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Preparation of both enantiomers of 1-allyl-1,2,3,4-tetrahydro-β-carboline using allyltin reagents and a chiral auxiliary derived from L-proline

Takashi Itoh, Yûji 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—β-Carboline, which had an acyl group derived from L-proline at the 9-position, reacted with allyltributyltin and 2,2,2-trichloroethyl chloroformate to afford an 1-allyl-1,2-dihydro-β-carboline derivative in a diastereoselective manner. The chiral acyl group at N-9 was readily eliminated by aqueous alkali to give a corresponding carboxylic acid. The formed 1-allyl-1,2-dihydro-β-carboline was transformed via two reduction steps to 1-allyl-1,2,3,4-tetrahydro-β-carboline in high ee. When the allylation was carried out using tetraallyltin instead of allyltributyltin, the stereoselectivity was reversed, and the antipode of the allyl adduct was obtained in high yield and ee in the presence of tin(IV) tetraiodide. Thus, it was found that both enantiomers of 1-allyl-β-carboline were obtained in good enantioselectivities by the use of the same chiral auxiliary.

1. Introduction

Introduction of functional groups to azaaromatics is one of the most important issues in organic synthesis, because products thus formed are versatile starting materials for a wide variety of complex molecules including pharmaceuticals and alkaloids.[1] We have recently been investigating the reactivity of *N*-acylated quaternary salts of azaaromatics toward nucleophiles, and found that allyltributyltin[2] and silyl enol ethers[3] react with these salts to form dihydro adducts which have a substituent at their 2-positions, namely at the vicinal position of the acyl groups. The results suggest that an asymmetric addition might be possible if the *N*-acyl group is chiral. Thus, we applied the reaction to the synthesis of optically pure homolaudanosine, one of the isoquinoline alkaloids via an asymmetric addition reaction using a chiral acyl chloride derived from L-alanine.[4] Continuing research of our group revealed that β-carboline was also a suitable substrate for the asymmetric addition of allyltributyltin using an auxiliary derived from L-proline attached at the 9-position, and that 1-allyl-1,2,3,4-tetrahydro-β-carboline was obtained in a enantioselective manner. In addition, the enantiomer of the allyl adduct was obtained by the reaction with tetraallyltin and tin(IV) halide using the same chiral auxiliary. This paper describes these results.[5] β-Carboline nucleus having a substituent at their C-1 position widely exists in nature as a part of indole alkaloids, and there are many reports concerning about their synthesis.[6] Pictet–Spengler reaction[7] and vinylogous Mannich reaction[8] are among the most representative methods for the synthesis of the nucleus, and the application toward asymmetric syntheses has been carried out using L-tryptophan[7,8] or tryptamine[9] as a starting material. On the other hand, asymmetric addition or substitution of β-carboline or its derivatives at C-1 position has been rarely reported. Although there have been several papers to claim that the addition reaction of 3,4-dihydro-β-carboline with nucleophiles in the presence of an acyl chloride afforded 1-substituted tetrahydro-β-carboline derivatives,[10] the methods were hardly applied to asymmetric syntheses. Yamaguchi et al., reported only in a review[11] that 3,4-dihydro-β-carboline-3-(*S*)-carboxylate underwent the addition reaction with tributyl(2,4-pentadienyl)tin in the presence of acryloyl chloride to give a yohimbane derivative in 86% yield (86% de), but the detailed procedure was not shown yet. Thus, there has been a sole method, that was developed by Meyers et al., to introduce directly a substituent on β-carboline framework.[12]

2. Results and discussion

In order to develop a new method for asymmetric synthesis of 1-substituted tetrahydro-β-carboline, we first tried the reaction of 3,4-dihydro-β-carboline (**1**) according to the reported procedure,[10] and observed almost no stereoselectivity despite of a good chemical yield (Scheme 1).[13] Next, the application of our previous method was carried out using 1,2-addition of a chiral acyl chloride and

Keywords: β-carboline; asymmetric addition; chiral auxliary; L-proline; allyltributyltin; tetraallyltin; pseudoyohimbane.

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

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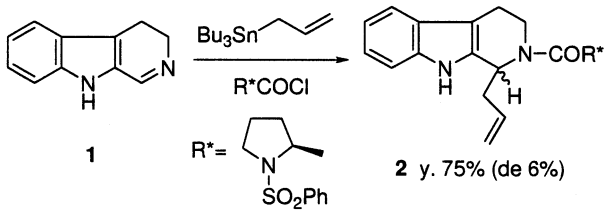
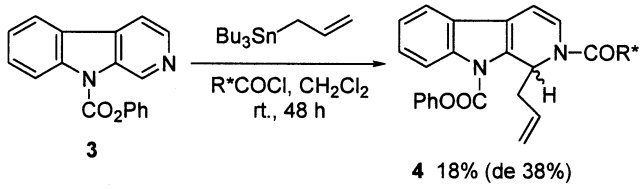
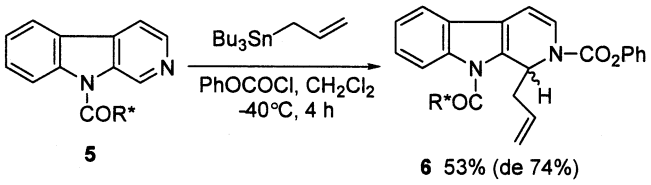


Scheme 1.



Scheme 2.



Scheme 3.

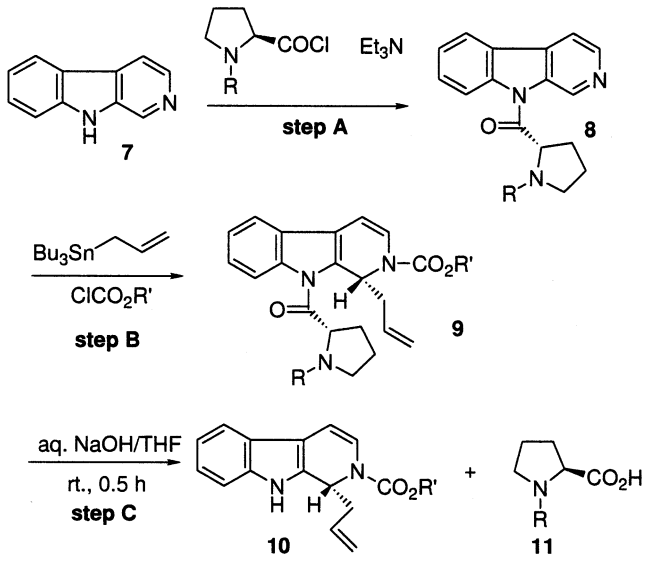
allyltributyltin to 9-phenoxycarbonyl-β-carboline (**3**), and it was found that the selectivity became better but the yield was very low (Scheme 2). The reason of the low yield was probably a weaker electron-withdrawing ability of *N*-acyl group than that of *N*-alkoxycarbonyl group. The exchange of the positions of these two groups, however, was revealed to improve both chemical yield and stereoselectivity (Scheme 3).

Accordingly, in spite of one atom further than *N*-2 position, the attachment of the chiral auxiliary to 9-position on β-carboline was found to be more effective for the asymmetric addition at C-1. Thus, for the purpose of further improvement of both chemical and chiral yields, we studied the effect of various acyl groups on N-9 derived from L-proline. Although we tested other amino acids such as alanine, phenylalanine, and valine as chiral auxiliaries, they were less effective than proline.[14] 9-Acyl-β-carbolines **8** were readily prepared by reaction of parent β-carboline **7** with acyl chlorides in the presence of triethylamine (or with corresponding carboxylic acids and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC·HCl)) in the yields over 80% (step A of Scheme 4). Then the addition of allyl group was carried out using allyltributyltin and phenyl chloroformate to afford **9** in high yields (step B). Compounds **9** was hydrolyzed smoothly at N-9 to give an allyl adduct **10** in quantitative yields accompanied by the complete recovery of the acyl group as the corresponding carboxylate (step C). These results are summarized in Table 1. The data show that the best result was obtained by the use of *N*-phenylsulfonyl group which had *t*-amyl group at para position (entry 9), although the effect of the substituents was rather slight. The other acyl groups afforded moderate chemical yields and the same stereoselectivity (entries 14–16), but neither yields nor stereoselectivity exceeded that of entry 9.

We next examined the reaction of tetraallyltin and 9-acyl-β-carboline **8**, expecting that the reagent would have the same stereoselectivity,[15] and the results are shown in Table 2. Unexpectedly, it was found that the opposite configuration *S* was obtained in every case, in spite of using the same chiral auxiliaries in Table 1.

The results prompted us to investigate the reaction mechanism, and the possibility of selective formation of both enantiomers with the same chiral auxiliary. At first, we thought that allyltributyltin and tetraallyltin had the same stereoselectivity and there must be another species that really reacted with the substrate. A distinguishing difference between these two allylic reagents is that tetraallyltin can transfer two or more allyl groups to the substrate. Thus triallyltin chloride formed by the first allylation might have the ability to bring about further allylation.[16] We assumed that the reversal of stereoselectivity was induced by the participation of these allyltin chlorides. Thus it was anticipated that the addition of tin(IV) halide would change the stereoselectivity.[17] The results of these experiments are shown in Table 3.

Addition of tin(IV) chloride emphasized the *S* selectivity, but the chemical yields decreased considerably (entries 2 and 3). Chlorinated tin(IV) has higher Lewis acidity than that of tetraallyltin, hence it was supposed that this



Scheme 4.

Table 1. Reaction of 9-acyi-β-carboline with allyltributyltin in the presence of chloroformate

Entry	R[a]	R′	Yield of **9** (%)	%ee[b,c] of **10**[d]
1[e]	$C_6H_5SO_2$–	Ph	53	74
2	$C_6H_5SO_2$–	Ph	0	–
3	$C_6H_5SO_2$–	CH_2CC1_3	90	78
4	I–$C_6H_4SO_2$–	CH_2CCl_3	60	73
5	Cl–$C_5H_4SO_2$–	CH_2CCl_3	75	74
6	MeO–$C_6H_4SO_2$–	CH_2CCl_3	70	74
7	Me–$C_6H_4SO_2$–	CH_2CC1_3	74	76
8	*i*-Pr–$C_6H_4SO_2$–	CH_2CC1_3	63	83
9	*t*-Am–$C_6H_4SO_2$–	CH_2CC1_3	98	86
10	Ph–$C_6H_4SO_2$–	CH_2CC1_3	72	77
11	PhC≡C–C_6H_4–SO_2–	CH_2CCl_3	63	70
12	neopentyl–$C_6H_4SO_2$–	CH_2CCl_3	71	82
13	cyclohexyl–$C_6H_4SO_2$–	CH_2CCl_3	62	81
14	PhCO–	CH_2CCl_3	80	57
15	MeCO–	CH_2CC1_3	71	58
16	CF_3CO–	CH_2CCl_3	85	76

[a] The substituents of phenylsulfonyl group are at *p*-position.
[b] Determined by HPLC using CHIRALCEL OD column.
[c] The configuration of **10** was *R* in every case.
[d] The yield of **10** and recoveries of **11** were over 90% in every case.
[e] All the reactions were carried out at −78° C except the entry 1 (−40°C).

Table 2. Reaction of 9-acyl-β-carboline with tetraallyltin in the presence of 2,2,2-trichloroethyl chloroformate

Entry	Compound	R	Yield of **9** (%)	%ee[a] of **10**[b]	Config.
1	**8a**	MeCO	71	9	*S*
2	**8b**	PhCO	52	12	*S*
3	**8c**	$C_6H_5SO_2$	54	29	*S*
4	**8d**	*t*-Am–$C_6H_4SO_2$	72	36	*S*

[a] Determined by HPLC using CHIRALCEL OD column.
[b] The yield of **10** was over 90% in every case.

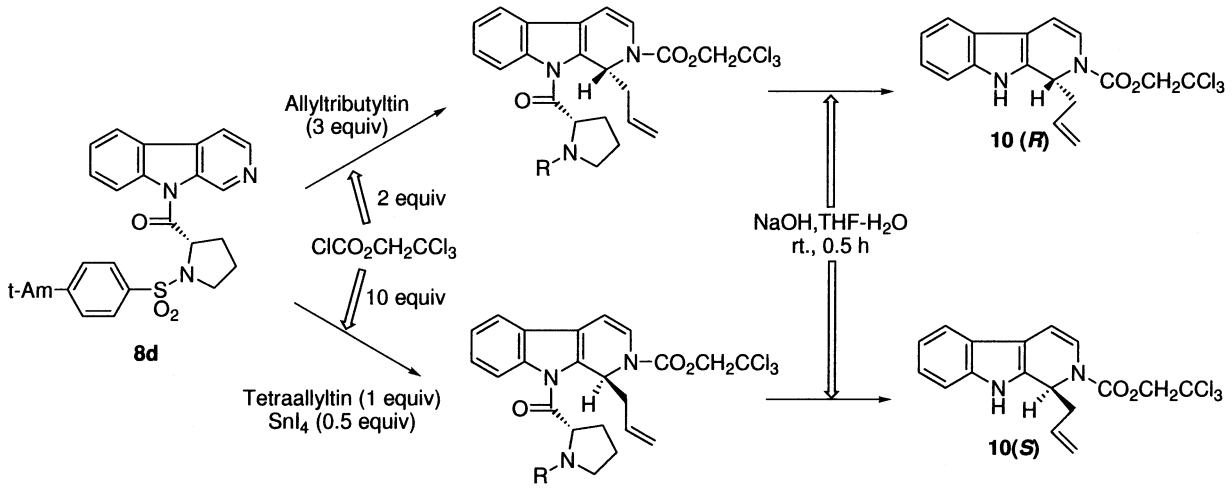
reduction of the yields was caused by the coordination of chlorinated tin to the nitrogen at 2-position of the substrate. The coordination could inhibit the quaternarization process by chloroformate, which is an essential step for succeeding addition reaction. Thus, tin(IV) bromide or iodide, which has lower Lewis acidity than that of tin(IV) chloride, was added to the reaction system. In the cases of tin(IV) bromide, the high ee was observed despite of low chemical yields (entries 4–6). It was found that the decrease of the amount of tin(IV) bromide resulted in the rise of the chemical yield without a loss of selectivity (entry 7 vs entry 4). Potential results were obtained when tin(IV) iodide was employed (entries 9–13), and the best one was gained by the reaction using 1 equiv. of tetraallyltin and 0.5 equiv. of tin(IV) iodide (entry 13). As a result of these data, a method for preparing (*S*)-1-allyl-1,2,3,4-tetrahydro-β-carboline was established as a counterpart of the reaction which affords the corresponding *R* isomer (Scheme 5).

Compound **10** thus obtained was readily transformed to

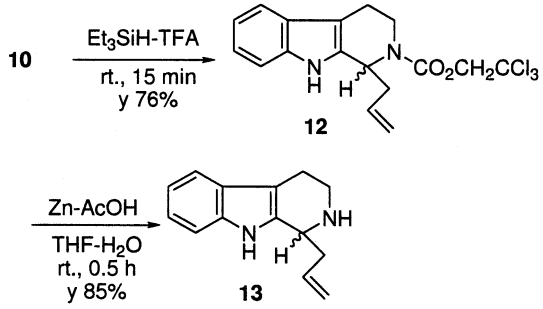
Table 3. Asymmetric allylation of 9-[*N*-(*t*-Amylphenylsulfonyl)prolinyI]-β-carboline with various allyltins formed in situ

Entry	Conditions of allyltin preparation			Chloroformate (equiv.)	Yield of **10** (%)	%ee[a]
	Tetraallyltin (equiv.)	Additive (equiv.)	Total tin (equiv.)			
1	3	None	3	2	72	36
2	2.25	$SnCl_4$ (0.75)	3	2	59	44
3	1.5	$SnC1_4$ (1.5)	3	2	4	74
4	1.5	$SnBr_4$ (1.5)	3	2	13	80
5	0.75	$SnBr_4$ (0.75)	1.5	2	17	83
6	0.5	$SnBr_4$ (0.5)	1	10	15	88
7	0.75	$SnBr_4$ (0.25)	1	10	43	83
8	1.5	SnI_4 (1.5)	3	2	13	87
9	0.75	SnI_4 (0.75)	1.5	2	32	90
10	0.5	SnI_4 (0.5)	1	10	50	87
11	0.75	SnI_4 (0.25)	1	2	72	72
12	0.67	SnI_4 (0.33)	1	10	62	85
13	1.0	SnI_4 (0.5)	1.5	10	91	84

[a] The configuration of **10** was *S* in every case.



Scheme 5.



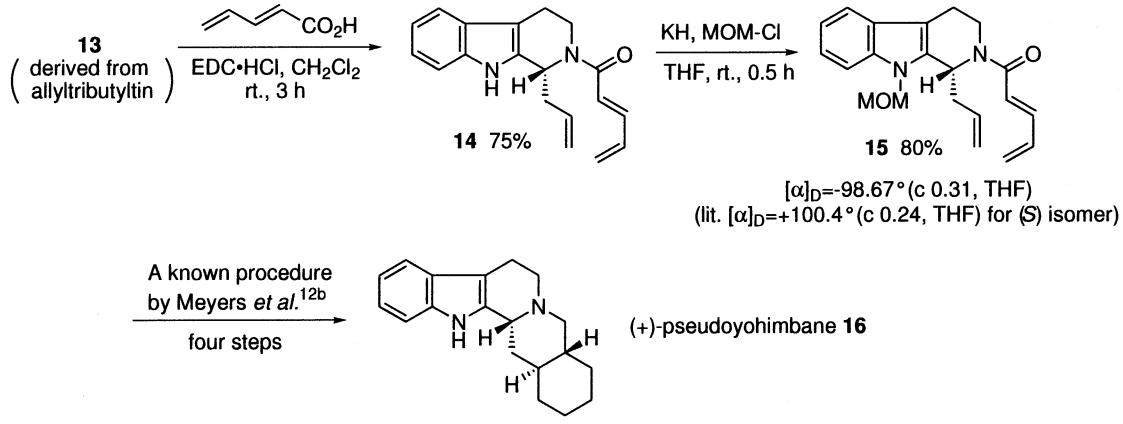
Scheme 6.

1-allyl-1,2,3,4-tetrahydro-β-carboline (**13**)[18] by the sequential reduction with triethylsilane–TFA and zinc–acetic acid in the yields of 76 and 85%, respectively (Scheme 6). No racemization was observed in these procedures.

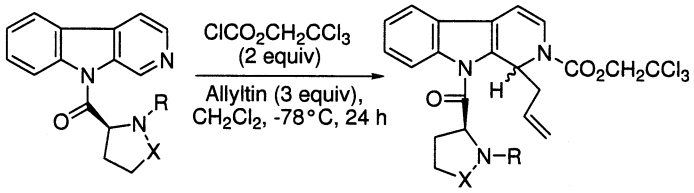
Allyl group is known to be transformed to a variety of other functional groups,[19] and most of the previous studies concerning direct modification of β-carboline moiety introduced allyl derivatives to the nucleus,[10] thus both enantiomers of the compound **13** are supposed to be versatile starting materials for diverse kinds of indole alkaloids.

In order to determine the absolute configuration and study the applicability to the synthesis of natural products, formal synthesis of pseudoyohimbane[20] was carried out from **13**, which was obtained from the reaction with allyltributyltin. The reaction of **13** with penta-2,4-dienoic acid and EDC·HCl followed by methoxymethylation with MOM–Cl and potassium hydride afforded 1-allyl-1,2,3,4-tetrahydro-9-methoxymethyl-2-(penta-2,4-dienoyl)-β-carboline (**15**) ($[\alpha]_D=-98.67°$(*c* 0.31, THF)) in 60% yield (two steps) (Scheme 7). Compound **15** is a known intermediate that Meyers et al., used for the synthesis of (−)-pseudoyohimbane.[12b] The reported configuration of **15** was *S* ($[\alpha]_D=+100.4°$). Therefore, the allyl adduct **13** derived from the reaction with allyltributyltin was determined to be an *R* isomer, whereas the reaction with tetraallyltin and tin(IV) iodide afforded an *S* isomer. Meyers transformed the compound *S*-15 to (−)-pseudoyohimbane in four steps. Thus the formation of the *R* isomer in our system was considered to complete the formal synthesis of (+)-pseudoyohimbane (**16**).

Though the mechanisms of the asymmetric addition remain unclear, several experiments were carried out to study the details of the mechanism (Scheme 8 and Table 4). It was supposed at first that allyltributyltin and tetraallyltin had the same stereoselectivity, and the opposite results were



Scheme 7.



Scheme 8.

Table 4. Allylation of **8** with allyltributyltin or tetraallyltin under various conditions

Entry	R	X	Allylation reagent[a]	Additive	Yield (%)	%ee[b]	Config.
1	*t*-Am$C_6H_4SO_2$	CH_2	A	–	98	86	*R*
2	*t*-Am$C_6H_4SO_2$	CH_2	A	HMPA	53	49	*R*
3	*t*-Am$C_6H_4SO_2$	CH_2	B	–	75	36	*S*
4	*t*-Am$C_6H_4SO_2$	CH_2	B	HMPA	69	0	–
5	*t*-Am$C_6H_4SO_2$	CH_2	B		23[c]	32[c]	*S*
6	$PhSO_2$	CH_2	A	–	90	78	*R*
7	$PhSO_2$	C=O	A	–	51	79	*R*
8	$PhCH_2$	C=O	A	–	15	43	
9	$PhCH_2$	C=O	C	–	95	37	*S*

[a] Al1ylation reagent: A=allyltributyltin; B=tetraallyltin; C=tetraallyltin+SnI_4.
[b] The ee was measured by HPLC after removal of the chiral auxiliary.
[c] The reaction was stopped at 2 h.

originated from allylchlorotin(s) which was formed in the reaction mixture. To confirm the presumption, the reaction with tetraallyltin was monitored at different times (Table 4, entries 3 and 5). The ee of the product, however, was not altered by the shortening of the reaction time, thus it was revealed that tetraallyltin itself had an *S* selectivity irrespective of the ligand exchange.[21] The addition of HMPA (3 equiv.) reduced the selectivity of both reagents (entries 1–4), and the effect was larger in the case of tetraallyltin (entries 3 and 4). These data suggest that the reagents might coordinate to the substrate for expressing the stereoselectivity, and that tetraallyltin was weaker ligand than allyltributyltin. For specifying the coordination site, other experiments shown in entries 7–9 were carried out (Table 4). The use of pyroglutamic acid instead of proline did not change the selectivity (entries 6 and 7), but the replacement of phenylsulfonyl group with benzyl group shifted the selectivity from *R* to *S* in spite of the use of allyltributyltin or tetraallyltin+SnI_4 (entries 7–9). Thus the coordination site seems to be an oxygen atom of sulfonyl group (or acyl group in Table 1, entries 14–16, and Table 2, entries 1 and 2). This supposition seems to be accord with the results that the *p*-substituent of phenylsulfonyl groups, which resides in the outside of a transition state, hardly affected the stereoselectivity (Table 1).

In this paper, we disclosed a first asymmetric allylation of β-carboline using a L-proline derivative as a chiral auxiliary. Moreover, the selection of the allylation reagents altered the stereoselectivity in the presence of the same auxiliary to give both enantiomers of 1-allyl-1,2,3,4-tetrahydro-β-carboline. These processes were readily performed by an inexpensive chiral source, which could be recovered quantitatively from the reaction mixture. The both enantiomers of the 1-allyl adduct might be useful starting material for asymmetric alkaloids syntheses. The study of the reaction mechanism, and the application of the allyl adducts to total syntheses of deplancheine, vincamine, and other alkaloids, are now under investigation.

3. Experimental

3.1. General

Melting points are uncorrected. ^1H and ^{13}C NMR spectra of $CDCl_3$, CD_2Cl_2, and DMSO-d_6 solutions were recorded at 500 and 125 MHz, respectively, with TMS as an internal standard. Mass spectra and high-resolution mass spectra (HRMS) were measured at 70 eV.

3.1.1. 9-Phenoxycarbonyl-β-carboline (3). In the solution of β-carboline (0.5 mmol) and triethylamine (1 mmol) in THF (2 ml), phenyl chloroformate (0.5 mmol) was added dropwise at room temperature, and the mixture was allowed to stir for 2 h. Then the solvent was evaporated off to leave a residue, which was chromatographed on silica gel (AcOEt) to give **3** in 70% yield. Colorless plates from hexane; mp 125–128.3°C; ^1H NMR ($CDCl_3$) δ 7.37–7.41 (3H, m), 7.49–7.55 (3H, m), 7.69 (1H, ddd, *J*=8.5, 7.3, 1.3 Hz), 7.99 (1H, dd, *J*=5.3, 0.9 Hz), 8.12 (1H, dt, *J*=7.7, 0.6 Hz), 8.46 (1H, d, *J*=8.5 Hz), 8.67 (1H, d, *J*=5.3 Hz), 9.68 (1H, s); ^{13}C NMR ($CDCl_3$) δ 114.2, 116.6, 121.2, 121.3, 123.7, 124.2, 126.6, 129.6, 130.4, 133.0, 134.3, 137.3, 138.8, 142.3, 149.6, 149.7. Anal. Calcd for $C_{18}H_{12}N_2O_2$: C, 74.99; H, 4.20; N, 9.72. Found: C, 75.06; H, 4.05; N, 9.79.

3.2. The formation of 2 and 4

3,4-Dihydro-β-carboline (**1**) was synthesized according to the reported method.[22] To the solution of *N*-phenylsulfonylproline (0.25 mmol) in dry benzene (0.5 ml), thionyl chloride (2.5 mmol) was added and the mixture was heated

for 1 h at 60°C. Then the solvent was evaporated off to leave the acid chloride, which was dissolved in CH_2Cl_2 (0.5 ml). The solution was added to the mixture of **1** or **3** (0.2 mmol) and allyltributyltin (0.3 mmol) in CH_2Cl_2 (0.5 ml), and the mixture was allowed to react for 1.5 h for **1**, and 48 h for **3** at room temperature. Thereafter, 3 M KF solution was added, and the mixture was reacted for 1 h to form a precipitate, which was filtered. The organic layer was separated, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel to give the product. The des of **2** and **4** were measured as 6 and 38%, respectively, using the HPLC analysis (CHIRALCEL OD, hexane–isopropanol=1:1).

3.2.1. 1-Allyl-1,2,3,4-tetrahydro-2-(*N*-phenylsulfonyl)-prolinyl-β-carboline (2). Yield 75%; Colorless powder; mp 100–104°C; The product was obtained as a mixture of conformational and diastereomeric isomers. ^{1}H- and ^{13}C NMR spectra were obtained as those of a mixture of at least four isomers. ^{1}H NMR ($CDCl_3$) δ 1.80–2.17 (4H, m), 2.47–2.88 (2.94–3.10) (4H, m), 3.43–3.64 (3.70–3.76) (3H, m), 4.23 (4.12, 4.65, 4.82) (1H, dd, J=12.9, 4.9 Hz), 4.87–5.24 (3H, m), 5.73 (5.55) (1H, dd, J=13.5, 6.9 Hz (8.6, 5.0 Hz)), 5.79–5.94 (6.00–6.08) (1H, m), 7.06–7.16 (2H, m), 7.24–7.34 (2H, m), 7.41–7.57 (3H, m), 7.84 (1H, dd, J=8.3, 1.2 Hz), 7.96 (1H, dd, J=7.0, 1.2 Hz), 8.55 (8.48, 8.60, 8.56) (1H, s); ^{13}C NMR ($CDCl_3$) δ 20.8 (21.1, 22.2, 22.4), 24.4 (24.6, 24.9, 25.2), 30.9 (31.1, 31.2, 31.6), 36.9 (38.6, 39.0, 39.5), 39.6 (40.5, 40.8), 48.2 (48.3, 48.8, 49.0), 49.8 (52.6, 53.2), 56.8 (58.7, 59.2), 107.3 (107.6, 109.0, 109.4), 111.1 (111.2), 117.9 (118.0, 118.1, 118.2), 118.6, 119.40 (119.44, 119.47, 119.58), 121.76 (121.81, 121.9, 122.1), 126.4 (126.5, 126.6), 127.4 (127.46, 127.54), 128.75 (128.77, 128.79, 128.9), 132.4 (132.5, 132.7), 133.2 (133.3, 133.6), 133.8 (134.1, 134.4), 136.07 (136.09, 136.2, 136.3), 139.0 (139.1, 139.3), 170.3 (170.5, 171.2, 171.4). Anal. Calcd for $C_{25}H_{27}N_3O_3S\cdot 1/2H_2O$: C, 65.48; H, 6.15; N, 9.16. Found: C, 65.63; H, 6.13; N, 8.80.

3.2.2. 1-Allyl-1,2-dihydro-9-phenoxycarbonyl-2-(*N*-phenylsulfonyl)prolinyl-β-carboline (4). Yield 18%; Colorless powder; mp 87–92°C; The product was obtained as a mixture of conformational and diastereomeric isomers. ^{1}H- and ^{13}C NMR spectra were obtained as those of a mixture of at least four isomers. ^{1}H NMR ($CDCl_3$) δ 1.72–2.30 (4H, m), 2.41–2.63 (2H, m), 3.32–3.59 (2H, m), 4.85–5.30 (3H, m), 5.72–5.99 (1H, m), 6.26 (6.25, 6.34) (1H, d, J=7.3 Hz), 6.63 (6.70) (1H, t, J=6.5 Hz), 6.94 (6.97) (1H, d, J=7.3 Hz), 7.30–7.65 (11H, m), 7.83 (7.89) (1H, d, J=8.2 Hz), 7.93 (1H, d, J=8.2 Hz), 8.05 (8.25, 8.28) (1H, d, J=8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 18.3 (20.0), 24.5 (24.9), 30.9 (32.0), 37.7 (38.2), 48.2 (48.3, 50.6, 50.7), 58.4 (59.0, 59.5), 104.9 (105.0), 114.3 (114.5), 116.1, 118.21 (118.23), 121.27 (121.31), 121.8 (121.9, 122.0), 123.8 (123.9), 124.9 (125.0), 125.81 (125.82), 126.52 (126.53), 127.3 (127.4), 127.9, 128.6 (128.7), 128.9, 129.6 (129.7), 131.5 (132.2), 132.4 (132.5), 133.0 (133.8), 136.0 (136.1), 138.7 (139.1), 149.2 (149.7), 169.6 (170.3). Anal. Calcd for $C_{32}H_{29}N_3O_5S\cdot H_2O$: C, 65.62; H, 5.33; N, 7.17. Found: C, 65.86; H, 5.02; N, 6.88.

3.3. The synthesis of *N*-phenylsulfonylprolines

L-Proline (10 mmol) was dissolved to the aqueous solution (50 ml) of K_2CO_3 (36 mmol), and the THF solution (10 ml) of phenylsulfonyl chloride (10.5 mmol) was added. The mixture was allowed to react for 2–5 h at 60°C, then the pH of the solution was adjusted to 3 by diluted aq. HCl. The mixture was extracted with $CHCl_3$, which was dried over $MgSO_4$, then removed by evaporation. Phenylsulfonyl chlorides which were not commercially available (*p*-phenyl, *p*-neopentyl, and *p*-cyclohexyl) were synthesized according to the reported methods.[23]

3.3.1. (*S*)-*N*-Phenylsulfonyl-L-proline. The mp and ^{1}H NMR data were identical with those of reported ones.[24]

3.3.2. (*S*)-*N*-(*p*-Iodophenylsulfonyl)-L-proline. Yield 94%; Colorless needles from diisopropyl ether; mp 121–123°C; $[\alpha]^{20}_D$=−62.40 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.79–1.88 (1H, m), 1.95–2.14 (3H, m), 3.30 (1H, dt, J=9.4, 7.4 Hz), 3.50 (1H, ddd, J=9.4, 7.3, 4.5 Hz), 4.33 (1H, dd, J=7.4, 5.2 Hz), 7.61 (2H, d, J=8.6 Hz), 7.90 (2H, d, J=8.6 Hz), 9.83 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 24.6, 30.8, 48.4, 60.2, 100.3, 128.6, 137.3, 138.1, 176.8. Anal. Calcd for $C_{11}H_{12}INO_4S$: C, 34.66; H, 3.17; N, 3.67. Found: C, 34.86; H, 2.78; N, 3.62.

3.3.3. (*S*)-*N*-(*p*-Chlorophenylsulfonyl)proline. Yield 40%; Colorless needles from hexane–diisopropyl ether; mp 108–109°C; $[\alpha]^{20}_D$=−79.40 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.79–1.88 (1H, m), 1.95–2.15 (3H, m), 3.31 (1H, dt, J=9.5, 7.4 Hz), 3.50 (1H, ddd, J=9.5, 7.3, 4.6 Hz), 4.34 (1H, dd, J=7.2, 5.2 Hz), 7.52 (2H, d, J=8.9 Hz), 7.84 (2H, d, J=8.9 Hz), 9.56 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 24.7, 30.9, 48.6, 60.3, 128.8, 129.3, 136.3, 139.4, 177.0. Anal. Calcd for $C_{11}H_{12}ClNO_4S$: C, 45.60; H, 4.17; N, 4.83. Found: C, 45.75; H, 3.84; N, 4.83.

3.3.4. (*S*)-*N*-(*p*-Methoxyphenylsulfonyl)proline. Yield 91%; Colorless plates from hexane–AcOEt; mp 108.8–109.4°C; $[\alpha]^{20}_D$=−89.81 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.74–1.79 (1H, m), 1.92–2.15 (3H, m), 3.27 (1H, dt, J=9.5, 7.5 Hz), 3.50 (1H, ddd, J=9.5, 7.0, 4.6 Hz), 3.88 (3H, s), 4.28 (1H, dd, J=8.3, 4.0 Hz), 7.01 (2H, d, J=8.7 Hz), 7.82 (2H, d, J=8.7 Hz), 11.05 (1H, brs); ^{13}C NMR ($CDCl_3$) δ 24.6, 30.6, 48.6, 55.6, 60.2, 114.3, 128.9, 129.6, 163.2, 177.0. Anal. Calcd for $C_{12}H_{15}NO_5S$: C, 50.52; H, 5.30; N, 4.91. Found: C, 50.52; H, 5.18; N, 4.84.

3.3.5. (*S*)-*N*-(*p*-Tolylsulfonyl)proline. The mp and NMR spectra were identical to those of reported data.[25]

3.3.6. (*S*)-*N*-(*p*-Isopropylphenylsulfonyl)proline. Yield 96%; Colorless needles from hexane–AcOEt; mp 94.1–95.3°C; $[\alpha]^{20}_D$=−90.20 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.28 (6H, d, J=7.0 Hz), 1.75–1.80 (1H, m), 1.94–2.07 (2H, m), 2.11–2.14 (1H, m), 2.99 (1H, sep, J=7.0 Hz), 3.29 (1H, q, J=8.0 Hz), 3.51–3.55 (1H, m), 4.31 (1H, dd, J=8.3, 3.7 Hz), 7.39 (2H, d, J=7.9 Hz), 7.81 (2H, d, J=7.9 Hz), 11.17 (1H, br); ^{13}C NMR ($CDCl_3$) δ 23.5, 24.6, 30.7, 34.0, 48.6, 60.2, 127.2, 127.6, 134.7, 154.5, 177.2. Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71. Found: C, 56.55; H, 6.29; N, 4.68.

3.3.7. (*S*)-*N*-{*p*-(*t*-Amyl)phenylsulfonyl}proline. Yield

90%; Colorless needles from hexane–AcOEt; mp 113.6–114.2°C; $[\alpha]^{20}_D$=−84.83 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.67 (3H, t, *J*=7.3 Hz), 1.32 (6H, s), 1.68 (2H, q, *J*=7.3 Hz), 1.73–1.81 (1H, m), 1.93–2.04 (2H, m), 2.10–2.16 (1H, m), 3.27–3.32 (1H, m), 3.51–3.55 (1H, m), 4.31 (1H, dd, *J*=8.2, 4.0 Hz), 7.49 (2H, d, *J*=8.5 Hz), 7.81 (2H, d, *J*=8.5 Hz), 10.68 (1H, br); ^{13}C NMR ($CDCl_3$) δ 9.0, 24.7, 28.2, 30.7, 36.7, 38.5, 48.8, 60.4, 126.9, 127.4, 134.3, 155.5, 177.0. Anal. Calcd for $C_{16}H_{23}NO_4S$: C, 59.05; H, 7.12; N, 4.30. Found: C, 59.13; H, 6.81; N, 4.32.

3.3.8. (*S*)-*N*-(Biphenyl-4-sulfonyl)proline. Yield 79%; Colorless granules from hexane–AcOEt; mp 133.5–135.5°C; ^{1}H NMR ($CDCl_3$) δ 1.76–1.85 (1H, m), 1.92–2.05 (2H, m), 2.13–2.21 (1H, m), 3.32 (1H, dt, *J*=9.5, 7.3 Hz), 3.56 (1H, ddd, *J*=9.5, 6.9, 4.0 Hz), 4.33 (1H, dd, *J*=8.3, 3.6 Hz), 7.43 (1H, tt, *J*=7.2, 1.3 Hz), 7.47–7.51 (2H, m), 7.61–7.63 (2H, m), 7.76 (2H, d, *J*=8.7 Hz), 7.95 (2H, d, *J*=8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 24.8, 30.7, 48.9, 60.5, 127.2, 127.7, 128.0, 128.5, 129.0, 135.7, 139.0, 145.9, 175.2. Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.61; H, 5.17; N, 4.23. Found: C, 61.35; H, 4.85; N, 4.26.

3.3.9. (*S*)-*N*-(*p*-Neopentylphenylsulfonyl)proline. Yield 69%; Colorless powder from hexane–CH_2Cl_2; mp 136–137°C; $[\alpha]^{20}_D$=−80.02 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.92 (9H, s), 1.73–1.80 (1H, m), 1.94–2.04 (2H, m), 2.11–2.18 (1H, m), 2.58 (2H, s), 3.26–3.32 (1H, m), 3.50–3.55 (1H, m), 4.31 (1H, dd, *J*=8.2, 3.7 Hz), 7.29 (2H, d, *J*=8.2 Hz), 7.79 (2H, d, *J*=8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 24.7, 29.3, 30.7, 32.0, 48.8, 50.0, 60.4, 127.0, 131.1, 134.8, 145.8, 176.6. Anal. Calcd for $C_{16}H_{23}NO_4S$: C, 59.05; H, 7.12; N, 4.30. Found: C, 58.83; H, 7.04; N, 4.31.

3.3.10. (*S*)-*N*-(*p*-Cyclohexylphenylsulfonyl)proline. Yield 77%; Colorless granules from hexane–AcOEt; mp 128.1–132.8°C; $[\alpha]^{20}_D$=−80.55 (*c* 1.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.22–1.32 (1H, m), 1.36–1.48 (4H, m), 1.73–1.80 (2H, m), 1.83–1.91 (4H, m), 1.93–2.04 (2H, m), 2.06–2.17 (1H, m), 2.55–2.62 (1H, m), 3.27 (1H, dt, *J*=9.7, 7.6 Hz), 3.52 (1H, ddd, *J*=9.7, 6.7, 4.3 Hz), 4.29 (1H, dd, *J*=8.2, 3.7 Hz), 7.37 (2H, d, *J*=8.4 Hz), 7.79 (2H, d, *J*=8.4 Hz), 9.29 (1H, br); ^{13}C NMR ($CDCl_3$) δ 24.7, 26.0, 26.7, 30.6, 34.1, 44.6, 48.8, 60.4, 127.5, 127.7, 134.6, 153.8, 176.5. Anal. Calcd for $C_{17}H_{23}NO_4S$: C, 60.51; H, 6.87; N, 4.15. Found: C, 60.39; H, 6.88; N, 4.15.

3.4. The synthesis of *N*-acylprolines

N-Acyl-L-prolines were synthesized using the same method applied to *N*-phenylsulfonyl-L-prolines. *N*-Acetylproline: the mp was identical to that of reported data.[26]

3.4.1. *N*-Benzoyl-L-proline. Yield 85%; Colorless plates from isopropyl ether–AcOEt; mp 155.5–156.5°C; The NMR spectra were obtained as those of a mixture of two isomers (4:1) derived from restricted rotation of the amide bond. The signals originated from the minor one are shown in parentheses. $[\alpha]^{20}_D$=−136.34 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.81–1.91 (1H, m), 1.95–2.05 (1H, m), 2.09–2.20 (1H, m), 2.25–2.34 (1H, m), 3.49–3.63 (3.71–3.83) (2H, m), 4.72 (4.28) (1H, dd, *J*=8.3, 5.4 Hz), 7.29–7.45 (3H, m), 7.56 (8.06) (2H, dd, *J*=7.5, 1.4 Hz), 10.23 (1H, bs). ^{13}C NMR ($CDCl_3$) δ 25.2 (22.4), 29.0 (31.2), 50.2 (46.5), 59.4 (61.4), 127.0 (126.3), 128.06 (128.12), 130.2 (129.8), 135.2 (133.2), 170.4 (170.6), 174.85 (174.90). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.67; H, 5.74; N, 6.39. *N*-Acetyl-L-proline was obtained from the method shown below: to the acetonitrile solution (10 ml) of L-proline (10 mmol), acetic anhydride (20 mmol) was added at room temperature, and the mixture was allowed to react for 1 h, then diluted with water. The mixture was extracted with CH_2Cl_2, then the organic layer was dried over $MgSO_4$ and evaporated. The residue was suspended in hexane to crystallize the product, which was separated by filtration (11% yield). (*S*)-*N*-Trifluoroacetylprolinyl chloride is a commercially available compound.

3.5. The synthesis of (*S*)-*N*-{4-(Phenylethynyl)benzenesulfonyl}proline

4-Iodophenylsulfonylproline (2 mmol), *t*BuOH (2 mmol), EDC·HCl (2.2 mmol), and DMAP (0.2 mmol) were dissolved in CH_2Cl_2 (5 ml) and the mixture was allowed to react at room temperature for 18 h. Thereafter, the solvent was evaporated off to leave a residue, which was chromatographed on silica gel (CH_2Cl_2) to give a *t*-butyl ester as colorless crystals in 76% yield. The recrystallization was carried out from hexane to give colorless granules (mp 96–98°C). The *t*-butyl ester (0.98 mmol), phenylacetylene (1.08 mmol), $Pd(PPh_3)_2Cl_2$ (0.02 mmol), CuI (0.04 mmol), and Et_3N (3 ml) were mixed and was allowed to react for 3 h at room temperature. Then the mixture was diluted with water (20 ml), and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (CH_2Cl_2–AcOEt) to afford corresponding phenylethynyl derivative in 98% yield as pale yellow crystals (mp 100–102°C). To the CH_2Cl_2 solution of the compound (0.81 mmol) was added TFA (4.5 mmol), and the mixture was allowed to react for 4 h at room temperature. Then CH_2Cl_2 was added, and the combined organic layer was extracted with sat. $NaHCO_3$. 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. The residue was suspended in hexane, and the solid thus formed was filtered. The carboxylic acid was obtained as colorless powder in 76% yield (mp 137°C).

3.5.1. *t*-Butyl (*S*)-*N*-(*p*-Iodophenylsulfonyl)-L-prolinate. Yield 76%; Colorless granules from hexane; mp 96–98°C; $[\alpha]^{20}_D$=−50.51 (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.45 (9H, s), 1.78–1.85 (1H, m), 1.92–2.00 (2H, m), 2.00–2.11 (1H, m), 3.32–3.36 (1H, m), 3.43–3.47 (1H, m), 4.22 (1H, dd, *J*=8.5, 3.4 Hz), 7.60 (2H, d, *J*=8.5 Hz), 7.87 (2H, d, *J*=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 24.5, 27.8, 30.9, 48.2, 61.1, 81.7, 100.0, 128.8, 138.1, 138.6, 171.0. Anal. Calcd for $C_{15}H_{20}INO_4S$: C, 41.20; H, 4.61; N, 3.20. Found: C, 41.19; H, 4.39; N, 3.17.

3.5.2. *t*-Butyl (*S*)-*N*-{4-(Phenylethynyl)benzenesulfonyl}-L-prolinate. Yield 98%; Colorless needles from hexane; mp 99.5–102.1°C; $[\alpha]^{20}_D$=−59.99 (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.46 (9H, s), 1.77–1.82 (1H, m), 1.94–2.07 (3H, m), 3.36 (1H, dt, *J*=9.5, 7.2 Hz), 3.49 (1H, ddd, *J*=9.5, 7.4, 4.9 Hz), 4.23 (1H, dd, *J*=8.4, 3.5 Hz), 7.34–7.39 (3H, m), 7.52–7.57 (2H, m), 7.64 (2H, d, *J*=8.5 Hz),

7.86 (2H, d, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 24.6, 27.9, 31.0, 48.3, 61.2, 81.8, 87.9, 92.8, 122.4, 127.4, 128.0, 128.5, 129.0, 131.8, 131.9, 138.0, 171.1. Anal. Calcd for $C_{23}H_{25}NO_4S$: C, 67.13; H, 6.12; N, 3.40. Found: C, 66.96; H, 5.92; N, 3.41.

3.5.3. (*S*)-*N*-{4-(Phenylethynyl)benzenesulfonyl}-L-proline. Yield 76%; Colorless needles from hexane–AcOEt; mp 137–139°C; $[\alpha]^{20}_D$=−79.77 (c 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.76–1.84 (1H, m), 1.94–2.05 (2H, m), 2.14–2.22 (1H, m), 3.30 (1H, dt, J=9.2, 7.5 Hz), 3.55 (1H, ddd, J=9.2, 6.8, 4.0 Hz), 4.31 (1H, dd, J=8.2, 3.6 Hz), 7.37–7.40 (3H, m), 7.53–7.57 (2H, m), 7.68 (2H, d, J=8.6 Hz), 7.87 (2H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 24.6, 30.7, 48.7, 60.3, 87.7, 93.1, 122.3, 127.5, 128.4, 128.5, 129.0, 131.8, 132.1, 136.7, 176.8. Anal. Calcd for $C_{19}H_{17}NO_4S$: C, 64.21; H, 4.82; N, 3.94. Found: C, 64.11; H, 4.55; N, 3.92.

3.6. General procedure for the synthesis of 9-acyl-β-carbolines

Method A: To the benzene solution (1 ml) of *N*-acyl or *N*-sulfonylproline (0.5 mmol), thionyl chloride ($SOCl_2$) (5 mmol) was added at room temperature, and the mixture was heated at 60°C for 1 h, then the solvent and excess $SOCl_2$ were evaporated off. The residue was dissolved in THF (1 ml), and the solution was added to the THF solution (1 ml) of β-carboline (0.5 mmol) and Et_3N (1 mmol) at room temperature. The mixture was allowed to react for 1–4 h at room temperature, then the solvent was evaporated off to leave the residue, which was chromatographed on silica gel to give the product.Method B: Ethyl-(*N*,*N*-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) (0.6 mmol) was added to the mixture of *N*-acyl or *N*-sulfonylproline (0.5 mmol) and β-carboline (0.5 mmol) in CH_2Cl_2 (1 ml), and the mixture was reacted for 1–3 h. Then the solvent was evaporated off, and the residue thus formed was chromatographed on silica gel (AcOEt) to give the product.

3.6.1. (*S*)-9-{*N*-(Phenylsulfonyl)prolinyl}-β-carboline. Yield 76% by Method A; Colorless powder; mp 124°C; $[\alpha]^{20}_D$=−101.38 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.07–2.15 (1H, m), 2.17–2.28 (2H, m), 2.43–2.53 (1H, m), 3.58–3.64 (1H, m), 3.69 (1H, td, J=8.3, 3.5 Hz), 5.63 (1H, dd, J=8.8, 2.0 Hz), 7.48–7.52 (3H, m), 7.60 (1H, tt, J=7.4, 1.3 Hz), 7.67 (1H, ddd, J=8.5, 7.3, 1.3 Hz), 7.85–7.88 (2H, m), 7.97 (1H, dd, J=5.1, 0.7 Hz), 8.11–8.15 (2H, m), 8.66 (1H, d, J=5.1 Hz), 9.50 (1H, s); ^{13}C NMR ($CDCl_3$) δ 24.4, 31.4, 48.2, 62.0, 114.1, 116.2, 121.5, 124.3, 124.6, 127.3, 128.9, 130.0, 132.66, 132.74, 135.0, 137.9, 138.4, 138.5, 143.8, 171.2. Anal. Calcd for $C_{22}H_{19}N_3O_3S\cdot 1/2H_2O$: C, 63.75; H, 4.86; N, 10.14. Found: C, 64.01; H, 4.60; N, 9.90.

3.6.2. (*S*)-9-{*N*-(*p*-Iodophenylsulfonyl)prolinyl}-β-carboline. Yield 84% by Method A; Colorless needles from diisopropyl ether–AcOEt; mp 207–209°C; $[\alpha]^{20}_D$=−28.89 (c 0.60, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 1.97–2.10 (2H, m), 2.23–2.27 (1H, m), 2.54–2.64 (1H, m), 3.33–3.41 (1H, m), 3.58–3.63 (1H, m), 5.49 (1H, dd,J=8.9, 2.5 Hz), 7.53–7.60 (3H, m), 7.71–7.75 (1H, m), 7.98 (2H, d, J=8.6 Hz), 8.21 (1H, d, J=8.6 Hz), 8.24 (1H, dd, J=4.9, 0.7 Hz), 8.36 (1H, d, J=7.7 Hz), 8.65 (1H, d, J=4.9 Hz), 9.51 (1H, s); ^{13}C NMR (DMSO-d_6) δ 24.0, 30.6, 48.1, 62.0, 101.2, 114.5, 116.1, 121.9, 123.9, 124.2, 128.5, 130.1, 131.8, 134.4, 137.4, 137.6, 137.7, 137.9, 143.5, 171.3. Anal. Calcd for $C_{22}H_{18}IN_3O_3S$: C, 49.73; H, 3.41; N, 7.91. Found: C, 49.75; H, 3.18; N, 7.98.

3.6.3. (*S*)-9-{*N*-(*p*-Chlorophenylsulfonyl)prolinyl}-β-carboline. Yield 70% by Method A; Colorless powder; mp 166–169°C; $[\alpha]^{20}_D$=−62.16 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.06–2.27 (3H, m), 2.45–2.56 (1H, m), 3.56–3.66 (2H, m), 5.62 (1H, dd, J=8.9, 2.1 Hz), 7.43–7.46 (3H, m), 7.62 (1H, td, J=8.4, 1.3 Hz), 7.80 (2H, d, J=8.8 Hz), 7.88 (1H, dd, J=5.1, 0.9 Hz), 8.05 (1H, d, J=7.4 Hz), 8.09 (1H, d, J=8.4 Hz), 8.63 (1H, d, J=5.1 Hz), 9.48 (1H, s); ^{13}C NMR ($CDCl_3$) δ 24.3, 31.3, 48.0, 62.0, 114.0, 116.1, 121.3, 124.3, 124.4, 128.7, 129.0, 129.9, 132.5, 134.8, 137.1, 137.7, 138.2, 139.1, 143.7, 171.0. Anal. Calcd for $C_{22}H_{18}ClN_3O_3S$: C, 60.07; H, 4.12; N, 9.55. Found: C, 60.18; H, 4.12; N, 9.64.

3.6.4. (*S*)-9-{*N*-(*p*-Methoxyphenylsulfonyl)prolinyl}-β-carboline. Yield 84% by Method A; Colorless powder; mp 186–189°C; $[\alpha]^{20}_D$=−85.75 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.03–2.10 (1H, m), 2.17–2.24 (2H, m), 2.39–2.48 (1H, m), 3.55 (1H, q, J=8.4 Hz), 3.65 (1H, dt, J=8.4, 3.5 Hz), 3.83 (3H, s), 5.56 (1H, dd, J=8.9, 2.1 Hz), 6.92 (2H, d, J=9.0 Hz), 7.44 (1H, m), 7.61 (1H, ddd, J=8.5, 7.3, 1.3 Hz), 7.78 (2H, d, J=9.0 Hz), 7.88 (1H, dd, J=5.1, 0.9 Hz), 8.04 (1H, dd, J=7.7, 0.6 Hz), 8.10 (1H, d, J=8.5 Hz), 8.62 (1H, d, J=5.1 Hz), 9.49 (1H, s); ^{13}C NMR ($CDCl_3$) δ 24.4, 31.4, 48.1, 55.5, 61.8, 113.98, 114.0, 116.1, 121.4, 124.2, 124.4, 129.4, 129.93, 129.99, 132.5, 134.9, 137.7, 138.3, 143.6, 162.8, 171.4. Anal. Calcd for $C_{23}H_{21}N_3O_4S$: C, 63.43; H, 4.86; N, 9.65. Found: C, 63.68; H, 5.13; N, 9.64.

3.6.5. (*S*)-9-{*N*-(*p*-Tolylsulfonyl)prolinyl}-β-carboline. Yield 78% by Method A; Colorless powder; mp 161–162°C; $[\alpha]^{20}_D$=−101.3 (c 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.04–2.10 (1H, m), 2.14–2.26 (2H, m), 2.40 (3H, s), 2.40–2.45 (1H, m), 3.56 (1H, q, J=8.3 Hz), 3.68 (1H, td, J=8.3, 3.5 Hz), 5.56 (1H, dd, J=8.8, 1.4 Hz), 7.26 (2H, d, J=8.1 Hz), 7.45 (1H, t, J=7.7 Hz), 7.62 (1H, t, J=7.7 Hz), 7.72 (2H, d, J=8.1 Hz), 7.89 (1H, d, J=5.1 Hz), 8.05 (1H, d, J=7.7 Hz), 8.10 (1H, d, J=7.7 Hz), 8.62 (1H, d, J=5.1 Hz), 9.47 (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.5, 24.3, 31.4, 48.1, 62.1, 114.1, 116.1, 121.4, 124.2, 124.4, 127.2, 129.5, 130.0, 132.6, 134.9, 135.4, 137.7, 137.8, 138.4, 143.5, 171.2. Anal. Calcd for $C_{23}H_{21}N_3O_3S$: C, 65.85; H, 5.05; N, 10.02. Found: C, 65.59; H, 4.80; N, 9.91.

3.6.6. (*S*)-9-{*N*-(*p*-Isopropylphenylsulfonyl)prolinyl}-β-carboline. Yield 83% by Method A; Colorless powder; mp 75°C; $[\alpha]^{20}_D$=−86.67 (c 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.27 (6H, d, J=6.9 Hz), 1.99–2.11 (1H, m), 2.17–2.25 (2H, m), 2.41–2.50 (1H, m), 2.97 (1H, sep, J=6.9 Hz), 3.57 (1H, q, J=8.5 Hz), 3.69 (1H, td, J=8.5, 3.7 Hz), 5.61 (1H, dd, J=9.0, 1.5 Hz), 7.34 (2H, d, J=8.4 Hz), 7.47 (1H, t, J=7.7 Hz), 7.63 (1H, t, J=7.7 Hz), 7.79 (2H, d, J=8.4 Hz), 7.92 (1H, d, J=5.0 Hz),

8.08 (1H, d, J=7.7 Hz), 8.15 (1H, d, J=7.7 Hz), 8.64 (1H, d, J=5.0 Hz), 9.49 (1H, s); ^{13}C NMR ($CDCl_3$) δ 23.6, 24.3, 31.3, 34.1, 48.1, 61.8, 114.0, 116.2, 121.3, 124.2, 124.4, 126.9, 127.3, 130.0, 132.6, 134.9, 135.7, 137.6, 138.4, 143.4, 154.0, 171.3. Anal. Calcd for $C_{25}H_{25}N_3O_3S\cdot 1/2H_2O$: C, 65.77; H, 5.74; N, 9.20. Found: C, 66.17; H, 5.68; N, 8.98.

3.6.7. (*S*)-9-[*N*-{*p*-(*t*-Amyl)phenylsulfonyl}prolinyl]-β-carboline. Yield 86% by Method B; Colorless powder from hexane–diisopropyl ether; mp 100–102°C; $[\alpha]^{20}_D$=−84.24 (c 1.00, $CHCl_3$); ^{1}H NMR (CD_2Cl_2) δ 0.68 (3H, t, J=7.3 Hz), 1.31 (6H, s), 1.68 (2H, q, J=7.3 Hz), 2.00–2.06 (1H, m), 2.13–2.24 (2H, m), 2.37–2.45 (1H, m), 3.49 (1H, q, J=7.6 Hz), 3.69 (1H, td, J=7.6, 3.1 Hz), 5.52 (1H, dd, J=9.9, 2.5 Hz), 7.46–7.49 (3H, m), 7.64 (1H, ddd, J=8.5, 7.6, 1.2 Hz), 7.75 (2H, d, J=8.5 Hz), 7.93 (1H, dd, J=5.2, 0.9 Hz), 8.11 (1H, d, J=7.6 Hz), 8.14 (1H, d, J=8.5 Hz), 8.61 (1H, d, J=5.2 Hz), 9.46 (1H, s); ^{13}C NMR (CD_2Cl_2) δ 9.2, 24.7, 28.3, 31.7, 37.0, 38.8, 48.7, 62.5, 114.6, 116.7, 121.9, 124.7, 125.1, 127.2, 127.4, 130.4, 133.0, 135.6, 135.9, 138.3, 139.1, 144.2, 155.7, 172.1. Anal. Calcd for $C_{27}H_{29}N_3O_3S\cdot 1/2H_2O$: C, 66.92; H, 6.24; N, 8.67. Found: C, 66.89; H, 6.20; N, 8.70.

3.6.8. (*S*)-9-{*N*-(Biphenyl-4-sulfonyl)prolinyl}-β-carboline. Yield 47% by Method A; Colorless powder; mp 185–187°C; ^{1}H NMR ($CDCl_3$) δ 2.09–2.17 (1H, m), 2.20–2.29 (2H, m), 2.47–2.55 (1H, m), 3.63 (1H, q, J=8.5 Hz), 3.72 (1H, td, J=8.5, 3.7 Hz), 5.66 (dd, J=9.0, 2.3 Hz), 7.42 (1H, tt, J=7.3, 1.2 Hz), 7.47–7.50 (3H, m), 7.60–7.62 (2H, m), 7.65 (1H, ddd, J=8.3, 7.3, 1.4 Hz), 7.70 (2H, d, J=8.5 Hz), 7.93 (2H, d, J=8.5 Hz), 7.95 (1H, dd, J=5.7, 0.9 Hz), 8.10 (1H, d, J=8.0 Hz), 8.16 (1H, d, J=8.3 Hz), 8.65 (1H, d, J=5.7 Hz), 9.54 (1H, s); ^{13}C NMR ($CDCl_3$) δ 24.4, 31.4, 48.2, 62.0, 114.4, 116.4, 121.7, 124.57, 124.63, 127.4, 127.7, 128.0, 128.5, 129.0, 130.4, 133.2, 135.2, 137.3, 137.6, 138.8, 139.3, 143.5, 145.8, 171.6. Anal. Calcd for $C_{28}H_{23}N_3O_3S$: C, 69.83; H, 4.81; N, 8.73. Found: C, 69.85; H, 4.45; N, 8.66.

3.6.9. (*S*)-9-[*N*-{4-(Phenylethynyl)benzenesulfonyl}prolinyl]-β-carboline. Yield 78% by Method A; Colorless needles from hexane–AcOEt; mp 202–203°C; $[\alpha]^{20}_D$=+7.32 (c 0.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.07–2.14 (1H, m), 2.16–2.26 (2H, m), 2.44–2.52 (1H, m), 3.59 (1H, q, J=8.5 Hz), 3.69 (1H, td, J=8.5, 3.5 Hz), 5.62 (1H, dd, J=8.8, 2.1 Hz), 7.37–7.39 (3H, m), 7.46 (1H, t, J=8.2 Hz), 7.55–7.57 (2H, m), 7.61–7.65 (3H, m), 7.84 (2H, d, J=8.8 Hz), 7.90 (1H, dd, J=5.1, 0.9 Hz), 8.07 (1H, d, J=7.0 Hz), 8.12 (1H, d, J=8.2 Hz), 8.64 (1H, d, J=5.1 Hz), 9.51 (1H, s); ^{13}C NMR ($CDCl_3$) δ 24.3, 31.3, 48.1, 62.1, 87.8, 92.9, 114.2, 116.3, 121.6, 122.3, 124.4, 124.6, 127.4, 128.2, 128.4, 128.9, 130.2, 131.7, 131.9, 132.8, 135.0, 137.7, 137.9, 138.6, 143.9, 171.3. Anal. Calcd for $C_{30}H_{23}N_3O_3S$: C, 71.27; H, 4.59; N, 8.31. Found: C, 71.14; H, 4.27; N, 8.31.

3.6.10. (*S*)-9-{*N*-(*p*-Neopentylphenylsulfonyl)prolinyl}-β-carboline. Yield 43% by Method A; Colorless powder; mp 82–85°C; $[\alpha]^{20}_D$=−48.51 (c 0.47, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.90 (9H, s), 2.03–2.09 (1H, m), 2.16–2.24 (2H, m), 2.38–2.47 (1H, m), 2.54 (2H, s), 3.57 (1H, q, J=8.7 Hz), 3.69 (1H, td, J=8.7, 3.9 Hz), 5.59 (1H, dd, J=8.8, 1.8 Hz), 7.23 (2H, d, J=8.3 Hz), 7.43 (1H, t, J=7.3 Hz), 7.60 (1H, ddd, J=8.5, 7.3, 1.3 Hz), 7.77 (2H, d, J=8.3 Hz), 7.87 (1H, dd, J=5.1, 0.9 Hz), 8.03 (1H, d, J=7.3 Hz), 8.10 (1H, d, J=8.5 Hz), 8.61 (1H, d, J=5.1 Hz), 9.49 (1H, s); ^{13}C NMR ($CDCl_3$) δ 22.6, 24.3, 29.2, 31.3, 31.9, 49.9, 61.7, 114.0, 116.1, 121.3, 124.1, 124.4, 126.6, 129.9, 130.7, 132.5, 134.8, 135.8, 137.7, 138.3, 143.6, 145.2, 171.2. Anal. Calcd for $C_{27}H_{29}N_3O_3S$: C, 68.18; H, 6.15; N, 8.84. Found: C, 67.83; H, 6.16; N, 8.46.

3.6.11. (*S*)-9-{*N*-(*p*-Cyclohexylphenylsulfonyl)prolinyl-β-carboline. Yield 32% by Method A; Colorless powder; mp 83–86°C; $[\alpha]^{20}_D$=−68.05 (c 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.21–1.31 (2H, m), 1.35–1.45 (3H, m), 1.74–1.79 (1H, m), 1.82–1.90 (4H, m), 2.03–2.10 (1H, m), 2.16–2.24 (2H, m), 2.40–2.48 (1H, m), 2.52–2.60 (1H, m), 3.56 (1H, q, J=8.5 Hz), 3.68 (1H, td, J=8.5, 3.7 Hz), 5.59 (1H, dd, J=9.0, 1.9 Hz), 7.31 (2H, d, J=8.4 Hz), 7.44 (1H, t, J=7.1 Hz), 7.61 (1H, ddd, J=8.5, 7.1, 1.2 Hz), 7.77 (2H, d, J=8.4 Hz), 7.89 (1H, dd, J=5.2, 0.9 Hz), 8.05 (1H, d, J=7.1 Hz), 8.12 (1H, d, J=8.5 Hz), 8.62 (1H, d, J=5.2 Hz), 9.49 (1H, s); ^{13}C NMR ($CDCl_3$) δ 24.4, 26.0, 26.7, 31.4, 34.0, 44.5, 48.2, 61.9, 114.2, 116.4, 121.6, 124.4, 124.6, 127.5, 127.6, 130.2, 132.8, 135.1, 135.9, 138.0, 138.6, 143.8, 153.5, 171.6. Anal. Calcd for $C_{28}H_{29}N_3O_3S\cdot 1/4H_2O$: C, 68.34; H, 6.04; N, 8.54. Found: C, 68.46; H, 6.32; N, 8.23.

3.6.12. (*S*)-9-{*N*-(Benzoyl)prolinyl}-β-carboline. Yield 86% by Method B; Colorless powder; mp 72–75°C; The ^{1}H NMR spectrum was obtained as that of a mixture of two isomers (9:1) derived from restricted rotation of the amide bond. The signals originated from the minor one are shown in parentheses. $[\alpha]^{20}_D$=−25.96 (c 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.04–2.13 (1H, m), 2.22–2.33 (2H, m), 2.51–2.63 (1H, m), 3.73 (4.09) (1H, dt, J=10.1, 6.9 Hz), 3.88–3.95 (1H, m), 5.84 (5.36) (1H, dd, J=8.5, 3.4 Hz), 7.42–7.47 (6.84–6.91) (4H, m), 7.61–7.67 (7.23–7.24) (3H, m), 7.92 (7.84) (1H, dd, J=5.1, 0.9 Hz), 8.08 (8.01) (1H, d, J=7.7 Hz), 8.32 (1H, d, J=8.4 Hz), 8.63 (8.59) (1H, d, J=5.1 Hz), 9.65 (1H, s); ^{13}C NMR ($CDCl_3$) δ 25.1, 29.7, 50.1, 60.9, 114.0, 116.5, 121.2, 123.9, 124.4, 127.1, 128.1, 129.8, 130.1, 132.5, 135.1, 135.6, 138.1, 138.7, 143.4, 169.4, 171.8. Anal. Calcd for $C_{23}H_{19}N_3O_2\cdot 1/4H_2O$: C, 73.88; H, 5.26; N, 11.24. Found: C, 73.76; H, 5.18; N, 11.01.

3.6.13. (*S*)-9-{*N*-(Acetyl)prolinyl}-β-carboline. Yield quant. by Method B; Colorless powder; mp 144–147°C; The ^{1}H NMR spectrum was obtained as that of a mixture of two isomers (7:1) derived from restricted rotation of the amide bond. The signals originated from the minor one are shown in parentheses. ^{1}H NMR ($CDCl_3$) δ 2.09–2.27 (3H, m), 2.16 (3H, s), 2.41–2.48 (1H, m), 3.64 (1H, q, J=8.5 Hz), 3.86 (3.94) (1H, td, J=8.5, 3.3 Hz), 5.61 (5.43) (1H, dd, J=8.7, 2.5 Hz), 7.35 (7.43) (1H, t, J=7.5 Hz), 7.53 (7.61) (1H, m), 7.81 (1H, dd, J=5.2, 0.9 Hz), 7.96 (7.88) (1H, d, J=7.5 Hz), 8.13 (8.04) (1H, d, J=8.2 Hz), 8.55 (8.62) (1H, d, J=5.2 Hz), 9.56 (1H, s); ^{13}C NMR ($CDCl_3$) δ 22.2 (22.4), 24.4 (31.5), 29.7 (31.8), 48.0 (46.8), 60.4 (62.3), 114.0, 116.5, 121.3, 124.1, 124.5

(124.7), 129.9 (130.4), 132.5, 135.2, 138.3, 138.6, 143.6 (144.2), 169.4 (169.3), 171.9 (171.4). Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.57; N, 13.67. Found: C, 70.12; H, 5.44; N, 13.49.

3.6.14. (*S*)-9-{*N*-(Trifluoroacetyl)prolinyl}-β-carboline. Yield 73% by Method A; Colorless powder; mp 148–151°C; The ^{1}H NMR spectrum was obtained as that of a mixture of two isomers (7:1) derived from restricted rotation of the amide bond. The signals originated from the minor one are shown in parentheses. $[\alpha]^{20}_D=-112.6$ (*c* 0.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.03–2.38 (3H, m), 2.41–2.65 (1H, m), 3.79 (1H, q, *J*=8.5 Hz), 4.00–4.06 (1H, m), 5.62 (5.68) (1H, dd, *J*=8.8, 1.6 Hz), 7.31 (7.40) (1H, t, *J*=7.6 Hz), 7.48 (7.56) (1H, m), 7.77 (7.83) (1H, d, *J*=4.9 Hz), 7.92 (1H, d, *J*=7.6 Hz), 8.05 (8.01) (1H, d, *J*=8.1 Hz), 8.52 (8.57) (1H, d, *J*=4.9 Hz), 9.44 (1H, s); ^{13}C NMR ($CDCl_3$) δ 24.4 (20.5), 28.7 (31.6), 47.4 (48.6) (q, *J*=3 Hz), 62.0 (61.3), 114.1, 116.1 (q, *J*=288 Hz), 116.4, 121.4, 124.4, 124.6, 130.0, 132.8, 135.0, 138.1, 138.4, 144.0 (144.4), 155.9 (q, *J*=38 Hz), 169.7 (169.9). Anal. Calcd for $C_{18}H_{14}F_3N_3O_2$: C, 59.84; H, 3.91; N, 11.63. Found: C, 59.92; H, 3.56; N, 11.59.

3.7. Asymmetric addition of allyltributyltin to 8 in the presence of 2,2,2-trichloroethyl chloroformate (the synthesis of 9 and 10, and the recovery of 11)

To the CH_2Cl_2 solution (1 ml) of 9-acyl-β-carboline (0.1 mmol) and allyltributyltin (0.3 mmol), 2,2,2-trichloroethyl chloroformate (0.2 mmol) was added at −78°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. The residue was chromatographed on silica gel (CH_2Cl_2–AcOEt) to afford the adduct **9** as a colorless oil. The adduct **9** was rather unstable, and the NMR spectrum is complicated because of the existence of diastereomeric and conformational isomers. Accordingly, the adduct **9** was treated with alkaline hydrolysis without further purification. Thus, to the THF solution (1 ml) of **9**, 1 M aqueous NaOH solution (2 ml) was added and the mixture was allowed to stand for 30 min at room temperature. Then H_2O was added to the mixture, which was extracted with CH_2Cl_2. The organic layer thus obtained was dried over $MgSO_4$, and evaporated to leave a residue, which was confirmed to be almost pure **10** by ^{1}H- and ^{13}C NMR. The aqueous layer was treated with dil. HCl to be acidic, and extracted with CH_2Cl_2. The evaporation of the CH_2Cl_2 afforded pure **11**. The yields of **10** and **11** were quantitative in every case. The ee of **10** was measured with HPLC (CHIRALCEL OD, hexane–isopropanol=1:1), which is shown in Table 1.

3.7.1. 1-Allyl-1,2-dihydro-2-(2,2,2-trichloroethoxycarbonyl)-β-carboline. Yield>90%; Colorless viscous oil; The NMR spectra were obtained as those of a mixture of two conformational isomers. The signals originated from the minor one are shown in parentheses. 86%ee (*R*); $[\alpha]^{20}_D=-184.6$ (*c* 1.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.49–2.67 (2H, m), 4.75 (4.78) (1H, d, *J*=11.9 Hz), 4.99 (5.00) (1H, d, *J*=11.9 Hz), 5.05–5.14 (2H, m), 5.63–5.69 (1H, m), 5.77–5.85 (1H, m), 6.16 (6.22) (1H, d, *J*=7.6 Hz), 6.72 (6.73) (1H, d, *J*=7.6 Hz), 7.14–7.20 (2H, m), 7.33 (1H, t, *J*=7.2 Hz), 7.59 (1H, d, *J*=7.6 Hz), 7.93 (8.00) (1H, bs); ^{13}C NMR ($CDCl_3$) δ 38.9 (39.9), 53.4 (53.7), 75.46 (75.52), 95.2 (95.1), 104.20 (104.19), 107.3 (107.6), 111.4 (111.3), 118.3 (117.9), 118.4 (118.9), 119.3 (119.6), 120.5, 122.2 (122.3), 123.7, 130.8 (130.6), 133.00 (133.03), 136.0, 152.0 (151.9). HRMS (FAB+): Calcd for $C_{17}H_{16}Cl_3N_2O_2$ $(M+H)^+$: 385.0277. Found: 385.0298.

3.7.2. 1-Allyl-1,2-dihydro-2-phenoxylcarbonyl-β-carboline. Yield>90%; Colorless viscous oil; The NMR spectra were obtained as those of a mixture of three conformational isomers. The signals originated from the minor ones are shown in parentheses. ^{1}H NMR ($CDCl_3$) δ 2.51–2.63 (2H, m), 5.03–5.15 (2H, m), 5.75–5.86 (2H, m), 6.19 (6.23) (1H, d, *J*=7.6 Hz), 6.81 (6.79) (1H, d, *J*=7.6 Hz), 7.12–7.19 (5H, m), 7.26–7.30 (1H, m), 7.39–7.44 (2H, m), 7.58–7.61 (1H, m), 8.01 (8.36, 8.38) (1H, s); ^{13}C NMR ($CDCl_3$) δ 39.0 (40.0), 53.2 (53.6), 104.38 (104.2, 104.35), 107.1 (107.7), 111.50 (111.34, 111.48), 118.09 (118.13, 118.14), 118.4 (118.9), 119.1 (119.4), 120.3 (120.4), 121.7 (121.6), 121.91 (121.94, 122.2), 123.7 (123.8), 125.85 (125.93), 129.52 (129.50, 129.55), 131.3 (130.8), 133.28 (133.26, 133.06), 136.08 (136.10), 151.1 (150.9), 152.6 (152.3). HRMS (FAB+): Calcd for $C_{21}H_{18}N_2O_2$ $(M+H)^+$: 331.1447. Found 331.1468.

3.8. Asymmetric addition of 8 with tetraallyltin

The same procedure mentioned above was applied to the case of tetraallyltin. The estimation of the ee was performed similarly.

3.9. Typical procedure for the asymmetric addition of 8 with tetraallyltin and SnX_4

To the CH_2Cl_2 solution (0.5 ml) of SnI_4 (0.05 mmol), tetraallyltin (0.1 mmol) was added, and the mixture was allowed to react for 10 min at room temperature. Then the mixture was cooled to −78°C, and the CH_2Cl_2 solution (0.5 ml) of **8** (*p*-*t*-Amyl derivative, 0.1 mmol), and $ClCO_2CH_2CCl_3$ (1 mmol) were added successively. The mixture was reacted for 48 h at −78°C, then treated with 3M aqueous KF solution for 1 h at room temperature. The organic layer was separated and dried over $MgSO_4$, and evaporated off. The residue was chromatographed on silica gel (CH_2Cl_2–AcOEt) to afford the adduct **9**, which was hydrolyzed using the above method to afford **10** in 91% yield (84%ee).

3.10. The formation of 12 by the reduction of 10

To the CH_2Cl_2 solution (1 ml) of **10** (44 μmol), Et_3SiH (200 μl) and trifluoroacetic acid (TFA, 100 μl) were added sequentially. The solution color was turned to glaucous instantaneously by the addition of TFA, but changed to pale yellow after 15 min, and the starting material was entirely consumed by the time, which was confirmed by TLC. The mixture was diluted with CH_2Cl_2, and washed with aqueous Na_2CO_3. The organic layer was separated, dried over $MgSO_4$, and evaporated off to leave a residue, which was chromatographed on silica gel to give an

oily substance. When it was dispersed in hexane, the crystalline product **12** was obtained in 76% yield.

3.10.1. 1-Allyl-1,2,3,4-tetrahydro-2-(2,2,2-trichloroethoxycarbonyl)-β-carboline (12). Yield 76%; Colorless plates from hexane–AcOEt; mp 111.5–112.0°C; The NMR spectra were obtained as those of a mixture of two conformational isomers. The signals originated from the minor one are shown in parentheses. 86%ee; $[\alpha]^{20}_{D}=-64.75$ (*c* 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.63–2.91 (4H, m), 3.23–3.36 (1H, m), 4.49–4.56 (1H, m), 4.82 (4.67) (1H, d, *J*=11.9 Hz), 4.82 (4.94) (1H, d, *J*=11.9 Hz), 5.15–5.24 (2H, m), 5.31–5.38 (1H, m), 5.90–6.06 (1H, m), 7.11 (1H, td, *J*=7.4, 2.8 Hz), 7.17 (1H, td, *J*=7.4, 1.4 Hz), 7.30–7.32 (1H, m), 7.48 (7.50) (1H, d, *J*=7.4 Hz), 7.94 (7.90) (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.6 (21.1), 38.9 (39.26), 39.4 (39.30), 51.6 (51.5), 75.1 (75.2), 95.7 (95.5), 108.5 (109.0), 110.9 (111.0), 118.3 (118.1), 118.8 (119.2), 119.6 (119.7), 122.1 (122.0), 126.5 (126.4), 133.1 (132.8), 133.9 (134.1), 135.94 (135.92), 153.9 (153.5). Anal. Calcd for $C_{17}H_{17}Cl_3N_2O_2$: C, 52.67; H,4.42; N, 7.23. Found: C, 52.86; H, 4.70; N, 7.16.

3.11. The synthesis of 13 via the reduction of 12 with Zn

The compound **12** (0.1 mmol) and AcOH (30 μl) were dissolved in THF (0.5 ml)–H_2O (0.5 ml) solution, and Zn powder (0.5 mmol) was added to the mixture, then the reaction was continued for 30 min at room temperature. Then the excess Zn was filtered off, and the filtrate was diluted with H_2O. The solution was alkalized with K_2CO_3, and extracted with CH_2Cl_2. The organic layer was extracted with 1 M HCl, then the layer was alkalized again by K_2CO_3, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and evaporated to leave colorless crystals, which was almost pure **13** (85%).

3.11.1. 1-Allyl-1,2,3,4-tetrahydro-β-carboline (13). Yield 85%; Colorless granules from hexane; mp 118–119°C; 86%ee; $[\alpha]^{20}_{D}=+110.0$ (*c* 0.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.72–1.85 (1H, bs), 2.54–2.59 (2H, m), 2.68–2.81 (2H, m), 3.03 (1H, ddd, *J*=12.8, 8.6, 5.3 Hz), 3.37 (1H, ddd, *J*=12.8, 5.0, 3.7 Hz), 4.16 (1H, tt, *J*=6.3, 1.8 Hz), 5.20–5.29 (2H, m), 5.92 (1H, ddt, *J*=17.1, 10.2, 7.0 Hz), 7.09 (1H, td, *J*=7.0, 1.1 Hz), 7.15 (1H, td, *J*=7.0, 1.3 Hz), 7.29 (1H, d, *J*=7.0 Hz), 7.48 (1H, d, *J*=7.0 Hz), 7.96 (1H, bs); ^{13}C NMR ($CDCl_3$) δ 22.7, 39.5, 42.9, 51.6, 109.1, 110.6, 117.9, 118.4, 119.2, 121.4, 127.1, 134.6, 135.4, 135.6. Anal. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H,7.60; N, 13.20. Found: C, 79.01; H, 7.71; N, 13.21.

3.12. The synthesis of 14

To the CH_2Cl_2 solution (2 ml) of **13** (0.26 mmol) and 2,4-pentadienoic acid (0.78 mmol), EDC·HCl (0.78 mmol) was added, and the mixture was allowed to react for 3 h at room temperature. The solution was diluted with CH_2Cl_2, and washed with 1 M HCl and 1 M NaOH, successively. The organic layer was dried with $MgSO_4$, and evaporated off to leave a residue, which was chromatographed on silica gel (CH_2Cl_2 to AcOEt) to give the product **14** in 75% yield.

3.12.1. 1-Allyl-2-(penta-2,4-dienoyl)-1,2,3,4-tetrahydro-β-carboline (14). Yield 75%; Colorless oil. The product was slowly decomposed at ambient temperature, and the NMR spectra were obtained as those of a mixture of two conformational isomers. The signals originated from the minor one are shown in parentheses., ^{1}H NMR ($CDCl_3$) δ 2.65–2.75 (2H, m), 2.75–2.89 (2H, m), 3.50–3.57 (1H, m), 4.19–4.24 (1H, m), 5.08–5.28 (2H, m), 5.45 (1H, d,*J*=9.9 Hz), 5.59 (1H, d, *J*=16.9 Hz), 5.85 (1H, t, *J*=6.7 Hz), 5.93–6.05 (1H, m), 6.39–6.57 (2H, m), 7.10 (1H, t, *J*=7.0 Hz), 7.16 (1H, t, *J*=7.0 Hz), 7.28–7.35 (2H, m), 7.45–7.52 (1H, m), 8.15 (7.93) (1H, bs); ^{13}C NMR ($CDCl_3$) δ 22.5 (21.2), 38.9 (37.0), 41.0 (39.9), 49.4 (50.3), 107.7, 110.9, 117.8, 118.3, 119.3 (119.5), 121.4, 121.7 (122.0), 124.2, 126.3, 133.7 (133.4), 134.3, 135.0, 135.9, 143.1, 165.7.

3.13. The synthesis of 15

The excess amount of KH, which was washed with pentane, was suspended in THF (0.5 ml), then the THF solution (1 ml) of **14** (0.12 mmol) was added and the mixture was allowed to stir for 5 min at 0°C. After the addition of methoxymethyl chloride (0.48 mmol), the reaction was continued for 30 min at 0°C. Then water was added, and the mixture was extracted with CH_2Cl_2, which was dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (CH_2Cl_2–AcOEt=3:1) to afford colorless oil in 80% yield. The ^{1}H and ^{13}C NMR of the product were in accord with those reported by Meyers et al.,[12b,27] The $[\alpha]^{20}_{D}$ was −98.67 (*c* 0.31, THF) (lit.[12b] $[\alpha]^{20}_{D}=+100.4$ (*c* 0.24, THF) for the *S* isomer) thus the configuration of **15** was determined as *R*.

3.14. The synthesis of chiral auxiliaries dserived from pyroglutamic acid (Table 4, entries 7–9)

The *N*-sulfonyl derivative (entry 7): Sodium hydride (0.6 mmol) was suspended in THF (1 ml), and *t*-butyl pyroglutamate (0.5 mmol) was added at room temperature, then the mixture was allowed to stir for 5 min. After the gas evolution, phenylsulfonyl chloride (0.55 mmol) was added and the reaction was continued for another 30 min. Then the mixture was quenched with water, and 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 (CH_2Cl_2–AcOEt) to give the *t*-butyl *N*-(phenylsulfonyl)pyroglutamate as a viscous oil (69%). The ester (0.07 mmol) was dissolved in CH_2Cl_2 (1.5 ml), and the reaction was started by the addition of trifluoroacetic acid (0.35 mmol), and continued for 15 h at room temperature. The mixture was diluted with CH_2Cl_2 and extracted with sat. $NaHCO_3$. The aqueous layer was acidified by dil. HCl, and extracted with CH_2Cl_2, which was dried over $MgSO_4$, and evaporated. The oily residue was suspended in hexane to crystallize, and the solid thus formed was filtered, and had a melting point of 158–160°C (76%). The addition of the carboxylic acid to β-carboline was carried out according to the Method B applied to the synthesis of **8**.

3.14.1. *t*-Butyl pyroglutamate. Yield 32%; Colorless powder; mp 99.8–102.5°C; ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 2.14–2.22 (1H, m), 2.31–2.48 (3H, m), 4.14 (1H, dd, *J*=7.6, 5.5 Hz), 6.31 (1H, bs); ^{13}C NMR ($CDCl_3$) δ 24.9,

28.0, 29.4, 56.1, 82.3, 170.8, 177.6. Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.12; H, 8.14; N, 7.77.

3.14.2. *t*-Butyl *N*-(phenylsulfonyl)pyroglutamate. Yield 69%; Colorless viscous oil; $[\alpha]^{20}_D=-49.40$ (*c* 0.10, $CHCl_3$); ^{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.

3.14.3. *N*-(Phenylsulfonyl)pyroglutamic acid. Yield 76%; Colorless powder; mp 158.0–160.5°C; $[\alpha]^{20}_D=-51.33$ (*c* 0.10, $CHCl_3$); ^{1}H 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.

3.14.4. 9-{*N*-(Phenylsulfonyl)pyroglutamyl}-β-carboline. Yield 91%; Colorless plates from diisopropyl ether–AcOEt; mp 203.1–204.0°C; $[\alpha]^{20}_D=-82.31$ (*c* 0.18, $CHCl_3$); ^{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, brs); ^{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.

3.15. The *N*-benzyl derivatives (entries 8 and 9)

The above procedure was applied with the use of benzyl bromide instead of phenylsulfonyl chloride and after the same work-up procedure, the colorless crystals were obtained by recrystallization.

3.15.1. *t*-Butyl *N*-benzylpyroglutamate. Yield 81%; Colorless needles from diisopropyl ether–AcOEt; mp 51.0–58.9°C; $[\alpha]^{20}_D=-38.08$ (*c* 0.20, $CHCl_3$); ^{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.

To the CH_2Cl_2 solution (2 ml) of the obtained compound (0.81 mmol) was added TFA (0.5 ml), and the mixture was allowed to react for 7 h at room temperature. The same work-up procedure mentioned above was carried out, and the product was obtained as colorless crystals (91%, mp 85–88°C). The addition to β-carboline was performed by the Method B, and the colorless needles were obtained.

3.15.2. *N*-Benzylpyroglutamic acid. The mp and ^{1}H NMR data were identical with those of reported ones.[28]

3.15.3. 9-(*N*-Benzylpyroglutamyl)-β-carboline. Yield 71%; Colorless needles from ether–AcOEt; mp 175–178°C; $[\alpha]^{20}_D=-125.4$ (*c* 0.40, $CHCl_3$); ^{1}H 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, brs); ^{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.

References

1. (a) Comins, D. L.; O'Conner, S. *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: San Diego, 1988; Vol. 44, pp. 199–267. (b) Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903–931.
2. (a) Itoh, T.; Hasegawa, H.; Nagata, K.; Ohsawa, A. *J. Org. Chem.* **1994**, *59*, 1319–1325. (b) Itoh, T.; Hasegawa, H.; Nagata, K.; Okada, M.; Ohsawa, A. *Tetrahedron* **1994**, *50*, 13089–13100.
3. (a) Itoh, T.; Miyazaki, M.; Hasegawa, H.; Nagata, K.; Ohsawa, A. *Chem. Commun.* **1996**, 1217–1218. (b) Itoh, T.; Miyazaki, M.; Nagata, K.; Ohsawa, A. *Tetrahedron* **2000**, *56*, 4383–4395.
4. (a) Itoh, T.; Miyazaki, M.; Nagata, K.; Hasegawa, H.; Ohsawa, A.; Nakamura, K. T. *Heterocycles* **1998**, *47*, 125–128. (b) Itoh, T.; Nagata, K.; Miyazaki, M.; Ohsawa, A. *Synlett* **1999**, 1154–1156.
5. Preliminary communications: (a) Itoh, T.; Matsuya, Y.; Enomoto, Y.; Nagata, K.; Miyazaki, M.; Ohsawa, A. *Synlett* **1999**, 1799–1801. (b) Matsuya, Y.; Itoh, T.; Enomoto, Y.; Ohsawa, A. *Heterocycles* **2000**, *53*, 2357–2361.
6. Saxton, J. E., Ed.; *The Chemistry of Heterocyclic Compounds Part 4*; Wiley: Chichester, 1994; Suppl. of Vol. 25.
7. (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842. (b) Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennet, D.; Cook, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 6998–7010. (c) Yu, S.; Berner, M.; Cook, J. M. *J. Am. Chem. Soc.* **2000**, *122*, 7827–7828 and references cited therein.
8. Martin, S. F.; Chen, K. X.; Eary, C. T. *Org. Lett.* **1999**, *1*, 79–81 and references cited therein.
9. (a) Waldmann, H.; Schmidt, G.; Henke, H.; Burkard, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2402–2403. (b) Tietze, L. F.; Zhou, Y.; Topken, E. *Eur. J. Org. Chem.* **2000**, 2247–2252.
10. (a) Martin, S. F.; Benage, B.; Hunter, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 5925–5927. (b) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161–6171. (c) Yamaguchi, R.; Hamasaki, T.; Sasaki, T.; Ohta, T.; Utimoto, K.; Kozima, S.; Takaya, H. *J. Org. Chem.*

1993, *58*, 1136–1143. (d) Birman, V. B.; Rawal, V. H. *J. Org. Chem.* **1998**, *63*, 9146–9147.
11. Yamaguchi, R. *Yuki Gosei Kagaku Kyokaishi* **1991**, *49*, 128–137 (*Chem. Abstr.*, **1991**, 114 185149u).
12. (a) Meyers, A. I.; Miller, D. B.; White, F. H. *J. Am. Chem. Soc.* **1988**, *110*, 4778–4787. (b) Meyers, A. I.; Highsmith, T. K.; Buonora, P. T. *J. Org. Chem.* **1991**, *56*, 2960–2964.
13. Comins et al., reported that non-aromatic *N*-acyliminium salts resulted in a lower degree of stereocontrol than the aromatic ones when α-attack of nucleophiles was controlled by the chiral acyl group, see: Comins, D. L.; Thakker, P. M.; Baevsky, M. F.; Badawa, M. M. *Tetrahedron* **1997**, *53*, 16327–16340.
14. For example, when *N*-protected alanine or phenylalanine was used for the chiral auxiliary, the de of the addition product was lower than 10%.
15. Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987 pp 185–258.
16. There are some reports to claim that allyltin halides and methoxides are more reactive to carbonyl compounds than tetraallyltin or allyltributyltin, see: (a) Boaretto, A.; Marton, D.; Tagliavini, G.; Ganis, P. *J. Organomet. Chem.* **1987**, *321*, 199–207. (b) Marshall, R. L.; Young, D. J. *Tetrahedron Lett.* **1992**, *33*, 2369–2370. (c) Miyake, H.; Yamamura, K. *Chem. Lett.* **1992**, 1369–1372. (d) Yanagisawa, A.; Inoue, H.; Morodome, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10356–10357. (e) Colkey, T. M.; Marshall, R. L.; McCluskey, A.; Young, D. J. *Tetrahedron Lett.* **1996**, *37*, 1905–1908. (f) Yanagisawa, A.; Morodome, M.; Nakashima, H.; Yamamoto, H. *Synlett* **1997**, 1309–1311.
17. Wardell, J. L. In *Chemistry of Tin*; Harrison, P. G., Ed.; Blackie & Sons: Glasgow, 1989; pp. 145–186.
18. The compound **15** was recently synthesized by Nakamura et al., but the characterization was carried out as *N*-trifluoroacetyl derivative, see:Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489–8490.
19. Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293 and references cited therein.
20. (a) Naito, T.; Miyata, O.; Tada, Y.; Nishiguchi, Y.; Kiguchi, T.; Ninomiya, I. *Chem. Pharm. Bull.* **1986**, *34*, 4144–4149. (b) Yamaguchi, R.; Otsuji, A.; Utimoto, K.; Kozima, S. *Bull. Chem. Soc. Jpn* **1992**, *65*, 298–300.
21. When allyltrimethyltin was used under the same conditions, the *R* isomer was obtained in 52% yield (71%ee). Thus, the change of alkyl groups (methyl or butyl) to allyl group caused the reversal of the stereoselectivity.
22. Whittaker, N. *J. Chem. Soc. C* **1969**, 85–89.
23. Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1988**, *53*, 2367–2371.
24. Cupps, T. L.; Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3972–3979.
25. Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111.
26. Yamada, K.; Takeda, M.; Iwakuma, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 265–270.
27. The ^{13}C NMR showed that **15** was obtained as a mixture of two conformers.
28. (a) Petersen, J. S.; Fels, G.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 4539–4547. (b) Campaigne, E.; Matthews, D. P. *Heterocycl. Chem.* **1975**, *12*, 391–392.