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Commercial Scale Process of Galanthamine Hydrobromide Involving Luche Reduction: Galanthamine Process Involving Regioselective 1,2-Reduction of α,β-Unsaturated Ketone

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ABSTRACT: Effect of lanthanide chloride in the Luche regioselective 1,2-reduction of 1-bromo-11-formyl-nornarwedine (**5**) was studied. Thus, 1-bromo-11-formyl-nornarwedine (**5**) is reduced with sodium borohydride in the presence of lanthanide chloride to yield 1-bromo-11-formyl-galanthamine isomers (**6**), which is a key intermediate for the commercial production of highly pure galanthamine hydrobromide (**1**), a modern drug against Alzheimer's disease.

INTRODUCTION

Galanthamine (**1**) is a tertiary alkaloid which is chemically known as [4*aS*,6*R*,8*aS*]-4*a*,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-ef][2]benzazepine-6-ol. The chemical structure of galanthamine hydrobromide (**1**) is as shown in Figure 1.

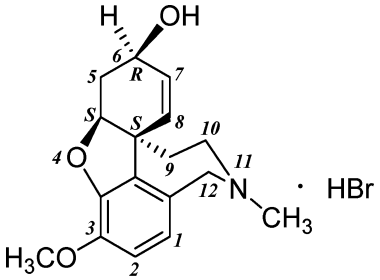

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Figure 1. Structure of galanthamine hydrobromide.

The molecular structure of galanthamine has three chiral centers, and hence, theoretically eight stereoisomers are possible. However, due to steric constraints, it could exist only in two racemic pairs (four stereoisomers), viz., [(4*aS*,6*R*,8*aS*)-isomer, (−)-galanthamine] (**1a**), [(4*aR*,6*S*,8*aR*)-isomer, (+)-galanthamine] (**2**), [(4*aS*,6*S*,8*aS*)-isomer, (−)-epigalanthamine] (**3**), and [(4*aR*,6*R*,8*aR*)-isomer, (+)-epigalanthamine] (**4**) (Figure 2). The naturally occurring and therapeutically active isomer is (−)-galanthamine (**1a**), which has the configuration of (4*aS*,6*R*,8*aS*).

(−)-Galanthamine is a competitive and reversible acetylcholinesterase inhibitor, which is approved for the treatment of mild to moderate Alzheimer's disease and is under development for other indications such as vascular dementia,

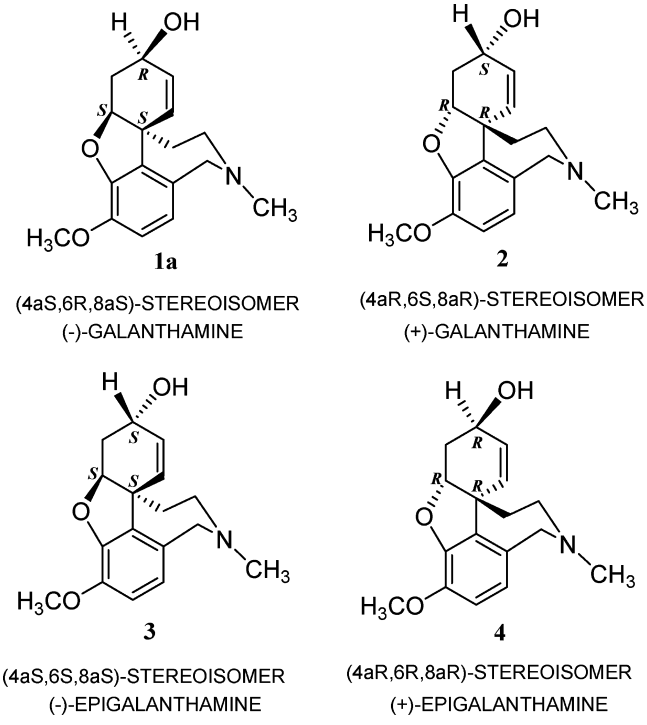

Figure 2. Structures of galanthamine stereoisomers.

Alzheimer's disease with cerebrovascular disease, mild cognitive impairment, schizophrenia, Parkinson's disease, and other diseases wherein cognition is impaired.

(−)-Galanthamine is usually isolated from plants belonging to the Amaryllidaceae family, such as the daffodil (*Narcissus*

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pseudomarcissus), snowdrop (*Galanthus nivalis*), and snowflake (*Leucojum aestivum*). These plants have (−)-galanthamine in concentrations up to 0.3% with only small amounts of companion alkaloids, so that the extraction method can be used. This process of extraction is expensive and time-consuming, hence not feasible for industrial scale operations.[1]

Barton and Kirby first reported the reduction of (−)-narwedine (**9**) by lithium aluminum hydride to prepare (−)-galanthamine along with (−)-epigalanthamine.[2] Szeczyk et al. prepared (−)-galanthamine along with (+)-galanthamine, i.e., (±)-galanthamine from 1-bromo-11-formyl-nornarwedine (**5**) and separated both (−)-galanthamine and (+)-galanthamine by resolving (±)-galanthamine with (1*S*)-(−)-camphanic chloride followed by column chromatography and fractional crystallization from methanol.[3] Chaplin et al. prepared (−)-galanthamine by dynamic diastereomeric salt resolution of (±)-narwedine (**8**) with di-*p*-toluoyl-D-tartaric acid salt of (−)-narwedine (**9**) and subsequently converting to (−)-galanthamine by using L-selectride.[4] Many other synthetic approaches have been reported in the literature for the preparation of (−)-galanthamine.[5−8]

We chose 1-bromo-11-formyl-nornarwedine (**5**) as a key intermediate to develop commercial scale process for galanthamine hydrobromide as shown in the Scheme 1. Conversion of 1-bromo-11-formyl-nornarwedine (**5**) to galanthamine involves 1,2-reduction of cyclic enone group. In this present work, we have studied the 1,2-reduction of cyclic enone of 1-bromo-11-formyl-nornarwedine (**5**) to yield 1-bromo-11-formyl-galanthamine isomers (**6**) and further converting these 1-bromo-11-formyl-galanthamine isomers (**6**) to (−)-galanthamine hydrobromide (**1**), as shown in Scheme 1.

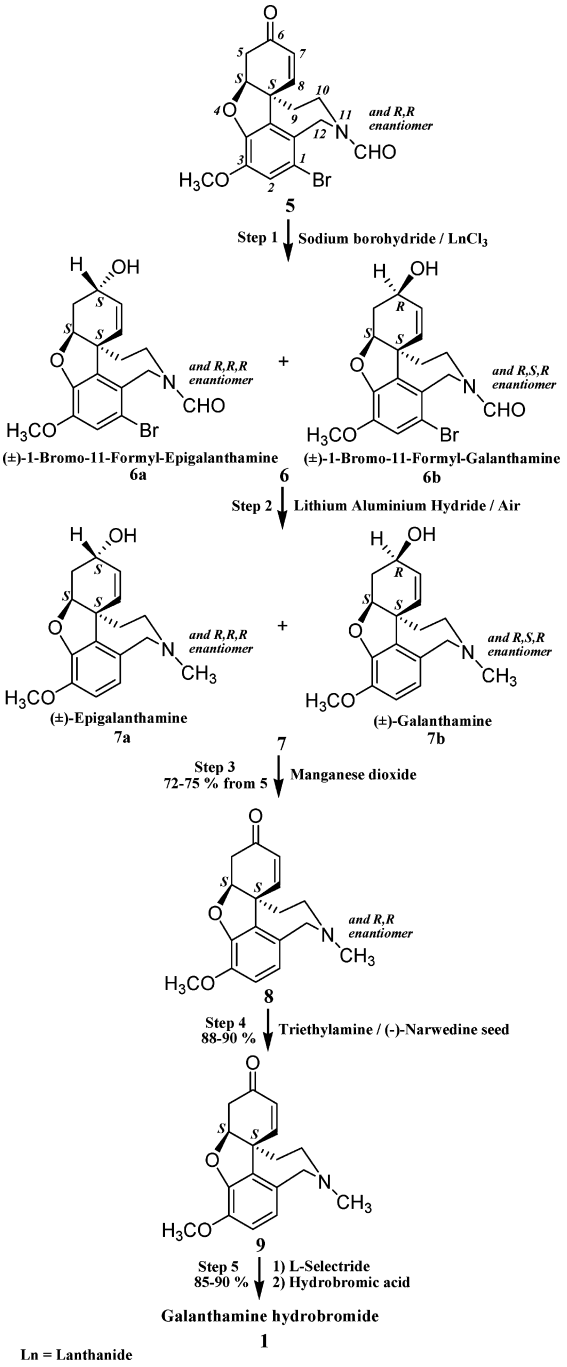
RESULTS AND DISCUSSION

Synthesis of galanthamine involves a complex chemistry and requires selective reagents to bring about the desired transformations. The use of reagents quantity, catalyst, and reaction conditions plays an important role to achieve desired regioselective intermediates with lesser amount of impurities. Reduction of keto group in 1-bromo-11-formyl-nornarwedine (**5**) is bound to form secondary alcohol at C-6 along with the reduction of double bond at C-7. This would result in the production of galanthamine final product contaminated with C-7 double bond reduced alcohol (1,4-reduction product) which is known as lycoramine (**11**)[9−11] as shown in Scheme 2.

In this scenario, it is required to find a synthetic strategy for the regioselective reduction of keto group in 1-bromo-11-formyl-nornarwedine (**5**), without disturbing the double bond at C-7 to produce 1-bromo-11-formyl-galanthamine isomers (**6**) and subsequently conversion of **6** to highly pure galanthamine with the least formation of impurities.

The pharmacopoeial monograph of galanthamine hydrobromide prescribed the limit for lycoramine impurity to <0.35% (in U.S. pharmacopoeia) and <0.4% (in European pharmacopoeia) in the active substance of the drug, galanthamine hydrobromide (**1**).[12] The reduction of the keto group of 1-bromo-11-formyl-nornarwedine (**5**) was performed initially with sodium borohydride and it was observed that the undesired reduction of the C-7 double bond occurred simultaneously with reduction of the keto group. The double bond reduced alcohol was obtained around ∼75%, which is identified as 1,4-addition product 1-bromo-11-formyl-lycoramine (**10**).

Scheme 1



From these experiments, we concluded that sodium borohydride predominantly favors 1,4-reduction yielding 1-bromo-11-formyl-lycoramine (**10**) rather than the desired 1,2-reduction products, 1-bromo-11-formyl-galanthamine isomers (**6**). Therefore, to prevent the formation of this undesired intermediate, we decided to adopt the conditions of the Luche reduction in which regioselective reduction was carried out using sodium borohydride in the presence of lanthanide halide such as cerium(III) chloride heptahydrate. The lanthanide chlorides are useful catalysts and are reported to result in regioselective 1,2-reduction of α,β-unsaturated ketone.[13] Initial experiments were performed by using cerium(III) chloride heptahydrate along with sodium borohydride, it was observed that the formation of the undesired intermediate was drastically

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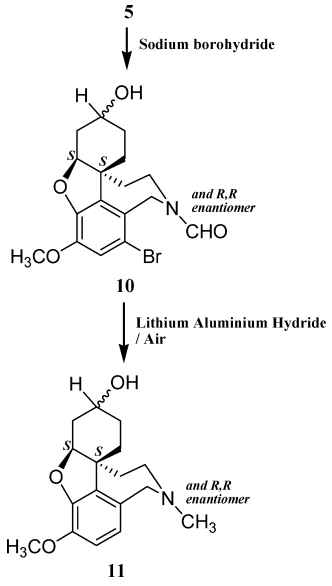
Scheme 2

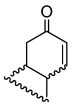
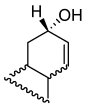
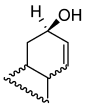
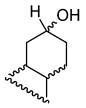


reduced and the reaction yielded the desired intermediate 1-bromo-11-formyl-galanthamine isomers (**6**).

Initially, we have studied the effect of solvent in this Luche regioselective reduction of 1-bromo-11-formyl-nornarwedine (**5**) by using different solvents such as methylene chloride, methanol, ethanol, isopropyl alcohol, acetone, and mixtures such as methanol and methylene chloride (1:1), methanol and tetrahydrofuran (1:1), and methanol and water (1:1). It was reported that protic solvents favored the Luche reduction.[14−18] However, solubility of 1-bromo-11-formyl-nornarwedine (**5**) in methanol was found to be poor, so the Luche reaction in methanol was slow and incomplete. Hence, we added methylene chloride or THF as cosolvent to increase the solubility of 1-bromo-11-formyl-nornarwedine (**5**). It has been observed that, among the solvents tried, the mixture of methylene chloride and methanol (1:1) is the best combination to obtain the desired regioselective transformation of **5** and to obtain highly pure 1-bromo-11-formyl-galanthamine isomers (**6**). When we have carried out the Luche reduction of **5** in methylene chloride alone, it was observed that the reaction failed to proceed and this indicates that methanol, a protic solvent, is a requirement for Luche reduction. Other protic solvents such as ethanol and isopropyl alcohol failed to give the desired products, 1-bromo-11-formyl-galanthamine isomers (**6**). So, we presume that the reduction reaction failed to proceed due to the poor solubility of **5** in the respective solvent system. The results obtained by the use of different solvents and combinations are summarized in Table 1.

The nature of metallic ion was found to be an important factor for the regioselective reduction of 1-bromo-11-formyl-nornarwedine (**5**). Our aim was to study the effect of lanthanide ions in the Luche reduction of 1-bromo-11-formyl-nornarwedine (**5**). In addition, we proposed to study the reduction of 1-bromo-11-formyl-nornarwedine (**5**) with sodium borohydride in the presence of other metal ions such as Cu^{1+}, Fe^{3+}, and Zn^{2+}. Replacement of the lanthanide with Cu^{1+} ion favored 1,4- reduction rather than 1,2-reduction of 1-bromo-11-formyl-nornarwedine (**5**). In the presence of other ions such as Fe^{3+} and Zn^{2+}, complete decomposition of the reducing agent occurred very rapidly and the unreacted starting material remained as the major component of the reaction mixture. We have carried out the Luche reduction in the presence of Lanthanide ions such as lanthanum, cerium, neodymium, samarium, europium, terbium, and ytterbium. The results obtained by use of different metal salts are summarized in Table 2. Among the lanthanide chlorides tested, cerium chloride is the most favored for economical reasons, as cerium is one of the less expensive rare earth elements. For the same reasons, we first optimized the quantity of $CeCl_3 \cdot 7H_2O$ required for the Luche reduction of 1-bromo-11-formyl-

Table 1. Effect of Solvent on Reduction of 1-Bromo-11-Formyl-Nornarwedine (5)

	% of Product[c]			
	Enone	1,2 addition products		1,4 addition product
Solvent used				
	1-Bromo-11-Formyl-Nornarwedine[d]	(±)-1-Bromo-11-Formyl-Epigalanthamine[d]	(±)-1-Bromo-11-Formyl-Galanthamine[d]	1-Bromo-11-Formyl-Lycoramine[d]
	(5)	**(6a)**	**(6b)**	**(10)**
MDC[a]	89.90	3.17	3.91	0.85
MeOH[a]	28.18	52.93	18.13	Not detected
MDC+MeOH[b]	0.02	74.03	25.15	Not detected
EtOH[a]	46.95	36.85	15.59	Not detected
IPA[a]	95.80	2.26	1.23	Not detected
THF+MeOH[a]	4.43	67.95	26.89	0.32
MeOH+H_2O[a]	88.45	7.66	2.88	Not detected
Acetone[a]	95.71	1.00	0.82	6.80

[a]Reaction conditions: 1.0 mol equiv of $CeCl_3$ and 1.0 mol equiv of $NaBH_4$; 1 h at 0−5 °C. [b]Reaction conditions: 0.5 mol equiv of $CeCl_3$ and 1.0 mol equiv of $NaBH_4$; 1 h at 0−5 °C. [c]Chromatographic purity (by HPLC, by area normalization). [d]HPLC sum of two rotamers area percentage.

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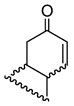
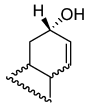
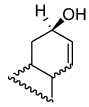
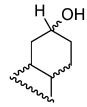
Table 2. Reduction of 1-Bromo-11-Formyl-Nornarwedine (5) in the Presence of Metallic Salts[e]

	% of Product[c]			
	Enone	1,2 addition products		1,4 addition product
Metallic salt used				
	1-Bromo-11-Formyl-Nornarwedine[d]	(±)-1-Bromo-11-Formyl-Epigalanthamine[d]	(±)-1-Bromo-11-Formyl-Galanthamine[d]	1-Bromo-11-Formyl-Lycoramine[d]
	(5)	(6a)	(6b)	10
Without salt	Not detected	23.03	17.61	58.46
$CeCl_3.7H_2O$[a]	0.02	74.03	25.15	Not detected
$LaCl_3.7H_2O$[a]	0.02	72.22	26.93	Not detected
$NdCl_3.6H_2O$[a]	0.03	73.19	26.16	Not detected
$SmCl_3.6H_2O$[a]	0.03	74.53	24.58	Not detected
$EuCl_3.6H_2O$[a]	0.02	74.44	24.77	Not detected
$TbCl_3.6H_2O$[a]	0.01	74.38	22.65	Not detected
$YbCl_3.6H_2O$[a]	0.01	79.29	19.09	Not detected
CuI[b]	Not detected	9.57	2.73	71.58
$FeCl_3$[b]	97.61	0.42	0.24	Not detected
$ZnBr_2$[b]	63.90	4.93	3.00	6.22

[a]0.5 mol equiv of metallic salt. [b]1.0 mol equiv of metallic salt. [c]Chromatographic purity (by HPLC, by area normalization). [d]HPLC sum of two rotamers area percentage. [e]Reaction conditions: 0.10 M solution of enone (5) in a 1:1 mixture of methanol and methylene chloride; 1.0 mol equiv of $NaBH_4$; 30 min at 0−5 °C.

nornarwedine (5). It was found that 0.5 mol equiv of $CeCl_3{\cdot}7H_2O$ is sufficient to carry out the regioselective Luche reduction of 1-bromo-11-formyl-nornarwedine (5) rather than an equimolar quantity of $CeCl_3{\cdot}7H_2O$.

Based on the above experiments, we concluded the optimized conditions of the Luche reduction of 1-bromo-11-formyl-nornarwedine (5) to obtain maximum yield and highest regioselectivity: the 1-bromo-11-formyl-nornarwedine (5) is reduced with 1 mol equiv of $NaBH_4$ in the presence of 0.5 mol equiv of cerium(III) chloride heptahydrate in solvent mixture of methylene chloride and methanol (1:1 ratio) at 0−5 °C. Further, the desired allylic alcohols and 1-bromo-11-formyl-galanthamine isomers (6) were obtained with high chromatographic purity (>99% by HPLC).

The next task was converting of 1-bromo-11-formyl-galanthamine isomers (6) to the drug compound galanthamine hydrobromide (1). Reduction of formyl group and debromination of the intermediates 1-bromo-11-formyl-galanthamine isomers (6) may be achieved by treating with lithium aluminium hydride (LAH). However, debromination of the intermediates 1-bromo-11-formyl-galanthamine isomers (6) was incomplete when they were treated either with excess lithium aluminium hydride (LAH) at reflux temperature or by continuation of the reaction for several hours. However, debromination is successfully completed by purging of air into the reaction mass as reported in the literature.[5,19] Thereafter, galanthamine isomer (7) intermediates were isolated and further oxidized with freshly prepared active manganese dioxide to get (±)-narwedine intermediate (8). We have studied different grades of manganese dioxide prepared by different literature methods.[20] The best results were obtained by using active manganese dioxide prepared by the procedure given in Vogel's textbook[21] and acetone was used as the reaction solvent to obtain the desired purity of the product (±)-narwedine (8). (±)-Narwedine is further subjected to kinetic dynamic resolution induced by (−)-narwedine seed in an aqueous ethanolic solution containing triethylamine to obtain a single isomer (−)-narwedine (9). This kinetic dynamic resolution was reported to be carried out at 40−42 °C for 16 h to 7 days.[22−24] We have optimized the process conditions and the resolution of (±)-narwedine was achieved effectively in aqueous ethanolic solution of (±)-narwedine containing triethylamine at 70−73 °C with (−)-narwedine seed and by gradual cooling over 3−4 h period to achieve desired isomer (9) of >99.5% e.e. (by Chiral HPLC) as well as >99.5% chromatographic purity (by HPLC).

In the final step of the synthesis, diastereoselective reduction of (−)-narwedine (9) was achieved by treating it with L-selectride in tetrahydrofuran at lower temperature conditions to produce (−)-galanthamine.[22] We have studied the behavior of this reaction at different temperatures and the best result was obtained when this reaction was carried out at −50 to −45 °C. After aqueous workup of the reaction mixture, (−)-galanthamine base was obtained and it was further treated with hydrobromic acid in aqueous ethanol to furnish the desired final product, (−)-galanthamine hydrobromide (1) with the chromatographic purity of >99.7% (by HPLC), chiral purity of >99.9% (by HPLC), and the 1,4-reduction product, lycoramine, is controlled to <0.3% (by HPLC).

The above optimized process was successfully scaled up to 60 kg input of 1-bromo-11-formyl-nornarwedine (5), and (−)-galanthamine hydrobromide obtained from this process meets all desired quality parameters.

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CONCLUSION

An efficient, scalable method for the preparation of galanthamine hydrobromide (**1**) involving Luche reduction was elaborated. Luche reduction of 1-bromo-11-formyl-nornarwedine (**5**) gives 1-bromo-11-formyl-galanthamine isomers (**6**), and the process for conversion of 1-bromo-11-formyl-galanthamine isomers (**6**) is optimized to obtain highly pure galanthamine hydrobromide (**1**) drug active substance.[25] Galanthamine hydrobromide is obtained with an overall yield of 56% from 1-bromo-11-formyl-nornarwedine (**5**).

EXPERIMENTAL SECTION

General. 1-Bromo-11-formyl-nornarwedine (**5**) was prepared from readily available Isovanilline and Tyramine according to the literature procedure.[3] Lanthanide salts of laboratory grades were used which were procured from Central Drug House (P) Ltd., New Delhi, India. Other reagents and solvents were obtained from commercial suppliers and used without further purification. Narwedine and narwedine salts are classified as moderate to severe sensitizing agents and, after prolonged exposure, cause severe allergic skin reactions.[5] For this reason, suitable personal protective equipment should be used while handling. Melting points were determined on a Polmon MP96 capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz spectrometer in DMSO-d_6; chemical shift data are reported in ppm from the internal standard TMS. The reaction monitoring and chromatographic purity (area percentage) were analyzed qualitatively by HPLC on Waters 2695 with 2996 PDA detector using Phenomenex Gemini C_{18} column (250 mm × 4.6 mm, 5 μ). HRMS were taken on Xevo G2 Q TOF HRMS instrument with electrospray ionization (positive) mode in units of mass (m/z). The IR spectra were recorded on KBr pellets on Perkin-Elmer FTIR (spectrum one) spectrophotometer.

*General Procedure for the Preparation of 1-Bromo-4a,5,9,10-tetrahydro-3-methoxy-6-hydroxy-6H-benzofuro-[3a,3,2-ef][2]benzazepin-11(12H)carboxaldehyde Isomers [(±)-1-Bromo-11-Formyl-Epigalanthamine (**6a**) and (±)-1-Bromo-11-Formyl-Galanthamine (**6b**) mixture](**6**).* A mixture of 1-Bromo-4*a*,5,9,10-tetrahydro-3-methoxy-6-oxo-6*H*-benzofuro[*3a,3,2-ef*]-[2]benzazepin-11(12*H*)carboxaldehyde (1-bromo-11-formyl nornarwedine) (**5**, 200 g, 0.529 mol), lanthanide chloride ($LnCl_3{\cdot}nH_2O$, 0.5 mol equiv) was taken in methylene chloride/methanol mixture (1:1 v/v, 6000 mL). The mixture was stirred at 25−30 °C for 30 min and cooled to 0−5 °C. Sodium borohydride (20g, 0.529 mol) was added in portions at 0−5 °C for 30 min and the completion of the reaction was monitored by qualitative HPLC analysis. Water (1200 mL) was added to the reaction mixture and then concentrated under reduced pressure to a volume of ∼2500 mL. The concentrated mass was extracted with methylene chloride (3000 mL) and washed with water (400 mL). The methylene chloride extract was concentrated under reduced pressure to obtain mixtures of (±)-1-bromo-11-formyl-epigalanthamine and (±)-1-bromo-11-formyl-galanthamine mixture (**6**) as a viscous oily mass (210 g).

Chromatographic purity: 99.13% (by HPLC, sum of four peaks corresponding to **6a** and **6b**). IR (KBr) (cm^{-1}): 3431, 1654, 1617−1491. HRMS: m/z = 380.0493/382.0475 [M + H]$^{+}$. ^{1}H NMR (DMSO-d_6, mixture of two rotamers): δ 1.23−2.45 (m, 4H), 3.60 (m, 1H), 3.75 (s, 3H), 4.15−4.23 (m, 2H), 4.44−4.61 (m, 2H), 4.90−4.95 (m, 1H), 5.73−5.76 (m, 1H), 6.05−6.11 (m, 1H), 6.98−7.02 (d, 1H), 8.05 (d, 1H).

*Preparation of 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol isomers [(±)-Epigalanthamine (**7a**) and (±)-Galanthamine (**7b**) mixture](**7**).* A solution of 1-Bromo-4*a*,5,9,10-tetrahydro-3-methoxy-6-hydroxy-6*H*-benzofuro[*3a,3,2-ef*][*2*]benzazepin-11-(12*H*)carboxaldehyde isomers [(±)-1-bromo-11-formyl-epigalanthamine and (±)-1-bromo-11-formyl-galanthamine mixture] (**6**, 210 g, 0.553 mol) in tetrahydrofuran (2000 mL) was added to a suspension of lithium aluminium hydride (80.40 g, 1.84 mols) in tetrahydrofuran (2000 mL) at 25−50 °C. The reaction mixture was stirred at reflux (55−60 °C) for about 1 h and reaction mixture was cooled to 25−30 °C. Air (∼80% N_2, ∼20% O_2) was purged into the reaction mass with a flow rate of 600 mL/min while stirring at 25−30 °C for 2 h, and completion of the reaction was monitored by qualitative HPLC analysis . The reaction mass was quenched by sequential addition of DM water (80 mL), 15% (w/v) sodium hydroxide solution (80 mL), and DM water (250 mL). The reaction mass was stirred at 50−55 °C for 1 h and the inorganic residue was removed by filtration. The filtrate was concentrated under reduced pressure and the product was extracted with chloroform (2000 mL). The chloroform extract was washed with water (400 mL) and concentrated under reduced pressure to obtain (±)-epigalanthamine and (±)-galanthamine mixture (**7**) as a pale yellow semisolid mass (165 g).

Chromatographic purity: 95.33% (by HPLC, sum of two peaks corresponds to **7a** and **7b**). IR (KBr) (cm^{-1}): 3388, 1623, 1508, 1444. HRMS: m/z = 288.1609 [M + H]$^{+}$. ^{1}H NMR (DMSO-d_6): δ 1.35−2.03 (m, 2H), 2.07−2.18 and 2.43 (m, 2H), 2.21 (bs, 3H) 2.88 and 3.14 (dd, 2H), 3.52 and 4.04 (dd, 2H), 3.70 (d, 3H), 4.21 (d, 1H), 4.46 (brt, 1H), 4.93 (d, 1H, exchangeable with D_2O), 5.67 (m, 1H), 5.99 (m, 1H), 6.51and 6.65 (2m, 1H each).

*Preparation of (±)-4a,5,9,10,11.12-Hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-one [(±)-Narwedine] (**8**).* To a mixture of 4*a*,5,9,10,11.12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[*3a,3,2-ef*][*2*]-benzazepin-6-ol isomers [(±)-Epigalanthamine and (±)-Galanthamine mixture] (7, 165 g, 0.575 mols) in acetone (6000 mL), active manganese dioxide (600 g, 6.9 mol) was added and stirred for 20 h at 25−30 °C. The completion of the reaction was monitored by qualitative HPLC analysis. After the completion of the reaction, the inorganic residue was removed by filtration, and the filtrate was concentrated under reduced pressure at 40−50 °C. The concentrated mass was triturated with ethyl acetate (200 mL) for 1 h at 25−30 °C and the product was filtered, washed with ethyl acetate (100 mL), and dried at 50−55 °C under reduced pressure to yield (±)-Narwedine (**8**) as a pale yellow powder (110 g, 72.94% yield from **5**).

Chromatographic purity: 99.29% (by HPLC). (−)-Narwedine content: 49.43% (by chiral HPLC) and (+)-Narwedine content: 50.57% (by chiral HPLC). Mp: 186−189 °C. IR (KBr) (cm^{-1}): 1682, 1620, 1507, 1439. HRMS: m/z = 286.1454 [M + H]$^{+}$. ^{1}H NMR (DMSO-d_6): δ 1.81 and 2.16 (dd, 2H), 2.28 (s, 3H), 2.76 and 3.01 (dd, 2H), 3.07 and 3.18 (dd, 2H), 3.33 and 4.13 (dd, 2H), 3.65 (s, 3H), 4.71 (d, 1H), 5.90 (d, 1H), 6.63 and 6.76 (2d, 1H each), 7.14 (d, 1H).

*Preparation of [4aS,8aS]-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepin-6-one [(−)-Narwedine](**9**).* (±)-4*a*,5,9,10,11.12-Hexahydro-3-

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methoxy-11-methyl-6*H*-benzofuro-[*3a,3,2-ef*][2]benzazepin-6-one [(±)-Narwedine] (**8**, 95 g, 0.333 mol) was dissolved in a mixture of DM water (72.2 mL), ethanol (1381 mL), and triethylamine (161.5 mL) at 75−80 °C. Thereafter, the reaction mixture was cooled to 70−73 °C and (−)-Narwedine (1.9 g) was added as seed to the solution. The resulting mixture was gradually cooled to 40−42 °C and stirred at the same temperature for 3 h for complete kinetic dynamic resolution of (−)-Narwedine. The completion of the reaction was monitored by qualitative chiral HPLC analysis. After completion of the reaction, the slurry mass was cooled to 25−30 °C, and the product filtered and dried at 55−65 °C under reduced pressure to get (−)-Narwedine (**9**) as cream-colored crystalline powder (85.5 g, 90% yield).

Chromatographic purity: 99.90% (by HPLC). (+)-Narwedine content: 0.20% (by chiral HPLC). Mp 190−192 °C. $[\alpha]_D^{25}$ (c = 1, in $CHCl_3$): −411.1°. IR (KBr) (cm^{-1}): 1682, 1620, 1507, 1439. HRMS: m/z = 286.1453 $[M + H]^+$. ^1H NMR (DMSO-d_6): δ 1.81 and 2.12 (dd, 2H), 2.28 (s, 3H), 2.76 and 2.96 (dd, 2H) 3.01 and 3.18 (dd, 2H), 3.60 and 4.13 (dd, 2H), 3.71 (s, 3H), 4.71(brs, 1H), 5.90 (d, 1H), 6.63 and 6.76 (2d, 1H each), 7.14 (d, 1H).

*Preparation of [4aS,6R,8aS]-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a,3,2-ef][2]-benzazepine-6-ol [(−)-Galanthamine hydrobromide] (**1**).* Lithium tri-*sec*-butyl borohydride [L-selectride] (1 molar solution in THF, 433 mL) was added dropwise to a suspension of [*4aS,8aS*]-4*a*,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[*3a,3,2-ef*][2]benzazepin-6-one [(−)-Narwedine] (**9**, 65 g, 0.228 mol) in THF (1300 mL) at −50 to −45 °C for 1 h and the reaction mixture stirred at −50 to −45 °C for 3 h. The completion of the reaction was monitored by qualitative HPLC analysis. The reaction mixture was quenched by adding aqueous hydrogen peroxide (40% w/w, 110.5 g, 1.3 mol), and the excess peroxide was destroyed by stirring the reaction mixture with aqueous sodium sulfite solution. The reaction mixture was concentrated under reduced pressure and the product was extracted with toluene (1625 mL). The organic extract was concentrated under reduced pressure at 50−55 °C to obtain galanthamine base as an oily mass, and galanthamine base was dissolved in a mixture of ethanol (260 mL) and DM water (65 mL). Aqueous hydrobromic acid (48% w/w, 40.42 g, 0.24 mols) was added to the galanthamine base solution and stirred at 15−20 °C for 2 h to obtain galanthamine hydrobromide. The product was filtered and dried under vacuum at 50−55 °C to obtain (−)-galanthamine hydrobromide (**1**) as a white crystalline powder (71.5 g, 85.4% yield).

Chromatographic purity: 99.79% (by HPLC). Lycoramine content: 0.12% (by HPLC). (+)-Galanthamine content: Not detected (by chiral HPLC). Mp 253 °C (dec.). $[\alpha]_D^{25}$ (c = 0.1, in Water): −97.5°. IR (KBr) (cm^{-1}): 3561, 3043, 3022, 2946, 2922, 2619, 2482, 1625, 1512, 1465, 1439, 1282, 1068. HRMS: m/z = 288.1604 $[M + H]^+$. ^1H NMR (DMSO-d_6): δ 1.91 and 2.04 (2m, 4H), 2.97 (m, 3H), 3.45 (m, 1H), 3.76 (brs, 4H), 4.10 (s, 1H), 4.34 and 4.48 (m, 2H), 4.60 (s, 1H), 4.80 (dd, 1H), 5.87 (dd, 1H), 6.13 (dd, 1H), 6.79 and 6.85 (2d, 1H each), 9.84 and 10.59 (2brs, 1H). ^{13}C NMR (DMSO-d_6): δ 31.8 (2 × CH_2), 35.6 (CH_3), 47.3, 55.4 (CH_2), 56.5 (OCH_3), 59.7 (CH_2), 60.4 (CH), 87.3 (CH), 112.8 (CH), 121.5, 123.7 (CH), 126.2 (CH), 130.7 (CH), 133.8, 145.8, 147.3.

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Notes

The authors declare no competing financial interest.

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