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A general method for the asymmetric synthesis of both enantiomers of 1-substituted 1,2,3,4-tetrahydro-β-carbolines employing pyroglutamic acid derivatives as chiral auxiliaries

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

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

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Abstract—9-(*S*)-Pyroglutaminyl-β-carbolines were allowed to react with a nucleophile (allyltributyltin or a silyl enol ether) in the presence of 2,2,2-trichloroethyl chloroformate to give 1,2-addition products in good yields and high diastereoselectivity. The chiral auxiliary at *N*-9 was readily removed by a mild hydrolysis. The same chiral source afforded both enantiomers by simply altering a protecting group of the amide nitrogen. That is, (*S*)-pyroglutaminyl groups which had an *N*-alkyl group afforded the (*S*) isomer, whereas the ones having an *N*-acyl group produced the (*R*) isomer of the addition products.

1. Introduction

β-Carboline (**1**) is a common nucleus of various indole alkaloids, and many of these have a chiral center at its C-1 position.[1] Thus, there have been several studies concerning the synthesis of chiral 1-substituted 1,2,3,4-tetrahydro-β-carboline derivatives using Pictet–Spengler reaction,[2] nucleophilic addition,[3] electrophilic substitution,[4] and reduction.[5] We have recently developed the asymmetric addition of allyltin reagents to a β-carboline derivative which has an (*S*)-proline-derived chiral auxiliary at *N*-9 position.[6] In addition, it was found that both enantiomers of a 1-allyl-1,2-dihydro-β-carboline derivative were obtained using allyltributyltin or tetraallyltin as a nucleophile in the presence of the same chiral auxiliary. The results indicate that the stereoselectivity of the allylation is not governed only by steric bias originated from the chiral auxiliary, and there might be some electrostatic interaction between the substrate and the nucleophiles. In fact, this peculiar stereoselectivity was not observed in the cases of other nucleophiles such as silyl enol ethers.

In order to develop a more general asymmetric addition, we have investigated other chiral auxiliaries than the proline derivatives and found that the one derived from (*S*)-pyroglutamic acid afforded good stereoselectivity using both allyltin and silyl enol ethers as nucleophiles. Moreover, it was revealed that the *N*-alkyl- and *N*-acylpyroglutamic acids afforded opposite enantiomers by the attack of the same nucleophiles. This paper describes these results.[7]

2. Results and discussion

At first, we tried reactions using standard amino acids such as alanine, valine, or phenylalanine as a chiral auxiliary, and they were found not to install at *N*-9 position of **1** in good yields.[8] Thus, we chose (*S*)-pyroglutamic acid as a candidate for a new chiral auxiliary, because it has a similar, but more rigid conformation with compared to proline due to carbonyl group in the pyrrolidine ring. Although pyroglutamic acid has been used for versatile building blocks for asymmetric synthesis,[9] there are few examples using its derivatives as chiral auxiliaries.[10] An *N*-protection step and succeeding addition to β-carboline proceeded without an event. Thus, *t*-butyl (*S*)-pyroglutamate (**2**) reacted with various *N*-protecting reagents in the presence of sodium hydride to give the derivatives **3**, which were transformed to the corresponding carboxylic acid **4** (Scheme 1 and Table 1).

The compound **4** thus obtained readily reacted with β-carboline by the use of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) to give 9-acyl-β-carbolines **5** (Scheme 2 and Table 2). Therefore, the substrates **5** for asymmetric addition were prepared in good yields via three steps.

Firstly, asymmetric addition reaction was carried out using

Keywords: β-carboline; (*S*)-pyroglutamic acid; chiral auxiliary; asymmetric addition; allyltributyltin; silyl enol ether; indole alkaloid.

* Corresponding author. Tel.: +81-3-3784-8183; fax: +81-3-3784-5982; e-mail: ohsawa@pharm.showa-u.ac.jp

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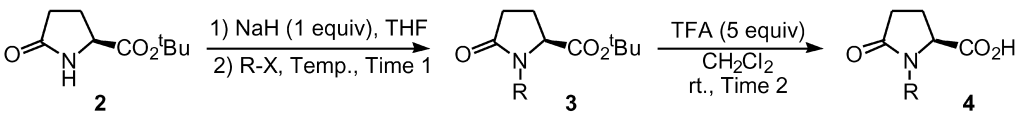
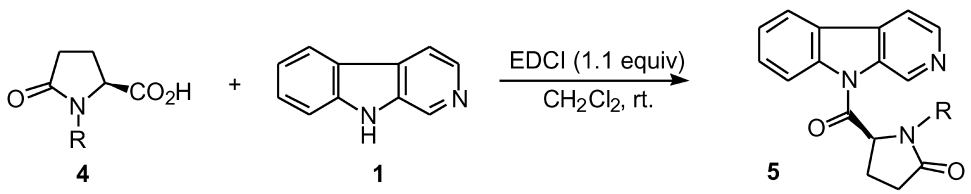


Scheme 1.

Table 1. Synthesis of the chiral auxiliary **4** from *t*-butyl (*S*)-pyroglutamate

Entry	Compound	R	Temperature	Time 1 (h)	Yield of **3** (%)	Time 2 (h)	Yield of **4** (%)
1	**a**	Me	Room temperature	1	94	4	71
2	**b**	$PhCH_2$	Reflux	1	81	7	91
3	**c**	1-Naphthylmethyl	Reflux	4	83	7	87
4	**d**	2-Naphthylmethyl	Reflux	1	83	7	97
5	**e**	9-Anthracenylmethyl	Reflux	10	75	22[a]	94
6	**f**	MeCO	Reflux	4.5	75	24	73
7	**g**	PhCO	Room temperature	24	74	24	90
8	**h**	9-Anthracenyl-CO	Reflux	9	83	25	85
9	**i**	*p*-NO_2–PhCO	Room temperature	17	69	43	91
10	**j**	$PhSO_2$	Room temperature	1	69	15	76

[a] 10 equiv. of TFA was used for the deprotection.



Scheme 2.

Table 2. Synthesis of 9-(pyroglutamyl)-β-carbolines (**5**)

Entry	Compound	R	Time (h)	Yield of **5** (%)
1	**a**	Me	3	86
2	**b**	$PhCH_2$	2	71
3	**c**	1-Naphthylmethyl	1.5	77
4	**d**	2-Naphthylmethyl	1.5	88
5	**e**	9-Anthracenylmethyl	4	95
6	**f**	MeCO	24	71
7	**g**	PhCO	20	99
8	**h**	9-Anthracenyl-CO	6	73
9	**i**	*p*-NO_2–PhCO	24	74
10	**j**	$PhSO_2$	2	91

allyltributyltin as a nucleophile (Scheme 3 and Table 3). In the event, the compound **5** was allowed to react with allyltributyltin and 2,2,2-trichloroethyl chloroformate to give a 1,2-dihydro adduct **6**, which was subsequently hydrolyzed to **7** in a quantitative yield. The chiral auxiliary was completely recovered under mild hydrolytic conditions. The absolute configuration of the product **7** was determined according to the method reported earlier.[6]

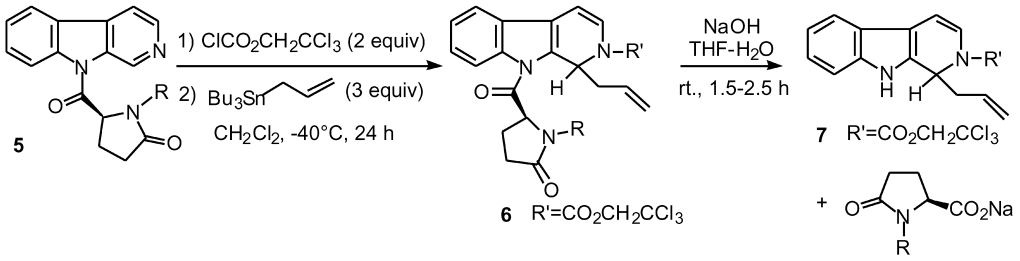
As shown in Table 3, the chiral auxiliaries which have an alkyl *N*-protecting group afforded the *S* isomer of the product, while the use of the auxiliaries having an acyl *N*-protecting group resulted in the formation of the *R* isomer. Thus, it was revealed that both enantiomers were obtained in good to high chemical and optical yields by the simple change of *N*-protecting groups of the auxiliary.

In the cases of entries 1–5, the steric hindrance of the *N*-protecting group played an important role in the induction of the stereoselectivity, that is, the ee of the *S* isomer was increased with the bulkiness of the protecting groups. In the cases of *N*-acyl groups, however, the bulkiness seldom affected the selectivity, and only the chemical yields were lowered (entries 6–10).

Secondly, silyl enol ethers were used as nucleophiles,[11] and the results are summarized in Table 4 (Scheme 4).

In the previous system using a (*S*)-proline derivative as the auxiliary, silyl enol ethers added to the substrate only in low stereoselectivity.[12] In the present system, however, the reaction proceeded in a highly diastereoselective manner to give the dihydro adducts **8a**–**e** in good yields after a mild hydrolysis. The change of the stereoselectivity was also observed in the cases of entries 6–8, and the same configurations (see below) as in the cases of Table 3 were obtained according to the used chiral auxiliaries. Thus, a general method for the synthesis of both enantiomers of 1-substituted 1,2,3,4-tetrahydro-β-carboline was accomplished using (*S*)-pyroglutamic acid as a chiral auxiliary.

For the determination of the configuration of the product in the reaction of silyl enol ethers, the adduct **8d** (entry 4 of Table 4) was transformed to a tetrahydro derivative **10** according to the process mentioned in Scheme 5. The dihydro adduct was reduced with triethylsilane to give the corresponding tetrahydro derivative **9**, which was further reduced with zinc–acetic acid, and succeeding esterification



Scheme 3.

Table 3. Asymmetric addition reaction of allyltributyltin with β-carboline which has a chiral auxiliary derived from pyroglutamic acid at *N*-9

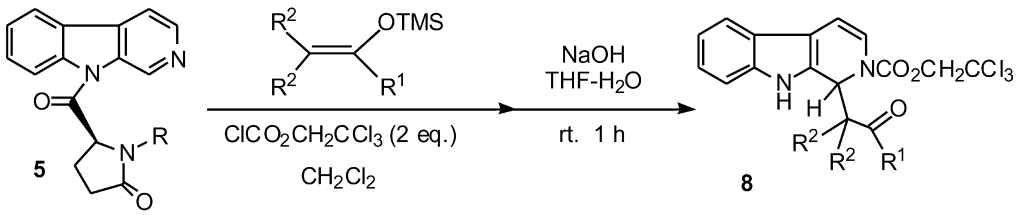
Entry	Compound	R	Yield of **6** (%)	Ee of **7** (%)[a]	Config. of **7**
1	**a**	Me	22	7	*S*
2	**b**	$PhCH_2$	95	21	*S*
3	**c**	1-Naphthylmethyl	87	58	*S*
4	**d**	2-Naphthylmethyl	Quant.	66	*S*
5	**e**	9-Anthracenylmethyl	98	91	*S*
6	**f**	MeCO	Quant.	89	*R*
7	**g**	PhCO	92	83	*R*
8	**h**	9-Anthracenyl-CO	56	83	*R*
9	**i**	*p*-NO_2–PhCO	Quant.	88	*R*
10	**j**	$PhSO_2$	51	79	*R*

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

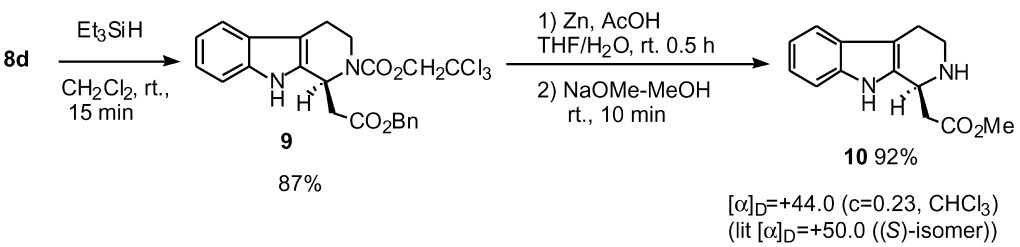
Table 4. Asymmetric addition reaction of silyl enol ethers with 9-(*N*-protected)-β-carboline

Entry	R	R^1	R^2	Temperature (°C)	Time (h)	Product	Yield (%)	Ea (%)[a]	Config. of **8**
1	Anthracenylmethyl	Me	H	0	24	**8a**	40	79	*S*
2	Anthracenylmethyl	Ph	H	0	2.5	**8b**	79	86	*S*
3	Anthracenylmethyl	OMe	Me	0	0.5	**8c**	Quant.	82	*S*
4	Anthracenylmethyl	OBn	H	−40	12	**8d**	81	88	*S*
5	Anthracenylmethyl	SBn	H	−40	19	**8e**	83	87	*S*
6	MeCO	OBn	H	−78	40	**8d**	93	76	*R*
7	PhCO	OBn	H	−78	40	**8d**	Quant.	76	*R*
8	*p*-NO_2–PhCO	OBn	H	−78	40	**8d**	Quant.	75	*R*

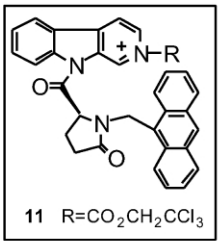
[a] The ee was estimated by HPLC after removal of the chiral auxiliary.



Scheme 4.



Scheme 5.



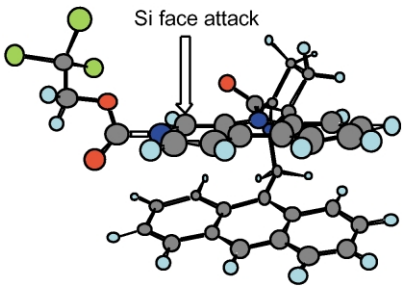


Figure 1. Calculated PM3 structures of 2-(trichloroethoxycarbonyl)-9-(*N*-anthracenylmethylpyroglutamyl)-β-carbolinium cation (**11**). The optimized conformation in which the *Re* face is blocked ΔH_f=117.4253 kcal/mol.

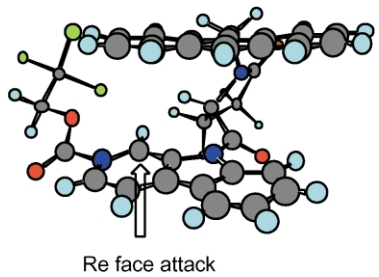


Figure 2. Calculated PM3 structures of 2-(trichloroethoxycarbonyl)-9-(*N*-anthracenylmethylpyroglutamyl)-β-carbolinium cation (**11**). A local minimal conformation in which the *Si* face is blocked ΔH_f=120.6484 kcal/mol.

of a free carboxylic acid afforded methyl ester of tetrahydro-β-carboline 1-acetic acid **10**. The absolute configuration was determined as *S* in comparison with the specific rotation of the reported one.[13] Thus, it was proved that the reaction proceeded in an *S* selective manner using the chiral auxiliary **5e** irrespective of the nucleophile to be allyltributyltin or silyl enol ether.

The unique stereoselectivities of the present reaction prompted us to consider factors controlling the stereochemistry. In the reaction using *N*-alkyl pyroglutaminyl groups (entries 1–5 in Table 3), the increment of the steric hindrance linearly increased the stereoselectivity of the addition. These results indicate that the selectivity was originated from shielding of one side of the substrate plane. Thus, PM3 calculations[14] were carried out for the intermediary *N*2-acylated quaternary salts of β-carboline whose optimized structures are shown in Figures 1 and 2.

In the optimized conformation in Figure 1, anthracenyl group is located on the *syn* position to the β-carboline group due to the π–π interaction of these two groups. The *Re* face of the reaction site (C1) of β-carboline ring is considerably shielded. A conformation in which the *Si* face is shielded was obtained as a local minimum structure as shown in Figure 2, but it is 3.22 kcal/mol less stable than that of Figure 1. Thus, the stereoselectivity using *N*-alkylpyroglutaminyl groups could be accounted for by the shielding of the *Re* face by the anthracenyl group.

In the cases of *N*-acylpyroglutaminyl groups (entries 6–10 of Table 3), however, the opposite stereoisomer was obtained. The bulkiness of the protecting group had little effect on the selectivity, and sterically less demanding *N*-acetyl derivative afforded the best result (entry 6).

These facts indicate that entirely different mechanism controls the stereochemistry. The PM3 calculation of the intermediates **12a** and **12b** showed that the carbonyl group **A** (in Figure 3) bends the methyl (in **12a**) or phenyl (in **12b**) group toward the far side of the reaction site because the carbonyl group **A** and another carbonyl group **B** in the pyroglutaminyl ring tend to reside in an antiperiplanar position to each other probably due to dipolar repulsion. It is suggested from the conformation that the steric influence of the methyl or phenyl group is weak. Though the reason of *R* selectivity (*Re* face attack) in the case of the substrate **12** remained unclear, the coordination of the nucleophiles to two carbonyl groups **A** and **C** might cause the *Re* face attack because these two groups exist near the reaction site on the *Re* face.[15] In fact, the addition of hexamethylphosphoric triamide (HMPA), which can act as a ligand for organometallic reagents, to the reaction system lowered the stereoselectivity.[16] The result suggests that the coordination

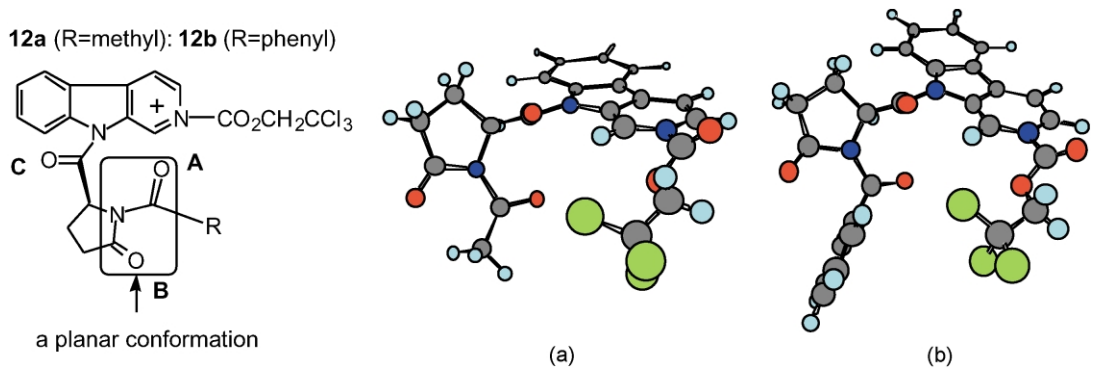


Figure 3. The Optimized structure of 2-(trichloroethoxycarbonyl)-9-(*N*-acylpyroglutamyl-β-carbolinium cation (**12a** and **12b**). (a) The optimized conformation of **12a**. ΔH_f=6.5927 kcal/mol. (b) The optimized conformation of **12b**. ΔH_f=43.1778 kcal/mol.

of the nucleophiles to the substrate might affect the selectivity.

3. Conclusion

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. Application of the adducts obtained by this method to the total synthesis of indole alkaloids is now under investigation.[17]

4. Experimental

4.1. General remarks

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra of $CDCl_3$ and CD_3OD solutions were recorded at 500 and 125 MHz, respectively, with tetramethylsilane (TMS) as an internal standard. High-resolution mass spectra (FAB-HRMS) were measured using *p*-nitrobenzyl alcohol as a matrix.

4.2. Preparation of the chiral auxiliaries

4.2.1. *N*-Protection of *tert*-butyl (*S*)-pyroglutamate (2). To the suspension of NaH (2 mmol) in THF (5 ml) was added *tert*-butyl (*S*)-pyroglutamate (**2**) (2 mmol), and the mixture was allowed to react for 5 min at room temperature, and an alkyl halide or acyl halide (2 mmol) was added to the mixture. The reaction was continued until the starting material was entirely consumed, then water was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and evaporated off to leave a residue, which was chromatographed on silica gel to give the product **3**.

4.2.2. *tert*-Butyl *N*-methyl-(*S*)-pyroglutamate (3a). Yield 94%; colorless plates from hexane; mp 69–71°C; $[\alpha]_D^{20}=-10.8$ (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.48 (9H, s), 2.01–2.08 (1H, m), 2.26–2.38 (2H, m), 2.43–2.51 (1H, m), 2.85 (3H, s), 3.98 (1H, dd, *J*=8.7, 3.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 22.6, 28.0, 28.8, 29.3, 62.6, 82.3, 170.9, 175.3. Anal. calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.31; H, 8.84; N, 6.95.

4.2.3. *tert*-Butyl *N*-benzyl-(*S*)-pyroglutamate (3b). Yield 81%; colorless needles from ^{i}Pr$_2$O–AcOEt; mp 51.0–58.9°C; $[\alpha]_D^{20}=+40.3$ (*c* 0.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.44 (9H, s), 1.99–2.06 (1H, m), 2.16–2.26 (1H, m), 2.40 (1H, ddd, *J*=13.6, 9.6, 4.0 Hz), 2.51–2.60 (1H, m), 3.83 (1H, dd, *J*=9.2, 3.3 Hz), 3.96 (1H, d, *J*=14.7 Hz), 5.06 (1H, d, *J*=14.7 Hz), 7.20–7.23 (2H, m), 7.26–7.35 (3H, m); ^{13}C NMR ($CDCl_3$) δ: 22.9, 28.0, 29.7, 45.6, 59.6, 82.2, 127.6, 128.4, 128.6, 135.8, 170.6, 174.9. Anal. calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.65; H, 7.55; N, 5.09.

4.2.4. *tert*-Butyl *N*-(naphthalen-1-ylmethyl)-(*S*)-pyroglutamate (3c). Yield 83%; colorless needles from hexane; mp 76–77°C; $[\alpha]_D^{20}=+51.5$ (*c* 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.40 (9H, s), 1.90–1.98 (1H, m), 2.09 (1H, ddd, *J*=18.8, 13.3, 9.2 Hz), 2.40 (1H, ddd, *J*=16.9, 9.6, 3.8 Hz), 2.52–2.62 (1H, m), 3.61 (1H, dd, *J*=9.2, 3.2 Hz), 4.39 (1H, d, *J*=14.6 Hz), 5.56 (1H, d, *J*=14.6 Hz), 7.34 (1H, dd, *J*=6.8, 1.0 Hz), 7.40 (1H, dd, *J*=8.1, 7.0 Hz), 7.48–7.56 (2H, m), 7.81–7.88 (2H, m), 8.08 (1H, dt, *J*=6.8, 1.1 Hz); ^{13}C NMR ($CDCl_3$) δ: 22.9, 28.0, 29.8, 43.8, 59.4, 82.0, 123.7, 125.0, 126.0, 126.7, 128.0, 128.5, 128.8, 131.3, 131.6, 133.7, 170.7, 174.5. Anal. calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.84; H, 7.22; N, 4.30.

4.2.5. *tert*-Butyl *N*-(naphthalen-2-ylmethyl)-(*S*)-pyroglutamate (3d). Yield 83%; colorless needles from hexane; mp 98–99°C; $[\alpha]_D^{20}=+69.7$ (*c* 0.54, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.41 (9H, s), 1.98–2.05 (1H, m), 2.19 (1H, ddd, *J*=18.7, 13.2, 9.2 Hz), 2.42 (1H, ddd, *J*=16.9, 9.7, 4.0 Hz), 2.53–2.62 (1H, m), 3.83 (1H, dd, *J*=9.2, 3.3 Hz), 4.14 (1H, d, *J*=14.7 Hz), 5.21 (1H, d, *J*=14.7 Hz), 7.35 (1H, dd, *J*=8.4, 1.7 Hz), 7.43–7.50 (2H, m), 7.65 (1H, s), 7.77–7.83 (3H, m); ^{13}C NMR ($CDCl_3$) δ: 22.8, 27.9, 29.6, 45.7, 59.4, 82.0, 125.8, 126.1, 126.2, 127.3, 127.4, 127.5, 128.4, 132.6, 133.0, 133.2, 170.5, 174.8. Anal. calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.74; H, 7.23; N, 4.32.

4.2.6. *tert*-Butyl *N*-(anthracen-9-ylmethyl)-(*S*)-pyroglutamate (3e). Yield 75%; Yellow needles from isopropyl ether; mp 169–172°C; $[\alpha]_D^{20}=+141.4$ (*c* 0.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.35 (9H, s), 1.82–1.89 (1H, m), 1.90–2.01 (1H, m), 2.38 (1H, ddd, *J*=16.9, 9.3, 2.6 Hz), 2.50–2.59 (1H, m), 3.43 (1H, dd, *J*=9.5, 2.0 Hz), 5.22 (1H, d, *J*=15.3 Hz), 5.94 (1H, d, *J*=15.3 Hz), 7.47 (2H, ddd, *J*=7.7, 6.4, 1.1 Hz), 7.52 (2H, ddd, *J*=8.1, 6.4, 1.5 Hz), 8.01 (2H, dd, *J*=8.1, 1.5 Hz), 8.33 (2H, dd, *J*=7.7, 1.1 Hz), 8.46 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 23.6, 27.9, 29.5, 37.5, 58.7, 82.0, 123.9, 125.0, 126.50, 126.52, 128.3, 129.0, 131.0, 131.2, 171.2, 174.5. Anal. calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.56; H, 6.70; N, 3.49.

4.2.7. *tert*-Butyl *N*-acetyl-(*S*)-pyroglutamate (3f). Yield 75%; colorless oil; $[\alpha]_D^{23}=-37.6$ (*c* 0.61, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.47 (9H, s), 2.01–2.07 (1H, m), 2.25–2.36 (1H, m), 2.52 (3H, s), 2.52–2.59 (1H, m), 2.66–2.76 (1H, m), 4.63 (1H, dd, *J*=9.4, 2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.2, 24.6, 27.8, 31.8, 58.4, 82.3, 170.1, 170.9, 174.6. HRMS (FAB$^+$) *m*/*z*: Calcd for $C_{11}H_{18}O_4N$ 228.1236, found 228.1218.

4.2.8. *tert*-Butyl *N*-benzoyl-(*S*)-pyroglutamate (3g). Yield 74%; colorless needles from hexane–dichloromethane; mp 150.9–151.4°C; $[\alpha]_D^{23}=-30.6$ (*c* 0.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.98 (9H, s), 2.10 (1H, ddt, *J*=13.4, 9.0, 4.7 Hz), 2.42 (1H, dq, *J*=13.4, 9.0 Hz), 2.55 (1H, ddd, *J*=17.5, 9.0, 4.7 Hz), 2.70 (1H, dt, *J*=17.5, 9.0 Hz), 4.77 (1H, dd, *J*=9.0, 4.7 Hz), 7.41 (2H, t, *J*=7.6 Hz), 7.52 (1H, t, *J*=7.6 Hz), 7.66 (2H, d, *J*=7.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 21.8, 27.9, 31.8, 59.5, 82.5, 127.8, 129.1, 132.2, 133.9, 170.0, 170.4, 173.6. Anal. calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.38; H, 6.62; N, 4.84.

4.2.9. *tert*-Butyl *N*-(9-anthracenecarbonyl)-(*S*)-pyroglutamate (3h). Yield 83%; mp 82.9–84.3°C; $[\alpha]_D^{23}=-88.1$ (*c* 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.65

(9H, s), 2.08–2.14 (1H, m), 2.29–2.40 (2H, m), 2.51–2.62 (1H, m), 5.08 (1H, dd, J=9.2, 3.1 Hz), 7.41–7.50 (3H, m), 7.54–7.57 (1H, m), 7.77 (1H, d, J=7.6 Hz), 8.02 (2H, d, J=8.2 Hz), 8.26 (1H, d, J=8.5 Hz), 8.52 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 21.4, 27.9, 31.2, 58.6, 82.7, 123.9, 124.7, 125.1, 125.3, 126.5, 126.7, 127.6, 128.2, 128.3, 128.4, 128.7, 129.9, 130.8, 130.9, 169.7, 170.1, 172.2. Anal. calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 73.87; H, 6.23; N, 3.36.

4.2.10. *tert*-Butyl *N*-(*p*-nitrobenzoyl)-(*S*)-pyroglutamate (3i). Yield 69%; Pale yellow powder from hexane–dichloromethane; mp 111.1–120.0°C; $[\alpha]_D^{23}$=−17.3 (c 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.51 (9H, s), 2.17 (1H, ddt, J=13.2, 9.4, 4.2 Hz), 2.48 (1H, ddt, J=13.2, 9.2, 9.0 Hz), 2.59 (1H, ddd, J=17.8, 9.3, 4.5 Hz), 2.74 (1H, dt, J=18.0 Hz), 4.82 (1H, dd, J=8.9, 3.9 Hz), 7.77 (2H, d, J=9.0 Hz), 8.27 (2H, d, J=9.0 Hz); ^{13}C NMR ($CDCl_3$) δ: 21.8, 27.9, 31.5, 59.0, 83.0, 123.1, 129.6, 139.9, 149.5, 168.5, 169.6, 173.7. Anal. calcd for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.54; H, 5.31; N, 8.23.

4.2.11. *tert*-Butyl *N*-benzenesulfonyl-(*S*)-pyroglutamate (3j). Yield 69%; colorless viscous oil; $[\alpha]_D^{20}$=−47.8 (c 0.52, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.49 (9H, s), 2.01–2.08 (1H, m), 2.33–2.45 (2H, m), 2.46–2.59 (1H, m), 4.74 (1H, dd, J=9.0, 2.6 Hz), 7.52 (2H, t, J=8.0 Hz), 7.64 (1H, tt, J=8.0, 1.3 Hz), 8.08 (2H, dd, J=8.0, 1.3 Hz); ^{13}C NMR ($CDCl_3$) δ: 23.2, 27.7, 30.3, 60.0, 82.7, 128.3, 128.5, 133.8, 137.7, 169.4, 172.4. HRMS (FAB$^+$): Calcd for $C_{15}H_{20}NO_5S$ $(M+H)^+$: 326.1062. Found: 326.1031.

4.3. Transformation of 3 to corresponding carboxylic acid 4

To the CH_2Cl_2 solution of *N*-protected *tert*-butyl (*S*)-pyroglutamate **3**, trifluoroacetic acid (5 equiv.) was added dropwise, and the mixture was allowed to react at room temperature. Then CH_2Cl_2 was added and the mixture was extracted with saturated aqueous $NaHCO_3$. The aqueous layer was acidified with dil. HCl, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and evaporated off to leave a residue. The residue was suspended in hexane to precipitate crystals, which was separated from the solution by filtration, and dried under vacuum to give *N*-protected pyroglutamic acid **4**.

4.3.1. *N*-Methyl-(*S*)-pyroglutamic acid (4a). Yield 71%; colorless prisms from ^{i}Pr$_2$O–AcOEt; mp 148–150°C; $[\alpha]_D^{20}$=−20.8 (c 0.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 2.16–2.24 (1H, m), 2.38–2.64 (3H, m), 2.92 (3H, s), 4.19 (1H, dd, J=9.2, 3.4 Hz), 10.61 (1H, bs); ^{13}C NMR ($CDCl_3$) δ: 20.8, 22.8, 29.4, 62.1, 174.0, 176.9. Anal. calcd for $C_6H_9NO_3$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.32; H, 6.34; N, 9.76.

4.3.2. *N*-Benzyl-(*S*)-pyroglutamic acid (4b). The mp and NMR spectra of this compound were identical to those of the reported data.[18] Yield 91%; colorless powder; mp 85–88°C (lit.[18] mp 92–93°C); $[\alpha]_D^{20}$=+78.6 (c 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 2.13–2.21 (1H, m), 2.30 (1H, ddd, J=18.9, 13.4, 9.3 Hz), 2.52 (1H, ddd, J=17.1, 9.3, 3.7 Hz), 2.60–2.69 (1H, m), 3.99 (1H, d, J=14.8 Hz), 4.03 (1H, dd, J=9.3, 3.1 Hz), 5.16 (1H, d, J=14.8 Hz), 7.21–7.23 (2H, m), 7.26–7.35 (3H, m), 10.06 (1H, bs).

4.3.3. *N*-(Naphthalen-1-ylmethyl)-(*S*)-pyroglutamic acid (4c). Yield 87%; colorless needles from isopropyl ether; mp 184–185°C; $[\alpha]_D^{20}$=+97.5 (c 0.53, $CHCl_3$); ^{1}H NMR (CD_3OD) δ: 1.97–2.08 (1H, m), 2.10–2.18 (1H, m), 2.35–2.43 (1H, m), 2.50–2.58 (1H, m), 3.72 (1H, dd, J=9.4, 3.1 Hz), 4.36 (1H, d, J=14.7 Hz), 5.56 (1H, d, J=14.7 Hz), 7.35–7.43 (2H, m), 7.49–7.51 (2H, m), 7.83–7.89 (2H, m), 8.01–8.04 (1H, m); ^{13}C NMR (CD_3OD) δ: 23.8, 30.7, 44.6, 60.0, 124.2, 126.1, 126.9, 127.5, 128.9, 129.7, 129.9, 132.0, 132.7, 135.2, 174.4, 177.2. Anal. calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.18; H, 5.42; N, 5.15.

4.3.4. *N*-(Naphthalen-2-ylmethyl)-(*S*)-pyroglutamic acid (4d). Yield 97%; colorless needles from hexane–^{i}Pr$_2$O; mp 149–152°C; $[\alpha]_D^{20}$=+73.6 (c 0.50, CH_3OH); ^{1}H NMR ($CDCl_3$) δ: 2.11–2.17 (1H, m), 2.25 (1H, ddd, J=18.9, 13.4, 9.5 Hz), 2.44 (1H, ddd, J=16.8, 9.5, 3.7 Hz), 2.56–2.63 (1H, m), 3.96 (1H, dd, J=9.3, 3.3 Hz), 4.18 (1H, d, J=14.9 Hz), 5.24 (1H, d, J=14.9 Hz), 7.37 (1H, dd, J=8.5, 1.8 Hz), 7.44–7.49 (2H, m), 7.68 (1H, s), 7.79–7.82 (3H, m); ^{13}C NMR ($CDCl_3$) δ: 22.9, 29.7, 45.6, 58.6, 126.0, 126.2, 126.4, 127.3, 127.6, 127.8, 128.6, 132.8, 133.3, 133.6, 173.7, 175.4. Anal. calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.10; H, 5.59; N, 5.18.

4.3.5. *N*-(Anthracen-9-ylmethyl)-(*S*)-pyroglutamic acid (4e). Yield 94%; Pale green prisms from ethanol; mp 277–280°C; $[\alpha]_D^{20}$=+151.2 (c 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 1.83–2.00 (2H, m), 2.31 (1H, ddd, J=16.9, 9.5, 2.4 Hz), 2.39–2.48 (1H, m), 3.41 (1H, dd, J=9.4, 1.7 Hz), 5.13 (1H, d, J=15.1 Hz), 5.84 (1H, d, J=15.1 Hz), 7.55 (2H, t, J=8.2 Hz), 7.60 (2H, t, J=8.2 Hz), 8.12 (2H, d, J=8.2 Hz), 8.35 (2H, d, J=8.2 Hz), 8.62 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 22.7, 28.9, 36.8, 57.5, 123.4, 125.0, 126.4, 126.6, 128.0, 129.0, 130.4, 130.7, 173.4, 173.7. Anal. calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 74.86; H, 5.18; N, 4.33.

4.3.6. *N*-Acetyl-(*S*)-pyroglutamic acid (4f). Yield 73%; colorless powder from hexane; mp 75.9–77.0°C; $[\alpha]_D^{20}$=−29.90 (c 0.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.19 (1H, ddt, J=13.4, 9.5, 3.0 Hz), 2.33–2.48 (1H, m), 2.55 (3H, s), 2.60 (1H, ddd, J=17.8, 9.3, 3.1 Hz), 2.76 (1H, dt, J=17.8, 10.1 Hz), 4.79 (1H, dd, J=9.7, 2.6 Hz), 9.16 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.1, 24.5, 31.7, 57.5, 171.3, 174.4, 176.2. Anal. calcd for $C_7H_9NO_4$: C, 49.12; H, 5.30; N, 8.18. Found: C, 49.01; H, 5.12; N, 8.01.

4.3.7. *N*-Benzoyl-(*S*)-pyroglutamic acid (4g). Yield 90%; colorless needles from hexane–ethyl acetate; mp 168.2–168.6°C; $[\alpha]_D^{25}$=+15.43 (c 0.3, CH_3OH); ^{1}H NMR ($CDCl_3$) δ: 2.27 (1H, ddt, J=13.2, 9.2, 4.5 Hz), 2.51 (1H, dq, J=13.2, 9.2 Hz), 2.62 (1H, ddd, J=17.7, 9.2, 4.5 Hz), 2.78 (1H, dt, J=17.7, 9.2 Hz), 4.92 (1H, dd, J=9.2, 4.5 Hz), 7.42 (2H, tt, J=7.5, 1.4 Hz), 7.54 (1H, tt, J=7.5, 1.5 Hz), 7.65–7.68 (2H, m); ^{13}C NMR ($CDCl_3$) δ: 21.7, 31.6, 58.5, 127.9, 129.2, 132.5, 133.4, 170.5, 173.3, 175.5. Anal. calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.77; H, 4.54; N, 5.80.

4.3.8. *N*-(Anthracene-9-carbonyl)-(*S*)-pyroglutamic acid

(4h). Yield 85%; Pale yellow powder; mp 150–155°C; $[\alpha]_D^{17}=-36.38$ (*c* 0.40, CH_3OH); ^1H NMR ($CDCl_3$) δ: 2.32 (1H, ddt, *J*=12.6, 9.8, 2.7 Hz), 2.40–2.47 (1H, m), 2.54 (1H, dq, *J*=12.9, 9.2 Hz), 2.67 (1H, dt, *J*=16.7, 9.5 Hz), 5.24 (1H, dd, *J*=9.2, 2.6 Hz), 7.43–7.51 (4H, m), 7.73–7.75 (1H, m), 8.00–8.04 (2H, m), 8.22 (1H, d, *J*=7.9 Hz), 8.52 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 21.8, 31.5, 57.9, 123.9, 124.8, 125.3, 125.6, 126.8, 126.9, 127.7, 128.4, 128.5, 128.6, 128.9, 130.0, 130.9, 131.1, 170.3, 172.7, 173.0. HRMS (FAB^+) *m/z*: Calcd for $C_{20}H_{16}NO_4$ $(M+H)^+$ 334.1079, found 334.1061.

4.3.9. *N*-(*p*-Nitrobenzoyl)-(*S*)-pyroglutamic acid (4i). Yield 91%; Pale yellow powder; mp 150.4–151.0°C; $[\alpha]_D^{20}=+12.46$ (*c* 0.5, CH_3OH); ^1H NMR ($CDCl_3$) δ: 2.32 (1H, ddt, *J*=13.1, 9.4, 3.7 Hz), 2.57 (1H, ddt, *J*=13.3, 9.3, 9.1 Hz), 2.66 (1H, ddd, *J*=17.7, 8.9, 3.7 Hz), 2.79 (1H, ddt, *J*=17.6, 9.0, 8.9 Hz), 4.98 (1H, dd, *J*=9.1, 3.6 Hz), 7.77 (2H, d, *J*=9.0 Hz), 8.29 (2H, d, *J*=9.0 Hz); ^{13}C NMR ($CDCl_3$+CD_3OD) δ: 21.9, 31.6, 58.4, 123.2, 129.6, 140.0, 149.5, 168.8, 172.6, 174.3. Anal. calcd for $C_{12}H_{10}N_2O_6$: C, 51.80; H, 3.62; N, 10.07. Found: C, 51.45; H, 3.30; N, 9.68.

4.3.10. *N*-(Benzenesulfonyl)-(*S*)-pyroglutamic acid (4j). Yield 76%; colorless powder; mp 158–160.5°C; $[\alpha]_D^{20}=-41.0$ (*c* 0.50, CH_3OH); ^1H NMR ($CDCl_3$) δ: 2.20–2.29 (1H, m), 2.43–2.70 (3H, m), 4.94 (1H, dd, *J*=9.2, 2.5 Hz), 5.72 (1H, br), 7.56 (2H, t, *J*=8.0 Hz), 7.68 (1H, t, *J*=8.0 Hz), 8.11 (2H, dd, *J*=8.0, 1.3 Hz); ^{13}C NMR ($CDCl_3$) δ: 23.4, 30.5, 59.0, 128.7, 128.8, 134.3, 137.5, 172.3, 175.0. Anal. calcd for $C_{11}H_{11}NO_5S$: C, 49.06; H, 4.12; N, 5.20. Found: C, 48.97; H, 3.74; N, 5.15.

4.4. The synthesis of 9-pyroglutaminyl-β-carbolines 5

To the CH_2Cl_2 (1 ml) solution of *N*-substituted pyroglutamic acid **4** (0.5 mmol) and β-carboline (0.5 mmol) was added EDCI (0.6 mmol), and the mixture was allowed to react for 1–3 h at room temperature. Then the mixture was chromatographed on silica gel (AcOEt) to give the product.

4.4.1. 9-(*N*-Methyl-(*S*)-pyroglutamyl)-β-carboline (5a). Yield 86%; colorless powder; mp 175–178°C; $[\alpha]_D^{20}=-148.9$ (*c* 0.30, CH_3OH); ^1H NMR ($CDCl_3$) δ: 2.31–2.37 (1H, m), 2.51–2.80 (3H, m), 2.95 (3H, s), 5.19 (1H, dd, *J*=9.3, 1.8 Hz), 7.52 (1H, t, *J*=7.3 Hz), 7.68 (1H, ddd, *J*=8.6, 7.3, 1.3 Hz), 7.94 (1H, dd, *J*=5.1, 0.9 Hz), 8.12 (1H, dd, *J*=7.3, 0.6 Hz), 8.18 (1H, br), 8.68 (1H, d, *J*=5.1 Hz), 9.55 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 23.6, 28.8, 29.2, 63.4, 114.1, 116.1, 121.5, 122.0, 124.6, 132.8, 134.6, 137.6, 138.2, 144.0, 147.5, 170.1, 174.9. Anal. calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.35; H, 5.02; N, 14.15.

4.4.2. 9-(*N*-Benzyl-(*S*)-pyroglutamyl)-β-carboline (5b). Yield 99%; colorless needles from Et_2O–AcOEt; mp 175–178°C; $[\alpha]_D^{20}=-124.7$ (*c* 0.13, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 2.26–2.32 (1H, m), 2.55–2.64 (2H, m), 2.66–2.75 (1H, m), 4.00 (1H, d, *J*=14.8 Hz), 5.01 (1H, dd, *J*=8.9, 1.9 Hz), 5.22 (1H, d, *J*=14.8 Hz), 7.12–7.18 (5H, m), 7.48 (1H, t, *J*=8.4 Hz), 7.60 (1H, t, *J*=8.4 Hz), 7.85–8.20 (1H, br), 7.91 (1H, dd, *J*=5.1, 0.9 Hz), 8.09 (1H, d, *J*=8.4 Hz), 8.64 (1H, d, *J*=5.1 Hz), 9.31 (1H, bs); ^{13}C NMR ($CDCl_3$) δ: 23.8, 29.3, 45.9, 60.2, 114.2, 116.1, 121.5, 124.5, 124.6, 127.7, 128.2, 128.7, 130.3, 132.9, 134.6, 135.3, 137.4, 138.3, 143.9, 170.6, 174.8. Anal. calcd for $C_{23}H_{19}N_3O_2$: C, 74.78; H, 5.18; N, 11.37. Found: C, 74.47; H, 4.79; N, 11.46.

4.4.3. 9-[*N*-(Naphthalen-1-ylmethyl)-(*S*)-pyroglutamyl]-β-carboline (5c). Yield 77%; colorless powder; mp 88–92°C; $[\alpha]_D^{20}=-114.1$ (*c* 0.17, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 2.21 (1H, ddt, *J*=11.9, 9.5, 2.4 Hz), 2.46 (1H, ddd, *J*=19.2, 13.1, 9.5 Hz), 2.60 (1H, ddd, *J*=16.8, 9.5, 2.4 Hz), 2.76 (1H, dt, *J*=16.8, 9.5 Hz), 4.47 (1H, d, *J*=14.6 Hz), 4.79 (1H, dd, *J*=9.5, 2.4 Hz), 5.62 (1H, d, *J*=14.6 Hz), 6.95 (1H, dd, *J*=8.2, 7.0 Hz), 7.06 (1H, d, *J*=7.0 Hz), 7.40–7.54 (4H, m), 7.55 (1H, d, *J*=7.9 Hz), 7.72–7.75 (1H, m), 7.87 (1H, dd, *J*=4.9, 0.9 Hz), 8.05 (2H, d, *J*=8.9 Hz), 8.61 (1H, d, *J*=4.9 Hz); ^{13}C NMR ($CDCl_3$) δ: 23.5, 29.5, 43.9, 59.8, 114.2, 121.5, 123.5, 124.7, 124.8, 126.2, 126.9, 127.8, 128.7, 129.0, 130.3, 130.9, 131.6, 132.8, 133.7, 144.2, 170.9, 174.8. Anal. calcd for $C_{27}H_{21}N_3O_2{\cdot}1/2H_2O$: C, 75.68; H, 5.17; N, 9.81. Found: C, 75.61; H, 5.21; N, 9.37.

4.4.4. 9-[*N*-(Naphthalen-2-ylmethyl)-(*S*)-pyroglutamyl]-β-carboline (5d). Yield 88%; colorless needles from $^iPr_2O$–AcOEt; mp 149–152°C; $[\alpha]_D^{20}=-104.2$ (*c* 0.52, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 2.31–2.35 (1H, m), 2.55–2.67 (2H, m), 2.71–2.81 (1H, m), 4.19 (1H, d, *J*=14.9 Hz), 5.04 (1H, dd, *J*=9.0, 2.4 Hz), 5.27 (1H, d, *J*=14.9 Hz), 7.26–7.43 (6H, m), 7.50 (1H, t, *J*=7.4 Hz), 7.67 (2H, t, *J*=8.1 Hz), 7.81 (1H, d, *J*=4.9 Hz), 7.86 (1H, br), 7.99 (1H, d, *J*=7.7 Hz), 8.57 (1H, d, *J*=4.9 Hz), 9.29 (1H, bs); ^{13}C NMR ($CDCl_3$) δ: 23.8, 29.4, 46.2, 60.1, 114.1, 116.0 (br), 121.5, 124.4, 124.6, 125.92, 125.94, 126.1, 127.3, 127.4, 128.7, 130.2, 132.57, 132.64, 132.8, 132.9, 134.5 (br), 137.3 (br), 138.2 (br), 143.7, 170.7, 174.9. Anal. calcd for $C_{27}H_{21}N_3O_2$: C, 77.31; H, 5.05; N, 10.02. Found: C, 77.07; H, 4.80; N, 9.98.

4.4.5. 9-[*N*-(Anthracen-9-ylmethyl)-(*S*)-pyroglutamyl]-β-carboline (5e). Yield 95%; colorless powder; mp 190–193°C (decomp.); $[\alpha]_D^{20}=-75.9$ (*c* 0.51, $CHCl_3$); ^1H NMR ($CDCl_3$, 60°C) δ: 2.10–2.15 (1H, m), 2.28–2.36 (1H, m), 2.57 (1H, ddd, *J*=16.8, 9.5, 2.1 Hz), 2.82 (1H, dt, *J*=17.1, 9.5 Hz), 4.56 (1H, dd, *J*=9.1, 1.5 Hz), 5.34 (1H, d, *J*=15.3 Hz), 5.79 (1H, d, *J*=15.3 Hz), 7.04 (2H, t, *J*=7.6 Hz), 7.15 (2H, t, *J*=8.2 Hz), 7.35 (1H, br), 7.65 (2H, d, *J*=8.5 Hz), 7.71 (1H, d, *J*=4.9 Hz), 7.88–7.90 (1H, m), 8.02 (1H, s), 8.07 (2H, d, *J*=8.9 Hz), 8.51 (1H, br); ^{13}C NMR ($CDCl_3$, 60°C) δ: 23.7, 29.4, 37.8, 59.3, 113.9, 121.2 (br), 123.3, 124.5 (br), 124.9, 125.5, 126.6, 128.4, 129.1, 130.0 (br), 130.9, 131.1, 132.8 (br), 143.7, 171.4, 174.9. Anal. calcd for $C_{31}H_{23}N_3O_2$: C, 79.30; H, 4.94; N, 8.95. Found: C, 78.93; H, 5.00; N, 8.77.

4.4.6. 9-(*N*-Acetyl-(*S*)-pyroglutamyl)-β-carboline (5f). Yield 71%; colorless needles from $^iPr_2O$–CH_2Cl_2; mp 195–196°C; $[\alpha]_D^{20}=-68.39$ (*c* 0.59, $CHCl_3$); ^1H NMR ($CDCl_3$) δ: 2.30–2.38 (1H, m), 2.57–2.79 (2H, m), 2.63 (3H, s), 7.50 (1H, td, *J*=7.6, 0.8 Hz), 7.64 (1H, ddd, *J*=8.6, 7.3, 1.3 Hz), 7.93 (1H, dd, *J*=5.1, 1.1 Hz), 8.11 (1H, ddd, *J*=7.8, 1.3, 0.6 Hz), 8.17 (1H, bs), 8.66 (1H, d, *J*=5.1 Hz), 9.50 (1H, bs); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.7, 24.6, 31.6, 59.0, 114.5, 116.4, 121.7, 124.7, 124.8, 130.5, 133.3, 135.0, 137.5, 138.7, 143.8, 170.2, 171.2, 174.2. Anal. calcd for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.00; H, 4.50; N, 12.85.

4.4.7. 9-[*N*-(Benzoyl)-(*S*)-pyroglutamyl]-β-carboline (5g). Yield 99%; colorless powder from hexane; mp 170.0–171.2°C; $[\alpha]_D^{25}$=+13.91 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 2.36–2.43 (1H, m), 2.68–2.79 (2H, m), 2.91–3.03 (1H, m), 6.00 (1H, dd, *J*=8.9, 2.3 Hz), 7.43 (2H, t, *J*=7.6 Hz), 7.49–7.57 (2H, m), 7.65–7.73 (3H, m), 7.98 (1H, dd, *J*=5.1, 0.9 Hz), 8.12 (1H, d, *J*=7.1 Hz), 8.2 (1H, d, *J*=5.9 Hz), 8.67 (1H, d, *J*=5.1 Hz), 9.57 (1H, bs); ^{13}C NMR($CDCl_3$) δ: 22.1, 31.4, 59.9, 114.3, 116.3, 121.6, 124.7, 124.7, 127.8, 129.2, 130.3, 132.3, 133.0, 133.3, 135.0, 137.8, 138.5, 144.1, 170.30, 170.34, 173.1. Anal. calcd for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 4.47; N, 10.96. Found: C, 72.24; H, 4.21; N, 10.90.

4.4.8. 9-[*N*-(Anthracene-9-carbonyl)-(*S*)-pyroglutamyl]-β-carboline (5h). Yield 73%; colorless powder; mp 180–183°C (decomp); $[\alpha]_D^{23}$=−139.36 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 2.44–2.48 (1H, m), 2.53–2.61 (1H, m), 2.80–2.88 (2H, m), 6.41 (1H, dd, *J*=9.0, 1.4 Hz), 7.45–7.57 (4H, m), 7.65 (1H, t, *J*=7.2 Hz), 7.76 (1H, td, *J*=7.8, 1.1 Hz), 7.84 (1H, d, *J*=8.2 Hz), 8.02–8.05 (3H, m), 8.16 (1H, d, *J*=7.6 Hz), 8.30 (1H, bs), 8.34 (1H, d, *J*=8.9 Hz), 8.54 (1H, s), 8.66 (1H, d, *J*=5.2 Hz), 9.77 (1H, bs); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.1, 31.1, 59.1, 114.5, 116.4, 121.8, 123.8, 124.9, 125.2, 125.7, 126.7, 127.2, 127.7, 128.45, 128.53, 128.7, 129.0, 129.4, 130.5, 130.8, 131.1, 133.3, 135.2, 138.0, 138.7, 144.2, 170.1, 170.2, 171.8. Anal. calcd for $C_{31}H_{21}N_3O_3$: C, 77.00; H, 4.38; N, 8.69. Found: C, 76.80; H, 4.11; N, 8.58.

4.4.9. 9-[*N*-(*p*-Nitrobenzoyl)-(*S*)-pyroglutamyl]-β-carboline (5i). Yield 74%; Pale yellow needles from ^{i}Pr$_2$O–CH_2Cl_2; mp 223–225°C; $[\alpha]_D^{20}$=+8.12 (*c* 0.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 2.42–2.50 (1H, m), 2.73–2.87 (2H, m), 2.91–3.04 (1H, m), 6.07 (1H, dd, *J*=9.0, 2.0 Hz), 7.54 (1H, td, *J*=7.6, 0.6 Hz), 7.70 (1H, td, *J*=7.9, 1.3 Hz), 7.85 (2H, d, *J*=8.8 Hz), 7.98 (1H, dd, *J*=5.1, 0.7 Hz), 8.15 (1H, dd, *J*=7.8, 0.6 Hz), 8.23 (1H, bs), 8.31 (2H, d, *J*=8.8 Hz), 8.70 (2H, d, *J*=5.1 Hz), 9.57 (1H, bs); ^{13}C NMR ($CDCl_3$) δ: 22.2, 31.2, 59.7, 114.5, 116.4, 121.8, 123.2, 124.96, 125.01, 129.7, 130.6, 135.0, 137.8, 138.6, 139.4, 144.4, 149.6, 168.4, 169.8, 173.3. HRMS (FAB$^+$) *m/z*: Calcd for $C_{23}H_{17}O_5N_4$ $(M+H)^+$ 429.1199, found 429.1245.

4.4.10. 9-[*N*-(Benzenesulfonyl)-(*S*)-pyroglutamyl]-β-carboline (5j). Yield 91%; colorless plates from ^{i}Pr$_2$O–AcOEt; mp 203.1–204.0°C; $[\alpha]_D^{20}$=−94.6 (*c* 0.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 2.32–2.40 (1H, m), 2.57–2.66 (1H, m), 2.71–2.85 (2H, m), 6.07 (1H, dd, *J*=9.2, 1.5 Hz), 7.53–7.60 (3H, m), 7.69–7.75 (2H, m), 8.01 (1H, d, *J*=4.9 Hz), 8.03–8.16 (1H, br), 8.09–8.12 (2H, m), 8.16 (1H, d, *J*=7.5 Hz), 8.71 (1H, d, *J*=4.9 Hz), 9.59 (1H, bs); ^{13}C NMR ($CDCl_3$) δ: 23.9, 30.2, 60.7, 114.3, 115.9, 121.8, 124.8, 128.5, 129.3, 130.4, 133.1, 134.3, 134.9, 137.1, 138.0, 144.2, 169.5, 172.1. Anal. calcd for $C_{22}H_{17}N_3O_4S$: C, 63.00; H, 4.09; N, 10.02. Found: C, 62.94; H, 3.74; N, 9.96.

4.5. Asymmetric addition of allyltributyltin to 9-pyroglutamyl-β-carbolines 5 in the presence of 2,2,2-trichloroethyl chloroformate

To the CH_2Cl_2 solution (1 ml) of **5** (0.1 mmol) and allyltributyltin (0.3 mmol) was added 2,2,2-trichloroethyl chloroformate (0.2 mmol) at −78°C under Ar atmosphere, and the reaction was continued for 24 h at the same temperature. After 3 M aqueous KF solution (10 ml) and CH_2Cl_2 (10 ml) were added, the mixture was stirred vigorously for another 1 h. Then the organic layer was separated, dried over $MgSO_4$, and evaporated off. The residue was chromatographed on silica gel (CH_2Cl_2–AcOEt) to give the adduct **6** as a colorless oil. The compound **6** was found to be unstable, and its NMR spectra were given as those of a mixture of diastereomers and conformational isomers. Thus, the adduct **6** was subjected to alkaline hydrolysis without further purification. To the THF solution (1 ml) of **6** was added 1 M aqueous NaOH solution (2 ml), and the mixture was allowed to react for 30 min at room temperature. After H_2O was added, the mixture was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$ and evaporated. A residue thus obtained was confirmed by NMR to be a pure compound **7**.[6] The aqueous layer was acidified with dil. HCl and extracted with CH_2Cl_2. The organic layer thus obtained was dried over $MgSO_4$, and evaporated off to leave almost pure compound **4** in a quantitative yield.

4.6. The reaction of 9-pyroglutamyl-β-carboline 5 with silyl enol ethers

2,2,2-Trichloroethyl chloroformate (0.2 mmol) was added to the mixture of compound **5** (0.1 mmol) and a silyl enol ether (0.3 mmol) in CH_2Cl_2 (1 ml) at the temperature shown in Table 4 under Ar, and the mixture was allowed to react for 0.5–40 h until the complete consumption of **5**. After diluted with THF (1 ml), 1 M NaOH (1 ml) was added to the mixture, which was allowed to stir for 1 h at room temperature. Then the mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and evaporated off to leave the residue, which was chromatographed on silica gel to give the product **8**. The aqueous layer was acidified with dil. HCl and extracted with CH_2Cl_2. The organic layer thus obtained was dried over $MgSO_4$, and evaporated off to leave almost pure compound **4** in a quantitative yield.

4.6.1. 1,2-Dihydro-1-(2-oxopropyl)-2-(2,2,2-trichloroethoxycarbonyl)-β-carboline (8a). Yield 40%; Pale yellow powder; mp 145–150°C; $[\alpha]_D^{20}$=−219.4 (*c* 0.22, $CHCl_3$). The product was obtained as a mixture of two conformational isomers. The ^{1}H and ^{13}C NMR spectra of minor one are shown in parentheses. ^{1}H NMR ($CDCl_3$, 60°C) δ: 2.12 (3H, s), 2.97–3.20 (2H, m), 4.73 (4.64) (1H, d, *J*=11.9 Hz), 4.99 (5.13) (1H, d, *J*=11.9 Hz), 6.03 (6.09) (1H, dd, *J*=10.3, 3.0 Hz (9.8, 2.8 Hz)), 6.16 (6.22) (1H, d, *J*=7.7 Hz), 6.69 (6.71) (1H, d, *J*=7.7 Hz), 7.11–7.20 (2H, m), 7.34 (7.33) (1H, d, *J*=7.8 Hz), 7.57 (1H, d, *J*=7.5 Hz), 8.76 (8.68) (1H, s); ^{13}C NMR ($CDCl_3$) δ: 30.3 (30.2), 48.4 (48.8), 48.9 (50.2), 75.5 (75.2), 95.0 (95.1), 104.0, 106.3 (106.4), 111.52 (111.47), 117.1 (118.0), 118.0 (118.2), 120.21 (120.23), 122.17 (122.19), 123.40 (123.44), 130.6 (130.5), 135.78 (135.81), 151.5 (151.3), 208.3 (208.2). Anal. calcd for $C_{17}H_{15}C_{l3}N_2O_3$: C, 50.83; H, 3.76; N, 6.97. Found: C, 50.60; H, 3.42; N, 6.69.

4.6.2. 1,2-Dihydro-1-(2-oxo-2-phenylethyl)-2-(2,2,2-trichloroethoxycarbonyl)-β-carboline (8b). Yield 79%;

colorless needles from hexane–AcOEt; mp 152–155°C; $[\alpha]_D^{20}=-335.0$ (*c* 0.30, $CHCl_3$); The product was obtained as a mixture of two conformational isomers. The ^1H and ^{13}C NMR spectra of minor one are shown in parentheses. ^1H NMR ($CDCl_3$, 60°C) δ: 3.48 (3.61) (1H, dd, *J*=18.0, 2.7 Hz), 3.65 (3.70) (1H, dd, *J*=18.0, 10.4 Hz), 4.76 (4.67) (1H, d, *J*=11.9 Hz), 4.99 (5.07) (1H, d, *J*=11.9 Hz), 6.21 (6.27) (1H, d, *J*=7.6 Hz), 6.28 (6.33) (1H, dd, *J*=10.4, 2.7 Hz), 6.77 (6.78) (1H, d, *J*=7.6 Hz), 7.10–7.18 (2H, m), 7.36 (7.35) (1H, d, *J*=7.9 Hz), 7.41–7.45 (2H, m), 7.54–7.58 (2H, m), 7.89 (1H, d, *J*=8.2 Hz), 8.91 (8.84) (1H, s); ^{13}C NMR ($CDCl_3$) δ: 43.9 (45.7), 49.4 (49.3), 75.6 (75.3), 95.1 (95.0), 104.3 (104.2), 106.5 (106.6), 111.63 (111.57), 117.3 (118.2), 118.1 (118.3), 120.29 (120.31), 122.26 (122.28), 123.56 (123.60), 127.9 (128.0), 128.7 (128.8), 131.0 (130.9), 133.8 (133.9), 135.95 (135.94), 136.1 (136.00), 151.7 (151.6), 199.60 (199.56). Anal. calcd for $C_{22}H_{17}Cl_3N_2O_3$: C, 56.98; H, 3.69; N, 6.04. Found: C, 57.28; H, 3.49; N, 5.77.

4.6.3. 1,2-Dihydro-1-(1-methoxycarbonyl-1-methylethyl)-2-(2,2,2-trichloroethoxycarbonyl)-β-carboline (8c). Yield quant; colorless powder; mp 146–148°C; $[\alpha]_D^{18}=+110.52$ (*c* 2.32, $CHCl_3$); The product was obtained as a mixture of two conformational isomers. The ^1H and ^{13}C NMR spectra of minor one are shown in parentheses. ^1H NMR ($CDCl_3$, 60°C) δ: 1.10 (3H, s), 1.32 (1.40) (3H, s), 3.71 (3H, s), 4.76 (4.82) (1H, d, *J*=11.9 Hz), 5.06 (4.90) (1H, d, *J*=11.9 Hz), 6.24–6.35 (2H, m), 6.78 (1H, d, *J*=7.5 Hz), 7.12–7.20 (2H, m), 7.35 (1H, d, *J*=7.7 Hz), 7.59 (1H, d, *J*=7.7 Hz), 8.53 (8.47) (1H, s); ^{13}C NMR ($CDCl_3$) δ: 19.3 (18.8), 23.1 (23.8), 50.5 (50.4), 32.3, 56.36 (56.43), 75.3 (75.6), 95.0 (94.5), 106.1 (106.8), 108.7 (109.0), 111.2, 117.9 (118.0), 119.4 (120.1), 120.0 (120.6), 121.97 (122.03), 123.2, 128.7 (128.6), 135.6, 153.2 (152.7), 177.7 (178.0). Anal. calcd for $C_{19}H_{19}Cl_3N_2O_4$: C, 51.20; H, 4.30; N, 6.28. Found: C, 51.33; H, 4.22; N, 6.06.

4.6.4. 1-Benzyloxycarbonylmethyl-1,2-dihydro-2-(2,2,2-trichloroethoxycarbonyl)-β-carboline (8d). Yield 81%; colorless powder; mp 138–142°C; $[\alpha]_D^{20}=-200.7$ (*c* 0.27, $CHCl_3$); The product was obtained as a mixture of two conformational isomers. The ^1H and ^{13}C NMR spectra of minor one are shown in parentheses. ^1H NMR ($CDCl_3$, 60°C) δ: 2.87–3.04 (2H, m), 4.74 (4.70) (1H, d, *J*=11.9 Hz), 4.98 (5.04) (1H, d, *J*=11.9 Hz), 5.05 (5.03) (1H, d, *J*=12.2 Hz), 5.19 (5.23) (1H, d, *J*=12.2 Hz), 6.05–6.10 (1H, m), 6.17 (6.23) (1H, d, *J*=7.9 Hz), 6.69 (6.70) (1H, d, *J*=7.9 Hz), 7.12–7.20 (2H, m), 7.27–7.31 (3H, m), 7.33–7.36 (3H, m), 7.58 (1H, d, *J*=7.9 Hz), 8.57 (8.54) (1H, s); ^{13}C NMR ($CDCl_3$) δ: 38.6 (40.3), 49.44 (49.46), 67.0 (66.9), 75.6 (75.4), 95.05 (94.96), 104.13 (104.11), 106.87 (106.92), 111.61 (111.57), 117.2, 118.2 (118.3), 120.4, 122.4, 123.5 (123.6), 128.4 (128.3), 128.28 (128.61), 128.7, 130.04 (129.96), 135.1 (135.2), 135.99 (136.03), 151.7 (151.4), 171.7 (171.9). Anal. calcd for $C_{23}H_{19}Cl_3N_2O_4$: C, 55.95; H, 3.88; N, 5.67. Found: C, 55.83; H, 3.58; N, 5.54.

4.7. Transformation of compound 8d to 10

To the CH_2Cl_2 solution (2 ml) of **8d** (24 mg, 0.049 mmol) and triethylsilane (200 μl, 1.26 mmol) was added trifluoroacetic acid (100 μl, 1.30 mmol), and the mixture was allowed to react for 15 min. Then the mixture was diluted with CH_2Cl_2, washed with 10% Na_2CO_3, dried over $MgSO_4$, and evaporated off in vacuo to leave a residue, which was chromatographed on silica gel (CH_2Cl_2) to give compound **9** (21 mg, 0.042 mmol, 87% yield). To the THF (0.35 ml)/H_2O (0.25 ml) solution of compound **9** (20 mg, 0.04 mmol) was added acetic acid (20 μl, 0.35 mmol) and zinc powder (11 mg, 0.17 mmol) successively, and the mixture was allowed to react for 3 h. Then ethyl acetate (15 ml) was added, and the organic layer was washed with 5% Na_2CO_3 (3 ml) and brine (1 ml) respectively, dried over $MgSO_4$, and evaporated off. The residue was dissolved in MeOH (1 ml), and the solution was treated with sodium methoxide (0.016 mmol) for 2.5 h at room temperature. Then the solution was neutralized with 1N HCl, and the methanol was evaporated off. The aqueous layer thus obtained was basified by the addition of 5% Na_2CO_3, and extracted with CH_2Cl_2 (8 ml×2). The organic layer was dried over $MgSO_4$, and evaporated off to leave a residue, which was chromatographed on silica gel (AcOEt–EtOH=5:1) to give the product **10** (9.0 mg, 0.037 mmol) in 92% yield.

4.7.1. 1-Benzyloxycarbonylmethyl-1,2,3,4-tetrahydro-2-(2,2,2-trichloroethoxycarbonyl)-β-carboline (9). Colorless needles from hexane; mp 114–115°C; $[\alpha]_D^{20}=+200.7$ (*c* 0.27, $CHCl_3$); The product was obtained as a mixture of two conformational isomers. The ^1H and ^{13}C NMR spectra of minor one are shown in parentheses. ^1H NMR ($CDCl_3$) δ: 2.79 (1H, dt, *J*=15.9, 4.6 Hz), 2.86–2.95 (1H, m), 3.01 (1H, d, *J*=7.0 Hz), 3.06 (1H, d, *J*=7.0 Hz), 3.18 (3.24) (1H, td, *J*=12.8, 4.6 Hz), 4.55 (1H, td, *J*=12.8, 4.9 Hz), 4.79 (4.63) (1H, d, *J*=11.9 Hz), 4.83 (4.98) (1H, d, *J*=11.9 Hz), 5.18 (5.17) (1H, d, *J*=12.2 Hz), 5.25 (5.29) (1H, d, *J*=12.2 Hz), 5.72 (5.73) (1H, t, *J*=7.0 Hz), 7.08–7.12 (1H, m), 7.16–7.19 (1H, m), 7.27 (1H, d, *J*=8.6 Hz), 7.34–7.39 (5H, m), 7.48 (1H, t, *J*=7.9 Hz), 8.67 (8.63) (1H, s); ^{13}C NMR ($CDCl_3$) δ: 21.6 (21.1), 39.67 (39.2), 39.70 (39.9), 48.0 (47.8), 67.2, 75.2 (75.1), 95.6 (95.5), 108.4 (108.6), 111.2, 118.2 (118.3), 119.5 (119.6), 122.2 (122.3), 126.2, 128.4 (128.5), 128.6 (128.7), 128.8, 131.9 (132.3), 135.2, 135.7 (135.8), 153.4 (153.0), 172.3 (172.6). Anal. calcd for $C_{23}H_{21}Cl_3N_2O_4$: C, 55.72; H, 4.27; N, 5.65. Found: C, 55.60; H, 3.96; N, 5.48.

4.7.2. 1,2,3,4-Tetrahydro-1-methoxycarbonylmethyl-β-carboline (10). Colorless powder; mp 140–143°C. The NMR spectrum of **10** was identical with that of the reported one.[13] ^1H NMR ($CDCl_3$) δ: 2.22–2.31 (1H, m), 2.59 (1H, ddd, *J*=17.6, 6.6, 4.2 Hz), 2.79–2.98 (3H, m), 4.82 (1H, dd, *J*=13.6, 4.0 Hz), 4.98–5.06 (1H, m), 5.27 (1H, d, *J*=17.3 Hz), 5.32 (1H, d, *J*=17.3 Hz), 6.06 (1H, dd, *J*=9.7, 2.9 Hz), 6.53 (1H, ddd, *J*=9.7, 6.6, 2.0 Hz), 6.96–6.99 (1H, m), 7.11–7.17 (3H, m), 7.25–7.32 (3H, m), 7.36–7.38 (1H, m), 7.57–7.61 (1H, m).

4.8. Molecular orbital calculations

The molecular orbital calculations were carried out using the PM3 procedure[14] with the standard parameters, as implemented in the MOPAC2000 program.

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