SYNTHESIS OF (Z)-3-BUTYLIDENE-6,7-DIHYDROXYPHTHALIDE

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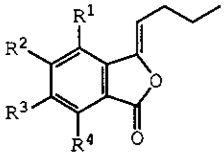
Abstract —— (Z)-3-Butylidene-6,7-dihydroxyphthalide (2) was first synthesized from 6,7-dimethoxyphthalide (4) and its structure was synthetically confirmed.

(Z)-3-Butylidene-6,7-dihydroxyphthalide (2) was isolated from the rhizome of Ligusticum wallichii Franch (Japanese name 'senkyu').[1] The structure of this compound was erroneously assigned to (Z)-3-butylidene-4,5-dihydroxyphthalide (1),[2] but recently corrected by the investigation into the ^{1}H-nmr spectra in comparison with those of 4-hydroxy- and/or 7-hydroxy-3-butylidenephthalides.[1]

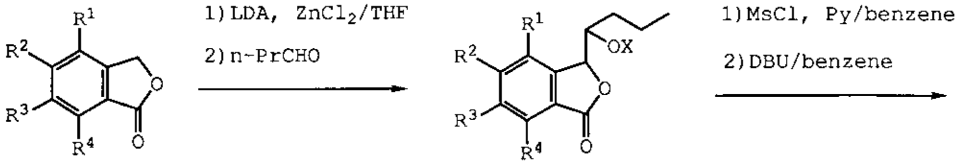


1: $R^1=R^2=OH$, $R^3=R^4=H$
2: $R^1=R^2=H$, $R^3=R^4=OH$

In this paper we wish to describe a convenient synthesis of both (Z)-3-butylidene-6,7-dihydroxyphthalide (2) and (Z)-3-butylidene-4,5-dihydroxyphthalide (1) and a comfirmation of the structure of the compound (2) from L. wallichii by comparison of their ^{1}H-nmr spectra.

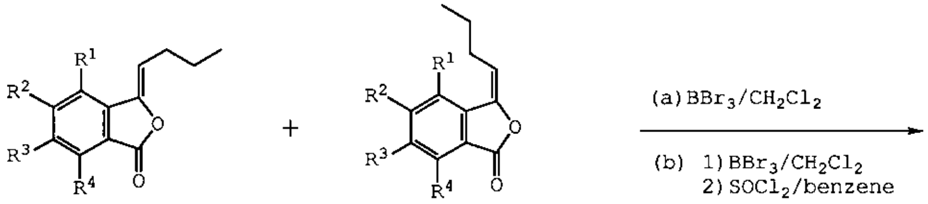
The alcohols (5 and 6) were obtained, as a diastereomeric mixture (threo/erythro), by lithiation of the corresponding phthalides (3 and 4) with LDA,[3] followed by transmetalation with zinc chloride and reaction with n-butyraldehyde.

Then the alcohols (5 and 6) were treated with methanesulfonyl chloride to afford their corresponding mesylates (7 and 8)



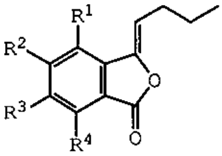
3: $R^1=R^2=OMe$, $R^3=R^4=H$
4: $R^1=R^2=H$, $R^3=R^4=OMe$

5: $R^1=R^2=OMe$, $R^3=R^4=H$, X=H
6: $R^1=R^2=H$, $R^3=R^4=OMe$, X=H
7: $R^1=R^2=OMe$, $R^3=R^4=H$, X=Ms
8: $R^1=R^2=H$, $R^3=R^4=OMe$, X=Ms

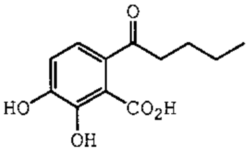


9a: $R^1=R^2=OMe$, $R^3=R^4=H$
10a: $R^1=R^2=H$, $R^3=R^4=OMe$

9b: $R^1=R^2=OMe$, $R^3=R^4=H$
10b: $R^1=R^2=H$, $R^3=R^4=OMe$



1: $R^1=R^2=OH$, $R^3=R^4=H$
2: $R^1=R^2=H$, $R^3=R^4=OH$



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Without separation of stereoisomers, the mesylates (7 and 8) were treated with DBU affording 3-butylidene-4,5-dimethoxyphthalide (9) and 3-butylidene-6,7-dimethoxyphthalide (10), respectively (9;Z/E=20/1, 10; Z/E=1/1). The ratio of Z/E was calculated on the basis of the intensities of vinyl proton signals in their ^{1}H-nmr spectra.).[4] The compound (9a) was further converted to 1 by demethylation with boron tribromide.[5] On the other hand, the demethylation of the compound (10a) with boron tribromide afforded 11 which was presumably generated as the result of addition of water when the reaction mixture was worked up. The compound (2) was obtained by treatment of 11 with thionyl chloride. The spectral data[2] of the natural product were identical with those of 2, but not those of 1. Thus the revised structure (2) for the natural product was confirmed.

EXPERIMENTAL

Melting points were measured on a YANACO micromelting point apparutus and are uncorrected. Infrared spectra were recorded on a Hitachi 270-30 spectrophotometer. Nuclear magnetic resonance spectra were obtained with a JEOL FX-200 spectrometer using tetramethylsilane as an internal standard. Mass spectra were determined on a JEOL DX-300 spectrometer.

4,5-Dimethoxyphthalide (3)

A solution of n-BuLi (1.6M in n-hexane, 96.0 ml) was injected into a stirred solution of *2-(3,4-dimethoxyphenyl)-4,4-dimethyl-2-oxazoline*[6] (30.0 g, 0.127 mol) in dry THF (280 ml) under argon atomosphere at -45℃ . The mixture was stirred at this temperature for 2 h, and then paraformaldehyde (11.5 g, 0.382 mol) was added at -45℃ . The mixture was stirred at this temperature for 1 h and then overnight at room temperature. The mixture was poured into ice water and then extracted twice with ether. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give a yellow oil. Then 3N HCl (1.2 l) was added to the yellow oil, and the mixture was refluxed under mechanical stirring for 3 h, and then left overnight at room temperature. The crystalline precipitate was separated from the mixture by filtration, washed with water, dried under vacuum and recrystallized from benzene to give colorless prisms of 3 (19.14 g, 77%) : mp 119-120℃ ; ir (KBr) ν max cm^{-1}: 1752 (C=O); ^{1}H-nmr ($CDCl_3$) δ : 3.95 (3H, s), 3.96 (3H, s), 5.32 (2H, s), 7.08 (1H, d, J=8.3 Hz), 7.62 (1H, d, J=8.3 Hz); ms m/z : 194 (M$^+$), 165 (M$^+$-CHO).

6,7-Dimethoxyphthalide (4)

The mixture of 2,3-dimethoxybenzoic acid (10.0 g, 54.89 mmol), 35% HCl (100 ml) and dimethoxymethane (5.4 ml, 60.38 mmol) was heated at 70-80℃ for 3 h under stirring. The mixture was extracted twice with $CHCl_3$. The organic layer was washed with 5% NaOH then brine, and dried ($MgSO_4$) and evaporated to give a residue. The residue was recrystallized from AcOEt-n-hexane to give colorless prisms of 4 (3.46 g, 32%) : mp 103-104℃ ; ir (KBr) ν max cm^{-1}: 1752 (C=O); ^{1}H-nmr ($CDCl_3$) δ : 3.92 (3H, s), 4.11 (3H, s), 5.20 (2H, s), 7.08 (1H, d, J=8.3 Hz), 7.24 (1H, d, J=8.3 Hz); ms m/z : 194 (M^+), 165 (M^+-CHO).

3-(1-Hydroxybutyl)-4,5-dimethoxyphthalide (5)

A solution of LDA [3] (51.5 mmol) was prepared in situ from diisopropylamine (7.2 ml), dry THF (90 ml) and n-BuLi (1.6M in hexane, 36 ml). A solution of 3 (10.0 g, 51.5 mmol) in dry THF (150 ml) was injected into the above solution of LDA under argon atomosphere at -70℃ and the mixture was stirred at this temperature for 30min. A s olution of $ZnCl_2$ (8.42 g, 61.8 mmol) in dry THF (80 ml) was injected into the above mixture at -40℃ and the mixture was stirred for 30 min. A solution of n-butyraldehyde (6.8 ml, 77.2 mmol) in dry THF (20 ml) was injected into the above mixture at -40℃ and the mixture was stirred at this temperature for 1 h and then overnight at room temperature. The mixture was poured into iced 5% HCl and extracted twice with ether. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give a residue, which was purified by flash column chromathography (SiO_2 ; eluent, AcOEt: n-hexane=1 : 1) followed by recrystallization from benzene to give colorless prisms of 5 (13.2 g, 97%, 3:1 mixture of unassigned stereoisomers) : mp 122-124℃ ; ir (KBr) ν max cm^{-1}: 3488(OH), 1746 (C=O); ^{1}H-nmr ($CDCl_3$) δ : 0.88 (9/4H, t, J=6.8 Hz), 0.96 (3/4H, t, J=6.8 Hz), 1.20-1.70 (4H, m), 1.92 (1/4H, d, J=10.0 Hz, D_2O exchangeable), 2.79 (3/4H, d, J=6.8 Hz, D_2O exchangeable), 3.95 (9/4H, s), 3.96 (3/4H, s), 3.98 (9/4H, s), 3.98 (3/4H, s), 5.50 (1/4H, d, J=2.2 Hz), 5.53 (3/4H, d, J=4.9 Hz), 7.09 (1/4H, d, J=8.3 Hz), 7.10 (3/4H, d, J=8.3 Hz), 7.64 (1/4H, d, J=8.3 Hz), 7.65 (3/4H, d, J=8.3 Hz); ms m/z : 266 (M^+), 248 (M^+-H_2O), 194 ($M^+-C_4H_8$).

3-(1-Hydroxybutyl)-6,7-dimethoxyphthalide (6)

The mixture of LDA[3] (51.5 mmol), 4 (10.0 g, 51.5 mmol), $ZnCl_2$ (8.42 g, 61.8 mmol), n-butyraldehyde (6.8 ml, 77.2 mmol) and dry THF (420 ml) was treated according to the conditions used for the preparation of 5. The reaction mixture was poured into iced 5% HCl and extracted twice with ether. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give a residue, which was purified by flash column chromathography (SiO_2 ; eluent, AcOEt : n-hexane=1 : 1) to give a colorless oil of 6 (10.7 g, 78%, 3:1 mixture of unassigned stereoisomers) : Ir (KBr) ν max cm^{-1}: 3464 (OH), 1758 (C=O); ^1H-nmr ($CDCl_3$) δ : 0.94 (9/4H, t, J=6.8 Hz), 0.97 (3/4H, t, J=6.8 Hz), 1.30-1.80 (4H, m), 1.30-1.80 (1H, br, D_2O exchangeable) 3.80-4.00 (1H, m), 3.91 (3H, s), 4.10 (9/4H, s), 4.11 (3/4H, s), 5.20 (1/4H, d, J=0.9 Hz), 5.26 (1H, d, J= 4.9 Hz), 7.10-7.30 (2H, m); ms m/z : 266 (M^+), 194 (M^+-C_4H_8).

3-(1-Methanesulfonyloxybutyl)-4,5-dimethoxyphthalide (7)

The mixture of 5 (12.42 g, 46.64 mmol), dry benzene (30 ml), dry pyridine (7.6 ml, 93.29 mmol) and methanesulfonyl chloride (7.2 ml, 93.29 mmol) was refluxed under argon atomosphere for 1 h. The mixture was poured into ice water and extracted twice with ether. The organic layer was washed with water then brine, and dried ($MgSO_4$) and evaporated to give a residue, which was purified by flash column chromathography (SiO_2 ; eluent, $CHCl_3$: CH_2Cl_2=1 : 1) to give a colorless oil of 7 (16.0 g, 99%) : Ir (KBr) ν max cm^{-1}: 1770 (C=O); ^1H-nmr ($CDCl_3$) δ : 0.84 (9/4H, t, J=7.3 Hz), 1.03 (3/4H, t, J=7.3 Hz), 1.20-2.10 (4H, m), 2.55 (3/4H, s), 3.13 (9/4H, s), 3.97 (3/4H, s), 3.98 (9/4H, s), 3.99 (9/4H, s), 4.05 (3/4H, s), 5.26 (1/4H, ddd, J=8.0, 1.5, 1.0 Hz), 5.41 (3/4H, ddd, J=10.0, 3.0, 2.0 Hz), 5.55 (1/4H, d, J=1.5 Hz), 5.92 (3/4H, d, J=2.0 Hz), 7.11 (1/4H, d, J=8.3 Hz), 7.12 (3/4H, d, J=8.3 Hz), 7.60 (1/4H, d, J=8.3 Hz), 7.64 (3/4H, d, J=8.3 Hz); ms m/z : 344 (M^+), 248 (M^+-$MeSO_3H$), 193.

(Z)- and (E)-3-Butylidene-4,5-dimethoxyphthalide (9a, 9b)

The mixture of 7 (16.0 g, 46.55 mmol), dry benzene (150 ml) and DBU (9.75 ml, 65.19 mmol) was refluxed under argon atomosphere for 1 h. The mixture was poured into iced 2% HCl (100 ml) and extracted twice with ether. The organic layer was washed with water then brine, and dried ($MgSO_4$) and evaporated to give a residue, which was recrystallized from n-hexane to give colorless needles of 9a (8.6 g, 74%) : mp 85-87℃ ; ir (KBr) ν max cm^{-1} : 1774 (C=O), 1680 (C=C); ^{1}H-nmr ($CDCl_3$) δ : 1.00 (3H, t, J=7.3 Hz), 1.56 (2H, tq, J=7.3, 7.3 Hz), 2.45 (2H, dt, J=7.9, 7.3 Hz), 3.95 (3H, s), 3.97 (3H, s), 5.98 (1H, t, J=7.9 Hz), 7.04 (1H, d, J=8.3 Hz), 7.62 (1H, d, J=8.3 Hz); ms m/z : 248 (M^+), 219 ($M^+-C_2H_5$), 206 ($M^+-C_3H_6$). The mother liquor was purified by flash column chromathography (SiO_2 ; eluent, CH_2Cl_2) followed by recrystallization from n-hexane to give colorless needles of 9b (0.46 g, 4%) : mp 79-81℃ ; ir (KBr) ν max cm^{-1} : 1784 (C=O), 1668 (C=C); ^{1}H-nmr ($CDCl_3$) δ : 1.00 (3H, t, J=7.3 Hz), 1.56 (2H, tq, J=7.3, 7.3 Hz), 2.73 (2H, dt, J=8.4, 7.3 Hz), 3.90 (3H, s), 4.00 (3H, s), 5.91 (1H, t, J=8.4 Hz), 7.12 (1H, d, J=8.3 Hz), 7.67 (1H, d, J=8.3 Hz); ms m/z : 248 (M^+), 219 ($M^+-C_2H_5$), 206 ($M^+-C_3H_6$).

(Z)- and (E)-3-Butylidene-6,7-dimethoxyphthalide (10a, 10b)

The mixture of 6 (10.0 g, 37.55 mmol), dry benzene (30 ml), dry pyridine (7.6 ml, 93.88 mmol) and methanesulfonyl chloride (5.8 ml, 75.11 mmol) was refluxed under argon atomosphere for 1 h. The mixture was poured into ice water and extracted twice with ether. The organic layer was washed with water then brine, and dried ($MgSO_4$) and evaporated to give a residue, which was purified by flash column chromathography (SiO_2 ; eluent, $CHCl_3$: CH_2Cl_2=1 : 1) to give a colorless oil of 8 : ^{1}H-Nmr ($CDCl_3$) δ : 0.95 (9/4H, t, J=6.4 Hz), 0.98 (3/4H, t, J=6.4 Hz), 1.20-1.90 (4H, m), 2.78 (3/4H, s), 3.09 (9/4H, s), 3.92 (3/4H, s), 3.93 (9/4H, s), 4.11 (3H, s), 5.01 (1/4H, dt, J=6.4, 3.7 Hz), 5.06 (3/4H, dt, J=6.4, 3.2 Hz), 5.50 (1/4H, d, J=3.7 Hz), 5.58 (3/4H, d, J=3.2 Hz), 7.13 (3/4H, d, J=8.3 Hz), 7.19 (1/4H, d, J=8.3 Hz), 7.24 (3/4H, d, J=8.3 Hz), 7.25 (1/4H, d, J=8.3 Hz); ms m/z : 344 (M^+), 248 (M^+-MeSO_3H).

Without further purification, 8 was dissolved in dry benzene (150 ml) and DBU (8.4ml, 56.33mmol) and refluxed under argon atomosphere for 1 h. The mixture was poured into iced 2% HCl (100 ml) and extracted twice with ether. The organic layer was washed with water then brine, and dried ($MgSO_4$) and evaporated to give a residue, which was purified by flash column chromathography (SiO_2 ; eluent, $CHCl_3$) to give 10a as a colorless amorphous powder (3.75 g, 40%) : Ir (KBr) ν max cm^{-1}: 1778 (C=O), 1688 (C=C); ^{1}H-nmr ($CDCl_3$) δ : 0.98 (3H, t, J=7.3 Hz), 1.53 (2H, tq, J=7.6, 7.3 Hz), 2.41 (2H, dt, J=7.8, 7.6 Hz), 3.92 (3H, s), 4.13 (3H, s), 5.46 (1H, t, J=7.8 Hz), 7.22 (1H, d, J=8.5 Hz), 7.28 (1H, d, J=8.5 Hz); ms m/z : 248 (M^+), 219 ($M^+-C_2H_5$), 206 ($M^+-C_3H_6$), and 10b *as a colorless oil (2.1 g, 22%) : Ir (KBr)* ν *max* cm^{-1} : 1778 (C=O), 1686 (C=C); ^{1}H-nmr ($CDCl_3$) δ : 1.02 (3H, t, J=7.3 Hz), 1.60 (2H, tq, J=7.6, 7.3 Hz), 2.46 (2H, dt, J=8.2, 7.6 Hz), 3.94 (3H, s), 4.12 (3H, S), 5.70 (1H, t, J=8.2 Hz), 7.25 (1H, d, J=8.3 Hz), 7.46 (1H, d, J=8.3 Hz); ms m/z : 248 (M^+), 219 ($M^+-C_2H_5$), 206 ($M^+-C_3H_6$).

(Z)-3-Butylidene-4,5-dihydroxyphthalide (1)

A solution of BBr_3 (0.8 M in CH_2Cl_2, 151 ml, 120.8mmol) was added to a stirred solution of 9a (7.5 g, 30.21 mmol) in dry CH_2Cl_2 (75 ml) under argon *atomosphere at* 0℃ . The mixture was stirred at 0℃ for 30 min and then at room temperature for 3 h. The mixture was poured into ice water and extracted with CH_2Cl_2 and then twice with AcOEt. The organic layer was washed with brine and evaporated to give a residue, which was purified by flash column chromathography (SiO_2 ; eluent, acetone: AcOEt=1: 10) and recrystallization from AcOEt-n-hexane to give colorless needles of 1 (5.38 g, 81%): mp 191-193℃ ; ir (KBr) ν max cm^{-1}: 3388 (OH), 3170 (OH), 1724 (C=O), 1678 (C=C); ^{1}H-nmr (CD_3OD) δ : 1.00 (3H, t, J=7.3 Hz), 1.56 (2H, tq, J=7.3, 7.3 Hz), 2.41 (2H, dt, J=7.8, 7.3 Hz), 5.95 (1H, t, J=7.8 Hz), 6.95 (1H, d, J=8.1 Hz), 7.23 (1H, d, J=8.1 Hz); ms m/z : 220 (M^+), 191 ($M^+-C_2H_5$), 178 ($M^+-C_3H_6$).

6,7-Dihydroxy-3-valerylbenzoic acid (11)

A solution of BBr_3 (0.8 M in CH_2Cl_2, 40 ml, 32mmol) was added to a stirred solution of 10a (2.0 g, 8.05 mmol) in dry CH_2Cl_2 (40 ml) under argon atomosphere at 0℃ . The mixture was stirred at 0℃ for 30 min, then at room temperature for 3 h. The mixture was poured into ice water. The crystalline precipitate was separated from the mixture by filtration, dried under vacuum and recrystallized from AcOEt-n-hexane to give colorless needles of 11 (1.20 g, 68%) : mp 98-100℃ ; ir (KBr) ν max cm^{-1}: 3364 (OH), 3232 (OH), 1726 (C=O); ^{1}H-nmr (CD_3OD) δ : 0.88 (3H, t, J=6.0 Hz), 1.10-1.40 (4H, m), 1.90-2.40 (2H, m), 6.87 (1H, d, J=7.6 Hz), 7.06 (1H, d, J=7.6 Hz); ms m/z : 238

(M^+), 181 ($M^+-C_4H_9$).

(Z)-3-Butylidene-6,7-dihydroxyphthalide (2)

The mixture of 11 (300 mg, 1.26 mmol), thionyl chloride (0.3 ml, 4.11mmol) and dry benzene (6 ml) was heated at 60-70℃ for 30 min under stirring. The mixture was evaporated to give a residue, which was purified by column chromathography (Sephadex LH-20 ; eluent, $CHCl_3$) and then recrystallized from $CHCl_3$-n-hexane to give colorless needles of 2 (167 mg, 60%): mp 113-115℃ (lit.[2] amorphous powder); ir (KBr) ν max cm^{-1}: 3560 (OH), 3242 (OH), 1740 (C=O), 1685 (C=C); ^1H-nmr (CD_3OD) δ : 0.98 (3H, t, J=7.3 Hz), 1.53 (2H, tq, J=7.3, 7.3 Hz), 2.36 (2H, dt, J=7.8, 7.3 Hz), 5.52 (1H, t, J=7.8 Hz), 7.06 (1H, d, J=8.1 Hz), 7.13 (1H, d, J=8.1 Hz); ms m/z : 220 (M^+), 191 ($M^+-C_2H_5$).

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Received, 21st May, 1991