A novel total synthesis of (±)-aspidospermidine

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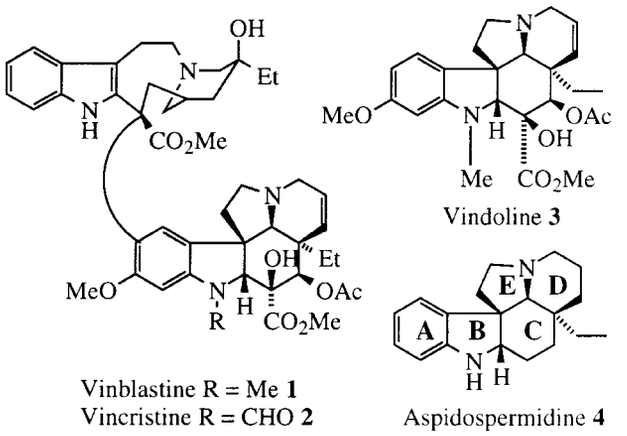
The tetrathiafulvalene-induced 'radical–polar crossover' reaction has been applied to the total synthesis of the pentacyclic *Aspidosperma* alkaloid aspidospermidine.

Introduction

The *Aspidosperma* alkaloids have long been the subject of synthetic interest[1–3] since the initial clinical success of two derivatives, vinblastine **1** and vincristine **2**, as anti-cancer agents.



These 'dimeric' alkaloids include the *Aspidosperma* skeleton, either as vindoline **3** or as its N-formyl analogue as one of their two 'monomeric' components. Despite their enormous value, vinblastine and vincristine have pronounced and serious side-effects. Synthesis[4] and semi-synthesis have allowed significant studies[5] to be conducted on the mode of action of the anti-tumour agents and have produced the new clinically useful derivative[6] vinorelbine® (navelbine). Further studies will benefit from versatile new synthetic routes to the agents. The synthesis of aspidospermidine **4** announced here is a prologue to such studies in our laboratories.

The key issues in this synthesis of aspidospermidine **4** (Scheme 1) relate to the stereochemistry at the four chiral centres on ring **C**, the creation of the tetrasubstituted carbon at the **BCE** ring junction, and the introduction of the C–N bond at the top of ring **C**. As the four stereocentres are contiguous, it should in principle be possible to establish the stereochemistry by initially defining one stereocentre and allowing it to control the neighbouring centre and then repeating the process twice in a relay effect.

The construction of the tetrasubstituted carbon provided initial difficulties using polar chemistry[1b] for steric reasons; however this is much less problematic for radical chemistry, both because the attacking radical would be unsolvated and therefore less encumbered, and also because the radical process leaves a longer distance between the bonding atoms at the crucial point in the reaction, *i.e.* at the transition state.[7]

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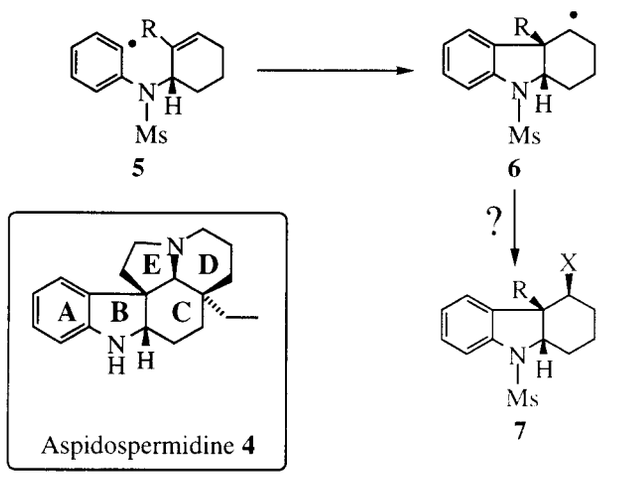
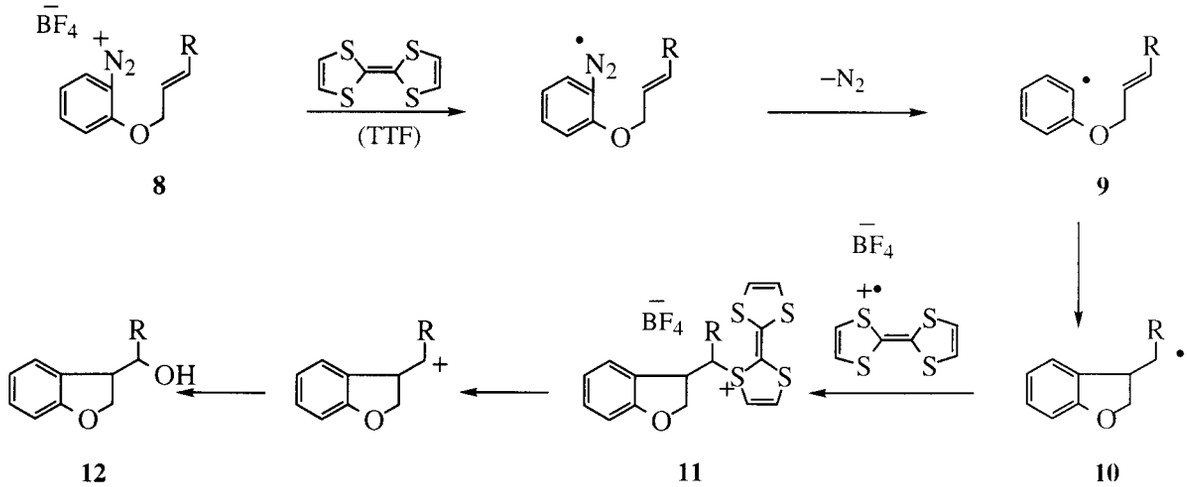


Scheme 1

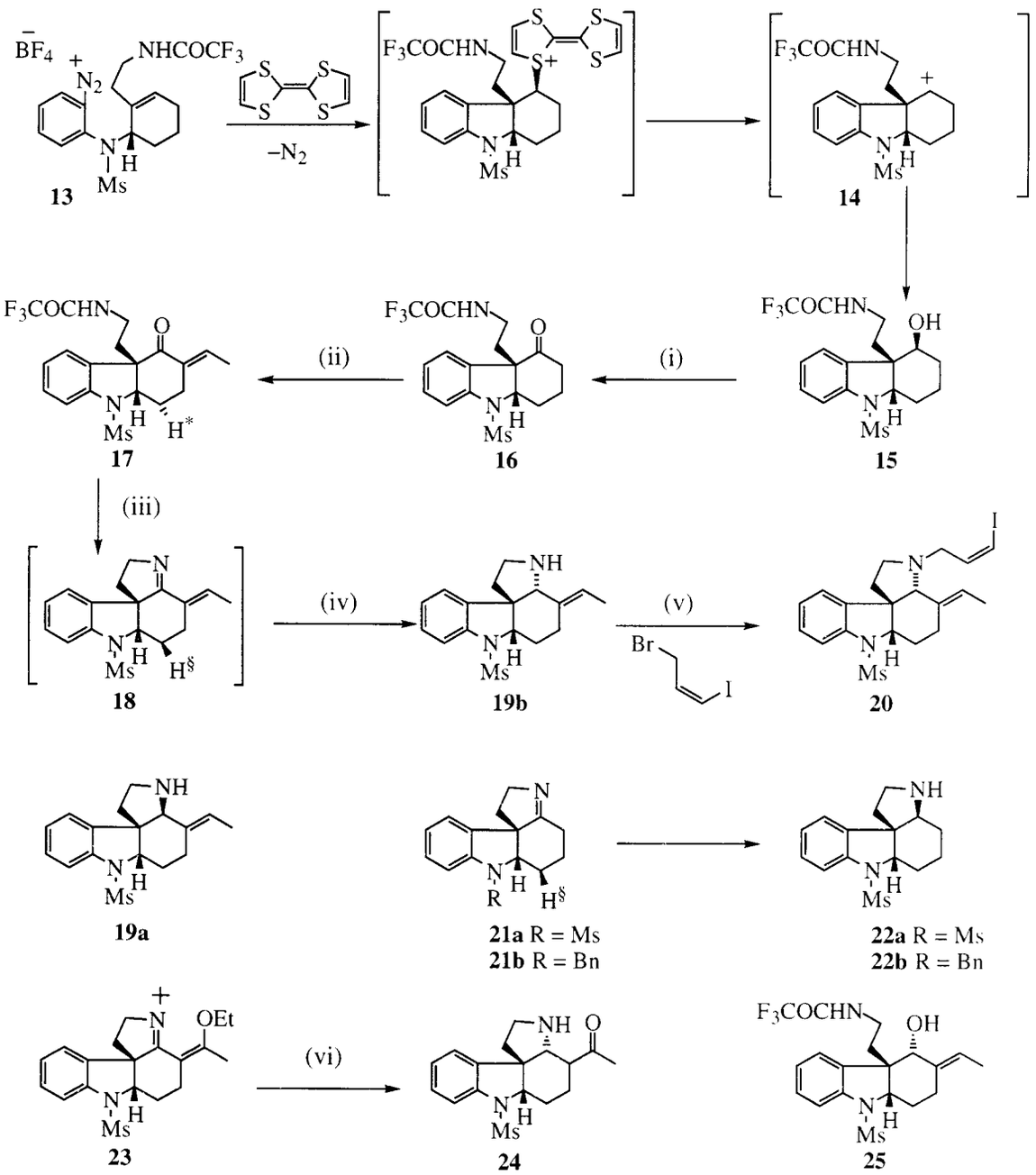
Accordingly, the plan envisaged cyclising aryl radical **5** to form alkyl radical **6** and functionalisation of **6** to form **7**. The initial cyclisation forms a [5,6]-fused system which, from precedent, must form with a *cis*-ring junction.[8] Although the final functionalisation could be achieved with a number of different groups,[9] the presence of an hydroxy group at this position would prove uniquely useful for later elaboration of the natural product. Such a substitution reaction is readily accomplished by the recently discovered radical–polar crossover reaction[10] when performed in moist acetone. This process permits an ordered sequence of radical and ionic steps to be followed in one pot. Specifically, electron transfer from TTF to a diazonium salt **8** is followed by loss of dinitrogen; the aryl radical **9** cyclises rapidly and the resulting alkyl radical **10** then couples to $TTF^{+\bullet}$ to form a sulfonium salt **11**. This salt undergoes unimolecular solvolysis in moist acetone yielding the corresponding alcohol **12** (Scheme 2).

Results and discussion

Extending this reaction to the current series of molecules, diazonium salt **13**[11] had been treated with TTF under these conditions to form the alcohol **15** as a single isomer (Scheme 3). The stereochemistry at the alcohol in this compound was not established, but previous studies would suggest complete stereoselectivity in favour of top-face attack on carbocation **14** due to effective shielding of the lower face by the indoline. Oxidation of the alcohol cleanly afforded the ketone **16**, which could now be used to introduce the two carbons which would ultimately form the ethyl side-chain of aspidospermidine. Mukaiyama aldol reaction[12] followed by spontaneous dehydration afforded **17**. Hydrolysis of the trifluoroacetamide group was carried out efficiently under mild conditions to afford the unstable imine **18**.



Scheme 2



Scheme 3 *Reagents and conditions:* (i) PCC, SiO_2, CH_2Cl_2, 18 h, 82%; (ii) TMSCl, Et_3N, DMF, 80 °C, 48 h, then $TiCl_4$, paraldehyde, CH_2Cl_2, −78 °C, 0.5 h, then room temp., 48 h, 51%; (iii) K_2CO_3, MeOH, H_2O, 18 h; (iv) $NaBH_4$, $CeCl_3$, 15 min, 79%; (v) K_2CO_3, Bu_4NCl, DMF, 46%; (vi) $NaBH_4$, then 'hydrolysis'.

The stereoselectivity of reduction of this imine was crucial. We had previously investigated[9] the stereochemistry of reduction of the imine **21a** which afforded **22a** as principal product. Semi-empirical molecular modelling[13] studies (AM1) indicated a close similarity between the preferred conformations of imine **21a** and **18**. The most stable conformers of both imines feature ring **C** in a boat conformation in which attack on the upper face of the imine group is inhibited by 'flagpole' hydrogen H§. The next most stable conformation for both imines shows ring **C** as a chair. Here it appears that either face of the imines may be attacked. The similarity between the conformations of the two imines raised expectations that **18** could be selectively reduced to **19a**. Moreover, if product stability is reflected to any extent in the transition state for reduction, then the reduction of **18** should be more selective (**19a** is 16 kcal mol^{-1} more stable than **19b**, whereas **22a** is only 3 kcal mol^{-1} more stable than its epimer). Luche reduction of imine **18** was performed *in situ* and afforded a single amine. However, alkylation of this amine with (*Z*)-3-bromo-1-iodopropene afforded an alkylated product which crystallised and was subjected to X-ray structure determination, showing it to be compound **20** (Fig. 1) and implying that the Luche reduction had afforded **19b** exclusively. The difference in stereochemistry of reduction of the two imines **18** and **21** was intriguing.[14] It may result from the effect of the cerium salt on the conformations of **18**. No parameters for cerium are available to us, so it was not possible to incorporate this into our computational studies. However, the closest analogy to reduction of **18** arises in the work of Gramain and co-workers,[14b] who had shown that, whereas **21b** could be reduced to **22b** with good to excellent selectivity depending on the conditions employed, the ethoxyiminium salt **23** was reduced by borohydride exclusively to afford **24** after hydrolysis of the vinyl ether. Iminium cation **23** bears close resemblance to imine **18** in having an alkylidene side-chain at the same position.

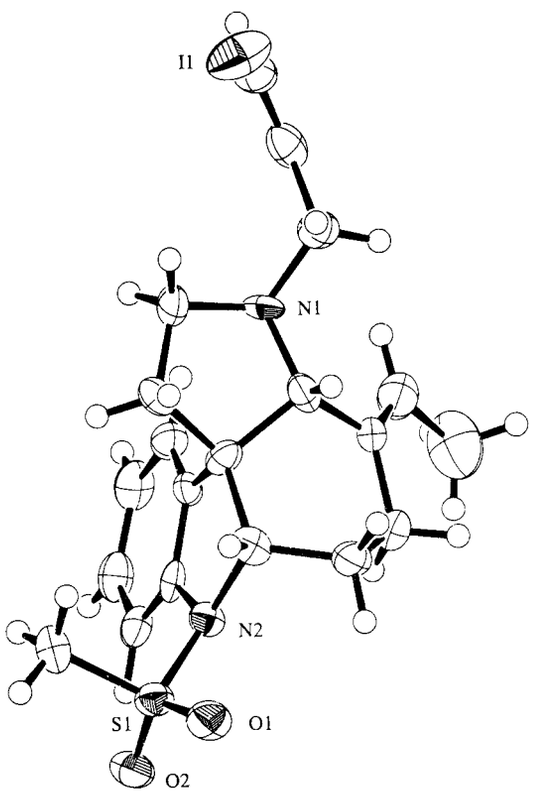
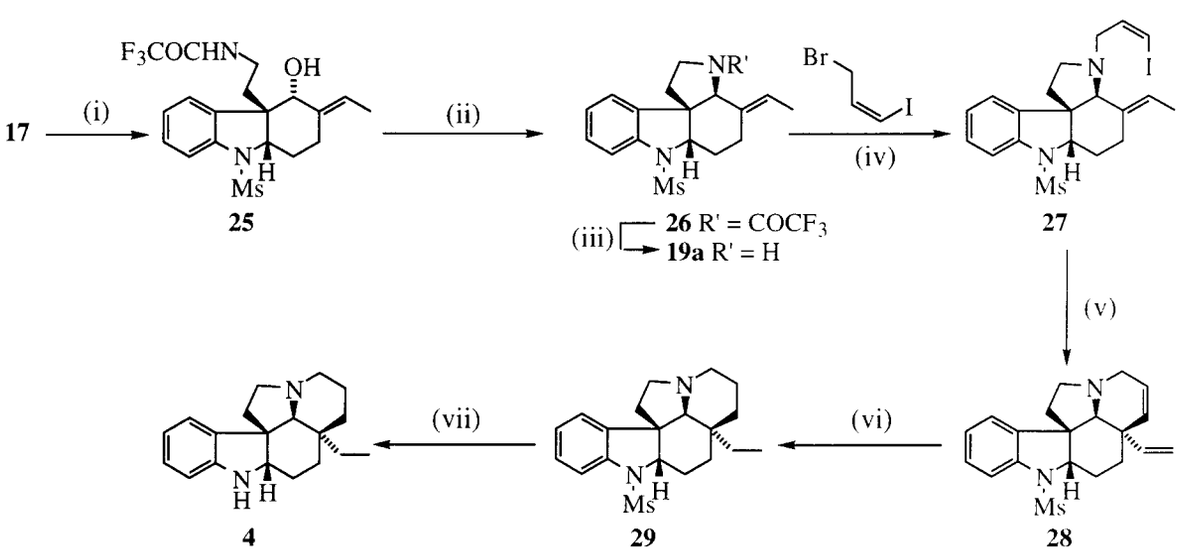


Fig. 1 Molecular structure of **20** with non-H atoms drawn as 50% probability ellipsoids and H atoms as small spheres of arbitrary size.

This posed a major problem for the synthesis. To address this, a conformational analysis of the ketone **17** was performed. This molecule adopts conformations quite different from the imines. Again a boat form in ring **C** is the most favourable conformation for **17** (about 11 kcal mol^{-1} more stable than the next most stable conformer, featuring ring **C** as a chair form) but the boat is now inverted relative to **18** and **21**, and the flagpole hydrogen, H*, now inhibits access to the ketone from the *lower* face. Luche reduction supported this analysis and pleasingly afforded exclusive top-face delivery of hydride to afford alcohol **25** (Scheme 4). With a single clean stereoisomer in hand, it was possible to proceed with the synthesis.

Intramolecular Mitsunobu reaction of this alcohol, exploiting the inherent acidity of the trifluoroacetamide group, neatly closed ring **E** affording **26**. Reductive cleavage of the trifluoroacetamide and alkylation[15] of the resulting amine **19a** yielded the *Z*-iodoalkene **27** and ring closure under the conditions[16] of Kuehne *et al.* gave the pentacycle **28**. The stereoselectivity of this cyclisation is governed by the *cis*-fused **CE** ring junction in **27**. Hydrogenation proceeded rapidly for the terminal alkene and more slowly for the ring alkene to afford **29**. Deprotection of the methylsulfonyl group occurred cleanly to afford aspidospermidine **4**, with the data in agreement with the literature.[1]

This novel synthesis of aspidospermidine[17] allows all of the



Scheme 4 *Reagents and conditions:* (i) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 100%; (ii) DEAD, PPh_2Me, THF, 0 °C→room temp., 99%; (iii) $NaBH_4$, EtOH, 60 °C, 82%; (iv) K_2CO_3, dry THF, 80%; (v) $Pd(OAc)_2$, Et_3N, PPh_3, dry MeCN, reflux, 37%; (vi) 10% Pt / C, 40 psi, EtOH, 5 days, 58%; (vii) Red-Al, toluene, 100 °C, 84%.

stereochemistry to be controlled by the configuration of the single stereocentre [18] in **13**. It also demonstrates for the first time the synthetic utility of the radical–polar crossover reaction. Whereas the use of free radicals in organic synthesis has expanded dramatically over the last twenty years, many of these gains have arisen as a result of the use of organotin reagents. However, these reagents are generally unacceptable for use in the pharmaceutical industry, so excluding this important sector from these advances. The application of radical–polar crossover reaction to total synthesis of the complex alkaloid aspidospermidine reinforces the message that radical chemistry need not be dependent on tin-derived reagents.

We thank the EPSRC for funding and the EPSRC National Mass Spectrometry Laboratory, Swansea, for high resolution mass spectra.

Experimental

General

Melting points were carried out on a Kofler hot stage apparatus and are uncorrected. Microanalyses were determined using a Perkin-Elmer 240B elemental analyser. Infrared spectra were obtained on a Perkin-Elmer 1720-X FTIR or a Pye-Unicam SP3-100 spectrometer. Ultraviolet spectra were recorded on a Philips PU8700 series instrument. ^{1}H NMR spectra were recorded at 90 MHz on a Perkin-Elmer R32, at 250 MHz on a Bruker WM250, at 270 MHz on a JEOL EX270 or at 400 MHz on a Bruker DPX400 instrument. ^{13}C NMR spectra were recorded at 63.5 MHz on a JEOL EX270 or at 100 MHz on a Bruker AM400 machine. NMR experiments were carried out in chloroform-*d*, methanol-d_4, acetone-d_6, acetonitrile-d_3 or dimethyl sulfoxide-d_6 with tetramethylsilane as internal reference. Chemical shifts are quoted in parts per million (ppm). The following abreviations are used for multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (*J*) are reported in hertz (Hz). In cases where superimposition of the signals of two, or more, isomers occurred, the signals have been reported as multiplets (m), unless the coupling constants of each isomer could be ascertained. Peaks which are clearly due to minor isomers are indicated by an asterisk (*). Mass spectra were recorded on a VG Micromass 70E or an AEI MS902 instrument. High resolution FAB or CI spectra were recorded at the EPSRC Mass Spectrometry Service Centre, Swansea.

Where necessary, solvents were dried and/or distilled before use. Tetrahydrofuran was distilled from sodium–benzophenone. Acetonitrile was distilled from phosphorus(v) oxide. Dichloromethane was distilled from calcium hydride. Diethyl ether, toluene and benzene were dried over sodium wire. Unless otherwise stated all light petroleum was of boiling range 40–60 °C and was distilled before use. Chromatography was performed using Sorbsil C60 (May and Baker), Kieselgel 60 (Art 9385) or Kieselgel HF254 silica gels.

2,2,2-Trifluoro-*N*-{2-[9-(methylsulfonyl)-4-oxo-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl]ethyl}acetamide 16

2,2,2-Trifluoro-*N*-{2-[9-(methylsulfonyl)-4-hydroxy-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl]ethyl}acetamide **15** (212 mg, 0.52 mmol), pyridinium chlorochromate (449.3 mg, 2.08 mmol) and silica gel (449.3 mg) were stirred in dichloromethane (50 ml) for 18 hours. Diethyl ether (100 ml) was added and the mixture stirred for an hour before being passed through a 10 cm column of silica and flushed through with a large excess of diethyl ether. The solvent was removed *in vacuo* to give *2,2,2-trifluoro-N-{2-[9-(methylsulfonyl)-4-oxo-2,3,4,4a,9,9a-hexahydro-1H-carbazol-4a-yl]ethyl}acetamide* **16** as a white solid (173 mg, 82%); mp 117.5–118 °C (from ethyl acetate–light petroleum) (Found: M^+, 404.1035. $C_{17}H_{19}F_3N_2O_4S$ requires *M*, 404.1018); ν_{max}(KBr)/cm^{-1} 3437, 2928, 2856, 1719, 1701 (shoulder), 1596, 1538, 1460, 1354, 1242, 1164 and 1104; δ_H($CDCl_3$, 400 MHz) 1.63–1.76 (1H, m, CH_2), 1.81–1.97 (2H, m, CH_2), 2.00–2.17 (2H, m, CH_2), 2.25–2.45 (3H, m, CH_2), 3.07 (3H, s, CH_3SO$_2$N), 3.25–3.43 (2H, m, CH_2N), 4.67 (1H, dd, *J* 5.5, 5.5, C*H*N), 6.98 (1H, d, *J* 7.6, Ar*H*), 7.06 (1H, dd, *J* 7.5, 7.5, Ar*H*), 7.10–7.20 (1H, br s, N*H*), 7.30 (1H, ddd, *J* 8.0, 7.5, 1.0, Ar*H*) and 7.46 (1H, dm, *J* 8.0, Ar*H*); δ_C($CDCl_3$, 100 MHz) 17.72 (t), 31.04 (t), 36.23 (t), 37.11 (t), 38.03 (q), 38.44 (t), 60.04 (d), 68.57 (s), 114.72 (d), 115.87 (q, $J_{^{13}C-^{19}F}$ 286), 124.48 (d), 124.69 (d), 130.37 (d), 131.34 (s), 141.33 (s), 157.65 (q, $J_{^{13}C-^{19}F}$ 37) and 209.59 (s); *m*/*z* (EI$^+$) 404 (M^+, 25%), 376 (5), 325 (100), 297 (15), 212 (63), 184 (64) and 130 (53).

N-{2-[3-[(*E*)-Ethylidene]-9-(methylsulfonyl)-4-oxo-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl]ethyl}-2,2,2-trifluoroacetamide 17

A stirred solution of 2,2,2-trifluoro-*N*-{2-[9-(methylsulfonyl)-4-oxo-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl]ethyl}-acetamide **16** (4.33g, 10.72 mmol), trimethylsilyl chloride (5.46 ml, 42.95 mmol) and triethylamine (8.87 ml, 64.43 mmol) in dry DMF (10 ml) was heated at 80 °C for 2 days. The reaction mixture was then cooled and poured into saturated sodium hydrogen carbonate (300 ml), extracted with diethyl ether (3 × 100 ml), washed successively with hydrochloric acid (2 M, 2 × 200 ml), saturated sodium hydrogen carbonate (2 × 200 ml) and water (2 × 200 ml). The combined organic extracts were dried over sodium sulfate, filtered and evaporated to dryness to afford the silyl enol ether of **16** as a yellow foam which was used directly in the next step.

Titanium tetrachloride (1 M solution in dichloromethane, 9.17 ml, 9.17 mmol) was added to dry dichloromethane (23 ml) at −78 °C, under nitrogen. Paraldehyde (0.49 ml, 3.67 mmol) was added, followed by dropwise addition of a solution of the silyl enol ether prepared above (4.36 g, 9.17 mmol) in dry dichloromethane (12 ml). The reaction was stirred at −78 °C for 0.5 h and then allowed to warm to room temperature over 30–40 min. The reaction was then stirred at room temperature for 2 days. The resulting mixture was poured into water (500 ml) and potassium carbonate added until the solution was basic. The mixture was extracted with dichloromethane (3 × 200 ml) and the combined organic extracts dried over magnesium sulfate, filtered and evaporated to dryness to give a brown oil which was purified by column chromatography (30 : 70 ethyl acetate–light petroleum) to afford *N-{2-[3-[(E)-ethylidene]-9-(methylsulfonyl)-4-oxo-2,3,4,4a,9,9a-hexahydro-1H-carbazol-4a-yl]ethyl}-2,2,2-trifluoroacetamide* **17** as a white powder (2.33 g, 51%); mp 54.5–57 °C (Found: MNH_4^+, 448.1518. $C_{19}H_{21}F_3N_2O_4S$ requires MNH_4, 448.1518); ν_{max}(KBr)/cm^{-1} 3314, 2933, 2861, 1713, 1683, 1624, 1479, 1350, 1211, 1160 and 1015; δ_H($CDCl_3$, 400 MHz) 1.70 (3H, dd, *J* 7.3, 0.8, CH_3), 1.82–1.96 (2H, m, CH_2), 2.36–2.54 (4H, m, 2 × CH_2), 3.02 (3H, s, CH_3), 3.34–3.49 (2H, m, CH_2), 4.71 (1H, dd, *J* 4.2, 3.0, C*H*N), 6.84 (1H, qdd, *J* 7.2, 1.6, 1.6, =C*H*), 6.98–7.10 (3H, m, Ar*H* and N*H*), 7.24–7.31 (1H, m, Ar*H*) and 7.48–7.50 (1H, d, *J* 6, Ar*H*); δ_C($CDCl_3$, 62.5 MHz) 13.93 (q), 20.15 (t), 29.86 (t), 35.97 (t), 36.27 (q), 38.21 (t), 58.47 (s), 67.64 (d), 114.35 (d), 115.77 (s, $J_{^{13}C-^{19}F}$ 285.5), 124.76 (d), 124.91 (d), 129.96 (d), 131.69 (s), 135.44 (s), 137.26 (d), 141.84 (s), 157.52 (s, $J_{^{13}C-^{19}F}$ 36.9) and 197.38 (s); *m*/*z* (CI$^+$) 448 (MNH_4^+, 48%), 430 (3), 355 (100), 327 (10) and 214 (47).

4-[(*E*)-Ethylidene]-7-(methylsulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazole 19b

N-{2-[3-[(*E*)-Ethylidene]-9-(methylsulfonyl)-4-oxo-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl]ethyl}-2,2,2-trifluoroacetamide **17** (900 mg, 2.10 mmol) was dissolved in methanol (75 ml) and a solution of potassium carbonate (637 mg, 4.60 mmol) in water (30 ml) was added. The mixture was stirred for 18 h.

Cerium(III) chloride (939 mg, 2.52 mmol) was added and the

mixture cooled in an ice bath. Sodium borohydride (96 mg, 2.52 mmol) was added and the mixture stirred for 15 min. Water (600 ml) was added and the mixture extracted with ethyl acetate (3 × 120 ml). The extracts were washed with water (500 ml) and extracted with aqueous hydrochloric acid (2 M, 3 × 60 ml). The extracts were made basic with solid sodium hydrogen carbonate and extracted with ethyl acetate (3 × 100 ml). The extracts were dried over sodium sulfate, filtered and evaporated to dryness to give a crude product that was purified by column chromatography on silica gel eluted with ethyl acetate to give *4-[(E)-ethylidene]-7-(methylsulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1H-pyrrolo[2,3-d]carbazole* **19b** (530 mg, 79%) as a white foam; mp 68–73 °C (Found: MH^+, 319.1473. $C_{17}H_{22}N_2O_2S$ requires *MH*, 319.1480); ν_{max}(KBr)/cm^{-1} 3435, 2928, 2865, 1635, 1476, 1459, 1347, 1158, 762 and 550; δ_H($CDCl_3$, 270 MHz) 1.31 (3H, d, *J* 6.5, CH_3), 1.58–2.27 (7H, m, N*H* and CH_2 × 3), 2.78 (3H, s, CH_3), 3.15–3.30 (2H, m, CH_2), 3.90 (1H, s, C*H*N), 4.46 (1H, dm, *J* 4.3, C*H*N), 5.19–5.22 (1H, m, C*H*=), 6.92 (1H, ddd, *J* 7.6, 7.6, 1.1, Ar*H*), 7.08–7.20 (2H, m, Ar*H*) and 7.33 (1H, dm, *J* 7.8, Ar*H*); δ_C($CDCl_3$, 67.5 MHz) 12.39 (q), 21.50 (t), 29.09 (t), 36.33 (q), 40.95 (t), 43.36 (t), 54.48 (s), 63.71 (d), 67.31 (d), 114.24 (d), 115.88 (d), 124.37 (d), 125.95 (d), 127.95 (d), 134.51 (s), 136.92 (s) and 141.25 (s); *m/z* (CI^+) 319 (MH^+, 100%), 317 (50).

4-[(*E*)-Ethylidene]-3-[(*Z*)-3-iodoprop-2-enyl]-7-methylsulfonyl-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazole 20

4-[(*E*)-Ethylidene]-7-(methylsulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazole **19b** (220 mg, 0.69 mmol), tetra-*n*-butylammonium chloride (306 mg, 1.04 mmol) and potassium carbonate (285 mg, 2.07 mmol) were dissolved in dimethylformamide (5 ml), under argon, and cooled to −5 °C (ice–salt bath). *cis*-3-Bromo-1-iodopropene (170 mg, 0.69 mmol) (weighed in a 100 μl syringe and handled under argon) was added and the mixture stirred for 2.5 h. Further *cis*-3-bromo-1-iodopropene (43 mg, 0.173 mmol) was added and the mixture stirred for a further 1 h.

The mixture was poured into water (30 ml) and extracted with diethyl ether (3 × 20 ml). The extracts were washed with aqueous sodium hydroxide (30 ml) and then extracted with aqueous hydrochloric acid (2 M, 3 × 20 ml). The acid extracts were washed with diethyl ether (30 ml) and made basic with solid sodium hydrogen carbonate and extracted with diethyl ether (3 × 30 ml), dried over sodium sulfate, filtered and evaporated to dryness to give a white solid. Purification by column chromatography on silica gel eluted with a 20% solution of hexane in dichloromethane gave *4-[(E)-ethylidene]-3-[(Z)-3-iodoprop-2-enyl]-7-methylsulfonyl-2,3,3a,4,5,6,6a,7-octahydro-1H-pyrrolo[2,3-d]carbazole* **20** (153 mg, 46%) as a white solid; mp 170.5–171.5 °C (Found: C, 49.48; H, 4.98; N, 5.51. $C_{20}H_{25}IN_2O_2S$ requires C, 49.59; H, 5.20; N, 5.78%) (Found: MH^+, 485.0760. $C_{20}H_{25}IN_2O_2S$ requires *MH*, 485.0760); ν_{max}(KBr)/cm^{-1} 2949, 2930, 2868, 2829, 1474, 1341, 1159, 970, 764 and 559; δ_H($CDCl_3$, 400 MHz) 1.33 (3H, dd, *J* 6.8, 1.9, CH_3), 1.83 (1H, ddd, *J* 10.7, 8.0, 2.6, CH_2), 1.88–2.28 (5H, m, CH_2), 2.71 (1H, ddd, *J* 10.7, 10.7, 2.6, NCH_2CH_2), 2.86 (3H, s, CH_3), 3.09 (1H, ddd, *J* 14.8, 7.0, 1.4, =CHCH_2), 3.42 (1H, ddd, *J* 10.6, 8.3, 8.3, NCH_2CH_2), 3.54 (1H, s, =CC*H*N), 3.65 (1H, ddd, *J* 14.8, 14.8, 2.1, =CHCH_2), 4.45–4.47 (1H, m, C*H*N), 5.29 (1H, qd, *J* 6.8, 2.0, C*H*=), 6.38 (1H, ddd, *J* 7.6, 2.0, 1.4, IC*H*=), 6.51 (1H, ddd, *J* 7.5, 7.0, 4.8, C*H*=CHI), 6.97 (1H, ddd, *J* 7.5, 7.5, 1.1, Ar*H*), 7.16 (1H, ddd, *J* 7.5, 7.5, 1.4, Ar*H*), 7.36 (1H, dm, *J* 8.0, Ar*H*) and 7.47 (1H, dm, *J* 7.2, Ar*H*); δ_C($CDCl_3$, 62.5 MHz) 12.45 (q), 22.60 (t), 29.10 (t), 36.76 (q), 37.97 (t), 51.68 (t), 56.01 (s), 59.88 (t), 68.22 (d), 68.68 (d), 82.66 (d), 114.17 (d), 116.56 (d), 124.16 (d), 127.23 (d), 128.24 (d), 132.42 (s), 136.71 (s), 139.11 (d) and 140.81 (s); *m/z* (CI^+) 485 (MNH_4^+, 62%), 484 (2), 359 (100), 357 (40), 319 (47) and 315 (53).

Crystal data for 20. A colourless needle was cut to 0.35 × 0.15 × 0.12 mm and mounted in oil on a Rigaku AFC7S diffractometer at 233 K. Monoclinic, space group *C*2/*c*, *a* = 32.927(5), *b* = 11.611(4), *c* = 11.161(5) Å, *β* = 108.51(2)°, *U* = 4046(2) Å^3, *Z* = 8. Measurements on the weakly diffracting sample were made with *λ* = 0.71069 Å radiation to 2*θ* = 52° and were corrected for absorption effects. Solution program DIRDIF92. Of 4265 reflections, 4190 were unique, R_{int} = 0.0560. Final refinement[21] to convergence was on *F* with 1719 observed reflections, $I > 1.5\sigma(I)$, and 235 parameters. *R* = 0.0587, *Rw* = 0.0603, *S* = 1.538. H atoms were placed in calculated positions.

Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/304. See http://www.rsc.org/suppdata/p1/1999/995/ for crystallographic files in .cif format.

N-{2-[3-[(*E*)-Ethylidene]-4-hydroxy-9-(methylsulfonyl)-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl]ethyl}-2,2,2-trifluoroacetamide 25

To a stirred solution of *N*-{2-[3-[(*E*)-ethylidene]-9-(methylsulfonyl)-4-oxo-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl]-ethyl}-2,2,2-trifluroacetamide **17** (2.33 g, 5.59 mmol) and cerium trichloride heptahydrate (2.09 g, 5.59 mmol) in methanol (100 ml) was added portionwise sodium borohydride (211 mg, 5.59 mmol) and the reaction stirred for 0.5 h under nitrogen at 0 °C. Water (50 ml) was added and the solvent was removed *in vacuo*. Further water (150 ml) and hydrochloric acid (2 M, 50 ml) were added and the resulting aqueous solution extracted with dichloromethane (3 × 80 ml). The combined organic extracts were dried over magnesium sulfate and evaporated under reduced pressure to dryness to give a colourless oil which was purified by column chromatography (5:95 ethyl acetate–dichloromethane) to afford *N-{2-[3-[(E)-ethylidene]-4-hydroxy-9-(methylsulfonyl)-2,3,4,4a,9,9a-hexahydro-1H-carbazol-4a-yl]-ethyl}-2,2,2-trifluoroacetamide* **25** as a white crystalline solid (2.33 g, 100%); mp 66–68 °C (Found: C, 52.46; H, 5.50; N, 6.57. $C_{19}H_{23}F_3N_2O_4S$ requires C, 52.77; H, 5.36; N, 6.48%); ν_{max}(KBr)/cm^{-1} 3508 (O–H), 3342 (N–H), 3106 (=C–H), 2929 (C–H), 1712 (C=O), 1568 (C=C), 1156 (–SO_2–N); δ_H($CDCl_3$, 250 MHz) 1.48 (3H, d, *J* 6.6, CH_3), 1.88–2.48 (7H, m, CH_2, OH), 2.96 (3H, s, CH_3), 3.11–3.20 (1H, m, CH_2N), 3.30–3.42 (1H, m, CH_2N), 4.23–4.26 (1H, m, C*H*OH), 4.34–4.39 (1H, br m, NCH), 5.44 (1H, q, *J* 6.5, CH=), 6.98 (1H, br, NH), 7.05 (1H, dd, *J* 7.4, 7.4, ArH), 7.13–7.29 (2H, m, ArH), 7.35 (1H, d, *J* 8.0, ArH); *m/z* 352 (M − HSO_2Me, 70%), 335 (M − CF_3CO, 100).

1-{4-[(*E*)-Ethylidene]-7-(methylsulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-3-yl}-2,2,2-trifluoroethan-1-one 26

To a stirred solution of *N*-{2-[3-[(*E*)-ethylidene]-4-hydroxy-9-(methylsulfonyl)-2,3,4,4a,9,9a-hexahydro-1*H*-carbazol-4a-yl]-ethyl}-2,2,2-trifluoroacetamide **25** (246 mg, 0.59 mmol) and methyldiphenylphosphine (0.16 ml, 0.59 mmol) in dry THF (10 ml) at 0 °C was added dropwise diethyl azodicarboxylate (0.14 ml, 0.89 mmol) and the reaction stirred for 48 h under nitrogen. The solvent was removed *in vacuo*, water (60 ml) added and the resulting aqueous solution extracted with dichloromethane (3 × 30 ml). The combined organic extracts were dried over magnesium sulfate and evaporated under reduced pressure to dryness to give a yellow oil which was purified by column chromatography (1:3 ethyl acetate–light petroleum) to afford *1-{4-[(E)-ethylidene]-7-(methylsulfonyl)-2,3,3a,4,5,6,6a,7-octa-*

hydro-1H-pyrrolo[2,3-d]carbazol-3-yl}-2,2,2-trifluoroethan-1-one **26** as a white crystalline solid (233 mg, 99%); mp 156–158 °C (Found: C, 55.09; H, 5.29; N, 6.66; M^+, 414.1205. $C_{19}H_{21}F_3N_2O_3S$ requires C, 55.06; H, 5.11; N, 6.76%; *M*, 414.1225); ν_{max}(KBr)/cm^{-1} 3061 (=C–H), 2930 (C–H), 2863 (C–H), 1694 (C=O), 1600 (C=C), 1159 (–SO_2–N); δ_H($CDCl_3$, 250 MHz) 1.55 and 1.58 [3H, 2 × d, *J* 6.6, CH_3], 1.72–2.50 (6H, m, CH_2), 2.83 and 2.88 (3H, 2 × s, CH_3), 3.62–3.99 (3H, m, CH_2N, NCH), 4.55 and 4.75 (1H, 2 × br m, NCH), 5.20 (1H, q, *J* 6.6, CH=), 6.80 and 6.92 (1H, 2 × d, *J* 7.5, ArH), 7.02 (1H, dd, *J* 7.4, 7.3, ArH), 7.19-7.25 (1H, m, ArH), 7.32-7.40 (1H, m, ArH); *m*/*z* 414 (M^+, 40%), 335 (M^+ − SO_2Me, 70).

4-[(*E*)-Ethylidene]-7-(methylsulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazole 19a

To a stirred solution of 1-{4-[(*E*)-ethylidine]-7-(methylsulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazol-3-yl}-2,2,2-trifluoroethan-1-one **26** (2.09 g, 5.0 mmol) in ethanol (100 ml) was added sodium borohydride (376 mg, 10.0 mmol) and the mixture heated at 60 °C, under nitrogen for 24 h . The reaction was cooled, water (100 ml) was added and the solvent was removed *in vacuo*. The resulting aqueous solution was extracted with dichloromethane (3 × 70 ml). The combined organic phases were extracted with hydrochloric acid (2 M, 3 × 60 ml), basified with solid sodium hydrogen carbonate and then re-extracted with dichloromethane (3 × 70 ml), dried over magnesium sulfate and evaporated under reduced pressure to dryness to give a brown oil which was purified by column chromatography (neat ethyl acetate) to afford *4-[(E)-ethylidene]-7-(methylsulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1H-pyrrolo[2,3-d]carbazole* **19a** as a brown solid (1.32 g, 82%); mp 52–54 °C (Found: MH^+, 319.1455. $C_{17}H_{21}N_2O_2S$ requires *MH*, 319.1480); ν_{max}(KBr)/cm^{-1} 3368 (N–H), 2956 (C–H), 2930 (C–H), 1663 (C=C), 1599 (C=C), 1158 (–SO_2–N); δ_H($CDCl_3$, 400 MHz) 1.55 (3H, d, *J* 6.7, CH_3), 1.67–1.70 (1H, m, CH_2), 1.92–2.35 (6H, m, CH_2, NH), 2.95 (3H, s, CH_3), 3.17–3.21 (2H, m, CH_2N), 3.82 (1H, s, NCH), 4.15 (1H, dd, *J* 9.1, 4.7, NCH), 5.42 (1H, q, *J* 6.7, CH=), 7.05 (1H, dd, *J* 7.4, 7.5, ArH), 7.17–7.22 (2H, m, ArH), 7.34 (1H, d, *J* 7.9, ArH); δ_C($CDCl_3$, 100 MHz) 13.4 (q), 20.6 (t), 29.1 (t), 38.1 (q), 42.4 (t), 44.9 (t), 55.4 (s), 63.8 (d), 69.3 (d), 114.3 (d), 122.1 (d), 123.6 (d), 124.5 (d), 128.7 (d), 134.1 (s), 136.4 (s), 141.1 (s); *m*/*z* 319 (MH^+, 100%), 240 (M^+ − SO_2Me, 25).

4-[(*E*)-Ethylidene]-3-[(*Z*)-3-iodoprop-2-enyl]-7-(methylsulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazole 27

To a stirred solution of 4-[(*E*)-ethylidene]-7-(methylsulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazole **19a** (220 mg, 0.68 mmol) and potassium carbonate (356 mg, 2.59 mmol) in dry THF (7 ml) was added dropwise (*Z*)-3-bromo-1-iodopropene (255 mg, 1.02 mmol) and the reaction stirred for 24 h under nitrogen. The resulting mixture was then heated at reflux for 1 h, cooled and the solvent was removed *in vacuo* to afford a brown oil which was purified by column chromatography (1 : 4 ethyl acetate–light petroleum) to afford *4-[(E)-ethylidene]-3-[(Z)-3-iodoprop-2-enyl]-7-(methylsulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1H-pyrrolo[2,3-d]carbazole* **27** as a brown oil (269 mg, 80%) (Found: M^+, 484.0684. $C_{20}H_{25}IN_2O_2S$ requires *M*, 484.0681); ν_{max}(film)/cm^{-1} 3080 (=C–H), 2934 (C–H), 2863 (C–H), 1606 (C=C), 1472 (CH_2), 1459 (CH_2), 1158 (–SO_2–N); δ_H($CDCl_3$, 400 MHz) 1.62 (3H, d, *J* 6.7, CH_3), 1.68–1.78 (1H, m, CH_2), 1.97 (1H, ddd, *J* 9.9, 9.9, 4.0, CH_2), 2.17–2.25 (2H, m, CH_2), 2.39–2.57 (3H, m, CH_2), 2.94 (1H, dd, *J* 15.2, 6.5, CH_2), 3.01 (3H, s, CH_3), 3.05 (1H, s, NCH), 3.34 (1H, ddd, *J* 13.0, 8.9, 4.1, CH_2), 3.42 (1H, dd, *J* 15.2, 4.3, CH_2), 4.27 (1H, dd, *J* 4.7, 4.1, NCH), 5.43 (1H, q, *J* 6.4, CH=), 6.34–6.41 (2H, m, CH=CH), 7.13 (1H, dd, *J* 7.5, 7.5, ArH), 7.24–7.29 (2H, m, ArH), 7.39 (1H, d, *J* 7.9, ArH); δ_C($CDCl_3$, 100 MHz) 13.3 (q), 20.1 (t), 28.2 (t), 37.8 (q), 40.0 (t), 51.7 (t), 55.0 (s), 56.8 (t), 70.7 (d), 75.4 (d), 83.1 (d), 113.9 (d), 123.2 (d), 124.0 (d), 124.5 (d), 128.4 (d), 133.5 (s), 136.4 (s), 138.6 (d), 141.0 (s); *m*/*z* 484 (M^+, 10%), 405 (21), 194 (100).

6-(Methylsulfonyl)-3a-vinyl-3a,4,5,5a,6,11,12,13a-octahydro-1*H*-indolizino[8,1-*cd*]carbazole 28

A stirred solution of 4-[(*E*)-ethylidene]-3-[(*Z*)-3-iodoprop-2-enyl]-7-(methylsulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazole **27** (269 mg, 0.56 mmol), palladium(II) acetate (50 mg, 0.21 mmol), triphenylphosphine (111 mg, 0.42 mmol) and triethylamine (0.39 ml, 2.80 mmol) in dry acetonitrile (7 ml) was heated at reflux for 3 h under nitrogen. The resulting mixture was cooled and the solvent was removed *in vacuo* to afford a brown oil which was purified by column chromatography (1 : 1 ethyl acetate–light petroleum) to afford *6-(methylsulfonyl)-3a-vinyl-3a,4,5,5a,6,11,12,13a-octahydro-1H-indolizino[8,1-cd]carbazole* **28** as a brown oil (74 mg, 37%) (Found: M^+, 356.1575. $C_{20}H_{24}N_2O_2S$ requires *M*, 356.1558); ν_{max}(film)/cm^{-1} 2925 (C–H), 2853 (C–H), 1660 (C=C), 1634 (C=C), 1600 (C=C), 1157 (–SO_2–N); δ_H($CDCl_3$, 250 MHz) 1.55–1.71 (3H, m, CH_2), 1.79–1.85 (1H, m, CH_2), 2.01–2.07 (1H, m, CH_2), 2.17–2.42 (2H, m, CH_2, CH_2N), 2.79 (1H, s, NCH), 2.85 (1H dd, *J* 16.2, 1.9, CH_2N), 3.03 (3H, s, CH_3), 3.33 (1H, ddd, *J* 13.9, 8.8, 5.1, CH_2N), 3.49 (1H, dd, *J* 16.3, 4.8, CH_2N), 4.26 (1H, dd, *J* 6.0, 5.8, NCH), 4.90 (1H, d, *J* 10.8, =CH_2), 4.99 (1H, d, *J* 16.6, =CH_2), 5.46 (1H, dd, *J* 9.6, 1.7, =CH), 5.64–5.76 (2H, m, =CH), 7.02 (1H, dd, *J* 7.4, 7.4, ArH), 7.16-7.19 (2H, m, ArH), 7.30 (1H, d, *J* 7.8, ArH); δ_C($CDCl_3$, 62.5 MHz) 25.8 (t), 28.9 (t), 39.7 (q), 40.4 (t), 42.1 (s), 52.6 (t), 52.7 (s), 53.3 (t), 68.7 (d), 70.4 (d), 113.8 (d), 114.4 (t), 123.4 (d), 123.7 (d), 123.8 (d), 128.3 (d), 134.1 (d), 137.1 (s), 139.8 (s), 142.3 (d); *m*/*z* 356 (M^+, 5%), 277 (M^+ − SO_2Me, 10), 79 (100).

N-Methylsulfonylaspidospermidine 29

6-(Methylsulfonyl)-3a-vinyl-3a,4,5,5a,6,11,12,13a-octahydro-1*H*-indolizino[8,1-*cd*]carbazole **28** (70 mg, 0.19 mmol) in ethanol (15 ml) was charged into an oven-dried Parr flask, cooled to room temperature under nitrogen. The solution was degassed by bubbling nitrogen gas through it for 20 min. 10% Pt/C (35 mg, 10% w/w) was added, and the flask was placed in a high pressure hydrogenation apparatus. The system was evacuated and filled with hydrogen gas (4 atm) three times, then filled again and the system was gently shaken for 5 days. The resulting suspension was filtered through Celite, washed repeatedly with ethanol and concentrated to afford a brown oil which was purified by column chromatography (1 : 1.5 ethyl acetate–light petroleum) to afford *N-methylsulfonylaspidospermidine* **29** as a brown oil (41 mg, 58%) (Found: M^+, 360.1878. $C_{20}H_{28}N_2O_2S$ requires *M*, 360.1871); ν_{max}(film)/cm^{-1} 2929 (C–H), 2855 (C–H), 2783 (C–H), 2727 (C–H), 1600 (C=C), 1474 (CH_2), 1459 (CH_2), 1348 (C–H), 1159 (–SO_2–N); δ_H($CDCl_3$, 400 MHz) 0.58 (3H, t, *J* 7.5, CH_3), 0.78–0.81 (1H, m, CH_2), 1.01–1.05 (2H, m, CH_2), 1.31–1.60 (5H, m, CH_2), 1.60–1.70 (1H, m, CH_2), 1.88–2.18 (5H, m, CH_2N, CH_2), 2.21 (1H, s, NCH), 2.93–2.98 [1H (partially overlapping), m, CH_2N], 2.94 (3H, s, CH_3), 3.05 (1H, ddd, *J* 11.9, 8.4, 3.4, CH_2N), 4.17 (1H, dd, *J* 6.5, 6.2, NCH), 6.95 (1H, ddd, *J* 8.0, 8.0, 0.9, ArH), 7.09–7.19 (2H, m, ArH), 7.24 (1H, dd, *J* 7.7, 1.0, ArH); δ_C($CDCl_3$, 100 MHz) 6.9 (q), 21.7 (t), 22.9 (t), 26.7 (t), 30.2 (t), 34.3 (t), 35.6 (s), 39.7 (q), 40.8 (t), 52.8 (t), 53.0 (s), 53.9 (t), 70.5 (d), 71.3 (d), 113.9 (d), 123.5 (d), 123.9 (d), 127.9 (d), 138.7 (s), 139.6 (s); *m*/*z* 360 (M^+, 4%), 281 (M^+ − SO_2Me, 6), 124 (100).

Aspidospermidine 4

To a stirred solution of *N*-methylsulfonylaspidospermidine **29** (32 mg, 0.086 mmol) in dry toluene (5 ml), under nitrogen was added sodium bis(2-methoxyethoxy)aluminium hydride (0.13

ml, 0.43 mmol) as a 70% w/w solution in toluene and the resulting mixture heated to 100 °C for 1 h. The reaction was then cooled, ethyl acetate was added and the mixture was left to stir for 20 min. The solvent was removed *in vacuo* to afford a brown oil which was purified by column chromatography (20 : 1 dichloromethane–methanol) to afford a colourless oil which was further purified by sublimation (110 °C, 0.05 Torr) to afford aspidospermidine **4** as a colourless solid (21 mg, 84%); mp 109–111 °C (Found: M^+, 282.2093. $C_{19}H_{26}N_2$ requires *M*, 282.2096); ν_{max}(KBr)/cm^{-1} 3373 (N–H), 3080 (=C–H), 2962 (C–H), 2780 (C–H), 2729 (C–H), 1608 (C=C); δ_H($CDCl_3$, 400 MHz) 0.63 (3H, t, *J* 7.5, CH_3), 0.84–0.90 (1H, m, CH_2), 1.03–1.15 (2H, m, CH_2), 1.32–1.52 (4H, m, CH_2), 1.61–1.64 (2H, m, CH_2), 1.64–1.72 (1H, m, CH_2), 1.95–1.98 (2H, m, CH_2, CH_2N), 2.22 (1H, s, NCH), 2.25–2.31 (2H, m, CH_2, CH_2N), 2.31–2.71 (1H, br m, NH), 3.04–3.07 (1H, br m, CH_2N), 3.07–3.12 (1H, br m, CH_2N), 3.40–3.50 (1H, br m, NCH), 6.63 (1H, d, *J* 7.7, ArH), 6.72 (1H, dd, *J* 7.7, 7.7, ArH), 7.01 (1H, dd, *J* 7.7, 7.7, ArH), 7.07 (1H, d, *J* 7.7, ArH); δ_C($CDCl_3$, 100 MHz) 7.0 (q), 21.9 (t), 23.2 (t), 28.3 (t), 30.2 (t), 34.7 (t), 35.9 (s), 39.0 (t), 53.2 (t), 53.6 (s), 54.1 (t), 65.9 (d), 71.5 (d), 110.6 (d), 119.2 (d), 123.0 (d), 127.3 (d), 135.9 (s), 149.6 (s); *m*/*z* 282 (M^+, 7%), 254 (8), 124 (100).

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