Esulatin G, a Novel Nor-diterpenoid from *Euphorbia esula*

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From aerial parts of *Euphorbia esula* esulatin G (**1**), a novel norparaliane diterpenoid, together with its biosynthetic precursor 5,8,14-triacetoxy-3-benzoyloxy-15-hydroxy-9-oxoparaliane (**2**) was isolated. Their structures were determined by extensive spectroscopic analysis (IR, MS, NMR, and X-ray diffraction).

Euphorbia esula L. is a perennial herb, distributed widely in China and used as folk medicine for treatment of cancer, swelling, and warts.[1] Previous chemical investigations revealed that this plant contains rich diterpenoids with injenane-type and jatrophane-type structures.[2,3] Some ingenane and jatrophane diterpenoids have been proven to have anticancer and antiHIV activities.[4,5] As a part of our search for bioactive compounds from the *Euphorbia* genus, a further chemical investigation towards the species *E. esula* has been carried out and led to characterization of a novel norparaliane diterpenoid named esulatin G (**1**) together with 5,8,14-triacetoxy-3-benzoyloxy-15-hydroxy-9-oxoparaliane (**2**),[6] a known diterpenoid (Figure 1), probably being the biosynthetic precursor of **1**.

The chloroform fraction of the plant ethanol extracts was purified by repeatedly column chromatography over silica gel with petroleum ether/acetone and Pharmadex LH-20 with methanol to afford compounds **1** and **2**.

Compound **1** was isolated as colorless needles. Its molecular formula was determined as $C_{30}H_{38}O_8$ by HREIMS (m/z 526.2561 $[M]^+$, calcd. 526.2567). The IR spectrum exhibited the presence of hydroxy (3442 cm^{-1}), ester carbonyl (1739 cm^{-1}), ketone carbonyl (1716 cm^{-1}), double bond (1655 cm^{-1}), and aromatic group (1610 cm^{-1}). The ^1H and ^{13}C NMR spectra showed the presence of one benzoyl group [δ 7.88 (2H, d, $J = 7.8$ Hz), 7.55 (1H, t, $J = 7.4$ Hz), 7.44 (2H, t, $J = 7.8$ Hz); δ 165.8, 129.3, 128.6, and 133.2] and two acetyl groups [δ 1.99 (3H, s), 2.12 (3H, s); δ 20.8 and 170.3; 20.8 and 169.5], making **1** a triester. The remaining moiety contained four methyl (one olefinic), four methylene (one terminal olefinic), six methine (three oxygenated), and five quaternary carbons (one oxygenated, one ketone and one olefinic), suggesting **1** to be a tricycle norditerpenoid.

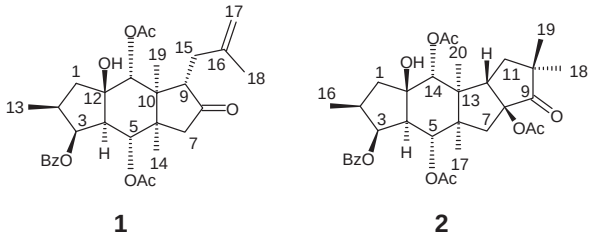


Figure 1. Structures of **1** and **2**.

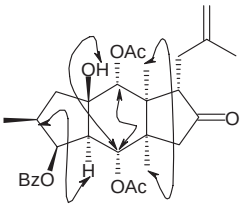


Figure 2. Key NOESY correlations of **1**.

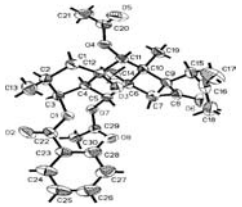
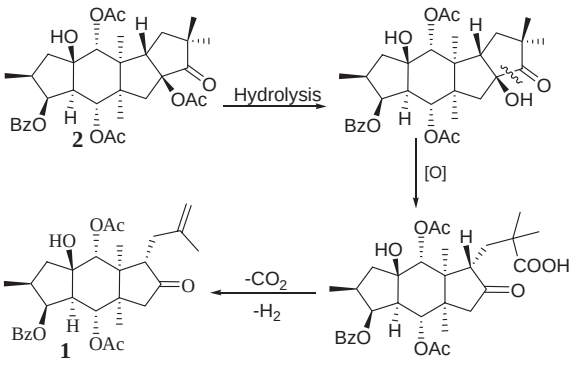


Figure 3. The ORTEP drawing of **1**.

Analysis of the ^1H–^1H COSY, HMQC, and HMBC spectra of **1** deduced the presence of –CH_2–CH(CH_3)–CH(OBz)–CH–CH(OAc)– and CH_2=C(CH_3)–CH_2–CH– fragments, indicating that **1** had a 5/6/5 tricyclic structure with an isobutenyl group. This structural feature was very similar with that of **2** except for the open terminal pentanone. In the HMBC spectrum, ^1H–^{13}C long-range correlations were observed between H-14 and C-5, C-7, C-10; H-19 and C-6, C-9, C-11; H-9 and C-7, C-16; H-11 and C-1, C-4, C-6, C-9; H-5 and C-3, C-7, C-12. The NOESY spectrum (Figure 2) exhibited the correlations of H-11 with H-5, H-9, and OH-12; OH-12 with H-5, and H-13; H-14 with H-19 and H-4 with H-2, showing that these protons are on the same side of the molecule.[7]

The assignment and stereochemistry of **1** was finally confirmed unambiguously by X-ray diffraction analysis of a single crystal obtained from methanol (Figure 3).[8] The esulatin G (**1**) is a novel norditerpenoid, probably derived from 5,8,14-triacetoxy-3-benzoyloxy-15-hydroxy-9-oxoparaliane (**2**), a known diterpenoid isolated from the same plant. Biogenetically, we suggest that **1** was produced from **2** via hydrolysis of the C-8 acetyl group followed by oxidative cleavage of the C-8 and C-9 bond and then decarboxylation. (Scheme 1).

Compound **2** was first reported from *Ephorbia paralias* in 1998 and its novel structure with a 5/6/5/5 ring system was named paraliane-type diterpenoid.[6] In our study the full assignment of its NMR data was made by various 2D technologies, from which the assignment of C-12 was revised from δ 40.4 reported before to δ 49.1.[9] Compound **2** was first isolated from this plant and second time from nature. It was suggested as a biosynthetic precursor of **1**.



Scheme 1. Proposed biogenesis of **1** from **2**.

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References and Notes

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7 Compound **1** colorless needles (MeOH); $[\alpha]^{24}$ +44.8 (*c* 0.29, $CHCl_3$); IR (KBr) ν_{max} 3442, 1739, 1716, 1232, 1027, 709 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.18 (m, H-1a), 1.18 (dd, $J = 5.8$ and 14.5 Hz, H-1b), 2.47 (m, H-2), 5.77 (t, $J = 4.7$ Hz, H-3), 2.47 (dd, $J = 4.3$, 11.9 Hz, H-4), 5.68 (d, $J = 11.9$ Hz, H-5), 2.36 (m, H-7), 3.95 (t, $J = 5.7$ Hz, H-9), 5.24 (s, H-11), 1.03 (d, $J = 7.8$ Hz, H-13), 1.23 (s, H-14), 2.09 (m, H-15a), 2.31 (m, H-1b), 1.83 (s, H-18), 1.86 (s, H-17), 0.82 (s, H-19), [7.88 (d, $J = 7.7$ Hz), 7.44 (t, $J = 7.7$ Hz), 7.55 (t, $J = 7.7$ Hz) for 3-OBz], 1.99 (s, 5-OAc), 2.12 (s, 11-OAc); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.3, C-1; 36.3, C-2; 76.5, C-3; 48.0, C-4; 70.1, C-5; 45.0, C-6; 47.1, C-7; 215.7, C-8; 54.3, C-9; 50.7, C-10; 73.0, C-11; 84.1, C-12; 16.0, C-13; 17.2, C-14; 33.1, C-15; 144.0, C-16; 112.3, C-17; 22.7, C-18; 15.9, C-19; 165.8, 129.3, 128.6, and 133.2 (3-OBz); 20.8 and 170.3 (5-OAc); 20.8 and 169.5 (11-OAc); EIMS *m/z* 526 $[M]^+$ (27), 511 (4), 466 (20), 164 (76), 105 (100); HREIMS *m/z*: $[M]^+$ calcd for $C_{30}H_{38}O_8$, 526.2567; found, 526.2561.
8 X-ray crystal data of **1**: $C_{30}H_{38}O_8$; crystal size (mm) 0.502 × 0.485 × 0.367 colorless prism; space group monoclinic, orthorhombic, $P2(1)2(1)2(1)$; unit cell dimensions $a = 12.0446(8)$ Å, $b = 15.0818(10)$ Å, $c = 15.9697(11)$ Å; volume 2901.0(3) $Å^3$; $Z = 4$; $Mr = 526.60$; density (calcd) 1.206 g/cm^3; absorption coefficient 0.091 mm^{-1}; $F(000) = 1128$. The reflection data were collected on a Bruker Smart Apex CCD diffractometer, using graphite-monochromated radiation Mo Kα $\lambda = 0.71073$ Å. A total of 17244 reflections was collected in the range $1.86 \leq \theta \leq 27.00^\circ$ of which 3521 unique reflections with $I > 2\sigma(I)$ utilized for the analysis, and were used for refinement. The final R and R_w were 0.065 and 0.0760 respectively, with goodness-of-fit of 0.820. Crystallographic data for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre, deposit No. CCDC 699582. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB21EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
9 Supporting Information is available electronically on the CSJ Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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