Pergamon

Tetrahedron 56 (2000) 6199–6207

TETRAHEDRON

Radical Cyclization in Heterocycle Synthesis. Part 10:[1] A Concise Synthesis of (−)-Kainic Acid via Sulfanyl Radical Addition–Cyclization–Elimination Reaction

Okiko Miyata, Yoshiki Ozawa, Ichiya Ninomiya and Takeaki Naito*

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan

Received 5 June 2000; accepted 27 June 2000

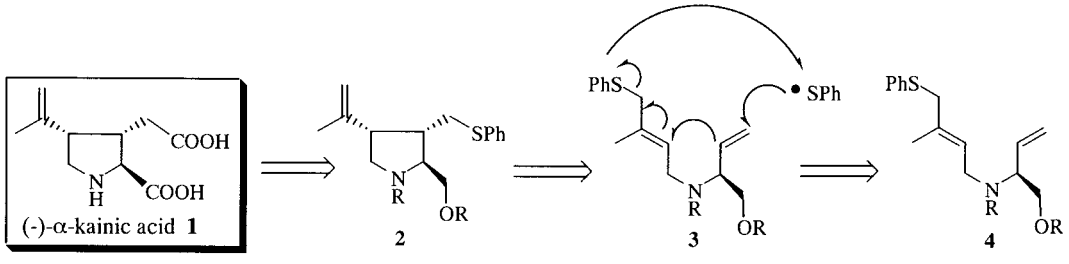
Abstract—Sulfanyl radical addition–cyclization–elimination of diallylamines in the presence of thiophenol and AIBN gave the 2,3,4-trisubstituted pyrrolidine in high yield. This reaction was extended to a radical cyclization using a catalytic amount of thiophenol. A successful application was demonstrated by the asymmetric synthesis of (−)-kainic acid.

Introduction

Radical cyclization continues to form a central methodology for synthesis of natural products containing heterocyclic rings.[2] These radical cyclization protocols commonly have several advantages over non-radical methods. The radical cyclization can be carried out in neutral organic solutions, and radical cascade reactions allow the construction of two or more rings in one-pot reactions. Most radical cyclizations used for the syntheses of heterocycles proceed in a 5-*exo-trig* manner. Therefore, a radical cyclization reaction is suitable for the construction of a 5-membered ring as exemplified in several syntheses[3] of (−)-α-kainic acid (**1**) having a pyrrolidine ring. In this paper, we describe full details of the sulfanyl radical-addition–cyclization–elimination[4] of diallylamines and its application to total synthesis of (−)-α-kainic acid.[5]

The marine product (−)-α-kainic acid[3] has attracted considerable interest since it was first isolated by Takemoto[6] in 1953, principally because of its potent neurotransmitting activity in the central nervous system. Several total syntheses of kainic acid and related compounds have been achieved during the last decade[3] since Oppolzer[7] reported an enantioselective synthesis of α-kainic acid via an intramolecular ene reaction.

As a disconnective analysis is shown in Scheme 1, our synthesis employs the newly developed sulfanyl radical addition–cyclization–elimination reaction as a key step (**4**→**3**→**2**). The advantage of this method is as follows: (1) substrate for the radical cyclization is easily prepared from (*S*)-methionine; (2) thiophenol used as a radical source, is of low toxicity and is inexpensive compared with tributyl tinhydride; (3) the key reaction involves the sequential formation of two bonds and one bond cleavage in one-pot construction of the trisubstituted pyrrolidine ring comprising kainic acid. We employed both cyclic and acyclic diallylamines as the substrate for radical reaction.

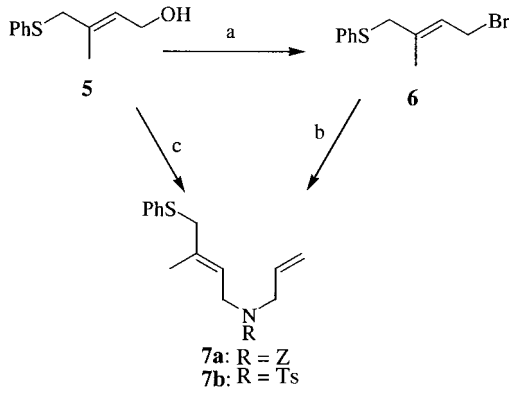


Scheme 1.

Keywords: kainic acid; thiophenol; radical cyclization; pyrrolidine.

* Corresponding author. Tel.: +81-78-441-7554; fax: +81-78-441-7556; e-mail: taknaito@kobepharma-u.ac.jp

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00579-2



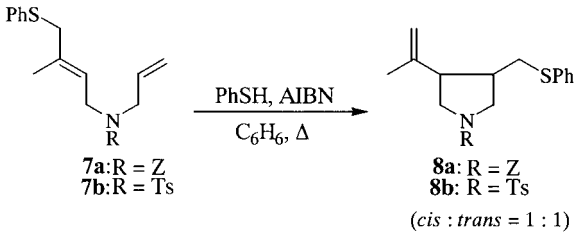
Scheme 2. Reagents and conditions: (a) CBr_4,Ph_3P, quant.; (b) (i) allylamine, (ii) ZCl, 19%; (c) *N*-tosylallylamine, DEAD, Ph_3P, 90%.

Results and Discussion

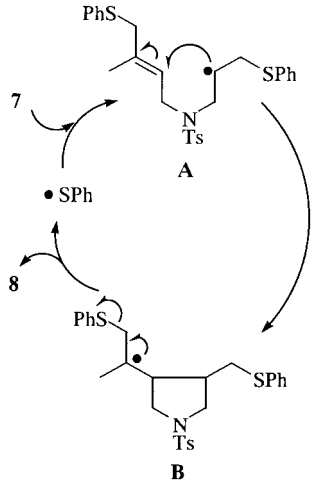
Preparation of substituted pyrrolidines having an isopropenyl group

We first investigated the phenylsulfanyl radical addition–cyclization–elimination reaction of model compounds **7a,b** (Scheme 2, Table 1). The requisite dienes **7a** and **7b** for the radical cyclization were prepared through either alkylation of allylamine with the allyl bromide **6** followed by acylation using benzyloxycarbonyl chloride (ZCl) or the Mitsunobu reaction of the *N*-tosylallylamine with the hydroxy sulfide **5**.[8] A solution containing thiophenol (1 equiv.) and AIBN (0.5 equiv.) in benzene was added dropwise with a syringe pump over 2 h to a solution of the carbamate **7a** in boiling benzene while stirring under nitrogen. The solution was then refluxed for further 2 h and the solvent was removed in vacuo. The resulting residue was purified by medium-pressure column chromatography (MPCC) to give a mixture of the *cis*- and *trans*-pyrrolidines **8a** having an isopropenyl group in 22% combined yield as an inseparable mixture (entry 1). When 2 equiv. of thiophenol was used, the reaction proceeded smoothly to give **8a** in 63% yield (entry 2). This result namely, that the pyrrolidine having an isopropenyl group was obtained in a one-pot procedure, suggests that the radical cyclization is suitable for the synthesis of kainic acid and the related kainoids.

Table 1. Sulfanyl radical addition–cyclization–elimination of **7a,b**



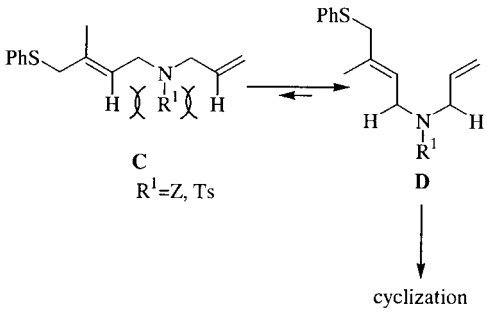
Entry	Substrate	PhSH (equiv.)	AIBN (equiv.)	Yield (%)
1	**7a**	1.0	0.5	22
2	**7a**	2.0	1.0	63
3	**7a**	0.2	0.2	16
4	**7b**	0.2	0.2	50



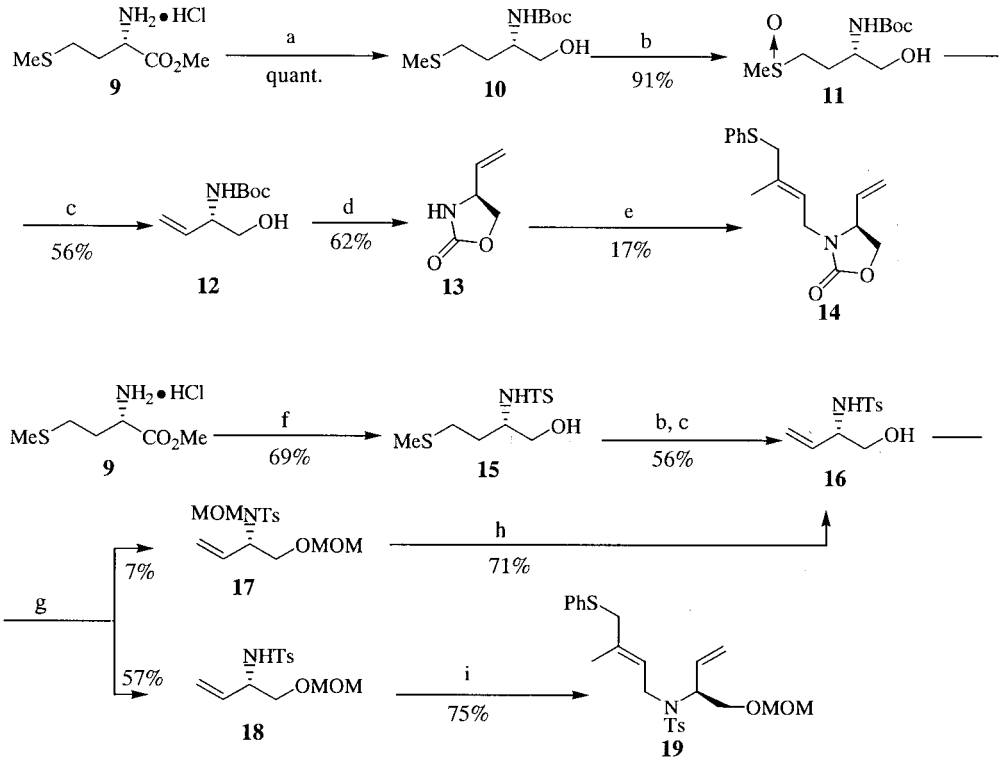
Scheme 3.

We next examined the reaction employing a catalytic amount of thiophenol (entries 3, 4). Treatment of **7b** having the *N*-tosyl group with 0.2 equiv. of thiophenol afforded a 1:1 mixture of the *cis*- and *trans*-**8b** in moderate yield, while **7a** gave the corresponding product **8a** in only 16% yield and the substrate **7a** was mostly recovered. This reaction mechanism is shown in Scheme 3. It involves a sequence of transformations including intermolecular addition of a phenylsulfanyl radical to the terminal olefin of **7**, generating the carbon-centered radical **A**, ring-closure to radical **B**, and subsequent β-elimination leading to the isopropenylpyrrolidine **8** and fanyl radical which reacts with **7** to give back the radical **A**. The different reactivities between **7a** and **7b** could be explained as follows (Scheme 4). The substrates **7a** and **7b** would exist in conformation **D** preferable for intramolecular cyclization over the less favored conformer **C** due to the steric repulsion between the substituent on nitrogen and vinyl protons.[2m,n] Since the tosyl group is more bulky than the Z-group, the radical cyclization of **7b** would take place smoothly because of large contribution of the conformer **D**.

Thus, we have developed a new and simple synthetic method for kainoids using the phenylsulfanyl radical addition–cyclization–elimination. Furthermore, we have now succeeded in extending the radical cyclization to a catalytic version which would be a potential synthetic weapon.



Scheme 4.



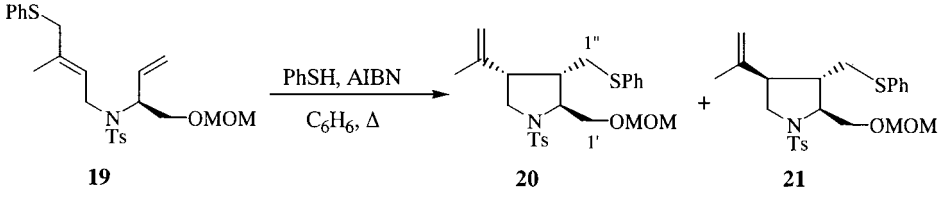
Scheme 5. Reagents and conditions: (a) (i) Boc_2O, (ii) $LiAlH_4$; (b) $NaIO_4$; (c) NaOAc, 200°C; (d) $SOCl_2$; (e) **6**, *n*-BuLi; (f) (i) TsCl, (ii) $LiAlH_4$; (g) MOMCl; (h) 10% HCl; (i) **5**, DEAD, Ph_3P.

Total synthesis of (−)-kainic acid

According to the results shown in the previous chapter, we undertook the synthesis of (−)-kainic acid. Based on our previous work,[3g] we employed **14** having an oxazolidinone ring as the chiral substrate for radical addition–cyclization–elimination. The oxazolidinone **14** was prepared from (*S*)-methionine methyl ester **9** as follows (Scheme 5): ester **9** was converted into *N*-Boc-vinylglycinol **12** via *t*-butoxycarbonylation, reduction of the ester, oxidation to the sulfinyl group, and pyrolysis of the resulting sulfoxide by the method reported previously.[9] Treatment of **12** with $SOCl_2$ followed by allylation of the resulting oxazolidinone **13** with allyl bromide **6** afforded **14**. Attempted sulfanyl radical addition–cyclization–elimination of **14** in the presence of thiophenol and AIBN was unsuccessful and the substrate **14** was mostly recovered.

Therefore, we next investigated synthesis of (−)-kainic acid via the radical addition–cyclization–elimination of the acyclic substrate (*S*)-**19** with no oxazolidinone ring which was prepared from **9** as follows (Scheme 5). Ester **9** was converted into (*S*)-*N*-tosylvinylglycinol (**16**) by sequential reactions involving *N*-tosylation, reduction of the ester, oxidation to the sulfoxide, and pyrolysis of the resulting sulfoxide. Alcohol **16** was treated with MOMCl to give **17**

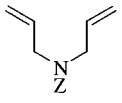
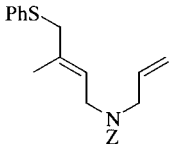
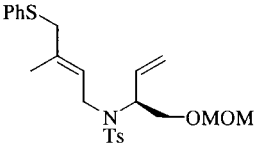
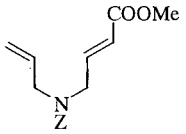
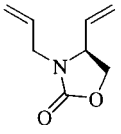
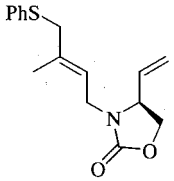
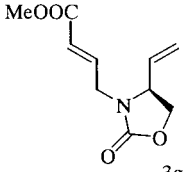
Table 2. Sulfanyl radical addition–cyclization–elimination of (*S*)-**19**

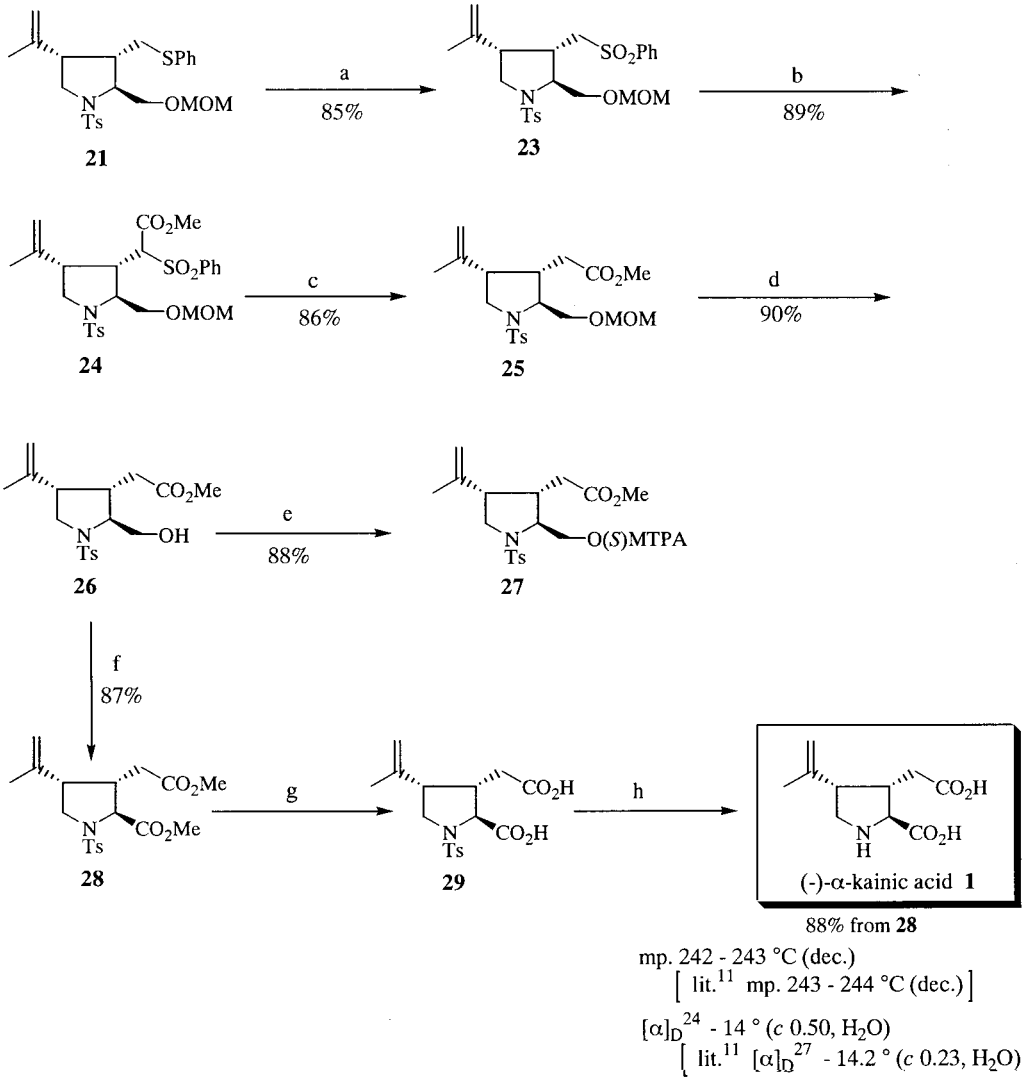


Entry	PhSH (equiv.)	AIBN (equiv.)	Additive	Solvent	Temp (°C)	Yield (%)	Ratio **20**:**21**
1	1.0	0.5	–	C_6H_6	80	94	1:1.3
2	0.2	0.2	–	C_6H_6	80	95	1:1.5
3	1.8	0.6[a]	–	C_6H_6	rt	27	1:1.4
4	1.0	0.5	–	C_6H_6	rt	64	1:1.6
5	1.5	0.75	–	EtOH	80	10	1:1.6
6	1.5	0.75	–	MeCN	80	9	1:1.5
7	1.5	0.75	$Yb(OTf)_3$ (1.0 equiv.)	C_6H_6	80	48	1:1.4

[a] Et_3B was used as a radical initiator.

Table 3. Cyclizability of various diallylamines in sulfanyl radical addition–cyclization

acyclic substrates	 **22a**[3g]	 **7a**	 **19**	 **22b**[3g]
yields of cyclized products	60%	63%	95%	81%
cyclic substrates	 **22c**	 **14**	 **22d**[3g]	
yields of cyclized products	---	---	85%	



Scheme 6. Reagents and conditions: (a) OXONE®; (b) (i) MeLi, (ii) ClCOOMe; (c) Na–Hg; (d) TFA; (e) (+)-MTPACl, py.; (f) (i) PDC, (ii) CH_2N_2; (g) LiOH; (h) Li/liq. NH_3.

and **18** in 7 and 57% yields, respectively. *N*,*O*-Diprotected compound **17** was recycled by converting into **16** by treatment with 10% HCl. The Mitsunobu reaction of **18** with the allyl alcohol **5** afforded the desired product **19** in 75% yield. Sulfanyl radical addition–cyclization–elimination of **19** in the presence of thiophenol and AIBN proceeded smoothly to give a 1:1.3 mixture of the cyclized products **20** and **21** in combined 94% yield (Table 2, entry 1). Similarly, treatment of **19** with a catalytic amount of thiophenol gave **20** and **21** in an almost similar ratio (Table 2, entry 2). Thus, sulfanyl radical addition–cyclization–elimination of **19** proceeded smoothly to give the cyclized products in excellent yield, while **14** having an oxazolidinone ring did not give the cyclized product as described above.

In order to improve the yield of the desired *cis*-product **20**, we investigated radical cyclization of **19** under other conditions. However, the conditions shown in Table 2, entry 3–7, were not so effective for improvement of the yield of the desired product **20**. The stereostructures of **20** and **21** were deduced from comparison of the ^{1}H NMR spectra with those of the related compounds[3g] and NOE correlations.

Having obtained different results in the cyclizability of two substrates **14** and **19**, we collected all the results of sulfanyl radical addition–cyclization of diallylamines reported previously[3g] and in this paper in Table 3. Thus, all acyclic diallylamines **22a**,[3g] **7a**, **19**, and **22b**[3g] with no oxazolidinone ring underwent smooth radical cyclization. On the other hand, the cyclizability of cyclic diallylamines having an oxazolidinone ring would depend on the substituent at the terminal olefin. In the case of **22c** and **14** with no alkoxycarbonyl group at the terminal olefin, any cyclized products could not be isolated while **22d**[3g] afforded the cyclized product in 85% yield. These results suggest that the existence of an oxazolidinone ring in **22c** and **14** leads to a less favorable transition state for ring closure except for **22d** having an α,β-unsaturated ester group which is a good radical acceptor. However, we are unable at this time to offer a detailed explanation of the influence of the oxazolidinone ring on the radical cyclization.

Next, we examined conversion of **20** into (−)-α-kainic acid (Scheme 6). Oxidation of the *cis*-product **20** with OXONE® (potassium peroxymonosulfate) gave the sulfone **23**, which was then subjected to methoxycarbonylation (MeLi, then ClCOOMe) to afford the sulfonyl ester **24** in high yield as a sole product. The stereochemistry at α-position of the ester group in **24** has not been established yet. Desulfonylation of **24** with 5% sodium-amalgam gave the ester **25**, which was identical with the authentic sample[10] upon comparison of their spectral data. The ester **25** had previously been transformed into (−)-kainic acid. According to Yoo's procedure,[10] the ester **25** was treated with TFA to give the hydroxy ester **26**. Optical purity of **26** was determined to be nearly 100% enantiomeric excess by ^{1}H NMR spectroscopic analysis of the corresponding (+)-MTPA ester **27**, which was derived from **26** by esterification using (+)-MTPA chloride. Finally, **26** was smoothly converted into (−)-kainic acid. Oxidation of the alcohol **26** with PDC followed by esterification of the resulting carboxylic acid with diazomethane gave the ester **28**. Hydrolysis of **28** with LiOH and subsequent deprotection under Birch conditions afforded (−)-kainic acid **1**. The physical (mp 242–243°C (dec.); $[\alpha]_D=-14.0$ (*c* 0.50, H_2O)) and spectral data of the synthetic (−)-kainic acid **1** were identical with those (mp 243–244°C (dec.); $[\alpha]_D=-14.2$ (*c* 0.23, H_2O)) of the authentic sample reported in the literature.[11]

Conclusion

We have integrated sulfanyl radical addition–cyclization of diallylamines to sulfanyl radical addition–cyclization–elimination by using an allyl phenyl sulfide in the substrate which allowed us to use a catalytic amount of thiophenol. The structure effect in sulfanyl radical addition–cyclization was also investigated by comparison of the cyclizability of diallylamines.

Experimental

General

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 200, 300, or 500 and at 50 MHz, respectively. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI method. Flash column chromatography was preformed using E. Merck Kieselgel 60 (230–400 mesh). MPCC was performed using Lober größe B (E. Merck 310-25, Lichroprep Si60).

Phenylmethyl (*E*)-*N*-[(3-methyl-4-(phenylsulfanyl)-2-butenyl)] (2-propenyl)carbamate (7a). To a stirred solution of the allyl alcohol **5**[8] (1.94 g, 10 mmol) in benzene (50 mL) was added CBr_4 (6.8 g, 20 mmol) and Ph_3P (5.4 g, 20 mmol) at 0°C under a nitrogen atmosphere. After the solution was stirred at the same temperature for 2 h, *n*-pentane (200 mL) was added to the reaction mixture. The reaction mixture was filtered to remove triphenylphosphine oxide. The filtrate was concentrated under reduced pressure to afford the crude (*E*)-1-bromo-3-methyl-4-(phenylsulfanyl)-2-butene **6** (2.55 g, quant.) as a yellow oil. After being characterized by NMR spectrum, **6** was immediately subjected to the following reaction. To a stirred solution of the bromide **6** (2.6 g, 10 mmol) in CH_2Cl_2 (50 mL) was added allylamine (1.8 mL, 24 mmol) at room temperature under a nitrogen atmosphere. After being stirred at room temperature for 4 h, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude (*E*)-*N*-[(3-methyl-4-(phenylsulfanyl)-2-butenyl)] (2-propenyl)amine. To a solution of the amine in benzene (30 mL) was added Et_3N (2 mL, 14 mmol) and Z-Cl (528 mg, 10 mmol) under a nitrogen atmosphere at room temperature. After the solution was stirred at the same temperature for 2 h, the reaction mixture was filtered to remove triethylamine hydrochloride. The filtrate was concentrated under reduced pressure, and the residue was purified by MPCC (hexane/AcOEt 1:1) to afford the carbamate **7a** (700 mg, 19%) as a yellow oil; IR ($CHCl_3$) 1691 (NCOO) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.74 (3H, br s), 3.48 (2H, br s), 3.62 (2H, m), 3.82 (2H, m), 4.92–5.26 (3H, m), 5.11 (2H, s), 5.53–5.78 (1H, m), 7.14–

7.42 (10H, m); HRMS (EI, *m/z*) calcd for $C_{22}H_{25}NO_2S$ (M^+) 367.1605, found 367.1601.

(*E*)-4-Methyl-*N*-[3-methyl-4-(phenylsulfanyl)-2-butenyl]-*N*-(2-propenyl)benzenesulfonamide (7b). To a stirred solution of allylamine (500 mg, 8.8 mmol) in CH_2Cl_2 (10 mL) was added triethylamine (1.6 mL, 12 mmol) and tosyl chloride (2 g, 10.6 mmol) at 0°C under a nitrogen atmosphere. After being stirred at the same temperature for 4 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by recrystallization (hexane/Et_2O) afforded 4-methyl-*N*-(2-propenyl)benzenesulfonamide (1.5 g, 96%) as pale yellow crystals: mp 59–61°C; IR ($CHCl_3$) 1335, 1160 (NSO_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.63 (2H, br d, J=7 Hz), 5.12–5.25 (2H, m), 5.62–5.82 (1H, m), 7.32 (2H, br d, J=8 Hz), 7.68 (2H, br d, J=8 Hz).

To a solution of the sulfonamide (1.5 g, 8.5 mmol) in benzene (50 mL) was added the alcohol **5** (682 mg, 3.5 mmol) and Ph_3P (2.9 g, 10.6 mmol) at 0°C under a nitrogen atmosphere. After being stirred at the same temperature for 15 min, diethyl azodicarboxylate (DEAD) (40% in toluene) (3.5 mL, 8.8 mmol) was added dropwise and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed and the residue was purified by MPCC (hexane/AcOEt 3:1) to afford the sulfonamide **7b** (2.48 g, 90%) as a yellow oil; IR ($CHCl_3$) 1341, 1158 (NSO_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.68 (3H, br s), 2.43 (3H, br s), 3.43 (2H, br s), 3.50 and 3.72 (each 2H, br d, J=7 Hz), 4.91–5.23 (3H, m), 5.39–5.61 (1H, m), 7.20–7.36 (7H, m), 7.64 (2H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{21}H_{25}NO_2S_2$ (M^+) 387.1325, found 387.1329.

General procedure for radical cyclization

Table 1, entry 1: To a boiling solution of the carbamate **7a** (110 mg, 0.3 mmol) in benzene (3 mL) under a nitrogen atmosphere was added a solution of thiophenol (0.03 mL, 0.3 mmol) and AIBN (24.6 mg, 0.15 mmol) in benzene (6 mL) by a syringe pump (5 mL/h) over 2 h. After the reaction mixture was heated at reflux for a further 4 h, the solvent was evaporated under reduced pressure. Purification of the residue by MPCC (hexane/AcOEt 4:1) afforded a 1:1 mixture of phenylmethyl *cis*/*trans*-4-(1-methylethenyl)-3-(phenylsulfanyl)methyl-1-pyrrolidinecarboxylate **8a** (24 mg, 22%) as an inseparable mixture. Pale yellow oil; IR ($CHCl_3$) 1693 (NCOO) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.65 (3/2H, br s), 1.70 (3/2H, br s), 2.44–3.93 (8H, m), 4.72 (1/2H, br s), 4.80 (1/2H, br s), 4.87 (1/2H, br s), 4.94 (1/2H, br s), 5.12 (2H, br s); HRMS (EI, *m/z*) calcd for $C_{22}H_{25}NO_2S$ (M^+) 367.1604, found 367.1601.

Table 1, entry 2: According to the procedure described for entry 1 (Table 1), treatment of **7a** with 2 equiv. of thiophenol and 1 equiv. of AIBN afforded **8a** (63%).

Table 1, entry 3: According to the procedure described for entry 1 (Table 1), treatment of **7a** with 0.2 equiv. of thiophenol and 0.2 equiv. of AIBN afforded **8a** (16%).

Table 1, entry 4: According to the procedure described for entry 1 (Table 1), treatment of **7b** with 0.2 equiv. of thiophenol and 0.2 equiv. of AIBN afforded a 1:1 mixture of *cis*/*trans*-4-(1-methylethenyl)-1-[(4-methylphenyl)sulfonyl]-3-[(phenylsulfanyl)methyl]pyrrolidine **8b** (50%) as an inseparable mixture. Pale yellow oil; IR ($CHCl_3$) 1341, 1158 (NSO_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.54 (3/2H, br s), 1.60 (3/2H, br s), 1.88 (1/2H, br t, J=12 Hz), 2.08–2.34 (1H, m), 2.38 (3/2H, br s), 2.43 (3/2H, br s), 2.40–2.74 (2H, m), 2.96–3.12 (3/2H, m), 3.23 (1/2H, t, J=10 Hz), 3.35–3.52 (3/2H, m), 3.63 and 3.64 (each 1/2H, t, J=8 Hz), 4.60 (1/2H, br s), 4.67 (1/2H, br s), 4.80 (1/2H, br s), 4.89 (1/2H, br s), 7.14–7.34 (7H, m), 7.71 (1H, br d, J=8 Hz), 7.74 (1H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{21}H_{25}NO_2S_2$ (M^+) 387.1325, found 387.1313.

(*S*)-4-Ethenyl-2-oxazolidinone (13). According to the literature,[9] L-methionine methyl ester **9** was converted into (*S*)-vinylglycinol **12** via *t*-butoxycarbonylation, reduction, oxidation, and pyrolysis. To a stirred solution of the (*S*)-vinylglycinol **12** (4.6 g, 25 mmol) in benzene (150 mL) was added thionyl chloride (2 mL, 25 mmol) at room temperature under a nitrogen atmosphere. After the solution was heated at reflux for 8 h, the reaction mixture was concentrated at reduced pressure and the residue was purified by MPCC (hexane/AcOEt 3:2) to afford **13** (1.7 g, 62%) as a yellow oil; IR ($CHCl_3$) 1766 (NCOO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.07 (1H, dd, J=8, 6 Hz), 4.39 (1H, qt, J=8, 2 Hz), 4.55 (1H, t, J=8 Hz), 5.30 (2H, m), 5.84 (1H, ddd, J=17, 10, 8 Hz); HRMS (EI, *m/z*) calcd for $C_5H_7NO_2$ (M^+) 113.0477, found 113.0452. $[\alpha]_D^{28}=-26.2$ (*c* 1.03, $CHCl_3$).

[*S*-(*E*)]-3-[3-Methyl-4-(phenylsulfanyl)-2-butenyl]-4-(2-propenyl)-2-oxazolidinone (14). To a stirred solution of the oxazolidinone **13** (112 mg, 1 mmol) in THF (3 mL) was added successively *n*-BuLi (1.65 M in THF) (0.6 mL, 1 mmol) and dropwise a solution of the bromide **6** (257 mg, 1 mmol) at −78°C under a nitrogen atmosphere. After being stirred at the same temperature for 0.5 h and then at 0°C for 2 h, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPCC (hexane/AcOEt 5:1) to afford **14** (49 mg, 17%) as a pale yellow oil; IR ($CHCl_3$) 1742 (NCOO) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.74 (3H, br s), 3.42 and 3.60 (2H, ABq, J=15 Hz), 3.46 (1H, dd, J=15, 9 Hz), 3.54 (1H, q, J=8 Hz), 3.82 (1H, dd, J=9, 7 Hz), 3.96 (1H, dd, J=15, 5 Hz), 4.21 (1H, t, J=9 Hz), 5.09 (1H, br d, J=15 Hz), 5.17 (1H, m), 5.25 (1H, br d, J=10 Hz), 5.53 (1H, ddd, J=17, 10, 9 Hz); HRMS (EI, *m/z*) calcd for $C_{16}H_{19}NO_2S$ (M^+) 289.1136, found 289.1141. $[\alpha]_D^{26}=-53.7$ (*c* 0.93, $CHCl_3$).

(*S*)-*N*-(1-Hydroxy-3-buten-2-yl)-4-methylbenzenesulfonamide (16). According to the procedure described for the preparation of **12**, L-methionine methyl ester **9** was converted into (*S*)-vinylglycinol **16** via tosylation, reduction, oxidation, and pyrolysis. Yellow crystals: mp 59–60°C (Et_2O); IR ($CHCl_3$) 3589 (OH), 1336, 1160 (NSO_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.41(3H, s), 3.53 (1H, dd, J=11, 6 Hz), 3.61 (1H, dd, J=11, 5 Hz), 3.87 (1H, br

quint., J=6 Hz), 5.05 (1H, dt, J=10, 2 Hz), 5.19 (1H, dt, J=16, 2 Hz), 5.52 (1H, br d, J=7 Hz), 5.61 (1H, ddd, J=16, 10, 6 Hz), 7.28 (2H, br d, J=8 Hz), 7.55 (2H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{11}H_{15}NO_3S$ (M^+) 241.0772, found 241.0790. $[\alpha]_D^{28}=-28.0$ (*c* 1.0, $CHCl_3$).

Methoxymethylation of Glycinol 16. To a solution of the glycinol **16** (723 mg, 3 mmol) in CH_2Cl_2 (5 mL) was added (i-Pr)$_2$NEt (0.76 mg, 4.5 mmol) and MOMCl (0.3 mL, 3.6 mmol) at room temperature under a nitrogen atmosphere. After being stirred at the same temperature for 4 h, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPCC (hexane/AcOEt 5:1) to afford (*S*)-*N*-(methoxymethyl)-*N*-[1-(methoxy)methoxy-3-buten-2-yl]-4-methylbenzenesulfonamide (**17**) (63 mg, 7%) and (*S*)-*N*-[1-(methoxy)methoxy-3-buten-2-yl]-4-methylbenzenesulfonamide (**18**) (487 mg, 57%).

17: Yellow oil; IR ($CHCl_3$) 1341, 1160 (NSO_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.42 (3H, s), 3.28 (3H, s), 3.32 (3H, s), 3.67 (2H, d, J=7 Hz), 4.45 (1H, br q, J=7 Hz), 4.50 (2H, br s), 4.71 and 4.83 (2H, ABq, J=10 Hz), 5.06–5.23 (2H, m), 5.71 (1H, br ddd, J=17, 10, 6 Hz), 7,27 (2H, br d, J=8 Hz), 7.74 (2H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{14}H_{20}NO_4S$ (M^+-OMe) 298.1112, found 298.1123.

18: Yellow oil; IR ($CHCl_3$) 1336, 1160 (NSO_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (3H, s), 3.30 (3H, s), 3.47 (1H, dd, J=10, 5 Hz), 3.52 (1H, dd, J=10, 5 Hz), 3.95 (1H, br quint., J=5 Hz), 4.51 and 4.52 (2H, ABq, J=6 Hz), 5.10 (1H, dt, J=10, 2 Hz), 5.17 (1H, dt, J=17, 2 Hz), 5.68 (1H, ddd, J=17, 10, 6 Hz), 7,28 (2H, br d, J=8 Hz), 7.75 (2H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{13}H_{19}NO_4S$ (M^+) 285.1033, found 285.1050. $[\alpha]_D^{26}=-6.3$ (*c* 0.96, $CHCl_3$).

Hydrolysis of 17. To a solution of **17** (67 mg, 0.2 mmol) in THF (3 mL) was added ethylene glycol (0.02 mL, 0.4 mmol) and 10% HCl (0.4 mL) at room temperature under a nitrogen atmosphere. After being stirred at reflux for 8 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated at reduced pressure. The residue was purified by MPCC (hexane/AcOEt 5:1) to afford **16** (39 mg, 71%). This compound was identical with **16** prepared from **15**.

[*S*-(*E*)]-*N*-[(1-Methoxy)methoxy-3-buten-2-yl]-4-methyl-*N*-[3-methyl-4-(phenylsulfanyl)-2-butenyl]benzenesulfonamide (19). To a solution of the alcohol **5** (194 mg, 1.0 mmol) in THF (26 mL) was added **18** (570 mg, 2.0 mmol) and Ph_3P (818 mg, 3.0 mmol) at 0°C under a nitrogen atmosphere. After being stirred at the same temperature for 15 min, DEAD (40% in toluene)(1.14 mL, 2.5 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h. The solvent was removed and the residue was purified by MPCC (hexane/AcOEt 3:1) to afford the sulfonamide **19** (360 mg, 75%) as a yellow oil; IR ($CHCl_3$) 1336, 1152 (NSO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.74 (3H, br s), 2.41 (3H, s), 3.29 (3H, s), 3.45 (2H, br s), 3.52 (1H, dd, J=10, 7 Hz), 3,56 (1H, dd, J=10, 7 Hz), 3.72 (1H, dd, J=17, 7 Hz), 3.86 (1H, dd, J=17, 7 Hz), 4.46 and 4.49 (2H, ABq, J=7 Hz), 4.54 (1H, m), 5.10 (1H, dt, J=17, 2 Hz), 5.15 (1H, dt, J=10, 2 Hz), 5.26 (1H, br tq, J=7, 2 Hz), 5.58 (1H, ddd, J=17, 10, 7 Hz), 7.18–7.31 (7H, m), 7.68 (2H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{24}H_{31}NO_4S_2$ (M^+) 461.1692, found 461.1701. $[\alpha]_D^{27}=+14.3$ (*c* 1.26, $CHCl_3$).

Phenylsulfanyl radical addition–cyclization–elimination of 19

Table 2, Entry 1: According to the procedure given for sulfanyl radical addition–cyclization–elimination of **7a,b,** reaction of **19** (260 mg, 0.56 mmol) using thiophenol (0.06 mL, 0.56 mmol) and AIBN (46 mg, 0.28 mmol) gave [2*S*-(2α,3β,4α)-[2-(methoxymethoxy)methyl-4-(1-methylethenyl)-1-(4-methylphenyl)sulfonyl-3-(phenylsulfanyl)methyl]pyrrolidine (**20**) (107 mg, 41%) and [2*S*-(2α,3β,4α)-[2-(methoxymethoxy)methyl-4-(1-methylethenyl)-1-(4-methylphenyl)sulfonyl-3-(phenylsulfanyl)methyl]pyrrolidine (**21**) (138 mg, 53%).

Table 2, Entry 2: According to the procedure given for sulfanyl radical addition–cyclization–elimination of **7a,b,** reaction of **19** (260 mg, 0.56 mmol) using a catalytic amount of thiophenol (0.01 mL, 0.11 mmol) and AIBN (18 mg, 0.11 mmol) gave **20** (99 mg, 38%) and **21** (147 mg, 57%) as shown in Table 2.

20: Yellow oil; IR ($CHCl_3$) 1347, 1164 (NSO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.04 (1H, t, J=13 Hz), 1.57 (3H, br s), 2.27 (1H, dq, J=13, 3 Hz), 2.33 (3H, s), 2.46 (1H, dd, J=13, 3 Hz), 3.04 (2H, m), 3.31 (3H, s), 3.56 (1H, m), 3.64 (1H, dd, J=10, 8 Hz), 3.77 (1H, dd, J=10, 4 Hz), 4.03 (1H, br dd, J=8, 4 Hz), 4.52 (1H, br s), 4.61 and 4.65 (2H, ABq, J=7 Hz), 4.86 (1H, br q, J=1 Hz), 7.13–7.26 (7H, m), 7.78 (2H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{24}H_{31}NO_4S_2$ (M^+) 461.1692, found 461.1709. $[\alpha]_D^{26}=-31.3$ (*c* 1.02, $CHCl_3$). NOEs were observed between 1′-H (δ 3.64) and 3-H (δ 2.27), 1″-H (δ2.46) and olefinic-H (δ 4.52), and 1″ H (δ 2.46) and 2-H (δ 4.03) in NOESY spectroscopy.

21: Yellow oil; IR ($CHCl_3$) 1345, 1161 (NSO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.57 (3H, br s), 2.05 (1H, br td, J=10, 8 Hz), 2.45 (3H, s), 2.50 (1H, m), 2.59 (1H, dd, J=13, 8 Hz), 2.93 (1H, dd, J=13, 5 Hz), 3.25 (1H, dd, J=12, 11 Hz), 3.26 (3H, s), 3.63 (1H, dd, J=12, 8 Hz), 3.79 (3H, m), 4 54 and 4.55 (2H, ABq, J=7 Hz), 4.65 (1H, br s), 4.79 (1H, br quint., J=1 Hz), 7.14–7.28 (5H, m), 7.33 (2H, br d, J=8 Hz), 7.76 (2H, br d, J=8 Hz); HRMS (EI, *m/z*) calcd for $C_{24}H_{31}NO_4S_2$ (M^+) 461.1692, found 461.1703. $[\alpha]_D^{26}=-62.9$ (*c* 0.81, $CHCl_3$). NOEs were observed between olefinic-H (δ 4.65, 4.79) and 3-H (δ 2.50), and 1″-H (δ 2.59, 2.93) and 4-H (δ 2.05) in NOESY spectroscopy.

(*S*)-3-Allyl-4-ethenyl-2-oxazolidinone (22c). According to the procedure described for the preparation of **14**, allylation of **13** (330 mg, 2.94 mmol) with allyl bromide gave **22c** (205 mg, 50%) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 3.52 (1H, ddt, J=15, 7, 1 Hz), 3.97 (1H, dd, J=9, 7 Hz), 4.12 (1H, ddt, J=15, 5, 2 Hz), 4.23 (1H, dt, J=9, 7 Hz), 4.44 (1H, t, J=9 Hz), 5.16–5.24 (2H, m), 5.30–5.37 (2H, m), 5.63 (2H, m).

[2*S*-(2α,3β,4β)]-[2-(Methoxymethoxy)methyl-4-(1-methylethenyl)-1-(4-methylphenyl)sulfonyl-3-(phenylsulfonyl)-methyl]pyrrolidine (23). To a solution of **20** (323 mg, 0.7 mmol) in MeOH (10 mL) was added dropwise a solution of OXONE® (2.17 g, 3.5 mmol) in H_2O (10 mL) at 0°C under a nitrogen atmosphere. After being stirred at room temperature for 3.5 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPCC (hexane/AcOEt 1:1) to afford **23** (293 mg, 85%) as colorless crystals: mp 120–121°C (Et_2O); IR ($CHCl_3$) 1348, 1166 (NSO_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (3H, br s), 1.48 (1H, dd, *J*=14, 11 Hz), 2.47 (1H, br d, *J*=14 Hz), 2.45 (3H, s), 2.65 (1H, br dd, *J*=11, 6 Hz), 2.89 (1H, dd, *J*=11, 9 Hz), 3.15 (1H, br dt, *J*=11, 7 Hz), 3.55 (1H, dd, *J*=9, 7 Hz), 3.65 (1H, dd, *J*=10, 7 Hz), 3.77 (1H, dd, *J*=10, 4 Hz), 4.07 (1H, br dd, *J*=7, 4 Hz), 4.48 (1H, br s), 4.67 and 4.68 (2H, ABq, *J*=7 Hz), 4.86 (1H, br s,), 7.36–7.84 (9H, m); HRMS (EI, *m/z*) calcd for $C_{24}H_{31}NO_6S_2$ (M^+) 493.1590, found 493.1584. Anal. calcd for $C_{24}H_{31}NO_6S_2$: C, 58.40; H, 6.33; N, 2.84; S, 12.99. Found: C, 58.33; H, 6.28; N, 2.83; S, 13.12. $[\alpha]_D^{27}=-17.5$ (*c* 0.97, $CHCl_3$).

Methyl [2*S*-(2α,3β,4β)]-[2-(methoxymethoxy)methyl-4-(1-methylethenyl)-1-[(4-methylphenyl)sulfonyl]-α-phenylsulfonyl]-3-pyrrolidineacetate (24). To a solution of **23** (179 mg, 0.36 mmol) in THF (6.5 mL) was added dropwise MeLi (1.04 M in Et_2O) (2.9 mL, 2.5 mmol) at −78°C under a nitrogen atmosphere. After being stirred at the same temperature for 0.5 h, methyl chloroformate (0.56 mL, 7.2 mmol) was added dropwise to the reaction mixture. After being stirred at 0°C for 4 h, the reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPCC (hexane/AcOEt 3:1) to afford **24** (178 mg, 89%) as colorless amorphous; IR ($CHCl_3$) 1741 (COO), 1329, 1152 (NSO_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.62 (3H, br s), 2.40 (3H, s), 3.17–3.34 (4H, m), 3.30 (3H, s), 3.57 (3H, s), 3.65 (1H, dd, *J*=11, 3 Hz), 3.78 (1H, dd, *J*=11, 4 Hz), 3.97 (1H, d, *J*=2 Hz), 4.50 and 4.55 (2H, ABq, *J*=6 Hz), 4.68 (1H, br s), 4.85 (1H, br t, *J*=4 Hz), 5.03 (1H, br s), 7.36–7.84 (9H, m); HRMS (EI, *m/z*) calcd for $C_{26}H_{33}NO_8S_2$ (M^+) 551.1646, found 551.1668.

Methyl [2*S*-(2α,3β,4β)]-[2-(methoxymethoxy)methyl-4-(1-methylethenyl)-1-[(4-methylphenyl)sulfonyl]-3-pyrrolidineacetate (25). To a solution of **24** (56 mg, 0.10 mmol) in MeOH (0.4 mL) was added Na_2HPO_4 (57 mg, 0.4 mmol) and 5% Na–Hg (112 mg, 0.24 mmol) at 0°C under a nitrogen atmosphere. After being stirred at the same temperature for 4 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPCC (hexane/AcOEt 3:1) to afford **25** (22 mg, 86%) as colorless crystals: mp 51.5–52°C (Et_2O) [lit.[10] mp 124–126°C (Et_2O)]; IR ($CHCl_3$) 1733 (COO), 1347, 1165 (NSO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (1H, dd, *J*=17, 11 Hz), 1.67 (3H, br s), 1.80 (1H, dd, *J*=17, 4 Hz), 2.45 (3H, s), 2.66 (1H, ddd, *J*=11, 6, 4 Hz), 3.03 (1H, dd, *J*=11, 9 Hz), 3.10 (1H, br dt, *J*=10, 6 Hz), 3.59 (3H, s), 3.52 (1H, dd, *J*=11, 6 Hz), 3.59 (3H, s), 3.65 (1H, br dd, *J*=7, 3 Hz), 3.67 (1H, dd, *J*=9, 7 Hz), 3.78 (1H,dd, *J*=9, 3 Hz), 4.52 (1H, br s), 4.64 and 4.67 (2H, ABq, *J*=6 Hz), 4.85 (1H, br q, *J*=6 Hz), 7.34 (2H, br d, *J*=8 Hz), 7.76 (2H, br d, *J*=8 Hz); HRMS (EI, *m/z*) calcd for $C_{20}H_{29}NO_6S$ (M^+) 411.1714, found 411.1703. $[\alpha]_D^{24}=-41.6$ (*c* 0.77, $CHCl_3$) [lit.[10] $[\alpha]_D^{15}=-31.1$ (*c* 1.0, $CHCl_3$)].

Methyl [2*S*-(2α,3β,4β)]-[2-(Hydroxymethyl)-4-(1-methylethenyl)-1-[(4-methylphenyl)sulfonyl]-3-pyrrolidineacetate (26). To a solution of **25** (140 mg, 0.34 mmol) in CH_2Cl_2 (1.2 mL) was added dropwise TFA (0.12 mL, 1.33 mmol) at room temperature under a nitrogen atmosphere at room temperature. After being stirred at the same temperature for 3 h, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPCC (hexane/AcOEt 4:1) to afford **26** (121 mg, 97%) as colorless crystals: mp 110–111°C (Et_2O) [lit.[10] mp 112–113°C]; IR ($CHCl_3$) 1732 (COO), 1345, 1163 (NSO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (1H, dd, *J*=17, 12 Hz), 1.65 (3H, br s), 1.81 (1H, dd, *J*=17, 3 Hz), 2.46 (3H, s), 2.54 (1H, br ddd, *J*=11, 6. 4 Hz), 3.00 (1H, br dt, *J*=11, 6 Hz), 3.07 (1H, dd, *J*=12, 9 Hz), 3.53 (1H, br t, *J*=6 Hz), 3.58 (1H, dd, *J*=9, 6 Hz), 3.59 (3H, s), 3.76 (1H, dd, *J*=11, 6 Hz), 3.80 (1H, dd, *J*=11, 6 Hz), 4.52 (1H, br s), 4.86 (1H, br q, *J*=2 Hz), 7.35 (2H, br d, *J*=8 Hz), 7.76 (2H, br d, *J*=8 Hz); HRMS (EI, *m/z*) calcd for $C_{18}H_{25}NO_5S$ (M^+) 367.1452, found 367.1430. Anal. calcd for $C_{18}H_{25}NO_5S$: C, 58.84; H, 6.86; N, 3.81; S, 8.73. Found: C, 58.72; H, 6.78; N, 3.80; S, 8.62. $[\alpha]_D^{25}=-21.1$ (*c* 0.97, $CHCl_3$) [lit.[10] $[\alpha]_D^{15}=-13.7$ (*c* 1.04, $CHCl_3$)].

Methyl [2*S*-[2α(*R),3β,4β]]-2-[(3,3,3-Trifluoro-2-methoxy-1-oxo-2-phenylpropoxy)methyl-4-(1-methylethenyl)-1-[(4-methylphenyl)sulfonyl]-3-pyrrolidineacetate (27).** To a solution of (−)-alcohol **26** (14 mg, 0.04 mmol) in CH_2Cl_2 (3 mL) was added pyridine (0.04 mL, 0.5 mmol) and (+)-MTPACl (100 mg, 0.4 mmol) at room temperature under a nitrogen atmosphere. After being stirred at the same temperature for 3 h, the solvent was evaporated under reduced pressure. Purification of the residue by MPCC (hexane/AcOEt 3:1) afford **27** (18 mg, 88%) as a colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (1H, dd, *J*=17, 11 Hz), 1.55 (3H, br s), 1.79 (1H, dd, *J*=17, 3 Hz), 2.42 (1H, m), 2.44 (3H, s), 2.88 (1H, br dt, *J*=12, 6 Hz), 2.97 (1H, dd, *J*=12, 9 Hz), 3.39 (1H, dd, *J*=9, 7 Hz), 3.52 (3H, s-like), 3.76 (1H, br dd, *J*=5, 3 Hz), 4.23 (1H, br s), 4.35 (1H, dd, *J*=12, 3 Hz), 4.74 (1H, dd, *J*=12, 5 Hz), 4.79 (1H, br q, *J*=2 Hz), 7.33 (2H, br d, *J*=8 Hz), 7.40 (3H, m), 7.54 (2H, m), 7.74 (2H, br d, *J*=8 Hz).

Methyl [2*S*-(2α,3β,4β)]-[2-(Methoxycarbonyl)-4-(1-methylethenyl)-1-[(4-methylphenyl)sulfonyl]-3-pyrrolidineacetate (28). To a solution of **26** (125 mg, 0.34 mmol) in DMF (0.65 mL) was added PDC (403 mg, 1 mmol) and molecular sieves (4 Å) (260 mg) at room temperature under a nitrogen atmosphere. After being stirred at the same temperature for 21 h, a solution of CH_2N_2 (0.41 mmol) in Et_2O (10 mL) was added to the reaction mixture. After being stirred at the same temperature for

1 h, the reaction mixture was diluted with H_2O and extracted with AcOEt. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by MPCC (hexane/AcOEt 2:1) to afford **28** (117 mg, 87%) as colorless crystals: mp 115.5–116°C (Et_2O) [lit.[10] mp 139–140°C]; IR ($CHCl_3$) 1737 (COO), 1352, 1166 (NSO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.59 (3H, dd, J=17, 11 Hz), 1.65 (3H, br s), 2.07 (1H, dd, J=17, 4 Hz), 2.44 (3H, s), 2.81 (1H, m), 3.09 (1H, m), 3.26 (1H, dd, J=9, 8 Hz), 3.56 (1H, dd, J=9, 7 Hz), 3.66 (3H, s), 3.77 (3H, s, OMe), 4.30 (1H, d, J=2 Hz), 4.59 (1H, br s), 4.89 (1H, br q, J=2 Hz), 7.33 (2H, br d J=8 Hz), 7.78 (2H, br d, J=8 Hz); HRMS (EI, m/z) calcd for $C_{19}H_{25}NO_6S$ (M^+) 395.1401, found 395.1381. Anal. calcd for $C_{19}H_{25}NO_6S$: C, 57.71; H, 6.37; N, 3.54; S, 8.11. Found: C, 57.42; H, 6.32; N, 3.50; S, 8.22. $[\alpha]_D^{24}=-46.3$ (c 1.08, $CHCl_3$) [lit.[10] $[\alpha]_D^{15}=-48.1$ (c 1.0, $CHCl_3$)].

(−)-α-Kainic acid (1). To a solution of **28** (56 mg, 0.14 mmol) in MeOH (0.5 mL) was added a solution of LiOH (126 mg, 3.0 mmol) in H_2O (0.5 mL) at room temperature under a nitrogen atmosphere. After being stirred at the same temperature for 1 h, the reaction mixture was acidified to pH 2 and extracted with AcOEt. The organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude dicarboxylic acid **29**. To liquid ammonia (3 mL) was added a solution of **29** in THF (0.5 mL) and then Li (8 mg, 1.1 mmol) at −78°C. After additional stirring at the same temperature for 30 min, the reaction mixture was quenched with isoprene. Ammonia was removed and the residue was dissolved in H_2O (1 mL) and neutralized to pH 7 with cold 2 M HCl. The resulting aqueous solution was loaded on resin (Amberlite CG-50) in a column and washed with water. After concentration, the residue was recrystallized from EtOH to give **1** (26 mg, 88%) as colorless crystals: mp 242–243°C (dec.) [lit.[11] mp 243–244°C (dec.)]; IR (nujol) 3520 (OH), 3130, 2600, 1680, 1621 (COOH, COO^-) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.68 (3H, br s), 2.18 (1H, dd, J=16, 8 Hz), 2.28 (1H, dd, J=16, 6.5 Hz), 2.91 (1H, br dt, J=11, 7 Hz), 2.97 (1H, m), 3.34 (1H, t, J=11 Hz), 3.62 (1H, J=11, 7 Hz), 3.98 (1H, br s), 4.94 (1H, br s); HRMS (EI, m/z) calcd for $C_{10}H_{15}NO_4$ (M^+) 213.1000, found 213.1020. $[\alpha]_D^{24}=-14.0$ (c 0.50, H_2O) [lit.[11] $[\alpha]_D^{24}=-14.2$ (c 0.23, H_2O)].

Acknowledgements

We are grateful to Professors S. Yoo and S. H. Lee, Korean Research Institute of Chemical Technology, for sending us the precious spectral data of the ester **25**. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan and a research grant from the Science Research Promotion Fund of the Japan Private School Promotion Foundation.

References

1. Part 9: Kiguchi, T.; Tajiri, K.; Ninomiya, I.; Naito, T.; *Tetrahedron*, **2000**, *32*, 5819–5833.

2. For reviews, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Baldwin, J. E., Ed.; Pergamon: Oxford, 1986. (b) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541–3676. (c) Curran, D. P. *Synthesis* **1988**, 417–439 and 489–513. (d) Jasperse, C. P.; Curran, D. P.; Fervig, T. *Chem. Rev.* **1991**, 1237–1286. (e) Crich, D. *Organosulfur Chemistry: Synthetic Aspects* Page, P., Ed.; Academic: London, 1995; Vol. 1, pp 49–88. (f) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React. (N. Y.)* Paquette, L. A., Ed.; Wiley: New York, 1996; Vol. 48, pp 301–856. (g) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177–194. (h) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543–17594. (i) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2562–2579. (j) Chatgilialoghi, C.; Bertrand, M. P.; Ferreri, C. *The Chemistry of Free Radicals: S-Centered Radicals*; Alfassi, Z. B., Ed.; Wiley: Chichester, 1999; pp 311–348. (k) Naito, T. *Heterocycles* **1999**, *50*, 505–541. (l) Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc. Perkin Trans. 1* **2000**, 1–14. (m) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746–2750. (n) Musa, O. M.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1999**, *64*, 1022–1025.

3. For reviews for syntheses of kainoids, see: (a) Hashimoto, K.; Shirahama, H. *J. Synth. Org. Chem. Jpn* **1989**, *47*, 212–223. (b) Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149–4174. For total synthesis of α-kainic acid using radical cyclization, see: (c) Baldwin, J. E.; Moloney, M. G.; Parson, A. F. *Tetrahedron* **1990**, *46*, 7263–7282. (d) Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1993**, 125–127. (e) Hannessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418–5424. (f) Bachi, M. D.; Melman, A. *J. Org. Chem.* **1997**, *62*, 1896–1898. (g) Miyata O.; Ozawa Y.; Ninomiya I.; Aoe K.; Hiramatsu H.; Naito T. *Heterocycles* **1997**, *46*, 321–333. (h) Cossy, J.; Cases, M.; Pardo, D. G. *Tetrahedron* **1999**, *55*, 6153–6166.

4. We have reported the sulfanyl radical addition–cyclization for heterocycle synthesis. (a) Naito, T.; Honda, Y.; Miyata, O.; Ninomiya, I. *Chem. Pharm. Bull.* **1993**, *41*, 217–219. (b) Naito, T.; Honda, Y.; Miyata, O.; Ninomiya, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 19–26. (c) Miyata O.; Nishiguchi, A.; Ninomiya, I.; Naito, T.; Aoe, K.; Okamura, K. *Tetrahedron Lett.* **1996**, *37*, 229–232. (d) Miyata, O.; Nishiguchi, A.; Ninomiya, I.; Naito, T. *Chem. Pharm. Bull.* **1996**, *44*, 1285–1287. (e) Naito, T.; Honda, Y.; Bhavakul, V.; Yamaguchi, S.; Fujiwara, A.; Miyata, O.; Ninomiya, I. *Chem. Pharm. Bull.* **1997**, *45*, 1932–1939. (f) Miyata, O.; Muroya, K.; Koide, J.; Naito, T. *Synlett* **1998**, 271–272.

5. Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Synlett* **1997**, 275–276.

6. Murakami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn* **1953**, *73*, 1026–1029.

7. Oppolzer, W.; Thirring, K. J. *J. Am. Chem. Soc.* **1982**, *104*, 4978–4979.

8. (a) Oroshnik, W.; Mallory, R. A. *J. Am. Chem. Soc.* **1950**, *72*, 4608–4613. (b) Sato, T.; Hanayama, K.; Fujisawa, T. *Tetrahedron Lett.* **1988**, *29*, 2197–2200.

9. Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1984**, *25*, 1071–1074.

10. Yoo, S.; Lee, S. H. *J. Org. Chem.* **1994**, *59*, 6968–6972.

11. Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467–6471.