Trichoverroid Stereoisomers

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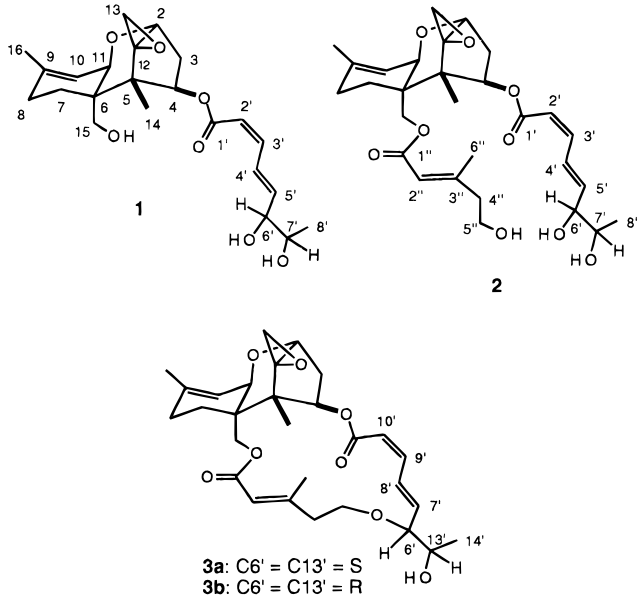
Trichoverroids, which lie along the biosynthetic path between the simple and the macrocyclic trichothecenes, have been characterized previously as sets of diastereomers that have the *S*-configuration at C-6′ and are epimeric at C-7′. An isolate of *Myrothecium verrucaria* (ATCC 20540), which is the only species of *Myrothecium* reported to produce the macrocyclic trichothecene isororidin E (**3a**), produces trichoverrols (**1**) and trichoverrins (**2**) that are epimeric at C-7′ but that have *R*-configurations at the C-6′ centers. Also reported are several additional naturally occurring C6′*R*-series trichoverroids that have varied structural modifications, including several *E*,*Z*-isomers **7**−**9**, 9*β*,10*β*-epoxides **11a** and **b**, 12,13-deoxyisotrichoverrin B (**10**), and 8α-hydroxyisotrichoverrin A (**12**).

The trichothecene complex of antibiotics can be divided into two classes: simple[1] and macrocyclic.[2] The trichoverroids lie along the biosynthetic path leading from the simple to the macrocyclic trichothecenes.[3] The two principal types of trichoverroids are the trichoverrols (e.g., **1**), which are C8 monoesterified simple trichothecenes at carbon-4, and the trichoverrins (e.g., **2**), which are simple trichothecenes esterified at both C-4 and C-15. The trichoverroids are produced by *Myrothecium* species of fungi,[2] and they are obtained as sets of diastereomers, epimeric at C-7′. The A-series are C6′(*S*),C7′(*S*) (*threo*), and the B-series are C6′(*S*),C7′(*R*) (*erythro*).[3] The A- and B-series trichoverroids can be distinguished by ^{1}H-NMR spectroscopy, wherein the H-6′ signal appears as a five-line multiplet ($J_{5',6'} \sim J_{6',7'} \sim 6.5$ Hz) in the A epimers but appears as an eight-line multiplet ($J_{5',6'} \sim 3.3$ Hz, $J_{6',7'} \sim 6.5$ Hz) in the B epimers. Whereas the C-6′ centers in the trichoverrols **1** and in the trichoverrins **2** are *S*, the corresponding centers in the ring-closed macrocyclic trichothecenes (e.g., roridins and baccharinoids) are *R*. There are a number of examples of roridins (especially the plant-derived baccharinoids)[4] that are epimeric at C-13′, the stereogenic center that corresponds to the C-7′ center in the trichoverroids; however, the only macrocyclic trichothecene reported to have the C6′*S* configuration is isororidin E (**3a**), in which both C-6′ and C-13′ are *S*.[5] These centers are both *R* in roridin E (**3b**). Furthermore, whereas roridin E (**3b**) is produced commonly by *Myrothecium verrucaria* and *Myrothecium roridum*,[2] the only *Myrothecium* species reported to produce isororidin E is *M. verrucaria* (ATCC 20540),[5] although **3a** was first isolated from a culture of *Cylindrocarpon* species.[6]



Results and Discussion

We have isolated the trichoverroids from a culture of *M. verrucaria* ATCC 20540 in order to compare them with those isolated earlier from *M. verrucaria* ATCC 24571.[3] The trichoverrols **1** and trichoverrins **2** isolated from *M. verrucaria* ATCC 20540 appeared at first to be identical to the trichoverroids isolated from other species of *Myrothecium* (e.g., *M. verrucaria* ATCC 24571).[3] In fact, the ^{13}C-NMR data for the trichoverrols isolated from *M. verrucaria* ATCC 20540 were identical to the ^{13}C-NMR data for the trichoverrols isolated from *M. verrucaria* ATCC 24571. There were, however, some subtle differences (e.g., optical rotations), which prompted us to determine the X-ray crystal structure of the "trichoverrol A" isolated from the culture of *M. verrucaria* ATCC 20540 for which an ORTEP diagram is presented in Figure 1. This analysis showed the "trichoverrol A" from ATCC 20540 to be **1**, C6′*R*,C7′*R* rather than **1**, C6′*S*,C7′*S*, as was found with **1** obtained from *M. verrucaria* ATCC 24571.[7] We call the C′6*S* series trichoverroids and the C6′*R* series isotrichoverroids. Thus, isolate ATCC 20540 produces isotrichoverrols A (**1**, C6′*R*,C7′*R*) and B (**1**, C6′*R*,C7′*S*). In a similar fashion we isolated the isotrichoverrins A (**2**, C6′*R*,C7′*R*) and B (**2**, C6′*R*,C7′*S*). The ^{1}H-NMR spectra of trichoverrin A (**2**, C6′*S*,C7′*S*) and isotrichoverrin A (**2**, C6′*R*,-C7′*R*) at 200 MHz are virtually identical, with the only discernible difference being a small (0.04 ppm) upfield shift of the C-5′ proton in isotrichoverrin **A** (**2**, C6′*R*,-C7′*R*) relative to the H-5′ signal in trichoverrin A (**2**, C6′*S*, C7′*S*). This difference could be verified only by obtaining the ^{1}H-NMR spectrum on a 50−50 mixture of trichoverrin A (**2**, C6′*S*,C7′*S*) and isotrichoverrin A (**2**, C6′*R*,C7′*R*). In the case of trichoverrin B (**2**, C6′*S*,-C7′*R*) and isotrichoverrin B (**2**, C6′*R*,C7′*S*), the ^{1}H-NMR spectrum of the 50−50 mixture at 400 MHz showed

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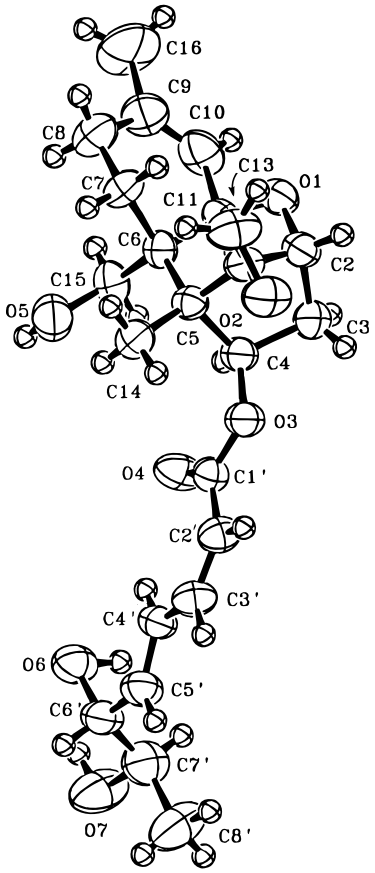
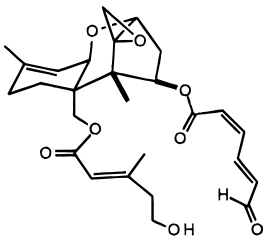


Figure 1. ORTEP diagram for isotrichoverrol (**1**C6′*R*,C7′*R*).

overlapping signals for the H-4 protons; all the other signals were superimposable.

To secure the stereochemical relationships between the trichoverrins (**2**, C6′*S*) and the isotrichoverrins (**2**, C6′*R*), we sought to oxidize the C6′ allylic alcohol to the corresponding ketone. Trichoverrin A (**2**, C6′*S*,C7′*S*) and isotrichoverrin B (**2**, C6′*R*,C7′*S*) would give the same C6′ ketone, and isotrichoverrin A (**2**, C6′*R*,C7′*R*) and trichoverrin B (**2**, C6′*S*,C7′*R*) would each give the same C6′ ketone, but one different from that obtained in the oxidation of trichoverrin A and isotrichoverrin B. Oxidation of the trichoverrins (**2**) with MnO_2 gave only cleavage of the *vic*-diol[8] to yield aldehyde **4**. However, oxidation with dichlorodicyanobenzoquinone (DDQ),[9] which does not cleave allylic *vic*-diols,[10] gave the desired C6′ ketones **5** accompanied by the 2′*E*-isomers **6**. Thus, trichoverrin A (**2**, C6′*S*,C7′*S*) and isotrichoverrin B (**2**, C6′*R*,C7′*S*), upon treatment with DDQ, gave ketones **5a** (40%) and **6a** (30%), whereas isotrichoverrin A (**2**, C6′*R*,C7′*R*) and trichoverrin B (**2**, C6′*S*,C7′*R*) gave ketones **5b** (40%) and **6b** (30%). On the basis of the known stereochemistries of the trichoverrins at C-6′ and C-7′,[7] these data clearly establish that isotrichoverrin A is C6′*R*,C7′*R* and isotrichoverrin B is C6′*R*,C7′*S*.

In addition to the previously reported trichoverrin C and the 2′*E*-isotrichoverrins A and B from *M. verrucaria* ATCC 20 540,[11] we now add to the list of minor metabolites produced by this fungus the following congeners: (2′*E*,4′*Z*′)-isotrichoverrins A (**7a**) and B (**7b**), (2′*E*)-isotrichverrols A (**8a**) and B (**8b**), (2′*E*)-roridin L-2 (**9**), (2′*E*)-12,13-deoxyisotrichoverrin B (**10**), 9β,10β-epoxyisotrichoverrins A (**11a**) and B (**11b**), and 8α-hydroxyisotrichoverrin A (**12**). These compounds were



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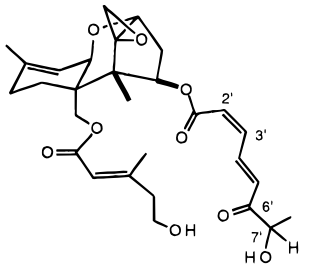
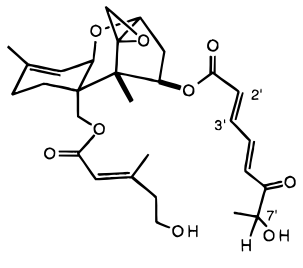


5a: C7′ = S
5b: C7′ = R



6a: C7′ = S
6b: C7′ = R

all isolated as minor metabolites from the *M. verrucaria* ATCC 20 540 culture after extensive chromatographic procedures (see Experimental Section) and characterized by ^{1}H- and ^{13}C-NMR spectroscopies and HRMS, which established their molecular formulas. Because this fungal isolate produces the *R*-series trichoverroids, we assume that all these minor trichoverroid metabolites have the C6′*R* configurations as well. The A- and B-series assignments were based on the observed proton couplings between H-6′ and H-7′.

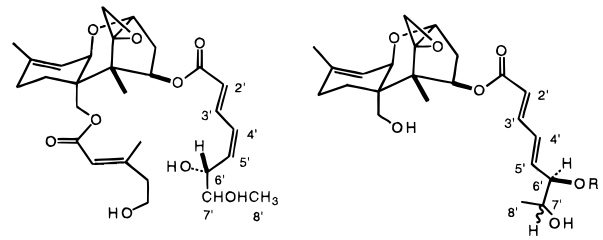
The 2′,4′-diene functionality found in the naturally occurring trichoverroids and macrocyclic trichothecenes nearly always has the 2′*Z*,4′*E* configuration, with the only reported exceptions being the (2′*E*)-isotrichoverrins A and B also isolated from *M. verrucaria* ATCC 20540.[11] However, Roush and Blizzard have prepared the *E*,*E* and the *E*,*Z* isomers of verrucarins B and J during the course of their total synthesis of these compounds.[12,13] Metabolites **7a** and **7b** are the first naturally occurring metabolites in this series reported to have the 2′*E*,4′*Z* configuration, and metabolites **8**−**10**, along with the previously reported (2′*E*)-isotrichoverrins A and B,[11] constitute the only reported naturally occurring 2′(*E*),4′-(*E*)-diene trichoverroids. The stereochemistries of the diene chains are readily apparent from analysis of the proton NMR spectra. Thus for the 2′(*E*),4′(*E*)-dienes, $J_{2',3'}$ and $J_{4',5} \sim 15-16$ Hz (e.g., **8a** and **8b**, Table 1). For the corresponding congeners with the 2′(*Z*),4′(*E*)-diene configuration, $J_{2',3'} = 11.3$ Hz and $J_{4',5'} = 15.5$ Hz (e.g., isotrichoverrins **2**, Table 1), and for the 2′(*E*),4′-(*Z*)-diene configuration, $J_{2',3'} \sim 15.2$ Hz and $J_{4',5'} \sim 11$ Hz (e.g., **7a** and **7b**, Table 1). In the typical (2′*Z*,4′*E*)-trichoverroids, the H-4′ proton is found at highest frequency (around 7.5 ppm) but moves upfield by about 1 ppm in the 2′*E*,4′*E* and 2′*E*,4′*Z* congeners. In these latter compounds, the H-3′ resonance moves downfield by about 1 ppm and becomes the highest-frequency signal in these compounds (see Table 1). Another notable effect is observed in the ^{13}C-NMR spectra of **7a** and **7b**, where both the C-3′ and C-6′ resonances shift upfield by about 4 ppm (relative to the carbon signals in the corresponding 4′*E* congeners; e.g., **8**−**10**) due to the *gauche* effect.

Table 1. ^{1}H-NMR Data for Protons 2′, 3′, 4′, 5′, and 6′ in Selected Trichoverroids[a]

H	**2A**[b]	**2b**[c]	**7a**	**7b**	**8a**	**8b**
2′	5.67 (11.3)	5.66 (11.3)	5.95 (15.2)	5.94 (15.1)	5.94 (15.4)	5.93 (15.3)
3′	6.59 (11.3, 11.3)	6.60 (11.3, 11.3)	7.64 (11.9, 15.2)	7.59 (11.8, 15.1)	7.29 (11.3, 15.4)	7.29 (10.9, 15.3)
4′	7.54 (11.3, 15.5)	7.52 (11.3, 15.5)	6.24 (10.7, 11.9)	6.26 (11.0, 11.8)	6.45 (11.3, 15.4)	6.42 (10.9, 15.9)
5′	6.07 (4.7, 15.5)	6.11 (5.2, 15.5)	5.79 (8.3, 10.7)	5.88 (8.6, 11.0)	6.10 (6.1, 15.4)	6.13 (5.9, 15.9)
6′	4.03 (m)	4.23 (m)	4.37 (6.7, 8.3)	4.60 (3.3, 8.6)	3.97 (6.1, 6.3)	4.21 (m)

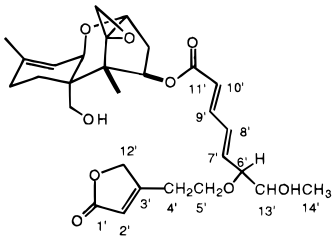
[a] Chemical shifts are in ppm and coupling constants (in Hz) are in parentheses. [b] **2A** is **2**,C6′*R*,C7′*R*. [c] **2B** is **2**, C6′*R*,C7′*S*.

Metabolite **9** exhibits NMR spectral characteristics very similar to those of roridin L-2,[14] though the proton data clearly show the diene to be 7′*E*,9′*E* ($J_{7',8'}$ and $J_{9',10'}$ ~ 15.3 Hz). In the same manner, metabolite **10** can be shown to be the *R*-series 2′*E* isomer of the previously characterized 12,13-deoxytrichoverrin B.[15] The NMR spectra of epoxides **11a** and **11b** resemble closely those of the isotrichoverrins with a few significant changes. The chemical shifts of H-10 and H-16 in **11** (cf. to these signals in **2**) are shifted upfield by 3.1 and 1.5 ppm, respectively, with $J_{10,11}$ ~ 5.5 Hz securing the assignment of the configuration of the 9β,10β-epoxide.[16] The C-9 and C-10 NMR signals have moved upfield to ca. 58 ppm, consistent with the presence of the 9,10-epoxide group. The NMR spectra of **12** resemble closely those of isotrichoverrin A, with the major difference being the shift of C-8 from ca. 28 ppm to 66.5 ppm. The corresponding proton signal also shifts from ca. 2 ppm (in **2**) to 4.11 ppm (in **12**). A downfield shift of the resonances of both H-15 and C-15 is consistent with the hydroxyl group at C-8 being α.[3,4]



7a: C7′ = R
7b: C7′ = S

8a: R = H; C7′ = R
8b: R = H; C7′ = S



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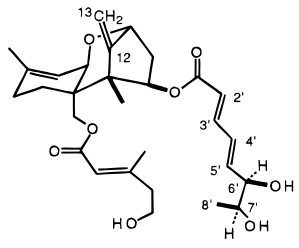

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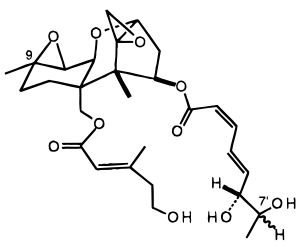
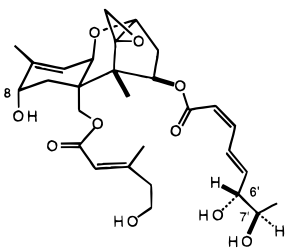


11a: C7′ = R
11b: C7′ = S



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The isolations of 12,13-deoxytrichothecenes **10** and epoxides **11** are notable in that there are few reports of naturally occurring trichothecenes with these structural variations, that is, 9,10-epoxides[16] and 12,13-deoxy congeners.[15,17,18]

During the course of these isolations, we relied very heavily on high speed countercurrent chromatography (CCC).[19] This technique has proven very powerful in several difficult isolations and has exhibited surprising selectivity. For example, in the separation of a fraction (S2F2, see Experimental Section) containing a number of isomeric trichoverrins, CCC not only gave base line separation of the A and B epimers of both isotrichoverrin (**2**, C6′*R*) and the 2′*E*-isotrichoverrins,[11] but also eluted (2′*E*)-isotrichoverrins A and B from the preparative CCC column with retention times of over an hour longer than those observed with the isotrichoverrins. The (2′*E*,4′*Z*)-isotrichoverrins (**7a** and **7b**) under these same conditions elute from the preparative CCC column with an intermediate retention time, about 30 min after the isotrichoverrins and 30 min before the 2′*E*-isotrichoverrins.

Experimental Section

General Experimental Procedures. IR spectra were determined on a Nicolet 5DXC FT spectrometer. NMR spectra were obtained in $CDCl_3$ on Bruker FT-NMR instruments (AMX-500, AM-400, and AF-200) using either the δ 0.00 signal of TMS or the δ 7.24 signal of $CDCl_3$ as an internal standard. ^{1}H-NMR signals were assigned by homonuclear (^{1}H−^{1}H) COSY 45, heteronuclear (^{1}H−^{13}C) COSY, and long-range heteronuclear (^{1}H-^{13}C) shift correlation (HETCOR) carried out in the inverse detection mode. ^{13}C-NMR signals were assigned by the above techniques as well as by IUNEPT and by comparison of chemical shift data with those in the literature. The δ 77.0 signal of $CDCl_3$ was used as an internal standard. HRMS data were collected on a VG 707OE mass spectrometer using direct probe by chemical ionization (CI) or by electron impact (EI) (70 eV) mode. TLC was performed on precoated TLC plates of Si gel 60F-254. Visualization was done by viewing the developed plates under short-wavelength UV light or by spraying with vanillin spray [40 g/L vanillin in EtOH−H_2SO_4 (1:4)]. Preparative TLC was achieved on the Model 7942 Chromatotron (Harrison Research Laboratories). The Chromatotron plates (1 mm) were prepared according to the instructions in the manual using E. Merck Si gel. All the CCC separations were performed with a high-speed countercurrent chromatograph, Model CCC-1000 (Pharm-Tech Research Corp., Baltimore, MD), equipped with interchangeable columns. The three columns used in this work were analytical (V_c = 55 mL), semipreparative (V_c = 355 mL), and preparative (V_c = 850 mL). Each column consisted of three multiple-layer coils of PTFE tubing (i.d. 0.85 mm for analytical, 1.6 mm for semipreparative, and 2.6 mm for preparative).

General operation conditions were as follows (if not otherwise noted): Lower organic layer was the mobile phase with solvent flow from head to tail [H-(T)]. Rotatory speeds were 1200 rpm (analytical column) and 1000 rpm (semipreparative and preparative columns). Samples were dissolved in the organic layer, and the volumes of samples for each injection were 0.5 mL (analytical column), 5.0 mL (semipreparative column), and 5−10 mL (preparative column). The eluent from the outlet of the column was continuously monitored by a Knauer variable wavelength monitor connected to a Fisher recorder. The wavelength of the monitor varied between 260 and 290 nm, depending on sample size. The solvent was delivered by a LDC/Milton minipump. The organic phase was used as the mobile phase.

The operating procedure of the CCC was as follows. The column was first filled with stationary phase, then the mobile phase was pumped into the column while the column rotated at the operation speed. After a certain amount of the stationary phase was displaced (the amount varied with column size and solvent system) and the flow of the mobile phase became steady, the sample was loaded onto the column. All the solvents used in CCC and TLC were commercial grade and were glass distilled before use, except MeOH, which was reagent grade (Fisher Scientific). The two solvent phases used in CCC were thoroughly equilibrated in a separatory funnel before use.

The fermentation procedures with *M. verrucaria* ATCC 20540 were carried out in a manner similar to those described previously.[3] Samples 1−4 (S1, S2, S3, and S4) from this isolate were the lower R_f fractions from Si gel chromatography (MeOH/CH_2Cl_2), given in the order of increasing polarity.

Isolation of Isotrichoverrol A (1, C6′*R*,C7′*R*). To sample 1, (S1, 5 g), which contained some solid material, was added 100 mL of cold EtOAc. The solid was collected and recrystallized from CH_2Cl_2/hexane to give isotrichoverrol A (170 mg), mp 180−183 °C. A portion was recrystallized from Me_2CO/EtOAc to give a crystal (mp 180−181 °C) suitable for X-ray crystallographic analysis. For isotrichoverrol A: $[\alpha]^{20}_D$ +54.0° (*c* 1.65, $CHCl_3$); HRMS (CI) *m*/*z* calcd for $C_{23}H_{33}O_7$ ($[M + H]^+$) 421.2226, found 421.2211; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.81 (3 H, s, H-14), 1.19 (3 H, d, J = 6.3 Hz, H-8′), 1.54 (1 H, br d, J = 7.6 Hz, H-7A), 1.70 (3 H, s, H-16), 1.98 (3 H, m, H-7B, H-8), 2.08 (1 H, ddd, J = 4.0, 5.1, 15.4 Hz, H-3β), 2.49 (1 H, dd, J = 8.0, 15.4 Hz, H-3α), 2.83 (1 H, d, J = 4.0 Hz, H-13A), 3.14 (1 H, d, J = 4.0 Hz, H-13B), 3.63 (1 H, d, J = 12.3 Hz, H-15A), 3.67, (1 H, dq, J = 6.3, 6.3 Hz, H-7′), 3.80 (1 H, d, J = 12.3 Hz, H-15B), 3.83 (1 H, d, J = 5.1 Hz, H-2′), 3.88 (1 H, br d, J = 5.0 Hz, H-11), 4.03 (1 H, m, H-6′), 5.47 (1 H, br d, J = 5.0 Hz, H-10), 5.70 (1 H, d, J = 11.5 Hz, H-2′), 6.06 (1 H, dd, J = 5.7, 15.5 Hz, H-5′), 6.08 (1 H, m, H-4), 6.61 (1 H, dd, J = 11.3, 11.5 Hz, H-3′), 7.59 (1 H, dd, J = 11.3, 15.5 Hz, H-4′). The ^{13}C NMR data are identical to those reported earlier for trichoverrol A (**1**, C6′*S*,-C7′*S*).[3]

Single Crystal X-Ray Analysis of Isotrichoverrol A. A colorless crystal of isotrichoverrol A (**1**, C6′*R*,C7′*R*) was obtained from Me_2CO/EtOAc and measured 0.1 × 0.25 × 0.3 mm. Data were acquired on a Enraf-Nonius CAD4 diffractometer with graphite monochromator and Cu radiation (I = 1.54178 Å): monoclinic, P21, a = 11.230(1), b = 7.0981(9), c = 14.118(2) Å, b = 97.01(1)°; 2q/q scans, maximum q = 69.9°. Eight standard were intensities measured every 1 h of X-ray exposure; mean intensity change = −5.0%; range = −8.4 to −3.1%; 2547 total data measured; 2407 without standards; 2312 unique; 1997$I \geq 3s(I)$. Structure solution was obtained by direct methods: least-squares refinement with anisotropic temperature factors for C, N, and O and isotropic terms for H; terms for 3 H's fixed with final R, weighted R, and goodness of-fit values of 0.060, 0.086, 2.37.[20]

Isolation of Isotrichoverrol B (1, C6′*R*,C7′*S*) and Related Trichoverroids. The remaining portion of S1 was subjected to semipreparative CCC (V_c = 355 mL) with a solvent system of MeOH/H_2O/$CHCl_3$/hexane (3:2:3:1.2), flow rate was 2.4 mL/min, (ca. 400 mg/injection, total 10 injections) to give 310 mg of isotrichoverrol A and 250 mg of isotrichoverrol B: an oil; $[\alpha]^{20}_D$ −4.0° (*c* 1.50, $CHCl_3$); HRMS (CI) *m*/*z* calcd for $C_{23}H_{33}O_7$ ($[M + H]^+$) 421.2226, found 421.2206; ^{1}H NMR ($CDCl_3$, 200 MHz), δ 0.80 (3 H, s, H-14), 1.12 (3 H, d, J = 6.4 Hz, H-8′), 1.57 (1 H, m, H-7A), 1.70 (3 H, s, H-16), 1.98 (3 H, m, H-7B, H-8), 2.08 (1 H, ddd, J = 4.0, 5.2, 15.4 Hz, H-3β), 2.49 (1 H, dd, J = 7.8, 15.4 Hz, H-3α), 2.82 (1 H, d, J = 3.9 Hz, H-13A), 3.12 (1 H, d, J = 3.9 Hz, H-13B), 3.61 (1 H, d, J = 12.3 Hz, H-15A), 3.81 (1 H, d, J = 12.3 Hz, H-15B), 3.83 (1 H, d, J = 5.2 Hz, H-2), 3.86 (1 H, br d, J = 5.1 Hz, H-11), 3.90 (1 H, dq, J = 3.5, 6.5 Hz, H-7′), 4.25 (1 H, m, H-6′), 5.45 (1 H, br d, J(= 5.1 Hz, H-10), 5.70 (1 H, d, J = 11.4 Hz, H-2′), 6.09 (1 H, m, H-4), 6.11 (1 H, dd, J = 6.0, 15.4 Hz, H-5′), 6.63 (1 H, dd, J = 11.3, 11.4 Hz, H-3′), 7.55 (1 H, dd, J = 11.3, 15.4 Hz, H-4′). The ^{13}C NMR data are identical to those reported earlier for trichoverrol B (**1**, C6′*S*,C7′*R*).[3]

Another fraction (780 mg) from this CCC was subjected to CCC (semipreparative column) with a solvent system of CH_2Cl_2/CCl_4/MeOH/H_2O (2:3:3:2) (ca. 400 mg/injection). The major fraction of this sample was eluted with little retention from the column, and there were no detectable trichothecenes in this fraction, according to TLC analysis. Seven additional fractions were collected: S1F1a (20 mg), S1F1b (24 mg), S1F1c (48 mg), S1F1d (67 mg), S1F1e (20 mg), S1F1f (17 mg), and S1F1g (55 mg of mixture of 2′*E*-isotrichoverrins A and B[11]).

S1F1d was subjected to reversed-phase TLC on C_8 (20 plates, 0.25 mm, 5 cm × 10 cm, 60% MeOH in H_2O) to give 34 mg of isotrichoverrin A and 3 mg of (9′*E*) roridin L-2 (**9**): an oil; HRMS (EI) *m*/*z* calcd for $C_{29}H_{38}O_9$ (M^+) 530.2516, found 530.2516; ^{1}H NMR δ 0.81 (3 H, s, H-14), 1.11 (3 H, d, J = 6.3 Hz, H-14′), 1.71 (3 H, s, H-16), 2.49 (1 H, dd, J = 7.9, 15.5 Hz, H-3α), 2.70 (2 H, t, J = 6.0 Hz, H-4′), 2.81 (1 H, d, J = 4.0 Hz, H-13A), 3.13 (1 H, d, J = 4.0 Hz, H-13B), 3.83 (1 H, d, J = 5.1 Hz, H-2), 3.92 (1 H, bd, J = 5.7 Hz, H-11), 4.77 (2 H, d, J = 1.5 Hz, H-12′), 5.48 (1 H, bd, J = 5.7 Hz, H-10), 5.90 (1 H, d, J = 1.5 Hz, H-2′), 5.90 (1 H, dd, J = 8.2, 15.3 Hz, H-7′), 5.97 (1 H, d, J = 15.4 Hz, H-10′), 6.12 (1 H, dd, J = 3.6, 7.9 Hz, H-4), 6.36 (1 H, dd, J = 11.0, 15.3 Hz, H-8′), 7.27 (1 H, dd, J = 11.0, 15.4 Hz, H-9′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 6.6 (C-14), 18.4 (C-14′), 19.0 (C-12′), 23.2 (C-16), 28.0 (C-8), 29.3 (C-4′), 31.3 (C-7), 35.9 (C-3), 44.2 (C-6), 48.2 (C-13), 49.0 (C-5), 63.0 (C-15), 65.6 (C-12), 66.2 (C-5′), 66.8 (C-11), 71.4 (C-13′), 75.8 (C-4), 79.0 (C-2), 85.9 (C-6′), 116.7 (C-2′), 118.8 (C-10), 122.6

(C-10′), 132.4 (C-8′), 138.6 (C-7′), 140.5 (C-9), 143.4 (C-9′), 166.8 (C-11′), 167.4 (C-3′), 173.2 (C-1′).

S1F1e was subjected to reversed-phase TLC of C_{18} (eight plates, 0.200 mm, 5 cm × 10 cm, 70% MeOH in 0.5 M NaCl aqueous solution) to give 8 mg of (2′*E*,4′*Z*)-isotrichoverrin A (**7a**), an amorphous solid: IR ($CHCl_3$) 3600 (OH), 1710 (C═O), 1652 (C═C) cm^{-1}; UV ($CHCl_3$) λ max (log ϵ) 261 (4.49) nm; HRMS (CI) *m/z* calcd for $C_{29}H_{41}O_9$ ($[M + H]^+$) 533.2751, found 533.2772; ^1H NMR ($CDCl_3$), δ 0.78 (3 H, s, H-14), 1.12 (3 H, d, J = 6.3 Hz, 8′-H), 1.69 (3 H, s, 16-H), 2.17 (3 H, d, J = 1.0 Hz, 6″-H), 2.40 (2 H, m, H-4″), 2.55 (1 H, dd, J = 7.9, 16.0 Hz, H-3α), 2.81 (1 H, d, J = 4 Hz H-13A), 3.13 (1 H, d, J = 4.0 Hz, H-13B), 3.66 (1 H, dq, J values ∼6.6 Hz, H-7′) 3.83 (1 H, d, J = 5.3 Hz, H-2), 3.94 (1 H, bd, J = 4.8 Hz, H-11), 4.10 (2 H, s, H-15), 4.37 (1 H, dd, J = 6.7, 8.1 Hz, H-6′), 5.46 (1 H, bd, J = 4.8 Hz, H-10), 5.79 (1 H, dd, J = 8.3, 10.7 Hz, H-5′), 5.81 (1 H, d, J = 1.0 Hz, H-2″), 5.95 (1 H, d, J = 15.2 Hz, H-2′), 6.13 (1 H, dd, J = 3.4, 7.9 Hz, H-4), 6.24 (1 H, dd, J = 10.7, 11.89 Hz, H-4′), 7.64 (1 H, dd, J = 11.9, 15.2 Hz, H-3′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 6.6 (C-14), 18.6 (C-8′), 19.0 (C-6″), 21.9 (C-7), 23.2 (C-16), 27.8 (C-8), 36.7 (C-3), 43.0 (C-6), 43.7 (C-4″), 48.1 (C-13), 48.6 (C-5), 59.7 (C-5″), 63.5 (C-15), 65.5 (C-12), 66.8 (C-11), 70.7 (C-7′), 72.4 (C-6′), 75.7 (C-4), 79.1 (C-2), 117.1 (C-2″), 118.5 (C-10), 123.1 (C-2′), 129.2 (C-4′), 138.6 (C-5′), 139.8 (C-3′), 140.5 (C-9), 157.0 (C-3″), 165.9 (C-1″), 166.9 (C-1′).

S1F1f was subjected to reversed-phase TLC on C_8 (five plates, 0.25 mm, 5 cm × 10 cm, 55% of MeOH in H_2O) to give 6 mg of (2′*E*)-12,13-deoxyisotrichoverrin B (**10**) as an oil: IR ($CHCl_3$) 1707 (C═O), 1652 (C═C) cm^{-1}; UV ($CHCl_3$) λ max (log ϵ) 260 (4.44) nm; HRMS (CI) *m/z* calcd for $C_{29}H_{41}O_8$ ($[M + H]^+$) 517.2801, found 517.2849; ^1H NMR δ 1.02 (3 H, s, H-14), 1.12 (3 H, d, J = 6.5 Hz, H-8′), 1.66 (3 H, s, H-16), 2.18 (3 H, d, J = 1.0 Hz, H-6″), 2.39 (2 H, t, J = 5.6 Hz, H-4″), 2.57 (1 H, dd, J = 7.7, 15.5 Hz, H-3α), 3.76∼3.90 (3 H, m, H-7′, H-5″), 3.96 (1 H, bd, J = 5.7 Hz, H-11), 4.11 (2 H, s, H-15), 4.18 (1H, m, H-6′), 4.42 (1 H, d, J = 5.1 Hz, H-2), 4.71 (1 H, s, H-13A), 5.13 (1 H, s, H-13B), 5.41 (1 H, bd, J = 5.7 Hz, H-10), 5.83 (1 H, d, J = 15.4 Hz, H-2′), 5.84 (1 H, d, J = 1.1 Hz, H-2″), 6.06 (1 H, dd, J = 3.0, 7.7 Hz, H-4), 6.11 (1 H, dd, J = 5.9, 15.6 Hz, H-5′), 6.39 (1 H dd, J = 10.9, 15.6 Hz, H-4′), 7.21 (1 H, dd, J = 10.9, 15.4 Hz, H-3′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.1 (C-14), 17.6 (C-8′), 19.0 (C-6″), 20.9 (C-7), 23.2 (C-16), 28.0 (C-8), 37.9 (C-3), 42.8 (C-6), 43.8 (C-4″), 51.6 (C-5), 59.8 (C-5″), 63.7 (C-15), 66.6 (C-11), 70.2 (C-7′), 75.4 (C-4), 75.6 (C-6′), 78.8 (C-2), 105.4 (C-13), 117.3 (C-2″), 118.8 (C-10), 121.8 (C-2′), 129.8 (C-4′), 140.2 (C-5′), 140.1 (C-9), 143.9 (C-3′), 152.3 (C-12), 156.7 (C-3″), 166.2 C-1″), 166.5 (C-1′).

Fraction S1F2 (700 mg) contained mainly trichoverrols according to TLC analysis. The sample was subjected to CCC (preparative column) with a solvent system of $CHCl_3$/hexane/MeOH/H_2O (3:1:3:2) and a flow rate of 3.2 mL/min to give six fractions: S1F2a (100 mg), S1F2b (160 mg), S1F2c (60 mg), S1F2d (160 mg), S1F2e (120 mg), and S1F2f (30 mg). S1F2e was further chromatographed on CCC (semipreparative column) with a solvent system of $CHCl_3$/hexane/MeOH/H_2O (3:1:3.2) and a flow rate of 2.0 mL/min. The chromatogram appeared as a single peak; however, the eluent was collected into two parts, A (80 mg) and B (30 mg). Fraction B was a mixture of 2′*E*-isotrichoverrol A (**8a**) and an uncharacterized trichoverroid as a minor component. Fraction A was subjected to CCC (analytical column) with a solvent system of CH_2Cl_2/CCl_4/hexane/MeOH/H_2O (3:5:2:6:4) and a flow rate of 1 mL/min (ca. 40 mg/injection) to give 60 mg of isotrichoverrol B (**1**, C6′*R*,C7′*S*) and 8 mg of **8a**: an oil; IR ($CHCl_3$) 3600, 3470 (OH), 1703 (C═O), 1644 (C═C) 1620 (C═C) cm^{-1}; UV ($CHCl_3$) λ max (log ϵ) 262 (4.36) nm; HRMS (EI) *m/z* calcd for $C_{23}H_{32}O_7$ (M^+) 420.2148, found 420.2164; ^1H NMR δ 0.80 (3 H, s, H-14), 1.19 (3 H, d, J = 6.3 Hz, H-8′), 1.70 (3 H, s, H-16), 2.47 (1 H, dd, J = 8.1, 15.3 Hz, H-3α), (1 H, d, J = 4.0 Hz, H-13A), 3.12 (1 H, d, J = 4.0 Hz, H-13B), 3.64 (1 H, d, J = 12.5 Hz, H-15A), 3.67 (1 H, dd, J ∼ 6.3 Hz, H-7′), 3.80 (1 H, d, J = 12.5 Hz, H-15B), 3.83 (1 H, d, J = 5.0 Hz, H-2), 3.92 (1 H, d, J = 5.2 Hz, H-11), 3.97 (1 H, dd, J = 6.1, 6.3 Hz, H-6′), 5.48 (1 H, bd, J = 5.2 Hz, H-10), 5.94 (1 H, d, J = 15.4 Hz, H-2′), 6.10 (1 H, dd, J = 6.1, 15.4 Hz, H-5′), 6.12 (1 H, dd, J = 3.7, 8.2 Hz, H-4) 6.45 (1 H, dd, J = 11.3, 15.4 Hz, H-4′), 7.29 (1 H, dd, J = 11.3, 15.4 Hz, H-3′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 6.4 (C-14), 19.1 (C-8′), 21.2 (C-7), 23.3 (C-16), 28.0 (C-8), 35.9 (C-3), 44.3 (C-6), 48.2 (C-13), 48.9 (C-5), 62.9 (C-15), 65.6 (C-12), 66.8 (C-11), 70.6 (C-7′), 75.6 (C-4), 76.5 (C-6′), 79.0 (C-2), 118.7 (C-10), 121.6 (C-2′), 129.6 (C-4′), 140.4 (C-9), 141.5 (C-5′), 144.4 (C-3′), 167.7 (C-1′).

S1F2f was subjected to CCC (analytical column) with a solvent system of CH_2Cl_2/CCl_4/MeOH/H_2O (2:3:3:2) and a flow rate of 1 mL/min to give 18 mg of a mixture of (2′*E*)isotrichoverrol B (**8b**) and another unknown trichoverroid. This mixture was chromatographed on CCC (analytical column) with a solvent system of CH_2Cl_2/CCl_4/hexane/MeOH/H_2O (3:5:2:6:4) and a flow rate of 1 mL/min to give 12 mg of the mixture and 3 mg of pure **8b**: an oil; IR ($CHCl_3$) 3600, 3470 (OH), 1705 (C═O), 1645, 1621 (C═C) cm^{-1}; UV ($CHCl_3$) λ max (log ϵ) 262 (4.44) nm; HRMS (EI) *m/z* calcd for $C_{23}H_{32}O_7$ (M^+) 420.2148, found 420.2188; ^1H NMR δ 0.79 (3 H, s, H-14), 1.12 (3 H, d, J = 6.5 Hz, H-8′), 1.69 (3 H, s, H-16), 2.47 (1 H, dd, J = 8.0, 15.3 Hz, H-3α), 2.80 (1 H, d, J = 4.0 Hz, H-13A), 3.11 (1 H, d, J = 4.0 Hz, H-13B), 3.63 (1 H, d, J = 12.2 Hz, H-15A), 3.80 (1 H, d, J = 12.2 Hz, H-15B), 3.82 (1 H, 3, J = 5.1 Hz, H-2), 3.88∼3.93 (2 H, m, H-11 and H-7′), 4.21 (1 H, m, H-6′), 5.47 (1 H, bd, J = 4.5 Hz, H-10), 5.93 (1 H, d, J = 15.3 Hz, H-2′), 6.10 (1 H, dd, J = 3.6, 8.2 Hz, H-4), 6.13 (1 H, dd, J = 5.9, 15.9 Hz, H-5′), 6.42 (1 H, dd, J = 10.9, 15.9 Hz, H-4′), 7.29 (1 H, dd, J = 10.9, 15.3 Hz, H-3′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 6.4 (C-14), 17.6 (C-8′), 21.2 (C-7), 23.2 (C-16), 28.0 (C-8), 35.9 (C-3), 44.3 (C-6), 48.1 (C-13), 48.9 (C-5), 62.8 (C-15), 65.6 (C-12), 66.8 (C-11), 70.1 (C-7′), 75.3 (C-6′), 75.6 (C-4), 79.0 (C-2), 118.8 (C-10), 121.5 (C-2′), 129.6 (C-4′), 140.5 (C-5′), 140.5 (C-9), 144.5 (C-3′), 167.7 (C-1′).

Isolation of Isotrichoverrins and Related Trichoverroids. Sample 2 (S2, 4 g) contained mainly trichoverrins according to TLC analysis. This sample was chromatographed on CCC (semipreparative column, V_c = 355 mL) with a solvent system of $CHCl_3$/hexane/MeOH/H_2O (3:1:3:2) and a flow rate of 3.2 mL/min (ca. 400 mg/injection). Like fractions were combined to give seven fractions: S1F1 (990 mg), S2F2 (1950 mg), S2F3 (190 mg), S2F4 (110 mg), S2F5 (170 mg), S2F6 (140 mg), and S2F7 (95 mg). A portion of S2F2 (1.6 g) was

subjected to CCC (semipreparative column) with a solvent system of $CH_2Cl_2/CCl_4/MeOH/H_2O$ (2:3:3:2) and a flow rate of 2.8 mL/min (500∼600 mg/injection). The components of the mobile phase (organic layer, CH_2Cl_2/CCl_4) were varied from 2:3 to 5:2, starting at $t = 120$ min and going to $t = 160$ min. Like portions were combined to give seven fractions: I [685 mg of isotrichoverrin A (**2**, C6′*R*,C7′*R*)], II [400 mg of isotrichoverrin B (**2**, C6′*R*,C7′*S*)], III (120 mg of a mixture of isotrichoverrin B and trichoverrin C),[11] IV (52 mg), V (20 mg), VI (70 mg of 2′*E*-isotrichoverrin A),[11] VII (45 mg of 2′*E*-isotrichoverrin B).[11]

Isotrichoverrin A (2, C6′*R*,C7′*R*): amorphous solid; $[\alpha]^{20}_D$ +5.6° (*c* 2.10, $CHCl_3$); HRMS (CI) *m/z* calcd for $C_{29}H_{41}O_9$ ($[M + H]^+$) 533.2751, found 533.2759; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.79 (3 H, s, H-14), 1.19 (3 H, d, J = 6.3 Hz, H-14′), 1.70 (3 H, s, H-16), 2.17 (3 H, d, J = 1.0 Hz, H-6″), 2.40 (2 H, m, H-4″), 2.56 (1 H, dd, J = 7.6, 15.5 Hz, H-3α), 2.82 (1 H, d, J = 4.0 Hz, H-13A), 3.14 (1 H, d, J = 4.0 Hz, H-13B), 3.66 (1 H, dq, J = 6.3, 6.3 Hz, H-7′), 3.80 (2 H, m, H-5″), 3.84 (1 H, d, J = 5.4 Hz, H-2), 3.98 (1 H, d, J = 4.7 Hz, H-11), 4.03 (1 H, m, H-6′), 4.07 (1 H, d, J = 12.5 Hz, H-15A), 4.14 (1 H, d, J = 12.5 Hz, H-15B), 5.46 (1 H, d, J = 4.7 Hz, H-10), 5.67 (1 H, d, J = 11.3 Hz, H-2′), 5.85 (1 H, d, J = 1.0 Hz, H-2″), 6.07 (1 H, dd, J = 4.7, 15.5 Hz, H-5′), 6.20 (1 H, dd, J = 7.6, 15.5 Hz, H-4), 6.59 (1 H, dd, J = 11.3, 11.3 Hz, H-3′), 7.54 (1 H, dd, J = 11.3, 15.5 Hz, H-4′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 6.7 (C-14), 18.9 (C-8′), 19.1 (C-6″), 21.9 (C-7), 23.2 (C-16), 27.9 (C-8), 36.9 (C-3), 42.9 (C-6), 43.6 (C-4″), 48.2 (C-13), 48.6 (C-5), 59.7 (C-5″), 63.4 (C-15), 65.8 (C-12), 66.6 (C-11), 70.6 (C-7′), 75.0 (C-4), 76.1 (C-6′), 79.1 (C-2), 117.0 (C-2″), 118.2 (C-2′), 118.5 (C-10), 127.1 (C-4′), 140.4 (C-9), 142.1 (C-5′), 143.7 (C-3′), 157.0 (C-3″), 165.9 (C-1″), 166.0 (C-1′).

Isotrichoverrin B (2, C6′*R*,C7′*S*): an oil; $[\alpha]^{20}_D$ −25.0° (*c* 2.20, $CHCl_3$); HRMS (CI) *m/z* calcd for $C_{29}H_{41}O_9$ ($[M + H]^+$) 533.2751, found 533.2786; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.78 (3 H, s, H-14), 1.12 (3 H, d, J = 6.5 Hz, H-14′), 1.69 (3 H, s, H-16), 2.16 (3 H, d, J = 1.1 Hz, H-6″), 2.39 (2 H, t, J = 6.0 Hz, H-4″), 2.55 (1 H, dd, J = 7.7, 15.5 Hz, H-3α), 2.82 (1 H, d, J = 4.0 Hz, H-13A), 3.14 (1 H, d, J = 4.0 Hz, H-13B), 3.75 (1 H, dt, J = 6.0, 11.5 Hz, H-5″A), 3.83 (1 H, dt, J = 6.0, 11.5 Hz, H-5″B), 3.84 (1 H, d, J = 5.1 Hz, H-2), 3.89 (1 H, dq, J = 3.6, 6.5 Hz, H-7′), 3.97 (1 H, d, J = 5.4 Hz, H-11), 4.10 (2 H, s, H-15), 4.23 (1 H, m, H-6′), 5.46 (1 H, d, J = 5.4 Hz, H-10), 5.66 (1 H, d, J = 11.3 Hz, H-2′), 5.83 (1 H, d, J = 1.0 Hz, H-6″), 6.11 (1 H, dd, J = 5.2, 15.5 Hz, H-5′), 6.19 (1 H, dd, J = 3.3, 7.7 Hz, H-4), 6.60 (1 H, dd, J = 11.3, 11.3 Hz, H-3′), 7.52 (1 H, dd, J = 11.3, 15.5 Hz, H-4′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 6.7 (C-14), 17.9 (C-8′), 19.2 (C-6″), 21.9 (C-7), 23.2 (C-16), 27.9 (C-8), 36.9 (C-3), 42.9 (C-6), 43.6 (C-4″), 48.2 (C-13), 48.6 (C-5), 59.7 (C-5″), 63.4 (C-15), 65.8 (C-12), 66.6 (C-11), 70.2 (C-7′), 75.0 (C-4), 75.4 (C-6′), 79.1 (C-2), 116.9 (C-2″), 118.0 (C-2′), 118.5 (C-10), 127.6 (C-4′), 140.4 (C-9), 141.1 (C-5′), 143.9 (C-3′), 157.0 (C-3″), 165.9 (C-1″), 166.0 (C-1′).

Fractions IV and V were subjected to CCC (semipreparative column) separately with the solvent system of $CH_2CL_2/CCl_4/MeOH/H_2O$ (2:3:3:2) and a flow rate of 1.8 mL/min to yield fractions (20 mg) rich in (2′*E*,4′*Z*)-isotrichoverrin B (**7b**). These fractions were combined and purified on TLC (Si gel, 1 mm, 20 cm × 20 cm, 5% MeOH in CH_2Cl_2, developed three times) to give 8 mg of pure **7b**: an amorphous solid; IR ($CHCl_3$) 3600 (OH), 1710 (C═O), 1646 (C═C) cm^{-1}; UV ($CHCl_3$) λ max (log ϵ) 262 (4.38) nm; HRMS (CI) *m/z* calcd for $C_{29}H_{41}O_9$ ($[M + H]^+$) 533.2751, found 533.2768; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.77 (3 H, s, H-14), 1.11 (3 H, d, J = 6.4 Hz, H-8′), 1.69 (3 H, s, H-16), 2.17 (3 H, s, H-6″), 2.40 (2 H, t, J = 5.7 Hz, H-4″), 2.55 (1 H, dd, J = 7.8, 15.5 Hz, H-3α), 2.81 (1 H, d, J = 4.0 Hz, H-13A), 3.13 (1 H, d, J = 4.0 Hz, H-13B), 3.75 ∼ 3.92 (3 H, m, H-7′, H-5″), 3.83 (1 H, d, J = 5.1 Hz, H-2), 3.95 (1 H, bd, J = 4.8 Hz, H-11), 4.11 (2 H, s, H-15), 4.60 (1 H, dd, J = 3.3, 8.6 Hz, H-6′), 5.46 (1 H, bd, J = 4.8 Hz, H-10), 5.83 (1 H, s, H-2″), 5.88 (1 H, dd, J = 8.6, 11.0 Hz, H-5′), 5.94 (1 H, d, J = 15.1 Hz, H-2′), 6.16 (1 H, dd, J = 3.5, 7.8 Hz, H-4), 6.26 (1 H, dd, J = 11.0, 11.8 Hz, H-4′), 7.59 (1 H, dd, J = 11.8, 15.1 Hz, H-3′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 6.6 (C-14), 17.3 (C-8′), 19.0 (C-6″), 21.9 (C-7), 23.2 (C-16), 27.9 (C-8), 36.7 (C-3), 42.9 (C-6), 43.7 (C-4″), 48.1 (C-13), 48.7 (C-5), 59.7 (C-5″), 63.5 (C-15), 65.5 (C-12), 66.8 (C-11), 70.4 (C-7′), 71.6 (C-6′), 75.6 (C-4), 79.1 (C-2), 117.2 (C-2″), 118.5 (C-10), 122.7 (C-2′), 128.9 (C-4′), 138.1 (C-5′), 139.9 (C-3′), 140.5 (C-9), 156.9 (C-3″), 165.9 (C-1″), 167.0 (C-1′).

Oxidation of Isotrichoverrin A with DDQ. To the solution of 80 mg (0.16 mmol) of isotrichoverrin A in dioxane (5 mL) was added 80 mg of DDQ. The reaction mixture was stirred at 65 °C for 16 h. The mixture was filtered through a cotton pad, and the filtrate was concentrated in rotary evaporator. The residue was precleaned by short silica column (2% $MeOH/CH_2Cl_2$) and subjected to CCC with a solvent system of CH_2Cl_2/CCl_4/hexane/MeOH/H_2O (4:3:3:6:4); lower organic phase was the mobile phase, and the flow rate was 2.0 mL/min to give 30 mg (35%) of 6′-oxotrichoverrin B (**5b**) and 26 mg (32%) of the 2′*E*-isomer **6b**.

6′-Oxotrichoverrin B (5b): colorless amorphous solid; HRMS (EI) *m/z* calcd for $C_{29}H_{38}O_9$ (M^+) 530.2516, found 530.2518; IR ($CHCl_3$) cm^{-1} 3500, 1718, 1650, 1587, 1182, 1080; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (3 H, s, H-14), 1.38 (3 H, d, J = 7.0 Hz, H-8′), 1.69 (3 H, s, *H*-16), 2.19 (3 H, d, J = 1.2 Hz, H-6″), 2.41 (2 H, t, J = 6.1 Hz, H-4″), 2.58 (1 H, dd, J = 7.8, 15.6 Hz, H-3α), 2.83 (1 H, d, J = 4.0 Hz, H-13A), 3.15 (1 H, d, J = 4.0 Hz, H-13B), 3.81 (2 H, t, J = 6.1 Hz, H-5″), 3.85 (1 H, d, J = 5.1 Hz, H-2), 3.89 (1 H, d, J = 5.7 Hz, H-11), 4.06 (1 H, d, J = 12.4 Hz, H-15A), 4.16 (1 H, d, J = 12.4 Hz, H-15B), 4.63 (1 H, q, J = 7.0 Hz, H-6′), 5.45 (1 H, d, J = 5.7 Hz, H-10), 5.83 (1 H, d, J = 1.2 Hz, H-6″), 6.05 (1 H, d, J = 11.5 Hz, H-2′), 6.08 (1 H, dd, J = 3.3, 7.8 Hz, H-4), 6.40 (1 H, d, J = 15.7 Hz, H-5′), 6.64 (1 H, dd, J = 11.5, 11.5 Hz, H-3′), 8.40 (1 H, dd, J = 11.5, 15.7 Hz, H-4′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 6.8 (C-14), 18.9 (C-6″), 20.8 (C-8′), 21.6 (C-7), 23.2 (C-16), 27.9 (C-8), 36.8 (C-3), 43.0 (C-6), 43.7 (C-4″), 48.1 (C-13), 48.7 (C-5), 59.9 (C-5″), 63.1 (C-15), 65.4 (C-12), 66.7 (C-11), 71.4 (C-7′), 76.0 (C-4), 79.0 (C-2), 117.0 (C-2″), 118.4 (C-10), 126.2 (C-5′), 131.6 (C-2′), 138.5 (C-3′), 140.6 (C-9), 140.8 (C-4′), 157.4 (C-3″), 164.8 (C-1′), 202.0 (C-6′).

6′-Oxo-(2′*E*)-trichoverrin B (6b): colorless oil; HRMS (EI) *m/z* calcd for $C_{29}H_{38}O_9$ (M^+) 530.2516, found 530.2478; IR ($CHCl_3$) cm^{-1} 3500, 1712, 1643, 1600; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (3 H, s, H-14), 1.37 (3 H, d, J = 7.1 Hz, H-8′), 1.69 (3 H, s, H-16), 2.18 (3 H, s, H-6″), 2.39 (2 H, t, J = 6.0 Hz, H-4″), 2.56 (1 H, dd, J

= 7.7, 15.6 Hz, H-3α), 2.82 (1 H, d, *J* = 4.0 Hz, H-15A), 3.13 (1 H, d, *J* = 4.0 Hz, H-13B), 3.79 (2 H, m, H-5″), 3.84 (1 H, d, *J* = 5.0 Hz, H-2), 3.86 (1 H, d, *J* = 4.9 Hz, H-11), 4.11 (2 H, AB, H-15), 4.43 (1 H, q, *J* = 7.1 Hz, H-7′), 5.44 (1 H, d, *J* = 4.9 Hz, H-10), 5.79 (1 H, s, H-2″), 6.01 (1 H, dd, *J* = 3.2, 7.7 Hz, H-4), 6.28 (1 H, d, *J* = 14.4 Hz, H-5′), 6.57 (1 H, d, *J* = 14.2 Hz, H-2′), 7.27 (1 H, dd, *J* = 11.5, 14.2 Hz, H-3′), 7.34 (1 H, dd, *J* = 11.5, 14.4 Hz, H-4′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 6.7 (C-14), 18.9 (C-6″), 20.0 (C-8′), 21.5 (C-7), 23.2 (C-16), 27.9 (C-8), 36.7 (C-3), 43.1 (C-6), 43.7 (C-4″), 48.0 (C-13), 48.9 (C-5), 59.8 (C-5″), 63.0 (C-15), 65.4 (C-12), 66.7 C-11), 72.1 (C-7′), 76.2 (C-4), 79.0 (C-2), 117.1 (C-2″), 118.3 (C-10), 130.0 (C-2′), 130.0 (C-6′), 140.3 (C-3′), 140.7 (C-9), 141.2 (C-4′), 157.7 (C-3″), 165.4 (C-1′), 165.8 (C-1″), 200.7 (C-6′).

Oxidation of Isotrichoverrin B with DDQ. A similar procedure was carried out on 30 mg (0.06 mmol) of isotrichoverrin B with 30 mg of DDQ to give 12 mg (40%) of 6′-oxotrichoverrin A (**5a**) and 8 mg (26%) of the 2′*E*-isomer **6a**.

6′-Oxotrichoverrin A (5a): an oil; HRMS (EI) *m/z* calcd for $C_{29}H_{38}O_9$ (M^+) 530.2516, found 530.2569; IR ($CHCl_3$) cm^{-1} 3500, 1712, 1650, 1578; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (3 H, s, H-14), 1.39 (3 H, d, *J* = 7.0 Hz, H-8′), 2.20 (3 H, d, *J* = 1.2 Hz, H-6″), 2.40 (2 H, m, H-4″), 2.58 (1 H, dd, *J* = 7.8, 15.5 Hz, H-3α), 2.83 (1 H, d, *J* = 4.0 Hz, H-13A), 3.16 (1 H, d, *J* = 4.0 Hz, H-13B), 3.82 (2 H, m, H-5″), 3.85 (1 H, d, *J* = 5.0 Hz, H-2), 3.90 (1 H, d, *J* = 5.3 Hz, H-11), 4.07 (1 H, d, *J* = 12.5 Hz, H-15A), 4.17 (1 H, d, *J* = 12.5 Hz, H-15B), 4.66 (1 H, q, *J* = 7.0 Hz, H-7′), 5.46 (1 H, d, *J* = 5.3 Hz, H-10), 5.84 (1 H, d, *J* = 1.2 Hz, H-2″), 6.06 (1 H, d, *J* = 11.4 Hz, H-2′), 6.11 (1 H, dd, *J* = 3.3, 7.7 Hz, H-4), 6.40 (1 H, d, *J* = 15.8 Hz, H-5′), 6.65 (1 H, t, *J* = 11.4 Hz, H-3′), 8.40 (1 H, dd, *J* = 11.4, 15.8 Hz, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.8 (C-14), 18.9 (C-6″), 20.9 (C-8′), 21.6 (C-7), 23.2 (C-16), 27.9 (C-8), 36.8 (C-3), 43.0 (C-6), 43.8 (C-4″), 48.1 (C-13), 48.7 (C-5), 59.9 (C-5″), 63.1 (C-15), 65.4 (C-12), 66.7 (C-11), 71.2 (C-7′), 76.0 (C-4), 79.0 (C-2), 117.0 (C-2″), 118.4 (C-10), 126.2 (C-5′), 131.7 (C-2′), 138.6 (C-3′), 140.7 (C-9), 140.9 (C-4′), 157.5 (C-3″), 164.9 (C-1′), 165.9 (C-1″), 202.1 (C-6′).

6′-Oxo-(2′*E*)-trichoverrin A (6a): an oil; HRMS (EI) *m/z* calcd for $C_{29}H_{38}O_9$ (M^+) 530.2516, found 530.2575; IR ($CHCl_3$) cm^{-1} 3500, 1706, 1648, 1584; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (1 H, s, H-14), 1.38 (3 H, d, *J* = 7.0 Hz, H-8′), 1.70 (3 H, s, H-16), 2.18 (3 H, d, *J* = 1.1 Hz, H-6″), 2.39 (2 H, t, *J* = 5.9 Hz, H-4″), 2.57 (1 H, dd, *J* = 7.8, 15.5 Hz, H-3α), 2.83 (1 H, d, *J* = 4.0 Hz, H-13A), 3.14 (1 H, d, *J* = 4.0 Hz, H-13B), 3.80 (2 H, m, H-5″), 3.84 (1 H, d, *J* = 5.0 Hz, H-2), 3.87 (1 H, d, *J* = 4.6 Hz, H-11), 4.11 (2 H, s, H-15), 5.45 (1 H, d, *J* = 4.6 Hz, H-10), 5.80 (1 H, d, *J* = 1.1 Hz, H-2″), 6.03 (1 H, dd, *J* = 3.2, 7.8 Hz, H-4), 6.28 (1 H, d, *J* = 14.4 Hz, H-5′), 6.57 (1 H, d, *J* = 14.2 Hz, H-2′), 7.26 (1 H, dd, *J* = 11.6, 14.2 Hz, H-3′), 7.34 (1 H, dd, *J* = 11.6, 14.4 Hz, H-4′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.7 (C-14), 19.0 (C-6″), 20.1 (C-8′), 21.6 (C-7), 23.2 (C-16), 28.0 (C-8), 36.7 (C-3), 43.1 (C-6), 43.7 (C-4″), 48.0 (C-13), 49.0 (C-5), 59.8 (C-5″), 63.1 (C-15), 65.4 (C-12), 66.8 (C-11), 72.2 (C-7′), 76.2 (C-4), 79.1 (C-2), 117.1 (C-2″), 118.4 (C-10), 138.1 (C-2′), 138.1 (C-5′), 140.4 (C-3′), 140.8 (C-9), 141.2 (C-4′), 157.2 (C-2″), 165.4 (C-1′), 165.8 (C-1″), 200.7 (C-6′).

Oxidation of Trichoverrins A and B with DDQ. A similar procedure was carried out with trichoverrin A (20 mg) to give 8 mg of **5a** and 6 mg of **6a**. A similar procedure with trichoverrin B (10 mg) gave 4 mg of **5b** and 3 mg of **6b**.

Manganese Dioxide Oxidation of Isotrichoverrin A. To a solution of isotrichoverrin A (25 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) in an ice bath was added 50 mg of activated MnO_2.[21] The mixture was stirred for 40 min. TLC analysis indicated that all the trichoverrin A was transformed to a less polar compound. The mixture was filtered through a Celite pad, the filtrate was concentrated, and the residue was passed through a small Si gel column to give 18 mg (78%) of an oil that was identified as aldehyde **4**: HRMS (EI) *m/z* calcd for $C_{27}H_{34}O_8$ (M^+) 486.2254, found 486.2258; IR ($CHCl_3$) cm^{-1} 3510, 1712, 1680, 1640, 1586; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (3 H, s, H-14), 1.70 (3 H, s, H-16), 2.19 (3 H, d, *J* = 1.2 Hz, H-6″), 2.39 (2 H, t, *J* = 5.9 Hz, H-4″), 2.60 (1 H, dd, *J* = 7.7, 15.6 Hz, H-3α), 2.83 (1 H, d, *J* = 4.0 Hz, H-13A), 3.15 (1 H, d, *J* = 4.0 Hz, H-13B), 3.79 (2 H, t, *J* = 5.9 Hz, H-5″), 3.86 (1 H, d, *J* = 5.2 Hz, H-2), 3.87 (1 H, d, *J* = 5.5 Hz, H-11), 4.12 (2 H, AB, H-15), 5.45 (1 H, d, *J* = 5.5 Hz, H-10), 5.80 (1 H, d, *J* = 1.2 Hz, H-2″), 6.02 (1 H, d, *J* = 11.5 Hz, H-2′), 6.03 (1 H, dd, *J* = 3.7, 7.7 Hz, H-4), 6.28 (1 H, dd, *J* = 8.0, 15.5 Hz, H-5′), 6.76 (1 H, dd, *J* = 11.5, 11.5 Hz, H-3′), 8.43 (1 H, dd, *J* = 11.5, 15.5 Hz, H-4′), 9.74 (1 H, d, *J* = 8.0 Hz, H-6′); ^{13}C NMR ($CDCl_3$) δ 7.0 (C-14), 18.9 (C-6″), 21.6 (C-7), 23.2 (C-16), 28.0 (C-8), 36.9 (C-3), 43.1 (C-6), 43.8 (C-4″), 48.1 (C-13), 48.9 (C-5), 59.9 (C-5″), 63.0 (C-15), 65.4 (C-12), 66.7 (C-11), 76.1 (C-4), 79.0 (C-2), 117.1 (C-2″), 118.4 (C-10), 125.9 (C-5′), 137.9 (C-2′), 140.4 (C-3′), 140.8 (C-9), 145.6 (C-4′), 157.3 (C-3″), 164.9 (C-1′), 165.8 (C-1″), 194.4 (C-6′).

Under these same conditions, isotrichoverrin B and trichoverrins A and B all gave **4** in similar yields.

Isolation of More Polar Trichoverroids. Sample 3 (S3, 1 g) from *M. verrucaria* isolate ATCC 20 540, which was more polar than those that contained trichoverrols (S1) and trichoverrins (S2), was partitioned between $CHCl_3$ (300 mL) and MeOH/H_2O mixture (50%, 300 mL). The organic fraction (0.6 g) was subjected to preparative TLC (chromatotron, 2 mm, Si gel) with MeOH/CH_2Cl_2 (3−10%). The most polar fraction (180 mg) was subjected to CCC with a solvent system of $CHCl_3$/hexane/MeOH/H_2O (12:8:15:5) at a flow rate of 1.8 mL/min to give 3 mg of 9β,10β-epoxyisotrichoverrin A (**11a**), and 3 mg of 9β,10β-epoxyisotrichoverrin B (**11b**).

9β,10β-Epoxyisotrichoverrin A (11a): an oil; $[\alpha]^{20}_D$ −16° (*c* 0.12, $CHCl_3$); HRMS (CI) *m/z* calcd for $C_{29}H_{41}O_{10}$ ($[M + H]^+$) 549.2700, found 549.2732; IR ($CHCl_3$) cm^{-1} 3487, 2931, 1712, 1643; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.72 (3 H, s, H-14), 1.20 (3 H, d, *J* = 6.5 Hz, H-8′), 1.34 (3 H, s, H-16), 1.60−2.00 (5 H, m, H-7, H-8, H-3β), 2.20 (3 H, d, *J* = 0.9 Hz, H-6″), 2.41 (2 H, t, *J* = 6.0 Hz, H-4″), 2.53 (1 H, dd, *J* = 7.9, 15.5 Hz, H-3α), 2.78 (1 H, d, *J* = 4.0 Hz, H-13A), 3.11 (1 H, d, *J* = 5.5 Hz, H-10), 3.19 (1 H, d, *J* = 4.0 Hz, H-13B), 3.67 (1 H, dq *J* = 6.5, 6.5 Hz, H-7′), 3.81 (2 H, m, H-5″), 3.89 (1 H, br d, *J* = 5.5 Hz, H-11), 3.93 (1 H, d, *J* = 5.1 Hz, H-2), 4.03 (1 H, m, H-6′), 4.04 (1 H, d, *J* = 12.5 Hz, H-15A), 4.15 (1 H, d, *J* = 12.5 Hz, H-15B), 5.68 (1 H, d, *J* = 11.3 Hz, H-2′), 5.82 (1 H, d, *J* = 0.9 Hz, H-2″), 6.03 (1 H, dd, *J* = 3.5, 7.5 Hz, H-4), 6.08 (1 H, dd, *J* = 5.8, 15.4 Hz, H-5′), 6.60 (1 H, dd, *J* = 11.3, 11.3 Hz, H-3′), 7.55 (1 H, dd, *J* =

11.3, 15.4 Hz, H-4′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 6.8 (C-14), 18.9 (C-8′), 19.2 (C-6″), 19.4 (C-7), 22.4 (C-16), 26.5 (C-8), 26.5 (C-8), 36.6 (C-3), 42.6 (C-6), 43.6 (C-4″), 48.0 (C-13), 48.5 (C-5), 57.3 (C-10), 57.5 (C-9), 59.7 (C-5″), 63.1 (C-15), 65.2 (C-12), 66.9 (C-11), 70.6 (C-7′), 74.8 (C-4), 76.2 (C-6′), 78.7 (C-2), 116.5 (C-2″), 118.1 (C-2′), 127.5 (C-4′), 142.2 (C-5′), 143.9 (C-3′), 158.1 (C-3″), 165.8 (C-1′), 166.0 (C-1″).

9*β*,10*β*-Epoxyisotrichoverrin B (11b): an oil; $[\alpha]^{20}_D$ −21° (*c* 0.13, $CHCl_3$); HRMS (CI) *m/z* calcd for $C_{29}H_{41}O_{10}$ ($[M + H]^+$) 549.2700, found 549.2754; IR ($CHCl_3$) cm^{-1} 3467, 2930, 1712, 1643; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.74 (3 H, s, H-14), 1.13 (3 H, d, J = 6.4 Hz, H-8′), 1.34 (3 H, s, H-16), 1.70−2.03 (5 H, m, H-3*β*, H-7, H-8), 2.20 (3, H, d, J = 0.9 Hz, H-6″), 2.41 (2 H, t, J = 6.1 Hz, H-4″), 2.53 (1 H, dd, J = 7.9, 15.5 Hz, H-3α), 2.78 (1 H, d, J = 4.0 Hz, H-13A), 3.10 (1 H, d, J = 5.6 Hz, H-10), 3.19 (1 H, d, J = 4.0 Hz, H-13B), 3.81 (2 H, m, H-5″), 3.90 (2 H, m, H-11, H-7′), 3.93 (1 H, d, J = 5.2 Hz, H-2), 4.04 (1 H, d, J = 12.6 Hz, H-15A), 4.15 (1 H, d, J = 12.6 Hz, H-15B), 5.67 (1 H, d, J = 11.3 Hz, H-2′), 5.81 (1 H, d, J = 0.9 Hz, H-2″), 6.03 (1 H, dd, J = 3.4, 7.9 Hz, H-4), 6.12 (1 H, dd, J = 5.3, 15.5 Hz, H-5′), 6.62 (1 H, dd, J = 11.3, 11.3 Hz, H-3′), 7.53 (1 H, dd, J = 11.3, 15.5 Hz, H-4′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 6.7 (C-14), 17.9 (C-8′), 19.2 (C-6″), 19.4 (C-7), 22.3 (C-16), 26.4 (C-8), 36.6 (C-3), 42.6 (C-6), 43.6 (C-4″), 48.0 (C-13), 48.5 (C-5), 57.3 (C-10), 57.5 (C-9), 59.7 (C-5″), 63.1 (C-15), 65.2 (C-12), 66.7 (C-11), 70.2 (C-7′), 74.7 (C-4), 75.4 (C-6′), 78.7 (C-2), 116.5 (C-2″), 118.0 (C-2′), 127.7 (C-4′), 142.1 (C-5′), 143.9 (C-3′), 158.4 (C-3″), 165.8 (C-1′), 165.9 (C-1″).

Sample 4 (S4, 5 g) was triturated with MeOH. The soluble portion was concentrated and dissolved in 50% aqueous MeOH solution (250 mL), and the solution was washed with CCl_4 (100 mL), $CHCl_3$/hexane (1:1, 150 mL), $CHCl_3$/hexane (7:3, 150 mL), and $CHCl_3$ (150 mL). The aqueous phase was concentrated to 150 mL by rotary evaporation and extracted with $CHCl_3$ (100 mL). The $CHCl_3$ extract was subjected to CCC with a solvent system of $CHCl_3$/hexane/MeOH/H_2O (7:3:5:5) to give 4 mg each of a 16-hydroxyisotrichodermadiendiols A and B[22] and 4 mg of 8α-hydroxyisotrichoverrin A (**12**).

8α-Hydroxyisotrichoverrin A (12): an oil; $[\alpha]^{20}_D$ −22° (c 0.37, $CHCl_3$); HRMS (CI) *m/z* calcd for $C_{29}H_{41}O_{10}$ ($[M + H]^+$) 549.2700, found 549.2710; IR ($CHCl_3$) cm^{-1} 3506, 2931, 1718, 1675, 1637; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (3 H, s, H-14), 1.19 (3 H, d, J = 6.3 Hz, H-14′), 1.69 (1 H, br d, J = 14.4 Hz, H-7*β*), 1.84 (3 H, s, H-16), 2.02 (1 H, m, H-3*β*), 2.17 (3 H, s, H-6″), 2.32 (1 H, dd, J = 6.5, 14.4 Hz, H-7α), 2.39 (2 H, m, H-4″), 2.58 (1 H, dd, J = 7.8, 15.5 Hz, H-3α), 2.85 (1 H, d, J = 4.0 Hz, H-13A), 3.14 (1 H, d, J = 4.0 Hz, H-13B), 3.66 (1 H, dq, J = 6.3, 6.3 Hz, H-7′), 3.78 (2 H, m, H-5″), 3.83 (1 H, d, J = 5.3 Hz, H-2), 4.03 (1 H, br d, J = 5.7 Hz, H-11), 4.09 (1 H, m, H-6′), 4.11 (1 H, br d, J = 6.5 Hz, H-8), 4.24 (1 H, d, J = 13.0 Hz, H-15A), 4.39 (1 H, d, J = 13.0 Hz, H-15B), 5.58 (1 H, br d, J = 5.7 Hz, H-10), 5.68 (1 H, d, J = 11.3 Hz, H-2′), 5.85 (1 H, s, H-2″), 6.07 (1 H, dd, J = 5.1, 15.5 Hz, H-5′), 6.30 (1 H, dd, J = 3.1, 7.8 Hz, H-4), 6.60 (1 H, dd, J = 11.3, 11.3 Hz, H-3′), 7.53 (1 H, dd, J = 11.3, 15.5 Hz, H-4′); ^{13}C NMR (50 MHz, $CDCl_3$) δ 6.6 (C-14), 18.9 (C-8′), 19.2 (C-6″), 20.4 (C-16), 31.3 (C-7), 36.8 (C-3), 42.9 (C-6), 43.5 (C-4″), 48.3 (C-13), 48.5 (C-5), 59.6 (C-5″), 64.6 (C-15), 65.8 (C-12), 66.5 (C-8), 66.8 (C-11), 70.5 (C-7′), 74.8 (C-4), 76.4 (C-6′), 79.0 (C-2), 116.9 (C-2″), 118.1 (C-2′), 120.9 (C-10), 127.3 (C-4′), 139.8 (C-9), 142.2 (C-5′), 144.0 (C-3′), 157.2 (C-3″), 165.2 (C-1′), 166.0 (C-1″).

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