Synthesis and nicotinic acetylcholine-binding properties of epibatidine homologues: homoepibatidine and dihomoepibatidine

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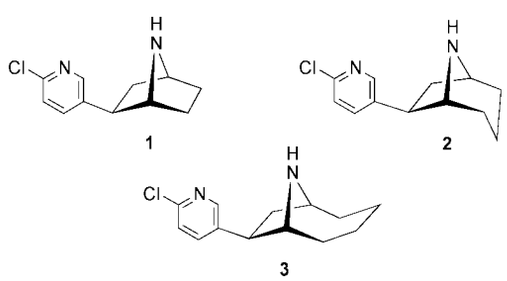
Received (in Cambridge, UK) 19th December 2000, Accepted 14th March 2001
First published as an Advance Article on the web 4th April 2001

Homoepibatidine **2** and dihomoepibatidine **3** have been synthesised from the 8-azabicyclo[3.2.1]oct-6-ene **8** and the 9-azabicyclo[4.2.1]oct-7-ene **9**, respectively, the key precursors for reductive Heck coupling reactions. Alternative routes starting from cyclohepta- and cycloocta-1,3-diene are described; deoxygenation of tropane and homotropane epoxides provides a convenient route to **8** and **9**. The enantiomers of **2** show similar potency at nicotinic receptors to the corresponding epibatidine enantiomers; the affinity of **3** is lower.

Introduction

Current interest in neuronal nicotinic acetylcholine receptors (nAChRs) and their potential as therapeutic targets is considerable. For many organic chemists, this area was opened to view by the discovery in 1992 of the natural product epibatidine **1**,[1] the first natural product based on the 7-azabicyclo[2.2.1]-heptane (7-azanorbornane) ring system. The powerful analgesic effects shown by **1** have stimulated a remarkable level of interest.[2] The fact that epibatidine acts at the nAChR rather than the opioid receptor (and is a much more effective ligand than nicotine itself) has prompted a substantial reappraisal of this receptor.[3] The toxicity of epibatidine has encouraged work on structurally related analogues in the search for ligands which show increased discrimination between receptor sub-types and are therefore less toxic.

We have a long-standing interest in the 7-azabicyclo[2.2.1]-heptane ring system based on synthesis,[4] structure and spectroscopy,[5,6] and reactivity.[7] The unusually high barrier to inversion at nitrogen in this system has been recognised for some time (the 'bicyclic effect'[5]) and we have utilised this feature in demonstrating control over reaction pathways based on the configuration of leaving groups at nitrogen.[7] Other key developments have included X-ray crystallographic studies on single invertomers[5b] which gave early indications of stabilising interactions involving the '7-azanorbornane' framework. Significantly, the first ^{15}N NMR studies[6] on 7-azanorbornanes (and higher homologues) showed dramatic deshielding of the bridging nitrogen compared with other bicyclic amines including tropanes, again indicating a substantial degree of delocalisation of nitrogen electron density into the bicyclic framework. This led us to consider the possibility that the unusual nature of the bridging nitrogen in **1** might be a factor in its equally unusual biological activity.



We therefore chose to synthesise the homologue **2**, based on the tropane (8-azabicyclo[3.2.1]octane) system, together with **3**, the homotropane (9-azabicyclo[4.2.1]nonane) homologue, building on our development of a general synthetic route to tropanes, homotropanes, and derivatives.[8–11] Molecular modelling studies showed that the N–N distances and orientation of the chloropyridyl substituent in the three compounds are very similar. The gradation of ring size was intended to probe: a) how well the receptor tolerates steric bulk on the opposite face to the nitrogen interaction points and any associated effect on enantioselectivity in binding; b) the extent to which the lower rigidity of the azabicyclic framework in **2** might provide a better indication of the N–N distance and orientation requirements of the pharmacophore; and c) the possible contribution of the 'special' characteristics of the bridging 'norbornyl' nitrogen to the remarkable biological properties of **1**. We have reported our synthetic methods in preliminary form[12] and now report the full experimental details together with activity data which bear on these issues.

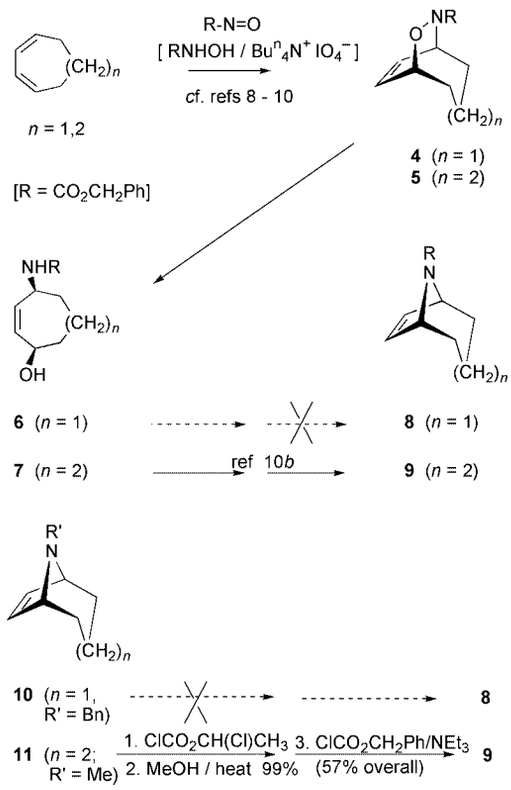
Independently of our work, Bai[13] has described an 8-step synthesis of **2** from commercially available 6β-hydroxytropinone together with an indication of potent analgesic activity based on hot-plate assays.

Results

We chose the Pd-catalysed reductive Heck procedure[14] for introduction of the chloropyridyl group into the azabicyclic skeleton and therefore required the *N*-protected precursors **8** and **9** (Scheme 1). We have synthesised the didehydrohomotropane **9** from cycloocta-1,3-diene *via* **5** and **7** as part of an earlier study[10b] (Scheme 1) but also chose to convert the *N*-methyl derivative **11**[10a] into **9** since quantities of **11** were already available. Thus, demethylation of **11** with α-chloroethyl chloroformate[15] followed by N-protection with benzyl chloroformate yielded **9** in an overall yield of 57% (Scheme 1).

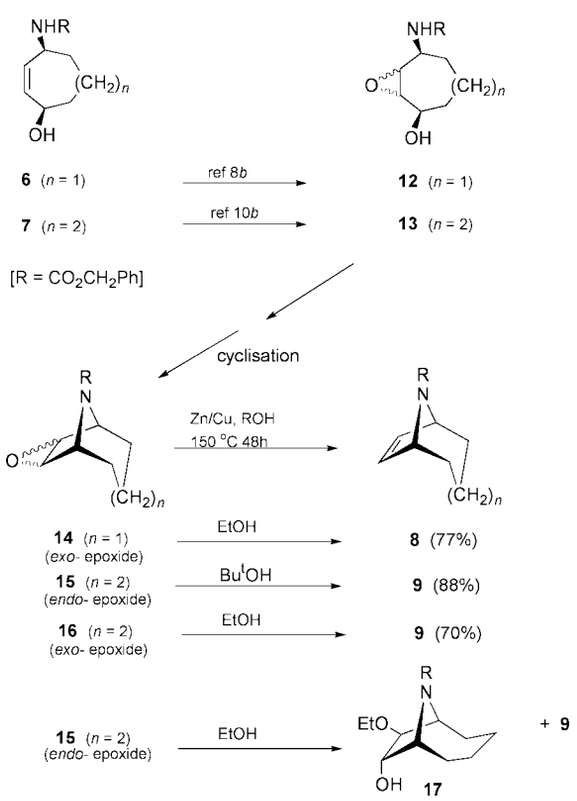
Unfortunately, the lower homologue **8** was not available using these routes since direct synthesis of the amines **8** (R = H, Me) from the corresponding precursors **6** had given low yields in earlier work.[8a] Furthermore, traditional N-debenzylation methods failed to give (**8**; R = H) when applied to *N*-benzylnortrop-6-ene (**10**; R′ = Bn).[15] A timely reminder that epoxides are effectively 'protected' alkenes was provided by the work of Bremner *et al.* who successfully deoxygenated the 6,7-epoxy-

 DOI: 10.1039/b010178h



Scheme 1

tropane derivative scopolamine with a zinc–copper couple.[16] Our work with simpler epoxytropanes had provided the N-protected *exo*-(β)-epoxide **14** from cycloheptadiene *via* the epoxide **12**[8b] and this was converted in good yield into the key alkene **8** by deoxygenation using a zinc/copper couple in ethanol in a sealed tube (Scheme 2). This is the most practical route to the N-protected alkene **8** which was produced in an overall yield of 33% from **6**.

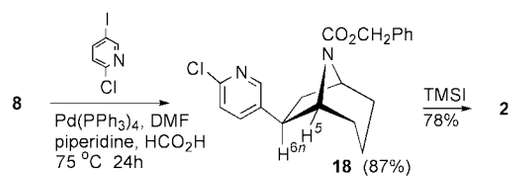


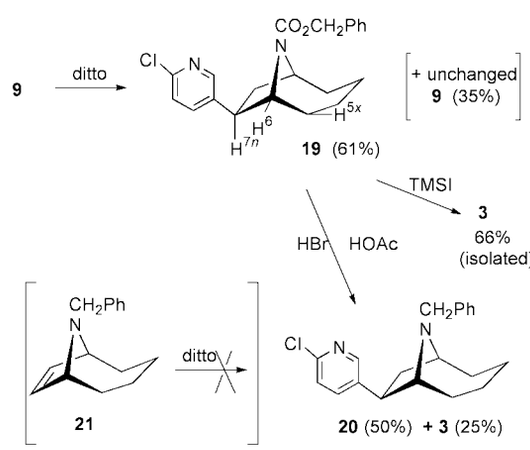
Scheme 2

Scheme 2 also summarises the adaptation of the same approach to the synthesis of the N-protected homotrop-7-ene **9**, *via* the epoxide **13**, demonstrating the successful application of deoxygenation to both the *endo*-(α)-epoxide **15** and the *exo*-isomer **16**, and providing a third route from **7** to **9**. We have already established that the *endo*-isomers of 6,7-epoxytropanes and 7,8-epoxyhomotropanes suffer ring-opening more readily that do the *exo*-isomers[8b,10b] and, in the case of *endo*-**15**, the consequence of this increased reactivity was competition from attack by the ethanol solvent, giving some **17**. However, this could be avoided completely by using *tert*-butyl alcohol instead of ethanol.

All of our routes to tropanes, homotropanes, and derivatives proceed *via cis*-1,4-amino alcohols such as **6** and **7**. These are formed, in turn, from cyclohepta- and cycloocta-1,3-diene by Diels–Alder addition of acylnitroso compounds formed *in situ* from hydroxycarbamates and a tetraalkylammonium periodate as oxidant (Scheme 1).[8,10,17] Despite the long-term use of tetramethylammonium periodate in this process without incident, *an unexpected and serious explosion occurred recently during transfer of this solid reagent into a reaction flask and we have therefore abandoned its use*.[9] The alternative tetra-*n*-butylammonium periodate is now available commercially and we confirm here that this reagent has provided a satisfactory alternative in the two key cycloaddition steps in Scheme 1 (details in the Experimental section). In response to low yields using tetraalkylammonium periodates in some related cycloaddition reactions, Martin[18a] has used a Swern procedure to oxidise the hydroxycarbamate; King[18b] has reported the use of the Dess–Martin periodinane.

Introduction of the chloropyridyl group into **8** using the conditions shown in Scheme 3 proceeded smoothly in 87% yield



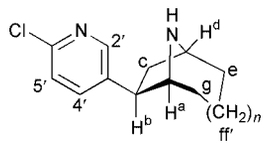


Scheme 3

to give **18** as the single isolated product. Most of the signals in the ^{1}H and ^{13}C NMR spectra of **18** were duplicated or broadened by slow rotation around the N–CO bond in the carbamate but there was no detectable spin–spin coupling between the bridgehead proton H^5 and the proton H^6, confirming that H^6 was indeed *endo*- and that addition of the chloropyridyl group had occurred exclusively from the *exo*-face. N-Deprotection of **18** using iodotrimethylsilane (TMSI) gave homoepibatidine **2** in 78% yield.

The analogous reductive Heck coupling on the homotrop-8-ene derivative **9** gave **19** as the major product in 61% yield,

Table 1 Selected ^{1}H and ^{13}C NMR data for **1**, **2**, and **3**



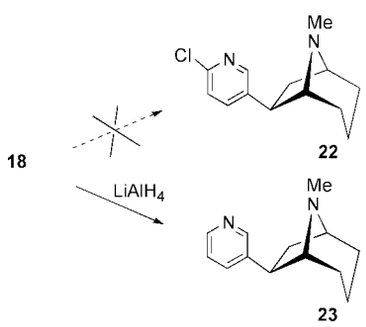
		1[a] (n = 0)		**2** (n = 1)		**3** (n = 2)	
		δ	*J*-Values/Hz	δ	*J*-Values/Hz	δ	*J*-Values/Hz
^{1}H	H^a	3.57 d	1.7	3.26 m	$w_{1/2}$ = 7.5	3.43 m	$w_{1/2}$ = 11.6
	H^b	2.77 dd	9.0, 5.1	3.08 dd	9.1, 5.0	3.05 br dd	9.2, 6.6, 2.0
	H^d	3.81 t	4.0, 4.0	3.62 br s	$w_{1/2}$ = 14.0	3.85 br dd	5.3, 2.0; $w_{1/2}$ = 16.2
^{13}C	a	62.6		62.7		66.8	
	b	44.4		44.3		49.3	
	c	40.2		39.3		42.8	
	d	56.4		55.6		58.6	
	e, g[b]	30.0, 31.2[b]		32.7, 33.3[b]		36.5, 36.8[b]	
	f, f	—		17.3		24.4, 24.6[b]	

[a] Data from ref. 19. [b] These signals may be interchanged.

together with unchanged **9**. Double irradiation of the downfield signal due to H^{7n} produced only minimal sharpening of the adjacent H^6, leaving a doublet ($J_{5exo,6}$ = 6.3 Hz). The small coupling betwen H^6 and H^{7n} again confirmed the *exo*-orientation of the chloropyridyl ring. Attempted Heck coupling using palladium acetate was unsuccessful, as was reaction using pre-formed $Pd(OAc)_2(PPh_3)_2$. Deprotection of **19** with TMSI provided a sample of dihomoepibatidine **3** in quantitative yield as shown by NMR spectroscopy, although chromatography reduced this to 66%. Treatment of **19** with HBr–ethanoic acid led to formation of the *N*-benzyl derivative **20** as the major product together with a modest amount of **3**. Attempts to achieve reductive Heck coupling with the *N*-benzyl compound **21** [10a] were unsuccessful.

Selected data for **1**, **2**, and **3** are summarised in Table 1. Data for the N-protected compounds are more complex as a result of slow N–CO bond rotation and are listed in the Experimental section.

Attempted conversion of the N-protected compound **18** into the *N*-methyl analogue of homoepibatidine, compound **22**, was unsuccessful. Reduction with lithium aluminium hydride (LAH) was slow even at room temperature and concomitant reductive removal of the chloro substituent from the pyridyl ring took place (Scheme 4) to yield **23** in 58% yield. This



Scheme 4

work was not pursued since N-methylation can be achieved by standard reductive amination techniques.[13]

Discussion

Affinity data for both enantiomers of homoepibatidine **2** and racemic **3** are shown in Table 2 together with comparison data for the enantiomers of epibatidine **1**, and (−)-nicotine.

The enantiomers of homoepibatidine **2** differ slightly in affinity but show a similar level of potency to epibatidine **1**; the affinity is approximately 10-fold higher than for nicotine. The affinity of dihomoepibatidine **3** is an order of magnitude lower

Table 2 Inhibition of binding at nicotinic receptors[a]

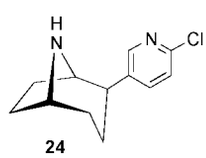
Compound	IC_{50}/ nM	Determinations	K_i/ nM[b]	nH[c]
(−)-Epibatidine **1**	0.1	5		
(+)-Epibatidine **1**	0.24	5		
(−)-Homoepibatidine **2**	0.3	2	0.13	0.55
(+)-Homoepibatidine **2**	0.8	2	0.35	0.72
(±)-Dihomoepibatidine **3**	2.85	2	1.25	0.6
(−)-Nicotine	7.8	5		

[a] Inhibition of (−)-[^{3}H] nicotine using rat brain homogenate (see Experimental section). [b] K_i = apparent affinity (IC_{50} corrected for ligand occupancy). [c] nH = Hill slope.

than **1** and **2** and no effort was made to resolve this compound. The similarity of **1** and **2** shows without doubt that the 'special' characteristics of the 7-azanorbornyl nitrogen are not a significant factor in the activity of **1**. Presumably the stabilising interactions between the bridging nitrogen and the carbocyclic framework are nullified on protonation but relative basicity data for **1** and **2** are unfortunately not available.

Clearly, the similar IC_{50}-values for epibatidine **1** and homoepibatidine **2** demonstrate that a somewhat less rigid azabicyclic framework can still support very high activity at nACh receptors despite the extra methylene group in **2** and the greater flexibility of the piperidine ring, which can adopt a boat or chair conformation, the latter being preferred.[20] The work of Bai, based on hot-plate assays, complements our own data; in this work, (±)-**2** elicited a similar level of antinociceptive activity at a dose of 40 μg kg^{-1} to that produced by 10 μg kg^{-1} of (±) − 1.[13]

It is not clear whether the lower activity of **3** is a consequence of the greater steric demands of the tetramethylene chain, the greater conformational flexibility of the bicyclic skeleton, or a combination of both. Certainly, a greater relative reduction in activity is found when the chloropyridyl moiety is relocated to the more flexible bridge in homoepibatidine isomers **24** and **25**.[21] Displacement of (±)-[^{3}H] epibatidine using electric organ membranes of the *Torpedo californica* eel, gave an IC_{50}-value for (−)-**24** of 7.19 μM (relative to 0.29 μM for (±)-epibatidine **1**; as expected, the value for (+)-**25** was much lower (674 μM).[21]



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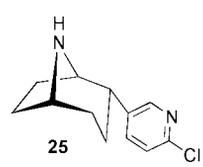

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Interestingly, the enantiomer affinity ratio for **2** [(+): (−) ≈ 2.6 : 1] is, within experimental error, identical to that of **1**

(2.4 : 1), indicating only very slight discrimination between enantiomers at the active site. A very recent report suggests that efficacy, as measured using voltage clamp electrophysiology, can vary according to whether ligands bind preferentially to open activated receptors, or to closed desensitised or closed resting states of the nACh receptors.[22] This work suggests that the activity difference between two enantiomeric ligands may be of different magnitude to that indicated by conventional affinity assays. Thus, it is reported that **2** acts as a full agonist at the α4β2 nAChR but the currents evoked by the two enantiomers differed, showing that the (+)-enantiomer was favoured strongly.[22] Similar responses were evoked at the α3β4 receptor but the difference was less marked. However, the response of the α7 receptor showed (−)-**2** to be at least 100 times less efficacious than the (+)-enantiomer. Our own recent studies to design agonists with greater enantiomeric selectivity (and greater sub-type selectivity) have concentrated on isomers of epibatidine based on the 2-azabicyclo[2.2.1]heptane[23] and 2-azabicyclo[2.1.1]hexane[24] frameworks, molecules which have greater intrinsic asymmetry than **1** or **2**. Initial results suggest that sub-type selectivity is increased in the 2-azabicyclo[2.2.1]-heptane derivatives.[23b]

Experimental

NMR spectra were recorded on Bruker ARX 250, DPX 300, or DRX 400 spectrometers. All spectra were obtained in $CDCl_3$ with tetramethylsilane (TMS) as internal reference unless indicated otherwise. Signal characteristics are described using standard abbreviations: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), br (broad); assignments were made with the aid of H–H COSY spectra and selective spin-decoupling experiments. In the ^{13}C spectra, quaternary, methine, methylene and methyl carbons, respectively, were identified using DEPT experiments; HC COSY experiments aided assignments but, in some cases, assignments of signals which have very similar chemical shifts may be interchanged. Many of the *N*-benzyloxycarbonyl compounds showed paired signals corresponding to two rotamers (1 : 1 ratio) in the ^1H and ^{13}C NMR spectra and these are quoted separately where possible; signals common to both rotamers are listed in italics.

IR spectra were recorded on a Perkin-Elmer 298 or PE 1604 FT spectrometer as solutions in 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. Accurate mass measurements were obtained using a Kratos Concept mass spectrometer. Mps were determined using a Kofler hot-stage apparatus and are uncorrected.

Optical-rotation measurements were made on a Perkin-Elmer 341 instrument and specific rotations are given in units of 10^{-1} deg cm^2 g^{-1} shown in the form $[\alpha]_D^{19}$ −31.0 (*c* 0.008 g mL^{-1} MeOH).

Reactions were performed under dry nitrogen using solvents dried by standard methods. 'Petroleum ether' and methanol used in chromatography were distilled prior to use; diethyl ether was distilled from LAH; 'petroleum ether' refers to the fraction distilled over the range 40–60 °C. Column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). TLC was conducted on standard commercial aluminium sheets pre-coated with a 0.2 mm layer of silica gel (Merck 60–254). All other solvents were purified as described by Perrin and Armarego.[25]

Biological assays

Displacement (−)-[3H] nicotine binding was determined using modification of the method described by Romano and Goldstein[26] Whole rat brains were homogenised in 1 : 10 (wet w/v) of 20 mM HEPES buffer, pH 4.7, and centrifuged at 17 500 ***g*** for 30 min. The pellet was resuspended in ten volumes of buffer. After a final centrifugation (17 500 ***g*** for 30 min) the pellet was resuspended in buffer at a concentration of 15 mg mL^{-1}. Binding assays were conducted in polypropylene tubes containing 100 μL of (−)-[3H] nicotine (final concentration 10 nM), 10 μL of displacing compound and 390 μL of buffer. Non-specific binding was defined by incorporation of 10 μL of carbachol (final concentration 1 mM). The reaction was initiated by adding 500 μL of the membrane suspension with vortex mixing. Samples were incubated for 60 min at 30 °C. The reaction was terminated by filtration over filters pre-soaked in 0.05% polyethyleneimine followed by washing with 10 mL of ice-cold saline, The radioactivity of filters was estimated by liquid scintillation spectroscopy. Data from binding assays were subjected to non-linear least squares regression analysis using RSI (BBN Research Systems, Cambridge, MA, USA) and a computerised iterative procedure written by Dr A. Richardson, NRC, Terlings Park.

***N*-(Benzyloxycarbonyl)-6-oxa-7-azabicyclo[3.2.2]non-8-ene 4.** Cyclohepta-1,3-diene (2.17 g, 0.023 mol) and tetra-*n*-butylammonium periodate[9] (10.0 g, 0.023 mol) in chloroform (50 mL) were stirred at 0 °C. A solution of benzyl *N*-hydroxycarbamate (3.84 g, 0.023 mol) in chloroform (30 mL) was added dropwise over a period of 15 min. On complete addition the mixture was allowed to warm to ambient temperature and was stirred for a further 19 h. The solution was filtered, and washed with water (10 × 50 mL). The organic layer was separated and the chloroform was removed on a rotary evaporator to yield a brownish oil which crystallised on storage. This was dissolved in diethyl ether (leaving a dark residue), washed with water (5 × 50 mL), dried over anhydrous magnesium sulfate, filtered, and the solvent removed using a rotary evaporator. The residual yellow oil crystallised on storage to yield 4 (4.616 g, 78%) as coloured crystals, mp 30–33 °C, showing identical spectra to those of an authentic sample.[8a] Chromatography on silica (1 : 4 diethyl ether–'petroleum ether') produced a colourless sample.[8a]

***N*-(Benzyloxycarbonyl)-7-oxa-8-azabicyclo[4.2.2]dec-9-ene 5.** Cycloocta-1,3-diene (0.921 g, 0.085 mol) was added to a stirred suspension of tetra-*n*-butylammonium periodate[9] (3.85 g, 0.089 mol) in dry chloroform (50 mL), which was maintained at 0 °C. A solution of benzyl *N*-hydroxycarbamate (1.473 g, 0.088 mol) in dry chloroform (30 mL), was added dropwise over a period of 10 min, after which time the mixture was allowed to come to RT and was stirred for a further 19 h. The mixture was worked up as described for compound **4**. The residual yellow oil (1.366 g, 59%) crystallised on storage to give **5** of good purity, mp 58–60 °C (lit.[10a] 61.0–61.5 °C). Spectroscopic data matched those of an authentic sample[10a] and a colourless sample could be obtained by chromatography on silica using 1 : 9 diethyl ether–'petroleum ether'.

***N*-(Benzyloxycarbonyl)-8-azabicyclo[3.2.1]oct-6-ene 8.** Zinc/copper couple (2.41 g; Lancaster Synthesis Ltd.) was added to a solution of the *exo*-epoxide **14**[8b] (134 mg, 0.52 mmol) in absolute ethanol (5 mL) and the mixture was heated in a Young's tube at 150 °C for 48 h. On cooling, the solution was filtered through Celite and the bulk of the solvent was removed using a rotary evaporator. The residual solution was partitioned between dichloromethane (30 mL) and water (10 mL). The organic layer was separated and repeatedly washed with water (2 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate. Filtration followed by rotary evaporation of the mixture yielded a crude oil (125 mg, 99%) which [from ^1H NMR integration against a known quantity of an internal standard (CH_2Cl_2)] was found to contain **8** (77%) and starting material. Column chromatography over silica (elution with diethyl ether–'petroleum ether' in ratios ranging

from 2 : 3 to 3 : 2) afforded recovered starting material (20%) and **8** as a pale yellow oil (68 mg, 54%), ν_{max} 3070w, 3030w, 2940br s, 2860m, 1700br s, 1595w, 1500w, 1440br s, 1420br s, 1365m, 1340m, 1305m, 1260m, 1225s, 1215m, 1165w, 1095br s, 1060s, 1035w, 1030w, 1010s, 955s, 920w, 825m, 760br m, 750br m, 715s, 695s cm^{-1}; δ_H (250 MHz) *1.30–1.85* (series of m, 6H, H^{2-4}), *4.58* (br m, $H^{1,6}$), *5.16* (s, CH_2Ph), *6.02/6.05* (2 × br s, $H^{6,7}$), *7.35* (m, 5H, Ph); δ_C (63 MHz) *16.7* (C^3), *23.9/24.8* (C^2, C^4), *58.9* (C^1, C^5), *66.8* (CH_2Ph), *128.2*, *128.3* and *128.8* (aryl CH), 130.5/130.9 (C^6, C^7), *137.5* (aryl C), 152.8 (C=O); *m/z* (FAB) 244 (MH^+); $C_{15}H_{18}NO_2$ [MH^+] requires *m/z* 244.1337; observed *m/z*, 244.1337.

***N*-(Benzyloxycarbonyl)-9-azabicyclo[4.2.1]non-7-ene 9 *via* demethylation of 11.** Compound **11**[10a] was converted into 9-azabicyclo[4.2.1]non-7-ene by demethylation using α-chloroethyl chloroformate and the secondary amine was stored as the picrate salt.[15] The free amine was released from the picrate (186.4 mg, 0.53 mmol) by dissolution in dichloromethane (2 mL) and addition of triethylamine (230 μL, 167 mg, 1.65 mmol, 3 eq.). To the stirred solution was added benzyl chloroformate (120 μL, 143 mg, 0.84 mmol, 1.5 eq.) by injection, and the solution was stirred overnight. The solution was washed successively with water (2 × 5 mL), dil. hydrochloric acid (2 × 5 mL) and dil. aq. sodium hydroxide (2 × 5 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure. The resulting oil was purified by flash chromatography, and elution with 1 : 1 diethyl ether–'petroleum ether' to yield **9** as a colourless oil (77.4 mg, 57%) showing spectra which matched those of an authentic sample.[10b] [Note: The signal due to the benzylic methylene group was omitted from the data in reference 10b and the full ^{13}C NMR data are therefore listed here: δ_C (75 MHz) 24.0/24.2 ($C^{3,4}$), 30.8/31.7 (C^2, C^5), 60.9/61.3 (C^1, C^6), *66.4* (CH_2Ph), *127.7, 127.8* and *128.4* (aryl CH), 130.9/131.0 (C^7, C^8), *137.1* (aryl C), *153.2* (C=O).]

***N*-(Benzyloxycarbonyl)-9-azabicyclo[4.2.1]non-7-ene 9 by deoxygenation of *endo*-(α)-epoxide 15.** Commercial zinc/copper couple (2.66 g; Lancaster Synthesis Ltd.) was added to a solution of the *endo*-epoxide **15**[21] (100 mg, 0.366 mmol) in dry *tert*-butyl alcohol (3 mL) in a dry Young's tube. The tube was flushed with nitrogen, sealed, and heated at 140 °C for 48 h. On cooling, the solution was filtered through Celite and the solid residue washed with dichloromethane (4 × 20 mL). The solution was washed with water (2 × 30 mL), dried over magnesium sulfate, and the solvent was evaporated off using a rotary evaporator. The residual oil was purified by column chromatography over silica (elution with 4 : 6 diethyl ether–'petroleum ether') to afford **9** as a colourless oil (49 mg, 52%), identified by comparison of spectra with an authentic sample.[10b]

Deoxygenation of *endo*-epoxide 15 using a Zn/Cu couple in ethanol; competitive formation of *N*-(benzyloxycarbonyl)-7β-ethoxy-8α-hydroxy-9-azabicyclo[4.2.1]non-7-ane 17. A sample of **15** (498 mg, 1.82 mmol) in absolute ethanol (10 mL) was treated with zinc–copper couple (2.44 g) in a Young's tube and heated at 120 °C for 72 h. The reaction mixture was worked up and chromatographed as described above to yield **9** (147 mg, 31%), unchanged **15** (101 mg, 20% recovery), and **17** (235 mg, 40%) as colourless oils having R_f-values of 0.69, 0.50, and 0.36, respectively, on TLC using 1 : 1 diethyl ether–'petroleum ether'. Compound **17** showed δ_H (250 MHz) *1.22* (t, J = 6.6 Hz, Me), *1.30–1.95* (series of m, 7H), 2.09/2.26 (m, H^5), *≈3.4* (br, OH), 3.48/3.52 (2 q, J = 6.6 Hz, CH_2Me), 3.68/3.72 (dd, J = 5.0, 1 8 Hz, H^7), 4.00/4.10 (2 × br dd, J = 6.1, 1.6 Hz, H^6), *4.23* (m, H^8), *4.39* (m, H^1), 5.10/5.12 (2 × ABq, ^2J = 12.6 Hz, CH_2Ph), *7.32* (m, 5H, Ph); δ_C (63 MHz; $CDCl_3$) *15.3* (Me), *24.2/24.4* (C^3C^4), 25.9/26.7 (C^5), 31.3/32.3 (C^2), 58.7/59.0 (C^1), 60.8/60.9 (C^6), *65.1* (CH_2Me), 66.7/66.8 (CH_2Ph), 76.7/76.8 (C^8), 92.2/92.9 (C^7), *127.7*, *127.8* and *128.4* (aryl CH), 136.7/136.8 (aryl C), 154.3/154.4 (C=O); *m/z* (EI) 319 (M^+, 8%), 301 (4), 273 (2), 228 (14), 184 (56), 138 (14), 96 (52), 91 (100); $C_{18}H_{25}NO_4$ [M^+] requires *m/z* 319.17836; observed *m/z*, 319.17835.

***N*-(Benzyloxycarbonyl)-9-azabicyclo[4.2.1]non-7-ene 9 by deoxygenation of *exo*-(β)-epoxide 16.** A sample of **16** (328 mg, 1.20 mmol) in absolute ethanol (20 mL) was treated with zinc–copper couple (4.14 g) in a Young's tube and heated at 150 °C for 24 h. The reaction mixture was worked up and chromatographed as described above to yield **9** (190 mg, 62%; 70% based on consumed **16**) as a colourless oil showing identical spectra to those of an authentic sample.

Tetrakis(triphenylphosphine)palladium(0). A mixture of palladium(II) chloride (5.00 g, 28.2 mmol) and triphenylphosphine (36.98 g, 141.0 mmol) in dimethyl sulfoxide (DMSO) (375 mL) was heated at 150 °C until all the solid had dissolved. The heater was removed and hydrazine hydrate (5.5.mL, 1129.7 mmol) was added carefully. The product separated as yellow crystals on cooling to RT and was filtered off under a nitrogen atmosphere. After washing with ethanol (4 × 100 mL) followed by diethyl ether (4 × 100 mL), traces of solvent were removed under vacuum to give tetrakis(triphenylphosphine)palladium(0) (30 g, 92%), δ_P (101 MHz; CD_2Cl_2) 12.0 (br s) (lit.,[27] 15.5).

***N*-(Benzyloxycarbonyl)-6β-(6′-chloro-3′-pyridyl)-8-azabicyclo[3.2.1]octane 18.** To a solution of **8** (86 mg, 0.35 mmol) in dry *N*,*N*-dimethylformamide (DMF) (570 μL) were added tetrakis(triphenylphosphine)palladium(0) (60.7 mg, 0.053 mmol), 2-chloro-5-iodopyridine (251 mg, 1.05 mmol), piperidine (121 μL, 1.23 mmol) and formic acid (39.6 μL, 1.05 mmol). The mixture was heated at 75 °C with stirring for 24 h and afterwards diluted with dichloromethane (15 mL), transferred to a separating funnel, and washed with water (3 × 5 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and the solvent evaporated off using a rotary evaporator. The crude oil was purified by flash chromatography and elution with diethyl ether–'petroleum ether' (in ratios ranging from 1 : 9 to 1 : 1) to afford **18** as a colourless oil (108.6 mg, 87%), ν_{max} 3062m, 2930s, 2863m, 1694s, 1587w, 1554w, 1454s, 1432s, 1339m, 1319s, 1267s, 1220m, 1185w, 1143m, 1102s, 1036s, 974w, 955w, 912w, 872w, 837w, 802w, 738br s, 696s cm^{-1}; δ_H (250 MHz) *1.2–1.9* (series of m, 6H), *1.95* (m, H^7_{exo}), *2.28* (m, H^7_{endo}), *3.21* (dd, J = 9.4, 4.7 Hz, H^6_{endo}), 4.12/4.22 (2 × br s, H^5), 4.47/4.53 (2 × br d, H^1), 5.16/5.20 (2 × ABq, ^2J = 12.4 Hz, CH_2Ph), 7.13/7.20 (2 d, J = 8.2 Hz, $H^{5'}$), 7.40/7.47 (2 dd, J = 8.2, 2.5 Hz, $H^{4'}$), *8.20* (br, $H^{2'}$), *7.28–7.40* (series of m, 5H, Ph); δ_C (63 MHz) *17.3* (C^3), 30.1/30.5/30.9/31.3 (C^2, C^4), 38.7/39.8 (C^7), 43.7/44.6 (C^6), 55.4/55.5 (C^1), 61.9/62.3 (C^5), *67.2* (CH_2Ph), *124.9* ($C^{5'}$), *128.3/128.4/128.9* (3 × aryl CH), *136.9* ($C^{4'}$) *137.2* (aryl C), *141.9* ($C^{3'}$), 148.5/148.6 ($C^{2'}$), *149.8* ($C^{6'}$), *153.8* (C=O); *m/z* 356 (M^+, 8%), 277 (2), 221 (17), 194 (1), 173 (3), 151 (2), 126 (4), 104 (3), 91 (100), 82 (27), 55 (15); $C_{20}H_{21}ClN_2O_2$ [M^+] requires *m/z* 356.1292; observed *m/z*, 356.1291.

***N*-(Benzyloxycarbonyl)-7β-(6′-chloro-3′-pyridyl)-9-azabicyclo[4.2.1]nonane 19.** Under a flow of nitrogen, *N*-(benzyloxycarbonyl)-9-azabicyclo[4.2.1]non-7-ene **9** (105 mg, 0.41 mmol) was placed in a thoroughly dried 3 mL Reacti-vial. 2-Chloro-5-iodopyridine (300 mg, 1.25 mmol, 3.1 eq.) was added followed by tetrakis(triphenylphosphine)palladium(0) (162 mg, 0.14 mmol). Dimethylformamide (800 μL) was injected into the sealed flask, followed by piperidine (150 μL, 129.2 mg, 1.52 mmol, 3.7 eq.) and formic acid (46 μL, 56.1 mg, 1.22 mmol, 3 eq.). The mixture was heated with stirring in a thermostatted bath at 75 °C for 24 h. Water (10 mL) was added, and the mixture extracted with dichloromethane (3 × 10 mL). The organic extracts were washed with water, dried over

anhydrous sodium sulfate, and the solvent removed under reduced pressure to leave an orange oil. Chromatography on silica, and elution with 4 : 6 diethyl ether–'petroleum ether' gave unchanged **9** (37.8 mg, 36%) and **19** as a colourless oil (92.5 mg, 61%; 97% based on consumed **9**), ν_{max} 3045br w, 2980br w, 2940 m, 1695s, 1440br m, 1415 m, 1330w, 1270br m, 1250br m, 1160br w, 895w cm^{-1}; δ_H (250 MHz) *1.4–1.8/2.0–2.3* (series of m, 10H, $H^{2,3,4,5,8}$), *3.19* (m, H^7), 4.20/4.31 (2 × br d, J = 6.3 Hz, H^6), 4.58/4.66 (2 m, H^1), 5.13/5.17 (2 × ABq, ^2J = 12.3 Hz, CH_2Ph), *7.11–7.42* (series of m, 6H, ArH and $H^{5'}$), *7.73* (m, $H^{4'}$), *8.21* (d, $J \approx 2.4$ Hz, $H^{2'}$); δ_C (63 MHz) *24.1/24.2* (C^3, C^4), 32.9/33.0/*34.1* (C^2, C^5), 40.2/41.4 (C^8), 46.7/47.8 (C^7), 56.2/56.7 (C^1), 64.1/64.3 (C^6), 66.7/66.8 (*C*H_2Ph), *124.5* ($C^{5'}$), *127.5–128.5* (complex, aryl CH), 135.1/135.2 ($C^{4'}$), 136.4/136.5 (aryl C), 141.2/141.4 ($C^{3'}$), *148.0* ($C^{2'}$), *149.5* ($C^{6'}$), *153.8* (C=O); *m/z* 370/372 (M^+, 12/4%), 279/281 (3/1), 262 (15), 235/237 (17/6), 183 (12), 96 (25), 91 (100), 77 (5); $C_{21}H_{23}ClN_2O_2$ requires *m/z* 370.1443; observed *m/z*, 370.1448.

6β-(6′-Chloro-3′-pyridyl)-8-azabicyclo[3.2.1]octane (2; homoepibatidine). Iodotrimethylsilane (63 μL, 0.44 mmol) was injected into a solution of **18** (35.3 mg, 0.099 mmol) in $CHCl_3$ (20 ml). Methanol (5 mL; acidified with gaseous HCl) was then added and the solvent removed using a rotary evaporator; this was followed by the addition of methanol (5 mL; basified with gaseous ammonia) after which the solvent was again removed. The residue was taken up in chloroform and the precipitate removed by filtration to yield a yellow oil after evaporation. Purification by flash column chromatography, and elution with diethyl ether–'petroleum ether' (in ratios ranging from 1 : 9 to 3 : 2), afforded **2** (17.2 mg, 78%), ν_{max} 3045w, 2920s, 2870w, 2850m, 1584w, 1560m, 1454s, 1405m, 1390m, 1290w, 1265s, 1140m, 1100s, 1084w, 862m, 840w, 825m, 805w, 790w, 735br s, 700s cm^{-1}; δ_H (250 MHz) 1.5–1.9 (series of m, 8H, incl. NH), 2.16 (dd, J = 13.2, 9.4 Hz, $H^{7\beta}$), 3.08 (dd, J = 9.1, 5.0, Hz, $H^{6\beta}$), 3.26 (br s, H^5), 3.62 (m, H^1), 7.15 (d, J = 8.2 Hz, $H^{5'}$), 7.67 (dd, J = 8.2, 2.5 Hz, $H^{4'}$), 8.20, (d, J = 2.5 Hz, $H^{2'}$); δ_C (63 MHz) 17.6 (C^3), 32.7/33.3 (C^2, C^4), 39.3 (C^7), 44.3 (C^6), 55.6 (C^1), 62.7 (C^5), 124.0 ($C^{5'}$), 137.1 ($C^{4'}$), 142.6 ($C^{3'}$), 148.2 ($C^{2'}$), 148.8 ($C^{6'}$); *m/z* 222/224 (M^+, 12/3%), 193/195 (3/1), 179/181 (9/3), 155 (5), 127 (4), 107 (4), 91 (10), 83 (100), 68 (18); $C_{12}H_{15}ClN_2$ [M^+] requires *m/z* 222.0924; observed *m/z*, 222.0924.

A sample of (±)-**18** was resolved using chiral HPLC on a semi-preparative Chiralpak AD column, eluted with 30% ethanol in hexane; samples were obtained in >99% ee as shown by analytical chiral HPLC. Pure samples of (+)-**2** and (−)-**2** were then obtained by separate deprotection using iodotrimethylsilane as described above. (+)-**18** $[a]_D^{19.2}$ +61.0 (*c* 0.0159 MeOH); (−)-**18** $[a]_D^{19.9}$ −61.4 (*c* 0.0174 MeOH); (+)-**2** $[a]_D^{19.0}$ +31.0 (*c* 0.008 MeOH). Insufficient material was available for reliable measurements on (−)-**2**.

7β-(6′-Chloro-3′-pyridyl)-9-azabicyclo[4.2.1]octane (3; dihomoepibatidine). Iodotrimethylsilane (210 μL, 295 mg, 1.48 mmol, 5.1 eq.) was injected into a solution of **19** (107 mg, 0.29 mmol) in dry CH_2Cl_2 (5 mL). The contents were mixed and stored for 30 min. Methanol (5 mL; acidified with gaseous HCl) was then added and the solvent removed using a rotary evaporator; this was followed by the addition of methanol (5 mL; basified with gaseous ammonia) after which the solvent was again evaporated off under reduced pressure. The residue was purified by chromatography on silica using 4 : 6 diethyl ether–'petroleum ether' to yield **3** (45 mg, 66%) as a colourless oil. A preliminary small-scale reaction gave a quantitative crude yield of **3** as shown by NMR integration against an internal standard but the deprotection reaction was not further optimised; δ_H (250 MHz; CD_2Cl_2) 1.5–1.9 (series of m, 9H incl. NH), 2.05 (m, 2H), 3.05 (br ddd, $J \approx 9.2$, 6.6, 2.0 Hz, $H^{7\alpha}$), 3.43 (br dd, J = 5.3, 2.0 Hz, H^6), 3.85 (m, H^1), 7.27 (d, J = 8.2 Hz, $H^{5'}$), 7.61 (dd, J = 8.2, 2.5 Hz, $H^{4'}$), 8.23 (d, J = 2.5 Hz, $H^{2'}$); δ_C (63 MHz, $CDCl_3$) 24.6/24.8 (C^3, C^4), 36.5/36.8 (C^2, C^5), 42.8 (C^8), 49.3 (C^7), 58.6 (C^1), 66.8 (C^6), 124.2 ($C^{5'}$), 136.9 ($C^{4'}$), 142.7 ($C^{3'}$), 148.2 ($C^{2'}$), 149.0 ($C^{6'}$); *m/z* 236/238 (M^+, 19/6%), 207/209 (3/1), 193/195 (15/5), 179/181 (30 : 10), 165 (4), 149 (11), 117 (12), 97 (100), 77 (14), 69 (44); $C_{13}H_{17}ClN_2$ requires *m/z* 236.1077; observed *m/z*, 236.1081.

***N*-Benzyl-7β-(6′-chloro-3′-pyridyl)-9-azabicyclo[4.2.1]nonane 20.** Hydrogen bromide (30% in acetic acid; 230 μL) was injected into a Reacti-vial containing **19** (12.4 mg, 33.5 μmol) and the mixture was stirred at RT for 3 days. Water (3 mL) was added, the solution was basified with dil. aq. sodium hydroxide, and sodium chloride was added to saturate the aqueous layer. The mixture was extracted with dichloromethane (5 × 2 mL), the combined extract was dried over anhydrous sodium sulfate, and the solvent evaporated to leave an oil (9.4 mg) which contained **3** together with a second compound. The mixture was subjected to preparative TLC on silica, with dichloromethane–methanol–ammonia (35% aq. solution, specific gravity 0.880) (90 : 10 : 3) as developer. The compound eluted first ($R_f \approx 0.85$) was shown to be the *N*-benzylated compound **20** (5.5 mg; 50%): δ_H (250 MHz) 1.4–1.8 (series of m, 6H), 1.8–2.1 (m, 4H), 3.03 (m, $H^{7\alpha}$), 3.15 (m, H^6), 3.53 (m, H^1), 3.90 (s, CH_2Ph), 7.10–7.31 (series of m, 6H, aryl H, $H^{5'}$), 7.60 (dd, J = 8, 2 Hz, $H^{4'}$), 8.20 (d, J = 2 Hz, $H^{2'}$); δ_C (63 MHz) 24.8/25.0 (C^3, C^4), 33.7/34.3 (C^2, C^5), 41.3 (C^8), 48.1 (C^7), 53.7 (C^1), 60.6 (C^6), 123.9 ($C^{5'}$), 126.7 (aryl CH), 128.1 (2 × aryl CH), 137.2 ($C^{4'}$), 140.3 (aryl C), 143.4 ($C^{3'}$), 148.3 ($C^{2'}$), 148.6 ($C^{6'}$); *m/z* 326/328 (M^+, 47 : 16%), 283/285 (11 : 4), 269/271 (21 : 7), 235/237 (9 : 3), 187 (38), 96 (34), 91 (100); $C_{20}H_{23}ClN_2$ requires *m/z* 326.1545; observed *m/z*, 326.1550. The second compound to be eluted ($R_f \approx 0.6$) (2 mg, 25% yield) was **3** contaminated with some **20** and was further purified by flash chromatography with the same elution conditions to yield a pure sample of **3**.

Attempted direct preparation of *N*-benzyl-7β-(6′-chloro-3′-pyridyl)-9-azabicyclo[4.2.1]nonane 20. The *N*-benzyl alkene **21** (44.8 mg, 0.21 mmol) was treated with 2-chloro-5-iodopyridine (166 mg, 0.69 mmol, 2.3 eq.) followed by tetrakis(triphenylphosphine)palladium(0) (314 mg, 0.27 mmol, 1.3 eq.), DMF (350 μL), piperidine (125 μL, 108 mg, 1.26 mmol, 6 eq.) and formic acid (48 μL, 58 mg, 1.25 mmol, 6 eq.) as described above and heated in a Reacti-vial at 95 °C for 48 h. Work-up and chromatography on silica using 3 : 7 diethyl ether–'petroleum ether' containing ammonia gave only unchanged **21**.

***N*-Methyl-6β-(3′-pyridyl)-8-azabicyclo[3.2.1]octane 23.** To a stirred solution of **18** (54 mg, 0.151 mmol) in THF (5 mL) at −78 °C was added LAH (23 mg, 0.604 mmol). The reaction mixture was allowed to warm slowly to ambient temperature. Analysis by TLC after 1.5 h showed only starting material. Further LAH (23 mg) was added at 0 °C and the reaction mixture allowed to warm to RT but TLC analysis still indicated that starting material was present after a further 2.5 h. Stirring was continued overnight, after which time no starting material remained. The reaction was quenched by the addition of the minimum quantity of water-saturated diethyl ether at 0 °C. The suspension was dried with anhydrous sodium sulfate and filtered through Celite. The inorganic residues were washed with ethyl acetate and the solvent evaporated off using a rotary evaporator to yield a crude yellow oil. Purification by column chromatography on silica using 3 : 7 diethyl ether–'petroleum ether' yielded **23** as a pale yellow oil (18 mg, 58%). ν_{max} 2930s, 2870w, 2860m, 1575w, 1460br m, 1425m, 1325br w, 1015br w, 850br s cm^{-1}; δ_H (400 MHz) 1.17 (m, 1H), 1.26 (m, 1H), 1.66 (m, 1H), 1.80 (m, 1H), 1.96–2.11 (series of m, 3H), 2.24 (dd, J = 13.1, 9.3 Hz, $H^{7\beta}$), 2.52 (s, 3H, NCH_3), 3.16 (br s, H^5), 3.19 (dd, J = 9.3, 5.0 Hz, $H^{6\beta}$), 3.34 (m, H^1), 7.21 (br dd, J = 8.0, 4.6, <1 Hz, $H^{5'}$), 7.80 (ddd, J = 8.0, 2.2, ≈1 Hz, $H^{4'}$), 8.43 (br dd, J = 4.6, ≈1, <1 Hz, $H^{2'}$), 8.58 (br d, J = 2.2, <1 Hz, $H^{6'}$); δ_C (106

MHz) 17.2 (C^3), 23.4/24.0 (C^2, C^4), 34.8 (CH_3), 38.8 (C^7), 45.0 (C^6), 59.7 (C^1), 66.1 (C^5), 123.4 ($C^{5'}$), 134.2 ($C^{4'}$), 144.0 ($C^{3'}$), 147.2/148.9 ($C^{2'}$, $C^{6'}$); *m*/*z* (FAB) 203 (MH^+); $C_{13}H_{19}N_2$ [MH^+] requires *m*/*z* 203.1548; observed *m*/*z*, 203.1548.

Acknowledgements

We are grateful to EPSRC for the award of a postgraduate studentship to A. L. W. We thank Mr Carl Williamson for preparing samples of **4** and **5**, and Dr G. A. Griffith for his assistance with selective spin-decoupling and 2-D NMR experiments.

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