DEFINITE TOTAL SYNTHESIS OF COUMARINOLIGNANS, DAPHNETICIN AND ITS REGIOISOMER

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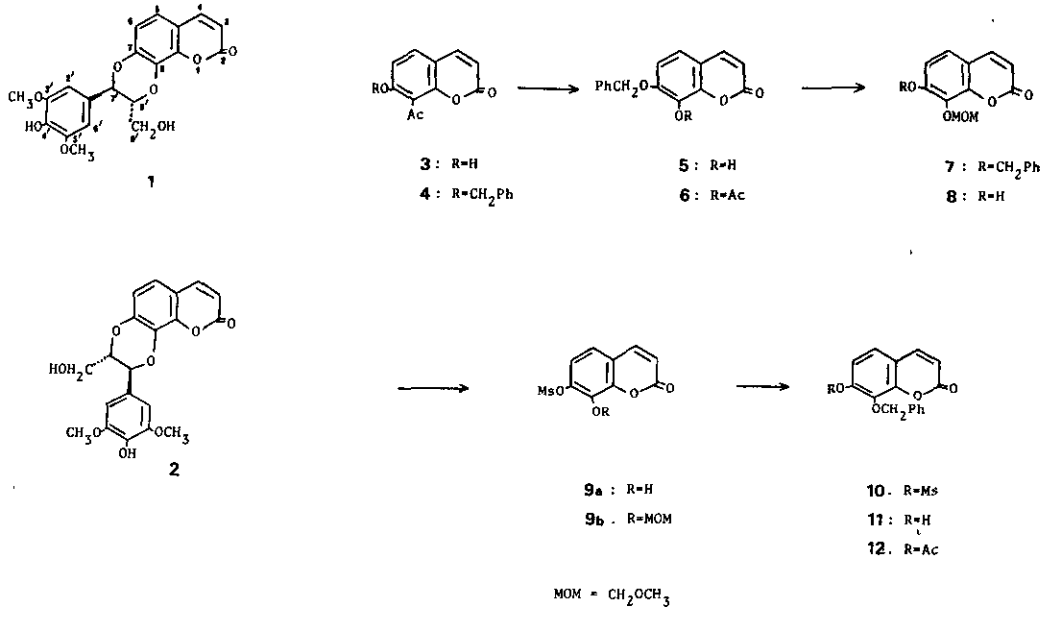
Abstract——The synthesis of 7-benzyloxy-8-hydroxycoumarin (5) and 8-benzyloxy-7-hydroxycoumarin (11) was described and further, by use of 5 as a starting material, daphneticin (1) was synthesized. On the other hand, its regioisomer (2) was also synthesized from (8), readily prepared via two steps from 5, according to the method described in the synthesis of daphneticin.

We have previously reported[1] a synthesis of a cytotoxic active compound,[2] daphneticin, which was isolated[3] from Daphne tangutica (Thymelaeaceae). In the synthesis[1] of daphneticin, 7,8-dibenzyloxycoumarin was treated with acid to give monobenzyloxycoumarin (7-benzyloxy-8-hydroxycoumarin) as a main product, which was used as a starting material. As the structure of monobenzyloxycoumarin (7-benzyloxy-8-hydroxycoumarin) was erroneously assigned[4] to that of 8-benzyloxy-7-hydroxycoumarin, we proposed the structure of daphneticin to be formula (2). However, G. A. Cordell and L-J. Lin[5] have recently published that the structure of daphneticin would be revised formula (1) by application of the selective INEPT pulse programme of the daphneticin diacetate.

Herein, we wish to report a definite synthesis of monobenzyloxycoumarins (7-benzyloxy-8-hydroxycoumarin (5) and 8-benzyloxy-7-hydroxycoumarin (11)) and further to describe a synthesis of daphneticin (1) and its regioisomer (2), respectively.

The compound (5) was prepared by benzylation of 8-acetyl-7-hydroxycoumarin (3)[6]

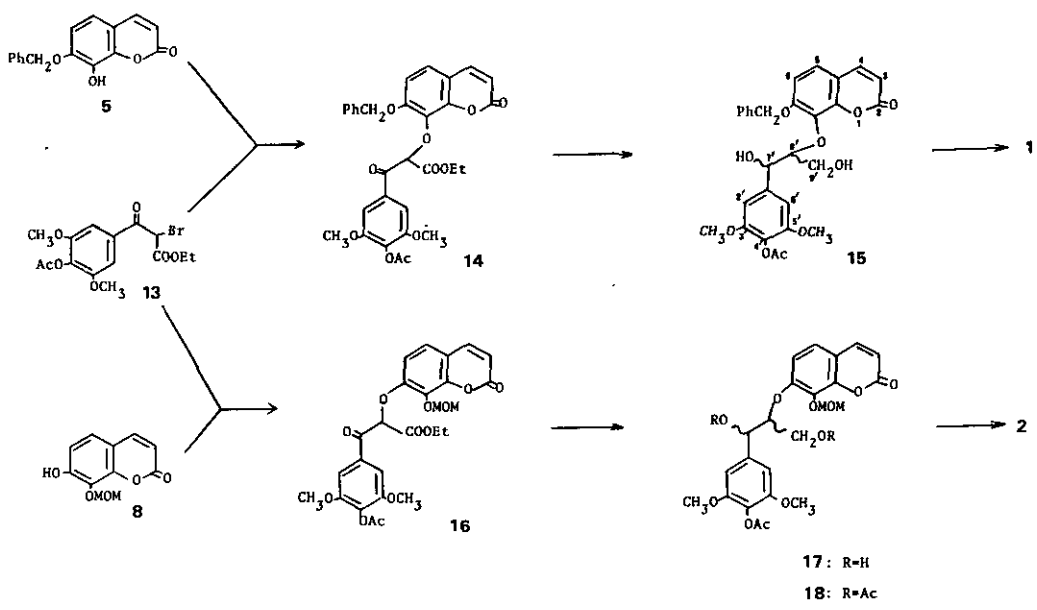
followed by treatment with hydrogen peroxide in alkaline dioxane solution (the Baeyer-Villiger reaction). On the other hand, the synthesis of the another monobenzyloxycoumarin (**11**) is as follows.



On treatment with chloromethyl methyl ether, the compound (**5**) was converted to the methoxymethyl ether (**7**) which was subjected to catalytic hydrogenation yielding a debenzylation product (**8**). Reaction of the compound (**8**) with methanesulfonyl chloride in pyridine for 15 h resulted in a mixture of a demethoxymethyl product (**9a**; main material) and a mesylated product (**9b**; minor material). Benzylation of **9a** with benzyl chloride was then transformed to a compound (**10**) and subsequent alkaline hydrolysis provided the compound (**11**). The obtained benzyloxyhydroxycoumarins (**5** and **11**) were derived to the corresponding acetyl products (**6** and **12**, respectively) by the normal acetylation reaction and were characterized.

The synthesis of daphneticin by use of **5** as the starting material (monobenzyloxycoumarin) has been described in the previous paper[1] and also expressed that the synthetic daphneticin (**1**) was identical with a natural specimen in all respects.

We also aimed at the synthesis of its regioisomer (**2**) by use of **8** as the starting material according to the method described in the synthesis of daphneticin.



Reaction of **8** and **13** in the presence of potassium tert-butoxide provided a condensation product (**16**) in 68% yield. The condensation product was reduced with lithium borohydride in tetrahydrofuran at 0°C to give the corresponding diols (**17**) which were homogeneous on tlc behavior in a variety of solvent systems and on spectroscopy measurement (^{1}H-nmr). Acetylation of the diols (**17**) by the usual manner gave triacetates (**18**) which were characterized as a mixture of the threo and erythro forms by measurement of the ^{1}H-nmr spectrum. The proton at C-7', in the ^{1}H-nmr spectrum of **18**, indicated signals as two doublets at δ 6.02 (J=4.7 Hz) and 6.06 (J=6.7 Hz) and therefore[7] the signal observed at δ 6.02 was attributed to the erythro isomer and the signal at δ 6.06 was ascribed to the threo isomer and the ratio of the erythro and threo isomers was about 2:5 by the ^{1}H-nmr spectral analysis.

Finally, the diols (**17**) cyclized upon heating in acetic acid in presence of conc. hydrochloric acid to yield regioisomer (**2**) of **1**, whose mass spectrum showed a characteristic peak at m/z 210 due to the retro Diels-Alder fragmentation of the benzodioxane moiety. The ^{1}H-nmr spectrum of the regioisomer exhibited a doublet signal of H-7' at δ 4.96 with J=8.1 Hz in accordance with trans orientation of the substituents on the dioxane nucleus. The spectra (ir and ms) of the regioisomer (**2**) were similar to those of daphneticin (**1**), but in a comparative study on the ^{13}C-nmr spectra of both compounds, the small difference in the value of chemical

shift is observed.

Thus, we have carried out the synthesis of daphneticin (1) and its regioisomer (2), and it is synthetically confirmed that the structure of daphneticin is represented to be formula 1.

EXPERIMENTAL

All melting points are uncorrected. Column chromatography was run on Merck silica gel 60 (70-230 mesh). Thin-layer chromatography (tlc) was performed on glass plates precoated with Kieselgel 60 F_{254} (Merck). Ms were recorded on a Hitachi M-52 spectrometer, high resolution ms and secondary ion mass spectrometry (sims) on a Hitachi M-80 spectrometer. Infrared (ir) spectra were obtained on a JASCO IRA-3 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 Fourier transform spectrometer operating at 25.00 MHz, with tetramethylsilane as an internal standard. Chemical shifts are quoted in parts per million (s=singlet, d=doublet, dd=doublet of doublets, t=triplet, q=quartet, m=multiplet, br=broad).

8-Acetyl-7-benzyloxycoumarin (4)———A mixture of 3[6] (14.36 g), benzyl chloride (12.1 ml) and anhydrous potassium carbonate (29.1 g) in DMF (150 ml) was heated with stirring at about 100°C for 30 min. After cooling, the reaction mixture was poured into water and then extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated. The crude product was recrystallized from benzene to afford colorless needles (4)(14.58 g, 70%), mp 115-117°C. Anal. Calcd for $C_{18}H_{14}O_4$: C, 73.46; H, 4.80. Found: C, 73.39; H, 4.80. ms m/z: 294 (M^+), 276, 252, 189 (100%), 175, 160, 147, 132. ir ν_{max} ($CHCl_3$): 1730, 1610, 1565 cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ: 2.61 (3H, s, $COCH_3$), 5.20 (2H, s, CH_2Ph), 6.27 (1H, d, J=9.4 Hz, C_3-H), 6.91 (1H, d, J=8.7 Hz, C_6-H), 7.37 (5H, br s, aromatic protons), 7.41 (1H, d, J=8.7 Hz, C_5-H), 7.61 (1H, d, J=9.4 Hz, C_4-H).

7-Benzyloxy-8-hydroxycoumarin (5)———A solution of 30% H_2O_2 (90 ml) was added dropwise to a mixture of 4 (3.0 g) in dioxane (90 ml) and 1N NaOH (60 ml) at 10°C, and stirred at the same temperature over than 10 min. The reaction mixture was poured into ice-water and neutralized with 5% HCl, then extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4, and evaporated. The crude product was recrystallized from benzene to afford colorless needles (5)(2.12 g, 78%), mp 163-164°C (lit.,[8] mp 162-163°C). tlc ($CHCl_3$-MeOH (20 : 1), Rf=0.39). Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51. Found: C, 71.56; H, 4.54. ms m/z: 268 (M^+, 100%), 178, 150, 121. ir ν_{max} ($CHCl_3$): 3550, 1730, 1630, 1570 cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ: 5.23 (2H, s, CH_2Ph), 6.05 (1H, br s, OH), 6.27 (1H, d, J=9.4 Hz, C_3-H), 6.89 (1H, d, J=8.7 Hz, C_6-H), 6.96 (1H, d, J=8.7 Hz, C_5-H), 7.36-7.43 (5H, m, aromatic protons), 7.61 (1H, d, J=9.4 Hz, C_4-H).

8-Acetoxy-7-benzyloxycoumarin (6)———A mixture of 5 (85 mg), acetic anhydride (0.5 ml), and pyridine (0.5 ml) was stirred at room temperature for 24 h. The reaction mixture was poured into water, and extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue

was recrystallized from MeOH to give colorless prisms (6)(88 mg, 90%), mp 128°C. High resolution ms m/z: 310.0840 Calcd for $C_{18}H_{14}O_5$ (M^+). Found: 310.0858. ms m/z: 310 (M^+), 268 (100%), 177, 149, 121. ir ν_{max} ($CHCl_3$): 1760, 1730, 1620, 1570 cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ: 2.39 (3H, s, $COCH_3$), 5.19 (2H, s, $C\underline{H}_2Ph$), 6.27 (1H, d, J=9.4 Hz, C_3-H), 6.92 (1H, d, J=8.7 Hz, C_6-H), 7.27 (1H, d, J=8.7 Hz, C_5-H), 7.37 (5H, br s, aromatic protons), 7.62 (1H, d, J=9.4 Hz, C_4-H).

7-Benzyloxy-8-methoxymethoxycoumarin (7)———A suspension of 5 (6.0 g) and t-BuOK (3.77 g) in CH_3CN (250 ml) was stirred for 30 min. The solution of chloromethyl methyl ether (3.6 g) in CH_3CN (10 ml) was added dropwise to the mixture and furthermore stirred for 15 min. The mixture was poured into water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography on a silica gel ($CHCl_3$-acetone (20 : 1)) giving a solid. The crude solid was recrystallized from EtOH to afford colorless needles (7)(5.8 g, 83%), mp 102°C. Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.15; H, 5.14. ms m/z: 312 (M^+), 267, 221, 190 (100%), 178, 163, 135. ir ν_{max} ($CHCl_3$): 1730, 1615, 1570 cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ: 3.65 (3H, s, OCH_3), 5.18 (2H, s, $OC\underline{H}_2OCH_3$ or $C\underline{H}_2Ph$), 5.25 (2H, s, $OC\underline{H}_2OCH_3$ or $C\underline{H}_2Ph$), 6.24 (1H, d, J=9.4 Hz, C_3-H), 6.90 (1H, d, J=8.7 Hz, C_6-H), 7.15 (1H, d, J=8.7 Hz, C_5-H), 7.35 (5H, m, aromatic protons), 7.60 (1H, d, J=9.4 Hz, C_4-H).

7-Hydroxy-8-methoxymethoxycoumarin (8)———A solution of 7 (5.37 g) in AcOEt (20 ml) and MeOH (20 ml) was subjected to catalytic reduction over 5% Pd-C (537 mg) at room temperature. After absorption of hydrogen had ceased, the catalyst was filtered off and the filtrate was evaporated. The crude product was recrystallized from benzene to give colorless needles (8)(3.38 g, 88%), mp 114°C. Anal. Calcd for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54. Found: C, 59.36; H, 4.51. ms m/z: 222 (M^+), 192(100%), 177, 149, 133, 121. ir ν_{max} ($CHCl_3$): 3530, 1720, 1610, 1580 cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ: 3.66 (3H, s, $OCH_2OC\underline{H}_3$), 5.25 (2H, s, $OC\underline{H}_2OCH_3$), 6.25 (1H, d, J=9.4 Hz, C_3-H), 6.92 (1H, d, J=8.7 Hz, C_6-H), 7.16 (1H, d, J=8.7 Hz, C_5-H), 7.62 (1H, br s, OH), 7.64 (1H, d, J=9.4 Hz, C_4-H).

8-Hydroxy-7-methanesulfonyloxycoumarin (9a) and 7-Methanesulfonyloxy-8-methoxymethoxycoumarin (9b)———A mixture of 8 (683 mg) and methanesulfonyl chloride (705 mg) in pyridine (5 ml) was stirred at room temperature for 15 h. The solvent was removed under reduced pressure to give the residue, which was poured into water. The reaction mixture was extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated to give crude product. The crude product was subjected by column chromatography on a silica gel ($CHCl_3$-acetone (20 : 1)) affording 9a (588 mg, 75%) and 9b (146 mg, 16%).

Compound 9a: Recrystallization from MeOH gave colorless needles, mp 202-204°C. tlc ($CHCl_3$-MeOH (20 : 1), Rf≈0.24). Anal. Calcd for $C_{10}H_8O_6S$: C, 46.88; H, 3.15. Found: C, 46.70; H, 3.16. ms m/z: 256 (M^+), 234, 206, 178 (100%), 150, 149. ir ν_{max} (KBr): 3300, 1730, 1610, 1580, 1355, 1160 cm^{-1}. ^{1}H-nmr (acetone-d_6) δ: 2.84 (1H, br s, OH), 3.40 (3H, s, SO_2CH_3), 6.43 (1H, d, J=9.4 Hz, C_3-H), 7.23 (1H, d, J=8.7 Hz, C_6-H), 7.28 (1H, d, J=8.7 Hz, C_5-H), 7.99 (1H, d, J=9.4 Hz, C_4-H).

Compound 9b: Recrystallization from benzene afforded colorless needles, mp 122°C. tlc ($CHCl_3$-MeOH (20 : 1), Rf=0.54). Anal. Calcd for $C_{12}H_{12}O_7S$: C, 48.00; H, 4.03.

Found: C, 47.89; H, 4.01. ms m/z: 300 (M^+), 279, 270, 256, 191, 178 (100%), 163, 150, 149. ir ν_{max} ($CHCl_3$): 1740, 1605, 1570, 1380, 1160 cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ: 3.25 (3H, s, SO_2CH_3), 3.70 (3H, s, $OCH_2O\underline{CH_3}$), 5.34 (2H, s, $O\underline{CH_2}OCH_3$), 6.45 (1H, d, J=9.4 Hz, C_3-H), 7.28 (1H, d, J=8.7 Hz, C_6-H), 7.32 (1H, d, J=8.7 Hz, C_5-H), 7.69 (1H, d, J=9.4 Hz, C_4-H).

8-Benzyloxy-7-methanesulfonyloxycoumarin (10)———A stirring mixture of **9a** (30 mg), benzyl chloride (29.6 mg), and anhydrous potassium carbonate (80.7 mg) in DMF (2 ml) was heated at about 70°C for 3.5 h. After cooling, the reaction mixture was poured into water and then extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated. The crude product was purified by preparative tlc ($CHCl_3$-acetone(20 : 1)), and then recrystallized from MeOH to afford colorless needles (**10**)(19 mg, 47%), mp 172°C. Anal. Calcd for $C_{17}H_{14}O_6S$: C, 58.95; H, 4.07. Found: C, 58.56; H, 4.05. ms m/z: 346 (M^+, 100%), 177, 149, 120. ir ν_{max} ($CHCl_3$): 1740, 1600, 1570, 1380, 1160 cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ: 3.07 (3H, s, SO_2CH_3), 5.31 (2H, s, $C\underline{H_2}Ph$), 6.45 (1H, d, J=9.4 Hz, C_3-H), 7.23 (1H, d, J=8.7 Hz, C_6-H), 7.28 (1H, d, J=8.7 Hz, C_5-H), 7.35-7.55 (5H, m, aromatic protons), 7.69 (1H, d, J=9.4 Hz, C_4-H).

8-Benzyloxy-7-hydroxycoumarin (11)———A mixture of **10** (100 mg) and fine powder KOH (10 mg) in DMF (3 ml) was stirred for 1 h. Then the reaction mixture was poured into ice-water, carefully neutralized with 1N HCl, and extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated. The crude product was purified by column chromatography on a silica gel ($CHCl_3$-acetone (30 : 1)), and recrystallized from benzene and ligroin to give colorless needles (**11**)(31 mg, 40%), mp 124°C. tlc ($CHCl_3$-MeOH(20 : 1), Rf=0.56). Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.50; H, 4.53. ms m/z: 268 (M^+), 178, 150, 121. ir ν_{max} ($CHCl_3$): 3550, 1730, 1610, 1580 cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ: 5.31 (2H, s, $C\underline{H_2}Ph$), 6.19 (1H, s, OH), 6.25 (1H, d, J=9.4 Hz, C_3-H), 6.84 (1H, d, J=8.7 Hz, C_6-H), 7.10 (1H, d, J=8.7 Hz, C_5-H), 7.36-7.46 (5H, m, aromatic protons), 7.63 (1H, d, J=9.4 Hz, C_4-H).

7-Acetoxy-8-benzyloxycoumarin (12)———A mixture of **11** (51 mg), acetic anhydride (1 ml), and pyridine (1 ml) was stirred for 24 h. The reaction mixture was poured into water, and extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated to dryness. The crude product was purified by preparative tlc ($CHCl_3$-acetone(20 : 1)) to give a solid. The solid was recrystallized from ether and n-hexane to afford colorless needles (**12**)(45 mg, 80%), mp 127°C. High resolution ms m/z: 310.0840 Calcd for $C_{18}H_{14}O_5$ (M^+). Found: 310.0870. ms m/z: 310 (M^+), 268(100%), 177, 149, 121. ir ν_{max} ($CHCl_3$): 1760, 1730, 1605, 1570 cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ: 2.19 (3H, s, $COCH_3$), 5.24 (2H, s, $C\underline{H_2}Ph$), 6.38 (1H, d, J=9.4 Hz, C_3-H), 6.98 (1H, d, J=8.7 Hz, C_6-H), 7.19 (1H, d, J=8.7 Hz, C_5-H), 7.32-7.48 (5H, m, aromatic protons), 7.66 (1H, d, J=9.4 Hz, C_4-H).

Condensation of 13 with 8 (Formation of 16)———A suspension of **8** (589 mg) and t-BuOK (387 mg) in CH_3CN (40 ml) was stirred for 15 min. A solution of **13** (860 mg) in CH_3CN (10 ml) was added dropwise to the mixture and furthermore stirred for 45 min. The mixture was poured into water and extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4, and evaporated. The crude product was

purified by column chromatography on a silica gel ($CHCl_3$-acetone(20 : 1)), and recrystallized from MeOH to give colorless needles (**16**)(794 mg, 68%), mp 147-149°C. High resolution ms m/z: 530.1422 Calcd for $C_{26}H_{26}O_{12}$ (M^+). Found: 530.1461. ms m/z: 530 (M^+), 498, 488, 456, 426, 383, 341, 322, 280, 268, 225, 223, 222. ir ν_{max} ($CHCl_3$): 1760, 1730, 1685, 1610 cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ: 1.24 (3H, t, J=7.1 Hz, OCH_2CH_3), 2.35 (3H, s, $COCH_3$), 3.65 (3H, s, OCH_2OCH_3), 3.88 (6H, s, OCH_3), 4.28 (2H, q, J=7.1 Hz, OCH_2CH_3), 5.27 and 5.32 (each 1H, d, J=6.1 Hz, OCH_2OCH_3), 5.88 (1H, s, $C_{8'}$-H), 6.28 (1H, d, J=9.4 Hz, C_3-H), 6.83 (1H, d, J=8.7 Hz, C_6-H), 7.15 (1H, d, J=8.7 Hz, C_5-H), 7.48 (2H, s, $C_{2'}$-H and $C_{6'}$-H), 7.61 (1H, d, J=9.4 Hz, C_4-H).

Reduction of 16 with Lithium Borohydride (Formation of 17)——A suspension of $LiBH_4$ (37.4 mg) in THF (3 ml) was added gradually to a solution of **16** (600 mg) in THF (12 ml) at 0°C. The mixture was stirred at the same temperature for 15 min under a nitrogen atmosphere. Then 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 a silica gel ($CHCl_3$-acetone-MeOH (20 : 2 : 1)) giving a colorless oil (**17**)(300 mg, 54%). sims m/z: 491 (M^++1). ir ν_{max} ($CHCl_3$): 3450, 1760, 1730, 1610 cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ: 2.31 (3H, s, $COCH_3$), 3.10 (1H, br s, OH), 3.63 (1H, s, OH), 3.66 (3H, s, OCH_2OCH_3), 3.78 and 3.79 (each 3H, s, OCH_3), 3.80-3.92 (2H, m, $C_{9'}$-H), 4.40-4.45 (1H, m, $C_{8'}$-H), 4.94-5.01 (1H, m, $C_{7'}$-H), 5.23 and 5.27 (each 1H, d, J=6.1 Hz, OCH_2OCH_3), 6.25 (1H, d, J=9.4 Hz, C_3-H), 6.68 and 6.69 (each 1H, s, $C_{2'}$-H and $C_{6'}$-H), 6.89 (1H, d, J=8.7 Hz, C_6-H), 7.13 (1H, d, J=8.7 Hz, C_5-H), 7.60 (1H, d, J=9.4 Hz, C_4-H).

Acetylation of 17 (Formation of 18)——A mixture of **17** (51 mg), acetic anhydride (1.0 ml), and pyridine (1.0 ml) was stirred at room temperature for 90 min. The reaction mixture was poured into 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 a silica gel (AcOEt-n-hexane(2 : 1)) to give colorless oil (**18**)(29 mg, 49%). High resolution ms m/z: 574.1684 Calcd for $C_{28}H_{30}O_{13}$ (M^+). Found: 574.1683. ms m/z: 574 (M^+), 542, 532, 482, 440, 428, 398, 368, 339, 252, 209. ir ν_{max} ($CHCl_3$): 1760, 1740, 1610 cm^{-1}. ^{1}H-nmr ($CDCl_3$) δ: 2.00 (15/7H, s, $COCH_3$), 2.03 (6/7H, s, $COCH_3$), 2.08 (15/7H, s, $COCH_3$), 2.11 (6/7H, s, $COCH_3$), 2.32 (3H, s, $COCH_3$), 3.69 (3H, s, OCH_2OCH_3), 3.81 (6H, s, OCH_3), 4.14 (5/7H, dd, J=12.1, 6.1 Hz, $C_{9'}$-H), 4.26 (2/7H, dd, J=12.1, 4.0 Hz, $C_{9'}$-H), 4.31 (5/7H, dd, J=12.1, 4.0 Hz, $C_{9'}$-H), 4.43 (2/7H, dd, J=12.1, 5.4 Hz, $C_{9'}$-H), 4.83 (5/7H, m, $C_{8'}$-H), 5.10 (2/7H, m, $C_{8'}$-H), 5.20 (2H, s, OCH_2OCH_3), 6.02 (2/7H, d, J=4.7 Hz, $C_{7'}$-H), 6.06 (5/7H, d, J=6.7 Hz, $C_{7'}$-H), 6.29 (1H, d, J=9.4 Hz, C_3-H), 6.65 (2H, s, $C_{2'}$-H and $C_{6'}$-H), 6.92 (1H, d, J=8.7 Hz, C_6-H), 7.17 (1H, d, J=8.7 Hz, C_5-H), 7.62 (1H, d, J=9.4, C_4-H).

A Regioisomer (2) of Daphneticin——A mixture of **17** (91 mg) in 36% HCl (3 ml) and AcOH (4 ml) was heated at 65°C for 20 min. Then 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 subjected to preparative tlc (AcOEt-n-hexane(2 : 1)), and furthermore purified by preparative tlc ($CHCl_3$-

MeOH (20 : 1)). The crude product was recrystallized from MeOH to give colorless needles (2)(8.2 mg, 11%), mp 238-239°C. High resolution ms m/z: 386.1000 Calcd for $C_{20}H_{18}O_8$ (M^+). Found: 386.0968. ms m/z: 386 (M^+), 368, 354, 219, 210, 191, 167. ir ν_{max} (KBr): 3450, 1720, 1610, 1565 cm^{-1}. ^{1}H-nmr (DMSO-d_6) δ: 3.26-3.62 (2H, m, $C_{9'}$-H), 3.78 (6H, s, OCH_3), 4.41 (1H, m, $C_{8'}$-H), 4.96 (1H, d, J=8.1 Hz, $C_{7'}$-H), 5.01 (1H, br s, OH), 6.30 (1H, d, J=9.4 Hz, C_3-H), 6.78 (2H, s, $C_{2'}$-H and $C_{6'}$-H), 6.99 (1H, d, J=8.7 Hz, C_6-H), 7.24 (1H, d, J=8.7 Hz, C_5-H), 8.00 (1H, d, J=9.4 Hz, C_4-H), 8.58 (1H, br s, OH). ^{13}C-nmr (pyridine-d_5) δ: 160.4 (s, C-2), 149.3 (s, C-9), 149.3 (s, C-3'), 149.3 (s, C-5'), 147.5 (s, C-7), 144.2 (d, C-4), 138.6 (s, C-8), 132.2 (s, C-4'), 126.3 (s, C-1'), 120.0 (d, C-5), 113.4 (d, C-3), 113.4 (s, C-10), 113.2 (d, C-6), 106.5 (d, C-2'), 106.5 (d, C-6'), 80.1 (d, C-8'), 77.4 (d, C-7'), 61.1 (t, C-9'), 56.3 (q, OCH_3).

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4) We previously reported[1] that 7,8-dibenzyloxycoumarin was hydrolyzed with trifluoroacetic acid or aluminum chloride to give 8-benzyloxy-7-hydroxycoumarin (11) as a main product and 7-benzyloxy-8-hydroxycoumarin (5) as a minor product. We here carried out the another synthesis of 5 and 11 and then each of 8-benzyloxy-7-hydroxycoumarin and 7-benzyloxy-8-hydroxycoumarin, prepared according to different synthesis routes, was compared. Consequently, the major material in debenzylation reaction of 7,8-dibenzyloxycoumarin must be revised to be 7-benzyloxy-8-hydroxycoumarin (5) and the minor material was 8-benzyloxy-7-hydroxycoumarin (11). The major product was condensed with 13 under alkaline condition to afford the condensation product, which was derived to daphneticin via few steps. From the above result, it is obvious that the descripton of daphneticin in the previous report[1] was erroneously represented as formula (2).
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