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Stereocontrolled Synthesis of (−)-Galanthamine

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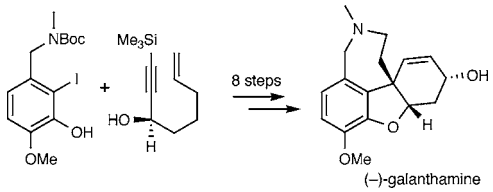
ABSTRACT



An enantioselective synthesis of (−)-galanthamine has been realized in 11 linear steps starting from isovanillin. A Mitsunobu aryl ether forming reaction was used to assemble the galanthamine backbone, which was stitched together using enyne ring-closing metathesis, Heck, and N-alkylation reactions affording the tetracyclic ring system. Control of relative and absolute stereochemistry was derived from an easily accessible enantiomerically enriched propargylic alcohol 13.

Galanthamine (**1**) is an *Amaryllidaceae* alkaloid,[1,2] which is in clinical use for the symptomatic treatment of Alzheimer's disease.[3] (−)-Galanthamine displays competitive reversible inhibition of acetylcholine esterase (AChE) and allosteric potentiation of nicotinic acetylcholine receptors.[4,5] These effects are believed to be associated with the therapeutic effect of the drug. (−)-Galanthamine is relatively expensive to obtain from natural sources, leading to the development of a synthetic process for its commercial production. This process utilizes oxidative phenolic coupling and crystallization-induced chiral conversion as key steps[6−8] and is effective for the synthesis of the natural product but somewhat limited in terms of analogue synthesis due to the requirement of electron-rich aryl groups. Alternative synthetic routes to galanthamine and structurally related alkaloids have been reported,[1,3,9−11] including an asymmetric total synthesis.[12]

Recognition of the benefits of a synthetic route to galanthamine with the potential to create structural analogues not available through the oxidative coupling approach[3,12,13] stimulated our initial synthetic efforts toward the natural product. Analysis of (−)-galanthamine (**1**) led us to consider a diene of general structure **2** as a key intermediate, which contains suitable functionality for the closure of the two

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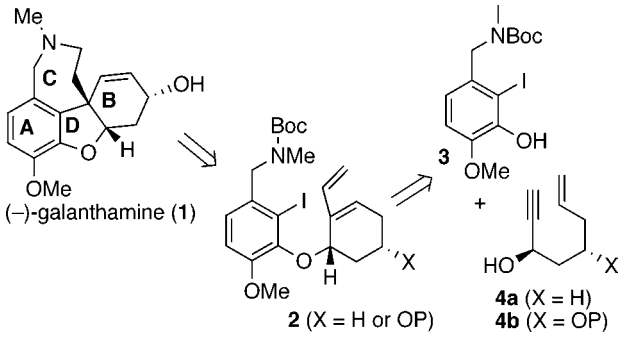
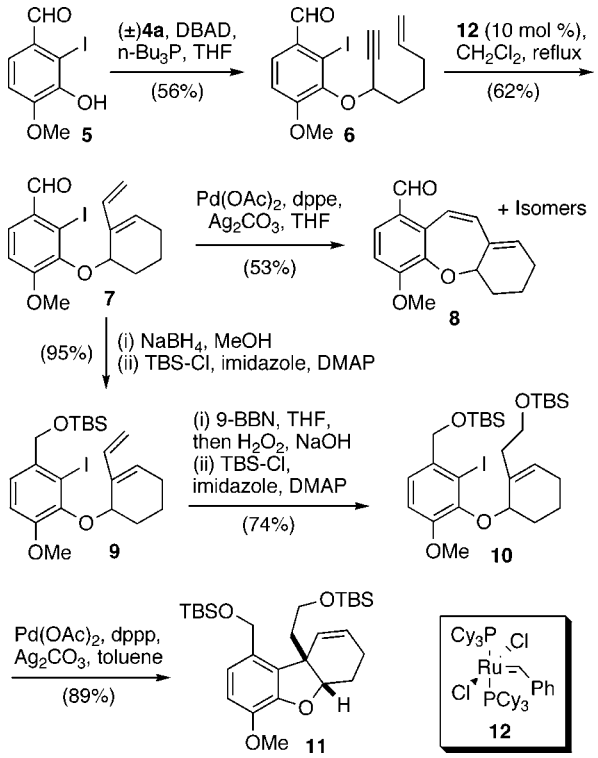
Scheme 1. Proposed Synthetic Route to (−)-Galanthamine



heterocyclic C and D rings (Scheme 1). Formation of the D ring, and corresponding quaternary stereogenic center, would be achieved by application of the Heck strategy introduced by Fels and Parsons.[11,12] The proposal centered on the use of an enyne ring-closing metathesis (RCM) reaction to create the vinyl-substituted cyclohexene ring within a structure containing all of the carbon atoms required in the final target.[14] Joining the two fragments would be effected through Mitsunobu coupling of a phenol **3** with an enantiomerically enriched propargylic alcohol **4a**,[15] readily available through asymmetric ketone reduction. Ultimately, we imagined that such an approach could be adapted to incorporate the galanthamine allylic hydroxyl group within the fragment **4b**.[16]

Our initial investigations, using a racemic propargylic alcohol (±)-**4a**[17] and phenol **5**,[18] established the enyne RCM reaction as a highly chemoselective means to create the vinylcyclohexene **7** (Scheme 2). However, it transpired that

Scheme 2. Synthesis of a Racemic ABD Ring System



Pd-catalyzed arylation of the diene **7** did not provide the desired product and instead favored C−C bond formation at the less sterically encumbered end of the 1,3-diene system, affording diene **8**.[19] Presumably, the intermediacy of a π-allyl palladium species also favors the observed regioselectivity. The required C−C bond formation was realized by selective hydration of the less-substituted olefin prior to the Heck reaction, securing the tricyclic ABD system **11** in high overall yield.[11,12,20,21]

Although the ultimately successful route to the tricycle **11** came at the expense of additional functional group interconversions and protecting group manipulations, it was easy to envisage its adaptation to provide a streamlined asymmetric synthesis of galanthamine. Accordingly, the

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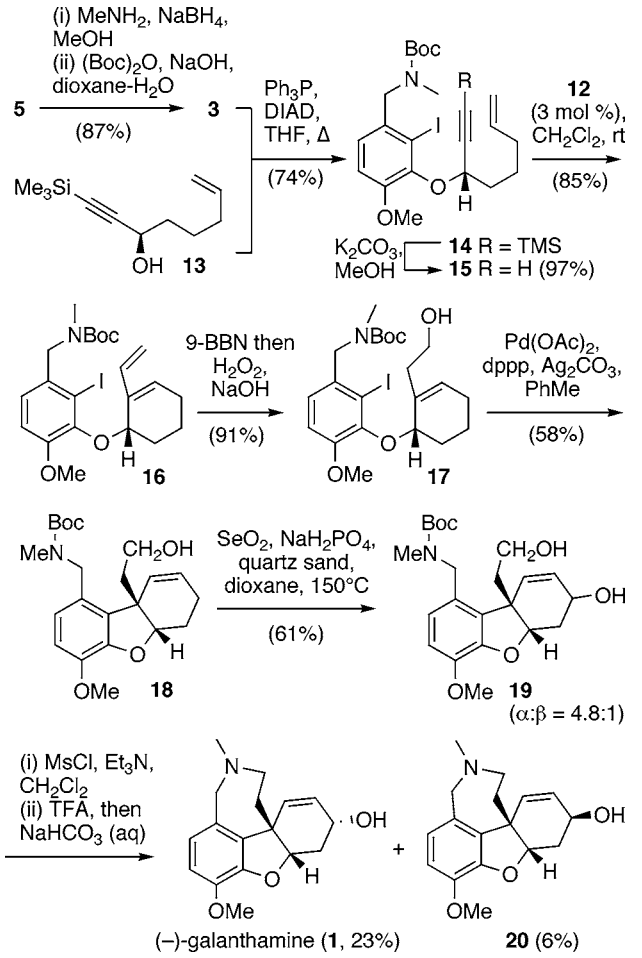
protected aminomethyl group was introduced into the aryl fragment **3** (Scheme 3). Mitsunobu coupling of **3** with the

Scheme 3. Asymmetric Synthesis of (−)-Galanthamine



enantiomerically enriched propargylic alcohol **13** delivered the aryl ether **14**. The enyne **15** (92% ee, HPLC), obtained after TMS deprotection of **14**, underwent an efficient RCM reaction in the presence of 3 mol % of the first-generation Grubbs' catalyst (**12**) at ambient temperature to give diene **16**. Hydroboration and oxidation of **16** was unaffected by the presence of the carbamate group, allowing access to the homoallylic alcohol **17** in excellent yield (91%).

The remaining steps to complete the total synthesis of (−)-galanthamine were carried out without protection of the primary hydroxyl group. An intramolecular Heck reaction of **17** led to successful formation of the central heterocyclic five-membered D ring in an acceptable yield. Trost's procedure was then applied to install the allylic hydroxyl group into **19**,[12] leading to an excess of the desired α-diastereoisomer (dr = 4.8:1 estimated by ^{1}H NMR). Separation of the diastereoisomers was not possible at this stage, so the mixture of epimers was taken through the remaining two steps. Activation of the 1° hydroxyl group was achieved through mesylation. Although some bismesylation was also observed under the conditions employed, no attempt was made to optimize this reaction. Finally, the azepine B ring formation was achieved in a one-pot process by sequential treatment with TFA and neutralization with $NaHCO_3$ (aq). Thus (−)-galanthamine and its epimer **19** were obtained after separation by column chromatography.[22]

In conclusion, an enantioselective synthesis of (−)-galanthamine has been described from commercially available materials in 11 linear steps (11 steps from isovanillin or 5-hexenoic acid, 14 steps in total). Control of absolute stereochemistry was achieved through an asymmetric reduction of a propargylic ketone. An efficient enyne metathesis reaction was used to close the B ring while generating the requisite functionality later used in the formation of the D and C rings.

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Supporting Information Available: Procedures and spectroscopic and analytical data for compounds **1**, **3**, **4a**, **6**−**11**, and **13**−**19**. Copies of ^{1}H and ^{13}C NMR spectra for compounds **1**, **3**, **6**−**11**, and **13**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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