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Synthetic Studies on Lignans and Related Compounds. VIII.[1] Synthesis of Justicidin B and Diphyllin and of Taiwanin C and E from 2,3-Dibenzylidenebutyrolactones *via* β-Apolignans: A Chemical Model for Natural Co-occurrence of 4-Hydrogen- and 4-Hydroxy-1-phenyl-2,3-naphthalides in Plants[2]

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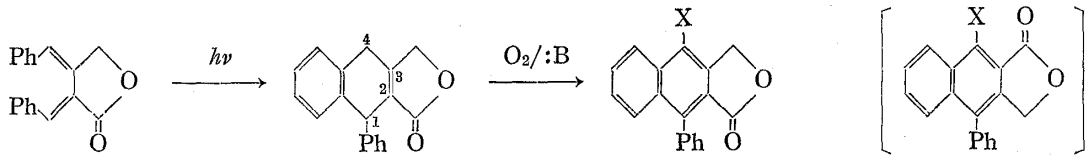
The concurrent synthesis of justicidin B (3) and diphyllin (4) coexistent in *Justicia procumbens* var. *leucantha* and of taiwanin C (1) and E (2) in *Taiwania cryptomerioides* was achieved by combination of the photocyclization of 2,3-dibenzylidenebutyrolactones (7 and 9) and subsequent air oxidation of the resulting β-apolignans (8a and 10a).

Keywords——synthesis; justicidin B; diphyllin; taiwanin C; taiwanin E; β-apolignan; 2,3-dibenzylidenebutyrolactone; photocyclization; air oxidation

We recently reported the specific photo-conversion[4] of 2,3-dibenzylidenebutyrolactones (I) into β-apolignans (II) and subsequent transformation of the latter (II) into 4-hydrogen- and 4-hydroxy-1-phenyl-2,3-naphthalides (III and IV) by a base-catalyzed air oxidation.[5]



I II III: X=H IV: X=OH V

Ph=phenyl

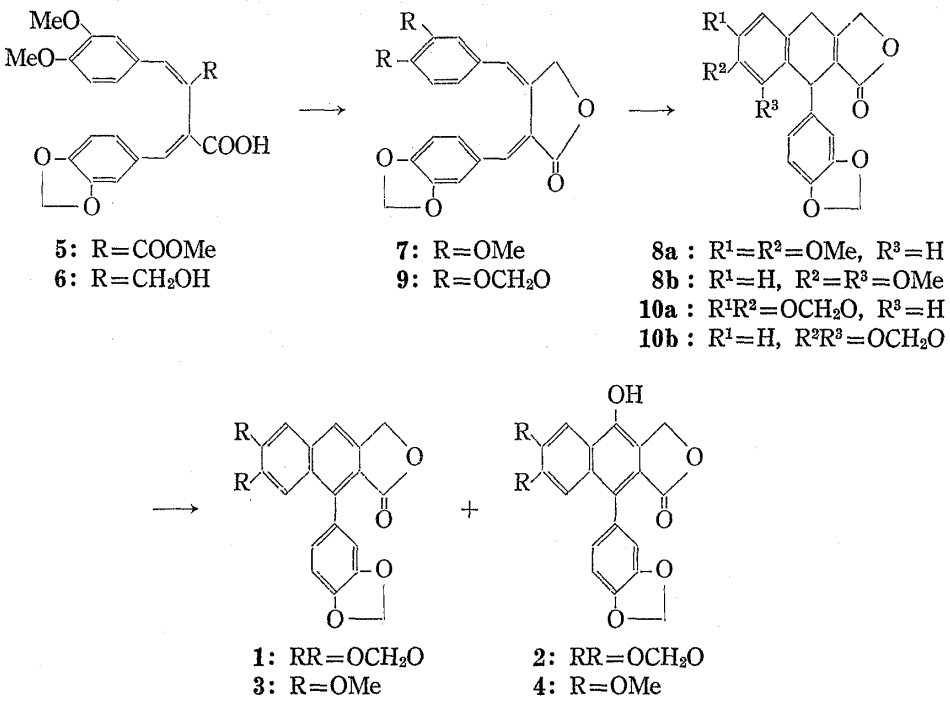
Chart 1

The transformation is of interest in association with a possible biogenetic pathway to naphthalide lignans from acyclolignans, and seems to provide a possible explanation for problems associated with the following facts: (i) the biogenesis[6] of podophyllotoxin (tetrahydro-IV) from phenylalanine *via* podorhizol (tetrahydro-I), (ii) the predominance[7] in natural occurrence of the 1-phenyl-2,3-naphthalide (III or IV) over 4-phenyl-2,3-naphthalide types (V), and (iii) the co-occurrence of taiwanin A (type I), C (1: type III), and E (2: type IV) in *Taiwania cryptomerioides*,[8] of β-apoplicatitoxin (type II),[9a] plicatinaphthalene (type III),[9b]

1) Part VII: T. Momose, T. Nakamura, and K. Kanai, *Chem. Pharm. Bull.* (Tokyo), **26**, 3186 (1978).
2) Presented at the 98th Annual Meeting of Pharmaceutical Society of Japan, Okayama, April 1978, Abstracts of Papers, p. 301.
3) Location: *133–1, Yamada-kami, Suita, Osaka 565, Japan.*
4) For model experiments, see T. Momose, K. Kanai, T. Nakamura, and Y. Kuni, *Chem. Pharm. Bull.* (Tokyo), **25**, 2755 (1977).
5) For a model experiment, see T. Momose and K. Kanai, *Heterocycles*, **9**, 207 (1978).
6) D.C. Ayres, *Tetrahedron Lett.*, **1969**, 883.
7) Z. Horii, M. Tsujiuchi, and T. Momose, *Tetrahedron Lett.*, **1969**, 1079.
8) *a*) Isolation of **1**, **2**, and **9**: Y.-T. Lin, T.-B. Lo, K.-T. Wang, and B. Weinstein, *Tetrahedron Lett.*, **1967**, 849; *b*) For unambiguous synthesis of **1** and **2**, see Z. Horii, M. Tsujiuchi, K. Kanai, and T. Momose, *Chem. Pharm. Bull.* (Tokyo), **25**, 1803 (1977).
9) *a*) B.F. MacDonald and G.M. Barton, *Can. J. Chem.*, **51**, 482 (1973); *b*) H. MacLean and B.F. MacDonald, *ibid.*, **47**, 4495 (1969); *c*) *Idem*, *ibid.*, **47**, 457 (1969).

and plicatinaphthol (type IV)[9c] in *Thuja plicata*, and of justicidin B (**3**: type III)[10a,b] and diphyllin (**4**: type IV)[10] in *Justicia procumbens* var. *leucantha*.

A combination of the photocyclization and air oxidation has now been utilized for the concurrent synthesis of **3** and **4** and of **1** and **2**.



5: R=COOMe
6: R=CH_2OH

7: R=OMe
9: R=OCH_2O

8a : $R^1=R^2=OMe$, $R^3=H$
8b : $R^1=H$, $R^2=R^3=OMe$
10a : $R^1R^2=OCH_2O$, $R^3=H$
10b : $R^1=H$, $R^2R^3=OCH_2O$

1: RR=OCH_2O
3: R=OMe

2: RR=OCH_2O
4: R=OMe

Chart 2

Synthesis of 3 and 4

The Stobbe condensation of dimethyl piperonylidenesuccinate[11] with veratraldehyde afforded the half ester (**5**), which was reduced with lithium aluminum hydride at −25° to a hydroxy acid (**6**). Treatment of **6** with *p*-toluenesulfonic acid (TsOH) in the dark gave a lactone (**7**).

A solution of **7** in dimethylformamide (DMF)[1] was irradiated with the light filtered through ordinary borosilicate glass in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO), and simultaneously bubbled with dry, oxygen-free nitrogen. Preparative thin-layer chromatography (TLC) of the crude product gave **8a** (56% yield) and **8b** (28% yield). These products exhibited infrared (IR) bands characteristic of β-apolignans at *ca.* 1750 (C=O) and *ca.* 1690 (C=C) cm^{-1}, and their substitutional isomerism was deduced from their proton magnetic resonance (^{1}H-NMR) spectra. The C_1–H signal at δ 5.13 for **8b** appeared at lower field than for **8a** (δ *ca.* 4.8) owing to the deshielding effect of the C_8-methoxyl, while the C_8-methoxyl protons (δ 3.46) in **8b** resonated at higher field than did the C_5-methoxyl ones (δ 3.89) in 1,4-dihydro-1-(3,4-dimethoxyphenyl)-3-hydroxymethyl-5-methoxy-2-naphthoic acid γ-lactone[12] owing to the shielding effect of the pendant phenyl ring. The marked deshielding effect of the C_8-methoxyl upon the C_1–H in **8b** can be explained by assuming that the phenyl ring is forced to be in a *quasi*-axial orientation, and hence the C_1–H in a *quasi*-equatorial

10) *a*) Isolation of **3** and **4**: M. Okigawa, T. Maeda, and N. Kawano, *Tetrahedron*, **26**, 4301 (1970); *b*) Isolation of **3** and **4**: K. Ohta and K. Munakata, Abstracts of Papers, 8th Shokubutsu-kagaku Symposium, Tokyo, Jan. 1972, p. 1; *c*) For the structure of **4**, see Z. Horii, K. Ohkawa, S.-W. Kim, and T. Momose, *Chem. Pharm. Bull.* (Tokyo), **19**, 535 (1971).
11) F.G. Baddar, L.S. El-Assal, N.A. Doss, and A.H. Shehab, *J. Chem. Soc.*, **1959**, 1016.
12) Unpublished data.

one, to minimize the steric interference with the C_8-methoxyl group. The feature established the structure of **8b**, and hence of **8a**.

Molecular oxygen was bubbled through a solution of **8a** and potassium *t*-butoxide in hexamethylphosphoric triamide (HMPA) at 25°. The crude product was subjected to preparative TLC to give **3** (28% yield) and **4** (27% yield), which were identical with justicidin B[10a] and diphyllin,[10c] respectively, on IR spectral comparison.

Synthesis of 1 and 2

Irradiation of taiwanin A (**9**)[13] afforded isomeric β-apolignans (**10a**: 35% yield) and (**10b**: 50% yield). The C_1–H signal was no longer a good landmark discriminating between the substitutional isomers (**10a** and **10b**): the C_1–H (δ *ca.* 4.74) in **10b** resonated at the field closely similar to that (δ 4.93) in **10a**. Ultimately, the structure of **10b** could be assigned from the presence of a pair of one-proton doublet signals at δ 5.86, 5.88, 5.89, and 5.91 ascribed to the C_7,C_8-methylenedioxy protons, which were not symmetrically arranged with respect to the pendant phenyl ring and were similar in its ^{1}H-NMR pattern to that in otobain.[14] The assignment of another one (**10a**) was furnished based on the presence of a singlet at δ 5.84 due to two methylenedioxy groups.

Oxidation of **10a** with molecular oxygen gave **1** (10% yield) and **2** (19% yield), which were identical with taiwanin C[8b] and taiwanin E,[8b] respectively, on IR spectral comparison.

Experimental

All melting points are uncorrected. ^{1}H-NMR spectra were obtained with a Hitachi R-22 (90 MHz) spectrometer with tetramethylsilane as an internal standard, IR spectra with a Hitachi EPI-G3 spectrophotometer, Ultraviolet (UV) spectra with a Shimadzu MPS-50L and UV-200 spectrophotometers, and Mass Spectra (MS) with a Hitachi RMU-6E spectrometer (direct inlet, at 70 eV). All organic extracts were dried over Na_2SO_4 before evaporation. Column chromatography was effected using Mallinckrodt silicic acid. Preparative TLC was performed on Merck Kieselgel 60 PF_{254}. The photochemical reactions were carried out in an immersion apparatus fitted with an Eikosha 100 W high-pressure mercury lamp.

Methyl Hydrogen α-Veratrylidene-β-piperonylidenesuccinate (**5**)——A solution of dimethyl piperonylidenesuccinate[11] (3.6 g) and veratraldehyde (2.3 g) in dry *t*-butanol (4.5 ml) was added to a stirred solution of potassium *t*-butoxide [from metallic K (0.7 g)] in dry *t*-butanol (10 ml) at room temperature over a period of 10 min. After heating under reflux for 30 min, the solution was poured into ice-water (80 ml), and the separated oil was taken in ether. The aqueous layer was acidified with 5% H_2SO_4, and the separated oil was extracted with AcOEt. The extract was washed with satd. NaCl and evaporated to give a pale yellow viscous oil (4.9 g), which was chromatographed on silica gel (100 g) in $CHCl_3$–EtOH (133: 1) to give **5** (4.1 g, 77%) as a pale yellow glass. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1712, 1688 (C=O), 1601 (arom.). ^{1}H-NMR ($CDCl_3$) δ: 3.73 (6H, s, OMe and –CO_2Me), 3.84 (3H, s, OMe), 5.90 (2H, s, –OCH_2O–), 6.6—7.3 (6H, m, Ar–H), 7.84 (1H, s, –CH=C–), 7.87 (1H, s, –CH=C–), 8.39 (1H, broad, –CO_2H). MS *m/e*: 412 (M^+, 42%), 380 (100%).

2-Piperonylidene-3-veratrylidene-4-hydroxybutyric Acid (**6**)——A solution of **5** (1.0 g) in dry tetrahydrofuran (4 ml) and dry ether (25 ml) was added to a stirred suspension of $LiAlH_4$ (1.5 g) in dry ether (44 ml) at −50°, and the suspension was stirred at −25° for 5 hr. After addition of AcOEt and subsequently of 5% H_2SO_4, the organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with satd. NaCl and evaporated *in vacuo* below room temperature to give a yellow glass (0.9 g), which was purified by preparative TLC on silica gel using benzene–acetone (4: 1) as a developing solvent to give **6** (0.5 g, 56%) as colorless needles (from benzene), mp 137—138°. IR ν_{max}^{KBr} cm^{-1}: 1691 (C=O), 1619 (C=C), 1598, 1582 (arom.). ^{1}H-NMR (d_6-acetone) δ: 3.67 (3H, s, OMe), 3.74 (3H, s, OMe), 4.26 (2H, broad s, –CH_2OH), *ca.* 4.6 (2H, broad, –CH_2OH and –CO_2H), 5.99 (2H, s, –OCH_2O–), 6.7—7.4 (7H, m, Ar–H and –CH=C–), 7.67 (1H, s, –CH=C–). *Anal.* Calcd. for $C_{21}H_{20}O_7$: C, 65.61; H, 5.24. Found: C, 65.22; H, 5.23.

2-Piperonylidene-3-veratrylidene-4-hydroxybutyric Acid γ-Lactone (**7**)——A solution of **6** (0.30 g) and TsOH (0.41 g) in dry ether (250 ml) was stirred in the dark for 40 hr at room temperature. The solution was washed with satd. $NaHCO_3$ and then satd. NaCl and evaporated *in vacuo* below room temperature to give **7** (0.27 g, 95%) as a yellow viscous oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1755 (C=O), 1630 (C=C), 1611, 1590 (arom.). ^{1}H-NMR ($CDCl_3$) δ: 3.62 (3H, s, OMe), 3.77 (3H, s, OMe), 5.00 (2H, d, J=2 Hz, –CH_2OCO–), 5.78 (2H, s,

13) G.A. Swoboda, K.-T. Wang, and B. Weinstein, *J. Chem. Soc.* (C), **1967**, 161.
14) T. Gilchrist, R. Hodges, and A.L. Porte, *J. Chem. Soc.*, **1962**, 1780.

$-OCH_2O-$), 6.58 (1H, t, $J=2$ Hz, $-CH=\overset{|}{C}-$), 6.1—7.0 (6H, m, Ar–H), 7.56 (1H, s, $-CH=\overset{|}{C}-$). UV λ_{max}^{EtOH} nm (log ε): 269 (4.15), 368 (3.93).

1,4-Dihydro-6,7-dimethoxy-3-hydroxymethyl-1-(3,4-methylenedioxyphenyl)-2-naphthoic Acid γ-Lactone (8a) and 1,4-Dihydro-7,8-dimethoxy-3-hydroxymethyl-1-(3,4-methylenedioxyphenyl)-2-naphthoic Acid γ-Lactone (8b)——A solution of **7** (272 mg) and DABCO (53 mg) in DMF (150 ml) was irradiated through an ordinary borosilicate glass sleeve (1.5 mm wall thickness) at 5° for 40 min under a stream of dry, oxygen-free N_2. After evaporation of the solution *in vacuo*, the crude product (230 mg) was purified by repeated preparative TLC on silica gel using $CHCl_3$–EtOH (50: 1) as solvent to give **8a** (152 mg, 56%) and **8b** (76 mg, 28%).

Compound **8a**: Colorless crystals (from ether), mp 145—146°. IR ν_{max}^{KBr} cm^{-1}: 1762 (C=O), 1693 (C=C), 1610 (arom.). ^{1}H-NMR ($CDCl_3$) δ: 3.75 (3H, s, OMe), 3.88 (3H, s, OMe), *ca.* 3.8 (2H, m, C_4–H), 4.82 (2H, broad s, $-CH_2OCO-$), *ca.* 4.8 (1H, m, C_1–H), 5.85 (2H, s, $-OCH_2O-$), 6.3—7.0 (5H, m, Ar–H). MS *m/e*: 366 (M^+, 100%). UV λ_{max}^{EtOH} nm (log ε): 286 (3.91). *Anal.* Calcd. for $C_{21}H_{18}O_6$: C, 68.84; H, 4.95. Found: C, 68.56; H, 4.97.

Compound **8b**: Colorless plates (from MeOH), mp 238—238.5°. IR ν_{max}^{KBr} cm^{-1}: 1752 (C=O), 1700 (C=C), 1607 (arom.). ^{1}H-NMR ($CDCl_3$) δ: 3.46 (3H, s, OMe), 3.82 (3H, s, OMe), *ca.* 3.8 (2H, m, C_4–H), 4.79 (2H, broad s, $-CH_2OCO-$), 5.13 (1H, m, C_1–H), 5.82 (2H, s, $-OCH_2O-$), 6.5—7.1 (5H, m, Ar–H). MS *m/e*: 366 (M^+, 100%). UV λ_{max}^{EtOH} nm (log ε): 285 (3.66). *Anal.* Calcd. for $C_{21}H_{18}O_6$: C, 68.84; H, 4.95. Found: C, 68.54; H, 4.94.

6,7-Dimethoxy-3-hydroxymethyl-1-(3,4-methylenedioxyphenyl)-2-naphthoic Acid γ-Lactone (Justicidin B) (3) and 6,7-Dimethoxy-4-hydroxy-3-hydroxymethyl-1-(3,4-methylenedioxyphenyl)-2-naphthoic Acid γ-Lactone (Diphyllin) (4)——Dry O_2 was bubbled through a stirred solution of **8a** (46 mg) and potassium *t*-butoxide (40 mg) in dry HMPA (5 ml) at 25° for 1 hr. The solution was poured into ice-water (30 ml), acidified with 5% H_2SO_4, and extracted with AcOEt. The extract was washed with satd. NaCl and evaporated to give a brown oil, which was purified by repeated preparative TLC on silica gel using $CHCl_3$–EtOH (40: 1) as solvent to give **3** (21 mg, 28%) as colorless crystals (from ether), mp 227—228° (lit.,[10a] 235—238°), and **4** (13 mg, 27%) as pale yellow crystals (from EtOH), mp 266—267° (lit.,[10c] 285—289°). Compounds **3** and **4** were identical with authentic justicidin B and diphyllin, respectively, on IR spectral comparison.

1,4-Dihydro-3-hydroxymethyl-6,7-methylenedioxy-1-(3,4-methylenedioxyphenyl)-2-naphthoic Acid γ-Lactone (10a) and 1,4-Dihydro-3-hydroxymethyl-7,8-methylenedioxy-1-(3,4-methylenedioxyphenyl)-2-naphthoic Acid γ-Lactone (10b)——A solution of taiwanin A (**9**)[13] (400 mg) and DABCO (80 mg) in DMF (200 ml) was irradiated for 40 min in a similar manner to that for **8a, b**. After evaporation of the solution *in vacuo*, the resulting pale brown solid was recrystallized from $CHCl_3$–EtOH to give **10b** (149 mg). The mother liquor was purified by repeated preparative TLC on silica gel using $CHCl_3$–EtOH (40: 1) as solvent to give **10a** (138 mg, 35%) and **10b** (50 mg). The total yield of **10b** was 50%.

Compound **10a**: Colorless prisms (from EtOH), mp 199—200°. IR ν_{max}^{KBr} cm^{-1}: 1759 (C=O), 1693 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 3.74 (2H, m, C_4–H), 4.81 (2H, broad s, $-CH_2OCO-$), 4.93 (1H, m, C_1–H), 5.84 (4H, s, $-OCH_2O-$), 6.3—6.8 (5H, m, Ar–H). MS *m/e*: 350 (M^+, 100%). UV λ_{max}^{EtOH} nm (log ε): 288.5 (3.88). *Anal.* Calcd. for $C_{20}H_{14}O_6$: C, 68.57; H, 4.03. Found: C, 68.60; H, 4.09.

Compound **10b**: Colorless prisms (from $CHCl_3$–EtOH), mp 248.5—250.5°. IR ν_{max}^{KBr} cm^{-1}: 1759 (C=O), 1695 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 3.72 (2H, m, C_4–H), 4.80 (2H, broad s, $-CH_2OCO-$), *ca.* 4.74 (1H, m, C_1–H), 5.84 (2H, s, $-OCH_2O-$), 5.86, 5.88, 5.89, and 5.91 (2H, dd, $-OCH_2O-$), 6.4—6.7 (5H, m, Ar–H). MS *m/e*: 350 (M^+, 100%). UV λ_{max}^{EtOH} nm (log ε): 289 (3.93). *Anal.* Calcd. for $C_{20}H_{14}O_6$: C, 68.57; H, 4.03. Found: C, 68.14; H, 3.98.

3-Hydroxymethyl-6,7-methylenedioxy-1-(3,4-methylenedioxyphenyl)-2-naphthoic Acid γ-Lactone (Taiwanin C) (1) and 4-Hydroxy-3-hydroxymethyl-6,7-methylenedioxy-1-(3,4-methylenedioxyphenyl)-2-naphthoic Acid γ-Lactone (Taiwanin E) (2)——The β-apolignan (**10a**, 60 mg) in dry HMPA (5 ml) was oxidized in the presence of potassium *t*-butoxide (54 mg) in a similar manner to that for **3** and **4** to give **1** (6 mg, 10%) as colorless crystals (from AcOEt), mp 240—245° (lit.,[8b] 260—266°), and **2** (12 mg, 19%) as pale yellow crystals (from AcOH), mp 298—300° (lit.,[8b] 302—305°). Compounds **1** and **2** were identical with authentic taiwanin C and E, respectively, on IR spectral comparison.

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