

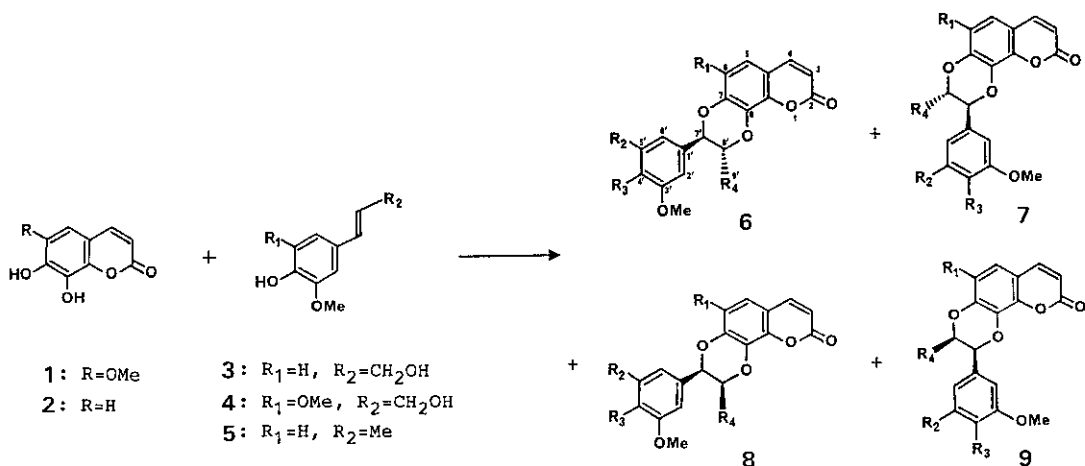
SYNTHESES OF NATURAL COUMARINOLIGNANS: OXIDATIVE COUPLING OF 7,8-DIHYDROXYCOUMARINS AND PHENYLPROPENES IN THE PRESENCE OF DIPHENYL SELENOXIDE

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Abstract—Oxidative coupling of 7,8-dihydroxycoumarins (1, 2) and phenylpropenes (3-5) using Ph₂SeO as oxidizing agent resulted in remarkably efficient synthesis of naturally occurring coumarinolignans (cleomiscosin A (6A), aquillochin (cleomiscosin C)(6B), daphneticin (6C), and propacin (6D)).

In the previous papers, we reported total syntheses of naturally occurring coumarinolignans (cleomiscosin A (6A),^{1a} cleomiscosin B (7A),^{1b} aquillochin (cleomiscosin C)(6B),^{1c} cleomiscosin D (7B),^{1c} daphneticin (6C),^{1d} and propacin (6D)^{1e}), which were prepared via condensation reaction of 7,8-dihydroxycoumarin derivatives with 3-aryl-2-bromo-3-oxopropionates or 1-aryl-2-bromo-1-oxopropane. On the other hand, Merlini^{2a} and Lin and Cordell^{2b} described that the coumarinolignans were also prepared by oxidative coupling of 7,8-dihydroxycoumarins (fraxetin (1) and daphnetin (2)) and phenylpropenes (coniferyl alcohol (3), sinapyl alcohol (4), and isoeugenol (5)) with Ag₂O, DDQ, or horseradish peroxidase. This procedure is known as the biomimetic synthesis and also utilized in the syntheses of naturally occurring benzodioxanes such as flavonolignans (silybin and isosilybin)³ and xanthonolignan (kielcorin).⁴ Though the syntheses of the benzodioxanes, using Ag₂O as oxidizing agent, is convenient, yields of the coumarinolignans were not satisfactory (poor yield). And we choose diphenyl selenoxide (Ph₂SeO) as oxidizing agent of phenolic hydroxyl groups, because Ph₂SeO is very effective⁵ for oxidation of catechols to ortho quinones (no effect on simple phenols) without over-oxidation. Herein, we wish to report an application of Ph₂SeO as oxidizing agent in oxidative coupling of 7,8-dihydroxycoumarins (1, 2) and phenylpropenes (3-5).

Treatment of fraxetin (1) and coniferyl alcohol (3) in MeOH and benzene in the presence of Ph₂SeO at room temperature followed by acetylation of oxidation products gave cleomiscosin A diacetate (6a) as a major product (39% yield)(Table 1) along with three isomers (cleomiscosin B diacetate (7a), cis cleomiscosin A diacetate (8a), and cis cleomiscosin B diacetate (9a)) as minor products.



- A: R₁=OMe, R₂=H, R₃=OH, R₄=CH₂OH
a: R₁=OMe, R₂=H, R₃=OAc, R₄=CH₂OAc
B: R₁=R₂=OMe, R₃=OH, R₄=CH₂OH
b: R₁=R₂=OMe, R₃=OAc, R₄=CH₂OAc
C: R₁=H, R₂=OMe, R₃=OH, R₄=CH₂OH
c: R₁=H, R₂=OMe, R₃=OAc, R₄=CH₂OAc
D: R₁=OMe, R₂=H, R₃=OH, R₄=CH₃
d: R₁=OMe, R₂=H, R₃=OAc, R₄=CH₃

The compound (6a) was obtained as pure crystals and the structure was assigned by direct comparison with an authentic sample.^{1a} And three isomers (7a-9a) were separated by column chromatography (silica gel) and subsequent HPLC, and their structures were elucidated by spectroscopic means (ir, mass, and particularly ¹H-nmr spectra). The spectral data (ir, mass, and ¹H-nmr) of 7a are closely similar to those of 6a. The ¹H-nmr spectrum of 7a displayed a proton signal due to C-7' at δ 5.05 (d, J=7.1 Hz) and the coupling constant was typical for trans orientation of the benzodioxane moiety. The remaining two compounds (8a, 9a) exhibited each other the great similarity of their spectra (ir, mass, and ¹H-nmr), and also indicated similar spectral data (ir and mass) except for the ¹H-

nmr spectra in comparison with that of **6a**. In the ^1H -nmr spectra of two compounds (**8a**, **9a**), C-7' proton signals were observed as doublets ($J=2.7$ Hz) at δ 5.37 and 5.36, respectively, in accordance with cis orientation of substituents on the benzodioxane nucleus. Therefore, two compounds (**8a**, **9a**) were cis regioisomers, which are spectroscopically indistinguishable each other.

Oxidation of fraxetin (**1**) and sinapyl alcohol (**4**) with Ph_2SeO followed by acetylation provided aquillochin diacetate (**6b**) as a main product (36% yield)(Table 1) along with three isomers (cleomiscosin D diacetate (**7b**), cis aquillochin diacetate (**8b**), and cis cleomiscosin D diacetate (**9b**)) as minor products. Four compounds (**6b-9b**) were separated according to the similar procedure described above. Each structure of **6b** and **7b** was confirmed by direct comparison of products, acetylated from the known materials $^{1\text{C}}$ (**6B** and **7B**). The remaining two compounds (**8b**, **9b**) showed spectral data (ir and mass spectra) similar to **6b**. However, in the ^1H -nmr spectra, the two compounds (**8b**, **9b**) revealed doublet signals ($J=2.7$ Hz) of $\text{C}_{7'}$ -H at δ 5.33 and 5.32, respectively, typical of cis orientation of the benzodioxane ring, and hence would be cis regioisomers.

Oxidation of daphnetin (**2**) and sinapyl alcohol (**4**) with Ph_2SeO and subsequent acetylation gave daphneticin diacetate (**6c**) as a main product (18% yield)(Table 1), which was proved identical with an authentic sample (**6c**) $^{1\text{d}}$ by direct comparison. And the remaining products were obtained as an inseparable mixture, which showed a single spot on tlc (silica gel) in a variety of solvent systems. Finally, similar oxidation of fraxetin (**1**) and isoeugenol (**5**) with Ph_2SeO followed by acetylation afforded propacin acetate (**6d**) as a main product (55% yield)(Table 1) and regioisomer of propacin acetate (**7d**), cis propacin acetate (**8d**) and cis regioisomer of propacin acetate (**9d**) as minor products. Four compounds (**6d-9d**) were separated according to the similar procedure described for **6a-9a**. The structure of **6d** was assigned by direct comparison of an authentic sample, $^{1\text{e}}$ and the structures of **7d** and **9d** were also established by direct comparison with the acetylation products of the known materials $^{1\text{e}}$ (regioisomer of propacin (**7D**) and cis regioisomer of propacin (**9D**)). Further, the last compound **8d** was very similar to **9d** in the spectral data (ir, mass, and ^1H -nmr). And the ^1H -nmr spectrum of **8d** displayed a doublet signal of $\text{C}_{7'}$ -H at δ 5.26 ($J=2.7$ Hz), due to cis orientation of the benzodioxane ring and hence formula of

this compound is represented to be 8d.

Table 1. Reaction of 7,8-Dihydroxycoumarins with Phenylpropenes in the Presence of Ph₂SeO

7,8-Dihydroxy-coumarins	Phenylpropenes	Product ^{a)}	Yield ^{b)} (%)
1	3	6a (6A) ^{c,d)}	39 (10.4) ^{c)} (8) ^{d)}
1	4	6b (6B) ^{c)}	36 (6.8) ^{c)}
2	4	6c (6C) ^{c)}	18 (1.0) ^{c)}
1	5	6d (6D) ^{c,d)}	55 (4.1) ^{c)} (22) ^{d)}

a) Isolated compound. b) Isolated yield.

c) Reaction carried out in the presence of Ag₂O; data from Lin and Cordell.^{2b}

d) Reaction carried out in the presence of Ag₂O; data from Merlini.^{2a}

Thus, the oxidative coupling of 7,8-dihydroxycoumarins (1, 2) and phenylpropenes (3-5) with Ph₂SeO afforded four kinds of coumarinolignans (6-9), among which isomer 6 of coumarinolignans was obtained in fairly good yields, as compared to the aforementioned Ag₂O oxidation (Table 1). Consequently, this method has highly regio- and stereo-selectivity and remarkable effect in the synthesis of naturally occurring coumarinolignans (cleomiscosin A (6A), aquillochin (cleomiscosin C)(6B), daphneticin (6C), and propacin (6D)). We postulate the mechanism of the oxidative coupling to be as follows. In the presence of Ph₂SeO, hydroxyl groups in 7,8-dihydroxycoumarins (1, 2) would be rapidly oxidized to generate the corresponding ortho quinones, in which the oxygen atom at C-8 position was immediately attacked by double bond (particularly C-2 position) of phenylpropenes (3-5) to afford the coumarinolignans (6) predominantly.

EXPERIMENTAL

All melting points are uncorrected. Column chromatography was run on Merck silica gel 60 (70-230 mesh). TLC was performed on glass plates precoated with Kieselgel 60 F₂₅₄ (Merck). Ms were recorded on a Hitachi M-52 spectrometer and high-resolution ms on a Hitachi M-80 spectrometer. Ir spectra were obtained on a JASCO IR-810 spectrophotometer. ¹H-Nmr spectra were recorded on a JEOL JNM-GX-270 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are quoted in parts per million (s=singlet, d=doublet, q=quartet, m=multiplet). Analytical HPLC, TOSOH CCPE and UV-8000 uv detector, was conducted on a Develosil pack ODS-5 column (4.6 x 250 mm) and the eluent of MeOH-H₂O (60 : 40)

was pumped at 1.0 ml/min. Preparative HPLC was carried on a Develosil pack ODS-10 column (20 x 250 mm) using the same solvent.

Oxidation of 1 and 2 with Ph₂SeO (Formation of 6a, 7a, 8a, and 9a)—A mixture of 1 (400 mg) and Ph₂SeO (814 mg) in MeOH (15 ml) and benzene (15 ml) was stirred at room temperature for 10 min and a solution of 3 (480 mg) in MeOH (5 ml) was added dropwise and then the reaction mixture was continued stirring. After 30 min, the reaction mixture was evaporated to give a brownish oil, which was acetylated with Ac₂O (2 ml) and pyridine (2 ml) at room temperature for 2 h. The reaction mixture was poured into ice-water and then extracted with AcOEt. The AcOEt layer was washed with water, dried over Na₂SO₄, and evaporated. The residue obtained was purified by column chromatography on a silica gel with CHCl₃-acetone (20 : 1) to yield a solid. The solid was recrystallized from benzene to afford 6a (356 mg). The mother liquor (320 mg) was rechromatographed on a silica gel column with CHCl₃-acetone (20 : 1) to yield three fractions. Following repeated HPLC of a small amount of each fraction provided 6a, 7a, 8a, and 9a.

Cleomiscosin A Diacetate (6a): Colorless prisms. mp 176-177°C. (lit.,^{1a} mp 180-181°C). Analytical HPLC, \underline{t}_R 12.5 min. Ms $\underline{m/z}$: 470(M⁺), 428, 368, 353, 291, 223, 222, 219, 180, 179, 162, 161, 147. Ir (CHCl₃): 1760, 1730, 1610, 1580 cm⁻¹. ¹H-Nmr (CDCl₃) δ : 2.06, 2.32 (6H, 2 x s, 2 x OAc), 3.85, 3.89 (6H, 2 x s, 2 x OCH₃), 4.11 (1H, dd, J=5.7, 13.1 Hz, 9'-H), 4.40 (2H, m, 8'-H and 9'-H), 5.05 (1H, d, J=7.1 Hz, 7'-H), 6.33 (1H, d, J=9.4 Hz, 3-H); 6.55 (1H, s, 5-H), 6.99 (1H, d, J=1.7 Hz, 2'-H), 6.99 (1H, dd, J=1.7, 8.1 Hz, 6'-H), 7.08 (1H, d, J=8.1 Hz, 5'-H), 7.61 (1H, d, J=9.4 Hz, 4-H). This compound was identical with an authentic sample^{1a} by mixed melting point, direct comparison of various spectra, and retention time in HPLC.

Cleomiscosin B Diacetate (7a): Amorphous powder. Analytical HPLC, \underline{t}_R 11.5 min. High-resolution ms $\underline{m/z}$: 470.1211 Calcd for C₂₄H₂₂O₁₀(M⁺). Found: 470.1215. Ms $\underline{m/z}$: 470(M⁺), 428, 368, 353, 291, 223, 222, 219, 180, 179, 162, 161, 147. Ir (CHCl₃): 1760, 1730, 1610, 1580 cm⁻¹. ¹H-Nmr (CDCl₃) δ : 2.06, 2.32 (6H, 2 x s, 2 x OAc), 3.85, 3.92 (6H, 2 x s, 2 x OCH₃), 4.13 (1H, dd, J=5.7, 13.1 Hz, 9'-H), 4.43 (2H, m, 8'-H and 9'-H), 5.05 (1H, d, J=7.1 Hz, 7'-H), 6.31 (1H, d, J=9.4 Hz, 3-H), 6.56 (1H, s, 5-H), 6.99 (1H, dd, J=1.7, 8.1 Hz, 6'-H), 7.01 (1H, d, J=1.7 Hz, 2'-H), 7.08 (1H, d, J=8.1 Hz, 5'-H), 7.60 (1H, d, J=9.4 Hz, 4-H).

8a (or 9a): Amorphous powder. Analytical HPLC, \underline{t}_R 12.4 min. High-resolution ms $\underline{m/z}$: 470.1211 Calcd for C₂₄H₂₂O₁₀(M⁺). Found: 470.1245. Ms $\underline{m/z}$: 470(M⁺), 428, 368, 353, 291, 223, 222, 219, 180, 179, 162, 161, 151, 147. Ir (CHCl₃): 1760, 1730, 1710, 1610, 1580 cm⁻¹. ¹H-Nmr (CDCl₃) δ : 1.99, 2.32 (6H, 2 x s, 2 x OAc), 3.86, 3.91 (6H, 2 x s, 2 x OCH₃), 4.08 (1H, dd, J=4.0, 12.1 Hz, 9'-H), 4.26 (1H, dd, J=8.1, 12.1 Hz, 9'-H), 4.87 (1H, ddd, J=2.7, 4.0, 8.1 Hz, 8'-H), 5.37 (1H, d, J=2.7 Hz, 7'-H), 6.34 (1H, d, J=9.4 Hz, 3-H), 6.57 (1H, s, 5-H), 7.04 (1H, dd, J=1.7, 8.1 Hz, 6'-H), 7.05 (1H, d, J=1.7 Hz, 2'-H), 7.09 (1H, d, J=8.1 Hz, 5'-H), 7.61 (1H, d, J=9.4 Hz, 4-H).

9a (or 8a): Amorphous powder. Analytical HPLC, \underline{t}_R 11.6 min. High-resolution ms $\underline{m/z}$: 470.1211 Calcd for C₂₄H₂₂O₁₀(M⁺). Found: 470.1192. Ms $\underline{m/z}$: 470(M⁺), 428,

368, 353, 291, 223, 222, 219, 180, 179, 162, 161, 147. Ir (CHCl₃): 1760, 1730, 1610, 1580 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 1.96, 2.33 (6H, 2 x s, 2 x OAc), 3.89, 3.94 (6H, 2 x s, 2 x OCH₃), 4.09 (1H, dd, J=4.0, 12.1 Hz, 9'-H), 4.28 (1H, dd, J=8.1, 12.1 Hz, 9'-H), 4.92 (1H, ddd, J=2.7, 4.0, 8.1 Hz, 8'-H), 5.36 (1H, d, J=2.7 Hz, 7'-H), 6.34 (1H, d, J=9.4 Hz, 3-H), 6.59 (1H, s, 5-H), 7.06 (1H, dd, J=1.7, 8.1 Hz, 6'-H), 7.10 (1H, d, J=8.1 Hz, 5'-H), 7.12 (1H, d, J=1.7 Hz, 2'-H), 7.62 (1H, d, J=9.4 Hz, 4-H).

Oxidation of 1 and 4 with Ph₂SeO (Formation of 6b, 7b, 8b, and 9b)——A mixture of 1 (400 mg) and 4 (555 mg) in MeOH (20 ml) and benzene (15 ml) in the presence of Ph₂SeO (806 mg) was treated by a procedure similar to that described for 6a, giving a residue. The residue was acetylated with Ac₂O (4 ml) and pyridine (4 ml) and worked up in the usual way to afford a product. The product was recrystallized from MeOH-CHCl₃ to yield crude solid and the mother liquor. The crude solid was recrystallized again from MeOH-CHCl₃ to give 6b (346 mg), and the mother liquor was purified by column chromatography on a silica gel with CHCl₃-acetone (30 : 1) to afford an oil (97 mg). A part of the oil was subjected to repeated HPLC, yielding 6b, 7b, 8b, and 9b.

Aquillochin (Cleomiscosin C) Diacetate (6b): Colorless prisms. mp 210°C. (lit.,⁶ mp 188°C). Analytical HPLC, tR 11.2 min. High-resolution ms m/z: 500.1317 Calcd for C₂₅H₂₄O₁₁(M⁺). Found: 500.1335. Ms m/z: 500(M⁺), 458, 398, 252, 209, 178, 161, 149. Ir (CHCl₃): 1770, 1730, 1610, 1580 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 2.07, 2.34 (6H, 2 x s, 2 x OAc), 3.83 (6H, s, 2 x OCH₃), 3.90 (3H, s, OCH₃), 4.15 (1H, dd, J=5.7, 13.1 Hz, 9'-H), 4.40 (2H, m, 8'-H and 9'-H), 5.00 (1H, d, J=7.1 Hz, 7'-H), 6.34 (1H, d, J=9.4 Hz, 3-H), 6.55 (1H, s, 5-H), 6.64 (2H, s, 2'-H and 6'-H), 7.61 (1H, d, J=9.4 Hz, 4-H). This compound was identical with an acetylation product, prepared from aquillochin (6B).^{1c}

Cleomiscosin D Diacetate (7b): Colorless prisms. mp 204°C. (lit.,⁷ mp 203-205°C). Analytical HPLC, tR 10.4 min. High-resolution ms m/z: 500.1317 Calcd for C₂₅H₂₄O₁₁(M⁺). Found: 500.1306. Ms m/z: 500(M⁺), 458, 398, 252, 209, 178, 161, 149. Ir (CHCl₃): 1770, 1730, 1610, 1580 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 2.07, 2.34 (6H, 2 x s, 2 x OAc), 3.83 (6H, s, 2 x OCH₃), 3.93 (3H, s, OCH₃), 4.17 (1H, dd, J=5.7, 13.1 Hz, 9'-H), 4.44 (2H, m, 8'-H and 9'-H), 5.01 (1H, d, J=7.1 Hz, 7'-H), 6.31 (1H, d, J=9.4 Hz, 3-H), 6.56 (1H, s, 5-H), 6.66 (2H, s, 2'-H and 6'-H), 7.61 (1H, d, J=9.4 Hz, 4-H). This compound was identical with an acetylation product, prepared from cleomiscosin D (7B).^{1c}

8b (or 9b): Amorphous powder. Analytical HPLC, tR 11.9 min. High-resolution ms m/z: 500.1317 Calcd for C₂₅H₂₄O₁₁(M⁺). Found: 500.1292. Ms m/z: 500(M⁺), 458, 398, 252, 209, 178, 161, 149. Ir (CHCl₃): 1770, 1730, 1610, 1580 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 2.00, 2.34 (6H, 2 x s, 2 x OAc), 3.85 (6H, s, 2 x OCH₃), 3.92 (3H, s, OCH₃), 4.10 (1H, dd, J=4.0, 12.1 Hz, 9'-H), 4.28 (1H, dd, J=8.1, 12.1 Hz, 9'-H), 4.88 (1H, ddd, J=2.7, 4.0, 8.1 Hz, 8'-H), 5.33 (1H, d, J=2.7 Hz, 7'-H), 6.34 (1H, d, J=9.4 Hz, 3-H), 6.57 (1H, s, 5-H), 6.71 (2H, s, 2'-H and 6'-H), 7.62 (1H, d, J=9.4 Hz, 4-H).

9b (or 8b): Amorphous powder. Analytical HPLC, tR 11.3 min. High-resolution ms m/z: 500.1317 Calcd for C₂₅H₂₄O₁₁(M⁺). Found: 500.1308. Ms m/z: 500(M⁺), 458,

398, 252, 209, 178, 161, 149. Ir (CHCl₃): 1770, 1730, 1610, 1580 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 1.97, 2.35 (6H, 2 x s, 2 x OAc), 3.87 (6H, s, 2 x OCH₃), 3.94 (3H, s, OCH₃), 4.12 (1H, dd, J=4.0, 12.1 Hz, 9'-H), 4.29 (1H, dd, J=8.1, 12.1 Hz, 9'-H), 4.91 (1H, ddd, J=2.7, 4.0, 8.1 Hz, 8'-H), 5.32 (1H, d, J=2.7 Hz, 7'-H), 6.34 (1H, d, J=9.4 Hz, 3-H), 6.59 (1H, s, 5-H), 6.74 (2H, s, 2'-H and 6'-H), 7.62 (1H, d, J=9.4 Hz, 4-H).

Oxidation of 2 and 4 with Ph₂SeO (Formation of 6c)——A mixture of 2 (400 mg) and 4 (654 mg) in MeOH (20 ml) and benzene (15 ml) in the presence of Ph₂SeO (951 mg) was treated by a procedure similar to that described for 6a. The resulting oil was acetylated with Ac₂O (4 ml) and pyridine (4 ml) and worked up in the usual way to afford a brownish oil. The oil was purified by column chromatography on a silica gel with CHCl₃-acetone (30 : 1) to give a solid. The solid was recrystallized from MeOH to yield 6c (188 mg) and the mother liquor (137.3 mg) was obtained as a yellowish oil.

Daphneticin Diacetate (6c): Colorless prisms. mp 209°C. (lit.,^{1d} mp 206-208°C). High-resolution ms $\underline{m/z}$: 470.1211 Calcd for C₂₄H₂₂O₁₀(M⁺). Found: 470.1219. Ms $\underline{m/z}$: 470(M⁺), 428, 368, 367, 340, 252, 210, 209, 191. Ir (CHCl₃): 1770, 1740, 1620, 1500 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 2.07, 2.35 (6H, 2 x s, 2 x OAc), 3.84 (6H, s, 2 x OCH₃), 4.15 (1H, dd, J=3.4, 12.1 Hz, 9'-H), 4.37 (1H, ddd, J=3.4, 3.4, 7.7 Hz, 8'-H), 4.42 (1H, dd, J=3.4, 12.1 Hz, 9'-H), 5.00 (1H, d, J=7.7 Hz, 7'-H), 6.31 (1H, d, J=9.4 Hz, 3-H), 6.63 (2H, s, 2'-H and 6'-H), 6.92 (1H, d, J=8.7 Hz, 6-H), 7.02 (1H, d, J=8.7 Hz, 5-H), 7.65 (1H, d, J=9.4 Hz, 4-H). This compound was identical with an authentic sample^{1d} in all respects.

Oxidation of 1 and 5 with Ph₂SeO (Formation of 6d, 7d, 8d, and 9d)——A mixture of 1 (400 mg) and 5 (442 mg) in MeOH (20 ml) and benzene (15 ml) in the presence of Ph₂SeO (814 mg) was treated by a procedure similar to that described for 6a, yielding an oil. Acetylation of the oil with Ac₂O (6 ml) and pyridine (6 ml) gave a crude solid, which was recrystallized from MeOH and benzene to afford 6d (432 mg). The mother liquor was purified by column chromatography on a silica gel with CHCl₃-acetone (20 : 1) affording an amorphous (403 mg), a part of which was chromatographed on a silica gel column with AcOEt-n-hexane (2 : 1) to provide three fractions. Each eluted fraction was further subjected to preparative HPLC, giving 6d, 7d, 8d, and 9d.

Propacin Acetate (6d): Colorless prisms. mp 214-215°C (from MeOH). (lit.,^{1e} mp 203-204°C (from EtOH)). Analytical HPLC, $\underline{t_R}$ 16.6 min. Ms $\underline{m/z}$: 412(M⁺), 370, 328, 327, 295, 233, 219, 206, 164, 149. Ir (CHCl₃): 1760, 1720, 1610 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 1.32 (3H, d, J=6.4 Hz, 9'-H), 2.32 (3H, s, OAc), 3.86, 3.88 (6H, 2 x s, 2 x OCH₃), 4.22 (1H, dq, J=8.1, 6.4 Hz, 8'-H), 4.72 (1H, d, J=8.1 Hz, 7'-H), 6.31 (1H, d, J=9.4 Hz, 3-H), 6.52 (1H, s, 5-H), 6.98 (1H, d, J=1.7 Hz, 2'-H), 6.98 (1H, dd, J=1.7, 8.1 Hz, 6'-H), 7.08 (1H, d, J=8.1 Hz, 5'-H), 7.61 (1H, d, J=9.4 Hz, 4-H). This compound was identical with an authentic sample^{1e} by direct comparison (various spectra and retention time in HPLC).

Regioisomer of Propacin Acetate (7d): Colorless prisms. mp 225-226°C (from MeOH). Analytical HPLC, $\underline{t_R}$ 15.8 min. High-resolution ms $\underline{m/z}$: 412.1157 Calcd for C₂₂H₂₀O₈(M⁺). Found: 412.1133. Ms $\underline{m/z}$: 412(M⁺), 370, 328, 327, 295, 233, 219,

206, 164, 149. Ir (CHCl₃): 1760, 1720, 1610 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 1.35 (3H, d, J=6.4 Hz, 9'-H), 2.33 (3H, s, OAc), 3.87, 3.93 (6H, 2 x s, 2 x OCH₃), 4.25 (1H, dq, J=8.1, 6.4 Hz, 8'-H), 4.71 (1H, d, J=8.1 Hz, 7'-H), 6.28 (1H, d, J=9.4 Hz, 3-H), 6.54 (1H, s, 5-H), 6.98 (1H, dd, J=1.7, 8.1 Hz, 6'-H), 7.01 (1H, d, J=1.7 Hz, 2'-H), 7.08 (1H, d, J=8.1 Hz, 5'-H), 7.60 (1H, d, J=9.4 Hz, 4-H). This compound was identical with a product acetylated from regioisomer of propacin (7D).^{1e}

cis Propacin Acetate (8d): Colorless oil. Analytical HPLC, *t*_R 15.5 min. High-resolution ms *m/z*: 412.1157 Calcd for C₂₂H₂₀O₈(M⁺). Found: 412.1153. Ms *m/z*: 412(M⁺), 370, 328, 327, 295, 233, 219, 206, 164, 149. Ir (CHCl₃): 1760, 1720, 1605 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 1.23 (3H, d, J=6.4 Hz, 9'-H), 2.32 (3H, s, OAc), 3.84, 3.91 (6H, 2 x s, 2 x OCH₃), 4.72 (1H, dq, J=2.7, 6.4 Hz, 8'-H), 5.26 (1H, d, J=2.7 Hz, 7'-H), 6.36 (1H, d, J=9.4 Hz, 3-H), 6.56 (1H, s, 5-H), 7.02 (1H, dd, J=1.7, 8.1 Hz, 6'-H), 7.04 (1H, d, J=1.7 Hz, 2'-H), 7.08 (1H, d, J=8.1 Hz, 5'-H), 7.62 (1H, d, J=9.4 Hz, 4-H).

cis Regioisomer of Propacin Acetate (9d): Colorless oil. Analytical HPLC, *t*_R 14.7 min. High-resolution ms *m/z*: 412.1157 Calcd for C₂₂H₂₀O₈(M⁺). Found: 412.1152. Ms *m/z*: 412(M⁺), 370, 328, 327, 295, 233, 219, 206, 164, 149. Ir (CHCl₃): 1760, 1720, 1610 cm⁻¹. ¹H-Nmr (CDCl₃) δ: 1.22 (3H, d, J=6.4 Hz, 9'-H), 2.33 (3H, s, OAc), 3.88, 3.94 (6H, 2 x s, 2 x OCH₃), 4.79 (1H, dq, J=2.7, 6.4 Hz, 8'-H), 5.25 (1H, d, J=2.7 Hz, 7'-H), 6.32 (1H, d, J=9.4 Hz, 3-H), 6.57 (1H, s, 5-H), 7.02 (1H, dd, J=1.7, 8.1 Hz, 6'-H), 7.09 (1H, d, J=1.7 Hz, 2'-H), 7.09 (1H, d, J=8.1 Hz, 5'-H), 7.61 (1H, d, J=9.4 Hz, 4-H). This compound was identical with a product acetylated from the known material (9D).^{1e}

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