Enantioselective Total Synthesis of (−)-Galanthamine

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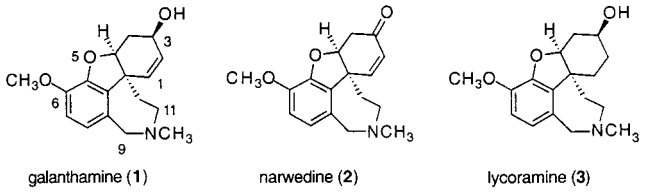
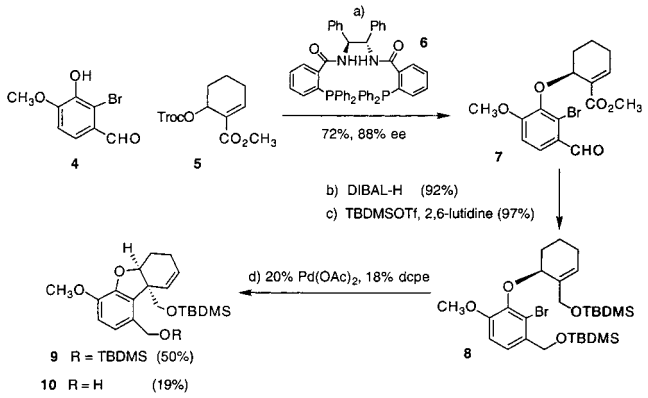
(−)-Galanthamine (**1**),[1] the parent member of the galanthamine-type *Amaryllidaceae* alkaloids, has recently received significant attention as a selective acetylcholinesterase inhibitor and, consequently, for its potential clinical application for the treatment of Alzheimer's disease.[2] An efficient synthesis of **1** is needed since its extraction from daffodils is low-yielding (0.1−2% dry weight)[3] and it has been reported that native sources are threatened.[4] To date, all syntheses of galanthamine have utilized a biomimetic oxidative bisphenol coupling[5] to create the critical spiro quaternary carbon[6] of narwedine **2**, which is converted into **1** by diastereoselective reduction. The only reported asymmetric synthesis of a galanthamine alkaloid relies on the oxidative coupling of L-tyrosine to prepare unnatural (+)-galanthamine.[7,8] Herein, we report a versatile approach for the enantioselective synthesis of the galanthamine alkaloids.



Our strategy was to first form the O5−C4a bond by a palladium-catalyzed asymmetric allylic alkylation (AAA)[9] of an *ortho*-halophenol and then employ an intramolecular Heck reaction[10] to prepare the crucial quaternary center. To this end, palladium-catalyzed reaction of 2-bromovanillin (**4**)[11] with carbonate **5**[12] (available in two steps from glutaraldehyde and the Emmons-Wadsworth-Horner reagent) in the presence of ligand **6**[13] furnished the required aryl ether (**7**) in 72% yield and with 88% enantiomeric excess on a 24 mmol scale (Scheme 1). Gratifyingly, good enantioselectivity could be obtained despite the fact that phenol **4** is *ortho*-disubstituted and that cyclohexene **5** bears a C2-substitutent. Surprisingly, the aryl ethers obtained from the palladium-catalyzed AAA of **5** are of the opposite absolute stereochemistry to those obtained in the AAA reactions of unsubstituted cyclohexenyl carbonates.[14] Investigation of the reasons for this reversal are ongoing and will be reported in due course.

Scheme 1. Asymmetric Synthesis of Tricyclic Core



(a) 3% **6**, 1% $[\eta^3\text{-}C_3H_5PdCl]_2$, $(C_2H_5)_3N$, CH_2Cl_2, rt. (b) $PhCH_3$, −78°. (c) 2,6-Lutidine, CH_2Cl_2, rt. (d) Proton sponge, DMA, 80°.

All attempts to effect the intramolecular Heck reaction of aryl ether **7** failed, resulting primarily in ionization of phenol **4**. An earlier report[15] suggested that the presence of electron-withdrawing subsitutents on the phenol favored the palladium-catalyzed ionization over the intramolecular Heck reaction. Therefore, **7** was reduced with DIBAL-H and the resulting diol protected with TBDMS-triflate to afford bis-TBDMS ether **8** in 89% yield from **7**. Heck reaction of **8** did not prove straightforward. The conditions developed by Overman[10,16] for formation of quaternary centers produced only poor yields of **9** as did the Jeffery-type conditions reported by Larock.[15] Under these conditions, ionization of the phenol persisted as the major pathway. Utilizing tri(tolyl)-phosphine as ligand (20% $Pd(OAc)_2$, 40% $(otol)_3P$ or 20% of the preformed palladacycle[17]) suppressed the ionization reaction;

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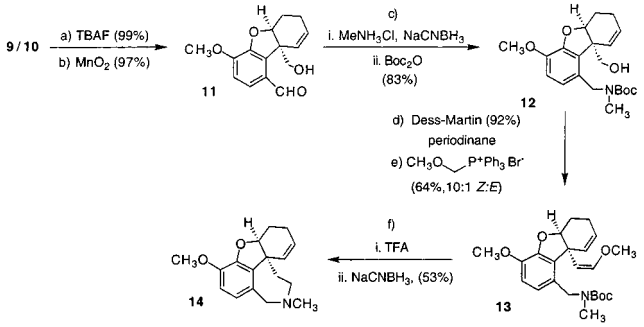
Scheme 2. Formation of Azepine Ring



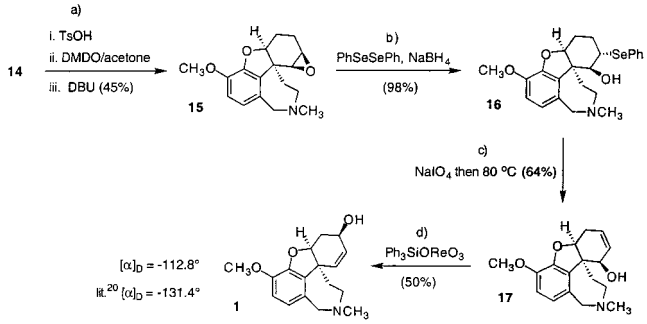
(a) THF, rt. (b) CH_3COCH_3, rt. (c) CH_3OH, reflux then CH_2Cl_2, $(C_2H_5)_3N$, rt. (d) $NaHCO_3$, CH_2Cl_2, rt. (e) $NaN(TMS)_2$, THF, 0°. (f) CH_2Cl_2, rt then CH_3OH, 4 Å MS, 0°.

however, tetrahydrobenzofuran **9** was isolated as a mixture of olefin isomers. On the other hand, use of 20% palladium acetate with bidentate ligands (18% dppb, dppe, dppf, or BINAP) prevented the olefin isomerization, but once again, phenol ionization dominated.

These results led us to the hypothesis that a sterically demanding bidentate phosphine ligand would suppress both the olefin isomerization reaction and the phenol ionization reaction. We thus turned our attention to bidentate alkylphosphine ligands.[18] 1,2-bis(Dicylohexylphosphino)ethane (dcpe) proved to be an excellent ligand for the intramolecular Heck reaction, affording benzofuran **9** in 50% yield along with 19% of the monodeprotected product **10** without detectable amounts of ionization (total yield of 69%). This selectivity may derive from a combination of factors. First, alkylphosphines are more electron-rich than their aryl counterparts, which has been shown to increase the rate of oxidative addition of palladium(0) to aryl halides.[19] Electron-rich ligands may also decrease the rate of coordination of palladium(0) to the trisubstituted olefin of **8** required for phenol ionization. Second, the steric hindrance of the dicyclohexylphosphine ligands is significantly greater than that of the corresponding diarylphosphine ligands. This factor may further decrease the rate of coordination of a trisubstituted olefin. This combination of electronic and steric factors present in the dicyclohexylphosphine ligands is presumably responsible for the sharp increase in the rate of the Heck reaction relative to the ionization.

The hydrobenzazepine ring of galanthamine was prepared in a six-step sequence (see Scheme 2). The TBAF deprotection of the mixture of **9** and **10** followed by chemoselective manganese dioxide oxidation of the resulting diol afforded aldehyde **11**. Reductive amination of aldehyde **11** was accomplished by formation of the imine with methylamine followed by reduction with sodium cyanoborohydride. The resulting secondary amine was protected without isolation to supply *tert*-butyl carbamate **12** in 83% yield. Dess−Martin oxidation of the amino alcohol **12** gave the amino aldehyde in 93% yield. The necessary one-carbon homologation was achieved by a Wittig olefination of the aldehyde with the ylide derived from methoxymethyltriphenylphosphonium bromide and NaHMDS producing **13** in 64% yield as a 10:1 mixture of olefin isomers. Concomitant deblocking of the secondary amine and hydrolysis of the methoxyvinyl group gave a seven-membered ring hemiaminal which was not isolated

Scheme 3. Adjustment of Oxidation Level



(a) CH_2Cl_2, rt. (b) C_2H_5OH, 80°. (c) THF, H_2O, rt then $CHCl_3$. (d) TsOH, PhH, 60°.

but immediately treated with sodium cyanoborohydride to afford (−)-3-deoxygalanthamine (**14**) in 53% overall yield.

Attempts to convert **14** to (−)-galanthamine (**1**) by direct allylic oxidation (SeO_2 or *tert*-butylperbenzoate, CuBr) were not successful. Therefore, we resorted to a four-step protocol to introduce the C3 hydroxyl group (see Scheme 3). Reaction of the tosylammonium salt of tertiary amine **14** with dimethyldioxirane[20] afforded a mixture of epoxide **15** and the corresponding α-hydroxy tosylate. Treatment of the crude mixture with DBU converted α-tosyl alcohol to epoxide **15** which was isolated in 45% from **14**. An nOe between the hydrogen on C-1 and one of the benzylic hydrogens (i.e., on C-9) established the stereochemistry as depicted in **15**. Regioselective opening of epoxide **15** with sodium phenylselenide produced α-hydroxy selenide **16** in 98% yield. Chemoselective oxidation of selenide **16** was readily achieved by treatment with sodium periodate to produce a 1:1 mixture of diastereomeric selenoxides. These selenoxides did not eliminate at room temperature but required heating (70 °C) to effect the desired conversion into (−)-isogalanthamine (**17**). Reaction of **17** with Osborn's rhenium(VII) catalyst[21] produced (−)-galanthamine ($[\alpha]_D = -112.8°$ ($c = 0.5$, EtOH), lit.[22] $[\alpha]_D = -131.4°$ ($c = 0.6$, EtOH)) with spectral characteristics identical to those of a sample of the natural product.

The asymmetric synthesis disclosed herein is the first total synthesis which does not utilize an oxidative phenol coupling to construct the quaternary center of (−)-galanthamine (**1**). Notably, aside from resolution, the sequential palladium-catalyzed AAA and intramolecular Heck reaction provides the only entry into the natural enantiomer of the (−)-galanthamine-type alkaloids. This strategy should allow for entry into a variety of clinically important natural and unnatural galanthamine-type *Amaryllidaceae* alkaloids.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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