

Development of a Pilot Scale Process for the Anti-Alzheimer Drug (–)-Galanthamine Using Large-Scale Phenolic Oxidative Coupling and Crystallisation-Induced Chiral Conversion

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Abstract:

(–)-Galanthamine has been synthesised using an efficient nine-step procedure, which in large scale affords 12.4 (6.7–19.1)% overall yield. The process improvements and optimization of each step are described. Notable steps include (i) an oxidative phenol coupling and (ii) crystallisation-induced chiral conversion of (±)-narwedine to (–)-narwedine. This is a practical and cost-effective synthesis of (–)-galanthamine which is amenable to pilot plant scale-up to afford sufficient material for use in clinical trials.

Introduction

Galanthamine, an *Amaryllidaceae* alkaloid, has been used clinically for 30 years for treatment of myasthenia gravis¹ and other neurological illnesses such as poliomyelitis,² as an anti-curare agent,³ and as a parasympathomimetic.⁴ More importantly, it has been approved for the treatment of Alzheimer's disease in Austria and is in phase III clinical trials both in the United Kingdom and the United States.^{5–6} Galanthamine is produced by isolation from botanical sources (e.g. *Galanthus nivalis*, *G. narcissus*, *G. leucojum*, or *G. crinum*^{7–9}); despite renewed efforts,⁹ these sources are not suitable for generation of large enough quantities of galanthamine (Figure 1).

We had requirements for large quantities of galanthamine for in vitro and in vivo efficacy studies and pharmacokinetic studies. Galanthamine was first synthesised by Barton¹⁰ with a pivotal synthetic step being an oxidative phenol cyclization (0.5% yield). Other researchers were able to increase both the yields and the scale of the Barton procedure. Other syntheses of galanthamine have been reported.^{11–13} While

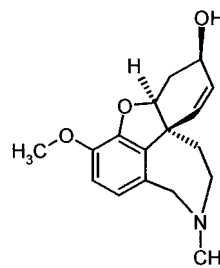


Figure 1. Structure of (–)-galanthamine, **1**; HBr-salt (**10**): nivalin, reminyll.

these procedures are workable on a laboratory scale, their scale-up to multi-kilogram scale is operationally prohibitive. We have recently communicated a more efficient route.¹² We report herein refinements to our earlier process which allows for large-scale synthesis of galanthamine (Scheme 1).

Results and Discussion

Step 1: 2-Bromo-4,5-dimethoxybenzaldehyde (1). Bromination of 3,4-dimethoxybenzaldehyde in acetic acid has been reported previously.¹⁴ By substituting methanol for acetic acid, we obtained **1** in 90–92% yield. While it has been reported that reaction of bromine with methanol may be vigorously exothermic,¹⁵ on the scale indicated in our experimental only a mildly exothermic reaction occurred (temperature increase from room temperature to about 40 °C) when bromine was added with water-cooling. On a 50 g laboratory scale in experiments using the same concentrations as the 4.0 kg experiment, designed to identify potential hazards, bromine was added at once without cooling, resulting in an exotherm, but the reaction temperature never exceeded 45–50 °C. The product contained less than 1% of the 3-bromo-4,5-dimethoxy-benzaldehyde as determined by HPLC and NMR. This procedure has been scaled up to 100 kg quantities with similar yields of 90–92%. Ethanol was less suitable because of decreased solubility and lower yields.

Step 2: 2-Bromo-5-hydroxy-4-methoxybenzaldehyde (2) by Regioselective Demethylation of 1. Substituted

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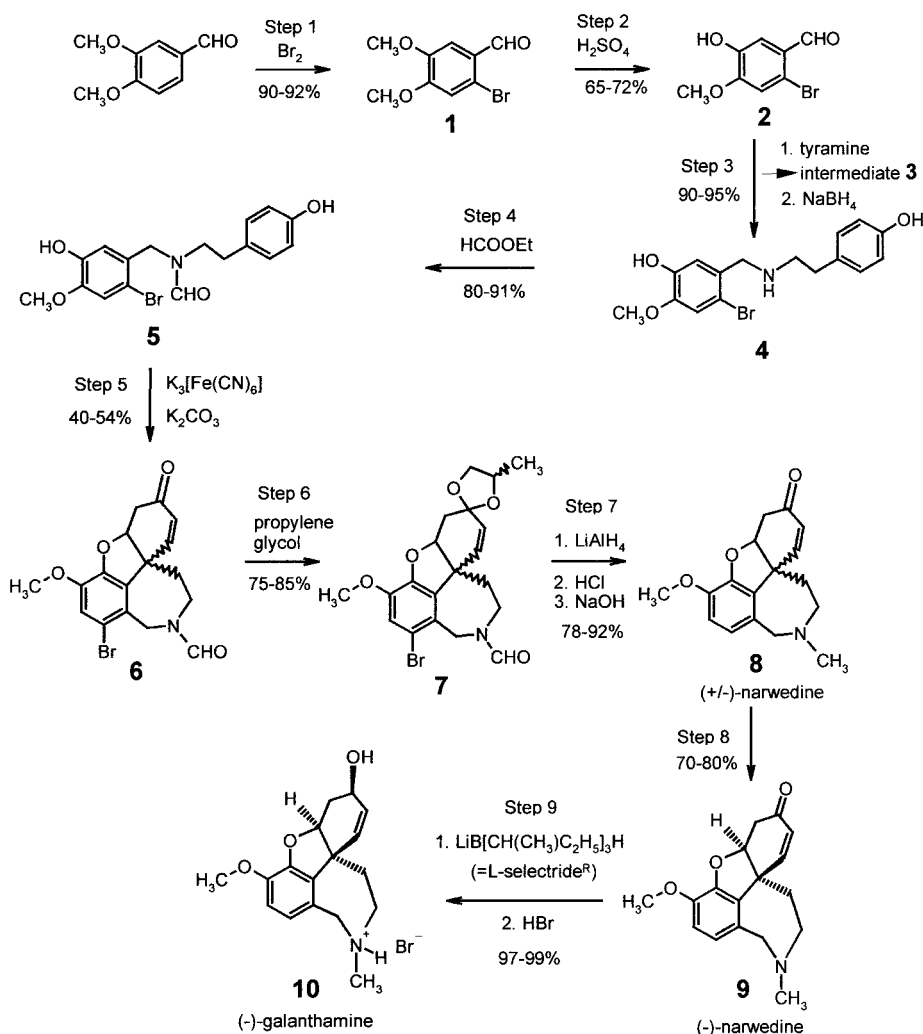
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Scheme 1



dimethoxybenzaldehydes can be demethylated regioselectively.¹⁶⁻¹⁷ Other methods for the preparation of **2**, such as the bromination of isovanilline with bromine¹⁸⁻²⁰ or thionyl bromide²¹ provided poor regioselectivity and/or mediocre yields. Selective 5-O-demethylation of **1** was achieved with concentrated sulfuric acid at 90 °C. Optimal conversion and yield is obtained after 6 h with a 5:1 sulfuric acid/substrate ratio.

Increased reaction times afforded increased side products (2-bromo-4,5-dihydroxybenzaldehyde and tar). The quality of sulfuric acid used is important for ease of work-up. Technical grade sulfuric acid gives a dark coloured product that is difficult to filter. While high quality sulfuric acid still afforded a dark colored product, it was easier to filter. Crystallisation of the crude product required adding water to an acetone solution of the crude product (and not vice versa), and cooling to 0–5 °C in order to obtain nicely

filterable crystals. On a 100 kg scale, yields ranged from 65 to 72%.

Step 3: Reductive Amination. The condensation of **2** with tyramine was performed in ethanol instead of a mixture of toluene and *n*-butanol (as reported previously). The crude 2-bromo-5-hydroxy-4-methoxybenzylidene-2-(4-hydroxyphenyl)ethanamine **3** is subsequently reduced to intermediate **4** using sodium borohydride in 90–95% yield. This step has been performed on 100 kg scale uneventfully.

Step 4: Formylation. Intermediate **4** is formylated with a mixture of ethyl formate and formic acid in dioxane. On smaller scales we found it advantageous to catalyse the reaction using 4-(dimethylamino)pyridine, but on larger scale this is not necessary. For process safety considerations, substitution of dioxane with ethylene glycol monomethyl ether had no detrimental effects on the productivity of the reaction. Product **5** is isolated by crystallisation, with yields of 80–91% on 100 kg of starting material.

Step 5: Oxidative Phenol Coupling. This step (conversion of **5** to **6**) was optimised for 12-kg production scale by multifactorial analysis of reaction parameters. We studied reaction temperature, concentration, and mode-of-addition of reagents, cosolvent effects (toluene, chloroform, methylene chloride, ethyl acetate, xylene, or anisole), phase-transfer

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Table 1. Influence of varying amounts of $K_3Fe(CN)_6$ and K_2CO_3

entry	amount 5 (g)	$K_3Fe(CN)_6$ (g)	10% K_2CO_3 soln (L)	physical yield (%)	content by HPLC (%)	active yield (%)
1	50	208	1	52.6	84.6	44.5
2	100	416	2	49.5	83.6	41.1
3	200	832	4	43.4	87.8	38.1
4	200	832	2a	30.7	75	23.0
5	100	300	2	42.8	84.5	36.2
6	100	416	2	49.5	83.6	41.1
7	100	500	2	51.3	82.5	42.3
8	200	600	2a	30.7	75	23.0

^a Heterogeneous reaction due to incomplete solubility of $K_3Fe(CN)_6$

catalysts, various bases (potassium carbonate, sodium hydrogen carbonate, lithium carbonate, sodium hydroxide), and various oxidizing agents (nickel peroxide, Fremy's salt, manganese dioxide, iron chloride, lead acetate). Our results continue to support the reaction mechanism summarised by Barton.²² Further, the mode of agitation of the reaction mixture had profound effect on product yield, irrespective of reaction scale. On the scale indicated in the experimental, the best results were obtained using a vertical stream agitator (IKA, driven by a 10 kW electric motor). Using conventional impeller agitators and baffles resulted in a decrease of the yield of 10–15%. The highest yields (50–54%) were obtained on a 20-g scale with higher dilution factor. Operationally, it was more economical to use reaction conditions with higher concentrations and compromise on product yields. As described in the experimental, yields of 40–42% have been consistently obtained on scales up to 12 kg.

Multifactorial Analysis of Parameters for the Oxidative Ring Closure Reaction. After numerous experimental permutations, we focused on optimising reaction conditions that employed toluene, water, K_2CO_3 , and $K_3Fe(CN)_6$. These studies are described below.

Varying the Amount of $K_3Fe(CN)_6$ and K_2CO_3 . These reactions were conducted using 13.5 L of toluene at 60° with a reaction time of 15 min. Results are summarised in Table 1.

Thus, lower concentrations resulted in higher yields, with the concentration of the aqueous phase limited by the solubility of $K_3Fe(CN)_6$. Further, at higher reaction concentrations, the filtration time of the reaction by-products increased significantly. In more dilute reaction conditions, filtration was accomplished in 10–15 min; in contrast, at higher concentrations, filtration and washing times ranged 3–12 h.

Once an optimal reagent and substrate combination was established, we then studied the effect of variations on reaction times and reaction temperatures on process throughput. These runs were done using 100 g of **5**, 416 g of $K_3Fe(CN)_6$, 2 L of K_2CO_3 solution, and 13.5 L of toluene. The results are summarised in Table 2. Additional experi-

Table 2. Influence of reaction temperature and of reaction time

entry	temp (°C)	stirring time (min)	isolated yield (%)	content by HPLC (%)	chemical yield (%)
9	60	15	49.5	83.6	41.1
10	80	5	48.2	84.4	40.7
11	45	30	48.7	85.6	41.7
12	20	60	47.9	85.2	40.8

Table 3. Reproducibility of the cyclization reaction

entry	isolated yield (%)	content by HPLC (%)	chemical yield (%)
13	47.1	85.3	40.2
13	48.2	85.2	41.1
15	49.1	85.9	42.2
16	49.2	83.6	41.1

mentson a gram scale at 0 °C resulted in reaction times of 4–6 h for completion and yields around 40%.

While the mode of the addition of **5** (in one or in several portions, powdered, lumpy, or as a slurry) did not influence the yields, the more critical aspect was to add **5** to a vigorously agitated two-phase reaction mixture of the other reactants.

Reproducibility. In four identical campaigns (100 g of **5**, 13.5 L of toluene, 416 g of $K_3Fe(CN)_6$ and 2 L of 10% potassium carbonate solution at 60° and 15 min reaction time) similar yields and product purity was obtained (Table 3).

Step 6: Ketal Formation. In earlier studies it was found that lithium aluminum hydride reduction of the ethylene ketal of **6** was problematic: poor reproducibility and inferior purity. In contrast, reduction of the 1,2-propylene glycol ketal of **6** occurred cleanly. Further, ketal **7** can be purified by crystallisation. While **7** is obtained as a mixture of diastereoisomers, it is not relevant strategically since the protecting group is removed during the work-up in step 7. The ketal is formed with *p*-toluenesulfonic acid catalysis and azeotropic removal of the water using toluene as solvent. The 1,2-propylene glycol ketal **7** is obtained, after extractive work-up, as a solid that can be used in the subsequent reduction without further purification. Yields range from 75 to 85% on batch runs up to 10 kg.

Step 7: Reduction of 7 Using Lithium Aluminum Hydride and Air: (±)-Narwedine (8). CAUTION: Narwedine and narwedine salts are classified as moderate to severe sensitising agents and, after prolonged exposure, cause severe allergic skin reactions. For this reason, personnel handling narwedine are equipped with full protective clothing, including protective helmet with controlled air stream, to avoid any contact with this substance.

Initially we had carried out lithium aluminum hydride reductions on reaction scales up to 10–20 g. However, on a 100-g scale, product formation was negligible; neither prolonging reaction times nor adding excess $LiAlH_4$ were effective in producing satisfactory reactivity. It was discovered that aeration of the solution resulted in complete

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Table 4. Reproducibility of the crystallisation-induced chiral transformation

entry	physical yield (g)	content by HPLC (%)	active yield (%)
17	78.5	95.3	70.0
18	78.3	96.0	70.3
19	77.0	95.8	73.0

substrate reduction.²³ Details of this reaction are reported elsewhere.²⁴ The reduction of **7** is monitored by TLC. Careful quenching of the reaction with water and extractive work-up gives the crystalline product **8**. The batch size of 14.4 kg was the largest performed so far by us with yields of 78–92%. On larger scale campaigns, **8** was not dried but used as a wet cake to avoid dust.

Step 8: (–)-Narwedine. A consistently reproducible procedure has been developed for the crystallisation-induced chiral transformation of **8** to **9** without the use of a chiral auxiliary other than seed crystals of **9**. Barton¹⁰ first reported that **8** can be converted to **9**, with further refinements by Shieh and Carlson.²⁵ The success of the crystallisation-induced chiral transformation is based on two phenomena – (i) narwedine crystallises as a conglomerate and (ii) (–)-narwedine equilibrates with (+)-narwedine via a retro-Michael intermediate. Chaplin²⁶ recently reported the dynamic diastereomeric resolution of salts of narwedine with di-*p*-toluoyl-D-tartaric acid followed by L-Selectride reduction to **10**. Using the conditions detailed in our experimental, on scales up to 7 kg, reproducible yields of 70–80% of **9** with a specific rotation of –400 to –410° (*c* = 1 in CHCl₃) are obtained. Our results are in contrast to the report of McCague^{13b} who reported difficulties in performing this method.

Reproducibility. In three identical campaigns [**8** (106.8 g dry weight), 1170 mL of ethanol 96% and 113 mL of triethylamine and seeding with 1.07 g of **9**] similar yields and product purity were obtained (Table 4).

Step 9: L-Selectride Reduction of (–)-Narwedine (9**) to (–)-Galanthamine·HBr (**10**).** We examined various reducing reagents for their ability to stereoselectively reduce narwedine (details will be reported elsewhere). L-Selectride was optimally suited, as galanthamine hydrobromide (nivalin) is isolated in nearly quantitative yield which can be used for the pharmaceutical bulk material. Since solutions of **9** in tetrahydrofuran undergo racemisation, it is important that solid **9** be added to solutions of L-Selectride at temperatures below –15 °C to minimise formation of epi-galanthamine. We have consistently obtained yields of 97–99% with reaction batches as large as 4.2 kg.

Summary

An efficient nine-step process for the synthesis of galanthamine hydrobromide (nivalin, remenyl) is reported. The process successfully generates multikilogram quantities of the bulk drug that is used in phase II and III clinical studies.

Experimental Section

General Procedures. ¹H and ¹³C NMR spectra were recorded using a Bruker AC 200 spectrometer (TMS as internal standard, CDCl₃ or DMSO-*d*₆ as solvent, δ values in ppm). Melting points were determined with a Kofler melting point apparatus; results are uncorrected. Optical rotation was recorded at 20 °C at 589, 578, 546, 436, and 365 nm and is reported for 589 nm. Elemental analyses were performed by the Microanalytical Laboratory, Institute of Physical Chemistry, University of Vienna (Mag. J. Theiner). HPLC analyses were performed using a Waters 600 pump and 486 detector at 285 nm. The column, Phenomenex C18 ODS3 (5 μ m) 250 \times 4.6 mm, was eluted with mixtures of 0.0015 M 3-cyclohexylamino-propane sulfonic acid (= CAPS) pH 2.0, MeOH, and THF.

Step 1: 2-Bromo-4,5-dimethoxybenzaldehyde (1**).** A 30-L (nominal capacity: 30 L, total capacity: 45 L, manufactured by Schott) glass reactor is charged with 25 L of methanol, and mill-powdered 3,4-dimethoxybenzaldehyde (4.0 kg, 24.07 mol) is added with stirring, resulting in a 5–8 °C temperature drop. The filling tube is rinsed with 2 L of methanol and closed. The mixture is heated to 30 °C, if necessary, to achieve a homogeneous solution. Bromine (4.4 kg, 27.53 mol) is added, with cooling (*T* < 40 °C), followed by stirring at this temperature for 1 h. The reaction mixture is then heated under reflux to remove 9.5 L of methanol by distillation. At this point, the product may start to precipitate from solution. After cooling to 20 °C, 15 L water is added with stirring. The resultant slurry is filtered using a 60-L pressure filter and washed with cold methanol (3 \times 5 L). The colourless to slightly yellowish product is dried in vacuo at 50 °C and 40 mbar for 18–24 h. Product yield is 5.4 kg (91.4%), mp 143–146 °C (lit.¹⁴ 149–150 °C). TLC: *R*_f = 0.55 (hexane/ethyl acetate, 6:4).

¹H NMR (CDCl₃) δ 3.9 (s, 3H), 3.98 (s, 3H), 7.05 (s, 1H), 7.40 (s, 1H), 10.20 (s, 1H). ¹³C NMR (CDCl₃) δ 190.3, 154.2, 148.6, 126.2, 120.1, 115.2, 110.1, 56.3, 55.9

Step 2: 2-Bromo-5-hydroxy-4-methoxybenzaldehyde (2**).** A 100-L glass vessel is charged with 95% sulphuric acid (80 L, 1.42 kmol), under argon, is heated with stirring at 90 °C. Stirring is stopped, and 2-bromo-4,5-dimethoxybenzaldehyde (**1**) (16.0 kg, 65.3 mol) is added within 10 min, and the reaction is allowed to proceed at 90 °C for 6 h. This mixture is then added quickly, using a glass transfer tube, to a 500-L reactor charged with 300 L of water, and 60 kg of ice to precipitate the product. The resultant temperature rise (to 60 °C) is further reduced by cooling with water, until a temperature of 20 °C is reached. The mixture is filtered using a 60-L pressure filter, and the crude product is washed with water (4 \times 15 L) to pH 5–7. The product is distributed between four trays and dried in a vacuum desiccator overnight at 60 °C and 40–50 mbar. A 100-L glass vessel is charged with acetone (80 L) and the dried, dark brown,

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crude material is added. Initial stirring at 20 °C results in a dark brown solution. Undissolved product is solubilised by heating to 30 °C. Activated carbon (1.2 kg) is added, and the mixture is stirred for 30 min at 20 °C. Then diatomaceous earth (1.2 kg) is added, and stirring is continued for 15 min. The suspension is filtered using a 60-L filter press, and the filtrate is pumped into a 500-L reactor. Water (120 L) is added, with stirring, followed by the addition of ice (40 kg). The precipitated product is filtered using a 60-L filter press and washed with ice-cold acetone/water (3 × 15 L, 1:1 v/v). The solid is distributed between four trays and dried in the vacuum desiccator overnight at 60 °C and 40–50 mbar to yield 13.34 kg (88.5%) of **2** as gray powder, mp 104–106 °C [lit.¹⁸ 105–108 °C].

¹H NMR (CDCl₃) δ 3.95 (s, 3 H), 5.80 (s, 1 H), 7.05 (s, 1 H), 7.48 (s, 1 H), 10.15 (s, 1H); ¹³C NMR (DMSO-*d*₆) δ 189.9, 152.9, 145.8, 125.8, 117.1, 114.9, 114.1, 55.6.

Step 3: (2-Bromo-5-hydroxy-4-methoxybenzylidene)-2-(4-hydroxyphenyl)ethylamine (3) and (2-Bromo-5-hydroxy-4-methoxybenzyl)-2-(4-hydroxyphenyl)ethylamine (4). A double-walled 30-L (nominal capacity: 30 L, total capacity: 45 L, Schott) glass reactor is charged with ethanol (30 L), and intermediate **2** (3500 g, 15.15 mol) is added with stirring. Following the addition of tyrosine (2.05 kg, 15.0 mol), the mixture is heated at reflux for 4 h. Ethanol (15 L) is removed by distillation, and the resulting suspension of intermediate **3** is cooled to 5 °C. A solution of sodium borohydride (465 g, 11.6 mol) in water (750 mL), stabilized by addition of 30% sodium hydroxide (1.5 mL), is added slowly, at such a rate so as to minimize foaming and to maintain the temperature <30 °C. The mixture is stirred for 1 h at room temperature and then added, with stirring, to water (80 L) in an open 120-L polypropylene container. The suspension is left to settle overnight, filtered using a 60-L filter press, and washed with water (3 × 10 L). After drying at 70 °C at 40 mbar, 5.02 kg (94.2%) of product **4** is recovered, mp 122–125 °C. TLC: *R*_f = 0.25 (EtOAc: methanol 9:1).

IR (KBr) 3370–3200 (br), 1554, 1511, 1448, 1409, 1246, 1166, 1023, 825, 800, 656 cm⁻¹; ¹H NMR (CDCl₃) δ 2.45 (s, 1H), 2.50–2.65 (m, 4H), 3.50 (s, 2H), 3.70 (s, 3H), 6.60–6.95 (m, 6H); ¹³C NMR (CDCl₃ + DMSO-*d*₆ = 1:1) δ 155.5, 147.3, 146.0, 130.5, 129.7, 129.2, 116.9, 115.6, 115.0, 111.0, 55.8, 51.8, 50.2, 34.5;

Step 4: *N*-(4-Hydroxyphenethyl)-*N*-(2-bromo-5-hydroxy-4-methoxybenzyl)formamide (5). A double-walled 30-L (nominal capacity: 30 L, total capacity: 45 L, Schott) glass reactor is charged with dioxane (28 L), and intermediate **4** (5.00 kg, 14.2 mol) is added with stirring. Ethyl formate (1900 mL, 23.6 mol), dimethylformamide (900 mL), and formic acid (150 mL) are added, and the mixture is refluxed for 10 h, followed by removal of volatiles using a 10-L rotary evaporator. Methanol (20 L) is added to the residue; the mixture is transferred to an 80-L polypropylene container and water and ice (60 L) are added with stirring. The suspension is stirred for 1 h, filtered using a 60-L filter press, washed with water (3 × 5 L) and dried in a vacuum desiccator at 60 °C and 40 mbar overnight. Yield of product

5 is 4.88 kg (80%), mp 164–165 °C [lit.²⁷ 148–149 °C]. *R*_f = 0.25 (EtOAc/hexane, 8:2).

IR (KBr) 3381, 2976, 2802, 1626, 1503, 1440, 1388, 1345, 1268, 1207, 1159, 1016, 825, 792 cm⁻¹; ¹H NMR (mixture of two rotamers, CDCl₃) δ 2.60 (m, 2H), 3.25 (m, 2H), 3.80 (s, 3H), 4.35 (br d, 2H), 6.65–7.00 (m, 6H); 7.80 (br s, 1H, exchangeable with D₂O), 8.20 (s, 1H, exchangeable with D₂O), 9.00 (s, 1H, CHO); ¹³C NMR (mixture of two rotamers, CDCl₃) δ 163.0 and 162.8 (d), 155.7 and 155.8 (s), 148.2 and 147.9 (s), 146.4 and 146.3 (s), 129.7 and 129.4 (d), 128.7 and 128.4 (s), 127.7 and 127.4 (s), 116.9 and 116.3 (d), 116.1 and 115.8 (d), 115.8–115.1 (3*d), 111.2 and 110.8 (s), 55.9 and 55.5 (q), 50.0 and 47.9 (t), 43.8 and 43.2 (t), 33.5 and 31.9 (t).

Step 5: 4α,5,9,10,11,12-Hexahydro-1-bromo-3-methoxy-11-formyl-6H-benzofuro[3a,3,2-ef][2] benzazepine-6-one (6). An 800-L steel reactor is charged with toluene (600 L) and water (120 L). Potassium hexacyanoferrate (III) (48 kg, 66.8 mol) and potassium carbonate (2 kg) are added. The reactor is heated to 50 °C with steam. Intermediate **5** (12 kg, 31.5 mol) is added at once, and the biphasic mixture is stirred for 1 h at 50–60 °C. Diatomaceous earth (30 kg) is added, and the pulpy mixture is filtered under pressure in 12 portions. The partly polymeric, insoluble filtered solids are removed following the filtration of each portion and placed in the filter press. The filtrate is transferred to the phase separator vessel. The lower, aqueous phase is removed to the cyanide waste tank. The toluene phase is washed with water (2 × 40 L) and pumped into the 500-L reactor. Toluene (2 × 30 L) is used to rinse the 800-L reactor. The washings are added to the filter press to resuspend the solids, and then it is filtered into the phase separator. The toluene phase is added to the 500-L reactor, and the combined toluene extracts are reduced by distillation at normal pressure to 50 L. The hot solution is added rapidly (within 5 min), with stirring, to petroleum ether (60 L, Bp. 80–110 °C). The crystalline product, obtained after cooling to 10–20 °C, is pressure-filtered, washed with petroleum ether (2 × 5 L, bp 80–110 °C), and dried at 80 °C and 40 mbar to yield 4.75 kg (40%) of the product **6**, mp 200–205 °C [lit.²⁷ 181–183 °C]. TLC: *R*_f = 0.45 and 0.55 (2 spots corresponding to 2 rotamers) (CHCl₃/MeOH, 95:5).

IR (KBr) 3440 (br), 1655, 1590, 1491, 1449, 1280, 1212, 1190, 1058, 1030, 455 cm⁻¹; ¹H NMR (mixture of two rotamers, CDCl₃ + DMSO-*d*₆ = 1:1) δ 8.18 (s+s, 1 H), 6.95 (s, 1 H), 6.80 (dd, 1 H, *J* = 12.8 Hz, *J* = 6.4 Hz), 6.10 (d, 1 H, *J* = 12.8 Hz), 5.70 and 5.15 (d+d, 1 H, *J* = 16.0 Hz), 4.70 (bs, 1 H), 4.50 (d, 0.5 H, *J* = 15.0 Hz), 4.40 and 4.05 (d+d, 1 H, *J* = 16.0 Hz), 4.05–3.90 (m, 0.5 H), 3.85 (s+s, 3 H), 3.80–3.60 (m, 0.5 H), 3.40–3.20 (m, 0.5 H), 3.15 (d, 1 H, *J* = 18.0 Hz), 2.85–2.65 (m, 1 H), 2.30–1.90 (m, 2 H); ¹³C NMR (mixture of two rotamers, CDCl₃+DMSO-*d*₆) δ 193.3 (d), 162.0 and 161.6 (s), 146.8 and 146.6 (s), 144.2 and 143.9 (s), 143.0 and 142.6 (d), 130.48 and 134.43 (s), 127.2 and 127.1 (d), 126.9 and 126.8 (s), 116.0 (d), 113.2 (d), 112.0 (s), 87.3 and 87.2 (d), 55.9 (q), 51.1 and 45.7 (t),

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40.2 and 34.3 (t), 37.6 and 34.2 (t). Calcd. for $C_{17}H_{16}BrNO_3$ (378.23) C, 53.99; H, 4.26; N, 3.70. Found: C, 53.70; H, 4.47; N, 3.41.

Step 6: 4 α ,5,9,10,11,12-Hexahydro-1-bromo-3-methoxy-11-formyl-6H-benzofuro[3a,3,2-ef][2]benzazepine-6-(1,2-propanediol) Ketal (7). A 100-L glass reactor is charged with toluene (70 L), intermediate **6** (10.0 kg, 26.4 mol), *p*-toluene-sulfonic acid (150 g) and 1,2-propanediol (10 L, 133 mol) (Solution A). A separate 15-L addition vessel is charged with a solution of *p*-toluenesulfonic acid (350 g) in 1,2-propanediol (5 L, 66 mol) (Solution B). After Solution A was heated for 1 h, 250 mL aliquots of Solution B is added to the refluxing mixture at 15 min intervals for total of 5 h. The mixture is refluxed, with stirring, for 6 h to remove water. The reaction mixture is cooled to 20 °C. The lower phase is transferred to a 40-L polypropylene container and extracted with toluene (4 \times 10 L). The combined toluene phases are concentrated in the 100-L glass reactor to a volume of 70 L. This solution then is cooled to 20 °C and washed successively with 10% acetic acid (20 L), saturated sodium hydrogen carbonate solution (2 \times 20 L) and finally with water (2 \times 20 L). The toluene phase is evaporated to dryness using a 50-L rotary evaporator to yield the product **7** (9.22 kg, 80%) as a dry foam. The foam was crystallised using ligroin (25 L, bp 80–110 °C) to give the product as pale yellow crystals mp 170–171 °C. TLC: 2 interconvertible spots at R_f = 0.70 and 0.75 ($CHCl_3$ /MeOH, 95:5).

1H NMR (mixture of diastereoisomers and rotamers, $CDCl_3$) δ 8.12 (s+s, 1 H), 6.88 (s, 1 H), 5.96–6.17 (m, 1 H), 5.60–5.85 (m, 1.5 H), 5.10 (d, 0.5 H, J = 18.5 Hz), 4.53 (bs, 1 H), 3.90–4.40 (m, 5 H), 3.82 (s, 3H), 3.10–3.75 (m, 3 H), 2.56–2.80 (m, 1 H), 1.80–2.40 (m, 3 H), 1.30 (d+d, 3H); ^{13}C NMR (mixture of diastereoisomers and rotamers, $CDCl_3$) δ 162.5, 161.7, 147.2, 144.9, 144.6, 132.2, 129.0, 128.5, 128.6, 127.8, 127.7, 127.6, 115.7, 115.5, 127.1, 126.8, 126.5, 113.2, 111.7, 102.4, 102.2, 87.3, 87.1, 73.4, 72.5, 71.7, 71.4, 71.2, 70.6, 70.3, 55.9, 51.5, 46.2, 48.4, 40.8, 39.3, 36.1, 35.9, 34.6, 33.7, 33.4, 33.1, 18.7, 17.6, 17.5.

Step 7: (±)-Narwedine (8). CAUTION: Narwedine and narwedine salts are classified as moderate to severe sensitising agents and, after prolonged exposure, cause severe allergic skin reactions. For this reason, all personnel handling narwedine are equipped with full protective clothing, including protective helmet with controlled air stream, to avoid any contact with this substance.

A 100-L glass reactor is dried under argon and charged with anhydrous THF (30 L). Intermediate **7** (14.4 kg, 33 mol) is added and the addition funnel rinsed with THF (2 L). A 10% solution of $LiAlH_4$ in THF (22 L, 57.9 mol) is added slowly with stirring to the suspension. The addition vessel again is rinsed with THF (2 \times 2 L). Initially, the reaction is exothermic with hydrogen evolution. Synthetic air (80% nitrogen, 20% oxygen) is bubbled into the solution at a rate of 20–25 L/min, with stirring at 60–65 °C without external heating. The reaction is monitored by TLC and is allowed to continue until the starting material has been consumed completely (approximately 3 h). Toluene (20 L) is added, followed by dropwise addition of water (2.5 L) over the

course of 1 h. Again, this addition produces an exothermic reaction and results in the evolution of hydrogen. During this decomposition a gel is formed intermittently, which is difficult to stir. Continued addition of water returns the mixture to a stirrable suspension. At this stage, 15% sodium hydroxide (2.5 L) is added rapidly and stirred for 15 min followed by the addition of diatomaceous earth (2.5 kg) as a filter aid. The solution is stirred for 30 min at reflux and filtered while hot, using a process filter, into a 100-L glass cylinder. The precipitate is extracted with warm solvent (toluene/THF, 1:1 v/v, 3 \times 20 L) and the combined filtrates are evaporated with a 50-L rotary evaporator. The crude narwedine propylene ketal is deprotected by adding 4 N hydrochloric acid (25 L) with stirring (rotary evaporator) for 20 min at 60 °C. The pH of the solution is adjusted to <1 by addition of 4 N hydrochloric acid. The solution is transferred to the 100-L glass reactor, cooled to 40 °C by the addition of ice (5 kg), and extracted with ethyl acetate (2 \times 15 L). The acidic, aqueous phase is concentrated by vacuum distillation (40 °C, 20–30 mbar) to a volume of 15 L. The residue after evaporation is collected and then added slowly with stirring to a polypropylene container charged with 25% ammonium hydroxide (20 L). Ice (10 kg) is added, the suspension of crystalline material is stirred for 30 min, pressure filtered, and washed with water (3 \times 5 L). The wet cake is dried at 70 °C and 40 mbar to give the product **8** (7.53 kg, 80%) as white to pale yellow powder, mp 191–193 °C (lit.¹⁰ 186–190 °C). TLC: R_f = 0.45 ($CHCl_3$ /MeOH, 95:5).

IR (KBr) 3014, 2919, 2844, 1681, 1618, 1587, 1540, 1505, 1440, 1285, 1265, 1212, 1167, 1146, 1133, 1102, 1050, 1029, 1000 cm^{-1} ; 1H NMR ($CDCl_3$) δ 6.93 (d, 1 H, J = 12.8 Hz), 6.64 (AB, 2 H, J = 8.5 Hz), 6.00 (d, 1 H, J = 12.8 Hz), 4.68 (m, 1 H), 4.06 (d, 1 H, J = 16.0 Hz), 3.80 (s, 3 H), 3.70 (d, 1 H, J = 16.0 Hz), 3.02–3.28 (m, 3 H), 2.71 (dd, 1 H, J = 19.2 Hz, J = 3.2 Hz), 2.41 (s, 3 H), 2.15–2.30 (m, 1 H), 1.75–1.90 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 194.4, 147.0, 144.4, 144.0, 130.6, 129.4, 127.1, 122.0, 111.9, 88.0, 60.7, 56.0, 54.1, 49.0, 42.5, 37.3, 33.3.

Step 8: (–)-Narwedine (9). A 100-L glass reactor is charged with ethanol/triethylamine (9:1 v/v, 75 L), and racemic narwedine (**8**, 7.0 kg, 24.5 mol) is added. The mixture is heated to reflux, and ethanol/triethylamine (9:1 v/v, 10 L) is added to give a homogeneous solution. The solution is cooled to 65–68 °C, seeded with **9** (70 g, $[\alpha]^{20}_D$ = –400°, c = 1.5 in $CHCl_3$; lit.²⁵ $[\alpha]^{25}_D$ = –415°, c = 1 in $CHCl_3$), cooled to 40 °C within 1 h, and stirred for 3 h. The suspension is concentrated at 40 °C and 20–40 mbar to a volume of 25–30 L and transferred to a 40-L polypropylene container. The reactor is rinsed with ethanol (1 L); the washing is added to the polypropylene container. The suspension is cooled to 5–10 °C with stirring, pressure filtered, and washed with cold ethanol (4 L, 0–5 °C). After drying at 60 °C and 40 mbar, 5.6 kg (80%) of **9** ($[\alpha]_D$ = –400°, c = 1.5% in $CHCl_3$) is recovered.

IR (KBr) 3014, 2919, 2844, 1681, 1618, 1587, 1540, 1505, 1440, 1285, 1265, 1212, 1167, 1146, 1133, 1102, 1050, 1029, 1000 cm^{-1} ; 1H NMR ($CDCl_3$) δ 6.93 (d, 1 H, J =

12.8 Hz), 6.64 (AB, 2 H, $J = 8.5$ Hz), 6.00 (d, 1 H, $J = 12.8$ Hz), 4.68 (m, 1 H), 4.06 (d, 1 H, $J = 16.0$ Hz), 3.80 (s, 3 H), 3.70 (d, 1 H, $J = 16.0$ Hz), 3.02–3.28 (m, 3 H), 2.71 (dd, 1 H, $J = 19.2$ Hz, $J = 3.2$ Hz), 2.41 (s, 3 H), 2.15–2.30 (m, 1 H), 1.75–1.90 (m, 1 H); ^{13}C NMR (CDCl_3) δ 194.4, 147.0, 144.4, 144.0, 130.6, 129.4, 127.1, 122.0, 111.9, 88.0, 60.7, 56.0, 54.1, 49.0, 42.5, 37.3, 33.3.

Step 9: (–)-Galanthamine Hydrobromide (10). A double-walled 30-L (nominal capacity: 30 L, total capacity: 45 L, Schott) glass reactor, under argon, is charged with 1 M L-Selectride in THF (18.0 L, 18 mol). Anhydrous THF (4 L) is added, and the mixture is cooled, with stirring, to -20°C . While the reactor temperature is maintained below -15°C , solid (–)-narwedine **9** (4200 g, 14.72 mol) is added portionwise over the course of 2 h. The solid-addition funnel is rinsed with anhydrous THF (1 L), and the reaction mixture stirred at -15°C for 30 min. The mixture then is heated to 20°C over the course of 1 h to give an amber-coloured solution. Ethanol (1.5 L) is added dropwise, resulting in a temperature rise to 30°C , and the mixture stirred for an additional 30 min. The reaction mixture is transferred to a 60-L pressure filter, and the reactor is rinsed with THF (1 L). The filtrate is returned to the glass reactor and the filter is rinsed with THF (2×2 L). The solution is diluted with ethanol (5 L) and cooled to 0°C . While maintaining the

temperature below 20°C , 48% hydrobromic acid (3.5 L, 20.8 mol) is added with stirring over the course of 30 min. Seed crystals of **10** (10 g) are added, and the pH is adjusted to <1 using 48% hydrobromic acid. The suspension is stirred at 0 – 5°C for 1 h, pressure filtered, washed with ethanol (3×4 L), and dried at 60°C at 40 mbar to give **10** (5366 g, 99%) as colourless crystals, mp 264 – 267°C (lit.²⁸ 246 – 247°C). $[\alpha]_{\text{D}} = -92^\circ$ ($c = 1.5\%$, H_2O) [lit.²⁸ -93° ($c = 1.5\%$, H_2O)].

^1H NMR ($\text{DMSO-}d_6$) δ 10.50 (bs, 1 H), 6.85 (AB, 2 H, $J = 9.6$ Hz), 6.15 (d, 1 H, $J = 7.9$ Hz), 5.95 (dd, 1 H, $J = 7.9$ Hz, $J = 3.2$ Hz), 4.85 (d, 1 H, $J = 16.0$ Hz), 4.60 (s, 1 H), 4.47 (bs, 1 H), 4.35 (d, 1 H, $J = 16.0$ Hz), 4.10 (bs, 1 H), 3.70–3.90 (s+m, 4 H), 3.50 (d, 1 H, $J = 12.8$ Hz), 2.85 (bs, 3 H), 2.40–2.00 (m, 3 H), 1.90 (d, 1 H, $J = 16.0$ Hz); ^{13}C NMR ($\text{DMSO-}d_6$) (clearly distinguishable signals; b = very broad and small signals) δ 146.3, 144.8, 132.8, 129.8, 125.4, 122.9, 121.2 (b), 111.9, 86.3, 59.4, 57.5 (b), 55.6, 53.7 (b), 46.4, 30.9.

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