

Total Synthesis of (–)-Galanthamine and (–)-Lycoramine via Catalytic Asymmetric Hydrogenation and Intramolecular Reductive Heck Cyclization

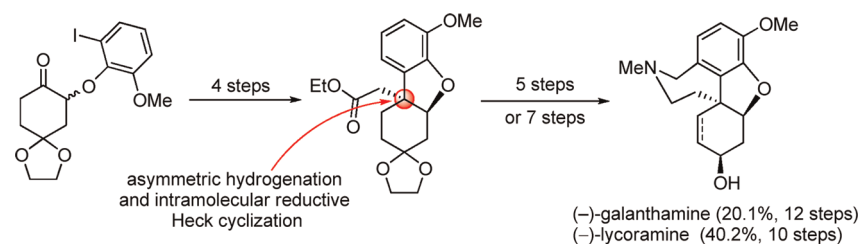
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ABSTRACT



A synthetic strategy featuring efficient ruthenium-catalyzed asymmetric hydrogenation of racemic α -aryloxy cyclic ketone via dynamic kinetic resolution and palladium-catalyzed intramolecular reductive Heck cyclization has been developed for the asymmetric total synthesis of (–)-galanthamine (20.1%, 12 steps) and (–)-lycoramine (40.2%, 10 steps)

The galanthamine-type alkaloids including (–)-galanthamine (**1**) and (–)-lycoramine (**2**) (Figure 1), isolated from the bulbs of different species of the Amaryllidaceae family, have attracted much attention of synthetic chemists because of their intriguing structures and potent biological activities.¹ (–)-Galanthamine (**1**) is a selective, reversible, and competitive acetylcholinesterase inhibitor and has been used in the early treatment of Alzheimer's disease.² (–)-Lycoramine (**2**) has a similar, albeit less potent, activity as an acetylcholinesterase inhibitor and an allosteric potentiating ligand.³ Because of the limited supplies of these alkaloids from natural sources, a number of synthetic strategies have been developed for the syntheses of galanthamine and its analogues since Barton and Kirby initiatively reported the total synthesis of galanthamine

in the early 1960s.⁴ However, most of the reported synthetic strategies provided the alkaloids in racemic form.⁵

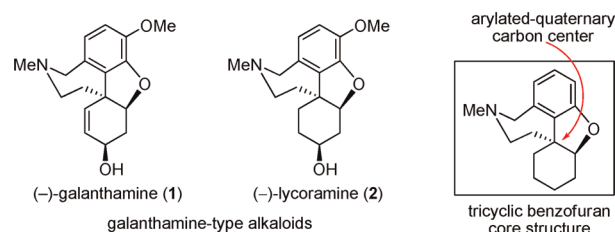


Figure 1. Representative galanthamine-type alkaloids and their core structure.

(1) Cordell, G. A., Ed. *The Alkaloids: Chemistry and Biology*; Amsterdam; Elsevier 2010 Vol. 68,.

(2) Sramek, J. J.; Frackiewicz, J. E.; Cutler, N. R. *Expert Opin. Invest. Drugs* **2000**, 9, 2393.

(3) Han, S.; Sweeney, J. E.; Bachman, E. S.; Schweiger, E. J.; Forloni, G.; Coye, J. T.; Davis, B. M.; Joullie, M. M. *Eur. J. Med. Chem.* **1992**, 27, 673.

(4) (a) Barton, D. H. R.; Kirby, G. W. *J. Chem. Soc.* **1962**, 806. (b) Barton, D. H. R.; Kirby, G. W.; Taylor, J. B. *J. Chem. Soc.* **1962**, 4545.

(5) For recent reviews on the synthesis of galanthamine and its analogues, see: (a) Marco-Contelles, J.; do Carmo Carreiras, M.; Rodríguez, C.; Villarroja, M.; García, A. G. *Chem. Rev.* **2006**, 106, 116. (b) Marco-Contelles, J.; Perez-Mayoral, E.; van Nhien, A. N.; Postel, D. *Targets Heterocycl. Syst.* **2007**, 11, 365. (c) Zhong, J. *Nat. Prod. Rep.* **2009**, 26, 363. (d) Fang, L.; Gou, S.; Zhang, Y. *Chin. J. Org. Chem.* **2011**, 31, 286.

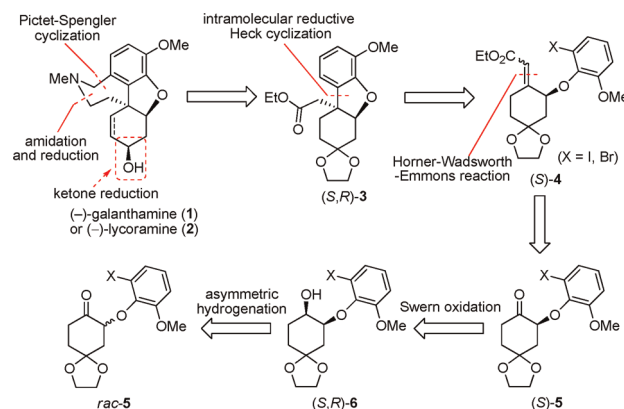
Galanthamine-type alkaloids feature a unique tricyclic benzofuran core structure with a chiral arylated-quaternary carbon center, and the enantioselective construction of this sterically congested quaternary carbon center is a major challenge in the synthesis of these alkaloids. Thus, a number of strategies have been developed to construct the chiral arylated-quaternary carbon center for the synthesis of galanthamine-type alkaloids by means of phenolic oxidative coupling,⁶ intramolecular Heck reaction,⁷ Claisen rearrangement,⁸ Brich–Cope sequence,⁹ phenolic oxidative coupling and crystallization-induced chiral conversion,¹⁰ and organocatalyzed Michael addition.¹¹ However, although being one of the most promising methods for the synthesis of chiral compounds, the asymmetric catalysis has been rarely used for the enantioselective synthesis of galanthamine-type alkaloids, and the reported catalytic asymmetric syntheses of (–)-galanthamine (**1**) and (–)-lycoramine (**2**) were not very efficient.^{7,11}

During the study on the catalytic asymmetric synthesis of chiral natural products, we found that the intramolecular reductive Heck reaction is a convenient access to the construction of tricyclic dihydrobenzofuran ring with a quaternary stereocenter.¹² This intramolecular reductive Heck reaction combining with the asymmetric hydrogenation of α -aryloxy cyclic ketone via a dynamic kinetic resolution (DKR), recently developed in our laboratory,¹³ provides a highly efficient strategy for the enantioselective synthesis of (–)-galanthamine (**1**, 20.1%, 12 steps) and (–)-lycoramine (**2**, 40.2%, 10 steps).

Our strategy is outlined in Scheme 1. We expected that the target molecules **1** and **2** could be synthesized from ester (*S,R*)-**3** via formation of the seven-membered aza ring through several steps including amidation and Pictet–Spengler cyclization. The ester (*S,R*)-**3** could be obtained

from α,β -unsaturated ester (*S*)-**4** containing an α -halogenated phenoxyl group via an intramolecular reductive Heck cyclization. The α,β -unsaturated ester (*S*)-**4** could be easily prepared from α -aryloxy cyclohexanone (*S*)-**5** via a Horner–Wadsworth–Emmons reaction, and the optically pure (*S*)-**5** could be obtained by ruthenium-catalyzed asymmetric hydrogenation of *rac*-**5** via DKR¹³ followed by a Swern oxidation.

Scheme 1. Synthetic Strategy for (–)-Galanthamine (**1**) and (–)-Lycoramine (**2**)



Since Larock¹⁴ and Trost^{7a,c} had reported that the intramolecular Heck reaction of aryl allyl ethers often suffers from a competitive palladium-catalyzed ionization of the aryloxy group, producing a phenol, the prevention of this unwanted side reaction inevitably became one of the

(6) (a) Tomioka, K.; Shimizu, K.; Yamada, S.; Koga, K. *Heterocycles* **1977**, *6*, 1752. (b) Shimizu, K.; Tomioka, K.; Yamada, S.; Koga, K. *Heterocycles* **1977**, *8*, 277. (c) Kodama, S.; Hamashima, Y.; Nishide, K.; Node, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2659. (d) Node, M.; Kodama, S.; Hamashima, Y.; Katoh, T.; Nishide, K.; Kajimoto, T. *Chem. Pharm. Bull.* **2006**, *54*, 1662.

(7) (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 11262. (b) Trost, B. M.; Tang, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2759. (c) Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785. Catalytic asymmetric synthesis of (–)-galanthamine (10 steps, 8% overall yield).

(8) (a) Tanimoto, H.; Kato, T.; Chida, N. *Tetrahedron Lett.* **2007**, *48*, 6267. (b) Kato, T.; Tanimoto, H.; Yamada, H.; Chida, N. *Heterocycles* **2010**, *82*, 563.

(9) Malachowski, W. P.; Paul, T.; Phounsavath, S. *J. Org. Chem.* **2007**, *72*, 6792.

(10) Magnus, P.; Sane, N.; Fauber, B. P.; Lynch, V. *J. Am. Chem. Soc.* **2009**, *131*, 16045.

(11) Chen, P.; Bao, X.; Zhang, L.-F.; Ding, M.; Han, X.-J.; Li, J.; Zhang, G.-B.; Tu, Y.-Q.; Fan, C.-A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8186. Catalytic asymmetric synthesis of (–)-galanthamine (16 steps, 2.8% overall yield) and (–)-lycoramine (14 steps, 8.1% overall yield).

(12) Reviews for reductive Heck reaction, see: (a) Oestreich, M., Ed. *The Mizoroki–Heck Reaction*; Wiley: Chichester, 2009. (b) Link, J. T.; Overman, L. E. *Metal-catalyzed Cross Coupling Reaction*; Diederick, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998, Chapter 6. (c) Tsuji, J. *Palladium Reagent and Catalysts. Innovation in Organic Synthesis*; John Wiley: New York, 1995. Selected papers for intramolecular reductive Heck reaction for the construction of dihydrobenzofuran ring: (d) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 13155. (e) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2002**, *124*, 11616.

(13) Bai, W.-J.; Xie, J.-H.; Li, Y.-L.; Liu, S.; Zhou, Q.-L. *Adv. Synth. Catal.* **2010**, *352*, 81.

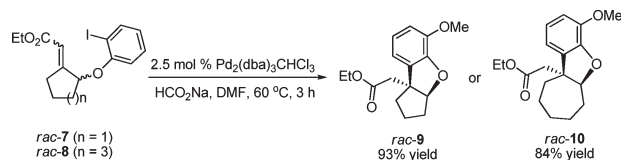
Table 1. Palladium-Catalyzed Cyclization of *rac*-**4** to *rac*-**3**^a

entry	X	[Pd]	reductive reagent (equiv)	temp (°C)	time (h)	yield ^b (%)
1	Br	Pd(OAc) ₂	HCO ₂ H (2.0)/Et ₃ N (2.5)	80	10	20
2	Br	Pd(OAc) ₂	HCO ₂ H (2.0)/Et ₃ N (2.5)	100	10	40
3	Br	Pd(OAc) ₂	HCO ₂ H (2.0)/Et ₃ N (2.5)	120	10	32
4	Br	Pd(OAc) ₂	HCO ₂ Na (2.0)	100	10	43
5	Br	Pd ₂ (dba) ₃ · CHCl ₃	HCO ₂ Na (2.0)	80	3	49
6 ^c	I	Pd ₂ (dba) ₃ · CHCl ₃	HCO ₂ Na (2.0)	60	3	95

^a Reaction conditions: 10 mmol of *rac*-**4**, 5 mol % of Pd catalyst, 10 mol % of PPh₃, DMF as solvent. ^b Isolated yield. ^c Without PPh₃.

major challenges of our synthetic strategy. We first evaluate the intramolecular reductive Heck cyclization of *rac-4a* (X = Br), which was prepared in good yield (67%, two steps) from 2-bromo-6-methoxyphenol and 7-bromo-1,4-dioxaspiro[4.5]decan-8-one¹⁵ (see the Supporting Information). When the reaction was performed in the presence of 5 mol % of Pd(OAc)₂, 10 mol % of PPh₃, 2.0 equiv of HCO₂H, and 2.5 equiv of Et₃N at 80 °C in DMF for 10 h, *rac-4a* was cyclized to *rac-3* in 20% yield accompanied by a significant amount of ionization product, 2-bromo-6-methoxyphenol (Table 1, entry 1). Increasing the reaction temperature led to a higher yield of *rac-3*, but still lower than 40% (entries 2 and 3). Use of HCO₂Na (2 equiv), instead of HCO₂H/Et₃N, as a reductive reagent resulted in a slight improvement of yield to 49% (entry 5). Fortunately, when the iodinated α,β -unsaturated ester *rac-4b* (X = I) was subjected to the reaction the ionization of aryloxy group was strongly suppressed and the desired reductive Heck cyclization product *rac-3* was obtained in 95% yield under milder conditions (60 °C, 3 h) (entry 6).¹⁶ This palladium-catalyzed intramolecular reductive Heck

Scheme 2. Palladium-Catalyzed Cyclization of *rac-7* and *rac-8*

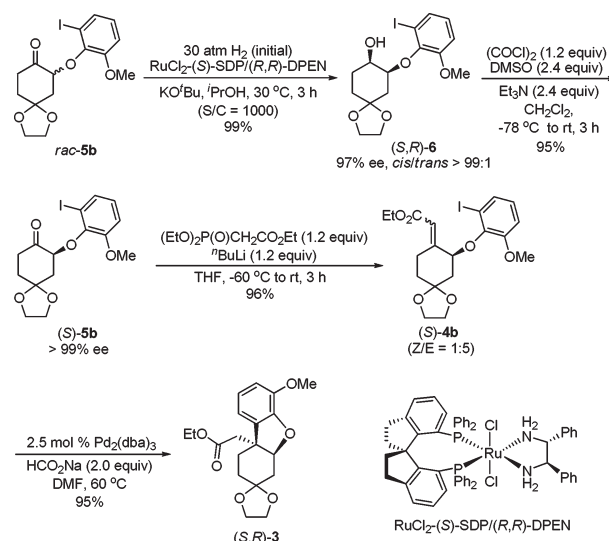


cyclization is also highly efficient for the cyclization of *rac-7* and *rac-8*, the analogues of *rac-4* derived from α -(2-iodophenoxy)cycloalkanones with five or seven-membered ring to the corresponding benzofurans *rac-9* (93%) and *rac-10* (84%) in high yields (Scheme 2).

Naturally, after the establishment of a highly efficient intramolecular reductive Heck cyclization to create the tricyclic benzofuran core structure of galanthamine-type alkaloids, we then tried the synthesis of (*S,R*)-**3** in optically pure form. To address this topic, the enantioselective synthesis of the optically pure α -aryloxy cyclohexanone (*S*)-**5b** is the key. Recently, we developed a highly efficient ruthenium-catalyzed asymmetric hydrogenation of racemic α -aryloxy cyclohexanones via DKR, producing chiral β -aryloxy cycloalkanols in excellent enantioselectivity.¹³ This provides an method for us to try the synthesis of the optically pure α -aryloxy cyclohexanone (*S*)-**5b** with a bulky ethylene ketal group at the 4-position of the cyclohexane ring. By using chiral ruthenium catalyst

RuCl₂-(*S*)-SDP/(*R,R*)-DPEN,¹⁷ *rac-5b* (obtained from the reaction of 2-iodo-6-methoxyphenol with 7-bromo-1,4-dioxaspiro[4.5]decan-8-one in 75% yield, see the Supporting Information) was hydrogenated to chiral β -aryloxy cyclohexanol (*S,R*)-**6** in high yield (99%) with excellent enantioselectivity (97% ee) and *cis*-selectivity (*cis/trans* > 99:1) (Scheme 3), indicating that the ethylene ketal group in the substrate has a negligible effect to the reaction. The β -aryloxy cyclohexanol (*S,R*)-**6** was then converted into α -aryloxy cyclohexanone (*S*)-**5b** in 95% yield without loss of its optical purity by Swern oxidation. Subsequently, a condensation of (*S*)-**5b** with ethyl 2-(dimethoxy-phosphoryl)

Scheme 3. Enantioselective Synthesis of (*S,R*)-**3** (DMSO = Dimethyl Sulfoxide)



acetate by a Horner-Wadsworth-Emmons reaction gave α,β -unsaturated esters (*S*)-**4b** in 96% yield with (*E*)-configuration as the major isomer (*Z/E* $\approx$ 1:5). The *Z,E*-mixture of (*S*)-**4b** was then submitted to the palladium-catalyzed intramolecular reductive Heck cyclization to give (*S,R*)-**3** in 95% yield.

With ester (*S,R*)-**3** in hand, we then focused our attention on its conversion into (–)-galanthamine (**1**) and (–)-lycoramine (**2**). As shown in Scheme 4, the ester (*S,R*)-**3** was hydrolyzed with sodium hydroxide in methanol/H₂O, followed by activation with ethyl chloroformate (ClCO₂Et) in the presence of triethylamine at –15 °C and amidation with aqueous methylamine (MeNH₂) to offer amide (*S,R*)-**11** in 83% yield (2 steps). Subsequent Pictet-Spengler cyclization of (*S,R*)-**11** with paraformaldehyde furnished the tetracyclic intermediate (*S,R*)-**12** with a seven-membered azepine ring in 89% yield.¹⁸ The intermediate (*S,R*)-**12** was then subjected to a selective

(14) Larock, R. C.; Stinn, D. E. *Tetrahedron Lett.* **1988**, 29, 4687.

(15) Laukhtien, G.; Volk, F.-J.; Frahm, A.-W. *Tetrahedron: Asymmetry* **1997**, 8, 3457.

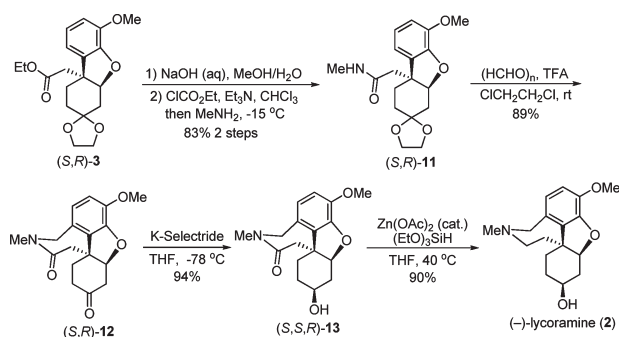
(16) Ester *rac-3* can also be synthesized in 65% yield by using radical cyclization (AIBN, *n*-Bu₃SnH, benzene, reflux, 3 h). However, the use of toxic metal tin compound made the radical cyclization less applicable. Selected papers for radical cyclization: (a) Parker, K. A.; Fokas, D. *J. Org. Chem.* **2006**, 71, 449. (b) Parker, K. A.; Kim, H.-J. *J. Org. Chem.* **1992**, 57, 752.

(17) (a) Xie, J.-H.; Wang, L.-X.; Zhu, S.-F.; Fu, Y.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2003**, 125, 4404. (b) Xie, J.-H.; Liu, S.; Huo, X.-H.; Cheng, X.; Duan, H.-F.; Fan, B.-M.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* **2005**, 70, 2967.

(18) Guillou, C.; Beunard, J.-L.; Gras, E.; Thal, C. *Angew. Chem., Int. Ed.* **2001**, 40, 4745.

reduction of the ketone group to the hydroxyl using K-Selectride and a further reduction of the amide motif to amine with triethoxysilane ((EtO)₃SiH) in the presence of Zn(OAc)₂ as a catalyst¹⁹ to give (–)-lycoramine (2) in 84.6% yield (2 steps).²⁰ The NMR spectroscopic data and the optical rotation ([α]_D²⁰ = –102 (c 0.35, EtOH), lit. [α]_D²⁰ = –100 (c 0.35, EtOH),⁹ [α]_D²⁰ = –92.7 (c 0.35, EtOH)¹¹) of our synthetic (–)-lycoramine are identical to those reported in the previous synthesis. Thus, enantioselective synthesis of (–)-lycoramine was achieved in 40.2% overall yield over 10 steps from the commercially available 2-iodo-6-methoxyphenol via a ruthenium-catalyzed asymmetric hydrogenation and a palladium-catalyzed intra-molecular reductive Heck cyclization as the key steps.

Scheme 4. Enantioselective Synthesis of (–)-Lycoramine (2) (K-Selectride = Potassium Tri-*sec*-butyl Borohydride)



The enantioselective synthesis of (–)-galanthamine (1) is outlined in Scheme 5. Using the procedure of Saegusa–Ito oxidation,²¹ the tetracyclic intermediate (S,R)-12 was treated with TBSOTf, followed by palladium-mediated oxidation to provide the desired enone (S,S)-14 in 51% yield (two steps).²² The (S,S)-14 was then reduced sequentially with K-Selectride and (EtO)₃SiH/Zn(OAc)₂ to yield (–)-galanthamine (1) in 83% yield. The data of NMR spectroscopy and optical rotation of our synthetic (–)-galanthamine (1) are identical to those reported in the literature ([α]_D²⁰ = –119.5 (c 0.30, EtOH), lit.^{6c} [α]_D²⁰ = –121.7 (c 0.30, EtOH)). The enantioselective

(19) Das, S.; Addis, D.; Zhou, S.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 1770.

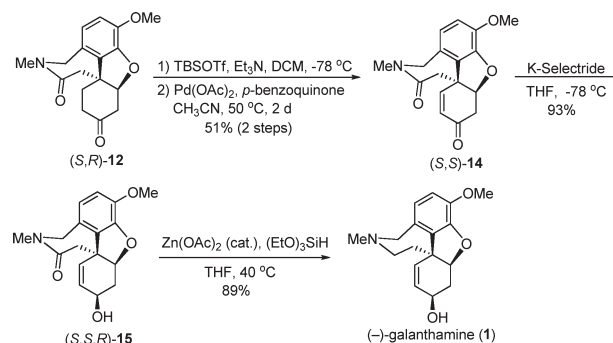
(20) The reduction of the amide group of (S,S,R)-9 with LiAlH₄ gave 2 in 81% yield.

(21) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(22) For improving the transformation of (S,R)-12 to (S,S)-14 other methods, such as DDQ oxidation of silyl enol ester, treatment with PhSeCl and oxidation with H₂O₂, and bromination followed with elimination of HBr, have also been tried; however, the desired product was obtained in very low yields.

synthesis of (–)-galanthamine (1) was thus accomplished in 12 steps with 20.1% overall yield.

Scheme 5. Enantioselective Synthesis of (–)-Galanthamine (1) (TBSOTf = *tert*-Butyldimethylsilyl Trifluoromethanesulfonate)



In conclusion, we have developed highly efficient enantioselective syntheses of (–)-galanthamine (1) and (–)-lycoramine (2) based on a ruthenium-catalyzed asymmetric hydrogenation and a palladium-catalyzed intramolecular reductive Heck cyclization as the key steps. The (–)-galanthamine (1) was synthesized in twelve steps with 20.1% overall yield and the (–)-lycoramine (2) was synthesized in ten steps with 40.2% overall yield from commercially available starting materials. These high yielding syntheses of (–)-galanthamine and (–)-lycoramine have good reproducibility. These results demonstrated that this catalytic enantioselective synthetic strategy is efficient for the asymmetric construction of the polycyclic benzofuran ring systems bearing an all-carbon quaternary center and has high potential for application to the syntheses of other galanthamine-type, morphine-type, and lunarine-type biologically significant alkaloids.

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Supporting Information Available. Experimental procedures, characterization data for the products, and HPLC spectra for (S)-5b and (S,R)-6. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.