Sesquiterpenes from *Ferula penninervis*

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The ethyl acetate soluble extract of the dried roots of *Ferula penninervis* gave 17 new sesquiterpenes [15 of the guaiane-type, ferupennins A−O (**1**−**15**), and two of the eudesmane-type, 1α-hydroxy-2-oxo-5α,7*β*,-11*β*H-eudesm-3-en-6α,12-olide (**16**) and penninervin (**17**)] and nine known sesquiterpenes. The structures of the new compounds were elucidated on the basis of spectroscopic evidence and X-ray analysis. The absolute configuration of ferupennin A (**1**) was determined by a modified Mosher method.

The chemical constituents of the genus *Ferula* (Apiaceae) have been studied by many groups. Compounds commonly found in this genus are sesquiterpenes (especially daucanes, humulanes, himachalanes, and guaianes),[1−6] sesquiterpene coumarins,[7,8] and dimeric coumarins.[9] Previous chemical studies on *F. penninervis* Regel and Schmalh also showed that the main components are sesquiterpenes.[10,11] We report herein the isolation and structure elucidation of 17 new compounds [15 guaiane-type sesquiterpenes, ferupennins A−O (**1**−**15**), 1α-hydroxy-2-oxo-5α,7*β*-11*β*H-eudesm-3-en-6α,12-olide (**16**), and penninervin (**17**)] along with nine known sesquiterpenes [decipienin F,[12] talassin B,[13] laferin,[13] oferin,[13] olgin,[14] carmenin,[15] 4*β*,10α-dihydroxyaromadendrane,[16] isolasolide,[17] and lasolide[17]]. The absolute configuration of ferupennin A (**1**) was determined by a modified Mosher method.[18] We examined the inhibitory effects of three of the isolated compounds, **6**, **8**, and **10**, on cytokine (IL-1*β*, IL-2, IL-4, and TNF-α) production, and compound **10** had a significant inhibitory effect on cytokine production (IL-2).

Results and Discussion

The IR spectrum of compound **1** indicated the presence of a hydroxyl group (3449 cm-1), a *γ*-lactone (1789 cm^{-1}), and an ester (1731 cm^{-1}). The UV spectrum revealed an α,*β*−α′,*β*′-unsaturated ketone (252 nm). The ^{1}H NMR spectrum showed the presence of an isopropyl group [δ_H 2.56 (1H, sept, J = 6.8 Hz) and 1.12 (6H, t, J = 6.8 Hz)], three methyl groups [δ_H 2.18 (6H, s) and 1.75 (3H, s)], a pair of methylene protons [δ_H 2.74 (1H, d, J = 18.0 Hz) and 2.50 (1H, dd, J = 10.4, 18.0 Hz)], and five methine protons [δ_H 6.11 (1H, s), 4.52 (1H, t, J = 10.7 Hz), 4.45 (1H, m), 3.47 (1H, d, J = 10.7 Hz), and 3.07 (1H, t, J = 10.7 Hz)]. The ^{13}C NMR spectrum (Table 1) of **1** showed 19 carbon signals, which could be resolved by a DEPT experiment into five methyls, one methylene, and two methines, as well as an additional two methines and one quaternary carbon attached to an oxygen function, two double bonds, and three carbonyl carbons (δ_C 195.8, 176.6, and 174.5). These observations agreed with a molecular formula of $C_{19}H_{24}O_6$, which was supported by HREIMS. On the basis of these findings, compound **1** was assumed to be a sesquiterpene with an isobutyrate ester substituent. The ^{13}C NMR data of **1** were similar to those of 2-oxo-8α-angeloyloxy-11α-acetoxy-5*β*H,6αH,7αH-guai-1(10),3-diene-6,12-olide (=laferin),[13] except for C-7, C-8, C-9, and the ester moiety. The ^{1}H−^{1}H COSY spectrum of **1** confirmed the connectivity of C-3 to C-9. The HMBC spectrum of **1** showed correlations of H-3 to C-1 and C-2, and H-13 to C-7, C-12, and C-11, which supported a guaiane skeleton in the structure of **1**. The NOESY spectrum of **1** showed correlations of H-5 to H-8 and H_3-13, H-6 to H-7, and H-9 to H_3-13. These findings showed that the relative stereochemistry at H-5, H-6, H-7, H-8, and H_3-13 in **1** was *β*, α, α, *β*, and *β*, respectively. The *cis* configuration of the lactone ring was also supported by the chemical shift of H-6 at δ_H 4.52 [*cis*: δ_H 4.5−4.9; *trans*: δ_H 3.2−3.9].[13] The remaining problem in the structure of **1** was the position (C-8 or C-11) of the ester group. It was very difficult to confirm that the ester is located on C-11 on the basis of the HMBC spectrum. Compound **1** was acetylated to give the monoacetate **1a**, the ^{1}H NMR spectrum of which showed a downfield shift of H-8 from δ_H 4.45 to δ_H 5.52. This clearly indicated that the isobutylate ester was located at C-11. To determine the absolute configuration of **1**, (*S*)- and (*R*)-MTPA esters were obtained after **1** was treated with (*R*)- and (*S*)-MTPA chloride, respectively. Thus, the 8*S* absolute configuration could be assigned on the basis of the $\Delta\delta$ values ($\Delta\delta = \delta S - \delta R$)[18] (Figure 1).

The ^{1}H NMR and ^{13}C NMR spectral data of ferupennins B (**2**; $C_{19}H_{22}O_6$), C (**3**; $C_{17}H_{20}O_6$), and D (**4**; $C_{20}H_{24}O_6$) were very similar to those of compound **1**, except for the ester units. The structures of the ester groups of **2**−**4** were determined on the basis of ^{1}H NMR and ^{13}C NMR spectral data and 2D NMR analysis to be methacrylate [**2**: δ_H 1.98 (3H, s), 5.67 and 6.21 (each 1H, s); δ_C 18.1 (CH_3), 127.8 (CH), 135.5 (C), 166.6 (COO)], acetate [**3**: δ_H 2.10 (3H, s); δ_C 22.0 (CH_3), 170.4 (COO)], and angelate [**4**: δ_H 1.91 (3H, s), 2.04 (3H, d, J = 7.0 Hz), 6.22 (1H, q, J = 7.0 Hz); δ_C 16.2 (CH_3), 20.2 (CH_3), 126.8 (C), 141.5 (CH), 166.9 (COO)], respectively. The similarity of the chemical shifts of H-8 (**1**: δ_H 4.45; **2**: δ_H 4.48; **3**: δ_H 4.46; **4**: δ_H 4.49) showed that the ester groups in compounds **2**−**4** were all located at C-11.

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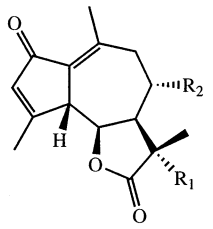
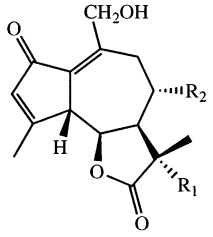
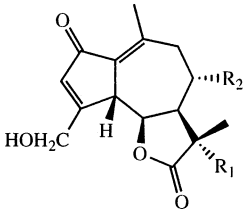
Chart 1



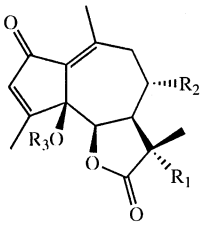
1 R_1 = i-But R_2 = H
2a R_1 = i-But R_2 = Ac
2 R_1 = MeAcr R_2 = H
3 R_1 = Ac R_2 = H
4 R_1 = Ang R_2 = H
5 R_1 = Ac R_2 = E-Ang
6 R_1 = Ac R_2 = A
7 R_1 = Ac R_2 = B



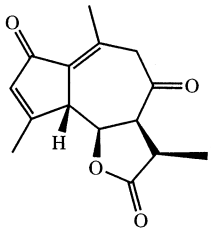
8 R_1 = Ac R_2 = Ang
10 R_1 = Ac R_2 = MeAcr



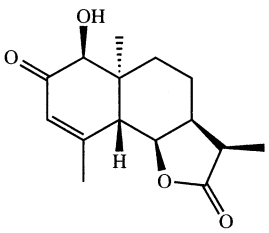
9 R_1 = Ac R_2 = Ang
11 R_1 = Ac R_2 = MeAcr



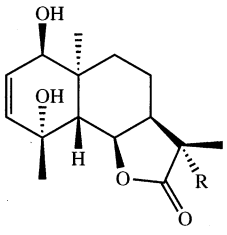
12 R_1 = H R_2 = Ang R_3 = Ac
13 R_1 = Ac R_2 = Ang R_3 = H
14 R_1 = H R_2 = MeAcr R_3 = Ac



15



16



17 R = Sen
18 R = Ang

Side chains in compound **1-18**

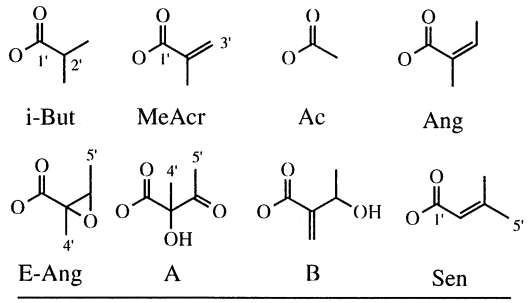


Table 1. ^{13}C NMR Spectral Data of Compounds **1**−**15** (100 MHz, δ, ppm)[a]

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
C-1	129.1	129.1	129.2	129.3	129.4	129.5	129.3	131.3	128.8	131.5	128.8	131.9	131.9	131.9	130.4
C-2	195.8	195.5	195.5	195.4	194.7	195.0	195.1	195.9	194.7	195.9	194.6	194.9	194.1	195.1	195.2
C-3	135.9	136.1	136.2	136.1	136.4	136.4	136.3	135.5	134.0	135.6	134.1	134.7	135.2	134.6	134.4
C-4	170.3	169.8	169.8	169.8	169.1[c]	169.2	169.2	172.6	171.3	172.6	170.8	171.5	171.3	171.8	170.4
C-5	48.2	48.3	48.3	48.3	48.1	47.9	48.2	47.9	45.1	48.0	45.1	79.6	79.3	79.4	49.9
C-6	78.9	78.8	78.7	78.7	78.3	78.2	78.4	78.2	78.2[b]	78.1	78.2	80.3	80.2	80.4	86.5
C-7	50.1	50.3	50.2	50.5	47.3	47.1	47.6	47.3	47.5	47.3	47.6	48.4	48.4	48.4	53.0
C-8	64.8	65.3	65.3	65.5	68.9	69.9	68.4	67.1	67.2	68.0	68.1	68.2	68.1	69.1	204.7
C-9	48.8	48.8	48.7	48.9	44.0	43.3	43.8	41.0	44.1	40.9	43.8	44.1	44.1	43.8	55.0
C-10	146.7	145.8	145.8	145.6	144.4	144.5	144.9	149.5	146.6	149.4	146.4	148.3	148.3	148.0	142.9
C-11	78.5	77.7	77.7	78.4	77.9	77.9	78.1	78.0	78.2[b]	78.0	78.1	79.3	79.8	79.3	36.7
C-12	174.5	174.0	174.1	173.7	173.1	173.0	173.1	173.3	173.8	173.2	173.6	174.2	174.2	174.1	176.6
C-13	20.3	20.3	20.3	20.4	19.1	20.3	20.4	20.6	20.5	20.6	20.5[b]	19.0	16.7	19.0	9.6
C-14	20.5[b]	20.5[b]	20.5	20.5	20.4[b]	20.8	20.9	63.3	20.2	63.4	20.5[b]	20.5	20.5	21.0	19.5
C-15	20.5[b]	20.5[b]	20.6	20.6	20.4[b]	20.5	20.7	20.9	62.7	20.6	62.7	16.9	19.0	16.8	18.5
C−1′	176.6	166.6		166.9	169.1[c]	170.4	165.5	166.3	166.5	166.2	166.3	166.8	166.9	166.6	
C-2′	33.8	135.5		126.8	59.6	81.0	143.6	126.7	126.8	135.9	135.9	127.1	127.3	136.1	
C-3′	18.1	127.8		141.5	60.3	204.2	66.6	141.5	141.4	127.2	127.1	141.0	141.0	126.9	
C-4′	18.6	18.1		20.2	20.8	22.7	125.5	20.5	20.4	18.3	18.3	21.0	21.0	18.2	
C-5′				16.2	13.8	24.2	22.6	14.3	16.1						
Ac			170.4		170.0	170.0	170.4	171.0	170.2	170.1	170.1	170.5	171.0	170.4	
			22.0		21.0	21.2	22.0	21.5	21.0	20.9	20.9	21.0	21.0	21.0	

[a] Measured in $CDCl_3$. [b,c]Overlapping signals in results; data with the same superscript symbol in any column are interchangeble.

Compound **5** ($C_{22}H_{26}O_8$) showed the presence of an epoxyangeloyl [δ_H 3.11 (1H, q, J = 5.8 Hz), 1.62 (3H, s), 1.39 (1H, d, J = 5.8 Hz), δ_C 169.1 (C-1′), 59.6 (C-2′), 60.3 (C-3′), 20.8 (C-4′), 13.8 (C-5′)] ester moiety in its ^1H NMR and ^{13}C NMR spectra. The ^{13}C NMR spectrum of **5** was closely comparable to that of compound **1** except for the signals due to the ester moiety. The ^1H NMR spectrum of **5** (ferupennin E) was also similar to those of compounds **1**−**4** except for the ester moiety and the chemical shift of H-8 (**5**: δ_H 5.64; **1**−**4**: δ_H 4.45−4.49). The correlation of H-8 (δ_H 5.64) to C-1′ (δ_C 169.1) in the HMBC spectrum confirmed that the epoxyangeloyl ester was located at C-8. The 2′*R* and 3′*S* relative stereochemistry of the epoxyangelate unit was confirmed by the correlation of H-3′ to H-4′ and H-5′ in the NOESY spectrum.

Compounds **6** ($C_{22}H_{26}O_9$) and **7** ($C_{22}H_{26}O_8$) (ferupennins F and G) showed ^1H NMR and ^{13}C NMR spectral data similar to those of compound **5** (guaiane skeleton and acetyl group) except for the ester unit [**6**: δ_H 1.49 (3H, s), 2.31 (3H, s); δ_C 22.7 (CH_3), 24.2 (CH_3), 81.0 (C), 170.4 (COO), 204.2 (CO); **7**: δ_H 1.42 (3H, d, J = 6.8 Hz), 4.64 (1H, q, J = 6.8 Hz), 5.96 (1H, J = 2.8 Hz). 6.27 (1H, d, J = 2.8 Hz); δ_C 22.6 (CH_3), 66.6 (CH), 125.5 (CH_2), 143.6 (C), 165.5 (COO)]. In the HMBC spectrum of **6**, the correlations of H-5′ (δ_H 2.31) with C-2′ (δ_C 81.0) and C-3′ (δ_C 204.2), and H-4′ (δ_H 1.49) with C-1′ (δ_C 170.4), C-2′ (δ_C 81.0), and C-3′

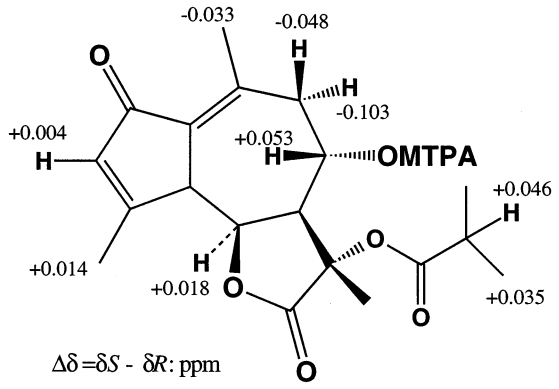


Figure 1. $\Delta\delta$ values of (*S*)- and (*R*)-MTPA esters of **1**.

(δ_C 204.2), confirmed that the ester unit of **6** is a 2′-hydroxy-2′-methyl-3′-oxobutanoyl unit. In the HMBC spectrum of **7**, the correlations of H-5′ (δ_H 1.42) with C-2′ (δ_C 143.6) and C-3′ (δ_C 66.6), and H_2-4′ (δ_H 6.27 and 5.96) with C-1′ (δ_C 165.5), C-2′ (δ_C 143.6), and C-3′ (δ_C 66.6), confirmed that the ester moiety of **7** is a 2′-exomethylene-3′-hydroxybutanoyl unit. The presence of these ester linkages at C-8 was determined on the basis of HMBC correlations [**6**: δ_H 5.59 (H-8) with δ_C 170.4 (C-1′); **7**: δ_H 5.56 (H-8) with δ_C 165.5 (C-1′)].

Compounds **8** and **9** (ferupennins H and I) were assigned the same molecular formula ($C_{22}H_{26}O_8$) and the same ester groups (acetate and angelate) on the basis of their ^{1}H NMR and ^{13}C NMR spectral data. On comparing the ^{1}H NMR spectral data of these compounds with those of laferin,[13] the methyl signal at δ_H 2.20 on the double bond in laferin was not seen in either **8** or **9**, while hydroxymethylene signals were observed at δ_H 4.34 (2H, s) and δ_H 4.79, 4.62 (each 1H, d, J = 16.4 Hz), respectively. In the HMBC spectra of **8** and **9**, correlations of H-14 with C-1 and C-9 in **8**, and H-15 with C-3 and C-5 in **9**, indicated that the hydroxymethyl groups are located on C-10 and C-4, respectively. The presence of the angelate on C-8 was confirmed by HMBC correlations: H-8 (δ_H 5.58) with C-1′ (δ_C 166.3) in **8**, and H-8 (δ_H 5.59) with C-1′ (δ_C 166.5) in **9**.

Compound **10** ($C_{21}H_{24}O_8$) (ferupennin J) showed ^{1}H NMR and ^{13}C NMR spectral data similar to compound **9**, except for the ester moiety (**9**: angelate; **10**: methacrylate). The positions of the ester groups were also confirmed by HMBC correlations. Compound **11** ($C_{21}H_{24}O_8$) (ferupennin K) was assigned the same molecular formula as **10**. Its ^{1}H NMR and ^{13}C NMR spectral data were also very similar to those of compound **9**, except for the ester group (**11**: methacrylate; **9**: angelate). The positions of the ester groups were also confirmed by its HMBC spectrum.

Compounds **12** and **13** (ferupennins L and M) had the same molecular formula ($C_{22}H_{26}O_8$) and very similar ^{1}H NMR and ^{13}C NMR spectral data. Comparison of the ^{1}H NMR and ^{13}C NMR spectral data of compounds **12** and **13** with those of compound **1**, except for their ester moieties, indicated that there were differences at C-5. The H-5 protons were not seen in compounds **12** and **13**, and the H-6 protons changed from a triplet [**1**: δ_H 4.52 (t, J = 10.7 Hz)] to doublets [**12**: δ_H 4.74 (d, J = 9.6 Hz); **13**: δ_H 4.78 (d, J = 10.0 Hz)]. In addition, the H-8 signal in compounds **12** and **13** was shifted downfield (0.45−0.48) compared to that in compound **1**. In the ^{13}C NMR spectra of **12** and **13**, the chemical shift of C-5 was found at δ_C 79.6 and 79.3 in compounds **12** and **13**, respectively. These findings suggested that an oxygen function was located on C-5 in the guaiane skeleton. In the HMBC spectrum of **12**, the correlations of H-15 with C-5, and H-7 with C-5, indicated

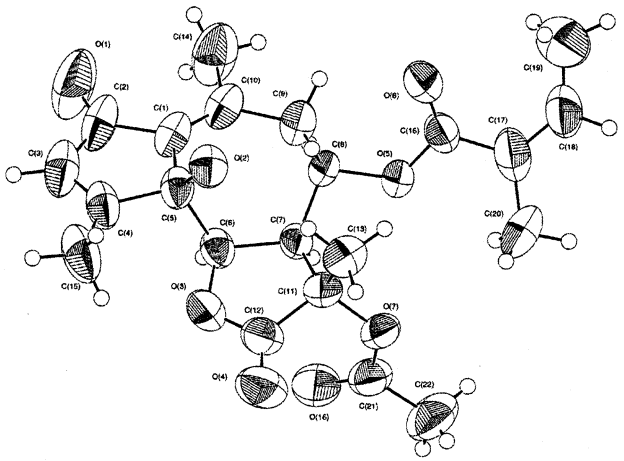


Figure 2. ORTEP drawing of **13**.

that the oxygen function was located at C-5. In their HMBC spectra, the signals at δ_H 6.04 (**12**, H-8) and δ_H 6.07 (**13**, H-8) correlated with those at δ_C 166.8 (**12**, angeloyl carbonyl) and δ_C 166.9 (**13**, angeloyl carbonyl). This shows that an angelate is located at C-8 in both compounds. The remaining problem was to determine whether the acetate is located on C-5 or C-11. Since, the HMBC and NOESY spectra of both compounds gave no effective correlations to determine the position of the ester, single-crystal X-ray analysis was performed on compound **13** (Figure. 2). On the basis of these results, the acetyl ester was determined to be located at C-11 in **13** and, by exclusion, at C-5 in **12**.

Compound **14** ($C_{21}H_{24}O_8$) (ferupennin N) had ^{1}H NMR and ^{13}C NMR spectral data very similar to those of **12**, except for the ester groups (**12**: angeloyl; **14**: methacryl). The methacrylate in compound **14** was confirmed as being located at C-8 on the basis of an HMBC analysis.

Compound **15** (ferupennin O) had a molecular formula of $C_{15}H_{16}O_4$, and its ^{1}H NMR spectrum showed three methyls at δ_H 1.33 (3H, d, J = 6.8 Hz), 2.21, and 2.37 (each 3H, s), one methylene at δ_H 3.30 and 3.48 (each 1H, d, J = 16.0 Hz), and four methines. The ^{13}C NMR spectrum showed signals similar to that of compound **1** for C-1−C-7, C-10, C-12, C-14, and C-15, except for the ester groups. The ^{13}C NMR spectra of the two compounds differed with regard to C-11 [**1**: δ_C 78.5 (C); **15**: 36.7 (CH)] and C-8 [**1**: δ_C 64.8 (CH); **15**: 204.7 (CO)]. On the basis of these findings, the structure of **15** was tentatively assigned as 2,8-dioxo-1(10),3-guaiadiene-12,6-olide. In the NOESY spectrum of **15**, the correlations of H-7 to H-6 and H-11 confirmed the *cis*-γ-lactone and 11β-methyl substituents. The structure of **15** was verified by singlet crystal X-ray analysis (Figure 3). Compound **16** was assigned a molecular formula of $C_{15}H_{20}O_4$ on the basis of HREIMS (*m*/*z* 264.1363). Its IR spectrum showed the presence of a hydroxy group (3346 cm^{-1}), a γ-lactone (1780 cm^{-1}), and an α,β-unsaturated ketone (1653 cm^{-1}). The ^{1}H NMR spectrum of **16** indicated the presence of three methyls [δ_H 2.10 , 0.97 (each 3H, s), and 1.21 (3H, d, J = 7.6 Hz)], one double-bond methine [δ_H 5.90 (1H, brs)], and a methine bearing an oxygen function [δ_H 4.66 (1H, dd, J = 6.4, 9.2 Hz)]. The ^{13}C NMR spectrum of **16** indicated the presence of an α,β-unsaturated ketone (δ_C 197.5, 124.6, 162.0), a γ-lactone (δ_C 178.9), three methyls, two methylenes, five methines (δ_C 78.7 × 2, 42.7, 38.1 × 2), and a quaternary carbon. In the ^{1}H−^{1}H COSY spectrum of **16**, correlations were observed between H-6 and both H-5 and H-7, and H-7 and both H-11 and H_2-8. Correlations of H-14 to C-1, C-5, C-9, and C-10, and H-15 to C-3, C-4, and C-15, were also observed in the

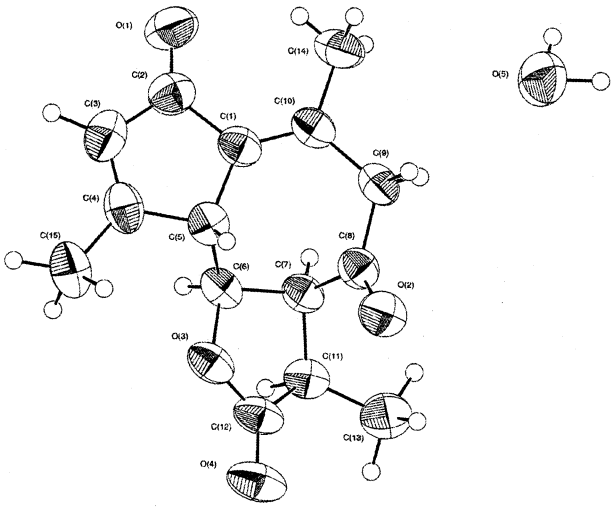


Figure 3. ORTEP drawing of **15**.

HMBC spectrum. These results suggested that compound **16** has the same structure as the known 1β-hydroxy-2-oxo-5β-11α-eudesm-3-en-6β,12-olide (**16a**),[19] but the chemical shifts of H-6 in the two compounds differed [**16**: δ_H 4.66 (dd, J = 6.4, 9.2 Hz); **16a**: δ_H 4.00 (dd, J = 9.0, 10.0 Hz)]. The compounds appeared to differ with regard to the relative stereochemistry of C-6. In the NOESY spectrum of **16**, the correlations of H-6 to H-7 and H_3-14 to H-6 and H-7 indicated that the γ-lactone in **16** was in a *cis* orientation. Therefore, the structure of compound **16** was assigned as 1α-hydroxy-5α,7β,11βH-eudesm-3-en-6α,12-olide.

The ^{1}H NMR spectrum of compound **17** ($C_{20}H_{28}O_6$) (penninnervin) showed the presence of five methyls, three double-bond methines [δ_H 5.68 (s), 5.74 (d, J = 9.6 Hz), 5.91 (dd, J = 5.6, 9.6 Hz)], and two methines bearing an oxygen function [δ_H 3.52 (d, J = 5.6 Hz), 5.45 (dd, J = 9.6, 10.4 Hz)]. The ^{13}C NMR spectrum of **17** suggested the presence of five methyls, two methylenes, two double bonds [δ_C 115.3 (CH), 126.1 (CH), 138.4 (CH), and 159.9 (C)], two ester carbonyls [δ_C 165.2 and 175.3], and three quaternary carbons [δ_C 36.8, 68.6, and 79.3]. In the ^{1}H−^{1}H COSY spectrum of **17**, the correlations of H-2 (δ_H 5.91) to H-1 (δ_H 3.52) and H-3 (δ_H 5.74); H-6 (δ_H 5.45) to H-5 (δ_H 1.89) and H-7 (δ_H 3.31); and H-7 to H-8 (δ_H 1.81) indicated that C-1 was connected to C-3 and C-5 was connected to C-8. In the HMBC spectrum, the correlations of H-14 to C-1, C-5, C-9, and C-10; H-15 to C-3, C-4, and C-5; H-6 to C-12; and H-13 to C-7 supported a partial structure of 1,4,11-trihydroxy-eudesm-2-en-6,12-olide for **17**. The ester group of **17** was determined to be a senicioate unit on the basis of spectral data and analysis of the HMBC spectrum. The relative stereochemistry and position of senicioate were determined on the basis of NOESY data [H-14 to H-1, H-6, and H-7; H_3-5′ to H_3-13; H-6 to H-7; and H-5 to H_3-15]. Therefore, the structure of compound **17** was assigned as shown.

Compound **18** ($C_{20}H_{28}O_6$) had ^{1}H NMR and ^{13}C NMR data very similar to those of compound **17**, except for the ester moieties [**17**: senicioate; **18**: angelate]. On the basis of an analysis of HMBC and NOESY spectral data, the structure of **18** was determined to be as shown. The spectral data of compound **18** were the same as decipienin D, which was the first compound reported with a *trans* configuration at C-6 and C-7,[20] but later it was corrected to the *cis* configuration.[12]

The effects of compounds **6**, **8**, and **10** on cytokine (IL-1β, IL-2, IL-4, and TNF-γ) production[21,22] were determined. The results are given in Table 2. Compound **10** had a moderate inhibitory effect on IL-2 production from liposaccharide-stimulated human peripheral mononuclear cells compared to the reference compound, prednisolone.

Table 2. Inhibitory Effects of Compounds **6**, **8**, and **10** and Prednisolone on Cytokine Production[a]

compound	IL1-β	IL-2	IL-4	TNF-α
6	18.9	38.6	33.8	31.6
8	25.3	14.3	−30.7	34.5
10	−4.6	90.9	48.9	15.9
prednisolone	24.8	30.6	40.7	47.9

[a] Inhibition (%), for test compounds at 10 μg/mL and prednisolone at 0.3 μg/mL.

Experimental Section

General Experimental Procedures. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. UV spectra were carried out on a UV2100 UV−vis recording spectrometer (Shimadzu), and IR spectra were recorded on a JASCO Fourier transform infrared spectrometer (FT/IR-420). NMR (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR, both use TMS as internal standard) were measured on a Bruker AM 400 spectrometer and MS on a JEOL JMSD-300 instrument. Column chromatography: silica gel 60 (Merck) and Toyopearl HW 40 (TOSHO). HPLC: GPC (Shodex H-2001, 2002, $CHCl_3$), silica gel (YMC-pack SIL-06 SH-043-5-06, 250 × 20 mm, Hibar RT 250-25 Si 60), ODS (YMC-R-ODS-5, Yamamura).

Plant Material. The dried roots of *Ferula penninervis* (1.9 kg) were collected in June 1998 from north of Angre, Uzbekistan. Herbarium specimens (EMS 4050) were deposited in the herbarium of the Academy of Sciences, Institute of Botany, Uzbekistan.

Extraction and Isolation. The EtOAc extract (139 g) of *F. penninervis* roots was chromatographed on a silica gel column and eluted with a solvent system of increasing polarity (*n*-hexane−EtOAc, 3:1, 2:1, 1:1, 1:2, 1:3, EtOAc, EtOAc−MeOH, 99:1, 19:1, 9:1, 8:2, 7:3, 1:1, MeOH) to give 32 fractions (fr. 1−32). Fraction 12 (3 g) was chromatographed on Toyopearl HW-40 ($CHCl_3$−MeOH, 2:1) to afford six fractions (fr. 12.1−12.6). Fraction 12.4 (520 mg) was purified by HPLC (silica gel 60, *n*-hexane−EtOAc, 1:1) to give talassin B (38 mg) and oferin (23 mg). Fraction 18 (9.2 g) was chromatographed on a silica gel column and eluted with $CHCl_3$−MeOH (100:1, 99:1, 98:2, 19:1) to give nine fractions (fr. 18.1−18.9). Fraction 18.3 (3.3 g) was chromatographed on Toyopearl HW-40 ($CHCl_3$−MeOH, 2:1) to afford five fractions (fr. 18.3.1−18.3.5). Fraction 18.3.2 (211 mg) was separated by HPLC (silica gel 60, *n*-hexane−EtOAc, 1:1) to give laferin (8 mg) and olgin (11 mg). Fraction 18.8 (3.4 g) was chromatographed on Toyopearl HW-40 ($CHCl_3$−MeOH, 2:1) to afford five fractions (fr. 18.8.1−18.8.5). Fraction 18.8.2 (499 mg) was separated by HPLC (silica gel 60, *n*-hexane−EtOAc, 1:1) and GPC ($CHCl_3$) to give **12** (10 mg), **13** (18 mg), and **14** (13 mg). Fraction 21 (9.6 g) was chromatographed on a silica gel column and eluted with $CHCl_3$−MeOH (19:1, 9:1, MeOH) to give eight fractions (fr. 21.1−21.8). Fraction 21.1 (577 mg) was purified by HPLC (silica gel 60, *n*-hexane−EtOAc, 1:1) and GPC ($CHCl_3$) to give **5** (4 mg), **15** (24 mg), isolasolide (19 mg), and lasolide (14 mg). Fraction 21.4 (3 g) was chromatographed on Toyopearl HW-40 ($CHCl_3$−MeOH, 2:1) to afford 13 fractions (fr. 21.4.1−21.4.13). Fraction 21.4.4 (110 mg) was separated by HPLC (silica gel 60, $CHCl_3$−MeOH, 98:2) to give **10** (24 mg) and **11** (6 mg). Fraction 21.4.10 (898 mg) was chromatographed on a silica gel column and eluted with $CHCl_3$−MeOH (19:1, 9:1, 8:2, 1:1, MeOH) to give six fractions (fr. 21.4.10.1−21.4.10.6). Fraction 21.4.10.2 (109 mg) was separated by HPLC (silica gel 60, $CHCl_3$−MeOH, 19:1) to give **16** (4 mg). Fraction 21.4.10.3 (219 mg) was separated by HPLC (ODS, MeOH−H_2O, 8:2) to give **1** (96 mg), **2** (7 mg), **4** (15 mg), and **9** (13 mg). Fraction 21.4.10.6 (67 mg) was purified by HPLC (ODS, MeOH−H_2O, 8:2) to give **3** (16 mg), **17** (3 mg), and **18** (3 mg).

Fraction 21.5 (2.6 g) was chromatographed on a silica gel column and eluted with $CHCl_3$−MeOH (19:1, 9:1, MeOH) to give eight fractions (fr. 21.5.1−21.5.8). Fraction 21.5.4 (113 mg) was separated by HPLC (silica gel 60, *n*-hexane−EtOAc, 1:4) to give **6** (42 mg), **7** (13 mg), and **8** (40 mg). Fraction 21.8 (347 mg) was chromatographed on a silica gel column and eluted with $CHCl_3$−MeOH (19:1, 9:1, MeOH) to give seven fractions (fr. 21.8.1−21.8.7). Fraction 21.8.4 (86 mg) was purified by HPLC (ODS, MeOH−H_2O, 7:3) to give carmenin (2 mg) and 4*β*,10α-dihydroxyaromadendrane (8 mg).

Ferupennin A (1): colorless oil; $[\alpha]_D$ +1.2° (*c* 0.5, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 252 (4.2) nm; IR (KBr) ν_{max} 3449, 2928, 1789, 1731, 1685, 1617, 1439, 1378, 1203, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 6.11 (1H, s, H-3), 4.52 (1H, t, *J* = 10.7 Hz, H-6), 4.45 (1H, m, H-8), 3.47 (1H, d, *J* = 10.7 Hz, H-5), 3.07 (1H, t, *J* = 10.7 Hz, H-7), 2.74 (1H, d, *J* = 18.0 Hz, H-9b), 2.50 (1H, dd, *J* = 10.4, 18.0 Hz, H-9a), 2.56 (1H, sept, *J* = 6.8 Hz, H-2′), 2.18 (6H, s, H-14, 15), 1.75 (3H, s, H-13), 1.12 (6H, t, *J* = 6.8 Hz, H-3′, 4′); ^{13}C NMR spectral data, see Table 1; EIMS *m*/*z* 348 $[M]^+$ (44), 296 (10), 278 (11), 218 (18), 205 (20), 192 (16), 183 (40), 167 (38), 149 (27), 137 (70), 120 (95), 110 (100), 95 (85), 85 (93), 67 (71), 59 (87), 49 (90), 39 (95); HREIMS *m*/*z* 348.1592 $[M]^+$ (calcd for $C_{19}H_{24}O_6$, 348.1573).

Ferupennin B (2): colorless oil; $[\alpha]_D$ +10.0° (*c* 0.6, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 251 (4.2) nm; IR (KBr) ν_{max} 3446, 2927, 1790, 1716, 1685, 1617, 1436, 1378, 1204, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 6.21 (1H, s, H-3′), 6.19 (1H, s, H-3), 5.67 (1H, s, H-3′), 4.64 (1H, t, *J* = 11.2 Hz, H-6), 4.48 (1H, ddd, *J* = 3.2, 11.2, 11.6 Hz, H-8), 3.50 (1H, d, *J* = 11.2 Hz, H-5), 3.19 (1H, t, *J* = 11.2 Hz, H-7), 2.80 (1H, dd, *J* = 3.2, 19.0 Hz, H-9b), 2.54 (1H, dd, *J* = 11.6, 19.0 Hz, H-9a), 2.26 (15, 6H, s, H-14), 1.98 (3H, s, H-4′), 1.87 (3H, s, H-13); ^{13}C NMR spectral data, see Table 1; EIMS *m*/*z* 346 $[M]^+$ (30), 296 (10), 278 (10), 261 (40), 218 (19), 205 (25), 192 (41), 183 (80), 167 (71), 149 (95), 137 (91), 120 (80), 110 (92), 95 (90), 85 (79), 72 (100), 71 (90), 59 (93), 39 (77); HREIMS *m*/*z* 346.1420 $[M]^+$ (calcd for $C_{19}H_{22}O_6$, 346.1416).

Ferupennin C (3): colorless oil; $[\alpha]_D$ +2.4° (*c* 0.5, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 252 (4.2) nm; IR (KBr) ν_{max} 3447, 2925, 1786, 1736, 1684, 1617, 1436, 1376, 1205, 1134 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 6.13 (1H, s, H-3), 4.61 (1H, t, *J* = 10.8 Hz, H-6), 4.46 (1H, ddd, *J* = 2.8, 10.4, 10.8 Hz, H-8), 3.49 (1H, d, *J* = 10.8 Hz, H-5), 3.15 (1H, t, *J* = 10.8 Hz, H-7), 2.75 (1H, dd, *J* = 2.8, 19.0 Hz, H-9b), 2.57 (1H, dd, *J* = 10.4, 19.0 Hz, H-9a), 2.21 (3H, s, H-14), 2.19 (3H, s, H-15), 2.10 (AcO), 1.83 (3H, s, H-13,); ^{13}C NMR spectral data, see Table 1; EIMS *m*/*z* 320 $[M]^+$ (83), 278 (10), 261 (17), 256 (21), 192 (92), 167 (42), 149 (80), 137 (39), 87 (92), 85 (86), 72 (66), 69 (75), 49 (92), 41 (100); HREIMS *m*/*z* 320.1254 $[M]^+$ (calcd for $C_{17}H_{20}O_6$, 320.1260).

Ferupennin D (4): colorless oil; $[\alpha]_D$ −2.0° (*c* 0.5, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 250 (4.1) nm; IR (KBr) ν_{max} 3447, 2927, 1791, 1736, 1685, 1617, 1457, 1377, 1205, 1142 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 6.22 (1H, q, *J* = 7.0 Hz, H-3′), 6.20 (1H, s, H-3), 4.65 (1H, t, *J* = 11.0 Hz, H-6,), 4.49 (1H, ddd, *J* = 3.2, 11.0, 11.6 Hz, H-8,), 3.52 (1H, d, *J* = 11.0 Hz, H-5), 3.23 (1H, t, *J* = 11.0 Hz, H-7), 2.80 (1H, dd, *J* = 3.2, 19.0 Hz, H-9b), 2.56 (1H, dd, *J* = 11.6, 19.0 Hz, H-9a), 2.28 (6H, s, H-14, 15), 2.04 (3H, d, *J* = 7.0 Hz, H-5′), 1.91 (3H, s, H-4′), 1.87 (3H, s, H-13); ^{13}C NMR spectral data, see Table 1; EIMS *m*/*z* 360 $[M]^+$ (53), 260 (42), 249 (58), 218 (12), 191 (21), 175 (51), 167 (50), 149 (35), 111 (33), 98 (92), 85 (90), 49 (34), 47 (100), 41 (82), 39 (23); HREIMS *m*/*z* 360.1558 $[M]^+$ (calcd for $C_{20}H_{24}O_6$, 360.1573).

Ferupennin E (5): amorphous powder; $[\alpha]_D$ −2.7° (*c* 0.4, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 252 (4.1) nm; IR (KBr) ν_{max} 3447, 2925, 1788, 1750, 1739, 1685, 1618, 1436, 1377, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 6.22 (1H, s, H-3,), 5.64 (1H, ddd, *J* = 3.2, 10.8, 14.0 Hz, H-8), 4.67 (1H, t, *J* = 10.8 Hz, H-6), 3.61 (1H, d, *J* = 10.8 Hz, H-7), 3.55 (1H, d, *J* = 10.8 Hz, H-5), 3.11 (1H, q, *J* = 5.8 Hz, H-3′), 2.75 (1H, dd, *J* = 3.2, 18.0 Hz, H-9b), 2.51 (1H, dd, *J* = 14.0, 18.0 Hz, H-9a), 2.27 (6H, s, H-14, 15), 2.13 (AcO), 1.63 (3H, s, H-13), 1.62 (H-4′,), 1.39 (3H, d, *J* = 5.8 Hz, H-5′); ^{13}C NMR spectral data, see Table 1; EIMS *m*/*z* 418 $[M]^+$ (97), 357 (28), 302 (45), 260 (19), 243 (95), 242 (90), 232 (35), 214 (73), 199 (81), 189 (60), 172 (100), 146 (95), 83 (37), 69 (90), 55 (41), 41 (81) 39 (22); HREIMS *m*/*z* 418.1619 $[M]^+$ (calcd for $C_{22}H_{26}O_8$, 418.1628).

Ferupennin F (6): amorphous powder; $[\alpha]_D$ +4.0° (*c* 0.8, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 252 (4.2) nm; IR (KBr) ν_{max} 3412, 2923, 1792, 1736, 1718, 1687, 1617, 1433, 1379, 1143 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 6.21 (1H, s, H-3), 5.59 (1H, ddd, *J* = 2.4, 10.6, 11.0 Hz, H-8), 4.64 (1H, t, *J* = 10.6 H z, H-6), 3.56 (1H, d, *J* = 10.6 Hz, H-7), 3.51 (1H, d, *J* = 10.6 Hz, H-5), 2.77 (1H, dd, *J* = 2.4, 18.8 Hz, H-9b), 2.56 (1H, dd, *J* = 11.0, 18.8 Hz, H-9a), 2.31 (3H, s, H-5′), 2.26 (3H, s, H-14), 2.25 (3H, s, H-15), 2.09 (AcO), 1.64 (3H, s, H-13), 1.49 (1H, s, H-4′); ^{13}C NMR spectral data, see Table 1; EIMS *m*/*z* 434 $[M]^+$ (79), 420 (100), 392 (42), 360 (37), 302 (45), 244 (65), 214 (77), 189 (95), 172 (78), 146 (95), 91 (82), 83 (26), 71 (94), 69 (81), 59 (77), 55 (72), 41(83); HREIMS *m*/*z* 434.1570 $[M]^+$ (calcd for $C_{22}H_{26}O_9$, 434.1577).

Ferupennin G (7): colorless oil; $[\alpha]_D$ +5.0° (*c* 1.0, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 248 (4.1) nm; IR (NaCl) ν_{max} 2959, 1794, 1720, 1685, 1644, 1432, 1363, 1159 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 6.27 (1H, d, *J* = 2.8 Hz, H-4′), 6.22 (1H, s, H-3,), 5.96 (1H, d, *J* = 2.8 Hz, H-4′), 5.56 (1H, ddd, *J* = 2.8, 10.4, 10.8 Hz, H-8), 4.70 (1H, t, *J* = 10.8 Hz, H-6), 4.64 (1H, q, *J* = 6.8 Hz, H-3′), 3.56 (1H, d, *J* = 10.8 Hz, H-7), 3.50 (1H, d, *J* = 10.8 Hz, H-5), 2.90 (1H, dd, *J* = 2.8, 19.0 Hz, H-9b), 2.52 (1H, dd, *J* = 10.4, 19.0 Hz, H-9a), 2.26 (6H, s, H-14, 15), 2.10 (AcO), 1.59 (3H, s, H-13), 1.42 (1H, d, *J* = 6.8 Hz, H-5′); ^{13}C NMR spectral data, see Table 1; EIMS *m*/*z* 418 $[M]^+$ (100), 304 (98), 244 (93), 232 (59), 214 (95), 189 (93), 181 (97), 172 (92), 159 (81), 146 (91), 71 (82), 59 (97), 55 (85), 41 (79); HREIMS *m*/*z* 418.1651 $[M]^+$ (calcd for $C_{22}H_{26}O_8$, 418.1625).

Ferupennin H (8): colorless oil; $[\alpha]_D$ +2.0° (*c* 1.0, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 252 (4.1) nm; IR (NaCl) ν_{max} 3469, 2928, 1793, 1739, 1716, 1686, 1617, 1457, 1352, 1154 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 6.20 (1H, s, H-3), 6.18 (1H, q, *J* = 7.2 Hz, H-3′), 5.58 (1H, ddd, *J* = 3.2, 10.8, 11.4 Hz, H-8), 4.66 (1H, t, *J* = 11.4 Hz, H-6), 4.34 (2H, s, H-14), 3.64 (1H, d, *J* = 11.4 Hz, H-5), 3.53 (1H, t, *J* = 11.4 Hz, H-7), 3.09 (1H, dd, *J* = 3.2, 19.0 Hz, H-9b), 2.64 (1H, dd, *J* = 10.8, 19.0 Hz, H-9a), 2.26 (3H, s, H-15), 2.13 (AcO), 2.01 (3H, d, *J* = 7.2 Hz, H-5′), 1.95 (3H, s, H-4′), 1.57 (3H, s, H-13); ^{13}C NMR spectral data, see Table 1; EIMS *m*/*z* 418 $[M]^+$ (90), 372 (63), 332 (25), 277 (25), 261 (41), 232 (52), 207 (26), 164 (95), 84 (47), 71 (100), 59 (95), 46 (50); HREIMS *m*/*z* 418.1607 $[M]^+$ (calcd for $C_{22}H_{26}O_8$, 418.1628).

Ferupennin I (9): colorless oil; $[\alpha]_D$ +0.8° (*c* 0.8, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) IR (NaCl) ν_{max} 3448, 2928, 1793, 1739, 1717, 1686, 1617, 1457, 1377, 1154 cm^{-1}; 250 (4.2), 226 (4.0) nm; ^1H NMR ($CDCl_3$) δ_H 6.43 (1H, s, H-3), 6.22 (1H, q, *J* = 6.4H z, H-3′), 5.59 (1H, ddd, *J* = 2.0, 10.6, 11.2 Hz, H-8), 4.79 (1H, d, *J* = 16.4 Hz, H-15), 4.62 (1H, t, *J* = 11.2 Hz, H-6), 4.52 (1H, d, *J* = 16.4 Hz, H-15), 3.86 (1H, d, *J* = 11.2 Hz, H-5), 3.56 (1H, t, *J* = 11.2 Hz, H-7), 2.90 (1H, dd, *J* = 2.0, 19.0 Hz, H-9b), 2.53 (1H, dd, *J* = 10.6, 19.0 Hz, H-9a), 2.27 (3H, s, H-14), 2.09 (AcO), 2.02 (3H, d, *J* = 6.4 Hz, H-5′), 1.91 (3H, s, H-4′), 1.59 (3H, s, H-13); ^{13}C NMR spectral data, see Table 1; EIMS *m*/*z* 418 $[M]^+$ (100), 372 (63), 332 (25), 278 (25), 261 (41), 232 (52), 208 (26), 165 (95), 84 (47), 46 (50); HREIMS *m*/*z* 418.1620 $[M]^+$ (calcd for $C_{22}H_{26}O_8$, 418.1628).

Ferupennin J (10): colorless oil; $[\alpha]_D$ +6.2° (*c* 1.0, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 250 (4.0) nm; IR (NaCl) ν_{max} 3640, 2956, 1793, 1719, 1687, 1646, 1431, 1361, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H 6.25 (1H, s, H-3), 6.16 (1H, s, H-3′), 5.69 (1H, s, H-3′), 5.52 (1H, ddd, *J* = 2.8, 10.4, 10.8 Hz, H-8), 4.69 (1H, t, *J* = 10.8 Hz, H-6), 4.34 (2H, s, H-14), 3.62 (1H, d, *J* = 10.8 Hz, H-5), 3.58 (1H, t, *J* = 10.8 Hz, H-7), 3.10 (1H, dd, *J* = 2.8, 19.0 Hz, H-9b), 2.65 (1H, dd, *J* = 10.4, 19.0 Hz, H-9a), 2.28 (3H, s, H-15), 2.10 (AcO), 1.97 (3H, s, H-4′), 1.57 (3H, s, H-13); ^{13}C NMR spectral data, see Table 1; EIMS *m*/*z* 404 $[M]^+$ (76), 376 (40), 318 (95), 276 (18), 258 (93), 243 (39), 229 (90), 213 (35), 201 (40), 187 (95), 159 (98), 146 (43), 91 (100), 77 (27), 69 (63), 55 (60), 41 (62); HREIMS *m*/*z* 404.1512 $[M]^+$ (calcd for $C_{21}H_{24}O_8$, 404.1471).

Ferupennin K (11): colorless oil; $[\alpha]_D$ +4.0° (*c* 0.3, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 249 (4.1) nm; IR (NaCl) ν_{max} 3646, 2959, 1794, 1723, 1687, 1645, 1431, 1362, 1158 cm^{-1}; ^1H NMR

($CDCl_3$) δ_H 6.40 (1H, s, H-3), 6.19 (1H, s, H-3′), 5.67 (1H, s, H-3′), 5.51 (1H, ddd, J = 2.0, 10.6, 11.2 Hz, H-8), 4.79 (1H, d, J = 16.4 Hz, H-15), 4.66 (1H, t, J = 11.2 Hz, H-6), 4.52 (1H, d, J = 16.4 Hz, H-15), 3.90 (1H, d, J = 11.2 Hz, H-5), 3.61 (1H, t, J = 11.2 Hz, H-7), 2.98 (1H, dd, J = 2.0, 19.0 H, H-9b), 2.56 (1H, dd, J = 10.6, 19.0 Hz, H-9a), 2.26 (3H, s, H-14), 2.09 (AcO), 1.99 (3H, s, H-4′), 1.69 (3H, s, H-13); ^{13}C NMR spectral data, see Table 1; EIMS m/z 404 $[M]^+$ (100), 343 (33), 317 (42), 276 (39), 259 (91), 240 (92), 212 (91), 188 (95), 162 (95), 129 (93), 105 (70), 91 (89), 77 (75), 71 (90), 55 (85), 39 (87); HREIMS m/z 404.1459 $[M]^+$ (calcd for $C_{21}H_{24}O_8$, 404.1471).

Ferupennin L (12): colorless oil; $[\alpha]_D$ +127.4° (c 1.0, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 259 (3.9), 222 (4.0) nm; IR (NaCl) ν_{max} 3423, 2928, 1790, 1741, 1695, 1640, 1437, 1354, 1152 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ_H 6.19 (1H, q, J = 6.8 Hz, H-3′), 6.04 (1H, ddd, J = 3.6, 9.6, 10.4 Hz, H-8), 6.01 (1H, s, H-3), 4.74 (1H, d, J = 9.6 Hz, H-6), 3.47 (1H, t, J = 9.6 Hz, H-7), 3.02 (1H, dd, J = 3.6, 18.6 H, H-9b), 2.40 (1H, dd, J = 10.8, 18.6 Hz, H-9a), 2.26 (3H, s, H-14), 2.23 (3H, s, H-15), 2.07 (AcO), 1.96 (3H, d, J = 6.8 Hz, H-5′), 1.90 (3H, s, H-4′), 1.65 (3H, s, H-13); ^{13}C NMR spectral data, see Table 1; EIMS m/z 418 $[M]^+$ (93), 358 (90), 318 (75), 276 (63), 262 (97), 248 (76), 218 (81), 205 (96), 190 (100), 166 (77), 160 (90), 144 (97), 112 (89), 97 (76), 66 (65); HREIMS m/z 418.1634 $[M]^+$ (calcd for $C_{22}H_{26}O_8$, 418.1628).

Ferupennin M (13): colorless needles; $[\alpha]_D$ +12.6° (c 0.7, $CHCl_3$); mp 90−91 °C; UV (MeOH) λ_{max} (log ϵ) 260 (3.8), 222 (4.0) nm; IR (NaCl) ν_{max} 3433, 2927, 1791, 1741, 1697, 1637, 1436, 1329, 1151 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ_H 6.22 (1H, q, J = 7.2 Hz, H-3′), 6.12 (1H, s, H-3), 6.07 (1H, ddd, J = 3.2, 10.0, 10.8 Hz, H-8), 4.78 (1H, d, J = 10.0 Hz, H-6), 3.50 (1H, t, J = 10.0 Hz, H-7), 3.08 (1H, dd, J = 3.2, 18.6 Hz, H-9b), 2.45 (1H, dd, J = 10.8, 18.6 H, H-9a), 2.28 (6H, s, H-14, 15), 2.09 (AcO), 2.05 (3H, d, J = 7.2 Hz, H-5′), 1.92 (3H, s, H-4′), 1.62 (3H, s, H-13); ^{13}C NMR spectral data, see Table 1; EIMS m/z 418 $[M]^+$ (20), 358 (43), 318 (98), 276 (25), 248 (49), 214 (61), 205 (95), 187 (27), 161 (77), 150 (100); HREIMS m/z 418.1618 $[M]^+$ (calcd for $C_{22}H_{26}O_8$, 418.1628).

X-ray Crystallographic Analysis of 13.[23] Crystal data for compound **13**: $C_{22}H_{26}O_8$, mol wt = 418.16, colorless orthorhombic crystal obtained from MeOH, crystal size 0.35 × 0.2 × 0.15 mm; space group $P2_12_12_1$, a = 11.5620(5) Å b = 16.1400(10) Å, c = 24.164(2) Å, V = 4509.3(5) Å^3, Z = 8, D_x = 1.251 Mg m^{-3}, D_m = 1.51 Mg m^{-3}. Data collection was performed on a DIP image plate, and the structure was solved by direct methods (maXus SIR92); 4520 reflections were measured, giving 4502 independent observations with 3211 having $I > 3\sigma$. All non-hydrogen atoms were refined with anisotropic Gaussian displacement parameters. Hydrogen atoms were refined as riding on the attached atom with isotopic displacement parameters. The final refinement converged with R(gt) = 0.0796, R_w(gt) = 0.2191, and S(ref) = 0.984. The final electron density map is featureless, with minimum and maximum peaks of −0.384 and 0.504 e Å^3.

Ferupennin N (14): colorless oil; $[\alpha]_D$ +99.3° (c 1.5, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 260 (3.6) nm; IR (NaCl) ν_{max} 3464, 2979, 1771, 1733, 1716, 1695, 1641, 1626, 1433, 1333, 1152 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ_H 6.12 (1H, s, H-3′), 6.03 (1H, ddd, J = 3.6, 9.6, 10.8 Hz, H-8), 6.00 (1H, s, H-3), 5.64 (1H, s, H-3′), 4.72 (1H, d, J = 9.6 Hz, H-6), 3.45 (1H, t, J = 9.6 Hz, H-7), 3.00 (1H, dd, J = 3.6, 18.6 Hz, H-9b), 2.39 (1H, dd, J = 10.8, 18.6 Hz, H-9a), 2.24 (6H, s, H-14,), 2.20 (3H, s, H-15), 2.07 (AcO), 1.93 (3H, s, H-4′), 1.62 (3H,, H-13); ^{13}C NMR spectral data, see Table 1; EIMS m/z 404 $[M]^+$ (89), 344 (84), 318 (91), 276 (42), 258 (80), 240 (100), 229 (93), 213 (97), 188 (98), 162 (66), 96 (90), 71 (99), 55 (82), 41 (69); HREIMS m/z 404.1469 $[M]^+$ (calcd for $C_{21}H_{24}O_8$, 404.1471).

Ferupennin O (15): colorless needles; $[\alpha]_D$ −20.0° (c 0.8, $CHCl_3$); mp 234−236° C; UV (MeOH) λ_{max} (log ϵ) 252 (3.9) nm; IR (NaCl) ν_{max} 3421, 2921, 1769, 1708, 1678, 1637, 1614, 1435, 1318, 1144 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ_H 6.13 (1H, s, H-3), 4.39 (dd, J = 6.6, 10.4 Hz, H-6), 3.70 (1H, t, J = 6.6 Hz, H-7), 3.48 (1H, d, J = 16.0 Hz, H-9), 3.41 (1H, d, J = 10.4 Hz, H-5), 3.30 (1H, d, J = 16.0 Hz, H-9), 2.73 (1H, m, H-11), 2.37 (3H, s, H-14), 2.21 (3H, s, H-15), 1.33 (3H, d, J = 6.8 Hz, H-13); ^{13}C NMR spectral data, see Table 1; EIMS m/z 260 $[M]^+$ (92), 246 (90), 187 (66), 173 (95), 165 (79), 147 (78), 135 (95), 119 (81), 105 (90), 91 (94), 81 (91), 72 (100), 67 (77), 59 (93), 53 (88), 43 (70), 39 (94); HREIMS m/z 260.1056; $[M]^+$ (calcd for $C_{15}H_{16}O_4$, 260.1049).

X-ray Crystallographic Analysis of 15.[23] Crystal data for compound **15**: $C_{15}H_{16}O_4$, mol wt = 260.29, a colorless monoclinic crystal was obtained from MeOH, crystal size 0.4 × 0.1 × 0.1 mm; space group $P2_1$, a = 9.060(2) Å, b = 5.0020(11) Å, c = 15.502(4) Å, V = 701.7(3) Å^3, Z = 2, D_x = 1.232 Mg m^{-3}. Data collection was performed on a DIP image plate, and the structure was solved by direct methods (maXus SIR92); 1440 reflections were measured, giving 1438 independent observations with 1077 having $I > 3\sigma$. All non-hydrogen atoms were refined with anisotropic Gaussian displacement parameters. Hydrogen atoms were refined as riding on the attached atom with isotopic displacement parameters. The final refinement converged with R(gt) = 0.0570, R_w(gt) = 0.1412, and S(ref) = 1.034. The final electron density map is featureless, with minimum and maximum peaks of −0.237 and 0.162 e Å^3.

1α-Hydroxy-2-oxo-5α,7β-11βH-eudesm-3-en-6α,12-olide (16): amorphous powder; $[\alpha]_D$ −17.0° (c 0.4, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 241 (3.9) nm; IR (NaCl) ν_{max} 3446, 2920, 1780, 1653, 1611, 1457, 1351, 1114 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ_H 5.90 (1H, br s, H-3), 4.66 (1H, dd, J = 6.4, 9.2 Hz, H-6), 3.40 (1H, br s, H-1), 2.92 (1H, d, J = 9.2 Hz, H-5), 2.85 (1H, q, J = 7.6 Hz, H-11), 2.79 (1H, m, H-7), 2.30 (1H, m, H-9), 2.10 (3H, s, H-15), 1.71 (1H, m, H-8), 1.48 (1H, m, H-8), 1.21 (3H, d, J = 7.6 Hz, H-13), 1.18 (1H, m, H-9), 0.97 (3H, s, H-14); ^{13}C NMR ($CDCl_3$) δ_C 197.5 (C-2), 178.9 (C-12), 162.0 (C-4), 124.6 (C-3), 78.7 (C-1, 6), 42.7 (C-5), 39.4 (C-10), 38.1 (C-7, 11), 29.8 (C-9), 23.1 (C-15), 22.0 (C-8), 19.3 (C-14), 10.5 (C-13); EIMS m/z 264 $[M]^+$ (98), 246 (40), 235 (95), 228 (20), 218 (66), 203 (42), 175 (94), 173 (56), 165 (83), 153 (92), 135 (62), 121 (78), 85 (90), 77 (88), 77 (75), 53 (77); HREIMS m/z 264.1363 $[M]^+$ (calcd for $C_{15}H_{20}O_4$, 264.1362).

Penninnervin (17): colorless oil; $[\alpha]_D$ −81.3° (c 0.3, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 221 (4.0) nm; IR (NaCl) ν_{max} 3434, 2921, 1773, 1718, 1647, 1457, 1382, 1352, 1231, 1134 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ_H 5.91 (1H, dd, J = 5.6, 9.6 Hz, H-2), 5.74 (1H, d, J = 9.6 Hz, H-3), 5.68 (1H, s, H-2′), 5.45 (1H, dd, J = 9.6, 10.4 Hz, H-6), 3.52 (1H, d, J = 5.6 Hz, H-1), 3.31 (1H, ddd, J = 5.8, 9.6, 11.6 Hz, H-7), 2.16 (3H, s, H-4′), 2.08 (1H, m, H-9), 1.89 (1H, d, J = 10.4 Hz, H-5), 1.86 (3H, s, H-5′), 1.81 (2H, m, H-8), 1.61 (3H, s, H-13), 1.50 (3H, s, H-15), 1.15 (1H, m, H-9), 0.93 (3H, s, H-14); ^{13}C NMR ($CDCl_3$) δ_C: 175.3 (C-12), 165.2 (C-1′), 159.9 (C-3′), 138.4 (C-3), 126.1 (C-2), 115.3 (C-2′), 79.3 (C-11), 76.5 (C-6), 72.2 (C-1), 68.6 (C-4), 44.7 (C-5), 39.3 (C-7), 36.8 (C-10), 32.4 (C-15), 31.2 (C-9), 27.8 (C-5′), 20.8 (C-13), 20.6 (C-4′), 20.4 (C-14), 18.8 (C-8); EIMS m/z 364 $[M]^+$ (99), 349 (92), 265 (90), 250 (92), 228 (93), 204 (95), 177 (95), 147 (100), 135 (87), 119 (82), 105 (92), 79 (87), 67 (87), 53 (91); HREIMS m/z 364.1896 $[M]^+$ (calcd for $C_{20}H_{28}O_6$, 364.1886).

Compound 18 (=decipenin D):[19] colorless oil; $[\alpha]_D$ −76.6° (c 0.3, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 220 (4.0) nm; IR (NaCl) ν_{max} 3488, 2927, 1763, 1718, 1649, 1458, 1385, 1354, 1334, 1134 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ_H 6.17 (1H, q, J = 7.4 Hz, H-3′), 5.91 (1H, dd, J = 5.9, 9.8 Hz, H-2), 5.75 (1H, d, J = 9.8 Hz, H-3), 5.36 (1H, dd, J = 9.6, 10.8 Hz, H-6), 3.53 (1H, d, J = 5.9 Hz, H-1), 3.32 (1H, ddd, J = 5.8, 9.6, 11.5 Hz, H-7), 2.07 (1H, m, H-9), 2.00 (1H, d, J = 7.4 Hz, H-5′), 1.93 (1H, d, J = 10.8 Hz, H-5), 1.90 (3H, s, H-4′), 1.82 (2H, m, H-8), 1.63 (3H, s, H-13), 1.50 (3H, s, H-15), 1.13 (1H, m, H-9), 0.94 (3H, s, H-14); ^{13}C NMR ($CDCl_3$) δ_C 175.0 (C-12), 166.6 (C-1′), 140.5 (C-3′), 138.4 (C-3), 127.2 (C-2′), 126.1 (C-2), 79.9 (C-11), 76.5 (C-6), 72.2 (C-1), 68.6 (C-4), 44.7 (C-5), 39.3 (C-7), 36.8 (C-10), 32.4 (C-15), 31.1 (C-9), 20.7 (C-13), 20.5 (C-14), 20.4 (C-4′), 18.8 (C-8), 16.1 (C-5′); EIMS m/z 364 $[M]^+$ (10), 349 (100), 265 (95), 250 (96), 231 (98), 213 (91), 176 (70), 166 (93), 135 (55), 119 (79), 100 (92), 79 (50), 55 (92); HREIMS m/z 364.1888 $[M]^+$ (calcd for $C_{20}H_{28}O_6$, 364.1886);

Esterification of 1 with Chiral Anisotropic Reagents [(*R*,*S*)-MTPA]. Three equivalents of 2,4,6-trinitrochlorobenzene, (*R*,*S*)-methoxytrifluorom ethylphenylacetic acid, and an

alcohol [**1** (3 mg)] were dissolved in pyridine and dehydrated (2 mL). After the mixture was stirred for 24 h, ether was added, and the organic layer was washed with 8% aqueous sodium hydrogen carbonate and brine, dried over Na_2SO_4, and concentrated to yield (*R*,*S*)-MTPA-**1** (each 1 mg). (+)-MTPA-**1**: ^{1}H NMR ($CDCl_3$) δ_H 6.2032 (H-3), 5.6714 (H-8), 4.6012 (H-6), 2.9142 (H-9b), 2.5550, (H-9a), 2.3882 (H-2′), 2.2642 (H-14), 2.2475 (H-15), 1.1289, 1.0750, (H-3′, H-4′). (−)-MTPA-**1**: ^{1}H NMR ($CDCl_3$) δ_H 6.2075 (H-3), 5.7245 (H-8), 4.6191 (H-6), 2.8664 (H-9b), 2.4519, (H-9a), 2.4345 (H-2′), 2.2315 (H-14), 2.2618 (H-15), 1.1636, 1.0750, (H-3′, H-4′).

Acetylation of 1. Compound **1** (5 mg) was acetylated with acetic anhydride (1 mL) and pyridine (1 mL) at room temperature overnight. The products were purified by using GPC eluted with $CHCl_3$, to provide compound **1a**: ^{1}H NMR ($CDCl_3$) δ_H 6.19 (H-3), 5.52 (H-8), 4.63 (H-6), 3.57 (H-5), 3.47 (H-7), 2.82 (H-9b), 2.61 (H-2′), 2.45 (H-9a), 2.21 (H-14, 15), 2.07 (AcO), 1.59 (H-13), 1.19 (H-3′, H-4′).

Biological Testing. The effects on cytokines (IL-1β, IL-2, IL-4, and TNFα) were investigated in peripheral whole blood collected from healthy volunteers as previously described by Yesilada et al.[22] In brief, heparinized blood was stimulated with bacterial lipopolysaccharide (LPS) and incubated in the presence of test samples or reference compound. The cultured supernatants were obtained, and concentrations of the cytokines produced from macrophages were directly determined by enzyme-linked immunosorbant assay (ELISA).

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(23) Crystallographic data for compounds **13** and **15** have been deposited with the Cambridge Crystallographic Data Center (**13**: CCDC191355, **15**: CCDC191356). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: 44-(091223-306033 or e-mail: deposit@ccdc.cam.ac.uk).

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