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Synthesis of (−)- and (+)-8-fluoro-galanthamine

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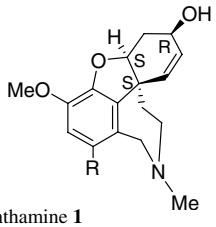
Abstract—The synthesis of racemic 8-fluorogalanthamine and its separation into (−)- and (+)-8-fluorogalanthamine (= (4a*S*,6*R*, 8a*S*)- and (4a*R*,6*S*,8a*R*)-1-fluoro-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3*a*,3,2-*ef*][2]benzazepin-6-ol) is described.

The approved anti-Alzheimer drug galanthamine **1** is a natural Amaryllidaceae alkaloid that was originally marketed for the treatment of polio, paralysis, facial neuralgia and in anesthesia. It acts as a selective, reversible and competitive acetylcholinesterase (AChE) inhibitor[1] as well as an allosteric ligand of nicotine acetylcholine receptors (nAChRs).[2] The synthesis and pharmacology of galanthamine have been reviewed recently.[3]

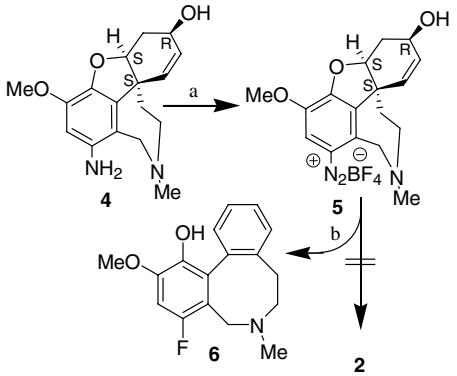
We report the synthesis of both enantiomers of 8-fluorogalanthamine **2** and **3** using the phenolic oxidative coupling approach followed by separation using chiral chromatography.



R= H : (-)-Galanthamine **1**
R= F : (-)-8-Fluorogalanthamine **2**
3 : *ent-* ***2***

The interest to prepare this substance originates from the fact, that this substance is covered by the Markush structure of patents[4,5] but has never been prepared before. Additionally we were interested in the influence of the fluorine substituent for the acetylcholine esterase inhibition and allosterically potentiating ligand (APL) activity at nicotinic acetylcholine receptors. The results of these biological tests will be reported elsewhere.

First we subjected galanthamine-8-diazonium tetrafluoroborate (**5**), prepared from 8-amino-(−)-galanthamine[4,5] (**4**) to a Balz–Schieman reaction in the presence of MgO.[6] The desired product **2** was formed only in traces. Instead the rearranged product **6** was isolated and the structure confirmed by ^{1}H NMR, ^{13}C NMR, DEPT, H–C COSY, and H–H COSY experiments (Scheme 1). This rearrangement is analogous to the known rearrangement of galanthamine to apogalanthamine[7] or apochlorine[8] on heating in strong acids.



Scheme 1. Reagents and conditions: (a) $NaNO_2$, HBF_4 and (b) MgO, 170 °C.

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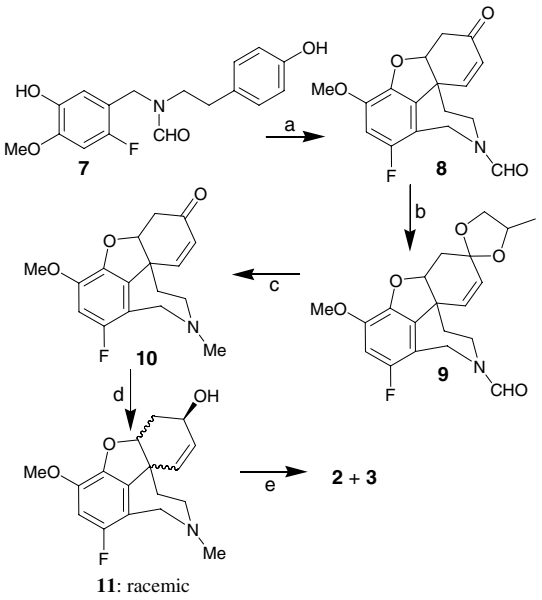

Scheme 2. Reagents and conditions: (a) $K_3[Fe(CN)_6]$, K_2CO_3, toluene/water, 50 °C; (b) 1,2-propanediol, PTSA, toluene (c) $LiAlH_4$; (d) L-selectride, THF and (e) preparative separation on chiral column.

After this unsuccessful attempt to prepare **2** starting from **1** we decided to incorporate the fluorine atom at the beginning and follow the method for the preparation of (−)-galanthamine on a kilogram scale,[9] based on the phenolic oxidative intramolecular coupling of **7**. This reaction was carried out under the previously optimized conditions[9] to afford the intermediate **8** in 40% yield. Protection followed by $LiAlH_4$ reduction of **9** furnished the (+/−)-8-fluoro-narwedine (**10**) (Scheme 2).

The centrosymmetric crystal structure of solid **10** (monoclinic space group $P2_1/n$) revealed, that this compound is not a conglomerate and thus the crystallization-induced chiral conversion, as used for (+/−) narwedine, could not be applied (Fig. 1). Reduction of the carbonyl group using L-selectride gave (+/−)-8-fluorogalanthamine (**11**) in 90% yield and >99% HPLC purity. The enantiomers of **11** were separated using chiral preparative column chromatography (Chiracel OD, 5 μm, 5 × 50 cm, 80% *n*-heptane/ 20% *i*-PrOH) to afford the products **2** and **3** which were converted to the corresponding hydrobromide salts. The progress and the result of this chiral separation was analyzed by chiral HPLC (Chiracel I OD–H, 80% *n*-heptane + 0.1% diethyl amine/20% *i*-PrOH). The crystal structure of (−) **2**·HBr was determined thus confirming the expectation, that (−)-8-fluorogalanthamine (**2**) has the same absolute configuration as (−)galanthamine. Interestingly, (−) **2**·HBr is isostructural with **1**·HBr in the solid state,[10,11] both crystallizing in the chiral orthorhombic space group $P2_12_12_1$ with practically identical galanthamine conformation, similar atomic coordinates and similar lattice parameters: $a = 7.3591$ (4), $b = 14.3683$ (8), $c = 15.9288$ (9) Å for **2**·HBr, $a = 7.3706$ (3), $b = 14.3273$ (7), $c = 15.9318$ (8) Å for **1**·HBr (room temperature for both). In the solid state and after mutual least-squares fit, the C, N, and O atoms of (−)-8-fluoro-galanthamine in **2**·HBr and (−)-galanthamine in **1**·HBr show positional differences of between 0.011 and 0.071 Å (F-bonded carbon), mean value 0.031 Å, and the bond lengths exhibit a rms disagreement of only 0.009 Å.

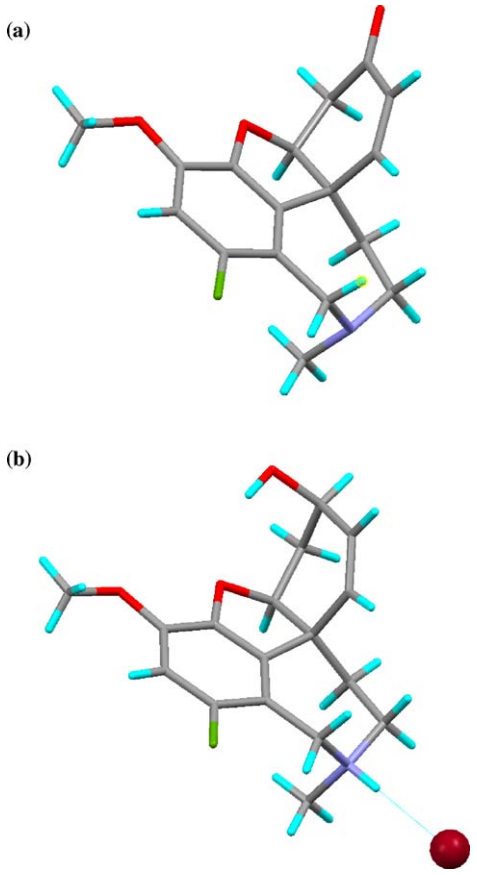

Figure 1. (a) (+/−)-8-fluoro-narwedine (**10**); (b) (−)-8-fluoro-galanthamine (**2**)·HBr.

Acknowledgements

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References and notes

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