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

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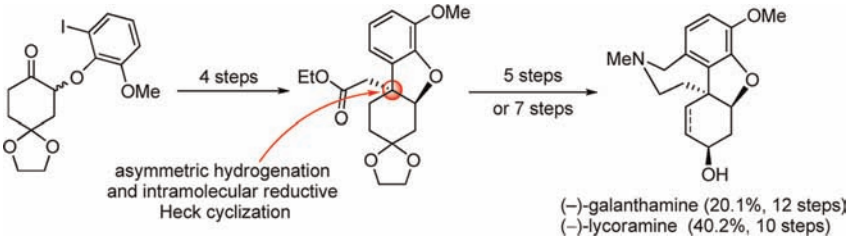
ABSTRACT



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]

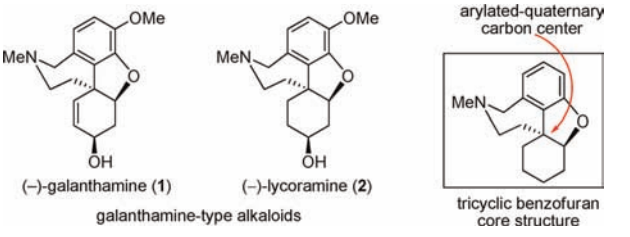


Figure 1. Representative galanthamine-type alkaloids and their core structure.

(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. Investig. 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.; Villarroya, 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.

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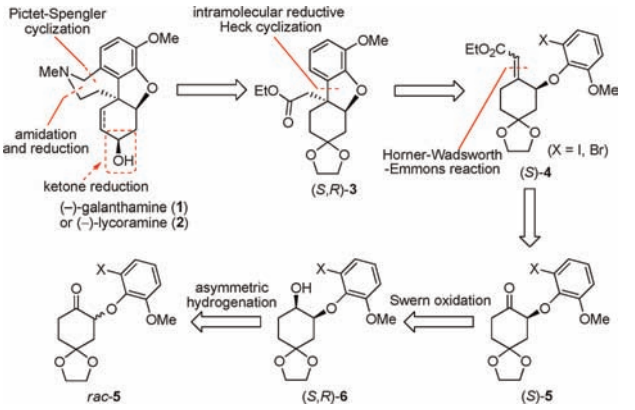
Galanthamine-type alkaloids feature a unique tricyclic benzofuran core structure with a chiral arylated-quaternary carbon center, and the enantioselective construction of this sterically congested quaternary carbon center is a major challenge in the synthesis of these alkaloids. Thus, a number of strategies 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 enentioselective 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).

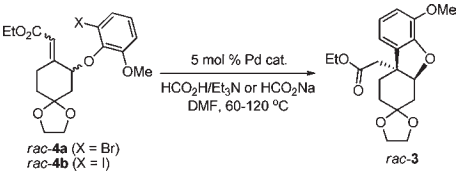
Our strategy is outlined in Scheme 1. We expected that the target molecules **1** and **2** could be synthesized from ester (*S*,*R*)-**3** via formation of the seven-membered aza ring through several steps including amidation and Pictet-Spengler cyclization. The ester (*S*,*R*)-**3** could be obtained 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 DKR[13] followed by a Swern oxidation.

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



Since Larock[14] 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

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_2H (2.0)/ Et_3N (2.5)	80	10	20
2	Br	$Pd(OAc)_2$	HCO_2H (2.0)/ Et_3N (2.5)	100	10	40
3	Br	$Pd(OAc)_2$	HCO_2H (2.0)/ Et_3N (2.5)	120	10	32
4	Br	$Pd(OAc)_2$	HCO_2Na (2.0)	100	10	43
5	Br	$Pd_2(dba)_3 \cdot CHCl_3$	HCO_2Na (2.0)	80	3	49
6[c]	I	$Pd_2(dba)_3 \cdot CHCl_3$	HCO_2Na (2.0)	60	3	95

[a] Reaction conditions: 10 mmol of *rac*-**4**, 5 mol % of Pd catalyst, 10 mol % of PPh_3, DMF as solvent. [b] Isolated yield. [c] Without PPh_3.

(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.

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(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.

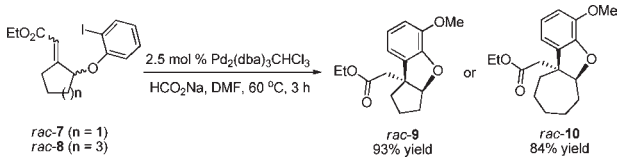
(11) Chen, P.; Bao, X.; Zhang, L.-F.; Ding, M.; Han, X.-J.; Li, J.; Zhang, G.-B.; Tu, Y.-Q.; Fan, C.-A. *Angew. Chem., Int. Ed.* **2011**, *50*, 8186. Catalytic asymmetric synthesis of (−)-galanthamine (16 steps, 2.8% overall yield) and (−)-lycoramine (14 steps, 8.1% overall yield).

(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.

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-one[15] (see the Supporting Information). When the reaction was performed in the presence of 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3, 2.0 equiv of HCO_2H, and 2.5 equiv of Et_3N 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 HCO_2Na (2 equiv), instead of HCO_2H/Et_3N, 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

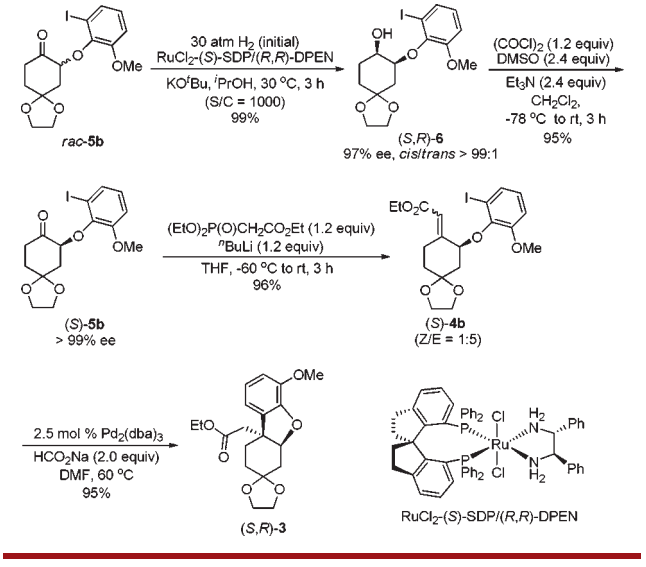
Scheme 2. Palladium-Catalyzed Cyclization of *rac*-**7** and *rac*-**8**



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 $RuCl_2$-(*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* ≈ 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/H_2O, followed by activation with ethyl chloroformate ($ClCO_2Et$) in the presence of triethylamine at −15 °C and amidation with aqueous methylamine ($MeNH_2$) 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) Lauktien, G.; Volk, F.-J.; Frahm, A.-W. *Tetrahedron: Asymmetry* **1997**, *8*, 3457.

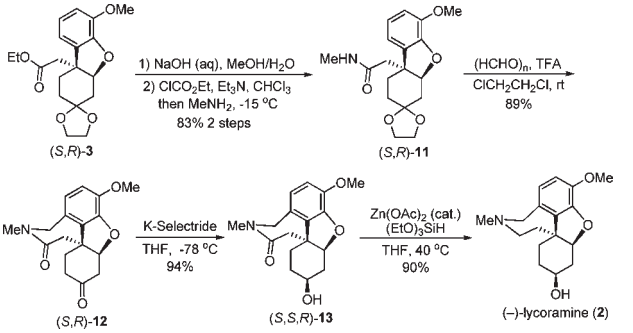
(16) Ester *rac*-**3** can also be synthesized in 65% yield by using radical cyclization (AIBN, *n*-Bu_3SnH, benezene, reflux, 3 h). However, the use of toxic metal tin compound made the radical cyclization less applicable. Selected papers for radical cyclization: (a) Parker, K. A.; Fokas, D. *J. Org. 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.

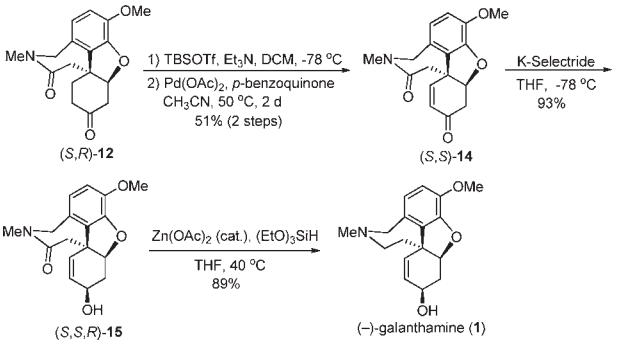
reduction of the ketone group to the hydroxyl using K-Selectride and a further reduction of the amide motif to amine with triethoxysilane ($(EtO)_3SiH$) in the presence of $Zn(OAc)_2$ as a catalyst[19] to give (−)-lycoramine (**2**) in 84.6% yield (2 steps).[20] The NMR spectroscopic data and the optical rotation ($[\alpha]_D^{20} = -102$ (*c* 0.35, EtOH), lit. $[\alpha]_D^{20} = -100$ (*c* 0.35, EtOH),[9] $[\alpha]_D^{20} = -92.7$ (*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 intramolecular 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 ($[\alpha]_D^{20} = -119.5$ (*c* 0.30, EtOH), lit.[6c] $[\alpha]_D^{20} = -121.7$ (*c* 0.30, EtOH)). The enantioselective 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.

(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 $LiAlH_4$ 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 H_2O_2, and bromination followed with elimination of HBr, have also been tried; however, the desired product was obtained in very low yields.