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The Synthesis of Isoquinoline Alkaloid and Its Related Compounds Using Alanine Derivatives as Chiral Auxiliaries

Takashi ITOH, Kazuhiro NAGATA, Masashi YOKOYA, Michiko MIYAZAKI, Keiko KAMEOKA,
Shigeru NAKAMURA, and Akio OHSAWA*

School of Pharmaceutical Sciences, Showa University; 1–5–8 Hatanodai, Shinagawa-ku, Tokyo 142–8555, Japan.

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Chiral 1-substituted isoquinoline derivatives, which were obtained by the reaction using alanine derivatives as chiral auxiliaries, were transformed to (*S*)-2,3,9,10,11-pentamethoxyhomoprotoberberine (7) and a synthetic intermediate for *O*-methylkreysigine (9) in good yields and high stereoselectivity. The corresponding chiral allyl derivative of isoquinoline was transformed to a pyrrolidinoisoquinoline (16) in a highly enantioselective manner.

Key words asymmetric synthesis; indole alkaloid; chiral auxiliary; pentamethoxyhomoprotoberberine; *O*-methylkreysigine; hexahydropyrrolo[2,1-*a*]isoquinoline

In the course of our study concerning asymmetric synthesis of 1-substituted isoquinoline and β-carboline derivatives, we found that chiral auxiliaries derived from simple amino acids afforded good stereoselectivity on the addition of silyl enol ethers or allyltributyltin to the C-1 position of the isoquinoline[1] or β-carboline[2,3] nucleus. In the case of isoquinolines, 5,8-dibromo derivatives which were readily obtained by reaction of the parent aromatics with Br_2 were found to be good substrates, and some *N*-substituted alanines were suitable chiral auxiliaries. Since both enantiomers of alanine are readily obtained from a commercial source, it is a useful method for making desirable enantiomers on demand.

With the method in hand, we have been investigating the total synthesis of natural products, and have already reported the asymmetric synthesis of an isoquinoline alkaloid homolaudanosine.[1] In this paper, we describe further application of our asymmetric addition products to the synthesis of (*S*)-2,3,9,10,11-pentamethoxyhomoprotoberberine (**7**), a synthetic intermediate for (*S*)-*O*-methylkreysigine (**9**), and an unnatural bioactive compound (*R*)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline (**16**).[4,5]

Since 1-substituted tetrahydroisoquinoline alkaloids exhibit a variety of biological activities,[6,7] several synthetic methods for these compounds have been developed.[8] There has been, however, only one report concerning the direct asymmetric addition of nucleophiles to an aromatic isoquinoline nucleus.[9] Thus, Comins *et al.*[9] reported the synthesis of (+)-carnegine *via* simple procedures, but the stereoselectivity of the product was low (62% ee). Although there have been several studies using the 3,4-dihydroisoquinoline nucleus as a substrate of asymmetric addition,[10] high stereoselectivity was seldom accomplished. Thus, we focused our attention on preparing chiral isoquinoline alkaloids and related compounds in order to confirm the generality and compatibility of our reaction method.

(*S*)-2,3,9,10,11-Pentamethoxyhomoprotoberberine (**7**) is a closely related compound of homoaporphine alkaloids, and its total syntheses were reported in two papers.[11—13] The most recent one was carried out by Czarnocki *et al.*,[12,13] who converted (*R*)-2-ethoxycarbonyl-1-formyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline to the compound in 4 steps. It was reported, however, that the starting material synthesized *via* 5 steps from D-tartaric acid and 3,4-dimethoxyphenethylamine tended to racemize, thus the product obtained from this process showed slightly lower stereoselectivity (87% ee). Our synthesis was commenced with a reaction using 5,8-dibromo-6,7-dimethoxyisoquinoline (**1**) and an (*R*)-alanine derivative.[14] Our previous study indicated that chiral auxiliaries derived from (*R*)-alanine would afford the desired stereoisomer,[1] thus the reaction of **1** with 1-(3,4,5-trimethoxyphenyl)-1-trimethylsilyloxyethylene was carried out in the presence of *N*-protected (*R*)-alanyl chloride in order to construct a required carbon skeleton with a chiral center at the C-1 position. Various *N*-protecting groups were tested, and a *p*-nitrobenzenesulfonyl group afforded the best selectivity.[15]

As a result, a 1-substituted 1,2-dihydroisoquinoline **2** was obtained in a high yield and good diastereoselectivity (Chart 1). The adduct **2** was purified to be a single diastereomer by recrystallization.

Reduction of **2** with HCO_2NH_4 in the presence of 10% Pd/C[16] resulted in the formation of 1,2,3,4-tetrahydroisoquinoline **3** *via* simultaneous debromination, reductions of the 3,4-double bond, and the nitro group in 95% yield. There was a small amount of a side product whose structure was supposed to be an alcohol derived from the reduction of the keto group of **2** (see Experimental). A standard debromination protocol such as radical reduction using tributyltin hydride resulted in the recovery of the starting material. The keto group in **3** was transformed to a methylene by a catalytic hydrogenation of **3** under acidic conditions using trifluoroacetic acid (TFA). Then, we planned removal of the chiral auxiliary using hydrolysis or reduction of the amide group of **4**, but all of our attempts failed under the following conditions. That is, the starting material **4** was recovered when **4** was treated with KOH, NaOH, LiOH–H_2O_2 or $LiAlH_4$ in various solvents. And, only when **4** was treated with KOH in ethylene glycol at 170 °C, the desired **6** was obtained, but in a low yield of 37% with partial racemization (66% ee), which was confirmed by measurement of the specific rotation of the product. In order to change the reactivity of **4** toward the nucleophile, compound **4** was subjected to trifluoroacetylation at an aromatic amino group to give **5** in 91% yield. The trifluoroacetylated compound **5** was allowed to react with $LiAlH_4$ at 0 °C to give **6** in 64% yield with no loss of enantiopurity. Finally, **6** was treated with 48% HBr solution in H_2O and formalin at 100 °C under the reported conditions[13]

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* To whom correspondence should be addressed. e-mail: ohsawa@pharm.showa-u.ac.jp

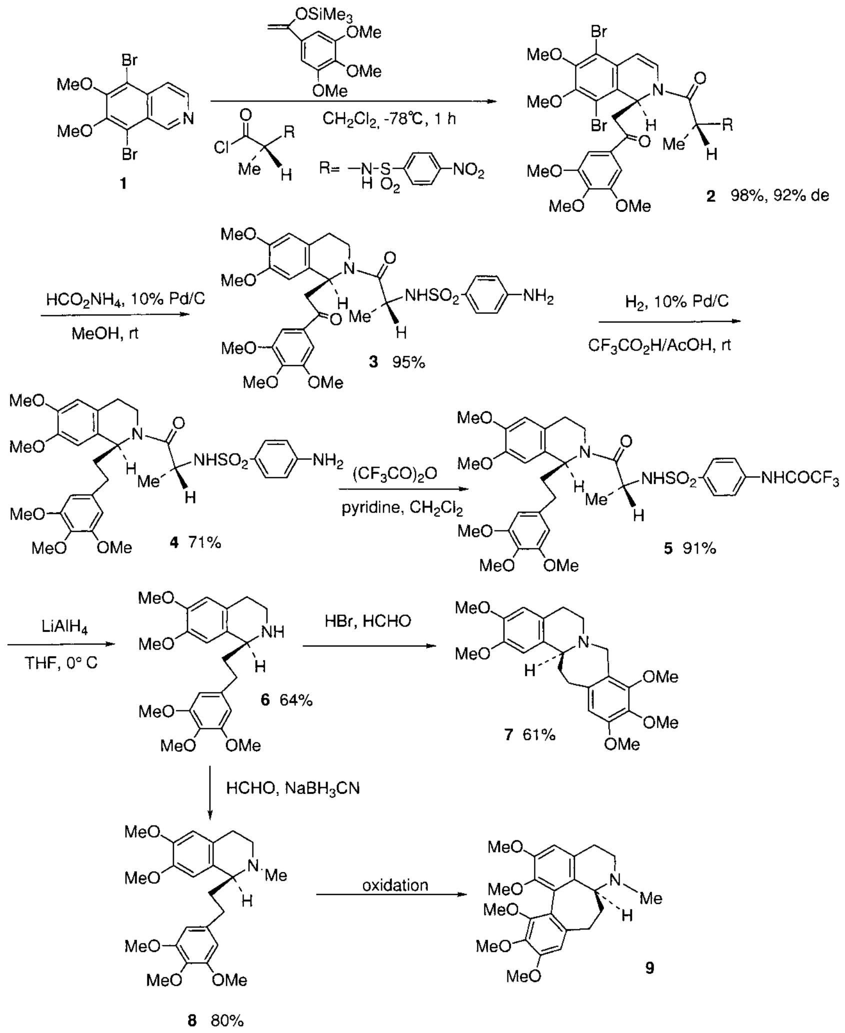

Chart 1

to give (S)-2,3,9,10,11-pentamethoxyhomoprotoberberine (**7**) in 61% yield (99% ee). This was converted to a hydrochloride salt to compare the optical rotation with that of the reported one.[11] The overall yield of **7** from 5,8-dibromo-6,7-dimethoxyisoquinoline (**1**) was 23%, which was superior to the reported one[13] (3.5% from tartaric acid). In addition, N-methylation of **6** using formaldehyde and $NaBH_3CN$ gave a synthetic precursor (**8**) of (S)-O-methylkreysigine (**9**) in 80% yield ($[\alpha]_D^{25}=+6.1°$ (c=0.92, MeOH), lit.[13] $[\alpha]_D^{25}=+4.8°$ (MeOH)).

Next, an allyl adduct **11** was adopted as a starting material for biologically active isoquinoline derivatives. Although we already reported that 5,8-dibromoisoquinoline (**10**) reacted with allyltributyltin in the presence of N-phthaloyl-(S)-alanyl chloride to give the 1,2-adduct **11** in a highly diastereoselective manner, the absolute configuration of the chiral center formed was not determined definitely.[1] Pyrrolidinoisoquinoline moieties widely exist in plant products such as erythrinane and related alkaloids, and many of them exhibit interesting biological activity.[17] Thus, a lot of synthetic studies have focused on the development of general approaches to these compounds.[18—20] In spite of these efforts, there are few general methods for the asymmetric synthesis of these compounds.[21—24] Lee *et al.* reported the total synthesis of both enantiomers of parent **16**.[25,26] The overall yields of their synthesis are 10.0% for the R isomer (6 steps from L-tartaric acid and 2-phenethylamine), and 6.1% for the S isomer (8 steps from malic acid and 2-phenethylamine), respectively. Therefore, we decided to carry out the asymmetric synthesis of (R)-**16** to determine the absolute configuration of **11** unambiguously, and also to improve the reported synthetic method (Chart 2).

The known compound **10**[27] was allowed to react with allyltributyltin and N-phthaloyl-(S)-alanyl chloride in the presence of tetrabutylammonium iodide to give the 1-allyl-1,2-dihydro adduct **11** in 95% yield (95% de). Contrary to the case of the 6,7-dimethoxyisoquinoline derivative **1**,[1] the N-(p-nitrobenzenesulfonyl)alanyl group did not afford a good result (65% yield, 83% de). Then, hydroboration and subsequent oxidation were carried out using BH_3–THF complex and $NaOH–H_2O_2$ to give **12** in a moderate yield of 70%. The reduction of **12** under catalytic hydrogenation conditions rapidly proceeded to give a debrominated derivative **13** in quantitative yield. Further reduction under the same conditions slowly transformed **13** to **14** in a moderate yield. Direct formation of **14** from **12** was also possible by elongation of the reaction time (6 h) to give a comparable yield of 62%. Then, the chiral auxiliary was removed by reduction of

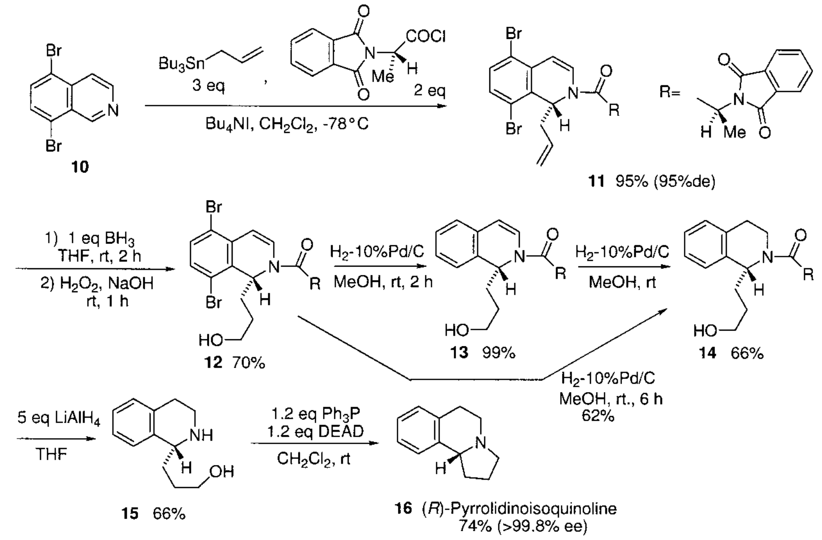

Chart 2

$LiAlH_4$ in THF to afford **15** without any racemization. In the last step, a Mitsunobu procedure[28] was applied to **15**, and the ring-closed product **16** was obtained in good yield with high enantiopurity. The overall yield from **10** was 20% (5 steps), and both enantiomers of the chiral auxiliary were readily obtained from a commercial source, thus the reaction in Chart 2 seems to be a good alternative for the reported one.[25,26]

In this paper, we described the application of the chiral adducts derived from isoquinoline to the synthesis of (*S*)-2,3,9,10,11-pentamethoxyhomoprotoberberine (**7**) and a pyrrolidinoisoquinoline **16**, as well as the formal synthesis of (*S*)-*O*-methylkreysigine (**9**) in short straightforward steps. The results indicate that our method was useful and convenient for the concise synthesis of chiral isoquinoline alkaloids. Application of the asymmetric addition to the synthesis of other alkaloids is now under investigation.

Experimental

General Remarks Melting points were measured with a Büchi micro melting point apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on JEOL GX400 and LA500 spectrometers using tetramethylsilane (TMS) as an internal standard. High-resolution mass spectra (FAB-HR-MS) were measured with JEOL JMS-MS700V using *p*-nitrobenzyl alcohol as a matrix. The enantiomeric excess of the products was determined by HPLC analysis using a JASCO UV2070 PU2080 system and chiralcel OD-R column.

1-(3,4,5-Trimethoxyphenyl)-1-(trimethylsilyloxy)ethene[29] To the 2.0 M lithium diisopropylamide solution of heptane/tetrahydrofuran/ethylbenzene (19 ml, 38 mmol) was added the THF solution (30 ml) of 3′,4′,5′-trimethoxyacetophenone (4.87 g, 23.2 mmol) and trimethylsilyl chloride (5.8 ml, 60 mmol) at −78 °C, and the mixture was allowed to react for 1 h. Then, the mixture was warmed to room temperature, and the solvent was evaporated off. The residue was extracted with pentane, and the solution was evaporated to leave an oil, which was distilled under reduced pressure (158 °C/7 mmHg) to give 1-(3,4,5-trimethoxyphenyl)-1-(trimethylsilyloxy)ethene (4.85 g, 17 mmol) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.28 (9H, s), 3.85 (3H, s), 3.88 (6H, s), 4.41 (1H, d, J=1.6 Hz), 4.84 (1H, d, J=1.6 Hz), 6.83 (2H, s). ^{13}C-NMR ($CDCl_3$) δ: 0.1, 56.0, 60.8, 90.8, 102.6, 133.2, 138.3, 152.8, 155.3. FAB HR-MS: Calcd for $C_{14}H_{23}O_4Si$ $(M+H)^+$: 283.1366. Found 283.1387.

5,8-Dibromo-1,2-dihydro-6,7-dimethoxy-2-[*N*-(4-nitrobenzenesulfonyl)-(*R*)-alanyl]-1-(*S*)-(3,4,5-trimethoxyphenacyl)isoquinoline (2) To the suspension of *N*-(4-nitrobenzenesulfonyl)-(*R*)-alanine (1.1 g, 4.30 mmol) in benzene (40 ml), 6 ml of $SOCl_2$ was added and the mixture was allowed to react at 60 °C for 8 h. Then, the solvent and excess $SOCl_2$ were removed completely *in vacuo*, and the residue was dissolved in CH_2Cl_2. To the mixture was added 5,8-dibromo-6,7-dimethoxyisoquinoline[1] (1.0 g, 2.89 mmol) under Ar, then the solution was cooled to −78 °C. The CH_2Cl_2 (10 ml) solution of 1-(3,4,5-trimethoxyphenyl)-1-(trimethylsilyloxy)ethene (1.63 g, 5.78 mmol) was added to the mixture, and the reaction was continued at −78 °C for 1 h. Then the mixture was warmed to room temperature, and the solvent was evaporated off to leave a residue. Next, the residue was chromatographed on a silica gel column (CH_2Cl_2/Et_2O=10) to give the addition product **2**, which was recrystallized from CH_2Cl_2/hexane to afford 2.30 g of a pale yellow powder (98%, 92% de). $[\alpha]_D^{25}=+272.9°$ (c=0.68, $CHCl_3$). mp 173 °C (dec). ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, d, J=7.2 Hz), 2.68 (1H, dd, J=12.8, 10.4 Hz), 3.10 (1H, dd, J=12.0, 3,6 Hz), 3.88 (6H, s), 3.90 (3H, s), 3.99 (3H, s), 4.04 (3H, s), 4.26 (1H, dq, J=7.2, 6.8 Hz), 5.64 (1H, d, J=10.4 Hz), 5.86 (1H, dd, J=10.4, 2.8 Hz), 6.47 (1H, d, J=8.0 Hz), 6.51 (1H, d, J=8.0 Hz), 7.11 (2H, s), 7.80 (2H, d, J=9.2 Hz), 7.88 (2H, d, J=9.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 19.2, 39.0, 48.8, 50.6, 56.3, 60.8, 60.9, 61.1, 105.7, 111.9, 115.9, 116.6, 122.9, 123.5, 126.2, 127.8, 128.5, 131.5, 142.7, 144.1, 149.3, 150.6, 151.0, 152.8, 169.6, 194.5. *Anal.* Calcd for $C_{31}H_{31}Br_2N_3O_{11}S$: C, 45.74; H, 3.85; N, 5.17. Found: C, 45.99; H, 3.91; N, 5.06.

2-[*N*-(4-Aminobenzenesulfonyl)-(*R*)-alanyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(*S*)-(3,4,5-trimethoxyphenacyl)isoquinoline (3) To the suspension of **2** (1.90 g, 2.34 mmol) in MeOH (150 ml) was added saturated aqueous HCO_2NH_4 solution (20 ml), and the reaction was initialized by the addition of 50% aqueous suspension of 10% Pd/C (4 g). The mixture was allowed to react for 4 h at room temperature. Then the mixture was filtrated with Celite, and the solvent was evaporated off. To the residue thus formed was added ethyl acetate, and the organic layer was washed with H_2O and brine, dried over $MgSO_4$, and evaporated. The residue was chromatographed on a silica gel (CH_2Cl_2/AcOEt=1), and the crude product was recrystallized from AcOEt–hexane to give **3** (1.39 g, 95%) as a colorless powder. $[\alpha]_D^{20}=+36.9°$ (c=0.55, $CHCl_3$). mp 122—124 °C. The product was obtained as a mixture of several conformational isomers. Thus the NMR spectra of the major isomer are shown; ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d, J=6.4 Hz), 2.62—2.90 (2H, m), 3.06 (1H, dd, J=14.0, 8.2 Hz), 3.38 (1H, dd, J=13.7, 5.8 Hz), 3.50—3.60 (2H, m), 3.75 (3H, s), 3.87 (3H, s), 3.92 (6H, s), 3.94 (3H, s), 4.13 (1H, dq, J=8.5, 7.3 Hz), 5.54 (1H, t, J=6.7 Hz), 5.66 (1H, d, J=9.2 Hz), 6.29 (2H, d, J=7.9 Hz), 6.43 (1H, s), 6.61 (1H, s), 7.27 (2H, s), 7.44 (2H, d, J=8.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 19.7, 28.1, 40.4, 45.2, 49.1, 50.8, 56.00, 56.03, 56.4, 61.0, 106.0, 109.0, 110.3, 111.2, 113.9, 125.1, 127.4, 129.1, 129.4, 132.0, 142.8, 147.5, 148.2, 153.2, 170.8, 196.1. *Anal.* Calcd for $C_{31}H_{39}N_3O_{10}S$ (monohydrate): C, 57.66; H, 6.09; N, 6.51. Found: C, 57.61; H, 6.20; N, 6.40.

In the above reaction, a minor product was obtained as an oil. The product was transformed to compound **3** by reduction under the same reaction conditions. This result and NMR spectral data suggested the structure of the minor compound as 2-[*N*-(4-aminobenzenesulfonyl)-(*S*)-alanyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(*S*)-[2-(3,4,5-trimethoxyphenyl)-2-hydroxyethyl]isoquinoline. The NMR data of the product are as follows: ^{1}H-NMR (CDCl$_3$) δ:1.43 (3H, d, J=7.0 Hz), 2.01—2.10 (2H, m), 2.66—2.88 (2H, m), 3.39—3.46 (1H, m), 3.80 (3H, s), 3.84 (6H, s), 3.87 (3H, s), 3.88 (3H, s), 4.25—4.32 (2H, m), 5.20 (1H, dd, J=10.3, 5.0 Hz), 5.69 (1H, d, J=9.9 Hz), 6.20 (2H, d, J=8.6 Hz), 6.55 (2H, s), 6.56 (1H, s), 6.60 (1H, s), 7.45 (2H, d, J=8.6 Hz). ^{13}C-NMR (CDCl$_3$) δ: 20.3, 28.1, 39.3, 45.8, 49.3, 50.2, 55.9, 56.0, 56.2, 60.8, 69.4, 102.5, 102.6, 109.9, 111.1, 114.3, 124.3, 128.1, 129.1, 138.1, 138.8, 140.0, 147.8, 148.0, 153.2, 172.5.

2-[*N*-(4-Aminobenzenesulfonyl)-(*R*)-alanyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(*S*)-(3,4,5-trimethoxyphenethyl)isoquinoline (4) To the AcOH/TFA (20 ml/2 ml) solution of compound **3** (310 mg, 0.49 mmol) was added a 50% aqueous suspension of 10% Pd/C (1.05 g), and the mixture was allowed to stand for 20 h at room temperature under H$_2$ atmosphere. Then, the mixture was filtrated with Celite, and the solvent was evaporated off. To the residue thus formed was added ethyl acetate, and the organic layer was washed with saturated aqueous NaHCO$_3$, dried over MgSO$_4$, and evaporated off. The crude product thus obtained was recrystallized from AcOEt–hexane to give compound **4** (210 mg, 71%) as a colorless powder. $[\alpha]_{\mathrm{D}}^{20}=+6.3°$ (c=0.45, CHCl$_3$). mp 108—110 °C. The product was obtained as a mixture of several conformational isomers. The NMR spectra of the major isomer are shown; ^{1}H-NMR (CDCl$_3$) δ: 1.37 (3H, d, J=6.8 Hz), 1.89—2.01 (2H, m), 2.46 (1H, ddd, J=15.6, 10.0, 5.6 Hz), 2.57—2.66 (3H, m), 3.46 (1H, ddd, J=13.6, 8.8, 5.6 Hz), 3.62 (1H, dt, J=13.2, 4.0 Hz), 3.79 (3H, s), 3.81 (6H, s), 3.84 (3H, s), 3.86 (3H, s), 4.19 (1H, dq, J=8.8, 7.2 Hz), 5.26 (1H, dd, J=8.8, 4.8 Hz), 5.80 (1H, d, J=9.2 Hz), 6.27 (2H, d, J=8.8 Hz), 6.37 (2H, s), 6.47 (1H, s), 6.56 (1H, s), 7.45 (2H, d, J=8.4 Hz). ^{13}C-NMR (CDCl$_3$) δ: 20.5, 22.9, 28.2, 32.8, 37.7, 39.1, 49.2, 52.4, 56.1, 56.2, 60.9, 105.2, 105.4, 110.30, 111.32, 111.7, 114.3, 124.6, 129.0, 129.1, 136.3, 137.1, 147.5, 147.8, 153.2, 170.9. *Anal.* Calcd for $C_{31}H_{39}N_3O_8S$: C, 60.64; H, 6.42; N, 6.85. Found: C, 60.45; H, 6.70; N, 6.47.

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-{*N*-[4-(trifluoroacetylamino)benzenesulfonyl]-(*R*)-alanyl}-1-(*S*)-(3,4,5-trimethoxyphenethyl)-isoquinoline (5) To the CH$_2$Cl$_2$ solution of compound **4** (44 mg, 0.072 mmol) was added trifluoroacetic anhydride (27 μl, 0.30 mmol) and pyridine (18 μl, 0.22 mmol), and the mixture was allowed to react for 5 h at room temperature. The solvent was evaporated off to leave a residue, which was dissolved in AcOEt. The organic layer thus formed was washed with 5% aqueous HCl and H$_2$O, dried over MgSO$_4$, and evaporated off. The crude product thus obtained was recrystallized from Et$_2$O–hexane to give **5** (47 mg, 91%) as a colorless powder. $[\alpha]_{\mathrm{D}}^{20}$ +21.35° (c=1.05, CHCl$_3$). mp 111—113 °C. The product was obtained as a mixture of several conformational isomers, thus the NMR spectra of the major isomer are shown; ^{1}H-NMR (CDCl$_3$) δ: 1.42 (3H, d, J=7.0 Hz), 1.92—2.18 (2H, m), 2.44 (1H, ddd, J=16.5, 11.0, 5.8 Hz), 2.53—2.67 (3H, m), 3.44—3.51 (1H, m), 3.62—3.69 (1H, m), 3.80 (3H, s), 3.82 (6H, s), 3.83 (3H, s), 3.84 (3H, s), 4.26 (1H, dq, J=8.9, 7.0 Hz), 5.27 (1H, dd, J=9.8, 5.2 Hz), 6.14 (1H, d, J=8.8 Hz), 6.35 (2H, s), 6.40 (1H, s), 6.50 (1H, s), 7.40 (2H, d, J=8.5 Hz), 7.72 (2H, d, J=8.9 Hz), 8.12 (1H, br). ^{13}C-NMR (CDCl$_3$) δ: 20.6, 22.7, 28.2, 32.8, 37.5, 39.0, 49.3, 52.3, 56.0, 56.1, 60.9, 105.1, 110.0, 111.4, 115.4 (q, $J_{\text{C-F}}$=288.6 Hz), 119.9, 124.0, 128.4, 128.5, 136.2, 136.7, 137.0, 138.9, 147.7, 148.0, 153.2, 170.1 (q, $J_{\text{C-F}}$=50.7 Hz), 170.46. *Anal.* Calcd for $C_{33}H_{38}F_3N_3O_9S$: C, 55.85; H, 5.40; N, 5.92. Found: C, 56.27; H, 5.65; N, 5.52.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(*S*)-(3,4,5-trimethoxyphenethyl)-isoquinoline (6) To the CH$_2$Cl$_2$ solution (2 ml) of compound **5** (151 mg, 0.21 mmol) was added lithium aluminum hydride LiAlH$_4$ (121 mg, 3.18 mmol) at 0 °C, and the mixture was allowed to stand for 2 h. Then, the additional LiAlH$_4$ (42 mg, 1.11 mmol) was applied to the mixture, and the reaction continued for another 3 h. Water was introduced to quench the reducing agent, and the mixture was warmed to room temperature. The mixture was extracted with AcOEt, and the organic layer thus obtained was washed with brine, dried over MgSO$_4$, and evaporated off. The residue was chromatographed on silica gel (CHCl$_3$/MeOH=10) to give the product **6** (52 mg, 64%) as a colorless oil. Although the yield was moderate, no side products were detected in the reaction. $[\alpha]_{\mathrm{D}}^{25}=-14.1°$ (c=0.34, CHCl$_3$); ^{1}H-NMR (CDCl$_3$) δ: 1.83 (1H, br), 2.03—2.19 (2H, m), 2.66—2.85 (4H, m), 3.04 (1H, ddd, J=12.8, 7.6, 5.2 Hz), 3.28 (1H, dt, J=12.8, 5.2 Hz), 3.82 (3H, s), 3.83 (3H, s), 3.84 (6H, s), 3.85 (3H, s), 4.02 (1H, dd, J=8.4, 3.6 Hz), 6.47 (2H, s), 6.576 (1H, s), 6.582 (1H, s). These data are identical with the reported ones.13)

(*S*)-2,3,9,10,11-Pentamethoxyhomoprotoberberine (7) The compound **6** (27 mg, 0.07 mmol) was mixed with 48% aq. HBr (43 mg) in water (2.5 ml), then 1.7 ml of 37% aqueous HCHO was added to the mixture. The reaction was carried out under reflux for 3 h. After cooling to room temperature, 20% aqueous NaOH was added to make the mixture basic, and the mixture was extracted with CHCl$_3$. The organic layer was extracted with 10% aq. HCl, and the acidic aqueous layer was basified using 20% aqueous NaOH. The aqueous mixture was extracted with CHCl$_3$. The organic layer was dried over MgSO$_4$, and evaporated off to give **7** (17 mg, 61%). In order to compare the $[\alpha]_{\mathrm{D}}$ value with that of the reported one, compound **7** (15 mg) was dissolved in EtOH (0.5 ml) and reacted with concentrated HCl (1 drop) at 80 °C. The solvent was evaporated off to leave a hydrochloride salt of **7**, which was recrystallized from MeOH/Et$_2$O (mp 224—226 °C, lit.11); mp 228—229 °C). Colorless oil. ^{1}H-NMR (CDCl$_3$) δ: 1.85—1.96 (2H, m), 2.60—2.79 (4H, m), 2.91—2.99 (1H, m), 3.12—3.19 (1H, m), 3.82 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 3.86 (3H, s), 3.88 (3H, s), 3.95 (1H, d, J=14.8 Hz), 4.14 (1H, dd, J=9.0, 5.0 Hz), 4.54 (1H, d, J=14.8 Hz). FAB-MS: 400 (M+H)$^+$. Hydrochloride salt $[\alpha]_{\mathrm{D}}^{25}=-111.3°$ (c=0.13, MeOH). These data are identical with the reported ones (lit. $[\alpha]_{\mathrm{D}}^{25}=-112.5°$ (MeOH)).13)

2-Methyl-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(*S*)-(3,4,5-trimethoxyphenethyl)isoquinoline (8) To the CH$_3$CN solution of the compound **6** (23 mg, 0.059 mmol) were added 37% aqueous HCHO (22 μl, 0.29 mmol) and NaBH$_3$CN (6 mg, 0.095 mmol), and the mixture was allowed to react for 2.5 h at room temperature. Then, 4 ml of 10% aqueous NaOH was added, and the mixture was extracted with AcOEt (6 ml×3). The organic layer was extracted with 10% aqueous HCl, and the acidic aqueous layer thus obtained was basified with 20% aqueous NaOH. The basic aqueous layer was extracted with AcOEt. The AcOEt layer was washed with brine, dried over MgSO$_4$, and evaporated off to give the product **8** (19 mg, 80%) as a colorless oil. In order to compare the $[\alpha]_{\mathrm{D}}$ value with that of the reported one, compound **8** was further purified using preparative TLC (silica 5717, Merck) (CHCl$_3$/MeOH=10). $[\alpha]_{\mathrm{D}}^{25}=+6.1°$ (c=0.92, MeOH). ^{1}H-NMR (CDCl$_3$) δ: 2.02—2.10 (2H, m), 2.49 (3H, s), 2.49—2.55 (1H, m), 2.62—2.83 (4H, m), 3.13—3.21 (1H, m), 3.45 (1H, t, J=5.5 Hz), 3.82 (3H, s), 3.83 (3H, s), 3.84 (6H, s), 3.86 (3H, s), 6.40 (2H, s), 6.55 (1H, s), 6.58 (1H, s). ^{13}C-NMR (CDCl$_3$) δ: 25.33, 32.07, 36.92, 42.71, 47.97, 52.95, 55.82, 56.03, 56.07, 60.86, 62.70, 105.32, 110.14, 111.31, 126.71, 129.62, 135.95, 138.70, 147.31, 153.08. These data are identical with the reported ones (lit. $[\alpha]_{\mathrm{D}}^{25}=+4.8°$ (MeOH)).13)

1-(*R*)-Allyl-5,8-dibromo-1,2-dihydro-2-[*N*-phthaloyl-(*S*)-alanyl]isoquinoline (11) The reaction was carried out according to the reported method,1) except that tetrabutylammonium iodide was used as an additive. The addition of the quaternary salt increased the reaction yield of **11** up to 95% from 75%.1)

5,8-Dibromo-1,2-dihydro-1-(*R*)-(3-hydroxypropyl)-2-[*N*-phthaloyl-(*S*)-alanyl]isoquinoline (12) To the THF solution (30 ml) of the compound **11** (2.0 g, 3.8 mmol) was added 1 M BH$_3$–THF solution (3.8 ml, 3.8 mmol) under Ar atmosphere at room temperature, and the mixture was allowed to react for 2 h. Water was added to quench the remaining BH$_3$–THF. Then, 30% aqueous H$_2$O$_2$ (0.8 ml) and 3 N aqueous NaOH (0.8 ml) were added to the mixture, and the reaction continued for another 1 h. Thereafter, water was added, and the mixture was extracted with ether. The organic layer was washed with water and brine, dried over MgSO$_4$, and evaporated off. A residue thus obtained was chromatographed on a silica gel (CH$_2$Cl$_2$/AcOEt=5) to give the crude product. It was recrystallized from AcOEt/Hexane to give **12** as a colorless powder (1.46 g, 70%). $[\alpha]_{\mathrm{D}}^{25}=-572.3°$ (c=1.04, MeOH). mp 173.2—174.6 °C. ^{1}H-NMR (CDCl$_3$) δ: 1.60—1.66 (3H, m), 1.70 (3H, d, J=6.9 Hz), 1.80 (1H, m), 3.69 (2H, t, J=5.5 Hz), 5.18 (1H, q, J=6.8 Hz), 6.07 (2H, d, J=7.7 Hz), 6.52 (1H, d, J=7.9 Hz), 7.20 (1H, d, J=8.8 Hz), 7.22 (1H, d, J=8.8 Hz), 7.70—7.78 (4H, m). ^{13}C-NMR (CDCl$_3$) δ: 15.8, 28.5, 28.8, 47.1, 53.9, 62.4, 110.4, 119.3, 120.3, 123.4, 125.5, 130.7, 131.1, 132.2, 134.2, 135.5, 166.8, 167.7. *Anal.* Calcd for $C_{23}H_{20}Br_2N_2O_4$: C, 50.39; H, 3.68; N, 5.11. Found C, 50.11; H, 3.45; N, 4.99.

1,2,3,4-Tetrahydro-1-(*R*)-(3-hydroxypropyl)-2-[*N*-phthaloyl-(*S*)-alanyl]-isoquinoline (14) To the MeOH solution (80 ml) of the compound **12** (1.37 g, 2.5 mmol) was added 10% Pd/C (880.0 mg, 0.8 mmol) under H$_2$ atmosphere at room temperature, and the mixture was allowed to react for 6 h at room temperature. Thereafter, AcOEt was added, and the mixture was filtered with Celite. The filtrate was evaporated off to leave a residue, which was chromatographed on silica gel (CH$_2$Cl$_2$/MeOH=20) to give the product **14** as a colorless, amorphous product (610 mg, 62%). $[\alpha]_{\mathrm{D}}^{25}=-71.7°$ (c=1.03, MeOH). The product was obtained as a mixture of two isomers (1 : 0.4). The NMR spectra of the major isomer are shown; ^{1}H-NMR (CDCl$_3$) δ: 1.59—1.67 (1H, m), 1.80 (3H, d, J=7.3 Hz), 1.82—2.02 (2H, m), 2.81 (1H, t, J=7.3 Hz), 3.58—3.76 (4H, m), 5.26 (1H, q, J=7.3 Hz), 5.56 (1H, dd, J=8.5, 4.9 Hz), 7.02 (1H, d, J=8.1 Hz), 7.11—7.22 (3H, m), 7.70—7.72 (2H, m), 7.81—7.83 (2H, m). ^{13}C-NMR (CDCl$_3$) δ: 15.6, 28.8, 29.1, 33.3, 40.2, 47.5, 53.2, 62.3, 123.5, 126.4, 126.6, 127.5, 128.4, 131.6, 133.1, 134.1, 137.3, 167.7, 168.5. HR-FAB-MS: Calcd for $C_{23}H_{25}N_2O_4$ $[M+H]^+$: 393.1814. Found 393.1806.

1,2-Dihydro-1-(*R*)-(3-hydroxypropyl)-2-[*N*-phthaloyl-(*S*)-alanyl]isoquinoline (13) The same procedure as above was carried out except the shortening of the reaction time to 2 h to give the intermediary compound **13** as a yellow oil (99%). ^{1}H-NMR ($CDCl_3$) δ: 1.44—1.86 (4H, m), 1.71 (3H, d, $J=7.0$ Hz), 3.67 (2H, m), 3.85 (1H, m), 5.20 (1H, q, $J=7.0$ Hz), 5.74 (1H, d, $J=7.5$ Hz), 6.09 (1H, dd, $J=9.5$, 3.1 Hz), 6.46 (1H, d, $J=6.6$ Hz), 6.80 (1H, d, $J=7.3$ Hz), 6.97 (1H, d, $J=7.9$ Hz), 7.35 (1H, dd, $J=7.9$, 0.9 Hz), 7.68—7.81 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 15.7, 28.6, 29.3, 47.3, 53.2, 62.6, 110.1, 121.5, 123.4, 123.8, 128.4, 131.2, 131.3, 131.6, 133.6, 134.1, 166.7, 167.4. HR-FAB-MS: Calcd for $C_{23}H_{23}N_2O_4$ $[M+H]^+$: 391.1658. Found 391.1628.

1,2,3,4-Tetrahydro-1-(*R*)-(3-hydroxypropyl)isoquinoline (15) To the THF solution of the compound **14** (565 mg, 1.4 mmol) was added $LiAlH_4$ (273 mg, 7.2 mmol) under Ar at 0 °C, and the mixture was allowed to react for 6 h at room temperature. Then the mixture was cooled to 0 °C, and water was added to quench the remaining $LiAlH_4$. The mixture was extracted with AcOEt, which was washed with water and brine, dried over $MgSO_4$, and evaporated off. The residue was chromatographed on silica gel (CH_2Cl_2/MeOH=10 to MeOH) to give the product **15** as a yellow oil (176 mg, 66%). Although the yield was moderate, no side products were detected in the reaction. $[\alpha]_D^{17}=+55.2°$ ($c=1.05$, CH_3OH). The enantiomeric excess (100%) was determined by chiral HPLC (chiralcel OD-R, λ254, MeOH/H_2O=7/3, 0.5 v/v% Et_3N, F.R. 0.5). ^{1}H-NMR ($CDCl_3$) δ: 1.66—1.82 (2H, m), 1.99 (2H, q, $J=6.2$ Hz), 2.74 (1H, dt, $J=16.7$, 6.3 Hz) 2.85 (1H, dt, $J=16.5$, 5.9 Hz), 3.06 (1H, dt, $J=12.6$, 5.3 Hz), 3.21 (1H, dt, $J=12.5$, 5.5 Hz), 3.54 (1H, ddd, $J=14.7$, 11.2, 3.3 Hz), 3.64 (1H, ddd, $J=11.0$, 6.0, 3.7 Hz), 4.02 (1H, t, $J=5.9$ Hz), 4.09 (2H, br s), 7.06—7.21 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 29.1, 30.5, 35.4, 39.8, 55.6, 62.8, 126.0, 126.2, 126.4, 129.3, 134.6, 138.4. HR-FAB-MS: Calcd for $C_{12}H_{18}NO$ $[M+H]^+$: 192.1388. Found 192.1383.

(*R*)-1,2,3,5,6,10b-Hexahydropyrrolo[2,1-*a*]isoquinoline (16) To the CH_2Cl_2 solution of compound **15** (46 mg, 0.24 mmol) were added triphenyl phosphine (76 mg, 0.29 mmol) and diethyl azodicarboxylate (36 ml, 0.29 mmol) under Ar at room temperature, then the mixture was allowed to react for 4 h. Next, the mixture was diluted with CH_2Cl_2, and the organic layer was washed with saturated aqueous $NaHCO_3$ and water, dried over $MgSO_4$, and evaporated. The residue thus obtained was chromatographed on silica gel (CH_2Cl_2/MeOH=5) to give the product **16** as a yellow oil (31 mg, 74%). $[\alpha]_D^{20}=+82.2°$ ($c=0.49$, CH_3OH). The enantiomeric excess (>99.8%) was determined by chiral HPLC (chiralcel OD-R, λ254, MeOH/H_2O=7/3, 0.5 v/v% Et_3N, F.R. 0.5). ^{1}H-NMR ($CDCl_3$) δ: 1.78 (1H, m), 1.90—1.99 (2H, m), 2.40 (1H, m), 2.69—2.81 (2H, m), 2.89 (1H, dt, $J=16.3$, 4.4 Hz), 3.05—3.13 (2H, m), 3.20 (1H, ddd, $J=11.0$, 6.0, 3.5 Hz), 3.62 (1H, br s), 7.07—7.17 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 23.1, 29.1, 31.2, 49.0, 54.4, 64.6, 126.9, 127.1, 127.3, 129.4, 135.0, 139.5. HR-FAB-MS: Calcd for $C_{12}H_{16}N$ $[M+H]^+$: 174.1283. Found 174.1295.

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References and Notes

1) Itoh T., Nagata K., Miyazaki M., Kameoka K., Ohsawa A., *Tetrahedron*, **57**, 8827—8839 (2001), and references cited therein.
2) Itoh T., Matsuya Y., Enomoto Y., Ohsawa A., *Tetrahedron*, **57**, 7277—7289 (2001).
3) Itoh T., Nagata K., Yokoya M., Miyazaki M., Ikeda S., Matsuya Y., Enomoto Y., Ohsawa A., *Synlett*, **2002**, 1005—1007 (2002).
4) Parts of this work were reported in preliminary communications: Nagata K., Itoh T., Kameoka K., Miyazaki M., Ohsawa A., *Heterocycles*, **55**, 2269—2272 (2001).
5) Parts of this work were reported in preliminary communications: Itoh T., Miyazaki M., Nagata K., Yokoya M., Nakamura S., Ohsawa A., *Heterocycles*, **58**, 115—118 (2002).
6) Herbert R. B., "The Chemistry and Biology of Isoquinoline Alkaloids," ed. by Philipson J. D., Roberts M. F., Zenk M. H., Springer-Verlag, Berlin, 1985, p. 213.
7) Shamma M., "Isoquinoline Alkaloids, Chemistry and Pharmacology," Academic Press, New York, 1972.
8) Rozwadowska M. D., *Heterocycles*, **39**, 903—931 (1994), and references cited therein.
9) Comins D. L., Badawi M. M., *Heterocycles*, **32**, 1869—1873 (1991).
10) Wanner K. T., Praschak, I., *Heterocycles*, **29**, 29—33 (1989).
11) Brossi A., Teitel S., *Helv. Chim. Acta*, **52**, 1228—1237 (1969).
12) Czarnocki Z., MacLean D. B., Szarek W., *J. Chem. Soc., Chem. Commun.*, **1987**, 493—494 (1987).
13) Czarnocki Z., MacLean D. B., Szarek W., *Can. J. Chem.*, **65**, 2356—2361 (1987).
14) In our previous report, compound **1** was proved to be a good substrate for the asymmetric addition of silyl enol ethers in the presence of *N*-protected alanyl chloride; see ref. 1.
15) The use of a phthaloyl group gave an 85% yield and 82% (de) selectivity.
16) Anwer M. K., Spatola A. F., *Tetrahedron Lett.*, **26**, 1381—1384 (1985).
17) Maryanoff B. E., McComsey D. F., Gardocki J. F., Shank R. P., Costanzo M. J., Nortey S. O., Schneider C. R., Setler P. E., *J. Med. Chem.*, **30**, 1433—1454 (1987), and references cited therein.
18) Tsuda Y., Sakai Y., Kaneko M., Ishiguro Y., *Heterocycles*, **15**, 431—436 (1981).
19) Speckamp W. N., Hiemstra H., *Tetrahedron*, **41**, 4367—4416 (1985).
20) Lete E., Egiarte A., Sotomayor N., Vicente T., Villa M.-J., *Synlett*, **1993**, 41—42 (1993).
21) Maryanoff B. E., McComsey D. F., *J. Heterocycl. Chem.*, **22**, 911—914 (1985).
22) Maryanoff B. E., McComsey D. F., Almond H. R., Jr., Mutter M. S., Bemis G. W., Whittle R. R., Olofson R. A., *J. Org. Chem.*, **51**, 1341—1346 (1986).
23) Maryanoff B. E., McComsey D. F., Mutter M. S., Sorgi K. L., Maryanoff C. A., *Tetrahedron Lett.*, **29**, 5073—5076 (1988).
24) Sorgi K. L., Maryanoff C. A., McComsey D. F., Graden D. W., Maryanoff B. E., *J. Am. Chem. Soc.*, **112**, 3567—3579 (1990).
25) Lee Y. S., Kang D. W., Lee S. J., Park H., *Synth. Commun.*, **25**, 1947—1956 (1995).
26) Lee Y. S., Kang D. W., Lee S. J., Park H., *J. Org. Chem.*, **60**, 7149—7152 (1995).
27) Gordon M., Pearson D. E., *J. Org. Chem.*, **27**, 329—332 (1964).
28) Bernotas R. C., Cube R. V., *Tetrahedron Lett.*, **32**, 161—164 (1991).
29) The silyl enol ether was synthesized according to the literature method; see, Colvin E. W., "Silicon Reagents in Organic Synthesis," Academic Press, London, 1998, pp. 99—105.