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Euphorikanin A, a Diterpenoid Lactone with a Fused 5/6/7/3 Ring System from *Euphorbia kansui*

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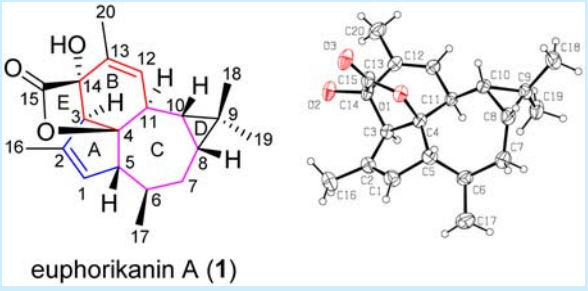
Supporting Information

ABSTRACT: Euphorikanin A (**1**), an unprecedented diterpenoid lactone which possesses a novel 5/6/7/3-fused tetracyclic ring skeleton, was isolated from the roots of *Euphorbia kansui*. The chemical structure and absolute stereochemistry were elucidated on the basis of extensive spectroscopic methods and single-crystal X-ray diffraction analysis. Compound **1** exhibited moderate cytotoxicity against two human tumor cell lines HeLa and NCI-446. A proposed biosynthetic pathway of compound **1** is also described.



Plants in the spurge family (Euphorbiaceae) are famous for the chemical diversity of their isoprenoid (sesqui-, di-, and triterpene) constituents.[1] The genus *Euphorbia* is the largest in this family, comprising more than 2000 species in the world and over 80 species in the mainland of China.[2] It has been found that sesquiterpenoids, diterpenoids, triterpenoids, steroids, flavonoids, phenolic acids, tannins, and other constituents exist in *Euphorbia*.[3] Diterpenoids (more than 871 compounds) are the characteristic constituents in the genus *Euphorbia*.[4] Many secondary metabolites based on specific types of diterpene skeletons (e.g., jatrophane, lathyrane, tigliane, daphnane, ingenane, myrinane, etc.) have been isolated from different parts (leaves, aerial parts, milky latex, roots, and seeds) of plants of the *Euphorbia* species and are of chemotaxonomial significance.[5] These diterpenoids can be formed in several steps of intramolecular cyclization of a casbene precursor, many of which retain the *gem*-dimethylcyclopropane ring in their final structures, such as lathyranes, tiglianes, and ingenanes.[6] A casbene synthase has also been shown to cyclize geranylgeranyl pyrophosphate (GGPP) to casbene.[7] Moreover, *Euphorbia* diterpenes possess a number of interesting biological activities, such as skin-irritant and tumor-promoting activities, and also antiproliferative, antiviral and multidrug resistance-reversing activities.[3] Their fascinating structures and important bioactivities have attracted increasing interest from both synthetic and natural products chemists over the past few years.[4a,8]

Euphorbia kansui is a perennial herb widely distributed in northern China, including Gansu, Shanxi, and Ningxia provinces. In traditional Chinese medicine, *E. kansui* is called "Gan Sui". Its roots have been extensively applied for the treatment of various diseases such as edema, ascites, asthma, epilepsy, and soreness.[9] Previous chemical studies have shown that the plant *E. kansui* contained diterpenoids, triterpenes, and phenolic derivatives.[10] Diterpenoids were found to be the major bioactive components of *E. kansui*, exhibiting various activities, e.g., antiviral[11] and anticancer[12] effects.

These results suggested that *E. kansui* could be an important source of structurally diverse diterpenoids with potent bioactivity. As part of our ongoing search for structurally interesting biologically active compounds from important Chinese medicinal herbs,[13] euphorikanin A (**1**) (Figure 1), a

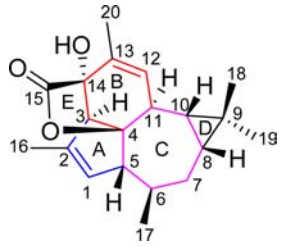


Figure 1. Structure of euphorikanin A (**1**).

structurally novel diterpenoid lactone with an unprecedented carbon skeleton featuring an unique tetradecahydrobenzo[*cd*]-cyclopropa[*f*]azulene core, was isolated from *E. kansui*. This paper describes the isolation, structural elucidation, and plausible biosynthetic pathway of **1** as well as its cytotoxicities against two human carcinoma cell lines.

The dried and pulverized roots of *E. kansui* were extracted four times (each time for 7 days) with 95% ethanol. The filtrated extract was concentrated under reduced pressure to

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yield the crude extract, which was resuspended in water and extracted sequentially with ethyl acetate and *n*-BuOH. The ethyl acetate extract, upon concentration, was subjected to a silica gel column (petroleum ether/acetone 40:1 to 0:1) to furnish fractions A–F. Fraction B was fractionated and chromatographed repeatedly on silica gel and Sephadex LH-20 columns to give the new compound **1**.

Euphorikanin A (**1**)[14] was obtained as an optically active ($[\alpha]_D^{25}$ +70 (*c* 0.10, $CHCl_3$)) needle crystal (in petroleum ether–acetone, 5:1). The molecular formula, $C_{20}H_{26}O_3$, was derived from the positive HRESIMS of the protonated molecular ion $[M + H]^+$ (*m*/*z* found 315.1955, calcd 315.1955) and was in accord with ^1H and ^{13}C NMR spectroscopic data. From this formula, it was suggested that **1** has eight degrees of unsaturation. The IR spectrum in KBr clearly suggested the presence of an ester carbonyl group based on one intense sharp band at 1756 cm^{-1}[15] as well as a characteristic band for the hydroxyl group at 3442 cm^{-1}. The ^1H NMR spectrum of **1** in $CDCl_3$ showed a secondary methyl group at δ_H 0.89 (d, *J* = 6.6 Hz, H_3-17), two tertiary methyl groups at δ_H 1.05 (s, H_3-18) and 1.00 (s, H_3-19), one vinylic methyl singlet at δ_H 1.81 (brs, H_3-20), and a vinylic methyl doublet at δ_H 1.84 (d, *J* = 1.8 Hz, H_3-16). The ^1H NMR spectrum also displayed resonances attributed to two olefinic methines at δ_H 5.53 (s, H-1) and δ_H 5.40 (s, H-12), an exchangeable hydroxyl proton at δ_H 2.72 (s, 14-OH), as well as other signals belonging to other methylene and methines with complex coupling patterns between δ_H 0.68–3.09 (Table 1).

Table 1. ^1H NMR (600 MHz) and ^{13}C NMR (150 MHz) Spectral Data of Compound 1 in $CDCl_3$ (δ in ppm, *J* in Hz)

no.	δ_C	δ_H mult (*J*, Hz)	HMBC
1	130.6, CH	5.53, s	3, 4
2	137.3, qC		
3	59.6, CH	3.09, s	2, 4, 13, 14, 15
4	97.3, qC		
5	54.5, CH	2.71, d (12.6)	3, 4
6	31.3, CH	1.34, m	4, 5, 8, 17
7	32.7, CH_2	1.79, m	6, 8, 9, 10, 17
		1.68, m	
8	20.8, CH	0.68, m	6
9	18.8, qC		
10	26.5, CH	0.81, m	8, 12, 18, 19
11	39.1, CH	2.34, dd (11.4, 2.4)	
12	126.1, CH	5.40, s	4, 14
13	139.5, qC		
14	80.4, qC		
15	177.0, qC		
16	16.2, CH_3	1.84, d (1.8)	1, 2, 3
17	20.9, CH_3	0.89, d (6.6)	5, 7
18	28.6, CH_3	1.05, s	8, 10
19	15.3, CH_3	1.00, s	9, 18
20	16.6, CH_3	1.81, brs	12, 13, 14
OH		2.72, s	3, 14, 15

The ^{13}C NMR and DEPT spectra of **1** showed a total of 20 carbon resonances which were assigned to five methyls, one methylene, eight methines (including two olefinic carbons), together with six quaternary carbons (including one ester carbonyl, two olefinic carbons, and two oxygenated carbons). From the number of carbon resonances in the ^{13}C NMR, in combination with the molecular formula, it could be inferred that compound **1** could be a diterpenoid. Moreover, deducting three degrees of unsaturation accounted for one ester carbonyl and two olefinic bonds, and the remaining five degrees of unsaturation were indicative of the pentacyclic ring system of **1**.

Interpretation of the 2D NMR data, including ^1H–^1H COSY, heteronuclear single-quantum coherence (HSQC), and heteronuclear multiple-bond correlation (HMBC) spectra, led to the construction of the planar structure of **1**. In the ^1H–^1H COSY spectrum (Figure 2), the cross peaks of H-1/H-5/H-

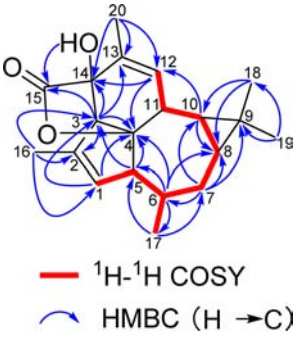

Figure 2. Key ^1H–^1H COSY, and HMBC correlations of **1**.

6(H_3-17)/H_2-7/H-8/H-10/H-11/H-12 suggested the presence of one key fragment (C-1/C-5/C-6(C-17)/C-7/C-8/C-10/C-11/C-12). In the HMBC spectrum of **1** (Figure 2), key correlations from the olefinic proton H-1 to C-3, C-4; from H_3-16 to C-1, C-2, C-3; from H-5 to C-3, C4; from H-3 to C-2, C-4, indicated that C-1, C-2, C-3, C-4, C-5 constructed a five-membered carbon ring A, which was substituted with a methyl group (CH_3-16) at C-2 and a double bond at C-1 and C-2. A octahydro-1*H*-indene core was constructed by a six-menbered ring B fused with five-menbered ring A, on the basis of the observation of the HMBC correlations from H-3 to C-13, C-14; from H_3-20 to C-12, C-13, C-14; from the olefinic proton H-12 to C-4, C-14, which was substituted with a methyl group (CH_3-20) at C-13, a double bond at C-12 and C-13, and a hydroxyl at C-14. HMBC correlations from H_3-17 to C-5, C-7; from H-6 to C-4, C-5, C-8, C-17; from H_2-7 to C-17, C-6, C-8, C-9, C-10; from H-8 to C-6; from H-10 to C-8, C-12 revealed the presence of a seven-menbered ring C that was fused to the rings A and B at C-5, C-4, and C-11, which was substituted with a methyl group (CH_3-17) at C-6. HMBC correlations from H_3-18 to C-8, C-10; from H_3-19 to C-9, C-18, together with their shifts, demonstrated the presence of a cyclopropane ring fused to the seven-menbered ring C at C-8 and C-10, which was substituted with two tertiary methyl groups (CH_3-18 and CH_3-19) at C-9. The "loose end" of ester carbonyl C-15 and the severely downfield-shifted signal at δ_C 97.3 ppm (C-4), coupled with the remaining one degree of unsaturation, revealed that an unusual 15,4-γ-lactone ring (E) was formed between C-15 and C-4 through an ester bond. In addition, the HMBC correlations from H-3 to C-14 and C-15 and from OH-14 to C-15 also indicated that C-15, C-14, C-3, and C-4 comprised a lactone ring E. Therefore, the planar structure of **1** was established to possess a 5/6/7/3 tetracyclic backbone, together with a γ-lactone ring, as shown in Figure 1.

The relative configuration of **1** was elucidated by analyzing the correlations detected in a NOESY spectrum. As depicted in the Chemdraw 3D molecular model (Figure 3), the NOE interactions between H_3-17 and H-5, H-5 and H-7β, H-5 and H-10, H-10 and H-8, H-8 and H_3-18 indicated the β-position of

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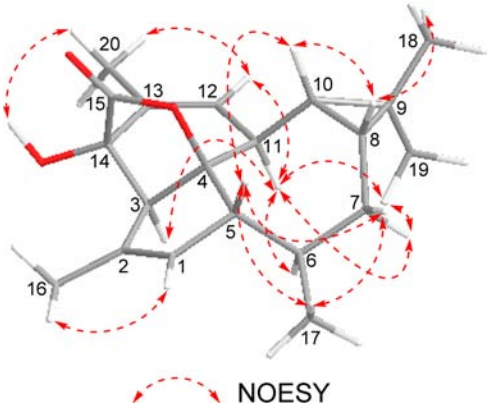


Figure 3. Key NOESY correlations observed for euphorikanin A (**1**).

H-5, H-7β, H-8, H-10 and C-17- and C-18-methyl groups. On the other hand, NOESY cross-peaks between H-6 and H-11, H-11 and H_3-19, H-11 and H-7α, and H-11 and H-3 dictated an α-arrangement of H-6, H-7α, H-11, H-3, and C-19-methyl groups. For lacking direct correlations, the relative configurations of 14-OH were not able to be determined by NOESY experiment.

To determine the absolute configuration and confirm the unique structure of **1**, X-ray crystallographic analysis was next carried out. After repeated attempts, a high-quality single crystal of **1** was obtained from petroleum ether/acetone solution. The X-ray crystallographic data (Figure 4)[16] corroborated the planar

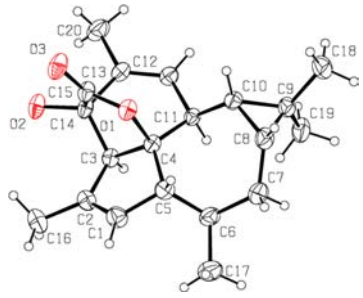
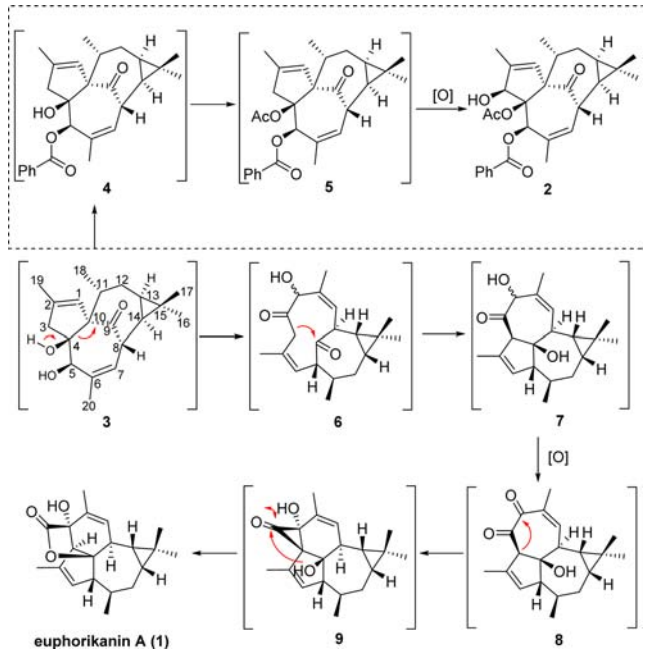


Figure 4. Single-crystal X-ray diffraction of euphorikanin A (**1**) (Cu Kα).

structure and relative configuration of **1** elucidated via NMR data and further allowed the assignment of its absolute configuration as 3*S*,4*R*,5*R*,6*R*,8*R*,10*R*,11*S*,14*S* [Flack parameter: 0.12 (11)].[17] The structure of **1** was named euphorikanin A.

Spectroscopic and X-ray crystallographic methods suggested that **1** represented a new diterpenoid carbon skeleton possessing a rare 5/6/7/3-membered ring fused tetracyclic ring architecture. To the best of our knowledge, compound **1** bears an unprecedented carbon skeleton, not previously reported in the natural kingdom. We propose that the named "euphorikanane" be used for this new diterpenoid carbon skeleton type. A plausible biosynthetic pathway for compound **1** is proposed as shown in Scheme 1. Compound **1** possesses a previously undescribed 5/6/7/3 ring system, which could be derived from the hypothetical precursor **3**, an ingenol-like diterpenoid that may be related to coisolated ingenane-type diterpene 4-*O*-acetyl-5-*O*-benzoyl-3β-hydroxy-20-deoxyingenol (**2**).[10j] In this pathway, a diketone **6** could be formed via a retro-aldol reaction in **3**, and when the aldol reaction proceeded between C-3 and C-9, tertiary alcohol **7** was formed. 5-OH was

Scheme 1. Proposed Biosynthetic Pathway for 1



oxidized to be a ketone group on **8**; subsequently, the cyclopropanone structure was constructed via an aldol condensation between C-3 and C-5. With the assistance of 9-OH, a retro-benzoin condensation was forwarded and euphorikanin A (**1**) could be obtained. This compound is of great interest for its biogenetic pathway. Therefore, euphorikanin A (**1**) will be an interesting target and challenge for synthetic chemistry.

Compound **1** was evaluated for its cytotoxic activities against two human tumor cell lines, HeLa and NCI-446 cell lines using MTT assay with etoposide as the positive control. As a result, compound **1** exhibited moderate cytotoxic activities with IC_{50} values of 28.85 and 20.89 μM, respectively (Table 2).

Table 2. In Vitro Cytotoxic Activity of Compound 1

	IC_{50} (μM)[a]	
compd	HeLa	NCI-446
1	28.85 ± 1.41	20.89 ± 1.67
etoposide[b]	26.23 ± 0.50	30.68 ± 1.10

[a]IC_{50} is defined as the concentration that resulted in a 50% decrease in cell number. [b]Etoposide was used as a positive control.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01093.

Experimental procedures; NMR, HRESIMS, and IR spectra of compound **1** (PDF)

X-ray data of compound **1** (CIF)

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Notes

The authors declare no competing financial interest.

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(14) Euphorikanin A (**1**): colorless crystals (petroleum ether−acetone, 5:1); mp 148−150 °C; $[\alpha]_D^{25}$ +70 (*c* 0.10, $CHCl_3$); IR (KBr) ν_{max} 3442, 2956, 2917, 2850, 1756, 1637, 1446, 1381, 1362, 1264, 1241, 1181, 1156, 1145, 1084, 1009, 953, 928, 881, 838, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) data, see Table 1; ^{13}C NMR ($CDCl_3$, 150 MHz) data, see Table 1; (+) HRESIMS *m*/*z* 315.1955 $[M + H]^+$ (calcd for $C_{20}H_{27}O_3$, 315.1955).

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(16) Crystal data for euphorikanin A (**1**): $C_{20}H_{26}O_3$, M_r = 314.41, orthorhombic, space group $P2_12_12_1$, *a* = 6.66247(9) Å, *b* = 16.2362(2) Å, *c* = 16.4824(3) Å, α = 90.00°, β = 90.00°, γ = 90.00°, *V* = 1782.96(4) $Å^3$, *T* = 293.7(3) K, *Z* = 4, *d* = 1.717 g/cm^3, μ(Cu Kα) = 0.612 mm^{-1}, *F*(000) = 680.0, crystal dimensions 0.27 × 0.12 × 0.04 mm were used for measurement on an Agilent Technologies SuperNova, Dual source, EOS CCD with mirror optics, using graphite monochromated Cu Kα radiation (λ = 1.54180). The total of 8123 reflections measured, 3140 independent reflections (R_{int} = 0.032). The final R_1 value was 0.0702 ($I > 2\sigma(I)$). The final w$R(F^2)$ value was 0.1736 (($I > 2\sigma(I)$). The final R_1 value was 0.0950 (all data). The final w$R(F^2)$ value was 0.2074 (all data). The goodness of fit on F^2 was 1.020. Crystallographic data for the structure of compound **1** have been deposited with the Cambridge Crystallographic Data Centre (deposition no. CCDC1455755). Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, U.K.; fax (+44) 1223-336-033 or deposit@ccdc.cam.uk).

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