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Synthesis of (±)-6*H*-benzofuro[3a,3,2,ef][3]benzazepine: an unnatural analog of (−)-galanthamine

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Abstract—The first total synthesis of an unnatural analog of the anti-Alzheimer drug (−)-galanthamine has been accomplished using $K_3[Fe(CN)]_6$ in the key step to build up the heterocyclic ring system via an oxidative tandem cyclization.

1. Introduction

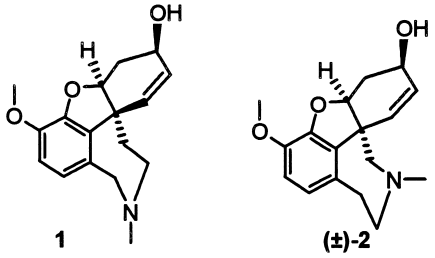
Galanthamine, which has been introduced into the European market and approved by the FDA for the treatment of Alzheimer's disease, is a reversible, competitive cholinesterase inhibitor that also allosterically modulates nicotinic acetylcholine receptors.[1,2] Earlier we have developed a kg-synthesis[3] for (−)-galanthamine **1**, a natural product also currently being isolated from daffodils.[4]

2. Results and discussion

As part of a program to study structure activity relationships of novel galanthamine analogs we formally changed the position of the nitrogen atom in the heterocyclic ring system from a benzylamine to a phenethylamine substructure (Scheme 1, compare galanthamine **1** with (±)-**2**).

The procedure was designed to apply the synthesis of galanthamine invented by Barton[5] to a new substrate and provide further insight into the scope and limitations of this oxidative tandem cyclization reaction.

In this paper we report on the total synthesis of the 3-benzazepine derivative **2** termed 'isogalanthamine'.



Scheme 1.

For the synthesis of the key intermediate **9** we studied two reductive amination pathways (Scheme 2) starting with 6-bromoisovanillin, now available in large quantities from the industrial galanthamine synthesis.[3] Our first approach was to synthesize benzeneacetaldehyde **4** with a Wittig-type homologation and subsequent hydrolysis[6] of **3**.

Since the reductive amination of **4** with 4-OH benzylamine resulted in unsatisfactory yields of **8**, we investigated an alternative pathway and prepared phenylethylamine **6**. We increased the yield for the preparation of **5**[7] from 79 to 92% and converted bromoisovanillin in an overall yield of 56% to **6**. Previously Battersby[8] used the same starting material to prepare **6** in a six-step-reaction in an overall yield of 10%. The other preparation of **6** from **4** via the oxime **7** proved less favorable. Having achieved a good synthesis for **6**, the reductive amination of **6** with 4-hydroxybenzaldehyde gave **8** in 97% yield, which was formylated to afford **9**.

The key intermediate **9** was subjected to an oxidative cyclization to form the narwedine analog (±)-**10** (Scheme 3). By using chloroform instead of toluene as described in the industrial galanthamine synthesis[3] as an organic solvent

Keywords: Alzheimer; galanthamine; tandem cyclization; phenolic coupling.
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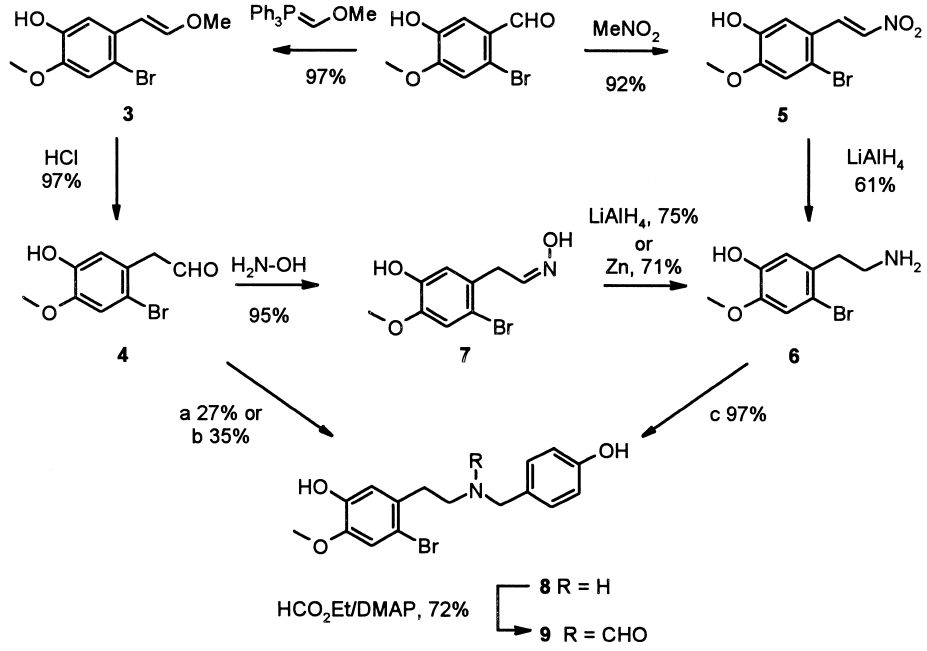
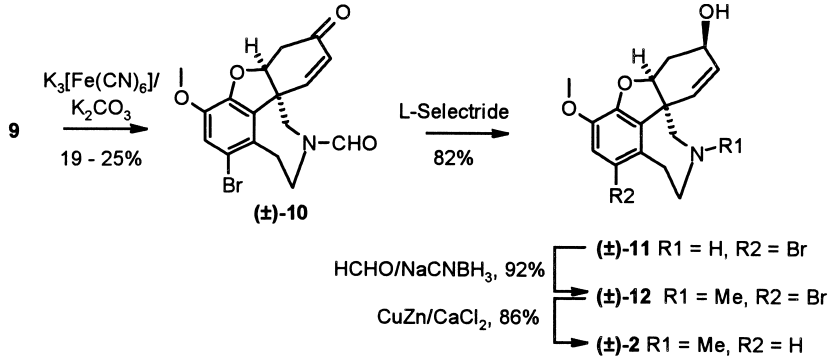


Scheme 2. (a): 4-hydroxybenzaldehydeoxime/Zn/HCl; (b): 4-hydroxybenzylamine/$NaBH_4$; (c): 4-hydroxybenzaldehyde/$NaBH_4$.



Scheme 3.

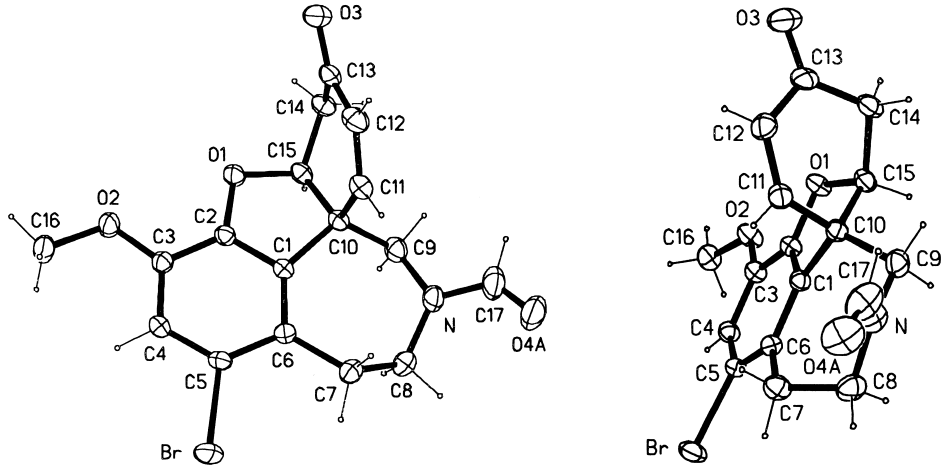


Figure 1. Molecular structure of (±)-**10** in crystalline state (30% ellipsoids, two views) with crystallographic atom numbering. Selected geometric data [Å, °]: Br–C5 1.914(2), O1–C2 1.374(2), O1–C15 1.463(2), O2–C3 1.362(2), O3–C13 1.224(2), N–C8 1.458(3), N–C9 1.453(3), N–C17 1.352(3), C11–C12 1.329(3), C17–O4A 1.104(4), C8–N–C9=118.3(2), C8–N–C17=121.1(2), C9–N–C17=120.5(2), N–C17–O4A=133.4(4).

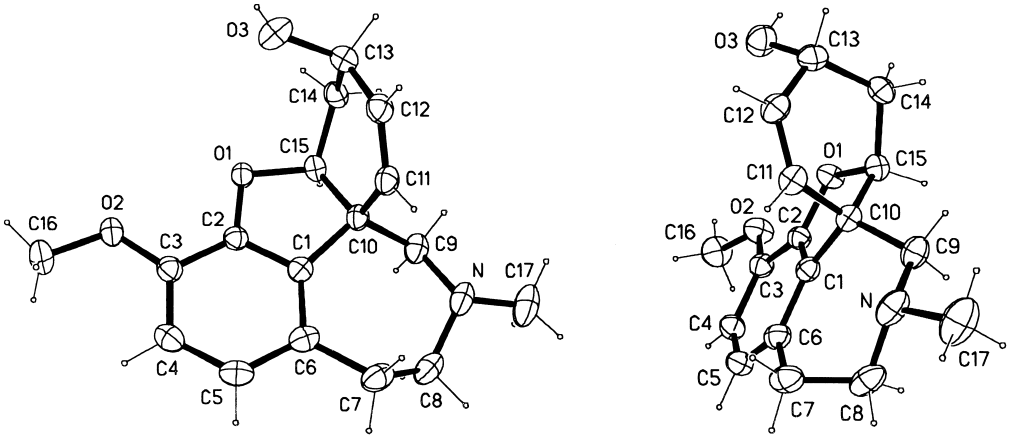


Figure 2. Molecular structure of (±)-**2** in crystalline state (30% ellipsoids, two views) with crystallographic atom numbering. Selected geometric data [Å, °]: O1–C2 1.373(2), O1–C15 1.466(2), O2–C3 1.364(2), O3–C13 1.433(2), N–C8 1.464(2), N–C9 1.463(2), N–C17 1.464(2), C11–C12 1.324(2), C8–N–C9=113.1(1), C8–N–C17=110.7(1), C9–N–C17=109.8(1), intermolecular hydrogen bond O3→O1($-x+1$, $-y$, $-z$)=3.002(2).

for the heterogeneous reaction system the tetracyclic compound (±)-**10** was obtained in 19% yield on a 3 g scale. The isolated yield could be improved to 25% on a 5 g scale, which is satisfactory for this type of tandem reaction. The use of VOF_3[9] as an alternative oxidant instead of $K_3[Fe(CN)_6]$ did not lead to any of the desired products. Ketone (±)-**10** was stereoselectively reduced to alcohol (±)-**11** using L-selectride. The total synthesis of (±)-isogalanthamine ((±)-**2**) was completed by using a reductive methylation with formaldehyde under Eschweiler–Clarke conditions[10] followed by debromination using a copper–zinc couple[11] in the presence of calcium chloride.

The crystal structures of the key intermediate (±)-**10** and of the final product (±)-**2** have been determined by X-ray diffraction (for details see Section 4). The molecular structures are shown in Figs. 1 and 2 with selected geometric data reported in the captions. The structure determinations confirmed the anticipated chemical structures and showed that both compounds retain the general shape characteristics of the tetracyclic ring system of the galanthamine family including the highly preferred chair-conformation of the azepine ring.[12a,d] The change of the nitrogen from a benzylamine position in galanthamine **1** to a phenethylamine position in (±)-**2** has distinct stereochemical consequences, however: whereas in both **1**[12a] and **2** the *N*-methyl groups are in equatorial positions relative to the azepine ring, the electron lone-pair of nitrogen is pointing approximately antiparallel to the C10–C11 bond in **1**, and approximately synparallel to this bond in (±)-**2** (cf. Fig. 2). Thus, significant differences in the bioactivity of both compounds have to be expected.

To summarize, we have developed an eight step synthesis starting from 6-bromoisovanillin with an overall yield of 6.3% using Barton's tandem cyclization as the key step of the synthesis. The results of current pharmacological investigations of (±)-**2** will be reported separately. Attempts to utilize this synthetic scheme for the preparation of structurally related galanthamine analogs and enantiomeric separation via second-order asymmetric transformation are under way.

3. Conclusion

To summarize, we have demonstrated that tandem cyclization can be successfully developed further to access new members of the galanthamine family. Further research in this field is being actively pursued in our laboratory.

4. Experimental

4.1. General

Melting points were measured on a Kofler melting point apparatus.

^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 MHz) pulse Fourier-transform NMR spectrometer in $CDCl_3$ or DMSO-d_6 using tetramethylsilane as an internal standard. Thin layer chromatography (TLC) was performed on Merck TLC aluminum sheets silica 60 F_{254}). Visualization was by UV light or spray reagents (molybdophosphoric acid or ninhydrine and heating). Column chromatography was performed using silica gel (Baker).

All reactions were magnetically stirred under an argon atmosphere.

MPLC (medium pressure liquid chromatography) was performed using a LC-8A pump (Shimadzu), a SPD-6AV UV-detector (Shimadzu) and Büchi preparative glass columns.

4.1.1. 4-Bromo-2-methoxy-5-(2-methoxyethenyl)phenol (3). To a stirred suspension of methoxymethyltriphenylphosphonium bromide (44.51 g, 129.8 mmol) in anhydrous THF (250 mL) KO*t*Bu (30.35 g, 270.5 mmol) was added at 0°C within 30 min and stirred for 30 min at this temperature. 2-Bromo-5-hydroxy-4-methoxybenzaldehyde (25.0 g, 108.2 mmol) was added within 30 min, stirred for 5 h at rt and hydrolyzed with water (100 mL). The solvent was removed in vacuo, and the residue was acidified with 2N HCl and extracted with EtOAc (3×150 mL). The combined organic layers were washed with water (2×200 mL) and

brine (200 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by MPLC (450 g SiO_2, hexane/EtOAc=4:1) to yield **3** as colorless crystals (27.2 g, 97%). Mp 64–66°C; ^{1}H NMR (CDCl) δ 7.72 (s, 0.6H, *Z*-isomer), 7.00 (s, 1H), 6.94 (s, 0.4H, *E*-Isomer), 6.87 (d, *J*=12.8 Hz, 0.4H, *E*-isomer), 6.16 (d, *J*=7.3 Hz, 0.6H, *Z*-isomer), 5.99 (d, *J*=12.8 Hz, 0.4H, *E*-isomer), 5.51 (d, *J*=7.3 Hz, 0.6H, *Z*-isomer), 3.87 (s, 3H), 3.76 and 3.69 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 149.5 and 148.0 (d), 145.5 and 145.1 (s), 145.0 and 144.4 (s), 129.1 and 128.3 (s), 115.7 and 111.2 (d), 114.9 and 114.6 (d), 111.9 (s), 104.0 and 103.4 (d), 60.6 and 56.5 (q), 56.0 and 56.2 (q).

4.1.2. 2-Bromo-5-hydroxy-4-methoxybenzeneacetaldehyde (4). **3** (5.90 g, 22.6 mmol) in THF (50 mL)/2N HCl (8 mL) was stirred under reflux for 2.5 h. Water (50 mL) was added, and the solution was concentrated in vacuo to a volume of 45 mL. The residue was extracted with EtOAc (3×80 mL), the combined organic layers were washed with water (2×100 mL), saturated $NaHCO_3$ (2×100 mL) and brine (1×100 mL), dried (Na_2SO_4), filtered and evaporated in vacuo to yield **4** as colorless crystals (5.40 g, 97%). Mp 106–108°C; ^{1}H NMR ($CDCl_3$) δ 9.71 (t, *J*=1.7 Hz, 1H), 7.06 (s, 1H), 6.80 (s, 1H), 5.62 (b, 1H), 3.90 (s, 3H), 3.73 (d, *J*=1.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 198.5 (d), 146.5 (s), 145.2 (s), 124.9 (s), 117.1 (s), 115.0 (d), 113.7 (d), 56.1 (q), 49.8 (t).

4.1.3. 4-Bromo-2-methoxy-5-(2-nitroethenyl)phenol (5). 2-Bromo-5-hydroxy-4-methoxybenzaldehyde (40.0 g, 173 mmol) and ammonium acetate (13.3 g, 173 mmol) in dry nitromethane (400 mL) were stirred under reflux for 15 min. The solvent was removed in vacuo, and the residue was partitioned between EtOAc (500 mL) and water (500 mL). The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with water (2×500 mL) and brine (500 mL), dried (Na_2SO_4), filtered and evaporated in vacuo. The residue was recrystallized from MeOH (200 mL) to yield **5** as yellow crystals (43.6 g, 92%). Mp 152–154°C; ^{1}H NMR ($CDCl_3$) δ 8.16 (d, *J*=13.4 Hz, 1H), 8.03 (d, *J*=13.4 Hz, 1H), 7.38 (s, 1H), 7.30 (s, 1H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.2 (s), 146.5 (s), 137.6 (d), 136.8 (d), 121.4 (s), 116.6 (s), 116.1 (d), 114.7 (d), 56.3 (q).

4.1.4. 4-Bromo-2-methoxy-5-(2-aminoethyl)phenol (6). *Method A*. To a suspension of $LiAlH_4$ (15.0 g, 394 mmol) in refluxing anhydrous THF (1000 mL), **5** (18.0 g, 65.7 mmol) in anhydrous THF (200 mL) was added within 2 h and stirred for 1 h. After hydrolysis with water (20 mL), the solvent was removed in vacuo. The residue was dissolved in 2N HCl (500 mL) and washed with EtOAc (2×250 mL). The combined organic layers were extracted with 2N HCl (2×100 mL), and the combined aqueous layers were treated with tartaric acid (70.0 g, 467 mmol), the pH was adjusted to >10 with conc. NH_3, and the aqueous layer was extracted with chloroform (3×500 mL). The combined organic layers were washed with water (2×300 mL) and brine (300 mL), dried (Na_2SO_4), filtered and evaporated to yield **6** as colorless crystals (9.92 g, 61%). Mp 170–172°C; ^{1}H NMR ($CDCl_3$) δ 7.00 (s, 1H), 6.73 (s, 1H), 3.98 (b, 3H), 3.75 (s, 3H), 2.49 (t, *J*=6.31 Hz, 2H), 2.35 (t, *J*=6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 146.9 (s), 146.3 (s), 131.3 (s), 117.5 (s), 115.9 (d), 111.1 (d), 55.9 (q), 42.1 (t), 38.7 (t).

Method B. To a suspension of **7** (200 mg, 0.77 mmol) in refluxing anhydrous Et_2O (20 mL) $LiAlH_4$/THF (1 M, 5 mL, 5 mmol) was added and refluxed for 48 h. After hydrolysis with water (20 mL), the solvent was removed in vacuo. The residue was dissolved in 2N HCl (50 mL) and washed with EtOAc (2×30 mL). The combined organic layers were extracted with 2N HCl (2×20 mL), and the combined aqueous layers were treated with tartaric acid (750 mg, 5 mmol), the pH was adjusted to >10 with conc. NH_3, and the aqueous layer was extracted with chloroform (3×20 mL). The combined organic layers were washed with water (2×30 mL) and brine (30 mL), dried (Na_2SO_4), filtered and evaporated to yield **6** as colorless crystals (142 mg, 75%). Mp 170–172°C. NMR data identical to the product obtained using Method A.

Method C. To a solution of **7** (200 mg, 0.77 mmol) in THF (20 mL)/2N HCl (8 mL) zinc (1.0 g, 15.3 mmol) was added and refluxed for 24 h. The suspension was filtered and concentrated in vacuo to a volume of 6 mL. This aqueous layer was washed with chloroform (2×4 mL), the pH was adjusted to >10 with conc. NH_3, and the aqueous layer was extracted with chloroform (3×5 mL). The combined organic layers were washed with water (2×10 mL) and brine (20 mL), dried (Na_2SO_4), filtered and evaporated to yield **6** as colorless crystals (135 mg, 71%). Mp 170–172°C. NMR data identical to the product obtained using Method A.

4.1.5. 2-Bromo-5-hydroxy-4-methoxybenzeneacetaldehyde oxime (7). **4** (1.98 g, 8.08 mmol), triethylamine (2.04 g, 20.2 mmol) and hydroxylamine hydrochloride (1.12 g, 16.2 mmol) in EtOH (30 mL) were refluxed for 2 h. The solvent was removed in vacuo, and the residue was partitioned between 2N HCl (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (2×15 mL), and the combined organic layers were washed with 2N HCl (2×50 mL), water (2×50 mL), saturated $NaHCO_3$ (2×50 mL) and brine (1×50 mL), dried (Na_2SO_4), filtered and concentrated. The residue was triturated with cold chloroform (3 mL) to yield **7** as colorless crystals (2.0 g, 95%). Mp 157–158°C; ^{1}H NMR ($CDCl_3$) δ 7.10 (s), 6.79 (s, 1H), 6.67 (t, *J*=5.0 Hz), 3.78 (s, 3H), 3.54 (d, *J*=5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 147.4 (d), 147.3 (s), 146.3 (s), 128.7 (s), 117.5 (s), 116.0 (d), 111.5 (d), 56.0 (q), 31.2 (t).

4.1.6. 4-Bromo-5-[*N*-[(4-hydroxyphenyl)methyl]-2-aminoethyl]-2-methoxyphenol (8). *Method A*. To **4** (500 mg, 2.04 mmol) and 4-hydroxyphenylbenzaldehyde oxime (278 mg, 2.04 mmol) in anhydrous THF (30 mL), zinc dust (1.30 g, 20.4 mmol) and 2N HCl (15 mL) were added and stirred under reflux for 24 h. The suspension was filtered and concentrated in vacuo to a volume of 10 mL. 2N HCl (20 mL) was added, and the aqueous layer was washed with EtOAc (2×30 mL). The combined organic layers were extracted with 2N HCl (2×20 mL), the pH of the combined aqueous layers was adjusted to >10 with conc. NH_3, and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were

washed with water (2×30 mL) and brine (1×30 mL), dried (Na_2SO_4), filtered and evaporated in vacuo to yield **8** as colorless crystals (194 mg, 27%). Mp 69–72°C; ^{1}H NMR (DMSO-d_6) δ 7.14–6.60 (m, 6H), 3.73 (s), 3.58 (s, 2H), 2.78–2.55 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 156.0 (s), 146.8 (s), 146.0 (s), 131.4 (s), 130.7 (s), 129.1 (d), 117.3 (d), 115.9 (d), 114.8 (d), 111.3 (s), 55.9 (q), 52.2 (t), 48.7 (t), 35.2 (t).

Method B. To **4** (300 mg, 1.22 mmol) and 4-hydroxybenzenemethaneamine hydrochloride (586 mg, 3.66 mmol) in anhydrous THF (20 mL), zinc dust (1.50 g, 22.9 mmol) and 2N HCl (16 mL) were added and stirred under reflux for 5 h. The suspension was filtered and concentrated in vacuo to a volume of 10 mL. 2N HCl (20 mL) was added, and the aqueous layer was washed with EtOAc (2×30 mL). The combined organic layers were extracted with 2N HCl (2×20 mL), the pH of the combined aqueous layers was adjusted to >10 with conc. NH_3, and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water (2×30 mL) and brine (1×30 mL), dried (Na_2SO_4), filtered and evaporated in vacuo to yield **8** as colorless crystals (150 mg, 35%). Mp 69–72°C. NMR data identical to the product obtained using Method A.

Method C. **6** (6.40 g, 26.0 mmol) and 4-hydroxybenzaldehyde (3.21 g, 26.0 mmol) in anhydrous EtOH (150 mL) were refluxed for 3 h. After cooling to 0°C sodium borohydride (5.0 g, 132.0 mmol) was added and refluxed for additional 30 min. AcOH (1 mL) and water (50 mL) were added, and the solvent was removed in vacuo. The residue was partitioned between 2N HCl (100 mL) and chloroform (100 mL). The organic layer was extracted with 2N HCl (2×25 mL), the pH of the combined aqueous layers was adjusted to >10 with conc. NH_3, and the aqueous layer was extracted with EtOAc (3×80 mL). The combined organic layers were washed with water (2×100 mL) and brine (1×100 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to yield **8** as colorless crystals (8.92 g, 97%). Mp 69–72°C. NMR data identical to the product obtained using Method A.

4.1.7. *N*-[2-(2-Bromo-5-hydroxy-4-methoxyphenyl)-ethyl]-*N*-[(4-hydroxyphenyl)methyl]-formamide (9). 8 (8.53 g, 24.1 mmol), cat. DMAP and ethyl formate (10 mL) were refluxed in anhydrous dioxane (150 mL)/DMF (10 mL)/formic acid (2.5 mL) for 24 h. Water (50 mL) was added and the mixture was concentrated to a volume of 80 mL and extracted with EtOAc (5×50 mL). The combined organic layers were washed with water (3×100 mL) and brine (1×100 mL), dried (Na_2SO_4), filtered and concentrated. The residue was purified by MPLC (SiO_2, $CHCl_3$/MeOH=97:3) to yield **9** as colorless crystals (6.66 g, 72%). Mp 104–106°C; ^{1}H NMR (DMSO-d_6) δ 9.30 and 9.48 (s, 1H), 7.11–6.67 (m, 6H), 4.14 (dd, 2H), 3.72 (s, 3H), 3.53–3.43 (m, 2H), 2.87–2.56 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 163.0 and 162.7 (d), 157.5 and 157.1 (s), 147.6 and 147.5 (s), 146.6 and 146.5 (s), 130.0 (s), 129.4 (d), 127.0 and 126.8 (s), 118.0 and 117.7 (d), 115.7 and 115.6 (d), 115.2 and 115.1 (d), 111.6 and 111.4 (s), 56.1 (q), 50.4 and 46.1 (t), 44.3 and 41.5 (t), 34.2 and 32.6 (t).

4.1.8. (4a*R,8a*R**)-4a,5,9,10,11-Hexahydro-1-bromo-3-methoxy-6-oxo-6*H*-benzofuro[3a,3,2-ef][3]benzazepine-10-carbaldehyde ((±)-10).** To a vigorously stirred mixture of $K_3[Fe(CN)_6]$ (13.2 g, 39.5 mmol), 10% aqueous K_2CO_3 (50 mL) and chloroform (300 mL) **9** (3.00 g, 7.9 mmol) was added at 60°C and stirred for 10 min. The resulting mixture was filtered using diatomaceous earth and washed with water (2×100 mL). The combined aqueous layers were extracted with chloroform (2×50 mL), the combined organic layers were washed with water (2×100 mL) and brine (1×100 mL), dried (Na_2SO_4), filtered and concentrated. The crude product was purified by MPLC (SiO_2, $CHCl_3$/MeOH=97:3) to yield (±)-**10** as colorless crystals (580 mg, 19%).

On a 5 g-scale a yield of 25% was obtained.

Mp 218–220°C; ^{1}H NMR ($CDCl_3$) δ 8.30 and 8.10 (s, 1H), 7.01 (s, 1H), 6.53 (dd, 1H), 6.09 (dd, 1H), 4.85 (dd, 1H), 3.80 (s, 3H), 4.27–2.58 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 193.4 and 193.0 (s), 162.3 and 161.7 (d), 146.8 (s), 144.0 and 143.8 (s), 141.7 and 141.5 (d), 130.8 and 129.8 (s), 128.8 and 128.0 (d), 128.9 and 127.6 (s), 117.0 and 116.8 (d), 115.7 and 115.3 (s), 84.3 and 83.8 (s), 56.2 (q), 51.4 and 50.9 (s), 49.0 and 48.7 (t), 43.7 (t), 37.4 and 37.2 (t), 35.3 and 33.4 (t); Anal. calcd for $C_{17}H_{16}BrNO_4$: C, 53.99; H, 4.26; N, 3.70. Found: C, 53.70; H, 4.47; N, 3.41.

4.1.9. (4aα,6β,8a*R)-4a,5,9,10,11-Hexahydro-1-bromo-3-methoxy-6*H*-benzofuro[3a,3,2-ef][3]benzazepine-6-ol ((±)-11).** To (±)-**10** (500 mg, 1.32 mmol) in anhydrous THF (12 mL) L-selectride® (1 M in THF, 4 mL, 4 mmol) was added at −12°C and stirred for 1 h at 10°C. Methanol (3 mL) was added and stirred for 2 h at rt. The solvent was removed in vacuo, and the residue was dissolved in 2N HCl (50 mL) and stirred vigorously. The aqueous layer was washed with EtOAc (1×50 mL), and the organic layer was extracted with 2N HCl (2×20 mL). The pH of the combined aqueous layers was adjusted to >10 with conc. NH_3, and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were washed with water (2×50 mL) and brine (1×50 mL), dried (Na_2SO_4), filtered and evaporated in vacuo to yield (±)-**11** as colorless crystals (380 mg, 82%). Mp 132–136°C; ^{1}H NMR ($CDCl_3$) δ 6.96 (s, 1H), 6.15 (d, J=10.2 Hz, 1H), 6.08 (dd, J=10.2 Hz, 1H), 4.08 (m, 1H), 4.50 (dd, 1H), 3.80 (s, 3H), 3.37 (m, 1H), 3.30 (m, 1H), 2.98 (d, J=12.6 Hz, 1H), 2.85 (m, 1H), 2.78 (d, J=12.6 Hz, 1H), 2.68 (m, 1H), 2.62 (m, 1H), 1.87 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 145.4 (s), 143.5 (s), 134.2 (s), 130.5 (s), 127.7 (d), 127.3 (d), 115.7 (d), 114.9 (s), 85.5 (d), 62.0 (d), 57.3 (t), 56.0 (q), 51.6 (s), 49.7 (t), 36.7 (t), 30.2 (t).

4.1.10. (4aα,6β,8a*R)-4a,5,9,10,11-Hexahydro-1-bromo-3-methoxy-10-methyl-6*H*-benzofuro[3a,3,2-ef][3]benzazepine-6-ol ((±)-12).** To (±)-**11** (370 mg, 1.05 mmol) in acetonitrile (12 mL) formaldehyde (35% in water, 1 mL) and sodium cyanoborohydride (165 mg, 2.63 mmol) were added and stirred at rt for 1 h. The solution was acidified with 2N HCl and washed with CH_2Cl_2 (2×10 mL). The combined organic layers were extracted with 2N HCl (2×10 mL), the pH was adjusted to >10 with conc. NH_3, and the combined aqueous layers were extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were

washed with water (2×50 mL) and brine (1×50 mL), dried (Na_2SO_4), filtered and evaporated in vacuo to yield (±)-**12** as off-white crystals (355 mg, 92%). Mp 158–161°C; ^{1}H NMR ($CDCl_3$) δ 6.92 (s, 1H), 6.18 (d, J=10.2 Hz, 1H), 6.02 (dd, J=10.2 Hz, J=5.1 Hz, 1H), 4.58 (b, 1H), 4.25–4.13 (m, 1H), 3.34 (dd, J=6.4, 16.5 Hz, 1H), 3.16–2.92 (m, 2H), 2.81–2.60 (m, 2H), 2.41 (s, 3H), 2.48–2.27 (m, 2H), 2.04–1.91 (m, 1H).

4.1.11. (4aα,6β,8a*R)-4a,5,9,10,11-Hexahydro-3-methoxy-10-methyl-6*H*-benzofuro[3a,3,2-ef]-[3]benzazepin-6-ol ((±)-2).** Zinc powder (1.00 g) and copper(I)iodide (1.00 g) in 50% EtOH (50 mL) were sonicated under argon for 2 h. $CaCl_2$ (722 mg, 6.51 mmol) and (±)-**12** (340 mg, 0.93 mmol) were added and refluxed for 12 h. The mixture was filtered and concentrated in vacuo. The residue was partitioned between water (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2×10 mL), the combined organic layers were washed with water (2×20 mL) and brine (1×30 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by MPLC (SiO_2, $CHCl_3$/MeOH=97:3) to yield (±)-**2** as colorless crystals (230 mg, 86%). Mp 152–155°C; ^{1}H NMR ($CDCl_3$) δ 6.66 (d, J=8.2 Hz, 1H), 6.61 (d, J=8.2 Hz, 1H), 6.22 (dd, J=10.2, 1.1 Hz, 1H), 6.01 (ddd, J=10.2, 5.2, 1.0 Hz, 1H), 4.57 (b, 1H), 4.22–4.12 (m, 1H), 3.83 (s, 3H), 3.29–3.12 (m, 1H), 3.12–3.01 (m, 1H), 2.80–2.62 (m, 3H), 2.42 (s, 3H), 2.46–2.26 (m, 2H), 2.04–1.90 (m); ^{13}C NMR ($CDCl_3$) δ 145.3 (s), 142.9 (s), 132.7 (s), 130.9 (s), 128.3 (d), 126.5 (d), 121.5 (d), 111.1 (d), 85.6 (d), 66.3 (t), 62.0 (d), 59.1 (t), 55.6 (q), 49.3 (q), 48.9 (s), 34.5 (t), 30.0 (t).

4.1.12. X-Ray structure analyses of (±)-10 and (±)-2. Crystal data for (±)-**10**: $C_{17}H_{16}BrNO_4$, M_r=378.22, orthorhombic, space group *Pbca* (No. 61), a=14.784(4) Å, b=10.805(3) Å, c=19.546(6) Å, V=3122.3(15) Å^3, Z=8, D_x=1.609 g cm^{-3}, T=295(2) K, $F(000)$=1536, λ(Mo Kα)=0.71073 Å, μ=2.65 mm^{-1}, colorless crystal (0.64×0.54×0.28 mm^3). Data were collected on a Siemens/Bruker SMART 3-circle diffractometer with a CCD area detector and graphite monochromatized Mo Kα radiation by recording 4×606 ω-scan frames ($\Delta\omega$=0.3°, t=15 s) covering a complete sphere of the reciprocal space, θ_{max}<30.0°. Corrections for absorption applied. Structure solution by direct methods, refinement by full-matrix least-squares on F^2 (SHELX-97);[13] N-bonded formyl group disordered with oxygen O(4) and C(17)-bonded H in two orientations; data/restraints/parameters=4550/0/220; final $R1$=0.048, $wR2$=0.080 (all data). CCDC 16/165137.[14]

Crystal data for (±)-**2**: $C_{17}H_{21}NO_3$, M_r=287.35, triclinic, space group $P\bar{1}$ (No. 2), a=7.991(3) Å, b=9.634(4), 10.549(5) Å, α=92.02(2)°, β=106.86(2)°, γ=107.69(2)°, V=3122.3(15) Å^3, Z=8, D_x=1.301 g cm^{-3}, $F(000)$=308, λ(Mo Kα)=0.71073 Å, μ=0.089 mm^{-1}, T=298(2) K, colorless crystal (0.7×0.46×0.24 mm^3). Data collected on a Siemens/Bruker SMART diffractometer (given earlier), θ_{max}<25.0°. Corrections for absorption applied. Structure solution by direct methods, refinement by full-matrix least-squares on F^2, data/restraints/parameters=2580/0/193; final $R1$=0.042, $wR2$=0.101 (all data). CCDC 16/165138.[14]

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14. Complete crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 165137–165138. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ (fax: +44-1223-336033, email: deposit@ccdc.cam.ac.uk).