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New Kilogram-Synthesis of the Anti-Alzheimer Drug (-)-Galanthamine

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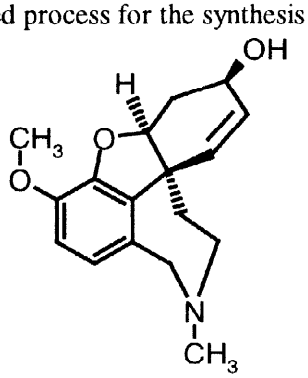
Abstract:
A concise, scalable synthesis of (−)-galanthamine, a drug being used for the treatment of Alzheimer's disease, is described. The yield of the critical phenolic coupling step was optimized to 45-50%. For the reduction of the aryl bromide, air-activated $LiAlH_4$ was used and racemic narwedine was converted to (−)-narwedine by a second order asymmetric transformation.

Keywords Asymmetric synthesis, phenols, polycyclic heterocyclic compounds

(−)-Galanthamine [1] (**1**) is a natural product being used to treat Alzheimer's disease in Austria and is currently in phase III clinical trials in Europe and the United States. An efficient industrial synthesis [2] is needed, as its isolation from natural sources suffers from high costs and limited supplies.

In this paper we report an improved process for the synthesis of chiral (−)-galanthamine (**1**)



(−)-Galanthamine (1)

with optimized yields of the individual steps. The bromination of 3,4-dimethoxybenzaldehyde using bromine in methanol (92 %) and subsequent demethylation with concentrated sulfuric acid (83%) was conducted on a one-ton scale to give 6-bromoisovanillin. This was condensed with tyramine and reduced with $NaBH_4$ to **2a** (95% in a single-vessel reaction) and formylated with ethyl formate (90%) to **2b**. The oxidative cyclization, performed on a 12-kg scale using potassium ferricyanide in toluene/aqueous sodium carbonate (45-50%), generated the bromoformylnarwedine (**3**). Following protection of **3** using propylene glycol (89.5%), **4** was reduced to (+/-)-narwedine (**5**) using $LiAlH_4$ and dry air [3] (95% on a 14-kg scale).

CAUTION narwedine is a sensitizing agent and can cause allergic skin reactions.

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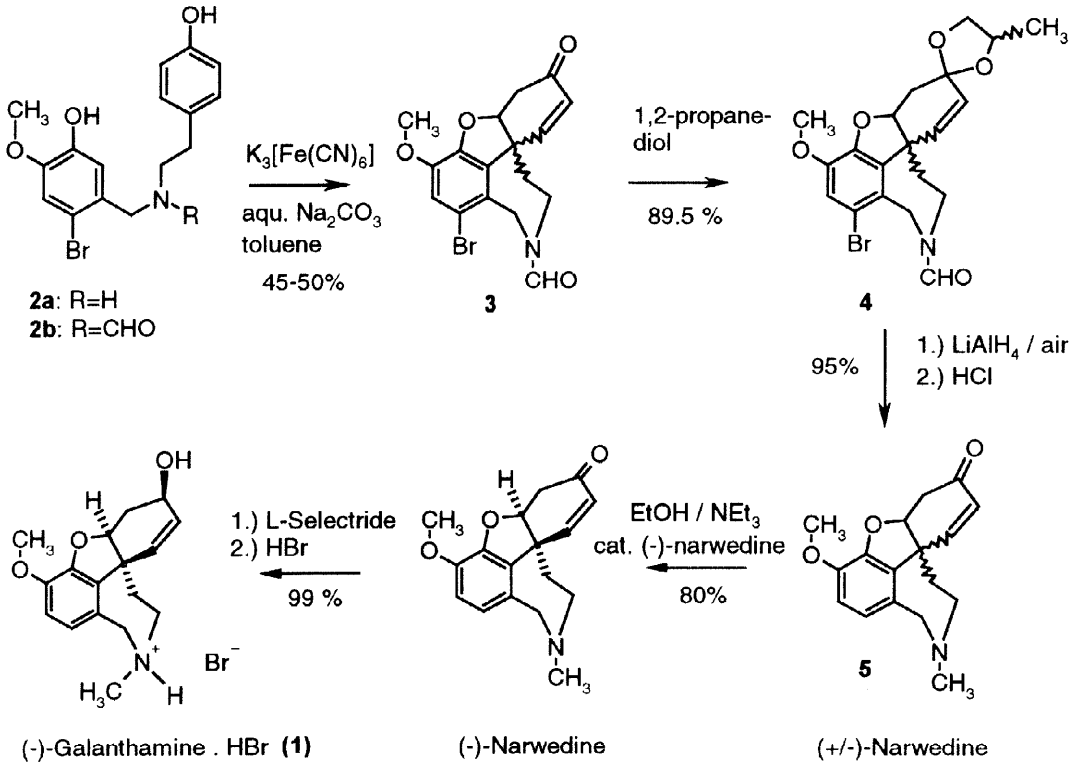
The second-order asymmetric transformation of (+/−)-**5**, in the presence of (−)-narwedine (8-kg scale), resulted in 80% yield of (-)-narwedine [4]. Reduction of (−)-**5** to (−)-galanthamine using L-Selectride followed by treatment with HBr yielded the hydrobromide of (−)-galanthamine (99% on a 4-kg scale). (Scheme 1).

Scheme 1



The yield of the phenolic coupling of **2b**, greatly improved by efficient stirring equipment, is substantially higher than that of the recently reported [5] coupling of the N-methylated amine (**2**, R = Me). The purity of the synthetic (−)-galanthamine was determined by HPLC [6].

In summary, we have developed a nine step synthesis of (−)-galanthamine from 3,4-dimethoxybenzaldehyde, with an overall yield of 18-21%, without the need for low-temperature reactions or chromatographic purifications.

References and notes

[1] Review: Bores GM Kosley Jr. RW *Drugs Future*, **1996**, *21*, 621-635.

[2] For small-scale syntheses of galanthamine see: a) Barton DHR, Kirby GW. *J. Chem. Soc.* **1962**, 806. b) Kametani T, Yamaki T, Yagi H, Fukumoto K. *J. Chem. Soc.* **1969**, 2602. c) Szewczyk J, Lewin A, Caroll FI, *J. Het. Chem.***1988**, *25*, 1809-1811. d) Shieh WC, Carlson JA. *J. Org. Chem.***1994**, *59*, 5463. e) Czollner L; Fröhlich J; Jordis U, Küenburg B. AT 401058 (Waldheim), Chem. Abstr. 125:196086. f) references cited by Chaplin [5].

[3] The scope and limitations of the novel reduction of aromatic bromides using air-activated LiAlH4 will be reported elsewhere.

[4] The details of this chiral transformation, including the determination of the optical purity of **1** and **5** by chiral capillary electrophoresis (CE) and their x-ray crystallography, will be reported elsewhere.

[5] For a recent reference on the synthesis of narwedine see: Chaplin DA; Fraser N, Tiffin PD. *Tetrahedron Lett.* **1997**, 38, 7931 .

[6] Phenomenex Prodigy 5µ ODS3 column, 0.0015 M CAPS to pH 2.00 (H_3PO_4) / MeOH 92.5:7.5 at 1.2 mL/min (isocratic) and UV detection at 285 nm.