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CONVENIENT SYNTHESIS OF A SIMPLE COUMARIN FROM SALICYLALDEHYDE AND WITTIG REAGENT. IV[1a-c]: IMPROVED SYNTHETIC METHOD OF SUBSTITUTED COUMARINS †

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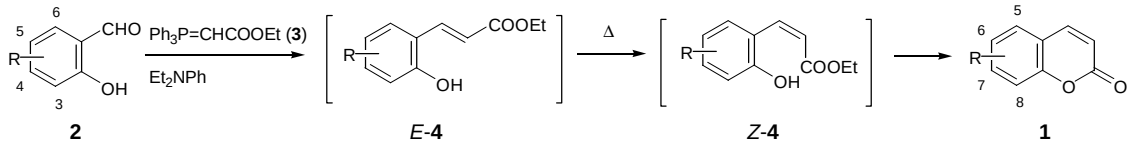
Abstract - The reaction of salicylaldehydes (**2**) with Horner-Wadsworth-Emmons (HWE) or Ando-HWE reagents was attempted to afford intramolecular phosphonate derivatives (**6**). A new synthetic method for coumarins (**1**) was achieved by using protected **2**.

Previously, we reported a convenient method for synthesizing a coumarin (**1**) by the Wittig reaction of a variety of salicylaldehydes (**2**) with carbethoxymethylenetriphenylphosphorane (**3**) in *N*,*N*-diethylaniline under reflux (Scheme 1).[1a-c] This method afforded the desired coumarin in high yield. However, there was a problem in applying it to some coumarins, especially those with a substituent at the 6 or 8 position. In this paper, we describe an improved synthetic method for coumarins.



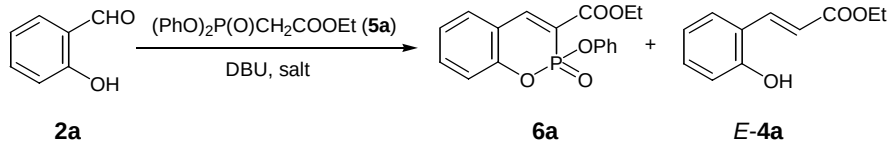
Scheme 1

We attempted *Z*-olefination (the Ando-HWE reaction)[2] of **2**, which is known as the *Z*-selective Horner-Wadsworth-Emmons (HWE) reaction (Table 1). Treatment of salicylaldehyde (**2a**) with ethyl diphenylphosphonoacetate (**5a**) at 0°C in the presence of NaI gave an unexpected intramolecular

† Dedicated to Professor Yuichi Kanaoka for the celebration of his 75th birthday.

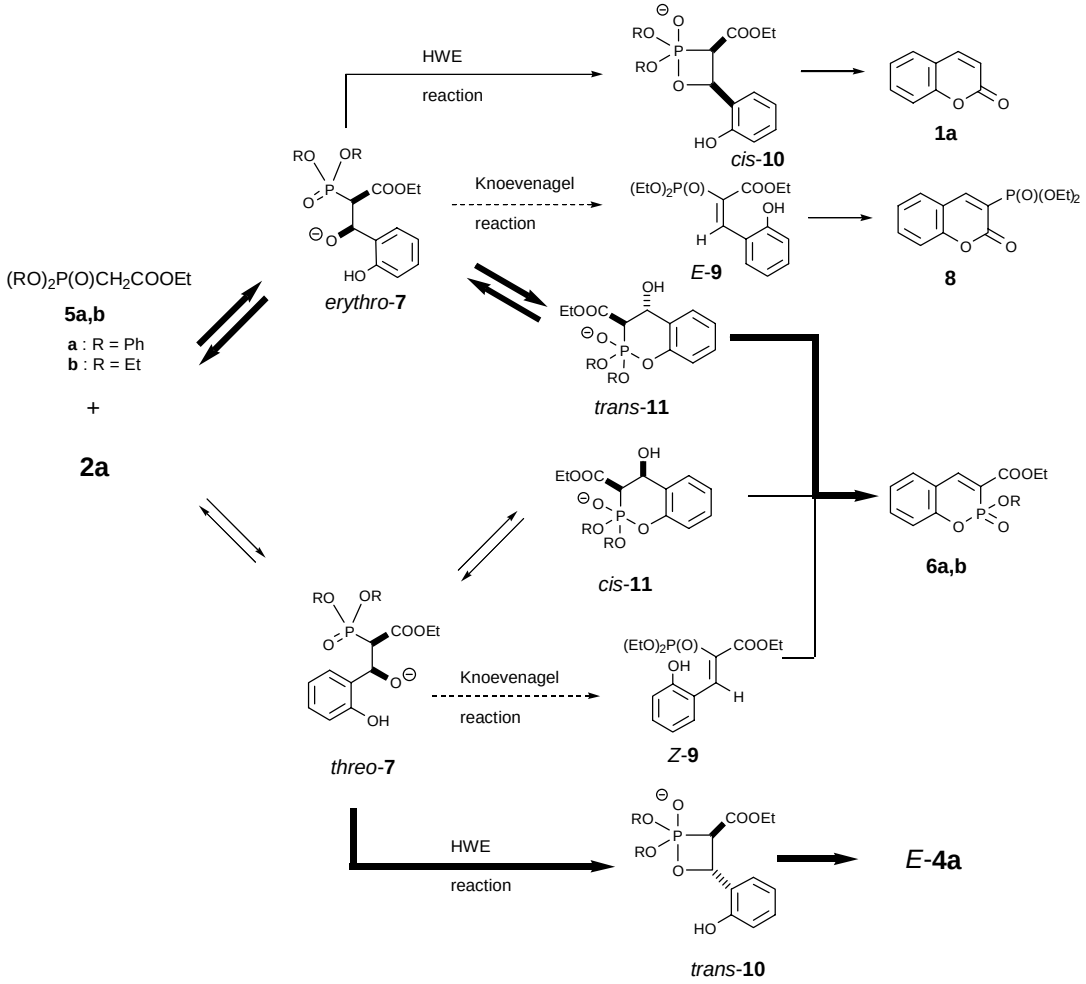
phosphonate derivative (**6a**) in 33% yield along with the *E*-olefinated product (*E*-**4a**) in 37% yield. An increase in the selectivity for **6a** (61% yield) versus *E*-**4a** (12% yield) was observed when the reaction was conducted at low temperatures (-78°C). Of the additive salts (NaI, LiCl, KI, or $MgBr_2$), the addition of NaI afforded the highest selectivity for **6a** (Table 1).

Table 1. Reaction of Salicylaldehyde with $(PhO)_2P(O)CH_2COOEt$ (**5a**).



2a **6a** *E*-**4a**

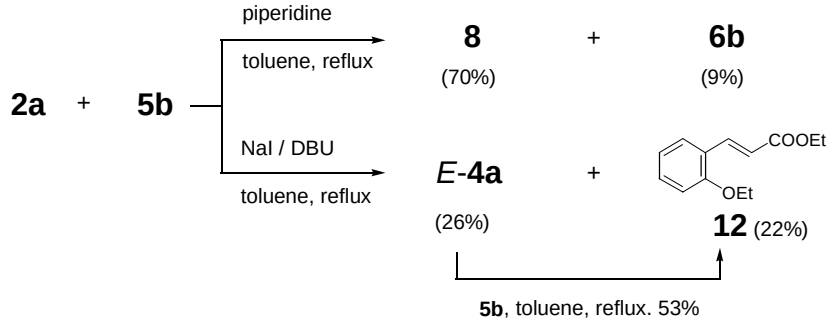
Salt	Temp (°C)	Time (h)	Product (Yield, %)	
			6a	*E*-**4a**
NaI	0	1.5	33	37
NaI	-78	2.0	61	12
LiCl	-78	7.0	26	53
KI	-78	3.0	36	33
$MgBr_2$	-78	12.8	15	29



Scheme 2

A mechanistic study of the HWE reaction reported that the *trans* 4-membered oxaphosphetane intermediate (*trans*-**10**) was more stable than the *cis* intermediate (*cis*-**10**), but that the *erythro*-aldol adduct (*erythro*-**7**) was more stable than *threo*-**7** (Scheme 2).[3] We postulated that **6a** might be formed *via* another intermediate of coumarin (**1a**) from *erythro*-**7**. Namely, the six-membered phosphonate (*trans*-**11**) is an intermediate in the production of **6a** from *erythro*-**7,** and the occurring dehydration of *trans*-**11** is a transforms **6a**, while *threo*-**7** gives *E*-**4a** *via* the stable intermediate, *trans*-**10**.

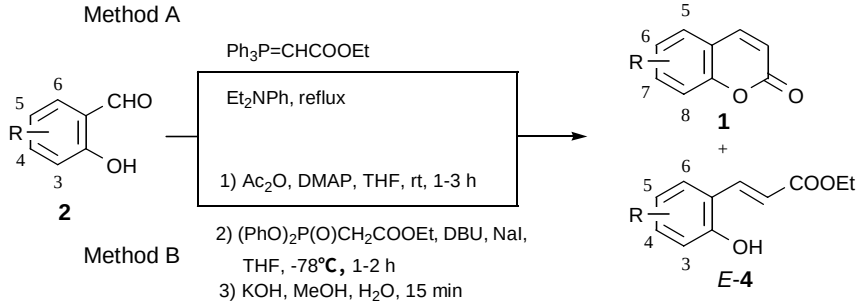
N. A. Rodios and co-workers[4] reported that the Knoevenagel reaction of **2a** with ethyl diethylphosphonoacetate (**5b**) afforded **6b** *via Z*-olefin (*Z*-**9**) from the *threo*-aldol adduct (*threo*-**7**) and coumarin-7-phosphonate (**8**) *via E*-olefin (*E*-**9**) from *erythro*-**7** (Scheme 2). Of the differences in the conditions of the HWE and Knoevenagel reactions, we focused on which base to use in the reaction of **2a** with **5b** in the presence of NaI/DBU under refluxing toluene (Scheme 3). This reaction afforded neither **6b** nor **8**, but *E*-**4a** in 26% yield, along with the ethylated product (**12**) of *E*-**4a** in 22% yield. The production of **12** was confirmed by heating *E*-**4a** with **5b**. Consequently, we understood that the reaction of **2** with **5** in the presence of NaI/DBU runs not *via* the Knoevenagel reaction, but *via* the HWE reaction, and that the intermediate in the transformation of **6a** or **6b** is *erythro*-**7**.



Scheme 3

A new synthetic method for **1** was developed using the acetate of **2** (Table 2, Method B). Successive acetylation of **2**, Ando-HWE reaction, and hydrolysis afforded **1** and *E*-**4** without a high reaction temperature. In comparison with Method A, this method was adopted for the synthesis of **1** with substituents at the 8 position, and should be very useful for the synthesis of **1b**,**d**,**e**,**f**. While the selectivity for **1** and *E*-**4** was high in most of the reaction, the selectivity for **1j,k** and *E*-**4j,k** produced from **2** with an electron-withdrawing group (COOMe, NO_2) at the 5 position decreased.

Table 2. A synthetic method of coumarin (**1**).



Run	R	Method	Product (yield, %) 1	E-4
1	H	A	89 (**1a**)	-
2		B	72 (**1a**)	1 (**4a**)[a]
3	3-OH	A	45 (**1b**)[a]	-
4		B	83 (**1b**)	4 (**4b**)[b]
5	3-OMe	A	81 (**1c**)[a]	11 (**4c**)[a]
6		B	78 (**1c**)	10 (**4c**)
7	3-Br	A	59 (**1d**)[c]	-
8		B	97 (**1d**)	-
9	3-COOMe	A	-	22 (**4e**)
10		B	85 (**1e**)	-
11	3-NO_2	A	10 (**1f**)	-
12		B[d]	49 (**1f**)[e]	-
13	5-OH	A	70 (**1g**)[a]	-
14		B	83 (**1g**)	4 (**4g**)[f]
15	5-OMe	A	93 (**1h**)[a]	-
16		B	62 (**1h**)	4 (**4h**)[g]
17	5-Br	A	65 (**1i**)[c]	-
18		B	84 (**1i**)	9 (**4i**)
19	5-COOMe	A	77 (**1j**)[c]	-
20		B	39 (**1j**)	12 (**4j**)[h]
21	5-NO_2	A	28 (**1k**)[e]	-
22		B	21 (**1k**)	64 (**4k**)[e]

a) Ref. 1a. *b*) Ref. 7. *c*) Ref. 1b. *d*) Acetate of **2f** was isolated. *e*) Ref. 1c. *f*) Ref. 6. *g*) Ref. 8. *h*) Bis(methoxycarbonyl) compound was obtained.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO A-102 spectrophotometer. MS spectra were recorded on a VG-70SE spectrometer. ^{1}H-NMR spectra were run on a JASCO MY 60FT or a Varian VXR-200 spectrometer. Analytical HPLC was performed with Chemcosorb 5Si-U (Chemco). Merck silica gel 60 (230-400 mesh) was employed for column chromatography. Extracts were dried over anhydrous $MgSO_4$.

Reaction of salicylaldehyde (2a) with ethyl diphenylphosphonoacetate (5a) Sodium iodide (0.36 g, 2.4 mmol) and DBU (0.32 mL, 2.2 mmol) were added at 0°C to a solution of **5a** (0.64 g, 2.0 mmol) in dry THF (20 mL) and the mixture was stirred at the same temperature for 10 min. After

cooling at -78°C, **2a** (0.24 mL, 2.2 mmol) was added to the mixture and the mixture was stirred at the same temperature for 2 h. The mixture was acidified by 10% aqueous HCl solution and extracted with AcOEt (80 mL). The organic layer was washed with brine (80 mL), dried and the solvent was removed *in vacuo*. The residue was subjected to column chromatography (SiO_2, AcOEt:hexane = 1:5). The first eluant gave ethyl (*E*)-3-(2-hydroxyphenyl)propenate (*E*-**4a**, 0.048 g, 12%) as colorless plates, mp 83—86°C (hexane and ether, lit.,[1a] 84—86°C). The second eluant gave ethyl 2-oxo-2-phenoxy-2*H*-benzo[*e*][1,2]oxaphosphine-3-carboxylate (**6a**, 0.400 g, 61%) as colorless plates, mp 66—69°C. IR (KBr) cm^{-1}: 1720. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.29 (t, 3H, *J* = 7.1 Hz), 4.35 (qd, 2H, *J* = 7.1, 2.5 Hz), 6.80—7.53 (m, 9H), 8.32 (d, 1H, *J* = 38.4 Hz). *Anal.* Calcd for $C_{17}H_{15}O_5P$: C, 61.82; H, 4.58. Found: C, 62.00; H, 4.74. FAB–MS (positive ion mode) *m/z*: 331 $(M+1)^+$, 285 $(M^+-OC_2H_5)$.

The reaction of **2a** with **5a** using other inorganic salt (LiCl, KI, $MgBr_2$) was treated by the same method as the above described method to afford the results in Table 1.

Reaction of salicylaldehyde (2a) with ethyl diethylphosphonoacetate (5b) Sodium iodide (0.36 g, 2.4 mmol) and DBU (0.32 mL, 2.2 mmol) were added at 0°C to a solution of **5b** (0.45 g, 2.0 mmol) in dry toluene (6 mL). After stirring for 10 min, **2a** (0.24 mL, 2.2 mmol) was added to the mixture and the mixture was stirred at reflux for 6 h. The mixture was acidified by 10% aqueous HCl solution and extracted with AcOEt (80 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ solution (60 mL) and brine (80 mL), dried and the solvent was removed *in vacuo*. The residue was subjected to column chromatography (SiO_2, AcOEt:hexane = 1:4). The first eluant gave a mixture (0.168 g) of **2a** and ethyl (*E*)-3-(2-ethoxyphenyl)propionate (**12**). The second eluant gave *E*-**4a** (0.0996 g, 26%). A mixture of **2a** and **12** was subjected to re-column chromatography (SiO_2, hexane) to give **12** (0.0962 g, 22%) as colorless oil, whose ^{1}H-NMR spectral data were agreed with reported one[5]. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.33 (t, 3H, *J* = 7.3 Hz), 1.45 (t, 3H, *J* = 7.3 Hz), 4.01 (q, 2H, *J* = 7.3 Hz), 4.26 (q, 2H, *J* = 7.3 Hz), 6.53 (d, 1H, *J* = 17.2 Hz), 6.81—7.56 (m, 4H), 8.03 (d, 1H, *J* = 17.2 Hz).

Reaction of ethyl (*E*)-3-(2-hydroxyphenyl)propenoate (*E*-4a) with ethyl diethylphosphonoacetate (5b) Sodium iodide (0.36 g, 2.4 mmol) and DBU (0.32 mL, 2.2 mmol) were added at 0°C to a solution of **5b** (0.22 g, 1.0 mmol) in dry toluene (6 mL). After stirring for 10 min, *E*-**4a** (0.211 g, 1.1 mmol) was added to the mixture and the mixture was stirred at reflux for 4 h. The solvent was removed *in vacuo*. The residue was subjected to column chromatography (SiO_2, AcOEt:hexane=1:4). The first eluant gave **12**

(0.128 g, 53%). The second eluant gave *E*-**4a** (0.100 g, 47%).

8-Hydroxycoumarin (1b) Acetic anhydride (0.40 mL, 4.2 mmol) and DMAP (0.513 g, 4.2 mmol) were added at 0°C for 5 min to a solution of 2,3-dihydroxybenzaldehyde (0.276 g, 2.0 mmol) in dry THF (2 mL). The mixture was stirred at rt for 2 h. A phosphonoacetate solution, which was prepared by stirring a mixture of NaI (0.564 g, 3.1 mmol), DBU (0.46 mL, 3.1 mmol), and **5a** (0.897 g, 2.8 mmol) in dry THF (18 mL) at 0°C for 10 min, was added at -78°C for 3 h to the mixture. Potassium hydroxide (0.56 g, 10.0 mmol) in MeOH/H_2O (3:1, 2.0 mL) was added to the mixture. After stirring for 15 min, the mixture was acidified with 10% aqueous HCl solution and extracted with AcOEt (90 mL). The organic layer was washed with brine (110 mL), dried and the solvent was removed *in vacuo*. The residue was subjected to column chromatography (SiO_2, AcOEt:hexane = 1:7). The first eluant gave starting material (0.021 g, 8%). The second eluant gave **1b** (0.270 g, 83%) as light yellow needles, mp 161—162°C (AcOEt and hexane, lit.,[1a] 152—156°C). The second eluant gave ethyl (*E*)-3-(2,3-dihydroxyoxyphenyl)propenate (*E*-**4b**, 0.016 g, 4%) as colorless needles, mp 143—145°C (ether and hexane, lit.,[7] 137—139°C).

8-Bromocoumarin (1d) Acetic anhydride (0.20 mL, 2.1 mmol) and DMAP (0.257 g, 2.1 mmol) were added at 0°C for 5 min to a solution of methyl 3-bromo-2-hydroxybenzaldehyde (0.402 g, 2.0 mmol) in dry THF (2 mL). The mixture was stirred at rt for 40 min. A phosphonoacetate solution, which was prepared by stirring a mixture of NaI (0.414 g, 2.8 mmol), DBU (0.38 mL, 2.5 mmol), and **5a** (0.737 g, 2.3 mmol) in dry THF (18 mL) at 0°C for 10 min, was added at -78°C for 1 h to the mixture. Potassium hydroxide (0.56 g, 10.0 mmol) in MeOH/H_2O (3:1, 2.0 mL) was added to the mixture. The mixture was stirred at rt for 15 min. The mixture was acidified with 10% aqueous HCl solution and extracted with AcOEt (100 mL). The organic layer was washed with brine (40 mL), dried and the solvent was removed *in vacuo*. The residue was subjected to column chromatography (SiO_2, hexane) to give **1d** (0.43 g, 97%) as yellow needles, mp 135—136°C (MeOH, lit.,[1b] 136.5—137°C).

8-Methoxycarbonylcoumarin (1e) Acetic anhydride (0.20 mL, 2.1 mmol) and DMAP (0.257 g, 2.1 mmol) were added at 0°C for 5 min to a solution of methyl 3-formyl-2-hydroxybenzoate (0.360 g, 2.0 mmol) in dry THF (2 mL). The mixture was stirred at rt for 1.5 h. A phosphonoacetate solution, which was prepared by stirring a mixture of NaI (0.414 g, 2.8 mmol), DBU (0.38 mL, 2.5 mL), and **5a** (0.737 g, 2.3 mmol) in dry THF (22 mL) at 0°C for 10 min, was added at -78°C for 1 h to the mixture. Potassium hydroxide (0.56 g, 10.0 mmol) in MeOH/H_2O (3:1, 2.0 mL) was added to the mixture. The

mixture was stirred at rt for 20 min. The mixture was acidified with 10% aqueous HCl solution and extracted with AcOEt (80 mL). The organic layer was washed with brine (90 mL), dried and the solvent was removed *in vacuo*. The residue was subjected to column chromatography (SiO_2, AcOEt:hexane = 1:6) to give **1e** (0.349 g, 86%) as colorless needles, mp 164.5—165.5°C (AcOEt and hexane). IR (KBr) cm^{-1}: 1710, 1730. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 4.01 (s, 3H), 6.47 (d, 1H, *J* = 9.8 Hz), 7.31—8.00 (m, 4H). *Anal.* Calcd for $C_{11}H_8O_4$: C, 64.71; H, 3.95. Found: C, 64.52; H, 4.09. FAB–MS (positive ion mode) *m/z*: 205 $(M+1)^+$.

8-Nitrocoumarin (1f) Acetic anhydride (0.23 mL, 2.4 mmol) was added at 0°C for 5 min to a solution dissolved 2-hydroxy-3-nitrobenzaldehyde (0.167 g, 1.0 mmol) in dry pyridine (1 mL). The mixture was stirred at rt for 1 h. The reaction mixture was poured into 10% aqueous HCl solution (40 mL), and extracted with AcOEt (50 mL). The organic layer washed with saturated aqueous $NaHCO_3$ solution (40 mL) and brine (40 mL), dried, and the solvent was removed *in vacuo.* The residue was recrystallized from a mixture of ether and hexane to give 2-acetoxy-3-nitrobenzaldehyde (0.123 g, 59%) as yellow needles, mp 89—90°C. IR (KBr) cm^{-1}: 1715, 1770. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.49 (s, 3H), 7.58—7.71 (m, 1H), 8.15—8.28 (m, 2H), 10.23 (s, 1H). *Anal.* Calcd for $C_9H_7NO_5$: C, 51.68; H, 3.37. Found: C, 51.51; H, 3.53.

A phosphonoacetate solution, which was prepared by stirring a mixture of NaI (0.200 g, 1.3 mmol), DBU (0.18 mL, 1.2 mL), and **5a** (0.35 g, 1.1 mmol) in dry THF (10 mL) at 0°C for 10 min, 2-acetoxy-3-nitrobenzaldehyde (0.21 g, 1.0 mmol) was added at -78°C for 1 h to the mixture. The mixture was neutralized with saturated aqueous NH_4Cl solution and extracted with AcOEt (90 mL). The organic layer was washed with brine (80 mL), dried, and the solvent was removed *in vacuo.* The mixture of the residue and K_2CO_3 (1.50 g, 10.9 mml) in EtOH/H_2O (1:1, 20ml) was stirred at rt for 21 h. The mixture was acidified with 10% aqueous HCl solution and extracted with AcOEt (80 mL). The organic layer was washed with brine (80 mL), dried and the solvent was removed *in vacuo*. Recrystallization ($CHCl_3$ and hexane) gave **1f** (0.159 g, 49% based on 2-hydroxy-3-nitrobenzaldehyde) as yellow needles, mp 190—191°C ($CHCl_3$ and hexane, lit.,[1c] 190—191°C).

The reaction of **2a,c,g,h,i,j,k** with **5a** was carried out by the same method as the preparation of **1d** to afford the results in Table 2. The following are the physicochemical properties of new compounds ((*E*)-**4i,j**) and ^{1}H-NMR spectral data of other compounds were agreed with the reported one.

Ethyl (*E*)-3-(5-bromo-2-hydroxyphenyl)propenoate (4i) colorless needles, mp 122.5—123.5°C (ether and hexane). IR (KBr) cm^{-1}: 1685. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.35 (t, 3H, *J* = 7.3 Hz), 4.30 (q, 2H, *J* = 7.3 Hz), 6.62 (d, 1H, *J* = 15.9 Hz), 6.83—7.60 (m, 3H), 7.98 (d, 1H, *J* = 15.9 Hz). *Anal.* Calcd for $C_{11}H_{11}O_3Br$: C, 48.73; H, 4.09. Found: C, 48.48; H, 4.23. FAB–MS (positive ion mode) *m/z*: 272 $(M+1)^+$.

Methyl (*E*)-3-(2-hydroxy-5-methoxycarbonylphenyl)propenoate (4j) colorless needles, mp 150—154°C (ether and hexane). IR (KBr) cm^{-1}: 1690, 1725. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.84 (s, 3H), 3.90 (s, 3H), 6.71 (d, 1H, *J* = 15.9 Hz), 6.95 (d, 1H, *J* = 7.8 Hz), 7.93 (dd, 1H, *J* = 7.8, 2.3 Hz), 8.06 (d, 1H, *J* = 15.9 Hz), 8.20 (d, 1H, *J* = 2.3 Hz). *Anal.* Calcd for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 60.99; H, 5.23. FAB–MS (positive ion mode) *m/z*: 237 $(M+1)^+$.

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