Neoclerodane Diterpenoids from *Scutellaria caerulea*

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Five new neoclerodane diterpenoids have been isolated from *Scutellaria caerulea*: (11*S**)-6α-acetoxy-7β,11-diisobutiryloxy-1β,8β-dihydroxy-4(18),13-neoclerodadien-15,16-olide (scuterulein A) (**1**); (13*R**)-1β-6α-7β-triacetoxy-11β-benzoyloxy-8β,13-epoxy-4(18)-neocleroden-15,16-olide (scuterulein B) (**2**); (11*S**)-1β,6α,11-triacetoxy-7β-isobutiryloxy-8β-hydroxy-4(18),13-neoclerodadien-15,16-olide (scuterulein C) (**3**); (11*S**)-6α,11-diacetoxy-7β-isobutiryloxy-1β,8β-dihydroxy-4(18),13-neoclerodadien-15,16-olide (deacetyl scuterulein C) (**4**), and (11*E*)-6α-acetoxy-7β-isobutiryloxy-1β,8β-dihydroxy-4(18),11,13-neoclerodatrien-15,16-olide (scuterulein D) (**5**). Structures were established by spectroscopic and chemical methods. An X-ray analysis was carried out on scuterulein B (**2**).

Scutellaria L. (Labiatae) is a large subcosmopolitan genus with 360 currently recognized species.[1] In America, it is represented by 113 species, with the greatest concentration in Central Mexico and with secondary centers in the southeastern United States and the northern Andes.[2] Recently, plants belonging to this genus have attracted attention owing to interesting biological activities observed for some neoclerodane diterpenoids isolated from them.[3]

In Mexico, *Scutellaria* is represented by 36 species, most of them growing in the mountains near the center of the country. As a part of our ongoing chemical studies on Mexican *Scutellaria* spp.,[4−6] we now describe the structure of five new neoclerodane diterpenoids, named scuteruleines A−D and deacetylscuterulein C (**1**−**5**), isolated from *Scutellaria caerulea* Moc. et Sessé (subgenus Scutellaria, section Scutellaria).[1] The structures of **1**−**5** were established from their spectroscopic data including extensive NMR analysis. An X-ray analysis was performed on scuterulein B (**2**).

Results and Discussion

Scuterulein A (**1**) was assigned the molecular formula $C_{30}H_{44}O_{10}$ by FAB$^+$ HRMS. Its IR spectrum showed absorptions for hydroxyl (3585 cm^{-1}), α,β-unsaturated γ-lactone (1783 cm^{-1}), ester carbonyl groups (1747 cm^{-1}), and an exocyclic double bond (1642, 893 cm^{-1}). The ^{1}H and ^{13}C NMR spectra of **1** (Table 1) showed signals for one acetoxyl and two isobutyryloxy groups.[7] These spectra also showed characteristic signals for the methyl groups of a neoclerodane diterpene with an oxygenated substituent at C-8.[6,8−10] A broad doublet at δ 4.69 (J = 1 Hz) and a broad singlet at δ 4.61 indicated the presence of an exocyclic methylene group at C-4:C-18. A singlet at δ 152.2 and a triplet at δ 105.6 in the ^{13}C NMR spectrum of **1** (Table 1) were consistent with the presence of this feature common to all the diterpenoids isolated from this plant.

Other relevant signals in the ^{1}H NMR spectrum of **1** were those of an ABX system which was assigned to the protons of a β-substituted α,β-unsaturated γ-lactone, i.e., H-14 and the C-16 methylene protons. The characteristic signals of this group were also observed in the ^{13}C NMR spectrum of **1**.[11] A one-proton double doublet at δ 5.76 was assigned to the X part of another ABX system. The AB part, which was observed at δ 3.38 and 3.18, showed strong correlation with the signal assigned to C-16 (δ_C 73.1, t) in the HMBC spectrum of **1**. This fact led us to assign the AB part of the system to the C-12 methylene protons and the X part to H-11, which must be geminal to an ester group. Two one-proton doublets (AB system) at δ 5.60 (J = 10.5 Hz) and δ 5.39 were assigned to the geminal protons of two additional ester groups. The multiplicity and the magnitude of the coupling constants indicated that these groups are located at the C-6 and C-7 positions with an *equatorial* orientation, as in scutebaicalin from *Scutellaria baicalensis*[8] and several neoclerodane derivatives isolated previously from *Scutellaria alpina*.[12−14] A doublet at δ 2.09

Table 1. ^{13}C NMR Data for Compounds **1** and **3**−**5**[a]

C	**1**	**3**	**4**	**5**
1	67.3 d	69.1 d	67.2 d	68.1 d
2	36.3 t	34.7 t	36.3 t	37.7 t
3	31.1 t	30.8 t	31.2 t	31.0 t
4	152.2 s	151.3 s	152.2 s	152.0 s
5	45.3 s	45.7 s	45.4 s	45.6 s
6	72.1 d	71.83 d	72.1 d	73.0 d
7	74.5 d	74.6 d	74.5 d	74.6 d
8	79.4 s	80.0 s	79.3 s	77.7 s
9	47.9 s	48.5 s	48.0 s	47.4 s
10	49.4 d	47.6 d	49.4 d	53.8 d
11	74.2 d	73.9 d	74.8 d	150.6 d
12	33.5 t	33.3 t	33.4 t	117.3 d
13	168.1 s	168.6 s	168.0 s	162.5 s
14	116.7 d	116.7 d	116.6 d	114.1 d
15	173.9 s	173.8 s	173.9 s	174.2 s
16	73.1 t	73.1 t	73.1 t	70.8 t
17	23.2 q	23.3 q	23.2 q	18.0 q
18	105.6 t	106.1 t	105.6 t	105.3t
19	16.7 q	17.0 q	16.7 q	21.4 q
20	16.4 q	15.6 q	16.3 q	15.3 q
CH_3COO-	170.5 s	169.9 s	170.4 s	170.4 s
		170.5 s	169.5 s	
		171.0 s		
CH_3COO-	21.0 q	22.4 q	20.8 q	21.1 q
		21.1 q	21.1 q	
		20.6 q		
$(CH_3)_2CHCOO-$	176.1 s	175.9 s	176.0 s	176.3 s
	175.8 s			
$(CH_3)_2CHCOO-$	34.3 d	34.1 d	34.1 d	34.1 d
	34.1 d			
$(CH_3)_2CHCOO-$	19.2 q	19.2 q	18.7 q	19.3 q
	19.0 q	18.7 q	19.2 q	18.7 q
	18.9 q			
	18.7 q			

[a] Assignments confirmed with the aid of HMBC and HMQC spectra.

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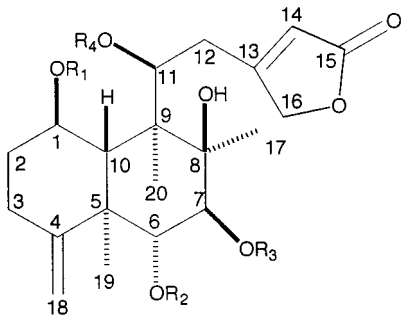
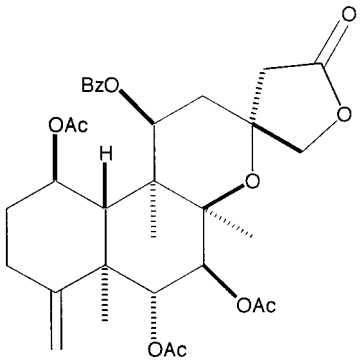


	R_1	R_2	R_3	R_4
1	H	Ac	$-COC_3H_7$	$-COC_3H_7$
3	Ac	Ac	$-COC_3H_7$	Ac
4	H	Ac	$-COC_3H_7$	Ac



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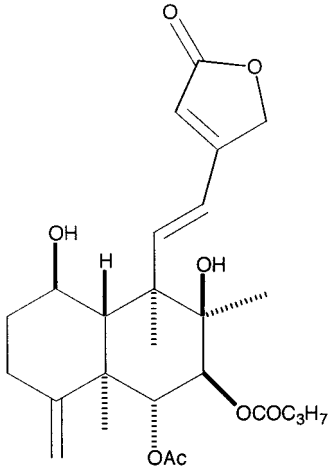

5

(J = 10 Hz) was attributed to the *axially* oriented H-10 and a double triplet at δ 4.26 (J = 10 and 3.5 Hz) to the geminal proton of a secondary hydroxyl group. The COSY spectrum of **1** showed strong correlation between these two signals, indicating that the secondary hydroxyl group is located at C-1 with an *equatorial* orientation.

The location of the ester substituents in compound **1** was established from the heteronuclear multiple bond connectivity (HMBC) spectrum. The HMBC showed cross-peaks of correlation through three bonds between the signal at δ 170.5 (acetoxyl carbonyl) with the proton at δ 5.60 (H-6). This proton correlated with the singlet attributed to C-4 (δ 152.2), which in turn showed a cross-peak with H-10. These facts established the acetoxyl group at the C-6 position. On the other hand, the signal at δ 176.1 (one of the isobutyryloxy carbonyls) correlated in the HMBC spectrum with the proton at δ 5.39, ascribed to H-7, indicating the presence of one of the isobutyryloxy groups at C-7. The second isobutyryloxy moiety must be located at the C-11, since the singlet at δ 175.8 correlated with the double doublets at δ 5.76, ascribed to H-11. On the basis of the previous discussion and the molecular formula, the oxygenated substituent at C-8, vide supra, corresponds to an additional hydroxyl group.

The relative stereochemistry depicted in **1** was firmly established from the ^{13}C NMR data and its NOESY spectrum. The chemical shifts observed, in the ^{13}C NMR spectrum of **1**, for the Me-19 and Me-20 at δ 16.7 and 16.4, respectively, indicated a *trans* fusion for the A/B rings.[11] The coupling constant observed for H-10 is in agreement with this feature present in all the diterpenoids isolated from this plant. In the NOESY spectrum of **1**, H-7 showed significant cross-peaks with Me-17, Me-19, and Me-20, whereas Me-19 and Me-20 correlated with H-1, indicating that H-1, H-7, and the methyl groups are on the same side of the decalin. On the other hand H-6 axial correlated with H-10 and one of the H-18 (pro *Z*). These facts indicated that H-10 and H-6 are on the opposite side of the decalin regarding H-7 and the methyl groups. The correlation between H-6 β-axial and one of the H-18 (pro *Z*) led us to distinguish between these protons.

On the basis of the previous discussion, it was concluded that scuterulein A possessed the structure depicted in **1**, except for the relative configuration at the C-11 stereogenic center. Comparison of the chemical shift and coupling constants observed for H-11 (δ 5.76, J = 10.5, 1.5 Hz) in **1** with those reported for scutalpin B[15] (δ, 5.52, J = 10.7, 1.2 Hz), a neoclerodane diterpenoid with similar oxidation pattern in the side chain, suggested an 11*S** relative configuration for this center in scuterulein A. In the NOESY spectrum of **1** the signal ascribed to H-11 showed a cross-peak of correlation with Me-20, Me-17, and H-16 pro *S*. These facts suggested that in the preferred conformation of the pendant chain, H-11 is close in space to these groups. AM1 semiempirical calculations[16] applied to scuterulein A (**1**) indicated that, in the minimum energy conformation of the side chain, the dihedral angle defined by C-20, C-9, C-11, and the oxygen atom bonded to C-11 is 29.3°. In this conformation the isobutyryloxy group points toward the A ring and H-11 is close to the Me-20, Me-17, and H-16 pro *S*. The calculated interatomic distances are H-11···Me-20 = 2.73 Å; H-11···Me-17 = 1.89 Å, and H-11···H-16 pro *S* = 2.23 Å, thus accounting for the cross-peaks observed in the NOESY spectrum and in agreement with an 11*S** relative stereochemistry. A similar conformation was proposed, based on difference NOE data, for the side chain of scuterivulactone A.[9] On the basis of the previous discussion scuterulein A (**1**) must be (11*S**)-6α-acetoxy-7β,-11-diisobutiryloxy-1β,8β-dihydroxy-4(18),13-neoclerodadien-15,16-olide.

Compound **2**, named scuterulein B, was assigned the molecular formula $C_{33}H_{40}O_{11}$ by FAB$^+$ HRMS. Its IR spectrum showed absorptions for a γ-spirolactone (1784 cm^{-1}), ester carbonyls (1744 and 1731 cm^{-1}), and an exocyclic double bond (1641 and 919 cm^{-1}). The ^1H and ^{13}C NMR spectra of **2** showed signals for three acetoxyl and one benzoyloxy groups. In agreement with the presence of the benzoyloxy group, the base peak in the EIMS corresponds to *m*/*z* 105. The UV spectrum confirmed this assumption. The ^1H and ^{13}C NMR spectra of **2** indicated a

substitution pattern in the decalin moiety similar to that found for **1**. These spectra were consistent with the existence of a γ-spirolactone function in **2**, instead of the α,β-substituted butenolide ring of **1**. A two-proton broad singlet at δ 2.85 (C-14 methylene protons) and an AB system at δ 4.43 and 4.19 were attributed to the protons of the γ-spiro lactone. This functional group has been frequently found in other neoclerodane derivatives previously isolated from *Scutellaria* species.[5−6,12−14]

Other relevant signals in the ^{1}H NMR spectrum of **2** are those due to the geminal protons of the ester groups at δ 5.59 (2H, m), 5.55 (A part of an AB system, d, J = 10.35), and 5.32 (B part). A broad singlet at δ 2.66 was attributed to H-10. The assignments of the signals ascribed to H-1, H-11, and H-10 were accomplished with the aid of COSY and HMQC spectra since these signals appeared highly distorted. The upfield shift of one of the acetoxyl methyl groups in the ^{1}H NMR spectrum of **2** at δ 1.79 (3H) indicated that the aromatic ring of the benzoyloxy group must be closer in space to one of the acetoxyl groups, modifying its chemical shift. Signals ascribed to H-10 (broad singlet), H-1, and H-11 (overlapped and distorted multiplets) suggested that the A ring of scuterulein B is in a rapid conformational exchange which could be due to the spatial proximity of the ester groups located at the C-1 and C-11 positions, which are closer to each other due to the six-membered 8,13 epoxy ring. Since this phenomenon was not observed in scutegutemalin, a neoclerodane diterpenoid with a γ-spiro lactone system with ester groups at C-1β and C-11β (isobutyroyloxy and acetoxyl respectively),[6] we can deduce that the benzoate group must be attached to either C-1 or C-11, producing steric repulsion due to its volume and therefore the conformational movement of the A ring. Supporting this assumption, the HMBC spectrum indicated that the acetate groups were bonded to C-6 and C-7. Although HMBC data were not conclusive regarding the position of the benzoyloxy group, the location of this ester moiety was possible since in the NOESY spectrum a strong correlation was observed between the signals ascribed to the aromatic *ortho* protons and one of the protons on C-16. This established unambiguously that the benzoate group is attached to C-11. To confirm the rapid exchange of the A ring in product **2**, the ^{1}H NMR spectrum was recorded at low temperature. At −50 °C H-1 was clearly observed at δ 5.64 as a double triplet (J = 10.5 and 5.5 Hz) and H-10 as a doublet at δ 2.61 (J = 5.5 Hz). On the other hand, H-11 was observed as a double doublet at δ 5.55 (J = 13.0 and 4 Hz), partially overlapped with the signal ascribed to H-6. The C-14 methylene protons were observed at this temperature as an AB system at δ 2.99 (d, J = 17.0 Hz) and δ 2.92 (d).

The relative stereochemistry depicted in **2** was established from the NOESY spectrum and confirmed by a single-crystal X-ray diffraction analysis. The molecular structure is illustrated in Figure 1. This analysis confirmed the location and orientation of the ester groups as well as the boat conformation of the A ring.

Compound **3**, scuterulein C, $C_{30}H_{42}O_{11}$ (HRMS) had an IR spectrum similar to **1**. The ^{1}H and ^{13}C NMR spectra of **3** (Table 1) indicated a substitution pattern in the decalin moiety similar to scuterulein A (**1**). The observed differences were consistent with the presence of three acetoxyl groups and only one isobutyryloxy group. A double triplet observed at δ 5.47 in the ^{1}H NMR spectrum of **3** was assigned to H-1. The downfield shift of this signal in regard to the corresponding one in scuterulein A indicated that, in compound **3**, this proton is geminal to an ester group.

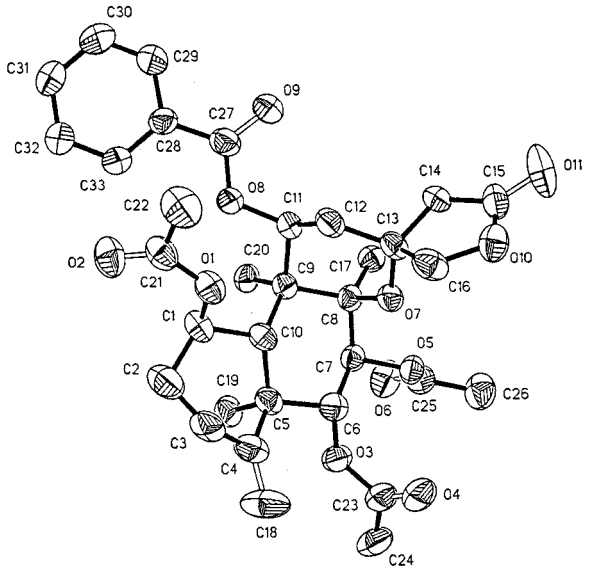

Figure 1. Computer-generated perspective drawing of scuterulein B (**2**).

The HMBC spectrum of **3** showed a cross-peak of correlation between the signals at δ 175.9 (isobutyryloxy carbonyl) and the signal ascribed to H-7 (δ 5.37). This indicated that the isobutyryloxy group is located at C-7, and the remaining acetoxyl substituents are located at the C-1, C-6, and C-11 positions. The relative configuration of **3** was the same as in **1**, as determined by ^{13}C NMR and NOESY data. Thus, scuterulein C (**3**) must be (11*S**)-1β,6α,11-triacetoxy-7β-isobutiryloxy-8β-hydroxy-4(18),13-neoclerodadien-15,16-olide.

The structure proposed for **4**, (11*S**)-6α,11-diacetoxy-7β-isobutiryloxy-1β,8β-dihydroxy-4(18),13-neoclerodadien-15,-16-olide, was deduced from its spectral data. Its ^{1}H and ^{13}C NMR spectra (Table 1) are almost identical to that of **3**. The upfield shift observed for H-1 at δ 4.25 compared to the same signal in **3** (δ 5.47) indicated that **4** is the 1-deacetyl derivative of **3**. Acetylation of **4** with Ac_2O in pyridine afforded a product identical in all respects to **3**.

The HRMS of compound **5**, named scuterulein D, is consistent with the molecular formula $C_{26}H_{36}O_8$. The ^{1}H NMR spectrum of **5** indicated a substitution pattern similar to that of **1**, **3**, and **4**. In the ^{1}H NMR spectrum of **5**, instead of the characteristic signal of H-11 (dd, about δ 5.7) found in the other scuteruleines, the signals of an additional double bond were observed at δ 6.49 (d, J = 16.75 Hz) and 6.27 (d, J = 16.75 Hz). These signals were assigned to the vinylic H-11 and H-12 protons, respectively. The coupling constants indicated an *E* configuration for this double bond. The ^{1}H NMR spectrum of **5** also showed one double triplet at δ 4.13, which was ascribed to the geminal proton of the secondary hydroxyl group attached to C-1. The presence of one acetoxyl and one isobutyryloxy group was also revealed by the ^{1}H NMR spectrum. HMBC data led to the location of these ester groups as depicted in **5**. The relative stereochemistry of scuterulein D was established with the aid of NOESY and ^{13}C NMR spectra.

Although the absolute stereochemistry of compounds **1**−**5** was not ascertained, we can assume that **1**−**5** belong to the same neocleordane series as other diterpenoids isolated from *Scutellaria* spp., whose absolute stereochemistry was firmly established by X-ray diffraction analysis or the CD exciton chirality methods.[6]

From a chemotaxonomic point of view, it is of interest to note that scuteruleines **1**−**5** lack an oxygenated sub-

stituent at C-19 found in almost all of the neoclerodane diterpenoids from European *Scutellaria* species.[17] Compounds **1**−**5** share this feature with scutebaicalin[8] and scuterbarbatine A[18] from the Chinese species *S. baicalensis* and *S. barbata*, with several compounds isolated from *S. rivularis* (also a Chinese plant),[19] and the neoclerodane diterpenoids isolated from the Mexican species[4−6] *S. drummondii, S. seleriana,* and *S. guatemalensis*. The only neoclerodane diterpenoid lacking a C-19 oxygenated substituent isolated from a Mediterranean species until now is scupontin G, from *S. pontica*.[17] The oxidation pattern of the neoclerodane diterpenoids isolated from Mexican Scutellarias in comparison with that found for the compounds from several Chinese representatives of this genus indicates a phytogeographical and an evolutionary relation between some Asiatic and American *Scutellaria* species. This relation has been proposed previously, based on both botanical considerations and the global distribution of the genus.[20] Although botanical similarities between some areas of vegetation in Mexico and Asia (China) are well documented,[21] this is, to the best of our knowledge, the first time that this relationship is chemically supported for the genus *Scutellaria*. The same chemical relationship has been found in some Mexican *Salvia* spp.[22]

Experimental Section

General Experimental Procedures. Melting points were determined on a Mel-Temp II apparatus and are uncorrected. Optical rotations were measured on a Jasco DIP-360 polarimeter. IR spectra ($CHCl_3$) were obtained on a FT-IR Magna 750 spectrophotometer. UV spectra (MeOH) were determined on a Perkin-Elmer 552 apparatus. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions using a Varian Unity Plus 500 apparatus at 500 and 125 MHz, respectively. Chemical shifts (δ values) are reported with respect to residual $CHCl_3$ (δ 7.25) for ^1H and to the solvent signal (δ 77.0) for ^{13}C. ^{13}C NMR assignments were confirmed with the aid of HMQC and HMBC spctra. EIMS were obtained at 70 eV by direct inlet on a JEOL JMS-AX505HA and HRMS on a JEOL JMS-SX102A apparatus using FAB+ technique. Merck Si gel no. 60 (230−400 mesh) was used for vacuum and flash column chromatography.

Plant Material. *Scutellaria caerulea* was collected in the state of Puebla (México) in August 1994, and a voucher specimen (MEXU PT14122) was deposited in the herbarium of the Instituto de Biología UNAM.

Extraction and Isolation. Dried and powdered aerial parts of *S. caerulea* (180 g) were extracted twice with Me_2CO (5 L) for 7 days at room temperature. The solvent of the combined extracts was removed in vacuo at low temperature (38 °C) to yield 4.6 g of a gummy residue, which was subjected to vacuum chromatography over silica gel 230−400 mesh. Mixtures of petroleum ether−Me_2CO of increasing polarity were used as eluents. Some fractions eluted with petroleum ether−Me_2CO (4:1) were combined (261 mg) and subjected to successive purification by flash chromatography (petroleum ether−^{i}PrOH, 9.5:0.5) to yield 44.1 mg of **1**. From other fractions (305 mg) eluted with the same polarity, 34 mg of compound **2** was isolated by crystallization and the mother liquors (212 mg) were rechromatographed using a mixture of CH_2Cl_2−Me_2CO (9.9−0.1) as eluent to yield an additional 7 mg of **2** and 37 mg of compound **3**. Some fractions eluted with petroleum ether−Me_2CO (3:2) of the original chromatography were combined (499 mg) and subjected to purification by flash chromatography. Elution with C_6H_6−EtOAc (9:1) yielded an additional 140 mg of **2** and an additional 61 mg of **3**. Some other fractions eluted with petroleum ether−Me_2CO (3:2) of the original chromatography were combined (183 mg) and subjected to purification by flash chromatography (C_6H_6−EtOAc, 9:1) to yield an additional 10 mg of **2**, 16 mg of **4**, and 10 mg of **5**. Oroxilin A (54 mg) and dihydrooroxilin A (32 mg) were obtained after flash chromatography (C_6H_6−EtOAc, 9.8:0.2) of some fractions eluted with petroleum ether−Me_2CO (4:1) from the original vacuum chromatography separation. Physical properties found for these compounds were identical to that described in the literature.[23]

Scuterulein A (1): colorless crystalline solid; mp 120−122 °C (C_6H_6); $[\alpha]^{25}_D$ −18° (*c* 0.01, MeOH); UV (MeOH) λ_{max} nm (log ϵ) 202 (4.31); IR ($CHCl_3$) ν_{max} 3585, 1783, 1747, 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (1H, m, $W_{1/2}$ = 4 Hz, H-14), 5.76 (1H, dd, *J* = 10.5, 1.5 Hz, H-11), 5.60 (1H, d, *J* = 10.5 Hz, H-6), 5.39 (1H, d, *J* = 10.5 Hz, H-7), 4.83 (1H, dd, *J* = 17.5, 2 Hz, H-16 pro *S*), 4.69 (1H, br d, *J* = 1 Hz, H-18 pro *E*), 4.64 (1H, dd, *J* = 17.5, 2 Hz, H-16 pro *R*), 4.61 (1H, br s, H-18 pro *Z*), 4.26 (1H, dt, *J* = 10, 3.5, H-1), 3.38 (1H, dd, *J* = 15.5, 10.5 Hz, H-12A), 3.18 (1H, br d, *J* = 15.5 Hz, H-12B), 2.60 (1H, sept, *J* = 7 Hz, $(CH_3)_2CH$−), 2.54 (1H, sept, *J* = 7 Hz, $(CH_3)_2CH$−), 2.09 (1H, d, *J* = 10 Hz, H-10), 1.94 (3H, s, CH_3COO−), 1.33 (3H, s, H-19), 1.31 (3H, s, H-17), 1.21 (3H, d, *J* = 7 Hz, $(CH_3)_2$-CH−), 1.18 (3H, d, *J* = 7 Hz, $(CH_3)_2CH$−), 1.15, (3H, d, *J* = 7 Hz, $(CH_3)_2CH$−), 1.13 (3H, d, *J* = 7 Hz, $(CH_3)_2CH$−), 1.0 (3H, s, H-20); ^{13}C NMR ($CDCl_3$), see Table 1; EIMS *m*/*z* (rel int) [M^+] 564 (4.3), 493 (2.7), 476 (5.5), 398 (10), 328 (15), 290 (25), 257 (15), 220 (28.8), 187 (38.9), 159 (15), 105 (22.6), 71 (79.0), 43 (100); FAB+ HRMS *m*/*z* 564.3042 (calcd for $C_{30}H_{44}O_{10}$ 564.3013).

Scuterulein B (2): colorless crystalline solid; mp 130−133 °C (Me_2CO−C_6H_6); $[\alpha]^{25}_D$ −101° (*c* 0.02, MeOH); UV (MeOH) λ_{max} nm (log ϵ) 201 (4.45), 228 (4.23), 272 (3.06); IR ($CHCl_3$) ν_{max} 1784, 1744, 1731, 1641 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.0 (2H, dt, *J* = 8, 1.3 Hz, H-2′,6′), 7.6 (1H, tt, *J* = 7.5, 1.3 Hz, H-4′), 7.47 (2H, dt, *J* = 8, 7.5 Hz, H-3′, H-5′), 5.59 (1H, m, H-11), 5.59 (1H, m, H-1), 5.55 (1H, d, *J* = 10.35, H-6), 5.32 (1H, d, *J* = 10.35 Hz, H-7), 4.77 (1H, d, *J* = 1.3 Hz, H-18 pro *E*), 4.74 (1H, br s, H-18 pro *Z*), 4.43 (1H, d, *J* = 9.4 Hz, H-16A), 4.19 (1H, br d, *J* = 9.4 Hz, H-16B), 2.85 (2H, br s, 2H-14), 2.66 (1H, br s, H-10), 2.10 (3H, s, CH_3COO−), 1.98 (3H, s, CH_3-COO−), 1.79 (3H, s, CH_3COO−), 1.40 (3H, s, H-19), 1.39 (3H, s, H-17), 1.23 (3H, s, H-20); ^{13}C NMR ($CDCl_3$) δ 174.0 (s, C-15), 170.8 (s, $OCOCH_3$), 170.1 (s, $OCOCH_3$), 169.9 (s, $OCOCH_3$), 167.0 (s, C_6H_5COO−), 150.9 (s, C-4), 133.6 (d, C *para*), 130.0 (d, 2C-*ortho*), 129.0 (s, C *ipso*), 128.4 (d, 2C *meta*), 106.5 (t, C-18), 84.0 (s, C-8), 79.2 (t, C-16), 74.6 (d, C-11), 77.8 (s, C-13), 74.1 (d, C-7), 72.5 (d, C-6), 71.7 (d, C-1), 46.4 (d, C-10), 44.7 (s, C-5), 44.1 (s, C-9), 42.8 (t, C-14), 34.8 (t, C-12), 30.0 (t, C-2), 27.0 (t, C-3), 21.4 (q, CH_3COO−), 20.9 (q, CH_3COO−), 20.7 (q, CH_3COO−), 20.0 (q, C-17), 18.7 (q, C-19), 17.9 (q, C-20); EIMS *m*/*z* (rel int) 552 (1.2), 432 (10.6), 310 (15.5), 183 (11.4), 105 (100), 43 (24.5). FAB+ HRMS *m*/*z* 612.2642 (calcd for $C_{33}H_{40}O_{11}$ 612.2649).

Scuterulein C (3): colorless crystalline solid; mp 155−156 °C (Me_2CO−C_6H_6); $[\alpha]^{25}_D$ −3.5° (*c* 0.02, MeOH); UV (MeOH) λ_{max} nm (log ϵ) 205 (4.40), 265 (2.91); IR ($CHCl_3$) ν_{max} 3463, 1781, 1740, 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (1H, m, $W_{1/2}$ = 4 Hz, H-14), 5.68 (1H, dd, *J* = 10.64, 1.57 Hz, H-11), 5.64 (1H, d, *J* = 10.38 Hz, H-6), 5.47 (1H, dt, *J* = 11.1, 4.9 Hz, H-1), 5.37 (1H, d, *J* = 10.38, H-7), 4.88 (1H, dd, *J* = 17.46, 1.82 Hz, H-16 pro *S*), 4.69 (1H, br d, *J* = 1 Hz, H-18 pro *E*), 4.66 (1H, br s, H-18 pro *Z*), 4.65 (1H, dd, *J* = 17.46, 1.81 Hz, H-16 pro *R*), 3.28 (1H, dd, *J* = 15.14, 10.64 Hz, H-12A), 3.11 (1H, br d, *J* = 15.14 Hz, H-12B), 2.59 (1H, sept, *J* = 7 Hz, $(CH_3)_2CH$−), 2.31 (1H, d, *J* = 11.1 Hz, H-10), 2.11 (3H, s, CH_3COO−), 1.98 (3H, s, CH_3COO−), 1.94 (3H, s, CH_3COO−), 1.37 (3H, s, H-19), 1.31 (3H, s, H-17), 1.20 (3H, d, *J* = 7 Hz, $(CH_3)_2CH$−), 1.17 (3H, d, *J* = 7 Hz, $(CH_3)_2CH$−), 0.89 (3H, s H-20); ^{13}C NMR ($CDCl_3$), see Table 1; EIMS *m*/*z* (rel int) [M^+] 578 (1.2), 518 (3.2), 202 (34.0), 184 (60.3), 159 (20.6), 71 (57.5), 43 (100); FAB+ HRMS *m*/*z* 578.2789 (calcd for $C_{30}H_{42}O_{11}$ 578.2805).

Deacetylscuterulein C (4): colorless crystalline solid; mp 180−189 °C (CH_2Cl_2−Me_2CO); $[\alpha]^{25}_D$ −6° (*c* 0.01, MeOH); UV (MeOH) λ_{max} nm (log ϵ) 210 (4.24), 222 (3.83); IR ($CHCl_3$) ν_{max} 3585, 1783, 1747, 1642 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.83 (1H, br s, $W_{1/2}$ = 4 Hz, H-14), 5.73 (1H, dd, *J* = 10.5, 1 Hz, H-11), 5.60 (1H, d, *J* = 10.5 Hz, H-6), 5.38 (1H, d, *J* = 10.5 Hz, H-7), 4.82 (1H, dd, *J* = 17.5, 2 Hz, H-16 pro *S*), 4.68 (1H, br s, H-18 pro *E*), 4.63 (1H, dd, *J* = 17.5, 1.5 Hz, H-16 pro *R*), 4.61 (1H, br s, H-18 pro *Z*), 4.25 (1H, dt, *J* = 10.5, 4 Hz, H-1), 3.35 (1H, dd,

J = 15.5, 10.5 Hz, H-12A), 3.16 (1H, br d, J = 15.5 Hz, H-12B), 2.60 (1H, sept, J = 7 Hz, $(CH_3)_2CH-$), 2.07 (1H, d, J = 10.5 Hz, H-10), 2.07 (3H, s, CH_3COO-), 1.94 (3H, s, CH_3COO-), 1.32 (3H, s, H-19), 1.31 (3H, s, H-17), 1.21 (3H, d, J = 7 Hz, $(CH_3)_2CH-$), 1.18 (3H, d, J = 7 Hz, $(CH_3)_2CH-$), 1.01 (3H, s, H-20); ^{13}C NMR ($CDCl_3$), see Table 1; EIMS m/z (rel int) [M^+] 536 (6.7), 493 (2.9), 476 (6.3), 290 (21.8), 220 (29.3), 187 (40.2), 159 (22.6), 105 (22.2), 71 (57.7), 43 (100); FAB+ HRMS m/z 536.2719 (calcd for $C_{28}H_{40}O_{10}$ 536.2700).

Scuterulein D (5): colorless crystalline solid; mp 162−165 °C (CH_2Cl_2−Me_2CO); UV (MeOH) λ_{max} nm (log ϵ) 271 (4.21); IR ($CHCl_3$) ν_{max} 3595, 1782, 1744, 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.49 (1H, d, J = 16.75 Hz, H-11), 6.27 (1H, d, J = 17.75 Hz, H-12A), 5.85 (1H, br s, $W_{1/2}$ = 3 Hz, H-14), 5.77 (1H, d, J = 10 Hz, H-6), 5.37 (1H, d, J = 10 Hz, H-7), 4.98 (1H, dd, J = 16.75, 1.25 Hz, H-16 pro S), 4.94 (1H, dd, J = 16.75, 1.25 Hz, H-16 pro R), 4.66 (2H, br s, H-18), 4.13 (1H, dt, J = 10.5, 4.5 Hz, H-1), 2.97 (1H, sept, J = 7 Hz, $(CH_3)_2CH-$), 2.20 (1H, d, J = 10.75 Hz, H-10), 1.96 (3H, s, CH_3COO-), 1.33 (2 × 3H, s, H-17, H-19), 1.20 (3H, d, J = 7 Hz, $(CH_3)_2CH-$), 1.17 (3H, d, J = 7 Hz, $(CH_3)_2CH-$), 0.99 (3H, s, H-20); ^{13}C NMR ($CDCl_3$), see Table 1; EIMS m/z (rel int) [M^+] 476 (8.0), 416 (2.1), 398 (22.4), 388 (3.8), 328 (29.5), 205 (30.8), 187 (30.8), 165 (27.9), 159 (31.7), 105 (25.3), 71 (60.8), 43 (100); FAB+ HRMS m/z 476.2400 (calcd for $C_{26}H_{36}O_8$ 476.2410).

Acetylation of 4. Compound **4** (10 mg) in pyridine (0.5 mL) was treated with Ac_2O (0.5 mL) at room temperature for 1 h. After usual workup 8 mg (75% yield) of a solid was obtained, identical in all respects to **3**.

Single-Crystal X-ray Crystallography of Scuteruleine B (2).[24] Suitable colorless crystals of **2** were obtained from a solution in Me_2CO. The crystal (0.52 × 0.24 × 0.10 mm) belongs to the orthorhombic system, space group $P2_12_12_1$ with a = 10.007 (3) Å, b = 18.388 (4) Å, c = 19.449 (7) Å, V = 3578.8 (18) Å^3, Z = 4, D_{calcd} = 1.245 g/cm^3, λ(Cu Kα) = 1.54178 Å. Intensity data were measured at 293(2) K on a Nicolet P3/F diffractometer. θ range of data collection = 1.5−52.58°; 4663 reflections were collected. The structure was solved by direct methods and refined by full matrix least-squares with anisotropic temperature factors for the non-hydrogen atoms. The refinement converged to a final R = 0.0553 for 4078 observed reflections.

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(24) Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre (deposit number CCDC161589). A copy of the data can be obtained, free of charge, on application to the director, CCDC, 12 Union Road, CambridgeCB2 1EZ, UK (fax: + 44-(0)-1223-336003 or e-mail: deposit@ccdc.cam.ac.uk).

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