The total synthesis of the analgesic alkaloid epibatidine

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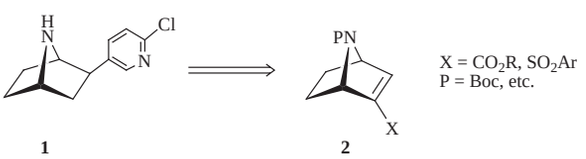
Several synthetic routes to the analgesic alkaloid epibatidine have been explored. Approaches starting from tropinone, involving either ring-cleavage followed by intramolecular aldol reaction, or Favorskii ring-contraction, were not successful. A successful route was established, involving cycloaddition of an *N*-protected pyrrole with ethynyl *p*-tolyl sulfone to prepare the required azabicyclo[2.2.1] skeleton. Completion of the synthesis required subsequent partial hydrogenation, addition of a metallated pyridine to an alkenyl sulfone, desulfonylation and brief functional group interchange and nitrogen deprotection. The synthesis proceeds in only six steps from the starting *N*-Boc pyrrole and furnishes the natural product in about 24% yield overall.

Introduction

The novel alkaloid epibatidine **1** has attracted a great deal of



1 **2**

synthetic attention since its isolation in 1986 from the skin extracts of the brightly coloured Ecuadorian poison frog *Epipedobates tricolor*.[1–3] This activity has been stimulated by the simple but unique nature of the 7-azabicyclo[2.2.1]heptane structure, and more importantly by the finding that epibatidine exhibits potent non-opioid analgesic activity.[4]

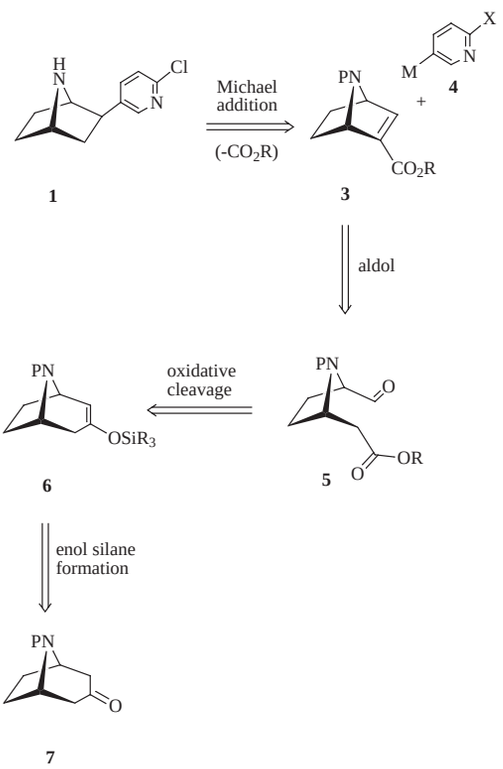
We recently described a total synthesis of epibatidine in racemic form,[5] and in a later communication we indicated how the synthesis could be modified in order to provide the natural product in optically active form.[6] Herein we describe in full detail our synthetic work aimed at the synthesis of this novel alkaloid. We have explored a number of different options, and have uncovered a very direct and efficient route to this target.

(i) Basic strategy

Our synthetic plans centred on the idea of constructing epibatidine by addition of a suitable pyridine nucleophile to an alkene of general structure **2**, activated by an electron-withdrawing group X. This group could be a carboxylic ester or sulfone, which would need to be removed following the key coupling step. It was anticipated that this approach would assure that the pyridine group would be installed in the required *exo*-configuration, and we expected that removal of the activating group X would be readily carried out by either decarboxylation or desulfonylation, as appropriate.

(ii) The tropane route: the aldol approach

Our initial plans centred on the idea that the desired azabicyclic nucleus of the alkaloid target could be derived by a ring contraction strategy, starting with a readily available tropane derivative. One retrosynthetic outline is shown in Scheme 1, in which the required 2-substituted pyridine would be introduced by conjugate addition of a pyridine-derived organometallic **4**

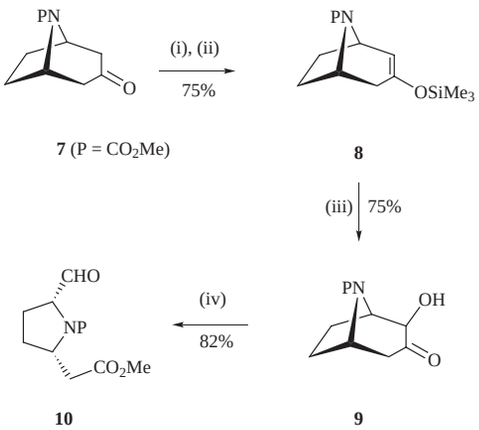


1 **3** **4** **5** **6** **7**

Scheme 1

(*e.g.* X = Cl) to a suitable acceptor, such as the α,β-unsaturated ester **3** (P = appropriate nitrogen protection group). The Michael acceptor **3** might be prepared by intramolecular aldol reaction of **5**, which in turn would be available by oxidative cleavage of the enol silane **6**. This strategy appeared especially attractive to us because we had previously shown that enolisation of tropinone derivatives to give enol silanes such as **6** was possible in highly enantioselective fashion by use of chiral lithium amide base reagents.[7] Therefore, this strategy would allow enantioselective access to epibatidine (either enantiomer would be available) using established asymmetric methodology.

Access to the desired aldol precursor in racemic form proved straightforward, according to the sequence outlined in Scheme 2. The enol silane **8**, prepared by standard techniques, was



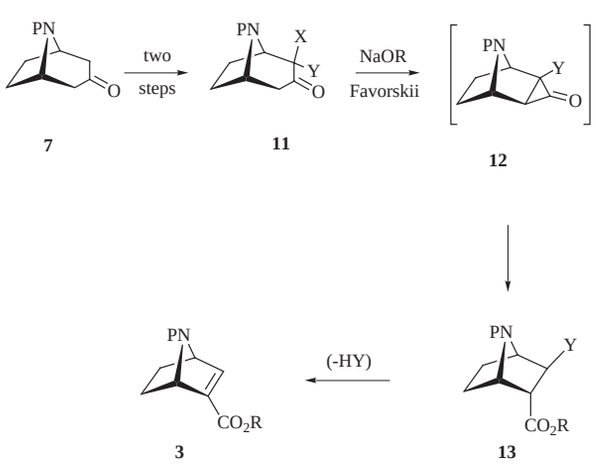
Scheme 2 *Reagents and conditions:* (i) LDA, THF, −78 °C (ii) Me_3SiCl (iii) DMDO, CH_2Cl_2, room temp. (iv) $Pb(OAc)_4$, MeOH, 0 °C.

reacted with dimethyldioxirane (DMDO) to give the α-hydroxy ketone **9** (assigned as the *exo*-alcohol, as indicated by $^3J_{1\text{-H},2\text{-H}}$ <1 Hz, which is typical of an *endo*-proton in the tropinone system), which was then subjected to oxidative cleavage using lead(IV) acetate in methanol to give the ester aldehyde **10**.[8]

Attempts to effect intramolecular aldol condensation of **10** were problematic, none of the desired aldol products being obtained under conditions ranging from LDA at −78 °C to KO^{t}Bu at 0 °C. Instead, only destruction of the starting material was observed. We associated these difficulties with the likelihood of deprotonation at both aldehyde and ester sites, and the possibility of ring-opening β-elimination following ester enolate formation. Attempts to trace the site of enolisation by trapping with Me_3SiCl (including *in situ* quench) were unsuccessful, as were deuterium incorporation experiments. In a last effort to progress this route we prepared the dimethyl acetal corresponding to aldehyde **10**, but were unable to then convert the remaining ester function into the silyl ketene acetal required for attempted ring closure *via* a Mukaiyama Lewis-acid mediated procedure.[9] These failures led us to examine alternative strategies for a ring-contraction route starting with a tropinone derivative.

(iii) The tropane route: the Favorskii approach

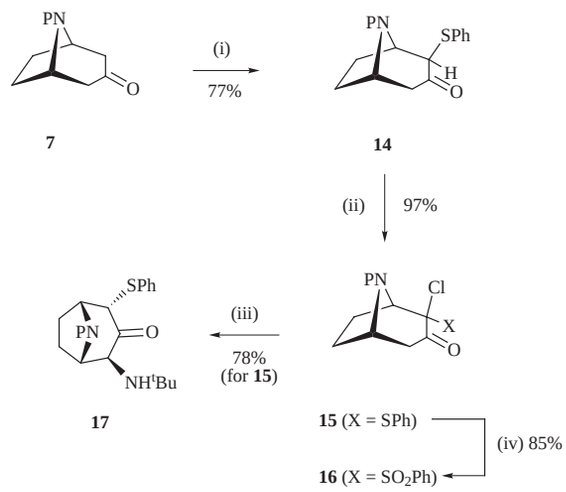
An alternative approach to our key Michael acceptor, starting from a tropinone-derived starting material, was anticipated *via* a modified Favorskii reaction, as indicated in Scheme 3.



Scheme 3

Exposure of a ketone **11**, substituted with two potential leaving groups X and Y, to base, would effect Favorskii ring contraction *via* **12** to give ester **13**, which would then undergo elimination to give the required α,β-unsaturated ester **3** (it should be noted that this sequence would allow enantioselective variants through desymmetrisation of **7** using a chiral lithium amide base). Although this type of reaction has been examined mainly using α,α-dihalo ketones, we chose to explore sequences in which the ketone was substituted with one sulfur-containing group (Y = SAr or SO_2Ar) and one halogen (X = Cl).[10]

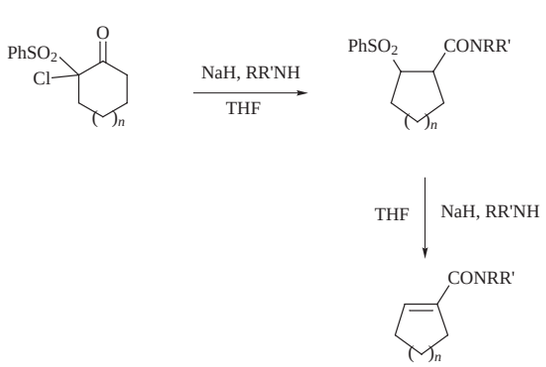
Reaction of tropinone derivative **7** with LDA, followed by addition of $PhSSO_2Ph$ gave the α-sulfenyl ketone **14** as a single (*exo*) diastereoisomer, Scheme 4. Reaction of this compound



Scheme 4 *Reagents and conditions:* (i) LDA, THF, −78 °C; $PhSSO_2Ph$ (ii) SO_2Cl_2, CCl_4 (iii) NaH, ^{t}BuNH$_2$, (iv) MCPBA, CH_2Cl_2, room temp.

with SO_2Cl_2 in CCl_4 then furnished the desired chlorinated compound **15** in excellent yield as an 8:1 mixture of diastereoisomers. The major product is presumably that with the *exo*-orientated chlorine substituent, as shown. This compound was our first Favorskii substrate, and was also oxidised to the corresponding sulfone **16**, which we regarded as another potential candidate for ring contraction.

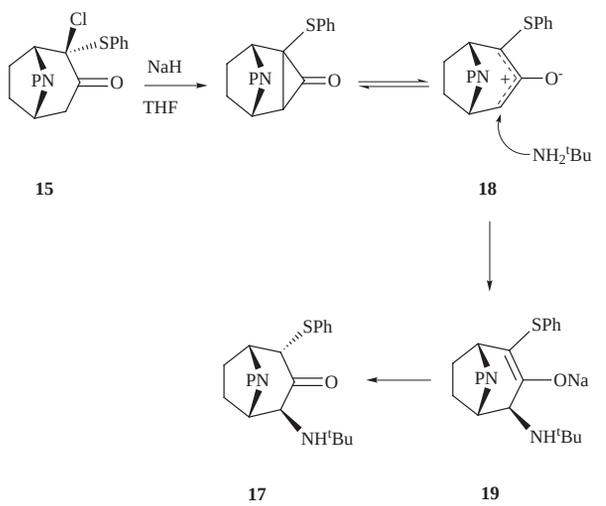
However, attempts to effect the desired ring contraction under classical types of Favorskii conditions, such as treatment of **15** with excess sodium methoxide in methanol, appeared too harsh for our system and resulted only in destruction of the starting material. Changing the reaction solvent to dimethoxyethane, reported as the optimum solvent for a related reaction, gave no improvement.[11] A report from the group of Yamakawa described a Favorskii-type of ring contraction on treatment of α-chloro-α-sulfonyl ketones with a mixture of sodium hydride and a secondary amine, Scheme 5.[12]



Scheme 5

We attempted to apply this method to the sulfone **16**, but reaction with sodium hydride in combination with several amines gave none of the desired products. Instead we chose to try these reaction conditions with the chloro sulfide **15**, and

found that reaction with sodium hydride and *tert*-butylamine resulted in clean conversion to a new compound. The ^{1}H NMR data for this compound led to initial optimism that a ring contracted β-phenylthio amide had been formed. However, more detailed consideration of the chemical shifts of downfield signals, along with ^{13}C NMR data which indicated a ketone and not an amide was present (207 ppm), forced us to conclude that ring contraction had not occurred. Instead, we assign the product of this reaction as the ketone **17**, formed in a highly stereoselective fashion *via exo*-selective attack of the amine on zwitterionic intermediate **18**,[13] followed by *exo*-selective protonation of the so-formed enolate **19**, Scheme 6.



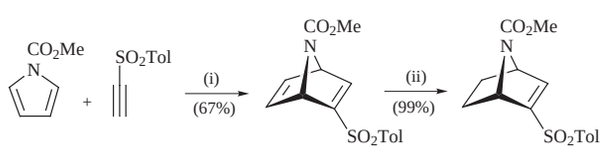
Scheme 6

This failure signalled the end of our investigations in this area, but a successful approach to epibatidine *via* a Favorskii ring contraction was subsequently published by the group of Bai.[14] Their independent studies again indicated the difficulty in achieving a one step Favorskii ring contraction–β-elimination (in this case starting with an α,α′-dibromo ketone), but this problem was circumvented by effecting a normal Favorskii reaction, and then using selenium chemistry to achieve the synthesis of a Michael acceptor of structure **3**.

(iv) The cycloaddition route

Our retrosynthetic analysis of epibatidine **1** suggested the Michael acceptor **2** as a key intermediate, which would incorporate either an unsaturated carboxylic acid derivative, or an unsaturated sulfone. Following our failure to exploit the Favorskii reaction to access the former type of intermediate, attention was focused on the alternative alkenyl sulfone.

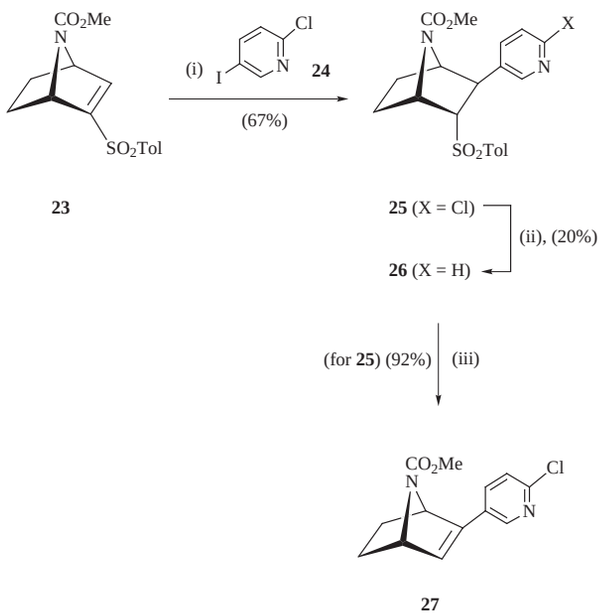
An established route to the 7-azabicyclo[2.2.1]hept-2-ene skeleton involves the cycloaddition of an *N*-protected pyrrole with an ethynyl sulfone.[15] For example reaction of pyrrole **20** with sulfone **21** gives cycloadduct **22**, which can be converted into alkenyl sulfone **23** (*cf.* **2**) by selective hydrogenation of the more electron rich double bond, Scheme 7. This route formed



Scheme 7 *Reagents and conditions:* (i) Δ (neat, 85–90 °C) (ii) H_2, Pd(C), MeCN.

part of one of the earliest (and still the shortest) synthetic routes to epibatidine, in which subsequent desulfonylation of **23** was followed by palladium catalysed coupling with 5-iodo-2-chloropyridine **24**.[16] We too adopted this route, Scheme 7 showing the results we obtained, which are similar to those reported previously.

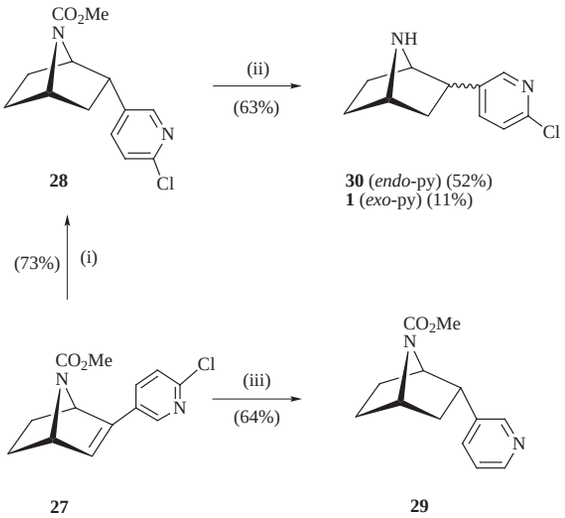
Metallation of 5-iodo-2-chloropyridine **24** was readily achieved by treatment with n-butyllithium at −78 °C, and addition of the alkenyl sulfone **23** to the resulting aryllithium resulted in smooth conversion to the required adduct **25**, Scheme 8. The product sulfone was obtained as a single diastereoisomer, assigned the *trans*-stereochemistry shown following extensive COSY experiments (both ^{1}H–^{1}H and ^{1}H–^{13}C), with the newly introduced pyridine group in the required *exo*-orientation.[17]



Scheme 8 *Reagents and conditions:* (i) BuLi (added to **24**), THF −78 °C (ii) Ra-Ni, THF, room temp. (iii) ^{t}BuOK, THF, 0 °C.

Desulfonylation of **25** proved problematic however, the use of well-established procedures, using sodium or aluminium amalgam, or magnesium in methanol, proving ineffectual.[18] Reaction of **25** with Raney nickel gave the undesired dechlorinated sulfone **26** in modest yield, leading us to conclude that competitive pyridine reduction in this type of attempted desulfonylation was the source of our difficulties. Instead, we treated sulfone **25** with base and succeeded in effecting very clean elimination of sulfinate to give the unsaturated chloropyridine intermediate **27**. Hydrogenation of this intermediate, albeit bearing different nitrogen protecting groups, such as Boc or Tosyl, had been described by several research groups to give mixtures of *exo*/*endo* epimers at the pyridine-bearing centre.[19] In our case, hydrogenation of **27** using PtO_2 under an atmosphere of hydrogen gave exclusively the undesired *endo*-product **28**, whilst the use of palladium on carbon in an acidic medium gave the dechlorinated *endo*-pyridine **29**, Scheme 9. Since base mediated epimerisation of the *endo*-compounds into the required *exo*-epimers had been reported for both the N-Boc and N-H series,[19,20] we did not consider this to be an insurmountable problem. However, in our hands the epimerisation of **28** was accompanied by nitrogen deprotection, and gave a poor ratio (*ca.* 1:5) of epibatidine **1** to its epimer **30**. Resubmitting **30** to the basic reaction conditions gave similar ratios, and rather than persist with efforts to correct the stereochemical problems inherent in this route, we chose to investigate an alternative.

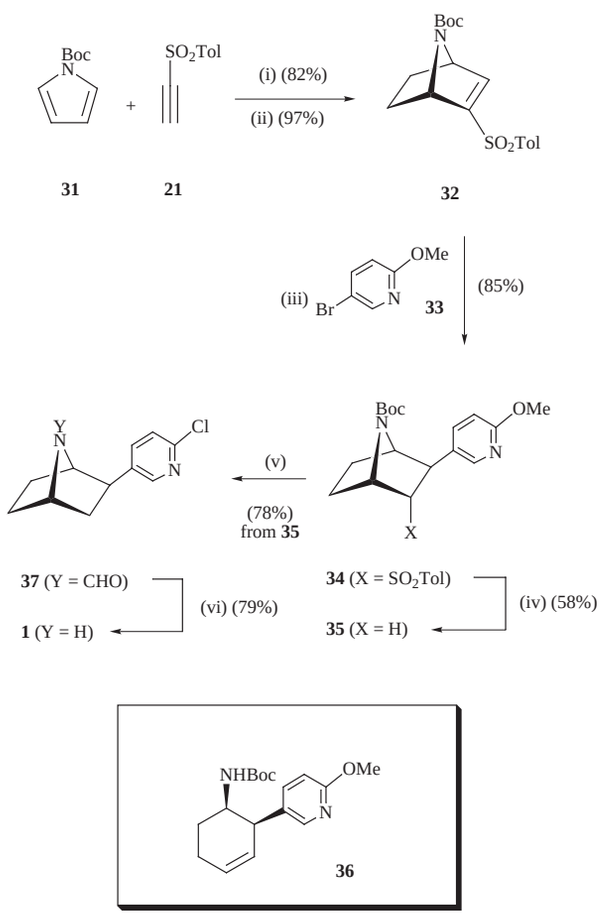
The route to epibatidine involving desulfonylation of key intermediate **25** had been foiled by the propensity of the chloropyridine group present to undergo dechlorination. We chose to re-examine a variant of this approach, which involved the installation of a 2-methoxypyridine group, which would be



Scheme 9 *Reagents and conditions:* (i) PtO_2, H_2, EtOAc (ii) ^tBuOK, ^tBuOH, Δ (iii) Pd(C), H_2, ^iPrOH, H_2O, HCl.

later converted into the desired chloropyridine,[21] once the difficult desulfonylation was complete. At the start of this fresh phase of the work, we took the opportunity to swap to the N-Boc series, because of the prospect of improved ease of protecting group removal at the end of the synthesis.

The first part of the synthesis proceeded as indicated earlier in Scheme 7. Cycloaddition of *N*-Boc pyrrole with *p*-tolyl ethynyl sulfone gave an adduct which was hydrogenated to give alkenyl sulfone **32**, Scheme 10. Addition of the methoxy-



Scheme 10 *Reagents and conditions:* (i) Δ (neat) 85–90 °C (ii) H_2, Pd(C), MeCN (iii) BuLi (added to **33**), THF −78 °C (iv) 6% Na(Hg), THF, MeOH, −20 °C (v) $POCl_3$, DMF, 0 °C then 95 °C (vi) 2 M HCl, Δ, THF.

substituted metallated pyridine proceeded similarly to the chloro derivative, this time using the bromopyridine **33** as a precursor to the required aryllithium. As before, desulfonylation proved problematic, the desired product **35** being accompanied by the unwanted ring opening product **36**. Buffering of the reaction gave no improvement, and this undesired mode of reaction was even observed when the free secondary amine corresponding to **34** was subjected to the desulfonylation conditions. Under optimal conditions sulfone **34** gave the desired product **35** in a reasonable 58% yield, accompanied by 11% of **36**. Subsequent reaction of **35** under Vilsmeier conditions effected the desired methoxypyridine to chloropyridine conversion, along with concomitant exchange of nitrogen protecting groups (due to Boc removal followed by *N*-formylation). This latter transformation proved very helpful in facilitating chromatographic separation of the alkaloid product from polar by-products, small amounts of free epibatidine, also formed at this stage, being much more difficult to obtain in pure form. Finally, the synthesis was completed by heating of **37** with dilute hydrochloric acid, to give the free alkaloid, epibatidine **1**, following basic work-up. Our synthetic epibatidine furnished spectroscopic data in accord with those described previously.

In summary, several alternative approaches to the novel alkaloid epibatidine have been explored, and a concise cycloaddition route established, which is summarised in Scheme 10. The route proceeds in only six steps from the starting *N*-Boc pyrrole and furnishes the natural product in about 24% overall, making it very competitive with other routes published to date. Furthermore, subsequent studies have established that the key alkenyl sulfone **32** can be accessed in non-racemic form *via* a novel enantioselective elimination reaction. At present this reaction is not very efficient, but work aimed at further developing this chemistry is underway and details will be reported elsewhere in due course.

Experimental

General procedures

Melting points were determined on a Reichert Hot Stage apparatus and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 1600 series FTIR spectrophotometer as either sample solutions in chloroform or films. High resolution mass spectra were acquired on a VG Micromass 70E or AEI MS-902 mass spectrometer using electron impact (EI), chemical ionization (CI) or fast atom bombardment (FAB) using *m*-nitrobenzyl alcohol (NBA) as the matrix. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser. Optical rotations were recorded using a JASCO DIP-370 digital polarimeter. Proton NMR spectra were recorded on a Bruker WM 250 (250 MHz), a Bruker AM 400 (400 MHz), a Bruker DRX 500 (500 MHz) or a JEOL EX-270 (270 MHz) spectrometer either at ambient temperature or 333 K. The chemical shifts were recorded relative to an internal tetramethylsilane standard. All coupling constants, *J*, are reported in hertz and abbreviations used are s—singlet, d—doublet, t—triplet, q—quartet, m—multiplet, dd—double doublet *etc*., also bs—broad singlet, bd—broad doublet *etc*. The ratio of isomer mixtures were determined using ^1H NMR spectroscopy. Carbon-13 NMR spectra were either recorded on a JEOL EX 270 (68 MHz) spectrometer or a Bruker AM 400 (100 MHz) at ambient temperature. The multiplicities indicated were obtained using a DEPT sequence. Proton and carbon assignments were frequently assisted by obtaining ^1H–^1H COSY and ^1H–^{13}C COSY spectra, which were recorded on a JEOL EX 270 spectrometer. Reaction progress was monitored by thin layer chromatography (TLC) using Merck silica gel 60 F_{254} precoated plates which were visualised with ultraviolet light and developed by staining with either basic potassium permanganate solution or acidic ammonium molybdate(IV). Liquid chromatography was per-

formed using forced flow (flash chromatography) of the indicated solvent system on Fluka silica gel 60 (220–440 mesh).

Organic solvents and reagents were dried from the following as required: THF and Et_2O (sodium–benzophenone ketyl), methanol (from magnesium methoxide onto 3 Å molecular sieves), CH_2Cl_2 and chlorotrimethylsilane (calcium hydride). Petroleum ether refers to the fraction with bp 40–60 °C which was distilled prior to use. All other reagents were used as received from commercial suppliers unless otherwise stated.

N-Methoxycarbonyl-3-trimethylsilyloxy-8-azabicyclo[3.2.1]oct-2-ene 8

n-BuLi (1.6 M in hexanes) (4.44 ml, 7.1 mmol) was added dropwise over 3 min to a stirred solution of diisopropylamine (1.0 ml, 7.1 mmol) in THF (40 ml) under N_2 at −78 °C. After 50 min a solution of the ketone **7** (1.0 g, 5.5 mmol) in THF (6 ml) was added dropwise over 5 min then followed after a further 35 min by chlorotrimethylsilane (1.39 ml, 10.9 mmol). The solution was stirred for a furthur 20 min before adding sat. aq. $NaHCO_3$ (10 ml), warming to room temp. and concentrating *in vacuo*. The aqueous layer was extracted with petroleum ether (3 × 50 ml), the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. Purification on silica gel (50% diethyl ether–petroleum ether) yielded the *title compound* **8** as a pale yellow oil (1.04 g, 75%); ν_{max}(film)/cm^{-1} 2955, 2913, 2871, 1708, 1651, 1448, 1108, 878 and 842; δ_H(250 MHz; $CDCl_3$) 0.16 (9H, s, -Si(CH_3)$_3$), 1.58–1.68 (1H, m), 1.76 (1H, d, *J* 15.8, 4-CH_{endo}), 1.82–1.99 (2H, m), 2.02–2.21 (1H, m), 2.56–2.87 (1H, m, 4-CH_{exo}), 3.66 (3H, s, -CO_2CH_3), 4.21–4.47 (2H, bs, 1 and 5-CH) and 5.13 (1H, bs, 2-CH); δ_C(68 MHz; $CDCl_3$) (rotamers) 0.0 ($SiMe_3$), 29.0 and 29.5 (6 or 7-CH_2), 35.0 and 35.6 (6 or 7-CH_2), 38.6 and 39.4 (4-CH_2), 52.0 (1 and 5-CH), 52.1 (-CO_2Me), 109.3 (2-CH), 148.9 (3-C) and 154.5 (-CO_2Me).

N-Methoxycarbonyl-2-*exo*-hydroxy-8-azabicyclo[3.2.1]octan-3-one 9

Dimethyldioxirane (0.05 M acetone solution[22]) (44 ml, 2.2 mmol) was added in one portion to a stirred solution of the silyl enol ether **8** (0.47 g, 1.8 mmol) in CH_2Cl_2 (5 ml) under N_2 at room temp. After 90 min the reaction mixture was concentrated *in vacuo* to yield an orange oil which was purified on silica gel (75% EtOAc–petroleum ether) to yield the *title compound* **9** as a yellow oil (0.24 g, 75%); ν_{max}(film)/cm^{-1} 3404, 2958, 2888, 1692, 1462, 1404, 1116, 993 and 764; δ_H(250 MHz; $CDCl_3$) 1.47–1.59 (2H, m, 6,7-CH), 2.00–2.12 (2H, m, 6,7-CH), 2.26 (1H, d, *J* 15.4, 4-CH_{endo}), 3.06 (1H, dd, *J* 15.4 2.8, 4-CH_{exo}), 3.77 (3H, s, -CO_2CH_3), 3.84 (1H, bs, 2-CH) and 4.60 (2H, bs, 1 and 5-CH); δ_C(68 MHz; $CDCl_3$) 23.7 (6 or 7-CH_2), 27.5 (6 or 7-CH_2), 45.6 (4-CH_2), 52.6 (-CO_2Me), 53.0 (1 or 5-CH), 58.0 (1 or 5-CH), 78.2 (2-CH), 155.4 (-CO_2Me) and 207.1 (C=O); *m*/*z*(EI) 199 (M^+, 22%), 171 (24), 142 (25), 126 (100) and 69 (11) (Found: [M − CO_2CH_3]$^+$, 140.0703. $C_7H_{10}NO_2$ requires M^+, 140.0711).

N-Methoxycarbonyl-5β-formyl-2β-(methoxycarbonylmethyl)-pyrrolidine 10

Lead tetraacetate (1.6 g, 3.6 mmol) was added in one portion to a stirred solution of the hydroxy ketone **9** (0.60 g, 3.0 mmol) in MeOH (25 ml) under N_2 at 0 °C. After 30 min the reaction mixture was concentrated *in vacuo*, water (60 ml) added and the aqueous layer extracted with CH_2Cl_2 (3 × 20 ml). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow gum which was purified on silica gel (60% EtOAc–petroleum ether) to yield the *title compound* **10** as a yellow oil (0.56 g, 82%); ν_{max}(film)/cm^{-1} 2956, 1737, 1452, 1381, 1122, 992 and 974; δ_H(250 MHz; $CDCl_3$) (rotamers) 1.74–1.75 (1H, m), 1.96–2.19 (3H, m), 2.41–2.47 (1H, m), 2.82–3.18 (1H, bm), 3.66 (3H, s, -CO_2CH_3), 3.73–3.77 (3H, bs, -CO_2CH_3), 4.17 and 4.30 (2H, m), 9.48 and 9.54 (1H, bs, -CHO); δ_C(68 MHz; $CDCl_3$) (rotamers) 24.4 and 25.4 (3 or 4-CH_2), 29.6 and 30.5 (3 or 4-CH_2), 38.3 and 39.2 (-CH_2CO_2Me), 51.6 (-CO_2Me), 52.7 (-CO_2Me), 55.0 and 55.7 (5-CH), 65.8 and 66.1 (2-CH), 156.2 (-CO_2Me), 171.3 (-CO_2Me) and 199.8 (C=O); *m*/*z*(EI) 200 ([M − COH]$^+$, 33%), 168 (11), 156 (19) and 126 (100) (Found: [M − COH]$^+$, 200.0915. $C_9H_{14}NO_4$ requires M^+, 200.0923).

N-Methoxycarbonyl-2-*exo*-(phenylsulfanyl)-8-azabicyclo[3.2.1]-octan-3-one 14

n-BuLi (1.6 M in hexanes) (3.69 ml, 5.9 mmol) was added dropwise over 3 min to a stirred solution of diisopropylamine (0.78 ml, 5.9 mmol) in THF (30 ml) under N_2 at −78 °C. After 40 min a solution of the ketone **7** (0.90 g, 4.9 mmol) in THF (10 ml) was added dropwise over 4 min. After stirring for a further 70 min a solution of phenyl benzenethiosulfonate (1.35 g, 5.4 mmol)[23] in THF (10 ml) was added dropwise over 5 min. The reaction mixture was stirred for 60 min before addition of sat. aq. $NaHCO_3$ (40 ml) in one portion, the reaction mixture was warmed to room temp. and then concentrated *in vacuo*. The aqueous layer was extracted with diethyl ether (3 × 20 ml), the combined organic layers were washed with brine (2 × 20 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. Purification on silica gel (16:4:1 $CHCl_3$–petroleum ether–diethyl ether) gave the *title compound* **14** as a pale yellow oil which crystallised on storage in a freezer to yield a white solid (1.10 g, 77%), mp 118–119 °C (diethyl ether) (Found: C, 61.40; H, 5.99; N, 4.85; S, 10.87. $C_{15}H_{17}NO_3S$ requires C, 61.83; H, 5.99; N, 4.81; S, 11.01%); ν_{max}(film)/cm^{-1} 2994, 2958, 1698, 1456, 1116 and 979; δ_H(250 MHz; $CDCl_3$) 1.61–1.79 (2H, m, 6 and 7-CH_{endo}), 1.96–2.18 (2H, m, 6 and 7-CH_{exo}), 2.23 (1H, d, *J* 15.4, 4-CH_{endo}), 3.26 (1H, bd, 4-CH_{exo}), 3.55 (1H, s, 2-CH), 3.80 (3H, s, -CO_2CH_3), 4.68 (1H, bs, 5-CH), 4.80 (1H, bs, 1-CH), 7.27–7.34 (3H, m) and 7.42–7.45 (2H, m); δ_C(68 MHz; $CDCl_3$) 27.8 (6 or 7-CH_2), 28.8 (6 or 7-CH_2), 45.0 (4-CH_2), 52.6 (-CO_2Me), 53.3 (5-CH), 56.9 (1-CH), 61.4 (2-CH), 127.9 (Ar-CH), 128.9 (Ar-CH), 132.4 (Ar-CH), 132.6 (Ar-C), 154.2 (-CO_2Me) and 203.2 (C=O); *m*/*z*(EI) 291 (M^+, 15%), 182 (10), 166 (49) and 126 (100) (Found: M^+, 291.0930. $C_{15}H_{17}NO_3S$ requires M^+, 291.0930).

N-Methoxycarbonyl-2-*exo*-chloro-2-*endo*-(phenylsulfanyl)-8-azabicyclo[3.2.1]octan-3-one 15

A solution of sulfuryl chloride (0.67 ml, 8.3 mmol) in CCl_4 (4 ml) was added dropwise over 25 min to a stirred solution of the sulfenyl ketone **14** (1.10 g, 3.8 mmol) in CCl_4 (10 ml). After 30 min the reaction mixture was concentrated *in vacuo* to yield a yellow gum which was purified on silica gel (35% EtOAc–petroleum ether) to yield the *title compound* **15** as a colourless gum which crystallised on storage in a freezer to give a white solid (1.19 g, 97%), mp 112–114 °C (Found: C, 55.31; H, 5.00; N, 4.36; Cl, 10.81; S, 9.57. $C_{15}H_{16}NO_3SCl$ requires C, 55.30; H, 4.95; N, 4.30; Cl, 10.88; S, 9.84%); ν_{max}(film)/cm^{-1} 3058, 2957, 2886, 1713, 1454, 1402, 1115 and 755; δ_H(250 MHz; $CDCl_3$; 333 K) 1.55–1.63 (1H, m), 1.96–2.05 (2H, m), 2.33–2.41 (1H, m), 2.37 (1H, dd, *J* 15.4 1.9, 4-CH_{endo}), 3.33 (1H, dd, *J* 15.4 4.6, 4-CH_{exo}), 3.62 (3H, s, -CO_2CH_3), 4.34 (1H, bs, 5-CH), 4.62 (1H, bs, 1-CH), 7.35–7.43 (3H, m) and 7.63–7.67 (2H, m); δ_C(68 MHz; $CDCl_3$) (rotamers) 25.5 and 26.3 (6 or 7-CH_2), 27.4 and 28.3 (6 or 7-CH_2), 44.0 (4-CH_2), 52.4 (-CO_2Me), 52.9 (5-CH), 61.7 (1-CH), 84.9 (2-C), 127.1 (Ar-C), 129.1 (Ar-CH), 129.9 (Ar-CH), 136.6 (Ar-CH), 153.6 (-CO_2Me) and 197.6 (C=O); *m*/*z*(EI) 325 (M^+, 11%), 200 (7) and 126 (100) (Found: M^+, 325.0535. $C_{15}H_{16}NO_3S^{35}Cl$ requires M^+, 325.0539).

N-Methoxycarbonyl-2-*exo*-chloro-2-*endo*-(phenylsulfonyl)-8-azabicyclo[3.2.1]octan-3-one 16

3-Chloroperoxybenzoic acid (60%) (1.18 g, 3.96 mmol) was

added in two portions over 30 min to a stirred, cooled (0 °C) solution of the sulfenyl ketone **15** (0.59 g, 1.80 mmol) in CH_2Cl_2 (8 ml), which was then warmed to room temp. After stirring for 18 h CH_2Cl_2 (30 ml) was added and the organic layer washed with 5% NaOH (2 × 15 ml), sat. aq. NH_4Cl (2 × 15 ml) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a colourless gum. Purification on silica gel (40% EtOAc–petroleum ether) yielded the *title compound* **16** as a white foam (0.55 g, 85%) (8:1 inseparable mixture of diastereomers), mp 137–138 °C (EtOAc) (Found: C, 50.28; H, 4.46; N, 4.12; Cl, 9.95. $C_{15}H_{16}NO_5SCl$ requires C, 50.35; H, 4.51; N, 4.51; Cl, 9.92%); ν_{max}(film)/cm^{-1} 3066, 2958, 1714, 1454, 1322, 1115, 992, 759 and 687; δ_H(250 MHz; $CDCl_3$; 333 K) (major diastereomer) 1.64–1.76 (1H, m), 2.03–2.33 (2H, m), 2.37 (1H, d, *J* 16.0, 4-CH_{endo}), 2.84–3.97 (1H, m), 3.09 (1H, dd, *J* 16.0 5.1, 4-CH_{exo}), 3.74 (3H, s, -CO_2CH_3), 4.69 (1H, bs, 5-CH), 5.15 (1H, d, *J* 7.3, 1-CH), 7.51–7.66 (3H, m) and 8.15–8.17 (2H, m); δ_C(68 MHz; $CDCl_3$) 27.0 (6 or 7-CH_2), 27.8 (6 or 7-CH_2), 45.4 (4-CH_2), 52.8 (-CO_2Me), 53.0 (5-CH), 59.6 (1-CH), 83.0 (2-C), 128.3 (Ar-CH), 131.8 (Ar-CH), 134.6 (Ar-CH), 136.2 (Ar-C), 153.6 (-CO_2Me) and 195.2 (C=O); *m*/*z*(EI) 359 (M[^{37}Cl]$^+$, 4%), 357 (M[^{35}Cl]$^+$, 11), 216 ([M − SO_2Ph]$^+$, 23), 174 (27) and 126 (100) (Found: M$^+$, 359.0415. $C_{15}H_{16}NO_5S^{37}Cl$ requires M$^+$, 359.0408).

N-Methoxycarbonyl-2-*endo*-(phenylsulfanyl)-4-*exo*-(*tert*-butylamino)-8-azabicyclo[3.2.1]octan-3-one 17

Sodium hydride (0.32 g, 7.99 mmol) was added in one portion to a solution of the sulfanyl ketone **15** (0.81 g, 2.50 mmol) in THF (12 ml) at 0 °C under N_2. After 20 min *tert*-butylamine (0.84 ml, 7.99 mmol) was added in one portion and the reaction mixture stirred for 23 h at 4 °C before adding sat. aq. NH_4Cl (20 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 ml), the combined organics dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. Purification on silica gel (30% EtOAc–petroleum ether) yielded the *title compound* **17** as a pale red oil (0.70 g, 78%); ν_{max}(film)/cm^{-1} 2960, 1738, 1704, 1448, 1112, 741 and 692; δ_H(250 MHz; $CDCl_3$) 1.04 (9H, s, -C(CH_3)$_3$), 1.09–1.25 (1H, m), 1.54–2.05 (4H, m), 3.36 (1H, d, *J* 2.7, 2-CH), 3.74 (3H, s, -CO_2CH_3), 4.43 (2H, bs, 1 and 5-CH), 4.86 (1H, m, 4-CH), 7.23–7.35 (3H, m) and 7.43–7.46 (2H, m); δ_C(68 MHz; $CDCl_3$) 26.1 (6 or 7-CH_2), 26.3 (6 or 7-CH_2), 29.5 (CMe_3), 51.5 (CMe_3), 52.8 (-CO_2Me), 57.9 (CH), 58.5 (CH), 59.8 (CH), 67.5 (CH), 126.8 (Ar-CH), 129.1 (Ar-CH), 130.6 (Ar-CH), 133.4 (Ar-C), 155.1 (-CO_2Me) and 206.1 (C=O); *m*/*z*(EI) 360 ([M − 2H]$^+$, 5%), 334 ([M − CO]$^+$, 16), 253 ([M − SPh]$^+$, 100), 225 (54), 172 (75) and 126 (79) (Found: [M − 2H]$^+$, 360.1521. $C_{19}H_{24}N_2O_3S$ requires M$^+$, 360.1508).

N-Methoxycarbonyl-2-(*p*-tolylsulfonyl)-7-azabicyclo[2.2.1]-hepta-2,5-diene 22

N-Methoxycarbonylpyrrole (2.5 g, 20 mmol) was added to ethynyl *p*-tolyl sulfone (7.2 g, 40 mmol),[24] the reaction mixture protected from light, then heated to 85 °C under N_2. After 26 h the brown oil obtained was cooled to room temp. and then purified on silica gel (30% to 50% EtOAc–petroleum ether) to yield the product as a pale brown oil. Crystallisation with diethyl ether yielded the *title compound* **22** as a white solid (4.1 g, 67%), mp 87–88 °C (Found: C, 59.08; H, 4.90; N, 4.57. $C_{15}H_{15}NO_4S$ requires C, 59.00; H 4.95; N 4.59%); ν_{max}($CHCl_3$)/cm^{-1} 2956, 1714, 1597, 1450, 1347, 1322, 1304 and 1084; δ_H(250 MHz; $CDCl_3$; 333 K) 2.45 (3H, s, -CO_2Me), 3.50 (3H, s, -$SO_2C_6H_4Me$), 5.23 (1H, bs, 4-CH), 5.42 (1H, d, *J* 2.4, 1-CH), 6.90 (1H, dd, *J* 5.3, 2.4, 5 or 6-CH), 6.98 (1H, dd, *J* 5.3, 2.4, 5 or 6-CH), 7.35 (2H, d, *J* 8.2, Tol-CH), 7.56 (1H, d, *J* 2.1, 3-CH) and 7.75 (2H, d, *J* 8.2, Tol-CH); δ_C(68 MHz; $CDCl_3$) 21.6 (Tol-CH_3), 52.8 (-OCH_3), 66.5 (1 or 4-CH), 67.7 (1 or 4-CH), 128.0 (Tol-CH), 130.0 (Tol-CH), 141.8 (CH), 142.9 (CH), 144.9 (C), 150.9 (C), 152.4 (CH), 154.6 (C) and 159.0 (C=O); *m*/*z*(CI) 306 (M + H$^+$, 32%), 274 (63), 182 (49), 150 (71) and 125 (100) (Found: M + H$^+$, 306.0784. $C_{15}H_{16}NO_4S$ requires M$^+$, 306.0800).

N-Methoxycarbonyl-2-(*p*-tolylsulfonyl)-7-azabicyclo[2.2.1]hept-2-ene 23

The diene **22** (3.28 g, 10.7 mmol) was dissolved in acetonitrile (40 ml) and added under N_2 to 10% palladium on carbon (0.1 mass equiv., 0.33 g). The suspension was stirred under a hydrogen atmosphere until the required volume of hydrogen was absorbed (240 ml, 10.7 mmol), the reaction mixture was then filtered through Celite with EtOAc. The filtrate was concentrated *in vacuo* to yield a pale yellow oil which crystallised on standing to give the *title compound* **23** as a white solid (3.28 g, 99%), mp 69.5–70.5 °C (Found: C, 58.44; H, 5.77; N, 4.74. $C_{15}H_{17}NO_4S$ requires C, 58.44; H 5.57; N 4.74%); ν_{max}($CHCl_3$)/cm^{-1} 2955, 1714, 1596, 1318, 1152, 1091 and 674; δ_H(250 MHz; $CDCl_3$; 333 K) 1.22–1.40 (2H, m), 1.87–2.09 (2H, m), 2.43 (3H, s, -$SO_2C_6H_4Me$), 3.47 (3H, s, -CO_2Me), 4.80–4.90 (2H, m, 1 and 4-CH), 6.98 (1H, d, *J* 1.9, 3-CH), 7.34 (2H, d, *J* 8.2, Tol-CH) and 7.77 (2H, d, *J* 8.2, Tol-CH); δ_C(68 MHz; $CDCl_3$) 19.6 (Tol-CH_3), 22.1 (5 or 6-CH_2), 22.8 (5 or 6-CH_2), 50.5 (-OCH_3), 58.4 (1 or 4-CH), 59.6 (1 or 4-CH), 125.7 (Tol-CH), 127.9 (Tol-CH), 134.4 (C), 141.2 (3-CH), 142.8 (C), 146.8 (C) and 153.6 (C=O); *m*/*z*(CI) 308 (M + H$^+$, 18%), 294 (23), 279 (100), 233 (42) and 139 (50) (Found: M + H$^+$, 308.0948. $C_{15}H_{18}NO_4S$ requires M$^+$, 308.0956).

N-Methoxycarbonyl-3-*exo*-(2-chloro-5-pyridyl)-2-*endo*-(*p*-tolylsulfonyl)-7-azabicyclo[2.2.1]heptane 25

n-BuLi (1.6 M in hexanes) (3.15 ml, 5.0 mmol) was added dropwise over 1 min to a stirred solution of 5-iodo-2-chloropyridine **24** (1.0 g, 4.2 mmol) in THF (30 ml) under N_2 at −78 °C. After 10 min a solution of the alkenyl sulfone **23** (1.28 g, 4.16 mmol) in THF (15 ml) was added dropwise over 6 min to the metallated pyridine. After 15 min at −78 °C, sat. aq. $NaHCO_3$ (5 ml) was added and the solution warmed to room temp. The orange mixture was concentrated *in vacuo*, diluted with brine (20 ml) and extracted with EtOAc (3 × 25 ml). The combined organics were dried ($MgSO_4$), filtered then concentrated *in vacuo* to yield a brown oil. Purification on silica gel (16:6:2 $CHCl_3$–petroleum ether–diethyl ether) gave recovered alkenyl sulfone **23** (0.16 g, 12%) followed by the *title compound* **25** as a white crystalline solid (1.19 g, 67%), mp 171–172 °C (Found: C, 56.80; H, 5.29; N, 6.70. $C_{20}H_{21}N_2O_4SCl$ requires C, 57.07; H 5.03; N 6.66%); ν_{max}($CHCl_3$)/cm^{-1} 2954, 1704, 1322, 1108 and 962; δ_H(250 MHz; $CDCl_3$) 1.69–2.00 (3H, m), 2.41 (3H, s, -$SO_2C_6H_4Me$), 2.63–2.74 (1H, m, 6-CH_{endo}), 3.36 (1H, d, *J* 5.9, 3-CH), 3.61 (1H, m, 2-CH), 3.68 (3H, s, -O*Me*), 4.35 (1H, d, *J* 4.6, 4-CH), 4.52 (1H, dd, *J* 4.2 4.2, 1-CH), 7.15 (1H, d, *J* 8.3, 3′-CH), 7.28 (2H, d, *J* 8.2, Tol-CH), 7.51 (1H, dd, *J* 8.3 2.6, 4′-CH), 7.62 (2H, d, *J* 8.2, Tol-CH) and 8.17 (1H, d, *J* 2.6, 6′-CH); δ_C(68 MHz; $CDCl_3$) 21.5 (Tol-CH_3), 23.9 (5 or 6-CH_2), 29.4 (5 or 6-CH_2), 46.8 (3-CH), 52.9 (-OCH_3), 58.3 (1-CH), 64.1 (4-CH), 72.8 (2-CH), 124.0 (3′-CH), 127.7 (Tol-CH), 130.1 (Tol-CH), 135.8 (C), 136.5 (C), 137.1 (4′-CH), 145.4 (C), 148.4 (6′-CH), 150.1 (C) and 155.1 (C=O); *m*/*z*(FAB) 423 (M[^{37}Cl] + H$^+$, 41%), 421 (M[^{35}Cl] + H$^+$, 100), 265 (30) (Found: M + H$^+$, 421.0995. $C_{20}H_{22}N_2O_4S^{35}Cl$ requires M + H$^+$, 421.0989).

N-Methoxycarbonyl-3-*exo*-(3-pyridyl)-2-*endo*-(*p*-tolylsulfonyl)-7-azabicyclo[2.2.1]heptane 26

Raney nickel (5 mass equiv., 0.3 g) was added in one portion to a stirred solution of the sulfone **25** (0.06 g, 0.14 mmol) in THF (3 ml) at 0 °C. The suspension was warmed to room temp. over 1 h and then additional Raney nickel (0.5 g) added and stirred for a further 8 h. The reaction mixture was filtered through Celite, concentrated *in vacuo* and the residue purified on silica

gel (90% EtOAc–petroleum ether) to yield the *title compound* **26** as a colourless oil (0.011 g, 20%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3030, 2957, 1704, 1447, 1322 and 1088; δ_H(250 MHz; $CDCl_3$) 1.64–2.00 (3H, m), 2.39 (3H, s, -$SO_2C_6H_4Me$), 2.65–2.78 (1H, m), 3.36 (1H, d, *J* 5.7, 3-CH), 3.67 (4H, m, 2-CH and -O*Me*), 4.36 (1H, d, *J* 4.1, 4-CH), 4.53 (1H, dd, *J* 4.3 4.3, 1-CH), 7.13 (1H, dd, *J* 8.0 4.8, 5′-CH), 7.26 (2H, d, *J* 8.2, Tol-CH), 7.52 (1H, ddd, *J* 8.0 1.9 1.9, 4′-CH), 7.66 (2H, d, *J* 8.2, Tol-CH) and 8.40–8.42 (2H, m, 2′ and 6′-CH); δ_C(100 MHz; $CDCl_3$) 21.6 (Tol-CH_3), 24.2 (5 or 6-CH_2), 29.6 (5 or 6-CH_2), 47.9 (3-CH), 52.9 (-OCH_3), 58.4 (1-CH), 64.4 (4-CH), 72.9 (2-CH), 123.4 (5′-CH), 127.9 (Tol-CH), 130.1 (Tol-CH), 134.2 (4′-CH), 136.2 (C), 137.5 (C), 145.3 (C), 148.5 (2′ or 6′-CH), 148.7 (2′ or 6′-CH) and 155.3 (C=O); *m*/*z*(FAB) 387 (M + H^+, 29%), 307 (31), 154 (100) and 136 (67) (Found: M + H^+, 387.1379. $C_{20}H_{23}N_2O_4S$ requires M^+, 387.1379).

N-Methoxycarbonyl-2-(2-chloro-5-pyridyl)-7-azabicyclo[2.2.1]-hept-2-ene 27

A solution of potassium *tert*-butoxide (0.19 g, 1.7 mmol) in THF (5 ml) was added dropwise over 2 min to a stirred solution of the sulfone **25** (0.56 g, 1.3 mmol) in THF (20 ml) under N_2 at 0 °C. After 15 min sat. aq. NH_4Cl (1 ml) was added, the solution warmed to room temp. then concentrated *in vacuo*. The residue was diluted with brine (20 ml), extracted with EtOAc (3 × 30 ml), the organics were dried ($MgSO_4$) and then concentrated *in vacuo* to yield a yellow oil. Purification on silica gel (25% EtOAc–petroleum ether) yielded the *title compound* **27** as a pale yellow oil (0.32 g, 92%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2990, 2954, 1694, 1627, 1460, 1360, 1310, 1107 and 978; δ_H(250 MHz; $CDCl_3$) 1.14–1.36 (2H, m, 5 and 6-CH_{endo}), 1.93–2.06 (2H, m, 5 and 6-CH_{exo}), 3.67 (3H, s, -O*Me*), 4.90 (1H, bs, 1 or 4-CH), 5.13 (1H, bs, 1 or 4-CH), 6.58 (1H, bs, 3-CH), 7.30 (1H, d, *J* 2.5, 3′-CH), 7.65 (1H, dd, *J* 8.3 2.5, 4′-CH) and 8.42 (1H, d, *J* 2.5, 6′-CH); δ_C(68 MHz; $CDCl_3$) 24.2 (5 or 6-CH_2), 25.7 (5 or 6-CH_2), 52.6 (-OCH_3), 60.2 (1 or 4-CH), 60.9 (1 or 4-CH), 124.2 (3'-CH), 127.6 (C), 130.7 (3-CH), 135.1 (4'-CH), 143.5 (C), 146.2 (6'-CH), 150.3 (C) and 155.7 (C=O); *m*/*z*(CI) 265 (M + H^+, 100%), 251 (50), 190 (21) and 91 (12) (Found: M + H^+, 265.0741. $C_{13}H_{14}N_2O_2{}^{35}Cl$ requires M^+, 265.0744).

N-Methoxycarbonyl-2-*endo*-(2-chloro-5-pyridyl)-7-azabicyclo-[2.2.1]heptane 28

The vinylpyridine **27** (0.10 g, 0.38 mmol) was dissolved in EtOAc (5 ml), platinum oxide (0.2 mass equiv., 0.02 g) added, and the mixture stirred under hydrogen for 50 min. The black suspension was filtered through Celite and concentrated *in vacuo* to yield a colourless oil. Purification on silica gel (30% EtOAc–petroleum ether) gave the *title compound* **28** as a colourless oil (0.074 g, 73%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2984, 2957, 1695, 1459, 1370, 1167, 1105 and 1025; δ_H(250 MHz; $CDCl_3$; 333 K) 1.41–1.50 (2H, m), 1.58–1.68 (2H, m), 1.80–1.89 (1H, m), 2.31 (1H, dddd, *J* 12.2 12.2 4.1 3.0, 3-CH_{exo}), 3.42–3.50 (1H, m, 2-CH), 3.72 (3H, s, -O*Me*), 4.37–4.44 (2H, m, 1 and 4-CH), 7.28 (1H, d, *J* 8.2, 3′-CH), 7.49 (1H, ddd, *J* 8.2 2.5 0.6, 4′-CH) and 8.25 (1H, d, *J* 2.5, 6′-CH); δ_C(68 MHz; $CDCl_3$) 23.2 (5 or 6-CH_2), 30.0 (5 or 6-CH_2), 34.1 (3-CH_2), 43.4 (2-CH), 52.3 (-OCH_3), 56.9 (4-CH), 60.0 (1-CH), 123.7 (3′-CH), 124.0 (C), 134.3 (C), 138.3 (4′-CH), 149.3 (6′-CH) and 155.7 (C=O); *m*/*z*(FAB) 269 (M[^{37}Cl] + H^+, 25%), 267 (M[^{35}Cl] + H^+, 78), 154 (100) and 136 (65) (Found: M + H^+, 267.0892. $C_{13}H_{16}N_2O_2{}^{35}Cl$ requires M^+, 267.0900).

N-Methoxycarbonyl-2-*endo*-(3-pyridyl)-7-azabicyclo[2.2.1]-heptane 29

The vinylpyridine **27** (0.05 g, 0.19 mmol) and 10% palladium on carbon (0.25 mass equiv., 0.025 g) were suspended in propan-2-ol (12 ml), water (1 ml) and 10% HCl (1.3 ml). The suspension was stirred under a hydrogen atmosphere for 50 min before filtering through Celite and concentrating *in vacuo*. Purification on silica gel (60% EtOAc–petroleum ether) yielded the *title compound* **29** as a colourless oil (0.028 g, 64%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2955, 2880, 1698, 1446, 1367, 1165, 1103 and 1026; δ_H(400 MHz; $CDCl_3$) 1.43–1.51 (2H, m), 1.58–1.70 (2H, m), 1.82–1.89 (1H, m), 2.31 (1H, dddd, *J* 12.1 12.1 5.1 3.1, 3-CH_{exo}), 3.49–3.52 (1H, m, 2-CH), 3.73 (3H, s, -O*Me*), 4.41–4.44 (2H, m, 1 and 4-CH), 7.26–7.28 (1H, m, 4′-CH), 7.53 (1H, bd, 5′-CH) and 8.51 (2H, bs, 2′ and 6′-CH); δ_C(100 MHz; $CDCl_3$) 23.4 (5 or 6-CH_2), 30.2 (5 or 6-CH_2), 34.1 (3-CH_2), 44.3 (2-CH), 52.5 (-OCH_3), 57.2 (4-CH), 60.3 (1-CH), 123.2 (5′-CH), 135.5 (4′-CH), 147.8 (2′ or 6′-CH), 149.8 (2′ or 6′-CH) and 156.0 (C=O); *m*/*z*(FAB) 233 (M + H^+, 100%), 154 (8), 127 (8) and 106 (11) (Found: M + H^+, 233.1289. $C_{13}H_{17}N_2O_2$ requires M^+, 233.1290).

2-*exo*-(2-Chloro-5-pyridyl)-7-azabicyclo[2.2.1]heptane 1 (epibatidine) and 2-*endo*-(2-chloro-5-pyridyl)-7-azabicyclo-[2.2.1]heptane 30

Potassium *tert*-butoxide (0.29 g, 2.6 mmol) was added to a solution of **28** (0.07 g, 0.26 mmol) in *tert*-butyl alcohol (14 ml) under N_2, and the mixture heated under reflux for 26 h. After cooling to room temp. the solution was concentrated *in vacuo* to yield a white solid. Purification on silica gel (98:2:1 then 96:4:1 CH_2Cl_2–MeOH–NH_3) gave firstly *epibatidine* **1** as a white solid (0.006 g, 11%), mp 59–60 °C (lit.,[19a] 50–51 °C); $\nu_{max}(CHCl_3)/cm^{-1}$ 3265, 2961, 2872, 1582, 1562, 1457, 1104, 1025 and 754; δ_H(400 MHz; $CDCl_3$) 1.50–1.62 (6H, m, 5-CH_2, 6-CH_2, 3-CH_{exo} and NH), 1.90 (1H, dd, *J* 12.0, 9.0, 3-CH_{endo}), 2.75 (1H, dd, *J* 9.0 4.9, 2-CH), 3.54 (1H, d, *J* 1.1, 1-CH), 3.78 (1H, dd, *J* 3.9 3.9, 4-CH), 7.22 (1H, d, *J* 8.3, 3′-CH), 7.76 (1H, dd, *J* 8.3 2.5, 4′-CH) and 8.27 (1H, d, *J* 2.5, 6′-CH); δ_C(100 MHz; $CDCl_3$) 30.2 (5 or 6-CH_2), 31.4 (5 or 6-CH_2), 40.3 (3-CH_2), 44.5 (2-CH), 56.4 (4-CH), 62.8 (1-CH), 123.9 (3′-CH), 137.9 (4′-CH), 141.1 (5′-C), 148.8 (6′-CH) and 149.0 (2′-C); *m*/*z*-(EI) 210 (M[^{37}Cl]$^+$, 7%), 267 (M[^{35}Cl]$^+$, 27), 179 (9), 140 (20) and 68 (100) (Found: M^+, 208.0760. $C_{11}H_{13}N_2{}^{35}Cl$ requires M^+, 208.0767), followed by its *epimer* **30** as a pale yellow oil (0.028 g, 52%), $\nu_{max}(CHCl_3)/cm^{-1}$ 3402, 2961, 2968, 2878, 1605, 1494, 1461, 1028 and 754; δ_H(250 MHz; $CDCl_3$) 1.32–1.47 (3H, m), 1.51 (1H, dd, *J* 12.4, 5.8, 3-CH_{endo}), 1.57–1.71 (1H, m), 1.82 (1H, bs, NH), 2.13 (1H, dddd, *J* 12.4 11.8 5.0 3.0, 3-CH_{exo}), 3.31 (1H, ddd, *J* 11.8 5.8 4.9, 2-CH), 3.76–3.93 (2H, m, 1 and 4-CH), 7.28 (1H, d, *J* 8.2, 3′-CH), 7.48 (1H, ddd, *J* 8.2, 2.4, 4′-CH) and 8.25 (1H, d, *J* 2.4, 6′-CH); *m*/*z*(FAB) 211 (M[^{37}Cl] + H^+, 33%), 209 (M[^{35}Cl] + H^+, 100), 109 (16), 95 (28) and 69 (62) (Found: M + H^+, 211.0815. $C_{11}H_{14}N_2{}^{37}Cl$ requires M^+, 211.0816).

N-(*tert*-Butyloxycarbonyl)-2-(*p*-tolylsulfonyl)-7-azabicyclo-[2.2.1]hept-2,5-diene 32

N-(*tert*-Butyloxycarbonyl)pyrrole **31** (7.4 ml, 44 mmol) was added to ethynyl *p*-tolyl sulfone **21** (15.9 g, 88 mmol), the reaction mixture protected from light, then heated to 85 °C under N_2. After 25 h the black oil obtained was cooled to room temp. and then purified on silica gel (20% to 35% EtOAc–petroleum ether) to yield recovered ethynyl *p*-tolyl sulfone (5.2 g, 33%) followed by the required cycloadduct as a white crystalline solid (12.6 g, 82%), mp 97–98 °C (diethyl ether–pentane), lit.,[25] 97–98 °C (Found: C, 62.37; H, 6.29; N, 4.06. $C_{18}H_{21}NO_4S$ requires C, 62.23; H 6.09; N 4.03%); $\nu_{max}(CHCl_3)/cm^{-1}$ 2978, 2930, 1713, 1321, 1152 and 859; δ_H(400 MHz; $CDCl_3$) 1.18–1.40 (9H, bs, -$CO_2{}^tBu$), 2.45 (3H, s, -$SO_2C_6H_4Me$), 5.18 (1H, bs, 1-CH), 5.42–5.30 (1H, bm, 4-CH), 6.88 (1H, dd, *J* 5.3, 2.6), 6.93–7.10 (1H, bm), 7.36 (2H, bd, Tol-CH), 7.58 (1H, bs, 3-CH) and 7.76 (2H, d, *J* 8.1, Tol-CH); δ_C(68 MHz; $CDCl_3$) 21.6 (Tol-CH_3), 27.8 (CMe_3), 66.8 (1 or 4-CH), 67.6 (1 or 4-CH), 81.3 (CMe_3), 128.0 (Tol-CH), 130.0 (Tol-CH), 135.6 (C), 141.5 (CH), 143.0 (CH), 144.9 (C), 152.6 (CH), 153.8 (C) and 158.9 (C=O);

m/*z*(FAB) 348 (M + H^+, 9%), 292 (27), 248 (14), 154 (100) and 136 (71).

This diene (2.57 g, 7.4 mmol) was then dissolved in acetonitrile (30 ml) and 10% palladium on carbon (0.1 mass equiv., 0.25 g) added in one portion. The suspension was stirred under a hydrogen atmosphere until the required volume of hydrogen was absorbed (200 ml, 8.9 mmol). The reaction mixture was then filtered through Celite with EtOAc and the filtrate concentrated *in vacuo* to give an off-white residue which was recrystallised from absolute ethanol to yield the *title compound* **32** as a white solid (2.51 g, 97%), mp 147–148 °C (Found: C, 62.17; H, 6.83; N, 4.05. $C_{18}H_{23}NO_4S$ requires C, 61.87; H, 6.63; N, 4.01%); ν_{max}($CHCl_3$)/cm^{-1} 2953, 1704, 1597, 1354, 1091 and 895; δ_H(250 MHz; $CDCl_3$; 333 K) 1.21 (10H, bs, -$CO_2{}^tBu$ + 1H), 1.32–1.43 (1H, s), 1.89–2.08 (2H, m), 2.45 (3H, s, -$SO_2C_6H_4$*Me*), 4.73–4.82 (2H, m, 1 and 4-CH), 7.06 (1H, d, *J* 1.9, 3-CH), 7.36 (2H, d, *J* 8.1, Tol-CH), 7.81 and (2H, d, *J* 8.1, Tol-CH); δ_C(68 MHz; $CDCl_3$) 21.5 (Tol-CH_3), 24.1 (5 or 6-CH_2), 25.1 (5 or 6-CH_2), 27.7 (C*Me*$_3$), 60.8 (1 or 4-CH), 61.7 (1 or 4-CH), 80.6 (*C*Me_3), 127.9 (Tol-CH), 129.9 (Tol-CH), 136.6 (C), 143.9 (3-CH), 144.7 (C), 148.9 (C), 154.6 (C) and 158.9 (C=O); *m*/*z*(FAB) 350 (M + H^+, 16%), 294 (100), 250 (57) and 154 (92) (Found: M + H^+, 350.1432. $C_{18}H_{24}NO_4S$ requires M, 350.1426).

2-Methoxy-5-bromopyridine 33[26]

A solution of bromine (2.35 ml, 45.8 mmol) in 1.0 M aqueous potassium bromide solution (270 ml, 0.27 mol) was added to a stirred emulsion of 2-methoxypyridine (4.82 ml, 45.8 mmol) and potassium hydroxide (1.52 g, 23.0 mmol) in water (270 ml). After 3 h 45 min 2 M NaOH (70 ml) was added to the colourless solution which was then extracted with CH_2Cl_2 (3 × 200 ml). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a brown oil. Bulb to bulb distillation gave the *title compound* **33** as a colourless oil (4.9 g, 57%); δ_H(250 MHz; $CDCl_3$) 6.66 (1H, d, *J* 8.8, 3-CH), 7.63 (1H, dd, *J* 8.8, 2.4, 4-CH) and 8.20 (1H, d, *J* 2.4, 6-CH); δ_C(68 MHz; $CDCl_3$) 53.7 (-OCH_3), 111.6 (5-C), 112.6 (3-CH), 141.0 (4-CH), 147.4 (6-CH) and 162.8 (2-C); *m*/*z*(EI) 188 (M[^{81}Br]$^+$, 48%), 170 (M[^{79}Br]$^+$, 32), 151 (100) and 120 (35) (Found: M^+, 186.9659. $C_6H_6ON^{79}Br$ requires M^+, 186.9633).

N-(*tert*-Butyloxycarbonyl)-3-*exo*-(2-methoxy-5-pyridyl)-2-*endo*-(*p*-tolyluenesulfonyl)-7-azabicyclo[2.2.1]heptane 34

n-BuLi (1.3 M in hexanes) (3.70 ml, 4.8 mmol) was added dropwise over 3 minutes to a stirred solution of 5-bromo-2-methoxypyridine (1.03 g, 5.5 mmol) in THF (35 ml) under N_2 at −78 °C. After 10 min a solution of the alkenyl sulfone **32** (1.2 g, 3.4 mmol) in THF (18 ml) was added dropwise over 3 min to the metallated pyridine. After 3 h at −78 °C the reaction mixture was allowed to warm to −60 °C over 30 min then sat. aq. NH_4Cl (5 ml) was added and the solution warmed to room temp. The orange mixture was concentrated *in vacuo*, diluted with brine (30 ml) and extracted with CH_2Cl_2 (3 × 40 ml). The combined organics were dried ($MgSO_4$), filtered then concentrated *in vacuo* to yield a brown oil. Purification on silica gel (20% EtOAc–petroleum ether) yielded recovered alkenyl sulfone **32** (0.10 g, 12%) followed by the *title compound* **34** as a colourless foam (1.33 g, 85%); ν_{max}($CHCl_3$)/cm^{-1} 2946, 2884, 1682, 1086 and 880; (Found: C, 62.01; H, 6.76; N, 6.19. $C_{24}H_{30}N_2O_5S$ requires C, 62.86; H 6.59; N 6.19%); δ_H(250 MHz; $CDCl_3$; 333 K) 1.42 (9H, s, -$CO_2{}^tBu$), 1.76–1.96 (3H, m), 2.38 (3H, s, -$SO_2C_6H_4$*Me*), 2.63–2.73 (1H, m), 3.25 (1H, d, *J* 5.8, 3-CH), 3.62 (1H, m, 2-CH), 3.87 (3H, s, -O*Me*), 4.23 (1H, d, *J* 4.5, 4-CH), 4.48 (1H, dd, *J* 4.2 4.2, 1-CH), 6.55 (1H, d, *J* 8.6, 3′-CH), 7.24 (2H, d, *J* 8.2, Tol-CH), 7.40 (1H, dd, *J* 8.6, 2.3, 4′-CH), 7.66 (2H, d, *J* 8.2, Tol-CH) and 7.89 (1H, d, *J* 2.3, 6′-CH); δ_C(68 MHz; $CDCl_3$) 21.3 (Tol-CH_3), 23.8 (5 or 6-CH_2), 27.9 (C*Me*$_3$), 29.2 (5 or 6-CH_2), 46.9 (3-CH), 53.1 (-OCH_3), 58.1 (1-CH), 64.3 (4-CH), 72.8 (2-CH), 80.5 (*C*Me_3), 110.4 (3′-CH), 127.6 (Tol-CH), 129.8 (Tol-CH), 130.3 (C), 136.1 (5′-C), 136.8 (4′-CH), 144.8 (C), 145.2 (6′-CH), 154.2 (2′-C) and 162.9 (C=O); *m*/*z*(FAB) 459 (M + H^+, 100%), 403 (47) and 203 (47) (Found: M + H^+, 459.1994. $C_{24}H_{31}N_2O_5S$ requires M, 459.1954).

N-(*tert*-Butyloxycarbonyl)-2-*exo*-(2-methoxy-5-pyridyl)-7-azabicyclo[2.2.1]heptane 35 and 1β-(*tert*-butyloxycarbonylamino)-2β-(2-methoxy-5-pyridyl)cyclohex-3-ene 36

To a solution of the adduct **34** (0.1 g, 0.22 mmol) in THF (4 ml)–MeOH (4 ml) at −20 °C under N_2, finely crushed 6% sodium amalgam (0.83 g, 2.2 mmol) was added in one portion. After 2 h 30 min the reaction mixture was filtered through Celite and concentrated *in vacuo* to yield a white residue. The residue was diluted with sat. aq. $NaHCO_3$ (20 ml), extracted with CH_2Cl_2 (3 × 15 ml), and the organics were dried ($MgSO_4$), filtered then concentrated *in vacuo* to yield a yellow oil. Purification on silica gel (10% EtOAc–petroleum ether) yielded firstly the *ring opened product* **36** as a colourless oil (0.0074 g, 11%); ν_{max}(film)/cm^{-1} 3309, 2976, 1696, 1491, 1366, 1170, 1027 and 738; δ_H(250 MHz; $CDCl_3$; 333 K) 1.40 (9H, s, -$CO_2{}^tBu$), 1.62–1.67 (2H, m, 6-CH_2), 2.24–2.28 (2H, m, 5-CH_2), 3.70 (1H, bs), 3.93 (3H, s, -OCH_3), 4.02–4.18 (2H, bs), 5.64–5.70 (1H, m, 3 or 4-CH), 6.00–5.90 (1H, m, 3 or 4-CH), 6.71 (1H, d, *J* 8.4, 3′-CH), 7.41 (1H, dd, *J* 8.4 2.3, 4′-CH) and 7.97 (1H, d, *J* 2.3, 6′-CH); δ_C(68 MHz; $CDCl_3$) 24.2 (6-CH_2), 28.9 (C*Me*$_3$), 29.6 (5-CH_2), 41.2 (CH), 49.0 (CH), 53.4 (-OCH_3), 79.2 (*C*Me_3), 110.1 (CH), 127.0 (CH), 127.8 (C), 128.3 (CH), 140.3 (CH), 147.6 (CH), 155.1 (2′-C) and 163.3 (C=O); *m*/*z*(FAB) 305 (M + H^+, 6%), 249 ([M-^{t}Bu] + H^+, 11), 109 (24), and 69 (84) (Found: [M-^{t}Bu] + H^+, 248.1149. $C_{13}H_{16}N_2O_3$ requires M, 248.1161), followed by the *desulfonylated product* **35** as a pale yellow oil (0.039 g, 58%); ν_{max}(film)/cm^{-1} 2974, 1698, 1494, 1153, 1029 and 757; δ_H(250 MHz; $CDCl_3$; 333 K) 1.43 (9H, s, -$CO_2{}^tBu$), 1.49–1.58 (1H, m), 1.76–1.84 (3H, m), 1.91–2.04 (1H, m, 3-CH_{endo}), 2.80 (1H, dd, *J* 8.8 4.9, 2-CH), 3.91 (3H, s, -OCH_3), 4.12 (1H, m, 1-CH), 4.35 (1H, bs, 4-CH), 6.68 (1H, d, *J* 8.6, 3′-CH), 7.57 (1H, dd, *J* 8.6, 2.5, 4′-CH) and 7.99 (1H, d, *J* 2.5, 6′-CH); δ_C(68 MHz; $CDCl_3$) 28.3 (C*M*$_3$), 28.8 (5 or 6-CH_2), 29.7 (5 or 6-CH_2), 40.4 (3-CH_2), 44.8 (2-CH), 53.3 (-OCH_3), 56.0 (4-CH), 62.2 (1-CH), 79.6 (*C*Me_3), 110.7 (3′-CH), 134.0 (5′-C), 137.4 (4′-CH), 145.1 (6′-CH), 155.3 (2′-C) and 162.9 (C=O); *m*/*z*(FAB) 249 ([M-^{t}Bu] + H^+, 67%), 205 ([M − $CO_2{}^tBu$] + H^+, 47), 73 (100) and 69 (77) (Found: M + H^+, 304.1792. $C_{17}H_{24}N_2O_3$ requires M, 304.1787).

N-Formyl-2-*exo*-(2-chloro-5-pyridyl)-7-azabicyclo[2.2.1]heptane 37

A solution of **35** (0.016 g, 0.052 mmol) in DMF (0.3 ml) was cooled to 0 °C and phosphorous oxychloride ($POCl_3$) (0.04 ml, 0.42 mmol) added under N_2. After stirring for 60 min the solution was heated to 95 °C for 3 h 15 min before cooling to room temp. Sat. aq. NaOAc (0.5 ml) and 2 M NaOH (1 ml) were added before extraction with CH_2Cl_2 (6 × 3 ml), combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a brown oil. Remaining traces of DMF were removed under high-vacuum (<2 mmHg) before purification on silica gel (EtOAc) to yield the *title compound* **37** as a yellow oil (0.0096 g, 78%); ν_{max}(film)/cm^{-1} 2980, 2877, 1660, 1457, 1380, 1106, 1023 and 754; δ_H(400 MHz; $CDCl_3$) (rotamers) 1.62–1.93 (5H, m), 2.10 (0.5H, dd, *J* 12.7 9.1, 3-CH_{endo}), 2.19 (0.5H, d, *J* 12.3 8.8, 3-CH_{endo}), 3.02–3.06 (1H, m, 2-CH), 3.92 (0.5H, d, *J* 4.1, 1-CH), 4.31 (0.5H, t, *J* 4.4, 4-CH), 4.66 (0.5H, d, *J* 4.4, 1-CH), 4.83 (0.5H, t, *J* 4.3, 4-CH), 7.25 (0.5H, d, *J* 8.3, 3′-CH), 7.28 (0.5H, d, *J* 8.3, 3′-CH), 7.47 (0.5H, dd, *J* 8.3 2.6, 4′-CH), 7.58 (0.5H, dd, *J* 8.3 2.6, 4′-CH), 8.03 (0.5H, s, C*H*O), 8.20 (0.5H, d, *J* 2.6, 6′-CH), 8.22 (0.5H, s, C*H*O) and 8.24 (1H, d, *J* 2.6, 6′-CH); δ_C(100 MHz; $CDCl_3$) (rotamers) 28.3 and 29.2 (5 or 6-CH_2),

26.9 and 30.9 (5 or 6-CH_2), 38.9 and 41.4 (3-CH_2), 44.2 and 45.0 (2-CH), 51.7 (0.5 CH), 55.4 (0.5 CH), 56.7 (0.5 CH), 61.9 (0.5 CH), 124.3 and 124.4 (3′-CH), 136.4 and 136.6 (4′-CH), 138.6 and 139.0 (5-C'), 148.8 and 148.6 (6′-CH), 149.7 and 150.0 (2-C'), 157.3 and 157.6 (C=O); *m*/*z*(EI) 238 ($M[^{37}Cl]^+$, 7%) 236 ($M[^{35}Cl]^+$, 19), 223 (11), 140 (61), 97 (100) and 68 (81) (Found: M^+, 236.0716. $C_{12}H_{13}N_2O^{35}Cl$ requires M, 236.0716).

2-*exo*-(2-Chloro-5-pyridyl)-7-azabicyclo[2.2.1]heptane 1 (epibatidine)

2 M HCl (2 ml) was added to a solution of **37** (0.016 g, 0.067 mmol) in THF (2 ml) then heated under N_2 to 55–60 °C for 2 h before cooling to room temp. The reaction mixture was concentrated *in vacuo*, 2 M NaOH (1 ml) added then the mixture extracted with chloroform (4 × 5 ml). The combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo* to yield a yellow solid. Purification on silica gel (98 : 2 : 1 then 96 : 4 : 1 CH_2Cl_2–MeOH–NH_3) yielded the *title compound* **1** as a white solid (0.011 g, 79%). All data were consistent with those described above.

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