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Total Synthesis of Cleomiscosin A, a Coumarinolignoid

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The coumarinolignoid cleomiscosin A (**1**), having antitumor activity, has been synthesized *via* the keto-ester (**10**), which was prepared from readily available starting materials (**6** and **9**). Removal of the methoxymethyl group of **10** followed by reduction with lithium borohydride gave a mixture of diols (**12a**, **b**). Treatment of **12a**, **b** with 5% sulfuric acid in acetic acid provided cleomiscosin A monoacetate (**14**) and subsequent hydrolysis with sodium hydroxide afforded **1**.

Keywords——coumarinolignoid; cleomiscosin A; benzodioxane; fraxetin; antitumor activity; coumarin

The coumarinolignoid cleomiscosin A (**1**) has been isolated[1] from the defatted seeds of *Cleome viscosa* (Capparidaceae), and was recently found[2] in *Simaba multiflora* (Simaroubaceae), *Soulamea soulameoides* (Simaroubaceae), and *Matayba arborescens* (Sapindaceae). The structure of cleomiscosin A was first represented[1] as formula **15**, but recently the revised structure **1** was proposed[3] on the basis of studies of selective heterodecoupling in the carbon-13 nuclear magnetic resonance (^{13}C-NMR) and proton nuclear magnetic resonance (^{1}H-NMR) spectra of cleomiscosin A diacetate (**2**).

Cleomiscosin A, having no optical activity (racemic compound), shows[4] antitumor activity *in vivo* in the P-388 lymphocytic leukemia test system. Further, it possesses a novel skeleton in which a phenylpropane unit is linked to a coumarin nucleus through a dioxane bridge. Recently, two groups have independently accomplished the synthesis of cleomiscosin A by an oxidative coupling reaction of fraxetin (**5**) and coniferyl alcohol. Namely, Merlini and co-workers[5] reported that the oxidative coupling of fraxetin (**5**) and coniferyl alcohol in the presence of silver oxide afforded cleomiscosin A in 8% yield together with a regioisomer cleomiscosin B (**15**) in 4% yield. On the other hand, Cordell and Lin[6] reported that treatment of the same reactants in buffered aqueous solution with horseradish peroxidase produced cleomiscosin A in 23% yield as the main product.

Herein, we wish to describe a large-scale synthesis of cleomiscosin A from readily available materials (**6** and **9**). The starting material, 8-acetyl-7-hydroxy-6-methoxycoumarin (**3**), prepared according to the literature,[7] was converted to the corresponding methoxymethyl (MOM) ether (**4**) by treatment with chloromethyl methyl ether. The Baeyer–Villiger oxidation of **4** with alkaline hydrogen peroxide in dioxane gave the expected phenolic compound (**6**) in 58% yield. The latter compound was also easily prepared in 65% yield by treatment of commercially available fraxetin (**5**) with chloromethyl methyl ether. Compound **6** was condensed with ethyl 2-bromo-3-(4-benzyloxy-3-methoxyphenyl)-3-oxopropionate (**9**)[8] in the presence of potassium butoxide in *N*,*N*-dimethylformamide (DMF) to give an ether (**10**) in excellent yield. Next, we investigated simultaneous reduction of the keto and ethyl ester groups in **10** with various reagents (sodium borohydride, potassium borohydride, lithium borohydride, and L-selectride). However, all attempts were unsuccessful and gave an intractable tar. Since attack of reagents on the ethyl ester group is thought to be difficult because of steric hindrance by the MOM group, **10** was transformed to a less-hindered ethyl

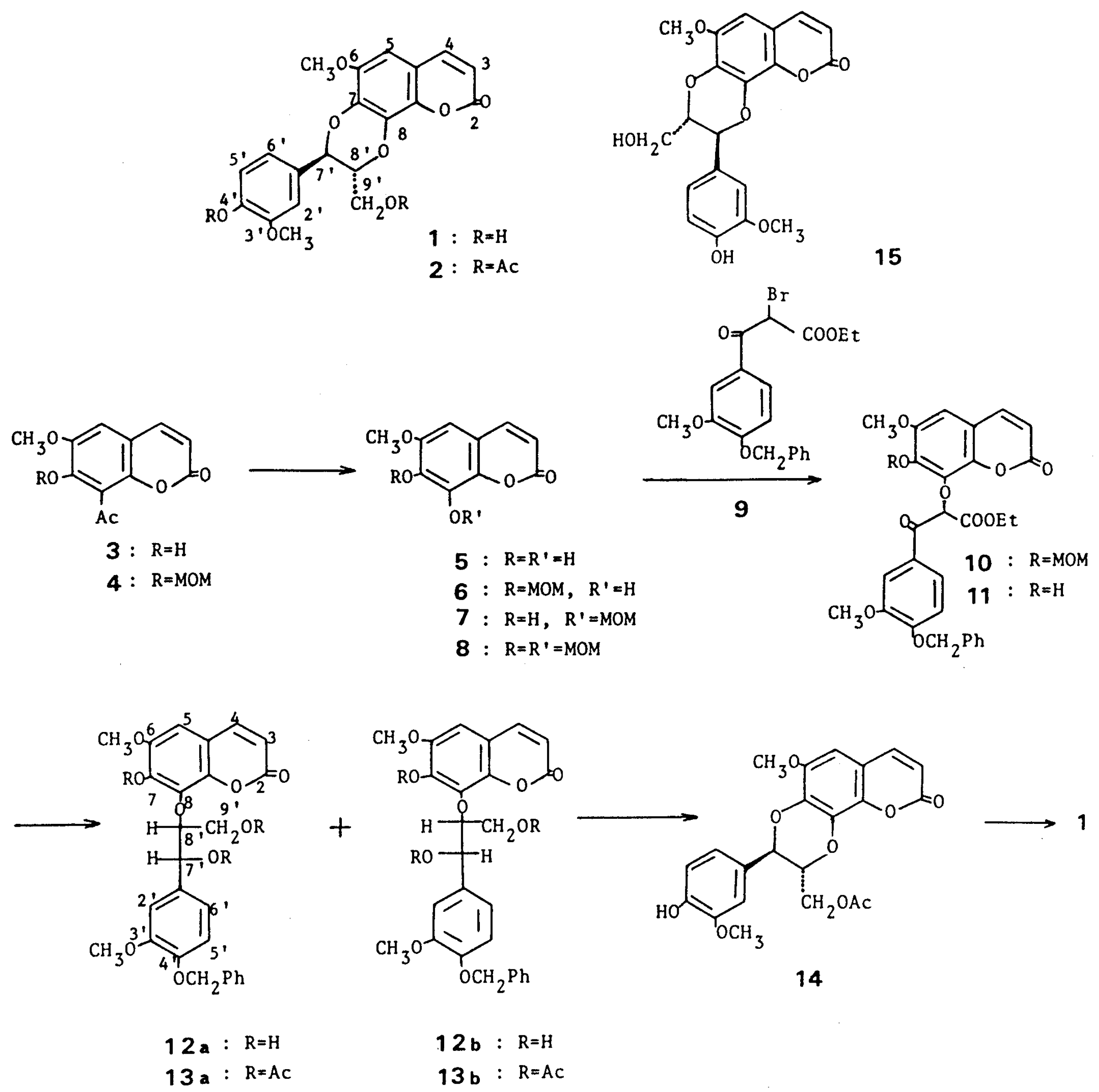

Chart 1

ester (**11**) by hydrolysis with hydrochloric acid. It was reported⁹⁾ that sodium borohydride is a good reagent for reduction of a β-ketoester to form prominently the *erythro* diastereomer of the corresponding diols. In the case of **11**, however, reduction using sodium borohydride did not proceed satisfactorily in several solvents such as methanol, ethanol, and 2-propanol at 10—30 °C. Eventually, the successful reduction of **11** to the diols (**12a**, **b**) was accomplished with lithium borohydride¹⁰⁾ in tetrahydrofuran (THF) at room temperature. These diols were homogeneous on thin-layer chromatography (TLC) in a variety of solvent systems. The high resolution mass spectrum (MS) gave the molecular formula $C_{27}H_{26}O_9$ and the infrared (IR) spectrum lacked both of the carbonyl bands (1675 and 1745 cm^{-1}) which were found in the keto ester (**11**). In the ^{1}H-NMR spectrum, signals due to two methoxyl groups at δ 3.68 and 3.72, one methylene group at δ 4.92, and one aromatic proton of the coumarin ring at δ 6.48 were each observed as a singlet. Furthermore, the proton assigned to the C-7′ position gave split signals at δ 5.08 (d, $J=8$ Hz) and δ 5.18 (d, $J=4$ Hz), and the protons at C-3 and C-4 similarly appeared as doublets at δ 6.04 and 6.05 ($J=9.5$ Hz, C_3-H), and δ 7.39 and 7.40 ($J=9.5$ Hz, C_4-H), respectively. Hence, these compounds (**12a**, **b**) were found to be a mixture of the *erythro* and *threo* forms. The ratio of the two isomers was estimated to be about 2 : 1 by ^{1}H-NMR spectral analysis. Attempts to separate the diols by chromatography were unsuccessful under various conditions. Therefore, the diols were led to the corresponding triacetates (**13a**, **b**) by normal acetylation, and these were successfully separated into **13a** and **13b** in pure form by preparative TLC. In order to clarify the stereochemistry of the triacetates, the ^{1}H-NMR spectra were measured. The stereochemical assignaments of **13a**, **b** were made on the basis of comparison of the J values for coupling between $C_{7'}$-H and $C_{8'}$-H. The ^{1}H-NMR spectrum of the major product (**13a**) exhibited a doublet at δ 6.07 ($J=4$ Hz) attributable to $C_{7'}$-H, whereas that of the minor product (**13b**) showed a doublet at δ 6.02 ($J=8$ Hz) ascribable to $C_{7'}$-H. It is known[11] that the vicinal coupling constant (J_{AB}) of the *erythro* isomer is smaller than that of the *threo* isomer. Accordingly, the structure of the major reduction product was assigned as the *erythro* form (**12a**) and the minor product was assigned as the *threo* form (**12b**).

Finally, the mixture (**12a**, **b**) underwent[12] cyclization with 5% sulfuric acid to give cleomiscosin A monoacetate (**14**) in 50% yield. The MS showed the characteristic fragment peak at *m*/*z* 222 due to the retro Diels–Alder reaction[1] of the benzodioxane moiety in addition to the parent peak at *m*/*z* 428. The coupling constant between the $C_{7'}$-H and $C_{8'}$-H signals in the ^{1}H-NMR spectrum was 8 Hz, demonstrating that the two hydrogens are *trans*-oriented. Subsequent treatment of **14** with 1% sodium hydroxide afforded the desired cleomiscosin A (**1**) in 96% yield.

Experimental

All melting points are uncorrected. Column chromatography was run on Merck Silica gel 60 (70—230 mesh) and 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 and secondary ion mass spectrometry (SIMS) on a Hitachi M-80 spectrometer. IR spectra were obtained on a JASCO IRA-3 spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-PS-100 nuclear magnetic resonance 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, br = broad).

8-Acetyl-6-methoxy-7-methoxymethoxycoumarin (4)——A mixture of 3[7] (1.869 g) and DMF (20 ml) was added to a suspension of NaH (60% in mineral oil) (480 mg) in THF (4 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 1 h and then chloromethyl methyl ether (0.91 ml) was added gradually. The mixture was stirred at room temperature for 3 h, then poured into water and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and acetone (10 : 1, v/v) to afford a solid (**4**). The solid was recrystallized from EtOH. Colorless needles (1.50 g) (68%). mp 108—109 °C. *Anal.* Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.26; H, 4.96. MS *m*/*z*: 278 (M^+), 246, 233, 216, 204 (100%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1725, 1570. ^{1}H-NMR ($CDCl_3$) δ: 2.62 (3H, s, $COCH_3$), 3.49 (3H, s, $OCH_2OC\underline{H}_3$), 3.88 (3H, s, OCH_3), 5.16 (2H, s, $OC\underline{H}_2OCH_3$), 6.33 (1H, d, $J=9.5$ Hz, C_3-H), 6.95 (1H, s, C_5-H), 7.62 (1H, d, $J=9.5$ Hz, C_4-H).

8-Hydroxy-6-methoxy-7-methoxymethoxycoumarin (6)——a) A solution of 30% hydrogen peroxide (20 ml) was added at once to a solution of **4** (400 mg) in dioxane (5 ml) and 1 N sodium hydroxide (4 ml) under ice-cooling. The mixture was stirred at room temperature for 2 d and poured into water. The resulting mixture was acidified by the dropwise addition of 5% acetic acid and extracted with ether. The ether layer was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and acetone (10 : 1, v/v) to yield a solid (**6**). The solid was recrystallized from EtOH. Colorless needles (211 mg) (58%). mp 161—163 °C. *Anal.* Calcd for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 56.95; H, 4.77. MS *m*/*z*: 252 (M^+), 222 (100%), 220, 207, 123. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 1720, 1570. ^{1}H-NMR (acetone-d_6) δ: 2.88 (1H, br s, OH), 3.56 (3H, s, $OCH_2OC\underline{H}_3$), 3.88 (3H, s, OCH_3), 5.22 (2H, s, $OC\underline{H}_2OCH_3$), 6.30 (1H, d, $J=9.5$ Hz, C_3-H), 6.80 (1H, s, C_5-H), 7.85 (1H, d, $J=9.5$ Hz, C_4-H).

b) A solution of fraxetin (**5**) (500 mg) in THF (0.5 ml) and DMF (0.5 ml) was added to a suspension of NaH (60% in mineral oil) (96 mg) in THF (1 ml) under ice-cooling. The reaction mixture was stirred at room temperature for 1 h and then chloromethyl methyl ether (0.185 ml) was added dropwise. The mixture was stirred at room temperature for 3 h, then poured into water and extracted with AcOEt. The organic layer was washed with water, dried over Na_2SO_4, and evaporated to yield a semisolid. The crude solid was crystallized from a small amount of

EtOH to yield unreacted fraxetin (**5**) (230 mg), and concentration of the mother liquor afforded a brown oil, which was subjected to column chromatography on silica gel with a mixture of $\mathrm{CHCl_3}$ and acetone (10 : 1, v/v). The substance eluted first was the dimethoxymethyl ether (**8**) (56 mg) (15% based on consumed starting material) and the compound eluted second was the monomethoxymethyl ether (**7**) (24 mg) (7%). The last elution product was the desired monomethoxymethyl ether (**6**) (211 mg) (65%).

8: The substance was recrystallized from EtOH. Colorless needles. mp 125—126 °C. TLC (silica gel/$\mathrm{CHCl_3}$–acetone (10 : 1, v/v), *Rf* = 0.62). *Anal.* Calcd for $\mathrm{C_{14}H_{16}O_7}$: C, 56.75; H, 5.44. Found: C, 56.81; H, 5.52. MS *m/z*: 296 ($\mathrm{M^+}$), 251, 235, 220 (100%), 205, 192. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1720, 1570. ^{1}H-NMR (acetone-d_6) δ: 3.56, 3.63 (6H, 2 × s, $2\times\mathrm{OCH_2OC\underline{H}_3}$), 3.90 (3H, s, $\mathrm{OCH_3}$), 5.20, 5.25 (2H, 2 × s, $2\times\mathrm{OC\underline{H}_2OCH_3}$), 6.32 (1H, d, J = 9.5 Hz, $\mathrm{C_3}$-H), 7.70 (1H, s, $\mathrm{C_5}$-H), 7.88 (1H, d, J = 9.5 Hz, $\mathrm{C_4}$-H).

7: The compound was recrystallized from EtOH. Colorless needles. mp 134—135 °C. TLC (silica gel/$\mathrm{CHCl_3}$–acetone (10 : 1, v/v), *Rf* = 0.43). *Anal.* Calcd for $\mathrm{C_{12}H_{12}O_6}$: C, 57.14; H, 4.80. Found: C, 57.27; H, 4.84. MS *m/z*: 252 ($\mathrm{M^+}$), 222 (100%), 220, 207, 123. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3550, 1720, 1570. ^{1}H-NMR (acetone-d_6) δ: 3.15 (1H, br s, OH), 3.64 (3H, s, $\mathrm{OCH_2OC\underline{H}_3}$), 3.91 (3H, s, $\mathrm{OCH_3}$), 5.25 (2H, s, $\mathrm{OC\underline{H}_2OCH_3}$), 6.21 (1H, d, J = 9.5 Hz, $\mathrm{C_3}$-H), 7.03 (1H, s, $\mathrm{C_5}$-H), 7.86 (1H, d, J = 9.5 Hz, $\mathrm{C_4}$-H).

6: The recrystallization of **6** was carried out from EtOH. Colorless needles. mp 159—161 °C. TLC (silica gel/$\mathrm{CHCl_3}$–acetone (10 : 1, v/v), *Rf* = 0.40). This compound was identical with the product obtained in a) on the basis of a comparison of spectral (IR, ^{1}H-NMR, and MS) properties and mixed melting point determination.

Condensation of 6 with 9 (Formation of 10)——A solution of **6** (197 mg) in DMF (0.5 ml) was added to a suspension of *tert*-BuOK (96 mg) in DMF (0.5 ml) at room temperature. The mixture was stirred for 1 h at the same temperature, then a solution of **9**[8)] (343 mg) in DMF (0.7 ml) was added under ice-cooling. Stirring was continued for a further 3 h at room temperature. The resulting mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried over $\mathrm{Na_2SO_4}$, and evaporated to dryness. Purification of the residue by column chromatography on silica gel with a mixture of $\mathrm{CHCl_3}$ and acetone (10 : 1, v/v) gave an oil (**10**). A colorless oil (444 mg) (98%). High MS *m/z*: 578.1786. Calcd for $\mathrm{C_{31}H_{30}O_{11}}$ ($\mathrm{M^+}$). Found: 578.1818. MS *m/z*: 578 ($\mathrm{M^+}$), 328 (100%), 285, 252, 241. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1750, 1720, 1675, 1565. ^{1}H-NMR ($\mathrm{CDCl_3}$) δ: 1.20 (3H, t, J = 7 Hz, $\mathrm{CH_2C\underline{H}_3}$), 3.49 (3H, s, $\mathrm{OCH_2OC\underline{H}_3}$), 3.86, 3.95 (6H, 2 × s, $2\times\mathrm{OCH_3}$), 4.24 (2H, q, J = 7 Hz, $\mathrm{OC\underline{H}_2CH_3}$), 5.24 (4H, s, $\mathrm{C\underline{H}_2Ph}$ and $\mathrm{OC\underline{H}_2OCH_3}$), 6.16 (1H, s, $\mathrm{C_{8'}}$-H), 6.29 (1H, d, J = 9.5 Hz, $\mathrm{C_3}$-H), 6.69 (1H, s, $\mathrm{C_5}$-H), 6.97 (1H, d, J = 8 Hz, $\mathrm{C_{5'}}$-H), 7.18—7.56 (5H, m, 5 × aromatic protons), 7.57 (1H, d, J = 9.5 Hz, $\mathrm{C_4}$-H), 7.71 (1H, d, J = 3 Hz, $\mathrm{C_{2'}}$-H), 7.88 (1H, dd, J = 8, 3 Hz, $\mathrm{C_{6'}}$-H).

Demethoxymethylation of 10 (Formation of 11)——A mixture of **10** (100 mg) and 2 N HCl–MeOH (5 ml) was stirred at room temperature for 30 min. The mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried over $\mathrm{Na_2SO_4}$, and evaporated to give a solid (**11**), which was recrystallized from AcOEt. Colorless needles (91 mg) (99%). mp 157—158 °C. *Anal.* Calcd for $\mathrm{C_{29}H_{26}O_{10}}$: C, 65.16; H, 4.90. Found: C, 64.96; H, 4.86. SIMS *m/z*: 535 ($\mathrm{M^+}$ + 1), 517, 372, 329, 281, 241 (100%), 219. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3630, 1745, 1730, 1675, 1580. ^{1}H-NMR ($\mathrm{CDCl_3}$) δ: 1.24 (3H, t, J = 7 Hz, $\mathrm{OCH_2C\underline{H}_3}$), 3.90, 3.94 (6H, 2 × s, $2\times\mathrm{OCH_3}$), 4.31 (2H, q, J = 7 Hz, $\mathrm{OC\underline{H}_2CH_3}$), 5.24 (2H, s, $\mathrm{C\underline{H}_2Ph}$), 6.20 (1H, s, $\mathrm{C_{8'}}$-H), 6.26 (1H, d, J = 9.5 Hz, $\mathrm{C_3}$-H), 6.72 (1H, s, $\mathrm{C_5}$-H), 7.02 (1H, d, J = 8 Hz, $\mathrm{C_{5'}}$-H), 7.36 (5H, br s, 5 × aromatic protons), 7.59 (1H, d, J = 9.5 Hz, $\mathrm{C_4}$-H), 7.70 (1H, d, J = 3 Hz, $\mathrm{C_{2'}}$-H), 7.98 (1H, dd, J = 8, 3 Hz, $\mathrm{C_{6'}}$-H).

Reduction of 11 with Lithium Borohydride (Formation of 12a, b)——A mixture of **11** (81 mg) and $\mathrm{LiBH_4}$ (13 mg) in THF (5 ml) was stirred at room temperature for 1.5 h. The mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried over $\mathrm{Na_2SO_4}$, and evaporated to dryness. Purification of the residue by column chromatography on silica gel with a mixture of $\mathrm{CHCl_3}$ and acetone (10 : 1, v/v) afforded an oil (**12a**, **b**). A colorless oil (56 mg) (75%). High MS *m/z*: 494.1575 Calcd for $\mathrm{C_{27}H_{26}O_9}$ ($\mathrm{M^+}$). Found: 494.1610. MS *m/z*: 494 ($\mathrm{M^+}$), 476, 385, 286, 270, 234 (100%), 208. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3350, 1720, 1615, 1575. ^{1}H-NMR ($\mathrm{CDCl_3}$) δ: 3.40—4.16 (3H, m, $\mathrm{C_{9'}}$-H and $\mathrm{C_{8'}}$-H), 3.68, 3.72 (6H, 2 × s, $2\times\mathrm{OCH_3}$), 4.92 (2H, s, $\mathrm{C\underline{H}_2Ph}$), 5.08 (1/3H, d, J = 8 Hz, $\mathrm{C_{7'}}$-H), 5.18 (2/3H, d, J = 4 Hz, $\mathrm{C_{7'}}$-H), 6.04 (1/3H, d, J = 9.5 Hz, $\mathrm{C_3}$-H), 6.05 (2/3H, d, J = 9.5 Hz, $\mathrm{C_3}$-H), 6.48 (1H, s, $\mathrm{C_5}$-H), 6.56—6.92 (3H, m, $\mathrm{C_{2'}}$-H, $\mathrm{C_{5'}}$-H, and $\mathrm{C_{6'}}$-H), 7.19 (5H, br s, 5 × aromatic protons), 7.39 (1/3H, d, J = 9.5 Hz, $\mathrm{C_4}$-H), 7.40 (2/3H, d, J = 9.5 Hz, $\mathrm{C_4}$-H).

Acetylation of 12a, b——A mixture of **12a**, **b** (50 mg), acetic anhydride (0.3 ml), and pyridine (0.5 ml) was stirred at room temperature for 2 h, then poured into water and extracted with AcOEt. The extract was washed with water, dried over $\mathrm{Na_2SO_4}$, and evaporated to give a crude oil (**13a**, **b**). The oil was subjected to preparative TLC with a mixture of $\mathrm{CHCl_3}$ and acetone (50 : 1, v/v) as a developing solvent. Elution of the adsorbent corresponding to *Rf* 0.46 with the same solvent gave **13a** (30 mg) (48%) and the band at *Rf* 0.42 afforded **13b** (9 mg) (14%).

13a: A colorless oil. TLC (silica gel/$\mathrm{CHCl_3}$–acetone (50 : 1, v/v), *Rf* = 0.46). High MS *m/z*: 620.1891 Calcd for $\mathrm{C_{33}H_{32}O_{12}}$ ($\mathrm{M^+}$). Found: 620.1870. MS *m/z*: 620 ($\mathrm{M^+}$), 518, 458, 427, 367 (100%), 335, 312, 293, 251, 208. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1765, 1740, 1575. ^{1}H-NMR ($\mathrm{CDCl_3}$) δ: 1.90 (3H, s, $\mathrm{COCH_3}$), 2.16 (6H, s, $2\times\mathrm{COCH_3}$), 3.78, 3.86 (6H, 2 × s, $2\times\mathrm{OCH_3}$), 4.07 (1H, dd, J = 13, 4 Hz, $\mathrm{C_{9'}}$-H), 4.45 (1H, dd, J = 13, 7 Hz, $\mathrm{C_{9'}}$-H), 4.99 (1H, m, $\mathrm{C_{8'}}$-H), 5.07 (2H, s, $\mathrm{C\underline{H}_2Ph}$), 6.07 (1H, d, J = 4 Hz, $\mathrm{C_{7'}}$-H), 6.30 (1H, d, J = 9.5 Hz, $\mathrm{C_3}$-H), 6.62 (1H, s, $\mathrm{C_5}$-H), 6.67—7.70 (3H, m, 3 × aromatic protons), 7.29 (5H, br s, 5 × aromatic protons), 7.50 (1H, d, J = 9.5 Hz, $\mathrm{C_4}$-H).

13b: A colorless oil. TLC (silica gel/$CHCl_3$–acetone (50 : 1, v/v), Rf=0.42). High MS m/z: 620.1891 Calcd for $C_{33}H_{32}O_{12}$ (M^+). Found: 620.1853. MS m/z: 620 (M^+), 518, 458, 427, 367 (100%), 335, 312, 293, 251, 208. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765, 1740, 1575. ^{1}H-NMR ($CDCl_3$) δ: 1.95, 1.97, 2.28 (9H, 3 × s, 3 × $COCH_3$), 3.82, 3.85 (6H, 2 × s, 2 × OCH_3), 3.89 (1H, dd, J=11, 4 Hz, $C_{9'}$-H), 4.29 (1H, dd, J=11, 3 Hz, $C_{9'}$-H), 4.95 (1H, m, $C_{8'}$-H), 5.07 (2H, s, $C\underline{H}_2Ph$), 6.02 (1H, d, J=8 Hz, $C_{7'}$-H), 6.32 (1H, d, J=9.5 Hz, C_3-H), 6.64 (1H, s, C_5-H), 6.53—6.93 (3H, m, 3 × aromatic protons), 7.29 (5H, br s, 5 × aromatic protons), 7.52 (1H, d, J=9.5 Hz, C_4-H).

Cleomiscosin A Monoacetate (14)——A mixture of **12a**, **b** (62 mg) and acetic acid (10 ml) was heated in the presence of 5% sulfuric acid (1.5 ml) under stirring at 60 °C for 10 min. After cooling, the reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4, and evaporated. The resulting oil was purified by column chromatography on silica gel with a mixture of $CHCl_3$ and acetone (10 : 1, v/v) to yield an oil (**14**). A colorless oil (27 mg) (50%). High MS m/z: 428.1106 Calcd for $C_{22}H_{20}O_9$ (M^+). Found 428.1107. MS m/z: 428 (M^+), 368 (100%), 222, 179, 162. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 1740, 1720, 1570. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s, $COCH_3$), 3.91 (6H, s, 2 × OCH_3), 3.93—4.49 (3H, m, $C_{8'}$-H and $C_{9'}$-H), 4.91 (1H, d, J=8 Hz, $C_{7'}$-H), 5.81 (1H, br s, OH), 6.33 (1H, d, J=9.5 Hz, C_3-H), 6.55 (1H, s, C_5-H), 6.77—7.01 (3H, m, 3 × aromatic protons), 7.61 (1H, d, J=9.5 Hz, C_4-H).

Cleomiscosin A (1)——A mixture of **14** (23 mg), MeOH (2 ml), and 1% NaOH (20 drops) was stirred at 0 °C for 30 min. The mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4, and evaporated to afford a solid (**1**), which was recrystallized from MeOH. Colorless needles (20 mg) (96%). mp 252—253 °C (lit.,[1] mp 247—249 °C; lit.,[2] mp 250—252 °C; lit.,[5] mp 257 °C). *Anal.* Calcd for $C_{20}H_{18}O_8$: C, 62.17; H, 4.70. Found: C, 61.90; H, 4.69. MS m/z: 386 (M^+), 368, 356, 249, 219, 208, 181, 180, 162, 161, 152, 151, 150, 138, 137, (100%), 124. IR ν_{max}^{KBr} cm^{-1}: 3460, 1710, 1610, 1575. ^{1}H-NMR (pyridine-d_5) δ: 3.74, 3.82 (6H, 2 × s, 2 × OCH_3), 3.94 (1H, dd, J=13, 3 Hz, $C_{9'}$-H), 4.35 (1H, dd, J=13, 2 Hz, $C_{9'}$-H), 4.51 (1H, m, $C_{8'}$-H), 5.01 (1H, br s, OH), 5.62 (1H, d, J=8 Hz, $C_{7'}$-H), 6.49 (1H, d, J=9.5 Hz, C_3-H), 6.78 (1H, s, C_5-H), 7.22—7.56 (3H, m, $C_{2'}$-H, $C_{5'}$-H, and $C_{6'}$-H), 7.32 (1H, br s, OH), 7.81 (1H, d, J=9.5 Hz, C_4-H). ^{13}C-NMR (pyridine-d_5) δ: 160.9 (s, C-2), 149.8 (s, C-3′), 149.1 (s, C-4′), 146.5 (s, C-6), 144.6 (s, C-4), 139.4 (s, C-9), 138.5 (s, C-7), 133.1 (s, C-8), 127.6 (s, C-1′), 121.8 (d, C-6′), 116.7 (d, C-5′), 113.9 (d, C-3), 112. 4 (d, C-2′), 112.0 (s, C-10), 101.2 (d, C-5), 80.0 (d, C-8′), 77.6 (d, C-7′), 60.8 (t, C-9′), 56.3 (q, OCH_3), 55.9 (q, OCH_3).

This compound was identical with an authentic sample[1] on the basis of mixed melting point determination and direct comparison of IR spectra (KBr).

Cleomiscosin A Diacetate (2)——A mixture of **1** (50 mg), acetic anhydride (0.42 ml) and pyridine (0.50 ml) was heated at 100 °C for 1 h. After cooling, the reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4, and evaporated to afford a solid (**2**), which was recrystallized from EtOH. Colorless needles (59 mg) (97%). mp 180—181 °C (lit.,[2] mp 178—180 °C). *Anal.* Calcd for $C_{24}H_{22}O_{10}$: C, 61.27; H, 4.72. Found: C, 61.52; H, 4.63. MS m/z: 470 (M^+), 428, 368 (100%), 291, 223, 222, 219, 180, 179, 162, 161, 147. IR ν_{max}^{KBr} cm^{-1}: 1755, 1725, 1715, 1610, 1560. ^{1}H-NMR ($CDCl_3$) δ: 2.01, 2.27 (6H, 2 × s, 2 × $COCH_3$), 3.80, 3.85 (6H, 2 × s, 2 × OCH_3), 4.06 (1H, m, $C_{8'}$-H), 4.38 (2H, m, $C_{9'}$-H), 4.99 (1H, d, J=7 Hz, $C_{7'}$-H), 6.24 (1H, d, J=9.5 Hz, C_3-H), 6.49 (1H, s, C_5-H), 6.82—7.10 (3H, m, $C_{2'}$-H, $C_{5'}$-H, and $C_{6'}$-H), 7.52 (1H, d, J=9.5 Hz, C_4-H). ^{13}C-NMR ($CDCl_3$) δ: 170.2 (s, $COCH_3$), 168.5 (s, $COCH_3$), 160.5 (s, C-2), 151.7 (s, C-3′), 145.8 (s, C-6), 143.6 (d, C-4), 140.8 (s, C-9), 138.8 (s, C-4′), 137.0 (s, C-7), 133.6 (s, C-1′), 131.7 (s, C-8), 123.4 (d, C-5′), 120.0 (d, C-6′), 114.4 (d, C-3), 111.9 (s, C-10), 111.5 (d, C-2′), 100.6 (d, C-5), 76.7 (d, C-7′), 75.1 (d, C-8′), 62.5 (t, C-9′), 56.4 (q, OCH_3), 56.0 (q, OCH_3), 20.6 (q, $COCH_3$).

Spectral (IR, ^{1}H-NMR, ^{13}C-NMR, and MS) properties of this substance were identical with those of the product prepared by Professor G. A. Cordell.[2]

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