Expeditious Syntheses of Conjugated Allenyl Esters and Oxazoles through a Cascade Reaction of α-Alkynyl Malonates under Alkaline Conditions

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Diethyl α-alkynyl-α-methoxymalonates (2a—e) were smoothly hydrolyzed and then decarboxylated under alkaline conditions employing 1 N KOH in EtOH to give conjugated allenyl esters (6a—e) in high yields, and similar alkaline treatment of diethyl α-alkynyl-α-acetylaminomalonates (5a, b, d, e) furnished unexpectedly the oxazoles (7a, b, d, e) having three substituent groups in excellent yields.

Key words conjugated allenyl ester; oxazole; α-alkynyl methoxymalonate; α-alkynyl acetylaminomalonate; hydrolysis; decarboxylation

Since the development of various synthetic methods for the achiral and chiral allenes, extensive studies on the structure and reactivity of the characteristic allenes have been performed.[1—9] Allenylic compounds have been efficiently utilized as a key intermediate to synthesize biologically active natural products.[10—12] The specific reactivities of allenylic compounds have been widely applied to carbon–carbon and carbon–hetero atom cyclizations, aldol reactions, Diels–Alder reactions, [2+2] and [4+2] cycloadditions, *etc.*[13—19] Because of this usefulness of allenes, there have been many reports on methods for constructing the allenylic moieties.[1—9,20—26] Previously, we communicated a characteristic synthetic method for conjugated allenyl esters and trisubstituted oxazoles *via* alkaline hydrolysis of diethyl α-alkynyl-α-methoxy(or acetylamino)malonates followed by decarboxylation of the corresponding resultant monocarboxylates in a cascade reaction manner.[27]

We now describe, in detail, expeditious syntheses of conjugated allenyl esters and trisubstituted oxazoles and the related reactions based on the following concept and background.[28] Cysteine proteases of the papain family have been implicated in the pathogenesis of a various of serious diseases. Hence, the development of cysteine protease inhibitors has been extensively studied worldwide.[29] We thus designed diethyl α-alkynyl-α-methoxy(or acetylamino)malonates (DAM, **A**) as new lead compounds for developing cysteine protease inhibitors, as shown in Chart 1.[27] Chart 1 illustrates our idea of the enzyme inhibition and latent function of DAM (**A**), readily obtained from the reaction of diethyl keto(or acetylimino)malonate with alkynyl anionic species, against cysteine proteases. Namely, enzymatic and/or non-enzymatic hydrolysis of an ethoxycarbonyl group (a "trigger" moiety leading compounds **A** to the conjugated allenyl ester) of the DAM (**A**) followed by enzymatic and/or non-enzymatic decarboxylation of the corresponding resultant monocarboxylic acids **B** may generate the conjugated allenyl esters **C**. The conjugated allenyl esters **C** must be capable of trapping an active-site nucleophile (SH group of the cysteine residue)[30] of the target enzyme, which may cause inhibition of the SH enzymes. In the molecule of DAM (**A**), the R group would be designed as the specific enzyme-recognition moiety bearing a di- or tripeptide substituent.

Diethyl α-alkynyl-α-methoxymalonates **2a**—**e**, employed for syntheses of conjugated allenyl esters (*vide infra*), were readily prepared from diethyl ketomalonate by its treatment with various ethynyl lithiums derived from **1a**—**e**, as shown

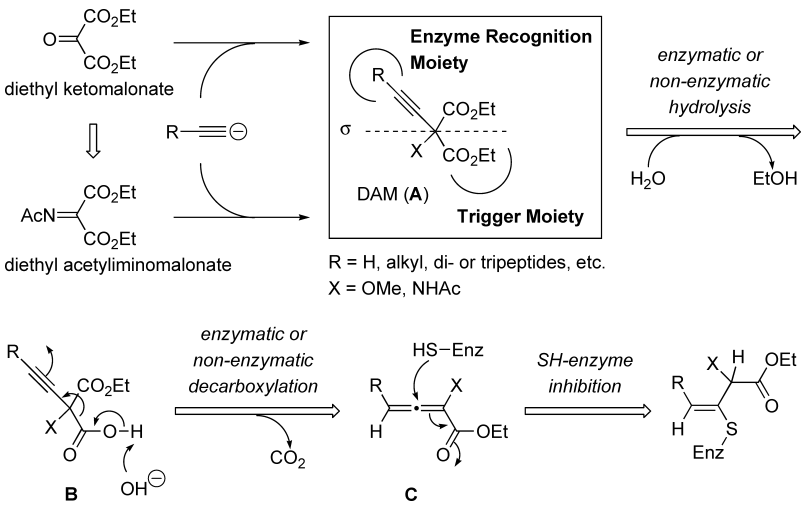

Chart 1

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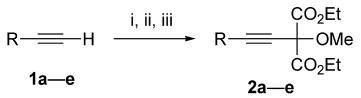
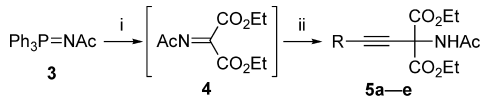
Table 1. Synthesis of α-Alkynyl-α-methoxymalonates **2a**—**e**



i) *n*-BuLi (1 mol eq), THF, -78 °C, 1 h
ii) diethyl ketomalonate (1 mol eq), -78 °C, THF, 1 h → r.t. , 1 h
iii) $(MeO)_2SO_4$ (1 mol eq), THF, reflux, 3.5 h

	R		Yield (%)
a	Me—	**2a**	55
b		**2b**	52
c	Me—	**2c**	50
d		**2d**	37
e	Me_3Si—	**2e**	67

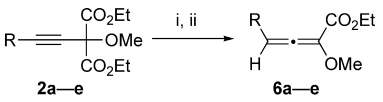
Table 2. Synthesis of α-Alkynyl-α-acetyliminomalonates **5a**—**e**



i) diethyl ketomalonate (1 mol eq), THF, reflux, 10-15 h
ii) R—≡—H (**1a—e**, 1 mol eq), *n*-BuLi (1 mol eq), THF, -78 °C, 4 h

	R		Yield (%)
a	Me—	**5a**	82
b		**5b**	67
c	Me—	**5c**	62
d		**5d**	90
e	Me_3Si—	**5e**	81

Table 3. Synthesis of Conjugated Allenyl Esters **6a**—**e**

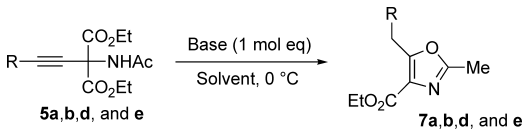


i) 1N KOH (1 mol eq), EtOH, 0 °C, 10-15 min
ii) 1N HCl (1 mol eq)

	R		Yield (%)
a	Me—	**6a**	94
b		**6b**	92
c	Me—	**6c**	100
d		**6d**	93
e	Me_3Si—	**6e**[a]	87

a) R=H.

Table 4. Synthesis of 2,4,5-Trisubstituted Oxazoles **7a**, **b**, **d**, and **e**



	R		Base	Solvent	Time		Yield (%)
a	Me—		1 N KOH	EtOH	20 min	**7a**	93
b			1 N KOH	EtOH	15 min	**7b**	98
d			1 N KOH	EtOH	5 min	**7d**	97
e	Me_3Si—		1 N KOH	EtOH	5 min	**7e**[a]	97
a	Me—		NaH	THF	2 h	**5a**	98 (recovery)
a	Me—		EtONa	THF	2 h	**5a**	96 (recovery)

a) R=H.

in Table 1. All desired products **2a**—**e** were obtained in 37—67% yields. The structures of **2a**—**e** were confirmed by the satisfaction of their spectroscopic requirements.

The synthesis of diethyl α-alkynyl-α-acetylaminomalonates **5a**—**e** was accomplished utilizing the aza-Wittig reaction of diethyl ketomalonate. Namely, acetyliminomalonate (**4**) was prepared by refluxing *N*-(triphenylphosphoranylidene)acetamide (**3**) and diethyl ketomalonate in THF for 10—15 h.[31] After the reaction mixture was cooled to −78 °C without isolation of **4**, a solution of each ethynyl lithium derived from **1a**—**e** in THF was added dropwise *via* cannula at −78 °C to give the corresponding products **5a**—**e** in 62—90% yields, as shown in Table 2. The structures of **5a**—**e** were reasonably assigned by their characteristic spectroscopic data.

As a model experiment for the enzymatic hydrolysis, alkaline hydrolyses of **2a**—**e** and **5a**—**e** were examined in order to realize our new idea illustrated in Chart 1. First, compounds **2a**—**e** were treated with 1 N KOH in EtOH at 0 °C. Thus, alkaline hydrolysis followed by decarboxylation and then formation of conjugated allenyl esters **6a**—**e** smoothly proceeded in a cascade reaction manner and in high yields, as anticipated. All results are summarized in Table 3. However, compounds **6a**—**e** were unstable at room temperature. In the case of **2e**, desilylated allenyl ester **6e** was obtained in 87% yield. The conjugated allenylic structures of **6a**—**e** were assigned by their characteristic spectroscopic data.

Next, we carried out alkaline hydrolysis of diethyl α-alkynyl-α-acetylaminomalonates **5a**, **b**, **d**, and **e** with 1 N KOH in EtOH at 0 °C in the same manner as for the compounds **2a**—**e**. Surprisingly, 2,4,5-trisubstituted oxazoles **7a**, **b**, **d**, and **e** were obtained in excellent yields instead of the corresponding allenyl ester-like compounds **6a**, **b**, **d**, and **e**, as shown in Table 4. Treatment of **5a** with EtONa or NaH in anhydrous THF resulted in recovery of the starting material (Table 4). Based on these results, initial alkaline hydrolysis of the ethyl ester moiety should play an important role in formation of the oxazole ring (*vide infra*).

The structure of oxazole **7a** was determined by X-ray crystallographic analysis (Fig. 1) of its alkaline hydrolysis product **7′a**,[32] which was readily converted to **7a** by esterification with EtBr in the presence of Et_3N, as shown in Chart 2. The structure of other oxazole derivatives **7b**, **d**, and **e** was determined on the basis of the similarity of characteristic ^{13}C-NMR spectrum data of the oxazole ring of **7b**, **d**, and **e** to those of **7′a**. Although there have been many useful methods for the syntheses of oxazoles,[33—38] this characteristic method giving the trisubstituted oxazoles in a cascade reaction manner (*vide infra*) seems to be unique.

Possible reaction mechanisms to generate conjugated allenyl esters **6a**—**e** from diethyl α-alkynyl-α-methoxymalonates **2a**—**e** and trisubstituted oxazole derivatives **7a**, **b**, **d**, and **e** from diethyl α-alkynyl-α-acetylaminomalonates **5a**, **b**, **d**, and **e** can be postulated, as shown in Chart 3. As anticipated in Chart 1, alkaline hydrolysis of an ethoxycarbonyl group of **2a**—**e** with KOH gave the corresponding malonic half-esters, which were instantly decarboxylated by OH^- to afford the conjugated allenyl esters **6a**—**e**. Similar alkaline hydrolysis of **5a**, **b**, **d**, and **e** with KOH also afforded the corresponding malonic half-esters, which were similarly decarboxylated by OH^- to form *in situ* the acetylamino allenyl esters **8a**, **b**, **d**, and **e**. Then, oxazole ring formation in the molecules **8** occurred *via* intramolecular 5-*endo-mode* cyclization. Thus, the overall reactions from **5a**, **b**, **d**, and **e** to trisubstituted oxazoles **7a**, **b**, **d**, and **e** proceeded in a cascade reaction manner,[28] as shown in Chart 3. The success of this intramolecular 5-*endo-mode* cyclization to give the trisubstituted oxazoles prompted us to develop various *endo-mode* carbocyclic and heterocyclic cyclization reactions by utilizing the conjugated allenyl ketone systems.[28,39]

In order to understand facile decarboxylation of ethyl hydrogen α-alkynyl-α-methoxymalonates **2′a**—**e** and ethyl hydrogen α-alkynyl-α-acetylaminomalonates **5′a**, **b**, **d**, and **e**, the following experiments were performed. Diethyl α-*cis*-styryl-α-methoxymalonate (**9**), obtained by hydrogenation of **2a** on 5% Pd–$BaSO_4$ in the presence of a catalytic amount of quinoline, was subjected to alkaline hydrolysis with 1 N KOH

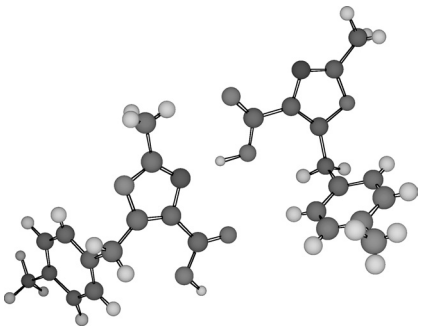
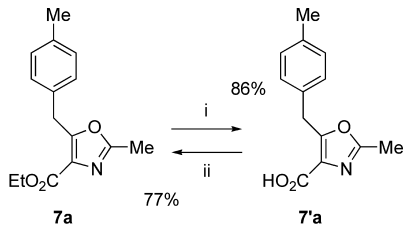
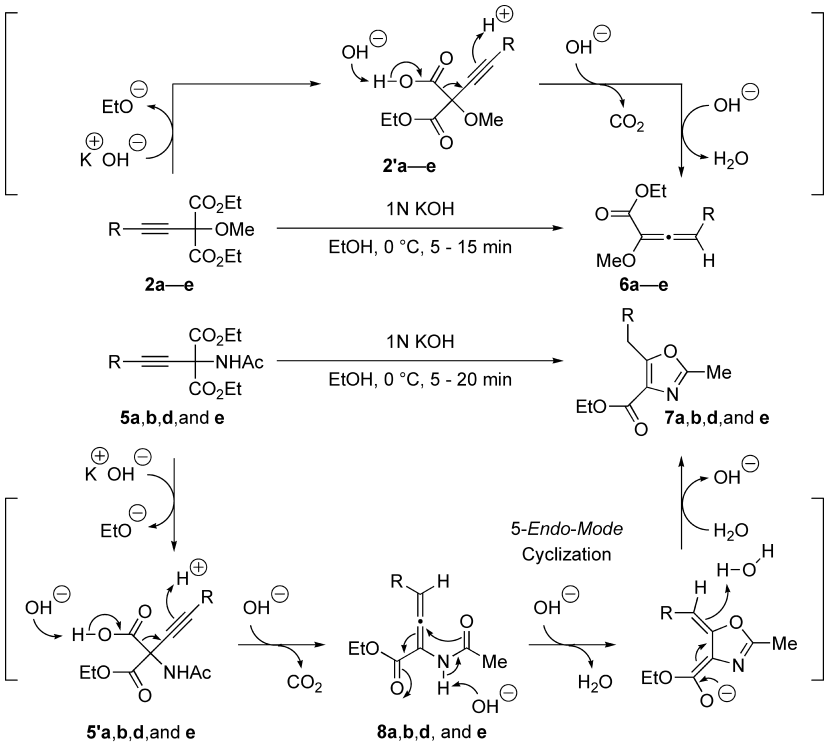


Fig. 1. Computer-Generated Drawing of the Crystallographic Structure of **7′a**



i) 1N KOH (2 mol eq), EtOH, 50 °C, 1 h
ii) EtBr (excess), Et_3N (1.2 mol eq), AcOEt—DMF (10 : 1), r.t., 48 h

Chart 2



2'e, **5'e**, **6e**, **7e**, and **8e** : R = H

Chart 3

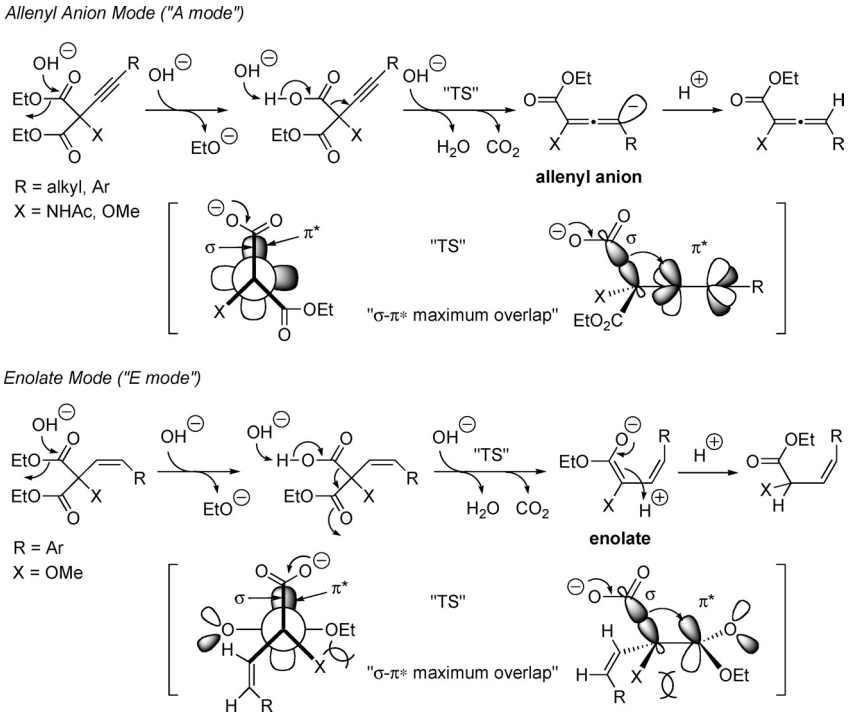


Fig. 2. Plausible Decarboxylation Modes in the Alkaline Hydrolysis of Malonic Half-Esters

in EtOH. The alkaline hydrolysis followed by decarboxylation took more reaction time (7 h) than that (5—20 min) of the cases of **2** and **5**, to furnish the desired decarboxylation *cis*-olefinic product **10** (30% yield), *trans*-olefinic product **11** (0.7% yield), and conjugated olefinic ester **12** (1.6% yield) together with 35% recovery of **9**, as shown in Chart 4. Based on the fact that the above reaction yielded **10** with its *cis*-olefinic geometry intact, the decarboxylation proceeded *via* exclusive enolization with the ethoxycarbonyl group. Decarboxylation based on the conjugation with the olefinic moiety to furnish **11** and **12** seemed to be negligible.

Decarboxylation of the α-alkynyl-malonic half-esters toward the conjugated allenyl ester formation *via* allenyl anion ("A" mode) may be facilitated by satisfying a stereoelectronic requirement ("TS") due to the maximum overlap of the s bond (alkynyl, EtO_2C, $XC–CO_2^-$) with the π^* bond of the alkynyl group, as shown in Fig. 2.[40] In this transition state, there is no specifically considerable steric repulsion for formation of the σ–π^* maximum overlap because of the linear alkynylic structure. On the other hand, in general, decarboxylation of the α-aryl- or α-alkyl-malonic half-esters in the enolization mode ("E" mode) seems to be difficult under the mild basic conditions.[41] Especially, in a possible transition state ("TS") involving the σ–π^* maximum overlap [σ bond (alkenyl, EtO_2C, $XC–CO_2^-$) and π^* bond of the ester carbonyl group], steric hindrance between the ethoxy group of EtO_2C– and the X (or olefinic) group may be enough to disturb the decarboxylation of **9**, as shown in Fig. 2 and Chart 4.

Proteases are principal enzymes for the functionalization of proteins, and their dysfunction is known to be cause of many serious diseases.[42—44] Therefore, in order to confirm the reactivity of the conjugated allenyl esters **6** and **8**, obtained by alkaline treatment of the corresponding precursors **2** and **5**, with the SH group of the cysteine residue of the enzymes, several biomimetic reactions of **2** and **5** with EtSH were investigated, as follows. After treatment of an EtOH solution of **2a**, **d** with 1 N KOH at 0 °C, EtSH was added to the solution and the mixture was stirred at 0 °C to obtain **13a** in 61% yield and **13d** in 69% yield, respectively (Chart 5).

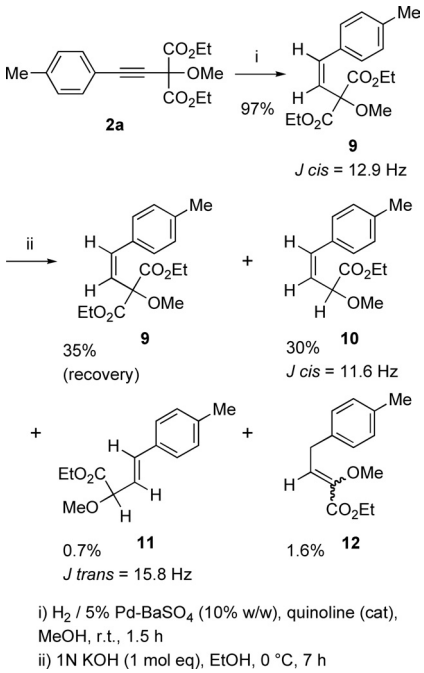
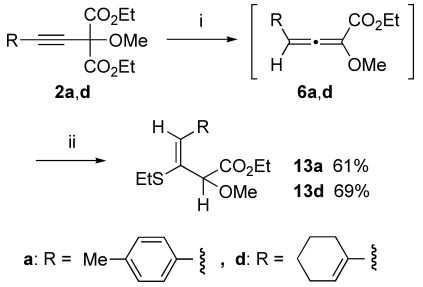


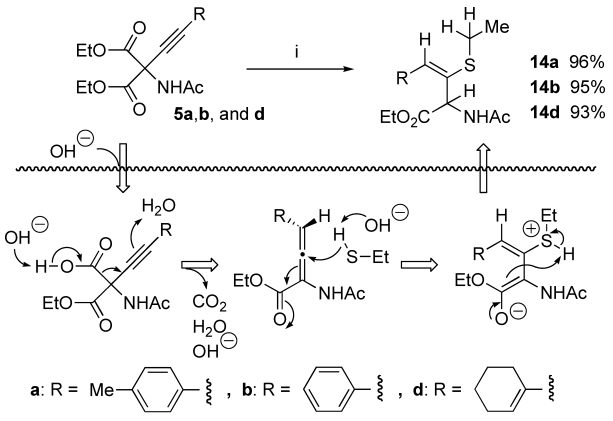
Chart 4

Diethyl α-alkynyl-α-acetylaminomalonates **5a**, **b**, and **d** were allowed to react with EtSH in the presence of 1 N KOH in EtOH at 0 °C. The Michael-type addition of EtSH to the allenyl esters **8a**, **b**, and **d** which were generated *in situ*, proceeded to afford the corresponding *E*-olefinic thiol adducts



i) 1N KOH (1 mol eq), EtOH, 0 °C, 15 min
ii) EtSH (1.1 mol eq), EtOH, 0 °C, 80 min

Chart 5



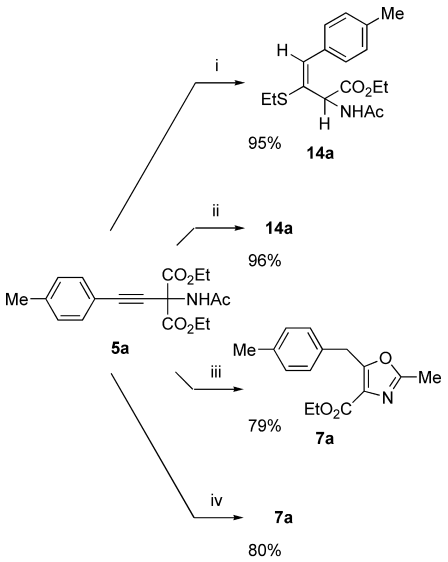
i) EtSH (1. mol eq), 1N KOH (1 mol eq), EtOH, 0 °C, 30 min

Chart 6

14a, **b** and **d** in high yields and in a highly stereoselective manner as expected (Chart 6).

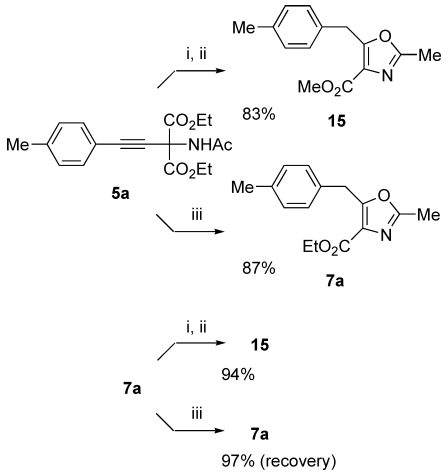
The *E*-geometry of **13a**, **d** and **14a**, **b**, and **d** was determined by their NOE measurement between the olefin proton and methylene protons of the ethyl thio group. This fact indicates that thiol addition to the *sp* carbon atom of the conjugated trisubstituted allenyl esters should occur from the opposite side ("less-hindered side") against the R group in the molecule **6** or **8**. Interestingly, this intermolecular thiol addition to the allenyl *sp* carbon atom proceeded more predominantly than the oxazole-ring formation *via* intramolecular 5-*endo-mode* cyclization. Furthermore, competitive intramolecular addition reactions onto the conjugated allenyl *sp* carbon atom of **8** among three kinds of nucleophiles, *i.e.*, EtSH (a cysteine-residue "mimic" in the molecule of various proteases), EtOH (a serine-residue "mimic"), and $EtNH_2$ or imidazole (a lysine- or histidine-residue "mimic") were examined by employing **5a** in the same flask. Thiol adduct **14a** was exclusively obtained in 95% or 96% yield, respectively (Chart 7). However, similar treatment of **5a** with an EtOH solution of $EtNH_2$ or imidazole without the use of EtSH afforded oxazole ester **7a** in 79% or 80% yield, respectively. Thus, the *sp* carbon atom of the conjugated allenyl ester moiety chemoselectively reacted with the SH group.[30] Specifically, the compounds **2**, **5**, and **6** must be expected to be cysteine protease inhibitors.[27]

Finally, an enzymatic hydrolysis of diethyl α-alkynyl-α-acetylaminomalonate **5a** using porcine liver esterase (PLE)



i) EtSH (2.4 mol eq), $EtNH_2$ (2.4 mol eq), 1N KOH (1 mol eq), EtOH, 0 °C, 30 min
ii) EtSH (2.4 mol eq), imidazole (2.4 mol eq), 1N KOH (1 mol eq), EtOH, 0 °C, 30 min
iii) $EtNH_2$ (2.4 mol eq), 1N KOH (1 mol eq), EtOH, 0 °C, 5 min
iv) imidazole (2.4 mol eq), 1N KOH (1 mol eq), EtOH, 0 °C, 5 min

Chart 7



i) Porcine Liver Esterase (Sigma Type I, 100 units), 0.1M phosphate buffer (pH 7.5)—acetone (10 : 1), 35-45 °C, 5 days
ii) CH_2N_2, Et_2O
iii) 0.1M phosphate buffer (pH 7.5)—acetone (10 : 1), 35-45 °C, 5 days

Chart 8

was tentatively investigated by using reaction conditions similar to those used for the enzymatic hydrolysis of prochiral σ-symmetrical esters with PLE,[45—49] as shown in Chart 8. Namely, **5a** was treated with PLE (Sigma Type I, 100 units) in a solution of 0.1 M phosphate buffer (pH 7.5)–acetone (10 : 1) at 35—45 °C for 5 d. After methylation of the resulting carboxylic acid with CH_2N_2, trisubstituted oxazole methyl ester **15** was obtained in 83%. In order to understand the oxazole ring formation in the PLE reaction, **5a** was subjected to the non-enzymatic conditions [0.1 M phosphate

buffer (pH 7.5)–acetone (10 : 1) at 35—45 °C for 5 d]. Then, the trisubstituted oxazole ethylester **7a** was obtained in 87% yield even without the use of PLE. Treatment of **7a** with PLE in a solution of 0.1 M phosphate buffer (pH 7.5)–acetone (10 : 1) at 35—45 °C for 5 d followed by methylation with CH_2N_2 gave **15** in 94% yield. An attempt at hydrolysis of **7a** in a solution of 0.1 M phosphate buffer (pH 7.5)–acetone (10 : 1) at 35—45 °C for 5 d resulted in 97% recovery of **7a**. Thus, it was ascertained that PLE would not cause the trisubstituted oxazole formation toward **7a** but only the ethyl ester group of **7a**, was hydrolyzed enzymatically.

In conclusion, we have established the characteristic synthetic methods for conjugated allenyl esters from diethyl α-alkynyl-α-methoxy malonates and for trisubstituted oxazole derivatives from α-alkynyl-α-acetylaminomalonate in a remarkable cascade reaction manner by utilizing a unique trigger system involving ester hydrolysis followed by decarboxylation to form the conjugated allenyl ester system. This trigger system should be highly useful for bioorganic and chemical design; *e.g.*, enediyne chemistry.[50,51] We have also demonstrated the important role of the alkynyl moiety for facile reactivity of α-alkynylmalonates to generate the conjugated allenyl system, and suggested the possibility of developing new cysteine protease inhibitors based on several biomimetic reactions using the conjugated alleny compounds and their precursor compounds.

Experimental

All melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. IR spectra were obtained using a Hitachi 260-50 or JASCO VALOR-III spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM-FX 200 (200, 50 MHz), JEOL JNM-EX 270 (270, 68 MHz), or JEOL GSX-400 (400, 100 MHz) spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane (TMS) as an internal standard. MS spectra were recorded on a JEOL JMS-D 300 or JEOL JMS SX-102A spectrometer. Elementary combustion analyses were performed using a Yanaco CHN CORDER MT-5. HPLC analyses were performed using a Shimadzu LC-10A equipped with ULTRON® Vx-octyl (0.46 cm i.d.×25 cm) column and UV/VIS detector (SPD-10A). All reactions were monitored by TLC employing 0.25-mm silica gel plates (Merck 5715; 60 F_{254}). Preparative TLC (PTLC) was performed on 0.5-mm silica gel plates (Merck 5744; 60 F_{254}). Column chromatography was carried out on silica gel (Wako Pure Chemical Industry; 74—149 mesh) using the indicated eluents. THF was distilled from sodium benzophenone ketyl under N_2. All reagents were used as purchased.

Typical Procedure for the Preparation of α-Alkynyl-α-methoxymalonates 2 To a solution of 4-ethynyltoluene (**1a**) (580 mg, 5 mmol) in THF (15 ml) was added dropwise *n*-BuLi (3 ml, 5 mmol) at −78 °C. After stirring at −78 °C for 1 h, the reaction mixture was added to a solution of diethyl ketomalonate (0.8 ml, 5 mmol) in THF (7.5 ml) *via* cannula at −78 °C over 1 h and stirred at room temperature for additional 1 h. Dimethyl sulfate (0.5 ml, 5 mmol) was then added and the resulting mixture was refluxed for 3.5 h. After the mixture was cooled down to room temperature, 1 N HCl was added and extracted with Et_2O. The organic layer was washed with saturated $NaHCO_3$, brine, and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel with *n*-hexane–AcOEt (8 : 2, v/v) to yield **2a** (798 mg, 55%) as a pale yellow oil.

Ethyl 2-Methoxy-2-(ethoxycarbonyl)-4-*p*-tolyl-3-butynoate (**2a**): Pale yellow oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.33 (6H, t, J=7.1 Hz), 2.36 (3H, s), 3.58 (3H, s), 4.34 (4H, q, J=7.1 Hz), 7.14 (2H, d, J=8.1 Hz), 7.41 (2H, d, J=8.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.99, 21.54, 54.37, 62.97, 79.87, 80.08, 89.52, 118.30, 129.10, 132.07, 139.58, 165.40; IR (neat) 2984, 2232, 1752, 1510, 1447 cm^{-1}. EI-MS Calcd for $C_{17}H_{20}O_5$ MW 304.1311, Found *m*/*z* 304.1295 (M^+).

Ethyl 2-Methoxy-2-(ethoxycarbonyl)-4-phenyl-3-butynoate (**2b**): Pale yellow oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.34 (6H, t, J=7.1 Hz), 3.60 (3H, s), 4.35 (4H, t, J=7.1 Hz), 7.27—7.38 (3H, m), 7.50—7.55 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.12, 54.44, 62.98, 80.06, 80.58, 89.31, 121.42, 128.39, 129.35, 132.20, 165.35; IR (neat) 2984, 2833, 2233, 1752, 1491 cm^{-1}. EI-MS Calcd for $C_{16}H_{18}O_5$ MW 290.1154, Found *m*/*z* 290.1158 (M^+).

Ethyl 2-Methoxy-2-(ethoxycarbonyl)-3-heptynoate (**2c**): Yellow oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.01 (3H, t, J=7.3 Hz), 1.30 (6H, t, J=7.1 Hz), 1.50—1.70 (2H, m), 2.30 (2H, t, J=7.0 Hz), 3.50 (3H, s), 4.30 (4H, q, J=7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.39, 13.98, 20.82, 21.67, 54.10, 62.80, 71.96, 79.67, 90.92, 165.70; IR (neat) 2967, 2833, 2242, 1752, 1465 cm^{-1}. FAB-MS Calcd for $C_{13}H_{20}O_5$ MW+Na 279.1208, Found *m*/*z* 279.1203 (M^++Na). *Anal.* Calcd for $C_{13}H_{20}O_5$: C, 60.91; H, 7.87. Found, C, 60.61; H, 8.07.

Ethyl 2-Methoxy-2-(ethoxycarbonyl)-4-(1-cyclohexen-1-yl)-3-butynoate (**2d**): Yellow oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.31 (6H, t, J=7.1 Hz), 1.46—1.72 (4H, m), 1.97—2.21 (4H, m), 3.51 (3H, s), 4.31 (4H, q, J=7.1 Hz), 6.20—6.32 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.95, 13.99, 21.32, 22.09, 25.67, 28.68, 54.20, 62.77, 62.86, 77.71, 79.99, 91.28, 119.35, 137.70, 137.75, 165.54; IR (neat) 2937, 2220, 1752, 1448 cm^{-1}. EI-MS Calcd for $C_{16}H_{22}O_5$ MW 294.1467, Found *m*/*z* 294.1475 (M^+). *Anal.* Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found, C, 64.82; H, 7.73.

Ethyl 2-Methoxy-2-(ethoxycarbonyl)-4-(trimethylsilyl)-3-butynoate (**2e**): Pale yellow oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.22 (9H, s), 1.31 (6H, t, J=7.1 Hz), 3.52 (3H, s), 4.31 (4H, q, J=7.1 Hz); IR (neat) 2964, 2361, 2171, 1756, 1466 cm^{-1}.

Typical Procedure for the Preparation of α-Alkynyl-α-acetyliminomalonates 5 To a solution of *N*-(triphenylphosphoranylidene)acetamide (**3**) (1.6 g, 5 mmol) in THF (25 ml) was added diethyl ketomalonate (0.8 ml, 5 mmol). The resulting mixture was warmed at reflux during 12 h. The reaction mixture was cooled down to −78 °C, a solution of *p*-tolylethynyl lithium that was prepared from 4-ethynyltoluene (**1a**) (0.6 ml, 5 mmol) and *n*-BuLi (3 ml, 5 mmol) in THF (5 ml) was added slowly at −78 °C over 1 h. The mixture was stirred for 3 h at −78 °C, and then 5% HCl was added. The mixture was extracted with Et_2O. The organic layer was washed with saturated $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel with *n*-hexane–Et_2O (1 : 5, v/v) to yield **5a** (1.32 g, 82%) as colorless needles.

Ethyl 2-(Acetylamino)-2-(ethoxycarbonyl)-4-(*p*-tolyl)-3-butynoate (**5a**): Colorless needles, mp 132—133 °C (*n*-hexane–CH_2Cl_2); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.32 (6H, t, J=7.1 Hz), 2.09 (3H, s), 2.33 (3H, s), 4.35 (4H, q, J=7.1 Hz), 7.04 (1H, br s), 7.10 (2H, d, J=8.3 Hz), 7.37 (2H, d, J=8.3 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.89, 21.53, 22.85, 60.73, 63.68, 81.74, 84.96, 118.79, 128.89, 132.08, 139.03, 165.18, 168.68; IR (KBr) 3363, 2985, 2238, 1757, 1682, 1505 cm^{-1}. *Anal.* Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found, C, 64.84; H, 6.56; N, 4.11.

Ethyl 2-(Acetylamino)-2-(ethoxycarbonyl)-4-phenyl-3-butynoate (**5b**): Yellow oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.33 (6H, t, J=7.1 Hz), 2.10 (3H, s), 4.36 (4H, q, J=7.1 Hz), 7.04 (1H, br s), 7.21—7.52 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.88, 22.80, 60.72, 63.71, 82.70, 84.70 121.87, 128.15, 128.86, 132.16, 165.08, 168.73; IR (neat) 3362, 2985, 2239, 1752, 1673, 1491 cm^{-1}. *Anal.* Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found, C, 63.88; H, 6.24; N, 4.28.

Ethyl 2-(Acetylamino)-2-(ethoxycarbonyl)-3-heptynoate (**5c**): White powder, mp 53—54 °C (*n*-hexane–Et_2O); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.97 (3H, t, J=7.3 Hz), 1.30 (6H, t, J=7.1 Hz), 1.48—1.60 (2H, m), 2.06 (3H, s), 2.23 (2H, t, J=7.0 Hz), 4.31 (4H, q, J=7.1 Hz), 6.94 (1H, br s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.33, 13.86, 20.80, 21.67, 22.79, 60.28, 63.49, 73.84, 86.01, 165.45, 168.68; IR (KBr) 3370, 2968, 2875, 2247, 1752, 1668, 1505, 1370, 1268, 1125, 1016 cm^{-1}. *Anal.* Calcd for $C_{14}H_{21}NO_5$: C, 59.33; H, 7.47; N, 4.95. Found, C, 59.40; H, 7.54; N, 4.72.

Ethyl 2-(Acetylamino)-2-(ethyoxycarbonyl)-4-(1-cyclohexen-1-yl)-3-butynoate (**5d**): Colorless needles, mp 82 °C (*n*-hexane–Et_2O); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.30 (6H, t, J=7.1 Hz), 1.50—1.80 (4H, m), 2.06 (3H, s), 2.00—2.35 (4H, m), 4.32 (4H, q, J=7.1 Hz), 6.17—6.28 (1H, m), 6.93 (1H, br s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.88, 21.36, 22.13, 22.86, 25.63, 28.71, 60.60, 63.57, 79.64, 86.61, 119.54, 137.07, 165.29, 168.54; IR (KBr) 3251, 2215, 1752, 1656, 1510 cm^{-1}. *Anal.* Calcd for $C_{17}H_{23}NO_5$: C, 63.52; H, 7.22; N, 4.36. Found, C, 63.39; H, 7.25; N, 4.12.

Ethyl 2-(Acetylamino)-2-(ethoxycarbonyl)-4-(trimethylsilyl)-3-butynoate (**5e**): Colorless needles, mp 97 °C (*n*-hexane–Et_2O); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.18 (9H, s), 1.30 (6H, t, J=7.1 Hz), 2.06 (3H, s), 4.31 (2H, q, J=7.1 Hz), 4.32 (2H, q, J=7.1 Hz), 6.88 (1H, br s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 0.34, 14.13, 23.14, 61.00, 63.91, 90.84, 97.85, 165.22, 168.8; IR (KBr) 3286, 2986, 2239, 1752, 1671, 1490 cm^{-1}. *Anal.* Calcd for $C_{14}H_{23}NO_5Si$: C, 53.65; H, 7.40; N, 4.47. Found, C, 53.39; H, 7.53; N, 4.22.

Typical Procedure for the Preparation of Conjugated Allenyl Esters 6 To a solution of **2a** (247 mg, 0.8 mmol) in EtOH (8 ml) was added 1 N KOH (0.8 ml) at 0 °C. After stirring at 0 °C for 15 min, 1 N HCl was added to the reaction mixture and extracted with Et_2O. The organic layer was washed with water, brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to yield **6a** (176 mg, 94%) as a pale yellow oil.

Ethyl 2-Methoxy-4-(*p*-tolyl)-2,3-butadienoate (**6a**): Pale yellow oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.28 (3H, t, J=7.1 Hz), 2.36 (3H, s), 3.53 (3H, s), 4.28 (2H, q, J=7.1 Hz), 7.08 (1H, s), 7.16 (2H, d, J=8.1 Hz), 7.27 (2H, d, J=8.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.25, 21.31, 56.60, 61.63, 111.28, 127.72, 129.42, 129.48, 131.89, 138.86, 163.49, 197.64; IR (neat) 2982, 1932, 1733, 1512, 1447 cm^{-1}. FAB-MS Calcd for $C_{14}H_{17}O_3$ MW+H 233, Found *m*/*z* 233 (M^++H).

Ethyl 2-Methoxy-4-phenyl-2,3-butadienoate (**6b**): Yellow oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.28 (3H, t, J=7.1 Hz), 3.54 (3H, s), 4.28 (2H, q, J=7.1 Hz), 7.11 (1H, s), 7.26—7.40 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.23, 56.68, 61.69, 111.43, 127.80, 128.73, 128.89, 131.98, 133.28, 163.39, 198.28; IR (neat) 2982, 1933, 1733, 1493 cm^{-1}. FAB-MS Calcd for $C_{13}H_{15}O_3$ MW+H 219, Found *m*/*z* 219 (M^++H).

Ethyl 2-Methoxy-2,3-heptadienoate (**6c**): Yellow oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.98 (3H, t, J=7.4 Hz), 3.51 (3H, s), 1.29 (3H, t, J=7.1 Hz), 1.50—1.61 (2H, m), 2.18—2.23 (2H, m), 4.23—4.30 (2H, m), 6.20 (1H, t, J=6.7 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.39, 13.95, 20.78, 21.65, 54.26, 63.28, 91.57, 110.19, 165.27, 196.07; FAB-MS Calcd for $C_{10}H_{17}O_3$ MW+H 185, Found *m*/*z* 185 (M^++H).

Ethyl 2-Methoxy-4-(1-cyclohexen-1-yl)-2,3-butadienoate (**6d**): Yellow oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.29 (3H, t, J=7.3 Hz), 1.50—1.76 (4H, m), 1.90—2.28 (4H, m), 3.48 (3H, s), 4.27 (2H, q, J=7.3 Hz), 5.86—6.00 (1H, m), 6.75 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.30, 22.15, 22.28, 25.73, 26.10, 56.49, 61.48, 114.72, 128.03, 132.09, 132.33, 163.81, 196.41; IR (neat) 2932, 1926, 1733, 1446, 1394, 1367, 1280, 1217, 1161, 1131, 1040 cm^{-1}. FAB-MS Calcd for $C_{13}H_{19}O_3$ MW+H 223, Found *m*/*z* 223 (M^++H).

Ethyl 2-Methoxy-2,3-butadienoate (**6e**): Yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.31 (3H, dt, J=0.98, 7.3 Hz), 3.51 (3H, s), 4.28 (2H, dq, J=0.03, 7.3 Hz), 5.83 (2H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 14.23, 61.61, 93.84, 56.69, 127.21, 163.88, 203.38; IR (neat) 2982, 2837, 1942, 1734 cm^{-1}. FAB-MS Calcd for $C_7H_{11}O_3$ MW+H 143, Found *m*/*z* 143 (M^++H).

Typical Procedure for the Preparation of 2,4,5-Trisubstituted Oxazoles 7 To a solution of **5a** (68 mg, 0.26 mmol) in EtOH (2.6 ml) was added 1 N KOH (0.26 ml) in one portion at 0 °C. After stirred at 0 °C for 20 min, 1 N HCl was added to the reaction mixture and extracted with Et_2O. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel with *n*-hexane–Et_2O (1 : 5, v/v) to yield **7a** (48 mg, 93%) as a yellow oil.

Ethyl 2-Methyl-5-(*p*-tolylmethyl)-4-oxazolecarboxylate (**7a**): Yellow oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.40 (3H, t, J=7.1 Hz), 2.32 (3H, s), 2.41 (3H, s), 4.30 (2H, s), 4.40 (2H, q, J=7.1 Hz), 7.12 (2H, d, J=8.2 Hz), 7.18 (2H, d, J=8.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.81, 14.40, 21.06, 31.55, 60.95, 127.29, 128.65, 129.38, 133.31, 136.64, 157.75, 160.04, 162.33; IR ($CHCl_3$) 3000, 2925, 1713, 1618, 1372 cm^{-1}. *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.47; H, 6.61N, 5.40. Found, C, 69.11; H, 6.58; N, 5.29.

Ethyl 2-Methyl-5-(phenylmethyl)-4-oxazolecarboxylate (**7b**): Yellow oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.40 (3H, t, J=7.1 Hz), 2.42 (3H, s), 4.34 (2H, s), 4.40 (2H, q, J=7.1 Hz), 7.15—7.45 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.79, 14.38, 31.97, 61.00, 127.00, 127.43, 128.71, 128.76, 136.36, 157.47, 160.14, 162.28; IR (neat) 3030, 2982, 1708, 1616, 1376 cm^{-1}. *Anal.* Calcd for $C_{14}H_{15}N_3O$: C, 68.54; H, 6.17; N, 5.71. Found, C, 68.26; H, 6.24; N, 5.53.

Ethyl 2-Methyl-5-(1-cyclohexen-1-ylmethyl)-4-oxazolecarboxylate (**7d**): Colorless crystalline powder, mp 30—31 °C (*n*-hexane–Et_2O); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.38 (3H, t, J=7.1 Hz), 1.45—1.78 (4H, m), 1.86—2.15 (4H, m), 2.45 (3H, s), 3.63 (2H, s), 4.37 (2H, q, J=7.1 Hz), 5.46—5.58 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.85, 14.38, 22.08, 22.71, 25.24, 28.20, 34.23, 60.81, 124.37, 127.83, 132.97, 157.64, 159.82, 162.33; IR ($CHCl_3$) 3010, 2949, 1718, 1612, 1375, 1342 cm^{-1}. *Anal.* Calcd for $C_{14}H_{19}NO_3$: C, 67.43; H, 7.69; N, 5.62. Found, C, 67.30; H, 7.92; N, 5.41.

Ethyl 2,5-Dimethyl-4-oxazolecarboxylate (**7e**): Yellow oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.39 (3H, t, J=7.1 Hz), 2.44 (3H, s), 2.59 (3H, s), 4.37 (2H, q, J=7.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 11.88, 13.71, 14.40, 60.81, 127.39, 156.07, 159.43, 162.45. IR (neat) 2999, 1710, 1620, 1340 cm^{-1}. EI-MS Calcd for $C_8H_{11}NO_3$ MW 169.0739, Found *m*/*z* 169.0736 (M^+).

Alkaline Hydrolysis of 7a To a solution of **7a** (120 mg, 0.46 mmol) in EtOH (4.6 ml) was added 1 N KOH (0.92 ml) at the room temperature. After being warmed at 50 °C for 1 h, the reaction mixture was treated with 10% HCl and then extracted with AcOEt. The extract was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. The residue was recrystallized from $CHCl_3$–acetone to yield **7′a** (91 mg, 86%) as colorless prisms.

2-Methyl-5-(*p*-tolylmethyl)-4-oxazolecarboxylic acid (**7′a**): Colorless prisms, mp 162 °C ($CHCl_3$–acetone); ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.32 (3H, s), 2.43 (3H, s), 4.32 (2H, s), 7.12 (2H, d, J=8.0 Hz), 7.20 (2H, d, J=8.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.58, 21.06, 31.48, 126.75, 128.74, 129.41, 133.00, 136.72, 158.63, 160.72, 165.43; IR (KBr) 3423, 2921, 2568, 1730, 1708, 1616, 1594, 1515, 1439, 1352, 1283, 1227, 1186, 1112, 1069 cm^{-1}. *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found, C, 67.33; H, 5.70; N, 5.69.

Esterification of 7′a To a solution of **7′a** (12 mg, 0.05 mmol) in AcOEt–DMF (10 : 1, v/v) (5 ml) was added triethylamine (0.01 ml, 0.06 mmol) and bromoethane (0.02 ml, 0.27 mmol) at room temperature. After stirring at room temperature for 48 h, water was added to the reaction mixture and extracted with Et_2O. The extract was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to yield **7a** (10 mg, 77%) as a yellow oil.

Hydrogenation of 2a The mixture of **2a** (912 mg, 3 mmol), 5% Pd–$BaSO_4$ (91 mg, 10% w/w), and quinoline (20 mg, 0.15 mmol) in MeOH (30 ml) was stirred at room temperature for 1.5 h. The reaction mixture was submitted to filtration with celite. The filtrate was concentrated *in vacuo* to afford a crude product **9**, which was purified by column chromatography on silica gel with *n*-hexane–AcOEt (85 : 15, v/v) to yield **9** (894 mg, 97%) as a pale yellow oil.

Ethyl (*Z*)-2-Methoxy-2(-ethoxycarbonyl)-4-(*p*-tolyl)-3-butenoate (**9**): Pale yellow oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.19 (6H, t, J=7.3 Hz), 2.33 (3H, s), 3.24 (3H, s), 4.07—4.24 (4H, m), 6.14 (1H, d, J=12.9 Hz), 6.80 (1H, d, J=12.9 Hz), 7.12 (2H, d, J=8.3 Hz), 7.43 (2H, d, J=8.3 Hz); IR (neat) 2983, 2938, 1740, 1514, 692 cm^{-1}. EI-MS Calcd for $C_{17}H_{22}O_5$ MW 306.1467, Found *m*/*z* 306.1494 (M^+). *Anal.* Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found, C, 66.16; H, 7.17.

Alkaline Hydrolysis of 9 To a solution of **9** (432 mg, 1.4 mmol) in EtOH (7 ml) was added 1 N KOH (1.4 ml) at 0 °C. After being stirred at 0 °C for 7 h, the reaction mixture was treated with 1 N HCl (1.4 ml) and then extracted with AcOEt. The extract was washed with saturated $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel with *n*-hexane–AcOEt (85 : 15, v/v) to yield **9** (151 mg, 35% recovery), **10** (99 mg, 30%), **11** (2.3 mg, 0.7%) and **12** (5.3 mg, 1.6%).

Ethyl (*Z*)-2-Methoxy-4-(*p*-tolyl)-3-butenoate (**10**): Yellow oil; ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.32 (3H, t, J=7.3 Hz), 2.37 (3H, s), 3.31 (3H, s), 4.28 (2H, q, J=7.3 Hz), 4.73 (1H, d, J=9.6 Hz), 5.63 (1H, dd, J=9.6 and 11.6 Hz), 6.84 (1H, d, J=11.6 Hz), 7.19 (2H, d, J=8.3 Hz), 7.32 (2H, d, J=8.3 Hz). IR (neat) 2984, 2930, 1750, 1514 cm^{-1}. EI-MS Calcd for $C_{14}H_{18}O_3$ MW 234.1256, Found *m*/*z* 234.1238 (M^+). *Anal.* Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74, Found, C, 71.23; H, 7.72.

Ethyl (*E*)-2-Methoxy-4-(*p*-tolyl)-3-butenoate (**11**): Pale yellow oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.30 (3H, t, J=7.3 Hz), 2.34 (3H, s), 3.44 (3H, s), 4.26 (2H, q, J=7.3 Hz), 4.38 (1H, d, J=6.9 Hz), 6.14 (1H, dd, J=6.9, 15.8 Hz), 6.74 (1H, d, J=15.8 Hz), 7.13 (2H, d, J=7.9 Hz), 7.29 (2H, d, J=7.9 Hz).

Ethyl 2-Methoxy-4-(*p*-tolyl)-2-butenoate (**12**): Pale yellow oil; ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.30 (3H, t, J=7.3 Hz), 2.31 (3H, s), 3.53 (2H, d, J=7.6 Hz), 3.72 (3H, s), 4.21 (2H, q, J=7.3 Hz), 6.38 (1H, t, J=7.6 Hz), 7.10 (4H, s).

Biomimetic Reactions of 2 with EtSH To a solution of **2a** (247 mg, 0.8 mmol) in EtOH (8 ml) was added 1 N KOH (0.8 ml) in one portion at 0 °C. After being stirred at 0 °C for 15 min, EtSH (0.07 ml, 0.9 mmol) was added. After being stirred at 0 °C for 80 min, 1 N HCl (0.8 ml) was added and then the reaction mixture was poured into water and extracted with Et_2O. The extract was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel with *n*-hexane–AcOEt (7 : 3, v/v) to yield **13a** (147 mg, 61%) as a pale yellow oil.

Ethyl (*E*)-2-Methoxy-3-ethylthio-4-(*p*-tolyl)-3-butenoate (**13a**): Pale yellow oil; ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.32 (3H, t, J=7.3 Hz), 1.33 (3H, t, J=7.3 Hz), 2.36 (3H, s), 2.77—3.02 (2H, m), 3.29 (3H, s), 4.29 (2H, q, J=7.3 Hz), 4.96 (1H, s), 6.81 (1H, s), 7.13 (2H, d, J=7.9 Hz), 7.26 (2H, d, J=7.9 Hz); IR (neat) 2926, 2825, 1752, 1607, 1510, 1447, 1369, 1265,

1191, 1110, 1029 cm^{-1}. EI-MS Calcd for $C_{16}H_{22}O_3S$ MW 294.1290, Found *m/z* 294.1313 (M^+). *Anal.* Calcd for $C_{16}H_{22}O_3S$: C, 65.27; H, 7.53. Found, C, 64.99; H, 7.55.

Ethyl (*E*)-2-Methoxy-3-ethylthio-4-(1-cyclohexen-1-yl)-3-butenoate (**13d**): Pale yellow oil; ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.26 (3H, t, J=7.3 Hz), 1.30 (3H, t, J=7.3 Hz), 1.56—1.70 (4H, m), 2.04—2.17 (4H, m), 2.68—2.83 (2H, m), 3.35 (3H, s), 4.25 (2H, q, J=7.3 Hz), 5.07 (1H, s), 5.84 (1H, br s), 6.15 (1H, br s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.63, 14.13, 21.90, 22.61, 25.50, 26.82, 28.97, 56.71, 61.31, 79.11, 128.05, 133.91, 136.24, 139.55, 169.90. IR (neat) 2940, 1746, 1625 cm^{-1}. EI-MS Calcd for $C_{15}H_{24}O_3S$ MW 284.1446, Found *m/z* 284.1426 (M^+).

Biomimetic Reactions of 5 with EtSH To a solution of **5a** (100 mg, 0.3 mmol) and EtSH (0.02 ml, 0.3 mmol) in EtOH (3 ml) was added 1 N KOH (0.3 ml) at 0 °C. After being stirred at 0 °C for 30 min, 1 N HCl (0.3 ml) was added and then the reaction mixture was poured into water and extracted with Et_2O. The extract was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel with *n*-hexane–AcOEt (7 : 3, v/v) to yield **14a** (92 mg, 96 %) as colorless needles.

Ethyl (*E*)-2-(Acetylamino)-3-ethylthio-4-(*p*-tolyl)-3-butenoate (**14a**): Colorless needles, mp 93.5 °C (*n*-hexane–Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, t, J=7.1 Hz), 1.32 (3H, t, J=7.3 Hz), 2.01 (3H, s), 2.34 (3H, s), 2.81 (2H, q, J=7.3 Hz), 4.22 (2H, q, J=7.1 Hz), 5.83 (1H, d, J=7.7 Hz), 6.40 (1H, br d, J=7.7 Hz), 6.76 (1H, s), 7.18 (2H, d, J=8.0 Hz), 7.33 (2H, d, J=8.0 Hz). IR (KBr) 3257, 3024, 2970, 1731, 1651, 1531 cm^{-1}. EI-MS Calcd for $C_{17}H_{23}NO_3S$ MW 321.1399, Found *m/z* 321.1370 (M^+).

Ethyl (*E*)-2-(Acetylamino)-3-ethylthio-4-phenyl-3-butenoate (**14b**): Colorless needles, mp 70 °C (*n*-hexane–Et_2O); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, t, J=7.1 Hz), 1.33 (3H, t, J=7.4 Hz), 2.02 (3H, s), 2.82 (2H, q, J=7.4 Hz), 4.22 (2H, q, J=7.1 Hz), 5.82 (1H, d, J=7.5 Hz), 6.41 (1H, br d, J=7.5 Hz), 6.76 (1H, s), 7.26—7.47 (5H, m). IR (KBr) 3282, 2907, 1752, 1651, 1521 cm^{-1}. EI-MS Calcd for $C_{16}H_{21}NO_3S$ MW 307.1242, Found *m/z* 307.1217 (M^+).

Ethyl (*E*)-2-(Acetylamino)-3-ethylthio-4-(1-cyclohexen-1-yl)-3-butenoate (**14d**): Pale yellow oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.24 (3H, t, J=7.3 Hz), 1.28 (3H, t, J=7.1 Hz), 1.55—1.75 (4H, m), 2.03 (3H, s), 2.12—2.78 (4H, m), 2.69 (2H, q, J=7.3 Hz), 4.19 (1H, dq, J=7.1, 10.9 Hz), 4.23 (1H, dq, J=7.1, 10.9 Hz), 5.88—5.93 (1H, m), 5.99 (1H, d, J=7.9 Hz), 6.15 (1H, s), 6.44 (1H, br d, J=7.9 Hz). IR (neat) 3425, 3000, 2945, 1732, 1675, 1508 cm^{-1}. EI-MS Calcd for $C_{16}H_{25}NO_3S$ MW 311.1555, Found *m/z* 311.1549 (M^+). *Anal.* Calcd for $C_{16}H_{25}NO_3S$: C, 61.71; H, 8.10; N, 4.50. Found. C, 61.47; H, 8.50; N, 4.33.

Enzymatic Hydrolysis of 5a PLE (Sigma; Type I, 100 units) was added to a stirred solution of **5a** (33 mg, 0.1 mmol) in 0.1 M phosphate buffer (pH 7.5)–acetone (10 : 1) (8.8 ml, v/v) at room temperature. After being stirred at 35—45 °C for 5 d, the reaction mixture was treated with 5% HCl and then Et_2O was added. The organic layer was washed with H_2O, brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo*. An excess amount of diazomethane was added to the residue at 0 °C. After being stirred at room temperature, the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel with *n*-hexane–AcOEt (7 : 3, v/v) to yield **15** (22 mg, 83%).

Methyl 2-Methyl-5-(*p*-tolylmethyl)-4-oxazolecarboxylate (**15**): Colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.32 (3H, s), 2.41 (3H, s), 3.92 (3H, s), 4.30 (2H, s), 7.10 (2H, d, J=8.1 Hz), 7.16 (2H, d, J=8.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.95, 21.24, 31.67, 52.07, 127.31, 128.88, 129.62, 133.46, 136.88, 158.16, 160.27, 162.93. IR (neat) 2952, 1713, 1618, 1515, 1439, 1359, 1299, 1220, 1111, 1075, 1023 cm^{-1}. EI-MS Calcd for $C_{14}H_{15}NO_3$ MW 245.1052, Found *m/z* 245.1043 (M^+).

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