Carbocyclic Galanthamin analogs: 4a,5,9,10,11,12-Hexahydro-6*H*-benzo[*b*]cyclohepta[*cd*]benzofurans

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Received April 23, 2002

The synthesis of a novel unnatural carbocyclic analog of the acetylcholine esterase inhibitor galanthamine with a $K_3[Fe(CN)_6]$ promoted oxidative tandem cyclization as the key step is reported.

J. Heterocyclic Chem., **39**, 1283(2002).

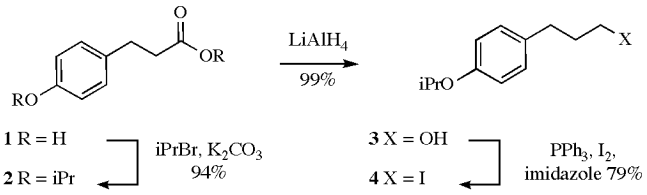
Introduction.

Galanthamine [1] - a natural product which can be isolated from caucasian snowdrops - is a selective, reversible acetylcholine esterase inhibitor [2] and is one of the few drugs approved for the treatment of Alzheimer's disease [3]. As an acetylcholine esterase (AChE) inhibitor, galanthamine was shown to elevate the level of acetylcholine in the brain. Galanthamine also exerts a second mechanism of action. This involves an allosteric potentiation of the nAChR function (APL) *via* a new class of noncompetitive cholinergic agonist binding sites [4]. The aim of this work was to prepare an isomer to galanthamine with the amine functionality as substituent instead of the benzazepine substructure. The key intermediate 4a,5,9,10,11,12-hexahydro-6*H*-benzo[*b*]cyclohepta[*cd*]benzofuran derivative (**10**) should be available by the extension of the tandem cyclization [1] to the novel precursor **9** and be elaborated into the target structure **13**.

Results and Discussion.

For the construction of the key intermediate of **10**, 3-(4-hydroxyphenyl)propionic acid (**1**) was reacted with isopropyl bromide in presence of potassium carbonate to give the ester (**2**) [5] in 94% yield, which was subsequently reduced using lithium aluminum hydride in dry THF. The resulting alcohol (**3**), which was obtained in 99% yield, was converted into the alkyl iodide (**4**) under Appelt conditions with a 79% yield (see Scheme 1).

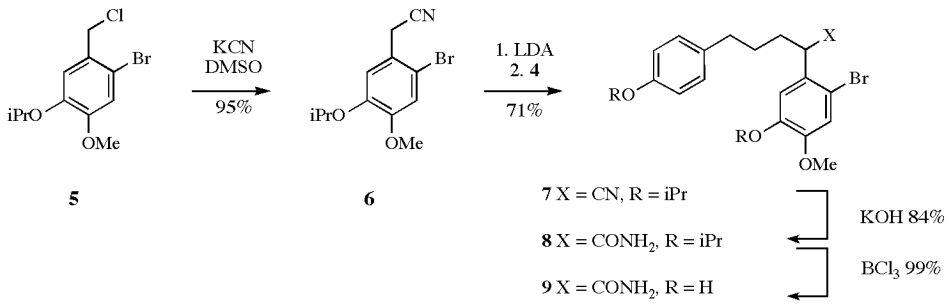
Scheme 1



1-Bromo-2-chloromethyl-5-methoxy-4-(1-methylethoxy)benzene (**5**) [6] was converted into the nitrile (**6**) using freshly ground KCN in DMSO with a 95% yield. As attempts to use NaH and $NaNH_2$ for the deprotonation of **6** failed, LDA was used as the base for linking **4** to **6**. The nitrile (**7**), which was obtained in a yield of 71%, was converted into the amide (**8**) by treatment with KOH in aqueous ethanol with an 84% yield. Cleavage of the isopropyl protecting group was performed using BCl_3 as lewis acid in dry CH_2Cl_2 and gave the diphenol (**9**) in a 99% yield (see Scheme 2).

Tandem cyclization [7] of **9** by vigorous stirring of a suspension of the starting material in $CHCl_3$ with an aqueous solution of $K_3[Fe(CN)_6]$ and potassium carbonate afforded the 4a,5,9,10,11,12-hexahydro-6*H*-benzo[*b*]cyclohepta-[*cd*]benzofuran derivative (**10**) as a mixture of diastereo-

Scheme 2



meric amides (**10a** and **10b**), the isomerization of **10b** into **10a** after separation of the isomers by MPLC was observed *via* TLC and ^{1}H-NMR spectroscopy.

Stereoselective reduction of the ketone (**10a**) gave rise to the allyl alcohol (**11**) with a yield of 83%. X-ray analysis of **10a** and **11** proved that no inversion at C-12 had taken place. (see Figures 1 and 2).

The use of phenyliodisyl bis(trifluoroacetate) (PIFA) [8,9] allowed the transformation of the amide (**11**) into the amine (**12**) with a 58% yield in the presence of the allyl alcohol substructure. The final debromination by treating **12** with a freshly prepared copper-zinc-couple [10] in the presence of $CaCl_2$ afforded the unnatural galanthamine analog (**13**) as a colorless solid with a yield of 78% (see Scheme 3).

The fact that **13** displayed no noticeable acetylcholine-(AChE) or butyrylcholine esterase (BuChE) inhibition was quite surprising. This information is intended to be used for a better understanding of binding mechanisms of galanthamine itself.

Conclusion.

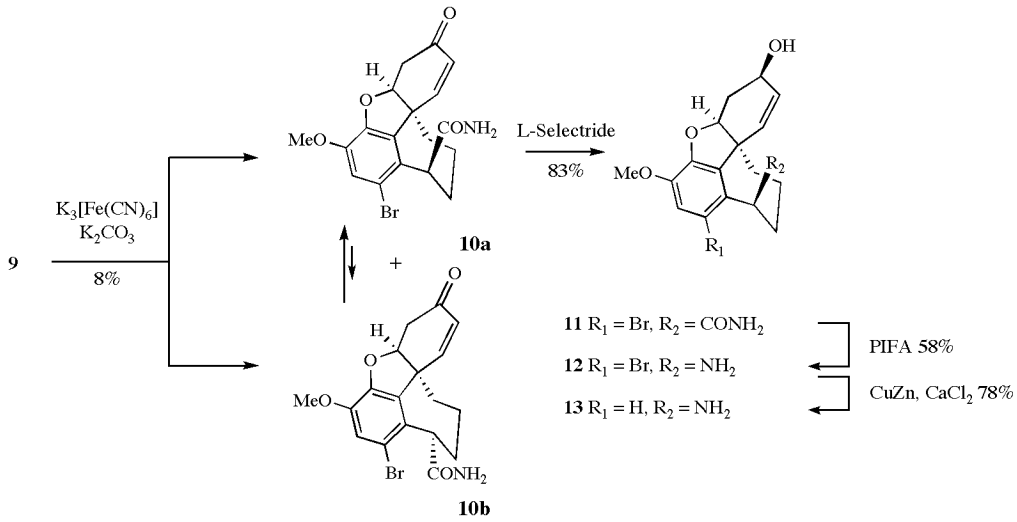
In summary we have extended the applicability of tandem cyclization by phenol oxidation towards the synthesis of members of the 4a,5,9,10,11,12-hexahydro-6*H*-benzo[*b*]cyclohepta[*cd*]benzofuran ring system and have thus provided access to novel unnatural analogs of the anti-Alzheimer drug galanthamine.

EXPERIMENTAL

General.

Melting points were determined on a Kofler melting point apparatus. ^{1}H and ^{13}C NMR-spectra were recorded on a Bruker AC-200 (200 MHz) pulse Fourier-transform NMR spectrometer

Scheme 3



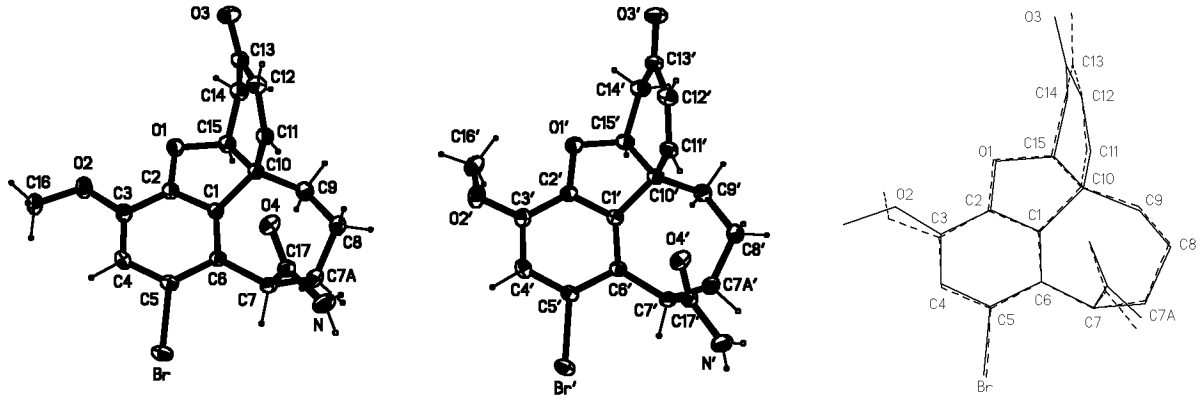


Figure 1. View of the two independent molecules present in the crystal structure of **10a** (20% ellipsoids, crystallographic atom numbering) and a superposition plot of the two (second molecule shown by broken lines; positional differences: r.m.s. 0.15 Å, O2-O2' 0.35 Å, O3-O3' 0.44 Å).

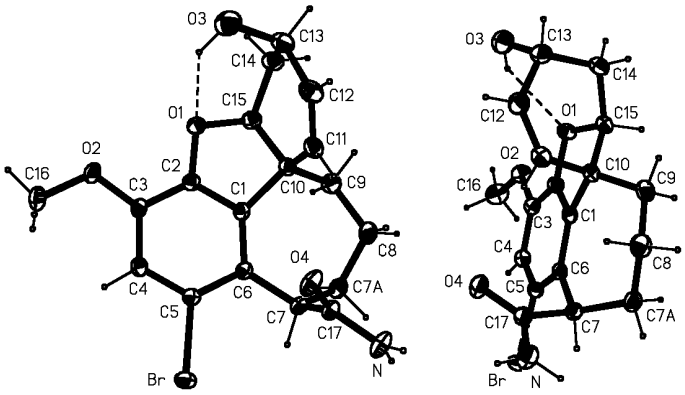


Figure 2. Molecular structure of **11** in crystalline **11**•~$^1/_2C_2H_5OH$ (20% ellipsoids) seen in two views (crystallographic atom numbering).

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 performed with magnetic stirring 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 97:3, *solvent B*: 20 mM CCl_3COOH: MeCN 97:3, *flow rate*: 0.5 mL/min, *injection volume*: 1 µL, *gradient*: see Table 1.

Table 1

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

4-(1-Methylethoxy)benzenepropanoic Acid, (1-Methyl)ethyl Ester (**2**).

A mixture of 4-hydroxybenzenepropanoic acid (**1**) (50.0 g, 300 mmol), potassium carbonate (210 g, 1.5 mol, anhydrous, freshly ground) and 2-bromopropane (221 g, 1.8 mol) in dry DMF (500 mL) was stirred at 60 °C for 24 hours. The mixture was filtered and evaporated *in vacuo*. The residue was partitioned between 2 *N* NaOH (500 mL) and Et_2O (500 mL), and the aqueous layer was extracted with Et_2O (2 x 100 mL). The combined organic layer was washed with 2 *N* NaOH (2 x 200 mL), water (2 x 500 mL) and brine (1 x 500 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by kugelrohr distillation (139 - 142 °C/0.025 mbar). Yield: colorless oil (70.8 g, 94%). TLC: petroleum ether:EtOAc = 9:1, R_f = 0.8; ^{1}H NMR ($CDCl_3$): δ 7.10 (d, *J* = 9.5 Hz, 2H), 6.81 (d, *J* = 9.5 Hz, 2H), 4.99 (septet, *J* = 6.3 Hz, 1H), 4.48 (septet, *J* = 6.3 Hz, 1H), 2.87 (t, *J* = 7.9 Hz, 2H), 2.54 (t, *J* = 7.9 Hz, 2H), 1.20 (d, *J* = 6.3 Hz, 6H), 1.31 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 172.4 (s), 156.2 (s), 132.4 (s), 129.1 (d), 115.8 (d), 69.7 (d), 67.4 (d), 36.4 (t), 30.1 (t), 22.0 (q), 21.7 (q).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.84; H, 8.75.

4-(1-Methylethoxy)benzenepropanol (**3**).

Compound **2** (10.0 g, 39.9 mmol) in dry THF (100 mL) was added to a suspension of $LiAlH_4$ (3.04 g, 80 mmol) in dry THF (100 mL) at 0 °C over 30 minutes and stirred at ambient temperature for 12 hours. Water (30 mL) was added, followed by concentrated HCl until the solution became clear. The mixture was partitioned between water (30 mL) and Et_2O (60 mL); the aqueous layer was extracted with Et_2O (2 x 20 mL), and the combined organic layer was washed with 2 *N* HCl (3 x 100 mL), water (1 x 100 mL), saturated $NaHCO_3$ (2 x 100 mL) and brine (1 x 100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Yield: colorless crystals (7.04 g, 99%), mp. 36 – 38 °C. TLC: petroleum ether : EtOAc = 4:1, R_f = 0.25. ^{1}H NMR ($CDCl_3$): δ 7.10 (d, *J* = 9.5 Hz, 2H), 6.82 (d, *J* = 9.5 Hz, 2H), 4.50 (septet, *J* = 6.3 Hz, 1H), 3.68 (t, *J* = 7.9 Hz, 2H), 2.66 (t, *J* = 7.9 Hz, 2H), 2.0 (b, 1H), 1.93 - 1.78 (m, 2H), 1.32 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 155.9 (s), 133.7 (s), 129.2 (d), 115.9 (d), 69.9 (d), 62.0 (t), 34.3 (t), 31.1 (t), 22.0 (q).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.93; H, 9.07.

1-(3-Iodopropyl)-4-(1-methylethoxy)benzene (**4**).

A mixture of triphenylphosphine (13.1 g, 49.9 mmol), iodine (19.9 g, 78.4 mmol) and imidazole (4.0 g, 58.8 mmol) in dry CH_2Cl_2 (250 mL) was stirred at ambient temperature for 20 minutes. At 15 °C, **3** (8.74 g, 45.0 mmol) in CH_2Cl_2 (100 mL) was added and stirred at ambient temperature for 12 hours. The mixture was then partitioned between water (300 mL) and CH_2Cl_2 (150 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL), and the combined organic layer was washed with water (1 x 100 mL), 10% $CuSO_4$ (2 x 200 mL), water (1 x 200 mL), saturated $NaHSO_3$ (2 x 200 mL) and brine (1 x 200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was slurried in iPr_2O (200 mL) and filtered. The filtrate was concentrated *in vacuo* and purified by MPLC (500 g SiO_2, petroleum ether:EtOAc = 95:5). Yield: colorless oil (10.9 g, 79%). TLC: petroleum ether:EtOAc = 4:1, R_f = 0.9. ^{1}H NMR ($CDCl_3$): δ 7.11 (d, *J* = 9.5 Hz, 2H), 6.82 (d, *J* = 9.5 Hz, 2H), 4.53 (septet, *J* = 6.3 Hz, 1H), 3.18 (t, *J* = 7.9 Hz, 2H), 2.67 (t, *J* = 7.9 Hz, 2H), 2.10 (Quintett, *J* = 7.9 Hz, 2H), 1.35 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 156.2 (s), 132.2 (s), 129.4 (d), 115.9 (d), 69.8 (d), 35.2 (t), 35.0 (t), 22.1 (q), 6.5 (t).

Anal. Calcd for $C_{12}H_{17}IO$: C, 47.39; H, 5.63. Found: C, 47.37; H, 5.41.

2-Bromo-4-methoxy-5-(1-methylethoxy)benzeneacetonitrile (**6**).

A mixture of 1-bromo-2-(chloromethyl)-5-methoxy-4-(1-methylethoxy)benzene (**5**) (7.00 g, 23.8 mmol) and potassium cyanide (1.70 g, 26.1 mmol, freshly ground) in dry DMSO (70

mL) was stirred at ambient temperature for 12 hours. Water (700 mL) was added, and the mixture was extracted with Et_2O (3 x 150 mL). The combined organic layer was washed with water (5 x 150 mL) and brine (1 x 200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was triturated with iPr_2O (2 x 15 mL). Yield: colorless crystals (6.46 g, 95%); mp. 92 - 94 °C. TLC: petroleum ether:EtOAc = 4:1, R_f = 0.55. ^{1}H NMR ($CDCl_3$): δ 7.02 (s, 1H), 6.97 (s, 1H), 4.50 (septet, *J* = 6.3 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 2H), 1.36 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 150.8 (s), 147.1 (s), 121.5 (s), 117.3 (s), 116.7 (d), 116.3 (d), 113.9 (s), 72.1 (d), 56.2 (q), 24.2 (t), 21.9 (q).

Anal. Calcd for $C_{12}H_{14}BrNO_2$: C, 50.72; H, 4.97; N, 4.93. Found: C, 50.73; H, 4.84; N, 4.89.

α-[2-Bromo-4-methoxy-5-(1-methylethoxy)phenyl]4-(1-methylethoxy)benzenepentanenitrile (**7**).

n-Butyllithium (12.7 mL, 27.5 mmol, 2.2 *M* in hexane) was added to a solution of diisopropylamine (3.55 g, 35.08 mmol) in dry THF (50 mL) at - 78 C° over a period of 15 minutes. The mixture was allowed to warm up to – 30 °C, stirred for 30 minutes and then cooled to - 78 C°. Compound **6** in dry THF (100 mL) was added, stirred for 20 minutes, warmed up to ambient temperature and stirred for an additional 60 minutes. The mixture was cooled to – 78 °C, then **4** in dry THF (50 mL) was added over 15 minutes and stirred for 45 minutes. Saturated NH_4Cl (50 mL) was added, the mixture was allowed to warm up to ambient temperature and partitioned between 2 *N* HCl (200 mL) and Et_2O (200 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layer was washed with water (5 x 150 mL), saturated $NaHCO_3$ (1 x 200 mL) and brine (1 x 200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by MPLC (1000 g SiO_2, petroleum ether:EtOAc = 98:2). Yield: colorless crystals (11.46 g, 71%), mp. 63 - 65 °C. TLC: petroleum ether: Et_2O = 1:4, R_f = 0.85. ^{1}H NMR ($CDCl_3$): δ 7.06 (d, *J* = 7.9 Hz, 2H), 7.01 (s, 1H), 7.02 (s, 1H), 6.82 (d, *J* = 7.9 Hz, 2H), 4.51 (septet, *J* = 6.3 Hz, 2H), 4.20 (t, *J* = 7.0 Hz, 1H), 3.82 (s, 3H), 2.68 - 2.56 (m, 2H), 1.99 - 1.68 (m, 4H), 1.31 (d, *J* = 6.3 Hz, 6H), 1.36 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ 156.1 (s), 150.7 (s), 147.2 (s), 133.0 (s), 129.2 (d), 127.1 (s), 120.5 (s), 116.2 (s), 115.9 (d), 115.5 (d),113.2 (s), 72.0 (d), 69.8 (d), 56.2 (q), 36.5 (t), 34.1 (d), 33.9 (t), 28.6 (t), 22.0 (q), 21.9 (q), 21.8 (q).

Anal. Calcd for $C_{24}H_{30}BrNO_3$: C, 62.61; H, 6.57; N, 3.04. Found: C, 62.32; H, 6.31; N, 2.97.

α-[2-Bromo-4-methoxy-5-(1-methylethoxy)phenyl]-4-(1-methylethoxy)benzenepentaamide (**8**).

Compound **7** (30.0 g, 65.2 mmol) in EtOH (600 mL) was treated with KOH (60.0 g, 1.07 mol) in water and refluxed for 6 hours. The mixture was concentrated under reduced pressure, and the residue was partitioned between 2 *N* HCl (200 mL) and Et_2O (300 mL). The aqueous layer was extracted with Et_2O (3 x 75 mL). The combined organic layer was washed with water (3 x 200 mL), saturated $NaHCO_3$ (1 x 200 mL) and brine (1 x 200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by MPLC (1000 g SiO_2, petroleum ether: Et_2O = 1:2) giving two fractions. The fraction eluted first (the acid **8**, X = COOH) was collected, concentrated *in vacuo*, dissolved in dry CH_2Cl_2 (100 mL), cooled to 0 °C and treated with oxalyl chloride (3 mL) in presence of a catalytic amount of DMF. The mixture was stirred for 2 hours and then evaporated to dryness. The residue was dissolved in dry THF (100 mL), and NH_3 was bubbled through the stirred solution for 2 hours. The mixture was concentrated and partitioned between water (100 mL) and Et_2O (100 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layer was washed with water (3 x 150 mL) and brine (1 x 200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was added to the fraction with the lower R_f, and the solvent was removed under reduced pressure. The residue was triturated with iPr_2O (2 x 50 mL). Yield: colorless crystals, (26.0 g, 83.5%), mp. 183 - 185 °C. TLC: petroleum ether: Et_2O = 1:4, R_f = 0.45. ^{1}H NMR ($CDCl_3$): δ 7.01 (d, *J* = 8.9 Hz, 2H), 6.98 (s, 1H), 6.92 (s, 1H), 6.75 (d, *J* = 8.9 Hz, 2H), 5.98 (b, 1H), 5.52 (b, 1H), 4.47 (septet, *J* = 6.3 Hz, 2H), 3.91 (t, *J* = 7.0 Hz, 1H), 3.82 (s, 3H), 2.74 - 2.40 (m, 2H), 2.22 - 2.00 (m, 1H), 1.91 - 1.36 (m, 3H), 1.35 - 1.22 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 175.2 (s), 155.8 (s), 149.9 (s), 147.0 (s), 133.9 (s), 130.8 (s), 129.1 (d), 115.7 (d), 114.8 (d), 114.7 (d), 71.4 (d), 69.7 (d), 56.0 (q), 49.7 (d), 34.6 (t), 31.9 (t), 29.1 (t), 22.0 (q), 21.8 (q), 21.7 (q).

Anal. Calcd for $C_{24}H_{32}BrO_4$: C, 60.25; H, 6.74; N, 2.93. Found: C, 60.00; H, 6.49; N, 2.80.

α-[2-Bromo-5-hydroxy-4-methoxyphenyl]-4-hydroxybenzenepentanamide (**9**).

To **8** (24.0 g, 50.2 mmol) in dry CH_2Cl_2 (300 mL) BCl_3 (150 mL, 150 mmol, 1 *M* in CH_2Cl_2) was added at -78 °C and stirred at ambient temperature for 4 hours. Water (200 mL) was added dropwise, and the mixture was concentrated to 150 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 (19.7 g, 99%), mp. 183 - 184 °C. TLC: EtOAc, R_f = 0.7. ^{1}H NMR (DMSO-d_6): δ 9.25 (s, 1H), 9.13 (s, 1H), 7.32 (s, 1H), 7.04 (s, 1H), 7.02 (s, 1H), 6.93 (d, *J* = 7.6 Hz, 2H), 6.91 (s, 1H), 6.66 (d, *J* = 7.6 Hz, 2H), 3.81 - 3.61 (m, 1H), 3.71 (s, 3H), 2.58 - 2.38 (m, 2H), 1.95 - 1.68 (m, 1H), 1.65 - 1.38 (m, 3H); ^{13}C NMR (DMSO-d_6): δ 174.1 (s), 155.3 (s), 147.2 (s), 146.1 (s), 132.1 (s), 129.1 (d), 115.7 (d), 115.4 (d), 115.1 (d), 111.8 (s), 55.9 (q), 49.1 (d), 34.2 (t), 29.6 (t), 26.9 (t).

Anal. Calcd for $C_{18}H_{20}BrNO_4$: C, 54.84; H, 5.11; N, 3.55. Found: C, 54.56; H, 5.40; N, 3.25.

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

To a suspension of **9** (3.00 g, 7.61 mmol) in $CHCl_3$ (300 mL) a mixture of $K_3[Fe(CN)_6]$ (13.2 g, 40.0 mmol) and K_2CO_3 (7.50 g, 53.1 mmol) in water (75 mL) was added at once and stirred vigorously using a mechanical stirrer at ambient temperature for 45 minutes. The mixture was filtered using diatomaceous earth, and the filtrate was washed with water (3 x 200 mL) and brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2, $CHCl_3$: MeOH = 96:4). Yield of diastereomer with the higher R_f: colorless crystals (0.24 g, 8%), mp. 257 - 258 °C (dec.). TLC: EtOAc, R_f = 0.6. ^{1}H NMR (DMSO-d_6): δ 7.57 (s, 1H), 7.48 (d, *J* = 14.5 Hz, 1H), 7.14 (s, 2H), 5.89 (d, *J* = 14.5 Hz, 1H), 4.66 (s, 1H), 4.32 (s, 1H), 4.01 (q, *J* = 7.7 Hz, 1H), 3.78 (s, 3H), 3.02 (d, *J* = 19.6 Hz, 1H), 2.79 (d, *J* = 19.6 Hz, 1H), 2.52 (d, *J* = 16.5 Hz, 1H), 2.16 (d, *J* = 16.5 Hz, 1H), 1.96 - 1.67 (m, 2H), 1.14 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 195.6 (s), 174.6 (s), 149.5 (d), 147.9 (s), 144.4 (s), 133.6 (s), 130.6 (s), 126.5 (d), 117.5 (s), 117.1 (d), 88.4 (d), 56.8 (q), 52.1 (s), 51.6 (d), 37.9 (t), 36.6 (t), 33.3 (t), 21.5 (t).

Anal. Calcd for $C_{18}H_{18}BrNO_4$: C, 55.12; H, 4.63; N, 3.57. Found: C, 55.15; H, 4.71; N, 3.38.

The diastereomer with the lower R_f **10b** which was formed as a minor byproduct was observed *via* TLC and NMR spectroscopy to isomerize to **10a**.

Anal. Calcd for $C_{18}H_{18}BrNO_4$: C, 55.12; H, 4.63; N, 3.57. Found: C, 55.10; H, 4.59; N, 3.46.

X-Ray Structure Determination of **10a**.

Crystal data: $C_{18}H_{18}BrNO_4$, M_r = 392.24, monoclinic, space group $P2_1/n$ (no. 14), a = 15.447(6) Å, b = 12.289(5) Å, c = 17.426(7) Å, β = 99.55(1)°, V = 3262(2) Å^3, Z = 8, D_x = 1.597 Mg/m^{-3}, λ(Mo-Kα) = 0.71073 Å, μ= 2.54 mm^{-1}, T = 297(2) K. X-ray data collection with a Bruker SMART CCD area detector diffractometer and graphite monochromatized Mo Kα radiation. 46429 reflections with θ < 30.0° were measured, corrected for *LP* and absorption, and merged to 9457 unique reflections, R_{int} = 0.030. 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 resided on the atoms to which they were bonded. The final refinement varied 442 parameters and converged at $R1 = \Sigma||F_o|-|F_c||/\Sigma|F_o| = 0.056$, $wR2 = [\Sigma(w(F_o^2-F_c^2)^2)/\Sigma(w(F_o^2)^2)]^? = 0.083$, and S = 0.97 for the 9457 unique reflections; $R1$ = 0.032 for the 6493 observed data [$I>2\sigma(I)$] [12].

The molecular structure of **10a** in the crystalline state is shown in Figure 1. The compound contains two crystallographically independent molecules the tetracyclic cores of which agree well in conformation, bond lengths, and bond angles whereas terminal atoms and groups show moderate (carbonyl oxygen O3, carboxamide group) to significant differences (methoxy group). The orientation of the methoxy group in the first molecule corresponds to what is usually observed in narwedine- and galanthamine-like compounds (*e.g.* compound **11**, Figure 2), whereas the "upward" orientation of the methoxy group of the second molecule is uncommon [13]. All differences between the two molecules are attributable to crystal packing and van-der-Waal forces assisted by intermolecular hydrogen bonds between the NH_2-groups as donors and the C=O groups of O(3) and O(4) of both molecules as acceptors (four bonds with N Æ O distances from 2.884 to 3.014 Å). Bond distances are (Å; first/second molecule; all e.s.d.'s 0.002-0.003 Å): Br-C5 1.907/1.912, O1-C2 1.365/1.375, O1-C15 1.461/1.454, O2-C3 1.367/1.367, O2-C16 1.403/1.410, O3-C13 1.219/1.231, O4-C17 1.226/1.229, N-C17 1.330/1.337, C1-C2 1.389/1.397, C1-C6 1.396/1.393, C1-C10 1.535/1.535, C2-C3 1.376/1.380, C3-C4 1.374/1.384, C4-C5 1.397/1.380, C5-C6 1.399/1.406, C6-C7 1.521/1.512, C7-C17 1.525/1.528, C7-C7A 1.550/1.545, C7A-C8 1.511/1.514, C8-C9 1.531/1.519, C9-C10 1.532/1.534, C10-C11 1.506/1.508, C10-C15 1.539/1.536, C11-C12 1.324/1.339, C12-C13 1.462/1.448, C13-C14 1.491/1.493, C14-C15 1.504/1.509.

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

To a suspension of **10a** (600 mg, 1.52 mmol) in dry THF (5 mL) L-Selectride® (4.6 mL, 4.6 mmol, 1 *M* in THF) was added dropwise at - 5 °C within 15 minutes and stirred at room temperature for 4 hours. The mixture was hydrolyzed with water (3 mL) and then 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 *invacuo*. The crude product was purified by flash chromatography (50 g SiO_2, EtOAc). Yield: colorless solid (798 mg, 83%), mp. 200 - 202 °C. TLC: EtOAc, R_f = 0.45. ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ 6.97 (s, 1H), 6.79 (b, 1H), 6.49 (b, 1H), 6.12 (d, J = 11.4 Hz, 1H), 5.83 (dd, J = 11.4 Hz, J = 5.1 Hz, 1H), 4.42 (s, 1H), 4.31 - 4.21 (m, 1H), 3.78 (s, 3H), 3.42 - 3.18 (m, 2H), 2.68 - 2.29 (m, 2H), 2.14 - 1.38 (m, 5H); ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ 173.4 (s), 146.3 (s), 143.6 (s), 134.2 (s), 128.8 (d), 128.6 (d), 126.8 (s), 116.1 (s), 115.6 (d), 87.1 (d), 60.1 (q), 55.6 (d), 50.1 (s), 49.5 (d), 37.5 (t), 31.0 (t), 29.8 (t), 20.3 (t).

Anal. Calcd for $C_{18}H_{20}BrNO_4$: C, 54.84; H, 5.11; N, 3.55. Found: C, 54.67; H, 5.10; N, 3.46.

X-Ray Structure Determination of **11** in the Form of the Solvate **11**•~$^1/_2C_2H_5OH$.

Crystal data: $C_{19}H_{23}BrNO_{4.5}$ ($C_{18}H_{20}BrNO_4$•$^1/_2C_2H_5OH$, idealized), M_r = 417.29, monoclinic, space group C2/c (no. 15), a = 24.820(9) Å, b = 11.447(5) Å, c = 17.097(7) Å, β = 131.14(1)°, V = 3658(3) Å^3, Z = 8, D_x = 1.515 Mg/m^{-3}, λ(Mo-Kα) = 0.71073 Å, μ= 2.27 mm^{-1}, T = 297(2) K. A colorless prism (0.64 x 0.38 x 0.32 mm) obtained from ethanol on slow evaporation (uptake of moisture likely) was used for X-ray data collection with a Bruker SMART CCD diffractometer and graphite monochromatized Mo Kα radiation. 21449 reflections with θ < 30.0° were measured, corrected for *LP* and absorption, and merged to 5223 unique reflections, R_{int} = 0.019. 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 resided on the atoms to which they were bonded, except for the hydroxyl H-atom that was refined without restraints. Three solvent peaks – C(1s), C(2s), and C(3s), attributed to the presence of disordered ethanol and possibly some water – were refined in coordinates, site occupation factors, and anisotropic thermal parameters. The final refinement varied 253 parameters and converged at $R1 = \Sigma||F_o|-|F_c||/\Sigma|F_o| = 0.038$, $wR2 = [\Sigma(w(F_o^2-F_c^2)^2)/\Sigma(w(F_o^2)^2)]^? = 0.075$, and S = 1.06 for all 5223 unique reflections; $R1$ = 0.028 for the 4146 observed data [$I>2\sigma(I)$] [12].

The molecular structure of **11** in its crystalline solvate **11**•~$^1/_2C_2H_5OH$ is shown in Figure 2. The compound contains between eight symmetry equivalent molecules of **11** per unit cell four cavities occupied by disordered ethanol solvent molecules (about one per cavity). A partial replacement of ethanol by water cannot be ruled out. Each cavity has a solvent accessible volume of about 100 Å^3 and a scattering power of *ca.* 27 electrons closely corresponding to the idealized chemical formula **11**•~$^1/_2C_2H_5OH$ with 26 electrons solvent scattering power per cavity (= 13 electrons or $^1/_2C_2H_5OH$ per molecule of **11**). Compound **11** adopts a conformation agreeing well with galanthamine and its derivatives [13]. Bond distances (Å; all e.s.d.'s ~0.002 Å): Br-C5 1.909, O1-C2 1.373, O1-C15 1.468, O2-C3 1.364, O2-C16 1.420, O3-C13 1.440, O4-C17 1.227, N-C17 1.329, C1-C2 1.380, C1-C6 1.403, C1-C10 1.530, C2-C3 1.389, C3-C4 1.383, C4-C5 1.394, C5-C6 1.394, C6-C7 1.517, C7-C17 1.532, C7-C7A 1.542, C7A-C8 1.521, C8-C9 1.520, C9-C10 1.527, C10-C11 1.518, C10-C15 1.543, C11-C12 1.323, C12-C13 1.490, C13-C14 1.510, C14-C15 1.506. Torsion angles (°): C16-O2-C3-C2 -176.8, C6-C7-

C17-N 175.8. Hydrogen bonds: O3 Æ O1 = 2.937 Å (intramolecular), N Æ O1 = 3.075 Å (intermolecular), and N Æ O4 = 2.886 Å (intermolecular).

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

To bis(trifluoracetoxy)iodobenzene (PIFA, 300 mg, 0.76 mmol) in MeCN (1.5 mL, HPLC grade) water (1.5 mL, HPLC grade) was added. Within 2 hours **11** was added 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:concentrated NH_3 = 96:3:1). Yield: colorless foam (161 mg, 58%), mp. 156 - 159 °C. TLC: $CHCl_3$:MeOH:conc. NH_3 = 89:10:1, R_f = 0.6. ^{1}H NMR (MeOH-d_4): δ 7.08 (s, 1H), 6.41 (d, *J* = 14.5 Hz, 1H), 5.83 (dd, *J* = 14.5 Hz, *J* = 5.1 Hz, 1H), 4.72 (s, 1H), 4.58 (s, 1H), 4.13 (t, *J* = 3.6 Hz, 1H), 3.82 (s, 3H), 2.49 (d, *J* = 17.2 Hz, 1H), 2.45 - 2.07 (m, 4H), 1.92 - 1.58 (m, 4H); ^{13}C NMR (MeOH-d_4): δ 147.2 (s), 144.7 (s), 134.5 (s), 133.3 (s), 130.9 (d), 126.4 (d), 116.6 (d), 115.5 (s), 87.8 (d), 61.2 (d), 57.3 (q), 54.0 (d), 48.6 (s), 38.3 (t), 35.2 (t), 30.1 (t), 17.9 (t). HPLC/MS *m/z* (relative intensity): NI: 366.1 (44%), 364.1 (100%), 349.1 (34%), 329.2 (37%) ; PI: 349.9 (98%), 348.8 (100%), 347.7 (16%), 332.8 (42%), 331.8 (38%).

Anal. Calcd for $C_{17}H_{20}BrNO_2$•0.66H_2O: C, 54.02; H, 5.68; N, 3.71. Found: C, 53.93; H, 5.52; N, 3.60.

(4aβ,6α,8aβ,12*R**)-12-Amino-4a,5,9,10,11,12-hexahydro-3-methoxy-6*H*-benzo[*b*]cyclohepta[*cd*]benzofuran-6-ol (**13**).

A suspension of zinc powder (500 mg) and Cu(I)I (500 mg) in water (4 mL)/EtOH (4 mL) was sonicated under argon for 45 minutes. Compound **12** (70 mg, 0.19 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 purified by flash chromatography (30 g SiO_2, $CHCl_3$:MeOH: concentrated NH_3 = 96:3:1). Yield: colorless crystals (42 mg, 78%), mp. 158 - 160 °C. TLC: $CHCl_3$:MeOH:concentrated NH_3 = 89:10:1, R_f = 0.55. ^{1}H NMR ($CDCl_3$): δ 6.81 - 6.61 (m, 3H), 6.97 (dd, *J* = 14 Hz, *J* = 4 Hz, 1H), 4.44 (s, 1H), 4.30 (s, 1H), 4.24 (t, *J* = 3Hz, 1H), 3.85 (s, 3H), 2.63 (dd, *J* = 17 Hz, *J* = 6 Hz, 1H), 2.40 (q, *J* = 15 Hz, 1H), 2.19 - 2.08 (m, 1H), 2.02 (dd, *J* = 18 Hz, *J* = 4 Hz, 1H), 1.97 - 1.52 (m, 7 H); ^{13}C NMR ($CDCl_3$): δ 145.4 (s), 143.2 (s), 134.1 (s), 132.6 (s), 129.9 (d), 125.4 (d), 121.9 (d), 109.9 (d), 87.7 (d), 61.1 (d), 54.8 (q), 48.5 (s), 37.0 (t), 34.4 (t), 29.0 (t), 25.8 (t), 16.9 (t). HPLC/MS *m/z* (relative intensity): NI: 287.1 (17%), 286.1 (54%), 285.2 (8%), 284.2 (36%), 279.2 (5%), 268.2 (28%), 266.1 (5%), 265.1 (8%), 253.1 (6%), 252.2 (18%), 251.2 (100%), 247.1 (5%), 240.2 (6%), 237.1 (10%), 236.1 (24%); PI: 272.0 (19%), 270.9 (100%), 270.0 (13%), 253.9 (11%), 253.0 (15%).

Acknowledgements.

The authors wish to thank Sanochemia Pharmazeutika AG for their financial support and donation of chemicals.

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