Synthesis and Antitumor Activity of Duocarmycin Derivatives: Modification of Segment-A of A-Ring Pyrrole Compounds

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A series of 3-substituted A-ring pyrrole compounds of duocarmycin were synthesized and evaluated for in vitro anticellular activity against HeLa S_3 cells and in vivo antitumor activity against murine sarcoma 180 in mice. These compounds were evaluated on the peripheral blood toxicity and delayed lethal toxicity. Further, to expand our investigation of their peripheral blood toxicity, the toxicity to bone marrow cells (CFU-GM, CFU-Meg) was investigated. Among 3-substituted A-ring pyrrole compounds of duocarmycin bearing a 5′,6′,7′-trimethoxy-2′-indolecarboxyl group as segment-B (Seg-B), several analogues showed remarkably potent antitumor activity with low peripheral blood toxicity. The 3-formyl compound **12h**, one of such analogues, showed stronger antitumor activity with lower toxicity to bone marrow cells compared to DU-86 (**2a**), an active metabolite of KW-2189 (**2b**). However, compound **12h** caused delayed death. On the other hand, the 3-bromo compound **15f**, one of the 3-substituted A-ring pyrrole derivatives bearing a 4′-methoxycinnamoyl group as Seg-B, showed the most potent antitumor activity among the 4′-methoxycinnamate analogues with low toxicity to bone marrow cells. Furthermore, compound **15f** did not cause delayed death similarly to **2d**. These results would indicate the importance of the C-3 substituents of A-ring pyrrole duocarmycin derivatives for exhibiting antitumor activity and decreasing toxicity.

Introduction

Duocarmycins (DUM) (A, **1a**; SA, **1b**; B1, **1e**; B2, **1c**; C1, **1f**; C2, **1d**) are novel antitumor antibiotics isolated from the culture broth of *Steptomyces* sp. (Chart 1).[1] DUMs are known to exhibit potent growth-inhibitory activity against human uterine cervix carcinoma HeLa S_3 in vitro and also exhibit modest broad antitumor spectrum against murine transplantable solid tumor.[2,3] Since DUMB1 (**1e**), -B2 (**1c**), -C1 (**1f**), and -C2 (**1d**) readily yield DUMA (**1a**) in aqueous solution, DUMA is thought to be an active form among these antibiotics. DUMA and DUMSA have a unique cyclopropane ring responsible for the sequence-selective alkylation of double-stranded DNA mediating N3 adenine covalent adduct formation.[4] This mechanism is similar to that of CC-1065 (**1g**) which has been reported to show high cytotoxicity.[5,6] The segment-B (Seg-B) of DUM has been considered to play an important role for noncovalent binding to the minor groove of DNA.[7] With the objective to identify novel promising candidates, we have previously synthesized a series of DUM analogues bearing simplified DNA-binding moieties.[8,9] Among these Seg-B derivatives, some of the A-ring pyrrole DUMs bearing a cinnamoyl group as Seg-B showed strong antitumor activity and low peripheral blood toxicity.[9]

On the other hand, Seg-A has the electrophilic cyclopropane ring necessary for the formation of covalent bonding to DNA. In previous papers,[10c] we have reported that the A-ring structure influences the electrophilicity of the cyclopropane. To investigate the reactivity of the cyclopropane subunit of DUMA (**1a**), DUMSA (**1b**), **2a**, and **2c**, we evaluated the chemical stability of these drugs under aqueous neutral conditions by reverse-phase HPLC analysis. The results indicate that the electrophilicity of the cyclopropane of DUMs is as follows: DUMA > **2a** > DUMSA = **2c**. Further, we have observed that the DNA-alkylating reaction of DUMA (**1a**), SA (**1b**), and analogues is reversible.[11] The rate of regeneration of these compounds from the covalent DNA adducts (**2c** > DUMSA > **2a** ≫ DUMA) was correlated to the electrophilicity of these compounds. Moreover, DUMA (**1a**) is unstable in the culture medium to give the inactive hydrolytic product.[12,13] This hydrolytic conversion seems to decrease the potency of analogues having Seg-A of the natural type. Among the several modification product of Seg-A, KW-2189 (**2b**)[10] having an A-ring pyrrole demonstrated excellent in vivo antitumor activity and good stability in the culture medium. KW-2189 (**2b**)[10] is currently under phase II clinical evaluation. In addition, several modifications of the alkylation subunits on duocarmycin or CC-1065 (**1g**) analogues have been previously reported.[14]

It is expected that our approach to synthesize the new Seg-A analogues may enhance the potency and decrease the toxicity by structural modifications of the A-ring pyrrole moiety which influences the association between DNA and drugs. From this viewpoint, new candidates for antitumor drugs would be found by further modification of the A-ring pyrrole moiety. Our study showed a new approach in the modification at the C-3 position of the A-ring pyrrole moiety in Seg-A for investigating anticellular and antitumor activities, peripheral blood toxicity, and structure−activity relationships of these derivatives. Furthermore, we studied the evaluation of delayed lethal toxicity and toxicity to bone marrow cells (CFU-GM, CFU-Meg) of these derivatives in order to investigate their peripheral blood toxicity in detail.

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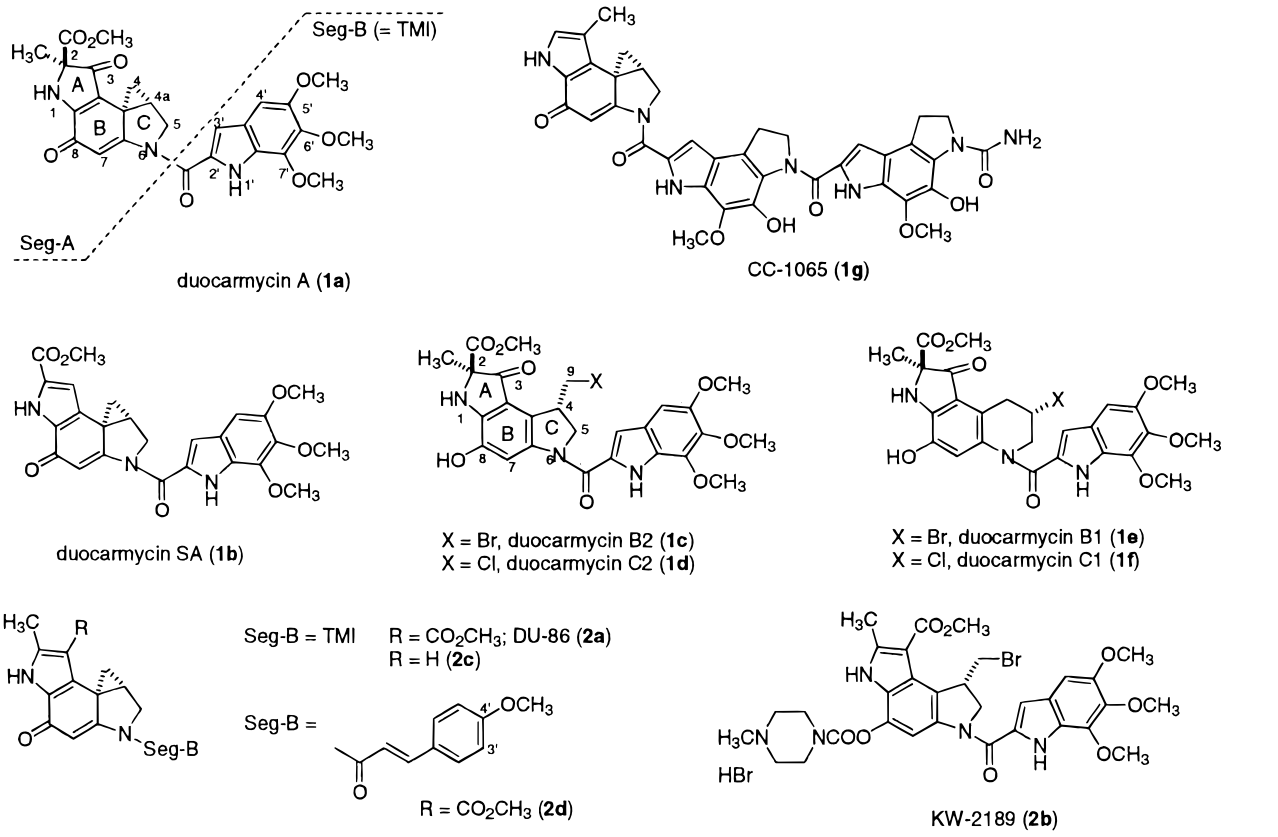
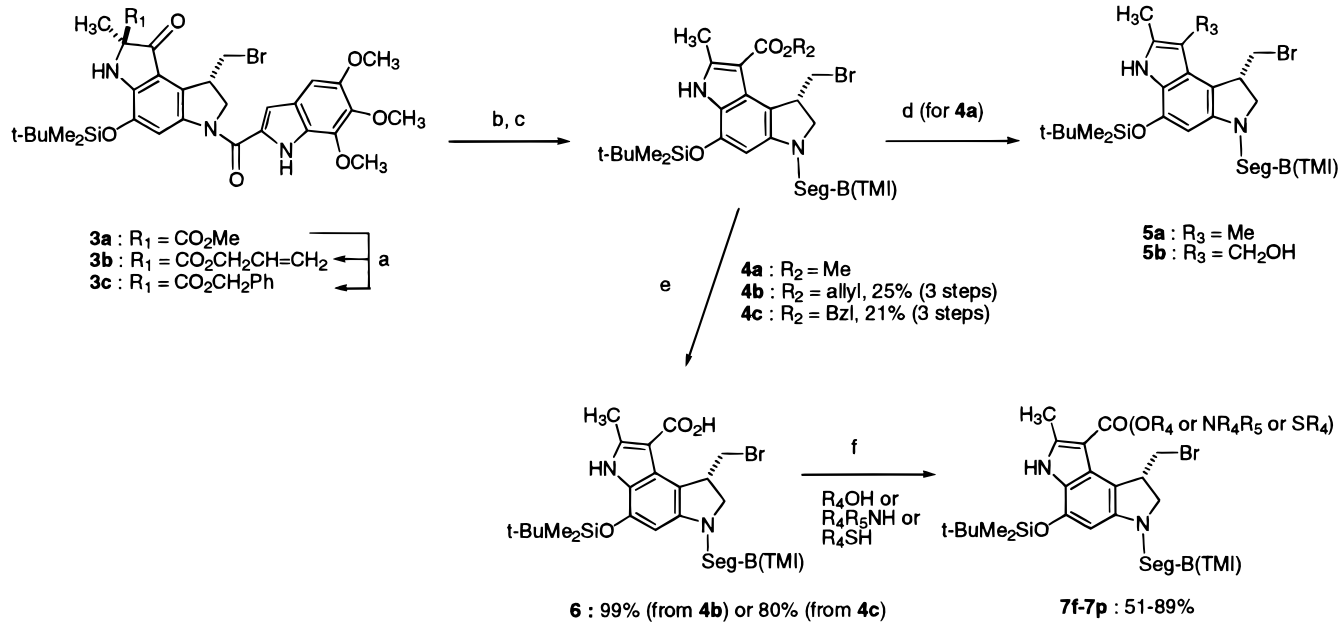
Chart 1. Structures of Duocarmycins, CC-1065, and Duocarmycin Derivatives



Scheme 1[a]

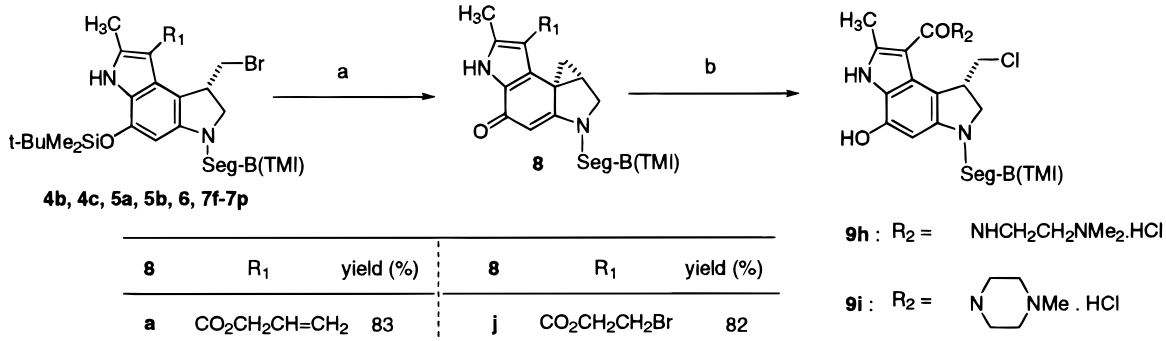


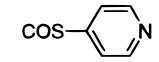
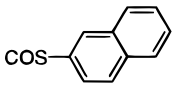
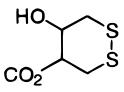
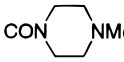
[a] (a) Allyl alcohol or benzyl alcohol, K_2CO_3, 0 °C; (b) $NaBH_4$, allyl alcohol, 0 °C; (c) BF_3-Et_2O, $CHCl_3$, rt; (d) DIBAL-H, THF, rt; (e) R_2 = allyl: $Pd(PPh_3)_4$, dimedone, THF, rt, or R_2 = Bzl: Pd/C, 25% HCO_2NH_4(aq), THF, rt; (f) method 1: DECP, Et_3N, THF, 0 °C−rt, method 2: EDCI, CH_2Cl_2, rt, method 3: EDCI, DMAP, CH_2Cl_2, rt.

Chemistry

In a previous paper, we reported that the 2-methyl-3-methoxycarbonyl A-ring pyrrole compound of duocarmycin (**4a**) was prepared by employing the Wagner−Meerwein type rearrangement of the 8-*O*-protected-3-hydroxyduocarmycin B2.[15] The 3-allyloxycarbonyl compound **4b** and 3-benzyloxycarbonyl compound **4c** were prepared by employing the same type of rearrangement of the corresponding 3-ester compounds **3b** and **3c** obtained by the treatment of compound **3a** with alcohols in the presence of K_2CO_3 (Scheme 1). Compound **4a** was reduced with DIBAL-H in THF at room temperature to afford the 3-methyl and 3-hydroxymethyl compounds **5a** and **5b**. The production ratio of **5a** and **5b** was greatly

Scheme 2[a]



8	R_1	yield (%)	8	R_1	yield (%)
a	$CO_2CH_2CH{=}CH_2$	83	j	$CO_2CH_2CH_2Br$	82
b	CO_2CH_2Ph	78	k	COSPh	78
c	Me	97	l		64
d	CH_2OH	47			
e	CO_2H	79	m		78
f	CONHPh	76			
g	$CONH^nPr$	80	n	$COSCH_2Ph$	57
h	$CONHCH_2CH_2NMe_2$	50	o		71
i		70	p	$CO_2CH_2CH_2SO_2Me$	61

[a] (a) $^nBu_4NF$, THF, rt; (b) 4 N HCl in AcOEt, CH_2Cl_2, rt.

affected by the equivalent of DIBAL-H and the reaction time [**5a** (56%), **5b** (7%): DIBAL-H (12 equiv), 23 h; **5a** (17%), **5b** (35%): DIBAL-H (4 equiv), 1.3 h]. The 3-carboxyl compound **6** was prepared by deprotection of the allyl group of **4b** using $Pd(PPh_3)_4$/dimedone[16] or the benzyl group of **4c** using palladium on carbon in the presence of 25% aqueous HCO_2NH_4. Compound **6** was converted to the 3-amides, 3-esters, and 3-thioesters **7f**−**7p** by the reaction with various amines, alcohols, and thiols using diethyl cyanophosphonate (DECP) in the presence of Et_3N (method 1) or only 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (method 2) or EDCI in the presence of 4-dimethylaminopyridine (DMAP) (method 3). The desilylation of 3-substituted compounds **4b**, **4c**, **5a**, **5b**, **6**, and **7f**−**7p** was carried out with $^nBu_4NF$ in THF to give **8a**−**8p**, respectively (Scheme 2). Compounds **8h** and **8i** were treated with 4 N HCl in AcOEt to afford **9h** and **9i** carrying a chloromethyl group in the C-ring part. The aqueous solubility of these HCl salts (**9h**, **9i**) was found to be more than 10 mg/mL.

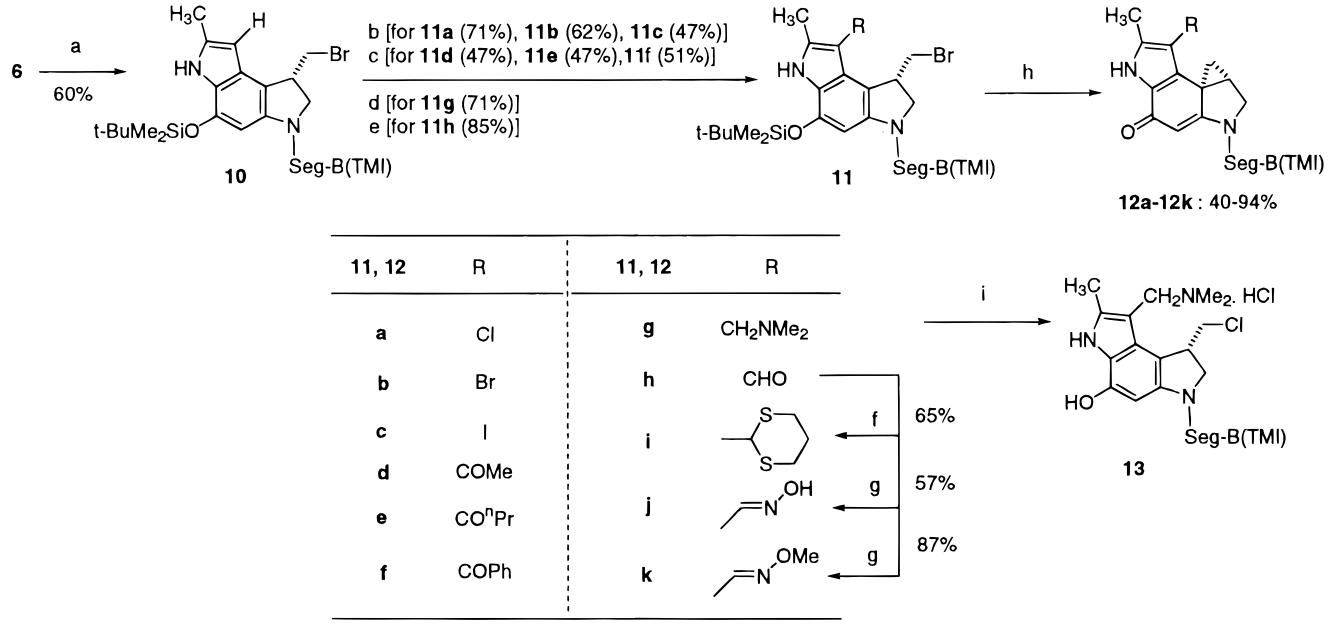
We have already reported that the 2-decarbomethoxy-3-hydroxy compound treated with camphorsulfonic acid (CAS) affords the dehydration product **10**.[10a] Further, we have found another synthesis of the 3-hydro compound **10** (Scheme 3). The 3-carboxyl compound **6** was decarboxylated at reflux in bromobenzene to give the 3-hydro compound **10**. Compound **10** was converted to the 3-halogeno compounds **11a**−**11c** by the reaction with NCS or NBS or NIS in the presence of silica gel under darkness.[17] Moreover, the 3-hydro compound **10** was reacted with various electrophiles (Friedel−Crafts acylation, Mannich reaction, Vilsmeier reaction) to yield the corresponding 3-acyls **11d**−**11f**, 3-dimethylaminomethyl compound **11g**, and 3-formyl compound **11h**. Treatment of **11h** with 1,3-dithiopropane in the presence of Amberlyst-15 afforded the 3-dithioacetal **11i**.[18] The 3-oximes **11j** and **11k** were synthesized by the reaction of **11h** with hydroxyamine or methoxyamine in EtOH. Compounds **11a**−**11k** were converted to the cyclopropane compounds **12a**−**12k** by the same method as Scheme 2. Compound **12g** was converted to the HCl salt **13** with high aqueous solubility (>10 mg/mL).

The preparation of the 3-substituted A-ring pyrrole derivatives bearing a 4′-methoxycinnamoyl group is outlined in Scheme 4. Synthesis of compounds **14a**−**14h** (Seg-A) was performed by the desilylation of 8-*O*-TBDMS-3-substituted compounds with $^nBu_4NF$, followed by methanolysis with sodium methoxide without isolation. The obtained compounds **14a**−**14h** were allowed to react with 4′-methoxy-*trans*-cinnamic *p*-nitrophenyl ester in the presence of NaH to yield the corresponding 3-substituted A-ring pyrrole derivatives bearing a 4′-methoxycinnamoyl group **(15a**−**15h)** in reasonable yield, as described previously.[9] Compound **15a** was treated with 4 N HCl in AcOEt for protection of the cyclopropane ring to afford an intermediate compound carrying a chloromethyl group in the C-ring part. After Mannich reaction, the obtained product was then treated with DBU to yield 3-dimethylaminomethyl compound **16**. The HCl salt (**17**) of **16** was also prepared by the same procedure as that of **9h** and **9i**. The aqueous solubility of compound **17** was found to be more than 10 mg/mL.

Results and Discussion

Tables 1 and 2 show anticellular activity of 3-substituted A-ring pyrrole derivatives against HeLa S_3 cells

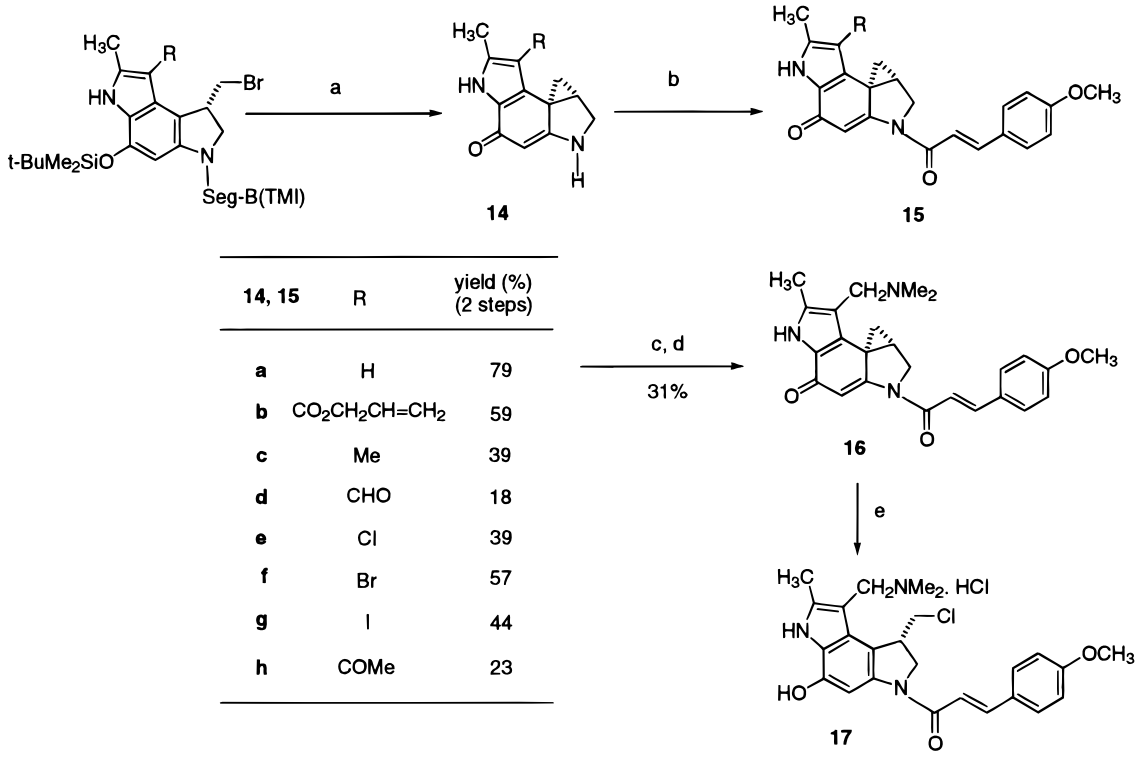
Scheme 3[a]



11, 12	R	11, 12	R
a	Cl	g	CH_2NMe_2
b	Br	h	CHO
c	I	i	
d	COMe	j	
e	CO^nPr	k	
f	COPh		

[a] (a) PhBr, reflux; (b) NCS or NBS or NIS, silica gel, CH_2Cl_2, rt; (c) Ac_2O or $(^nPrO)_2O$ or $(PhO)_2O$, BF_3-Et_2O or $TiCl_4$, CH_2Cl_2, rt or 50 °C; (d) $Me_2NCH_2NMe_2$, TFA, −10 °C; (e) $POCl_3$, DMF, rt; (f) $HS(CH_2)_3SH$, Amberlyst-15, THF, rt; (g) H_2NOH or H_2NOMe, EtOH, rt; (h) $^nBu_4NF$, THF, rt; (i) 4 N HCl in AcOEt, CH_2Cl_2, rt.

Scheme 4[a]



14, 15	R	yield (%) (2 steps)
a	H	79
b	$CO_2CH_2CH{=}CH_2$	59
c	Me	39
d	CHO	18
e	Cl	39
f	Br	57
g	I	44
h	COMe	23

[a] (a) (1) $^nBu_4NF$, THF, rt, (2) NaOMe, MeOH, rt; (b) (1) NaH, (2) 4-methoxycinnamic *p*-nitrophenyl ester, DMF, −20 °C; (c) (1) 4 N HCl in AcOEt, CH_3CN, rt, (2) $Me_2NCH_2NMe_2$, TFA, −10 °C; (d) DBU, CH_3CN, rt; (e) 4 N HCl in AcOEt, CH_2Cl_2, rt.

in vitro, antitumor activity against sarcoma 180 solid tumor in mice, and hematotoxicity (WBC, PL) in vivo. The efficacy in vivo is expressed as T/C, where T and C represent means of tumor volume in treated and control mice, respectively.

Among 3-substituted A-ring pyrrole analogues bearing a 5′,6′,7′-trimethoxy-2′-indolecarbonyl group as Seg-B of the natural type, 3-methyl (**8c**), 3-hydroxymethyl (**8d**), 3-halogeno (**12a**−**12c**), and 3-formyl (**12h**) derivatives showed strong anticellular activity comparable to the 3-methoxycarbonyl compound **2a** (DU-86), a cyclopropane compound of KW-2189 (**2b**).[10] In contrast, the 3-amides, 3-esters, and 3-thioesters showed a tendency to decrease anticellular activity. It is assumed that their 3-substituted groups are a steric hindrance to the DNA minor groove.

On the other hand, the relationship between the in vitro activity and the in vivo activity is somewhat

Table 1. Anticellular Activity, Antitumor Activity, and Hematotoxicity of Duocarmycin Derivatives Bearing a 5′,6′,7′-Trimethoxy-2′-indolecarboxyl Group

	HeLa S_3 IC_{50} (nM)[a]		sarcoma 180 (sc-iv)[b]		hematotoxicity	
			dose		WBC[d]	PL[e]
no.	1 h	72 h	(mg/kg)	T/C[c]	(%)	(%)
8a	0.43	0.26	0.13	0.24	43	73
8b	0.74	0.18	0.13	0.20	53	75
8c	0.098	0.022	0.031	0.31	35	66
8d	0.093	0.010	0.031	0.38	75	toxic
8e	14	0.28	0.25	0.26	67	107
8f	16	3.6	4.0	0.18	32	NT[f]
8g	24	5.3	2.0	0.25	38	55
8h	39	3.5	0.13	0.58	62	84
8i	34	3.0	2.0	0.38	37	83
8j	0.21	0.12	0.13	0.22	28	59
8k	19	8.1	4.0	0.18	35	85
8l	4.0	1.4	0.5	0.43	83	94
8m	130	18	2.0	0.60	130	91
8n	0.72	0.22	0.25	0.23	56	53
8o	2.7	1.1	0.5	0.30	75	105
8p	30	12	8.0	0.49	36	81
9h	9.1	0.78	0.25	0.59	93	93
9i	60	4.1	8.0	0.45	33	84
12a	0.018	0.009	0.063	0.22	31	36
12b	0.025	0.014	0.031	0.34	27	70
12c	0.092	0.039	0.016	0.24	55	NT
12d	0.27	0.39	0.25	0.24	32	64
12e	3.0	1.4	4.0	0.24	17	26
12f	2.5	0.78	1.0	0.31	32	90
12g	0.25	0.10	0.13	0.24	53	81
12h	0.08	0.046	0.031	0.18	86	56
12i	3.1	1.1	0.5	0.36	38	77
12j	0.13	0.082	0.13	0.39	88	98
12k	8.7	1.7	1.0	0.25	22	59
13	0.28	0.16	0.5	0.30	47	82
2a	0.045	0.0052	0.25	0.21	22	38

[a] Drug concentration required to inhibit the growth of HeLa S_3 cells by 50%. [b] Mice (5 mice/group) were implanted subcutaneously (sc) with tumor cells, and the drug was dosed (mg/mg) intravenously (iv). [c] T and C are the values of the mean tumor volume of treated and control mice, respectively. [d] Number of peripheral platelets of normal mice on day 7 (percent of control). [e] Number of white blood cells of tumor-bearing mice on day 4 (percent of control). [f] Not tested.

different. Although the analogues having a steric hindrance group at the C-3 position of the A-ring pyrrole indicated lower anticellular activity than **2a**, several analogues showed efficient antitumor activity in vivo (T/C < 0.3). It is conceivable that good stability in the culture medium and the association between DNA and drugs may cause strong antitumor activity.[13] Moreover, many 3-substituted A-ring pyrrole DUMs having a trimethoxyindole skeleton in Seg-B showed lower peripheral blood toxicity than **2a**, an active metabolite of KW-2189 (**2b**). We evaluated the toxicity to bone marrow cells (CFU-GM, CFU-Meg) of duocarmycin derivatives in order to investigate their peripheral blood toxicity in detail. First, comparative examination of compound **2a** bearing a 5′,6′,7′-trimethoxy-2′-indolecarbonyl group and compound **2d** bearing a 4′- methoxycinnamoyl group was performed (Figure 1). The results indicated that the toxicity of compound **2d** to bone marrow cells was lower and its recovery was also more rapid than that of compound **2a**, like the tendency of peripheral blood toxicity. Next, the 3-formyl compound **12h**, demonstrating potent antitumor activity with low peripheral blood toxicity, was evaluated in vivo on its toxicity to bone marrow cells (Figure 2). Compound **12h** showed lower toxicity than **2a** in the level of bone marrow cells. Modification at the C-3 position of the A-ring pyrrole resulted in a decreased toxicity not only to peripheral blood toxicity but also to bone marrow cells. Furthermore, the evaluation of delayed toxicity was performed (Table 3).[10b] No toxic death was observed in mice on and after day 30 by the administration of compound **2d**, indicating that compound **2d** did not cause delayed death in ddY mice. However, compounds **2a** and **12h** caused delayed death even when administered below the maximum tolerated dose predetermined in the evaluation of antitumor activity against murine sarcoma 180 in ddY mice. It was assumed that delayed death by **2a** and **12h** was caused by the strong noncovalent interaction between DNA and Seg-B of the natural type.

Table 2. Anticellular Activity, Antitumor Activity, and Hematotoxicity of Duocarmycin Derivatives Bearing a 4′-Methoxycinnamoyl Group

	HeLa S_3 IC_{50} (nM)[a]		sarcoma 180 (sc-iv)[b]		hematotoxicity	
			dose		WBC[d]	PL[e]
no.	1 h	72 h	(mg/kg)	T/C[c]	(%)	(%)
15a	7.0	0.17	0.5	0.34	30	63
15b	11	1.1	1.0	0.51	42	98
15c	7.5	0.22	0.5	0.15	21	83
15d	0.96	0.37	0.13	0.41	59	80
15e	1.4	0.029	0.25	0.21	19	64
15f	2.9	0.065	0.21	0.11	24	67
15g	2.4	0.63	0.25	0.16	23	70
15h	3.3	0.92	1.0	0.37	52	86
16	3.6	0.39	0.25	0.35	65	83
17	7.8	0.57	1.0	0.37	48	88
2d	2.9−7.0	0.26−0.94	0.83	0.34	50	63

[a] Drug concentration required to inhibit the growth of HeLa S_3 cells by 50%. [b] Mice (5 mice/group) were implanted subcutaneously (sc) with tumor cells, and the drug was dosed (mg/mg) intravenously (iv). [c] T and C are the values of the mean tumor volume of treated and control mice, respectively. [d] Number of peripheral platelets of normal mice on day 7 (percent of control). [e] Number of white blood cells of tumor-bearing mice on day 4 (percent of control).

Table 2 shows the anticellular and antitumor activity and hematotoxicity of the 3-substituted A-ring pyrrole derivatives bearing a 4′-methoxycinnamoyl group. We expected that 4′-methoxycinnamates would show lower toxicity to bone marrow toxicity than the derivatives bearing a trimethoxyindole skeleton in Seg-B. The 3-chloro (**15e**) and 3-bromo (**15f**) compounds exhibited the most remarkable anticellular activity of all the derivatives having a 4′-methoxycinnamoyl group as Seg-B with IC_{50} values below 0.1 nM at 72-h exposure.[9] Compound **15f** showed the strongest antitumor activity among 4′-methoxycinnamates with a T/C value of 0.11. Among 4′-methoxycinamates, compounds **15d** and **15f** were studied on efficacy against human xenografted carcinoma (LC-6) and toxicity to bone marrow cells (Figure 2). Compound **15f** showed excellent activity in vivo with a T/C value of 0.099 (0.25 mg/kg dose); however, compound **15d** showed weak antitumor activity. Bone marrow toxicity of **15d** and **15f** was lower than that of **2a** bearing Seg-B of the natural type and was equal to that of 4′-methoxycinnamate (**2d**) (Figures 1 and 2). Moreover, compound **15f** did not cause delayed death at a dose below the maximum tolerated dose in the evaluation of antitumor activity against murine sarcoma 180 in ddY mice (Table 3). These results indicate

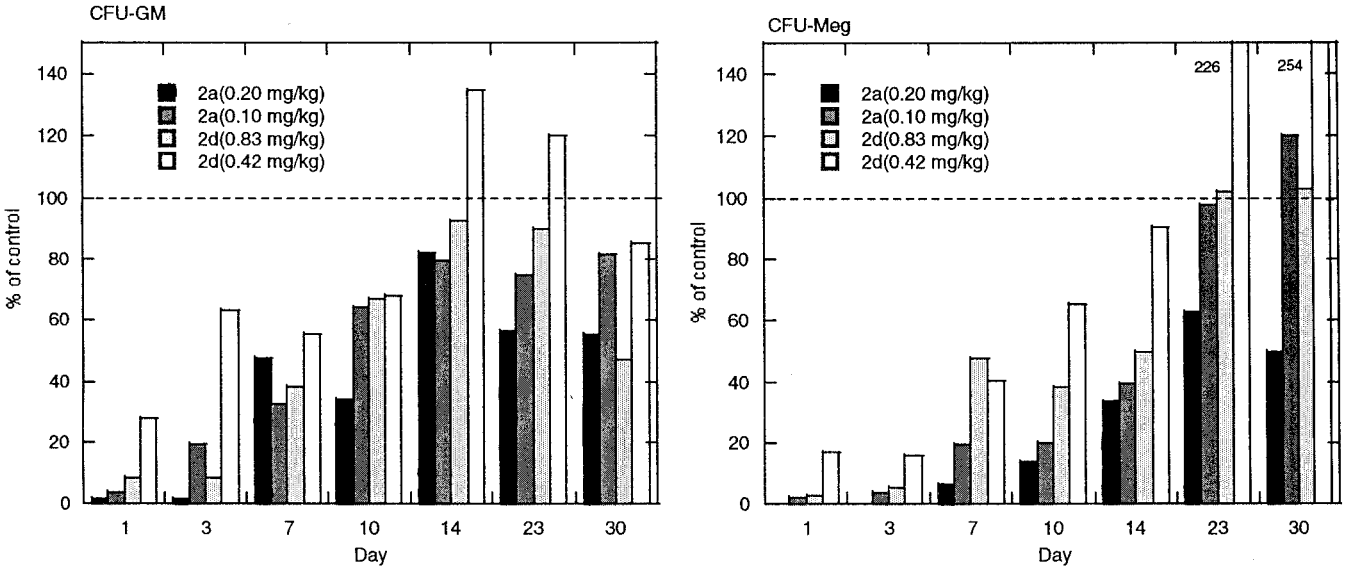


Figure 1. Suppression and recovery of hematopoietic functions after drug administration. Drug was administered iv in ddY mice on day 0, and the ratios of colony-forming unit−granulocytes and macrophages (CFU-GM) and colony-forming unit−megakaryocytes (CFU-Meg) per femur to those of control were calculated on the days indicated.

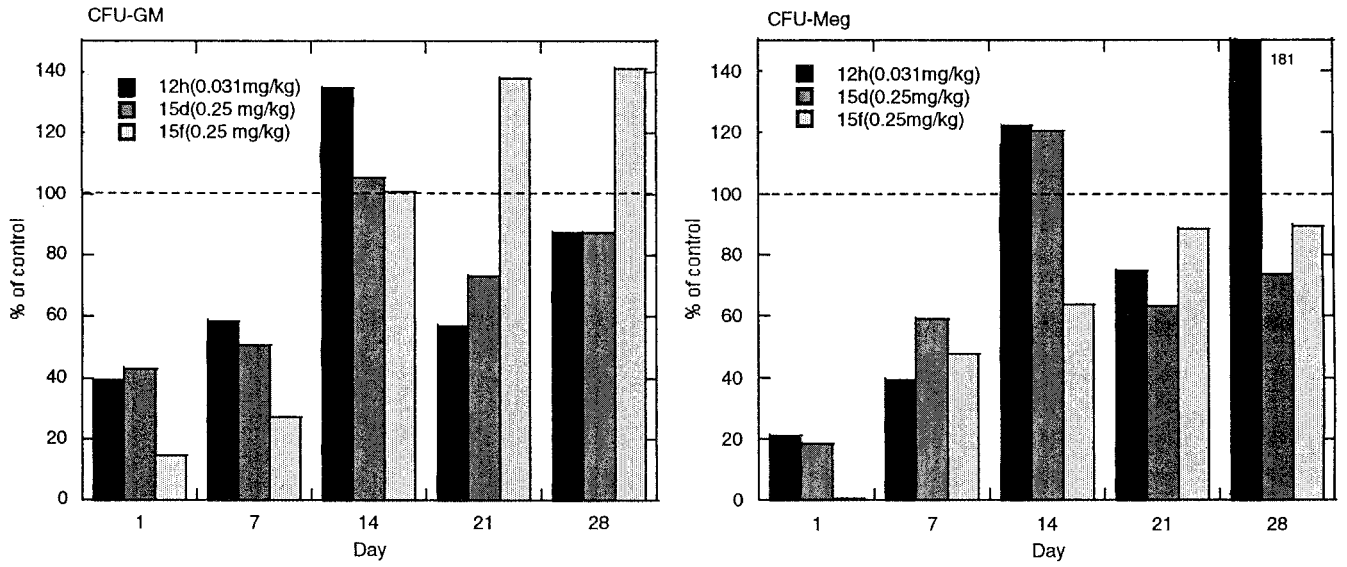


Figure 2. Suppression and recovery of hematopoietic functions after drug administration. Drug was administered iv in ddY mice on day 0, and the ratios of colony-forming unit−granulocytes and macrophages (CFU-GM) and colony-forming unit−megakaryocytes (CFU-Meg) per femur to those of control were calculated on the days indicated.

that compound **15f** is as promising a candidate as compound **2d** for a novel antitumor agent.

In addition, compounds **9g**, **9h**, **13**, and **17**, having an amino group at the C-3 position of the A-ring pyrrole, were found to possess adequate water solubility in excess of 10 mg/mL.

Conclusions

A series of 3-substituted A-ring pyrrole compounds of duocarmycin were prepared and evaluated for their anticellular activity against Hela S_3 cells and antitumor activity against sarcoma 180 murine solid tumor and LC-6 human lung tumor xenograft. Moreover, we performed the evaluation on these derivatives regarding delayed lethal toxicity and bone marrow toxicity in order to investigate their peripheral blood toxicity in detail. The 3-bromo A-ring pyrrole compound **15f** of duocarmycin bearing a 4′-methoxycinnamoyl group showed remarkably potent antitumor activity with low peripheral blood toxicity and low bone marrow toxicity. Moreover, compound **15f** did not cause delay death similarly to **2d**. Modification at the C-3 position was shown to be a promising approach for preparing new candidates for antitumor drugs.

Experimental Section

Infrared spectra (IR) were recorded on a JASCO IR-810 spectrometer. ^{1}H-NMR spectra were measured on JEOL JNM-EX270 and Bruker AM-400 spectrometers and are reported in δ units. Mass spectra were measured with JEOL JMS-DX303 and SHIMAZU QP-1000 spectrometers. Elemental analyses were performed with a Perkin-Elmer 2400 C, H, N analyzer. For column chromatography, silica gel (SiO_2, Merck Kieselgel 60 F_{254}) was used. Preparative TLC (PTLC) was carried out on glass plates coated with Merck Kieselgel 60 F_{254s}. Usual workup refers to washing of organic layers with brine, drying over anhydrous Na_2SO_4, and evaporating off the solvents under reduced pressure.

Table 3. Lethal Toxicity of Duocarmycin Derivatives in Mice

no.	dose (mg/kg)	deceased day	mortality[a]
2a	0.17	65	1/10
	0.20	46, 48, 48, 49, 66	5/10
	0.24	5, 12, 12, 58, 58, 62	6/10
	0.29	5, 5, 5, 5, 5, 5, 5, 6, 7, 7	10/10
	0.35	5, 5, 5, 5, 5, 5, 5, 5, 5, 5	10/10
	0.42	2, 2, 2, 2, 5, 6, 6, 6, 6, 6	10/10
	0.50	2, 2, 2, 2, 2, 2, 2, 2, 2, 2	10/10
2d	0.58	not deceased	0/10
	0.69	not deceased	0/10
	0.83	not deceased	0/10
	1.0	5, 5, 5, 5, 5, 5, 5, 6, 6, 9	10/10
	1.2	5, 5, 5, 5, 5, 5, 5, 5, 5, 6	10/10
	1.4	2, 2, 2, 2, 2, 3, 5, 5, 5, 5	10/10
	1.7	2, 2, 2, 2, 2, 2, 2, 2, 2, 2	10/10
12h	0.031	49	1/10
	0.044	59, 60, 65	3/10
	0.063	49, 50, 59, 60, 64, 65, 65	7/10
	0.088	4, 4, 4, 4, 4, 7, 7, 7, 7, 7	10/10
	0.13	3, 3, 3, 3, 3, 4, 4, 4, 4, 4	10/10
15f	0.099	not deceased	0/10
	0.15	not deceased	0/10
	0.22	not deceased	0/10
	0.33	5, 5, 5, 5, 6, 6, 6, 29	8/10
	0.50	2, 2, 4, 4, 4, 4, 4, 4, 4, 4	10/10
	0.75	2, 2, 2, 2, 2, 2, 2, 2, 2, 2	10/10

[a] Observed for 60−71 days. Each compound was administered iv in male ddY mice on day 0.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-(allyloxycarbonyl)-A-ring-pyrrole-DUMB2 (4b). To a solution of **3a** (3.58 g, 5.10 mmol) in allyl alcohol (100 mL) was added K_2CO_3 (2.01 g, 15.2 mmol), and the mixture was stirred at 0 °C for 41 h 40 min; 0.5 N HCl was added, and the whole was extracted with AcOEt and then washed with aqueous $NaHCO_3$. Usual workup afforded 5.70 g of **3b**. To a solution of **3b** (5.70 g) in allyl alcohol (39 mL) was added $NaBH_4$ (577 mg, 15.2 mmol), and the mixture was stirred at 0 °C for 1 h 45 min; 0.5 N HCl was added, and the whole was extracted with $CHCl_3$, washed with aqueous $NaHCO_3$, and worked up as usual. The residue was purified by column chromatography (hexane−AcOEt, 4:1−2:1) to give 1.29 g (35%) of 8-*O*-(*tert*-butyldimethylsilyl)-3-hydroxy-DUMB2. To a solution of 8-*O*-(*tert*-butyldimethylsilyl)-3-hydroxy-DUMB2 (200 mg) in $CHCl_3$ (6 mL) was added BF_3-Et_2O (0.101 mL, 0.822 mmol), and the mixture was stirred at room temperature for 17 h 30 min. Aqueous $NaHCO_3$ was added, and the whole was extracted with $CHCl_3$, then washed with aqueous $NaHCO_3$, and worked up as usual. The residue was purified by PTLC (hexane−AcOEt, 3:1) to give 139 mg (71%) of **4b**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.44 (1 H, brs), 8.36 (1 H, brs), 7.98 (1 H, brs), 6.99 (1 H, d, J = 2.3 Hz), 6.89 (1 H, s), 6.12 (1 H, ddt, J = 19.6, 10.4, 5.9 Hz), 5.44 (1 H, ddd, J = 17.2, 1.6, 1.3 Hz), 5.31 (1 H, ddd, J = 10.2, 1.3, 1.3 Hz), 4.82−4.98 (2 H, m), 4.73 (1 H, d, J = 9.2 Hz), 4.55−4.62 (1 H, m), 4.52 (1 H, dd, J = 8.3, 8.3 Hz), 4.06 (3 H, s), 3.94 (3 H, s), 3.92 (3 H, s), 3.80 (1 H, dd, J = 7.6, 3.0 Hz), 3.21 (1 H, dd, J = 9.9, 9.9 Hz), 2.76 (3 H, s), 1.06 (9 H, s), 0.38 (3 H, s), 0.36 (3 H, s); FAB-MS m/z 714, 712 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-(benzyloxycarbonyl)-A-ring-pyrrole-DUMB2 (4c): yield 21%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.45 (1 H, brs), 8.40 (1 H, brs), 7.98 (1 H, s), 7.48−7.52 (2 H, m), 7.31−7.43 (3 H, m), 6.98 (1 H, d, J = 2.3 Hz), 6.89 (1 H, s), 5.54 (1 H, d, J = 12.2 Hz), 5.35 (1 H, d, J = 12.2 Hz), 4.71 (1 H, d, J = 9.9 Hz), 4.56 (1 H, m), 4.49 (1 H, dd, J = 9.6, 8.6 Hz), 4.06 (3 H, s), 3.94 (3 H, s), 3.92 (3 H, s), 3.80 (1 H, dd, J = 9.9, 2.3 Hz), 3.21 (1 H, dd, J = 9.9, 9.9 Hz), 2.71 (3 H, s), 1.05 (9 H, s), 0.37 (3 H, s), 0.36 (3 H, s); FAB-MS m/z 764, 762 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2,3-dimethyl-A-ring-pyrrole-DUMB2 (5a) and 8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-(hydroxymethyl)-A-ring-pyrrole-DUMB2 (5b). To a solution of **4a** (50 mg, 0.073 mmol) in THF (2 mL) was added DIBAL-H (0.98 M, 0.89 mL, 0.87 mmol), and the mixture was stirred under Ar atmosphere at room temperature for 23 h; 0.5 N HCl was added, and the whole was extracted with $CHCl_3$, then washed with aqueous $NaHCO_3$, and worked up as usual. The residue was purified by PTLC (hexane−AcOEt, 3:2) to give 26 mg (56%) of **5a** and 3.4 mg (7%) of **5b**. **5a**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.45 (1 H, brs), 7.79 (1 H, brs), 7.76 (1 H, s), 6.96 (1 H, d, J = 2.3 Hz), 6.88 (1 H, s), 4.74 (1 H, d, J = 10.9 Hz), 4.54 (1 H, dd, J = 10.2, 8.3 Hz), 4.08−4.15 (1 H, m), 4.07 (3 H, s), 3.94 (3 H, s), 3.92 (3 H, s), 3.71 (1 H, dd, J = 10.4, 1.8 Hz), 3.25 (1 H, dd, J = 10.9, 10.6 Hz), 2.38 (3 H, s), 2.32 (3 H, s), 1.06 (9 H, s), 0.36 (3 H, s), 0.34 (3 H, s); FAB-MS m/z 644, 642 $(M + H)^+$. **5b**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.44 (1 H, brs), 7.94 (1 H, s), 7.85 (1 H, brs), 6.96 (1 H, d, J = 2.0 Hz), 6.88 (1 H, s), 4.89 (1 H, d, J = 12.2 Hz), 4.74 (1 H, d, J = 12.5 Hz), 4.73 (1 H, d, J = 10.9 Hz), 4.54 (1 H, dd, J = 10.2, 8.3 Hz), 4.13−4.20 (1 H, m), 4.06 (3 H, s), 4.00 (1 H, dd, J = 10.2, 2.0 Hz), 3.94 (3 H, s), 3.91 (3 H, s), 3.29 (1 H, dd, J = 10.6, 10.6 Hz), 2.48 (3 H, s), 1.06 (9 H, s), 0.36 (3 H, s), 0.35 (3 H, s); FAB-MS m/z 660, 658 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethsilyl)-2-methyl-3-carboxy-A-ring-pyrrole-DUMB2 (6). The case of 4b: To a solution of **4b** (60 mg, 0.085 mmol) in THF (3 mL) were added dimedone (59.4 mg, 0.424 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol), and the mixture was stirred under Ar atmosphere at room temperature for 1 h; 0.01 M phosphoric buffer (pH 7) was added, and the whole was extracted with $CHCl_3$ and then worked up as usual. The residue was purified by PTLC (hexane−AcOEt, 3:2) to give 56 mg (99%) of **6**.

The case of 4c: To a solution of **4c** (48 mg, 0.062 mmol) in THF (2 mL) were added 25% HCO_2NH_4(aq) (0.46 mL) and 10% Pd/C (30 mg), and the mixture was stirred under Ar atmosphere at room temperature for 30 min. The mixture was filtered through Celite. Then, the filrate was poured into 0.01 M phosphoric buffer (pH 7). The whole was extracted with $CHCl_3$ and worked up as usual. The residue was purified by PTLC (hexane−AcOEt, 3:2) to give 33 mg (80%) of **6**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.59 (1 H, brs), 8.52 (1 H, s), 8.00 (1 H, brs), 7.01 (1 H, d, J = 2.3 Hz), 6.89 (1 H, s), 4.74 (1 H, d, J = 10.2 Hz), 4.70−4.75 (1 H, m), 4.54 (1 H, dd, J = 9.9, 8.9 Hz), 4.06 (3 H, s), 3.95 (3 H, s), 3.91 (3 H, s), 3.90 (1 H, br), 3.29 (1 H, dd, J = 9.9, 9.6 Hz), 2.82 (3 H, s), 1.07 (9 H, s), 0.39 (3 H, s), 0.38 (3 H, s); FAB-MS m/z 674, 672 $(M + H)^+$; IR (KBr) 3458, 2856, 1630, 1495, 1466, 1443, 1419, 1389, 1308, 1228, 1203, 1111, 845 cm^{-1}.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-(*N*-phenylcarbamoyl)-A-ring-pyrrole-DUMB2 (7f). Method 1: To a solution of **6** (60 mg, 0.089 mmol) in THF (3 mL) were added aniline (0.016 mL, 0.18 mmol), DECP (0.020 mL, 0.13 mmol), and Et_3N (0.025 mL, 0.18 mmol), and then the mixture was stirred at 0 °C for 1 h. After the mixture stirred at room temperature for 12 h, 0.01 M phosphoric buffer (pH 7) was added, and the whole was extracted with AcOEt and then worked up as usual. The residue was purified by PTLC (hexane−AcOEt, 1:1) to give 41 mg (61%) of **7f**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.40 (1 H, brs), 8.17 (1 H, s), 8.00 (1 H, s), 7.65 (2 H, d, J = 8.6 Hz), 7.50 (1 H, s), 7.40 (2 H, dd, J = 7.9, 7.6 Hz), 7.11−7.20 (1 H, m), 6.92 (1 H, d, J = 2.3 Hz), 6.87 (1 H, s), 4.51−4.58 (2 H, m), 4.39 (1 H, m), 4.06 (3 H, s), 3.94 (3 H, s), 3.90 (3 H, s), 3.73 (1 H, dd, J = 9.9, 3.0 Hz), 3.26 (1 H, dd, J = 9.6, 9.6 Hz), 2.67 (3 H, s), 1.07 (9 H, s), 0.38 (3 H, s), 0.37 (3 H, s); FAB-MS m/z 749, 747 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-(*N*-*n*-propylcarbamoyl)-A-ring-pyrrole-DUMB2 (7g). Method 2: To a solution of **6** (30 mg, 0.045 mmol) in CH_2Cl_2 (1.2 mL) were added ^{n}PrNH$_2$ (0.011 mL, 0.13 mmol) and EDCI (26 mg, 0.13 mmol), and the mixture was stirred at room temperature for 9 h; 0.01 M phosphoric buffer (pH 7) was added, and the whole was extracted with $CHCl_3$ and then worked up as usual. The residue was purified by PTLC (hexane−AcOEt, 1:1) to give 28 mg (89%) of **7g**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.41 (1 H, brs), 8.19 (1 H, s), 7.95 (1 H, brs), 6.90 (1 H, d, J = 2.0 Hz), 6.87 (1 H, s), 5.83 (1 H, t, J = 5.8 Hz), 4.56 (1 H, dd, J = 10.6, 2.6 Hz), 4.48 (1 H, dd, J = 10.6, 8.6 Hz), 4.28−4.42 (1 H, m), 4.05 (3 H, s), 3.93 (3 H, s), 3.89 (3 H, s), 3.65 (1 H, dd, J = 9.9,

3.0 Hz), 3.38−3.58 (2 H, m), 3.19 (1 H, dd, J = 9.6, 9.6 Hz), 2.56 (3 H, s), 1.71 (2 H, dt, J = 7.6, 7.3 Hz), 1.05 (9 H, s), 1.02 (3 H, t, J = 7.3 Hz), 0.35 (3 H, s), 0.34 (3 H, s); FAB-MS m/z 715, 713 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-[*N*-(2-dimethylaminoethyl)carbamoyl]-A-ring-pyrrole-DUMB2 (7h): method 2; yield 72%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.49 (1 H, brs), 8.21 (1 H, s), 7.95 (1 H, brs), 6.93 (1 H, d, J = 1.7 Hz), 6.88 (1 H, s), 6.60 (1 H, br), 4.51−4.65 (2 H, m), 4.35−4.48 (1 H, m), 4.05 (3 H, s), 3.93 (3 H, s), 3.90 (3 H, s), 3.60−3.71 (3 H, m), 3.18 (1 H, dd, J = 10.2, 9.9 Hz), 2.60−2.68 (2 H, m), 2.60 (3 H, s), 2.33 (6 H, s), 1.05 (9 H, s), 0.35 (3 H, s), 0.34 (3 H, s); FAB-MS m/z 744, 742 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-(4-methyl-1-piperazinylcarbonyl)-A-ring-pyrrole-DUMB2 (7i): method 2; yield 71%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.47 (1 H, brs), 8.17 (1 H, s), 7.93 (1 H, brs), 6.96 (1 H, d, J = 2.0 Hz), 6.88 (1 H, s), 4.59 (2 H, brd, J = 5.6 Hz), 4.20−4.70 (1 H, br), 4.05 (3 H, s), 3.93 (3 H, s), 3.90 (3 H, s), 3.41−3.56 (7 H, br), 3.19 (1 H, dd, J = 10.2, 9.9 Hz), 2.45 (3 H, s), 2.33 (3 H, s), 2.29−2.52 (2 H, br), 1.05 (9 H, s), 0.36 (3 H, s), 0.35 (3 H, s); FAB-MS m/z 756, 754 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-(2-bromoethoxycarbonyl)-A-ring-pyrrole-DUMB2 (7j): method 2; yield 63%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.45 (1 H, brs), 8.44 (1 H, brs), 7.99 (1 H, s), 7.00 (1 H, d, J = 2.0 Hz), 6.89 (1 H, s), 4.53−4.75 (5 H, m), 4.06 (3 H, s), 3.94 (3 H, s), 3.92 (3 H, s), 3.80 (1 H, dd, J = 10.2, 2.6 Hz), 3.72 (1 H, td, J = 5.6, 1.7 Hz), 3.21 (1 H, dd, J = 9.9, 9.9 Hz), 2.78 (3 H, s), 1.06 (9 H, s), 0.38 (3 H, s), 0.36 (3 H, s); FAB-MS m/z 782, 780, 778 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethysilyl)-2-methyl-3-(phenylthiocarbonyl)-A-ring-pyrrole-DUMB2 (7k): method 1; yield 61%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.43 (1 H, brs), 8.42 (1 H, s), 8.04 (1 H, s), 7.47−7.61 (5 H, m), 6.97 (1 H, d, J = 2.0 Hz), 6.89 (1 H, s), 4.64 (1 H, d, J = 8.6 Hz), 4.54 (1 H, dd, J = 8.6, 8.3 Hz), 4.45−4.51 (1 H, m), 4.06 (3 H, s), 3.94 (3 H, s), 3.91 (3 H, s), 3.60 (1 H, dd, J = 8.6, 3.0 Hz), 3.19 (1 H, dd, J = 9.6, 9.2 Hz), 2.94 (3 H, s), 1.07 (9 H, s), 0.39 (3 H, s), 0.38 (3 H, s); FAB-MS m/z 766, 764 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-(4-pyridinylthiocarbonyl)-A-ring-pyrrole-DUMB2 (7l): method 1; yield 77%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.50 (1 H, brs), 9.00 (1 H, brs), 8.70 (2 H, d, J = 4.6 Hz), 8.05 (1 H, brs), 7.55 (2 H, d, J = 5.0 Hz), 6.97 (1 H, d, J = 1.7 Hz), 6.88 (1 H, s), 4.65 (1 H, d, J = 9.9 Hz), 4.54 (1 H, dd, J = 10.6, 8.6 Hz), 4.42−4.50 (1 H, m), 4.04 (3 H, s), 3.93 (3 H, s), 3.91 (3 H, s), 3.59 (1 H, dd, J = 9.9, 2.6 Hz), 3.17 (1 H, dd, J = 9.6, 9.2 Hz), 2.93 (3 H, s), 1.04 (9 H, s), 0.37 (3 H, s), 0.36 (3 H, s); FAB-MS m/z 767, 765 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-(1-naphthalenylthiocarbonyl)-A-ring-pyrrole-DUMB2 (7m): method 1; yield 55%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.44 (1 H, brs), 8.46 (1 H, brs), 8.12 (1 H, s), 8.04 (1 H, brs), 7.88−7.96 (3 H, s), 7.51−7.64 (3 H, m), 6.96 (1 H, d, J = 2.0 Hz), 6.88 (1 H, s), 4.63 (1 H, d, J = 8.6 Hz), 4.54 (1 H, dd, J = 8.6, 7.3 Hz), 4.45−4.54 (1 H, m), 4.06 (3 H, s), 3.94 (3 H, s), 3.91 (3 H, s), 3.63 (1 H, dd, J = 8.6, 2.6 Hz), 3.21 (1 H, dd, J = 9.6, 9.2 Hz), 2.98 (3 H, s), 1.07 (9 H, s), 0.40 (3 H, s), 0.38 (3 H, s); FAB-MS m/z 816, 814 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-(benzylthiocarbonyl)-A-ring-pyrrole-DUMB2 (7n). Method 3: To a solution of **6** (50 mg, 0.074 mmol) in CH_2Cl_2 (2 mL) were added benzyl mercaptan (0.0262 mL, 0.223 mmol), EDCI (71 mg, 0.372 mmol), and DMAP (45.4 mg, 0.372 mmol), and then the mixture was stirred at room temperature for 69 h 40 min; 0.01 M phosphoric buffer (pH 7) was added, and the whole was extracted with $CHCl_3$ and then worked up as usual. The residue was purified by PTLC ($CHCl_3$−MeOH, 70:1) to give 44 mg (75%) of **7n**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.44 (1 H, brs), 8.31 (1 H, s), 8.01 (1 H, s), 7.42−7.46 (2 H, m), 7.28−7.37 (3 H, m), 7.00 (1 H, d, J = 2.0 Hz), 6.90 (1 H, s), 4.67−4.75 (1 H, m), 4.51−4.58 (2 H, m), 4.44 (1 H, d, J = 13.9 Hz), 4.32 (1 H, d, J = 13.5 Hz), 4.06 (3 H, s), 3.94 (3 H, s), 3.92 (3 H, s), 3.61 (1 H, brd, J = 9.9 Hz), 3.13 (1 H, dd, J = 9.9, 9.2 Hz), 2.83 (3 H, s), 1.05 (9 H, s), 0.37 (3 H, s), 0.36 (3 H, s); FAB-MS m/z 780, 778 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-(5-hydroxy-1,2-dithian-4-yloxycarbonyl)-A-ring-pyrrole-DUMB2 (7o): method 1; yield 51%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.44 (1 H, brs), 8.46 (1 H, brs), 8.00 (0.5 H, brs), 7.98 (0.5 H, brs), 6.98 (1 H, d, J = 2.0 Hz), 6.88 (1 H, s), 5.16−5.26 (1 H, m), 4.73 (0.5 H, d, J = 8.9 Hz), 4.71 (0.5 H, d, J = 9.2 Hz), 4.51−4.57 (2 H, m), 4.06 (1.5 H, s), 4.05 (1.5 H, s), 4.03 (1 H, br), 3.94 (3 H, s), 3.91 (3 H, s), 3.80 (0.5 H, brd, J = 10.6 Hz), 3.72 (0.5 H, dd, J = 9.5, 2.5 Hz), 3.04−3.42 (5 H, m), 2.77 (3 H, s), 1.06 (9 H, s), 0.37 (3 H, s), 0.36 (3 H, s); FAB-MS m/z 808, 806 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-[2-(methylsulfonyl)ethoxycarbonyl]-A-ring-pyrrole-DUMB2 (7p): method 1; yield 56%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.45 (1 H, brs), 8.47 (1 H, s), 7.99 (1 H, s), 6.99 (1 H, d, J = 2.0 Hz), 6.89 (1 H, s), 4.88 (1 H, td, J = 12.5, 6.3 Hz), 4.81 (1 H, td, J = 12.5, 6.3 Hz), 4.72 (1 H, d, J = 9.2 Hz), 4.49−4.56 (2 H, m), 4.06 (3 H, s), 3.94 (3 H, s), 3.92 (3 H, s), 3.76 (1 H, brd, J = 8.9 Hz), 3.54−3.58 (2 H, m), 3.19 (1 H, dd, J = 9.9, 9.9 Hz), 3.02 (3 H, s), 2.75 (3 H, s), 1.05 (9 H, s), 0.38 (3 H, s), 0.36 (3 H, s); FAB-MS m/z 780, 778 $(M + H)^+$.

2-Methyl-3-(allyloxycarbonyl)-A-ring-pyrrole-DUMA (8a). To a solution of **4b** (40 mg, 0.056 mmol) in THF (1.5 mL) was added ^{n}Bu$_4$NF (1.0 M in THF, 0.19 mL, 0.17 mmol), and the mixture was stirred at room temperature for 45 min; 0.01 M phosphoric buffer (pH 7) was added, and the whole was extracted $CHCl_3$ and then worked up as usual. The residue was purified by PTLC ($CHCl_3$−MeOH, 15:1) to give 24 mg (83%) of **8a**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 11.92 (1 H, brs), 9.52 (1 H, brs), 7.13 (1 H, s), 6.95 (1 H, d, J = 2.0 Hz), 6.80 (1 H, s), 6.01 (1 H, ddt, J = 19.5, 10.6, 5.6 Hz), 5.36 (1 H, dq, J = 17.2, 1.3 Hz), 5.27 (1 H, dq, J = 10.4, 1.2 Hz), 4.73 (1 H, d, J = 5.6 Hz), 4.44 (2 H, br), 4.06 (3 H, s), 3.93 (3 H, s), 3.89 (3 H, s), 3.67 (1 H, m), 2.65 (3 H, s), 2.37 (1 H, dd, J = 7.3, 3.3 Hz), 1.36 (1 H, dd, J = 4.3, 4.0 Hz); FAB-MS m/z 518 $(M + H)^+$; FAB-HRMS calcd for $C_{28}H_{28}N_3O_7$ $(M + H)^+$ m/z 518.1927, found 518.1917; IR (KBr) 1701, 1645, 1605, 1583, 1489, 1385, 1263, 1211, 1105 cm^{-1}. Anal. ($C_{28}H_{27}N_3O_7 \cdot 1.0H_2O$) C, H, N.

2-Methyl-3-(benzyloxycarbonyl)-A-ring-pyrrole-DUMA (8b): yield 78%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 11.84 (1 H, brs), 9.47 (1 H, brs), 7.31−7.42 (5 H, m), 7.11 (1 H, s), 6.93 (1 H, d, J = 2.0 Hz), 6.80 (1 H, s), 5.26 (2 H, s), 4.36−4.40 (2 H, br), 4.06 (3 H, s), 3.94 (3 H, s), 3.89 (3 H, s), 3.61−3.67 (1 H, m), 2.62 (3 H, s), 2.35 (1 H, dd, J = 7.4, 3.5 Hz), 1.33 (1 H, d, J = 4.6, 3.6 Hz); FAB-MS m/z 568 $(M + H)^+$; FAB-HRMS calcd for $C_{32}H_{30}N_3O_7$ $(M + H)^+$ m/z 568.2084, found 568.2059; IR (KBr) 1701, 1638, 1603, 1583, 1489, 1396, 1292, 1265, 1211, 1105 cm^{-1}. Anal. ($C_{32}H_{29}N_3O_7 \cdot 1.7H_2O$) C, N; H: calcd, 5.46; found, 5.01.

2,3-Dimethyl-A-ring-pyrrole-DUMA (8c): yield 97%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 10.64 (1 H, brs), 9.51 (1 H, brs), 6.95 (1 H, s), 6.92 (1 H, d, J = 2.3 Hz), 6.78 (1 H, s), 4.39 (2 H, br), 4.05 (3 H, s), 3.92 (3 H, s), 3.88 (3 H, s), 2.90−2.99 (1 H, m), 2.26 (3 H, s), 1.98 (1 H, dd, J = 7.4, 2.5 Hz), 1.92 (3 H, s), 1.34 (1 H, dd, J = 4.6, 4.6 Hz); FAB-MS m/z 448 $(M + H)^+$; IR (KBr) 1637, 1606, 1578, 1560, 1468, 1385, 1306, 1265, 1230, 1109 cm^{-1}. Anal. ($C_{25}H_{25}N_3O_5 \cdot 1.8H_2O$) C, N; H: calcd, 6.01; found, 5.50.

2-Methyl-3-(hydroxymethyl)-A-ring-pyrrole-DUMA (8d): yield 47%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 6.86 (1 H, s), 6.82 (1 H, s), 6.71 (1 H, s), 4.42 (1 H, dd, J = 10.2, 4.6 Hz), 4.36 (1 H, d, J = 12.5 Hz), 4.32 (1 H, d, J = 9.6 Hz), 4.28 (1 H, d, J = 12.5 Hz), 3.96 (3 H, s), 3.86 (3 H, s), 3.82 (3 H, s), 3.08−3.15 (1 H, m), 2.27 (3 H, s), 2.09 (1 H, dd, J = 7.4, 4.1 Hz), 1.30 (1 H, dd, J = 4.6, 4.6 Hz); FAB-MS m/z 464 $(M + H)^+$; FAB-HRMS calcd for $C_{25}H_{26}N_3O_6$ $(M + H)^+$ m/z 464.1822, found 464.1830; IR (KBr) 3234, 1637, 1618, 1603, 1578, 1560, 1527, 1466, 1389, 1306, 1267, 1107 cm^{-1}. Anal. ($C_{25}H_{25}N_3O_6 \cdot 2.0H_2O$) C, N; H: calcd, 5.85; found, 5.41.

2-Methyl-3-carboxy-A-ring-pyrrole-DUMA (8e): yield 79%; ^{1}H-NMR (270 MHz, DMSO-d_6) δ 12.29 (1 H, brs), 12.23 (1 H, brs), 11.58 (1 H, brs), 7.01 (1 H, s), 6.93 (1 H, s), 6.48 (1 H, s), 4.45 (1 H, dd, J = 10.7, 4.8 Hz), 4.27 (1 H, d, J = 10.9

Hz), 3.90 (3 H, s), 3.80 (3 H, s), 3.79 (3 H, s), 3.51−3.53 (1 H, m), 2.47 (3 H, s), 2.18 (1 H, dd, J = 7.3, 2.6 Hz), 1.43 (1 H, dd, J = 3.6, 3.3 Hz); FAB-MS m/z 478 (M + H)$^+$; IR (KBr) 3460, 2837, 1643, 1636, 1616, 1581, 1489, 1466, 1387, 1267, 1230, 1180, 1109 cm^{-1}. Anal. ($C_{25}H_{23}BrN_3O_7$·1.3H_2O) C, H, N.

2-Methyl-3-(*N*-phenylcarbamoyl)-A-ring-pyrrole-DUMA (8f): yield 76%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3-OD) δ 7.50 (2 H, d, J = 7.6 Hz), 7.30 (2 H, dd, J = 8.3, 7.6 Hz), 7.08 (1 H, dd, J = 7.6, 7.3 Hz), 6.94 (1 H, s), 6.86 (1 H, s), 6.74 (1 H, s), 4.41 (1 H, dd, J = 10.2, 4.6 Hz), 4.33 (1 H, d, J = 10.2 Hz), 3.99 (3 H, s), 3.86 (3 H, s), 3.81 (3 H, s), 3.40−3.46 (1 H, m), 2.51 (3 H, s), 2.16 (1 H, dd, J = 7.3, 3.6 Hz), 1.30−1.36 (1 H, m); FAB-MS m/z 553 (M + H)$^+$; IR (KBr) 1653, 1647, 1635, 1601, 1578, 1525, 1489, 1389, 1263, 1107 cm^{-1}. Anal. ($C_{31}H_{28}N_4O_6$·1.5H_2O) C, H, N.

2-Methyl-3-(*N*-*n*-propylcarbamoyl)-A-ring-pyrrole-DUMA (8g): yield 80%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3-OD) δ 6.92 (1 H, s), 6.86 (1 H, s), 6.74 (1 H, s), 6.33 (1 H, br), 4.39 (1 H, br), 4.32 (1 H, d, J = 10.2 Hz), 3.96 (3 H, s), 3.85 (3 H, s), 3.81 (3 H, s), 3.42 (1 H, br), 3.23−3.28 (2 H, m), 2.40 (3 H, s), 2.09 (1 H, br), 1.52−1.55 (2 H, m), 1.29 (1 H, br), 0.90 (3 H, t, J = 7.6 Hz); FAB-MS m/z 519 (M + H)$^+$; IR (KBr) 1639, 1618, 1579, 1527, 1466, 1389, 1304, 1263, 1109 cm^{-1}. Anal. ($C_{28}H_{30}N_4O_6$·1.5H_2O) C, H, N.

2-Methyl-3-[*N*-(2-dimethylaminoethyl)carbamoyl]-A-ring-pyrrole-DUMA (8h): yield 50%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 6.88 (1 H, s), 6.85 (1 H, s), 6.72 (1 H, s), 4.39 (1 H, dd, J = 10.2, 4.6 Hz), 4.30 (1 H, d, J = 10.2 Hz), 3.96 (3 H, s), 3.83 (3 H, s), 3.80 (3 H, s), 3.31−3.44 (1 H, m), 3.39 (2 H, t, J = 6.1 Hz), 2.45 (2 H, t, J = 6.1 Hz), 2.41 (3 H, s), 2.21 (6 H, s), 2.09 (1 H, dd, J = 7.6, 3.6 Hz), 1.29 (1 H, dd, J = 4.3, 4.3 Hz); FAB-MS m/z 548 (M + H)$^+$; FAB-HRMS calcd for $C_{29}N_{34}N_5O_6$ (M + H)$^+$ m/z 548.2509, found 548.2504; IR (KBr) 1633, 1616, 1581, 1525, 1464, 1385, 1304, 1265, 1230, 1107 cm^{-1}. Anal. ($C_{29}H_{33}N_5O_6$·0.9H_2O·0.6$CHCl_3$) C, H, N.

2-Methyl-3-[(4-methyl-1-piperazinyl)carbonyl]-A-ring-pyrrole-DUMA (8i): yield 70%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 11.45 (1 H, s), 9.41 (1 H, s), 7.04 (1 H, s), 6.93 (1 H, d, J = 2.3 Hz), 6.80 (1 H, s), 4.45 (1 H, dd, J = 10.1, 4.5 Hz), 4.38 (1 H, d, J = 10.2 Hz), 4.06 (3 H, s), 3.93 (3 H, s), 3.89 (3 H, s), 3.40−3.70 (3 H, br), 2.30−2.60 (6 H, br), 2.36 (3 H, s), 2.32 (3 H, s), 2.27 (1 H, br), 1.44 (1 H, br); FAB-MS m/z 560 (M + H)$^+$; FAB-HRMS calcd for $C_{30}H_{34}N_5O_6$ (M + H)$^+$ m/z 560.2509, found 560.2502; IR (KBr) 1633, 1614, 1585, 1470, 1392, 1298, 1261, 1228, 1138, 1109, 999 cm^{-1}. Anal. ($C_{30}H_{33}N_5O_6$·0.8H_2O·0.5$CHCl_3$) C, H; N: calcd, 11.05; found, 10.59.

2-Methyl-3-(2-bromoethoxycarbonyl)-A-ring-pyrrole-DUMA (8j): yield 82%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 11.55 (1 H, brs), 9.39 (1 H, brs), 7.13 (1 H, s), 6.96 (1 H, d, J = 2.0 Hz), 6.81 (1 H, s), 4.56 (2 H, t, J = 5.6 Hz), 4.46 (2 H, br), 4.08 (3 H, s), 3.94 (3 H, s), 3.90 (3 H, s), 3.67−3.69 (1 H, m), 3.63 (2 H, t, J = 5.6 Hz), 2.69 (3 H, s), 2.39 (1 H, dd, J = 7.3, 3.3 Hz), 1.38 (1 H, dd, J = 4.3, 4.0 Hz); FAB-MS m/z 586, 584 (M + H)$^+$; FAB-HRMS calcd for $C_{27}H_{27}{}^{79}BrN_3O_7$ (M + H)$^+$ m/z 554.1927, found 554.1907; IR (KBr) 1643, 1605, 1487, 1387, 1294, 1265, 1230, 1209, 1105 cm^{-1}. Anal. ($C_{27}H_{26}BrN_3O_7$·0.5H_2O) C, H, N.

2-Methyl-3-(phenylthiocarbonyl)-A-ring-pyrrole-DUMA (8k): yield 78%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 12.00 (1 H, brs), 9.40 (1 H, s), 7.43−7.52 (5 H, m), 7.18 (1 H, s), 6.92 (1 H, d, J = 2.0 Hz), 6.81 (1 H, s), 4.42 (1 H, dd, J = 10.6, 4.6 Hz), 4.37 (1 H, d, J = 9.9 Hz), 4.07 (3 H, s), 3.94 (3 H, s), 3.89 (3 H, s), 3.57−3.63 (1 H, m), 2.94 (3 H, s), 2.28 (1 H, dd, J = 7.4, 3.5 Hz), 1.31 (1 H, dd, J = 4.6, 4.0 Hz); FAB-MS m/z 570 (M + H)$^+$; FAB-HRMS calcd for $C_{31}H_{28}N_3O_6S$ (M + H)$^+$ m/z 570.1699, found 570.1689; IR (KBr) 1647, 1630, 1479, 1427, 1396, 1385, 1304, 1263, 1228, 1109, 858 cm^{-1}. Anal. ($C_{31}H_{27}N_3O_6S$·0.8H_2O) C, H, N.

2-Methyl-3-(4-pyridinylthiocarbonyl)-A-ring-pyrrole-DUMA (8l): yield 64%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 12.38 (1 H, brs), 9.48 (1 H, brs), 8.65 (2 H, d, J = 5.0 Hz), 7.42 (2 H, d, J = 5.0 Hz), 7.21 (1 H, s), 6.91 (1 H, brs), 6.80 (1 H, s), 4.42 (2 H, br), 4.06 (3 H, s), 3.94 (3 H, s), 3.89 (3 H, s), 3.57 (1 H, m), 2.93 (3 H, s), 2.24 (1 H, dd, J = 7.4, 3.4 Hz), 1.32 (1 H, br); FAB-MS m/z 571 (M + H)$^+$; FAB-HRMS calcd for $C_{30}H_{27}N_4O_6S$ (M + H)$^+$ m/z 571.1651, found 571.1641; IR (KBr) 1626, 1606, 1579, 1481, 1427, 1385, 1306, 1265, 1228, 1107 cm^{-1}. Anal. ($C_{30}H_{26}N_4O_6S$· 0.6H_2O·0.4$CHCl_3$) C, H, N.

2-Methyl-3-(1-naphthalenylthiocarbonyl)-A-ring-pyrrole-DUMA (8m): yield 78%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 12.14 (1 H, brs), 9.45 (1 H, brs), 8.00 (1 H, brs), 7.79−7.88 (3 H, m), 7.47−7.56 (3 H, m), 7.20 (1 H, s), 6.90 (1 H, d, J = 2.0 Hz), 6.79 (1 H, s), 4.41 (1 H, dd, J = 10.2, 4.6 Hz), 4.35 (1 H, d, J = 9.9 Hz), 4.07 (3 H, s), 3.93 (3 H, s), 3.88 (3 H, s), 3.53−3.59 (1 H, m), 3.00 (3 H, s), 2.28 (1 H, dd, J = 7.6, 3.3 Hz), 1.30 (1 H, dd, J = 4.6, 3.6 Hz); FAB-MS m/z 620 (M + H)$^+$; IR (KBr) 1647, 1616, 1481, 1427, 1385, 1304, 1265, 1176, 1109, 858 cm^{-1}. Anal. ($C_{35}H_{29}N_3O_6S$·1.5H_2O) C, H, N.

2-Methyl-3-(benzylthiocarbonyl)-A-ring-pyrrole-DUMA (8n): yield 57%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 11.78 (1 H, brs), 9.39 (1 H, brs), 7.23−7.37 (5 H, m), 7.14 (1 H, s), 6.95 (1 H, d, J = 2.0 Hz), 6.81 (1 H, s), 4.42−4.51 (2 H, m), 4.26 (2 H, s), 4.07 (3 H s), 3.94 (3 H, s), 3.89 (3 H, s), 3.67−3.70 (1 H, br), 2.77 (3 H, s), 2.31 (1 H, dd, J = 7.6, 3.3 Hz), 1.35 (1 H, dd, J = 4.3, 4.0 Hz); FAB-MS m/z 584 (M + H)$^+$; IR (KBr) 1633, 1605, 1576, 1481, 1429, 1385, 1304, 1263, 1228, 1109 cm^{-1}. Anal. ($C_{32}H_{29}N_3O_6S$·0.7H_2O) C, H, N.

2-Methyl-3-(5-hydroxy-1,2-dithian-4-yloxycarbonyl)-A-ring-pyrrole-DUMA (8o): yield 71%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 6.91 (1 H, s), 6.87 (1 H, d, J = 0.7 Hz), 6.73 (1 H, s), 4.92−5.01 (1 H, m), 4.40 (1 H, dd, J = 10.2, 4.3 Hz), 4.34 (1 H, d, J = 10.2 Hz), 3.98 (1.5 H, s), 3.97 (1.5 H, s), 3.85 (1.5 H, s), 3.82 (1.5 H, s), 3.78−3.89 (1 H, m), 3.55−3.64 (1 H, m), 3.47 (3 H, s), 3.12−3.23 (2 H, m), 2.92−3.05 (2 H, m), 2.53 (3 H, s), 2.34 (0.5 H, dd, J = 7.8, 3.5 Hz), 2.25 (0.5 H, dd, J = 7.4, 3.5 Hz), 1.28−1.30 (1 H, m); FAB-MS m/z 612 (M + H)$^+$; FAB-HRMS calcd for $C_{29}H_{30}N_3O_8S$ (M + H)$^+$ m/z 612.1475, found 612.1475; IR (KBr) 3205, 2941, 1643, 1612, 1527, 1446, 1387, 1304, 1265, 1105 cm^{-1}. Anal. ($C_{29}H_{29}N_3O_8S_2$· 0.5H_2O) C, H, N.

2-Methyl-3-[2-(methylsulfonyl)ethoxycarbonyl]-A-ring-pyrrole-DUMA (8p): yield 61%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 11.46 (1 H, brs), 9.40 (1 H, brs), 7.11 (1 H, s), 6.87 (1 H, d, J = 2.3 Hz), 6.76 (1 H, s), 4.66−4.77 (2 H, m), 4.46 (1 H, dd, J = 10.6, 4.6 Hz), 4.42 (1 H, d, J = 10.6, Hz), 4.03 (3 H, s), 3.92 (3 H, s), 3.88 (3 H, s), 3.66−3.67 (1 H, m), 3.60 (1 H, brt, J = 6.1 Hz), 3.50 (1 H, brt, J = 5.8 Hz), 3.03 (3 H, s), 2.60 (3 H, s), 2.31 (1 H, dd, J = 7.4, 3.1 Hz), 1.32 (1 H, dd, J = 4.3, 4.0 Hz); FAB-MS m/z 584 (M + H)$^+$; IR (KBr) 1645, 1537, 1616, 1489, 1398, 1302, 1265, 1103 cm^{-1}. Anal. ($C_{28}H_{29}N_3O_9S$· 1.0H_2O) C, H, N.

2-Methyl-3-[*N*-(2-dimethylaminoethyl)carbamoyl]-A-ring-pyrrole-DUMC2 Hydrochloride (9h). A solution of **8h** (19 mg, 0.034 mmol) in CH_2Cl_2 (1.74 mL) was treated with 4 N HCl in AcOEt (0.026 mL) at room temperature for 30 min. The mixture was concentrated under reduced pressure to give 23 mg of **9h**: ^{1}H-NMR (270 MHz, DMSO-d_6) δ 11.45 (1 H, s), 11.32 (1 H, s), 10.16 (1 H, br), 9.98 (1 H, brs), 8.00 (1 H, t, J = 5.3 Hz), 7.66 (1 H, brs), 6.97 (1 H, s), 6.96 (1 H, s), 4.57 (1 H, dd, J = 10.9, 8.6 Hz), 4.35 (1 H, d, J = 11.2 Hz), 4.10−4.23 (1 H, m), 3.93 (3 H, s), 3.81 (3 H, s), 3.79 (3 H, s), 3.60−3.72 (3 H, m), 3.38 (1 H, dd, J = 9.9, 9.6 Hz), 3.13−3.33 (2 H, m), 2.84 (6 H, t, J = 5.3 Hz), 2.55 (3 H, s); IR (KBr) 1525, 1495, 1466, 1429, 1390, 1315, 1224, 1128, 1107, 1045 cm^{-1}. Anal. ($C_{29}H_{34}ClN_5O_6$·HCl·1.5H_2O) C, H; N: calcd, 10.82; found, 9.72.

2-Methyl-3-[(4-methyl-1-piperazinyl)carbonyl]-A-ring-pyrrole-DUMC2 hydrochloride (9i): ^{1}H-NMR (270 MHz, DMSO-d_6) δ 11.51 (1 H, s), 11.33 (1 H, brs), 10.88 (1 H, br), 10.01 (1 H, brs), 7.67 (1 H, brs), 6.96 (2 H, brs), 4.62 (1 H, dd, J = 10.2, 9.2 Hz), 4.33 (1 H, d, J = 11.2 Hz), 4.17−4.30 (1 H, m), 3.93 (3 H, s), 3.81 (3 H, s), 3.79 (3 H, s), 3.00−3.75 (10 H, br), 2.81 (3 H, brs), 2.42 (3 H, s); IR (KBr) 1612, 1495, 1466, 1427, 1390, 1315, 1223, 1117, 1047, 974 cm^{-1}. Anal. ($C_{30}H_{34}$-ClN_5O_6·HCl·4.0H_2O) C, H, N.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-A-ring-pyrrole-DUMB2 (10). A solution of **6** (138 mg, 0.205 mmol) in bromobenzene (11.4 mL) was stirred at reflux (165 °C) for 10

h. Then the resulting mixture was concentrated in vacuo. The residue was purified by PTLC (hexane−AcOEt, 2:1) to give 77 mg (60%) of **10**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.44 (1 H, brs), 7.90 (1 H, s), 7.83 (1 H, s), 6.95 (1 H, d, J = 2.4 Hz), 6.88 (1 H, s), 6.14 (1 H, q, J = 1.1 Hz), 4.85 (1 H, m), 4.50 (2 H, m), 4.06 (3 H, s), 3.94 (3 H, s), 3.91 (3 H, s), 3.90 (1 H, m), 3.38 (1 H, dd, J = 10.3, 10.3 Hz), 2.48 (3 H, s), 1.07 (9 H, s), 0.36 (6 H, s); EI-MS m/z 629, 627 $(M)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-chloro-A-ring-pyrrole-DUMB2 (11a). To a solution of **10** (150 mg, 0.239 mmol) in CH_2Cl_2 (6 mL) were added NCS (38.3 mg, 0.287 mmol) and silica gel (49.5 mg), and the mixture was stirred under darkness at room temperature for 3 h; 0.01 M phosphoric buffer (pH 7) was added, and the whole was extracted with $CHCl_3$ and then worked up as usual. The residue was purified by PTLC (hexane−AcOEt, 2:1) to give 113 mg (71%) of **11a**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.53 (1 H, brs), 8.12 (1 H, s), 7.89 (1 H, brs), 6.95 (1 H, d, J = 1.7 Hz), 6.88 (1 H, s), 4.72 (1 H, d, J = 10.6 Hz), 4.54 (1 H, dd, J = 10.6, 8.6 Hz), 4.16−4.25 (1 H, m), 4.04 (3 H, s), 3.97 (1 H, dd, J = 10.2, 3.0 Hz), 3.93 (3 H, s), 3.90 (3 H, s), 3.30 (1 H, dd, J = 10.2, 10.2 Hz), 2.42 (3 H, s), 1.05 (9 H, s), 0.35 (6 H, s); FAB-MS m/z 664, 662 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethysilyl)-2-methyl-3-bromo-A-ring-pyrrole-DUMB2 (11b): yield 62%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.46 (1 H, brs), 8.10 (1 H, s), 7.87 (1 H, brs), 6.97 (1 H, d, J = 2.3 Hz), 6.89 (1 H, s), 4.75 (1 H, d, J = 10.9 Hz), 4.56 (1 H, dd, J = 10.2, 8.9 Hz), 4.27−4.33 (1 H, m), 4.06 (3 H, s), 4.01 (1 H, dd, J = 10.2, 2.6 Hz), 3.94 (3 H, s), 3.92 (3 H, s), 3.27 (1 H, dd, J = 10.6, 10.2 Hz), 2.45 (3 H, s), 1.06 (9 H, s), 0.36 (3 H, s), 0.35 (3 H, s); FAB-MS m/z 710, 708, 706 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-iodo-A-ring-pyrrole-DUMB2 (11c): yield 47%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.48 (1 H, brs), 8.33 (1 H, brs), 7.88 (1 H, brs), 6.96 (1 H, d, J = 2.3 Hz), 6.89 (1 H, s), 4.76 (1 H, d, J = 10.9 Hz), 4.55 (1 H, dd, J = 10.6, 8.3 Hz), 4.37−4.43 (1 H, m), 4.05 (3 H, s), 4.02 (1 H, dd, J = 10.9, 1.8 Hz), 3.94 (3 H, s), 3.91 (3 H, s), 3.22 (1 H, dd, J = 10.9, 10.2 Hz), 2.48 (3 H, s), 1.05 (9 H, s), 0.36 (3 H, s), 0.35 (3 H, s); FAB-MS m/z 755, 753 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-acetyl-A-ring-pyrrole-DUMB2 (11d). To a solution of **6** (15 mg, 0.024 mmol) in CH_2Cl_2 (0.8 mL) were added Ac_2O (0.0068 mL, 0.072 mmol) and BF_3−Et_2O (0.0088 mL, 0.072 mmol), and the mixture was stirred at room temperature for 14 h 40 min. Aqueous $NaHCO_3$ was added, and the whole was extracted with $CHCl_3$ and then worked up as usual. The residue was purified by PTLC (hexane−AcOEt, 1:1) to give 7.6 mg (47%) of **11d**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.46 (1 H, brs), 8.50 (1 H, brs), 8.02 (1 H, s), 6.99 (1 H, d, J = 1.3 Hz), 6.88 (1 H, s), 4.70 (1 H, d, J = 9.9 Hz), 4.65−4.75 (1 H, br), 4.51 (1 H, dd, J = 9.9, 9.6 Hz), 4.05 (3 H, s), 3.93 (3 H, s), 3.91 (3 H, s), 3.74 (1 H, dd, J = 9.2, 2.6 Hz), 3.18 (1 H, dd, J = 9.6, 9.6 Hz), 2.77 (3 H, s), 2.56 (3 H, s), 1.05 (9 H, s), 0.37 (3 H, s), 0.36 (3 H, s); FAB-MS m/z 672, 670 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-butyryl-A-ring-pyrrole-DUMB2 (11e): yield 47%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.43 (1 H, brs), 8.28 (1 H, brs), 8.02 (1 H, s), 7.00 (1 H, s), 6.89 (1 H, s), 4.71−4.77 (1 H, m), 4.69 (1 H, d, J = 10.2 Hz), 4.54 (1 H, dd, J = 10.2, 8.9 Hz), 4.06 (3 H, s), 3.94 (3 H, s), 3.92 (3 H, s), 3.64 (1 H, dd, J = 9.6, 3.0 Hz), 3.17 (1 H, dd, J = 9.9, 9.6 Hz), 2.83 (2 H, t, J = 7.4), 2.77 (3 H, s), 1.83 (2 H, tq, J = 7.3, 7.3 Hz), 1.06 (9 H, s), 1.04 (3 H, t, J = 7.6 Hz), 0.38 (3 H, s), 0.36 (3 H, s); FAB-MS m/z 700, 698 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-benzoyl-A-ring-pyrrole-DUMB2 (11f): yield 51%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.54 (1 H, brs), 8.43 (1 H, brs), 8.04 (1 H, brs), 7.78 (2 H, d, J = 6.9 Hz), 7.56−7.58 (1 H, m), 7.48 (2 H, dd, J = 7.6, 6.9 Hz), 6.96 (1 H, d, J = 2.0 Hz), 6.86 (1 H, s), 4.58 (1 H, dd, J = 10.6, 2.3 Hz), 4.50 (1 H, dd, J = 10.6, 8.6 Hz), 4.06 (3 H, s), 3.94 (3 H, s), 3.90 (3 H, s), 3.87−3.93 (1 H, m), 3.51 (1 H, dd, J = 10.1, 3.1 Hz), 3.11 (1 H, dd, J = 9.9, 9.9 Hz), 2.27 (3 H, s), 1.07 (9 H, s), 0.41 (3 H, s), 0.39 (3 H, s); FAB-MS m/z 734, 732 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-(dimethylaminomethyl)-A-ring-pyrrole-DUMB2 (11g). $Me_2NCH_2NMe_2$ (0.0434 mL, 0.318 mmol) was added to TFA (1 mL), and the mixture was stirred under Ar atmosphere at −10 °C for 20 min. Then, **27** (40 mg, 0.064 mmol) was added, and stirring was continued at −10 °C for 50 min. Aqueous $NaHCO_3$ was added, and the whole was extracted with $CHCl_3$ and then worked up as usual. The residue was purified by PTLC ($CHCl_3$−MeOH, 8:1) to give 31.1 mg (71%) of **11g**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.47 (1 H, s), 7.89 (1 H, brs), 7.82 (1 H, brs), 6.95 (1 H, d, J = 2.0 Hz), 6.87 (1 H, s), 4.71 (1 H, d, J = 10.9 Hz), 4.53 (1 H, dd, J = 9.9, 8.3 Hz), 4.16−4.27 (2 H, m), 4.05 (3 H, s), 3.93 (3 H, s), 3.91 (3 H, s), 3.58 (1 H, d, J = 13.2 Hz), 3.36 (1 H, d, J = 13.2 Hz), 3.20 (1 H, dd, J = 10.6, 10.2 Hz), 2.42 (3 H, s), 2.29 (6 H, s), 1.06 (9 H, s), 0.36 (3 H, s), 0.34 (3 H, s); FAB-MS m/z 687, 685 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-formyl-A-ring-pyrrole-DUMB2 (11h). To a solution of **10** (905 mg, 1.44 mmol) in DMF (36 mL) was added $POCl_3$, (0.161 mL, 1.73 mmol), and the mixture was stirred at room temperature for 1 h 15 min; 0.01 M phosphoric buffer (pH 7) was added, and the whole was extracted with AcOEt and then worked up as usual. The residue was purified by column chromatography (hexane−AcOEt, 3:1−1:1) to give 808 mg (85%) of **11h**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 10.06 (1 H, s), 9.43 (1 H, brs), 8.56 (1 H, s), 8.02 (1 H, s), 7.00 (1 H, d, J = 2.3 Hz), 6.89 (1 H, s), 4.69−4.75 (1 H, m), 4.54−4.58 (2 H, m), 4.06 (3 H, s), 3.94 (3 H, s), 3.92 (3 H, s), 3.80 (1 H, brd, J = 9.2 Hz), 3.27 (1 H, dd, J = 9.2, 9.2 Hz), 2.77 (3 H, s), 1.06 (9 H, s), 0.39 (3 H, s), 0.37 (3 H, s); FAB-MS m/z 658, 656 $(M + H)^+$.

8-*O*-(*tert*-Butyldiethylsilyl)-2-methyl-3-(1,3-dithianyl)-A-ring-pyrrole-DUMB2 (11i). To a solution of **11h** (70 mg, 0.11 mmol) in THF (2.8 mL) were added 1,3-propanedithiol (0.0215 mL, 0.214 mmol) and Amberlyst-15 (12 mg), and then the mixture was stirred at room temperature for 17 h. After addition of 1,3-propanedithiol (0.0215 mL, 0.214 mmol) and Amberlyst-15 (12 mg), the mixture was stirred for 5 h 15 min. Aqueous $NaHCO_3$ was added, and the whole was extracted with $CHCl_3$ and then worked up as usual. The residue was purified by column chromatography (hexane−AcOEt, 4:1) to give 52 mg (65%) of **11i:** ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.44 (1 H, brs), 7.94 (1 H, s), 7.82 (1 H, brs), 6.96 (1 H, d, J = 2.0 Hz), 6.89 (1 H, s), 5.58 (1 H, s), 4.71 (1 H, d, J = 10.9 Hz), 4.59 (1 H, dd, J = 10.6, 7.9 Hz), 4.28 (1 H, br), 4.60−4.12 (1 H, m), 4.06 (3 H, s), 3.94 (3 H, s), 3.92 (3 H, s), 3.25 (1 H, dd, J = 10.9, 10.9 Hz), 3.10−3.19 (2 H, td, J = 12.5, 1.0 Hz), 2.94 (2 H, dd, J = 13.9, 1.0 Hz), 2.70 (3 H, s), 2.21 (1 H, brd, J = 13.9 Hz), 1.92−2.02 (1 H, m), 1.05 (9 H, s), 0.36 (3 H, s), 0.34 (3 H, s); FAB-MS m/z 748, 746 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-(hydroxyiminomethyl)-A-ring-pyrrole-DUMB2 (11j). To a solution of **11h** (25 mg, 0.038 mmol) in ethanol (1 mL) was added hydroxyamine hydrochloric acid (5.3 mg, 0.076 mmol), and then the mixture was stirred at room temperature for 1 h 40 min. After addition of hydroxyamine hydrochloric acid (5.3 mg, 0.076 mmol), the mixture was stirred for 15 h; 0.01 M phosphoric buffer (pH 7) was added, and the whole was extracted with $CHCl_3$ and then worked up as usual. The residue was purified by PTLC (hexane−AcOEt, 1:1) to give 15 mg (57%) of **11j**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.46 (1 H, brs), 8.34 (1 H, s), 8.16 (1 H, brs), 7.95 (1 H, brs), 7.20 (1 H, br), 6.97 (1 H, d, J = 2.0 Hz), 6.88 (1 H, s), 4.72 (1 H, d, J = 9.9 Hz), 4.45 (1 H, dd, J = 10.9, 9.9 Hz), 4.41−4.52 (1 H, m), 4.05 (3 H, s), 3.95 (1 H, br), 3.94 (3 H, s), 3.91 (3 H, s), 3.29 (1 H, dd, J = 10.2, 9.9 Hz), 2.53 (3 H, s), 1.06 (9 H, s), 0.37 (3 H, s), 0.36 (3 H, s); FAB-MS m/z 673, 671 $(M + H)^+$.

8-*O*-(*tert*-Butyldimethylsilyl)-2-methyl-3-(methoxyiminomethyl)-A-ring-pyrrole-DUMB2 (11k): yield 87%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.46 (1 H, brs), 8.29 (1 H, d, J = 1.0 Hz), 8.20 (1 H, brs), 7.97 (1 H, brs), 6.99 (1 H, d, J = 1.6 Hz), 6.88 (1 H, s), 4.78 (1 H, d, J = 9.9 Hz), 4.57−4.62 (1 H, m), 4.53 (1 H, dd, J = 9.9, 8.6 Hz), 4.07 (3 H, s), 4.06 (3 H, d, J = 1.0 Hz), 3.94 (3 H, s), 3.92 (3 H, s), 3.90 (1 H, dd, J = 10.2, 2.3

Hz), 3.17 (1 H, dd, J = 10.2, 9.9 Hz), 2.51 (3 H, s), 1.06 (9 H, s), 0.38 (3 H, s), 0.36 (3 H, s); FAB-MS m/z 687, 685 $(M + H)^+$.

The synthesis of compounds **12a**−**12k** was performed according to the same procedure as for **8a**.

2-Methyl-3-chloro-A-ring-pyrrole-DUMA (12a): yield 78%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 11.59 (1 H, brs), 9.55 (1 H, brs), 7.00 (1 H, s), 6.93 (1 H, s), 6.78 (1 H, s), 4.43 (2 H, m), 4.05 (3 H, s), 3.93 (3 H, s), 3.88 (3 H, s), 3.14 (1 H, br), 2.33 (3 H, s), 2.28 (1 H, dd, J = 7.6, 4.3 Hz), 1.35 (1 H, dd, J = 4.6, 4.0 Hz); FAB-MS m/z 468 $(M + H)^+$; FAB-HRMS calcd for $C_{24}H_{23}ClN_3O_5$ $(M + H)^+$ m/z 468.1326, found 468.1328; IR (KBr) 1637, 1608, 1581, 1527, 1473, 1385, 1304, 1265, 1105 cm^{-1}. Anal. ($C_{24}H_{22}ClN_3O_5 \cdot 1.0H_2O$) C, H; N: calcd, 8.65; found, 8.04.

2-Methyl-3-bromo-A-ring-pyrrole-DUMA (12b): yield 78%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 6.87 (1 H, s), 6.85 (1 H, s), 6.74 (1 H, s), 4.33−4.42 (2 H, m), 4.00 (3 H, s), 3.87 (3 H, s), 3.82 (3 H, s), 3.19 (1 H, m), 2.30 (1 H, dd, J = 7.4, 4.1 Hz), 2.25 (3 H, s), 1.31 (1 H, dd, J = 4.6, 4.6 Hz); FAB-MS m/z 514, 512 $(M + H)^+$; FAB-HRMS calcd for $C_{24}H_{23}{}^{79}BrN_3O_5$ $(M + H)^+$ m/z 512.0821, found 512.0840; IR (KBr) 1633, 1608, 1581, 1470, 1387, 1304, 1263, 1111, 1051 cm^{-1}. Anal. ($C_{24}H_{22}BrN_3O_5 \cdot 0.5H_2O$) C, H; N: calcd, 8.05; found, 7.45.

2-Methyl-3-iodo-A-ring-pyrrole-DUMA (12c): yield 83%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 11.66 (1 H, s), 9.50 (1 H, s), 7.02 (1 H, s), 6.94 (1 H, d, J = 1.7 Hz), 6.79 (1 H, s), 4.39−4.51 (2 H, m), 4.06 (3 H, s), 3.93 (3 H, s), 3.89 (3 H, s), 3.36 (1 H, m), 2.37 (3 H, s), 2.30−2.45 (1 H, br), 1.32 (1 H, dd, J = 4.6, 4.6 Hz); FAB-MS m/z 560 $(M + H)^+$; FAB-HRMS calcd for $C_{24}H_{23}IN_3O_5$ $(M + H)^+$ m/z 560.0682, found 560.0673; IR (KBr) 1633, 1605, 1581, 1466, 1385, 1304, 1261, 1109, 1039 cm^{-1}. Anal. ($C_{24}H_{22}IN_3O_5$) C, H, N.

2-Methyl-3-acetyl-A-ring-pyrrole-DUMA (12d): yield 70%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 6.97 (1 H, s), 6.88 (1 H, s), 6.75 (1 H, s), 4.37 (2 H, m), 3.99 (3 H, s), 3.86 (3 H, s), 3.82 (3 H, s), 3.65−3.75 (1 H, m), 2.59 (3 H, s), 2.38 (3 H, s), 2.29 (1 H, dd, J = 7.4, 3.1 Hz), 1.23 (1 H, dd, J = 4.6, 3.6 Hz); FAB-MS m/z 476 $(M + H)^+$; IR (KBr) 1649, 1603, 1483, 1460, 1387, 1302, 1265, 1228, 1109 cm^{-1}. Anal. ($C_{26}H_{25}N_3O_6 \cdot 0.5H_2O$) C, H, N.

2-Methyl-3-butyryl-A-ring-pyrrole-DUMA (12e): yield 63%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 12.10 (1 H, brs), 9.44 (1 H, brs), 7.18 (1 H, s), 6.95 (1 H, d, J = 2.0 Hz), 6.82 (1 H, s), 4.45 (2 H, br), 4.07 (3 H, s), 3.94 (3 H, s), 3.89 (3 H, s), 3.83 (1 H, m), 2.74 (3 H, s), 2.67 (2 H, t, J = 7.1 Hz), 2.33 (1 H, dd, J = 7.3, 3.3 Hz), 1.68 (2 H, tq, J = 7.6, 7.3 Hz), 1.28 (1 H, dd, J = 4.6, 3.6 Hz), 0.96 (3 H, t, J = 7.4 Hz); FAB-MS m/z 504 $(M + H)^+$; IR (KBr) 1647, 1618, 1605, 1439, 1396, 1385, 1303, 1265, 1230, 1109 cm^{-1}. Anal. ($C_{28}H_{29}N_3O_6 \cdot 0.6H_2O$) C, H, N.

2-Methyl-3-benzoyl-A-ring-pyrrole-DUMA (12f): yield 40%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 11.96 (1 H, brs), 9.45 (1 H, brs), 7.68 (2 H, d, J = 7.6 Hz), 7.54−7.59 (1 H, m), 7.46 (2 H, dd, J = 7.9, 6.9 Hz), 7.14 (1 H, s), 6.95 (1 H, s), 6.80 (1 H, s), 4.50 (1 H, dd, J = 10.4, 4.5 Hz), 4.43 (1 H, d, J = 10.2 Hz), 4.06 (3 H, s), 3.93 (3 H, s), 3.88 (3 H, s), 3.50−3.52 (1 H, m), 2.19 (1 H, dd J = 7.4, 3.5 Hz), 2.09 (3 H, s), 1.41 (1 H, dd, J = 4.0, 4.0 Hz); FAB-MS m/z 538 $(M + H)^+$; IR (KBr) 1641, 1614, 1601, 1470, 1385, 1302, 1263, 1230, 1107 cm^{-1}. Anal. ($C_{31}H_{27}N_3O_6 \cdot 1.5H_2O$) C, H, N.

2-Methyl-3-(dimethylaminomethyl)-A-ring-pyrrole-DUMA (12g): yield 55%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.88 (1 H, brs), 9.30 (1 H, brs), 6.95 (1 H, s), 6.93 (1 H, d, J = 2.3 Hz), 6.78 (1 H, s), 4.41 (1 H, dd, J = 10.4, 4.5 Hz), 4.35 (1 H, d, J = 10.2 Hz), 4.07 (3 H, s), 3.93 (3 H, s), 3.89 (3 H, s), 3.18−3.22 (1 H, m), 3.13 (1 H, d, J = 13.5 Hz), 3.07 (1 H, d, J = 13.5 Hz), 2.48 (1 H, dd, J = 7.4, 3.8 Hz), 2.31 (3 H, s), 2.17 (6 H, s), 1.31 (1 H, dd, J = 4.6, 4.3 Hz); FAB-MS m/z 491 $(M + H)^+$; IR (KBr) 1641, 1610, 1579, 1527, 1468, 1427, 1396, 1385, 1304, 1263, 1155, 1109 cm^{-1}. Anal. ($C_{27}H_{30}N_4O_5 \cdot 1.0H_2O$) C, H; N: calcd, 11.02; found, 10.25.

2-Methyl-3-formyl-A-ring-pyrrole-DUMA (12h): yield 72%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 12.27 (1 H, brs), 9.83 (1 H, s), 9.47 (1 H, brs), 7.17 (1 H, s), 6.96 (1 H, d, J = 2.4 Hz), 6.82 (1 H, s), 4.48 (2 H, br), 4.07 (3 H, s), 3.94 (3 H, s), 3.90 (3 H, s), 3.65 (1 H, m), 2.70 (3 H, s), 2.36 (1 H, dd, J = 9.0, 3.3 Hz), 1.38 (1 H, dd, J = 4.3, 4.1 Hz); FAB-MS m/z 462 $(M + H)^+$; FAB-HRMS calcd for $C_{25}H_{24}N_3O_6$ $(M + H)^+$ m/z 462.1665, found 462.1649; IR (KBr) 1647, 1610, 1585, 1527, 1487, 1468, 1387, 1265, 1228, 1109 cm^{-1}. Anal. ($C_{25}H_{23}N_3O_6 \cdot 1.0H_2O$) C, H, N.

2-Methyl-3-(1,3-dithianyl)-A-ring-pyrrole-DUMA (12i): yield 78%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 10.81 (1 H, brs), 9.42 (1 H, brs), 6.99 (1 H, s), 6.93 (1 H, d, J = 2.3 Hz), 6.80 (1 H, s), 5.04 (1 H, s), 4.47 (1 H, dd, J = 10.2, 4.3 Hz), 4.40 (1 H, d, J = 10.2 Hz), 4.06 (3 H, s), 3.93 (3 H, s), 3.90 (3 H, s), 3.36 (1 H, br), 3.01 (2 H, td, J = 12.2, 0.8 Hz), 2.87 (2 H, dd, J = 12.0, 0.8 Hz), 2.55 (3 H, s), 2.31 (1 H, br), 2.16 (1 H, brd, J = 14.2 Hz), 1.85−1.94 (1 H, m), 1.43 (1 H, dd, J = 4.6, 4.6 Hz); FAB-MS m/z 552 $(M + H)^+$; IR (KBr) 1637, 1618, 1579, 1527, 1466, 1396, 1383, 1304, 1261, 1109 cm^{-1}. Anal. ($C_{28}H_{29}N_3O_5S$) C, H, N.

2-Methyl-3-(hydroxyiminomethyl)-A-ring-pyrrole-DUMA (12j): yield 94%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 7.96 (1 H, s), 6.87 (1 H, s), 6.85 (1 H, s), 6.72 (1 H, s), 4.34 (1 H, dd, J = 10.2, 4.3 Hz), 4.28 (1 H, d, J = 10.2 Hz), 3.97 (3 H, s), 3.84 (3 H, s), 3.80 (3 H, s), 3.43−3.49 (1 H, m), 2.34 (1 H, dd, J = 7.6, 3.3 Hz), 2.31 (3 H, s), 1.19 (1 H, dd, J = 4.6, 4.0 Hz); FAB-MS m/z 477 $(M + H)^+$; FAB-HRMS calcd for $C_{25}H_{25}N_4O_6$ $(M + H)^+$ m/z 477.1774, found 477.1767; IR (KBr) 3463, 1579, 1527, 1491, 1468, 1425, 1385, 1306, 1263, 1198, 1109 cm^{-1}. Anal. ($C_{25}H_{24}N_4O_6 \cdot 0.7H_2O \cdot 0.2CHCl_3$) C, H; N: calcd, 10.92; found, 10.32.

2-Methyl-3-(methoxyiminomethyl)-A-ring-pyrrole-DUMA (12k): yield 90%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 11.74 (1 H, s), 9.55 (1 H, s), 8.01 (1 H, s), 7.09 (1 H, s), 6.94 (1 H, d, J = 2.0 Hz), 6.78 (1 H, s), 4.40−4.44 (2 H, m), 4.06 (3 H, s), 3.93 (3 H, s), 3.92 (3 H, s), 3.89 (3 H, s), 3.60−3.67 (1 H, m), 2.48 (1 H, dd, J = 7.4, 3.5 Hz), 2.42 (3 H, s), 1.27 (1 H, dd, J = 4.0, 3.7 Hz); FAB-MS m/z 491 $(M + H)^+$; IR (KBr) 1603, 1583, 1527, 1489, 1466, 1385, 1306, 1263, 1109, 1051 cm^{-1}. Anal. ($C_{26}H_{26}N_4O_6 \cdot 0.8H_2O$) C, H; N: calcd, 11.10; found, 10.38.

The synthesis of compound **13** was performed according to the same procedure as for **9h**.

2-Methyl-3-(dimethylaminomethyl)-A-ring-pyrrole-DUMC2 hydrochloride (13): ^{1}H-NMR (270 MHz, DMSO-d_6) δ 11.50 (1 H, brs), 11.38 (1 H, brs), 10.01 (1 H, s), 9.61 (1 H, br), 7.62 (1 H, br), 6.98 (1 H, s), 6.96 (1 H, s), 4.57 (1 H, dd, J = 10.6, 7.3 Hz), 4.45 (1 H, d, J = 11.2 Hz), 4.38−4.46 (1 H, m), 4.11−4.16 (1 H, m), 3.95−4.04 (1 H, m), 3.92 (3 H, s), 3.83−3.88 (1 H, br), 3.82 (3 H, s), 3.79 (3 H, s), 3.51 (1 H, dd, J = 9.6, 9.5 Hz), 2.81 (3 H, d, J = 4.3 Hz), 2.71 (3 H, d, J = 3.6 Hz), 2.46 (3 H, s); IR (KBr) 1637, 1608, 1527, 1495, 1466, 1427, 1390, 1315, 1223, 1107, 1047 cm^{-1}. Anal. ($C_{27}H_{31}ClN_4O_5 \cdot HCl \cdot 1.0H_2O$) C, H; N: calcd, 9.63; found, 8.76.

2-Methyl-A-ring-pyrrole-DUM-Seg-A (14a). To a solution of **10** (600 mg, 0.954 mmol) in THF (40.9 mL) was added ^{n}Bu$_4$NF (1.0 M in THF, 3.17 mL, 2.86 mmol), and then the mixture was stirred at room temperature for 30 min. The mixture was concentrated under reduced pressure, and NaOMe (28 wt % in MeOH, 0.551 mL) was added to a solution of the residue in MeOH (40.9 mL). After the mixture stirred at room temperature for 60 min, 0.01 M phosphoric buffer (pH 7) was added, and the whole was extracted with $CHCl_3$ and then worked up as usual. The residue was purified by column chromatography ($CHCl_3$−MeOH, 40:1−20:1) to give 170 mg (89%) of **14a:** ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 5.60 (1 H, s), 5.41 (1 H, s), 3.77 (1 H, dd, J = 10.9, 5.3 Hz), 3.59 (1 H, d, J = 9.2 Hz), 2.73−2.80 (1 H, m), 2.32 (3 H, s), 1.58 (1 H, dd, J = 7.9, 3.6 Hz), 1.28 (1 H, dd, J = 5.0, 3.6 Hz); FAB-MS m/z 201 $(M + H)^+$.

2-Methyl-3-(allyloxylcarbonyl)-A-ring-pyrrole-DUM-Seg-A (14b): yield 74%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 5.93 (1 H, ddt, J = 19.6, 10.6, 5.6 Hz), 5.36 (1 H, s), 5.28 (1 H, ddd, J = 17.3, 1.7, 1.3 Hz), 5.19 (1 H, ddd, J = 10.4, 1.3, 1.0 Hz), 4.63 (1 H, brd, J = 5.9 Hz), 3.68 (1H, dd, J = 10.9, 5.6 Hz), 3.53 (1 H, d, J = 10.9 Hz), 3.44−3.50 (1 H, m),

2.47 (3 H, s), 2.08 (1 H, dd, J = 7.9, 3.0 Hz), 1.02 (1 H, dd, J = 4.8, 3.1 Hz); FAB-MS m/z 285 $(M + H)^+$.

2,3-Dimethyl-A-ring-pyrrole-DUM-Seg-A (14c): yield 77%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 5.38 (1 H, s), 3.69 (1 H, dd, J = 10.6, 5.3 Hz), 3.54 (1 H, d, J = 10.6 Hz), 3.39 (3 H, s), 2.88−2.94 (1 H, m), 2.16 (3 H, s), 1.82 (3 H, s), 1.78 (1 H, dd, J = 7.6, 3.6 Hz), 1.06 (1 H, dd, J = 4.6, 4.0 Hz); FAB-MS m/z 215 $(M + H)^+$.

2-Methyl-3-formyl-A-ring-pyrrole-DUM-Seg-A(14d): yield 48%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 12.43 (1 H, brs), 9.71 (1 H, s), 5.94 (1 H, brs), 5.60 (1 H, s), 3.75 (1 H, dd, J = 10.1, 5.4 Hz), 3.57 (1 H, d, J = 10.6 Hz), 3.45−3.47 (1 H, m), 2.55 (3 H, s), 2.09 (1 H, dd, J = 7.6, 2.6 Hz), 1.07 (1 H, dd, J = 4.7, 4.3 Hz); FAB-MS m/z 229 $(M + H)^+$.

2-Methyl-3-chloro-A-ring-pyrrole-DUM-Seg-A(14e): yield 95%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 5.35 (1 H, s), 3.69 (1 H, dd, J = 10.9, 5.3 Hz), 3.54 (1 H, d, J = 10.9 Hz), 3.03−3.10 (1 H, m), 2.18 (3 H, s), 2.02 (1 H, dd, J = 7.8, 3.5 Hz), 1.04 (1 H, dd, J = 4.3, 4.3 Hz); FAB-MS m/z 235 $(M + H)^+$.

2-Methyl-3-bromo-A-ring-pyrrole-DUM-Seg-A (14f): yield 92%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 5.37 (1 H, s), 3.71 (1 H, dd, J = 10.7, 5.4 Hz), 3.56 (1 H, d, J = 10.9 Hz), 3.12−3.19 (1 H, m), 2.21 (3 H, s), 2.09 (1 H, dd, J = 7.9, 3.6 Hz), 1.05 (1 H, dd, J = 4.6, 4.0 Hz); FAB-MS m/z 281, 279 $(M + H)^+$.

2-Methyl-3-iodo-A-ring-pyrrole-DUM-Seg-A (14g): yield 70%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 5.36 (1 H, s), 3.71 (1 H, dd, J = 10.9, 5.3 Hz), 3.56 (1 H, d, J = 10.6 Hz), 3.25−3.31 (1 H, m), 2.22 (3 H, s), 2.12 (1 H, dd, J = 7.6, 3.6 Hz), 1.02 (1 H, dd, J = 4.3, 4.3 Hz); FAB-MS m/z 327 $(M + H)^+$.

2-Methyl-3-acetyl-A-ring-pyrrole-DUM-Seg-A(14h): yield 69%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 5.38 (1 H, s), 3.66 (1 H, dd, J = 10.6, 5.3 Hz), 3.57−3.62 (1 H, m), 3.52 (1 H, d, J = 10.6 Hz), 2.52 (3 H, s), 2.33 (3 H, s), 2.08 (1 H, dd, J = 7.6, 2.6 Hz), 0.94 (1 H, dd, J = 4.5, 2.8 Hz); FAB-MS m/z 243 $(M + H)^+$.

4′-Methoxycinnamoyl 2-Methyl-A-ring-pyrrole-DUM (15a). To a solution of 60% NaH (6.0 mg, 0.15 mmol) in DMF (0.36 mL) was added a DMF solution (0.48 mL) of **14a** (25 mg, 0.12 mmol), and the mixture was stirred under Ar atmosphere at −20 °C for 2 h. Then, a solution of the *p*-nitrophenyl ester of 4-methoxycinnamic acid (41 mg, 0.14 mmol) in DMF (0.48 mL) was added and stirred for 50 min; 0.01 M phosphoric buffer (pH 7) was added, and the whole was extracted with AcOEt and then worked up as usual. The residue was purified by column chromatography ($CHCl_3$−MeOH, 100:1) to give 40 mg (89%) of **15a**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ 9.44 (1 H, brs), 7.76 (1 H, d, J = 15.5 Hz), 7.52 (2 H, d, J = 8.6 Hz), 6.91 (2 H, d, J = 8.6 Hz), 6.79 (1 H, d, J = 15.5 Hz), 6.41 (1 H, br), 5.67 (1 H, d, J = 1.7 Hz), 4.22 (1 H, d, J = 11.6 Hz), 4.10 (1 H, dd, J = 11.2, 5.0 Hz), 3.85 (3 H, s), 2.58−2.62 (1 H, m), 2.36 (3 H, s), 1.71 (1 H, dd, J = 7.8, 4.1 Hz), 1.47 (1 H, dd, J = 4.6, 4.6 Hz); FAB-MS m/z 361 $(M + H)^+$; IR (KBr) 1666, 1601, 1574, 1510, 1479, 1242, 1227, 1173 cm^{-1}. Anal. ($C_{22}H_{20}N_2O_3$) C, H, N.

4′-Methoxycinnamoyl 2-methyl-3-(allyloxylcarbonyl)-A-ring-pyrrole-DUM (15b): yield 80%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 7.70 (1 H, d, J = 15.5 Hz), 7.47 (2 H, d, J = 8.9 Hz), 6.86 (2 H, d, J = 8.9 Hz), 6.67 (1 H, d, J = 15.2 Hz), 6.62 (1 H, br), 5.96 (1 H, ddt, J = 19.5, 10.2, 5.6 Hz), 5.32 (1 H, ddd, J = 17.3, 1.7, 1.3 Hz), 5.23 (1 H, ddd, J = 10.4, 1.3, 1.0 Hz), 4.67 (2 H, dt, J = 5.6, 1.3 Hz), 4.18 (1 H, d, J = 10.9 Hz), 4.09 (1 H, dd, J = 10.9, 4.6 Hz), 3.49−3.56 (1 H, m), 2.54 (3 H, s), 2.34 (1 H, dd, J = 7.6, 3.3 Hz), 1.26 (1 H, dd, J = 5.0, 3.6 Hz); FAB-MS m/z 445 $(M + H)^+$; IR (KBr) 1554, 1512, 1489, 1390, 1292, 1242, 1225, 1173, 1111, 1072 cm^{-1}. Anal. ($C_{26}H_{24}N_2O_5 \cdot 1.0H_2O$) C, H, N.

4′-Methoxycinnamoyl 2,3-dimethyl-A-ring-pyrrole-DUM (15c): yield 51%; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 10.30 (1 H, brs), 7.75 (1 H, d, J = 15.2 Hz), 7.51 (2 H, d, J = 8.6 Hz), 6.90 (2 H, d, J = 8.9 Hz), 6.79 (1 H, d, J = 15.5 Hz), 6.43 (1 H, br), 4.24 (1 H, d, J = 11.2 Hz), 4.10 (1 H, dd, J = 11.2, 4.6 Hz), 3.84 (3 H, s), 2.26 (3 H, s), 2.01 (1 H, dd, J = 6.9, 4.6 Hz), 1.92 (3 H, s), 1.29 (1 H, dd, J = 4.6, 4.6 Hz); FAB-MS m/z 375 $(M + H)^+$; FAB-HRMS calcd for $C_{23}H_{23}N_2O_3$ $(M + H)^+$ m/z 375.1708, found 375.1703; IR (KBr) 1664, 1618, 1603, 1572, 1560, 1512, 1468, 1390, 1281, 1240, 1173 cm^{-1}. Anal. ($C_{23}H_{22}N_2O_3 \cdot 0.3H_2O$) C, H, N.

4′-Methoxycinnamoyl 2-methyl-3-formyl-A-ring-pyrrole-DUM (15d): yield 38%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 9.66 (1 H, s), 7.62 (1 H, d, J = 15.2 Hz), 7.41 (2 H, d, J = 8.6 Hz), 6.79 (2 H, d, J = 8.9 Hz), 6.60 (1 H, d, J = 15.5 Hz), 4.13 (1 H, d, J = 10.9 Hz), 4.04 (1 H, dd, J = 10.9, 4.6 Hz), 3.72 (3 H, s), 3.37−3.43 (1 H, m), 2.49 (3 H, s), 2.24 (1 H, dd, J = 7.6, 3.6 Hz), 1.22 (1 H, dd, J = 5.0, 3.6 Hz); FAB-MS m/z 389 $(M + H)^+$; IR (KBr) 1664, 1601, 1578, 1512, 1479, 1394, 1390, 1242, 1173 cm^{-1}. Anal. ($C_{23}H_{20}N_2O_4 \cdot 0.6H_2O$) C, H, N.

4′-Methoxycinnamoyl 2-methyl-3-chloro-A-ring-pyrrole-DUM (15e): yield 41%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 7.66 (1 H, d, J = 15.5 Hz), 7.44 (2 H, d, J = 8.3 Hz), 6.83 (2 H, d, J = 8.3 Hz), 6.65 (1 H, d, J = 15.2 Hz), 6.45 (1 H, br), 4.17 (1 H, d, J = 11.2 Hz), 4.06 (1 H, dd, J = 11.1, 4.8 Hz), 3.76 (3 H, s), 2.96−3.09 (1 H, m), 2.25 (1 H, dd, J = 7.6, 4.3 Hz), 2.21 (3 H, s), 1.24 (1 H, dd, J = 4.6, 4.3 Hz); FAB-MS m/z 395 $(M + H)^+$; IR (KBr) 1601, 1574, 1512, 1475, 1392, 1286, 1240, 1225, 1171, 1061 cm^{-1}. Anal. ($C_{22}H_{19}ClN_2O_3 \cdot 0.8H_2O$) C, H, N.

4′-Methoxycinnamoyl 2-methyl-3-bromo-A-ring-pyrrole-DUM (15f): yield 62%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 7.70 (1 H, d, J = 15.5 Hz), 7.47 (2 H, d, J = 8.6 Hz), 6.86 (2 H, d, J = 8.9 Hz), 6.68 (1 H, d, J = 15.2 Hz), 6.47 (1 H, br), 4.20 (1 H, d, J = 10.9 Hz), 4.09 (1 H, dd, J = 11.2, 5.0 Hz), 3.79 (3 H, s), 3.10−3.16 (1 H, m), 2.34 (1 H, dd, J = 7.4, 4.1 Hz), 2.25 (3 H, s), 1.26 (1 H, dd, J = 5.0, 4.3 Hz); FAB-MS m/z 441, 439 $(M + H)^+$; FAB-HRMS calcd for $C_{22}H_{20}{}^{79}BrN_2O_3$ $(M + H)^+$ m/z 439.0657, found 439.0673; IR (KBr) 1666, 1597, 1574, 1512, 1470, 1390, 1284, 1240, 1171, 1051 cm^{-1}. Anal. ($C_{22}H_{19}BrN_2O_3$) C, H, N.

4′-Methoxycinnamoyl 2-methyl-3-iodo-A-ring-pyrrole-DUM (15g): yield 63%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 7.62 (1 H, d, J = 15.5 Hz), 7.41 (2 H, d, J = 8.9 Hz), 6.80 (2 H, d, J = 8.9 Hz), 6.62 (1 H, d, J = 15.5 Hz), 6.45 (1 H, br), 4.14 (1 H, d, J = 11.2 Hz), 4.04 (1 H, dd, J = 11.2, 4.6 Hz), 3.73 (3 H, s), 3.18−3.23 (1 H, m), 2.33 (1 H, dd, J = 7.6, 4.3 Hz), 2.21 (3 H, s), 1.17 (1 H, dd, J = 5.0, 4.3 Hz); FAB-MS m/z 487 $(M + H)^+$; IR (KBr) 1666, 1601, 1574, 1464, 1392, 1240, 1171, 1038, 822 cm^{-1}. Anal. ($C_{22}H_{19}IN_2O_3$) C, H, N.

4′-Methoxycinnamoyl 2-methyl-3-acetyl-A-ring-pyrrole-DUM (15h): yield 33%; ^{1}H-NMR (270 MHz, $CDCl_3$ + CD_3OD) δ 7.68 (1 H, d, J = 15.2 Hz), 7.46 (2 H, d, J = 8.6 Hz), 6.85 (2 H, d, J = 8.6 Hz), 6.67 (1 H, br), 6.65 (1 H, d, J = 15.2 Hz), 4.16 (1 H, d, J = 10.9 Hz), 4.07 (1 H, dd, J = 10.9, 4.6 Hz), 3.59−3.66 (1 H, m), 2.58 (3 H, s), 2.37 (3 H, s), 2.31 (1 H, dd, J = 7.4, 3.1 Hz), 1.17 (1 H, dd, J = 4.3, 4.0 Hz); FAB-MS m/z 403 $(M + H)^+$; IR (KBr) 1662, 1601, 1576, 1512, 1390, 1240, 1225, 1173, 1006, 825 cm^{-1}. Anal. ($C_{24}H_{22}N_2O_4 \cdot 0.5H_2O$) C, H, N.

4′-Methoxycinnamoyl 2-Methyl-3-(dimethylaminomethyl)-A-ring-pyrrole-DUM (16). To a solution of **15a** (47 mg, 0.13 mmol) in THF (1.8 mL) was added 4 N HCl in AcOEt (0.098 mL, 0.39 mmol), and the mixture was stirred at room temperature for 45 min. The mixture was concentrated under reduced pressure, and a solution of $Me_2NCH_2NMe_2$ (0.089 mL, 0.65 mmol) in TFA (0.5 mL) was stirred at −10 °C for 25 min and then was added to a solution of the residue in TFA (0.8 mL) at −10 °C. After the mixture stirred for 1 h 45 min, aqueous $NaHCO_3$ was added, and the whole was extracted with $CHCl_3$ and then worked up as usual. The residue was purified by PTLC ($CHCl_3$−acetone, 10:1) to give 22 mg (36%) of 4′-methoxycinnamoyl 2-methyl-3-(dimethylaminomethyl)-A-ring-pyrrole-DUMC2. To a solution of 4′-methoxycinnamoyl 2-methyl-3-(dimethylaminomethyl)-A-ring-pyrrole-DUMC2 (22 mg, 0.047 mmol) in CH_3CN (1.5 mL) was added DBU (0.0354 mL, 0.0237 mmol), and the mixture was stirred at room temperature for 40 min; 0.01 M phosphoric buffer (pH 7) was

added, and the whole was extracted with $CHCl_3$ and then worked up as usual. The residue was purified by PTLC ($CHCl_3$−acetone, 10:1) to give 17 mg (87%) of **16:** ^{1}H-NMR (270 MHz, $CDCl_3$) δ 10.45 (1 H, brs), 7.76 (1 H, d, J = 15.5 Hz), 7.51 (2 H, d, J = 8.6 Hz), 6.91 (2 H, d, J = 8.6 Hz), 6.80 (1 H, J = 15.5 Hz), 6.46 (1 H, br), 4.21 (1 H, d, J = 11.2 Hz), 4.09 (1 H, dd, J = 11.4, 4.8 Hz), 3.84 (3 H, s), 3.08−3.14 (1 H, m), 2.54 (1 H, dd, J = 7.3, 3.6 Hz), 2.31 (3 H, s), 2.15 (6 H, s), 1.24 (1 H, dd, J = 4.6, 4.0 Hz); FAB-MS m/z 418 $(M + H)^+$; FAB-HRMS calcd for $C_{25}H_{28}N_3O_3$ $(M + H)^+$ m/z 418.2131, found 418.2106; IR (KBr) 1616, 1601, 1576, 1512, 1473, 1394, 1284, 1240, 1171, 1018 cm^{-1}. Anal. ($C_{25}H_{27}N_3O_3 \cdot 0.2H_2O$) C, H, N.

4′-Methoxycinnamoyl 2-Methyl-3-(dimethylaminomethyl)-A-ring-pyrrole-DUMC2 Hydrochloride (17). A solution of **16** (11 mg, 0.026 mmol) in CH_2Cl_2 (1 mL) was treated with 4 N HCl in AcOEt (0.0326 mL) at room temperature for 30 min. The mixture was concentrated under reduced pressure to give 12 mg of **17**: ^{1}H-NMR (270 MHz, DMSO-d_6) δ 11.46 (1 H, s), 9.97 (1 H, brs), 9.50−9.53 (1 H, br), 7.81 (1 H, s), 7.75 (2 H, d, J = 8.6 Hz), 7.59 (1 H, d, J = 14.9 Hz), 7.08 (1 H, d, J = 15.5 Hz), 7.00 (2 H, d, J = 8.3 Hz), 4.29−4.49 (3 H, m), 3.96−4.13 (2 H, m), 3.81 (3 H, s), 3.78 (3 H, br), 3.52−3.56 (1 H, br), 2.81 (3 H, d, J = 4.0 Hz), 2.69 (3 H, d, J = 4.0 Hz), 2.45 (3 H, s); FAB-MS m/z 454 $(M + H)^+$; IR (KBr) 1633, 1601, 1512, 1495, 1441, 1427, 1252, 1174 cm^{-1}. Anal. ($C_{25}H_{28}ClN_3O_3 \cdot HCl \cdot 2.5H_2O$) C, H, N.

Biological Studies. Human uterine cervix carcinoma HeLa S_3 cells were obtained from American Type Culture Collection through Dainippon Pharmaceutical Co. (Osaka, Japan). The cells (2×10^4/well) were precultured in the culture medium in 24-well multidishes (Nunc, Roskilde, Denmark) for 24 h at 37 °C in a humidified atmosphere of 5% CO_2. For the pulse exposure experiment, cells were treated with each compound for 1 h, washed with Dulbecco's phosphate-buffered saline [Ca^{2+}- and Mg^{2+}-free, PBS(−)], and further incubated in fresh medium for 71 h. For the continuous exposure experiment, cells were treated with each compound for 72 h. Then, cells were treated with PBS(−) containing 0.05% trypsin (Difco Laboratories, Detroit, MI) and 0.02% EDTA (Wako Pure Chemical Industries Co., Ltd., Osaka, Japan) and counted by using a Microcell Counter (CC-180A, Toa Medical Electronics Co., Ltd., Kobe, Japan). The IC_{50} values (drug concentration required for 50% inhibition of the cell growth) were determined.

Sarcoma 180 cells were kindly supplied by the National Cancer Center (Tokyo, Japan). Sarcoma 180 cells were passaged and used for the experiment in adults male ddY mice. Murine solid tumor was inoculated subcutaneously (sc) at the axillary region of mice. Drugs were administered intravenously (iv) beginning 1 day after tumor inoculation. Antitumor efficacy is expressed as T/C, where T and C are the values of mean tumor volume of treated and control mice. The length and width of the tumors were measured, and tumor volume was calculated as:

$$\text{tumor volume (mm}^3\text{)} = \text{length (mm)} \times [\text{width (mm)}]^2/2$$

according to the method of the National Cancer Institute.[19]

The criteria for effectiveness against murine solid tumors were the percentage T/C values with 42% and less, and statistical significance was determined by the Mann−Whitney U-test ($p < 0.05$). Drug efficacy against human xenografts was expressed as the percentage of mean V/V_0 value against that of the control group, where V is the tumor volume on the day of evaluation and V_0 is the tumor volume on the day of initial drug treatment. The criteria for effectiveness were T/C values with 50% and less, and statistical significance was determined by the Mann−Whitney U-test ($p < 0.01$, one-sided).[20]

Hematotoxicity (effect of compounds on peripheral blood (PB) platelet counts and white blood cell counts). Effect on PB platelet counts: Each drug was dissolved with saline and was administered into the tail vein of normal male ddY mice (mean weight 20 ± 1 g). After 7 days, PB was obtained from the orbital vein to measure the platelet counts using a microcell counter (CC-180A, Toa Medical Electronics Co., Ltd., Kobe, Japan). Results are presented as percentage of the absolute value of the treated group versus that of control (percent of control).

Effect on PB white blood cell counts: Drugs were administered iv beginning 1 day after tumor inoculation. After 4 days, PB was obtained from the orbital vein of tumor-bearing mice to measure the white blood cell counts using a microcell counter (CC-180A, Toa Medical Electronics Co., Ltd., Kobe, Japan). Results are presented as percentage of the absolute value of the treated group versus that of control (percent of control).

Lethal Toxicity. For the evaluation of delayed lethal toxicity, each drug was given by single iv administration in adult male ddY mice (mean weight 20 ± 1 g), and their survival days were observed over 60 days.

Evaluation of Bone Marrow Toxicity. Bone marrow cells: Male ddY mice received a single iv dose of the drug by tail vein injection on day 0 of the experiment. Then bone marrow (BM) cells were harvested by flushing from the limbs of mice with Iscove's modified Dulbecco's medium (IMDM, Gibco, Grand Island, NY) using a 23-G needle on a 1-mL syringe and were prepared at the concentration of 1.0×10^6 cells/mL using a microcell counter.

Colony-forming unit−granulocytes and macrophages (CFU-GM) assay: BM cells (2.5×10^4) were plated in 0.3% agar (agar noble, Difco Lab., Detroit, MI) with IMDM, 20% FBS (Filtron, Brooklyn, Australia), and 100 units/mL GM-CSF (Boehringer Mannheim, Tokyo, Japan). Cultures were incubated in humidified air containing 5% CO_2 at 37 °C, and colonies (>40 cells/colony) were counted after 7 days of incubation after staining using a Wright's eosin methylene blue solution (Omron, Tokyo, Japan).

Colony-forming unit−megakaryocytes (CFU-Meg) assay: BM cells (1.0×10^5) were plated in 0.3% agar (agar noble, Difco Lab., Detroit, MI) with IMDM, 10% FBS (Filtron, Brooklyn, Australia), 50 units/mL IL-3 (Boehringer Mannheim, Tokyo, Japan), and 1000 units/mL IL-6 (Boehringer Mannheim, Tokyo, Japan). Cultures were incubated in humidified air containing 5% CO_2 at 37 °C, and colonies (>4 cells/colony) were counted after 7 days of incubation after staining for the presence of acetylcholinesterase.

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Supporting Information Available: HPLC analytical data of compounds **8b**−**8d**, **8i**, **9h**, **12a**, **12b**, **12g**, **12j**, **12k**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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