Facile Synthesis of (±)-, (+)-, and (-)-Galanthamine

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The Amarylidacea alkaloid galanthamine (**1a**) is an acetylcholinesterase inhibitor that has been evaluated as a potential agent for the treatment of Alzheimer's disease. We report a very efficent synthesis of (±)-galanthamine [(±)-**1a**] from readily available isovanillin and tyramine. We have separated racemic galanthamine into its diastereoisomeric (1*S*)-camphanate esters and obtained both natural (-)- and unnatural (+)-galanthamine by lithium aluminum hydride removal of the acyl group.

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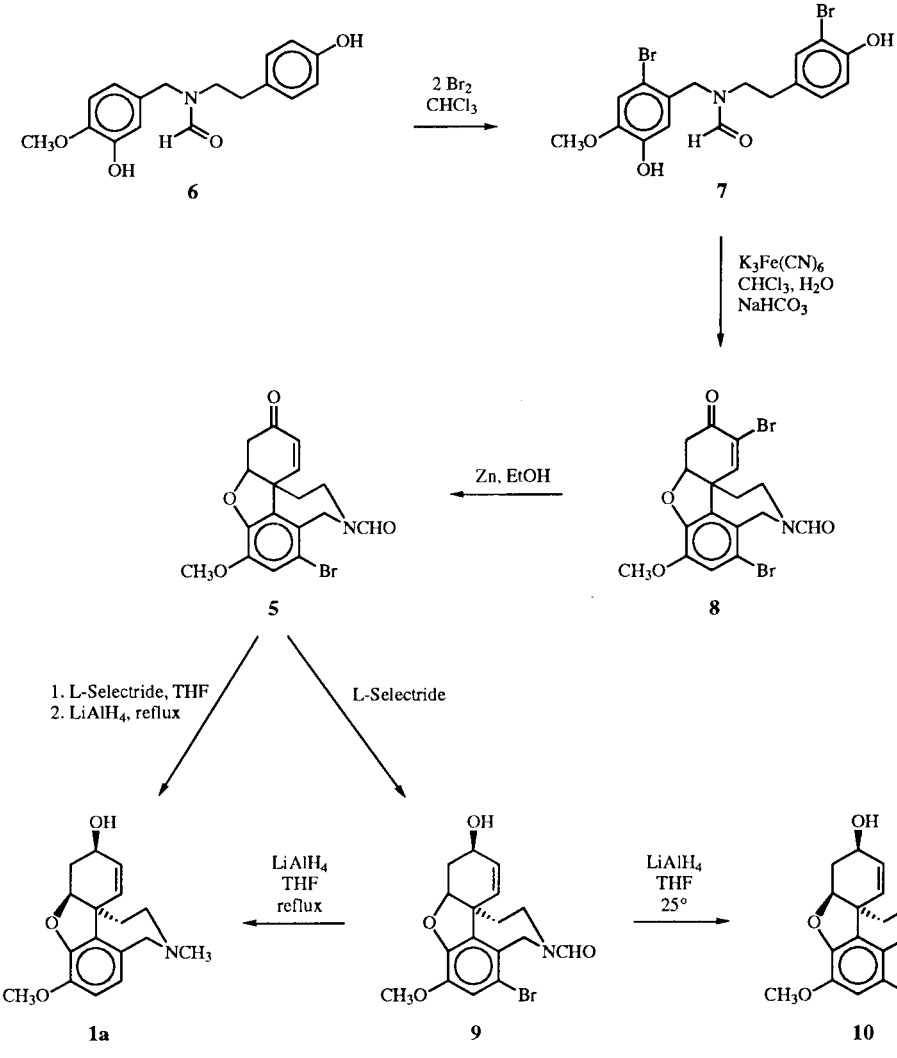
Introduction.

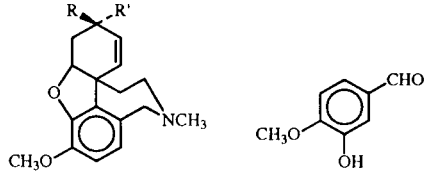
The enzyme choline acetyltransferase (ChAT) catalyzes the synthesis of acetylcholine (ACh) from choline. The loss of this enzyme in the hippocampus and cerebral cortex of Alzheimer's patients suggested an association between the degeneration of cholinergic neurons and senile dementia of the Alzheimer's type (SDAT) and, combined with other information, has led to the cholinergic hypothesis of SDAT [1]. The clinical improvement resulting from the treatment of Alzheimer's patients with the acetylcholinesterase (AChE) inhibitor tacrine hydrochloride (Cognex®) has generated interest in this class of agents [2]. Galanthamine (**1a**), an alkaloid originally isolated from *Galanthus woronowii* (Caucasian snowdrops) [3] and characterized as an AChE inhibitor [4,5,6,7], its epimer epigalanthamine (**1b**), and its oxidized analog narwedine (**1c**), have been evaluated as potential agents for treatment of Alzheimer's disease [8,9]. However, although **1a** is also found in *Galanthus nivalis* (common snowdrops) [10] and, in *Leucopium aestivum* [11], the supply of **1a** has been limited. The synthesis of racemic galanthamine [(±)-**1a**] was accomplished by Barton [10] employing a biomimetic route in which phenolic oxidative cyclization was the crucial step in the formation of the tetracyclic framework. The overall yield of this synthesis was extremely low. Numerous papers describing alternative routes for the synthesis of (±)-galanthamine [(±)-**1a**], epigalanthamine (**1b**), and narwedine (**1c**) have appeared in the chemical literature [8,9,11,12,13]. Most of these reports utilized the same biomimetic strategy, and involved multistep sequences resulting in very low overall yields. The best yield, 5%, was reported by Kametani [11]; however, an approximately 2% yield was reported by Vlahov [13] on repeating the Kametani procedure. There are three reports describing the preparation of the active enantiomer, (-)-galanthamine. In the original synthesis of (±)-**1a**, induced isomerization of (±)-narwedine (**1c**) followed by reduction afforded (-)-galanthamine [10]. Alternatively, fractional crystallization of diastereoisomeric dibenzoyltartrate salts of racemic galanthamine was reported [14] to provide (-)-galanthamine in low yield, and in a third procedure reported by Shimizu [12], (-)-galanthamine was prepared by an asymmetric synthesis from L-tyrosine in less then 1% overall yield. In 1988 we published an improved synthesis of (±)-galanthamine [15], which reduced the number of steps and afforded the final product in higher overall yield than in previous methods. We now present significant improvements to our reported synthesis of racemic galanthamine and describe an efficient resolution to give (+)- and (-)-**1a**.

Results and Discussion.

We previously reported that (±)-**1a** could be prepared in 11% overall yield starting with commercially available isovanillin (**2**) and tyramine (**3**) [15]. The critical step in the synthesis was the oxidative cyclization of *N*-(4-hydroxyphenethyl)-*N*-(2-bromo-5-hydroxy-4-methoxybenzyl)formamide (**4**) to (±)-2-bromo-*N*-formyl-*N*-nornarwedine (**5**). The best conditions involved treatment of **4** with potassium ferricyanide in a chloroform/sodium bicarbonate biphase which gave 21% of **5** [15]. Analysis of the reaction suggested that iron-chelation and the extent of partitioning of **4** in the reaction biphase were important factors. Since we expected increased chloroform solubility and steric hindrance to chelation to improve the cyclization, a relatively less polar analog of **4**, *N*-(3-bromo-4-hydroxyphenethyl)-*N*-(2-bromo-5-hydroxy-4-methoxybenzylformamide (**7**), was considered as a useful substrate. In fact, synthesis of **7** by bromination of *N*-(4-hydroxyphenethyl)-*N*-(3-hydroxy-4-methoxybenzyl)formamide (**6**) with two equivalents of bromine at -65° (93% yield), followed by oxidative cyclization gave (±)-2,7-dibromo-*N*-formyl-*N*-nornarwedine (**8**) in 38 to 43% yields, depending upon the scale. Selective debromination of **8** using activated zinc in ethanol provided a quantitative yield of **5**. In our previous study, we reported that lithium aluminum hydride reduction of **5** provided an 84% yield of a 1.7 to 1 mixture of (±)-galanthamine [(±)-**1a**] and (±)-epigalanthamine [(±)-**1b**] which could be separated by chromatography [15]. To

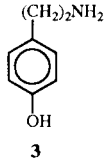
Scheme 1





1a, R = OH, R' = H
b, R = H, R' = OH
c, R,R' = O

2



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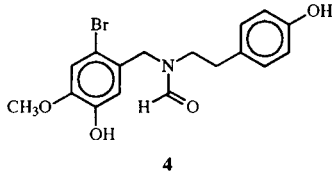

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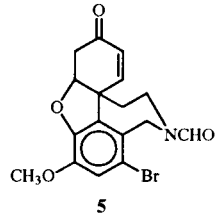


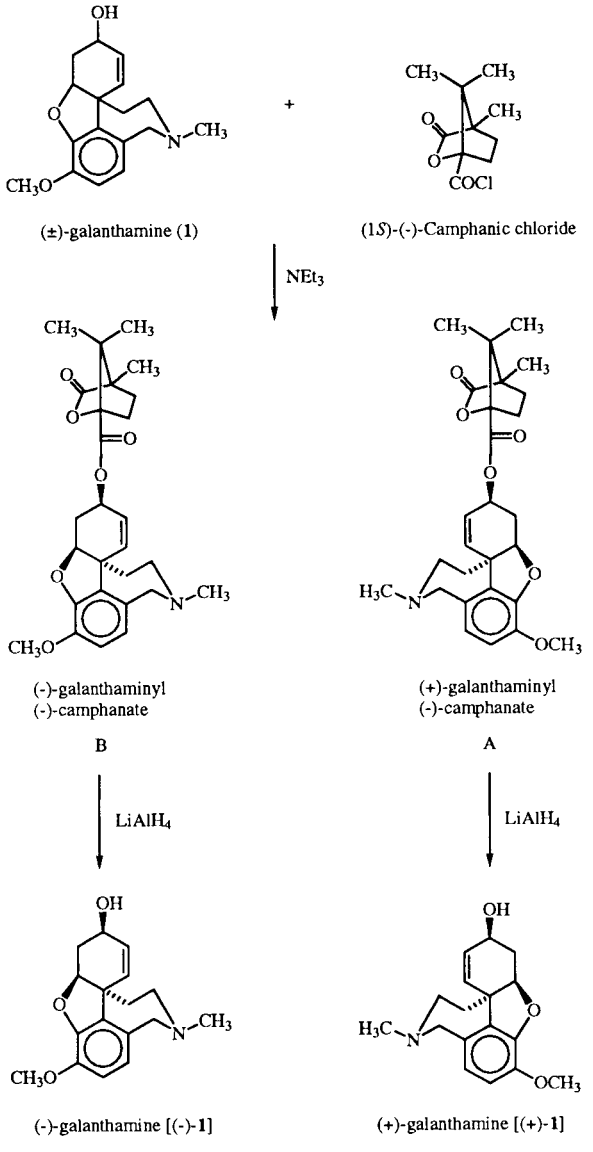
5

eliminate the formation of **1b**, we investigated other methods for the reduction of **5**. We found that use of L-Selectride in tetrahydrofuran at -78° proceeded stereoselectively to give exclusively (±)-1-bromo-*N*-formyl-*N*-norgalanthamine (**9**) in 76% yield. Lithium aluminum hydride reduction of **9** at 25° in refluxing tetrahydrofuran gives a mixture of (±)-1-bromogalanthamine (**10**) and (±)-galanthamine [(±)-**1a**]. Treatment of **5** with L-Selectride followed by lithium aluminum hydride affords (±)-**1a** directly in 69% yield. Thus, the procedure outlined in Scheme 1 provides a 24% overall yield of (±)-**1a**, with only **8** requiring chromatographic purification.

It had been reported that optically active narwedine (**1c**) could be prepared by the crystallization of racemic narwedine in the presence of optically active galanthamine (**1a**) or epigalanthamine (**1b**) [10]. In addition, the resolution of (±)-**1a** *via* its ditoluoyl-(+)-tartrate salt has also been reported [14]. However, since these reported resolutions did not appear practical to the preparation of the relatively large amounts of (+)- and (-)-**1a**, we investigated other methods of resolution.

Success was achieved by using fractional crystalliza-

Scheme 2



tion of galanthaminyl camphanate (Scheme 2). Thus, treatment of (±)-galanthamine with (1*S*)-(-)-camphanic chloride gave a mixture of diastereomeric galanthaminyl camphanate esters **A** and **B**. These esters were distinguishable by hplc; ester **B** coeluted with (-)-galanthaminyl camphanate (prepared from natural galanthamine). Fractional crystallization afforded the pure diastereomers **A** and **B** in 39% and 37% overall yield, respectively, and cleavage of the esters with lithium aluminum hydride proceeded in 96% yield to give (+)- and (-)-**1a**.

Conclusion.

We have developed a very efficient method, amenable to large-scale synthesis, for the preparation of (±)-galanthamine [(±)-**1a**] with overall yield of 20% from isovanillin (**3**) and tyramine (**4**). We have separated racemic galanthamine into its (1*S*)-camphanic diastereoisomeric esters and obtained both natural (-)- and unnatural (+)-galanthamine by lithium aluminum hydride removal of the acyl group.

EXPERIMENTAL

Melting points were determined on a Koffler hot stage. Proton magnetic resonance (^{1}H nmr) spectra were obtained on either a Bruker WM250 or AMX-500 spectrometer. Chemical shifts are reported in ppm, and δ values are relative to tetramethylsilane. All optical rotations were determined at the sodium D line using a Rudolph Research Autopol III Polarimeter (1-dm cell). Analysis (hplc) was carried out using a Macintosh-controlled system consisting of two Rainin pumps, a Gilson 811B Dynamic Mixer, Rheodyne injector and, Knauer Model 87 variable wavelength uv detector.

N-(3-Bromo-4-hydroxyphenethyl)-*N*-(2-bromo-5-hydroxy-4-methoxybenzyl)formamide (**7**).

To a solution of *N*-(4-hydroxyphenethyl)-*N*-(3-hydroxy-4-methoxybenzyl)formamide (**6**) [15] (10 g, 0.032 mole) in 500 ml of methanol/chloroform (5:1) at room temperature was added dropwise a solution of bromine (11.31 g, 0.071 mole) in chloroform. After the addition was complete, the mixture was stirred for several minutes, washed with water until the *p*H of the aqueous layer was 7, and the solvent was evaporated. The product was recrystallized from chloroform to give 12.20 g (80%) of the dibrominated formamide **7** as an off-white solid, mp 158-159°; ^{1}H nmr (500 MHz, deuteriochloroform + 3 drops DMSO-d_6): showed the amide to exist in two equally populated rotamers, δ (ppm) 2.62 (t, J = 7.6 Hz, 1, CH_2CH_2), 2.71 (t, J = 6.9 Hz, 1, CH_2CH_2), 3.33 (m, 2, CH_2CH_2), 3.84 (s, 1.5, OCH_3), 3.85 (s, 1.5, OCH_3), 4.32 (s, 1, $ArCH_2N$), 4.51 (s, 1, $ArCH_2N$), 6.77 (s, 0.5, H-2(Tyr)), 6.82 (s, 0.5, H-2(Tyr)), 6.87 (d, J = 8.0 Hz, 0.5, H-6(Tyr)), 6.88 (s, 1, ArH(isovan)), 6.92 (d, J = 8.0 Hz, 1, H-6(Tyr)), 7.01 (d, J = 8.0 Hz, 1, H-5(Tyr)), 7.23 (m, 1, ArH(isovan)), 8.00 (s, 0.5, CHO); 8.26 (s, 0.5, CHO); ^{13}C nmr (500 MHz, deuteriochloroform + 3 drops DMSO-d_6): showed two rotamers, δ (ppm) are shown in pairs, 30.7, 32.4 (CH_2), 42.4, 43.1 (CH_2), 47.1, 49.6 (CH_2), 54.9 (OCH_3), 108.8, 108.4 (ArH), 110.2, 110.4 (ArH), 114.4, 114.8 (ArH), 115.2, 115.5 (ArH), 115.3 (ArH), 125.8, 126.5 (ArH), 127.4, 127.6 (ArH), 128.8, 129.5 (ArH), 131.0, 131.1 (ArH), 146.8, 147.1 (ArH), 151.3, 151.5 (ArH), 161.5, 161.7 (CHO).

Anal. Calcd. for $C_{17}H_{17}Br_2NO_4 \cdot 0.5H_2O$: C, 43.62; H, 3.88; N, 2.99. Found: C, 43.43; H, 3.63; N, 2.99.

(±)-(4aα)-4a,5,9,10,11,12-Hexahydro-1,5-dibromo-11-formyl-3-methoxy-6*H*-benzofuro[3a,3,2-*e*,*f*][2]benzazepin-6-one [**8**, (±)-2,7-Dibromo-*N*-formyl-*N*-nornarwedine].

In a Morton flask a well-stirred mixture of 3000 ml of chloroform and a solution of potassium ferricyanide (54.60 g, 0.166 mole) in 547 ml 5% sodium bicarbonate was heated at 60° in a water bath for 2 hours. All at once the dibromoformamide **7** (15.0 g, 0.032 mole) was added, and the reaction mixture was stirred vigorously for 2 h at 60°. The chloroform layer was separated, and the aqueous layer was extracted with chloroform (1 x 300 ml). The combined organic phase was evaporated, the

residue was adsorbed onto 60 g of silica gel and purified by column chromatography (1% methanol/chloroform) to give 5.77 g (39%) of the dibromoenone **8** as a yellow foam: ^{1}H nmr shows two conformers (500 MHz, deuteriochloroform): δ (ppm) major, 2.05 (m, 1, H-9a or H-9e), 2.20 (ddd, J = 2.5, 2.5, 13.9 Hz, 1, H-9a or H-9e), 2.92 (dd, J = 3.5, 17.8 Hz, 1, H-5a or H-5e), 3.32 (m, 1, H-10a or H-10e), 3.41 (m, 1, H-5a or H-5e), 3.86 (s, 3, OCH_3), 4.41 (d, J = 16.9 Hz, 1, H-12a or H-12e), 4.59 (m, 1, H-10a or H-10e), 5.20 (d, J = 16.9 Hz, 1, H-12a or H-12e), 7.00 (s, 1, H-2), 7.25 (d, J = 1.8 Hz, 1, H-8), 8.20 (s, 1, CHO); minor, 2.05 (m, 1, H-9a or H-9e), 2.32 (ddd, J = .24, 2.4, 13.7 Hz, 1, H-9a or H-9e), 2.91 (dd, J = 3.5, 17.8 Hz, 1, H-5a or H-5e), 3.41 (m, 1, H-5a or H-5e), 3.711 (ddd, J = 15.0, 12.7, 2.1 Hz, 1, H-10a or H-10e), 3.85 (s, 3, OCH3), 4.04 (m, 2, H-10a or H-10e and H-12a or H-12e), 4.72 (m, 1, H-4), 5.75 (d, J = 15.9 Hz, 1, H-12a or H-12e), 7.00 (s, 1, H-2), 7.29 (d, J = 1.8 Hz, 1, H-8), 8.17 (s, 1, CHO); ^{13}C nmr (500 MHz, deuteriochloroform): δ (ppm) major, 34.6 (12), 37.2 (5), 40.9 (10), 51.9 (9), 52.8 (OCH_3), 56.4 (4a), 87.4 (4), 113.1 (vinyl), 116.8 (vinyl), 123.6 (Ar), 127.0 (Ar), 129.6 (Ar), 142.7 (Ar), 145.0 (Ar), 147.6 (Ar), 162.5 (CO), 185.7 (CO); minor, 37.2 (5), 38.0 (10), 46.2 (12), 46.5 (9), 52.8 (OCH_3), 56.4 (4a), 87.2 (4), 114.6 (vinyl), 117.0 (vinyl), 123.7 (Ar), 126.8 (Ar), 129.5 (Ar), 142.4 (Ar), 139.8 (Ar), 147.3 (Ar), 161.8 (CO), 185.7 (CO).

Anal. Calcd. for $C_{17}H_{15}Br_2NO_4 \cdot 0.5H_2O$: C, 43.81; H, 3.46; N, 3.00. Found: C, 43.73; H, 3.44; N, 2.93.

(±)-(4aα)-4a,5,9,10,11,12-Hexahydro-1-bromo-3-methoxy-11-formyl-6*H*-benzofuro[3a,3,2-*e*,*f*][2]benzazepin-6-one [**5**, (±)-2-Bromo-*N*-formyl-*N*-nornarwedine].

To a solution of the dibromoenone **8** (1.6 g, 0.0035 mole) in ethanol (50 ml) was added activated zinc powder (3.2 g, 0.05 g-atom). The mixture was refluxed until hplc (silica gel, 2% methanol/chloroform) showed completion of the reaction (overnight). The solution was filtered hot, and the zinc was washed thoroughly with hot ethanol. Evaporation of the solvent and separation of the residue on a silica gel column (2% methanol/chloroform) afforded the product as a white foam (1.3 g, 98%). The ^{1}H nmr was identical with that previously reported [15].

(±)-(4aα,6β)-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*e*,*f*][2]benzazepin-6-ol [**1a**, (±)-Galanthamine].

A solution of **5** (2 g, 0.0053 mole) in dry THF (60 ml) was cooled to -78°. After stirring at this temperature under dry argon for 20 minutes, 1 *M* L-Selectride (22 ml, 0.022 mole) was added dropwise, and the reaction was stirred at -78° for an additional 2 hours. The mixture was then allowed to come to 0°, and 1 *M* lithium aluminum hydride/THF (11 ml, 0.011 mole) was added dropwise. Stirring was continued overnight and excess of reducing agents was decomposed by sequential addition of water (1 ml) and 10% sodium hydroxide (5 ml). The inorganic salts were removed by filtration, and the filtrate was dried over magnesium sulfate. The residue remaining after evaporation of the solvent was dissolved in dry THF (20 ml), added to a 1 *M* solution of lithium aluminum hydride in THF (10 ml, 0.01 mole), and the mixture was refluxed for 24 hours. After cooling to 0°, the excess of lithium aluminum hydride was decomposed by addition of water (1 ml) and 10% sodium hydroxide (3 ml). The inorganic salts were removed by filtration and washed thoroughly with ethyl acetate. The combined organic filtrate and washings were dried over magnesium sulfate, and the solvent was evaporated. Chromatography on silica gel (3% methanol/chloroform) provided 1.3 g (70% yield) of (±)-galanthamine [(±)-**1a**], identical with previously obtained material [15].

Resolution of (±)-Galanthamine [(±)-**1a**].

To a solution of (±)-galanthamine [(±)-**1a**] (1.74 g, 0.006 mole) in a mixture of dry THF (20 ml) and chloroform (pentene stabilized, 75 ml) was added (1*S*)-(-)-camphanic chloride (2.00 g, 0.009 mole) and triethylamine (2 ml, 0.014 mole). After stirring overnight in the dark, the solvents were evaporated, and the residue dissolved in chloroform (100 ml). The resulting solution was washed with aqueous sodium bicarbonate (2 x 50 ml), dried and evaporated. Column chromatography (silica gel, methanol/chloroform 98:2) provided 2.45 g (86%) of a yellow, semi-crystalline product. Fractional crystallization from methanol afforded 1.1 g (45%) of isomer **A** and 1.05 g (43%) of isomer **B**. Both were found to be pure by hplc [Dynamax C_8 (25 cm x 8 mm), water/methanol 45:55 with 4.1 ml of diisopropylamine and 1.5 ml of acetic acid per liter at a flow rate of 2 ml/minute]. The retention times were 12.5 and 14.1 minutes for **A** and **B**, respectively.

Isomer **A**. (+)-Galanthaminyl (-)-Camphanate.

This compound had mp 196-198°; ^{1}H nmr (250 MHz, deuteriochloroform): δ 0.85 and 0.86 (two s, 6, 2 x CH_3 on C-7'), 1.06 (s, 3, CH_3 on C-4'), 1.55-1.65 (m, 1, H-9a), 1.65-2.10 (m, 3, 2 x H-5', H-6'), 2.05-2.22 (m, 2, H-9b and H-5a), 2.41 (s, 3, NCH_3), 2.52-2.68 (m, 1, H-6'), 2.65-2.72 (m, 1, H-5b), 3.00-3.15 (m, 1, H-10b), 3.23-3.38 (m, 1, H-10a), 3.67 (d, J = 15.1 Hz, 1, H-12b), 3.81 (s, 3, OCH_3), 4.11 (d, J = 15.1 Hz, 1, H-12a), 4.58 (m, 1, H-4), 5.45 (d-d, J = 4.7 Hz, 1, H-6), 5.95 (d-d, J = 4.7 Hz, J = 9.2 Hz, 1, H-7), 6.34 (d, J = 9.2 Hz, 1, H-8), 6.58 (d, J = 8.5 Hz, 1, H-2), 6.64 (d, J = 8.5 Hz, 1, H-1).

Anal. Calcd. for $C_{27}H_{34}NO_6$: C, 69.36; H, 7.11; N, 3.00. Found: C, 69.43; H, 7.10; N, 2.91.

Isomer B. (-)-Galanthaminyl (-)-Camphanate.

This compound had mp 163-165°; ^{1}H nmr (250 MHz, deuteriochloroform): δ 0.99 (s, 3, CH_3 on C-4'), 1.10 (s, 6, 2 x CH_3 on C-7'), 1.55-1.65 (m, 1, H-9a), 1.60-1.65 (m, 1, H-6'), 1.85-2.10 (m, 2, 2 x H-5'), 2.05-2.22 (m, 2, H-9a and H-5a), 2.40 (s, 3, NCH_3), 2.30-2.45 (m, 1, H-6'), 2.65-2.72 (m, 1, H-5b), 3.00-3.15 (m, 1, H-10b), 3.23-3.38 (m, 1, H-10a), 3.67 (d, J = 15.1 Hz, 1, H-12b), 3.81 (s, 3, OCH_3), 4.08 (d, J = 15.1 Hz, 1, H-12a), 4.58 (m, 1, H-4), 5.43 (d-d, J = 4.7 Hz, J = 4.7 Hz, 1, H-6), 5.92 (d-d, J = 4.7 Hz, J = 9.8 Hz, 1, H-7), 6.34 (d, J = 9.8 Hz, 1, H-8), 6.58 (d, J = 8.5 Hz, 1, H-2), 6.64 (d, J = 8.5 Hz, 1, H-1).

Anal. Calcd. for $C_{27}H_{34}NO_6$: C, 69.36; H, 7.11; N, 3.00. Found: C, 69.14; H, 7.11; N, 2.92.

(+)-Galanthamine [(+)-**1a**].

A solution of (+)-galanthaminyl (-)-camphanate (300 mg, 0.65 mmole) in dry THF (10 ml) was added to a solution of lithium aluminum hydride (5 mmoles) in THF (50 ml) at 0°. The mixture was stirred at 0° for 10 minutes and was then allowed to come to room temperature. Stirring was continued for 1 hour at which time 10% sodium hydroxide (0.2 ml) was added to decompose the excess lithium aluminum hydride. After the inorganic salts were removed by filtration, the filtrate was dried over magnesium sulfate and evaporated. The residue had ^{1}H nmr (250 MHz, deueteriochloroform): δ 1.52-1.58 (m, 1, H-9a), 1.96-2.06 (m, 1, H-5a), 2.01-2.11 (m, 1, H-9b), 2.38 (s, 3,

NCH_3), 2.51 (bs, 1, OH), 2.60-2.70 (m, 1, H-5b), 2.93-3.08 (m, 1, H-10b), 3.24-3.35 (m, 1, H-10a), 3.66 (d, J = 15.1 Hz, 1, H-12b), 3.81 (s, 3, OCH_3), 4.07 (d, J = 15.1 Hz, 1, H-12a), 4.05-4.17 (m, 1, H-6), 4.55-4.64 (m, 1, H-4), 5.97 (d-d, J = 10.0 Hz, J = 4.7 Hz, 1, H-7), 6.06 (d, J = 10.0 Hz, 1, H-8), 6.61 (d, J = 8.1 Hz, 1, H-2), 6.65 (d, J = 8.1 Hz, 1, H-1).

The hydrochloride salt was prepared by passing dry hydrogen chloride through a methanolic solution of the free base. The product was recrystallized from methanol/ether providing 200 mg (96%) of (+)-galanthamine hydrochloride as white crystals, mp 245° dec; $[\alpha]^{25}_{589}$ = + 107.0° (c 1.97, methanol).

Anal. Calcd. for $C_{17}H_{22}ClNO_3 \cdot 1/4H_2O$: C, 62.19; H, 6.86; N, 4.27. Found: C, 62.02; H, 6.76; N, 4.12.

(-)-Galanthamine [(-)-**1**].

The procedure described for (+)-galanthamine was followed. From 6.7 g (0.014 mole) (-)-galanthaminyl (-)-camphanate, 4.0 g (97%) of semicrystalline (-)-galanthamine was obtained. The ^1H nmr was identical to the spectrum of (+)-**1**.

The hydrochloride salt was prepared from 2.2 g of (-)-**1** to give 2.3 g (93%) of (-)-**1**•HCl: mp 249-249.5°; $[\alpha]^{25}_{589}$ -106.6° (c 1.25, methanol), lit [10] mp 253-257°, $[\alpha]_D$ -103° (c 0.6, water).

Anal. Calcd. for $C_{17}H_{22}ClNO_3 \cdot 1/2H_2O$: C, 61.35; H, 6.91; Cl, 10.67; N, 4.21. Found: C, 61.58; H, 6.86; Cl, 10.54; N, 4.16.

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