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Stereoselective syntheses of galanthamine and its stereoisomers by complementary Luche and L-selectride reductions

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ABSTRACT

A diastereodivergent approach for the stereoselective syntheses of all four stereoisomers of galanthamine, (−)-galanthamine **1**, (+)-galanthamine **2**, (−)-epigalanthamine **3**, and (+)-epigalanthamine **4**, from (±)-narwedine **5** is reported. Thus (±)-narwedine **5** was resolved by dynamic kinetic resolution to obtain enantiomerically pure (−)-narwedine **6** and (+)-narwedine **7**. Each enantiomerically pure isomer of narwedine was subjected to Luche and L-selectride reactions to obtain all four isomers of galanthamine. In these reactions, the (−)-galanthamine **1** and (+)-galanthamine **2** isomers were obtained with an enantiomeric purity of >99.5%, whereas (−)-epigalanthamine **3** and (+)-epigalanthamine **4** are obtained with a chiral purity of >97%. The axial hydride attack by the Luche reduction and the equatorial hydride attack by the L-selectride reduction on the cyclic enone system are explored in the stereoselective synthesis of the galanthamine isomers and thus it was demonstrated that the stereoselective synthesis involving the Luche and L-selectride reductions are complementary in yielding enantiomeric stereogenic centers from a prochiral carbonyl group on the cyclic enone system.

1. 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 naturally occurring and therapeutically active isomer is (−)-galanthamine **1**, which has a configuration of (4*aS*,6*R*,8*aS*) and has been approved for the treatment of mild to moderate Alzheimer's disease. The chemical structures of galanthamine **1** and its stereoisomers **2**, **3**, and **4** are shown in Figure 1.[1]

The first successful synthesis of (−)-galanthamine **1** was reported by Barton and Kirby in 1962 in which (±)-narwedine **5** was resolved to obtain (−)-narwedine **6**, which was then reduced with lithium aluminum hydride to obtain a mixture of (−)-galanthamine **1** and (−)-epigalanthamine **3**. Barton also reported on the reduction of (+)-narwedine **7** with $LiAlH_4$ to obtain a mixture of (+)-galanthamine **2** and (+)-epigalanthamine **4**. The residue obtained after the reduction was subjected to chromatographic separation to obtain both (+)-galanthamine **2** (36% yield) and (+)-epigalanthamine **4** (25% yield), which indicates that the selectivity of the $LiAlH_4$ reduction of (+)-narwedine **7** favors the formation of (+) galanthamine **2** rather than (+)-epigalanthamine **4** in a ratio of 1.4:1.[2] Szewczyk et al. prepared (−)-galanthamine **1** and (+)-galanthamine **2** from 1-bromo-11-formyl-nornarwedine; this synthetic approach involved

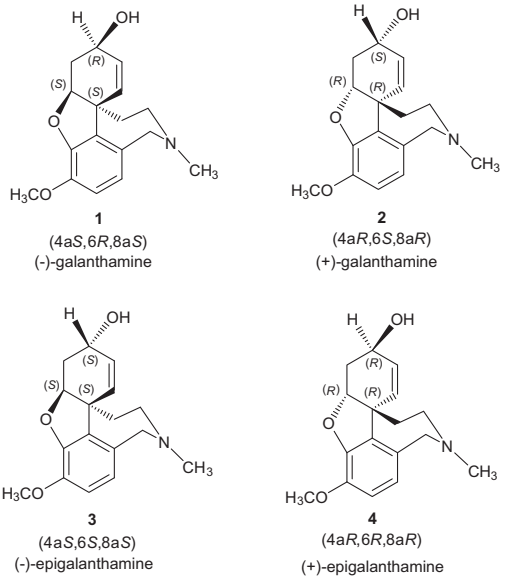

Figure 1. Structures of the galanthamine stereoisomers.

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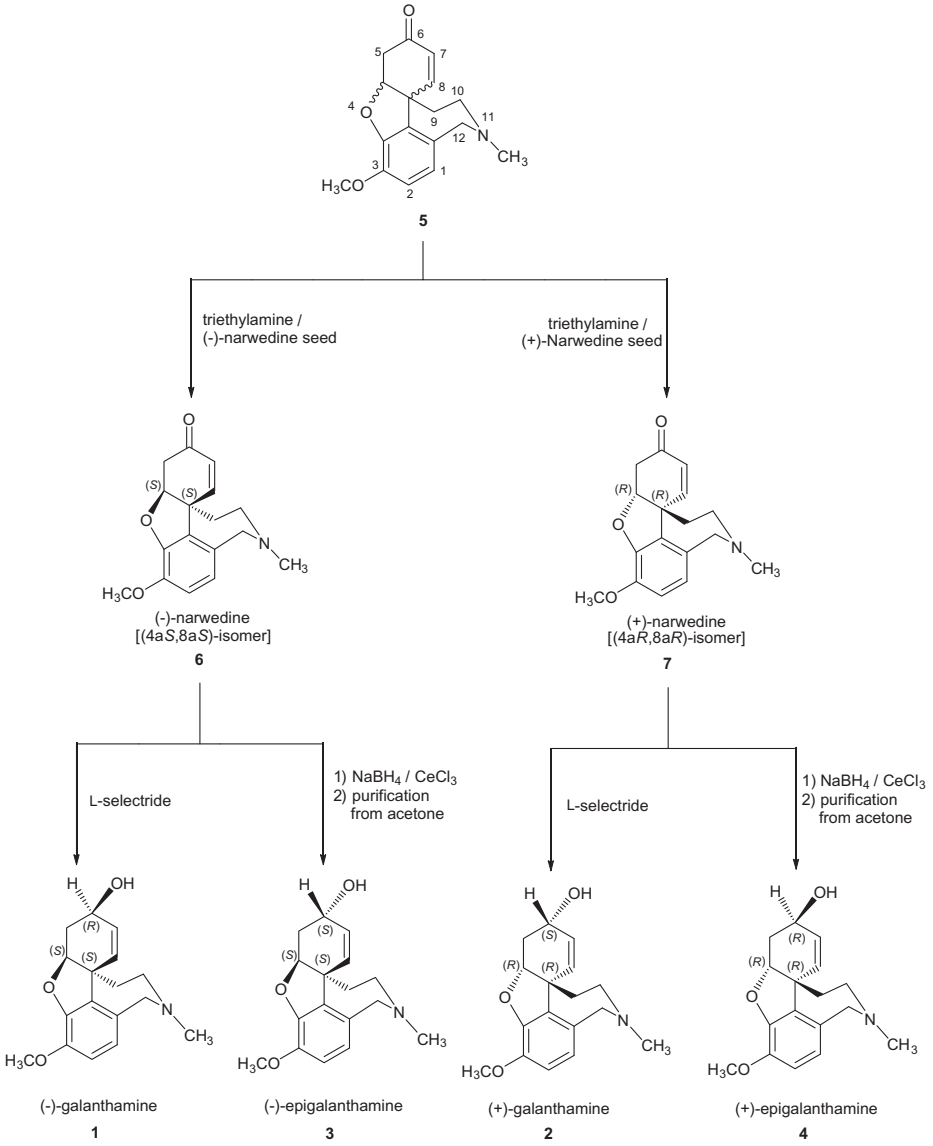
(1*S*)-(−)-camphanic chloride as a resolving agent and fractional crystallization from methanol to obtain (−)-galanthamine **1** and (+)-galanthamine **2**.[3] Many other synthetic routes for the preparation of (−)-galanthamine have also been reported in the literature.[4–8] Valhov et al. prepared (−)-epigalanthamine **3** via microbial reductive transformations of 1-bromo narwedine-12-one to a (−)-epigalanthamine derivative with an isolated yield of 50% pure product, which was further reduced with lithium aluminum hydride to obtain (−)-epigalanthamine **3** in 92% yield. The selectivity obtained here is due to the microbial reductive transformation and not because of the $LiAlH_4$ reduction.[9] Tomioka et al. synthesized (+)-galanthamine **2** from L-tyrosine in seven steps.[10] Dyer et al. prepared a 1:1 mixture of (+)-galanthamine **2** and (+)-epigalanthamine **4** by reducing (+)-narwedine **7** with lithium aluminum hydride in the presence of *N*-methylephedrine and *N*-ethyl-2-aminopyridine. This clearly signifies that there is no selectivity during the reduction, hence the selectivity is almost equal with regard to the formation of both diastereoisomers. Flash chromatography of this 1:1 mixture yielded (+)-galanthamine **2** (98% ee, 30% yield) and (+)-epigalanthamine **4** (95% ee, 26% yield).[11] To the best of our knowledge, there is no report that prepares all four isomers in a diastereodivergent approach. In a continuation of our interests in synthesizing tertiary alkaloids, we herein report the synthesis of the galanthamine isomers in a diastereodivergent synthetic approach.

2. Results and discussion

The synthesis of all four stereoisomers of galanthamine in a diastereodivergent approach is shown in Scheme 1. Herein we chose (±)-narwedine **5** as a key starting material for the synthesis of the galanthamine isomers. This approach involves two critical synthetic stages; the first is the kinetic dynamic resolution of (±)-narwedine **5** and the second is the reduction of the narwedine isomers by complementary stereoselective reduction reactions to give all four isomers of galanthamine with an enantiomeric purity of >97%. The resolution of (±)-narwedine **5** to obtain (−)-narwedine **6** was first reported by Barton.[2] Shieh et al. explained the mechanism of this kinetic dynamic resolution process of (±)-narwedine **5** with a retro-Michael ring opening and ring closing dienone system.[12] It has also been reported that either (−)-narwedine **6** or (+)-galanthamine **2** can be used to induce the resolution to produce (−)-narwedine **6** as a single pure isomer.[12,13] The resolution was reported to be



Scheme 1. The synthesis of all four stereoisomers of galanthamine **1**, **2**, **3**, and **4**.

carried out with an appropriate enantiomerically pure enantiomer seeding a supersaturated ethanolic solution of (±)-narwedine **5** in the presence or absence of triethylamine. The resolution was achieved by stirring the mixture at 40 °C for 12 h to 7 days.[12–16] We carried out the kinetic dynamic resolution of (±)-narwedine **5** by following the reported procedures and observed that these reported procedures were inconsistent in yielding an impure (−)-narwedine **6** isomer, which was contaminated with the undesired enantiomer, (+)-narwedine **7**. For the successful synthesis of enantiomerically pure galanthamine isomers, the resolution process of (±)-narwedine **5** should consistently yield the narwedine isomers with high enantiomeric purity. We presume that the resolution time and temperature play an important role in yielding the narwedine isomers with a higher enantiomeric purity. Hence we decided to optimize these two key parameters in the kinetic dynamic resolution of (±)-narwedine **5**.

To investigate this kinetic dynamic resolution process of (±)-narwedine **5**, we monitored the resolution process of (±)-narwedine **5** by analyzing aliquots at different stages by chiral HPLC methods. As expected, we observed that prior to adding the seed of (−)-narwedine, the ethanolic solution of (±)-narwedine **5** at reflux temperature contains both stereoisomers (−)-narwedine **6** and (+)-narwedine **7** in almost equal amounts in an equilibrium state. The resolution mixture was cooled to 72–73 °C and (−)-narwedine **6** was added as a seed. (−)-Narwedine **6** started to crystallize from the solution after the addition of the (−)-narwedine **6** seed and the mixture was slowly cooled to room temperature over a period of 4 h. During this process, aliquots of the resolution slurry were collected at different temperatures. The aliquots collected at different temperatures were filtered and the solids were analyzed by chiral HPLC to check the contents for (+)-narwedine **6** and (−)-narwedine **7**. The results obtained by the kinetic dynamic resolution of (±)-narwedine **5** to obtain (−)-narwedine **6** at different temperature are summarized in Table 1.

The initial solution of narwedine and the filtrates obtained from the aliquots collected at different temperatures during the resolution process, contain a racemic mixture of narwedine. It is well known that narwedine in solution exists as a racemic mixture and while crystallizing out from the solution, it separates out as enantiomerically pure (−)-narwedine **6**. Herein we have shown that the resolution of narwedine to obtain (−)-narwedine **6** isomer can be achieved in a shorter time period.

Secondly, since the reported procedures[12–15] for this resolution recommend an optimized temperature of approximately 40 °C, we studied this resolution at 40–42 °C at different intervals of the process in order to check the content of (+)-and (−)-narwedine after seeding and cooling the reaction. In this experiment, aliquots of the slurry collected at different intervals were filtered and the filtered solids as well as mother liquors were analyzed by chiral HPLC method. The results obtained from this resolution study at different intervals of time are given in Table 2.

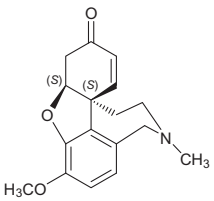
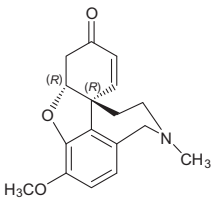
The above experimental results showed that the filtrates obtained from the aliquots contain a racemic mixture of narwedine. It was also concluded that stirring the resolution mixture for 3–4 h at 40–42 °C was required to obtain an enantiomerically pure product with very good yield. Based on these studies, we summarized this kinetic dynamic resolution of (±)-narwedine **5** to obtain a pure enantiomer of (−)-narwedine **6** as follows: (±)-narwedine **5** is dissolved in aqueous ethanol solution containing triethylamine at 75–80 °C to obtain a saturated solution and cooled to 70–73 °C. (−)-Narwedine **6** seed crystals were added at 70–73 °C. This resolution mixture was then gradually cooled to 40–42 °C and stirring was continued at 40–42 °C for 3–4 h to obtain enantiomerically pure (−)-narwedine **6**. The slurry mass was cooled to 25–30 °C and filtered to obtain (−)-narwedine **6** with an enantiomeric purity of >99.5% and purity of >99.5% (by HPLC).

The resolution of (+)-narwedine **7** from (±)-narwedine **5** requires (+)-narwedine **7** seed crystals, which were prepared by the resolution of (±)-narwedine **5** by using (−)-galanthamine **1** as the seed, as reported in the literature.[2,13] Thereafter, (+)-narwedine **7** was successfully prepared by seeding the ethanolic solution of (±)-narwedine **5** containing triethylamine at 70–73 °C with (+)-narwedine **7** seed crystals; the resolution process was continued as described for the preparation of (−)-narwedine.

Our next goal was to prepare all four stereoisomers of galanthamine diastereoselectively from enantiomerically pure narwedine isomers. The prochiral carbonyl group of narwedine has to be reduced diastereoselectively to obtain all fours isomers of galanthamine. Hence we evaluated two complementary reducing agents, which could either predominantly facilitate an axial hydride attack to yield an equatorial alcohol or facilitate equatorial hydride attack to give an axial alcohol.[17]

It was reported in the literature[18] that the bulk of the reagent appears to dictate the hydride approach from the less sterically hindered face to facilitate an equatorial hydride attack to yield an axial alcohol; thus (−)-narwedine **6** was reduced with L-selectride to yield exclusively (−)-galanthamine **1**.[12,13] Sodium borohydride could facilitate axial attack[19] and thus initially, we carried out the reduction reaction of (−)-narwedine **6** with sodium borohydride in methanol solvent and anticipated the product as

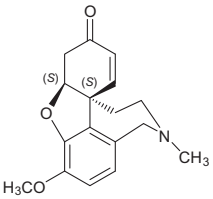
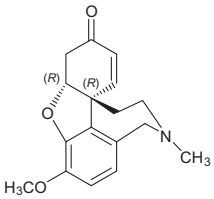
Table 1
Resolution of (±)-narwedine **5** at different temperatures

Particulars	Time (h)	Content of isomers[a]	
			
After dissolution at 75 °C and before addition of seed	0	49.43	50.57
Solid obtained from the aliquot of slurry collected at 60 °C and filtered	1	99.28	0.72
Solid obtained from the aliquot of slurry collected at 50 °C and filtered	2	99.60	0.40
Solid obtained from the aliquot of slurry collected at 40 °C and filtered	3	99.47	0.53
Solid obtained from the aliquot of slurry collected at 25 °C and filtered	4	99.76	0.24

Reaction conditions: (±)-Narwedine **5** was dissolved in aqueous ethanol containing triethylamine at reflux and seeded with (−)-narwedine at 72–73 °C and then cooled to 25 °C over a 4 h period.

[a] Chromatographic purity (by chiral HPLC, by area normalization).

Table 2
Resolution process of (±)-narwedine **5** at different intervals of time at 40–42 °C

Particulars	Content of isomers[a]	
		
Crystallized solid after cooling to 40 °C in 3–4 h period	99.12	0.88
Mother liquor at 40 °C	49.83	50.17
Crystallized solid after stirring at 40–42 °C for 1 h	99.40	0.60
Mother liquor at 40–42 °C for 1 h	49.31	50.69
Crystallized solid after stirring at 40–42 °C for 2 h	99.61	0.39
Mother liquor at 40–42 °C for 2 h	48.87	51.13
Crystallized solid after stirring at 40–42 °C for 3 h	99.74	0.26
Mother liquor at 40–42 °C for 3 h	49.89	50.11
Final filtered solid after cooling to 25–30 °C in 1–2 h period	99.77	0.23

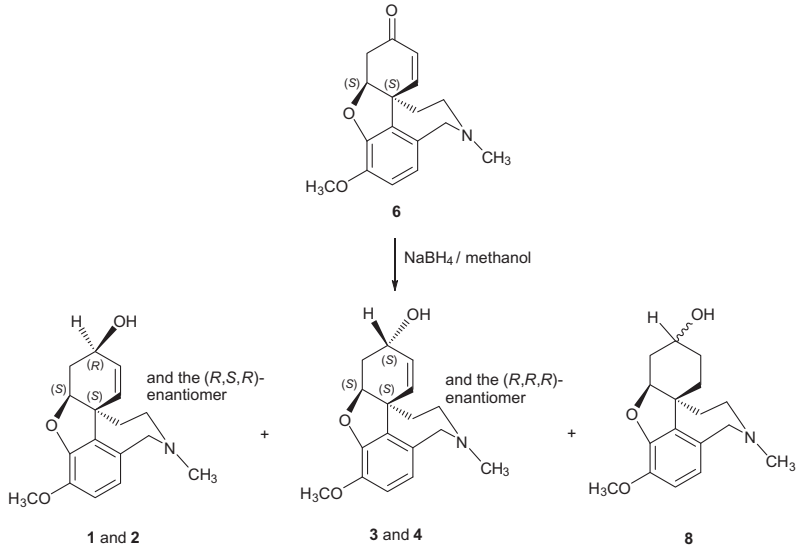
Reaction conditions: (±)-Narwedine **5** was dissolved in aqueous ethanol containing triethylamine at reflux and seeded with (−)-narwedine **6** at 72–73 °C and further cooled to 40–42 °C over a 3–4 h period. The reaction mass was then stirred for 3–4 h after cooling (during which time aliquots were taken), then finally cooled to 25–30 °C and filtered.
[a] Chromatographic purity (by chiral HPLC, by area normalization).

predominantly being (−)-epigalanthamine **3** and lycoramine **8**.[20] However this reaction gave a mixture of (±)-galanthamine **1** and **2**, (±)-epigalanthamine **3** and **4** and lycoramine **8** (Scheme 2).

The formation of lycoramine **8** was anticipated due to the conjugate reduction of the C-7 double bond. However, the reduction of (−)-narwedine **6** in yielding (±)-galanthamine and (±)-epigalanthamine has not been understood. Similar results were obtained when (+)-narwedine **7** was reduced with sodium borohydride in methanol, in which the formation of a (±)-galanthamine and (±)-epigalanthamine racemic mixture was observed instead of the expected product of predominantly (+)-epigalanthamine **4**. We decided to evaluate the enantiomeric purity of the (−)-narwedine **6** isomer while it was suspended in a protic solvent. Therefore, (−)-narwedine **6** was suspended in methanol at 25–30 °C and stirred at this temperature for 1 h. Aliquots were drawn from the slurry mass after 15 min and 1 h and filtered. The filtrates, as well as the solids, were analyzed for (−)-narwedine **6** and (+)-narwedine **7** contents by chiral HPLC and we found that the amount of (+)-narwedine **7** slightly increases in the solid sample. However, the solution contained a racemic mixture of narwedine. The results from this experiment are shown in Table 3.

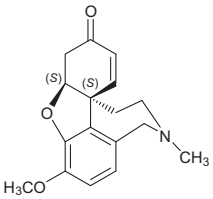
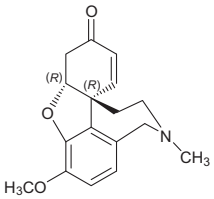
When (−)-narwedine **6** was suspended in a protic solvent, the chirality remained intact as long as (−)-narwedine **6** existed as a solid and thus no significant racemization occurred. However, racemization of (−)-narwedine **6** occurs spontaneously when it is dissolved in a protic solvent. (+)-Narwedine **7** also behaves in a similar way in methanol. Hence it was understood that the racemization of the narwedine isomer, which occurred spontaneously due to the dissolution during the reduction reaction of narwedine with sodium borohydride in methanol, and further reduction of racemic narwedine resulted in the formation of (±)-galanthamine and (±)-epigalanthamine.

We also studied the stability of a homogenous solution of enantiopure (−)-narwedine **6** in methylene chloride and methanol solvent mixture in the presence and absence of cerium (III) chloride. Enantiopure (−)-narwedine **6** in a solvent mixture of methylene chloride and methanol (1:1 v/v) was stirred at −50 °C and aliquots were analyzed by chiral HPLC at different intervals. We observed



Scheme 2. Reduction of (−)-narwedine with sodium borohydride in the absence of $CeCl_3$.

Table 3
Stability of (−)-narwedine **6** in methanol solvent

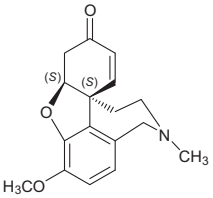
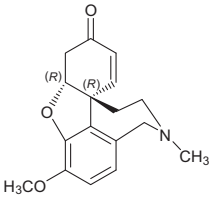
Particulars	Time	Content of isomers[a] 	
Input (−)-narwedine **6**	—	99.95	00.05
Analysis of the solid obtained after filtration of slurry	15 min	99.71	0.29
Analysis of the filtrate obtained after filtration of slurry	15 min	53.31	46.69
Analysis of the solid obtained after filtration of slurry	1 h	99.80	0.20
Analysis of the filtrate obtained after filtration of slurry	1 h	49.66	50.36

[a] Chromatographic purity (by chiral HPLC, by area normalization).

that spontaneous racemization of (−)-narwedine **6** occurred in the absence of cerium (III) chloride, whereas the chirality of (−)-narwedine **6** remained intact in the homogenous solution containing cerium (III) chloride (Luche condition). These experimental results are summarized in Tables 4 and 5.

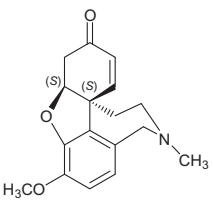
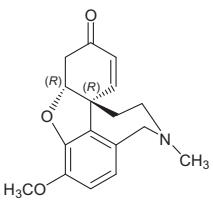
In order to achieve a diastereoselective reduction, we decided to carry out a Luche reaction for the reduction of the narwedine isomers. The Luche reduction has advantages such as it being regiospecific to facilitate 1,2-reduction of cyclic enones and thus formation of the 1,4-reduction product, lycoramine **8** can be controlled. The Luche reduction also favors an axial hydride attack and so facilitates the formation of a predominantly equatorial alcohol.[19,21] The Luche reduction was carried with sodium borohydride in the presence of cerium (III) chloride to reduce (−)-narwedine **6**; this reaction was also carried out in different solvents such as tetrahydrofuran, methanol, methylene chloride and acetonitrile and mixtures of solvents such as tetrahydrofuran and methanol (1:1), methylene chloride and methanol (1:1). It was observed that the reduction of (−)-narwedine **6** with sodium borohydride in the presence of cerium (III) chloride in a mixture of methylene chloride and methanol (1:1) predominantly yielded an equatorial alcohol, (−)-epigalanthamine **3** along with a lesser amount of axial alcohol, (−)-galanthamine **1**. We also studied the effect of temperature on the stereoselectivity of the Luche reduction of (−)-narwedine **6**. Thus, the Luche reaction of (−)-narwedine **6** was carried out with sodium borohydride in the presence of cerium (III) chloride at different temperatures and the results are given in Table 6.

Table 4
The stability of (−)-narwedine **6** in a methanol and methylene chloride solution at −50 °C

Time	Content of isomers[a] 	
Initial	99.73	0.27
15 min	71.23	28.77
1 h	63.94	36.06
2 h	60.62	39.38

[a] Chromatographic purity (by chiral HPLC, by area normalization).

Table 5
The stability of (−)-narwedine **6** in a methanol and methylene chloride solution at −50 °C in the presence of $CeCl_3 \cdot 7H_2O$

Time	Content of isomers[a] 	
Initial	99.73	0.27
15 min	99.19	0.81
1 h	99.13	0.87
2 h	99.11	0.89

[a] Chromatographic purity (by chiral HPLC, by area normalization).

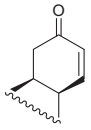
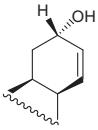
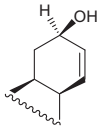
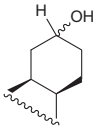
The balance of material in all cases comprised of the sum of all of the other peaks observed in the chromatogram.

The above studies showed that when the Luche reduction of (−)-narwedine **6** was carried out at −55 to −50 °C, effective diastereoselectivity was observed and this yielded the desired equatorial alcohol, (−)-epigalanthamine **3** (~83%) along with axial alcohol (−)-galanthamine **1** (~14%). The diastereoselectivity of this reaction was observed to be ~6:1. This crude product was further purified by stirring with acetone at reflux temperature to obtain the desired equatorial alcohol, (−)-epigalanthamine **3** with an enantiomeric purity of >97%. It was also found that (−)-epigalanthamine **3** had a chromatographic purity of >96% (by HPLC) and a specific rotation of −230 (*c* 1, $CHCl_3$).

Similarly, (+)-narwedine **7** was subjected to a Luche reduction with sodium borohydride in the presence of cerium (III) chloride at −55 to −50 °C to give ~83% of the equatorial alcohol (+)-epigalanthamine **4** along with ~14% of the axial alcohol (+)-galanthamine **2**; purification of this crude product by stirring with acetone at reflux temperature afforded the desired stereoisomer of the equatorial alcohol, (+)-epigalanthamine **4**, which showed a purity of >96% (by HPLC), enantiomeric purity of >97% (by HPLC) and a specific rotation of +232 (*c* 1, $CHCl_3$).

The diastereoselectivity of the Luche reduction increases at a lower temperature (−55 to −50 °C) which is due to the ligation of the cerium ion with the carbonyl group, which means that the protic solvent is more effective at a low temperature and thus predominantly yields the equatorial alcohol, epigalanthamine.

Table 6
The effect of temperature on the formation of equatorial and axial alcohols during the reduction of (−)-narwedine **6** with sodium borohydride in the presence of $CeCl_3 \cdot 7H_2O$

		% of product[a]			
		Enone	Equatorial alcohol	Axial alcohol	C-7 reduced product
					
		(-)-Narwedine	(-)-Epigalanthamine	(-)-Galanthamine	Lycoramine
Temperature	Quantity of $NaBH_4$ used (m. eq.)	**5**	**3**	**1a**	**8**
Without $CeCl_3 \cdot 7H_2O$	1.20	0.02	34.78	38.48	24.60
25–30 °C	1.20	0.60	60.18	38.32	0.46
10–15 °C	1.50	0.14	61.62	37.27	0.44
0–5 °C	1.80	0.65	69.70	29.14	0.23
−15 to −10 °C	2.10	0.71	71.55	24.59	0.16
−30 to −25 °C	2.30	0.53	73.47	24.01	0.12
−55 to −50 °C	2.50	0.03	82.87	13.94	Not detected
−65 to −60 °C	2.70	0.02	81.50	14.50	1.94
−75 to −70 °C	3.00	2.25	73.90	18.85	1.05

Reaction conditions: a 0.10 M solution of enone **5** in a 1:1 mixture of methanol and methylene chloride; 1.0 m. eq. of $CeCl_3$.
[a] Chromatographic purity (by HPLC, by area normalization).

Secondly, the ligation of the cerium ion with the carbonyl group through methanol completely prevents the racemization of narwedine and thus controls the formation of the other isomers of galanthamine as observed when narwedine was reduced with sodium borohydride in the absence of cerium (III) chloride. Thirdly, the Luche reduction is regiospecific in favoring 1,2-reduction, and thus controlled the formation of lycoramine **8**. Thus Luche reduction of the narwedine isomers is better in yielding their respective epigalanthamine isomers with high enantiomeric purity than other reducing agents such as lithium aluminum hydride, sodium borohydride and so on.

Diastereoselective reduction of (−)-narwedine **6** was carried out with L-selectride in tetrahydrofuran at −50 to −45 °C to exclusively produce axial alcohol (−)-galanthamine **1**. After the reaction was completed, the reaction was quenched with hydrogen peroxide and the excess peroxide was destroyed with sodium sulfite. After aqueous work-up of the reaction, (−)-galanthamine base was obtained and then treated with hydrobromic acid in aqueous ethanol to give the desired product, (−)-galanthamine hydrobromide **1** with a chromatographic purity of >99.7% (by HPLC) and an enantiomeric purity of >99.9% (by HPLC). The specific rotation of this axial alcohol **1** was −96.5 (*c* 0.1, water).

Similarly the diastereoselective reduction of (+)-narwedine **7** with L-selectride in tetrahydrofuran at −50 to −45 °C gave the axial alcohol, (+)-galanthamine **2**, which is the enantiomer of (−)-galanthamine **1** with the chromatographic purity of >99% (by HPLC) and an enantiomeric purity of >99.5% (by HPLC). The specific rotation of this axial alcohol **2** was +97.7 (*c* 0.1, water).

3. Conclusion

In conclusion, we have developed an efficient diastereodivergent approach for the synthesis of all four stereoisomers of galanthamine from (±)-narwedine **5**. The resolution of (±)-narwedine **5** was optimized to obtain narwedine isomers with an enantiomeric purity of >99.7%. Luche and L-selectride reduction of the cyclic enone system have been demonstrated as being complementary to yield the axial and equatorial alcohols, meaning that epigalanthamine isomers were prepared with an enantiomeric purity of >97% and galanthamine isomers were prepared with an enantiomeric purity of >99.5%.

4. Experimental

4.1. General

Starting material, (±)-narwedine **5** was prepared by following the literature,[22] L-selectride was procured from BASF. 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 NMR spectra were recorded on a Bruker 300 MHz spectrometer and ^{13}C NMR spectra were recorded on a Bruker 100 MHz spectrometer in DMSO-d_6 or $CDCl_3$, chemical shift data are reported in ppm from the internal standard TMS. The reaction monitoring and chromatographic purities of samples were analyzed qualitatively by High Performance Liquid Chromatography (HPLC) on a Waters 2695 with a 2996 PDA detector using Phenomenex Gemini C_{18} column (250 mm × 4.6 mm, 5 μ). The enantiomeric purity of the narwedine and galanthamine isomers were analyzed on a Waters 2695 with a 2996 PDA detector using Chiralpak AD-H (250 mm × 4.6 mm, 5 μ) column, respectively. High Resolution Mass spectra (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 using KBr pellets on Perkin–Elmer FTIR (spectrum one) spectrophotometer.

4.2. (4*aS*,8*aS*)-4*a*,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2]benzazepin-6-one [(−)-narwedine] 6

(±)-4*a*,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2]benzazepin-6-one [(±)-narwedine] **5** (75 g, 0.263 mol) was dissolved in a mixture of demineralised water (57 mL), ethanol (1090 mL), and triethylamine (127.5 mL) at 75–80 °C. The reaction mixture was cooled to 70–73 °C and (−)-narwedine (1.5 g) was added as seed to the dissolved solution. The resulting mixture was gradually cooled to 40–42 °C and stirred at the same temperature for 3 h. The completion of the resolution was

monitored by qualitative chiral HPLC analysis. Thereafter, the slurry was cooled to 25–30 °C, the product filtered and dried at 55–65 °C under reduced pressure to give (−)-narwedine **6** as a cream crystalline powder (67.5 g, 90%). Chromatographic purity: 99.92% (by HPLC); enantiomeric purity: 99.95% (by HPLC); mp: 190–192 °C; $[\alpha]_D^{25} = -409.1$ (*c* 1, $CHCl_3$); IR(KBr) (cm^{-1}): 1682 (C=O), 1620 (C=C), 1507, 1439; δ_H (300 MHz, DMSO-d_6): 1.81 and 2.12 (dd, *J* = 14.1, 3.0 Hz, 2H), 2.28 (s, 3H), 2.76 and 2.96 (dd, *J* = 2.1, 2.1 Hz, 2H) 3.01 and 3.18 (dd, *J* = 3.3, 13.2 Hz, 2H), 3.60 and 4.13 (dd, *J* = 15.6, 15.3 Hz, 2H), 3.71 (s, 3H), 4.71(brs, 1H), 5.90 (d, *J* = 9 Hz, 1H), 6.63 and 6.76 (2d, *J* = 9, 6 Hz, 2H), 7.14 (d, *J* = 9 Hz, 1H); HRMS (ESI^+): $[M+H]^+$ *m*/*z* 286.1453.

4.3. (4*aR*,8*aR*)-4*a*,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2]benzazepin-6-one [(+)-narwedine] 7

(±)-4*a*,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2]benzazepin-6-one [(±)-narwedine] **5** (50 g, 0.333 mol) was dissolved in a mixture of demineralised water (38 mL), ethanol (1381 mL), and triethylamine (85 mL) at 75–80 °C. Thereafter the reaction mass was cooled to 70–73 °C and (+)-narwedine (1 g) was added as a seed to the solution. The resulting mixture was gradually cooled to 40–42 °C and stirred at the same temperature for 3 h. The completion of the resolution was monitored by qualitative chiral HPLC analysis. The slurry mass was further cooled to 25–30 °C, the product filtered and dried at 55–65 °C under reduced pressure to give (+)-narwedine **7** as a cream crystalline powder (45 g, 90% yield). Chromatographic purity: 99.89% (by HPLC); enantiomeric purity: 99.77% (by HPLC); mp: 190–191 °C; $[\alpha]_D^{25} = +412.3$ (*c* 1, $CHCl_3$); IR(KBr) (cm^{-1}): 1681 (C=O), 1619 (C=C), 1507, 1439; δ_H (300 MHz, DMSO-d_6): 1.80 and 2.13 (dd, *J* = 13.8, 2.7 Hz, 2H), 2.27 (s, 3H), 2.75 and 3.01 (dd, *J* = 2.4, 3.3 Hz, 2H) 3.07 and 3.18 (dd, *J* = 3.6, 13.8 Hz, 2H), 3.59 and 4.12 (dd, *J* = 15.3, 15.6 Hz, 2H), 3.71 (s, 3H), 4.71(brs, 1H), 5.89 (d, *J* = 10.2 Hz, 1H), 6.63 and 6.75 (2d, *J* = 8.1, 8.1 Hz, 2H), 7.14 (d, *J* = 10 Hz, 1H); HRMS (ESI^+): *m*/*z* 286.1474 $[M+H]^+$.

4.4. (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 hydrobromide [(−)-galanthamine hydrobromide] 1

Lithium tri-*sec*-butyl borohydride (L-selectride), (1 molar solution in THF, 360.8 mL) was added dropwise to a suspension of (4*aS*,8*aS*)-4*a*,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2]benzazepin-6-one, [(−)-narwedine] **6** (50 g, 0.175 mol) in THF (1000 mL) at −50 to −45 °C for 1 h after which the reaction mixture was stirred at −50 to −45 °C for 3 h. The completion of the reaction was monitored by qualitative HPLC analysis. Next, the reaction mixture was quenched by adding aqueous hydrogen peroxide (40% w/w, 85 g, 1 mol) and the excess peroxide was destroyed by stirring the reaction with an aqueous sodium sulfite solution. The reaction mixture was concentrated under reduced pressure and the product was extracted into toluene (1250 mL). The organic extract was concentrated under reduced pressure at 50–55 °C to obtain (−)-galanthamine base as an oily mass, which was dissolved in a mixture of ethanol (200 mL) and DM water (50 mL). Aqueous hydrobromic acid (48% w/w, 31.09 g, 0.185 mol) was then added to the (−)-galanthamine base solution and stirred at 15–20 °C for 2 h. The product was filtered and dried under vacuum at 50–55 °C to obtain (−)-galanthamine **1** as a hydrobromide salt as white crystalline powder (55 g, 85.4% yield). Chromatographic purity: 99.85% (by HPLC); enantiomeric purity: 100% (by HPLC); mp: 253 °C (dec); $[\alpha]_D^{25} = -96.5$ (*c* 0.1, water); IR(KBr) (cm^{-1}): 3561, 3043,3022, 2946, 2922, 2619, 2482, 1625, 1512, 1465, 1439, 1282, 1068; δ_H (300 MHz, DMSO-d_6): 1.90 (brs, 1H), 2.04 (dd, *J* = 15.6, 5.1 Hz, 2H), 2.23 (dd, *J* = 15.6 Hz, 1H), 2.49 (s, 3H), 2.97 (brs, 2H), 3.34 (m, 1H), 3.76 (s, 3H), 3.82 (brs, 1H), 4.09 (s, 1H), 4.48 (m, 2H), 4.59 (s, 1H), 4.78 (d, *J* = 14.1 Hz, 1H), 5.87 (dd, *J* = 6, 3 Hz, 1H), 6.12 (d, *J* = 9 Hz, 1H), 6.79 and 6.85 (2d, *J* = 8.4, 8.4 Hz, 2H), 9.82 (2brs, 1H); δ_C (100 MHz, DMSO-d_6): 30.9 (2×CH_2), 35.1 (CH_3), 46.4 (CH_2), 55.6 (OCH_3), 59.4 (CH_2), 86.4 (CH), 111.9 (CH), 120.4, 122.8 (CH), 125.4 (CH), 129.8 (CH), 132.8, 144.8, 146.3; HRMS (ESI^+): *m*/*z* 288.1608 $[M+H]^+$.

4.5. (4*aR*,6*S*,8*aR*)-4*a*,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2] benzazepine-6-ol [(+)-galanthamine] 2

Lithium tri-*sec*-butyl borohydride [L-selectride] (1 molar solution in THF, 67 mL) was added dropwise to a suspension of (4*aR*,8*aR*)-4*a*,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2]benzazepin-6-one, [(+)-narwedine] **7** (10 g, 0.0351 mol) in THF (200 mL) at −50 to −45 °C for 1 h after which the reaction mixture was 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, 17 g, 1.3 mol) and the excess peroxide was destroyed by stirring the reaction with an aqueous sodium sulfite solution. The reaction mixture was concentrated under reduced pressure and the product was extracted into toluene (250 mL). The organic extract was concentrated under reduced pressure at 50–55 °C to obtain (+)-galanthamine base **2**, which was dissolved in a mixture of ethanol (40 mL) and DM water (10 mL). Aqueous hydrobromic acid (48% w/w, 6.22 g, 0.0878 mol) was added to the (+)-galanthamine base solution and stirred at 15–20 °C for 2 h to obtain (+)-galanthamine as its hydrobromide salt. The product was filtered and dried under vacuum at 50–55 °C to obtain (+)-galanthamine hydrobromide **2** as a white crystalline powder (11 g, 85.4% yield). Chromatographic purity: 99.08% (by HPLC); enantiomeric purity: 99.60% (by HPLC); mp: 244 °C (dec); $[\alpha]_D^{25} = +97.7$ (*c* 0.1, water); IR (KBr) (cm^{-1}): 3561, 3043, 3022, 2946, 2923, 2620, 2482, 1625, 1513, 1466, 1438, 1282, 1068; δ_H (300 MHz, DMSO-d_6): 1.97–2.28 (2dd, *J* = 14.1, 10.8, 10 Hz, 4H), 2.56 (s, 1H), 2.98 (brs, 2H), 3.57 (d, *J* = 14.7 Hz, 1H), 3.77 (brs, 4H), 4.10 (s, 1H), 4.37 and 4.80 (2m, 2H), 4.58 and 4.65 (2m, 2H), 5.90 (dd, *J* = 6, 3 Hz, 1H), 6.12 (d, *J* = 9 Hz, 1H), 6.78 and 6.85 (2d, *J* = 8.1, 8.1 Hz, 2H), 9.81 and 10.54 (2brs, 1H); δ_C (100 MHz, DMSO-d_6): 30.9 (2×CH_2), 34.8 (CH_3), 46.2 (CH_2), 55.6 (OCH_3), 59.4 (CH_2), 86.4 (CH), 111.9 (CH), 120.6, 122.5 (CH), 125.12 (CH), 130.0 (CH), 133.0, 145.0, 146.5; HRMS (ESI^+): *m*/*z* 288.1609 $[M+H]^+$.

4.6. (4*aS*,6*S*,8*aS*)-4*a*,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2] benzezapine-6-ol [(−)-epigalanthamine] 3

A mixture of (4*aS*,8*aS*)-4*a*,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2]benzezapin-6-one [(−)-narwedine] **6** (10 g, 0.035 mol), cerium chloride heptahydrate (13.07 g, 0.035 mol) in methylene chloride–methanol (1:1 v/v, 300 mL) was stirred at −55 to −50 °C for 30 min after which sodium borohydride (3.33 g, 0.088 mol) was added in portions at −55 to −50 °C over a period of 30 min. The reaction mixture was stirred at −55 to −50 °C for 2 h and the completion of the reaction was monitored by qualitative HPLC analysis. Water (10 mL) was then added to the reaction mixture and the temperature was raised to 25–30 °C. The reaction mixture was concentrated under reduced pressure and the concentrated mass was stirred with chloroform (100 mL). The inorganic residue was removed by filtration. The filtrate was washed with water (60 mL) and the organic layer was concentrated under reduced pressure. The crude product was stirred

with acetone (50 mL) at reflux temperature. The slurry mass was cooled to 25–30 °C, filtered and dried at 45–50 °C under reduced pressure to yield (−)-epigalanthamine **3** as a white crystalline powder (6.85 g, 68% yield). Chromatographic purity: 96.49% (by HPLC); enantiomeric purity: 97.71% (by HPLC); mp: 181–182 °C; $[\alpha]_D^{25} = -229.9$ (c 1, $CHCl_3$); IR (KBr, cm^{-1}): 3151, 3031, 3011, 2945, 2916, 1623, 1508, 1459, 1445, 1436, 1272, 1053; δ_H (300 MHz, $CDCl_3$): 1.61–1.75 (m, 2H), 2.18 and 2.75 (dd, J = 12, 12 Hz, 2H), 2.36 (s, 3H), 3.07 and 3.22 (dd, J = 12.9, 12.1 Hz, 2H), 3.59 and 4.05 (dd, J = 15.3, 15 Hz, 2H), 3.83 (s, 3H), 4.60 (m, 2H), 5.79 (d, J = 10.2 Hz, 1H), 6.05 (d, J = 11.7 Hz, 2H), 6.55 and 6.62 (2d, J = 8.1, 8.1 Hz, 2H); δ_C (100 MHz, $CDCl_3$): 32.3 ($2\times CH_2$), 34.1 (CH_3), 41.6 (CH_2), 48.0, 53.8 (CH_2), 55.8 (OCH_3), 60.1 (CH_2), 62.7 (CH), 88.4 (CH), 110.8 (CH), 121.5, 126.2 (CH), 128.9 (CH), 131.9 (CH), 132.9, 143.8, 146.6; HRMS (ESI^+): m/z 288.1614 $[M+H]^+$.

4.7. (4*aR*,6*R*,8*aR*)-4*a*,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2] benzezapine-6-ol [(+)-epigalanthamine] 4

A mixture of [4*aR*,8*aR*]-4*a*,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2]benzezapin-6-one, [(+)-narwedine] **7** (10 g, 0.035 mol), cerium chloride heptahydrate (13.07 g, 0.035 mol) in methylene chloride–methanol (1:1 v/v, 300 mL) was stirred at −55 to −50 °C for 30 min and sodium borohydride (3.33 g, 0.088 mol) was added in portions at −55 to −50 °C over period of 30 min. The reaction mixture was stirred at −55 to −50 °C for 2 h and the completion of the reaction was monitored by qualitative HPLC analysis. Water (10 mL) was then added to the reaction mixture and the temperature was raised to 25–30 °C. The mixture was concentrated under reduced pressure and the concentrated mass was stirred with chloroform (100 mL). The inorganic residue was removed by filtration. The filtrate was washed with water (60 mL) and the organic layer was concentrated under reduced pressure. The crude product was stirred with acetone (50 mL) at reflux temperature and then cooled to 25–30 °C. The product slurry was stirred for 1 h, filtered and dried at 45–50 °C under reduced pressure to yield (+)-epigalanthamine **4** as a white crystalline powder (6.95 g, 69% yield). Chromatographic purity: 96.66% (by HPLC); enantiomeric purity: 97.06% (by HPLC); mp: 182–183 °C; $[\alpha]_D^{25} = +232.6$ (c 1, $CHCl_3$);IR (KBr) (cm^{-1}): 3151, 3031, 3011, 2945, 2916, 1624, 1508, 1460, 1445, 1436, 1272, 1070; δ_H (300 MHz, $CDCl_3$): 1.63–1.76 (m, 2H), 2.15 and 2.76 (dd, J = 12, 12 Hz, 2H), 2.37 (s, 3H), 3.03 and 3.22 (dd, J = 15, 15 Hz, 2H), 3.60 and 4.10 (dd, J = 15, 15 Hz, 2H), 3.84 (s, 3H), 4.60 (m, 2H), 5.79 (d, J = 12 Hz, 1H), 6.05 (d, J = 9 Hz, 2H), 6.55 and 6.62 (2d, J = 9, 9 Hz, 2H); δ_C (100 MHz, $CDCl_3$): 32.3 ($2\times CH_2$), 34.1 (CH_3), 41.7 (CH_2), 48.1, 53.8 (CH_2), 55.8 (OCH_3), 60.2 (CH_2), 62.9 (CH), 88.4 (CH), 110.8 (CH), 121.5, 126.3 (CH), 128.9 (CH), 131.8 (CH), 132.9, 143.8, 146.6; HRMS (ESI^+): m/z 288.1616 $[M+H]^+$.

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