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

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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-pentamethoxyhomoprotobemerine (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 pyrroldinodoxoisouquinoline (16) in a highly enantioselective manner.

Key words: asymmetric synthesis; indole alkaloid; chiral auxiliary; pentamethoxyhomoprotobemerine; O-methylkreysigine; hexahydropyrrolo[2,1-α]isouquinoline

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 isoquinoline13) or β-carboline2,3) nucleus. In the case of isoquinolines, 5,8-dibromo derivatives which were readily obtained by reaction of the parent aromatics with Br₂ 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.11) In this paper, we describe further applications of our asymmetric addition products to the synthesis of (S)-2,3,9,10,11-pentamethoxyhomoprotobemerine (7), a synthetic intermediate for (S)-O-methylkreysigine (9), and an unnatural bioactive compound (R)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-α]isouquinoline (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.5) There has been, however, only one report concerning the direct asymmetric addition of nucleophiles to an aromatic isoquinoline nucleus.8) 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,9) 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-Pentamethoxyhomoprotobemerine (7) is a closely related compound of homoaquiphrine 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-dimethoxyphenethyl-amino 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,15) thus the reaction of 1 with 1-(3,4,5-trimethoxyphenyl)-1-trimethylsilylloxyethylene 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 HCO₂NH₂ in the presence of 10% Pd/C 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•H₂O, or LiAlH₄ 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 LiAlH₄ at 0°C to give 6 in 64% yield with no loss of enantiopurity. Finally, 6 was treated with 48% HBr solution in H₂O and formalin at 100°C under the reported conditions13)
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. The overall yield of 7 from 5,8-dibromo-6,7-dimethoxyisoquinoline (1) was 23%, which was superior to the reported one (3.5% from tartaric acid). In addition, N-methylation of 6 using formaldehyde and NaBH₄CN gave a synthetic precursor (8) of (S)-O-methylkreysigine (9) in 80% yield ([α]_D^25 = +6.1° (c=0.92, MeOH), lit. [α]_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. Pyrrolidinoisoquinoline moieties widely exist in plant products such as erythrinane and related alkaloids, and many of them exhibit interesting biological activity. Thus, a lot of synthetic studies have focused on the development of general approaches to these compounds. In spite of these efforts, there are few general methods for the asymmetric synthesis of these compounds. Lee et al. reported the total synthesis of both enantiomers of parent 16. 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 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, 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 BH₃–THF complex and NaOH–H₂O₂ 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
LiAlH₄ in THF to afford 15 without any racemization. In the last step, a Mitsunobu procedure 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 auxiliaries derived from isoquinoline to the synthesis of (S)-2,3,9,10,11-pentamethoxyxomproteobberine (7) and a pyrrolidinoisoquinoline 16, as well as the formal synthesis of (S)-O-methylkreyssigne (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. 1H- and 13C-NMR spectra were recorded on JEOL GXS-400 and LA500 spectrometers using tetramethylsilane (TMS) as an internal standard. High-resolution mass spectra (FAB-HR-MS) were recorded on JEOL GX400 and LA500 spectrometers using tetramethylsilane as an internal standard. The enantiomeric excess of the products was determined by HPLC analysis using a JASCO UV2070 PU2080 system and chiralcel OD-R column. The enantiomeric purity was determined by HPLC analysis using a chiralpak AD-H column.

**C31H31Br2N3O11S: C, 45.74; H, 3.85; N, 5.17. Found: C, 45.92; 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 HCO₂NH₄ 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 filtered with Celite, and the solvent was evaporated off. To the residue thus formed was added ethyl acetate, and the organic layer was washed with H₂O and brine, dried over MgSO₄, and evaporated. The residue was chromatographed on a silica gel (CH₂Cl₂/AcOEt 1:2) column, and the crude product was recrystallized from AcOEt-hexane to give 3 (1.39 g, 95%) as a colorless powder.

**C₂₉H₂₃N₂O₇S: 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 recrystallized from AcOEt–hexane to give 4 (1.39 g, 95%) as a colorless powder.

**C₂₉H₂₃N₂O₇S (monohydrate): C, 57.66; H, 6.09; N, 6.51. Found: C, 57.61; H, 6.20; N, 6.40.**

Chart 2

8.0 Hz), 7.11 (2H, s), 7.80 (2H, d, J = 9.2 Hz). 13C-NMR (CDCl₃) 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. Caled for C₁₇H₂₁BrN₃O₇S: C, 57.40; H, 5.36; N, 6.13. 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-hydroxy-
ethylisoquinoline. The nitrogen of the product are as follows: 

\[ ^{1}H-NMR \] (CDCl₃) 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 (3H, m), 3.80 (8H, 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), 7.45 (5H, d, J = 8.6 Hz). 

\[ ^{13}C-NMR \] (CDCl₃) δ: 20.3, 28.1, 37.9, 45.8, 50.2, 55.9, 56.1, 60.9, 71.0, 109.9, 114.1, 114.3, 124.3, 128.1, 129.1, 131.8, 138.8, 140.0, 147.8, 148.0, 153.2, 172.5.

2-[4-(Aminobenzensulfonyl)-(R)-allyl]-3,3,4-tetrahydro-6,7-dimethoxy-1-(S)-(3,4,5-trimethoxyphenethyl)isoquinoline (4) To the AcOH/TF(A solution (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 H₂ atmosphere. Then, the mixture was filtered with Celite, and the solvent was evaporated off. To the crude product thus obtained were added ethyl acetate, and the organic layer was washed with saturated aqueous NaHCO₃, dried over MgSO₄, and evaporated off. The crude product thus obtained was recrystallized from AcOEt–hexane to give compound 4 (210 mg, 71%) as a colorless powder. 

\[ [\alpha]_{D}^{25} = +6.3^* \] (c = 0.45, CHCl₃), mp 108—110°C. The product was obtained as a mixture of several conformational isomers. The NMR spectra of the major isomer are shown; 

\[ ^{1}H-NMR \] (CDCl₃) 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, 8.5, 5.6 Hz), 3.62 (1H, dt, J = 13.2, 4.8 Hz), 3.81 (3H, s), 3.88 (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, 6.47) (1H, s). 6.56 (1H, s). 7.45 (1H, d, J = 8.4 Hz). 

\[ ^{13}C-NMR \] (CDCl₃) 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, 110.3, 113.2, 117.1, 124.3, 124.9, 129.0, 129.1, 130.4, 137.1, 147.5, 147.8, 153.2, 170.9. Anal. Calc. C₃₄H₃₈F₃N₃O₉S: C, 55.85; H, 5.40; N, 8.8, 7.2 Hz). The mixture was allowed to react for 6 h at room temperature. Thereafter, AcOEt was added, and the mixture was filtered with Celite, and the solvent was evaporated off. The residue thus formed was added ethyl acetate, and the organic layer was washed with saturated aqueous NaHCO₃, dried over MgSO₄, and evaporated off. The crude product thus obtained was recrystallized from Et₂O–hexane to give 5 (47 mg, 91%) as a colorless powder. 

\[ [\alpha]_{D}^{25} = +4.8^* \] (c = 0.45, MeOH). In order to compare the \[ [\alpha]_{D}^{25} \] value with that of the reported one, compound 8 was further purified using preparative TLC (silica 5717, Merck) (CHCl₃/MEOH = 10). 

\[ [\alpha]_{D}^{25} = +6.1^* \] (c = 0.92, MeOH). \[ ^{1}H-NMR \] (CDCl₃) δ: 2.03—2.10 (2H, m), 2.49 (3H, s), 2.49—2.55 (1H, m), 2.62—2.83 (4H, m), 3.45 (1H, br, J = 20.3 Hz), 3.80 (6H, s), 3.81 (3H, s), 4.26 (1H, dq, 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). 

\[ ^{13}C-NMR \] (CDCl₃) 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 = 21.3 Hz) 119.9, 124.0, 128.4, 128.5, 136.2, 136.7, 137.0, 138.9, 147.7, 148.0, 152.3, 170.1 (q, J = 50.7 Hz), 170.46. Anal. Calc. C₃₄H₃₈F₃N₃O₉S: C, 55.8; H, 5.4. N, 5.2. Found C, 56.27; H, 5.65; N, 5.52.

2,3,4-Tetrahydro-6,7-dimethoxy-1-(S)-(3,4,5-trimethoxyphenethyl)benzene-1-sulfonate (5) To the CH₃Cl₂ 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 CH₂Cl₂, and the solution was added trifluoroacetic anhydride to the mixture, and the mixture was allowed to react for 2 h. Water was added to quench the remaining BH₃–THF. Then, the mixture was chromatographed on silica gel (CH₂Cl₂/MeOH 95:5) to give the crude product. It was recrystallized from AcOEt–hexane to compare the \[ [\alpha]_{D}^{25} \] value with that of the reported one, compound 5 was obtained as a mixture of two isomers (610 mg, 62%). 

\[ [\alpha]_{D}^{25} = -112.5^* \] (c = 0.13, MeOH). 

2-Methyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(S)-(3,4,5-trimethoxyphenethyl)isoquinoline (8) To the CH₂CN solution of the compound 6 (23 mg, 0.059 mmol) was added 37% aqueous HCHO (22 ml, 0.29 mmol) and NaBH₄ (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 evaporated off to give the product 8 (19 mg, 80%) as a colorless oil. In order to compare the \[ [\alpha]_{D}^{25} \] value with that of the reported one.
29, 31, 33, 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_{12}H_{16}N_{2}O [M + H]⁺: 293.1814. Found 293.1806.

2.1-Dihydro-1-(R)-(3-hydroxypropyl)-2-[(N-phthaloyl-(S)-alanly)]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%). ¹H-NMR (CDCl₃) δ: 1.44—1.86 (2H, m), 7.40 (1H, d, J = 7.5 Hz), 2.89 (1H, dt, J = 11.0, 6.0, 3.5 Hz), 3.54 (1H, d, J = 5.9 Hz), 4.09 (2H, br s), 7.06—7.21 (4H, m). ¹³C-NMR (CDCl₃) 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]⁺: 293.1887. Found 293.1838.

(R)-1,2,3,5,6,10b-Hexahydropyrido[1,2-a]isoquinoline (16) To the THF solution of the compound 14 (565 mg, 1.4 mmol) was added LiAlH₄ (56 mg, 0.24 mmol) under Ar at 0 °C, and the mixture was allowed to react for 4 h at room temperature. Then the mixture was cooled to 0 °C, and water was added to quenching the LiAlH₄. The mixture was extracted with AcOEt, which was washed with water and brine, dried over MgSO₄, and evaporated off. The residue was chromatographed on silica gel (CH₂Cl₂/MeOH = 10 to MeOH) to give the product 16 as a yellow oil (176 mg, 66%).

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References and Notes
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).
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.