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Synthesis of Epibatidine Isomers: Reductive Heck Coupling of 2-Azabicyclo[2.2.1]hept-5-ene derivatives

Caroline D. Cox and John R. Malpass*

Department of Chemistry, University of Leicester, Leicester LE1 7RH, U.K.

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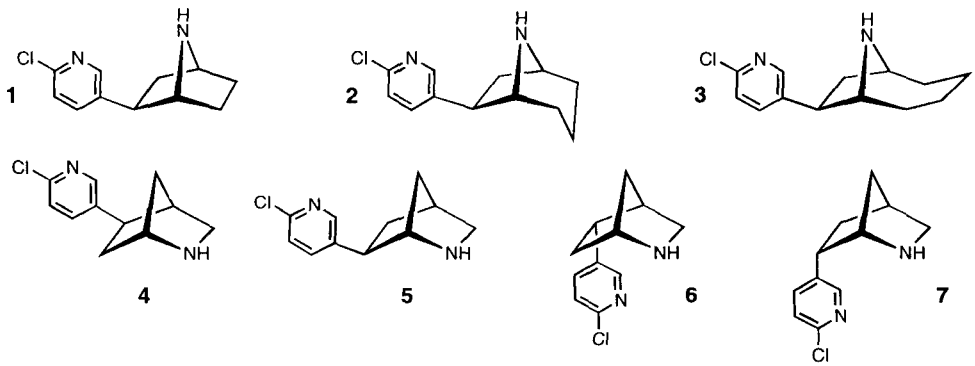
Abstract: The coupling of *N*-protected 2-azabicyclo[2.2.1]hept-5-enes and 2-chloro-5-iodopyridine under reductive Heck conditions gives approximately equal amounts of *exo*-5- and *exo*-6- (6′-chloro-3′-pyridyl)-2-azabicyclo-[2.2.1]heptanes. The ratio varies slightly under a range of conditions but both products are isolated in every case (and in the corresponding reaction with 3-iodopyridine) contrary to a recent report that only the 5-*exo*- isomers are formed.

Introduction

The discovery of the natural product epibatidine **1** in 1992[1] and recognition of its powerful analgesic properties has led to a remarkable level of synthetic interest. The fact that epibatidine acts at the nicotinic acetylcholine receptor (nAChR) and is a much more effective ligand than nicotine itself has prompted a substantial reappraisal of this receptor.[2] The toxicity of epibatidine itself has encouraged work on structurally related analogues in the search for lower toxicity and also higher discrimination between receptor sub-types.

As part of our studies of epibatidine analogues, we have synthesised the tropane-based homoepibatidine **2** and the *bis*- homologue, the homotropane derivative **3**.[3] Both of these compounds show activity at the nAChR receptor, indeed, **2** is as active as epibatidine itself.[4] This has encouraged us to explore further azabicyclic variants of **1** which retain the chloropyridyl moiety. The rigidity of the bicyclo[2.2.1]-heptane skeleton offers considerable advantages in defining *N-N* distance and orientation, and we chose to make novel epibatidine isomers based on 2-aza- (as opposed to 7-aza-) bicyclo[2.2.1]heptane. NAChRs in the central and autonomic nervous system show little discrimination between the enantiomers of either epibatidine or homoepibatidine and we felt that the inherent asymmetry of the '2-aza-' system might allow greater enantioselectivity. Whilst we anticipated that the *endo*-5- (**6**) and *endo*-6- (6-chloro-3-pyridyl) derivatives (**7**) might well have higher activity at the receptor than **4** and **5**,[5] we required all four regio- and stereoisomers (**4** - **7**) in order to have appropriate points of reference for both structural and activity studies.[6]



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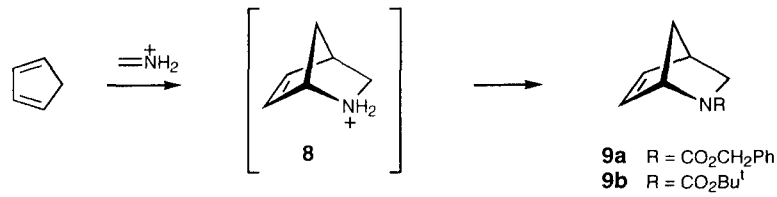
On the basis of successful use of the reductive Heck reaction[7] in the formation of **2** and **3**,[3] we chose to apply this methodology to *N*-protected derivatives of 2-azabicyclo[2.2.1]hept-5-ene in the expectation of isolating **4** and **5**. In addition to the question of regioselectivity, we were also interested in facial selectivity since *endo*- attack to yield **6** and **7** was a real possibility if interactions occurred between the 2-nitrogen and the palladium reagent. In the event, only 5-*exo*- and 6-*exo*- derivatives were isolated (leading to compounds **4** and **5**);[6] a successful alternative approach to the *endo*- compounds **6** and **7**[6] will be described in full separately.[8] Our results on the synthesis of **4** and **5** are given added relevance by a very recent report that reductive Heck reactions in this system gave only the 5-*exo*- isomer;[9a] this claimed selectivity was thought to be a consequence of a reduction of electron density at C-5 through hyperconjugation ($\pi \rightarrow \sigma^*_{C\text{-}N}$).

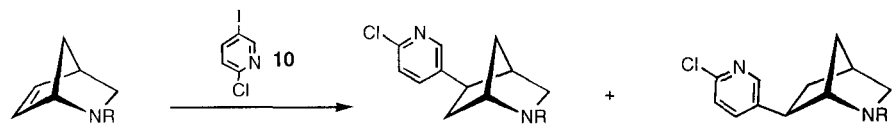
The 2-azabicyclo[2.2.1]hept-5-ene precursors were obtained by means of the established cycloaddition of iminium salts to cyclopentadiene[10] (Scheme 1). The amino nitrogen of **8** was protected using both the benzyloxycarbonyl group (**9a**) and the *t*-butyloxycarbonyl (BOC) group (**9b**).

Scheme 1



Treatment of **9a** with 2-chloro-5-iodopyridine (**10**) under reductive Heck conditions[7] (using an excess of (**10**) gave a mixture of two products, **11a** and **12a** (Scheme 2) in an isolated yield of 95%. Chromatographic separation on silica gave pure **11a** and **12a**

Scheme 2



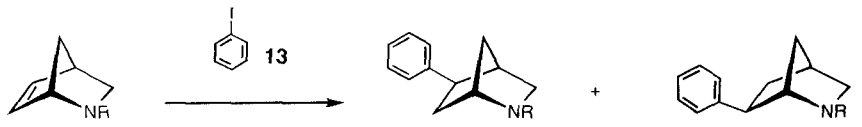
The presence of two compounds was indicated in the ^{1}H NMR spectra of the crude reaction products by two pairs of signals in the δ 4.0 - 4.4 region, assigned to H_1 in **11** and **12**. The duplication of signals resulted from the presence of two rotamers in each case and complicated most of the ^{1}H NMR spectra of the *N*-protected compounds, but key features were apparent. For example, in the case of **11a**, $H_{5\text{-endo}}$ was unaffected by N-CO rotation of the distant urethane and appeared as a doublet of doublets at δ 3.01 (vicinal coupling to $H_{6\text{-exo}}$ and $H_{6\text{-endo}}$)[11] but with no significant coupling to the bridgehead proton H_4. The bridgehead protons H_1 appeared downfield in both **11a** and in **12a** (above); predictably, the HH COSY spectrum showed coupling of H_1 to $H_{6\text{-}exo}$ in the former but not the latter case ($J_{1,6\text{-endo}} < 1$ Hz) and the larger value for the half-width ($W_{½}$) for H_1 in **11a** (compared with H_1 in **12a**) was consistent with the additional presence of $J_{1,6\text{-exo}}$ in **11a**. The COSY spectrum of **12a** also showed cross peaks corresponding to $J_{3\text{-endo},7\text{-anti}}$ and $J_{6\text{-endo},7\text{-syn}}$ allowing $H_{7\text{-anti}}$ (δ1.57) and $H_{7\text{-syn}}$ (δ1.66) to be assigned. Analysis of the simpler spectra obtained for the deprotected compounds is summarised below and in Table 2.

Turning to the *N*-BOC-protected compounds, the reaction with **9b** gave a mixture of the analogous 5- and 6-*exo*-chloropyridyl compounds **11b** and **12b** when $Pd(PPh_3)_4$ was used as catalyst. Variation of the reaction conditions led to modest differences in the *N*-BOC series; product ratios and isolated yields are summarised in Table 1. Compound **11b** showed spectroscopic properties which differed in some respects from those reported by Maier[9] (see Experimental section); the spectra of **12b** were similar to those of **12a** (above). When $Pd_2(dba)_3$ was used, the yield was lower. Moving to $Pd(OAc)_2(PPh_3)_2$, the use of one equivalence of **10** produced a yield

of 64% of **11b** and **12b** in the crude product after 24h (as shown by integration against an internal standard of CH_2Cl_2 prior to chromatography), although the isolated yield was lower (40% after chromatography). The proportion of the 5-*exo*-isomer was higher under these conditions but the 6- isomer was still evident (ratio of **11b**:**12b** = *ca.* 65:35). A final, shorter, reaction which duplicated exactly the reaction and work-up conditions described by Maier [5h at 80 C using $Pd(OAc)_2(PPh_3)_2$ and one molar equivalent of **10**], also gave a product containing both **11b** and **12b**. The ^1H NMR spectrum of the crude product was more complex and a yield of 40 ± 10 % was estimated using an internal standard (CH_2Cl_2). Following spectroscopic analysis, the crude products were chromatographed in every case and shown to contain both compounds. Clearly, $Pd(PPh_3)_4$ was the most effective catalyst in our hands and an excess of **10** improved the yields substantially and consistently.

As an additional check on the regioselectivity, we performed the reductive Heck procedure using iodobenzene **13**. The yield using $Pd(OAc)_2(PPh_3)_2$ was modest (Table 1) but the presence of both regioisomers in the crude product was again indicated by the presence of two pairs of signals in the δ 4.0 - 4.4 region corresponding to H_1 in **14** and **15**. Compound **15** was only partially separated from the mixture chromatographically but the secondary amines **16** and **17** were separated later.

Scheme 3



9b **14** R = CO_2Bu^t **15** R = CO_2Bu^t

16 R = H **17** R = H

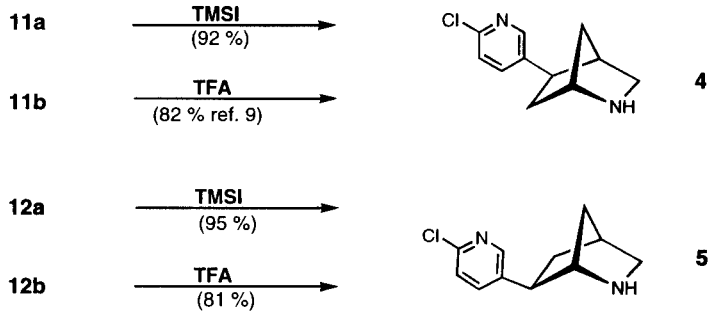
Table 1 Reductive Heck reactions on 2-azabicyclo[2.2.1]hept-5-ene derivatives 9a and 9b

Compound	Reaction conditions	Products and ratio[a]	yield[b]
9a	**10** (3 eq.), $Pd(PPh_3)_4$, piperidine, HCO_2H, DMF, 75 C, 21h	**11a : 12a** 60 : 40	95%
9b	**10** (3 eq.), $Pd(PPh_3)_4$, piperidine, HCO_2H, DMF, 75 C, 24h	**11b : 12b** 55 : 45	85%
9b	**10** (3 eq.), $Pd_2(dba)_3$, piperidine, HCO_2H, ethyl ethanoate, 75 C, 22h	**11b : 12b** 45 : 55	68%
9b	**10** (1 eq.), $Pd(OAc)_2(PPh_3)_2$, piperidine, HCO_2H, DMF, 80 C, 24h	**11b : 12b** *ca.* 65 : 35	40%
9b	**10** (1 eq.), $Pd(OAc)_2(PPh_3)_2$, piperidine, HCO_2H, DMF, 80 C, 5h[c]	**11b : 12b** complex[d]	46%[d]
9b	**13** (3 eq.), $Pd(OAc)_2(PPh_3)_2$, piperidine, HCO_2H, DMF, 80 C, 23h	**14 : 15** 55 : 45	47%

a. Ratios are measured from ^1H NMR spectra of crude reaction products and are approximate owing to peak overlap with minor by-products of the reaction work-up; they are considered accurate to *ca.* ± 5%.
b. Overall yields are of isolated material after chromatography, except for the fifth entry in the table.
c. Conditions as used in ref. 9. Conditions were not optimised in our work.
d. The ^1H NMR spectrum of the crude product was complex but showed clear evidence of both **11b** and **12b** (overall yield estimated by integration relative to an internal standard); **11b** and **12b** were also identified after chromatography.

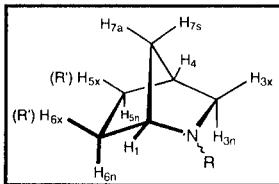
Deprotection of the nitrogen in both the **a** and **b** series gave the nor-compounds **4** and **5** (Scheme 4). Despite routine use of TMSI in other cases,[3] some contamination of **4** and **5** with the corresponding *N*-benzyl-derivatives was observed in early work when using this reagent to deprotect the *N*-benzyloxycarbonyl derivatives **11a** and **12a**. This occurred during work-up if samples containing the secondary amine were concentrated in the presence of benzyl iodide formed during the reaction. However, excellent yields and clean products were obtained if the reaction mixture was acidified prior to work-up. Deprotection of the *N*-BOC derivative **11b** with TFA to give **4** and of **12b** to give the secondary amine **5** was straightforward (Scheme 4). Deprotection of the phenyl analogues **14** and **15** completed the series. The secondary amines **16** and **17** were easier to separate chromatographically than the *N*-protected precursors.

Scheme 4



The novel 6-*exo*-chloropyridyl isomer **5** was examined extensively by NMR spectroscopy and diagnostic spin-spin interactions were identified with the aid of HH COSY experiments. The *exo*-location of the substituent on C-6 was confirmed by the fact that H_6 showed no significant interaction with H_1 but did show a cross-peak as a result of W-coupling to $H_{7\text{-syn}}$. The geminal protons on C-5 ($J_{5,5}$ = 12.5 Hz) were identified by vicinal coupling to H_4 ($J_{4,5\text{-exo}}$ = 3.5 Hz) and 'W'-coupling to $H_{3\text{-exo}}$ ($J_{3\text{-exo},5\text{-exo}}$ = 3.0 Hz). The location of the substituent at the 5- position in isomer **4** was confirmed by coupling between $H_{5\text{-endo}}$ and the proton $H_{4'}$ on the chloropyridyl ring. Ultimately, comparison with the 5-*endo*- and 6-*endo*- isomers **6** and **7** (prepared *via* an alternative route)[6] left no room for doubt regarding the *exo*- assignments. The spectra of compounds **4** and **5** were quite similar to each other and to the spectrum reported by Maier[9] for **4**. However, closer inspection of the latter revealed important differences between the claimed **4** and our *exo*-5- isomer and disclosed features in common with our *exo*-6- isomer **5** (detailed spectral analysis including J values is given in the experimental section). Investigation of the ^{13}C NMR spectra supported this reassignment (Table 3 below).

Table 2. Selected ^1H NMR data for compounds 11a, 12a, 4 and 5

	**11a** (5-*exo*- pyr-Cl; R = CO_2CH_2Ph)		**12a** (6-*exo*- pyr-Cl; R = CO_2CH_2Ph)		**4** (5-*exo*- pyr-Cl; R = H)		**5** (6-*exo*- pyr-Cl; R = H)	
	δ (ppm)		**δ (ppm)**		**δ (ppm)**		**δ (ppm)**	
H_1	**4.41**, 4.48	bs	**4.22**, 4.35	bs	3.63	bs	3.46	bs
H_{3x}	**3.43**, 3.45	dd	*ca. 3.4*	m	3.03	dd	2.99	bddd
H_{3n}	**3.28**, 3.24	d	**3.19**, 3.16	d	2.81	d	2.71	d
H_4	*2.68*	bs	*2.72*	bs	2.55	m	2.58	bs
H_{5x}	--		*ca. 1.9*	m	--		1.73	dddd
H_{5n}	*3.01*	dd	*ca. 2.0*	m	2.97	dd	1.96	ddd
H_{6x}	*ca. 1.6-1.8*	m	--		1.74	ddd	--	
H_{6n}	**2.28**, 2.37	dddd	*ca. 3.3*	m	2.09	ddd	2.96	bdd
H_{7a}	*ca. 1.6-1.8*	m	*1.57*	AB(b)	1.62	AB(b)	1.59 *	AB(b)
H_{7s}	*ca. 1.6-1.8*	m	*1.66*	AB(b)	1.55	AB(b)	1.52 *	AB(b)
$H_{2'}$	8.25	d	**8.26**, 8.18	d	8.27	d	8.24	d
$H_{5'}$	*7.27*	d	*ca. 7.2 - 7.4*	m	7.25	dd	7.25	d
$H_{4'}$	*7.48*	dd	*ca. 7.4 - 7.5*	dd	7.49	ddd #	7.46	dd
Benzylic CH_2	*5.15*	AB	*5.08-5.27*	AB				
Phenyl	*7.30-7.40*	m	*7.21-7.41*	m				

Figures in bold refer to the major rotamer, though ratios were close to 1:1 in most cases (see experimental section); figures in italics refer to overlapping peaks including signals due to two rotamers. * H_{7s} and H_{7a} are too close to assign with confidence. # Coupling between $H_{5\text{-endo}}$ and $H_{4'}$ was resolved in this case ($J_{4',5n}$ = 0.5 Hz) and was confirmed by selective spin-decoupling.

Just as the ^{1}H NMR spectra for the *N*-protected adducts were complicated by N-CO rotation, so the chemical shifts for the secondary amines were influenced by traces of acid and careful basification was necessary. However, the ^{13}C NMR shifts were relatively less sensitive and are listed in Table 3; assignments were checked with the aid of CH COSY spectra. The shifts for C_1, C_5, and C_6 were diagnostic for the 5- and 6-series and the agreement within each family is reassuring. Comparison of the ^{13}C spectra for compounds **4** & **5** with that for the claimed 5-*exo*- isomer *7*[9a] strengthens the suggestion that the data actually quoted for *7* fit the 6-*exo*- isomer **5**. Similar comparisons between the *N*-BOC-protected compounds **11b**, **12b**, and *6*[9a] again favour the 6-*exo*- assignment (**12b**) for *6*. We conclude that both 5- and 6- isomers were formed in the earlier work and that varying isomer ratios were present but were not recognised. Separation may have occurred at various stages since ratios are not easy to assess using ^{1}H NMR spectroscopy or TLC (see below). The isolation of a single 5-*exo*-*N*-tosyl derivative *8*[9a] prior to X-ray determination may have been the result of adventitious separation early or late in the sequence. However, it would not be possible to reproduce this work exactly.[9b]

Table 3. ^{13}C NMR data for 5- and 6-*exo*- derivatives

	5-Clpyr *N*-CO_2Bn **11a** *	5-Clpyr *N*-BOC **11b** *	5-Clpyr *N*-H **4** *	5-phenyl *N*-BOC **14** *	5- phenyl *N*-H **16** *	6-Clpyr *N*-CO_2Bn **12a** *	6-Clpyr *N*-BOC **12b** *	6-Clpyr *N*-H **5** *	6-phenyl *N*-BOC **15** *	6-phenyl *N*-H **17** *	Clpyr *N*-BOC *6* ‡	Clpyr *N*-H *7* ‡	phenyl *N*-BOC *10* ‡	phenyl *N*-H *11* ‡
C_1	56.9 57.1	56.2 57.2	56.4	56.3 57.3	56.1	61.2 61.8	60.6 62.3	61.3	61.2 62.6	61.7	60.5 62.2	61.2	62.2 63.6	62.6
C_3	53.4 53.5	53.1 53.6	51.4	53.3 53.8	52.1	52.4 52.5	52.0 52.6	50.2	52.2 52.7	53.4	52.0 52.5	50.3	53.1 53.7	52.5
C_4	43.3	43.4	42.3 #	43.0 43.6	42.9	37.0 37.6	37.1 37.6	36.8	37.0 37.5	37.0	37.0 37.6	36.8	39.7 # 39.9 #	37.7 #
C_5	42.6	42.6 42.7	42.9 #	45.4 45.6	46.1	34.6 # 35.0 #	34.6 # 34.8 #	36.3	34.5 # 34.7 #	36.6 #	34.4 † 34.7 †	36.4	38.0 # 38.5 #	37.3 #
C_6	39.4 39.9	39.5 39.9	39.7	39.5 39.9	41.4	45.2 45.9	45.2 45.8	46.3	48.3 49.0	50.8	45.1 45.7	46.7	46.4 46.6	46.6
C_7	35.3 35.8	35.2 35.7	35.6	35.2 35.7	35.6	34.4 #	33.9 # 34.5 #	35.5	34.0 # 34.4 #	35.4 #	34.4 † 34.7 †	35.4	35.0 # 35.3 #	36.3 #
$C_{2'}$	148.4 148.5	148.4 148.5	148.5	-	-	148.6 148.8	148.5 149.0	148.7	-	-	148.6	148.7	-	-
$C_{3'}$	139.3	139.5	139.4	-	-	137.0 137.2	137.2	138.0	-	-	138.0	138.4	-	-
$C_{4'}$	136.9	137.2	137.2	-	-	137.5 137.9	137.3 138.0	137.5	-	-	137.3 137.4	137.4	-	-
$C_{5'}$	124.0	124.0	124.0	-	-	124.0	123.9 124.0	123.9	-	-	124.0	123.9	-	-
$C_{6'}$	149.3	149.2	149.2	-	-	149.4	149.3	149.2	-	-	149.1	149.0	-	-
$PhCH_2$	66.6 66.8	-	-	-	-	66.7 66.9	-	-	-	-	-	-		
aryl	127.9 128.0 128.5 137.2	-	-	126.0 126.8 128.5 145.4	125.8 126.9 128.4 146.0	127.8 § 128.0 128.1 128.5 128.6 136.8	-	-	126.0 126.1 127.2 127.3 128.3 128.4 143.0 143.1	125.9 127.2 128.4 144.6	-	-	127.1 127.9 128.3 129.55 129.61 144.2 146.5	127.1 127.9 129.6 146.4
C-Me_3	-	79.4	-	79.0 79.2	-	-	79.4 79.7	-	79.1 79.3	-	79.4	-	79.9 80.2	
CH_3	-	28.5	-	28.6 28.7	-	-	28.55 28.62	-	29.0 29.1	-	28.46 28.53	-	29.6 29.9	
C=O	154.5 154.8	154.2 154.5	-	154.7	-	154.4 154.5	154.2 154.3	-	154.2 154.5	-	no data	-	no data	

* data from this work # values may be interchanged ‡ data and compound numbers from reference 9 - plausible assignments are given here but these are conjectural (^{13}C shifts are rounded to 1 decimal place except where 2 signals would otherwise appear to be identical) † signals for C_5 and C_7 cannot be assigned with confidence § The duplicate aryl carbon signals are not all resolved

In the case of the claimed 5-*exo*-phenyl compound ***10***,[9] the ^{1}H NMR spectrum also has more in common with our 6-*exo*-phenyl derivative **15** than with the 5- isomer (**14**) but some **14** may also be present. It is noteworthy that a minimal set of aryl signals (1 aryl C and 3 CH) is seen for the 5-*exo*-compound **14** since the phenyl is as far as is possible from the N-CO rotation; in contrast, the aryl signals in the 6-*exo*- isomer **15** are duplicated, as were the signals quoted earlier for ***10***. There are also suggestions of a mixture in the ^{13}C data for the deprotected amine ***11***[9] when compared with **16** and **17** but the agreement with **17** is closer (Table 3).

Certainly, the similarities between the complex ^{1}H NMR spectra for **11** & **12** (and **14** & **15**), together with the difficulty of separating the *N*-protected isomers, did not lead to simple analysis. Furthermore, we noted a substantially lower response of **12b** to PMA stain on TLC, making it more difficult to detect than **11b** under these conditions. At first sight, our isolated yields of **11b** (*ca.* 30 - 47%; c.f. 42% in reference 9) suggested to us that the isomer **12b** might have decomposed, or was not isolated, in the earlier work. However, the stability of the 6-*exo*- compound **12b** (eluted first from silica), together with the spectroscopic evidence, removed this possibility. The differences between our conclusions and those of the Maier group are explicable on the basis of revised spectroscopic assignments and a degree of incomplete or adventitious separation, unrecognised in the earlier work. We are confident that our results are reproducible and that the choice of catalyst is not a controlling factor. The lower yield in the case of $Pd_2(dba)_3$ is probably a consequence of the greater sensitivity of this reagent to steric interactions with the substrate. It is clear that the use of an excess of the aryl or chloropyridyl component leads to much-improved yields. In no case did we see evidence of *endo*- attack.

The variations in the **11b** : **12b** ratio in Table 1 show only a modest dependence on reaction conditions. There is no support for the claim of complete regioselectivity and no need to invoke stabilising ground-state interactions in the substrates. The results in both the chloropyridyl and phenyl series show that application of the reductive Heck procedure to the 2-azanorbornene ring system provides a practical route to both 5-*exo*- and 6-*exo*- regioisomers.

Acknowledgements

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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 (b.p. 40 - 60°) for chromatography. Formic acid was distilled from phthalic anhydride. Silica Gel 60 (Fischer) was used for column and chromatotron separations. 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.

_N_-(Benzyloxycarbonyl)-2-azabicyclo[2.2.1]hept-5-ene (9a).

This compound was prepared as described earlier.[10,13] δ_H (250 MHz, $CDCl_3$) (rotamer ratio *ca.* 53:47); signals common to both rotamers are listed in italics): *1.58* (bs, 2H, $H_{7s/7a}$), *2.71* (2 overlapping bd, 2H, H_{3n}), *3.19* (bs, 1H, H_4), *3.39* (dd, J = 9.5, 3.0 Hz, 1H, H_{3x}), [4.70 (s, major rotamer) and 4.80 (s, minor rotamer) 1H,

H_{1s},], *5.12* (m, 2H benzylic CH_2), *6.28* (bs, 1H, H_5), [6.38 (bs, major rotamer) and 6.28 (bs, minor rotamer) 1H, H_{6n},], *7.35* (bs, 5H, Ph). Many signals remained broad at this temperature/field but all the expected spin-spin interactions (including long-range 'W' interactions) were revealed by the HH COSY spectrum.

N-(Benzyloxycarbonyl)-5-*exo*-(6′-chloro-3′-pyridyl)-2-azabicyclo[2.2.1]heptane (11a)
N-(Benzyloxycarbonyl)-6-*exo*-(6′-chloro-3′-pyridyl)-2-azabicyclo[2.2.1]heptane (12a)

In a 2ml reactivial were placed **9a** (50mg, 0.218mmol), $Pd(PPh_3)_4$ (23mg, 0.020mmol), 2-chloro-5-iodopyridine **10**[7] (156mg, 0.654mmol), DMF (0.5 ml) and piperidine (75µl, 0.763mmol). To the stirred solution was added formic acid (25µl, 0.654mmol) and the solution was heated at 75°C for 21 hours. Dichloromethane (12ml) was added to the crude reaction mixture which was washed with water (2 x 1ml), dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure. The crude product was examined by ^{1}H NMR spectroscopy and shown to contain **11a** and **12a** in a ratio of 60:40 respectively. Purification by flash chromatography, eluting with 1:1 petroleum ether : diethyl ether yielded **12a** (R_f 0.17) and **11a** (R_f 0.10) (combined yield 71mg, 0.207mmol, 95%) as pale yellow oils. The sample of **11a** was contaminated with a small amount of **12a**. Complete separation was performed using a chromatotron; a sample of 363 mg of the chromatographed mixture gave pure samples of **11a** (255 mg) and **12a** (108 mg) as colourless oils using 1:1 diethyl ether: petroleum ether as solvent. Two rotamers were observed for each of the bicyclic urethanes; ^{1}H and ^{13}C NMR signals common to both rotamers are listed in italics.

11a: δ_H (300 MHz, $CDCl_3$) (rotamer ratio: 52:48) *major rotamer*: *1.62-1.82* (m, 3H. H_{7s}, H_{7a} & H_{6x}), 2.28 (dddd, 1H, $J_{6,6}$ = 13.5, $J_{5n,6n}$ = 9.0, $J_{6n,7s}$ = 1.5, $J_{1,6n}$ <1 Hz, H_{6n}), *2.68* (bs, 1H, H_4), *3.01* (dd, 1H, $J_{5n,6n}$ = 9.0, $J_{5n,6x}$ = 5.5 Hz, H_{5n}), 3.28 (bd, 1H, $J_{3,3}$ = 10.0 Hz, H_{3n}), 3.43 (dd, 1H, $J_{3,3}$ = 10.0, $J_{3x,4}$ = 3.5 Hz, H_{3x}), 4.41 (bs, 1H, H_1), *5.15* (AB, 2H, J = 13.0 Hz, benzylic), *7.30-7.40* (m, 5H, aryl), *7.27* (d, 1H, $J_{4',5'}$ = 8.0 Hz, $H_{5'}$), *7.48* (dd, 1H, $J_{4',5'}$ = 8.0, $J_{2',4'}$ = 3.0 Hz, $H_{4'}$), *8.25* (d, 1H, $J_{2',4'}$ = 3.0 Hz, $H_{2'}$); *minor rotamer: 1.62-1.82* (m, 3H. H_{7s}, H_{7a} & H_{6x}), 2.37 (dddd, $J_{6,6}$ = 13.5, $J_{5n,6}$ = 9.0, $J_{6n,7s}$ =1.5, $J_{1,6n}$ <1 Hz, 1H, H_{6n}), *2.68* (bs, 1H, H_4), *3.01* (dd, 1H, $J_{5n,6n}$ = 9.0, $J_{5n,6x}$ = 5.5 Hz, H_{5n}), 3.24 (bd, 1H, $J_{3,3}$ = 10.0 Hz, H_{3n}), 3.45 (dd, $J_{3,3}$ = 10.0, $J_{3x,4}$ = 3.5 Hz, 1H, H_{3x}), 4.48 (bs, 1H, H_1), *5.15* (AB, 2H, J = 13.0 Hz, benzylic), *7.30-7.40* (m, 5H, aryl), *7.27* (d, $J_{4',5'}$ = 8.0 Hz, 1H. $H_{5'}$), *7.48* (dd, $J_{4',5'}$ = 8.0, $J_{2',4'}$ = 3.0 Hz, 1H, $H_{4'}$), *8.25* (d, $J_{2',4'}$ = 3.0 Hz, 1H, $H_{2'}$); δ_c (62.90 MHz, $CDCl_3$): see Table 3; ν_{max} ($CDCl_3$): 2960w, 2240w, 1690s, 1430ss, 1560m, 1160w, 1105s, 925-890s, 760-695s cm^{-1}; $^m/_z$: 343 (MH^+), 365 (MNa^+); $C_{19}H_{20}N_2O_2Cl$ [MH^+] requires $^m/_z$ 343.12133; observed 343.12140

12a: δ_H (250 MHz, $CDCl_3$) (rotamer ratio: 53:47): *major rotamer: 1.57 & 1.66* (broad AB, 2H, $J_{7,7} \approx 11$ Hz, H_{7a} & H_{7s}), *ca. 1.9 & 2.0* (m, 2H, H_{5n} & H_{5x}), *2.72* (bs, 1H, H_4), 3.19 (d, 1H, $J_{3,3}$ = 10.0 Hz, H_{3n}), *ca. 3.3* (m, 1H, H_{6n}), *ca. 3.4* (m, 1H, H_{3x}), 4.22 (bs, 1H, H_1), *5.08-5.27* (AB, 2H, $J_{gem} \approx 12$ Hz, benzylic), *7.21-7.41* (m, 6H, aryl & $H_{5'}$), *ca.* 7.4 & 7.5 (dd, 1H, $J_{4',5'}$ = 8.5, $J_{2',4'}$ = 2.5 Hz, $H_{4'}$), 8.26 (d, $J_{2',4'}$ = 2.5 Hz, 1H, $H_{2'}$); *minor rotamer: 1.57 & 1.65* (broad AB, 2H, $J_{7,7} \approx 11$ Hz, H_{7a} & H_{7s}), ca. *1.9 & 2.0* (m, 2H, H_{5n} & H_{5x}), *2.72* (bs, 1H, H_4), 3.16 (d, 1H, $J_{3,3}$ = 10.0 Hz, H_{3n}), *ca. 3.3* (m, 1H, H_{6n}), *ca. 3.4* (m, 1H, H_{3x}), 4.35 (bs, 1H, H_1), *5.08-5.27* (AB, 2H, $J_{gem} \approx 12$ Hz, benzylic), *7.21-7.41* (m, 6H. aryl & $H_{5'}$), *ca.* 7.4 & 7.5 (dd, 1H, $J_{4',5'}$ = 8.5, $J_{2',4'}$ = 2.5 Hz, $H_{4'}$), 8.18 (d, 1H, $J_{2',4'}$ = 2.5 Hz, $H_{2'}$); δ_c (62.90 MHz, $CDCl_3$): see Table 3; ν_{max} ($CDCl_3$): 2950w, 2230w, 1685s, 1420s, 1360m, 1100s cm^{-1}; $^m/_z$: 343 (MH^+), 365 (MNa^+); $C_{19}H_{20}N_2O_2Cl$ [MH^+] requires $^m/_z$ 343.12133; observed 343.12142.

N-(*t*-Butyloxycarbonyl)-2-azabicyclo[2.2.1]hept-5-ene (9b)

The method used for preparation of **(9b)** was similar to that described in reference 9. For example, a sample of crude **(9b)** was obtained from cyclopentadiene (0.15g). Purification using a chromatotron, eluting with 9:1 petroleum ether : diethyl ether (R_f 0.10), yielded 0.14g of material contaminated with an impurity having the same polarity. Further purification by Kugelrohr distillation (50°C, 1 x 10^{-3} bar) afforded pure **9b** (93mg, 0.48mmol, 21%) as a colourless oil. Two rotamers were observed in a ratio of 56:44. ^{1}H NMR data were in agreement with earlier work.[9]

N-(*t*-Butyloxycarbonyl)-5-*exo*-(6′-chloro-3′-pyridyl)-2-azabicyclo[2.2.1]heptane (11b)
N-(*t*-Butyloxycarbonyl)-6-*exo*-(6′-chloro-3′-pyridyl)-2-azabicyclo[2.2.1]heptane (12b)
a. using $Pd(PPh_3)_4$ catalyst

In a 2ml reactivial were placed **9b** (26mg, 0.13mmol), $Pd(PPh_3)_4$ (15mg, 0.013mmol), 2-chloro-5-iodopyridine **10** (95mg, 0.40mmol), DMF (0.5 ml) and piperidine (46µl, 0.46mmol). To the stirred solution was added formic acid (15µl, 0.39mmol) and the solution heated at 75°C for 24 hours. Dichloromethane (7ml) was added to the reaction mixture which was washed with water (3 x 2ml), dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure. The crude product was examined by NMR and shown to contain **11b** and **12b** in a ratio of 55:45. The sample was purified by flash chromatography, eluting

with 7:3 petroleum ether : diethyl ether to yield **12b** (R_f 0.19, spot visualised by u.v., did not stain in PMA) and **11b** (R_f 0.11, spot visualised by u.v. and PMA) (combined yield 35mg, 0.112mmol, 85%) as colourless oils. Rotamer ratios for **11b** and **12b** were similar; signals common to both rotamers are shown in italics below.

11b: δ_H (250 MHz, $CDCl_3$) (rotamer ratio 55:45): *major rotamer*: *1.48* (s, 9H, Bu^t), *1.62* (half of broad AB, 1H, H_7) *1.64 - 1.80* (half of broad AB, 1H, H_7), *1.71* (ddd, 1H, $J_{6,6} \approx 12.5$ Hz, $J_{5n,6x} \approx 5.5$ Hz, $J_{1,6x} \approx 2.5$ Hz, H_{6x}), *2.2 - 2.4* (m, 1H, H_{6n}), *2.64* (bs, 1H, H_4), *3.00* (dd, 1H, $J_{5n,6n} = 9.0$ Hz, $J_{5n,6x} = 5.5$ Hz, H_{5n}), 3.20 (bd, 1H, $J_{3,3} = 10.0$ Hz, H_{3n}), *3.36* (bd, 1H, J = 10.0 Hz, H_{3x}), 4.28 (bs, 1H, H_1), *7.26* (d, 1H, $J_{4',5'} = 8.3$ Hz, $H_{5'}$), *7.48* (dd, 1H, $J_{4',5'} = 8.3$, $J_{2',4'} = 2.5$ Hz, $H_{4'}$), *8.26* (d, 1H, $J_{2',4'} = 2.5$ Hz, $H_{2'}$); *minor rotamer*: *1.48* (s, 9H, Bu^t), *1.62* (half of broad AB, 1H, H_7) *1.64 - 1.80* (m, 1H, H_7), *1.71* (ddd, 1H, $J_{6,6} \approx 12.5$ Hz, $J_{5n,6x} \approx 5.5$ Hz, $J_{1,6x} \approx 2.5$ Hz, H_{6x}), *2.2 -2.4* (m, 1H, H_{6n}), *2.64* (bs, 1H, H_4), *3.00* (dd, 1H, $J_{5n,6n} = 9.0$ Hz, $J_{5n,6x} = 5.5$ Hz, H_{5n}), 3.15 (bd, 1H, $J_{3,3} = 10.0$ Hz, H_{3n}), *3.36* (bd, 1H, J = 10.0 Hz, H_{3x}), 4.40 (bs, 1H, H_1), *7.26* (d, 1H, $J_{4',5'} = 8.3$ Hz, $H_{5'}$), *7.48* (dd, 1H, $J_{4',5'} = 8.3$, $J_{2',4'} = 2.5$ Hz, $H_{4'}$), *8.26* (d, 1H, $J_{2',4'} = 2.5$ Hz, $H_{2'}$); δc (100.61 MHz, $CDCl_3$): see Table 3; ν_{max} ($CDCl_3$): 2975w, 1675s, 1455m, 1410s, 1370m, 1255w, 1155m, 1105m, 900w, 830w; $^m/_z$: 309 (MH^+), 331 (MNa^+); $C_{16}H_{22}N_2O_2Cl$ [MH^+] requires $^m/_z$ 309.13698; observed 309.13694.

12b: δ_H (400 MHz, $CDCl_3$) (rotamer ratio 54:46): *major rotamer:* 1.52 (s, 9H, Bu^t), 1.64 & *ca.*1.53 (broad AB, 2H, $J_{7,7} = 11$ Hz, H_{7s}/H_{7a}), *1.86-2.04* (m, 2H, H_{5x} & H_{5n}), *2.69* (bs, 1H, H_4), 3.15 (d, 1H, $J_{3,3} = 9.5$ Hz, H_{3n}), 3.18 (bdd, 1H, $J_{5n,6n} \approx$ *ca.* 8.5, $J_{5x,6n} \approx 5.5$ Hz, H_{6n}), 3.33 (bddd, 1H, $J_{3,3} \approx 9.5$, $J_{3x,4x} \approx 2.5$, $J_{3x,5x} \approx 2.5$ Hz, H_{3x}), 4.10 (bs, 1H, H_1), 7.30 (d, 1H, $J_{4',5'} = 8.5$ Hz, $H_{5'}$), 7.47 (dd, 1H, $J_{4',5'} = 8.5$, $J_{2',4'} = 2.2$ Hz, $H_{4'}$), *8.27* (d, 1H, $J_{2',4'} = 2.2$ Hz, $H_{2'}$); *minor rotamer*: 1.49 (s, 9H, Bu^t),), 1.61 & *ca.*1.53 (AB, 2H, H_{7s}/H_{7a}), *1.86-2.04* (m, 2H, H_{5x} & H_{5n}), *2.69* (bs, 1H, H_4), 3.06 (d, 1H, J = 9.5 Hz, H_{3n}), 3.25 (bdd, 1H, $J_{5n,6n} \approx 8.5$ Hz, $J_{5x,6n} \approx 5.5$ Hz, H_{6n}), 3.31 (bddd, 1H, $J_{3,3} \approx 9.5$ Hz, $J_{3x,4x} \approx 2.5$ Hz, $J_{3x,5x} \approx 2.5$ Hz, H_{3x}), 4.31 (bs, 1H, H_1), 7.26 (d, 1H, $J_{4',5'} = 8.5$ Hz, $H_{5'}$), 7.54 (dd, 1H, $J_{4',5'} = 8.5$, $J_{2',4'} = 2.2$ Hz, $H_{4'}$), *8.27* (d, $J_{2',4'} = 2.2$ Hz, 1H, $H_{2'}$); δc (100.61 MHz, $CDCl_3$): see Table 3; ν_{max} ($CDCl_3$): 2970m, 2880w, 1675s, 1455m, 1410s, 1370m, 1250w, 1150s, 1105s, 870w, 830w, 700w; $^m/_z$: 309 (MH^+), 331 (MNa^+), $C_{16}H_{22}N_2O_2Cl$ [MH^+] requires $^m/_z$ 309.13698; observed 309.13696.

Comparative literature data for **11b**:[9] ^{1}H NMR δ_H (500 MHz, $CDCl_3$): 0.79-0.86 (m, 1H) [we assume that these signals correspond to petrol residues], 1.45, 1.47 (2s, 9H), 1.54-1.62 (m, 1H), 1.90-1.94 (m, 2H), 2.66 (s, br.,1H), 3.03-3.28 (m, 3H), 4.06, 4.26 (2s, 1H), 7.20-7.27 (m, 1H), 7.41-7.47 (m, 1H), 8.23 (d, J = 2.3 Hz, 1H). ^{13}C NMR δc (125 MHz, $CDCl_3$): 28.46, 28.53, 34.42, 34.67, 37.02, 37.58, 45.13, 45.72, 51.97, 52.52, 60.54, 62.21, 79.40, 124.01, 137.25, 137.35, 138.02, 148.63, 149.07. Some variations in chemical shift may be due to changes of concentration and/or pH; even traces of acid give rise to downfield shifts as a result of *N*-protonation. Nevertheless, some differences of interpretation remain and the quoted signals at δ 4.06 and 4.26[9] actually correspond quite closely to our shifts for H_1 in the two rotamers of **12b**, rather than **11b**.

b. Synthesis of 11b and 12b using $Pd_2(dba)_3$ as catalyst.

In a 2ml reactivial were placed **9b** (21mg, 0.11mmol), $Pd_2(dba)_3$ (11mg, 0.011mmol), 2-chloro-5-iodopyridine **10** (79mg, 0.33mmol), ethyl ethanoate (0.5 ml) and piperidine (38μl, 0.39mmol). To the stirred solution was added formic acid (13μl, 0.33mmol) and the solution heated at 75°C for 21.5 hours. Work-up as described above gave a sample containing **11b** and **12b** in a ratio of 45:55 (NMR). Purification by flash chromatography, eluting with 7:3 petroleum ether : diethyl ether yielded **12b** (12.9 mg; R_f 0.19, visualised by u.v., did not stain in PMA; contaminated with **11b** 1.7 mg) and **11b** (8.6 mg; R_f 0.11, spot visualised both by u.v. and PMA) (combined yield 23mg, 0.075mmol, 68%) as colourless oils.

c. Synthesis of 11b and 12b using $Pd(OAc)_2(PPh_3)_2$ as catalyst

In a 2ml reactivial were placed **9b** (40mg, 0.20mmol), $Pd(OAc)_2$ (2.4mg, 0.01mmol), triphenylphosphine (6.0mg, 0.021mmol), 2-chloro-5-iodopyridine (48mg, 0.20mmol), DMF (0.6 ml) and piperidine (64μL, 0.65mmol). To the slightly basic, stirred solution was added formic acid (21μL, 0.55mmol) and the solution was heated at 80°C for 5 hours. Work-up as above (using ethyl ethanoate as solvent) gave crude product (46% relative to an internal standard) showing a complex ^{1}H NMR spectrum. Chromatography (7:3 petroleum ether : diethyl ether) yielded a mixture of **11b** and **12b** (15.5mg, 0.05mmol, 25%).

A similar small-scale reaction (58 mg of **10**) using identical ratios of reagents but a longer reaction time (24h) gave a mixture of **11b** and **12b** (ratio 65:35) in 40% yield after chromatography.

***N*-(*t*-Butyloxycarbonyl)-5-*exo*-phenyl-2-azabicyclo[2.2.1]heptane (14)**
***N*-(*t*-Butyloxycarbonyl)-6-*exo*-phenyl-2-azabicyclo[2.2.1]heptane (15)**

In a 2ml reactivial were placed **9b** (31mg, 0.16mmol), $Pd(OAc)_2$ (5mg, 0.02mmol), triphenylphosphine (10mg, 0.04mmol), benzyl iodide (53μL, 0.48mmol), DMF (0.5 ml) and piperidine (55μL, 0.56mmol). To the

slightly basic, stirred solution was added formic acid (18μL, 0.48mmol) and the solution was heated at 75°C for 23 hours. The usual work-up gave a sample which was purified by flash chromatography using a chromatotron, eluting with 9.5: 0.5 petroleum ether : diethyl ether to give **15** (R_f 0.1, spot visualised by u.v., did not stain in PMA) (7.0mg, 0.026mmol) and a mixture of the two regioisomers (compound **14** had R_f 0.05, spot visualised both by u.v. and PMA) (13.5mg, 0.075mmol) as pale yellow oils in a yield of 47% and a ratio of 55:45 (**14**:**15**). ^{13}C NMR data for **14** and **15** are summarised in Table 3. Rotamer ratios differed for **14** and **15**; signals common to both rotamers are shown in italics below.

14: δ_H (400 MHz, $CDCl_3$) (rotamer ratio 35:65): *major rotamer:* 1.52 (s, 9H, Bu^t), *1.60-1.73* (m, 2H, H_{7a}/H_{7s}), *1.78* (m, 1H H_{6x}), 2.21 (dd, 1H, $J_{6,6}$ = 12.5, $J_{5n,6n}$ = 9.0 Hz, H_{6n}), *2.64* (bs, 1H, H_4), *3.01* (dd, 1H, $J_{5n,6n}$ = 9.0, $J_{5n,6x}$ = 5.5 Hz, H_{5n}), 3.12, 3.19 (cannot determine which is major rotamer) (d, 1H, $J_{3,3}$ = 10.0 Hz, H_{3n}), *3.34* (dd, 1H, $J_{3,3}$ = 10.0, $J_{3x,4}$ = 3.0 Hz, H_{3x}), 4.24 (bs, 1H, H_1), *7.16-7.35* (m, 5H, aryl); *minor rotamer:* 1.48 (s, 9H, Bu^t), *1.60-1.73* (m, 2H, H_{7a}/H_{7s}), *1.78* (m, 1H H_{6x}), 2.29 (dd, 1H, $J_{6,6}$ = 12.5, $J_{5n,6n}$ = 9.0 Hz, H_{6n}), *2.64* (bs, 1H, H_4), *3.01* (dd, 1H, $J_{5n,6n}$ = 9.0, $J_{5n,6x}$ = 5.5 Hz, H_{5n}), 3.12, 3.19 (cannot determine which is major rotamer) (d, 1H, $J_{3,3}$ = 10.0 Hz, H_{3n}), *3.34* (dd, 1H, $J_{3,3}$ = 10.0, $J_{3x,4}$ = 3.0 Hz, H_{3x}), 4.37 (bs, 1H, H_1), *7.16-7.35* (m, 5H, aryl). $C_{17}H_{24}NO_2$ [MH^+] requires $^m/_z$ 274.18070; observed 274.18068.

15: δ_H (400 MHz, $CDCl_3$) (rotamer ratio 45:55,): *major rotamer:* 1.52 (s, 9H, Bu^t), *1.55-1.63* (m, 2H, H_{7s}/H_{7a}), *1.90* (ddd, 1H, $J_{5,5}$ = 13.0, $J_{5n,6n}$ =8.5, $J_{5n,7s}$ = 2.0 Hz, H_{5n}), *1.99* (m, 1H, H_{5x}), *2.64* (bs, 1H, H_4), 3.12 (d, 1H, $J_{3,3}$ = 9.5 Hz, H_{3n}), 3.16 (dd, 1H, $J_{5n,6n}$ = 8.5, $J_{5x,6n}$ = 5.5 Hz, H_{6n}), 3.30 (ddd, 1H, $J_{3,3}$ = 9.5, $J_{3x,4}$ = 2.5, $J_{3x,5x}$ = 2.5 Hz, H_{3x}), 4.13 (bs, 1H, H_1), *7.15-7.35* (m, 5H, aryl); *minor rotamer:* 1.48 (s, 9H, Bu^t), *1.55-1.63* (m, 2H, H_{7s}/H_{7a}), *1.90* (ddd, 1H, $J_{5,5}$ = 13.0, $J_{5n,6n}$ =8.5, $J_{5n,7s}$ = 2.0 Hz, H_{5n}), *1.99* (m, 1H, H_{5x}), *2.64* (bs, 1H, H_4), 3.03 (d, 1H, $J_{3,3}$ = 9.5 Hz, H_{3n}), 3.27 (dd, 1H, $J_{5n,6n}$ = 8.5, $J_{5x,6n}$ = 5.5 Hz, H_{6n}), 3.27 (ddd, 1H, $J_{3,3}$ = 9.5, $J_{3x,4}$ = 2.5, $J_{3x,5x}$ = 2.5 Hz, H_{3x}), 4.31 (bs, 1H, H_1), *7.15-7.35* (m, 5H, aryl).

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

A solution of **11a** (20mg, 0.058mmol) in CH_2Cl_2 (2ml) was stirred in a round-bottom flask under a nitrogen atmosphere. TMSI (41μl, 0.29mmol) was added and the solution stirred for 7 mins at which point HBF_4.diethyl ether complex (43μl, 0.29mmol) was added. The reaction was quenched with water (0.5ml), and the solvent removed under reduced pressure. Petroleum ether (1ml) was added to the residue and the amine salt extracted with water (3 x 3ml). The aqueous layers were combined and basified with ammonia gas. The water was removed under reduced pressure and the residue extracted with chloroform (3 x 3ml), the extracts combined, dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography, eluting with 9:1 dichloromethane:methanol, saturated with ammonia gas (R_f 0.42) to yield the free amine **4** (11mg, 0.052mmol, 92%) as a pale yellow oil. δ_H (400 MHz, $CDCl_3$): 1.55 (half of broad AB, 1H, $J_{7,7} \approx$ 10.5 Hz, H_{7s}), 1.62 (half of broad AB, 1H, $J_{7,7} \approx$ 10.5 Hz, H_{7a}), 1.74 (ddd, 1H, $J_{6,6}$ = 13.5, $J_{5n,6x}$ = 5.5, $J_{1,6x}$ = 3.0 Hz, H_{6x}), 1.96 (bs, NH; variable shift), 2.09 (ddd, 1H, $J_{6,6}$ = 13.5, $J_{5n,6n}$ = 9.0, $J_{6n,7s}$ = 1.5 Hz, H_{6n}), 2.55 (m, 1H, H_4), 2.81 (d, 1H, $J_{3,3}$ = 10.0 Hz, H_{3n}), 2.97 (dd, 1H, $J_{5n,6n}$ = 9.0, $J_{5n,6x}$ = 5.5 Hz, H_{5n}), 3.03 (dd, 1H, $J_{3,3}$ = 10.0, $J_{3x,4}$ = 3.5 Hz, H_{3x}), 3.63 (bs, 1H, H_1), 7.25 (dd, 1H, $J_{4',5'}$ = 8.0, $J_{2',5'}$ = 0.3 Hz, $H_{5'}$), 7.49 (ddd, 1H, $J_{4',5'}$ = 8.0, $J_{2',4'}$ = 3.0, $J_{4',5n}$ = 0.5 Hz, $H_{4'}$), 8.27 (bd, 1H, $J_{2',4'}$ = 3.0 Hz, $H_{2'}$); δ_C (100.61 MHz, $CDCl_3$): see Table 3; ν_{max} ($CDCl_3$): 2980s, 2220w, 1560w, 1455m, 1260s, 1090s, 1010s, 800s cm^{-1}; $^m/_z$: 209 (MH^+); $C_{11}H_{14}N_2Cl$ [MH^+] requires $^m/_z$ 209.08455; observed 209.08459

Comparative literature data for **4**:[9] NMR δ_H (200 MHz, $CDCl_3$): 1.47-1.57 (m, 2H), 1.64-1.72 (m, 1H), 1.86-1.95 (m, 1H), 2.23 (s, br.,1H), 2.54 (s, 1H), 2.73 (d, J = 9.5 Hz, 1H), 2.95-2.99 (m, 1H), 3.02-3.06 (m, 1H), 3.52 (s, 1H), 7.23 (d, 1H, J = 8.2 Hz,), 7.45 (dd, 1H, J = 2.6, 5.7 Hz), 8.24 (d, 1H, J = 2.5 Hz). ^{13}C NMR δ_C (50 MHz, $CDCl_3$): 35.41, 36.35, 36.82, 46.71, 50.31, 61.17, 123.86, 137.37, 138.35, 148.70, 149.02.

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

A solution of the *N*-benzyloxycarbonyl-protected amine **12a** (8.0mg, 0.023mmol) in CH_2Cl_2 (2ml) was treated with TMSI (16μl, 0.12mmol) as described for conversion of **11a** into **4** above. The crude product was purified by flash chromatography, eluting with 19:1 dichloromethane:methanol saturated with ammonia gas (R_f 0.28), to yield the free amine **5** (4.6mg, 0.022mmol, 95%) as a pale yellow oil. δ_H (400 MHz, $CDCl_3$): 1.52 & 1.59 (broad AB, 2H, $J_{7,7}$ = 13 Hz, H_{7s}/H_{7a}), 1.73 (dddd, 1H, $J_{5,5}$ = 12.5, $J_{5x,6n}$ = 6.0, $J_{4,5x}$ = 3.5, $J_{3x,5x}$ = 3.0 Hz, H_{5x}), 1.82 (bs, NH), 1.96 (ddd, 1H, $J_{5,5}$ = 12.5, $J_{5n,6n}$ = 9.0, $J_{5n,7s}$ = 2.0 Hz, H_{5n}), 2.58 (bs, 1H, H_4), 2.71 (d, 1H, $J_{3,3}$ = 10 Hz, H_{3n}), 2.99 (bddd, 1H, $J_{3,3}$ = 10, $J_{3x,4}$ = 3.5, $J_{3x,5x}$ = 3.0 Hz, H_{3x}), 2.96 (bdd, 1H, $J_{5n,6n}$ = 9.0, $J_{5x,6n}$ = 6.0 Hz, H_{6n}), 3.46 (bs, 1H, H_1), 7.25 (d, 1H, $J_{4',5'}$ = 8.5 Hz, $H_{5'}$), 7.46 (dd, 1H, $J_{4',5'}$ = 8.5, $J_{2',4'}$ = 2.5 Hz, $H_{4'}$), 8.24 (d, 1H, $J_{2',4'}$ = 2.5 Hz, $H_{2'}$); δ_C (100.61 MHz, $CDCl_3$): 35.9 (C_7), 36.7 (C_5), 37.2 (C_4), 46.7 (C_6), 50.6 (C_3), 61.7 (C_1), 124.4 ($C_{5'}$), 137.9 ($C_{4'}$), 138.4 ($C_{3'}$), 149.1 ($C_{2'}$), 149.6 ($C_{6'}$); ν_{max} ($CDCl_3$): 2980s, 2220m,

1560m, 1460s, 1380m, 1100s, 900m cm^{-1}; $^m/_z$: 209 (MH^+); $C_{11}H_{14}N_2Cl$ [MH^+] requires $^m/_z$ 209.08455; observed 209.08450.

Deprotection of the *N*-BOC analogue **12b** with TFA (method below) also gave **5** in 81% yield.

***exo*-5-Phenyl-2-azabicyclo[2.2.1]heptane (16) and *exo*-6-phenyl-2-azabicyclo[2.2.1]heptane (17)**

A mixture of **14** and **15** (13.5mg, 0.0494mmol) was stirred in dichloromethane (0.5ml) under a nitrogen atmosphere. TFA (50μL, 0.66mmol) was added and left for 4 hours. The mixture was quenched with sodium hydrogen carbonate soln. (0.5ml) and basified to pH 10. After extraction with dichloromethane (4 x 2ml), the organic layers were combined, dried with anhydrous magnesium sulphate and the solvent removed under reduced pressure. Separation by flash chromatography, eluting with dichloromethane : methanol (9.5:0.5) saturated with ammonia gave **17** (3.6mg, 0.021mmol) (r.f. 0.22) and **16** (4.2mg, 0.024mmol) (r.f. 0.13) as pale yellow oils (combined yield 92%). Separate conversion of pure **15** into **17** gave a similar yield.

16: δ_H (250 MHz, $CDCl_3$): 1.51 (half of broad AB, 1H, $J_{7,7} \approx 10.5$ Hz, H_{7s}), 1.70 (half of broad AB, 1H, $J_{7,7} \approx 10.5$ Hz, H_{7a}), 1.82 (ddd, 1H, $J_{6,6} = 13.0$, $J_{5n,6x} = 5.0$, $J_{1,6x} = 3.0$ Hz, H_{6x}), 2.05 (bs, NH; variable shift), 2.05 (m, 1H, H_{6n}), 2.58 (bs, 1H, H_4), 2.80 (d, 1H, $J_{3,3} = 10.0$ Hz, H_{3n}), 2.98 (dd, 1H, $J_{5n,6n} = 9.0$, $J_{5n,6x} = 5.0$ Hz, H_{5n}), 3.00 (dd, 1H, $J_{3,3} = 10.0$, $J_{3x,4} = 3.5$ Hz, H_{3x}), 3.60 (bs, 1H, H_1), 7.14 - 7.34 (m, 5H, phenyl); δ_C data in table 3; $^m/_z$: 173 (M^+, E.I.); $C_{12}H_{15}N$ [M^+] requires $^m/_z$ 173.12045; observed 173.12045.

17: δ_H (250 MHz, $CDCl_3$): 1.46 (ddddd, 1H, $J_{7,7} = 10.5$, $J_{1,7s} \approx 1.5$, $J_{4,7s} \approx 1.5$, $J_{5n,7s} \approx 2.5$, $J_{6n,7s} \approx 1.5$ Hz, H_{7s}), 1.67 (half of broad AB, 1H, $J_{7,7} = 10.5$ Hz, H_{7a}), 1.82 (dddd, 1H, $J_{5,5} = 13.0$, $J_{5x,6n} = 6.0$, $J_{4,5x} = 3.5$, $J_{3x,5x} = 3.0$ Hz, H_{5x}), 1.69 (bs, NH), 1.91 (ddd, 1H, $J_{5,5} = 13.0$, $J_{5n,6n} = 9.0$, $J_{5n,7s} \approx 2.5$ Hz, H_{5n}), 2.53 (bs, 1H, H_4), 2.70 (d, 1H, $J_{3,3} = 9.5$ Hz, H_{3n}), 2.95 (ddd, 1H, $J_{3,3} = 9.5$, $J_{3x,4} = 3.0$, $J_{3x,5x} = 3.0$ Hz, H_{3x}), 3.00 (dd, 1H, $J_{5n,6n} = 9.0$, $J_{5x,6n} = 6.0$ Hz, H_{6n}), 3.48 (bs, 1H, H_1), 7.13 - 7.34 (m, 5H, phenyl); δ_C data in table 3; $^m/_z$: 173 (M^+, E.I); $C_{12}H_{15}N$ [M^+] requires $^m/_z$ 173.12045; observed 173.12044.

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