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Synthesis of 5- and 6- chloropyridyl-substituted 2-azabicyclo[2.2.1]heptanes; novel epibatidine isomers

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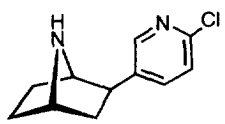
Abstract

A synthetic route to the epibatidine analogue *endo*-5-(6-chloro-3-pyridyl)-2-azabicyclo[2.2.1]heptane and the corresponding *endo*-6- isomer is described, starting from a readily-available 2-azabicyclo[2.2.1]hept-5-ene derivative. Both the *exo*-5- and *exo*-6- compounds are also shown to be accessible from the same substrate using reductive Heck chemistry.

The alkaloid epibatidine **1**, isolated in 1992, has excited sufficient attention to have stimulated approximately 30 syntheses to date [1]. The very high analgesic activity of **1** is a consequence of its high potency as an agonist at nicotinic acetylcholine receptors (nAChRs) in the central and autonomic nervous system [2]. However, the potential benefit of this high activity is offset by the toxicity of **1** and the search continues for compounds having high antinociceptive activity but lower toxicity. With this in mind, we have reported the synthesis of homoepibatidine **2** [3], a compound which retains the very high activity of **1** in contrast with other tropane-based isomers such as the 2-chloropyridyl derivative [4] and the higher homologue bis-homoepibatidine [3], which presumably have a less favourable orientation of the two amine nitrogens. We have resolved **2** and find the same, intriguing similarity between the activity of the two enantiomers which is a feature of epibatidine itself. We reasoned that greater discrimination between enantiomers at the receptor would be likely in analogues having the secondary nitrogen placed asymmetrically in the azabicyclic framework and that higher nAChR sub-type selectivity [2] might then follow.



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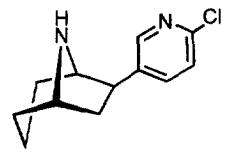

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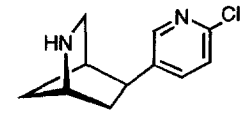

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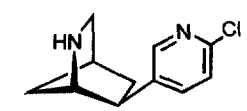

4

We therefore chose as targets the isomers **3** and **4**, based on the 2-azabicyclo-[2.2.1]heptane ring system, having established that the *N-N* distances were within the limits imposed by current models of the nAChR pharmacophore [5]. *N-N* Distances estimated from simple molecular mechanics calculations are shown in Table 1. Activity has been shown to fall off rapidly if the *N-N* distance is substantially less, or greater, than *ca.* 5.5 Å [5].

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Table 1. Calculated *N-N* distances (values from DTMM3)

compound	in minimum energy conformation (Å)	after 180° rotation about the C-pyridyl bond (Å)
(1)	4.3	5.5*
(2)	4.5	5.5
(3)	5.5	5.4
(4)	4.2	5.0

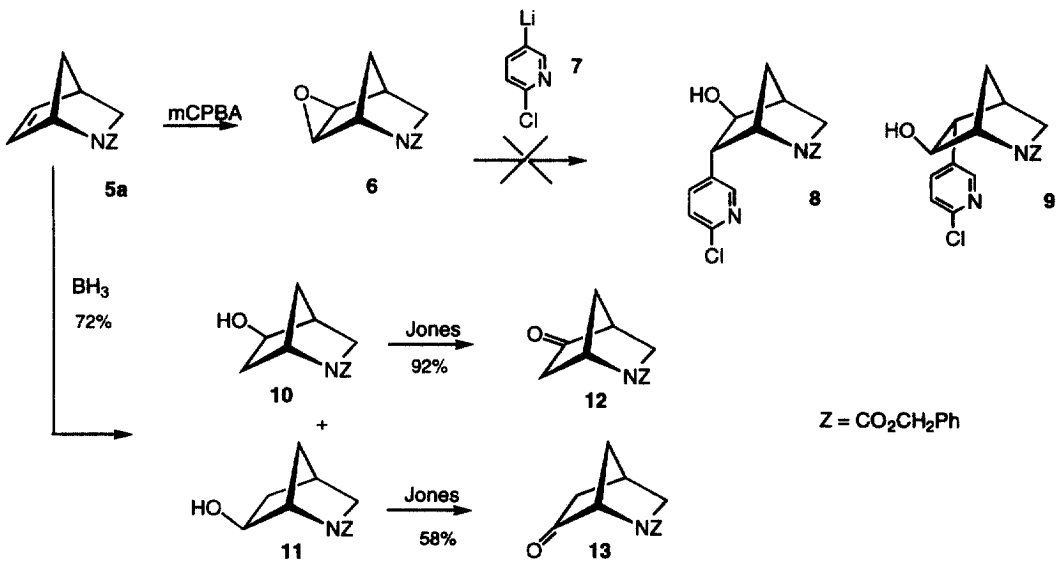
Note: both conformations have very similar energies using DTMM; figures are for guidance only. * compare the value of 5.51Å for the minimum energy: [5]

The 5-*endo*- isomer **3** appears a very attractive candidate based on a comparison with **1** and **2**, the two azabicylic compounds which show the highest activity to date. Compound **3** also offers the unique possibility that, based simply on *N-N* distances, both minimum energy rotamers might offer an acceptable fit. Clearly, other factors are likely to play a part [5] but the 2-azabicyclo[2.2.1]heptane framework provides a useful rigid 'test-bed' to aid definition of the pharmacophore. The estimated *N-N* distance for isomer **4** should still place it amongst a group of compounds having significant activity, certainly greater than that of nicotine itself [5].

We describe here a simple route to both **3** and **4** [6,7] which is summarised in Schemes 1 and 2. The 2-azabicyclo[2.2.1]heptane derivatives are drawn in a more conventional format to emphasise the *exo- / endo-* relationships and *exo-* facial selectivity in the reactions.

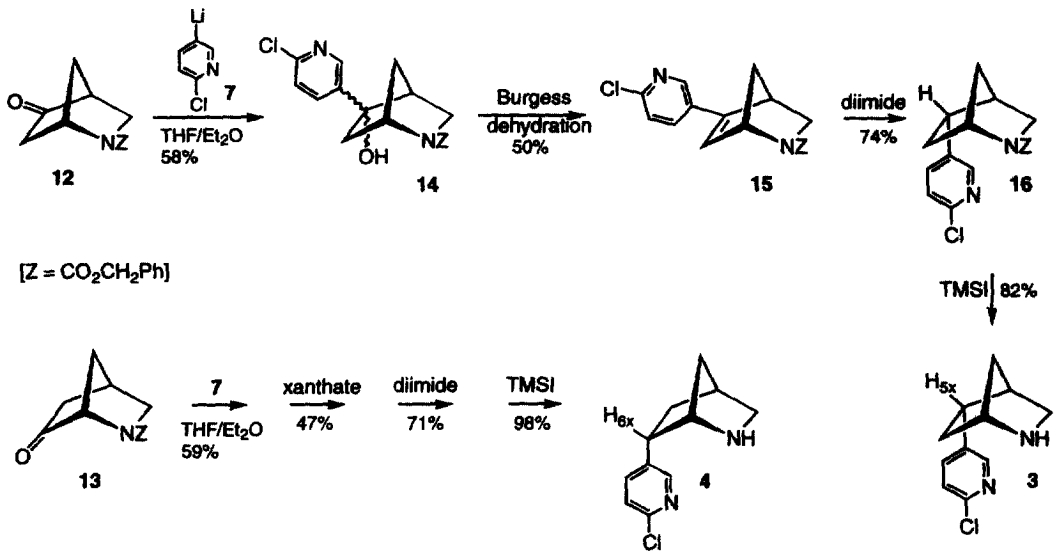
Initial attempts to open the epoxide **6** with the chloropyridyl-lithium reagent **7** (from 2-chloro-5-iodopyridine [8] and Bu^{n}Li in THF/Et_2O) were unsuccessful; attempts using alternative nucleophiles including cuprates are under way. Building on earlier work on the oxymercuration of **5a** and derivatives [9], we converted **5a** into the alcohols **10** and **11** using diborane (ratio of **10** : **11** = 36 : 64). Chromatographic separation was followed by Jones oxidation of each alcohol to give the key N-protected amino-ketones **12** and **13**, respectively (Scheme 1) [10].

Scheme 1



Treatment of the ketone **12** with **7** gave the chloropyridyl derivatives **14** (ratio of stereoisomers not determined) which was dehydrated using Burgess reagent to **15**. The required *endo-* configuration at C-5 was then obtained by reduction using diimide which occurred cleanly from the *exo-* face. The use of hydrogen and a palladium catalyst usually led to some dechlorination in our hands. *N*-Deprotection with TMSI gave **3** in good yield.

Scheme 2

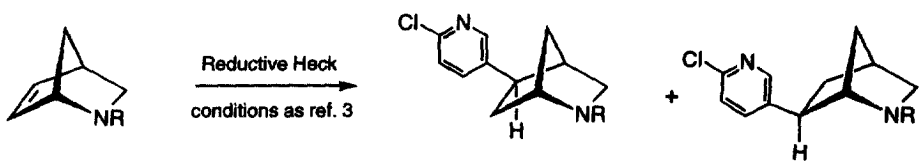


Similar treatment of the ketone **13** provided the 6-*endo-* isomer **4**. In this case, the dehydration step was accomplished using thermal decomposition of the xanthate ester [11].

Regio- and stereochemical assignments followed from full analysis of the ^{1}H NMR spectra. For example, selective spin-decoupling experiments allowed extraction of J values from the complex signal for the proton H_{5x} in **3**: $J_{5x,6x} = 11.5$, $J_{5x,6n} = 5.5$ Hz and, significantly, $J_{4,5x}$ = *ca.* 4 and $J_{3x,5x}$ = *ca.* 2 Hz (W-coupling) [12]. The corresponding proton H_{6x} in **4** appeared as a (doublet)^3 with $J_{5x,6x} = 12.0$, $J_{5n,6x} = 5.5$, and $J_{1,6x} = 2.5$ Hz. The low-field position of the α-*N* bridgehead proton H_1 distinguished it from H_4 in each case [12]. Comparative spectral analysis for all four isomers (c.f. Scheme 3) secured the assignments unambiguously.

The two *exo-* isomers **17** and **18** (Scheme 3) were obtained using 2-chloro-5-iodo-pyridine and standard conditions for the reductive Heck reaction (conditions employed in the synthesis of epibatidine [8], and homoepibatidine [3]).

Scheme 3



5a R = CO_2CH_2Ph
5b R = CO_2Bu^t

17a,b
19 R = H

18a,b
20 R = H

We obtained **17b** and **18b** (each as a pair of rotamers about the N-CO bond) in a ratio of *ca.* 55 : 45 respectively (85% isolated yield) using the *N*-BOC-protected derivative **5b** and $Pd(PPh_3)_4$ as catalyst [13]. A similar ratio was obtained using $Pd_2(dba)_3$ and also starting with the N-benzyloxycarbonyl-protected substrate **5a** (60% yield using $Pd(PPh_3)_4$). Following separation of **17** and **18** on silica and efficient deprotection (with TMSI for **17a** and **18a** and with TFA for **17b** and **18b**), the two epibatidine isomers **19** and **20** were isolated in high overall yields. These results contrast with the very recent claim [14] that reductive Heck chemistry on **5b** proceeds with complete regioselectivity to yield only the 5-*exo*- product.

Resolution of **3** and **4** and investigations into the biological activity of **3**, **4**, **19**, and **20** will be reported in due course.

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References and Notes

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