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SESQUITERPENE LACTONES FROM *MICHELIA FUSCATA*

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Key Word Index—*Michelia fuscata*; *Magnolia fuscata*; Magnoliaceae; sesquiterpene lactones; germacranolides; guaianolide; lignan; desacetyllanuginolide; michefuscalide.

Abstract—Two new sesquiterpene lactones, desacetyllanuginolide and michefuscalide were isolated from *Michelia fuscata* along with two known lactones, dehydrolanuginolide, lipiferolide and a lignan, syringaresinol. The structures of desacetyllanuginolide and michefuscalide were determined by spectral and chemical methods.

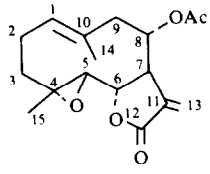
INTRODUCTION

During previous studies, it was shown that *Michelia fuscata* Blume (synonym: *Magnolia fuscata* Andr.) contained several types of alkaloids; biscoclaurines (magnoline and magnolamine), benzylisoquinoline (magnocurarine) and aporphines (liriodenine and magnofloline) [1–6].

As part of our investigation of the sesquiterpene lactones from plants belonging to the Magnoliaceae, we have investigated the neutral components of *M. fuscata*. Four sesquiterpene lactones and a lignan were isolated from this plant. Three of the compounds were already known: dehydrolanuginolide (**1**) [7], lipiferolide (**2**) [8] and syringaresinol (**6**) [9]. The other two substances were new lactones, desacetyllanuginolide (**3**) and michefuscalide (**4**). We now report the isolation and structural elucidation of these new compounds.

RESULTS AND DISCUSSION

The minor neutral constituent (**3**) was obtained as a pale yellow oil. The mass spectrum indicated a molecular ion at *m/z* 266 in agreement with the molecular formula $C_{15}H_{22}O_4$. The IR spectrum showed the presence of a saturated γ-lactone (1765 cm^{-1}). The ^1H NMR spectrum (see Experimental) revealed the presence of CH–Me, O–C–Me and HC=C–Me as well as an epoxy proton coupled with a lactone methine proton. The ^1H NMR spectrum was very similar to those of dehydrolanuginolide (**1**) and lipiferolide (**2**) previously isolated from this plant, and showed similar chemical shifts and the same complexity of the signals for the C-1 proton, and the C-4 and C-10 Me groups. The major differences in the spectrum of **3** compared with the spectra of **1** and **2** were the absence of the C-13 exomethylene protons and an acetoxyl group and the presence of a three proton



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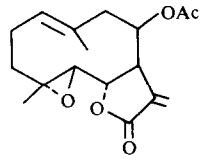

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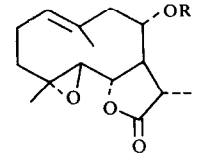

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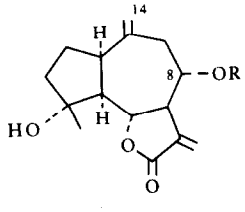
3a R=Ac



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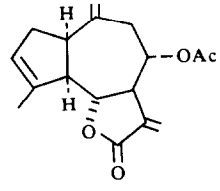
4a R=H



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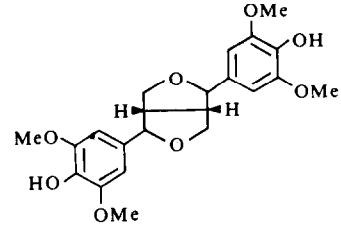

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doublet ($J = 7$ Hz) at δ 1.44. This doublet could be attributed to a C-11 Me group, which was produced by reduction of the 11,13-exomethylene on the γ-lactone ring of **1** and **2**.

Treatment of **3** with Ac_2O and pyridine gave a monoacetate identical to lanuginolide by comparison with its reported physical data (^{1}H NMR and IR spectra) [7]. Furthermore, the spectra of the monoacetate of **3** were completely consistent with those of an authentic sample prepared by the catalytic hydrogenation (Pd–C) of dehydrolanuginolide (**1**). On the other hand, the stereochemistry of lanuginolide at C-1, C-5, C-6, C-7 and C-10 had already been established [6]. Therefore compound **3** must be desacetyllanuginolide.

The second sesquiterpene lactone, michefuscalide (**4**) was obtained as a viscous oil. From the mass spectrum, the MW of this compound was found to be 306 daltons in agreement with a molecular formula of $C_{17}H_{22}O_5$. The ^{1}H NMR spectrum revealed the presence of exomethylene protons as doublets (J = 3 Hz) at δ 5.75 and 6.27 which are characteristic of an α,β-unsaturated-γ-lactone. Two signals attributable to methyl groups were observed. A singlet at 1.36 could be assigned to a Me group attached to a carbon bearing a hydroxyl group. A sharp singlet was observed at 2.16 and assigned to an acetoxyl Me group. Double doublets at 4.08 (J = 10, 11 Hz) and double singlets at 5.11 and 5.17 were assigned to a methine proton (C-6) and exomethylene protons (C-14), respectively. From the above data and the ^{13}C NMR spectrum, it was concluded that michefuscalide must be a guaian sesquiterpene lactone having an exomethylene group on the seven-membered ring, an acetoxyl and a methyl tertiary hydroxyl group.

Hydrolysis of **4** with 2% aqueous KOH in dioxane gave the corresponding diol (**4a**). As a result, in its ^{1}H NMR spectrum, one C-13 proton signal shifted to a lower field (below 6 ppm) because of a paramagnetic effect, showing the presence of a α-hydroxyl group at C-8 in a 6,7-lactonized compound (**4a**) [10]. Therefore, an acetoxyl group of michefuscalide is α-orientated. The relative stereochemistry of C-5, C-6 and C-7 was deduced from the coupling constant (J = 10, 11 Hz) of these protons with the adjacent protons, which is characteristic of a guaianolide having 5α-, 6β- and 7α-protons.

The presence of a tertiary methyl group at C-4 was established by conversion of (**4**) to dehydrocumanbrin A (**5**).* The configuration of the hydroxyl group at C-4 was determined by partial synthesis of michefuscalide (**4**) from dehydrolanuginolide (**1**), the absolute stereochemistry of which has been clarified [6]. Treatment of **1** with BF_3–Et_2O in ether at room temp. gave a product resulting from transannular cyclization, and after purification by prep. TLC the product was shown to be identical with michefuscalide (**4**) by comparison of their ^{1}H NMR and IR spectra. The hydroxyl group at C-4 in michefuscalide therefore had the α-configuration, and the stereostructure of michefuscalide is confirmed to be **4**.

*Cumanbrin A was isolated from *Chrysanthemum ornatum* Hemsl. var. *spontaneum* Kitam. in our laboratory. This compound was converted to dehydrocumanbrin A by treatment with thionyl chloride and pyridine.

In addition to the two new sesquiterpene lactones discussed above, two known lactones and a lignan were isolated. The former compounds were identified as dehydrolanuginolide (**1**) and lipiferolide (**2**), and the latter was syringaresinol (**6**).

EXPERIMENTAL

Mps are uncorr. ^{1}H NMR (100 MHz) and ^{13}C NMR (25 MHz) spectra were determined in $CDCl_3$. Spots were detected after TLC in UV light (254 nm) and by spraying with 10% H_2SO_4 and then heating at 100°.

Extraction and separation of compounds. The MeOH extract of fresh leaves (4 kg) of *Michelia fuscata* Blume collected in May 1980 at the Botanical Garden of the Faculty of Sciences, Kyoto University, Kyoto was divided into the *n*-hexane- and the $CHCl_3$-soluble fractions (10 g). The residue was chromatographed over a column of Si gel (200 g) using C_6H_6 with gradually increasing proportions of EtOAc as eluent.

The first fraction (C_6H_6–EtOAc, 20:1) gave dehydrolanuginolide (**1**, 1.2 g) and lipiferolide (**2**, 0.8 g). The second fraction (C_6H_6–EtOAc, 1:1) gave michefuscalide (**4**, 55 mg). The third fraction (EtOAc) gave desacetyllanuginolide (**3**, 15 mg) and syringaresinol (**6**, 30 mg).

Desacetyllanuginolide (**3**). Yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1765, 1740. MS *m/z*: 266 (M^+, $C_{15}H_{22}O_4$), 248, 239, 208, 205. ^{1}H NMR: δ 1.28 (3H, *s*, 15-H), 1.44 (3H, *d*, J = 7 Hz, H-13), 1.76 (3H, *s*, H-14), 2.64 (1H, *d*, J = 8 Hz, H-5), 3.80 (1H, *m*, H-8), 3.88 (1H, *t*, J = 8 Hz, H-6), 5.20 (1H, *m*, H-1).

Monoacetate of **3**. Oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770, 1740. $[\alpha]_D$ − 37.7° (*c* 0.18, $CHCl_3$). MS *m/z*: 308 (M^+, $C_{17}H_{24}O_5$), 266, 248, 220, 205, 191, 190. ^{1}H NMR: δ 1.30 (3H, *s*, H-15), 1.45 (3H, *d*, J = 7 Hz, H-13), 1.82 (3H, *s*, H-14), 2.10 (3H, *s*, OCOMe), 2.62 (1H, *d*, J = 8 Hz, H-5), 3.94 (1H, *t*, J = 8 Hz, H-6), 4.90 (1H, *m*, H-8), 5.20 (1H, *m*, H-1).

Hydrogenation of **1** *to lanuginolide* (**3a**). A soln of **1** (10 mg) in EtOH (6 ml) was hydrogenated at room temp. for 1 hr using 10% Pd–C (3 mg) as a catalyst. The reaction mixture was filtered and evaporated to afford lanuginolide (10 mg), which was identical with the monoacetate of **3** by comparison of their physical data (IR and ^{1}H NMR spectra) and TLC behavior.

Michefuscalide (**4**). Colourless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1770, 1740, 1660, 1640. MS *m/z*: 306 (M^+, $C_{17}H_{22}O_5$), 291, 249, 246, 229, 228. CD curve $[\theta]_{254}$ − 1399. ^{1}H NMR: δ 1.36 (3H, *s*, H-15), 2.16 (3H, *s*, OCOMe), 2.39 (1H, *t*, J = 11 Hz, H-5), 4.08 (1H, *dd*, J = 10, 11 Hz, H-6), 4.86 (1H, *m*, H-8), 5.11, 5.17, (2H, each *s*, H-14), 5.75 (1H, *d*, J = 3 Hz, H-13), 6.27 (1H, *d*, J = 3 Hz, H-13). ^{13}C NMR: δ 44.0 (*d*, C-1), 26.1 (*t*, C-2), 44.8 (*t*, C-3), 79.9 (*s*, C-4), 55.4 (*d*, C-5), 78.7 (*d*, C-6), 49.2 (*d*, C-7), 74.3 (*d*, C-8), 39.8 (*t*, C-9), 141.1 (*s*, C-10), 135.5 (*s*, C-11), 168.5 (*s*, C-12), 123.7 (*t*, C-13), 115.7 (*t*, C-14), 23.9 (*q*, C-15), 21.0 (*q*, $\underline{C}H_3COO$) 169.3 (*s*, $CH_3\underline{C}OO$).

Hydrolysis of **4**. To a soln of **4** (10 mg) in dioxane (2 ml) was added 2% KOH (2 ml) and the soln was allowed to stand overnight. This soln was acidified and extracted with EtOAc. The extract was evaporated and the residue passed through a column of Si gel (1 g, $CHCl_3$–Me_2CO, 40:1) to give an oil (**4a**, 1 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1765. ^{1}H NMR: δ 5.02 (2H, *br s*, 14-H), 6.24, 6.26 (2H, each *d*, J = 3 Hz, 13-H), 3.80 (1H, *m*, 8-H).

Dehydration of **4**. Compound **4** (3 mg) was dissolved in pyridine (1 ml), and mesyl chloride (1 drop) was added. The resulting soln was left overnight at room temp. The reactant was treated in the usual manner. Colourless oil (**5**, 1 mg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1730, 1640. MS *m/z*: 288 (M^+, $C_{17}H_{20}O_4$).

^{1}H NMR: δ 1.85 (3H, *s*, H-15), 2.12 (3H, *s*, OCOMe), 4.04 (1H, *dd*, $J = 9$, 11 Hz, 6-H), 4.88, 5.02 (2H, each *s*, H-14), 4.92 (1H, *m*, H-8), 5.48 (1H, *br s*, H-3), 5.58 (1H, *d*, $J = 3$ Hz, H-13), 6.18 (1H, *d*, $J = 3$ Hz, H-13). These physical data were identical with those of dehydrocumanbrin A.

Transannular cyclization of **1**. To a soln of **1** (50 mg) in dry Et_2O (10 ml), BF_3–Et_2O (2 ml) was gradually added at 0° and the soln was left at room temp. for 3 hr. The Et_2O layer was washed successively with H_2O, satd $NaHCO_3$ and NaCl soln, dried and evaporated to afford a gummy residue. The latter was purified by prep. TLC ($CHCl_3$–Me_2CO, 10:1) to give michefuscalide (4 mg). This compound was identical to an authentic sample.

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