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Synthesis of (−)-Homogalanthamine from Naltrexone

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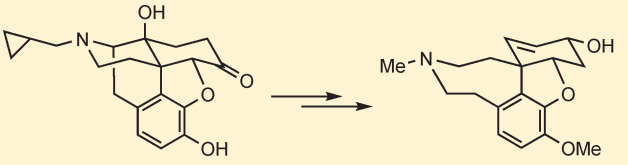
Supporting Information

ABSTRACT: Acetylcholinesterase inhibitor (−)-homogalanthamine **3** was synthesized from μ opioid antagonist naltrexone (**2**) in 16% total yield. The synthesis features Grob fragmentation as a key reaction, which was especially accelerated in the presence of 15-crown-5.



(−)-Galanthamine (**1**),[1] an alkaloid isolated from the Caucasian snowdrop, *Galanthus woronowii*, and also from another species of the Amaryllidaceae family, *Lycoris radiate*, is a prescription drug for the treatment of Alzheimer's disease in Europe and the United States.[2] It has a unique dual mechanism on the cholinergic system, not only inhibiting acetylcholinesterase (AChE) activity but also allosterically modulating the nicotinic acetylcholine receptor.[3] Moreover, it exhibits less toxicity than tacrine, rivastigmine, and donepezil.[4] Therefore, many reports have described the syntheses of galanthamine[5] and its derivatives,[5a] including a C-ring,[6] D-ring,[7] quaternary ammonium, and bis-interacted derivatives,[8] to evaluate their inhibitory effects on AChE. However, to the best of our knowledge, no report has previously described the synthesis of (−)-homogalanthamine **3**.

In the course of our opioid research, commonalities in the structures of (−)-galanthamine (**1**), (−)-homogalanthamine **3**, and μ opioid antagonist naltrexone (**2**) (Figure 1) prompted us to attempt the synthesis of (−)-homogalanthamine **3** from naltrexone (**2**). We were also interested in whether a transformation from **2** to **3** would impact the pharmacological effects of **3** on either AChE or the opioid receptor. Herein, we report the practical synthesis of (−)-homogalanthamine **3** from naltrexone (**2**) and some preliminary results of the inhibitory effect of **3** on AChE.

Our retrosynthetic analysis is outlined in Scheme 1. We reasoned that (−)-homogalanthamine **3** could be synthesized from ketone **4** by the following sequential reactions; dehydrogenation, transposition of the oxygen functionality, and reduction of the carbamate. The key intermediate **4** could be constructed by Grob fragmentation of *N*-chloroamine **5** due to its favorable geometry; the C9−C14 bond being broken is in an antiperiplanar relationship to the leaving group (N−Cl bond).[9] In turn, compound **5** could be obtained from naltrexone (**2**) by the reductive removal of the 6-ketone group in **2**, removal of the *N*-substituent, and *N*-chlorination.

First, naltrexone (**2**) was converted to naltrexone methyl ether (**6**)[10] (Scheme 2). Next, we attempted the reductive removal of the 6-ketone group in **6** by general methods for converting a ketone to a methylene. Our attempts included Wolff−Kishner[11] or Clemmensen reduction and desulfurization of the dithioacetal

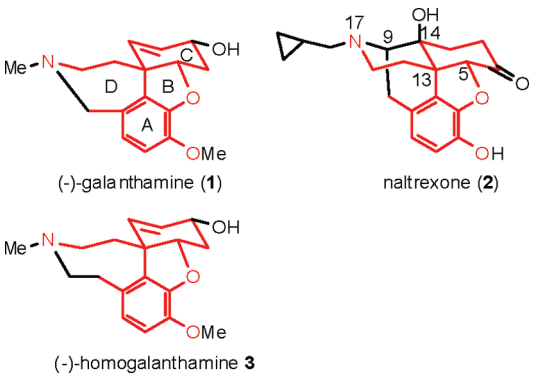
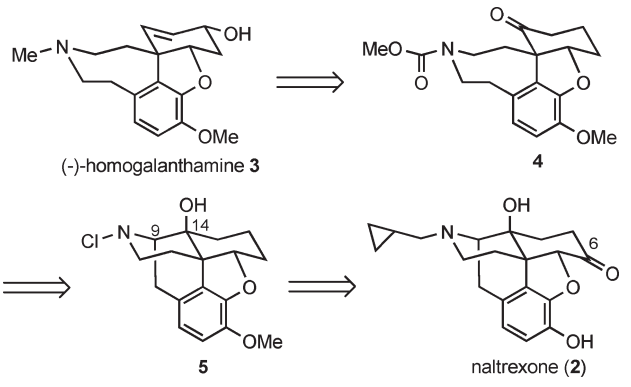


Figure 1. Commonalities in the structures of (−)-galanthamine (**1**), naltrexone (**2**), and (−)-homogalanthamine **3**.

Scheme 1. Retrosynthetic Analysis of (−)-Homogalanthamine 3



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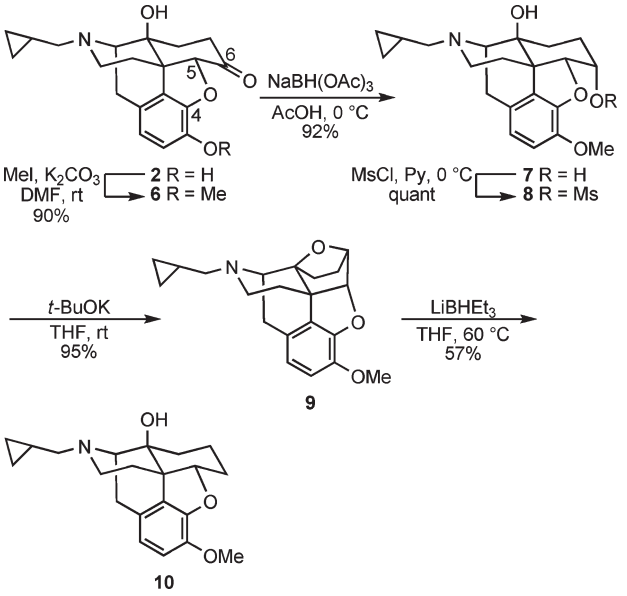
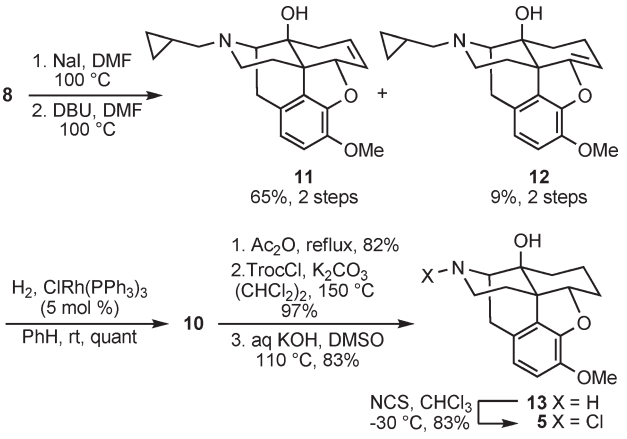
Scheme 2. Removal of the 6-Ketone Group in Naltrexone Methyl ether (6)

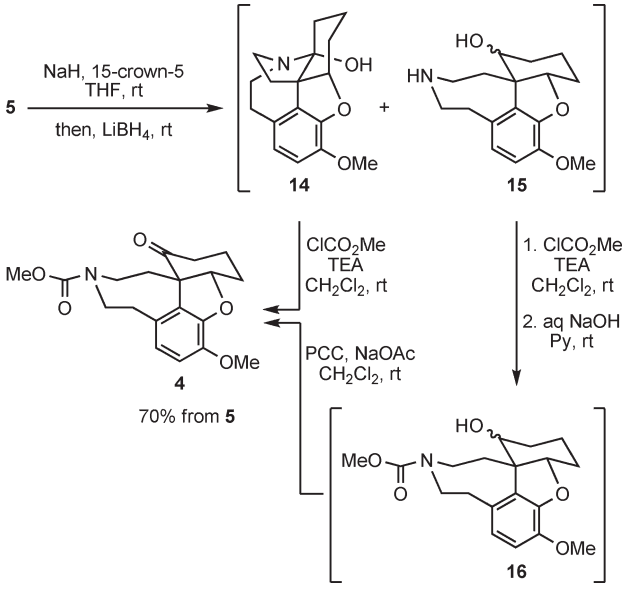


Scheme 3. Synthesis of *N*-Chloroamine 5

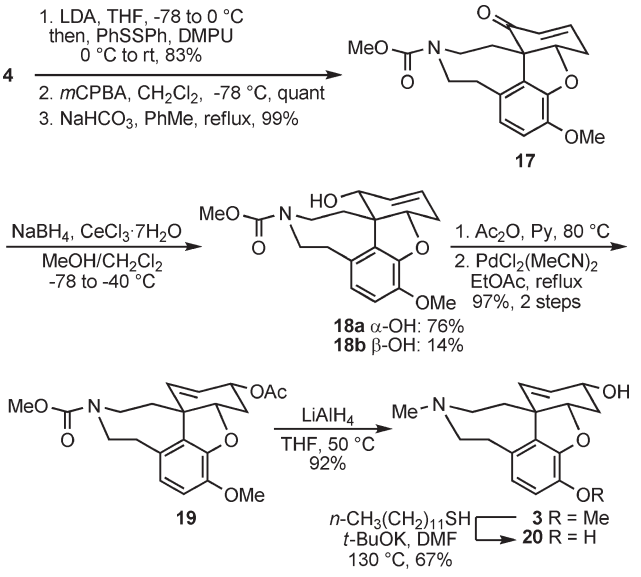


of **6** with Raney Ni, but all procedures led to a cleavage of the 4,5-ether bond. Next, we attempted to synthesize **10** by E2 elimination of mesylate **8** and subsequent hydrogenation of the resulting olefin. Stereoselective reduction of **6** with $NaBH(OAc)_3$ in acetic acid[12] and subsequent mesylation of 6-alcohol **7** afforded mesylate **8** (Scheme 2). Unfortunately, treatment of **8** with *t*-BuOK gave bicyclic compound **9** by intramolecular S_N2 reaction.[13] The successful conversion of the resulting **9** to the objective compound **10** was achieved by $LiBHEt_3$ reduction,[14] but the yield was less than 57% (Scheme 2). To suppress the intramolecular S_N2 reaction[13] and to accelerate the rate of the objective elimination reaction, the mesylate group in **8** was substituted with iodide (Scheme 3). The resulting iodide was subjected to E2 elimination reaction with DBU to give olefin **11** along with its isomer **12**. The mixture of olefins **11** and **12** was hydrogenated with Wilkinson's catalyst (5 mol %) in benzene to afford the objective compound **10** quantitatively. Compound **10** was converted to the secondary amine **13** by a previously reported

Scheme 4. Grob Fragmentation of *N*-Chloroamine 5



Scheme 5. Synthesis of (−)-Homogalanthamine 3 from the Key Intermediate 4



method;[15] this was followed by *N*-chlorination with NCS[9a,16] in $CHCl_3$ at −30 °C to give *N*-chloroamine **5** in 83% yield.

With *N*-chloroamine **5** in hand, Grob fragmentation of **5** was investigated (Scheme 4). Fortunately, the reaction of **5** with NaH in the presence of 15-crown-5 proceeded smoothly.[17] The C9−C14 bond was cleaved, followed by a $LiBH_4$ reduction to afford a mixture of hemiaminal **14** and amine **15**. This mixture was then treated with $ClCO_2Me$. This opened the five-membered hemiaminal ring in **14** and simultaneously protected the nitrogen to give the carbamate **4**. In parallel, treatment of **15** with $ClCO_2Me$ formed a carbonate that was hydrolyzed to give alcohol **16**. Then, **16** was oxidized by PCC to provide **4**. Thus, the key intermediate **4** was prepared from **5** in 4 steps with a 70% yield.

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Finally, the key intermediate **4** was converted into (−)-homogalanthamine **3** (Scheme 5). The intermediate **4** was treated with LDA and PhSSPh, followed by *m*-CPBA, and then refluxed in toluene to afford **17**[18] in 82% total yield. The desired α-allylic alcohol **18a** was synthesized by Luche reduction[19] at −78 °C, followed by separation of the β-isomer by column chromatography and recrystallization in 76% yield. The allylic rearrangement of the oxygen functionality in **18a** was achieved by acetylation of the allylic alcohol and the $PdCl_2(MeCN)_2$-catalyzed [3,3] sigmatropic rearrangement in refluxing EtOAc to give **19** in two steps (97% yield).[20] Simultaneous reduction of both the carbamate and acetate groups in **19** with $LiAlH_4$ at 50 °C afforded the desired (−)-homogalanthamine **3** in 92% yield. Demethylation of **3** was carried out with thiolate anion,[21] prepared in situ from an orderless dodecanethiol[12f,22,23] with *t*-BuOK, to provide crystalline compound **20**. The structure of **20** was determined by X-ray analysis (see the Supporting Information).

The inhibitory activity of the obtained **3** (IC_{50} = 3.0 μM) toward AChE was about 1/5 as potent as that of (−)-galanthamine (**1**) (IC_{50} = 0.6 μM). Phenolic compound **20**[24] derived from **3** showed no binding affinity for the opioid receptors in the competitive binding assay, indicating that the cleavage of the C9−C14 bond in naltrexone (**2**) abolished its affinity for opioid receptors.

In conclusion, we succeeded in the synthesis of (−)-homogalanthamine **3** in 16% total yield from the μ opioid antagonist, naltrexone (**2**). The key reaction was a Grob fragmentation to obtain the important intermediate **4**. This synthesis is advantageous, because naltrexone (**2**) is readily available, our synthetic route for the (-)-homogalanthamine **3** is practical, and the total yield was very high. Thus, we can easily obtain the intermediates of (-)-homogalanthamine **3** and their derivatives. We are currently examining the application of this synthetic route to the synthesis of compounds that are more active and less toxic than (−)-galanthamine (**1**).

EXPERIMENTAL SECTION

Grob Fragmentation of *N*-Chloroamine 5 and the Subsequent Reductions (Synthesis of Ketone 4). To a suspension of NaH (dry, 1.4 g, 56 mmol) in THF (30 mL) was added 15-crown-5 (3.7 mL, 18.7 mmol) and the mixture stirred at rt for 15 min under an argon atmosphere. A solution of *N*-chloroamine **5** (6.0 g, 18.7 mmol) in THF (120 mL) was gradually added to the suspension. After the disappearance of **5** was observed by TLC analysis, $LiBH_4$ (46 mL, 2.0 M in THF, 92 mmol) was added to the reaction mixture. After being stirred for 11 h, the mixture was treated with *i*-PrOH (100 mL), followed by 6 M HCl (100 mL) at 0 °C, and stirred at rt for additional 2 h. The reaction mixture was treated with 12 M aqueous NaOH to adjust to pH 9−10 and then concentrated under reduced pressure and extracted with *i*-PrOH/$CHCl_3$ (1:3) (200 mL, 100 mL, 50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The obtained residue was filtered through a short silica gel column (NH_4OH/MeOH/$CHCl_3$, 1:9:100) and concentrated under reduced pressure to afford a pale yellow oil (a mixture of **14** and **15**). To a solution of the oil in CH_2Cl_2 (120 mL) were added Et_3N (7.8 mL, 56 mmol) and methyl chloroformate (2.2 mL, 28 mmol) at 0 °C under an argon atmosphere. After being stirred at rt for 1 h, the mixture was concentrated under reduced pressure. To a solution of the residue in pyridine (100 mL) was added 4 M aqueous NaOH (50 mL), and the mixture was stirred at rt for 14 h under an argon atmosphere. The mixture was treated with saturated aqueous NH_4Cl to adjust to pH 9−10 and then concentrated under reduced pressure and extracted with $CHCl_3$ (100 mL, 50 mL, 25 mL). The combined organic layer was washed with brine, dried over $NaSO_4$, and evaporated under reduced pressure to afford a yellow solid (a mixture of **4** and **16**). To a solution of the solid in CH_2Cl_2 (200 mL) were added NaOAc (92 g, 1.12 mol) and PCC (24 g, 112 mmol). After being stirred for 3 h at rt, the reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (EtOAc/*n*-hexane, 3:2) and recrystallized from a $CHCl_3$−*n*-hexane solution to afford ketone **4** (4.5 g, 70%) as a colorless prismatic crystal. Ketone **4** was a mixture of rotamers. **4**: mp 126−128 °C; IR (KBr) 2950, 1703, 1623, 1507, 1478, 1437, 1404, 1274, 1239, 1203, 1170, 1123, 1041, 1002, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.54−1.78 (m, 2H), 1.88−2.05 (m, 1H), 2.06−2.64 (m, 7H), 3.16−3.32 (m, 1H), 3.37−3.54 (m, 1.8H), 3.45 (s, 1.2H), 3.60 (s, 1.8H), 3.61−3.80 (m, 1.2H), 3.88 (s, 1.2H), 3.89 (s, 1.8H), 4.69−4.77 (m, 1H), 6.60 (d, *J* = 8.4 Hz, 0.4H), 6.66 (d, *J* = 8.4 Hz, 0.6H), 6.76 (d, *J* = 8.4 Hz, 0.4H), 6.79 (d, *J* = 8.4 Hz, 0.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 18.2, 29.0, 29.5, 30.8, 36.1, 37.1, 38.2, 38.4, 43.8, 44.4, 48.8, 49.3, 52.2, 52.4, 55.9, 56.0, 60.5, 60.6, 93.2, 93.6, 112.5, 112.8, 121.8, 122.1, 127.9, 128.2, 128.9, 129.0, 142.7, 142.8, 149.6, 149.9, 156.4, 157.0, 213.0, 213.2; HRMS (ESI) $[M + Na]^+$ calcd for $C_{19}H_{23}NO_5Na$ 368.1474, found 368.1462.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, full characterization of compounds, and ^1H NMR spectra and X-ray crystallographic file of compound **20** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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