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1-Methylgalanthamine Derivatives#

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Summary. The syntheses of pharmaceutically interesting galanthamine analogues bearing a methyl group at the C1 position are described.

Keywords. Acetylcholine esterase inhibitor; Drug research; Galanthamine analogue; Tandem cyclization; Total synthesis.

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 [1–3]. For SAR studies 1-methylgalanthamine derivatives were prepared.

Results and Discussion

1-Methylgalanthamine (**6**) was prepared in a sequence analogous to the industrial synthesis of (−)-galanthamine [4, 5] starting from 5-hydroxy-4-methoxy-2-methylbenzaldehyde [6]. Reductive amination with tyramine gave rise to the phenethylbenzylamine **1** in 96% yield. N-Formylation using methyl formate/formic acid in dioxane led to **2** in 83% yield. Tandem cyclization by phenol oxidation yielded the 1-methylnarwedine derivative **3** in 55%. Ketal formation using propylene glycol gave rise to the protected species **4** with a yield of 73%. By reduction of the amide moiety and subsequent cleavage of the protecting group under acidic conditions

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# Dedicated to Professor *Peter Stanetty* on the occasion of his 60th birthday

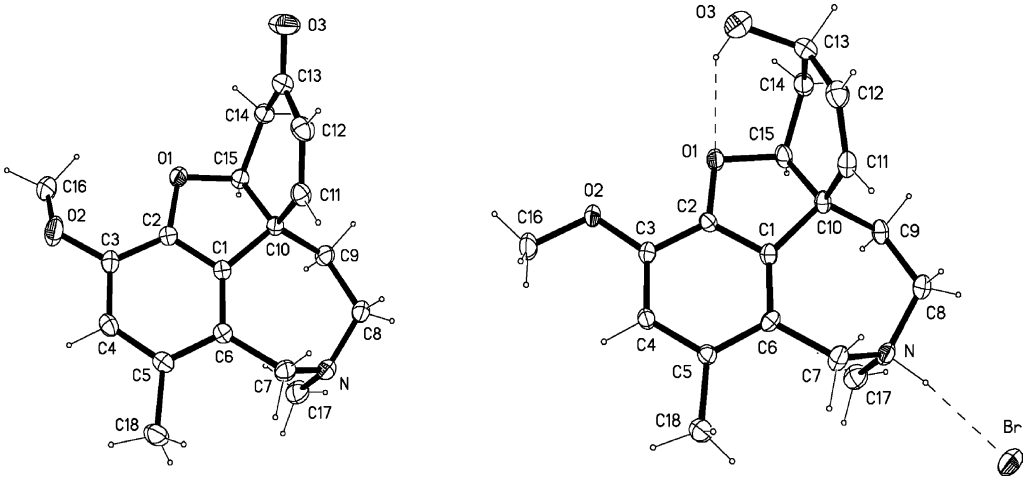
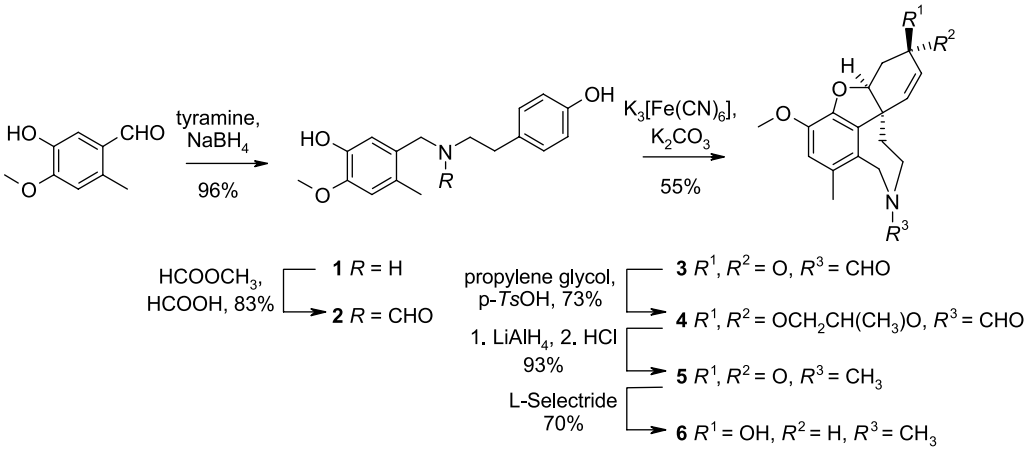


Fig. 1. Molecular structures of **5** (left) and (−)-**6** · HBr (right) in crystalline state (20% ellipsoids)

1-methylnarwedine (**5**) was synthesized in 93% yield. An X-ray crystallographic study of racemic **5** (Fig. 1, for further details see experimental section) showed it to crystallize in the non-chiral centrosymmetric, monoclinic space group $P2_1/n$. This made a crystallization-induced asymmetric transformation [7] to enantiopure **5** impossible that works so well with narwedine. In this case crystallization of the compound in the chiral space group $P2_12_12_1$ combined with chiral seeding and continuous re-equilibration of its enantiomers in solution *via* a base-catalyzed *retro*-Michael addition opened an elegant and efficient access to either (−) or (+)-narwedine starting with racemic educt [4, 5]. Attempts to resolve the racemate **5** employing tartaric acid derivatives failed. Final stereoselective reduction of ketone **5** using L-Selectride® gave 1-methylgalanthamine (**6**) in 70% yield. For analytical purposes and for X-ray analysis the free base was converted into the crystalline HBr-salt by treatment with concentrated HBr (Scheme 1). Interestingly,



Scheme 1

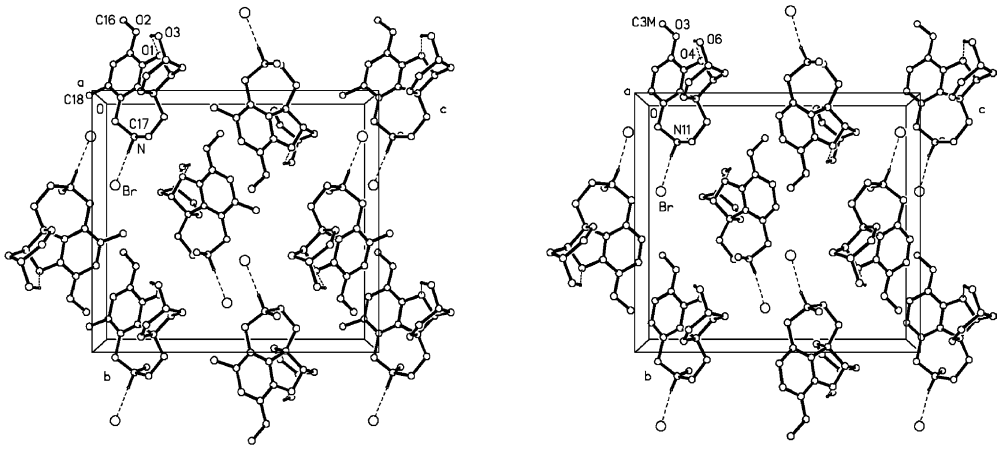
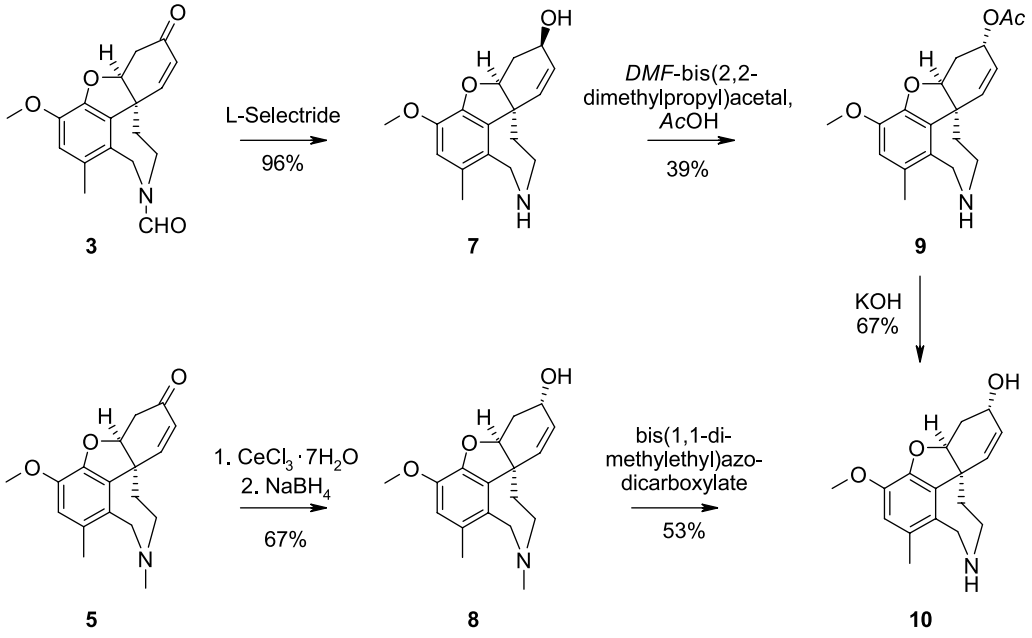


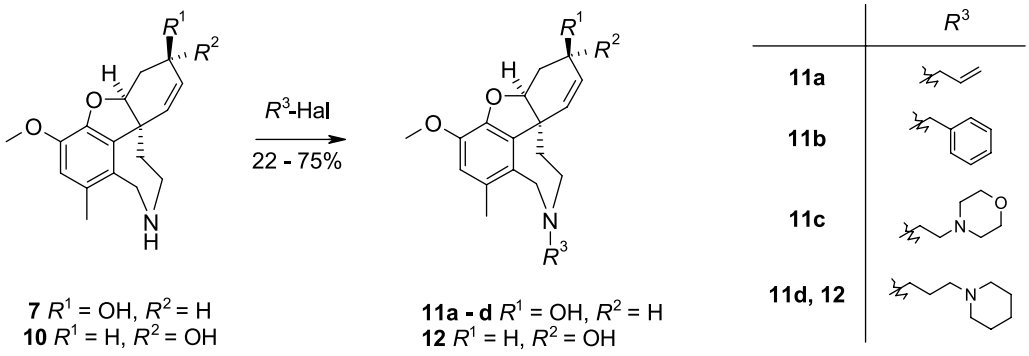
Fig. 2. Comparison of the two isomorphic structures of (−)-**6** · HBr (left) and (−)-galanthamine hydrobromide [8] (right) viewed down the a-axis of their orthorhombic unit cells (space group $P2_12_12_1$; left: $a = 7.499$, $b = 14.395$, $c = 15.937$ Å, $V = 1720$ Å^3; right: $a = 7.371$, $b = 14.327$, $c = 15.932$ Å, $V = 1682$ Å^3)

this salt (**6** · HBr) crystallizes spontaneously in the chiral space group $P2_12_12_1$ and is, moreover, isostructural with (−)-galanthamine hydrobromide [8] (Figs. 1 and 2, see also experimental section). This crystallographic property of **6** · HBr would in principle permit the separation of the enantiomers by crystallization techniques [7], but was not tested due to lacking sufficiently large amounts of the compound.

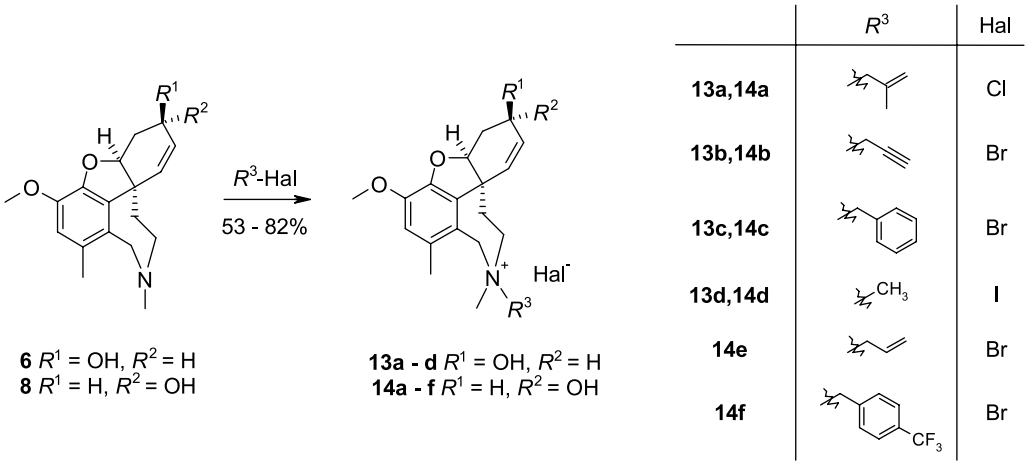
As a key intermediate for the synthesis of the 6-*epi*-derivatives, *epi*-1-methylgalanthamine (**8**) was prepared by stereoselective reduction of **5** using



Scheme 2



Scheme 3



Scheme 4

L-Selectride® in the presence of $CeCl_3 \cdot 7H_2O$ in 67% yield. N-Demethylation employing bis(1,1-dimethylethyl)azodicarboxylate yielded the secondary amine **10** in 53%. L-Selectride® reduction of the keto group of **3** with concomitant loss of the *N*-formyl group gave rise to the isomeric **7** in 96% yield. Conversion of **7** into **10** *via* the intermediate acetate **9** was disfavored due to low yields for both steps (see Scheme 2). N-Alkylation of **7** and **10** led to derivatives of 1-methylgalanthamine (**11a**–**11d**) and *epi*-1-methylgalanthamine (**12**) (see Scheme 3).

Quarternary ammonium salts **13a**–**13d** and **14a**–**14f** were prepared by treatment of **6** and **8** with various alkyl halides (see Scheme 4).

Experimental

Melting points were measured on a *Kofler* micro hot stage. ^1H and ^{13}C NMR-spectra were recorded on a Bruker AC-200 or a Bruker Avance 400 FT-NMR spectrometer in $CDCl_3$ or *DMSO*-d_6 using TMS as internal standard. Thin layer chromatography (TLC) was performed on precoated plates (Merck TLC aluminum sheets silica 60 F_{254}) with detection by UV light or with phosphomolybdic acid in aqueous

*Et*OH by heating. All reactions were magnetically stirred under Ar. All liquid reagents were freshly distilled prior to use. Elemental analyses were found to agree favorably with the calculated values.

5-[N-[2-(4-Hydroxyphenyl)ethyl]aminomethyl]-2-methoxy-4-methylphenol (**1**, $C_{17}H_{21}NO_3$)

2-Methyl-4-methoxy-5-hydroxybenzaldehyde (27.8 g, 168 mmol) and 23.0 g of tyramine (168 mmol) were refluxed in 300 cm^3 of dry *Et*OH for 8.5 h. The mixture was cooled to 0°C, and 5.20 g of $NaBH_4$ (134 mmol) in 20 cm^3 of H_2O were added and stirred for 30 min. Then the mixture was poured into 4.5 dm^3 of ice/H_2O, and the precipitate was collected by filtration and dried at 50°C/50 mbar. Yield 43.3 g of colorless solid (96%); mp 122–124°C (H_2O); TLC: $CHCl_3$:*Me*OH:conc. NH_4OH = 89:10:1, R_f = 0.2; ^{1}H NMR (200 MHz, *DMSO*-d_6): δ = 6.90 (m, 2H), 6.67 (s, 1H), 6.62 (m, 2H), 6.55 (s, 1H), 3.72 (s, 3H), 3.51 (s, 2H), 2.73 (t, J = 6.5 Hz, 2H), 2.60 (t, J = 6.5 Hz, 2H), 2.10 (s, 3H) ppm; ^{13}C NMR (50 MHz, *DMSO*-d_6): δ = 155.4 (s), 145.8 (s), 143.9 (s), 130.9 (s), 130.4 (s), 129.3 (d), 126.0 (s), 116.2 (d), 115.0 (d), 114.3 (d), 55.7 (q), 51.1 (t), 50.3 (t), 35.0 (t), 17.9 (q) ppm.

N-[(5-Hydroxy-4-methoxy-2-methylphenyl)methyl]-N-[2-(4-hydroxyphenyl)ethyl]-formamide (**2**, $C_{18}H_{21}NO_4$)

1 (55.0 g, 191 mmol) and 23.5 cm^3 of methyl formiate (383 mmol) were refluxed in 400 cm^3 of dioxane/11 cm^3 of *DMF*/1.5 cm^3 of formic acid for 7 h. Then the mixture was concentrated *in vacuo*. The residue was dissolved in 55 cm^3 of *Me*OH, and 2.7 dm^3 of ice/H_2O were added under vigorous stirring. The precipitate was collected by filtration and dried at 50°C/50 mbar. Yield 49.8 g of colorless crystals (83%); mp 170–171°C (H_2O); TLC: $CHCl_3$:*Me*OH:conc. NH_4OH = 89:10:1, R_f = 0.35; ^{1}H NMR (200 MHz, *DMSO*-d_6): δ = 9.20 (s, 1H), 8.74 (d, J = 15.3 Hz, 1H), 8.19 (s, 0.5H), 7.88 (s, 0.5H), 7.00–6.87 (m, 2H), 6.74 (s, 1H), 6.72–6.56 (m, 2H), 6.59 (s, 1H), 4.31 (s, 1H), 4.23 (s, 1H), 3.73 (s, 3H), 3.21 (dd, J = 15.3, 7.6 Hz, 2H), 2.60 (t, J = 7.6 Hz, 2H), 2.12 (s, 3H) ppm; ^{13}C NMR (50 MHz, *DMSO*-d_6): δ = 162.7 and 162.3 (2d), 155.7 (s), 146.7 and 146.5 (2s), 144.4 and 144.2 (2s), 129.7 and 129.4 (2d), 128.9 and 128.4 (2s), 126.5 (s), 126.4 and 126.3 (2s), 116.3 and 115.9 (2d), 115.1 (d), 114.6 and 114.4 (2d), 55.6 (q), 48.0 and 47.4 (2t), 43.3 and 41.6 (2t), 33.2 and 31.9 (2t), 18.1 and 18.0 (2q) ppm.

[(±)-(4aα,8aR)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-1-methyl-6-oxo-6H-benzofuro[3a,3,2-ef][2]benzazepine-11-carboxaldehyde* (**3**, $C_{18}H_{19}NO_4$)

To a vigorously stirred mixture of 47.0 g of K_2CO_3 (338 mmol), 47.0 g of $K_3[Fe(CN)_6]$ (142 mmol), 1.6 dm^3 of toluene, and 470 cm^3 of H_2O 11.4 g of **2** (69.8 mmol) were added at 80°C and it was stirred for 1 h at this temperature. Then 40 g of diatomaceous earth were added and it was stirred for additional 10 min. The mixture was filtered, and the solid was triturated with 100 cm^3 of water and 3×200 cm^3 of hot toluene. The aqueous layer was extracted with 200 cm^3 of toluene and the combined organic layer was washed with 2 × 500 cm^3 of 1 *N* HCl, 2 × 500 cm^3 of H_2O, and 500 cm^3 of brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was triturated with 2 × 10 cm^3 of *i-Pr*$_2$O. Yield 6.17 g of light yellow crystals (55%); mp 215°C (decomp) (*i-Pr*$_2$O); TLC: $CHCl_3$:*Me*OH:conc. NH_4OH = 89:10:1, R_f = 0.5 and 0.4; ^{1}H NMR (mixture of 2 rotamers, 200 MHz, *DMSO*-d_6): δ = 8.18 (s, 0.2H), 8.10 (s, 0.8H), 7.25 (dd, J = 10.4, 1.9 Hz, 0.8H), 7.15 (dd, J = 10.4, 1.9 Hz, 0.2H), 6.73 (s, 0.2H), 6.69 (s, 0.8H), 5.95 (d, J = 10.3 Hz, 0.8H), 5.93 (d, J = 10.3 Hz, 0.2H), 5.14 (d, J = 15.4 Hz, 0.8H), 4.83 (d, J = 15.4 Hz, 0.2H), 4.67 (bs, 1H), 4.51 (d, J = 15.4 Hz, 0.2H), 4.07 (d, J = 15.4 Hz, 0.8H), 3.97 (bs, 1H), 3.78–3.60 (m, 4H) 3.07 (dd, J = 17.4, 3.4 Hz, 1H), 2.78 (dd, J = 17.4, 1.9 Hz, 1H), 2.33 (s, 3H), 2.30 (s, 0.8H), 2.22 (s, 0.2H), 1.86 (dt, J = 13.5, 3.7 Hz, 1H) ppm; ^{13}C NMR (mixture of 2 rotamers, 50 MHz, *DMSO*-d_6): δ = 194.9 (s), 162.8 and 162.1 (2d), 145.2 and 144.8 (2d), 145.5 and 145.3 (2s), 142.9 and 142.8 (2s), 130.6 and 130.3 (2s), 128.2 (s), 127.5 and

127.0 (2s), 126.4 and 126.2 (2d), 114.5 and 114.2 (2d), 87.0 and 86.8 (2d), 55.6 (q), 49.2 and 49.0 (2s), 47.4 and 45.6 (2t), 41.8 and 40.1 (2t), 37.7 (t), 37.5 (t) 37.4 (t), 34.1 (t), 19.2 and 18.9 (2q) ppm.

[(±)-(4aα,8aR)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-1,4′-dimethylspiro[6H-benzofuro[3a,3,2-ef][2]benzazepine-6,2′-[1,3]-dioxolane]-11-carboxaldehyde* (**4**, $C_{21}H_{25}NO_5$)

Compound **3** (6.17 g, 19.7 mmol), 11.1 cm^3 of propylene glycol (149 mmol), and 375 mg of *p-Ts*OH (1.97 mmol) were refluxed in 40 cm^3 of dry toluene for 13 h using a *Dean-Stark*-apparatus. The toluene layer was separated, and the remaining glycol was extracted with 7×5 cm^3 of toluene. The combined organic layer was washed with 2×50 cm^3 of 8% *Ac*OH, 2×50 cm^3 of satd. $NaHCO_3$ solution and 50 cm^3 of brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Yield 5.34 g of off-white foam (73%); TLC: $CHCl_3$:*Me*OH = 90:10, $R_f = 0.7$; ^1H NMR (mixture of diastereomers and rotamers, 200 MHz, $CDCl_3$): $\delta = 8.14$–8.01 (m, 1H), 7.30–7.09 (m, 2H), 6.51 (s, 1H), 6.22–5.97 (m, 1H), 5.85–5.61 (m, 1H), 5.38 and 4.77 (d, $J = 15.7$ Hz, 1H), 4.49 (bs, 1H), 4.37–4.01 (m, 2H), 3.93–3.74 (m, 5H), 3.71–3.10 (m, 1H), 2.79–2.58 (m, 1H), 2.41 (s, 2H), 2.32 (d, $J = 10.2$ Hz, 3H), 2.25–1.74 (m, 3H) ppm; ^{13}C NMR (mixture of diastereomers and rotamers, 50 MHz, $CDCl_3$): $\delta = 162.5$ (d), 161.7 (d), 143.7 (s), 143.6 (s), 143.3 (d), 142.7 (d), 129.9 (s), 129.6 (s), 127.8 (d), 127.6 (d), 126.0 (s), 125.7 (s), 114.6 (d), 114.4 (d), 87.5 (d), 87.4 (d), 68.2 (d), 68.0 (t), 56.1 (q), 56.0 (q), 49.2 (s), 49.0 (s), 48.7 (t), 46.7 (t), 43.2 (t), 41.2 (t), 38.7 (t), 37.2 (t), 37.1 (t), 34.8 (t), 19.7 (q), 19.4 (q), 18.9 (q) ppm.

[(±)-(4aα,8aR)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-1,11-dimethyl-6H-benzofuro[3a,3,2-ef][2]benzazepine-6-one* (**5**, $C_{18}H_{21}NO_3$)

To 5.34 g of **4** (14.4 mmol) in 20 cm^3 of dry *THF* 25.2 cm^3 of a $LiAlH_4$ solution (1 *M* in *THF*, 25.2 mmol) were added at ambient temperature and stirred for 15 min. 10 cm^3 of toluene, 1.5 cm^3 of H_2O, and 1.5 cm^3 of 15% aqueous NaOH were subsequently added and stirred for 15 min. 1.5 g of diatomaceous earth were added, then the mixture was stirred under reflux for 1 h and filtered. The remainder was triturated with 3×10 cm^3 of hot toluene:*THF* = 1:1, the combined organic layer was concentrated *in vacuo*, dissolved in 25 cm^3 of 4 *N* HCl, stirred for 25 min at 60°C and washed with 2×5 cm^3 of *Et*O*Ac* (discard). The *pH* of the aqueous solution was adjusted to >8.5 using conc. NH_4OH and the mixture was extracted with 5×15 cm^3 of $CHCl_3$. The combined organic layer was washed with 50 cm^3 of brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was recrystallized from 15 cm^3 of *i-Pr*$_2$O:*Et*O*Ac* = 9:1. Yield 4.01 g of yellow crystals (93%); mp 121–122°C (*i-Pr*$_2$O/*Et*O*Ac*); TLC: $CHCl_3$:*Me*OH = 95:5, $R_f = 0.4$; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.01$ (dd, $J = 10.4$, 1.6 Hz, 1H), 6.56 (s, 1H), 5.99 (d, $J = 10.4$ Hz, 1H), 4.68–4.62 (m, 1H), 3.97 (d, $J = 15.7$ Hz, 1H), 3.80 (s, 3H), 3.79 (d, $J = 15.7$ Hz, 1H), 3.22–2.95 (m, 3H), 2.71 (dd, $J = 17.8$, 3.7 Hz, 1H), 2.44 (s, 3H), 2.23 (s, 3H), 2.20–2.01 (m, 1H), 1.87 (dt, $J = 13.8$, 3.4 Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 194.4$ (s), 145.2 (s), 142.9 (s), 131.0 (s), 128.9 (s), 126.8 (2d + s), 114.3 (d), 87.7 (d), 55.9 (q), 55.8 (t), 54.1 (t), 48.9 (s), 43.5 (q), 37.1 (t), 33.4 (t), 19.4 (q) ppm.

[(±)-(4aα,6β,8aR)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-1,11-dimethyl-6H-benzofuro[3a,3,2-ef][2]benzazepine-6-ol* (**6**, $C_{18}H_{23}NO_3$)

To a suspension of 170 mg of **5** (0.57 mmol) in 5 cm^3 of dry *THF* 0.70 cm^3 of an L-Selectride solution (1 *M* in *THF*, 0.70 mmol) were added at −25°C and stirred for 30 min at −15°C. The mixture was allowed to warm up to ambient temperature, then 0.25 cm^3 of H_2O and 1 cm^3 of conc. NH_4OH were added and it was stirred for 10 min. Additional 2 cm^3 of conc. NH_4OH were added, and the aqueous solution was extracted with 3×10 cm^3 of CH_2Cl_2. The combined organic layer was washed with 2×10 cm^3 of H_2O and 10 cm^3 of brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue

was purified by MPLC (10 g SiO_2, $CHCl_3$:*Me*OH = 90:10) and triturated with $2 \times 2\,cm^3$ of Et_2O. Yield 120 mg of colorless foam (70%); TLC: $CHCl_3$:*Me*OH = 95:5, $R_f = 0.4$; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 6.54$ (s, 1H), 6.10 (dd, $J = 10.2$, 1.2 Hz, 1H), 5.98 (dd, $J = 10.2$, 4.7 Hz, 1H), 4.56 (bs, 1H), 4.12 (bs, 1H), 3.99 (d, $J = 15.6$ Hz, 1H), 3.82 (s, 3H), 3.81 (d, $J = 15.6$ Hz, 1H), 3.20 (ddd, $J = 14.2$, 12.1, 2.1 Hz, 1H), 2.96 (dt, $J = 14.2$, 3.4 Hz, 1H), 2.65 (ddd, $J = 15.7$, 3.2, 1.5 Hz, 1H), 2.41 (s, 3H), 2.24 (s, 3H), 1.99 (ddd, $J = 15.5$, 5.0, 2.5 Hz, 2H), 1.60 (ddd, $J = 13.7$, 4.0, 2.4 Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 144.0$ (s), 143.0 (s), 133.4 (s), 128.9 (s), 127.4 (2d), 127.0 (s), 126.6 (s), 113.6 (d), 88.3 (d), 61.9 (d), 55.7 (q), 55.4 (t), 53.8 (t), 48.2 (s), 42.7 (q), 33.8 (t), 29.8 (t), 19.4 (q) ppm.

Conversion into the HBr salt: The above reaction solution was quenched with $3\,cm^3$ of *Et*OH and stirred for 30 min. Then the *pH* of the solution was adjusted to ≤ 1 using conc. HBr, and the mixture was stirred for 12 h. The precipitate was collected by filtration and triturated with *Et*OH. Colorless crystals; mp 246–250°C (*Et*OH).

[(±)-(4aα,6β,8aR)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-1-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepine-6-ol* (**7**, $C_{17}H_{21}NO_3$)

To a suspension of 500 mg of **3** (1.60 mmol) in $12\,cm^3$ of dry *THF* $6.0\,cm^3$ of an L-Selectride solution (1 *M* in *THF*, 6.0 mmol) were added at 0°C and stirred for 1 h. Then $0.25\,cm^3$ of H_2O and $1\,cm^3$ of conc. NH_4OH were added and stirred for 10 min. The mixture was concentrated to a volume of $5\,cm^3$, additional $10\,cm^3$ of conc. NH_4OH were added, and the aqueous solution was extracted with $3 \times 15\,cm^3$ of CH_2Cl_2. The combined organic layer was washed with $2 \times 10\,cm^3$ of 2 *N* NH_4OH, $2 \times 10\,cm^3$ of H_2O, and $10\,cm^3$ of brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by MPLC (20 g SiO_2, $CHCl_3$:*Me*OH:conc. NH_4OH = 89:10:1). Yield 440 mg of colorless foam (96%); TLC: $CHCl_3$:*Me*OH:conc. NH_4OH = 89:10:1, $R_f = 0.4$; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 6.51$ (s, 1H), 6.06 (d, $J = 10.2$ Hz, 1H) , 5.97 (dd, $J = 10.2$, 4.5 Hz, 1H), 4.57 (bs, 1H), 4.27 (d, $J = 16.0$ Hz, 1H), 4.11 (t, $J = 4.4$ Hz, 1H), 3.80 (s, 3H), 3.77 (d, $J = 16.0$ Hz, 1H), 3.40–3.10 (m, 2H), 2.65 (dd, $J = 15.6$, 3.2 Hz, 1H), 2.23 (s, 3H), 1.99 (ddd, $J = 15.6$, 4.9, 2.3 Hz, 1H), 1.89–1.63 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 144.4$ (s), 142.9 (s), 133.4 (s), 130.5 (s), 127.8 (s), 127.5 (d), 127.1 (d), 113.5 (d), 88.1 (d), 61.4 (d), 55.8 (q), 49.0 (s), 48.9 (t), 46.9 (t), 39.7 (t), 29.8 (t), 19.4 (q) ppm.

[(±)-(4aα,6α,8aR)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-1,11-dimethyl-6H-benzofuro[3a,3,2-ef][2]benzazepine-6-ol* (**8**, $C_{18}H_{23}NO_3$)

Compound **5** (2.0 g, 6.68 mmol) was dissolved in $150\,cm^3$ of boiling *Me*OH, then 2.50 g of $CeCl_3 \cdot 7H_2O$ (6.68 mmol) were added at 0°C and stirred for 1 h. 0.50 g of $NaBH_4$ (13.4 mmol) were added and stirred at 0–5°C for 2 h. $5\,cm^3$ of 2 *N* HCl were added, the mixture was concentrated *in vacuo* to a volume of $10\,cm^3$, and the residue was diluted with $150\,cm^3$ of H_2O. The *pH* of the solution was adjusted to >8.5 using conc. NH_4OH, and the mixture was extracted with $5 \times 30\,cm^3$ of *Et*O*Ac*. The combined organic layer was washed with $100\,cm^3$ of brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by MPLC (100 g SiO_2, $CHCl_3$:*Me*OH:conc. NH_4OH = 89.5:10:0.5). Yield 1.34 g of colorless oil (67%); TLC: $CHCl_3$:*Me*OH = 90:10, $R_f = 0.2$; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 6.51$ (s, 1H), 6.10 (d, $J = 10.2$ Hz, 1H), 5.79 (d, $J = 10.2$ Hz, 1H), 4.69–4.56 (m, 1H), 4.55 (bs, 1H), 3.96 (d, $J = 15.3$ Hz, 1H), 3.82 (s, 3H), 3.79 (d, $J = 15.3$ Hz, 1H), 3.21 (td, $J = 13.1$, 1.7 Hz, 1H), 2.97 (dt, $J = 14.1$, 3.3 Hz, 1H), 2.75 (dddd, $J = 14.1$, 5.3, 4.0, 1.2 Hz, 1H), 2.38 (s, 3H), 2.23 (s, 3H), 2.10 (dd, $J = 13.1$, 3.2 Hz, 1H), 2.03 (bs, 1H), 1.69 (ddd, $J = 13.6$, 10.7, 2.6 Hz, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 145.0$ (s), 142.9 (s), 133.5 (s), 131.7 (d), 128.5 (s), 126.7 (d), 126.6 (s), 113.5 (d), 88.3 (d), 63.1 (d), 55.8 (q), 55.2 (t), 54.1 (t), 48.3 (s), 42.6 (q), 34.6 (t), 32.4 (t), 19.5 (q) ppm.

Conversion into the HBr salt: The free base was dissolved in *Et*OH, treated with conc. HBr, and stored at −20°C for 24 h. The precipitate was collected by filtration and triturated with cold *Et*OH. Colorless crystals; mp 254–255°C (*Et*OH).

[(±)-(4aα,6α,8aR)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-1-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepine-6-ol* (**10**, $C_{17}H_{21}NO_3$)

Method A. Step 1: Preparation of *[(±)-(4aα,6α,8aR*)]-6-Acetyloxy-4a,5,9,10,11,12-hexahydro-3-methoxy-1-methyl-6H-benzofuro[3a,3,2-ef][2]benzazepine* (**9**, $C_{19}H_{23}NO_4$)

To 100 mg of **7** (0.35 mmol) in 12 cm^3 of dry toluene a mixture of 0.50 cm^3 of *N,N*-dimethylformamide-bis(2,2-dimethylpropyl)acetal (1.74 mmol) and 0.10 cm^3 of *Ac*OH (1.74 mmol) in 2 cm^3 of dry toluene was added at 80°C over a period of 1 h. The mixture was stirred at 80°C for 22 h, cooled to ambient temperature, and extracted with 2×5 cm^3 of H_2O and 5×10 cm^3 of 2 *N* HCl. The *pH* of the combined aqueous layer was adjusted to >8.5 using conc. NH_4OH, and the mixture was extracted with 5×10 cm^3 of *Et*OAc. The combined organic layer was washed with 100 cm^3 of brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by MPLC (5 g SiO_2, $CHCl_3$:*Me*OH = 95:5). Yield 45 mg of colorless oil (39%); TLC: $CHCl_3$:*Me*OH = 95:5, $R_f = 0.2$; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 6.50$ (s, 1H), 6.14 (d, $J = 10.2$ Hz, 1H), 5.72 (d, $J = 10.2$ Hz, 1H), 5.67–5.58 (m, 1H), 4.57 (bs, 1H), 4.24 (d, $J = 16.0$ Hz, 1H), 3.83 (s, 3H), 3.75 (d, $J = 16.0$ Hz, 1H), 3.40–3.09 (m, 2H), 2.90–2.70 (m, 1H), 2.23 (s, 3H), 2.07 (s, 3H), 2.01–1.73 (m, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 170.2$ (s), 145.3 (s), 142.8 (s), 133.0 (s), 130.5 (s), 128.4 (d), 127.2 (d), 127.0 (s), 113.5 (d), 87.3 (d), 66.4 (d), 55.8 (q), 48.8 (s + t), 47.1 (t), 40.4 (t), 28.2 (t), 21.1 (q), 19.4 (q) ppm.

Step 2: Saponification. 17 mg of **9** (0.05 mmol), 17 mg of K_2CO_3 (0.12 mmol) and 0.1 cm^3 of 2 *N* KOH were stirred in 0.5 cm^3 of *Me*OH at ambient temperature. When complete conversion was detected by TLC, 1 cm^3 of H_2O was added, the mixture was concentrated *in vacuo* to a volume of 1 cm^3, and diluted with 4 cm^3 of 2 *N* HCl. The aqueous layer was washed with 3×5 cm^3 of *Et*OAc (discard), the *pH* was adjusted to >8.5 using conc. NH_4OH, and the mixture was extracted with 5×5 cm^3 of *Et*OAc. The combined organic layer was washed with 10 cm^3 of brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Yield 10 mg of colorless foam (67%).

Method B. A solution of 0.80 g of **8** (2.65 mmol) and 1.50 g of bis(1,1-dimethylethyl)azodicarboxylate (6.63 mmol) in 80 cm^3 of dry *THF* was stirred for 24 h at ambient temperature. The mixture was concentrated *in vacuo*, and the residue was dissolved in 20 cm^3 of 20% *TFA* in CH_2Cl_2, stirred for 30 min, and cooled to 0°C. The *pH* was adjusted to >8.5 using conc. NH_4OH, and the mixture was extracted with 5×5 cm^3 of CH_2Cl_2. The combined organic layer was washed with 10 cm^3 of brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by MPLC (30 g SiO_2, $CHCl_3$:*Me*OH = 90:10). Yield 400 mg of colorless oil (53%); $CHCl_3$:*Me*OH = 95:5, $R_f = 0.1$; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 6.50$ (s, 1H), 6.08 (d, $J = 10.3$ Hz, 1H), 5.80 (d, $J = 10.3$ Hz, 1H), 4.70–4.62 (m, 1H), 4.57 (bs, 1H), 4.26 (d, $J = 15.7$ Hz, 1H), 3.83 (s, 3H), 3.75 (d, $J = 15.7$ Hz, 1H), 3.35–3.20 (m, 1H), 2.85–2.70 (m, 1H), 2.50–2.29 (m, 2H), 2.23 (s, 3H), 2.00–1.64 (m, 2H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 145.4$ (s), 142.9 (s), 133.5 (s), 131.6 (d), 130.7 (s), 127.2 (d), 126.8 (s), 113.3 (d), 88.2 (d), 63.1 (d), 55.9 (q), 48.9 (t), 48.8 (s), 47.2 (t), 32.2 (t), 28.2 (t), 19.5 (q) ppm.

*General Procedure for the Preparation of N-Substituted Compounds **11a–11d***

200 mg of **7** (0.70 mmol), 195 mg of K_2CO_3 (1.40 mmol), and 115 mg of NaI (0.77 mmol) were freshly ground and stirred under reflux with 1.2 equiv of alkylating agent in 5 cm^3/100 mg of dry acetone. The conversion was monitored by TLC. Then the mixture was concentrated *in vacuo*, and the residue was dissolved in 2 *N* HCl and washed with 2×25 cm^3 of *Et*OAc (discard). The *pH* of the aqueous solution was adjusted to >8.5 using conc. NH_4OH, and the mixture was extracted with 5×25 cm^3 of *Et*OAc. The combined organic layer was washed with 50 cm^3 of brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by MPLC (SiO_2, $CHCl_3$:*Me*OH:conc. NH_4OH = 89:10:1).

[(±)-(4aα,6β,8aR)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-1-methyl-11-(2-propenyl)-6H-benzofuro[3a,3,2-ef][2]benzazepine-6-ol* (**11a**, $C_{20}H_{25}NO_3$)

Reagent 0.07 cm^3 of 1-bromo-2-propene (0.84 mmol); reaction time 10 h. Yield 50 mg of colorless foam (22%); TLC: $CHCl_3$:*Me*OH:conc. NH_4OH = 89:10:1, $R_f = 0.2$; ^1H NMR (200 MHz, $CDCl_3$):

$\delta = 6.52$ (s, 1H), 6.12 (d, $J = 10.3$ Hz, 1H), 6.03–5.78 (m, 2H), 5.18 (bs, 1H), 5.11 (d, $J = 4.5$ Hz, 1H), 4.57 (bs, 1H), 4.12 (bs, 1H), 4.09 (d, $J = 15.0$ Hz, 1H), 3.81 (s, 3H), 3.78 (d, $J = 15.0$ Hz, 1H), 3.32–3.02 (m, 4H), 2.72–2.58 (m, 1H), 2.21 (s, 3H), 2.07–1.89 (m, 2H), 1.57 (ddd, $J = 13.7$, 3.4, 2.7 Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 144.0$ (s), 143.0 (s), 136.0 (d), 133.6 (s), 129.1 (s), 127.4 (d), 127.2 (d), 126.9 (s), 117.5 (t), 113.7 (d), 88.4 (d), 62.0 (d), 57.2 (t), 55.8 (q), 52.9 (t), 52.0 (t), 48.4 (s), 33.9 (t), 29.8 (t), 19.4 (q) ppm.

[(±)-(4aα,6β,8aR)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-1-methyl-11-(phenylmethyl)-6H-benzofuro[3a,3,2-ef][2]benzazepine-6-ol* (**11b**, $C_{24}H_{27}NO_3$)

Reagent 0.1 cm^3 of benzyl bromide (0.84 mmol); reaction time 24 h. Yield 140 mg of colorless foam (53%); TLC: $CHCl_3$:*Me*OH:conc. $NH_4OH = 89:10:1$; $R_f = 0.4$; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.30$ (m, 5H), 6.50 (s, 1H), 6.16 (d, $J = 10.2$ Hz, 1H), 5.99 (dd, $J = 10.2$, 4.9 Hz, 1H), 4.61 (bs, 1H), 4.13 (bs, 1H), 4.00 (d, $J = 15.7$ Hz, 1H), 3.82 (s, 3H), 3.81 (d, $J = 15.7$ Hz, 1H), 3.69 (s, 2H), 3.34 (ddd, $J = 14.1$, 12.4, 1.8 Hz, 1H), 3.13 (td, $J = 14.1$, 3.5 Hz, 1H), 2.74–2.37 (m, 2H), 2.19–1.93 (m, 2H), 1.90 (s, 3H), 1.57 (dt, $J = 13.7$, 3.0 Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 143.9$ (s), 143.0 (s), 138.9 (s), 133.6 (s), 129.2 (s), 128.7 (d), 128.2 (d), 127.4 (d), 127.3 (d), 127.2 (s), 126.9 (d), 113.7 (d), 88.4 (d), 62.0 (d), 57.4 (t), 55.8 (q), 52.4 (t), 52.2 (t), 48.5 (s), 33.7 (t), 29.8 (t), 19.1 (q) ppm.

[(±)-(4aα,6β,8aR)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-1-methyl-11-[2-(4-morpholinyl)ethyl]-6H-benzofuro[3a,3,2-ef][2]benzazepine-6-ol* (**11c**, $C_{23}H_{32}N_2O_4$)

Reagent 155 mg of 4-(2-chloroethyl)morpholine · HCl (0.84 mmol); reaction time 24 h. Yield 210 mg of colorless foam (75%); TLC: $CHCl_3$:*Me*OH:conc. $NH_4OH = 89:10:1$, $R_f = 0.5$; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 6.52$ (s, 1H), 6.10 (d, $J = 10.3$ Hz, 1H), 5.97 (dd, $J = 10.3$, 4.8 Hz, 1H), 4.55 (bs, 1H), 4.13 (bs, 1H), 4.12 (d, $J = 15.9$ Hz, 1H), 3.88 (d, $J = 15.9$ Hz, 1H), 3.81 (s, 3H), 3.75–3.65 (m, 4H), 3.30 (ddd, $J = 14.3$, 12.4, 2.0 Hz, 1H), 3.10 (dt, $J = 14.3$, 3.3 Hz, 1H), 2.76–2.58 (m, 4H), 2.55–2.41 (m, 5H), 2.25 (s, 3H), 2.08–1.90 (m, 2H), 1.55 (dd, $J = 13.7$, 2.8 Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 144.1$ (s), 143.0 (s), 133.5 (s), 128.9 (s), 127.4 (d), 127.1 (d), 126.9 (s), 113.7 (d), 88.4 (d), 66.7 (2t), 66.6 (t), 61.9 (d), 57.1 (t), 55.8 (q), 54.0 (2t), 53.4 (t), 52.0 (t), 48.4 (s), 33.4 (t), 29.8 (t), 19.4 (q) ppm.

[(±)-(4aα,6β,8aR)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-1-methyl-11-[3-(1-piperidinyl)propyl]-6H-benzofuro[3a,3,2-ef][2]benzazepine-6-ol* (**11d**, $C_{25}H_{36}N_2O_3$)

Reagent 166 mg of 1-(3-chloropropyl)piperidine · HCl (0.84 mmol); reaction time 24 h. Yield 180 mg of colorless foam (63%); TLC: $CHCl_3$:*Me*OH:conc. $NH_4OH = 89:10:1$, $R_f = 0.3$; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 6.52$ (s, 1H), 6.10 (d, $J = 10.4$ Hz, 1H), 5.96 (dd, $J = 10.4$, 4.7 Hz, 1H), 4.55 (bs, 1H), 4.12 (bs, 1H), 4.08 (d, $J = 15.7$ Hz, 1H), 3.83 (d, $J = 15.7$ Hz, 1H), 3.81 (s, 3H), 3.24 (ddd, $J = 14.2$, 12.2, 2.0 Hz, 1H), 3.07 (dt, $J = 14.2$, 3.5 Hz, 1H), 2.71–2.13 (m, 10H), 2.24 (s, 3H), 2.07–1.88 (m, 2H), 1.77–1.35 (m, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 144.0$ (s), 142.9 (s), 133.5 (s), 128.9 (s), 127.3 (2d), 127.2 (s), 113.7 (d), 88.4 (d), 62.0 (d), 57.2 (t), 55.8 (q), 54.5 (3t), 53.3 (t), 51.4 (t), 48.5 (s), 33.4 (t), 29.8 (t), 25.7 (2t), 25.0 (t), 24.2 (t), 19.5 (q) ppm.

[(±)-(4aα,6α,8aR)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-1-methyl-11-[3-(1-piperidinyl)propyl)-6H-benzofuro[3a,3,2-ef][2]benzazepine-6-ol* (**12**, $C_{25}H_{36}N_2O_3$)

This compound was prepared following the general procedure given for the synthesis of compounds **11a**–**11d**. Reagents 100 mg of **10** (0.35 mmol), 83 mg of 1-(3-chloropropyl)piperidine · HCl (0.42 mmol); reaction time 28 h. Yield 60 mg of colorless oil (42%); TLC: $CHCl_3$:*Me*OH = 90:10, $R_f = 0.1$;

^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 6.50$ (s, 1H), 6.10 (d, $J = 10.2$ Hz, 1H), 5.78 (dd, $J = 10.2$, 1H), 4.70–4.57 (m, 1H), 4.54 (bs, 1H), 4.05 (d, $J = 15.2$ Hz, 1H), 3.82 (d, $J = 15.2$ Hz, 1H), 3.82 (s, 3H), 3.25 (ddd, $J = 13.5$, 12.8, 1.6 Hz, 1H), 3.09 (dt, $J = 13.5$, 2.5 Hz, 1H), 2.75 (dt, $J = 13.7$, 4.1 Hz, 1H), 2.56–2.27 (m, 8H), 2.23 (s, 3H), 2.08 (td, $J = 13.1$, 4.0, 2H), 1.81–1.38 (m, 9H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 144.9$ (s), 142.7 (s), 133.4 (s), 131.3 (s), 128.3 (2d), 127.0 (s), 113.3 (d), 88.1 (d), 63.0 (d), 57.2 (t), 55.7 (q), 54.4 (3t), 53.1 (t), 51.6 (t), 48.4 (s), 33.1 (t), 29.5 (t), 25.6 (2t), 24.8 (t), 24.1 (t), 19.5 (q) ppm.

General Procedure for the Preparation of Quarternary Ammonium Salts ***13a–14f***

The tertiary amine was dissolved in a minimum amount of dry *DMF*, then the alkylating agent was added and stirred at elevated temperature. The conversion was monitored *via* TLC. The mixture was slowly poured into Et_2O, the precipitate was collected by filtration and washed with Et_2O. The crude product was dissolved in *Et*OH and precipitated using *Et*OA*c*.

[(±)-(4aα,6β,8aR)]-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-1,11-dimethyl-11-(2-methyl-2-propenyl)-6H-benzofuro[3a,3,2-ef][2]benzazepinium chloride* (**13a**, $C_{22}H_{30}ClNO_3$)

Amine 280 mg of **6** (0.94 mmol); reagent 0.30 cm^3 of 1-chloro-2-methylprop-2-ene (3.08 mmol); reaction conditions 2 h, 70°C. Yield 270 mg of colorless crystals (73%); mp 239–241°C; ^{13}C NMR (50 MHz, *DMSO*-d_6): $\delta = 144.6$ (s), 134.2 (s), 133.5 (s), 131.1 (s), 130.9 (d), 127.5 (t), 124.9 (d), 115.9 (s), 114.4 (d), 86.3 (d), 73.0 (t), 60.8 (t), 59.4 (d), 55.5 (q), 46.3 (s), 43.0 (q), 31.1 (t), 23.8 (q), 18.9 (q) ppm.

[(±)-(4aα,6β,8aR)]-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-1,11-dimethyl-11-(2-propinyl)-6H-benzofuro[3a,3,2-ef][2]benzazepinium bromide* (**13b**, $C_{21}H_{26}BrNO_3$)

Amine 350 mg of **6** (1.16 mmol); reagent 0.13 cm^3 of 3-bromo-1-propine (1.16 mmol); reaction conditions 19 h, 60°C. Yield 300 mg of colorless crystals (62%); mp 216–218°C; ^{13}C NMR (50 MHz, *DMSO*-d_6): $\delta = 144.8$ (s), 144.7 (s), 133.4 (s), 131.0 (s), 125.2 (d), 115.3 (s), 114.5 (d), 86.2 (d), 83.7 (d), 72.6 (t), 60.6 (t), 59.7 (d), 55.6 (q), 46.2 (s), 43.0 (q), 31.0 (t), 18.8 (q) ppm.

[(±)-(4aα,6β,8aR)]-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-1,11-dimethyl-11-(phenylmethyl)-6H-benzofuro[3a,3,2-ef][2]benzazepinium bromide* (**13c**, $C_{25}H_{30}BrNO_3$)

Amine 240 mg of **6** (0.80 mmol); reagent 0.25 cm^3 of benzyl bromide (1.00 mmol); reaction conditions 10 min, 60°C. Yield 262 mg of colorless crystals (69%); mp 246–248°C; ^{13}C NMR (50 MHz, *DMSO*-d_6): $\delta = 144.7$ (s), 133.4 (d), 130.7 (s), 130.4 (d), 129.0 (d), 128.1 (s), 114.5 (d), 86.3 (d), 59.7 (t), 59.5 (d), 55.6 (q), 46.2 (s), 18.6 (q) ppm.

[(±)-(4aα,6β,8aR)]-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-1,11,11-trimethyl-6H-benzofuro[3a,3,2-ef][2]benzazepinium iodide* (**13d**, $C_{19}H_{26}INO_3$)

Amine 140 mg of **6** (0.46 mmol); reagent 200 mg of methyl iodide (1.40 mmol); reaction conditions 1.5 h, 40°C. Yield 146 mg of colorless crystals (71%); mp 278–280°C; ^{13}C NMR (50 MHz, *DMSO*-d_6): $\delta = 144.6$ (s), 144.1 (s), 132.8 (s), 131.6 (s), 114.2 (d), 86.3 (d), 62.6 (t), 59.5 (d), 55.4 (q), 45.9 (s), 31.0 (t), 18.4 (q) ppm.

[(±)-(4aα,6α,8aR)]-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-1,11-dimethyl-11-(2-methyl-2-propenyl)-6H-benzofuro[3a,3,2-ef][2]benzazepinium chloride* (**14a**, $C_{22}H_{30}ClNO_3$)

Amine 150 mg of **8** (0.50 mmol); reagent 45 mg of 1-chloro-2-methylprop-2-ene (1.50 mmol); reaction conditions 10 min, 70°C. Yield 160 mg of colorless crystals (82%); mp 162–164°C; ^{13}C NMR (50 MHz, *DMSO*-d_6): $\delta = 144.7$ (s), 134.2 (s), 134.1 (s), 131.1 (d), 127.5 (t), 114.4 (d), 87.3 (d), 73.0 (t), 60.7 (d), 59.4 (t), 55.6 (q), 46.3 (s), 23.8 (q), 18.9 (q) ppm.

[(±)-(4aα,6α,8aR)]-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-1,11-dimethyl-11-(2-propinyl)-6H-benzofuro[3a,3,2-ef][2]benzazepinium bromide* (**14b**, $C_{21}H_{26}BrNO_3$)

Amine 150 mg of **8** (0.50 mmol); reagent 180 mg of 3-brom-1-propine (1.50 mmol); reaction conditions 2.5 h, 70°C. Yield 167 mg of colorless crystals (82%); mp 158–162°C; ^{13}C NMR (50 MHz, *DMSO*-d_6): $\delta = 144.8$ (s), 133.9 (s), 131.2 (s), 114.5 (d), 87.2 (d), 83.7 (d), 72.6 (d), 55.6 (q), 46.3 (s), 31.9 (t), 18.8 (q) ppm.

[(±)-(4aα,6α,8aR)]-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-1,11-dimethyl-11-(phenylmethyl)-6H-benzofuro[3a,3,2-ef][2]benzazepinium bromide* (**14c**, $C_{25}H_{30}BrNO_3$)

Amine 153 mg of **8** (0.51 mmol); reagent 92 mg of benzyl bromide (0.51 mmol); reaction conditions 3 h, 70°C. Yield 150 mg of colorless crystals (63%); mp 169–175°C; ^{13}C NMR (50 MHz, *DMSO*-d_6): $\delta = 144.6$ (s), 134.1 (s), 133.4 (d), 131.0 (s), 130.4 (d), 128.9 (d), 128.1 (s), 114.4 (d), 87.2 (d), 61.8 (d), 59.4 (t), 55.6 (q), 46.3 (s), 31.5 (t), 18.6 (q) ppm.

[(±)-(4aα,6α,8aR)]-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-1,11,11-trimethyl-6H-benzofuro[3a,3,2-ef][2]benzazepinium iodide* (**14d**, $C_{19}H_{26}INO_3$)

Amine 210 mg of **8** (0.70 mmol); reagent 290 mg of methyl iodide (2.10 mmol); reaction conditions 2 h, 40°C. Yield 240 mg of colorless crystals (77%); mp 280°C (decomp); ^{13}C NMR (50 MHz, *DMSO*-d_6): $\delta = 144.7$ (s), 133.6 (s), 131.1 (s), 114.4 (d), 87.1 (d), 62.2 (t), 60.7 (q), 55.5 (q), 48.4 (d), 46.2 (s), 31.5 (t), 18.9 (q) ppm.

[(±)-(4aα,6α,8aR)]-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-1,11-dimethyl-11-(2-propenyl)-6H-benzofuro[3a,3,2-ef][2]benzazepinium bromide* (**14e**, $C_{21}H_{28}BrNO_3$)

Amine 150 mg of **8** (0.50 mmol); reagent 0.13 cm^3 of 3-bromo-1-propene (1.50 mmol); reaction conditions 2 h, 60°C. Yield 150 mg of colorless crystals (64%); mp 140–145°C; ^{13}C NMR (50 MHz, *DMSO*-d_6): $\delta = 144.7$ (s), 134.5 (d), 134.0 (s), 131.1 (s), 128.3 (s), 126.1 (d), 115. 3 (d), 114.4 (d), 87.2 (d), 60.7 (d), 59.8 (t), 55.6 (q), 46.3 (s), 31.5 (t), 18.8 (q) ppm.

[(±)-(4aα,6α,8aR)]-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-1,11-dimethyl-11-(4-(trifluoromethyl)phenylmethyl)-6H-benzofuro[3a,3,2-ef][2]benzazepinium bromide* (**14f**, $C_{26}H_{29}BrF_3NO_3$)

Amine 150 mg of **8** (0.50 mmol); reagent 357 mg of 4-(trifluoromethyl)benzylbromide (1.50 mmol); reaction conditions 1 h, 70°C. Yield 140 mg of colorless crystals (53%); mp 178–182°C; ^{13}C NMR (50 MHz, *DMSO*-d_6): $\delta = 144.8$ (s), 134.4 (d + d), 134.2 (d), 132.6 (s), 131.2 (s), 130.9 (s), 130.3 (s), 126.6 (d), 125.8 (s), 121.2 (d), 114.5 (d), 87.3 (d), 60.8 (d), 55.6 (q), 46.3 (s), 34.3 (t), 18.7 (q) ppm.

*X-Ray Structure Determinations of **5** and **6** · HBr*

Crystal data of **5**: $C_{18}H_{21}NO_3$, $M_r = 299.36$, colorless block of $0.80 \times 0.52 \times 0.22$ mm from $CHCl_3/MeOH$, monoclinic, space group $P2_1/n$ (no. 14), $a = 11.591(2)$ Å, $b = 9.925(2)$ Å, $c = 13.267(3)$ Å, $\beta = 92.11(1)^\circ$, $V = 1525.2(5)$ Å^3, $Z = 4$, $D_x = 1.304$ Mg/m^3, λ(Mo-Kα) = 0.71073 Å, $\mu = 0.088$ mm^{-1}, $T = 300(2)$ K. X-Ray data collection with a Bruker SMART CCD area detector diffractometer and graphite monochromatized Mo-Kα radiation. 19740 reflections with $\theta < 27.5^\circ$ were measured, corrected for absorption, and merged to 3470 unique reflections, $R_{int} = 0.027$. Structure solved with direct methods, structure refinement on F^2 using program SHELXL97. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms had isotropic temperature factors and rided on the atoms to which they were bonded. The final refinement varied 204 parameters and converged at $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.052$, $wR2 = [\Sigma(w(F_o^2 - F_c^2)^2)/\Sigma(w(F_o^2)^2)]^{1/2} = 0.121$, and $S = 1.04$ for the 3470 unique reflections; $R1 = 0.040$ for the 2767 observed data [$I > 2\sigma(I)$].

The molecular structure of **5** in crystalline state is shown in Fig. 1. The compound differs from racemic narwedine mainly in two respects. It does not crystallize spontaneously in a chiral space group ($P2_12_12_1$ in case of narwedine [12]), and the methoxy group adopts an unusual orientation being approximately *syn*-oriented to O1 (torsion angle C2–C3–O2–C16 = 36.4°, Fig. 1).

Crystal data of **6** · *HBr:* $C_{18}H_{24}BrNO_3$, $M_r = 382.29$, colorless prism of $0.26 \times 0.10 \times 0.06$ mm from 96% ethanol, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 7.499(2)$ Å, $b = 14.395(4)$ Å, $c = 15.937(4)$ Å, $V = 1720.4(8)$ Å^3, $Z = 4$, $D_x = 1.476$ Mg/m^3, λ(Mo-Kα) = 0.71073 Å, $\mu = 2.404$ mm^{-1}, $T = 300(2)$ K. X-Ray data collection with a Bruker SMART CCD area detector diffractometer and graphite monochromatized Mo-Kα radiation. 14235 reflections with $\theta < 25.0^\circ$ were measured, corrected for *LP* and absorption, and merged to 3021 unique reflections, $R_{int} = 0.056$ [9]. Structure solved with direct methods, structure refinement on F^2 using program SHELXL97 [10]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms had isotropic temperature factors, the OH and NH hydrogen atoms were refined without restraints, all other hydrogen atoms rided on the atoms to which they were bonded. The absolute structure was determined via a highly significant *Flack* parameter of −0.014(12) and showed that the molecules of **6** in the investigated crystal corresponded to (−)-galanthamine [8] in configuration. The final refinement varied 220 parameters and converged at $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.061$, $wR2 = [\Sigma(w(F_o^2 - F_c^2)^2)/\Sigma(w(F_o^2)^2)]^{1/2} = 0.074$, and $S = 1.03$ for the 3021 unique reflections; $R1 = 0.037$ for the 2351 observed data [$I > 2\sigma(I)$] [11].

The asymmetric unit of **6** · HBr is shown in Fig. 1. The compound turned out to be practically isostructural with (−)-galanthamine hydrobromide [8] (Fig. 2). Corresponding atom positions of the two structures differ on the average only by 0.30 Å and the differences can be attributed to the extra space requirement of the additional CH_3 group in **6** · HBr.

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[12] Unpublished crystallographic data of (−)-narwedine: $C_{17}H_{19}NO_3$, $M_r = 285.33$, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 9.659(2)$ Å, $b = 10.184(2)$ Å, $c = 15.061(3)$ Å, $V = 1481.5(5)$ Å^3, $Z = 4$, $D_x = 1.279$ Mg/m^3, λ(Mo-Kα) = 0.71073 Å, $\mu = 0.088$ mm^{-1}, $T = 297(2)$ K, $R1 = 0.0524$, $wR2 = 0.1054$ (all 4291 data)