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EPIBATIDINE ANALOGS SYNTHESIZED FOR CHARACTERIZATION OF NICOTINIC PHARMACOPHORES—A REVIEW

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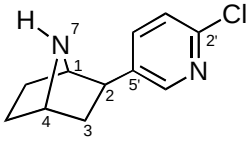
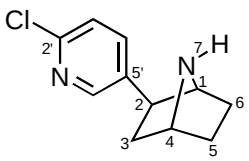
Abstract – In 1992 Daly and co-workers reported the isolation of a new natural product, epibatidine. Future studies showed that epibatidine was an nAChR ligand with analgesic potency 200-400 times greater than that of morphine. However, its potential as a new drug was limited by its toxic side effects, probably resulting from its activity at a number of nAChR subtypes. Epibatidine's unique structure and potent activity made it an ideal lead structure for the development of nAChR ligands with reduced side effects and better nAChR subtype selectivity. This review presents the synthetic methods we have used to synthesize a number of epibatidine agonists, antagonists, and mixed agonists/antagonists to better characterize the α4β2 nAChR pharmacophore and hopefully provide compounds that have potential for treating nicotine addiction.

INTRODUCTION

In 1992 Daly and co-workers were able to isolate trace amounts of a natural product from the skin of the Ecuadorian poison frog Epipedobates tricolor that was found to be 200-400 times more potent than morphine as an analgesic.[1] The analgesic activity was not blocked by naloxone, showing that the activity was not due to interaction with opioid receptors. Subsequent studies showed that the analgesic activity resulted from interaction with nicotinic acetylcholine receptors (nAChRs).[2, 3] Daly reviewed these early studies.[4] Epibatidine (**1a**) has a 7-azabicyclo[2.2.1]heptane structure to which is attached an *exo*-5-(2'-chloropyridinyl) substituent. Fletcher and co-workers[5] showed that the natural alkaloid possessed the (1*R*,2*R*,4*S*)-stereochemistry. Epibatidine (**1a**) and its enantiomer possess negative and positive rotations of the plane of polarized light, respectively (Figure 1). However, salts showed opposite signs of rotation from the free bases.



(*1R,2R,4S*)-epibatidine [**(-)-1a**], natural freebase, (-)-isomer



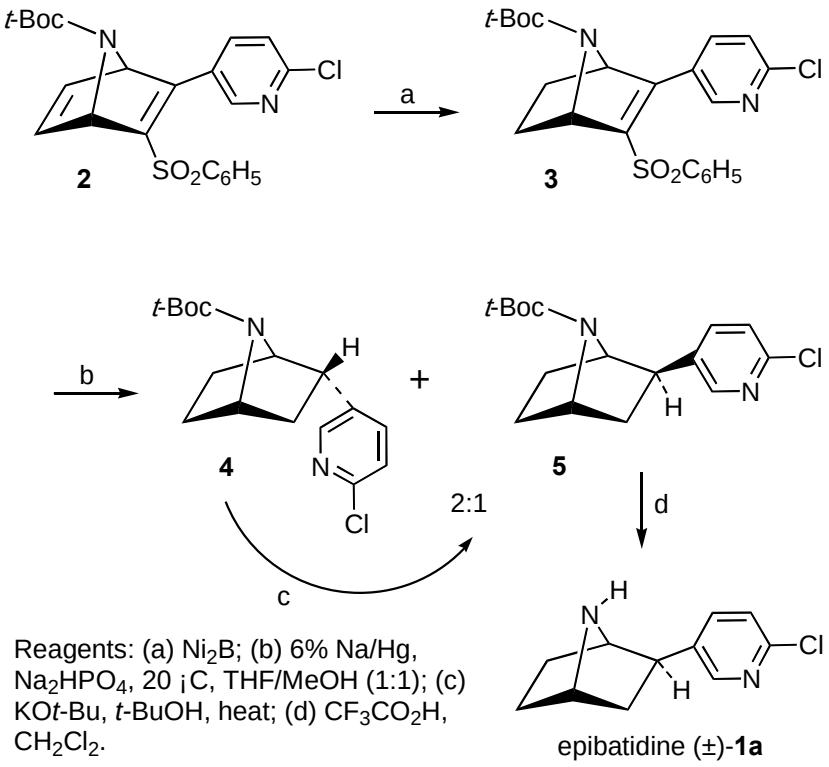
(*1S,2S,4R*)-epibatidine [**(+)-1a**], freebase, (+)-isomer

Figure 1

The unique structure and biological activity of epibatidine generated considerable interest in this compound and precipitated the development of numerous routes for its synthesis from simple starting materials. A number of these syntheses have been detailed in prior reviews.[6,7,8,9,10,11,12,13] In this review, we report the synthetic methods we used to prepare epibatidine as well as a number of epibatidine analogs that were used in a structure activity relationship (SAR) study to help characterize the pharmacophores for nAChRs and hopefully lead to new pharmacotherapies for treating nicotine addiction.

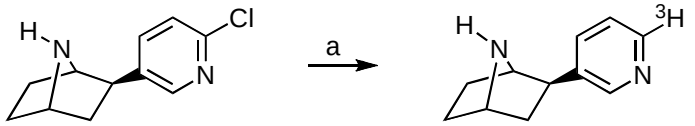
SYNTHESIS OF EPIBATIDINE

Our first synthesis of epibatidine was based on a synthesis reported by Huang and Shen[14] (see Scheme 1).[15] In this approach, the least substituted double bond of the cycloadduct **2**, prepared by a method similar to that used by Huang and Shen to prepare the *N*-carbomethoxy analog, was selectively reduced using nickel boride to give 96% of **3**. Desulfonation and concomitant reduction of **3** proceeded cleanly to give 65% of a 2:1 mixture of the *endo* and *exo* isomers **4** and **5**. The *endo* isomer **4** was epimerized to the *exo* isomer **5** in 46% yield using the reported procedure of Fletcher and co-workers.[5] Deprotection of the *N*-Boc epibatidine (**5**) with trifluoroacetic acid at room temperature gave 97% of racemic epibatidine as a white solid. Optical resolution of (±)-**1** using di-*p*-toluoyltartaric acid gave (+)- and (-)-**1a**, which were converted to their hydrochloride salts.



Scheme 1

Tritium labeled (+)- and (-)-norchloroepibatidine [(+)- and (-)-**6**] were synthesized by reductive tritiation of epibatidine (Scheme 2).[16] These radiolabeled compounds proved useful for in vivo labeling of nAChRs.[16]



(+)- or (-)-**1a** (+)- or (-)-**6**

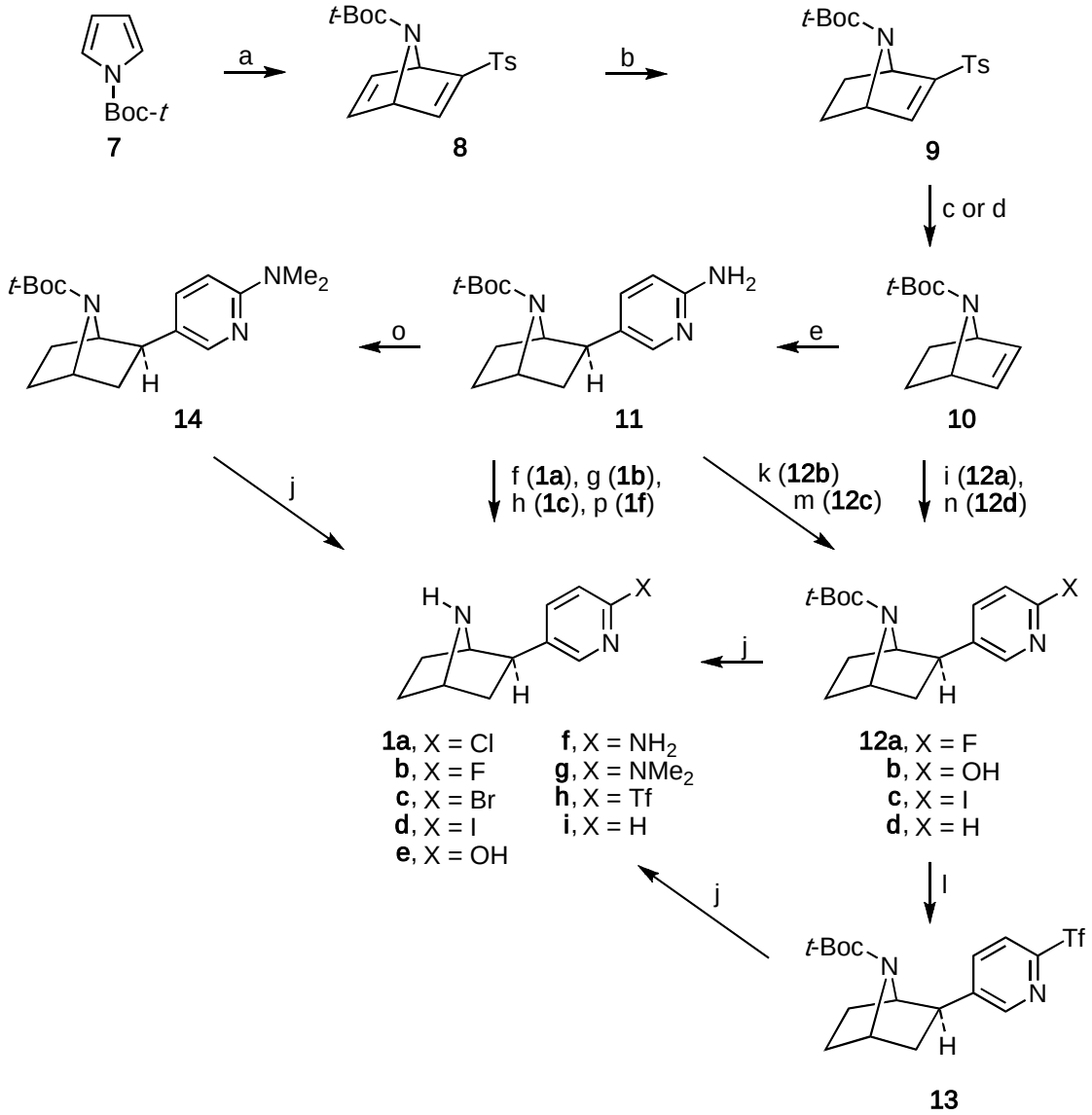
Reagents: (a) $^3H_2$, 10% Pd/C, 1 N KOH/MeOH.

Scheme 2

IMPROVED SYNTHESIS OF EPIBATIDINE AND 2'-SUBSTITUTED DESCHLORO-EPIBATIDINE ANALOGS

In 2001 we reported an improved synthesis of **1a**.[17] The new route also proved useful for the synthesis of the 2'-substituted deschloroepibatidine analogs **1b-i** (Scheme 3).[17] Heating a solution of *N*-(*tert*-butoxycarbonyl)pyrrole (**7**)[18] and *p*-tolylsulfonylacetylene[19] at 80 °C yielded diene **8**. Selective reduction of the 5,6-double bond using nickel boride[15] in ethanol gave monoolefin **9**. Originally, desulfonation of **9** to give **10** was carried out in 55% yield using 2.5% sodium amalgam in a 1:1 mixture of ethyl acetate and *tert*-butyl alcohol containing disodium hydrogen phosphate.[20] Later we discovered that **9** could be converted to **10** in higher yield and on larger scale by adding tributyltin hydride to **9** in benzene containing 2,2'-azabisisobutyronitrile (AIBN) followed by treatment of the resulting addition product with tetrabutylammonium fluoride in tetrahydrofuran.[21] Coupling of **10** with 2-amino-5-iodopyridine using palladium acetate as catalyst in dimethylformamide containing tetrabutylammonium chloride and potassium formate at 100 °C for 12 h provided 7-*tert*-butoxycarbonyl-*exo*-2-(2'-amino-5'-pyridinyl)-7-azabicyclo[2.2.1]heptane (**11**). Diazotization[22] of **11** in pyridine containing 70% hydrogen fluoride effected conversion of the 2-amino group to a fluoro group and deprotection of the *N*-Boc group gave 46% of the 2'-fluoro analog **1b**. Compound **1b** could also be obtained by direct reductive Heck coupling of 2-fluoro-5-iodopyridine (obtained by diazotization of 2-amino-5-iodopyridine[19] in pyridine•HF) with **10** to give intermediate **12a**, which gave the desired **1b** on removal of the *N*-Boc-protecting group with trifluoroacetic acid. However, this route was less desirable since the overall yield was 39% and the coupling of 2-fluoro-5-iodopyridine with **10** took 4 days, whereas the coupling of 2-amino-5-iodopyridine with **10** was complete in 12 h. We also found that diazotization of **11** in hydrochloric acid in the presence or absence of cuprous chloride gave a 76% yield of epibatidine (**1a**) which was identical to an authentic sample, thus, providing an improved synthesis of **1a**.[15] Diazotization of **11** using sodium nitrite in hydrobromic acid containing bromine or acetic acid containing potassium carbonate gave the 2'-bromo analogs **1c** and the *N*-*tert*-butoxycarbonyl 2'-hydroxy compound **12b**, respectively. Treatment of **12b** with trifluoromethanesulfonic anhydride gave the 2'-triflate **13**.

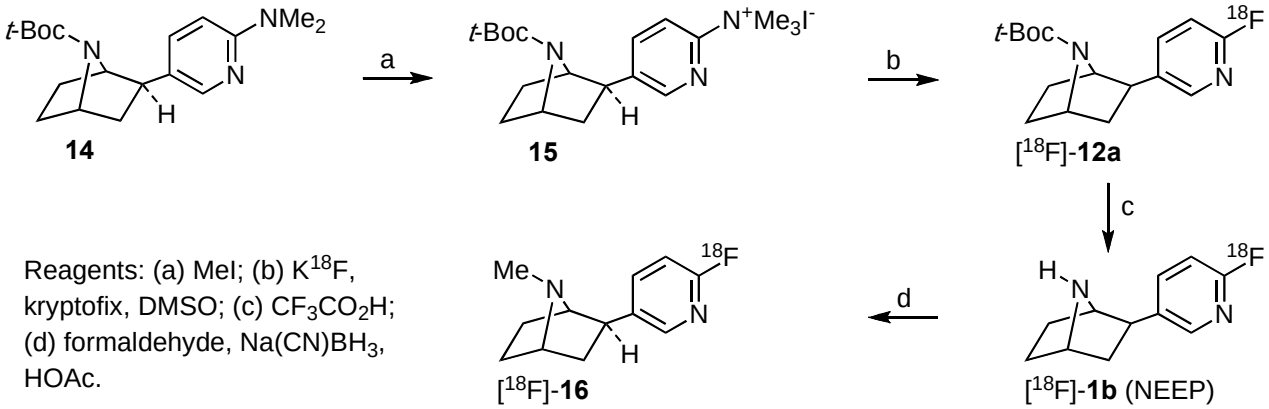
Diazotization of **11** with isoamyl nitrite in methylene iodide containing hydrogen iodide afforded the *N-tert*-butoxycarbonyl 2'-iodo compound **12c**. Reductive Heck coupling of **10** with 3-iodopyridine yielded *N-tert*-butoxycarbonyl 2'-norchloro analog **12d**. Reductive methylation of **11** with formaldehyde using sodium cyanoborohydride yielded the *N-tert*-butoxycarbonyl 2'-dimethylamino analog **14**. Treatment of **12b-d**, **13**, and **14** with trifluoroacetic acid yielded the 2'-substituted epibatidine analogs **1d**, **1e**, and **lg-i**. Treatment of **11** with methanolic hydrogen chloride provided **1f**.



Reagents: (a) HC≡CTs, 80 °C; (b) Ni_2B, EtOH; (c) Na/Hg (2.5%), Na_2HPO_4, EtOAc:*t*-BuOH (1:1); (d) (i) Bu_3SnH, AIBN, benzene, (ii) Bu_4NF, THF; (e) 2-amino-5-iodopyridine, $Pd(OAc)_2$, *n*-Bu_4NCl, KO_2CH, DMF, 100 °C, 12 h; (f) $NaNO_2$, HCl, CuCl; (g) $NaNO_2$, pyridine•HF; (h) $NaNO_2$, Br_2, HBr; (i) 2-fluoro-5-iodopyridine, $Pd(OAc)_2$, *n*-Bu_4NCl, KO_2CH, DMF, 100 °C, 4 days; (j) CF_3CO_2H; (k) $NaNO_2$, HOAc, K_2CO_3; (l) Tf_2O, pyridine; (m) isoamyl nitrite, CH_2I_2, HI; (n) 3-iodopyridine, $Pd(OAc)_2$, *n*-Bu_4NCl, KO_2CH, DMF, 80 °C, 24 h; (o) $NaBH_3CN$, formaldehyde; MeOH; (p) HCl.

Scheme 3

[^{18}F]-2'-Fluorodeschloroepibatidine and [^{18}F]-*N*-methyl-2'-fluorodeschloroepibatidine proved useful as positron emission tomography (PET) imaging agents.[22,23,24,25] Scheme 4 outlines the method used to synthesize these two PET ligands. Methylation of **14** with iodomethane affords the 2'-(*N,N,N*-trimethylammonium) analog **15**.[20] Nucleophilic heteroaromatic substituents of **15**, using no-carrier added potassium [^{18}F]fluoride followed by deprotection with trifluoroacetic acid, afforded [^{18}F]-2'-fluorodeschloroepibatidine ([^{18}F]-**1b**).[26] Reductive *N*-methylation with formaldehyde and sodium cyanoborohydride yielded [^{18}F]-*N*-methyl-2'-fluorodeschloroepibatidine ([^{18}F]-**16**).[26]



Scheme 4

SYNTHESIS OF 2',3'-DISUBSTITUTED DESCHLOROEPIBATIDINE ANALOGS

As a continuation of our SAR studies, we synthesized 2',3'-disubstituted deschloroepibatidine analogs **17a-n** (Figure 2).[27]

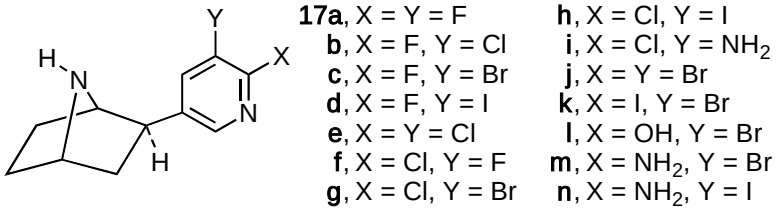
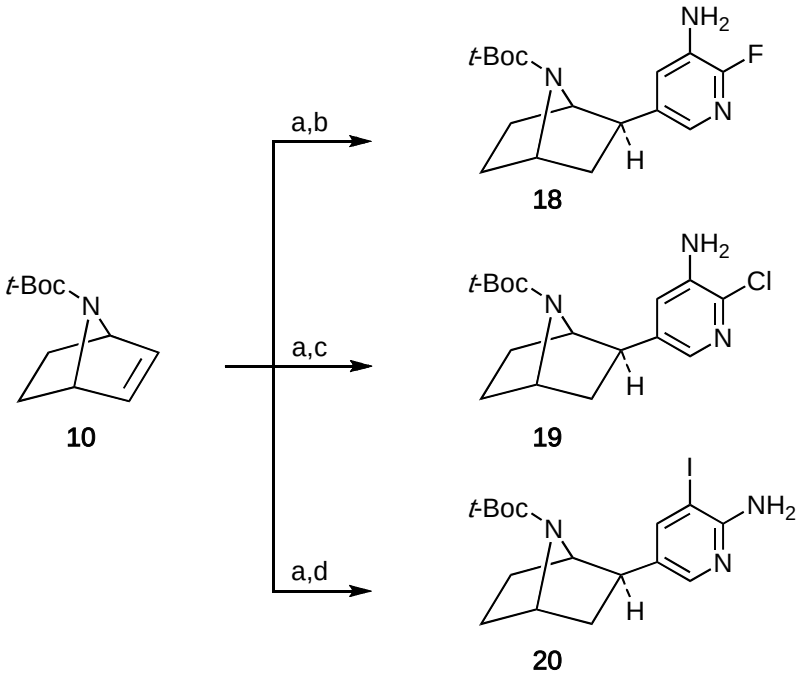


Figure 2

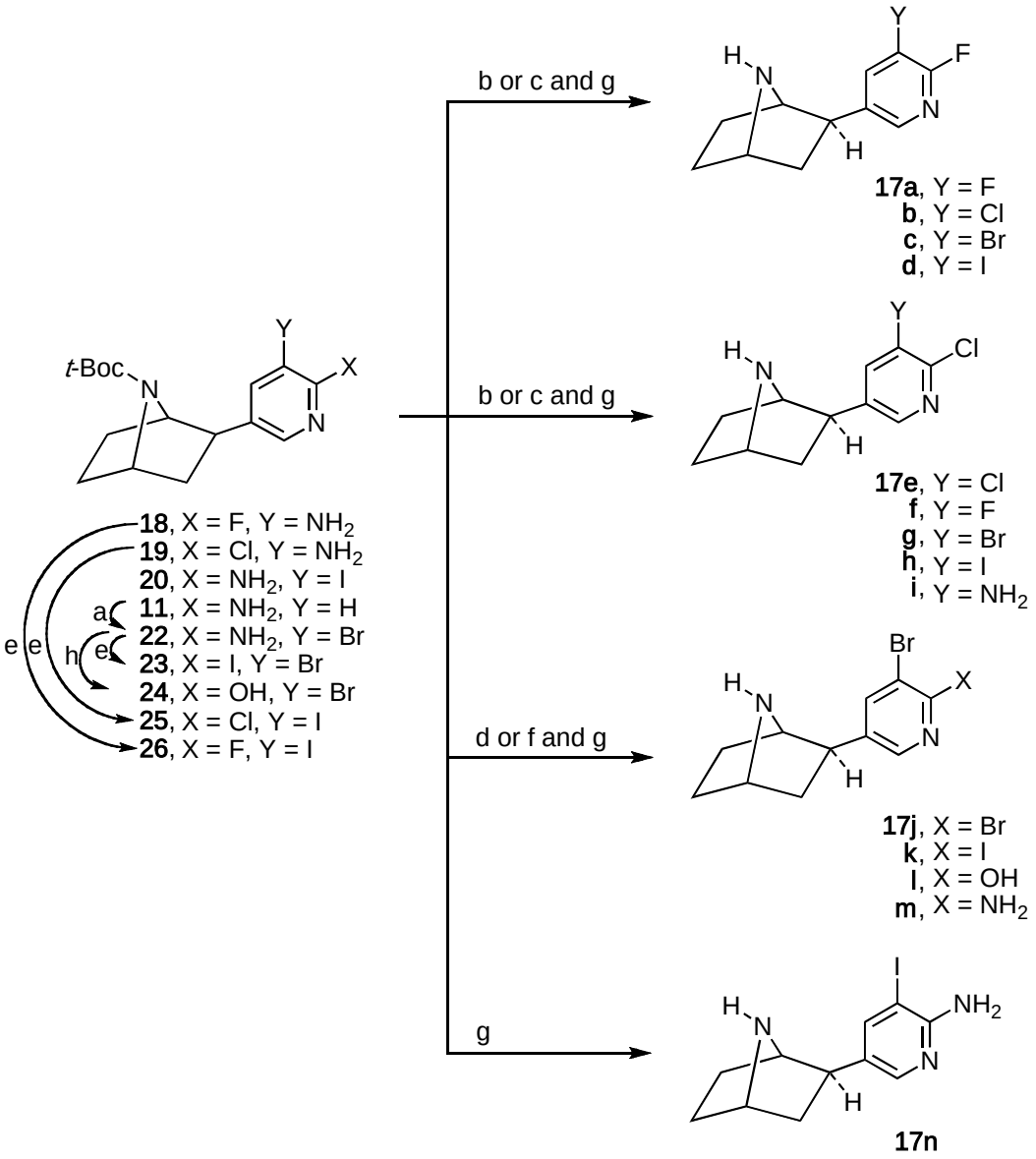
Scheme 5 outlines the synthesis of the intermediates **18-20**, which were used to prepare target compounds **17a-n**. The reductive palladium acetate-catalyzed addition of 3-amino-2-fluoro-5-iodopyridine (**21a**), 3-amino-2-chloro-5-iodopyridine (**21b**), and 2-amino-3,5-diidopyridine (**21c**) to 7-*tert*-butoxy-carbonyl-7-azabicyclo[2.2.1]hept-2-ene (**10**) in dimethylformamide (DMF) containing tetrabutyl-ammonium chloride and potassium formate at 100 °C provided the intermediates **18-20**.



Reagents: (a) $Pd(OAc)_2$, Bu_4NCl, KO_2CH, DMF, 100 °C, 12 h; (b) 3-amino-2-fluoro-5-iodopyridine (**21a**); (c) 3-amino-2-chloro-5-iodopyridine (**21b**); (d) 2-amino-3,5-diiodopyridine (**21c**).

Scheme 5

Scheme 6 outlines the routes used to prepare *tert*-butoxycarbonyl intermediates **22-26** and their conversion to target compounds **17a–n**. Bromination of 7-*tert*-butoxycarbonyl-2'-aminodeschloroepibatidine (**11**)[20] using bromine in acetic acid provided intermediate **22**. Diazotization of **18**, **19**, and **22** with isoamyl nitrite containing hydroiodic acid in methylene iodide gave **26**, **25**, and **23**, respectively. Diazotization of **22** with *tert*-butyl nitrite in DMF yielded intermediate **24**. Diazotization of **18** and **19** with sodium nitrite in pyridine containing 70% hydrogen fluoride-pyridine affected conversion of the 3-amino group to a fluoro group and deprotection of the *N*-*tert*-butoxycarbonyl group to give **17a**,**f**, respectively. Diazotization of **18** and **19** with sodium nitrite in hydrochloric acid in the presence of cuprous chloride gave **17b**,**e**, respectively. Diazotization of **22** with pyridine containing 70% hydrogen fluoride-pyridine provided **17c**. Diazotization of **22** using sodium nitrite in hydrochloric acid in the presence of copper (I) chloride or hydrobromic acid in the presence of copper (I) bromide yielded **17g** and **17j**, respectively. Treatment of **26**, **25**, **19**, **23**, **24**, **22**, and **20** with trifluoroacetic acid provided **17d**,**h**,**i**,**k-n**, respectively.

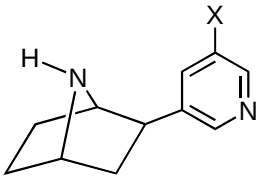


Reagents: (a) Br_2, HOAc; (b) HF-pyridine, $NaNO_2$; (c) HCl, CuCl, $NaNO_2$; (d) HBr, $NaNO_2$, CuBr; (e) isoamyl nitrite, HI, CH_2I_2; (f) HCl, dioxane; (g) CF_3CO_2H; (h) *tert*-butyl nitrite, DMF.

Scheme 6

SYNTHESIS OF 3'-SUBSTITUTED DESCHLOROEPIBATIDINE ANALOGS

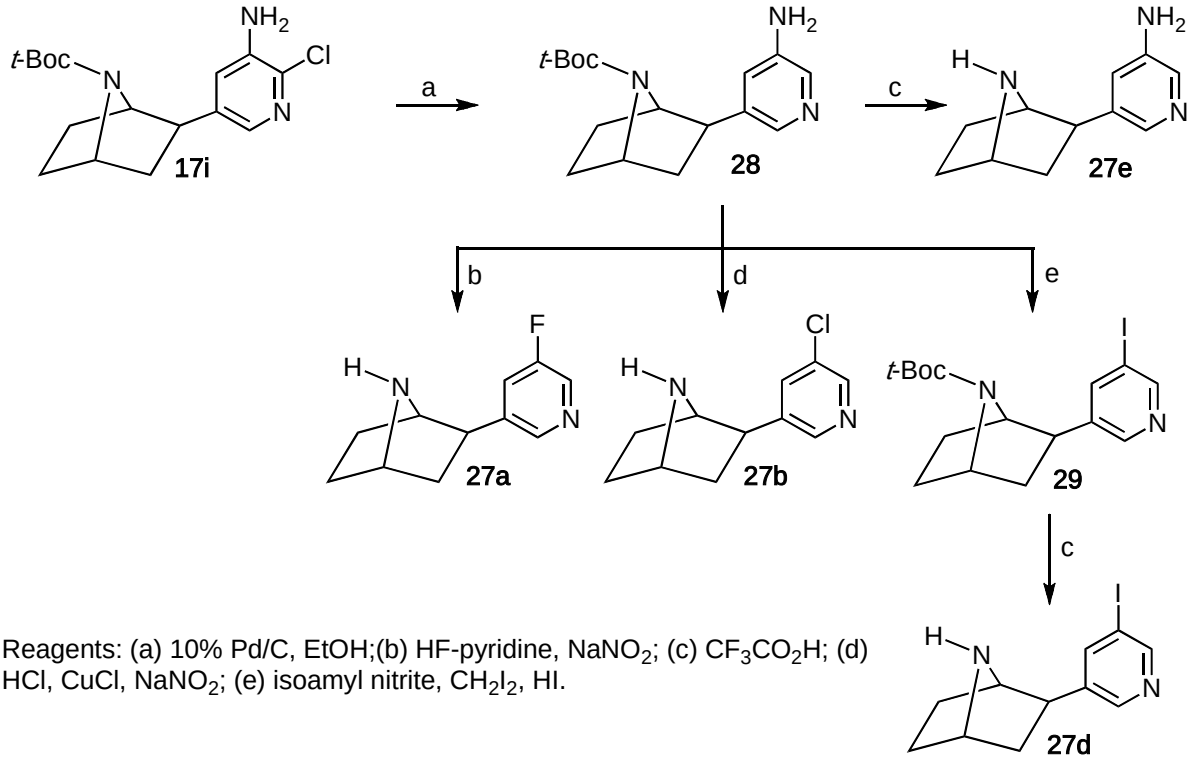
In efforts to further characterize the nAChR pharmacophore, we synthesized 3'-substituted deschloroepibatidine analogs **27a-g** (Figure 3).[28]



27a, X = F
b, X = Cl
c, X = Br
d, X = I
e, X = NH_2
f, X = CH_2=CH-
g, X = HC≡C-

Figure 3

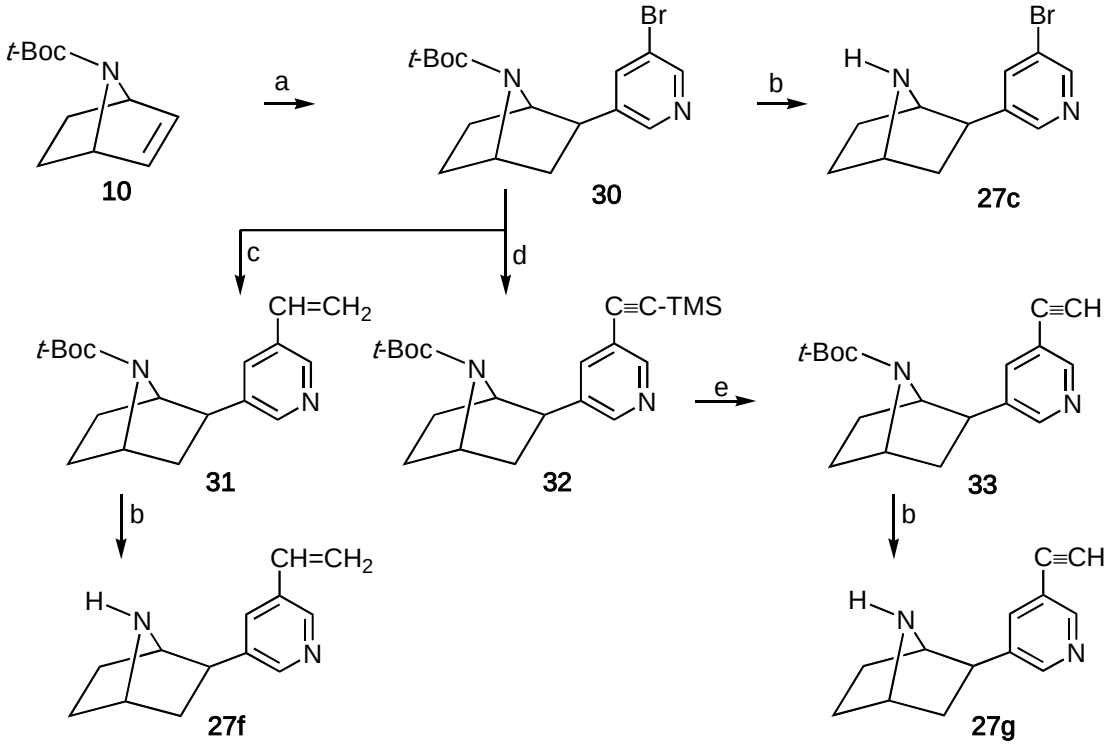
Scheme 7 outlines the synthesis of 3'-substituted deschloroepibatidine analogs of **27a**,**b**,**d**,**e**. Catalytic reductive dechlorination of 3'-aminoepibatidine (**17i**) using 10% palladium on carbon catalyst in ethanol provided the intermediate 7-*tert*-butoxycarbonyl-3'-aminodeschloroepibatidine (**28**). Diazotization of **28** with sodium nitrite in pyridine containing 70% hydrogen fluoride-pyridine affected conversion of the 3'-amino group to a fluoro group and deprotection of the *N*-*tert*-butoxycarbonyl group to give the 3'-fluoro analog **27a**. Diazotization of **28** with sodium nitrite in hydrochloric acid in the presence of cuprous chloride yielded the 3'-chloro analog **27b**. Diazotization of **28** with isoamyl nitrite containing hydroioidic acid in methylene iodide gave the 3'-iodo intermediate **29**. Treatment of **28** and **29** with trifluoroacetic acid provided the 3'-amino and 3'-iodo analogs **27e** and **27d**, respectively. Resolution of **27d** with (+)- and (-)-di-*p*-toluoyl-tartaric acid afforded (-)- and (+)-**27d**.



Reagents: (a) 10% Pd/C, EtOH;(b) HF-pyridine, $NaNO_2$; (c) CF_3CO_2H; (d) HCl, CuCl, $NaNO_2$; (e) isoamyl nitrite, CH_2I_2, HI.

Scheme 7

The 3'-bromo-(**27c**), 3'-vinyl-(**27f**), and the 3'-ethynyl-(**27g**) analogs were prepared as shown in Scheme 8. Reductive palladium acetate-catalyzed addition of 3,5-dibromopyridine to 7-*tert*-butoxy-carbonyl-7-azabicyclo[2.2.1]hept-2-ene (**10**) in DMF containing tetrabutylammonium chloride and potassium formate at 80 °C provided the intermediate 7-*tert*-butoxy-carbonyl-3'-bromodeschloroepibatidine (**30**). Coupling of **30** with vinyltributyltin, catalyzed by tris(dibenzylideneacetonyl)bis-palladium, in *N*-methyl-2-pyrrolidinone (NMP) containing tris(2-furyl)-phosphine (TFP) at 80 °C afforded the 7-*tert*-butoxycarbonyl-protected 3'-vinyl intermediate **31**. The reaction of **30** with trimethylsilylacetylene in the presence of a catalytic amount of copper (I) iodide and bis(triphenylphosphine)-palladium (II) chloride in degassed disopropylamine in a sealed tube at 50 °C produced **32**. Removal of the silyl protecting group with tetrabutyl ammonium fluoride in THF afforded the *tert*-butoxycarbonyl 3'-ethynyl intermediate **33**. Treatment of **30**, **31**, and **33** with trifluoroacetic acid in methylene chloride yielded the 3'-bromo, 3'-vinyl-, and 3'-ethynyl- analogs **27c**,**f**,**g**, respectively.

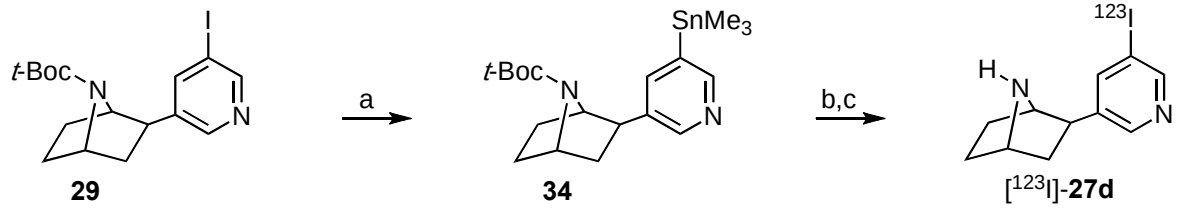


Reagents: (a) $Pd(OAc)_2$, $(n\text{-}Bu)_4NCl$, KO_2CH, DMF, 80 °C, 3,5-dibromopyridine; (b) CF_3CO_2H, CH_2Cl_2; (c) $CH_2{=}CHSn(C_4H_9)_3$, $Pd_2(dba)_3$, NMP, TFP, 80 °C; (d) HC≡CTMS, $Pd(Cl)_2[PC_6H_5)_3]_2$, $[Me_2CH]_2NH$, CuI; (e) Bu_4NF, THF.

Scheme 8

The iodine-123 analog of **27d** and [^{11}C]-*N*-methyl-3'-iododeschloroepibatidine (**35**) have been shown to be useful single photon emission computed tomography (SPECT) and PET agents for in vivo imaging of α4β2 nAChRs.[29, 30] The synthesis of these two compounds is shown in Scheme 9[29] and Scheme 10,[30] respectively.

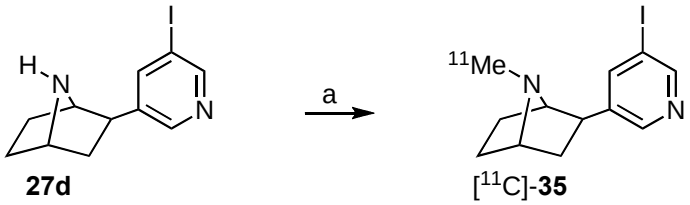
Treatment of **29** with hexamethylditin in the presence of tetrakis(triphenylphosphine)palladium (0) yielded the trimethyltin precursor **34**. Reaction of iodine-123 sodium iodide with **34** in the presence of chloramine-T followed by deprotection with trifluoroacetic acid afforded [^{123}I]-**27d**. Treatment of **27d** with [^{11}C]methyliodide in dimethylforamide gives [^{11}C]-**35**.



29 **34** [^{123}I]-**27d**

Reagents: (a) $[Me_3Sn]_2$, $Pd[P(C_6H_5)_3]_4$; (b) $Na^{123}I$, chloramine-T; (c) CF_3CO_2H.

Scheme 9



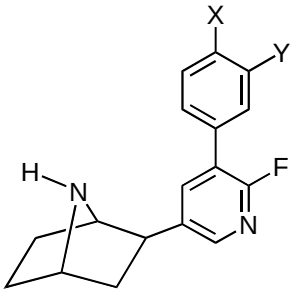
27d [^{11}C]-**35**

Reagents: (a) ^{11}MeI, DMF.

Scheme 10

SYNTHESIS OF 2'-FLUORO-3'-(SUBSTITUTED PHENYL)DESCHLOROEPIBATIDINE ANALOGS

In a preliminary study we found that 2'-fluoro-3'-phenyldeschloroepibatidine (**36a**) (Figure 4) was, to our knowledge, the first epibatidine analog reported to show nAChR antagonist properties.[31] In order to further develop this finding, compounds **36b-k** (Figure 4) were synthesized and evaluated.[32]

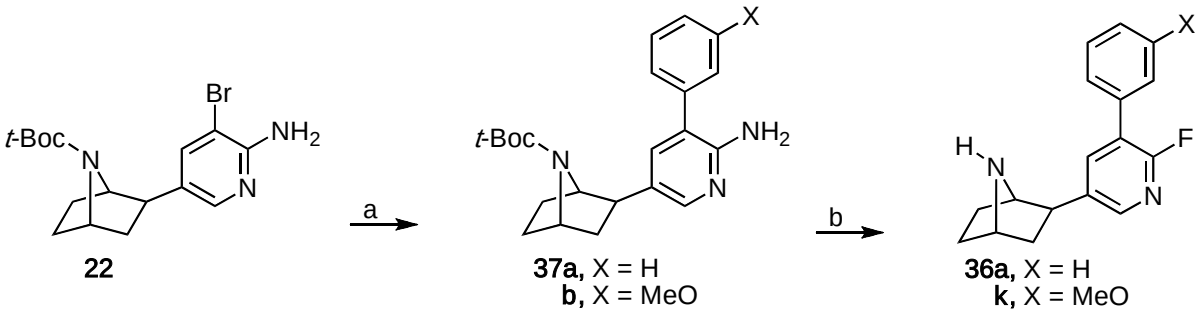


36a, X = Y = H
b, X = H, Y = F
c, X = F, Y = H
d, X = H, Y = Cl
e, X = Cl, Y = H
f, X = H, Y = NO_2
g, X = NO_2, Y = H
h, X = H, Y = NH_2
i, X = NH_2, Y = H
j, X = H, Y = MeO
k, X = MeO, Y = H

Figure 4

The synthesis of **36a** and **36k** is outlined in Scheme 11. Palladium acetate-catalyzed reaction of **22** with phenylboronic acid or 3-methoxyphenylboronic acid in dimethoxyethane (DME) in the presence of tri-(*o*-tolyl)phosphine and sodium carbonate gave the *tert*-butoxycarbonyl-protected 2'-amino-3'-phenyl

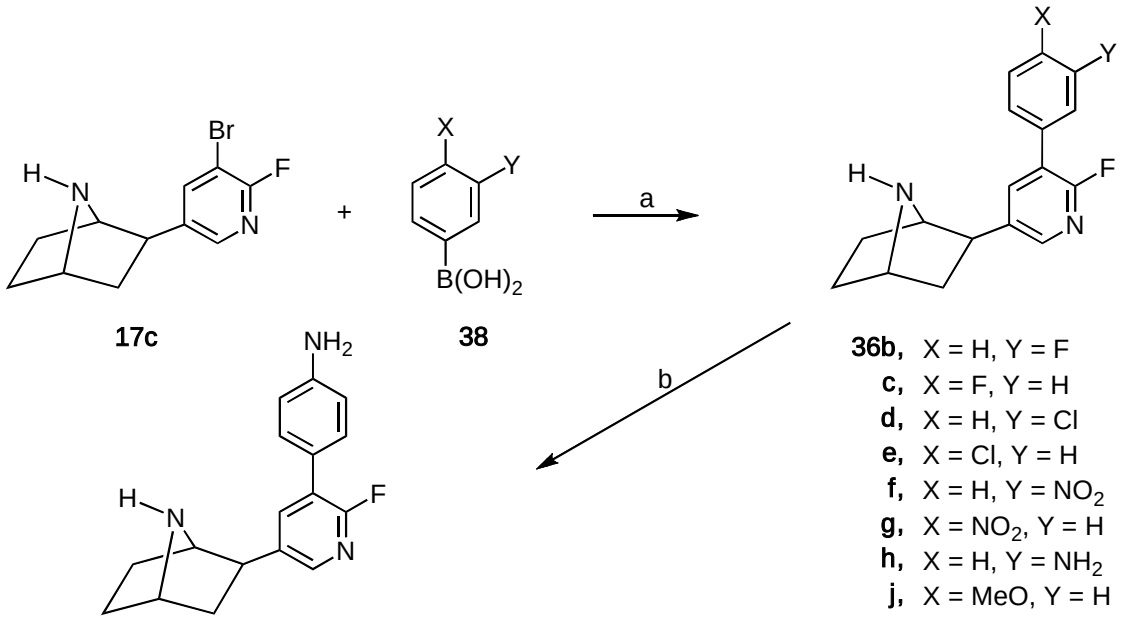
analog **37a** and **37b**, respectively. Diazotization of **37a,b** using sodium nitrite in pyridine containing 70% hydrogen fluoride/pyridine yielded the desired compounds **36a** and **36k**, respectively. Resolution of **36a** using (+)- and (-)-di-*p*-toluoyltartaric acid afforded (+)- and (-)-**36a**. After completion of the synthesis of **36a** and **37k**, we discovered that the palladium catalyzed coupling of arylboronic acids could be carried out without protecting the azabicyclo[2.2.1]heptane amino group. This provided a more efficient route to compounds **36b-j**, which is outlined in Scheme 12. Palladium acetate catalyzed reaction of **17c** with the appropriate 3- or 4-substituted phenyboronic acid (**38**) in dimethoxyethane (DME) in the presence of tri(*o*-tolyl)phosphine and sodium carbonate gave the desired compounds **36b–h** and **36j**. Reduction of the 4'-nitro analog **36g** using iron and hydrochloride acid afforded the 4'-amino analog **36i**.



Reagents: (a) $C_6H_5B(OH)_2$ or $MeOC_6H_4B(OH)_2$, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, DME, Na_2CO_3; (b) $NaNO_2$, pyridine•HF.

Scheme 11

It was particularly interesting to note that compounds **36a-k** possessed varying degrees of nAChR agonist and antagonist properties in studies using mice.[32]

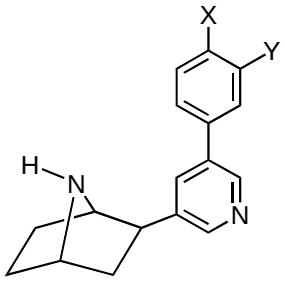


Reagents: (a) $Pd(OAc)_2$, P(*o*-tolyl)$_3$, DME, Na_2CO_3; (b) Fe, HCl

Scheme 12

SYNTHESIS OF 3'-(SUBSTITUTED PHENYL)DESCHLOROEPIBATIDINE ANALOGS

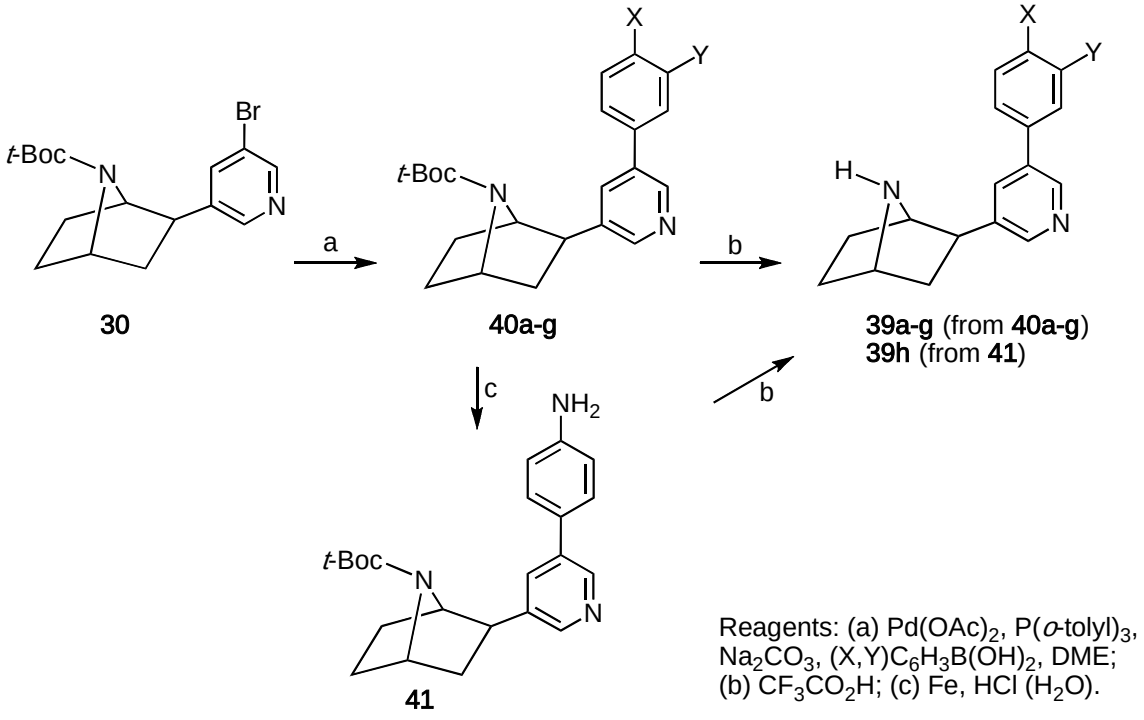
In a continuation of our SAR studies to identify compounds having antagonist and mixed agonist/antagonist properties, we synthesized the 3'-(substituted phenyl)deschloroepibatidine analogs **39a-j** (Figure 5).



39a, X = Y = H
b, X = Cl, Y = H
c. X = H, Y = Cl
d, X = F, Y = H
e, X = H, Y = F
f, X = NO_2, Y = H
g, X = H, Y = NO_2
h, X = NH_2, Y = H
i, X = H, Y = NH_2
j, X = H, Y = MeO

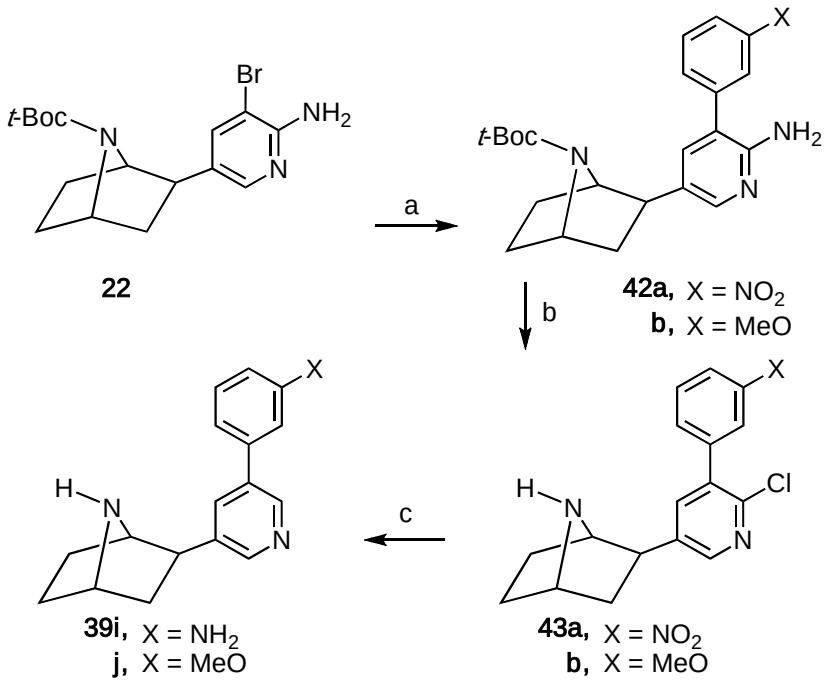
Figure 5

The synthesis of **39a-h** is shown in Scheme 13.[33] Palladium acetate catalyzed coupling of *tert*-butoxycarbonyl-3'-bromodeschloroepibatidine (**30**) with the appropriately substituted phenylboronic acid in dimethoxyethane (DME) in the presence of tri-(*o*-tolyl)phosphine and sodium carbonate gave the *tert*-butoxycarbonyl-protected 3'-(substituted phenyl)deschloroepibatdine analogs (**40a-g**). Reduction of the 4-nitrophenyl intermediate **40f** with iron powder in hydrochloric acid gave the 4-aminophenyl compound **41**. Treatment of **40a-g** and **41** with trifluoroacetic acid in methylene chloride removed the protecting *tert*-butoxycarbonyl group and afforded the desired 3-(substituted phenyl)deschloroepibatidine analogs **39a-h**.



Scheme 13

The 3'-(3-aminophenyl)- and 3'-(3-methoxyphenyl)deschloroepibatidine analogs **39i** and **39j**, respectively, were synthesized as outline in Scheme 14 before the more efficient synthesis used for **39a-g** was developed. Palladium acetate catalyzed addition of 3-nitrophenylboronic acid or 3-methoxyphenylboronic acid to 7-*tert*-butoxycarbonyl-2'-amino-3'-bromodeschloroepibatidine (**22**) provided the *tert*-butoxy-carbonyl-protected 3'-(3-nitrophenyl)- and 3'-(3-methoxyphenyl)deschloroepibatidine analogs **42a** and **42b**, respectively. Diazotization of **42a** and **42b** using sodium nitrite in hydrochloric acid yielded the 3'-(3-methoxyphenyl)epibatidine analog **43a** and the 3'-(3'-nitrophenyl)epibatidine analog **43b**, respectively. Catalytic hydrogenation of **43a** and **43b** using 10% palladium on carbon catalyst in methanol yielded the desired **39i** and **39j**, respectively.



Reagents: (a) $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Na_2CO_3, DME, H_2O, 3-$NO_2C_6H_4B(OH)_2$ or $MeOC_6H_4B(OH)_2$; (b) $NaNO_2$, HCl; (c) 10% Pd/C, MeOH.

Scheme 14

SYNTHESIS OF BRIDGED AND FUSED RING ANALOGS OF EPIBATIDINE

Since reduction of the conformational freedom of a lead compound like epibatidine can provide useful SAR information concerning the nAChR pharmacophore, we synthesized the conformationally restricted epibatidine analogs **44-49** (Figure 6).[34]

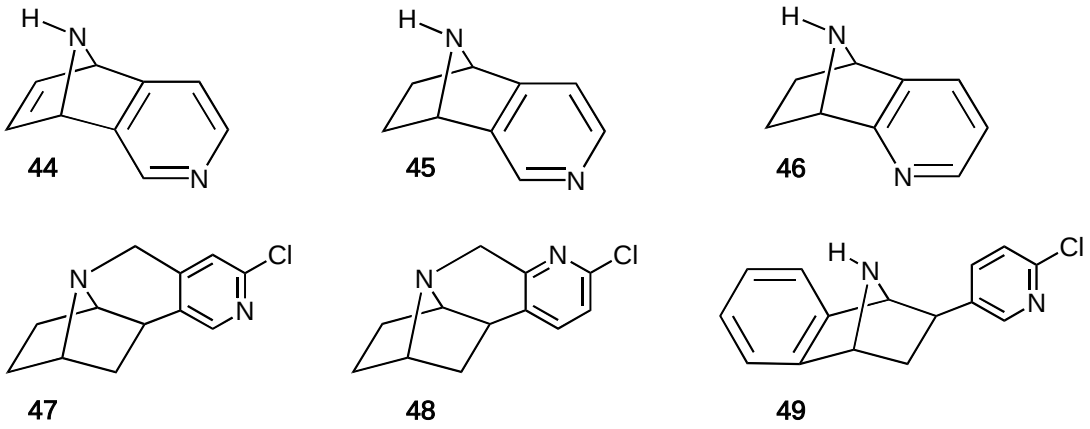
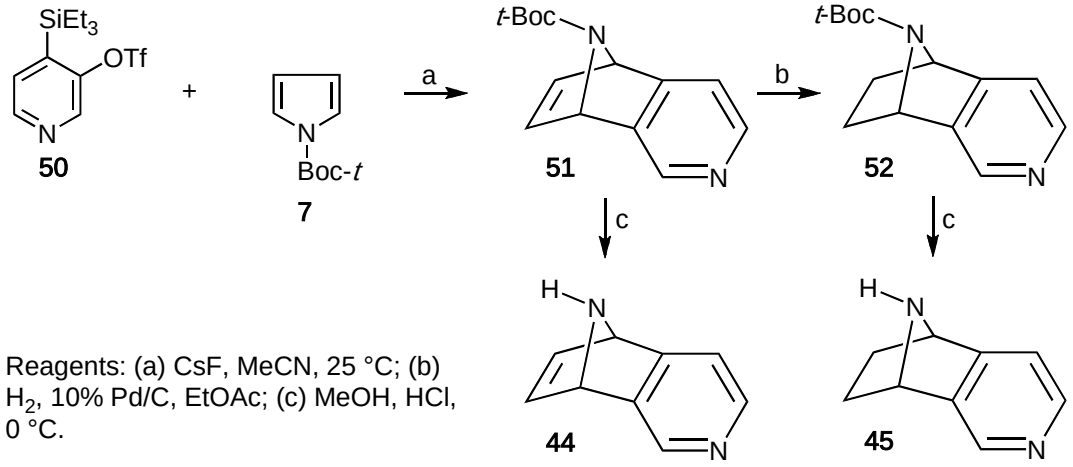


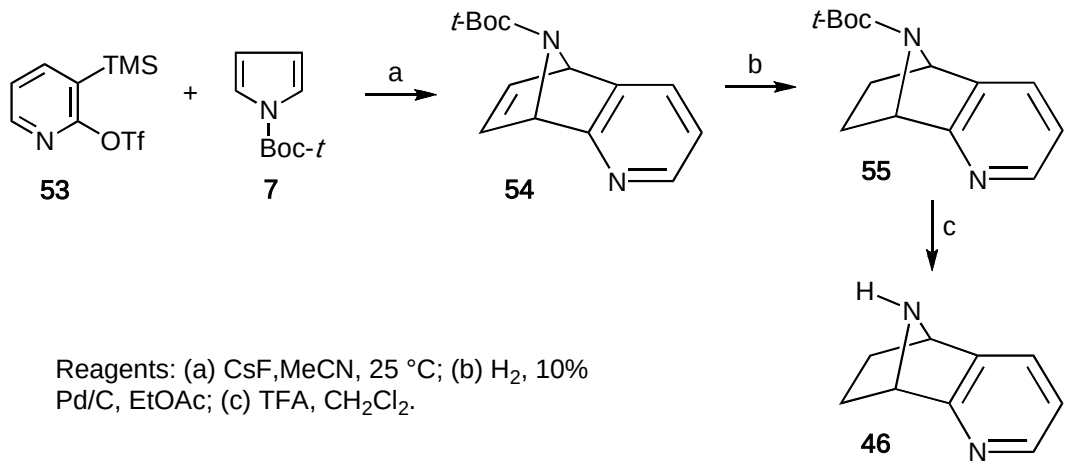
Figure 6

The fused ring epibatidine analogs **44** and **45** were synthesized as outlined in Scheme 15. 3-Pyridyne, generated by treating 4-triethylsilylpyridin-3-yl trifluoromethanesulfonate (**50**)[35] with cesium fluoride in acetonitrile, was added to **7** to give **51**. Catalytic hydrogenation of **51** using 10% palladium on carbon in ethyl acetate yielded **52**. Treatment of **51** and **52** with hydrogen chloride in methanol provided the desired 3,4-pyridine fused ring epibatidine analogs **44** and **45**, respectively. A totally different synthesis of **45** which involved sixteen steps and a very low overall yield has been reported.[36]



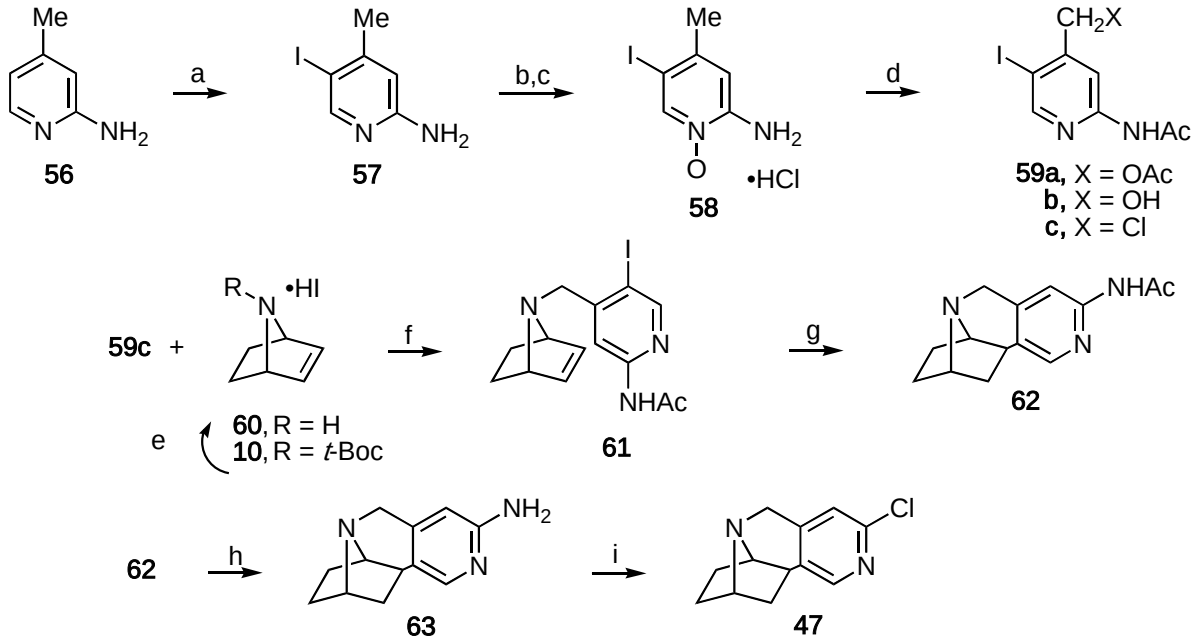
Scheme 15

The 2,3-pyridine ring based analog **46** was synthesized by a procedure similar to that for **45** (Scheme 16).[34] 2-Pyridyne, generated by treating 3-trimethylsilylpyridin-2-yl trifluoromethanesulfonate (**53**)[37] with cesium fluoride in acetonitrile, was added to **7** to give **54**. Catalytic reduction of **54** in ethyl acetate using 10% palladium on carbon catalyst yielded **55**. Removal of the *tert*-butoxycarbonyl protecting group using trifluoroacetic acid in methylene chloride provided **46**.



Scheme 16

The bridged epibatidine analog **47** was synthesized as shown in Scheme 17 starting with 2-amino-4-methylpyridine (**56**). Iodination of **56** using iodine in a periodic, sulfuric, acetic acid mixture afforded a 71% yield of 2-amino-5-iodo-4-methylpyridine (**57**).[34]

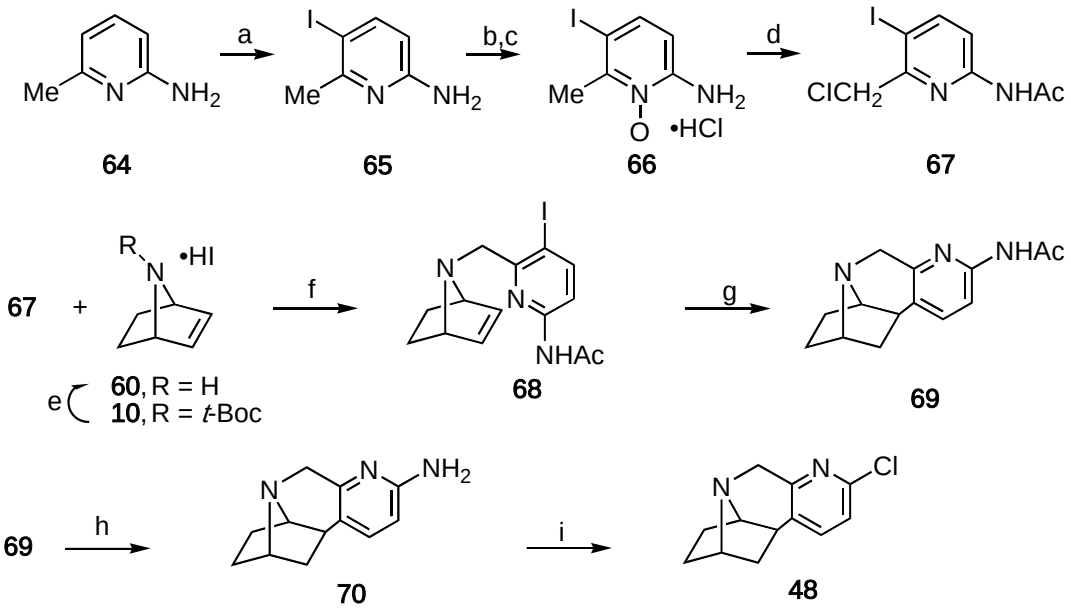


Scheme 17

Reaction of **57** with *m*-chloroperbenzoic acid in acetone gave the *N*-oxide **58**, which was isolated as the hydrochloride salt in 85% yield. Treatment of the hydrochloride salt of **58** with acetic anhydride in dioxane was expected to give the 4-acetoxymethyl or 4-hydroxymethyl compounds **59a** or **59b**, respectively.

Surprisingly, 2-acetamido-4-chloromethyl-5-iodopyridine (**59c**) was isolated in 56% yield. Apparently, chloride ion displaced the acetoxy or hydroxy group from the expected 4-acetoxymethyl or 4-hydroxymethyl intermediate to give **59c**. Alkylation of 7-azabicyclo[2.2.1]hept-2-ene (**60**), generated from *tert*-butoxycarbonyl-7-azabicyclo[2.2.1]hept-2-ene (**10**) using trimethylsilyl iodide in chloroform, with **59c** provided the *N*-alkylated product **61** in 43% yield. Two possible approaches for the conversion of **61** to **62** were the Heck cyclization[38, 39, 40, 41] and a radical initiated cyclization.[42, 43] We found that intramolecular cyclization of **61** using reductive Heck conditions similar to that used for intermolecular coupling[20] (palladium diacetate, potassium formate, and tetrabutyl ammonium chloride in dimethylformamide at 90 °C) provided the hexahydro-7,10-methanopyrrolo-2-[1,2-b]-2,6-naphthyridine **62** in 45% yield. Hydrolysis of **62** using refluxing 3 N hydrochloric acid gave a 90% yield of the 3-amino analog **63**. Diazotization of **63** using sodium nitrite in concentrated hydrochloric acid yielded the desired epibatidine analog **47** in 28% yield.

Bridged epibatidine analog **48** was synthesized from 2-amino-6-methylpyridine (**64**) by a set of reactions exactly analogous to those used to prepare analog **47** that proceeded through intermediate **65-70** (see Scheme 18).[34] The yield in each step was similar to the analogous step in the synthesis of **47**.

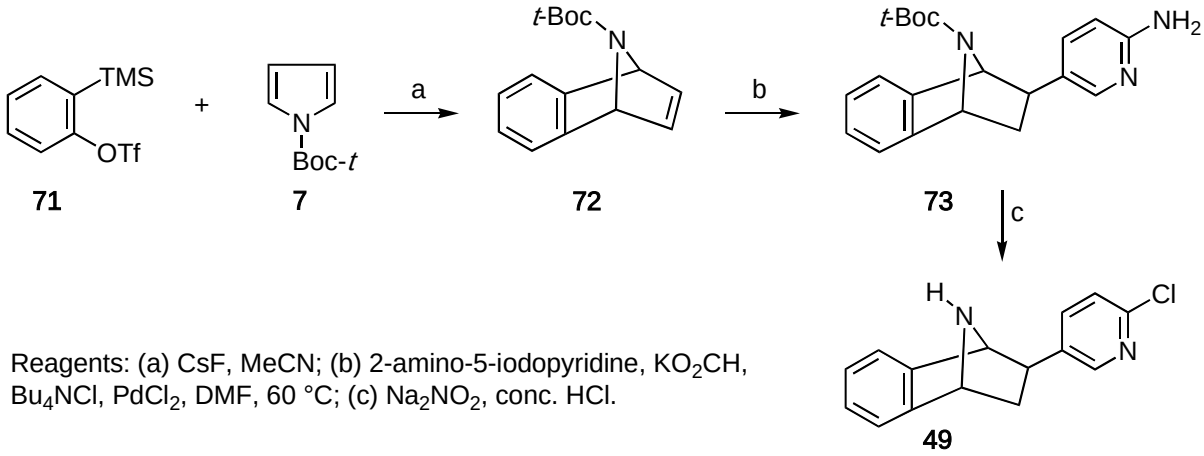


Reagents: (a) H_5IO_6, I_2, H_2SO_4, HOAc, H_2O, 80 °C; (b) MCPBA; (c) ethereal HCl; (d) Ac_2O, dioxane; (e) Me_3SiI, $CHCl_3$; (f) NaOMe, MeOH; (g) KO_2CH, $Pd(OAc)_2$, Bu_4NCl, DMF, 90 °C; (h) 3 N HCl, reflux; (i) $NaNO_2$, conc. HCl.

Scheme 18

The 5,6-benzofusion ring epibatidine analog **49** was synthesized as outlined in Scheme 19.[34] Benzyne, generated by treating 2-trimethylsilyl trifluoromethanesulfonate (**71**)[44, 45, 46] with cesium fluoride in

acetonitrile, was added to **7** to give **72**. Subjection of **72** to reductive Heck conditions using 2-amino-5-iodopyridine gave **73**. Diazotization of **73** using sodium nitrite in concentrated hydrochloride acid yielded the desired **49**.



Scheme 19

SYNTHESIS OF *EXO*-2-(2'-CHLORO-5-PYRIDINYL)-7-(*ENDO* AND *EXO*)-AMINOBICYCLO-[2.2.1]HEPTANES

In one of our SAR studies, we reported the syntheses of epibatidine analogs where the nitrogen in the 7-azabicyclo[2.2.1]heptane ring was moved outside the ring (see structures **74** and **75**, Figure 7).[47]

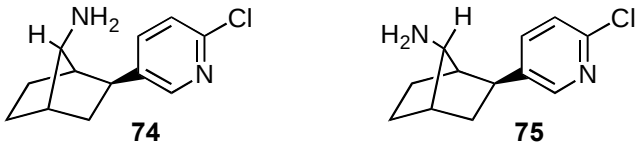
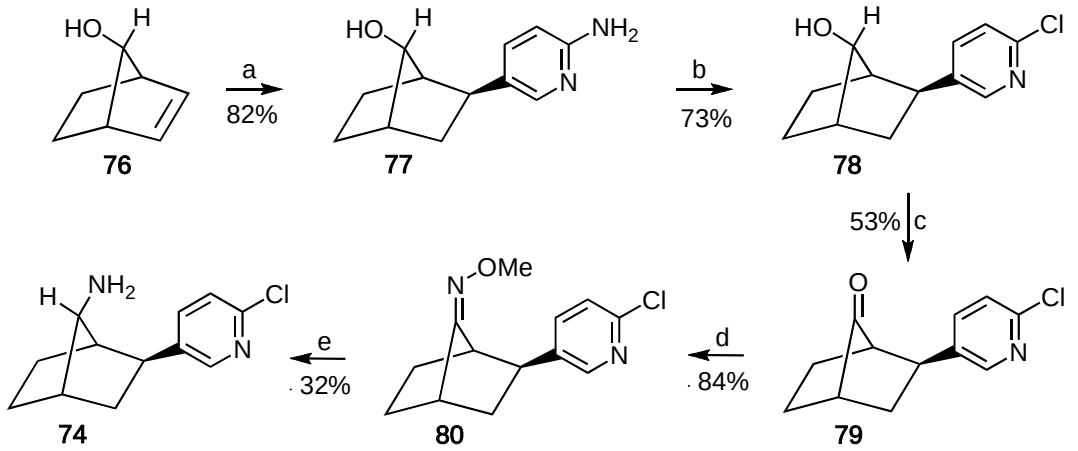


Figure 7

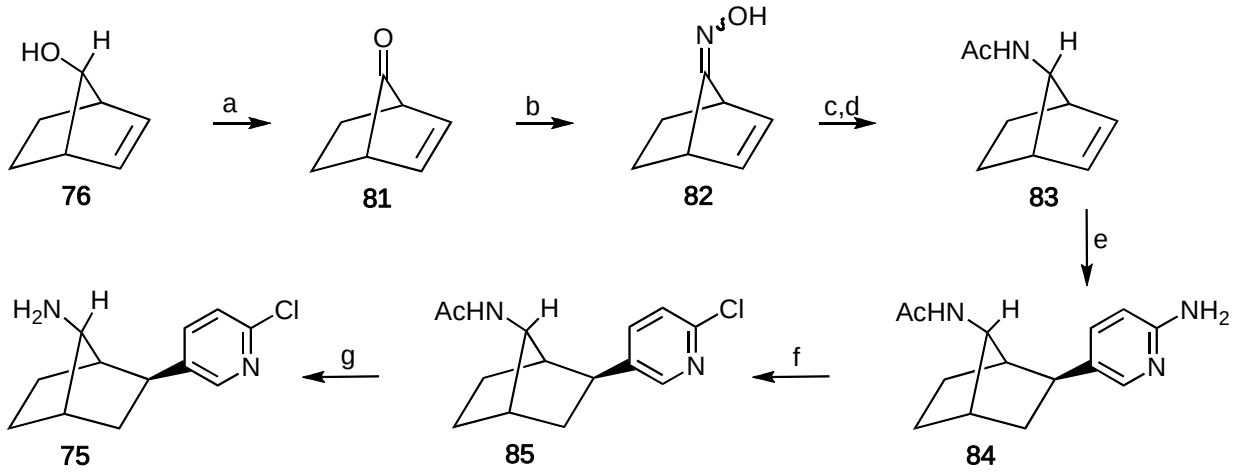
The synthesis of **74** is outlined in Scheme 20.[47] The reductive palladium acetate catalyzed addition of 2-amino-5-iodopyridine to *exo*-7-hydroxybicyclo[2.2.1]heptane (**76**)[48] in dimethylformamide (DMF) containing potassium formate and tetrabutylammonium chloride at 110 °C provided an 82% yield of less sterically hindered *exo*-2-(2'-amino-5'-pyridinyl)-7-*exo*-hydroxybicyclo[2.2.1]heptane (**77**).[49,50] Diazotization of **77** using sodium nitrite in concentrated hydrochloric acid afforded the 2'-chloro compound **(78)** in a 73% yield. Oxidation of **78** using pyridine sulfur trioxide complex in DMSO provided a 50% yield of the 7-oxo compound **79**. Potassium carbonate catalyzed condensation of **79** with methoxylamine in ethanol provided an 84% yield of the *O*-methyloxime compound **80**. Reduction of **80** from the least hindered face with diborane in tetrahydrofuran afforded *exo*-2-(2'-chloro-5'-pyridinyl)-7-*endo*-aminobicyclo[2.2.1]heptane **(74)** in 32% yield.



Reagents: (a) 2-amino-5-iodopyridine, $Pd(OAc)_2$, KO_2CH, DMF, Bu_4NCl, 110 °C; (b) $NaNO_2$, HCl; (c) pyridine sulfur trioxide, Et_3N, DMSO; (d) $MeONH_2$, K_2CO_3, EtOH; (e) B_2H_6,THF.

Scheme 20

We were able to obtain **75** by the route shown in Scheme 21.[47] Swern oxidation of **76** using oxalyl chloride, dimethyl sulfoxide, and triethylamine gave ketone **81** in 70% yield. Treatment of **81** with hydroxylamine hydrochloride in aqueous methanol containing sodium acetate provided a 36% yield of oxime **82**. Lithium aluminum hydride reduction of **82** followed by acetylation gave the *N*-acetamido protected intermediate **83** (69%). Reductive palladium acetate catalyzed addition of 2-amino-5-iodopyridine to **83** in DMF containing potassium formate and tetrabutylammonium chloride yielded 20% of the less sterically hindered *exo*-2-(2'-amino-5'-pyridinyl)-7-exo- acetamidobicyclo[2.2.1]heptane **(84)**.[49,50] Diazotization of **84** using sodium nitrite in concentrated hydrochloric acid afforded a 40% yield of 2'-chloro compound **85**. Removal of the protecting acetyl group from **85** using potassium hydroxide in ethylene glycol at 150 °C provided the desired **75** in 73% yield.



Reagents: (a) $(COCl)_2$, DMSO, Et_3N; (b) NH_2OH HCl, NaOAc; (c) $LiA1H_4$, Et_2O; (d) Ac_2O, pyridine; (e) KO_2CH, 2-amino-5-iodopyridine, Bu_4NCl, $Pd(OAc)_2$, DMF; (f) $NaNO_2$, HCl; (g) KOH, $HO(CH_2)_2OH$.

Scheme 21

SUMMARY

In this review, synthetic methods used to prepare a number of different types of epibatidine analogs have been presented. In addition, the epibatidine analogs have been evaluated for their biological activity. For example, K_i values for the inhibition of [^{3}H]epibatidine binding at α,β-nAChR in male rat cerebral cortex and inhibition of binding to the α7 nAChR using [^{125}I]iodoMLA for the epibatidine analogs were determined and compared to epibatidine (**1a**), nicotine, and the α4β2 mixed agonist/antagonist varenicline, which is now an approved drug for treating smokers.

The compounds were also evaluated for analgesic activity in the tail-flick and hot-plate tests as well as for spontaneous activity and hypothermia in the mouse. Compounds whose in vivo activity was less than that expected from their K_i values in the α,β-nAChR screens were evaluated for antagonism of nicotine-induced activity in the mouse test. The Ki values for the 2'-substituted deschloroepibatidine analogues **1b-d** possessing electron withdrawing groups and the unsubstituted analogue **1i** were essentially identical to that of epibatidine (**1a**).[17] Analogues with electron releasing groups had higher K_i values than epibatidine (**1a**). A good correlation was found between K_i binding affinity and ED_{50} values in the tail flick test.[17] The 2',3'-disubstituted deschloroepibatidine analogues **17a-k** and **17m-n** and the 3'-substituted deschloroepibatidine analogues **27a-g** had high affinity for the α4β2 nAChR.[27,28] In contrast to the 2'-substituted deschloroepibatidine analogues, the agonist activity seen in the tail flick for 2',3'-disubstituted or the 3'-substituted analogues did not correlate well with their binding affinity.[27, 28] The 2'-chloro-3'-amino disubstituted analogue **17i** and most of the 3'-substituted analogs **27a-g** were found to have both agonist and antagonist properties in the mouse tests.[27, 28] Several epibatidine analogs from the 2'-fluoro-3-(substituted phenyl)deschloroepibatidine (**36a-k**) and the 3'-(substituted phenyl)deschloroepibatidine (**39a-j**) classes possessed high affinity for the α4β2 nAChR and showed varying degrees of mixed agonist/antagonist activity in the mouse functional test, some with activity similar to varenicline.[32, 33] Future nicotine drug discrimination (DD), condition place preference (CPP), and self-administration (SE) studies may suggest that one or more of these analogs should be considered for development as a pharmacotherapy for treating nicotine addiction.

All bridged and fused ring analogues of epibatidine possessed low nAChR affinity.[34] The binding affinity and in vivo functional activity of the (*endo* and *exo*)-aminobicyclo[2.2.1]heptane analogs **74** and **75** were comparable to those of nicotine.[47]

ACKNOWLEDGEMENTS

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Dr. Carroll has authored 409 publications, 33 book chapters, and 34 patents. A few awards and honors recognizing Dr. Carroll's research accomplishments include: the 2000 Southern Chemist Award from the Memphis Section of the American Chemical Society, the 2001 Herty Award from the Georgia Section of the American Chemical Society, the 2002 American Chemical Society Medicinal Chemistry Award, the 2006 Nathan B. Eddy Award from the College on Problems of Drug Dependence, and the 2006 Research Achievement Award in Drug Design and Discovery from the American Association of Pharmaceutical Scientists.