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7-Substituted 2-Azabicyclo[2.2.1]heptanes as Key Intermediates for the Synthesis of Novel Epibatidine Analogues; Synthesis of *syn*- and *anti*-Isoepiboxidine

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Neighboring group participation by the 2-nitrogen in *anti*-7-bromo-2-benzyl-2-azabicyclo[2.2.1]-heptane allows ready nucleophilic substitution at the 7-position by C, N, O, and halogen nucleophiles and opens the way to a range of novel 7-substituted 2-azabicyclo[2.2.1]heptanes. Conversion of an *anti*-7-ethoxycarbonyl group into a methylisoxazole ring provides *anti*-isoepiboxidine, a conversion that is possible even without protection of the secondary bicyclic nitrogen. Successful base-induced epimerization α to the carbonyl of the *anti*-7-ethoxycarbonyl derivative gives the *syn*-stereoisomer and hence *syn*-isoepiboxidine.

Introduction

Interest in the 7-azabicyclo[2.2.1]heptane (7-azanorbornane) ring system has increased dramatically since the discovery of epibatidine **1a**, a natural product with unusually high activity at the nicotinic acetylcholine receptor (nAChR).[1] Intense synthetic interest has led to a large number of approaches to **1a**, together with an ever-increasing variety of analogues bearing different heterocycles;[2] prominent among these is epiboxidine **2a** in which replacement of the chloropyridyl substituent by methylisoxazole leads to high nAChR affinity but lower toxicity compared to **1a**.[2a] Homologous systems showing high nAChR affinity include homoepibatidine **1b**,[3] and interest in the methylisoxazole substituent has been further reinforced by the very recent report of the potent nAChR agonist homoepiboxidine **2b** by the Daly group.[4] The emphasis in the search for therapeutically useful compounds is now on high nAChR subtype selectivity.[5] We have recently reported analogues based on the more highly strained 2-azabicyclo[2.1.1]hexane ring system[6a] together with epibatidine isomers **3**−**6** in which the heterocycle is attached to the 5- and 6-positions of 2-azanorbornane.[6b−d] Compounds **3** and **4** have shown sufficient promise in this and other work[6b,e,f] to encourage us to explore routes to the remaining 2-azanorbornane derivatives *syn*-**7** and *anti*-**7** in which the positions of the bicyclic nitrogen and the heterocycle of **1a** have simply

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(1) (a) 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: (b) 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. (c) Wei, Z.-L.; George, C.; Kozikowski, A. P. *Tetrahedron Lett.* **2003**, *44*, 3847−3850.

(2) Recent examples of alternative heterocycles incorporated into the epibatidine framework and into analogues include the following. (a) Methylisoxazole: Badio, B.; Garraffo, H. M.; Plummer, C. V.; Padgett, W. L.; Daly, J. W. *Eur. J. Pharmacol.* **1997**, *321*, 189−194. (b) Isoxazoles: Silva, N. M.; Tributino, J. L. M.; Miranda, A. L. P.; Barreiro, E. J.; Fraga, C. A. M. *Eur. J. Med. Chem.* **2002**, *37*, 163−169. (c) Pyridazines: Che, D.; Wegge, T.; Stubbs, M.; Seitz, G.Meier, H.; Methfessel, C. *J. Med. Chem.*, **2001**, *44*, 47−57. (d) Substituted pyridines: 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. Avalos, M.; Parker, M. J.; Maddox, F. N.; Carroll, F. I.; Luetje, C. W. *J. Pharmacol. Exp. Ther.* **2002**, *302*, 1246−1252. Carroll, F. I.; Lee, J. R.; Navarro, H. A.; Brieaddy, L. E.; Abraham, P.; Damaj, M. I.; Martin, B. R. *J. Med. Chem.* **2001**, *44*, 4039−4041. (e) 6-Chloropyridazin-3-yl derivatives: Toma, L.; Quadrelli, P.; Bunnelle, W. H.; Anderson, D. J.; Meyer, M. D.; Cignarelli, G.; Gelain, A.; Barlocco, D. *J. Med. Chem.* **2002**, *45*, 4011−4017. (f) See also: Gohlke, H.; Schwarz, S.; Gündisch, D.; Tilotta, M. C.; Weber. A.; Wegge, T.; Seitz, G. *J. Med. Chem.* **2003**, *46*, 2031−2048 for recent work on 3D QSAR analysis in the design of heterocyclic substituents for high nAChR subtype selectivity in epibatidine analogues and homologues.

(3) (a) 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.; Hemmings, D. A.; Wallis, A. L. *Tetrahedron Lett.* **1996**, *37*, 3911−3914. (b) Xu, R.; Bai, D. L.; Chu, G. H.; Tao, J. N.; Zhu, X. Z. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 279−282. Bai, D. L.; Xu, R.; Chu G. H.; Zhu, X. Z. *J. Org. Chem.* **1996**, *61*, 4600−4606.

(4) Fitch, R. W.; Pei, X.-F.; Kaneko, Y.; Gupta, T.; Shi, D.; Federova, I.; Daly, J. W. *Bioorg. Med. Chem.* **2004**, *12*, 179−190.

(5) For leading reviews and references to nAChR affinities, see: (a) Carroll, F. I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1889−1896. (b) Bunnelle, W. H.; Dart, M. J.; Schrimpf, M. R. *Curr. Top. Med. Chem.* **2004**, *4*, 299−334. (c) Astles, P. C.; Baker, S. R.; Boot, J. R.; Broad, L. M.; Dell, C. P.; Keenan, M. *Curr. Drug Targets: CNS Neurol. Disord.* **2002**, *1*, 337−348. (d) Tønder, J. E.; Olesen, P. H. *Curr. Med. Chem.* **2001**, *8*, 651−674. (e) Lloyd, G. K.; Williams, M. *J. Pharmacol. Exp. Ther.* **2000**, *292*, 461−467. (f) Curtis, L.; Chiodini, F.; Spang, J. E.; Bertrand, S.; Patt, J. T.; Westera, G.; Bertrand, D. *Eur. J Pharmacol.* **2000**, *393*, 155−163. (g) Tønder, J. E.; Hansen, J. B.; Begtrup, M.; Petterson, I.; Rimvall, K.; Christensen, B.; Ehrbar, U.; Olesen, P. H. *J. Med. Chem.* **1999**, *42*, 4970−4980. (h) Holladay, M. W.; Dart M. J.; Lynch, J. K. *J. Med. Chem.* **1997**, *40*, 4169−4194.

(6) (a) Malpass, J. R.; Patel, A. B.; Davies, J. W.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 9348−9355. (b) Cox, C. D.; Malpass, J. R.; Rosen, A.; Gordon, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2372−2379. (c) Malpass, J. R.; Cox, C. D. *Tetrahedron* **1999**, *55*, 11879−11888. (d) Malpass, J. R.; Cox, C. D. *Tetrahedron Lett.* **1999**, *40*, 1419−1422. (e) Dart, M. J.; Wasicak, J. T.; Ryther, K. B.; Schrimpf, M. R.; Kim, K. H.; Anderson, D. J.; Sullivan, J. P.; Meyer, M. D. *Pharm. Acta Helv.* **2000**, *74*, 115−123. (f) 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. Hodgson, D. M.; Maxwell, C. R.; Matthews, I. R. *Synlett* **1998**, *12*, 1349−1350.

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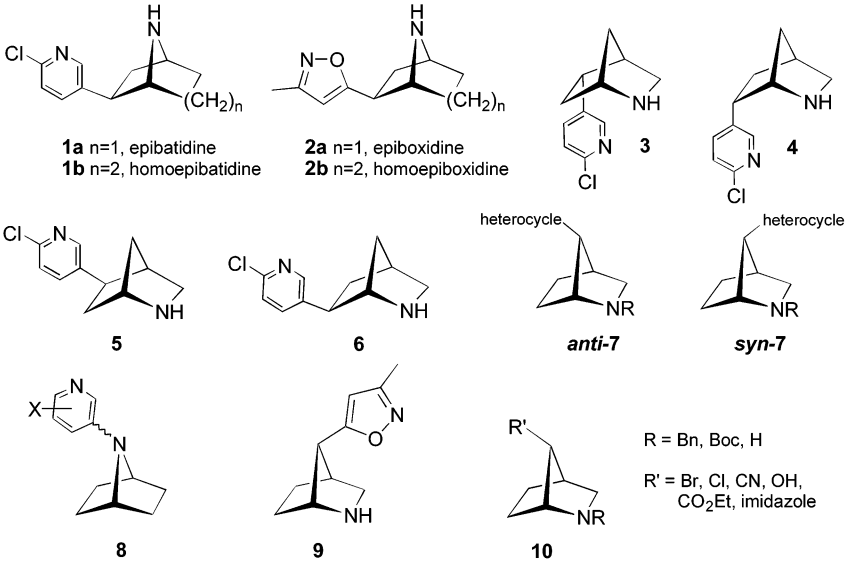
CHART 1



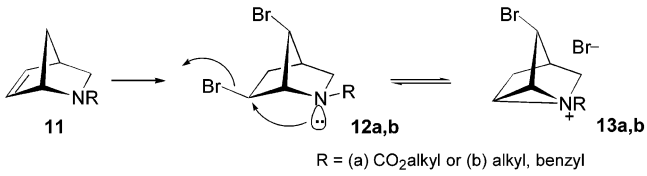
been reversed.[7] Although 7-substituted-7-azabicyclo[2.2.1]-heptyl (7-azanorbornyl) derivatives **8** have been reported recently,[8] we are not aware of any compounds having heterocycles directly attached to the 7-position of 2-azanorbornanes.

We chose *syn*-isoepiboxidine **9** as our first target. We demonstrate here that this and related 7-substituted-2-azanorbornanes are available by way of the key *anti*-7-substituted intermediates **10**. Neighboring group participation by the 2-azanorbornyl nitrogen is the key to displacements from the 7-position, extending its established role in the loss of 6-substituents. Epimerization at the 7-position [e.g., for the ester **10** (R = CO_2Et)] provides the essential first entry into the 7-*syn* series and hence a route to **9**.

Discussion

Neighboring group participation by σ and π bonds is a key feature of the rearrangement chemistry of bicyclo-[2.2.1]heptanes (norbornanes), and similar participation has also been established in the chemistry of azanorbornanes and -enes; σ or π electrons can participate in displacement of a nucleofuge from nitrogen in the 2-[9] or the 7-position[10] of the azanorbornane skeleton. More usually, nitrogen is seen to participate in the displacement of leaving groups from carbon,[9,11] and the nitrogen lone pair can also overlap with centers of developing positive charge during electrophilic addition to double bonds, leading again to skeletal rearrangement.[11,12] Such involvement of *N*-acyl and *N*-alkoxycarbonyl nitrogen in skeletal rearrangement is well established during electrophilic addition to derivatives of the 2-azanorborn-5-ene system **11**,[12] leading for example to dibromo derivatives such as **12a**.[12b] In the case of *N*-alkyl derivatives, the pioneering work of Raasch[11] has been developed, leading to isolation of the aziridinium intermediates **13b** during bromination.[13a] Indeed when R is alkyl, the equilibrium shown in Scheme 1 is biased completely in favor of the aziridinium salt **13b** with none of the dibromide **12b**.

SCHEME 1



We had hoped that addition of nucleophiles to the *N*-ethoxycarbonyl derivative **12a** ⇌ **13a** might allow interception of a small equilibrium concentration of **13a** (effectively achieving substitution at the 6-position), but we were unable to demonstrate any replacement of the 6-bromine in **12a**,[14a] despite the fact that carbamate

(7) Clearly, the N−N distances and orientation will be important in determining the binding ability of these ligands. Compounds **3** and **4** show much higher affinities and subtype selectivity than **5** and **6**,[6b] and it is reasonable to expect *syn*-**7** to be a better ligand than *anti*-**7**.

(8) Cheng, J.; Zhang, C.; Stevens, E. D.; Izenwasser, S.; Wade, D.; Chen, S.; Paul, D.; Trudell, M. L. *J. Med. Chem.* **2002**, *45*, 3041−3047. In addition, 7-substituted 1-azabicyclo[2.2.1]heptanes have been reported: Ullrich, T.; Binder, D.; Pyerin, M. *Tetrahedron Lett.* **2002**, *43*, 177−179.

(9) (a) Davies, J. W.; Malpass J. R.; Walker, M. P. *J. Chem. Soc., Chem. Commun.* **1985**, 686−687. (b) Durrant, M. L.; Malpass J. R.; Walker, M. P. *J. Chem. Soc., Chem. Commun.* **1985**, 687−688 and references to earlier work.

(10) Durrant, M. L.; Malpass J. R. *Tetrahedron* **1995**, *51*, 7063−7076. Davies, J. W.; Durrant, M. L.; Naylor, A.; Malpass, J. R. *Tetrahedron* **1995**, *51*, 8655−8664.

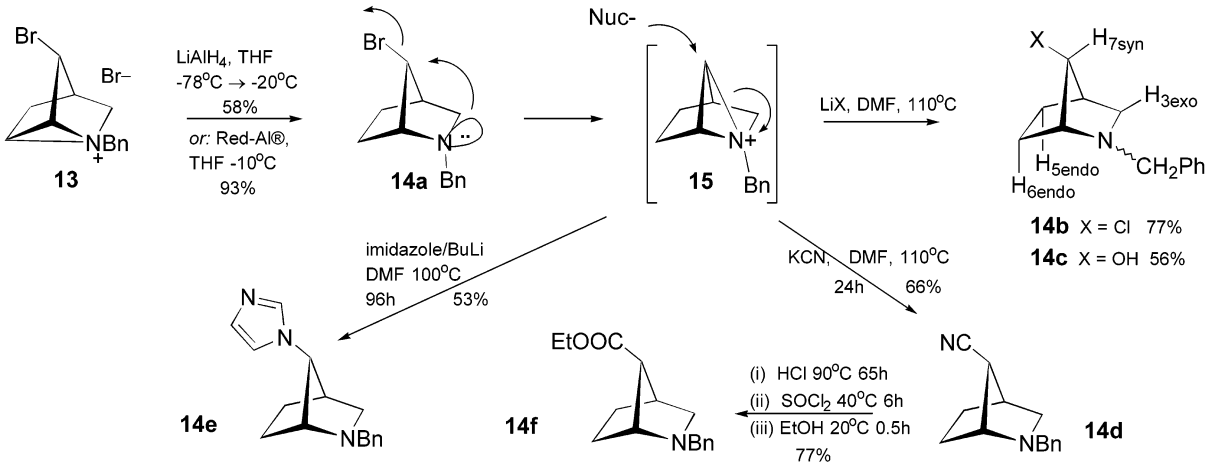
(11) Raasch, M. S. *J. Org. Chem.* **1975**, *40*, 161−172.

(12) (a) For work in the 2-azabicyclo[2.2.1]hept-5-ene-3-one system, see: Faith, W. C.; Booth, C. A.; Foxman, B. M.; Snider, B. B. *J. Org. Chem.* **1985**, *50*, 1983−1985. Evans, C.; McCague, R.; Roberts, S. M.; Sutherland, A. G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 656−657. Palmer, C. F.; McCague, R. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2977−2978. (b) Bromination of *N*-ethoxycarbonyl-2-azanorborn-5-ene also proceeds smoothly with rearrangement to give **12a** (R = CO_2CH_2-Ph): Cox, C. D. PhD thesis, University of Leicester, 2000.

(13) (a) Sosonyuk, S. E.; Bulanov, M. N.; Leshcheva, I. F.; Zyk, N. V. *Russ. Chem. Bull.* **2002**, *51*, 1254−1261. For other azatricyclene intermediates, see: Portoghese, P. S.; Sepp, D. T. *Tetrahedron* **1973**, *29*, 2253−2256 and ref 9. (b) A 6-methoxy derivative was isolated on treatment of **13** (R = Me) with sodium methoxide in MeOH (ref 12a). A very recent paper from the same group has widened the range of nucleophiles: Bulanov, M. N.; Sosonyuk, S. E.; Zyk, N. V.; Zefirov, N. S. *Russ. J. Org. Chem.* **2003**, *39*, 415−421.

(14) (a) Barth, G. S.; (b) Fulford, S. Y.; (c) Rimmington, S. Unpublished work, University of Leicester.

SCHEME 2



nitrogen participates during additions to *N*-alkoxycarbonyl-2-azanorborn-5-enes and also electrophilic ring opening of the derived *exo*-5,6-epoxides.[14b] However, interception of **13** using a wider range of nucleophiles is possible in the *N*-alkyl series and has been used to make 6-substituted 2-azabicyclo[2.2.1]heptanes following reductive removal of the 7-substituent.[13b]

We were concerned to do the opposite: to remove the 6-substituent and introduce a range of functional groups at the 7-position. Treatment of **13b** (R = Bn) with hydride allows effective removal of the 6-bromine yielding the 7-bromo derivative **14a** (Scheme 2). At low temperature (−78 °C followed by warming to −20 °C over 1 h), $LiAlH_4$ gave **14a** in 58% yield after chromatography on silica.[15] The use of Red-Al[16] is preferable.

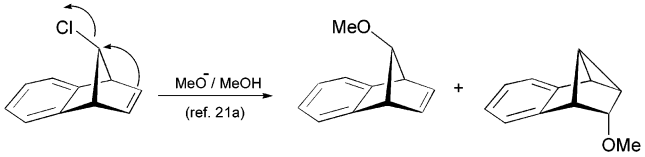
Nucleophilic substitution at the 7-position of **14a** was then attempted, despite the fact that direct (S_N2) substitution is difficult to achieve at this position in simple norbornanes.[17] The key substitution reactions occurred at elevated temperatures (ca. 100 °C). Thus, treatment of **14a** with LiCl in DMF gave the chloro analogue **14b** in 77% yield (Scheme 2),[18] and LiOH in DMF provided **14c** in 56% yield.[16b]

All of the substitutions based on **14a** occurred with complete retention of configuration at C-7. For example, the *anti* stereostructure of **14b** was confirmed by COSY experiments that identified "W" coupling between H_{7syn} and H_{5endo}/H_{6endo}.[19] In addition, NOE interactions were seen between H_{7syn} and H_{3exo} and between the CH_2 of the inverting *N*-benzyl group and both H_{7syn} and H_{6endo}. Similar reaction of **14a** with KCN in DMF yielded **14d** in 66% yield, and use of the imidazolyl anion followed the same pathway, producing **14e** in 53% yield. Here, the protons H_{5exo} and H_{6exo} appeared ca. 0.5 ppm upfield of the corresponding signals in **14b**−**d**, shielded by the ring current of the *anti* imidazole ring.

The *anti* stereochemistry in all of the 7-derivatives **14a**−**f** was confirmed by detailed spectroscopic analysis and is presumably the result of participation by nitrogen, as shown by **14a** → **15** (Scheme 2). Such involvement of the 2-nitrogen in displacements from the 7-position is clearly more energetically demanding than in displacement from the 6-position (**12** → **13**, Scheme 1) so that there was no competition during the earlier substitution at C-6 in the 6,7-dibromo compound **12b**.

Participation by the nitrogen lone pair in displacement of an *anti* substituent from C-7 is closely analogous to the involvement of π-electrons in the overall retention of stereochemistry observed in the classic studies by Cristol, Winstein, and others on the solvolysis of 7-substituted norbornenyl tosylates and brosylates[21] (e.g., Scheme 3). Similar π-participation has been observed in the loss of chloride ion from a range of *N*-chloro-7-azanorbornadienes.[10]

SCHEME 3



It is not unreasonable, in principle, that S_N2 substitution at the 7-position might proceed (with inversion), and on the basis of existing work in norbornanes[17] a slow reaction would be expected and a high temperature would

(15) Addition of $NaBH_4$ in MeOH to **13** led only to isolation of the 6-methoxy compound (17% yield).[13b] Treatment of **13** with $LiAlH_4$ at room temperature led to loss of both bromines and gave *N*-benzyl-2-azanorbornane, which was identical to a sample obtained by careful hydrogenation[14c] of **11**.

(16) (a) Mitch, C. H.; Quimby, S. J. Patent WO 00/75140 A1, 2000; US 6,559,171 B1, 2003. (b) The reaction conditions described in this patent were different to ours and were claimed to provide the 7-*endo*-hydroxy compound (OH *syn* to nitrogen). In our hands they gave only the *anti* stereoisomer, identical to our sample **14c**.

(17) (a) See: Jenkins, M. N.; Nash, J. J.; Morrison, H. *Tetrahedron Lett.* **2002**, *43*, 3773−3775 and references therein to earlier work. (b) The work in ref 17a indicates, for example, that carbonyl groups in the 2-/3-position(s) of the norbornyl skeleton can exert a significant effect on substitution at C-7.

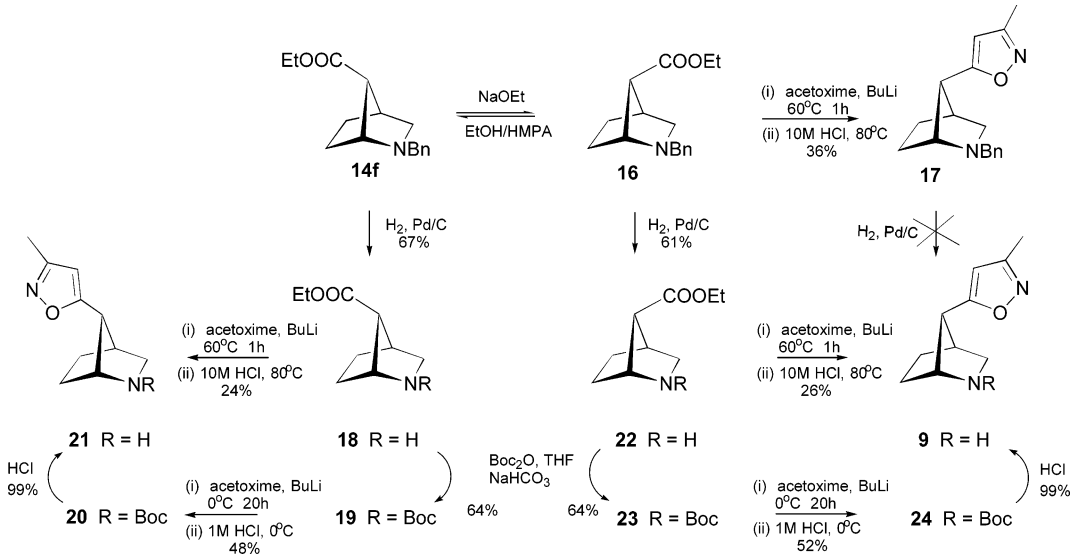
(18) Yields in these reactions have not been optimized in all cases. Typical reactions were performed on a 5−20 mmol scale but smaller-scale reactions in sealed reaction vials were effective down to a 0.1 mmol scale.

(19) See: Belkacemi, D.; Malpass, J. R. *Tetrahedron* **1993**, *40*, 9105−9116 for examples of W-coupling in 2-azanorbornanes.

(20) (a) We and others have previously exchanged *N*-benzyl for *N*-Cbz or *N*-Boc groups, e.g., ref 6a and references therein. (b) Conversion of *N*-benzyl into *N*-Boc was carried out prior to methylisoxazole formation in the recent work by Fitch et al.[4]

(21) (a) Cristol, S. J.; Nachtigall, G. W. *J. Am. Chem. Soc.* **1968**, *90*, 7132−7133; 7133−7134. (b) Tanida, H. *Acc. Chem. Res.* **1968**, *1*, 239−245. (c) Winstein, S. *J. Am. Chem. Soc.* **1961**, *83*, 1516−1517 and earlier references therein.

SCHEME 4



be required. However, our demonstration of *anti* stereochemistry for all of the derivatives **14a**−**f** strongly suggests that participation of the 2-nitrogen is general and provides a lower-energy alternative to S_N2 displacement for all of the nucleophilic substitutions studied. We are currently exploring alternative routes to the *syn*-7-hydroxy compound. Calculations make it clear that *syn*-7-heterocyclic derivatives will have more appropriate N−N distances for interaction with nicotinic receptors than *anti* stereoisomers, and it was thus important to achieve inversion of configuration at C-7.

The conversion of **14d** into the ester **14f** proceeded in an overall yield of 77% (Scheme 2). Crucially, epimerization of **14f** with base led to a mixture containing approximately 55% of the *syn*-epimer **16** (Scheme 4).[22,23] Base-induced epimerization at the 7-position in norbornanes is precedented[24] but is more difficult than at normal unstrained sp^3 carbon. This area is currently under active investigation, as is the influence of substituents elsewhere in the azanorbornyl ring system on the ease of bimolecular nucleophilic substitution at the 7-position.[17b]

Chromatographic separation of the stereoisomers **14f** and **16** was straightforward. The *syn*-ester **16** was converted into the *syn*-methylisoxazole derivative **17** using standard methods[2a,4] in 36% yield. However, attempts to deprotect the *N*-benzyl compound **17** by hydrogenolysis were unsuccessful (Scheme 4); not surprisingly, the methylisoxazole ring did not survive such treatment.

Our failure to obtain **9** from **17** prompted exchange of the *N*-benzyl for an *N*-alkoxycarbonyl protecting group in the 7-esters prior to heterocycle formation.[20] In the *anti* series, hydrogenolysis of **14f** gave the secondary amine **18**, which was *N*-Boc-protected to give **19** prior to heterocycle formation and *N*-deprotection of **20**; *anti*-isoepiboxidine **21** was formed in an overall yield of 30% from **18**. However, an unexpected observation avoided this reprotection/deprotection strategy and compensated for our earlier inability to enter the *N*-alkoxycarbonyl series by direct interception of **13a** (R = CO_2Alkyl) with nucleophiles. Thus, treatment of **18** with the dianion of acetoxime[2a] gave the methylisoxazole derivative *anti*-isoepiboxidine **21** directly (Scheme 4) in 24% yield. In similar fashion, debenzylation of **16** gave **22**, which was successfully converted into the target *syn*-isoepiboxidine **9** directly in 26% yield. The overall yield using the alternative 3-step procedure (via **23** and **24**) was 33%. Reported yields for the construction of methylisoxazoles are consistently low,[2a,4,6a] and mechanistic interest in this conversion[4] deserves to be extended. In the meantime, we believe that formation of the methylisoxazole ring without protection of the secondary amino-nitrogen (previously assumed to be an essential requirement) is a significant observation that will have wider application.

Further studies of substitution at the 7-position of the 2-azabicyclo[2.2.1]heptane ring system are under way. The application of coupling reactions to 7-halo compounds is being explored as a means of extending the range of available heterocyclic substituents as part of our program of synthesis of compounds having potential as high-affinity nAChR ligands.

Experimental Section

NMR spectra were recorded in $CDCl_3$ using tetramethylsilane as internal standard. Routine mass spectra were measured using electrospray and accurate mass measurements

(22) This situation is reminiscent of early syntheses of epibatidine **1a**, which gave predominantly the *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.

(23) The methylene protons of the *syn*-ester ethyl group in **16** appeared as a complex pattern, interpreted as an overlapping pair of doublets of quartets. These complex signals collapsed to an AB pattern on double irradiation of the ester methyl triplet, confirming the diastereotopic relationship (in keeping with the position over the unsymmetrical C−N bond). The *syn*-ester **22** showed similar complexity for the methylene "quartet". The ester CH_2 protons in the *anti* isomers **14f** and **18** sit over a near-symmetrical C−C linkage and do not show diastereotopicity. In the case of **16**, the CH_2 protons of the *N*-benzyl group appear as a singlet; benzyl protons in these compounds often show accidental equivalence, and in this case this may be a consequence of the shift in the inversion equilibrium[19] towards the *endo*-*N*-benzyl invertomer as a result of steric interactions between the *exo*-invertomer and the *syn*-7 substituent.

(24) Buske, G. R.; Ford, W. T. *J. Org. Chem*. **1976**, *41*, 1998−2006.

using FAB or EI. IR spectra were measured as films. All reactions were performed in oven-dried glassware under dry nitrogen unless stated otherwise. Commercially available solvents were purified and dried, when necessary, prior to use. "Ether" refers to diethyl ether and "petrol" to petroleum ether, bp 40−60 °C.

Flash chromatography was carried out using silica gel (60). Thin-layer chromatography was conducted on silica 60-254 plates. Chromatography solvents were routinely saturated with ammonia gas for amine (and *N*-protected amine) separations.

3-Bromo-1-benzyl-1-azoniatricyclo[2.2.1.0^{2,6}]heptane Bromide (13). Using the procedure described by Sosonyuk et al.,[13a] 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene (**11**)[25] (12.03 g, 64.9 mmol) was dissolved in dry CH_2Cl_2 (120 mL). Bromine (6.0 mL, 129.5 mmol) was added dropwise at −78 °C. The mixture was stirred as the temperature rose to 20 °C. Evaporation in vacuo gave an orange oil, which was dissolved in dry CH_3CN (100 mL), cooled to 0 °C, and stirred vigorously while more **11** (12.06 g, 65.0 mmol) in dry CH_3CN (60 mL) was added dropwise. After warming to 20 °C, the solvents were evaporated in vacuo, yielding **13** as pale yellow crystals (22.3 g, 100%), mp 128−130 °C. [The NMR spectra are broadly similar to those described for the corresponding *N*-Me compound and the *N*-benzyl derivative having a Br_3^- counterion[13a]]. δ_H (250 MHz, $CDCl_3$) 2.42 (brs, 2H), 2.83 (brs, 1H), 3.41 (d, J = 8.9 Hz, 1H), 3.94 (d, J = 8.9 Hz, 1H), 4.42 (m, 2H), 4.86 (brs, 1H), 5.34 (s, 2H), 7.42−7.73 (m, 5H). δ_C (62.9 MHz, $CDCl_3$) 30.9, 37.6, 44.5, 44.8, 46.2, 55.1, 55.3, 129.4, 129.5, 130.3, 131.1. ν_{max} 3049s, 3003w, 2318w, 1426m, 1278m, 898m cm^{-1}. *m/z* 264/266 (1:1) (M^+). $C_{13}H_{15}NBr$ [M^+] requires *m/z* 264.03879; observed 264.03884.

***anti*-7-Bromo-2-benzyl-2-azabicyclo[2.2.1]heptane (14a).** $LiAlH_4$ (0.53 g, 13.97 mmol) and **13** (3.056 g, 8.85 mmol) were cooled to −78 °C in a dry flask. Dry THF (100 mL) was added with stirring, and the mixture allowed to warm to −20 °C over a period of 1 h followed by addition of water-saturated ether until effervescence stopped. The mixture was filtered, the residue was washed with CH_2Cl_2, and after drying with $MgSO_4$ the solvents were removed in vacuo to give crude **14a**, which was chromatographed (petrol/ether 7:3; NH_3) to give a pale yellow oil (1.359 g, 58%), R_f (7:3, petrol/ether). δ_H (250 MHz, $CDCl_3$) 1.42, 1.77−2.13 (m, 4H), 2.43 (brs, 1H), 2.47 (d, J = 9.2 Hz, 1H), 2.82 (ddd, $J \approx$ 9.2, 3.3, 3.3 Hz, 1H), 3.23 (brs, 1H), 3.67, 3.69 (AB, J = 13.4 Hz, 2H), 4.24 (d, J = 1.7 Hz, 1H), 7.18 (m, 5H). δ_C (62.9 MHz, $CDCl_3$) 25.2, 26.7, 44.0, 53.4, 58.0, 59.0, 64.9, 126.9, 128.1, 128.2, 139.2. ν_{max} 3064s, 2982m, 2276w, 1504m, 1463m, 1430m, 1380w, 1279s, 1150w, 907m cm^{-1}. *m/z* 266/268 (1:1) (MH^+). $C_{13}H_{16}NBr$ [EI, M^+] requires *m/z* 265.04661; observed 265.04659.

Alternatively, reduction using Red-Al[16] (65+ wt % solution in toluene, 7.65 mL, 26.0 mmol) and **13** (8.96 g, 26.0 mmol) in dry THF (225 mL) at −10 °C for 2 h gave **14a** as a pale yellow oil (6.42 g, 24.1 mmol, 93%).

***anti*-7-Chloro-2-benzyl-2-azabicyclo[2.2.1]heptane (14b).** To a solution of **14a** (63.7 mg, 0.24 mmol) in anhydrous DMF (1.0 mL) in a reaction vial was added LiCl (217.5 mg, 5.13 mmol). The mixture was heated to 100 °C for 24 h, cooled, and poured into water (2 mL), followed by extraction with ether (3 × 2 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, and the solvents were evaporated in vacuo, yielding **14b** as a pale yellow oil (41 mg, 77%). R_f 0.79 (EtOAc/MeOH, 9:1). δ_H (250 MHz, $CDCl_3$) 1.41 (m, 1H), 1.80−2.08 (m, 3H), 2.34 (brs, 1H), 2.38 (d, J = 9.2 Hz, 1H), 2.85 (ddd, $J \approx$ 9.2, 3.2, 3.2 Hz, 1H), 3.16 (brs, 1H), 3.66 (brs, 2H), 4.20 (brs, 1H), 7.27 (m, 5H). δ_C (62.9 MHz, $CDCl_3$) 24.2, 26.2, 43.5, 58.0, 58.5, 62.0, 64.5, 126.8, 128.1, 128.3, 139.1. ν_{max} 3064m, 2991m, 2318w, 1683s, 1500w, 1453w, 1289w, 1256s, 843w cm^{-1}. *m/z* 222.10500 (MH^+); $C_{13}H_{17}NCl$ requires 222.10495.

***anti*-7-Hydroxy-2-benzyl-2-azabicyclo[2.2.1]heptane (14c).** The 7-bromo compound **14a** (110 mg, 0.41 mmol) and LiOH (173 mg, 4.1 mmol) in dry DMF (8 mL) were stirred at 100 °C for 24 h. The reaction mixture was cooled, added to water (30 mL), and extracted with ether (4 × 25 mL). The combined extracts were washed with water (3 × 35 mL), dried over $MgSO_4$, and then filtered. Removal of solvents in vacuo gave a yellow oil that was chromatographed (9:1, EtOAc/MeOH, NH_3), yielding **14c** as a pale yellow oil (47 mg, 56%). R_f 0.53. δ_H (300 MHz, $CDCl_3$) 1.34−1.43 (m, 1H), 1.70−1.78 (m, 1H), 1.88−2.00 (m, 2H), 2.11 (brs, 1H), 2.19 (d, J = 9.3 Hz, 1H), 2.40 (brs, OH), 3.03 (brs, 1H), 3.05 (ddd, $J \approx$ 9.3, 3.6, 3.0 Hz, 1H), 3.65, 3.70 (AB, J = 13.4 Hz, 2H), 4.29 (brs,1H), 7.21−7.35 (m, 5H). δ_C (75.5 MHz, $CDCl_3$) 22.7, 26.5, 41.6, 57.7, 58.0, 62.9, 76.3, 126.8, 128.2, 128.5, 139.2. ν_{max} 3053m, 2970m, 2303w, 1421w, 1265s cm^{-1}. *m/z* 204.13886 (MH^+); $C_{13}H_{18}NO$ requires 204.13884.

Using the procedure described in ref 16a, **14a** (3.06 g, 11.5 mmol) and 1-methyl-2-pyrrolidinone (containing 15% v/v H_2O; 56 mL) were stirred at 100 °C for 67 h. The reaction mixture was diluted with water (150 mL), basified with aqueous NaOH, and extracted with ether (4 × 100 mL). The combined organic extracts were washed with water (4 × 100 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to yield **14c** as a yellow oil (1.54 g, 66%) showing NMR spectra identical to those of the sample obtained above.

***anti*-7-Cyano-2-benzyl-2-azabicycl[2.2.1]heptane (14d).** KCN (2.36 g, 35.70 mmol) and 18-crown-6 (∼1 mg) were added to **14a** (0.765 g, 2.88 mmol) in anhydrous DMF (10 mL), and the mixture was stirred vigorously at 110 °C for 24 h. After filtration, the solid residue was washed with ether, and the combined organic extracts were dried prior to removal of solvent in vacuo to give a yellow oil that was chromatographed (3:7 petrol/ether, NH_3), yielding **14d** as a yellow oil (0.405 g, 66%), R_f 0.32. δ_H (250 MHz, $CDCl_3$) 1.49 (m, 1H), 1.94 (m, 3H), 2.45 (d, J = 9.4 Hz, 1H), 2.73 (m, 3H), 3.47 (brs, 1H), 3.59, 3.67 (AB, J = 13.4 Hz, 2H), 7.29 (m, 5H). δ_C (62.9 MHz, $CDCl_3$) 26.2, 26.6, 35.3, 42.6, 58.6, 58.7, 64.3, 119.5, 127.0, 128.2, 128.3, 138.7. ν_{max} 2973s, 2874s, 2234s, 1494s, 1453s cm^{-1} *m/z* 213.13914; $C_{14}H_{17}N_2$ (MH^+) requires *m/z* 213.13917.

***anti*-7-(Imidazole-1-yl)-2-benzyl-2-azabicyclo[2.2.1]-heptane (14e).** Butyllithium (0.31 mL, 1.6 M in hexanes, 0.49 mmol) was added dropwise to imidazole (34 mg, 0.50 mmol) in anhydrous DMF (1.5 mL), and the mixture was stirred at 20 °C for 0.25 h. A solution of **14a** (103 mg, 0.39 mmol) in anhydrous DMF (4 mL) was added, and after stirring at 100 °C for 96 h the mixture was filtered, the residue was washed with diethyl ether, the combined organic extracts were washed with water (4 × 2 mL), and the solvents were removed in vacuo. After chromatography (ether, NH_3), **14e** was isolated as a yellow oil (52 mg, 53%), R_f 0.20. δ_H (250 MHz, $CDCl_3$) 1.42 (m, 1H), 1.47 (m, 1H), 1.68 (m, 1H), 2.00 (m, 1H), 2.45 (d, J = 9.4 Hz, 1H), 2.81 (brs, 1H), 3.15 (ddd, $J \approx$ 9.4, 3.2, 3.2 Hz, 1H), 3.63 (brs, 1H), 3.69 (brs, 2H), 4.36 (brs, 1H), 6.87 (brs, 1H), 7.06 (brs, 1H), 7.14 (m, 5H), 7.46 (brs, 1H). δ_C (62.9 MHz, $CDCl_3$) 23.9, 26.6, 41.1, 57.9, 58.2, 61.6, 62.9, 118.5, 127.0, 128.2, 128.3, 129.0, 136.6, 139.0. ν_{max} 3052m, 2972m, 2305w, 1501w, 1452w, 1374w, 1265s, 1082w, 910w cm^{-1}. *m/z* 254.16572; $C_{16}H_{20}N_3$ [MH^+] requires 254.16564.

***anti*-2-Benzyl-2-azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (14f).** Aqueous HCl (4 mL, 8 M) was added to **14d** (0.309 g, 1.46 mmol) and stirred at 90 °C for 65 h. The mixture was evaporated to dryness; thionyl chloride (4 mL) was added, and the mixture was stirred at 40 °C for 6 h. Excess thionyl chloride was removed in vacuo, dry ethanol (5 mL) was added, and the mixture stirred at 20 °C for 0.5 h. After removal of the solvents in vacuo, the resulting yellow oil was dissolved in HCl (4 mL, 1 M) and washed with CH_2Cl_2 (3 × 4 mL). The aqueous layer was basified with ammonium hydroxide solution (8 mL, 35% ammonia) and extracted with CH_2Cl_2 (3 × 4 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. Removal of solvents in vacuo gave **14f** as a yellow oil (0.290 g, 77%; the sample was sufficiently pure for the epimerization to give **16**). R_f 0.41 (3:2

(25) Larsen, P. A.; Grieco, P. A. *Org. Synth.* **1990**, *68*, 206−209.

ether/petrol). δ_H (250 MHz, $CDCl_3$) 1.24 (t, J = 7.1 Hz, 3H), 1.40, 1.60−1.95 (m, 4H), 2.40 (d, J = 9.4 Hz, 1H), 2.61 (brs, 1H), 2.86 (ddd, $J \approx$ 9.4, 3.4, 3.4 Hz, 1H), 2.93 (brs, 1H), 3.44 (brs, 1H), 3.66, 3.74 (AB, J = 13.5 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H), 7.33 (m, 5H). δ_C (62.9 MHz, $CDCl_3$) 14.0, 25.5, 26.9, 40.1, 51.2, 58.4, 59.9, 60.0, 62.2, 126.8, 128.2, 128.2, 128.4, 138.9, 171.7. ν_{max} 3053s, 2982s, 2305w, 1725s, 1452m, 1370m, 1265s, 1214m, 1180m, 1043m, 896w cm^{-1}. *m/z* 260.16510; $C_{16}H_{22}NO_2$ [MH^+] requires *m/z* 260.16505.

***syn*-2-Benzyl-2-azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (16).** To the ester **14f** (3.387 g, 13.10 mmol) was added NaOEt in EtOH (0.63 M, 42 mL) and dry HMPA (0.1 mL), and the mixture was stirred at 65 °C for 24 h. After addition of the mixture to water (50 mL) and extraction with CH_2Cl_2 (5 × 60 mL), the organic extracts were combined, dried over anhydrous $MgSO_4$, and filtered. Capillary GC analysis [25 m HP−FFAP column] indicated the presence of both **14f** and **16** (*anti*/*syn* = 45:55). Chromatography (3:2 ether/petrol, NH_3) yielded **14f** (1.399 g; 41%), R_f 0.41**,** and **16** (1.56 g, 6.02 mmol, 46%), R_f 0.59. δ_H (300 MHz, $CDCl_3$) 1.28 (t, J = 7.1 Hz, 3H), 1.32−1.54, 1.54−1.69, 1.84 (3 × m, 2H, 1H, 1H), 1.93 (d, J = 8.4 Hz, 1H), 2.48 (brs, 1H), 2.55 (brs, 1H), 3.28 (ddd, $J \approx$ 8.4, 3.5, 3.5 Hz, 1H), 3.48 (brs, 1H), 3.68 (brs, 2H), 4.18, 4.20 (complex, 2 overlapping dq,[23] J = 7.1 Hz, 2H), 7.25−7.28 (m, 5H). δ_C (75.5 MHz, $CDCl_3$) 14.3, 23.7, 29.7, 39.4, 53.7, 55.5, 56.5, 60.0, 62.7, 126.5, 128.0, 140.0, 172.2. ν_{max} 2976s, 2870s, 1733s, 1453s, 1186s cm^{-1}. *m/z* 260.16509 (MH^+); $C_{16}H_{22}NO_2$ [MH^+] requires *m/z* 260.16505.

***syn*-2-Benzyl-7-(3-methyl-isoxazol-5-yl)-2-azabicyclo-[2.2.1]heptane (17).** Using the procedure described by Badio et al.,[2a] acetoxime (129 mg, 1.77 mmol) was dissolved in dry THF (4 mL) and held at 0 °C. Butyllithium (2.21 mL, 1.6 M, 3.53 mmol) was added, and the mixture was stirred at 20 °C for 0.8 h. The ester **16** (174 mg, 0.67 mmol) dissolved in dry THF (2 mL) was added. After stirring at 60 °C for 1 h the solvent was evaporated using nitrogen. HCl (8 mL, 10.2 M) was added, and the mixture was stirred at 80 °C for 4.5 h and then 12 h at room temperature. The reaction mixture was basified with saturated $NaHCO_3$ solution (∼15 mL) and extracted with CH_2Cl_2 (4 × 40 mL). The organic layers were combined, and removal of the solvents in vacuo gave an orange oil that was dissolved in HCl (1 M, 3 mL) and washed with ether (4 × 2 mL). The aqueous layer was basified (NH_4OH solution) and extracted with CH_2Cl_2 (4 × 2 mL). The CH_2Cl_2 extracts were dried over $MgSO_4$ and filtered. Flash chromatography (9:1, ether/MeOH, NH_3) gave **17** as a colorless oil (65 mg, 36%), R_f 0.56. δ_H (300 MHz, $CDCl_3$) 1.45−1.62 (m, 2H), 1.74−1.87 (m, 1H), 2.00−2.13 (m, 1H), 2.02 (d, J = 9.1 Hz, 1H), 2.30 (s, 3H), 2.52 (brs, 1H), 2.88 (brs, 1H), 3.09 (ddd, $J \approx$ 9.1, 3.5, 3.5 Hz, 1H), 3.46 (brs, 1H), 3.68, 3.74 (AB, J = 13.8 Hz, 2H), 6.16 (s, 1H), 7.17−7.33 (m, 5H). δ_C (75.5 MHz, $CDCl_3$) 11.5, 24.1, 29.9, 41.8, 46.6, 55.8, 56.2, 63.0, 102.3, 126.6, 128.1, 138.8, 159.6, 172.3. ν_{max} 2961s, 1601s, 1494m, 1418s, 1370m, 1184m, 1010m. *m/z* 269.16537; $C_{17}H_{21}N_2O$ [MH^+] requires *m/z* 269.16539.

***anti*-2-Azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (18).** A solution of **14f** (1.399 g, 5.40 mmol) in dry MeOH (40 mL) was hydrogenolyzed over Pd/C (10%, 0.25 g) with stirring for 24 h. The reaction mixture was filtered through Celite, and the solvent was removed in vacuo to leave a yellow oil that was chromatographed (17:3, ether/MeOH, NH_3) to provide **18** (0.612 g, 67%), R_f 0.29. δ_H (300 MHz, $CDCl_3$) 1.25 (t, J = 7.1 Hz, 3H), 1.48−1.57, 1.77−1.98 (2 × m, 2H, 2H), 2.62 (brs, 1H), 2.69 (d, J = 9.5 Hz, 1H), 2.73 (brs, 1H), 3.01 (ddd, $J \approx$ 9.5, 3.0, 3.0 Hz, 1H), 3.61 (brs, 1H), 4.12 (q, J = 7.1 Hz, 2H). δ_C (75.5 MHz, $CDCl_3$) 13.9, 26.8, 30.9, 39.2, 51.9, 53.6, 57.4, 60.0, 171.5. ν_{max} 3407b, 2979s, 1730s, 1541m, 1372m, 1226s, 1051m cm^{-1}. *m/z* 170.11811; $C_9H_{16}NO_2$ [MH^+] requires 170.11810.

***anti*-2-Boc-2-azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (19).** The *anti*-ethyl ester **18** (103 mg, 0.61 mmol), Boc_2O (202 mg, 0.93 mmol), and $NaHCO_3$ (187 mg, 2.23 mmol) were stirred in THF (2 mL) and water (6 mL) at room temperature for 20 h. The reaction mixture was extracted with ether (4 × 4 mL), the organic extracts were combined, dried over anhydrous $MgSO_4$, and filtered, and the solvents were removed in vacuo. The resulting colorless oil was chromatographed (7:3 ether/petrol, NH_3) yielding **19** (105 mg, 64%), R_f 0.54. δ_H [300 MHz, $CDCl_3$; where there is signal duplication (slow N−CO rotation, ratio ∼52:48) the minor rotamer signal is shown in italics] 1.27 (bt, J = 7.0 Hz, 3H), *1.45*, 1.46 (2 × s, 9H), 1.57−1.88 (m, 4H), 2.76 (m, 2H), *3.01*, 3.07 (2 × d, J = 9.7 Hz, 1H), 3.32, *3.35* (2 × brs, 1H), 4.15 (bq, J = 7.0 Hz, 2H), 4.31, *4.45* (2 × brs, 1H). δ_C (75.5 MHz, $CDCl_3$) 14.1, *25.8* & 26.0, 28.5, *29.1* & 29.3, 39.1 & *39.6*, *52.6* & 53.0, 53.1 & *53.7*, *57.3* & 58.1, 60.5, *79.2* & 79.3, *153.7* & 154.1, 170.5. ν_{max} 2977s, 1736s, 1697s, 1408s, 1173s, 1101s, 1048s cm^{-1}. *m/z* 270.17050; $C_{14}H_{24}NO_4$ (MH^+) requires 270.17053.

***anti*-2-Boc-7-(3-methyl-isoxazol-5-yl)-2-azabicyclo[2.2.1]-heptane (20).** Using the procedure described by Fitch et al.,[4] a solution of butyllithium (0.58 mL, 1.6 M in hexanes, 0.93 mmol) was added dropwise over 10 min to a solution of acetoxime (34 mg, 0.47 mmol) in dry THF (1 mL) under argon at 0 °C. After stirring for 2 h at 0 °C, a solution of the *anti*-ethyl ester **19** (58 mg, 0.22 mmol) in dry THF (1 mL) was added over 10 min. The reaction mixture was stirred under argon at 0 °C for 20 h and then transferred to vigorously stirred 1 M HCl (8 mL) over 40 min. This mixture was neutralized ($NaHCO_3$) and extracted with CH_2Cl_2 (5 × 15 mL), the combined organic extracts were dried over anhydrous $MgSO_4$ and filtered, and the solvents were removed in vacuo. The resulting yellow oil was chromatographed (7:3 ether/petrol), yielding **20** (19 mg, 48% based on recovered **19**), R_f 0.21 and **19** (19 mg). NMR signals were broadened; where there is signal duplication (slow N−CO rotation, ratio ∼2:3) the minor rotamer signal is shown in italics. δ_H (300 MHz, $CDCl_3$) 1.47 (s, 9H), 1.60−1.86 (m, 4H), 2.28 (s, 3H), 2.85 (brs, 1H), 3.14 (brs, 1H), 3.45 (bddd, $J \approx$ 9.6, 2.7, 2.7 Hz, 1H), 4.43, *4.51* (2 × brs, 1H), 5.88 (brs, 1H). δ_C (100.6 MHz, $CDCl_3$) 11.4, 25.9, 28.5, *28.9* & 29.2, 40.1 & *40.7*, *46.0* & 46.3, 53.2 & *53.7*, *58.3* & 59.3, 79.6, 102.6, 154.2, 159.7, 170.0. ν_{max} 2976m, 1694s, 1406s, 1173m, 1112m cm^{-1}. *m/z* 279.17085; $C_{15}H_{23}N_2O_3$ (MH^+) requires 279.17087.

***anti*-7-(3-Methyl-isoxazol-5-yl)-2-azabicyclo[2.2.1]-heptane (21) from 20.** The ester **20** (8.3 mg, 0.030 mmol) was stirred in a mixture of EtOH (0.435 mL), ethyl acetate (1.205 mL), and acetyl chloride (0.359 mL) at 0 °C for 1 h. The reaction mixture was evaporated to dryness to give the hydrochloride salt of **21** (6.4 mg, 99%). Data for the free amine **21**: δ_H (300 MHz, $CDCl_3$) 1.40−1.75 (m, 4H), 1.9 (brs, NH), 2.27 (s, 3H), 2.71 (brs, 1H), 2.77 (d, J = 9.6 Hz, 1H), 3.09 (brs, 1H), 3.13 (m,1H), 3.71 (brs, 1H), 5.85 (s, 1H). δ_C (75.5 MHz, $CDCl_3$) 11.4, 26.8, 31.0, 40.4, 47.2, 52.3, 58.7, 102.3, 159.6, 171.4. ν_{max} 3392b, 2968s, 2876m, 1725w, 1602s, 1534m, 1415s cm^{-1}. *m/z* 179.11839; $C_{10}H_{15}N_2O$ [MH^+] requires *m/z* 179.11844.

Direct Formation of 21 from 18. The procedure described for **17** was followed using acetoxime (76 mg, 1.04 mmol) in dry THF (3 mL), butyllithium (1.43 mL, 1.6 M, 2.29 mmol), and the ester **18** (65 mg, 0.38 mmol) in dry THF (2 mL). HCl (8 mL, 10.2 M) was used in the second step, and after workup **21** was isolated as an orange oil (28 mg). Quantitative ^1H NMR analysis gave a yield of 16.2 mg, 24%.

***syn*-2-Azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (22).** The ester **16** (1.56 g, 6.02 mmol) in dry MeOH (40 mL) was hydrogenolyzed as described for **14f** to yield **22** as a yellow oil (0.625 g, 61%), R_f 0.30. δ_H (300 MHz, $CDCl_3$) 1.27 (t, J = 7.1 Hz, 3H), 1.40−1.77 (m, 4H), 2.0 (brs NH), 2.59 (brs, 1H), 2.61 (d, J = 9.8 Hz, 1H), 2.51 (brs, 1H), 3.13 (ddd, $J \approx$ 9.8, 3.1, 3.1 Hz, 1H), 3.61 (bd, ≈ 2.6 Hz, 1H), 4.14 (complex "q",[23] J = 7.1 Hz, 2H). δ_C (75.5 MHz, $CDCl_3$) 13.9, 28.8, 30.8, 40.0, 49.8, 52.2 & 52.4, 58.27 & 58.31, 60.0, 172.3 & 172.7. ν_{max} 3406b, 2977s, 1728s, 1542m, 1409s, 1303m, 1192m, 1037m cm^{-1}. *m/z* 170.11812; $C_9H_{16}NO_2$ [MH^+] requires *m/z* 170.11810.

***syn*-2-Boc-2-azabicyclo[2.2.1]heptane-7-carboxylic Acid Ethyl Ester (23).** Treatment of the ester **22** (128 mg, 0.76 mmol) with Boc_2O (262 mg, 1.20 mmol) and $NaHCO_3$ (200 mg, 2.38 mmol) in THF (2 mL) and water (6 mL) using the method described for **19** gave **23** (130 mg, 64%), R_f (7:3, ether/petrol, NH_3) 0.39. δ_H [300 MHz, $CDCl_3$; where there is signal duplication due to slow N−CO rotation (ratio ∼45:55) the minor rotamer signal is shown in italics.] 1.24 (t, J = 7.1 Hz, 3H), *1.44* & 1.46 (2 × s, 9H), 1.64−1.80 (m, 4H), 2.53 (brs, 1H), *2.72* & 2.75 (2 × brs, 1H), *2.94* & 3.00 (2 × d, J = 9.8 Hz, 1H), 3.51 (m, 1H), 4.13 (m, 2H), 4.39 & *4.51* (2 x brs, 1H). δ_C (75.5 MHz, $CDCl_3$) 14.2, 27.4, 28.5, 30.7, 39.4, 40.0, 50.6, 51.2, 52.2, 53.0, 58.2, 58.9, 60.4, 60.5, 79.0, 79.1, 154.2, 154.5, 170.6, 170.9. ν_{max} 2974m, 1735s, 1696s, 1406s, 1163s, 1104s cm^{-1}. *m*/*z* 270.17057; $C_{14}H_{24}NO_4$ [MH^+] requires *m*/*z* 270.17053.

***syn*-2-Boc-7-(3-methyl-isoxazol-5-yl)-2-azabicyclo[2.2.1]-heptane (24).** Acetoxime (74 mg, 1.01 mmol), butyllithium in hexanes (1.27 mL, 1.6 M, 2.03 mmol), and the ester **23** (133 mg, 0.49 mmol) were reacted using the procedure described for **20** to give **24** (61 mg, 52% based on recovered **23**), R_f (7:3, ether/petrol, NH_3) 0.35, and recovered **23** (19 mg). δ_H [300 MHz, $CDCl_3$; where there is signal duplication because of slow N−CO rotation (ratio ∼45:55), the minor rotamer signal is shown in italics.] *1.43* & 1.47 (2 × s, 9H), 1.57−1.95 (m, 4H), *2.24* & 2.25 (2 × s, 3H), 2.74 & *2.80* (2 × brs, 1H), 2.94 & *2.95* (2 × brs, 1H), *2.96* & 3.03 (2 × d, J = 10.1 Hz, 1H), 3.15 & *3.27* (2 × ddd, $J \approx$ 9.9, 2.7, 2.7 Hz, 1H), *4.35* & 4.51 (2 × brs, 1H), 5.84 & *5.91* (2 × brs, 1H). δ_C (100.6 MHz, $CDCl_3$) 11.4, *28.5* & 28.6, *30.6* & 30.9, *40.8* & 41.4, 45.6 & *46.1*, 50.1 & *50.8*, *58.6* & 59.7, *79.4* & 79.6, 102.1 & *102.3*, 154.5, 159.8, *170.2* & 170.4. ν_{max} 2976s, 2359s, 1694s, 1406s, 1150s, 1112s cm^{-1}. *m*/*z* 279.17088; $C_{13}H_{23}N_2O_3$ [MH^+] requires *m*/*z* 279.17087.

***syn*-7-(3-Methyl-isoxazol-5-yl)-2-azabicyclo[2.2.1]-heptane (*syn*-isoepiboxidine) (9).** The *N*-Boc compound **24** (12.5 mg, 0.0450 mmol) was deprotected as described for compound **20**, yielding the hydrochloride salt of compound **9** (9.6 mg, 99%). Data for the free amine **9**: δ_H (300 MHz, $CDCl_3$) 1.49−1.68 (m, 2H), 1.72−1.91 (m, 2H), 2.27 (bs, 3H & NH), 2.66 (brs, 1H), 2.67 (d, J = 9.9 Hz, 1H), 2.91 (brs, 1H), 2.99 (ddd, $J \approx$ 9.9, 3.2, 3.2 Hz, 1H), 3.66 (bd, J = 2.5 Hz, 1H), 5.96 (s, 1H). δ_C (75.5 MHz, $CDCl_3$) 11.3, 29.0, 31.9, 40.8, 46.5, 49.9, 59.2, 102.4, 159.7, 171.6). ν_{max} 3400b, 2966s, 2877s, 1602s, 1418s cm^{-1}. *m*/*z* 179.11842; $C_9H_{16}NO_2$ [MH^+] requires 179.11844.

Direct Formation of 9 from 22 Acetoxime (72 mg, 0.99 mmol) in dry THF (3 mL) was treated with butyllithium (1.30 mL, 1.6 M, 2.08 mmol) and the ester **22** (54 mg, 0.32 mmol) in dry THF (2 mL) following the procedure described for **17**. Following workup using HCl (8 mL, 10.2 M), **9** was isolated as an orange oil (30 mg). Quantitative ^1H NMR analysis using an internal standard gave a yield of 14.6 mg, 26%.

Supporting Information Available: Spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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