Synthesis of galanthamine

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Abstract
The synthesis of (±)- and (-)-galanthamine via 3,4-dihydro-6,7-dimethoxy-4'-oxo-spiro[5H]-2-benzazepine-5,1'-[2]cyclohexene]-2(1H)-carboxylic acid ethyl ester (2) is described.

Keywords: Narwedine, apogalanthamine enone-dienone conversion, O-demethylation

Introduction
In the course of our numerous investigations into the industrial synthesis of galanthamine, we also considered using the known 3,4-dihydro-6,7-dimethoxy-4'-oxo-spiro[5H]-2-benzazepine-5,1'-[2]cyclohexene]-2(1H)-carboxylic acid ethyl ester (2) as the key intermediate.

Results and Discussion
Compound 2 was brominated using either dibromo Meldrum’s acid (method A) or benzyl trimethyl ammonium tribromide (method B) to produce a mixture of mono- and dibrominated spiro compounds 3a and 3b. The conditions described in method B are those that gave the highest yield of pure 3a after optimized efforts. The mono- and dibrominated species were separated by column chromatography and converted to dienones 4. As an alternative, hydrogen bromide was eliminated from the crude mixture of 3a and 3b, and 4a was isolated by chromatography. Various reagent systems (boron tribromide, boron tribromide / ethyl sulfide, aluminum chloride / pyridine, and aluminum chloride / ethyl sulfide) were tested for the O-demethylation of 4a to initiate the intramolecular Michael addition and the formation of the skeleton of the narwedine type enone 5a. Under these reaction conditions, the principal products were identified as apogalanthamine derivatives 10a or 10b (see Scheme 3). 5a was obtained in 5% yield using AlCl3 / Et2S in methylene chloride, and converted to (±)-galanthamine ((±)-1) by
methylation and successive L-Selectride and lithium aluminum hydride reductions. As another alternative, the intermediate 7c was prepared starting with narwedin derivative 6, now available in large quantities due to successful industrial synthesis. L-Selectride reduction with concomitant N-deformylation produced 7a, which was debrominated to 7b and, reacted with ethyl chloroformate, yielded 7c (see Scheme 1).

(a) 5,5-Dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane, CCl₄, reflux; (b) BnMe₃N⁺Br³⁻, THF, rt; (c) DBN, CHCl₃, rt; (d) Et₂S, AlCl₃, CH₂Cl₂, rt; (e) MeI, K₂CO₃, acetone, reflux; (f) L-Selectride, THF, - 20 °C; (g) L-Selectride, THF, - 20 °C; (h) CuZn, CaCl₂, EtOH, water, reflux; (i) ClCO₂Et, Et₃N, CH₂Cl₂, 0 °C; (j) LiAlH₄, THF, reflux; (k) oxalyl chloride, DMSO, Et₃N, - 78 °C

Scheme 1

To synthesize (-)-galanthamine ((-)-1), 5b was converted to (±)-narwedine ((±)-9) which was subjected to the crystallization induced chiral transformation to (-)-narwedine ((-)-9), followed by stereoselective L-Selectride reduction (see Scheme 2).
(a) LiAlH₄, THF, 60 °C, then acid workup; (b) EtOH/Et₃N, reflux; (c) L-Selectride, THF, - 20 °C; (d) propylene glycol, TsOH, toluene, reflux

Scheme 2

To confirm the structure, 10b was converted to the known apogalanthamine derivative 10d by methylation and reduction (see Scheme 3).

(a) AlCl₃, pyridine, 0 °C; (b) BBr₃, Et₂S, CH₂Cl₂, rt; (c) BBr₃, CH₂Cl₂, 0 °C; (d) MeI, K₂CO₃, acetone, reflux; (e) LiAlH₄, THF, 0 °C → rt

Scheme 3

Experimental Section

5'-Bromo-3,4-dihydro-6,7-dimethoxy-4'-oxo-spiro[5H-2-benzazepine-5,1'-[2]cyclohexene]-2(1 H)-carboxylic acid, ethyl ester (3a). Method A. 5,5-Dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane (Dibromomeldrum's acid) (120 mg, 0.40 mmol) was added to the spiroenone 2 (140 mg, 0.43 mmol) in CCl₄ (10 mL), and the reaction mixture was refluxed for 21 h. After concentration the residue was purified by flash chromatography (30 g SiO₂, petrol ether : EtOAc, 80 : 20 to 60 : 40) to give the monobrominated species 3a (50 mg, 26.5%) and the dibromo product 3b (20 mg, 9.1%) both as yellow oils.

Method B. Benzyltrimethylammonium tribromide (480 mg, 1.23 mmol) was added to the spiroenone 2 (320 mg, 6.89 mmol) in THF (5 mL) at 0 °C within 30 min, and the reaction mixture was stirred at room temperature for 3 h. CHCl₃ (30 mL) was added and the organic layer was washed with a saturated aqueous NaHCO₃ solution (2 x 40 mL), dried (Na₂SO₄), filtered and
concentrated to give the crude mixture of products, which were separated by flash chromatography using the same eluents as described in method A to yield the monobromo product 3a (228 mg, 53%) and dibrominated species 3b (20 mg, 24%). Analytical data of 3a: \(^1\text{H NMR (CDCl}_3\):} \delta 7.02 (d, 1 H), 7.20 - 7.00 (m, 2 H), 6.05 (d, 1 H), 4.60 - 4.40 (m, 2 H), 4.30 - 3.95 (m, 3 H), 3.85 (s, 3 H), 3.68 (s, 3 H), 3.72 (dd, 1 H), 3.60 (m, 1 H), 3.00 (dd, 1 H), 2.65 (m, 1 H), 2.35 (m, 2 H), 1.2 (m, 3 H). Analytical data of 3b: \(^1\text{H NMR (CDCl}_3\):} \delta 7.10 – 6.85 (m, 2 H), 6.05 (d, 1 H), 4.90 (dd, 1 H), 4.65 (m, 1 H), 4.40 (m, 1 H), 4.20 – 3.95 (m, 2 H), 3.88 (s, 3 H). 3.75 (s, 3 H), 3.50 (m, 1 H), 3.00 (m, 1 H), 2.65 (m, 1 H), 2.45 (m, 1 H), 2.15 (m, 2 H), 1.20 (m, 3 H).

3,4-Dihydro-6,7-dimethoxy-4'-oxo-spiro[5\text{H}-2-benzazepine-5,1'-[2,5]cyclohexa-diene]-2(1\text{H})-carboxylic acid, ethyl ester (4a). Method B was performed on a 6.67 mmol scale and the crude bromination product obtained in almost quantitative yield was dissolved in CHCl\(_3\) (50 mL), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (2.1 mL, 17.6 mmol) was added and the reaction mixture was stirred ad room temperature for 16 h. CHCl\(_3\) (30 mL) was added, and the organic layer was washed with a saturated aqueous NaHCO\(_3\) solution (2 x 25 mL), dried (Na\(_2\)SO\(_4\)), filtered and concentrated. Flash chromatography (50 g SiO\(_2\), hexane : EtOAc, 60 : 40 to 50 : 50) gave compound 4a as a yellow oil (1.55 g, 65% for 2 steps) and bromodienone 4b (1.0 g, 34%) as a colorless solid. Analytical data of 4a: IR (KBr): 3465 br, 2948.6 m, 1680.9 s, 1663.4 s, 1525.4 w, 1470.2 m, 1419.5 m, 1252.6 m, 1124.8 m, 1094.5 m, 1054.6 m; 1H NMR (CDCl\(_3\)) \(\delta 7.46 (d, 1 H), 6.94 (m, 2 H), 6.81 (m, 1 H), 6.38 (d, 1 H), 4.60 (d, 1 H), 4.13 (m, 2 H), 3.81 (s, 3 H), 3.69 (m, 2 H), 3.59 (s, 3 H), 2.26 (m, 2 H), 1.22 (m, 3 H); 13C NMR (CDCl\(_3\)) \(\delta 178.2 (s), 154.9 and 154.5 (s), 154.1 and 153.8 (d), 153.2 (d), 151.8 (s), 148.5 (s), 130.4 (s), 129.2 (s), 125.4 and 125.1 (d), 124.5 and 123.8 (d), 121.9 and 121.4 (s), 111.4 and 111.1 (d), 61.2 and 61.0 (t), 60.5 (q), 55.2 (q), 50.4 (s), 47.3 (t), 43.6 (t), 37.5 and 37.3 (t), 14.2 and 14.1 (q); MS (EI, 70 eV, m/e): 43 8 (2.3), 437 (15.1), 435 (114.8), 498 (14.6), 406 (16.0), 357 (19.1), 356 (100), 321 (10.5), 319 (10.6), 268 (17.6), 267 (53.2), 255 (49.8), 254 (43.8), 253 (10.3), 252 (20.0), 130 (9.5), 129 (28.5), 128 (37.5), 127 (23.3), 119 (17.7), 118 (32.5), 117 (29.5), 116 (10.1), 109 (18.8), 108 (20.8), 107 (12.9), 106 (13.3), 100 (15.5), 99 (30.2), 98 (25.7), 97 (19.4), 88 (18.8), 87 (17.1), 86 ((28.5), 85 (10.4 ), 76 (10.1), 75 (24.27), 74 (17.2), 73 (13.2), 72 (9.3), 71 (27.7). 62 (12.8), 61 (11.5), 60 (22.2), 59 (39.35), 58 (35.1), 57 (8.1), 45 (18.4), 43 (24.7); TLC: hexane : EtOAc = 3 : 2, Rf = 0.4. Analytical data of 4b: IR (KBr): 3480 br, 2948.6 m, 1680.9 s, 1663.4 s, 1525.4 w, 1470.2 m, 1419.5 m, 1252.6 m, 1124.8 m, 1094.5 m, 1054.6 m; 1H NMR (CDCl\(_3\)) \(\delta 7.00 (m, 2 H), 6.80 (m, 2 H), 6.28 (m, 2 H), 4.60 (d, 2 H), 4.08 (m, 2 H), 3.80 (s, 3 H), 3.68 (m, 2 H), 3.55 (s, 3 H), 2.20 (t, 2 H), 1.15 (m, 3 H); 13C NMR (CDCl\(_3\)) \(\delta 185.6 (s), 155.4 (s), 154.5 (d), 154.5 (d), 154.5 (s), 154.2 (s), 148.9 (s), 130.9 and 130.7 (s), 125.8 (d), 125.8 (d), 125.5 and 125.2 (d), 111.3 and 111.0 (d), 61.1 (t), 60.4 (q), 55.4 (q), 47.5 (s), 47.5 (t), 43.9 (t), 38.2 and 38.1 (t), 14.5 and 14.3 (q).

5,6,9,10,11,12-Hexahydro-3-hydroxy-6-oxo-4H-benzo[f][3a,3,2-ef][2]benzazepin-11-carboxylic acid ethyl ester (5a). Dienone 4a (200 mg, 0.61 mmol) in CH\(_2\)Cl\(_2\) (5 mL) was added
to a solution of AlCl₃ (freshly sublimed, 300 mg, 2.24 mmol) and diethyl sulfide (1.4 mL, 13.2 mmol) in CH₂Cl₂ (10 mL) at room temperature and stirred for 4 h. A mixture of MeOH (4 mL), water (1 mL) and CH₂Cl₂ (5 mL) was added, and the organic layer was washed with water (1 x 20 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 15 mL), the combined organic layers were washed with brine (1 x 30 mL), dried (Na₂SO₄), filtered and concentrated. Flash chromatography (20 g SiO₂, hexane : EtOAc = 60 : 40) gave compound 5a as a colorless oil (10 mg, 5.2%). IR (KBr): 3454 br, 2942 m, 2938 m, 2935 s, 1694 s, 1617 s, 1490 s, 1427 s, 1240 s, 1101 m, 1067 m, 1031 m, 973 m, 947 m, 917 m, 851 m, 772 m, 699 w cm⁻¹; ¹H NMR (CDCl₃) δ 6.95 (dd, 1 H), 6.75 (m, 2 H), 6.03 (d, 1 H), 5.60 (s, OH), 4.90 (dd, 1 H), 4.62 (d, 1 H), 4.40 (d, 1 H), 4.20 – 3.90 (m, 3 H), 3.35 (m, 1 H), 3.10 (m, 1 H), 2.75 (dd, 1 H), 2.28 – 1.92 (m, 2 H), 1.22 (m, 3 H); TLC: hexane : EtOAc = 3 : 2, Rf = 0.4.

5,6,7,8-Tetrahydro-11-hydroxy-1,2-dimethoxydibenz[c,e]azocine-6-carboxylic acid ethyl ester (10b). Method A. Dienone 4a (100 mg, 0.31 mmol) in CH₂Cl₂ (3 mL) was added to a solution of BBr₃ (228 mg, 0.91 mmol) and diethyl sulfide (279 mg, 3.10 mmol) in CH₂Cl₂ (5 mL) at room temperature and stirred for 20 min. A saturated aqueous NaHCO₃ solution (80 mL) was added, the layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were washed with brine (1 x 30 mL), dried (Na₂SO₄), filtered and concentrated. Flash chromatography (20 g SiO₂, hexane - EtOAc, 70 : 30 to 60 : 40) yielded compound 10b as colorless oil (80 mg, 80%).

Method B. Dienone 4a (178 mg, 0.55 mmol) was added to a solution of AlCl₃ (freshly sublimated, 2.30 g, 17.2 mmol) in pyridine (14 mL) at 0 °C and stirred at room temperature for 28 h. After concentration the residue was dissolved in CHCl₃ (80 mL) and washed with 2 N HCl (1 x 80 mL). The aqueous layer was extracted with CHCl₃ (2 x 20 mL), the combined organic layers were washed with brine (1 x 30 mL), dried (Na₂SO₄), filtered and concentrated. Flash chromatography (20 g SiO₂, hexane - EtOAc, 70 : 30 to 60 : 40) yielded compound 10b as colorless oil (80 mg, 54%). ¹H NMR (CDCl₃) δ 7.55 and 7.32 (d, 1 H), 7.15 (m, 1 H), 6.90 (d, 1 H), 6.78 (m, 2 H), 6.30 (d, OH), 4.80 (dd, 1 H), 4.62 – 4.30 (m, 1 H), 4.25 - 4.00 (m, 2 H), 3.95 (s, 3 H), 3.48 (s, 3 H), 3.20 (t, 1 H), 2.95 (t, 1 H), 2.80 (m, 1 H), 1.84 (dd, 1 H), 1.50 – 1.15 (m, 3 H); ¹³C NMR (CDCl₃) δ 156.1 s, 155.9 (s), 152.2 and 152.1 (s), 146.2 and 145.9 (s), 141.7 and 141.5 (s), 134.5 and 134.1 (s), 132.2 (d), 130.9 and 130.8 (s), 127.3 and 126.9 (s), 126.3 and 125.7 (d), 115.5 (d), 113.1 (d), 111.3 and 111.2 (d), 61.5 and 61.4 (t), 60.3 (q), 55.7 (q), 47.5 and 47.2 (t), 47.1 and 46.9 (t), 34.9 and 34.8 (t), 14.7 and 14.5 (q); TLC: hexane - EtOAc = 3 : 2, Rf = 0.3.

5,6,7,8-Tetrahydro-1,2,11-trimethoxydibenz[c,e]azocine-6-carboxylic acid ethyl ester (10c). To a suspension of K₂CO₃ (1.30 g, 9.40 mmol) in acetone (30 mL) phenol 10b (310 mg, 0.86 mmol) an methyl iodide (681 mg, 4.80 mmol) were added, and the mixture was refluxed for 15 h. After concentration water (60 mL) was added to the residue. The aqueous phase was extracted with EtOAc (3 x 30 mL), the combined organic layers were washed with brine (1 x 50 mL), dried (Na₂SO₄), filtered and concentrated. Flash chromatography (60 g SiO₂, hexane : EtOAc, 60 : 40) yielded compound 10c as colorless oil (304 mg, 94%). ¹H NMR (CDCl₃) δ 7.55
and 7.35 (d, 1 H), 7.25 (m, 1 H), 6.95 – 6.75 (m, 3 H), 5.00 – 4.70 (dd, 1 H), 4.65 – 4.45 (m, 1 H), 4.40 – 4.00 (m, 2 H), 3.91 (s, 3 H), 3.86 (s, 3 H), 3.42 (s, 3 H), 3.13 (t, 1 H), 2.85 (m, 2 H), 2.40 (dd, 1 H), 1.50 – 1.20 (m, 3 H); 13C NMR (CDCl3) δ 159.4 (s), 155.7 (s), 152.2 and 152.2 (s), 146.3 and 146.1 (s), 141.8 and 141.5 (s), 134.5 and 134.1 (s), 132.2 (d), 131.1 and 131.0 (s), 127.7 and 127.5 (s), 126.4 and 125.7 (d), 114.3 and 114.1 (d), 111.4 (d), 111.3 (d), 61.3 (t), 60.3 (q), 55.8 (q), 55.1 (q), 47.5 (t), 47.2 and 47.0 (t), 35.2 (t), 14.8 and 14.6 (q).

5,6,7,8-Tetrahydro-1,2,11-trihydroxydibenzo[c,e]azocine-6-carboxylic acid ethyl ester (10a).

Dienone 4a (250 mg, 0.78 mmol) in CH2Cl2 (5 mL) was added to a solution of BBr3 (876 mg, 3.50 mmol) in CH2Cl2 (10 mL) at 0 °C and stirred for 60 min at this temperature. Water (10 mL) was added and the pH was adjusted to 9 using 2 N NaOH. The layers were separated and the aqueous layer was acidified with 2 N HCl and extracted with CHCl3 (3 x 50 mL). The combined organic layers were washed with brine (1 x 50 mL), dried (Na2SO4), filtered and concentrated. Flash chromatography (22 g SiO2, hexane : EtOAc, 70 : 30 to 60 : 40 to 50 : 50) yielded compound 10a as colorless solid (155 mg, 67%). IR (KBr): 3307 br, 1633 s, 1470 s, 1440 s, 1408 m, 1270 s, 1288 s, 1113 s, 1075 m, 1026 w, 991 m, 910 w, 902 w, 890 w, 810 w, 590 w, 418 cm⁻¹; 1H NMR (DMSO-d6) δ 8.65 (s, OH), 8.43 (s, OH), 6.95 – 6.40 (m, 5H), 6.25 (s, OH), 4.45 (dd, 1 H), 4.35 – 3.98 (m, 1 H), 3.95 – 3.70 (m, 2 H), 2.85 (t, 1 H), 2.50 (m, 2 H), 2.05 (t, 1 H), 1.20 – 0.90 (m, 3 H); 13C NMR (DMSO-d6) δ 156.7 (s), 155.1 (s), 143.9 and 143.7 (s), 141.5 (s), 141.2 and 141.1 (s), 131.6 (d), 129.3 and 129.3 (s), 127.1 and 126.9 (s), 125.5 and 125.7 (s), 121.3 and 120.9 (d), 115.4 (d), 113.7 (d), 112.8 (d), 60.6 (t), 46.5 and 46.7 (t), 46.8 and 47.0 (t), 34.5 (t), 14.4 and 14.7 (q); TLC: hexane : EtOAc = 3 : 2, Rf = 0.1; m.p.: 213 - 218 °C.

5,6,7,8-Tetrahydro-1,2,11-trimethoxy-6-methyl-dibenz[c,e]azocine (10d).

Carbamate 10c (175 mg, 0.47 mmol) was added to a suspension of LiAlH4 (39 mg, 1.02 mmol) in anhydrous THF (10 mL) at 0 °C and stirred at room temperature overnight. Water (100 mL) was added, and the aqueous layer was extracted with EtOAc (4 x 100 mL). The combined organic layers were washed with brine (1 x 50 mL), dried (Na2SO4), filtered and concentrated. Flash chromatography (30 g SiO2, EtOAc : hexane, 90 : 10) gave compound 10d as colorless oil (90 mg, 61%). m.p. 165 – 169 °C (perchlorate, Lit. 6: 167 – 170 °C); 1H NMR (DMSO-d6) δ 7.28 (d, 1 H), 7.10 (d, 1 H), 6.95 (d, 1 H), 6.65 (m, 2 H), 3.90 (s, 3 H), 3.85 (s, 3 H), 3.50 (d, 1 H), 3.42 (s, 3 H), 3.20 (d, 1 H), 3.00 (d, 1 H), 2.70 – 2.35 (m, 3 H), 3.40 (s, 3 H); 13C NMR (DMSO-d6) δ 158.8 (s), 151.3 (s), 145.7 (s), 142.3 (s), 133.6 (s), 131.2 (s), 131.0 (d), 127.1 (s), 125.6 (d), 113.5 (d), 110.8 (d), 110.4 (d), 59.7 (q), 58.2 (q), 57.0 (t), 55.3 (t), 54.5 (q), 44.8 (q), 32.0 (t); TLC: EtOAc : Et3N = 95 : 5, Rf = 0.3.

4a,5,9,10-Tetrahydro-3-methoxy-6-oxo-6H-benzofuro[3a,3,2-ef][2]benzazepine-11(12H)-carboxylic acid ethyl ester (5b). To a suspension of K2CO3 (0.50 g, 6.62 mmol) in acetone (20 mL) phenol 5a (100 mg, 0.29 mmol) and methyl iodide (454 mg, 3.20 mmol) were added, and the mixture was refluxed for 6 h. After concentration water (60 mL) was added to the residue. The aqueous phase was extracted with EtOAc (3 x 30 mL), the combined organic layers were washed with brine (1 x 50 mL), dried (Na2SO4), filtered and concentrated. Flash
chromatography (50 g SiO₂, CHCl₃ : MeOH, 99 : 1) yielded compound 5b as colorless solid (65 mg, 65%). IR (KBr): 3441 br, 2975 m, 2902 m, 1699 s, 1624 m, 1511 s, 1432 s, 1289 s, 1249 s, 1217 s, 1194 s, 1139 m, 1107 m, 1057 m, 1020 m, 993 m, 930 w, 880 w, 837 w, 809 w, 775 m cm⁻¹; ¹H NMR (CDCl₃)  δ 6.85 (d, 1 H), 6.90 – 6.60 (m, 2 H), 6.03 (d, 1 H), 4.90 (dd, 1 H), 4.70 (s, 1 H), 4.30 (dd, 1 H), 4.20 – 3.90 (m, 3 H), 3.80 (s, 3 H), 3.35 (m, 1 H), 3.15 (dd, 1 H), 2.75 (dd, 1 H), 2.28 – 1.90 (m, 2 H), 1.20 (t, 3 H); ¹³C NMR (CDCl₃)  δ 193.7 (s), 155.1 and 155.0 (s), 147.2 (s), 143.8 (s), 143.3 and 143.2 (d), 129.5 and 129.2 (s), 129.0 (s), 126.9 (d), 121.1 and 120.6 (d), 111.5 and 111.3 (d), 87.3 (d), 61.1 (t), 55.6 (q), 51.4 and 51.0 (t), 48.7 (s), 45.5 and 45.2 (t), 36.8 (t), 36.1 and 35.2 (t), 14.2 and 14.1 (q); TLC: CHCl₃ : MeOH = 99 : 1, Rf = 0.4; m. p.: 154 – 156 °C.

(6R)-1-Bromo-3-methoxy-5,6,9,10,11,12-hexahydro-4aH-benzofuro[3a,3,2-eff][2]benzazepin-6-ol (7a). To a suspension of ketone 6 (15.0 g, 39.7 mmol) in dry THF (400 mL) L-Selectride® (120 mL, 1 N in THF) was added at – 20 °C. The mixture was stirred for 2 h at this temperature, then water (100 mL) was added dropwise. After stirring for 10 min. the mixture was concentrated, and the residue was dissolved in EtOAc (300 mL). The organic layer was washed with a saturated aqueous NaHCO₃ solution (1 x 300 mL), the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with a saturated aqueous NaHCO₃ solution (2 x 300 mL), water (1 x 100 mL), brine (1 x 300 mL), dried (Na₂SO₄), filtered and concentrated. Flash chromatography (500 g SiO₂, CH₂Cl₂ : MeOH : aqueous ammonia = 96 : 3.5 : 0.5) gave compound 7a as a colorless solid (8.51 g, 61%). ¹H NMR (CDCl₃):  δ 6.85 (s, 1 H), 4.56 (b, 1 H), 6.05 - 5.90 (m, 2 H), 4.48 (d, 1 H), 4.10 (dd, 1 H), 3.85 (d, 1 H), 3.80 (s, 3 H), 3.35 - 3.05 (m, 2 H), 2.62 (m, 1 H), 2.02 (NH, OH), 1.98 (m, 1 H), 1.85 -1.65 (m, 2 H); ¹³C NMR (CDCl₃)  δ 145.8 (s), 144.0 (s), 134.1 (s), 131.6 (s), 127.9 (d), 126.8 (d), 115.5 (d), 113.0 (s), 88.4 (d), 61.7 (d), 56.0 (q), 52.7 (t), 49.3 (s), 46.6 (t), 39.8 (t), 29.7 (t); TLC: CH₂Cl₂: MeOH = 9 : 1, Rf = 0.65; m. p.: 152 – 153 °C.

(6R)-3-Methoxy-5,6,9,10,11,12-hexahydro-4aH-benzofuro[3a,3,2-eff][2]benzazepin-6-ol (7b). A suspension of zinc dust (19.0 g, 290 mmol) and copper(I)iodide (19.0 g, 100 mmol) in ethanol (200 mL)/water (200 mL) was sonicated for 1 h under an argon atmosphere. Calcium chloride (14.0 g, 126 mmol) and 7a (7.0 g, 19.9 mmol) were added, and the mixture was refluxed for 3 h, filtered and concentrated. The residue was dissolved in CHCl₃ (100 mL) and washed with water (1 x 100 mL). The aqueous layer was extracted with CHCl₃ (2 x 100 mL), the combined organic layers were washed with aqueous NaHCO₃ solution (2 x 300 mL), water (1 x 100 mL), brine (1 x 300 mL), dried (Na₂SO₄), filtered and concentrated. The crystalline residue was washed with diisopropyl ether (50 mL) to give the debrominated compound 7b (4.45 g, 82%). ¹H NMR (CDCl₃):  δ 6.65 - 6.52 (m, 2 H), 6.06 - 5.92 (m, 2 H), 4.57 (b, 1 H), 4.15 - 4.08 (m, 1 H), 3.95 (d, J = 5.7 Hz, 2 H), 3.79 (s, 3 H), 3.34 (ddd, J = 14.6, 3.5, 3.5 Hz, 1 H), 3.18 (ddd, J = 13.2, 11.4, 2.6 Hz, 1 H), 2.66 (ddd, J = 15.7, 1.63, 1.63 Hz, 1 H), 1.98 (ddd, J = 15.7, 5.0, 2.4 Hz, 1 H), 1.88 - 1.61 (m, 2 H); ¹³C NMR (CDCl₃):  δ 146.2 (s), 143.9 (s), 133.1 (s), 133.0 (s), 127.6 (d), 127.0 (d), 120.5 (d), 111.0 (d), 88.5 (d), 61.9 (d), 55.8 (q), 53.8 (t), 48.7 (s), 47.0 (t), 40.3 (t), 29.9 (t); TLC: CHCl₃: MeOH = 9 : 1; Rf = 0.35; m. p.: 233 – 235°C.
(6R)-3-Methoxy-5,6,9,10,11,12-hexahydro-6-hydroxy-4aH-benzofuro[3a,3,2-ef][2]benzazepin-11-carboxylic acid ethyl ester (7c) Method A. A solution of norgalanthamine 7b (300 mg, 1.10 mmol) and Et₃N (121 mg, 1.20 mmol) in dry CH₂Cl₂ (5 mL) was treated with ethyl chloroformate (121 mg, 1.12 mmol) in CH₂Cl₂ (1 mL) at 0 °C. The reaction mixture was stirred at this temperature for 1 h, then 2 N HCl (10 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (3 x 3 mL), the combined organic layers were washed with 2 N HCl (2 x 5 mL), water (1 x 10 mL), a saturated aqueous NaHCO₃ solution (2 x 10 mL), water (1 x 100 mL), brine (1 x 10 mL), dried (Na₂SO₄), filtered and concentrated to give carbamate 7c as a colorless foam (349 mg, 92%).

Method B. To a suspension of carbamate 5b (100 mg, 0.29 mmol) in dry THF (4 mL) L-Selectride® (1.46 mL, 1 N in THF, 1.46 mmol) was added at – 20 °C. The mixture was stirred for 2 h at this temperature, then water (2 mL) was added dropwise. After stirring for 10 min. the mixture was concentrated, and the residue was dissolved in EtOAc (10 mL). The organic layer was washed with a saturated aqueous NaHCO₃ solution (1 x 10 mL), the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with a saturated aqueous NaHCO₃ solution (2 x 10 mL), water (1 x 10 mL), brine (1 x 10 mL), dried (Na₂SO₄), filtered and concentrated. Flash chromatography (10 g SiO₂, CH₂Cl₂ : MeOH : aqueous ammonia = 96 : 3.5 : 0.5) gave compound 7c as a colorless solid (76.5 mg, 76%).

1H NMR (CDCl₃) δ 6.82 – 6.56 (m, 2 H), 6.07 – 5.88 (m, 2 H), 4.99 – 4.60 (m, 1 H), 4.56 (s, 1 H), 4.38 – 3.89 (m, 6 H), 3.78 (s, 3 H), 3.50 – 3.18 (m, 1 H), 2.62 (dd, 1 H), 2.40 (s, 1 H), 2.09 – 1.60 (m, 3 H), 1.31 – 1.09 (m, 3 H); 13C NMR (CDCl₃) δ 155.4 and 155.3 (s), 146.3 (s), 144.1 (s), 132.2 and 131.9 (s), 129.2 (s), 127.9 (d), 126.2 (d), 121.3 and 120.7 (d), 111.1 and 110.8 (d), 88.1 and 88.0 (d), 61.6 (d), 61.2 (t), 55.7 (q), 51.6 and 51.2 (t), 48.2 (s), 45.5 and 45.2 (t), 37.1 and 36.2 (t), 29.7 (t), 14.4 and 14.3 (q); TLC: CHCl₃ : MeOH = 9 : 1, Rf = 0.75; EtOAc, Rf=0.65.

3-Methoxy-11-methyl-5,6,9,10,11,12-hexahydro-4aH-benzofuro[3a,3,2-ef][2]benzazepine-6,2'-[1,3]dioxolane-11-carboxylic acid, ethyl ester (8). Ketone 5b (10.0 g, 29.1 mmol), p-toluene sulfonic acid (150 mg) and 1,2-propanediol (10 mL) mixture were refluxed with stirring in toluene (70 mL) for 10 hours using a Dean-Stark type apparatus. A dropping funnel was charged with a solution of p-toluene sulfonic acid (350 mg) in 1,2-propanediol (5 mL). After the first hour of refluxing and then every 15 min. for the remaining 5 h, 250 µL of this solution were added to the refluxing mixture. The reaction mixture was cooled to 20°C, and the lower phase was separated and extracted with toluene (4 x 10 mL). The combined toluene phases were concentrated to a volume of 70 mL. This solution then was cooled to 20°C and washed successively with 10% acetic acid (20 mL), saturated sodium hydrogen carbonate solution (2 x 20 mL), water (2 x 20 mL), brine (20 mL), dried (Na₂SO₄), filtered and evaporated to dryness to yield the product 8 (9.56 g, 82%) as a dry foam, which was directly used in the next step.

3-Methoxy-11-methyl-5,6,9,10,11,12-hexahydro-4aH-benzofuro[3a,3,2-ef][2]benzazepin-6-one, (±)-narwedine ((±)-9). To ketal 8 (14.4 g, 35.9 mol) in anhydrous THF (30 mL) a 10% solution of LiAlH₄ in THF (24 mL, 63.0 mmol) is added slowly with stirring to the suspension.
Synthetic air (80% nitrogen, 20% oxygen) is introduced into the solution 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 mL) is added, followed by dropwise addition of water (2.5 mL). 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 mL) is added rapidly and stirred for 15 min. followed by the addition of diatomaceous earth (2.5 g) as a filtration aid. The solution is stirred for 30 min at reflux and filtered while hot. The precipitate is hot-extracted with toluene : THF = 1:1 (3 x 20 mL) and the combined filtrates are evaporated to dryness. The crude product is deprotected by adding 4N HCl (25 mL) and stirring for 20 min at 60°C. After adjusting the pH of the solution to < 1 by addition of 4N HCl the solution is cooled and washed with EtOAc (2 x 15 mL). The acidic, aqueous phase is concentrated by vacuum distillation (40°C, 20 - 30 mbar) to a volume of 15 mL. To the residue 25% ammonium hydroxide (20 mL) and ice (10 g) are added, the suspension of crystalline material is stirred for 30 min, filtered, washed with water (3 x 5 mL) and dried at 70°C and 40 mbar to give the product (±)-9 (8.09 g, 79%) as white to pale yellow powder. 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 (CDCl₃) 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); ¹³C NMR (CDCl₃) δ 194.4, 147.0, 144.4, 144.0, 130.6, 129.4, 127.1, 127.1, 122.0, 111.9, 88.0, 60.7, 56.0, 54.1, 49.0, 42.5, 47.7, 37.3, 33.3; TLC: CHCl₃ : MeOH = 95 : 5, Rf = 0.45; m. p.: 191 - 193°C.

(−)-Narwedine ((−)-9). (±)-9 (7.0 g) in ethanol : triethylamine = 9 : 1 (75 mL) is heated to reflux and ethanol : triethylamine = 9 : 1 (10 mL) is added to give a homogeneous solution. The solution is cooled to 65 - 68°C, seeded with (−)-9 (70 mg) 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 30 mL, cooled to 5 - 10°C with stirring, filtered and washed with cold ethanol (4 mL). After drying at 60°C and 40 mbar, 5.61 g (80%) of (−)-9 is recovered. α = - 400, c = 1.5% in CHCl₃, Lit.⁷: α₂₀ = - 405. D

5,6,9,10,11,12-Hexahydro-3-methoxy-6-oxo-4aH-benzofuro[3a,3,2-ef][2]benzazepin-11-carboxylic acid ethyl ester (5b). To a solution of oxalyl chloride (110 mg, 0.87 mmol) in dry CH₂Cl₂ (3 mL), DMSO (68 mg, 0.87 mmol) in dry CH₂Cl₂ (1 mL) was added at − 78 °C and stirred for 1 h at this temperature. Carbamate 7c (150 mg, 0.34 mmol) in dry CH₂Cl₂ (2 mL) was added and stirred at − 60 °C for 5 h. After addition of triethylamine (200 mg, 1.98 mmol) the mixture was stirred for 1 h at − 60 °C and 1 h at room temperature. The reaction mixture was washed with 2 N HCl, the aqueous layer was extracted with CH₂Cl₂ (2 x 4 mL), the combined organic layers were washed with 2 N HCl (2 x 10 mL), a saturated aqueous NaHCO₃ solution (2 x 10 mL), water (1 x 10 mL), brine (1 x 10 mL), dried (Na₂SO₄), filtered and concentrated to give ketone 5b as a colorless solid (143 mg, 96%).

(+)-Galanthamine ((+)-1). To a suspension of LiAlH₄ (55 mg, 1.44 mmol) in dry THF (1 mL) carbamate 7c (100 mg, 0.29 mmol) in dry THF (0.5 mL) was added dropwise. After stirring at
reflux temperature for 12 h a saturated aqueous NaHCO₃ solution (3 mL) was added, and the mixture was concentrated. The residue was dissolved in CHCl₃ (5 mL) and washed with a saturated aqueous NaHCO₃ solution (3 x 3 mL). The aqueous layer was extracted with CHCl₃ (4 x 3 mL). The combined organic layers were washed with a saturated aqueous NaHCO₃ solution (2 x 5 mL), water (1 x 5 mL), brine (1 x 10 mL), dried (Na₂SO₄), filtered and concentrated. Flash chromatography (10 g SiO₂, CHCl₃ : MeOH : aqueous ammonia = 97 : 2.5 : 0.5) gave compound 1 as a colorless solid (75 mg, 90%), which was identical to galanthamine (HPLC, NMR).

(-)-Galanthamine ((-)-1). To a suspension of (-)-Narwedine ((-)-9) (1.0g, 3.50 mmol) in dry THF (10 mL) L-Selectride® (5.3 mL, 1 N in THF) was added at – 20 °C. The mixture was stirred for 2 h at this temperature, then water (100 mL) was added dropwise. After stirring for 10 min. the mixture was concentrated, and the residue was dissolved in EtOAc (20 mL). The organic layer was washed with a saturated aqueous NaHCO₃ solution (1 x 30 mL), the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with a saturated aqueous NaHCO₃ solution (2 x 30 mL), water (1 x 10 mL), dried (Na₂SO₄), filtered and concentrated. Flash chromatography (50 g SiO₂, CH₂Cl₂ : MeOH : aqueous ammonia = 96 : 3.5 : 0.5) gave compound (-)-1 as a colorless solid (0.91 g, 91%), which was identical to Galanthamine (HPLC, NMR). α = -95, c = 1% in CHCl₃, Lit. 5: α₂₅ = -93.4 D

1H NMR (CDCl₃) δ 6.68 - 6.56 (m, 2 H), 6.08 (d, 1 H), 5.98 (dd, 1 H), 4.59 (b, 1 H), 4.12 (b, 1 H), 4.07 (d, 1 H), 3.66 (d, 1 H), 3.82 (s, 3 H), 2.38 (s, 3 H), 3.26 (ddd, 1 H), 3.03 (ddd, 1 H), 2.68 (dd, 1 H), 2.17 - 1.92 (m, 2 H), 1.55 (ddd, 1 H); 13C NMR (CDCl₃) δ 145.6 (s), 143.8 (s), 132.8 (s), 129.2 (s), 127.4 (d), 111.0 (d), 126.7 (d), 121.8 (d), 88.4 (d), 61.8 (d), 60.4 (t), 55.6 (q), 41.9 (q), 53.6 (t), 48.0 (s), 33.6 (t), 29.8 (t).

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References and Notes