Tetrathiafulvalene-mediated stereoselective synthesis of the tetracyclic core of *Aspidosperma* alkaloids

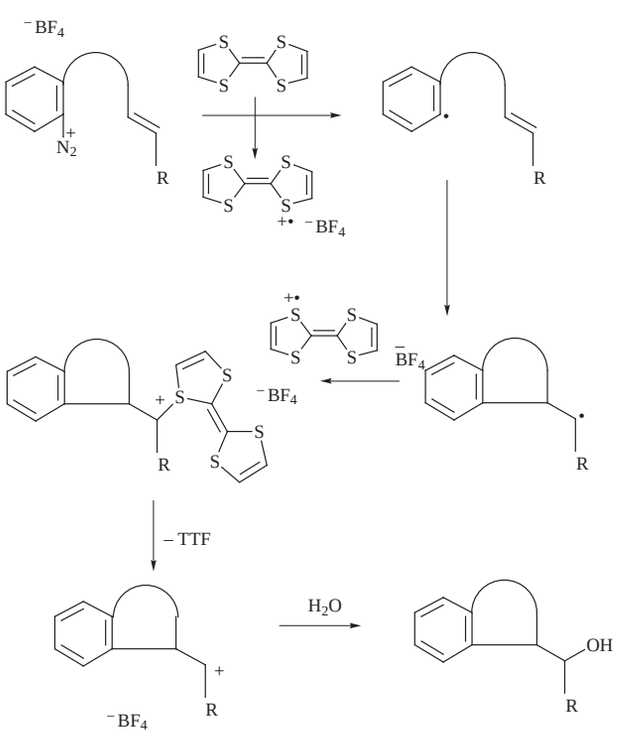
Rodney Fletcher,[b] Murat Kizil,[b] Christopher Lampard,[a,b] John A. Murphy *[,a,b] and Stephen J. Roome[b]

[a] *Department of Pure and Applied Chemistry, The University of Strathclyde, 295 Cathedral Street, Glasgow, UK G1 1XL*
[b] *Department of Chemistry, University of Nottingham, University Park, Nottingham, UK NG7 2RD*

A novel route to advanced synthetic precursors of *Aspidosperma* alkaloids is described, utilising radical-polar crossover reactions.

Introduction

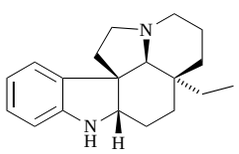
In previous papers,[1] we have demonstrated a novel one-pot reaction cascade featuring (i) aryl radical generation, (ii) cyclisation, (iii) radical trapping on sulfur with the radical-cation of tetrathiafulvalene ($TTF^{\bullet+}$) to form a sulfonium salt, and (iv) S_N1 substitution — a sequence of reactions which was named a 'radical-polar crossover' sequence (Scheme 1). The efficiency of



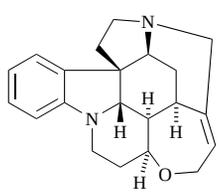
Scheme 1

this sequence, the mildness of the conditions (room temperature, acetone as solvent) and the catalytic use of TTF all suggested that the reaction had synthetic promise, so the prospect of extending this chemistry to the synthesis of generic precursors of complex molecules was attractive.

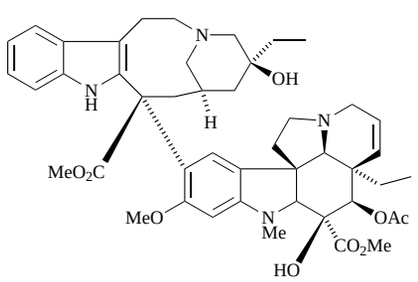
The alkaloids aspidospermidine **1**, strychnine **2** and vinblastine **3** feature a common tetracyclic core **4** which is a worthy synthetic target.[2,3] Our approaches to this heterocyclic skeleton *via* 'radical-polar crossover' reactions are described in this paper.[4]



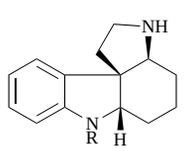
Aspidospermidine **1**



Strychnine **2**



Vinblastine **3**



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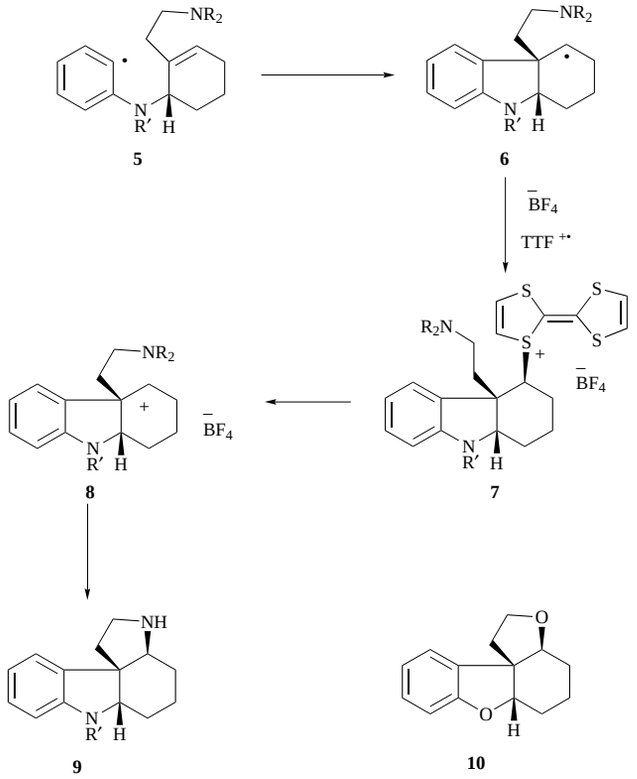
Results and discussion

Our initial strategy to synthesise this tetracyclic core is shown in Scheme 2 featuring cyclisation of an aryl radical **5**, functionalisation and substitution. Ample precedent in radical cyclisation chemistry indicates the cyclisation to the indoline **6** to give a *cis* ring-junction, and this would place the pendant side-chain above the cyclohexyl cation ring in cation **8** to afford tetracyclic product **9** of required stereochemistry.

Our first aim was to see if it was possible to prepare a tetracyclic skeleton. The use of two oxygen heteroatoms as in **10** was expected to provide an easier initial target than the nitrogen heterocycle **9**, and so **10** became the initial target. This molecule was successfully prepared as follows. Anisic acid **11** was reduced *via* a precedented Birch reduction, adding allyl bromide to quench the intermediate dianion.[5] Acid hydrolysis afforded allyl enone **12** (Scheme 3). Luche reduction of this compound afforded the cyclohexenol **13**. The stereochemistry of this molecule governs the relative stereochemistry at all other centres in the tetracycle **10**. Although **13** was used as a racemic mixture, it has previously been prepared in an enantiomerically pure form,[6] and this suggests that any racemic product prepared in this paper may ultimately be prepared as an enantiomerically pure product. (Mitsunobu reactions on cyclohexenols such as **13** have been demonstrated[7] to proceed by an S_N2 mechanism).

Mitsunobu coupling of **13** with *o*-nitrophenol **14a** yielded **15a**, the terminal allyl group of which was then oxidised to an aldehyde **17a**. This was achieved in a two stage process with



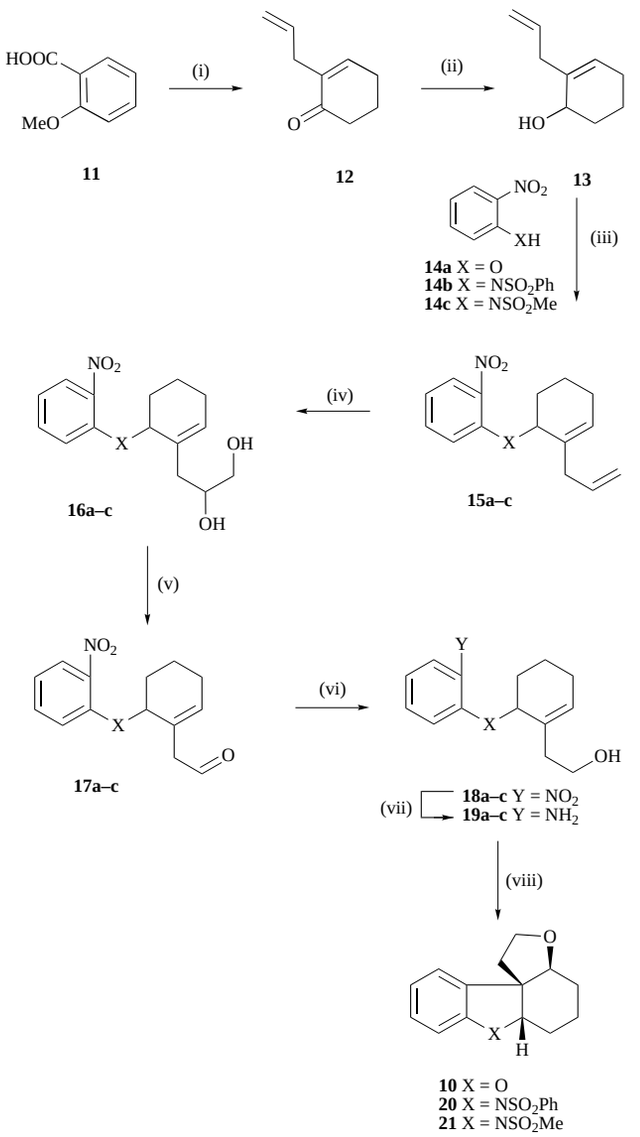
Scheme 2

excellent selectivity. Reduction afforded alcohol **18a**, and this nitro-compound was converted to the corresponding amine **19a** and, following diazotisation, treated with TTF, affording a single isomer of a tetracyclic ether **10**. It was not possible to confirm the relative stereochemistry by X-ray crystallography at this stage (for information regarding stereochemistry of cyclisation, see below).

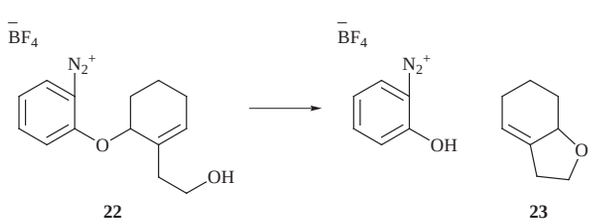
The intermediate diazonium tetrafluoroborate **22**, unlike most salts previously encountered in our work, could not be isolated as a solid from these reactions, and hence was used *in situ*. However the low yield of the tetracycle was noted. By-product **23** (Scheme 4) was tentatively identified in some of these reactions and provided a possible explanation for this. This compound could arise by attack of the pendant alcohol group in **22** on the ring-alkene to cause elimination of the arene; the activation of the leaving group by the electron-withdrawing diazonium group would play an important role in this reaction. The formation of **23** was minimised by performing the diazotisation reaction at low temperature and adding the TTF as soon as diazotisation was complete.

If this theory was correct, then replacing the oxygen linkage between the two rings in **22** by a nitrogen should afford a more robust molecule, and presumably a higher yield in the crucial TTF cyclisation reaction. Accordingly, the amines **19b** and **19c** were prepared and, following diazotisation, treated with TTF in acetone. These reactions afforded significantly improved yields of the corresponding tetracycles **20** and **21**, and again, both compounds were obtained as single isomers. Both were also crystalline solids and so, by obtaining an X-ray crystal structure determination on **20**, the expected relative stereochemistry of the cyclisation steps was confirmed.[1h]

The next problem to solve was how to introduce the second nitrogen of **9**. In principle this could easily be achieved by using an appropriate nitrogen nucleophile to intercept the intermediate cation **8**. However, the only nitrogen nucleophile which had so far been employed successfully in radical-polar crossover reactions was acetonitrile, and so questions now arose about the nature of the nitrogen nucleophile in this step. An intramolecular nitrile group would require severe distortion to

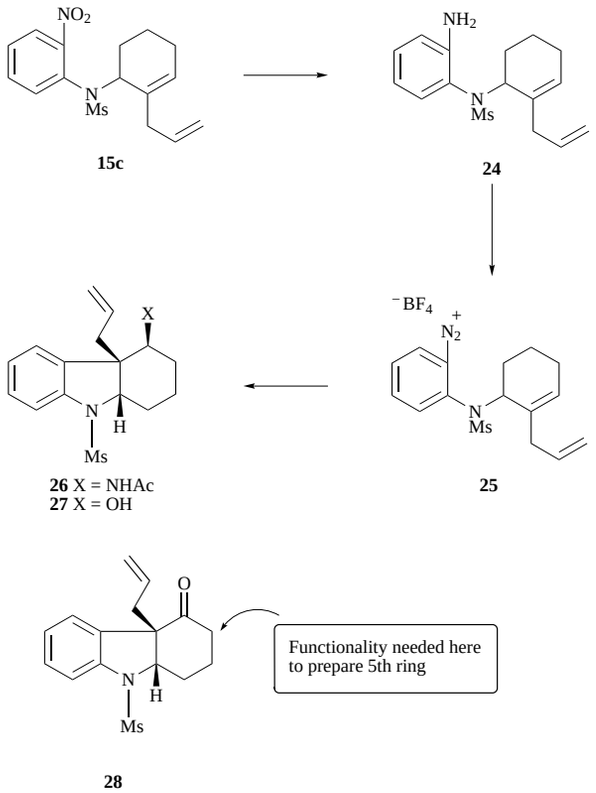


Scheme 3 *Reagents and conditions*: (i) NH_3(l), Na, −78 °C; CH_2=CH-CH_2Br, −78 °C to rt; HCl, H_2O, reflux, 33%; (ii) $CeCl_3$, $NaBH_4$, MeOH, 15 min, 71%; (iii) Ph_3P, DEAD, THF, 0 °C to rt, (a) 2-NO_2-C_6H_4OH, 2 h, 96%; Ph_3P, DEAD, THF, 0 °C to rt, (b) 2-NO_2-$C_6H_4NHSO_2Ph$ 2 h, 97%; Ph_3P, DEAD, THF, 0 °C to rt, (c) 2-NO_2-$C_6H_4NHSO_2Me$ 1h, 76%; (iv) OsO_4, NMO, acetone, H_2O, Bu^{t}OH, (a) 15 h, 99%; (b) 24 h, 72%; (c) 20 h, 62%; (v) $NaIO_4$, Et_2O, H_2O, MeOH, (a) 17 h, 100%; (b) 20 h, 91%; (c) 4.5 h, 97%; (vi) $NaBH_4$, MeOH, (a) 5 min, 92%; (b) 2 min, 86%; (c) 10 min, 91%; (vii) $Cu(acac)_2$, $NaBH_4$, EtOH, (a) 1.5 h, 98%; (b) 2.5 h, 24%; (c) 2 h, 60%. (viii) $NOBF_4$, DCM, −10 °C, (a) 5 min; (b) and (c) 1.5 h and then TTF, acetone, (a) 30 min, 27%; (b) 2 h, 68%; (c) 2 h, 75%



Scheme 4

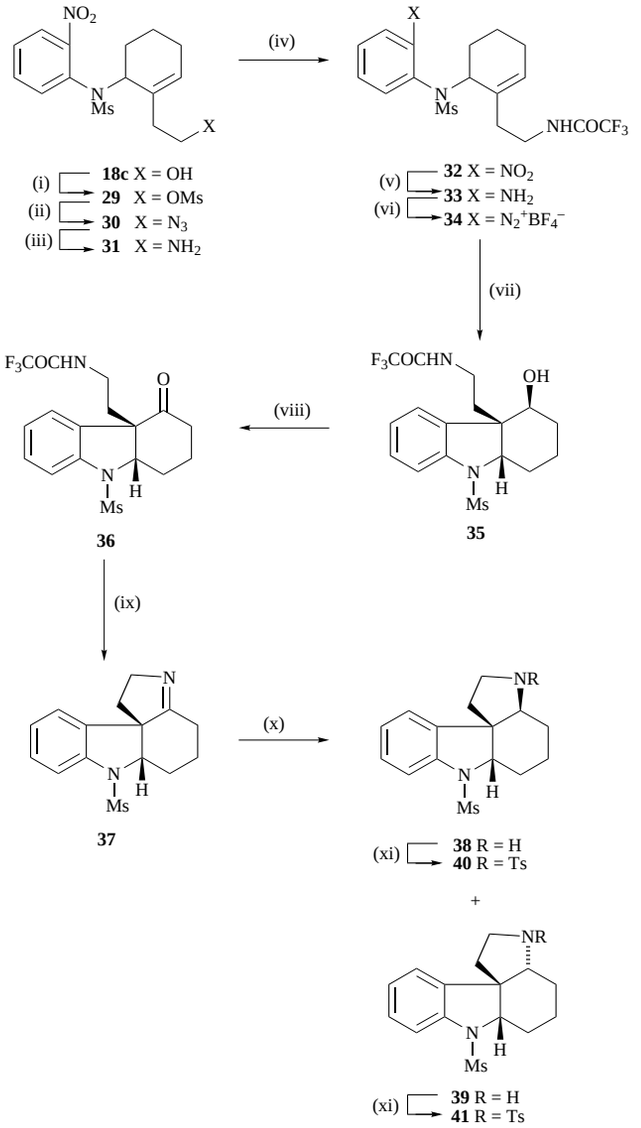
achieve the trajectory needed to trap the carbocation intermediate using the *sp* orbital containing its N-lone pair. An alternative approach would use acetonitrile and TTF to convert diazonium salt **25** to amide **26** (Scheme 5). Subsequent transformation to **9** should be achieved by standard reactions. However, at this stage we contemplated the possibility of natural product synthesis using TTF chemistry and the difficult ques-



Scheme 5

tion of how to introduce the fifth ring of aspidospermidine or the vindoline portion of vinblastine. Plainly, this would be very difficult using **26** as a synthetic intermediate, and so modification was needed. A solution would be to cyclise **25** in moist acetone rather than acetonitrile. Oxidation of the resulting alcohol **27** to ketone **28** would then allow further functionalisation at the desired position α to the carbonyl group, by enolate chemistry; the ketone group would also be convenient for the formation of the five-membered ring of **9**.

The route followed is shown in Scheme 6. Here, to facilitate the formation of the five-membered ring, the side-chain alcohol function of **18c** was converted to the corresponding trifluoroacetamide **32**. Reduction to the corresponding amine **33**, diazotisation to **34** and treatment with TTF in moist acetone afforded alcohol **35** which was oxidised to ketone **36**. Deprotection of the trifluoroacetamide liberated the primary amine which spontaneously afforded the imine **37**. Reduction of the imine[2] in turn yielded the tetracycles **38** and **39** in a 7:3 ratio, isolated following protection as the corresponding toluenesulfonamides **40** and **41**. Compound **40**, the major isomer, was identical by spectroscopy and mixed melting point with a sample prepared by another route[8] the structure of which had been confirmed by X-ray crystallographic analysis.[9]



Scheme 6 *Reagents and conditions*: (i) $MeSO_2Cl$, Et_3N, DCM, 19 h, 70%; (ii) NaN_3, DMF, 96%; (iii) $HS(CH_2)_3SH$, Et_3N, Pr^iOH, $NaBH_4$, 48 h followed by (iv) $(CF_3CO)_2O$, Et_3N, DMAP, THF, 0 °C to rt, 4 d, 87% over 2 steps; (v) $NaBH_4$, $Cu(acac)_2$, EtOH, 1 h, 70%, (vi) $NOBF_4$, DCM, 0 °C, 1 h (vii) TTF, acetone, H_2O, 2 d, 45% over two steps; (viii) PCC, DCM, 18 h, 83%; (ix) K_2CO_3, H_2O, MeOH, 24 h, 79%; (x) $NaBH_4$, MeOH, 2 h and then (xi) TsCl, DMAP, pyridine, reflux, 20 h, 100%

Conclusion

In summary, this paper details[4] the application of radical-polar crossover chemistry to the synthesis of a tetracyclic synthetic precursor of complex alkaloids.

Experimental

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 AM400 machine. ^{13}C NMR spectra were recorded at 67.5 MHz on a JEOL EX270 or at 100 MHz on a Bruker AM400 machine. NMR experiments were carried out in deuterochloroform, [$^2H_4$]methanol, [$^2H_6$]acetone, [$^2H_3$]acetonitrile or [$^2H_6$]dimethyl sulfoxide with tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (ppm). The following abbreviations are used for multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants 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. 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-(Prop-2-enyl)cyclohex-2-en-1-ol 13

To a solution of 2-(prop-2-enyl)cyclohex-2-en-1-one[5] **12** (1 g, 7.4 mmol, 1.0 equiv.) in methanol (20 ml) was added cerium trichloride heptahydrate (2.76 g, 7.4 mmol, 1.0 equiv.) and the mixture stirred at 0 °C for 5 min before the addition of sodium boranuide (279 mg, 7.4 mmol, 1.0 equiv.). After 10 min the reaction was quenched by the addition of water (20 ml) and then the methanol was removed by rotary evaporation. The resulting aqueous mixture was extracted with diethyl ether (5 × 50 ml), dried over magnesium sulfate, filtered and evaporated and purified by distillation [bp 60–64 °C at 0.3 mmHg] to give 2-(prop-2-enyl)cyclohex-2-en-1-ol[6] **13** as a clear colourless oil (721 mg, 5.2 mmol, 71%); ν_{max}(film)/cm^{-1} 3342, 3076, 2935, 2835, 1639, 1434; δ_H(250 MHz, $CDCl_3$) 1.53–2.03 (6H, m, $CH_2CH_2CH_2$), 2.84–2.86 (2H, m, CCH_2CH), 4.05 (1H, s, HOCH), 5.01–5.11 (2H, m, $CH{=}CH_2$), 5.57 (1H, m, C=CH), 5.83 (1H, ddt, *J* 11.9, 10.1 and 6.9, $CH{=}CH_2$); δ_C(67.5 MHz, $CDCl_3$) 17.6 (t), 25.4 (t), 31.9 (t), 38.7 (t), 66.6 (d), 115.9 (t), 126.1 (d), 136.9 (d), 137.6 (s); *m*/*z* (FAB) 139 [$(MH)^+$, 3%], 121 (18), 95 (25), 91 (30), 79 (36), 41 (100).

1-(2-Nitrophenoxy)-2-(prop-2-enyl)cyclohex-2-ene 15a

o-Nitrophenol **14a** (938 mg, 6.75 mmol, 1.5 equiv.) and triphenylphosphine (1.77 g, 6.75 mmol, 1.5 equiv.) were dissolved in dry tetrahydrofuran (50 ml). 2-(Prop-2-enyl)cyclohex-2-en-1-ol **13** (621 mg, 4.5 mmol, 1.0 equiv.) was added and the mixture cooled to 0 °C. Diethyl azodicarboxylate (1.17 g, 1.06 ml, 6.75 mmol, 1.5 equiv.) was added dropwise over 15 min. After 2 h, the mixture was evaporated to dryness, dissolved in dichloromethane (100 ml) and washed with sodium hydroxide (2 M, 2 × 100 ml) and hydrochloric acid (2 M, 2 × 100 ml) before drying over magnesium sulfate. The solution was evaporated to dryness and purified by column chromatography on silica gel [2% diethyl ether–light petroleum] to give 1-(2-*nitrophenoxy*)-2-(*prop*-2-*enyl*)*cyclohex*-2-*ene* **15a** as a clear yellow oil (1.12 g, 4.3 mmol, 96%) (Found MNH_4^+, 277.1552. $C_{15}H_{17}NO_3$ requires MNH_4 277.1552) ν_{max}(film)/cm^{-1} 3076, 2916, 1604, 1581, 1524, 1482, 1355, 744; δ_H(400 MHz, $CDCl_3$) 1.56–1.81 (2H, m, $OCHCH_2$), 1.97–2.02 (2H, m, $CH_2CH_2CH{=}C$), 2.12–2.17 (1H, m, $CH_2CH{=}C$), 2.87–2.89 (2H, m, $CHCH_2C$), 4.81 (1H, m, OCH), 4.96–5.01 (2H, m, $CH_2{=}CH$), 5.74–5.84 (1H, m, $CH_2{=}CH$), 5.78 (1H, m, $C{=}CHCH_2$), 6.98 (1H, dd, *J* 8.3 and 8.3, ArH), 7.13 (1H, d, *J* 8.4, ArH), 7.48 (1H, dd, *J* 8.5 and 8.5, ArH), 7.73 (1H, d, *J* 8.3, ArH); δ_C(100 MHz, $CDCl_3$) 17.9 (t), 25.3 (t), 27.8 (t), 38.7 (t), 74.4 (d), 115.7 (d), 116.4 (t), 120.0 (d), 125.3 (d), 129.0 (d), 133.6 (d), 134.0 (s), 136.3 (d), 141.2 (s), 151.6 (s); *m*/*z* (FAB) 260 [$(MH)^+$, 2%]. 213 (2), 137 (7), 122 (39), 121 (100).

1-(2-Nitrophenoxy)-2-(2,3-dihydroxypropyl)cyclohex-2-ene 16a

To a stirred solution of 1-(2-nitrophenoxy)-2-(prop-2-enyl)-cyclohex-2-ene **15a** (550 mg, 2.1 mmol, 1.0 equiv.) in acetone–water (20 ml, 9 : 1) was added a solution of osmium tetroxide (7.55 ml of 5 mg ml^{-1} solution in *tert*-butyl alcohol, 38 mg, 0.15 mmol, 7 mol%) followed by *N*-methylmorpholine *N*-oxide (298 mg, 2.55 mmol, 1.2 equiv.) and the mixture stirred for 15 h. Aqueous sodium bisulfite (5% w/v, 10 ml) was then added and the mixture evaporated to remove acetone before extracting with dichloromethane (5 × 30 ml). The organic phase was washed with hydrochloric acid (2 M, 2 × 50 ml) and water (3 × 50 ml) before drying over magnesium sulfate, evaporating to dryness and purifying by column chromatography on silica gel eluting with diethyl ether to give 1-(2-*nitrophenoxy*)-2-(2,3-*dihydroxypropyl*)*cyclohex*-2-*ene* **16a** as a clear yellow oil [615 mg, 2.09 mmol, 99% (as a mixture of diastereoisomers, combined yield)]; ν_{max}(film)/cm^{-1} 3385, 3012, 2935, 2867, 1604, 1581, 1523, 1480, 1051, 747; a small quantity of each separate isomer was isolated during this chromatography. Data for the diastereoisomer 1 (Found MNH_4^+, 311.1607. $C_{15}H_{19}NO_5$ requires MNH_4 311.1607); δ_H(250 MHz, $CDCl_3$) 1.26–1.85 (3H, m, $CH_2CH_2CH_2$), 1.95–2.23 (4H, m, $CH_2CH_2CH_2$ and CH_2C), 2.48 (1H, dd, *J* 14.6 and 2.6, $CH_2CH{=}C$), 2.50–3.00 (2H, br s, 2 × OH), 3.39–3.48 (1H, m, CH_2OH), 3.64–3.70 (1H, dd, *J* 11.2 and 3.0, CH_2OH), 3.79–3.88 (1H, m, C*H*OH), 4.90 (1H, m, ArOCH), 5.90 (1H, m, C=CH), 7.01 (1H, dd, *J* 8, 8, ArH), 7.15 (1H, d, *J* 8, ArH), 7.15 (1H, dd, *J* 8, 8, ArH), 7.77 (1H, d, *J* 8, ArH); δ_C(67.5 MHz, $CDCl_3$) 15.5 (t), 25.7 (t), 27.4 (t), 40.0 (t), 66.8 (t), 70.9 (d), 75.3 (d), 115.9 (d), 120.7 (d), 126.2 (d), 131.5 (s), 132.5 (d), 134.5 (d), 141.2 (s) and 151.2 (s). Data for diastereoisomer 2 (Found MNH_4^+, 311.1607. $C_{15}H_{19}NO_5$ requires MNH_4 311.1607); δ_H(250 MHz, $CDCl_3$) 1.56–1.75 (3H, m, $CH_2CH_2CH_2$), 2.01–2.05 (3H, m, $CH_2CH_2CH_2$), 2.21 (1H, d, *J* 13.7, $CH_2C{=}CH$), 2.32 (1H, dd, *J* 13.5 and 9.6, $CH_2C{=}CH$), 3.46 (1H, dd, *J* 11.2 and 7.2, CH_2OH), 3.60 (1H, dd, *J* 11.2 and 3.3, CH_2OH), 3.87 (1H, m, C*H*OH), 4.91 (1H, m, CHOAr), 5.93 (1H, m, C=CH), 7.00 (1H, dd, *J* 8, 8, ArH), 7.17 (1H, d, *J* 8, ArH), 7.53 (1H, dd, *J* 8, 8, ArH), 7.83 (1H, d, *J* 8, ArH); δ_C(67.5 MHz, $CDCl_3$) 17.5 (t), 25.1 (t), 26.9 (t), 38.4 (t), 66.1 (t), 70.4 (d), 74.4 (d), 115.5 (d), 120.1 (d), 125.3 (d), 131.4 (d), 131.6 (s), 133.7 (d), 140.8 (s) and 150.8 (s); *m*/*z* (FAB) 155 (16%), 137 (12), 91 (33), 55 (83).

[6-(2-Nitrophenoxy)cyclohex-1-enyl]acetaldehyde 17a

To a stirred solution of 1-(2-nitrophenoxy)-2-(2,3-dihydroxypropyl)cyclohex-2-ene **16a** (98.1 mg, 0.33 mmol, 1.0 equiv.) in diethyl ether (5 ml) was added sodium periodate (88.3 mg, 0.41 mmol, 1.25 equiv.) followed by water (0.2 ml) and the mixture stirred. After 16 h another portion of sodium periodate was added (35 mg, 0.16 mmol, 0.5 equiv.) and the mixture stirred for a further 1 h. The two-phase reaction mixture was then extracted with diethyl ether (3 × 20 ml) which was then dried over magnesium sulfate and evaporated to dryness to give [6-(2-*nitrophenoxy*)*cyclohex*-1-*enyl*]*acetaldehyde* **17a** as a yellow oil (91.5 mg, 0.35 mmol, 100%) (Found MNH_4^+, 279.1345. $C_{15}H_{19}NO_5$ requires MNH_4 279.1345). ν_{max}(film)/cm^{-1} 2937, 2866, 2836, 1721, 1603, 1582, 1524, 1482, 745; δ_H(400 MHz, $CDCl_3$) 1.60–1.70 (1H, m, $CH_2CH_2CH_2$), 1.72–1.85 (1H, m, $CH_2CH_2CH_2$), 1.87–2.03 (2H, m, $OCHCH_2$), 2.05–2.14 (1H, m, $C{=}CHCH_2$), 2.16–2.27 (1H, m, $C{=}CHCH_2$), 3.32 (1H, br d, *J* 16.6, $OHCCH_2$), 3.39 (1H, br d, *J* 16.6, $OHCCH_2$), 4.90 (1H, m, ArOCH), 5.92 (1H, t, *J* 3.6, C=CH), 7.01 (1H, dd, *J* 8, 8, ArH), 7.11 (1H, d, *J* 8, ArH), 7.49 (1H, dd, *J* 8, 8, ArH), 7.76 (1H, d, *J* 8, ArH), 9.66 (1H, t, *J* 1.9, CHO); δ_C(100 MHz, $CDCl_3$) 17.7 (t), 25.1 (t), 27.3 (t), 49.0 (t), 74.9 (d), 115.5 (d), 120.3 (d), 125.2 (d), 127.9 (s), 133.1 (d), 133.6 (d), 140.8 (s), 150.7 (s) and 200.2 (d); *m*/*z* (FAB) 137 (10%) 123 (29), 95 (52), 81 (50), 69 (82).

2-[6-(2-Nitrophenoxy)cyclohex-1-enyl]ethanol 18a

To a stirred solution of [6-(2-nitrophenoxy)cyclohex-1-enyl]-acetaldehyde **17a** (91.5 mg, 0.35 mmol, 1.0 equiv.) in methanol (5 ml) was added sodium boranuide (13.4 mg, 0.35 mmol, 1.0 equiv.) and the mixture stirred for 5 min. Water (5 ml) was added and then the mixture evaporated to remove methanol before extracting with dichloromethane (5 × 20 ml). The organic phase was washed with water (2 × 20 ml), dried over magnesium sulfate and evaporated to dryness to give 2-[6-(2-*nitrophenoxy*)*cyclohex*-1-*enyl*]*ethanol* **18a** as a clear yellow oil (84.7 mg, 0.32 mmol, 92%) (Found M^+, 263.1158. $C_{14}H_{17}NO_4$ requires *M* 263.1158). ν_{max}(film)/cm^{-1} 3379, 3076, 2838, 1603, 1581, 1523, 1451, 1354, 744; δ_H(400 MHz, $CDCl_3$) 1.70–1.80 (2H, m, $OCHCH_2CH_2$), 1.97–2.07 (3H, m, $CH_2CH_2CH_2$), 2.16–2.21 (1H, m, $C{=}CHCH_2$), 2.30 (1H, dtd, *J* 14.4, 7.6 and 1.2,

CH_2CH_2C), 2.51 (1H, dtd, *J* 14.4, 7.8 and 1.1, CH_2CH_2C), 3.68–3.72 (2H, m, CH_2OH), 4.88 (1H, m, ArOCH), 5.89 (1H, t, *J* 3.6, C=CH), 7.01 (1H, dd, *J* 8, 8, ArH), 7.16 (1H, d, *J* 8, ArH), 7.51 (1H, dd, *J* 8, 8, ArH), 7.79 (1H, d, *J* 8, ArH); δ_C(67.5 MHz, $CDCl_3$) 17.2 (t), 25.1 (t), 27.0 (t), 38.1 (t), 60.8 (t), 74.4 (d), 115.3 (d), 120.0 (d), 125.4 (d), 130.8 (d), 131.7 (s), 133.7 (d), 140.6 (s), 150.8 (s); *m*/*z* (FAB) 139 (5%), 125 (43), 93 (25).

2-[6-(2-Aminophenoxy)cyclohex-1-enyl]ethanol 19a

Copper(II) acetylacetonate (65 mg, 0.25 mmol, 0.2 equiv.) was suspended in ethanol (65 ml). Sodium boranuide (0.24 g, 6.2 mmol, 5 equiv.) was then added forming a brown solution which gradually faded and a granular precipitate formed. A solution of 2-[6-(2-nitrophenoxy)cyclohex-1-enyl]ethanol **18a** (327 mg, 1.24 mmol, 1.0 equiv.) in ethanol (5 ml) was then added followed by a further addition of sodium boranuide (0.48 g, 12.4 mmol, 10 equiv.). The mixture was stirred at room temperature until TLC indicated complete reaction (2 h). Water (60 ml) was added and the ethanol was removed by rotary evaporation. The residue was extracted with dichloromethane, dried over magnesium sulfate and evaporated to afford 2-[6-(2-*aminophenoxy*)*cyclohex*-1-*enyl*]*ethanol* **19a** as a clear yellow oil (282 mg, 1.22 mmol, 98%) (Found M^+, 233.1454. $C_{14}H_{19}NO_2$ requires *M* 233.1416); ν_{max}(film)/cm^{-1} 3373, 3004, 2937, 1612, 1502, 753; δ_H(400 MHz, $CDCl_3$) 1.54–1.72 (3H, m, OCH-CH_2CH_2), 1.95–2.02 (2H, m, CH_2CH_2CH=C), 2.10–2.16 (1H, m, C=CHCH_2), 2.24–2.31 (1H, ddd, *J* 14, 7 and 7, CH_2C=CH), 2.40–2.45 (1H, ddt, *J* 14, 7 and 7, CH_2C=CH), 3.30–3.60 (3H, m, OH and NH_2), 3.65 (2H, m, CH_2OH), 4.64 (1H, s, ArOCH), 5.80 (1H, m, C=CH), 6.67–6.85 (4H, m, ArH); δ_C(100 MHz, $CDCl_3$) 17.7 (t), 25.4 (t), 27.5 (t), 38.3 (t), 61.2 (t), 73.3 (d), 113.2 (d), 115.6 (d), 118.4 (d), 121.3 (d), 129.7 (d), 133.3 (s), 137.1 (s), 145.4 (s); *m*/*z* (FAB) 234 [$(MH)^+$, 3.1%)] 125 (6), 109 (42), 93 (23), 55 (100).

1,2,4,5,6,6a-Hexahydro-3a*H*-benzofuro[4,3a-*b*]benzofuran 10

To a stirred solution of 2-[6-(2-aminophenoxy)cyclohex-1-enyl]ethanol **19a** (119 mg, 0.52 mmol, 1.0 equiv.) in dichloromethane (3 ml) at 0 °C was added nitrosonium tetrafluoroborate (60 mg, 0.52 mmol, 1.0 equiv.) and the mixture stirred for 5 min. The solvent was removed under a strong stream of nitrogen and the red oil obtained dissolved immediately in acetone (3 ml). Tetrathiafulvalene (106 mg, 0.52 mmol, 1.0 equiv.) was added and the mixture stirred for 30 min. The mixture was poured into cold diethyl ether (50 ml) and then filtered. The filtrate was evaporated to dryness, dissolved in chloroform (50 ml), washed with water (3 × 50 ml), dried over magnesium sulfate and evaporated to dryness to give a brown oil that was purified by chromatography on silica gel (5% diethyl ether–light petroleum) to give a pale yellow solid. Upon recrystallisation (ethyl acetate–diethyl ether), 1,2,4,5,6,6a-*hexahydro*-3aH-*benzofuro*[4,3*a*-b]*benzofuran* **10** (30 mg, 0.14 mmol, 27%) was obtained as white prisms, mp 53–55 °C (Found M^+, 216.1151. $C_{14}H_{16}O_2$ requires *M*, 216.1150) ν_{max}(disc)/cm^{-1} 2959, 2924, 2861, 1592, 1479, 758; δ_H(250 MHz, $CDCl_3$) 1.49–1.63 (4H, m, $CH_2CH_2CH_2$), 1.77–1.82 (1H, m, $CH_2CH_2CH_2$), 1.91–2.09 (1H, m, $CH_2CH_2CH_2$), 2.11 (1H, ddd, *J* 12.8, 8.6 and 8.6, CH_2-CH_2O), 2.26 (1H, ddd, *J* 12.8, 8.6 and 8.4, CH_2CH_2O), 3.96–4.14 (2H, m, CH_2O), 4.17 (1H, dd, *J* 4.6 and 3.2, CH_2CHO), 4.54 (1H, dd, *J* 6.9 and 6.8, ArOCH), 6.82 (1H, d, *J* 7.9, ArH), 6.90 (1H, dd, *J* 7.7 and 7.7, ArH), 7.11–7.19 (2H, m, ArH); δ_C(100 MHz, $CDCl_3$) 16.1 (t), 26.9 (t), 29.8 (t), 40.1 (t), 53.2 (s), 66.4 (t), 80.2 (d), 86.7 (d), 110.3 (d), 121.0 (d), 122.7 (d), 128.8 (d), 131.8 (s) and 159.0 (s); *m*/*z* (EI^+) 216 (M^+, 100%), 188 (20), 171 (85), 144 (38), 131 (37).

***N*-(2-Nitrophenyl)benzenesulfonamide 14b**

2-Nitroaniline (10 g, 72 mmol), benzenesulfonyl chloride (15.26 g, 86.4 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (2.4 g, 20 mmol) were dissolved in pyridine (80 ml) and heated at reflux for 18 h. The cooled reaction mixture was diluted with dichloromethane (500 ml), washed with aqueous hydrochloric acid (2 M, 2 × 200 ml) and extracted with aqueous sodium hydroxide (2 M, 3 × 300 ml). The combined aqueous layers were acidified with concentrated hydrochloric acid and then extracted with dichloromethane (2 × 300 ml). The combined organic extracts were dried over magnesium sulfate, filtered and evaporated to dryness to give *N*-(2-nitrophenyl)benzenesulfonamide **14b** as a red–brown solid, mp 97–99 °C (lit.,[8] 101–102 °C) (14.2 g, 71%), δ_H($CDCl_3$, 400 MHz) 7.17 (1H, dt, *J* 1.3, 8.0, ArH), 7.46–7.61 (4H, m, ArH), 7.83–7.86 (3H, m, ArH), 8.10 (1H, dd, *J* 1.3, 8.0, ArH) and 9.87 (1H, s, NH); δ_C($CDCl_3$, 67.5 MHz) 120.65 (d), 123.79 (d), 125.95 (d), 126.94 (d), 129.20 (d), 133.42 (d), 133.57 (d), 135.76 (d), 136.80 (s) and 138.29 (s).

***N*-(2-Nitrophenyl)-*N*-(2-prop-2-enylcyclohex-2-enyl)benzenesulfonamide 15b**

N-(2-Nitrophenyl)benzenesulfonamide **14b** (500 mg, 1.8 mmol) and triphenylphosphine (0.71 g, 2.7 mmol) were dissolved in tetrahydrofuran (25 ml) and, under nitrogen, 2-prop-2-enylcyclohex-2-enol **13** (373 mg, 2.7 mmol) and diethyl azodicarboxylate (470 mg, 2.7 mmol) were added. The mixture was stirred for 2 h and then evaporated to dryness. The resulting slurry was recrystallised from ethyl acetate to remove triphenylphosphine oxide and then from tetrachloromethane to remove reduced diethyl azodicarboxylate. Finally, purification by column chromatography on silica gel (6:1 petrol–ethyl acetate) gave N-(2-*nitrophenyl*)-N-(2-*prop*-2-*enylcyclohex*-2-*enyl*)-*benzenesulfonamide* **15b** as a light brown solid (696 mg, 97%), mp 102–103.5 °C (ethyl acetate–light petroleum) (Found: C, 63.29; H, 5.72; N, 6.96. $C_{21}H_{22}N_2SO_4$ requires C, 63.3; H, 5.56; N, 7.03%); ν_{max}(disc)/cm^{-1} 3073, 2939, 2833, 1601, 1535, 1446, 1351, 1160, 1092 and 721; δ_H($CDCl_3$, 400 MHz) (This compound and many of the subsequent compounds were present as rotameric mixtures; the spectra quoted are those at the ambient operating temperature of the spectrometer) 0.10–0.20 and 0.85–2.70 (8H, m, 4 × CH_2), 4.45–4.70 (1H, m, HCN), 4.75–5.10 (2H, m, CH_2=), 5.50–5.70 (2H, m, CH= × 2), 6.85–6.95, 7.40–7.75 and 7.90–8.05 (9H, m, ArH); δ_C($CDCl_3$, 67.5 MHz) 16.58 (t), 17.38 (t), 23.94 (t), 24.64 (t), 27.26 (t), 29.63 (t), 37.76 (t), 38.19 (t), 56.17 (d), 58.10 (d), 115.35 (t), 115.71 (t), 124.89 (d), 125.64 (d), 127.21 (d), 128.09 (d), 128.84 (d), 128.90 (d), 130.89 (d), 131.14 (s), 131.98 (d), 132.49 (d), 132.78 (d), 133.03 (d), 133.69 (d), 135.50 (d), 136.57 (d), 139.93 (s), 140.22 (s), 149.79 (s) and 149.94 (s); *m*/*z* (CI^+) 416 [(MNH_4^+), 25%] 369 (20), 229 (65), 121 (45) and 109 (100).

***N*-[2-(2,3-Dihydroxypropyl)cyclohex-2-enyl]-*N*-(2-nitrophenyl)-benzenesulfonamide 16b**

To a solution of *N*-(2-nitrophenyl)-*N*-(2-prop-2-enylcyclohex-2-enyl)benzenesulfonamide **15b** (200 mg, 0.5 mmol) in acetone–water (9:1) (40 ml), osmium tetroxide (12.8 mg, 0.05 mmol) and then 4-methylmorpholine *N*-oxide (70.6 mg, 0.6 mmol) were added and the mixture stirred under nitrogen for 24 h. Then, aqueous sodium bisulfite (5%, 10 ml) was added and most of the acetone evaporated *in vacuo*. The resulting aqueous solution was extracted with dichloromethane (5 × 30 ml) and the combined extracts washed with aqueous hydrochloric acid (2 M, 2 × 30 ml) and water (30 ml), dried over magnesium sulfate, filtered and evaporated to dryness. Purification by column chromatography on silica gel eluting with (6:4 dichloromethane–diethyl ether) gave N-[2-(2,3-*dihydroxypropyl*)-*cyclohex*-2-*enyl*]-N-(2-*nitrophenyl*)*benzenesulfonamide* **16b** (157 mg, 72%) as two separate diastereoisomers. Higher R_F isomer: fluffy yellow solid, mp 68.5–71 °C (ethyl acetate–light petroleum) (Found: MH^+, 433.1447. $C_{21}H_{24}N_2O_6S$ requires *MH*, 433.1433); ν_{max}(disc)/cm^{-1} 3442, 2927, 1643, 1535, 1350, 1161 and 721; δ_H($CDCl_3$, 250 MHz) 0.05–0.15 and 0.75–2.20 (8H, m, CH_2 × 4), 2.40–3.70 (5H, m, CH_2OH + $CHOH$), 4.65–4.85 (1H, m, CHN), 5.65–5.80 (1H, m, CH=) and 6.85–6.95 and

7.30–8.15 (9H, m, Ar*H*): δ_C($CDCl_3$, 100 MHz) 16.82 (t), 17.83 (t), 24.26 (t), 25.04 (t), 27.44 (t), 29.63 (t), 37.06 (t), 38.30 (t), 57.16 (d), 59.40 (d), 66.10 (t), 66.63 (t), 72.44 (d), 73.53 (d), 125.26 (d), 124.92 (d), 127.78 (d), 128.45 (d), 129.14 (d), 129.29 (d), 129.72 (d), 130.73 (s), 131.17 (s), 132.15 (d), 132.23 (d), 132.32 (d), 132.68 (d), 133.05 (d), 133.39 (d), 133.50 (d), 133.67 (d), 140.12 (s), 140.41 (s), 150.05 (s) and 150.39 (s); *m*/*z* (FAB) 455 (MNa^+, 78%), 433 (19), 391 (49), 307 (100) and 289 (57). Lower R_F isomer: fluffy white solid, mp 64–66 °C (ethyl acetate–light petroleum) (Found: C, 58.58; H, 5.69; N, 6.28. $C_{21}H_{24}N_2O_6S$ requires C, 58.32; H, 5.59; N, 6.48%); ν_{max}(disc)/cm^{-1} 3435, 2929, 1628, 1536, 1349 and 1160: δ_H($CDCl_3$, 250 MHz) 0.05–0.20 and 0.80–3.00 (10H, m, CH_2 × 4 and OH × 2), 3.05–3.75 (3H, m, CH_2OH + CHOH), 4.55–4.75 (1H, m, CHN), 5.65–5.85 (1H, m, CH=) and 6.85–7.20 and 7.30–8.15 (9H, m, Ar*H*); δ_C($CDCl_3$, 100 MHz) 16.82 (t), 17.81 (t), 24.17 (t), 24.97 (t), 27.54 (t), 29.71 (t), 37.55 (t), 38.29 (t), 55.65 (d), 58.17 (d), 66.35 (t), 66.61 (t), 69.44 (d), 73.03 (d), 125.27 (d), 125.94 (d), 127.61 (d), 128.48 (d), 129.20 (d), 129.30 (d), 129.42 (d), 129.73 (d), 130.70 (s), 130.95 (s), 131.17 (s), 132.15 (s), 132.73 (d), 132.11 (d), 133.46 (d), 133.56 (d), 133.63 (d), 133.77 (d), 133.87 (d), 134.15 (d), 134.26 (d), 134.30 (d), 139.97 (s), 140.53 (s), 150.03 (s) and 150.30 (s).

N-(2-Nitrophenyl)-*N*-[2-(2-oxoethyl)cyclohex-2-enyl]benzenesulfonamide 17b

To a stirred solution of *N*-[2-(2,3-dihydroxypropyl)cyclohex-2-enyl]-*N*-(2-nitrophenyl) benzenesulfonamide **16b** (512 mg, 1.19 mmol) in diethyl ether (18 ml) and ethanol (2 ml), sodium periodate (317 mg, 1.48 mmol) and then water (0.71 ml) were added and the resulting mixture was stirred for 20 h under nitrogen gas. The mixture was diluted with ethyl acetate (50 ml) and washed with water (50 ml). The aqueous phase was extracted with ethyl acetate (2 × 50 ml) and the combined organic extracts were washed with water (3 × 75 ml), dried over magnesium sulfate, filtered and evaporated to dryness to give N-(2-*nitrophenyl*)-N-[2-(2-*oxoethyl*)*cyclohex*-2-*enyl*]*benzenesulfonamide* **17b** as a yellow solid (433 mg, 91%), mp 115–117.5 °C (ethyl acetate–light petroleum) (Found: MH^+, 401.1129. $C_{20}H_{20}N_2O_5S$ requires *MH*, 401.1171); ν_{max}(disc)/cm^{-1} 2964, 2827, 1722, 1534, 1346, 1162, 730 and 588; δ_H($CDCl_3$, 400 MHz) 0.05–0.15, 0.80–0.95, 1.05–1.45, 1.50–1.55, 1.70–1.95 and 2.30–2.45 (6H, m, CH_2 × 3), 2.85–3.05 and 3.15–3.25 (2H, m, CH_2CHO), 4.50–4.75 (1H, m, CHN), 5.55–5.80 (1H, m, CH=), 7.05–7.10, 7.30–7.75 and 7.85–8.00 (9H, m, ArH) and 9.45 (1H, t, *J* 1.6) CHO; δ_C($CDCl_3$, 67.5 MHz) 16.67 (t), 18.11 (t), 24.25 (t), 25.03 (t), 27.07 (t), 29.12 (t), 48.57 (t), 49.02 (t), 56.31 (d), 59.25 (d), 125.17 (d), 125.83 (d), 127.27 (d), 127.57 (d), 128.19 (d), 128.58 (d), 128.98 (d), 129.19 (d), 129.29 (d), 129.35 (d), 129.84 (d), 130.58 (s), 131.10 (s), 132.35 (d), 132.84 (d), 133.21 (d), 133.39 (d), 133.56 (d), 134.91 (d), 135.90 (d), 139.91 (s), 140.20 (s), 149.93 (s), 150.25 (s), 199.10 (d) and 200.26 (d); *m*/*z* (CI^+) 418 (MNH_4^+, 75%), 353 (35), 213 (47), 211 (100), 199 (18), 156 (16), 123 (21) and 109 (32).

N-[2-(2-Hydroxyethyl)cyclohex-2-enyl]-*N*-(2-nitrophenyl)-benzenesulfonamide 18b

To a stirred solution of *N*-(2-nitrophenyl)-*N*-[2-(2-oxoethyl)-cyclohex-2-enyl]benzenesulfonamide **17b** (359 mg, 0.898 mmol), dissolved in methanol (15 ml) and under nitrogen gas, was added sodium boranuide (34 mg, 0.898 mmol) and the mixture stirred for two min. Water (10 ml) was added and the solution evaporated to dryness. The residue was dissolved in water (50 ml), extracted with dichloromethane (3 × 50 ml) and the combined organic extracts dried over magnesium sulfate, filtered and evaporated to dryness to give a sticky white solid. Purification by column chromatography on silica gel eluted with diethyl ether gave N-[2-(2-*hydroxyethyl*)*cyclohex*-2-*enyl*]-N-(2-*nitrophenyl*)*benzenesulfonamide* **18b** as a yellow solid (312 mg, 86%), mp 107–109 °C (from ethyl acetate–light petroleum) (Found: C, 59.43; H, 5.65; N, 6.90. $C_{20}H_{22}N_2O_5S$ requires C, 59.69; H, 5.51; N, 6.95%); ν_{max}(disc)/cm^{-1} 3442, 2918, 2886, 1600, 1535, 1351, 1160, 1092, 718 and 593; δ_H($CDCl_3$, 400 MHz) 0.00–0.25, 0.80–2.20 and 2.45–2.55 (9H, m, CH_2 × 4 and OH), 3.45–3.60 (1H, m, CH_2OH), 4.55–4.70 (1H, m, CHN), 5.65–5.70 (1H, m, CH=) and 7.00–7.10, 7.40–7.75 and 7.85–8.05 (9H, m, ArH); δ_C($CDCl_3$, 67.5 MHz) 16.86 (t), 17.90 (t), 24.12 (t), 24.89 (t), 27.48 (t), 29.62 (t), 36.71 (t), 37.61 (t), 56.05 (d), 58.10 (d), 61.24 (t), 61.92 (t), 125.09 (d), 125.86 (d), 127.46 (d), 128.46 (d), 129.02 (d), 129.09 (d), 129.54 (d), 130.66 (s), 131.16 (s), 131.75 (d), 131.99 (d), 132.20 (d), 132.58 (d), 132.94 (d), 133.21 (d), 133.28 (d), 133.87 (d), 139.86 (s), 140.49 (s), 150.06 (s) and 150.26 (s); *m*/*z* (CI^+) 420 [(MNH_4^+), 17%)], 353 (7), 296 (11), 249 (8), 211 (28), 142 (22) and 109 (100).

N-(2-Aminophenyl)-*N*-[2-(2-hydroxyethyl)cyclohex-2-enyl]-benzenesulfonamide 19b

To a stirred suspension of copper(II) acetylacetonate (26.5 mg, 0.1 mmol) in ethanol (10 ml), under nitrogen, was added sodium boranuide (18.9 mg, 0.5 mmol) and the mixture stirred for 20 min, after which time the solution was clear and a black solid had formed. To this were added *N*-[2-(2-hydroxyethyl)-cyclohex-2-enyl]-*N*-(2-nitrophenyl)benzenesulfonamide **18b** (200 mg, 0.50 mmol) in ethanol (5 ml) and sodium boranuide (37.8 mg, 1 mmol) with ethanol (10 ml). After stirring for a further 2.5 h, water (50 ml) was added and the solution was filtered through cotton wool and evaporated *in vacuo* to remove ethanol. The solution was then extracted with ethyl acetate (3 × 50 ml) and the combined extracts dried over magnesium sulfate, filtered and evaporated to dryness to give a brown oil which was purified by high performance liquid chromatography on a 20 × 250 mm YMC S-15Sil column, using 70 : 30 light petroleum ethyl acetate as eluent to give N-(2-*aminophenyl*)-N-[2-(2-*hydroxyethyl*)*cyclohex*-2-*enyl*]*benzenesulfonamide* **19b** as a clear oil (45 mg, 24%), ν_{max}(film)/cm^{-1} 3502, 3377, 3065, 2937, 2872, 1618, 1497, 1446, 1328, 1155 and 1019; δ_H($CDCl_3$, 400 MHz) 0.70–0.95, 1.15–1.45, 1.70–2.25, 2.50–2.60 and 2.75–2.85 (9H, m, CH_2 × 4 and OH), 3.40 (2H, very broad s, NH_2), 3.45–3.60 and 3.80–3.95 (2H, m, CH_2OH), 4.65, 4.95 (1H, 2 × m, CHN), 5.65, 5.85 (1H, 2 × m, CH=), 6.40–6.60 (2H, m, ArH), 6.70–6.80 (1H, m, ArH), 7.05–7.15 (1H, m, ArH) and 7.45–7.85 (5H, m, ArH); δ_C($CDCl_3$, 67.5 MHz) 17.56 (t), 18.71 (t), 24.39 (t), 24.80 (t), 28.03 (t), 30.60 (t), 36.93 (t), 37.83 (t), 55.87 (d), 58.69 (d), 61.51 (t), 117.22 (d), 117.52 (d), 117.72 (d), 118.11 (d), 123.67 (s), 127.67 (d), 128.67 (d), 128.82 (d), 129.67 (d), 129.79 (d), 131.36 (d), 131.73 (d), 132.00 (d), 132.35 (s), 132.61 (d), 140.14 (s), 140.38 (s), 147.53 (s) and 147.67 (s); *m*/*z* (FAB) 373 (MH^+, 1%), 249 (6), 219 (8) and 133 (36).

7-Phenylsulfonyl-1,2,3a,4,5,6,6a,7-octahydrofuro[2,3-*d*]-carbazole 20

Nitrosonium tetrafluoroborate (8.42 mg, 0.072 mmol) was added to a stirred solution of *N*-(2-aminophenyl)-*N*-[2-(2-hydroxyethyl)cyclohex-2-enyl]benzenesulfonamide **19b** (22.5 mg, 0.06 mmol) in dichloromethane (5 ml) at 0 °C under nitrogen, and the mixture stirred for 1.5 h. The dichloromethane was evaporated by a stream of nitrogen and the resulting black residue dissolved in acetone (0.3 ml) and tetrathiafulvalene (14.7 mg, 0.072 mmol, 1 equiv.) in acetone (0.3 ml) added. After 2 h, the solution was evaporated to dryness, absorbed onto silica gel from dichloromethane and purified by column chromatography on silica gel eluted with an 85 : 15 mixture of ethyl acetate in light petroleum to give 7-*phenylsulfonyl*-1,2,3a,4,5,6,6a,7-*octahydrofuro*[2,3-d]*carbazole* **20** as a pale yellow solid (14.4 mg, 68%), mp 184–186 °C (ethyl acetate–light petroleum) (Found: MH^+, 356.1289. $C_{20}H_{21}NO_3S$ requires *MH*, 356.1320); ν_{max}-(disc)/cm^{-1} 2915, 2920, 1471, 1456, 1351, 1167, 1097, 1053, 760 and 596; δ_H($CDCl_3$, 400 MHz) 0.85–0.93 (1H, m, CH_2), 1.24–

1.63 (5H, m, $CH_2 \times 3$), 1.90–2.02 (1H, m, CH_2), 2.20–2.30 (1H, m, CH_2), 3.68–3.76 (1H, m, CH_2O), 3.81 (1H, ddd, *J* 8.9, 8.9, 2.7, CH_2O), 3.95 (1H, dd, *J* 11.0, 6.3, CHO), 4.27–4.31 (1H, m, CHN), 7.04–7.09 (2H, m, ArH), 7.27 (1H, ddd, *J* 7.6, 7.6, 1.7, ArH), 7.42 (2H, ddm, *J* 6.8, 6.8, ArH), 7.51–7.54 (1H, m, ArH), 7.70 (1H, d, *J* 8.1, ArH) and 7.81–7.83 (2H, m, ArH); δ_C($CDCl_3$, 67.5 MHz) 16.26 (t), 26.65 (t), 30.64 (t), 42.90 (t), 52.44 (q), 65.75 (t), 66.85 (d), 77.88 (d), 116.05 (d), 122.30 (d), 124.47 (d), 126.47 (d), 128.54 (d), 129.04 (d), 133.05 (d), 134.21 (s), 139.28 (s) and 140.38 (s); *m*/*z* (CI^+) 373 (MNH_4^+, 23%), 356 (11) and 216 (100).

N-(2-Nitrophenyl)methanesulfonamide 14c

Methanesulfonyl chloride (14.87 g, 130 mmol, 1.2 equiv.), 2-nitroaniline (15 g, 109 mmol, 1.0 equiv.) and 4-(dimethylamino)pyridine (3.20 g, 26.2 mmol, 0.1 equiv.), were dissolved in pyridine (55 ml) and the resulting mixture heated under reflux for 18 h. The cooled reaction mixture was diluted with dichloromethane (200 ml), washed with aqueous hydrochloric acid (2 M, 2 × 200 ml) and aqueous sodium hydroxide (2 M, 3 × 150 ml). The combined aqueous extracts were acidified with concentrated hydrochloric acid, and then extracted with dichloromethane (4 × 150 ml). The combined organic extracts were dried over magnesium sulfate, filtered and evaporated to dryness to give N-(2-*nitrophenyl*)*methanesulfonamide* **14c** as a red–brown solid (13 g, 60 mmol, 56%) mp 105–107 °C (diethyl ether); [Found: M^+ (EI), 216.0204. $C_7H_8N_2SO_4$ requires: *M* 216.0204]; ν_{max}($CHCl_3$)/cm^{-1} 3288, 1613, 1581, 1352, 1325, 966; δ_H(400 MHz, $CDCl_3$) 3.16 (3H, s, CH_3), 7.24 (1H, ddd, *J* 8.5, 8.5, 0.7, ArH), 7.69 (1H, ddd, *J* 8.5, 8.5, 1.5, ArH), 7.88 (1H, dd, *J* 8.5, 0.7, ArH), 8.26 (1H, dd, *J* 8.5, 1.5, ArH), 9.74 (1H, br s, N*H*); δ_C(67.5 MHz, $CDCl_3$) 40.5 (q), 119.2 (d), 123.4 (d), 126.4 (d), 134.1 (s), 136.1 (d), 136.2 (d); *m*/*z* (EI) 216 (M^+, 61%), 138 (100).

N-(2-Nitrophenyl)-*N*-(2-prop-2-enylcyclohex-2-enyl)methanesulfonamide 15c

N-(2-Nitrophenyl)methanesulfonamide **14c** (1.83 g, 8.5 mmol, 1.0 equiv.) and triphenylphosphine (3.34 g, 12.75 mmol, 1.5 equiv.) were dissolved in dry tetrahydrofuran (100 ml). 2-Prop-2-enylcyclohex-2-en-1-ol **13** (1.76 g, 12.75 mmol, 1.5 equiv.) was added and the mixture cooled to 0 °C. Diethyl azodicarboxylate (2.22 g, 2.0 ml, 12.75 mmol, 1.5 equiv.) was added dropwise over a 15 min period. After 2 h the mixture was evaporated to dryness, dissolved in dichloromethane (100 ml) and washed with sodium hydroxide (2 M, 2 × 100 ml), aqueous sodium carbonate (saturated, 2 × 100 ml) and water (2 × 100 ml). It was then dried over sodium sulfate and filtered and the solvent removed under reduced pressure to give a yellow solid. This was purified by column chromatography on silica gel (9 : 1 light petroleum–ethyl acetate) to give N-(2-*nitrophenyl*)-N-(2-*prop*-2-*enylcyclohex*-2-*enyl*)*methanesulfonamide* **15c** as a clear yellow oil (2.18 g, 6.49 mmol, 76%) (Found: C, 57.14; H, 6.05; N, 8.54; $C_{16}H_{20}O_4N_2S$ requires C, 57.13; H, 5.99; N, 8.33%) [Found: $(MH)^+$ (FAB) 337.1219. $C_{16}H_{20}O_4N_2S$ requires: *MH*, 337.1222]; ν_{max}($CHCl_3$)/cm^{-1} 3082, 2946, 1601, 1579, 1542, 1347, 969; δ_H(400 MHz, CD_3SOCD_3 at 400 K) 1.08 (1H, m, CH_2), 1.37 (1H, m, CH_2), 1.85 (3H, m, C*H*$_2$C*H*$_2$), 2.18 (1H, m, CH_2), 2.74 (2H, m, CC*H*$_2$C=CH), 3.15 (3H, s, *C*H_3), 4.55 (1H, br m, NCH), 5.07 (2H, m, C*H*$_2$=CH), 5.70 (1H, m, C=C*H*), 5.85 (1H, m, CH_2=C*H*), 7.63 (3H, m, ArH), 7.87 (1H, dd, *J* 8.0, 1.6, ArH); δ_C(67.5 MHz, $CDCl_3$) 18.2 (t), 18.5 (t), 24.4 (t), 24.8 (t), 29.3 (t), 30.5 (t), 38.9 (t), 39.2 (t), 39.5 (q), 55.7 (d), 58.3 (d), 116.1 (t), 116.5 (t), 117.4 (d), 118.2 (d), 123.0 (s), 129.9 (d), 130.2 (d), 131.5 (d), 132.1 (s), 136.0 (d), 147.8 (s); *m*/*z* (FAB) 337 [$(MH)^+$, 6%], 154 (24), 121 (100).

N-[2-(2,3-Dihydroxypropyl)cyclohex-2-enyl]-*N*-(2-nitrophenyl)-methanesulfonamide 16c

Osmium tetroxide (16.1 mg, 0.063 mmol) and then 4-methylmorpholine *N*-oxide (126.5 mg, 1.08 mmol) were added to a solution of *N*-(2-nitrophenyl)-*N*-(2-prop-2-enylcyclohex-2-enyl)methanesulfonamide **15c** (300 mg, 0.9 mmol) in acetone–water (9 : 1) (60 ml), and the mixture stirred under nitrogen for 20 h. Aqueous sodium bisulfite (5%, 30 ml) was added and most of the acetone was evaporated *in vacuo*. The resulting aqueous solution was extracted with dichloromethane (5 × 30 ml) and the combined extracts washed with aqueous hydrochloric acid (2 M, 2 × 50 ml) and water (30 ml), dried over magnesium sulfate, filtered and evaporated to dryness. Purification by column chromatography on silica gel (ethyl acetate) gave N-[2-(2,3-*dihydroxypropyl*)*cyclohex*-2-*enyl*]-N-(2-*nitrophenyl*)*methanesulfonamide* **16c** (208 mg, 62%) as a mixture of two diastereoisomers. A small amount of the mixture was separated to obtain the following spectroscopic and analytical data. The higher R_F isomer was obtained as a glassy yellow solid mp 58–64 °C (ethyl acetate–light petroleum) (Found: C, 51.53; H, 6.04, N, 7.46. $C_{16}H_{22}N_2O_6S$ requires C, 51.88; H, 5.99; N, 7.56%); ν_{max}(disc)/cm^{-1} 3482, 3388, 2953, 2927, 2880, 2859, 1598, 1525, 1352, 1347, 1143, 1022 and 776; δ_H($CDCl_3$, 400 MHz) 0.20–0.40, 0.95–1.65, 1.70–2.45 and 3.01–3.95 (16H, m, $CH_2 \times 5$ + OH × 2 + C*H*OH + C*H*$_3$), 4.75–4.85 (1H, m, CHN), 5.65–5.85 (1H, m, CH=) and 7.20–7.90 (4H, m, ArH); δ_C($CDCl_3$, 67.5 MHz) 16.80 (t), 16.97 (t), 24.00 (t), 24.60 (t), 28.05 (t), 28.92 (t), 36.75 (t), 37.95 (t), 40.47 (q), 56.70 (d), 58.24 (d), 65.81 (t), 66.08 (t), 72.65 (d), 73.14 (d), 124.56 (d), 125.21 (d), 129.10 (d), 129.38 (d), 130.05 (s), 132.15 (d), 132.85 (d), 133.26 (d), 134.92 (d), 149.16 (s) and 149.70 (s); *m*/*z* (FAB) 393 (MNa^+, 100%), 371 (22), 291 (33), 289 (16), 129 (49) and 177 (51); lower R_F isomer was obtained as a white solid mp 133–136 °C (ethyl acetate–light petroleum) (Found: C, 51.57; H, 6.06; N, 7.47. $C_{16}H_{22}N_2O_6S$ requires C, 51.88; H, 5.99; N, 7.56%); [Found: MNH_4^+ (CI) 388.1542. $C_{16}H_{22}N_2O_6S$ requires: MNH_4 388.1542]: ν_{max}(disc)/cm^{-1} 3482, 3386, 2926, 2877, 2854, 1530, 1354, 1326, 1148, 1027, 969 and 776; δ_H($CDCl_3$, 400 MHz) 0.20–0.40, 0.95–1.50, 1.70–2.50 and 2.65–3.95 (16H, m, $CH_2 \times 5$ + OH × 2 + C*H*OH + CH_3), 4.55–4.75 (1H, m, CHN), 5.65–5.90 (1H, m, CH=) and 7.20–7.95 (4H, m, ArH); δ_C($CDCl_3$, 67.5 MHz) 16.75 (t), 16.93 (t), 23.92 (t), 24.53 (t), 28.03 (t), 28.88 (t), 37.23 (t), 37.90 (t), 40.51 (q), 55.42 (d), 57.20 (d), 66.02 (t), 70.21 (d), 70.44 (d), 124.78 (d), 125.10 (d), 129.06 (d), 129.43 (d), 130.05 (s), 130.69 (d), 132.27 (d), 132.83 (d), 133.67 (d), 133.98 (d), 134.47 (d), 149.18 (s) and 149.74 (s); *m*/*z* (CI) 388 [$(MNH_4)^+$, 38%], 187 (100), 172 (94).

N-(2-Nitrophenyl)-*N*-[2-(2-oxoethyl)cyclohex-2-enyl]methanesulfonamide 17c

Sodium periodate (133.8 mg, 0.625 mmol) and then water (0.3 ml) were added to a stirred solution of *N*-[2-(2,3-dihydroxypropyl)cyclohex-2-enyl]-*N*-(2-nitrophenyl)methanesulfonamide **16c** (183 mg, 0.45 mmol) in diethyl ether (8 ml) and ethanol (0.5 ml), and the resulting mixture was stirred for 4.5 h under nitrogen gas. The mixture was diluted with water (50 ml) and extracted with ethyl acetate (3 × 50 ml). The combined organic extracts were washed with water (2 × 50 ml), dried over magnesium sulfate, filtered and evaporated to give N-(2-*nitrophenyl*)-N-[2-(2-*oxoethyl*)*cyclohex*-2-*enyl*]*methanesulfonamide* **17c** as a yellow oil that crystallised when refrigerated (146 mg, 97%), mp 123–124 °C (ethyl acetate–light petroleum) (Found: C, 53.3; H, 5.56; N, 8.43. $C_{15}H_{18}N_2O_5S$ requires C, 53.24; H, 5.36; N, 8.28%); ν_{max}(disc)/cm^{-1} 3015, 2937, 1729, 1527, 1349, 1321, 1148, 1034 and 774; δ_H($CDCl_3$, 400 MHz) 0.30–0.45 and 1.05–2.10 (6H, m, $CH_2 \times 3$), 3.00–3.30, 3.35–3.45 and 3.85–3.90 (5H, m, CH_2 + CH_3), 4.55–4.65 (1H, m, CHN), 5.76–5.90 (1H, m, CH=), 7.20–7.85 (4H, m, ArH) and 9.62, 9.75 (1H, 2 × br s, CHO); δ_C($CDCl_3$, 67.5 MHz) 16.84 (t), 18.46 (t), 24.09 (t), 24.59 (t), 27.68 (t), 28.36 (t), 40.31 (q), 40.42 (q), 48.36 (t), 48.51 (t), 55.98 (d), 58.33 (d), 124.78 (d), 125.08 (d), 126.92 (s), 127.55 (s), 129.20 (d), 129.60 (d), 130.09 (s), 132.42 (d), 132.84 (d), 133.43 (d), 133.99 (d), 134.77 (d), 135.26 (d), 149.09 (s), 149.67 (s),

199.58 (d) and 199.98 (d); *m/z* (FAB) 361 (MNa^+, 99%), 337 (43), 293 (99), 259 (100), 239 (98) and 217 (58).

N-[2-(2-Hydroxyethyl)cyclohex-2-enyl]-*N*-(2-nitrophenyl)-methanesulfonamide 18c

Sodium boranuide (15 mg, 0.39 mmol) was added to a stirred solution of *N*-(2-nitrophenyl)-*N*-[2-(2-oxoethyl)cyclohex-2-enyl]methanesulfonamide **17c** (130 mg, 0.39 mmol), dissolved in methanol (8 ml) and under nitrogen gas, and the mixture stirred for 10 min. Water (20 ml) was added and the solution evaporated to dryness. The residue was dissolved in water (50 ml) and extracted with ethyl acetate (3 × 50 ml). The combined organic extracts were washed with water (3 × 50 ml), dried over magnesium sulfate, filtered and evaporated. Purification by column chromatography on silica gel (ethyl acetate–dichloromethane 1:4) gave N-[2-(2-*hydroxyethyl*)*cyclohex*-2-*enyl*]-N-(2-*nitrophenyl*)*methanesulfonamide* **18c** as a yellow solid (120 mg, 91%), mp 78–80 °C (ethyl acetate–light petroleum) (Found: MH^+, 341.1167. $C_{15}H_{20}N_2O_5S$ requires *MH*, 341.1171); ν_{max}(disc)/cm^{-1} 3419, 2927, 2870, 1603, 1530, 1331, 1148, 1027 and 771; δ_H(CD_3SOCD_3, 250 MHz, 400 K) 0.84–1.02 (1H, m, CH_2), 1.29–1.43 (1H, m, CH_2), 1.65–1.93 (3H, m, CH_2), 2.11–2.29 (2H, m, CH_2), 2.32–2.51 (1H, m, CH_2), 3.16, 3.17 (3H, 2 × s, CH_3), 3.54–3.64 (2H, m, C*H*$_2$OH), 4.60–4.70 (1H, m, CHN), 5.72 (1H, t, *J* 4.0, CH=), 7.53–7.71 (3H, m, ArH) and 7.87 (1H, dd, *J* 7.7, 1.8, ArH); δ_C($CDCl_3$, 100 MHz) 16.95 (t), 18.05 (t), 23.92 (t), 24.45 (t), 28.04 (t), 28.85 (t), 36.57 (t), 37.21 (t), 40.49 (q), 56.30 (d), 57.90 (d), 61.62 (t), 124.63 (d), 125.07 (d), 129.00 (d), 129.34 (d), 130.11 (s), 131.50 (d), 131.89 (d), 132.22 (s), 132.74 (d), 133.65 (d), 134.62 (d), 149.18 (s) and 149.65 (s); *m/z* (FAB) 363 (MNa^+, 36%), 341 (33), 307 (62), 289 (41) and 239 (22).

N-(2-Aminophenyl)-*N*-[2-(2-hydroxyethyl)cyclohex-2-enyl]-methanesulfonamide 19c

Sodium boranuide (3.8 mg, 0.1 mmol) was added to a stirred suspension of copper(II) acetylacetonate (5.3 mg, 0.02 mmol) in ethanol (2 ml), under nitrogen, and the mixture stirred for 20 min, after which time a clumpy black solid had formed. To this were added *N*-[2-(2-hydroxyethyl)cyclohex-2-enyl]-*N*-(2-nitrophenyl)methanesulfonamide **18c** (34 mg, 0.1 mmol) in ethanol (1 ml) and sodium boranuide (7.6 mg, 0.2 mmol) with ethanol (2 ml). The mixture was stirred for 2 h, water (50 ml) was added and the solution was filtered through cotton wool and evaporated *in vacuo* to remove ethanol. The solution was then extracted with ethyl acetate (3 × 50 ml) and the combined extracts dried over magnesium sulfate, filtered and evaporated to dryness to give a brown oil. Purification of the crude residue on silica gel (4% ethyl acetate in dichloromethane) gave *N*-(2-*aminophenyl*)-N-[2-(2-*hydroxyethyl*)*cyclohex*-2-*enyl*]*methanesulfonamide* **19c** as a viscous yellow oil (22.1 mg, 60%) (Found: MH^+, 311.1442. $C_{15}H_{22}N_2O_3S$ requires *MH*, 311.1429); δ_H($CDCl_3$, 250 MHz) 0.7–2.42 (9H, m, CH_2 × 4 + O*H*), 3.20 (3H, s, CH_3), 3.70–4.62 (4H, m, CH_2 + NH_2) 4.65–4.70 (1H, m, CHN), 5.65–5.70 (1H, m, CH=) and 6.63–7.30 (4H, m, ArH); δ_C($CDCl_3$, 100 MHz) 18.02 (t), 19.43 (t), 24.48 (t), 24.78 (t), 28.84 (t), 29.95 (t), 36.95 (t), 38.04 (t), 39.49 (q), 55.43 (d), 59.93 (d), 61.35 (t), 61.95 (t), 117.73 (d), 118.29 (d), 118.68 (d), 122.61 (s), 123.98 (s), 129.91 (d), 130.09 (d), 131.10 (d), 131.79 (d), 132.20 (s), 133.31 (s) and 147.17 (s); *m/z* (FAB) 333 (MNa^+, 40%), 311 (31), 307 (32), 289 (22), 187 (100) and 176 (85).

7-Methylsulfonyl-1,2,3a,4,5,6,6a,7-octahydrofuro[2,3-*d*]-carbazole 21

Nitrosonium tetrafluoroborate (8.43 mg, 0.072 mmol) was added to a stirred solution of *N*-(2-aminophenyl)-*N*-[2-(2-hydroxyethyl)cyclohex-2-enyl]methanesulfonamide **19c** (22.1 mg, 0.06 mmol) in dichloromethane (5 ml) at 0 °C under nitrogen, and the mixture stirred for 1.5 h. The dichloromethane was evaporated by a stream of nitrogen and the resulting black residue dissolved in acetone (0.3 ml) and tetrathiafulvalene (14.7 mg, 0.072 mmol) in acetone (0.13 ml) was added. After a further 2 h, the solution was evaporated to dryness, adsorbed onto silica gel from dichloromethane and purified by column chromatography on silica gel (85:15 ethyl acetate–light petroleum) to give 7-*methylsulfonyl*-1,2,3a,4,5,6,6a,7-*octahydrofuro*[2,3-d]*carbazole* **21** as a white solid (13.1 mg, 75%), mp 162–164 °C (ethyl acetate–light petroleum) (Found: M^+, 293.1086. $C_{15}H_{19}NO_3S$ requires *M*, 293.1086); δ_H($CDCl_3$, 400 MHz) 1.27–1.49 (3H, m, CH_2), 1.56–1.67 (1H, m, CH_2), 1.92–2.05 (2H, m, CH_2), 2.18–2.28 (1H, m, CH_2), 2.32 (1H, ddd, *J* 12.6, 6.6, 3.0, CH_2), 3.06 (3H, s, CH_3), 3.99–4.09 (2H, m, CH_2O), 4.16 (1H, dd, *J* 11.0, 6.0, CHO), 4.28 (1H, dd, *J* 2.8, 2.8, CHN), 7.08 (1H, ddd, *J* 8, 8, 1.0, ArH), 7.17 (1H, br d, *J* 8, ArH), 7.26 (1H, td, *J* 8, 1.3, ArH) and 7.34 (1H, br d, *J* 8.0, ArH); δ_C($CDCl_3$, 100 MHz) 16.59 (t), 26.86 (t), 29.68 (t), 39.93 (q), 42.74 (t), 52.70 (s), 66.44 (t), 68.09 (d), 78.19 (d), 114.18 (d), 123.03 (d), 124.21 (d), 129.00 (d), 133.97 (s) and 140.87 (s); *m/z* (EI^+) (M^+, 293 (10%), 253 (50), 168 (32) and 115 (65).

N-[2-(2-Methylsulfonyloxyethyl)cyclohex-2-enyl]-*N*-(2-nitrophenyl)methanesulfonamide 29

Methanesulfonyl chloride (0.37 ml, 4.74 mmol) was added dropwise over 5 min to a stirred solution of *N*-[2-(2-hydroxyethyl)cyclohex-2-enyl]-*N*-(2-nitrophenyl)methanesulfonamide **18c** (1.07 g, 3.16 mmol), triethylamine (0.87 ml, 6.32 mmol) and 4-(dimethylamino)pyridine (50 mg, 0.41 mmol) in dichloromethane (100 ml) at 0 °C. Once the addition was complete the ice bath was removed and the solution stirred for 18 h. Further methanesulfonyl chloride (0.25 ml, 3.16 mmol) was added and the mixture stirred for 1 h.

The reaction mixture was washed with water (100 ml) and dried over magnesium sulfate, filtered and evaporated to give a colourless oil. Purification by column chromatography on silica gel (1:4 diethyl ether–dichloromethane) gave N-[2-(2-*methylsulfonyloxyethyl*)*cyclohex*-2-*enyl*]-N-(2-*nitrophenyl*)*methanesulfonamide* **29** as a white foam (930 mg, 70%) (Found: M^+, 418.0874. $C_{16}H_{22}N_2O_7S_2$ requires *M*, 418.0868); ν_{max}(disc)/cm^{-1} 3036, 2940, 2876, 1604, 1533, 1348, 1174, 1152, 973 and 731; δ_H($CDCl_3$, 250 MHz) 0.20–0.40, 0.90–1.60, 1.70–2.05 and 2.40–2.60 (8H, m, C*H*$_2$ × 4), 3.02 (3H, s, C*H*$_3$), 3.16 (3H, s, CH_3), 4.30–4.40 (2H, m, CH_2), 4.60–4.80 (1H, m, CHN), 5.75–5.90 (1H, m, HC=) and 7.25–7.85 (4H, m, ArH); δ_C($CDCl_3$, 100 MHz) 16.94 (t), 18.37 (t), 24.12 (t), 24.74 (t), 28.06 (t), 28.79 (t), 33.32 (t), 33.90 (t), 37.22 (q), 40.65 (q), 40.93 (q), 55.35 (d), 57.45 (d), 68.99 (t), 125.01 (d), 125.23 (d), 129.37 (s), 129.70 (d), 130.07 (s), 130.36 (s), 132.51 (d), 133.96 (d), 133.30 (d), 134.17 (d), 134.39 (d), 149.41 (s), 149.93 (s); *m/z* (EI^+) 418 (M^+, 4%), 339 (100), 258 (84), 217 (23), 200 (44) and 182 (15).

N-[2-(2-Azidoethyl)cyclohex-2-enyl]-*N*-(2-nitrophenyl)methanesulfonamide 30

N-[2-(2-Methylsulfonyloxyethyl)cyclohex-2-enyl]-*N*-(2-nitrophenyl)methanesulfonamide **29** (900 mg, 2.15 mmol) and sodium azide (282 mg, 4.30 mmol) were dissolved in dimethylformamide and heated at 70 °C for 4 h. The solution was then poured into water (200 ml) and extracted with ethyl acetate (3 × 100 ml). The combined ethyl acetate extracts were washed with water (5 × 200 ml), dried over magnesium sulfate, filtered and evaporated to dryness to yield a brown oil. Purification by column chromatography on silica gel eluted with dichloromethane as solvent gave N-[2-(2-*azidoethyl*)*cyclohex*-2-*enyl*]-N-(2-*nitrophenyl*)*methanesulfonamide* **30** as a light yellow, viscous oil (750 mg, 96%) (Found: MNH_4^+, 383.1501. $C_{15}H_{19}N_5O_4S$ requires MNH_4, 383.1502); ν_{max}(disc)/cm^{-1} 3042, 2938, 2873, 2094, 1601, 1532, 1338, 1151, 1025, 971 and 734; δ_H($CDCl_3$, 270 MHz) 0.05–0.15, 0.45–1.20, 1.25–2.20 and 2.80–2.90 (8H, m, CH_2 × 4), 3.02 (3H, s, CH_3), 3.05–3.25 (2H, m, CH_2), 4.35–4.60 (1H, m, CHN), 5.35–5.60 (1H, m, CH=) and 7.10–7.80 (4H, m,

ArH); δ_C($CDCl_3$, 67.5 MHz) 17.36 (t), 18.61 (t), 24.50 (t), 25.10 (t), 28.62 (t), 29.18 (t), 33.56 (t), 34.17 (t), 41.07 (q), 41.37 (q), 50.53 (t), 55.88 (d), 57.63 (d), 125.22 (d), 125.50 (d), 129.63 (d), 129.82 (d), 130.52 (s), 130.77 (s), 131.46 (s), 131.87 (s), 132.61 (d), 133.12 (d), 134.02 (d), 134.37 (d), 134.75 (d), 135.31 (d), 149.83 (s) and 150.15 (s); *m/z* (CI^+) 383 (MNH_4^+, 42%), 338 (19), 306 (15), 234 (17), 187 (88) and 122 (100).

N-(2-Nitrophenyl)-*N*-{2[2-(trifluoroacetamido)ethyl]cyclohex-2-enyl}methanesulfonamide 32

Reduction of *N*-[2-(2-azidoethyl)cyclohex-2-enyl]-*N*-(2-nitrophenyl)methanesulfonamide **30** by propane-1,3-dithiol, followed by protection as a trifluoroacetamide.

A solution of *N*-[2-(2-azidoethyl)cyclohex-2-enyl]-*N*-(2-nitrophenyl)methanesulfonamide **30** (109 mg, 0.3 mmol), propane-1,3-dithiol (0.15 ml, 1.5 mmol), triethylamine (0.206 ml, 1.5 mmol) and methanol (1.5 ml) was stirred for 48 h. Water (100 ml) was added and the solution extracted with ethyl acetate (3 × 100 ml). These extracts were then extracted with aqueous hydrochloric acid (2 M, 3 × 50 ml) and the acid layer made basic with solid sodium hydrogen carbonate. Extraction into dichloromethane (3 × 100 ml) and drying of these extracts over magnesium sulfate, filtration and evaporation to dryness gave a viscous yellow oil (123 mg, >100% based on the desired compound) that was not further purified at this stage.

The residue was dissolved in tetrahydrofuran (20 ml) and triethylamine (0.413 ml, 3 mmol) and 4-(dimethylamino)-pyridine (37 mg, 0.3 mmol) was added and the mixture cooled to 0 °C in an ice bath. Trifluoroacetic anhydride (0.423 ml, 3 mmol) in tetrahydrofuran (10 ml) was added dropwise over 10 min. The ice bath was removed and the mixture stirred for 24 h after which further triethylamine (2.07 ml, 15 mmol) was added. The mixture was stirred for a further 3 days.

Water (100 ml) was added and most of the tetrahydrofuran was removed *in vacuo*. Extraction with dichloromethane (3 × 50 ml), drying over magnesium sulfate and evaporation to dryness gave an oily residue. Purification by column chromatography on silica gel (30:70 ethyl acetate–light petroleum) gave N-(2-*nitrophenyl*)-N-{2-[2-(*trifluoroacetamido*)*ethyl*]*cyclohex*-2-*enyl*}*methanesulfonamide* **32** as a yellow solid (113 mg, 87%), mp 139–141 °C (ethyl acetate–light petroleum) (Found: C, 46.75; H, 4.46; N, 9.46. $C_{17}H_{20}F_3N_3O_5S$ requires C, 46.89; H, 4.63; N, 9.65%); ν_{max}(disc)/cm^{-1} 3347, 3105, 2941, 1717, 1576, 1535, 1359, 1335, 1210, 1180 and 1152; δ_H(CD_3SOCD_3, 400 MHz) 0.05–0.35, 0.75–1.40, 1.45–1.90, 1.95–2.20 and 2.30–2.75 (8H, m, CH_2 × 4), 3.10–3.65 (5H, br m, CH_3 and CH_2N), 4.45–4.75 (1H, m, CHN), 5.45–5.75 (1H, m, CH=), 7.15–8.10 (4H, m, ArH) and 9.15–9.50 (1H, m, NH); δ_C(CD_3SOCD_3, 62.5 MHz) 16.59 (t), 17.67 (t), 23.98 (t), 24.57 (t), 27.20 (t), 29.04 (t), 33.14 (t), 33.86 (t), 37.56 (t), 40.18 (q), 40.52 (q), 53.96 (d), 56.28 (d), 116.06 (q, $J_{^{13}C-^{19}F}$ 287), 124.95 (d), 125.51 (d), 129.58 (d), 130.01 (d), 130.30 (s), 131.50 (s), 131.64 (d), 132.13 (d), 132.83 (d), 133.37 (d), 133.48 (d), 134.03 (d), 149.47 (s), 150.20 (s), 156.36 (q, $J_{^{13}C-^{19}F}$ 35); *m/z* (FAB) 458 (MNa^+, 79%), 436 (37), 435 (13) and 329 (100).

N-(2-Aminophenyl)-*N*-{2-[2-(trifluoroacetamido)ethyl]cyclohex-2-enyl}methanesulfonamide 33

Sodium boranuide (185 mg, 4.88 mmol) was added to a stirred suspension of copper(II) acetylacetonate (776 mg, 2.93 mmol) in ethanol (50 ml), under nitrogen, and the mixture stirred for 20 min, after which time a heavy black solid had formed. To this were added *N*-(2-nitrophenyl)-*N*-{2-[2-(trifluoroacetamido)-ethyl]cyclohex-2-enyl}methanesulfonamide **32** (1.062 g, 2.44 mmol) in ethanol (50 ml) and sodium boranuide (277 mg, 7.32 mmol). After stirring for 1 h, water (500 ml) was added and the solution was filtered through cotton wool and evaporated *in vacuo* to remove ethanol. The solution was extracted with dichloromethane (3 × 100 ml) and the combined extracts dried over magnesium sulfate, filtered and evaporated to give a brown oil which was purified by column chromatography (SiO_2, 4% solution of ethyl acetate in dichloromethane) to give N-(2-*aminophenyl*)-N-{2-[2-(*trifluoroacetamido*)*ethyl*]*cyclohex*-2-*enyl*}*methanesulfonamide* **33** as a cream solid (685 mg, 70%), mp 152–154 °C (from ethyl acetate–light petroleum) (Found: M^+, 405.1358. $C_{17}H_{22}F_3N_3O_3S$ requires *M*, 405.1334); ν_{max}-(disc)/cm^{-1} 3478, 3381, 3343, 3105, 2954, 1722, 1621, 1306, 1214, 1179, 1141, 1037 and 755; δ_H(CD_3SOCD_3, 400 MHz) 0.72–0.95, 1.05–1.39, 1.60–2.35 and 2.60–2.70 (8H, m, CH_2 × 4), 3.07 (2H, s, NH_2), 3.25–3.60 (2H, m, CH_2N), 3.34 (3H, s, CH_3), 4.75–4.85 (1H, m, CHN), 5.50–5.60 (1H, m, CH=), 6.42–6.52 (1H, m, ArH), 6.70–6.85 (2H, m, ArH), 7.05–7.15 (1H, m, ArH) and 9.20–9.30 (1H, m, NH); δ_C(CD_3SOCD_3, 100 MHz) 17.14 (t), 18.38 (t), 24.43 (t), 24.79 (t), 28.03 (t), 29.23 (t), 33.61 (t), 34.00 (t), 37.70 (t), 40.33 (q), 40.76 (q), 53.65 (d), 56.13 (d), 116.22 (q, $J_{^{13}C-^{19}F}$ 286), 116.15 (d), 116.52 (d), 121.33 (s), 122.01 (s), 129.49 (d), 129.66 (d), 130.60 (d), 131.98 (d), 132.50 (s), 132.65 (d), 132.85 (s), 148.53 (s), 148.67 (s) and 156.43 (q, $J_{^{13}C-^{19}F}$ 36); *m/z* (EI^+) 405 (M^+, 12%), 326 (17), 220 (34), 186 (100) and 171 (20).

9-Methylsulfonyl-4-hydroxy-4a*H*-[2-(trifluoroacetamido)ethyl]-1,2,3,4,9,9a-hexahydrocarbazole 35

N-(2-Aminophenyl)-*N*-{2-[2-(trifluoroacetamido)ethyl]cyclohex-2-enyl} methanesulfonamide **33** (202.5 mg, 0.5 mmol) and nitrosonium tetrafluoroborate (88 mg, 0.75 mmol) were reacted in dichloromethane (10 ml) at 0 °C for 2 h, after which time all the starting material had been consumed as determined by thin layer chromatography. The solvent was removed *in vacuo* and the residue dissolved in acetone (5 ml) and poured into diethyl ether (100 ml). A brown solid was precipitated, which when filtered proved to be very hygroscopic, rapidly forming a brown oil on the filter paper. The oil was redissolved in acetone (5 ml) and tetrathiafulvalene (112.2 mg, 0.55 mmol) was added, followed by water (1 ml) after 10 min. The mixture was then reacted for 2 days.

The solvent was removed *in vacuo* and the residue partitioned between water (20 ml) and dichloromethane (20 ml). The aqueous portion was extracted with dichloromethane (2 × 10 ml) and the combined organic phases were washed with water (3 × 20 ml), dried over magnesium sulfate, filtered and evaporated to dryness. The product was purified by column chromatography on silica gel eluted with a 10% solution of ethyl acetate in dichloromethane to give 9-*methylsulfonyl*-4-*hydroxy*-4aH-[2-(*trifluoroacetamido*)*ethyl*]-1,2,3,4,9,9a-*hexahydrocarbazole* **35** as a white solid (92.2 mg, 45%), mp 92–93 °C (ethyl acetate–light petroleum) (Found: M^+, 406.1131. $C_{17}H_{21}F_3N_2O_4S$ requires *M*, 406.1174); ν_{max}(disc)/cm^{-1} 3508, 3345, 2925, 2854, 1716, 1457, 1345, 1212, 1159, 766 and 546; δ_H($CDCl_3$, 400 MHz) 1.45–1.91 (7H, m, CH_2 × 3 and OH), 2.15–2.23 (1H, m, CH_2), 2.24–2.32 (1H, m, CH_2), 3.06 (3H, s, CH_3), 3.37–3.47 (1H, m, CH_2), 3.15–3.23 (1H, m, CH_2), 4.23 (1H, dd, *J* 8.4, 5.7, C*H*OH), 4.31–4.35 (1H, m, CHN), 7.02–7.09 (1H, br s, NH), 7.06 (1H, ddd, *J* 7.4, 7.4, 1.1, ArH), 7.13–7.17 (1H, m, ArH), 7.27 (1H, ddd, *J* 7.7, 7.7, 1.4, ArH) and 7.35–7.38 (1H, m, ArH); δ_C(100 MHz, $CDCl_3$) 15.51 (t), 27.46 (t), 28.50 (t), 32.76 (t), 35.21 (t), 38.56 (q), 49.84 (s), 68.14 (d), 68.30 (d), 113.90 (d), 115.66 (q, $J_{^{13}C-^{19}F}$ 287), 123.22 (d), 123.92 (d), 128.60 (d), 134.09 (s), 140.12 (s), 157.28 (q, $J_{^{13}C-^{19}F}$ 37); *m/z* (EI^+) 406 (M^+, 10%), 327 (21), 309 (100), 256 (9), 214 (19), 200 (31) and 130 (88).

9-Methylsulfonyl-4-oxo-4a*H*-[2-(trifluoroacetamido)ethyl)]-1,2,3,4,9,9a-hexahydrocarbazole 36

9-Methylsulfonyl-4-hydroxy-4a*H*-[2-(trifluoroacetamido)ethyl]-1,2,3,4,9,9a-hexahydrocarbazole **35** (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 h. 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 9-*methylsulfonyl*-4-*oxo*-4aH-[2-(*trifluoroacetamido*)*ethyl*]-1,2,3,4,9,9a-*hexahydrocarbazole* **36** as a white solid (173 mg, 83%), 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}(disc)/cm^{-1} 3437, 2928, 2856, 1719, 1701 (sh), 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_2N), 3.25–3.43 (2H, m, CH_2N), 4.67 (1H, dd, *J* 5.5, 5.5, CHN), 6.98 (1H, dm, *J* 8, ArH), 7.06 (1H, ddm, *J* 8, 8, ArH), 7.10–7.20 (1H, s, NH), 7.30 (1H, ddd, *J* 8, 8, 1.0, ArH) and 7.46 (1H, dm, *J* 8, ArH); 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).

7-Methylsulfonyl-2,4,5,6,6a,7-hexahydro-1*H*-pyrrolo[2,3-*d*]-carbazole 37

Methylsulfonyl-4-oxo-4a*H*-[2-(trifluoracetamido)ethyl]-1,2,3,4,9,9a-hexahydrocarbazole **36** (30 mg, 0.074 mmol) and potassium carbonate (22.53 mg, 0.163 mmol) were dissolved in a mixture of methanol (2 ml) and water (0.9 ml) and stirred for 24 h. The solvent was removed *in vacuo* and the residue partitioned between water (50 ml) and dichloromethane (50 ml). The aqueous layer was extracted with two further portions of dichloromethane (2 × 20 ml) and the combined organic extracts were dried over magnesium sulfate, filtered and evaporated to give 7-*methylsulfonyl*-2,4,5,6,6a,7-*hexahydro*-1H-*pyrrolo*[2,3-d]*carbazole* **37** (17 mg, 79%) as a white solid, mp 144.5–146 °C (ethyl acetate–light petroleum) (Found: M^+, 290.1090. $C_{15}H_{18}N_2O_2S$ requires *M*, 290.1089); ν_{max}(disc)/cm^{-1} 3010, 2964, 2928, 2856, 1646, 1597, 1471, 1354, 1160, 1059, 958, 778 and 548; δ_H($CDCl_3$, 400 MHz) 1.43–1.54 (1H, m, CH_2), 1.62–1.71 (1H, m, CH_2), 1.83–1.91 (1H, m, CH_2), 2.00–2.27 (4H, m, CH_2), 2.74 (1H, ddd, *J* 15.0, 4.1, 4.1, CH_2), 2.98 (3H, s, CH_3), 3.80 (1H, m, CH_2), 4.00 (1H, ddm, *J* 15.5, 8.2, CH_2), 4.29 (1H, dd, *J* 9.0, 5.8, CHN), 6.90 (1H, ddd, *J* 7.5, 1.2, 0.5, ArH), 7.07 (1H, ddd, *J* 7.5, 7.5, 1, ArH), 7.29 (1H, ddd, *J* 7.5, 7.5, 1.3, ArH) and 7.45 (1H, ddd, *J* 7.5, 0.9, 0.6, ArH); δ_C($CDCl_3$, 100 MHz) 20.07 (t), 29.17 (t), 30.16 (t), 38.81 (q), 42.08 (t), 56.77 (t), 61.90 (s), 72.07 (d), 115.63 (d), 123.31 (d), 124.84 (d), 129.58 (d), 134.31 (s), 139.67 (s) and 178.00 (s); *m*/*z* (EI^+) 290 (M^+, 91%), 222 (100), 211 (4), 194 (12), 182 (20), 162 (22), 144 (31), 130 (17) and 115 (19).

7-Methylsulfonyl-3-(4-methylphenylsulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazole 40 and 7-methylsulfonyl-3-(methylphenylsulfonyl)-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazole 41

7-Methylsulfonyl-2,4,5,6,6a,7-hexahydro-1*H*-pyrrolo[2,3-*d*]-carbazole **37** (260 mg, 0.90 mmol) was dissolved in methanol (20 ml) and sodium boranuide (34 mg, 0.9 mmol) was added and the mixture stirred for 10 min. Water (50 ml) was added and the solution extracted with dichloromethane (3 × 20 ml). The extracts were dried over sodium sulfate, filtered and evaporated to give an oily residue. (^{1}H NMR analysis of the mixture showed that two compounds were present. Analysis of the relative sizes of the integrals of the ^{1}H NMR signals corresponding to the methyl groups of the product showed the two isomers were present in a 7 : 3 ratio.)

The residue was dissolved in dichloromethane (8 ml) and 4-methylbenzenesulfonyl chloride (182.11 mg, 0.95 mmol) and triethylamine (0.142 ml, 1.032 mmol) were added and the mixture stirred for 2.5 days. The mixture was partitioned between dichloromethane (20 ml) and aqueous hydrochloric acid (2 M, 20 ml). The dichloromethane layer was separated and the aqueous portion extracted with dichloromethane (2 × 25 ml). The combined dichloromethane portions were dried over sodium sulfate, filtered and evaporated to dryness. The product was purified by column chromatography (SiO_2, CH_2Cl_2) to give a mixture of 7-*methylsulfonyl*-3-(4-*methylphenylsulfonyl*)-2,3,3a,4,5,6,6a,7-*octahydro*-1H-*pyrrolo*[2,3-d]*carbazole* **40** and 7-*methylsulfonyl*-3-(4-*methylphenylsulfonyl*)-2,3,3a,4,5,6,6a,7-*octahydro*-1H-*pyrrolo*[2,3-d]*carbazole* **41** as a white solid (396 mg, 100%). A second column (SiO_2, 1 : 4 petrol–dichloromethane) gave firstly 7-*methylsulfonyl*-3-(4-*methylphenylsulfonyl*)-2,3,3a,4,5,6,6a,7-*octahydro*-1H-*pyrrolo*[2,3-d]*carbazole* **40** as a white solid (280 mg, 70%) mp 180–181 °C (from ethyl acetate–hexane) [lit.,[7,9] 180–181 °C (mixed mp 180–181 °C)] (Found: C, 59.38; H, 5.96; N, 6.61; $C_{22}H_{26}S_2O_4N_2$ requires: C, 59.17; H, 5.87; N, 6.27%) [Found: M^+ (EI), 446.1320. $C_{22}H_{26}S_2O_4N_2$ requires: *M*, 446.1334]; ν_{max}/cm^{-1} ($CHCl_3$) 2927, 2854, 1600, 1460, 1350, 1159, 1102; δ_H(400 MHz, $CDCl_3$) 1.22–1.55 (5H, m, CH_2CH_2CH_2), 1.89–1.94 (1H, m, CH_2), 2.14–2.18 (1H, m, CH_2), 2.26–2.29 (1H, m, CH_2), 2.46 (3H, s, $ArCH_3$), 2.99 (3H, s, SO_2CH_3), 3.48–3.53 (1H, m, CH_2NTs), 3.62–3.68 (1H, m, CH_2NTs), 3.94–3.95 (1H, br m, CCHN), 4.05–4.10 (1H, dd, *J* 6.1, 5.8, NCH), 6.64 (1H, d, *J* 7.5, ArH), 6.89 (1H, ddd, *J* 7.5, 7.5, 1.0, ArH), 7.20 (1H, ddd, *J* 7.5, 7.5, 1.0, ArH), 7.25–7.28 (1H, m, ArH), 7.37 (2H, d, *J* 8.3, ArH), 7.79 (2H, d, *J* 8.3, ArH); δ_C(100 MHz, $CDCl_3$) 16.5 (t), 21.6 (t), 27.4 (t), 28.3 (t), 36.2 (t), 39.5 (q), 47.5 (q), 53.7 (s), 61.2 (d), 67.3 (d), 114.0 (d), 122.5 (d), 123.6 (d), 127.5 (d), 129.1 (d), 129.9 (d), 133.6 (s), 134.9 (s), 140.1 (s), 143.9 (s); *m*/*z* (EI) 446 (M^+, 63%), 367 (100) and secondly 7-*methylsulfonyl*-3-(4-*methylphenylsulfonyl*)-2,3,3a,4,5,6,6a,7-*octahydro*-1H-*pyrrolo*[2,3-d]*carbazole* **41** as a white solid (110 mg, 27%), mp >320 °C (Found: MH^+, 447.1412. $C_{22}H_{27}N_2O_4S_2$ requires *MH* 447.1412); ν_{max}(disc)/cm^{-1} 2964, 2933, 2880, 1610, 1478, 1461, 1348, 1161 and 664; δ_H($CDCl_3$, 250 MHz) 1.34–1.78 (6H, m, CH_2 × 3), 1.93–2.04 (1H, m, CH_2), 2.37–2.44 (1H, m, CH_2), 2.48 (3H, s, CH_3), 2.92–3.01 (1H, m, C*H*N), 2.94 (3H, s, CH_3), 3.37–3.40 (1H, br t, *J* 10, CH_2N), 3.53–3.63 (1H, m, CH_2N), 4.19 (1H, t, *J* 6, CHN), 7.09 (1H, br dd, *J* 7.6, 7.6, ArH), 7.23–7.29 (1H, m, ArH), 7.34–7.41 (3H, m, ArH), 7.59 (1H, br d, *J* 7.3, ArH) and 7.73 (2H, d, *J* 8.4, ArH); δ_C($CDCl_3$, 67.5 MHz) 19.63 (t), 21.61 (q), 24.53 (t), 28.32 (t), 36.64 (t), 38.87 (q), 46.46 (t), 54.17 (s), 61.91 (d), 67.46 (d), 114.55 (d), 124.14 (d), 125.89 (d), 127.75 (d), 128.88 (d), 129.92 (d), 132.33 (s), 133.96 (s), 140.55 (s) and 144.03 (s); *m*/*z* (CI^+) 447 (MH^+, 11%), 293 (65), 291 (50), 215 (90) and 213 (100).

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