Efficient Syntheses of 1-Arylnaphthalene Lignan Lactones and Related Compounds from Cyanohydrins

Tsuyoshi Ogiku, Shin-ichi Yoshida, Hiroshi Ohmizu,* and Tameo Iwasaki*

Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co., Ltd., 3-16-89, Kashima, Yodogawa, Osaka 532, Japan

Received December 21, 1994[⊗]

1-Arylnaphthalene lignan lactones were synthesized in good yields from *O*-(*tert*-butyldimethylsilyl)-cyanohydrins in two steps based on a conjugate addition–aldol reaction, followed by acid-catalyzed closure to form the naphthalene ring. 4-Hydroxy-1-arylnaphthalene lignan lactones were also synthesized by conjugate addition–aldol reaction, followed by aromatization–lactonization.

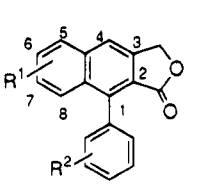
Introduction

1-Arylnaphthalene lignan lactones, e.g., taiwanin C (**1a**), chinensin (**1b**), diphyllin (**2a**), and dehydropodophyllotoxin (**2b**), have attracted considerable interest with the discovery of their intriguing biological activities such as antitumor and antihyperlipidemic activities (Chart 1).[1] We became interested in the synthesis of this series in connection with our synthetic studies in search of new lignan derivatives. Existing synthetic methods for lignan lactones[2] include those based on the Diels–Alder reaction of phenylpropionic acid derivatives[3] or 1-arylisobenzofurans,[4] cyclization of Stobbe condensation products,[5] nucleophilic addition of aryllithium to naphthyloxazolines,[6] and the conjugate addition–aldol reaction of thioacetals.[7] In a preliminary effort to use these methods, we found that some had defects such as the use of a number of steps and complex reagents, and some were not effective for the preparation of the naturally occurring lignans. This prompted us to develop an alternative method. In this paper, we describe efficient methods based on the conjugate addition–aldol reaction using *O*-(*tert*-butyldimethylsilyl)cyanohydrins. Some preliminary results have been published.[8]

Results and Discussion

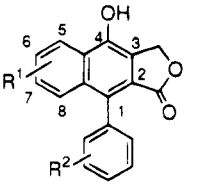
We considered that the conjugate addition–aldol reaction would be one of the methods having the highest potential in the synthesis of this series of lignans. We first planned the strategy on the basis of the conjugate addition–aldol reaction sequence as illustrated in Scheme 1. The key intermediate **4** would be synthesized by this sequence followed by cyclization. 1-Arylnaphthalene lignan lactone **1** would be formed by aromatization involving elimination of HCN and TBDMSOH from **4**. The 4-hydroxy-1-arylnaphthalene lignan lactone **2** would be formed by the aromatization–lactonization reaction initiated by formylation of **5**.

Chart 1



1

R^1	R^2
a: 6,7-OCH_2O-	3,4-OCH_2O-
b: 6,7-OCH_2O-	3,4-$(OMe)_2$
c: 6,7-$(OMe)_2$	3,4-OCH_2O-
d: 6,7-$(OMe)_2$	3,4,5-$(OMe)_3$



2

R^1	R^2
a: 6,7-$(OMe)_2$	3,4-OCH_2O-
b: 6,7-OCH_2O-	3,4,5-$(OMe)_3$
c: 6,7-OCH_2O-	3,4-$(OMe)_2$
d: 6,7-OCH_2O-	3,4-OCH_2O-
e: 6,7,8-$(OMe)_3$	3,4-$(OMe)_2$

Synthesis of 1-Arylnaphthalene Lignan Lactones. Hünig and his co-workers studied the chemistry of *O*-(trimethylsilyl)cyanohydrins and demonstrated the conjugate addition of these materials to α,β-unsaturated esters.[9] However, they did not examine the conjugate addition of the reaction with 2-butenolide. Ziegler et al. found that conjugate addition of *O*-(1-ethoxyethyl)cyanohydrin to 2-butenolide did not occur cleanly.[7a] Accordingly, our study began with examination of the conjugate addition of **7**, prepared by Cava's method,[10] to 2-butenolide (Scheme 2).

Conjugate addition of the anion generated by reaction of **7** with LDA to 2-butenolide cleanly took place in THF at −78 °C. Without isolation of the addition product, the resulting enolate was trapped by addition of piperonal to afford **8** in 88% yield after purification. Treatment of **8** with TFA–CH_2Cl_2 (1:1) at room temperature for 30 min afforded **9** in 80% yield as a 1:1 mixture of the two diastereomers, which were separated by silica gel chro-

[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1995.

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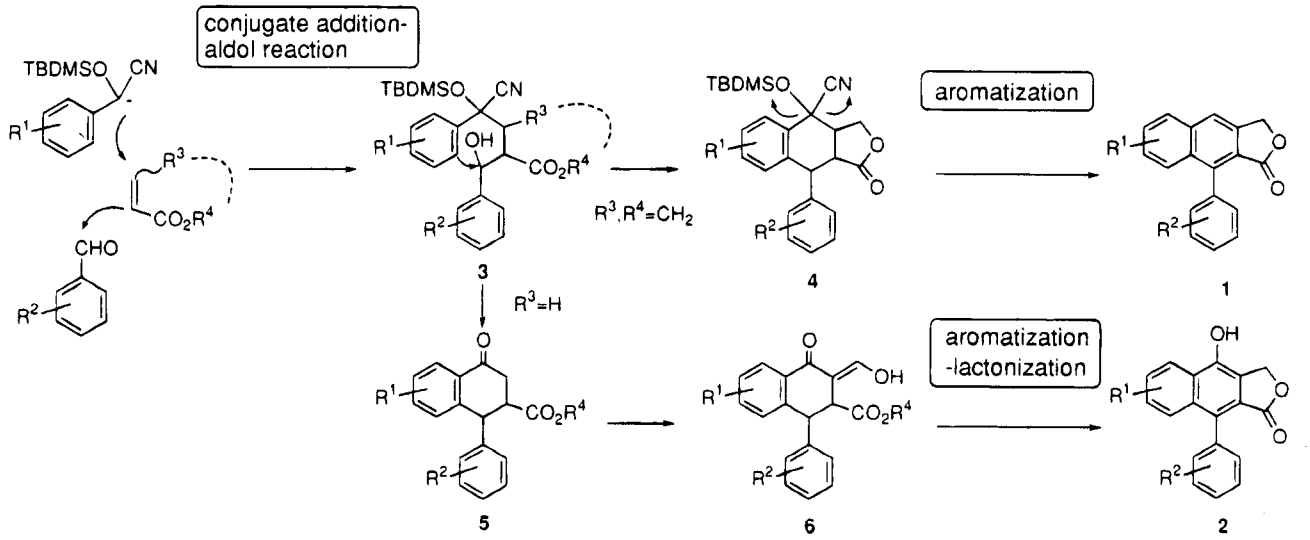
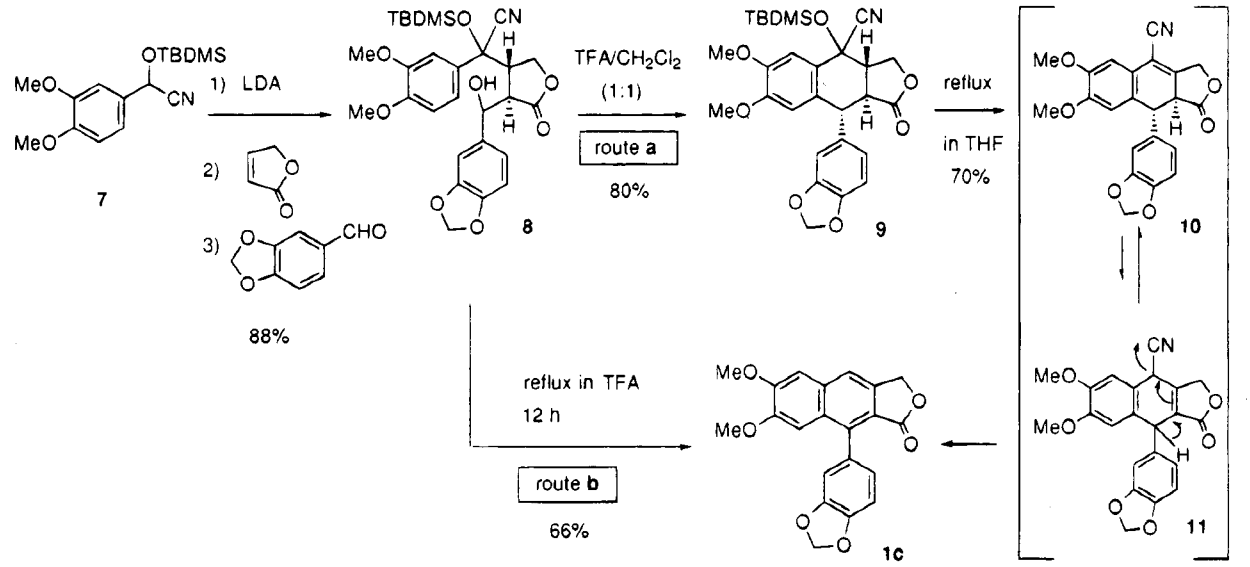
Scheme 1



Scheme 2



matography. Their structures were unambiguously determined by X-ray crystallographic and/or NMR analyses. Refluxing the mixture of the diastereomers in TFA for 12 h gave rise to the aromatized 1-arylnaphthalene lignan **1c**, identical with justicidin B, in 70% yield.[11]

When the reaction of **9** leading to **1c** was quenched after 2 h, the intermediate **10** was isolated in 17% yield together with **9** (33%) and **1c** (29%). When isolated **10** was refluxed in TFA, **1c** was formed in quantitative yield. Thus, the sequence of events leading to aromatization can be accounted for by the sequential formation of intermediates **10** and **11**. These results prompted us to investigate the one-pot conversion of **8** to **1c** under TFA conditions (route b in Scheme 2). When **8** was treated with refluxing TFA for 12 h, **1c** was formed in 66% yield. In this one-pot conversion, crude **8** could be used without purification.

This two-step synthesis of 1-arylnaphthalene lignans was extended to taiwanin C (**1a**),[12] chinensin (**1b**), and **1d** as shown in Scheme 3. α,β-Unsaturated esters other than 2-butenolide could also be used to afford other 1-arylnaphthalene lignans **14** and **16**. A small amount of the lactone **17** was produced in the second step in the use of dimethyl maleate as a Michael acceptor. This undesired production of lactone was easily avoided by the pretreatment of the adduct of the conjugate addition–aldol reaction with Ac_2O at 60 °C.

Synthesis of 4-Hydroxy-1-arylnaphthalene Lignan Lactones. Our attention next turned to the synthesis of 4-hydroxy-1-arylnaphthalene lignans. In order to evaluate the validity of the strategy, we first examined the conversion of thuriferic acid (**19**)[13] into naphthoic acid **20** as a model reaction (Chart 2). Treatment of **19** with 2 equiv of NaOMe in MeOH at room temperature gave **20** quantitatively. This result suggested that **2** could be formed in a one-pot procedure through formylation of the corresponding tetralone derivative.

On the basis of the results of the model reaction, we initiated the synthesis of diphyllin (**2a**), a representative 4-hydroxy-1-arylnaphthalene lignan lactone (Scheme 4). Conjugate addition of the anion generated from **7** with LDA to methyl acrylate in THF at −78 °C followed by

(11) Munakata, K.; Maruo, S.; Ohta, K. *Tetrahedron Lett.* **1965**, 4167.
(12) Lin, Y.; Li, T.-B.; Wang, K. T. *Tetrahedron Lett.* **1967**, 849.
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Scheme 3

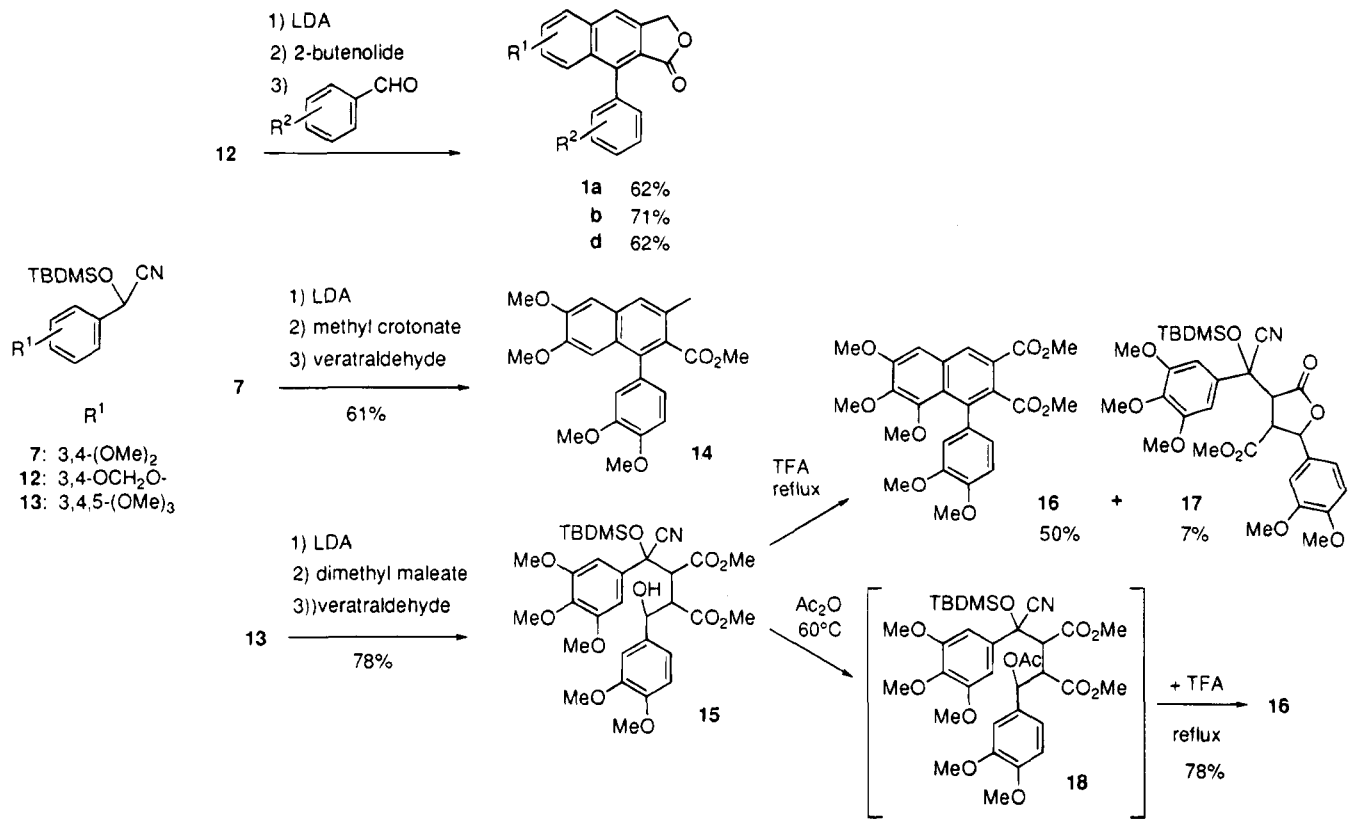
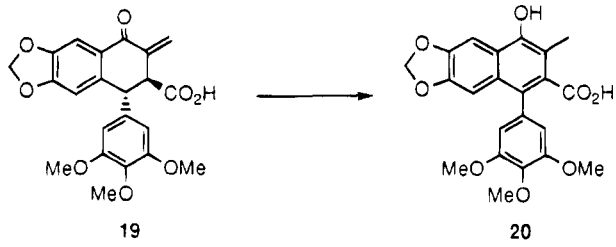


Chart 2



addition of piperonal gave a mixture of the four diastereomers **21** in quantitative yield. The mixture was treated with TFA–CH_2Cl_2 (1:1) at room temperature for 12 h to afford **26** in 72% yield; **26** is formed by elimination of TBDMSOH from **22**.

This result is in marked contrast with the cyclization reaction leading to **9**, where the analogous elimination reaction was not observed at all under the same reaction conditions.

In order to obtain **22** and to prevent elimination, various cyclization reaction conditions were examined. As a result, **22** was obtained in 65% yield by treatment of **21** with TFA–CH_2Cl_2 (1:6) at 0 °C for 2 h. Treatment of **22** thus obtained with tetra-*n*-butylammonium fluoride in CH_2Cl_2 at room temperature gave **23a** in quantitative yield; no cis diastereomer was observed. Thus, **23a** was obtained from **7** in 65% overall yield in only three steps. The structure of **23a** was unambiguously determined on the basis of spectral data.

Upon treatment of **23a** with 3 molar equiv of HCO_2-Me in the presence of 2 molar equiv of NaOMe in benzene at 80 °C for 2 h, formylation followed by isomerization (aromatization) took place, to afford **25** in 71% yield. When the reaction was carried out at 50 °C for 30 min, the intermediate **24** was isolated in 76% yield. It was obtained as an inseparable mixture of the *syn* and the *anti* enolisomers with structures based on the ^1H NMR, IR, and MS spectra of the mixture. Without isolation of **25**, the reaction mixture was treated with concd HCl to afford **2a** in 57% overall yield from **23a** (Chart 3). The physical and spectroscopic properties of **2a** are in accord with those of diphyllin reported by Okigawa et al.[14]

Four analogous example of 4-hydroxy-1-arylnaphthalene lignan lactones are shown in Table 1.

In conclusion, we have descrived an efficient route to 4-unsubstituted and 4-hydroxy-1-arylnaphthalene lignan lactones. These efficient methods should find wide application in the synthesis of this series of lignan lactones.

Experimental Section

α-[(*tert*-Butyldimethylsilyl)oxy]-α-(3,4-dimethoxyphenyl)acetonitrile (7). To a solution of veratraldehyde (166 g, 1 mol) in acetonitrile (5 L) was added successively KCN (260 g, 4 mol), TBDMSCl (180 g, 1.2 mol), and ZnI_2 (0.5 g) under vigorous stirring at room temperature. The mixture was stirred for 1 day. The insoluble materials were removed by filtration and rinsed thoroughly with Et_2O (ca. 100 mL). The filtrate was concentrated to dryness *in vacuo*, and the residue was dissolved in Et_2O (500 mL). The solution was washed with water (100 mL), dried ($MgSO_4$), and concentrated to dryness *in vacuo* to afford yellow oil. The oil was crystallized from $^iPr_2O$ to give **7** (270 g, 88%): mp 54–55 °C; IR (KBr) 2251, 1595 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 0.15 (s, 3H), 0.22 (s, 3H), 0.94 (s, 9H), 3.91 (s, 6H), 5.46 (s, 1H), 6.8–7.11 (m, 3H); MS *m/z* 307 (M^+).

Compounds **12**[11] and **13** were prepared in the same manner described above.

α-[(*tert*-Butyldimethylsilyl)oxy]-α-(3,4,5-trimethoxyphenyl)acetonitrile (13). From 196 g (1 mol) of 3,4,5-trimethoxybenzaldehyde was obtained 242 g (66%) of **13**. **13:**

(14) Okigawa, M.; Maeda, T.; Kawano, N. *Tetrahedron* **1970**, *26*, 4301.

Scheme 4

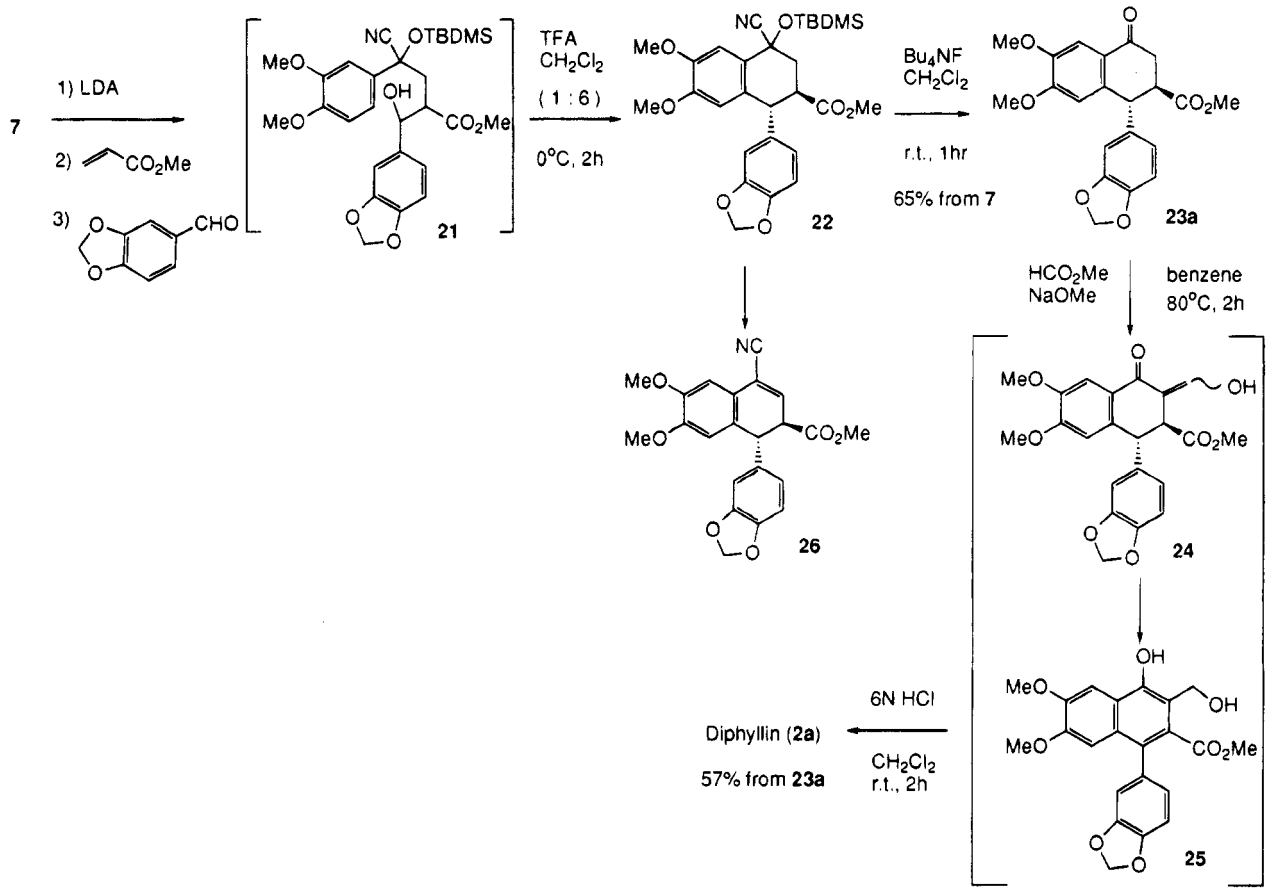
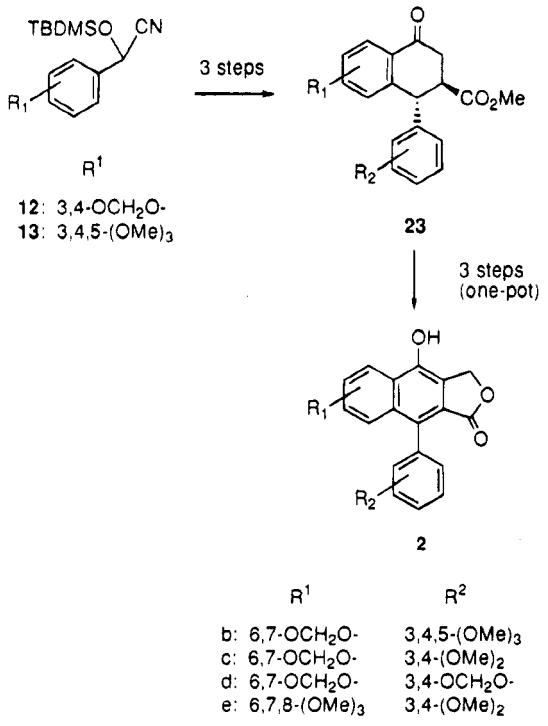


Chart 3



mp 43 °C; IR (KBr) 2240, 1595 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 0.15 (s, 3H), 0.23 (s, 3H), 0.93 (s, 9H), 3.76 (s, 3H), 3.78 (s, 6H), 5.34 (s, 1H), 6.55 (s, 2H); MS *m/z* 337 (M^+).

***trans*-β-[α-[(*tert*-Butyldimethylsilyl)oxy]-α-cyanoveratryl]-α-(α-hydroxypiperonyl)-γ-butyrolactone (8).** To a solution of LDA in THF (prepared from 2.22 g (22 mmol) of diisopropylamine and 13.8 mL (22 mmol) of butyllithium (1.6 M in hexane) in 15 mL of THF) was added **7** (6.14 g, 20 mmol) in 20 mL of THF under vigorous stirring, followed by successive addition of 2-butenolide (1.68 g, 20 mmol) in 20 mL of THF and piperonal (3.0 g, 20 mmol) in 10 mL of THF at −78 °C. After 10 min, AcOH (20 mL) was added. The reaction mixture was poured into a mixture of H_2O and AcOEt. The organic layer was washed with water, dried ($MgSO_4$), and concentrated to dryness *in vacuo*. Purification of the residue by silica gel column chromatography using hexane−AcOEt (2:1) as an eluent to afford **8** (9.52 g, 88%) as a mixture of four diastereoisomers. The mixture was used in the next step without further separation.

Table 1. Synthesis of 4-Hydroxy-1-arylnaphthalene Lignans

starting material	yield of **23b−e**[a]	yield of **2b−e**[a]
12	**23b** (68%)	**2b** (54%)
12	**23c** (58%)	**2c** (48%)
12	**23d** (62%)	**2d** (55%)
13	**23e** (64%)	**2e** (57%)

[a] Isolated yield. All new compounds were fully characterized on the basis of the ^1H NMR, IR, and mass spectra and elemental analyses. The physical properties of **2b−d** are in accord with those reported in the literature.

(1*R,2*S**,3*S**,4*S**)-4-[(*tert*-Butyldimethylsilyl)oxy]-4-cyano-1-[3,4-(methylenedioxy)phenyl]-3-(hydroxymethyl)-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic Acid Lactone (9a) and (1*R**,2*S**,3*S**,4*R**)-4-[(*tert*-Butyldimethylsilyl)oxy]-4-cyano-1-(3,4-dimethoxyphenyl)-3-(hydroxymethyl)-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic Acid Lactone (9b).** To a stirred solution of diastereomers (**8**) (9.5 g, 17.5 mmol) in 40 mL of CH_2Cl_2 was added TFA (40 mL) at room temperature. After 8 h, the reaction mixture was poured into water (100 mL). The organic layer was washed with water (3 × 100 mL), dried ($MgSO_4$), and concentrated to dryness *in vacuo*. The residue was purified by silica gel chromatography using

hexane–AcOEt (2:1) as an eluent to afford **9a** (3.75 g, 41%) and **9b** (3.61 g, 39%).

9a: mp 216–218 °C; IR (KBr) 1784 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 0.48 (s, 3H), 0.57 (s, 3H), 0.96 (s, 9H), 2.8–3.1 (m, 2H), 3.65 (s, 3H), 3.90 (s, 3H), 4.08 (d, 1H, J = 9.6 Hz), 4.36 (t, 1H, J = 9.2 Hz), 4.59 (dd, 1H, J = 6.2, 8.8 Hz), 6.6–6.9 (m, 3H), 5.95 (dd, 2H, J = 1.6, 1.8 Hz), 6.31 (s, 1H), 7.05 (s, 1H); MS m/z 523 (M^+). Anal. Calcd for $C_{28}H_{33}NO_7Si$: C, 64.22; H, 6.35; N, 2.67. Found: C, 64.48; H, 6.33; N, 2.46.

9b: mp 188–189 °C; IR (KBr) 1785 cm^{-1}; ^1H NMR (δ in $CDCl_3$) −0.03 (s, 3H), 0.44 (s, 3H), 0.90 (s, 9H), 2.9–3.1 (m, 1H), 3.16 (dd, 1H, J = 11, 14 Hz), 3.70 (s, 3H), 3.95 (s, 3H), 4.33 (dd, 1H, J = 8.4, 10 Hz), 4.07 (d, 1H, J = 11 Hz), 4.59 (dd, 1H, J = 6.8, 8.4 Hz), 5.96 (s, 2H), 6.59 (s, 1H), 6.7–6.9 (m, 2H), 6.62 (s, 1H), 7.13 (s, 1H); MS m/z 523 (M^+). Anal. Calcd for $C_{28}H_{33}NO_7Si$: C, 64.22; H, 6.35; N, 2.67. Found: C, 63.93; H, 6.39; N, 2.68.

Justicidin B (1c). A solution of **9a,b** (**a**:**b** = 1:1, 5.23 g, 10 mmol) in TFA (20 mL) was refluxed for 12 h. The reaction mixture was concentrated to dryness *in vacuo*. The residue was crystallized from MeOH to give **1c** (2.52 g, 70%): mp 241–243 °C (lit.[11] mp 240 °C).

Two-Step Synthesis of Taiwanin C (1a). A solution of diisopropylamine (11 mmol) in 50 mL of THF was treated with 7.5 mL of butyllithium (1.6 M in hexane) at −50 °C for 20 min. To this solution were added dropwise **12** (2.57 g, 10 mmol) in THF (10 mL), 2-butenolide (840 mg, 10 mmol) in THF (20 mL), and piperonal (1.50 g, 10 mmol) in THF (10 mL) under vigorous stirring at −78 °C. After 10 min, AcOH (10 mL) was added to quench the reaction. The reaction mixture was poured into a mixture of H_2O and AcOEt. The organic layer was dried ($MgSO_4$) and concentrated to dryness *in vacuo*. The residue was dissolved in TFA (20 mL), and the solution was refluxed for 12 h. The reaction mixture was evaporated to dryness *in vacuo*. The crystals were recrystallized from MeOH to afford **1a** (2.15 g, 62%): mp 267–70 °C (lit.[12] 275 °C).

Compounds **1b**, **1d**, and **14** were prepared in the same manner described above.

Chinensin (1b) (2.58 g, 71%) was obtained from **12** (2.57 g, 10 mmol). **1b**: mp 225–227 °C (lit.[7c] 227 °C).

3-(Hydroxymethyl)-6,7-dimethoxy-1-(3,4,5-trimethoxyphenyl)-2-naphthoic Acid Lactone (1d). From **12** (3.03 g, 10 mmol) was obtained 2.54 g (62%) of **1d**. **1d**: mp 205–206 °C; IR (KBr) 1739, 1620 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 3.70 (s, 3H), 3.79 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 3.96 (s, 3H), 6.70 (s, 2H), 7.12 (s, 1H), 7.50 (s, 1H), 7.95 (s, 1H), 8.31 (s, 1H); MS m/z 410 (M^+). Anal. Calcd for $C_{23}H_{22}O_7$: C, 67.31; H, 5.40. Found: C, 67.19; H, 5.41.

1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-2-(methoxycarbonyl)-3-methylnaphthalene (14). From **7** (3.03 g, 10 mmol) was obtained 2.41 g (61%) of **14**. **14**: mp 201–203 °C; IR (KBr) 1740 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 2.51 (s, 1H), 3.70 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.96 (s, 3H), 6.6–6.9 (m, 3H), 7.50 (s, 1H), 7.95 (s, 1H), 8.31 (s, 1H); MS m/z 396 (M^+). Anal. Calcd for $C_{23}H_{24}O_6$: C, 69.68; H, 6.10. Found: C, 69.69; H, 6.01.

1-(3,4-Dimethoxyphenyl)-6,7,8-trimethoxy-2,3-bis(methoxycarbonyl)naphthalene (16). A solution of diisopropylamine (11 mmol) in 50 mL of THF was treated with 7.5 mL of butyllithium (1.6 M in hexane) at −50 °C for 20 min. To this solution were added dropwise **13** (3.03 g, 10 mmol) in THF (10 mL), 2-butenolide (840 mg, 10 mmol) in THF (20 mL), and veratraldehyde (1.96 g, 10 mmol) in THF (10 mL) under vigorous stirring at −78 °C. After 10 min, AcOH (10 mL) was added to quench the reaction. The reaction mixture was poured into a mixture of H_2O and AcOEt. The organic layer was dried ($MgSO_4$) and concentrated to dryness *in vacuo*. The residue was dissolved in Ac_2O (10 mL), and the solution was heated at 60 °C for 30 min. To this solution was added dropwise TFA (30 mL) and the mixture was refluxed for 12 h. The reaction mixture was evaporated to dryness *in vacuo*. The crystals were recrystallized from MeOH to afford **16** (3.67 g, 78%): mp 214–216 °C; IR (KBr) 1740, 1718 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 3.55 (s, 3H), 3.68 (s, 3H), 3.74 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 3.85 (s, 3H), 3.99 (s, 3H), 6.6–6.9 (m, 3H), 7.50 (s, 1H), 8.30 (s, 1H); MS m/z 470 (M^+). Anal. Calcd for $C_{25}H_{26}O_9$: C, 63.82; H, 5.57. Found: C, 63.59; H, 5.41.

4-Hydroxy-3-methyl-6,7-(methylenedioxy)-1-(3,4,5-trimethoxyphenyl)-2-naphthoic Acid (20). Model Reaction. To a solution of thuriferic acid (**19**)[14] (406 mg, 1 mmol) in MeOH (2 mL) was added NaOMe (104 mg, 2 mmol) in one portion at room temperature. The mixture was stirred for 2 h at the same temperature. The resulting mixture was diluted with AcOEt (20 mL), washed with water (10 mL), 1 N HCl (10 mL), and brine (10 mL), dried ($MgSO_4$), and concentrated to give **20** as a foam (398 mg, 98%): IR (KBr) 1710 cm^{-1}; ^1H NMR (δ $CDCl_3$) 2.24 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 6.0 (s, 2H), 6.31 (s, 2H), 6.40 (s, 1H), 7.55 (s, 1H); MS m/z 412 (M^+).

Methyl (1*R,2*R**)-6,7-Dimethoxy-1-[3,4-(methylenedioxy)phenyl]-4-oxotetralin-2-carboxylate (23a).** In a dried flask was prepared LDA (11 mmol) by addition of butyllithium (1.6 M in hexane, 7.5 mL, 11 mmol) to a solution of diisopropylamine (1.11 g, 11 mmol) in THF (10 mL) at −78 °C under a nitrogen atmosphere. The solution was stirred for 10 min at the same temperature. To the mixture were successively added dropwise cyanohydrin (**7**, 3.07 g, 10 mmol) in THF (10 mL), methyl acrylate (860 mg, 10 mmol) in THF (5 mL), and piperonal (1.5 g, 10 mmol) in THF (5 mL) at −78 °C. The resulting mixture was allowed to warm to −50 °C and stirred for 10 min, resulting in a pale yellow solution. The reaction was then quenched with AcOH (1.32 g, 22 mmol) in water (100 mL). The solution was allowed to warm to room temperature. The organic layer was separated, and the aqueous layer was extracted with EtOAc (50 mL). The combined organic layer was washed with brine (50 mL) and dried ($MgSO_4$). Evaporation of the solvent provided crude **21** (5.4 g, 98%) as an oil. To a solution of **21** (5.0 g, 9.2 mmol) in CH_2Cl_2 (60 mL) was added dropwise TFA (10 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C. To this was added water (100 mL). The organic layer was separated, washed successively with saturated aqueous $NaHCO_3$ (2 × 50 mL) and brine (50 mL), and dried ($MgSO_4$). To the resulting solution was added tetra-*n*-butylammonium fluoride (1 M in THF, 10 mL, 10 mmol) at room temperature. After stirring for 1 h, the mixture was washed with 20% citric acid (2 × 50 mL) and brine (50 mL), dried ($MgSO_4$), and then concentrated to dryness *in vacuo*. Crystallization from MeOH afforded **23a** (2.26 g, 65% from **7**) as a colorless solid: mp 141–144 °C (MeOH); IR (KBr) 1735, 1671 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 2.6–2.9 (m, 2H), 3.2–3.4 (m, 1H), 3.55 (s, 3H), 3.75 (s, 3H), 380 (s, 3H), 4.52 (d, 1H, J = 7.2 Hz), 5.99 (dd, J = 1.2, 0.8 Hz), 6.40 (s, 1H), 6.5–6.7 (m, 3H), 7.54 (s, 1H); MS m/z 384 (M^+), 369 (M^+ − CH3). Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.62; H, 5.24. Found: C, 65.66; H, 5.51.

The cyclized compounds **23b-e** were prepared in the same manner described above.

Methyl (1*R,2*R**)-6,7-(methylenedioxy)-4-oxo-1-(3,4,5-trimethoxyphenyl)tetralin-2-carboxylate (23b)** (2.75 g, 68%) was obtained from the cyanohydrin (**12**, 2.91 g, 10 mmol), methyl acrylate (860 mg), and 3,4,5-trimethoxybenzaldehyde (1.96 g, 10 mmol). **23b**: mp 171–173 °C (MeOH); IR (KBr) 1743, 1674 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 2.6–2.9 (m, 2H), 3.2–3.4 (m, 1H), 3.55 (s, 3H), 3.77 (s, 3H), 3.81 (s, 6H), 4.52 (d, 1H, J = 7.1 Hz), 6.00 (dd, J = 0.8, 1.1 Hz), 6.31 (s, 2H), 6.41 (s, 1H), 7.55 (s, 1H); MS m/z 414 (M^+), 399 ($M^+ - CH_3$). Anal. Calcd for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35. Found: C, 64.00; H, 5.38.

Methyl (1*R,2*R**)-6,7-(methylenedioxy)-4-oxo-1-(3,4-dimethoxyphenyl)tetralin-2-carboxylate (23c)** (2.23 g, 58%) was obtained from the cyanohydrin (**12**, 2.91 g, 10 mmol), methyl acrylate (860 mg), and veratraldehyde (1.66 g, 10 mmol). **23c**: mp 161–163 °C (MeOH); IR (KBr) 1740, 1670 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 2.3–2.9 (m, 2H), 3.2–3.4 (m, 1H), 3.57 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.51 (d, 1H, J = 7.2 Hz), 6.00 (dd, J = 0.8, 1.2 Hz), 6.40 (s, 1H), 6.6–6.9 (m, 3H), 7.51 (s, 1H); MS m/z 384 (M^+). Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.62; H, 5.24. Found: C, 65.67; H, 5.45.

Methyl (1*R,2*R**)-6,7-(methylenedioxy)-1-[3,4-(methylenedioxy)phenyl]-4-oxotetralin-2-carboxylate (23d)** (2.28 g, 62%) was obtained from the cyanohydrin (**12**, 2.91 g, 10

mmol), methyl acrylate (860 mg), and piperonal (1.5 g, 10 mmol). **23d**: mp 101–103 °C (AcOEt–hexane); IR (KBr) 1735, 1672 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 2.3–2.7 (m, 2H), 3.7–3.9 (m, 1H), 3.55 (s, 3H), 4.61 (d, 1H, J = 7.4 Hz), 5.97 (s, 2H), 6.01 (s, 2H), 6.55 (s, 1H), 6.5–6.5 (m, 2H), 6.80 (s, 1H, J = 8 Hz), 7.52 (s, 1H); MS m/z 368 (M^+). Anal. Calcd for $C_{20}H_{16}O_7$: C, 65.22; H, 4.38. Found: C, 65.33; H, 4.40.

Methyl (1*R,2*R**)-1-(3,4-dimethoxyphenyl)-6,7,8-trimethoxy-4-oxotetralin-2-carboxylate (23e)** (2.76 g, 64%) was obtained from the cyanohydrin (**13**, 3.37 g, 10 mmol), methyl acrylate (860 mg), and veratraldehyde (1.66 g, 10 mmol). **23e**: mp 152–4 °C (MeOH); IR (KBr) 1740, 1670 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 2.65 (dd, 1H, J = 4.8, 17 Hz), 2.90 (dd, 1H, J = 1.4, 17 Hz), 3.2–3.4 (m, 1H), 3.54 (s, 1H), 3.65 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 5.03 (brs, 1H), 6.43 (dd, 1H, J = 2.0, 3.0 Hz), 6.7–6.8 (m, 2H), 7.48 (s, 1H); MS m/z 430 (M^+). Anal. Calcd for $C_{23}H_{26}O_8$: C, 64.17; H, 6.09. Found: C, 64.21; H, 6.10.

Diphyllin (2a). A mixture of **23a** (1.0 g, 2.83 mmol), NaOMe (288 mg, 5.6 mmol), HCO_2Me (676 mg, 7.2 mmol), and benzene (3 mL) was heated at 50 °C for 30 min and then at 80 °C for 2 h. To the mixture was added concd HCl (10 mL) at 0 °C. The resulting mixture was vigorously stirred for 2 h at room temperature. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), and dried ($MgSO_4$). The solvent was evaporated to dryness *in vacuo*. Trituration of the residue with MeOH afforded **2a** (570 mg, 57%) as a colorless solid: mp 280 °C dec (lit.[15] 284–7 °C dec); IR (KBr) 3300, 1725 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 3.72 (s, 3H), 3.91 (s, 3H), 5.35 (s, 2H), 6.02 (s, 2H), 6.6–7.3 (m, 4H), 7.65 (s, 1H), 8.45 (brs, 1H); MS m/z 380 (M^+). Anal. Calcd for $C_{21}H_{16}O_7$: C, 66.31; H, 4.24. Found: C, 66.11; H, 4.39.

4-Hydroxy-1-arylnaphthalene lignan lactones **2b–e** were prepared under the same conditions as described above.

Dehydropodophyllotoxin (2b). From **23b** (2.7 g, 6.5 mmol), NaOMe (700 mg, 13 mmol), and HCO_2Me (1.6 g, 26 mmol) was obtained **2b** (1.46 g, 54%). **2b**: mp 284–6 °C (MeOH) (lit.[15] mp 286–8 °C); IR (KBr) 3300, 1725 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 3.74 (s, 3H), 3.76 (s, 3H), 3.91 (s, 3H), 5.36 (s, 2H), 6.01 (s, 2H), 6.6–7.3 (m, 3H), 7.65 (s, 1H), 8.45 (brs, 1H); MS m/z 410 (M^+). Anal. Calcd for $C_{22}H_{18}O_8$: C, 64.39; H, 4.42. Found: C, 64.38; H, 4.33.

Isodiphyllin (2c). From **23c** (2.2 g, 5.7 mmol), NaOMe (616 mg, 11.4 mmol) and HCO_2Me (1.4 g, 2.3 mmol) was obtained **2c** (1.06 g, 48%). **2c**: mp 252 °C dec (lit.[7c] 256 °C dec); IR (KBr) 3300, 1743 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 3.76 (s, 3H), 3.88 (s, 3H), 5.35 (s, 2H), 6.12 (s, 2H), 6.6–7.3 (m, 4H), 7.65 (s, 1H), 9.45 (brs, 1H); MS m/z 380 (M^+). Anal. Calcd for $C_{21}H_{16}O_7$: C, 66.31; H, 4.24. Found: C, 66.34; H, 4.29.

Taiwanin E (2d). From **23d** (2.2 g, 5.8 mmol), NaOMe (621 mg, 11.6 mmol), and HCO_2Me (1.4 g, 23 mmol) was obtained **2d** (1.21 g, 55%). **2d**: mp 263–265 °C (lit.[16] 263–267 °C); IR (KBr) 3200, 1741 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 5.35 (s, 2H), 6.02 (s, 2H), 6.12 (s, 2H), 6.6–6.9 (m, 4H), 7.65 (s, 1H), 9.45 (brs, 1H); MS m/z 364 (M^+). Anal. Calcd for $C_{20}H_{12}O_7$: C, 65.93; H, 3.32. Found: C, 65.99; H, 3.39.

1-(3,4-Dimethoxyphenyl)-4-hydroxy-3-(hydroxymethyl)-6,7,8-trimethoxynaphthalene-2-carboxylic Acid Lactone (2e). From **23e** (2.7 g, 6.2 mmol), NaOMe (656 mg, 12.4 mmol), and HCO_2Me (1.5 g, 25 mmol) was obtained **2e** (1.54 g, 57%). **2e**: mp 261 °C dec; IR (KBr) 3200, 1740, 1720 cm^{-1}; ^1H NMR (δ in DMSO-d_6) 3.32 (s, 3H), 3.71 (s, 3H), 3.80 (s, 3H), 3.82 (s, 3H), 4.00 (s, 3H), 5.35 (s, 2H), 6.6–7.1 (m, 3H), 7.55 (s, 1H), 10.45 (brs, 1H); MS m/z 426 (M^+). Anal. Calcd for $C_{23}H_{22}O_8$: C, 64.78; H, 5.20. Found: C, 64.58; H, 5.19.

Methyl (1*R,2*R**)-3-(Hydroxymethylidene)-6,7-dimethoxy-1-[3,4-(methylenedioxy)phenyl]-4-oxotetralin-2-carboxylate (24)**. A mixture of **23a** (1.0 g, 2.83 mmol), NaOMe (288 mg, 5.6 mmol), HCO_2Me (676 mg, 7.2 mmol), and benzene (3 mL) was heated at 50 °C for 30 min. Upon cooling, the mixture was washed with 5% citric acid (2 × 3 mL) and brine (3 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the residue on silica gel using hexane–AcOEt (1:2) as an eluent gave **24** (864 mg, 76%) as a yellow oil. The ^1H NMR spectrum showed that **24** was a mixture of inseparable *syn* and *anti* isomers. **24** was used in the next step without purification.

Methyl 4-Hydroxy-3-(hydroxymethyl)-6,7-dimethoxy-1-[3,4-(methylenedioxy)phenyl]naphthalene-2-carboxylate (25). To a solution of **24** (804 mg, 2 mmol) in MeOH (2 mL) was added NaOMe (108 mg, 4 mmol) at room temperature. After 14 h, 1 N HCl (10 mL, 10 mmol) was added to the reaction mixture. The resulting mixture was extracted with $CHCl_3$ (3 × 50 mL). The organic layer was dried ($MgSO_4$) and concentrated to dryness under reduced pressure. Purification of the residue by silica gel chromatography using AcOEt–hexane (2:1) as an eluent gave **25** (410 mg, 51%) as an oil.

Diphyllin (2a) from 25. To a solution of **25** (400 mg, 1 mmol) in $CHCl_3$ (2 mL) was added 6 N HCl (10 mL) at 0 °C. The mixture was vigorously stirred for 2 h at room temperature. The organic layer was separated, washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), and dried ($MgSO_4$). The solvent was evaporated to dryness *in vacuo*. The residue was triturated with MeOH to afford **2a** (345 mg, 91%) as a colorless solid.

Methyl (1*R,2*R**)-4-Cyano-6,7-dimethoxy-1-[3,4-(methylenedioxy)phenyl]-1,2-dihydronaphthalene-2-carboxylate (26)**. To a solution of **22** (884 mg, 2 mmol) in CH_2Cl_2 (10 mL) was added dropwise TFA (10 mL) at 0 °C. After stirring at room temperature for 12 h, the reaction mixture was washed with water (3 × 10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried ($MgSO_4$), and concentrated to give **26** as a pale yellow oil (580 mg, 72%): IR (KBr) 2010, 1743 cm^{-1}; ^1H NMR (δ in $CDCl_3$) 3.55 (s, 3H), 3.95 (s, 3H), 3.99 (s, 3H), 4.52 (d, 1H, J = 7.2 Hz), 5.20 (d, 1H, J = 10.0 Hz), 6.0 (dd, 1H, J = 0.8, 1.2 Hz), 6.4–7.5 (m, 5H, ArH); MS m/z 393 (M^+), 367 ($M^+ - CN$).

JO942162H

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