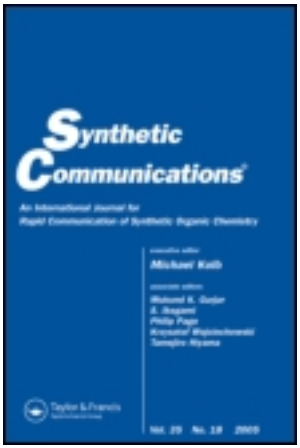

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Stereochemistry of Phellinsin A: A Concise Synthesis of α-Arylidene-γ-Lactones

Eungsoo Kim [a], Hyeong Kyu Lee [a], Eui-Il Hwang [a], Sung-Uk Kim [a], Woo Song Lee [a], Sangku Lee [a] & Sang-Hun Jung [b]

[a] Korea Research Institute of Bioscience and Biotechnology, Yusong, Taejon, Republic of Korea
[b] College of Pharmacy, Chungnam National University, Taejon, Republic of Korea

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Stereochemistry of Phellinsin A: A Concise Synthesis of α-Arylidene-γ-Lactones

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Korea Research Institute of Bioscience and Biotechnology, Yusong, Taejon, Republic of Korea

Sang-Hun Jung
College of Pharmacy, Chungnam National University, Taejon, Republic of Korea

Abstract: Phellinsin A (**1a**) was prepared in a concise way, thereby elucidating the relative stereochemistry of the aryl and carboxylic acid groups in **1a**. The synthesis employed selective monohydrolysis of the dilactones derived from oxidative dimerization of cinnamic acid derivatives. This approach provided a practical synthetic route to α-arylidene-γ-lactones.

Keywords: α-Arylidene-γ-lactone, cinnamic acid, dilactone, hydrolysis

Phellinsin A (**1a**), isolated from the cultured broth of *Phellinus* sp. PL3, is an inhibitor of chitin synthases II, which renders it a potentially useful antifungal agent.[1] Structurally, phellinsin A is a phenolic lignan featuring a dehydrodimerized γ-lactone form of caffeic acid, and it occurs in a racemic form despite the presence of two asymmetric centers. The connectivity of **1a** was established by NMR analysis; however, the relative stereochemistry of two neighboring aryl and carboxylic acid moieties in **1a** was not elucidated. For the

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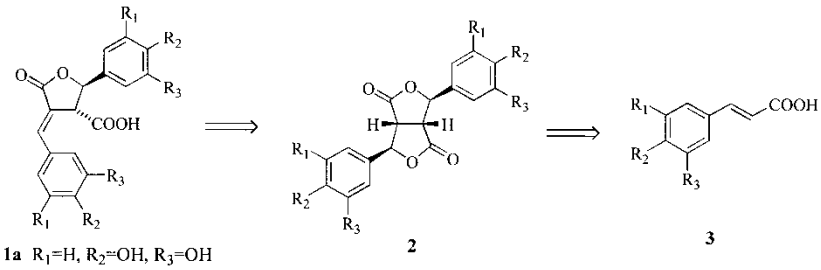
Address correspondence to Sangku Lee, Korea Research Institute of Bioscience and Biotechnology, 52 Oun,, Yusong, Taejon 305-333, Republic of Korea. Tel.: + 82-42-860-4552; Fax: +82-42-860-4309; E-mail: sangku@kribb.re.kr

development of new potent analogues of **1a**, the stereochemistry of **1a** needs to be established. Herein we describe the synthesis of phellinsin A (**1a**), thereby establishing the relative stereochemistry of **1a** and providing an efficient synthetic route to α-arylidene-γ-lactones,[2] which constitute an important group in natural products.[3]

Oxidative dimerization of free phenolic cinnamic acids, ferulic acid, and sinapic acid to the corresponding dilactones using $FeCl_3$ as an one-electron oxidant was reported in nearly sixty years ago.[4] Recently, Yuzikhin and coworkers utilized lead dioxide in CF_3COOH-CH_2Cl_2 as an one-electron oxidant for the oxidative dimerization of cinnamic acid derivatives to the corresponding dilactones.[5] They showed that alkoxy-, alkyl-, and halogen-substituted cinnamic acids provided the corresponding dilactones. It is known that the oxidative dimerization reaction involves the formation of relatively stable radical cations and the dimerization of the resulting radicals, followed by intramolecular cyclization to yield the corresponding dilactone.[5,6]

We have interested in the construction of the ring skeleton of phellinsin A (**1a**) via oxidative dimerization of cinnamic acid derivatives **3** to the corresponding dilactones **2** and monohydrolysis of the resulting dilactones, followed by dehydration to furnish the α-arylidene-γ-lactone moieties **1** as shown in retrosynthetic analysis (Scheme 1). One-electron oxidation would be expected to provide thermodynamically more stable *cis*-ring fused-dilactones positioning *exo*-orientation of aryl groups, which upon mono-hydrolysis of the dilactone would generate the *trans*-relationship of the carboxylic acid and aryl moieties in **1**. We envisioned that this strategy could provide a simple way of preparing phellinsin A (**1a**), thereby establishing the relative stereochemistry of **1a** and providing an efficient synthetic route to α-arylidene-γ-lactones **1**.

Dehydrodiferulic dilactone (**2b**) was obtained in 56% yield from ferulic acid (**3b**) by slight modification of Haworth's method.[4] The stage was set for the mono-hydrolysis of the dilactone **2b**, followed by dehydration to

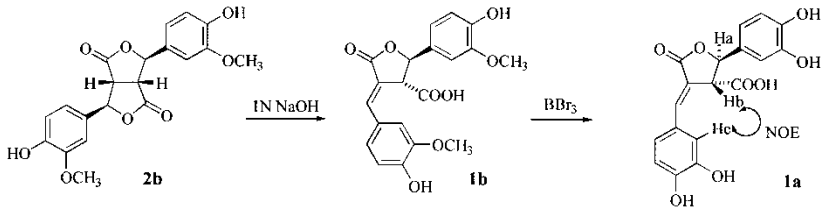


Scheme 1.

produce α-arylidene-γ-lactone **1b** (Scheme 2). To this end, dilactone **2b** was treated with 1 NaOH at room temperature for 5 min to furnish γ-lactone **1b** in 86% yield. For the preparation of phellinsin A (**1a**), compound **1b** was demethylated by treatment with BBr_3 in methylene chloride at 0°C to afford **1a**. The *E*-configuration of the double bond in **1a** was established by NOESY and COSY experiments. We observed NOE effects between Hb and Hc. The *trans*-orientation of the aryl and carboxylic acid groups in **1a** was confirmed by a small coupling constant (Ja,b = 2.0–2.4 Hz) and a comparison to literature data of the methyl esters of **1b**[7] and **1f**.[8] The synthetic compound **1a** was in good accord with a natural authentic sample in all aspects including IR, ^{1}H-NMR, ^{13}C-NMR, and TLC in three different solvent systems. Accordingly, the relative stereochemistry of the aryl and carboxylic acid groups in phellinsin A (**1a**) was determined to be *trans*-relation. This approach, a sequence of oxidative dimerization of substituted cinnamic acid to the corresponding dilactone and subsequent monohydrolysis of the dilactone, provided a practical way to synthesize phellinsin A (**1a**).

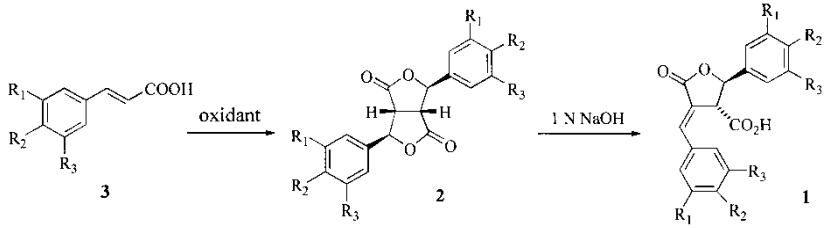
Having clarified the synthesis of phellinsin A (**1a**) via monohydrolysis of the corresponding dilactone, we demonstrated the synthetic approach to α-arylidene-γ-lactones **1** by preparing analogues of phellinsin A. To this end, a series of dilactones **2** were prepared from cinnamic acid derivatives **3** using $FeCl_3$ or PbO_2 as an oxidant (Table 1).[9] $FeCl_3$ was effective for the oxidative dimerization of *para*-hydroxy-substituted cinnamic acids,[4] whereas PbO_2 was used for nonphenolic cinnamic acid derivatives.[5] Treatment of the dilactones **2** in THF with 1N NaOH at room temperature for 5 min underwent monohydrolysis of the dilactones, followed by dehydration, to furnish the corresponding α-arylidene-γ-lactones **1** in moderate to good isolated yields.[10] The synthesis of α-arylidene-γ-lactones was completed in two steps starting from cinnamic acid derivatives.

In summary, we have prepared phellinsin A (**1a**) and its analogs in a concise way, thereby elucidating the *trans*-relation of the aryl and carboxylic acid groups in **1a**. The synthesis features monohydrolysis of the dilactones derived from oxidative dimerization of cinnamic acid derivatives and followed by dehydration to yield α-arylidene-γ-lactones.



Scheme 2.

Table 1. Hydrolysis of dilactones **2** to the corresponding α-arylidene-γ-lactones **1**



Entry	**3**	R_1	R_2	R_3	Oxidant	**2** (%)[a]	**1** (%)[a]
1	**3b**	H	OH	OCH_3	$FeCl_3$	**2b** (56)	**1b** (86)
2	**3c**	H	OH	H	$FeCl_3$	**2c** (52)	**1c** (75)
3	**3d**	H	OC_2H_5	H	PbO_2	**2d** (42)	**1d** (78)
4	**3e**	H	H	H	PbO_2	**2e** (36)	**1e** (62)
5	**3f**	OCH_3	OH	OCH_3	$FeCl_3$	**2f** (75)	**1f** (62)
6	**3g**	H	OCH_3	OCH_3		**2g** (90)[b]	**1g** (80)
7	**3h**	OCH_3	OCH_3	OCH_3		**2h** (84)[c]	**1h** (74)

[a]Isolated yield, not optimized.
[b]Prepared by treatment of **2b** with diazomethane.
[c]Prepared by treatment of **2f** with diazomethane.

EXPERIMENTAL

All reactions were conducted under a nitrogen atmosphere using oven-dried glassware unless otherwise noted. Analytical TLC was done on 0.25 mm E. Merck precoated silica-gel 60 F_{254} plates. Visualization was accomplished with UV light at 254 nm and with phosphomolybdic acid or anisaldehyde stain. Flash chromatography was performed on silica gel 60 (E. Merck 9385, 230–400 mesh). ^1H and ^{13}C NMR spectra were recorded on a Varian Unity 300 or Varian Inova 400 spectrometer at ambient temperature. Chemical shifts are reported in ppm relative to tetramethylsilane/$CHCl_3$.

General Procedure for Oxidative Dimerization of 4-Hydroxy-substituted Cinnamic Acids using $FeCl_3$

To a solution of ferric chloride (9.2 g, 56.7 mmol) in ethanol (100 mL) was added a solution of 4-hydroxy-3-methoxycinnamic acid (**3b**, 5.0 g, 25.7 mmol) in ethanol (30 mL) at room temperature. The reaction mixture was stirred for 1 h and concentrated in vacuo. The residue was diluted with water, extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (1:1 hexane–EtOAc) to afford 5.6 g (56%) of **2b** as a white solid.

2b: Mp 206–208°C (lit.[4b] mp 207–211°C); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.86 (s, 2H), 7.06 (d, $J = 1.8$ Hz, 2H), 6.92 (dd, $J = 7.8$, 1.8 Hz, 2H), 6.86 (d, $J = 7.8$ Hz, 2H), 5.78 (brs, 2H), 4.09 (brs, 2H), 3.87 (s, 6H); ^{13}C NMR (75 MHz, acetone-d_6) δ 176.1, 148.9, 148.4, 131.0, 119.7, 116.2, 110.5, 83.3, 56.5, 49.2; HRMS (FAB) m/z 387.1092 [$(M + H)^+$, calcd. for $C_{20}H_{19}O_8$ 387.1080].

2c: Compound **2c** was prepared in 52% yield as a yellow solid from **3c** according to the general procedure. **2c:** mp 185–188°C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.23 (dd, $J = 6.6$, 1.8 Hz, 4H), 6.82 (dd, $J = 6.6$, 1.8 Hz, 4H), 5.75 (s, 2H), 3.93 (s, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 177.3, 159.5, 130.6, 128.3, 116.8, 84.1, 49.7; HRMS (FAB) m/z 327.0851 [$(M + H)^+$, calcd. for $C_{18}H_{15}O_6$ 327.0869].

2f: Compound **2f** was prepared in 75% yield as a pale brown solid from **3f** according to the general procedure. **2f:** mp 230–234°C (lit.[4b] mp 227–235°C); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.47 (s, 2H), 6.75 (s, 4H), 5.76 (brs, 2H), 4.12 (brs, 2H), 3.84 (s, 12H); ^{13}C NMR (75 MHz, acetone-d_6) δ 176.7, 149.7, 138.2, 130.5, 105.0, 84.1, 57.4, 49.8; HRMS (FAB) m/z 447.1288 [$(M + H)^+$, calcd. for $C_{22}H_{23}O_{10}$ 447.1291].

General Procedure for Oxidative Dimerization of Nonphenolic Cinnamic Acids using PbO_2

To a solution of trifluoroacetic acid (3 mL) in methylene chloride (18 mL) was added 4-ethoxycinnamic acid (**3d**, 1.0 g, 5.2 mmol) at 0°C. Then, PbO_2 (1.24 g, 5.2 mmol) was added and the reaction mixture was sirred for 1 h. The mixture was poured into ethyl acetate (100 mL), and the organic layer was washed in succession with water, saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (4 : 1 hexane–EtOAc) to afford 0.84 g (42%) of **2d** as a white solid.

2d: Mp 163–164°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, $J = 8.7$ Hz, 4H), 6.90 (dd, $J = 6.6$, 1.8 Hz, 4H), 5.88 (s, 2H), 4.02 (q, $J = 6.9$ Hz, 4H), 3.56 (s, 2H), 1.41 (t, $J = 6.9$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 159.6, 129.8, 126.2, 115.1, 81.9, 63.7, 48.3, 14.7; HRMS (FAB) m/z 383.1485 [$(M + H)^+$, calcd. for $C_{22}H_{23}O_6$ 383.1495].

2e: Compound **2e** was prepared in 36% yield as a pale brown solid from **3e** according to the general procedure. **2e:** mp 161–163°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.30 (m, 10H), 5.93 (s, 2H), 3.56 (s, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 138.0, 129.2, 129.1, 124.5, 81.7, 48.2; HRMS (FAB) m/z 295.0982 [$(M + H)^+$, calcd. for $C_{18}H_{15}O_4$ 295.0970].

General Procedure for Methylation of Hydroxy-substituted Dilactones

To a solution of dehydrodiferulic dilactone (**2b**, 0.3 g, 0.77 mmol) in acetone (20 mL) was added excess of diazomethane in ethyl ether at room temperature. The reaction mixture was stirred overnight and concentrated in vacuo. The residue was recrystallized from methanol to yield 0.27 g (90%) of **2g** as a white solid.

2g: Mp 200–203°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03–7.00 (m, 6H), 5.80 (s, 2H), 4.22 (s, 2H), 3.79 (s, 6H), 3.77 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 149.4, 149.0, 130.5, 118.8, 111.7, 109.9, 81.7, 55.7, 55.6, 48.1; HRMS (FAB) m/z 415.1394 [$(M + H)^+$, calcd. for $C_{22}H_{23}O_8$ 415.1393].

2h: Compound **2h** was prepared in 84% yield as a white solid from **2f** according to the general procedure. **2h:** mp 200–202°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.73 (s, 4H), 5.79 (s, 2H), 4.26 (s, 2H), 3.81 (s, 12H), 3.66 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 175.3, 153.2, 137.8, 133.9, 103.5, 81.6, 60.0, 56.1, 47.8; HRMS (FAB) m/z 475.1601 [$(M + H)^+$, calcd. for $C_{24}H_{27}O_{10}$ 475.1604].

General Procedure for Hydrolysis of Dilactones to the Corresponding α-Arylidene-γ-lactones

To a solution of dehydrodiferulic dilactone (**2b**, 1.40 g, 3.63 mmol) in THF (10 mL) was added 1N NaOH (100 mL) at room temperature. The reaction mixture was stirred for 5 min, acidified with 2N HCl to pH 4, extracted with ethyl acetate, dried over $MgSO_4$, and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (9:1 CH_2Cl_2–CH_3OH) to afford 1.2 g (86%) of **1b** as a yellow solid.

1b: Mp 116–119°C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (s, 1H), 7.36 (s, 1H), 7.15 (d, $J = 8.0$ Hz, 1H), 6.86 (s, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 6.75 (bs, 2H), 5.69 (d, $J = 2.0$ Hz, 1H), 3.98 (bs, 1H), 3.87 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 178.8, 175.2, 150.4, 149.2, 149.1, 148.0, 140.2, 133.5, 127.5, 126.8, 123.1, 119.3, 116.5, 116.4, 114.6, 110.3, 84.4, 58.1, 56.7, 56.4; HRMS (FAB) m/z 387.1082 [$(M + H)^+$, calcd. for $C_{20}H_{19}O_8$ 387.1080].

1c: Compound **1c** was prepared in 75% yield as a white solid from **2c** according to the general procedure. **1c:** mp decomp.; ^{1}H NMR (300 MHz, CD_3OD) δ 7.57 (s, 1H), 7.56 (d, $J = 8.7$ Hz, 2H), 7.12 (d, $J = 9.0$ Hz, 2H), 6.81 (d, $J = 9.0$ Hz, 2H), 6.76 (d, $J = 8.7$ Hz, 2H), 5.68 (d, $J = 2.4$ Hz, 1H), 4.00 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 178.1, 174.9, 161.2, 159.0, 140.2, 134.0, 132.6, 128.0, 126.8, 122.2. 116.8, 116.6, 84.0, 57.1; HRMS (FAB) m/z 327.0857 [$(M + H)^+$, calcd. for $C_{18}H_{15}O_6$ 327.0869].

1d: Compound **1d** was prepared in 78% yield as a brown solid from **2d** according to the general procedure. **1d:** mp 100–102°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.85 (d, $J = 8.7$ Hz, 2H), 7.39 (s, 1H), 7.10 (d, $J = 8.7$ Hz, 2H), 6.92 (d, $J = 8.7$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 5.76 (s, 1H), 4.04 (q, $J = 7.2$ Hz, 2H), 3.96 (q, $J = 6.6$ Hz, 2H), 3.65 (s, 1H), 1.31 (t, $J = 7.2$ Hz, 3H), 1.28 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.3, 159.7, 158.2, 133.3, 132.4, 126.9, 126.5, 114.6, 114.5, 63.2, 63.0, 14.6, 14.5; HRMS (FAB) m/z 383.1490 [$(M + H)^+$, calcd. for $C_{22}H_{23}O_6$ 383.1495].

1e: Compound **1e** was prepared in 62% yield as a white solid from **2e** according to the general procedure. **1e:** mp 144–146°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.50–7.28 (m, 10H), 5.81 (s, 1H), 4.25 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 177.1, 174.6, 142.3, 139.4, 135.6, 131.7, 131.1, 129.9, 129.8, 129.4, 127.0, 126.3, 84.5, 58.7; HRMS (FAB) m/z 295.0974 [$(M + H)^+$, calcd. for $C_{18}H_{15}O_4$ 295.0970].

1f: Compound **1f** was prepared in 62% yield as a yellow solid from **2f** according to the general procedure. **1f:** mp decomp.; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, $J = 1.8$ Hz, 1H), 6.77 (s, 2H), 6.51 (s, 2H), 5.69 (d, $J = 2.4$ Hz, 1H), 4.12 (m, 1H), 3.85 (s, 6H), 3.84 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 171.4, 147.4, 147.2, 141.9, 137.7, 135.2, 130.2, 124.4, 118.1, 107.7, 101.9, 80.5, 56.4, 56.3, 53.5; HRMS (FAB) m/z 447.1286 [$(M + H)^+$, calcd. for $C_{22}H_{23}O_{10}$ 447.1291].

1g: Compound **1g** was prepared in 80% yield as a yellow solid from **2g** according to the general procedure. **1g:** mp decomp.; ^{1}H NMR (300 MHz, CD_3OD) δ 7.59 (s, 1H), 7.34 (s, 1H), 7.13 (d, $J = 7.8$ Hz, 1H), 6.91 (d, $J = 7.8$ Hz, 2H), 6.88 (s, 1H), 6.82 (d, $J = 7.8$ Hz, 1H), 5.70 (s, 1H), 4.02 (s, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.78 (s, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 175.8, 174.9, 150.7, 150.6, 150.4, 149.2, 134.6, 127.3, 127.1, 122.4, 119.0, 116.4, 114.2, 112.9, 110.3, 80.9, 56.6, 56.5, 56.4; HRMS (FAB) m/z 415.1397 [$(M + H)^+$, calcd. for $C_{22}H_{23}O_8$ 415.1393].

1h: Compound **1h** was prepared in 74% yield as a yellow solid from **2h** according to the general procedure. **1h:** mp decomp.; ^{1}H NMR (300 MHz,

CD_3OD) δ 7.59 (d, $J = 2.4$ Hz, 1H), 7.03 (s, 2H), 6.64 (s, 2H), 5.60 (d, $J = 2.4$ Hz, 1H), 3.90 (d, $J = 2.4$ Hz, 1H), 3.87 (s, 6H), 3.81 (s, 6H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 177.3, 174.7, 154.8, 154.6, 140.9, 139.9, 139.0, 138.2, 131.4, 125.9, 109.3, 103.6, 84.3, 61.1, 61.0, 56.9, 56.6; HRMS (FAB) m/z 475.1602 [$(M + H)^+$, calcd. for $C_{24}H_{27}O_{10}$ 475.1604].

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