A New Entry to Asymmetric Synthesis of 1-Substituted 1,2,3,4-Tetrahydro-β-carbolines Employing a Pyroglutamic Acid Derivative as a Chiral Auxiliary

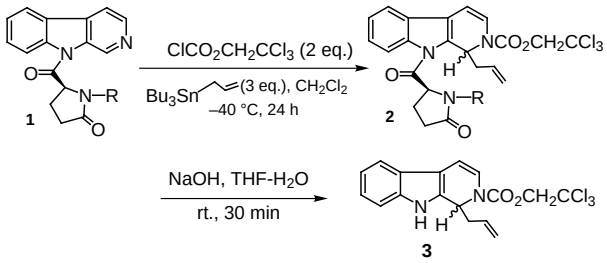
Takashi Itoh, Kazuhiro Nagata, Masashi Yokoya, Michiko Miyazaki, Sachiko Ikeda, Yuji Matsuya, Yasuko Enomoto, Akio Ohsawa*

School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan
Fax +81(3)37845982; E-mail: ohsawa@pharm.showa-u.ac.jp

Received 4 April 2002

Abstract: β-Carboline which was protected at N-9 by an acyl group derived from L-pyroglutamic acid reacted with allyltributyltin or silyl enol ethers in the presence of an alkyl chloroformate in a highly diastereoselective manner to give 1-substituted 1,2-dihydro-β-carbolines. The compounds were readily transformed to the corresponding asymmetric 1-substituted tetrahydro-β-carbolines that are common partial structures in a variety of indole alkaloids.

Key words: β-carboline, allyltributyltin, silyl enol ether, pyroglutamic acid, asymmetric addition, indole alkaloid



Scheme 1

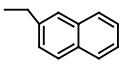
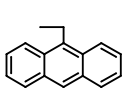
β-Carboline nucleus which has a chiral center at C-1 position exists widely in nature as a part of various indole alkaloids.[1] In the course of our study of the asymmetric synthesis of 1-substituted 1,2,3,4-tetrahydro-β-carbolines, we found that allyltin reagents reacted with β-carboline having a chiral auxiliary derived from L-proline at N-9 position to give 1-allyl-1,2-dihydro derivatives in good yields with high diastereoselectivity.[2] Moreover, it was also found that the synthesis of the both enantiomers was readily performed in the presence of the same chiral auxiliary by simply selecting allyltributyltin or tetraallyltin.[3] Thus the previous reaction was proved to be useful for the synthesis of chiral 1-allyl derivatives of β-carboline.

To our disappointment, however, nucleophiles other than allyltins gave poor results.[4] To overcome the disadvantage, we have investigated other chiral auxiliaries at N-9 position of β-carboline, and found that a pyroglutamic acid derivative gave a good stereoselectivity for the reaction with both allyltributyltin and silyl enol ethers. This paper describes these results.

In the previous study,[2,3] the asymmetric induction was supposed to be originated from the coordination of an allyltin reagent to a sulfonyl group in the chiral auxiliary.[5] Thus, it was thought that removal of the sulfonyl group would simplify the reaction mechanism and that the use of a simple steric factor would improve the reaction system toward a more general procedure. Our study revealed that *N*-(9-anthracenylmethyl)pyroglutamyl group was a good chiral auxiliary (Scheme 1 and Table 1).[6]

In the event, the compound **1**[7] was allowed to react with allyltributyltin and 2,2,2-trichloroethyl chloroformate to give a 1,2-dihydro adduct **2**, which was successively hydrolyzed to **3** in a quantitative yield.[8] The chiral auxiliary was completely recovered under the mild hydrolytic conditions. When the amide hydrogen of L-pyroglutamyl group was displaced with phenylsulfonyl group, the *R* isomer was obtained through the mechanism in which was supposed to involve coordination of the sulfonyl group of the chiral auxiliary to allyltributyltin (entry 1). When methyl group was introduced instead of sulfonyl group, the stereoselectivity was changed from *R* to *S* despite the low ee (entry 2). The ee was increased by the use of bulkier benzyl and naphthylmethyl groups (entries 3–5), and the employment of *N*-anthracenylmethyl group afforded a

Table 1 Asymmetric Addition Reaction of Allyltributyltin with β-Carboline, which have a Chiral Auxiliary Derived from Pyroglutamic Acid at N-9

Entry	Compound	R	Yield of **2** (%)	ee of **3**[a] (%)
1	**a**	-SO_2Ph	51	79 (*R*)
2	**b**	-Me	22	7 (*S*)
3	**c**	-CH_2Ph	95	21 (*S*)
4	**d**		87	58 (*S*)
5	**e**		Quant.	66 (*S*)
6	**f**		98	91 (*S*)

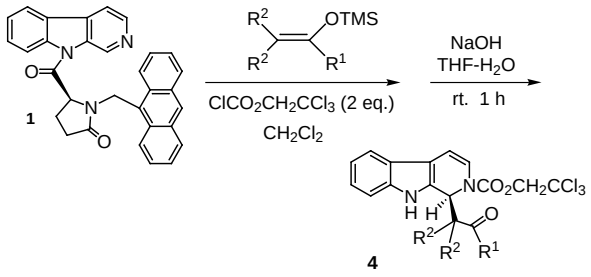
[a] The ee was estimated by HPLC after removal of the chiral auxiliary.

Synlett 2002, No. 6, 04 06 2002. Article Identifier:
1437-2096,E;2002,0,06,1005,1007,ftx,en;Y04502ST.pdf.

ISSN 0936-5214

higher yield and the best stereoselectivity (entry 6).[9] Thus, we found that the naturally more required *S* isomer was obtained from the naturally dominant *S* isomer of pyroglutamyl group.

Next, silyl enol ethers were adopted as nucleophiles instead of allyltributyltin, and the results are summarized in Table 2 (Scheme 2).



Scheme 2

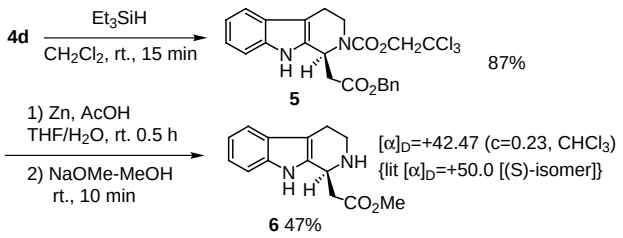
Table 2 Asymmetric Addition Reaction of Silyl Enol Ethers with 9-(*N*-Anthracenylmethylpyroglutamyl)-β-carboline

Entry	R^1	R^2	Temp. (°C)	Time (h)	Product	Yield (%)	ee[a] (%)
1	Me	H	0	24	**4a**	40	79
2	Ph	H	0	2.5	**4b**	79	86
3	OMe	Me	0	0.5	**4c**	quant.	82
4	OBn	H	–40	12	**4d**	81	88
5	SBn	H	–40	19	**4e**	83	87

[a] The ee was estimated by HPLC after removal of the chiral auxiliary.

In our previous system, silyl enol ethers afforded poor results because the reagents do not have coordinative interaction with the substrate. In the present reaction, however, the reaction proceeded in a highly diastereoselective manner to give the dihydro adducts **4** in good yields after a hydrolytic process.[10] Thus, a general method for the synthesis of naturally occurring *S* isomer of 1-substituted 1,2,3,4-tetrahydro-β-carboline was accomplished using L-pyroglutamic acid as a chiral auxiliary.

For the determination of stereoselectivity using silyl enol ethers, the adduct **4d** was transformed to a tetrahydro derivative as mentioned in Scheme 3.



Scheme 3

The dihydro adduct was reduced with triethylsilane to give the corresponding tetrahydro derivative, which was further reduced with zinc-acetic acid, and succeeding esterification (the yield not optimized) of a free carboxylic acid afforded methyl ester of tetrahydro-β-carboline 1-acetic acid. The absolute configuration was determined as *S* by the comparison of the specific rotation with the reported one.[11] Thus, it was proved that the reaction proceeded in an *S* selective manner regardless the nucleophilic species.

In order to investigate the origin of stereoselectivity, PM3 calculations[12] were carried out for the intermediary N-2 acylated quaternary salts of β-carboline **7** whose optimized structures are shown in Figure.

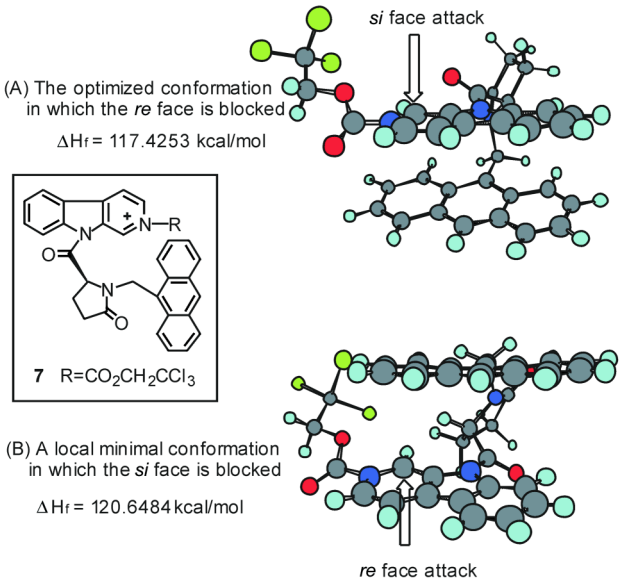


Figure Calculated PM3 structures of 2-(trichloroethoxycarbonyl)-9-(*N*-anthracenylmethylpyroglutamyl)-β-carbolinium cation (**7**)

In the optimized conformation (A), anthracenyl group is located at the *syn* position to the β-carboline group probably due to π-π interaction of these two groups. The *re* face of the C-1 reaction site of β-carboline ring is effectively shielded. A conformation in which the *si* face is shielded was obtained as a local minimum structure (B), but it was 3.22 kcal/mol less stable than (A). Thus, the stereoselectivity could be accounted for by the shielding of the *re* face by the anthracenyl group.

In this paper, we described a new method for the asymmetric addition of allyltributyltin or silyl enol ethers to β-carboline at C-1 position using a novel chiral auxiliary derived from (*S*)-pyroglutamic acid. The auxiliary was readily recovered quantitatively by hydrolysis. Although pyroglutamic acid has been used for a versatile building block for asymmetric synthesis,[13] there are few examples using its derivatives as chiral auxiliaries.[14] Application of the adducts obtained by this method to the total synthesis of indole alkaloids is now under investigation.

References

(1) *The Chemistry of Heterocyclic Compounds*, Vol. 25, Part 4; Saxton, J. E., Ed.; John Wiley & Sons: Chichester, **1994**.

(2) Itoh, T.; Matsuya, Y.; Enomoto, Y.; Nagata, K.; Miyazaki, M.; Ohsawa, A. *Synlett* **1999**, 1799.

(3) (a) Matsuya, Y.; Itoh, T.; Enomoto, Y.; Ohsawa, A. *Heterocycles* **2000**, *53*, 2357. (b) Itoh, T.; Matsuya, Y.; Enomoto, Y.; Ohsawa, A. *Tetrahedron* **2001**, *57*, 7277.

(4) In the previous reaction which adopted *N*-phenylsulfonylprolinyl group as a chiral auxiliary, the addition using silyl enol ethers afforded the products in good yields but poor diastereoselectivity (<20%).

(5) The coordination mechanism was supposed to participate only in the reaction of β-carbolines. In the cases of isoquinoline derivatives, only the steric factor might control the stereochemistry; see: (a) Itoh, T.; Nagata, K.; Miyazaki, M.; Ohsawa, A. *Synlett* **1999**, 1154. (b) Itoh, T.; Nagata, K.; Miyazaki, M.; Kameoka, K.; Ohsawa, A. *Tetrahedron* **2001**, *57*, 8827. (c) Nagata, K.; Itoh, T.; Kameoka, K.; Miyazaki, M.; Ohsawa, A. *Heterocycles* **2001**, *55*, 2269.

(6) *N*-Protected L-pyroglutamic acids were readily prepared from the reaction of *t*-butyl L-pyroglutamate and an alkyl halide in the presence of NaH, followed by hydrolysis.

(7) The compound **1** was obtained as follows: To the mixture of *N*-alkyl L-pyroglutamic acid (0.5 mmol) and β-carboline (0.5 mmol) in CH_2Cl_2 (1 mL) was added ethyl-(*N*,*N*′-dimethylaminopropyl)carbodiimide hydrochloride (0.6 mmol), and the mixture was reacted for 3 h at room temperature. Then the solvent was evaporated off, and the residue thus formed was chromatographed on silica gel (EtOAc) to give 9-acyl-β-carbolines **1**.

(8) Experimental procedure: To the CH_2Cl_2 solution (1 mL) of 9-acyl-β-carboline **1** (0.1 mmol) and allyltributyltin (0.3 mmol), 2,2,2-trichloroethyl chloroformate (0.2 mmol) was added at -40 °C under Ar atmosphere, and the reaction was continued for 24 h at the same temperature. Then 3 M aqueous KF solution was added to the solution, and the mixture was allowed to stir vigorously for 1 h. The organic layer was separated, dried over $MgSO_4$, and evaporated off to leave the residue, which was chromatographed on silica gel to afford the adduct **2**. The compound **2** was dissolved in THF (1 mL), and treated with 1 M aqueous KOH solution (2 mL) for 30 min. Then H_2O was added to the mixture, which was extracted with CH_2Cl_2 to give pure **3**. The aqueous layer was acidified with HCl and extracted with CH_2Cl_2 to afford the recovered chiral auxiliary.

(9) The absolute configuration of the allyl adduct **3** was determined by the previous mentioned method; see ref.[3b]

(10) In these cases, the dihydro adduct initially obtained was hydrolyzed without the isolation to give the compound **4**, because of the instability of the intermediate.

(11) Tietze, L. F.; Zhou, Y.; Töpken, E. *Eur. J. Org. Chem.* **2000**, 2247.

(12) The molecular orbital calculations were carried out using the PM3 procedure with the standard parameters, as implemented in the MOPAC2000 program.

(13) Najera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245; and references cited therein.

(14) (a) Menezes, R. F.; Zazza, C. A.; Sheu, J.; Smith, M. B. *Tetrahedron Lett.* **1989**, *30*, 3295. (b) O'Meara, J. A.; Jung, M.; Durst, T. *Tetrahedron Lett.* **1995**, *36*, 2559. (c) Roth, E.; Altman, J.; Kapon, M.; Ben-Ishai, D. *Tetrahedron* **1995**, *51*, 801. (d) Behr, J. B.; Defoin, A.; Pires, J.; Streith, J.; Kacko, J. L.; Zehnder, M. *Tetrahedron* **1996**, *52*, 3283. (e) Ezquerra, J.; Prieto, L.; Avendano, C.; Martos, J. L.; de la Cuesta, E. *Tetrahedron Lett.* **1999**, *40*, 1575.