WITTIG-HORNER REACTION OF DIMETHYL PHTHALIDE-3-PHOSPHONATES WITH ALDEHYDES: SYNTHESIS OF 3-YLIDENEPHTHALIDES AND CHARACTERIZATION OF THEIR *E*- AND *Z*-ISOMERS

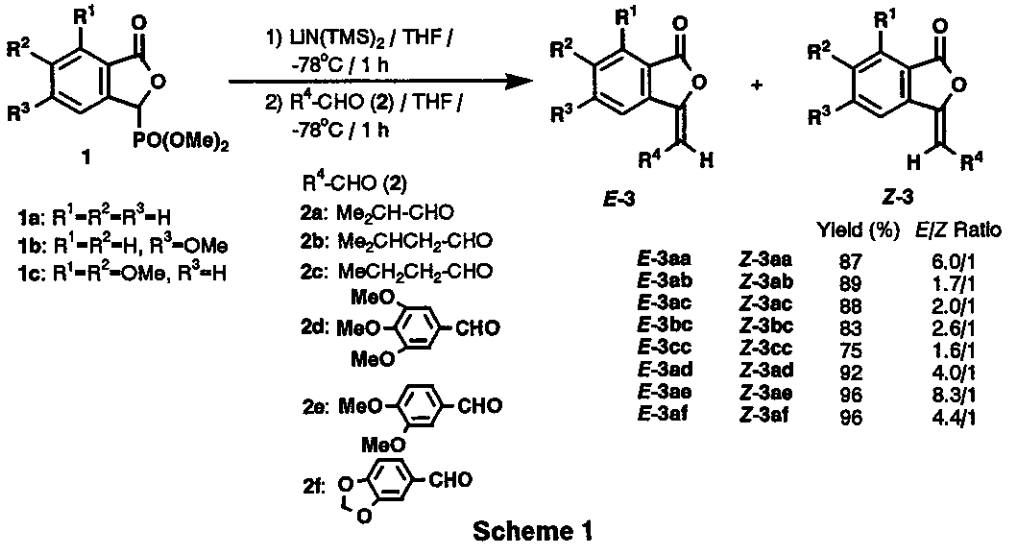
Mitsuaki Watanabe,*[a] Saori Ijichi,[b] Hitoshi Morimoto,[b] Kayoko Nogami,[b] and Sunao Furukawa[b]

Center for Instrumental Analysis, [a] School of Pharmaceutical Sciences, [b]
Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852, Japan

Abstract- Wittig-Horner reaction of dimethyl phthalide-3-phosphonates with aldehydes in the presence of lithium bis(trimethylsilyl)amide was investigated. Using their NOE experiments, both the *E*- and *Z*-isomers of 3-ylidenephthalides were clearly characterized.

Recently, we reported a facile regioselective synthetic method for dimethyl phthalide-3-phosphonates having various substituents on the aromatic ring, based on the reaction of *N,N*-diethyl-2-formylbenzamides with dimethyl *tert*-butyldimethylsilyl phosphite.[1] In order to develop the utility of phthalide-3-phosphonates in organic synthesis, Wittig-Horner reactions[2] of these compounds with aldehydes were investigated. The Wittig-Horner reaction of phthalide-3-phosphonates in the presence of NaH at room temperature has already been reported,[3] but characterization of the *E*- and *Z*-isomers of the synthesized 3-ylidenephthalides had not been reported except that of several thermally stable (*Z*)-3-benzylidenephthalides.[3b] Although the 3-alkylidenephthalides may occur as the *E*- or *Z*-isomers, their configuration in natural or synthesized products had been confused for a long time.[4] In 1980, Gijbels and coworkers reported that natural 3-butylidenephthalide was confirmed to be the *Z*-isomer by means of ^{1}H and ^{13}C nmr measurements.[4] However no nuclear Overhauser effect (NOE), which is necessary for the determination of stereochemistry, was made in their experiments. In this paper, we describe a convenient synthesis of 3-alkylidene- and 3-benzylidenephthalides using the Wittig-Horner reaction of dimethyl phthalide-3-phosphonates with aldehydes in the presence of lithium bis(trimethylsilyl)amide and the characterization of their *E*- and *Z*-isomers based on the NOE experiments.

Reaction of dimethyl phthalide-3-phosphonate (**1a**)[1,3b] with 1.1 eq. of lithium bis(trimethylsilyl)amide in THF at -78°C for 1 h resulted in the formation of the yellow anion, which, upon treatment with 1.1 eq. of isobutyraldehyde (**2a**) at -78°C for 1 h followed by quenching with saturated NH_4Cl solution at -78°C, gave 3-isobutylidenephthalide (**3aa**) as *E/Z* mixtures in 87% yield. Lithium diisopropylamide (LDA) was also used instead of lithium bis(trimethylsilyl)amide and **3aa** was obtained in almost the same yield (85%). When the reaction mixture using LDA as a base was allowed to warm to room temperature for 1 h and then quenched, however, the yield of **3aa** was decreased to 50% yield.[5] For the efficient synthesis of 3-ylidenephthalides, quenching of the reaction mixture at -78°C is necessary. Although we have tested NaH as a base (THF, 0°C, 6 h), the yield of **3aa** was much lower (64%). As shown in Scheme 1, various 3-ylidenephthalides (**3**), which were mixtures of *E/Z*-isomers, were synthesized in high yields starting from



1a: $R^1=R^2=R^3=H$
1b: $R^1=R^2=H$, $R^3=OMe$
1c: $R^1=R^2=OMe$, $R^3=H$

R^4-CHO (2)
2a: Me_2CH-CHO
2b: Me_2CHCH_2-CHO
2c: $MeCH_2CH_2$-CHO

		Yield (%)	*E/Z* Ratio
E-3aa	*Z*-3aa	87	6.0/1
E-3ab	*Z*-3ab	89	1.7/1
E-3ac	*Z*-3ac	88	2.0/1
E-3bc	*Z*-3bc	83	2.6/1
E-3cc	*Z*-3cc	75	1.6/1
E-3ad	*Z*-3ad	92	4.0/1
E-3ae	*Z*-3ae	96	8.3/1
E-3af	*Z*-3af	96	4.4/1

Scheme 1

1a-c and **2b-f** under the reaction conditions using lithium bis(trimethylsilyl)amide as a base.

The pure samples of *E*-isomers and *Z*-isomers were easily obtained by silica gel column chromatography using benzene as the eluent for 3-alkylidenephthalides (**3aa**,[3b,6] **ab**,[6] **ac**,[4] **bc**, **cc**[7]) or dichloromethane for 3-benzylidenephthalides (**3ad**, **ae**, **af**[3b,8]). In the cases of *E*-**3aa** and *Z*-**3aa**, their ir and mass spectra were almost identical. However, characteristic differences between *E*-**3aa** and *Z*-**3aa** were observed in their ^1H and ^{13}C nmr spectra; *i. e.* the proton signal of the vinyl protons for these compounds appeared at different chemical shifts [*E*-**3aa**: δ 5.72 (δ, *J*=10.26 Hz); *Z*-**3aa**: δ 5.48 (δ, *J*=9.53 Hz)]. In the NOE experiments, the irradiation of the methine proton of *E*-**3aa** produced NOE enhancement at the signal of aromatic C4-H, but no NOE enhancement at the same proton was observed by the irradiation of the vinyl proton (Figure 1). In the NOE experiments of *Z*-**3aa**, the irradiation of the vinyl proton produced NOE enhancement at the signal of aromatic C4-H. On the other hand, no enhancement at the signals of aromatic protons was observed by the irradiation of the methine proton of *Z*-**3aa** (Figure 2).[7,9]

In the cases of 3-benzylidenephthalides, bathochromic shifts of the uv spectra of the *Z*-isomers compared with those of the *E*-isomers were observed. In their ^1H nmr spectra; *i. e.* *E*-**3ad** and *Z*-**3ad**, the vinyl protons of *E*-**3ad** and *Z*-**3ad** appeared at δ 6.86 (s) and δ 6.35 (s), respectively. The irradiation of the vinyl proton of *E*-**3ad** gave NOEs at aromatic C2′-H and C6′-H and no NOE enhancement at the signal of aromatic C4-H was observed (Figure 3). On the other hand, the irradiation of the vinyl proton of *Z*-**3ad** caused NOEs at aromatic C4-H along with aromatic C2′-H and C6′-H (Figure 4). From the above NOE observations, the relative configurations of the 3-ylidenephthalides were clearly determined. The NOE observations and chemical shifts of the vinyl proton of *E*- and *Z*-ylidenephthalides synthesized here are summarized in Figure 5 and Table I, respectively. ^{13}C Nmr data of a series of *E*- and *Z*-3-alkylidenephthalides are summarized in Table II. Using differentiation of the chemical shift of the vinyl protons, the *E*/*Z* ratios of each of the reaction products were calculated and the results are listed in Scheme 1. By comparison with the Perkin synthesis,[4] which mainly gave thermally stable *Z*-isomers, the Wittig-Horner reaction of dimethyl phthalide-3-phosphonates (**1**) under the conditions described here predominantly lead to *E*-isomers due to the formation of *erythro*-intermediates.[2,6,8] From our spectral data, the following observations allow the determination of the stereochemistry of 3-ylidenephthalides: i) in

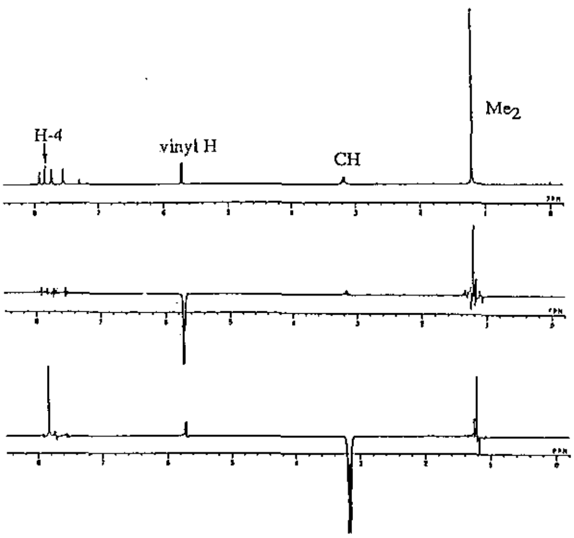


Figure 1. ^{1}H Nmr Spectrum and NOE Spectra of *E*-3aa

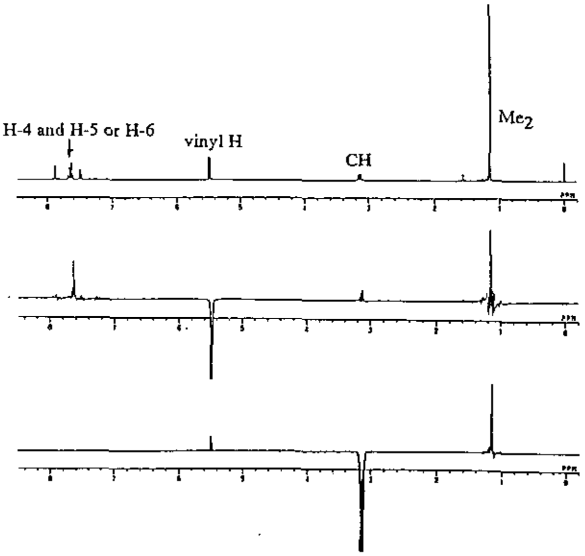


Figure 2. ^{1}H Nmr Spectrum and NOE Spectra of *Z*-3aa

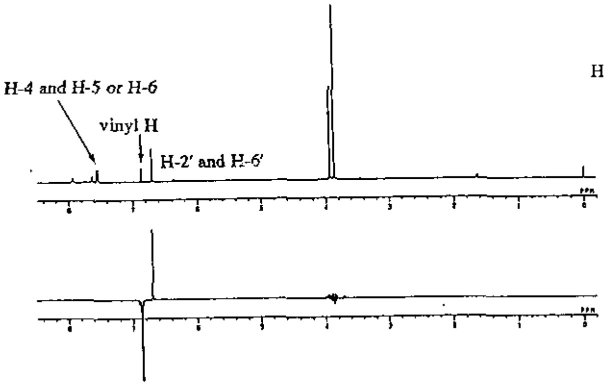


Figure 3. ^{1}H Nmr Spectrum and NOE Spectrum of *E*-3ad

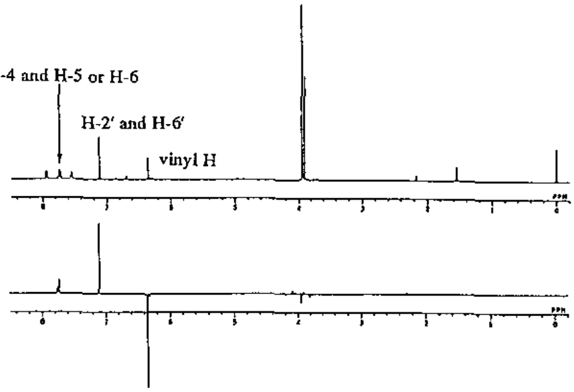
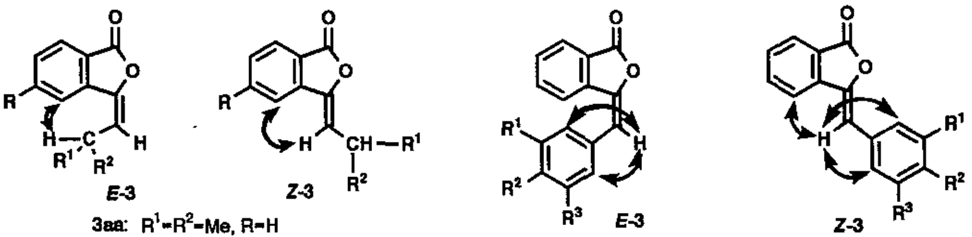


Figure 4. ^{1}H Nmr Spectrum and NOE Spectrum of Z-3ad



(*E*)- and (*Z*)-3-Alkylidenephthalides

3aa: R^1=R^2=Me, R=H
3ab: R^1=H, R^2=CHMe, R=H
3ac: R^1=H, R^2=CH$_2$Me, R=H
3bc: R^1=H, R^2=CH$_2$Me, R=OMe

(*E*)- and (*Z*)-3-Benzylidenephthalides

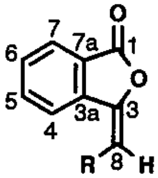
3ad: R^1=R^2=R^3=OMe
3ae: R^1=R^2=OMe, R^3=H
3af: R^1=R^2=OCH$_2$O, R^3=H

Figure 5. NOE Correlations of (*E*)- and (*Z*)-3-Ylidenephthalides

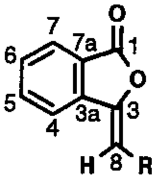
Table I. Chemical Shift of Vinyl Protons of (*E*)- and (*Z*)-3-Ylidenephthalides
(400 MHz, δ from TMS in $CDCl_3$)

	3aa	3ab	3ac	3bc	3cc	3ad	3ae	3af
E-	5.72 (d)	5.87 (t)	5.83 (t)	5.78 (t)	5.67 (t)	6.86 (s)	6.87 (s)	6.82 (s)
Z-	5.48 (d)	5.67 (t)	5.64 (t)	5.59 (t)	5.47 (t)	6.35 (s)	6.36 (s)	6.35 (s)
Δ	0.24	0.20	0.19	0.19	0.20	0.51	0.51	0.47

Table II. ^{13}C Nmr Data for (*E*)- and (*Z*)-3-Alkylidenephthalides



E-3



Z-3

3aa: $R=\overset{9}{C}H\overset{10}{Me_2}$
3ab: $R=\overset{9}{C}H_2\overset{10}{C}H\overset{11}{Me_2}$
3ac: $R=\overset{9}{C}H_2\overset{10}{C}H_2\overset{11}{Me}$

Carbons	*E*-3aa	*E*-3ab	*E*-3ac	*Z*-3aa	*Z*-3ab	*Z*-3ac
1	166.97	166.89	166.67	167.13	167.20	167.13
3a	138.13	138.32	138.03	139.80	139.61	139.57
3	144.47	146.07	145.58	144.05	146.19	145.80
4	123.11	123.18	122.89	119.64	119.68	119.68
5	134.39	134.28	134.10	134.16	134.24	134.24
6	129.57	129.57	129.35	129.33	129.37	129.33
7	125.52	125.44	125.15	125.25	125.25	125.13
7a	126.26	126.26	125.88	124.51	124.55	124.43
8	121.12	113.03	113.62	116.33	108.39	109.41
9	26.00	34.99	27.73	25.92	34.76	27.83
10	23.12	29.19	22.63	22.81	28.72	22.54
11		22.34	13.52		22.38	13.78

Assignments were made by heteronuclear multiple bond connectivity.

the ^1H nmr spectra, the vinyl protons of *E*-isomers of 3-ylidenephthalides appear further downfield than those of *Z*-isomers (Table I); ii) in the ^{13}C nmr spectra of 3-alkylidenephthalides, the carbon signals of the aromatic C4 are remarkably different for *E*- and *Z*-isomers; in *E*-isomers, signals appear further downfield compared with those in *Z*-isomers (Table II).[4]

Among the (*Z*)-3-alkylidenephthalides synthesized here, both 3-isobutylidenephthalide (**3aa**) and 3-isovalidenephthalide (**3ab**) were isolated as components of the flavor of celery plants,[10] and 3-butylidenephthalide (**3ac**) was isolated from umbelliferous plants.[4,11] Moreover, (*Z*)-3-butylidene-6,7-dihydroxyphthalide isolated from *Ligusticum wallichii* Franch[12] was recently synthesized by Ogawa and coworkers through its dimethyl derivative (**3cc**: *E*/*Z*=1/1.8).[7]

In conclusion, we have shown that the Wittig-Horner reaction of dimethyl phthalide-3-phosphonate with aldehydes in the presence of lithium bis(trimethylsilyl)amide provided a efficient synthetic method for the preparation of various (*E*)- and (*Z*)-3-ylidenephthalide derivatives. Each assignment of configuration of the *E*- and *Z*-isomers in 3-alkylidene- and 3-benzylidenephthalides were clarified by their NOE experiments.

EXPERIMENTAL

General. Melting points were determined with a Yanagimoto micromelting point apparatus and were uncorrected. The ir spectra were measured with a JASCO 810 spectrophotometer. The uv spectra were recorded in 95% ethanol on a Hitachi 323 spectrophotometer. The nmr spectra were obtained on a JEOL GX-400 spectrometer operating at 399.65 MHz for ^{1}H and 100.40 MHz for ^{13}C nuclei using $CDCl_3$ as a solvent and tetramethylsilane as an internal reference. The ms were determined on a JEOL DX-303 mass spectrometer. Elemental analyses were performed at the Microanalytical Laboratory of the Center for Instrumental Analysis in Nagasaki University. Conventional column chromatography was carried out on a column of Kiesekgel 60 (230-400 mesh).

General Procedure for the Reaction of Dimethyl Phthalide-3-phosphonates (1) with Aldehydes (2). A solution of lithium bis(trimethylsilyl)amide (3.3 mmol, 1.0 M solution of hexane) was injected into a stirred solution of **1**[1,3b] (3 mmol) in THF (50 ml) at -78°C under an argon atmosphere. The mixture was stirred at -78°C for 1 h and then a solution of aldehydes (**2**; 3.3 mmol) in THF (20 ml) was injected into the yellow solution at -78°C. Stirring was continued for an additional 1 h at -78°C. The reaction was quenched with saturated NH_4Cl solution and 10% HCl solution at -78°C. THF was removed under reduced pressure. The residue was extracted with CH_2Cl_2 and the CH_2Cl_2 layer was dried over Na_2SO_4, and then evaporated to give 3-ylidenephthalides (**3**). The analytically pure samples of *E*- and *Z*-isomers of **3** were obtained by silica gel column chromatography. For the purification of 3-alkylidenephthalides, benzene was used as eluent and the *Z*-isomers elured faster than the *E*-isomers. For a purification of 3-benzylidenephthalides, CH_2Cl_2 was used as eluent and the *E*-isomers eluted faster than the *Z*-isomers except for **3af** which was reversed.

(*E*)-3-Isobutylidenephthalide (*E*-3aa): mp 56-57°C (ether/hexane). Ms *m/z*: 188 (M^+, 18), 173 (100), 155 (7), 104 (10). Ir (KBr) νco: 1780 cm^{-1}. Uv nm (log ε): 210 (4.24), 215 (4.22), 235 (4.21), 250 (s)(4.21), 260 (4.26), 270 (s)(4.15), 308 (3.82). ^{1}H Nmr (400 MHz) δ: 1.21 (6H, d, *J*=7.0 Hz), 3.13-3.22 (1H, m), 5.72 (1H, d, *J*=10.3 Hz), 7.54 (1H, dd, *J*=7.7, 0.7 Hz), 7.72 (1H, dd, *J*=8.1, 1.1 Hz), 7.83 (1H, d, *J*=8.1 Hz), 7.92 (1H, d, *J*=7.7 Hz). *Anal.* Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.31; H, 6.46.

(*Z*)-3-Isobutylidenephthalide (*Z*-3aa): an oil. Ms *m/z*: 188 (M^+, 33), 173 (100), 155 (9), 103 (79). Ir (neat) νco: 1780 cm^{-1}. Uv nm (log ε): 205 (4.11), 215 (s)(4.07), 233 (s)(3.99), 258 (s)(3.81), 270 (s)(3.65), 308 (3.26). ^{1}H Nmr (400 MHz) δ: 1.15 (6H, d, *J*=7.0 Hz), 3.09-3.18 (1H, m), 5.38 (1H, d, *J*=9.5 Hz), 7.50 (1H, dd, *J*=8.1, 1.5 Hz), 7.61-7.69 (2H, m), 7.89 (1H, d, *J*=7.7 Hz). *Anal.* Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.23; H, 6.74.

(*E*)-3-Isovalidenephthalide (*E*-3ab): an oil. Ms *m/z*: 202 (M^+, 24), 159 (100), 148 (26), 132 (32), 104 (68). Ir (neat) νco: 1770 cm^{-1}. Uv nm (log ε): 210 (4.45), 215 (s)(4.43), 235 (s)(4.42), 260 (4.49), 270 (s)(4.37), 308 (4.06). ^{1}H Nmr (400 MHz) δ: 1.03 (6H, d, *J*=6.6 Hz), 1.84-1.91 (1H, m), 2.45 (2H, dd, *J*=8.4, 6.6 Hz), 5.87 (1H, t, *J*=8.4 Hz), 7.54 (1H, t, *J*=7.3 Hz), 7.72 (1H, dt, *J*=7.7, 1.1 Hz), 7.85 (1H, d, *J*=7.7 Hz), 7.91 (1H, d, *J*=7.7 Hz). *Anal.* Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.49; H, 7.27.

(*Z*)-3-Isovalidenephthalide (*Z*-3ab): an oil (this compound is gradually solidified in a refrigerator; mp 108-110°C). Ms *m/z*: 202 (M^+, 12), 159 (48), 148 (82), 132 (9), 104 (100). Ir (neat) νco: 1780 cm^{-1}. Uv nm (log ε): 215 (s)(4.07), 232.5 (4.11), 257.5 (4.02), 270 (s)(3.89), 310 (3.51). ^{1}H Nmr (400 MHz) δ: 0.984 (6H, d, *J*=7.0 Hz), 1.77-1.88 (1H, m), 2.37 (2H, dd, *J*=8.1, 7.0 Hz), 5.66 (1H, t, *J*=8.1 Hz), 7.49-7.52 (1H, m), 7.66-7.68 (2H, m), 7.88 (1H, d, *J*=7.7 Hz). *Anal.* Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.31; H, 7.16.

(*E*)-3-Butylidenephthalide (*E*-3ac): an oil (lit.,[11b] bp 125-135°C/2 mmHg). Ms *m/z*: 188 (M^+, 36), 159 (100), 146 (29), 132 (19), 104 (33). Ir (neat) νco: 1770 cm^{-1}. Uv nm (log ε): 208 (4.15), 214 (s)(4.14), 235 (4.13), 258 (4.18), 268 (s)(4.06), 308 (3.74). ^{1}H Nmr (400 MHz) δ: 1.03 (3H, t, *J*=7.3 Hz), 1.62 (2H, sext, *J*=7.3 Hz), 2.53 (1H, q, *J*=7.3 Hz), 5.83 (1H, t, *J*=8.1 Hz), 7.53 (1H, dt, *J*=7.0, 0.7 Hz), 7.71 (1H, dt, *J*=7.3, 1.1 Hz), 7.82 (1H, d, *J*=7.7 Hz), 7.89 (1H, dd, *J*=7.7, 1.1 Hz). *Anal.* Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.42; H, 6.50.

(*Z*)-3-Butylidenephthalide (*Z*-3ac): an oil. Ms *m/z*: 188 (M^+, 19), 159 (52), 146 (63), 132 (42), 104 (100). Ir (neat) vco: 1780 cm^{-1}. Uv nm (log ε): 210 (s)(3.93), 215 (3.95), 234 (4.05), 256 (4.05), 268 (s)(3.93), 315 (3.61). ^{1}H Nmr (400 MHz) δ: 0.98 (3H, t, *J*=7.3 Hz), 1.55 (2H, sext, *J*=7.3 Hz), 2.44 (2H, q, *J*=7.7 Hz), 5.64 (1H, t, *J*=7.7 Hz), 7.46-7.50 (1H, m), 7.62-7.68 (2H, m), 7.84-7.86 (1H, m). *Anal.* Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.70; H, 6.56.

(*E*)-5-Methoxy-3-butylidenephthalide (*E*-3bc): an oil (this compound is gradually solidified in a refrigerator; mp 42-43°C). Ms *m/z*: 218 (M^+, 34), 189 (100), 176 (72), 161 (15), 134 (33), 106 (20). Ir (neat) vco: 1770 cm^{-1}. Uv nm (log ε): 226 (4.17), 257 (4.41), 305 (s)(3.56), 318 (3.34). ^{1}H Nmr (400 MHz) δ: 1.03 (3H, t, *J*=7.3 Hz), 1.62 (2H, sext, *J*=7.3 Hz), 2.48 (2H, q, *J*=7.7 Hz), 3.93 (3H, s), 5.78 (1H, t, *J*=8.1 Hz), 7.04 (1H, dd, *J*=8.4, 2.2 Hz), 7.18 (1H, d, *J*=2.2 Hz), 7.77 (1H, d, J=8.4 Hz). ^{13}C nmr δ: 13.66, 22.73, 27.83, 55.77, 107.30, 113.57, 116.49, 118.55, 126.69, 140.31, 145.45, 164.64, 166.46. *Anal.* Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.62 ; H, 6.55.

(*Z*)-5-Methoxy-3-butylidenephthalide (*Z*-3bc): an oil (this compound is gradually solidified in a refrigerator; mp 50-51°C). Ms *m/z*: 218 (M^+, 35), 189 (100), 176 (78), 161 (16), 134 (10), 116 (4), 106 (7). Ir (neat) vco: 1780 cm^{-1}. Uv nm (log ε): 220 (s)(4.06), 225 (4.13), 255 (4.50), 275 (s)(4.20), 303 (s)(3.67), 315 (3.47). ^{1}H Nmr (400 MHz) δ: 0.98 (3H, t, *J*=7.3 Hz), 1.55 (2H, sext, *J*=7.3 Hz), 2.43 (2H, q, *J*=7.7 Hz), 3.91 (3H, s), 5.59 (1H, t, *J*=7.7 Hz), 7.01 (1H, dd, *J*=9.2, 2.2 Hz), 7.02 (1H, d, J=2.2 Hz), 7.74 (1H, d, *J*=9.2 Hz). ^{13}C Nmr δ: 13.82, 22.54, 27.79, 55.89, 102.63, 109.17, 117.11, 117.77, 126.65, 142.18, 145.68, 164.98, 166.89. *Anal.* Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.84 ; H, 6.68.

(*E*)-6,7-Dimethoxy-3-butylidenephthalide (*E*-3cc): an oil (lit.,[7] an oil). Ms *m/z*: 248 (M^+, 43), 219 (100), 206 (9). Ir (neat) vco: 1780 cm^{-1}. Uv nm (log ε): 224 (4.29), 238 (4.26), 266 (4.15), 278 (s)(4.05), 338 (3.90). ^{1}H Nmr (400 MHz) δ: 1.02 (3H, t, *J*=7.3 Hz), 1.60 (2H, sext, *J*=7.3 Hz), 2.46 (2H, q, *J*=7.7 Hz), 3.95 (3H, s), 4.10 (3H, s), 5.67 (1H, t, *J*=8.1 Hz), 7.28 (1H, d, *J*=8.4 Hz), 7.45 (1H, d, *J*=8.4 Hz). ^{13}C Nmr δ : 13.78, 22.89, 27.95, 56.86, 62.27, 111.16, 118.28, 119.53, 131.94, 145.02, 147.98, 153.08, 164.56. The above ms, ir, uv, ^{1}H, and ^{13}C nmr data agreed well with those of an authentic sample of *E*-

3cc.[7]

(*Z*)-6,7-Dimethoxy-3-butylidenephthalide (*Z*-3cc): an oil (lit.,[7] an amorphous powder). Ms *m/z*: 248 (M^+, 44), 219 (100), 206 (10). Ir (neat) νco: 1770 cm^{-1}. Uv nm (log ε): 225 (4.06), 240 (4.07), 268 (3.95), 283 (s)(3.75), 340 (3.72). ^1H Nmr (400 MHz) δ: 0.97 (3H, t, *J*=7.3 Hz), 1.53 (2H, sext, *J*=7.3 Hz), 2.39 (2H, q, *J*=7.7 Hz), 3.93 (3H, s), 4.11 (3H, s), 5.47 (1H, t, *J*=7.7 Hz), 7.25 (1H, d, *J*=8.4 Hz), 7.29 (1H, d, *J*=8.4 Hz). ^{13}C Nmr δ: 13.82, 22.65, 27.75, 56.94, 62.20, 106.92, 114.58, 116.65, 120.03, 133.23, 145.10, 147.74, 152.80, 164.75. The above ms, ir, uv, ^1H, and ^{13}C nmr data agreed well with those of an authentic sample of *Z*-3cc.[7]

(*E*)-3-(3′,4′,5′-Trimethoxy)benzylidenephthalide (*E*-3ad): mp 148°C (CH_2Cl_2/ether). Ms *m/z*: 312 (M^+, 100), 297 (65), 269 (13). Ir (KBr) νco: 1780 cm^{-1}. Uv nm (log ε): 209 (4.50), 233 (s)(4.20), 253 (s)(4.13), 333 (4.08). ^1H Nmr (400 MHz) δ: 3.86 (6H, s), 3.93 (3H, s), 6.70 (1H, s), 6.71 (1H, s), 6.86 (1H, s), 7.72-7.57 (2H, m), 7.61-7.64 (1H, m), 7.91-7.96 (1H, m). *Anal.* Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.15; H, 5.14.

(*Z*)-3-(3′,4′,5′-Trimethoxy)benzylidenephthalide (*Z*-3ad): mp 162°C (ether/pentane). Ms *m/z*: 312 (M^+, 100), 297 (59), 269 (10). Ir (KBr) νco: 1780 cm^{-1}. Uv nm (log ε): 210 (4.38), 242 (4.17), 305 (s)(4.17), 354 (4.35). ^1H Nmr (400 MHz) δ: 3.90 (3H, s), 3.95 (6H, s), 6.35 (1H, s), 7.11 (2H, s), 7.52-7.57 (1H, m), 7.70-7.79 (2H, m), 7.95 (1H, d, *J*=7.7 Hz). *Anal.* Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 68.90; H, 5.18.

(*E*)-3-(3′,4′-Dimethoxy)benzylidenephthalide (*E*-3ae): mp 154-155°C (CH_2Cl_2/hexane). Ms *m/z*: 282 (M^+, 100), 267 (39), 239 (12), 221 (17). Ir (KBr) νco: 1775 cm^{-1}. Uv nm (log ε): 203 (4.53), 230 (s)(4.23), 255 (4.14), 345 (4.12). ^1H Nmr (400 MHz) δ: 3.89 (3H, s), 3.96 (3H, s), 6.87 (1H, s), 6.95 (1H, d, *J*=8.1 Hz), 6.97 (1H, d, *J*=1.8 Hz), 7.05-7.08 (1H, m), 7.50-7.54 (2H, m), 7.59-7.63 (1H, m), 7.90-7.94 (1H, m). *Anal.* Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 71.97; H, 5.00.

(*Z*)-3-(3′,4′-Dimethoxy)benzylidenephthalide (*Z*-3ae): mp 128-129°C (ethyl acetate/ether). Ms *m/z*: 282 (M^+, 100), 267 (22), 239 (9), 221 (11). Ir (KBr) νco: 1780 cm^{-1}. Uv nm (log ε): 201 (4.33), 235 (s)(4.32), 232 (4.18), 260 (s)(4.10), 303 (4.15), 362 (4.38). ^1H Nmr (400 MHz) δ: 3.92 (3H, s), 3.97 (3H, s), 6.36 (1H, s), 6.89 (1H, d, *J*=8.4 Hz), 7.35 (1H, dd, *J*=8.4, 1.8 Hz), 7.49-7.53 (2H, m), 7.67-7.74 (2H, m), 7.92 (1H, d,

J=8.1 Hz). *Anal.* Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.25; H, 5.10.

(*E*)-3-(3′,4′-Methylenedioxy)benzylidenephthalide (*E*-3af): mp 125-126°C (CH_2Cl_2/hexane) (lit.,[8] mp 139-140°C). Ms m/z: 266 (M^+, 100), 160 (10), 152 (23). Ir (KBr) νco: 1770 cm^{-1}. Uv nm (log ε): 203 (4.56), 232 (s)(4.23), 255 (4.25), 348 (4.07). ^1H Nmr (400 MHz) δ: 6.05 (2H, s), 6.82 (1H, s), 6.89 (1H, d, J=8.1 Hz), 6.93-6.98 (2H, m), 7.31-7.57 (2H, m), 7.61-7.64 (1H, m), 7.91-7.95 (1H, m). *Anal.* Calcd for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79. Found: C, 71.77; H, 3.99.

(*Z*)-3-(3′,4′-Methylenedioxy)benzylidenephthalide (*Z*-3af): mp 202-203°C (CH_2Cl_2/hexane) (lit.,[3b] mp 201-203°C; lit.,[8] mp 202-204°C). Ms m/z: 266 (M^+, 100), 160 (7), 152 (17). Ir (KBr) νco: 1760 cm^{-1}. Uv nm (log ε): 201 (4.43), 220 (s)(4.36), 240 (s)(4.19), 255 (s)(4.08), 300 (4.08), 363 (4.36). ^1H Nmr (400 MHz) δ: 6.01 (2H, s), 6.35 (1H, s), 6.84 (1H, d, J=8.1 Hz), 7.22 (1H, dd, J=8.1, 1.8 Hz), 7.51-7.55 (2H, m), 7.68-7.75 (2H, m), 7.93 (1H, d, J=7.7 Hz). *Anal.* Calcd for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79. Found: C, 72.22; H, 3.95.

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