1 PERKIN

6-Substituted 2-azabicyclo[2.2.1]hept-5-enes by nitrogen-directed radical rearrangement: synthesis of an epibatidine analogue with high binding affinity at the nicotinic acetylcholine receptor †

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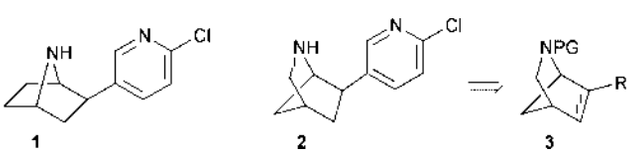
Base-induced isomerisation of epoxide **13** gives an azanortricyclanol **17** which is a precursor for a novel free-radical induced rearrangement to 6-substituted 2-azabicyclo[2.2.1]hept-5-enes **28**–**31**. Compound **31** undergoes selective *exo*-face hydrogenation to give the 6-substituted 2-azabicyclo[2.2.1]heptane **33** (structure confirmed by X-ray crystallographic analysis). Deprotection of **33** gives epibatidine analogue **2** which has been shown to bind with high affinity at rat brain nicotinic acetylcholine receptors.

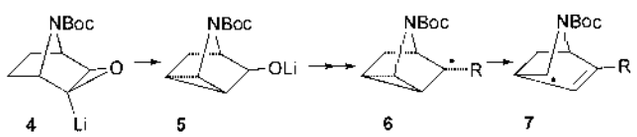
Introduction

In 1992 Daly and co-workers reported the isolation and structural elucidation of the alkaloid epibatidine **1**.[1] Epibatidine has attracted considerable attention from the scientific community due to its novel structure combined with the fact that it is a highly potent non-opioid analgesic nicotinic acetylcholine receptor (nAChR) agonist.[2] Unfortunately, epibatidine **1** is toxic or even lethal at doses only slightly higher than its effective analgesic dose. However it is a significant therapeutic lead in the important search for nAChR modulators having a wider separation between antinociceptive and toxic effects.[3] In this context we considered a structurally interesting target would be *endo*-6-(6-chloropyridin-3-yl)-2-azabicyclo[2.2.1]heptane **2**, since it represents an isomer of epibatidine in which the nitrogen in the rigid bicyclo[2.2.1]heptyl framework is translocated from the 7- to the 2-position but maintains the same connectivity and similar relative orientation to the chloropyridyl substituent. We envisaged the epibatidine analogue **2** being derived from *exo*-selective hydrogenation of a 6-substituted 2-azabicyclo[2.2.1]hept-5-ene **3** and detail here our results on a method to prepare such systems, and the synthesis and biological studies of **2**.[4]



1 **2** **3**

The 2-azabicyclo[2.2.1]heptyl ring system can be most easily prepared by an aza Diels–Alder reaction using cyclopentadiene.[5] However, at the outset of our work a regiocontrolled access to 6-substituted systems was not available. Our strategy (Scheme 1) employs a rearrangement *via* lithiation of an achiral epoxide (**4** to **5**) (making it amenable to asymmetric synthesis by enantioselective deprotonation),[6] followed by a radical rearrangement (**6** to **7**). A related radical rearrangement (8-aza- to 6-azabicyclo[3.2.1]oct-2-en-7-yl radical) was reported by Rigby and Pigge in 1996.[7]

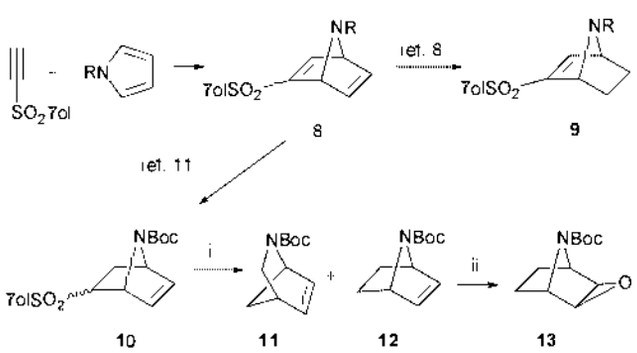


4 **5** **6** **7**

Scheme 1

Results and discussion

In order to examine this chemistry, a synthesis of the achiral epoxide **13** was required (Scheme 2). The potential precursor of



Scheme 2 *Reagents and conditions*: i, 6% Na–Hg, Na_2HPO_4, MeOH, −10 °C to 25 °C, 3 h; ii, Oxone, Na_2EDTA, acetone, Bu_4NHSO_4, $NaHCO_3$, CH_2Cl_2–H_2O, 25 °C, 48 h.

epoxide **13**, alkene **12**, was known (albeit protected as the methyl carbamate) from the studies of Vogel and co-workers.[8] We focused on the Boc derivative **12** in order to ensure compatibility in the base-induced epoxide rearrangement and

† Electronic supplementary information (ESI) available: details of biological studies. See http://www.rsc.org/suppdata/p1/b1/b107414h/

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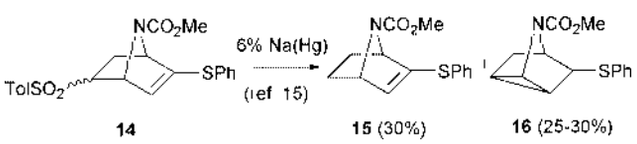
because of the relative ease of deprotection. The method developed by Vogel involves cycloaddition of protected pyrrole with an arylsulfonyl-substituted acetylene to give the diene **8** (R = CO_2Me), followed by hydrogenation of the less-substituted olefin and desulfonylation of the resultant vinyl sulfone **9** (R = CO_2Me).[8] Although we initially adapted this route to the Boc-protected series,[9] we observed (similarly to others)[10] that the sodium amalgam-mediated desulfonylation of vinyl sulfone **9** (R = Boc) was low yielding (~30% in our hands). However, we found that sodium amalgam-mediated desulfonylation of the related known alkene **10** [easily available from diene **8** (R = Boc) using $NaBH_4$][11] was slightly more satisfactory in terms of yield (up to 62% of alkene **12**). During the course of our studies, alternative methods for the synthesis of alkene **12** were reported which, although adding additional steps, achieve desulfonylation from vinyl sulfone **9** without the use of sodium amalgam.[12]

A by-product isolated in the desulfonylation of alkene **10** was subsequently identified as the known 2-azabicyclo[2.2.1]-heptene **11** (18%, Scheme 2).[13] By-product alkene **11** may be derived from homolysis of the intermediate aryl radical anion in desulfonylation[14] and radical cyclisation to azatricyclic radical **6** (R = H), followed by cyclopropyl carbinyl radical ring-opening to **7** (R = H). The latter process provides encouragement for the radical rearrangement that we wished to investigate. Support for formation of the azatricyclic radical **6** (R = H) as an intermediate in this mechanism is found in the sodium amalgam-mediated desulfonylation of a 5-phenylsulfonyl-substituted 7-azabicyclo[2.2.1]heptene **14**, which has been previously observed to give approximately equal proportions of the simple reduced 7-azabicyclo[2.2.1]heptene **15** together with 5-phenylthio-substituted 3-azatricyclo[2.2.1.$0^{2,6}$]-heptane **16** (Scheme 3),[15] the latter presumably being isolated due to the radical stabilising effect of the phenylthio substituent.

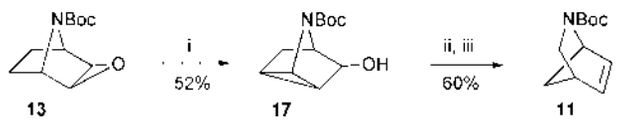


Scheme 3

Contemporaneously with our own studies, a by-product was reported in desulfonylation of the methyl carbamate system analogous to **10**, and this by-product was tentatively characterised as *N*-methoxycarbonyl-6-azabicyclo[3.3.1]hept-2-ene,[16] although the data provided, together with our studies reported herein (and elsewhere recently),[17] would suggest that this by-product should be reassigned as a 2-azabicyclo[2.2.1]hept-5-ene.

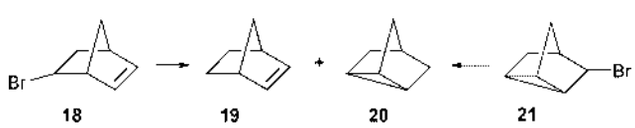
Epoxidation of the alkene **12** using MCPBA buffered with Na_2HPO_4 (CH_2Cl_2, 25 °C, 20 h)[18] afforded the desired epoxide **13** (Scheme 2) in only 41% yield after a difficult purification. Peracetic acid in the presence of Na_2CO_3 (CH_2Cl_2, 25 °C, 48 h)[19] gave a similar yield of epoxide **13** (42%). Use of freshly prepared dimethyldioxirane[20] (0.1 M in acetone; 6 equiv., CH_2Cl_2, 25 °C, 36 h) gave a clean reaction, but obtaining significant conversion was problematic (a maximum of 25% conversion was observed). *In situ* methods of generating dimethyldioxirane are now known to be more efficient, although a phase transfer catalyst is required.[21] Treatment of the alkene **12** with Oxone, $NaHCO_3$, Bu_4NHSO_4 and Na_2EDTA in acetone–CH_2Cl_2–H_2O resulted in a highly satisfactory 76% yield of *N*-Boc-azanorbornene ‡ oxide **13**. As found for the epoxidation of other bicyclo[2.2.1] derivatives,[22] the epoxidation occurred exclusively from the *exo* face, as determined by ^{1}H NMR NOE studies (irradiation at the chemical shift corresponding to the epoxide CH's produced enhancement at the chemical shift assigned for the *endo*-protons of the CH_2's). An alternative route to epoxide **13** was briefly examined. Epoxidation (49%) of alkene **10** (MCPBA, Na_2HPO_4) followed by sodium amalgam-mediated desulfonylation (30%) did give the epoxide **13**, but the poor yields in this sequence led us to prefer the sequence of desulfonylation of alkene **10** followed by epoxidation using dimethyldioxirane generated *in situ*.

On reaction with LDA, epoxide **13** underwent a similar lithiation–transannular C–H insertion (**4** to **5**, Scheme 1) to that originally observed by Crandall with *exo*-norbornene oxide.[23] In the present case, azanortricyclanol§ **17** was obtained (52%, Scheme 4) and the spectral data compared well with those for the related azatricycle **16**[15b] (Scheme 3). The reaction of epoxide **13** with LDA was found to be most effective if carried out at 0 °C, although it was important to quench the reaction immediately or the yield of azanortricyclanol **17** was diminished (stirring over 10 h resulted in 21% yield of **17**).



Scheme 4 *Reagents and conditions*: i, LDA, Et_2O, 0 °C, 5 min; ii, KH, THF, 0 °C, 20 min, then CS_2, 0 °C, 10 min, then MeI, 20 min; iii, Bu_3SnH, AIBN, toluene, 100 °C, 1 h.

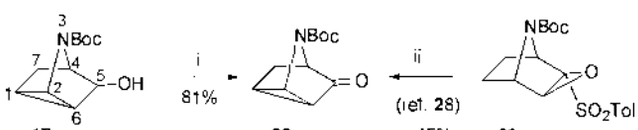
Formation of the xanthate ester of azanortricyclanol **17** and radical deoxygenation[24] by heating with Bu_3SnH–AIBN in toluene gave the 2-azabicyclo[2.2.1]heptene **11**[13] (60%) as the only isolated product (Scheme 4). A careful analysis of the ^{1}H NMR of the crude material, using comparisons with a reference sample of alkene **12** and the predicted chemical shifts of **17** (OH = H), did not indicate the presence of either of these latter two compounds. Radical reduction of norbornenyl bromide **18** or nortricyclyl bromide **21** is known to produce the same (~1 : 1) mixture of norbornene **19** and nortricyclene **20** (Scheme 5).[25] In the present case the radical **7** (R = H) which leads to the



Scheme 5

2-aza alkene **11** may be strongly preferred due to a stabilising effect of the radical by the NBoc group[26] and/or a larger CH–N–CH angle in **7** (compared with **6**) which promotes amide-type resonance (*vide infra*).[27]

So as to provide a way to introduce substituents in order to see their effect on the radical rearrangement [**6** to **7** (R = alkyl, aryl)], azanortricyclanol **17** was oxidised (81%) to the ketone **22** (Scheme 6). Subsequent to our studies,[4] Plumet and co-workers



Scheme 6 *Reagents and conditions*: i, $(CO)_2Cl_2$, DMSO, CH_2Cl_2, −78 °C, 20 min, then NEt_3; ii, LiHMDS, Et_2O, 0 °C, 1 h.

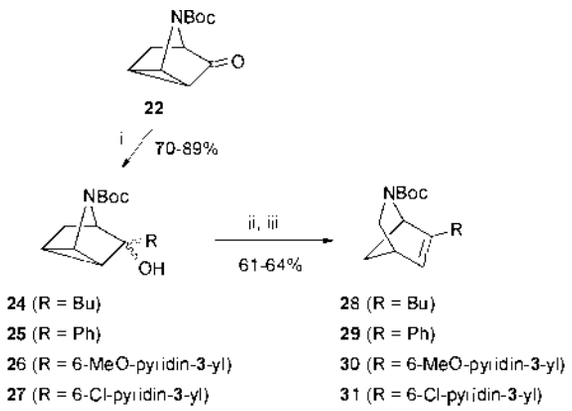
have reported an interesting route to ketone **22** (45%) from epoxy sulfone **23** using LiHMDS (Scheme 6).[28] With LDA or $LiNEt_2$ and epoxy sulfone **23**, low yields (~30–37%) of azanortricyclanol **17** were obtained and ketone **22** was not

‡ The IUPAC name for norbornene is bicyclo[2.2.1]heptene.

§ The IUPAC name for azanortricyclanol is 3-azatricyclo[2.2.1.$0^{2,6}$]-heptan-5-ol.

observed. Although not currently having the potential to be an enantioselective process,[6] the route to ketone **22** reported by Plumet is noteworthy because it proceeds in four steps from commercially available starting materials [*via* addition of Bu′OOLi to alkene **9** (R = Boc)], with the additional benefit of avoiding the use of sodium amalgam.

Addition of BuLi and PhLi to the ketone **22** gave epimeric mixtures (inconsequential) of tertiary alcohols **24** (70%) and **25** (88%) respectively, which were best deoxygenated by the procedure of Dolan and MacMillan (Scheme 7).[29] Smooth



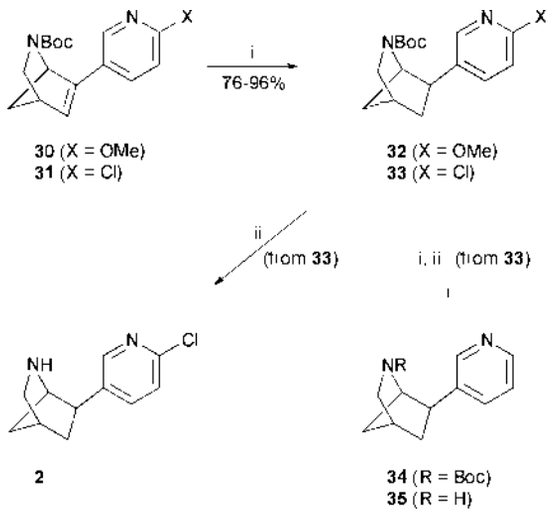
Scheme 7 *Reagents and conditions*: i, RLi, THF–Et_2O, −78 °C (1 h) to 25 °C, 1 h; ii, $ClCOCO_2Me$, DMAP, MeCN, 25 °C, 30 min; iii Bu_3SnH, AIBN, toluene, 100 °C, 45 min.

rearrangement to give the 6-substituted 2-azabicyclo[2.2.1]-hept-5-enes **28** and **29** (64% and 61%) was observed, despite the potential additional radical stabilising effects present in the supposed intermediates **6** (R = alkyl, aryl) compared with **6** (R = H). The presence of a stabilising group adjacent to the intermediate radical **6** (R = alkyl, aryl) could potentially have slowed radical cyclisation and hence promoted formation of 5-substituted 3-azatricyclo[2.2.1.$0^{2,6}$]heptanes (*i.e.* deoxygenation without rearrangement).

In order to access the desired 2-azabicyclic analogue of epibatidine **2**, alkene hydrogenation would be required following rearrangement. Literature precedent suggested that a pyridyl chlorine substituent might be cleaved under typical hydrogenation conditions.[30] Indeed, several syntheses of epibatidine requiring a late-stage alkene reduction have used methoxypyridyl functionality, with subsequent conversion to chloropyridyl using $POCl_3$–DMF.[31] Thus, initially the methoxypyridyl alkene **30** was prepared (Scheme 7).

Hydrogenation of the methoxypyridyl alkene **30** (in EtOAc, since **30** is unstable to protic solvents) gave the desired *endo*-6-substituted-2-azabicyclo[2.2.1]heptane **32** exclusively in 78% yield (Scheme 8). Careful analysis by TLC and examination of the ^{1}H NMR of the crude isolate suggested only one product was formed in the reduction, and NOE studies indicated that the pyridyl substituent was *syn* to the NBoc group (see Experimental section). However under $POCl_3$–DMF conditions, only decomposition of 2-azabicyclo[2.2.1]heptane **32** was observed. The synthesis and hydrogenation (10% Pd/C, 1 atm H_2) of the chloropyridyl alkene **31** was therefore carried out, with careful monitoring of the hydrogenation. The loss of the chloro substituent was not as facile as expected on the basis of related literature examples,[30] and a reaction time of 3 h led to complete reduction of the double bond, selectively from the *exo* face to give 2-azabicyclo[2.2.1]heptane **33** in 96% yield, and importantly without loss of chlorine. The stereochemistry obtained from hydrogenation was confirmed by X-ray crystallographic analysis of 2-azabicyclo[2.2.1]heptane **33** (Fig. 1).

The X-ray structure also indicates planarity of the 2-azabicyclic nitrogen. Nitrogen atoms in amides are believed to



Scheme 8 *Reagents and conditions*: i, H_2 (1 atm), 10% Pd/C, EtOAc, 25 °C, 2–3 h (48 h for **34**); ii, TFA, CH_2Cl_2, 25 °C, 2 h.

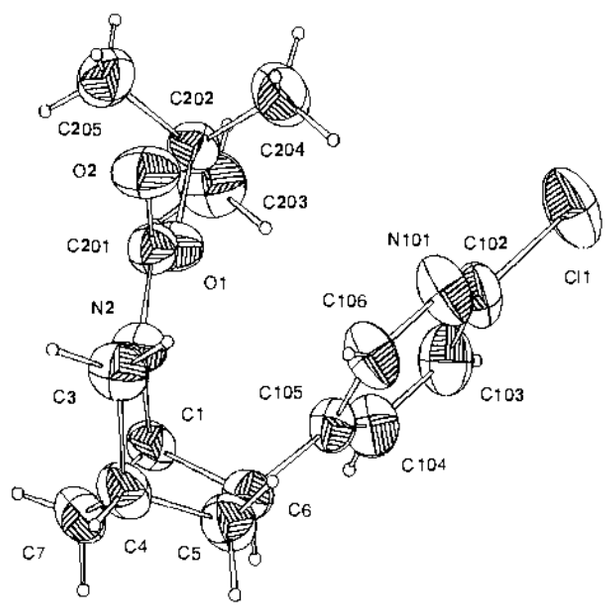
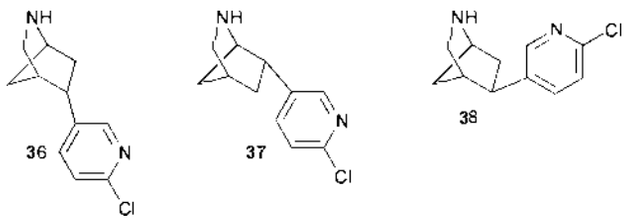


Fig. 1 Molecular structure of 2-azabicyclo[2.2.1]heptane **33** (thermal ellipsoids are at the 50% level).

be planar-trigonal due to conjugation with the carbonyl group.[27] In contrast, 7-azabicyclo[2.2.1]heptanes are known to have a more pyramidal amide nitrogen.[27] The increased planarity in 2-azabicyclo[2.2.1]heptanes could promote greater amide type resonance compared to 7-azabicyclo[2.2.1]heptanes (and probably 3-azatricyclo[2.2.1.$0^{2,6}$]heptanes). Stabilisation by amide type resonance could therefore favour the rearrangement from the 3-azatricyclo[2.2.1.$0^{2,6}$]heptane radical **6** to the 2-azabicyclo[2.2.1]heptane radical **7**.

The face selectivity in the hydrogenation of 2-azabicyclo-[2.2.1]heptenes **30** and **31** is higher than that observed in the related 7-azabicyclo[2.2.1]heptene systems. For example, a 4 : 1 ratio of *endo–exo* isomers was observed by Fletcher and co-workers in their synthesis of epibatidine.[32] The higher selectivity observed in our system is possibly due to increased steric hindrance from the Boc protecting group, as well as from the ring methylenes of the azabicycle. TFA deprotection of 2-azabicyclo[2.2.1]heptane **33** gave the target epibatidine analogue **2** in 93% yield (Scheme 8). The des-chloro analogue **35** was also prepared for biological testing by dechlorination of 2-azabicycle **33** (10% Pd/C, 1 atm H_2, EtOAc, 2 days, 50% yield) followed by TFA deprotection (37% yield, unoptimised).

In 1998 Maier and co-workers reported the selective preparation of the 5-*exo*-substituted-2-azabicyclic analogue **36**, in which the chloropyridyl substituent was introduced by a reductive Heck coupling with alkene **11**.[13] More recently, Malpass and Cox have also reported the synthesis of 2-azabicyclo-[2.2.1]heptane epibatidine analogues.[33,34] They found that the reductive Heck reaction reported by Maier in fact gave a 55 : 45 mixture of 5- and 6-*exo*-substituted-azabicycles **36** and **37**, respectively.[33] Malpass and Cox also synthesised the 5- and 6-*endo*-substituted-2-azabicyclo[2.2.1]heptanes **38** and **2** respectively.[34] Their strategy proceeded *via* hydroboration of 2-azabicyclo[2.2.1]hept-5-ene **11** (Boc = Z), which proceeded with low regioselectivity (36 : 64[34a] or 45 : 55[34b] in favour of hydroboration at the 6-position). A strategy similar to that of Malpass and Cox to **2** was recently outlined by Dart and co-workers.[35]



Biological studies

Among the numerous neuronal nAChR subtypes, the α4β2 receptor is the predominant central nervous system (CNS) receptor subtype exhibiting high affinity for nicotine, and it has been suggested that β2-containing nAChRs (likely α4β2) may play a fundamental role in mediating several important physiological processes including cognition, neurotransmitter release, and antinociception. Therefore, ligands that selectively bind and activate α4β2 receptors could potentially provide novel therapeutics for the treatment of a variety of debilitating CNS disorders such as Alzheimer's disease, as well as the management of pain.[3,35] Analogue **2** has recently been shown to display subnanomolar binding affinity (K_i = 0.032 nM) for α4β2 receptors {where binding affinity was determined by measuring the displacement of [^{3}H]-(−)-cytisine from a preparation of whole rat brain},[35] which is a 30-fold increase in binding affinity over *S*-nicotine. This makes **2** one of the few epibatidine analogues for which a study has shown binding affinity at least as high as (actually marginally higher) than (−)-epibatidine **1** (for which K_i = 0.04 nM) at α4β2 receptors.[3,35] During the review process of the current paper, Malpass and co-workers also reported high binding affinity with analogue **2** (K_i = 0.045 nM; for (−)-epibatidine **1**: K_i = 0.019 nM) in competition assays against [^{3}H]-(−)-nicotine.[34b]

In our own studies, binding affinity was measured in competition binding assays using [^{3}H]-epibatidine to label nicotinic binding sites in rat brain P2 membranes. Analogue **2** and des-chloro analogue **35** both displayed lower binding affinity (K_i = 0.22 nM and K_i = 0.7 nM respectively) than epibatidine **1** (K_i = 0.026 nM).† The lower affinity, relative to epibatidine **1**, observed in the present study is likely to reflect the fact that [^{3}H]-epibatidine will label both α4β2 and α3β2* subtypes of nAChR under the conditions used for the competition assays.[36] This suggests that **2** may be more discriminating than epibatidine with respect to nAChR subtypes. In the mouse hot plate assay,[37] full efficacy of analogue **2** relative to epibatidine was found at a dose of 0.062 mmol kg^{-1}. At lower doses, analogue **2** failed to show statistically significant activity. The compound was also tested in the rat hot box model.[38] Seizures were observed at a dose of 0.62 mmol kg^{-1}, intraperitoneal and no statistically significant analgesic effects were noted at a dose 10-fold lower (0.062 mmol kg^{-1}).

In contrast to nicotine and anatoxin-a, the enantiomers of epibatidine **1** have surprisingly been shown to be approximately equipotent. This could be explained by the relative space occupied by the bicyclic ring of the two enantiomers when the drug binds to the receptor.[39] An illustration of this is shown in Fig. 2, where the two enantiomers are depicted so that both nitrogens (considered to be important in binding) are in the same plane and aligned vertically.

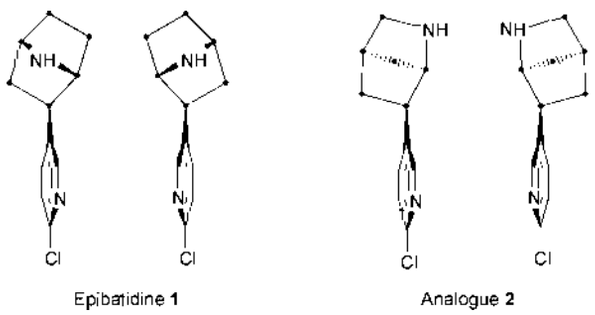


Fig. 2

However, for analogue **2**, the azabicyclic portion of the enantiomers appears to have a very different spatial area and this suggests a potential difference in activity (Fig. 2). In order to begin to probe this aspect, the enantiomers of 2-azabicyclo[2.2.1]heptane **33** were separated by chiral HPLC (see Experimental) and individually deprotected with TFA to give the epibatidine analogues (+)-**2** and (−)-**2**. The individual enantiomers were evaluated in electrophysiological studies.†[3b,40] Like epibatidine **1** and (*R*)-5-(azetidin-2-ylmethoxy)-2-chloropyridine (ABT-594),[3b] (+)-**2** was effective at reducing pain related activity in the anaesthetised rat, with no effect on non-noxious inputs. Interestingly (−)-**2** was ineffective, suggesting that either (−)-**2** does not bind or it is too weak to activate and then desensitise the receptor. Further studies are required to help clarify this intriguing latter issue.

In summary, this work demonstrates the strategic utility of combining base induced epoxide rearrangements and free radical rearrangements, providing a novel entry into the 2-azabicyclo[2.2.1]heptenyl system and, in particular, an epibatidine analogue with high binding affinity at α4β2 subtype nAChRs. The process demonstrates a new approach to the 2-azabicyclo[2.2.1]heptyl ring system, which uses a nitrogen atom to promote and guide cyclopropane ring opening. Extensions of this principle to addition reactions,[17] different ring systems and manipulation of the adducts towards other targets of biological interest, are under investigation.

Experimental

General details

All reactions requiring anhydrous conditions were conducted in flame- or oven-dried apparatus under an atmosphere of argon. Syringes and needles for the transfer of reagents were dried at 140 °C and allowed to cool in a desiccator over P_2O_5 before use. Ethers were distilled from sodium benzophenone ketyl; (chlorinated) hydrocarbons, amines and DMF from CaH_2. Internal reaction temperatures are reported unless stated otherwise. Reactions were monitored by TLC using commercially available glass-backed plates, pre-coated with a 0.25 mm layer of silica containing a fluorescent indicator (Merck). Organic layers were dried over $MgSO_4$ unless stated otherwise. Column chromatography was carried out on Kieselgel 60 (40–63 μm). Light petroleum refers to the fraction with bp 40–60 °C. $[\alpha]_D$ Values are given in 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded as thin films unless stated otherwise. Peak intensities are specified as strong (s), medium (m) or weak (w). ^{1}H and ^{13}C NMR spectra

were recorded in $CDCl_3$ unless stated otherwise with Varian Gemini 200, Bruker AC200, Bruker WM250, JEOL GSX270, Bruker WH300, JEOL EX400, Bruker AM500 or Bruker AMX500 spectrometers. Chemical shifts are reported relative to $CHCl_3$ [δ_H 7.26, δ_C(central line of t) 77.0]. Coupling constants (J) are given in Hz.

2-(*tert*-Butoxycarbonyl)-2-azabicyclo[2.2.1]hept-5-ene 11 [13] and 7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]hept-2-ene 12 [10]

Freshly prepared 6% Na–Hg [41] (100 g) and Na_2HPO_4 (40 g, 0.28 mol) were added to a stirred solution of alkene **10** [11] (10 g, 29 mmol) in anhydrous MeOH (250 cm^3) at −10 °C under argon. The reaction mixture was warmed to 25 °C over 3 h, then water (10 cm^3) was added and the reaction mixture filtered. The filtrate was extracted with CH_2Cl_2 (4 × 75 cm^3) and the organic extracts combined, washed with brine, dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was purified by column chromatography (20% Et_2O–light petroleum). First to elute was *alkene* **12**, a clear colourless oil (3.5 g, 62%); R_f (50% Et_2O–light petroleum) 0.63; ν_{max}/cm^{-1} 2977m, 1704s, 1365s, 1285m and 1160m; δ_H(200 MHz) 6.21 (2 H, s, HC=CH), 4.65 (2 H, s, 2 × CH), 1.83 (2 H, br d, J 8.0, 2 × H of CH_2), 1.39 (9 H, s, Bu^t) and 1.09 (2 H, d, J 8.0, 2 × H of CH_2); δ_C(50 MHz) 155.4 (C=O), 135.0 (*C*=C), 134.7 (C=*C*), 79.6 (*C*Me$_3$), 59.5 (2 × CH), 28.0 (3 × Me) and 23.6 (2 × CH_2); *m*/*z* (CI) 196 (M + H^+, 18%) and 96 (M − Boc, 100) (Found: M + H^+, 196.1338. $C_{11}H_{18}NO_2$ requires *M*, 196.1338).

Second to elute was *alkene* **11**, a clear colourless oil (1.0 g, 18%); R_f (50% Et_2O–light petroleum) 0.53; ν_{max}(film)/cm^{-1} 2977s, 1694s, 1391s, 1365s and 1161s; δ_H(500 MHz, DMSO, 90 °C) 6.29 (2 H, s, HC=CH), 4.53 (1 H, d, J 1.5, C(1)H), 3.22 (1 H, dd, J 9.0, 3.0, C(3)H *exo*), 3.15 (1 H, s, C(4)H), 2.49 (1 H, dd, J 9.0, 1.5, C(3)H *endo*), 1.51 (1 H, d, J 8.5, H of CH_2), 1.46 (1 H, dd, J 8.5, 1.5, H of CH_2) and 1.38 (9 H, s, Bu^t); δ_C(125 MHz) (3 : 2 mixture of rotational isomers observed) 155.9 (C=O), 136.5 (*C*=C), 134.4 and 133.7 (C=*C*), 79.0 (*C*Me$_3$), 61.1 and 59.9 (C1), 48.0 (C3), 46.2 and 45.8 (C7), 43.4 and 42.9 (C4) and 28.4 (3 × Me); *m*/*z* (CI) 196 (M + H^+, 4%), 157 (10), 96 (27) and 66 (100).

exo-2,3-Epoxy-7-(*tert*-butoxycarbonyl)-7-azabicyclo[2.2.1]-heptane 13

Oxone (63 g, 0.10 mol) and Na_2EDTA (200 mg, 0.50 mmol) in water (260 cm^3) was added slowly over 2 h to a vigorously stirred mixture of alkene **12** (2.0 g, 10 mmol), $NaHCO_3$ (17 g), Bu_4NHSO_4 (680 mg, 2.0 mmol), acetone (8.0 cm^3) and CH_2Cl_2 (120 cm^3). The pH was maintained at 7.8–8.0 by the addition of $NaHCO_3$. After 24 h further Oxone (30 g) was added. After a further 24 h, the reaction mixture was filtered and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 and the organic extracts were combined, dried and evaporated under reduced pressure. Purification by column chromatography (50% Et_2O–light petroleum) gave *epoxide* **13** as a white solid (1.6 g, 76%); R_f (50% Et_2O–light petroleum) 0.22; mp (from Et_2O) 91–94 °C (Found: C, 62.8; H, 8.1; N, 6.6. $C_{11}H_{17}NO_3$ requires C, 62.5; H, 8.1; N, 6.6%); ν_{max}(CH_2Cl_2)/cm^{-1} 2950m, 1695s, 1375s, 1360s and 1170m; δ_H(500 MHz) 4.36 (1 H, d, J 4.5, CH), 4.21 (1 H, d, J 4.5, CH), 3.26 (1 H, d, J 3.5, CH–O), 3.23 (1 H, d, J 3.5, CH–O), 1.85–1.76 (2 H, m, 2 × H of CH_2), 1.46 (9 H, s, Bu^t) and 1.36 (2 H, d, J 7.0, 2 × H of CH_2); ^{1}H NMR NOE experiments: irradiation at δ 4.36 saw enhancement at 3.26 and 3.23 (4.4%), 1.85–1.76 (5.0%) and 1.36 (3.1%); irradiation at δ 3.26 saw enhancement at 4.36 and 4.21 (4.3%) and 1.36 (3.5%); δ_C(125 MHz) 158.0 (C=O), 79.8 (*C*Me$_3$), 57.0 (CH–O), 56.4 (CH–O), 50.1 (CH), 49.7 (CH), 28.2 (3 × Me), 26.0 (CH_2) and 25.1 (CH_2); *m*/*z* (CI) 212 (M + H^+, 8%) and 112 (M − Boc, 100) (Found: M + H^+, 212.1285. $C_{11}H_{18}NO_3$ requires *M*, 212.1286).

3-(*tert*-Butoxycarbonyl)-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ol 17¶

Bu^{n}Li (2.1 mol dm^{-3} in hexanes; 3.81 cm^3, 8.00 mmol) was added to a stirred solution of diisopropylamine (1.19 cm^3, 8.44 mmol) in Et_2O (15 cm^3) at 0 °C under argon. After 1 h, epoxide **13** (845 mg, 4.00 mmol) in Et_2O (20 cm^3) was added over 10 minutes (solution changed from colourless to yellow) and the reaction mixture was stirred for 5 min. HCl (1 mol dm^{-3} in H_2O; 10 cm^3) was added and the aqueous layer extracted with Et_2O (3 × 30 cm^3). The organic extracts were combined, washed with brine, dried and the solvent evaporated under reduced pressure. Purification of the residue by column chromatography (75% Et_2O–light petroleum) gave *azanortricyclanol* **17** as a clear colourless oil (439 mg, 52%); R_f (60% Et_2O–light petroleum) 0.11; ν_{max}/cm^{-1} 3404s, 2975s, 1678s, 1417s, 1252m, 1173s and 1114s; δ_H(500 MHz) 3.92 (1 H, br s, C*H*OH), 3.88 (1 H, br s, C(4)H), 3.61 (1 H, t, J 4.5, C(2)H), 1.75 (1 H, br s, OH), 1.54 (1 H, d, J 11.0, H of CH_2), 1.52–1.50 (1 H, m, C(6)H), 1.47 (9 H, s, Bu^t), 1.44–1.42 (1 H, m, C(1)H) and 1.32 (1 H, dt, J 11.0, 2.0, H of CH_2); δ_C(125 MHz) 157.3 (C=O), 80.2 (*C*Me$_3$), 75.4 (CHOH), 56.0 (C4), 31.1 (C2), 29.7 (CH_2), 28.3 (3 × Me), 17.2 (C6) and 14.7 (C1); *m*/*z* (CI) 212 (M + H^+, 10%) and 112 (100) (Found: M + H^+, 212.1287. $C_{11}H_{18}NO_3$ requires *M*, 212.1287).

2-(*tert*-Butoxycarbonyl)-2-azabicyclo[2.2.1]hept-5-ene 11 [13]

A solution of azanortricyclanol **17** (100 mg, 0.47 mmol) in THF (2.5 cm^3) was added dropwise to a suspension of KH (35% dispersion in mineral oil; 81 mg, 0.71 mmol) in THF (2.5 cm^3) at 0 °C under argon. After stirring for 20 min at 25 °C, the solution was re-cooled to 0 °C and then CS_2 (0.04 cm^3, 0.67 mmol) was added. After 10 min, MeI (0.04 cm^3, 0.64 mmol) was added and the reaction mixture stirred for 20 min at 25 °C. Water (5 cm^3) was added and the aqueous layer was extracted with Et_2O (3 × 20 cm^3). The organic layers were combined, washed with brine, dried and the solvent evaporated under reduced pressure to give the xanthate as a yellow oil (192 mg, characteristic singlet in the ^{1}H NMR at δ 2.50 assigned as SMe). The xanthate was co-evaporated twice with toluene (10 cm^3) and used without further purification. AIBN (12 mg) and Bu_3SnH (0.20 cm^3, 0.74 mmol) in toluene (1 cm^3) were added dropwise over 0.5 h to a solution of the crude xanthate in dry, degassed toluene (20 cm^3) at 100 °C. The solvent was then removed under reduced pressure to give a yellow oil which was treated exactly according to the procedure of Curran and Chang [42] to remove tin by-products. Final purification by column chromatography (30% Et_2O–hexane) gave the *2-azabicyclo[2.2.1]hept-5-ene* **11** as a clear colourless oil (55 mg, 60%, 66% based on recovered **17**).

3-(*tert*-Butoxycarbonyl)-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-one 22¶

DMSO (0.81 cm^3, 11 mmol) was added to a stirred solution of $(COCl)_2$ (0.50 cm^3, 5.7 mmol) in CH_2Cl_2 (17 cm^3) at −78 °C under argon. After 10 min, azanortricyclanol **17** (1.0 g, 4.74 mmol) in CH_2Cl_2 (13 cm^3) was added dropwise to the reaction mixture. After stirring for 20 min at −78 °C, NEt_3 (4.0 cm^3, 29 mmol) was added and the reaction mixture allowed to warm to 25 °C. Water (2 cm^3) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 cm^3). The organic extracts were combined, washed with brine, dried and the solvent evaporated under reduced pressure. Purification by column chromatography (50% Et_2O–light petroleum) gave *ketone* **22** as a pale yellow oil (800 mg, 81%); R_f (50% Et_2O–light petroleum) 0.30; ν_{max}/cm^{-1} 2979–2939, 1778s, 1706s, 1478m, 1369s, 1290s, 1254s, 1171s, 1124s and 1097s; δ_H(200 MHz) 4.33 (1 H, t, J 4.5,

¶ The numbering in the NMR follows that given in structure **17** in Scheme 6.

C(4)H), 3.74 (1 H, br s, C(2)H), 2.32 (1 H, t, *J* 5.0, C(6)H), 2.03 (1 H, d, *J* 10.5, H of CH_2), 1.76 (1 H, dt, *J* 10.5, 2.0, H of CH_2), 1.60 (1 H, t, *J* 5.0, C(1)H) and 1.46 (9 H, s, Bu^t); δ_C(125 MHz) 206.0 (C=O), 155.4 (C=O), 81.1 (*C*Me$_3$), 54.7 (C4), 39.2 (C2), 30.6 (CH_2), 28.2 (3 × Me), 21.5 (C6) and 17.9 (C1); *m*/*z* (CI) 227 (100%), 210 (M + H$^+$, 22%), 171 (43) and 110 (M − Boc, 100) (Found: M + H$^+$, 210.1130. $C_{11}H_{15}NO_3$ requires *M*, 210.1130).

3-(*tert*-Butoxycarbonyl)-5-(*n*-butyl)-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ol 24¶

BuLi (2.0 mol dm^{-3} in pentane; 0.54 cm^3, 1.08 mmol) was added dropwise to a stirred solution of ketone **22** (150 mg, 0.72 mmol) in THF (5 cm^3) at −78 °C under argon. After 1 h, the reaction mixture was allowed to warm to 25 °C. Saturated aqueous NH_4Cl (10 cm^3) was added and the reaction mixture was extracted with Et_2O (3 × 20 cm^3). The organic extracts were combined, washed with brine, dried and the solvent evaporated under reduced pressure to give a yellow oil. Purification by column chromatography (50% Et_2O–light petroleum) gave *alcohol* **24** as a clear colourless oil (135 mg, 70%); R_f (Et_2O) 0.60; ν_{max}/cm^{-1} 3425m, 2957s, 1679s, 1366s, 1293s, 1177s and 1101s; δ_H(270 MHz) 3.75–3.47 (2 H, m, C(4)H and C(2)H), 2.15–2.11 (1 H, d, *J* 11.0, H of CH_2), 1.79–1.64 (1 H, m, CH), 1.59–1.19 (18 H, m, CH, OH, H of CH_2, 3 × Me and 3 × CH_2) and 0.92 (3 H, t, *J* 7.0, Me); δ_C(100 MHz) (3 : 1 mixture of rotational isomers observed) 155.5 (C=O), 83.5 (*C*–OH, quat.), 79.6 (*C*Me$_3$), 56.8 and 56.0 (C4), 34.3 and 33.8 (C2), 33.3 (CH_2), 31.0 and 30.6 (CH_2), 28.3 and 28.2 (3 × Me), 26.5 (CH_2), 23.1 (CH_2), 20.7 and 20.6 (CH) and 14.1 and 13.5 (CH and Me); *m*/*z* (CI) 268 (M + H$^+$, 20%), 229 (10), 212 (5) and 168 (M − Boc, 100) (Found: M + H$^+$, 268.1911. $C_{15}H_{26}NO_3$ requires *M*, 268.1913).

3-(*tert*-Butoxycarbonyl)-5-phenyl-3-azatricyclo[2.2.1.0^{2,6}]-heptan-5-ol 25¶

PhLi (1.8 mol dm^{-3} in 30% Et_2O–cyclohexane; 0.79 cm^3, 1.42 mmol) was added dropwise to a stirred solution of ketone **22** (150 mg, 0.72 mmol) in THF (5 cm^3) at −78 °C under argon. After 1 h, the reaction mixture was allowed to warm to 25 °C and saturated aqueous NH_4Cl (10 cm^3) added. The mixture was extracted with Et_2O (3 × 20 cm^3) and the organic extracts were combined, washed with brine, dried and the solvent evaporated under reduced pressure to give a yellow oil. Purification was by column chromatography (50% Et_2O–light petroleum). First to elute was *endo alcohol* **25**, isolated as a clear colourless oil (107 mg, 52%); R_f (50% Et_2O–hexane) 0.21; ν_{max}/cm^{-1} 3392m, 2976m, 1674s, 1427s, 1366s, 1296m, 1171s and 1079s; δ_H-(270 MHz) 7.49 (2 H, dd, *J* 8.5, 2.0, 2 × CH of Ph), 7.38–7.27 (3 H, m, 3 × CH of Ph), 3.90 (1 H, br s, C(4)H), 3.78 (1 H, t, *J* 4.5, C(2)H), 2.60 (1 H, br s, OH), 1.82 (1 H, t, *J* 5.0, C(6)H), 1.68–1.70 (1 H, m, C(1)H), 1.50 (9 H, s, Bu^t), 1.42 (1 H, d, *J* 11.0, H of CH_2) and 1.24 (1 H, d, *J* 11.0, H of CH_2); δ_C(100 MHz) 157.2 (C=O), 139.4 (C of Ph, quat.), 128.3, 128.2, 128.1, 128.0 and 126.9 (5 × CH of Ph), 84.6 (C–OH, quat.), 80.4 (*C*Me$_3$), 60.2 (C4), 33.0 (C2), 29.8 (CH_2), 28.4, 28.3 and 28.1 (3 × Me), 20.5 (C6) and 15.4 (C1); *m*/*z* (CI) 288 (M + H$^+$, 20%), 249 (10), 232 (10) and 188 (M − Boc, 100) (Found: M + H$^+$, 288.1604. $C_{17}H_{22}NO_3$ requires *M*, 288.1600). Second to elute was *exo alcohol* **25**, isolated as a clear colourless oil (75 mg, 36%); R_f (50% Et_2O–hexane) 0.16; ν_{max}/cm^{-1} 3391m, 2976m, 1670s, 1430s, 1366s, 1297m, 1171s and 1081s; δ_H(270 MHz) 7.53 (2 H, dd, *J* 8.5, 2.0, 2 × CH of Ph), 7.37–7.31 (3 H, m, 3 × CH of Ph), 3.75–3.40 (2 H, m, C(4)H and C(2)H), 2.39 (1 H, d, *J* 10.5, H of CH_2), 2.15 (1 H, br s, OH), 1.75 (1 H, d, *J* 5.0, C(1)H), 1.67–1.65 (1 H, m, C(6)H), 1.57 (1 H, d, *J* 10.5, H of CH_2) and 1.27 and 1.08 (9 H, 2 × s, Bu^t); δ_C(100 MHz) (3 : 1 mixture of rotational isomers observed) 154.6 (C=O), 141.4 (C of Ph, quat.), 128.4, 128.2, 128.1, 126.9 and 126.8 (5 × CH of Ph), 84.9 (*C*–OH, quat.), 79.2 (*C*Me$_3$), 59.0 and 57.5 (C4), 35.0 and 34.6 (C2), 32.1 and 31.5 (CH_2), 28.3 and 28.2 (3 × Me), 21.2 and 20.6 (C6) and 14.6 and 13.9 (C1); *m*/*z* (CI) 288 (M + H$^+$, 20%), 249 (10), 232 (10) and 188 (M − Boc, 100) (Found: M + H$^+$, 288.1604. $C_{17}H_{22}NO_3$ requires *M*, 288.1600).

3-(*tert*-Butoxycarbonyl)-5-(6-methoxypyridin-3-yl)-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ol 26¶

Bu^{n}Li (2.5 mol dm^{-3} in hexanes; 2.22 cm^3, 5.55 mmol) was added dropwise to a stirred solution of 5-bromo-2-methoxy-pyridine[30,43] (1.21 g, 6.44 mmol) in Et_2O (18 cm^3) and THF (8.0 cm^3) at −78 °C under argon. After 30 min, ketone **22** (450 mg, 2.15 mmol) in Et_2O (8 cm^3) was added. The reaction mixture was stirred for 3 h at −78 °C and then warmed to 25 °C before saturated aqueous NH_4Cl (15 cm^3) was added. The aqueous layer was extracted with Et_2O (3 × 25 cm^3) and the organic extracts were combined, washed with brine, dried and the solvent evaporated under reduced pressure to give a yellow oil which was purified by column chromatography (50% Et_2O–light petroleum). First to elute was the *endo alcohol* **26**, isolated as a white foam (300 mg, 44%); R_f (Et_2O) 0.45; ν_{max}/cm^{-1} 3401s, 2978s, 1694s, 1694m, 1496s, 1368s, 1289s, 1173m and 1114m; δ_H(500 MHz) 8.26 (1 H, d, *J* 2.0, C(2 of pyridine)H), 7.70 (1 H, dd, *J* 8.5, 2.0, C(4 of pyridine)H), 6.74 (1 H, d, *J* 8.5, C(5 of pyridine)H), 3.94 (3 H, s, OMe), 3.86 (1 H, br s, C(4)H), 3.79 (1 H, br s, C(2)H), 2.65 (1 H, br s, OH), 1.81 (1 H, t, *J* 5.0, C(6)H), 1.70 (1 H, t, *J* 5.0, C(1)H), 1.50 (9 H, s, Bu^t), 1.43 (1 H, d, *J* 10.5, H of CH_2) and 1.26 (1 H, d, *J* 10.5, H of CH_2); ^{1}H NMR NOE experiments: irradiation at δ 8.26 saw enhancement at 1.81 (5.5%) and 1.70 (1.4%); irradiation at δ 3.86 saw enhancement at 8.26 (2.2%) and 7.70 (4.0%); irradiation at δ 3.79 saw enhancement at 1.81 (5.3%) and 1.70 (3.2%); δ_C-(125 MHz) 164.0 (C3 of pyridine, quat.), 154.0 (C=O), 145.4 (C2 of pyridine), 137.6 (C4 of pyridine), 127.8 (C6 of pyridine, quat.), 110.7 (C5 of pyridine), 82.8 (C–OH, quat.), 80.7 (*C*Me$_3$), 60.5 (C4), 53.5 (OMe), 33.0 (C2), 29.7 (CH_2), 28.3 (3 × Me), 20.5 (C6) and 15.4 (C1); *m*/*z* (CI) 319 (M + H$^+$, 50%), 263 (60) and 201 (100) (Found: M + H$^+$, 319.1655. $C_{17}H_{23}N_2O_4$ requires *M*, 319.1658). Second to elute was *exo alcohol* **26** isolated as a white solid (300 mg, 44%); R_f (Et_2O) 0.34; mp (from Et_2O) 121–122 °C; δ_H(500 MHz) 8.31 (1 H, br s, C(2 of pyridine)H), 7.74–7.72 (1 H, m, C(4 of pyridine)H), 6.72 (1 H, d, *J* 8.5, C(5 of pyridine)H), 3.91 (3 H, s, OMe), 3.85–3.81 (1 H, m, C(4)H), 3.74–3.66 (1 H, m, C(2)H), 2.36 (1 H, d, *J* 10.0, H of CH_2), 2.17 (1 H, br s, OH), 1.78 (1 H, t, *J* 4.5, C(1)H), 1.68 (1 H, br s, C(6)H), 1.57 (1 H, dt, *J* 10.0, 1.5, H of CH_2) and 1.30 and 1.17 (9 H, 2 × s, Bu^t); δ_C(125 MHz) (3 : 2 mixture of rotational isomers observed) 163.9 (C3 of pyridine, quat.), 154.8 (C=O), 145.4 and 144.9 (C2 of pyridine), 137.6 (C4 of pyridine), 129.7 (C6 pyridine, quat.), 110.6 and 110.3 (C5 of pyridine), 83.2 and 83.0 (C–OH, quat.), 79.8 and 79.6 (*C*Me$_3$), 58.9 and 57.6 (C4), 53.5 (OMe), 35.1 and 34.6 (C2), 31.9 and 31.3 (CH_2), 28.3 (3 × Me), 21.0 and 20.6 (C6) and 14.6 and 13.9 (C1); *m*/*z* (CI) 319 (M + H$^+$, 70%), 263 (100) and 201 (50) (Found: M + H$^+$, 319.1655. $C_{17}H_{23}N_2O_4$ requires *M*, 319.1658).

3-(*tert*-Butoxycarbonyl)-5-*exo*-(6-chloropyridin-3-yl)-3-azatricyclo[2.2.1.0^{2,6}]heptan-5-ol 27¶

Bu^{n}Li (2.1 mol dm^{-3} in hexanes; 1.20 cm^3, 2.52 mmol) was added dropwise to a stirred solution of 2-chloro-5-iodo-pyridine[32,44] (688 mg, 2.87 mmol) in Et_2O (15 cm^3) and THF (5.0 cm^3) at −78 °C under argon. After 30 min, ketone **22** (200 mg, 0.96 mmol) in Et_2O (6 cm^3) was added. The reaction mixture was stirred for 3 h at −78 °C and then warmed to 25 °C over 15 min and then saturated aqueous NH_4Cl (10 cm^3) was added. The aqueous layer was extracted with Et_2O (3 × 20 cm^3) and the organic extracts were combined, washed with brine, dried and the solvent evaporated under reduced pressure. Purification by column chromatography (50% Et_2O–light petrol-

eum) gave *tertiary alcohol* **27** as a cream foam (230 mg, 74%); R_f (Et_2O) 0.32; ν_{max}/cm^{-1} 3362m, 2978m, 1674s, 1458m, 1368s, 1295s, 1170m and 1108s; δ_H(200 MHz) 8.58–8.52 (1 H, m, C(2 of pyridine)H), 7.86–7.83 (1 H, m, C(4 of pyridine)H), 7.32 (1 H, d, *J* 9.5, C(5 of pyridine)H), 3.99–3.76 (2 H, m, C(4)H and C(2)H), 2.70 (1 H, br s, OH), 2.41 (1 H, d, *J* 10.5, H of CH_2), 1.86 (1 H, t, *J* 5.0, C(1)H), 1.74 (1 H, br s, C(6)H), 1.63 (1 H, d, *J* 10.5, H of CH_2) and 1.37 and 1.23 (9 H, 2 × s, Bu^t); ^{1}H NMR NOE experiments: irradiation at δ 8.56 saw enhancement at 3.88 (3.2%) and 1.74 (3%); irradiation at δ 3.88 saw enhancement at 8.56 (1.5%), 7.85 (2.7%), 2.41 (1%), 1.86 (4%), 1.74 (3.3%) and 1.63 (1.8%); irradiation at δ 2.41 saw enhancement at 3.88 (1.3%) and 1.63 (3%); δ_C(125 MHz) (3 : 2 mixture of rotational isomers observed) 154.8 (C=O), 150.8 (C6 of pyridine, quat.), 148.6 and 148.4 (C2 of pyridine), 148.0 (C3 of pyridine, quat.), 137.8 and 137.5 (C4 of pyridine), 123.8 and 123.5 (C5 of pyridine), 82.7 (C–OH, quat.), 80.0 (CMe_3), 59.1 and 57.8 (C4), 35.3 and 34.8 (C2), 32.0 and 31.5 (CH_2), 28.2, 28.1 and 28.0 (3 × Me), 21.3 and 20.8 (C6) and 14.6 and 14.0 (C1); *m*/*z* (CI) 323 (M + H^+, 35%), 267 (100) and 223.0 (M − Boc, 68) (Found: M + H^+, 323.1162. $C_{16}H_{20}{}^{35}ClN_2O_3$ requires *M*, 323.1162).

2-(*tert*-Butoxycarbonyl)-6-(*n*-butyl)-2-azabicyclo[2.2.1]-hept-5-ene 28

DMAP (34 mg, 0.28 mmol) and $ClCOCO_2Me$ (0.03 cm^3, 0.33 mmol) were added to a stirred solution of alcohol **24** (50 mg, 0.19 mmol) in MeCN (3 cm^3) at 25 °C under argon. After 0.5 h, the reaction mixture was diluted with EtOAc (10 cm^3) and washed with saturated aqueous $NaHCO_3$ (10 cm^3) and H_2O (10 cm^3). The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the crude oxalyl ester as a yellow oil (80 mg) which then was co-evaporated twice with toluene. AIBN (*ca.* 5 mg) and Bu_3SnH (0.08 cm^3, 0.30 mmol) were added to a stirred solution of the crude oxalyl ester in dry, degassed toluene (5 cm^3) and the reaction mixture was then heated to 100 °C. After 45 min the reaction mixture was allowed to cool and the solvent was removed under reduced pressure to give a yellow oil which was treated exactly according to the procedure of Curran and Chang[42] to remove tin by-products. Final purification by column chromatography (40% Et_2O–hexane) gave *alkene* **28** as a colourless oil (30 mg, 63%): R_f (30% Et_2O–hexane) 0.47; ν_{max}/cm^{-1} 2960s, 1697s, 1391s, 1182m and 1141m; δ_H(270 MHz) (3 : 1 mixture of rotational isomers observed) 5.73–5.72 (1 H, m, C=CH), 4.55 and 4.42 (1 H, 2 × br s, C(1)H), 3.29 (1 H, d, *J* 9.0, H of $C(3)H_2$), 3.06 (1 H, d, *J* 3.5, C(4)H), 2.66 and 2.57 (1 H, 2 × d, *J* 9.0, H of $C(3)H_2$), 2.27–2.15 (2 H, m, $C(7)H_2$), 1.48–1.43 (9 H, m, Bu^t) and 1.27–0.85 (9 H, m, Bu^n); δ_C(100 MHz) (3 : 1 mixture of rotational isomers observed) 151.9 (C=O), 149.6 (CH=*C*, quat.), 127.6 (*C*H=C), 78.9 (CMe_3), 63.6 and 62.7 (C1), 48.1 and 47.8 (C7), 47.3 and 46.7 (C3), 43.1 and 42.6 (C4), 31.6 (CH_2), 29.6 and 29.4 (CH_2), 28.5 (3 × Me), 22.6 and 22.5 (CH_2) and 14.1 and 13.9 (Me); *m*/*z* (CI) 252 (M + H^+, 15%), 213 (35), 196 (50) and 123 (100) (Found: M + H^+, 252.1962. $C_{15}H_{26}NO_2$ requires *M*, 252.1964).

2-(*tert*-Butoxycarbonyl)-6-phenyl-2-azabicyclo[2.2.1]hept-5-ene 29

Alcohol **25** (70 mg, 0.24 mmol) was deoxygenated following the procedure described for **28**. Purification by column chromatography (40% Et_2O–hexane) gave *alkene* **29** as a colourless oil (40 mg, 62%): R_f (50% Et_2O–hexane) 0.44; ν_{max}/cm^{-1} 2977m, 1692s, 1402s, 1365m, 1155s and 758s; δ_H(270 MHz; 55 °C) 7.55 (2 H, br s, 2 × CH of Ph), 7.31 (2 H, t, *J* 7.5, 2 × CH of Ph), 7.22 (1 H, t, *J* 7.5, CH of Ph), 6.45 (1 H, br s, C=CH), 5.09 (1 H, br s, C(1)H), 3.44 (1 H, dd, *J* 9.5 and 3.0, H of $C(3)H_2$), 3.26 (1 H, br s, C(4)H), 2.79 (1 H, m, H of $C(3)H_2$), 1.76 (2 H, br s, $C(7)H_2$) and 1.40 (9 H, s, Bu^t); δ_C(100 MHz) (3 : 1 mixture of rotational isomers observed) 154.8 (C=O), 149.1 and 147.7 (CH=*C*), 134.0 (C of Ph, quat.), 129.1 and 128.8 (*C*H=C), 128.5 and 128.3 (2 × CH of Ph), 127.5 and 127.3 (CH of Ph), 125.6 (2 × CH of Ph), 79.5 and 79.0 (CMe_3), 62.0 and 61.4 (C1), 48.1 and 48.0 (C7), 47.0 and 46.5 (C3), 43.8 and 43.3 (C4) and 28.5 and 28.4 (3 × Me); *m*/*z* (CI) 272 (M + H^+, 20%), 233 (70), 216 (80) and 143 (100) (Found: M + H^+, 272.1649. $C_{17}H_{22}NO_2$ requires *M*, 272.1651).

2-(*tert*-Butoxycarbonyl)-6-(6-methoxypyridin-3-yl)-2-azabicyclo[2.2.1]hept-5-ene 30

Alcohol **26** (130 mg, 0.41 mmol) was deoxygenated following the procedure described for **28**. Purification by column chromatography (50% Et_2O–light petroleum) gave *alkene* **30** as a clear colourless oil (70 mg, 57%); R_f (50% Et_2O–light petroleum) 0.33; ν_{max}/cm^{-1} 2977m, 1692s, 1603s, 1500s, 1409s, 1290s, 1158s and 1023m; δ_H(500 MHz) 8.38 (1 H, s, C(2 of pyridine)H), 7.72 (1 H, d, *J* 8.5, C(4 of pyridine)H), 6.71 (1 H, d, *J* 8.5, C(5 of pyridine)H), 6.41 (1 H, br s, C=CH), 5.06 (1 H, m, C(1)H), 3.94 (3 H, s, OMe), 3.44 (1 H, dd, *J* 9.5, 3.0, H of $C(3)H_2$), 3.28 (1 H, br s, C(4)H), 2.80 (1 H, d, *J* 9.0, H of $C(3)H_2$), 1.76–1.60 (2 H, m, $C(7)H_2$) and 1.40 (9 H, s, Bu^t); δ_C(125 MHz) (3 : 1 mixture of rotational isomers observed) 163.4 (C6 of pyridine, quat.), 154.9 and 154.0 (C=O), 146.6 and 145.4 (HC=*C*, quat.), 144.2 and 144.0 (C2 of pyridine), 137.8 and 135.8 (C4 of pyridine), 127.9 and 127.6 (H*C*=C), 123.2 and 122.2 (C3 of pyridine, quat.), 110.4 and 110.3 (C5 of pyridine), 79.8 and 79.6 (CMe_3), 61.6 and 61.4 (C1), 54.1 (OMe), 48.0 and 47.2 (C7), 43.8 and 43.2 (C3), 38.9 and 38.0 (C4) and 28.6, 28.4 and 28.3 (3 × Me); *m*/*z* (CI) 319.2 (100%), 303.2 (M + H^+, 15), 263 (50) and 219 (80). **30** is unstable especially in protic solvents. Accurate mass not measured due to decomposition.

2-(*tert*-Butoxycarbonyl)-6-(6-chloropyridin-3-yl)-2-azabicyclo[2.2.1]hept-5-ene 31

Alcohol **27** (200 mg, 0.62 mmol) was deoxygenated following the procedure described for **28**. Purification by column chromatography (40% Et_2O–light petroleum) gave *alkene* **31** as a clear colourless oil (115 mg, 61%); R_f (75% Et_2O–light petroleum) 0.61; ν_{max}/cm^{-1} 2975m, 1691s, 1464m, 1408s, 1367s, 1157s and 1106s; δ_H(270 MHz; 60 °C) 8.57 (1 H, dd, *J* 2.5, 0.5, C(2 of pyridine)H), 7.94 and 7.78 (1 H, 2 × br s, C(4 of pyridine)H), 7.27 (1 H, dd, *J* 8.0, 0.5, C(5 of pyridine)H), 6.57 (1 H, br s, C=CH), 5.05–5.03 (1 H, m, C(1)H), 3.47 (1 H, dd, *J* 9.0 and 3.0, H of $C(3)H_2$), 3.31 (1 H, br s, C(4)H), 2.78 (1 H, br s, H of $C(3)H_2$), 1.77 (2 H, s, $C(7)H_2$) and 1.41 (9 H, s, Bu^t); δ_C(100 MHz) (2 : 1 mixture of rotational isomers observed) 154.9 and 154.8 (C=O), 150.1 (CH=*C*), 147.0 (C2 of pyridine), 145.3 and 143.8 (C6 of pyridine, quat.), 136.5 and 135.5 (C4 of pyridine), 132.0 and 131.7 (*C*H=C), 129.7 and 128.9 (C3 of pyridine, quat.), 124.1 and 124.0 (C5 of pyridine), 80.2 and 79.7 (CMe_3), 61.7 and 61.5 (C1), 48.4 and 48.1 (C7), 47.0 and 46.5 (C3), 44.3 and 43.7 (C4) and 28.6 (3 × Me); *m*/*z* (CI, CH_4) 325/323 (35%), 309/307 (M + H^+, 90), 269/267 (10), 253/251 (20) and 225/223 (100) (Found: M + H^+, 307.1224. $C_{16}H_{20}{}^{35}ClN_2O_2$ requires *M*, 307.1213).

endo-2-(*tert*-Butoxycarbonyl)-6-(6-methoxypyridin-3-yl)-2-azabicyclo[2.2.1]heptane 32

10% Pd/C (15 mg) was added to a solution of alkene **30** (19 mg, 0.063 mmol) in EtOAc (4 cm^3). The flask was evacuated and then flushed with H_2, and the reaction mixture was stirred under 1 atm of H_2 for 2 h. The reaction mixture was filtered through Celite and the solvent evaporated under reduced pressure to give a clear colourless oil. Purification by column chromatography (gradient elution 50–75% Et_2O–light petroleum) gave *2-azabicyclo[2.2.1]heptane* **32** as a clear colourless oil (15 mg, 78%); R_f (Et_2O) 0.51; ν_{max}/cm^{-1} 2974s, 2880m, 1690s,

1606m, 1497s, 1411s, 1288s and 1151s; δ_H(500 MHz) (2 : 1 mixture of rotational isomers observed) 7.98 and 7.96 (1 H, d, *J* 2.5, C(2 of pyridine)H), 7.40 and 7.35 (1 H, 2 × dd, *J* 8.5, 2.5, C(4 of pyridine)H), 6.69 and 6.65 (1 H, 2 × d, *J* 8.5, C(5 of pyridine)H), 4.29 and 4.12 (1 H, 2 × s, C(1)H), 3.91 and 3.89 (3 H, s, OMe), 3.45–3.35 (1 H, m, H of $C(3)H_2$), 3.30–3.20 (1 H, m, C(6)H), 3.13 and 3.08 (1 H, 2 × d, *J* 10.0, H of $C(3)H_2$), 2.66–2.63 (1H, m, C(4)H), 2.18–2.09 (1 H, m, H of $C(5)H_2$), 1.82–1.68 (2 H, m, $C(7)H_2$), 1.55–1.46 (1 H, m, $C(5)H_2$) and 1.33 and 1.10 (9 H, 2 × s, Bu^t); ^{1}H NMR NOE experiments: irradiation at δ 7.40 saw enhancement at 6.67 (9.7%), 3.25 (2.3%), 3.08 (2.8%) and 1.50 (3.7%); irradiation at δ 3.25 saw enhancement at 7.97 (6%), 7.37 (1.2%), 4.29 and 4.12 (1.9 and 4%), 2.15 (6.8%) and 1.70 (3.2%); δ_C(125 MHz) (3 : 1 mixture of rotational isomers observed) 162.9 (C6 of pyridine, quat.), 154.1 (C=O), 146.4 and 145.7 (C2 of pyridine), 138.5 and 138.0 (C4 of pyridine), 129.6 (C3 of pyridine, quat.), 110.2 and 110.1 (C5 of pyridine), 78.9 and 78.7 (CMe_3), 62.1 and 60.4 (C1), 53.4 and 53.2 (OMe), 52.6 (C3), 45.8 and 45.6 (C6), 39.7 and 39.2 (C7), 38.0 and 37.5 (C4), 34.3 and 33.3 (C5) and 28.4 and 28.1 (3 × Me); *m*/*z* (EI) 304 (M^+, 45%) and 231 (100) (Found: M^+, 304.1794. $C_{17}H_{25}N_2O_3$ requires *M*, 304.1787).

endo-2-(*tert*-Butoxycarbonyl)-6-(6-chloropyridin-3-yl)-2-azabicyclo[2.2.1]heptane 33

10% Pd/C (Aldrich; 10 mg) was added to a solution of alkene **31** (90 mg, 0.29 mmol) in EtOAc (18 cm^3). The flask was immediately evacuated, flushed with H_2 and the reaction mixture was stirred under 1 atm of H_2 for 3 h. The reaction mixture was filtered through Celite and the solvent evaporated under reduced pressure to give a clear colourless oil. Purification by column chromatography (50% Et_2O–light petroleum) gave *2-azabicyclo[2.2.1]heptane* **33** as a white solid (86 mg, 96%); R_f (75% Et_2O–light petroleum) 0.47; mp (from Et_2O) 124–125 °C; ν_{max}/cm^{-1} 2927s, 1686s, 1456s, 1412s and 1151s; δ_H (500 MHz) 8.22 and 8.20 (1 H, 2 × d, *J* 2.5, C(2 of pyridine)H), 7.64–7.61 (1 H, m, C(4 of pyridine)H), 7.38 and 7.33 (1 H, 2 × d, *J* 8.0, C(5 of pyridine)H), 4.20 and 4.17 (1 H, 2 × s, C(1)H), 3.48–3.45 (1 H, m, $C(3)H_2$), 3.41–3.31 (1 H, m, C(6)H), 3.19 and 3.15 (1 H, 2 × d, *J* 9.5, H of $C(3)H_2$), 2.70 (1H, br s, C(4)H), 2.25–2.14 (1 H, m, H of $C(5)H_2$), 1.86–1.77 (2 H, m, $C(7)H_2$), 1.66–1.55 (1 H, m, H of $C(5)H_2$) and 1.32 and 1.08 (9 H, 2 × s, Bu^t); δ_C(125 MHz) (2 : 1 mixture of rotational isomers observed) 155.8 (C=O), 150.8 and 150.3 (C2 of pyridine), 150.1 (C6 of pyridine, quat.), 140.6 and 140.3 (C4 of pyridine), 138.4 (C3 of pyridine, quat.), 125.2 and 125.0 (C5 of pyridine), 80.7 and 80.5 (CMe_3), 63.9 and 62.3 (C1), 54.5 and 53.7 (C3), 48.5 and 47.1 (C6), 40.6 and 40.1 (C7), 39.5 and 39.0 (C4), 34.3 and 33.3 (C5) and 28.7 and 28.4 (3 × Me); *m*/*z* (CI) 309/311 (M + H^+, 100%), 275/276 (48) and 209/211 (M − Boc, 47) (Found: M + H^+, 309.1374. $C_{16}H_{22}{}^{35}ClN_2O_2$ requires *M*, 309.1370). The enantiomers were separated by chiral HPLC [Daicel Chiralcel OD column (20 mm × 250 mm)] on a Gilson system and a 118 UV–VIS detector set at 254 nm using 10 : 90 EtOH–hexane as eluent (5 cm^3 min^{-1}) t_R 12.1 min; $[\alpha]_D^{24}$ +40.0 (*c* 1.0 in $CHCl_3$) and 14.8 min; $[\alpha]_D^{24}$ −39.4 (*c* 1.0 in $CHCl_3$).

Crystal data for **33**: $C_{16}H_{21}ClN_2O_2$, *M* = 308.81, triclinic, space group $P\bar{1}$, *a* = 6.225(1), *b* = 10.446(1), *c* = 12.497(2) Å, *α* = 85.74(1)°, *β* = 87.21(1)°, *γ* = 83.12(1)°, *V* = 803.84(2) Å^3, *Z* = 2. 3474 reflections measured on an Enraf Nonius DIP2000 diffractometer. Cu-K*α* radiation. 2841 reflections observed with $I > 3\sigma(I)$ yield *R* = 0.0579, R_w = 0.0643. CCDC reference number 168194. See http://www.rsc.org/suppdata/p1/b1/b107414h/ for crystallographic data in .cif or other electronic format.

endo-6-(6-Chloropyridin-3-yl)-2-azabicyclo[2.2.1]heptane 2

TFA (0.10 cm^3, 1.3 mmol) was added to a solution of 2-azabicycle **33** (10 mg, 0.032 mmol) in CH_2Cl_2 (0.5 cm^3) at 0 °C under argon. After stirring for 2 h at 25 °C, saturated aqueous Na_2CO_3 (1 cm^3) was added and the aqueous layer was extracted with EtOAc (3 × 10 cm^3). The organic layers were combined, dried (Na_2SO_4) and the solvent evaporated under reduced pressure. Purification by column chromatography (1 : 10 : 90 NH_3–MeOH–CH_2Cl_2) gave *2-azabicyclo[2.2.1]heptane* **2** as a clear colourless oil (6.2 mg, 93%); R_f (1 : 10 : 90 NH_3–MeOH–CH_2Cl_2) 0.52; ν_{max}/cm^{-1} 3402br s, 2927s, 1682s, 1462s, 1202s and 1106s; δ_H(500 MHz; CD_3OD) 8.31 (1 H, d, *J* 2.5, C(2 of pyridine)H), 7.78 (1 H, dd, *J* 8.5, 2.5, C(4 of pyridine)H), 7.45 (1 H, d, *J* 8.5, C(5 of pyridine)H), 3.63 (1 H, s, C(1)H), 3.45–3.41 (1 H, m, C(6)H), 2.95–2.92 (1 H, m, H of $C(3)H_2$), 2.77 (1 H, d, *J* 9.5, H of $C(3)H_2$), 2.60 (1H, s, C(4)H), 2.22–2.15 (1 H, m, H of $C(5)H_2$), 1.90–1.88 (1 H, m, H of $C(7)H_2$), 1.82–1.79 (1 H, m, H of $C(7)H_2$) and 1.67–1.63 (1 H, m, H of $C(5)H_2$); ^{1}H NMR NOE experiments: irradiation at δ 7.78 saw enhancement at 7.45 (6.8%), 3.63 (1.4%), 3.45 (1.7%), 2.77 (1.3%) and 1.65 (3%); irradiation at δ 3.45 saw enhancement at 8.31 (3.6%), 7.78 (2.4%), 3.63 (2.7%), 2.20 (5.3%) and 1.89 (4.8%); δ_C(125 MHz; CD_3OD) 149.3 (C2 of pyridine), 139.5 (C4 of pyridine), 124.1 (C5 of pyridine), 60.2 (C1), 50.8 (C3), 44.6 (C6), 38.9 (C7), 37.5 (C4) and 32.8 (C5); *m*/*z* (CI) 209/211 (M + H^+, 100%) and 122 (30) (Found: M + H^+, 209.0844. $C_{11}H_{13}{}^{35}ClN_2$ requires *M*, 209.0846). The separate enantiomers had optical rotations $[\alpha]_D^{24}$ +81.0 (*c* 1.0 in $CHCl_3$) and $[\alpha]_D^{24}$ −81.1 (*c* 1.0 in $CHCl_3$).

endo-2-(*tert*-Butoxycarbonyl)-6-(pyridin-3-yl)-2-azabicyclo-[2.2.1]heptane 34

10% Pd/C (40 mg) was added to a solution of 2-azabicycle **33** (35 mg, 0.11 mmol) in EtOAc (6 cm^3). The flask was evacuated, flushed with H_2, and the reaction mixture was stirred under 1 atm of H_2 for 48 h. The reaction mixture was filtered through Celite and the solvent evaporated under reduced pressure to give a clear colourless oil (30 mg). Purification by column chromatography (gradient elution 50%–100% Et_2O–light petroleum) gave *2-azabicyclo[2.2.1]heptane* **34** as a clear colourless oil (15 mg, 50%); R_f (75% Et_2O–light petroleum) 0.16; ν_{max}/cm^{-1} 2976m, 1690s, 1412s, 1179m and 1150s; δ_H(400 MHz) (3 : 1 mixture of rotational isomers) 8.47 (2 H, br s, C(2 of pyridine)H) and C(6 of pyridine)H), 7.54 and 7.44 (1 H, 2 × d, *J* 8.0, C(4 of pyridine)H), 7.25–7.18 (1 H, m, C(5 of pyridine)H), 4.38 and 4.20 (1 H, 2 × s, C(1)H), 3.49–3.40 (1 H, m, $C(3)H_2$), 3.38–3.32 (1 H, m, C(6)H), 3.15 and 3.09 (1 H, 2 × d, *J* 9.5, $C(3)H_2$), 2.70–2.67 (1H, m, C(4)H), 2.23–2.13 (1 H, m, C(5)H), 1.84 (1 H, d, *J* 10.0, $C(7)H_2$), 1.76 (1 H, d, *J* 10.5, $C(7)H_2$), 1.60–1.47 (1 H, m, C(5)H) and 1.32 and 1.07 (9 H, 2 × s, Bu^t); δ_C(100 MHz) (3 : 1 mixture of rotational isomers observed) 154.0 (C=O), 150.4 (C2 of pyridine), 147.3 (C6 of pyridine), 137.1 and 135.5 (C3 of pyridine), 134.6 (C4 of pyridine), 123.2 (C5 of pyridine), 78.8 (CMe_3), 62.0 and 60.2 (C1), 53.4 and 52.6 (C3), 46.5 and 46.4 (C6), 39.8 and 39.2 (C7), 38.0 and 37.5 (C4), 34.1 and 33.2 (C5) and 28.3 and 28.0 (3 × Me); *m*/*z* (EI) 275 (M^+, 100%) (Found: M^+, 274.1684. $C_{16}H_{22}N_2O_2$ requires *M*, 274.1681).

endo-6-(Pyridin-3-yl)-2-azabicyclo[2.2.1]heptane 35

2-Azabicycle **34** (9 mg, 0.033 mmol) was deprotected following the procedure described for **2**. Purification by column chromatography (1 : 15 : 85 NH_3–MeOH–CH_2Cl_2) gave *2-azabicycle* **35** as a clear colourless oil (2.1 mg, 37%); R_f (1 : 10 : 90 NH_3–MeOH—CH_2Cl_2) 0.10; ν_{max}/cm^{-1} 3380br s, 2923s, 1652m, 1424m, 1261m and 1027m; δ_H (500 MHz; CD_3OD) 8.51 (1 H, d, *J* 2.0, C(2 of pyridine)H), 8.44 (1 H, dd, *J* 5.0, 2.0, C(6 of pyridine)H), 7.81 (1 H, d, *J* 8.0, C(4 of pyridine)H), 7.45 (1 H, dd, *J* 8.0, 5.0, C(5 of pyridine)H), 3.69 (1 H, s, C(1)H), 3.50–3.45 (1 H, m, C(6)H), 2.97–2.94 (1 H, m, H of $C(3)H_2$), 2.84–2.82 (1 H, d, *J* 9.5, H of $C(3)H_2$), 2.62 (1H, t, *J* 3.5, C(4)H), 2.24–2.16 (1 H, m, H of $C(5)H_2$), 1.92 (1 H, d, *J* 10.0, H of

C(7)H_2), 1.83 (1 H, dd, *J* 10.0, 2.0, H of C(7)H_2) and 1.99–1.70 (1 H, m, H of C(5)H_2); *m*/*z* (CI) 175 (M + H^+, 100%).

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