Addition of Nucleophiles to Immonium Galanthamines

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

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Four galanthamine derivatives were converted into immonium bromides by treatment with NBS. The nucleophilic addition of cyanide and methylmagnesium iodide to these galanthaminium halides was studied and the structures and conformations of two products were investigated by NMR spectroscopy and X-ray diffraction.

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 which also allosterically modulates nicotinic acetylcholine receptors.[1] Several routes for the total synthesis of (−)-galanthamine (**1**) have been developed in recent years, one of which is now applied in industrial scale production.[2] In continuation of previous research on novel derivatives of **1**,[3] the title reaction was investigated as a tool for the preparation of 12-substituted galanthamines.

Results and Discussion

Immonium Glanthamines

When (−)-galanthamine (**1**) was treated with bromine in order to obtain 1-bromogalanthamine, the formation of a side product was observed in 50 % conversion which was identified as (−)-galanthaminium bromide (**5**). Since **5** was supposed to be a promising key intermediate for the preparation of galanthamine derivatives substituted in position 12 (for the numbering of the galanthamine skeleton see Figure 1), the focus of our interest was set on the synthesis of pure galanthaminium halides. Under optimised reaction conditions (similar to results published for analogous compounds),[4] (−)-galanthamine (**1**) and its analogues **2**−**4** were oxidised in yields of 86−92% using N-bromosuccinimide (NBS) in $CHCl_3$ (see Scheme 1 and Table 1).

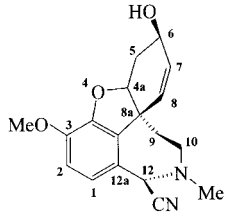

Figure 1. Galanthamine-12-carbonitrile **9**

Since this research was part of a long term pharmaceutically oriented project, the nucleophiles chosen for addition to these immonium halides were selected in connection with bio-activity issues.

Galanthamine-12-carbonitriles

Following a procedure reported by Leonard and Hauck,[5] the galanthaminium bromides **5**−**8** were converted into the corresponding carbonitriles by treatment with freshly ground KCN. Compounds **9**−**12** were formed as mixtures of geometric isomers in yields of 51−77% (see Table 2; the ratios were estimated from the integration of H12 in the ^{1}H NMR spectra). Their chromatographic separation was found to be unsuccessful despite sufficiently different R_f values. An equilibrium, due to smooth interconversion of the two isomers in solution shown by 2D TLC analysis, turned out to be the reason for this failure. Only in the case of **9**, owing to its favourable isomeric ratio, could the major isomer be isolated by crystallisation from EtOH in 33% yield. Surprisingly, a large amount of galanthamine (**1**) was found in the mother liquor of this separation which

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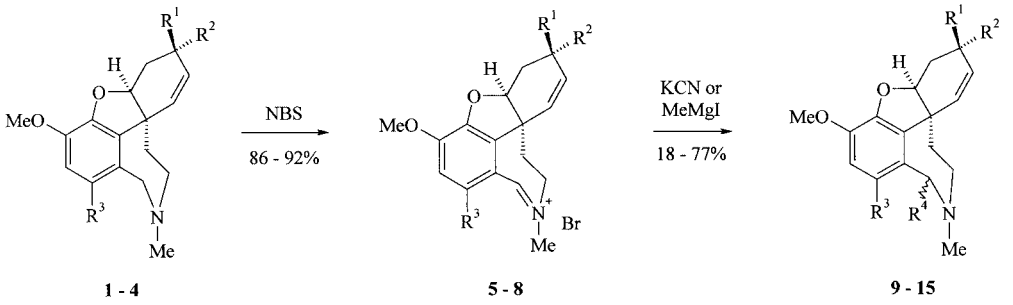


Scheme 1

Table 1. Synthesis of galanthaminium bromides

Product	Stereo-chemistry	Reactant	R^1	R^2	R^3	Yield (%)
5	(−)	**1**	OH	H	H	90
6	(+/−)	**2**	OH	H	Me	86
7	(−)	**3**	H	OH	H	92
8	(+/−)	**4**	H	OH	Me	not isolated[a]

[a] **8** could not be purified since it failed to crystallise.

Table 2. Synthesis of galanthamine-12-carbonitriles

Product	Reactant	R^1	R^2	R^3	R^4	Isomeric mixture Yield (%)	Ratio	Major isomer Yield (%)[a]
9	**5**	OH	H	H	CN	67	90:10	33
10	**6**	OH	H	Me	CN	59	60:40	—[b]
11	**7**	H	OH	H	CN	77	70:30	—[b]
12	**8**	H	OH	Me	CN	51	50:50	—[b]

[a] After crystallisation. [b] See text.

might have been formed by a competing reduction of the starting galanthaminium salt by ethanol.

The structure of the predominant isomer of **9** was investigated by NMR spectroscopy. The signals were assigned by means of 2D spectra and NOE measurements revealed interactions between protons H4a/H9, H1/H12 (shown in Figure 2) and H8/H10. These results indicate a *cis* orientation of the cyano group relative to the double bond and a boat-type conformation of the azepine ring. The single-crystal X-ray diffraction analysis (see Exp. Sect.) verified this structural assignment (Figure 2).

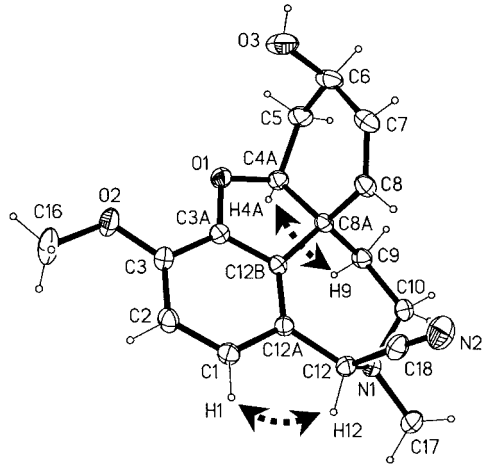
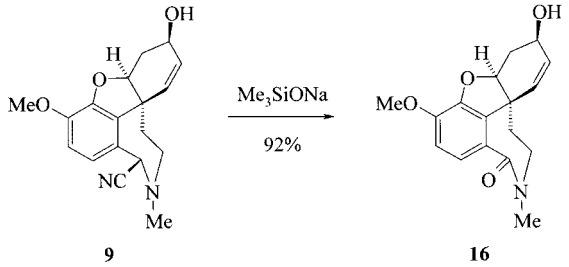


Figure 2. Molecular structure of **9** in the solid state (20% ellipsoids) and NOE interactions

After having thus elucidated the configuration of **9**, a comparison of the NMR spectra of both of its isomers with those of **11** seemed a promising approach for a structural determination of the latter. In fact the chemical shifts of protons and carbon atoms for the major as well as for the minor isomers of **9** and **11** are very similar, in particular in the region of C1/H1−C12a−C12/H12−CN, where the influence of the different stereochemistry at position 6 should be very low and the orientation of the nitrile group the predominant feature affecting the NMR shifts. It can thus be concluded that in the preferentially formed isomer of **11**, the cyano group is also in a *cisoid* position to the olefinic bond.

It should be pointed out that when utilising 1-methylgalanthamines (**6** and **8**) as substrates, there is almost no selectivity and the yields are also slightly lower. This might be explained by the sterically hindered approach of the cyanide ion through the methyl group along the preferred reaction path.

One important reason for the introduction of the nitrile group was the intention of using it as a starting point for further modifications of the galanthamine skeleton, mainly via conversion into the aminomethyl group. First attempts to reduce **9** using $LiAlH_4$ unexpectedly led to the isolation of the amide **16**. Efforts utilising $BH_3{\cdot}Me_2S$,[6] $Pd/C/H_2/CHCl_3$ [7] or $Al/NiCl_2{\cdot}6H_2O$[8] were also unsuccessful. Mechanistic studies with Me_3SiONa showed that the formation of the amide can be promoted by a base (in accordance with earlier observations;[9] see Scheme 2), presumably via a cyanohydrin-type intermediate formed from the anion of **9** and traces of O_2 present in the reaction mixture. Thus,



Scheme 2

it can be assumed that the basic properties of $LiAlH_4$ are responsible for the formation of **16**.

12-Methylgalanthamines

Since the addition of organometallic compounds to iminium ions is a well-known method for C−C bond formation,[10] a Grignard reagent was chosen as an additional type of nucleophile to be added to the galanthaminium halides. Treatment of **5**−**7** with methylmagnesium iodide yielded the 12-methyl galanthamine derivatives **13**−**15** which were also obtained as mixtures of two geometric isomers (see Table 3; ratios again by integration of H12). The rather low yields can at least be partially attributed to problems caused by the extremely low solubility of the immonium bromides in aprotic solvents.

Table 3. Synthesis of 12-methylgalanthamines

Product	Reactant	R^1	R^2	R^3	R^4	Isomeric mixture Yield (%)	Ratio	Major isomer Yield (%)[a]
13	**5**	OH	H	H	Me	46	75:25	28
14	**6**	OH	H	Me	Me	18	80:20	−[b]
15	**7**	H	OH	H	Me	48	80:20	24

[a] After separation by liquid chromatography. [b] The difference in the R_f values was too small for chromatographic separation.

Due to the enhanced stability of these compounds, chromatographic separation was possible and the major isomers of **13** and **15** could be isolated as pure compounds. In the case of **13**, NOE experiments revealed interactions completely analogous to those of **9** and a *cis* orientation of the methyl group and a conformation similar to that depicted in Figure 2 can therefore be deduced for the major isomer of **13**. For **15**, the analysis of the NMR spectroscopic data in the region of C1/H1−C12a−C12/H12−CH_3 as described for the nitrile **11** again showed that the isomer with the CH_3 group pointing upwards was predominantly formed.

Conclusion

Four galanthamine derivatives were converted into immonium bromides by treatment with *N*-bromosuccinimide. The nucleophilic addition of cyanide and methylmagnesium iodide to these galanthaminium halides was studied and the structures and conformations of two products were investigated by NMR spectroscopy and X-ray diffraction. Thus, the potential of the method for the derivatisation of the galanthamine skeleton in position 12 has been demonstrated.

Experimental Section

General Remarks: Melting points were measured with a Kofler micro hot stage apparatus. ^1H and ^{13}C NMR spectra were recorded with a Bruker AC-200 or a Bruker Avance 400 FT NMR spectrometer at 300 K in $CDCl_3$ or $[D_6]$DMSO using tetramethylsilane as an internal standard. MALDI-TOF mass spectra were obtained with a Shimadzu AXIMA LNR spectrometer using sinapinic acid as the matrix. IR spectra were recorded with a BioRad FTS 135 spectrometer. 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 with heating. Starting materials were obtained by total synthesis according to known (**1**,[2] **3**[11]) or recently developed procedures[3a] (**2** and **4**). All reactions were magnetically stirred under argon. Liquid reagents were freshly distilled prior to use.

General Procedure for the Preparation of Galanthaminium Bromides (Procedure A): To a stirred solution of galanthamine or a galanthamine analogue (1 equiv.) in dry $CHCl_3$ (50 mL/g galanthamine) was added *N*-bromosuccinimide (1 equiv.). The resultant precipitate was collected by filtration, triturated with the given solvent and dried.

[4a*S*-(4aα,6β,8a*R)]-4a,5,9,10-Tetrahydro-6-hydroxy-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepinium Bromide (5):** This was prepared according to procedure A using (−)-galanthamine (**1**, 200 mg). Reaction time: 10 min. Yield: bright yellow crystals (230 mg, 90%); m.p. 216−219 °C (EtOH). $C_{17}H_{20}BrNO_3 \times 0.1$ HBr: calcd. C 54.55, H 5.41, N 3.74; found C 54.52, H 5.36, N 3.66. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.15 (m, 3 H), 2.38 (d, J = 15.3 Hz, 1 H), 3.79 (s, 3 H), 3.94 (s, 3 H), 4.11 (s, 2 H), 4.59 (s, 1 H), 4.74 (s, 1 H), 5.73 (d, J = 10.3 Hz, 1 H), 5.92 (dd, J = 10.3, 4.5 Hz, 1 H), 7.27 (d, J = 8.5 Hz, 1 H), 7.54 (d, J = 8.5 Hz, 1 H), 9.10 (s, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.7 (t), 31.1 (t), 45.9 (s), 51.5 (q), 54.0 (t), 56.4 (q), 58.9 (d), 87.0 (d), 112.9 (d), 115.0 (s), 126.4 (d), 129.8 (d), 133.0 (d), 136.9 (s), 146.2 (s), 151.3 (s), 167.3 (d) ppm. IR (KBr): $\tilde{\nu}$ = 3011, 2939, 2887, 2845, 1723, 1658, 1609 cm^{-1}. MALDI-MS: m/z = 286.26 $[M - Br]^+$ (calcd. for $C_{17}H_{20}NO_3$: 286.14).

[(±)-(4aα,6β,8a*R)]-4a,5,9,10-Tetrahydro-6-hydroxy-3-methoxy-1,11-dimethyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepinium Bromide (6):** This was prepared according to procedure A using (+/−)-1-methylgalanthamine (**2**, 200 mg). Reaction time: 15 min. The precipitate (162 mg) was triturated twice with Et_2O. The filtrate was concentrated in vacuo, dissolved in EtOH (0.5 mL) and precipitated with Et_2O to obtain an additional 54 mg. Total yield: orange crystals (216 mg, 86%); m.p. 223−226 °C (EtOH). $C_{18}H_{22}BrNO_3 \times 0.21$ HBr: calcd. C 54.42, H 5.64, N 3.53; found C 54.39, H 5.58, N 3.99. ^1H NMR (200 MHz, $[D_6]$DMSO): δ = 1.96−2.40 (m, 4 H), 2.53 (s, 3 H), 3.86 (s, 3 H), 3.91 (s, 3 H), 3.95−4.17 (m, 4 H), 4.74 (s, 1 H), 5.54 (d, J = 10.2 Hz, 1 H), 5.81 (dd, J = 10.1, 4.5 Hz, 1 H), 7.04 (s, 1 H), 9.06 (s, 1 H) ppm. ^{13}C NMR (50 MHz, $[D_6]$DMSO): δ = 18.9 (q), 29.4 (t), 35.1 (t), 47.0 (s), 50.5 (q), 54.4 (t), 56.3 (q), 58.7 (d), 86.5 (d), 113.9 (s), 114.9 (d), 127.9 (d), 128.4 (d), 136.7 (s), 140.4 (s), 144.7 (s), 150.5 (s), 166.4 (d) ppm. IR (KBr): $\tilde{\nu}$ = 3017, 2972, 2908, 2857, 1707, 1641, 1600 cm^{-1}. MALDI-MS: m/z = 300.31 $[M - Br]^+$ (calcd. for $C_{18}H_{22}NO_3$: 300.16).

[4a*S*-(4aα,6α,8a*R)]-4a,5,9,10-Tetrahydro-6-hydroxy-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepinium Bromide (7):** This was prepared according to procedure A using (−)-epi-galanthamine (**3**, 780 mg). Reaction time: 3 min. The precipitate was triturated twice with Et_2O. The filtrate was concentrated in vacuo, dissolved in EtOH (0.5 mL) and precipitated with Et_2O to obtain an additional fraction of **7**. Total yield: yellow crystals (910 mg, 92%); m.p. 205−210 °C (EtOH). $C_{17}H_{20}BrNO_3 \times 0.3$ HBr: calcd. C

52.28, H 5.24, N 3.59; found C 52.12, H 5.18, N 3.88. ^{1}H NMR (200 MHz, [D$_6$]DMSO): δ = 1.60−1.81 (m, 1 H), 2.10−2.30 (m, 2 H), 2.60 (s, 1 H), 3.77 (s, 3 H), 3.94 (s, 3 H), 4.04−4.21 (m, 2 H), 4.21−4.40 (m, 1 H), 4.80 (bs, 1 H), 5.68 (d, J = 12.7 Hz, 1 H), 5.82 (d, J = 12.7 Hz, 1 H), 7.20 (d, J = 11.5 Hz, 1 H), 7.51 (d, J = 11.5 Hz, 1 H), 9.10 (s, 1 H) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 30.8 (t), 31.5 (t), 46.2 (s), 51.4 (q), 54.2 (t), 56.4 (q), 60.7 (d), 88.0 (d), 113.0 (d), 115.0 (s), 126.0 (d), 133.0 (d), 134.4 (d), 137.3 (s), 146.5 (s), 151.2 (s), 167.3 (d) ppm. IR (KBr): $\tilde{\nu}$ = 3003, 2975, 2943, 2887, 2848, 1704, 1658, 1610 cm^{-1}. MALDI-MS: m/z = 286.24 [M − Br]$^+$ (calcd. for $C_{17}H_{20}NO_3$: 286.14).

General Procedure for the Preparation of Galanthamine-12-carbonitriles (Procedure B): The starting material was dissolved in water (30 mL/g galanthaminium compound) in a separating funnel and Et_2O (10 mL/g galanthaminium compound) and KCN (freshly ground, 3 equiv.) were added. After 2−3 min, the aqueous layer was extracted exhaustively with Et_2O or $CHCl_3$. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo. If required, the crude product was purified by LC (SiO_2, $CHCl_3$/MeOH, 90:10).

[4a*S*-(4aα,6β,8a*R,12*S**)]-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepine-12-carbonitrile (9):** This was prepared according to procedure B using **5** (3.50 g). The crude isomeric mixture (2.01 g, 67%, ratio 90:10) was dissolved in the minimum amount of EtOH and crystallised. Yield: colourless crystals (990 mg, 33%); m.p. 151−155 °C (EtOH). Attempts to separate both isomers from mother liquor by LC failed due to isomerisation. TLC: $CHCl_3$/MeOH, 90:10; R_f = 0.75 (major isomer), 0.65 (minor isomer). $C_{18}H_{20}N_2O_3$: calcd. C 69.21, H 6.45, N 8.97; found C 68.85, H 6.32, N 8.69. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78 (ddd, J = 13.7, 5.0, 1.2 Hz, 1 H), 2.08−1.98 (m, 2 H), 2.38 (d, J = 11.4 Hz, 1 H), 2.61 (s, 3 H), 2.61−2.74 (m, 1 H), 2.91 (dt, J = 15.0, 3.2 Hz, 1 H), 3.50 (dd, J = 15.0, 13.6 Hz, 1 H), 3.85 (s, 3 H), 4.15 (dt, J = 11.1, 5.0 Hz, 1 H), 4.61 (m, 1 H), 4.71 (s, 1 H), 6.07 (dd, J = 10.2, 5.3 Hz, 1 H), 6.35 (d, J = 10.2 Hz, 1 H), 6.70 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.7 (t), 36.4 (t), 46.1 (q), 48.1 (s), 49.9 (t), 55.9 (q), 61.6 (d + d), 88.9 (d), 111.6 (d), 116.4 (s), 122.5 (d), 124.2 (s), 126.9 (d), 128.2 (d), 132.9 (s), 145.6 (s), 146.7 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3036, 2978, 2926, 2869, 2218, 1622, 1590 cm^{-1}. MALDI-MS: m/z = 286.16 [M − HCN + H]$^+$ (calcd. for $C_{17}H_{20}NO_3$: 286.14).

X-ray Structure Determination of 9: Crystal data: $C_{18}H_{20}N_2O_3$, M_r = 312.36, monoclinic, space group $P2_1$ (no. 3), a = 7.676(3) Å, b = 8.812(3) Å, c = 12.418(4) Å, β = 107.72(1)°, V = 800.1(5) Å^3, Z = 2, D_x = 1.297 Mg·m^{-3}, λ(Mo-K_α) = 0.71073 Å, μ = 0.089 mm^{-1}, T = 295(2) K. X-ray data collection with a Bruker SMART CCD area detector diffractometer and graphite-monochromated Mo-K_α radiation. 11661 reflections with $\theta < 30.0°$ were measured, corrected for LP and absorption and merged to 4589 unique reflections, R_{int} = 0.018. The structure was solved by direct methods and the structure refinement on F^2 was carried out using SHELXL-97.[12] All nonhydrogen atoms were refined anisotropically. Hydrogen atoms had isotropic temperature factors and ride on the atoms to which they are bonded. The absolute structure could not be determined by diffraction but was deduced from the compound's chemistry. The final refinement varied 213 parameters and converged at $R1 = \Sigma F_o - F_c / \Sigma F_o = 0.039$, $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2} = 0.097$ and $S = 1.06$ for the 4589 unique reflections; $R1 = 0.035$ for the 4205 observed data [$I > 2\sigma(I)$].[13] The molecular structure of **9** in the crystalline state is shown in Figure 2 with the crystallographic atom designations. Galanthamine-type compounds are based on a relatively stiff tetracyclic core with some flexibility only in the azepine ring which may adopt a chair or boat conformation depending on the relative position of atom C10 (Figure 2). In **9**, the molecule exhibits the usual chair conformation for the azepine ring with the cyano group axial and the *N*-bound methyl group equatorial on this ring. The bond lengths correspond well with related compounds[14] and are as follows (Å; all e.s.d. values 0.001−0.002 Å): O1−C2 1.366, O1−C15 1.468, O2−C3 1.359, O2−C16 1.431, O3−C13 1.438, N1−C7 1.459, N1−C8 1.470, N1−C17 1.468, C1−C2 1.382, C1−C6 1.392, C1−C10 1.521, C2−C3 1.394, C3−C4 1.388, C4−C5 1.391, C5−C6 1.391, C6−C7 1.512, C7−C18 1.500, C8−C9 1.523, C9−C10 1.538, C10−C11 1.510, C10−C15 1.546, C11−C12 1.327, C12−C13 1.501, C13−C14 1.513, C14−C15 1.508, C18−N2 1.137. In the crystalline state, the OH group O3−H3 forms an intramolecular hydrogen bond to O1 of a neighbouring molecule, O3···O1 = 2.921(2) Å. The H−H distances for the NOE interactions, shown in Figure 2, are both 2.25 Å based on C−H bond lengths according to the X-ray riding model.

[(±)-(4aα,6β,8a*R)]-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-1,11-dimethyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepine-12-carbonitrile (10):** This was prepared according to procedure B using **6** (300 mg). Yield: mixture of two isomers as colourless crystals (151 mg, 59%); m.p. 72−73 °C. TLC: $CHCl_3$/MeOH, 90:10; R_f = 0.3 and 0.65. $C_{19}H_{22}N_2O_3 \times 0.5\ H_2O$: calcd. C 68.04, H 6.91, N 8.35; found C 67.91, H 6.62, N 8.20. ^{1}H NMR (isomeric mixture, 200 MHz, $CDCl_3$): δ = 1.68−1.87 (m, 1 H), 1.92−2.10 (m, 2 H), 2.31 (s, 3 H), 2.60 (s, 1.2 H), 2.62 (s, 1.8 H), 2.70 (bs, 1 H), 2.88 (dt, J = 14.6, 3.8 Hz, 1 H), 3.47 (ddd, J = 13.9, 9.8, 3.4 Hz, 1 H), 3.83 (s, 3 H), 4.12 (dt, J = 15.5, 4.9 Hz, 1 H), 4.50 (bs, 0.4 H), 4.57 (bs, 0.6 H), 4.83 (s, 0.4 H), 4.96 (s, 0.6 H), 6.01 (dd, J = 9.2, 5.0 Hz, 1 H), 6.27 (d, J = 8.9 Hz, 0.6 H), 6.31 (d, J = 8.9 Hz, 0.4 H), 6.59 (s, 1 H) ppm. ^{13}C NMR (isomeric mixture, 100 MHz, $CDCl_3$): δ = 19.3 (q), 20.3 (q), 30.2 (t), 33.7 (t), 36.8 (t), 47.2 (s), 47.2 (q), 47.9 (s), 49.0 (s), 50.3 (t), 51.0 (t), 56.3 (q), 56.5 (q), 56.6 (d), 57.9 (d), 62.2 (d), 62.3 (d), 88.9 (d), 89.4 (d), 114.4 (d), 114.5 (d), 115.3 (s), 116.7 (s), 122.8 (s), 122.9 (s), 127.7 (d), 128.4 (d), 128.7 (s), 129.6 (s), 129.3 (d), 129.7 (d), 133.6 (s), 135.7 (s), 144.8 (s), 145.3 (s), 145.4 (s), 145.5 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3027, 2928, 2874, 2224, 1683, 1615 cm^{-1}. MALDI-MS: m/z = 300.22 [M − HCN + H]$^+$ (calcd. for $C_{18}H_{22}NO_3$: 300.16).

[4a*S*-(4aα,6α,8a*R)]-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-ef][2]benzazepine-12-carbonitrile (11):** This was prepared according to procedure B using **7** (500 mg). Yield: mixture of two isomers as colourless crystals (330 mg, 77%); m.p. 90−96 °C. TLC: $CHCl_3$/MeOH, 90:10; R_f = 0.75. ^{1}H NMR (isomeric mixture, 200 MHz, $CDCl_3$): δ = 1.71 (ddd, J = 13.5, 10.7, 2.5 Hz, 1.4 H), 1.85 (dd, J = 13.5, 4.2 Hz, 1.4 H), 2.04−2.27 (m, 1.2 H), 2.38 (s, 0.9 H), 2.58 (s, 2.1 H), 2.70−2.98 (m, 1.7 H), 3.12 (dt, J = 14.8, 3.2 Hz, 0.3 H), 3.85 (s, 2.1 H), 3.86 (s, 0.9 H), 4.58 (bs, 1 H), 4.64 (s, 0.7 H), 5.22 (s, 0.3 H), 5.85 (d, J = 10.3 Hz, 1 H), 6.03 (d, J = 10.5 Hz, 0.3 H), 6.31 (dt, J = 10.5, 1.6 Hz, 0.7 H), 6.62 (d, J = 8.3 Hz, 0.7 H), 6.68 (d, J = 8.0 Hz, 0.7 H), 6.72 (d, J = 8.0 Hz, 0.3 H), 6.92 (d, J = 8.3 Hz, 0.3 H) ppm. ^{13}C NMR (isomeric mixture, 50 MHz, $CDCl_3$): δ = 31.7 and 32.0 (t), 36.9 (t), 45.9 (q), 47.9 (s), 50.0 (t), 55.8 (q), 58.4 and 61.4 (d), 62.8 (d), 88.4 and 88.7 (d), 111.2 and 111.3 (d), 116.5 (s), 120.1 and 121.8 (d), 123.3 and 124.0 (s), 126.6 (d), 131.9 and 132.5 (d), 132.6 (s), 145.0 and 145.2 (s), 147.2 and 147.5 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3027, 2928, 2848, 2212, 1692, 1614 cm^{-1}. MALDI-MS: m/z = 286.23 [M − HCN + H]$^+$ (calcd. for $C_{17}H_{20}NO_3$: 286.14).

[(±)-(4aα,6α,8a*R)]-4a,5,9,10,11,12-Hexahydro-6-hydroxy-3-methoxy-1,11-dimethyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepine-12-carbonitrile (12):** Crude (+/-)-epi-1-methylgalanthaminium bromide (**8**) prepared from (±)-epi-1-methylgalanthamine (**4**) according to procedure A (500 mg) was used without further purification according to procedure B. Crude **12** was purified by LC (SiO_2, $CHCl_3$/MeOH, 90:10). Yield: mixture of two stereoisomers as a colourless foam (220 mg, 51%). TLC: $CHCl_3$/MeOH, 90:10; R_f = 0.6 and 0.7. ^{1}H NMR (isomeric mixture, 200 MHz, $CDCl_3$): δ = 1.63−1.93 (m, 2 H), 2.07−2.23 (m, 1 H), 2.30 and 2.33 (s, 3 H), 2.57 and 2.58 (s, 3 H), 2.68−3.05 (m, 2 H), 3.32−3.55 (m, 1 H), 3.84 and 3.87 (s, 3 H), 4.45 and 4.50 (m, 1 H), 4.55−4.74 (m, 1 H), 4.82 and 4.94 (s, 1 H), 5.82 (d, J = 10.4 Hz, 1 H), 6.26 (d, J = 10.4 Hz, 1 H), 6.57 (s, 1 H) ppm. ^{13}C NMR (isomeric mixture, 50 MHz, $CDCl_3$): δ = 18.8 (q), 19.8 (q), 31.7 (t), 34.1 (t), 36.9 (t), 46.7 (q), 47.3 (s), 48.4 (s), 50.0 (t), 50.7 (t), 55.8 (q), 56.0 (q), 56.4 (d), 57.2 (d), 62.6 (d), 63.0 (d), 88.4 (d), 88.5 (d), 113.8 (d), 113.9 (d), 114.8 (s), 116.4 (s), 122.2 (s), 122.4 (s), 127.1 (d), 127.6 (s), 128.5 (s), 129.5 (d), 131.7 (d), 132.2 (d), 133.0 (s), 135.0 (s), 144.1 (s), 144.5 (s), 145.8 (s), 146.0 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3027, 2934, 2872, 2217, 1680, 1605 cm^{-1}. MALDI-MS: m/z = 300.28 [M − HCN + H]$^+$ (calcd. for $C_{18}H_{22}NO_3$: 300.16).

General Procedure for the Preparation of 12-Methylgalanthamine Derivatives (Procedure C): To MeMgI (3 M in Et_2O, 2−4 equiv.) was added the solid galanthaminium compound (1 equiv.) under nitrogen. After the given reaction time, dry Et_2O (20 mL/g galanthaminium compound) was added and the resultant mixture stirred for the prescribed period. The mixture was hydrolysed with water and a pH > 9 was attained using concentrated NH_4OH. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated in vacuo.

[4a*S*-(4aα,6β,8a*R,12*R**)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-11,12-dimethyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol (13):** This was prepared according to procedure C using **5** (2.00 g). Reaction time: 40 min, then stirring for 5 min. Yield: mixture of two isomers as a colourless solid (760 mg, 46%). The major isomer was isolated by LC (SiO_2, $CHCl_3$/MeOH/concd. NH_4OH, 89:10:1); m.p. 46−48 °C. TLC: $CHCl_3$/MeOH/concd. NH_4OH, 89:10:1; R_f = 0.65. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (d, J = 13.3 Hz, 1 H), 1.51 (d, J = 7.3 Hz, 3 H), 1.95 (ddd, J = 16.5, 5.0, 1.8 Hz, 1 H), 2.11 (dt, J = 13.3, 2.4 Hz, 1 H), 2.43 (s, 3 H), 2.63 (d, J = 15.6 Hz, 1 H), 2.85 (td, J = 15.5, 3.5 Hz, 1 H), 3.62 (dd, J = 14.6, 13.2 Hz, 1 H), 3.78 (s, 3 H), 3.88 (q, J = 7.4 Hz, 1 H), 4.08 (t, J = 4.4 Hz, 1 H), 4.54 (bs, 1 H), 5.94 (dd, J = 10.1, 4.4 Hz, 1 H), 6.07 (d, J = 10.1 Hz, 1 H), 6.57 (d, J = 8.3 Hz, 1 H), 6.66 (d, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9 (q), 29.8 (t), 31.7 (t), 41.5 (q), 44.2 (t), 48.9 (s), 55.8 (q), 61.8 (d), 64.0 (d), 88.8 (d), 111.6 (d), 122.2 (d), 127.4 (d), 129.4 (d), 131.4 (s), 135.1 (s), 143.5 (s), 146.2 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3031, 2947, 2911, 2843, 1621 cm^{-1}. MALDI-MS: m/z = 302.38 [M + H]$^+$ (calcd. for $C_{18}H_{24}NO_3$: 302.18).

[(±)-(4aα,6β,8a*R)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-1,11,12-trimethyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol (14):** This was prepared according to procedure C using **6** (500 mg). Reaction time: 30 min (additional 15 mL of dry Et_2O were added), then stirring for 2.5 h. Yield: Mixture of two isomers as a colourless solid (73 mg, 18%); m.p. 45−50 °C. TLC: $CHCl_3$/MeOH/concd. NH_4OH, 89:10:1; R_f = 0.5. ^{1}H NMR (isomeric mixture, 200 MHz, $CDCl_3$): δ = 1.18−1.30 (m, 1 H), 1.51 (d, J = 7.3 Hz, 3 H), 1.87−2.15 (m, 2 H), 2.25 (s, 3 H), 2.46 (s, 2.5 H), 2.51 (s, 0.5 H), 2.55−2.73 (m, 1 H), 2.77−2.97 (m, 1 H), 3.55−3.75 (m, 1 H), 3.81 (s, 3 H), 4.03−4.17 (m, 2 H), 4.44−4.59 (m, 1 H), 5.95 (dd, J = 10.2, 4.5 Hz, 1 H), 6.06 (d, J = 10.2 Hz, 1 H), 6.57 (s, 1 H) ppm. ^{13}C NMR (isomeric mixture, 50 MHz, $CDCl_3$): δ = 18.8 (q), 19.2 and 19.7 (q), 29.9 (t), 31.7 (t), 41.5 (q), 44.3 (t), 48.4 and 49.4 (s), 55.8 and 56.0 (q), 58.8 and 59.3 (d), 61.8 and 62.2 (d), 88.4 and 88.7 (d), 114.0 and 114.3 (d), 127.5 (d), 126.8 and 127.8 (s), 129.3 (d), 129.0 and 130.4 (s), 131.7 and 132.5 (s), 142.9 (s), 144.7 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3031, 2925, 2866, 1673, 1616 cm^{-1}. MALDI-MS: m/z = 316.38 [M + H]$^+$ (calcd. for $C_{19}H_{26}NO_3$: 316.19).

[4a*S*-(4aα,6α,8a*R,12*R**)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-11,12-dimethyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol (15):** For the preparation of **15**, procedure C was modified: MeMgI (3.7 equiv.) was added to **7** (300 mg) over a period of 30 min and the mixture stirred for 20 min. Et_2O (15 mL) was then added and the mixture stirred for 3 h. The crude product (120 mg, 48%) was purified by LC ($CHCl_3$/MeOH, 90:10). Yield: Colourless foam (60 mg, 24%). TLC: $CHCl_3$/MeOH/concd. NH_4OH, 89:10:1; R_f = 0.8. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.44−1.59 (m, 1 H), 1.52 (d, J = 7.3 Hz, 3 H), 1.69 (ddd, J = 13.6, 10.6, 2.0 Hz, 1 H), 2.20 (td, J = 13.2, 2.4 Hz, 1 H), 2.41 (s, 3 H), 2.67−2.94 (m, 3 H), 3.61 (t, J = 13.6 Hz, 1 H), 3.81 (s, 3 H), 3.93−3.82 (m, 1 H), 4.54 (bs, 1 H), 4.57−4.70 (m, 1 H), 5.76 (d, J = 10.4 Hz, 1 H), 6.04 (d, J = 10.4 Hz, 1 H), 6.53 (d, J = 8.3 H, 1 H), 6.65 (d, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.8 (q), 32.0 (t + t), 41.2 (q), 44.4 (t), 48.6 (s), 55.6 (q), 62.7 (d), 64.1 (d), 88.6 (d), 111.2 (d), 121.5 (d), 128.9 (d), 131.1 (s), 131.3 (d), 134.5 (s), 143.2 (s), 147.0 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3027, 2927, 2887, 2842, 1659, 1621 cm^{-1}. MALDI-MS: m/z = 302.35 [M + H]$^+$ (calcd. for $C_{18}H_{24}NO_3$: 302.18).

[4a*S*-(4αa,6β,8a*R)]-4a,5,9,10-Tetrahydro-6-hydroxy-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-12(11*H*)-one (16): 5** (200 mg, 0.64 mmol) and sodium trimethylsilanolate (1 M in CH_2Cl_2, 0.64 mL, 0.64 mmol) were stirred in dry THF for 72 h at ambient temperature. The precipitate was collected by filtration, triturated with THF (2 × 2 mL) and dried. Yield: Off-white crystals (177 mg, 92%); m.p. 251−255 °C. TLC: $CHCl_3$/MeOH, 90:10; R_f = 0.65. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.83 (dt, J = 14.6, 2.5 Hz, 1 H), 2.06 (ddd, J = 15.7, 5.0, 2.3 Hz, 1 H), 2.31 (dt, J = 14.1, 3.9 Hz, 1 H), 2.71 (dt, J = 15.7, 1.7 Hz, 1 H), 3.19 (s, 3 H), 3.16−3.25 (m, 1 H), 3.80 (dt, J = 14.1, 2.1 Hz, 1 H), 3.91 (s, 3 H), 4.13 (dt, J = 10.1, 4.8 Hz, 1 H), 4.74 (bs, 1 H), 5.53 (d, J = 9.8 Hz, 1 H), 5.87 (dd, J = 9.8, 5.3 Hz, 1 H), 6.89 (d, J = 8.5 Hz, 1 H), 7.49 (d, J = 8.5 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.3 (t), 34.9 (q), 38.3 (t), 48.0 (s), 49.5 (t), 55.8 (q), 61.0 (d), 89.2 (d), 111.9 (d), 123.4 (s), 124.4 (d), 125.2 (d), 131.6 (d), 131.7 (s), 145.1 (s), 146.9 (s), 168.3 (s) ppm. IR (neat): $\tilde{\nu}$ = 2994, 2924, 2863, 1628, 1611, 1582 cm^{-1}. MALDI-MS: m/z = 302.35 [M + H]$^+$ (calcd. for $C_{17}H_{20}NO_4$: 302.14).

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