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Chemoenzymatic total synthesis of (+)-galanthamine and (+)-narwedine from phenethyl acetate

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Abstract

The stereoselective total synthesis of unnatural (+)-galanthamine starting from phenethyl acetate is described. Chirality was introduced via microbial dihydroxylation of phenethyl acetate with the recombinant strain JM109 (pDTG601A) to the corresponding *cis*-cyclohexadienediol whose configuration provides for the absolute stereochemistry of the ring C of (+)-galanthamine. Intramolecular Heck cyclization was used to form the quaternary carbon and dibenzofuran functionality. The synthesis of (+)-galanthamine was completed in a total of 10 steps and an overall yield of 5.5%. Experimental and spectral data are provided for all new compounds.

Key words: enzymatic dihydroxylation, total synthesis, galanthamine, narwedine

The natural product, (-)-galanthamine (**1**), Figure 1, was isolated from the bulbs of different species of the Amaryllidaceae family.[1] It has been shown to be a centrally acting, selective, reversible, and competitive acetylcholine esterase (AChE) inhibitor,[2] as well as an allosteric modulator of the neuronal nicotinic receptor for acetylcholine.[3] Galanthamine hydrobromide, commercially available as Radazyne®, is the most recently approved AChE inhibitor in Europe (European Registration Bureau, ERB) and in the USA (Federal Drug Administration, FDA) for the symptomatic treatment of Alzheimer's disease.[4]

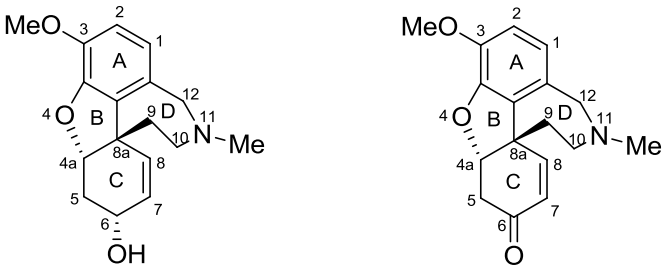


Figure 1. Structure of (-)-galanthamine and (-)-narwedine (with numbering system shown).

Because of the biological activities of (-)-galanthamine, and the high cost of isolation from natural sources,[5] several total syntheses[6] have been reported to produce this drug. A summary of the most recent synthetic approaches to (-)-galanthamine is shown in Table 1. The strategy in these approaches has been classified according to the sequence the rings of galanthamine (see Figure 1) are constructed. It can be seen that the most recent syntheses are predominantly relying on Pd-catalyzed coupling reactions for the formation of the quaternary center C-8a. Two of the approaches (Banwell[7f] and Chida[7j]) involve chemoenzymatic steps and/or the use of starting materials from a chiral pool. Chida's approach started with D-glucose while Banwell made use of a chiral cyclohexadienediol obtained from the microbial dihydroxylation of bromobenzene. Our approach employs the toluene dioxygenase-mediated dihydroxylation of phenethyl acetate to the corresponding cyclohexadiene diol and this maneuver considerably shortens the synthesis. In this paper we report a new and stereoselective synthesis of (+)-galanthamine, the enantiomer of the natural product, starting from an enantiomerically pure cyclohexanediol derived enzymatically from phenethyl acetate.

Table 1. Some recent syntheses of galanthamine.[7]

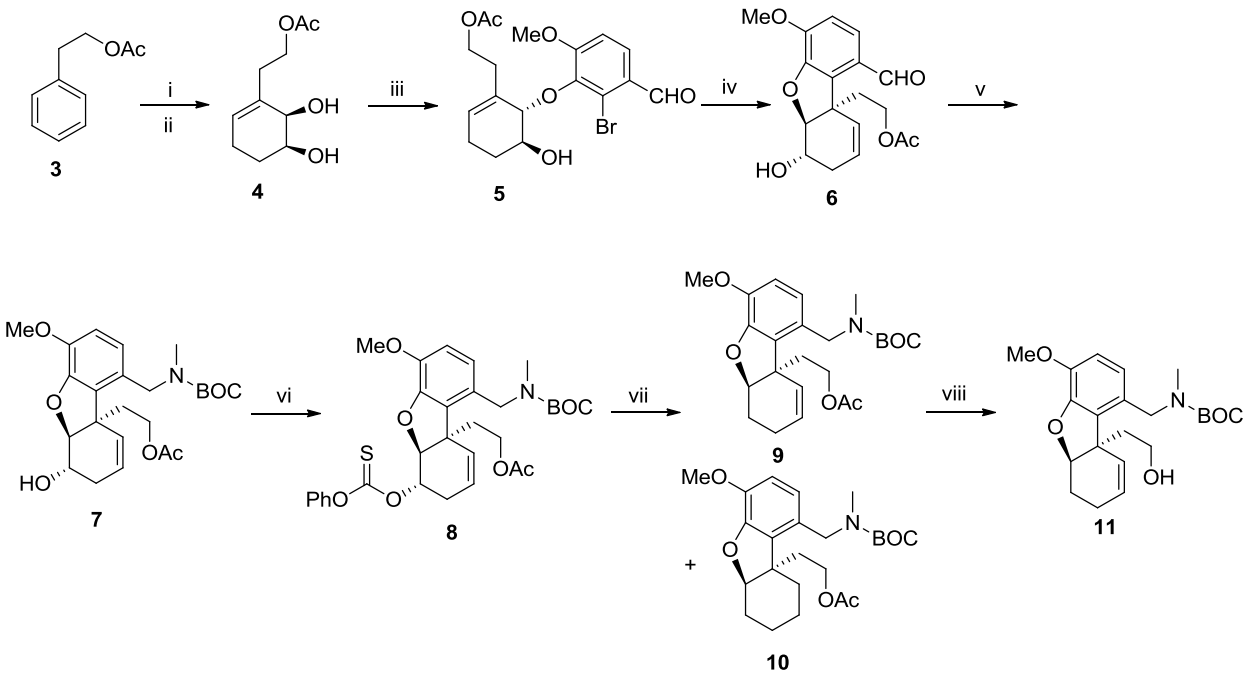
Strategy for Galanthamine Synthesis/Key step	Number of steps/overall yield	Author/year of publication	Comments	Reference
ABDC, Pd-catalyzed intramolecular Larock annulation	14 steps, 9.3%	Jia, Y. 2015	(-)-galanthamine	7a
ACBD, ring-closing	14 steps, 3.0%	Tae, J. 2013	(-)-galanthamine	7b

metathesis				
ACBD, Pd-catalyzed asymmetric allylic etherification	5 steps, 61%	Ojima, I. 2013	Formal synthesis, preparation of Trost intermediate with a higher %ee, 4 remaining steps, (-)-galanthamine	7c
ACBD, Pd-catalyzed intramolecular reductive Heck cyclization	12 steps, 20.1%	Zhou, Q.-L. and Xie, J.-H. 2012	(-)-galanthamine	7d
ACBD, catalytic asymmetric intramolecular Michael addition	15 steps, 2.8%	Fan, C.-A. 2011	(-)-galanthamine	7e
ACBD, Eschenmoser-Claisen rearrangement	21 steps, 7.7%	Banwell, M. G. 2010	(+)-galanthamine	7f
ACBD, Stille coupling, intramolecular Diels-Alder reaction	10 steps, 1.9%	Cho, C.-G. 2010	(±)-galanthamine	7g
ACBD, intramolecular alkylation of phenol	8 steps, 63%	Magnus, P. 2009	Formal synthesis, (-)-narwedine was prepared and converted to (-)-galanthamine	7h
ACBD, enyne ring-closing metathesis	11 steps, 4.1%	Brown, R.C.D. 2007	(-)-galanthamine	7i

ACBD, Claisen rearrangement	19 steps, 4.9%	Chida, N. 2007	(+)-galanthamine	7j
ACBD, Pd-catalyzed asymmetric allylic alkylation	10 steps, 8.0%	Trost, B.M. 2005	(-)-galanthamine	7k
ACDB, hypervalent iodine-catalyzed phenolic oxidative coupling	14 steps, 23.0%	Node, M. 2004	(-)-galanthamine	7l
ACBD, Pd-catalyzed intramolecular Heck cyclization, dehydrogenation reaction	8 steps, 12.0%	Guillou, C. 2001	(±)-galanthamine	7m
ACDB, crystallization-induced chiral conversion	10 steps, 12.4%	Jordis, U. and Frohllich, J. 1999	(-)-galanthamine, pilot scale	7n
ACDB, hypervalent iodine-catalyzed phenolic coupling	9 steps, 36%	Kita, Y. 1998	(±)-galanthamine	7o

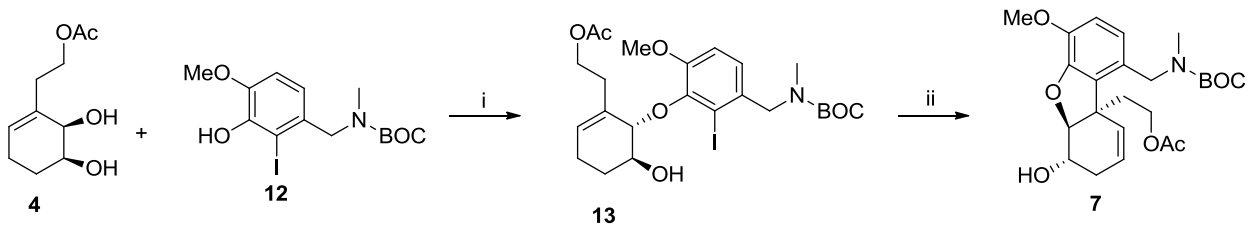
The synthesis began with the microbial dihydroxylation of phenethyl acetate **3** to afford an intermediate cyclohexadiene diol,[8] which was subjected to a selective reduction of the less hindered alkene to afford the known diol **4**,[9] Scheme1. The coupling of diol **4** with bromo-isovanillin was accomplished via a Mitsunobu reaction at the more reactive allylic alcohol functionality to afford ether **5**. A subsequent intramolecular Heck reaction of **5** allowed for the assembly of the ABC rings of galanthamine present in the intermediate aldehyde **6**. The aldehyde functionality was converted to carbamate **7** via reductive amination with methylamine followed by protection of the resulting amine with Boc group. With the attainment of **7**, the rest of the

synthesis needs only the closure of ring D and the transposition of the alcohol functionality from C-5 to C-6, as required for galanthamine. A Barton-McCombie deoxygenation followed by allylic hydroxylation of C-6 was originally intended for this transformation. The alcohol in **7** was converted to thionocarbonate **8**, which was subjected to a free-radical reduction (*n*-Bu_3SnH, AICN (cat.) in refluxing toluene to afford the desired product **9** along with the over-reduced compound **10** in a ratio of 4:1. The intermediate **9** was successfully converted to the known compound **11**,[7h] thus completing a formal synthesis of (+)-galanthamine.



Scheme 1. Preparation of Intermediate **8**. i) *E. coli* JM 109 (pDTG601A), 80%; ii) PAD, MeOH, HOAc, 85%; iii) bromo isovanillin, Bu_3P, TMAD, THF, 87%; iv) Ag_2CO_3, dppf, $Pd(OAc)_2$, toluene, reflux, 87%; v) a. $Ti(iPrO)_4$, $NH_2Me.HCl$, NEt_3, MeOH, b. $NaBH_4$, c. Boc_2O, NEt_3, EtOH, 80%, ; vi) PhOCSCl, pyridine, DCM, 84%; vii) *n*-Bu_3SnH, AICN, toluene, 80 °C, 60%; viii. Aq. NaOH, MeOH, 89%.

The synthetic sequence was shortened by one step by preparing the intermediate **7** directly from a Mitsunobu product **13**, as shown in Scheme 2. Thus, diol **4** was coupled to the phenol **12** as shown in Scheme 2. As it is known that the presence of electron-donating groups on the aromatic coupling partner for the intramolecular Heck reaction retards the reaction rate, the halide used was iodide instead of bromide.[7k]

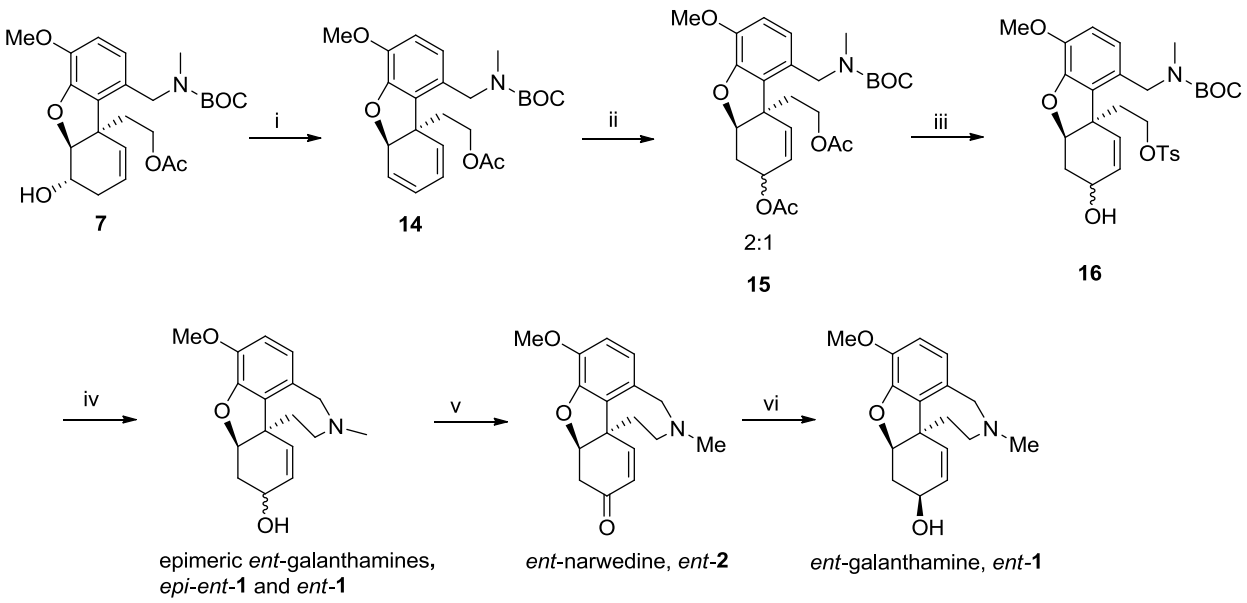


Scheme 2. Shorter route for preparing **7**. i) TMAD, nBu_3P, THF, 85%; ii) bis-diphenylphosphino)propane, Ag_2CO_3, DMF, 150 °C, 80%.

In order to install a hydroxyl group at C-6,[7h] an allylic oxidation of **9** was investigated. The standard method for this purpose, the SeO_2-mediated allylic oxidation, failed under a variety of conditions[10] and did not lead to appreciable amounts of either the enone or the allylic alcohol.

To facilitate the subsequent installation of C-6 hydroxyl, an elimination-hydroxylation (indirect) sequence was utilized, as shown in Scheme 3. The alcohol **7** was converted to diene **14** via mesylation followed by elimination with DBU. A Prevost reaction was conducted on the diene **14** to afford a diastereomeric mixture of iodo acetates, which were immediately subjected to reduction with sodium borohydride in DMSO to afford a 2:1 mixture of diastereomeric acetates **15**. This method proved superior to other alternatives (Ni-Raney, $LiAlH_4$).

Hydrolysis of the acetyl groups of **15** with aqueous sodium hydroxide in methanol afforded the desired intermediate diol, which was immediately converted to the tosylate **16** by selective tosylation of the primary alcohol. Deprotection of the BOC group was accomplished with TFA in dichloromethane provided the intermediate secondary amine. Simple evaporation of solvents and TFA followed by the addition of excess potassium carbonate in ethanol and heating the resulting mixture to reflux resulted in the conversion of the tosylates to epimeric *ent*-galanthamines in a 2:1 ratio favoring the C-6 β-epimer, Scheme 3.



Scheme 3. Completion of the synthesis of *ent*-galanthamine i) a. MsCl, NEt_3, CH_2Cl_2, b. DBU, toluene, reflux; ii) a. I_2, AgOAc, HOAc, THF, b. $NaBH_4$, DMSO, 80 °C, 63%; iii. a. aq NaOH, MeOH, b. *p*TsCl, NEt_3, DMAP, CH_2Cl_2, 67%. iv) a. TFA, CH_2Cl_2, b. K_2CO_3, EtOH, reflux; v) PCC, CH_2Cl_2, 75%; vi) L-Selectride, THF, -60 °C, 66%.

The mixtures of epimers was subjected to oxidation using pyridinium chlorochromate to afford the desired *ent*-narwedine,[11] whose spectral and physical properties were consistent with those published in the literature.[12] The *ent*-narwedine obtained was reduced stereoselectively with L-selectride to afford *ent*-galanthamine, whose spectral and physical properties matched those provided in the literature.[7f] In conclusion, a short chemoenzymatic synthesis of *ent*-galanthamine has been accomplished in 10 steps from phenethyl acetate. Further improvements in this short synthesis will address a more direct conversion of diene **14** to narwedine (**2**) by adjustments in the oxidative functionalization of the diene with $Co(acac)_2/O_2$ (previously reported in the synthesis of kibdelone[13]) that may lead to a one-pot conversion. Among other methods for the direct conversion of a diene to an allylic alcohol include hydroboration-oxidation[14] and acid-catalyzed hydration.[15] These improvements, as well as the 2nd generation of the natural enantiomer are currently being investigated and will be reported in due course.

Supplemental Information: experimental and spectral data are provided for the following compounds: **5**, **6**, **7**, **8**, **9**, **10**, **11**, **13**, **14**, **15**, **16**, ***epi-ent*-1**, ***ent*-1** and ***ent*-2**.

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