Synthesis of epibatidine isomers: *endo*-5- and 6- (6′-chloro-3′-pyridyl-2-azabicyclo[2.2.1]heptanes

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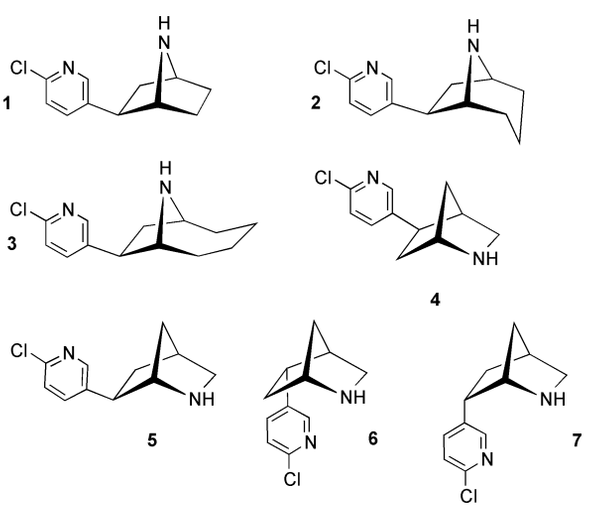
Synthesis of the title compounds is described; detailed NMR data are provided in support of the proposed stereostructures. The 5- and 6-*endo*-compounds show high selectivity for α4β2 *versus* α7 nAChR subtypes; in contrast, the *exo*-stereoisomers show comparatively weak affinity at both subtypes.

Introduction

The level of interest in epibatidine[1] **1** and analogues remains high. Following the recognition that epibatidine acts at the nicotinic acetylcholine receptor (nAChR) but shows high toxicity, work on structurally related analogues has developed rapidly in the search for higher discrimination between nAChR receptor sub-types.[2]

We have earlier synthesised the tropane-based homoepibatidine **2** and the homotropane derivative **3**. Both of these compounds show activity at the nAChR receptor, indeed **2** is as active as epibatidine itself[3] and this encouraged us to explore further azabicyclic variants of **1** which retain the chloropyridyl moiety but which retain the rigidity of the bicyclo[2.2.1]heptane skeleton. We have reported novel epibatidine isomers **4**–**7** based on 2-aza- (as opposed to 7-aza-) bicyclo[2.2.1]heptane[4] and a full account of the synthesis of the *exo*-isomers **4** and **5** using reductive Heck chemistry has appeared.[5] We now report full details of the synthesis of **6** and **7** and binding data for all four isomers **4**–**7** at the α4β2 and α7 nAChR subtypes together with comparison data for **1** and **2**.



We felt that the inherent asymmetry of the '2-aza-' system might allow increased selectivity and we anticipated that the *endo*-5- (**6**) and *endo*-6-(6′-chloro-3′-pyridyl) derivatives (**7**) should offer interesting comparisons with the highly potent compounds **1** and **2** on the base of modelling of N–N distances (Table 1). The structural relationships in **4** and **5** suggested that these isomers were likely to have low affinity at the receptor but they were included in the binding assays for comparison. In addition, following controversy over structural assignments of **4** and **5**,[5] these compounds provided important reference data leading to secure assignments for **6** and **7**.

Table 1 Calculated N–N distances[a] (DTMM)

Compound (protonated)	In minimum energy conformation/Å	After 180° rotation about the C-pyridyl bond/Å
1	4.3	5.5[b]
2	4.5	5.5
6	4.7	5.7
7	4.1	4.9

[a] Both conformations have very similar energies using DTMM; figures are for guidance only. [b] Compare the value of 5.51 Å for the minimum energy.[2b]

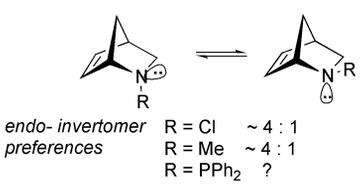


Fig. 1

Results and discussion

Whilst the reductive Heck reaction had been very effective in the synthesis of **2**–**5**,[3–5] the established preference for *exo*-attack on the etheno-bridge in 2-azabicyclo[2.2.1]hept-5-enes and 8-azabicyclo[3.2.1]oct-6-enes suggested that it would be of limited value in the synthesis of *endo*-isomers and our own studies[5] showed only *exo*-attack. Nevertheless, it is worth noting that *endo*-attack has been observed during epoxidation of 2-azabicyclo[2.2.1]hept-5-en-3-one.[6] Attempts were made to attach a group to the azabicycle which might co-ordinate to the palladium catalyst during a reductive Heck reaction and bring the aryl group into the *endo*-face. The *endo*-invertomer preference shown by *N*-substituents in 2-azabicyclo[2.2.1]hept-5-enes (Fig. 1) has been established for *N*-halo-[7a] and *N*-alkyl-[7b] derivatives.

It was envisaged that a diphenylphosphine moiety attached to the nitrogen might also prefer the *endo*-orientation and the lone-pair of electrons associated with the phosphorus would then be available for co-ordination to the palladium catalyst.

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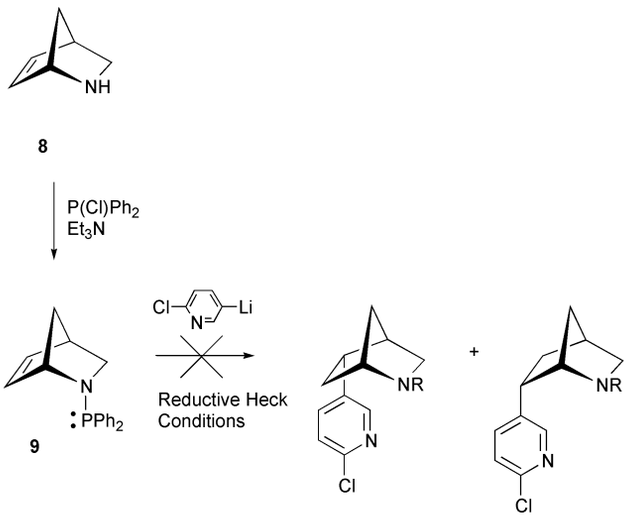
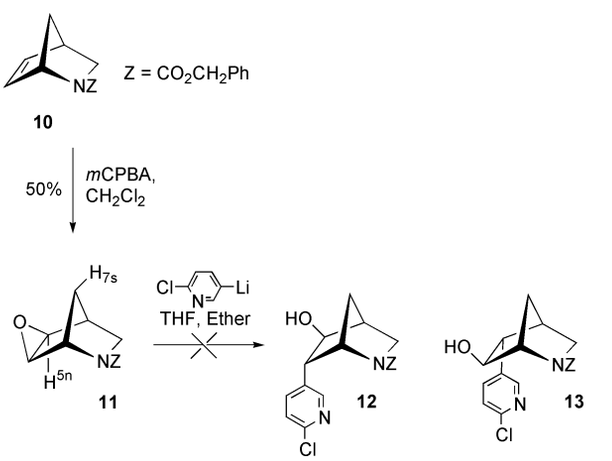


Scheme 1

Synthesis of **9** from 2-azabicyclo[2.2.1]hept-5-ene **8**[5,8] was attempted (Scheme 1). The amine **8** was dried over molecular sieves, transferred to an NMR tube in deuteriochloroform and, after addition of diphenylphosphine chloride, the sample was monitored by NMR spectroscopy. Observation of a new peak at 45 ppm in the ^{31}P NMR spectrum suggested that **9** had been formed but the compound could not be isolated and was subjected immediately to reductive Heck conditions using 2-chloro-5-iodopyridine. None of the expected Heck adducts having either the *endo*- or *exo*-configuration were obtained.

A second strategy directed towards the synthesis of the *endo*-chloropyridyl analogues involved attempted ring-opening of the *exo*-epoxide **11** using a chloropyridyllithium reagent (Scheme 2) to give one or both of the regioisomers **12** and **13**.



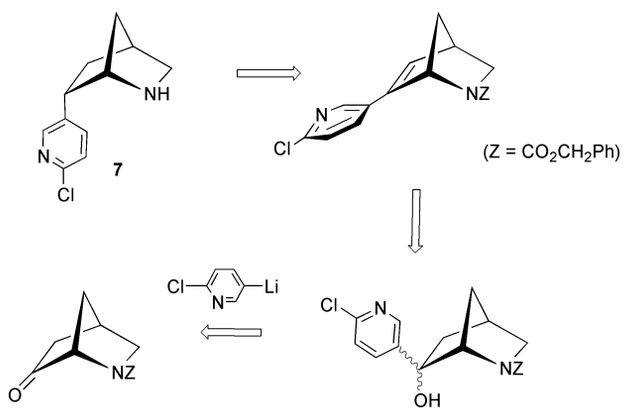
Scheme 2

Dehydration, followed by hydrogenation from the *exo*-face, would then give the *N*-protected, *endo*-substituted targets **6** and **7**.

The epoxide **11**, originally made by Carroll,[9] was generated from the *N*-protected amine **10** using *m*CPBA in dichloromethane. A thorough spectroscopic analysis of this compound was carried out using HH COSY spectra and selective double-irradiation experiments, leading to a full ^{1}H NMR assignment (see Experimental section). The observation of 'W'-coupling ($J_{5endo,7syn}$) confirmed the *exo*-configuration of the epoxide in **11**.

The aryllithium reagent (Scheme 2) was formed by dropwise addition of *n*-butyllithium (in hexanes) to 2-chloro-5-iodopyridine in diethyl ether–THF at −78 °C. Reaction with the epoxide **11** under a range of conditions failed to achieve ring-opening. Nucleophilic opening of the *exo*-epoxide in azabicyclo[4.2.1]nonane analogues has been shown to occur but this work has demonstrated that the reaction was much slower than for the *endo*-isomer.[10] Clearly, the *endo*-isomer of **11** would be susceptible to nucleophilic ring-opening but *endo*-epoxidation has only been observed in reactions of the 3-keto-derivative of **10**.[6] In more recent work, the remarkable resistance of *exo*-epoxide **11** to nucleophilic ring-opening has been confirmed;[11] the epoxide does react in the presence of Lewis acid catalysts but the opening is accompanied by skeletal rearrangement.[11]

We therefore chose to make use of nucleophilic attack on the appropriate ketones, following the general approach used successfully by Fletcher in his synthesis of epibatidine.[12] The approach is illustrated for the 6-*endo*-chloropyridyl-substituted azabicycle **7** (Scheme 3).



Scheme 3

Oxymercuration of the alkene **10** has been reported to give the alcohols **14** and **15**. Jones oxidation was then used to convert a sample of **14** into the ketone **17**.[9] We chose to hydroxylate **10** using diborane (Scheme 4). We required both ketones **17** and **18** and therefore chose to separate, purify, and fully characterise **14** and **15**. The NMR spectra of the *N*-protected compounds were complicated by the presence of two rotamers in each case and, in order to be certain of assignments, **15** was deprotected by hydrogenolysis to give **16** (Scheme 4).

The secondary amino-alcohol **16** was fully characterised using ^{1}H and HH COSY NMR spectra. Confirmation that the hydroxy group was at the 6-position was provided by identification of H^{5x} at δ 1.36 which showed vicinal coupling to H^4 ($J_{4,5exo}$ = 5.5 Hz) and geminal coupling $J_{5exo,5endo}$ (13.0 Hz). The *exo*-stereochemistry at C6 was confirmed by the absence of significant coupling between H^6 and H^1 and by 'W' coupling ($J_{6endo,7syn} \approx$ 1.5 Hz). Corresponding signal assignments for alcohols **14** and **15** were deduced in a similar fashion and a full evaluation of the ^{1}H NMR data is given in Table 2.[13]

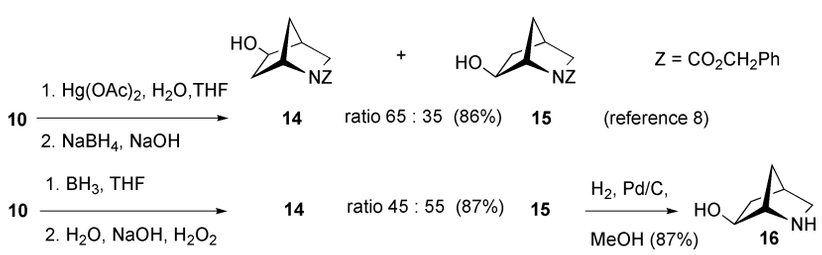
Oxidation of **14** to give **17** was accomplished most effectively using Jones' reagent (Scheme 5) and **15** was converted into **18** most effectively using *N*-methylmorpholine *N*-oxide catalysed by tetrapropylammonium perruthenate. Nucleophilic addition of 5-lithio-2-chloropyridine, again generated from 2-chloro-5-iodopyridine and *n*-butyllithium at −78 °C gave the adducts **19** and **20** respectively each, predominately, as one stereoisomer as judged by NMR spectroscopy. Whilst the *exo*-orientation of the chloropyridyl substituents was assumed, determination of stereostructure was not pursued since loss of configuration occurred in the next step.

The dehydration steps to form alkenes **21** and **22** (Scheme 5) were not straightforward. Several dehydrating agents were investigated before reasonable yields were achieved. Attempted dehydration involving the conversion of the hydroxy group into a methyl oxalyl ester followed by radical deoxygenation[14] was

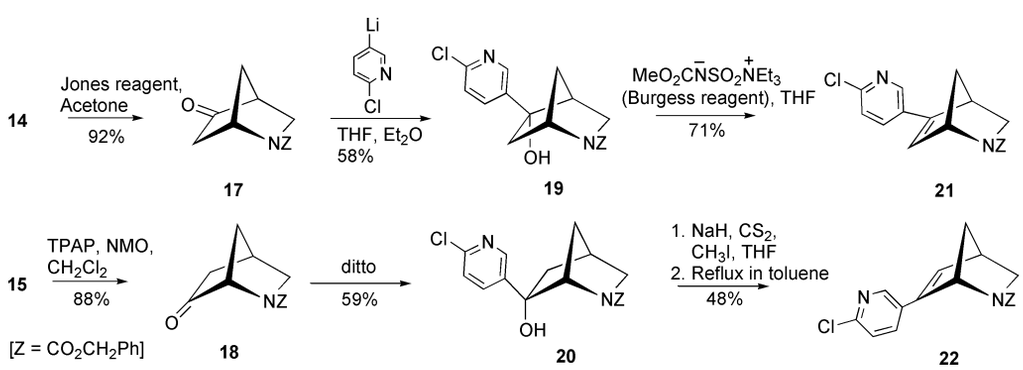
Table 2 ^{1}H NMR data for **14**–**16**[a]

Signal[b]	**14** (Z = CO_2CH_2Ph) δ		**15** δ		**16** δ	
H^1	**4.27**, 4.32	br s	**4.14**, 4.08	br s	3.27	br s
H^{3x}	**3.27**, 3.28	d	**3.22**, 3.23	ddd	2.78	ddd
H^{3n}	**2.93**, 2.91	dd	**2.89**, 2.91	dd	2.34–2.44	m
H^4	*2.49*	br s	*2.56*	br s	2.34–2.44	m
H^{5x}	—		**1.48**, 1.45	dddd	1.36	dddd
H^{5n}	*4.02*	d	**1.83**, 1.84	ddd	1.81	ddd
H^{6x}	**1.47**, 1.49	dddd	—		—	
H^{6n}	**2.07**, 2.15	ddd	**4.04**, 3.98	d	3.83	ddd
H^{7a}	*1.85*	d	**1.82**, 1.78	m	1.70	dddd
H^{7s}	**1.59**, 1.57	ddddd	**1.54**, 1.57	d	1.44	ddddd
OH(NH)	*2.77*	s	*2.30*	s	2.34–2.44	m
Benzylic	*5.05–5.20*	m	*5.05–5.20*	m	—	
Phenyl	*7.25–7.50*	m	*7.25–7.50*	m	—	
J values/Hz	$^4J_{1,4}$ <1		$^4J_{1,4}$ <1		$^3J_{1,6n}$ 1.0	
	$^3J_{1,6x}$ 2.5		$^3J_{1,7a}$ ~1		$^3J_{1,7a}$ ~1.5	
	$^3J_{1,6n}$ <1		$^3J_{1,7s}$ ~1		$^3J_{1,7s}$ ~1.5	
	$^3J_{1,7a}$ ~1.5		$^2J_{3,3}$ 9.0		$^2J_{3,3}$ 9.5	
	$^3J_{1,7s}$ ~1.5		$^3J_{3x,4}$ 3.0		$^3J_{3x,4}$ ~3.0	
	$^2J_{3,3}$ 10.0		$^4J_{3x,5x}$ 3.0		$^4J_{3x,5x}$ ~3.0	
	$^3J_{3x,4}$ 3.0		$^4J_{3n,7s}$ <1		$^4J_{3n,7a}$ 1.5	
	$^4J_{3n,7a}$ ~1		$^4J_{3n,7a}$ 1.5		$^3J_{4,5x}$ 5.5	
	$^3J_{4,7a}$ 1.5		$^3J_{4,5x}$ 5.0		$^3J_{4,7s}$ ~1.5	
	$^3J_{4,7s}$ ~1.5		$^3J_{4,7s}$ ~1		$^3J_{4,7a}$ ~3.0	
	$^3J_{4,5n}$ <1		$^3J_{4,7a}$ ~1		$^2J_{5,5}$ 13.0	
	$^3J_{5n,6n}$ 6.5		$^2J_{5,5}$ 13.5		$^3J_{5x,6n}$ 3.0	
	$^3J_{5n,6x}$ 2.5		$^3J_{5x,6n}$ 2.5		$^3J_{5n,6n}$ 7.0	
	$^4J_{5n,7s}$ 2.5		$^3J_{5n,6n}$ 7.0		$^4J_{5n,7s}$ 2.5	
	$^2J_{6,6}$ 13.5		$^4J_{5n,7s}$ 4.0		$^4J_{6n,7s}$ ~1.5	
	$^4J_{6n,7s}$ 2.5		$^2J_{7,7}$ ~11		$^2J_{7,7}$ 10.0	
	$^4J_{6x,7a}$ ~10.0					
	$^2J_{7,7}$ ~10.0					

[a] Spectra in $CDCl_3$ at 400 MHz; *x* = *exo*- and *n* = *endo*- [b] Two sets of rotamer signals were shown by both **14** (ratio 53 : 47) and **15** (55 : 45); where distinguishable, the major rotamer is shown in bold type. Signals common to both rotamers are shown in italics.



Scheme 4



Scheme 5

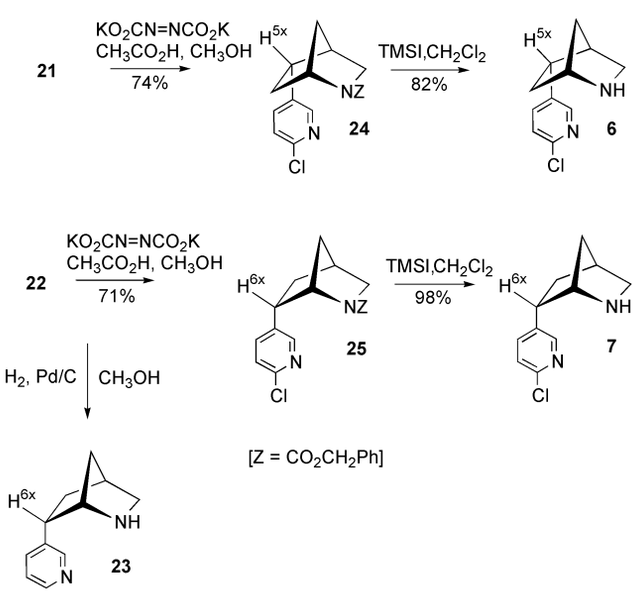
unsuccessful in both cases. Dehydration with $POCl_3$ produced some alkene product, but in very low yield which could not be improved by variation of the reaction conditions.

The use of Burgess' reagent led to successful dehydration of **19** in 71% yield, but the corresponding yield for **20** was only 10%. Thermolysis of the xanthate ester of **20** was more successful (Scheme 5). Hydrogenation of **22** occurred from the *exo*-face as anticipated but resulted in complete removal of the chloropyridyl substituent (Scheme 6). The use of diimide, generated *in situ*, gave **24** and **25** in good yield. *N*-Deprotection

Table 3 Comparative ^{1}H NMR data for epibatidine isomers **4**–**7** [a]

Signal	**6** δ		**7** δ		**4** δ		**5** δ	
H^1	3.56	br s	3.44	br s	3.63	br s	3.46	br s
H^{3x}	2.70	d	3.00	ddd	3.03	dd	2.99	br ddd
H^{3n}	2.50–2.60	m	2.68	d	2.81	d	2.71	d
H^4	2.50–2.60	m	2.54	br s	2.55	m	2.58	br s
H^{5x}	3.24	dddd	2.12	dddd	—		1.73	dddd
H^{5n}	—		1.46	ddd	2.97	dd	1.96	ddd
H^{6x}	2.07	ddd	3.25	ddd	1.74	ddd	—	
H^{6n}	1.65	dd	—		2.09	ddd	2.96	bdd
H^{7a}	1.70–1.74	m	1.75–1.80	m	1.62	AB(br)	1.59 [b]	AB(br)
H^{7s}	1.70–1.74	m	1.75–1.80	m	1.55	AB(br)	1.52 [b]	AB(br)
$H^{2'}$	8.22	d	8.25	d	8.27	d	8.24	d
$H^{5'}$	7.22	d	7.29	d	7.25	dd	7.25	d
$H^{4'}$	7.54	ddd	7.53	ddd	7.49	ddd	7.46	dd
J values/Hz	$^3J_{1,6x}$ 3.0		$^3J_{1,6x}$ 2.5		$^3J_{1,6x}$ 3.0		—	
	$^2J_{3,3}$ 10.5		$^2J_{3,3}$ 9.5		$^2J_{3,3}$ 10.0		$^2J_{3,3}$ 10.0	
	$^3J_{3x,4}$ [c]		$^3J_{3x,4}$ 3.0		$^3J_{3x,4}$ 3.5		$^3J_{3x,4}$ 3.5	
	$^3J_{3x,5x}$ 2.5		$^3J_{3x,5x}$ 3.0		—		$^3J_{3x,5x}$ 3.0	
	$^3J_{4,5x}$ 4.0		$^3J_{4,5x}$ 4.3		—		$^3J_{4,5x}$ 3.5	
	$^3J_{5x,6x}$ 11.5		$^3J_{5x,6x}$ 12.0		$^3J_{5n,6n}$ 9.0		$^3J_{5n,6n}$ 9.0	
	$^3J_{5x,6n}$ 5.5		$^3J_{5n,6x}$ 5.5		$^3J_{5n,6x}$ 5.5		$^3J_{5x,6n}$ 6.0	
	$^2J_{6,6}$ 13.5		$^2J_{5,5}$ 13.0		$^2J_{6,6}$ 13.5		$^2J_{5,5}$ 12.5	
	$^2J_{7,7}$ [c]		$^2J_{7,7}$ [c]		$^2J_{7,7}$ 10.5		$^2J_{7,7}$ 13.0	
	$^4J_{2',4'}$ 3.0		$^4J_{2',4'}$ 2.5		$^4J_{2',4'}$ 3.0		$^4J_{2',4'}$ 2.5	
	$^3J_{4',5'}$ 8.5		$^3J_{4',5'}$ 8.3		$^3J_{4',5'}$ 8.0		$^3J_{4',5'}$ 8.5	
	$^4J_{4',5x}$ <1		$^4J_{4',6x}$ <1		$^4J_{4',5n}$ 0.5; $^4J_{2',5'}$ 0.3			

[a] Spectra in $CDCl_3$ at 400 MHz (**4** & **5**) and 250 MHz (**6** & **7**); s = *syn*-, a = *anti*-. [b] Interchangeable. [c] Signal overlap. br = broad.



Scheme 6

with iodotrimethylsilane gave the target molecules **6** and **7** as pale yellow oils. ^{1}H NMR data are summarised in Table 3. Key observations confirming the stereostructure of **6** included identification of H^{6exo} as a doublet of doublet of doublets at δ 2.07 showing geminal coupling ($J_{6endo,6exo}$ = 13.5 Hz) and vicinal coupling ($J_{1,6exo}$ = 3.0 Hz); the proton at C^5 showed vicinal coupling ($J_{4,5exo}$ = 4.0 Hz) and 'W'-coupling ($J_{3exo,5exo}$ = 2.5 Hz) which was confirmed by double irradiation experiments. In the case of **7**, the *endo*-orientation of the 6-chloropyridyl substituent was indicated by vicinal coupling ($J_{1,6exo}$ = 2.5 Hz). Finally the proton signals for **6** and **7** were compared with their *exo*-chloropyridyl epimers[5] to confirm the consistency of the assignments for all four compounds (Table 3). On completion of our synthesis of **6** and **7**, an alternative route to **7** was reported involving a free-radical-induced rearrangement of a 7-azanorbornyl system to a 2-azabicyclonorbornyl derivative.[15]

Table 4 Inhibition of binding at nicotinic receptors [a]

Compound	α7 K_i/nM	α4β2 K_i /nM	α4/α7
(+)-Epibatidine **1**	4.9 ± 0.7 (*n* = 3)	0.019	0.0039
(−)-Epibatidine **1**	7.0 ± 1.8 (*n* = 4)	0.020	0.0029
(±)-Homoepibatidine **2**	13 (*n* = 2)	0.23	0.018
(±)-5-*exo*-**4**	3300	> 38 [b]	> 0.012
(±)-6-*exo*-**6**	1600	> 38 [b]	> 0.024
(±)-5-*endo*-**5**	6.3	0.056	0.089
(±)-6-*endo*-**7**	3.9	0.045	0.012

[a] α7 (^{125}I-α-bungarotoxin binding to rat hippocampal membranes), α4 (^{3}H-nicotine binding to rat cortical membranes). [b] Approximately 40 nM.

The α4β2 and α7 nAChR subtypes are strong candidates to mediate nicotine's known effects on neurotransmission, cognition, sensory gating, and anxiety because of their distribution in the brain and because of their high relative abundance in the mammalian central nervous system (CNS).[2a] Consequently, samples of the epibatidine analogues **4**–**7** were tested for their affinity at the agonist binding sites of these subtypes.

Affinity at the α7 nAChR subtype was measured by displacement of ^{125}I-α-bungarotoxin (a competitive α7 selective antagonist) to rat hippocampal membranes, while affinity for the α4β2 subtype was measured using displacement of [^{3}H]-(−)-nicotine (an α4-selective agonist) to rat cortical membranes. The results (Table 4) indicate that both *endo*-analogues retain the potent nicotinic binding properties of the epibatidine

enantiomers: very high affinity (pM) at the α4β2 subtype, high affinity (nM) at the α7 subtype, and high α4β2 *vs.* α7 subtype selectivity. In sharp contrast, the *exo*-derivative exhibited comparatively weak affinity at both subtypes, as expected on the basis of the spatial relationship of the two nitrogen centres.

Experimental

NMR spectra were recorded on Bruker ARX 250, DPX 300, or DRX 400 spectrometers ($CDCl_3$ solvent) with TMS as internal reference. Signal characteristics are described using standard abbreviations. In the ^{13}C spectra, quaternary, methine, methylene and methyl carbons respectively, were identified using DEPT experiments. Many of the *N*-protected compounds showed signals corresponding to two rotamers in the ^{1}H and ^{13}C NMR spectra and these are quoted separately where possible; signals common to both rotamers are listed in italics. NMR data for the secondary amines in this work refer to samples basified using anhydrous potassium carbonate.

IR spectra were recorded on a Perkin-Elmer 298 spectrometer as solutions (CH_2Cl_2) unless indicated otherwise. Band intensities are described using standard abbreviations: s (strong), m (medium), w (weak), br (broad), v (very). Mass spectra were measured routinely on a Micromass Quattro LC spectrometer using ionisation by FAB (unless stated otherwise). Accurate mass measurements were obtained using a Kratos Concept mass spectrometer.

Reactions were performed under dry nitrogen. $Pd(PPh_3)_4$ was prepared using a literature method;[12] other palladium reagents were commercial samples, as were solvents and other reagents. Piperidine was distilled before use, as was petroleum ether (bp 40–60 °C) for chromatography. Formic acid was distilled from phthalic anhydride. Silica Gel 60 (Fischer) was used for column and chromatotron separations; in all cases, the silica gel was immersed in the eluting solvent saturated with ammonia gas, prior to use. TLC was conducted on standard commercial aluminium sheets pre-coated with a 0.2 mm layer of silica gel. *N*-Protected compounds were visualised on TLC using UV and then a phosphomolybdic acid (PMA) dip; deprotected secondary amino-compounds were detected using UV and then a vanillin dip.

Biological assays

Binding reactions had a volume of 0.5 mL and were conducted in 96 deep well plates. Reactions were incubated with shaking for the indicated time and temperature, then the membranes were collected by filtration (GF/C filters pre-treated for 2 hours with 0.01 %PEI–1%BSA solution (PEI = polyethyleneimine, BSA = bovine serum albumin) were used for the α7 assay; GF/B filters pre-treated for 2 hours with 0.5% PEI were used for the α4β2 assay), washed 4× with cold assay buffer and then counted for radioactivity in the presence of scintillation fluid. Assay conditions: α7nAChR: 5 nM [^{125}I]α-bungarotoxin, rat hippocampal membranes, 0.1 mg mL^{-1} BSA in buffer (120 NaCl, 5 KCl, 1 $MgCl_2$, 2 $CaCl_2$, 50 Tris, pH 7.4; mM) and incubated for 2 h at 20 °C. α4β2nAChR: 3 nM[^{3}H]nicotine, rat cortical membranes, buffer and incubated for 1 h at 4 °C. IC_{50} values were determined from 5–7 drug concentrations (triplicates). K_i values were determined using the Cheng–Prusoff equation: $K_i = [IC_{50}]/(2+([Ligand]/K_d)^{½} - 1)$,[17] where $n = 2$ for the α7 binding assay and $n = 1$ for α4β2 assay. SEM (standard error of the mean) for values were determined ≥3 times.

exo-5-(6′-Chloro-3′-pyridyl)-2-azabicyclo[2.2.1]heptane 4 and *exo*-6-(6′-chloro-3′-pyridyl)-2-azabicyclo[2.2.1]heptane 5

The synthesis and properties of these compounds are described in Ref. 5.

exo-5,6-Epoxy-*N*-(benzyloxycarbonyl)-2-azabicyclo[2.2.1]-heptane 11

N-(Benzyloxycarbonyl)-2-azabicyclo[2.2.1]hept-5-ene **10**[5] (0.50 g, 2.2 mmol) was dissolved in dry dichloromethane (50 ml) to which *m*CPBA (71.5%, 0.63 g, 2.6 mmol) was added and the solution stirred at room temperature for 130 hours. The reaction solution was washed with sodium hydrogen carbonate solution (2 × 10 ml) and water (2 × 10 ml). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography eluting with 5 : 5 diethyl ether–petroleum ether (bp 40–60 °C) (R_f 0.17) to yield **11** (0.27 g, 1.1 mol, 51%); ν_{max} (CH_2Cl_2) 3020w, 2960w, 2900w, 1700s, 1400s, 1360s, 1305m, 1215m, 1165m, 1100s, 1005m, 860s, 695w cm^{-1}; δ_H (400 MHz, $CDCl_3$) (rotamer ratio 54 : 46) *major rotamer*: 1.19 (br d, J = 10, <1 Hz, 1H, H^{7s}), *1.64* (br d, J = 10 Hz, 1H, H^{7a}), *2.82* (ddd, J = 3.0, 1.5, <1 Hz, 1H, H^4), 3.09 (d, J = 10.0 Hz, 1H, H^{3n}), *3.26* (dd, J = 3.5,<1 Hz, 1H, H^5), *3.31* (d, J = 10.0 Hz, 1H, H^{3x}), 3.38 (br s, 1H, H^6), 4.45 (br s, 1H, H^1), *5.10–5.20* (br s, 2H, benzylic CH_2), *7.20–7.40* (m, 5H, Ph); *minor rotamer*: 1.15 (br d, J = 10 Hz, 1H, H^{7s}), *1.64* (br d, J = 10, <1 Hz, 1H, H^{7a}), *2.82* (ddd, J = 3.0, 1.5, <1 Hz, 1H, H^4), 3.05 (d, J = 10.0 Hz, 1H, H^{3n}), *3.26* (br d, J = 3.5, <1 Hz, 1H, H^5), *3.31* (d, J = 10.0 Hz, 1H, H^{3x}), 3.49 (br s, 1H, H^6), 4.54 (br s, 1H, H^1), *5.10–5.20* (br s, 2H, benzylic CH_2), *7.20–7.40* (m, 5H, Ph); δ_C (62.90 MHz, $CDCl_3$) 37.2, 37.8, 57.2, 57.5 (2 × CH), *49.0, 49.3* (2 × epoxy CH), 25.5, 26.0, 46.9, 47.1 (2 × CH_2), *66.8* (CH_2Ph), *127.8, 128.0, 128.4* (5 × aryl CH), *136.6* (1 × aryl C), *155.1* (urethane C=O); *m*/*z*: 246 (MH^+), 268 (MNa^+); $C_{14}H_{16}NO_3$ [MH^+] requires *m*/*z* 246.11301; observed 246.11302.

exo-*N*-(Benzyloxycarbonyl)-2-azabicyclo[2.2.1]heptan-5-ol 14 and *exo*-*N*-(benzyloxycarbonyl)-2-azabicyclo[2.2.1]heptan-6-ol 15

A solution of *N*-(benzyloxycarbonyl)-2-azabicyclo[2.2.1]hept-5-ene **10**[5] (6.38 g, 27.8 mmol) in THF (340 mL) was placed in a flame-dried 3-necked flask equipped with a septum cap under a nitrogen atmosphere, and stirred at −78 °C. BH_3·THF complex (1 M, 720 mL, 72.0 mmol) was injected dropwise through the septum and after 10 min the solution allowed to warm to room temperature. Stirring was continued for 2.5 hours when the reaction was quenched by sequential addition of water (16 mL), sodium hydroxide (6 M, 16 mL, 96 mmol) and hydrogen peroxide (30% w/v, 16 mL, 141 mmol). The reaction mixture was then stirred for a further 30 min after which the solvent was removed under reduced pressure. The white residue was partitioned between diethyl ether (300 mL) and water (50 mL), the organic layer was washed with water (50 mL) then brine (50 mL), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography using diethyl ether to yield **15** (R_f 0.38) (3.26 g, 13.2 mmol) and **14** (R_f 0.18) (2.69 g, 10.9 mmol) in an overall yield of 87% as pale yellow oils, ratio 55 : 45 (**15** : **14**). Compound **14** showed ν_{max} (CH_2Cl_2) 3600w, 2940w, 2240w, 1680brs, 1420s, 1360m, 1330w, 1260w, 1100m, 1075m cm^{-1}; δ_H see Table 2; δ_C (100.61 MHz, $CDCl_3$) (signals common to both rotamers are in italics) 44.3, 44.3, 55.8, 56.0, 72.3, 72.2 (3 × CH), 33.5, 34.0, 42.7, 42.9, 47.9, 48.0 (3 × CH_2), 66.4, 66.6 (*C*H_2Ph), *127.6, 127.8, 128.3* (5 × aryl CH), *136.6* (1 × aryl C), 154.3, 154.6 (C=O); *m*/*z*: 248 (MH^+), 270 (MNa^+); $C_{14}H_{18}NO_3$ [MH^+] requires *m*/*z* 248.12860; observed 248.12867. Compound **15** showed: ν_{max} (CH_2Cl_2) 3620w, 2980w, 2890w, 2240w, 1695br s, 1430s, 1360m, 1160w, 1100m, 890m cm^{-1}; δ_H see Table 2; δ_C (100.61 MHz, $CDCl_3$) 35.8, 35.3, *60.9*, 72.2, 71.6 (3 × CH), 33.1, 33.7, 39.4, 38.9, *51.6* (3 × CH_2), *66.6* (*C*H_2Ph), *127.7, 127.8, 128.4* (5 × aryl CH), 136.8, 136.7 (1 × aryl C), *154.7* (C=O); *m*/*z*: 248 (MH^+), 270 (MNa^+); $C_{14}H_{18}NO_3$ [MH^+] requires *m*/*z* 248.12866; observed 248.12867.

Broad ^{1}H NMR ranges for a sample of **15** have been reported[9] but the sample was not characterised.

exo-2-Azabicyclo[2.2.1]heptan-6-ol 16

The *N*-protected alcohol **15** (0.033 g, 0.13 mmol) was dissolved in dry methanol (5 mL) in a round-bottomed flask equipped with a 3-way tap. Palladium on carbon catalyst (5%, 0.01 mmol) was added and the reaction mixture stirred under hydrogen for 5 hours. The catalyst was filtered off through Celite and the solvent removed under reduced pressure to yield **16** (13 mg, 87%) as a pale yellow oil, ν_{max} ($CDCl_3$) 3640m, 2940m, 2250m, 1020s, 890s, 700m cm^{-1}; δ_H see Table 2; δ_C (100.61 MHz, $CDCl_3$) 33.5, 41.0, 50.0 (3 × CH_2), 36.0, 61.5 (2 × CH), 74.5 (CH(OH)); *m*/*z*: 113 (M^+) (EI); $C_6H_{11}NO$ [M^+] requires *m*/*z* 113.08405; observed 113.08406.

N-(Benzyloxycarbonyl)-2-azabicyclo[2.2.1]heptan-5-one 17

The *N*-protected alcohol **14** (0.52 g, 2.10 mmol) was dissolved in acetone (200 mL) with stirring and cooled to 0 °C. Jones reagent [prepared from chromium trioxide (12.35 g), concentrated sulfuric acid (11.5 mL) and water (20 mL)] was added dropwise until in excess and the mixture stirred for 30 minutes. After ensuring that the solution remained orange, the excess chromic acid was destroyed by dropwise addition of propan-2-ol. The solution was basified with 6 M sodium hydroxide and the solvent removed under reduced pressure. Water (150 mL) was added and the solution extracted with dichloromethane (4 × 100 mL). The organic extracts were combined, dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, eluting with diethyl ether (R_f 0.41) to yield **17** (0.48 g, 1.96 mmol, 92%) as a pale yellow oil, ν_{max} (CH_2Cl_2) 3050w, 2990w, 1755s, 1700s, 1420s, 1360w, 1260m, 1100m, 770–590w cm^{-1}; δ_H (250 MHz, $CDCl_3$; two rotamers were observed in a ratio of 54 : 46) *1.96* (d, *J* = 10.0 Hz, 1H, H^{7a}), *2.25* (d, *J* = 10.0 Hz, 1H, H^{7s}), *2.14–2.42* (m, 2H, H^{6x} and H^{6n}), *2.91* (br s, 1H, H^4), *3.40* (d, *J* = 11.0 Hz, 1H, H^{3n}), *3.54* (d, *J* = 11.0 Hz, 1H, H^{3x}), 4.66 (br s, 1H, H^1, minor rotamer), 4.71 (br s, 1H, H^1, major rotamer), *5.05–5.20* (m, 2H, benzylic), *7.20–7.50* (m, 5H, Ph); δ_C (62.90 MHz, $CDCl_3$) 50.0, 50.7, 55.9, 56.1 (2 × CH), 37.2, 37.6, 45.5, 45.7, *47.3* (3 × CH_2), *66.9* (CH_2Ph), *127.8, 128.0, 128.4* (5 × aryl CH), *136.4* (aryl C), *154.5* (urethane C=O), 212.5, 213.0 (C=O); *m*/*z*: 246 (MH^+), 268 (MNa^+); $C_{14}H_{16}NO_3$ [MH^+] requires *m*/*z* 246.11300; observed 246.11302. Broad ^{1}H NMR ranges for a sample of **17** have been reported but the sample was not characterised.[9]

N-(Benzyloxycarbonyl)-2-azabicyclo[2.2.1]heptan-6-one 18

The alcohol **15** (3.26 g, 13.2 mmol) was dissolved in dichloromethane (27 mL) in a 3-necked flask containing powdered molecular sieves (4 Å, 6.7 g) under an argon atmosphere and stirred for 10 min. To the stirred mixture was added *N*-methylmorpholine *N*-oxide (NMO) (2.31 g, 19.7 mmol) followed by tetrapropylammonium perruthenate (TPAP, 230 mg, 0.65 mmol) and the reaction was judged to be complete by TLC after 30 minutes. The crude reaction mixture was immediately subject to flash chromatography, eluting with dichloromethane (R_f 0.10) to yield **18** (2.83 g, 11.5 mmol, 87.5%) as a colourless oil, ν_{max} ($CDCl_3$) 2960w, 1760s, 1695s, 1420m, 1360m, 1100m, 910s, 750–700s cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.72 (d, *J* = 11.0 Hz, 1H, H^{7a}), 1.91 (d, *J* = 11.0 Hz, 1H, H^{7s}), 2.00 (dd, *J* = 17.5, 4.0 Hz, 1H, H^{5n}), 2.23 (ddd, *J* = 17.5, 4.5, 1.5 Hz, 1H, H^{5x}), 2.85 (br s, 1H, H^4), 3.23 (d, *J* = 10.0 Hz, 1H, H^{3n}), 3.51 (ddd, *J* = 10.0, 2.5, 1.5 Hz, 1H, H^{3x}), 4.27 (br s, 1H), 5.05–5.25 (m, 2H, benzylic CH_2), 7.25–7.50 (m, 5H, Ph); δ_C (62.90 MHz, $CDCl_3$) 34.0, 61.9 (2 × CH), 36.3, 41.4, 50.7 (3 × CH_2), 67.0 (CH_2Ph), 127.6, 127.8, 128.3 (5 × aryl CH), 136.2 (aryl C), 154.6 (urethane C=O), 205.0 (C=O); *m*/*z*: 246 (MH^+), 268 (MNa^+); $C_{14}H_{16}NO_3$ [MH^+] requires *m*/*z* 246.11308; observed 246.11302.

5-(6′-Chloro-3′-pyridyl)-*N*-(benzyloxycarbonyl)-2-azabicyclo[2.2.1]heptan-5-ol 19

2-Chloro-5-iodopyridine (0.25 g, 1.00 mmol) was dissolved in diethyl ether (7 mL) and THF (4 mL) in a flame-dried flask under a nitrogen atmosphere and cooled to −78 °C. Butyllithium (1.6 M, 625 μL, 1.00 mmol) was added dropwise and the solution stirred for 20 min. A solution of **17** (0.202 g, 0.83 mmol) in THF (4 mL) was added dropwise and stirring continued for 2 hours. The reaction was warmed to −50 °C and maintained at this temperature for 30 min, before it was quenched by the addition of ammonium chloride (0.5 mL) and warmed to room temperature. Water (1.5 mL) was added and the organic layer separated off. The aqueous layer was extracted with diethyl ether (4 × 5 mL), the organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography eluting with diethyl ether (R_f 0.31) to yield **19** (0.17 g, 0.48 mmol, 58%) as a pale yellow foam, ν_{max} (CH_2Cl_2) 3050s, 2995s, 2300m, 1700m, 1420s, 1275s, 1260s, 900m, 760m, 720m cm^{-1}; δ_H (250 MHz, $CDCl_3$) (rotamer ratio 51 : 49) *major rotamer*: *1.63* (d, *J* = 11.0 Hz, 1H, H^{7a}), *1.81* (m, 1H, H^{7s}), 2.05 (dd, *J* = 11.0, 3.5 Hz, 1H, H^{6n}), 2.21 (dd, *J* = 11.0, 2.5 Hz, 1H, H^{6x}), 2.78 (br s, 1H, H^4), 3.29 (dd, *J* = 9.5, 3.5 Hz, 1H, H^{3x}), 3.71 (s, 1H, OH), 4.05 (d, *J* = 9.5 Hz, 1H, H^{3n}), *4.32* (br s, 1H, H^1), *5.05–5.20* (m, 2H, benzylic CH_2), *7.20–7.50* (m, 6H, Ph and H$^{5′}$), *7.79* (dd, *J* = 8.0, 2.5 Hz, 1H, H$^{4′}$), *8.40* (m, 1H, H$^{2′}$); *minor rotamer: 1.63* (d, *J* = 11.0 Hz, 1H, H^{7a}), *1.81* (m, 1H, H^{7s}), 2.00 (dd, *J* = 11.0, 3.5 Hz, 1H, H^{6n}), 2.26 (dd, *J* = 11.0, 2.5 Hz, 1H, H^{6x}), 2.73 (br s, 1H, H^4), 3.26 (dd, *J* = 9.5, 3.5 Hz, 1H, H^{3x}), 3.54 (s, 1H, OH), 3.99 (d, *J* = 9.5 Hz, 1H, H^{3n}), *4.32* (br s, 1H, H^1), *5.05–5.20* (m, 2H, benzylic CH_2), *7.20–7.50* (m, 6H, Ph and H$^{5′}$), *7.79* (dd, *J* = 8.0, 2.5 Hz, 1H, H$^{4′}$), *8.40* (m, 1H, H$^{2′}$); δ_C (62.90 MHz, $CDCl_3$) 47.5, 48.3, 57.4, 57.6 (2 × CH), 37.4, 38.0, 46.0, 46.1, 46.6, 47.3 (3 × CH_2), *65.7* (*C*-OH), 66.5, 66.7 (CH_2Ph), 127.5, 127.7, 127.8, 127.9, *128.4* (5 × aryl CH), 136.6, 136.8 (1 × aryl C), *124.0, 137.0*, 146.8, 146.9 (3 × pyridyl CH), *142.0* (pyridyl C), *150.1* (pyridyl *C*-Cl), *154.5* (urethane C=O); *m*/*z*: 359 (MH^+), 381 (MNa^+); $C_{19}H_{20}N_2O_3Cl$ [MH^+] requires *m*/*z* 359.11618; observed 359.11625.

6-(6′-Chloro-3′-pyridyl)-*N*-(benzyloxycarbonyl)-2-azabicyclo-[2.2.1]heptan-6-ol 20

2-Chloro-5-iodopyridine (0.36 g, 1.52 mmol) was dissolved in diethyl ether (7.5 mL) and THF (4 mL) in a flame-dried flask under a nitrogen atmosphere and cooled to −78 °C. Butyllithium (1.6 M, 152 μL, 1.52 mmol) was added dropwise and stirred for 20 min. A solution of **18** (0.37 g, 1.52 mmol) in diethyl ether (4 mL) was added dropwise and stirring continued for 2 hours. The reaction was warmed to −50 °C and maintained at this temperature for 30 min. The reaction was quenched by the addition of aqueous ammonium chloride (0.75 mL) and warmed to room temperature. Water (2.5 mL) was added and the organic layer separated off. The aqueous layer was extracted with diethyl ether (4 × 5 mL), the organic extracts were combined, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography eluting with diethyl ether (R_f 0.21) to yield **20** (0.32 g, 0.89 mmol, 59%) as a pale yellow foam; ν_{max} (CH_2Cl_2) 2960w, 1695s, 1420s, 1320m, 1050s, 685m cm^{-1}; (Signals due to major and minor rotamer overlapped in both ^{1}H and ^{13}C NMR spectra of **20**) δ_H (250 MHz, $CDCl_3$) 1.57–1.84 (m, 2H, H^{7a}, H^{7s}), 1.92–2.44 (m, 2H, H^{5x}, H^{5n}), 2.63 (br s, 1H, H^4), 3.28 (d, *J* = 9.5 Hz, 1H, H^{3n}), 3.47 (dd, *J* = 9.5, 1.5 Hz, 1H, H^{3x}), 4.20–4.53 (m, 1H, H^1), 5.03–5.25 (m, 2H, benzylic CH_2), 7.23–7.42 (m, 5H, Ph), 7.25 (d, *J* = 8.5 Hz, 1H, H$^{5′}$), 7.74 (d, *J* = 8.5 Hz, 1H, H$^{4′}$), 8.43 (br s,

1H, H$^{2'}$); δ_C (62.90 MHz, $CDCl_3$) 37.6, 64.3 (2 × CH), 36.8, 43.5, 52.0 (3 × CH_2), 66.7 (*C*H_2Ph), 80.2 (*C*-OH), 127.4, 127.7, 128.3 (5 × aryl CH), 136.5 (1 × aryl C), 123.7, 137.0, 147.2 (3 × pyridyl CH), 149.9 (pyridyl *C*-Cl) [signals for pyridyl C and urethane C=O were lost in the noise]; *m*/*z*: 359 (MH^+), 381 (MNa^+); $C_{19}H_{20}N_2O_3Cl$ [MH^+] requires *m*/*z* 359.11620; observed 359.11625.

5-(6′-Chloro-3′-pyridyl)-*N*-(benzyloxycarbonyl)-2-azabicyclo-[2.2.1]hept-5-ene 21

Burgess reagent [16] (0.385 g, 1.62 mmol) was dissolved in THF (3 mL) under a nitrogen atmosphere. A solution of vacuum-oven dried **19** (0.433 g, 1.21 mmol) in THF (3 mL) was added dropwise and stirring continued for 17.5 hours at room temperature. The reaction was heated for 30 min at 50 °C and then left to cool to room temperature. The reaction was quenched by the addition of water (0.2 mL), neutralised with sodium hydroxide solution and the solvent removed under reduced pressure. The reaction mixture was extracted with chloroform (4 × 3 mL), the organic layers were combined, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, eluting with 7 : 3 diethyl ether–petroleum ether (bp 40–60 °C) (R_f 0.23) to yield **21** (0.290 g, 0.852 mmol, 70.7%), as a pale yellow oil; ν_{max} (CH_2Cl_2) 3060w, 2950w, 1695s, 1580w, 1450m, 1410s, 1355s, 1160m, 1105s, 830m, 800w; δ_H (250 MHz, $CDCl_3$) (rotamer ratio 51 : 49) *major rotamer*: *1.66–1.80* (m, 2H, H^{7a}, H^{7s}), *2.71–2.85* (m, 1H, H^{3n}), 3.49 (d, *J* = 9.5 Hz, 1H, H^{3x}), *3.57* (br s, 1H, H^4), 4.85 (br s, 1H, H^1), *4.96–5.12* (m, 2H, benzylic CH_2), 6.69 (br s, 1H, H^6), *7.18–7.33* (m, 6H, Ph, H$^{4'}$), *7.56* (d, *J* = 7.5 Hz, 1H, H$^{5'}$), *8.35* (d, *J* = 2.0 Hz, 1H, H$^{2'}$); *minor rotamer*: *1.66–1.80* (m, 2H, H^{7a}, H^{7s}), *2.71–2.85* (m, 1H, H^{3n}), 3.47 (d, *J* = 9.5 Hz, 1H, H^{3x}), *3.57* (br s, 1H, H^4), 4.77 (br s, 1H, H^1), *4.96–5.12* (m, 2H, benzylic CH_2), 6.54 (br s, 1H, H^6), *7.18–7.33* (m, 6H, Ph, H$^{4'}$), *7.56* (d, *J* = 7.5 Hz, 1H, H$^{5'}$), *8.35* (d, *J* = 2.0 Hz, 1H, H$^{2'}$); δ_C (100.61 MHz, $CDCl_3$) (signals common to both rotamers are listed in italics) 44.1, 44.6, 61.4, 61.8 (2 × CH), 46.1, 46.3, 47.4, 47.7 (2 × CH_2), *66.8* (CH_2Ph), *128.8* (C_5), 129.7, 130.3 (C_6), *127.9, 128.0, 128.4* (5 × aryl CH), *136.7* (1 × aryl C), *124.2, 135.2, 146.4* (3 × pyridyl CH), *145.2* (pyridyl C), *150.5* (pyridyl C-Cl), *155.7* (C=O); *m*/*z*: 341 (MH^+), 363 (MNa^+); $C_{19}H_{18}N_2O_2Cl$ [MH^+] requires *m*/*z* 341.10567; observed 341.10568.

6-(6′-Chloro-3′-pyridyl)-*N*-(benzyloxycarbonyl)-2-azabicyclo-[2.2.1]hept-6-ene 22

Sodium hydride (95%, 120 mg, 4.75 mmol) was stirred in THF (4.5 mL) in a flame-dried flask fitted with a septum, under a nitrogen atmosphere at 0 °C. Compound **20** (283 mg, 0.789 mmol), dissolved in THF (2.7 mL), was added dropwise and the mixture stirred for 50 min at room temperature. The reaction flask was cooled to 0 °C and carbon disulfide (60 μL, 0.98 mmol) added through the septum, after which the reaction was allowed to warm to room temperature and stirred for 15 min. Iodomethane (61 μL, 0.99 mmol) was added dropwise, and stirring continued for a further 25 minutes. Water (1.5 mL) was added and the solvent removed under reduced pressure. The residue was partitioned between water (4 mL) and dichloromethane (4 × 4 mL), the organic layers were combined, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The crude xanthate was dissolved in toluene (15 mL) and heated at reflux for 5 hours. The toluene was removed under reduced pressure and the crude product purified by flash chromatography, eluting with 7 : 3 diethyl ether–petroleum ether (bp 40–60 °C) (R_f 0.12) to yield **22** (120 mg, 0.353 mmol, 44.7%) as a pale yellow oil; ν_{max} ($CDCl_3$) 2960w, 1685s, 1450m, 1420s, 1355m, 1250w, 1160w, 1105m, 900w, 820w, 690w; δ_H (400 MHz, $CDCl_3$) (rotamer ratio 56 : 44) *major rotamer*: *1.76–1.85* (m, 2H, H^{7a}, H^{7s}), 2.85 (d, *J* = 9.0 Hz, 1H, H^{3n}), *3.39* (m, 1H, H^4), *3.58* (dd, *J* = 9.0, 3.0 Hz, 1H, H^{3x}), *5.00–5.20* (m, 3H, H^1, benzylic CH_2), 6.59 (d, *J* = 1.5 Hz, 1H, H^5), *7.20–7.40* (m, 5H, Ph), 7.03 (d, *J* = 8.5 Hz, 1H, H$^{5'}$), 8.00 (dd, *J* = 8.5, 2.0 Hz, 1H, H$^{4'}$), 8.60 (d, *J* = 2.0 Hz, 1H, H$^{2'}$); *minor rotamer*: *1.76–1.85* (m, 2H, H^{7a}, H^{7s}), 2.91 (d, *J* = 9.0 Hz, 1H, H^{3n}), *3.39* (m, 1H, H^4), *3.58* (dd, *J* = 9.0, 3.0 Hz, 1H, H^{3x}), *5.00–5.20* (m, 3H, H^1, benzylic CH_2), 6.64 (d, *J* = 1.5 Hz, 1H, H^5), *7.20–7.40* (m, 5H, Ph), 7.31 (d, *J* = 8.5 Hz, 1H, H$^{5'}$), 7.59 (dd, *J* = 8.5, 2.0 Hz, 1H, H$^{4'}$), 8.49 (d, *J* = 2.0 Hz, 1H, H$^{2'}$); δ_C (100.61 MHz, $CDCl_3$) 43.5, 44.2, 61.6, 61.9 (2 × CH), 46.7, 46.9, 47.9, 48.3 (2 × CH_2), 66.8, 67.2 (*C*H_2Ph), 131.5, 131.7 (C_5), *129.2* (C_6), 127.8, 127.9, *128.3*, 128.4, 128.6 (5 × aryl CH), 136.2, 136.7 (1 × aryl C), 123.8, 124.1, 135.3, 135.9, 146.6, 146.8 (3 × pyridyl CH), 143.9, 145.1 (pyridyl C), *149.9* (pyridyl C-Cl), *155.1* (C=O); *m*/*z*: 341 (MH^+), 363 (MNa^+); $C_{19}H_{18}N_2O_2Cl$ [MH^+] requires *m*/*z* 341.10561; observed 341.10568.

endo-5-(6′-Chloro-3′-pyridyl)-*N*-(benzyloxycarbonyl)-2-aza-bicyclo[2.2.1]heptane 24

Potassium azodicarboxylate (74 mg, 0.38 mmol) and **21** (21.0 mg, 0.062 mmol) were dissolved in dry methanol (0.65 mL) under a nitrogen atmosphere. Dry glacial ethanoic acid (44 μL, 0.76 mmol) was added dropwise and the solution stirred for 20 hours at room temperature. Further potassium azodicarboxylate (20 mg, 0.10 mmol) was added and the reaction stirred for 3 more hours. The reaction was quenched with water (0.5 mL) and the solvent removed under reduced pressure. The residue was partitioned between dichloromethane (4 mL) and sodium hydrogen carbonate solution (1.0 mL). The dichloromethane fraction was washed with sodium hydrogen carbonate solution (0.5 mL) and brine (1 mL), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, eluting with 4 : 1 diethyl ether–petroleum ether (bp 40–60 °C) (R_f 0.46). Compound **24** (16 mg, 0.045 mmol, 74%) was isolated as a pale yellow oil; ν_{max} ($CDCl_3$) 2595w, 1690s, 1450m, 1425s, 1360m, 1330m, 1290w, 1160m, 1110s, 1250w, 900w, 835w, 700w; δ_H (300 MHz, $CDCl_3$) (rotamer ratio 55 : 45) *major rotamer*: *1.76–1.85* (m, 2H, H^{7a}, H^{7s}), *1.88–1.98* (m, 1H, H^{6n}), *2.15* (ddd, *J* = 12.5, 11.0, 2.5 Hz, 1H, H^{6x}), *2.71* (br s, 1H, H^4), 3.07 (dd, *J* = 10.5, 1.0 Hz, 1H, H^{3n}), 3.17 (ddd, *J* = 10.5, 3.5, 1.5 Hz, 1H, H^{3x}), 3.40 (ddd, *J* = 11.0, 5.5, 3.5 Hz, 1H, H^{5x}), 4.45 (br s, 1H, H^1), *5.05–5.21* (m, 2H, benzylic CH_2), 7.17 (d, *J* = 8.0 Hz, 1H, H$^{5'}$), *7.29–7.41* (m, 7H, Ph, H$^{4'}$), 8.23 (d, *J* = 2.5 Hz, 1H, H$^{2'}$); *minor rotamer*: 1.76–1.85 (m, 2H, H^{7a}, H^{7s}), *1.88–1.98* (m, 1H, H^{6n}), *2.15* (ddd, *J* = 12.5, 11.0, 2.5 Hz, 1H, H^{6x}), *2.71* (br s, 1H, H^4), 3.02 (dd, *J* = 10.5, 1.0 Hz, 1H, H^{3n}), 3.19 (ddd, *J* = 10.5, 3.5, 1.5 Hz, 1H, H^{3x}), 3.43 (ddd, *J* = 11.0, 5.5, 3.5 Hz, 1H, H^{5x}), 4.39 (br s, 1H, H^1), *5.05–5.21* (m, 2H, benzylic CH_2), 7.25 (d, *J* = 8.0 Hz, 1H, H$^{5'}$) *7.29–7.41* (m, 7H, Ph, H$^{4'}$), 8.22 (d, *J* = 2.5 Hz, 1H, H$^{2'}$); δ_C (75.81 MHz, $CDCl_3$) *40.6*, 43.1, 43.6, 57.5, 57.7 (3 × CH), 35.4, 36.2, 39.5, 40.0, *46.9* (3 × CH_2), 66.5, 66.8 (*C*H_2Ph), *127.9, 128.0, 128.5* (5 × aryl CH), *136.9* (1 × aryl C), 123.9, 124.0, 137.8, 137.9, 149.8, 149.9 (3 × pyridyl CH), 135.7, 135.8 (pyridyl C), *149.4* (pyridyl C-Cl), 154.3, 154.5 (urethane C=O); *m*/*z*: 343 (MH^+), 365 (MNa^+); $C_{19}H_{20}N_2O_2Cl$ [MH^+] requires *m*/*z* 343.12130; observed 343.12133.

endo-6-(6′-Chloro-3′-pyridyl)-*N*-(benzyloxycarbonyl)-2-aza-bicyclo[2.2.1]heptane 25

Potassium azodicarboxylate (341 mg, 1.76 mmol) and **22** (115 mg, 0.351 mmol) were dissolved in dry methanol (3 mL) under a nitrogen atmosphere. Glacial ethanoic acid (200 μL, 3.51 mmol) was added dropwise and the solution stirred for 22 hours at room temperature after which further potassium azodicarboxylate (100 mg, 0.515 mmol) was added. Stirring was continued for a further 7 hours, the reaction was quenched with water (0.5 mL), and the solvent removed under reduced

pressure. The residue was partitioned between dichloromethane (15 mL) and sodium hydrogen carbonate solution (3 mL). The dichloromethane fraction was washed with sodium hydrogen carbonate solution (3 mL) and brine (3 mL), dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, eluting with 7 : 3 diethyl ether–petroleum ether (bp 40–60 °C) (R_f 0.22). Compound **25** (81.7 mg, 0.238 mmol, 71%) was isolated as a pale yellow oil; ν_{max} ($CDCl_3$) 2980w, 2880w, 1690vs, 1455s, 1425s, 1360m, 1340w, 1155m, 1110s, 1025w, 900m, 700m; δ_H (400 MHz, $CDCl_3$) (rotamer ratio 62 : 38) *major rotamer*: *1.51* (dddd, J = 13.0, 5.5, 2.5, 2.5 Hz, 1H, H^{5n}), *1.75–1.82* (m, 1H, H^{7s}), *1.86* (ddd, J = 10.0, 3.5, 2.0 Hz, 1H, H^{7a}), *2.19–2.33* (m, 1H, H^{5x}), *2.70–2.76* (m, 1H, H^4), 3.15 (dd, J = 10.0, 1.0 Hz, 1H, H^{3n}), *3.32* (ddd, J = 11.5, 5.5, 2.5 Hz, 1H, H^{6x}), 3.53 (ddd, J = 10.0, 3.0, 3.0, 1H, H^{3x}), 4.29 (br s, 1H, H^1), 4.71, 4.78 (d, J = 12 Hz, 2H, benzylic CH_2), *6.98* (dd, J = 8.5, 2.5 Hz, 1H, $H^{4\prime}$), 7.13 (d, J = 8.5 Hz, 1H, $H^{5\prime}$), *7.27–7.40* (m, 5H, Ph), 8.22 (d, J = 2.5 Hz, 1H, $H^{2\prime}$); *minor rotamer*: *1.51* (dddd, J = 13.0, 5.5, 2.5, 2.5 Hz, 1H, H^{5n}), *1.75–1.82* (m, 1H, H^{7s}), *1.86* (ddd, J = 10.0, 3.5, 2.0 Hz, 1H, H^{7a}), *2.19–2.33* (m, 1H, H^{5x}), *2.70–2.76* (m, 1H, H^4), 3.24 (dd, J = 10.0, 1.0 Hz, 1H, H^{3n}), *3.32* (ddd, J = 11.5, 5.5, 2.5 Hz, 1H, H^{6x}), 3.48 (ddd, J = 10.0, 3.0, 3.0, 1H, H^{3x}), 4.49 (br s, 1H, H^1), 4.95, 5.05 (d, J = 12 Hz, 2H, benzylic CH_2), *6.98* (dd, J = 8.5, 2.5 Hz, 1H, $H^{4\prime}$), 7.07 (d, J = 8.5 Hz, 1H, $H^{5\prime}$), *7.27–7.40* (m, 5H, Ph), 8.23 (d, J = 2.5 Hz, 1H, $H^{2\prime}$); δ_C (100.61 MHz, $CDCl_3$) 37.5, 38.0, 45.5, 45.8, 60.7, 61.8 (3 × CH), 33.9, 34.2, 39.2, 39.9, *53.4* (3 × CH_2), 65.9, 66.5, *66.7* (CH_2Ph), 127.89, 127.93, *128.0*, 128.4, 128.5 (5 × aryl CH), 136.1, 136.9 (1 × aryl C), *123.6*, 137.4, 138.0, 149.4, 150.0 (3 × pyridyl CH), *135.8* (pyridyl C), *149.5* (pyridyl C-Cl), *154.7* (urethane C=O); *m/z*: 343 (MH^+), 365 (MNa^+); $C_{19}H_{20}N_2O_2Cl$ [MH^+] requires *m/z* 343.12143; observed 343.12133.

endo-5-(6′-Chloro-3′-pyridyl)-2-azabicyclo[2.2.1]heptane 6

Compound **24** (13.4 mg, 0.0391 mmol) was dissolved in chloroform (0.5 mL) and stirred under a nitrogen atmosphere. TMSI (28 μL, 0.20 mmol) was added and stirred for 7 min followed by hydrofluoroboric acid–diethyl ether complex (11 μL, 0.078 mmol) stirring for a further 5 min. The reaction mixture was quenched with water (100 μl) and the solvent removed under reduced pressure. Water (0.5 mL) was added and the solution washed with petroleum ether (bp 40–60 °C) (2 × 0.1 mL). The solution was neutralised with solid potassium carbonate and the product extracted with dichloromethane (4 × 2 mL), the dichloromethane layer dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The crude was passed through a pipette half-filled with flash silica, eluting with methanol saturated with ammonia gas. The product **6** (6.7 mg, 0.032 mmol, 82%) was isolated as a pale yellow oil; ν_{max} (CH_2Cl_2) 2970s, 1590m, 1565m, 1460s, 1400m, 1335w, 1270m, 1150w, 1110s, 1025m, 840w, 800w, 700w; δ_H see Table 3; δ_C (100.61 MHz, $CDCl_3$) 34.7 (C^7), 39.9 (C^3), 41.5 (C^5), 42.6 (C^4), 44.2 (C^6), 57.0 (C^1), 123.9 ($C^{5\prime}$), 135.7 ($C^{4\prime}$), 138.6 ($C^{3\prime}$), 149.5 ($C^{6\prime}$), 149.9 ($C^{2\prime}$); *m/z*: 209 (MH^+); $C_{11}H_{14}N_2Cl$ [MH^+] requires *m/z*: 209.08451; observed 209.08455.

endo-6-(6′-Chloro-3′-pyridyl)-2-azabicyclo[2.2.1]heptane 7

Compound **25** (51 mg, 0.15 mmol) was dissolved in dichloromethane (0.5 mL) and stirred under a nitrogen atmosphere. TMSI (105 μL, 0.74 mmol) was added and stirred for 7 min followed by hydrofluoroboric acid–diethyl ether complex (44 μL, 0.30 mmol) stirring for a further 5 min. The reaction mixture was worked up as described for **6** above. The product **7** was isolated as a pale yellow oil (31 mg, 0.15 mmol, 98%), ν_{max} (CH_2Cl_2) 3050m, 2960m, 2930m, 1730w, 1705w, 1590w, 1565w, 1460s, 1420m, 1260s, 1110s, 1025w, 895w, 750m; δ_H see Table 3; δ_C (62.89 MHz, $CDCl_3$) 33.9 (C^7), 37.8 (C^4), 39.8 (C^5), 45.5 (C^6), 51.7 (C^3), 60.3 (C^1), 123.7 ($C^{5\prime}$), 136.3 ($C^{4\prime}$), 138.6 ($C^{3\prime}$), 149.2 ($C^{6\prime}$), 149.6 ($C^{2\prime}$); *m/z*: 209 (MH^+); $C_{11}H_{14}N_2Cl$ [MH^+] requires *m/z* 209.08458; observed 209.08455.

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