Facile Construction of the 1-Phenylnaphthyl Skeleton *via* an Ester-mediated Nucleophilic Aromatic Substitution Reaction. Applications to the Synthesis of Phenylnaphthalide Lignans

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A convenient method is presented for the construction of the 1-phenylnaphthyl skeleton *via* an ester-mediated nucleophilic displacement of a methoxy group from an aromatic nucleus by Grignard nucleophiles. Thus, treatment of isopropyl 1-methoxy-2-naphthoate **1** with a phenyl Grignard reagent **2** or **8** affords the 1-phenyl-2-naphthoate ester **3** or **9** in good to excellent yield. Similarly, treatment of a 2,6-dialkylphenyl 2-methoxybenzoate **4b** or **c** with a 1-naphthyl Grignard reagent **5** gives the 2-(1-naphthyl)benzoate ester **7**. The methodology has been utilized in the synthesis of the naturally occurring phenylnaphthalide lignans, taiwanin C **12a** and chinensin **12b**.

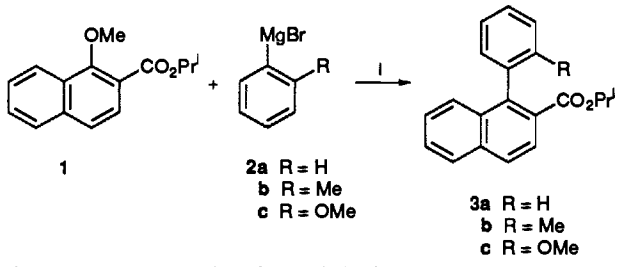
Structural units containing the phenyl-naphthyl linkage are frequently found in naturally occurring products.[1,2] Some of these have attracted much interest because of their broad spectrum of biological activities, as exemplified by the benzo[*d*]naphtho[1,2-*b*]pyran-6(*H*)-ones occurring in aryl *C*-glycoside antibiotics (*e.g.*, gilvocarcins),[3] naphthylisoquinoline alkaloids (*e.g.*, ancistrocladines)[2,4] and the like.[5,6]

Phenylnaphthalide lignans, such as taiwanins and justicidins, constitute another family of such natural products which are also characterized by the 1-phenylnaphthyl skeleton.[1,7] Although a wide variety of methods have been proposed for the synthesis of this class of lignans,[1,8] the key step for the construction of the phenyl-naphthyl skeleton can be classified roughly into two methodologies: The first relies on assembling the B-ring of the naphthalene nucleus *via* the annulation of a properly substituted benzene derivative followed by an aromatization process, such as those based on the Diels–Alder reaction,[9a,b] the Stobbe condensation[9c] and a conjugate addition followed by cyclization,[9d] or *via* a ring cleavage of phenyl(cyclopropyl)methanols followed by a recyclization to form the six-membered ring system.[9e] The second, more direct route, is the joining of the pertinent aryl and naphthyl half. Meyers *et al.* have reported the oxazoline-mediated nucleophilic aromatic substitution (S_NAr) of 2-oxazoline-substituted 1-methoxynaphthalenes by a phenyllithium reagent, where the oxazoline serves both as a protecting group for the carboxylic function and as an activating group of the *ortho*-methoxy group for the S_NAr reaction (the Meyers reaction).[9f]

In previous papers, we reported that an ester group significantly activates an *ortho* alkoxy substituent for S_NAr displacement, and thus, the oxazoline functionality required in the conventional Meyers reaction can be replaced by a readily prepared and an easily removable ester functionality.[10] By use of this methodology, axially chiral and/or achiral biphenyls[10a,b] and binaphthyls[10c,d] have been conveniently prepared in excellent yields. In view of the increasing interest in the phenylnaphthalide lignans,[6] we report herein an extension of the ester-mediated S_NAr process for the construction of 1-phenylnaphthyl skeleton and its applications to the synthesis of taiwanin C **12a** and chinensin **12b**.

Results and Discussion

Construction of the 1-Phenylnaphthyl Skeleton.—First, construction of the 1-phenylnaphthyl skeleton was studied *via* the nucleophilic displacement on 1-methoxy-2-naphthoate esters (Scheme 1). The reaction of isopropyl 1-methoxy-2-naphthoate **1** with the phenyl Grignard reagents **2a–c** in diethyl ether–benzene was found to give the 1-phenyl-2-naphthoate esters **3a–c** in good to excellent yields (Table 1). Although the reaction conditions were not optimized, addition of about 1.2–1.4 equiv. of the Grignard reagents **2** seemed suitable. Less bulky phenyl nucleophiles than the 1-naphthyl counterparts may also attack the isopropyl ester **1** in a 1,2-fashion, resulting in a reduced yield of the coupling product, as exemplified by the reaction using 2.0 equiv. of the Grignard reagent **2c** (entry 4). Alternatively, it has been reported that 1-naphthyl Grignard reagents do not add to the ester carbonyl function of isopropyl 2-naphthoate **1**, and thus, the synthesis of binaphthyls could be carried out even in the presence of a large excess of the naphthyl Grignard reagents.[10c]



1 **2a** R = H, **b** R = Me, **c** R = OMe **3a** R = H, **b** R = Me, **c** R = OMe

Scheme 1 *Reagents and conditions:* i, Et_2O–PhH

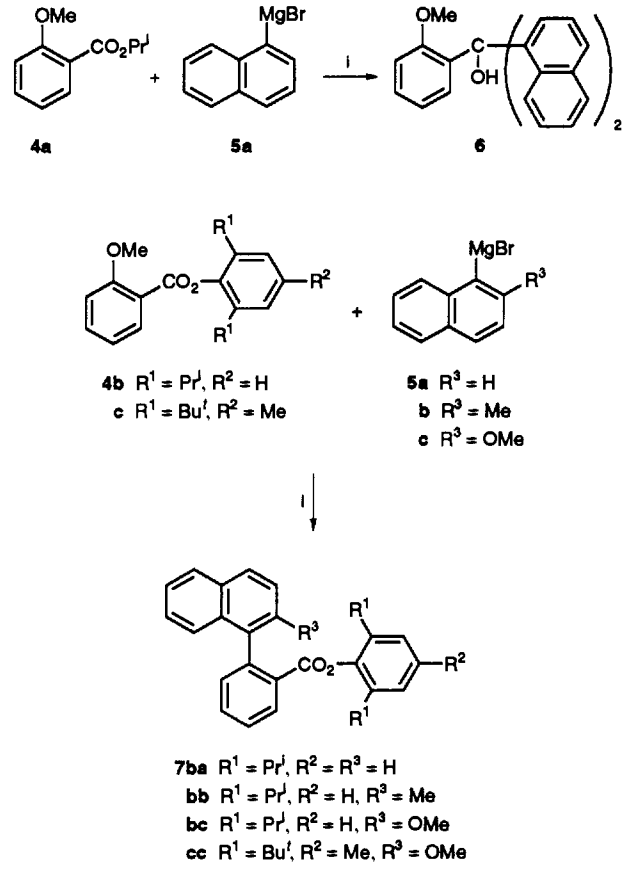
Table 1 Synthesis of the 1-phenyl-2-naphthoate esters **3** and the 2-(1-naphthyl)benzoate esters **7**

Entry	Substrate	Nucleophile (equiv.)	[time (*t*/h)]	Product	Yield[a] (%)
1	**1**	**2a** (1.4)	[1][b]	**3a**	84
2	**1**	**2b** (1.4)	[1][b]	**3b**	96
3	**1**	**2c** (1.4)	[1][b]	**3c**	79
4	**1**	**2c** (2.0)	[1][b]	**3c**	64
5	**4b**	**5a** (2.0)	[20][b]	**7ba**	83
6	**4b**	**5b** (2.0)	[20][c]	**7bb**	72
7	**4b**	**5c** (2.0)	[20][b]	**7bc**	0
8	**4c**	**5c** (2.0)	[14][b]–[3][c]	**7cc**	84

[a] Isolated yield based on the substrate **1** or **4**. [b] Room temp. [c] Reflux.

In the next step, our effort was directed toward the construction of the (1-naphthyl)phenyl structure *via* the reaction of 2-methoxybenzoate esters **4** with a 1-naphthyl Grignard reagent **5**. An attempt to protect the carboxyl group of 2-methoxybenzoic acid by conversion into the isopropyl ester

4a gave rise to only carbonyl addition upon reaction with the 1-naphthyl Grignard reagent **5a** to yield the carbinol **6** (63%) (Scheme 2). This is apparently due to the inferior reactivity of

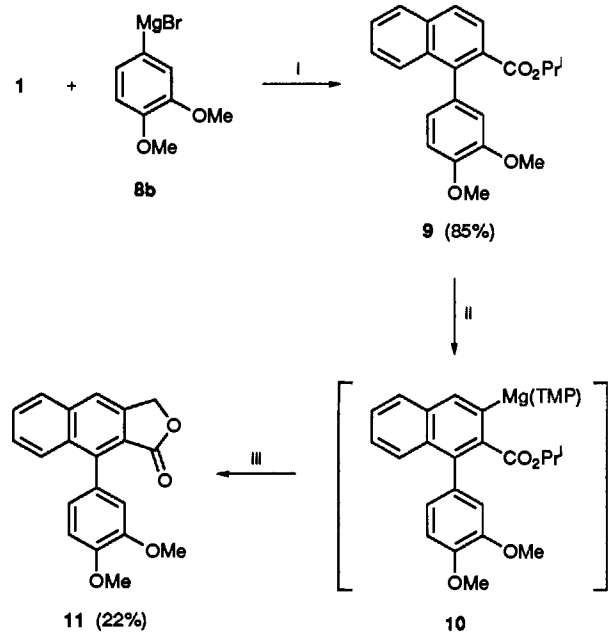


Scheme 2 *Reagents and conditions:* i, Et_2O–PhH

the methoxy group in the benzoate ester **4a** toward nucleophilic displacement, as compared to that of the naphthoate ester 1.[10a,c] Therefore, implementing the procedures devised for the synthesis of biphenyls by the ester-mediated S_NAr process,[10a] 2,6-dialkylphenyl protecting groups were introduced into 2-methoxybenzoic acid. The resulting benzoate esters **4b** and **4c** were allowed to react with 1-naphthyl Grignard reagents **5a–c** (Scheme 2). The results listed in Table 1 show that the correct combination of a 2-methoxybenzoate ester **4** and the naphthyl Grignard nucleophile **5** afforded the 2-(1-naphthyl)benzoate ester **7** in satisfactory yields. It is of interest to note that the reaction of the 2,6-diisopropylphenyl ester **4b** with the 1-naphthyl Grignard reagent **5a** afforded the coupled product **7ba** in good yield, whilst the steric hindrance provided by the same ester was insufficient for the 2-methoxy-1-naphthyl Grignard reagent **5c** (entry 7); intramolecular coordination of the 2-methoxy oxygen to the magnesium metal presumably reduces the effective steric bulk of the nucleophile.[10c]

Total Synthesis of Taiwanin C and Chinensin.—From the foregoing results, the 1-phenyl-2-naphthoate esters **3** or the 2-(1-naphthyl)benzoate ester **7** are now readily available in substantial quantities for the elaboration of 1-phenylnaphthyl derivatives. From a practical point of view, the first route, *i.e.* the nucleophilic displacement on 1-methoxy-2-naphthoate ester 1 by a phenyl Grignard reagent **2**, is of particular interest because of its facile nature and the mildness of the reaction conditions. It can be seen that taiwanin C **12a** and chinensin **12b**, both being 1-phenyl-2-naphthoic acid derivatives, are suitable synthetic targets to demonstrate the utility of this S_NAr process.

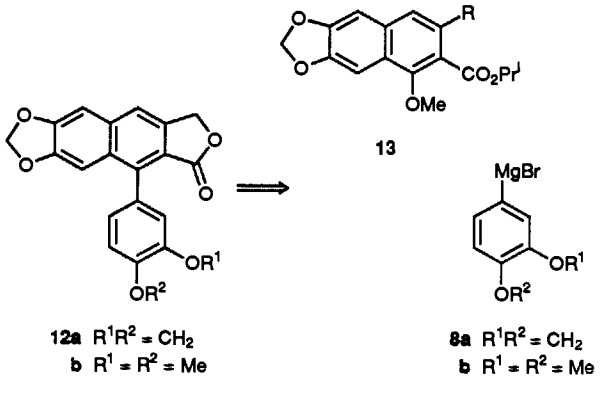
Directed *ortho* metallation of substituted aromatics has been widely utilized for organic synthesis,[11] and specifically the ester-directed *ortho* magnesiation[12] attracted our interest. Thus, we performed model studies to test the feasibility of metallation of the initially constructed 1-phenyl-2-naphthoate ester, followed by trapping by an electrophile to assemble the requisite substituents on the naphthalene B-ring (Scheme 3).



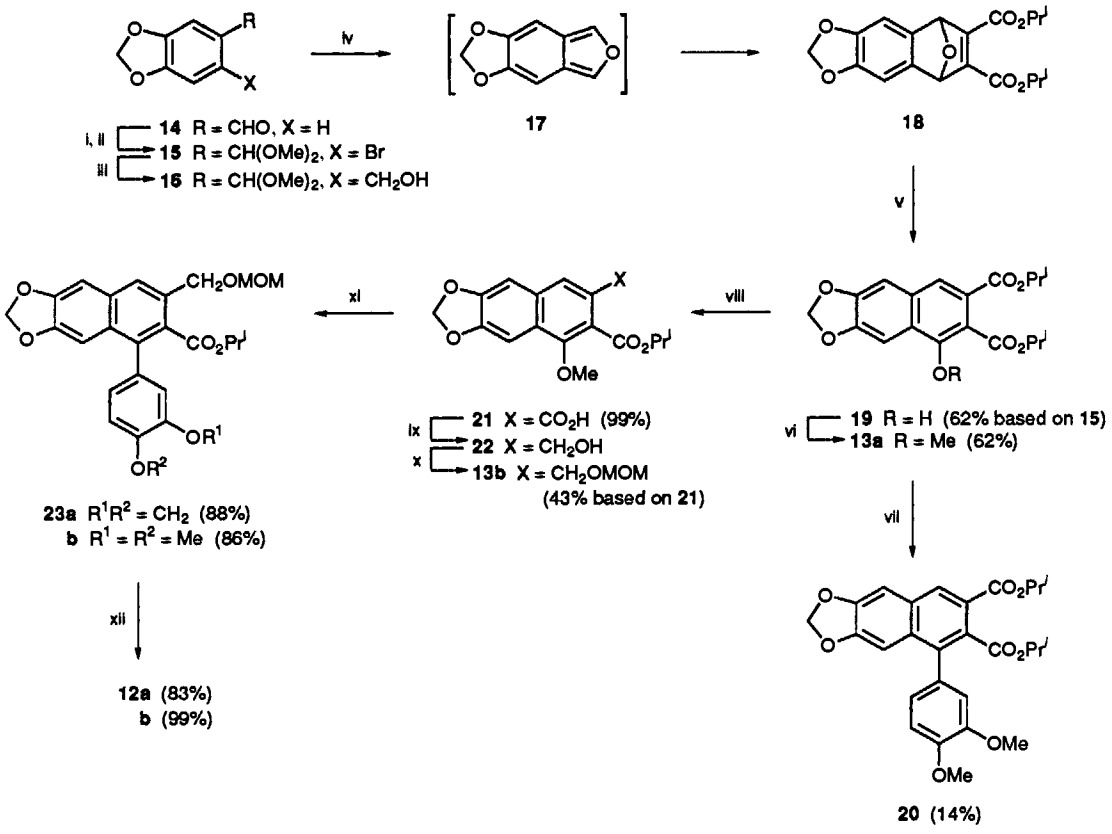
Scheme 3 *Reagents and conditions:* i, THF, room temp.; ii, $(TMP)_2Mg$, THF, room temp.; iii, paraformaldehyde, THF, room temp.

The Grignard reagent **8b** smoothly displaced the methoxy group of the naphthoate ester 1 to give the biaryl compound **9** in good yield (85%). Magnesiation of this 2-naphthoate ester **9** with bis(2,2,6,6-tetramethylpiperidinido)magnesium $[(TMP)_2Mg]$[12] followed by reaction with paraformaldehyde caused lactonization of the intermediary magnesium alkolate to give the chinensin derivative 11 directly, but only in a low yield (22%). The poor result may be ascribed to a reluctant magnesiation due to steric congestion imposed by the *meta* phenyl group. It is in sharp contrast to lithiation which does not seem so prone to steric hindrance, as judged by an oxazoline-directed *ortho* lithiation of a similar 1-phenylnaphthyl system.[9f]

As the ester-directed magnesiation of the sterically congested system did not work well, an alternative retrosynthetic route to chinensin-type natural products required the relevant Grignard reagents **8** and a substrate **13**, which bears a 7-substituent amenable to the later elaborations (Scheme 4). It was obvious



Scheme 4



Scheme 5 *Reagents and conditions:* i, lit.,[18]; ii, $CH(OMe)_3$, MeOH, $TsOH{\cdot}H_2O$, reflux; iii, BuLi, THF, −78 °C; then HCHO −78 °C ⟶ room temp.; iv, DPAD, AcOH, 100 °C; v, TsOH, PhMe, reflux; vi, MeI, NaH, DMF, 60 °C; vii, **8b**, THF, room temp.; viii, KOH, aq. EtOH, 60 °C; then conc. HCl; ix, $NaBH_4$, $BF_3{\cdot}Et_2O$, DGM, room temp.; x, MOMCl, Pr^i_2EtN, PhH, room temp.; xi, **8a** or **b**, THF, room temp.; xii, HCl (4 mol dm^{-3}), THF, room temp. ⟶ reflux

that the isopropoxycarbonyl group was the ideal choice for the protection of the 6-carboxylic acid functionality. Our synthetic plan suggested that diisopropyl 5-methoxynaphtho[2,3-*d*]-1,3-dioxole-6,7-dicarboxylate **13a** should be the key intermediate, since it was readily obtainable from the Diels–Alder reaction of an isobenzofuran and an acetylenedicarboxylate ester, according to the method developed by Rodrigo and co-workers (Scheme 5).[13]

Bromination of the commercial piperonal **14**, followed by acetalization gave the bromo-acetal **15**, which was in turn treated with butyllithium and then with formaldehyde to give benzyl alcohol **16**. Acidic treatment of the benzyl alcohol **16** with acetic acid generated the isobenzofuran **17**, which, *in situ*, was allowed to react with diisopropyl acetylenedicarboxylate (DPAD) to give the Diels–Alder adduct **18**. This was aromatized by treatment with toluene-*p*-sulfonic acid to give hydroxy diester **19** in 62% yield, based on the acetal **15**. This diester **19** was then methylated with methyl iodide to give the methyl ether diester **13a**.

In an attempted reaction of compound **13a** with 3,4-dimethoxyphenyl Grignard reagent **8b**, the S_NAr displacement of the methoxy group proceeded to give the coupled product **20** in only a poor yield, but the Grignard reagent preferentially added to the ester carbonyl group at the 7-position.

Several methods have already been presented for the regioselective partial reduction of naphthalene-2,3-dicarboxylate esters, including the L-Selectride reduction of the acid anhydride[14a] and the hydrogenation catalysed by a ruthenium–phosphine complex.[14b] However, these methods generally require multistep processes. To our pleasure, however, the trivial alkaline hydrolysis of the diester **13a** was found to give rise to the mono carboxylic acid **21** in quantitative yield. Then, the carboxylic acid function of mono acid **21** was reduced to the hydroxymethyl group (**22**) with diborane, which was then converted into methoxymethyl (MOM) ether **13b**. Treatment of the MOM-ether **13b** with the Grignard reagent **8a** proceeded smoothly to give the coupled product **23a** in good yield, which, on treatment with dil. HCl, underwent a hydrolytic removal of the MOM-protecting group and a spontaneous lactonization to afford taiwanin C **12a**. As expected, the reaction of MOM-ether **13b** with the Grignard reagent **8b** also gave the coupled product **23b** and subsequent similar treatment as above afforded chinensin **12b**.

Conversions of the 9-phenylnaphtho[2,3-*c*]furan-1(3*H*)-ones into the 4-phenylnaphtho[2,3-*c*]furan-1(3H)-ones, *e.g.* a conversion of taiwanin C **12a** into justicidin E,[7] have already been well documented.[14b] Therefore, the facile experimental procedures and the ready availability of the starting materials suggest that the ester-mediated S_NAr biaryl coupling methodology shown in Scheme 5 should provide a useful route to such a family of phenylnaphthalide lignans.

Experimental

M.p.s were taken using a Yamato MP-21 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-460 spectrophotometer. ^1H NMR spectra were recorded on a Bruker AC-250T spectrometer using tetramethylsilane as the internal standard and $CDCl_3$ as the solvent, unless otherwise stated. *J*-Values are given in Hz. Mass spectra were recorded on a JEOL JMS-D300 spectrometer using the field desorption (FD) technique. Microanalyses were carried out in the Microanalytical Laboratory of the Institute for Chemical Reaction Science, Tohoku University. Merck silica gel $60GF_{254}$ was used for analytical and preparative TLC (PLC). A Merck Lobar column (2.5 cm i.d. × 31 cm) packed with LiChroprep Si

60 was used for preparative LC. Silica gel columns were prepared by use of Nacalai silica gel 60 (70–230 mesh). Water- and air-sensitive reactions were routinely carried out under nitrogen. Grignard reactions were performed by a similar procedure to that described in the previous papers.[10a,c] Diethyl ether, benzene and THF were distilled from sodium diphenylketyl just before use. Other solvents for experiments requiring anhydrous conditions were purified by usual methods. Commercial materials were used as purchased unless otherwise noted. 2,2,6,6-Tetramethylpiperidine (TMPH) was distilled from calcium hydride (38 °C/1600 Pa) and stored under nitrogen. Isopropyl 1-methoxy-2-naphthoate 1,[10c] the 2-methoxybenzoate esters **4**[10a] and 1-bromo-2-methylnaphthalene[10d] were obtained as before. Dibutylmagnesium was prepared according to the literature procedure[15] and was used as a THF solution, concentration of which was determined to be 0.56 mol dm^{-3} by titration with sulfuric acid.[16] DPAD was prepared according to the literature procedure.[17]

Synthesis of 1-*Phenyl*-2-*naphthoate Esters* **3**. *General Procedure*.—To a solution of the ester **1** (2.00 mmol) in dry benzene (7.0 cm^3) was added a Grignard reagent **2**, which had been prepared from the corresponding aryl bromide (2.80 mmol) and magnesium turnings (110 mg) in dry diethyl ether (7.0 cm^3) and dissolved by the addition of benzene (7.0 cm^3). The mixture was stirred at room temperature for 1 h and was worked up as usual. See Table 1 for the yield of the corresponding product **3**. Chromatography on a silica gel column was used for purification of the products using indicated eluent.

Isopropyl 1-*phenyl*-2-*naphthoate* **3a**. Hexane–ethyl acetate (97:3) as the eluent; a pale yellow oil (Found: C, 82.85; H, 6.5. $C_{20}H_{18}O_2$ requires C, 82.7; H, 6.2%); ν_{max}(neat)/cm^{-1} 1702 (CO); δ_H(250 MHz) 0.97 (6 H, d, *J* 6.2, CHMe_2), 4.95 (1 H, sept, *J* 6.2, CH) and 7.29–7.91 (11 H, m, ArH).

Isopropyl 1-(2-*methylphenyl*)-2-*naphthoate* **3b**. Hexane–benzene (1:1) as the eluent; a pale yellow oil (Found: C, 82.9; H, 6.8. $C_{21}H_{20}O_2$ requires C, 82.9; H, 6.6%); ν_{max}(neat)/cm^{-1} 1698 (CO); δ_H(250 MHz) 0.87 (3 H, d, *J* 6.2, CHMe_2), 1.02 (3 H, d, *J* 6.2, CHMe_2), 1.96 (3 H, s, Me), 4.95 (1 H, sept, *J* 6.2, CH) and 7.06–7.98 (10 H, m, ArH).

Isopropyl 1-(2-*methoxyphenyl*)-2-*naphthoate* **3c**. Benzene as the eluent; a pale yellow oil (Found: C, 78.9; H, 6.4. $C_{21}H_{20}O_3$ requires C, 78.7; H, 6.3%); ν_{max}(neat)/cm^{-1} 1696 (CO); δ_H(250 MHz) 0.88 (3 H, d, *J* 6.2, CHMe_2), 0.99 (3 H, d, *J* 6.2, CHMe_2), 3.60 (3 H, s, OMe), 4.92 (1 H, sept, *J* 6.2, CH) and 6.94–7.93 (10 H, m, ArH).

A similar reaction was performed using 2.0 mol equiv. of the Grignard reagent **2c** to give the biarylcarboxylate ester **3c** in a somewhat reduced yield (64%).

Synthesis of 2-(1-*Naphthyl*)*benzoate Esters* **7**. *General Procedure*.—To a solution of an ester **4** (2.00 mmol) in dry benzene (7.0 cm^3) was added a Grignard reagent **5**, which had been prepared from the corresponding aryl bromide (4.00 mmol) and magnesium turnings (160 mg) in dry diethyl ether (7.0 cm^3) and dissolved by the addition of benzene (7.0 cm^3). The mixture was stirred at an appropriate temperature for 17–20 h and was worked up as usual. In case of the reaction using the Grignard reagent **5c**, which was not sufficiently soluble in the above-mentioned volume of the mixed solvent, the Grignard reagent was prepared in diethyl ether (14 cm^3) and dissolved by the addition of benzene (14 cm^3), and this solution was added to a solution of an ester **4** in benzene (14 cm^3). See Table 1 for reaction conditions and the yield of the corresponding product **7**. Chromatography on a silica gel column was used for purification of the products using the indicated eluent, unless otherwise noted.

2,6-*Diisopropylphenyl* 2-(1-*naphthyl*)*benzoate* **7ba**. Hexane–benzene (7:3) as the eluent; crystals, m.p. 130–132 °C (Found: C, 85.3; H, 7.0. $C_{29}H_{28}O_2$ requires C, 85.25; H, 6.9%); ν_{max}(KBr)/cm^{-1} 1736 (CO); δ_H(250 MHz) 0.85 (6 H, d, *J* 5.9, CHMe_2), 0.96 (6 H, d, *J* 6.8, CHMe_2), 2.48 (2 H, br, CH) and 6.96–8.29 (14 H, m, ArH).

2,6-*Diisopropylphenyl* 2-(2-*methyl*-1-*naphthyl*)*benzoate* **7bb**. Hexane–benzene (11:9) as the eluent; crystals, m.p. 98.7–99.4 °C (Found: C, 85.05; H, 7.2. $C_{30}H_{30}O_2$ requires C, 85.3; H, 7.15%); ν_{max}(KBr)/cm^{-1} 1736 (CO); δ_H(250 MHz) 0.73 (3 H, d, *J* 6.5, CHMe_2), 0.84 (3 H, d, *J* 6.7, CHMe_2), 0.89 (3 H, d, *J* 7.3, CHMe_2), 0.93 (3 H, d, *J* 7.1, CHMe_2), 2.25 (3 H, s, Me), 2.25–2.50 (2 H, m, CH) and 6.94–8.31 (13 H, m, ArH).

2,6-*Di*-tert-*butyl*-4-*methylphenyl* 2-(2-*methoxy*-1-*naphthyl*)*benzoate* **7cc**. The crude product was purified by preparative LC with hexane–ethyl acetate (9:1) as the eluent; crystals, m.p. 247–249 °C (Found: C, 82.3; H, 7.6. $C_{33}H_{36}O_3$ requires C, 82.5; H, 7.5%); ν_{max}(KBr)/cm^{-1} 1742 (CO); δ_H(250 MHz) 1.11 (9 H, s, Bu^t), 1.31 (9 H, s, Bu^t), 2.21 (3 H, s, Me), 3.72 (3 H, s, OMe) and 6.96–8.64 (12 H, m, ArH).

Reaction of Isopropyl 2-*Methoxybenzoate* **4a** *with* 1-*Naphthylmagnesium Bromide* **5a**.—This reaction was performed by the same procedure as mentioned for the preparation of compounds **7**. The ester **4a** (389 mg, 2.00 mmol) was treated with 2.0 mol equiv. of the Grignard reagent **5a** in diethyl ether (7.0 cm^3)–benzene (14 cm^3) at room temperature for 3 h. Chromatography on a silica gel column with hexane–benzene (3:2) as the eluent gave (2-methoxyphenyl)di(1-naphthyl)-methanol **6** (490 mg, 63%) as crystals, m.p. 205 °C (decomp.) (Found: C, 86.1; H, 5.6. $C_{28}H_{22}O_2$ requires C, 86.1; H, 5.7%); ν_{max}(KBr)/cm^{-1} 3485 (OH); δ_H(250 MHz) 3.74 (3 H, s, OMe), 5.90 (1 H, s, OH) and 6.44–8.63 (18 H, m, ArH).

Isopropyl 1-(3,4-*Dimethoxyphenyl*)-2-*naphthoate* **9**.—This compound was prepared by a similar procedure to that used for the preparation of compounds **3**, using THF instead of the mixed solvent that did not sufficiently dissolve the Grignard reagent **8b**: To a solution of the ester **1** (1.46 g, 5.98 mmol) in dry THF (21 cm^3) was added the Grignard reagent **8b** which had been prepared from 1-bromo-3,4-dimethoxybenzene (1.83 g, 8.43 mmol) and magnesium turnings (330 mg) in dry THF (21 cm^3). The mixture was stirred at room temperature for 1 h and was worked up as usual. Recrystallization from ethanol gave the biarylcarboxylate ester **9** (1.78 g, 85%) as crystals, m.p. 128–129 °C (Found: C, 75.4; H, 6.45. $C_{22}H_{22}O_4$ requires C, 75.4; H, 6.3%); ν_{max}(KBr)/cm^{-1} 1703 (CO); δ_H(250 MHz) 1.02 (3 H, d, *J* 6.3, CHMe_2), 1.05 (3 H, d, *J* 6.3, CHMe_2), 3.85 (3 H, s, OMe), 3.97 (3 H, s, OMe), 4.99 (1 H, sept, *J* 6.3, CH) and 6.85–7.91 (9 H, m, ArH).

9-(3,4-*Dimethoxyphenyl*)*naphtho*[2,3-c]*furan*-1(3H)-*one* **11**.—To a solution of TMPH (3.73 g, 26.4 mmol) in dry THF (25 cm^3) was added dibutylmagnesium (0.56 mol dm^{-3} in THF; 22 cm^3, 12.3 mmol) and the mixture was refluxed for 3 h. The cooled mixture was added to a solution of the ester **9** (702 mg, 2.00 mmol) in THF (5.0 cm^3) and the resulting mixture was stirred at room temperature. After 24 h, a suspension of paraformaldehyde (1.20 g) in THF (10 cm^3) was added and the mixture was stirred at room temperature for a further 6 h and was then quenched with sat. NH_4Cl (10 cm^3). After most of the THF had been evaporated, the residue was dissolved in diethyl ether (100 cm^3)–sat. NH_4Cl (100 cm^3) and the two layers were separated. The aqueous layer was extracted with diethyl ether and the combined organic layer was washed successively with sat. NH_4Cl and water and then dried over $MgSO_4$. After the solvent had been evaporated, the residue was chromatographed on a silica gel column with benzene–ethyl acetate (9:1) as the

eluent to give the lactone **11** (138 mg, 22%) as crystals, m.p. 211–212 °C (from ethanol) (lit.,[9f] 208–209 °C) (Found: C, 74.9; H, 5.2. $C_{20}H_{16}O_4$ requires C, 75.0; H, 5.0%); ν_{max}(KBr)/cm^{-1} 1750 (CO); δ_H(250 MHz) 3.87 (3 H, s, OMe), 3.99 (3 H, s, OMe), 5.45 (2 H, s, $ArCH_2$) and 6.92–7.98 (8 H, m, ArH).

6-Bromopiperonal Dimethyl Acetal **15**.—Piperonal **14** was brominated[18] to give 6-bromopiperonal, m.p. 129–130 °C (lit.,[19] 127–129 °C). The bromide (9.55 g, 41.7 mmol) and dry methanol (6.69 g, 209 mmol) were heated under reflux for 1 h in trimethyl orthoformate (100 cm^3) in the presence of toluene-*p*-sulfonic acid monohydrate (447 mg, 2.35 mmol). The cooled mixture was diluted with diethyl ether and washed successively with sat. $NaHCO_3$ and water and dried over $MgSO_4$. After the solvent had been evaporated, the residue was distilled under reduced pressure by use of a Kugelrohr (70–80 °C/27–13 Pa) to give the acetal **15**[13a] (11.0 g, 96%) as an oil, ν_{max}(neat)/cm^{-1} 3000–2825 (CH) and 1120–1038 (C–O); δ_H(250 MHz) 3.37 (6 H, s, OMe), 5.47 (1 H, s, CH), 5.98 (2 H, s, OCH_2O), 7.00 (1 H, s, ArH) and 7.09 (1 H, s, ArH).

Diisopropyl 5-Hydroxynaphtho[2,3-d]-1,3-*dioxole*-6,7-*dicarboxylate* **19**.—To a solution of the bromo-acetal **15** (6.88 g, 25.0 mmol) in dry THF (50 cm^3) was added dropwise butyllithium (1.6 mol dm^{-3} in hexane; 18.8 cm^3, 30.1 mmol) at −78 °C, and the mixture was stirred at this temperature for 30 min. Formaldehyde gas, generated by the pyrolysis of paraformaldehyde (7.66 g), was bubbled through the solution and the resulting mixture was warmed to room temperature over a period of 1 h and was then quenched with brine (5 cm^3). After most of the THF had been evaporated, the residue was dissolved in diethyl ether (200 cm^3)–brine (200 cm^3) and the two layers were separated. The aqueous layer was extracted with diethyl ether and the combined organic layer was washed successively with brine and water and then dried over $MgSO_4$. After the solvent had been evaporated, the residue was dried *in vacuo* to give the crude alcohol **16** (5.54 g) as a pale yellow oil, δ_H(250 MHz; [$^2H_6$]benzene) 2.50 (1 H, br s, OH), 2.98 (6 H, s, OMe), 4.51 (2 H, s, CH_2OH), 5.30 (1 H, s, CH), 5.30 (2 H, s, OCH_2O), 6.87 (1 H, s, ArH) and 7.27 (1 H, s, ArH).

A mixture of the crude alcohol **16** (5.54 g), DPAD (25 cm^3) and glacial acetic acid (1.7 cm^3) was heated at 100 °C for 20 min. The volatiles were distilled off under reduced pressure [100 °C (bath temp.)/107 Pa] to give a brown residue (8.43 g), an aliquot of which was purified by PLC with dichloromethane–ethyl acetate (99 : 1) as the developer to give the spectromerically pure adduct diisopropyl 5,8-epoxy-5,8-dihydroxynaphtho[2,3-*d*]-1,3-dioxole-6,7-dicarboxylate **18** as a pale yellow oil, δ_H(250 MHz) 1.30 (12 H, d, *J* 6.3, $CHMe_2$), 5.10 (2 H, sept, *J* 6.3, CH), 5.85 (2 H, s, ArCH), 5.93 (1 H, d, *J* 1.4, OCH_2O), 5.98 (1 H, d, *J* 1.4, OCH_2O) and 6.95 (2 H, s, ArH).

The above residue (8.41 g) was heated under reflux for 12 h in dry toluene (200 cm^3) in the presence of toluene-*p*-sulfonic acid monohydrate (638 mg, 3.35 mmol). After cooling, the mixture was poured into sat. $NaHCO_3$ (200 cm^3) and the two layers were separated. The aqueous layer was extracted with diethyl ether and the combined organic layer was washed successively with sat. $NaHCO_3$ and water and then dried over $MgSO_4$. After the solvents had been evaporated, the residue was chromatographed on a silica gel column with hexane–acetone (9 : 1) as the eluent to give the tricycle **19** (5.59 g, 62% based on the bromo-acetal **15**) as crystals, m.p. 84.8–85.2 °C (from ethanol) (Found: C, 63.1; H, 5.7. $C_{19}H_{20}O_7$ requires C, 63.3; H, 5.6%); ν_{max}(KBr)/cm^{-1} 1721 (CO); δ_H(250 MHz) 1.38 (6 H, d, *J* 6.3, $CHMe_2$), 1.41 (6 H, d, *J* 6.3, $CHMe_2$), 5.21 (1 H, sept, *J* 6.3, CH), 5.29 (1 H, sept, *J* 6.3, CH), 6.10 (2 H, s, OCH_2O), 7.05 (1 H, s, ArH), 7.17 (1 H, s, ArH), 7.66 (1 H, s, ArH) and 11.96 (1 H, s, OH).

Diisopropyl 5-Methoxynaphtho[2,3-d]-1,3-*dioxole*-6,7-*dicarboxylate* **13a**.—To a suspension of NaH (550 mg, 22.9 mmol) in dry DMF (20 cm^3) was added dropwise a solution of the tricycle **19** (5.50 g, 15.3 mmol) in DMF (60 cm^3) and the mixture was stirred at room temperature for 2 h. To the mixture was added iodomethane (3.25 g, 22.9 mmol) and the resulting mixture was stirred for 1 h at 60 °C. After cooling, the mixture was poured into 2 mol dm^{-3} HCl (200 cm^3) and extracted with diethyl ether. The extract was washed successively with 2 mol dm^{-3} HCl, 20% w/w Na_2SO_3, 2 mol dm^{-3} Na_2CO_3 and water and finally dried over $MgSO_4$. After the solvent had been evaporated, the residue was chromatographed on a silica gel column with hexane–ethyl acetate (19 : 1 to 4 : 1) as the eluent to give the ether **13a** (3.52 g, 62%) as pale yellow crystals, m.p. 81.2–81.7 °C (from methanol) (Found: C, 64.3; H, 5.9. $C_{20}H_{22}O_7$ requires C, 64.2; H, 5.9%); ν_{max}(KBr)/cm^{-1} 1729 and 1693 (CO); δ_H(250 MHz) 1.38 (6 H, d, *J* 6.3, $CHMe_2$), 1.43 (6 H, d, *J* 6.3, $CHMe_2$), 3.97 (3 H, s, OMe), 5.25 (1 H, sept, *J* 6.3, CH), 5.37 (1 H, sept, *J* 6.3, CH), 6.11 (2 H, s, OCH_2O), 7.19 (1 H, s, ArH), 7.38 (1 H, s, ArH) and 8.12 (1 H, s, ArH).

Diisopropyl 5-(3,4-Dimethoxyphenyl)naphtho[2,3-d]-1,3-*dioxole*-6,7-*dicarboxylate* **20**.—To a solution of the ether **13a** (375 mg, 1.00 mmol) in dry THF (3.5 cm^3) was added the Grignard reagent **8b**, which had been prepared from 1-bromo-3,4-dimethoxybenzene (300 mg, 1.38 mmol) and magnesium turnings (55 mg) in dry THF (3.5 cm^3). The mixture was stirred at room temperature for 3 h and was worked up as usual. PLC with hexane–ethyl acetate (1 : 1) as the developer gave the biaryldiester **20** (65.0 mg, 14%) as crystals, m.p. 190–191 °C; ν_{max}(KBr)/cm^{-1} 1717 and 1707 (CO); δ_H(250 MHz) 1.01 (3 H, d, *J* 6.2, $CHMe_2$), 1.02 (3 H, d, *J* 6.2, $CHMe_2$), 1.38 (6 H, d, *J* 6.2, $CHMe_2$), 3.85 (3 H, s, OMe), 3.95 (3 H, s, OMe), 4.99 (1 H, sept, *J* 6.2, CH), 5.28 (1 H, sept, *J* 6.2, CH), 6.06 (2 H, s, OCH_2O), 6.85–6.97 (4 H, m, ArH), 7.23 (1 H, s, ArH) and 8.36 (1 H, s, ArH).

6-(Isopropyloxycarbonyl)-5-methoxynaphtho[2,3-d]-1,3-*dioxole*-7-*carboxylic Acid* **21**.—A mixture of the diester **13a** (1.85 g, 4.94 mmol), KOH (1.30 g), ethanol (10 cm^3) and water (1.0 cm^3) was stirred at 60 °C for 15 min. After the mixture had been cooled to room temperature, most of the ethanol was evaporated and the residue was dissolved in water. The solution was washed with diethyl ether and acidified by addition of conc. HCl to liberate the free acid, which was collected by filtration, washed with water and dried *in vacuo* to give the mono acid **21** (1.63 g, 99%) as crystals, m.p. 235 °C (decomp.) (Found: C, 61.1; H, 4.8. $C_{17}H_{16}O_7$ requires C, 61.4; H, 4.85%); ν_{max}(KBr)/cm^{-1} 2955 (OH), 1723 and 1686 (CO); δ_H(250 MHz; [$^2H_6$]-acetone) 1.35 (6 H, d, *J* 6.2, $CHMe_2$), 3.98 (3 H, s, OMe), 5.27 (1 H, sept, *J* 6.2, CH), 6.24 (2 H, s, OCH_2O), 7.42 (1 H, s, ArH), 7.46 (1 H, s, ArH) and 8.26 (1 H, s, ArH).

Isopropyl 5-Methoxy-7-(methoxymethoxymethyl)naphtho-[2,3-d]-1,3-*dioxole*-6-*carboxylate* **13b**.—To a mixture of the mono acid **21** (1.55 g, 4.66 mmol), $NaBH_4$ (801 mg, 21.2 mmol) and dry bis(2-methoxyethyl) ether (DGM) (125 cm^3) was added dropwise boron trifluoride–diethyl ether (*d* 1.15; 3.5 cm^3, 28.4 mmol) and the mixture was stirred at room temperature for 1 h. The mixture was poured onto crushed ice and was extracted with diethyl ether. The extract was washed with water and dried over $MgSO_4$. After the solvent had been evaporated, the residue was dried *in vacuo* to give a pale yellow oil (1.32 g), an aliquot of which was purified by PLC with hexane–ethyl acetate (1 : 1) as the developer to give spectromerically pure alcohol isopropyl 7-(hydroxymethyl)-5-methoxynaphtho[2,3-*d*]-1,3-dioxole-6-carboxylate **22** as an oil, ν_{max}(neat)/cm^{-1} 3435 (OH) and 1716 (CO); δ_H(250 MHz) 1.44 (6 H, d, *J* 6.1, $CHMe_2$), 2.97 (1 H, br s, OH), 3.97 (3 H, s, OMe), 4.67 (2 H, s, $ArCH_2$), 5.38 (1 H, sept, *J*

6.1, CH), 6.07 (2 H, s, OCH_2O), 7.08 (1 H, s, ArH), 7.39 (1 H, s, ArH) and 7.44 (1 H, s, ArH).

The above residue (1.30 g) was treated with chloromethyl methyl ether (*d* 1.07; 2.25 cm^3, 29.9 mmol) in dry benzene (35 cm^3) in the presence of Hünig's base [ethyldiisopropylamine (*d* 0.742; 10 cm^3, 57.4 mmol)] at room temperature. The reaction was monitored by TLC and another aliquot of chloromethyl methyl ether (500 mm^3, 6.64 mmol) and Hünig's base (2.0 cm^3, 11.5 mmol) were added every 3 h. After 10 h the mixture was poured into HCl (2 mol dm^{-3}; 100 cm^3) and the two layers were separated. The aqueous layer was extracted with diethyl ether and the combined organic layer was washed successively with Na_2CO_3 (2 mol dm^{-3}) and water and then dried over $MgSO_4$. After the volatiles had been removed by evaporation, the residue was chromatographed on a silica gel column with hexane–ethyl acetate (6:1 to 4:1) as the eluent, to give the MOM-ether isopropyl 5-methoxy-7-(methoxymethoxymethyl)naphtho[2,3-*d*]-1,3-dioxole-6-carboxylate **13b** (720 mg, 43% based on the acid **21**) as a pale yellow oil (Found: C, 63.0; H, 6.1. $C_{19}H_{22}O_7$ requires C, 63.0; H, 6.1%); ν_{max}(neat)/cm^{-1} 1719 (CO); δ_H(250 MHz) 1.41 (6 H, d, *J* 6.3, $CHMe_2$), 3.41 (3 H, s, CH_2OMe), 3.97 (3 H, s, OMe), 4.68 (2 H, s, CH_2), 4.73 (2 H, s, CH_2), 5.35 (1 H, sept, *J* 6.3, CH), 6.07 (2 H, s, OCH_2O), 7.09 (1 H, s, ArH), 7.38 (1 H, s, ArH) and 7.45 (1 H, s, ArH).

Isopropyl 5-(1,3-Benzodioxol-5-yl)-7-(methoxymethoxymethyl)naphtho[2,3-d]-1,3-*dioxole-6-carboxylate* **23a**.—The Grignard reagent **8a** was prepared from 5-bromo-1,3-benzodioxole (203 mg, 1.01 mmol) and magnesium turnings (40 mg) in dry THF (3.0 cm^3). Seven-tenths of this mixture was added dropwise to a solution of the ether **13b** (183 mg, 505 μmol) in dry THF (1.75 cm^3) and the mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC and the remaining Grignard reagent was added to the mixture. The resulting mixture was stirred for a further 2 h and was worked up as usual. PLC with hexane–acetone (2:1) as the developer gave the biaryl ester **23a** (202 mg, 88%) as an amorphous solid (Found: C, 66.4; H, 5.4. $C_{25}H_{24}O_8$ requires C, 66.4; H, 5.3%); ν_{max}(neat)/cm^{-1} 1710 (CO); δ_H(250 MHz) 0.99 (3 H, d, *J* 6.3, $CHMe_2$), 1.05 (3 H, d, *J* 6.3, $CHMe_2$), 3.42 (3 H, s, CH_2OMe), 4.70 (2 H, s, CH_2), 4.78 (2 H, s, CH_2), 4.96 (1 H, sept, *J* 6.3, CH), 6.00 (1 H, d, *J* 1.3, OCH_2O), 6.02 (2 H, s, OCH_2O), 6.03 (1 H, d, *J* 1.3, OCH_2O), 6.75–6.90 (4 H, m, ArH), 7.13 (1 H, s, ArH) and 7.70 (1 H, s, ArH).

5-(1,3-Benzodioxol-5-yl)furo[3′,4′:6,7]*naphtho*[2,3-d]-1,3-*dioxol-6*(8 H)-*one* (*Taiwanin C*) **12a**.—To a solution of biaryl ester **23a** (98.0 mg, 217 μmol) in THF (2.5 cm^3) was added HCl (4 mol dm^{-3}; 2.0 cm^3) and the mixture was stirred at room temperature for 20 h and was then refluxed for 1 h.

After the mixture had been cooled to room temperature, further HCl (2 mol dm^{-3}; 30 cm^3) was added and the mixture was extracted with chloroform. The extract was washed successively with Na_2CO_3 (2 mol dm^{-3}) and water and then dried over $MgSO_4$. After the solvents had been evaporated, the residue was recrystallized from ethyl acetate to give taiwanin C **12a** (62.4 mg, 83%) as crystals, m.p. 272–277 (lit.,[6] 273–277 °C); ν_{max}(KBr)/cm^{-1} 1761 (CO); δ_H(250 MHz) 5.37 (2 H, s, $ArCH_2$), 6.06 (1 H, d, *J* 1.4, OCH_2O), 6.08 (3 H, br, OCH_2O), 6.79 (1 H, dd, *J* 7.5 and 1.5, ArH), 6.81 (1 H, d, *J* 1.5, ArH), 6.96 (1 H, d, *J* 7.5, ArH), 7.11 (1 H, s, ArH), 7.20 (1 H, s, ArH) and 7.69 (1 H, s, ArH); *m/z* 349 (18%, $M^+ + 1$) and 348 (100, M^+).

Isopropyl 5-(3,4-Dimethoxyphenyl)-7-(methoxymethoxymethyl)naphtho[2,3-d]-1,3-*dioxole-6-carboxylate* **23b**.—The Grignard reagent **8b** was prepared from 1-bromo-3,4-dimethoxybenzene (306 mg, 1.41 mmol) and magnesium turnings (55 mg) in dry THF (4.0 cm^3). Half the quantity of the Grignard reagent was added dropwise to a solution of the ether **13b** (183 mg, 505 μmol) in dry THF (1.75 cm^3) and the mixture was stirred at room temperature for 1 h. The reaction was monitored by TLC and then the remaining Grignard reagent was added to the mixture. The resulting mixture was stirred for a further 2 h and then worked up as usual. PLC with hexane–ethyl acetate (2:1) as the developer gave crystals, which were further purified by PLC with dichloromethane–acetone (50:1) to give the biaryl ester **23b** (203 mg, 86%), m.p. 108–109 °C (Found: C, 66.4; H, 6.15. $C_{26}H_{28}O_8$ requires C, 66.65; H, 6.0%); ν_{max}(KBr)/cm^{-1} 1712 (CO); δ_H(250 MHz) 0.95 (3 H, d, *J* 6.3, $CHMe_2$), 0.98 (3 H, d, *J* 6.3, $CHMe_2$), 3.43 (3 H, s, CH_2OMe), 3.85 (3 H, s, OMe), 3.94 (3 H, s, OMe), 4.71 (2 H, s, CH_2), 4.78 (2 H, s, CH_2), 4.91 (1 H, sept, *J* 6.3, CH), 6.02 (2 H, s, OCH_2O), 6.87–6.96 (4 H, m, ArH), 7.14 (1 H, s, ArH) and 7.70 (1 H, s, ArH).

5-(3,4-Dimethoxyphenyl)furo[3′,4′:6,7]*naphtho*[2,3-d]-1,3-*dioxol-6*(8H)-*one* (*Chinensin*) **12b**.—Chinensin **12b** was prepared by the same procedure as mentioned for the preparation of taiwanin C **12a** using the biaryl ester **23b** (102 mg, 218 μmol). PLC with dichloromethane–ethyl acetate (20:1) as the developer gave chinensin **12b** (78.8 mg, 99%) as crystals, m.p. 220–221 (lit.,[20] 220–221 °C); ν_{max}(KBr)/cm^{-1} 1764 (CO); δ_H(250 MHz) 3.87 (3 H, s, OMe), 3.98 (3 H, s, OMe), 5.37 (2 H, s, $ArCH_2$), 6.08 (2 H, s, OCH_2O), 6.86 (1 H, d, *J* 1.8, ArH), 6.91 (1 H, dd, *J* 8.1 and 1.8, ArH), 7.03 (1 H, d, *J* 8.1, ArH), 7.12 (1 H, s, ArH), 7.20 (1 H, s, ArH) and 7.69 (1 H, s, ArH); *m/z* 365 (9%, $M^+ + 1$) and 364 (100, M^+).

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