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DEVELOPMENT OF NOVEL NICOTINIC RECEPTOR MEDIATED THERAPEUTIC AGENTS: SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL EPIBATIDINE ANALOGS AND THE FIRST TOTAL SYNTHESIS OF (±)-ANABASAMINE AND RELATED ANALOGS

A Dissertation

Submitted to the Graduate Faculty of the
University of New Orleans
in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy
in
The Department of Chemistry

by

Stassi C. DiMaggio

B.S., Tulane University, 1998

August 2003

Dedicated to:

My mother, Vita O. DiMaggio

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to my advisor, Professor Mark L. Trudell, for his guidance, support, and encouragement. His confidence helped me to stay focused on my goals. I would also like to thank my committee members, Professor Branko Jursic, Professor John Wiley, Professor Guijun Wang, and Professor Steven Rick. In addition, I would like to thank Professor Bruce C. Gibb for always taking the time to answer any questions I have had as well as Dr. Matthew Tarr and Dr. Paul Hanson.

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ABSTRACT

In an effort to search for a more selective, less toxic neuronal nicotinic acetylcholine receptor analgesic agent in comparison to epibatidine, a series of analogs with hybrid structures of epibatidine and ABT-594 were designed and synthesized. The 1-(pyridyloxymethyl)-7-azabicyclo[2.2.1]heptane ring systems were furnished via an intramolecular cyclization from a trans 1,4 disubstitituted amino-cyclohexane derivative. The functionalized cyclohexane ring was formed *via* a [4+2] Diels-Alder cyclization reaction between the acetamidoacrylate and Danishefsky's diene. These 1-(pyridyloxymethyl)-7-azabicyclo[2.2.1]heptane ring systems were then tested *in vitro* as potential $\alpha 4\beta 2$ nicotinic acetylcholine receptor ligands with high potency and selectivity.

In addition, a series of rigid acetylcholine analogs were synthesized from cocaine to study the conformation of acetylcholine, the endogenous neurotransmitter at the nicotinic acetylcholine receptor. A stereoselective reduction of 2-tropinone led to the enantioselective synthesis of the desired acetoxytropane systems. These compounds were also tested in *in vivo* models for binding affinity and efficacy responses.

Anabasamine, an alkaloid isolated from the Central Asian shrub, *Anabasis aphylla*, was synthesized for the first time. It was targeted due to interesting preliminary biological activity such as exhibiting anticholinesterase activity, anti-inflammatory activity, and facilitated an increase in hepatic alcohol dehydrogenase levels. Only preliminary studies were performed as anabasamine is limited in quantity due to its

difficult isolation. A versatile synthetic methodology was developed for the synthesis of anabasamine and related nicotine analogs. This new methodology employed a pyridyl anion addition to valerolactone, for anabasamine, or butyrolactone for the nicotine analog, to afford 5-hydroxy-1-(6-methoxy-pyridin-3-yl)-pentan-1-one or 4-hydroxy-1-(6-methoxy-pyridin-3-yl)-butan-1-one, respectively. A reductive amination provided the piperidine ring moiety and a Suzuki coupling reaction introduced the bipyridyl moiety to anabasamine in five steps and 23% overall yield. In addition, this methodology was applied successfully to the synthesis of nicotine and other related analogs. In particular the synthesis of 6-methoxynicotine, a useful drug intermediate, was generated improving the yield from 16% over five steps to 54% over three steps.

INTRODUCTION

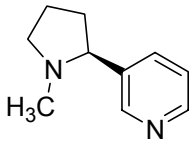
Nicotinic Acetylcholine Receptors (nAChRs)

Though the nicotinic acetylcholine receptor (nAChR) was one of the first receptors to be cloned, its full mechanistic function is still elusive to scientists today. Its importance however is greatly appreciated. A progressive understanding of the active site has led to advances in formulating treatment for a variety of devastating central nervous system disorders. Additionally, understanding the binding mechanism of human nicotinic agonists and antagonists will lead the way to new nAChR drug discovery.

Studying the active site of a receptor whose three-dimensional topology is unknown requires a multifaceted approach. One method is to carefully design molecules that incorporate the structural qualities of known biologically active compounds to achieve increasingly greater receptor potency. Such hybrids should take into account the assets of known drugs such as favorable distances between atoms, functional group moieties, and structural similarities resulting in potency without toxicity. Natural products have repeatedly lead to the development of many beneficial drugs and usually display unprecedented potencies. Using nature's designs in conjunction with some pharmacologically interesting synthetic compounds can afford drugs that not only give insight to the active site of the receptor, but also may solve some medical dilemmas.

Nicotinic Acetylcholine Receptor Structure and Subtypes

Nicotinic acetylcholine receptors (nAChRs), named for their affinity for nicotine (**1**) versus muscarine, are pentameric, transmembrane proteins that belong to a superfamily of ligand-gated ion channel receptors.[1] Other well-known members of this family include the glycine receptor, the γ-aminobutyric acid (GABA) receptors, and the 5-hydroxytryptamine$_3$ (serotonin) receptor.[2] The approximately 300 kDa glycoprotein complex is widely distributed throughout the body, moderating the function of the central nervous system (CNS), peripheral nervous system (PNS), cardiovascular and immune systems. They direct cholinergic transmission at the neuromuscular junction of striated muscles, at the synapse of the autonomous peripheral ganglia, as well as within certain sections of the brain.[3] Individually, these functions are performed by a different nAChR subtype, unique in its structure and composition. A subtype is classified according to the type and arrangement of subunits it contains. Different subunit compositions result in a variety of biophysical profiles, and likewise, pharmacological properties.[4]



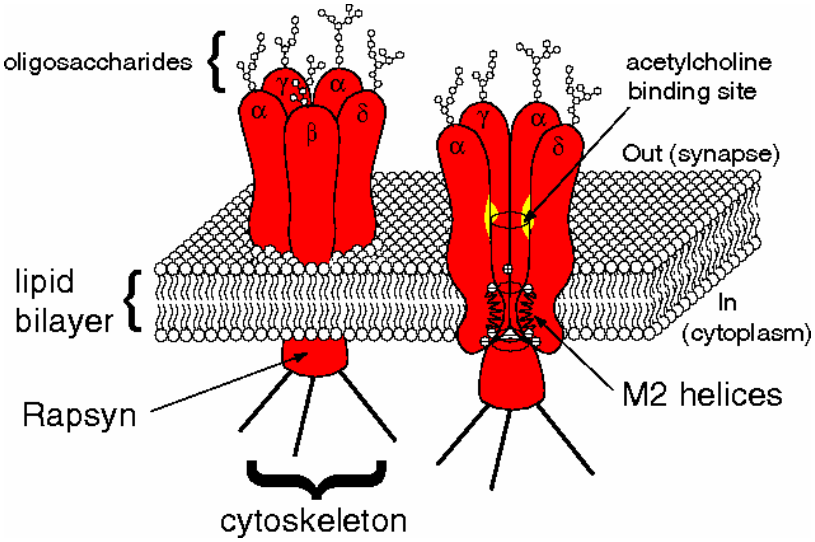
(*S*)-nicotine **1**

Through amino acid sequencing of the primary structure of these distinctive subunits, nicotinic receptors have been divided into three major sub-families.[5] The first consists of neuro-muscular nicotinic receptors found in skeletal muscle and the electric organs of certain fish. These nAChRs are heteromeric proteins that are selectively labeled and blocked by the antagonist α-bungarotoxin present in snake venom. The

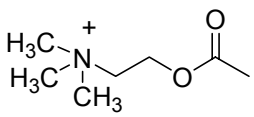
second consists of central nervous system neuronal nAChRs that do not bind α-bungarotoxin, but have high affinity for nicotine. This subtype is also a heteromeric protein found in the brain and central nervous system. The third subfamily contains homoligomeric neuronal nAChRs that do bind α-bungarotoxin, but do not exhibit affinity for nicotine.[6] These ganglionic receptors are considered to be the most primordial forms of the receptors, from which all others evolved.[7]

The first nAChR subclass, located in the neuro-muscular junction, is primarily associated with regulation of skeletal muscle contractions. It has been widely studied and classified based on its abundance in the electric organ of the *Torpedo* ray (*Torpedo californica)*.[1] The meuro-muscular subtype is composed of five subunits, two identical α subunits (α1), one β (β2), one γ, and one δ, and referred to as α1β2δγ. These subunits are differentiated by the makeup of their primary amino acid sequence. The five subunits are arranged around a central pore that traverses the cell membrane. This organization creates a pore that functions as an ion channel, selectively allowing a particular cation to traverse the cell membrane (Figure 1).[5]

Figure 1: Pentameric transmembrane nAChR; ion-channel surrounded by the subunits.[5]



When the endogenous neurotransmitter, acetylcholine (ACh), (**2**) binds to the active site of the receptor, the cation-specific channel opens, and allows for the cation to pass through (Na+ or K+ in the peripheral subtype), depolarizing the cell and propagating the nerve impulse. When complete, the ion pore is shut and impermeable.[2] Because it is the ligand acetylcholine (**2**) that activates the receptor into its open state, the nAChR is classified as a ligand-gated ion channel receptor



acetylcholine **2**

Numerous details of the receptor class as a whole have been revealed following the sequencing of the primary structure of each of the subunits by Shosaka Numa and his coworkers.[8, 9] The cloned cDNA sequences revealed that each subunit ($\alpha 1$, $\beta 1$, γ, δ) ranges in size from 40-65 kDa.[8] Hydropathy plots of the primary structures reveal that each subunit contains four hydrophobic stretches, which are thought to form four membrane spanning segments labeled M1, M2, M3, and M4 (Figure 2). Each segment traverses the membrane as an α-helix and it is the M2 helix of each subunit that faces the ion channel surrounding the receptor's central axis and constituting the wall of the ion pore (Figure 3). An extracellular 200 amino acid sequence amino-terminal domain precedes the M1, M2, and M3 helices, however a 109-142 amino acid loop connects the M3 and M4 helix. The M1-M4 domains are truncated by an extracellular C-terminus sequence.[5]

Figure 2: Trans-membrane M1-M4 helices

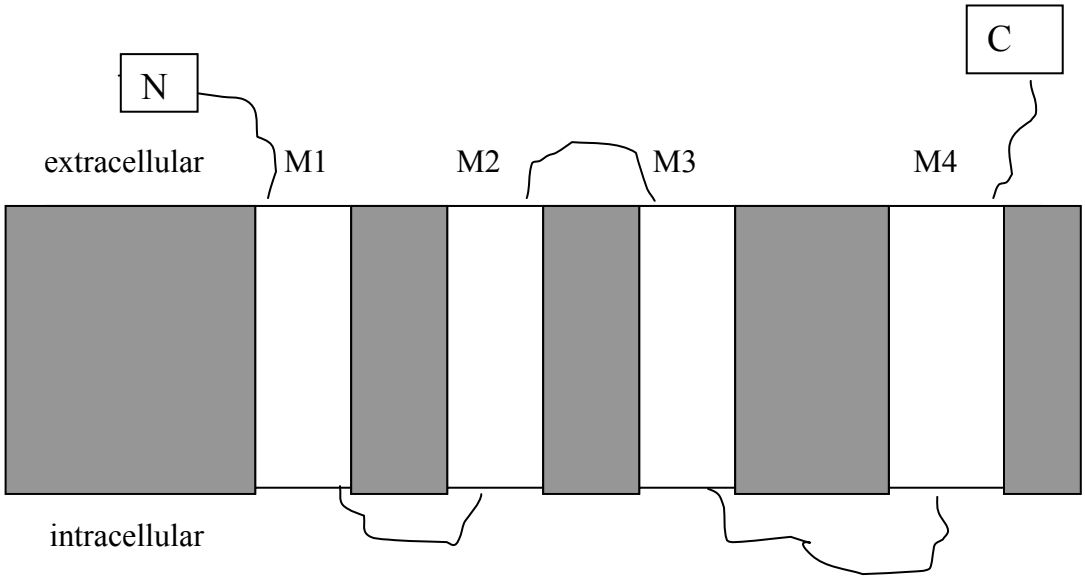
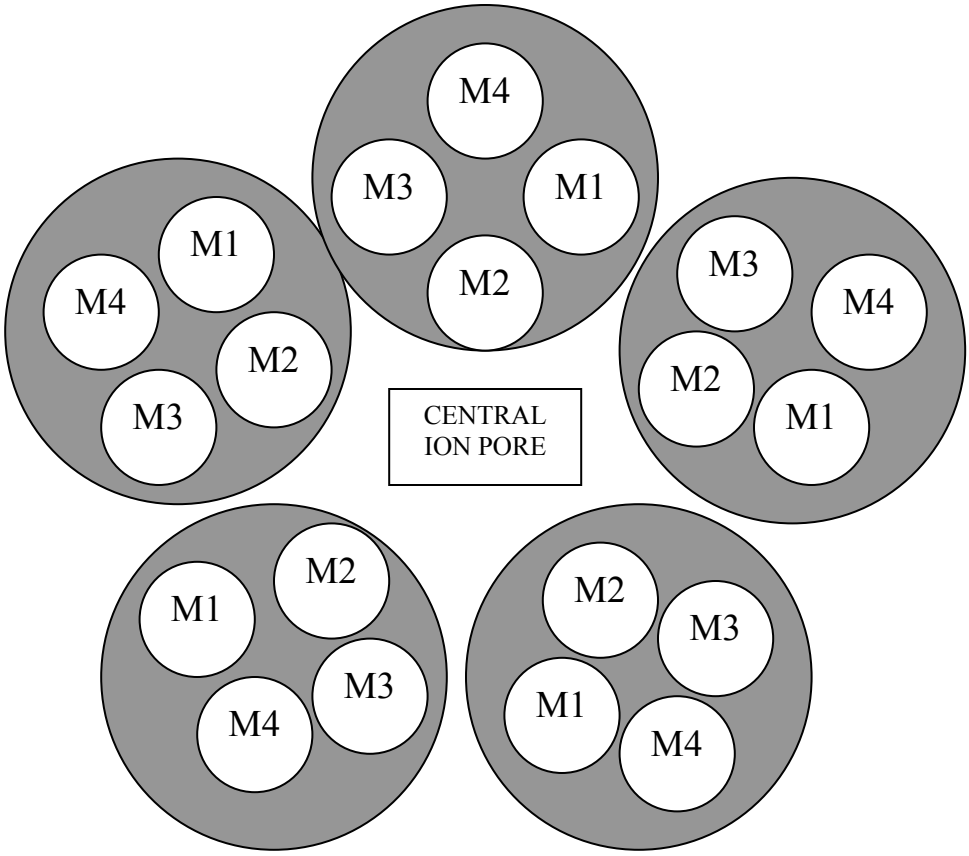


Figure 3: M2 helices surrounding the ion channel of the receptor



The neuronal nicotinic acetylcholine receptor, the second subclass, is believed to have homologous construction to the muscular subtype. However much of its structure and function has not been well characterized due to the wide diversity of the genes encoding for the subunits.[6] Regardless, the information obtained from the muscular subtype has allowed scientists insight into other members of the nAChR family where no atomically resolved structure has been completed. The three-dimensional map of the

neuronal nicotinic acetylcholine is ever evolving from a series of studies including chemical labeling, mutagenisis experiments, electronmicroscope imaging, and patch-clamp investigations.[5]

The neuronal nicotinic acetylcholine receptor was first introduced in 1889 by J. H. Langley and W. L. Dickinson when they discovered that nicotine could block neuronal transmission in the superior cervical ganglion.[10] This physiological discovery led to the concept of the presence of nicotinic receptors.[11, 12] More recently, characteristics of the neuronal structure have emerged from a combination of muscular subtype data and advanced investigations into this biologically significant protein.

The central nervous system neuronal nicotinic acetylcholine receptor is, like the muscular subtype, a pentameric arrangement of proteins arranged around a central pore, creating an ion channel specific for Ca+. This protein consists of 2α subunits and 3β subunits. The α subunits are identified by a characteristic disulfide bond between adjacent cysteine (Cys) residues and eight α-subunits (α2-α9) have been identified in neuronal subtypes. Neuronal β-subunits, sometimes referred to as "non-α" subunits, do not contain the Cys-Cys moiety and are subdivided into β2, β3, and β4.[13] The α4β2 combination (2α4:3β2) is the heteromeric neuronal subtype that does not bind α-bungarotoxin and the most prominent subtype dispersed throughout the central nervous system, especially in the mammalian brain.[14] The active site for ligand binding is considered to be primarily within the α subunit, but distinctly at the interface of the α and β subunits.[6] These sites are believed to be responsible for binding nicotine.

A homomeric pentamer of α7 subunits is also prevalent in the central nervous system, but is found in the peripheral nervous system (PNS) as well.[15] Its distribution in

the brain is comparable to the α4β2 subtype, but its function is yet to be fully determined. This subtype is thought to play a role in learning, memory, and other cognitive functioning as well as neuroprotection.[6] Because it consisted solely of α subunits, it is predicted to have five high affinity binding sites for ligands such as α-bungarotoxin, but not nicotine.[16]

Heteromeric combinations of α3, α7, β2, β3, and β4 and homomeric α9 and α7 subunits constitute the final subtype, ganglionic neuronal nicotinic acetylcholine receptors, that has a binding affinity for α-bungarotoxin.[17] This subtype is responsible for synaptic transmission in the autonomic nervous system, adrenal catecholamine release, and various cellular functions.[6]

Table 1 summarizes the various nicotinic acetylcholine receptor subtypes discussed, their subunit makeup and location, and perceived primary function. This is only a partial list of the subtypes found in mammals, but describes the subtypes that are most relevant to our research.

Table 1: Nicotinic Acetylcholine Receptor Subtypes

Classification	Subunits	Location	Proposed Function
Neuronal (CNS)	$\alpha4\beta2$	CNS	Memory and learning, neurotransmitter release, pain propagation, role in addiction
	$\alpha7$	CNS	Cognitive functions, neuroprotection
Neuronal (Ganglionic)	$\alpha7$	PNS	Cellular functions and regulation
Muscular	$\alpha1\beta1\delta\gamma$	Neuromuscular Junction	Skeletal muscle contractions

$\alpha4\beta2$ Function in the Mammalian Brain

Though the full function of the $\alpha4\beta2$ subunit is unknown, activation of these nAChRs produces a variety of behavioral and physiological effects in experimental animals and humans, including effects on cognitive performance, locomotor activity, body temperature, respiration, cardiovascular function, and pain perception.[18] Neuronal nAChRs, which play a role in neurotransmitter release, interact with nicotine resulting in a stimulation of acetylcholine, dopamine, norepinephrine, serotonin, GABA, and glutamate. These neurotransmitters have been linked to the mediation and modulation of a multitude of behaviors and disorders.[13]

Acetylcholine and nicotine bind with high affinity to the $\alpha4\beta2$ subunit which is the most prominent subtype in the mammalian brain, although precise distribution is species dependent.[6] The role of the $\alpha4\beta2$ subtype in nicotine binding was supported by the finding that mice with knockout genes for $\beta2$, the most widely expressed subunit in

the central nervous system, lost their high affinity binding site for nicotine.[19] The role of this subtype has been explored in various central nervous system diseases as well as the possibility for nicotine therapy.

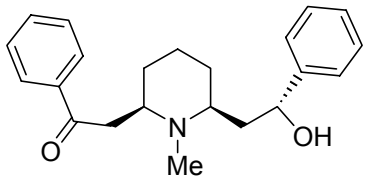
Nicotine has been looked at for its ability to increase cognitive function, as it is known to increase attention and alertness in its users. This is attributed to its ability to increase certain catecholamine release (dopamine and norepinephrine) which are believed to be involved in learning and memory.[20] Nicotine has since been used to increase the cognitive ability in patients with Alzheimer's Disease, where dysfunction is associated at the catecholaminergic systems.[21] Alzheimer's Disease is the most common form of dementia, and as of yet there are no definite treatments or prophylactic agents. Nicotine, its structural analogs, and other nAChR agonists are being looked at for possible treatment catalyzed by the findings that there are a decreased amount of $\alpha 4\beta 2$ subunits in the brains of Alzheimer's patients resulting in cholinergic deficits.[22] The stimulation of the $\alpha 4\beta 2$ subunit with agonists exerts a neuroprotective effect against β-amyloids, the neurodegenerative component in senile plaques.[23] Interestingly, there is also a decrease in incidence of Alzheimer's disease amongst smokers.[24]

The neuroprotective effect of nicotine is also observed in Parkinson's Disease- a motor disorder characterized by tremors, rigidity, bradykinesia, and impaired reflexes, which are caused by a loss of dopamine neurons in the brain. The ability of nicotine to increase dopamine concentrations is what precisely brings about this effect.[25] The dopamine release is also seen as a therapeutic benefit for the treatment of Schizophrenia. It is thought that Schizophrenics self-medicate with nicotine to increase their own dopamine levels since nicotine potentially overcomes the effects of the dopamine

antagonists commonly prescribed to Schizophrenics. This theory might explain why there is an overwhelming number of Schizophrenia patients who smoke excessively.[26]

The sale of drugs to treat anxiety and depression generated over 20 billion dollars in 2000.[27] While nAChR drugs will probably never replace current selective-serotonin reuptake inhibitor (SSRI) drugs (i.e. Prozac™), mood elevation was seen amongst major depression patients after using transdermal nicotine over four days probably due to serotonin and norepinephrine release.[28] In addition to anti-depressive properties of nicotine, smokers uniformly report a calming effect after a cigarette. The anxiolytic effect of nicotine may be a result of receptor desensitization. This is evident when desensitizing doses are continually administered and the anxiolytic activity remains.[29] Though the anti-anxiety effects of nicotine analogs are much lower than that of the benzodiazapines, they do not impair motor function or cognitive performance.

Nicotine addiction involves a myriad of physiological responses including cognition enhancement, psychological conditioning, stress relief, withdrawal relief, and other reinforcing properties. Some of these properties can be attributed to the dopaminergic release system, but the oral fixation, hand-to-mouth coordination, and social associations make curing nicotine addiction a daunting challenge. Nicotine itself has had only modest success as a smoking cessation agent. Nicotine delivered via a gum or transdermal patch does not produce the significant effects exhibited by inhaled nicotine. Several nAChR agonists/antagonists are currently being studied for their ability to substitute nicotine and block the reinforcement effects. (-)-Lobeline (**3**) has a high binding affinity at the $\alpha 4\beta 2$ subunit and it is currently in clinical trials as a smoking cessation drug.[30]



(-)-lobeline **3**

The modest, but definite, anti-nociceptive properties of nicotine were first reported in the 1930s.[31] More recently, injected nicotine has been thought to activate pain inhibiting pathways and antinociceptive mechanisms via a process that appears to involve calcium ions.[32] The relatively short-lasting and modest efficacy of nicotine as a pain-killer, coupled with its numerous side effects, will prevent nicotine from ever being marketed as an analgesic agent. However, the discovery of the natural alkaloid, (-)-epibatidine (**4**)**,** which produces potent antinociceptive responses in rodents, has renewed interest in a nAChR mediated painkiller. Epibatidine will be discussed in detail in future sections.

The diverse possibilities for the subunits of the neuronal nicotinic acetylcholine receptors give rise to a multitude of functions in the central nervous system. It is this disparate activity that makes these receptors significant targets for a wide variety of therapeutic agents. The characterization of functionally relevant subunit concentrations in conjunction with their locations is necessary in order to identify potent and selective ligands. Since no full three-dimensional structure has been mapped, the number of active pharmacophores developed has increased drastically over the past ten years. These have provided, and will continue to provide, the tools necessary for understanding the

functional importance of nAChR subtype diversity. Consequently, the potential for developing ligands for use in disorders such as Alzheimer's Disease, Parkinson's Disease, anxiety and depression, schizophrenia, and pain management is encouraging.

Inhibition Constants and Effective Concentrations

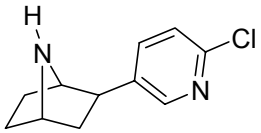
Compounds are measured for their binding affinity for the nicotine receptor by determining the concentration at which the compound displaces (or inhibits) 50% of a radiolabeled ligand with known binding affinity. For example, [H^3] nicotine or [^{3}H]cytisine can be used as the standard to measure binding affinity at the nAChR. The concentration of prepared ligand required for the response is reported in molar units as an IC_{50} value-the effective concentration. The usefulness of this value is limited due to variances in technique and tissue samples between labs. Cheng and Prusoff derived an equation (Equation 1) that incorporates the concentration of the ligand tested [L] and the dissociation constant (K_d) of the standard compound from the receptor.[33] This value is reported in molar units as an inhibition constant (K_i). Inhibition constants are more useful for comparison between labs.

$$K_i = \frac{IC_{50}}{[L]/K_d + 1} \qquad \text{(Eq 1)}$$

Another measurement used to determine the potency of a ligand at a receptor is the effective concentration (EC_{50}). The EC_{50} of a compound is the concentration at which the drug illicits 50% of the biological response seen when acetylcholine, the endogenous neurotransmitter, is bound.

Epibatidine

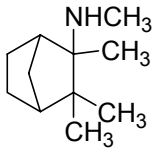
One of the most potent nAChR ligands discovered was originally isolated from the poison dart frog *Epipedobates tricolor* in 1974 by Dr. John Daly.[34] The compound was originally identified from two populations of the *E. tricolor* in southwestern Ecuador and termed 208/210 based upon mass spectrometry analysis. When the structure was finally determined in the early 1990s to be [(*1R, 2R, 5S*)- 2-(2-chloro-5-pyridinyl)-7-azabicyclo [2.2.1]heptane, epibatidine (**4**) became the topic of much research.



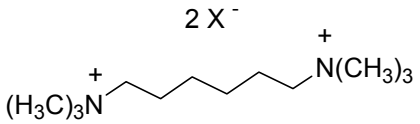
(-)-epibatidine **4**

In a routine toxicity test, the alkaloid was injected into a mouse and the Straub-tail response was observed. This is defined when a mouse arches its tail over its back in a manner inherent to an opioid response. Rat tail flick assays showed that epibatidine had incredibly potent antinociceptive properties 200 times that of morphine.[35,36] The studies also showed that the analgesic effect is mediated through neuronal nAChRs, not opioid receptors, due to its inability to be blocked by the opioid antagonist naltrexone. The analgesic effects of epibatidine, however, could be blocked by the neuronal nAChR antagonist mecamylamine (**5**).[37] The peripheral nAChR antagonist, hexamethonium (**6**), which is incapable of passing through the blood-brain-barrier, had no effect on the analgesic effects of epibatidine.[38] The therapeutic effects of epibatidine, as well as its

toxicity are both a result of its high binding affinity to the nAChR, which is in the low picomolar range (K_i = 55 pM).[34] This is approximately 300 times more potent than nicotine at these receptors. Epibatidine will not, however, ever be developed as an analgesic agent due to its very narrow therapeutic index. At concentrations only slightly higher than those alleviating pain, severe hypertension, convulsions, respiratory depression and death has been observed in animal models.[36]

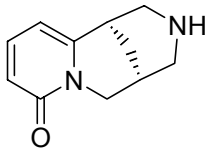


mecamylamine, **5**



hexametonium, **6**

The idea of a potent analgesic agent that is not mediated by opioid receptors was very exciting. While opioids, such as morphine, can be used successfully to treat moderate to severe pain, there is a ceiling to their therapeutic effects for chronic pain. Also, opioids have many undesirable side effects associated with their use including severe constipation, respiratory depression, tolerance, and significant potential for addiction.[39] By discovering an analgesic agent mediated through the neuronal nAChR, a whole new level of non-narcotic pain management therapy became possible.



(-)-cytisine **7**

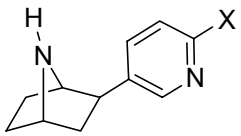
For specific receptor subtype affinity, *in vitro* competitive binding studies were preformed comparing (-)-epibatidine with [^{3}H](-)-nicotine (**1**) and [^{3}H](-)-cytisine (**7**), agents known to be highly selective for the α4β2 subunit. Epibatidine displaced [^{3}H]nicotine with a K_i = 55 pM and [^{3}H]cytisine with a K_i = 45 pM, lower concentrations than any other compound used to date in this assay. Epibatidine (**4**) was also tested for its affinity for the peripheral α7 subtype by a competitive binding assay with α-bungarotoxin. The inhibition constant was calculated to be only 230 nM, thus demonstrating the selectivity of epibatidine for the α4β2 subunit as well as a 20-fold higher potency than nicotine at the α7 subunit.[36,38] Even though epibatidine displays a selectivity for neuronal subtypes over peripheral, it exhibits high binding affinity at numerous binding sites throughout the brain of rodents.[40] It has also been shown that both enantiomers of epibataine offer high binding affinity, with the unnatural (+) enantiomer only slightly less potant that the natural (-) enantiomer.[38]

Epibatidine was tested for its ability to stimulate dopamine release in rat brains as compared to nicotine. Sullivan and his coworkers found that epibatidine has an EC_{50} of 0.4 $\pm$ 0.1 nM versus 60 $\pm$ 12 nM for nicotine. To implicate the α4β2 subunit, the stimulated dopamine release by epibatidine was blocked by known antagonists to the

receptor.[36] Epibatidine also stimulates the release of the neurotransmitter norepinephrine. In this paradigm, epibatidine has an EC_{50} = 19.6 nM compared to 34.6 nM of nicotine. The lower potency observed for norepinephrine release relative to dopamine release implies that a subunit other than the α4β2 is involved in norepinephrine release.[41]

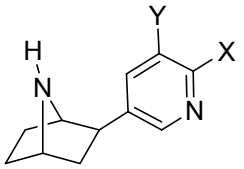
Structure-Activity Relationships of Epibatidine at the nAChR

In order to build a more complete pharmacophore model for the nAChR, structure-activity relationships of biologically active compounds are studied to a great extent. By comparing structure similarities of more potent compounds, better new compound designs can be achieved. One of the first atructure-activity relationship studies was of substituent effect on the pyridyl ring.



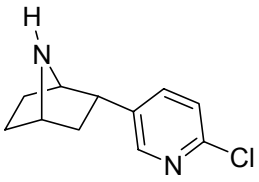
8a, X = H
8b, X = CH_3
8c, X = F
8d, X = Br
8e, X = I
8f, X = NH_2
8g, X = OH
8h, X = $N(CH_3)_2$
8i, X = CF_3SO_3

The 2-position on the pyridyl ring can tolerate a variety of substituents without compromising the potency.[36, 37] The analogs **8a-e** bind to the α4β2 subunit with similar affinity to epibatidine. The amino moity **8f** was found to exhibit decreased binding affinity with respect to epibatidine, but maintained a potency comparable to nicotine. The 2-position was not tolerant of a hydroxy group **8g**, a dimethyl amino group **8h**, and a triflate **8i** as seen by lower binding affinities for these analogs.[42]



9a, X = Cl, Y = Cl
9b, X = Cl, Y = F
9c, X = Cl, Y = Br
9d, X = Cl, Y =I
9e, X = Cl, Y = NH_2
9f, X =OH, Y = Br

The addition of an electron-releasing halogen substituents ortho- to the chlorine atom of epibatidine resulted in ligands **9a-d** with equipotent binding affinity to epibatidine. Interestingly enough, the 3'-amino analog **9e** was 26 times more potent than [^{3}H] epibatidine (K_i = .001 nM) at the α4β2 receptor subtype.[43] This compound displayed potent, but decreased affinity for the α7 subtype (K_i = 13.9 nM) with a K_i ratio α4β2/α7 approximately 14,000—which is two times more selective than epibatidine in this assay. Though the binding data proves **9e** to be more potent as well as more selective than epibatidine, it is not more efficacious. The compound did not produce the analagesic activity of epibatidine with comparable EC_{50} (effective concentration) values. More of the drug would be required to attempt reproducing the analgesic effects of epibatidine, which may conflict with the toxicity levels of the compound. The 2-bromo, 3-hydroxy **9f** was inactive in all analgesia tests. The *endo* isomer of epiatidine (**10**) exhibits lower binding affinity than the natural *exo* isomer,[44] as does the *N*-methylated analog (**11**). However, the analgesic activity was not significantly diminished by methylation.[38]



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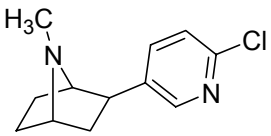

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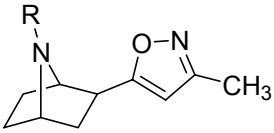
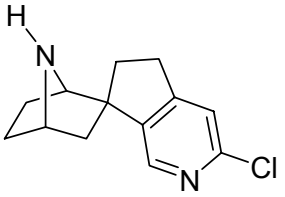


12a, R = H
12b, R = CH_3

Epiboxidine (**12a**), first synthesized in the Daly group, replaced the chloropyridine ring with an isoxazole ring. The N-H compound proved to have only 10-fold less binding affinity in rat-brain than epibatidine (K_i =0.6 nM) as well as a 10-fold decrease in analgesic effects. It was, however, 10-fold less toxic than epibatidine in mice. The biological properties of the methylated analog **12b** corresponded to methylated epibatidine in that it displayed a lower binding affinity than the desmethylated epiboxidine.



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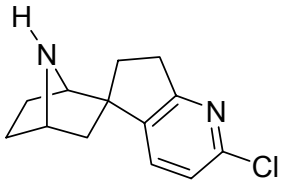

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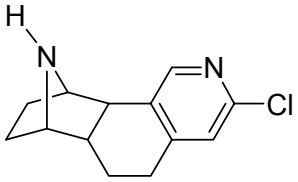

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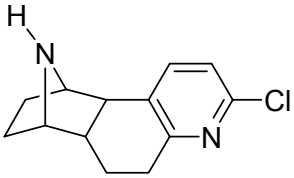
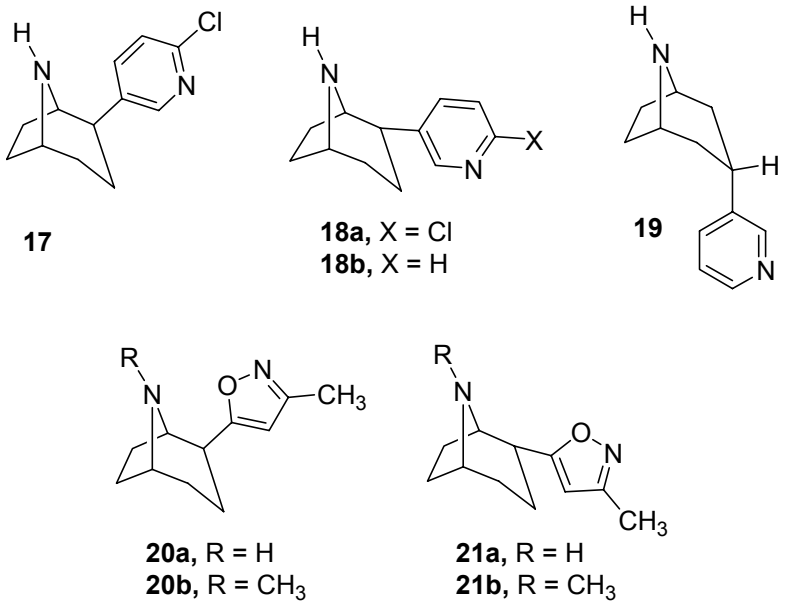


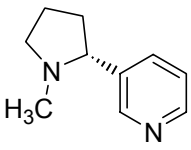
16

Some constrained analogs of epibatidine **13-16** synthesized in the Kozikowski group recently provided some insight as to the relative positioning of the pyridine ring in the receptor. The two spiro compounds **13** and **14** exhibited very low binding affinity (with K_i in the μM range) for all subtypes tested including the α4β2. This was consistant with other 2-endo epibatidine analogs. The fused ring compounds **15** and **16** exhibit high binding affinities at α4β2 albeit, still significantly lower than that of epibatidine (α4β2 K_i = 73, 295 nM, respectively). Even though similarities exist between the internitrogen distances of the fused ring compounds (**15**, **16**) and epibatidine, there is enough variation to be discriminated by the receptor.[45]

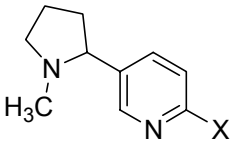


The 8-azabicyclo[3.2.1]octane ring system homologs of epibatidine were synthesized in our lab from 2-tropinone and 3-tropinone (**17-19**).[46, 47] The *endo* and *exo* chloropyridyl compounds **17** and **18a** exhibited a 30-fold decrease in binding affinity for the nicotine receptor as well as a 30-fold decrease in analgesic activity. This implied that the rigid 7-azabicyclo[2.2.1]heptane ring system is necessary to maintain the high binding of epibatidine. When the chlorine was substituted with hydrogen (**18b**), the binding affinity was five-fold less potent than the chloro derivatives. Moving the pyridyl group to the 3-position of the tropane ring also reduced the affinity (**19**). Epiboxidine analogs **20-21** of the 2-tropane ring system were also synthesized in our labs. The 2β analog **20a** was to exhibit high affinity for the α4β2 subtype (K_i =3.3 nM).[47]

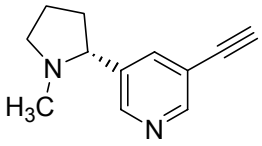
The Structure-Activity Relationship of Nicotine Related Analogs



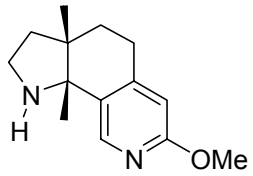
(R)-nicotine, **22**



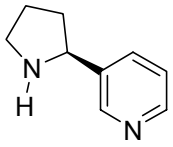
23a, R = Cl
23b, R = Br
23c, R = CH_3
23d, R = OCH_3



SIB-1508Y, **24**



SIB-1926, **25**



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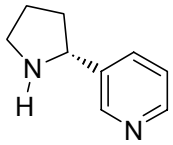

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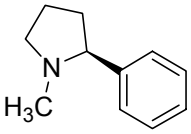
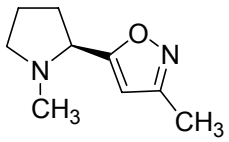


28

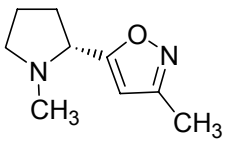
Since the biological activity of nicotine has been known for some time, many structurally related compounds have been synthesized and tested. The unnatural enantiomer, (*R*)-nicotine (**22**), maintains potency at the nAChR, with only a 10-fold decrease in binding affinity.[48] A series of racemic 6-substituted nicotine analogs **23a-d** were synthesized to study the effects of electron-withdrawing and electron-releasing groups on the aromatic ring.[66] As compared to racemic nicotine, the halogens **23a**, **23b** and the methyl group **23c** did not effect the binding assay while the methoxy group **23d** decreased the binding. The halogens did increase the analgesic activity fifteen-fold in tail-flick assays.

SIB-1508Y (**24**) is presently being tested in patients with Parkinson's Disease after its high binding affinity was reported (K_i = 3 nM). The promise of drugs such as these beckons scientists to create a better nicotinic pharmacphore model. The rigid nicotine analog SIB-1926 (**25**) was created to achieve just that.[49] While SIB-1926 did produce an analgesic effect in mouse models, as well as stimulate dopamine release, it was not as potent as nicotine at the native receptor.

After the discovery of epibatidine, NH compounds were looked at for the same biophysical properties. The demethylated nicotine compounds were tested for their potency and both enantiomers (**26, 27**) were less potent than nicotine. Also, replacing the pyridine ring with phenyl (**28**) resulted in a 100-fold decrease in binding affinity.



ABT-418, **29**



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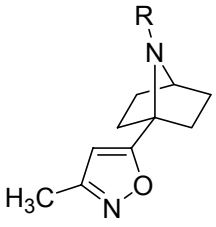


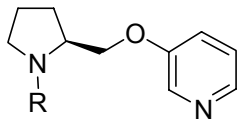
31a, R = H
31b, R = Me

The pyridyl ring was replaced with an isoxazole moity to furnish ABT-418 (**29**). This compound maintained high binding affinity to the α4β2 subunit (K_i =4.2 nM).[50] In addition this compound showed significant promise in the treatment of Alzheimer's disease as it increased the cognitive function of Alzheimer's patients in high doses.[51] ABT-418 exhibits the cognitive and anxiolytic effects seen of nicotine, but in the absence of many side effects associated with nicotine. This is a result of the greater

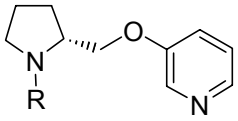
selectivity ABT-418 has for the α4β2 subtype over the ganglionic α7, as compared to nicotine.[52] As seen in the paradigm for nicotine, the (*S*)- enantiomer (**29**) is more potent than the corresponding (*R*)-enantiomer (**30**).[16] Placing the isoxazole ring at the bridgehead position of the rigid 7-azabicyclo[2.2.1]heptane ring system (**31a**, **31b**) decreased the activity greatly.[53]

Structure-Activity Relationships of Pyridyl Ethers

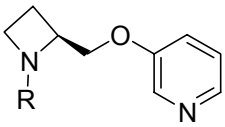
Though many potent ligands for the nAChR have been developed, most were not as subtype selective as a therapeutic agent should be. Nor did they contain a high thereputic index (defined as the range between the biologically effective concentration and the concentration at which the compound is toxic). A series of 3-pryidyl ethers developed by Abbott Laboratories marked a new breakthrough in nicotine receptor drugs.



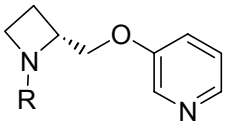
32a, R=CH_3
32b, R=H



33a, R=H
33b, R=CH_3



34a, R=CH_3
34b, R=H

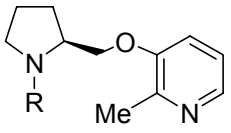


35a, R=CH_3
35b, R=H

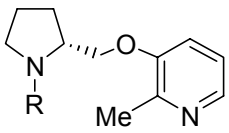
In 1996, Holladay *et al.* synthesized a series of methylated and desmethylated pyrrolidine and azetidine rings with 3-pyridyl ether functional groups. The (*S*)-pyrrolidine enantiomer, A-84543 (**32a**), and both desmethyl analogs **32b**, **33a** showed

sub-nanomolar binding affinity at the α4β2 nicotine receptor (K_i = 0.15, 0.16, and 0.14 nM, respectively).[54] The methylated (*R*)-pyrrolidine enantiomer **33b** showed a 100-fold decrease in binding activity. Even more promising was their selectivity for α4β2 when compared with another central nervous system subtype (α3βx).

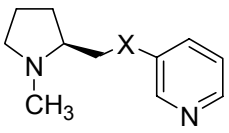
The ring reduction to an azetidine offered a new structural class of nicotinic agonists **34-35**. These compounds followed the trend of the pyrrolidine analogs, with the *N*-methylated (*R*)-enantiomer **35a** showing a lower binding affinity than the others in the series, albeit still in the nanomolar range.[54] The desmethylated compounds **34b**, **35b** exhibited K_i values in the picomolar range—similar to epibatidine—as well as similar EC_{50} values. The EC_{50} values were 160% greater than that of nicotine. Unfortunately, these compounds are 20-40-fold less potent than epibatidine to activate the receptor.



36a, R=H
36b, R=Me



37a, R=H
37b, R=Me

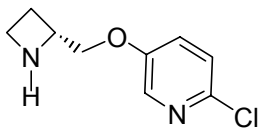


38a, X=S
38b, X=CH_2
38c, X=CH_2O

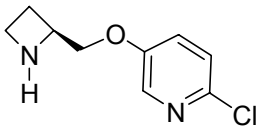
These findings led to the exploration of substituted derivatives as well as the nature of recognition with respect to the ether linkage.[55] The 2-methyl pyridine ring **36-37** analogs paralleled the non-methlyated versions with all compounds exhibiting nanomolar binding with the exception of the (*R*) enantiomer **37b** which exhibited greatly decreased binding affinity. In addition to high binding affinity, **36**, **37a** showed substantial selectivity over the ganglionic α7 subtype. The derivative ABT-089 (**36a**), with K_i = 16 nM, is also orally bioavailable with reduced degradation in liver

metabolism. Activity characterization studies were preformed in an aged primate model and cognitive enhancing properties were observed as well as anxiolytic properties.[54]

The ether linkage and chain length of **36-37** appear to be crucial for high molecular recognition. The sulfur derivative **38a** exhibits a 2000-fold decrease in binding affinity relative to the oxygen analog **38a**. Removal of the electronegative element altogether **38b** decreased the binding by 150-fold. If the ether linkage is removed from the pyrrolidine ring by an ethylene linkage versus a methylene **38c**, a 120-fold decrease is also seen.[56] Finally, if the pyridine ring is replaced by phenyl, the high binding affinity is lost.[57]



ABT-594, **39**



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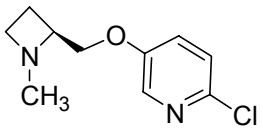

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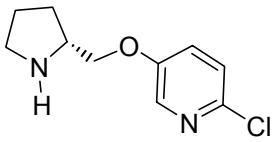

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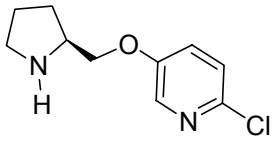
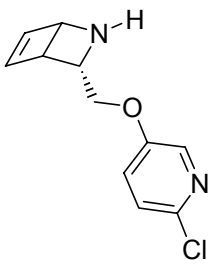


43

The 6-chloro-analogs **39-43** of the Abbott Laboratory pyridyl ethers were synthesized for comparison to epibatidine [58] All of the chlorinated ethers in this series bound to the α4β2 subunit at picomolar concentrations, with the exception of **40** and **42**. In addition to equipotent binding affinity to epibatidine, ABT-594 (**39**) also exhibited the same level of orally active analgesia. A more significant feature of ABT-594 (**39**) is that

it had a much lower toxicity and is more selective for the α4β2 subtype over the α7. The higher therapeutic index and lower risk of side effects brought ABT-594 **(39)** though Phase II and Phase III clinical trials as a pain-killer. For the pyridyl ether series of compounds, it is clear that the pyridine ring and the 6-chloro substituant are major factors in the high binding affinity/low toxicity/high selectivity properties displayed.



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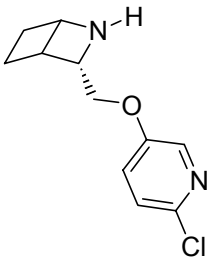

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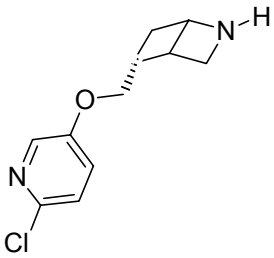
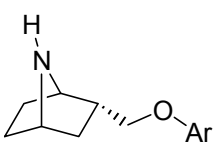
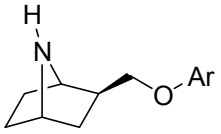


46

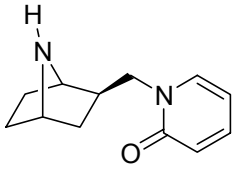
Various conformationally constrained analogs **44-46** have been synthesized to study the possible conformation geometry in the binding site.[59] Though the 2-azabicyclo[2.2.0] hexane rings retained nanomolar binding affinity for the neuronal nAChR, their EC_{50} values were between 11-34% of the maximum response (**46**<**44**<**45**). These compounds were also less effective than epibatidine and ABT-594 in producing analgesic activity. This shows that the conformation adopted by ABT-594 probably does not resemble **44** or **45**.



47a
47b
47c

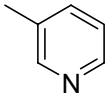


48a
48b
48c

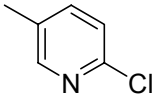


49

Ar=



a



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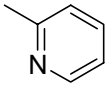
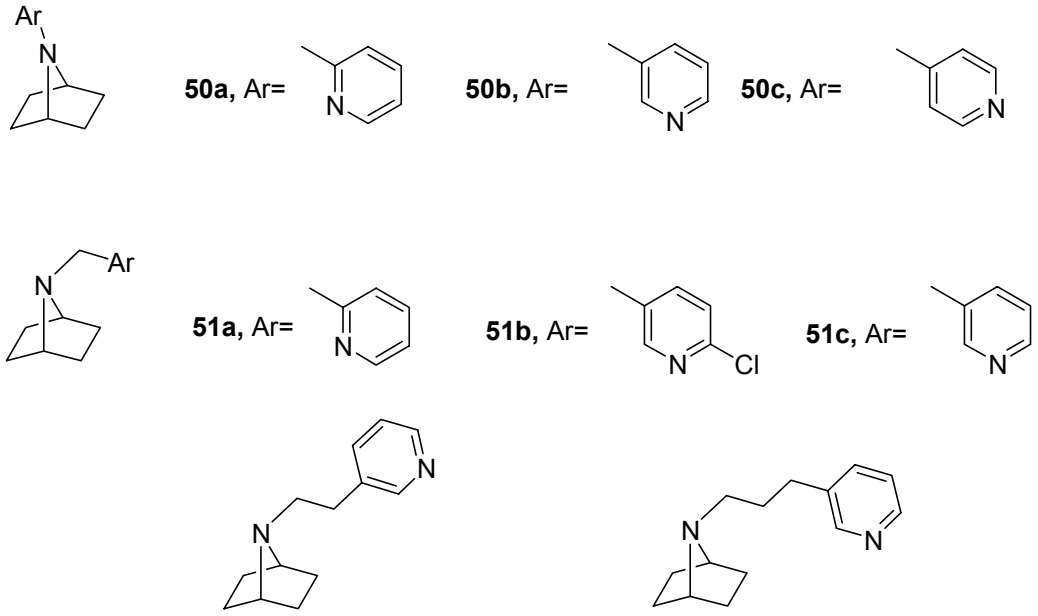


c

Recently in our labs, 2-substituted rigid 7-azabicyclo[2.2.1]heptanes **47-49** were synthesized.[60] All compounds showed a lower binding affinity than epibatidine and nicotine, with the *endo* **47a-c** exhibiting low to moderate micromolar concentrations as well as the deschlorinated exo compounds **48a, 48c**. The exo 6-chloropyridine **48b** offered the best binding, in the submicromolar range, and though still too low for potent therapeutic use, the structure-activity relationships of the ethers were consistent with those of epibatidine and its analogs. The 2-pyridyl derivatives **47c, 48c** and the amide analog **49** did, however, display comparable potency to the 3-pyridyl homologs, which had not been seen in other series. With the ether linkage in the 2-position of the bicyclic system, the 7-azabicyclo[2.2.1]heptane ring does not substitute for the azetidine ring as recognized by the $\alpha 4\beta 2$ receptor.

Structure-Activity Relationship of *N*-substituted Bicyclic Rings



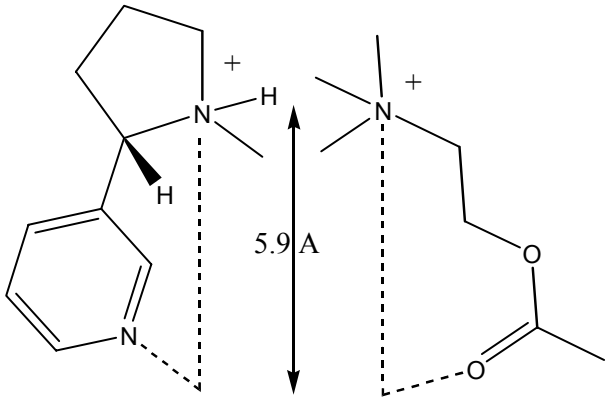
Also synthesized in our labs were a series of *N*-substituted and *N*-tethered 7-azabicyclo[2.2.1]heptane ring derivatives **50-53**.[61, 62] All of these compounds displayed decreased binding affinity when compared to epibatidine, nicotine, and cytisine. The *N*-aryl derivatives **50a-c** only displayed 50% inhibition of [^{3}H]Cytisine at 100 μM concentrations. The *N*-methylene-aryl derivatives were also poor nAChR activators, with the 3-pyridyl analog **51c**, being by far the most active, with a K_i of approximately only 100 nM. Increasing the tethered chain to an ethylene **52** and a propylene **53** decreased the binding accordingly.

The Nicotine Receptor Pharmacophore Model

A pharmacophore can be defined as a "minimal ensemble of structural features common to a series of agents, seemingly responsible for a specific effect."[63] Specifically, a pharmacophore for the nAChR should possess the physiochemical properties necessary to stimulate activity at the receptor. There is a long history of research groups proposing pharmacophore models for the nicotine receptor dating back to 1952.

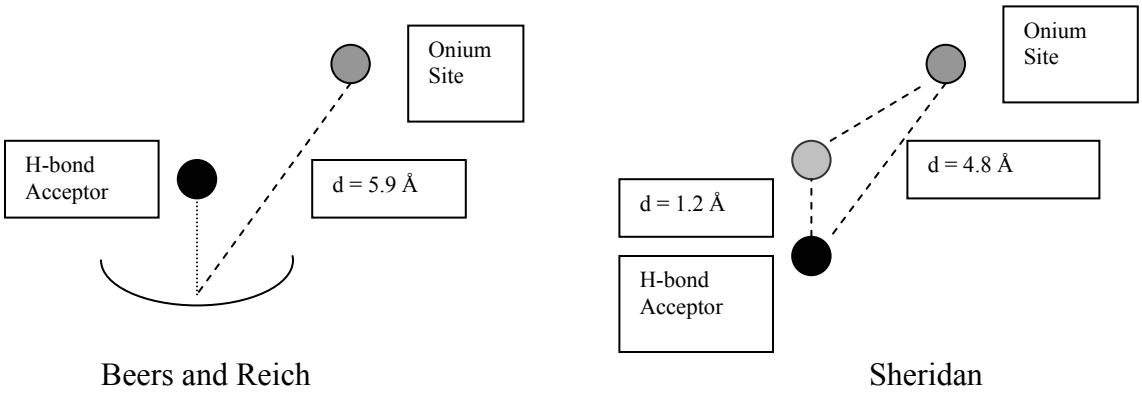
The first pharmacophores were based on the internitrogen distance of nicotine and structurally similar acetylcholine. The most recent and accepted theories were devised starting in 1970 when Beers and Reich advanced their previous studies using Dreiding and CPK space filling models.[64] They found two common structural features necessary for nicotinic agonist and antagonist activity: a couloumbic interaction involving an alkylammonium moiety and an H-bond that depends upon an acceptor 5.9 Å away from the center of the positive charge (Figure 4).[64] The internitrogen distance, however is 4.85 Å, a consistent measurement with earlier models.

Figure 4: The Beers and Reich Pharmacophore Model[64]



Sheridan extrapolated the Beers and Johnson model to essentially describe a pharmacophore with an H-bond acceptor and a more basic nitrogen in the molecule that can become protonated and likewise became a center of positive charge. They also noted a distance of 1.2 Å between the H-bond acceptor and a third atom that resides above the plane of the internitrogen space.[65] This model, based on nicotine, cytisine, and ferruginine, corresponds with Beers and Reich distance of 5.9 Å between the onium site and the van der Waals surface (Figure 5).[64, 65]

Figure 5: Comparison of the Beers and Reich Pharmacophore with the Sheridan Model.[63]



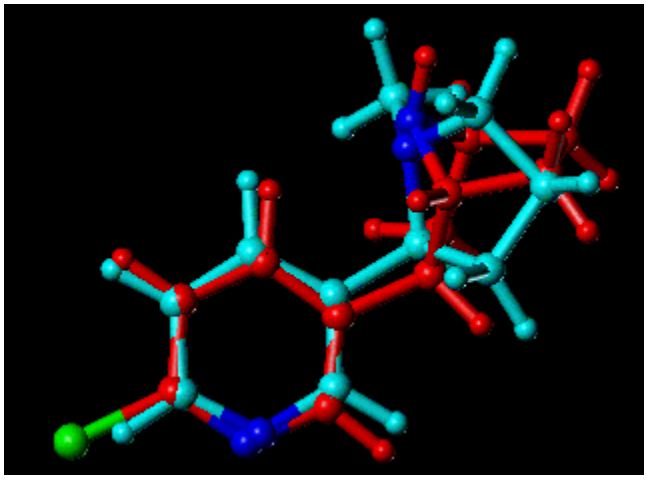
54 **55**

Glennon and coworkers added to the pharmacophore requirements a stipulation on the basic nitrogen substituents. A series of simple aminomethylpyridines **54-55** were synthesized where the internitrogen distance did not vary greatly amongst analogs. Nevertheless, the pharmacology changed greatly. The disubstituted nitrogen (R_1= Me, R_2= Et) bound much higher (K_i= 28 nM) than the primary amine (R_1= R_2= H) whose inhibition constant was greater than 10,000 nM.[66]

The discovery of epibatidine (**4**) offers exception to an industry standard. Although there are some structural similarities, there are some obvious differences.

Even though the two structures are superimposeable, the internitrogen distance of epibatidine is 5.5 Å instead of the 4.97 Å seen in nicotine. This distance is longer than both the previous models and would seem to predict a low affinity for the receptor. On the contrary, epibatidine has one of the highest affinities for the nAChR known to date. Glennon and coworkers proposed a new model in 1994 with the optimum internitrogen distance of 5.1-5.5 Å taking into account the structure of epibatidine. A reasonable structural resemblance between epibatidine and nicotine can be seen through overlapping the basic and pyridinium nitrogens of each (Figure 6).

Figure 6: Epibatidine (red) and nicotine (blue). Nitrogen atoms in dark blue overlap.[67]



In 1996 Abbott Laboratories based molecular modeling studies on their series of pyridyl ether compounds **(39-43)** known to have potent nicotinic agonist activity. They found the optimum internitrogen distance for ligand receptor interaction to be 6.1 Å.[68] Obviously, much work is still needed to identify concrete nicotinic pharmacophores. To

date no pharmacophore model has been successful in incorporating all active nAChR ligands. However, with every new active class of compounds, the picture of a nicotinic pharmacophore becomes potentially more clear.

Rigid Acetylcholine Analogs

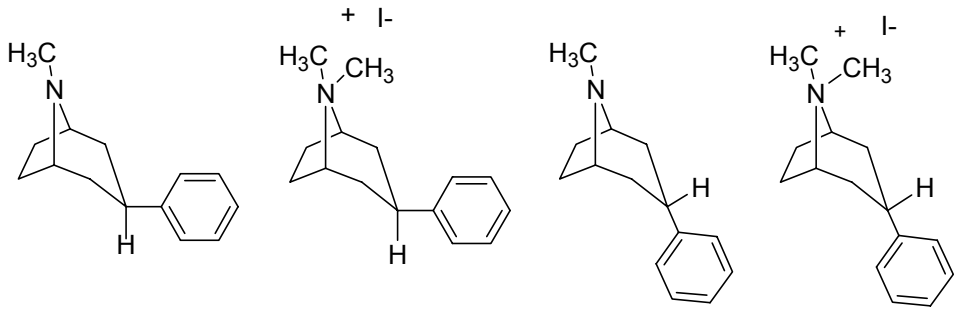
The nicotinic acetylcholine receptors are responsible for recognition and binding of the neurotransmitter, acetylcholine (**2**). The junction at which neurons pass signals to other neurons, muscles, or glands are called synapses. In these synapses, the arriving action potential triggers the release of a neurotransmitter from the presynaptic neuron which diffuses across the cleft and binds to its corresponding receptor on the postsynaptic membrane. Neurotransmitter binding stimulates membrane depolarization, thereby triggering an action potential on the postsynaptic membrane.[69]

Acetylcholine binds to the receptor activating the ligand gated ion channel and stimulating the central and parasympathetic nervous system. Its transmission plays a role in numerous physiological functions including stimulation of the vagal nerve that decreases the heart rate and cardiac output, dilation of blood vessels to decrease blood pressure, stimulates gut motility, stimulates genitourinary smooth muscle, and regulates muscle constriction.[70]

Those compounds that are active at these receptors, as agonists or antagonists, are of particular interest in treating several central and peripheral nervous conditions such as Parkinson's disease, Alzheimer's disease, Tourette's syndrome, myasthenia gravis, and depression-anxiety disorders. Some common natural agonists, including acetylcholine, nicotine, and epibatidine, and antagonists as hexamethonium, succinylcholine, and α-

bungarotoxin are commonly used as models in current drug synthesis. An agonist is a drug that increases or decreases the activity of the particular cell with which the receptors are associated versus an antagonist which counteracts or prevents the action of another drug or endogenous body chemical.

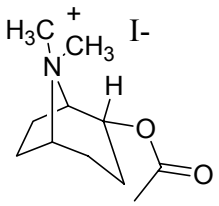
Acetylcholine is a flexible molecule with many possible conformations. The topography of the ion-channel of the acetylcholine receptor is not fully known. Likewise the binding conformation of acetylcholine is unknown. By constructing several rigid conformations of acetylcholine and its derivatives, a better understanding of its spatial geometry within the receptor, and ultimately the three-dimensional receptor structure can be achieved.



56 **57** **58** **59**

The tropane ring system has been studied for its binding capabilities at the nicotine receptor. A series of 3-phenyl tropane rings **56-59** were synthesized and tested for their effects on blood pressure in dog models.[71] All increased the blood pressure at or near the levels of nicotine, with the exception to **59**, which was inactive. Though less

toxic than nicotine, there was still a modest therapeutic index. Also, the drugs caused convulsions, respiratory depression, and death.



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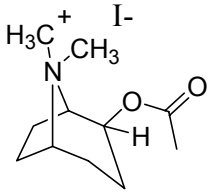


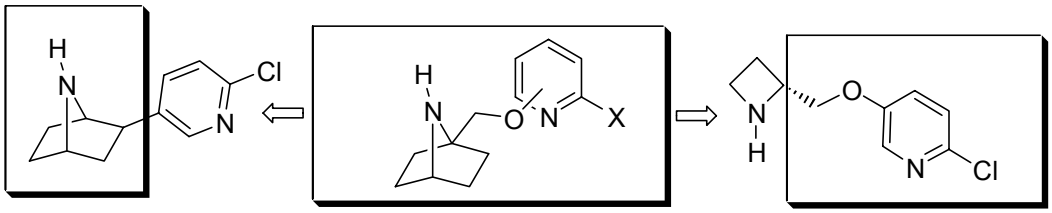
61

In 1962, Archer[72] had made 2-acetoxy-tropane derivatives **60** and **61**. These quaternary 2-acetoxy-tropane isomers were found to mimic acetylcholine. They activated the ligand gated ion channel and ultimately stimulated the parasympathetic nervous system, but only preliminary biological studies were performed.

Specific Aims and Design Strategy of Epibatidine Analogs

New compounds that incorporate the chloro pyridyl group of epibatidine tethered to a nitrogen containing ring via an ether linkage have proven to have similar potencies as that of epibatidine at the nAChR. These compounds have potential as analgesic agents because of significant decrease in toxicity. Though encouraging, none of these pyridyl ethers have yet been viable drug candidates for either pain control or central nervous disorder treatment. To this end, a series of pyridyl ether derivatives have been envisaged to explore the structure-activity relationship of epibatidine related compounds. The

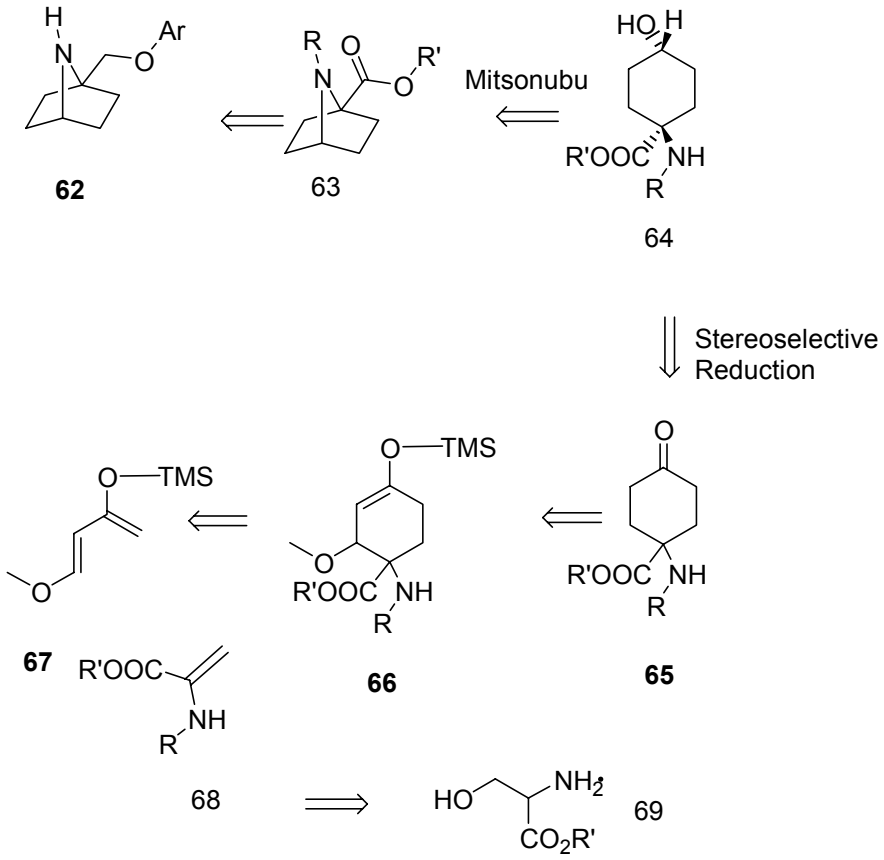
derivatives were designed to be hybrid structures of epibatidine and ABT-594 (Scheme 1). In this series, we will study the effects of the bridgehead substituted ring system on the proximity of the basic and pyridyl nitrogen. Attaching a heteroaromatic ring onto the rigid system with the nitrogen in varying positions will fine-tune our understanding of the nAChR binding site.



X= H, Cl

Scheme 1

The synthesis of 1-substituted 7-azabicyclo[2.2.1]heptane ring system analogs will exploit chemistry previously developed for epibatidine. An intramolecular ring closing reaction will be employed to generate the 7-azabicyclo[2.2.1]heptane ring system. The appropriately functionalized cyclohexane derivative will be prepared via a stereoselective reduction of a functionalized cyclohexanone. The cyclohexanone can be afforded through a [4+2] Diels-Alder cycloaddition between a diene and appropriately substituted dienophile (Scheme 2).

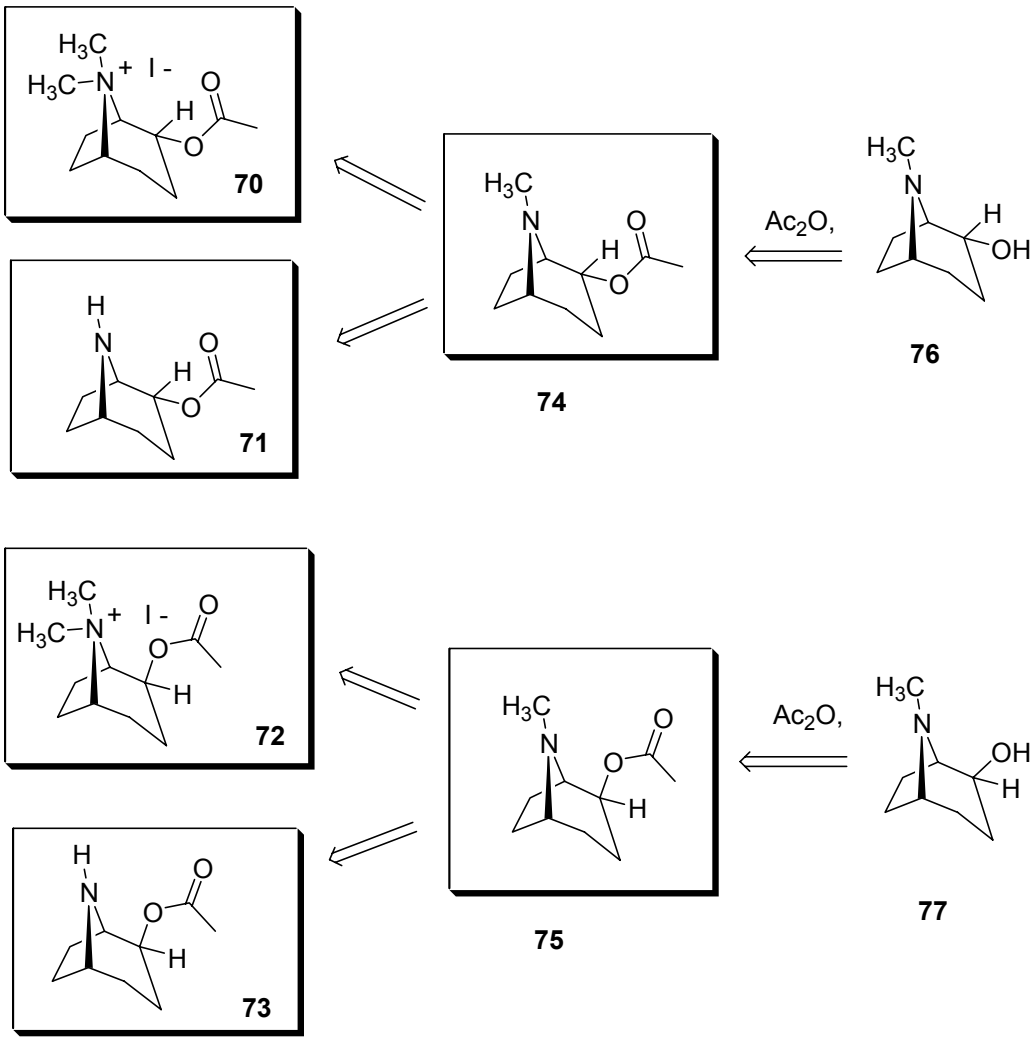


Scheme 2

Specific Aims and Design Strategy of Rigid Acetylcholine Derivatives

The second specific aim is to study the binding conformation of acetylcholine at the active site of the nAChR. To this end, a series of rigid 2-acetoxytropane analogs will be prepared. Demethylated forms of the acetylcholine moeity will also be synthesized, as many bicyclic N-H compounds, such as epibatidine, show potency at the nicotinic acetylcholine receptor.

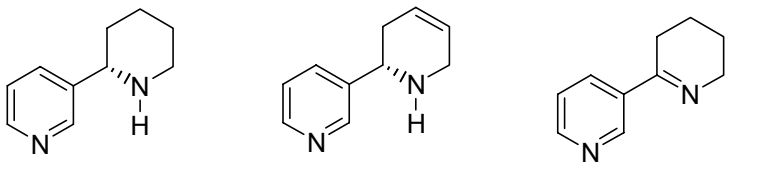
The 2-acetoxy tropanes **70-75** will be prepared by converting the corresponding 2-tropinol alcohols **76-77** into acetates.[73] The chiral alcohols will be synthesized stereoselectively from (*R*)-2-tropinone obtained by degradation from (-)-cocaine.[74] The individual α- and β- stereoisomers will be tested for binding affinity at the nicotinic acetylcholine receptor in several assays.



Scheme 3

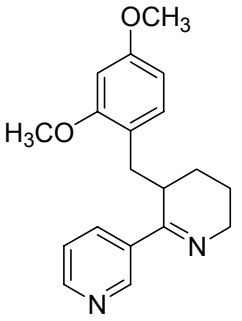
Natural Product Synthesis: (*S*)-Anabasamine

During the past decade, over 12,000 compounds containing a piperidine ring have been employed in various stages of clinical trials.[75] Efficient synthesis of piperidine based compounds is of particular interest to medicinal chemists. Naturally occurring alkaloids that incorporate piperidine and pyrrolidine rings have already been proven to possess important biological activities.

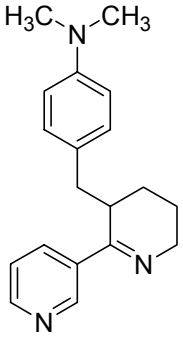


78 (*S*)-anabasine **79** (*S*)-anatabine **80** (*S*)-anabaseine

(*S*)-Anabasine (**78**), and (*S*)-anatabine (**79**) are found in the plant *Nicotina tobaccum*, the species most prominently used in cigarette tobacco, and are quite potent at the nAChR.[16] Anabasine (**78**) has a 30-fold lower affinity for mouse brain than nicotine and 40% the efficacy. It has a K_i of 210 nM at the α4β2 subunit. Anatabine exhibits approximately half the potency of anabasine. Anabaseine (**80**) a paralytic toxin found in the marine worm *Paranemertes peregina*, is a partial agonist at the α4β2 subunit. It possesses a 20-fold weaker affinity for the α4β2 subunit when compared to nicotine and only 10% the efficacy. It does, however, show high efficacy at the ganglionic α7 subunit, and therefore exhibits selectivity for this receptor subtype.[16]



81 GTS-21



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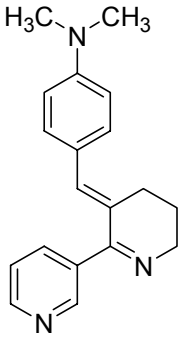
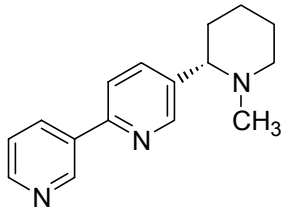


83

The analog of anabaseine, GTS-21 (**81**), has been tested in clinical trials and shown to have positive effects on cognition in rats and rabbits. It has also exhibited cytoprotective effects on learning and memory and against β-amyloids toxicity, the plaques associated with Alzheimer's Disease. The analogs **82** and **83** had lower binding affinities than GTS-21 and did not exhibit the same level of therapeutic benefits.[16]



84 (*S*)-Anabasamine

A related alkaloid, (*S*)-anabasamine (**84**), is found in the poisonous semi-shrub *Anabasis aphylla* of Central Asia.[75] Limited preliminary studies on the biological effects of anabasamine were conducted during the 1980s in the Soviet Union.[76] Only recently, anabasamine was shown to inhibit the catalytic activity of the enzyme

acetylcholinesterase, which causes the rapid hydrolysis of acetylcholine at the nerve synapse.[77]

When anabasamine was administered orally to rats, anti-inflammatory activity similar to indomethain was observed.[78] It also inhibited the inhibitory effects of steroids such as hydrocortisone.[79] This effect appears to be a result of activation of the adrenal cortex-hypothalamus-pituitary system. The piperidine alkaloid may also strengthen the adrenergic system as it reduces the ptosis caused by reserpine, a compound that blocks the dopamine-norepinephrine transformation in mice.[79]

Another interesting discovery is that anabasamine was found to increase the activity of hepatic alcohol dehydrogenase and proportionally decrease ethanol levels in the blood stream of rats.[80] It also stimulated the adrenal regulated production of tryptophan pyrrolase in the liver of rats when administered.[81]

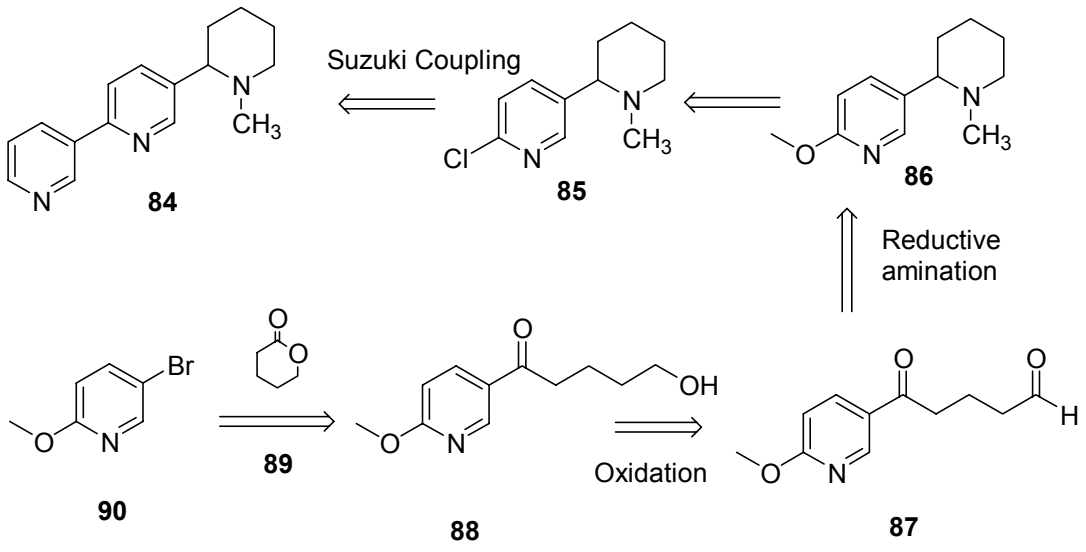
Most of the studies found on (*S*)-anabasamine (**84**) revolve around how to isolate and purify the compound from the other alkaloids found in the plant specimen. The limited concentrations in plants as well as difficulty in isolation make this compound an attractive target for synthesis. Further studies of anabasamine as well as its analogs could be conducted with greater ease if a more practical source of the compound were available to scientists.

Specific Aims and Design Rational of Anabasamine

The specific aim of this research is to develop a short, practical, and efficient synthesis of the plant alkaloid, anabasamine (**84**) and related nicotine analogs. The

tricyclic compound will be synthesized as a racemic mixture. The racemate will then be tested at the nAChR for binding affinity.

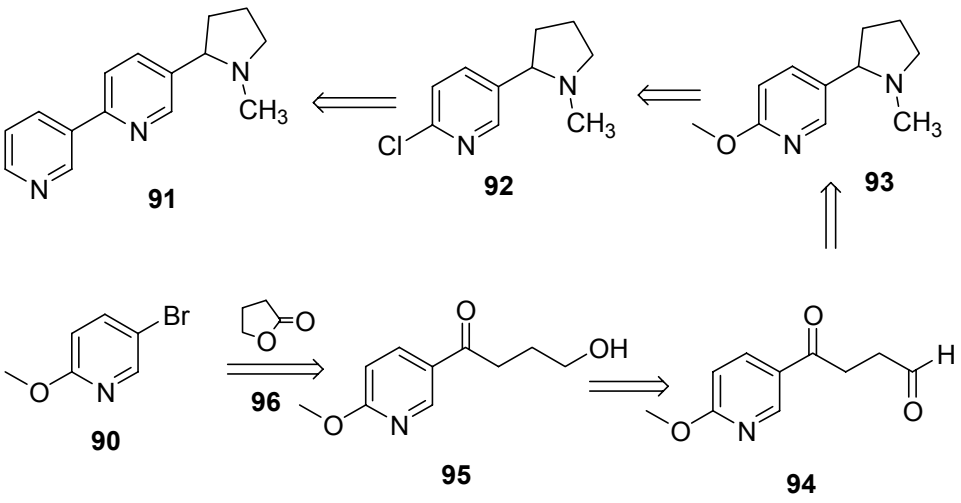
The synthesis will employ a Suzuki aromatic ring coupling of 3-pyridine boronic acid to the 2-chloropyridine derivative **85** to afford anabasamine (**84)**. The chlorinated pyridine **85** will be prepared via chlorination of the aryl ether **86**. The piperidine moiety of the bicyclic compound **86** will be prepared through reductive amination of the keto-aldehyde **87**. The corresponding alcohol will be prepared via an addition of δ-valerolactone (**89**) to the 2-methoxypyridyl anion derived from commercially available 5-bromo-2-methoxypyridine (**90**) (Scheme 4).



Scheme 4

In a similar synthetic scheme (Scheme 5), the nicotine analog of anabasamine **91** will be prepared via the Suzuki coupling reaction of 3-pyridineboronic acid and 6-

chloronicotine (**92**). 6-Methoxynicotine (**93**) will be prepared via reductive amination of the 4-oxo-butanal **94**. The corresponding alcohol will be afforded through an addition reaction of a pyridine anion to γ-butyrolactone (**95**). In this synthetic route, the common drug intermediate 6-methoxynicotine (**93**) will be prepared in three steps.



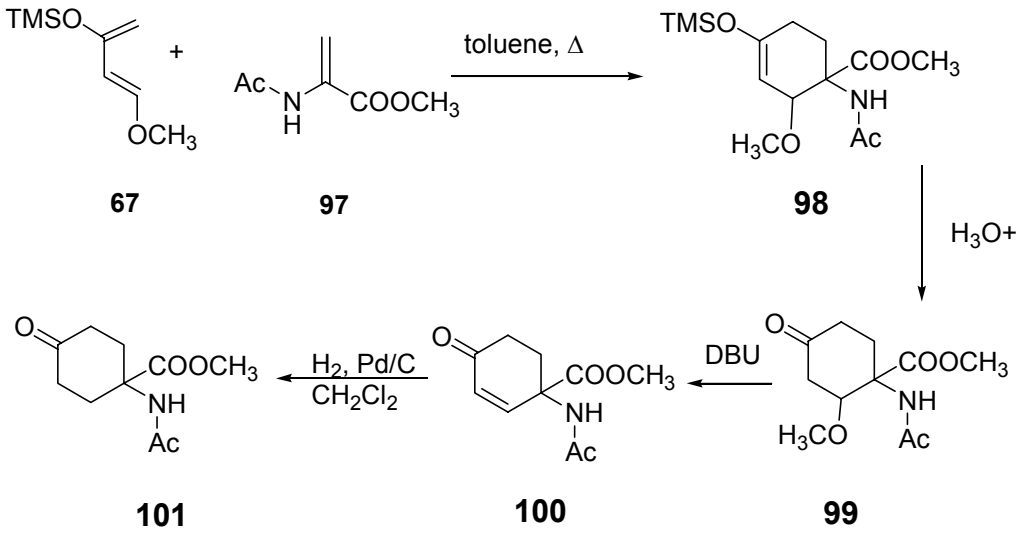
Scheme 5

RESULTS AND DISCUSSION

Synthesis 1-(Pyridyloxymethyl)-7-aza-bicyclo[2.2.1]heptanes

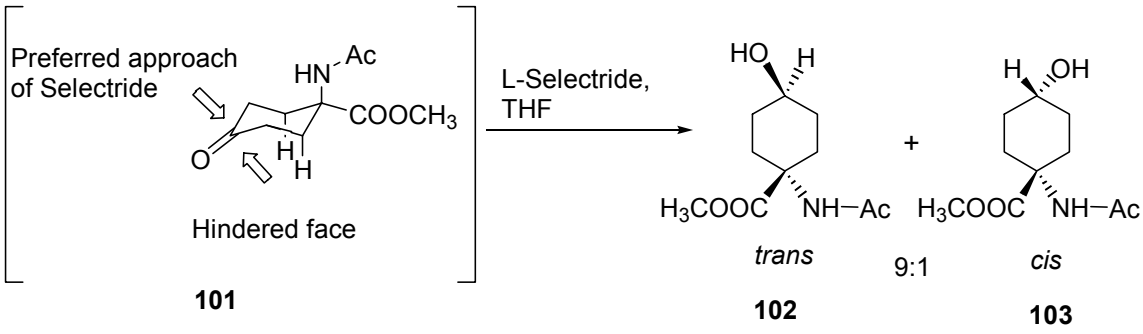
Attempted Synthesis with Acetyl Protecting Group

Several synthetic routes were attempted to prepare a 1-substituted [2.2.1] bicyclic ring system. The first route investigated was designed to incorporate the commercially available Danishefski's diene (**67**) with commercially available dienophile, methyl 2-acetamidoacrylate (**97**), in a method proven successful to make monocyclic rigid proline analogs.[82] Scheme 6 illustrates the Diels-Alder cycloaddition using an excess of the diene **7** (2:1 ratio) to the dienophile **97** and the components were stirred under an atmosphere of nitrogen in refluxing toluene for 3 days. This furnished the cycloaddition adduct that was directly carried on to the next step. After hydrolysis of the trimethylsilyl group of **98**, the elimination of the methoxy moiety of **99** was performed to yield the enone **100** in 34% yield over the three steps. The enone **100** was then hydrogenated (H_2, 1 atm) over palladium on carbon to afford the 4-substituted cyclohexanone **101** in 90% yield.



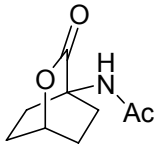
Scheme 6

With the ketone **101** in hand, a selective reduction was performed on the cyclohexanone employing the bulky borohydride reagent, L-Selectride ® (lithium tri-*sec*-butylborohydride). The adjacent axial hydrogen atoms prevented the indiscriminant reduction of the carbonyl by the bulky reagent from either face. This procedure furnished a 9:1 ratio of the *trans*-cyclohexane derivative **102** over the *cis* configuration **103** as determined by NMR peak integration of the methyl ester peaks (Scheme 7). The isomers were not separated at this time.



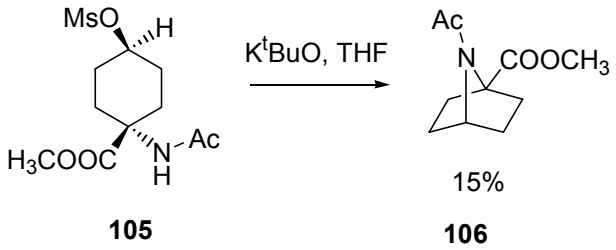
Scheme 7

The work up of the L-Selectride reduction proved to be very important. The borohydride reagent was quenched with saturated ammonium chloride and the THF was removed under reduced pressure on a rotary evaporator. When heat was used to aid in the THF evaporation in the presence of the aqueous acid, the major product that was obtained resulted from intramolecular cyclization to furnish the bicyclic lactone **104** in 94% yield. The formation of **104** served to confirm the relative stereochemistry of the L-selectride reduction of ketone **101**. Only the trans isomer **102** could form the bicyclic lactone **104**. The problem of intramolecular lactone formation was corrected by filtration of excess precipitated ammonium chloride followed by a solvent evaporation under reduced pressure at temperatures no greater than 40 °C.



104, 94%

The isomeric alcohols **102** and **103** were converted into their corresponding mesylates with mesityl chloride. Separation of the mesylate isomers by gravity column produced the pure *trans*-1, 4-disubstituted cyclohexane derivative **105** appropriate for an intramolecular ring closing transformation. With the mesolate **105** in hand, the ring closure was attempted (Scheme 8). With potassium *tert*-butoxide, the 7-azabicyclo[2.2.1]heptane **106** was only formed in poor yield (15%). This was due to the acetyl protecting group being a poor electron- withdrawing group and likewise, rendering the hydrogen atom on the nitrogen atom less acidic. As a result, the proton was not acidic enough to facilitate the ring closing reaction.



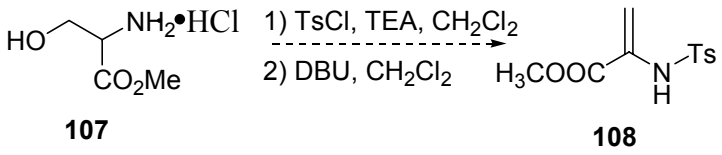
105 **106**

Scheme 8

Attempted Synthesis with Toluenesulfonyl Protecting Group

An alternative protecting group was sought that would provide sufficient proton acidity. For this, the *p*-toluenesulfonyl group was chosen. The corresponding acrylate dienophile was not commercially available. The attempted synthesis from the inexpensive reagent, *d,l*-serine methyl ester hydrochloride (**107**) is illustrated in Scheme 9. The amino and the hydroxyl groups were converted simultaneously into the sulfamide and tosylate in one step using an excess of *p*-toluenesulfonyl chloride in the presence of triethylamine (Scheme 9). After removing excess unreacted *p*-toluenesulfonylchloride,

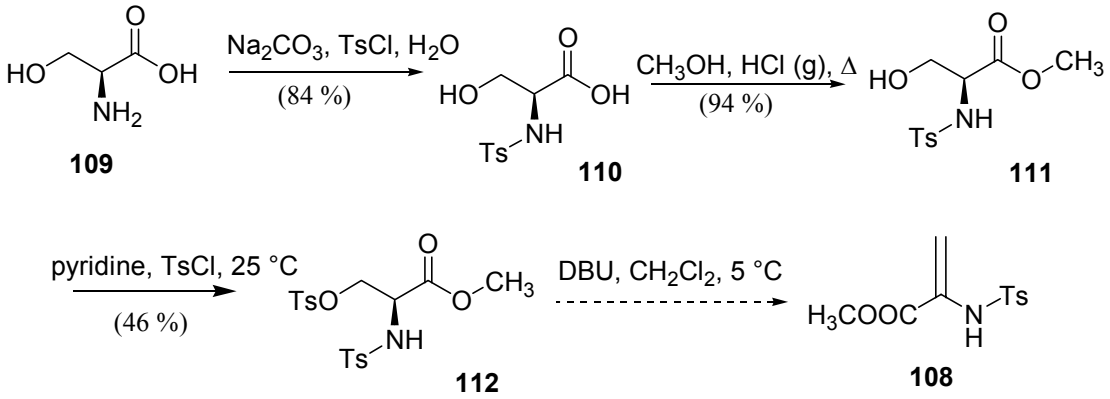
the resulting oil was used without purification in a DBU (1,8-diazobicyclo[5.4.0]undec-7-ene) mediated elimination reaction. The elimination to the corresponding acrylate **108** was not successful. Despite using various bases, reaction temperatures, and solvents, the desired acrylate was never obtained. Trace amounts of starting material were recovered, but mostly intractable decomposition products were observed.



107 **108**

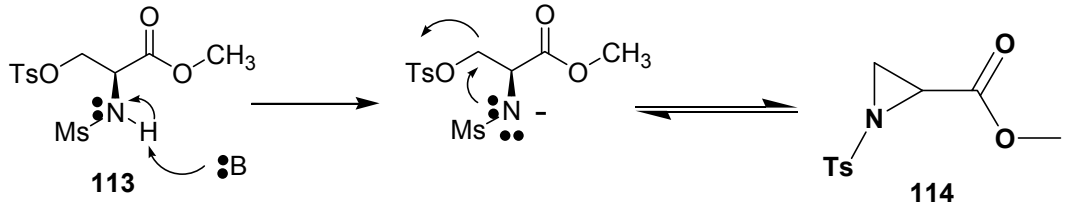
Scheme 9

Stepwise tosylation of the nitrogen followed by tosylation of the alcohol moiety was performed to ensure that the proper intermediate was formed (Scheme 10). The desired sulfamide **110** was made by treating *L*-serine (**109**) with an excess of sodium carbonate in water. This afforded the *N*-tosyl serine **110** in 84% yield. The carboxylic acid moiety was converted into the corresponding methyl ester **111** by refluxing in HCl-methanol in 94% yield. Tosylation of the alcohol employed pyridine as a base and gave only modest yields (46%) of the desired tosylate **112**. With the alcohol converted into the tosylate and the nitrogen protected appropriately, the desired DBU mediated elimination to the acrylate dienophile was attempted. Despite numerous attempts and varied reaction conditions, the desired acrylate **108** was not obtained.



Scheme 10

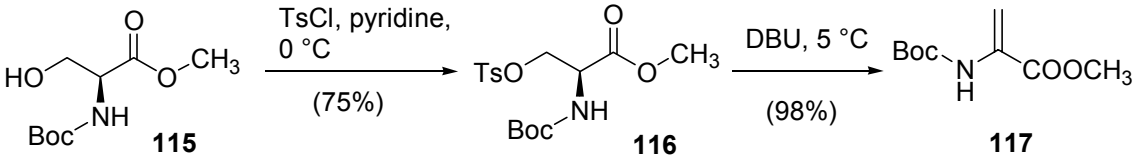
The same sequence was followed for the preparation of a mesylate leaving group **113** in an attempt to produce the elimination product **108** (Scheme 11). A multitude of different bases and conditions were explored (DBU, pyridine, sodium hydroxide, triethylamine, 1,4-diazabicyclo[2.2.2]octane, tetrabutylammonium fluoride, potassium *tert*-butoxide), however none of which resulted in the desired acrylate The reason the elimination product **108** was not obtained is envisaged to be due to the competing azetidine ring formation **114** and subsequent decomposition. Though this compound was never characterized by NMR due to its instability, this is predicted based on the relative reactivity of the *N*-hydrogen atom vicinal to the tosyl group.



Scheme 11

Attempted Synthesis with *tert*-Butoxycarbonyl Protecting Group

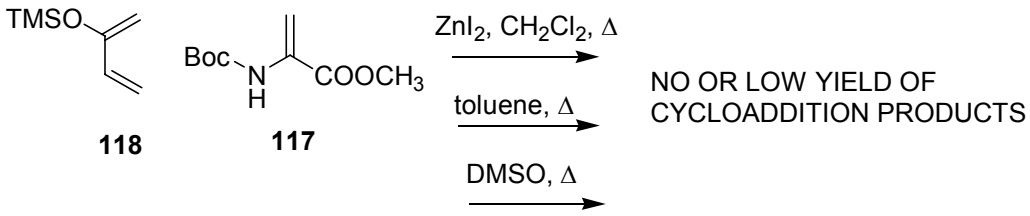
Even after attempts to trap the dienophile **108** during its formation by placing it in excess diene **67**, it was clear that the protecting group was poorly suited for this task. The *tert*-butoxycarbonyl (Boc) group, a less electron-withdrawing protecting group, was utilized (Scheme 12). Commercially available *N*-*t*-butoxycarbonyl-*d*-serine methyl ester (**115**) was converted into the corresponding tosylate utilizing the procedure of Boggs, *et al*.[83] Upon recrystallization, the white solid **116** was obtained in 75% yield. This was subsequently subjected to the DBU (1,8-diazobicyclo[5.4.0]undec-7-ene) mediated conditions to give the desired acrylate **117** in 98% yield.[84]



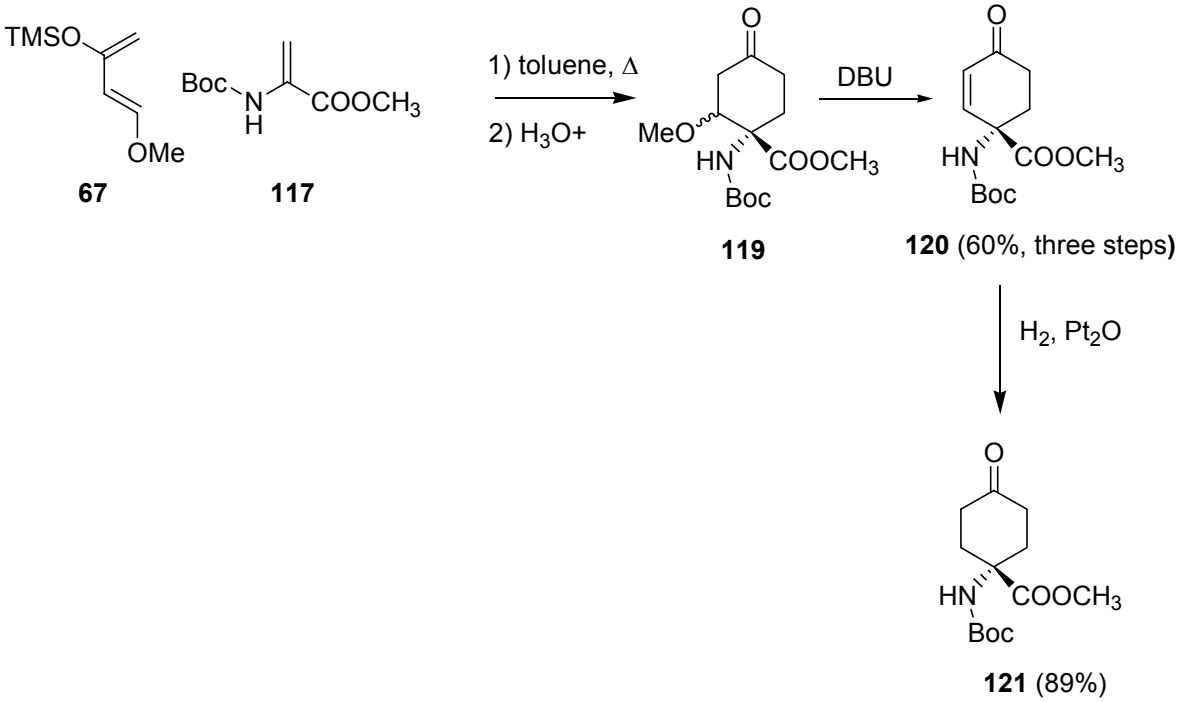
Scheme 12

With the Boc-protected dienopohile **117** in hand, the Diels-Alder [4+2] cycloaddition was studied. 2-Trimethylsiloxy-1,3-butadiene (**118**) was selected as the diene in order to minimize the number of steps in the synthesis, but this proved not to be as successful in the Diels-Alder cycloaddition as Danishefsky's diene[1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene] (**67**) (Scheme 13). Even when the Lewis Acid catalyst ZnI_2 was employed, the results were not as favorable as when the methoxy group was present on the diene. The best results were obtained when one equivalent of the dienophile **117** was heated with four equivalents of Danishefksi's diene (**67**) in refluxing

toluene under an atmosphere of argon for 24 hours, at which time 1 more equivalent of the dienophile was added and the mixture was heated to reflux for an additional 48 hours. The excess diene was necessary to discourage the dienophile from reacting with itself. This was immediately followed by hydrolysis of the trimethylsilyl group to afford the ketone **119** (Scheme 14).



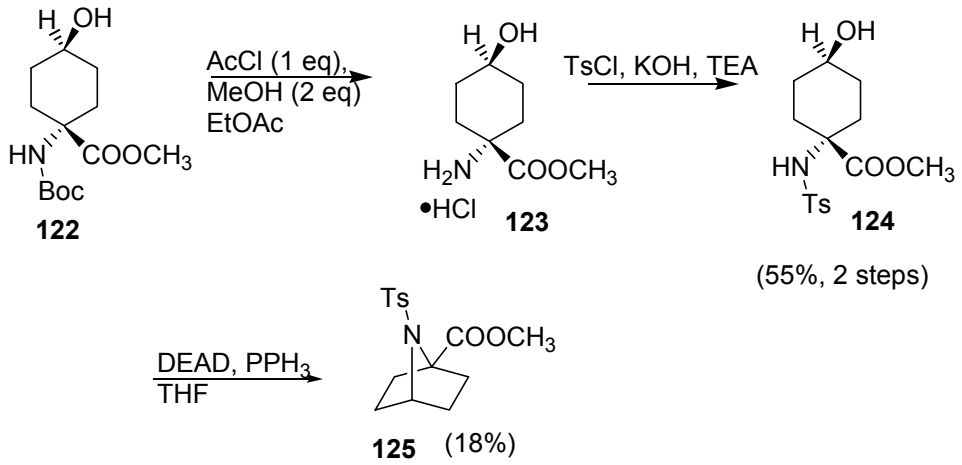
Scheme 13



Scheme 14

The same procedures (Scheme 14) were preformed to eliminate the methoxy group of **119** as employed for **99**. The absolute purification of the enone **120** became and important step in the procedure. After gravity silica gel column chromatography using a gradient solvent system of pure chloroform gradually increasing to 10% methanol:90% chloroform, a single compound was obtained. The H^1 NMR showed only a slight impurity. However, the compound was a very viscous oil. This made the compound very difficult to handle in subsequent steps. The enone **120** was then hydrogenated over 10% palladium on carbon in methanol to furnish the ketone **121**. Following the hydrogenation, filtration of the catalyst through Celite®, a fritted funnel, or even filter paper became almost impossible owing to the viscosity of the compound. Recrystalliazation of the enone in a 3% MeOH solution in chloroform offered absolute purity and a yellow crystalline solid in 60% yield.

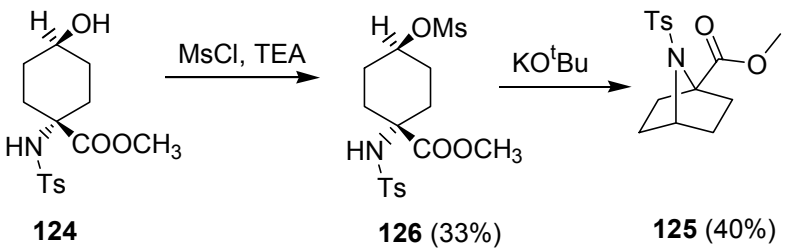
Selective reduction of the ketone was again achieved with L-Selectride® to afford the alcohol **122** in 77% yield without the complication of the lactone formation. The Boc group was converted into the tosyl group in order to prepare the molecule for a Mitsonubu ring closing reaction. Attempts to remove the Boc group with trimethlysilyl iodide caused cleavage of the methyl ester and standard conditions employing trifluoroacetic acid resulted in dehydration of the alcohol to the corresponding cyclohexene. The amino group was successfully deprotected to afford the quaternary ammonium salt **123** by HCl/methanol/ethyl acetate that was generated from acetyl chloride and methanol. The ammonium salt **123** was dissolved in a solution of potassium hydroxide, *p*-toluenesulfonyl chloride, and triethylamine. This furnished the sulfonamide **124** in a modest 55% over two steps (Scheme 15).[85]



Scheme 15

The *p*-toluenesulfonyl protecting group had recently been reported in the literature to facilitate an intramolecular Mitsonubu ring closure where other protecting groups failed. This reaction occurs in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (PPh_3).[62] However, no Mitsonubu ring closures have been reported where a functional group was attached to the same carbon as the protected amine. To our dismay, the Mitsonubu cyclization gave only very poor yields (18%) of the desired 7-azabicyclo[2.2.1]heptane derivative **125**. A small amount of starting material was recovered along with numerous intractable side products after reaction times of 48 hours.

In order to facilitate the ring closure, the alcohol **124** was converted into the mesylate leaving group **126** (Scheme 16). Potassium *tert*-butoxide mediated intramolecular cyclization also did not afford enough of the 7-azabicyclo[2.2.1]heptane **125** to generate the desired analogs (Scheme 16).



124 **126** (33%) **125** (40%)

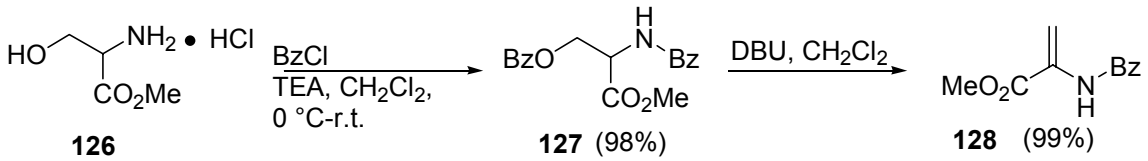
Scheme 16

Synthesis Employing Benzoyl Protecting Group

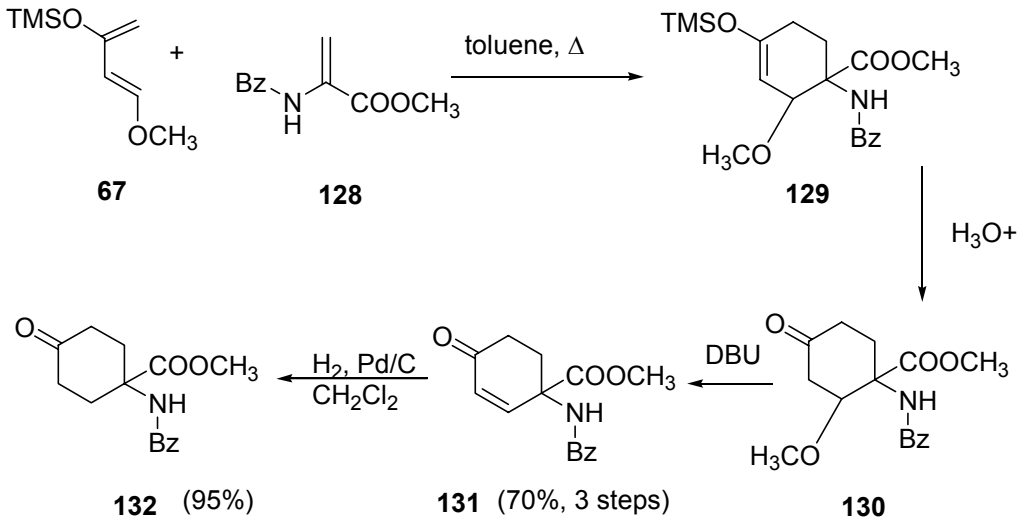
At this point, a modified procedure used to study rigid proline analogs was employed to obtain higher yields of the necessary intermediate (Scheme 17).[86] If the literature procedure was followed, for the one-pot benzoyl protection of the amine as well as the alcohol of *d,l*-serine methyl ester (**126**), a poor yield was obtained of the desired product **127**. The yield was improved over the reported literature value by adding the reagents to the salt slurry at 0 ºC instead of 25 ºC. Also, adding the benzoyl chloride (BzCl) and the triethylamine (TEA) in alternating portions of TEA followed by BzCl prevented the reaction mixture from becoming too hot. This sequence was repeated until the complete volume of each reagent was added. At that point the reaction was stirred at room temperature until no starting material was apparent by thin layer chromatography (TLC). The resulting yellow solid was triturated with hexanes to afford the white, crystalline benzyl-amino acid derivative **127** in almost quantitative yield.

The subsequent elimination of the benzoate moiety of **127** was achieved by slow addition of 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) to the stirred solution of **127**. If the temperature did not exceed 5 ºC, the dienophile **128** was furnished in 99% yield. Removal of the solvent was achieved under reduced pressure at room temperature. If

heat is applied, the resulting product will be a viscous, insoluble gel that was very difficult to work with and produced significantly lower yields if used in the cycloaddition reaction. Also, it should be noted that the dienophile should be used in the subsequent cycloaddition as soon after its synthesis as possible, as it can transform into the viscous material upon standing, even in the refrigerator, over time. This material generally gave lower yields of the cycloaddition adduct **129**.



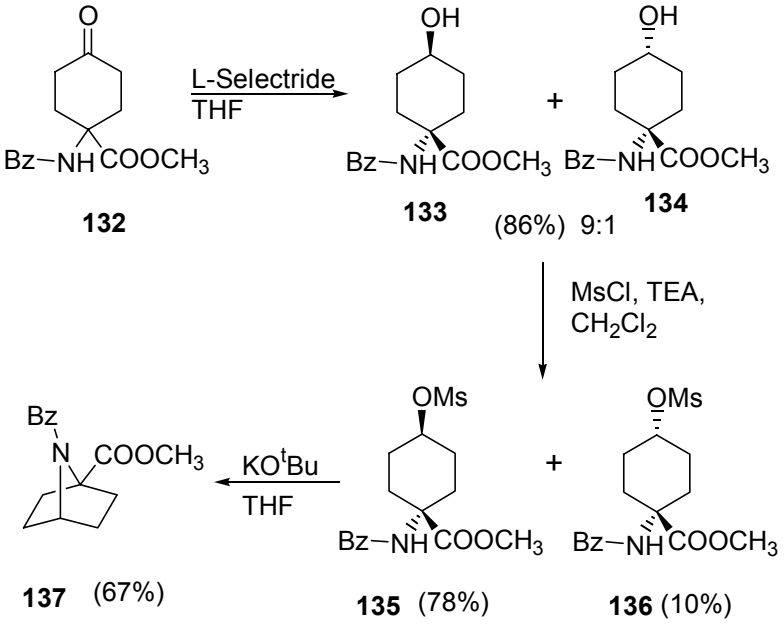
Scheme 17



Scheme 18

Utilizing 2-trimetyhylsiloxy-1,3-butadiene would be preferable in the Diels-Alder [4+2] cycloaddition as it alleviates two time consuming steps. However, its limited

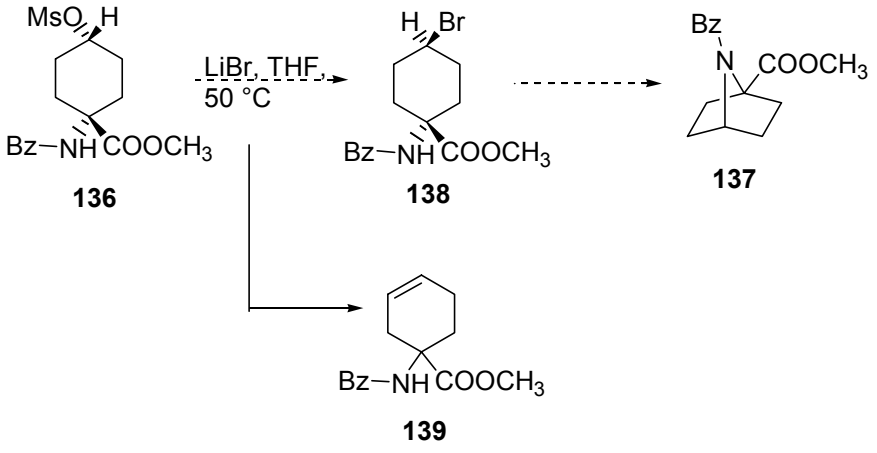
availability eliminated the diene as a precursor in the synthesis. Danishefsky's Diene (1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene **67**) was an acceptable alternative being sufficiently activated with electron-donating groups to facilitate the cycloaddition with the acrylate dienophile **128**. The diene and the dienophile were heated in toluene to give the cycloaddition adduct **129** (Scheme 8) in 3-4 days. The trimethylsiloxy group hydrolysis and elimination of the methoxy group were carried out as previously described to afford the enone **131** in 70% yield over three steps (Scheme 18). The enone **131** was hydrogenated over 10% palladium on activated carbon in methylene chloride to afford the 4-substituted cyclohexanone derivative **132** in 95% yield.



Scheme 19

The cyclohexanone derivative **132** was selectively reduced with L-Selectride® (lithium tri-*sec*-butylborohydride) to produce the inseparable alcohol isomers

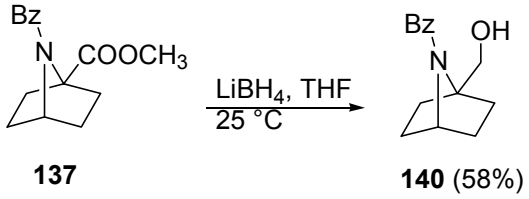
133 and **134** (9:1) (Scheme 19). The dropwise addition of the borohydride reagent over 1 hour at -78 ºC followed by vigorous stirring at –78 ºC for 20 hours afforded the highest yield of 86%. The isomeric alcohols **133** and **134** were converted into their corresponding mesolates **135** and **136** in high yield. Separation of the mesylate isomers by gravity column chromatography afforded the produced a pure *trans* 1,4-disubstituted cyclohexane derivative **135** in 78% isolated yield. Potassium *tert*-butoxide was added to the *trans* cyclohexane derivative **135** at –78 ºC and the solution was stirred for 1 hour at this temperature. The reaction was then allowed to stir overnight at room temperature to furnish the 7-azabicyclo[2.2.1]heptane ring **137** in 67% yield (Scheme 19).



Scheme 20

If the conversion of the isomeric alcohols **133** and **134** into the corresponding mesylates **135** and **136** in Scheme 19 was performed on a large scale, a significant quantity of the *cis* cyclohexane derivative **136** was obtained. With the *cis*-mesylate **136** in hand, an attempt to convert it into the desired bicyclic intermediate **137** was made (Scheme 20).[87] Substituting the mesylate with bromine would afford a bromo-

cyclohexane derivative **138** with the appropriate stereochemistry for the intramolecular cyclization. However, treatment of the *cis*-mesylate **136** with lithium bromide and heat only furnished the cyclohexene **139** as the major product.

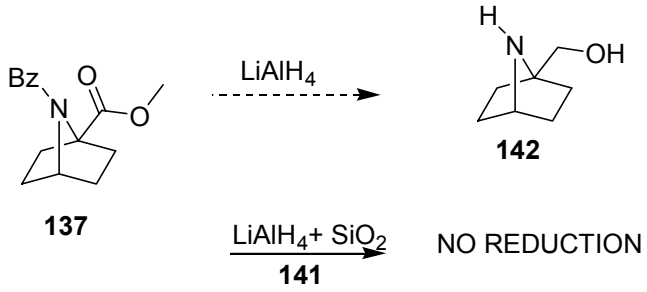


137 **140** (58%)

Scheme 21

An attempt to reduce the methyl ester moiety of **137** to the primary alcohol **140** in the presence of a benzoyl protecting group was made. The addition of lithium borohydride in refluxing tetrahydrofuran (THF) resulted in the consumption of the starting material within several hours, however a negligible amount of the desired product was obtained.[60] A variety of temperatures were tested, but even moderate temperatures (e.g. 40 °C) produced a significantly lower yield than if the reaction proceeded at room temperature (Scheme 21). Unsuccessful methods employed include refluxing the ester in diethyl ether as well as in THF at 32 ºC. The highest yields were obtained when 1.5 equivalents of lithium borohydride was added initially to the stirred reaction with an additional 0.5 equivalents added every 12 hours until a total of 2.5 equivalents were added.

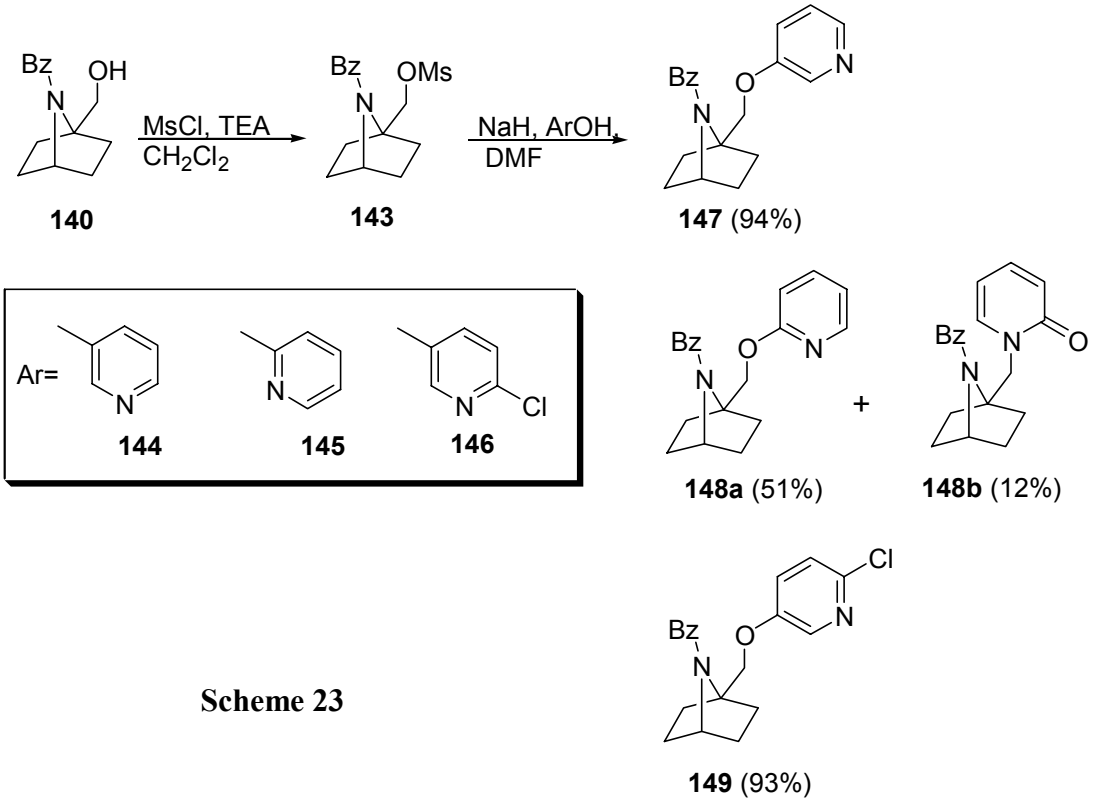
Other reducing methods were attempted to increase the yield of the bicyclic alcohol **140** (Scheme 22). The careful stoichiometric addition of lithium aluminum hydride in THF reduced the benzamide protecting group concurrently with the ester resulting in a side product that did not contain the benzoyl functionality. The by-product proposed is the secondary amine **142**, which was not isolated due to possible water solubility. The deactivated lithium aluminum hydride in the presence of silica gel (SiO_2) was also attempted with no observed reduction to the desired alcohol **140**.[88] This bulky reagent complex **141** is thought to be too sterically demanding to react with an ester on the hindered bridgehead position.



Scheme 22

The bicyclic alcohol **140** was converted into the corresponding mesylate **143** with methanesulfonyl chloride and triethylamine (Scheme 23). It is important to note that the mesylate **143** cannot be purified by column chromatography, as decomposition readily occurs. For this reason it was used in its crude form in the following Williamson ether synthesis with hydroxypyridine derivatives **144-146**. 3-Hydroxypyridine (**144**) and 2-hydroxypyridine (**145**) are commercially available while 2-chloro-5-hydroxypyridine was synthesized according to the literature procedure.[89] As illustrated in Scheme 23, sodium

hydride (NaH) was stirred in dimethylformamide under an atmosphere of nitrogen with a corresponding hydroxypyridine **144-146** in dry dimethylformamide for 1 hour at room temperature to generate the alkoxide ion from the alcohol moiety. The mesylate **143** was then added to the alkoxide and the solution was stirred at 80 ºC until the ether formation was complete (TLC). The reaction of the mesylate **143** with 3-hydroxypyridine (**144**) afforded the 3-pyridyl ether derivative **147** in high yield (94%). The reaction of the mesylate **143** with 2-hydroxypyridine (**145**) furnished the 2-pyridyl ether **148a** in moderate yield (51%) and the 2-pyridone side product **148d** in 12% yield. This is the result of a tautamerization that readily occurs in 2-hydroxypyridine. The pyridone **146d** was characterized by NMR and X-ray crystallography (Figure 7). The reaction of the mesylate **143** with 2-chloro-5-hydroxypyridine (**146**) furnished the 2-chloropyridyl ether **149** in high yield (93%). The chlorinated ether structure was unequivocally established by X-ray chrystallography (Figure 8).



Scheme 23

Figure 7. ORTEP Drawing of 1-(7-Benzoyl-7-aza-bicyclo[2.2.1]hept-1-ylmethyl)-1H-pyridin-2-one (**148b**). (Courtesy of E. D. Stevens and Z. Moore, University of New Orleans)

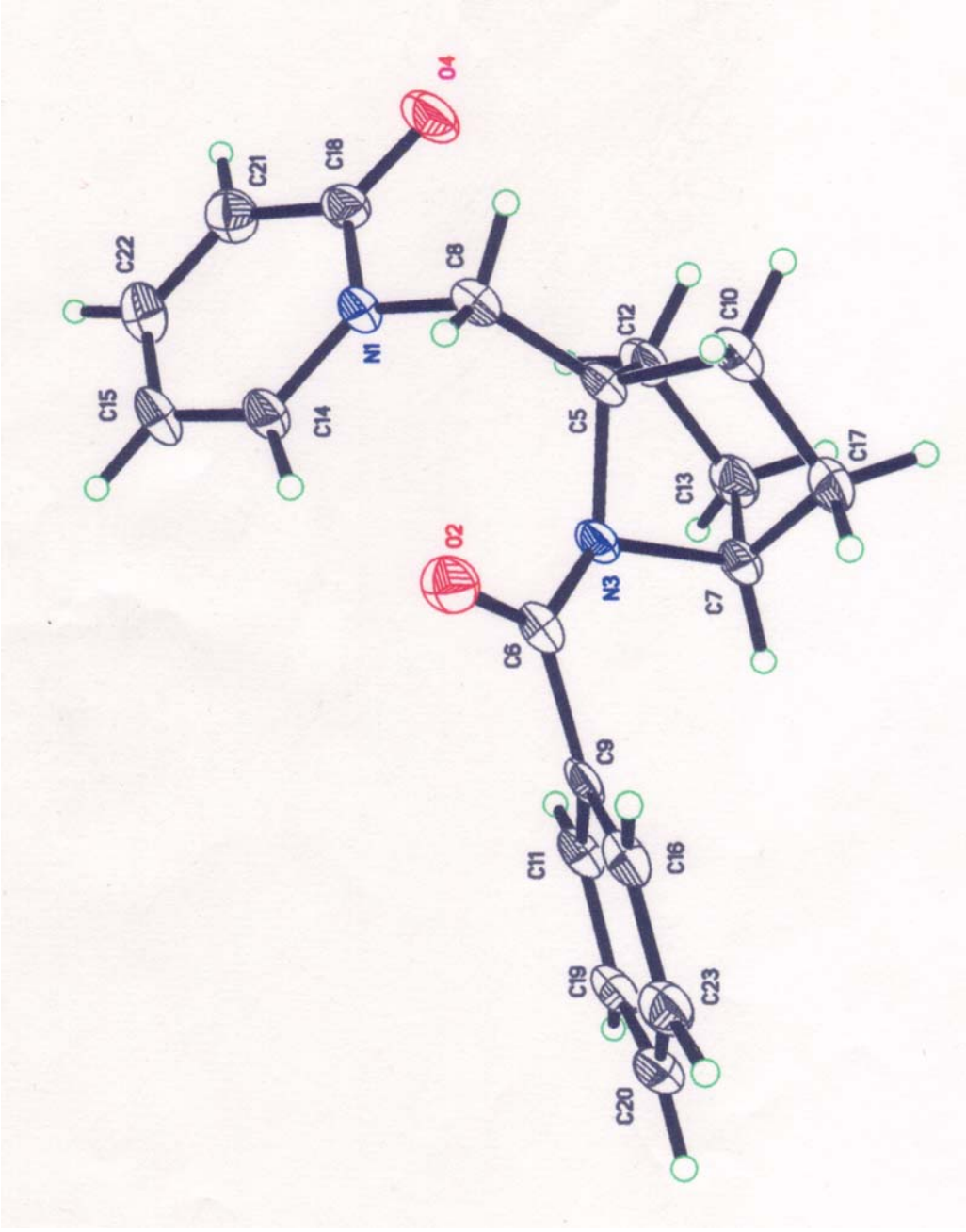
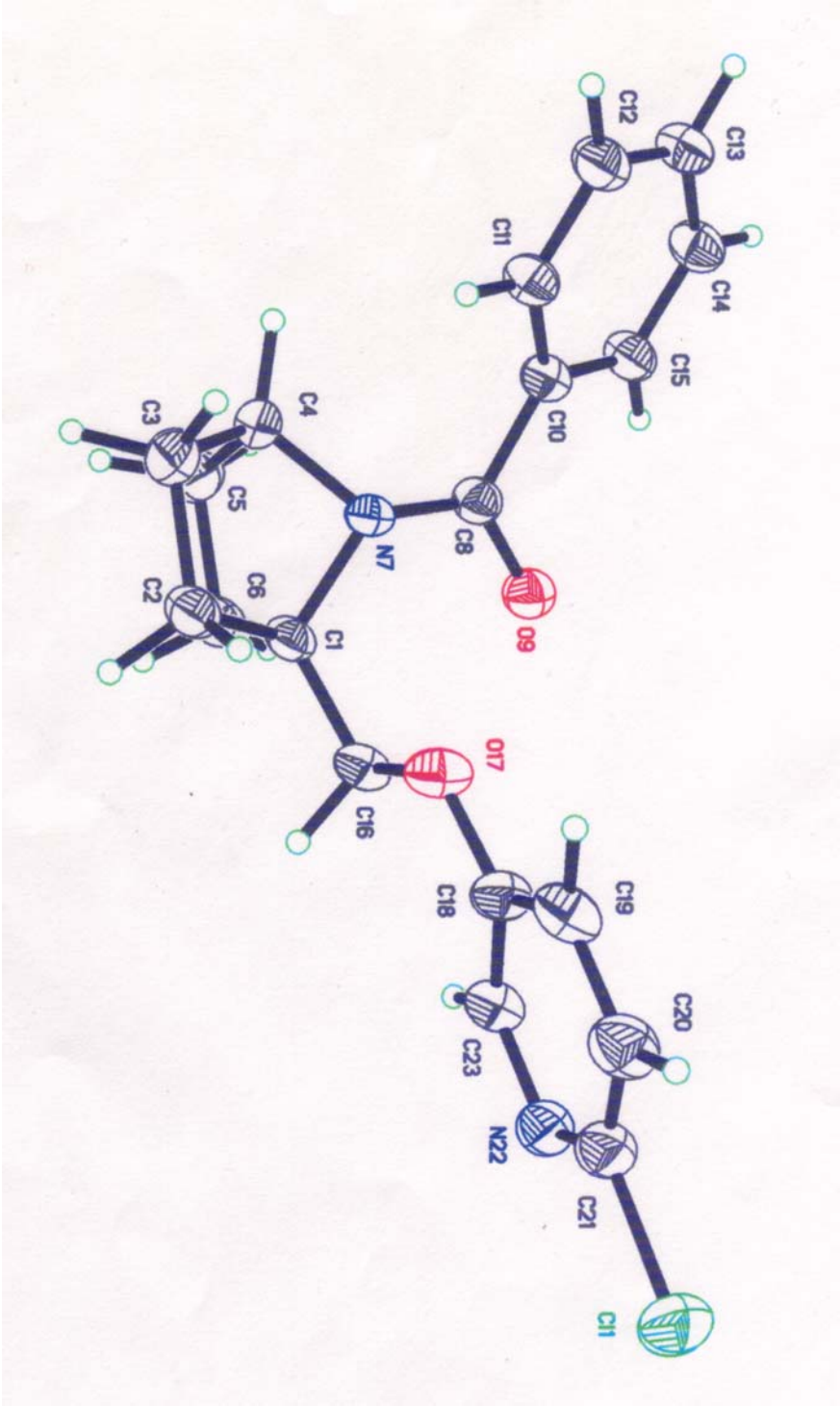
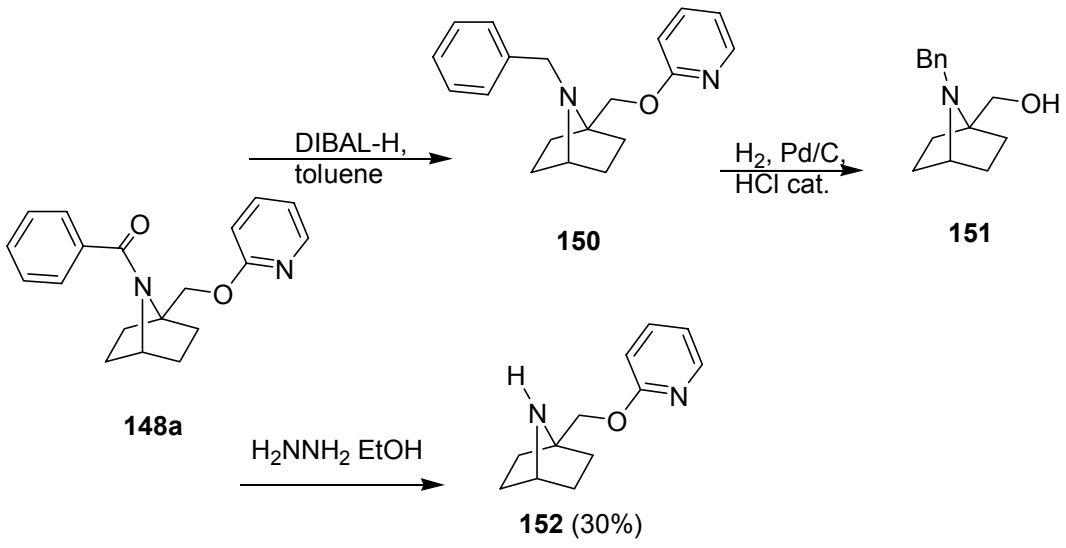


Figure 8. ORTEP Drawing of [1-(6-Chloro-pyridin-3-yloxymethyl)-7-aza-bicyclo[2.2.1]hept-7-yl]-phenyl-methanone (**149**). (Courtesy of E. D. Stevens and Z. Moore, University of New Orleans)

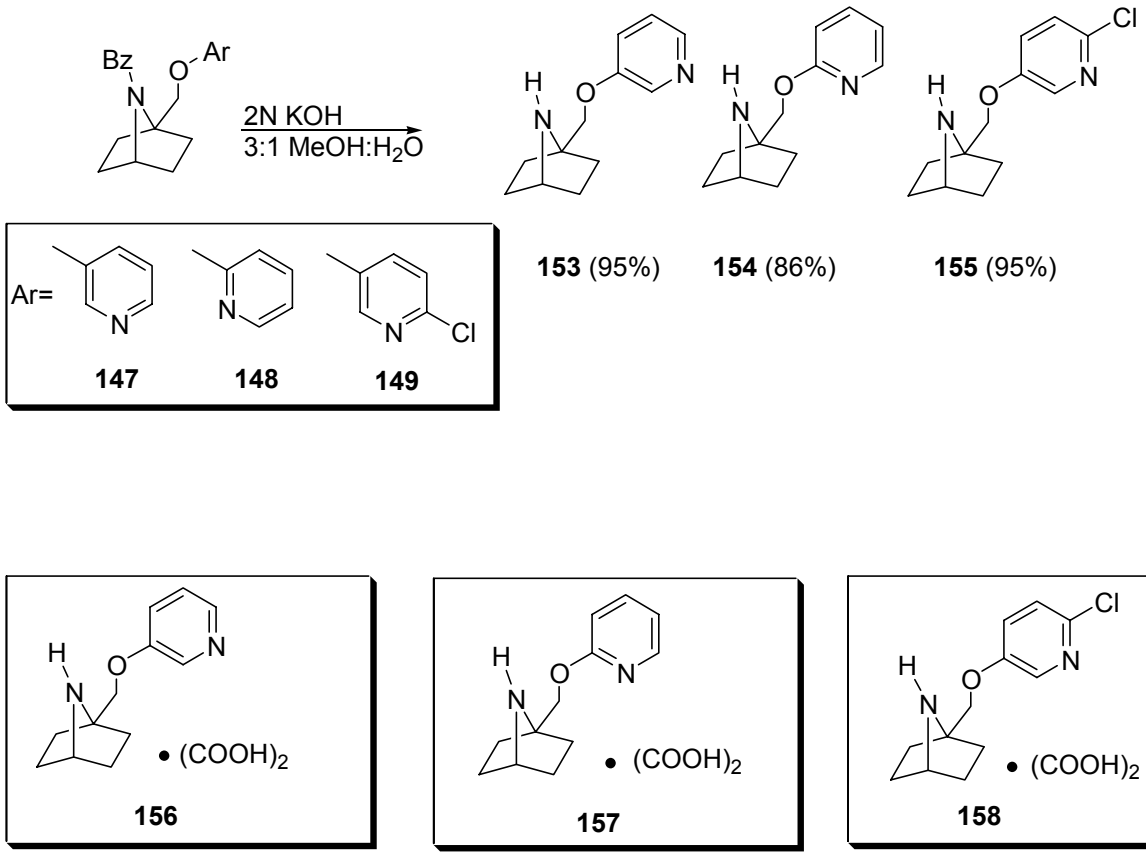


Deprotection of the benzamide was attempted several ways (Scheme 24). Converting the amide directly into a secondary amine with diisobutyl aluminum hydride (DIBAL-H) in toluene at –78 ºC was attempted.[90] However, when this procedure was applied to the pyridyl ether **148a**, 50-60% of the product formed was the benzyl amine **150**. The resulting benzyl group was attempted to be removed by hydrogenation over palladium on carbon with catalytic amounts of hydrochloric acid. However, even catalytic amounts of concentrated HCl resulted in the cleavage of the pyridyl ether to furnish **151**. The benzoyl protecting group of **148a** was attempted to be removed with hydrazine (NH_2NH_2) in ethanol.[91] After two days at reflux, only one third of the starting material **148a** was converted into the desired product **152**. In addition, it must be noted that this method should not be employed for the chlorinated analog **149**, as it will substitute hydrazine for the chlorine atom adjacent to the nitrogen atom.



Scheme 24

The amides **147-149** were deprotected in a refluxing solution of 2 N KOH in a 3:1 mixture of methanol to water (Scheme 25).[92] This afforded the deprotected amines **153-155** in high yield without the formation of the benzylated product and without risk of ether cleavage. The amines were converted into the oxalic acid salts **156-158** to be used in subsequent biological testing (Scheme 25).



Scheme 25

Internitrogen Distance Calculations

Though the nicotinic acetylcholine receptor pharmacophore model is incomplete, many structural features of ligands have been proposed to enhance binding at the receptor. One such feature is an optimum internitrogen distance between the basic nitrogen of a molecule and the nitrogen of a pyridine ring present within the structure. The original model of Beers and Reich predicted an optimum internitrogen distance of 4.97 Å based on the structure of nicotine. The discovery of epibatidine contributed to the proposal of a new internitrogen distance of 5.1 Å-5.5 Å. The series of pyridyl ethers **32-43**, which are less toxic than epibatidine, suggests that the internitrogen distance of a ligand should be within 5.9-6.4 Å where the optimum distance is 6.1 Å.

The distance between the basic nitrogen of the 7-azabicyclo[2.2.1]heptane ring and the pyridine nitrogen of **149** was determined to be 6.48 Å by the X-ray crystal structure (Figure 8). It should be noted that the crystal packing structure may not represent the ligand's conformation in solution. Modeling calculations based on the minimum energy conformation (Chem3D® drawing) of the deprotected 7-azabicyclo[2.2.1]heptane ring **155** show an internitrogen distances 6.36 Å (Figure 9). Rotation of the pyridine ring about the oxygen-sp^2-hybridized carbon in 30º increments offers internitrogen distances of 6.21-6.59 Å (Δ 0.38 Å). Based on the structural similarity of **155** and **153** to ABT-594 (**39**), as well as similar internitrogen distances, we predict this series to have potent binding affinities similar to ABT-594. The 2-pyridyl derivative **154** was calculated to have an internitrogen distance of 4.90 Å based on the lowest energy conformation (Figure 10). The range of internitrogen distances calculated

by rotation of the pyridine ring encompasses 4.70-5.20 Å (Δ 0.38 Å). Though less than the optimum internitrogen distance calculated for the pyridyl ethers, these values correspond with those calculated for epibatidine and nicotine. We also predict high binding affinity similar to epibatidine based on the structural similarities of **154** and epibatidine. Chem-3D calculations of the lowest energy conformation of (*S*)-nicotine compute an internitrogen distance of 4.6 Å compared to the literature value of 4.97 Å. The Chem-3D computations of the newly synthesized pyridyl ether analogs may have an error of up to 0.37 Å.

Figure 9. Lowest energy conformation of **155** based on Chem3D calculations. N7-N13 distance equals 6.36 Å.

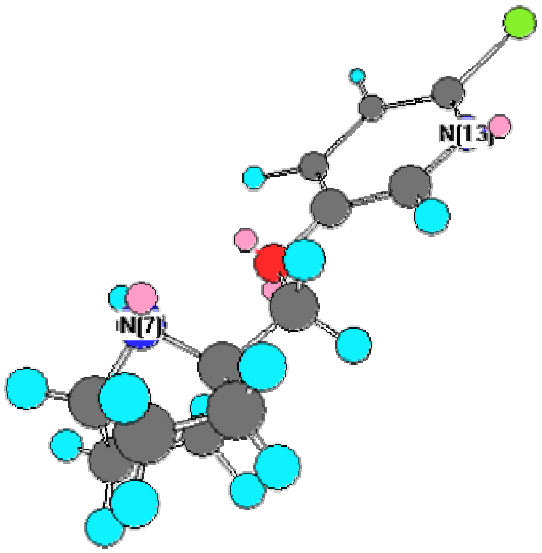
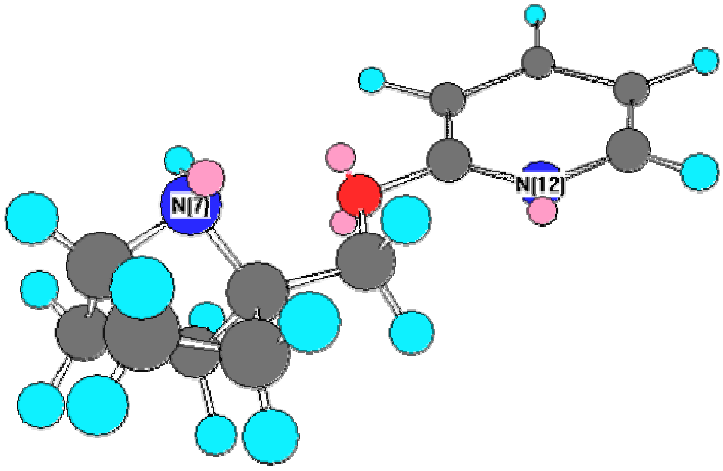


Figure 10. Lowest energy conformation of 154 based on Chem3D calculations. N7-N13 distance equals 4.90 Å.

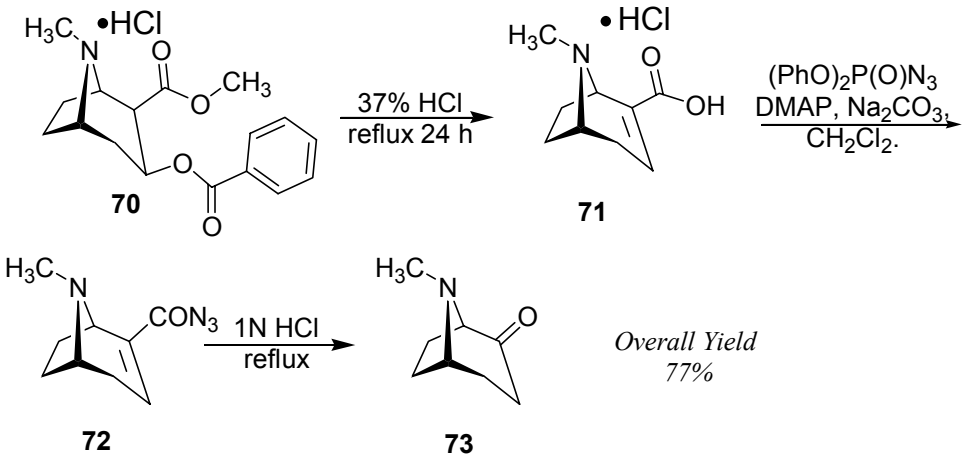


Synthesis and Binding Affinity of Rigid Acetylcholine Analogs

Chemistry

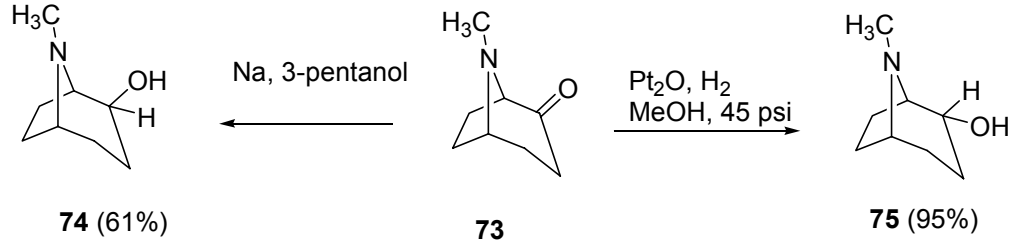
The synthesis of the rigid acetylcholine analogs begins with the formation of 2-tropanone (**73**). This system can easily be derived from (-)-cocaine (**70**) as outlined by Zhang, Lomenzo, and Trudell (Scheme 26).[74] The confiscation grade cocaine was heated to reflux in 12 M hydrochloric acid to afford (-)-anhydroecgonine hydrochloride (**71**). The acid was thoroughly dried at 100 ºC (oil bath) under vacuum overnight and pulverized before use in the following step. A suspension of the carboxylic acid **71** was treated with diphenylphosphoryl azide (DPPA) and catalytic amounts of

dimethylaminopyridine (DMAP). The slurry was stirred over 48 h at room temperature to afford the azide **72**. The crude azide was converted directly into the ketone **73** *via* a Curtius rearrangement performed in 1N hydrochloric acid. The pure ketone **73** was obtained by Kugehlohr bulb-to-bulb distillation in 77% overall yield.



70 **71** **72** **73**

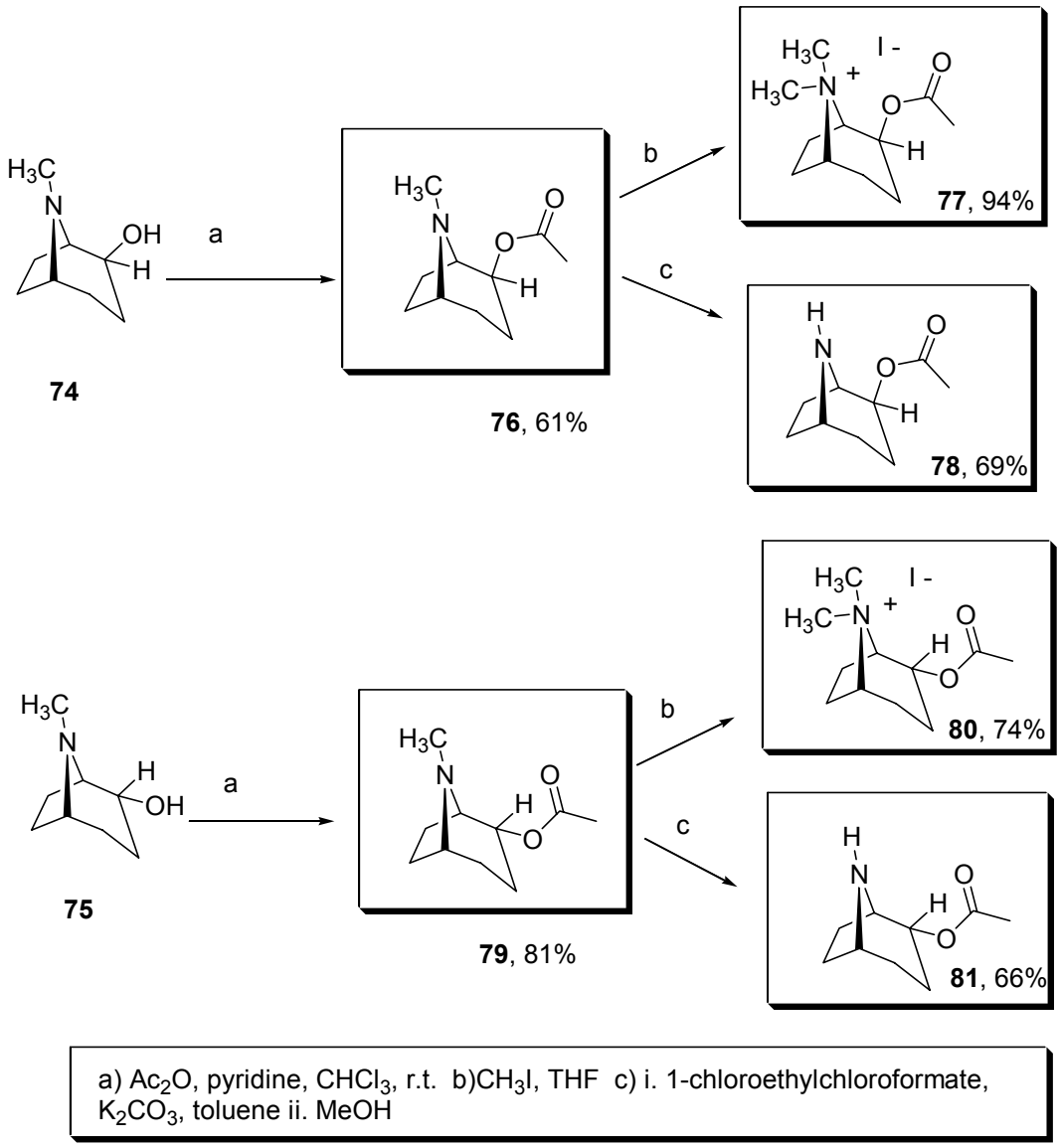
Scheme 26



74 (61%) **73** **75** (95%)

Scheme 27

The β-2-tropanol (**74**) could be made from 2-tropanone (**73**) in the absence of any α-2-tropanol *via* a dissolving metal reduction of sodium metal in 3-pentanol (Scheme 27).[73] During this reaction, both *endo* and *exo* isomers were formed, however the β-tropinol (*exo*) isomer is thermodynamically preferred to the α-2-tropanol, and after 20 hours at elevated temperatures any α-tropinol (**75**) formed was converted to β-2-tropanol (**74**). The 2-tropanone (**73**) was selectively converted into the α-2-tropanol (**75**) by hydrogenation in methanol catalyzed by PtO_2 (Scheme 27). Elevated pressures of 45 psi were necessary for the reaction to proceed to completion. The platinum catalyst coordinates to the basic nitrogen of the tropane ring, thereby delivering the hydrogen from the *exo* face of the ring that results in the *endo* alcohol **75** in 95% yield. It should be noted that both alcohols **74** and **75** can be purified by column chromatography.[93] However, the basic tropanes have an affinity for 'sticking' to the acidic silica gel of the column and would decompose if not eluted in a timely fashion. Solvent systems with high polarity (88:10:2 $CHCl_3$:MeOH:NH_4OH) and flash chromatography were employed in order to ensure optimum yield.



Scheme 28

Conversion of the β-2-tropinol (**74**) into its corresponding ester **76** was not achieved in high yields by treatment of the alcohol with acetyl chloride, catalytic amounts of dimethylaminopyridine (DMAP) and triethylamine (TEA). This conversion was

accomplished by treatment of the β-alcohol **74** with freshly distilled acetic anhydride (Ac_2O) and freshly distilled pyridine at room temperature. High yields were achieved if the chromatography solvent system contained NH_4OH in order to neutralize the acidic sites of the silica gel. The β-2-acetoxytropane (**76**) was converted into the oxalic acid salts for biological testing.

The quaternary 2-acetoxy-8-methyl-8-azabicyclo[3.2.1]octane methlyiodide (**77**) was synthesized by treating the starting material **76** with methyl iodide (CH_3I) in refluxing tetrahydrofuran. Upon completion of the methylation, the solvent was removed under reduced pressure and the resultant white solid was triturated with hexanes to afford the quaternary salt **77** in almost quantitative yields.[72] The purity of the resulting salt **77** was suitable for biological testing.

Demethylation of the β-acetoxytropane to the corresponding secondary amines **78** required a two step process. The tropane ring is first reacted with 1-chloroethyl-chloroformate (ACE-Cl) to form the *N*-chloroformate intermediate. Subsequent heating in MeOH furnished the amine in moderate yields. Purification was accomplished by formation of the hydrochloride salt. Anhydrous HCl gas was bubbled through cold diethyl ether and the solution was slowly dropped into a solution of the free base until a precipitate formed. The salts were only obtained in crystalline form by slow crystal growth in THF at –20 ºC over several days.[94]

The α-acetoxytropane **78-81** derivatives were synthesized in the same manner as the β-acetoxytropanes (Scheme 28). α-2-Tropinol (**76**) was converted into its corresponding ester, α-2-acetoxytropane (**78**), with acetic anhydride in the presence of pyridine. The ester **78** was transformed into the oxalic acid salt derivative for subsequent

biological testing. The α-2-acetoxy-8-methyl-8-azabicyclo[3.2.1]octane methlyiodide (**79**) was synthesized in the same fashion as the β-derivative. The demethylated β-acetxytropane **81** was also synthesized as outlined in Scheme 28 and converted into the HCl salt for biological testing.

Biology

The acetoxytropanes **77**, **78**, **80**, **81** were tested at the neuronal nicotinic acetylcholine receptor for comparison of their relative binding affinity to epibatidine (Table 2). The values reported are concentrations at which 50% of the radiolabeled epibatidine was displaced from the receptor active site. Rat cortex membrane tissue was used, as it contained a high concentration of the α4β2 receptor subtype. The compounds exhibited no measurable affinity for the central nervous system nicotinic acetylcholine receptor affinity up to the highest dose tested (50 μM). The acetoxytropanes **77**, **78**, **80**, **81** were also tested in Torpedo electric organ preparation to determine if the compounds displayed affinity for the 2αβγδ neuromuscular nicotinic acetylcholine receptor. No measurable response was detected at concentrations up to 5 μM. This translates to a 100-1,000 fold decrease in affinity relative to nicotine and 1,000-10,000 fold decrease in affinity relative to epibatidine at these receptor subtypes. Since binding in the subnanomolar range was desired these compounds were deemed inactive, and therefore not representitive of the conformation of acetylcholine inside the active site of the nicotinic receptor.

Table 2. Nicotinic Ligand Binding at CNS nAChRs (^{3}H-Epibatidine displacement)

	4	**77**	**78**	**80**	**81**
Agent	(-)-Epibatidine	SD-I-94	SD-I-103	SD-I-70	SD-I-80
Rat Cortex Membranes ($\alpha4\beta2$)	1.5 pM	> 50 μM	> 50 μM	> 50 μM	> 50 μM
Torpedo Electric Organ ($\alpha1\beta1\delta\gamma$)	0.006 μM	> 5 μM	> 5 μM	> 5 μM	> 5 μM

Since the acetoxytropane derivatives were not active at the neuronal nicotinic acetylcholine receptor, they were tested at muscarinic acetylcholine receptors to determine if they resembled the conformation of acetylcholine at this receptor subtype. One source that contains a high concentration of muscarinic receptors of $\alpha x\beta y$ subtype is the guinea pig ileum. The compounds were tested for their minimum effective concentration, or the concentration necessary produce the response seen with acetylcholine binding (Table 3). Table 3 shows that the necessary stimulating concentrations for **76-81** as agonists are 100-1,000 times higher than those for acetylcholine. This revealed that the compounds are likewise 100-1,000 times less potent than acetylcholine in this paradigm.

Antagonist properties of **76-81** were also measured as relative to atropine, a known muscarinic antagonist (Table 3). This activity was reported as the minimal effective blocking dose against acetylcholine. The α-2-acetoxytropane **79**, the α-2-acetoxytropane methiodide **80**, and the desmethyl α-2-acetoxytropane **81** are 200-fold

less potent than atropine. The β-2-acetoxytropane **76** and the desmethyl β-2-acetoxytropane were also 200-fold less potent and the β-2-acetoxytropane was 400-fold less potent than atropine in this paradigm.

Table 3. Acetylcholine-like potency in isolated guinea pig ileum

Agent	Agonist EC min (μg/mL) (range) [N]*	Antagonists EC_{50} against ACh (range) [N]
SD-I-70 (**79**)	>40 [2]	15 [2]
SD-I-71 (**80**)	100 (30-240) [4]	30 [3]
SD-I-80 (**81**)	120	25 [2]
SD-I-94 (**76**)	400 (120-800) [7]	25 [3]
SD-I-103 (**77**)	80 (30-160) [7]	40 [3]
SD-I-109 (**78**)	10 (4-20) [6]	7 (5-20) [6]
ACh Cl	0.2 (0.05-0.4) [7]	-----
Atropine SO_4	-----	0.02 (0.007-0.05) [7]

*EC min = minimal stimulant concentration, [N] = number of tests

A paradigm similar to the guinea pig ileum was investigated to study possible agonist and antagonist activity at the muscarinic acetylcholine receptor in rat (Table 4). Rat jejunum preparation displays concentration of a distinct muscarinic acetylcholine receptor αxβyβz, different from the subtype present in guinea pig illeum. The series proved to be inactive in this paradigm as well. The analogs **79, 80,** and **81** were 200-300-fold less potent than acetylcholine as an agonist and **80** and **81** were 500-1,000-fold less potent as antagonists when compared to atropine.

Table 4. Acetylcholine-like muscarinic potency in isolated rat jejunun

Agent	Agonist EC min μg/mL (range) [N]*	Antagonnist EC_{50} against ACh (range) [N]
SD-I-70 (**78**)	100 [4]	-----
SD-I-71 (**80**)	100 [3]	50 [2]
SD-I-80 (**81**)	150 [2]	20 [2]
ACh Cl	0.5 (0.2-1.0) [4]	-----
Atropine SO_4	-----	0.05 [2]

*EC min = minimal stimulant concentration, [N] = number of tests

Advanced testing was performed on the β-acetoxytropanes **76** and **77**. A live animal model was used to study the acetylcholine derivatives' effects on rat blood pressure. Atropine blocks the acetylcholine response and causes a decrease in blood pressure in animal models. Where 0.5-1 μg of atropine per 1 kg of rat is required to illicit an acetylcholine blocking response, 500 μg or more was required of the rigid acetylcholine derivatives **76** and **77** to achieve the same response. The β-2-acetoxytropanes were 1000-fold less potent in this paradigm. Potency was also measured at the ganglionic α7 nAChR subtype found in rat spinal cord by observing nicotinic pressor response. Where nicotine produces an increase in blood pressure at concentrations as low as 120 μg/mL, compounds **76** and **77** were completely inactive, even at concentrations up to 2 mg/mL.

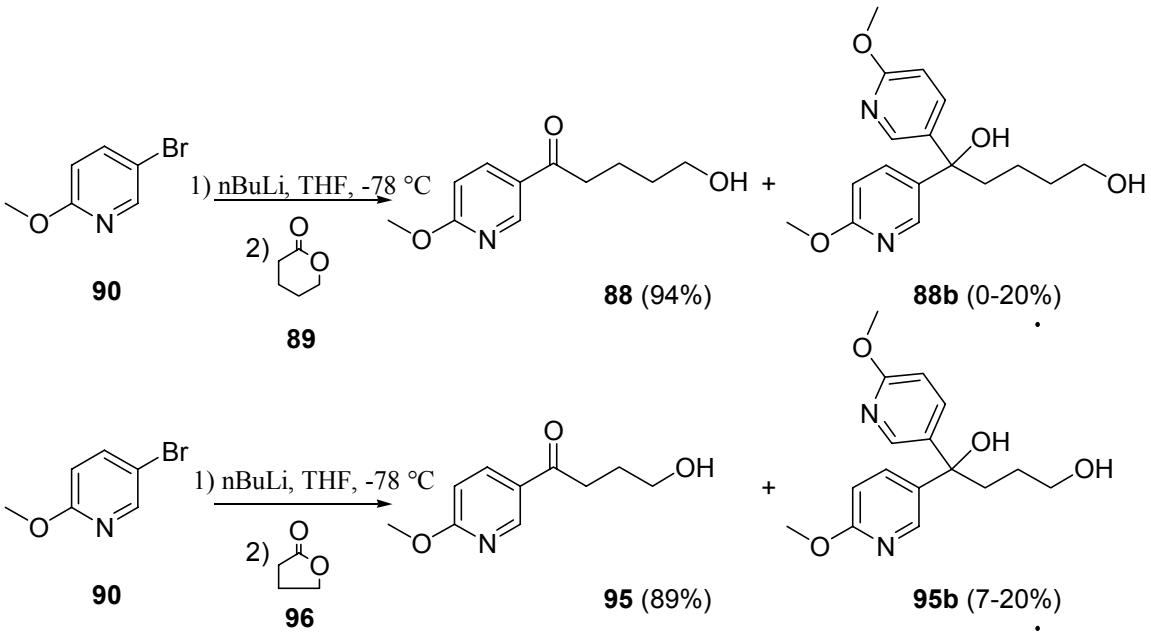
Table 5. Rat blood pressure and spinal rat preparation tests on **76** and **77**

Agent	Minimal Ach Blocking Dose in Rat Blood Pressure Model	Spinal Rat Preparation
SD-I-94 (**76**)	>500 μg/kg	Inactive up to 2 mg/mL
SD-I-103 (**77**)	500 μg/kg	Inactive up to 2 mg/mL
Atropine	0.5-1 μg/kg	---
Nicotine	---	120 g/mL

Though a search was performed to determine if acetylcholine adopts a conformation similar to the one held in the rigid acetylcholine derivatives synthesized in this study, no significant biological activity was observed. We can conclude that acetylcholine adopts a conformation when bound to the active site of the nicotinic and muscarinic receptor subtypes tested that does not resemble the conformation imparted by the rigid tropane system. Alternatavely, the low binding affinity of the 2-acetoxytropanes may be ascribed to the additional steric interactions at the nAChR introduced by the tropane ring.

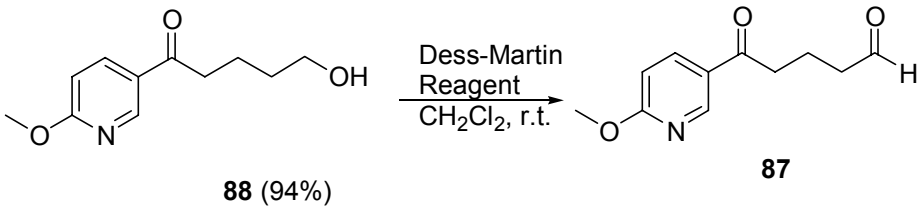
Synthesis of Anabasamine and Related Alkaloids

The synthesis of (±)-anabasamine was designed to be a versatile synthetic route with variability at each step to produce a number of different analogs and series of compounds. The first step in the synthesis involved the lithiation of commercially available 5-bromo-2-methoxypyridine (**90**). n-Butyllithium was added to a stirred solution of the pyridine in diethyl ether at –78 ºC over 15 minutes.[95] When the pyridyl lithium reagent was generated, the diluted δ-valerolactone (**89**) was added over 15 minutes. Stirring for 2 hours at room temperature was suffucient to facilitate the ring opening of the lactone and acylation of the pyridine ring. This afforded the keto-alcohol **88** in 94% yield. The concentration of the reaction proved to have an effect on the yield of the keto-alcohol **88**. Concentrations less than 0.04 M of 5-bromo-2-methoxypyridine increased the yield by decreasing the possibility of a second pyridyl anion addition to the ketone product **88**. The pyridyl anion addition to the ketone resulted in the formation of the biaryl diol **88b**. Another factor that effected the yield was the purity of the valerolactone. The reagent is only be available in technical grade and may contain up to 25% of an unreactive polymer. When the reagent was stored at –20 ºC, polymerization was minimized and yields of **88** were generally increased.



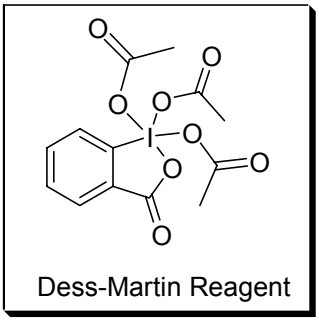
Scheme 29

Employing alternate lactones furnished keto-alcohols of varied chain-length. The butanol derivative **95** was generated in a similar manner to the pentanol **88** with the addition of δ-butyrolactone to the pyridine anion of **90** (Scheme 29). This afforded **95** in 89% yield. Up to 20% of the side product **95b** was isolated with higher concentrations of the reagents. However, lower concentrations of the reagents resulted in a decreased occurrence of the second addition product **95b**. It is important to note that reaction times increased for the less concentrated solution. The biaryl compound **95b** was identified by mass spectroscopy and by 2D COSY ^{1}H NMR.



88 (94%)

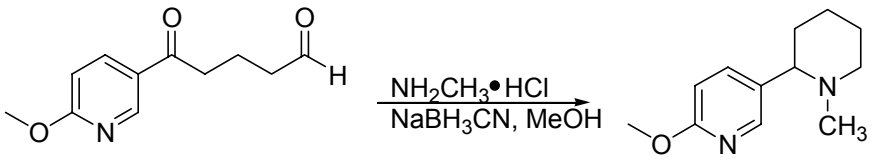
87



Scheme 30

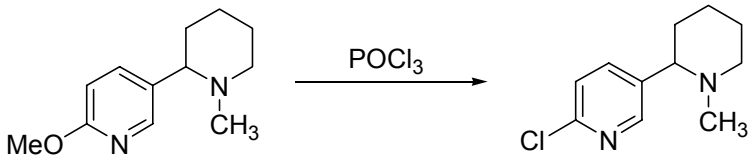
A variety of different oxidation agents were employed to oxidize the primary alcohol of **88** to afford the keto-aldehyde **87**. Oxidation of the alcohol with chromium regents (pyridinium dichromate and pyridinium chlorochromate) did not afford the product in sufficient purity. Due to the instability of the aldehyde to purification by column chromatography, an oxidation that proceeded with the formation of efficiently removed by-products in the workup was required. The Dess-Martin reagent was successful in oxidizing the primary alcohol **88** to afford the keto-aldehyde **87** in almost quantitative yield with negligible impurities as detected by TLC and NMR (Scheme 30).[96] The reaction was performed at room temperature in methylene chloride with 1.45 equivalents of the Dess-Martin reagent. The excess reagent allowed the reaction to be completed in 1.5 h. During the work-up, excess oxidizing agent was quenched with sodium thiosulfate in a saturated solution of $NaHCO_3$. It was beneficial to vigorously stir the reaction mixture and the aqueous mixture together for 10-20 minutes until the organic layer was rendered colorless. This thoroughly extracted excess oxidizing agent, acetic

acid, and other byproducts of the Dess-Martin reagent, from the organic solution. The presence of acetic acid or oxidizing agent was formed to effect the yield of the following step by reacting with the reducing reagent utilized in the reductive amination (Scheme 31). With the keto-aldehyde **87** in hand, the reductive amination was performed employing methylamine hydrochloride and sodium cyanoborohydride in methanol to yield the piperidine analog.[97]



87 **86** (58%)

Scheme 31



86 **85** (77%)

Scheme 32

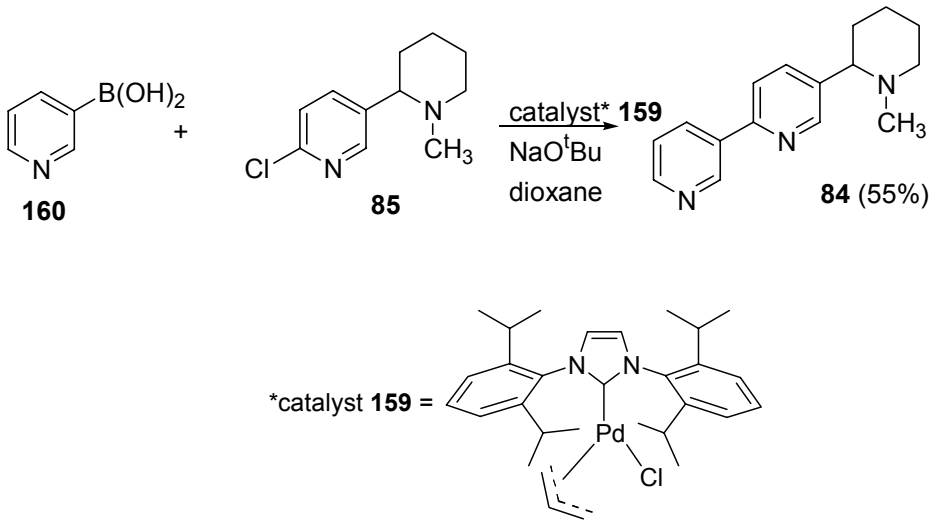
At this point, chlorination at the 2-position of the pyridine ring of **86** was desired for several reasons. First, it was of interest to study the binding affinity of the chlorinated piperidine analog **85** at the nicotinic acetylcholine receptor in comparison to epibatidine. Second, the chlorine moiety was desired in the subsequent coupling step to introduce the second 3-pyridyl ring of anabasamine. Chlorination methods utilizing

dimethylformamide (DMF) resulted in the formylation of the pyridine ring. Also, since the chloroinated product **85** exhibited higher water solubility than ether solubility, separation of DMF from the compound by ether extraction proved to be very difficult. Also, refluxing the aryl ether **86** in $POCl_3$ using standard reflux apparatus did not yield the desired chlorination products. The chlorination was achieved by heating the aryl ether **86** in phosphorous oxychloride in a sealed reactor tube at 115 ºC for 24 hours. Larger scales required 48 hours. The chlorinated pyridine derivative **85** could then be obtained if careful work-up conditions were employed.

The workup for this reaction proved to be very important and must be performed with extreme care in order to obtain the desired product. Once the reaction was cooled, most of the $POCl_3$ was removed by rotary evaporation. This minimized the amount of reagent to be neutralized. The viscous residue was then dissolved in a small amount of dichloromethane. Because the compound exists as the salt at this point, the salt is not readily soluble in organic solvents. However, attempting to dissolve the residue in even a small amount of cold water resulted in an exothermic reaction with residual phosphorous oxychloride that led to decomposition of the product **85**. The residue must then be first added dropwise to ice water to quench the $POCl_3$. The resulting aqueous mixture was then added dropwise to a saturated solution of ice-cold sodium carbonate and a pH 10 is maintained. If the base was added to the salt, or the salt was added to the base prior to dilution with water, even at cold temperatures, the reaction bubbled violently and decomposition occured. The basic aqueous layer was thoroughly extracted with copious amounts of dichloromethane to retrieve the compound from the water layer. Purification

by column chromatography resulted in the desired chlorinated pyridine **85** in moderate to good yields (49-77%).

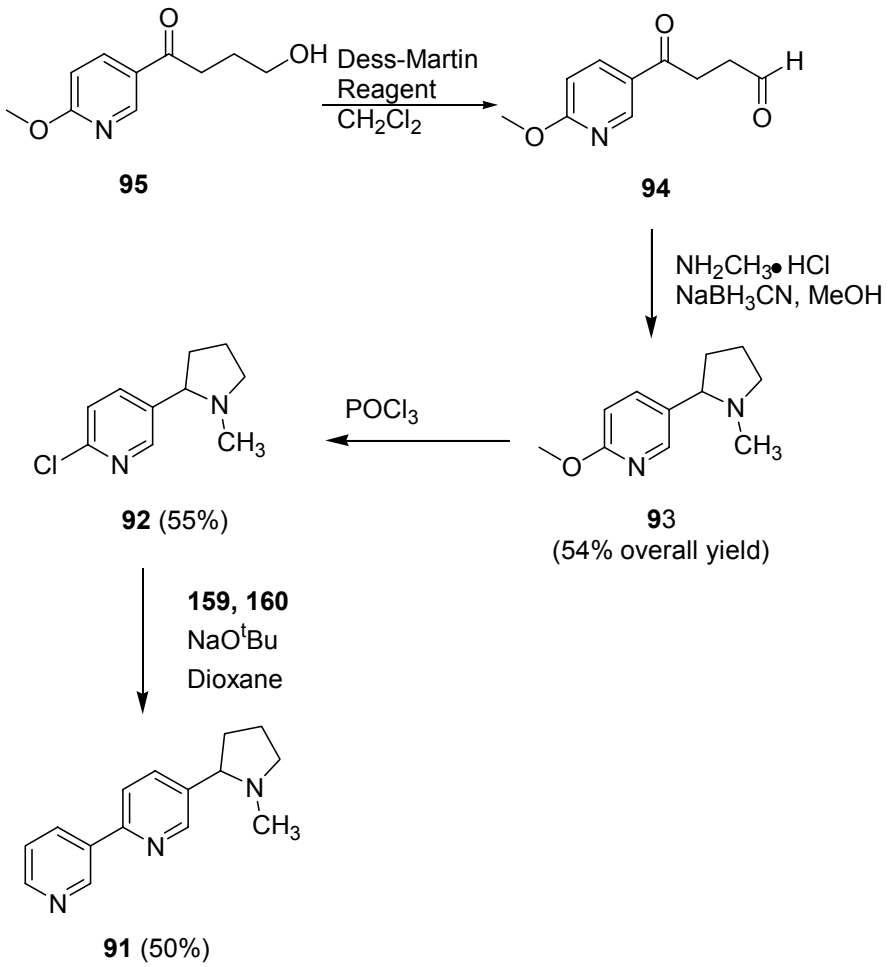
With the chloropyridine 85 in hand, the Suzuki-Miyaura coupling was then employed utilizing a palladium catalyst **159** developed by Viciu, *et al* for aromatic ring coupling reaction (Scheme 33).[98] Much research has been devoted to attempting aromatic coupling reactions utilizing chlorine atoms instead of the more expensive and more reactive bromine or other derivatives. This catalyst **159** proved successful for sufficient coupling of a 2-pyridyl chloride to a pyridyl boronic acid. To carry out the coupling, a reaction tube was charged with 3-pyridine boronic acid (**160**), the palladium catalyst **159**, and the sodium *tert*-butoxide in an argon glove box. To the heterogeneous mixture, a solution of the aryl chloride **85** in dry dioxane was added. The reaction was stirred vigorously at 80 ºC for 9 hours to afford the biaryl natural product, (±)-anabasamine (**84**) in 55% yield.[99] The limitation of this procedure is primarily the insolubility of the pyridyl boronic acid in dioxane. Pyridine boronic acids exhibit even lower solubilities than their benzene counterparts and more dilute reaction conditions were required than desired. The rate of the reaction varies directly with concentration. Though the reaction is run under dry conditions, water is not the greatest concern as interference in the mechanism. However, the reaction must be performed under anaerobic conditions to prevent deactivation of the palladium catalyst and to ensure high conversion.



Scheme 33

The pyrrolidine analog of anabasamine **91** was synthesized in a similar fashion to anabasamine (Scheme 34). Starting with 4-hydroxy-1-(6-methoxy-pyridin-3-yl)-butan-1-one (**95**) the Dess-Martin oxidation and reductive amination were subsequently employed as illustrated in Schemes 30 and 31. At this point, racemic 6-methoxy nicotine (**93**) was made in three steps with an overall yield of 54%. This is a marked improvement over the previous methods described in the literature of 16% overall yield in 5 steps. The nicotine analog **93** had been used, and continues to be used as a common drug intermediate for the development of a number of substituted nicotine analogs.

The methoxy moiety of 6-methoxynicotine (**93**) was substituted with a chlorine to generate the aryl chloride **92** appropriate for the Sizuki-Myaura coupling reaction. With the aryl chloride **92** in hand, the biaryl coupling was carried out with 3-pyridine boronic acid as described in Scheme 33 to afford the nicotine analog **91** in 50% yield.



95

94

92 (55%)

93
(54% overall yield)

91 (50%)

Scheme 34

CONCLUSION

In conclusion, three new classes of nicotinic acetylcholine receptor ligands have been developed. The first series of analogs (**147-149**) consists of hybrid structures of epibatidine (**4**) and ABT-594 (**39**). The 1-pyridyl ether-7-azabicyclo[2.2.1]heptane derivatives **147-149** were synthesized in 14 steps in a 7-13% overall yield. Previous studies have demonstrated that an optimum distance between the basic nitrogen and the pyridyl nitrogen of many nAChR ligands, such as epibatidine and ABT-594, is crucial for potent activity. The 1-pyridyl ether-7-azabicyclo[2.2.1]heptane derivatives are structurally similar to ABT-594 with a 3-atom extension (C-C-O) between the basic nitrogen of the heptane ring and the pyridyl ring. The most recent pharmacophore model for the nicotinic receptor calculates an optimum internitrogen distance to be 6.1 Å based on the structure of ABT-594 and other pyridyl ethers. Chem3D® calculations of the internitrogen distances of **147** and **148** revealed lengths (6.2-6.6 Å) that correspond to the optimum distance. The internitrogen distance of the 2-pyridyl ether **154** weas calculated in the same fashion to reveal distances of 4.7-5.2 Å, similar to the 5.1 Å internitrogen distance of epibatidine. The oxalic acid salts of the bicyclic pyridyl ethers are presently being tested for binding affinity at the nicotinic acetylcholine receptor. This new class of compounds will potentially aid in the ever-developing nicotinic receptor pharmacophore model. The results of these studies will be reported elsewhere.

A stereoselective synthesis was developed for a series of rigid acetylcholine analogs, the second class of nAChR ligands. These 2-acetoxytropanes were synthesized in five steps from (-)-cocaine *via* the isomeric alcohols, α-2-tropinol and β-2-tropinol. The previous synthesis of the alcohols required a difficult isomer separation, which was alleviated by the method reported herein. The 2-acetoytropanes were tested for binding affinity to the central nervous system subtype of the nicotinic acetylcholine receptor. The assay showed low potency at the receptor with high concentrations necessary to displace the [^{3}H]epibatidine. Subsequent tests were performed to study if the compounds displayed high binding affinity for the muscarinic acetylcholine receptor. All compounds tested displayed low potencies in this assay as well. This suggested that the flexible endogenous neurotransmitter, acetylcholine, adopts a conformation other than the one imparted by the rigid tropane ring when in the active site of the receptor. Alternatively, the low binding of the acetoxytropanes could also be due to unfavorable steric bulk of the ligand created by the tropane ring.

Finally, the first total synthesis of the plant alkaloid, anabasamine, was developed. The synthetic sequence for (±)-anabasamine (**84**) is concise and consists of only five steps with a 29% overall yield. The route is equally efficient for both large and small scale preparations. Two intermediates of the sequence, **85** and **86**, as well as anabasamine, will be tested as novel nicotinic acetylcholine ligands. Using a similar synthesis, the pyrrolidine analog **91** of anabasamine was synthesized. This novel hybrid structure of nicotine and anabasamine will be tested for nicotinic acetylcholine receptor binding affinity. 6-Methoxynicotine (**93**), an intermediate in this synthesis, is a common drug intermediate from which batteries of compounds are made to study the nicotinic

receptor. The synthetic procedure for the synthesis of the tricyclic nicotine analog **91** offers the intermediate, 6-methoxynicotine (**93**), in three steps in 54% overall yield. This is a marked increase over the previously accepted synthesis which afforded **93** in five steps in 16% overall yield.

EXPERIMENTALS

General Information

All chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, unless otherwise noted. Anhydrous THF, CH_2Cl_2, Et_2O, CH_3CN and MeOH were purchased from Mallinkrodt Baker. Anhydrous DMF was purchased in a sure-seal bottle from Aldrich Chemical Co. Toluene and benzene were dried by distillation over Na/benzophenone. Chromatography refers to column chromatography on silica gel (Sorbent Technologies Silica Gel, 60Å, 32 – 63 μm Standard Grade). Reported melting points were recorded on a Hoover Mel-Temp apparatus and are uncorrected. NMR spectra were recorded on a Varian-Gemini 400 MHz spectrometer or as noted on a Varian-Gemini 300 MHz or 500 MHz multiprobe spectrometer. Chemical shifts are reported as δ values with deuterated chloroform ($CDCl_3$) and tetramethylsilane (TMS) (Cambridge Isotope Laboratories) employed as the internal standard. Elemental analyses were obtained from Atlantic Microlabs, Inc., Norcross, GA. Mass spectra (LRMS) were recorded on a Hewlett-Packard 5855 GC-MS (University of New Orleans).

8-Methyl-8-azabicyclo[3.2.1]octan-2-ol (75): 2-Tropinone (4.4g, 32 mmol) was hydrogenated over PtO_2 (150 mg) in MeOH (67 mL) at a constant pressure of 45 psi for 4 h. The solution was filtered and the residue was purified flash chromatography (SiO_2, $CHCl_3$, MeOH, NH_4OH 89:10:1) to yield **75** as a white solid (4.4 g, 99% yield) mp 76-77 ºC. ^1H NMR (400 MHz, $CDCl_3$) δ 2.04-1.96 (m, 1H), 1.87-1.80 (m, 1H), 1.76-1.49 (m,

2H), 1.47-1.38 (m, 2H), 1.30-1.21 (m, 1H). ^{13}C NMR: (400 MHz, $CDCl_3$) δ 69.0, 67.5, 60.7, 41.0, 30.1, 25.3, 25.0, 20.6.

Acetic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-2-yl ester (79): To a stirred solution of α-2-tropinol **75** (1.0 g, 7.1 mmol) in dry CH_2Cl_2 (10 mL) under an atmosphere of nitrogen was added dry pyridine (1.90 mL) and freshly distilled acetic anhydride (1.9 mL). This was stirred overnight at room temperature. The organic mixture was washed with a solution of saturated $NaHCO_3$ (11 mL). The aqueous layer was extracted with additional $CHCl_3$ (2 × 20 mL). The organic fractions were combined and the solvent removed under reduced pressure. The oil was purified by column chromatography (SiO_2, $CHCl_3$: MeOH: NH_4OH, 90:9:1) to yield **79** as a colorless oil (1.1 g, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (q, J = 5.6 Hz, 1H), 3.17-3.14 (m, 1H), 3.08-3.06 (m, 1H), 2.29 (s, 3H), 1.86-1.73 (m, 4H), 1.48-1.35 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.7, 72.1, 63.6, 60.4, 40.3, 29.8, 25.0, 21.9, 21.5, 20.9.

Acetic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-2-yl ester · oxalic acid: A solution of acetoxy tropane (81 mg, 0.44 mmol) in a minimum amount of propanol was added to a warm solution of oxalic acid (47 mg, 0.53 mmol, 1.2 eq) in propanol. THF was added dropwise to crystallize the salt as a white solid mp 100-102 °C, $[\alpha]_D^{25}$ = +6.7 (c=1, EtOH) *Anal*. Calcd. for $C_{12}H_{17}O_2N \bullet C_2O_4H \bullet 0.75\ H_2O$: C, 50.25; H, 7.20; N, 4.88. Found: C, 50.44; H, 7.01; N, 4.83.

2-Acetoxy-8-methyl-8-azabicyclo[3.2.1]octane · methyliodide (80): To a stirred solution of **79** (67 mg, 0.37 mmol) in freshly distilled THF (10 mL) under an atmosphere of nitrogen was added CH_3I (0.34 mL, 0.55 mmol) dropwise. The solution was heated to reflux for 2 h. The solvent was removed under reduced pressure and the resulting fine

powder was triturated with warm ether and then warm acetone to yield **80** as a white powder (73 mg, 74%). mp 274°C. $[\alpha]_D^{25}$= +9.3 (c=1, EtOH). ^{1}H NMR (400 MHz, D_2O) δ 4.41-5.43 (q, *J* = 1.6 Hz, 1H), 3.94-3.90 (m, 2H), 3.28 (s, 3H), 3.14 (s, 3H), 2.53-2.24 (m, 4H), 2.11 (s, 3H), 2.06-2.10 (m, 2H), 1.69-1.85, (m, 2H) ^{13}C NMR (400 MHz, d-DMSO) 175.0, 74.0, 69.2, 68.5, 66.4, 52.8, 45.0, 26.25, 25.8, 21.8, 20.2. *Anal.* Calcd. for $C_{11}H_{20}NO_2$: C, 40.63; H, 6.20; N, 4.31. Found: C, 40.81; H, 6.22; N, 4.13.

2-Acetoxy-8-azonia-bicyclo[3.2.1]octane · HCl (81): To a stirred solution of the ester **6** (0.75g, 4.1 mmol) and K_2CO_3 (0.57g, 4.1 mmol) in dry toluene (35 mL) sealed under an atmosphere of nitrogen was added 1-chloroethyl chloroformate (1.4 mL). The solution was heated to reflux overnight. The solution was diluted with toluene, washed with 1N HCl and then with brine. The organic layers were dried over Na_2SO_4, concentrated and passed through a short column, first with CH_2Cl_2, then with EtOAc. These fractions were concentrated to give a pale yellow oil. The oil was dried and dissolved in MeOH, sealed under N_2 and stirred at 25°C overnight. The crude pale yellow oil was converted into the HCl salt by bubbling HCl (g) into dry diethyl ether at 0 ºC and slowly dropping the HCl-ether into a solution of the free amine in ether. The resulting HCl salt was triterated 3 times with ether to give a pure white powder (460 mg , 66% yield). Mp 242-244 °C (decomposed) $[\alpha_D]^{25}$ = +31.3, (c=1, EtOH). ^{1}H NMR (400 MHz, D_2O) δ 5.04 (m, 1H), 4.08 (m, 2H), 2.11 (s, 3H), 2.37-1.71 (m, 10 H). ^{13}C NMR (400 MHz, d-DMSO) δ 169.4, 67.7, 55.2, 53.7, 25.9, 25.4, 21.7, 21.5, 20.8. *Anal*. Calcd. for $C_9H_{15}NO_2$•HCl: C, 52.56; H, 7.84; N, 6.81. Found: C, 52.29; H, 7.70; N, 6.72.

8-Methyl-8-aza-bicyclo[3.2.1]octan-2-ol (74): To a solution of 2-tropinone **73** (5.0g, 36 mmol) in dry toluene (10 mL) under an atmosphere of nitrogen was added 3-pentanol (23

mL, 0.22 mol). The resulting mixture was added to sodium powder (0.25 g, 0.11 mol) in dry THF (20 mL) under nitrogen and over 45 minutes. This was heated to reflux overnight. The organic layer was washed with deionized H_2O (94 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 100 mL). The combined organic layers were dried over Na_2SO_4 and condensed. Purification by gravity column (SiO_2: $CHCl_3$: MeOH: NH_4OH 90:9:1) afforded **74** (3.3 g, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (br s, 1H), 3.51 (m, 1H), 3.04 (m, 2H), 2.20 (s, 3H), 2.01-1.56 (m, 3H), 1.56-1.41 (m, 4H), 1.30-1.26 (m, 1H).

Acetic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-2-yl ester (79): To a stirred solution of β-2-tropinol **74** (1.9g, 14 mmol) in dry $CHCl_3$ (19 mL) under an atmosphere of nitrogen was added dry pyridine (4 mL, 46 mmol) and dry acetic anhydride (3.7 mL, 39 mmol). The solution was stirred at room temperature overnight. The reaction was quenched with a saturated solution of $NaHCO_3$ (22 mL) and the organic layer was removed. The aqueous layer was washed with $CHCl_3$ (3 × 45 mL) and the organic fractions were combined and concentrated. Purification was achieved by flash chromatography (SiO_2, $CHCl_3$: MeOH, 90:10) to yield **79** as a colorless oil (0.83 g, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (br s, 1H), 3.22 (br s, 1H), 3.19 (br s, 1H), 2.25 (s, 3H), 2.12 (s, 3H), 2.06-1.53 (m, 10 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.6, 72.0, 64.1, 61.0, 41.1, 28.5, 23.7, 23.1, 21.2, 20.7.

Acetic acid 8-methyl-8-aza-bicyclo[3.2.1]oct-2-yl ester · oxalate: The acetoxy tropane **79** (100 mg, 0.55 mmol) was dissolved in a minimum amount of propanol and added to a warm solution of oxalic acid (59 mg, 0.65 mmol, 1.2 eq) in propanol. THF was added dropwise to prompt the salt to crystallize as a white solid, mp 90-92°C, $[\alpha]_D^{25}$ = -9.2,

(c=1, EtOH). *Anal*. Calcd. for $C_{10}H_{17}NO_2 \bullet C_2O_4H \bullet 1/2\ H_2O$: C, 51.06 H, 7.14; N, 4.96. Found: C, 51.12; H, 6.95; N, 4.96.

2-Acetoxy-8-methyl-8-azabicyclo[3.2.1]octane · methyliodide (77): To a stirred solution of the ester **10** (.270 g, 1.4 mmol) in dry THF (35 mL) under an atmosphere of nitrogen was added CH_3I (1.27 mL). The reaction was heated to reflux overnight to give **77** as a white solid (64 mg, 24% yield). mp 276-278°C $[\alpha_D]^{25}$= -6.2, (c=1, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5-44-5.42 (m, 1H), 3.91-3.95 (m, 2H), 3.28 (s, 3H), 3.14 (s, 3H), 2.29-2.22 (m, 4H) 2.11 (s, 3H0, 2.11-2.05 (m, 2H), 1.87-1.69 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 173.5, 76.4, 67.3, 52.4, 44.6, 30.5, 25.7, 25.3, 21.4, 21.3, 19.6. *Anal*. Calcd. for $C_{11}H_{20}NO_2$: C, 40.63; H, 6.20; N, 4.31. Found: C, 40.86; H, 6.23; N, 4.30.

2-Acetoxy-8-azabicyclo[3.2.1]octane · HCl (78): To a stirred solution of the ester **76** (1.0 g, 6.1 mmol) and K_2CO_3 (840 mg, 6.1 mmol) in dry toluene (50 mL) under an atmosphere of nitrogen was added 1-chloroethyl chloroformate (ACE-Cl) (1.8 mL, 12 mmol). The reaction was heated to reflux for 30 h and then two more equivalents of ACE-Cl (1.8 mL, 12 mmol) were added. The reaction mixture was refluxed for an additional 18 h. The solution was filtered and the filtrate rinsed with CH_2Cl_2. The toluene was removed under reduced pressure and dried over Na_2SO_4. The resulting brown oil was stirred under nitrogen in dry MeOH (40 mL) at 25 °C for 24 h. The solvent was removed under reduced pressure. The resulting residue was converted to the HCl salt by bubbling HCl (g) into dry diethyl ether at 0 ºC and slowly dropping the HCl-ether into a solution of the free amine in ether. The salt was recrystallized from MeOH and THF at –20 ºC over 4 days. The resulting HCl salt was triturated 3 times with ether

to give a pure white crystalline solid. mp 228-230 ºC (dec.) $[\alpha]_D^{25}$= -18.6, (c=1, EtOH). ^{1}H NMR (400 MHz, MeOD) δ 6.48 (br s, NH) 4.88 (m, 1H), 4.15 (s, 1H), 4.08 (s, 1H) 2.36 (m, 2 H), 2.24 (s, 3H), 1.95-1.75 (m, 4H), 1.67 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.2, 68.42, 56.5, 54.1, 24.8, 24.0, 23.5, 21.0, 20.2. *Anal*. Calcd. for $C_9H_{15}NO_2$•HCl: C, 52.56; H, 7.84; N, 6.81. Found: C, 52.50; H, 7.90; N, 6.79.

5-Hydroxy-1-(6-methoxy-pyridin-3-yl)-pentan-1-one (88): To a stirred solution of 5-bromo-2-methoxypyridine (2.50, 1.72 mL) in dry Et_2O (50 mL) was added a solution of n-BuLi in hexanes (9.14 mL, 1.6 M) dropwise over 15 minutes at –78ºC. The solution was stirred for an additional 15 minutes at –78 ºC and then a solution of δ-valerloactone (1.23 mL, 13 mmol) in Et_2O was added dropwise. The reaction was stirred at room temperature for 2 h. Brine (25 mL) was added to quench the reaction and the organic layer was removed. The aqueous layer was extracted with EtOAc (2 × 50 mL) and $CHCl_3$ (2 × 50 mL) and condensed under reduced pressure. The residue was purified by flash column chromatography (SiO_2: EtOAc) to afford a pale yellow solid (2.5 g, 89 %), yield mp 34-36 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, J = 2.4 Hz, 1H), 8.15 (dd J_1 = 8.8 Hz, J_2 = 2.4, 1H), 6.80 (d, J = 8.4 Hz, 1H), 4.01 (s, 3H), 3.68 (m, 2H), 2.98 (t, J = 6.8 Hz, 2H), 1.85 (q, J = 7.2 Hz, 2H), 1.66 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 198.4, 166.8, 149.1, 138.3, 126.7, 111.2, 62.3, 54.2, 38.1, 32.2, 20.4. *Anal*. Calc. for $C_{11}H_{15}NO_3$ C, 63.14; H, 7.23; N, 6.69. Found: C, 63.32; H, 7.33; N, 6.68.

5-(6-Methoxy-pyridin-3-yl)-5-oxo-pentanal (87): To a stirred solution of the alcohol **88** (0.61 g, 2.9 mmol) in CH_2Cl_2 (60 mL) under an atmosphere of nitrogen was added a 25% weight solution of prepared Dess-Martin reagent in CH_2Cl_2 (8.8 mL, 4.3 mmol). The reaction was stirred at room temperature for 1.5 h. The reaction was then diluted

with Et_2O and poured into a solution of $Na_2S_2O_3$ in saturated $NaHCO_3$ (60 mL) and stirred for 5 min until clear. A pH 7 buffer was added and the mixture was extracted with Et_2O (3 × 50 mL). The organic layer was washed an additional time with saturated $NaHCO_3$ (60 mL) and H_2O (60 mL). The organic fractions were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude aldehyde in almost quantitative yield. The aldehyde was used in the following step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8. 79 (d, J = 1.6 Hz, 1H), 8.13 (dd, J_1 = 8.8 Hz, J_2 = 2.8, 2H) 6.79 (d, J = 8.8 Hz, 1H), 4.01 (s, 3H), 3.00 (t, J = 6.8 Hz, 2H), 2.61 (t, J = 6.8, 2H), 2.07 (q, J = 7.6 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 201.8, 197.0, 166.7, 148.9, 138.0, 111.1, 54.0, 43.0, 37.1, 16.4.

6'-Methoxy-1-methyl-1,2,3,4,5,6-hexahydro-[2,3']bipyridinyl (86): The aldehyde (3.70 g, 17.9 mmol), NH_2CH_3· HCl (1.21 g, 17.9 mmol) and $NaBH_3CN$ (1.68 g, 26.8 mmol) were dissolved in dry MeOH (100 mL) under an atmosphere of nitrogen. The reaction was stirred for 48 h at room temperature. The MeOH was removed under reduced pressure and saturated Na_2CO_3 (aq) was added to the residue. The aqueous layer was extracted $CHCl_3$ (3 × 100 mL). The residue was purified by gravity column chromatography (SiO_2, MeOH:CH_2Cl_2 1:9) to afford the product as a yellow oil (2.0 g, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 2 Hz, 1H), 7.61 (dd, $_1$ = 8.6 Hz J_2 = 2.4, 1H), 6.71 (d, J = 8.4 Hz, 1H), 3.93 (s, 3H), 3.02 (d, J = 11.6 Hz, 1H), 2.75 (dd, J_1 = 11 Hz, J_2 = 2.4, 1H), 2.14-2.06 (m, 1H), 1.99 (s, N-CH_3), 1.81 (d, J = 12.8, 1H), 1.73-1.52 (m, 4H), 1.42-1.30 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.6, 145.8, 137.7, 111.0, 67.5, 57.5, 53.4, 44.4, 35.7, 26.0, 24.9. *Anal*. Calc. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58.

6'-Chloro-1-methyl-1,2,3,4,5,6-hexahydro-[2,3']bipyridinyl (85): (80 mg, 0.42 mmol) The aryl ether **86** was dissolved in $POCl_3$ (3 mL) and sealed in a high pressure reactor tube. The reaction was stirred at 115 ºC for 24 h. The excess $POCl_3$ was removed of under reduced pressure. The viscous residue was slowly added dropwise into ice water. The aqueous solution was slowly added to ice cold saturated Na_2CO_3 at pH=10. The aqueous phase was extracted with CH_2Cl_2 (5 × 25 mL), dried with Na_2SO_4, and condensed under reduced pressure. The residue was purified by gravity column chromatography (SiO_2, MeOH:CH_2Cl_2 1:9) to afford the product as a brown oil (55 mg, 77% yield based on recovered starting material). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, J = 2 Hz, 1H), 7.67 (dd, J_1 = 7.6 Hz J_2 = 2.4, 1H), 7.29 (d, J = 8.4 Hz, 1H), 3.02 (d, J = 11.6 Hz, 1H), 2.82 (dd, J_1 = 12 Hz, J_2 = 3.2, 1H), 2.14-2.08 (m, 1H), 1.98 (s, N-CH_3), 1.82 (d, J = 12, 1H), 1.73-1.66 (m, 4H), 1.55-1.33 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 150.1, 149.1, 139.5, 137.9, 124.4, 65.5, 57.3, 44.6, 36.2, 26.0, 24.8.

(±)-Anabasamine (84): A reaction tube was charged with the *N,N'*-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidine (20 mg, 0.35 mmol), pyridine-3-boronic acid (64 mg, 0.53 mmol), and sodium *tert*-butoxide (67 mg, 0.69 mmol) in an atmosphere of argon. A solution of the 2-chloropyridine **85** (73 mg, 35 mmol) in dry dioxane (5 mL) was added to the heterogenous mixture. The reaction mixture was stirred vigorously in an 85 ºC oil bath for 8 h. The reaction was cooled and the catalyst filtered through a short column (SiO_2, MeOH:CH_2Cl_2 1:9) to furnish the natural product **84** as a brown oil (48 mg, 75% yield based on recovered starting material). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (d, J = 1.6, 1H), 8.65 (d, J = 1.6, 1H), 8.63 (s, 1H), 8.33 (dd, J = 8, J = 1.2, 1H), 7.81 (dd, J = 8, J = 2, 1H), 7.73 (d, J = 8, 1H), 7.40 (m, 1H), 3.06 (d, J = 11.6,

1H), 2.89 (dd, J = 11.2, J = 2.4, 1H), 2.18-2.12 (m, 1H), 2.04 (s, 3H), 1.86-1.54 (m, 6H) ^{13}C NMR (400 MHz, $CDCl_3$) δ 153.9, 149.9, 149.8, 148.3, 139.8, 136.1, 135.0, 134.4, 123.8, 120.7, 68.1, 57.5, 44.8, 36.1, 26.1, 24.9.

4-Hydroxy-1-(6-methoxy-pyridin-3-yl)-butan-1-one (95): To a stirred solution of 5-bromo-2-methoxypyridine (5.0 g, 26 mmol) in dry Et_2O (100 mL) was added a solution of n-BuLi in hexanes (18.2 mL, 1.6 M) dropwise over 15 minutes at –78ºC. The solution was stirred for an additional 15 minutes at –78 ºC and then a solution of γ-butyroloactone (1.91 mL, 26.6 mmol) in Et_2O was added dropwise. The reaction was stirred at room temperature for 2 h. Brine was added to quench the reaction and the organic layer was removed. The aqueous layer was extracted with EtOAc (2 × 50 mL) and $CHCl_3$ (2 × 50 mL) and condensed. The residue was purified by column chromatography (SiO_2: $CHCl_3$:MeOH 95:5) to afford a pale yellow solid (2.5 g, 55 % yield), mp 32-34 ºC, and the bipyridyl by-product **95b** (20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, J = 2, 4 Hz, 1H), 8.15 (dd, J_1 = 8 Hz, J_2 = 2.4 Hz, 1H) 6.79 (d, J = 8.8 Hz, 1H), 3.75 (m, 2H), 3.08 (t, J = 7.6 Hz, 2H) 2.02 (q, J = 6.4, 2H), 1.85 (OH). ^{13}C NMR (400 MHz, $CDCl_3$) δ 198.3, 166.8, 149.1, 138.2, 126.6, 111.2, 62.1, 54.1, 35.1, 26.8. Mass Spec (ES) *m/z* 196.1 (M+). *Anal*. Calc. for $C_{10}H_{12}NO_2Cl \cdot 1/8\ H_2O$ C, 160.82; H, 6.70; N, 7.09. Found: C, 60.88; H, 6.72; N, 7.09.

5-(6-Methoxy-pyridin-3-yl)-4-oxo-butanal (94): To a stirred solution of the alcohol **95**(0.44 g, 2.3 mmol) in CH_2Cl_2 (60 mL) under an atmosphere of nitrogen was added a 25% weight solution of prepared Dess-Martin reagent in CH_2Cl_2 (5.8 mL, 2.6 mmol). The reaction was stirred at room temperature for 1.5 h. The reaction was then diluted with Et_2O and poured into a solution of $Na_2S_2O_3$ in saturated $NaHCO_3$ (60 mL) and

stirred for 5 min until clear. A pH 7 buffer was added and the mixture was extracted with Et_2O (3 × 50 mL). The organic layer was washed an additional time with saturated $NaHCO_3$ and H_2O. The organic fractions were combined and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford the crude aldehyde **94** (0.42 g) in almost quantitative yield. The aldehyde was used in the following step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8. 34 (s 1H), 8.15 (dd, J_1 = 8.8 Hz, J_2 = 2.0, 1H) 6.79 (d, J = 8.8 Hz, 1H), 3.27 (t, J = 6.0 Hz, 2H), 2.94 (t, J = 6.4, 2H).

2-Methoxy-5-(1-methyl-pyrrolidin-2-yl)-pyridine (93): The aldehyde **94** (1.52 g, 7.81 mmol), NH_2CH_3· HCl (0.527 g, 7.81 mmol) and $NaBH_3CN$ (0.736 g, 11.7 mmol) were dissolved in dry MeOH (100 mL) under an atmosphere of nitrogen. This was stirred for 48 h at room temperature. The MeOH was removed under reduced pressure and saturated Na_2CO_3 (aq) was added to the residue. The aqueous layer was extracted with $CHCl_3$ (3 × 100 mL). The residue was purified by gravity column chromatography (SiO_2, MeOH:CH_2Cl_2 1:9) to afford **93** as a yellow oil (800 mg, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 2.4 Hz, 1H), 7.62 (dd, $_1$ = 8.6 Hz J_2 = 2.4, 1H), 6.74 (d, J = 8.8 Hz, 1H), 3.93 (s, 3H), 3.24 (t, J = 8 Hz, 1H), 3.01 (t,„J_2 = 8.4, 1H), 2.28 (q, J = 8.8 Hz, 1H) 2.15 (s, 3H), 2.01-1.68 (m, 5H), ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.8, 146.1, 137.8, 131.0, 111.1, 68.4, 57.0, 53.4, 40.2, 34.7, 22.4. *Anal*. Calc. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58.

2-Chloro-5-(1-methyl-pyrrolidin-2-yl)-pyridine (92): The 2-methoxypyridine **93** (80 mg, 0.39 mmol) was dissolved in $POCl_3$ (3 mL) and sealed in a high pressure reactor tube. The reaction was stirred at 115 ºC for 24 h. The excess $POCl_3$ was then removed under reduced pressure. The viscous residue was slowly dropped into ice water. The

aqueous solution was added dropwise to cold Na_2CO_3 the pH=10. The aqueous phase was extracted with CH_2Cl_2 (5 × 25 mL), dried over Na_2SO_4, and condensed under reduced pressure. The residue was purified by gravity column chromatography (SiO_2, MeOH:CH_2Cl_2 1:9) to afford the product as a brown oil (45 mg, 55% based on recovered starting material). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, J = 2 Hz, 1H), 7.68 (dd, J_1 = 8.4 Hz J_2 = 5.2, 1H), 7.29 (d, J = 8.4 Hz, 1H), 3.23 (m, 1H), 3.09 (t, J = 8 Hz), 2.31 (m, 2H), 2.16 (s, N-CH_3), 2.01-1.91 (m, 1H), 1.90-1.78 (m, 1H), 1.72-1.64 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 150.2, 149.3, 138.0, 137.5, 124.4, 68.2, 57.1, 40.5, 35.5, 22.7

5-(1-Methyl-pyrrolidin-2-yl)-[2,3']bipyridinyl (91): A reaction tube was charged with the *N,N'*-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidine (45 mg, 0.23 mmol), pyridine-3-boronic acid (42 mg, 0.34 mmol), and sodium *tert*-butoxide (44 mg, 0.46 mmol) in an atmosphere of argon. A solution of the 2-chloropyridine **92** (45 mg, 0.23 mmol) in dry dioxane (4 mL) and added to the heterogenous mixture. The reaction mixture was stirred vigorously in an 85 ºC oil bath for 8 h. The reaction was cooled and the catalyst filtered through a short column (SiO_2, MeOH:CH_2Cl_2 1:9) to furnish the natural product as a brown oil (11 mg, 64% based on recovered starting material).m/z = 240 (M + 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (s, 1H), 8.64 (s, 2H), 8.32 (d, J = 8.4,1H), 7.84 (dd, J = 8, J = 1.6, 1H), 7.74 (d, J = 8.4, 1H), 7.41 (q, J = 4.1, 1H), 3.29 (t, J = 8, 1H), 3.18 (t, J = 8.4, 1H), 2.39-2.33 (m, 2H), 2.22 (s, 3H), 2.07-1.74 (m, 4H) ^{13}C NMR (400 MHz, $CDCl_3$) δ 150.1, 150.0, 148.4, 136.2, 135.5, 134.5, 123.8, 120.8, 68.8, 57.2, 40.6, 35.4, 22.8.

1-Acetylamino-4-oxo-cyclohex-2-enecarboxylic acid methyl ester (100). To a stirred solution of Danishefsky's Diene (20 g, 0.12 mol) in dry toluene (360 mL) under an

atmosphere of nitrogen was added a solution of methyl-2-acetamidoacrylate (4.2 g, 0.03 mol) dissolved in toluene (30 mL). The solution was heated to reflux for 24 h and then an additional equivalent of the dienophile (4.2 g, 0.03 mol) in of toluene (30 mL) was added. The reaction mixture was then heated to reflux for an additional 68 h. The toluene was removed under reduced pressure and the resulting brown residue was dissolved in a 1:4 mixture of 0.005 M HCl :THF (60 mL: 240 mL). The solution was then stirred at room temperature for 15 h. After the hydrolysis of the trimethylsilyl group was completed by TLC, the THF was removed under reduced pressure. The crude material was dissolved in CH_2Cl_2 (160 mL), washed with brine (2 × 160 mL) and saturated $NaHCO_3$. The aqueous layers were additionally extracted with CH_2Cl_2 (2 × 160 mL) and EtOAc (2 × 160 mL). The organic fractions were combined and dried over Na_2SO_4 and condensed to an amber oil. This was brought to the next step without purification. To a stirred solution of the crude residue dry CH_2Cl_2 (320 mL) under an atmosphere of nitrogen was added DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (4.2 mL) dropwise at 0 ºC and stirred at this temperatue for 24 h. When all of the starting material was consumed (TLC), the organic layer was washed with 0.5 M HCl (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (5 × 50 mL). The organic fractions were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The brown oil was purified by column chromatography (SiO_2, $CHCl_3$:MeOH, 9:1) to afford **100** (9.2 g, 75% yield) as an amber oil. ^{1}H NMR ($CDCl_3$) δ 7.05 (d, J = 12 Hz, 1H), 6.47 (br s, NH), 6.11 (d, J= 12 Hz, 1H), 3.74 (s, 3H), 2.59-2.40 (m, 4H), 1.98 (s, 3H). ^{13}C NMR ($CDCl_3$): 197.4, 171.2, 170.2, 147.1, 129.9, 57.8, 53.1, 33.5, 31.4, 22.7.

1-Acetylamino-4-oxo-cyclohexanecarboxylic acid methyl ester (101): The enone **100** (9.2 g) was hydrogenated at 1 atm over 10% Pd/ carbon (1.3 g) in CH_2Cl_2 (250 mL) for 36 h. The solution was filtered through a pad of Celite. The solvent was removed under reduced pressure and the resulting residue was recrystallized from hexane:EtOAc (1:9) to yield **101** as a white solid (7.7 g, 82% yield). ^{1}H NMR ($CDCl_3$): δ 6.66 (br s, NH), 3.75 (s, 3H), 2.49-2.46 (m, 4H), 2.38-2.35 (m, 4H), 2.05 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 209.7, 173.3, 171.2, 57.4, 52.4, 36.4, 31.9 (2), 22.7 (2).

Trans-1-Acetylamino-4-hydroxy-cyclohexanecarboxylic acid methyl ester (102): To a stirred solution of the ketone (1.9 g, 8.9 mmol) in dry THF (140 mL) under an atmosphere of nitrogen at –78 ºC was added a solution of L-Selectride (14 mL, 1 M) over 25 minutes. The reaction was stirred at this temperature for 3 h. Saturated NH_4Cl (60 mL) was added and the mixture was allowed to come to room temperature. The solutiuon was filtered and condensed under reduced pressure at room temperaure. The aqueous mixture was extracted with CH_2Cl_2 (5 × 50 mL) and the organic fractions combined, dried (Na_2SO_4) condensed to afford a yellow residue. This was chromatographed (SiO_2 $CHCl_3$: MeOH 9:1) to give the mixture of alcohols (cis:trans 1:9) as a white solid (1.6 g, 81% yield). Data for ***102***: ^{1}H NMR ($CDCl_3$): δ 5.69 (br s, NH), 3.92 (br s, OH), 3.73 (s, 3H), 2.33 (m, 1H), 2.01 (s, 3H), 1.84-1.67 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 175.8, 169.9, 75.5, 55.1, 26.4 (2), 25.8 (2), 24.2.

***N*-(3-Oxo-2-oxa-bicyclo[2.2.2]oct-4-yl)-acetamide (104):** To a stirred solution of the ketone (1.9 g, 8.9 mmol) in dry THF (140 mL) under an atmosphere of nitrogen at –78 ºC was added a solution of L-Selectride (14 mL, 1 M) over 25 minutes. The reaction was stirred at this temperature for 3 h. Saturated NH_4Cl (60 mL) was added and the mixture

was allowed to come to room temperature. The solutiuon was filtered and condensed under reduced pressure at 65 ºC. The residue was washed with CH_2Cl_2 (5 × 50 mL) and the organic fractions combined, dried (Na_2SO_4) condensed to afford a yellow residue. This was purified by chromatography (SiO_2 $CHCl_3$: MeOH 9:1) to give the bicyclic lactone **104** as a white solid (2.1 g, 95% yield). MS (CI) *m/z* 184 (M^+, 1), 142. ^{1}H NMR ($CDCl_3$): δ 6.76 (br s, NH), 4.75 (t, *J* = 4.4, 1H), 3.12 (td, $J_{1\text{-}2}$ = 12.2 Hz, $J_{2\text{-}3}$ = 5.2 Hz, 2H), 2.15-2.04 (m, 2H), 2.00 (s, 3H), 1.90 (t, *J* = 12.4 2H), 1.67 (t, *J* = 13, 2H). ^{13}C NMR ($CDCl_3$): δ 175.5, 169.8, 75.2, 54.9, 26.3 (2), 25.6 (2), 24.0.

1-Acetylamino-4-methanesulfonyloxy-cyclohexanecarboxylic acid methyl ester (105): To a stirred solution of the alcohols **102, 103** (3.5 g, 17 mmol) and dimethylaminopyridine (200 mg, 1.7 mmol) in dry CH_2Cl_2 (240 mL) was added freshly distilled Et_3N (3.4 mL, 25 mmol) followed by methanesulfonyl chloride (3.2 mL, 33 mmol). The mixture was refluxed under an atmosphere of nitrogen for 41 h. The reaction was allowed to cool to room temperature. The organic layer was washed with 5% $NaHCO_3$ (aq), dried over Na_2SO_4, and condensed under reduced pressure. The resulting solid was triturated with EtOAc to yield the mesylate as a white solid (1.9 g, 42% yield). ^{1}H NMR ($CDCl_3$): δ 5.67 (br s, NH), 4.92 (m, 1H), 3.74 (s, 3H), 3.05 (s, 3H), 2.27 (t, *J* = 10.8, 2 H), 2.06-1.95 (m, 4H), 2.06 (s, 3H), 1.88-1.81 (m, 2H). ^{13}C NMR ($CDCl_3$): 173.5, 170.2, 79.0, 58.12, 52.8, 39.0, 27.6 (2), 27.2 (2), 23.5.

7-Acetyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid methyl ester (106): To a stirred solution of the mesylate **105** (1.6 g, 5.9 mmol) in dry THF (55 mL) was added a 1 M solution of potassium *tert*-butoxide in THF (12 mL, 1M) at –78 ºC over 20 minutes. The reaction was stirred at –78 ºC for 80 min. The ice bath was removed and the reaction

was stirred for 20 h at room temperature. The reaction was quenched with 0.5 M HCl (25 mL) and extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The residue was purified by gravity column chromatography (SiO_2, EtOAc) to afford **106** as a white solid (170 mg, 15% yield). ^{1}H NMR ($CDCl_3$): δ 4.24 (t, 1H), 3.81 (s, 3H), 2.27-2.20 (m, 2H), 2.05 (s, 3H), 1.97-1.77 (m, 2H), 1.77-1.72 (m, 2H), 1.63-1.57 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 171.5, 171.3, 66.9, 59.5, 52.4, 32.4 (2), 30.4 (2), 21.7. *Anal*. Calc. for $C_{10}H_{15}NO_3$: C, 60.9; H, 7.67; N, 7.1 Found: C, 60.1; H, 7.72; N, 7.0

3-Hydroxy-2-(toluene-4-sulfonylamino)-propionic acid (110): To a stirred solution of L-Serine (5.0 g, 48 mmol) and Na_2CO_3 (14 g, 130 mmol) in deionized water (150 mL) was added toluenesulfonylchloride (11 g, 55 mmol). The mixture was stirred vigorously at 25 ºC for 4 h. The solution was then filtered to removed NaCl and the filtrate was acidified to pH = 2 with ice cold concentrated HCl. The product was collected and washed with water and ethanol to yield the tosylate **110** as a pure white solid (7.9 g, 84% yield) mp 240-242 ºC, (dec.) ^{1}H NMR ($CDCl_3$): δ 7.76 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 3.90 (t, J = 7.2 Hz, 1H), 3.78-3.66 (m, 2H) 2.41 (s, 3H). *Anal*. Calc. for $C_{10}H_{13}NO_5S$: C, 46.32; H, 5.05; N5.40. Found: C, 46.31; H, 5.09; N, 5.39.

3-Hydroxy-2-(toluene-4-sulfonylamino)-propionic acid methyl ester (111): Anhydrous HCl (g) was bubbled through MeOH (300 mL) for 45 minutes. The methanolic HCl (300 mL) was added to a solution of **110** (1.0 g, 3.9 mmol) and the mixture was heated to reflux for 24 h. The solvent was removed and the residue dissolved in EtOAc. The organic layer was washed with saturated Na_2CO_3 (200 mL) and the aqueous phase was extracted with EtOAc (3 × 150 mL). The organic fractions were

combined and dried over Na_2SO_4 followed by evaporation under reduced pressure to yield a white solid (3.8 g, 94% yield), mp 71-73 ºC. ^{1}H NMR ($CDCl_3$): δ 7.75 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 4.03 (t, J = 4, 1H) 3.85 (qd, J_1= 12.6, J_2 = 4 2H), 3.55 (s, 3H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 170.5, 144.0, 136.7, 129.9 (2), 127.4 (2), 63.8, 57.8, 53.0, 21.7. *Anal*. Calc. for $C_{11}H_{15}O_5NS$: C, 48.34; H, 5.53; N, 5.12. Found: C, 48.51; H, 5.58; N, 5.16.

3-Methanesulfonyloxy-2-(toluene-4-sulfonylamino)-propionic acid methyl ester (113): To a stirred solution of the alcohol **109** (1.0 g, 3.6 mmol) and dimethylaminopyridine (4 mg) in dry CH_2Cl_2 (50 mL) was added distilled triethylamine (0.76 mL, 5.5 mmol) and methanesulfonylchloride (1.5 mL, 0.35 mL) dropwise at 0 ºC. The solution was allowed to come to ambient temperature and stirred for 36 h. The organic layer was washed with deionized H_2O (1 × 50 mL) and with 5% Na_2CO_3 (2 × 50 mL), dried over Na_2SO_4, and condensed under reduced pressure. The mesylate **113** was recrystallized from EtOAc to afford a white solid (1.1 g, 91%). ^{1}H NMR ($CDCl_3$): δ 7.74 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 5.59 (d, J = 7.6 Hz, NH), 4.56-4.52 (m, 1H), 4.54-4.42 (m, 1H), 4.21-4.18 (m, 1H), 3.68 9s, 3H), 3.04 (s, 3H), 2.43 (s, 3H).

***N*- (*tert*-Butoxycarbonyl)-O-tosyl-*d,l*-serine Methyl Ester (116):** To a stirred solution of *p*-toluenesulfonic acid (23 g, 0.12 mol) in dry pyridine (30 mL) was added *N*-*tert*-butoxycarbonyl-*d*-serine methyl ester (20 g, 0.09 mol) dissolved in dry pyridine (70 mL) at –15 ºC. The mixture was stirred at this temperature for 6 h and then 0 ºC overnight. The heterogenous mixture was poured over crushed ice. The aqueous mixture was extracted with EtOAc (2 × 100 mL) and combined organic fractions were washed with 20% citric acid (100 mL), saturated $NaHCO_3$ (100 mL), and brine (2 × 100 mL). The

organic layer was washed again with ice cold 1N HCl (100 mL), saturated $NaHCO_3$ (100 mL), and brine (2 × 100 mL). The solution was dried over Na_2SO_4 and the solvent removed under reduced pressure. The golden yellow oil was dried on a high vacuum pump until it solidified. The pale yellow solid was then recrystallized from pure EtOAc at 0 ºC to yield the product as a white crystalline solid (28 g, 87% yield), mp 72 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 5.29 9 (br s, NH), 4.51 (d, J = 8, 1H), 4.40 (dd, J_1 = 10.6, J = 2.8, 1H), 4.28 (dd, J_1 = 10.6, J = 2.8, 1H), 3.70 (s, 3H), 2.43 (s, 3H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$, 400 MHz): 172.0, 152.5, 131.9, 130.7, 127.8, 70.6, 62.5, 55.8, 50.4, 28.7, 20.9. *Anal*. Calc. for $C_9H_{15}O_4N$: C, 51.46; H, 6.21; N, 3.75. Found: C, 51.44; H, 6.20; H, 3.88.

2-*tert*-Butoxycarbonylamino-acrylic acid methyl ester (117). To a stirred solution of **116** (12. g, 0.03 mol) in dry CH_2Cl_2 (350 mL) under an inert atmosphere DBU (6.0 mL, 0.08 mol) was added dropwise at 0 ºC. The reaction was stirred at 0 ºC until no more starting material was visible by TLC (6 h). The reaction was quenched and washed with water. The combined organic fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by flash chromatography (SiO_2 to yield a tan solid (6.6 g, 98%) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.04 (br s, NH), 6.16 (s, 1H), 5.72 (s, 1H), 3.83 (s, 3H)1.49 (s, 9H). ^{13}C NMR ($CDCl_3$, 400 MHz): 164.5, 152.6, 131.4, 105.2, 80.6, 52.9, 28.2. *Anal*. Calc. for $C_9H_{15}O_4N$: C, 53.72; H, 7.51; N, 6.96.

1-*tert*-Butoxycarbonylamino-4-oxo-cyclohex-2-enecarboxylic acid methyl ester (120): To a solution of Danishefsky's Diene (20 g, 0.12 mol) in dry toluene (360 mL) under an atmosphere of nitrogen was added a solution of the acrylate **117** (6.0 g, 0.03 mol) in dry toluene (30 mL). The solution was heated to reflux for 24 h and then an

additional equivalent of the dienophile (6.0 g, 0.03 mol) in toluene (30 mL) was added. The reaction mixture was then heated to reflux for an additional 48 h. The toluene was removed under reduced pressure and the resulting residue was dissolved in a soultion of 1:4 0.005 M HCl :THF (60 mL: 240 mL). The solution was then stirred at room temperature for 15 h. After the hydrolysis of the trimethylsilyl group was completed by TLC, the THF was removed under reduced pressure. The crude material was dissolved in CH_2Cl_2 (160 mL), washed with brine (2 × 160 mL) and then saturated $NaHCO_3$ (2 × 160 mL). The aqueous layers were then extracted with CH_2Cl_2 (2 × 160 mL) and EtOAc (2 × 160 mL). The organic fractions were combined and dried over Na_2SO_4 and condensed to an amber oil. This was brought to the next step without purification. To a stirred solution of the residue in dry CH_2Cl_2 (320 mL) under an atmosphere of nitrogen DBU (9.8 mL) was added dropwise at 0 ºC. The mixture was stirred at room temperature for 24 h. When the elimination of the methoxy group was complete by TLC, the organic layer was washed with 0.5 M HCl (200 mL) and the aqueous layer extracted with CH_2Cl_2 (5 × 50 mL). The organic fractions were combined, dried over Na_2SO_4, and concentrated. The brown oil was purified by gradient column chromatography (SiO_2, $CHCl_3$: MeOH, 9:1) to afford **120** (9.7 g, 60% yield) as an amber oil. This could be recrystallized in pure EtOAc to give a colorless solid. ^{1}H NMR ($CDCL_3$) δ 7.05 (d, *J* = 10.4 Hz, 1H), 6.11 (d, *J*= 10.4 Hz, 1H), 5.36 (br s, NH), 3.81 (s, 3H), 2.55 (t, *J* = 6.4, 2H), 2.46-2.30 (m, 2H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$): 197.4, 171.2, 170.2, 147.1, 129.9, 57.8, 53.1, 33.5, 31.4, 22.7. *Anal*. Calc. for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11; N, 5.20.

1-*tert*-Butoxycarbonylamino-4-oxo-cyclohexanecarboxylic acid methyl ester (121): The enone **120** (3.0 g) was hydrogenated (1 atm) over PtO_2 (30 mg) in CH_2Cl_2 (150 mL) for 48 h. The solution was filtered through a pad of Celite. The solvent was removed under reduced pressure and the resulting residue was recrystallized from hexane:EtOAc (1:9) to yield **121** as a white solid (2.7 g, 89% yield) mp 116-118 ºC. ^{1}H NMR ($CDCl_3$): δ 3.76 (s, 3H), 2.57-2.25 (m, 8H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 209.1, 173.9, 155.3, 57.9, 52.6, 36.5, 32.7 (2), 28.2 (2). Analysis calculated for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.30; H, 7.73; N, 5.08.

1-*tert*-Butoxycarbonylamino-4-hydroxy-cyclohexanecarboxylic acid methyl ester (122): To a solution of the ketone **121** (5.1 g, 19 mmol) in dry THF (180 mL) under an atmosphere of nitrogen at –78 ºC was added a 1 M solution of L-Selectride (2.8 mL, 1 M) over 25 minutes. The reaction was stirred at this temperature for 6 h. The reaction was quenched by the addition of saturated NH_4Cl (100 mL) and the mixture was allowed to come to room temperature. The solvent was removed under reduced pressure to afford a yellow residue. This was chromatographed (SiO_2 $CHCl_3$: MeOH 9.5:0.5) to give the mixture of alcohols (cis:trans 1:9) as a white solid (5.2 g, 87% yield). Data for the *trans* isomer: ^{1}H NMR ($CDCl_3$): δ 4.81 (br s, NH), 3.94 (br s, OH), 3.73 (s, 3H), 2.25-2.30 (m, 1H), 1.88-1.66 (m, 8H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 174.9, 155.3, 69.2, 66.1, 58.6, 52.3, 30.2, 29.0, 28.4.

4-Hydroxy-1-(toluene-4-sulfonylamino)-cyclohexanecarboxylic acid methyl ester (123): To a stirred solution of **122** (310 mg, 1.2 mmol) in EtOAc (previously dried over Na_2SO_4) under an atmosphere of nitrogen was added MeOH (0.9 mL, 2.3 mmol) followed by the careful, dropwise addition of acetyl chloride (0.9 mL, 1.2 mmol) at 0 ºC.

The reaction was stirred at ambient temperature overnight. The solvent was removed under reduced pressure to afford the quaternary ammonium salt as a white powder (180 mg, 75%, crude yield). The solid was triterated with EtOAc and dried thoroughly under vacuum. The recrystallized material was used in the following tosylation reaction without further purification. To a stirred solution of the crude salt (250 mg, 1.2 mmol) in dry CH_3CN (5 mL) was added a solution of KOH (160 mg, 3.0 mmol) in CH_3CN (5 mL) at 0 ºC. Triethylamine (.03 mL, .12 mmol) and a solution of tosyl chloride (270 mg, 1.4 mmol) in CH_3CN (5 mL) were added dropwise to the stirred solution. The mixture was stirred at room temperature overnight until the reaction was complete by TLC. The solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (20 mL). The organic solution was washed with deionized H_2O. The aqueous layer was extracted with methylene chloride (2 × 20 mL). The combined organic fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The resultant oil was purified by column chromatography (SiO_2, 9.5 $CHCl_3$: 0.5 MeOH) to afford the sulfamide **124** as a brown oil (270 mg, 69 % yield): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 MHz, 2H), 5.31, (br s, NH), 3.81 (m, 1H) 3.46 (s, 3H), 2.42 (s, 3H), 2.23-2.17 (m, 2H), 1.75-1.67 (m, 4H), 1.50-1.43 (m, 2H).

7-(Toluene-4-sulfonyl)-7-azabicyclo[2.2.1]heptane-1-carboxylic acid methyl ester (125): To a stirred solution of triphenylphosphine (41 mg, 0.16 mmol) in dry THF (1 mL) under an atmosphere of nitrogen was added a solution of **123** (34 mg, 0.10 mmol) in dry THF (3 mL). DEAD (diethylaminodicarboxylate) (30 µL, 0.02 mmol) was added slowly to the reaction mixture. The reaction was stirred at room temperature for 48 h. The THF was removed under reduced pressure. The resulting residue was purified by

column chromatography (SiO_2, $CHCl_3$) to yield a white solid **125** in poor yield (6 mg, 18 %) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 8 MHz, 2H), 4.32, (t, *J* = 4.8 Hz, 1H), 3.73 (s, 3H), 2.42 (s, 3H), 2.35-2.26 (m, 2H), 2.07-1.98 (m, 2H), 1.83-1.77 (m, 2H), 1.56-1.49 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 173.0, 143.9, 137.6, 129.7 (2), 127.5 (2), 60.2, 52.5, 38.7, 27.3, 26.3, 21.6.

Acetic acid 4-methanesulfonyloxy-1-(toluene-4-sulfonylamino)-cyclohexyl ester (126). To a stirred solution of the **124** alcohol (266 mg, 0.78 mmol) in dry CH_2Cl_2 (10 mL) under an atmosphere of nitrogen was added freshly distilled diisopropylethylamine (DIEA) (0.27 mL, 1.6 mmol) followed by addition of methanesulfonyl chloride (0.15 mL, 0.16 mmol). The mixture was stirred at room temperature for 36 h. The organic layer was washed with 5% $NaHCO_3$ (aq), dried over Na_2SO_4, and condensed under reduced pressure. The resulting solid was triturated with EtOAc to yield the mesylate **126** as a tan solid (109 mg, 33% yield). ^{1}H NMR ($CDCl_3$): δ 7.74 (d, *J* = 8.4 Hz, 2H) 7.30 (d, *J* = 8.4 Hz, 2H) 4.99 (br s, NH), 4.84 (m, 1H), 3.47 (s, 3H), 2.99 (s, 3H), 2.43 (s, 3H) 2.15-2.08 (m, 2H), 1.92-1.80 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 173.3, 144.1, 137.8, 129.9 (2), 127.6 (2), 60.4, 52.7, 38.9, 27.8 (2), 26.5 (2), 21.7.

7-(Toluene-4-sulfonyl)-7-azabicyclo[2.2.1]heptane-1-carboxylic acid methyl ester

Method B: To a stirred solution of the mesolate **126** (1.60 g, 5.9 mmol) in dry THF (55 mL) under an atmosphere of nitrogen at –78 ºC was added a solution of potassium *tert*-butoxide in THF (11.7 mL, 1 M) over 20 minutes. The reaction was stirred at –78 ºC for 80 min. The reaction was stirred for an additional 20 h at 20 ºC. The reaction was quenched with 0.5 M HCl (25 mL) and was extracted with EtOAc (3 × 50 ml). The organic layers were combined, dried over Na_2SO_4, and condensed. ^{1}H NMR ($CDCl_3$, 400

MHz): δ 7.80 (d, *J* = 8 Hz, 2H), 7.28 (d, *J* = 8 MHz, 2H), 4.32, (t, *J* = 4.8 Hz, 1H), 3.73 (s, 3H), 2.42 (s, 3H), 2.35-2.26 (m, 2H), 2.07-1.98 (m, 2H), 1.83-1.77 (m, 2H), 1.56-1.49 (m, 2H).

Benzoic acid 2-benzoylamino-2-methoxycarbonyl-ethyl ester (127): To a stirred solution of d,l serine methylester (4.5 g, 29 mmol) in dry CH_2Cl_2 (150 mL) under an atmosphere of nitrogen was added distilled triethylamine (13 mL, 98 mmol) and benzoyl chloride (7.7 mL, 67 mmol) in alternating portions of 2 mL triethylamine followed by 1 mL benzoyl chloride at 0 ºC. The reaction was stirred at room temperature for 7 h. The reaction was then washed with saturated $NaHCO_3$ (2 × 50 mL) and the organic layer was dried over Na_2SO_4 and condensed to yield 127 as a white solid (9.1 g, 97% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (d, J = 7.20 Hz, 2H), 7.82 (d, J = 7.2 Hz, 2H), 7.60-7.43 (m, 6H), 7.07 (d, J = 6.8 Hz, 1H), 5.19, (q, J = 4 Hz, 1H), 4.78 (d, J = 3.6 Hz, 2H), 3.84 (s, 3H).

2-Benzoylamino-acrylic acid methyl ester (128). To a stirred solution of **127** (9.1 g, 28 mmol) dry CH_2Cl_2 (300 mL) under an inert atmosphere of nitrogen DBU (5.1 mL, 0.07 mol) was added dropwise at 0 ºC. The reaction was stirred at 0 ºC for 6 h. When the elimination was completed by TLC, the reaction was quenched and washed with water (300 mL). The combined organic fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The product was purified by flash chromatography (SiO_2 6:4 hexanes:EtOAC) to yield 128 as a thick, brown oil (5.9 g, 99% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.54 (br s, NH), 7.84 (d, *J* = 7.6 Hz, 2H) 7.55-7.46 (m, 3H), 6.80 (s, 1H), 6.00 (s, 1H), 3.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 400 MHz): 165.5, 164.5, 134.0, 131.8, 130.8, 126.8, 126.7, 108.6, 52.9.

1-Benzoylamino-4-oxo-cyclohex-2-enecarboxylic acid methyl ester (131): To a stirred solution of Danishefsky's Diene (6.5 mL, 33 mol) in dry toluene (80 mL) under an atmosphere of nitrogen was added a solution of the acrylate **128** (1.7 g, 8.3 mmol) in dry toluene (20 mL). The solution was heated to reflux for 24 h and then an additional equivalent of the dienophile (1.7 g, 8.3 mmol) in toluene (20 mL) was added. The reaction mixture was heated to reflux for an additional 48 h. The toluene was removed under reduced pressure and the resulting residue was dissolved in a solution of 1:4 0.005 M HCl :THF (40 mL). The solution was then stirred at room temperature for 15 h. After the hydrolysis of the trimethylsilyl group was complete (TLC), the THF was removed under reduced pressure. The crude material was dissolved in methylene chloride (160 mL), washed with brine (2 × 160 mL) and saturated $NaHCO_3$. The aqueous layers were then extracted with CH_2Cl_2 (2 × 160 mL) and EtOAc (2 × 160 mL). The organic fractions were combined and dried over Na_2SO4 and condensed to an amber oil. The material was carried on to the next step without purification. The residue was dissolved in dry CH_2Cl_2 (180 mL) under an atmosphere of nitrogen. DBU (5.4 mL) was added dropwise at 0 ºC. The mixture was stirred at room temperature for 24 h. When the elimination of the methoxy group was completed by TLC, the organic layer was washed with 0.5 M HCl (120 mL) and the aqueous layer extracted with CH_2Cl_2 (5 × 60 mL). The organic fractions were combined, dried over Na_2SO_4, and concentrated. The brown oil was purified by gradient column chromatography (SiO_2, hexanes:EtOAc, 1:1) to afford **131** (5.4, 60% yield over 3 steps) as an yellow oil. This was recrystallized from EtOAc to give a colorless solid. ^1H NMR ($CDCL_3$) δ 7.80 (d, J = 6.8 Hz, 2H), 7.57-7.44 (m, 3H)

7.14 (d, *J*= 10.4 Hz, 1H), 6.89 (br s, NH), 3.85 (s, 3H), 2.66-2.54 (m, 4H), 1.45. ^{13}C NMR ($CDCl_3$): 197.4, 171.2, 170.2, 147.1, 129.9, 57.8, 53.1, 33.5, 31.4, 22.7.

1-Benzoylamino-4-oxo-cyclohexanecarboxylic acid methyl ester (132): The enone **131**(5.4 g 20 mmol) was hydrogenated (1 atm, H_2) over 10% Pd/C (1.4 g) in CH_2Cl_2 (270 mL) for 48 h. The solution was filtered through a pad of Celite and the solvent was removed under reduced pressure. The resulting residue was recrystallized from hexane:EtOAc (1:9) to yield **132** as a white solid (5.1 g, 92.% yield), mp 133.134 ºC. ^1H NMR ($CDCl_3$): δ 7.80 (d, *J* = 6.8 Hz, 2H), 7.56-7.45 (m, 3H), 6.39 (br s, NH) 3.80 (s, 3H), 2.78-2.52 (m, 8H).

1-*tert*-Butoxycarbonylamino-4-hydroxy-cyclohexanecarboxylic acid methyl ester (133): To a stirred solution of the ketone **132** (5.1 g, 18 mmol) in dry THF (100 mL) under an atmosphere of nitrogen at –78 ºC was added a solution of L-Selectride (22 mL, 1 M) over 25 minutes. The reaction was stirred at this temperature for 3 h. Saturated NH_4Cl (25 mL) was added to quench the mixture was allowed to come to room temperature. The solutiuon was filtered and condensed under reduced pressure at room temperaure. The residue was washed with EtOAc (50 mL) and a 1:3 mixture of isopropanol: $CHCl_3$ (2 × 60). The resulting residue was chromatographed (SiO_2 hexanes:EtOac 1:9) to give the mixture of alcohols **133, 143** (cis:trans 1:9) as a white solid (5.3 g, 86% yield) Isomer ratio was determined by ^1H NMR peak integration. Data for the desired trans product **133** is as follows: ^1H NMR ($CDCl_3$): δ 7.80 (d *J* = 6.8 Hz, 2H) 7.56-7.45 (m, 3H), 6.22 (br s, NH), 3.98 (m, 1H), 3.77 (s, 3H), 2.50-2.41 (m, 2H), 1.97-2.05 (m, 2H), 1.72-1.80 (m, 4H).

1-Benzoylamino-4-methanesulfonyloxy-cyclohexanecarboxylic acid methyl ester (135): To a stirred solution of the alcohols **133, 134** (3.8 g, 14 mmol) in dry CH_2Cl_2 (100 mL) under an atmosphere of nitrogen was added diisopropylethylamine (DIEA) (4.7 mL, 27 mmol) followed by methanesulfonyl chloride (2.1 mL, 27 mmol). The mixture was stirred at room temperature for 36 h. The resulting solid chromatographed by gravity column chromatography (SiO_2, hexanes:EtOAc 1:1) to isolate the trans isomer **135** as a white solid (4.4 mg, 90% yield). ^{1}H NMR ($CDCl_3$): δ 7.76 (d, *J* = 7.2 Hz, 2H) 7.54 (t, *J* = 7.6 Hz, 1H) 7.45 (t *J* = 8.0 Hz, 2H), 6.20 (br s, NH), 4.97 (m, 1H), 3.77 (s, 3H), 3.06 (s, 3H), 2.42-2.34 (m, 3H) 2.18-2.08 (m, 4H), 1.96-1.89 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 173.3, 144.1, 137.8, 129.9 (2), 127.6 (2), 60.4, 52.7, 38.9, 27.8 (2), 26.5 (2), 21.7.

7-Benzoyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid methyl ester (137): To a stirred solution of the mesylate (2.4 g, 6.8 mmol) in dry THF (70 mL) under an atmosphere of nitrogen was added a solution of KO^{t}Bu in THF (7.4 mL, 1 M) at –78 ºC over 20 minutes. The reaction was stirred at –78 ºC for 80 min and then stirred for 16 h at 20 ºC. The reaction was quenched with 0.5 M HCl (8 mL) and the aqueous layer extracted with EtOAc (1 × 60 ml) and CH_2Cl_2 (2 × 60 mL). The organic layers were combined, dried with Na_2SO_4, and the THF removed under reduced pressure. The oil was dissolved in benzene and the solvent was removed under reduced pressure to yield **137** a white solid (2.3 g, 67% yield) mp 100-102 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (dd, J_1 = 8.2 Hz J_2 = 1.2 Hz, 2H), 7.51-7.39 (m, 3H), 4.27, (t, *J* = 4.8 Hz, 1H), 3.82 (s, 3H), 2.39-2.33 (m, 2H), 1.96-1.90 (m, 2H), 1.85-1.79 (m, 2H), 1.59-1.53 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 172.3, 171.5, 134.6, 131.4, 128.6, 67.5, 61.2, 52.4, 32.1, 30.4. *Anal*.

Calc. for $C_{15}H_{17}NO_3 \cdot 1/8\ H_2O$: C, 68.88; H, 6.74; N, 5.34. Found: C, 68.90; H, 6.75; N, 5.24.

1-Hydroxymethyl-7-benzoyl-azabicyclo[2.2.1]heptane (140): To a stirred solution of the methyl ester **137** (0.47 g, 1.8 mmol) in dry THF (20 mL) under an atmosphere of nitrogen was added a solution of $LiBH_4$ in THF (1.4 mL, 2 M) at 0 ºC. The reaction was stirred at room temperature for 24 h. At this time an additional 0.5 eq of $LiBH_4$ (0.7 mL, 2 M) was added. The reaction mixture was then stirred for an additional 24 h at 25 ºC. When the reduction was completed by TLC, 0.5 M HCl (10 mL) was added to neutralize the reaction mixture. The solution was extracted with EtOAc (3 × 20 mL) and the organic fractions dried over Na_2SO_4, filtered and evaporated under reduced pressure. The resulting solid was purified by gravity column chromatography (SiO_2, hexanes:EtOAc 1:1) to yield a pale yellow crystalline solid (0.24 g, 58% yield) mp 75-77 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48-7.39 (m, 5H) 5.58 (t, *J* = 7.2 Hz, 1H), 4.11 (t, 1H), 4.01 (d, *J* = 7.2 Hz, 2H), 2.08-2.03 (m, 2H), 1.87-1.84 (m, 2H), 1.57-1.50 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 168.4, 136.8, 130.5, 128.6 (2), 127.3 (2), 71.0, 61.5, 61.3, 31.3, 29.7. *Anal*. Calc. for $C_{15}H_{17}NO_3 \cdot 1/8\ H_2O$: C, 72.00; H, 7.44; N, 6.00. Found: C, 71.85; H, 7.37; N, 5.94.

Methanesulfonic acid 7-benzoyl-7-aza-bicyclo[2.2.1]hept-1-yl-methyl ester (143): To a stirred solution of the alcohol **140** (0.25 g, 1.1 mmol) in CH_2Cl_2 (25 mL) was added triethylamine (0.22 mL) and methanesulfonyl chloride (0.09 mL) at 0 ºC for 36 h. The organic layer was washed with H_2O and brine. The organic layer was dried over Na_2SO_4 and condensed. The mesylate **143** was used without further purification in the following reactions.

7-Benzoyl-[1-(pyridin-3-yloxymethyl)-7-azabicyclo[2.2.1]heptane (147): To a stirred solution of 60% NaH dispersion in mineral oil (.07 g, 1.8 mmol,) in dry DMF (20 mL) under an atmosphere of nitrogen was added a solution of 3-hydroxypyridine (0.13 g, 1.3 mmol) in DMF (10 mL). The solution was stirred for 1 h at 25 ºC. A solution of the mesylate **143** (0.27 g, 0.83 mmol) in DMF (10 mL) was added and the reaction was stirred at 80 ºC for 24 h. The DMF was removed under reduced pressure and the dark brown residue was purified by column chromtography (SiO_2, $CHCl_3$:MeOH 98:2) to afford **147** as a white solid (0.24g, 94% yield), mp 79-80 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.41 (d, *J* = 4.8 Hz, 1H) 8.26 (d, *J* = 4.8 Hz 1H) 8.54 (m, 2H) 7.46-7.39 (m, 3H) 7.31-7.27 (m, 1H) 7.23-7.20 (m, 1H) 4.88 (s, 1H), 4.21 (t, 1H), 2.10-2.02 (m, 2H), 1.95-1.89 (m, 4H), 1.58-1.53 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 170.7, 155.5, 142.2, 138.9, 136.9, 130.8, 128.5 (2), 127.9 (2), 124.0, 121.0, 71.6, 67.5, 61.6, 33.2 (2), 29.9 (2). *Anal*. Calc. for $C_{19}H_{20}N_2O_3 \cdot 1/4\ H_2O$: C, 72.01; H, 6.52; N, 8.84. Found: C, 72.01; H, 6.45; N, 8.86.

7-Benzoyl-[1-(pyridin-2-yloxymethyl)-7-aza-bicyclo[2.2.1]heptane] (148a): To a stirred solution of 60% NaH dispersion in mineral oil (0.13 g, 3.3 mmol,) in dry DMF (30 mL) under an atmosphere of nitrogen was added a solution of 2-hydroxypyridine (0.25 g, 2.7 mmol) in DMF (20 mL). The solution was stirred for 1 h at 25 ºC. A solution of the mesylate **143** (0.41 g, 1.3 mmol) in DMF (10 mL) was added and the reaction was stirred at 80 ºC for 24 h. The DMF was removed under reduced pressure and the dark brown residue was purified by column chromtography (SiO_2, $CHCl_3$:MeOH 98:2) to furnish a white solid (200 mg, 51% yield) mp 135-137 ºC and the 2-pyridinone isomer **148b** as a crystalline solid (50 mg, 12%) mp 142 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15 (d, *J* = 4.8 Hz, 1H), 7.58-7.51 (m, 2H) 7.42-7.34 (m, 3H), 6.83 (t, *J* = 6 Hz, 1H) 6.75 (d, *J* = 8.4

Hz, 1H), 4.88 (s, 1H), 5.12 (s 2H), 4.21 (t, J = 4 Hz, 1H) 2.13-2.07 (m, 2H), 1.90-1.74 (m, 4H), 1.53-1.47 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 170.5, 164.0, 147.0, 138.6, 137.2, 130.4, 128.3 (2), 127.9 (2), 116.8, 110.9, 67.5, 66.9, 61.4, 53.8, 32.9 (2), 29.9 (2). *Anal*. Calc. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.90; H, 6.57; N, 9.13.

1-(7-Benzoyl-7-azabicyclo[2.2.1]hept-1-ylmethyl)-1H-pyridin-2-one (148b): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.23 (dd, J_1 = 7, J_2 = 1.6 Hz, 1H), 7.58 (d, J = 6.8 Hz, 2H), 7.50-7.47 (m, 1H), 7.42 (t, J = 8 Hz, 2H), 7.34-7.28 (m, 2H), 6.58 (d, J = 9.2, 1H), 6.11 (td, J_1 = 6.8 Hz J_2 = 1.6 Hz, 1H), 5.14 (s, 2H), 4.13 9t, J = 4.4 Hz, 1H), 1.96 (m, 2H), 1.82-1.70 (m, 4H), 1.49-1.43 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 173.8, 163.4, 139.7, 138.7, 137.0, 128.6 (2), 128.0 (2), 120.8, 106.1, 69.0, 62.7, 48.0, 32.6, 29.5. *Anal*. Calc. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.90; H, 6.57; N, 9.13.

7-Benzoyl(6-Chloro-pyridin-3-yloxymethyl)-7-aza-bicyclo[2.2.1]heptane (149): To a stirred solution of 60% NaH dispersion in mineral oil (0.04 g, 0.9 mmol,) in dry DMF (5 mL) under an atmosphere of nitrogen was added a solution of 3-hydroxy-5-chloropyridine (90 mg, 0.67 mmol) in DMF (5 mL). The solution was stirred for 1 h at 25 ºC. A solution of the mesylate (0.14 g, 0.44 mmol) in DMF (10 mL) was added and the reaction was stirred at 80 ºC for 24 h. The DMF was removed under reduced pressure and the dark brown residue was purified by column chromtography (SiO_2, hexanes:EtOAc 3:1) to elude a white solid (140 mg, 93% yield), mp 85 ºC. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (s, 1H) 7.55 (d, J = 6.8 Hz 2H), 7.48-7.38 (m, 3H) 7.31-7.27 (m, 1H) 7.22 (m, 1H) 4.80 (s, 2H), 4.21 (t, 1H), 2.10-2.04 (m, 2H), 1.94-1.85 (m, 4H), 1.58-1.52 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 170.8, 154.8, 142.7, 137.6, 136.7, 130.9, 128.6

(2), 127.9 (2), 125.0, 124.6, 71.0, 67.4, 61.7, 33.1 (2), 29.9 (2). *Anal*. Calc. for $C_{19}H_{19}N_2O_2 \cdot 1/4\ H_2O$: C, 72.01; H, 6.52; N, 8.84. Found: C, 72.01; H, 6.45; N, 8.86.

6-Chloro-pyridin-3-ol (146): To a stirred solution of 3-amino-5-chloropyridine (.500 g, 3.9 mmol) in a 3:1 THF:CH_2Cl_2 solution (40 mL) was added $BF_3 \cdot (CH_3CH_2O)$ (1.2 g, 8.3 mmol) followed by *tert*-butyl nitrite (0.48 g, 4.7 mmol) at –10 ºC. The reaction was stirred for 10 min at –10 ºC then 0 ºC for 30 min. Pentane was then added to the reaction mixture. The resulting diazonium salt precipitate was collected by suction filtration and washed with cold pentane resulting in an orange solid that was used in the next step without further purification. The salt was dissolved in acetic anhydride (6 mL) and stirred at 75 ºC for 3 h until N_2 evolution was complete. The crude product was purified by flash chromatography (SiO_2, EtOAc:hexanes 3:7) to yield a yellow oil (0.11g, 16 % yield over 2 steps) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (d, J = 2.4 Hz, 1H), 7.47 (dd, J_1 = 8 Hz, J_2 = 2.8 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 2.34 (s, 3H).

To a stirred solution of the acetate (0.11 g) in MeOH (5 mL) was added K_2CO_3 (0.04 g, 0.32 mmol). The reaction was stirred at ambient temperature for 8 h. When the reaction was complete by TLC, the solvent was removed under reduced pressure. The residue was dissolved in H_2O and extracted with Et_2O (3 × 15 mL). The organic layer was dried with Na_2SO_4 and condensed to yield **146** as a pure white solid (80 mg, 99% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (s, 1H), 7.26 (s, 1H), 7.22 (s, 1H).

1-(Pyridin-3-yloxymethyl)-7-azabicyclo[2.2.1]heptane (153): The amine **147** (0.18 g, 0.05 mmol) was dissolved in a 2N KOH solution in 3:1 MeOH/H_2O (15 mL) and heated to reflux for 48 h. When no starting material was detected by TLC, water was added to the reaction mixture and the MeOH was removed under reduced pressure. The remaining

aqueous mixture was extracted with CH_2Cl_2 (5 × 50 mL) and the combined organic layers dried over Na_2SO_4 and condensed to yield **153** a yellow oil (120 mg, 99% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.34 (s, 1H), 8.21 (d, *J* = 2.8 Hz, 1H), 7.25-7.18 (m, 2H), 4.24 (s, 2H), 3.66 (t, 4.4 Hz, 1H), 1.80-1.65 (m, 4H), 1.58-1.47 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 155.2, 142.0, 138.0, 123.7, 120.9, 70.4, 65.9, 56.9, 31.9 (2), 31.4 (2).

1-(Pyridin-2-yloxymethyl)-7-aza-bicyclo[2.2.1]heptane (154): The protected amine **148a** (0.06 g, 0.02 mmol) was dissolved in a 2N KOH solution in 3:1 MeOH/H_2O (10 mL) and refluxed for 48 h. When no starting material was detected by TLC, water was added and the MeOH was removed under reduced pressure. The remaining aqueous layer was extracted with CH_2Cl_2 (5 × 50 mL) and the organic layer dried with Na_2SO_4 and condensed to yield **154** as a yellow oil (38 mg, 95% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.34 (s, 1H), 8.21 (d, *J* = 2.8 Hz, 1H), 7.25-7.18 (m, 2H), 4.24 (s, 2H), 3.66 (t, 4.4 Hz, 1H), 1.80-1.65 (m, 4H), 1.58-1.47 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 155.2, 142.0, 138.0, 123.7, 120.9, 70.4, 65.9, 56.9, 31.9 (2), 31.4 (2).

1-(6-Chloro-pyridin-3-yloxymethyl)-7-aza-bicyclo[2.2.1]heptane (155): The protected amine (0.06 g, 0.02 mmol) was dissolved in a 2N KOH solution in 3:1 MeOH/H_2O (10 mL) and heated to reflux for 48 h. When no starting material was detected by TLC, water was added and the MeOH was removed under reduced pressure. The remaining aqueous layer was extracted with CH_2Cl_2 (5 × 50 mL) and the organic layer dried with Na_2SO_4 and condensed to yield **155** as a yellow solid (36 mg, 86% yield). ESI *m/z* = 239.3 ($M+H^+$) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (s, 1H), 7.23 (s, 2H), 4.23 (s, 2H), 3.68 (t, *J* = 4.44 Hz, 1H), 1.81-1.75 (m, 2H), 1.70-1.64 (m, 2H), 1.57-1.50 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 154.7, 142.7, 137.0, 125.0, 124.5, 71.2, 66.1, 57.2, 32.1 (2), 31.6 (2).

General procedure for preparation of oxalate salts:

Oxalic acid (1.2 eq) was dissolved in a minimal amount of diethyl ether. The oxalic acid solution was added dropwise to a dissolved solution of the free base in diethyl ether until a white precipitate formed. The ether was evaporated and the white solid was rinsed with cold ether to afford the salt as an analytically pure crystalline solid.

1-(Pyridin-3-yloxymethyl)-7-aza-bicyclo[2.2.1]heptane·oxalic acid (156): *Anal*. Calc. for $C_{12}H_{16}N_2O\cdot(COOH)_2\cdot 1/2H_2O$: C, 55.44; H, 6.63; N, 9.24. Found: C, 55.44; H, 6.03; N, 9.06.

1-(Pyridin-2-yloxymethyl)-7-aza-bicyclo[2.2.1]heptane·oxalic acid(157): *Anal*. Calc. for $C_{12}H_{16}N_2O\cdot(COOH)_2$: C, 57.13; H, 6.16; N, 9.52. Found: C, 56.79; H, 6.16; N, 9.43.

1-(6-Chloro-pyridin-3-yloxymethyl)-7-aza-bicyclo[2.2.1]heptane·oxalic acid (158): *Anal*. Calc. for $C_{12}H_{15}ClN_2O\cdot(COOH)_2$: C, 51.15; H, 5.21; N, 8.52. Found: C, 51.10; H, 5.12; N, 8.31.

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APPENDIX

X-ray Crystallographic Data, Positional Parameters, General Displacement,

Parameter Expressions, Bond Distances, and Bond Angles

for

Phenyl-[1-(pyridin-2-yloxymethyl)-7-azabicyclo[2.2.1]hept-7-yl]methanone (**148b**)

and

[1-(6-Chloro-pyridin-3-yloxymethyl)-7-azabicyclo[2.2.1]hept-7-yl]phenylmethanone (**149**)

Table 1. X-Ray Crystallographic Data for **149**

Empirical formula	$C_{20}H_{20}ClN_2O_2$
Formula weight	355.83
Temperature	150(2) K
Wavelength	0.71073 Å
Space	P2(1)/c
Volume, Z	4
Unit cell dimensions	
a, Å	11.5922(15)
α, deg.	90
b, Å	13.1468(17)
β, deg.	117.549(2)
c, Å	12.3797(16)
γ, deg.	90
v, Å ^{3}	1672.8(4)
density (calc), Mg/m^3	1.413
Absorption coefficient	0.245 mm^{-1}
F(000)	748
Crystal size	0.5 x 0.3 x 0.4 mm
θ range for data collection	2.42 to 22.50 deg.
Limiting indices	$-12\leq h\leq 12$, $-14\leq k\leq 14$, $-13\leq l\leq 13$
Reflections collected / unique	10983 / 2190 [R(int) = 0.1216]
Completeness to theta	22.50 100.0 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2190 / 357 / 293
Goodness-of-fit on F^2	0.968
Final R indices [I>2σ(I)]	R1 = 0.0755, wR2 = 0.1861
R indices (all data)	R1 = 0.1255, wR2 = 0.2045
Largest diff. peak and hole	0.312 and -0.557 e/ Å ^{3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for **149**
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Cl(1)	5479(2)	1754(1)	2796(2)	50(1)
C(1)	1073(5)	6366(4)	-1246(4)	26(1)
C(2)	2127(6)	6892(5)	-1471(5)	31(1)
C(3)	1367(6)	7397(5)	-2730(5)	35(1)
C(4)	-44(5)	7133(4)	-3051(5)	29(1)
C(5)	-480(6)	7730(5)	-2223(5)	34(1)
C(6)	312(6)	7195(5)	-963(5)	32(1)
N(7)	128(4)	6080(3)	-2534(4)	25(1)
C(8)	-900(5)	5447(3)	-2826(5)	25(1)
O(9)	-1002(3)	4912(3)	-2036(3)	31(1)
C(10)	-1760(5)	5221(3)	-4130(5)	25(1)
C(11)	-1415(5)	5404(3)	-5057(5)	30(1)
C(12)	-2242(5)	5170(3)	-6250(5)	35(1)
C(13)	-3449(5)	4738(3)	-6552(5)	35(1)
C(14)	-3819(5)	4541(3)	-5660(5)	34(1)
C(15)	-2975(5)	4780(3)	-4453(5)	31(1)
C(16)	1571(6)	5521(5)	-316(5)	28(1)
O(17)	2218(3)	4782(3)	-720(3)	34(1)
C(18)	2893(4)	4015(3)	90(5)	30(1)
C(19)	3656(4)	3384(4)	-228(5)	34(1)
C(20)	4451(4)	2681(4)	590(5)	39(2)
C(21)	4454(4)	2639(3)	1716(5)	34(1)
C(23)	2965(5)	3897(4)	1238(5)	30(1)
N(22)	3739(4)	3210(3)	2043(4)	34(1)

Table 3. Bond lengths [Å] and angles [deg] for **149**.

Cl(1)-C(21)	1.756(6)
C(1)-N(7)	1.505(6)
C(1)-C(16)	1.509(7)
C(1)-C(2)	1.538(7)
C(1)-C(6)	1.542(8)
C(2)-C(3)	1.542(8)
C(3)-C(4)	1.534(8)
C(4)-N(7)	1.500(7)
C(4)-C(5)	1.549(8)
C(5)-C(6)	1.564(8)
N(7)-C(8)	1.358(6)
C(8)-O(9)	1.254(6)
C(8)-C(10)	1.483(7)
C(10)-C(11)	1.400(7)
C(10)-C(15)	1.400(7)
C(11)-C(12)	1.374(7)
C(12)-C(13)	1.392(7)
C(13)-C(14)	1.381(7)
C(14)-C(15)	1.391(7)
C(16)-O(17)	1.452(6)
O(17)-C(18)	1.382(6)
C(18)-C(23)	1.393(7)
C(18)-C(19)	1.396(7)
C(19)-C(20)	1.366(7)
C(20)-C(21)	1.393(8)
C(21)-N(22)	1.314(7)
C(23)-N(22)	1.337(7)
N(7)-C(1)-C(16)	117.3(4)
N(7)-C(1)-C(2)	99.8(4)
C(16)-C(1)-C(2)	114.4(5)
N(7)-C(1)-C(6)	101.8(4)
C(16)-C(1)-C(6)	113.8(4)
C(2)-C(1)-C(6)	108.0(5)
C(1)-C(2)-C(3)	104.3(4)
C(4)-C(3)-C(2)	101.9(5)
N(7)-C(4)-C(3)	100.5(4)
N(7)-C(4)-C(5)	101.9(4)
C(3)-C(4)-C(5)	110.4(5)
C(4)-C(5)-C(6)	102.2(5)
C(1)-C(6)-C(5)	103.0(4)
C(8)-N(7)-C(4)	121.6(4)

C(8)-N(7)-C(1)	123.6(4)
C(4)-N(7)-C(1)	96.3(4)
O(9)-C(8)-N(7)	121.6(5)
O(9)-C(8)-C(10)	118.5(4)
N(7)-C(8)-C(10)	118.6(5)
C(11)-C(10)-C(15)	117.9(5)
C(11)-C(10)-C(8)	123.7(5)
C(15)-C(10)-C(8)	118.4(5)
C(12)-C(11)-C(10)	121.4(5)
C(11)-C(12)-C(13)	119.6(5)
C(14)-C(13)-C(12)	120.5(5)
C(13)-C(14)-C(15)	119.5(5)
C(14)-C(15)-C(10)	121.0(5)
O(17)-C(16)-C(1)	107.8(4)
C(18)-O(17)-C(16)	116.6(4)
O(17)-C(18)-C(23)	124.7(5)
O(17)-C(18)-C(19)	116.6(5)
C(23)-C(18)-C(19)	118.4(5)
C(20)-C(19)-C(18)	119.4(5)
C(19)-C(20)-C(21)	117.3(5)
N(22)-C(21)-C(20)	125.1(5)
N(22)-C(21)-Cl(1)	116.4(4)
C(20)-C(21)-Cl(1)	118.4(4)
N(22)-C(23)-C(18)	122.6(5)
C(21)-N(22)-C(23)	117.3(5)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for **149**
The anisotropic displacement factor exponent takes the form:
$-2\pi^2$ [$h^2 a^{*2}$ U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
Cl(1)	37(1)	44(1)	52(1)	11(1)	8(1)	8(1)
C(1)	27(3)	30(3)	19(2)	-4(2)	9(2)	-4(2)
C(2)	31(3)	38(3)	24(3)	-2(3)	11(3)	-6(3)
C(3)	42(3)	34(3)	31(3)	0(3)	18(3)	-8(3)
C(4)	35(3)	23(3)	26(3)	-1(2)	12(2)	-3(2)
C(5)	39(4)	32(3)	31(3)	3(3)	16(3)	0(3)
C(6)	38(4)	33(3)	25(3)	-4(3)	14(3)	0(3)
N(7)	27(2)	27(2)	18(2)	2(2)	7(2)	-3(2)
C(8)	28(3)	26(3)	24(3)	0(2)	13(2)	3(2)
O(9)	31(2)	33(2)	29(2)	2(2)	13(2)	-3(2)
C(10)	24(3)	26(3)	24(3)	-2(2)	10(2)	5(2)
C(11)	31(3)	34(3)	26(3)	-5(3)	14(2)	0(3)
C(12)	37(3)	39(3)	26(3)	-3(3)	13(3)	-4(3)
C(13)	36(3)	38(3)	21(3)	-2(3)	5(3)	-1(3)
C(14)	25(3)	39(3)	31(3)	-2(3)	8(2)	-4(3)
C(15)	31(3)	36(3)	25(3)	-3(3)	12(3)	-5(3)
C(16)	23(3)	35(3)	22(3)	-4(2)	6(3)	1(3)
O(17)	33(2)	45(2)	24(2)	4(2)	12(2)	7(2)
C(18)	23(3)	36(3)	25(3)	2(2)	7(2)	4(2)
C(19)	27(3)	46(3)	25(3)	-7(3)	9(3)	-2(3)
C(20)	27(3)	46(3)	38(3)	-3(3)	9(3)	2(3)
C(21)	28(3)	36(3)	32(3)	3(3)	8(3)	-3(2)
C(23)	23(3)	39(3)	25(3)	-4(2)	8(3)	0(3)
N(22)	23(3)	34(3)	36(3)	1(2)	7(2)	-4(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for **149**

	x	y	z	U(eq)
H(2A)	2770(50)	6330(40)	-1410(50)	41(17)
H(2B)	2710(60)	7320(50)	-760(60)	70(20)
H(3A)	1450(50)	8190(50)	-2680(50)	51(17)
H(3B)	1480(60)	7070(50)	-3410(60)	60(20)
H(4)	-710(50)	7280(40)	-4000(50)	29(14)
H(5A)	-1490(50)	7590(40)	-2520(40)	25(14)
H(5B)	-220(50)	8500(40)	-2120(50)	39(15)
H(6A)	-410(60)	6950(40)	-650(50)	60(18)
H(6B)	850(50)	7650(40)	-430(40)	24(15)
H(11)	-563(19)	5709(8)	-4831(16)	30(15)
H(12)	-2003(16)	5302(7)	-6898(18)	43(17)
H(13)	-4032(17)	4574(7)	-7402(19)	70(20)
H(14)	-4663(19)	4238(8)	-5865(17)	60(20)
H(15)	-3232(16)	4643(7)	-3820(18)	25(14)
H(6A)	2240(40)	5800(30)	470(40)	15(12)
H(16B)	890(70)	5230(60)	-320(70)	90(30)
H(19)	3601(12)	3464(10)	-1036(18)	26(14)
H(20)	5011(14)	2230(12)	417(16)	70(20)
H(23)	2440(20)	4320(20)	1500(40)	43(17)

Table 6. Crystal data and structure refinement for **148b**

Empirical formula	$C_{19}H_{21}N_2O_2$
Formula weight	309.38
Temperature	150(2) K
Wavelength	0.71073 Å
Space group	P2(1)/c
Unit cell dimensions	
a, Å	13.830(2)
α, deg.	90
b, Å	7.3959(12)
β, deg.	97.495(3)
c, Å	15.141(2)
γ, deg.	90
Volume, Z	4
Calculated density	1.338 Mg/m^3
Absorption coefficient	0.087 mm^{-1}
F(000)	660
Crystal size	0.5 x 0.4 x 0.2 mm
Θ range for data collection	3.75 to 22.49 deg.
Limiting indices	$-14\leq h\leq 14$, $-7\leq k\leq 7$, $-16\leq l\leq 16$
Reflections collected / unique	10999 / 1987 [R(int) = 0.0487]
Completeness to Θ	22.49 99.5 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1987 / 0 / 289
Goodness-of-fit on F^2	1.063
Final R indices [$I>2\sigma(I)$]	R1 = 0.0458, wR2 = 0.1145
R indices (all data)	R1 = 0.0498, wR2 = 0.1183
Extinction coefficient	0.0052(17)
Largest diff. peak and hole	0.268 and -0.312 $e/Å^3$

Table 7. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å ^{2} x 10^3) for **148b**
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
N(1)	1508(1)	1778(2)	1023(1)	22(1)
O(2)	3493(1)	-329(2)	151(1)	29(1)
N(3)	2670(1)	1858(2)	-716(1)	21(1)
O(4)	916(1)	4478(2)	1460(1)	36(1)
C(5)	2561(1)	3256(2)	-16(1)	23(1)
C(6)	3233(1)	336(2)	-588(1)	22(1)
C(7)	2795(1)	3164(2)	-1447(1)	26(1)
C(8)	2441(1)	2633(2)	914(1)	23(1)
C(9)	3494(1)	-578(2)	-1408(1)	21(1)
C(10)	3501(1)	4373(2)	-39(1)	28(1)
C(11)	2806(1)	-956(2)	-2136(1)	24(1)
C(12)	1707(1)	4354(2)	-492(1)	27(1)
C(13)	1875(2)	4288(2)	-1479(1)	29(1)
C(14)	1404(1)	-53(2)	884(1)	25(1)
C(15)	604(1)	-945(3)	1060(1)	31(1)
C(16)	4452(1)	-1103(2)	-1422(1)	24(1)
C(17)	3670(2)	4262(3)	-1026(1)	31(1)
C(18)	787(1)	2826(2)	1338(1)	25(1)
C(19)	3075(1)	-1856(2)	-2863(1)	26(1)
C(20)	4030(1)	-2364(2)	-2883(1)	28(1)
C(21)	-53(1)	1848(2)	1518(1)	30(1)
C(22)	-139(1)	41(3)	1388(1)	32(1)
C(23)	4719(1)	-1984(2)	-2164(1)	28(1)

Table 8. Bond lengths [Å] and angles [deg] for **148b**

N(1)-C(14)	1.375(2)
N(1)-C(18)	1.395(2)
N(1)-C(8)	1.465(2)
O(2)-C(6)	1.231(2)
N(3)-C(6)	1.368(2)
N(3)-C(7)	1.496(2)
N(3)-C(5)	1.503(2)
O(4)-C(18)	1.245(2)
C(5)-C(8)	1.511(2)
C(5)-C(12)	1.533(2)
C(5)-C(10)	1.545(2)
C(6)-C(9)	1.500(2)
C(7)-C(13)	1.516(3)
C(7)-C(17)	1.525(3)
C(9)-C(16)	1.384(3)
C(9)-C(11)	1.387(2)
C(10)-C(17)	1.545(3)
C(11)-C(19)	1.379(2)
C(12)-C(13)	1.542(3)
C(14)-C(15)	1.345(3)
C(15)-C(22)	1.403(3)
C(16)-C(23)	1.389(3)
C(18)-C(21)	1.425(3)
C(19)-C(20)	1.377(3)
C(20)-C(23)	1.379(3)
C(21)-C(22)	1.353(3)
C(14)-N(1)-C(18)	122.34(15)
C(14)-N(1)-C(8)	118.89(14)
C(18)-N(1)-C(8)	118.52(14)
C(6)-N(3)-C(7)	121.18(13)
C(6)-N(3)-C(5)	124.96(13)
C(7)-N(3)-C(5)	96.30(12)
N(3)-C(5)-C(8)	118.74(13)
N(3)-C(5)-C(12)	100.04(13)
C(8)-C(5)-C(12)	115.36(14)
N(3)-C(5)-C(10)	100.94(13)
C(8)-C(5)-C(10)	112.28(14)
C(12)-C(5)-C(10)	107.77(14)
O(2)-C(6)-N(3)	123.45(15)
O(2)-C(6)-C(9)	119.96(14)
N(3)-C(6)-C(9)	116.53(14)

N(3)-C(7)-C(13)	101.51(13)
N(3)-C(7)-C(17)	101.32(14)
C(13)-C(7)-C(17)	109.72(15)
N(1)-C(8)-C(5)	116.20(14)
C(16)-C(9)-C(11)	119.37(16)
C(16)-C(9)-C(6)	118.27(15)
C(11)-C(9)-C(6)	122.33(15)
C(17)-C(10)-C(5)	103.10(14)
C(19)-C(11)-C(9)	120.17(17)
C(5)-C(12)-C(13)	103.58(14)
C(7)-C(13)-C(12)	102.64(14)
C(15)-C(14)-N(1)	121.66(17)
C(14)-C(15)-C(22)	118.35(18)
C(9)-C(16)-C(23)	119.96(17)
C(7)-C(17)-C(10)	102.83(15)
O(4)-C(18)-N(1)	120.05(15)
O(4)-C(18)-C(21)	125.13(16)
N(1)-C(18)-C(21)	114.80(15)
C(20)-C(19)-C(11)	120.58(17)
C(19)-C(20)-C(23)	119.55(17)
C(22)-C(21)-C(18)	122.19(17)
C(21)-C(22)-C(15)	120.64(18)
C(20)-C(23)-C(16)	120.35(17)

Symmetry transformations used to generate equivalent atoms:

Table 9. Anisotropic displacement parameters ($Å^2$ x 10^3) for **148b**
The anisotropic displacement factor exponent takes the form:
$-2\pi^2$ [$h^2 a^{*2}$ U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
N(1)	27(1)	14(1)	26(1)	1(1)	4(1)	-1(1)
O(2)	36(1)	22(1)	27(1)	3(1)	1(1)	8(1)
N(3)	30(1)	11(1)	23(1)	0(1)	3(1)	1(1)
O(4)	44(1)	17(1)	47(1)	-6(1)	10(1)	1(1)
C(5)	30(1)	10(1)	28(1)	-2(1)	5(1)	-1(1)
C(6)	23(1)	13(1)	28(1)	1(1)	1(1)	-2(1)
C(7)	42(1)	11(1)	27(1)	3(1)	9(1)	1(1)
C(8)	27(1)	15(1)	28(1)	-2(1)	2(1)	-1(1)
C(9)	29(1)	7(1)	26(1)	3(1)	3(1)	-2(1)
C(10)	33(1)	16(1)	36(1)	-2(1)	4(1)	-5(1)
C(11)	26(1)	12(1)	33(1)	2(1)	1(1)	1(1)
C(12)	33(1)	14(1)	34(1)	0(1)	5(1)	3(1)
C(13)	41(1)	16(1)	30(1)	5(1)	1(1)	2(1)
C(14)	32(1)	14(1)	29(1)	2(1)	4(1)	3(1)
C(15)	36(1)	13(1)	43(1)	4(1)	4(1)	-1(1)
C(16)	28(1)	15(1)	29(1)	2(1)	0(1)	-4(1)
C(17)	40(1)	16(1)	39(1)	2(1)	14(1)	-3(1)
C(18)	32(1)	18(1)	25(1)	-1(1)	3(1)	5(1)
C(19)	35(1)	13(1)	28(1)	0(1)	-2(1)	-3(1)
C(20)	40(1)	14(1)	30(1)	-1(1)	9(1)	1(1)
C(21)	28(1)	26(1)	37(1)	1(1)	8(1)	5(1)
C(22)	29(1)	26(1)	43(1)	6(1)	6(1)	-5(1)
C(23)	31(1)	19(1)	36(1)	2(1)	7(1)	2(1)

Table 10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for **148b**

	x	y	z	U(eq)
H(7)	2893(12)	2560(20)	-2012(12)	26(4)
H(8A)	2962(13)	1800(20)	1116(11)	24(4)
H(8B)	2491(12)	3720(20)	1282(12)	24(4)
H(10A)	4040(14)	3830(30)	356(13)	31(5)
H(10B)	3416(13)	5660(30)	168(12)	28(5)
H(11)	2139(15)	-590(20)	-2132(12)	28(5)
H(12A)	1075(14)	3810(20)	-398(12)	28(5)
H(12B)	1715(14)	5610(30)	-241(13)	36(5)
H(13A)	1312(14)	3750(20)	-1849(12)	29(5)
H(13B)	1990(13)	5530(30)	-1731(13)	35(5)
H(14)	1978(14)	-600(20)	655(11)	27(5)
H(15)	560(13)	-2200(30)	962(12)	35(5)
H(16)	4915(13)	-840(20)	-915(13)	25(5)
H(17A)	4288(13)	3590(30)	-1082(11)	28(5)
H(17B)	3693(14)	5520(30)	-1309(13)	36(5)
H(19)	2584(14)	-2080(20)	-3364(13)	33(5)
H(20)	4222(13)	-2960(30)	-3374(13)	32(5)
H(21)	-552(15)	2500(30)	1734(13)	37(5)
H(22)	-713(14)	-520(20)	1523(12)	26(5)
H(23)	5435(14)	-2330(30)	-2185(12)	31(5)

VITA

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