

ENANTIOSELECTIVE SYNTHESIS OF (S)-2,3,9,10,11-PENTAMETHOXYHOMOPROTOBERBERINE AND (S)-O-METHYLKREYSIGINE USING AN ASYMMETRIC ADDITION TO AN ISOQUINOLINE RING

Kazuhiro Nagata, Takashi Itoh, Keiko Kameoka, Michiko Miyazaki, and Akio Ohsawa*

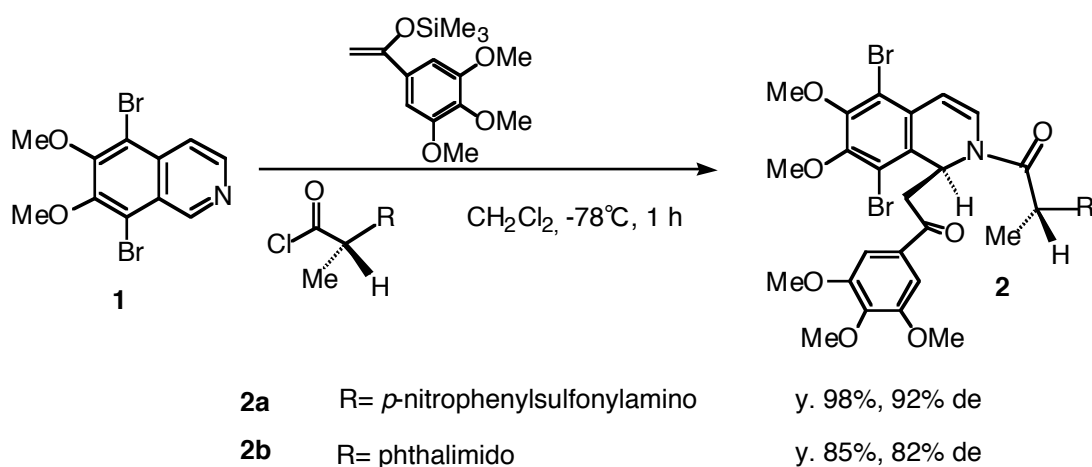
School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan

Abstract – Total synthesis of (S)-2,3,9,10,11-pentamethoxyhomoprotoberberine (**7**) was carried out using an asymmetric nucleophilic addition of a silyl enol ether to 5,8-dibromo-6,7-dimethoxyisoquinoline (**1**) in the presence of an acid chloride derived from alanine. The addition proceeded in high diastereoselectivity to give a 1-substituted 1,2-dihydroisoquinoline (**2**), which was converted to the target alkaloid in short steps. One of the intermediates was readily transformed to a product (**8**) which was known as a precursor for synthesis of O-methylkreysigine (**9**).

Recently we have found that nucleophilic additions of silyl enol ethers¹ and allyltin² reagents to *N*-acylated azaaromatics generated *in situ* were effective methods for introduction of a substituent to azaaromatics. It was also demonstrated that asymmetric additions to isoquinolines³ and β -carboline⁴ at C1 position proceeded in good yields with high diastereoselectivities using *N*-protected amino acid chlorides as an acylating reagent. It was therefore presumed that optically active 1-substituted tetrahydroisoquinoline derivatives would be synthesized straightforwardly by this method. Since 1-substituted tetrahydroisoquinoline alkaloids have important physiological and pharmacological activities,⁵ there have been many synthetic methods⁶ for them. Only one example, however, was reported in which isoquinoline ring was used as a starting material.⁷ In the paper, Comins *et al.* reported the synthesis of (+)-carnegine *via* simple procedures, but the stereoselectivity of the product was low (62% ee).

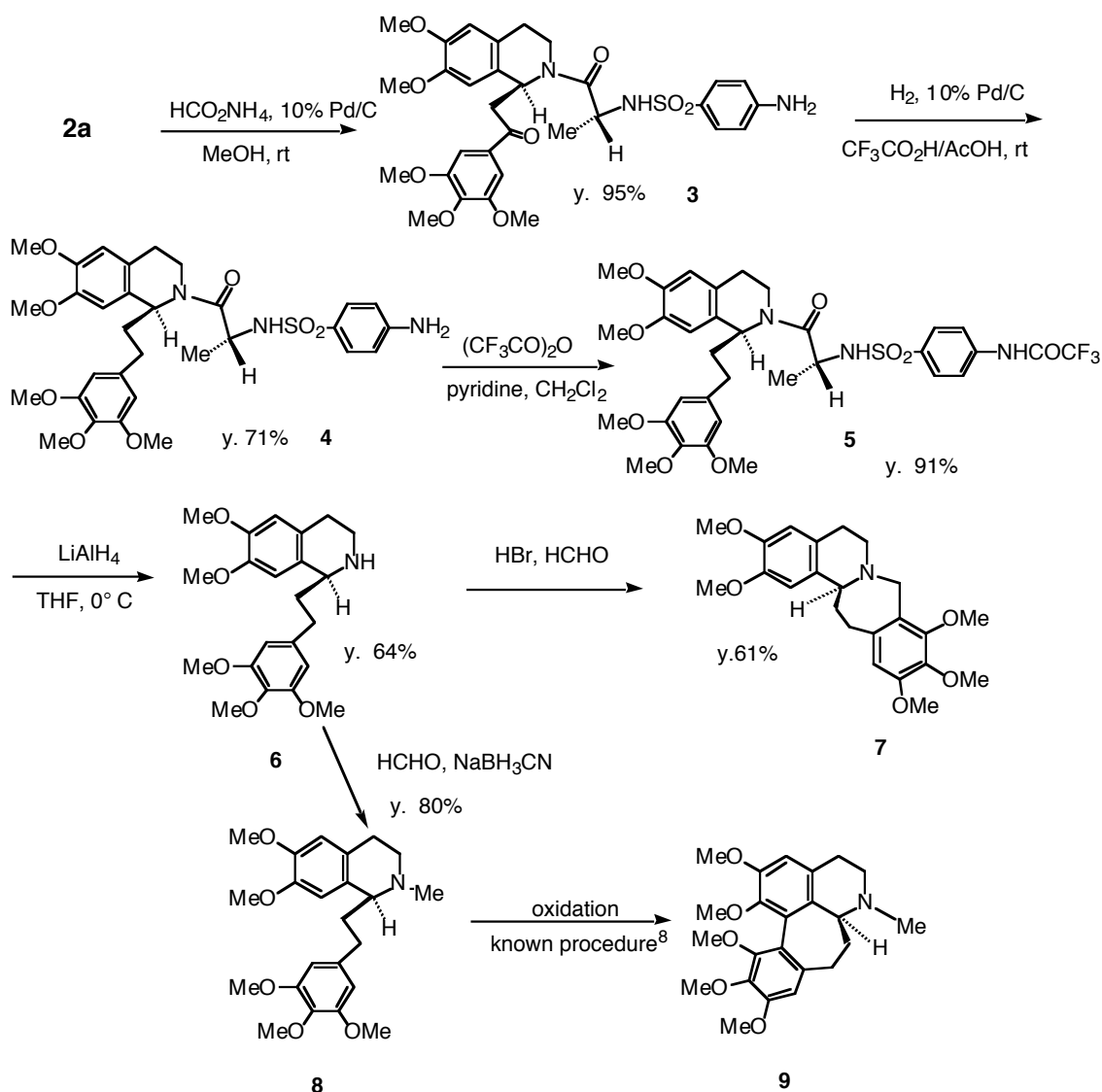
We would like to report here a new and direct route to the titled compounds using an isoquinoline derivative as a starting material. The latest synthesis of (S)-2,3,9,10,11-pentamethoxyhomoprotoberberine was reported by Czarnocki *et al.*⁸ In their procedure, (*R*)-2-ethoxycarbonyl-1-formyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline, which was obtained through several steps from D-(-)-tartaric acid, was converted to the alkaloid in 4 steps. However, it was reported that the starting material was proved to racemize easily, thus the product obtained from this process showed only moderate stereoselectivity.

The synthesis of the titled compound was commenced using 5,8-dibromo-6,7-dimethoxyisoquinoline as a starting material, because it has been found that the compound affords corresponding 1-substituted dihydroisoquinolines in high yields with high diastereoselectivity in the reaction with silyl enol ethers in the presence of *N*-protected L-alanyl chloride.³ This asymmetric addition reaction with 1-(3,4,5-trimethoxyphenyl)-1-trimethylsilyloxyethylene in the presence of *N*-protected D-alanyl chloride was applied to construct a required carbon skeleton and absolute configuration at C-1. Our previous study showed that *p*-nitrophenylsulfonyl and phthaloyl groups acted as good *N*-protecting groups, thus they were also adopted in this procedure. As a result, 1-substituted 1,2-dihydroisoquinolines (**2a**) and (**2b**) were obtained in high diastereoselectivities (Scheme 1). Each of the adducts (**2a**) and (**2b**) was purified to be a single diastereomer by recrystallization.



Scheme 1

Reduction of **2a** with HCO₂NH₄ in the presence of 10% Pd/C⁹ gave a debrominated 1,2,3,4-tetrahydroisoquinoline (**3**) in 95% yield. The reduction of **2b**, however, did not give a desired 1,2,3,4-tetrahydro product,¹⁰ and thus subsequent conversions were carried out by using tetrahydroisoquinoline (**3**) (Scheme 2). The keto group in **3** was transformed to methylene by a catalytic hydrogenation of **3** under acidic conditions. At the next step, all of our attempts failed to remove the chiral auxiliary from the compound (**4**) under mild conditions, for example by treatment with KOH and/or NaOH in MeOH/H₂O at 70°C, with LiOH- H₂O₂ in THF, and with LiAlH₄ in THF. Only under harsh conditions with KOH in HOCH₂CH₂OH at 170°C was obtained the desired compound (**6**), but the yield was low (37%) and partial racemization was observed. Therefore, 1,2,3,4-tetrahydroisoquinoline (**4**) was subjected to trifluoroacetylation at aromatic amino group in order to increase electron deficiency of **4**. Then trifluoroacetylated compound (**5**) was allowed to react with LiAlH₄ at 0°C to give **6** ($[\alpha]_D^{25} = -14.1^\circ$ (c 0.34, CHCl₃)) in 64% yield. Finally, **6** was treated with 48% HBr solution in H₂O and formaldehyde at 100°C under reported conditions,^{8b} to give (*S*)-2,3,9,10,11-pentamethoxyhomoprotoberberine (**7**) in 61% yield. It was converted to a hydrochloride salt to compare the optical rotation with that of reported one.¹¹ Its specific rotation showed $[\alpha]_D^{25} = -111.3^\circ$ (c 0.13, MeOH) (literature value $[\alpha]_D^{25} = -112.5^\circ$ (MeOH)). In addition, *N*-methylation of **6** using formaldehyde in NaBH₃CN gave a precursor (**8**) of (*S*)-*O*-methylkreysigine (**9**) in 80% yield ($[\alpha]_D^{25} = +6.1^\circ$ (c 0.92,



Scheme 2

MeOH)) (literature¹² value $[\alpha]_{\text{D}}^{25} = +4.8^\circ$ (MeOH)).

In conclusion, optically active (*S*)-2,3,9,10,11-pentamethoxyhomoprotoberberine was synthesized concisely with 99% ee using an asymmetric nucleophilic addition of a silyl enol ether to 5,8-dibromo-4,7-dimethoxyisoquinoline as a key step, and subsequent treatment resulted in short steps preparation of the target molecule. The overall yield from 5,8-dibromo-4,7-dimethoxyisoquinoline was 23%. In addition, a precursor of (*S*)-*O*-methylkreysigine (9) was also synthesized from an intermediary compound. Application of the asymmetric addition to synthesis of other alkaloids is now under investigation.

ACKNOWLEDGEMENT

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

REFERENCES

1. a) T. Itoh, M. Miyazaki, H. Hasegawa, K. Nagata, and A. Ohsawa, *Chem. Commun.* 1996, 1217.
b) T. Itoh, Y. Matsuya, H. Hasegawa, K. Nagata, M. Okada, and A. Ohsawa, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2511. c) T. Itoh, M. Miyazaki, K. Nagata, and A. Ohsawa, *Heterocycles*, 1997, **46**, 83. d) T. Itoh, M. Miyazaki, K. Nagata, H. Hasegawa, A. Ohsawa, and K. T. Nakamura, *Heterocycles*, 1998, **47**, 125. e) T. Itoh, M. Miyazaki, K. Nagata, and A. Ohsawa, *Tetrahedron*, 2000, **56**, 4383.
2. a) T. Itoh, H. Hasegawa, K. Nagata, and A. Ohsawa, *J. Org. Chem.*, 1994, **59**, 1319. b) T. Itoh, H. Hasegawa, K. Nagata, M. Okada, and A. Ohsawa, *Tetrahedron*, 1994, **50**, 13089.
3. T. Itoh, K. Nagata, M. Miyazaki, and A. Ohsawa, *Synlett*, 1999, 1154.
4. T. Itoh, Y. Matsuya, Y. Enomoto, K. Nagata, M. Miyazaki, and A. Ohsawa, *Synlett*, 1999, 1799.
5. a) R. B. Herbert, In *The Chemistry and Biology of Isoquinoline Alkaloids*, ed. by J. D. Philipson, M. F. Roberts, and M. H. Zenk, Springer-Verlag, Berlin, 1985, p. 213. b) M. Shamma, *Isoquinoline Alkaloids, Chemistry and Pharmacology*, Academic Press, New York, 1972.
6. M. D. Rozwadowska, *Heterocycles*, 1994, **39**, 903.
7. D. L. Comins and M. M. Badawi, *Heterocycles*, 1991, **32**, 1869.
8. a) Z. Czarnocki, D. B. MacLean, and W. Szarek, *J. Chem. Soc., Chem. Commun.*, 1987, 493.
b) Z. Czarnocki, D. B. MacLean, and W. Szarek, *Can. J. Chem.*, 1987, **65**, 2356.
9. M. K. Anwer and A. F. Spatola, *Tetrahedron Lett.*, 1985, **26**, 1381.
10. When **2b** was reduced with HCO_2NH_4 in the presence of 10% Pd/C, corresponding debrominated 1,2- dihydroderivative was obtained, but further reduction to a tetrahydro derivative did not proceed.
11. A. Brossi and S. Teitel, *Helv. Chim. Acta*, 1969, **52**, 1228.
12. A. Brossi, J. O'Brine, and S. Teitel, *Helv. Chim. Acta*, 1969, **52**, 678.