Pergamon

Tetrahedron Letters, Vol. 38, No. 11, pp. 1965-1968, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00235-9

Novel Epoxyeremophilanolides, Eremopetasitenins A1, A2, B1, and B2, from *Petasites japonicus*

Motoo Tori,* Makiko Kawahara, and Masakazu Sono

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

Abstracts: Eremopetasitenins A1, A2, B1, and B2 have been isolated from the fresh rhizomes of *Petasites japonicus* and their structures determined by spectroscopic methods to have eremophilane skeletons with epoxylactones.

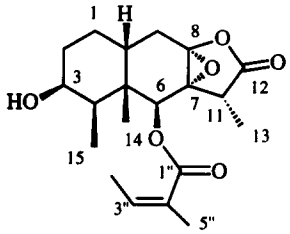
Eremophilane-type sesquiterpenoids have been found in Compositae,[1] especially *Petasites japonicus*[2], *Ligularia*,[3] or *Senecio*[4] species and its related plants studied by Naya, Takahashi, or Bohlmann, respectively. *P. japonicus* (Sieb. et Zucc.) Maxim. is a common plant in the mountain area in Japan and quite recently Yaoita and Kikuchi reported a number of compounds from its dried rhizome,[5] which prompted us to report our preliminary results on the isolation and structure determination of novel sesquiterpenoids from the methanol extracts of its fresh rhizomes.

The MeOH extracts (66 g from 860 g of dried rhizomes) were partitioned between EtOAc and water. The EtOAc soluble fraction (16 g) was separated by silica-gel and Sephadex LH-20 chromatography as well as normal- and reversed-phase HPLC, repeatedly, to isolate eremopetasitenins A1 (14.1 mg), A2 (11.7 mg), B1 (4.0 mg), and B2 (4.1 mg) (**1** - **4**).

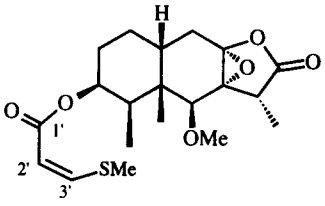
The molecular formula of eremopetasitenin A1 (**1**),[6] $C_{30}H_{28}O_6$, $[\alpha]_D$ -23.2°, was determined by HRMS. The presence of a hydroxyl group was indicated by the IR (3400 cm^{-1}) spectrum and the ^{13}C NMR spectrum showed the presence of two carbonyl groups (δ_C 175.9 and 166.5) and one double bond (δ_C 141.8 and 126.4) as well as four carbons attached to oxygen functions (Table 1). There were two *sec*-methyl (δ_H 0.95 and 1.29), one *tert*-methyl (δ_H 1.03), and two olefinic methyl (δ_H 1.99 and 2.11) groups, one of which resonated as doublet in the lower field (δ_H 2.11) and coupled with the proton at δ_H 6.30 (q). These observation and the HMBC spectrum (Fig. 1) suggested an eremophilane skeleton for this compound. The presence of the epoxide ring was inferred by the chemical shifts (δ_C 65.4 and 86.9)[7,8] and seven degrees of unsaturation. The stereochemistry was determined by the NOESY correlations as shown in Fig.2. The angerate moiety was also shown by the NOE between H-3" and H-5". The position of this ester moiety was determined by the correlation of H-6α and C-1" in the HMBC spectrum. The structure of Eremopetasitenin A1 was established as depicted in the formula **1**.

This compound is probably identical with the one isolated by Bohlmann in 1979.[9] Although the ^1H NMR, IR, and MS data were reported, the stereochemistry was not determined.

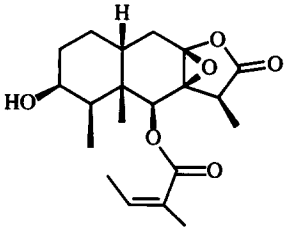
The ^1H NMR of eremopetasitenin A2 (**2**),[10] $C_{20}H_{28}O_6S$ (HRMS), $[\alpha]_D$ -27.8°, indicated the presence of SMe (δ_H 2.40 and δ_C 19.2) and OMe (δ_H 3.74 and δ_C 62.5) groups and other signals were similar to those of **1**.



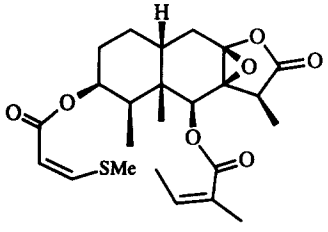
eremopetasitenin A1 (**1**)



eremopetasitenin A2 (**2**)



eremopetasitenin B1 (**3**)



eremopetasitenin B2 (**4**)

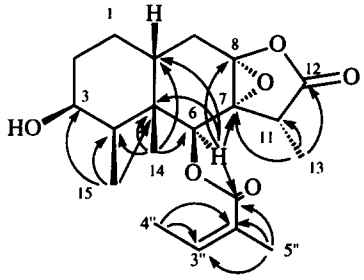


Fig.1. HMBC correlations found for **1**.

Table 1. ^{13}C NMR data for **1-4**.

C	1	2	3	4
1	27.5	27.3	28.2	29.0
2	29.3	26.2	28.6	25.4
3	68.0	71.2	68.3	71.3
4	39.0	35.5	39.7	36.6
5	41.3	42.4	41.0	41.0
6	67.0	76.6	68.2	68.0
7	65.4	67.0	63.6	63.7
8	86.9	86.9	87.8	87.6
9	25.0	25.0	26.7	26.7
10	33.9	33.4	35.7	35.5
11	40.7	40.3	43.0	43.0
12	175.9	176.7	175.8	176.0
13	10.9	11.5	11.2	11.2
14	20.4	19.3	19.6	19.3
15	6.8	7.7	6.4	8.1
1'	-	165.9	-	165.5
2'	-	113.3	-	113.2
3'	-	151.7	-	151.7
1"	166.5	-	167.7	167.2
2"	126.4	-	126.8	127.0
3"	141.8	-	140.8	140.1
4"	16.1	-	16.0	15.9
5"	20.6	-	20.6	20.5
OMe	-	62.5	-	-
SMe	-	19.2	-	19.3

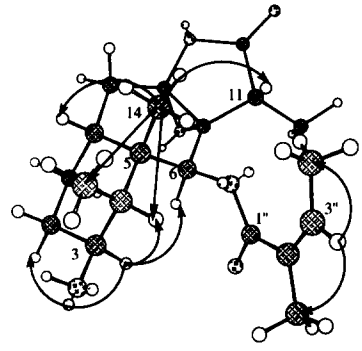


Fig.2. NOESY correlations detected for **1**.

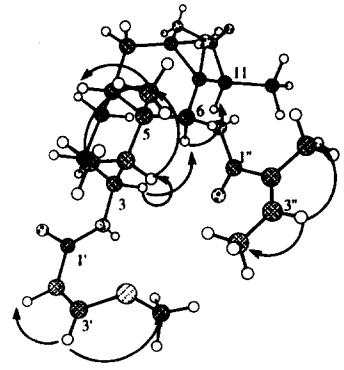


Fig.3. NOESY correlations detected for **4**.

The HMBC spectrum of this compound also indicated an eremophilane skeleton with the SMe group attached to acrylate side chain, connecting to C-3, and with the OMe group substituted at C-6. The presence of the epoxide ring was suggested by the chemical shifts (δ_C 67.0 and 86.9)[7,8] and seven degrees of unsaturation. The stereochemistry was suggested by the similar arguments on the NOESY spectrum. Thus the structure of eremopetasitenin A2 was determined as depicted in the formula **2**.

The third compound, eremopetasitenin B1 (**3**),[11] $C_{20}H_{28}O_6$ (HRMS), $[\alpha]_D$ -55.6°, showed very similar ^1H NMR spectrum to that of eremopetasitenin A1 (**1**). The presence of a hydroxyl group (3400 cm^{-1}), a lactone (1800 cm^{-1}), and angerate moiety (1690 cm^{-1}) was indicated by the IR spectrum. The HMQC and HMBC spectra also indicted an eremophilane skeleton having an epoxide ring at C-7 and C-8 positions (δ_C 63.6 and 87.8)[7,8] (see Table 1) for this compound. However, the proton at δ 5.76 assigned to H-6α of eremopetasitenin A1 (**1**) shifted to 5.09 in the case of eremopetasitenin B1 (**3**), suggesting that **3** was the isomer of **1** concerning the lactone part. The NOESY spectrum clearly showed the following correlations; between H-6α and 3α, H-6α and H-4α, H-6α and H-11α, H-14 and H-15, H-14 and H-10β, and H-3" and H-5". From these evidence the structure of eremopetasitenin B1 was established as displayed in the formula **3**.

Eremopetasitenin B2 (**4**),[12] $C_{24}H_{32}O_7S$ (HRMS), $[\alpha]_D$ -66.9°, had Z-3'-methylthiopropenoyl moiety at the 3-position and angerate ester at the 6-position of the eremophilane skeleton, revealed by the 2D NMR spectra. This compound also had an epoxide ring at C-7 and C-8 positions, suggested by the chemical shifts (δ_C 63.7 and 87.6)[7,8] and nine degrees of unsaturation. The stereochemistry was inferred by the NOESY spectrum. NOE's between H-6α and H-11α, H-6α and H-3α, H-14 and H-10β, H-14 and H-15, H-14 and H-4α, H-2' and H-3', and H-3" and H-5" clearly suggested that this compound had A/B cis juncture, an epoxide ring orienting β direction, and the geometry of two ester side chains as shown in Fig. 3. Therefore structure of eremopetasitenin B2 was established as depicted in the formula **4**.

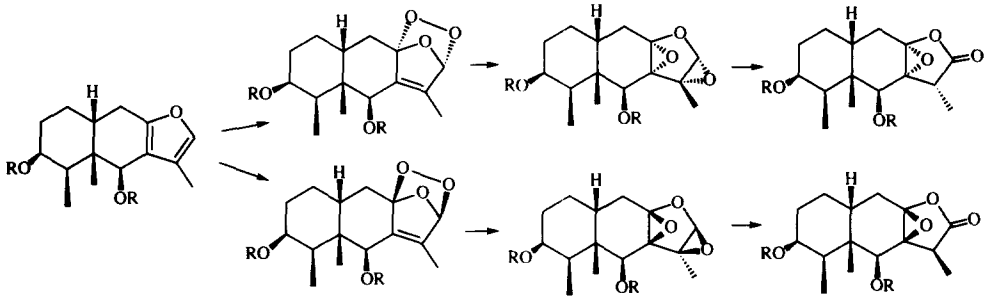


Fig. 4. Possible biosynthetic pathway to eremopetasitenins.

It is very important to note that the biosynthesis of these compounds presumably derived from oxidation of such as furans followed by rearrangement into diepoxides and epoxylactones (Fig. 4), as discussed in the case of fusicoccane diterpenoids.[13] Although this is the third case to isolate epoxy lactones having eremophilane skeleton, namely Bohlmann first isolated the compound very similar to eremopetasitenin A1[9] and later the diepoxide from *Senecio* species,[14] it is not very often that such compounds are found in the nature.

References and Notes

1. Novotny, L.; Jizba, J.; Herout, V.; Sorm, F. *Coll. Czech. Chem. Commun.*, **1962**, *27*, 1393-1399 and references cited therein.
2. Naya, K.; Okayama, T.; Fujiwara, M.; Nakata, M.; Ohtsuka, T.; Kurio, S. *Bull. Chem. Soc. Jpn.*, **1990**, *63*, 2239-2245 and references cited therein.
3. Tanahashi, Y.; Ishizaki, Y.; Takahashi, T.; Tori, K. *Tetrahedron Letters*, **1968**, 3739-3742 and references cited therein.
4. Bohlmann, F.; Knoll, K. H.; Zdero, C.; Mahanta, P. K.; Grenz, M.; Suwita, A.; Ehlers, D.; Le Van, N.; Abraham, W. R.; Natu, A. A. *Phytochemistry*, **1977**, *16*, 965-985 and references cited therein.
5. Yaoita, Y.; Kikuchi, M. *Chem. Pharm. Bull.*, **1996**, *44*, 1731-1735 and references cited therein.
6. **1**: HRCIMS obs. *m/z* 365.1955. $C_{20}H_{29}O_6$ requires 365.1964; CIMS *m/z* 365 $(M+1)^+$, 347, 283, 265, 247, 237, 219, 191, 165, 121, 101, 83 (base), 55; δ_H (400 MHz; $CDCl_3$) 6.30 (1H, q, 7.3, H-3''), 5.76 (1H, s, H-6α), 4.19 (1H, dt, 12.0, 4.5, H-3α), 2.98 (1H, q, 7.3, H-11β), 2.48 (1H, dd, 15.2, 7.5, H-9β), 2.24 (1H, d, 15.2, H-9α), 2.11 (3H, dq, 7.3, 1.5, H-4''), 1.99 (3H, s, H-5''), 1.94 (1H, m, H-10β), 1.84 (1H, H-1a), 1.81 (1H, m, H-4α), 1.76 (1H, m, H-2a), 1.53 (1H, m, H-2b), 1.49 (1H, m, H-1b), 1.29 (3H, d, 7.3, H-13), 1.03 (3H, s, H-14), 0.95 (3H, d, 7.1, H-15); ν 3400, 1807, 1720 cm^{-1}.
7. Iguchi, K.; Mori. K.; Matsushima, M.; Yamada, Y. *Chem. Pharm. Bull.*, **1987**, *35*, 3531-3533.
8. Wiemer, D. F.; Wolfe, L. K.; Fenical, W.; Strobel, S. A.; Clardy, J. *Tetrahedron Letters*, **1990**, *31*, 1973-1976.
9. Bohlmann, F.; Zdero, C.; Berger, D.; Suwita, A.; Mahanta, P.; Jefferey, C. *Phytochemistry*, **1979**, *18*, 79-93.
10. **2**: HRCIMS obs. *m/z* 397.1668. $C_{20}H_{29}O_6S$ requires 397.1685; CIMS *m/z* 397 $(M+1)^+$, 379, 331, 307, 279 (base), 261, 247, 229, 155, 123, 101; δ_H (600 MHz; $CDCl_3$) 7.05 (1H, d, 10.3, H-3'), 5.83 (1H, d, 10.3, H-2'), 5.20 (1H, dt, 12.0, 4.8, H-3α), 3.87 (1H, s, H-6α), 3.74 (3H, s, 6-OMe), 3.09 (1H, q, 7.3, H-11β), 2.40 (3H, s, SMe), 2.4-2.3 (2H, m, H-4α, H-9β), 2.10 (1H, d, 15.1 , H-9α), 1.85 (1H, m, H-10β), 1.88-1.60 (3H, m, H-1β, H-2), 1.44 (3H, d, 7.3, H-13), 1.44 (1H, m, H-1α), 0.91 (3H, d, 7.2, H-15), 0.83 (3H, s, H-14); ν 1800, 1690 cm^{-1}.
11. **3**: HRCIMS obs. *m/z* 365.1971. $C_{20}H_{29}O_6$ requires 365.1964; CIMS *m/z* 365 $(M+1)^+$, 265, 247, 237, 209, 191, 149, 123, 101, 83 (base); δ_H (600 MHz; $CDCl_3$) 6.23 (1H, qq, 7.3, 1.5, H-3''), 5.09 (1H, br s, H-6α), 4.25 (1H, dt, 11.8, 4.2, H-3), 2.95 (1H, q, 7.1, H-11), 2.61 (1H, dd, 15.4, 6.0, H-9β), 2.05 (3H, dq, 7.4, 1.5, H-4''), 2.02 (1H, br s, H-9α), 1.95 (3H, dq, 1.5, 1.5, H-5''), 1.88 (1H, m, H-10β), 1.78 (1H, m, H-2α), 1.73 (1H, qd, 7.4, 4.2, H4α), 1.56 (2H, m, H-1β, 2β), 1.35 (1H, td, 13.2, 4.1, H-1α), 1.25 (3H, d, 7.1, H-13), 1.09 (3H, s, H-14), 0.90 (3H, d, 7.4, H-15); ν 3400, 1800, 1690 cm^{-1}.
12. **4**: HRCIMS obs. *m/z* 465.1953. $C_{24}H_{33}O_7S$ requires 465.1947; CIMS *m/z* 465 $(M+1)^+$, 447, 419, 391, 365, 347, 309, 265, 247 (base), 231, 219, 203, 191; δ_H (600 MHz; $CDCl_3$) 7.02 (1H, d, 10.2, H-3'), 6.18 (1H, q, 7.2, H-3''), 5.94 (1H, br s, H-6α), 5.79 (1H, d, 10.2, H-2'), 5.26 (1H, dt, 16.2, 5.6, H-3α), 3.01 (1H, q, 7.2, H-11α), 2.60 (1H, dd, 15.6, 6.0, H-9β), 2.38 (3H, s, SMe), 2.06 (3H, d, 7.2, H-4''), 2.02 (1H, m, H-9α), 1.94 (3H, t, 1.8, H-5''), 1.93-1.87 (3H, m, H-2, H-4, H-10β), 1.65 (1H, m, H-2β), 1.40 (2H, m, H-1), 1.26 (3H, d, 7.2, H-13), 1.10 (3H, s, H-14), 0.92 (3H, d, 6.6, H-15); ν 1820, 1725, 1705 cm^{-1}.
13. Tori, M.; Nakashima, K.; Takaoka, S.; Asakawa, Y. *Chem. Pharm. Bull.*, **1994**, *42*, 2650-2653.
14. Ahmad, M.; Jakupovic, J.; Bohlmann, F.; Niemeyer, H. M. *Phytochemistry*, **1991**, *30*, 2407-2409.

(*Received in Japan* 6 *January* 1997; *revised* 27 *January* 1997; *accepted* 30 *January* 1997)