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

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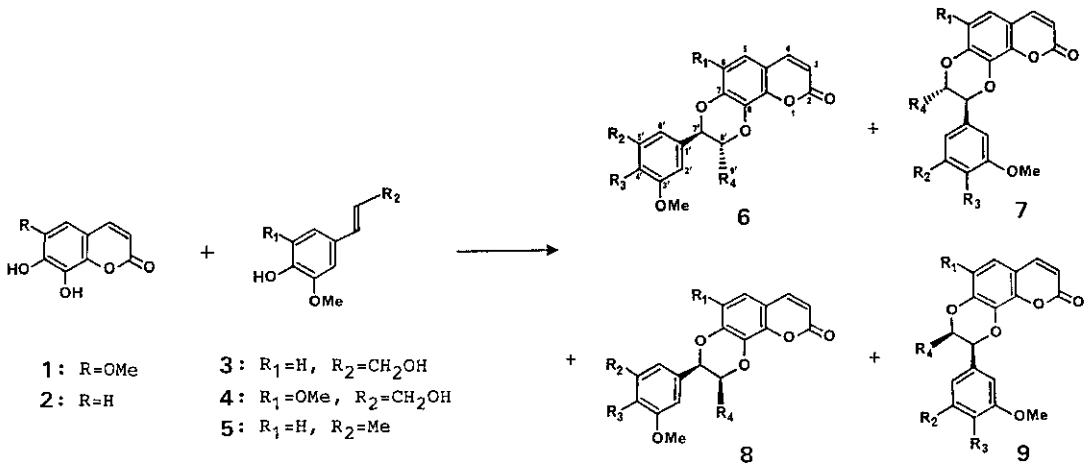
Abstract——Oxidative coupling of 7,8-dihydroxycoumarins (1, 2) and phenylpropenes (3-5) using Ph_2SeO as oxidizing agent resulted in remarkably efficient synthesis of naturally occurring coumarinolignans (cleomiscosin A (**6A**), aquillochin (cleomiscosin C)(**6B**), daphneticin (**6C**), and propacin (**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 Ag_2O, 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 Ag_2O as oxidizing agent, is convenient, yields of the coumarinolignans were not satisfactory (poor yield). And we choose diphenyl selenoxide (Ph_2SeO) as oxidizing agent of phenolic hydroxyl groups, because Ph_2SeO is very effective[5] for oxidation of catechols to *ortho* quinones (no effect on simple phenols) without over-oxidation.
Herein, we wish to report an application of Ph_2SeO 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 Ph_2SeO 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: R_1=OMe, R_2=H, R_3=OH, R_4=CH_2OH
a: R_1=OMe, R_2=H, R_3=OAc, R_4=CH_2OAc
B: R_1=R_2=OMe, R_3=OH, R_4=CH_2OH
b: R_1=R_2=OMe, R_3=OAc, R_4=CH_2OAc
C: R_1=H, R_2=OMe, R_3=OH, R_4=CH_2OH
c: R_1=H, R_2=OMe, R_3=OAc, R_4=CH_2OAc
D: R_1=OMe, R_2=H, R_3=OH, R_4=CH_3
d: R_1=OMe, R_2=H, R_3=OAc, R_4=CH_3

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 ^{1}H-nmr spectra). The spectral data (ir, mass, and ^{1}H-nmr) of **7a** are closely similar to those of **6a**. The ^{1}H-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 ^{1}H-nmr), and also indicated similar spectral data (ir and mass) except for the ^{1}H-

nmr spectra in comparison with that of **6a**. In the ^{1}H-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[1c] (**6B** and **7B**). The remaining two compounds (**8b, 9b**) showed spectral data (ir and mass spectra) similar to **6b**. However, in the ^{1}H-nmr spectra, the two compounds (**8b, 9b**) revealed doublet signals (J=2.7 Hz) of $C_{7'}$-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**)[1d] 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,[1e] and the structures of **7d** and **9d** were also established by direct comparison with the acetylation products of the known materials[1e] (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 ^{1}H-nmr). And the ^{1}H-nmr spectrum of **8d** displayed a doublet signal of $C_{7'}$-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 Ph_2SeO

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 Ag_2O; data from Lin and Cordell.[2b]
d) Reaction carried out in the presence of Ag_2O; data from Merlini.[2a]

Thus, the oxidative coupling of 7,8-dihydroxycoumarins (**1**, **2**) and phenylpropenes (**3-5**) with Ph_2SeO afforded four kinds of coumarinolignans (**6-9**), among which isomer **6** of coumarinolignans was obtained in fairly good yields, as compared to the aforementioned Ag_2O 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 Ph_2SeO, hydroxyl groups in 7,8-dihydroxycoumarins (**1**, **2**) would be rapidly oxidized to generate the corresponding ortho guinones, 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 F_{254} (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. ^{1}H-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-H_2O (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 Ph_2SeO (Formation of 6a, 7a, 8a, and 9a)———A mixture of **1** (400 mg) and Ph_2SeO (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 Ac_2O (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 Na_2SO_4, and evaporated. The residue obtained was purified by column chromatography on a silica gel with $CHCl_3$-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 $CHCl_3$-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, tR 12.5 min. Ms m/z: 470(M^+), 428, 368, 353, 291, 223, 222, 219, 180, 179, 162, 161, 147. Ir ($CHCl_3$): 1760, 1730, 1610, 1580 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.06, 2.32 (6H, 2 x s, 2 x OAc), 3.85, 3.89 (6H, 2 x s, 2 x OCH_3), 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, tR 11.5 min. High-resolution ms m/z: 470.1211 Calcd for $C_{24}H_{22}O_{10}$(M^+). Found: 470.1215. Ms m/z: 470(M^+), 428, 368, 353, 291, 223, 222, 219, 180, 179, 162, 161, 147. Ir ($CHCl_3$): 1760, 1730, 1610, 1580 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.06, 2.32 (6H, 2 x s, 2 x OAc), 3.85, 3.92 (6H, 2 x s, 2 x OCH_3), 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, tR 12.4 min. High-resolution ms m/z: 470.1211 Calcd for $C_{24}H_{22}O_{10}$(M^+). Found: 470.1245. Ms m/z: 470(M^+), 428, 368, 353, 291, 223, 222, 219, 180, 179, 162, 161, 151, 147. Ir ($CHCl_3$): 1760, 1730, 1710, 1610, 1580 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.99, 2.32 (6H, 2 x s, 2 x OAc), 3.86, 3.91 (6H, 2 x s, 2 x OCH_3), 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, tR 11.6 min. High-resolution ms m/z: 470.1211 Calcd for $C_{24}H_{22}O_{10}$(M^+). Found: 470.1192. Ms m/z: 470(M^+), 428,

368, 353, 291, 223, 222, 219, 180, 179, 162, 161, 147. Ir ($CHCl_3$): 1760, 1730, 1610, 1580 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.96, 2.33 (6H, 2 x s, 2 x OAc), 3.89, 3.94 (6H, 2 x s, 2 x OCH_3), 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 Ph_2SeO (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 Ph_2SeO (806 mg) was treated by a procedure similar to that described for **6a**, giving a residue. The residue was acetylated with Ac_2O (4 ml) and pyridine (4 ml) and worked up in the usual way to afford a product. The product was recrystallized from MeOH-$CHCl_3$ to yield crude solid and the mother liquor. The crude solid was recrystallized again from MeOH-$CHCl_3$ to give **6b** (346 mg), and the mother liquor was purified by column chromatography on a silica gel with $CHCl_3$-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 $C_{25}H_{24}O_{11}(M^+)$. Found: 500.1335. Ms m/z: 500(M^+), 458, 398, 252, 209, 178, 161, 149. Ir ($CHCl_3$): 1770, 1730, 1610, 1580 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.07, 2.34 (6H, 2 x s, 2 x OAc), 3.83 (6H, s, 2 x OCH_3), 3.90 (3H, s, OCH_3), 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 $C_{25}H_{24}O_{11}(M^+)$. Found: 500.1306. Ms m/z: 500(M^+), 458, 398, 252, 209, 178, 161, 149. Ir ($CHCl_3$): 1770, 1730, 1610, 1580 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.07, 2.34 (6H, 2 x s, 2 x OAc), 3.83 (6H, s, 2 x OCH_3), 3.93 (3H, s, OCH_3), 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 $C_{25}H_{24}O_{11}(M^+)$. Found: 500.1292. Ms m/z: 500(M^+), 458, 398, 252, 209, 178, 161, 149. Ir ($CHCl_3$): 1770, 1730, 1610, 1580 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.00, 2.34 (6H, 2 x s, 2 x OAc), 3.85 (6H, s, 2 x OCH_3), 3.92 (3H, s, OCH_3), 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 $C_{25}H_{24}O_{11}(M^+)$. Found: 500.1308. Ms m/z: 500(M^+), 458,

398, 252, 209, 178, 161, 149. Ir ($CHCl_3$): 1770, 1730, 1610, 1580 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.97, 2.35 (6H, 2 x s, 2 x OAc), 3.87 (6H, s, 2 x OCH_3), 3.94 (3H, s, OCH_3), 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 Ph_2SeO (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 Ph_2SeO (951 mg) was treated by a procedure similar to that described for **6a**. The resulting oil was acetylated with Ac_2O (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 $CHCl_3$-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 m/z: 470.1211 Calcd for $C_{24}H_{22}O_{10}(M^+)$. Found: 470.1219. Ms m/z: 470(M^+), 428, 368, 367, 340, 252, 210, 209, 191. Ir ($CHCl_3$): 1770, 1740, 1620, 1500 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.07, 2.35 (6H, 2 x s, 2 x OAc), 3.84 (6H, s, 2 x OCH_3), 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 Ph_2SeO (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 Ph_2SeO (814 mg) was treated by a procedure similar to that described for **6a**, yielding an oil. Acetylation of the oil with Ac_2O (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 $CHCl_3$-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, tR 16.6 min. Ms m/z: 412(M^+), 370, 328, 327, 295, 233, 219, 206, 164, 149. Ir ($CHCl_3$): 1760, 1720, 1610 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) 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 OCH_3), 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, tR 15.8 min. High-resolution ms m/z: 412.1157 Calcd for $C_{22}H_{20}O_8(M^+)$. Found: 412.1133. Ms m/z: 412(M^+), 370, 328, 327, 295, 233, 219,

206, 164, 149. Ir ($CHCl_3$): 1760, 1720, 1610 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) 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 OCH_3), 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, tR 15.5 min. High-resolution ms m/z: 412.1157 Calcd for $C_{22}H_{20}O_8(M^+)$. Found: 412.1153. Ms m/z: 412(M^+), 370, 328, 327, 295, 233, 219, 206, 164, 149. Ir ($CHCl_3$): 1760, 1720, 1605 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) 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 OCH_3), 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, tR 14.7 min. High-resolution ms m/z: 412.1157 Calcd for $C_{22}H_{20}O_8(M^+)$. Found: 412.1152. Ms m/z: 412(M^+), 370, 328, 327, 295, 233, 219, 206, 164, 149. Ir ($CHCl_3$): 1760, 1720, 1610 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) 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 OCH_3), 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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