$ and NCHCH$_2$CH$_2$C*H*$_2$), 1.70–1.82 (m, 2H, NCHCH$_2$C*H* and NCH$_2$C*H*CH$_2$C), 2.00–2.03 (m, 1H, NCHC*H*$_{eq}$), 2.05–2.11 (m, 1H, NCH$_2$C*H*CH$_2$C), 2.65 (td, 1H, *J* 11.8, 3.0 Hz, NCHCH$_2$CH$_2$CH$_2$C*H*), 2.72–2.86 (m, 3H, NC*H*$_2$CH$_2$CH$_2$C and NCH$_2$CH$_2$C*H*C), 3.01 (br d, 1H, *J* 11.9 Hz, NCHCH$_2$CH$_2$CH$_2$C*H*), 3.24 (dddd, 1H, *J* 15.7, 11.2, 7.2, 1.5 Hz, NCH$_2$CH$_2$C*H*$_{ax}$C), 3.63 (br d, 1H, *J* 10.6 Hz, NC*H*C), 7.15–7.25 (m, 2H, Ar*H*) and 7.34–7.42 (m, 2H, Ar*H*); *m*/*z* (%) 241 (M^+, 100), 226 (7), 212 (61), 199 (85), 185 (57), 170 (22), 158 (30), 128 (19), 115 (18), 99 (12) and 77 (10); ν_{max} (DCM) 3060, 2930, 1460, 1120 and 740 cm^{-1}.

4.5.3. 8-[(4-Methylphenyl)sulfonyl]-1,2,3,4,6,7,8,12c-octahydroindolo[3,2-a]quinolizine (**36**)



Prepared from (**29**) (0.283 g, 1.10 mmol) and BH_3/THF (11.0 mL, 11.0 mmol) by the general procedure. After 3 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 99:1 v/v ether/triethylamine gave the product (0.20 g, 81%) as a pale yellow oil, which darkened on standing. (Found: C, 69.30; H, 6.55; N, 7.2; S, 8.60. $C_{22}H_{24}N_2O_2S$ requires C, 69.45; H, 6.35; N, 7.35; S, 8.45%.); δ (500 MHz, CD_2Cl_2) 1.24 (ddd, 1H, *J* 24.2, 11.3, 3.7 Hz, NCHC*H*$_{ax}$), 1.38–1.47 (m, 1H, NCHCH$_2$C*H*$_{ax}$), 1.55–1.60 (m, 2H, NCHCH$_2$CH$_2$C*H*$_2$), 1.76 (br d, *J* 12.9 Hz, NCHCH$_2$C*H*$_{eq}$), 2.24 (s, 3H, C*H*$_3$), 2.31–2.38 (m, 2H, NCHC*H*$_{eq}$ and NCHCH$_2$CH$_2$CH$_2$C*H*), 2.45 (td, 1H, *J* 11.4, 10.4, 4.5 Hz, NC*H*CH$_2$C), 2.85–2.92 (m, 2H, NCHCH$_2$CH$_2$CH$_2$C*H* and CHNC*H*CH$_2$C), 2.97–3.10 (m, 2H, NCH$_2$C*H*$_2$C), 3.16 (dd, 1H, *J* 11.2, 2.4 Hz, NC*H*C), 7.07–7.16 (m, 4H, Ar*H*), 7.38 (d, 1H, *J* 7.5 Hz, Ar*H*), 7.57 (dt, 2H, *J* 8.4, 2.1 Hz, Ar*H*) and 8.01 (dt, 1H, *J* 8.3, 0.9 Hz, Ar*H*); *m*/*z* (%) 380 (M^+, 12), 379 (15), 225 (100), 197 (6), 169 (11), 91 (15) and 65 (6); ν_{max} (DCM) 3080, 2940, 1450, 1375, 1180 and 750 cm^{-1}.

4.5.4. 9-[(4-Methylphenyl)sulfonyl]-1,3,4,6,7,8,9,13c-octahydro-2H-pyrido[1′,2′:1,2]azepino[4,3-b]indole (**37**)



Prepared from (**31**) (0.341 g, 0.83 mmol) and BH_3/THF (0.264 g, 6.96 mmol) by the general BH_3 procedure. After 2 h, the resulting mixture was worked up in the normal manner. Flash chromatography eluting with 66:33:1 v/v/v ether/petroleum ether/triethylamine gave the product (**37**) (0.201 g, 61%) as a colourless oil. (Found: 394.1720$C_{23}H_{26}N_2O_2S$ requires 394.1715.) δ (500 MHz, CD_2Cl_2) 1.35–1.42 (m, 3H, 3×C*H*), 1.60–1.62 (m, 2H, C*H*$_2$), 1.71–1.73 (m, 1H, C*H*), 1.84–1.86 (m, 1H, C*H*), 1.92–1.98 (m, 1H, C*H*), 2.32 (s, 3H, C*H*$_3$), 2.44–2.54 (m, 2H, NC*H*$_2$ and C*H*), 2.93 (br d, C*H*), 3.31 (tdd, 1H, *J* 12.9, 6.2, 1.2 Hz), 3.43–3.50 (m, 2H, 2×C*H*), 7.18–7.25 (m, 4H, Ar*H*), 7.32 (m, 2H, *J* 7.5 Hz, Ar*H*), 7.55 (d, 2H, *J* 7.7 Hz) and 8.16 (d, 1H, *J* 7.7 Hz, Ar*H*); *m*/*z* (%) 394 (M^+, 7), 240 (20), 239 (100), 211 (11), 197 (8), 183 (16), 167 (5), 156 (8) and 91 (18).

Acknowledgements

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References and notes

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