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Abstract: An alternative total synthesis of (−)-galanthamine (**1**) hydrobromide, employing ecofriendly amidation, oxidative coupling, and classical resolution strategies is accomplished.

Keywords: Amidation; Galanthamine; Oxidative coupling

INTRODUCTION

Galanthamine **1**, active against the acetylcholinesterase enzyme that increases postsynaptic membrane susceptibility to acetylcholine,[1] is an alkaloid base extracted from the leaves of the plant *Galanthus nivalis* L.[2] Hydrobromide salt of **1** is commercially available as a registered drug under the trade name Nivalin and many others for the treatment of Alzheimer's disease.[2] In the search for more robust, ecofriendly, and cost-effective synthetic routes, we are engaged in developing an alternate synthesis of **1**.

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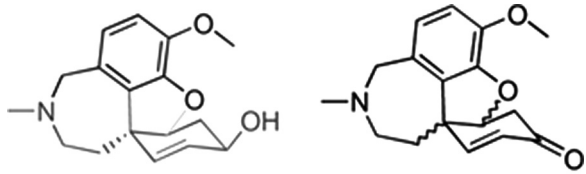


1 2

Figure 1. (–)-Galanthamine and norwedine.

The nonscalable and uneconomical isolation process of **1** from its natural source ($50,000 per kilogram)[3] has prompted various research groups to devise several syntheses, particularly involving biomimetic oxidative phenol coupling[4] and palladium-catalyzed enantio-divergent synthesiss,[5] to create the structural type unique to **1** and its derivative (Figure 1).

All hitherto known biomimetic syntheses[4] are poor yielding whereas asymmetric syntheses[5] are not cost-effective nor high yielding and therefore cannot be implemented in the industries for commercial production. Classical resolution, the *trivial but most reliable* technique, has been employed as one of the key strategies on a pilot-scale production of **1**.[4] Another key reaction, in the precedented synthesis, was an oxidative ring closure that afforded severe skin allergen intermediate narwedine **2** in the later course of the synthesis of **1**.

RESULTS AND DISCUSSION

The retrosynthetic analysis of **1**, as shown in Figure 2, starts with the installation of the northern part (i.e., bisphenol derivative **5**) and the southern part (*p*-hydroxy ethyl-*N*-methyl-phenyl amine derivative **8)**.

These two units (northern and southern) were bridged through an amide tether. An oxidative coupling strategy was employed to forge the spirocylic center, followed by furan ring formation. Finally, reduction cascades and dehalogenation afforded the desired product (±) **1**. Classical resolution provided the enantiomerically pure (–)-galanthamine **1**.

The synthesis of the northern part,[6] bromobenzoic acid derivative **5**, commences with the isovanilline **3**.

Benzylation of **3** afforded corresponding product **4** in 98% yield and excellent purity. Bromination of resultant and subsequent $KMnO_4$-mediated oxidation gave rise to the bromobenzoic acid derivative **5** in good yield (Scheme 1).

The synthesis of the southern part,[7] *p*-benzyloxy ethyl-*N*-methyl-phenyl amine derivative **8**, begins with the *p*-hydroxybenzylmethyl carboxylate. Benzylation of carboxylate **6** afforded corresponding

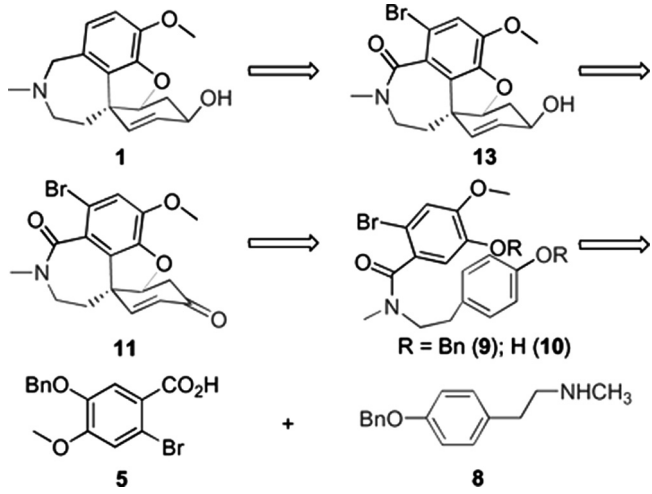


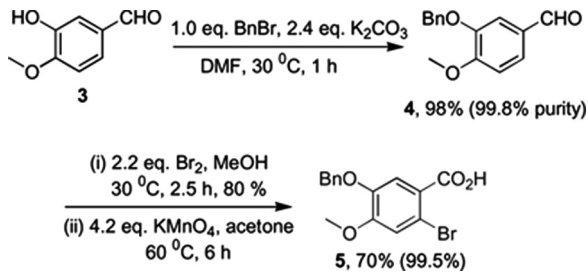
Figure 2. Retrosynthetic analysis.

product **7** in 98% yield. Amidation of the resultant and subsequent borohydride-mediated reduction furnished the *p*-benzyloxy ethyl-*N*-methyl-phenyl amine derivative **8** as an advanced synthonin good yield (78% for two steps) as depicted in Scheme 2.

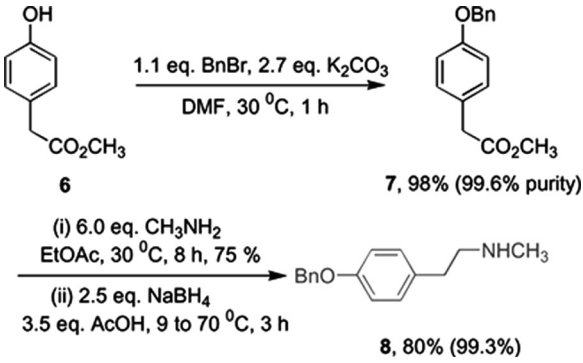
Ecofriendly phenyl boronic acid–catalyzed amidation[7] reaction of intermediates **5** and **8** was performed to obtain amide **9**.

In this reaction, as shown in Scheme 3, the acid moiety of **5** gets activated with phenyl boronic acid, which in turn provides an electron-deficient acid carbonyl center that reacts with amine **8** to afford amide **9** in 93% yield.

Hydrogenolysis on **9** to afford **10** and efficient intramolecular oxidative coupling, *in the presence of an amide bond*, occurred with the substrate **10**, resulting in a tetracyclic framework **11** in 62% yield. Formation of radicals in both northern and southern units, mechanistically as shown



Scheme 1. Synthesis of northern part **5**.

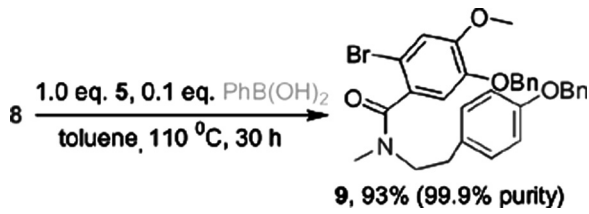


Scheme 2. Synthesis of southern part **8**.

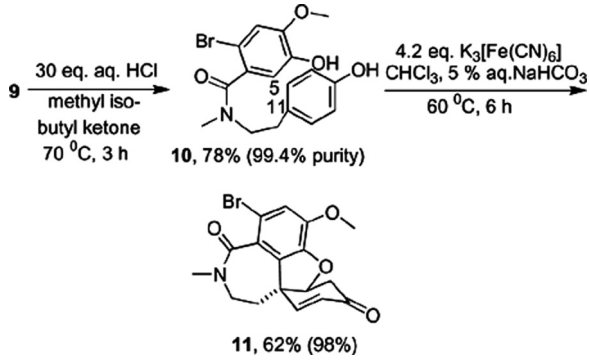
in Scheme 4, is mediated by redox potential of ferric ions.[8] These two radicals intimately succeeded to create a bond and furnished spirocyclic intermediate **12**. The southern part serves as a source of Michael acceptor that facilitates the caging to form the furan ring, whereas *o*-quinonoid (northern part), as a donor, afforded the tetracyclic skeleton **11** at the expense of salvaging its aromaticity as depicted in Scheme 5.

Noticeably, we observed the formation of only one set of stereoisomer **11**. The stereochemical outcome, supported by PM3 calculations, may be considered as such because of an amide bond strain that brought both the subunits in a close proximity (C5–C11 = 5.218 Å) followed by aligning them in an *endo* fashion and facilitating the formation of the spirocyclic center in **12**. Thus, an amide tether in framework **10** proved to be advantageous over the amine intermediate.[9] Oxidative coupling involving amine **14** (similar motif; Fig. 3)[9] is not high yielding, presumably because of the sp^3 hybridized carbon that kept both the units away (C5–C11 = 5.768 Å) from each other.

In the cyclic ether formation events, spontaneous Michael addition in the intermediate **12** progressed well, affording precursor **11** with the desired diastereoselectivity.



Scheme 3. Ecofriendly amidation: Synthesis of amide **5**.

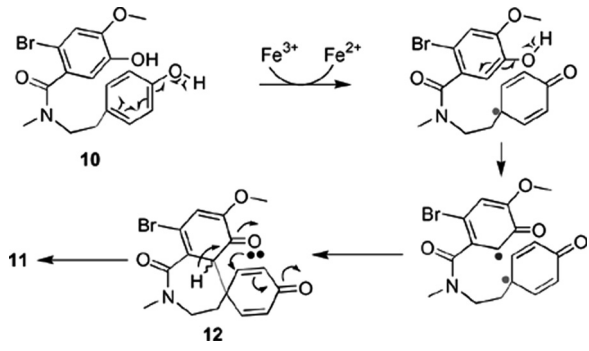


Scheme 4. Debenzylation and oxidative phenolic intramolecular cyclization.

PM3 calculation revealed that **12** (phenolic form) had a shorter distance between the phenolic oxygen and Cβ_1 (2.510 Å) than that between the oxygen and Cβ_2 (3.864 Å) (Fig. 3c). Cβ_1 and Cβ_2 are the equivalent Michael acceptor positions in the same plane that allows the formation of only one set of enantiomers (*RR* and*SS*). The resulting stereoselectivity can be presumed as a result of furan ring formation in the β plane.

A wide range of reagents for substrate-controlled stereoselective reduction of α,β-unsaturated ketone was intensively investigated. Among reagents screened, L-selectride was found to be a reagent of choice. The L-selectride-mediated reaction of α,β-unsaturated ketone **11** (Table 1) proceeded smoothly, affording alcohol **13** in excellent yield (80%) and diastereoselectivity (de; 99.6%) (entry 9).

Vitride-mediated debromination and amide reduction[10] of **11** both happened simultaneously in one pot to afford a diastereomeric mixture



Scheme 5. Plausible oxidative coupling mechanism.

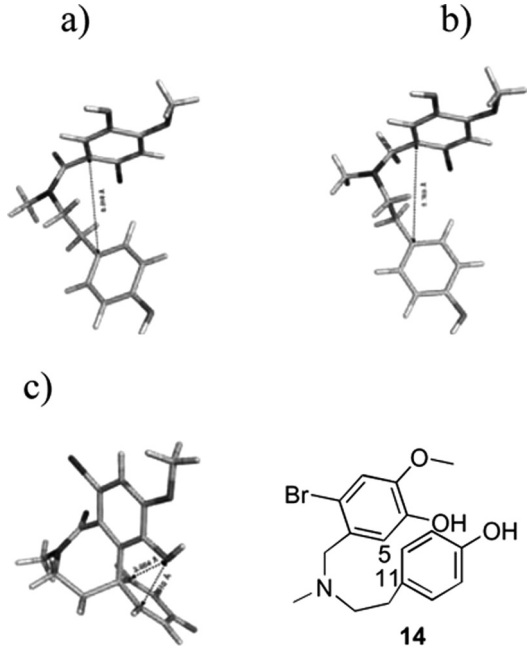


Figure 3. (a) Distance between C5-C11 = 5.218 Å in amide **10**; (b) Distance between C5-C11 = 5.768 Å in amine **14**; (c) Phenolic O-Cβ_1 & Cβ_2 bond lengths in intermediate **12**.

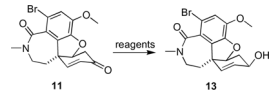
of **1** in good yield (75%). Classical resolution of the diastereomeric mixture of **1** employing (+)-DPTTA monohydrate[11] furnished the enatiomerically pure product (–)-**1** with scalable yield (70% based on available enantiomer in the racemate) and chiral purity (99.91%).

A conventional method for the HBr salt formation using aq. HBr afforded (–)-galanthamine hydrobromide [(–) **1** HBr] in 85% yield as shown in Scheme 6.

EXPERIMENTAL

Unless otherwise stated, all nonaqueous reactions and distillations were carried out under an atmosphere of dry nitrogen in dried glassware. Commercially available starting materials and reagents were purchased from Suven Pharmaceuticals, Hyderabad, India, and were used as received. When necessary, solvents and reagents were dried prior to use. Laboratory reagents (LR)-grade toluene, tetrahydrofuran, diethyl ether, methanol, ethanol, and dichloromethane were used as received from the supplier.

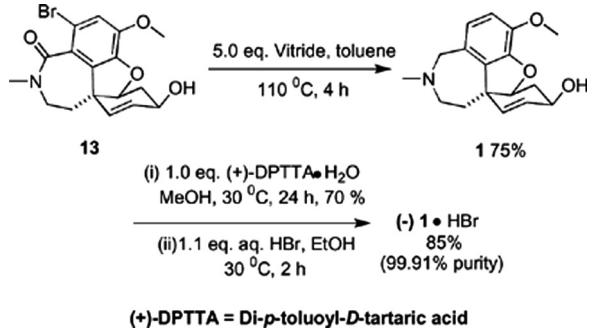
Table 1. Stereoselective reduction to **13**



No.	Reagents (eq.)	Solvents	Time (h)	Temp. (°C)	*dr* (α:β)	Yield (%)
1	HCO_2H (3.0)	AcOH	12	100	50:50	60
2	$NaBH_4$(2.5)	AcOH	3	80	65:35	65
3	$NaBH_4$ (3.0)/ I_2 (cat.)	AcOH	2.5	80	65:35	60
4	$NaBH_4$ (3.0)	Sec. BuOH	2.5	80	25:75	70
5	Vitride (5.0)	Toluene	8	110	55:45	55
6	DIBALH (3.5)	1,4-Dioxane	6	110	30:70	60
7	BH_3.DMS (4.5)	Toluene	9	70	30:70	65
8	Camphenyl borane (3.0)	Toluene	10	80	70:30	40
9	L-selectride (2.5)	THF	3	−10 to −0	0.2:99.8	80

Analytical thin-layer chromatography (TLC) was performed on EM reagents 0.25-mm silica-gel aluminium support plates bought from Merck. Visualization was accomplished by irradiation under a 254-nm UV lamp.

^{1}H NMR spectra were recorded on a Varian 400 MHz instrument ^{13}C NMR spectra were recorded on a Varian 200-MHz spectrometer. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane (0 ppm) or with the solvent resonance as the internal standard ($CDCl_3$ 7.26 ppm, DMSO-d_6 2.49 ppm, acetone-d_6 2.04 ppm, benzene-d_6



Scheme 6. End-game strategy to (–) **1** HBR.

7.15 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, app qui = apparent quintet, br = broad, m = multiplet), coupling constants, and number of protons. IR spectra were taken on a Perkin-Elmer equipment. Mass spectra were obtained on a low-resonance Q-trap machine in electron spray mode. Melting points were obtained on a Polmon apparatus and are uncorrected.

2-Bromo-4-methoxy-5-(4-methoxy-benzyloxy)-benzoic Acid 5

To a stirred solution of benzylated isovanilline **4** (100 g, 0.31 mol) in methanol (1.0 L), bromine (190 g, 1.18 mol) was added over a period of 30–45 min at 25–35°C. After stirring at 25–35°C for 1 h, water (3.0 L) was added and cooled to 5–10°C; the reaction mixture was further stirred for 1 h. The precipitated material was separated by filtration, and the wet solid was taken in water (600 mL), stirred for 30 min, filtered, and washed with water (400 mL) and toluene (100 mL). Ethyl acetate was added to the wet solid, heated to reflux, stirred for 30 min, and cooled to 10–15°C with continuous stirring for an additional 30 min. The precipitate was filtered, washed with toluene (50 mL), and dried at 40 to 45°C for 5 h to obtain 106 g of the corresponding bromo intermediate in 80% yield. This intermediate (100 g 0.31 mol) was dissolved in acetone (2.0 L) and heated to reflux. A mixture of water (1.5 L) and $KMnO_4$ (100 g, 0.63 mol) was added at refluxing temperature and stirred for 60–90 min at 50–55°C. The solvent was removed by distillation below 60°C. The undesired by-product MnO_2 was removed by filtration on a Celite® bed and washed with 10% KOH solution (100 mL). The pH of the filtrate was adjusted to 2–2.5 using 1 N aq. HCl at 0–5°C, and the contents were stirred for about 30–45 min. The separated solid was isolated by filtration and dried at 65–70°C to afford **5** (73.4 g) in 70% yield as a white solid. ^{1}H NMR (DMSO, 400 MHz): δ 3.87 (s, 3H), 5.12 (s, 2H), 7.25–7.40 (m, 7H), 13.1 (s, 1H).

p-Benzyloxy-*N*-methyl Phenethyl-amine 8

To a solution of *p*-benzyloxy phenyl methyl acetate **7** (144 g, 0.576 mol), 17% aqueous methyl amine (636 mL, 3.46 mol) was added and stirred for 3 h at 25–35°C. The precipitated solid was filtered, and the wet cake was taken into ethyl acetate (576 mL) and refluxed for 30 min. The resultant solution cooled to 25–35°C to obtain a precipitate that was isolated by filtration to obtain *p*-benzyloxy phenyl acetic acid- *N*-methyl amide (107.5 g) in 75% yield. The resultant *p*-benzyloxy phenyl acetic acid N-methyl amide (50.0 g, 0.196 mol) was dissolved in 1,4 dioxane (500 mL)

and stirred for 15–20 min, and sodium borohydride (18.6 g, 0.48 mol) was added at 15–20°C. After stirring for 5 min, a solution of acetic acid (41.2 g, 0.68 mol) in 1,4-dioxane (250 mL) was added slowly at 15–20°C. The reaction mass was heated to 60–70°C and stirred for 3 h. The solvents were distilled off under reduced pressure. Water (500 mL) was added to the residue and stirred for about 45 min. A white solid appeared and was isolated by filtration, washed with water (100 mL), and dried at 60°C for 3 h to obtain **8** (37.8 g) in 80% yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.65 (s, 3H), 3.19 (m, 4H), 5.02 (s, 2H), 6.86 (d, 2H, $J = 8.0$ Hz), 7.09 (d, 2H, $J = 8.0$ Hz), 7.29 (m, 5H), 9.62 (s, 1H).

5-Benzyloxy-*N*-[2-(4-benzyloxy-phenyl)-ethyl]-2-bromo-4-methoxy-*N*-methyl-benzamide 9[1]

Phynylboronic acid (1.8 g, 0.148 mmol) was added to a solution of 5-benzyloxy-2-bromo-4-methoxy-benzoic acid (50 g, 1.48 mmol) in *o*-xylene (850 mL). The reaction mixture was heated to 120°C. To this mixture, [2-(4-benzyloxy-phenyl)-ethyl] methylamine (44.69 g, 1.48 mmol) was added in one portion. The reaction mixture was heated at reflux for 30 h, and water was collected in the Dean–Stark trap. The solvent was completely distilled and cooled to 25°C, and methanol (50 mL) was charged. The reaction mixture was heated to reflux and maintained for 15 min to get a clear solution. At reflux, 5% alkaline methanol (150 mL) was added and maintained for 45 min before cooling to 0–5°C for 4 h. Then the precipitate was filtered and washed with 2×50-mL portions of methanol and dried in vacuum at 60°C for 6 h to afford **9** (71.4 g) in 86% yield. ^{1}H NMR (400 MHz, DMSO-d6): δ 2.61 (t, 2H, $J = 4.0$ Hz), 3.10 (t, 2H, $J = 4.0$ Hz), 3.30 (s, 3H), 3.81 (s, 3H), 4.98 (d, 2H, $J = 12.0$ Hz), 5.02 (s, 2H), 6.90 (s, 1H), 6.98 (d, 1H, $J = 8.0$ Hz), 7.18–7.48 (m, 14H).

Debenzylated Amide 10[1]

To asolution of **9** (162 g, 0.289 mol) in MIBK (91.6 L), 36.5% aqueous hydrochloric acid (2.1 L) was added and heated to 70°C. After 2 h of stirring, the reaction content was cooled to 30°C and water (810 mL) was added. pH was adjusted to 3 using caustic lye at 20–45°C. After stirring at 45°C for 30 min, the aqueous layer was separated and extracted with MIBK (812 mL). Solvents were distilled off, and the residue was dissolved in 500 mL of dichloromethane and cooled to 0–5°C. After 90 min, the precipitated solid was filtered and washed with dichloromethane (160 mL). Solid material was dried at 75°C under reduced pressure for 5 h to obtain **10** (86 g) in 78% yield.^{1}H NMR (400 MHz, DMSO-d6) δ

2.72 and 2.98 (2 × s, 3H), 2.69–2.71 (m, 2H), 3.23 and 3.60 (2 × m, 2H), 3.84 (s, 3H), 6.50–6.84 (m, 4H), 7.01–7.07 (m, 2H), 9.09 (s, 1H), 9.22 and 9.70 (2 × s, 1H).

Tetracyclic System 11

To a refluxed solution of potassium ferricyanide (327.6 g, 0.996 mol) in chloroform (18 L), 5% $NaHCO_3$ (3.3 L) solution was added followed by **10** (90 g, 0.237 mol) for a period of 45 min in two portions under continuous stirring. After refluxing for **1** h, the reaction mixture was cooled to 50°C, filtered through a Celite® bed, washed with chloroform (2.7 L), and separated into organi layers. The organic layer was washed with water (2.7 L). Solvents were removed, n-heptane (2.0 L) was added, and the reaction content was cooled, stirred for 30 min, and filtered to afford the desired compound **11** (55.5 g) in 62% yield. ^{1}H NMR (400 MHz, DMSO-d6): δ 2.08–2.16 (m, 1H), 2.40 (ddd, 1H, $J = 14.5$, 2.4, 2.4 Hz), 2.84 (dd, 1H, $J = 17.5$, 3.9 Hz), 3.18–3.21 (m, 4H), 3.40 (ddd, 1H, $J = 14.8$, 2.4, 3.7 Hz), 3.65–3.79 (m, 1H), 3.90 (s, 3H), 5.01 (s, 1H), 5.95 (d, 1H, $J = 10.1$ Hz), 6.22 (dd, 1H, $J = 10.1$, 2.3 Hz), 7.29 (s, 1H); ^{13}C NMR (200 MHz, $CDCL_3$) δ192.9, 164.7, 146.7, 146.2, 145.7, 129.4, 125.9, 122.9, 118.7, 114.1, 89.3, 56.4, 48.7, 48.6, 36.7, 36.6, 34.1; IR (neat) 3374, 2853, 1698 cm^{-1}; MS (CI) calcd. for $C_{17}H_{16}BrNO_4$ (M^+); 378.22 found (MH^+) 379.00, 381.00.

Alcohol 13[11]

To a solution of **11** (20 g, 0.053 mol) in THF (1.0 L), a 1.0 M solution of L-selectride (134 mL, 0.134 mol) in THF was slowly added over 2 h at −10 to 0°C. After stirring for 2 h, the reaction mixture was quenched with water (40 mL) and hydrogen peroxide solution (35 mL of hydrogen peroxide in 110 mL of water) at −10 to 0°C. Sodium hydroxide solution (10%, 8.0 g in 88 mL of water) was added below 35°C and stirred for about 60 min at 35°C, then extracted with dichloromethane (110 mL). Solvents were removed, and the isolated solid was washed with sodium hydroxide solution (4 g in 50 mL of water) followed by water (100 mL). The solid material was under vacuum at 75°C for 4 h to obtain **13** (16.0 g) in 80% yield. ^{1}H NMR (400 MHz, DMSO): δ 1.82 (d, 1H, $J = 8.0$ Hz), 2.00–2.03 (m, 3H), 3.20–3.30 (m, 1H), 3.40–3.50 (m, 1H), 3.70 (s, 3H), 3.82 (s, 3H), 4.07–4.09 (m, 1H), 4.79–4.81 (m, 1H), 5.32 (d, 1H, $J = 8.0$ Hz), 5.79 (dd, 1H, $J = 4.0$, 8.0 Hz), 7.19 (s, 1H); ^{13}C NMR (200 MHz, $CDCL_3$) δ 164.9, 146.0, 144.7, 131.9, 130.7, 126.3, 123.2, 117.8, 113.6, 89.8, 60.8, 56.2,

48.7, 48.2, 38.1, 33.9, 29.7; MS (CI) calcd. for $C_{17}H_{18}BrNO_4$ (M^+) 380.23; found 381.00, 383.00.

Galanthamine 1 HBr

To a refluxing solution of 70% vitride (152 g, 0.526 mol) in toluene (1.2 L), a solution of compound **13** (40 g, 0.105 mol) in toluene (2.4 L) was added in about 3 h. After stirring for an additional 1 h, the reaction mixture was cooled to 0–10°C, and 5% sodium potassium tartarate solution (121 g in 700 mL of water) was added in 20 min. The precipitate was filtered through the Celite® bed and washed with toluene (200 mL). The organic layer was washed with saturated sodium chloride solution (120 mL). Solvents were distilled off completely under the reduced pressure at less then 60°C, and the resultant crude material (25 g, 0.087 mol, 83.3%) was dissolved in 100 mL of methanol. (+)-Di-*p*-tolyl tartaric acid (37.6 g, 0.093 mol), was added, and the resultant mixture was stirred for about 24 h at 35°C. The precipitated solid was filtered and washed with methanol (25 mL). The residue was taken into methanol (100 mL) and stirred for 10 min, and 47% aq HBr (12.5 mL) in methanol (25 mL) was added over a period of 45 min at 25–30°C. The contents were stirred for about 1 h at less then 25–30°C. Further, the temperature was reduced to 0–5°C and stirred for about 60 min. The desired product was isolated by filtration and washed with 25 mL of methanol. The solid product was dried at 65°C under reduced pressure for 6 h to afford bromide salt of galanthamine **1** (10 g) in 80% yield. Spectral data matched perfectly with the standard sample.

In conclusion, we have succeeded in developing a novel synthetic route that has been implemented at our facility.

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