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Eremofarfugin A and eremopetasitenin B_3, two new eremophilanolides from *Farfugium japonicum*

Motoo Tori,* Yasuko Shiotani, Masami Tanaka, Katsuyuki Nakashima and Masakazu Sono

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro cho, Tokushima 770-8514, Japan

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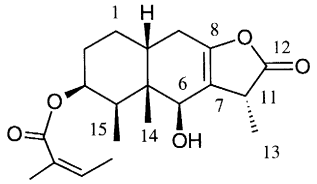
Abstract

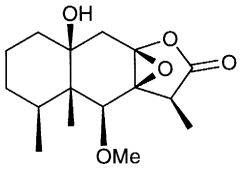
Two new eremophilanolides, eremofarfugin A and eremopetasitenin B_3, have been isolated from the methanol extract of fresh rhizomes of *Farfugium japonicum* (Compositae) and their structures have been determined on the basis of high resolution 2D NMR analysis.

Keywords: epoxide; terpenes and terpenoids; plants; lactones.

Eremophilanes[1] are widely distributed in Compositae, especially in *Ligularia*,[2] *Petasites*,[3] *Farfugium*,[4] and *Senecio*[5] tribes. Among eremophilanolides isolated so far, epoxyeremophilanes are very rare in nature, although there are precedents.[6] We previously isolated four epoxyeremophilanes from the fresh rhizomes of *Petasites japonicum* and reported their structures.[7] We have found two new lactones having an enol lactone and an epoxide at the C-7 and 8 positions from the fresh rhizomes of close species *Farfugium japonicum* and determined their structures. Now we report the preliminary results on the structures of these new compounds.



eremofarfugin A (**1**)



eremopetasitenin B_3 (**2**)

The EtOAc soluble part (52 g) of the MeOH extract (279 g) from the fresh rhizomes of *F. japonicum* (8.05 kg) collected in Tokushima Prefecture was separated by silica gel column chromatography, followed by Sephadex LH-20 ($CHCl_3$–MeOH, 1:1) and HPLC (Nucleosil 50-5, hexane–EtOAc) to isolate eremofarfugin A (**1**) (5.6 mg)[8] and eremopetasitenin B_3 (**2**) (30.1 mg).[9] Eremofarfugin A (**1**), $C_{20}H_{28}O_5$, obviously had an angeloyl moiety from the ^1H NMR spectrum.[8] Some peaks in the ^{13}C NMR spectrum

* Corresponding author. Tel: +81-88-622-9611; fax: +81-88-655-3051; e-mail: tori@ph.bunri-u.ac.jp (M. Tori)

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in $CDCl_3$ at rt are very broad presumably due to slow molecular movement. Therefore, measurement of 2D NMR spectra was carried out both in $CDCl_3$ at rt and in C_6D_6 at 50°C. The presence of the double bond between the C-7 and C-8 was inferred by the HMBC spectrum as shown in Fig. 1. The connectivity between H-3 and C-1′ was revealed by the HMBC spectrum in C_6D_6 at 50°C. The stereochemistry was established by the NOESY spectrum (Fig. 2). The A/B *cis* arrangement was determined by the NOE between H-14 and H-10. The angeloyl moiety was β-oriented, because H-3 had an NOE into H-6, which also indicated the configuration at C-6. Therefore, this molecule adopts non-steroid conformation and H-3 should be axial [δ 5.28 (dt, J=12.1, 4.3)]. Because the NOE between H-6 and H-13 was observed, the methyl group at the C-11 must be α-oriented. Thus, the total structure was established as depicted in the formula **1**. Enol lactones are very rare in nature and this probably is the intermediate of the biosynthesis of eremophilanes, although the real route is not obvious yet.

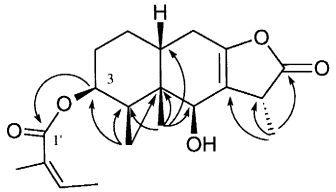

Fig. 1. Selected long-range correlations for **1**

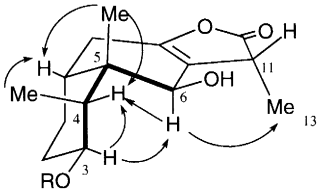

Fig. 2. Selected NOEs for **1** (R=Ang)

Eremopetasitenin B_3 (**2**)[9] exhibited the quasi molecular ion peak at *m/z* 297 $(M+H)^+$ and the molecular formula was determined by the HRMS as $C_{16}H_{24}O_5$. The IR spectrum showed the presence of a hydroxyl group (3550 cm^{-1}) and a lactone (1820 cm^{-1}). The doublet peaks at δ 1.48 are relatively low compared to ordinary methyl groups, suggesting the presence of electronegative substituents. There was only one sp^2 carbon at δ 175.4, which should be assigned for a lactone carbonyl group. Therefore, this compound must have four rings in the molecule, indicating the presence of an epoxide ring. The two singlets at δ_C 61.5 and 86.0 seem to be due to an epoxide, one of which must have two oxygen atoms judging from its chemical shift (δ_C 86.0). The HMBC spectrum showed the correlations between H-13 and C-12, C-11, and C-7; H-6 and C-7, C-8, C-5, C-10, and C-11; H-14 and C-4, C-5, C-6, and C-10; H-15 and C-3, C-4, and C-5 (Fig. 3). The planar structure for compound **2** was determined by this evidence. The NOESY spectrum (Fig. 4) indicated the stereochemistry. If the epoxide ring is α-oriented, the observed NOEs are not reasonably explained. Therefore, the structure was established as depicted in the formula **2**. The importance of this type of molecule in biosynthesis is described in Ref. 7.

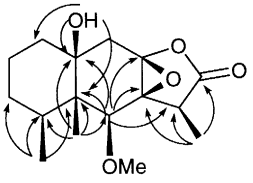

Fig. 3. Selected long-range correlations for **2**

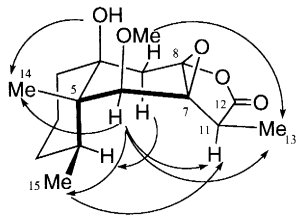

Fig. 4. Selected NOEs for **2**

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8. $[\alpha]_D^{22}$ −16.2 (c 0.65, $CHCl_3$); IR 3450, 1800, 1700, 1650 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.96 (3H, s, H-14), 0.99 (3H, d, *J*=7.1, H-15), 1.40 (3H, d, *J*=7.7, H-13), 1.43 (1H, qd, *J*=12.6, 4.3, H-1α), 1.56 (1H, m, H-1β), 1.71 (1H, qd, *J*=12.6, 4.3, H-2β), 1.83 (1H, dq, *J*=12.6, 4.3, H-2α), 1.90 (3H, quint., *J*=1.4, H-5′), 1.94 (1H, br d, *J*=15.4, H-9α), 2.00 (3H, dq, *J*=7.1, 1.4, H-4′), 2.03 (1H, m, H-10β), 2.34 (1H, m, H-4α), 2.61 (1H, br d, *J*=15.4, H-9β), 3.36 (1H, qd, *J*=6.0, 1.3, H-11β), 4.71 (1H, br s, H-6α), 5.28 (1H, dt, *J*=12.1, 4.3, H-3α), 6.09 (1H, qq, *J*=7.1, 1.4, H-3′); ^{13}C NMR (150 MHz, $CDCl_3$) δ 7.8 (C-15), 14.4 (C-13), 15.8 (C-4′), 19.1 (C-14), 20.6 (C-5′), 25.7 (C-9), 25.8 (C-2), 27.4 (C-1), 35.2 (C-10), 35.9 (C-4), 39.2 (C-11), 42.0 (C-5), 65.7 (C-6), 71.6 (C-3), 116.1 (C-7), 127.9 (C-2′), 138.3 (C-3′), 147.6 (C-8), 167.6 (C-1′), 180.0 (C-12); ^{13}C NMR (100 MHz, C_6D_6, 50°C) δ 8.1 (C-15), 14.3 (C-13), 15.8 (C-4′), 19.0 (C-14), 20.7 (C-5′), 25.8 (C-9), 26.1 (C-2), 27.2 (C-1), 35.2 (C-10), 36.1 (C-4), 39.2 (C-11), 42.1 (C-5), 65.5 (C-6), 71.9 (C-3), 116.2 (C-7), 128.0 (C-2′), 138.0 (C-3′), 147.7 (C-8), 167.1 (C-1′), 178.9 (C-12); MS *m/z* 377 $(M+CH_5)^+$, 349 $(M+H)^+$, 331, 303, 249, 231 (base), 203, 109, 83; HRMS *m/z* 349.1989 $(M+CH_5)^+$. $C_{20}H_{29}O_5$ requires 349.2016.
9. $[\alpha]_D^{22}$ −15.8 (c 1.2 $CHCl_3$); IR 3550, 1820 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.85 (3H, d, *J*=6.6, H-15), 1.04 (3H, s, H-14), 1.28 (1H, m, H-4α), 1.38 (1H, m, H-1α), 1.41 (1H, m, H-3β), 1.44 (1H, m, H-3α), 1.48 (3H, d, *J*=7.4, H-13), 1.49 (1H, m, H-2α), 1.66 (1H, m, H-1β), 1.69 (1H, m, H-2β), 2.40 (1H, d, *J*=15.7, H-9β), 2.72 (1H, q, *J*=7.4, H-11α), 2.76 (1H, d, *J*=15.7, H-9α), 3.42 (3H, s, -OMe), 3.71 (1H, s, H-6α), 3.77 (1H, s, -OH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.6 (C-14), 10.8 (C-13), 16.2 (C-15), 21.6 (C-2), 28.7 (C-3), 31.4 (C-9), 32.1 (C-4), 32.8 (C-1), 42.7 (C-11), 45.0 (C-5), 58.9 (OMe), 61.5 (C-7), 72.8 (C-10), 79.1 (C-6), 86.0 (C-8), 175.4 (C-12); MS *m/z* 297 $(M+H)^+$, 279, 264, 247 (base), 236, 191, 169, 157, 125, 97, 83; HRMS *m/z* 297.1687 $(M+H)^+$. $C_{16}H_{25}O_5$ requires 297.1702.