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Catalytic Asymmetric Allylation of 3,4-Dihydroisoquinolines and Its Application to the Synthesis of Isoquinoline Alkaloids

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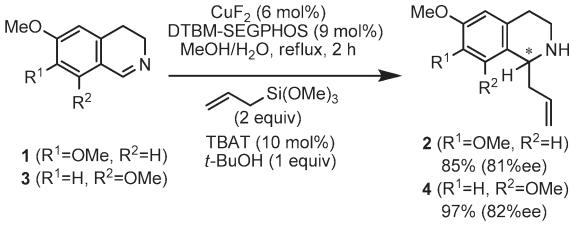
Received October 16, 2010



A catalytic asymmetric allylation of 3,4-dihydroisoquinoline was carried out with allyltrimethoxylsilane-Cu as the nucleophile in the presence of DTBM-SEGPHOS as the chiral ligand to afford corresponding chiral 1-allyltetrahydroisoquinoline derivatives in good yield and stereoselectivity. The allyl adduct thus obtained was applied to the synthesis of several isoquinoline alkaloids such as crispine A and homolaudanosine. The reaction was further used for the synthesis of the isoquinoline moiety of schulzeine A.

Introduction

A variety of isoquinoline alkaloids exist in nature, and have various biological activities.[1] A specific structural feature of many of these alkaloids is a chiral center at C-1 (based on isoquinoline numbering),[2] thus the construction of a chiral carbon at C-1 is a key step for the asymmetric total synthesis of these compounds. The Pictet−Spengler reaction[3] and Bischler−Napieralski reaction[4] are representative procedures for the synthesis of isoquinoline moieties. However, these methods require a stoichiometric amount of a chiral source to introduce the chirality at C-1.[5]

Recently, enantioselective syntheses of C-1 substituted tetrahydroisoquinoline have been developed. Chong et al. reported an allylation using a variety of cyclic imines, including 3,4-dihydroisoquinoline, to give the corresponding chiral C-1 allyl adducts with high enantioselectivity.[6] In this process, a stoichiometric amount of a chiral auxiliary was used. Although few methods allow the synthesis of chiral 1-substituted tetrahydroisoquinoline derivatives using catalysts, one of the best methods for asymmetric catalytic synthesis is the reduction of the imine in 3,4-dihydroisoquinoline using asymmetric Ru(II) catalyst, as reported by Noyori.[7] It is difficult, however, to apply this procedure to compounds which have a functional group sensitive to reduction. In part to address this limitation, Sodeoka et al. reported a Pd(II)-catalyzed addition reaction of malonate to dihydroisoquinoline to give 1-substituted tetrahydroisoquinoline derivatives in a highly stereoselective manner.[8]

(1) (a) Shamma, M. *Organic Chemistry, A series of Monographs*; Academic Press, Inc.: New York; Vol. 25 (b) Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903. (c) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341.

(2) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic Publishers: Amsterdam, The Netherlands, 1998.

(3) (a) Brossi, A.; Focella, A.; Teitel, S. *Helv. Chim. Acta* **1972**, *55*, 15. (b) Kawai, M.; Deng, Y.; Kimura, I.; Yamamura, H.; Araki, S.; Naoi, M. *Tetrahedron: Assymmetry* **1997**, *8*, 1487. (c) Gremmen, C.; Wanner, M.; Koomen, G.-J. *Tetrahedron Lett.* **2001**, *42*, 8885. (d) Pedrosa, R.; Andrês, C.; Iglesias, J. M. *J. Org. Chem.* **2001**, *66*, 243.

(4) (a) Polniaszek, R. P.; Kaufman, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 4859. (b) Czarnocki, Z.; Suh, D.; MacLean, D. B.; Hultin, P. G.; Szarek, W. A. *Can. J. Chem.* **1992**, *70*, 1555. (c) Miyatani, K.; Ohno, M.; Tatsunami, K.; Ohishi, Y.; Kunitomo, J.; Kawasaki, I.; Yamashita, M.; Ohta, S. *Heterocycles* **2001**, *55*, 589.

(5) Although several papers reported asymmetric catalytic Pictet−Spengler reactions, the substrate was limited to indole derivatives. See: Muratore, M. E.; Holloway. C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796 and references cited therein.

(6) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 9646.

(7) (a) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.

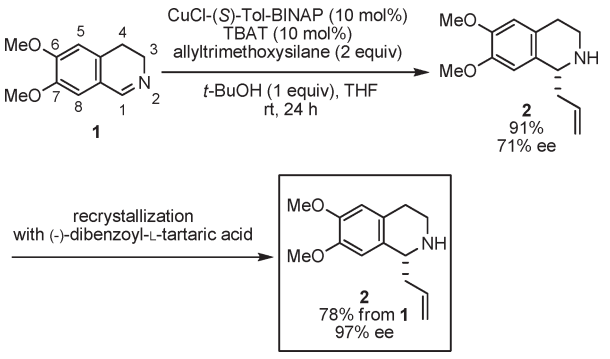
Published on Web 12/28/2010 DOI: 10.1021/jo101956m

The allyl group is versatile due to its ready modification to other functional groups.[9] Thus, we investigated an asymmetric allylation reaction at the C-1 position of the isoquinoline nucleus. Shibasaki et al. reported catalytic allylation of a carbonyl group using allyltrimethoxysilane, and in the presence of a chiral phosphine ligand, asymmetric induction was observed.[10] In a previous paper, we applied this reaction system to 6,7-dimethoxy-3,4-dihydroisoquinoline as a cyclic imine to obtain the corresponding C-1 allyl adduct with moderate stereoselectivity, and after recrystallization in the presence of dibenzoyltartaric acid, applied this adduct to the total synthesis of (−)-emetine.[11] To improve the stereoselectivity of the 1-allyl adduct, we studied other chiral ligands and found that DTBM-SEGPHOS gave better results. The resulting allyl adduct was used for the synthesis of several isoquinoline alkaloids described herein.

Results and Discussion

Asymmetric Allylation to the Cyclic Imine. We previously reported[11] that an asymmetric catalytic allylation of 6,7-dimethoxy-3,4-dihydroisoquinoline (**1**) proceeded in a stereoselective manner to afford 1-allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2**), using allyltrimethylsilane-Cu as the nucleophile in the presence of tol-BINAP as the chiral ligand (Scheme 1). After recrystallization of allyl adduct **2** with a chiral tartaric acid, compound **2** was obtained in 78% yield (97% ee) from **1**.

SCHEME 1



We next applied this reaction system to the synthesis of an isoquinoline moiety of schulzeine A, a natural product from the marine sponge *Penares schulzei* (Figure 1).[12] Schulzeine A is comprised of a tricyclic structure that includes a 6,8-dihydroxyisoquinoline nucleus and a C28 fatty acid side chain. To synthesize the tricyclic core in a stereoselective manner, the present reaction system was applied to 6,8-dimethoxy-3,4-dihydroisoquinoline, but the selectivity was found to be moderate (62% ee; Scheme 2 and Table 1, entry 6), and subsequent attempts to recrystallize **4** in the presence of a chiral acid were unsuccessful.

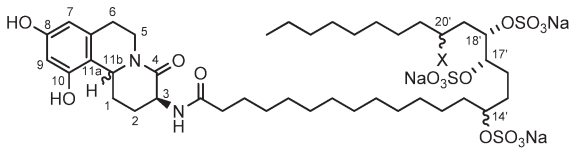
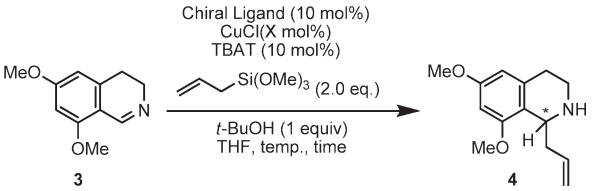


FIGURE 1

SCHEME 2



The results from using several other phosphine ligands for the catalytic allylation of **3** (Scheme 3) are summarized in Table 1. Higher reaction temperature improved the reaction yield without significantly decreasing stereoselectivity (Table 1, entries 5, 7 vs 6, 8), but the ee did not exceed 70%.[13] Thus, other systems for the addition reaction were studied. We found that the reaction conditions used by Shibasaki's group for asymmetric vinylation[14] were effective. This reaction system was applied to the allylation of compound **3** by using allyltrimethoxysilane instead of trimethoxyvinylsilane. The results are shown in Table 2.

First, a catalytic amount of a chiral phosphine ligand and CuF_2 in wet methanol was refluxed for 2 h. After removal of the solvent in vacuo, tetrabutylammonium triphenyldifluorosilicate (TBAT), allyltrimethoxysilane, and substrate **3** were added to the residue as THF solutions. In the case of Tol-BINAP, the allyl adduct was obtained in poor yield and with poor stereoselectivity (Table 2, entry 1). The use of SEGPHOS as a ligand improved both yield and selectivity. This result prompted us to use the more bulky DTBM-SEGPHOS as a ligand, and we observed that yield increased with increasing reaction temperature without loss of stereoselectivity. To minimize the amount of ligand required, the reaction was carried out at various ratios of ligand and CuF_2 (entries 7−12). At a phosphine ligand:metal ratio of 2:1,[14] 20 mol % of DTBM-SEGPHOS was needed to obtain satisfactory results. By increasing the relative amount of CuF_2, the reaction proceeded smoothly, and 9 mol % of the ligand was sufficient at a ligand:metal ratio of 3:2. Thus, a high chemical yield of 97% and 82% ee was accomplished by using 9 mol % of DTBM-SEGPHOS and 6 mol % of CuF_2 (Table 2, entry 11).

This reaction condition was applied to 6,7-dimethoxy-3,4-dihydroisoquinoline (**1**) and yielded improved results (entries 13 and 14), demonstrating that a reaction system with DTBM-SEGPHOS as a chiral source is a practical

(8) (a) Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2006**, *128*, 14010. (b) Dubs, C.; Hamashima, Y.; Sasamoto, N.; Seidel, T. M.; Suzuki, S.; Hashizume, D.; Sodeoka, M. *J. Org. Chem.* **2008**, *73*, 5859.

(9) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763 and references cited therein.

(10) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536.

(11) Itoh, T.; Miyazaki, M.; Fukuoka, H.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2006**, *8*, 1295.

(12) Takeda, K.; Uehara, T.; Nakao, Y.; Matsunaga, S.; van Soest, R. W.; Fusetani, N. *J. Am. Chem. Soc.* **2004**, *126*, 187.

(13) Although several solvents other than THF were used as a reaction solvent, the yields were lower in every case.

(14) Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138.

TABLE 1. Allylation of 3 in the Presence of a Chiral Ligand

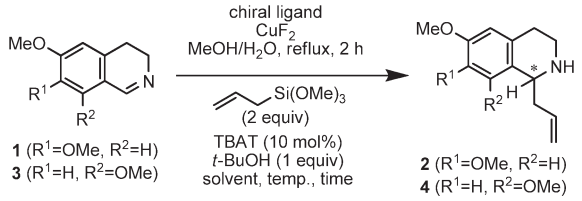
entry	chiral ligand	X (mol %)	temp (°C)	time	yield (%)	ee (%)
1	(*R*)-QUINAP[a]	10	rt	23 h	0	
2	(*S*)-SEGPHOS[b]	10	rt	23 h	0	
3	(*S*)-SEGPHOS	10	70	6 h	39	28 (*R*)
4	(*R*)-DTBM-SEGPHOS[c]	10	50	6 h	9	0.3
5	(*S*)-Tol-BINAP[d]	10	rt	1 d	5	64 (*R*)
6	(*S*)-Tol-BINAP	10	50	2.5 h	73	62 (*R*)
7	(*S*)-Tol-BINAP	3	rt	7 d	6	69 (*R*)
8	(*S*)-Tol-BINAP	3	50	3 h	61	51 (*R*)

[a]QUINAP: 1-(2-diphenylphosphino-1-naphthyl)isoquinoline. [b]SEGPHOS: 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole. [c]DTBM-SEGPHOS: 5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole. [d]Tol-BINAP: 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl.

TABLE 2. Allylation of 1 or 3 with Allylsilane and Cu(II) in the Presence of a Chiral Ligand

entry	SM	chiral ligand (mol %)	CuF_2 (mol %)	solvent	temp (°C)	time (h)	product	yield (%)	ee (%)
1	**3**	(*S*)-Tol-BINAP (20)	10	THF	50	6	**4**	17	53 (*R*)
2	**3**	(*S*)-SEGPHOS (20)	10	THF	70	4	**4**	61	61 (*R*)
3	**3**	(*R*)-DTBM-SEGPHOS (20)	10	THF	rt	24	**4**	50	87 (*S*)
4	**3**	(*R*)-DTBM-SEGPHOS (20)	10	THF	50	22	**4**	31	84 (*S*)
5	**3**	(*R*)-DTBM-SEGPHOS (20)	10	THF	70	1.5	**4**	quant	83 (*S*)
6	**3**	(*R*)-DTBM-SEGPHOS (20)	10	DMF	70	0.5	**4**	77	82 (*S*)
7	**3**	(*R*)-DTBM-SEGPHOS (2)	1	THF	70	21	**4**	16	26 (*S*)
8	**3**	(*R*)-DTBM-SEGPHOS (10)	5	THF	70	28	**4**	26	81 (*S*)
9	**3**	(*R*)-DTBM-SEGPHOS (15)	7.5	THF	70	14	**4**	42	84 (*S*)
10	**3**	(*R*)-DTBM-SEGPHOS (6)	4	THF	70	8	**4**	72	56 (*S*)
11	**3**	(*R*)-DTBM-SEGPHOS (9)	6	THF	70	4.5	**4**	97	82 (*S*)
12	**3**	(*R*)-DTBM-SEGPHOS (15)	10	THF	70	1.5	**4**	88	84 (*S*)
13	**1**	(*R*)-DTBM-SEGPHOS (20)	10	THF	70	1	**2**	87	80 (*S*)
14	**1**	(*R*)-DTBM-SEGPHOS (20)	6	THF	70	2.5	**2**	85	81 (*S*)

SCHEME 3



method for the asymmetric catalytic allylation of cyclic imines.

Determination of the Absolute Configuration of the Allyl Adduct. The absolute configuration of the allyl adduct **4** was determined as follows. First, racemic **4** was obtained quantitatively by the reaction of **3** and allyl magnesium bromide. The racemate was reacted with *N*-phthaloyl-(*S*)-alanine in the presence of EDCI to give diastereomeric amides **5a** and **5b** (Scheme 4). The products were recrystallized from hexane−dichloromethane, and **5a** was obtained as a colorless crystal. The structure of **5a** was determined by X-ray crystallographic analysis and showed that the absolute configuration at the C-1 position is *R* (Scheme 4). Next, compound **4**, which was obtained from the reaction with use of (*R*)-DTBM-SEGPHOS, was reacted with *N*-phthaloyl-(*S*)-alanine to give **5b** as the main product. The C-1 absolute configuration of **5b** was determined to be *S*, indicating that the use of (*R*)-DTBM-SEGPHOS provides **4** in the *S* form. The stereoselectivity was found to be consistent with those of Shibasaki's reaction.[14]

Asymmetric Synthesis of Crispine A. To demonstrate the usefulness of chiral allyl adducts **2** and **4**, several isoquinoline alkaloids were synthesized by using these as starting materials. First, we selected crispine A, one of the simplest isoquinoline alkaloids, as the target molecule. Crispine A was isolated in 2002 by Cheng's group, and was found to show cytotoxicity in vitro.[15] Although several groups have reported the total synthesis of crispine A,[16] asymmetric synthesis of the compound has published only recently.[17,6] Thus, we carried out the asymmetric total synthesis of crispine A using (*R*)-**2**.

After protecting the N-2 position of (*R*)-allyl adduct **2** with $(Boc)_2O$, product **6** was subjected to hydroboration−oxidation to give primary alcohol **7** (Scheme 5, top). Deprotection of **7** gave amino alcohol **8** in moderate yield, and Mitsunobu reaction with DEAD and PPh_3 (Scheme 5, bottom) afforded the ring-closing product, crispine A (**9**).

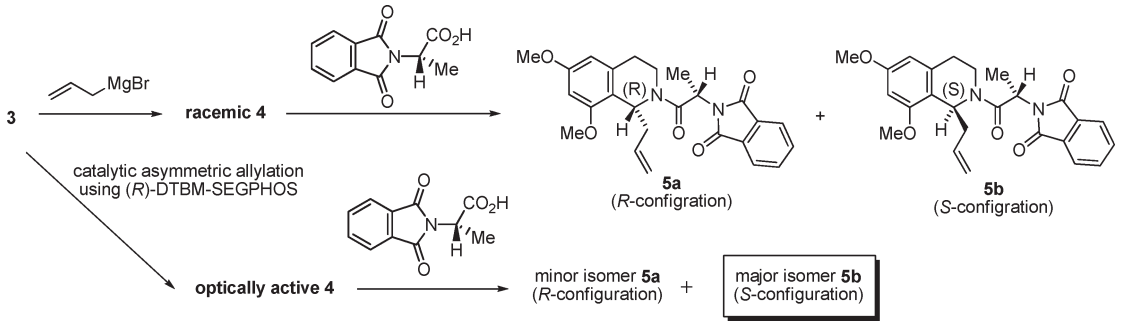
In this procedure, the yield of the last step was only 50%, and the overall yield of crispine A (**9**) was 26.7% in 5 steps. Therefore, other cyclization processes were investigated. As a result, alcohol **7** was activated with TsCl, and subsequent deprotection with TMSOTf in air resulted in spontaneous cyclization to obtain **9** in 2 steps with 74% yield (5 steps, 54% yield from **2**). The specific rotation of **9** was identical with that of crispine A, and the synthesis proceeded without racemization.

(15) Zhang, Q.; Tu, G.; Zhao, Y.; Cheng, T. *Tetrahedron* **2002**, *58*, 6795.

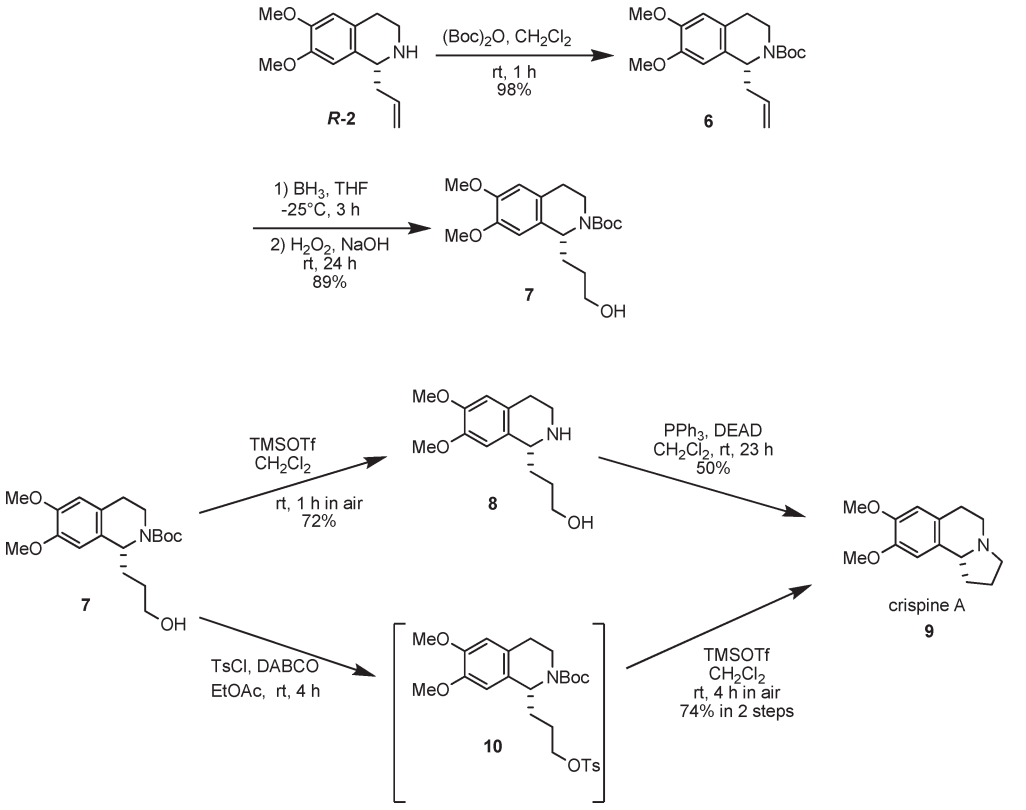
(16) (a) King, F. D. *Tetrahedron* **2007**, *63*, 2053. (b) Knölker, H.-J.; Agawal, S. *Tetrahedron Lett*. **2005**, *46*, 1173. (c) Orito, K.; Matsuzaki, T.; Suginome, H. *Heterocycles* **1988**, 2403. (d) Schell, F. M.; Smith, A. M. *Tetrahedron Lett*. **1983**, *24*, 1883.

(17) (a) First enantioselective synthesis of crispine A: Szawkalo, J.; Zawadzka, A.; Wojtasiewicz, K.; Leniewski, A.; Drabowicz, J.; Czarnocki, Z. *Tetrahedron: Asymmetry* **2005**, *16*, 3619. (b) Allin, S. M.; Gaskell, S. N.; Towler, J. M. R.; Bulman Page, P. C.; Saha, B.; McKenzie, M. J.; Martin, W. P. *J. Org. Chem.* **2007**, *72*, 8972. (c) Szawkalo, J.; Czarnocki, S. J.; Zawadzka, A.; Wojtasiewicz, K.; Leniewski, A.; Maurin, J. K.; Czarnocki, Z.; Drabowicz, J. *Tetrahedron: Asymmetry* **2007**, *18*, 406. (d) Hou, G.-H.; Xie, J.-H.; Yan, P.-C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2009**, *131*, 1366. (e) Amat, M.; Elias, V.; Llor, N.; Subrizi, F.; Molins, E.; Bosch, J. *Eur. J. Org. Chem*. **2010**, 4017. (f) Deracemization of racemic crispine A: Bailey, K. R.; Ellis, A. J.; Reiss, R.; Snape, T. J.; Turner, N. J. *Chem. Commun*. **2007**, 3640.

SCHEME 4



SCHEME 5



Synthesis of Homolaudanosine. Homolaudanosine (**14**), an alkaloid identified in 1983 by Leary, has a chiral center at the C-1 position.[18] Several total syntheses have been reported,[19] including our paper that described the asymmetric synthesis of (*R*)-homolaudanosine using a chiral auxiliary derived from an amino acid.[20]

To evaluate the synthetic value of chiral allyl adduct **2** as a stating material, the synthesis of **14** was reinvestigated (Scheme 6).

After protection of N-2 in **2** with ethyl chloroformate, allyl adduct **11** was transformed to aldehyde **12** using OsO_4-NaIO_4 oxidation. Compound **12** was subjected to the Grignard reaction with 3,4-dimethoxyphenylmagnesium bromide to give secondary alcohol **13**. The hydroxyl group of **13** was converted to the Cl group with $SOCl_2$ in pyridine, and subsequent reduction with $LiAlH_4$ afforded (*S*)-homolaudanosine **14** in an overall yield of 29.1% from compound **2**.

Compound *S*-**2** also could be transformed into (−)-emetine[21] according to the previously described strategy.[11]

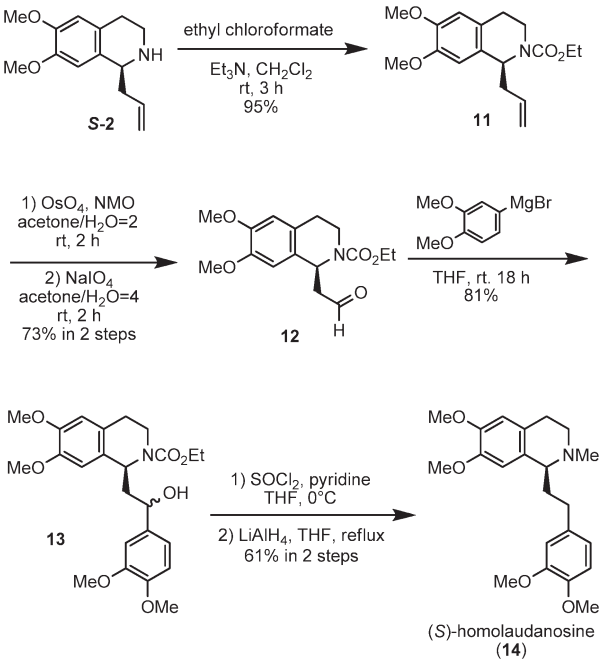
Synthesis of Schulzeine A (Isoquinoline Framework). Schulzeines (A, B, and C), which are alkaloids first isolated by Fusetani et al. in 2003,[12] have high α-glucosidase inhibition activity (Figure 1). Their intriguing structure and bioactivity prompted four groups to attempt the synthesis

(18) Aladesanmi, A. J.; Kelly, C. J.; Leary, J. D. *J. Nat. Prod.* **1983**, *46*, 127.

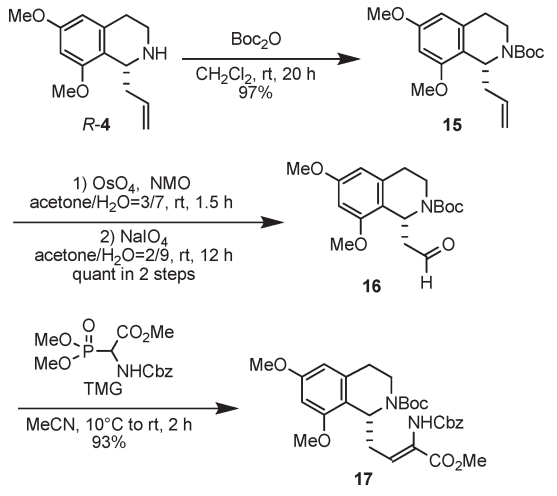
(19) (a) Czarnocki, Z.; MacLean, D. B.; Szarek, W. A. *J. Chem. Soc., Chem. Commun.* **1987**, 493. (b) Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095. (c) Yamato, M.; Hashigaki, K.; Qais, N.; Ishikawa, S. *Tetrahedron* **1990**, *46*, 5909. (d) Wanner, K. T.; Praschak, I. *Heterocycles* **1991**, *32*, 1869. (e) Pedrosa, R.; Andres, C.; Iglesias, J. M. *J. Org. Chem.* **2001**, *66*, 243. (f) Taylor, A. M.; Schreiber, S. L. *Org. Lett.* **2006**, *8*, 143. (g) Zang, Z.; Leitch, D. C.; Lu, M.; Patrick, B. O.; Scafer, L. L. *Chem.—Eur. J.* **2007**, *13*, 2012.

(20) Itoh, T.; Nagata, K.; Miyazaki, M.; Ohsawa, A. *Synlett* **1999**, 1154.

SCHEME 6

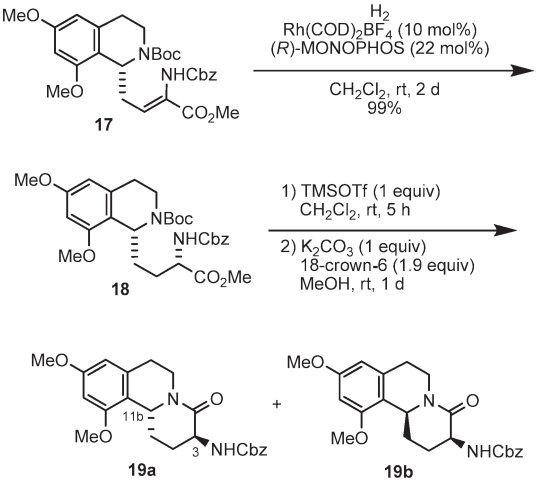


SCHEME 7



of these compounds.[22] Recently, Wardrop reported the first total synthesis of schulzeine A, leading to revision of

SCHEME 8



the original structure at C-20′.[22d] The four reports used similar approaches for the synthesis of the tricyclic isoquinoline derivative, that is, the chiral center at C-3 was derived from glutaminic acid and the C-11b chiral center was obtained by the diastereoselective Pictet–Spengler reaction. The purity of C-11b was not always high, and the separation of the diastereomer was crucial in every case. Since satisfactory yields and stereoselectivity were not obtained, allylation product **2** was applied to the synthesis of the isoquinoline fragment in schulzeine A (Scheme 7).

R-Allyl adduct **4** obtained from the reaction of 6,8-dimethoxy-3,4-dihydroisoquinoline (**3**) and (*S*)-DTBM-SEGPHOS was protected by $(Boc)_2O$, and oxidized with OsO_4–$NaIO_4$ to aldehyde **16**. Horner–Wadsworth–Emmons olefination of aldehyde **16** with dimethylphosphate derived from glycine gave dehydroamino acid **17** in high yield.[23]

Asymmetric reduction of the olefin was needed to introduce another chiral center in the heterotricyclic schulzeines. The reaction was carried out by Feringa's method, using Rh-catalysis[24] with the chiral ligand (*R*)-[4-*N*,*N*-dimethylamino]dinaphtho[2,1-*d*:1′,2′-*f*][1,3,2]dioxaphosphepine ((*R*)-MONOPHOS), to obtain **18** (Scheme 8). Due to the presence of complicated conformational isomers in **18**, it was difficult to determine the stereoselectivity of the reduction at this point. Deprotection of the Boc group and successive cyclization of **18** provided a diastereomeric mixture of **19a** and **19b**. The mixture was successfully separated by column chromatography.

To determine the ratio and enantiomeric excess of diastereomer **19**, reduction–cyclization was studied by using racemic and optically active (82% ee) **17**.

To determine the configuration of **19a** and **19b** obtained by the asymmetric reduction, the Cbz group was removed under catalytic hydrogenation conditions to give amines **20a** and **20b** (Scheme 9), respectively. NOEs showed a correlation between H-3 and H-11b in **20b**, whose 11b position has

(21) (a) Brossi, A.; Baumann, M.; Schnider, O. *Helv. Chim. Acta* **1959**, *42*, 1515. (b) Szantay, C.; Toke, L. *Tetrahedron Lett.* **1963**, 1323. (c) Szantay, C.; Toke, L.; Kolonis, P. *J. Org. Chem.* **1966**, *31*, 1447. (d) van Tamelen, E. E.; Placeway, C.; Schiemenz, G. P.; Wright, I. G. *J. Am. Chem. Soc.* **1969**, *91*, 7359. (e) Takano, S.; Sasaki, M.; Kanno, H.; Shishido, K.; Ogasawara, K. *Heterocycles* **1977**, *7*, 143. (f) Kametani, T.; Suzuki, Y.; Terasawa, H.; Ihara, M.; Fukumoto, K. *Heterocycles* **1977**, *8*, 119. (g) Fujii, T.; Ohba, M.; Akiyama, S. *Heterocycles* **1984**, *22*, 159. (h) Naito, T.; Kojima, N.; Miyata, O.; Ninomiya, I. *J. Chem. Soc., Chem. Commun.* **1985**, *22*, 1611. (i) Ihara, M.; Yasui, K.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1469. (j) Gulles, J. W.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 6873. (k) Stearman, C. J.; Wilson, M.; Padwa, A. *J. Org. Chem.* **2009**, *74*, 3491. (l) Tietze, L. F.; Rackelmann, N.; Sekar, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4254. (m) Tietze, L. F.; Rackelmann, N.; Müller, I. *Chem.—Eur. J.* **2004**, *10*, 2722.

(22) (a) Kuntiyong, P.; Akkarasamiyo, S.; Eksinitkun, G. *Chem. Lett.* **2006**, *35*, 1008. (b) Gurjar, M. K.; Pramanik, C.; Bhattasali, D.; Ramana, C. V.; Mohapatra, D. K. *J. Org. Chem.* **2007**, *72*, 6591. (c) Liu, G.; Romo, D. *Org. Lett.* **2009**, *11*, 1143. (d) Wardrop, D. J.; Bowen, E. G. *J. Am. Chem. Soc.* **2009**, *131*, 6062.

(23) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, N.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552.

(24) Van Den Berg, M.; Minnaard, A. J.; Schudde, E. P.; Van Esch, J.; De Vries, A. H. M.; De Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539.

SCHEME 9

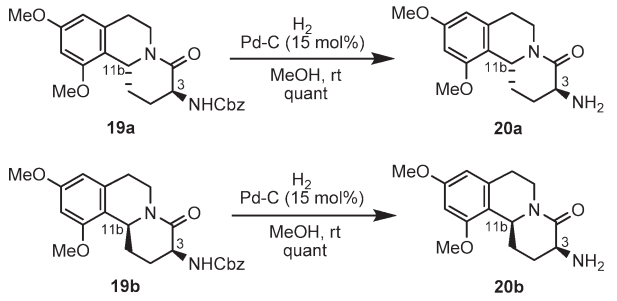


TABLE 3

substrate	yield (%) of **18**	yield (%) of **19**	ratio **19a**:**19b**	ee (%) **19a**	ee (%) **19b**
racemic **17**	quant	93	53:47	78	80
17 (82% ee) (*R*:*S* = 91:9)	99	96	82:18	98	62

S-configuration, but no correlation in **20a**, which has an *R*-isomer at H-11b. The results indicated that asymmetric reduction by Feringa's method was accomplished in a highly *S*-selective manner. The results summarized in Table 3 suggested that the reduction process is stereospecific regardless of the pre-existing chiral center at C-11b.

The asymmetric synthesis of **20a**, an intermediate of schulzeine A, was accomplished with an overall yield of 68.1% via 9 steps from 6,8-dimethoxy-3,4-dihydroisoquinoline (**3**) and (*S*)-DTBM-SEGPHOS.

In this paper, we described the catalytic asymmetric allylation of 3,4-dihydroisoquinolines, and its application in the synthesis of several isoquinoline alkaloids. The results show the usefulness of the allyl adduct as a starting material for optically active isoquinoline alkaloid synthesis. Further applications and the total synthesis of schulzeine A are now in progress.

Experimental Section

General. The reagents were commercially available and used without further purification. Thin-layer chromatography (TLC) was conducted with silica gel, using UV light (254 nm), an acetone solution of potassium permangarate, and iodine as monitoring methods. Silica gel (spherical, neutral, 100−200 μm) and NH silica gel (100−200 mesh) were used for column chromatography. All the reaction temperatures shown are bath temperatures. The nuclear magnetic resonance spectra (NMR) were measured with 400 and 500 MHz spectrometers. Chemical shifts for ^{1}H NMR were reported downfield from tetramethylsilane (TMS) as the internal standard. The signal multiplicities were shown as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. The standard chemical shifts for ^{13}C NMR were derived from the used solvent.

Preparation of 3,4-Dihydroisoquinolines 1 or 3.[25] Hexamethylenetetramine (7.74 g, 55.2 mmol) was added to the mixture of 2-(dimethoxyphenyl)ethylamine (5 g, 27.6 mmol), AcOH (30 mL), and trifluoroacetic acid (7.5 mL) under Ar, and the mixture was allowed to stir at 90 °C for 30 min (for 3,4-dimethoxyphenethylamine) or 3 h (for 3,5-dimethoxyphenethylamine), respectively. To the reaction mixture cooled to room temperature was added H_2O, and the mixture was basified with potassium carbonate and then extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and then the solvent was removed in vacuo. The residue was purified by column chromatography (EtOAc/MeOH = 20 to 4) to give 3,4-dihydroisoquinolines **1** or **3** as a yellow solid in 90% (for **1**) or 96% (for **3**) yield, respectively.

6,7-Dimethoxy-3,4-dihydroisoquinoline (1):[26] colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.68 (2H, t, J = 7.9 Hz), 3.73 (2H, td, J = 8.7, 1.8 Hz), 3.91 (3H, s), 3.93 (3H, s), 6.68 (1H, s), 6.81 (1H, s), 8.23 (1H, t, J = 2.1 Hz); ^{13}C NMR ($CDCl_3$) δ 24.1, 46.8, 55.4, 55.5, 109.8, 109.9, 120.9, 129.2, 147.2, 150.6, 159.0. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.97; H, 6.85; N, 7.18. HR-FAB MS calcd for $C_{11}H_{14}NO_2$ $[M + H]^+$ 192.1025, found 192.1024.

6,8-Dimethoxy-3,4-dihydroisoquinoline (3):[27] colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.66 (2H, t, J = 7.7 Hz), 3.67 (2H, td, J = 7.7, 1.9 Hz), 3.83 (3H, s), 3.85 (3H, s), 6.27 (1H, s), 6.31 (1H, s), 8.61 (1H, t, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 26.0, 46.6, 55.3, 55.4, 96.3, 103.8, 111.5, 139.9, 155.1, 158.5, 162.6. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.77; H, 6.84; N, 7.21. HR-FAB MS calcd for $C_{11}H_{14}NO_2$ $[M + H]^+$ 192.1025, found 192.1026.

Preparation of Chiral 1-Allyl-1,2,3,4-tetrahydroisoquinolines 2 or 4. After heating a mixture of CuF_2 (1.2 mg, 0.012 mmol) and DTBM-SEGPHOS (21.2 mg, 0.018 mmol) in MeOH (1 mL) and H_2O (100 μL) at 80 °C for 2 h, the solvent was removed in vacuo, and subsequently azeotropically dehydrated by using toluene twice (each 0.5 mL). To the residue dissolved in THF (1 mL) was added tetra-*n*-butylammonium difluorotriphenylsilicate (10.8 mg, 0.02 mmol) and the reaction mixture was cooled to 0 °C. To the cooled reaction mixture were added 3,4-dihydroisoquinoline (**1** or **3**) (38.2 mmol, 0.2 mmol) and allyltrimethoxysilane (68 μL, 0.4 mmol). Again the reaction mixture was warmed to room temperature and *t*-BuOH (20 mL, 0.2 mol) was added to the mixture. After stirring at 70 °C for 4.5 h under Ar, saturated aqueous sodium bicarbonate solution (10 mL) was added to the mixture, which was extracted with EtOAc, and the combined organic layer was dried over $MgSO_4$, filterd, and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/MeOH = 10 to 1) to give the allyl adduct (**2** or **4**) as a colorless oil.

To determine the enantiomeric excesses, thus obtained allyl adduct was subjected to *N*-trifluoroacetylation, and the ee was subsequently detected by HPLC, using Daicel Chiralcel OD-H (eluent was hexane/2-propanol = 100). The compound **2a** was obtained in 97% yield, and the ee was determined as 82% by using the HPLC method.

1-Allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (2): colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.82 (1H, br s), 2.49 (1H, dtd, J = 15.3, 8.0, 1.0 Hz), 2.60−2.67 (1H, m), 2.67−2.79 (2H, m), 2.95 (1H, ddd, J = 12.6, 7.8, 4.9 Hz), 3.22 (1H, dt, J = 12.3, 5.3 Hz), 3.85 (6 H, s), 4.00 (1H, dd, J = 8.7, 3.6 Hz), 5.13−5.21 (2H, m), 5.79−5.89 (1H, m), 6.58 (1H, s), 6.66 (1H, s); ^{13}C NMR ($CDCl_3$) δ 29.5, 40.8, 41.1, 54.7, 55.8, 56.0, 109.1, 111.8, 117.9, 127.5, 130.5, 135.6, 147.2, 147.4. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.81; H, 8.34; N, 5.94. HR-FAB MS calcd for $C_{14}H_{20}NO_2$ $[M + H]^+$ 234.1494, found 234.1480.

1-Allyl-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4): colorless oil; (*R*)-**4** (82% ee) $[\alpha]^{18}_D$ +38.8 (*c* 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.31 (1H, br s), 2.34 (1H, dt, J = 14.1, 9.2 Hz), 2.58−2.64 (1H, m), 2.66 (1H, dt, J = 12.2, 4.0 Hz), 2.86 (1H, ddd, J = 16.3, 10.0, 6.0 Hz), 2.94 (1H, ddd, J = 12.4, 5.9, 3.2 Hz), 3.16 (1H, ddd, J = 12.5, 10.2, 4.4 Hz), 3.78 (3H, s), 3.79 (3H, s), 4.15 (1H, dd, J = 9.5, 2.6 Hz), 5.09−5.13 (2H, m), 5.84−5.92 (1H, m),

(25) Ivanov, I.; Venkov, A. *Heterocycles* **2001**, *55*, 1569.

(26) (a) Whalley, W. M.; Meadow, M. *J. Chem. Soc.* **1953**, *23*, 1067. (b) Warrener, R. N.; Liu, L.; Russell, R. A. *Tetrahedron* **1998**, *54*, 7485.

(27) Gray, von R. W.; Dreiding, A. S. *Helv. Chim. Acta* **1980**, *63*, 315.

6.23 (1H, d, J = 2.3 Hz), 6.29 (1H, d, J = 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 29.5, 37.58, 37.62, 50.2, 55.17, 55.22, 96.4, 104.4, 117.2, 119.6, 136.57, 136.62, 157.2, 158.8; HR-FAB MS calcd for $C_{14}H_{20}NO_2$ $[M + H]^+$ 234.1494, found 234.1488.

The Purification of 2 (71% ee, *R* isomer), Using (−)-Dibenzoyl-L-tartaric Acid. Compound **2** (123.7 mg, 0.53 mmol) and (−)-dibenzoyl-L-tartaric acid (190 mg, 0.53 mmol) were recrystallized from CH_3CN/H_2O (20), and the solid thus obtained was filtrated, dissolved in EtOAc, and extracted with aq Na_2CO_3. The organic layer was dried over $MgSO_4$, and evaporated off to leave optically more active **2** (97%ee, *R*) in 78% yield (96.5 mg).

The Protection of *N*-2 Position of Compound 2 by the Use of the Boc Group. To the solution of $(Boc)_2O$ (580.2 mg, 2.5 mmol) in CH_2Cl_2 (8 mL) was added 1-allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2**) (307.7 mg, 1.3 mmol) in CH_2Cl_2 (7 mL) at room temperature, and the mixture was allowed to stir for 1 h. Then the reaction was quenched by the addition of H_2O, and the mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was purified by column chromatography (CH_2Cl_2/EtOAc = 20) to give **6** (98%) as a colorless powder.

***tert*-Butyl 1-allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (6):** colorless powder, mp 71−74 °C; (*R*)-**6** (98.7% ee) $[\alpha]^{18}_D$ −105.3 (*c* 1.15, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 100 °C) δ 1.44 (9H, s), 2.45−2.57 (2H, m), 2.65 (1H, dt, J = 16.2, 4.2 Hz), 2.72 (1H, ddd, J = 16.2, 10.4, 5.8 Hz), 3.19 (1H, ddd, J = 13.1, 10.4, 4.3 Hz), 3.74 (3H, s), 3.75 (3H, s), 3.94 (1H, dt, J = 12.8, 4.5 Hz), 4.99−5.06 (3H, m), 5.82 (1H, ddt, J = 17.1, 10.1, 7.1 Hz), 6.70 (1H, s), 6.77 (1H, s); ^{13}C NMR (DMSO-d_6, 100 °C) δ 27.2, 27.8, 37.2, 40.4, 53.2, 55.7, 55.9, 78.6, 111.5, 112.8, 116.2, 126.1, 129.1, 135.1, 147.4, 147.7, 153.8. Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.43; H, 8.37; N, 4.04. HR-FAB MS calcd for $C_{19}H_{28}NO_4$ $[M + H]^+$ 334.2018, found 334.2029.

Hydroboration−Oxidation of the Compound 6. To the allyl derivative **6** (427.1 mg, 1.28 mmol) dissolved in THF (5 mL) solution was added BH_3−THF (1 M solution, 3.9 mL, 3.9 mmol) at −25 °C under Ar, and the mixture was allowed to stir for 3 h. After addition of H_2O into the reaction mixture, 3 M NaOH (1 mL) and H_2O_2 (30%, 1 mL) were added, and the reaction was continued for 24 h at room temperature. Then brine (15 mL) was added to the reaction mixture, which was extracted with EtOAc. The collected organic layer was dried with $MgSO_4$ and removed in vacuo. The residue was purified with silica gel column chromatography (EtOAc) to give the primary alcohol product **7** in 89% yield.

***tert*-Butyl 1-(3-hydroxypropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (7):** colorless oil; (*R*)-**7** (99.6% ee) $[\alpha]^{18}_D$ −90.0 (*c* 0.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 60 °C) δ 1.48 (9H, s), 1.61−1.76 (2H, m), 1.78−1.86 (2H, m), 2.61 (1H, dt, J = 16.1, 3.9 Hz), 2.83 (1H, ddd, J = 16.1, 10.5, 5.7 Hz), 3.21 (1H, br s), 3.65−3.76 (2H, m), 3.83 (3H, s), 3.84 (3H, s), 4.06 (1H, br s), 5.06 (1H, br s), 6.58 (1H, s); ^{13}C NMR ($CDCl_3$, 60 °C) δ 25.5, 28.1, 28.5, 29.5, 33.4, 54.0, 56.1, 56.3, 62.7, 79.8, 110.9, 112.2, 126.4, 130.4, 147.8, 155.1. Anal. Calcd for $C_{19}H_{29}NO_5 \cdot {}^1/_4H_2O$: C, 64.11; H, 8.35; N, 3.94. Found: C, 64.16; H, 8.35.37; N, 3.80. HR-FAB MS calcd for $C_{19}H_{30}NO_5$ $[M + H]^+$ 352.2131, found 352.2124.

Deprotection of N-Boc to the Formation of an Aminoalcohol 8. To compound **7** (177.5 mg, 0.51 mmol) in CH_2Cl_2 was added TMSOTf (0.4 mL, 2.21 mmol) at room temperature under air, and the mixture was allowed to stir for 1 h. The mixture was basified with saturated sodium bicarbonate, and extracted with CH_2Cl_2. The collected organic layer was dried over $MgSO_4$ and removed in vacuo to leave the residue, which was purified with NH silica gel column chromatography (EtOAc/MeOH = 5) to give an aminoalcohol **8** (72%) as a colorless solid.

1-(3-Hydroxypropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8):[28] colorless powder; ^{1}H NMR ($CDCl_3$) δ 1.67−1.85 (2H, m), 1.91−2.04 (2H, m), 2,67 (1H, dt, J = 16.4, 6.2 Hz), 2.77 (1H, dt, J = 16.5, 5.8 Hz), 3.06 (1H, ddd, J = 13.1, 6.1, 5.3 Hz), 3.20 (1H, ddd, J = 12.9, 7.3, 5.4 Hz), 3.55 (1H, ddd, J = 11.1, 8.1, 3.0 Hz), 3.66 (1H, ddd, J = 17.3, 6.2, 3.2 Hz), 3.85 (3H, s), 3.85 (3H, s), 3.94 (1H, dd, J = 7.8, 3.9 Hz), 6.57 (1H, s), 6.59 (1H, s); ^{13}C NMR ($CDCl_3$) δ 28.8, 30.7, 35.6, 39.7, 55.4, 55.8, 56.0, 62.8, 109.3, 111.6, 126.6, 130.3, 147.2, 147.4. Anal. Calcd for $C_{14}H_{21}NO_3 \cdot {}^1/_3H_2O$: C, 65.34; H, 8.49; N, 5.44. Found: C, 65.59, H, 8.59; N, 5.24. HR-FAB MS calcd for $C_{14}H_{22}NO_3$[M + H]$^+$ 252.1586, found 252.1600.

Crispine A (9). To a solution of **7** (124.0 mg, 0.38 mmol) in ethyl acetate (1 mL) was added DABCO (92.7 mg, 0.83 mmol) and *p*-toluenesulfonyl chloride (119.0 mg, 0.62 mmol) at 0 °C under Ar, and the mixture was allowed to stir at room temperature for 4 h. The insoluble material was filtered through the Celite pad and filtrate was evaporated in vacuo to give the crude Ts-adduct **10** as a colorless oil. Compound **10** thus obtained was dissolved in CH_2Cl_2 (5 mL), and trimethylsilyl trifluoromethanesulfonate (0.33 mL, 1.81 mmol) was added in air. After 3 h, the reaction mixture was basified with saturated sodium bicarbonate aqueous solution and extracted with CH_2Cl_2. The collected organic layer was dried over $MgSO_4$ and removed in vacuo. The residue was purified with silica gel column chromatography (EtOAc to MeOH) to give the ring closing product crispine A (**9**) in 74% in two steps.

***tert*-Butyl 6,7-dimethoxy-1-[3-(toluene-4-sulfonyloxy)propyl]-1,2,3,4-tetrahydroisoquinoline- 2-carboxylate (10):** colorless oil; (*R*)-**10** (99.6% ee) $[\alpha]^{18}_D$ −69.8 (*c* 0.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 60 °C) δ 1.44 (9H, s), 1.75−1.83 (4H, m), 2.43 (3H, s), 2.57 (1H, dt, J = 15.9, 3.7 Hz), 2.77−2.86 (1H, m), 3.11 (1H, br s), 3.83 (3H, s), 3.84 (1H, s), 4.01−4.09 (2H, m), 4.16−4.22 (1H, m), 4.98 (1H, br s), 6.56 (1H, s), 6.57 (1H, s), 7.31 (2H, d, J = 8.5 Hz), 7.77 (2H, d, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 60 °C) δ 21.4, 26.0, 28.0 28.4, 32.5, 47.1, 53.4, 56.1, 56.3, 70.2, 79.8, 110.8, 112.2, 126.4, 127.8, 129.8, 130.4, 133.7, 144.6, 147.9, 148.1, 154.9. Anal. Calcd for $C_{26}H_{35}NO_7S$: C, 61.76; H, 6.98; N, 2.77. Found: C, 61.34, H, 7.15; N; 2.72. HR-FAB MS calcd for $C_{26}H_{36}NO_7S$ $[M + H]^+$ 506.2212, found 506.2205.

Crispine A (9):[15] colorless powder, mp 85−88 °C; (*R*)-**9** (99.3% ee) $[\alpha]^{18}_D$ +90.4 (*c* 0.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$,) δ 1.67−1.77 (1H, m), 1.81−2.00 (2H, m), 2,28−2.36 (1H), 2.55 (1 h, q, J = 8.5 Hz), 2.63 (1H, td, J = 10.7, 4.8 Hz), 2.73 (1H, dt, J = 16.3, 3.7 Hz), 2.94−3.04 (1H, m), 3.85 (3H, s), 6.57 (1H, s), 6.61 (1H, s); ^{13}C NMR ($CDCl_3$) δ 22.3, 28.2, 30.5, 48.2, 53.2, 55.9, 56.0, 63.0, 108.8, 111.3, 126.2, 131.0,. 147.1, 147.2; HR-FAB MS calcd for $C_{14}H_{19}NO_2$ $[M + H]^+$ 234.1479, found 234.1494.

***N*-Protection of Compound 2 with Ethyl Chloroformate.** To a solution of **2** (253.2 mg, 1.09 mmol) in CH_2Cl_2 (10 mL) was added triethylamine (0.23 mL, 1.65 mmol) and ethyl chloroformate (0.16 mL, 1.67 mmol) at room temperature under Ar, and the mixture was allowed to stir for 3 h. After addition of H_2O (10 mL), the reaction mixture was extracted with CH_2Cl_2 and the collected organic layer was dried over $MgSO_4$ and removed in vacuo. The residue was purified with column chromatography (EtOAc) to give **11** as a colorless oil.

Ethyl 1-allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (11): colorless oil; (*S*)-**11** (97% ee) $[\alpha]^{16}_D$ +123.6 (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 60 °C) δ 1.25 (3H, t, J = 7.1 Hz), 2.53 (2H, t, J = 6.7 Hz), 2.62 (1H, dt, J = 15.9, 3.9 Hz), 2.79−2.87 (1H, m), 3.26 (1H, br s), 3.82 (6H, s), 4.07−4.17 (3H, m), 5.00−5.04 (2H, m), 5.10 (1H, br s), 5.78−5.88 (1H, m), 6.57 (1H, s), 6.60 (1H, s); ^{13}C NMR ($CDCl_3$, 60 °C) δ 14.7, 28.1, 38.0, 41.3, 54.1, 56.1, 56.2, 61.2, 110.9, 112.2, 117.1, 126.4, 129.3,

(28) Lazar, L.; Fulop, F.; Bernath, G.; Mattinen, J. *Org. Prep. Proced. Int.* **1993**, *25*, 91.

135.1, 147.8, 148.2, 155.7; HR-FAB MS calcd for $C_{17}H_{24}NO_4$ $[M + H]^+$ 306.1705, found 306.1693.

Transformation of the Allyl Adduct 11 to the Aldehyde 12. To a solution of **11** (636.7 mg, 2.09 mmol) in acetone (10 mL) and H_2O (5 mL) was added OsO_4 (1.9 mL, 4% aqueous solution, 0.31 mmol) and 4-methylmorpholine *N*-oxide (0.16 mL, 1.67 mmol) at room temperature, and the mixture was allowed to stir for 2.3 h. After addition of a 10% $NaHSO_3$ aqueous solution (30 mL), the reaction mixture was extracted with ethyl acetate and the collected organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. Then $NaIO_4$ (957 mg, 4.48 mmol) in H_2O (4 mL) was added into the residue dissolved in acetone (16 mL), and the mixture was stirred for 2 h at room temperature. Saturated NaCl aqueous solution (20 mL) was added into the reaction mixture, which was extracted with ethyl acetate. The collected organic layer was dried over $MgSO_4$, and evaporated off in vacuo. The resultant was purified by column chromatography (EtOAc) to obtain **12** as a colorless solid (465.5 mg, 73% in two steps).

Ethyl 6,7-dimethoxy-1-(2-oxoethyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (12): colorless solid; (*S*)-**12** (97% ee) $[\alpha]^{18}_D$ +55.3 (*c* 0.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 60 °C) δ 1.27 (3H, t, J = 7.1 Hz), 2.67 (2H, dt, J = 16.1, 4.0 Hz), 2.82−2.90 (3H, m), 3.28 (1H, br s), 3.83 (6H, s), 4.13−4.21 (3H, m), 5.63 (1H, br s), 6.62 (1H, s), 6.66 (1H, s), 9.83 (1H, t, J = 2.6 Hz); ^{13}C NMR ($CDCl_3$, 60 °C) δ 14.4, 27.8, 38.2, 49.8, 51.0, 55.9, 56.0, 61.4, 110.1, 112.1, 126.3, 127.9, 148.1, 148.4, 155.2, 199.6; HR-FAB MS calcd for $C_{16}H_{22}NO_5[M + H]^+$ 308.1498, found 308.1501.

The Grignard Reaction to the Aldehyde 12. To Mg (145.9 mg, 6 mmol) in THF (2 mL) were added 4-bromoveratorole (0.87 mL, 6.05 mmol) and a small amout of I_2 and the mixture was stirred at 110 °C for 2 h under Ar. Thus prepared Grignard reagent solution was cooled to 0 °C, the aldehyde **12** dissolved in THF (2 mL) was added to the Grignard reagent solution, and the mixture was allowed to stir for 18 h under Ar. Then 10% NH_4Cl aqueous solution was added to stop the reaction. The reaction mixture was extracted with ethyl acetate, which was dried over $MgSO_4$, and removed in vacuo. The residue thus formed was purified with column chromatography (CH_2Cl_2 to EtOAc) to give the alcohol **13** (48.8 mg, 81%).

Ethyl 1-[2-(3,4-dimethoxyphenyl)-2-hydroxyethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (13): colorless oil; ^{1}H NMR ($CDCl_3$, 60 °C) δ 1,24−1,33 (4H, m), 2.08−2.13 (1H, m), 2.34 (1H, qui, J = 7.4 Hz), 2.66 (1H, dt, J = 16.0, 4.4 Hz), 2.82−2.89 (1H, m), 3.28−3.34 (1H, m), 3.79−3.88 (12H, m), 4.09−4.27 (3H, m), 4.60−4.84 (1H, m), 5.21−5.41 (1H, m), 6.56−6.63 (2H, m), 6.78−7.00 (3H, m); ^{13}C NMR ($CDCl_3$, 60 °C) [those derived from a minor diastereomer and/or a conformational isomer are shown in parentheses] δ 14.5 (14.6), 27.8 (28.0), 38.5 (38.3), 46.1 (46.5), 51.6 (51.3), 55.72 (55.66), 55.77 (55.82), 55.98 (56.0), 56.1 (56.2), 61.9 (61.4), 72.0 (69.2), 109.7 (110.3), 110.6 (110.7), 111.2 (111.4), 111.7 (112.0), 117.8 (118.0), 127.3 (125.5), 129.3 (129.7), 137.5 (136.7), 148.05 (147.8), 148.08 (148.11), 149.2 (149.3), 155.5 (155.9); HR-FAB MS calcd for $C_{24}H_{32}NO_7$ $[M + H]^+$ 446.2179, found 446.2170.

The Synthesis of Homolaudanosine (14). To compound **13** (47.0 mg, 0.11 mmol) dissolved in THF (3 mL) was added pyridine (30 μL, 0.37 mmol) and thionyl chloride (25 μL, 0.34 mmol), and the mixture was stirred for 2.3 h at 0 °C under Ar. Then $LiAlH_4$ (63 mg, 1.66 mmol) was added, and the mixture was warmed to 100 °C with stirring for 6.7 h. The reaction was quenched with 10% HCl aqueous solution, and saturated aqueous sodium bicarbonate (20 mL) was added. Insoluble material was filtered through a Celite pad, and the filtrate was extracted with ethyl acetate. The Celite pad used was washed with hot $CHCl_3$, and the combined organic layers were dried over $MgSO_4$, filtered, and removed in vacuo to obtain the desired product homolaudanosine as a colorless oil, which was further purified with column chromatography (CH_2Cl_2/MeOH = 10) (24.0 mg, 61%).

Homolaudanosine (14):[29] colorless oil; (*S*)-**14** $[\alpha]^{18}_D$ +10.5 (*c* 0.16, EtOH); ^{1}H NMR ($CDCl_3$, 60 °C) δ 2.01−2.07 (2H, m), 2.48 (3H, s), 2.50−2.56 (1H, m), 2.66−2.81 (4H, m), 3.12−3.18 (1H, m), 3.43 (1H, t, J = 5.4 Hz), 3.83 (3H, s), 3.851 (3H, s), 3.856 (3H, s), 3.858 (3H, s), 6.54 (1H, s), 6.58 (1H, s), 6.71−6.74 (2H, m), 6.79 (1H, d, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 60 °C) δ 24.8, 31.1, 36.8, 42.4, 47.5, 55.71, 55.72, 55.81, 55.83, 62.4, 110.5, 111.2, 111.3, 111.8, 120.0, 126.3, 129.3, 135.2, 146.8, 147.21, 147.23, 148.7; HR-FAB MS calcd for $C_{22}H_{30}NO_4$ $[M + H]^+$ 372.2175, found 372.2184.

The Protection of N-2 of Compound 4 with the Boc Group. Compound **4** (997 mg, 4.3 mmol) and $(Boc)_2O$ (1.18 mL, 5.1 mmol) were dissolved in CH_2Cl_2 (30 mL) and the mixture was stirred for 20 h under Ar at room temperature. The reaction was quenched by addition of H_2O (60 mL) and the aqueous solution thus obtained was extracted with CH_2Cl_2 and the combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc = 4 to 2) to obtain the desired product **23** (1.39 g) as a colorless oil in 97% yield.

***tert*-Butyl 1-allyl-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (15):** HPLC: CHIRALPAK IA, hexane: CH_2Cl_2 = 10:1, 0.5 mL/min, retention times 23.9 and 25.2 min (*R*)-**15** (82% ee) $[\alpha]^{20}_D$ −53.8 (*c* 0.55, $CHCl_3$); colorless oil; ^{1}H NMR (DMSO-d_6, 100 °C) δ 1.40 (9H, s), 2.30−2.38 (1H, m), 2.45−2.52 (1H, m), 2.69−2.73 (2H, m), 3.21−3.28 (1H, m), 3.73 (3H, s), 3.79 (3H, s), 3.82−3.90 (1H, m), 4.91−5.01 (2H, m), 5.21 (1H, dd, J = 8.9, 3.9 Hz), 5.72−5.82 (1H, m), 6.30 (1H, d, J = 2.2 Hz), 6.40 (1H, d, J = 2.2 Hz); ^{13}C NMR (DMSO-d_6, 100 °C) δ 27.4, 27.6, 37.9, 48.6, 54.7, 55.0, 78.1, 96.4, 104.7, 104.9, 115.3, 118.2, 135.2, 135.4, 153.5, 155.9, 158.5; HR-FAB MS calcd for $C_{19}H_{28}NO_4$ $[M + H]^+$ 334.2018, found 334.2034.

The Conversion of the Allyl Adduct 15 to the Aldehyde 16. To the allyl adduct **15** (1.28 g, 3.8 mmol) dissolved in a mixture of acetone (35 mL) and H_2O (15 mL) were added NMO (50% aqueous solution, 3.7 mL, 17.5 mmol) and OsO_4 (4% aqueous solution 1.1 mL, 0.18 mmol), and the mixture was allowed to stir at room temperature for 1.5 h. Then the reaction was quenched with 10% $NaHSO_3$ aqueous solution (40 mL), and the resultant solution was extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue thus obtained was dissolved in the mixture of acetone (90 mL) and H_2O (20 mL), and $NaIO_4$ (1.9 g, 2.3 mmol) was added at room temperature and the mixture was stirred for 12 h. The reaction mixture was diluted with brine (100 mL) and extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$, filterd, and concentrated in vacuo. The residue thus formed was purified with column chromatography (EtOAc) to give the aldehyde **16** as a yellow oil (1305 mg, quant).

***tert*-Butyl 6,8-dimethoxy-1-(2-oxoethyl)-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (16):** pale yellow oil; (*R*)-**16** (82% ee) $[\alpha]^{19}_D$ −68.0 (*c* 1.03, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 100 °C) δ 1.41 (9H, s), 2.61 (1H, ddd, J = 14.9, 8.5, 3.7 Hz), 2.67−2.80 (3H, m), 3.20−3.27 (1H, m), 3.74 (3H, s), 3.80 (3H, s), 3.88−3.91 (1H, m), 5.59 (1H, dd, J = 8.4, 4.6 Hz), 6.34 (1H, d, J = 2.2 Hz), 6.42 (1H, d, J = 2.2 Hz), 9.68 (1H, dd, J = 2.7, 3.5 Hz); ^{13}C NMR (DMSO-d_6, 100 °C) δ 28.0, 28.1, 37.6, 45.6, 48.8, 55.4, 55.6, 79.5, 97.1, 105.7, 117.5, 136.1, 153.9, 156.2, 159.5, 200.3; HR-FAB MS calcd for $C_{18}H_{26}NO_5$ $[M + H]^+$ 336.1811, found 336.1818.

Horner−Wadsworth−Emmons Reaction of 16. To the aldehyde **16** (329.4 mg, 0.98 mmol) solution of acetonitrile (30 mL) were added benzyloxycarbonyl-α-phosphonoglycine trimethyl

(29) Itoh, T.; Nagata, K.; Miyazaki, M.; Kameoka, K.; Ohsawa, A. *Tetrahedron* **2001**, *57*, 8827.

ester (390 mg, 1.2 mmol) and tetramethylguanidine (185 μL, 1.5 mmol) at 10 °C. After stirring at room temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2, and washed by 10% citric acid aqueous solution, saturated aqueous sodium bicarbonate solution, and brine, respectively. The resulting organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (hexane/EtOAc = 1) to obtain the dehydroamino acid **17** as a colorless amorphous solid (501.2 mg, 95%).

***tert*-Butyl 1-(3-benzyloxycarbonylamino-3-methoxycarbonylallyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinoline-2-carboxylate (17):** colorless amorphous, mp 55−63 °C; (*R*)-**17** (82% ee) $[\alpha]^{19}_D$ −42.2 (*c* 2.3, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 100 °C) δ 1.42 (9H, s), 2.51−2.76 (4H, m), 3.17−3.20 (1H, m), 3.64 (3H, s), 3.75 (3H, s), 3.77 (3H, s), 3.84 (1H, br s), 5.05 (2H, d, *J* = 2.9 Hz), 5.247−5.254 (1H, m), 6.33 (1H, d, *J* = 2.3 Hz), 6.41 (1H, d, *J* = 2.3 Hz), 6.52 (1H, t, *J* = 6.9 Hz), 7.31−7.34 (5H, m), 8.23 (1H, br s); ^{13}C NMR (DMSO-d_6) [those derived from conformational isomer are shown in parentheses] δ 27.4, 27.5, 31.9, 36.7, 48.0, 51.0, 54.8, 55.0, 65.3 (65.4), 78.62 (78.4 and 78.58), 96.4, 105.0, 117.6, 126.9, 127.1, 127.65, 127.72, 133.3, 135.5, 136.3, 153.7, 153.4, 155.9, 158.7, 164.1. Anal. Calcd for $C_{29}H_{36}N_2O_8$: C, 64.43; H, 6.71; N, 5.18. Found: C, 64.15; H, 6.79; N, 5.19. HR-FAB MS calcd for $C_{29}H_{37}N_2O_8$ $[M + H]^+$ 541.2550, found 541.2595.

Reduction of 25 by the Use of MONOPHOS Ligand. Compound **17** (161.8 mg, 0.33 mmol), (*R*)-MONOPHOS (23.5 mg, 0.073 mmol), and $Rh(COD)_2BF_4$ (12.2 mg, 0.033 mmol) were dissolved in CH_2Cl_2 (7 mL). The reaction mixture was charged with H_2 gas at room temperature and stirred for 2 days. The reaction mixture was adsorbed on the surface of silica gel and sequentially purified by column chromatography (hexane/EtOAc = 1) to give an amino acid derivative **18** as a colorless amorphous solid (160.7 mg, 99%).

***tert*-Butyl 1-(3-benzyloxycarbonylamino-3-methoxycarbonylpropyl)-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (18):** colorless amorphous; ^{1}H NMR (DMSO-d_6, 100 °C) δ 1.41 (9H, s), 1.56−1.79 (4H, m), 2.63−2.77 (2H, m), 3.19−3.25 (1H, m), 3.62 (3H, s), 3.72 (3H, s), 3.74 (3H, d, *J* = 8.4 Hz), 3.80−3.90 (1H, m), 4.07−4.20 (1H, m), 5.03−5.04 (2H, m), 5.11 (1H, br s), 6.29 (1H, br s), 6.38 (1H, t, *J* = 3.2 Hz), 7.25−7.34 (5H, m); ^{13}C NMR ($CDCl_3$) [those derived from a minor isomer and/or a conformational isomer are shown in parentheses] δ 28.4, 28.7, 29.7 (29.4), 30.1 (30.3), 36.2 (36.1), 37.7 (37.5), 49.1, 49.7, 52.2, 54.6 (54.1), 55.3 (55.2), 66.9 (66.7), 79.6 (79.9), 96.4 (96.6), 104.2 (104.3), 119.4 (119.0), 128.1 (127.9), 128.5 (128.4), 135.7, 136.2 (136.7), 155.2 (154.8), 156.1 (155.8), 156.8 (156.6), 159.1, 173.0 (173.2); HR-FAB MS calcd for $C_{29}H_{39}N_2O_8$ $[M + H]^+$ 543.2706, found 543.2706

The Ring Formation to Compound 19. To the solution of compound **18** (1.34 g, 2.5 mmol) in CH_2Cl_2 (20 mL) was added TMSOTf (0.45 mL, 2.5 mmol), and the mixture was allowed to stand for 11 h under air. The reaction was quenched with MeOH (20 mL) and the solvent was removed in vacuo. The residue thus obtained was dissolved in MeOH (20 mL), and 18-crown-6 (1.23 g, 4.7 mmol) and K_2CO_3 (0.34 g, 2.5 mmol) were added, then the mixture was allowed to stir for 1 d under Ar. H_2O (20 mL) and saturated aqueous $NaHCO_3$ solution (20 mL) were added to the reaction mixture and the obtained aqueous solution was extracted with CH_2Cl_2. After washed with brine, the organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The mixture of the diastereomeric compounds was separated with column chromatography (hexane/EtOAc = 4 to 0.25) to obtain **19a** (796 mg, 79%) and **19b** (171.3 mg, 17%) as colorless amorphous solids, respectively.

Benzyl (9,11-dimethoxy-4-oxo-1,3,4,6,7,11b-hexahydro-2*H*-pyrido[2,1-*a*]isoquinolin-3-yl)carbamate (19a, 19b): colorless amorphous. **19a** (yield 79%, 98% ee): mp 61−65 °C; R_f 0.49 (silica gel, EtOAc:hexane = 4:1); HPLC: CHIRALPAK AD-H, hexane:*i*-PrOH = 1:1, 0.5 mL/min, retention times 22.5 and 35.0 min (3*S*,11b*R*)-**19a** (98% ee) $[\alpha]^{20}_D$ +198.6 (*c* 0.26, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.26−1.38 (1H, m), 1.72−1.82 (1H, m), 2.36 (1H, br s), 2.47−2.54 (2H, m), 2.72−2.79 (1H, m), 2.88−2.91 (1H, m), 3.695 (3H, s), 3.702 (3H, s), 3.97−4.06 (1H, m), 4.62−4.64 (1H, m), 4.81−4.84 (1H, m), 5.03 (2H, d, *J* = 3.6 Hz), 5.81 (1H, br s), 6.17 (1H, s), 6.26 (1H, d, *J* = 2.4 Hz), 7.18−7.28 (5H, m); ^{13}C NMR ($CDCl_3$) δ 27.4, 27.8, 30.4, 39.4, 52.8, 55.1, 55.2, 55.9, 66.6, 97.1, 104.6, 117.6, 127.87, 127.92, 128.3, 136.4, 137.6, 156.5, 157.6, 159.0, 168.4; HR-FAB MS calcd for $C_{23}H_{27}N_2O_5$ $[M + H]^+$ 411.1920, found 411.1942.

19b (yield 17%, 62% ee): mp. 55−59 °C; R_f 0.60 (silicagel, EtOAc:hexane = 4:1); HPLC: CHIRALPAK AD-H, hexane:*i*-PrOH = 1:1, 0.5 mL/min, retention times 20.9 and 25.2 min. (3*S*,11b*S*)-**19b** (62% ee) $[\alpha]^{19}_D$ −117.0 (*c* 0.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.19−1.38 (3H, m), 2.26−2.37 (1H, m), 2.50−2.74 (4H, m), 3.69 (3H, s), 3.72 (3H, s), 4.28−4.34 (1H, m), 4.57−4.64 (1H, m), 4.74 (1H, dd, *J* = 11.0, 3.8 Hz), 5.04 (2H, d, *J* = 5.2 Hz), 6.06 (1H, d, *J* = 4.8 Hz), 6.20 (1H, d, *J* = 2.0 Hz), 6.26 (1H, d, *J* = 2.4 Hz), 7.17−7.30 (5H, m); ^{13}C NMR ($CDCl_3$) δ 25.8, 28.5, 29.8, 39.1, 48.8, 50.4, 55.5, 55.6, 66.9, 97.2, 104.6, 116.9, 128.27, 128.31, 128.7, 136.8, 137.3, 156.3, 157.1, 159.7, 170.4; HR-FAB MS calcd for $C_{23}H_{27}N_2O_5$ $[M + H]^+$ 411.1920, found 411.1895.

Elimination of the Cbz Group To Give the Isoquinoline Moiety of Schulzeine. Compound **19a** (207 mg, 0.5 mmol) and Pd−C (10 wt.% Pd/C, 79.5 mg, 0.075 mmol) were dissolved in MeOH (20 mL), then hydrogen gas was purged and the mixture was allowed to stir at room temperature for 21 h. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated in vacuo. The residue thus obtained was purified by column chromatography (EtOAc/MeOH = 10 to 2) to give the desired amine **20a** as a yellow oil (150.7 mg, quant). The same procedure was applied to compound **19b** (182 mg, 0.44 mmol) to give amine **20b** (129 mg, quant).

3-Amino-9,11-dimethoxy-1,2,3,6,7,11b-hexahydropyrido[2,1-*a*]-isoquinolin-4-one (20a, 20b). 20a: ^{1}H NMR (CD_3OD) δ 1.43 (1H, dddd, *J* = 13.9, 12.5, 12.5, 2.6 Hz), 1.95 (1H, dddd, *J* = 12.9, 12.9, 12.7, 2.5 Hz), 2.27−2.33 (1H, m), 2.62−2.69 (2H, m), 2.76−2.87 (1H, m), 3.03−3.09 (1H, m), 3.77 (3H, s), 3.74−3.83 (1H, m), 3.81 (3H, s), 4.78−4.85 (2H, m), 6.33 (1H, d, *J* = 2.0 Hz), 6.43 (1H, d, *J* = 2.0 Hz); ^{13}C NMR (CD_3OD) δ 27.0, 28.6, 31.1, 40.6, 52.2, 55.78, 55.80, 57.2, 98.2, 106.1, 117.9, 138.7, 159.0, 160.9, 168.3; HR-FAB MS calcd for $C_{15}H_{21}N_2O_3$ $[M + H]^+$ 277.1552, found 277.1535.

20b: ^{1}H NMR ($CDCl_3$) δ 1.38−1.50 (1H, m), 1.66−1.77 (1H, m), 2.38−2.49 (2H, m), 2.73−2.79 (3H, m), 3.78 (3H, s), 3.83 (3H, s), 4.04−4.09 (1H, m), 4.61−4.69 (1H, m), 4.86 (1H, dd, *J* = 3.2, 11.2 Hz), 6.37 (1H, d, *J* = 2.0 Hz), 6.44 (1H, d, *J* = 2.0); ^{13}C NMR ($CDCl_3$) δ 24.8, 28.8, 30.2, 40.1, 50.0, 50.8, 55.8, 55.9, 98.0, 105.8, 117.0, 138.3, 158.3, 161.1, 170.1; HR-FAB MS calcd for $C_{15}H_{21}N_2O_3$ $[M + H]^+$ 277.1552, found 277.1574.

Acknowledgment. This work was supported by a "High-Tech Research Center" Project for Private Universities: matching fund subsidy from MEXT (Ministry of Education, Culture, Sports, Science and Technology), and a Grant-in-Aid for Scientific Research (C) from Japan Society for the Promotion of Science. We thank Dr. Saito of Takasago International Corporation for providing us with DTBM-SEGPHOS and SEGPHOS, and Ms. K. Shiohara of Showa University for measuring the HRMS spectra.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **1**−**13**, **15**−**16**, and **18**−**20**, and ORTEP drawing of the X-ray crystal structure of compound **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.