

Natural Product Synthesis

Total Synthesis of (–)-Galanthamine by Remote Asymmetric Induction

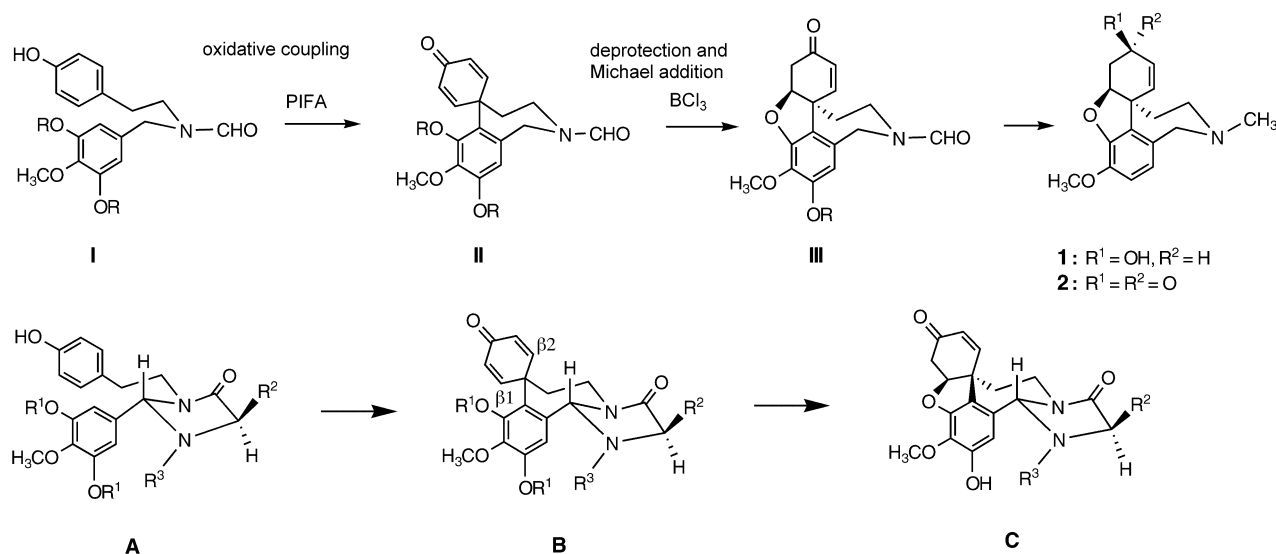
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(–)-Galanthamine (**1**),^[1] an alkaloid isolated from the *Amaryllidaceae* family, has attracted the attention of synthetic chemists because of its use as a selective acetylcholinesterase inhibitor in the clinical treatment of Alzheimer's disease.^[2] Its limited supply and the high costs associated with isolating this compound from natural sources^[3] are two compelling reasons for the need for an efficient synthesis. (–)-Galanthamine (**1**) has usually been prepared industrially through the crystallization-induced asymmetric transformation^[3,4] of the intermediate (±)-narwedine (**2**).^[5] As the latter compound is highly allergenic, chemists must be extremely careful when working with it, which underscores the necessity for safer and more efficient methods for the synthesis of (–)-**1**. In addition to the classical and biomimetic phenolic oxidative coupling^[4a,b,6] in the presence of metal oxidants, an asymmetric allylic alkylation and intramolecular Heck reaction sequence has also been used in an excellent synthetic strategy toward (–)-**1**.^[7] We recently improved the phenolic oxidative coupling of norbelladine-type derivatives **I**, which contain a pyrogallol moiety, and applied it in a synthesis of (±)-**2** and (±)-**1**.^[8] Herein we report a new asymmetric synthesis of (–)-galanth-

amine (**1**), through remote asymmetric induction with a chiral imidazolidinone auxiliary derived from phenylalanine.

Our strategy for the asymmetric synthesis of (–)-**1** involved the modification of our previous racemic synthesis^[8] by using phenyliodine(III) bis(trifluoroacetate) (PIFA) as the “clean” oxidant, as shown in Scheme 1. The key step in this asymmetric version of the synthesis is the intramolecular Michael addition of the coupling product **II** to give the cyclic ether **III**. This step requires the preferential attack by the phenolic oxygen atom on one olefin of the symmetrical dienone moiety. Therefore, we designed conformational restriction into the seven-membered ring in **II** by introducing an α -amino acid at the benzylic position, α to the N atom in the ring. More precisely, the conformation of the seven-membered ring in the coupling product **B** of the chiral imidazolidinone **A** would be restricted by a fused five-membered ring. It could be reasoned that the intramolecular Michael addition of **B** would then proceed diastereoselectively to afford the cyclic ether **C** by this new type of remote asymmetric induction. Through semiempirical PM3 calculations based on the Monte Carlo techniques for conformer analysis,^[9] we calculated the most stable conformer of the intermediate **B** ($R^1 = H$, $R^2 = Bn$, $R^3 = COCF_3$). The distance between the phenolic O atom and C β 1 (2.61 Å) is 0.55 Å shorter than that between the O atom and C β 2 (3.15 Å). The intramolecular Michael addition should be highly regio- and diastereoselective, thus leading to the desired enantiomer corresponding to (–)-galanthamine.

For the substrate in the coupling reaction, we chose D-phenylalanine as the chiral auxiliary, as its bulky substituent

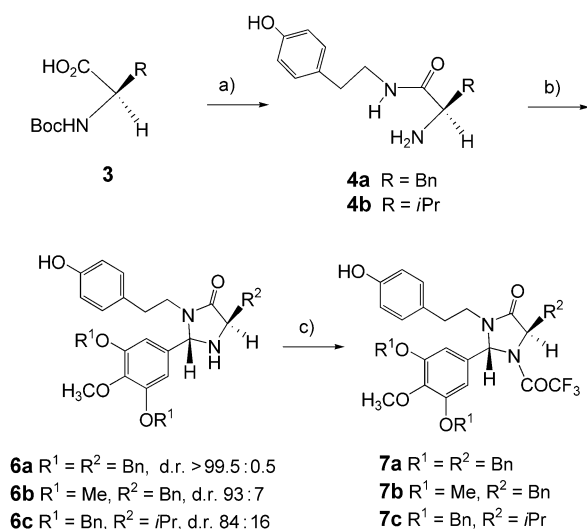


Scheme 1. Strategy for the synthesis of (–)-galanthamine.

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($R^2 = \text{benzyl}$) was expected to be effective in the diastereoselective formation of the chiral imidazolidinone corresponding to **A**. (*R*)-*N*-Boc-D-phenylalanine (**3**, $R = Bn$) was condensed with tyramine in the presence of the dehydrating agent *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl). Removal of the *N*-Boc group then gave the amine **4a** in 92% yield (over two steps; Scheme 2).



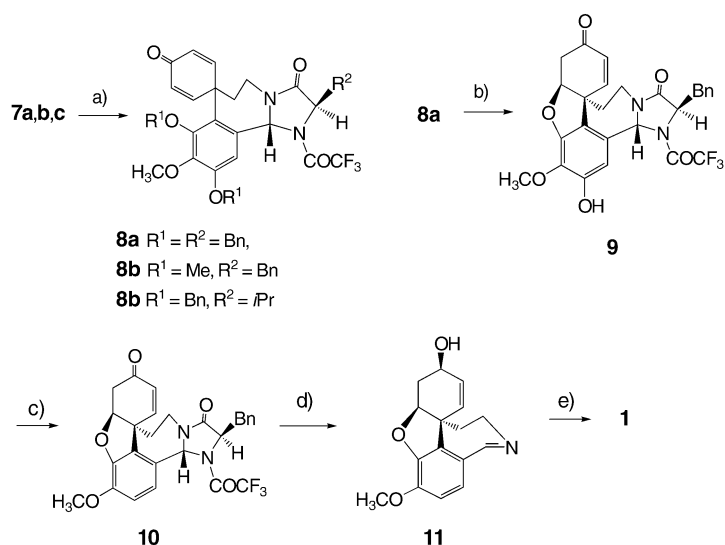
Scheme 2. Synthesis of the oxidative-coupling precursors **7**. Reagents and conditions: a) 1. tyramine (1.2 equiv), EDC·HCl (1.2 equiv), HOBT (0.1 equiv), THF, room temperature, 2 h, 95%; 2. MsOH (2 equiv), MeOH, 40°C, 3 h, 97%; b) for **6a** and **6c**: 1. **5a**, dioxane, room temperature, 1 day; 2. HCl (4 M)/dioxane, room temperature, 2 days, 80% from **4a** and 66% from **4b**, respectively; for **6b**: 1. **5b**, dioxane, room temperature, 12 h; 2. HCl (4 M)/dioxane, room temperature, 12 h, 43% from **4a**; c) (CF₃CO)₂O (2.4 equiv), pyridine, 0°C, 15 min, 94% (**7a**). Boc = *tert*-butoxycarbonyl, HOBT = 1-hydroxy-1*H*-benzotriazole, Ms = methanesulfonyl.

Upon treatment with the pyrogallol-type aldehyde 3,5-dibenzyloxy-4-methoxybenzaldehyde (**5a**), the amine **4a** was transformed into the desired imine intermediate, which underwent cyclization in the presence of 4 M hydrochloric acid to the imidazolidinone **6a** in 80% yield. Exclusive formation of **6a** (R¹ = Bn) was observed in this cyclization, whereas the diastereoselectivity observed in the reaction of **4a** with 3,4,5-trimethoxybenzaldehyde (**5b**) to form **6b** (R¹ = Me) was just 86%. The relative configuration of the two substituents in the imidazolidinone ring was confirmed to be *trans* by NOE experiments.^[10] In the case of the cyclization with **4b**, in which D-valine is incorporated as the chiral auxiliary instead of D-phenylalanine, the desired product **6c** was obtained as a diastereomeric mixture (5.4:1). Phenylalanine was selected as a chiral auxiliary based on the results of these three cyclizations. The secondary amino group in the imidazolidinone ring of **6a** was protected with a trifluoroacetyl group to give the precursor **7a** to the oxidative coupling in high yield. For comparison of the coupling reactions, the imidazolidinone derivatives **7b** and **7c** were also prepared.

The phenolic oxidative coupling of **7a–c** with PIFA in trifluoroethanol resulted in moderate yields (41–61%) of **8a–b** (Scheme 3). In these coupling reactions the yields were lower than we had anticipated based on our earlier studies.^[8] However, **8a** was produced from **7a** in a higher yield (61%) than any reported previously for such a reaction of a norbelladine-type compound.^[4,6] Debenzylation of **8a** with boron trichloride afforded the cyclic ether **9** in 95% yield.

During the debenzylation, an intramolecular Michael addition proceeded smoothly to give the single diastereomer **9**. The stereochemistry of the product **9** was consistent with that predicted by calculation, as confirmed below.

The remaining phenolic hydroxy group in **9** was converted into the triflate and then subjected to palladium(0)-catalyzed reduction with formic acid^[11] to give **10** in 83% yield, as shown in Scheme 3. The stereoselective reduction of the enone **10** with L-selectride, followed by alkaline hydrolysis of the chiral imidazolidinone auxiliary, afforded the imine **11**. Reduction of the imine with sodium borohydride, and *N*-methylation of the product via the corresponding *N*-formamide, completed the asymmetric total synthesis of (–)-galanthamine (**1**). The specific rotation of the synthetic (–)-**1** ([α]_D²⁴ = –121.7 (*c* = 0.30, EtOH)) was consistent with the reported value.^[12] The optical purity of the synthetic (–)-**1** (100% *ee*) was confirmed by HPLC analysis on a chiral phase.^[13]

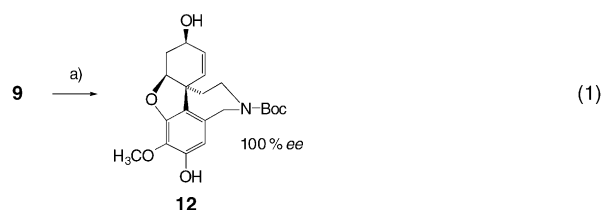


Scheme 3. Synthesis of (–)-galanthamine. Reagents and conditions: a) PIFA (1.1 equiv), CF₃CH₂OH, (for **8a**: –40°C, 10 min, 61%; for **8b**: –40°C, 1.5 h, 41%; for **8c**: –40°C, 15 min, 45%); b) BCl₃ (3.0 equiv), CH₂Cl₂, –78°C, 2 days, 95%; c) 1. Tf₂O (2.4 equiv), pyridine, 0°C, 2.5 h, 83%; 2. Pd(OAc)₂ (0.2 equiv), PPh₃ (0.4 equiv), Et₃N (15 equiv), HCO₂H (10 equiv), DMF, 60°C, 3 days, 100%; d) 1. L-selectride (2.4 equiv), THF, –78°C, 3 h, 78%; 2. KOH (10%), Bu₄NBr (0.5 equiv), EtOH, 80°C, 1 day, 96%; e) 1. NaBH₄ (1.2 equiv), MeOH, 0°C, 5 h; 2. HCO₂Et, 60°C, 2 days, 100% (2 steps); 3. LiAlH₄, THF, 7 h, 94%. DMF = *N,N*-dimethylformamide, Tf = trifluoromethanesulfonyl.

In conclusion, we have described a new and efficient total synthesis of (–)-galanthamine (**1**), which was carried out in 14 steps and 23% overall yield from readily available (*R*)-*N*-Boc-D-phenylalanine. A chiral phenylalanine auxiliary regulated the formation of **6a** as a single diastereomer, then controlled the regio- and stereochemistry of the intramolecular Michael addition of the phenol moiety to the spirodienone in **8a** (R¹ = H) in a novel remote asymmetric induction. This work has provided a straight-forward synthetic route to (–)-galanthamine (**1**) that does not involve the highly allergenic intermediate narwedine (**2**).

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Keywords: alkaloids · asymmetric synthesis · Michael addition · natural products · total synthesis



Reagents and conditions: a) 1. L-selectride (2.0 equiv), THF, -78°C , 1 day, 92%; 2. NaOH (10%), room temperature, 7.5 days, 83%; 3. NaBH_4 (4.0 equiv), MeOH, room temperature, 4 h; 4. $(\text{Boc})_2\text{O}$ (3.0 equiv), THF, room temperature, 2 h, 58% (2 steps).

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- [13] The optical purity of **12**, derived from **9** [Eq (1)], was measured by HPLC on a chiral stationary phase (Daicel CHIRALCEL OD, iPrOH/hexane (9:1), 1.0 mL min⁻¹); (–)-**12**: $R_{\text{t}} = 50.2$ min, (+)-**12**: $R_{\text{t}} = 74.0$ min.