Carbocyclic Galanthamine Analogs: Incorporating the Phenethylamine Motif

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An unnatural analog of the anti-Alzheimer drug galanthamine bearing a phenethylamine moiety has been prepared as a racemic mixture using $K_3[Fe(CN)_6]$ induced tandem cyclization techniques in the key step to form derivatives of a novel heterocyclic ring system.

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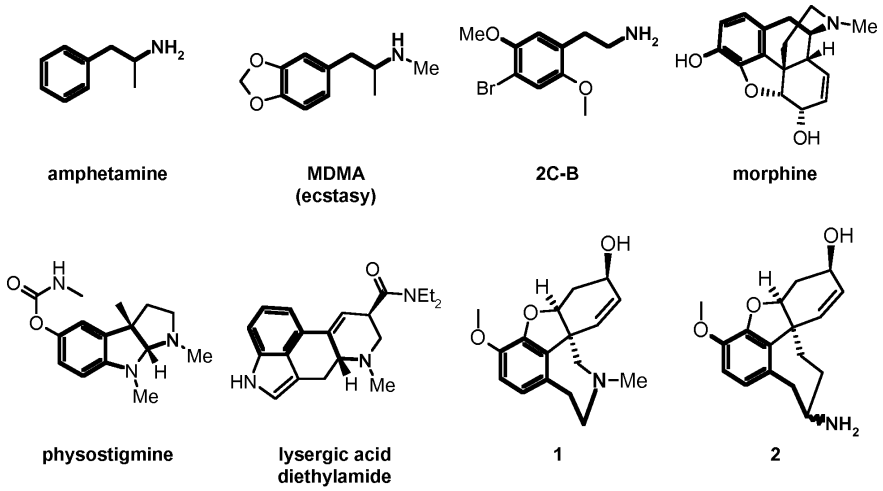
Introduction.

Phenethylamine is known to be the essential pharmacophore of a large number of CNS-active compounds. The array of these drugs starts with amphetamine and related designer drugs (*e.g.* ecstasy or 2C-B) and ends with complex natural products like morphine, physostigmine or lysergic acid diethyl amide (LSD). The first attempts to incorporate the phenethylamine substructure into the core of the anti-Alzheimer drug galanthamine [1,2] led to the synthesis of (4aα,6β,8aR*)-4a,5,9,10,11,12-hexahydro-3-methoxy-10-methyl-6*H*-benzofuro[3a,3,2-*ef*][3]benzazepine-6-ol (**1**), termed "isogalanthamine" [3]. The isomeric compound (**2**) was expected to show promising biological properties, and the tetracyclic ring system should be accessible utilizing tandem cyclization by phenol oxidation [3-7]. (see Table 1).

Results and Discussion.

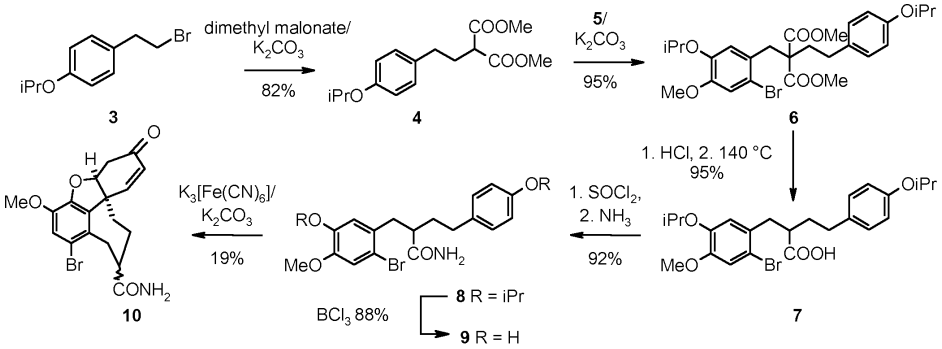
For the synthesis of the norbelladine analog (**9**) 1-(2-bromoethyl)-4-(1-methylethoxy)benzene (**3**), which was prepared starting from 4-hydroxyacetophenone [5], was reacted with dimethyl malonate in the presence of potassium carbonate to give the substituted malonic ester **4** in 82% yield. 4-Isopropyloxystyrene was detected as a minor side product. Reacting 1-bromo-2-chloromethyl-5-methoxy-4-(1-methylethoxy)benzene (**5**), available from bromo-isovanilline in 3 steps [5], with **4** under the same conditions gave **6** in 95% yield after purification by Kugelrohr distillation. Ester cleavage and decarboxylation under reduced pressure gave rise to the carboxylic acid (**7**), which was obtained as colorless solid in 95% yield. The conversion of **7** into the amide (**8**) was performed by successive treatment with thionyl chloride in dry dichloromethane and ammonia in dry formamide and gave **8** in 92% yield. Isopropyl ether cleavage of **8** using boron trichloride in dry dichloromethane afforded the diphenol (**9**) in 88% yield, which was then subjected to a $K_3[Fe(CN)_6]$ induced tandem cyclization. After chromatographic purification (4aR*,8aR*)-1-bromo-4a,5,9,10,11,12-hexahydro-3-methoxy-6-oxo-6*H*-benzo[*a*]cyclohepta[*hi*]benzofuran-11-carboxamide (**10**) was isolated as a mixture of diastereomeric amides with a total yield of 19% and was used directly in the next reaction steps (see Scheme 1).

Table 1: The Phenethylamine Motif

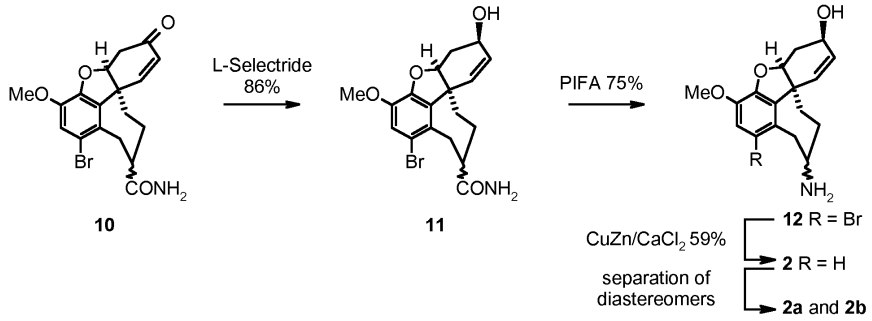


The cyclization product (**10**) was converted into the corresponding allyl alcohol (**11**) using L-Selectride® in dry tetrahydrofuran as the stereoselective reducing agent with 86% yield as a diastereomeric mixture (relative *R*- and *S*-configuration at C-11) as confirmed by the corresponding signals in NMR. Due to the presence of the cyclohexene ring the degradation of the amide (**11**) required very mild reaction conditions to avoid epoxide formation. Applying phenyliodisyl bis(trifluoroacetate) (PIFA) [8,9] in acetonitrile/water as the selective oxidant led to the desired amine (**12**) in 75% yield without formation of major byproducts. After debromination using a freshly prepared copper-zinc-couple [10] the diastereomeric galanthamine analogs **2a** and **2b** were separated by medium pressure liquid chromatography (MPLC) (see Scheme 2) and were both obtained as colorless solids.

Scheme 1



Scheme 2



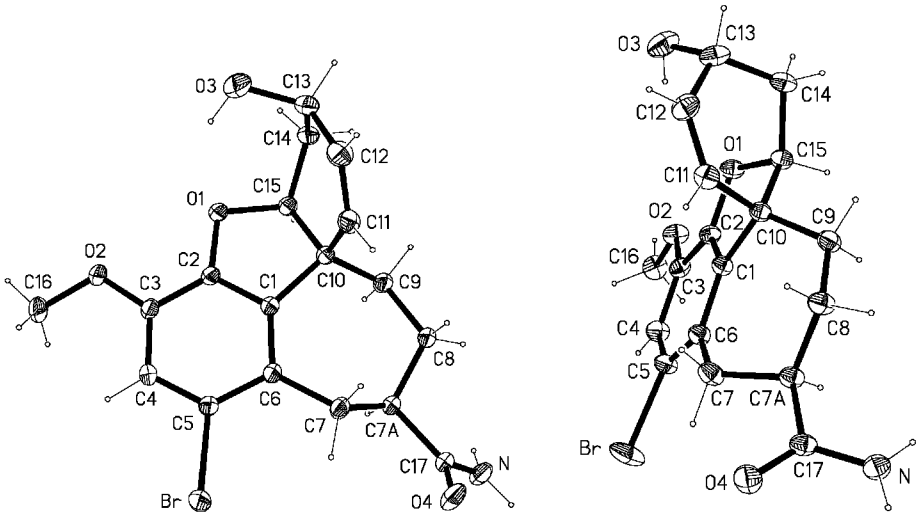


Figure 1. Molecular structure of **11** (crystallographic atom numbering), the diastereomer with the lower R_f (20% ellipsoids). For crystallography see experimental section.

For structural investigations the diastereomer with the lower R_f of an analytical sample of **11** was isolated by MPLC and crystallized from ethanol. X-ray diffraction confirmed the relative *R*-configuration at C11 for this compound. (see Figure 1).

Conclusion.

In summary, we have demonstrated that tandem cyclization by phenol oxidation can be successfully applied to access new members of the galanthamine family. Specifically we have prepared derivatives of the novel 6*H*-benzo[*a*]cyclohepta[*hi*]benzofuran ring system. The biological data of these compounds should allow conclusions on the binding mechanisms of galanthamine itself as well as valuable insights into structure-activity-relationships and will be published elsewhere.

EXPERIMENTAL

General.

Melting points were determined 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 precoated plates (Merck TLC aluminum sheets silica 60 F_{254}) with detection by UV light or with phosphomolybdic acid in aqueous EtOH by heating. All reactions were magnetically stirred under an argon atmosphere. MPLC (medium pressure liquid chromatography) was performed using SiO_2 (Baker), a LC-8A pump (Shimadzu), a SPD-6AV UV-detector (Shimadzu) and Büchi glass columns. All the HPLC-MS data were obtained using a HP1100 liquid chromatography system equipped with a diode array detector (Hewlett-Packard) and a 1100 Series MSD with Atmospheric Pressure Chemical Ionization Interface (APCI) in positive and negative ion mode, scanning m/z 200 - 550. *Column*: Merck Purospher RP18e, 5 µm, *solvent A*: MeCN:H_2O (97:2), *solvent B*: 20 mM CCl_3COOH:MeCN (97:3), *flow rate*: 0.5 mL/min, *injection volume*: 1 µL. *Gradient*: see Table 2.

Table 2. HPLC-gradient

Time	%A	%B
	20.0	80.0
5.00	20.0	80.0
17.00	60.0	40.0
22.00	60.0	40.0
22.50	20.0	80.0

2-[2-[4-(1-Methylethoxy)phenyl]ethyl]propanedioic Acid Dimethyl Ester (**4**).

1-(2-Bromoethyl)-4-(1-methylethoxy)benzene (**3**) [5] (19.0 g, 78.1 mmol), dimethyl malonate (40.0 g, 300 mmol) and potassium carbonate (42.0 g, 300 mmol, anhydrous, freshly ground) in dry DMF (400 mL) were stirred for 10 hours at 70 °C. The suspension was filtered and concentrated, and the residue was partitioned between water (250 mL) and Et_2O (250 mL). The aqueous layer was extracted with Et_2O (1 x 100 mL), the combined organic layer was washed with water (3 x 200 mL) and brine (1 x 150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The excess of dimethylmalonate was removed by distillation (160 °C/15 mbar), and the crude product was purified by Kugelrohr distillation (140 °C/0.001 mbar). Yield: colorless oil (18.9 g, 82%). TLC: petroleum ether:EtOAc = (90:10), R_f = 0.4. ^1H NMR ($CDCl_3$): δ 7.08 (d, *J* = 10.0 Hz, 2H), 6.81 (d, *J* = 10.0 Hz, 2H), 4.50 (septet, *J* = 6.5 Hz, 1H), 3.71 (s, 6H), 3.32 (t, *J* = 7.5 Hz, 1H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.19 (q, *J* = 7.5 Hz, 2H), 1.31 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 169.8 (s), 156.3 (s), 132.3 (s), 129.4 (d), 115.9 (d), 69.9 (d), 52.5 (q), 50.8 (d), 32.4 (t), 30.6 (t), 22.1 (q).

2-[2-Bromo-4-methoxy-5-(1-methylethoxy)phenylmethyl]-2-[2-[4-(1-methylethoxy)-phenyl]ethyl]propanediacid Dimethyl Ester (**6**).

Compound **4** (18.9 g, 64.2 mmol), 1-bromo-2-chloromethyl-5-methoxy-4-(1-methylethoxy)benzene (**5**) [5] (18.9 g, 64.2 mmol) and potassium carbonate (45.0 g, 321 mmol, anhydrous, freshly ground) in dry DMF (300 mL) were stirred for 12 hours at 60 °C. The suspension was filtered and concentrated, and the residue was partitioned between water (250 mL) and Et_2O (250 mL). The aqueous layer was extracted with Et_2O (1 x 100 mL), the combined organic layer was washed with water (3 x 200 mL) and brine (1 x 150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by Kugelrohr distillation (160 °C/0.005 mbar). Yield: colorless oil (33.7 g, 95%). TLC: petroleum ether: EtOAc = 90 : 10, R_f = 0.5; ^1H NMR ($CDCl_3$): δ 7.04 (s, 1H), 7.01 (d, *J* = 10.0 Hz, 2H), 6.79 (d, *J* = 10.0 Hz, 2H), 6.73 (s, 1H), 4.47 (septet, *J* = 6.5 Hz, 1H), 4.36 (septet, *J* = 6.5 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 6H), 3.48 (s, 2H), 2.65 - 2.47 (m, 2H), 2.26 - 2.06 (m, 2H), 1.31 (d, *J* = 6.5 Hz, 12H); ^{13}C NMR ($CDCl_3$): δ 171.4 (s), 156.1 (s), 149.8 (s), 146.2 (s), 133.0 (s), 129.3 (s), 129.1 (d), 118.2 (s), 116.2 (d), 116.0 (d), 115.8 (d), 71.6 (d), 69.7 (d), 58.7 (s), 55.9 (q), 52.3 (q), 37.4 (t), 34.5 (t), 29.9 (t), 22.0 (q), 21.9 (q).

Anal. Calcd for $C_{27}H_{35}BrO_7$: C, 58.81; H, 6.40. Found: C, 59.00; H, 6.26.

2-(2-Bromo-5-isoproxy-4-methoxybenzyl)-4-(4-isopropoxyphenyl)butyric Acid (**7**).

Compound **6** (33.7 g, 61.1 mmol) and KOH (17.5 g, 312 mmol) were stirred in EtOH (150 mL)/water (30 mL) under reflux for 12 hours. The solution was concentrated to 30 mL *in vacuo*, the pH was adjusted to less than 1 by the dropwise addition of concentrated HCl, and the mixture was partitioned between water (250 mL) and Et_2O (250 mL). The aqueous layer was extracted with Et_2O (2 x 100 mL), the combined organic layer was washed with water (3 x 200 mL) and brine (1 x 150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was decarboxylated using a Kugelrohr apparatus (30 minutes, 140 °C/0.005 mbar), and the formed carboxylic acid was purified by subsequent distillation (150 °C/0.005 mbar). Yield: colorless crystals (27.5 g, 94%); mp. 114 - 116 °C. TLC: $CHCl_3$:MeOH = 90:10, R_f =0.65; ^1H NMR (DMSO-d_6): δ 7.09, (s, 1H), 7.01 (d, *J* = 7.3 Hz, 2H), 6.80 (s, 1H), 6.78 (d, *J* = 7.3 Hz, 2H), 4.69 - 4.37 (m, 2H), 3.72 (s, 3H), 3.00 - 2.33 (m, 5H), 1.99 - 1.58 (m, 2H), 1.18 (d, *J* = 6.4 Hz, 12H); ^{13}C NMR (DMSO-d_6): δ 176.0 (s), 155.6 (s), 149.3 (s), 145.8 (s), 133.1 (s), 130.3 (s),

129.1 (d), 118.1 (d), 116.0 (d), 115.5 (s), 114.1 (d), 70.6 (d), 69.0 (d), 55.8 (q), 44.9 (d), 33.5 (t), 31.9 (t), 21.9 (q), 21.8 (q).

Anal. Calcd for $C_{24}H_{31}BrO_5$: C, 60.13; H, 6.52. Found: C, 60.38; H, 6.55.

2-(2-Bromo-5-isoproxy-4-methoxybenzyl)-4-(4-isopropoxyphenyl)butyramide (**8**).

To **7** (10.0 g, 20.8 mmol) in dry CH_2Cl_2 (100 mL) thionyl chloride (50 mL) was added within 15 minutes at 0 °C and stirred for 2 hours at this temperature. The mixture was concentrated *in vacuo*, and the residue was dissolved in dry formamide (15 mL), treated with a saturated solution of NH_3 in dry formamide (100 mL) at 0 °C and stirred for 1 hour at the same temperature. The solution was poured into water (1500 mL), and the precipitate was collected by filtration and triturated with water (4 x 400 mL). Yield: colorless crystals (9.21 g, 92%); mp. 154 - 156 °C. TLC: $CHCl_3$: MeOH = 90:10, R_f = 0.7; ^{1}H NMR (DMSO-d_6): δ 7.32 (s, 1H), 7.08, (s, 1H), 7.02 (d, *J* = 7.3 Hz, 2H), 6.83 (s, 1H), 6.80 (s, 1H), 6.78 (d, *J* = 7.3 Hz, 2H), 4.68 - 4.32 (m, 2H), 3.77 (s, 3H), 3.39 (s, 3H), 3.00 - 2.62 (m, 2H), 2.00 - 1.58 (m, 2H), 1.18 (d, *J* = 6.4 Hz, 12H); ^{13}C NMR (DMSO-d_6): δ 175.8 (s), 155.5 (s), 149.1 (s), 145.8 (s), 133.5 (s), 130.9 (s), 129.9 (d), 118.1 (d), 115.8 (d), 115.5 (s), 114.1 (d), 70.9 (d), 69.0 (d), 55.8 (q), 45.9 (d), 34.2 (t), 32.1 (t), 21.9 (q), 21.8 (q).

Anal. Calcd for $C_{24}H_{32}BrNO_4$: C, 60.25; H, 6.74; N, 2.93. Found: C, 59.99; H, 6.56; N, 2.82.

α-(2-Bromo-5-hydroxy-4-methoxyphenylmethyl)-4-hydroxybenzenebutaneamide (**9**).

To **8** (9.30 g, 19.4 mmol) in dry CH_2Cl_2 (150 mL) BCl_3 (40 mL, 1.6 *M* in CH_2Cl_2) was added at -78 °C and stirred for 1 hour. The solution was allowed to warm up to ambient temperature and stirred for an additional 2 hours. Water (300 mL) was added dropwise, and the mixture was concentrated to 300 mL *in vacuo*. The formed precipitate was collected by filtration and triturated with water (6 x 200 mL) and iPr_2O (2 x 40 mL). Yield: colorless crystals (6.76 g, 88%); mp. 177 - 179 °C. TLC: $CHCl_3$:MeOH = 90:10, R_f = 0.4; ^{1}H NMR (DMSO-d_6): δ 9.18 (s, 2H), 7.18 (s, 1H), 7.04, (s, 1H), 6.97 (d, *J* = 7.3 Hz, 2H), 6.72 (s, 1H), 6.65 (s, 1H), 6.66 (d, *J* = 7.3 Hz, 2H), 3.77 (s, 3H), 3.48 (s, 3H), 2.92 - 2.38 (m, 4H); ^{13}C NMR (DMSO-d_6): δ 175.6 (s), 155.5 (s), 147.0 (s), 145.8 (s), 131.3 (s), 129.9 (s), 129.8 (d), 117.9 (s), 115.8 (d), 115.0 (d), 111.9 (d), 56.0 (q), 48.1 (d), 37.6 (t), 37.0 (t).

Anal. Calcd for $C_{18}H_{20}NO_4$: C, 54.84; H, 5.11; N, 3.55. Found: C, 54.55; H, 4.90; N, 3.28.

(4a*R**,8a*R**)-1-Bromo-4a,5,9,10,11,12-hexahydro-3-methoxy-6-oxo-6*H*-benzo[*a*]cyclohepta[*hi*]-benzofuran-11-carboxamide (**10**).

To a suspension of **9** (3.00 g, 7.61 mmol) in $CHCl_3$ (300 mL) $K_3[Fe(CN)_6]$ (13.2 g, 40.0 mmol) and K_2CO_3 (7.50 g, 54 mmol) in water (75 mL) were added at once and stirred vigorously using a mechanical stirrer for 45 minutes at ambient temperature. The mixture was filtered using diatomaceous earth, and the filtrate was washed with water (3 x 100 mL) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (50 g SiO_2, EtOAc). Yield: colorless crystals (0.576 g, 19.2%); mp. 231 - 235 °C (dec.). TLC: $CHCl_3$:MeOH = 90:10, R_f =0.4 and 0.5; ^{1}H NMR ($CDCl_3$): δ 7.00 (s, 1H); 6.86 (dd, *J* = 12.3 Hz, *J* = 1.0Hz, 1H), 6.06 (d, *J* = 1.0 Hz, 1H), 5.02 (bs, 2H), 4.70 (s, 1H), 3.82 (s, 3H), 3.62 (d, *J* = 16.2 Hz, 1H), 3.23 (dd, *J* = 16.2 Hz, *J* = 3.0 Hz, 1H), 3.08 - 2.89 (m, 1H), 2.77 (dd, *J* = 16.2 Hz, *J* = 6.0 Hz, 1H), 2.62 - 1.70 (m, 5H); ^{13}C NMR (DMSO-d_6): δ 202.5 (s), 184.9 and 179.1 (s), 146.5 and 146.1 (d), 145.0 and 145.9 (s), 143.3 and 142.0 (s), 132.0 and 131.8 (s), 128.9 and 128.0 (s), 126.7 and 126.2 (d), 116.3 and 115.0 (s), 114.4 (d), 87.4 and 87.3 (d), 56.0 (q), 49.5 and 49.3 (s), 45.3 (d), 37.3 and 37.0 (t), 35.4 (t), 34.4 (t), 30.4 (t).

Anal. Calcd for $C_{18}H_{18}BrNO_4$: C, 55.12; H, 4.63; N, 3.57. Found: C, 54.91; H, 4.66; N, 3.41.

(4aα,6β,8a*R**)-1-Bromo-4a,5,9,10,11,12-hexahydro-3-methoxy-6-hydroxy-6*H*-benzo[*a*]cyclohepta[*hi*]benzofuran-11-carboxamide (**11**).

To a suspension of **10** (860 mg, 2.19 mmol) in dry THF (5 mL) L-Selectride® (6.6 mL, 6.6 mmol, 1 *M* in THF) was added dropwise at - 5 °C within 15 minutes and stirred for 4 hours at room temperature. The mixture was hydrolyzed with water (3 mL) and concentrated *in vacuo*. The residue was partitioned between EtOAc (30 mL) and 2 *N* HCl (20 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL), the combined organic layer was washed with 2 *N* HCl (2 x 25 mL), water (1 x 25 mL), saturated $NaHCO_3$ (1 x 25 mL) and brine (1 x 25 mL), dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude product was purified by flash chromatography (50 g SiO_2, EtOAc). Yield: colorless solid (741 mg, 86%). TLC: $CHCl_3$:MeOH = 90:10, R_f = 0.35 and 0.45; ^{1}H NMR ($CDCl_3$): δ 6.92 (s, 1H), 6.10 - 5.89 (m, 2H), 5.82 - 5.53 (m, 2H), 4.54 (s, 1H), 4.13 (s, 1H), 3.81 (s, 3H), 3.51 (d, *J* = 15.4 Hz, 1H), 3.05 (dd, *J* = 17.0 Hz, *J* = 6.5 Hz, 1H), 2.96 - 2.84 (m, 1H), 2.65 (d, *J* = 16.2 Hz, 1H), 2.83 (dd, *J* = 16.2 Hz, *J* = 6.5 Hz, 1H), 2.44 - 1.40 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 177.7 and 175.2 (s), 145.3 (s), 145.7 (s), 144.2 and 143.9 (s), 133.8 and 134.2 (s), 128.3 and 128.2 (d), 126.5 (d), 116.1 and 115.9 (s), 115.3 and 115.1 (d), 88.5 (d), 61.8 (d), 56.1 (q), 49.1 and 49.0 (s), 46.0 (d), 41.9 (t), 35.9 and 35.7 (t), 29.8 and 29.6 (t), 28.8 and 26.2 (t).

Anal. Calcd for $C_{18}H_{20}BrNO_4$: C, 54.84; H, 5.11; N, 3.55. Found: C, 54.84; H, 5.18; N, 3.43.

X-Ray Analysis.

For X-ray analysis the diastereomer ((4aβ,6α,8aβ,11*R**)-1-bromo-4a,5,9,10,11,12-hexahydro-3-methoxy-6-hydroxy-6*H*-benzo[*a*]cyclohepta[*hi*]benzofuran-11-carboxamide) with the lower R_f was isolated by MPLC and crystallized from EtOH.

Crystal Data.

$C_{18}H_{20}BrNO_4$, M_r = 394.26, monoclinic, space group $P2_1/c$ (no. 14), *a* = 10.417(4) Å, *b* = 14.375(5) Å, *c* = 11.722(4) Å, β = 107.57(1)°, *V* = 1673.4(10) Å^3, *Z* = 4, D_x = 1.565 Mg/m^{-3}, λ(Mo-Kα) = 0.71073 Å, μ = 2.48 mm^{-1}, *T* = 297(2) K. X-ray data collection with a Bruker SMART CCD area detector diffractometer and graphite monochromatized Mo Kα radiation. 24015 reflections with θ < 30.0° were measured, corrected for *LP* and absorption, and merged to 4813 unique reflections, R_{int} = 0.034. Structure solved with direct methods, structure refinement on F^2 using program SHELXL97 [11]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms had isotropic temperature factors and rided on the atoms to which they were bonded (exception: hydroxyl hydrogen H(3o), which was refined without restraints). The final refinement varied 223 parameters and converged at $R1 = \Sigma||F_o|-|F_c||/\Sigma|F_o| = 0.050$, $wR2 = [\Sigma(w(F_o^2-F_c^2)^2)/\Sigma(w(F_o^2)^2)]^? = 0.091$, and $S = 1.05$ for the 4813 unique reflections; $R1 = 0.034$ for the 3664 observed data [$I>2\sigma(I)$] [12].

The molecular structure of **11** in crystalline state is shown in Figure 1. The tetracyclic core corresponds in bond lengths, bond angles, and conformation well with galanthamine and derivatives thereof, except for small bond geometry differences at C7A which in the galanthamine family is a nitrogen atom [13]. Different from the galanthamine family where the N-bonded methyl group or related substituents prefer the axial orientation relative to the 7-membered ring (*e.g.* references [13b,13d]) although they are free to adopt also the equatorial orientation, the axial orientation of the $CONH_2$ group in **11** is stereochemically fixed. Bond distances are (Å; all e.s.d.'s 0.002-0.003 Å): Br-C5 1.903, O1-C2 1.373, O1-C15 1.471, O2-C3 1.363, O2-C16 1.429, O3-C13 1.446, O4-C17 1.228, N-C17 1.337, C1-C2 1.384, C1-C6 1.401, C1-C10 1.523, C2-C3 1.392, C3-C4 1.383, C4-C5 1.398, C5-C6 1.396, C6-C7 1.511, C7-C7A 1.531, C7A-C8 1.538, C7A-C17 1.536, C8-C9 1.531, C9-C10 1.536, C10-C11 1.510, C10-C15 1.550, C11-C12 1.318, C12-C13 1.501, C13-C14 1.508, C14-C15 1.511. Hydrogen bonds: O3ÆO1 2.945 (intramolecular and distinctly bent), NÆO3 3.094 (intermolecular), NÆO4 2.989 (intermolecular).

(4aα,6β,8a*R**)-11-Amino-1-bromo-4a,5,9,10,11,12-hexahydro-3-methoxy-6*H*-benzo[*a*]cyclohepta[*hi*]benzofuran-6-ol (**12**).

To bis(trifluoracetoxy)iodobenzene (PIFA, 787 mg, 1.78 mmol) in MeCN (3.5 mL, HPLC grade) water (3.5 mL, HPLC grade) was added. Compound **11** was added within 3 hours and stirred at ambient temperature for 24 hours. The reaction solution was concentrated *in vacuo*, dissolved in $CHCl_3$ (5 mL), filtered and purified by flash chromatography (30 g SiO_2, $CHCl_3$: MeOH:conc. NH_3 = 96: 3:1). Yield: colorless foam (490 mg, 75%). TLC: $CHCl_3$: MeOH: conc. NH_3 = 89:10:1, R_f =0.2 and 0.25. ^{1}H NMR (MeOH-d_4): δ 7.07 (s, 1H), 6.12 - 5.87 (m, 2H), 5.82 - 5.53 (m, 2H), 4.53 (s, 1H), 4.14 (s, 1H), 3.80 (s, 3H), 3.59 (d, *J* = 20.0 Hz, 1H), 3.14 - 2.92 (m, 1H), 2.47 (d, *J* = 17.0 Hz, 1H), 2.16 (s, 3H), 2.01 - 2.62 (m, 2H); ^{13}C NMR (MeOH-d_4): δ 148.3 and 148.2 (s), 146.5 and 146.1(s), 135.8 (s), 129.9 and 129.3 (s), 128.5 and 127.9 (d), 125.9 and 123.9(d), 118.4 and 118.1 (s), 116.9 and 116.0 (d), 118.4 and 118.0 (s), 116.8 and 116.0 (d), 89.0 and 88.9 (d), 62.4 and 62.3 (d), 57.2 (q), 50.6 and 50.4 (s), 49.8 (d), 38.5 (t), 36.0 and 35.0 (t), 31.8 and 31.0 (t), 31.4 and 28.3 (t). LC-MS: NI: 367.1 (21%), 366.1 (90%), 364.1 (100%), 362.1 (11%), 361.1 (10%), 348.2 (16%), 346.2 (6%); PI: 367.8 (18%), 365.9 (23%), 363.8 (6%), 351.8 (58%), 350.8 (10%), 349.9 (100%), 348.8 (63%), 347.9 (87%).

(4aα,6β,8a*R**)-11-Amino-4a,5,9,10,11,12-hexahydro-3-methoxy-6*H*-benzo[*a*]cyclohepta[*hi*]benzofuran-6-ol (**2**).

Zinc powder (600 mg) and Cu(I)I (600 mg) in water (4 mL)/EtOH (4 mL) were sonicated for 45 minutes under argon. **12** (80 mg, 0.22 mmol) and $CaCl_2$ (300 mg, 2.7 mmol) were added and refluxed for 12 hours. Concentrated NH_3 (1 mL) was added, and the mixture was concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (15 mL), filtered and the isomers separated by flash chromatography (30 g SiO_2, $CHCl_3$:MeOH:conc. NH_3 = 96:3:1).

(4aα,6β,8aα,11*R**)-11-Amino-4a,5,9,10,11,12-hexahydro-3-methoxy-6*H*-benzo[*a*]cyclohepta[*hi*]benzofuran-6-ol (**2a**).

Compound **2a** was obtained as colorless foam, yield 10 mg; ^{1}H NMR ($CDCl_3$): δ 6.73 - 6.62 (m, 2H), 6.05 (s, 2H), 4.62 (s, 1H), 4.14 (s, 1H), 3.82 (s, 3H), 3.57 (s, 1H), 3.22 (d, *J* = 16.2 Hz, 1H), 2.83 (dd, *J* = 16.2 Hz, *J* = 6.5 Hz, 1H), 2.24 - 1.60 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 146.2 (s), 144.3 (s), 133.6 (s), 128.4 (s), 128.1 (d), 127.2 (d), 124.8 (d), 111.9 (d), 89.0 (d), 62.6 (d), 56.3 (q) 49.0 (s), 48.3 (d, C-11), 41.8 (t, C-9), 32.5 (t, C-12), 30.4 (t, C-10), 30.4 (t). HPLC/MS *m/z* (relative intensity): PI: 289.0 (11%), 288.0 (59%), 271.0 (29%), 269.9 (100%), 252.9 (10%).

(4aβ,6α,8aβ,11*R**)-11-Amino-4a,5,9,10,11,12-hexahydro-3-methoxy-6*H*-benzo[a]cyclohepta[hi]benzofuran-6-ol (**2b**).

Compound **2b** was obtained as colorless foam, yield 26 mg; ^{1}H NMR ($CDCl_3$): δ 6.70 - 6.58 (m, 2H), 6.07 - 5.91 (m, 2H), 4.54 (s, 1H), 4.12 (s, 1H), 3.82 (s, 3H), 2.99 (s, 1H), 2.86 (t, *J* = 15.0 Hz, 1H), 2.72 (d, *J* = 16.0 Hz, 1H), 2.63 (dd, *J* = 16.0 Hz, *J* = 3.3 Hz, 1H), 2.30 - 1.60 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 146.4 (s), 143.9 (s), 133.7 (s), 128.5 (s), 128.1 (d), 127.5 (d), 123.3 (d), 111.7 (d), 88.9 (d), 62.4 (d), 56.3 (q), 52.8 (d, C-11), 48.3 (s), 45.1 (t, C-9), 35.8 (t, C-12), 35.6 (t, C-10), 30.4 (t). HPLC/MS *m/z* (relative intensity): PI: 287.0 (5%), 272.0 (7%), 271.0 (46%), 270.0 (100%).

The total combined yield of compounds **2a** and **2b**, as colorless foam, was 36 mg (59%).

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