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Approaches to Syn-7-Substituted 2-Azanorbornanes as Potential Nicotinic Agonists; Synthesis of *syn*- and *anti*-Isoepibatidine

John R. Malpass,* Sandeep Handa, and Richard White

Department of Chemistry, University of Leicester, Leicester LE1 7RH, United Kingdom

jrm@le.ac.uk

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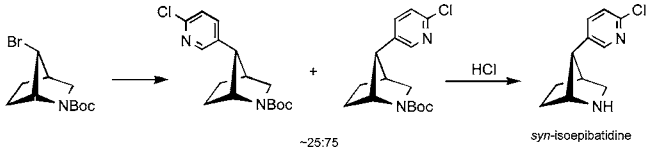
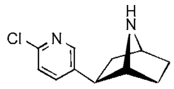
ABSTRACT

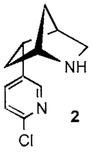


Coupling of *N*-Boc-7-bromo-2-azabicyclo[2.2.1]heptane with aryl and pyridyl boronic acids incorporates aryl and heterocyclic substituents at the 7-position and leads to a preference for syn over anti stereoisomers. Incorporation of a chloropyridyl group followed by N-deprotection gives *syn*-isoepibatidine. Facial selectivity in attack on 7-keto-2-azanorbornanes depends heavily on the N-protecting group leading to the first *syn*-7-hydroxy-2-azabicyclo[2.2.1]heptane derivative.

The discovery of epibatidine **1**, a naturally occurring derivative of the 7-azabicyclo[2.2.1]heptane (7-azanorbornane) ring system that has unusually high activity at the nicotinic acetylcholine receptor (nAChR),[1] has stimulated intense synthetic activity. The search for therapeutically useful compounds having higher nAChR subtype selectivity and lower toxicity has encouraged the synthesis of a wide range of analogues and isomers.[2]



1 epibatidine



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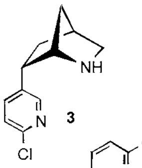

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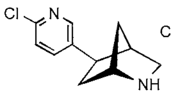

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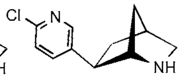

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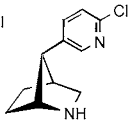
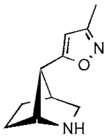


6 isoepibatidine



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We have been intrigued by the potential of the elusive isomer isoepibatidine **6** in which all the key features of **1** are retained but the positions of the bicyclic nitrogen and the heterocycle are simply reversed. Other epibatidine isomers **2** and **3** (having the heterocycle attached to the 5- and 6-*endo* positions of 2-azanorbornane)[3a] retain high nAChR affinity, as do many homologues and analogues.[4]

The *exo* orientation of the heterocycle in the isomers **4** and **5** leads to a much greater N−N distance and reduced nAChR affinity as anticipated.[3a]

We have recently reported the synthesis of novel syn- and anti-7-derivatives of 2-azanorbornane, including *syn*-isoepiboxidine **7** (and the anti stereoisomer) via the corre-

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(1) Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475−3478. For leading references to epibatidine analogue synthesis, see: Carroll, F. I.; Lee, J. R.; Navarro, H. A.; Ma, W.; Brieaddy, L. E.; Abraham, P.; Damaj, M. I.; Martin, B. R. *J. Med. Chem.* **2002**, *45*, 4755−4761.

(2) For reviews and leading references to analogues and to nAChR affinities, see: Carroll, F. I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1889−1896. Bunnelle, W. H.; Dart, M. J.; Schrimpf, M. R. *Curr. Top. Med. Chem.* **2004**, *4*, 299−334.

(3) See: (a) Cox, C. D.; Malpass, J. R.; Rosen, A.; Gordon, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2372−2379 (**2**−**5**). (b) Hodgson, D. M.; Maxwell, C. R.; Wisedale, R.; Matthews, I. R.; Carpenter, K. J.; Dickenson, A. H.; Wonnacott, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3150−3158 (**3**).

(4) Malpass, J. R.; Hemmings, D. A.; Wallis, A. L.; Fletcher, S.; Patel, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1044−1050. Malpass, J. R.; Patel, A. B.; Davies, J. W.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 9348−9355.

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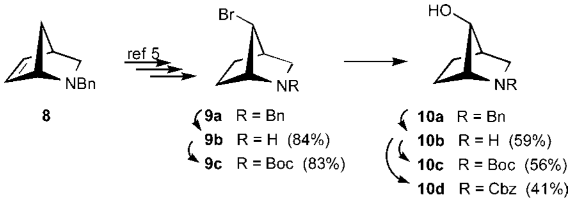
sponding 7-ethoxycarbonyl derivatives.[5] Interest in 7-substituted 2-azanorbornanes has also been extended to their use as precursors to α-kainic acids.[6] We now report the first successful direct attachment of aryl and heterocyclic rings to the 7-position of 2-azanorbornanes via metal-catalyzed coupling reactions, opening the way to *syn*-isoepibatidine **6** and a wider range of analogues.[2,7] Additionally, further investigation of the manipulation of syn/anti stereochemistry in 7-substituted 2-azanorbornanes has allowed us to resolve a disagreement over the stereochemical assignment of the 7-hydroxy compounds unambiguously.

The key anti-7-substituted intermediate **9a** is available from *N*-benzyl-2-azanorborn-5-ene **8** as described earlier.[5] The conversion of **9a** into **10a** and modification to give the *N*-Boc and *N*-Cbz examples **10c** and **10d** was achieved using standard methods[5] (Scheme 1).

Scheme 1



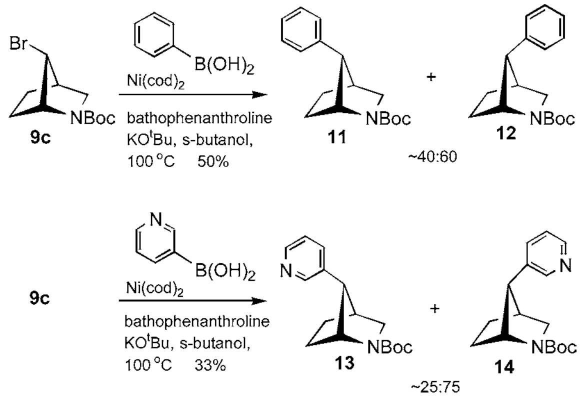
The anti stereochemistry is retained at C-7 during the substitution owing to neighboring group participation by the 2-azanorbornyl nitrogen. This allows smooth exchange of the bromine by a range of other nucleophilic groups[5] but clearly precludes direct S_N2 displacement with inversion, leading to the syn compounds which we had chosen as precursors for coupling chemistry. This is a problem since the syn-7-substituted derivatives are of much greater interest pharmacologically, bearing in mind the importance of N−N distances in achieving high nAChR affinity and the current level of understanding of the nAChR pharmacophore.[2] Our earlier synthesis of *syn*- and *anti*-isoepiboxidines involved the construction of the methylisoxazole ring in situ from a nitrile substituent via an ester group of established syn configuration.[5]

The key objective of the present work was the *direct* incorporation of pyridyl heterocycles at the 7-position of 2-azanorbornanes, preferably with control of syn stereochemistry. We hoped to use metal-catalyzed cross-coupling reactions to couple the heterocycle and the syn-bromo compound but were faced by two issues. First, studies of this type of reaction involving nonprimary sp^3 centers are in their infancy;[8] second, only the anti-7-bromo precursors **9** were available.

A significant recent report describing the coupling of nonactivated secondary bromo- and iodo- compounds with aryl boronic acids using a Ni(0) catalyst illustrates recent developments that are increasing the versatility of cross-coupling reactions substantially.[9] This work included examples of two (thiophene- and indole-based) heterocyclic boronic acids, and we applied this procedure to our more complex substrates, despite earlier observations on difficulties using functionalized alkyl electrophiles.[9]

We had intended to use the syn-7-bromo isomers of **9** as precursors but based our initial studies on the Boc-protected anti isomer **9c**, which was prepared from the readily available **9a** in 70% yield (Scheme 1). Coupling with phenylboronic acid required modification of the conditions described by Zhou and Fu.[9] A significantly higher catalyst loading was used (20 mol % instead of 4 mol %), and the low reactivity of **9c** necessitated a temperature of 100 °C for 48 h (rather than 60 °C for 5 h). Flash chromatography provided both epimers **11** and **12** in a total yield of 50%. The syn/anti ratio was 60:40 (Scheme 2).

Scheme 2



The same conditions were applied to the coupling of 3-pyridyl boronic acid with **9c** and gave **13** and **14** in a combined isolated yield of 33%. The syn epimer was again preferred (syn/anti ratio of 75:25). Yields were generally in line with those reported by Zhou and Fu.[9]

The fact that *β*-elimination is impossible in our system may contribute to the success of our reactions. Having demonstrated that this catalytic system can be utilized successfully with pyridyl boronic acids and functionalized secondary bromides, we applied similar conditions to the coupling of 4-chloro-3-pyridyl boronic acid[10] with **9c**. The

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(5) Malpass, J. R.; White, R. *J. Org. Chem.* **2004**, *69*, 5328−5334.

(6) Hodgson D. M.; Hachisu, S.; Andrews, M. D. *Org. Lett.* **2005**, *7*, 815−817.

(7) For recent examples of alternative heterocycles incorporated into the epibatidine framework and into analogues, see leading references in: Carroll, F. I.; Ma, W.; Yokota, T.; Lee, J. R.; Brieaddy, L. E.; Navarro, H. A.; Damaj, M. I.; Martin, B. R. *J. Med. Chem.* **2005**, *48*, 1221−1228. See also citations 2 and 4 in ref 5.

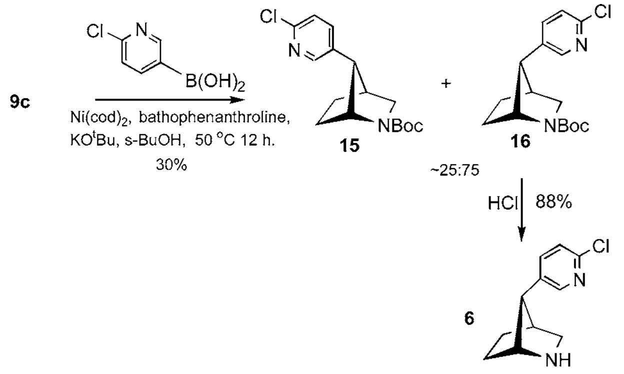
(8) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525−1532. Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674−688. Coupling of pyridylboronic acids and heteroaryl systems has been reported: Parry, P. R.; Wang, C.; Batsanov, A. S.; Bryce, M. R.; Tarbit, B. *J. Org. Chem.* **2002**, *67*, 7541−7543.

(9) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc*. **2004**, *126*, 1340−1341. This report concentrated on secondary alkyl halides that lacked functionality. A footnote in the paper states that “reactions of functionalized alkyl electrophiles proceed in lower yield”.

(10) Bouillon, A.; Lancelot, J.-C.; Collot, V.; Bovy, P. R.; Rault, S. *Tetrahedron* **2002**, *58*, 2885−2890. This reagent is now commercially available.

isolated material contained some of the desired products, but there was also evidence of defunctionalization[11] and solvolysis (incorporation of a 2-butoxy group in place of the 2-chloropyridyl substituent). Lowering the temperature to 50 °C and the reaction time to 12 h avoided loss of the pyridyl chlorine and produced the desired **15** and **16** in an overall 30% yield (Scheme 3).

Scheme 3



The mixture of N-protected products was not easy to separate, but the major epimer **16** was isolated by careful chromatography and characterized with the aid of a crystal structure (Figure 1). Removal of the *N*-Boc group was straightforward (using acetyl chloride in ethanol/ethyl acetate[5]), giving *syn*-isoepibatidine as the hydrochloride salt **6:HCl** in 88% isolated yield.

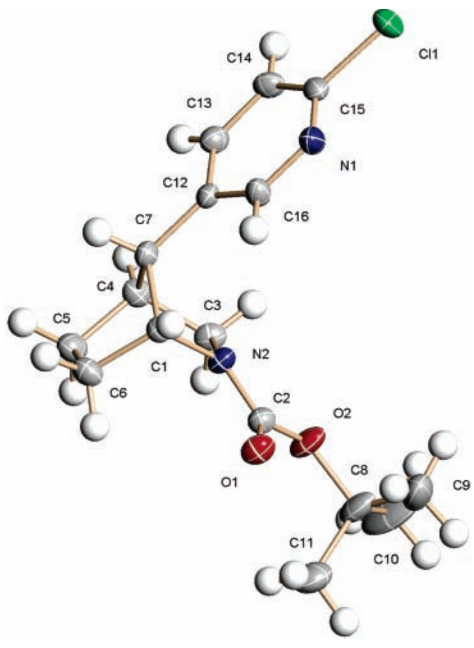


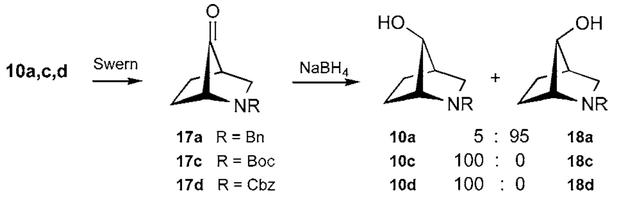
Figure 1. X-ray crystal structure of N-Boc isoepibatidine **16**.

The use of strong base and elevated temperatures inevitably raised the likelihood of epimerization at the 7-position[5,12] and made the question of stereocontrol in the actual coupling reactions somewhat academic.

Nevertheless, we performed a chloropyridyl coupling at room temperature and interrupted the conversion after 3 h (ca. 10% conversion). The ratio of **15** and **16** in the isolated sample was 75 anti:25 syn. When this same mixture was treated with base (KOᵗBu/BuOH) at 50 °C, the ratio reversed in favor of the syn isomer (25 anti:75 syn). This is in agreement with initial retention of configuration at C-7 followed by base-induced epimerization.

While it is now clear that syn-7 isomers of **9** are not required for synthesis of **6**, our early development work toward the syn-7-hydroxy isomers of **10** has allowed us to extend the range of syn derivatives and to resolve a recent disagreement over the orientation of the hydroxyl group.[5,13] We approached the syn-7-hydroxy compounds **18** via a simple oxidation/reduction strategy (Scheme 4).

Scheme 4



Swern oxidation of **10a**,**c**,**d** provided the corresponding 7-keto-compounds **17a**,**c**,**d**, but perversely, hydride reduction of the latter two derivatives using borohydride occurred only from the syn face, re-forming the starting compounds **10**. Fortunately, the facial selectivity was reversed in the case of the *N*-benzyl aminoketone **17a** and led to a substantial preference for the syn-hydroxy derivative **18a**.

The syn stereochemistry of **18a** was confirmed by an X-ray crystal structure of the 3,5-dinitrobenzoate derivative (Figure 2).

Standard methods allow attachment of a range of O-linked heterocycles using the oxy-anions of **10a**,**c**,**d**,[13] and it is now clear that a range of claimed syn derivatives that were synthesized as potential muscarinic antagonists[13] are in fact the anti isomers **19**. The availability of the syn compounds **18** now opens the way to the preferred range of syn derivatives **20**.

These include novel analogues of ABT-594[14] that contain the chloropyridyloxy group and have the same sequence of atoms between the two nitrogens.

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[11] Quantities of defunctionalised *N*-Boc-2-azanorbornane (ca. 20%) were isolated from each of the coupling reactions.

[12] This situation recalls early syntheses of epibatidine **1** that gave predominantly the unwanted *endo* stereoisomer, requiring subsequent epimerization at the 2-position of the 7-azanorbornyl ring system, for example: Fletcher, S. R.; Baker, R.; Chambers, M. S.; Herbert, R. H.; Hobbs, S. C.; Thomas, S. R.; Verrier, H. M.; Watt, A. P.; Ball, R. G. *J. Org. Chem.* **1994**, *59*, 1771−1778. For a significant improvement to the epimerization methodology for epibatidine, see: Habermann, J.; Ley, S. V.; Scott, J. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1253−1256.

[13] Mitch, C. H.; Quimby, S. J. Patent WO 00/75140 A1, 2000; U.S. Patent 6, 559, 171 B1 2003.

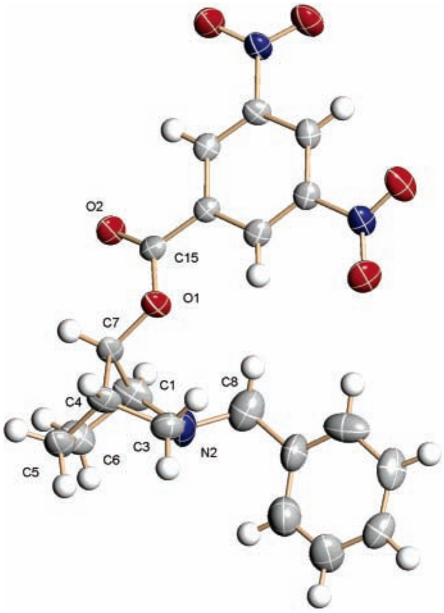
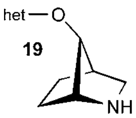


Figure 2. X-ray crystal structure of the 3,5-dinitrobenzoate of **18a**.

Syn-7 isomers have N−N distances that are more conducive to nAChR activity than the anti isomers but have less conformational freedom than ABT-594. We continue to explore this area and examine the factors that determine facial selectivity in attack on the 7-keto group.[15]



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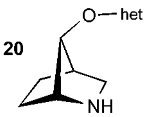

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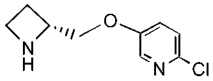

ABT-594

In summary, facial selectivity in attack on 7-keto-2-azanorbornanes is profoundly dependent on the N-protecting group and allows isolation and characterization of *syn*-7-hydroxy-2-azanorbornane (a precursor of novel potential nicotinic and muscarinic ligands). Significantly, we have demonstrated the first successful coupling of 4-chloro-3-pyridyl boronic acid with the functionalized secondary alkyl bromo compound **9c** and have shown that epimerization occurs under the reaction conditions. The observed thermodynamic preference for the *syn*-7-chloropyridyl derivative allows the use of the more readily accessible anti-7-bromo compound as the substrate in the synthesis of the novel epibatidine isomer *syn*-isoepibatidine **6**. This compound is a potential nicotinic agonist and will be screened for nAChR subtype selectivity. The coupling reaction itself has significance for the direct synthesis of other epibatidine analogues.

Acknowledgment. We are grateful to Dr. John Fawcett for the crystal structures and to Dr. Gerry Griffith for NMR data.

Supporting Information Available: Experimental procedures for coupling reactions and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Holladay, M. W.; Wasicak, J. T.; Lin, N. H.; He, Y.; Ryther, K. B.; Bannon, A. W.; Buckley, M. J.; Kim, D. J. B.; Decker, M. W.; Anderson, D. J.; Campbell, J. E.; Kuntzweiler, T. A.; Donnelly-Roberts, D. L.; Piattoni-Kaplan, M.; Briggs, C. A.; Williams, M.; Arneric, S. P. *J. Med. Chem.* **1998**, *41*, 407−412.

(15) For significant work on facial selectivity in attack on carbonyl groups in bicyclic environments, see: Kaselj, M.; Wen-Sheng, C.; Le Noble, W. J. *Chem. Rev.* **1999**, *99*, 1387−1413.