

EFFICIENT SYNTHESIS OF HYDROXYPHTHALIDES

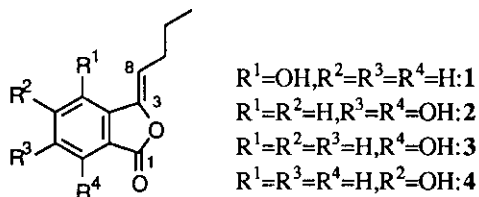
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Abstract--- Naturally occurring hydroxyphthalides were synthesized *via* migration of double bond regio- and stereoselectively. Isomerization of E-isomer to Z-isomer easily occurred under acidic or basic conditions.

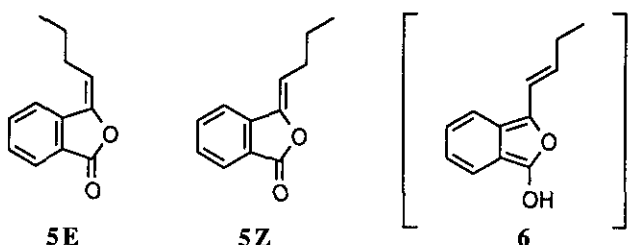
Several hydroxyphthalides such as senkyunolide-B (**1**),¹ (Z)-3-butylidene-6,7-dihydroxyphthalide (**2**),² (Z)-3-butylidene-7-hydroxyphthalide (**3**),³ and (Z)-3-butylidene-5-hydroxyphthalide (**4**)² were recently isolated from the rhizome of *Ligusticum* or *Cnidium* species which were applied frequently to traditional Chinese medicines. In these compounds, although **1**,⁴ **2**⁵ and **3**⁶ have already been synthesized, the synthesis of **4** has not been achieved so far. In this paper we wish to describe a efficient, regio- and stereoselective synthesis for these hydroxyphthalides (**1-4**) and isomerization of E-isomer to Z-isomer in this regard.



We have already reported the synthesis of **2** and the related compounds by the use of metallated phthalide in several steps. The stability of double bond of 3-alkylidene-phthalides was examined to clarify the reaction pathway of the previous method which afforded a mixture of Z- and E-isomers.⁵ Although it is known that a isomerization between Z- and E-isomer occurs by an only irradiation of light,⁷ it was found that the isomerization of E-isomer

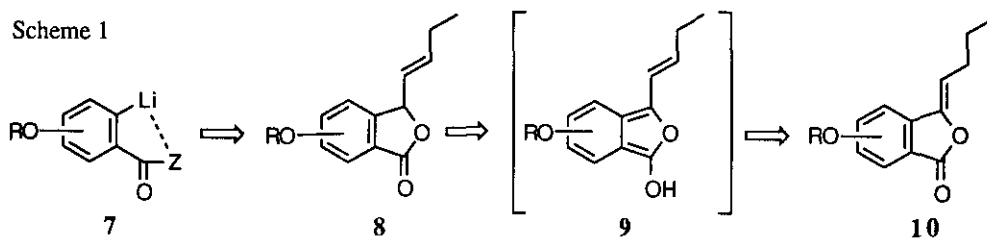
to thermodynamically stable *Z*-isomer occurred smoothly with acid or base as shown in Table 1. In particular, **5E** isomerized to **5Z** with *p*-toluenesulfonic acid (PTSA) in quantitative yield. It was suggested that **5E** isomerized to **5Z** via an intermediate (**6**).

Table 1. Stability of *E*- and *Z*-isomers with acid or base



Entry	Substrate	Reagent	Solvent	Temp.	Time(h)	E / Z (ratio) ^a	Recovery (%)
1	5E	DBU	Benzene	reflux	1	79 / 21	99
2	5E	DBU	Benzene	reflux	5	47 / 53	95
3	5E	PTSA	Benzene	reflux	1	0 / 100	100
4	5Z	DBU	Benzene	reflux	5	0 / 100	100
5	5Z	PTSA	Benzene	reflux	1	0 / 100	100

a) ratio of E/Z was determined by ¹H-nmr analysis



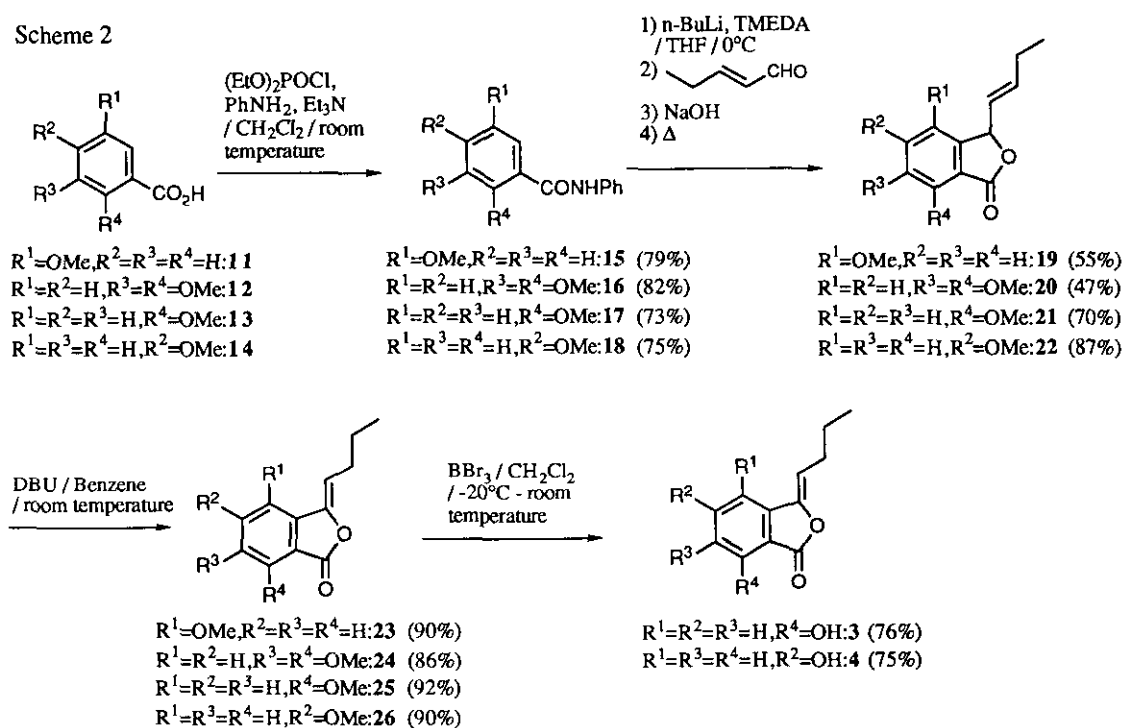
Z=Strong directed metallation group

Many different synthetic approaches to 3-alkylidene-phthalides have already been reported,⁸ but they are not enough to prepare various hydroxyphthalides easily in regio- and stereoselective manner. Some of these methods lead to mixtures of *E*- and *Z*-isomers or 5- and 6-membered ring compounds and others are not useful in broad scope owing to difficulty of synthesis of the corresponding precursors.

We turned our attention to effective approach for the synthesis of hydroxyphthalides. Aryllithium intermediate (**7**) regioselectively generated with the aid of strong directed metallation group⁹ reacted with an unsaturated aldehyde to give lactone (**8**) which should be successively converted into migration product (**10**) as shown in Scheme 1.

Amides (**15-18**) were obtained from commercially available **11-14** by use of condensing agent such as diethyl chlorophosphate. Then lithiation of **15-18** with *n*-butyllithium in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA), followed by reaction with *trans*-2-pentenal, hydrolysis with base, and cyclization by heat afforded **19-22**. The only *Z*-isomer of 3-ylideneephthalides (**23-26**)¹¹ were stereoselectively obtained *via* migration of the double bond of **19-22** by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). 3-Ylideneephthalides (**25, 26**) of them were further converted to hydroxyephthalides (**3, 4**)¹¹ by demethylation with boron tribromide¹⁰ (Scheme 2). Hydroxyephthalides (**1, 2**) have already been obtained from **23, 24** in the previous paper.⁴⁻⁵ The spectral data of these hydroxyephthalides were identical with those of natural products.

Scheme 2



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11. **26**: mp 56-57°C; ir (KBr) ν max cm^{-1} : 1782 (C=O), 1692 (C=C); $^1\text{H-nmr}$ (CDCl_3) δ : 0.99 (3H, t, J=7.4 Hz), 1.55 (2H, tq, J=7.4, 7.4 Hz), 2.44 (2H, dt, J=7.8, 7.4 Hz), 3.92 (3H, s), 5.59 (1H, t, J=7.8 Hz), 7.02 (1H, d, J=2.2 Hz), 7.02 (1H, dd, J=9.1, 2.2 Hz), 7.77 (1H, d, J=9.1 Hz), **25**: Colorless oil (lit.⁶ bp 200-203°C); ir (KBr) ν max cm^{-1} : 1776 (C=O), 1686 (C=C); $^1\text{H-nmr}$ (CDCl_3) δ : 0.98 (3H, t, J=7.4 Hz), 1.54 (2H, tq, J=7.4, 7.4 Hz), 2.43 (2H, dt, J=7.8, 7.4 Hz), 4.00 (3H, s), 5.60 (1H, t, J=7.8 Hz), 6.90 (1H, d, J=8.2 Hz), 7.18 (1H, d, J=7.7 Hz), 7.59 (1H, dd, J=8.2, 7.7 Hz), **4**: mp 117-119°C (lit.² amorphous powder); ir (KBr) ν max cm^{-1} : 1746 (C=O), 1682 (C=C); $^1\text{H-nmr}$ (CDCl_3) δ : 0.97 (3H, t, J=7.4 Hz), 1.54 (2H, tq, J=7.4, 7.4 Hz), 2.42 (2H, dt, J=7.8, 7.4 Hz), 5.59 (1H, t, J=7.8 Hz), 7.02 (1H, dd, J=8.4, 2.1 Hz), 7.07 (1H, d, J=2.1 Hz), 7.10 (1H, br, exchangeable with D_2O), 7.76 (1H, d, J=8.4 Hz), **3**: mp 75-76°C (lit.⁶ 69-70°C); ir (KBr) ν max cm^{-1} : 1752 (C=O), 1686 (C=C); $^1\text{H-nmr}$ (CDCl_3) δ : 0.99 (3H, t, J=7.4 Hz), 1.55 (2H, tq, J=7.4, 7.4 Hz), 2.44 (2H, dt, J=7.9, 7.4 Hz), 5.67 (1H, t, J=7.9 Hz), 6.91 (1H, d, J=8.2 Hz), 7.13 (1H, d, J=7.6 Hz), 7.45 (1H, br, exchangeable with D_2O), 7.54 (1H, dd, J=8.2, 7.6 Hz), The stereochemistry at C-8 of these compounds (**23-26**, **3**, **4**) was confirmed by the presence of NOE between the olefinic proton and the aromatic proton.

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