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SYNTHESIS OF HELILANDIN B, PASHANONE, AND THEIR ISOMERS

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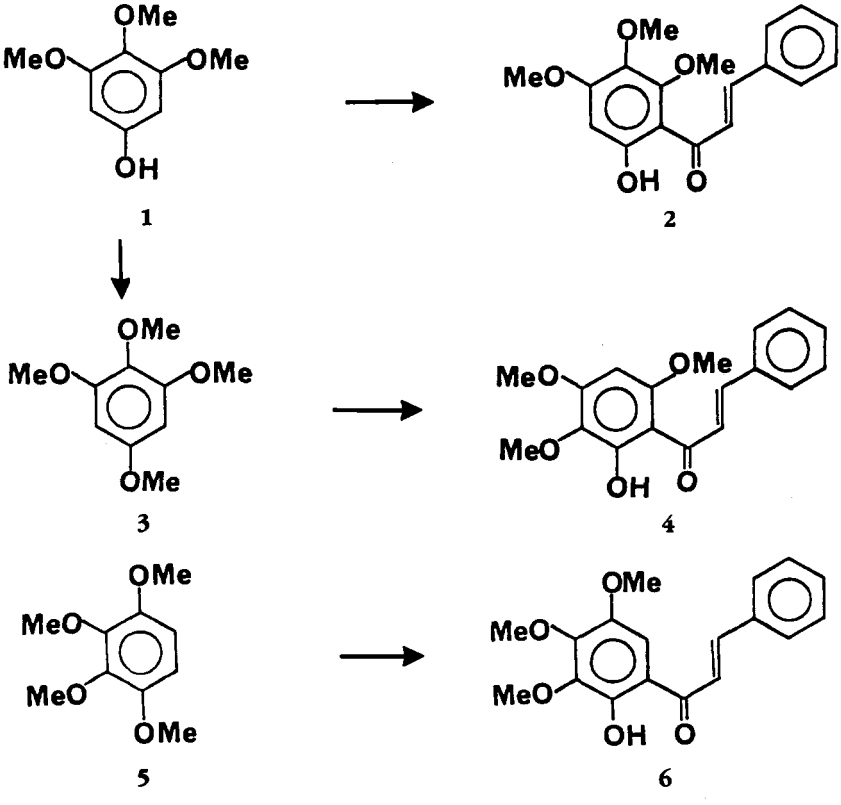
ABSTRACT.—The synthesis of helilandin B [**2**] and pashanone [**9**] from readily available 3,4,5-trimethoxyphenol [**1**] was achieved. The synthesis of other chalcones having the same oxygenation pattern as helilandin B and pashanone has also been performed.

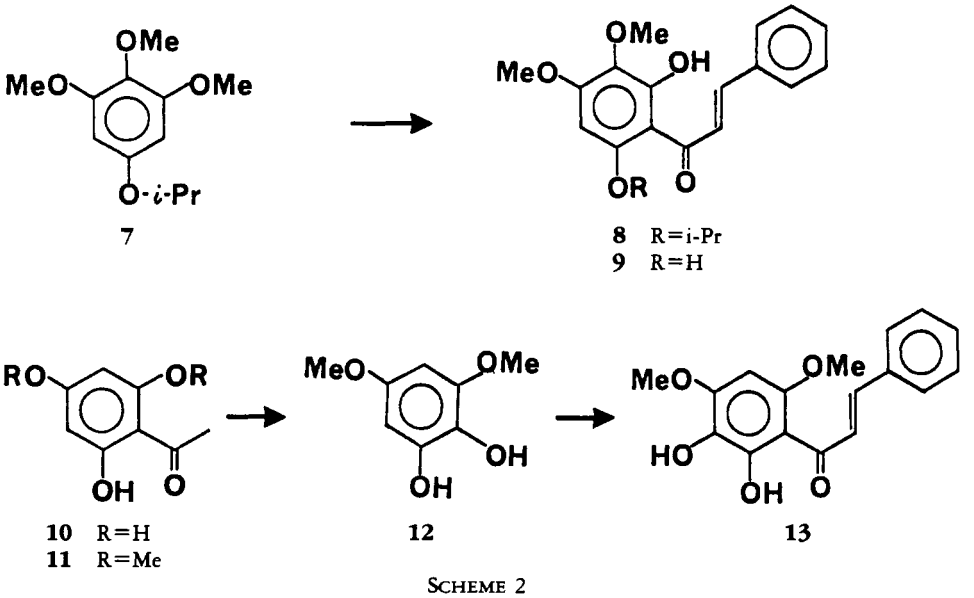
In a previous paper (1), we reported the isolation and structural elucidation of two chalcones, helilandin B [**2**] and pashanone [**9**], from *Lindera erythrocarpa* Makino (Lauraceae). In connection with our further interest in differences between the ^{1}H-nmr spectra of these chalcones **2** and **9** and their isomers **4**, **6**, **13**, **15**, **20**, and **28**, we have synthesized those eight compounds by the use of readily available tetrasubstituted benzenes **1**, **3**, and **5** and phloroacetophenone [**10**] as starting materials. Some of these compounds have already been synthesized by Bhaskar and Seshadri (2), but their assignments of the ^{1}H-nmr spectral data of those compounds were not acceptable for the identification of natural products. We synthesized these compounds via other routes in order to compare the ^{1}H-nmr spectral data of our synthetic products with those of the natural products in our previous work (1). We now report the facile synthesis of these chalcones and their ^{1}H-nmr spectra.



SCHEME 1

The synthesis of helilandin B [**2**] and its isomers **4** and **6** was performed by the Friedel-Crafts reaction of the readily available corresponding tetrasubstituted benzenes, 3,4,5-trimethoxyphenol [**1**], 1,2,3,5-tetramethoxybenzene [**3**], and 1,2,3,4-tetramethoxybenzene [**5**] (3), with cinnamoyl chloride (Scheme 1).

The synthesis of pashanone [**9**] and its isomers **13**, **15**, **20**, and **28** was achieved as follows. Isopropylation of 3,4,5-trimethoxyphenol [**1**] followed by Friedel-Crafts reaction with cinnamoyl chloride gave the chalcone **8** in good yield. Deisopropylation of **8** afforded pashanone [**9**]. Methylation of readily available phloroacetophenone [**10**] gave the dimethyl ether **11**, which was treated with H_2O_2 in alkaline solution followed by Friedel-Crafts reaction of **12** to give the 2′,3′-dihydroxy-4′,6′-dimethoxychalcone [**13**] (Scheme 2). This structure was supported by the presence of a chelated hydroxyl group in the ^{1}H-nmr spectrum.



SCHEME 2

We could not synthesize the remaining three chalcones, **15**, **20**, and **28**, by the same method because the corresponding tetrasubstituted benzenes were not available as starting materials. Consequently, these compounds were synthesized by aldol condensation. Elbs oxidation of 2-hydroxy-4,6-dimethoxyacetophenone [**11**] followed by aldol condensation with benzaldehyde afforded 2′,5′-dihydroxy-4′,6′-dimethoxychalcone [**15**]. Elbs oxidation of 2-hydroxy-4,6-diisopropoxyacetophenone [**16**] followed by methylation gave **18**, which was condensed with benzaldehyde and subjected to deisopropylation to give 2′,4′-dihydroxy-3′,6′-dimethoxychalcone [**20**]. Methylation of 2-hydroxy-4,6-dibenzyloxyacetophenone [**21**] followed by debenzylation gave monomethyl ether **23**. Isopropylation of **23** followed by Elbs oxidation gave **25**, which was methylated to afford **26**. Aldol condensation of **26** followed by deisopropylation afforded 2′,4′-dihydroxy-5′,6′-dimethoxychalcone [**28**] (Scheme 3).

In the ^{1}H-nmr spectra of the three monohydroxytrimethoxychalcones **2**, **4**, and **6**, significant differences were observed for the chemical shifts of an aromatic proton on the A ring (see Experimental).

The 3′-H in **2** (δ 6.30) and 5′-H in **4** (δ 6.02) were observed at extremely high field due to the presence of *o*-hydroxyl and *p*-hydroxyl groups, respectively. On the other hand, the 6′-H in **6** (δ 7.05) was observed at relatively low field owing to the *o*-acyl group.

MeO
OMe
OH
O
OH
11
MeO
OMe
OH
O
OH
14
MeO
OMe
OH
O
OH
15
i-PrO
O-i-Pr
OR
OR
17 R=H
18 R=Me
RO
OR
OMe
OMe
O
19 R=i-Pr
20 R=H
R2O
OR3
OR1
O
21 R1=R2=Bz, R3=H
22 R1=R2=Bz, R3=Me
23 R1=R2=H, R3=Me
24 R1=H, R2=i-Pr, R3=Me
i-PrO
OR
OMe
OH
O
25 R=H
26 R=Me
RO
OMe
OMe
OH
O
27 R=i-Pr
28 R=H

SCHEME 3

TABLE 1. ^{1}H-nmr Spectral Data of Dihydroxydimethoxychalcones **9**, **13**, **15**, **20**, and **28**.

Assignment	Compound									
	9[a]		**13**[b]		**15**[c]	**20**[b]		**28**[b]	
OMe	3.86	3.81	3.94	3.95	3.88	3.91	3.91	3.91	3.97
	3.91		3.99	4.00	3.95	3.94		3.93	
3′-H	6.10	6.05			6.33			6.36	6.43
5′-H			6.06	6.11		6.07	6.08		
OH	6.89		5.22		5.20	6.37		6.30	
		7.43 m		7.53 m			7.41 m		7.53 m
Ph	7.39–7.66 m		7.36–7.64 m		7.41–7.65 m	7.40–7.63 m		7.41–7.67 m	
β-H	7.86 d (15.8)		7.82 d (15.8)		7.85 d (15.8)	7.79 d (15.8)		7.83 d (15.8)	
		7.95 d (8)		7.95			7.86		7.97
α-H	8.15 d (15.8)		7.95 d (15.8)		7.97 d (15.8)	7.90 d (15.8)		7.93 d (15.8)	
chelated OH	13.92	13.82	14.11	—	13.31	14.35	—	13.48	13.75

[a]First column, spectra obtained in $CDCl_3$ (270 MHz), data in second column from Agarwal *et al.* (5).
[b]First column, spectra obtained in $CDCl_3$ (270 MHz), data in second column from Bhaskar and Seshadri (2).
[c]Spectra obtained in $CDCl_3$ (270 MHz).

The signal of the β-proton in **6** (δ 7.45) was observed at higher field than those of **2** (δ 7.83) and **4** (δ 7.80), and this difference may come from the substitution patterns on the A ring (2′,3′,4′,6′-oxygenated in **2** and **4**, and 2′,3′,4′,5′-oxygenated in **6**) of those chalcones.

Next, we carefully investigated the ^{1}H-nmr spectra of the remaining five chalcones, **9**, **13**, **15**, **20**, and **28** (Table 1). Bhaskar and Seshadri (2) had demonstrated that there were large differences in the chemical shifts of the methoxyl groups, rather than those of the aromatic protons. Thus the methoxyl group in **9** was observed at high field (δ 3.81) compared with those in **13** (δ 3.95 and 4.00), and, further, the chemical shifts of two methoxyl groups were equivalent in **9**, **20**, and **28**. However, in our ^{1}H-nmr spectra (270 MHz) of the five chalcones, the methoxyl groups had very similar chemical shifts and their spectra were thus not useful for structure elucidation.

We did find significant differences in the aromatic region of these compounds. Thus the 3′-H in **9** (δ 6.10), 5′-H in **13** (δ 6.06), and 3′-H in **20** (δ 6.07) were observed at high field due to the presence of *p*-hydroxyl groups, as expected, whereas 3′-H in **15** (δ 6.33) and 3′-H in **28** (δ 6.36) occurred at lower field. Further, **9** was easily distinguished from others because the signal of its α proton (δ 8.15) was observed at extremely low field.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All melting points are uncorrected. Cc was run on Merck Si gel 60 (70–230 mesh). Tlc was performed on glass plates precoated with Kieselgel 60 F_{254} (Merck). Mass spectra were recorded on a Hitachi M-52 spectrometer and high resolution mass spectra on a Hitachi M-80 spectrometer. Ir spectra were obtained on a JASCO IR-810 spectrophotometer. ^{1}H-nmr spectra were recorded on a JEOL JNM-GX-270 spectrometer operating at 270 MHz with TMS as an internal standard. Chemical shifts are quoted in ppm.

2′-HYDROXY-4′,5′,6′-TRIMETHOXYCHALCONE [**2**].—A solution of cinnamoyl chloride (300 mg) in dry nitrobenzene (10 ml) was added to a solution of 3,4,5-trimethoxyphenol [**1**] (300 mg) and $AlCl_3$ (240 mg) in dry nitrobenzene (10 ml), and the mixture was stirred at room temperature. After 3 h, the reaction mixture was poured into ice-H_2O, and the mixture was extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was purified by cc on SiO_2 ($CHCl_3$) to give yellow prisms (111 mg, 22%); mp 100–101° (from MeOH) [lit. (4) mp 101–102°]; eims *m/z* $[M]^+$ 314, 299, 237, 210, 195, 167; hrms *m/z* 314.1184 (calcd for $C_{18}H_{18}O_5$, 314.1154); ir ν max ($CHCl_3$) 3000, 1630, 1560 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 3.84, 3.91, 3.94 (9H, s × 3, 3 × OMe), 6.30 (1H, s, 3′-H), 7.36–7.67 (5H, m, Ar-H), 7.83 (1H, d, J = 15.8 Hz, β-H), 7.96 (1H, d, J = 15.8 Hz, α-H), 13.67 (1H, s, OH). This compound was identified as helilandin B [**2**] (1), isolated from *L. erythrocarpa*, by direct comparison (mmp and co-tlc).

1,2,3,5-TETRAMETHOXYBENZENE [**3**].—A solution of Me_2SO_4 (3.9 ml) in dry Me_2CO (50 ml) was added to a solution of **1** (3.0 g) and K_2CO_3 (9.0 g) in dry Me_2CO (50 ml), and the mixture was refluxed for 3 h. After cooling, the reaction mixture was filtered off, and the filtrate was diluted with same volume of H_2O and then extracted with EtOAc. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to give a colorless oil (3.0 g, 93%); eims *m/z* $[M]^+$ 198, 183; hrms *m/z* 198.0906 (calcd for $C_{10}H_{14}O_4$, 198.0892); ir ν max ($CHCl_3$) 1600, 1510 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 3.79, 3.85 (12H, s × 2, 4 × OMe), 6.15 (2H, s, Ar-H).

2′-HYDROXY-3′,4′,6′-TRIMETHOXYCHALCONE [**4**].—A solution of cinnamoyl chloride (130 mg) in dry nitrobenzene (1 ml) was added to a solution of **3** (130 mg) in dry nitrobenzene (1 ml), and the mixture was stirred at room temperature. After 3 h, the reaction mixture was treated as already described for **2**. Purification by a column of SiO_2 (C_6H_6) afforded yellow prisms (31 mg, 15%); mp 139.5–141° (from MeOH); eims *m/z* $[M]^+$ 314, 237, 210; hrms *m/z* 314.1144 (calcd for $C_{18}H_{18}O_5$, 314.1154); ir ν max ($CHCl_3$) 1635, 1620, 1570 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 3.85, 3.96 (9H, s × 2, 3 × OMe), 6.02 (1H, s, 5′-H), 7.40–7.63 (5H, m, Ar-H), 7.80 (1H, d, J = 15.8 Hz, β-H), 7.89 (1H, d, J = 15.8 Hz, α-H), 13.91 (1H, s, OH). No other chalcone was found in this reaction mixture.

2′-HYDROXY-3′,4′,5′-TRIMETHOXYCHALCONE [**6**].—A solution of cinnamoyl chloride (300 mg) in dry nitrobenzene (10 ml) was added to a solution of 1,2,3,4-tetramethoxybenzene [**5**] (300 mg) and $AlCl_3$ (240 mg) in dry nitrobenzene (10 ml), and the mixture was stirred at room temperature. After 3 h,

the reaction mixture was treated as previously described for **2**. Purification by a column of SiO_2 (C_6H_6) afforded orange prisms (205 mg, 43%); mp 64–66° (from MeOH); eims *m/z* $[M]^+$ 314, 237, 195; hrms *m/z* 314.1176 (calcd for $C_{18}H_{18}O_5$, 314.1154); ir ν max ($CHCl_3$) 1640, 1580 cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.83, 3.88, 4.00 (9H, s × 3, 3 × OMe), 7.05 (1H, s, 6′-H), 7.37–7.62 (5H, m, Ar-H), 7.45 (1H, d, J = 15.8 Hz, β-H), 7.85 (1H, d, J = 15.8 Hz, α-H), 13.00 (1H, s, OH).

1,2,3-TRIMETHOXY-5-ISOPROPOXYBENZENE [**7**].—A solution of 2-bromopropane (0.8 g) in dry DMF (10 ml) was added to a solution of **1** (1.0 g) and K_2CO_3 (1.8 g) in dry DMF (10 ml) during 15 min, and the mixture was stirred for 30 min at room temperature and then refluxed for 3.5 h. After cooling, the reaction mixture was filtered off, and the filtrate was diluted with ice-H_2O followed by extraction with $CHCl_3$. The organic layer was washed with 5% NaOH and H_2O, dried over Na_2SO_4, and evaporated to give a colorless oil (1.0 g, 81%); eims *m/z* $[M]^+$ 226, 184, 169; hrms *m/z* 226.1217 (calcd for $C_{12}H_{18}O_4$, 226.1205); ir ν max ($CHCl_3$) 1600, 1510 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.27 (6H, d, J = 6.0 Hz, 2 × Me), 3.76, 3.77 (9H, s × 2, 3 × OMe), 4.38–4.46 (1H, m, Me_2CH-), 6.09 (2H, s, Ar-H).

2′-HYDROXY-6′-ISOPROPOXY-3′,4′-DIMETHOXYCHALCONE [**8**].—A solution of cinnamoyl chloride (84 mg) in dry nitrobenzene (1 ml) was added to a solution of **7** (100 mg) and $AlCl_3$ (67 mg) in dry nitrobenzene (1 ml), and the mixture was stirred at room temperature. After 3 h, the reaction mixture was treated as previously described for **2**. Separation by a column of SiO_2 (C_6H_6) afforded yellow prisms (9 mg, 6%) and yellow prisms (42 mg, 28%). The former was identical with **2** and the latter was determined to be the desired product, compound **8**: mp 91–92.5° (from MeOH); eims *m/z* $[M]^+$ 342, 300, 285, 196, 181; hrms *m/z* 342.1441 (calcd for $C_{20}H_{22}O_5$, 342.1466); ir ν max ($CHCl_3$) 1635, 1620, 1570 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.44 (6H, d, J = 6.0 Hz, 2 × Me), 3.85, 3.93 (6H, s × 2, 2 × OMe), 4.61–4.68 (1H, m, Me_2CH-), 6.02 (1H, s, 3′-H), 7.36–7.62 (5H, m, Ar-H), 7.76 (1H, d, J = 15.8 Hz, β-H), 7.99 (1H, d, J = 15.8 Hz, α-H), 13.78 (1H, s, OH).

2′,6′-DIHYDROXY-4′,5′-DIMETHOXYCHALCONE [**9**].—A 1.0-M solution (0.5 ml) of BCl_3/CH_2Cl_2 was added to a solution of **8** (10 mg) in dry CH_2Cl_2 at −70°, and the mixture was gradually warmed to room temperature and then stirred for 15 min. The reaction mixture was added to ice-H_2O and then extracted with EtOAc. The organic layer was washed several times with H_2O and dried over Na_2SO_4. After removal of the solvent, the residue was purified by preparative tlc [C_6H_6-EtOAc (10:1)] to yield red prisms (4.7 mg, 54%); mp 147–148.5° (from $CHCl_3$) [lit. (5) mp 147–149°]; eims *m/z* $[M]^+$ 300, 285, 223, 196, 181; hrms *m/z* 300.1027 (calcd for $C_{17}H_{16}O_5$, 300.0997); ir ν max ($CHCl_3$) 3475, 3025, 1640, 1570, 1510 cm^{-1}; ^1H nmr ($CDCl_3$) see Table 1. This compound was identified as pashanone [**9**] (1), isolated from *L. erythrocarpa*, by direct comparison (mmp and co-tlc).

2-HYDROXY-4,6-DIMETHOXYACETOPHENONE [**11**].—The mixture of phloroacetophenone [**10**] (10.0 g), K_2CO_3 (39.4 g), and MeI (20.3 g) in dry Me_2CO (250 ml) was refluxed for 3 h. The reaction mixture was filtered, and the filtrate was concentrated. The resulting residue was diluted with H_2O and then extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated, and the residual solid was recrystallized from MeOH to afford colorless prisms (9.7 g, 83%); mp 78.5–79.5°; eims *m/z* $[M]^+$ 196, 181; hrms *m/z* 196.0732 (calcd for $C_{10}H_{12}O_4$, 196.0735); ir ν max ($CHCl_3$) 3025, 1620, 1595 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.54 (3H, s, Ac), 3.75, 3.79 (6H, s × 2, 2 × OMe), 5.85, 5.99 (2H, d × 2, J = 2.4 Hz, 3- and 5-H), 13.96 (1H, s, OH).

2′,3′-DIHYDROXY-4′,6′-DIMETHOXYCHALCONE [**13**].—A mixture of **11** (0.1 g), 6% NaOH (0.3 ml), and 3% H_2O_2 (0.4 ml) in pyridine (0.3 ml) was stirred overnight at room temperature. The reaction mixture was acidified with diluted HCl and extracted with EtOAc. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The resulting material (76 mg) was dissolved in dry nitrobenzene (2 ml) and $AlCl_3$ (0.77 g), and cinnamoyl chloride (1.1 g) was added to the solution and stirred vigorously at room temperature. After 3 h, the reaction mixture was treated as previously described for **2**. Purification by preparative tlc [$CHCl_3$-Me_2CO (10:1)] provided orange prisms (7 mg, 5%); mp 137–139° (from MeOH) [lit. (2) mp 138–140°]; eims *m/z* $[M]^+$ 300, 223; hrms *m/z* 300.0985 (calcd for $C_{17}H_{16}O_5$, 300.0997); ir ν max ($CHCl_3$) 3550, 1640, 1570 cm^{-1}; ^1H nmr see Table 1.

2,5-DIHYDROXY-4,6-DIMETHOXYACETOPHENONE [**14**].—A solution of $K_2S_2O_8$ (3.8 g) in H_2O (80 ml) was added dropwise to a stirring solution of **11** (2.5 g) in 10% NaOH (80 ml) for 2 h at room temperature. The mixture was left overnight in a refrigerator and then adjusted to pH 4 with HCl. The unreacted starting material was removed by extraction with EtOAc, and the aqueous solution was further acidified to pH 2 and then refluxed for 2 h after addition of Na_2SO_3 (1.8 g). The cooled solution was extracted with EtOAc, and the organic layer was evaporated. The residue was purified by preparative tlc [$CHCl_3$-Me_2CO (10:1)] and recrystallized from MeOH to give yellow prisms (196 mg, 7%); mp 161–162°; eims *m/z* $[M]^+$ 212, 197; hrms *m/z* 212.0703 (calcd for $C_{10}H_{12}O_5$, 212.0685); ir ν max ($CHCl_3$)

3550, 1635, 1610, 1495 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.68 (3H, s, Ac), 3.92, 3.96 (6H, s × 2, 2 × OMe), 5.11 (1H, s, 5-OH), 6.26 (1H, s, 3-H), 13.18 (1H, s, 2-OH).

2′,5′-DIHYDROXY-4′,6′-DIMETHOXYCHALCONE [**15**].—A solution of benzaldehyde (100 mg) in EtOH (2 ml) was added dropwise to a solution of **14** (100 mg) and 60% KOH (2 g) in EtOH (1 ml), and the mixture was stirred for 2 days at room temperature. After concentration of the reaction mixture, the residue was diluted with H_2O and extracted with EtOAc. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was purified by preparative tlc [$CHCl_3$-Me_2CO (20:1)] to afford orange needles (7 mg, 5%); mp 156–158° (from MeOH) [lit. (6) mp 156–158°]; eims *m/z* $[M]^+$ 300, 223; hrms *m/z* 300.0971 (calcd for $C_{17}H_{16}O_5$, 300.0997); ir ν max ($CHCl_3$) 3550, 1635, 1590, 1575 cm^{-1}; ^1H nmr see Table 1.

2-HYDROXY-4,6-DIISOPROPOXYACETOPHENONE [**16**].—A solution of 2-bromopropane (16.1 g) in dry DMF (50 ml) was added to a solution of **10** (10.0 g) and K_2CO_3 (9.0 g) in dry DMF (200 ml) during 15 min, and the mixture was stirred for 30 min at room temperature and then refluxed for 4 h. After cooling, the reaction mixture was filtered off, and the filtrate was diluted with ice-H_2O and extracted with $CHCl_3$. The organic layer was washed with 5% NaOH and H_2O, dried over Na_2SO_4, and evaporated to give a dark red oil (10.0 g, 67%); eims *m/z* $[M]^+$ 252, 210, 168, 153; hrms *m/z* 252.1353 (calcd for $C_{14}H_{20}O_4$, 252.1360); ir ν max ($CHCl_3$) 1620, 1585, 1435 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.30, 1.36 (12H, d × 2, J = 6.1 Hz, 4 × Me), 2.57 (3H, s, Ac), 4.48–4.62 (2H, m, 2 × Me_2CH-), 5.83, 5.95 (2H, d × 2, J = 2.0 Hz, 3- and 5-H), 13.97 (1H, s, OH).

2,5-DIHYDROXY-4,6-DIISOPROPOXYACETOPHENONE [**17**].—A solution of $K_2S_2O_8$ (2.4 g) in H_2O (100 ml) was added dropwise to a stirring solution of **16** (2.0 g) in 10% NaOH (40 ml) for 3 h at room temperature. The mixture was left overnight in a refrigerator and then treated as already described for **14**. Purification by preparative tlc [$CHCl_3$-Me_2CO (10:1)] to give an oil (248 mg, 12%); eims *m/z* $[M]^+$ 268, 226, 184, 153; hrms *m/z* 268.1322 (calcd for $C_{14}H_{20}O_5$, 268.1309); ir ν max ($CHCl_3$) 3550, 1635, 1610, 1490 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.32, 1.40 (12H, d × 2, J = 6.1 Hz, 4 × Me), 2.69 (3H, s, Ac), 4.60–4.69 (1H, m, Me_2CH-), 4.85–4.94 (1H, m, Me_2CH-), 5.20 (1H, s, 5-OH), 6.21 (1H, s, 3-H), 13.06 (1H, s, 2-OH).

2,4-DIISOPROPOXY-3,6-DIMETHOXYACETOPHENONE [**18**].—A mixture of **17** (214 mg), Me_2SO_4 (252 mg), and K_2CO_3 (441 mg) in Me_2CO (10 ml) was refluxed overnight. The reaction mixture was filtered, diluted with H_2O, and extracted with EtOAc. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to give a viscous oil (218 mg, 92%); eims *m/z* $[M]^+$ 296, 254, 212, 197; hrms *m/z* 296.1615 (calcd for $C_{16}H_{24}O_5$, 296.1622); ir ν max ($CHCl_3$) 1700, 1600, 1490 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.23, 1.38 (12H, d × 2, J = 6.1 Hz, 4 × Me), 2.48 (3H, s, Ac), 3.76, 3.78 (6H, s × 2, 2 × OMe), 4.52–4.62 (2H, m, 2 × Me_2CH-), 6.25 (1H, s, 5-H).

2′,4′-DIISOPROPOXY-3′,6′-DIMETHOXYCHALCONE [**19**].—A solution of benzaldehyde (218 mg) in EtOH (3 ml) was added dropwise to a solution of **18** (218 mg) and 60% KOH (4 g) in EtOH (3 ml), and the mixture was stirred overnight at room temperature. After concentration of the reaction mixture, the residue was diluted with H_2O and extracted with EtOAc. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residual oil was purified by preparative tlc [$CHCl_3$-Me_2CO (10:1)] to afford orange oil (90 mg, 32%); eims *m/z* $[M]^+$ 384, 342, 300; hrms *m/z* 384.1929 (calcd for $C_{23}H_{28}O_5$, 384.1934); ir ν max ($CHCl_3$) 1640, 1600, 1490 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.19, 1.40 (12H, d × 2, J = 6.1 Hz, 4 × Me), 3.74, 3.82 (6H, s × 2, 2 × OMe), 4.51–4.65 (2H, m, 2 × Me_2CH-), 6.30 (1H, s, 5′-H), 7.00 (1H, d, J = 15.8 Hz, β-H), 7.36–7.56 (5H, m, Ar-H), 7.41 (1H, d, J = 15.8 Hz, α-H).

2′,4′-DIHYDROXY-3′,6′-DIMETHOXYCHALCONE [**20**].—A 1.0-M solution (1.5 ml) of BCl_3-CH_2Cl_2 was added to a solution of **19** (7.8 mg) in dry CH_2Cl_2 (0.5 ml) at −70°, and the mixture was gradually warmed to room temperature and stirred for 5 min. The reaction mixture was poured into ice-H_2O and extracted with EtOAc. The EtOAc layer was washed several times with H_2O and dried over Na_2SO_4. After removal of the solvent, the residue was purified by preparative tlc [$CHCl_3$-Me_2CO (20:1)] to yield orange prisms (2.0 mg, 33%); mp 169–171° (from $CHCl_3$), [lit. (2) mp 170–172°]; eims *m/z* $[M]^+$ 300, 223; hrms *m/z* 300.0971 (calcd for $C_{17}H_{16}O_5$, 300.0996); ir ν max ($CHCl_3$) 3500, 1630, 1600 cm^{-1}; ^1H nmr see Table 1.

2-HYDROXY-4,6-DIBENZYLOXYACETOPHENONE [**21**].—A solution of benzyl chloride (18.1 g) in dry DMF (50 ml) was added to a stirring solution of **10** (11.1 g) and K_2CO_3 (41.1 g) in dry DMF (50 ml), and the mixture was heated at 100° for 2 h with stirring. The reaction mixture was filtered off, and the filtrate was evaporated. The residue was dissolved in $CHCl_3$, and the $CHCl_3$ solution was washed with 5% NaOH and then H_2O. After removal of the solvent, the solid was recrystallized from EtOAc to give colorless prisms (12.5 g, 54%); mp 119–120.5°; eims *m/z* $[M]^+$ 348, 306, 258; hrms *m/z* 348.1335 (calcd for

$C_{22}H_{20}O_4$, 348.1360); ir ν max ($CHCl_3$) 1620, 1600, 1435 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.55 (3H, s, Ac), 5.06 (4H, s, 2 × -CH_2Ph), 6.09, 6.16 (2H, d × 2, J = 2.4 Hz, 3- and 5-H), 7.33–7.44 (10H, m, Ar-H), 14.02 (1H, s, OH).

2,4-DIBENZYLOXY-6-METHOXYACETOPHENONE [**22**].—A mixture of **21** (1.1 g), Me_2SO_4 (0.8 g), and K_2CO_3 (1.4 g) in dry Me_2CO (20 ml) was refluxed for 3.5 h. After cooling, the reaction mixture was filtered off, and the filtrate was diluted with same volume of H_2O and then extracted with EtOAc. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to give a colorless oil (1.0 g, 87%); eims *m/z* $[M]^+$ 362, 272, 257; hrms *m/z* 362.1534 (calcd for $C_{23}H_{22}O_4$, 362.1518); ir ν max ($CHCl_3$) 1600, 1455, 1400 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.45 (3H, s, Ac), 3.92 (3H, s, OMe), 5.03 (4H, s, 2 × -CH_2Ph), 6.21, 6.24 (2H, d × 2, J = 2.0 Hz, 3- and 5-H), 7.28–7.40 (10H, m, Ar-H).

2,4-DIHYDROXY-6-METHOXYACETOPHENONE [**23**].—A mixture of **22** (1.0 g) and 10% Pd/C (0.5 g) in EtOAc (10 ml) was stirred under an H_2 atmosphere until uptake had ceased. After filtration, the reaction mixture was evaporated to give a solid, which was recrystallized from MeOH to afford colorless prisms (320 mg, 64%); mp 201–202°; eims *m/z* $[M]^+$ 182, 167, 124; hrms *m/z* 182.0555 (calcd for $C_9H_{10}O_4$, 182.0578); ir ν max ($CHCl_3$) 1640, 1580 cm^{-1}; ^1H nmr (Me_2CO-d_6) δ 2.55 (3H, s, Ac), 3.90 (3H, s, OMe), 5.95, 6.03 (2H, d × 2, J = 2.0 Hz, 3- and 5-H), 7.35 (1H, br s, 4-OH), 13.92 (1H, s, 2-OH).

2-HYDROXY-4-ISOPROPOXY-6-METHOXYACETOPHENONE [**24**].—A mixture of **23** (0.72 g), K_2CO_3 (1.09 g), and 2-bromopropane (0.58 g) in dry DMF (40 ml) was heated at 100–110° for 2 h. After cooling, the reaction mixture was filtered off, and the filtrate was diluted with ice-H_2O and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was recrystallized from MeOH to give colorless prisms (0.77 g, 87%); mp 71–72°; eims *m/z* $[M]^+$ 224, 182, 167; hrms *m/z* 224.1069 (calcd for $C_{12}H_{16}O_4$, 224.1048); ir ν max ($CHCl_3$) 1620, 1600 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.35 (6H, d, J = 6.1 Hz, 2 × Me), 2.60 (3H, s, Ac), 3.84 (3H, s, OMe), 4.53–4.62 (1H, m, Me_2CH-), 5.89, 6.03 (2H, d × 2, J = 2.4 Hz, 3- and 5-H), 14.03 (1H, s, OH).

2,5-DIHYDROXY-4-ISOPROPOXY-6-METHOXYACETOPHENONE [**25**].—A solution of $K_2S_2O_8$ (1.12 g) in H_2O (30 ml) was added dropwise to a mixture of **24** (0.77 g), pyridine (5 ml), and 10% NaOH (40 ml) with stirring for 3 h at room temperature. The mixture was left overnight in a refrigerator and then treated as already described for **14**. Purification by preparative tlc [$CHCl_3$-Me_2CO (10:1)] to give an oil (162 mg, 20%); eims *m/z* $[M]^+$ 240, 198, 183; hrms *m/z* 240.1020 (calcd for $C_{12}H_{16}O_5$, 240.0998); ir ν max ($CHCl_3$) 3550, 1635, 1610, 1490 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.41 (6H, d, J = 6.1 Hz, 2 × Me), 2.67 (3H, s, Ac), 3.97 (3H, s, OMe), 4.60–4.69 (1H, m, Me_2CH-), 6.24 (1H, s, 3-H), 7.26 (1H, s, 5-OH), 13.18 (1H, s, 2-OH).

2-HYDROXY-4-ISOPROPOXY-5,6-DIMETHOXYACETOPHENONE [**26**].—A mixture of **25** (162 mg), K_2CO_3 (186 mg), and Me_2SO_4 (102 mg) in dry Me_2CO (4 ml) was refluxed for 2 h. After cooling, the reaction mixture was filtered off, and the filtrate was diluted with same volume of H_2O and then extracted with EtOAc. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to give a colorless oil (140 mg, 82%); eims *m/z* $[M]^+$ 254, 197; hrms *m/z* 254.1179 (calcd for $C_{13}H_{18}O_5$, 254.1154); ir ν max ($CHCl_3$) 1620, 1600, 1485 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.41 (6H, d, J = 6.1 Hz, 2 × Me), 2.65 (3H, s, Ac), 3.76, 3.99 (6H, s × 2, 2 × OMe), 4.56–4.65 (1H, m, Me_2CH-), 6.21 (1H, s, 3-H), 13.43 (1H, s, OH).

2'HYDROXY-4'-ISOPROPOXY-5',6'-DIMETHOXYCHALCONE [**27**].—A solution of benzaldehyde (140 mg) in EtOH (1.5 ml) was added dropwise to a solution of **26** (140 mg) and 60% KOH (2 g) in EtOH (1.5 ml) and the mixture was stirred overnight at room temperature. After concentration of the reaction mixture, the residue was diluted with H_2O and extracted with EtOAc. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residual oil was purified by preparative tlc [$CHCl_3$-Me_2CO (10:1)] to afford an orange oil (164 mg, 87%); eims *m/z* $[M]^+$ 342, 299; hrms *m/z* 342.1439 (calcd for $C_{20}H_{22}O_5$, 342.1446); ir ν max ($CHCl_3$) 1630, 1585, 1480 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.43 (6H, d, J = 6.4 Hz, 2 × Me), 3.82, 3.94 (6H, s × 2, 2 × OMe), 4.59–4.68 (1H, m, Me_2CH-), 6.27 (1H, s, 3'-H), 7.39–7.66 (5H, m, Ar-H), 7.82 (1H, d, J = 15.8 Hz, β-H), 7.96 (1H, d, J = 15.8 Hz, α-H), 13.66 (1H, s, OH).

2',4'-DIHYDROXY-5',6'-DIMETHOXYCHALCONE [**28**].—A 1.0-M solution (1.5 ml) of BCl_3/CH_2Cl_2 was added to a solution of **27** (20 mg) in dry CH_2Cl_2 (0.5 ml) at −70°, and the mixture was gradually warmed to room temperature and stirred for 15 min. The reaction mixture was poured into ice-H_2O and extracted with EtOAc. The organic layer was washed several times with H_2O and dried over Na_2SO_4. After removal of the solvent, the residue was purified by preparative tlc [$CHCl_3$-Me_2CO (20:1)] to give orange prisms (3 mg, 17%); mp 180–182° (from $CHCl_3$) [lit. (2) mp 182–184°]; eims *m/z* $[M]^+$ 300,

223, 195; hrms *m/z* 300.0968 (calcd for $C_{17}H_{16}O_5$, 300.0997); ir ν max ($CHCl_3$) 3500, 1630, 1560, 1480 cm^{-1}; ^1H nmr see Table 1.

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