The Effect of Phenyl Substituents on the Release Rates of Esterase-Sensitive Coumarin-Based Prodrugs

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A coumarin-based prodrug system has been recently developed in our laboratory for the preparation of esterase-sensitive prodrugs of amines, peptides, and peptidomimetics. The drug release rates from this prodrug system were found to be dependent on the structural features of the drug moiety. In certain cases, the release can be undesirably slow for drugs that are secondary amines with relatively high pK_a's. Aimed at finding ways to manipulate the release rates to suit the need of different drugs, we have examined the effect of the phenyl ring substitutions on the release kinetics of such prodrugs and found that appropriately positioned alkyl substituents on the phenyl ring could help to facilitate the release by as much as 16-fold. Therefore, introduction of alkyl substituents on the phenyl ring should allow us to manipulate the release rates and, therefore, time profiles for different drugs.

Key words cyclic prodrug; opioid peptide; peptidomimetic; cyclization

Undesirable physicochemical properties of amine, peptide and peptidomimetic drugs often result in their low membrane permeabilities through the biological barriers and, therefore, low bioavailabilities.[1—4] Prodrug strategy[5] represents a promising approach to modifying the undesirable physicochemical properties of such drugs to aid in their delivery to the desired site of action.[1,2] However, the preparation of prodrugs of amines, peptides, and peptidomimetics is often challenging due to the complexity of peptide molecules and the lack of appropriate chemical method to bioreversibly derivatize an amino group.[6] Recently, our laboratory has developed a novel coumarin-based prodrug system for the preparation of esterase-sensitive prodrugs of amines,[7—10] peptides,[11—13] and peptidomimetics,[14—16] which are otherwise difficult to make.[1,2,6] The design takes advantage of the spontaneous lactonization of *cis*-coumarinic acid and its derivatives **2** (Chart 1).[17—19] In such a strategy, a latent nucleophile can be unmasked using an esterase triggering mechanism that initiates a lactonization reaction to release the parent drug (Chart 1). Using this prodrug strategy, we have prepared esterase-sensitive prodrugs of model amines (Chart 1),[7—10] esterase-sensitive cyclic prodrugs (Chart 2) of opioid peptides[11—13] and peptidomimetic glycoprotein IIb/IIIa antagonists[14—16] with greatly improved membrane permeability. We have also prepared an esterase-sensitive cyclic prodrug of tirofiban,[20—24] an FDA approved antithrombotic drug which can only be administered through the i.v. route. The coumarin-based prodrug of tirofiban, showed greatly improved oral bioactivities in preliminary studies in dogs,[15] further demonstrating the clinical potential of this coumarin-based prodrug approach.

Now that we have demonstrated the clinical potential of this prodrug system, it will be important for us to address one practical issue, *i.e.*, the ability to fine-tune the release rates so that the release time profile can be modulated to suit the need of individual drugs. In our earlier studies, we have found that the release rates are largely dictated by the rate of lactonization (**2** to **3**, Chart 1), which in turn depends on the structural features of the drug moieties.[7,9] The release rates are affected by the pK_a and the steric features of the amines to be released.[9] Amines with lower pK_a's tend to be released at faster rates. Steric hindrance on the amine part tends to slow down the release. Ideally, one would like to be able to modulate the release rates independent of the structural properties of the drug moiety. In order to find ways to modulate the release rates of this class of prodrugs, it is important that we achieve a basic understanding of the factors that could affect the release rates. Since both the acyl moiety and the amine moiety are integral components of the drug moiety in a cyclic prodrug system (Chart 2), our focus shifted to the effect of phenyl ring substitutions. There have been ample literature precedents indicating that ring substituents, which introduce steric congestion, could be used for modulating the rates of lactonization reactions.[17—19,25—29] Aimed at understanding the structure-release rate relationship of the coumarin-based prodrugs, a series of substituted coumarinic acid derivatives were synthesized. The release rates of these prodrugs were studied using porcine liver esterase (PLE) in phosphate buffer solution at pH 7.4. It was found that introduction of methyl substitutions *ortho* to the alkyl side chain and the phenol hydroxyl group results in significant increases in release rates.

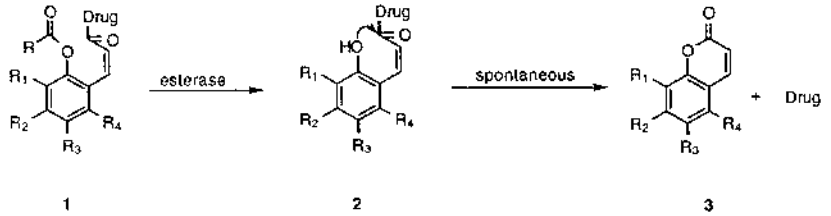

Chart 1. A Coumarin-Based Esterase-Sensitive Prodrug System

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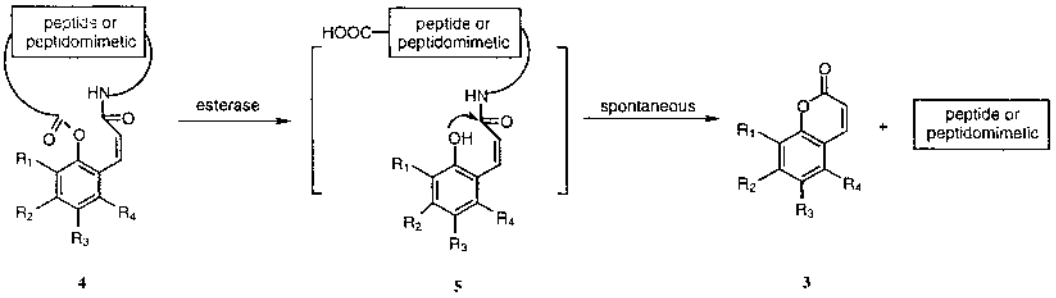

Chart 2. A Coumarin-Based Cyclic Prodrug System

Results and Discussion

For this study, we have designed a series of compounds with methyl substitutions at different positions of the phenyl ring to achieve a thorough understanding of the effect of alkyl substitution on the release kinetics. *N*-Methylbenzylamine and diethylamine were used as the model amines for the study.

Synthesis We have developed three approaches to the synthesis of coumarin-based prodrugs.[30] For this study, we chose to use the approach starting with substituted coumarins because of the ready availability of these compounds either commercially or synthetically. Substituted coumarins **3g**—**i** are commercially available. However, compounds **3a**—**f** need to be synthesized. There are several procedures reported for the preparation of substituted coumarins using methods ranging from palladium-catalyzed addition[31] to Wittig reactions[32—35] and other reactions.[36—38] We took a Friedel-Crafts type of reaction approach for the synthesis of substituted coumarins **3a**—**f** by heating the corresponding substituted phenol **5a**—**f** with propiolic acid or its ester in methanesulfonic acid to give the desired substituted coumarins **3a**—**f** in 40—90% yields (Chart 3). We studied this reaction using both propiolic acid and its methyl ester and found that both gave similar yields. Then the substituted coumarins (**3a**—**i**) were reduced using lithium aluminum hydride (LAH) at 0 °C to give the ring-opened diols **6a**—**i** in about 30—55% yields. The primary hydroxyl groups of diols **6a**—**i** were selectively protected as a silyl ether by reacting with *tert*-butyldimethyl silyl (TBDMS) chloride to give **7** in 80—90% yields. The acetylation of the free phenol hydroxyl group of **7** was accomplished by reaction with acetic anhydride in the presence of triethylamine (TEA) and 4-dimethylaminopyridine (DMAP) in about 90% yields. The free primary hydroxyl group of **9** after deprotection of the silyl group using acetic acid was converted to the carboxyl group in two steps. The oxidation to the aldehydes **10** was accomplished using manganese dioxide in dichloromethane (DCM) in about 90% yield. Conversion of the aldehydes **10** to the carboxylic acids **11** was accomplished in 60—100% yield by oxidation with sodium chlorite in the presence of hydrogen peroxide under acidic conditions. The free acids **11** were then coupled with *N*-methylbenzylamine or diethylamine using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) as the activating reagent in the presence of hydroxybenzotriazole (HOBt) and DMAP to give the model prodrugs **1a**—**r**.

Esterase Kinetics The esterase kinetic studies were carried out following procedures reported earlier using PLE.[7,9,11] Briefly the reaction was followed with UV. Upon incubation with PLE in phosphate buffer (0.05 M, pH 7.4, 37±0.5 °C) at an enzyme concentration of about 1 unit/ml, all model prodrugs **1a**—**r** completely released the amine moiety as designed. Figure 1 shows a typical set of UV spectra in a kinetic study. The *pseudo* first order rate constants were determined from linear curve-fittings. Data from the first 4—5 half-lives were used. Figure 2 shows some typical plots used for the determination of the rate constants.

The objectives of this study were to see how alkyl substitutions on the phenyl ring would affect the release rates and whether such substitutions could help to enhance the release rates as designed. As shown in Tables 1 and 2, with the monomethyl or dimethyl substituted model prodrug systems **1a**—**l** with at least one methyl group vicinal to either the side chain alkenyl group or the phenol hydroxyl group, significant release rate enhancements were observed compared with the un-substituted model prodrugs **1s** and **1t**. For example, the release rates for *N*-methylbenzylamine in the coumarin-based model prodrug system **1s**[7,9] (R_1=R_2=R_3=R_4=H) had a half-life of about 32 min (Table 1). With the dimethyl-substituted model prodrug systems **1a**, which has one methyl group next to the side chain alkenyl group and one methyl group next to the phenol hydroxyl group, the release was about 5-fold faster with a half-life of 4.8 min. This is not surprising. There have been literature precedents indicating that the steric hindrance at both positions facilitates similar lactonizations.[27,28,39,40] It is also logical that with only one substituent at either of the two vicinal position (R_1 and R_4) a significant increase in the release rates was observed, however, to a lesser degree compared with the di-substituted ones. For example, compounds **1c**, **1g**, and **1i** had release half-lives ranging from 6.3—8.5 min, which are significantly shorter than that of the unsubstituted one **1s** (32 min), but slightly longer than that of **1a** (4.8 min). One unexpected result was with compound **1e**, which has R_1 and R_2 as methyl groups. It has a half-life of about 3.2 min which is shorter than that of **1a** and has only one methyl substituent next to the phenol hydroxyl group. It is conceivable that the R_2 methyl group could help to facilitate the lactonization through either electronic or steric effect or a combination of both. As an electron donating group, the R_2 methyl group is expected to decrease the electrophilicity of the amide carbonyl and increase the charge on the phenol hydroxyl oxygen. To examine the effect of the R_2 substituent alone, we have also synthesized and evaluated compounds **1o** and **1q**, with a methyl and a methoxy group at the R_2 position, respectively. With a single electron donating group (methyl or methoxy) at the R_2 position, the release rates of **1o** and **1q** were similar to that of the

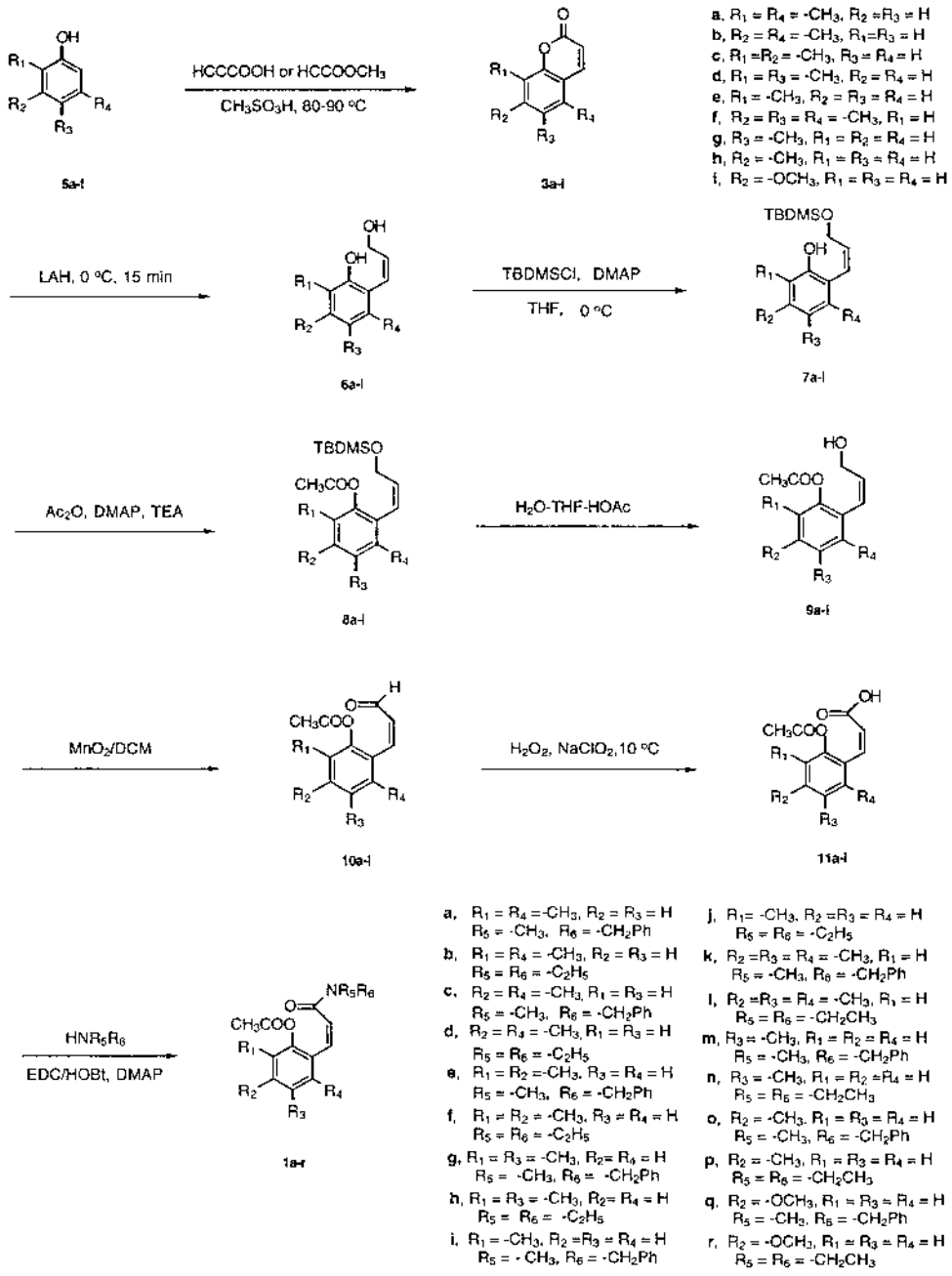

Chart 3. Synthesis of Substituted Coumarin-Based Prodrugs

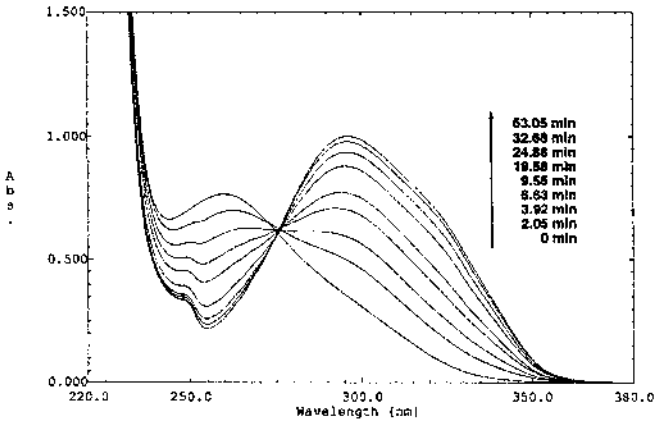

Fig. 1. The UV Reaction Profile for the Esterase-Catalyzed Hydrolysis of Prodrug **1a**

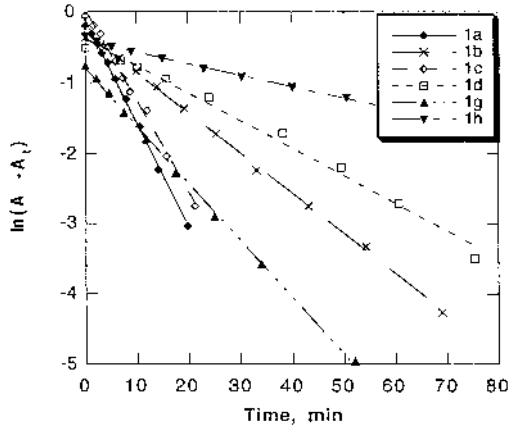

Fig. 2. The *Pseudo*-First-Order Kinetics of the Esterase-Triggered Release of Amines from Model Prodrugs **1a**—**d**, **1g**—**h**

Table 1. Esterase-Catalyzed Release Rates for Methylbenzylamine (R_5=–CH_3, R_6=–CH_2Ph)

Model prodrug	R_1	R_2	R_3	R_4	$k_{obs}\times10^2$ (min^{-1})	$t_{1/2}$ (min)
1a	CH_3	H	H	CH_3	14.4±0.4	4.8±0.1
1c	H	CH_3	H	CH_3	11.0±0.8	6.3±0.5
1e	CH_3	CH_3	H	H	21.8±0.5	3.2±0.1
1g	CH_3	H	CH_3	H	8.2±0.2	8.5±0.2
1i	CH_3	H	H	H	9.4±0.3	7.4±0.2
1k	H	CH_3	CH_3	CH_3	7.3±0.2	9.5±0.5
1m	H	H	CH_3	H	2.6±0.1	26.4±1.0
1o	H	CH_3	H	H	2.2±0.04	32.1±0.5
1q	H	OCH_3	H	H	2.0±0.01	34.5±0.2
1s	H	H	H	H	2.1±0.1	32.5±0.2

Table 2. Esterase-Catalyzed Release Rates for Diethylamine (R_5=R_6=–CH_2CH_3)

Model prodrug	R_1	R_2	R_3	R_4	$k_{obs}\times10^2$ (min^{-1})	$t_{1/2}$ (min)
1b	CH_3	H	H	CH_3	6.1±0.5	11.4±1.0
1d	H	CH_3	H	CH_3	3.7±0.4	18.8±1.9
1f	CH_3	CH_3	H	H	5.8±0.1	11.9±0.2
1h	CH_3	H	CH_3	H	1.5±0.1	46.4±1.4
1j	CH_3	H	H	H	2.3±0.3	30.6±3.6
1l	H	CH_3	CH_3	CH_3	1.5±0.1	45.1±1.8
1n	H	H	CH_3	H	0.34±0.02	204±11
1p	H	CH_3	H	H	0.32±0.02	212±13
1r	H	OCH_3	H	H	0.35±0.01	197±3.5
1t	H	H	H	H	0.37±0.03	188±12

unsubstituted compound **1s**. This suggests that the electronic effect of the R_2 substituent is minimal even with a strongly electron donating methoxy group at the R_2 position. Then the unexpected rate enhancement for **1e** is most likely due to the enhanced steric congestion introduced by the R_2 group next to R_1. However, similar effect was not observed when an additional methyl group was positioned next to R_4 (**1k**), which did not further enhance the release rate of compound **1c**. The effect of R_3 alone (**1m**) was also examined as a control and R_3 alone was found to have very little effect on the lactonization rate. All of these are consistent with steric factors being the predominant factors in determining the reaction rates.

The same study was also carried out with the release of diethylamine for two reasons. First, we would like to confirm that the substituent effect observed with the release of methylbenzylamine is generally applicable. Second, the release of diethylamine is much slower than that of methylbenzylamine, which would help to "spread out" the data so that experimental errors would not complicate the data interpretation as much. For example, the maximum $t_{1/2}$ difference for the release of methylbenzylamine among all the analogs (**1a**—**k**) with at least one methyl group *ortho* to either the alkene side chain or the phenol ester was less than 5 min. Minor experimental errors could significantly affect the outcome of the interpretation. With the corresponding diethylamine analogs (**1b**—**l**), the maximum difference in $t_{1/2}$ was about 35 min. Again, the highest release rates were observed with the methyl group at the R_1 and R_4 (**1b**, $t_{1/2}$=11.4 min) or R_1 and R_2 (**1f**, $t_{1/2}$=11.9 min) positions. The release rates were significantly slower with other substituted coumarinic acid analogs with only one methyl group next to either the side chain alkenyl or phenol hydroxyl group. For example, the releases rates of **1d**, **1h**, **1j**, and **1l** ranged from 18.8 to 46.4 min. However, all these substituted analogs released diethylamine at a much faster rates than that of the unsubstituted one **1t**, which has a half-life of about 188 min.[7,9] Similarly, mono-substitution at either R_2 or R_3 position alone had very little effect on the release rates. For example, the half-lives of **1n**, **1p**, and **1r** ranged from 197 to 214 min compared with the half-life of 188 min of the unsubstituted one (**1t**).

Therefore, the steric effect of the substituents *ortho* to either the side chain alkenyl group or the phenol carboxyl group is the most important factor in determining the lactonization rates of the substituted coumarinic acid derivatives. Electronic factors by substituents at the R_2 and R_3 position seem to have very little effect on the lactonization rates.

Conclusions

Aimed at understanding the structure-release rate relationship, we have designed, synthesized, and evaluated a series of substituted coumarinic acid analogs. Their esterase-catalyzed release rates have been studied using PLE. It was found that methyl substituents *ortho* to either the side chain alkenyl group or the phenol carboxyl group can greatly enhance the rate of lactonization of such systems through the introduction of steric congestion. The electronic effect of the substituents at the R_2 and R_3 positions are not important in influencing the release rates. The understanding of the structure–release rate relationship will help the design of prodrugs with different release time profiles.

Experimental

General Methods All ^{1}H-NMR spectra were recorded at 300 MHz with TMS as the internal standard. Column chromatography was performed using silica gel (200—400 mesh) from Aldrich. Elemental analyses were performed by Atlantic Microlab Inc. Mass spectral analyses were conducted by North Carolina State University Mass Spectrum Laboratory. Commercially available starting materials and reagents were purchased from Aldrich. THF was distilled from Na and benzophenone; methylene chloride (CH_2Cl_2) was distilled from CaH_2. A Shimadzu 1601 UV-visible spectrophotometer was used for the esterase kinetics study.

5,8-Dimethylcoumarin (3a)[41] To a solution of 2,5-dimethyl phenol (**5a**) (2.440 g, 20 mmol) in methansulfonic acid (40 ml) was added propiolic acid (1.479 ml, 24 mmol) at room temperature. After stirring at 85—90 °C under N_2 atmosphere for 4 h, the solution was diluted with 80 ml de-ionized water and extracted with 120 ml ethyl acetate (40 ml×3). The ethyl acetate layer was washed with saturated Na_2CO_3 (30 ml×3) and then saturated NaCl, and dried over $MgSO_4$ and concentrated to give a gray solid (3.123 g, 81%). ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s), 2.49 (3H, s), 6.42 (1H, d, J=9.6 Hz), 7.00 (1H, d), 7.26 (1H, d), 7.92 (1H, d, J=9.6 Hz).

2-[(*Z*)-3-Hydroxy-1-propenyl]-3,6-dimethylphenol (6a) A solution of 5,8-dimethyl coumarin (**3a**) (2.453 g, 14.1 mmol) in ether (60 ml) was treated at 0 °C with a suspension of LAH (1.072 g, 28.2 mmol) in ether (20 ml). After stirring for 15 min, 1 N HCl (85 ml) was added to dropwise the reaction at 0 °C. Then the solution was extracted with ether (3×100 ml). The combined ether layers was dried over $MgSO_4$ and concentrated to give a light yellow solid (2.431 g). Recrystallization from methylene chloride/ethyl acetate (7 : 1) gave **6a** (1.325 g, 52%) as gray white crystals: ^{1}H-NMR (CD_3OD) δ: 2.12 (3H, s), 2.23 (3H, s), 3.93 (2H, d, J=7.0 Hz), 5.97—6.02 (1H, m), 6.26 (1H, d, J=11.2 Hz), 6.98 (1H, d), 7.05 (1H, d). MS (EI) m/z: 178.1 (M^+). *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; O, 17.95. Found: C, 74.24; H, 7.98.

2-[(*Z*)-3-{[1-(*tert*-Butyl)-1,1-dimethyl-silanyl]oxy}-1-propenyl]-3,6-dimethylphenol (7a) To the stirred solution of **6a** (1.198 g, 10.1 mmol) in dry THF (15 ml), the solution of *tert*-butyldimethylsilyl chloride (2.273 g, 15.2 mmol) in dry THF (30 ml) was added at 0 °C, followed by the dropwise addition of DMAP (1.838 g, 38.7 mmol) in dry THF (20 ml). After stirring at 0 °C for 8 h, the solution was filtered and evaporated to remove the THF.

Ethyl acetate (50 ml) was added and the solution was washed with 1 N HCl (3×20 ml), 5% $NaHCO_3$ (2×20 ml) and water (20 ml). The ethyl acetate layer was dried over $MgSO_4$, filtered and evaporated to give a yellow oil (2.720 g). The oil was chromatographed on a silica gel column with ethyl acetate/hexane (1 : 15) to afford **7a** as a white solid (1.82 g, 82%). ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 2.12 (3H, s), 2.22 (3H, s), 3.99 (2H, d, J=6.9 Hz), 6.10—6.18 (1H, m), 6.36 (1H, d, J=11.4 Hz), 6.82—6.96 (2H, dd). MS (EI) m/z: 292.2 (M^+). *Anal.* Calcd for $C_{17}H_{28}O_2Si$: C, 69.81; H, 9.65; O, 10.94; Si, 9.60. Found: C, 69.62; H, 9.58.

2-[(*Z*)-3-{[1-(*tert*-Butyl)-1,1-dimethyl-silanyl]oxy}-1-propenyl]-3,6-dimethylphenyl Acetate (8a) To the solution of **7a** (1.68 g, 5.7 mmol) in dry CH_2Cl_2 (30 ml) was added dropwise acetic anhydride (0.808 ml, 7.32 mmol), DMAP (149 mg, 1.22 mmol) and TEA (1.56 ml, 11 mmol). After stirring at room temperature under N_2 atmosphere for 1 h, the reaction mixture was washed with 1 N HCl (2×20 ml), 5% $NaHCO_3$ (15 ml) and water (15 ml). Then the solution was dried over $MgSO_4$, filtered and evaporated to afford **5a** as a white solid (1.83 g, 90%). ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 2.14 (3H, s), 2.15 (3H, s), 2.25 (3H, s), 4.01 (2H, d, J=6.9 Hz), 6.10—6.20 (1H, m), 6.34 (1H, d, J=11.1 Hz), 6.84—7.00 (2H, dd). MS (EI) m/z: 334.2 (M^+). *Anal.* Calcd for $C_{19}H_{30}O_3Si$: C, 68.22; H, 9.04; O, 14.35; Si, 8.40. Found: C, 68.11; H, 9.12.

2-[(*Z*)-3-Hydroxy-1-propenyl]-3,6-dimethylphenyl Acetate (9a) To the solution of **8a** (1.425 g, 4.27 mmol) in THF (12 ml) was added water (12 ml) and then added dropwise acetic acid (36 ml). The mixture was stirred at room temperature for 3 h and then evaporated to remove THF, water and acetic acid. Ethyl acetate (50 ml) was added to the residue, which was washed with 5% $NaHCO_3$ (3×20 ml) and water (2×20 ml). It was dried over $MgSO_4$, filtered and evaporated to afford **9a** as a white oil (931 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 2.14 (3H, s), 2.16 (3H, s), 2.27 (3H, s), 3.94 (2H, t), 5.98—6.02 (1H, m), 6.28 (1H, d, J=11.4 Hz), 7.00 (1H, d), 7.06 (1H, d). MS (EI) m/z: 220.1 (M^+). *Anal.* Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; O, 21.79. Found: C, 71.02; H, 7.38.

3,6-Dimethyl-2-[(*Z*)-3-Oxo-1-propenyl]phenyl Acetate (10a) To the solution of **9a** (334 mg, 1.43 mmol) in dry CH_2Cl_2 (20 ml) was added in one portion 85% activated manganese(IV) oxide (292 mg, 2.86 mmol), which was dried with a drying tube containing anhydrous $CaSO_4$. Then every one hour manganese(IV) oxide (292 mg) was added in one portion for a period of five hours. The reaction mixture was filtered over Celite (5 g), washed with CH_2Cl_2 and evaporated to afford **10a** as a brown oil (329 mg, 99%). ^{1}H-NMR ($CDCl_3$) δ: 2.16 (3H, s), 2.20 (3H, s), 2.60 (3H, s), 6.19 (1H, d, J=11.4 Hz), 7.05 (1H, d, J=11.4 Hz), 7.16 (1H, d), 7.33 (1H, d); 9.53 (1H, d, J=8.2 Hz). MS (EI) m/z: 218.1 (M^+). *Anal.* Calcd for $C_{13}H_{16}O_3$: C, 71.54; H, 6.47; O, 21.99. Found: C, 71.63; H, 6.55.

(*Z*)-3-[2-(Acetyloxy)-3,6-dimethylphenyl]acrylic Acid (11a) A solution of 80% sodium chlorite (210 mg, 2.1 mmol) in water (1.86 ml) was added dropwise in 2 h to a stirred mixture of **10a** (252 mg, 1.09 mmol) in acetonitrile (1.33 ml), sodium phosphate (43 mg) in water (0.53 ml), and 30% hydrogen peroxide (0.156 ml), while its temperature was kept at 10 °C with an ice-water bath. Oxygen evolution from the solution was monitored until the end of the reaction (about 2 h) with a bubbler connected to the apparatus. A small amount of sodium sulfite was added to destroy the unreacted HOCl and H_2O_2. The solution was acidified with 1 N HCl to pH=1—2. The mixture was extracted with ethyl acetate (30 ml). The ethyl acetate layer was washed with saturated sodium chloride solution (2×30 ml) and dried over $MgSO_4$. Filtration and evaporation of the solvent afforded **11a** as a white solid (244 mg, 96%). ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, s), 2.22 (3H, s), 2.26 (3H, s), 6.14 (1H, d, J=11.9 Hz), 6.88 (1H, d, J=11.9 Hz), 7.02 (1H, d), 7.08 (1H, d). MS (FAB) m/z: 235.1 $(M+H)^+$. *Anal.* Calcd for $C_{13}H_{16}O_4$: C, 66.66; H, 6.02; O, 27.32. Found: C, 66.59; H, 6.00.

2-[(*Z*)-2-(Benzylmethylcarbamoyl)vinyl]-3,6-dimethylphenyl Acetate (1a) To the solution of **11a** (220 mg, 0.94 mmol) in dry CH_2Cl_2 (5 ml) was added EDC (217 mg, 1.128 mmol) at 0 °C. The mixture was stirred for 10 min. To the mixture was added dropwise methyl benzylamine (0.145 ml, 1.128 mmol) and DMAP (23 mg, 0.189 mmol). After stirring at 0 °C under N_2 atmosphere for 1 h, the ice bath was withdrawn and the reaction was kept stirring at room temperature for 3 h. Then CH_2Cl_2 (50 ml) was added. The CH_2Cl_2 layer was washed with saturated $NaHCO_3$ solution (3×20 ml), 10% citric acid solution (2×20 ml) and water (20 ml), and dried over $MgSO_4$. Filtration and evaporation gave a light yellow oil, which was chromatographed on a silica gel column with ethyl acetate/hexane (1 : 4) to give **1a** as a white solid (253 mg, 72%). ^{1}H-NMR ($CDCl_3$) δ: 2.12 (3H, s), 2.23 (3H, s), 2.24 (3H, s), 2.67/2.80 (3H, s/s, rotamer), 4.35/4.52 (2H, s/s, rotamer), 6.30 (1H, d, J=12.4 Hz), 6.58 (1H, d, J=12.4 Hz), 7.00 (1H, d), 7.07 (1H, brs); 7.23—7.29 (5H, brs). MS (FAB) m/z 338.2 $(M+H)^+$. *Anal.* Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.89; H, 6.98; N, 4.10.

2-[(*Z*)-2-(Diethylcarbamoyl-vinyl]-3,6-dimethylphenyl Acetate (1b) To the solution of **11a** (318 mg, 1.36 mmol) in dry CH_2Cl_2 (10 ml) was added EDC (261 mg, 1.36 mmol) at 0 °C, The mixture was stirred for 10 min. To the mixture was added dropwise diethylamine (0.168 ml, 1.63 mmol), HOBt (183 mg, 1.36 mmol) and DMAP (33 mg, 0.272 mmol). After stirring at 0 °C under N_2 atmosphere for 1 h, the ice bath was withdrawn and the reaction was kept stirring at room temperature for 3 h. Then CH_2Cl_2 (50 ml) was added. The CH_2Cl_2 layer was washed with saturated $NaHCO_3$ solution (3×20 ml), 10% citric acid solution (2×20 ml) and water (20 ml), and dried over $MgSO_4$. Filtration and evaporation gave a light yellow oil, which was chromatographed on a silica gel column with ethyl acetate/hexane (1 : 4) to give **1b** as a white solid (304 mg, 66%). ^{1}H-NMR ($CDCl_3$) δ: 0.96/1.00 (6H, t/t, rotamer), 2.10 (3H, s), 2.24 (3H, s), 2.28 (3H, s), 3.16/3.32 (4H, q/q, rotamer), 6.23 (1H, d, J=12.6 Hz), 6.54 (1H, d, J=12.6 Hz), 6.96 (1H, d), 7.07 (1H, d), 7.04 (1H, d). MS (FAB) m/z: 290.2 $(M+H)^+$. *Anal.* Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.48; H, 8.11; N, 4.79.

5,7-Dimethylcoumarin (3b)[42] In a manner similar to the preparation of **3a**, 3,5-dimethyl phenol (**5b**) (2.196 g, 18 mmol) and propiolic acid (1.331 ml, 21.6 mmol) were reacted in methansulfonic acid (40 ml) to give **3b** as a gray solid (2.184 g, 68%). ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 2.48 (3H, s), 6.36 (1H, d, J=9.7 Hz), 6.93 (1H, s), 6.90 (1H, s), 7.89 (1H, d, J=9.7 Hz).

2-[(*Z*)-3-Hydroxy-1-propenyl]-3,5-dimethylphenol (6b) In a manner similar to the preparation of **6a**, 5,7-dimethyl coumarin (**3b**) (2.104 g, 11.8 mmol) in ether (70 ml) was treated with a suspension of lithium LAH (896 mg, 23.6 mmol) in ether (40 ml) to afford **6b** (851 mg, 41%) as gray white crystals. ^{1}H-NMR (CD_3OD) δ: 2.15 (3H, s), 2.26 (3H, s), 4.06 (2H, d, J=6.9 Hz), 5.30 (1H, s), 5.46 (1H, s), 6.17 (1H, m), 6.38 (1H, d, J=11.1 Hz), 6.61(2H, s). MS (EI) m/z: 178.1 (M^+). *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; O, 17.95. Found: C, 74.19; H, 7.96.

2-[(*Z*)-3-{[1-(*tert*-Butyl)-1,1-dimethylsilanyl]oxy}-1-propenyl]-3,5-dimethylphenol (7b) In a manner similar to the preparation of **7a**, **6b** (610 mg, 3.35 mmol, in 8 ml dry THF), *tert*-butyldimethylsilyl chloride (553 mg, 3.687 mmol, in 4 ml dry THF) and DMAP (613 mg, 38.7 mmol, in 10 ml dry THF) were reacted to give **7b** as a white solid (948 mg, 91%). ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 2.14 (3H, s), 2.25 (3H, s), 4.02 (2H, d, J=7.0 Hz), 5.99 (1H, s), 6.10—6.18 (1H, m), 6.32 (1H, d, J=11.3 Hz), 6.59 (1H, s), 6.63 (1H, s). MS (EI) m/z: 292.2 (M^+). *Anal.* Calcd for $C_{17}H_{28}O_2Si$: C, 69.81; H, 9.65; O, 10.94; Si, 9.60. Found: C, 69.68; H, 9.62.

2-[(Z)-3-{[1-(*tert*-Butyl)-1,1-dimethyl-silanyl]oxy}-1-propenyl]-3,5-dimethylphenyl Acetate (8b) In a manner similar to the preparation of **8a**, **7b** (948 mg, 3.22 mmol), acetic anhydride (0.365 ml, 3.87 mmol), DMAP (78 mg, 0.645 mmol) and triethylamine (0.806 ml, 5.8 mmol) were treated to afford **8b** (1.042 g, 87%) as white solid. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 2.15 (3H, s), 2.21 (3H, s), 2.28 (3H, s), 4.01 (2H, d, J=6.9 Hz), 6.10—6.18 (1H, m), 6.32 (1H, d, J=11.1 Hz), 6.61 (1H, s), 6.65 (1H, s). MS (EI) m/z: 334.2 (M^+). *Anal.* Calcd for $C_{19}H_{30}O_3Si$: C, 68.22; H, 9.04; O, 14.35; Si, 8.40. Found: C, 68.29; H, 9.10.

2-[(*Z*)-3-Hydroxy-1-propenyl]-3,5-dimethylphenyl Acetate (9b) In a manner similar to the preparation of **9a**, **8b** (902 mg, 2.68 mmol, in 10 ml dry THF), water (10 ml) and acetic acid (30 ml) were reacted to give **9b** as a white oil (622 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 2.14 (3H, s), 2.18 (3H, s), 2.27 (3H, s), 3.94 (2H, t), 5.98—6.04 (1H, m), 6.30 (1H, d, J=11.4 Hz), 6.62 (1H, s), 6.68 (1H, s). MS (EI) m/z: 220.1 (M^+). *Anal.* Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; O, 21.79. Found: C, 70.62; H, 7.23.

3,5-Dimethyl-2-[(*Z*)-3-oxo-1-propenyl]phenyl Acetate (10b) In a manner similar to the preparation of **10a**, **9b** (502 mg, 2.28 mmol) and 85% activated manganese(IV) oxide (466 mg×6, 4.56 mmol×6) were treated to afford **10b** (438 mg, 92%) as brown oil. ^{1}H-NMR ($CDCl_3$) δ: 2.17 (3H, s), 2.18 (3H, s), 2.60 (3H, s), 6.17 (1H, dd, J=11.4 Hz), 7.03 (1H, d, J=11.4 Hz), 6.79 (1H, d), 6.87 (1H, d), 9.58 (1H, d, J=8.2 Hz). MS (EI) m/z: 218.1 (M^+). *Anal.* Calcd for $C_{13}H_{16}O_3$: C, 71.54; H, 6.47; O, 21.99. Found: C, 71.33; H, 6.25.

(*Z*)-3-[2-(Acetyloxy)-4,6-dimethylphenyl]acrylic Acid (11b) In a manner similar to the preparation of **11a**, 80% sodium chlorite (348 mg, 3.87 mmol) in water (3.10 ml), **10b** (402 mg, 1.09 mmol, in 2.2 ml acetonitrile), sodium phosphate (69 mg) in water (0.85 ml), and 30% hydrogen peroxide (0.156 ml) were reacted to give **11b** as a white solid (422 mg, 98%). ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, s), 2.24 (3H, s), 2.28 (3H, s), 6.15 (1H, d, J=11.8 Hz), 6.81 (1H, d, J=11.8 Hz), 7.04 (1H, d), 7.10 (1H, d). MS (FAB) m/z: 235.1 $(M+H)^+$.

2-[(*Z*)-2-(Benzylmethylcarbamoyl)-vinyl]-3,5-dimethylphenyl Acetate (1c) In a manner similar to the preparation of **1a**, **11b** (401 mg, 1.71 mmol, in 8 ml dry CH_2Cl_2), EDC (395 mg, 2.06 mmol), methyl benzylamine (0.265 ml, 2.06 mmol), and DMAP (42 mg, 0.343 mmol) were reacted to give **1c** as a white solid (353 mg, 52%). ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, s), 2.23 (3H, s), 2.28 (3H, s), 2.68/2.81 (3H, s/s, rotamer), 4.37/4.54 (2H, s/s, rotamer), 6.33 (1H, d, J=12.3 Hz), 6.61 (1H, d, J=12.3 Hz), 7.01 (1H, d), 7.09 (1H, brs), 7.25—7.30 (5H, brs). MS (FAB) *m/z*: 338.2 $(M+H)^+$. *Anal.* Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.97; H, 7.12; N, 4.07.

2-[(*Z*)-2-(Diethylcarbamoyl-vinyl]-3,5-dimethylphenyl Acetate (1d) In a manner similar to the preparation of **1b**, **11b** (83 mg, 1.175 mmol, in 10 ml dry CH_2Cl_2), EDC (68 mg, 0.355 mmol), diethylamine (0.031 ml, 0.426 mmol) and DMAP (9 mg, 0.071 mmol) were reacted to give **1d** as a white solid (102 mg, 85%). ^{1}H-NMR ($CDCl_3$) δ: 0.97/1.04 (6H, t/t, rotamer), 2.24 (6H, s), 2.28 (3H, s), 3.20/3.30 (4H, q/q, rotamer), 6.22 (1H, d, J=12.5 Hz), 6.53 (1H, d, J=12.5 Hz), 6.68 (1H, s), 6.88 (1H, s). MS (FAB) *m/z*: 290.2 $(M+H)^+$. *Anal.* Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.64; H, 8.12; N, 4.77.

7,8-Dimethylcoumarin (3c)[43] In a manner similar to the preparation of **3a**, 1,2-dimethyl phenol (**5c**) (2.440 g, 20 mmol) and propiolic acid (1.476 ml, 24 mmol) were reacted in methansulfonic acid (40 ml) to give **3c** as a gray solid (3.192 g, 90%). ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s), 2.40 (3H, s), 6.36 (1H, d, J=9.6 Hz), 7.10 (1H, d), 7.21 (1H, d), 7.67 (1H, d, J=9.6 Hz).

6-[(*Z*)-3-Hydroxy-1-propenyl]-2,3-dimethylphenol (6c) In a manner similar to the preparation of **6a**, 7,8-dimethyl coumarin (**3c**) (2.700 g, 15.3 mmol) in ether (70 ml) was treated with a suspension of LAH (1.166 g, 30.7 mmol) in ether (40 ml) to afford **6c** (1.096 g, 41%) as gray white crystals. ^{1}H-NMR (CD_3OD) δ: 2.18 (3H, s), 2.27 (3H, s), 4.22 (2H, d, J=7.0 Hz), 5.30 (1H, s), 6.05 (1H, m), 6.54 (1H, d, J=11.2 Hz), 6.71—6.80 (2H, dd). MS (EI) *m/z*: 178.1 (M^+). *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; O, 17.95. Found: C, 73.91; H, 7.69.

6-[(*Z*)-3-{[1-(*tert*-Butyl)-1,1-dimethylsilanyl]oxy}-1-propenyl]-2,3-dimethylphenol (7c) In a manner similar to the preparation of **7a**, **6c** (628 mg, 3.451 mmol, in 10 ml dry THF), *tert*-butyldimethylsilyl chloride (569 mg, 3.796 mmol, in 5 ml dry THF), and DMAP (632 mg, 5.177 mmol, in 10 ml dry THF) were reacted to give **7c** as a white solid (807 mg, 80%). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.90 (9H, s), 2.18 (3H, s), 2.26 (3H, s), 4.15 (2H, d, J=7.2 Hz), 6.00—6.03 (1H, m), 6.47 (1H, d, J=11.2 Hz), 6.82—6.96 (2H, dd). MS (EI) *m/z*: 292.2 (M^+). *Anal.* Calcd for $C_{17}H_{28}O_2Si$: C, 69.81; H, 9.65; O, 10.94; Si, 9.60. Found: C, 69.72; H, 9.47.

6-[(*Z*)-3-{[1-(*tert*-Butyl)-1,1-dimethylsilanyl]oxy}-1-propenyl]-2,3-dimethylphenyl Acetate (8c) In a manner similar to the preparation of **8a**, **7c** (212 mg, 0.72 mmol), acetic anhydride (0.081 ml, 0.085 mmol), DMAP (18 mg, 0.144 mmol) and TEA (0.188 ml, 1.8 mmol) were treated to afford **8c** (1.042 g, 87%) as white solid. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (6H, s), 0.88 (9H, s), 2.06 (3H, s), 2.29 (3H, s), 2.30 (3H, s), 4.29 (2H, d, J=7.0 Hz), 5.81—5.85 (1H, m), 6.31 (1H, d, J=11.1 Hz), 6.94—7.03 (2H, dd). MS (EI) *m/z*: 334.2 (M^+). *Anal.* Calcd for $C_{19}H_{30}O_3Si$: C, 68.22; H, 9.04; O, 14.35; Si, 8.40. Found: C, 68.35; H, 9.18.

6-[(*Z*)-3-Hydroxy-1-propenyl]-2,3-dimethylphenyl Acetate (9c) In a manner similar to the preparation of **9a**, **8c** (216 mg, 0.643 mmol, in 2.4 ml dry THF), water (2.4 ml) and acetic acid (7.2 ml) were reacted to give **9c** as a white oil (142 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s), 2.29 (3H, s), 2.30 (3H, s), 4.21 (2H, t), 5.90—5.94 (1H, m), 6.43 (1H, d, J=11.4 Hz), 6.91 (1H, d), 7.02 (1H, d). MS (EI) *m/z*: 220.1 (M^+). *Anal.* Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; O, 21.79. Found: C, 71.08; H, 7.61.

2,3-Dimethyl-6-[(*Z*)-3-oxo-1-propenyl]phenyl Acetate (10c) In a manner similar to the preparation of **10a**, **9c** (140 mg, 0.64 mmol) and 85% activated manganese(IV) oxide (131 mg×6, 1.28 mmol×6) were treated to afford **10c** (133 mg, 92%) as brown oil. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s), 2.31 (3H, s), 2.34 (3H, s), 6.16 (1H, dd, J=11.4 Hz), 7.10 (2H, s), 7.47 (1H, d, J=11.4 Hz), 9.81 (1H, d, J=8.2 Hz). MS (EI) *m/z*: 218.1 (M^+). *Anal.* Calcd for $C_{13}H_{16}O_3$: C, 71.54; H, 6.47; O, 21.99. Found: C, 71.27; H, 6.28.

(*Z*)-3-[2-(Acetyloxy)-3,4-dimethylphenyl]acrylic Acid (11c) In a manner similar to the preparation of **11a**, 80% sodium chlorite (116 mg, 1.285 mmol) in water (1.03 ml), **10c** (133 mg, 0.612 mmol, in 0.73 ml acetonitrile), sodium phosphate (23 mg) in water (0.28 ml), and 30% hydrogen peroxide (0.083 ml) were reacted to give **11c** as a white solid (117 mg, 82%). ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s), 2.30 (3H, s), 2.32 (3H, s), 6.00 (1H, d, J=11.9 Hz), 6.95 (1H, d, J=11.9 Hz), 7.04 (1H, d), 7.22 (1H, d). MS (FAB) *m/z*: 235.1 $(M+H)^+$. *Anal.* Calcd for $C_{13}H_{16}O_4$: C, 66.66; H, 6.02; O, 27.32. Found: C, 66.95; H, 6.23.

6-[(*Z*)-2-(Benzylmethylcarbamoyl)-vinyl]-2,3-dimethylphenyl Acetate (1e) In a manner similar to the preparation of **1a**, **11c** (115 mg, 0.49 mmol, in 4 ml dry CH_2Cl_2), EDC (94 mg, 0.49 mmol), methyl benzylamine (0.076 ml, 0.59 mmol), HOBt (66 mg, 0.49 mmol), and DMAP (42 mg, 0.343 mmol) were reacted to give **1e** as a white solid (137 mg, 83%). ^{1}H-NMR ($CDCl_3$) δ: 2.26 (3H, s), 2.31 (3H, s), 2.33 (3H, s), 2.67/2.87 (3H, s/s, rotamer), 4.32/4.57 (2H, s/s, rotamer), 6.09 (1H, d), 6.59 (1H, d), 6.81 (1H, d,), 7.03 (2H, br s), 7.20 (1H, d), 7.23—7.29 (3H, br s). MS (FAB) *m/z*: 338.2 $(M+H)^+$. *Anal.* Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.39; H, 7.17; N, 4.02.

6-[(*Z*)-2-(Diethylcarbamoyl)-vinyl]-2,3-dimethylphenyl Acetate (1f) In a manner similar to the preparation of **1b**, **11c** (244 mg, 1.043 mmol, in 10 ml dry CH_2Cl_2), EDC (200 mg, 1.043 mmol), diethylamine (0.129 ml, 1.251 mmol), HOBt (141 mg, 1.043 mmol), and DMAP (25 mg, 0.209 mmol) were reacted to give **1f** as a white solid (188 mg, 65%). ^{1}H-NMR ($CDCl_3$) δ: 0.90/1.09 (6H, t/t, rotamer), 2.05 (3H, s), 2.27 (3H, s), 2.35 (3H, s), 3.16/3.42 (4H, q/q, rotamer), 6.04 (1H, d), 6.52 (1H, d), 6.96 (1H, d), 7.32 (1H, d). MS (FAB) *m/z*: 290.2 $(M+H)^+$. *Anal.* Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.81; H, 8.18; N, 4.68.

6,8-Dimethylcoumarin (3d)[44] In a manner similar to the preparation of **3a**, 2,4-dimethyl phenol (**5d**) (2.440 g, 18 mmol) and propiolic acid (1.479 ml, 24 mmol) were reacted in methansulfonic acid (40 ml) to give **3d** as a gray solid (2.7552 g, 79%). ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s), 2.43 (3H, s), 6.36 (1H, d, J=9.7 Hz), 6.98 (1H, s), 7.83 (1H, s), 7.86 (1H, d, J=9.7 Hz).

2-[(*Z*)-3-Hydroxy-1-propenyl]-4,6-dimethylphenol (6d) In a manner similar to the preparation of **6a**, 6,8-dimethyl coumarin (**3d**) (2.4532 g, 14.1 mmol) in ether (60 ml) was treated with a suspension of LAH (1.072 g, 28.2 mmol) in ether (20 ml) to afford **6d** (986 mg, 38%) as gray white crystals. ^{1}H-NMR ($CDCl_3$) δ: 2.14 (3H, s), 2.25 (3H, s), 4.06 (2H, d, J=7.0 Hz), 5.32 (1H, s), 5.46 (1H, s), 6.18 (1H, m), 6.40 (1H, d, J=11.2 Hz), 6.62(2H, s). MS (EI) *m/z*: 178.1 (M^+). *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; O, 17.95. Found: C, 74.28; H, 7.71.

2-[(*Z*)-3-{[1-(*tert*-Butyl)-1,1-dimethyl-silanyl]oxy}-1-propenyl]-4,6-dimethylphenol (7d) In a manner similar to the preparation of **7a**, **6d** (926 mg, 5.10 mmol, in 15 ml dry THF), *tert*-butyldimethylsilyl chloride (840 mg, 5.60 mmol, in 30 ml dry THF) and DMAP (933 mg, 7.60 mmol, in 20 ml dry THF) were reacted to give **7d** as a white solid (1.280 g, 84%). ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.90 (9H, s), 2.15 (3H, s), 2.27 (3H, s), 4.03 (2H, d, J=7.1 Hz), 5.99 (1H, s), 6.10—6.18 (1H, m), 6.32 (1H, d, J=11.2 Hz), 6.63 (1H, s), 6.69 (1H, s). MS (EI) *m/z*: 292.2 (M^+). *Anal.* Calcd for $C_{17}H_{28}O_2Si$: C, 69.81; H, 9.65; O, 10.94; Si, 9.60. Found: C, 69.63; H, 9.71.

2-[(*Z*)-3-{[1-(*tert*-Butyl)-1,1-dimethyl-silanyl]oxy}-1-propenyl]-4,6-dimethylphenyl Acetate (8d) In a manner similar to the preparation of **8a**, **7d** (1.200 mg, 4.08 mmol), acetic anhydride (0.462 ml, 4.90 mmol), DMAP (100 mg, 0.816 mmol) and triethylamine (1.049 ml, 7.3 mmol) were treated to afford **8d** (1.332 g, 97%) as white solid. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 2.15 (3H, s), 2.21 (3H, s), 2.28 (3H, s), 4.01 (2H, d, J=6.9 Hz), 6.10—6.18 (1H, m), 6.32 (1H, d, J=11.1 Hz), 6.64 (1H, s), 6.69 (1H, s). MS (EI) *m/z*: 334.2 (M^+). *Anal.* Calcd for $C_{19}H_{30}O_3Si$: C, 68.22; H, 9.04; O, 14.35; Si, 8.40. Found: C, 68.48; H, 9.21.

2-[(*Z*)-3-Hydroxy-1-propenyl]-4,6-dimethylphenyl Acetate (9d) In a manner similar to the preparation of **9a**, **8d** (1.298 mg, 3.863 mmol, in 22 ml dry THF), water (22 ml) and acetic acid (65 ml) were reacted to give **9d** as a white oil (838 mg, 99%). ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s), 2.18 (3H, s), 2.27 (3H, s), 3.94 (2H, t), 6.00—6.06 (1H, m), 6.32 (1H, d, J=11.3 Hz), 6.67 (1H, s), 6.71 (1H, s). MS (EI) *m/z*: 220.1 (M^+). *Anal.* Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; O, 21.79. Found: C, 70.55; H, 7.22.

4,6-Dimethyl-2-[(*Z*)-3-oxo-1-propenyl]phenyl Acetate (10d) In a manner similar to the preparation of **10a**, **9d** (808 mg, 3.67 mmol) and 85% activated manganese(IV) oxide (749 mg×6, 7.34 mmol×6) were treated to afford **10d** (612 mg, 78%) as brown oil. ^{1}H-NMR ($CDCl_3$) δ: 2.16 (3H, s), 2.21 (3H, s), 2.58 (3H, s), 6.20 (1H, dd, J=11.4 Hz), 7.07 (1H, d), 7.17 (1H, d), 7.35 (1H, d, J=11.4 Hz), 9.53 (1H, d, J=8.2 Hz). MS (EI) *m/z*: 218.1 (M^+). *Anal.* Calcd for $C_{13}H_{16}O_3$: C, 71.54; H, 6.47. Found: C, 71.45; H, 6.50.

(*Z*)-3-[2-(Acetyloxy)-4,6-dimethylphenyl]acrylic Acid (11d) In a manner similar to the preparation of **11a**, 80% sodium chlorite (459 mg, 5.10 mmol) in water (4.08 ml), **10d** (530 mg, 2.43 mmol, in 2.9 ml acetonitrile), sodium phosphate (43 mg) in water (1.1 ml), and 30% hydrogen peroxide (0.35 ml) were reacted to give **11d** as a white solid (550 mg, 97%). ^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, s), 2.13 (3H, s), 2.28 (3H, s), 6.01 (1H, d, J=11.8 Hz), 6.93 (1H, d, J=11.8 Hz), 7.03 (1H, s), 7.08 (1H, s). MS (FAB)

m/z: 235.1 $(M+H)^+$. *Anal.* Calcd for $C_{13}H_{16}O_4$: C, 66.66; H, 6.02; O, 27.32. Found: C, 66.87; H, 6.17.

2-[(*Z*)-2-(Benzylmethylcarbamoyl)-vinyl]-4,6-dimethylphenyl Acetate (1g) In a manner similar to the preparation of **1a**, **11d** (275 mg, 1.175 mmol, in 10 ml dry CH_2Cl_2), EDC (225 mg, 1.175 mmol), methyl benzylamine (0.182 ml, 1.41 mmol), and DMAP (28 mg, 0.235 mmol) were reacted to give **1g** as a white solid (264 mg, 78%). ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s), 2.20 (3H, s), 2.36 (3H, s), 2.70/2.87 (3H, s/s, rotamer), 4.32/4.57 (2H, s/s, rotamer), 6.11 (1H, d, J=12.4 Hz), 6.60 (1H, d, J=12.4 Hz), 7.12 (1H, s), 7.22 (1H, s), 7.26 (5H, brs). MS (FAB) *m/z*: 338.2 $(M+H)^+$. *Anal.* Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.57; H, 6.79; N, 4.08.

2-[(*Z*)-2-(Diethylcarbamoylvinyl]-4,6-dimethylphenyl Acetate (1h) In a manner similar to the preparation of **1b**, **11d** (275 mg, 1.175 mmol, in 20 ml dry CH_2Cl_2), EDC (225 mg, 0.235 mmol), diethylamine (0.145 ml, 1.41 mmol), HOBt (159 mg, 1.175 mmol) and DMAP (28 mg, 0.235 mmol) were reacted to give **1h** as a white solid (221 mg, 76%). ^{1}H-NMR ($CDCl_3$) δ: 0.91/1.12 (3H, t/t, rotamer), 2.11 (3H, s), 2.24 (3H, s), 2.33 (3H, s), 3.15/3.41 (2H, q/q, rotamer), 6.05 (1H, d, J=12.6 Hz), 6.53 (1H, d, J=12.6 Hz), 6.97 (1H, s), 7.19 (1H, s). MS (FAB) *m/z*: 290.2 $(M+H)^+$. *Anal.* Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.69; H, 8.33; N, 4.75.

8-Methylcoumarin (3e)[45] In a manner similar to the preparation of **3a**, *o*-methylphenol (**5e**) (3.240 g, 30 mmol) and propiolic acid (2.488 ml, 36 mmol) were reacted in methansulfonic acid (30 ml) to give **3e** as a gray solid (1.916 g, 40%). ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s), 6.41 (1H, d, J=9.6 Hz), 7.17 (1H, t), 7.35 (2H, dd), 7.70 (1H, d, J=9.6 Hz).

2-[(*Z*)-3-Hydroxy-1-propenyl]-6-methylphenol (6e) In a manner similar to the preparation of **6a**, 8-dimethyl coumarin (**3e**) (415 mg, 2.60 mmol) in ether (20 ml) was treated with a suspension of LAH (198 mg, 5.20 mmol) in ether (5 ml) to afford **6e** (179 mg, 42%) as gray white crystals. ^{1}H-NMR (CD_3OD) δ: 2.27 (3H, s), 4.22 (2H, d, J=6.9 Hz), 6.08 (1H, m), 6.57 (2H, d, J=11.2 Hz), 6.81 (1H, t), 6.90 (1H, d), 7.07 (1H, d). MS (EI) *m/z*: 164.1 (M^+). *Anal.* Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37; O, 19.49. Found: C, 73.33; H, 7.39.

2-[(*Z*)-3-{[1-(*tert*-Butyl)-1,1-dimethyl-silanyl]oxy}-1-propenyl]-6-methylphenol (7e) In a manner similar to the preparation of **7a**, **6e** (142 mg, 0.87 mmol, in 6 ml dry THF), *tert*-butyldimethylsilyl chloride (143 mg, 0.95 mmol, in 3 ml dry THF) and DMAP (159 mg, 1.31 mmol, in 3 ml dry THF) were reacted to give **7e** as a white solid (176 mg, 73%). ^{1}H-NMR ($CDCl_3$) δ: 0.05 (6H, s), 0.89 (9H, s), 2.26 (3H, s), 4.16 (2H, d, J=7.2 Hz), 6.05 (1H, m), 6.50 (1H, d, J=11.3 Hz), 6.78 (1H, t), 6.87 (1H, d), 7.05 (1H, d). MS (EI) *m/z*: 278.2 (M^+). *Anal.* Calcd for $C_{16}H_{26}O_2Si$: C, 69.01 H, 9.41; O, 11.49; Si, 10.09. Found: C, 68.85; H, 9.29.

2-[(*Z*)-3-{[1-(*tert*-Butyl)-1,1-dimethylsilanyl]oxy}-1-propenyl]-6-methylphenyl Acetate (8e) In a manner similar to the preparation of **8a**, **7e** (176 mg, 0.63 mmol), acetic anhydride (0.071 ml, 0.76 mmol), DMAP (15 mg, 0.13 mmol) and triethylamine (0.163 ml, 0.134 mmol) were treated to afford **8e** (143 g, 71%) as white solid. ^{1}H-NMR ($CDCl_3$) δ: 0.03 (6H, s), 0.89 (9H, s), 2.14 (3H, s), 2.26 (3H, s), 4.26 (2H, d, J=6.9 Hz), 5.84 (1H, m), 6.32 (1H, d), 7.06 (3H, m). MS (EI) *m/z*: 320.2 (M^+). *Anal.* Calcd for $C_{18}H_{28}O_3Si$: C, 67.46; H, 8.81; O, 14.98; Si, 8.76. Found: C, 67.88; H, 8.59.

2-[(*Z*)-3-Hydroxy-1-propenyl]-6-methylphenyl Acetate (9e) In a manner similar to the preparation of **9a**, **8e** (43 mg, 0.134 mmol, in 1.0 ml dry THF), water (1.0 ml) and acetic acid (3.0 ml) were reacted to give **9e** as a white oil (30 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 2.18 (3H, s), 2.30 (3H, s), 4.20 (2H, t), 5.95 (1H, m), 6.45 (1H, d, J=11.4 Hz), 7.12 (3H, m). MS (EI) *m/z*: 206.1 (M^+). *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; O, 23.27. Found: C, 69.79; H, 6.78.

6-Methyl-2-[(*Z*)-3-oxo-1-propenyl]phenyl Acetate (10e) In a manner similar to the preparation of **10a**, **9e** (30 mg, 0.14 mmol) and 85% activated manganese(IV) oxide (29 mg×6, 0.28 mmol×6) were treated to afford **10e** (133 mg, 92%) as brown oil. ^{1}H-NMR ($CDCl_3$) δ: 2.21 (3H, s), 2.30 (3H, s), 6.19 (1H, dd, J=11.4 Hz), 7.20 (2H, d), 7.31 (1H, t), 7.50 (1H, d, J=11.4 Hz), 9.80 (1H, d, J=8.2 Hz). MS (EI) *m/z*: 204.1 (M^+). *Anal.* Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92; O, 23.50. Found: C, 70.11; H, 5.88.

(*Z*)-3-[2-(Acetyloxy)-3-methylphenyl]acrylic Acid (11e) In a manner similar to the preparation of **11a**, 80% sodium chlorite (22 mg, 0.24 mmol) in water (0.204 ml), **10e** (24 mg, 0.12 mmol, in 0.15 ml acetonitrile), sodium phosphate (43 mg) in water (0.055 ml), and 30% hydrogen peroxide (0.018 ml) were reacted to give **11e** as a white solid (25.8 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 2.16 (3H, s), 2.20 (3H, s), 6.15 (1H, d, J=11.9 Hz), 6.94 (1H, d, J=11.9 Hz), 7.14 (2H, d), 7.22 (1H, t). MS (FAB) *m/z*: 221.1 $(M+H)^+$. *Anal.* Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49; O, 29.06. Found: C, 65.33; H, 5.58.

2-[(*Z*)-2-(Benzylmethylcarbamoyl)-vinyl]-6-methylphenyl Acetate (1i) In a manner similar to the preparation of **1a**, **11e** (25.8 mg, 0.12 mmol, in 4 ml dry CH_2Cl_2), EDC (23 mg, 0.12 mmol), methyl benzylamine (0.020 ml, 0.15 mmol), HOBt (16 mg, 0.12 mmol), and DMAP (28 mg, 0.235 mmol) were reacted to give **1i** as a white solid (26.4 mg, 68%). ^{1}H-NMR ($CDCl_3$) δ: 2.17 (3H, s), 2.30 (3H, s), 2.66/2.86 (3H, s/s, rotamer), 4.32/4.57 (2H, s/s, rotamer), 6.14 (1H, d, J=12.3 Hz), 6.62 (1H, d, J=12.3 Hz), 6.92 (1H, t), 7.01 (1H, d), 7.14 (1H, d), 7.23 (5H, br s). MS (FAB) *m/z*: 324.2 $(M+H)^+$. *Anal.* Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.53; H, 6.70; N, 4.18.

2-[(*Z*)-2-(Diethylcarbamoylvinyl]-6-methylphenyl Acetate (1j) In a manner similar to the preparation of **1b**, **11e** (36 mg, 0.164 mmol, in 4 ml dry CH_2Cl_2), EDC (31 mg, 0.164 mmol), diethylamine (0.020 ml, 0.197 mmol), HOBt (22 mg, 0.164 mmol), and DMAP (4 mg, 0.033 mmol) were reacted to give **1j** as a white solid (35 mg, 75%). ^{1}H-NMR ($CDCl_3$) δ: 0.86/1.10 (3H, t/t, rotamer), 2.16 (3H, s), 2.35 (3H, s), 3.14/3.42 (2H, q/q, rotamer), 6.09 (1H, d, J=12.5 Hz), 6.57 (1H, d, J=12.5 Hz), 7.08 (1H, t), 7.17 (1H, d), 7.41 (1H, d). MS (FAB) *m/z*: 276.2 $(M+H)^+$. *Anal.* Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09; O, 14.84. Found: C, 70.02; H, 7.73; N, 4.96.

5,6,7-Trimethylcoumarin (3f) In a manner similar to the preparation of **3a**, 3,4,5-trimethyl phenol (**5f**) (1.362 g, 10 mmol) and propiolic acid (0.746 ml, 11 mmol) were reacted in methansulfonic acid (40 ml) to give **3f** as a gray solid (0.996 g, 53%). ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s), 2.45 (3H, s), 2.49 (3H, s), 6.42 (1H, d, J=9.7 Hz), 7.00 (1H, d), 7.92 (1H, d, J=9.7 Hz). MS (EI) *m/z*: 188.1 (M^+). *Anal.* Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43; O, 17.00. Found: C, 76.50; H, 6.61.

2-[(*Z*)-3-Hydroxy-1-propenyl]-3,4,5-trimethylphenol (6f) In a manner similar to the preparation of **6a**, 5,6,7-dimethyl coumarin (**3f**) (866 mg, 4.61 mmol) in ether (40 ml) was treated with a suspension of LAH (380 mg, 9.21 mmol) in ether (15 ml) to afford **6f** (258 mg, 30%) as gray white crystals. ^{1}H-NMR (CD_3OD) δ: 2.12 (3H, s), 2.13 (3H, s), 2.23 (3H, s), 3.93 (2H, d, J=7.0 Hz), 5.97—6.02 (1H, m), 6.26 (1H, d, J=11.1 Hz), 6.98 (1H, d); 7.05 (1H, d). MS (EI) *m/z*: 192.1 (M^+). *Anal.* Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39; O, 16.64. Found: C, 74.79; H, 8.41.

2-[(*Z*)-3-{[1-(*tert*-Butyl)-1,1-dimethylsilanyl]oxy}-1-propenyl]-3,4,5-trimethylphenol (7f) In a manner similar to the preparation of **7a**, **6f** (153 mg, 0.8 mmol, in 8 ml dry THF), *tert*-butyldimethylsilyl chloride (132 mg, 0.88 mmol, in 6 ml dry THF) and DMAP (146 mg, 1.2 mmol, in 10 ml dry THF) were reacted to give **7f** as a white solid (163 mg, 66%). ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.88 (9H, s), 2.11 (3H, s), 2.12 (3H, s), 2.25 (3H, s), 4.01 (2H, d, J=7.5 Hz), 6.10—6.15 (1H, m), 6.37 (1H, d, J=11.4 Hz), 6.66 (1H, s). MS (EI) *m/z*: 306.2 (M^+). *Anal.* Calcd for $C_{18}H_{30}O_2Si$: C, 70.53; H, 9.87; O, 10.44; Si, 9.16. Found: C, 70.58; H, 9.86.

2-[(*Z*)-3-{[1-(*tert*-Butyl)-1,1-dimethyl-silanyl]oxy}-1-propenyl]-3,4,5-trimethylphenyl Acetate (8f) In a manner similar to the preparation of **8a**, **7f** (63 mg, 0.205 mmol), acetic anhydride (0.030 ml, 245 mmol), DMAP (5 mg, 0.041 mmol) and TEA (0.052 ml, 0.369 mmol) were treated to afford **8f** (64 mg, 89%) as white solid. ^{1}H-NMR ($CDCl_3$) δ: 0.02 (6H, s), 0.87 (9H, s), 2.17 (3H, s), 2.19 (3H, s), 2.21 (3H, s), 2.29 (3H, s), 4.04 (2H, d, J=6.7 Hz), 5.86—5.92 (1H, m), 6.18 (1H, d, J=11.2 Hz), 6.73 (1H, s). MS (EI) *m/z*: 348.2 (M^+). *Anal.* Calcd for $C_{20}H_{32}O_3Si$: C, 68.92; H, 9.25; O, 13.77, Si, 8.06. Found: C, 68.92; H, 9.36.

2-[(*Z*)-3-Hydroxy-1-propenyl]-3,4,5-trimethylphenyl Acetate (9f) In a manner similar to the preparation of **9a**, **8f** (64 mg, 0.183 mmol, in 2.0 ml dry THF), water (2.0 ml) and acetic acid (6.0 ml) were reacted to give **9f** as a white oil (48 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s), 2.16 (3H, s), 2.22 (3H, s), 2.28 (3H, s), 3.94 (2H, t), 5.98—6.02 (1H, m), 6.30 (1H, d, J=11.4 Hz), 6.71 (1H, s). MS (EI) *m/z*: 234.1 (M^+). *Anal.* Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74; O, 20.49. Found: C, 71.18; H, 7.76.

3,4,5-Trimethyl-2-[(*Z*)-3-oxo-1-propenyl]phenyl Acetate (10f) In a manner similar to the preparation of **10a**, **9f** (48 mg, 0.205 mmol) and 85% activated manganese(IV) oxide (42 mg×6, 0.410 mmol×6) were treated to afford **10f** (133 mg, 92%) as brown oil. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s), 2.19 (3H, s), 2.23 (3H, s), 2.31 (3H, s), 6.18 (1H, dd, J=11.4 Hz), 6.79 (1H, s), 7.36 (1H, d, J=11.4 Hz), 9.53 (1H, d, J=8.2 Hz). MS (EI) *m/z*: 232.1 (M^+). *Anal.* Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94; O, 20.66. Found: C, 72.22; H, 6.98.

(*Z*)-3-[2-(Acetyloxy)-4,5,6-trimethylphenyl]acrylic Acid (11f) In a manner similar to the preparation of **11a**, 80% sodium chlorite (28 mg, 0.308 mmol) in water (0.220 ml), **10f** (32 mg, 0.147 mmol, in 0.2 ml acetonitrile), sodium phosphate (6.0 mg) in water (0.060 ml), and 30% hydrogen peroxide (0.020 ml) were reacted to give **11f** as a white solid (35 mg, 96%).

^{1}H-NMR ($CDCl_3$) δ: 2.16 (3H, s), 2.19 (3H, s), 2.23 (3H, s), 2.28 (3H, s), 6.14 (1H, d, J=11.9 Hz), 6.74 (1H, s), 6.94 (1H, d, J=11.9 Hz). MS (FAB) m/z: 249.1 $(M+H)^+$. *Anal.* Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50; O, 25.78. Found: C, 67.93; H, 6.52.

2-[(*Z*)-2-(Benzylmethylcarbamoyl)-vinyl]-3,4,5-trimethylphenyl Acetate (1k) In a manner similar to the preparation of **1a**, **11f** (17 mg, 0.0685 mmol, in 2.5 ml dry CH_2Cl_2), EDC (14 mg, 0.0685 mmol), methyl benzylamine (0.011 ml, 0.0823 mmol), HOBt (9 mg, 0.0685 mmol), and DMAP (2 mg, 0.0137 mmol) were reacted to give **1k** as a white solid (16 mg, 67%). ^{1}H-NMR ($CDCl_3$) δ: 2.14 (3H, s), 2.19 (3H, s), 2.21 (3H, s), 2.27 (3H, s), 2.69/2.80 (3H, s/s, rotamer), 4.40/4.50 (2H, s/s, rotamer), 6.30 (1H, d, J=12.2 Hz), 6.62 (1H, d, J=12.2 Hz), 6.73 (1H, s), 7.08 (2H, br s); 7.22—7.24 (3H, br s). MS (FAB) m/z: 352 $(M+H)^+$. *Anal.* Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99; O, 13.66. Found: C, 75.02; H, 7.36; N, 3.71.

2-[(*Z*)-2-(Diethylcarbamoylvinyl]-3,4,5-trimethylphenyl Acetate (1l) In a manner similar to the preparation of **1b**, **11f** (17 mg, 0.0685 mmol, in 2.5 ml dry CH_2Cl_2), EDC (14 mg, 0.0685 mmol), diethylamine (0.0168 ml, 0.0823 mmol), HOBt (9 mg, 0.0685 mmol) and DMAP (2 mg, 0.0137 mmol) were reacted to give **1l** as a white solid (10.2 mg, 49%). ^{1}H-NMR ($CDCl_3$) δ: 0.99/1.00 (6H, t/t, rotamer), 2.14 (3H, s), 2.17 (3H, s), 2.20 (3H, s), 2.24 (3H, s), 3.24/3.29 (4H, q/q, rotamer), 6.26 (1H, d, J=12.2 Hz), 6.63 (1H, d, J=12.2 Hz), 6.69 (1H, s). MS (FAB) m/z: 304.2 $(M+H)^+$. *Anal.* Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62; O, 15.82. Found: C, 71.06; H, 8.34; N, 4.55.

2-[(*Z*)-3-Hydroxy-1-propenyl]-4-methylphenol (6g) In a manner similar to the preparation of **6a**, 6-methylcoumarin (**3g**) (8.02 g, 50 mmol) in ether (200 ml) was treated with a suspension of LAH (3.79 g, 100 mmol) in ether (100 ml) to afford **6g** (2.50 g, 30%) as white crystals. ^{1}H-NMR (CD_3OD) δ: 2.23 (3H, s), 4.25 (2H, dd, J=6.4, 1.2 Hz), 5.78 (1H, m), 6.59 (1H, J=11.7 Hz), 6.67—6.91 (3H, m). MS (EI) m/z: 164 (M^+, 34), 145 (100), 131 (22), 91 (14), 77 (8). *Anal.* Calcd for $C_{10}H_{12}O_2$: C, 73.15; H,7.37. Found: C, 73.31; H, 7.41.

2-[(*Z*)-3-{[1-(*tert*-Butyl)-1,1-dimethylsilanyl]oxy}-1-propenyl]-4-methylphenol (7g) In a manner similar to the preparation of **7a**, **6g** (630 mg, 3.8 mmol, in 5.9 ml dry THF), *tert*-butyldimethylsilyl chloride (640 mg, 4.2 mmol, in 4.4 ml dry THF) and DMAP (700 mg, 5.7 mmol, in 7.4 ml dry THF) were reacted to give **7g** as a white solid (880 mg, 83%). ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.90 (9H, s), 2.26 (3H, s), 4.16 (2H, d, J=7.17 Hz), 6.02 (1H, m), 6.48 (1H, d, J=11.3 Hz), 6.79—6.97 (3H, m). MS (FAB) m/z: 278 (M^+, 65), 221 (100), 203 (24). *Anal.* Calcd for $C_{16}H_{26}O_2Si$: C, 69.01; H, 9.41. Found: C, 69.06; H, 9.43.

2-[(*Z*)-3-{[1-(*tert*-Butyl)-1,1-dimethylsilanyl]oxy}-1-propenyl]-4-methylphenyl Acetate (8g) In a manner similar to the preparation of **8a**, **7g** (870 mg, 3.1 mmol), acetic anhydride (0.40 ml, 3.7 mmol), DMAP (80 mg, 0.60 mmol) and triethylamine (0.8 ml, 5.6 mmol) were treated to afford **8g** (0.984 g, 87%) as colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.04 (6H, s), 0.89 (9H, s), 2.26 (3H, s), 2.33 (3H, s), 4.27 (2H, m), 5.86 (1H, m), 6.35 (1H, d, J=11.5 Hz), 6.93—7.10 (3H, m). MS (FAB) m/z: 321 $[(M+H)^+$, 63], 277 (20), 263 (100), 221 (52), 203 (30). *Anal.* Calcd for $C_{18}H_{28}O_3Si$: C, 67.46; H, 8.81. Found: C, 67.68; H, 8.78.

2-[(*Z*)-3-Hydroxy-1-propenyl]-4-methylphenyl Acetate (9g) In a manner similar to the preparation of **9a**, **8g** (960 mg, 2.68 mmol, in 8.5 ml dry THF), water (8.5 ml) and acetic acid (25.5 ml) were reacted to give **9g** as a yellow oil (640 mg, 100%). ^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s), 2.34 (3H, s), 4.23 (2H, t, J=5.6 Hz), 5.95 (1H, m), 6.44 (1H, d, J=11.6 Hz), 6.93—7.11 (3H, m). MS (FAB) m/z: 207 $[(M+H)^+$, 41], 189 (96), 164 (41). *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 70.07; H, 6.99.

4-Methyl-2-[(*Z*)-3-oxo-1-propenyl]phenyl Acetate (10g) In a manner similar to the preparation of **10a**, **9g** (586 mg, 2.84 mmol) and 85% activated manganese(IV) oxide (581 mg×6, 5.7 mmol×6) were treated to afford **10g** (490 mg, 85%) as brown oil. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (3H, s), 2.37 (3H, s), 6.19 (1H, dd, J=11.4, 8.2 Hz), 7.04 (1H, d, J=8.2 Hz), 7.16—7.29 (2H, m), 7.49 (1H, d, J=11.4 Hz), 9.82 (1H, d, J=8.2 Hz).

(*Z*)-3-[2-(Acetyloxy)-5-methylphenyl]acrylic Acid (11g) In a manner similar to the preparation of **11a**, 80% sodium chlorite (190 mg, 1.64 mmol) in water (1.50 ml), **10g** (210 mg, 1.01 mmol, in 1.0 ml acetonitrile), sodium phosphate (30 mg, 0.28 mmol) in water (0.4 ml), and 30% hydrogen peroxide (0.12 ml) were reacted to give **11g** as a white solid (130 mg, 57%). ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s), 2.33, (3H, s), 6.05 (1H, d, J=12.3 Hz), 6.95 (1H, s), 6.96 (1H, d, J=11.2 Hz), 7.16—7.25 (2H, m). MS (EI) m/z: 220 (M^+, 2), 178 (28), 160 (100), 132 (73), 104 (11), 77(12). *Anal.* Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.59; H, 5.53.

2-[(*Z*)-2-(Benzylmethylcarbamoyl)-vinyl]-4-methylphenyl Acetate (1m) In a manner similar to the preparation of **1a**, **11g** (230 mg, 1.10 mmol, in 5 ml dry CH_2Cl_2), EDC (250 mg, 1.3 mmol), methyl benzylamine (0.2 ml), and DMAP (30 mg, 0.2 mmol) were reacted to give **1m** as a yellow oil (310 mg, 90%). ^{1}H-NMR ($CDCl_3$) δ: 2.24 and 2.33 (3H, ss), 2.27 and 2.29 (3H, ss), 2.71 and 2.87 (3H, ss), 4.33 and 4.58 (2H, ss), 6.14 and 6.15 (1H, dd, J=12.6 Hz), 6.63 (1H, d, J=12.6 Hz), 6.91—7.37 (8H, m). MS (FAB) m/z: 324 $[(M+H)^+$, 100], 307 (86), 264 (42), 220 (10). *Anal.* Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.47; H, 6.65; N, 4.18.

2-[(*Z*)-2-(Diethylcarbamoylvinyl]-4-methylphenyl Acetate (1n) In a similar manner to **1a**, **11g** (0.059 g, 0.27 mmol) was coupled to diethylamine (0.06 ml, 0.57 mmol), using EDC (0.063 g, 0.32 mmol), HOBt (0.042 g, 0.31 mmol), and DMAP (0.007 g, 0.05 mmol). The solution was stirred at room temperature for 4.5 h. The crude was purified by chromatotron using EtOAc/Hexane (1/5) to give colorless oil (59.2 mg, 80% yield). ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, t, J=7.1 Hz), 1.13 (3H, t, J=7.1 Hz), 2.28 (3H, s), 2.32 (3H, s), 3.17 (2H, q, J=7.1 Hz), 3.42 (2H, q, J=7.1 Hz), 6.08 (1H, d, J=12.7 Hz), 6.57 (1H, d, J=12.6 Hz), 6.92 (1H, d, J=8.2 Hz), 7.10 (1H, dd, J=1.8, 8.4 Hz), 7.36 (1H, s). MS (CI) m/z: 276 $[(M+H)^+$, 100], 234 (41), 216 (28), 161 (17). *Anal.* Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.62; H, 7.70; N, 5.09.

2-[(*Z*)-3-Hydroxy-1-propenyl]-5-methylphenol (6h) In similar manner to procedure **6a**, a solution of 7-methylcoumarin (1.6 g, 10 mmol) in diethyl ether (220 ml) was reduced by suspension of LAH (0.78 g, 20 mmol) in Et_2O (50 ml) for 10 min, extracted with 3×80 ml of Et_2O, washed with 3×80 ml of water, 2×75 ml of brine. The crude (1.65 g) was recrystallized to give white solid (0.88 g, 54% yield). ^{1}H-NMR (CD_3OD) δ: 2.25 (3H, s), 4.26 (2H, d, J=6.4 Hz), 5.75 (1H, m), 6.59 (1H, J=12.5 Hz), 6.61—6.92 (3H, m). MS (EI) m/z: 164 (M^+, 30), 145 (100), 132 (4), 121 (26), 108 (19), 91 (24), 77 (18). *Anal.* Calcd for $C_{10}H_{12}O_2$: C, 73.15; H,7.37. Found: C, 73.37; H, 7.47.

2-[(*Z*)-3-{[1-(*tert*-Butyl)-1,1-dimethyl-silanyl]oxy}-1-propenyl]-5-methylphenol (7h) Using similar manner to **7a**, **6h** (0.60 g, 3.66 mmol) in THF (5.7 ml) was added to TBDMSCl (0.61 g, 4.03 mmol) in THF (4.3 ml), then dropwise of DMAP (0.67 g, 5.49 mmol) in THF (7.1 ml) to give white solid (79% yield). ^{1}H-NMR ($CDCl_3$) δ: 0.06 (6H, s), 0.81 (9H, s), 2.30 (3H, s), 4.17 (2H, d, J=7.1 Hz), 5.99 (1H, m), 6.48 (1H, d, J=11.3 Hz), 6.71—6.91 (3H, m). MS (FAB) m/z: 278 (M^+, 75), 221 (100), 203 (48). *Anal.* Calcd for $C_{16}H_{26}O_2Si$: C, 69.01; H, 9.41. Found: C, 69.19; H, 9.23.

2-[(*Z*)-3-{[1-(*tert*-Butyl)-1,1-dimethyl-silanyl]oxy}-1-propenyl]-5-methylphenyl Acetate (8h) In a manner similar to **8a**, **7h** (0.82 g, 2.9 mmol) in DCM (11 ml) was acetylated by Ac_2O (0.34 ml, 3.6 mmol), DMAP (0.07 g, 0.6 mmol), and TEA (0.75 ml, 5.4 mmol). After the reaction, the oil was dissolved into 40 ml of EtOAc, washed with 2×40 ml×1% HCl, 5% $NaHCO_3$ (40 ml), water (40 ml), brine (40 ml) to give colorless oil (0.94 g, 100%). ^{1}H-NMR ($CDCl_3$) δ: 0.03 (6H, s), 0.88 (9H, s), 2.27 (3H, s), 2.35 (3H, s), 4.29 (2H, d, J=6.1 Hz), 5.84 (1H, m), 6.34 (1H, d, J=11.6 Hz), 6.88 (1H, s), 7.02 (1H, d, J=7.9 Hz), 7.10 (1H, d, J=7.7 Hz). MS (FAB) m/z: 321 $[(M+H)^+$, 63], 277 (20), 263 (100), 221 (52), 203 (30).

2-[(*Z*)-3-Hydroxy-1-propenyl]-5-methylphenyl Acetate (9h) In a similar manner to **9a**, **8h** (0.93 g, 2.90 mmol) was treated with THF–water–HOAc: (8.5 : 8.5 : 25.5) for 8 h, dissolved into 50 ml of EtOAc, washed with 2×50 ml×5% $NaHCO_3$, 2×50 ml water, brine (50 ml) to give yellow oil (0.60 g, 100%). ^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s), 2.35 (3H, s), 4.23 (2H, d, J=6.6 Hz), 5.93 (1H, m), 6.43 (1H, d, J=11.5 Hz), 6.87 (1H, s), 7.03 (1H, d, J=8.1 Hz), 7.07 (1H, d, J=7.7 Hz). MS (FAB) m/z: 206 (M^+, 40), 189 (100), 164 (37). *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.61; H, 7.01.

5-Methyl-2-[(*Z*)-3-oxo-1-propenyl]phenyl Acetate (10h) In a similar manner to **10a**, **9h** (0.36 g, 1.76 mmol) was oxidized by MnO_2 (0.36 g, 3.52 mmol) to give dark yellow oil (0.28 g, 79%). ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s), 2.40 (3H, s), 6.17 (1H, dd, J=11.4, 8.2 Hz), 6.98 (1H, s), 7.10 (1H, d, J=7.7 Hz), 7.27 (1H, d, J=7.7 Hz), 7.49 (1H, d, J=11.4 Hz), 9.82 (1H, d, J=8.2 Hz).

(*Z*)-3-[2-(Acetyloxy)-4-methyl-phenyl]acrylic Acid (11h) In a similar manner to **11a**, **10h** (0.28 g, 1.39 mmol) in acetonitrile (1 ml), was oxidized by sodium chlorite (0.22 g, 1.94 mmol) in water (2 ml) in the presence of sodium monophosphate (0.04 g, 0.37 mmol) in water (0.55 ml), hydrogen peroxide (0.16 ml, 1.4 mmol). After the reaction, the sodium sulfite (0.1 g) was added, the solution was extracted with 3×20 ml EtOAc. The organic layer was then washed with 2×20 ml water and 2×20 ml brine. The crude was then purified to give light yellow solid (0.21 g, 70%). ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s), 2.33 (3H, s), 6.02 (1H. d, J=12.3 Hz), 6.90 (1H, s), 6.97 (1H, d, J=12.4 Hz), 7.04 (1H, d, J=7.9 Hz), 7.41 (1H, d, J=7.9 Hz). MS (EI) m/z: 221 (M^+, 1), 160 (100), 132 (67), 104 (12), 77 (17). *Anal.* Calcd

for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.45; H, 5.60.

2-[(*Z*)-2-(Benzylmethylcarbamoyl)-vinyl]-5-methylphenyl Acetate (1o) In a similar manner to **1a**, **11h** (0.21 g, 0.96 mmol) was coupled to *N*-benzylmethylamine (0.15 ml, 1.05 mmol), using DCC (0.24 g, 1.15 mmol), HOBt (0.14 g, 1.05 mmol), and DMAP (0.02 g, 0.19 mmol). After the reaction, the reaction mixture was cooled to −78 °C, and DCU was filtered. The crude was purified to give yellow oil (87 mg, 28% yield). ^{1}H-NMR ($CDCl_3$) δ: 2.28 and 2.30 (3H, ss), 2.31 and 2.37 (3H, ss), 2.69 and 2.87 (3H, ss), 4.35 and 4.58 (2H, ss), 6.11 and 6.13 (1H, dd, J=12.6 Hz), 6.61 and 6.62 (1H, dd, J=12.5 Hz), 6.80—7.49 (8H, m). MS (FAB) *m/z*: 324 [(M+H)$^+$, 100], 307 (86), 264 (42), 220 (10).

2-[(*Z*)-2-(Diethylcarbamoylvinyl]-5-methylphenyl Acetate (1p) In a similar manner to **1b**, **11h** (0.10 g, 0.45 mmol) was coupled to diethylamine (0.10 ml, 0.96 mmol), using EDC (0.11 g, 0.55 mmol), HOBt (0.068 g, 0.51 mmol), and DMAP (0.011 g, 0.09 mmol). The solution was stirred at room temperature for 3.5 h. The crude was purified by chromatotron using EtOAc–hexane (1 : 5) to give colorless light yellow oil (0.094 g, 75% yield). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7.1 Hz), 1.12 (3H, t, J=7.1 Hz), 2.32 (3H, s), 2.33 (3H, s), 3.19 (2H, q, J=7.2 Hz), 3.42 (2H, q, J=7.1 Hz), 6.06 (1H, d, J=12.6 Hz), 6.56 (1H, d, J=12.6 Hz), 6.85 (1H, s), 6.97 (1H, d, J=7.9 Hz), 7.47 (1H, d, J=8.0 Hz). MS (CI) *m/z*: 276 [(M+H)$^+$, 100], 234 (51), 216 (43), 161 (13). *Anal.* Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.60; H, 7.72; N, 5.10.

2-[(*Z*)-3-Hydroxy-1-propenyl]-5-methoxyphenol (6i) In similar manner to procedure **6a**, a solution of 7-methoxycoumarin (3.5 g, 20 mmol) in Et_2O (400 ml) was reduced by suspension of LAH (1.52 g, 40 mmol) in Et_2O (60 ml) for 5 min, extracted with 3×40 ml of Et_2O, washed with 3×200 ml of water, 2×150 ml of brine. The crude (3.63 g) was recrystallized from DCM to give white solid (1.42 g, 39% yield). ^{1}H-NMR (CD_3OD) δ: 3.30 (3H, s), 4.26 (2H, d, J=6.4 Hz), 5.70 (1H, m), 6.37 (1H, s), 6.40 (1H, s), 6.56 (1H, J=11.6 Hz), 6.96 (1H, J=7.9 Hz). MS (EI) *m/z*: 180 (M$^+$, 82), 161 (100), 147 (25), 137 (83), 124 (46), 91 (12), 77 (10). *Anal.* Calcd for $C_{10}H_{12}O_2$: C, 66.65; H, 6.71. Found: C, 66.49; H, 6.72.

2-[(*Z*)-3-{[1-(*tert*-Butyl)-1,1-dimethylsilanyl]oxy}-1-propenyl]-5-methoxyphenol (7i) Using similar manner to **7a**, **6i** (0.60 g, 3.31 mmol) in THF (5 ml) was added to TBDMSCl (0.55 g, 3.64 mmol) in THF (4 ml), then dropwise of DMAP (0.61 g, 4.96 mmol) in THF (6.5 ml) to give white solid (0.77 g, 80% yield). ^{1}H-NMR ($CDCl_3$) δ: 0.07 (6H, s), 0.90 (9H, s), 3.79 (3H, s), 4.16 (2H, d, J=7.5 Hz), 5.97 (1H, dt, J=11.2, 7.2 Hz), 6.45—6.49 (3H, m), 6.93 (1H, d, J=8.0 Hz). MS (FAB) *m/z*: 295 [(M+H)$^+$, 71], 237 (100), 207 (66). *Anal.* Calcd for $C_{16}H_{26}O_2Si$: C, 65.26; H, 8.90. Found: C, 65.31; H, 8.85.

2-[(*Z*)-3-{[1-(*tert*-Butyl)-1,1-dimethylsilanyl]oxy}-1-propenyl]-3-methoxyphenyl Acetate (8i) In a manner similar to **8a**, **7i** (0.77 g, 2.6 mmol) in DCM (14 ml) was acetylated by Ac_2O (0.3 ml, 3.1 mmol), DMAP (0.07 g, 0.5 mmol), and TEA (0.65 ml, 4.7 mmol). After the reaction, the oil was dissolved into 50 ml of EtOAc, washed with 2×30 ml of 1% HCl, 5% $NaHCO_3$ (50 ml), water (50 ml), brine (40 ml) to give colorless oil (0.87 g, 99%). ^{1}H-NMR ($CDCl_3$) δ: 0.03 (6H, s), 0.89 (9H, s), 2.28 (3H, s), 3.80 (3H, s), 4.29 (2H, dd, J=6.2, 1.4 Hz), 5.81 (1H, m), 6.31 (1H, d, J=11.5 Hz), 6.62 (1H, d, J=2.5 Hz), 6.77 (1H, dd, J=8.6, 2.5 Hz), 7.14 (1H, d, J=8.6 Hz). MS (FAB) *m/z*: 337 [(M+H)$^+$, 28], 293 (29), 279 (100), 237 (38), 205 (93). *Anal.* Calcd for $C_{18}H_{28}O_4Si$: C, 64.25; H, 8.39. Found: C, 64.13; H, 8.31.

2-[(*Z*)-3-Hydroxy-1-propenyl]-5-methoxyphenyl Acetate (9i) In a similar manner to **9a**, **8i** (0.85 g, 2.53 mmol) was treated with THF–water–AcOH (7.2 : 7.2 : 21.5) for 4.5 h, dissolved into 70 ml of EtOAc, washed with 2×50 ml of 5% $NaHCO_3$, water (70 ml), brine (50 ml) to give light yellow oil (0.56 g, 100%). ^{1}H-NMR ($CDCl_3$) δ: 2.28 (3H, s), 3.80 (3H, s), 4.24 (2H, d, J=6.1 Hz), 5.90 (1H, m), 6.40 (1H, d, J=11.4 Hz), 6.62 (1H, d, J=2.3 Hz), 6.78 (1H, dd, J=8.5, 2.4 Hz), 7.11 (1H, d, J=8.4 Hz). MS (FAB) *m/z*: 222 (M$^+$, 25), 205 (37). *Anal.* Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.12; H, 6.39.

5-Methoxy-2-[(*Z*)-3-oxo-1-propenyl]phenyl Acetate (10i) In a similar manner to **10a**, **9i** (0.55 g, 2.47 mmol) was oxidized by MnO_2 (0.50 g, 4.93 mmol) to give dark yellow oil (0.40 g, 74%). ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s), 3.84 (3H, s), 6.14 (1H, dd, J=11.3, 8.1 Hz), 6.72 (1H, d, J=2.4 Hz), 6.83 (1H, dd, J=8.4, 2.4 Hz), 7.32 (1H, d, J=8.4 Hz), 7.44 (1H, d, J=11.4 Hz), 9.84 (1H, d, J=8.2 Hz).

(*Z*)-3-[2-(Acetyloxy)-4-methoxyphenyl]acrylic Acid (11i) In a similar manner to **11a**, **10i** (0.633 g, 2.87 mmol) in acetonitrile (2.5 ml), was oxidized by sodium chlorite (0.476 g, 4.21 mmol) in water (4.2 ml) in the presence of sodium monophosphate (0.099 g, 0.83 mmol) in water (1 ml), hydrogen peroxide (0.36 ml, 3.13 mmol). After the reaction, the sodium sulfite (1 g) was added, the solution was extracted with 3×30 ml EtOAc. The organic layer was then washed with 2×30 ml water and 2×30 ml brine. The crude was then recrystallized from EtOAc–hexane (1 : 5) to give 0.53 g yellow to off-white solid (77%). ^{1}H-NMR ($CDCl_3$) δ: 2.29 (3H, s), 3.81 (3H, s), 5.96 (1H. d, J=12.4 Hz), 6.64 (1H, d, J=2.34 Hz), 6.79 (1H, dd, J=8.7, 2.4 Hz), 6.94 (1H, d, J=12.2 Hz), 7.59 (1H, d, J=8.8 Hz).

2-[(*Z*)-2-(Benzylmethylcarbamoyl)vinyl]-5-methoxyphenyl Ester (1q) In a similar manner to **1a**, **11i** (0.101 g, 0.42 mmol) was coupled to *N*-benzylmethylamine (0.10 ml, 0.47 mmol), using EDC (0.10 g, 0.51 mmol), HOBt (0.064 g, 0.47 mmol), and DMAP (0.01 g, 0.08 mmol). The solution was stirred at room temperature for 4.5 h. The crude was purified by chromatotron using EtOAc–hexane (1 : 5) to give yellow oil (52 mg, 37% yield). ^{1}H-NMR ($CDCl_3$) δ: 2.29 and 2.30 (3H, ss), 2.70 and 2.88 (3H, ss), 3.77 and 3.82 (3H, ss), 4.37 and 4.59 (2H, ss), 6.05 and 6.36 (1H, dd, J=12.5 Hz), 6.50—7.56 (9H, m). MS (CI) *m/z*: 339 [(M+H)$^+$, 100], 298 (53), 280 (32), 177 (42). *Anal.* Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.97; H, 6.24; N, 4.21.

2-[(*Z*)-2-(diethylcarbamoyl)vinyl]-5-methoxyphenyl Acetate (1r) In a similar manner to **1b**, **11i** (0.101 g, 0.43 mmol) was coupled to diethylamine (0.10 ml, 0.47 mmol), using EDC (0.10 g, 0.52 mmol), HOBt (0.064 g, 0.47 mmol), and DMAP (0.012 g, 0.098 mmol). The solution was stirred at room temperature for 1 h. The crude was purified by chromatotron using EtOAc–hexane (1 : 5) to give yellow oil (37 mg, 29% yield). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.1 Hz), 1.13 (3H, t, J=7.1 Hz), 2.33 (3H, s), 3.20 (2H, q, J=7.1 Hz), 3.43 (2H, q, J=7.1 Hz), 3.79 (3H, s), 6.01 (1H, d, J=12.6 Hz), 6.51 (1H, d, J=12.6 Hz), 6.59 (1H, d, J=2.3 Hz), 6.71 (1H, dd, J=8.7, 2.3 Hz), 7.53, (1H, d, J=8.6 Hz). MS (CI) *m/z*: 292 [(M+H)$^+$, 100], 250 (40), 232 (33), 177 (14). *Anal.* Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.94; H, 7.27; N, 4.80.

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