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Total Synthesis of Neolignans, Americanin A and Isoamericanin A

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The condensation reaction of 3-benzyloxy-4-hydroxybenzaldehyde with 2,3-epoxy-3-[(3,4-dimethoxymethoxy)phenyl]-1-propanol, prepared from caffeic acid in four steps, afforded the ether (**11**) in good yield. Mesylation of **11** followed by treatment with potassium carbonate, provided the epoxide (**13**), which was converted to the debenzylation product (**14**) by hydrogenolysis. Compound **14** underwent cyclization with potassium carbonate to yield the *trans* dioxane derivative (**15**). Reaction of **15** with the ylide (**16**) followed by hydrolysis furnished americanin A (**1**). Isoamericanin A (**3**) was similarly synthesized from another condensation product (**18**).

Keywords——Phytolaccaceae; *Phytolacca americana*; americanin A; isoamericanin A; regioisomer; benzodioxane; epoxide; neolignan; antihepatotoxic activity

The neolignan americanin A (**1**) has been isolated[1a] from the seeds of *Phytolacca americana* (Phytolaccaceae) together with americanin B and americanin D. Americanin A is a racemic compound (no optical activity),[1b] and shows antihepatotoxic activity.[1c] The structure of americanin A was first represented[1a,c] as the formula (**3**), but recently the revised structure (**1**) was proposed[1b] on the basis of a degradation study of its dimethylether.

Here we describe the synthetic confirmation of the structures of americanin A (**1**) and its regioisomer (isoamericanin A)[2] (**3**), in which a new dioxane formation[3-6] by treatment of compounds **14** and **21** with potassium carbonate was utilized.

The key intermediate (**14**) for the synthesis of **1** was prepared as follows. Caffeic acid (**5**) was converted to a methoxymethyl (MOM) ether (**7**) by esterification with acidic methanol followed by treatment with chloromethoxymethane. Reduction of **7** with lithium aluminum hydride gave the alcohol (**8**) in 78% yield, and this was transformed into an epoxide (**9**) in 84% yield by oxidation with *tert*-butyl hydroperoxide in the presence of vanadyl acetylacetonate. Condensation of **9** with 3-benzyloxy-4-hydroxybenzaldehyde (**10**) in the presence of sodium hydroxide gave the ether (**11**) as a stereochemically homogeneous product in good yield. The configuration (*erythro* or *threo*) of the ether (**11**) was ambiguous at this stage, but the following transformation (see below) of **11** to the *trans* dioxane (**15**) established its configuration as *erythro*. Mesylation of **11** in the usual manner gave the corresponding mesylate (**12**) in 72% yield, and subsequent treatment with potassium carbonate provided an epoxide (**13**) in an excellent yield. Debenzylation of **13** by hydrogenolysis yielded the first target substance (**14**).

Compound **14** underwent cyclization with potassium carbonate to yield the dioxane derivative (**15**) in 86% yield. The mass spectrum (MS) of **15** showed the characteristic peak at *m/z* 254 due to a retro Diels–Alder fragmentation of the benzodioxane moiety, and the proton nuclear magnetic resonance (^{1}H-NMR) spectrum revealed a doublet signal of H-7 at δ 5.01 with a coupling constant (J=8 Hz) typical of *trans* orientation of the benzodioxane ring.

Next, we investigated the Wittig synthesis of the α,β-unsaturated aldehyde moiety in americanin A. The attempted Wittig reaction of **15** with the ylide prepared from 1,3-dioxan-2-ylmethyltriphenylphosphonium bromide[7] or diethyl formylmethylphosphonate diethylacetal,[8] was unsuccessful, the starting material (**15**) being recovered unchanged. However, the

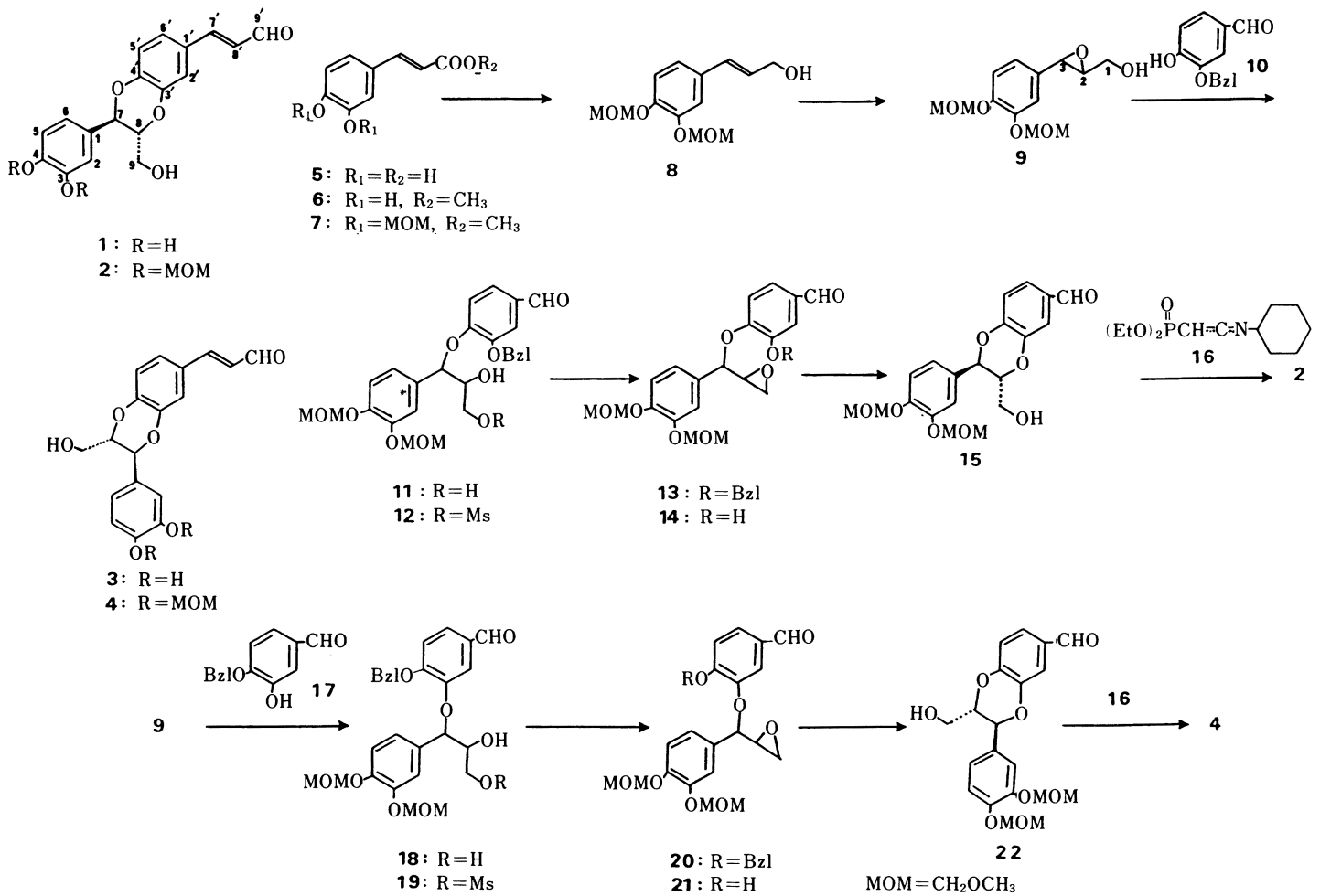
1: R=H
2: R=MOM
5: R1=R2=H
6: R1=H, R2=CH3
7: R1=MOM, R2=CH3
8
9
10
3: R=H
4: R=MOM
11: R=H
12: R=Ms
13: R=Bzl
14: R=H
15
16
17
18: R=H
19: R=Ms
20: R=Bzl
21: R=H
22
MOM=CH2OCH3

Chart 1

ylide (**16**)[9] prepared from diethyl 2-(cyclohexylimino)ethylphosphonate by treatment with sodium hydride, when reacted with **15** at room temperature for 1 h, yielded the desired α,β-unsaturated aldehyde (**2**). Acid hydrolysis of **2** gave americanin A (**1**), which was identical with the natural sample[1] on the basis of mixed melting point determination and direct comparison of infrared (IR) spectra.

We also attempted the synthesis of isoamericanin A (**3**) in a similar manner. Compound **18** was prepared by condensation of **9** with 4-benzyloxy-3-hydroxybenzaldehyde (**17**) under basic conditions in 80% yield. Mesylation of **18** followed by epoxidation and subsequent debenzylation, as described for **14**, afforded the epoxide (**21**) in 71% overall yield from **18**. Treatment of the epoxide (**21**) with potassium carbonate furnished the benzodioxane (**22**), in which the substituents on the benzodioxane nucleus are disposed in a *trans* orientation. Finally, **22** was reacted with the ylide (**16**) to yield the α,β-unsaturated aldehyde (**4**) which was converted to isoamericanin A (**3**) by acid treatment. The above syntheses of americanin A and isoamericanin A established that the correct structure for americanin A is represented by the 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 and high-resolution MS and secondary ion MS (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 carbon-13 nuclear magnetic resonance (^{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, t = triplet, q = quartet, m = multiplet, br = broad).

Methyl 3-(3,4-Dihydroxy)phenyl-2-propenoate (6)——A mixture of caffeic acid (**5**) (25 g) in conc. H_2SO_4 (1.3 ml) and MeOH (250 ml) was refluxed for 8 h. The organic solvent was removed *in vacuo*. The resulting precipitate was collected and washed with water. The crude product was recrystallized from MeOH to give **6** as colorless needles (26 g, 96%). mp 152—153 °C (lit.,[10] mp 152 °C).

Methyl 3-(3,4-Dimethoxymethoxy)phenyl-2-propenoate (7)——NaH (60% in mineral oil) (9.6 g), washed with dry ether, was suspended in dry tetrahydrofuran (THF) (100 ml). The slurry was cooled to 0 °C under a nitrogen atmopshere and a solution of **6** (26 g) in dry THF (100 ml) was slowly added. After the addition, the mixture was stirred at room temperature for 1 h. Then the mixture was cooled to 0 °C and a solution of chloromethoxymethane (30.5 ml) in dry THF (50 ml) was added dropwise. The mixture was stirred at room temperature for 8 h, then quenched by adding water (50 ml). The resulting mixture was extracted with $CHCl_3$. The organic layer was washed with water, dried over Na_2SO_4, and concentrated. The crude product was chromatographed on a silica gel column with a mixture of $CHCl_3$ and acetone (20 : 1), giving **7** as a colorless oil (34 g, 90%). High-resolution MS *m/z*: 282.1102. Calcd for $C_{14}H_{18}O_6$ (M^+). Found: 282.1116. MS *m/z*: 282 (M^+), 207, 206 (100%), 175, 146, 145. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705, 1640, 1600, 1585. ^{1}H-NMR ($CDCl_3$) δ: 3.47, 3.49, 3.75 (9H, 3 × s, 3 × OCH_3), 5.25 (4H, s, 2 × $OC\underline{H}_2OCH_3$), 6.35 (1H, d, J = 16 Hz, C_2-H), 7.14 (3H, m, 3 × aromatic protons), 7.63 (1H, d, J = 16 Hz, C_3-H).

3-(3,4-Dimethoxymethoxy)phenyl-2-propen-1-ol (8)——A suspension of lithium aluminum hydride (4.0 g) in dry ether was added dropwise to a solution of **7** (30 g) in dry ether (30 ml) and dry THF (30 ml) at −10 °C. After the addition, AcOEt (50 ml) and then water (30 ml) were added to the reaction mixture. The resulting mixture was filtered and the filtrate was concentrated. The residue was chromatographed on a silica gel column with a mixture of benzene and AcOEt (1 : 1), giving **8** as a colorless oil (21 g, 78%). High-resolution MS *m/z*: 254.1153 Calcd for $C_{13}H_{18}O_5$ (M^+). Found: 254.1164. MS *m/z*: 254 (M^+), 178 (100%), 162, 161, 150, 135, 122, 120, 119. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1580, ^{1}H-NMR ($CDCl_3$) δ: 2.08 (1H, br s, OH), 3.56 (6H, s, 2 × OCH_3), 4.33 (2H, d, J = 5 Hz, $C\underline{H}_2OH$), 5.28 (4H, s, 2 × $OC\underline{H}_2OCH_3$), 6.31 (1H, m, C_2-H), 6.64 (1H, d, J = 16 Hz, C_3-H), 7.00—7.40 (3H, m, 3 × aromatic protons).

2,3-Epoxy-3-[(3,4-dimethoxymethoxy)phenyl]-1-propanol (9)——A solution of *tert*-butyl hydroperoxide (70% in water) (8.21 ml) in CH_2Cl_2 (50 ml) was added to a mixture of vanadyl acetylacetonate (40 mg) and **8** (7.62 g) in CH_2Cl_2 (100 ml) and the reaction mixture was stirred at room temperature for 6 h. The organic solvent was evaporated off. The residue was chromatographed on a silica gel column with a mixture of benzene and AcOEt (1 : 1), giving **9** as a colorless oil (6.80 g, 84%). High-resolution MS *m/z*: 270.1102 Calcd for $C_{13}H_{18}O_6$ (M^+). Found: 270.1096. MS *m/z*: 270 (M^+), 256, 194, 180, 151, 149, 136, 135 (100%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1580. ^{1}H-NMR ($CDCl_3$) δ: 2.67 (1H, br s, OH), 3.44—4.00 (4H, m, C_1-H, C_2-H, and C_3-H), 3.57 (6H, s, 2 × OCH_3), 5.28 (4H, s, 2 × $OC\underline{H}_2OCH_3$), 6.80—7.32 (3H, m, 3 × aromatic protons).

Condensation of 9 with 10 (Formation of 11)——A solution of **10**[11] (6.83 g) in 1% aq NaOH (120 ml) was stirred at 70 °C under a nitrogen atmosphere and excess epoxide (**9**) (9.0 g) was added over 10 min at 70 °C. The mixture was stirred at the same temperature for 2.5 h and then poured into 1 N NaOH. After extraction with CH_2Cl_2, the organic layer was washed successively with 1 N NaOH and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed on a silica gel column with a mixture of $CHCl_3$ and acetone (5 : 1), giving **11** as a colorless oil (12.0 g, 81%; based on **10** consumed). SIMS *m/z*: 499 ($M^+ + 1$), 421, 271, 239. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 1685, 1600. ^{1}H-NMR ($CDCl_3$) δ: 3.31—3.95 (3H, m, C_8-H and C_9-H), 3.41, 3.46 (6H, 2 × s, 2 × OCH_3), 5.13 (4H, s, 2 × OCH_2), 5.14 (2H, s, OCH_2), 5.27 (1H, d, J=6 Hz, C_7-H), 6.65—7.51 (6H, m, 6 × aromatic protons), 9.66 (1H, s, CHO).

Mesylation of 11 (Formation of 12)——A solution of MsCl (0.31 ml) in CH_2Cl_2 (2 ml) was added to a solution of **11** (1.81 g) in pyridine (1 ml) at −10 °C. The mixture was stirred at the same temperature for 6 h, then the reaction mixture was poured into ice-water and extracted with $CHCl_3$. The organic layer was washed with water, dried over Na_2SO_4, and concentrated. The crude product was chromatographed on a silica gel column with a mixture of $CHCl_3$ and acetone (5 : 1), giving **12** as a colorless oil (1.5 g, 72%). SIMS *m/z*: 577 ($M^+ + 1$), 461, 349, 277. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1690, 1600. ^{1}H-NMR ($CDCl_3$) δ: 2.84 (3H, s, SO_2CH_3), 3.39, 3.43 (6H, 2 × s, 2 × OCH_3) 4.17 (1H, m, C_8-H), 4.40 (2H, d, J=4 Hz, C_9-H), 5.07 (2H, s, OCH_2), 5.15 (4H, s, 2 × OCH_2), 5.16 (1H, d, J=6 Hz, C_7-H), 6.70—7.66 (6H, m, 6 × aromatic protons), 9.62 (1H, s, CHO).

Epoxidation of 12 (Formation of 13)——A mixture of **12** (1.13 g) and anhydrous K_2CO_3 (270 mg) in MeOH (5 ml) was stirred at room temperature for 30 min. The reaction mixture was filtered, then the filtrate was evaporated to dryness, and the residue was dissolved in $CHCl_3$. The organic layer was washed with water, dried over Na_2SO_4, and concentrated. The crude product was chromatographed on a silica gel column with a mixture of $CHCl_3$ and acetone (5 : 1), giving **13** as a colorless oil (930 mg, 99%). $C_{27}H_{28}O_8$. MS *m/z*: 480 (M^+), 450, 437, 349, 253, 228, 221, 209, 189, 177, 149, 147, 135, 119. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685, 1600, 1585. ^{1}H-NMR ($CDCl_3$) δ: 2.62—2.95 (2H, m, C_9-H), 3.22—3.54 (1H, m, C_8-H), 3.42, 3.46 (6H, 2 × s, 2 × OCH_3), 5.10, 5.13, 5.14 (6H, 3 × s, 3 × OCH_2), 5.20 (1H, d, J=2 Hz, C_7-H), 6.78—7.50 (6H, m, 6 × aromatic protons), 9.68 (1H, s, CHO).

Debenzylation of 13 (Formation of 14)——A solution of **13** (923 mg) in AcOEt (20 ml) was hydrogenated over 5% Pd–C (100 mg) under an H_2 atmosphere. The reaction mixture was filtered and the filtrate was concentrated. The crude product was chromatographed on a silica gel column with a mixture of $CHCl_3$ and acetone (5 : 1), giving **14** as a colorless oil (710 mg, 95%). High-resolution MS *m/z*: 390.1313 Calcd for $C_{20}H_{22}O_8$ (M^+). Found: 390.1350. MS *m/z*: 390 (M^+), 254 (100%), 177, 149, 147, 135, 119. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 1680, 1600. ^{1}H-NMR ($CDCl_3$) δ: 2.72—3.42 (3H, m, C_8-H and C_9-H), 3.46 (6H, s, 2 × OCH_3), 4.90 (1H, d, J=2 Hz, C_7-H), 5.21 (4H, s, 2 × OCH_2OCH_3), 6.66—7.50 (6H, m, 6 × aromatic protons), 9.62 (1H, s, CHO).

Cyclization of 14 (Formation of 15)——A mixture of **14** (675 mg) and anhydrous K_2CO_3 (230 mg) in MeOH (10 ml) was stirred at room temperature for 30 min. The reaction mixture was filtered, then the filtrate was evaporated to dryness, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4, and concentrated. The crude product was chromatographed on a silica gel column with a mixture of $CHCl_3$ and acetone (5 : 1), giving **15** as a colorless oil (580 mg, 86%). High-resolution MS *m/z*: 390.1313 Calcd for $C_{20}H_{22}O_8$ (M^+). Found: 390.1290. MS *m/z*: 390 (M^+, 100%), 314, 296, 254, 253, 178, 177, 147, 136, 135. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1690, 1605, 1585. ^{1}H-NMR ($CDCl_3$) δ: 3.43—3.93 (2H, m, C_9-H), 3.49 (6H, s, 2 × OCH_3), 4.01 (1H, m, C_8-H), 5.01 (1H, d, J=8 Hz, C_7-H), 5.21 (4H, s, 2 × OCH_2OCH_3), 6.91—7.49 (6H, m, 6 × aromatic protons), 9.77 (1H, s, CHO).

Wittig Reaction of 15 (Formation of 2)——A solution of diethyl 2-(cyclohexylimino)ethylphosphonate[9] (430 mg) in dry THF (5 ml) was added to a suspension of dry ether–washed NaH (60% in mineral oil) (40 mg) in dry THF (5 ml) with stirring and ice-cooling under a nitrogen atmosphere, and the mixture was stirred for 1 h. A solution of **15** (320 mg) in dry THF (5 ml) was added, and the whole was stirred at room temperature for 1 h. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The organic layer was washed with saturated NaCl, dried over Na_2SO_4, and concentrated. The crude product was chromatographed on a silica gel column with a mixture of $CHCl_3$ and acetone (5 : 1), giving **2** as a colorless oil (290 mg, 85%). High-resolution MS *m/z*: 416.1470 Calcd for $C_{22}H_{24}O_8$ (M^+). Found: 416.1461. MS *m/z*: 416 (M^+, 100%), 340, 322, 281, 254, 251, 178, 160, 150, 136. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1670, 1620, 1610, 1580. ^{1}H-NMR ($CDCl_3$) δ: 3.48—3.92 (2H, m, C_9-H), 3.50 (6H, s, 2 × OCH_3), 4.04 (1H, m, C_8-H), 4.99 (1H, d, J=8 Hz, C_7-H), 5.22 (4H, s, 2 × OCH_2OCH_3), 6.54 (1H, dd, J=16, 8 Hz, $C_{8'}$-H), 6.88—7.24 (6H, m, 6 × aromatic protons), 7.32 (1H, d, J=16 Hz, $C_{7'}$-H), 9.59 (1H, d, J=8 Hz, CHO).

Americanin A (1)——A mixture of **2** (85 mg), 2 N HCl (1 ml) and MeOH (1 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into ice-water and extracted with AcOEt. The organic layer was washed with water, dried over Na_2SO_4, and concentrated. The crude product was recrystallized from MeOH to give **1** as colorless needles (51 mg, 76%). mp 245 °C (lit.,[1] mp 246—247 °C). High-resolution MS *m/z*: 328.0946 Calcd for $C_{18}H_{16}O_6$ (M^+). Found: 328.0924. MS *m/z*: 328 (M^+), 166, 164, 123, 110. IR ν_{max}^{KBr} cm^{-1}: 3300, 1645, 1605, 1575. ^{1}H-NMR (DMSO-d_6) δ: 3.11—3.71 (2H, m, C_9-H), 4.07 (1H, m, C_8-H), 4.87 (1H, d, J=8 Hz, C_7-H), 6.49—7.35 (6H, m, 6 × aromatic protons), 6.84 (1H, dd, J=16, 8 Hz, $C_{8'}$-H), 7.57 (1H, d, J=16 Hz, $C_{7'}$-H), 8.95 (2H, br s, 2 × OH), 9.53 (1H, d, J=8 Hz, CHO). ^{13}C-NMR (DMSO-d_6) δ: 194.0 (d, C-9′), 153.1 (d, C-8′), 146.5 (s, C-3′), 145.9 (s, C-4), 145.2 (s, C-3), 143.5 (s, C-4′), 127.5 (s, C-1′), 127.1 (s, C-1), 126.8 (d, C-7′), 122.6 (d, C-6′), 118.8 (d, C-6), 117.3 (d, C-5′), 116.7 (d, C-2′), 115.5 (d, C-5), 114.9 (d, C-2), 78.1 (d, C-8), 76.1 (d, C-7), 60.0 (t, C-9).

Condensation of 9 with 17 (Formation on 18)——A mixture of **17**[11] (4.2 g) and NaOH (736 mg) in water (74 ml) was stirred at 70 °C under a nitrogen atmosphere and excess epoxide (**9**) (6.7 g) was added over 10 min. The mixture was stirred at the same temperature for 2.5 h. The reaction mixture was treated in a manner similar to that descirbed for **11** to give **18** as a colorless oil (7.3 g, 80%; based on **17** consumed). SIMS *m/z*: 499 ($M^+ + 1$), 421, 271, 239. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: *3550, 1685, 1600.* ^{1}*H-NMR* ($CDCl_3$) *δ: 2.81, 3.14 (2H, 2×brs, 2×OH), 3.38, 3.41 (6H, 2×s,* $2\times OCH_3$), 3.56—4.00 (3H, m, C_8-*H and* C_9-*H), 5.11 (4H, s,* $2\times OCH_2$), *5.13 (2H, s,* OCH_2), *5.21 (1H, d, J=6 Hz,* C_7-H), 6.82—7.40 (6H, m, 6× aromatic protons), 9.56 (1H, s, CHO).

Mesylation of 18 (Formation of 19)——A solution of MsCl (1.11 ml) in CH_2Cl_2 (2 ml) was added dropwise to a mixture of **18** (6.5 g), CH_2Cl_2 (4 ml) and pyridine (3 ml) at −10 °C. The mixture was stirred at the same temperature for 6 h, then treated in a manner similar to that described for **12** to give **19** as a colorless oil (5.5 g, 73%). SIMS *m/z*: 577 ($M^+ + 1$), 461, 349, 277, 221. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 1685, 1600, 1355, 1170. ^{1}H-NMR ($CDCl_3$) *δ*: 2.88 (3H, s, SO_2CH_3), 3.42, 3.44 (6H, $2\times$s, $2\times OCH_3$), 4.16 (1H, m, C_8-H), 4.40 (2H, d, *J*=4 Hz, C_9-H), 5.12 (1H, d, *J*=6 Hz, C_7-H), 5.14 (6H, s, $3\times OCH_2$), 6.84—7.44 (6H, m, 6× aromatic protons), 9.60 (1H, s, CHO).

Epoxidation of 19 (Formation of 20)——A mixture of **19** (5.2 g) and anhydrous K_2CO_3 (1.25 g) in MeOH (20 ml) was stirred at room temperature for 30 min, then treated in manner similar to that described for **13** to give **20** as a colorless oil (4.3 g, 99%), $C_{27}H_{28}O_8$. MS *m/z*: 480 (M^+), 437, 393, 349, 317, 285, 253, 221, 209, 189, 177, 149, 147, 135, 119. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685, 1600. ^{1}H-NMR ($CDCl_3$) *δ*: 2.60—2.82 (2H, m, C_9-H), 3.10—3.40 (1H, m, C_8-H), 3.44 (6H, s, $2\times OCH_3$), 5.14 (1H, d, *J*=2 Hz, C_7-H), 5.16 (6H, s, $3\times OCH_2$), 6.84—7.44 (6H, m, 6× aromatic protons), 9.62 (1H, s, CHO).

Debenzylation of 20 (Formation of 21)——A solution of **20** (4.14 g) in AcOEt (50 ml) was hydrogenated over 5% Pd–C (400 mg) under an H_2 atmosphere, then treated in a manner similar to that described for **14** to give **21** as a colorless oil (3.3 g, 98%). High-resolution MS *m/z*: 390.1313 Calcd for $C_{20}H_{22}O_8$ (M^+). Found: 390.1329. MS *m/z*: 390 (M^+), 254 (100%), 177, 149, 147, 135, 119. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3530, 1680, 1600. ^{1}H-NMR ($CDCl_3$) *δ*: 2.86—3.01 (1H, m, C_9-H), 3.15—3.27 (1H, m, C_9-H), 3.29—3.43 (1H, m, C_8-H), 3.51 (6H, s, $2\times OCH_3$), 4.98 (1H, d, *J*=2 Hz, C_7-H), 5.23 (4H, s, $2\times OCH_2OCH_3$), 6.91—7.53 (6H, m, 6× aromatic protons), 9.65 (1H, s, CHO).

Cyclization of 21 (Formation of 22)——A mixture of **21** (3.3 g) and anhydrous K_2CO_3 (1.2 g) in MeOH (90 ml) was stirred at room temperature for 30 min, then treated in a manner similar to that described for **15** to give **22** as a colorless oil (2.8 g, 85%). High-resolution MS *m/z*: 390.1313 Calcd for $C_{20}H_{22}O_8$ (M^+). Found: 390.1288. MS *m/z*: 390 (M^+, 100%), 314, 296, 254, 253, 178, 177, 147, 136, 135. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1690, 1605, 1585. ^{1}H-NMR ($CDCl_3$) *δ*: 1.82 (1H, brs, OH), 3.50 (6H, s, $2\times OCH_3$), 3.55 (1H, dd, *J*=12.5, 3 Hz, C_9-H), 3.83 (1H, dd, *J*=12.5, 3 Hz, C_9-H), 4.08 (1H, m, C_8-H), 4.94 (1H, d, *J*=8 Hz, C_7-H), 5.20 (4H, s, $2\times OCH_2OCH_3$), 6.92—7.40 (6H, m, 6× aromatic protons), 9.78 (1H, s, CHO).

Wittig Reaction of 22 (Formation of 4)——A solution of diethyl 2-(cyclohexylimino)ethylphosphonate[9] (2.38 g) in dry THF (10 ml) was added to a suspension of dry ether-washed NaH (60% in mineral oil) (210 mg) in dry THF (10 ml) with stirring and ice-cooling under a nitrogen atmosphere, and the mixture was stirred for 1 h. A solution of **22** (1.77 g) in dry THF (10 ml) was added, and the whole was stirred at room temperature for 1 h. The reaction mixture was treated in a manner similar to that described for **2** to give **4** as a colorless oil (1.56 g, 83%). High-resolution MS *m/z*: 416.1470 Calcd for $C_{22}H_{24}O_8$ (M^+). Found: 416.1433. MS *m/z*: 416 (M^+, 100%), 340, 322, 281, 254, 251, 178, 160, 150, 136. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1670, 1620, 1610, 1580. ^{1}H-NMR ($CDCl_3$) *δ*: 1.98 (1H, brs, OH), 3.44—3.92 (2H, m, C_9-H), 3.48 (6H, s, $2\times OCH_3$), 4.05 (1H, m, C_8-H), 4.92 (1H, d, *J*=8 Hz, C_7-H), 5.20 (4H, s, $2\times OCH_2OCH_3$), 6.50 (1H, dd, *J*=16, 8 Hz, $C_{8'}$-H), 6.86—7.16 (6H, m, 6× aromatic protons), 7.29 (1H, d, *J*=16 Hz, $C_{7'}$-H), 9.56 (1H, d, *J*=8 Hz, CHO).

Isoamericanin A (3)——A mixture of **4** (492 mg), 2 N HCl (5 ml) and MeOH (5 ml) was stirred at room temperature for 2 h. The reaction mixture was treated in a manner similar to that described for **1** to give a solid, which was recrystallized from MeOH to give **3** as yellow needles (320 mg, 82%), mp 174—176 °C (lit.,[2] mp 177—178 °C). High-resolution MS *m/z*: 328.0946 Calcd for $C_{18}H_{16}O_6$ (M^+). Found: 328.0938. MS *m/z*: 328 (M^+), 166, 164, 123, 110. IR ν_{max}^{KBr} cm^{-1}: 3200, 1650, 1600, 1575. ^{1}H-NMR (DMSO-d_6) *δ*: 3.16—3.72 (2H, m, C_9-H), 4.14 (1H, m, C_8-H), 4.85 (1H, d, *J*=8 Hz, C_7-H), 6.66 (1H, dd, *J*=16, 8 Hz, $C_{8'}$-H), 6.68—7.36 (6H, m, 6× aromatic protons), 7.52 (1H, d, *J*=16 Hz, $C_{7'}$-H), 9.02 (1H, brs, OH). 9.52 (1H, d, *J*=8 Hz, CHO). ^{13}C-NMR (DMSO-d_6) *δ*: 194.0 (d, C-9′), 153.1 (d, C-8′), 146.3 (s, C-3′), 145.9 (s, C-4), 145.3 (s, C-3), 143.9 (s, C-4′), 127.4 (s, C-1′), 127.3 (s, C-1), 126.8 (d, C-7′), 123.0 (d, C-6′), 118.9 (d, C-6), 117.3 (d, C-5′), 116.8 (d, C-2′), 115.6 (d, C-5), 115.1 (d, C-2), 78.8 (d, C-8), 75.7 (d, C-7), 60.2 (t, C-9).

The IR, ^{1}H-NMR, and ^{13}C-NMR spectra of the product were superimposable on those of a natural specimen.[2]

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