Synthesis of 1,4-Diphenylbutadiene Derivatives: Novel Inducer of Tissue-Type Plasminogen Activator (t-PA) in Cultured Bovine Endothelial Cells

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Received August 9, 2006; accepted September 13, 2006; published online September 19, 2006

(*E*,*E*)-1,4-Diphenylbutadiene derivatives were synthesized by utilizing the Stobbe reaction of dimethyl succinate as a key step. Their stereoisomers were also synthesized stereoselectively by means of the cross-coupling reaction of the vinylstannanes and the vinylbromides, which were obtained from the propiolic acid esters by stereoselective hydrostannation, as a key step. To discover novel stimulators of fibrinolysis in vascular endothelial cells, the synthesized compounds were added to cultured bovine endothelial cells to determine the activity of the plasminogen activator in the conditioned medium. Of the synthesized compounds, three compounds were found to stimulate the activity of the plasminogen activator in endothelial cells. In addtition, these compounds inhibited thrombus formation in a rat model of venous thrombosis.

Key words plasminogen activator; dipheylbutadiene derivative; cross-coupling reaction; stereoselective olefin synthesis; Stobbe condensation; plasminogen activator inhibitor-1

It is well known that plasminogen activator in blood plays an important role in endogenous fibrinolysis by converting plasminogen to plasmin. Thus, stimulation of endogenous fibrinolysis by a pharmaceutical agent may be useful for prevention and treatment of patients with thrombosis. Since vascular endothelial cells synthesize and secrete plasminogen activator, cultured endothelial cells are suitable for the study of the modulation of endogenous fibrinolytic activity in an *in vitro* system.[1—4] It has been reported that physiological substances such as thrombin,[5,6] short-chain fatty acids[7] and retinoids[8,9] induce an increase in the fibrinolytic activity in cultured endothelial cells *via* enhancement of plasminogen activator synthesis. Of these, we have been interested in retinoids because the inducing activity of plasminogen activator synthesis could easily be improved by chemical modification of its conjugated polyene functionality.

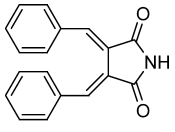
We performed random screening of polyene compounds in Tanabe libraries and found that (3*E*,4*E*)-3,4-dibenzylidenepyrrolidine-2,5-dione (**1a**) showed high potency of plasminogen activator induction (Fig. 1). We selected **1a** as the lead compound, and carried out its chemical modification to enhance the activity. In this paper, we describe stereoselective syntheses, structure–activity relationships (SAR), and antithrombotic activities of 1,4-diphenylbutadiene derivatives.

Chemistry

The typical synthetic route of the succinimide type derivatives of 1,4-diphenylbutadiene **1a**—**r** is shown in Chart 1. The key intermediate (*E*,*E*)-dibenzylidenesuccinic acid monomethyl esters **14a**—**c** were synthesized utilizing twice the Stobbe condensation.[10] The (*E*)-benzylidenesuccinic acid methyl ester obtained stereoselectively in the first Stobbe condensation of benzaldehyde **12a**, **b** with dimethyl succinate,[11] was transformed into the (*E*)-dimethyl esters **13a**, **b** by treatment with a catalytic amount of c.H_2SO_4 in MeOH. The second Stobbe condensation of **13a**, **b** with benzaldehyde or 3,4,5-trimethoxybenzaldehyde, steroselectively afforded the (*E*,*E*)-half-esters **14a**—**c**. Treatment of **14a**—**c** with $SOCl_2$ followed by excess aqueous NH_3 afforded the imide derivatives **1a**, **g**. The intermediate succinamate **2** was spontaneously cyclized to succinimide **1** in this reaction condition because of the basicity of ammonia. The Stobbe condensation of **13a**, **b** with substituted benzaldehyde and successive amidation with ammonia afforded the imide derivatives **1b**—**f**, **1h**—**m**. Instead of ammonia, various amines were used to afford *N*-substituted succinimide derivatives **1n**—**r** from **14b**. The syntheses of the succinamate type derivatives **2a**—**k** were performed by treatment of equimolar ammonia or amine and at low reaction temperature.

The syntheses of the (*E*,*E*)-dibenzylidenesuccinic anhydride **3**, (*E*,*E*)-dibenzylidene-γ-butyrolactone **4a**, **b** and (*E*,*E*)-dibenzylidene-γ-butyrolactam **5a**, **b** are shown in Chart 2. The anhydride **3** was obtained by treatment of half-ester **14b** with $SOCl_2$ and $SnCl_4$ successively. The half-ester **14b**, **c** was reduced with diisobutylaluminum hydride (DIBAL-H) to give the corresponding alcohol, which was successively treated with aqueous HCl to afford the lactone **4a**, **b**. Treatment of amide **2b**, **c** with PPh_3 and CCl_4 afforded the nitrile **15a**, **b**. Hydrogenation of the nitrile **15a**, **b** in the presence of Raney-Ni followed by cyclization by heating afforded the lactam **5a**, **b**.

In order to explore the effect of stereochemistry on butadiene moiety, we decided to synthesize all isomers of **1g** and **2b**, which possessed a high potency of t-PA induction. The stereoisomers of dibenzylidenesuccinimide **1g** and methyl dibenzylidenesuccinamate **2b** were synthesized by utilizing a cross-coupling reaction[12] as a key step, as shown in Chart 3.



1a

Fig. 1. Lead Compound

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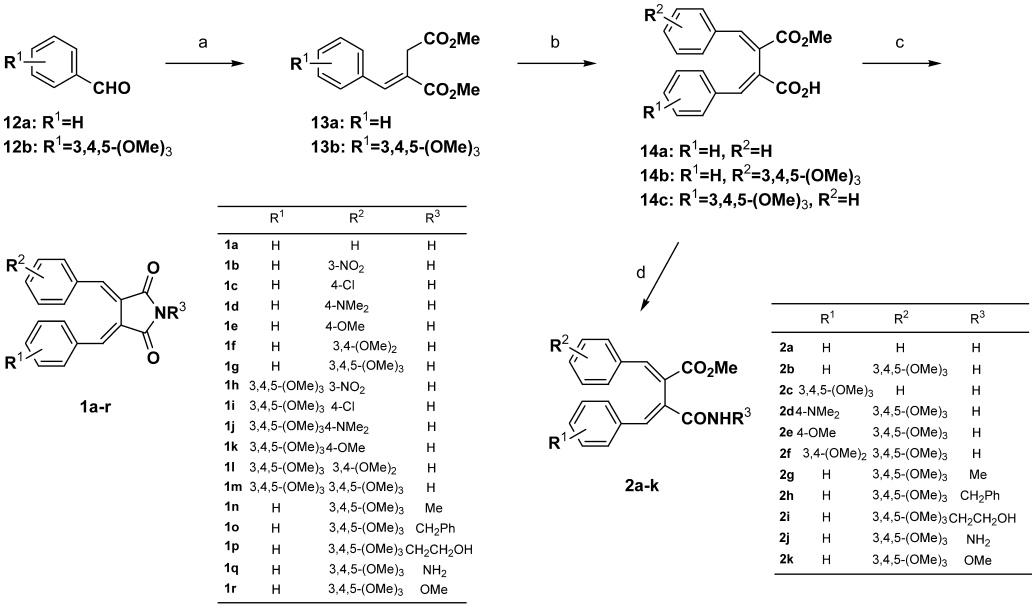
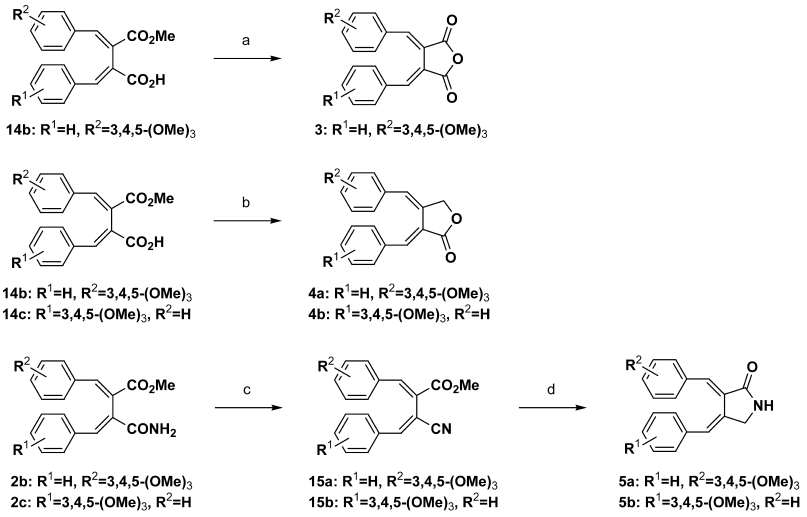


	R^1	R^2	R^3
1a	H	H	H
1b	H	3-NO_2	H
1c	H	4-Cl	H
1d	H	4-NMe_2	H
1e	H	4-OMe	H
1f	H	3,4-$(OMe)_2$	H
1g	H	3,4,5-$(OMe)_3$	H
1h	3,4,5-$(OMe)_3$	3-NO_2	H
1i	3,4,5-$(OMe)_3$	4-Cl	H
1j	3,4,5-$(OMe)_3$	4-NMe_2	H
1k	3,4,5-$(OMe)_3$	4-OMe	H
1l	3,4,5-$(OMe)_3$	3,4-$(OMe)_2$	H
1m	3,4,5-$(OMe)_3$	3,4,5-$(OMe)_3$	H
1n	H	3,4,5-$(OMe)_3$	Me
1o	H	3,4,5-$(OMe)_3$	CH_2Ph
1p	H	3,4,5-$(OMe)_3$	CH_2CH_2OH
1q	H	3,4,5-$(OMe)_3$	NH_2
1r	H	3,4,5-$(OMe)_3$	OMe

	R^1	R^2	R^3
2a	H	H	H
2b	H	3,4,5-$(OMe)_3$	H
2c	3,4,5-$(OMe)_3$	H	H
2d	4-NMe_2	3,4,5-$(OMe)_3$	H
2e	4-OMe	3,4,5-$(OMe)_3$	H
2f	3,4-$(OMe)_2$	3,4,5-$(OMe)_3$	H
2g	H	3,4,5-$(OMe)_3$	Me
2h	H	3,4,5-$(OMe)_3$	CH_2Ph
2i	H	3,4,5-$(OMe)_3$	CH_2CH_2OH
2j	H	3,4,5-$(OMe)_3$	NH_2
2k	H	3,4,5-$(OMe)_3$	OMe

Reagents and Conditions: (a) (1) dimethyl succinate,^{t}BuOK/^{t}BuOH 25°C; (2) c.H_2SO_4/MeOH 25°C; (b) aldehyde, ^{t}BuOK/^{t}BuOH 25°C; (c) (1) $SOCl_2$/$CHCl_3$ reflux; (2) R^3NH_2(excess)/$CHCl_3$ 25°C; (d) (1) $SOCl_2$/$CHCl_3$ reflux; (2) R^3NH_2(1eq.)/$CHCl_3$ 0°C

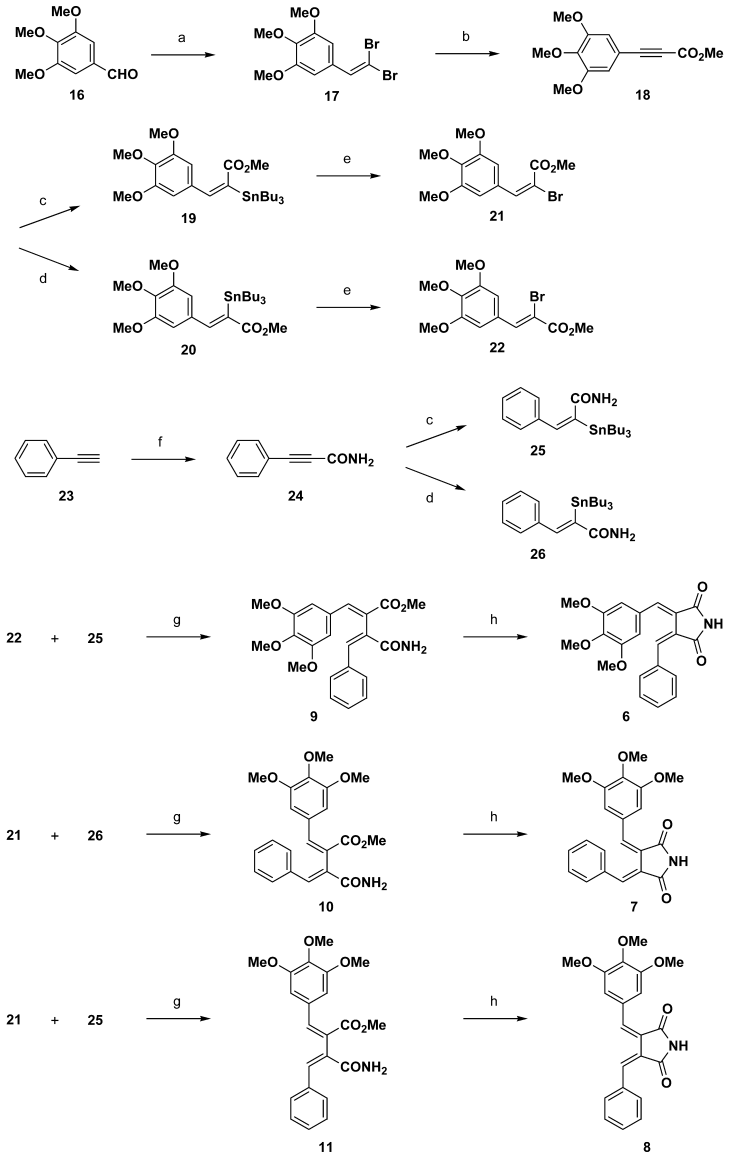
Chart 1. Synthesis of Dibenzylidenesuccinimide Derivatives **1a**—**r** and Dibenzylidenesuccinamate Derivatives **2a**—**k**



Reagents and Conditions: (a) (1) $SOCl_2$/toluene 80°C; (2) $SnCl_4$/toluene 25°C; (b) (1) DIBAL-H/CH_2Cl_2 25°C; (2) $ClCO_2Et$, Et_3N/THF 0°C; (c) PPh_3/CCl_4 50°C; (d) (1) H_2, Raney-Ni/MeOH 25°C (2) reflux

Chart 2. Synthesis of Other Ring Derivatives **3**, **4a**, **b** and **5a**, **b**

The bromide **21**, **22** and the stannane **25**, **26** were synthesized as follows. Methyl 3,4,5-trimethoxypropiolate (**18**) was prepared from 3,4,5-trimethoxybenzaldehyde (**16**) by Corey's method.[13] Treatment of the aldehyde **16** with CBr_4 and PPh_3 afforded the dibromoolefin **17**. Lithiation of **17** with 2 eq of *n*-butyllithium followed by addition of methyl chloroformate afforded the propiolate **18**. Hydrostannation of the propiolate **18** in the presence of $Pd(PPh_3)_4$[14,15] stereoselectively gave the (*E*)-vinylstannane **19**. On the other hand, hydrostannation of **18** in the presence of AIBN[16] proceeded stereoselectively to afford (*Z*)-vinylstannane **20**. Treatment of the vinylstannanes **19**, **20** with bromine gave the vinylbromides **21**, **22**[17] with retention of the configuration in high yields. The stannannes **25**, **26** were synthesized in a similar manner. Lithiation of phenylacetylene (**23**) followed by bubbling of carbon dioxide afforded the propiolic acid, which was converted to the amide **24**. Hydrostannation of the propiolic amide **24** in the presence of $Pd(PPh_3)_4$ or AIBN afforded (*E*)-vinylstannane **25** or (*Z*)-vinylstannane **26** steroselectively. The cross-coupling reaction of the (*Z*)-vinylbromide **22** with the (*E*)-vinylstannane **25** smoothly proceeded in the presence of $Pd(PPh_3)_2Cl_2$ in DMF at 60 °C[18] to provided the (*E*,*Z*)-amide **9**. The (*E*,*Z*)-imide **6** was obtained in high yield by treatment of **9** with aqueous NaOH. Similarly, the appropriate combination of the (*E*)-vinylbromide **21** and the (*Z*)-vinylstannane **26** gave the corresponding (*Z*,*E*)-amide **10** and (*Z*,*E*)-imide **7**. Next, the (*Z*,*Z*)-amide **11** and (*Z*,*Z*)-imide **8** was obtained from the (*E*)-vinylbromide **21** and the (*E*)-vinylstannane **25**.



Reagents and Conditions: (a) PPh_3, CBr_4/CH_2Cl_2 25°C; (b) (1) nBuLi/THF 25°C; (2) $ClCO_2Me$/THF 25°C; (c) Bu_3SnH, $Pd(PPh_3)_4$/THF 25°C; (d) Bu_3SnH, AIBN/toluene 25°C; (e) Br_2/CH_2Cl_2 0°C; (f) (1) nBuLi/THF -78°C; (2) CO_2/THF 0°C; (3) $SOCl_2/CHCl_3$ 25°C; (4) $NH_3/CHCl_3$ 25°C; (g) $PdCl_2(PPh_3)_2$/DMF 60°C; (h) aq.NaOH/THF 25°C

Chart 3. Synthesis of Stereoisomers **6**—**11**

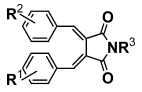
Biological Result and Discussion

To determine whether the synthesized compounds can stimulate the fibrinolytic activity in vascular endothelial cells, the cells were treated with the compounds for 24 h, and the activity of the plasminogen activator (PA) in the conditioned medium was measured.

Table 1 summarizes the relative PA activity of vascular endothelial cells treated with dibenzylidenesuccinimide derivatives **1a**—**r**, compared to the control cells treated with vehicle alone. First, the effect of the electron-withdrawing (**1b**, **c**) and electron-donating (**1d**—**g**) substituents R^1 of the dibenzylidenesuccinimide was examined. Among the compounds **1b**—**g**, the 3,4,5-trimethoxy-substituted derivative **1g** was revealed to possess good potency of the PA activity. Next, the effect of the electron-withdrawing (**1h**, **i**) and electron-donating (**1j**—**m**) substituents R^2 in **1g** was examined. All of the R^2-substituted derivatives **1h**—**m** exhibited much lower activity than **1g**. Finally, the effect of the *N*-substituents R^3 in **1g** was examined. As a result, all of the R^3-substituted derivatives **1n**—**r** exhibited much lower activity than **1g**.

Table 2 summarizes the relative PA activity of dibenzylidenesuccinamate derivatives **2a**—**k** compared to the control cells treated with vehicle alone. First, the 3,4,5-trimethoxy-substituted derivatives **2b**, **c** were examined due to effective substituent in dibenzylidenesuccinimide derivatives. The R^2-substituted derivative **2b** was revealed to possess equal potency with the dibenzylidenesuccinimide derivative **1g**. However, the R^1-substituted derivative **2c** was revealed to be less potent than **1g**. Next, the effect of substituents R^1 in **2b** was examined. All of the R^1-substituted derivatives **2d**—**f** exhibited much lower activity than **2b**. Finally, the effect of the *N*-substituents R^3 in **2b** was examined. Among the compounds of **2g**—**k**, the methyl-substituted derivative **2g** and the amino-substituted derivative **2j** were revealed to possess good potency of the PA activity. However, the potency did not exceed **2b**. These results suggest that a small substituent

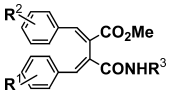
Table 1. Plasminogen Activator Stimulating Activity of Dibenzylidenesuccinimide Derivatives



Compound	R^1	R^2	R^3	Relative PA activity[a)]
1a	H	H	H	1.96
1b	3-NO_2	H	H	0.49
1c	4-Cl	H	H	1.32
1d	4-NMe_2	H	H	0.35
1e	4-OMe	H	H	0.75
1f	3,4-$(OMe)_2$	H	H	1.08
1g	3,4,5-$(OMe)_3$	H	H	2.33
1h	3,4,5-$(OMe)_3$	3-NO_2	H	1.23
1i	3,4,5-$(OMe)_3$	4-Cl	H	1.40
1j	3,4,5-$(OMe)_3$	4-NMe_2	H	1.53
1k	3,4,5-$(OMe)_3$	4-OMe	H	1.02
1l	3,4,5-$(OMe)_3$	3,4-$(OMe)_2$	H	0.95
1m	3,4,5-$(OMe)_3$	3,4,5-$(OMe)_3$	H	1.53
1n	3,4,5-$(OMe)_3$	H	Me	1.64
1o	3,4,5-$(OMe)_3$	H	CH_2Ph	1.26
1p	3,4,5-$(OMe)_3$	H	CH_2CH_2OH	1.54
1q	3,4,5-$(OMe)_3$	H	NH_2	1.23
1r	3,4,5-$(OMe)_3$	H	OMe	0.71

a) See Experimental. Retinyl palmitate, a reference compound, at 20 μM showed relative PA activity ranging from 2.00 to 3.00 in this assay.

Table 2. Plasminogen Activator Stimulating Activity of Dibenzylidenesuccinamate Derivatives



Compound	R^1	R^2	R^3	Relative PA activity[a)]
2a	H	H	H	1.74
2b	H	3,4,5-$(OMe)_3$	H	2.54
2c	3,4,5-$(OMe)_3$	H	H	1.33
2d	4-NMe_2	3,4,5-$(OMe)_3$	H	0.94
2e	4-OMe	3,4,5-$(OMe)_3$	H	1.50
2f	3,4-$(OMe)_2$	3,4,5-$(OMe)_3$	H	0.95
2g	H	3,4,5-$(OMe)_3$	Me	2.27
2h	H	3,4,5-$(OMe)_3$	CH_2Ph	1.06
2i	H	3,4,5-$(OMe)_3$	CH_2CH_2OH	1.55
2j	H	3,4,5-$(OMe)_3$	NH_2	2.16
2k	H	3,4,5-$(OMe)_3$	OMe	1.83

a) See Experimental. Retinyl palmitate, a reference compound, at 20 μM showed relative PA activity ranging from 2.00 to 3.00 in this assay.

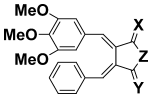
in R^3 is particularly favorable for good potency.

As shown in Table 3, the effect of the other ring derivatives was examined. The anhydride **3** and the lactams **5a**, **b** exhibited much lower activity than **1g**, whereas the lactones **4a**, **b** possessed the good potency of the PA activity. In particular, **4a** exhibited much higher activity than **1g**.

The activity of stereoisomers in **1g** and **2b** are summarized in Table 4. Both succinimide derivatives **6**—**8** and succinamate derivatives **9**—**11** showed no strong activity. These results show that the *E*,*E*-isomer is most effective.

In the compounds that showed strong activity, **1g**, **2b** and **4a** were evaluated the antithrombotic activity in a rat model

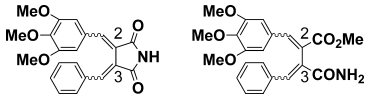
Table 3. Plasminogen Activator Stimulating Activity of Other Ring Derivatives



Compound	X	Y	Z	Relative PA activity[a)]
3	O	O	O	1.05
4a	H_2	O	O	2.69
4b	O	H_2	O	2.25
5a	O	H_2	NH	0.93
5b	H_2	O	NH	1.18

a) See Experimental.

Table 4. Plasminogen Activator Stimulating Activity for Stereoisomers of **1g** and **2b**



Compound	Configuration at C-2 and C-3 positions	Relative PA activity[a)]
1g	2*E*,3*E*	2.33
6	2*E*,3*Z*	1.60
7	2*Z*,3*E*	0.68
8	2*Z*,3*Z*	0.60
2b	2*E*,3*E*	2.54
9	2*E*,3*Z*	1.40
10	2*Z*,3*E*	1.15
11	2*Z*,3*Z*	1.05

a) See Experimental.

Table 5. Antithrombotic Activities of **1g**, **2b** and **4a** in the Rat Venous Thrombosis Model

Compound	Dose (mg/kg)	Decrease (%) in thrombus weight
1g	10	53
	100	73
2b	10	25
	100	52
4a	10	43
	100	79

of venous thrombosis (Table 5). In this model, the antithrombotic activity of **1g** was more potent than that of **2b** and **4a**.

Conclusion

On the basis of modification conjugated polyene functionality in retinoid, we have prepared 1,4-diphenylbutadiene derivatives to obtain a compound with plasminogen activator inducing activity. After identifying the optimum substituent on the two phenyl rings of dibenzylidenesuccinimide **1a**, various modifications to the *N*-substituent, the ring system, and the stereochemistry of double bonds have been investigated. Among the series of compounds obtained, we selected **1g** (T-686) for further evaluation as an antithrombotic agent.

Experimental

Melting points were measured using a Büchi 535 capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1640 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a Bruker AC-200 spectrometer with Me_4Si as an internal standard. Mass spectra were recorded on a Hitachi M-2000A spectrometer at 70eV, and high-resolution mass spectra (HR-MS) were measured with a JEOL JMS HX-100 spectrometer. Elemental analyses were carried out in this laboratory. Silica gel (Kieselgel 60, Merck) was used for column chromatography, and silica gel (Kieselgel 60 F_{254}, layer thickness 0.25 mm, Merck) for analytical thin layer chromatography (TLC).

Dimethyl (*E*)-2-Benzylidenesuccinate (13a) A solution of benzaldehyde (15.9 g, 0.15 mol) and dimethyl succinate (26.3 g, 0.18 mol) in *tert*-BuOH (20 ml) was added to a solution of potassium *tert*-butoxide (16.8 g, 0.15 mol) in *tert*-BuOH (150 ml) below 50 °C and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into ice-water and the aqueous layer was washed with *i*-Pr_2O and acidified with c.HCl. The organic layer was extracted with AcOEt and washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in MeOH (75 ml). To this solution was added c.H_2SO_4 (0.75 ml) and the mixture was refluxed for 5 h. After the removal of solvent, saturated aqueous $NaHCO_3$ was added and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel. Elution with hexane/AcOEt (4 : 1) gave **13a** (23.2 g, 66%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 3.55 (2H, s), 3.74 (3H, s), 3.83 (3H, s), 7.30—7.45 (5H, m), 7.91 (1H, s). IR (film) cm^{-1}: 3150, 1750, 1720. MS *m/z*: 234 (M^+). HR-MS Calcd for $C_{13}H_{14}O_4$ (M^+): 234.0892. Found: 234.0904.

Dimethyl (*E*)-2-(3,4,5-Trimethoxybenzylidene)-succinate (13b) This compound was prepared in 68% yield from 3,4,5-trimethoxybenzaldehyde by a method similar to that described for **13a**. ^{1}H-NMR ($CDCl_3$) δ: 3.58 (2H, s), 3.74 (3H, s), 3.75 (6H, s), 3.82 (3H, s), 3.83 (3H, s), 6.87 (2H, s), 7.87 (1H, s). IR (film) cm^{-1}: 3050, 1750, 1720. MS *m/z*: 324 (M^+). HR-MS Calcd for $C_{16}H_{20}O_7$ (M^+): 324.1209. Found: 324.3197.

Methyl Hydrogen (2*E*,3*E*)-2,3-Dibenzylidenesuccinate (14a) A solution of **13a** (23.2 g, 99 mmol) and benzaldehyde (10.6 g, 99 mmol) in THF (40 ml) was added to a solution of potassium *tert*-butoxide (11.1 g, 99 mmol) in *tert*-BuOH (100 ml) below 50 °C and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into ice-water and the aqueous layer was washed with *i*-Pr_2O and acidified with c.HCl. The organic layer was extracted with AcOEt and washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel. Elution with hexane/AcOEt (4 : 1) gave **14a** (19.9 g, 65%). mp 148—149 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.66 (3H, s), 7.25—7.35 (6H, m), 7.40—7.50 (4H, m), 7.85 (1H, s), 7.90 (1H, s). IR (KBr) cm^{-1}: 1730, 1680, 1595, 1510. MS *m/z*: 308 (M^+). *Anal.* Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 73.87; H, 5.05.

Methyl Hydrogen (2*E*,3*E*)-2-Benzylidene-3-(3,4,5-trimethoxybenzylidene)-succinate (14b) This compound was prepared in 78% yield from **13a** and 3,4,5-trimethoxybenzaldehyde by a method similar to that described for **14a**. mp 157—158 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.64 (9H, s), 3.73 (3H, s), 6.58 (2H, s), 7.10—7.40 (5H, m), 7.68 (1H, s), 7.82 (1H, s). IR (KBr) cm^{-1}: 1725, 1675, 1590, 1510. MS *m/z*: 398 (M^+). *Anal.* Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.16; H, 5.46.

Methyl Hydrogen (2*E*,3*E*)-3-Benzylidene-2-(3,4,5-trimethoxybenzylidene)-succinate (14c) This compound was prepared in 76% yield from **13b** by a method similar to that described for **14a**. mp 131—133 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.64 (3H, s), 3.66 (6H, s), 3.75 (3H, s), 6.56 (2H, s), 7.10—7.40 (5H, m), 7.66 (1H, s), 7.84 (1H, s). IR (KBr) cm^{-1}: 1715, 1665, 1590, 1510. MS *m/z*: 398 (M^+). *Anal.* Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.18; H, 5.47.

(3*E*,4*E*)-3,4-Dibenzylidenepyrrolidine-2,5-dione (1a) To a solution of **14a** (8.1 g, 26 mmol) in $CHCl_3$ (40 ml) were added $SOCl_2$ (1.9 ml, 26 mmol) and DMF (2 drops) below 10 °C and the mixture was refluxed for 30 min. This solutuon was added to 28% aqueous NH_3 (10 ml) and the mixture was stirred at room temperature for 1 h. To this solution, 2 N HCl was added to pH 7 and the mixture was extracted with $CHCl_3$ and dried ($MgSO_4$), and concentrated *in vacuo*. The residue was crystalized in AcOEt to give **1a** (4.4 g, 79%). mp 205—207 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.79—6.90 (8H, m), 7.08—7.12 (2H, m), 7.81 (2H, s), 8.79 (1H, bs). IR (KBr) cm^{-1}: 3150, 3185, 1760, 1710, 1620. MS *m/z*: 275 (M^+). *Anal.* Calcd for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.23; H, 4.82; N, 5.02.

The following compounds (**1b**—**r**) were prepared from the corresponding half-ester (**14a**—**c**) or diester (**13a**, **b**) by a method similar to that described for **1a**.

(3*E*,4*E*)-3-Benzylidene-4-(3-nitrobenzylidene)-pyrrolidine-2,5-dione (1b) Yield: 45%. mp 216—218 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.76—6.90 (4H, m), 7.08 (1H, m), 7.19 (1H, m), 7.36—7.48 (2H, m), 7.77 (1H, s), 7.92 (1H, s), 7.94 (1H, m), 8.67 (1H, bs). IR (KBr) cm^{-1}: 3160, 1765, 1705, 1625. MS *m/z*: 320 (M^+). *Anal.* Calcd for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.52; H, 3.65; N, 8.64.

(3*E*,4*E*)-3-Benzylidene-4-(4-chlorobenzylidene)-pyrrolidine-2,5-dione (1c) Yield: 62%. mp 263—265 °C. ^{1}H-NMR (DMSO-d_6) δ: 6.76—6.90 (4H, m), 7.08 (1H, m), 7.19 (1H, m), 7.36—7.48 (2H, m), 7.77 (1H, s), 7.92 (1H, s), 7.94 (1H, m), 8.67 (1H, bs). IR (KBr) cm^{-1}: 3160, 1765, 1705, 1625. MS *m/z*: 311, 309 (M^+). *Anal.* Calcd for $C_{18}H_{12}NClO_2$: C, 69.80; H, 3.90; Cl, 11.45; N, 4.52. Found: C, 69.56; H, 3.78; Cl, 11.72; N, 4.44.

(3*E*,4*E*)-3-Benzylidene-4-(4dimethylaminobenzylidene)-pyrrolidine-2,5-dione (1d) Yield: 62%. mp 220—222 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.90 (6H, s), 6.10 (2H, d, J=9.0 Hz), 6.71 (2H, d, J=9.0 Hz), 6.87 (2H, m), 6.90 (2H, s), 7.13 (1H, m), 7.71 (1H, s), 7.72 (1H, s), 8.12 (1H, bs). IR (KBr) cm^{-1}: 3165, 1750, 1705, 1580. MS *m/z*: 318 (M^+). *Anal.* Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.21; H, 5.94; N, 8.58.

(3*E*,4*E*)-3-Benzylidene-4-(4-methoxybenzylidene)-pyrrolidine-2,5-dione (1e) Yield: 66%. mp 181—183 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.69 (3H, s), 6.36 (2H, d, J=8.8 Hz), 6.80 (2H, d, J=8.8 Hz), 6.88 (2H, m), 6.90 (2H, s), 7.13 (1H, m), 7.76 (1H, s), 7.77 (1H, s), 8.40 (1H, bs). IR (KBr) cm^{-1}: 3170, 1760, 1705, 1620. MS *m/z*: 305 (M^+). *Anal.* Calcd for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.73; H, 5.02; N, 4.59.

(3*E*,4*E*)-3-Benzylidene-4-(3,4-dimethoxybenzylidene)-pyrrolidine-2,5-dione (1f) Yield: 86%. mp 162—163 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.56 (3H, s), 3.80 (3H, s), 6.41 (2H, m), 6.57 (1H, dd, J=8.4, 1.6 Hz), 6.94 (4H, m), 7.13 (1H, m), 7.75 (1H, s), 7.77 (1H, s), 8.68 (1H, bs). IR (KBr) cm^{-1}: 3160, 1760, 1705, 1620. MS *m/z*: 335 (M^+). *Anal.* Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.52; H, 5.22; N, 4.11.

(3*E*,4*E*)-3-Benzylidene-4-(3,4,5-trimethoxybenzylidene)-pyrrolidine-2,5-dione (1g) Yield: 70%. mp 158—159 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.57 (6H, s), 3.72 (3H, s), 6.18 (2H, s), 6.90 (1H, s), 6.95 (2H, s), 7.00—7.30 (2H, m), 7.71 (1H, s), 7.77 (1H, s), 9.22 (1H, bs). IR (KBr) cm^{-1}: 3150, 3050, 1760, 1710, 1620. MS *m/z*: 365 (M^+). *Anal.* Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 68.98; H, 5.22; N, 3.88.

(3*E*,4*E*)-3-(3-Nitrobenzylidene)-4-(3,4,5-trimethoxybenzylidene)-pyrrolidine-2,5-dione (1h) Yield: 46%. mp 239—242 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.49 (6H, s), 3.53 (3H, s), 6.26 (2H, s), 7.40 (2H, m), 7.63 (1H, s), 7.66 (1H, s), 7.76 (1H, d, J=7.8 Hz), 8.01 (1H, d, J=8.3 Hz), 11.81 (1H, bs). IR (KBr) cm^{-1}: 3165, 1760, 1710, 1625. MS *m/z*: 410 (M^+). *Anal.* Calcd for $C_{21}H_{18}N_2O_7$: C, 61.46; H, 4.42; N, 6.83. Found: C, 61.30; H, 4.42; N, 6.55.

(3*E*,4*E*)-3-(4-Chlorobenzylidene)-4-(3,4,5-trimethoxybenzylidene)-pyrrolidine-2,5-dione (1i) Yield: 65%. mp 148—150 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.62 (6H, s), 3.80 (3H, s), 6.25 (2H, s), 6.91 (2H, d, J=8.8 Hz), 6.97 (2H, d, J=8.8 Hz), 7.69 (1H, s), 7.73 (1H, s), 8.77 (1H, bs). IR (KBr) cm^{-1}: 3165, 1760, 1710, 1620. MS *m/z*: 401, 399 (M^+). *Anal.* Calcd for $C_{21}H_{18}ClNO_5$: C, 63.08; H, 4.54; Cl, 8.87; N, 3.50. Found: C, 62.87; H, 4.47; Cl, 8.59; N, 3.43.

(3*E*,4*E*)-3-(4-Dimethylaminobenzylidene)-4-(3,4,5-trimethoxybenzylidene)-pyrrolidine-2,5-dione (1j) Yield: 75%. mp 199—202 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.86 (6H, s), 3.50 (9H, s), 6.24 (2H, d, J=8.8 Hz), 6.36 (2H, s), 6.81 (2H, d, J=8.8 Hz), 7.46 (1H, s), 7.50 (1H, s), 11.42 (1H, bs). IR (KBr) cm^{-1}: 3155, 1745, 1695, 1580. MS *m/z*: 408 (M^+). *Anal.* Calcd for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.55; H, 6.04; N, 6.76.

(3*E*,4*E*)-3-(4-Methoxybenzylidene)-4-(3,4,5-trimethoxybenzylidene)-pyrrolidine-2,5-dione (1k) Yield: 87%. mp 185—186 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.59 (6H, s), 3.72 (3H, s), 3.74 (3H, s), 6.23 (2H, s), 6.48 (2H, d, J=8.8 Hz), 6.90 (2H, d, J=8.8 Hz), 7.68 (1H, s), 7.73 (1H, s), 8.34 (1H, bs). IR (KBr) cm^{-1}: 3160, 1755, 1705, 1600. MS *m/z*: 395 (M^+). *Anal.* Calcd for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54. Found: C, 66.88; H, 5.18; N, 3.46.

(3*E*,4*E*)-3-(3,4-Dimethoxybenzylidene)-4-(3,4,5-trimethoxybenzylidene)-pyrrolidine-2,5-dione (1l) Yield: 74%. mp 185—189 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.59 (3H, s), 3.61 (6H, s), 3.75 (3H, s), 3.81 (3H, s), 6.30 (2H, s), 6.47 (1H, d, J=1.8 Hz), 6.57 (1H, d, J=8.4 Hz), 6.73 (1H, dd, J=1.8, 8.4 Hz), 7.68 (1H, s), 7.72 (1H, s), 8.71 (1H, bs). IR (KBr) cm^{-1}: 3200, 1765, 1715, 1600. MS *m/z*: 425 (M^+). *Anal.* Calcd for $C_{23}H_{23}NO_7$: C, 64.93; H, 5.45; N, 3.29. Found: C, 64.76; H, 5.51; N, 3.17.

(3*E*,4*E*)-2,3-Bis-(3,4,5-trimethoxybenzylidene)-pyrrolidine-2,5-dione (1m) Yield: 77%. mp 186—187 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.64 (12H, s), 3.77 (6H, s), 6.29 (4H, s), 7.68 (2H, s), 8.49 (1H, bs). IR (KBr) cm^{-1}: 3180, 1755, 1710, 1580. MS *m/z*: 455 (M^+). *Anal.* Calcd for $C_{24}H_{25}NO_8$: C, 63.29;

H, 5.53; N, 3.08. Found: C, 62.57; H, 5.83; N, 2.86.

(3*E*,4*E*)-3-Benzylidene-1-methyl-4-(3,4,5-trimethoxybenzylidene)-pyrrolidine-2,5-dione (1n) Yield: 79%. mp 131—133 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.25 (3H, s), 3.58 (6H, s), 3.73 (3H, s), 6.19 (2H, s), 6.93 (2H, s), 6.96 (2H, s), 7.16 (1H, m), 7.72 (1H, s), 7.77 (1H, s). IR (KBr) cm^{-1}: 1750, 1700, 1615. MS *m/z*: 379 (M^+). *Anal.* Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.36; H, 5.43; N, 3.57.

(3*E*,4*E*)-1-Benzyl-3-benzylidene-4-(3,4,5-trimethoxybenzylidene)-pyrrolidine-2,5-dione (1o) Yield: 80%. mp 132—134 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.57 (6H, s), 3.72 (3H, s), 4.92 (2H, s), 6.17 (2H, s), 6.91 (2H, s), 6.94 (2H, s), 7.16 (1H, m), 7.30—7.40 (3H, m), 7.52 (2H, m), 7.71 (1H, s), 7.76 (1H, s). IR (KBr) cm^{-1}: 1765, 1705, 1625. MS *m/z*: 455 (M^+). *Anal.* Calcd for $C_{28}H_{25}NO_5$: C, 73.83; H, 5.53; N, 3.08. Found: C, 73.68; H, 5.35; N, 2.85.

(3*E*,4*E*)-3-Benzylidene-1-(2-hydroxyethyl)-4-(3,4,5-trimethoxybenzylidene)-pyrrolidine-2,5-dione (1p) Yield: 73%. mp 103—105 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.73 (1H, m), 3.57 (6H, s), 3.73 (3H, s), 3.85—4.05 (4H, m), 6.18 (2H, s), 6.91 (1H, s), 6.95 (2H, s), 6.95—7.25 (2H, m), 7.72 (1H, s), 7.77 (1H, s). IR (KBr) cm^{-1}: 3500, 1755, 1700, 1620. MS *m/z*: 409 (M^+). *Anal.* Calcd for $C_{23}H_{23}NO_6$: C, 67.47; H, 5.66; N, 3.42. Found: C, 67.72; H, 5.87; N, 3.30.

(3*E*,4*E*)-1-Amino-3-benzylidene-4-(3,4,5-trimethoxybenzylidene)-pyrrolidine-2,5-dione Hydrochloride (1q) Yield: 85%. mp 108—114 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.58 (6H, s), 3.73 (3H, s), 6.19 (2H, s), 6.93 (2H, s), 6.95 (2H, s), 7.19 (1H, m), 7.29 (2H, s), 7.72 (1H, s), 7.77 (1H, s). IR (KBr) cm^{-1}: 3300, 1765, 1700, 1620. MS *m/z*: 380 (M^+). *Anal.* Calcd for $C_{21}H_{20}N_2O_5 \cdot HCl$: C, 60.51; H, 5.08; Cl, 8.50; N, 6.72. Found: C, 60.71; H, 5.36; Cl, 8.25; N, 6.34.

(3*E*,4*E*)-3-Benzylidene-1-methoxy-4-(3,4,5-trimethoxybenzylidene)-pyrrolidine-2,5-dione (1r) Yield: 70%. mp 131—133 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.59 (6H, s), 3.73 (3H, s), 4.13 (3H, s), 6.19 (2H, s), 6.95 (4H, d, J=4.4 Hz), 7.18 (1H, m), 7.73 (1H, s), 7.78 (1H, s). IR (KBr) cm^{-1}: 1765, 1715, 1620. MS *m/z*: 395 (M^+). *Anal.* Calcd for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54. Found: C, 67.79; H, 5.32; N, 3.45.

Methyl (2*E*,3*E*)-2-Benzylidene-3-carbamoyl-4-phenylbut-3-enoate (2a) To a solution of **14a** (4.0 g, 13 mmol) in $CHCl_3$ (50 ml) were added $SOCl_2$ (1.0 ml, 13 mmol) and DMF (2 drops) below 10 °C and the mixture was refluxed for 30 min. This solutuon was added dropwise to 28% aqueous NH_3 (0.8 ml, 13 mmol) below 0 °C and the mixture was stirred at same temperature for 30 min. The organic layer was extracted with $CHCl_3$ and dried ($MgSO_4$), and concentrated *in vacuo*. The residue was crystalized in *i*-Pr_2O to give **2a** (3.7 g, 90%). mp 148—149 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.66 (3H, s), 5.61 (1H, m), 5.86 (1H, m), 7.25—7.35 (6H, m), 7.40—7.45 (2H, m), 7.55—7.60 (2H, m), 7.95 (1H, s), 8.00 (1H, s). IR (KBr) cm^{-1}: 3430, 1710, 1680, 1595, 1500. MS *m/z*: 307 (M^+). *Anal.* Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.57; N, 4.56. Found: C, 74.34; H, 5.67; N, 4.51.

The following compounds (**2b**—**k**) were prepared from the corresponding half-ester (**14a**—**c**) or diester (**13a**, **b**) by a method similar to that described for **2a**.

Methyl (2*E*,3*E*)-3-Carbamoyl-4-phenyl-2-(3,4,5-trimethoxybenzylidene)-but-3-enoate (2b) Yield: 95%. mp 179—180 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.66 (3H, s), 3.75 (6H, s), 3.83 (3H, s), 5.82 (2H, m), 6.87 (2H, s), 7.20—7.50 (5H, m), 7.88 (1H, s), 7.92 (1H, s). IR (KBr) cm^{-1}: 3400, 3200, 1725, 1675, 1590. MS *m/z*: 365 (M^+). *Anal.* Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.42; H, 5.78; N, 3.34.

Methyl (2*E*,3*E*)-2-Benzylidene-3-carbamoyl-4-(3,4,5-trimethoxyphenyl)-but-3-enoate (2c) Yield: 73%. mp 121—122 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.70 (3H, s), 3.73 (6H, s), 3.80 (3H, s), 5.94 (2H, bs), 6.70 (2H, s), 7.25—7.40 (3H, m), 7.50—7.65 (2H, m), 7.81 (1H, s), 7.96 (1H, s). IR (KBr) cm^{-1}: 3470, 3310,1700, 1655, 1630, 1580. MS *m/z*: 365 (M^+). *Anal.* Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.57; H, 5.82; N, 3.44.

Methyl (2*E*,3*E*)-3-Carbamoyl-4-(4-dimethylaminophenyl)-2-(3,4,5-trimethoxybenzylidene)-but-3-enoate (2d) Yield: 90%, mp 171—172 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.96 (6H, s), 3.70 (3H, s), 3.75 (6H, s), 3.82 (3H, s), 5.66 (2H, br), 6.58 (2H, d, J=8.8 Hz), 6.93 (2H, s), 7.41 (1H, d, J=8.8 Hz), 7.90 (2H, s). R (KBr) cm^{-1}: 3350, 3200, 1710, 1670, 1610. MS *m/z*: 440 (M^+). *Anal.* Calcd for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.41; N, 6.36. Found: C, 65.31; H, 6.39; N, 36.30.

Methyl (2*E*,3*E*)-3-Carbamoyl-4-(4-methoxyphenyl)-2-(3,4,5-trimethoxybenzylidene)-but-3-enoate (2e) Yield: 88%, mp 169—170 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.70 (3H, s), 3.78 (6H, s), 3.79 (3H, s), 3.85 (3H, s), 5.39 (1H, br), 5.80 (1H, br), 6.83 (2H, d, J=8.8 Hz), 6.91 (2H, s), 7.45 (2H, d, J=8.9 Hz), 7.91 (1H, s), 7.94 (1H, s). IR (KBr) cm^{-1}: 3440, 3200, 1705, 1670, 1610, 1590. MS *m/z*: 427 (M^+). *Anal.* Calcd for $C_{23}H_{25}NO_7$: C, 64.63; H, 5.89; N, 3.32. Found: C, 64.48; H, 5.75; N, 3.19.

Methyl (2*E*,3*E*)-3-Carbamoyl-4-(3,4-dimethoxyphenyl)-2-(3,4,5-trimethoxybenzylidene)-but-3-enoate (2f) Yield: 49%, mp 148—149 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.71 (3H, s), 3.79 (6H, s), 3.86 (3H, s), 3.87 (3H, s), 5.43 (1H, br), 5.81 (1H, br), 6.81 (1H, d, J=8.9 Hz), 6.92 (2H, s), 7.09—7.13 (2H, m), 7.92 (2H, s). IR (KBr) cm^{-1}: 3450, 3300,1720, 1690, 1605, 1585. MS *m/z*: 457 (M^+). *Anal.* Calcd for $C_{24}H_{27}NO_8$: C, 63.01; H, 5.95; N, 3.06. Found: C, 62.78; H, 5.79; N, 2.87.

Methyl (2*E*,3*E*)-3-Methylcarbamoyl-4-phenyl-2-(3,4,5-trimethoxybenzylidene)-but-3-enoate (2g) Yield: 87%, mp 155—157 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.89 (3H, d, J=4.8 Hz), 3.65 (3H, s), 3.77 (6H, s), 3.85 (3H, s), 5.97 (1H, m), 6.87 (2H, s), 7.20—7.50 (5H, m), 7.88 (1H, s), 7.94 (1H, s). IR (KBr) cm^{-1}: 3400, 1715, 1665, 1600. MS *m/z*: 411 (M^+). *Anal.* Calcd for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.19; H, 6.24; N, 3.31.

Methyl (2*E*,3*E*)-3-Benzylcarbamoyl-4-phenyl-2-(3,4,5-trimethoxybenzylidene)-but-3-enoate (2h) Yield: 88%, mp 130—132 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.61 (3H, s), 3.74 (6H, s), 3.88 (3H, s), 4.24 (1H, dd, J=6.8, 5.7 Hz), 4.61 (1H, dd, J=6.8, 5.7 Hz), 6.21 (1H, d, J=5.7 Hz), 6.86 (1H, s), 6.85 (2H, m), 7.14—7.47 (2H, m), 7.89 (1H, s), 8.03 (1H, s). IR (KBr) cm^{-1}: 3450, 3400, 1715, 1665, 1605, 1585. MS *m/z*: 487 (M^+). *Anal.* Calcd for $C_{29}H_{29}NO_6$: C, 71.44; H, 6.00; N, 2.87. Found: C, 71.30; H, 5.94; N, 2.67.

Methyl (2*E*,3*E*)-3-(2-Hydroxyethylcarbamoyl)-4-phenyl-2-(3,4,5-trimethoxybenzylidene)-but-3-enoate (2i) Yield: 81%, mp 110—111 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.19 (1H, bs), 3.23—3.76 (4H, m), 3.62 (3H, s), 3.77 (6H, s), 3.84 (3H, s), 6.40 (1H, m), 6.85 (2H, s), 7.23—7.48 (5H, m), 7.88 (1H, s), 7.93 (1H, s). IR (KBr) cm^{-1}: 3600, 3400, 1700, 1660. MS *m/z*: 441 (M^+). *Anal.* Calcd for $C_{24}H_{27}NO_7$: C, 65.29; H, 6.16; N, 3.17. Found: C, 65.24; H, 6.06; N, 3.01.

Methyl (2*E*,3*E*)-3-Hydrazinocarbonyl-4-phenyl-2-(3,4,5-trimethoxybenzylidene)-but-3-enoate (2j) Yield: 64%, mp 174—175 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.65 (3H, s), 3.75 (6H, s), 3.83 (3H, s), 3.65—4.04 (2H, m), 6.83 (2H, s), 7.12—7.48 (6H, m), 7.87 (1H, s), 7.93 (1H, s). IR (KBr) cm^{-1}: 3350, 3300, 1710, 1660. MS *m/z*: 412 (M^+). *Anal.* Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.86; N, 6.79. Found: C, 64.21; H, 6.05; N, 6.64.

Methyl (2*E*,3*E*)-3-Methoxycarbamoyl-4-phenyl-2-(3,4,5-trimethoxybenzylidene)-but-3-enoate (2k) Yield: 51%, mp 148—150 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.60 (3H, s), 3.65 (3H, s), 3.77 (6H, s), 3.83 (3H, s), 6.84 (2H, s), 7.21—7.50 (5H, m), 7.82 (1H, s), 7.88 (1H, s), 8.63 (1H, bs). IR (KBr) cm^{-1}: 3200, 1710, 1660. MS *m/z*: 427 (M^+). *Anal.* Calcd for $C_{23}H_{25}NO_7$: C, 64.63; H, 5.89; N, 3.28. Found: C, 64.69; H, 5.87; N, 3.04.

(3*E*,4*E*)-3-Benzylidene-4-(3,4,5-trimethoxybenzylidene)-dihydrofuran-2,5-dione (3) To a solution of **14b** (7.3 g, 18 mmol) in toluene (50 ml) were added $SOCl_2$ (1.3 ml, 18 mmol) and DMF (1 drop) and the mixture was stirred at 80 °C for 30 min. To this solutuon, $SnCl_4$ (2.7 ml, 23 mmol) was added below 10 °C and the mixture was stirred at room temperature for 16 h. The reaction mixture was poured into ice-water and the organic layer was extracted with AcOEt and washed with 1 N NaOH and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was crystalized in Et_2O to give **3** (4.8 g, 72%). mp 201—203 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.95 (3H, s), 4.00 (3H, s), 4.10 (3H, s), 6.52 (1H, s), 7.09 (1H, s), 7.35 (5H, s), 7.84 (1H, s), 9.70 (1H, s). IR (KBr) cm^{-1}: 1800, 1745. MS *m/z*: 366 (M^+). *Anal.* Calcd for $C_{21}H_{18}O_6$: C, 68.85; H, 4.95. Found: C, 68.76; H, 4.86.

(3*E*,4*E*)-3-Benzylidene-4-(3,4,5-trimethoxybenzylidene)-dihydrofuran-2-one (4a) To a solution of **14b** (5.0 g, 13 mmol) in CH_2Cl_2 (50 ml) was added 1.5 M diisobutylaluminum hydride in toluene (25 ml, 38 mmol) under nitrogen below 10 °C and the mixture was stirred at room temperature for 1 h. To this solution, 10% aqueous HCl was added carefully until pH 1 below 10 °C and the mixture was stirred at 50 °C for 1 h. The organic layer was extracted with $CHCl_3$ and dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane : AcOEt=2 : 1) to give **4a** (2.3 g, 53%); mp 145—146 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.49 (6H, s), 3.60 (3H, s), 4.92 (1H, d, J=2.0 Hz), 5.94 (2H, s), 6.47 (1H, s), 6.70—7.10 (5H, m), 7.54 (1H, s). IR (KBr) cm^{-1}: 1770, 1755, 1620, 1585, 1505. MS *m/z*: 352 (M^+). *Anal.* Calcd for $C_{21}H_{20}O_5$: C, 71.58; H, 5.72. Found: C, 71.73; H, 5.64.

(3*E*,4*E*)-4-Benzylidene-3-(3,4,5-trimethoxybenzylidene)-dihydrofuran-2-one (4b) This compound was prepared in 78% yield from **14c** by a method similar to that described for **4a**. mp 140—142 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.58 (6H, s), 3.73 (3H, s), 5.03 (2H, d, J=2.0 Hz), 6.24 (2H, s), 6.64 (1H, s), 6.70—7.15 (5H, m), 7.62 (1H, s). IR (KBr) cm^{-1}: 1750, 1585. MS *m/z*: 352 (M^+). *Anal.* Calcd for $C_{21}H_{20}NO_5$: C, 71.58; H, 5.72. Found: C, 71.74; H, 5.61.

Methyl (2*E*,3*E*)-3-Cyano-4-phenyl-2-(3,4,5-trimethoxybenzylidene)-but-3-enoate (15a) A solution of **2b** (4.0 g, 10 mmol) in THF (15 ml) was added to a solution of PPh_3 (5.2 g, 20 mmol) in CCl_4 (15 ml) and the mixture was stirreded at 50 °C for 3 h. The resulting precipitate was filtered off, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane : AcOEt=2 : 1) to give **15a** (3.1 g, 82%); mp 104—106 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.72 (3H, s), 3.81 (6H, s), 3.87 (3H, s), 6.83 (2H, s), 7.28—7.39 (5H, m), 7.45 (1H, s), 7.86 (1H, s). IR (KBr) cm^{-1}: 2230, 1720, 1630, 1605, 1590. MS *m/z*: 379 (M^+). *Anal.* Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.82; H, 5.60; N, 3.70.

Methyl (2*E*,3*E*)-2-Benzylidene-3-cyano-4-(3,4,5-trimethoxyphenyl)-but-3-enoate (15b) This compound was prepared in 85% yield from **2c** by a method similar to that described for **15a**. mp 112—114 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.73 (3H, s), 3.75 (6H, s), 3.85 (3H, s), 6.64 (2H, s), 7.33 (1H, s), 7.38—7.43 (3H, m), 7.55—7.60 (2H, m), 7.94 (1H, s). IR (KBr) cm^{-1}: 2240, 1725, 1620, 1600. MS *m/z*: 379 (M^+). *Anal.* Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.44; H, 5.32; N, 3.85.

(3*E*,4*E*)-4-Benzylidene-3-(3,4,5-trimethoxybenzylidene)-pyrrolidin-2-one (5a) A mixture of **15a** (5.7 g, 15 mmol) and Raney Ni (10 ml) in MeOH (250 ml) was stirred under hydrogen atmosphere (1 atm) at room temperature for 2 h. After removal of the catalyst by filtration, the filtrate was refluxed for 1 h and concentrated *in vacuo*. The residue was chromatographed on silica gel ($CHCl_3$: acetone=5 : 1) to give **5a** (3.6 g, 65%); mp 125—127 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.61 (6H, s), 3.72 (3H, s), 4.30 (2H, s), 6.27 (2H, s), 6.63 (1H, s), 6.63—7.05 (5H, m), 7.09 (1H, bs), 7.47 (1H, s). IR (KBr) cm^{-1}: 3200, 1695, 1630, 1605, 1580. MS *m/z*: 351 (M^+). *Anal.* Calcd for $C_{21}H_{21}NO_5$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.92; H, 6.05; N, 4.02.

(3*E*,4*E*)-3-Benzylidene-4-(3,4,5-trimethoxybenzylidene)-pyrrolidin-2-one (5b) This compound was prepared in 69% yield from **15b** by a method similar to that described for **5a**. mp 125—127 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.59 (6H, s), 3.67 (3H, s), 4.28 (2H, s), 6.12 (2H, s), 6.58 (1H, s), 6.87—7.13 (6H, m), 7.54 (1H, s). IR (KBr) cm^{-1}: 3460, 1700, 1685, 1615, 1585. MS *m/z*: 351 (M^+). *Anal.* Calcd for $C_{21}H_{21}NO_5$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.87; H, 6.07; N, 3.94.

1,1-Dibromo-2-(3,4,5-trimethoxyphenyl)-ethylene (17) A mixture of CBr_4 (67.6 g, 0.20 mol) and PPh_3 (106.9 g, 0.40 mol) in CH_2Cl_2 (400 ml) was stirred under nitrogen at room temperature for 1 h. To this mixture was added 3,4,5-trimethoxybenzaldehyde (20 g, 0.10 mol) at 0 °C and the mixture was stirred for 16 h at room temperature. The resulting precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane : AcOEt=5 : 1) to give **17** (35.5 g, 99%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 3.87 (9H, s), 6.80 (2H, s), 7.41 (1H, s). IR (film) cm^{-1}: 2940, 1580, 1505, 1240. MS *m/z*: 354, 352, 350 (M^+). HR-MS Calcd for $C_{11}H_{12}Br_2O_3$ (M^+): 349.9152. Found: 349.9164.

Methyl 3-(3,4,5-Trimethoxyphenyl)-propiolate (18) To a solution of **17** (10 g, 28 mmol) in dry THF (100 ml) was added *n*-butyllithium (1.6 M in hexane) (39 ml, 63 mmol) below −50 °C under nitrogen and the mixture was stirred at room temperature for 1 h. Then methyl chloroformate (2.6 ml, 34 mmol) in dry THF (20 ml) was added below −50 °C and the resulting mixture was stirred at room temperature for 30 min. The reaction was quenched by addition of saturated aqueous NH_4Cl and the reaction mixture was extracted with AcOEt. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane : AcOEt=3 : 1) to give **18** (6.3 g, 88%); mp 97—98 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.85 (3H, s), 3.86 (6H, s), 3.88 (6H, s), 6.84 (2H, s). IR (KBr) cm^{-1}: 2220, 1705, 1580, 1505, 1240. MS *m/z*: 250 (M^+). *Anal.* Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.26; H, 5.56.

Methyl (*E*)-2-(Tributylstannyl)-3-(3,4,5-trimethoxyphenyl)-acrylate (19) To a solution of **18** (15.0 g, 60 mmol) and $Pd(PPh_3)_4$ (1.4 g, 1.2 mmol) in dry THF (75 ml) was added dropwise Bu_3SnH (16.2 ml, 60 mmol) in dry THF (50 ml) over 2 h under nitrogen and stirred at room temperature for 3.5 h. Solvent was removed *in vacuo* and the residue was diluted with hexane. The resulting precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane : AcOEt=5 : 1) to give **19** (22.2 g, 73%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (9H, t, *J*=7.1 Hz), 1.03 (6H, t, *J*=7.8 Hz), 1.20—1.70 (12H, m), 3.71 (3H, s), 3.84 (9H, s), 6.58 (2H, s), 6.59 (1H, s). IR (film) cm^{-1}: 2955, 1705, 1580, 1510, 1240. MS (SI-MS) *m/z*: 542 (M^++1).

Methyl (*Z*)-2-(Tributylstannyl)-3-(3,4,5-trimethoxyphenyl)-acrylate (20) To a solution of **18** (4.0 g, 16 mmol) and Bu_3SnH (4.3 ml, 16 mmol) in toluene (80 ml) was added AIBN (40 mg, 0.24 mmol) under nitrogen and the mixture was stirred at room temperature for 1 h. Solvent was removed *in vacuo*. The residue was chromatographed on silica gel (hexane : AcOEt=8 : 1) to give **20** (7.4 g, 86 %) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.76—0.89 (15H, m), 1.16—1.42 (12H, m), 3.78 (3H, s), 3.86 (3H, s), 3.87 (6H, s), 6.51 (2H, s), 8.30 (1H, s). IR (film) cm^{-1}: 2955, 1710, 1575, 1505, 1235. MS (SI-MS) *m/z*: 542 (M^++1).

Methyl (*E*)-2-Bromo-3-(3,4,5-trimethoxyphenyl)-acrylate (21) To a stirred solution of **19** (5.0 g, 9.8 mmol) in dry CH_2Cl_2 (70 ml) was added dropwise bromine (0.51 ml, 9.8 mmol) in dry CH_2Cl_2 (100 ml) over 3.5 h under nitrogen below 10 °C. Solvent was removed *in vacuo*. Ether and aqueous KF were added to the residue and the mixture was stirred for 1 h. The insoluble material was filtered off and the filtrate was extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane : AcOEt=2 : 1) to give **21** (3.1 g, 94%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 3.79 (3H, s), 3.84 (6H, s), 3.86 (3H, s), 6.57 (2H, s), 7.26 (1H, s). IR (film) cm^{-1}: 2945, 1730, 1580, 1505, 1220. MS *m/z*: 332, 330 (M^+). HR-MS Calcd for $C_{13}H_{15}BrO_2$ (M^+): 330.0102. Found: 330.0115.

Methyl (*Z*)- 2-Bromo-3-(3,4,5-trimethoxyphenyl)-acrylate (22) This compound was prepared in 85% yield from **20** by a method similar to that described for **21**. mp 65—66 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.90 (6H, s), 3.91 (6H, s), 7.19 (2H, s), 8.16 (1H, s). IR (KBr) cm^{-1}: 2945, 1720, 1580, 1505, 1235. MS *m/z*: 332, 330 (M^+). *Anal.* Calcd for $C_{13}H_{15}BrO_2$: C, 47.15; H, 4.57. Found: C, 47.05; H, 4.67.

3-Phenylpropiolamide (24) To a solution of phenylacetylene (5.0 g, 49 mmol) in dry THF (100 ml) was added *n*-butyllithium (1.6 M in hexane) (34 ml, 54 mmol) below −50 °C under nitrogen and the mixture was stirred at −78 °C for 30 min. Then CO_2 gas was bubbled below 0 °C for 30 min. The reaction mixture was acidified to pH 1 with 10% aqueous HCl and extracted with $CHCl_3$. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (50 ml). To this solution was added $SOCl_2$ (4.3 ml, 59 mmol) and DMF (2 drops) and the mixture was stirred at room temperature for 1 h. This solution was added to 28% aqueous NH_3 (20 ml) below 10 °C and the mixture was stirred at room temperature for 30 min. The organic layer was extracted with $CHCl_3$ and dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel ($CHCl_3$: MeOH=20 : 1) to give **24** (2.5 g, 35%); mp 102—104 °C. ^{1}H-NMR ($CDCl_3$) δ: 5.89 (2H, br), 7.30—7.42 (3H, m), 7.52—7.58 (2H, m). IR (KBr) cm^{-1}: 3385, 3190, 2225, 1640, 1490. MS *m/z*: 145 (M^+). *Anal.* Calcd for C_9H_7NO: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.35; H, 4.81; N, 9.44.

(*E*)-3-Phenyl-2-(tributylstannyl)acrylamide (25) This compound was prepared in 38% yield from **24** by a method similar to that described for **19** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (9H, t, *J*=7.2 Hz), 1.09 (6H, m), 1.36 (6H, m), 1.60 (6H, m), 5.19 (2H, br), 6.66 (1H, s), 7.25—7.45 (m, 5H). IR (film) cm^{-1}: 3490, 3300, 1650, 1600. MS *m/z*: 436 (M^+).

(*Z*)-3-Phenyl-2-(tributylstannyl)acrylamide (26) This compound was prepared in 52% yield from **24** by a method similar to that described for **20**. mp 59—60 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.83 (9H, t, *J*=7.2 Hz), 0.87 (6H, m), 1.24 (6H, m), 1.40 (6H, m), 5.48 (2H, br), 7.79 (1H, s), 7.25 (m, 2H), 7.34 (m, 3H), 7.79 (1H, s). IR (KBr) cm^{-1}: 3400, 3200, 1630, 1600. MS *m/z*: 436 (M^+). *Anal.* Calcd for $C_{21}H_{35}NOSn$: C, 57.82; H, 8.09; N, 3.21. Found: C, 57.39; H, 8.13; N, 3.28.

Methyl (2*E*,3*Z*)-3-Carbamoyl-4-phenyl-2-(3,4,5-trimethoxybenzylidene)-but-3-enoate (9) A solution of **22** (5.4 g, 12.4 mmol), **25** (4.1 g, 12.4 mmol) and $PdCl_2(PPh_3)_2$ (0.43 g, 0.62 mmol) in DMF (25 ml) was stirred under nitrogen at 60 °C for 14 h. Solvent was removed *in vacuo*. AcOEt and aqueous KF was added to the residue and the mixture was stirred for 1 h. The insoluble material was filtered off and the filtrate was extracted with AcOEt. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel ($CHCl_3$: acetone=5 : 1) to give **9** (3.1 g, 63%); mp 146—147 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.81 (6H, s), 3.84 (3H, s), 3.86 (3H, s), 5.64 (1H, bs), 6.48 (1H, bs), 6.60 (1H, s), 7.23 (2H, s), 7.31 (3H, m), 7.46 (2H, m), 7.79 (1H, s). IR (KBr) cm^{-1}: 3470, 3200, 1690, 1660, 1580. MS *m/z*: 397 (M^+). *Anal.* Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.41; H, 5.77; N, 3.31.

(3*Z*,4*E*)-3-Benzylidene-4-(3,4,5-trimethoxybenzylidene)-pyrrolidine-2,5-dione (6) To a solution of **9** (2.0 g, 5.0 mmol) in THF (20 ml) was added 2 N NaOH (5 ml) and the mixture was stirreded for 30 min. To this solution, 2 N HCl (5 ml) was added and the mixture was extracted with $CHCl_3$ and dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel ($CHCl_3$: acetone=10 : 1) to give **6** (1.7 g, 93%); mp 176—178 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.80 (6H, s), 3.92 (3H, s), 6.88 (2H, s), 7.40 (3H, m), 7.62 (1H, s), 7.84 (2H, m), 7.86 (1H, s), 8.35 (1H, bs). IR (KBr) cm^{-1}: 3160, 1750, 1700, 1640, 1610, 1500. MS *m/z*: 365 (M^+). *Anal.*

Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 69.00; H, 5.19; N, 3.90.

Methyl (2*Z*,3*E*)-3-Carbamoyl-4-phenyl-2-(3,4,5-trimethoxybenzylidene)-but-3-enoate (10) This compound was prepared in 65% yield from **21** and **26** by a method similar to that described for **9**. mp 186—187 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.74 (3H, s), 3.84 (6H, s), 3.87 (3H, s), 5.74 (1H, bs), 6.38 (1H, bs), 6.61 (2H, s), 6.71 (1H, s), 7.33 (3H, m), 7.65 (2H, m), 7.81 (1H, s). IR (KBr) cm^{-1}: 3500, 3360, 1705, 1670, 1580. MS *m*/*z*: 397 (M^+). *Anal.* Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.47; H, 5.84; N, 3.50.

(3*E*,4*Z*)-3-Benzylidene-4-(3,4,5-trimethoxybenzylidene)-pyrrolidine-2,5-dione (7) This compound was prepared in 95% yield from **10** by a method similar to that described for **6**. mp 197—198 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.87 (6H, s), 3.91 (3H, s), 7.25 (2H, s), 7.42 (3H, m), 7.56 (1H, s), 7.61 (2H, m), 7.69 (1H, s), 8.65 (1H, bs). IR (KBr) cm^{-1}: 3170, 1750, 1710, 1575, 1510. MS *m*/*z*: 365 (M^+). *Anal.* Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 68.90; H, 5.26; N, 3.72.

Methyl (2*Z*,3*Z*)-3-Carbamoyl-4-phenyl-2-(3,4,5-trimethoxybenzylidene)-but-3-enoate (11) This compound was prepared in 68% yield from **21** and **25** by a method similar to that described for **9**. mp 158—160 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.82 (3H, s), 3.85 (6H, s), 3.87 (3H, s), 5.70 (2H, bs), 6.60 (2H, s), 6.64 (1H, s), 6.92 (1H, s), 7.29—7.41 (3H, m), 7.47—7.53 (2H, m). IR (KBr) cm^{-1}: 3455, 3345, 1730, 1670, 1575, 1510, 1250. MS *m*/*z*: 397 (M^+). *Anal.* Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.35; H, 5.76; N, 3.64.

(3*Z*,4*Z*)-3-Benzylidene-4-(3,4,5-trimethoxybenzylidene)-pyrrolidine-2,5-dione (8) This compound was prepared in 93% yield from **11** by a method similar to that described for **6**. mp 190—192 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.95 (9H, s), 7.28 (1H, s), 7.37 (1H, s), 7.44 (3H, m), 7.54 (2H, s), 8.00 (2H, m), 8.16 (1H, bs). IR (KBr) cm^{-1}: 3180, 1745, 1700, 1575, 1505. MS *m*/*z*: 365 (M^+). *Anal.* Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 69.03; H, 5.20; N, 3.91.

Plasminogen Activator Activity in Conditioned Medium from Bovine Endothelial Cells Endothelial cells from bovine carotid artery were grown to confluence on 24-well microplates in E'MEM supplemented with +10% fetal bovine serum (FBS) and 2 mM L-glutamine. The cell monolayer was washed twice with FBS-free E'MEM and then further incubated in fresh FBS-free MEM containing the test compound at a concentration of 3 μM for 24 h. The test compound was added as an ethanol (final 0.5%) solution and therefore control cells were incubated in the presence of 0.5% ethanol only. After the incubation, the conditioned medium was collected and centrifuged at 3000 rpm at 4 °C for 10 min to remove cellular debris. The conditioned medium was stored at −80 °C until measurement of the activity of plasminogen activator. Plasminogen activator (PA) activity in the conditioned medium was measured by the spectrophotometric method using a commercial kit (Spectrolyse^{TM}/fibrin, Biopool AB, Umea, Sweden). The relative PA activity in the cells treated with the test compounds was estimated on the assumption that the PA activity in the absence of any test compound is 100%.

Antithrombotic Activity in a Rat Model of Venous Thrombosis The oral antithrombotic activity of test compounds was evaluated in a rat model of venous thrombosis induced by the intravenous injection of thromboplastin followed by stasis of the inferior vena cava.[19] Test compounds were suspended in 0.1% Nikkol HCO-60 solution at concentrations of 1 and 10 mg/ml. Each solution of the test compounds was orally administered to rats in a volume of 10 ml/kg for 8 consecutive days. Control groups were treated with 0.1% Nikkol HCO-60 solution only. Two hours after the last administration of each compound, the thrombus was induced as described above. The thrombus formed was removed and its dry weight was measured. The percentage decrease in thrombus weight for each treatment group compared to the control group (vehicle) was estimated.

References and Notes

1) Sprengers E. D., Kluft C., *Blood*, **69**, 381—387 (1987).
2) Schneiderman J., Loskutoff D. J., *Trends Cardiovasc. Med.*, **1**, 99—102 (1991).
3) Schleef R. R., Higgins D. L., Pillemer E., Levitt L. J., *J. Clin. Invest.*, **83**, 1747—1752 (1989).
4) Kooistra T., Lansink M., Emeis J. J., *Drug Future*, **21**, 291—299 (1996).
5) Levin E. G., Marzec U., Anderson J., Harker L. A., *J. Clin. Invest.*, **74**, 33—39 (1990).
6) Van Hinsberg V. W. M., Sprengers E. D., Kooistra T., *Thromb. Haemost.*, **57**, 148—153 (1987).
7) Kooistra T., Van den Berg J., Tons A., Platenberg G., Rijken D. C., Van den Berg E., *Biochem. J.*, **247**, 605—612 (1987).
8) Bulens F., Nelles L., Van den Panhuyzen N., Collen D., *J. Cardiovasc. Pharmacol.*, **19**, 508—514 (1992).
9) Kojima S., Hagiwara H., Shimonaka M., Saito Y., Inada Y., *Biomed. Res.*, **7**, 155—159 (1986).
10) Johnson W. S., Daube G. H., *Org. React.*, **6**, 1—73 (1951).
11) The stereochemistry was decided by NMR date.
12) Sai H., Ogiku T., Nishitani T., Hiramatsu H., Horikawa H., Iwasaki T., *Synthesis*, **1995**, 582—586 (1995).
13) Corey E. J., Fuchs P. L., *Tetrahedron Lett.*, **13**, 3769—3772 (1972).
14) Ichinose Y., Oda H., Oshima K., Utimoto K., *Bull. Chem. Soc. Jpn.*, **60**, 3468—3470 (1987).
15) Rossi R., Carpita A., Cossi P., *Tetrahedron*, **48**, 8801—8824 (1992).
16) Corey E. J., Ulrich P., Fitzpatrick J. M., *J. Am. Chem. Soc.*, **98**, 222—224 (1976).
17) Baekelmans P., Gielen M., Malfroid P., Nasieski J., *Bull. Soc. Chem. Belg.*, **77**, 85—90 (1968).
18) Chen C., Cox P. B., Roberts S. M., *J. Chem. Soc., Chem. Commun.*, **1988**, 971—973 (1988).
19) Vogel G. M. T., Mueleman D. G., Bourgondien F. G. M., Hobbelen P. M. J., *Thromb. Res.*, **54**, 399—410 (1989).