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Total Synthesis of Coumarinolignans, Propacin and Its Regioisomer

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Compound **8** was reacted with **7** in the presence of potassium *tert*-butoxide to give the condensation product (**9**), which was reduced with lithium borohydride to afford a mixture of alcohols (**10a, b**). The alcohols underwent cyclization with concentrated hydrochloric acid to furnish propacin (**1**). Its regioisomer (**3**) was also synthesized from the condensation product (**13**) through a similar route.

Keywords——*Protium opacum*; coumarinolignoid; propacin; coumarin; fraxetin; benzodioxane

Comarinolignoids (propacin,[1a] cleomiscosin A,[1b-e] cleomiscosin B,[1b,c,e] daphneticin,[1f] and aquillochin[1e,g]) are a new class of natural products. These materials possess a novel skeleton in which a phenylpropane unit is linked to a coumarin nucleus through a dioxane bridge. These substances are interesting because of their cytotoxic and antihepatotoxic activities, and we have reported facile syntheses of cleomiscosin A,[2] cleomiscosin B,[3] and daphneticin.[4] Propacin (**1**), having no optical activity (racemic compound), was isolated[1a] from powdered trunk wood of *Protium opacum* (Burseraceae). The synthesis of propacin have been achieved in low yield, along with the formation of the regioisomer (**3**), by treatment of fraxetin and isoeugenol under oxidative reaction conditions (horseradish peroxidase,[5] 2,3-dichloro-5,6-dicyanobenzoquinone,[5] and silver oxide[6]).

Here, we wish to describe an effective synthesis of propacin from readily available materials (7-methoxymethylfraxetin (**8**) and 1-(4-benzyloxy-3-methoxyphenyl)-2-bromo-1-propanone (**7**)) and further to report the synthesis of the regioisomer (**3**).

The starting material (**7**) was synthesized as follows. On treatment with *N*-bromoacetamide in aqueous perchloric acid, isobenzyleugenol (**5**)[7] was converted to the corresponding bromohydrin (**6**), which was oxidized with active manganese dioxide in dichloromethane to give the expected compound (**7**).[8] Next, **7** was reacted with **8**, prepared[2] previously in this laboratory, in acetonitrile in the presence of potassium *tert*-butoxide to give a condensation product (**9**) in 51% yield. Reduction of the condensation product with lithium borohydride in tetrahydrofuran (THF) afforded a mixture of alcohols (**10a, b**), which was easily separated by preparative thin layer chromatography (TLC), giving **10a** as a main product and **10b** as a minor product. The infrared (IR) spectra of **10a, b** showed a hydroxyl band (3480 and 3500 cm^{-1}, respectively). In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **10a**, the methine proton at the C-7′ position was observed as a doublet at δ 4.71 (J=7.4 Hz) and the same proton in the spectrum of **10b** appeared as a doublet at δ 4.93 (J=3.0 Hz). It is well-known[9] that the vicinal coupling constant of the *threo* form is larger than that of the *erythro* form. Consequently, the signal at δ 4.71 was attributed to the *threo* isomer (**10a**) and **10b** was assigned as the *erythro* isomer. The mixture of **10a, b** cyclized upon heating in acetic acid in the presence of concentrated hydrochloric acid, *via* a quinone methide intermediate[3]

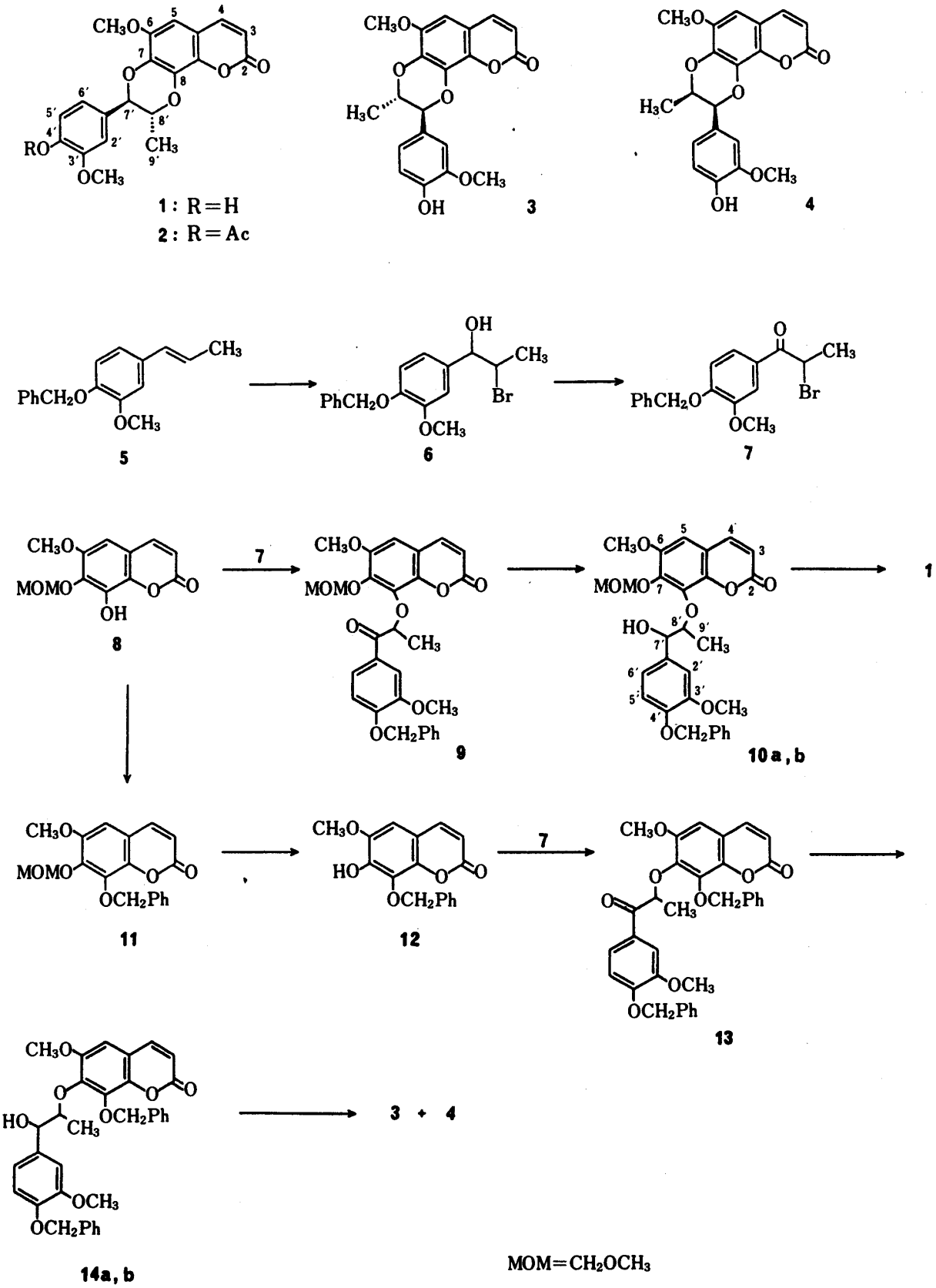

Chart 1

such as that involved in the synthesis of cleomiscosin B, to give propacin (**1**). The mass spectrum (MS) showed the characteristic fragment peak[1a] at *m/z* 164 due to the retro Diels–Alder reaction of the benzodioxane moiety. In the ^{1}H-NMR spectrum, the signal of the proton at the C-7′ position was observed as a doublet at δ 4.76 whose coupling constant (J=8.1 Hz) was typical for *trans*-orientation of the benzodioxane moiety. The synthetic propacin (**1**) was identical with an authentic specimen[6] by direct comparison of ^{1}H-NMR, ^{13}C-nuclear magnetic resonance (^{13}C-NMR), MS, and IR (KBr) spectra.

We also aimed at the synthesis of the regioisomer (**3**) of propacin according to the method described above.

The starting material (**12**) was readily prepared by benzylation of **8** followed by treatment with hydrochloric acid. Reaction of **12** with **7** in the presence of potassium *tert*-butoxide provided the condensation product (**13**) in 47% yield. The condensation product was reduced with lithium borohydride in THF to give alcohols (**14a, b**), which were separated by preparative TLC to afford the more-polar substance (**14a**) and the less-polar substance (**14b**), which were characterized spectroscopically. The high-resolution MS of the alcohols (**14a, b**) gave the molecular formula $C_{34}H_{32}O_8$ and the ^{1}H-NMR, MS, and IR spectra supported the structures (**14a, b**). In the ^{1}H-NMR spectrum of **14a**, the methine proton at the C-7′ position appeared as a doublet at δ 4.58 whose coupling constant was 7.7 Hz. On the other hand, the coupling constant of the doublet due to the C-7′ proton (δ 4.75) was 2.4 Hz in the case of **14b**. Hence, the alcohol (**14a**) was concluded to be the *threo* isomer and **14b**, the *erythro* isomer.

Finally, the alcohols (**14a, b**) were treated with concentrated hydrochloric acid in acetic acid at 60 °C for 30 min to furnish the regioisomer (**3**) of propacin and the *cis*-isomer (**4**).

The spectra (IR, MS, and ^{1}H-NMR) of the regioisomer (**3**) were closely similar to those of propacin (**1**). Namely, the MS of **3** showed the retro Diels–Alder fragmentation peak at *m/z* 164 and, in the ^{1}H-NMR spectrum, the C-7′ proton signal was observed as a doublet at δ 4.75 with J=8.1 Hz in accordance with the *trans*-orientation of the substituents on the dioxane nucleus. However, comparison of the ^{13}C-NMR spectrum of **3** with that of propacin (**1**) showed the small differences in the chemical shift values. The IR and MS spectra of the *cis*-isomer (**4**) were also similar to those of the regioisomer (**3**). However, in the ^{1}H-NMR spectrum, the C-7′ proton signal was observed as a doublet at δ 5.21 (J=2.7 Hz), demonstrating that the two hydrogens are *cis*-oriented. Therefore, this compound is represented by the formula (**4**).

We postulate the mechanism of the cyclization reaction to be as follows. On treatment of the alcohols (**14a, b**) with hydrochloric acid, the hydroxyl group at the C-7′ position was removed to give a cation (C-7′ position) and simultaneous elimination of the benzyl group (C-8 position) left a hydroxyl group (C-8 position) which can attack the cation (C-7′ position) from both α- and β- faces of the coumarin nucleus to afford a mixture of the *trans*-isomer (**3**) and the *cis*-isomer (**4**) (*SN*1-like reaction).

Thus, we have achieved syntheses of propacin (**1**) and the regioisomer (**3**).

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 and ^{13}C-NMR spectra on a JEOL JNM-FX-100, with tetramethylsilane as an internal standard. Chemical shifts are quoted in parts per million (s=singlet, d=doublet, dd=doublet-of-doublets, dq=doublet-of-quartets, t=triplet, q=quartet, m=multiplet, br=broad).

1-(4-Benzyloxy-3-methoxyphenyl)-2-bromo-1-propanol (6)——A solution of 14% aqueous $HClO_4$ (5.0 ml) was added to a mixture of isobenzyleugenol (**5**)[7] (2.0 g) in dioxane (30 ml) and ice-water (4.0 ml), and then *N*-bromo-

acetamide (1.1 g) was added portionwise to the stirred mixture at 0 °C over 1 h. A solution of 1% sodium dithionate (40 ml) was added to the reaction mixture, which was poured into ice-water and extracted with Et_2O. The Et_2O layer was washed with 5% sodium bicarbonate and brine, dried over Na_2SO_4, and evaporated to give a yellow oil. The oil was purified by column chromatography on a silica gel (benzene–AcOEt (10 : 1)) to give a colorless oil (**6**) (2.53 g, 92%). High-resolution MS *m/z*: 352.0497 Calcd for $C_{17}H_{19}{}^{81}BrO_3$ ($M^+ + 2$). Found: 352.0505. High-resolution MS *m/z*: 350.0516 Calcd for $C_{17}H_{19}{}^{79}BrO_3$ (M^+). Found: 350.0495. ^{1}H-NMR ($CDCl_3$) δ: 1.55 (3H, d, J=6.4 Hz, C_9-H), 2.81 (1H, brs, OH), 3.86 (3H, s, OCH_3), 4.35 (1H, dq, J=3.7, 6.4 Hz, C_8-H), 4.87 (1H, d, J=3.7 Hz, C_7-H), 5.12 (2H, s, OCH_2Ph), 6.79 (1H, dd, J=1.7, 8.1 Hz, C_6-H), 6.85 (1H, d, J=8.1 Hz, C_5-H), 6.94 (1H, d, J=1.7 Hz, C_2-H), 7.26—7.46 (5H, m, aromatic protons).

1-(4-Benzyloxy-3-methoxyphenyl)-2-bromo-1-propanone (7)——Active MnO_2 (2.24 g) was added gradually to a solution of **6** (320 mg) in dry CH_2Cl_2 (50 ml), and the mixture was stirred at room temperature for 30 min. The reaction mixture was filtered off and the filtrate was evaporated to dryness. The crude product was recrystallized from EtOH to give colorless prisms (**7**) (230 mg, 72%). mp 87—88 °C (lit.[8] mp 86—87 °C). ^{1}H-NMR ($CDCl_3$) δ: 1.88 (3H, d, J=6.4 Hz, C_9-H), 3.95 (3H, s, OCH_3), 5.24 (2H, s, OCH_2Ph), 5.26 (1H, q, J=6.4 Hz, C_8-H), 6.91 (1H, d, J=8.1 Hz, C_5-H), 7.32—7.46 (5H, brs, aromatic protons), 7.58 (1H, dd, J=1.7, 8.1 Hz, C_6-H), 7.60 (1H, d, J=1.7 Hz, C_2-H).

Condensation of 7 with 8 (Formation of 9)——A solution of **7** (83 mg) in acetonitrile (3.0 ml) was added dropwise to a mixture of **8**[2] (50 mg) and *tert*-BuOK (67 mg) in acetonitrile (3.0 ml). The mixture was stirred for 30 min at room temperature, then poured into ice-water and extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated. The residue was purified by preparative TLC ($CHCl_3$–acetone (10 : 1)) to give a colorless oil (**9**) (52.4 mg, 51%). High-resolution MS *m/z*: 520.1731 Calcd for $C_{29}H_{28}O_9$ (M^+). Found: 520.1713. MS *m/z*: 520 (M^+), 488, 429, 397, 368, 313, 285, 282, 258, 241, 195. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1680, 1600, 1560. ^{1}H-NMR ($CDCl_3$) δ: 1.62 (3H, d, J=6.4 Hz, $C_{9'}$-H), 3.53 (3H, s, OCH_2OCH_3), 3.86 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 5.21 (1H, d, J=5.7 Hz, OCH_2OCH_3), 5.22 (2H, s, OCH_2Ph), 5.27 (1H, d, J=5.7 Hz, OCH_2OCH_3), 6.01 (1H, q, J=6.4 Hz, $C_{8'}$-H), 6.29 (1H, d, J=9.4 Hz, C_3-H), 6.66 (1H, s, C_5-H), 6.93 (1H, d, J=8.1 Hz, $C_{5'}$-H), 7.30—7.45 (5H, m, aromatic protons), 7.58 (1H, d, J=9.4 Hz, C_4-H), 7.66 (1H, d, J=1.7 Hz, $C_{2'}$-H), 7.77 (1H, dd, J=1.7, 8.1 Hz, $C_{6'}$-H).

Reduction of 9 with Lithium Borohydride (Formation of 10a, b)——A suspension of $LiBH_4$ (3 mg) in dry THF (2.0 ml) was added dropwise to a solution of **9** (50 mg) in dry THF (2.0 ml) at 0 °C, and stirred for 10 min at the same temperature under a nitrogen atmosphere. The reaction mixture was poured into ice-water, and extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated. The residual product was separated by preparative TLC (benzene–AcOEt (3 : 1)) to give **10a** (46.8 mg, 93%) and **10b** (2.9 mg, 6%).

10a: A colorless oil. TLC (silica gel, benzene–AcOEt (1 : 1), Rf=0.49). High-resolution MS *m/z*: 522.1887 Calcd for $C_{29}H_{30}O_9$ (M^+). Found: 522.1884. MS *m/z*: 522 (M^+), 460, 369, 270, 265, 254, 235, 163. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480, 1725, 1610. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6.4 Hz, $C_{9'}$-H), 3.63 (3H, s, OCH_2OCH_3), 3.86 (6H, s, 2 × OCH_3), 4.21 (1H, brs, OH), 4.49 (1H, dq, J=6.4, 7.4 Hz, $C_{8'}$-H), 4.71 (1H, d, J=7.4 Hz, $C_{7'}$-H), 5.12 (2H, s, OCH_2Ph), 5.22 (1H, d, J=5.7 Hz, OCH_2OCH_3), 5.28 (1H, d, J=5.7 Hz, OCH_2OCH_3), 6.33 (1H, d, J=9.4 Hz, C_3-H), 6.65 (1H, s, C_5-H), 6.78 (1H, d, J=8.1 Hz, $C_{5'}$-H), 6.82 (1H, dd, J=1.7, 8.1 Hz, $C_{6'}$-H), 6.93 (1H, d, J=1.7 Hz, $C_{2'}$-H), 7.25—7.44 (5H, m, aromatic protons), 7.57 (1H, d, J=9.4 Hz, C_4-H).

10b: A colorless oil. TLC (silica gel, benzene–AcOEt (1 : 1), Rf=0.53). High-resolution MS *m/z*: 522.1887 Calcd for $C_{29}H_{30}O_9$ (M^+). Found: 522.1872. MS *m/z*: 522 (M^+), 460, 369, 270, 265, 254, 235, 163. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1725, 1610. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=6.4 Hz, $C_{9'}$-H), 3.63 (3H, s, OCH_2OCH_3), 3.89 (3H, s, OCH_3), 3.90 (3H, s, OCH_3) 4.70 (1H, dq, J=3.0, 6.4 Hz, $C_{8'}$-H), 4.93 (1H, d, J=3.0 Hz, $C_{7'}$-H), 5.12 (2H, s, OCH_2Ph), 5.22 (1H, d, J=5.7 Hz, OCH_2OCH_3), 5.27 (1H, d, J=5.7 Hz, OCH_2OCH_3), 6.37 (1H, d, J=9.4 Hz, C_3-H), 6.71 (1H, s, C_5-H), 6.73 (1H, dd, J=1.7, 8.1 Hz, $C_{6'}$-H), 6.81 (1H, d, J=8.1 Hz, $C_{5'}$-H), 6.99 (1H, d, J=1.7 Hz, $C_{2'}$-H), 7.26—7.44 (5H, m, aromatic protons), 7.62 (1H, d, J=9.4 Hz, C_4-H).

Propacin (1)——A mixture of **10a, b** (389.9 mg), 35% HCl (19.5 ml), and acetic acid (19.5 ml) was heated at 60 °C for 30 min. The reaction mixture was poured into ice-water and extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel (AcOEt–hexane (1 : 1)) to afford a crude solid. The solid was recrystallized from EtOH to give colorless prisms (**1**) (39.5 mg, 14%). mp 238—241 °C (lit.[1a] mp 226—228 °C, lit.[6] mp 225—227 °C). High-resolution MS *m/z*: 370.1051 Calcd for $C_{20}H_{18}O_7$ (M^+). Found: 370.1023. MS *m/z*: 370 (M^+), 327, 295, 233, 219, 164, 149. IR ν_{max}^{KBr} cm^{-1}: 3400, 1710, 1570. ^{1}H-NMR (DMSO-d_6) δ: 1.17 (3H, d, J=6.4 Hz, $C_{9'}$-H), 3.79 (6H, s, 2 × OCH_3), 4.44 (1H, dq, J=6.4, 8.1 Hz, $C_{8'}$-H), 4.76 (1H, d, J=8.1 Hz, $C_{7'}$-H), 6.34 (1H, d, J=9.4 Hz, C_3-H), 6.82 (1H, d, J=8.1 Hz, $C_{5'}$-H), 6.88 (1H, dd, J=1.7, 8.1 Hz, $C_{6'}$-H), 6.92 (1H, s, C_5-H), 7.03 (1H, d, J=1.7 Hz, $C_{2'}$-H), 7.96 (1H, d, J=9.4 Hz, C_4-H), 9.24 (1H, s, OH). ^{13}C-NMR (DMSO-d_6) δ: 159.9 (s, C-2), 147.7 (s, C-4'), 147.3 (s, C-6), 145.1 (s, C-3'), 144.7 (d, C-4), 137.3 (s, C-7), 131.3 (s, C-8), 126.8 (s, C-1'), 120.8 (d, C-6'), 115.4 (d, C-5'), 113.1 (d, C-3), 111.9 (d, C-2'), 111.2 (s, C-10), 100.8 (d, C-5), 80.1 (d, C-7'), 73.2 (d, C-8'), 55.8 (q, OCH_3), 55.8 (q, OCH_3), 16.7 (q, C-9').

Propacin Acetate (2)——A mixture of **1** (12.3 mg), acetic anhydride (0.2 ml), and pyridine (0.2 ml) was stirred at room temperature overnight. Water was poured into the reaction mixture and the mixture was extracted with AcOEt.

The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated. The residual product was recrystallized from EtOH to give colorless prisms (**2**) (11.6 mg, 85%). mp 203—204 °C (lit.[1a] mp 202—205 °C, lit.[6] mp 200—201 °C). High-resolution MS *m/z*: 412.1157 Calcd for $C_{22}H_{20}O_8$ (M^+). Found: 412.1145. MS *m/z*: 412 (M^+), 370, 328, 233, 206, 164, 149. IR ν_{max}^{KBr} cm^{-1}: 1760, 1720, 1610. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, d, J=6.4 Hz, $C_{9'}$-H), 2.32 (3H, s, OAc), 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.22 (1H, dq, J=6.4, 8.1 Hz, $C_{8'}$-H), 4.72 (1H, d, J=8.1 Hz, $C_{7'}$-H), 6.31 (1H, d, J=9.4 Hz, C_3-H), 6.52 (1H, s, C_5-H), 6.98 (1H, d, J=1.7 Hz, $C_{2'}$-H), 6.97 (1H, dd, J=1.7, 8.1 Hz, $C_{6'}$-H), 7.08 (1H, d, J=8.1 Hz, $C_{5'}$-H), 7.60 (1H, d, J=9.4 Hz, C_4-H).

8-Benzyloxy-6-methoxy-7-methoxymethoxycoumarin (11)——A mixture of **8**[2] (203 mg), benzyl chloride (107 mg), and anhydrous K_2CO_3 (333 mg) in *N*, *N*-dimethylformamide (DMF) (6.0 ml) was heated with stirring at 130 °C for 30 min. After cooling, the reaction mixture was poured into ice-water. The precipitate was collected by filtration, and recrystallized from MeOH to give colorless needles (**11**) (220 mg, 80%). mp 106 °C. *Anal.* Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.42; H, 5.28. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3020, 1720, 1570. ^{1}H-NMR ($CDCl_3$) δ: 3.55 (3H, s, OCH_2OCH_3), 3.87 (3H, s, OCH_3), 5.22 (4H, s, OCH_2OCH_3 and OCH_2Ph), 6.32 (1H, d, J=9.4 Hz, C_3-H), 6.68 (1H, s, C_5-H), 7.31—7.56 (5H, m, aromatic protons), 7.59 (1H, d, J=9.4 Hz, C_4-H).

8-Benzyloxy-7-hydroxy-6-methoxycoumarin (12)——A solution of **11** (105 mg) in saturated HCl–MeOH (10 ml) was stirred for 30 min at room temperature. The solvent was removed to give the residue, which was taken up in AcOEt. The AcOEt solution was washed with water, dried over Na_2SO_4, and evaporated to give a crude solid. The solid was recrystallized from benzene to afford colorless needles (**12**) (91 mg, 99%). mp 131 °C. *Anal.* Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.06; H, 4.69. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520, 1730, 1580. ^{1}H-NMR ($CDCl_3$) δ: 3.90 (3H, s, OCH_3), 5.30 (2H, s, OCH_2Ph), 6.15 (1H, br s, OH), 6.27 (1H, d, J=9.4 Hz, C_3-H), 6.64 (1H, s, C_5-H), 7.31—7.52 (5H, m, aromatic protons), 7.58 (1H, d, J=9.4 Hz, C_4-H).

Condensation of 7 with 12 (Formation of 13)——A solution of **7** (155 mg) in acetonitrile (5.0 ml) was added dropwise to a mixture of **12** (120 mg) and *tert*-BuOK (135.5 mg) in acetonitrile (5.0 ml) and the mixture was stirred for 30 min. The reaction mixture was worked up by the same procedure as used in the synthesis of **9**. The resulting residue was purified by preparative TLC ($CHCl_3$–acetone (20 : 1)) to give a colorless oil (**13**) (106 mg, 47%). High-resolution MS *m/z*: 566.1939 Calcd for $C_{34}H_{30}O_8$ (M^+). Found: 566.1966. MS *m/z*: 566 (M^+), 475, 359, 331, 304, 270, 241. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3020, 1720, 1690, 1600. ^{1}H-NMR ($CDCl_3$) δ: 1.57 (3H, d, J=6.4 Hz, $C_{9'}$-H), 3.72 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 5.20 (2H, s, OCH_2Ph), 5.21 (2H, s, OCH_2Ph), 5.75 (1H, q, J=6.4 Hz, $C_{8'}$-H), 6.31 (1H, d, J=9.4 Hz, C_3-H), 6.63 (1H, s, C_5-H), 6.79 (1H, d, J=8.1 Hz, $C_{5'}$-H), 7.27—7.46 (10H, m, aromatic protons), 7.49 (1H, dd, J=1.7, 8.1 Hz, $C_{6'}$-H), 7.55 (1H, d, J=1.7 Hz, $C_{2'}$-H), 7.57 (1H, d, J=9.4 Hz, C_4-H).

Reduction of 13 with Lithium Borohydride (Formation of 14a, b)——A suspension of $LiBH_4$ (2 mg) in dry THF (1.0 ml) was added dropwise to a solution of **13** (29 mg) in dry THF (1.0 ml) at 0 °C, and stirred for 10 min at the same temperature under a nitrogen atmosphere. The reaction mixture was treated by the same procedure as used in the synthesis of **10**. The resulting product was separated by preparative TLC (benzene–AcOEt (3 : 1)) to give **14a** (14 mg, 48%) and **14b** (12.9 mg, 44%).

14a: A colorless oil. TLC (silica gel, benzene–AcOEt (1 : 1), Rf=0.59). High-resolution MS *m/z*: 568.2095 Calcd for $C_{34}H_{32}O_8$ (M^+). Found: 568.2083. MS *m/z*: 568 (M^+), 550, 460, 459, 369, 298, 270, 235, 220. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3020, 1730. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, d, J=6.4 Hz, $C_{9'}$-H), 3.83 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.28 (1H, dq, J=6.4, 7.7 Hz, $C_{8'}$-H), 4.33 (1H, br s, OH), 4.58 (1H, d, J=7.7 Hz, $C_{7'}$-H), 5.11 (2H, s, OCH_2Ph), 5.19 (1H, d, J=10.4 Hz, OCH_2Ph), 5.29 (1H, d, J=10.4 Hz, OCH_2Ph), 6.35 (1H, d, J=9.4 Hz, C_3-H), 6.68 (1H, s, C_5-H), 6.76 (1H, dd, J=1.7, 8.1 Hz, $C_{6'}$-H), 6.79 (1H, d, J=8.1 Hz, $C_{5'}$-H), 6.85 (1H, d, J=1.7 Hz, $C_{2'}$-H), 7.28—7.53 (10H, m, aromatic protons), 7.60 (1H, d, J=9.4 Hz, C_4-H).

14b: A colorless oil. TLC (silica gel, benzene–AcOEt (1 : 1), Rf=0.63). High-resolution MS *m/z*: 568.2095 Calcd for $C_{34}H_{32}O_8$ (M^+). Found: 568.2114. MS *m/z*: 568 (M^+), 550, 460, 459, 369, 298, 270, 235, 220. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3020, 1730. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, d, J=6.4 Hz, $C_{9'}$-H), 3.65 (1H, br s, OH), 3.85 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.57 (1H, dq, J=2.4, 6.4 Hz, $C_{8'}$-H), 4.75 (1H, d, J=2.4 Hz, $C_{7'}$-H), 5.11 (2H, s, OCH_2Ph), 5.21 (1H, d, J=10.4 Hz, OCH_2Ph), 5.26 (1H, d, J=10.4 Hz, OCH_2Ph), 6.38 (1H, d, J=9.4 Hz, C_3-H), 6.65 (1H, dd, J=1.7, 8.1 Hz, $C_{6'}$-H), 6.73 (1H, s, C_5-H), 6.79 (1H, d, J=8.1 Hz, $C_{5'}$-H), 6.88 (1H, d, J=1.7 Hz, $C_{2'}$-H), 7.27—7.54 (10H, m, aromatic protons), 7.63 (1H, d, J=9.4 Hz, C_4-H).

Regioisomer of Propacin (3) and Its *cis* Isomer (4)——A mixture of **14a, b** (83 mg), 35% HCl (3.0 ml) and acetic acid (3.0 ml) was heated at 60 °C for 30 min. The reaction mixture was treated by the same procedure as used for **1**. The resulting precipitate was washed with a small amount of AcOEt and recrystallized from AcOEt to give a product (**3**) (15 mg, 28%). The mother liquor (the AcOEt solution) was subjected to preparative TLC ($CHCl_3$–acetone (20 : 1)), giving a crude solid. The product was recrystallized from AcOEt to afford the product (**4**) (13 mg, 24%).

3: Colorless prisms. mp >300 °C. TLC (silica gel, $CHCl_3$–acetone (10 : 1), Rf=0.52). High-resolution MS *m/z*: 370.1051 Calcd for $C_{20}H_{18}O_7$ (M^+). Found: 370.1070. MS *m/z*: 370 (M^+), 327, 295, 233, 219, 164, 149. IR ν_{max}^{KBr} cm^{-1}: 3420, 1710, 1620, 1580. ^{1}H-NMR (DMSO-d_6) δ: 1.14 (3H, d, J=6.4 Hz, $C_{9'}$-H), 3.80 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.42 (1H, dq, J=6.4, 8.1 Hz, $C_{8'}$-H), 4.75 (1H, d, J=8.1 Hz, $C_{7'}$-H), 6.31 (1H, d, J=9.4 Hz, C_3-H), 6.84 (1H, d, J=8.1 Hz, $C_{5'}$-H), 6.90 (1H, d, J=8.1 Hz, $C_{6'}$-H), 6.93 (1H, s, C_5-H), 7.05 (1H, s, $C_{2'}$-H), 7.95 (1H, d, J=9.4 Hz, C_4-H), 9.28 (1H, br s, OH). ^{13}C-NMR (DMSO-d_6) δ: 159.8 (s, C-2), 147.7 (s, C-4'), 147.3 (s, C-6), 145.1 (s, C-3'),

144.6 (d, C-4), 136.5 (s, C-7), 132.2 (s, C-8), 126.8 (s, C-1′), 120.7 (d, C-6′), 115.4 (d, C-5′), 113.0 (d, C-3), 111.9 (d, C-2′), 111.0 (s, C-10), 101.0 (d, C-5), 79.7 (d, C-7′), 73.7 (d, C-8′), 55.8 (q, OCH_3), 55.7 (q, OCH_3), 16.7 (q, C-9′).

4: Colorless needles. mp >300 °C. TLC (silica gel, $CHCl_3$–acetone (10 : 1), Rf=0.53). High-resolution MS m/z: 370.1051 Calcd for $C_{20}H_{18}O_7$ (M^+). Found: 370.1017. MS m/z: 370 (M^+), 327, 295, 233, 219, 164, 149. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3540, 1720, 1620, 1580. ^{1}H-NMR (DMSO-d_6) δ: 1.20 (3H, d, J=6.4 Hz, $C_{9'}$-H), 3.94 (6H, s, 2×OCH_3), 4.73 (1H, dq, J=2.7, 6.4 Hz, $C_{8'}$-H), 5.21 (1H, d, J=2.7 Hz, $C_{7'}$-H), 5.70 (1H, s, OH), 6.31 (1H, d, J=9.4 Hz, C_3-H), 6.56 (1H, s, C_5-H), 6.90 (1H, dd, J=1.7, 8.1 Hz, $C_{6'}$-H), 6.94 (1H, d, J=8.1 Hz, $C_{5'}$-H), 7.00 (1H, d, J=1.7 Hz, $C_{2'}$-H), 7.61 (1H, d, J=9.4 Hz, C_4-H). ^{13}C-NMR (DMSO-d_6) δ: 159.8 (s, C-2), 147.4 (s, C-4′), 146.6 (s, C-6), 145.5 (s, C-3′), 144.7 (d, C-4), 138.0 (s, C-9), 135.5 (s, C-7), 130.9 (s, C-8), 126.5 (s, C-1′), 119.6 (d, C-6′), 115.4 (d, C-5′), 113.1 (d, C-3), 111.3 (d, C-2′), 111.3 (s, C-10), 101.3 (d, C-5), 76.4 (d, C-7′), 72.5 (d, C-8′), 55.9 (q, OCH_3), 55.7 (q, OCH_3), 13.4 (q, C-9′).

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