Synthetic Method and Biological Activities of *cis*-Fused α-Methylene γ-Lactones

Yohsuke Higuchi,[†] Fumito Shimoma,[†] and Masayoshi Ando*[,‡]

Graduate School of Science and Technology, and Department of Chemistry and Chemical Engineering, Faculty of Engineering, Niigata University, 2-8050 Ikarashi, Niigata 950-2181, Japan

Received December 18, 2002

A reliable method was developed for the synthesis of *cis*-fused α-methylene γ-lactones via α-methyl γ-lactones. Bromination of α-methyl γ-lactones with LDA/CBr_4 or TMSOTf/PTAB and successive dehydrobromination with DBU or TBAF of the resulting α-bromo-α-methyl γ-lactones gave the desired α-methylene γ-lactones in high yield. This method was successfully applied to the synthesis of biologically active compounds. α-Methylene γ-lactone derivatives **1c**, **2c**, **4c**, and **17** showed cell growth inhibitory activity to P388 lymphocytic leukemia. They also showed significant activities to crop diseases. Thus, α-methylene γ-lactone **1c** showed preventive activity in controlling scab of apple caused by *Venturia inaequalis*. α-Methylene γ-lactones **2c**, **4c**, **17**, and **18** also showed significant preventive activities in controlling damping off of cucumber caused by *Pythium aphanidermatum*.

The sesquiterpene lactones with *cis*- and *trans*-fused α-methylene γ-lactone moieties are a rapidly expanding group of natural products comprising to date ca. 2000 compounds.[1] Some of them have been shown to possess biological activities such as antitumor,[2−15] antiulcer,[15] cardiotonic,[15] antischistosomal,[2,16,17] anthelmintic,[18] contraceptive,[19,20] allergy,[2] immunomodulation,[21] root-growth stimulatory,[2,22,23] root-growth and germination inhibitory activities,[2,3,12−14,24,25] and preventive or curative activities for crop diseases.[3,14] These compounds featuring α-methylene γ-lactone can be considered as playing the role of a Michael acceptor of biological nucleophiles, e.g., thiol groups of proteins[2] (Figure 1). This reaction is likely to explain many of their biological activities. Cytotoxic agents may irreversibly alkylate critical enzymes that control cell division, while allergenic compounds may conjugate with proteins to form antigens, which trigger the allergic response.

In the course of our studies of structure−activity relationships of sesquiterpene lactones, we encountered the necessity of an efficient conversion of α-methyl γ-lactones to the corresponding α-methylene γ-lactones. Grieco and Miyashita[26] had developed a general, high-yield α-methylenation sequence for the construction of *trans*-fused α-methylene γ-lactones employing alkyl phenylselenoxide,[27,28] which underwent facile *syn* elimination at low temperature[29] with exclusive formation of the exocyclic methylene unit[30] (Scheme 1). The method has been applied to the syntheses of a wide variety of sesquiterpene lactones with a *trans*-fused α-methylene γ-lactone moiety[3,11−14,31−44] such as eudesmanolides, guaianolides, elemanolides, and germacranolides. On the other hand, Ourisson and coworkers[45] had reported a synthetic sequence that permitted construction of a *cis*-fused α-methylene γ-lactone moiety from the corresponding α-methyl γ-lactone precursors (Scheme 2). They had also applied their method to the synthesis of (−)-frullanolide.[45]

We attempted α-methylenation of (3aα,8aα)-3β-methyloctahydro-2*H*-cyclohepta[*b*]furan-2-one (**1a**) by the Ourisson method. The reaction gave a complex mixture, and the only isolated product was an alkylated compound (Scheme 3). Thus, we sought to develop general, high-yield sequences of α-methylenation that were applicable to the chemical transformation of *cis*-fused α-methyl γ-lactones condensed with a six- or seven-membered ring to the corresponding α-methylene γ-lactone derivatives such as pseudoguaianolides and a part of eudesmanolides.

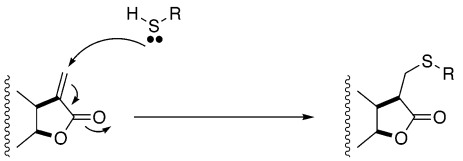
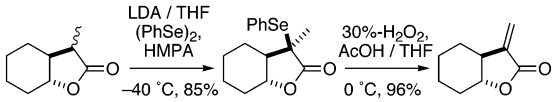
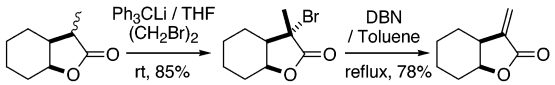


Figure 1.

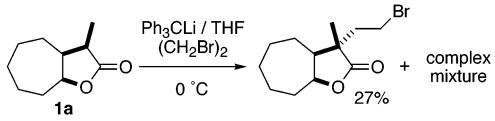
Scheme 1[26]



Scheme 2[45]



Scheme 3



Results and Discussion

In this paper, we report two general, high-yield α-methylenation sequences for *cis*-fused α-methyl γ-lactone precursors. Our first approach (method A) is based on bromination of the enolate anion of α-methyl γ-lactones (**a**) with CBr_4 [46] and subsequent dehydrobromination of the resulting α-bromo-α-methyl γ-lactones (**b**) with DBU (Figure 2). The results of this method, which was applied to the *cis*-fused α-methyl γ-lactone precursors condensed with a seven-membered ring, are summarized in Table 1. It is noteworthy that the α-methylenation of γ-lactone by this method is compatible with the presence of a double bond (entry 6). The limitation of this method is shown in the hydroxy γ-lactone **7a** of entry 7. The yield of bromination

* To whom correspondence should be addressed. Tel and Fax: +81-25-262-7326. E-mail: mando@eng.niigata-u.ac.jp.
[†] Graduate School of Science and Technology.
[‡] Department of Chemistry and Chemical Engineering, Faculty of Engineering.

10.1021/np020586y CCC: $25.00
Published on Web 05/30/2003

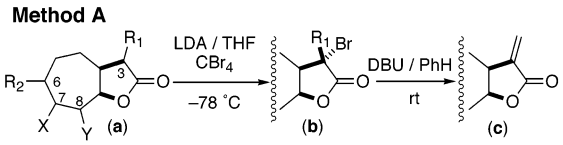


Figure 2. α-Methylenation sequence of *cis*-α-methyl γ-lactones condensed with a seven-membered ring by method A.

Table 1. Products and Yields of α-Methylenation of *cis*-α-Methyl γ-Lactones Condensed with a Seven-Membered Ring by Method A

entry	α-methyl γ-lactone	α-bromo-α-methyl γ-lactone (**b**) isolated yield (%)	α-methylene γ-lactone (**c**) isolated yield (%)
1	**1a**: $R^1 = \beta$-Me $R^2 = X = Y = H$	**1b**: 72	**1c**: 31
2	**2a**: $R^1 = \alpha$-Me $R^2 = \alpha$-Me $X = Y = H$	**2b**: 55	**2c**: 66
3	**3a**: $R^1 = \beta$-Me $R^2 = \alpha$-Me $X = Y = H$	**2b**: 77	**2c**: 66
4	**4a**: $R^1 = \alpha$-Me $R^2 = \beta$-Me $X = Y = H$	**4b**: 69	**4c**: 72
5	**5a**: $R^1 = \beta$-Me $R^2 = \beta$-Me $X = Y = H$	**4b**: 62	**4c**: 72
6	**6a**: $R^1 = \beta$-Me $R^2 = \beta$-Me $X = Y =$ double bond	**6b**: 72	**6c**: 65
7	**7a**: $R^1 = \beta$-Me $R^2 = \alpha$-Me $X = H$ $Y = \beta$-OH	**7b**: 44	**7c**: –

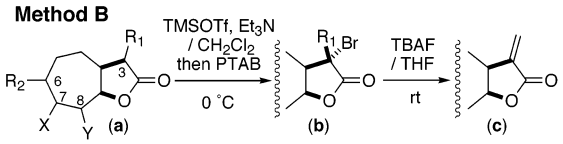


Figure 3. α-Methylenation sequence of *cis*-α-methyl γ-lactones condensed with a seven-membered ring by method B.

was low, and dehydrobromination of the resulting α-bromo-α-methyl γ-lactone **7b** with DBU gave a complex mixture, probably because of the participation of the alkoxide anion produced under the reaction conditions in the molecule.

Our second approach (method B) is based on the bromination of silyl enol ethers[47] of α-methyl γ-lactones (**a**) with phenyltrimethylammonium tribromide (PTAB) and successive dehydrobromination of the resulting α-bromo-α-methyl γ-lactones (**b**) with tetrabutylammonium fluoride (TBAF) (Figure 3). The fluoride anion was found to be effective as a base for *trans* elimination of *cis*-fused α-bromo-α-methyl γ-lactones (**b**) under mild conditions as well as the reagent for deprotection of the silyl protecting group. The results are summarized in Table 2.

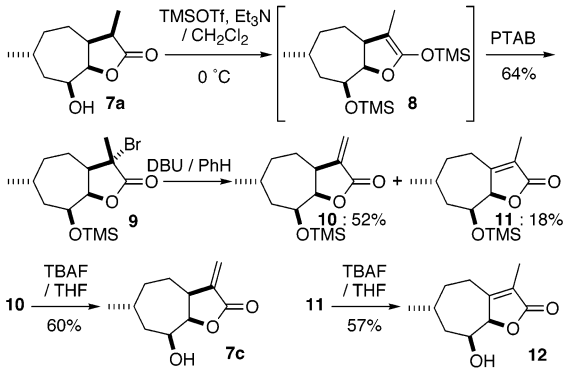
Although, as mentioned above, the attempted α-methylenation of the hydroxy γ-lactone **7a** by method A was unsuccessful, the modified method B was successfully applied to this compound (Scheme 4). Thus, treatment of the hydroxy γ-lactone **7a** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of Et_3N in CH_2Cl_2 gave the corresponding unstable silyl enol ether **8**. Without separation, bromination of **8** in situ with PTAB gave the α-bromo-α-methyl γ-lactone **9**, in which the hydroxy group at C-8 was protected as a TMS ether under the reaction conditions. Dehydrobromination of **9** with DBU and the successive deprotection of TMS ether at C-8 with

Table 2. Products and Yields of α-Methylenation of *cis*-α-Methyl γ-Lactones Condensed with a Seven-Membered Ring by Method B

entry	α-methyl γ-lactone	α-bromo-α-methyl γ-lactone (**b**) isolated yield (%)[a]	α-methylene γ-lactone (**c**) isolated yield (%)[a]
1	**1a**: $R^1 = \beta$-Me $R^2 = X = Y = H$	not attempted	not attempted
2	**2a**: $R^1 = \alpha$-Me $R^2 = \alpha$-Me $X = Y = H$	**2b**: 70	**2c**: 76
3	**3a**: $R^1 = \beta$-Me $R^2 = \alpha$-Me $X = Y = H$	**2b**: 69 (80)	**2c**: 76
4	**4a**: $R^1 = \alpha$-Me $R^2 = \beta$-Me $X = Y = H$	**4b**: 65 (97)	**4c**: 87
5	**5a**: $R^1 = \beta$-Me $R^2 = \beta$-Me $X = Y = H$	**4b**: 81	**4c**: 87
6	**6a**: $R^1 = \beta$-Me $R^2 = \beta$-Me $X = Y =$ double bond	**6b**: 77 (79)	**6c**: 84 (93)
7	**7a**: $R^1 = \beta$-Me $R^2 = \alpha$-Me $X = H$ $Y = \beta$-OH	(see Scheme 4 and text)	

[a] The yields in parentheses are based on recovered starting material.

Scheme 4

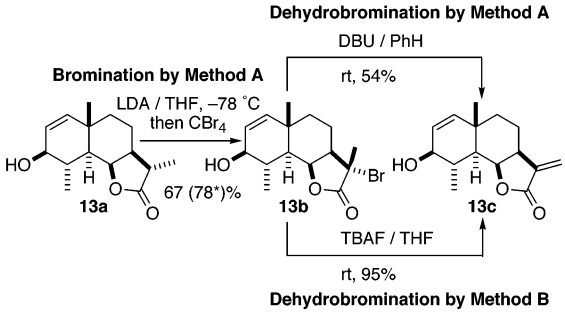


TBAF gave the desired α-methylene γ-lactone **7c** and the endocyclic α,β-unsaturated lactone **12** in 31% and 10% overall yields in two steps.

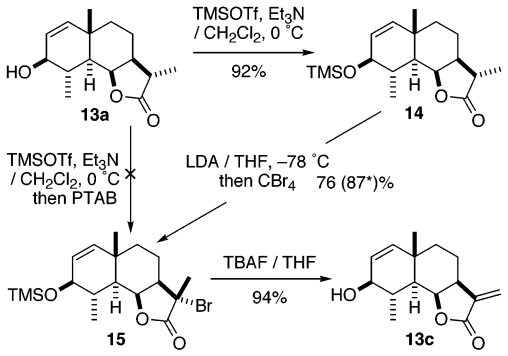
Finally, methods A and B have been applied to the α-methylenation of 6β-santonin derivatives such as an allylic alcohol **13a**. An attempt to apply method A to **13a** afforded the corresponding *cis*-fused α-methylene γ-lactone **13c** via α-bromo-α-methyl γ-lactone **13b** in unsatisfactory yields. The yield of **13c** from **13b** was improved by the application of dehydrobromination according to method B. Dehydrobromination of **13b** with TBAF in THF gave the α-methylene γ-lactone **13c** in 95% yield. The fluoride anion is much better than DBU for the dehydrobromination reaction of **13b**, which possesses an allylic alcohol moiety (Scheme 5).

Treatment of **13a** with TMSOTf and Et_3N in CH_2Cl_2, followed by treatment with PTAB, did not give the desired α-bromo-α-methyl γ-lactone **15** but a TMS ether **14**, which was also prepared under the mild conditions by the treatment of **13a** with TMSOTf-Et_3N. Bromination of **14** by the reaction of method A (LDA−CBr_4) gave α-bromo-α-methyl γ-lactone **15** in 76% yield (87% yield based on recovered material). It is noteworthy that the fluoride anion reacts on **15** as the reagent for dehydrobromination as well as deprotection of TMS ether (Scheme 6).

Scheme 5

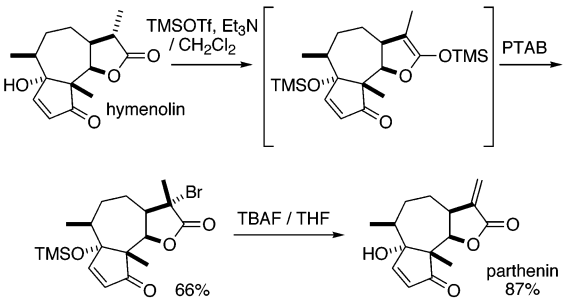


Scheme 6



* The yields in parentheses are based on recovered starting material.

Scheme 7



In a previous paper[48] we reported the total synthesis of an ambrosanolide, parthenin, by the application of this synthetic method as a key step to an intermediate, hymenolin, which was synthesized regio- and stereoselectively from 4-methyltropolone[49] (Scheme 7).

Biological Activities. 1. Cell Growth Inhibitory Activity of Compounds to P388 Lymphocytic Leukemia Test System.[50] The compounds **1c**, **2c**, **4c**, and **17** showed significant cell growth inhibitory activity against murine lymphocytic leukemia (P388) in vitro. The extent of growth inhibition of **1c**, **2c**, **4c**, and **17** was 76%, 50%, 69%, and 40%, respectively, at a concentration of 1 μg/mL, as shown in Table 3. As expected, α-methylene γ-lactones **1c**, **2c**, **4c**, and **17** were more active than **16**, which has an endo-unsaturated γ-lactone structure. Oxygen functional groups such as OH and OAc at the C-8 position of **17** and **18** decreased their activities. It is interesting that **4c**, which possesses the B, C ring partial structure of ambrosanolides (Figure 5), was the most active among the six compounds at a dose of 0.1 μg/mL (Table 3).

2. In Vitro Antimicrobial Spectral Activity of 17 and 19. From an interest in the principal functional group of active compounds to the microbes that cause plant diseases, we examined the in vitro antimicrobial activity of *cis*-fused octahydro-2*H*-cyclohepta[*b*]furan-2-one (**19**) and its 3-methylene derivative **17**. α-Methylene γ-lactone derivative **17** showed significant activity against five of the 14 microbes tested, while the corresponding saturated γ-lactone derivative **19** was inactive (Table 4). The results indicated that the α-methylene γ-lactone moiety was at least one of the principal functional groups involved in the antimicrobial activity of the compounds.

3. Control of Crop Diseases. The preventive activities in controlling crop diseases were examined by a pot test; the results are summarized in Table 5 and the pot test procedures are summarized in Table 6. The α-methylene γ-lactone **1c** showed significant preventive activity in controlling scab of apple caused by *Venturia inaequalis*. The evaluation of disease control is 99−90% at 500 ppm. The α-methylene γ-lactones **2c**, **17**, and **18** showed strong

Table 3. Cell Growth Inhibitory Activities against Murine Lymphocytic Leukemia (P388) in Vitro

	cell growth inhibitory ratio,[a] %			
compd	10 μg/mL	1 μg/mL	10^{-1} μg/mL	evaluation[b]
1c	102	76	9	+
2c	102	50	15	+
4c	101	69	38	+
16	43	4	7	−
17	100	40	11	+
18	102	21	9	−
acriamycin (control)	107	102	104	

[a] Cell growth inhibition ratio (%) was calculated according to cell growth inhibitory ratio (%) = $[1 - (T - C_0)/(C - C_0)] \times 100$ where T = cell count after culture with compound, C = cell count after culture without compound, and C_0 = cell count at the start of culture. [b] +: effective (growth inhibitory ratio >40%).

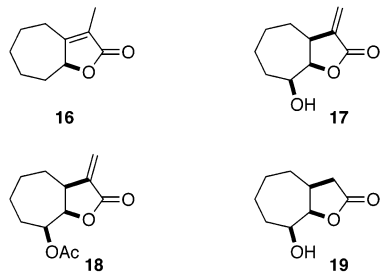


Figure 4. Structures of compounds **16**, **17**, **18**, and **19**.

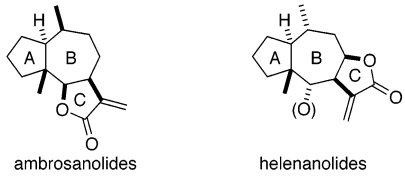


Figure 5. Stereochemistry of ambrosanolides and helenanolides.

Table 4. In Vitro Antimicrobial Spectra Data of **17** and **19**

		evaluated values of preventive activities[a]				
compd	conc (ppm)	Mym[b]	Hg[c]	Ak[d]	Vi[e]	Rse[f]
17	200	10	5	4	0	10
	100	8	0	2	5	6
	50	7	0	0	−	3
19	200	0	0	0	0	0
	100	0	0	0	0	0
	50	0	0	0	0	0

[a] The preventive activities are expressed as 10 scales (10, 100%; 9, 99−90%; 8, 89−80%; 7, 79−70%; 6, 69−60%; 5, 59−50%; 4, 49−40%; 3, 39−30%; 2, 29−20%; 1, 19−10%; 0, 9−0%). [b] Mym, *Mycosphaerella melonis*. [c] Hg, *Pyrenophora graminea* (*Helminthosporium gramineum*). [d] Ak, *alternaria kikuchiana*. [e] Vi, *Venturia inaequalis*. [f] Rse, *Rhynchosporium secalis*.

Table 5. Control of Crop Diseases by **1c**, **2c**, **4c**, **17**, **18**, and **19** at 500 ppm

	evaluated values of disease control[a]					
disease	**1c**	**2c**	**4c**	**17**	**18**	**19**
sheath blight of rice[b]	0	0	0	2	1	0
powdery mildew of wheat[c]	0	0	0	2	1	4
damping off of cucumber[d]	0	5	3	5	5	0
scab of apple[e]	4	0	0	0	0	0

[a] This assessment was made by rating disease severity of sheath blight, powdery mildew, and scab or number infecting seedling of damping off, and the indices are expressed by 5 scales (5, 100%; 4, 99−90%; 3, 89−70%; 2, 69−50%; 1, 49−30%; 0, 29−0%). [b] Caused by *Rhizoctonia solani*. [c] Caused by *Erysiphe graminis*. [d] Caused by *Pythium aphanidermatum*. [e] Caused by *Venturia inaequalis*.

preventive activities, and **4c** showed moderate preventive activities in controlling damping off of cucumber caused by *Pythium aphanidermatum*. The evaluation of disease control is 100% for **2c**, **17**, and **18** and 89−70% for **4c** at 500 ppm. The α-methylene γ-lactones **17** and **18** showed weak preventive activity and the saturated γ-lactone **19** showed significant preventive activity in controlling powdery mildew of wheat caused by *Erysiphe graminis*. The evaluation of disease control is 69−50% for **17**, 49−30% for **18**, and 99−90% for **19** at 500 ppm. The α-methylene γ-lactones **17** and **18** also showed weak preventive activity in controlling sheath blight of rice caused by *Rhizoctonia solani*. The evaluation of disease control is 69−50% for **17** and 49−30% for **18** at 500 ppm. It is interesting that saturated lactone **19** is more active than the corresponding α-methylene γ-lactones **17** and **18** in controlling powdery mildew of wheat. The results suggested that the interactions of compounds and microbes on the surface or inside of the infected plant are complex and do not always reflect the results of in vitro assays.

Experimental Section

General Experimental Procedures. All melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 (500) MHz and 50 (125) MHz, respectively, in $CDCl_3$. The assignments of ^{1}H NMR spectra were determined by decoupling and H−H COSY experiments. The assignments of ^{13}C NMR spectra were determined by DEPT, C−H COSY, HMQC, and HMBC experiments. All reactions were run under an atmosphere of N_2. Benzene, toluene, dichloromethane, diisopropylamine, and triethylamine were distilled from CaH_2. THF was distilled from sodium benzophenone ketyl. To describe HPLC conditions, the column, solvent, and flow rate are designated in this order. The column codes are as follows: A, 30 × 1.0 cm i.d. glass column packed with 10 μm silica gel; B, 25 × 0.8 cm i.d. stainless column packed with 10 μm silica gel. Silica gel (230−400 mesh) was employed for flash chromatography, and 70−230 mesh silica gel was employed for column chromatography. To describe the conditions of column and flash chromatographies, the weight of silica gel, column i.d., and solvent are designated in this order.

General Bromination Procedure of *cis*-γ-Lactone by Method A. Preparation of (3aα,8aα)-3α-Bromo-3β-methyloctahydro-2*H*-cyclohepta[*b*]furan-2-one (1b). A solution of **1a** (21.9 mg, 0.130 mmol) in THF (0.5 mL) was added into a solution of LDA [prepared from diisopropylamine (36.4 μL, 0.258 mmol) and 1.64 M BuLi in hexane (157 μL, 0.258 mmol)] in THF (1 mL) at −78 °C under stirring. The mixture was stirred at this temperature for 1 h, then CBr_4 (86.3 mg, 0.260 mmol) in THF (0.5 mL) was added dropwise at −78 °C. The mixture was warmed to room temperature, stirred for 20 min, poured into a saturated aqueous solution of NH_4Cl (10 mL), and extracted with EtOAc (4 × 20 mL). The combined extracts were washed with a saturated aqueous solution of NaCl (30 mL), dried (Na_2SO_4), and concentrated to give a brown oil (44 mg), which was purified by column chromatography [0.5 g; 0.5 cm i.d.; EtOAc−hexane (5:95)] to give **1b** (23.0 mg, 72%) as a colorless oil: IR ($CHCl_3$) ν_{max} 1765 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.02 (1H, ddd, J = 10.0, 5.6, 5.6 Hz, H-8a), 2.79 (1H, m, H-3a), 2.30 (1H, m, H-4), 1.88 (3H, s, H-9).

General Dehydrobromination Procedure of α-Bromo *cis*-γ-lactone for the Preparation of α-Methylene *cis*-γ-Lactone by Method A. Preparation of (3aα,8aα)-3-Methyleneoctahydro-2*H*-cyclohepta[*b*]furan-2-one (1c) by Method A. A solution of **1b** (10.0 mg, 0.0406 mmol) and DBU (30 μL, 0.201 mmol) in toluene (0.4 mL) was stirred at room temperature for 24 h, poured into 2 M HCl (10 mL), and extracted with Et_2O (4 × 20 mL). The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and a saturated aqueous solution of NaCl (10 mL), dried ($MgSO_4$), and concentrated to give an oily crude product (18 mg), which was purified by HPLC [column B; EtOAc−hexane (5:95); 7.5 mL/min; t_R 12.0 min] to give **1c** (2.1 mg, 31%) as a colorless oil: IR (neat) ν_{max} 1760, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.30 (1H, d, J = 3.2 Hz, H-9), 5.58 (1H, d, J = 2.8 Hz, H-9), 4.74 (1H, ddd, J = 10.5, 8.5, 3.8 Hz, H-8a), 3.26 (1H, m, H-3a); *anal.* C 72.50%, H 8.67%, calcd for $C_{10}H_{14}O_2$, C 72.26%, H 8.49%.

Preparation of (3aα,8aα)-3α-Bromo-3β,6α-dimethyloctahydro-2*H*-cyclohepta[*b*]furan-2-one (2b) from (3aα,-

Table 6. Pot Test Procedures

disease (pathogen)	host	test compounds application method	dosage,[a] ppm	inoculation method	incubation method for disease development	assessment method of disease severity
sheath blight (*R. solani*)	rice	preventive foliar spray a few hours preinoculn	500	infestation of water with mycelium grown in the chaff's medium	4 days, high humidity, darkness, 28 °C	evaluation by infection indices (0−5) depending on size of necrotic lesions
powdery mildew (*E. graminis*)	wheat	preventive foliar spray a few hours preinoculn	500	dusting of spore	10 days, fluorescent lamps, 22 °C	evaluation by infection indices (0−5) depending on rate of leaf coverage of powdery mildew
damping off (*P. aphanidermatum*)	cucumber	solid drench immed postsowing	500, 20 mL/pot	infestation of soil with mycelium grown in the bran's medium	14 days, greenhouse, ~25 °C	evaluation by infection indices (0−5) depending on number of infected seedlings
scab (*V. inaequalis*)	apple	preventive foliar spray a few hours preinoculn	500	foliar spray of spore suspension	5 days, high humidity, darkness, 15 °C; 10 days, fluorescent lamps	evaluation by infection indices (0−5) depending on rate of scab lesions

[a] Active ingredient.

8aα)-3α,6α-Dimethyloctahydro-2*H*-cyclohepta[*b*]furan-2-one (2a) by Method A. Using the general procedure for bromination, we obtained the crude product (80 mg), which was passed through a short column of silica gel. The eluate was concentrated and the residue was further purified by HPLC [column A; EtOAc−hexane (5:95); 6.0 mL/min; t_R 10.0 min] to give **2b** (37.2 mg, 55%) as colorless needles (hexane): mp 45−46 °C; IR ($CHCl_3$) ν_{max} 1770 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.99 (1H, ddd, J = 10.7, 6.0, 5.9 Hz, H-8a), 2.77 (1H, ddd, J = 12.5, 5.9, 2.4 Hz, H-3a), 2.36 (1H, ddd, J = 13.5, 9.5, 6.0 Hz, H-8), 1.87 (3H, s, H-10), 0.92 (3H, d, J = 6.6 Hz, H-9); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.3 (s, C-2), 80.7 (d, C-8a), 59.1 (s, C-3), 55.1 (d, C-3a), 37.8 (t), 36.7 (d, C-6), 29.6 (t), 28.9 (t, C-8), 23.6 (q, C-9), 23.5 (t, C-4), 23.1 (q, C-10); *anal.* C 50.70%, H 6.55%, calcd for $C_{11}H_{17}O_2Br$, C 50.59%, H 6.56%.

Preparation of (3aα,8aα)-6α-Methyl-3-methyleneoctahydro-2*H*-cyclohepta[*b*]furan-2-one (2c) by Method A. Using the general procedure for dehydrobromination, we obtained the crude product (20 mg), which was purified by column chromatography [2 g; 1.2 cm i.d.; EtOAc−hexane (5:95)] to give **2c** (12.2 mg, 66%) as a colorless oil: IR ($CHCl_3$) ν_{max} 1752, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.25 (1H, d, J = 3.0 Hz, H-10), 5.55 (1H, d, J = 2.7 Hz, H-10), 4.66 (1H, ddd, J = 12.0, 8.4, 3.9 Hz, H-8a), 3.19 (1H, m, H-3a), 2.10 (1H, dddd, J = 13.8, 8.4, 4.0, 1.3 Hz, H-8), 1.51 (1H, m, H-6), 1.07 (1H, ddd, J = 13.3, 11.6, 11.6 Hz, H-5), 1.01 (1H, ddd, J = 14.5, 11.7, 11.7 Hz, H-7), 0.93 (3H, d, J = 6.6 Hz, H-9); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2 (s, C-2), 140.4 (s, C-3), 121.9 (t, C-10), 82.2 (d, C-8a), 43.2 (d, C-3a), 36.9 (d, C-6), 36.5 (t, C-5), 32.8 (t, C-7), 30.4 (t, C-8), 30.1 (t, C-4), 23.3 (q, C-9); HREIMS *m/z* 180.1155 (calcd for $C_{11}H_{16}O_2$, 180.1150).

Preparation of (3aα,8aα)-3α-Bromo-3*β*,6*β*-dimethyloctahydro-2*H*-cyclohepta[*b*]furan-2-one (4b) from (3aα,8aα)-3α,6*β*-Dimethyloctahydro-2*H*-cyclohepta[*b*]furan-2-one (4a) by Method A. Using the general procedure for bromination, we obtained the crude product (49 mg), which was passed through a short column of silica gel. The eluate was concentrated and the residue was further purified by HPLC [column A; EtOAc−hexane (5:95); 9.0 mL/min; t_R 6.0 min] to give **4b** (26.9 mg, 69%) as colorless needles (hexane): mp 44−45.5 °C; IR ($CHCl_3$) ν_{max} 1768 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.09 (1H, ddd, J = 7.5, 5.6, 2.8 Hz, H-8a), 2.76 (1H, ddd, J = 11.2, 5.6, 2.2 Hz, H-3a), 2.20 (1H, dddd, J = 12.0, 7.5, 7.5, 2.4 Hz, H-8), 1.88 (3H, s, H-10), 0.89 (3H, d, J = 6.7 Hz, H-9); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.7 (s, C-2), 80.1 (d, C-8a), 59.4 (s, C-3), 54.1 (d, C-3a), 33.0 (d, C-6), 31.7 (t), 27.9 (t), 26.3 (t, C-8), 23.1 (q, C-10), 22.5 (t, C-4), 21.7 (q, C-9); *anal.* C 50.50%, H 6.39%, calcd for $C_{11}H_{17}O_2Br$, C 50.59%, H 6.56%.

Preparation of (3aα,8aα)-6*β*-Methyl-3-methyleneoctahydro-2*H*-cyclohepta[*b*]furan-2-one (4c) by Method A. Using the general procedure for dehydrobromination, we obtained the crude product (25 mg), which was purified by column chromatography [2 g; 1.2 cm i.d.; EtOAc−hexane (5:95)] to give **4c** (14.2 mg, 72%) as colorless prisms (hexane): mp 43−44.5 °C; IR ($CHCl_3$) ν_{max} 1756, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.35 (1H, d, J = 3.1 Hz, H-10), 5.53 (1H, d, J = 2.8 Hz, H-10), 4.82 (1H, ddd, J = 9.0, 7.0, 2.8 Hz, H-8a), 3.32 (1H, m, H-3a), 2.08 (1H, m, H-8), 0.90 (3H, J = 6.5 Hz, H-9); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.6 (s, C-2), 139.5 (s, C-3), 122.2 (t, C-10), 81.1 (d, C-8a), 41.6 (d, C-3a), 34.6 (d, C-6), 32.6 (t), 30.2 (t), 29.0 (t, C-8), 28.3 (t, C-4), 22.0 (q, C-9); *anal.* C 73.06%, H 8.95%, calcd for $C_{11}H_{16}O_2$, C 73.30%, H 8.95%.

Preparation of (3aα,8aα)-3α-Bromo-3*β*,6*β*-dimethyl-3,3a,4,5,6,8a-hexahydro-2*H*-cyclohepta[*b*]furan-2-one (6b) by Method A. To a cooled (−78 °C) solution of **6a** (23.5 mg, 0.130 mmol) in THF (0.7 mL) was added 0.609 M LDA (257 μL) [prepared from diisopropylamine (328 μL, 2.33 mmol), 1.55 M BuLi in hexane (1.50 mL, 2.33 mmol), and THF (2 mL)]. The mixture was stirred at −78 °C for 45 min, then CBr_4 (52.8 mg, 0.156 mmol) in THF (0.4 mL) was added slowly. The reaction mixture was stirred at this temperature for 30 min, poured into a saturated aqueous solution of NH_4Cl (5 mL), and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a brown oil (49 mg), which was purified by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (5:95)] to give **6b** (24.1 mg, 72%) as colorless prisms (EtOAc−hexane): mp 79−80 °C; IR ($CHCl_3$) ν_{max} 1778 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.65 (1H, ddd, J = 11.5, 2.0, 2.0 Hz, H-8), 5.62 (1H, m, H-8a), 5.50 (1H, ddd, J = 11.5, 5.3, 2.1 Hz, H-7), 2.92 (1H, ddd, J = 11.5, 5.1, 1.5 Hz, H-3a), 2.47 (1H, m, H-6), 1.90 (3H, s, H-10), 1.05 (3H, d, J = 6.8 Hz, H-9); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.5 (s, C-2), 135.8 (d, C-7), 123.5 (d, C-8), 80.8 (d, C-8a), 59.6 (s, C-3), 51.5 (d, C-3a), 31.3 (t, C-5), 29.9 (d, C-6), 23.7 (q, C-10), 21.5 (t, C-4), 21.0 (q, C-9); *anal.* C 50.70%, H 5.77%, calcd for $C_{11}H_{15}O_2Br$, C 50.98%, H 5.83%.

Preparation of (3aα,8aα)-6*β*-Methyl-3-methylene-3,3a,4,5,6,8a-hexahydro-2*H*-cyclohepta[*b*]furan-2-one (6c) by Method A. A solution of **6b** (24.0 mg, 0.0926 mmol) and DBU (27.7 μL, 0.185 mmol) in PhH (0.5 mL) was stirred at room temperature for 22 h. Then the mixture was treated with additional DBU (27.7 μL, 0.185 mmol) and stirred at this temperature for a further 11.6 h. The reaction mixture was poured into 1 M HCl (5 mL) and extracted with EtOAc (5 × 10 mL). The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), dried (Na_2SO_4), and concentrated to give a crude product (16 mg), which was purified by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (5:95)] to give **6c** (10.7 mg, 65%) as a colorless oil: IR ($CHCl_3$) ν_{max} 3012, 1760, 1662 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.27 (1H, d, J = 2.8 Hz, H-10), 5.59 (1H, d, J = 2.5 Hz, H-10), 5.57 (1H, ddd, J = 10.1, 3.2, 1.7 Hz, H-8), 5.46−5.35 (2H, H-7 and -8a), 3.09 (1H, m, H-3a), 2.34 (1H, m, H-6), 1.07 (3H, d, J = 6.7 Hz, H-9); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.0 (s, C-2), 140.1 (s, C-3), 134.2 (d), 126.4 (d), 122.4 (t, C-10), 79.4 (d, C-8a), 39.9 (d, C-3a), 31.4 (d, C-6), 30.3 (t), 29.0 (t), 21.0 (q, C-9); HREIMS *m/z* 178.0998 (calcd for $C_{11}H_{14}O_2$, 178.0994).

Preparation of (3aα,8aα)-3α-Bromo-8*β*-hydroxy-3*β*,6α-dimethyloctahydro-2*H*-cyclohepta[*b*]furan-2-one (7b) by Method A. To a cooled (−78 °C) solution of **7a** (28.4 mg, 0.143 mmol) in THF (0.6 mL) was added 0.609 M LDA (590 μL) [prepared from diisopropylamine (328 μL, 2.33 mmol), 1.55 M BuLi in hexane (1.50 mL, 2.33 mmol), and THF (2 mL)]. The mixture was stirred at −78 °C for 45 min, then CBr_4 (58.2 mg, 0.172 mmol) in THF (0.3 mL) was added slowly. The reaction mixture was stirred at this temperature for 30 min, poured into a saturated aqueous solution of NH_4Cl (5 mL), and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a brown oil (51 mg), which was purified by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (5:95)] to give **7b** (17.3 mg, 44%) as colorless crystals: mp 58−61 °C; IR ($CHCl_3$) ν_{max} 3608, 3500 (br), 1776 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.80 (1H, d, J = 2.3 Hz, H-8a), 4.13 (1H, br d, J = 6.1 Hz, H-8), 2.26 (1H, ddd, J = 10.8, 2.5, 2.3 Hz, H-3a), 2.07 (1H, dddd, J = 15.0, 6.1, 4.4, 1.9 Hz, H-7), 1.45 (3H, s, H-10), 1.41 (1H, ddd, J = 12.9, 2.6, 2.5 Hz, H-4), 1.17 (1H, ddd, J = 15.0, 11.2, 1.2 Hz, H-7), 0.94 (3H, d, J = 6.8 Hz, H-9); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.8 (s, C-2), 84.5 (d, C-8a), 83.5 (s, C-3), 81.3 (d, C-8), 50.7 (d, C-3a), 37.0 (t, C-7), 33.0 (t), 30.7 (d, C-6), 23.1 (q, C-9), 21.7 (t), 11.1 (q, C-10); HREIMS *m/z* 276.0361 (calcd for $C_{11}H_{17}O_3Br$, 276.0361).

General Bromination Procedure of *cis*-*γ*-Lactone by Method B. Preparation of 2b from 2a by Method B. To a stirred solution of **2a** (40.0 mg, 0.219 mmol) and Et_3N (91.0 μL, 0.656 mmol) in CH_2Cl_2 (1 mL) was added TMSOTf (63.3 μL, 0.328 mmol) at 0 °C. After 10 min, the mixture was treated with PTAB (102 mg, 0.271 mmol) in CH_2Cl_2 (0.6 mL) and stirred at this temperature for 1 h. The reaction was quenched with a mixture of a 10% aqueous solution of $Na_2S_2O_3$ (1 mL) and a saturated aqueous solution of NaCl (5 mL), and the mixture was extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were washed with a saturated aqueous solution of NaCl (2 × 10 mL), dried (Na_2SO_4), and concentrated to give a crude product (80 mg), which was purified by column chromatography [4 g; 1.5 cm i.d.; EtOAc−hexane (5:95)] to give **2b** (40.2 mg, 70%), which was identical in all respects with **2b** mentioned above.

General Dehydrobromination Procedure of α-Bromo-*cis*-γ-lactone for the Preparation of α-Methylene *cis*-γ-lactone by Method B. Preparation of 2c by Method B. A solution of **2b** (25.2 mg, 0.0965 mmol) and TBAF (1 M in THF, 96.5 μL) in THF (1.2 mL) was stirred at room temperature for 6 h. Then the solution was treated with additional TBAF (1 M in THF, 48.2 μL) and stirred at this temperature for a further 4 h. The reaction mixture was poured into a saturated aqueous solution of NH_4Cl (5 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were washed with a saturated aqueous solution of NaCl (2 × 10 mL), dried (Na_2SO_4), and concentrated to give a crude product (50 mg), which was purified by column chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (1:9)] to give **2c** (13.2 mg, 76%), which was identical in all respects with **2c** mentioned above.

Preparation of 4b from 4a by Method B. Using the general procedure for bromination, we obtained the crude product (40 mg), which was separated by column chromatography [2 g; 1.2 cm i.d.; EtOAc−hexane (5:95)]. The faster running gave **4b** (23.8 mg, 65%), which was identical in all respects with **4b** mentioned above. The slower running gave starting material **4a** (8.5 mg, 33%).

Preparation of 4c by Method B. Using the general procedure for dehydrobromination, we obtained the crude product, which was purified by flash chromatography [8 g; 1.6 cm i.d.; EtOAc−hexane (1:9)] to give **4c** (15.9 mg, 87%), which was identical in all respects with **4c** mentioned above.

Preparation of 6b by Method B. To a stirred solution of **6a** (36.7 mg, 0.204 mmol) and Et_3N (84.8 μL, 0.612 mmol) in CH_2Cl_2 (1 mL) was added TMSOTf (59.1 μL, 0.306 mmol) at 0 °C. After 14 min, the mixture was treated with PTAB (92.1 mg, 0.245 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at this temperature for 16 min, poured into a 10% aqueous solution of $Na_2S_2O_3$ (5 mL), and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a crude product (109 mg), which was separated by flash chromatography [8 g; 1.6 cm i.d.; EtOAc−hexane (3:97)]. The faster running gave **6b** (40.6 mg, 77%), which was identical in all respects with **6b** mentioned above. The slower running gave starting material **6a** (0.6 mg, 2%).

Preparation of 6c by Method B. A solution of **6b** (8.8 mg, 0.0340 mmol) and TBAF (1 M in THF, 68 μL) in THF (1 mL) was stirred at room temperature for 1.5 h, poured into a saturated aqueous solution of NH_4Cl (5 mL), and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a crude product (36 mg), which was separated by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (5:95)]. The faster running gave starting material **6b** (0.9 mg, 10%). The slower running gave **6c** (5.1 mg, 84%), which was identical in all respects with **6c** mentioned above.

Preparation of (3aα,8aα)-3α-Bromo-8β-trimethylsilyloxy-3β,6α-dimethyloctahydro-2*H*-cyclohepta[*b*]furan-2-one (9) by Method B. To a stirred solution of **7a** (9.7 mg, 0.0489 mmol) and Et_3N (34.0 μL, 0.245 mmol) in CH_2Cl_2 (0.5 mL) was added TMSOTf (23.6 μL, 0.122 mmol) at 0 °C. After 14 min, the mixture was treated with PTAB (22.1 mg, 0.0587 mmol) in CH_2Cl_2 (0.2 mL). The reaction mixture was stirred at this temperature for 14 min, poured into a 10% aqueous solution of $Na_2S_2O_3$ (5 mL), and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a crude product (32 mg), which was separated by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (3:97)]. The first running gave **9** (11.0 mg, 64%) as colorless crystals: mp 43−47 °C; IR ($CHCl_3$) ν_{max} 1774 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.61 (1H, dd, J = 9.4, 2.0 Hz, H-8a), 4.24 (1H, dd, J = 7.5, 2.0 Hz, H-8), 3.26 (1H, ddd, J = 12.0, 9.4, 5.6 Hz, H-3a), 1.89 (3H, s, H-10), 0.94 (3H, d, J = 6.5 Hz, H-9), 0.11 (9H, s, H-TMS); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 175.6 (s, C-2), 84.1 (d, C-8a), 71.0 (d, C-8), 58.2 (s, C-3), 52.6 (d, C-3a), 40.5 (t), 34.8 (t), 30.1 (d, C-6), 24.9 (q, C-10), 24.5 (t), 23.3 (q, C-9), −0.1 (q, C-TMS); HREIMS *m/z* 269.1582 (calcd for $C_{14}H_{25}O_3Si$ (−Br), 269.1573). The second running gave (3aα,8aα)-8β-trimethylsilyloxy-3α,6α-dimethyloctahydro-2*H*-cyclohepta[*b*]furan-2-one (1.3 mg, 10%) as colorless crystals: ^1H NMR ($CDCl_3$, 500 MHz) δ 4.35 (1H, dd, J = 9.0, 1.5 Hz, H-8a), 4.24 (1H, ddd, J = 6.4, 1.5, 1.5 Hz, H-8), 2.44 (1H, dq, J = 11.2, 7.5 Hz, H-3), 2.32 (1H, dddd, J = 11.2, 11.2, 9.0, 7.0 Hz, H-3a), 2.04 (1H, m), 1.18 (3H, d, J = 7.5 Hz, H-10), 0.97 (1H, ddd, J = 14.3, 11.4, 11.4 Hz, H-5), 0.94 (3H, d, J = 6.5 Hz, H-9), 0.10 (9H, s, H-TMS). The third running gave (3aα,8aα)-8β-trimethylsilyloxy-3β,6α-dimethyloctahydro-2*H*-cyclohepta[*b*]furan-2-one (1.2 mg, 9%) as a colorless oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 4.49 (1H, dd, J = 9.3, 2.0 Hz, H-8a), 4.20 (1H, ddd, J = 7.3, 2.0, 2.0 Hz, H-8), 2.83 (1H, m, H-3a), 2.72 (1H, dq, J = 11.2, 7.5 Hz, H-3), 1.63 (1H, ddd, J = 15.0, 13.9, 9.6 Hz), 1.22 (3H, d, J = 7.5 Hz, H-10), 1.14 (1H, ddd, J = 14.5, 11.3, 1.0 Hz, H-7), 0.93 (3H, d, J = 7.0 Hz, H-9), 0.12 (9H, s, H-TMS).

Preparation of (3aα,8aα)-8β-Trimethylsilyloxy-6α-methyl-3-methyleneoctahydro-2*H*-cyclohepta[*b*]furan-2-one (10) and 8β-Trimethylsilyloxy-3,6α-dimethyl-4,5,6,7,8,-8aα-hexahydro-2*H*-cyclohepta[*b*]furan-2-one (11) by Method A. A solution of **9** (30.0 mg, 0.0859 mmol) and DBU (38.6 μL, 0.258 mmol) in PhH (0.5 mL) was stirred at room temperature for 48 h, poured into a saturated aqueous solution of NH_4Cl (10 mL), and extracted with CH_2Cl_2 (5 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a crude product (52 mg), which was separated by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (5:95)]. The faster running gave **10** (12.0 mg, 52%) as colorless crystalline material: ^1H NMR ($CDCl_3$, 500 MHz) δ 6.09 (1H, d, J = 3.5 Hz, H-10), 5.36 (1H, d, J = 3.5 Hz, H-10), 4.51 (1H, dd, J = 9.2, 1.6 Hz, H-8a), 4.23 (1H, ddd, J = 7.0, 1.6, 1.6 Hz, H-8), 3.19 (1H, m, H-3a), 2.14 (1H, m), 1.15 (1H, dd, J = 14.0, 11.8 Hz, H-7), 1.03 (1H, ddd, J = 14.3, 11.6, 11.6 Hz, H-5), 0.94 (3H, d, J = 6.5 Hz, H-9), 0.06 (9H, s, H-TMS). The slower running gave **11** (4.1 mg, 18%) as colorless crystalline material: ^1H NMR ($CDCl_3$, 500 MHz) δ 4.86 (1H, br s, $W_{h/2}$ = 5 Hz, H-8a), 4.34 (1H, ddd, J = 5.1, 1.5, 1.5 Hz, H-8), 2.72 (1H, m, H-4), 2.46 (1H, m, H-4), 1.77 (3H, s, H-10), 1.00 (3H, d, J = 7.0 Hz, H-9), 0.05 (9H, s, H-TMS).

Preparation of (3aα,8aα)-8β-Hydroxy-6α-methyl-3-methyleneoctahydro-2*H*-cyclohepta[*b*]furan-2-one (7c). A solution of **10** (12.0 mg, 0.0447 mmol) and TBAF (1 M in THF, 49.2 μL) in THF (0.5 mL) was stirred at room temperature for 22 min, poured into a saturated aqueous solution of NH_4Cl (4 mL), and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a crude product (30 mg), which was purified by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (2:8)] to give **7c** (5.3 mg, 60%) as colorless prisms (EtOAc−hexane): mp 114−115 °C; IR ($CHCl_3$) ν_{max} 3616, 1760 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.21 (1H, dd, J = 3.3, 1.1 Hz, H-10), 5.50 (1H, dd, J = 3.0, 0.8 Hz, H-10), 4.57 (1H, dd, J = 9.3, 2.2 Hz, H-8a), 4.34 (1H, m, H-8), 3.23 (1H, m, H-3a), 1.19 (1H, dd, J = 14.4, 12.2 Hz, H-7), 1.06 (1H, ddd, J = 14.2, 11.5, 11.5 Hz, H-5), 0.96 (3H, d, J = 7.0 Hz, H-9); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6 (s, C-2), 140.6 (s, C-3), 120.4 (t, C-10), 83.8 (d, C-8a), 70.9 (d, C-8), 42.0 (d, C-3a), 39.5 (t, C-7), 35.5 (t, C-5), 30.0 (t, C-4), 29.9 (d, C-6), 23.4 (q, C-9); *anal.* C 67.44%, H 8.24%, calcd for $C_{11}H_{16}O_3$, C 67.32%, H 8.22%.

Preparation of 8β-Hydroxy-3,6α-dimethyl-4,5,6,7,8,8a-hexahydro-2*H*-cyclohepta[*b*]furan-2-one (12). A solution of **11** (4.1 mg, 0.0153 mmol) and TBAF (1 M in THF, 20.1 μL) in THF (0.2 mL) was stirred at room temperature for 24 min, poured into a saturated aqueous solution of NH_4Cl (5 mL), and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a crude product (15 mg), which was purified by flash chromatography [2 g; 1.2 cm i.d.; EtOAc−hexane (1:3)] to give **12** (1.7 mg, 57%) as colorless crystals: IR ($CHCl_3$) ν_{max} 3612, 3460, 1748, 1672 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.96 (1H, br s, $W_{h/2}$ = 5 Hz, H-8a), 4.39 (1H, br s, $W_{h/2}$ = 9 Hz, H-8), 2.75 (1H, br d, J = 19.6 Hz, H-4), 2.53 (1H, br dd, J = 19.6, 13.3 Hz, H-4), 2.10 (1H, dddd, J = 14.6, 5.0, 2.4, 2.4 Hz), 1.80 (3H, s, H-10), 1.02 (3H, d, J = 7.0 Hz, H-9).

Preparation of 11α-Bromo-3β-hydroxyeudesm-1-eno-12,6β-lactone (13b) by Method A. To a cooled (−78 °C) solution of **13a** (22.0 mg, 0.0879 mmol) in THF (0.5 mL) was

added 0.609 M LDA (362 μL) [prepared from diisopropylamine (328 μL, 2.33 mmol), 1.55 M BuLi in hexane (1.50 mL, 2.33 mmol), and THF (2 mL)]. The mixture was stirred at this temperature for 45 min, then CBr_4 (32.7 mg, 0.0966 mmol) in THF (0.2 mL) was added slowly. The reaction mixture was stirred at −78 °C for 25 min, poured into a saturated aqueous solution of NH_4Cl (5 mL), and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a brown oil (45 mg), which was separated by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (3:7)]. The faster running gave **13b** (19.3 mg, 67%) as colorless crystals: mp 113−118 °C; $[\alpha]^{20}_D$ +1.1° (*c* 1.52, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3612, 1782 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.57−5.46 (2H, H-1 and H-2), 4.98 (1H, dd, *J* = 3.5, 3.2 Hz, H-6), 3.85 (1H, d, *J* = 9.1 Hz, H-3), 2.55 (1H, m, H-7), 1.98 (1H, m, H-4), 1.91 (3H, s, H-13), 1.40 (1H, dd, *J* = 11.4, 3.2 Hz, H-5), 1.24 (3H, d, *J* = 6.4 Hz, H-15), 1.04 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.4 (s, C-12), 140.1 (d), 127.6 (d), 76.5 (d, C-6), 75.9 (d, C-3), 59.7 (s, C-11), 49.0 (d, C-7), 47.0 (d, C-5), 36.1 (t), 35.6 (d, C-4), 34.4 (s, C-10), 22.0 (q, C-13), 21.5 (q, C-14), 20.2 (t), 14.8 (q, C-15); HREIMS *m/z* 328.0657 (calcd for $C_{15}H_{21}O_3Br$, 328.0674). The slower running gave starting material **13a** (3.1 mg, 14%).

Preparation of 3β-Hydroxyeudesma-1,11(13)-dieno-12,6β-lactone (13c) by Method A. A solution of **13b** (19.3 mg, 0.0586 mmol) and DBU (26.3 μL, 0.176 mmol) in PhH (0.5 mL) was stirred at room temperature for 25.7 h. Then the mixture was treated with additional DBU (26.3 μL) and stirred at this temperature for 26 h. Since the recovered **13b** still existed, DBU (43.8 μL) was further added. The resulting mixture was stirred at room temperature for a further 39 h, poured into 1 M HCl (5 mL), and extracted with EtOAc (5 × 10 mL). The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), dried (Na_2SO_4), and concentrated to give a crude product (12 mg), which was purified by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (3:7)] to give **13c** (7.8 mg, 54%) as colorless needles (EtOAc−hexane): mp 118−121 °C; $[\alpha]^{20}_D$ −151.8° (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3608, 3496, 1764, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.13 (1H, d, *J* = 1.0 Hz, H-13), 5.57 (1H, d, *J* = 1.0 Hz, H-13), 5.52 (1H, d, *J* = 10.4 Hz), 5.49 (1H, d, *J* = 10.4 Hz), 4.54 (1H, dd, *J* = 5.2, 3.3 Hz, H-6), 3.83 (1H, br d, *J* = 8.9 Hz, H-3), 2.92 (1H, m, H-7), 1.99 (1H, m, H-4), 1.82 (1H, m, H-8), 1.59−1.50 (2H, H-8 and H-9), 1.38 (1H, dd, *J* = 11.6, 3.3 Hz, H-5), 1.34 (1H, ddd, *J* = 14.3, 14.3, 3.8 Hz, H-9), 1.20 (3H, d, *J* = 6.6 Hz, H-15), 1.08 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8 (s, C-12), 141.8 (s, C-11), 140.6 (d, C-2), 127.4 (d, C-1), 120.3 (t, C-13), 76.3 (d, C-6), 75.9 (d, C-3), 46.7 (d, C-5), 39.6 (d, C-7), 36.3 (t, C-9), 35.5 (d, C-4), 34.0 (s, C-10), 24.5 (t, C-8), 21.3 (q, C-14), 14.9 (q, C-15); HREIMS *m/z* 248.1406 (calcd for $C_{15}H_{20}O_3$, 248.1412).

Preparation of 13c by Dehydrobromination of 13b with TBAF. A solution of **13b** (10.0 mg, 0.0304 mmol) and TBAF (1 M in THF, 45.6 μL) in THF (0.5 mL) was stirred at room temperature for 16 h, then the solution was treated with additional TBAF (1 M in THF, 30.4 μL) and stirred at this temperature for 24 h. Since the recovered **13b** still existed in the reaction mixture, TBAF (1 M in THF, 30.4 μL) was further added. The reaction mixture was stirred for a further 7 h, poured into a saturated aqueous solution of NH_4Cl (5 mL), and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a crude product, which was purified by flash chromatography [1.5 g; 1.2 cm i.d.; EtOAc−hexane (3:7)] to give **13c** (7.2 mg, 95%), which was identical in all respects with **13c** mentioned above.

Preparation of (11*S*)-3β-Trimethylsilyloxyeudesm-1-eno-12,6β-lactone (14). To a stirred solution of **13a** (52.9 mg, 0.211 mmol) and Et_3N (87.7 μL, 0.633 mmol) in CH_2Cl_2 (1.5 mL) was added TMSOTf (61.3 μL, 0.317 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 26 min, poured into a saturated aqueous solution of $NaHCO_3$ (5 mL), and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a crude product (89 mg), which was purified by flash chromatography [7.5 g; 1.6 cm i.d.; EtOAc−hexane (5:95)] to give **14** (62.1 mg, 92%) as colorless crystals: ^1H NMR ($CDCl_3$, 200 MHz) δ 5.43 (1H, dd, *J* = 10.0, 1.3 Hz), 5.36 (1H, dd, *J* = 10.0, 1.6 Hz), 4.70 (1H, dd, *J* = 4.7, 3.0 Hz, H-6), 3.86 (1H, ddd, *J* = 8.8, 1.6, 1.3 Hz, H-3), 2.37 (1H, q, *J* = 7.7 Hz, H-11), 1.31 (3H, d, *J* = 7.7 Hz, H-13), 1.10 (3H, d, *J* = 6.5 Hz, H-15), 1.07 (3H, s, H-14), 0.16 (9H, s, H-TMS); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 180.4 (s, C-12), 139.7 (d), 128.0 (d), 76.8 (d, C-6), 76.7 (d, C-3), 47.1 (d, C-5), 44.5 (d, C-11), 42.0 (d, C-7), 36.6 (t), 35.1 (d, C-4), 34.5 (s, C-10), 23.7 (t), 21.3 (q, C-14), 14.8 (q), 14.6 (q), 0.5 (q, C-TMS).

Preparation of 11α-Bromo-3β-trimethylsilyloxyeudesm-1-eno-12,6β-lactone (15). To a cooled (−78 °C) solution of **14** (26.4 mg, 0.0819 mmol) in THF (0.5 mL) was added 0.637 M LDA (155 μL) [prepared from diisopropylamine (345 μL, 2.45 mmol), 1.63 M BuLi in hexane (1.50 mL, 2.45 mmol), and THF (2 mL)]. The mixture was stirred at this temperature for 50 min, then CBr_4 (33.3 mg, 0.100 mmol) in THF (0.2 mL) was added slowly. The reaction mixture was stirred at −78 °C for 22 min, poured into a saturated aqueous solution of NH_4Cl (5 mL), and extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a brown oil (46 mg), which was separated by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (5:95)]. The faster running gave **15** (25.0 mg, 76%) as colorless crystals: mp 110−115 °C; $[\alpha]^{20}_D$ +30.7° (*c* 1.22, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1782 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.45 (1H, dd, *J* = 10.0, 1.7 Hz), 5.39 (1H, dd, *J* = 10.0, 2.0 Hz), 4.97 (1H, dd, *J* = 3.6, 3.2 Hz, H-6), 3.88 (1H, ddd, *J* = 8.9, 2.0, 1.6 Hz, H-3), 2.53 (1H, ddd, *J* = 12.0, 6.8, 3.6 Hz, H-7), 2.06 (1H, m, H-4), 1.91 (3H, s, H-13), 1.74 (1H, m, H-8), 1.56 (1H, m, H-9), 1.39 (1H, dd, *J* = 11.5, 3.2 Hz, H-5), 1.35−1.24 (2H, H-8 and -9), 1.15 (3H, d, *J* = 6.5 Hz, H-15), 1.04 (3H, s, H-14), 0.16 (9H, s, H-TMS); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.5 (s, C-12), 139.0 (d), 128.5 (d), 76.7 (d), 76.6 (d), 59.8 (s, C-11), 49.0 (d, C-7), 47.0 (d, C-5), 36.2 (t, C-9), 35.0 (d, C-4), 34.5 (s, C-10), 22.0 (q, C-13), 21.4 (q, C-14), 20.2 (t, C-8), 14.7 (q, C-15), 0.5 (q, C-TMS); HREIMS *m/z* 400.1082 (calcd for $C_{18}H_{29}O_3SiBr$, 400.1069). The slower running gave starting material **14** (3.5 mg, 13%).

Preparation of 13c by Dehydrobromination of 15 with TBAF. A solution of **15** (21.8 mg, 0.0543 mmol) and TBAF (1 M in THF, 163 μL) in THF (2 mL) was stirred at room temperature for 2.7 h. Since the reaction was not completed, the reaction mixture was treated with additional TBAF (1 M in THF, 54.3 μL) and stirred at this temperature for a further 1 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (5 mL), and the mixture was extracted with CH_2Cl_2 (5 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give a crude product, which was purified by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (3:7)] to give **13c** (12.7 mg, 94%), which was identical in all respects with **13c** mentioned above.

3-Methyl-4,5,6,7,8,8aα-hexahydro-2*H*-cyclohepta[*b*]furan-2-one (16). Compound **16** was prepared by the procedures reported by us:[50] colorless oil; IR (neat) ν_{max} 1760, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 4.97−4.70 (1H, m, H-8a), 3.00−1.00 (10H, m), 1.79 (3H, m, $W_{h/2}$ = 5 Hz, H-9); MS *m/z* (relative intensity) 166 (M^+, 78), 138 (27), 137 (55), 110 (26), 109 (34), 96 (31), 95 (100), 82 (23), 81 (38), 67 (56); *anal.* C 72.08%, H 8.52%, calcd for $C_{10}H_{14}O_2$, C 72.26%, H 8.49%.

(3aα,8aα)-8β-Hydroxy-3-methyleneoctahydro-2*H*-cyclohepta[*b*]furan-2-one (17). Compound **17** was prepared by the procedures reported by us:[50] colorless needles (ether); mp 86.5 °C; IR (KBr) ν_{max} 3450, 1745, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.26 (1H, d, *J* = 3.3 Hz, H-9), 5.54 (1H, d, *J* = 3.0 Hz, H-9), 4.71 (1H, dd, *J* = 9.2, 2.0 Hz, H-8a), 4.27 (1H, d, *J* = 8.0 Hz, H-8), 3.31 (1H, m, H-3a), 2.96 (1H, br s, OH); MS *m/z* (relative intensity) 182 (M^+, 1.5), 164 (8), 154 (6), 139 (11), 138 (11), 136 (14), 135 (14), 125 (23), 123 (27), 112 (81), 107 (21), 94 (22), 93 (20), 81 (21), 79 (32), 58 (43), 55 (22), 43 (100); *anal.* C 65.50%, H 7.79%, calcd for $C_{10}H_{14}O_3$, C 65.91%, H 7.74%.

(3aα,8aα)-8β-Acetoxy-3-methyleneoctahydro-2*H*-cyclohepta[*b*]furan-2-one (18). Compound **18** was prepared by the procedures reported by us:[50] colorless oil; IR ($CHCl_3$) ν_{max} 3025, 1760, 1742, 1662 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.32 (1H,

d, J = 3.2 Hz, H-9), 5.57 (1H, d, J = 2.8 Hz, H-9), 5.24 (1H, br d, J = 9.0 Hz, H-8), 4.77 (1H, dd, J = 9.2, 1.8 Hz, H-8a), 3.46−3.29 (1H, m, H-3a), 2.04 (3H, s, H−Ac); MS *m*/*z* (relative intensity) 224 (M^+, 2), 182 (42), 164 (100), 163 (29), 154 (29), 136 (35), 135 (40), 112 (37), 107 (24); *anal.* C 64.00%, H 7.38%, calcd for $C_{12}H_{16}O_4$, C 64.27%, H 7.19%.

(3aα,8aα)-8β-Hydroxyoctahydro-2*H*-cyclohepta[*b*]furan-2-one (19). Compound **19** was prepared by the procedures reported by us:[50] colorless crystals (ether); mp 82−82.5 °C; IR (KBr) ν_{max} 3400, 1760 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.59 (1H, dd, J = 8.5, 1.7 Hz, H-8a), 4.31 (1H, dddd, J = 7.3, 5.5, 1.7, 1.7 Hz, H-8), 2.94−2.72 (1H, m, H-3a), 2.68 (1H, dd, J = 17.3, 9.5 Hz, H-3), 2.46 (1H, d, J = 5.5 Hz, OH), 2.44 (1H, dd, J = 17.3, 9.0 Hz, H-3), 2.07 (1H, m, H-7), 1.49 (1H, m, H-7); MS *m*/*z* (relative intensity) 170 (M^+, 20), 152 (39), 142 (59), 127 (43), 126 (41), 124 (48), 123 (27), 110 (58), 108 (28), 98 (36), 96 (31), 93 (43), 92 (32), 85 (70), 83 (100), 82 (33), 81 (31), 80 (20), 67 (20); *anal.* C 63.75%, H 8.37%, calcd for $C_9H_{14}O_3$, C 63.51%, H 8.29%.

Cell Growth Inhibitory Activity of Compounds to Murine Lymphocytic Cell (P388) in Vitro. Murine lymphocytic leukemia cells (P388) were incubated with compounds at 37 °C in a humidified atmosphere of 5% CO_2 for 48 h. After incubation, the cell number was counted with a Coulter counter, and the cell growth inhibition ratio (%) was calculated according to cell growth inhibitory ratio (%) = $[1-(T-C_0)/(C-C_0)] \times 100$ where T = cell count after culture with compound, C = cell count after culture without compound, and C_0 = cell count at the start of culture.

In Vitro Antimicrobial Activity of 17 and 19. For in vitro antimicrobial assay, medium was prepared from sucrose (20 g), malt extract (20 g), polypepton (5 g), agar (15 g), and distilled water (1 L). The tested compounds **17** and **19** were dissolved in this medium at concentrations of 200, 100, and 50 ppm, and the medium was solidified. Microbes were incubated on the surface of the solid medium and kept for 4 days at 28 °C for *Mycosphaerella melonis*, *Pyrenophora graminea* (*Helminthosporium gramineum*), and *Alternaria kikuchiana* and for 11 days at 18 °C for *Venturia inaequalis* and *Rhynchosporium secalis*. The preventive effect of microbe growth by compounds was observed. The preventive effect was evaluated in 10 scales of growth inhibition (10, 100%; 9, 99−90%; 8, 89−80%; 7, 79−70%; 6, 69−60%; 5, 59−50%; 4, 49−40%; 3, 39−30%; 2, 29−20%; 1, 19−10%; 0, 9−0%).

Preventive Activity of Compounds in Controlling Crop Diseases. The diseases and the test methods are shown in Table 6. Test samples, which were formulated as emulsions in water, were applied by spraying on the plants or drenching of the soil before inoculation. The plants were inoculated with spores or hypha of fungal pathogens. After incubation, disease severity of test plants was observed under desirable conditions for 4−15 days. The tested crop diseases are as follows: blast of rice, sheath blight of rice, powdery mildew of wheat, damping off of cucumber, downy mildew of grape, late blight of tomato, and scab of apple. Positive results by six tested samples were obtained in sheath blight of rice, powdery mildew of wheat, damping off of cucumber, and scab of apple and are shown in Table 5.

Acknowledgment. We express our thanks to Y. Yanagi of Sumitomo Pharmaceuticals Co., Ltd., for bioassay of cell growth inhibitory activity of compounds to P388 and to N. Hirata of Sumitomo Chemical Co., Ltd., for bioassay of compounds in controlling crop diseases.

References and Notes

(1) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman and Hall: London, 1991; Vol. 1.
(2) Rodriguez, E.; Towers, G. H. N.; Mitchell, J. C. *Phytochemistry* **1976**, *15*, 1573−1580.
(3) Ando, M. *J. Synth. Org. Chem.* **1992**, *50*, 858−874.
(4) Cordell, G. A.; Farnsworth, N. R. *J. Nat. Prod.* **1977**, *40*, 1−44.
(5) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147−1152.
(6) Lee, K.-H.; Huang, E.-S.; Piantadosi, C.; Pagano, J. S.; Geissman, T. A. *Cancer Res.* **1971**, *31*, 1649−1654.
(7) Kupchan, S. M.; Kelsey, J. E.; Maruyama, M.; Cassady, J. M. *Tetrahedron Lett.* **1968**, 3517−3520.
(8) Jolad, S. D.; Wiedhopf, R. M.; Cole, J. R. *J. Pharm. Sci.* **1974**, *63*, 1321−1322.
(9) Ogura, M.; Cordell, G. A.; Farnsworth, N. R. *Phytochemistry* **1978**, *17*, 957−961.
(10) Cassady, J. M.; Suffness, M. *Anticancer Agents Based on Natural Product Models*; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; pp 204−224.
(11) Ando, M.; Kusaka, H.; Ohara, H.; Takase, K.; Yamaoka, H.; Yanagi, Y. *J. Org. Chem.* **1989**, *54*, 1952−1960.
(12) Ando, M.; Isogai, K.; Azami, H.; Hirata, N.; Yanagi, Y. *J. Nat. Prod.* **1991**, *54*, 1017−1024.
(13) Ando, M.; Isogai, K.; Azami, H.; Hirata, N.; Yamazaki, H.; Yanagi, Y. *J. Nat. Prod.* **1992**, *55*, 1620−1625.
(14) Ando, M.; Wada, T.; Kusaka, H.; Takase, K.; Hirata, N.; Yanagi, Y. *J. Org. Chem.* **1987**, *52*, 4792−4796.
(15) Robles, M.; Aregullin, M.; West, J.; Rodriguez, E. *Planta Med.* **1995**, *61*, 199−203.
(16) Vichnewski, W.; Gilbert, B. *Phytochemistry* **1972**, *11*, 2563−2566.
(17) Garcia, M.; Da Silva, A. J. R.; Baker, P. M.; Gilbert, B.; Rabi, J. A. *Phytochemistry* **1976**, *15*, 331−332.
(18) Sánchez-Viesca, F.; Romo, J. *Tetrahedron* **1963**, *19*, 1285−1291.
(19) Bates, R. B.; Cekan, Z.; Procházka, V.; Herout, V. *Tetrahedron Lett.* **1963**, 1127−1130.
(20) Jöchle, W. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 537−549.
(21) Taniguchi, M.; Kataoka, T.; Suzuki, H.; Uramoto, M.; Ando, M.; Arao, K.; Magae, J.; Nishimura, T.; Otake, N.; Nagai, K. *Biosci. Biotech. Biochem.* **1995**, *59*, 2064−2067.
(22) Osawa, T.; Suzuki, A.; Tamura, S. *Agr. Biol. Chem.* **1971**, *35*, 1966−1972.
(23) Osawa, T.; Taylor, D.; Suzuki, A.; Tamura, S. *Tetrahedron Lett.* **1977**, 1169−1172.
(24) Asakawa, Y.; Takemoto, T. *Phytochemistry* **1979**, *18*, 285−288.
(25) Asakawa, Y.; Matsuda, R.; Takemoto, T. *Phytochemistry* **1980**, *19*, 567−569.
(26) Grieco, P. A.; Miyashita, M. *J. Org. Chem.* **1974**, *39*, 120−122.
(27) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137−6139.
(28) Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813−5815.
(29) Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, 1979−1982.
(30) (a) Jones, D. N.; Mundy, D.; Whitehouse, R. D. *J. Chem. Soc., Chem. Commun.* **1970**, 86−87. (b) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697−2699.
(31) Grieco, P. A.; Nishizawa, M. *J. Chem. Soc., Chem. Commun.* **1976**, 582−583.
(32) Edgar, M. T.; Greene, A. E.; Crabbé, P. *J. Org. Chem.* **1979**, *44*, 159−160.
(33) Ando, M.; Takase, K. *Tetrahedron* **1977**, *33*, 2785−2789.
(34) Ando, M.; Akahane, A.; Takase, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 283−289.
(35) Ando, M.; Yamaoka, H.; Takase, K. *Chem. Lett.* **1982**, 501−504.
(36) Ando, M.; Akahane, A.; Yamaoka, H.; Takase, K. *J. Org. Chem.* **1982**, *47*, 3909−3916.
(37) Ando, M.; Tajima, K.; Takase, K. *J. Org. Chem.* **1983**, *48*, 1210−1216.
(38) Ando, M.; Ono, A.; Takase, K. *Chem. Lett.* **1984**, 493−496.
(39) Ando, M.; Yoshimura, H. *J. Org. Chem.* **1993**, *58*, 4127−4131.
(40) Ando, M.; Ibayashi, K.; Minami, N.; Nakamura, T.; Isogai, K.; Yoshimura, H. *J. Nat. Prod.* **1994**, *57*, 433−445.
(41) Yamakawa, K.; Nishitani, K.; Tominaga, T. *Tetrahedron Lett.* **1975**, 2829−2832.
(42) Yamakawa, K.; Tominaga, T.; Nishitani, K. *Tetrahedron Lett.* **1975**, 4137−4140.
(43) Yamakawa, K.; Nishitani, K.; Yamamoto, A. *Chem. Lett.* **1976**, 177−180.
(44) Grieco, P. A.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 1717−1720.
(45) Greene, A. E.; Muller, J.-C.; Ourisson, G. *J. Org. Chem.* **1974**, *39*, 186−191.
(46) Arnold, R. T.; Kulenovic, S. T. *J. Org. Chem.* **1978**, *43*, 3687−3689.
(47) Reuss, R. H.; Hassner, A. *J. Org. Chem.* **1974**, *39*, 1785−1787.
(48) Shimoma, F.; Kusaka, H.; Azami, H.; Wada, K.; Suzuki, T.; Hagiwara, H.; Ando, M. *J. Org. Chem.* **1998**, *63*, 3758−3763.
(49) Shimoma, F.; Kusaka, H.; Wada, K.; Azami, H.; Yasunami, M.; Suzuki, T.; Hagiwara, H.; Ando, M. *J. Org. Chem.* **1998**, *63*, 920−929.
(50) Ando, M.; Kataoka, N.; Yasunami, M.; Takase, K.; Hirata, N.; Yanagi, Y. *J. Org. Chem.* **1987**, *52*, 1429−1437.

NP020586Y