Conversion of 4-Oxoproline Esters to 4-Substituted Pyrrole-2-carboxylic Acid Esters

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The Grignard, Wittig, Tebbe, Horner–Emmons, and Reformatsky reactions of the 4-oxoproline esters gave the corresponding 4-alylated or 4-alkylidenated products, respectively. The products were properly treated with bases to cause aromatization, giving 4-substituted pyrrole-2-carboxylic acid esters such as methyl 4-methylpyrrole-2-carboxylate, which is a trail pheromone of *Atta texana*.

Key words 4-oxoproline ester; Grignard reaction; Horner–Emmons reaction; Reformatsky reaction; aromatization; methyl 4-methylpyrrole-2-carboxylate

During our study of the synthesis of several compounds using 4-hydroxyproline (**1**) as a starting material,[1] when a *p*-toluenesulfonyl (Ts, tosyl) group was introduced to the nitrogen atom of **1** by the Schotten–Baumann method employing TsCl and aqueous NaOH according to Portoghese's method[2] in order to obtain compound **2**, thereby prolonging the reaction, we encountered a side reaction that caused the elimination of sulfinic acid and aromatization, giving pyrrole-2-carboxylic acid (**3**) (Chart 1). We therefore considered that the aromatization could be utilized for the synthesis of pyrrole-2-carboxylic acid derivatives such as methyl 4-methylpyrrole-2-carboxylate (**4**), which is a trail pheromone of *Atta texana*.[3—6]

Although aromatizations of the *N*-tosylproline derivatives giving pyrrole-2-carboxylic acid derivatives,[7—9] as well as other syntheses of the pyrrole-2-carboxylic acid derivatives,[10—12] have been reported by many workers, synthesis of the pyrrole-2-carboxylic acid derivatives using 4-oxoproline derivatives has not been reported. Therefore, we performed alkylation and alkylidenaion of *N*-tosyl-4-oxoproline ester, followed by aromatization of the products to give 4-substituted proline-2-carboxylic acid esters **7** (Chart 2). This method made it possible to introduce not only a simple alkyl group but also an alkyl possessing a functional group into 4-position of the pyrrole-2-carboxylic acid derivatives.

Thus we report here the conversion of 4-oxoproline esters **5** and **6** to the 4-substituted proline-2-carboxylic acid esters **7**.

Base Treatments of *N*-Tosyl-4-oxoproline Esters We chose the methyl and/or *tert*-butyl esters of *N*-tosyl-4-oxoproline **5**[13] and **6**[14] as substrates for the ketone reactions, and synthesized them from **1** according to the previously reported methods.[2] Next, we attempted the base treatments of **5** and **6** using appropriate bases to cause enolization and aromatization. As a result, 4-hydroxypyrrole-2-carboxylic acid esters **8** and **9** were successfully obtained in 76% and 60% yields, respectively. Only the benzyl ester of 4-hydroxypyrrole-2-carboxylic acid[15] has been reported previously; **8** and **9** are new compounds (Chart 3).

The Grignard Reactions of *N*-Tosyl-4-oxoproline Ester and Conversion into the Pyrrole Derivatives Grignard reactions were attempted with the *tert*-butyl ester of *N*-tosyl-4-oxoproline **6**, in order to prevent the reaction at the ester moiety. When the Grignard reagent was employed without addition of other reagent, the by-products were remarkably formed and yields of the desired products were much lower (mixture of epimers <70%). In order to prevent the aldol reaction and the aromatization of **6**, which seemed to be the side reactions, additions of $CeCl_3$[16,17] into the reaction systems were examined. Consequently, the numbers of the com-

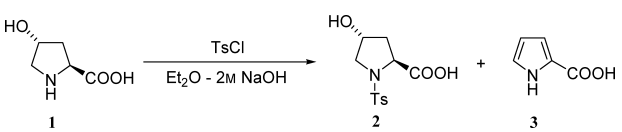

Chart 1

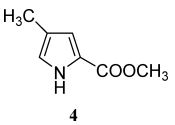

Fig. 1. Trail Pheromone of *Atta texana*

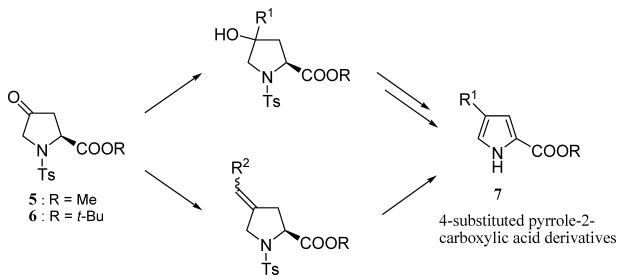

Chart 2

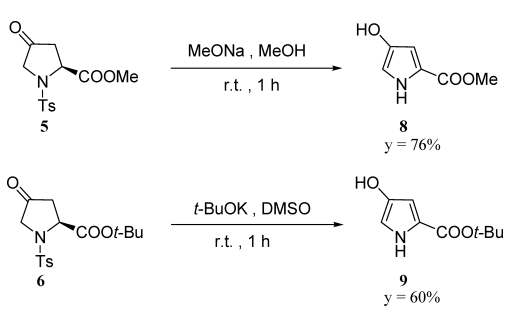

Chart 3

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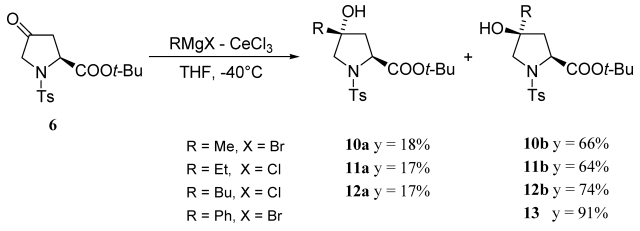


Chart 4. The Grignard Reactions of Compound **6**

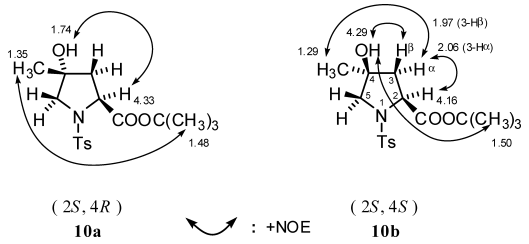


Fig. 2. Selected Decisive NOE Relationships of Compounds **10a** and **10b**

ponents of the reaction mixtures decreased in the TLC analyses and the yields of the desired products improved (Chart 4).

The obtained products were the epimers in each alkylation, and the ratio of the epimers seemed to change by the size of the alkyl (or phenyl) groups introduced to the 4-position. When a phenyl group was introduced, a single epimer, (2*S*,4*R*)-form **13** was generated. Although, by the IUPAC nomenclature, the absolute configuration of **13** is different from those of **10b**—**12b**, which were (2*S*,4*S*)-forms, the structure of **13** should be similar to those of **10b**—**12b**. The stereochemistries of the epimers were determined by differential nuclear Overhauser effect (NOE) experiments of ^{1}H-NMR (Fig. 2). As for **10a**, +NOEs were observed between a signal at δ 1.74 assigned to the hydroxy proton and a signal at δ 4.33 assigned to 2-H, and between a signal at δ 1.35 assigned to the 4-methyl protons and a signal at δ 1.48 assigned to methyl protons of the *tert*-butyl group. Therefore, **10a** was proved to have a (2*S*,4*R*)-configuration. As for **10b**, +NOEs were observed between a signal at δ 4.29 assigned to the hydroxy proton and signals at δ 1.97 assigned to 3-H$_\beta$ and δ 1.50 assigned to methyl protons of the *tert*-butyl group. +NOEs were also observed between a signal at δ 2.06 assigned to 3-H$_\alpha$ and signals at δ 4.16 assigned to 2-H and δ 1.29 assigned to 4-methyl protons. Therefore, **10b** was proved to have a (2*S*,4*S*)-configuration. In the case of **11**—**13**, +NOEs similar to those for compound **10** were observed, and the configurations of these compounds were confirmed.

Further, differences between the characteristics of the epimers **10a**—**12a** and **10b**—**12b** were observed in TLC (silica gel) analysis and IR spectra due to the probable intramolecular hydrogen bondings between a hydroxy group and an ester carbonyl group of **10b**—**12b**. The *Rf* values of **10b**—**12b** were higher than those of the corresponding epimers **10a**—**12a** in TLC analysis, because the intermolecular hydrogen bondings between the hydroxy groups of **10b**—**12b** and silica gel seem to have been prevented. Concerning the characteristic absorption bands of carbonyl groups in the IR spectra, those of **10b**—**12b** (1707, 1720, 1718 cm^{-1}) were located at lower wavenumbers than those of **10a**—**12a** (1728, 1751, 1730 cm^{-1}).

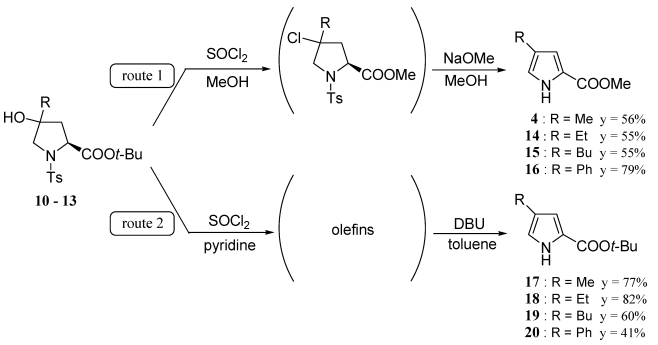


Chart 5

Next, aromatizations of the compounds **10**—**13** were attempted. In order to obtain methyl esters of 4-substituted pyrrole-2-carboxylic acids, **10b**—**12b** and **13** were treated with $SOCl_2$–MeOH, which should cause chlorination and transesterification, then treated with NaOMe in MeOH, affording compounds **4**, **14**, **15**, and **16** in 56%, 55%, 55%, and 79% yields, respectively (Chart 5, route 1). Compounds **10a**—**12a** were also treated similarly to **10b**—**12b**, and similar results were obtained.

Meanwhile, to obtain *tert*-butyl esters of 4-substituted pyrrole-2-carboxylic acids, **10b**—**12b** and **13** were treated with $SOCl_2$-pyridine, which should cause chlorination and elimination, then treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing toluene, affording compounds **17**, **18**, **19**, and **20** in 77%, 82%, 60%, and 41% yields, respectively (Chart 5, route 2).

Incidentally, the aromatizations are characteristic of *N*-tosylproline derivatives, and normally *N*-protected proline derivatives (urethanes and amides) do not undergo aromatization under the basic conditions. For example, treatment of *N*-*tert*-butoxycarbonyl-4-iodo-L-proline methyl ester with DBU provided 3,4- and 4,5-dehydroproline derivatives without aromatization.[18]

The Wittig, the Tebbe, and the Horner–Emmons Reactions of *N*-Tosyl-4-oxoproline Esters and Conversion into the Pyrrole Derivatives We examined the Wittig reaction of **5** with methylenetriphenylphosphorane, which was generated by treatment of methyltriphenylphosphonium bromide with phenyllithium in Et_2O,[19] at room temperature and the expected 4-methyleneproline derivative **21** was obtained in only 10% yield. A similar reaction was examined by Cheng *et al.*, and they reported that the low yield of the reaction was due to the propensity of the sulfonamide moiety to decompose under basic conditions.[20]

We next examined the Tebbe reaction[21] of **6**, and the desired product **22** was obtained in 16% yield together with the dimethylated product **23** in 22% yield (Chart 6).

Meanwhile, the Horner–Emmons reactions[22] of **5** and **6** gave satisfactory results, as shown in Table 1. However, the expected products underwent rearrangement at olefin or aromatization under the basic reaction conditions to give the secondary products, depending on the alkyl groups of esters **5** and **6**, temperatures, and reagents. For example, the Horner–Emmons reaction of **6** and triethyl phosphonoacetate at room temperature for 1 h (entry 3) gave *exo*-olefins **25a** (4*E*) and **25b** (4*Z*), *endo*-olefins **25c** (3-ene) and **25d** (4-ene), and pyrrole **29**, in 17%, 14%, 33%, 9%, and 23% yields. A

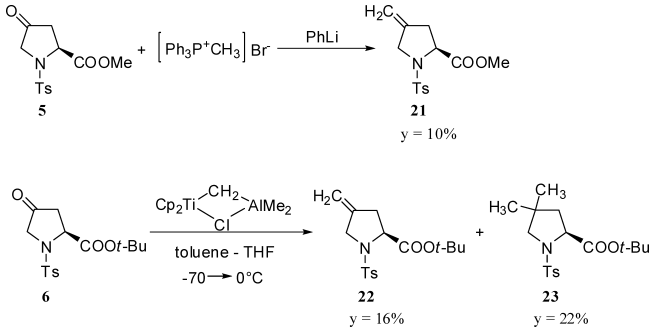


Chart 6

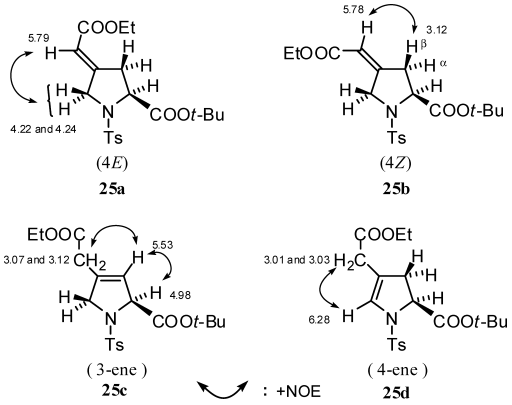
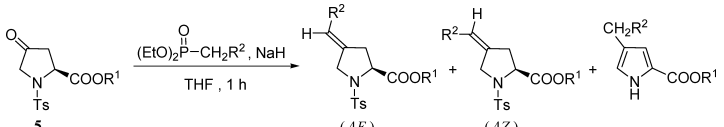


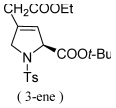
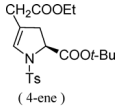
Fig. 3. Selected Decisive NOE Relationships of Compounds **25a**—**d**

Table 1. The Horner–Emmons Reactions of Compounds **5** and **6**



R^1 = Me , R^2 = COOEt	**24a**	**24b**	**28**
R^1 = *t*-Bu , R^2 = COOEt	**25a**	**25b**	**29**
R^1 = Me , R^2 = CN	**26a**	**26b**	**30**
R^1 = *t*-Bu , R^2 = CN	**27a**	**27b**	**31**

Entry	Substrate		R^2	Temp.	Yields (%)				
		R^1			Olefin	**a** (4*E*)	**b** (4*Z*)	Pyrrole	
1	**5**	Me	COOEt	r.t.	**24**	2	—	**28**	86
2				−40 °C		48	44		—
3	**6**	*t*-Bu		r.t.	**25**	17	14[a)]	**29**	23
4				0 °C		37	30[b)]		—
5	**5**	Me	CN	0 °C	**26**	—	4	**30**	56
6				−40 °C		37	33		3
7	**6**	*t*-Bu		15 °C	**27**	—	—	**31**	98
8				0 °C		48	36		5

a) The isomers  (3-ene) **25c** 33% and  (4-ene) **25d** 9% were obtained. *b*) **25c** 30%, **25d** 2%. r.t.: room temperature.

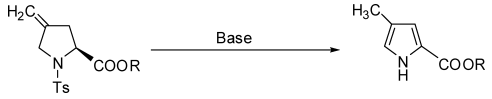
similar reaction at 0 °C for 1 h (entry 4) gave **25a**, **25b**, **25c**, and **25d** in 37%, 30%, 30%, and 2% yields without formation of **29**. In the case of the reactions using diethyl cyanomethylphosphonate (entry 5—8), aromatization occurred more easily.

The structures of **24**—**27** were determined by differential nuclear Overhauser effect (NOE) experiments of ^{1}H-NMR (Fig. 3). As for **25a**, +NOEs were observed between a signal at δ 5.79 assigned to the olefinic proton and signals at δ 4.22 and δ 4.24 assigned to 5-Hs. For **25b**, +NOEs were observed between a signal at δ 5.78 assigned to the olefinic proton and a signal at δ 3.12 assigned to 3-H$_\beta$. For **25c**, +NOEs were observed between a signal at δ 5.53 assigned to the olefinic 3-proton and signals at δ 3.07 and δ 3.12 assigned to methylene protons of the side chain, and δ 4.98 assigned to 2-H. For **25d**, +NOEs were observed between a signal at δ 6.28 assigned to the olefinic 5-proton and signals at δ 3.01 and δ 3.03 assigned to methylene protons of the side chain, and δ 7.70 assigned to aromatic protons. In the case of **24**, **26**, and **27**, discriminations of the (4*E*)-form from the (4*Z*)-form were done similarly (Fig. 3).

Aromatizations of the olefinic compounds **21** and **22** were then examined (Table 2). In these cases, similarly to the aromatization process of 4-alkylated proline derivatives **10**—**13**, treatments of **21** and **22** with DBU in refluxing toluene for 12 h (entry 1 and 3) afforded pyrrole derivatives **4** and **17** in 97% and 99% yields, respectively. Without heating, the aromatization reaction hardly proceeded. Compounds **21** and **22** were also treated with potassium *tert*-butoxide in tetrahydrofuran (THF) at room temperature for 1 h (entry 2 and 4), giving **4** and **17** in 77% and 85% yields, respectively.

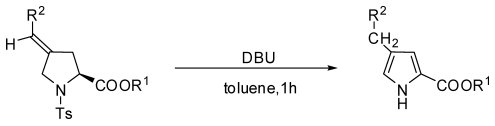
On the other hand, compounds **24**—**27** seemed to be more reactive (Table 3). Even at room temperature, treatments of **24a** and **26a** with DBU in toluene (using concentrations similar to that of **21**) for 1 h (entry 1 and 3) gave the corresponding pyrrole derivatives **28** and **30** in 97% and 99% yields,

Table 2. Aromatization of Compounds **21** and **22**



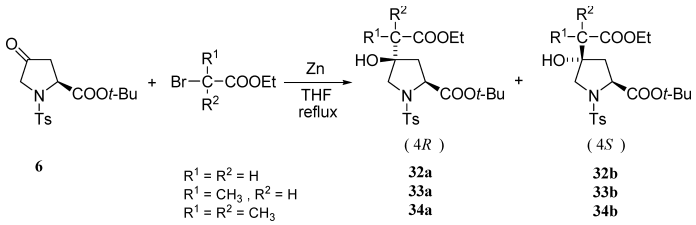
Entry	Substrate	R	Reaction conditions	Product	Yield (%)
1	**21**	Me	DBU, toluene, reflux, 12 h	**4**	97
2			*t*-BuOK, THF, r.t., 1 h		77
3	**22**	*t*-Bu	DBU, toluene, reflux, 12 h	**17**	99
4			*t*-BuOK, THF, r.t., 1 h		85

Table 3. Aromatization of Compounds **24**—**27**



Entry	Substrate	R^1	R^2	Temp.	Product	Yield (%)
1	**24a**	Me	COOEt	r.t.	**28**	97
2	**25a**	*t*-Bu	COOEt	Reflux	**29**	99
3	**26a**	Me	CN	r.t.	**30**	99
4	**27a**	*t*-Bu	CN	Reflux	**31**	99

Table 4. The Reformatsky Reactions of Compound **6**



Entry	R^1	R^2	Reaction conditions			Yields (%)	
			Reagents	Time (h)		**a** (4*R*)	**b** (4*S*)
1	H	H	Zn, $(CH_3O)_3B$	1		Complicated mixture	
2			Zn–Cu	1	**32**	45	10
3	CH_3	H	Zn, $(CH_3O)_3B$	1.5	**33**	55	21
4	CH_3	CH_3	Zn, $(CH_3O)_3B$	1	**34**	60	18

respectively. Compounds **24b** and **26b** were treated similarly to **24a** and **26a** and similar results were obtained. In the case of **25a** and **27a**, which have *tert*-butyl ester function, treatments with DBU at room temperature caused the aromatization, but slowly. So the reaction mixtures were heated under reflux for 1 h (entry 2 and 4), giving **29** and **31** in 99% and 99% yields, respectively. We attributed the lower reactivities of the *tert*-butyl esters to the steric hindrances around the 2-hydrogens, which would be abstracted by DBU. Treatment of the corresponding geometric isomers **25b** and **27b** in a manner similar to **25a** and **27a** gave similar results. Similar treatment of the regioisomers **25c** and **25d** also afforded **29** quantitatively.

The Reformatsky Reactions of *N*-Tosyl-4-oxoproline Ester and Conversion into the Pyrrole Derivatives It seems impossible that the Horner–Emmons reaction should induce a pyrrole derivative which has a tertiary alkyl group, so we next attempted the Reformatsky reaction. As the usual Reformatsky reaction condition (ketone, bromoacetate, and zinc) often generates side reactions such as an aldol reaction and a dehydration,[23] addition of trimethyl borate into the reaction system was examined. Unfortunately, methyl ester **5** gave complicated mixtures under the conditions employed for **6**. As shown in Table 4, when ethyl 2-bromopropionate and ethyl 2-bromoisobutyrate were used (entry 3 and 4), the desired 4-alkylated products **33a**, **33b**, **34a**, and **34b** were obtained in 55%, 21%, 60%, and 18% yields. Each of **33a** and **33b** is a mixture of the epimers based on the asymmetric carbons of side chains; each separation of the epimers was difficult and the ratios of epimers were estimated to be 56 : 44 for **33a**, and 66 : 34 for **33b**, by ^{1}H-NMR. The same result was obtained when optically active ethyl (*R*)-2-bromopropionate or ethyl (*S*)-2-bromopropionate was employed for the reaction in place of racemic ethyl 2-bromopropionate.

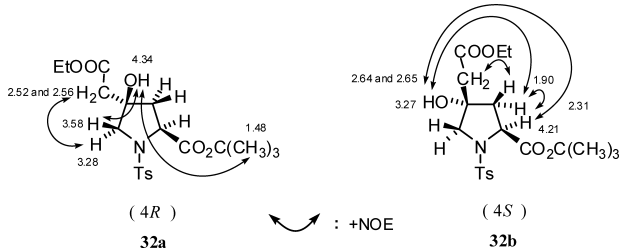


Fig. 4. Selected Decisive NOE Relationships of Compounds **32a** and **32b**

Meanwhile, a complicated mixture was obtained when ethyl bromoacetate was used (entry 1). We therefore attempted the method using Zn–Cu couple[24] for ethyl bromoacetate (entry 2), and compounds **32a** and **32b** were obtained in 45% and 10% yields.

The stereochemistries of **32a** and **32b** were determined by differential nuclear Overhauser effect (NOE) experiments of ^{1}H-NMR (Fig. 4). As for **32a**, +NOE was observed between a signal at δ 4.34 assigned to the hydroxy proton and a signal at δ 1.48 assigned to methyl protons of the *tert*-butyl group. Unfortunately, because the signals of 3-methylene protons overlapped at δ 2.16, no other effective information to deter-

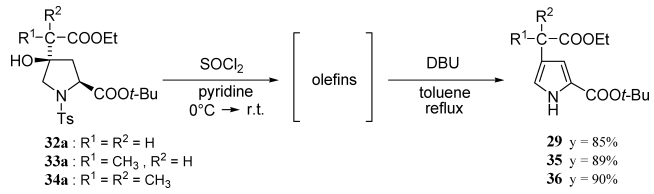


Chart 7

mine the stereochemistry at 4-position was obtained. Therefore, **32a** was proved to have a (2*S*,4*R*)-configuration. For **32b**, +NOEs were observed between a signal at δ 4.21 assigned to 2-H, a signal at δ 3.27 assigned to the hydroxy proton, and a signal at δ 2.31 assigned to 3-H_α. +NOEs were also observed between a signal at δ 1.90 assigned to 3-H_β and signals at δ 2.64 and δ 2.65 assigned to 4-methylene protons. Therefore, **32b** was proved to have a (2*S*,4*S*)-configuration.

Aromatizations of compounds **32a**—**34a** were done according to those of the Grignard products **10**—**13**, treated with $SOCl_2$-pyridine, then treated with DBU in refluxing toluene, giving the desired pyrrole derivatives **29**, **35**, and **36** in 85%, 89%, and 90% yields, respectively. Enantiomeric compounds **32b**—**34b** were also treated similarly to **32a**—**34a**, and similar results were obtained (Chart 7).

In conclusion, we accomplished the conversion of 4-oxoproline esters to 4-substituted pyrrole-2-carboxylic acid esters.

Experimental

Melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. Specific rotations were determined with a JASCO DIP-370 polarimeter. NMR spectra, except for the amino acids, were recorded in chloroform-*d* ($CDCl_3$) on a JEOL JNM-ECP500 spectrometer using tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Hitachi 270-30 spectrophotometer. Mass spectra (MS) and high resolution mass spectra (HR-MS) were obtained with a JEOL JMS-DX300 instrument. TLC was performed on Silica gel 60 F_{254} plates (0.25 mm; Merck). Column chromatography was performed on silica gel (Kieselgel 60, 70—230 mesh; Merck). Flash chromatography was performed on silica gel (Silica Gel 60, 230—400 mesh; Nacalai Tesque).

Methyl 4-Hydroxypyrrole-2-carboxylate (8) Under an argon atmosphere, compound **5** (1.00 g, 3.36 mmol) was suspended in MeOH (10 ml), and then 28% NaOMe (10 ml) was added at room temperature and the mixture was stirred for 1 h. A sufficient amount of carbon dioxide was bubbled into the mixture and the mixture was concentrated under reduced pressure. Water (25 ml) was added to the residue at 0 °C and the whole was extracted with AcOEt (25 ml×2). The organic layer was washed with water (25 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residual brown oil was subjected to column chromatography on silica gel (AcOEt) to give **8** (360 mg, 76%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 3.83 (3H, s, CH_3), 5.39 (1H, s, OH), 6.51 (1H, dd, J=2.8, 1.8 Hz, 3-H), 6.58 (1H, dd, J=3.0, 1.8 Hz, 5-H), 8.84 (1H, s, NH). ^{13}C-NMR ($CDCl_3$) δ: 51.63 (q), 104.47 (d), 108.98 (d), 119.22 (s), 143.81 (s), 161.79 (s). IR ν_{max}^{neat} cm^{-1}: 3403, 3134 (NH, OH), 1685 (C=O). HR-MS *m/z*: 141.0428 (Calcd for $C_6H_7NO_3$: 141.0426).

***tert*-Butyl 4-Hydroxypyrrole-2-carboxylate (9)** Under an argon atmosphere, compound **6** (1.00 g, 2.95 mmol) was dissolved in DMSO (5 ml), and then *t*-BuOK (800 mg) was added at room temperature and the mixture was stirred for 1 h. A sufficient amount of carbon dioxide was bubbled into the mixture and the mixture was concentrated under reduced pressure. Water (25 ml) was added to the residue at 0 °C and the whole was extracted with AcOEt (25 ml×2). The organic layer was washed with water (25 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residual brown oil was subjected to column chromatography on silica gel [hexane–Et_2O (1 : 1)] to give **9** (325 mg, 60%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.54 (9H, s, $C(CH_3)_3$), 5.30 (1H, br s, OH), 6.45 (1H, s, 3-H), 6.53 (1H, s, 5-H), 8.78 (1H, s, NH). ^{13}C-NMR ($CDCl_3$) δ: 28.36 (q), 81.17 (s), 103.97 (d), 108.04 (d), 120.96 (s), 143.66 (s), 160.83 (s). IR ν_{max}^{neat} cm^{-1}: 3415, 3315 (NH, OH), 1681 (C=O). HR-MS *m/z*: 183.0892 (Calcd for $C_9H_{13}NO_3$: 183.0895).

***tert*-Butyl (2*S*,4*R*)-4-Hydroxy-4-methyl-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (10a) and *tert*-Butyl (2*S*,4*S*)-4-Hydroxy-4-methyl-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (10b)** Under reduced pressure, powdered $CeCl_3 \cdot 7H_2O$ (1.62 g, 4.4 mmol) was heated at 90 °C for 1 h, then the temperature was slowly raised and kept at 140 °C for 2 h. After cooling, the vessel was filled with argon. THF (15 ml) was added and the vessel was irradiated with ultrasonic waves for 2 h. After the suspension was cooled at −40 °C under an argon atmosphere, 3 M CH_3MgBr in THF (1.33 ml, 4.0 mmol) was added dropwise and the mixture was stirred for 1.5 h. A solution of compound **6** (679 mg, 2.00 mmol) in THF (3 ml) was added dropwise to the suspension prepared as described above and stirred for 1 h. The reaction was quenched with 3% CH_3COOH (13 ml). The whole was extracted with AcOEt (15 ml×3) and the organic layer was washed with brine (15 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residual white solid was subjected to column chromatography on silica gel [benzene–AcOEt (10 : 1 then 8 : 1)] to give **10b** (472 mg, 66%) and then **10a** (130 mg, 18%). These compounds were recrystallized from *i*-Pr_2O, respectively.

10a: Colorless prisms, mp 213—214 °C (dec.), $[\alpha]_D^{30}$ −71.3° (c=0.7, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, s, CH_3), 1.48 (9H, s, $C(CH_3)_3$), 1.74 (1H, br s, OH), 1.90 (1H, dd, J=13.1, 9.6 Hz, 3-H_β), 2.25 (1H, ddd, J=13.1, 7.6, 2.0 Hz, 3-H_α), 2.41 (3H, s, Ar-CH_3), 3.34 (1H, d, J=11.3 Hz, 5-H_β), 3.40 (1H, dd, J=2.0, 11.3 Hz, 5-H_α), 4.33 (1H, dd, J=7.6, 9.6 Hz, 2-H), 7.30 (2H, d, J=8.3 Hz, Ar-H), 7.79 (2H, d, J=8.3 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 21.56 (q), 24.15 (q), 27.92 (q), 44.74 (t), 60.82 (t), 61.03 (d), 76.79 (s), 81.85 (s), 127.81 (d), 129.58 (d), 135.33 (s), 143.66 (s), 171.19 (s). IR ν_{max}^{KBr} cm^{-1}: 3483 (OH), 1728 (C=O). MS (FAB) *m/z*: 356 (M^++1). *Anal.* Calcd for $C_{17}H_{25}NO_5S$: C, 57.44; H, 7.09; N, 3.94. Found: C, 57.38; H, 6.92; N, 4.01.

10b: Colorless prisms, mp 127—129 °C, $[\alpha]_D^{30}$ −51.6° (c=0.7, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, s, CH_3), 1.50 (9H, s, $C(CH_3)_3$), 1.97 (1H, ddd, J=1.8, 2.8, 13.8 Hz, 3-H_β), 2.06 (1H, dd, J=10.3, 13.8 Hz, 3-H_α), 2.44 (3H, s, Ar-CH_3), 3.06 (1H, d, J=9.5 Hz, 5-H_α), 3.46 (1H, dd, J=9.5, 2.8 Hz, 5-H_β), 4.16 (1H, dd, J=10.3, 1.8 Hz, 2-H), 4.29 (1H, s, OH), 7.33 (2H, d, J=8.1 Hz, Ar-H), 7.75 (2H, d, J=8.1 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 21.83 (q), 23.50 (q), 28.00 (q), 43.90 (t), 60.72 (d), 61.34 (t), 77.00 (s), 83.51 (s), 127.96 (d), 130.03 (d), 134.76 (s), 144.21 (s), 173.53 (s). IR ν_{max}^{KBr} cm^{-1}: 3410 (OH), 1707 (C=O). MS (FAB) *m/z*: 356 (M^++1). *Anal.* Calcd for $C_{17}H_{25}NO_5S$: C, 57.44; H, 7.09; N, 3.94. Found: C, 57.38; H, 6.89; N, 4.14.

***tert*-Butyl (2*S*,4*R*)-4-Ethyl-4-hydroxy-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (11a) and *tert*-Butyl (2*S*,4*S*)-4-Ethyl-4-hydroxy-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (11b)** Compounds **11a** (128 mg, 17%) and **11b** (475 mg, 64%) were obtained from **6** (679 mg, 2.00 mmol) in a manner similar to that described for **10**, but using 2 M EtMgCl in Et_2O (2.0 ml, 4.0 mmol) and a reaction time of 1.5 h. These compounds were recrystallized from *i*-Pr_2O, respectively.

11a: Colorless prisms, mp 114—115 °C, $[\alpha]_D^{30}$ −77.2° (c=0.6, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7.6 Hz, $CH_2C\underline{H}_3$), 1.48 (9H, s, $C(CH_3)_3$), 1.61 (2H, q, J=7.6 Hz, $C\underline{H}_2CH_3$), 1.85 (1H, dd, J=13.0, 9.6 Hz, 3-H_α), 1.85 (1H, s, OH), 2.22 (1H, ddd, J=13.0, 7.5, 1.8 Hz, 3-H_β), 2.41 (3H, s, Ar-CH_3), 3.33 (1H, d, J=11.5 Hz, 5-H_β), 3.39 (1H, dd, J=11.5, 1.8 Hz, 5-H_α), 4.32 (1H, dd, J=9.6, 7.5 Hz, 2-H), 7.31 (2H, d, J=8.4 Hz, Ar-H), 7.80 (2H, d, J=8.4 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 8.48 (q), 21.56 (q), 27.92 (q), 30.52 (t), 42.84 (t), 59.80 (t), 61.00 (d), 79.81 (s), 81.82 (s), 127.80 (d), 129.57 (d), 135.34 (s), 143.64 (s), 171.35 (s). IR ν_{max}^{KBr} cm^{-1}: 3502 (OH), 1751 (C=O). MS (FAB) *m/z*: 370 (M^++1). *Anal.* Calcd for $C_{18}H_{27}NO_5S$: C, 58.51; H, 7.37; N, 3.79. Found: C, 58.56; H, 7.24; N, 3.78.

11b: Colorless prisms, mp 126—127 °C, $[\alpha]_D^{26}$ −48.9° (c=1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.4 Hz, $CH_2C\underline{H}_3$), 1.50 (9H, s, $C(CH_3)_3$), 1.56 (2H, q, J=7.4 Hz, $C\underline{H}_2CH_3$), 1.94 (1H, dt, J=13.7, 1.6 Hz, 3-H_α), 2.02 (1H, dd, J=13.7, 10.3 Hz, 3-H_β), 2.44 (3H, s, Ar-CH_3), 3.05 (1H, d, J=9.4 Hz, 5-H_β), 3.45 (1H, dd, J=9.4, 1.6 Hz, 5-H_α), 4.17 (1H, s, OH), 4.19 (1H, d, J=1.6 Hz, 2-H), 7.33 (2H, d, J=8.1 Hz, Ar-H), 7.76 (2H, d, J=8.1 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 8.67 (q), 21.56 (q), 27.81 (q), 30.32 (t), 42.05 (t), 59.96 (t), 60.31 (d), 79.57 (s), 83.17 (s), 127.68 (d), 129.76 (d), 134.57 (s), 143.91 (s), 173.29 (s). IR ν_{max}^{neat} cm^{-1}: 3465 (OH), 1720 (C=O). MS (FAB) *m/z*: 370 (M^++1). *Anal.* Calcd for $C_{18}H_{27}NO_5S$: C, 58.51; H, 7.37; N, 3.79. Found: C, 58.61; H, 7.31; N, 3.74.

***tert*-Butyl (2*S*,4*R*)-4-Butyl-4-hydroxy-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (12a) and *tert*-Butyl (2*S*,4*S*)-4-Butyl-4-hydroxy-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (12b)** Compounds **12a** (136 mg,

17%) and **12b** (588 mg, 74%) were obtained from **6** (679 mg, 2.0 mmol) in a manner similar to that described for **10**, but using 2 M BuMgCl in Et_2O (2.0 ml, 4.0 mmol), a reaction time of 2 h, and column chromatography on silica gel [benzene–AcOEt (15 : 1 then 10 : 1)]. These compounds were recrystallized from *i*-Pr_2O, respectively.

12a: Colorless oil, $[\alpha]_D^{26}$ −45.8° (c=0.8, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7.1 Hz, $(CH_2)_3C\underline{H}_3$), 1.23—1.30 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$), 1.48 (11H, s, $C(CH_3)_3$ and $C\underline{H}_2(CH_2)_2CH_3$), 1.51—1.58 (4H, m, $CH_2C\underline{H}_2CH_2CH_3$), 1.78 (1H, s, OH), 1.86 (1H, dd, J=13.1, 9.9 Hz, 3-H$_\alpha$), 2.22 (1H, ddd, J=13.1, 7.3, 1.8 Hz, 3-H$_\beta$), 2.42 (3H, s, Ar-CH_3), 3.33 (1H, d, J=11.5 Hz, 5-H$_\alpha$), 3.40 (1H, dd, J=11.5, 1.8 Hz, 5-H$_\beta$), 4.32 (1H, dd, J=9.9, 7.3 Hz, 2-H), 7.31 (2H, d, J=8.3 Hz, Ar-H), 7.80 (2H, d, J=8.3 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 13.93 (q), 21.57 (q), 22.96 (t), 26.39 (t), 27.93 (q), 37.47 (t), 43.31 (t), 60.05 (t), 60.89 (d), 79.55 (s), 81.82 (s), 127.81 (d), 129.58 (d), 135.37 (s), 143.66 (s), 171.29 (s). IR ν_{max}^{neat} cm^{-1}: 3485 (OH), 1730 (C=O). MS (FAB) m/z: 398 (M^++1).

12b: Colorless needles, mp 116—117 °C, $[\alpha]_D^{30}$ −41.8° (c=1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7.1 Hz, $(CH_2)_3C\underline{H}_3$), 1.25—1.31 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$), 1.32—1.39 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$), 1.50 (11H, s, $C(CH_3)_3$ and $C\underline{H}_2(CH_2)_2CH_3$), 1.95 (1H, ddd, J=13.7, 1.8, 1.6 Hz, 3-H$_\beta$), 2.02 (1H, dd, J=13.7, 10.3 Hz, 3-H$_\alpha$), 2.44 (3H, s, Ar-CH_3), 3.04 (1H, d, J=9.5 Hz, 5-H$_\alpha$), 3.45 (1H, dd, J=9.5, 1.6 Hz, 5-H$_\beta$), 4.16 (1H, dd, J=10.3, 1.8 Hz, 2-H), 4.18 (1H, s, OH), 7.32 (1H, d, J=8.3 Hz, Ar-H), 7.75 (2H, d, J=8.3 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 13.95 (q), 21.57 (q), 23.05 (q), 26.52 (t), 27.81 (q), 37.29 (t), 42.46 (t), 60.18 (t), 60.21 (d), 79.28 (s), 83.21 (s), 127.70 (d), 129.76 (d), 134.55 (s), 143.91 (s), 173.29 (s). IR ν_{max}^{KBr} cm^{-1}: 3467 (OH), 1718 (C=O). MS (FAB) m/z: 398 (M^++1). *Anal.* Calcd for $C_{18}H_{27}NO_5S$: C, 60.43; H, 7.86; N, 3.52. Found: C, 60.51; H, 7.71; N, 3.38.

***tert*-Butyl (2*S*,4*R*)-4-Hydroxy-4-phenyl-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (13)** Compound **13** (762 mg, 91%) was obtained from **6** (679 mg, 2.0 mmol) in a manner similar to that described for **10**, but using 1 M PhMgBr in THF (4.0 ml, 4.0 mmol), a reaction time of 2 h, and column chromatography on silica gel [benzene–Et_2O (40 : 1)]. The resulting white solid was recrystallized from *i*-PrOH to give colorless needles, 166—168 °C, $[\alpha]_D^{29}$ −80.9° (c=1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.54 (9H, s, $C(CH_3)_3$), 2.25 (1H, dd, J=14.0, 1.6 Hz, 3-H$_\beta$), 2.44 (3H, s, Ar-CH_3), 2.55 (1H, dd, J=14.0, 10.6 Hz, 3-H$_\alpha$), 3.44 (1H, d, J=9.6 Hz, 5-H$_\alpha$), 3.71 (1H, dd, J=9.6, 1.6 Hz, 5-H$_\beta$), 4.35 (1H, dd, J=10.6, 1.6 Hz, 2-H), 4.75 (1H, s, OH), 7.30 (5H, m, Ph), 7.38 (2H, d, J=7.6 Hz, Ar-H), 7.80 (2H, d, J=7.6 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 21.59 (q), 27.85 (q), 44.01 (t), 60.27 (d), 61.67 (t), 79.91 (s), 83.51 (s), 125.24 (d), 127.78 (d), 127.91 (d), 128.46 (d), 129.84 (s), 134.44 (d), 140.18 (s), 144.08 (s), 173.12 (s). IR ν_{max}^{KBr} cm^{-1}: 3398 (OH), 1703 (C=O). MS (FAB) m/z: 418 (M^++1). *Anal.* Calcd for $C_{22}H_{27}NO_5S$: C, 63.29; H, 6.52; N, 3.35. Found: C, 63.16; H, 6.45; N, 3.37.

Methyl 4-Methylpyrrole-2-carboxylate (4) Thionyl chloride (0.61 ml, 7.9 mmol) was added dropwise to MeOH (5 ml) at −10 °C. After 30 min, compound **10b** (200 mg, 0.56 mmol) was added to the solution. The whole was stirred at room temperature for 24 h and the reaction mixture was concentrated under reduced pressure. MeOH (15 ml) was added to the residue and the solution was concentrated under reduced pressure. This operation was repeated 3 times. The residual oil was dissolved in MeOH (3 ml) and 28% NaOMe solution (3 ml) was added. Then the mixture was stirred at room temperature for 1.5 h. A sufficient amount of carbon dioxide was bubbled into the mixture and the mixture was concentrated under reduced pressure. Water (20 ml) was added to the residue at 0 °C and the whole was extracted with AcOEt (20 ml×2). The organic layer was washed with brine (20 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (AcOEt) to give **4** (43 mg, 56%) as a white solid. It was recrystallized from cyclohexane to give colorless needles, mp 73—74 °C, (lit.[25] mp 73—74 °C). ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s, CH_3), 3.84 (3H, s, OCH_3), 6.72 (2H, s, 3-H and 5-H), 9.20 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 11.67 (q), 51.36 (q), 116.12 (d), 120.94 (s), 121.50 (d), 122.16 (s), 161.79 (s). IR ν_{max}^{neat} cm^{-1}: 3283 (NH), 1673 (C=O). MS m/z: 139 (M^+).

Methyl 4-Ethylpyrrole-2-carboxylate (14) Compound **14** (47 mg, 55%) was obtained from **11b** (207 mg, 0.56 mmol) in a manner similar to that described for **4** but with column chromatography on silica gel [hexane–AcOEt (1 : 1)]. It was recrystallized from hexane to give colorless needles, mp 56—57 °C, (lit.[11] mp 56—57 °C). ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, t, J=7.6 Hz, $CH_2C\underline{H}_3$), 2.50 (2H, q, J=7.6 Hz, $C\underline{H}_2CH_3$), 3.84 (3H, s, CO_2CH_3), 6.76 (2H, s, 3-H and 5-H), 8.87 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 15.17 (q), 19.86 (t), 51.35 (q), 114.56 (d), 120.08 (d), 122.23 (s), 128.42 (s), 161.57 (s). IR ν_{max}^{KBr} cm^{-1}: 3292 (NH), 1685 (C=O). MS m/z: 153 (M^+).

Methyl 4-Butylpyrrole-2-carboxylate (15) Compound **15** (56 mg, 55%) was obtained from **12b** (223 mg, 0.56 mmol) in a manner similar to that described for **4** but with column chromatography on silica gel [hexane–AcOEt (2 : 1)]. It was recrystallized from hexane to give colorless needles, mp 63—64 °C, (lit.[11] mp 59—60 °C). ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.3 Hz, $(CH_2)_3C\underline{H}_3$), 1.31—1.39 (2H, m, $(CH_2)_2C\underline{H}_2CH_3$), 1.51—1.57 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$), 2.46 (2H, t, J=7.3 Hz, benzylic H), 3.83 (3H, s, CO_2CH_3), 6.73 (1H, s, 3-H), 6.75 (1H, s, 5-H), 8.95 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 13.92 (q), 22.30 (t), 26.36 (t), 33.12 (t), 51.34 (q), 115.04 (d), 120.65 (d), 122.14 (s), 126.81 (s), 161.63 (s). IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1693 (C=O). MS m/z: 181 (M^+).

Methyl 4-Phenylpyrrole-2-carboxylate (16) Compound **16** (89 mg, 79%) was obtained from **13** (234 mg, 0.56 mmol) in a manner similar to that described for **4**. It was recrystallized from *i*-Pr_2O to give colorless prisms, mp 197—198 °C, (lit.[26] mp 176—180 °C). ^{1}H-NMR ($CDCl_3$) δ: 3.89 (3H, s, OCH_3), 7.20—7.25 (3H, m, Ar-H), 7.36 (2H, m, Ar-H), 7.52 (2H, m, 3-H and 5-H), 9.17 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 51.61 (q), 112.55 (d), 119.51 (d), 123.42 (s), 125.31 (d), 126.34 (d), 126.94 (s), 128.79 (d), 134.48 (s), 161.56 (s). IR ν_{max}^{KBr} cm^{-1}: 3280 (NH), 1677 (C=O). MS m/z: 201 (M^+). *Anal.* Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.46; H, 5.64; N, 6.97.

***tert*-Butyl 4-Methylpyrrole-2-carboxylate (17)** Thionyl chloride (4.0 ml, 55 mmol) was added dropwise to a solution of compound **10b** (200 mg, 0.56 mmol) in pyridine (12 ml) and the whole was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure. Toluene (12 ml) was added and the solution was concentrated under reduced pressure. This operation was repeated once. Water (20 ml) was added to the residue and the whole was extracted with benzene (20 ml×2). The organic layer was washed with brine (20 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in toluene (6 ml) and DBU (0.5 ml, 3.3 mmol), and the solution was refluxed for 12 h. The mixture was concentrated under reduced pressure and the residue was subjected to column chromatography on silica gel [hexane–AcOEt (10 : 1)] to give **17** (79 mg, 77%) as a white solid. It was recrystallized from hexane to give colorless prisms, mp 113—114 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.59 (9H, s, $C(CH_3)_3$), 2.10 (3H, s, CH_3), 6.66 (1H, s, 3-H), 6.68 (1H, s, 5-H), 9.08 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 11.69 (q), 28.39 (q), 80.57 (s), 115.40 (d), 120.55 (d), 120.64 (s), 123.98 (s), 160.82 (s). IR ν_{max}^{KBr} cm^{-1}: 3323 (NH), 1676 (C=O). MS (FAB) m/z: 182 (M^++1). *Anal.* Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.36; H, 8.40; N, 7.70.

***tert*-Butyl 4-Ethylpyrrole-2-carboxylate (18)** Compound **18** (90 mg, 82%) was obtained from **11b** (207 mg, 0.56 mmol) in a manner similar to that described for **17**. It was recrystallized from hexane to give colorless prisms, mp 75—76 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, t, J=7.6 Hz, $CH_2C\underline{H}_3$), 1.55 (9H, s, $C(CH_3)_3$), 2.49 (2H, q, J=7.6 Hz, $C\underline{H}_2CH_3$), 6.69 (2H, s, 3-H and 5-H), 9.03 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 15.28 (q), 19.91 (t), 28.40 (q), 80.57 (s), 113.89 (d), 119.41 (d), 123.97 (s), 128.07 (s), 160.79 (s). IR ν_{max}^{KBr} cm^{-1}: 3319 (NH), 1672 (C=O). MS (FAB) m/z: 196 (M^++1). *Anal.* Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.89; H, 8.72; N, 7.14.

***tert*-Butyl 4-Butylpyrrole-2-carboxylate (19)** Compound **19** (75 mg, 60%) was obtained from **12b** (223 mg, 0.56 mmol) in a manner similar to that described for **17**. It was recrystallized from hexane to give colorless prisms, mp 70—71 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7.4 Hz, $(CH_2)_3C\underline{H}_3$), 1.33 (2H, m, $(CH_2)_2C\underline{H}_2CH_3$), 1.55 (11H, s, $C(CH_3)_3$ and $CH_2C\underline{H}_2CH_2CH_3$), 2.45 (2H, t, J=7.7 Hz, $C\underline{H}_2(CH_2)_2CH_3$), 6.67 (2H, s, 3-H and 5-H), 8.87 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 13.93 (q), 22.36 (t), 26.43 (t), 28.41 (q), 33.22 (t), 80.56 (s), 114.35 (d), 119.79 (d), 123.96 (s), 126.55 (s), 160.69 (s). IR ν_{max}^{KBr} cm^{-1}: 3315 (NH), 1676 (C=O). MS (FAB) m/z: 224 (M^++1). *Anal.* Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.94; H, 9.29; N, 6.15.

***tert*-Butyl 4-Phenylpyrrole-2-carboxylate (20)** Compound **20** (56 mg, 41%) was obtained from **13** (234 mg, 0.56 mmol) in a manner similar to that described for **17**. It was recrystallized from hexane to give a white powder, mp 94—95 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.60 (9H, s, $C(CH_3)_3$), 7.12 (1H, m, Ar-H), 7.20 (2H, s, 3-H and 5-H), 7.35 (2H, t, J=8.0 Hz, Ar-H), 7.52 (2H, d, J=8.0 Hz, Ar-H), 9.45 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 28.41 (q), 81.14 (s), 111.95 (d), 118.88 (d), 125.13 (s), 125.30 (d), 126.15 (d), 126.61 (s), 128.72 (d), 134.77 (s), 160.79 (s). IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1678 (C=O). HR-MS (FAB) m/z: 243.1260 (Calcd for $C_{15}H_{17}NO_2$: 243.1259).

Methyl (2*S*)-4-Methylene-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (21) Ph_3P–CH_3Br (2.20 g, 6.2 mmol) was heated at 120 °C under reduced pressure for 1 h, then heated in a stream of dry N_2 at 120 °C. Under an

argon atmosphere, Et_2O (15 ml) and 1.9 M PhLi (1.8 ml, 3.4 mmol) were added and stirred at room temperature for 4 h. A solution of **5** (893 mg, 3.00 mmol) in THF (5 ml) was added and the mixture was stirred at room temperature for 30 h. The mixture was cooled at 0 °C and neutralized with 10% aqueous citric acid. The whole was extracted with AcOEt (30 ml) and water (20 ml). The aqueous layer was extracted with AcOEt (20 ml×3) and the combined organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residual reddish brown oil was subjected to flash chromatography on silica gel [hexane–$CHCl_3$ (1 : 1), then hexane–Et_2O (3 : 1)] to give **21** (91 mg, 10%) as a colorless oil. Colorless oil, $[\alpha]_D^{23}$ −30.8° (c=0.7, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.42 (3H, s, Ar-CH_3), 2.62 (1H, d, J=14.2, 3.5 Hz, 3-H$_\beta$), 2.75 (1H, m, 3-H$_\alpha$), 3.65 (3H, s, CO_2CH_3), 4.02 (2H, s, 5-H), 4.45 (1H, dd, J=9.2, 3.5 Hz, 2-H), 4.96 (2H, s, olefinic H), 7.31 (2H, d, J=8.4 Hz, Ar-H), 7.73 (2H, d, J=8.4 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 21.56 (q), 36.92 (t), 51.75 (t), 52.44 (q), 60.45 (d), 108.65 (t), 127.49 (d), 129.72 (d), 134.99 (s), 141.94 (s), 143.85 (s), 171.80 (s). IR ν_{max}^{neat} cm^{-1}: 1741 (C=O). HR-MS (FAB) m/z: 296.0957 (Calcd for $C_{14}H_{18}NO_4S$: 296.0957).

***tert*-Butyl (2*S*)-4-Methylene-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (22)** Under an argon atmosphere, 0.5 M Tebbe reagent in toluene (4.0 ml, 2.0 mmol) was added dropwise to a solution of **6** (339 mg, 1.00 mmol) in THF (10 ml) and the mixture was stirred at −70 °C for 4 h, then at 0 °C for 1 h. Water (5 ml) was added and the insoluble material was filtered out using Hyflo Super-Cel®. The filtrate was extracted with AcOEt (80 ml×2). The organic layer was washed with water (50 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residual reddish brown oil was subjected to flash chromatography on silica gel [hexane–AcOEt (6 : 1), then hexane–$CHCl_3$ (1 : 3)] to give **22** (54 mg, 16%) as a pale yellow oil and **23** (78 mg, 22%) as a white solid, which was recrystallized from hexane to give a white powder, mp 76—77 °C.

22: $[\alpha]_D^{31}$ −38.8° (c=0.4, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.41 (9H, s, $C(CH_3)_3$), 2.42 (3H, s, Ar-CH_3), 2.55 (1H, dd, J=15.8, 3.2 Hz, 3-H$_\beta$), 2.76 (1H, dd, J=15.8, 9.0 Hz, 3-H$_\alpha$), 4.02 (2H, s, olefinic H), 4.35 (1H, dd, J=3.2, 9.0 Hz, 2-H), 4.96 (2H, m, 5-H), 7.30 (2H, d, J=8.1 Hz, Ar-H), 7.74 (2H, d, J=8.1 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 21.53 (q), 27.83 (q), 37.29 (t), 51.72 (t), 61.22 (d), 81.96 (s), 108.20 (t), 127.46 (d), 129.64 (d), 135.73 (s), 142.54 (s), 143.56 (s), 170.45 (s). IR ν_{max}^{neat} cm^{-1}: 1743 (C=O). HR-MS (FAB) m/z: 338.1424 (Calcd for $C_{17}H_{23}NO_4S$: 338.1426).

23: $[\alpha]_D^{25}$ −85.7° (c=0.4, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.75 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.48 (9H, s, $C(CH_3)_3$), 1.76 (1H, dd, J=8.2, 17.6 Hz, 3-Ha), 1.95 (1H, dd, J=8.2, 17.6 Hz, 3-Hb), 2.42 (3H, s, Ar-CH_3), 3.13 (2H, m, 5-H), 4.17 (1H, t, J=8.2 Hz, 2-H), 7.30 (2H, d, J=8.1 Hz, Ar-H), 7.79 (2H, d, J=8.1 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 21.53 (q), 25.78 (q), 27.91 (q), 38.74 (s), 44.57 (t), 60.52 (t), 61.24 (d), 81.56 (s), 127.62 (d), 129.51 (d), 135.64 (s), 143.39 (s), 171.56 (s). IR ν_{max}^{KBr} cm^{-1}: 1745 (C=O). MS (FAB) m/z: 354 (M^++1). *Anal.* Calcd for $C_{18}H_{27}NO_4S$: C, 61.16; H, 7.70; N, 3.96. Found: C, 61.14; H, 7.56; N, 4.01.

Methyl (2*S*,4*E*)-4-Ethoxycarbonylmethylene-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (24a) and Methyl (2*S*,4*Z*)-4-Ethoxycarbonylmethylene-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (24b) THF (10 ml) was added to 60% NaH in oil (168 mg, 4.2 mmol), which was washed beforehand with hexane to remove the oil. Under an argon atmosphere, triethyl phosphonoacetate (1.12 g, 5.00 mmol) was added and the whole was stirred at room temperature for 2 h. After the mixture was cooled at −40 °C, a solution of **5** (297 mg, 1.00 mmol) in THF (5 ml) was added dropwise and the whole was stirred for 1 h. A sufficient amount of carbon dioxide was bubbled into the mixture and the mixture was concentrated under reduced pressure. Water (20 ml) was added to the residue at 0 °C and the whole was extracted with benzene (20 ml×3). The organic layer was washed with brine (20 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residual yellow oil was subjected to column chromatography on silica gel [hexane–AcOEt (4 : 1)] to give **24a** (177 mg, 48%) as a colorless oil, and then **24b** (163 mg, 44%) as a colorless oil.

24a: $[\alpha]_D^{29}$ −6.8° (c=1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 2.43 (3H, s, Ar-CH_3), 3.13 (1H, dd, J=19.0, 9.4 Hz, 3-H$_\alpha$), 3.32 (1H, br d, J=19.0 Hz, 3-H$_\beta$), 3.64 (3H, s, $COOCH_3$), 4.13 (2H, q, J=7.1 Hz, $C\underline{H}_2CH_3$), 4.22 (1H, d, J=16.0 Hz, 5-H$_\beta$), 4.24 (1H, d, J=16.0 Hz, 5-H$_\alpha$), 4.54 (1H, dd, J=9.0, 2.9 Hz, 2-H), 5.80(1H, br s, olefinic H), 7.32 (2H, d, J=7.9 Hz, Ar-H), 7.72 (2H, d, J=7.9 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 14.22 (q), 21.55 (q), 35.89 (t), 52.45 (q), 53.11 (t), 60.24 (t), 60.57 (d), 113.83 (d), 127.48 (d), 129.84 (d), 134.70 (s), 144.14 (s), 155.42 (s), 165.54 (s), 171.39 (s). IR ν_{max}^{neat} cm^{-1}: 1743, 1712 (C=O). HR-MS m/z: 367.1093 (Calcd for $C_{17}H_{21}NO_6S$: 367.1090).

24b: $[\alpha]_D^{29}$ −12.5° (c=1.1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 2.43 (3H, s, Ar-CH_3), 2.82 (1H, br d, J=17.4 Hz, 3-H$_\beta$), 2.94 (1H, ddd, J=17.4, 8.9, 1.1 Hz, 3-H$_\alpha$), 3.62 (3H, s, $COOC\underline{H}_3$), 4.15 (2H, q, J=7.1 Hz, $C\underline{H}_2CH_3$), 4.46—4.58 (3H, m, 2-H and 5-H), 5.78 (1H, s, olefinic H), 7.32 (2H, d, J=8.3 Hz, Ar-H), 7.32 (2H, d, J=8.3 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 14.21 (q), 21.56 (q), 37.91 (t), 52.03 (t), 52.47 (q), 59.03 (d), 60.34 (t), 114.29 (d), 127.52 (d), 129.77 (d), 134.99 (s), 143.96 (s), 155.74 (s), 165.40 (s), 171.18 (s). IR ν_{max}^{neat} cm^{-1}: 1745, 1711 (C=O). HR-MS m/z: 367.1092 (Calcd for $C_{17}H_{21}NO_6S$: 367.1090).

***tert*-Butyl (2*S*,4*E*)-4-Ethoxycarbonylmethylene-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (25a), *tert*-Butyl (2*S*,4*Z*)-4-Ethoxycarbonylmethylene-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (25b), *tert*-Butyl (2*S*)-4-Ethoxycarbonylmethyl-1-*p*-toluenesulfonyl-3-pyrroline-2-carboxylate (25c), and *tert*-Butyl (2*S*)-4-Ethoxycarbonylmethyl-1-*p*-toluenesulfonyl-4-pyrroline-2-carboxylate (25d)** THF (10 ml) was added to 60% NaH in oil (168 mg, 4.2 mmol), which was washed beforehand with hexane to remove the oil. Under an argon atmosphere, triethyl phosphonoacetate (1.12 g, 5.00 mmol) was added and the whole was stirred at room temperature for 2 h. After the mixture was cooled at 0 °C, a solution of **6** (339 mg, 1.00 mmol) in THF (5 ml) was added dropwise and the whole was stirred for 1 h. A sufficient amount of carbon dioxide was bubbled into the mixture and the mixture was concentrated under reduced pressure. Water (20 ml) was added to the residue at 0 °C and the whole was extracted with benzene (20 ml×3). The organic layer was washed with brine (20 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residual yellow oil was subjected to column chromatography on silica gel [hexane–Et_2O (4 : 1)] to give **25a** (152 mg, 37%) as a colorless oil, then **25b** (123 mg, 30%) as a colorless oil, then **25d** (9 mg, 3%) as a pale yellow oil, and then **25c** (124 mg, 30%) as a pale yellow oil.

25a: $[\alpha]_D^{21}$ −9.2° (c=0.72, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 1.40 (9H, s, $C(CH_3)_3$), 2.42 (3H, s, Ar-CH_3), 3.11 (1H, ddd, J=19.0, 9.2, 0.9 Hz, 3-H$_\alpha$), 3.28 (1H, br d, J= 19.0 Hz, 3-H$_\beta$), 4.14 (2H, q, J=7.1 Hz, $C\underline{H}_2CH_3$), 4.22 (1H, d, J=16.5 Hz, 5-Ha), 4.24 (1H, d, J=16.5 Hz, 5-Hb), 4.42 (1H, dd, J=9.2, 3.2 Hz, 2-H), 5.79 (1H, m, olefinic H), 7.32 (2H, d, J=8.0 Hz, Ar-H), 7.73 (2H, d, J=8.0 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 14.23 (q), 21.55 (q), 27.81 (q), 36.06 (t), 53.15 (t), 60.20 (t), 61.41 (d), 82.31 (s), 113.59 (d), 127.49 (d), 129.76 (d), 135.32 (s), 143.91 (s), 156.05 (s), 165.65 (s), 170.18 (s). IR ν_{max}^{neat} cm^{-1}: 1736, 1712 (C=O). HR-MS (FAB) m/z: 410.1634 (Calcd for $C_{20}H_{28}NO_6S$: 410.1637).

25b: $[\alpha]_D^{17}$ −16.6° (c=0.70, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 1.40 (9H, s, $C(CH_3)_3$), 2.42 (3H, s, Ar-CH_3), 3.12 (1H, dd, J=19.0, 9.2 Hz, 3-H$_\beta$), 3.28 (1H, d, J=19.0 Hz, 3-H$_\alpha$), 4.13 (2H, q, J=7.1 Hz, $C\underline{H}_2CH_3$), 4.23 (2H, d, J=3.3 Hz, 5-H), 4.42 (1H, dd, J=9.2, 3.3 Hz, 2-H), 5.78 (1H, s, olefinic H), 7.30 (2H, d, J=8.3 Hz, Ar-H), 7.73 (2H, d, J=8.3 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 14.23 (q), 21.55 (q), 27.81 (q), 36.06 (t), 53.15 (t), 60.21 (t), 61.42 (d), 82.31 (s), 113.60 (d), 127.49 (d), 129.77 (d), 135.31 (s), 143.91 (s), 156.05 (s), 165.65 (s), 170.18 (s). IR ν_{max}^{neat} cm^{-1}: 1736, 1712 (C=O). HR-MS (FAB) m/z: 410.1635 (Calcd for $C_{20}H_{28}NO_6S$: 410.1637).

25c: $[\alpha]_D^{23}$ −138.7° (c=0.7, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.2 Hz, $CH_2C\underline{H}_3$), 1.47 (9H, s, $C(CH_3)_3$), 2.42 (3H, s, Ar-CH_3), 3.07 (1H, d, J=16.3 Hz, $C\underline{H}_2COOEt$), 3.12 (1H, d, J=16.3 Hz, $C\underline{H}_2COOEt$), 4.11 (2H, q, J=7.1 Hz, $C\underline{H}_2CH_3$), 4.17 (1H, br dd, J=13.7, 5.7 Hz, 5-Ha), 4.22 (1H, d, J=13.7 Hz, 5-Hb), 4.98 (1H, d, J=2.1 Hz, 2-H), 5.53 (1H, dd, J=5.7, 2.1 Hz, 3-H), 7.31 (2H, d, J=8.1 Hz, Ar-H), 7.79 (2H, d, J=8.1 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 14.09 (q), 21.55 (q), 27.96 (q), 34.57 (t), 56.54 (t), 61.15 (t), 68.97 (d), 82.26 (s), 122.23 (d), 127.59 (d), 129.68 (d), 134.80 (s), 135.51 (s), 143.63 (s), 168.79 (s), 169.20 (s). IR ν_{max}^{neat} cm^{-1}: 1738 (C=O). HR-MS (FAB) m/z: 410.1639 (Calcd for $C_{20}H_{28}NO_6S$: 410.1637).

25d: $[\alpha]_D^{23}$ −120.9° (c=0.3, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 1.49 (9H, s, $C(CH_3)_3$), 2.43 (3H, s, Ar-CH_3), 2.62 (1H, dd, J=16.0, 7.1 Hz, 3-H$_\beta$), 2.79 (1H, dd, J=16.0, 11.5 Hz, 3-H$_\alpha$), 3.01 (1H, d, J=16.5 Hz, $C\underline{H}_2COOEt$), 3.03 (1H, d, J=16.5 Hz, $C\underline{H}_2COOEt$), 4.10 (2H, q, J=7.2 Hz, $C\underline{H}_2CH_3$), 4.15 (1H, dd, J=11.5, 7.1 Hz, 2-H), 6.28 (1H, s, 5-H), 7.31 (2H, d, J=8.2 Hz, Ar-H), 7.70 (2H, d, J=8.2 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 14.12 (q), 21.59 (q), 27.90 (q), 33.55 (t), 37.61 (t), 60.88 (t), 61.31 (d), 82.19 (s), 116.56 (s), 127.44 (s), 127.75 (s), 129.74 (d), 133.70 (s), 144.04 (s), 169.84 (s), 169.92 (s). IR ν_{max}^{neat} cm^{-1}: 1738 (C=O). HR-MS m/z: 409.1557 (Calcd for $C_{20}H_{27}NO_6S$: 409.1559).

Methyl (2*S*,4*E*)-4-Cyanomethylene-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (26a) and Methyl (2*S*,4*Z*)-4-Cyanomethylene-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (26b) Compound **5** (297 mg, 1.00 mmol) was treated in a manner similar to that described for **24**, but using diethyl cyanomethylphosphonate (886 mg, 5.00 mmol) and column chromatography on silica gel [hexane–Et_2O (1 : 1)], giving pyrrole derivative **28** (5 mg, 3%),

then **26a** (118 mg, 37%) as a white solid, and then **26b** (107 mg, 33%) as a white solid. Compounds **26a** and **26b** were recrystallized from *i*-Pr_2O-AcOEt, respectively.

26a: Colorless needles, mp 80—82 °C, $[\alpha]_D^{21}$ +9.4° (c=0.8, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s, Ar-CH_3), 2.98—3.02 (2H, m, 3-H), 3.66 (3H, s, $COOCH_3$), 4.23 (1H, d, J=16.5 Hz, 5-Ha), 4.27 (1H, d, J=16.5 Hz, 5-Hb), 4.60 (1H, t, J=6.1 Hz, 2-H), 5.34 (1H, m, olefinic H), 7.34 (2H, d, J=8.3 Hz, Ar-H), 7.71 (2H, d, J=8.3 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 21.60 (q), 36.70 (t), 52.14 (q), 52.73 (t), 59.81 (d), 93.73 (d), 115.31 (s), 127.44 (d), 129.95 (d), 134.62 (s), 144.50 (s), 161.30 (s), 170.62 (s). IR ν_{max}^{KBr} cm^{-1}: 2216 (CN), 1736 (C=O). MS *m/z*: 320 (M^+). *Anal.* Calcd for $C_{15}H_{16}N_2O_4S$: C, 56.24; H, 5.03; N, 8.74. Found: C, 56.10; H, 5.04; N, 8.72.

26b: Colorless needles, mp 102—104 °C, $[\alpha]_D^{21}$ −21.7° (c=0.7, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s, Ar-CH_3), 2.82 (1H, dd, J=17.6, 1.1 Hz, 3-H_β), 2.96 (1H, dd, J=17.6, 8.9 Hz, 3-H_α), 3.63 (3H, s, $COOCH_3$), 4.30 (1H, d, J=16.6 Hz, 5-H_α), 4.36 (1H, d, J=16.6 Hz, 5-H_β), 4.61 (1H, dd, J=8.9, 3.0 Hz, 2-H), 5.33 (1H, s, olefinic H), 7.35 (2H, d, J=8.2 Hz, Ar-H), 7.73(2H, d, J=8.2 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 21.60 (q), 37.25 (t), 51.83 (t), 52.67 (q), 60.15 (d), 93.56 (d), 115.04 (s), 127.50 (d), 129.94 (d), 134.65 (s), 144.44 (s), 161.53 (s), 170.60 (s). IR ν_{max}^{KBr} cm^{-1}: 2222 (CN), 1753 (C=O). MS *m/z*: 320 (M^+). *Anal.* Calcd for $C_{15}H_{16}N_2O_4S$: C, 56.24; H, 5.03; N, 8.74. Found: C, 56.22; H, 5.11; N, 8.68.

***tert*-Butyl (2*S*,4*E*)-4-Cyanomethylene-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (27a) and *tert*-Butyl (2*S*,4*Z*)-4-Cyanomethylene-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (27b)** Compound **6** (339 mg, 1.00 mmol) was treated in a manner similar to that described for **25**, but using diethyl cyanomethylphosphonate (886 mg, 5.00 mmol) and column chromatography on silica gel [hexane–Et_2O (2 : 1)], giving pyrrole derivative **29** (4 mg, 5%), then **27a** (174 mg, 48%) as a white solid, and then **27b** (131 mg, 36%) as a white solid. Compounds **27a** and **27b** were recrystallized from hexane–AcOEt, respectively.

27a: Colorless needles, mp 96—97 °C, $[\alpha]_D^{17}$ +9.9° (c=0.7, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.41 (9H, s, $C(CH_3)_3$), 2.44 (3H, s, Ar-CH_3), 2.94 (1H, br d, J=17.9 Hz, 3-H_β), 2.98 (1H, ddd, J=17.9, 8.5, 1.6 Hz, 3-H_α), 4.24 (1H, dd, J=16.5, 1.1 Hz, 5-Ha), 4.26 (1H, dd, J=16.5, 1.8 Hz, 5-Hb), 4.49 (1H, dd, J=8.5, 3.2 Hz, 2-H), 5.32 (1H, m, olefinic H), 7.32 (2H, d, J=8.1 Hz, Ar-H), 7.72 (2H, d, J=8.1 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 21.58 (q), 27.80 (q), 37.03 (t), 52.15 (t), 60.70 (d), 82.95 (s), 93.46 (d), 115.37 (s), 127.44 (d), 129.90 (d), 135.16 (s), 144.29 (s), 161.90 (s), 169.36 (s). IR ν_{max}^{neat} cm^{-1}: 2222 (CN), 1739 (C=O). MS (FAB) *m/z*: 363 (M^++1). *Anal.* Calcd for $C_{18}H_{22}N_2O_4S$: C, 59.65; H, 6.12; N, 7.73. Found: C, 59.56; H, 6.18; N, 7.77.

27b: Colorless needles, mp 120—121 °C, $[\alpha]_D^{17}$ −37.2° (c=0.6, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.38 (9H, s, $C(CH_3)_3$), 2.44 (3H, s, Ar-CH_3), 2.75 (1H, br d, J=17.6 Hz, 3-H_β), 2.96 (1H, dd, J=17.6, 9.0 Hz, 3-H_α), 4.34 (1H, br d, J=16.6 Hz, 5-H_β), 4.37 (1H, dd, J=16.6, 1.1 Hz, 5-H_α), 4.49 (1H, ddd, J=9.0, 2.5, 1.6 Hz, 2-H), 5.33 (1H, m, olefinic H), 7.33 (2H, d, J=8.1 Hz, Ar-H), 7.74 (2H, d, J=8.1 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 21.56 (q), 27.76 (q), 37.59 (t), 51.85 (t), 61.08 (d), 82.88 (s), 93.19 (d), 115.07 (s), 127.47 (d), 129.90 (d), 135.22 (s), 144.23 (s), 162.21 (s), 169.32 (s). IR ν_{max}^{KBr} cm^{-1}: 2220 (CN), 1743 (C=O). MS (FAB) *m/z*: 363 (M^++1). *Anal.* Calcd for $C_{18}H_{22}N_2O_4S$: C, 59.65; H, 6.12; N, 7.73. Found: C, 59.65; H, 6.14; N, 7.72.

Treatments of 21 with Bases Method a: DBU (0.21 ml, 1.4 mmol) was added to a solution of **21** (59 mg, 0.20 mmol) in toluene (1 ml) and the mixture was refluxed for 12 h. After cooling, the mixture was concentrated under reduced pressure and the residual brown oil was subjected to column chromatography on silica gel (AcOEt) to give **4** (27 mg, 97%).

Method b: To a solution of **21** (86 mg, 0.29 mmol) in THF (2 ml), 1 M *t*-BuOK in THF (0.7 ml) was added and the resulting solution was stirred at room temperature for 1 h. A sufficient amount of carbon dioxide was bubbled into the mixture and the mixture was concentrated under reduced pressure. Water (15 ml) was added to the residue at 0 °C and the whole was extracted with $CHCl_3$ (15 ml×2). The organic layer was washed with water (5 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel [hexane–AcOEt (3 : 1)] to give **4** (31 mg, 77%).

Treatments of 22 with Bases Method a: DBU (0.21 ml, 1.4 mmol) was added to a solution of **22** (68 mg, 0.20 mmol) in toluene (1 ml) and the mixture was refluxed for 12 h. After cooling, the mixture was concentrated under reduced pressure and the residual brown oil was subjected to column chromatography on silica gel [hexane–AcOEt (3 : 1)] to give **17** (36 mg, 99%).

Method b: To a solution of **22** (96 mg, 0.29 mmol) in THF (2 ml), 1 M *t*-BuOK in THF (0.7 ml) was added and the resulting solution was stirred at room temperature for 1 h. A sufficient amount of carbon dioxide was bubbled into the mixture and the mixture was concentrated under reduced pressure. Water (15 ml) was added to the residue at 0 °C and the whole was extracted with $CHCl_3$ (15 ml×2). The organic layer was washed with water (5 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel [hexane–AcOEt (3 : 1)] to give **17** (44 mg, 85%).

Methyl 4-(Ethoxycarbonylmethyl)pyrrole-2-carboxylate (28) DBU (0.21 ml, 1.4 mmol) was added to a solution of **24a** (72 mg, 0.20 mmol) in toluene (1 ml) and the mixture was stirred at room temperature for 1 h. It was concentrated under reduced pressure and the residual brown oil was subjected to column chromatography on silica gel (AcOEt) to give **28** (40 mg, 97%) as a white solid. It was recrystallized from hexane–AcOEt to give colorless needles, mp 66—68 °C, (lit.[27] mp 64—65 °C). ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 3.49 (2H, s, $C\underline{H}_2CO_2Et$), 3.84 (3H, s, $CO_2C\underline{H}_3$), 4.16 (2H, q, J=7.1 Hz, $C\underline{H}_2CH_3$), 6.85 (1H, s, 3-H), 6.91 (1H, s, 5-H), 9.41 (1H, s, NH). ^{13}C-NMR ($CDCl_3$) δ: 14.21 (q), 32.82 (t), 51.45 (q), 60.83 (t), 115.73 (d), 117.74 (s), 122.13 (d), 122.54 (s), 161.63 (s), 171.91 (s). IR ν_{max}^{KBr} cm^{-1}: 3325 (NH), 1736, 1689 (C=O). MS *m/z*: 211 (M^+). *Anal.* Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.87; H, 6.15; N, 6.59.

***tert*-Butyl 4-(Ethoxycarbonylmethyl)pyrrole-2-carboxylate (29)** DBU (0.21 ml, 1.4 mmol) was added to a solution of **25a** (82 mg, 0.20 mmol) in toluene (1 ml) and the mixture was refluxed for 1 h. After cooling, the mixture was concentrated under reduced pressure and the residual brown oil was subjected to column chromatography on silica gel [benzene–Et_2O (5 : 1)] to give **29** (50 mg, 99%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 1.55 (9H, s, $C(CH_3)_3$), 3.48 (2H, s, benzylic H), 4.16 (2H, q, J=7.1 Hz, $CO_2C\underline{H}_2CH_3$), 6.77 (1H, s, 3-H), 6.86 (1H, s, 5-H), 9.29 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 14.21 (q), 28.37 (q), 32.84 (t), 60.79 (t), 80.85 (s), 115.03 (d), 117.44 (s), 121.24 (d), 124.35 (s), 160.71 (s), 172.00 (s). IR ν_{max}^{neat} cm^{-1}: 3311 (NH), 1738, 1678 (C=O). HR-MS *m/z*: 253.1315 (Calcd for $C_{13}H_{19}NO_4S$: 253.1314).

Methyl 4-Cyanomethylpyrrole-2-carboxylate (30) DBU (0.21 ml, 1.4 mmol) was added to a solution of **26a** (65 mg, 0.20 mmol) in toluene (1 ml) and the mixture was stirred at room temperature for 1 h. It was concentrated under reduced pressure and the residual brown oil was subjected to column chromatography on silica gel [hexane–Et_2O (4 : 1)] to give **30** (33 mg, 99%) as a white solid. It was recrystallized from hexane–AcOEt to give colorless prisms, mp 92—93 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.60 (2H, s, $C\underline{H}_2CN$), 3.86 (3H, s, $CO_2C\underline{H}_3$), 6.85 (1H, s, 3-H), 6.70 (1H, s, 5-H), 9.74 (1H, s, NH). ^{13}C-NMR ($CDCl_3$) δ: 15.76 (t), 51.75 (q), 113.95 (s), 114.48 (d), 118.25 (s), 121.51 (d), 123.34 (s), 161.47 (s). IR ν_{max}^{KBr} cm^{-1}: 3303 (NH), 2249 (CN), 1685 (C=O). MS *m/z*: 164 (M^+). *Anal.* Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.50; H, 5.02; N, 17.04.

***tert*-Butyl 4-Cyanomethylpyrrole-2-carboxylate (31)** DBU (0.21 ml, 1.4 mmol) was added to a solution of **27a** (73 mg, 0.20 mmol) in toluene (1 ml) and the mixture was refluxed for 1 h. After cooling, the mixture was concentrated under reduced pressure and the residual brown oil was subjected to column chromatography on silica gel [benzene–Et_2O (5 : 1)] to give **31** (41 mg, 99%) as a white solid. It was recrystallized from hexane–AcOEt to give colorless needles, mp 112—113 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.57 (9H, s, $C(CH_3)_3$), 3.59 (2H, s, $C\underline{H}_2CN$), 6.78 (1H, s, 3-H), 6.90 (1H, s, 5-H), 9.61 (1H, s, NH). ^{13}C-NMR ($CDCl_3$) δ: 15.80 (t), 28.34 (q), 81.45 (s), 113.64 (s), 113.89 (d), 118.28 (s), 120.63 (d), 125.16 (s), 160.50 (s). IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 2252 (CN), 1662 (C=O). MS (FAB) *m/z*: 207 (M^++1). *Anal.* Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.20; H, 6.85; N, 13.67.

***tert*-Butyl (2*S*,4*R*)-4-Ethoxycarbonylmethyl-4-hydroxy-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (32a) and *tert*-Butyl (2*S*,4*S*)-4-Ethoxycarbonylmethyl-4-hydroxy-1-*p*-toluenesulfonylpyrrolidine-2-carboxylate (32b)** A mixture of granulated zinc (0.15 g), copper(II) acetate hydrate (15 mg), and acetic acid (1 ml) was stirred at room temperature for 12 h. The acetic acid was then decanted and the Zn–Cu couple was washed with Et_2O (1 ml×3) and benzene (1 ml). To the Zn–Cu couple, THF (2 ml) was added with stirring, then a solution of compound **6** (339 mg, 1.00 mmol) and ethyl bromoacetate (334 mg, 2.0 mmol) in THF (2 ml) was added dropwise. The mixture was heated under reflux for 1 h. After cooling, AcOEt (5 ml) and concentrated ammonium hydroxide (5 ml) were added at 0 °C and the mixture was stirred for 10 min. The whole was filtered and the organic layer was separated. The aqueous layer was extracted with AcOEt (5 ml×2) and the combined organic layer was washed with water (10 ml), then brine (10 ml). It was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residual yellow oil was subjected to flash chromatography on silica gel [hexane–AcOEt (4 : 1)], then column chromatography on silica gel [ben-

zene–AcOEt (10 : 1)], giving **32a** (192 mg, 45%) as a white solid and **32b** (43 mg, 10%) as a colorless oil. Compound **32a** was recrystallized from hexane–AcOEt.

32a: Colorless prisms (hexane–AcOEt) : mp 73—74 °C, $[\alpha]_D^{17}$ −37.4° (c=0.93, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 1.48 (9H, s, $C(CH_3)_3$), 2.16 (2H, m, 3-H), 2.43 (3H, s, Ar-CH_3), 2.52 (1H, d, J=15.4 Hz, $C\underline{H}_2CO_2Et$), 2.56 (1H, d, J=15.4 Hz, $C\underline{H}_2CO_2Et$), 3.28 (1H, d, J=9.9 Hz, 5-H$_\alpha$), 3.58 (1H, dd, J=9.9, 0.8 Hz, 5-H$_\beta$), 4.14 (2H, q, J=7.1 Hz, $C\underline{H}_2CH_3$), 4.27 (1H, dd, J=8.9, 3.2 Hz, 2-H), 4.34 (1H, s, OH), 7.32 (2H, d, J=8.3 Hz, Ar-H), 7.77 (2H, d, J=8.3 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 14.12 (q), 21.56 (q), 27.83 (q), 41.93 (t), 42.40 (t), 59.44 (t), 59.98 (d), 60.95 (t), 76.31 (s), 82.96 (s), 127.68 (d), 129.74 (d), 135.01 (s), 143.87 (s), 170.61 (s), 172.36 (s). IR ν_{max}^{KBr} cm^{-1}: 3438 (OH), 1736, 1714 (C=O). MS (FAB) m/z: 428 (M^++1). *Anal.* Calcd for $C_{20}H_{29}NO_7S$: C, 56.19; H, 6.84; N, 3.28. Found: C, 56.20; H, 6.75; N, 3.21.

32b: $[\alpha]_D^{26}$ −54.6° (c=0.40, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.2 Hz, $CH_2C\underline{H}_3$), 1.50 (9H, s, $C(CH_3)_3$), 1.90 (1H, dd, J=13.0, 9.0 Hz, 3-H$_\beta$), 2.31 (1H, ddd, J=13.0, 7.7, 1.8 Hz, 3-H$_\alpha$), 2.42 (3H, s, Ar-CH_3), 2.64 (1H, d, J=16.9 Hz, $C\underline{H}_2CO_2Et$), 2.65 (1H, d, J=16.9 Hz, $C\underline{H}_2CO_2Et$), 3.27 (1H, s, OH), 3.41 (1H, d, J=11.5 Hz, 5-H$_\beta$), 3.52 (1H, dd, J=11.5, 1.8 Hz, 5-H$_\alpha$), 4.15 (2H, q, J=7.2 Hz, $C\underline{H}_2CH_3$), 4.21 (1H, dd, J=9.0, 7.7 Hz, 2-H), 7.32 (2H, d, J=8.1 Hz, Ar-H), 7.78 (2H, d, J=8.1 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 14.09 (q), 21.57 (q), 27.92 (q), 41.30 (t), 42.98 (t), 59.59 (t), 60.79 (d), 61.25 (t), 79.14 (s), 81.96 (s), 127.88 (d), 129.55 (d), 134.63 (s), 143.66 (s), 171.02 (s), 171.98 (s). IR ν_{max}^{neat} cm^{-1}: 3506 (OH), 1738, 1732 (C=O). HR-MS (FAB) m/z: 428.1744 (Calcd for $C_{20}H_{30}NO_7S$: 428.1743).

An Epimeric Mixture of *tert*-Butyl (2*S*,4*R*)-4-[1-(Ethoxycarbonyl)-ethyl]-4-hydroxy-1-*p*-toluenesulfonylpyrrolidine-2-carboxylates (33a) and an Epimeric Mixture of *tert*-Butyl (2*S*,4*S*)-4-[1-(Ethoxycarbonyl) ethyl]-4-hydroxy-1-*p*-toluenesulfonylpyrrolidine-2-carboxylates (33b) Under an argon atmosphere, ethyl 2-bromopropionate (905 mg, 5.0 mmol) was added to a mixture of **6** (679 mg, 2.00 mmol), zinc powder (260 mg, 4.00 mg-atoms), trimethyl borate (1.04 g, 10.0 mmol), and THF (10 ml). The whole was stirred for a while at room temperature and heated under reflux for 1.5 h. After cooling, AcOEt (10 ml), concentrated ammonium hydroxide (10 ml), and glycerin (10 ml) were added at 0 °C and the mixture was stirred for 10 min. The whole was filtered and the organic layer was separated. The aqueous layer was extracted with AcOEt (10 ml×2) and the combined organic layer was washed with water (20 ml), then brine (20 ml). It was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residual brown oil was subjected to column chromatography on silica gel [hexane–AcOEt (3 : 1)] to give **33a** (486 mg, 55%) as a pale yellow oil and **33b** (186 mg, 21%) as a pale yellow oil.

***tert*-Butyl (2*S*,4*R*)-4-[2-(Ethoxycarbonyl)propan-2-yl]-4-hydroxy-1-*p*-toluenesulfonylpyrrolidene-2-carboxylate (34a) and *tert*-Butyl (2*S*,4*S*)-4-[2-(Ethoxycarbonyl)propan-2-yl]-4-hydroxy-1-*p*-toluenesulfonylpyrrolidene-2-carboxylate (34b)** Under an argon atmosphere, ethyl 2-bromoisobutyrate (975 mg, 5.0 mmol) was added to a mixture of **6** (679 mg, 2.00 mmol), zinc powder (260 mg, 4.00 mg-atoms), trimethyl borate (1.04 g, 10.0 mmol), and THF (10 ml). The whole was stirred for a while at room temperature and heated under reflux for 1 h. After cooling, AcOEt (10 ml), concentrated ammonium hydroxide (10 ml), and glycerin (10 ml) were added at 0 °C and the mixture was stirred for 10 min. The whole was filtered and the organic layer was separated. The aqueous layer was extracted with AcOEt (10 ml×2) and the combined organic layer was washed with water (20 ml), then brine (20 ml). It was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residual brown oil was subjected to flash chromatography on silica gel [hexane–Et_2O (2 : 1)] to give **34a** (550 mg, 60%) as a colorless oil and **34b** (164mg, 18%) as a pale yellow oil.

34a: $[\alpha]_D^{25}$ −40.1° (c=0.86, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (6H, s, CH_3), 1.26 (3H, t, J=7.1 Hz, $CO_2CH_2C\underline{H}_3$), 1.50 (9H, s, $C(CH_3)_3$), 2.00 (1H, dd, J=13.7, 0.9 Hz, 3-H$_\beta$), 2.28 (1H, dd, J=13.7, 10.3 Hz, 3-H$_\alpha$), 2.42 (3H, s, Ar-CH_3), 3.45 (2H, s, 5-H), 4.09 (2H, q, J=7.1 Hz, $C\underline{H}_2CH_3$), 4.20 (1H, s, OH), 4.27 (1H, dd, J=10.3, 0.9 Hz, 2-H), 7.31 (2H, d, J=8.3 Hz, Ar-H), 7.76 (2H, d, J=8.3 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 14.03 (q), 21.44 (q), 21.53 (q), 27.81 (q), 38.86 (t), 47.77 (s), 56.98 (t), 60.21 (d), 60.92 (t), 82.82 (s), 83.10 (s), 127.62 (d), 129.69 (d), 135.03 (s), 143.80 (s), 172.63 (s), 175.82 (s). IR ν_{max}^{neat} cm^{-1}: 3442 (OH), 1720 (C=O). HR-MS (FAB) m/z: 456.2055 (Calcd for $C_{22}H_{34}NO_7S$: 456.2056).

34b: $[\alpha]_D^{24}$ −43.6° (c=0.82, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.27 (6H, s, CH_3), 1.31 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 1.50 (9H, s, $C(CH_3)_3$), 2.04 (1H, m, 3-H$_\beta$), 2.14 (1H, ddd, J=12.8, 6.9, 1.8 Hz, 3-H$_\alpha$), 2.42 (3H, s, Ar-CH_3), 2.96 (1H, s, OH), 3.40 (1H, dd, J=11.7, 1.8 Hz, 5-H$_\alpha$), 3.62 (1H, d, J=11.7 Hz, 5-H$_\beta$), 4.13 (2H, q, J=7.1 Hz, $C\underline{H}_2CH_3$), 4.18 (1H, dd, J=9.9, 6.9 Hz, 2-H), 7.31 (2H, d, J=8.2 Hz, Ar-H), 7.79 (2H, d, J=8.2 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 14.04 (q), 21.76 (q), 21.90 (q), 27.78 (q), 31.60 (s), 38.90 (t), 47.19 (s), 56.93 (t), 61.04 (d), 61.37 (t), 81.82 (s), 82.47 (s), 127.91 (d), 129.52 (d), 134.64 (s), 143.59 (s), 171.18 (s), 177.12 (s). IR ν_{max}^{neat} cm^{-1}: 3506 (OH), 1736, 1728 (C=O). HR-MS (FAB) m/z: 456.2054 (Calcd for $C_{22}H_{34}NO_7S$: 456.2056).

Aromatization of Compound 32 Giving 29 Thionyl chloride (1.0 ml, 14 mmol) was added dropwise to a solution of compound **32a** (129 mg, 0.30 mmol) in pyridine (3.0 ml) at 0 °C and the whole was stirred at room temperature for 2 h. The reaction mixture was concentrated under reduced pressure. Toluene (12 ml) was added and the solution was concentrated under reduced pressure. This operation was repeated once. Water (20 ml) was added to the residue and the whole was extracted with benzene (20 ml×2). The organic layer was washed with brine (20 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in toluene (2 ml) and DBU (0.30 ml, 2.0 mmol), and the solution was refluxed for 3 h. The mixture was concentrated under reduced pressure and the residue was subjected to column chromatography on silica gel [hexane–AcOEt (1 : 1)] to give **29** (65 mg, 85%) as a colorless oil.

***tert*-Butyl 4-[1-(Ethoxycarbonyl)ethyl]pyrrole-2-carboxylate (35)** Compound **35** (72 mg, 89%) was obtained as a pale yellow oil from **33a** (133 mg, 0.30 mmol) in a manner similar to that described for **29** from **32**, but using column chromatography on silica gel [benzene–Et_2O (5 : 1)]. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 1.46 (3H, d, J=7.1 Hz, benzylic CH_3), 1.56 (9H, s, $C(CH_3)_3$), 3.64 (1H, q, J=7.1 Hz, benzylic H), 4.13 (2H, q, J=7.1 Hz, $C\underline{H}_2CH_3$), 6.78 (1H, s, 3-H), 6.83 (1H, s, 5-H), 9.77 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 14.16 (q), 18.44 (q), 28.38 (q), 38.07 (d), 60.66 (t), 80.87 (s), 113.45 (d), 120.19 (d), 124.11 (s), 124.69 (s), 128.33 (d), 161.03 (s), 175.02 (s). IR ν_{max}^{neat} cm^{-1}: 3112 (NH), 1736, 1676 (C=O). HR-MS m/z: 267.1469 (Calcd for $C_{14}H_{21}NO_4S$: 267.1471).

***tert*-Butyl 4-[2-(Ethoxycarbonyl)propan-2-yl]pyrrole-2-carboxylate (36)** Compound **36** (76 mg, 90%) was obtained as a white solid from **34a** (137 mg, 0.30 mmol) in a manner similar to that described for **29** from **32**, but using column chromatography on silica gel [hexane–AcOEt (10 : 1)]. It was recrystallized from hexane to give colorless prisms, mp 88—89 °C ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 1.52 (6H, s, benzylic CH_3), 1.56 (9H, s, $C(CH_3)_3$), 4.12 (2H, q, J=7.1 Hz, $C\underline{H}_2CH_3$), 6.80 (1H, s, 3-H), 6.83 (1H, s, 5-H), 9.43 (1H, s, NH). ^{13}C-NMR ($CDCl_3$) δ: 14.09 (q), 26.65 (q), 28.39 (q), 41.54 (s), 60.75 (t), 80.85 (s), 112.71 (d), 119.28 (d), 123.98 (s), 130.38 (s), 160.88 (s), 176.70 (s). IR ν_{max}^{KBr} cm^{-1}: 3311 (NH), 1738, 1678 (C=O). MS m/z: 281 (M^+). *Anal.* Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.19; H, 8.08; N, 4.68.

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