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Total Synthesis of (±)-Galanthamine via a C3-Selective Stille Coupling and IMDA Cycloaddition Cascade of 3,5-Dibromo-2-pyrone

Jay Hyok Chang, Ho-Ung Kang, In-Hak Jung, and Cheon-Gyu Cho*

Department of Chemistry, Hanyang University, Seoul 133-791, Korea

ccho@hanyang.ac.kr

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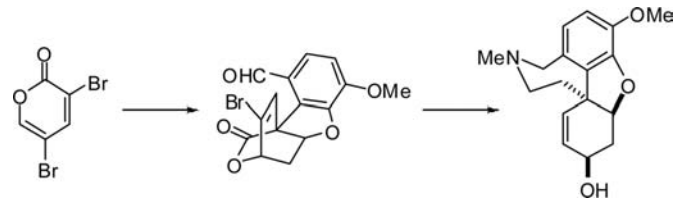
ABSTRACT



A new efficient synthetic route to (±)-galanthamine was devised by using a tandem C3-selective Stille coupling−IMDA cascade of 3,5-dibromo-2-pyrone as a key strategy.

Galanthamine (**1**, Figure 1), an alkaloid isolated from various plant sources including the bulbs and flowers of the Caucasian snowdrop (*Galanthus woronowii*), is a selective, competitive, and reversible inhibitor of acetylcholinesterase (Ache). It has also shown potent activity in allosteric modulation of the neural nicotinic receptors to increase acetylcholine release.[1] Being marketed as a hydrobromide salt under several brand names, galanthamine is a commercially available prescription drug for the symptomatic treatment of senile dementia of Alzheimer's disease (AD) patients.[2] The inefficiency in its isolation from natural sources has led to the development of effective synthetic methods and strategies, mainly based on biomimetic oxidative phenol coupling or an intramolecular Heck reaction.[3]

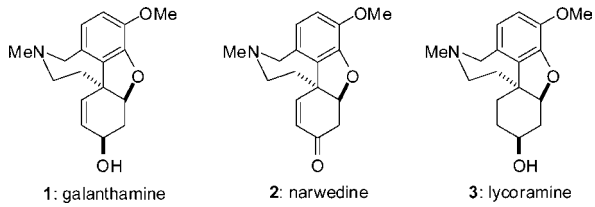


Figure 1. Galanthamine and its related congenors.

As part of our current study concerning the synthetic utility of 3,5-dibromo-2-pyrone in target-oriented synthesis,[4] we have envisaged that the tricyclic core of galanthamine with all required functional elements including the characteristic quaternary benzylic carbon could be readily forged from **6**-*endo*, the IMDA cycloaddition product of **7**. The IMDA precursor **7** is in turn attainable from the C3-selective Stille coupling reaction of 2-pyrone **8** with the corresponding aryl stannane **9** (Scheme 1).[5] In forward direction, ester **5**, the lactone ring-opening product of IMDA product **6**-*endo*, needs to be homologated by one carbon to provide the key intermediate **4**. Connection of two terminal groups, amine and aldehyde, would assemble the benzoazepin ring system. Inversion of the stereochemistry of the secondary hydroxyl group and the removal of the vinyl bromide would then complete the total synthesis of (±)-galanthamine.

Our synthetic study began with the preparation of aryltin **9** (Scheme 2). Installation of a vinyl ether group on commercial phenol **10** was made by employing the Cu(II)-promoted vinylation process reported by Blouin and co-

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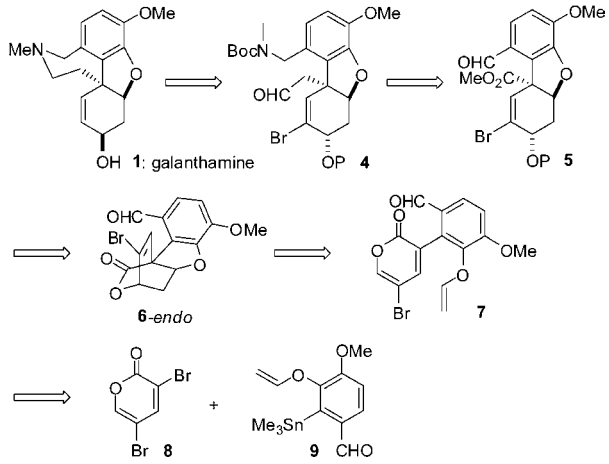
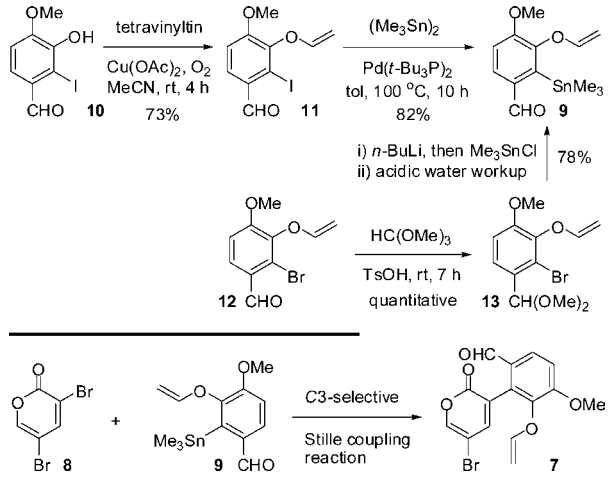
Scheme 1. Retrosynthesis of (±)-Galanthamine



workers,[6] which provided aryl vinyl ether **11** in 73% yield. Despite the potential interference of the neighboring vinyl ether function, the Pd-catalyzed stannylation[7] of iodide **11** proceeded surprisingly well to afford aryltin **9** in 82% yield. Alternatively, aryltin **9** could be made with a two-step sequence composed of the aldehyde protection and lithiation−stannylation−workup process in a more economical way. The easy access to aryltin **9** allowed the C3-selective Stille coupling reaction with 3,5-dibromo-2-pyrone toward the synthesis of the IMDA precursor **7**.

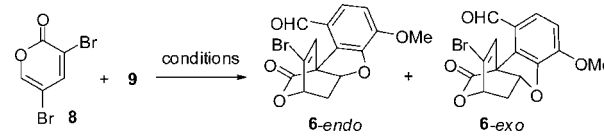
Scheme 2. Preparation of Aryltin **9** and Coupling Reaction with **8**



The actual coupling reaction afforded not the expected 2-pyrone **7**, but tetracyclolactones **6**-*endo* and **6**-*exo*, resulting from the intramolecular Diels−Alder reaction of the initially formed coupling product **7** (Table 1).[8]

Table 1. Tandem Stille/IMDA Cascade

a



entry	catalyst	additive	conditions	yield (ratio)
1	$Pd(PPh_3)_4$	none	toluene, 100 °C, 20 h	trace
2	$Pd(PPh_3)_4$	CuI	toluene, 90 °C, 6 h	10% (2:1)
3	$Pd(PPh_3)_4$	CuBr	toluene, 80 °C, 10 h	15% (2:1)
4	$Pd(PPh_3)_4$	CuI	DMF, 90 °C, 16 h	35% (2.5:1)
5	$Pd(PPh_3)_4$	CuI[b]	DMF, 90 °C, 12 h	26% (2.5:1)
6	**$Pd(PPh_3)_4$**	**CuI**	**DMF, 95 °C, 11 h**	**45% (2.5:1)**
7	$Pd(PPh_3)_4$	CuI	DMF, 110 °C, 12 h	12% (1:4)
8	$Pd(PPh_3)_4$	none	DMF, 95 °C, 12 h	trace
9	$Pd(t\text{-}Bu_3P)_2$	CuI	DMF, 80 °C, 8 h	trace

[a] 5 mol % catalyst and 10 mol % additive. [b] 20 mol %.

A thorough screening of reaction conditions indicated that this tandem Stille/IMDA cascade is quite sensitive to solvent, temperature, and cocatalyst, but not much on Pd catalyst. Shown in Table 1 is a partial list of our work. The best results were obtained when the reaction was performed with 5 mol % of $Pd(PPh_3)_4$ and 10 mol % of CuI in DMF at 95 °C (entry 6).[9] DMF proved to be a better solvent than toluene. The reactions without CuI provided only a trace of the IMDA products regardless of the solvent type (entries 1 and 8). It also turned out that **6**-*endo* is thermally more labile than **6**-*exo*, which accounts for the diminished product yield of the reaction conducted at elevated temperature (110 °C, entry

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(9) There is a peculiar temperature effect in the regiochemical outcome. A detailed account will be followed in due course.

7). The reaction at lower temperature also gave lower product yield due to the increased formation of byproducts (entry 4).

The stereochemistry of **6**-*endo* and **6**-*exo* was determined primarily by comparing the ^{1}H NMR chemical shifts and coupling constants of the C_5 and C_6 protons of the isolated **6**-*endo* and **6**-*exo* products (Figure 2). The H_{6a} of **6**-*endo*

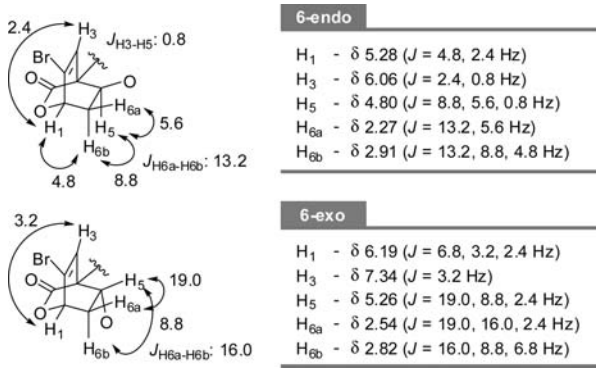
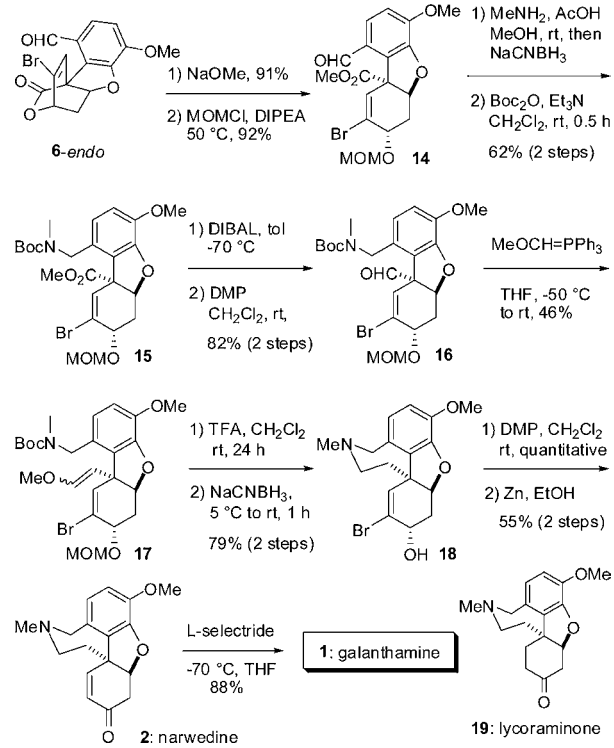


Figure 2. ^{1}H NMR assignment of **6**-*endo* and **6**-*exo*.

appears at higher field than the H_{6a} of **6**-*exo* (2.27 vs 2.54 ppm) because of the anisotropic effect of the bridgehead aromatic ring, generally observed in the series of similar bicyclolactones.[10]

Lactone ring opening of **6**-*endo* with NaOMe and protection of the resultant secondary hydroxyl group as a MOM ether furnished ester **14** in 84% yield over two steps. From this point, we adapted the procedures elaborated by Trost and co-workers for their synthesis of galanthamine,[3d] based on the structural similarity with their tricyclic intermediate. Nevertheless, an intensive optimization process was required for the transformation of tricyclic ester **14** to the final target in an acceptable total yield (see Supporting Information for the details). The reductive amination reaction of aldehyde **14** under the modified reaction conditions gave the corresponding secondary amine which was masked with the Boc group in 62% total yield over two steps (Scheme 3).[11] DIBAL reduction followed by oxidation provided aldehyde **16a**. Subsequent Wittig olefination with methoxymethyl phosphorus ylide furnished enol ether **17** as a mixture of *E*/*Z* isomers in reasonable yield (46%). The acid-promoted hydrolysis of the sterically hindered vinyl ether to aldehyde became more tricky, due to the presence of the MOM ether group. We found that the hydrolysis was best when reacted with TFA at rt, which accompanied deblocking of both *N*-Boc and MOM groups. Reduction of the resultant cyclic hemiaminal with $NaCNBH_3$ furnished tetracycle **18** in 79% total yield from **17**. Dess−Martin oxidation followed by Zn-

Scheme 3. Synthesis of (±)-Galanthamine



mediated debromination gave (±)-narwedine **2** and the over-reduction product (±)-lycoraminone **19** in 55% and 20% yield, respectively, from **18**.[12] Finally, the L-selectride reduction of the ketone furnished (±)-galanthamine **1** in 87% yield.[13] The hydride was delivered exclusively to the α-face of the ketone **2** as the *β*-face is blocked by the flanking benzofuran subunit.

In summary, we have devised a new synthetic route to (±)-galanthamine from 3,5-dibromo-2-pyrone by using a C3-selective Stille coupling/IMDA cascade as a key strategy. Our novel strategy would be a valuable addition to the current galanthamine synthesis predominated by the approaches involving either oxidative phenol coupling or an intramolecular Heck reaction.

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Supporting Information Available: Details of experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Submission of **14** to the literature conditions using methylamine hydrochloride in MeOH resulted in the formation of aromatic dimethyl acetal. Use of $MeNH_2$ dissolved in anhydrous MeOH was required to avoid the problematic acetal formation in our case.

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