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Enantioenriched N-(2-Chloroalkyl)-3-acetoxypiperidines as Potential Cholinotoxic Agents. Synthesis and Preliminary Evidence for Spirocyclic Aziridinium Formation.

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Abstract: The syntheses of six enantioenriched analogs representing cyclic forms of acetylcholine are reported. (S)- and (R)-N-(2-chloroethyl)-3-acetoxypiperidine and (R,R)-, (R,S)-, (S,R)-, and (S,S)-N-(2-chloropropyl)-3-acetoxypiperidine have been synthesized from (R)- or (S)-3-hydroxypiperidine in five steps. (R)- and (S)-3-hydroxypiperidine were accessed via parallel stereospecific routes from d- and l-glutamic acid, and through fractional recrystallization of diastereomeric tartranilic acid salts. (S)-N-(2-Chloroethyl)-3-acetoxypiperidine was reacted with silver perchlorate to form a spirocyclic aziridinium analog of acetylcholine as evidenced by a characteristic ^{1}H NMR shift for the aziridinium methylene groups.

Recent studies have revealed the importance of specific neurotransmitters in the etiology of various neuropsychiatric diseases. In parallel with these investigations, researchers have been greatly interested in developing and identifying neurotoxic or neurotoxin agents that could be used therapeutically to selectively extinguish or modify individual neurotransmitter systems. Such agents could be used to specifically alter neurotransmitter concentrations *in vivo* through substrate mimicry, inhibition of metabolizing enzymes, or blocking of a receptor, and could serve as chemical probes in the study of a basic neurochemical mechanism of action.

Acetylcholine (ACh; **1**) is a major neurotransmitter found in the ganglia, the neuromuscular junction, and the postganglionic synapses of the cholinergic nervous system. When released into the synaptic cleft, ACh can bind to either muscarinic or nicotinic receptor and initiate neurochemical cascades before being hydrolyzed to choline and acetic acid by the enzyme acetylcholinesterase.[1] Choline acetyltransferase catalyzes the synthesis of ACh *in vivo* from choline and acetyl CoA thereby establishing a continuous pool of available ACh and an interdependence of choline and ACh concentrations. Normally, the rate of ACh turnover is rapid, and the cholinergic system is highly resistant to insult. Available pharmacological agents that disturb the cholinergic

1: acetylcholine

2a: R = Ac, R^1 = Me; AChM
2b: R = H, R^1 = Et; AF64A

Figure 1.

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system generally act either as agonists (e.g., cholinesterase inhibitors, arecoline, etc.) or antagonists (atropine, etc.) and, because of their limited course of action, are particularly useful for studying acute responses. However, these agents are of less utility when a long-term cholinergic perturbation is sought, and persistent cholinotoxic agents would be valuable additions in the study of ACh-based and choline-based disease states.

In attempts to prolong the duration of interaction with the ACh system, researchers have substituted choline or ACh quaternary ammonium moiety with an aziridinium mustard group (via a β-haloethyl group), which react covalently with available nucleophilic sites on proteins. Whether the new covalent bond remains intact indefinitely, or eventually breaks owing to other factors, it has a far longer interaction with the target [protein or receptor] than the native neurotransmitter. As examples, acetylcholine mustard (AChM; **2a**) was first synthesized and its toxicology studied in 1947,[2] and several subsequent investigations of a variety of aziridinium analogues of choline and ACh have been reported.[3] The choline-based aziridinium analog AF64A (ethylcholine mustard aziridinium; **2b**) devised by Fisher and Hanin has been shown to simulate the neurochemical conditions that appear to cause a number of neuropsychiatric diseases including Alzheimer's disease.[4] However, because the aziridinium group is highly reactive and ACh and choline are conformationally flexible, many of these cholinotoxic agents are not selective. Since AChE[1] and the ACh receptor[5] can discriminate between stereoisomers,[5] it occurred to us that ACh analogs of defined configurations that bear a reactive aziridinium moiety could act as more selective cholinotoxic agents. We selected stereoisomeric N-(2-chloroalkyl)-3-acetoxypiperidines (Figure 2; **3-8**) as target molecules that, following aziridinium formation using base,[6] could increase selectivity owing to combined electronic and stereochemical features.[7] The target molecules were chosen based on the following criterion: (a) the cyclic piperidine structure imposes a cyclic restriction to the ethano bridge of ACh, (b) the acetoxy group is positioned at an asymmetric carbon and can probe protein stereochemical biases,[8] (c) the aziridinium moiety could be generated spirocyclic, a variation not yet examined for cholinotoxic agents, and (d) added asymmetry can be installed in the aziridinium ring that may influence

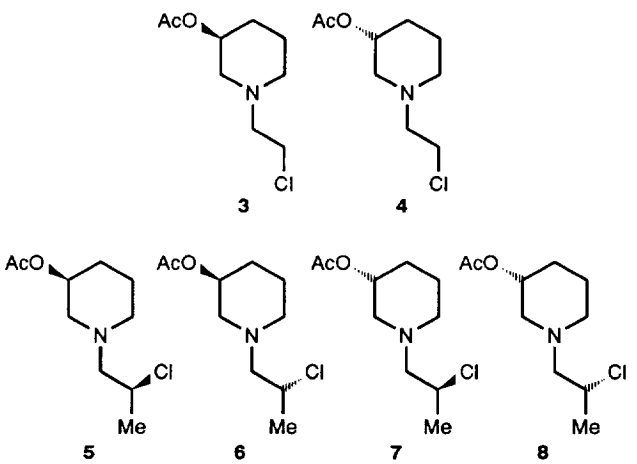


Figure 2.

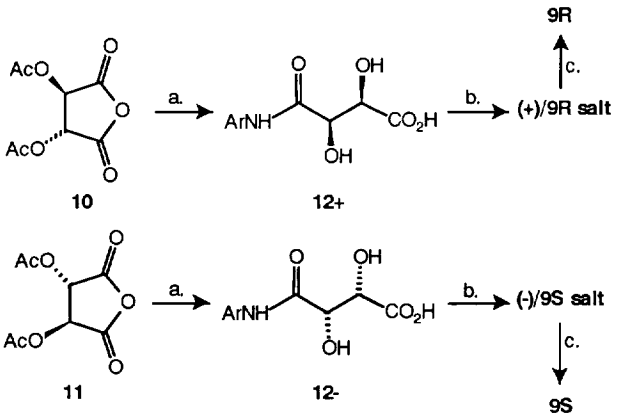
the orientation of covalent bond-forming reaction with the protein. In this paper, we report the synthesis of six enantioenriched β-chloroalkyl precursors to heterospirocyclic mustard analogs of ACh, and demonstrate an example of conversion to a spirocyclic aziridinium.

RESULTS AND DISCUSSION

Our strategy sought to take advantage of the fact that the target molecules **3-8** all share a heterocyclic 3-hydroxypiperidine structure differing only in the configuration at C-3 and the N-alkyl side chain. As a result, molecules **3-8** can be prepared from substituted 3-hydroxypiperidine enantiomers using various alkylating agents to install the desired exocyclic amino group. Preparation of the β-haloamine moiety was considered as a required last step in the synthetic sequence to avoid possible spontaneous aziridinium ring closure under subsequent reaction conditions. With these goals and restrictions, our initial synthetic plan focused on the preparation of (R)-3-hydroxypiperidine (**9R**) and (S)-3-hydroxypiperidine (**9S**).

The enantiomers of 3-hydroxypiperidine have been accessed through fractional recrystallization of tartranilic acid diastereomers.[8bc,9] Total syntheses of **9S** also have been reported from (S)-malic acid,[10] l-glutamic acid,[10] or a carbohydrate precursor.[11] We elected to emply Olsen's route,[10] and fractional crystallization[9] to access **9S** and **9R** and confirm the prior stereochemical assignments. We also envisioned conversion of **9S** into **9R** through conventional inversion methods to possibly avoid a parallel sequence with *d*-glutamic acid.

The enantiomers of **9** were first separated following conversion to their diastereomeric, 4-chlorotartranilic acid salts (Scheme 1). (+)-4-Chlorotartranilic acid (**12+**) was prepared by reaction of 4-chloroaniline with (+)-diacetoxysuccinic anhydride (**10**)[12] followed by basic hydrolysis of the acetyl groups.[13] The same procedure was conducted with (-)-diacetoxysuccinic anhydride (**11**)[12] to give (-)-4-chlorotartranilic acid (**13**). A 2:1 molar ratio of racemic **9** to **12+** was warmed to 40 °C and cooled to room temperature to provide the (+)/**9R** salt. Likewise, the (-)/**9S** salt was prepared from racemic **9** and **12-**. The individual enantiomers **9R** and **9S** were isolated as

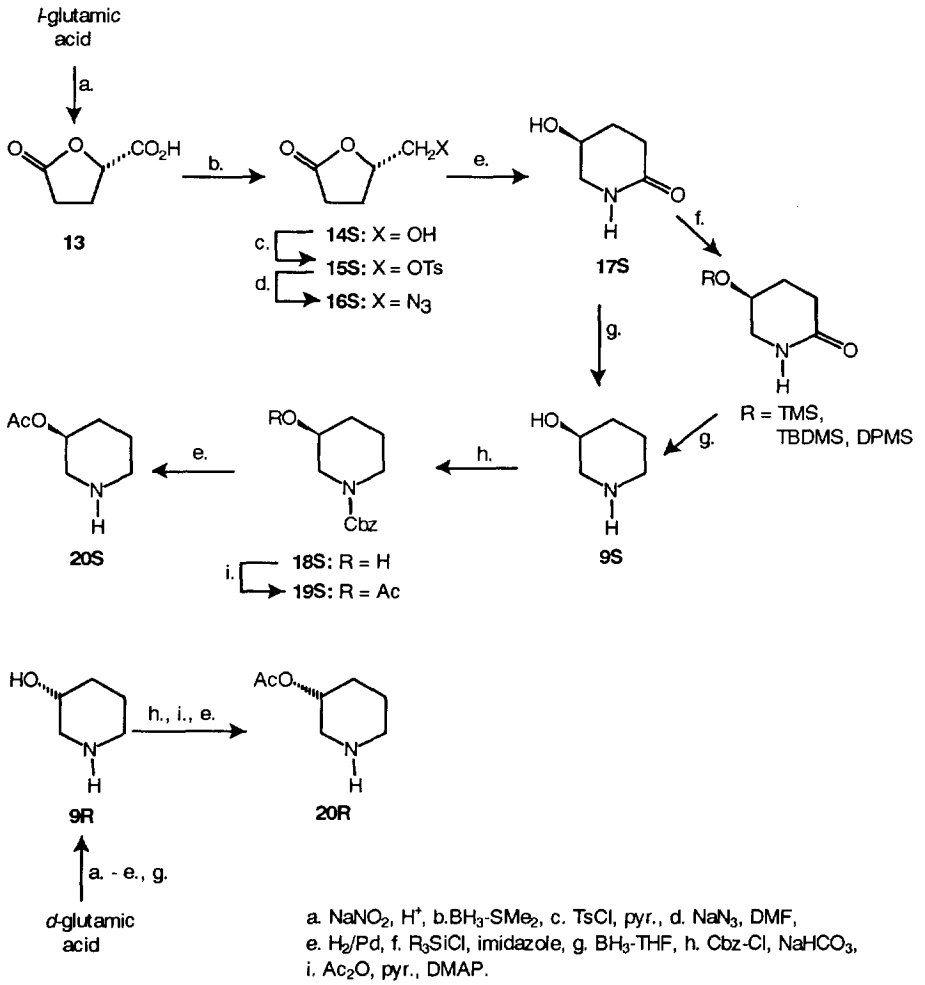


a. p-ClArNH$_2$, b. 3-hydroxypiperidine, c. K_2CO_3

Scheme 1

their free bases following reaction of the salts with K_2CO_3 in methanol/toluene. The overall yield of **9R** or **9S** from racemic **9** ranged from 35-42%, and the physical data agreed with that previously reported. Capillary gas chromatography showed the enantiomers were greater than 98% pure.

The synthetic pathway to **9S** is considered next (Scheme 2). Using diazotization conditions, l-glutamic acid was converted to (S)-5-oxo-2-tetrahydrofuran-carboxylic acid (**13S**) in 91% crude yield. Several recrystallizations gave highly purified material in 68% overall recovery. The carboxylic acid (**13S**) was reduced



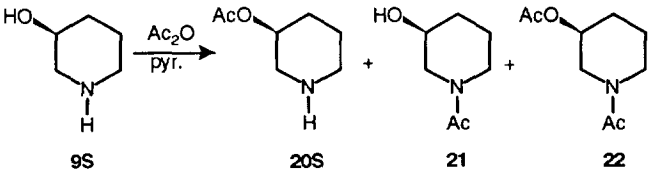
Scheme 2

to the primary alcohol (S)-(+)-γ-hydroxymethyl-γ-butyrolactone (**14S**) with borane-methyl sulfide complex in 90-92% yield. In attempts to obviate odor problems on large scale, we attempted the same reduction using borane-THF complex,[14] however, overreduction to the lactol occurred. The primary alcohol was converted to

the corresponding (S)-(+)-γ-p-tosyloxymethyl-γ-butyrolactone (**15S**) in 93% yield using pyridine/CH_2Cl_2 as cosolvents.[15] The sulfonate group was displaced with azide in DMF to give **16S** in 93% yield. Reduction of **16S** by catalytic hydrogenation (H_2, Pd/C) led to the amine, which undergoes ring expansion to form the lactam, (S)-5-hydroxypiperidin-2-one (**17S**) in 96% yield. The lactam carbonyl could be reduced to form (S)-3-hydroxypiperidine (**9S**) using $LiAlH_4$ or BH_3-THF (approx. 50%), but the yields on larger scale were lowered due to the high polarity and water solubility of **9S**. To increase recovery of **9S**, we first protected the hydroxy of **17S** as the TMS-, TBDMS-, or DPMS- derivative and conducted the reduction. Surprisingly, the silyl groups were removed under the reduction conditions. We next decided to trap **9S** as the carbobenzyloxy derivative. Following aqueous quench of borane reduction of **17S**, the crude mixture was treated directly with excess $NaHCO_3$, and reacted with a toluene solution of Cbz-Cl. The aqueous layer was periodically adjusted to pH 8.5 with 10% NaOH, and the reaction was stirred overnight to give (S)-(+)-N-carbobenzyloxy-3-hydroxypiperidine (**18S**) in 76% overall yield.

(S)-(+)-N-Carbobenzyloxy-3-hydroxypiperidine (**18S**) was converted to (S)-(-)-N-carbobenzyloxy-3-acetoxypiperidine (**19**) in 85% yield using acetic anhydride. The ^1H NMR of this compound gave a poorly resolved ^1H spectrum presumably due to conformational flexibility. However, all other physical and elemental data were consistent with this structure. Hydrogenolysis of the Cbz-group on small scale (H_2, Pd/C, 1 atm) gave the desired (S)-3-acetoxypiperidine (**20S**). It was noted during hydrogenolysis that the 24 h reaction time gave transacetylation (vide infra). Subsequent hydrogenolyses therefore were conducted on a Parr shaker at 35 psi over a 3 h period, and following removal of the catalyst, the product was either stored at -78 °C or used directly in the next step.

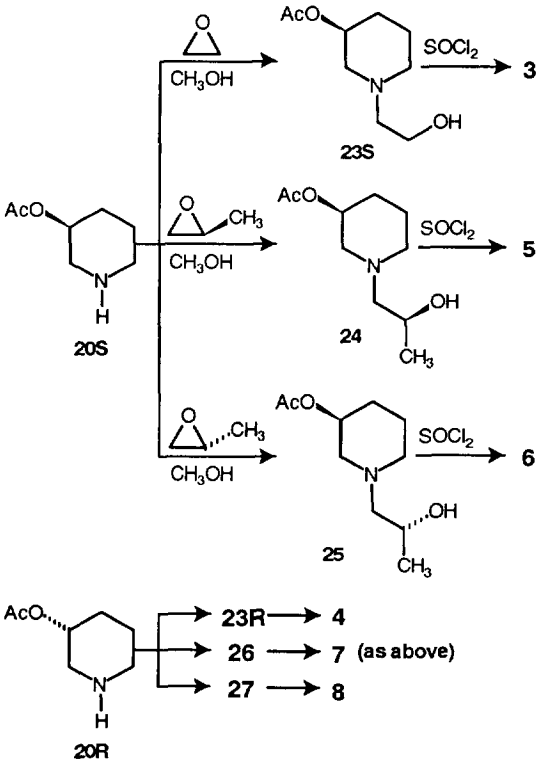
The isolation of some **9S** from the reduction permitted an examination of the acetylation step. If the hydroxyl group of **9S** could be converted directly to an acetoxy, protection as the Cbz would be avoided and only installation of the nitrogen side chain remained. However, all attempts to convert **9S** into its 3-acetoxy stereoisomer gave predominant formation of N-acetyl-3-hydroxypiperidine (**21**) even when the amine was fully protonated (pH 1) (Eq. 1). Minor amounts of the desired product **20S** and diacetylated side product **22** were separated from **21** using silica gel chromatography. Again, **20S** underwent facile transacetylation to **21** upon storage at 0 °C. Therefore, protection/blocking of the amine moiety was fortuitous because the Cbz-group permits easier isolation and better storage as a 3-acetoxy precursor.



(1)

The functionalization of the piperidine amino group was next undertaken (Scheme 3). (S)-3-acetoxypiperidine **20S**, freshly prepared from **19S**, was reacted with 1-bromo-2-chloroethane to give (S)-(-)-N-(2-chloroethyl)-3-acetoxypiperidine (**3**) although in poor yield (10-23%). The addition of sodium iodide did not increase the yield. The poor yields are likely due to both over alkylation and self-alkylation. Thus, we turned our attention to preparing precursors to the β-haloethyl side chain, namely, 2-hydroxyethylamine derivatives.

Alternative alkylating agents that install a 2-hydroxyethyl group including 2-bromoethanol, 2-chloroethanol, and ethylene carbonate, were tried. All reagents gave the product **23S** although in yields of 1-40%. The best result was obtained with 2-bromoethanol/triethylamine. *In situ* generation of ethylene oxide (from 2-bromoethanol and NaOH) resulted in the formation of **23S**, but the reaction was accompanied by significant ester hydrolysis. Reaction of a preformed solution of ethylene oxide in methanol at 0 ^{0}C with **20S** led to a reproducible 60% yield of **23S**. Minor amounts of the bis-(2-hydroxyethyl)-3-acetoxypiperidinium ion, which were easily separated, were observed when the reaction time exceeded 1.5 h. The reaction gave a poor yield of product when water was used as cosolvent. The primary alcohol was reacted with $SOCl_2$ to give the crystalline, hydrochloride salt of (S)-(-)-N-(2-chloroethyl)-3-acetoxypiperidine (**3**) in 80% yield. The desired product **3** was generated by treatment with $NaHCO_3$ in CH_2Cl_2, and purified on silica gel for spectral and elemental analyses. Compound **3** undergoes dimerization (self-alkylation) and/or cyclization at room temperature and storage as the hydrochloride is warranted. The overall yield for the sequence from l-glutamic acid is 31%.



Scheme 3

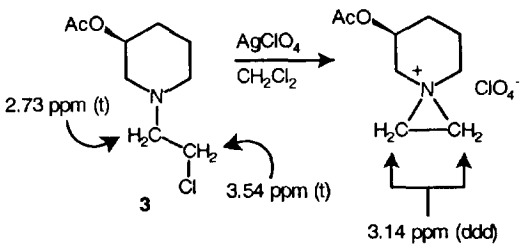
To avoid a parallel synthetic sequence from d-glutamic acid, we examined the possibility of transforming (S)-(+)-N-carbobenzyloxy-3-hydroxypiperidine (**18S**) directly into (R)-(-)-N-carbobenzyloxy-3-acetoxypiperidine (**19R**). The hydroxyl group was converted into a variety of leaving groups, and displacement reactions were

conducted with acetate ion under a variety of conditions. However, only scant conversion to the 3-acetoxy derivative was observed. Application of Mitsunobu conditions[16] led to partial racemization of the asymmetric center, and this approach was abandoned.

The corresponding enantiomer target (R)-(+)-N-(2-chloroethyl)-3-acetoxypiperidine (**4**) was synthesized in 30% overall yield using an identical synthetic sequence starting from d-glutamic acid and proceeding through (R)-(+)-3-hydroxypiperidine (Schemes 2 and 3). All intermediates showed identical spectral and physical data to that obtained from the l-glutamic acid route. Targets **5** and **6** were prepared from (S)-3-acetoxypiperidine (**20S**) in a manner similar to that described for the preparation of **3** (Scheme 3). (S)-3-Acetoxypiperidine (**20S**) was reacted with (S)- or (R)-propylene oxide to afford the corresponding (S)-N-[(2S)-hydroxypropyl]-3-acetoxypiperidines **24** and (S)-N-[(2R)-hydroxypropyl]-3-acetoxypiperidines **25** in 71 and 76% yield, respectively. Reaction of each secondary alcohol with thionyl chloride led to the corresponding β-chloropropyl hydrochloride derivatives of **5** and **6** with retention of configuration in 71-84% yield. The free bases were generated as noted prior. Again, storage as the hydrochloride salt is suggested. Targets **7** and **8** were prepared from (R)-3-hydroxypiperidine **9R** proceeding through intermediates **20R**, and **26/27** in a manner identical to that described for the preparation of **4** and **6** (Scheme 3).

The syntheses of the target molecules **3-8** were repeated from **9S** and **9R** obtained from the fractional crystallization method. Products **3-8** were virtually identical in all physical and spectral details to that obtained from the synthetic material.

Target molecules **3-8** represent precursors to possible cholinotoxic agents following conversion into the corresponding aziridinium ions, and therefore this process needs to be examined. In prior reports, aziridiniums have been produced *in situ* from the corresponding β-haloethylamino moiety under aqueous alkaline conditions, which also can lead to ester hydrolysis,[4h] concomitant aziridinium ring-opening by nucleophiles,[17] and dimerization.[18] These side reactions cause difficulty in measuring the correct concentration of aziridinium to be administered during bioassay. Therefore, we chose to generate the aziridinium cation under non-aqueous conditions as an ion pair to a weakly nucleophilic anion in an effort to possibly isolate and characterize the formation of these cholinotoxic agents. Leonard and coworkers used NMR to identify the spirocyclic aziridinium of N-2-chloroethylpiperidine, and its high melting, dimeric structure 1,1,4,4-tetraethylpiperazinium dication following reaction with silver perchlorate.[17f,19] Owing to the similarity of N-2-chloroethylpiperidine to **3**, we chose to react **3** with $AgClO_4$ in acetone, butanone and CH_2Cl_2 and found that a spirocyclic aziridinium ion had formed by the following evidence (Equation 2).



(2)

Filtration of a small quantity of crystals produced from the $AgClO_4$ gave a melting point of 85-90°C consistent with values reported for monomeric ion formation. The chemical shift of the N-CH_2- and -CH_2-Cl groups of **3** changed from 2.73 (t) ppm and 3.54 (t) ppm, respectively, to a single absorbance at 3.18 (ddd) ppm consistent with that reported by Nelson.[17f] It is noteworthy that traces (approx. 5%) of the aziridinium of **3** can be detected in the ^{1}H NMR immediately following dissolution of **3** in $CDCl_3$ without $AgClO_4$. However, the aziridinium precipitates from the solution and the cyclization rate could not be determined. The chemical shifts of the $CH_3C(O)$- group (and other proximous group) shifted downfield consistent with the formation of a more strongly electron-withdrawing group. The preliminary isolation of a crystalline, spirocyclic aziridinium offers great advantages in the use of these materials as cholinotoxins. Normally, aziridiniums are generated *in situ* by reaction of base with the precursor β-haloamine immediately prior to bioassay leading to errors in the exact amount of aziridinium used. Isolation as solids would greatly aid measures in concentration and application as potential cholinotoxins.

EXPERIMENTAL

Warning. The 2-haloethylamine compounds **3-8** are potential toxic agents and should be handled in a well ventilated hood by qualified persons. 2-Haloethylamine compounds may be destroyed by stirring overnight in warm (40°C) 6 M KOH.

Commercially available reagents and solvents were purified when necessary by standard literature methods. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was conducted on E. Merck aluminum-backed, 0.2 mm silica gel $60F_{254}$ plates. Visualization was conducted using an ultraviolet lamp and/or anisaldehyde stain (2% solution of *o*-anisaldehyde in 95:4:1 absolute EtOH-H_2SO_4-HOAc, PMA (phosphomolybdic acid in EtOH), or ninhydrin (5% in EtOH) with heating. Flash chromatography was performed with Kieselgel 60, 230-400 mesh (Merck). Elemental analyses were performed by Midwest Microlab Ltd., Indianapolis, Indiana.

^{1}H and ^{13}C NMR spectra were recorded at 300 MHz and 75.4 MHz, respectively, in deuterated chloroform ($CDCl_3$) unless specified otherwise. Proton and carbon spectral frequencies are relative to $CHCl_3$ (7.24 ppm) and $CDCl_3$ (triplet @ 77.0 ppm), respectively. Select infrared data, obtained as solutions in $CDCl_3$, are tabulated in decreasing wavenumber (cm^{-1}). Gas chromatographic analyses were performed using a capillary DB-1 column (30 m, 50-250 °C @ 20 °C/min). The optical rotations were recorded (Na lamp) at room temperature in the specified solvents.

***(S)-(-)-N-(2-Chloroethyl)-3-acetoxypiperidine* (3).** Compound **23S** (0.37 g, 2 mmol) was stirred in dry CH_2Cl_2 (6 mL) at 5 °C under argon. Freshly distilled $SOCl_2$ (0.16 mL, 2.2 mmol) was added by syringe and stirring was continued for 20 min. The cooling bath was removed and the reaction stirred an additional 3 h at rt. At completion, the reaction was diluted with CH_2Cl_2 (10 mL), chilled to 0 °C whereupon the addition of Et_2O resulted in crystallization of hydrochloride salt. The salt was filtered under argon and washed with dry Et_2O. Removal of traces of solvent under high vacuum gave white crystals of **3** as the hydrochloride salt (0.408 g, 80.4%). The hydrochloride salt was converted to the free base **3** by reaction with excess $NaHCO_3$ in CH_2Cl_2 (10 mL) with stirring. Chromatography on silica gel using petroleum ether-Et_2O (1:1) gave pure material: TLC (petroleum ether/Et_2O, 1:1), R_f 0.34; $[\alpha]_D^{24}$ = -31.1° (c 0.45, $CHCl_3$); ^{1}H NMR δ 1,38-1.46 (m, 1H), 1.52-1.62

(m, 1H), 1.71-1.87 (m, 2H), 2.03 (s, 3H), 2.25-2.34 (m, 2H), 2.56-2.63 (m, 1H), 2.73 (t, J = 7.2 Hz, 2H), 2.80 (dd_{br}, J = 3.55, 10.9, Hz, 1H), 3.54 (t, J = 7.2 Hz, 2H), 4.82 (t on dd, J = 7.8, 8.2, 15.9 Hz, 1H); ^{13}C NMR δ 21.3, 22.6, 29.2, 40.8, 53.3, 56.9, 59.7, 69.3, 170.5. Anal calcd for $C_9H_{16}NO_2Cl$: C, 52.55; H, 7.84; N, 6.81. Found: C, 52.55; H, 7.86; N, 6.74.

***(R)-(+)-N-(2-Chloroethyl)-3-acetoxypiperidine* (4).** The identical procedure as above using (R)-(+)-(**23**) gave 80% yield: $[\alpha]_D^{24}$ = +28.3° (c 0.50, $CHCl_3$). This compound showed identical spectral and physical data to **3**.

***Preparation of N-(2-chloropropyl)-3-acetoxypiperidines* (5-8).**

General procedure; Each diastereomer of N-(2-hydroxypropyl)-3-acetoxy-piperidine was stirred in dry CH_2Cl_2 (50 mg/mL) at 0 °C under argon. Freshly distilled $SOCl_2$ (1.5 equiv) was added and the reaction mixture was stirred for 20 min. The cooling bath was removed and the reaction was allowed to stir an additional 5 h at rt. Anhydrous ry Et_2O caused crystallization of the corresponding hydrochloride salt. Filtration and recrystallization from CH_2Cl_2 afforded white crystals (71-84%). Treatment with $NaHCO_3/CH_2Cl_2$ followed by chromatography on silica gel using petroleum ether-Et_2O (3:1) affords tertiary amines **5**, **6**, **7**, and **8**.

***(3S)-(-)-N-[(2S)-Chloropropyl]-3-acetoxypiperidine* (5).** mp 134-137 °C (HCl salt); TLC (petroleum ether/Et_2O, 3:1), R_f 0.32; $[\alpha]_D^{24}$ = -43.0° (c 2.6, $CHCl_3$); ^1H NMR δ 1.29-1.41 (m, 2H), 1.47 (d, J = 6.4 Hz, 3H), 1.51-1.62 (m, 1H), 1.66-1.77 (m, 1H), 1.79-1.89 (m, 1H), 2.01 (s, 3H), 2.19-2.29 (m, 2H), 2.46 (dd, J = 7.4, 13.1 Hz, 1H), 2.55-2.61 (m, 1H), 2.63 (dd, J = 6.4, 13.1 Hz, 1H), 2.80 (dd_{br}, J = 3.9, 10.8 Hz, 1H), 4.01 (dq, J = 6.7, 13.2 Hz, 1H), 4.78 (t on dd, J = 8.3, 8.6, 16.8 Hz, 1H); ^{13}C NMR δ 21.2, 22.9, 23.2, 29.4, 53.8, 54.6, 57.2, 66.1, 69.5, 170.4.

***(3S)-(+)-N-[(2R)-Chloropropyl]-3-acetoxypiperidine* (6).** mp 152-154 °C (HCl salt); $[\alpha]_D^{24}$ = +24.2° (c 1.2, CH_3OH) (HCl salt). This compound showed identical spectral and physical data to **7**. Anal calcd for $C_{10}H_{18}NO_2Cl$: C, 54.66; H, 8.26; N, 6.38. Found: C, 55.00; H, 8.10; N, 6.21.

***(3R)-(-)-N-[(2S)-Chloropropyl]-3-acetoxypiperidine* (7).** mp 153-155 °C (HCl salt); TLC (petroleum ether/Et_2O, 3:1), R_f 0.33; $[\alpha]_D^{24}$ = -21.1° (c 0.9, CH_3OH) (HCl salt); ^1H NMR δ 1.32-1.48 (m, 1H), 1.47 (d, J = 6.6 Hz, 3H), 1.51-1.59 (m, 1H), 1.61-1.79 (m, 1H), 1.80-1.89 (m, 1H), 2.02 (s, 3H), 2.15-2.30 (m, 2H), 2.46 (dd, J = 7.2, 14.3 Hz, 1H), 2.45-2.55 (m, 1H), 2.66 (dd, J = 6.6, 14.3 Hz, 1H), 2.83 (dd_{br}, J = 3.9, 10.8 Hz, 1H), 4.03 (dq, J = 6.7, 13.2 Hz, 1H), 4.82 (t on dd, J = 8.3, 8.6, 16.8 Hz, 1H); ^{13}C NMR δ 21.2, 22.9, 23.2, 29.4, 53.5, 54.8, 57.6, 66.2, 69.6, 180.1.

***(3R)-(+)-N-[(2R)-Chloropropyl]-3-acetoxypiperidine* (8).** mp 133-137 °C (HCl salt); $[\alpha]_D^{24}$ = +30.0° (c 1.8, $CHCl_3$). This compound showed identical spectral and physical data to **5**.

***(S)-(-)-3-Hydroxypiperidine* (9S).**[10,20] Method A. (S)-(-)-5-Hydroxy-2-piperidinone **17S** (0.97 g, 8.4 mmol) was stirred in 20 mL of dry THF at 0 °C under argon. Portions of $LiAlH_4$ (0.64 g, 2 eq.) were added slowly to the mixture, and following addition of all the $LiAlH_4$ the ice bath was removed. The reaction mixture was brought to reflux for 43.5 h, cooled, and diluted with EtOAc (50 mL). A minimum amount of 0.1 M NaOH was added

to destroy excess hydride reagent. The insoluble material was filtered, and the solution dried over Na_2SO_4. The drying agent was filtered and removal of the solvent left 1.4 g of a residue that was purified on silica gel (MeOH/$CHCl_3$, 3:7) to give the product **9S** (0.43 g, 59%) as pale yellow crystals.

Method B. To a suspension of (S)-(-)-5-Hydroxy-2-piperidinone **17S** in dry THF (33.3 mg/mL) was added 2 equiv. of 1M BH_3•THF complex in THF at 0 °C under argon. The ice bath was removed and reaction mixture was heated for 1.5 h. The reaction was quenched by cautious addition of anhydrous MeOH, and concentrated under reduced pressure. Identical chromatographic conditions as above gave **9S** (48-62%) as pale yellow crystals.

TLC (MeOH-$CHCl_3$, 3:7), R_f 0.01; mp 55-60 °C; $[\alpha]_D^{24}$ = -8.94° (c 4.7, CH_3OH), lit[10] $[\alpha]_D^{24}$ = -7.4° (c 0.4, CH_3OH); ^1H NMR δ 1.37-1.55 (m, 2H), 1.68-1.82 (m, 2H), 2.17 (s_{br}, 2H), 2.61 (dd, J = 6.8, 11.9 Hz, 1H), 2.63-2.76 (m, 2H), 2.94 (dd, J = 2.5, 11.9 Hz, 1H), 3.63-3.69 (m, 1H); ^{13}C NMR δ 23.4, 32.9, 46.4, 53.5, 66.6.

***(R)-(+)-3-Hydroxypiperidine* (9R).**[10,20] From Method B and **17R**: yield 58.3%; mp 56-60 °C; $[\alpha]_D^{24}$ = +9.4° (c 0.65, CH_3OH). This compound showed identical spectral and physical data to **9S**.

Fractional recrystallization of the diastereomeric salts (+)/9R and (-)/9S and recovery of enantioenriched 3-hydroxypiperidine from its diastereomeric salt.

(+)/9R-salt: To a solution of racemic 3-hydroxypiperidine in warm 95% ethanol was added 0.5 equivalents of (+)-4-chlorotartranilic acid (**12+**) in 95% EtOH. The solution was stirred at 40 °C to yield a clear solution, which was cooled to rt. Upon standing overnight at rt, the solution deposited a first crop of needle-shaped crystals in 70-74% yield. mp 152-155 °C; $[\alpha]_D^{24}$ = +77.6° (c 0.49, H_2O).

(-)/9S-salt: The identical procedure using (-)-4-chlorotartranilic acid (**12-**) led to formation of the **(-)/9S** diastereomeric salt. mp 153-155 °C; $[\alpha]_D^{24}$ = -76.1° (c 0.46, H_2O).

Each diastereomeric salt was dissolved in MeOH/toluene (3:7) and an equivalent amount of solid K_2CO_3 was added. After vigorous stirring for 3 h, the mixture was filtered, and the filtrate concentrated in vacuo to give a waxy solid. The solid was shaken with hot EtOAc and concentrated. Crystallization from EtOAc/benzene/hexane gave powdery, pale yellow crystals of (S)-(-)- or (R)-(+)-3-hydroxypiperidine in an overall recovery of 56-62%. The physical and spectral data for **9R** and **9S** obtained from recrystallization were identical to that obtained from synthesis.

***(R,R)-(+)-Diacetoxysuccinic anhydride* (10).**[12] (+)-Tartaric acid (15.1 g, 0.1 mol) was placed in 250 mL round bottom flask fitted with a condenser and additional funnel under argon. The additional funnel was charged with a solution of acetic anhydride (40 mL) and sulfuric acid (1.0 mL), which was added dropwise to the tartaric acid with stirring at 0 °C. Upon completion, the ice bath was removed and the mixture was refluxed gently for 30 min. The mixture was cooled to rt leaving a solid residue that was shaken with benzene (100 mL) and filtered. The crystals were washed with dry Et_2O. Removal of the last trace of solvent under vacuum afforded white crystals **10** in 76% yield: mp 133-135 °C (dec.), lit.[9] 133-134 °C; $[\alpha]_D^{24}$ = +97.2° (c, 0.5, $CHCl_3$); ^1H NMR δ 2.21 (s, 6H), 5.66 (s, 2H); ^{13}C NMR δ 20.16, 22.19, 72.07, 163.09, 169.50.

***(S,S)-(-)-Diacetoxysuccinic anhydride* (11).**[12] Prepared from (-)-tartaric acid in a procedure similar to that above: mp 133-134 °C; $[\alpha]_D^{24}$ = -97.0° (c 0.5, $CHCl_3$). This compound showed identical spectral and physical data to **10**.

***(R,R)-(+)-4-Chlorotartranilic acid* (12+).**[13] To a solution of **10** (10.0 g, 46 mmol) in CH_2Cl_2 (50 mL) was added 4-chloroaniline (6.0 g, 47 mmol) portionwise over 10 min. The solution was maintained at reflux for 15 h, and cooled to give a dark brown solution, which was washed with 10% KOH (3 x 30 mL). The aqueous layers were combined and neutralized by the addition of concentrated HCl resulting in the precipitation of the crude product. The wet crystals were recrystallized from EtOH/H_2O to give needle-shaped, colorless crystals **12+** in 68% yield: mp 192-194 °C; ^{1}H NMR δ 3.50-4.20 (br, 2H), 4.57 (s, 1H), 4.67 (s, 1H), 5.11-5.40 (br, 1H), 7.34 (d, *J* = Hz, 2H), 7.80 (d, *J* = Hz, 2H), 9.32 (s, 1H); ^{13}C NMR δ 72.67, 74.25, 121,75, 129.31, 170.45, 173.44.

***(S,S)-(-)-4-Chlorotartranilic acid* (12-).**[13] The identical procedure using **11** and 4-chloroaniline was conducted to give 65% yield of **12-**: mp 193-195 °C. This compound showed identical spectral and physical data to **12+**.

***(S)-(+)-5-Oxo-2-tetrahydrofurancarboxylic acid* (13S).**[10,20] (S)-(+)-Glutamic acid (29.9 g, 0.2 mol) was dissolved in 4 M HCl (130 mL) at 0 °C. A solution of $NaNO_2$ (20.7 g, 0.3 mol) in H_2O (45 mL) was added dropwise over 20 min. After stirring overnight at room temperature, a clear solution resulted. Removal of the water under reduced pressure yielded a white, oily solid. The residue was shaken with hot acetone (300 mL) and filtered. The insoluble material was washed with boiling acetone (100 mL), and the filtrates were combined. Evaporation of the acetone gave a pale yellow syrup (23.7 g, 91%) that was redissolved in hot $CHCl_3$ (500 mL), cooled, and stirred over Na_2SO_4 at 60 °C for 3 h. The sticky drying agent was removed and the volume of $CHCl_3$ solution was reduced to about 200 mL by rotary evaporation. A few seed crystals were added, the solution was chilled to -30 °C where crystallization ensued (17.7 g, 68%): white crystals; $[\alpha]_D^{24}$ = +14.8° (c 2.3, CH_3OH); mp 70-72 °C, lit[10] 71-73°C; ^{1}H NMR δ 2.32-2.42 (m, 1H), 2.52-2.68 (m, 3H), 4.95 (dd, *J* = 4.2, 8.4 Hz, 1H), 11.48 (s, 1H); ^{13}C NMR δ 25.7, 26.7, 75.2, 174.7, 176.5.

***(R)-(-)-5-Oxo-2-tetrahydrofurancarboxylic acid* (13R).**[10,20] Obtained from (R)-(-)-glutamic acid using the same procedure for the (S)-isomer (above): $[\alpha]_D^{24}$ = -13.8° (c 5.0, CH_3OH); mp 70-72 °C. This compound showed identical spectral and physical data to **13S**.

***(S)-(+)-γ-Hydroxymethyl-γ-butyrolactone* (14S).**[14] The lactone carboxylic acid **13S** (15.6 g, 0.12 mol) was dissolved in dry THF (80 mL) and stirred for 20 min at -78 °C under argon. A 2 M borane-methylsulfide solution in THF (65 mL, 0.13 mol) was added, warmed to room temperature, and stirred for 14 h. The reaction duration varied and required monitoring by TLC. The mixture was quenched by cautious addition of dry MeOH (80 mL), and the volatile materials removed by rotary evaporation. Methanol (50 mL) was added, stirred, and evaporated under reduced pressure. The residue was chromatographed on silica gel using 4% MeOH in $CHCl_3$ (91%, 12.75 g): colorless oil; TLC (MeOH-$CHCl_3$, 4:96), R_f 0.24; $[\alpha]_D^{24}$ = +44.7° (c 0.26, $CHCl_3$); ^{1}H NMR δ 1.99-2.25 (m, 2H), 2.39-2.60 (m, 2H), 3.51-3.60 (m, 2H), 3.75-3.82 (m, 1H), 4.52-4.59 (m, 1H); ^{13}C NMR δ 23.0, 28.5, 63.8, 80.9, 178.0.

***(R)-(-)-γ-Hydroxymethyl-γ-butyrolactone* (14R).**[14] This enantiomer was prepared from (R)-(-)-5-oxo-2-tetrahydrofuran-carboxylic acid using the above procedure: $[\alpha]_D^{24}$ = -54.4° (c 2.7, $CHCl_3$), lit[15] $[\alpha]_D^{24}$ = -53.1° (c 5.13, $CHCl_3$). This compound showed identical spectral and physical data to **14S**.

***(S)-(+)-γ-p-Tosyloxymethyl-γ-butyrolactone* (15S).**[10,15] A mixture of **14S** (2.32 g, 20 mmol) and TsCl (5.73 g, 30 mmol) in pyridine (4 mL) and CH_2Cl_2 (10 mL) was stirred at room temperature for 9 h. The mixture was diluted with CH_2Cl_2 (80 mL) and the solution was washed successively with 10% HCl (3 x 50 mL), 20% $NaHCO_3$ (2 x 50 mL), and brine. The organic layers were combined and dried over Na_2SO_4. The solution was filtered and the filtrate concentrated under reduced pressure. The product crystallized from a saturated solution in CH_2Cl_2 to which Et_2O had been added (93%, 5.0 g): needles; TLC (Et_2O), R_f 0.16; $[\alpha]_D^{24}$ = +46.2° (c 2.5, $CHCl_3$), lit[15] $[\alpha]_D^{24}$ = +44.5° (c 0.95, $CHCl_3$); mp 86-87 °C, lit[15] mp 87°C; ^{1}H NMR δ 2.04-2.14 (m, 1H), 2.25-2.37 (m, 1H), 2.42 (s, 3H), 2.46-2.56 (m, 2H), 4.13 (ddd, *J* = 4.18, 8.69, 11.0 Hz, 2H), 4.62-4.69 (m, 1H), 7.34 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR δ 21.6, 23.5, 27.8, 69.9, 76.4, 127.9, 130.0, 132.3, 145.4, 175.9.

***(R)-(-)-γ-Tosyloxymethyl-γ-butyrolactone* (15R).**[10,15] Prepared from (R)-(-)-γ-hydroxymethyl-γ-butyrolactone **14R** using the above procedure: $[\alpha]_D^{24}$ = -45.1° (c 2.6, $CHCl_3$). This compound showed identical spectral and physical data to **15S**.

***(S)-(+)-5-Azido-4-pentanolide* (16S).**[10] To a solution of **15S** (8.21 g, 30 mmol) in dry DMF (25 mL) was added NaN_3 (6.5 g, 100 mmol) in five portions and refluxed for 1.5 h. The solvent was removed, and resulted in a dark brown oily residue, which was shaken with $CHCl_3$ (50 mL) and filtered through a frit of Celite. The pad was washed with hot $CHCl_3$ (20 mL), and the filtrates were combined and concentrated *in vacuo*. Chromatography on silica gel (acetone-hexane, 1:4) afforded **16S** (3.98 g, 93%): yellow liquid; TLC (acetone-hexane, 1:4), R_f 0.09; IR (cm^{-1}) 2120 (N_3), 1780 (C=O); $[\alpha]_D^{24}$ = +91.9° (c 5.0, $CHCl_3$), lit[10] $[\alpha]_D^{24}$ = +92.9° (c 2.15, $CHCl_3$) ; ^{1}H NMR δ 1.95-2.08 (m, 1H), 2.23-2.35 (m, 1H), 2.44-2.64 (m, 2H), 3.49 (ddd, *J* = 3.62, 4.99, 13.3 Hz, 2H), 4.58-4.65 (m, 1H); ^{13}C NMR δ 24.5, 28.1, 54.1, 77.9, 176.0.

***(R)-(-)-5-Azido-4-pentanolide* (16R).** [10] The same procedure as above from **15R** yields **16R** in 89.2% yield: $[\alpha]_D^{24}$ = -86.3° (c 2.5, $CHCl_3$). This compound showed identical spectral and physical data to **16S**.

***(S)-(-)-5-Hydroxy-2-piperidinone* (17S).**[10,11] To a solution of the azide **16S** (1.44 g, 10 mmol) in MeOH (degassed; 80 mL) in a pressure bottle was added 5 mol% of 10% Pd-C. The mixture was shaken on a Parr Hydrogenator under H_2 pressure (50 psi) for 24 h. The solution was filtered through a Celite frit to remove spent catalyst, and the catalyst washed with portions of hot MeOH (2 x 20 mL). The filtrates were combined and concentrated under reduced pressure. Chromatography on silica gel was conducted using MeOH-$CHCl_3$ (1:9) to obtain **17S** following recrystallization from MeOH-Et_2O (1.15 g, 96%): white crystals; TLC (MeOH-$CHCl_3$, 1:9), R_f 0.16; mp 120-121 °C, lit[11] mp 124-125 °C; $[\alpha]_D^{24}$ = -12.4° (c 0.5, CH_3OH); ^{1}H NMR (D_2O) δ 1.74-1.82 (m, 2H), 2.13-2.36 (m, 2H), 3.13 (dd, *J* = 3.9, 13.2 Hz, 1H), 3.16 ($s_{ex.}$, 1H), 3.29 (dd, *J* = 3.8, 13.2 Hz, 1H), 3.53 (d_{br}, 1H), 3.98-4.04 (m, 1H); ^{13}C NMR (D_2O, ref CD_3OD: 49.0 ppm) δ 26.4, 26.6, 47.6, 62.5, 174.9.

***(R)-(+)-5-Hydroxy-2-piperidinone* (17R).**[10,11] From **16R** using the above procedure (92%): mp 120-123 °C; $[\alpha]_D^{24}$ = +13.3° (c 0.5, CH_3OH). This compound showed identical spectral and physical data to **17S.**

***(S)-(+)-N-Carbobenzyloxy-3-hydroxypiperidine* (18S).**[10] Method A. (S)-(-)-3-Hydroxypiperidine **9S** (1.01 g, 10 mmol) was suspended in 10 mL of water containing powdered $NaHCO_3$ (2 equiv.; 1.68 g). A solution of Cbz-Cl (2.85 mL, 20 mmol) in toluene (8 mL) was added dropwise while the pH was controlled at 8~9 by the addition of 50% NaOH. The solution was stirred overnight at room temperature and diluted with Et_2O (80 mL). The organic layer was washed successively with water (50 mL) and brine (50 mL), and dried with Na_2SO_4. The solution was filtered, concentrated by rotary evaporation, and chromatographed on silica gel using petroleum ether-Et_2O (2:3) to afford a colorless oil of **18S** (2.23 g, 88%).

Method B. (two-step procedure from lactam **17S**). A solution of **17S** (0.41 g, 3.6 mmol) in dry THF (15 mL) at 0 °C under argon was reacted with 1 M BH_3•THF complex (15 mL, 15 mmol). After all the borane was added, the solution was heated to 60 °C for 1.5 h. The reaction was cooled and then quenched by the cautious addition of MeOH. The solvent was removed under reduced pressure to give yellowish oily crystals of crude **9S** that was immediately dissolved in 7 mL of water containing $NaHCO_3$ (0.8 g). A solution of carbobenzyloxy chloride (1.4 mL) in toluene (5 mL) was added dropwise, and after adjusting the pH to 8 with 50% NaOH, the reaction was stirred overnight at rt. The work up (same as described in method A) affords **18S** as a colorless oil (overall yield 76%; 0.64 g): TLC (petroleum ether-Et_2O, 2:3), R_f 0.18; t_R 7.29 min; $[\alpha]_D^{24}$ = +5.79° (c 3.8, $CHCl_3$); ^1H NMR δ 1.38-1.59 (m, 2H), 1.71-1.93 (m, 2H), 3.08-3.28 (m, 2H), 3.51-3.67 (br, 1H), 3.68-3.78 (br, 1H), 3.76 (s, 1H), 3.80-3.83 (m, 1H), 5.23 (s, 2H), 7.26-7.38 (m, 5H); ^{13}C NMR δ 22.2, 32.3, 44.1, 50.7, 66.0, 67.2, 126.9, 128.0, 136.7, 155.7.

(R)-(-)-N-Carbobenzyloxy-3-hydroxypiperidine (18R).[10] From either **9R** (Method A) or **17R** (Method B), yields 85.4% (white oily crystals): t_R 7.28 min; $[\alpha]_D^{24}$ = -6.44° (c 2.64, $CHCl_3$). This compound showed identical spectral and physical data to **18S.**

***(S)-(-)-N-Carbobenzyloxy-3-acetoxypiperidine* (19S).** A solution of **18S** (1.12 g, 4.7 mmol) in 1 mL of pyridine containing 5-10 mg of DMAP was stirred at room temperature under argon. Anhydrous acetic anhydride (0.6 mL, 6.4 mmol) was added and the reaction was stirred for 3 h. The reaction was diluted with EtOAc (40 mL) and washed successively with 20% $NaHCO_3$ and brine. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to a residue that was purified on silica gel using petroleum ether-Et_2O (1:1) to yield **19S** (1.12 g; 85%): colorless liquid; TLC (petroleum ether-Et_2O, 1:1), R_f 0.21; t_R 10.10 min; $[\alpha]_D^{24}$ = -10.5° (c 4.0, $CHCl_3$); ^1H NMR δ 1.43-1.60 (m, 1H), 1.63-1.90 (m, 3H), 1.98 (s_{br}, 3H), 3.29-3.43 (m, 1H), 3.45-3.67 (m, 3H), 4.72-4.86 (m, 1H), 5.13 (s_{br}, 2H), 7.25-7.38 (m,5H); ^{13}C NMR δ 20.9, 21.8, 28.9, 44.0, 47.3, 67.0, 67.7, 127.7, 127.9, 128.4, 136.7, 155.4, 170.2. Anal. calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.93; H, 6.91; N, 5.10.

***(R)-(+)-N-Carbobenzyloxy-3-acetoxypiperidine* (19R).** The identical procedure from **18R** yields 82.6%: t_R 10.09 min; $[\alpha]_D^{24}$ = +11.2° (c 4.3, $CHCl_3$). This compound showed identical spectral and physical data to **19S.**

***(S)-(-)-3-Acetoxypiperidine* (20S).** A solution of **19S** (1.01 g, 3.6 mmol) in MeOH (degassed; 80 mL) containing 5 mol% of 10% Pd/C was reacted overnight with H_2 (35 psi) using a Parr Hydrogenator. The catalyst was filtered through a Celite frit, and the frit was washed with MeOH (10 mL). The filtrates were combined and concentrated under reduced pressure. Chromatography on silica gel was conducted with $CHCl_3$-MeOH (9:1) to give **20S** (0.47 g, 90%): colorless liquid; TLC ($CHCl_3$-MeOH, 9:1), R_f 0.10; t_R 4.49 min; $[\alpha]_D^{24}$ = -8.43° (c 7.0, $CHCl_3$); ^{1}H NMR δ 1.37-1.55 (m, 2H), 1.55-1.78 (m, 2H), 1.82-1.93 (m, 1H), 2.01 (s, 3H), 2.63-2.75 (m, 3H), 2.96-3.08 (d_{br}, 1H), 4.67-4.76 (m, 1H); ^{13}C NMR δ 21.3, 24.2, 29.6, 45.9, 50.1, 69.6, 170.5. Anal. Calcd for $C_7H_{13}NO_2$: C, 58.67; H, 9.15; N, 9.78. Found: C, 58.81; H, 9.16; N, 9.64.

***(R)-(+)-3-Acetoxypiperidine* (20R).** The identical procedure as above using **19R** yields **20R** in 85.4% yield: t_R 4.48 min; $[\alpha]_D^{24}$ = +9.14° (c 5.8, $CHCl_3$). This compound showed identical spectral and physical data to **20S**.

***(S)-(-)-N-(2-Hydroxyethyl)-3-acetoxypiperidine* (23S).** Compound **20S** (0.40 g, 2.8 mmol) was stirred in methanol (20 mL) at 0 °C. Ethylene oxide was bubbled into the solution and the progress of the reaction was monitored by TLC, and the flow stopped when the formation of the quaternary ammonium was observed by TLC (baseline). Excess ethylene oxide and solvent was removed in vacuo using an aqueous $MeNH_2$ trap. Chromatography on silica gel using MeOH-$CHCl_3$ (2:98) afforded **23S** (0.33 g, 64%): colorless liquid; TLC (MeOH-$CHCl_3$, 1:9), R_f 0.29; t_R 6.49 min; $[\alpha]_D^{24}$ = -24.0° (c 0.9, $CHCl_3$), ^{1}H NMR δ 1.40-1.57 (m, 2H), 1.70-1.83 (m, 2H), 2.00 (s, 3H), 2.20-2.30 (m, 2H), 2.47-2.51 (t, J = 5.9 Hz, 2H), 2.53-2.58 (m, 1H), 2.72-2.77 (dd, J = 3.4, 11.0 Hz, 2H), 3.53-3.56 (t, J = 5.9 Hz, 2H), 4.76-4.84 (m, 1H); ^{13}C NMR δ 21.2, 22.7, 29.3, 53.0, 56.9, 57.7, 59.1, 69.4, 170.4. Anal calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.62; H, 9.11; N, 7.19.

***(R)-(+)-N-(2-Hydroxyethyl)-3-acetoxypiperidine* (23R).** The identical procedure using **20R** yielded 58.8%: t_R 6.48 min; $[\alpha]_D^{24}$ = +22.1° (c 1.1, $CHCl_3$). This compound showed identical spectral and physical data to **23S**.

***(3S)-(+)-N-[(2S)-Hydroxypropyl]-3-acetoxypiperidine* (24).** (S)-(-)-3-Acetoxypiperidine **20S** (0.58 g, 4 mmol) was dissolved in MeOH (5 mL) at 5 °C and (S)-(-)-propylene oxide (0.4 mL, 5.7 mmol) was added dropwise. The reaction was stirred for 14-17 h at 5 °C. At completion, the MeOH and excess propylene oxide were removed under reduced pressure, and the residue was chromatographed on silica gel using Et_2O to yield **24** (0.61 g, 76%): TLC (Et_2O), R_f 0.25; t_R 6.65 min; $[\alpha]_D^{24}$ = +24.4° (c 3.6, $CHCl_3$); ^{1}H NMR δ 1.07 (d, J = 6.2 Hz, 3H), 1.39-1.60 (m, 2H), 1.67-1.84 (m, 2H), 1.99 (s, 3H), 2.11-2.22 (m, 2H), 2.28 (dd, J = 3.1, 12.5 Hz, 1H), 2.42 (t_{br}, J = 5.3 Hz, 2H), 2.86 (dd, J = 3.2, 11.0 Hz, 1H), 3.72-3.80 (m, 1H), 4.78 (t on dd, J = 7.8, 7.9, 15.7 Hz, 1H); ^{13}C NMR δ 19.9, 21.2, 22.7, 29.2, 52.8, 57.5, 62.2, 65.5, 69.2, 170.4. Anal calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.63, H, 9.54, N, 6.92.

***(3S)-(-)-N-[(2R)-Hydroxypropyl]-3-acetoxypiperidine* (25).** Stereoisomer **25** was obtained from (S)-(-)-3-acetoxypiperidine **20S** and (R)-(+)-propylene oxide (yield 78%): t_R 6.55 min; $[\alpha]_D^{24}$ = -68.9° (c 6.3, $CHCl_3$). This compound showed identical spectral and physical data to **26**.

***(3R)-(+)-N-[(2S)-Hydroxypropyl]-3-acetoxypiperidine* (26).** Stereoisomer **26** was obtained from (R)-(+)-3-acetoxypiperidine **20R** and (S)-(-)-propylene oxide as indicated in the experiment for isomer **24** (71% yield): TLC (Et_2O), R_f 0.19; t_R 6.64 min; $[\alpha]_D^{24}$ = +73.3° (c 3.6, $CHCl_3$); ^1H NMR δ 1.08 (d, J = 8.3 Hz, 3H), 1.41-1.56 (m, 2H), 1.72-1.84 (m, 2H), 2.00 (s, 3H), 2.10-2.19 (m, 2H), 2.31 (dd, J = 3.1, 12.3 Hz, 1H), 2.44 (t_{br}, J = 7.6 Hz, 1H), 2.62-2.72 (m, 2H), 3.73-3.79 (m, 1H), 4.82 (t on dd, J = 7.7, 7.8, 15.3 Hz, 1H); ^{13}C NMR δ 19.9, 21.2, 22.7, 29.2, 52.8, 57.5, 62.2, 65.5, 69.2, 170.4.

***(3R)-(-)-N-[(2R)-Hydroxypropyl]-3-acetoxypiperidine* (27).** Obtained from (R)-(+)-3-acetoxypiperidine (**20R**) and (R)-(+)-propylene oxide as indicated in the experiment for isomer **24** (68% yield): TLC (Et_2O), R_f 0.25; t_R 6.64 min; $[\alpha]_D^{24}$ = -22.6° (c 3.4, $CHCl_3$). This compound showed identical spectral and physical data to **24**.

Reaction of 3 with $AgClO_4$; Spirocyclic Aziridinium Formation. (S)-N-(2-chloroethyl)-acetoxypiperidine (**3**) hydrochloride (0.45 g, 1.9 mmol) was dissolved in CH_2Cl_2 (15 mL) at room temperature. To this solution was added $NaHCO_3$ (1 eq.) and the mixture stirred for 70 min. The solution was transferred to a 10 mL flask using a cotton plug to remove excess carbonate and Na_2SO_4 (1 g) was added. The solution was stirred 10 min and $AgClO_4 \cdot XH_2O$ (0.39 g, 1.9 mmol) was added precipitating AgCl immediately. The reaction was stirred an additional 1 h at rt, filtered through Whatman 42 filter paper, and concentrated. Crystallization from CH_2Cl_2-ether afforded white crystals of (S)-5-acetoxy-3-azaniospiro[2.5]octane perchlorate. mp 85-89°C. ^1H NMR: δ 1.85-197 (m, 2H), 1.98-2.04 (m, 2H), 2.13 (s, 3H), 3.00-3.12 (m, 2H), 3.18 (ddd, 2H), 3.7 (t_{br}, 2H), 3.88-3.95 (dd, 2H), 5.21-5.26 (m, 1H). Resonances broadened due to trace Ag.

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