PERGAMON

Phytochemistry 61 (2002) 373–377

PHYTOCHEMISTRY

www.elsevier.com/locate/phytochem

# Jatrophane and lathyrane diterpenoids from *Euphorbia hyberna* L.

Ana Margarida V.D. Ferreira[a], Luís H.M. Carvalho[a,*], Maria João M. Carvalho[a], Miguel M. Sequeira[b], Artur M.S. Silva[c]

[a]*Department of Chemistry, University of Trás-os-Montes and Alto Douro, Quinta de Prados, 5001-911 Vila Real, Portugal*
[b]*Department of Biology, University of Madeira, Campus da Penteada, 9000 Funchal, Portugal*
[c]*Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal*

Received 18 March 2002; received in revised form 13 May 2002

**Abstract**

A new diterpene tetraester, from the jatrophane family, and two new diterpene triesters, with a lathyrane skeleton, have been isolated from the chloroform extract of the roots of *Euphorbia hyberna* L. The structures of these compounds have been established by spectroscopic methods, including 2D NMR experiments. 

*Keywords:* *Euphorbia hyberna* L; Euphorbiaceae; Jatrophane polyesters; Lathyrane polyesters; Macrocyclic diterpenes

## 1. Introduction

The Euphorbiaceae family is one of the largest families in the plant kingdom. It comprises 263 genera and about 7300 species of almost cosmopolitan distribution. *Euphorbia*, the largest genus of Euphorbiaceae, with about 1600 species is characterized by the presence of milky latex. This genus has been the subject of numerous chemical studies (Singla and Pathak, 1990; Ahmad and Jassbi, 1998; Öksüz et al., 1999; Vogg et al., 1999; Ferreira and Ascenso, 1999; Hohmann et al., 1999, 2000; Marco et al., 1999).

As a part of our programme on the chemistry of plants of NE of Portugal, we have investigated *Euphorbia hyberna* L., subsp. *hyberna*, which is native from the West and South of Europe. It is a small shrub growing in damp or shady places, mainly on mountains (Moore et al., 1968). This species is chemically investigated by the first time. In this study, we report the isolation and structure elucidation of three hitherto unknown polyesters of macrocyclic diterpenes with the jathrophane and lathyrane skeletons.

## 2. Results and discussion

The acetone-soluble fraction obtained from the chloroform extract of the roots of *E. hyberna* L. was subjected to silica gel column chromatography and eluted with hexane/chloroform mixtures, giving one jatrophane tetraester **1** and two lathyrane derivatives **2** and **3**.

The $^{1}H$ and $^{13}C$ NMR of compound **1** spectra revealed the presence of one benzoate group [$\delta_H$ 8.04 *br d* (2H), 7.46 *t* (2H), 7.60 *t* (1H); $\delta_C$ 129.7, 129.6 (2×CH), 128.4 (2×CH), 133.3 (CH), 165.6 (C=O)] and three acetate groups [$\delta_H$ 2.25, 1.83, 2.06, $\delta_C$ 169.1, 168.6, 170.1 (C=O) and 21.5, 20.6, 20.5 ($CH_3$)]. The $^{1}H$ NMR and COSY spectra revealed the presence of two tertiary methyl groups ($\delta_H$ 1.24, 1.43), two secondary methyl groups ($\delta_H$ 1.35 *d*, 6H) and the structural fragments with sequences of correlated protons: $\delta_H$ 2.16 *m*, 3.10 *dd*, 2.48 *m* and 1.35 *d* [–$CH_2$–CH($CH_3$)–]; $\delta_H$ 5.45 *dd*, 2.89 *dd*, 5.90 *d* [–CH(OR)–CH–CH(OR)–]; $\delta_H$ 5.53 *d*, 5.94 *dd*, 3.54 *m*, 1.35 *d* [*trans* –CH=CH–CH($CH_3$)]. Additionally $^{13}C$ NMR and DEPT spectra indicated the presence of two ketones (C-9 and C-14), a double bond with a *trans* configuration ($J$=16 Hz, C11=C12), and an exomethylene group at C-6. The connectivities of these partial structures and the ester groups position were established by the long-range C–H correlations found in the HMBC spectrum of **1** (Table 1). In this spectrum C–H correlations between the protons of the exomethylene

* Corresponding author. Tel.: +351-259-350285; fax: +351-259-350480.
*E-mail address:* lcarv@utad.pt (L.H.M. Carvalho).

0031-9422/02/$ - see front matter 
PII: S0031-9422(02)00182-6

group (H-17a and H-17b) and C-7 (29.7 ppm) and between H-8 and C-6 confirm the location of the acetoxyl group at C-8.

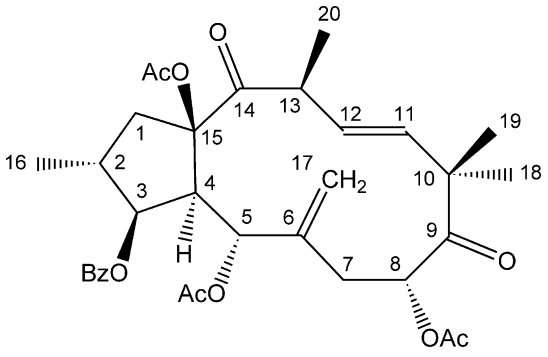
The relative stereochemistry of compound **1** was studied through the analysis of the coupling constants and NOESY spectrum. H-4 was used as a convenient reference point and was assumed to be α (Günther et al., 1998). NOE cross peaks between H-4, H-3 and H-13 supported the β orientation of the benzoate group on C-3 and the methyl group located on C-13. A NOE correlation between H-3 and H-16 pointed to an α orientation of this methyl group. The absence of NOE cross peaks between H-4 and H-5 required that H-5 have also an α orientation. A NOE cross peak between H-5 and H-8, proved the β orientation of H-8 and the α orientation of the 8-OAc. The NOE cross-peaks between H-11 and H-13 and H-18, and also between H-12 and H-19 and H-20 proved that these two groups of protons have an opposite orientation. No NOE correlation was observed between H-4 and 15-OAc, supporting the β orientation of the acetyl group on C-15. The coupling between H-4 and H-5 ($J_{4,5}=10$ Hz) suggests that the compound adopts a conformation in which the 6,17 exomethylene group is perpendicular to the mean plan of the macrocyclic ring (Jakupovic et al., 1998; Marco et al., 1998). With regard to the above data the structure of compound **1** was established as a derivative of the bicyclic diterpenoid jatrophane (Fig. 1).

Compound **2** (Fig. 2) is a 2-epiisomer of a known compound, lathyrol diacetate benzoate isolated from *Euphorbia lathyris* (Adolf and Hecker, 1971). Its $^{1}H$ and $^{13}C$ NMR spectra (Table 2) revealed the presence of one benzoate group [$\delta_H$ 8.04 *br d* (2H), 7.46 *t* (2H), 7.58 *t* (1H), $\delta_C$ 130.1, 129.6 (2×CH), 128.3 (2×CH), 133.1

Table 1
NMR spectral data of the jatrophane **1**

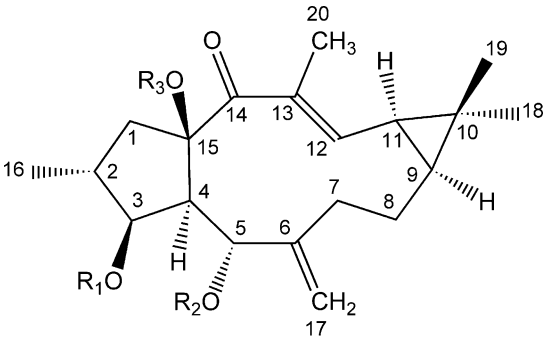
| Atom | $^{1}H$ (*J* in Hz) | $^{13}C$ | $^{1}H$–$^{1}H$ COSY | HMBC | NOESY |
|---|---|---|---|---|---|
| 1a | 2.16, *m* | 42.3 *t* | H-1b | – | H-1b, H-4, H-13, H-16 |
| 1b | 3.10, *dd* (15.9, 9.0) | | H-1a; H-2 | C-2, C-4, C-15 | H-1a, H-2 |
| 2 | 2.48, *m* | 38.4 *d* | H-1a; H-16 | – | H-1b, H-3, H-16 |
| 3 | 5.45, *dd* (5.1, 1.2) | 81.2 *d* | H-4 | C-1, C-15, C-1′ | H-2, H-4, H-16 |
| 4 | 2.89, *dd* (9.9, 5.4) | 46.6 *d* | H-3; H-5 | C-5, C-6, C-14 | H-1a, H-3, H-13 |
| 5 | 5.90, *d* (9.9) | 72.6 *d* | H-4 | 5-COMe | H-8 |
| 6 | – | 137.1 *s* | – | – | – |
| 7 | 2.16, *m* | 29.7 *t* | H-8 | – | – |
| 8 | 5.32, *br d* (7.2) | 72.2 *d* | H-7 | C-6 | H-7, H-12, H-17b, H-19 |
| 9 | – | 207.8 *s* | – | – | – |
| 10 | – | 49.5 *s* | – | – | – |
| 11 | 5.53, *d* (15.9) | 135.2 *d* | H-12 | C-10, C-13, C-19, C-18 | H-7, H-13, H-18 |
| 12 | 5.94, *dd* (15.9, 9.9) | 132.9 *d* | H-11; H-13 | C-10, C-20 | H-17a, H-19, H-20 |
| 13 | 3.54, *m* | 44.7 *d* | H-12; H-20 | C-11, C-12, C-20 | H-1a, H-4, H-11, H-20 |
| 14 | – | 203.6 *s* | – | – | – |
| 15 | – | 92.7 *s* | – | – | – |
| 16 | 1.35, *d* (7.2)a | 19.6 *q*a | H-2 | C-1, C-2, C-3 | H-1a, H-2, H-3 |
| 17a | 5.28, *br s* | 117.4 *t* | – | C-5, C-6, C-7 | H-5, H-17b |
| 17b | 4.96, *br* s | – | H-7 | C-7 | H-17a |
| 18 | 1.24, *s* | 24.0 *q* | – | C-9, C-10, C-11, C-18 | H-11 |
| 19 | 1.43, *s* | 24.6 *q* | – | C-9, C-10, C-11, C-19 | H-8, H-12 |
| 20 | 1.35, *d* (6.5)a | 19.7 *q*a | H-13 | C-12, C-13, C-14 | H-12, H-13 |
| *OAc* | | | | | |
| 5-CO | – | 168.6 *s* | – | – | – |
| 5-COMe | 1.83, *s* | 20.6 *q* | – | 5-COMe | – |
| 8-CO | – | 169.1 *s* | – | – | – |
| 8-COMe | 2.25, *s* | 21.5 *q* | – | 8-COMe | – |
| 15-CO | – | 170.1 *s* | – | – | – |
| 15-COMe | 2.06, *s* | 20.5 *q* | – | 15-COMe | – |
| *OBz* | | | | | |
| 1′ | – | 165.6 *s* | – | – | – |
| 2′ | – | 129.7 *s* | – | – | – |
| 3′, 7′ | 8.04, *br d* (7.2) | 129.6 *d* | H-4′,6′ | C-1′, C-5′ | – |
| 4′, 6′ | 7.46, *t* (7.5) | 128.4 *d* | H-3′,5′ | C-2′ | – |
| 5′ | 7.60, *t* (7.5) | 133.3 *d* | H-4′,6′ | – | – |

All $^{1}H$–$^{13}C$ connectivities were assigned by HETCOR and multiplicities were determined by DEPT experiments. Values with the same letter may be interchanged.




**1**

Fig. 1. Compound 1.




| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| **2** | Bz | Ac | Ac |
| **3** | Ac | Ac | Ac |

Fig. 2. Compounds 2 and 3.

(CH) and 166.0 (C=O)], two acetate groups [$\delta_H$ 1.84, 2.12, $\delta_C$ 20.7, 21.9 ($CH_3$), 169.7, 169.9 (C=O)], two tertiary methyl groups ($\delta_H$ 1.19, 1.24), two secondary methyl groups ($\delta_H$ 1.24 *d*, 1.76 *d*), one ketone (C-14), a double bond (C12=C13) with a *trans* configuration (supported by the absence of NOE cross-peak between H-12 and 20-$CH_3$ in the NOESY spectrum) and an exomethylene group at C-6.

The connectivities between protons and carbons were deduced from HETCOR and HMBC experiments (Table 3) and allowed the establishment of the lathyrane framework and to conclude that **2** is structurally close to a triester of lathyrol bearing two acetate groups at C-5 and C-15 and a benzoate group at C-3. However, the resonances of H-1b, H-2 and H-3, their multiplicity and the $^{13}C$ NMR spectrum are quite different from those observed for similar lathyrol derivatives (Adolf and Hecker, 1971; Appendino et al., 1999; Itokawa et al., 1990; Onwukaeme and Rowan, 1992). In particular the $^{13}C$ NMR resonance value of C-16 (18.7 ppm) is located

Table 2
$^1H$ and $^{13}C$ NMR spectral data of lathyranes **2** and **3**

| Atom | **2** $^1H$ (*J* in Hz) | **3** $^1H$ (*J* in Hz) | **2** $^{13}C$ (2) | **3** $^{13}C$ (3) |
|---|---|---|---|---|
| 1a | 2.3[a] | 2.39, *m* | 44.0 *t* | 42.7 *t* |
| 1b | 2.94, *d* (9.3) | 2.78, *dd* (15.0, 7.7) | – | – |
| 2 | 2.33[a] | 2.20, *m* | 37.3 *d* | 37.0 *d* |
| 3 | 5.26, *dd* (5.2, 2.2) | 4.94, *m* | 84.1 *d* | 82.6 *d* |
| 4 | 3.03, *dd* (8.9, 5.3) | 2.89, *dd* (8.4, 6.0) | 48.6 *d* | 48.6 *d* |
| 5 | 6.26, *d* (8.9) | 6.10, *br d* (8.5) | 66.0 *d* | 66.4 *d* |
| 6 | – | – | 144.7 *s* | 144.9 *s* |
| 7a | 2.3[a] | 2.3[a] | 34.6 *t* | 34.4 *t* |
| 7b | 2.0[a] | 2.0[a] | – | – |
| 8a | 1.6[a] | 1.8[a] | 21.7 *t* | 21.6 *t* |
| 8b | 2.0[a] | 2.0[a] | – | – |
| 9 | 1.2[a] | 1.2[a] | 35.7 *d* | 35.7 *d* |
| 10 | – | – | 25.8 *s* | 26.0 *s* |
| 11 | 1.45, *dd* (11.5, 8.4) | 1.45, *dd* (11.5, 8.4) | 28.6 *d* | 28.4 *d* |
| 12 | 6.52, *dd* (11.5, 1.0) | 6.42, *br d* (11.5) | 145.3 *d* | 145.2 *d* |
| 13 | – | – | 134.5 *s* | 134.2 *s* |
| 14 | – | – | 195.7 *s* | 195.4 *s* |
| 15 | – | – | 93.2 *s* | 92.6 *s* |
| 16 | 1.24, *d* (5.2) | 1.15, *d* (7.1) | 18.7 *q* | 18.5 *q* |
| 17a | 4.71, *s* | 4.72, *s* | 114.1 *t* | 113.5 *t* |
| 17b | 4.90, *s* | 4.92, *s* | – | – |
| 18 | 1.19, *s* | 1.20, *s* | 29.0 *q* | 28.8 *q* |
| 19 | 1.24, *s* | 1.25, *s* | 16.8 *q* | 16.6 *q* |
| 20 | 1.76, *d* (0.7) | 1.73, *s* | 12.6 *q* | 12.4 *q* |
| *OAc* | | | | |
| 3-CO | – | – | – | 170.0 *s*e |
| 3-COMe | – | 2.01, *s*d | – | 20.9 *q*f |
| 5-CO | – | – | 169.7 *s* | 169.7 *s*e |
| 5-COMe | 1.84, *s* | 2.02, *s*d | 20.7 *q* | 21.0 *q*f |
| 15-CO | – | – | 169.9 *s* | 170.7 *s*e |
| 15-COMe | 2.12, *s* | 2.05, *s*d | 21.9 *q* | 21.7 *q*f |
| *OBz* | | | | |
| 1′ | – | – | 166.0 *s* | – |
| 2′ | – | – | 130.1 *s* | – |
| 3′, 7′ | 8.04, *br d* (8.0) | – | 129.6 *d* | – |
| 4′, 6′ | 7.46, *t* (7.5) | – | 128.3 *d* | – |
| 5′ | 7.58, *t* (7.4) | – | 133.1 *d* | – |

[a] Approximate central values due to overlapped signals. Values with the same letter may be interchanged.
All $^1H$–$^{13}C$ connectivities were assigned by HETCOR and multiplicities were determined by DEPT experiments.

Table 3
HMBC connectivities of lathyranes **2** and **3**

| **2** | **3** |
|---|---|
| H-1b: C-2, C-16 | H-1b: C-2, C-16 |
| H-3: C-15 | H-3: C-15 |
| H-4: C-5, C-6 | H-4: C-5, C-6 |
| H-5: C-4, C-6, C-17, 5-COMe | H-5: C-4, C-6, C-17, 5-COMe |
| H-12: C-14, C-20 | H-12: C-14, C-20 |
| H-17a: C-5, C-7 | H-17a: C-5, C-7 |
| H-17b: C-5, C-7 | H-17b: C-5, C-7 |
| H-20: C-14 | H-20: C-14 |
| H-3′,7′: C-1′,C-4′,6′,C-5′ | |
| H-4′, H-6′: C-3′,7′ | |
| H-5′: C-4′,6′ | |

more downfield than usual suggesting a *trans*-relationship between the methyl group and the oxygen function at C-3 (the same is observed for jatrophane derivatives like **1**). The similarity of the resonances and coupling constants values in the fragment of C-5 to C-13 of **2** with those published for lathyrol esters led us to conclude that the configuracional and conformational aspects of the 11-membered ring are essentially the same in both systems. The stereochemical differences were centred on the five membered rings, which were confirmed by the coupling pattern between H-2 and H-1b and the analysis of the NOESY spectrum of compound **2** (Table 4). H-4 was again used as a reference point and assumed to be α. A NOE cross peak between H-4 and H-3 proved the β orientation of the benzoate group on C-3, while a NOE cross peak between H-3 and 16-C$H_3$ proved the α orientation of the methyl group on C-2 and confirmed that compound **2** is a 2-epiisomer of a lathyrol ester. The absence of NOE correlation between H-4 and H-5 proved the α orientation of the acetate group on C-5.

The $^1$H and $^{13}$C NMR spectra (Table 2) of compound **3** (Fig. 2) have a close similarity with those of compound **2** and revealed the presence of three acetate groups [$\delta_H$ 2.01, 2.02, 2.05, $\delta_C$ 170.0, 169.7, 170.7 (C=O), 20.9, 21.0, 21.7 (*C*$H_3$)], two tertiary methyl groups ($\delta_H$ 1.25, 1.20), two secondary methyl groups ($\delta_H$ 1.15 *d*, 1.73 *d*), one ketone (C-14), a double bond (C12=C13) with a *trans* configuration (supported by the absence of NOE cross-peak between H-12 and 20-$CH_3$ in the NOESY spectrum) and an exomethylene group at C-6. The proton and carbon connectivities deduced from HETCOR, HMBC and NOESY experiments (Tables 3 and 4) allowed to establish the carbon framework and to assign the position of the acyl residues. All these spectral features of compound **3** and their comparison with literature data (Adolf and Hecker, 1971; Appendino et al., 1999; Itokawa et al., 1990; Onwukaeme and Rowan, 1992) led us to assign its structure as depicted in Fig. 2.

Table 4
NOESY correlations of lathyranes **2** and **3**

| **2** | **3** |
|---|---|
| H-1b: H-1a | H-1b: H-1a |
| H-3: H-4, H-16 | H-3: H-4, H-17a, H-16 |
| H-4: H-3, H-17a | H-4: H-3, H-17a |
| H-5: H-12 | H-5: H-12 |
| H-12: H-5, H-20 | H-12: H-5, H-20 |
| H-17a: H-4, H-17b | H-17a: H-4, H-17b |
| H-17b: H-7a, H-17a | H-17b: H-3,[a] H-4,H-17a |
| H-16: H-2, H-3, H-12 | H-16: H-3, H-12 |
| H-20: H-5, H-12 | H-20: H-5, H-12 |
| H-3′,7′: H-4′,6′H-5′ | |
| H-4′,6′: H-3′,7′H-5′ | |
| H-5′: H-4′,6′ | |

[a] Ambiguous due to the overlapping with diagonal peaks.

## 3. Experimental

### 3.1. General

$^1$H and $^{13}$C NMR (300.13 and 75.47 MHz, respectively) and 2D NMR (COSY, NOESY, HETCOR and HMBC) spectra were recorded in $CDCl_3$ and referenced to TMS signal ($^1$H) and to solvent signal ($^{13}$C) on a Bruker AMX spectrometer. HR-FABMS was measured in a VG AutoSpec M mass spectrometer. CC: silica gel 100 (35–70 mesh, Merck) and silica gel 60 (230–400 mesh, Merck). TLC: silica gel 60 $F_{254}$ aluminum-backed sheets (Merck); PTLC: silica gel 60 $F_{254}$ plates (2 mm, Merck). The TLC sheets were checked for spots spraying with 50% (v/v) $H_2SO_4$:EtOH and heating.

### 3.2. Plant material

The whole root system of *E. hyberna* L., subsp. *hyberna*, was collected in the Alvão mountains, near Vila Real (Trás-os-Montes and Alto Douro, NE of Portugal) in March 1996. Voucher specimens have been deposited in the Herbarium of the University of Trás-os-Montes and Alto Douro.

### 3.3. Extraction and isolation

The air-dried and powdered roots (634 g) were extracted exhaustively with chloroform (6 × 2.5 l), at room temperature. Removal of the solvent from the organic extract, at 40 °C under reduced pressure, gave a residue (15.1 g) that was partitioned with acetone. The acetone-soluble fraction, furnished a yellow oil residue (9.0 g) that was fractionated using silica gel CC (1 kg silica gel 100 using $CHCl_3$ as eluent) collecting 500 ml frs. The combined frs. 21–27 (4.0 g) were then subjected to a second CC (CCII) using 200 g of silica gel 60, eluting with EtOAc–*n*-hexane (2:8) and collecting 100 ml frs. All the collected frs. were monitored by TLC, and combined, in accordance with their composition. Solvent evaporation of the combined frs. 21–34 (CCII) precipitated pure compound **1** (130 mg, $R_f$ 0.50, EtOAc-$CHCl_3$, 1:9). Frs. 3–7 (1.73 g), which were eluted from CCII, were chromatographed on a silica gel 60 (60 g) column, using EtOAc–$CHCl_3$ (5:95) as eluent, and gave pure compound **2** (30 mg, $R_f$ 0.60, EtOAc–$CHCl_3$, 5:95). Frs. 9–15, obtained from CCII, afforded a residue (0.82 g) that was subjected to repeated CC on silica gel 60 (EtOAc–$CHCl_3$ 1:9) and gave a residue (0.38 g) that was further purified by PTLC (EtOAc–$CHCl_3$ 1:9, 2×) yielding pure compound **3** (26 mg, $R_f$ 0.56, EtOAc–$CHCl_3$, 1:9).

*3.3.1. (2R*, 3S*, 4R*, 5R*, 8R*, 13S*, 15R*)-5,8,15-Triacetoxy-3-benzoyloxy-9,14-dioxojatropha-6(17),11E-diene (**1**)*

Colourless to white needles; IR $\nu_{max}$ $cm^{-1}$: 2987 (C–H), 1743, 1724 (ester and ketone C=O), 1652, 1602, 1452, 1371, 1270, 1224, 1114, 1070, 1025; EIMS (probe) 70 eV, *m*/*z* (rel. int.): 596 [$M^+$] (4), 581 (2), 494 (4), 476 (3), 372 (7), 312 (5), 284 (5), 229 (9), 216 (7), 188 (16), 177 (7), 160 (5), 123 (15), 105 (100), 96 (45), 77 (14), 59 (7); HR-FAB MS (positive ion mode) *m*/*z*: $[M+H]^+$ 597.2718, calculated for $[C_{33}H_{40}O_{10}+H]^+$ 597.2700; NMR spectral data: see Table 1.

*3.3.2. (2R*, 3S*, 4R*, 5R*, 9S*, 11S*, 15R*)-5,15-Diacetoxy-3-benzoyloxy-14-oxolathyra-6(17),12E-diene (**2**)*

Colorless oil; IR $\nu_{max}$ $cm^{-1}$: 2925 (C–H), 1741, 1716 (ester and ketone C=O), 1648, 1625, 1452, 1371, 1276, 1226, 1114; HR-FAB MS (positive ion mode) *m*/*z*: $[M+H]^+$ 523.2711, calculated for $[C_{31}H_{38}O_7+H]^+$ 523.2696; NMR spectral data: see Tables 2–4.

*3.3.3. (2R*, 3S*, 4R*, 5R*, 9S*, 11S*, 15R*)-3,5,15-Triacetoxy-14-oxolathyra-6(17),12E-diene (**3**)*

Colorless oil; IR $\nu_{max}$ $cm^{-1}$: 2927 (C–H), 1739 (ester and ketone C=O), 1650, 1625, 1452, 1371, 1253, 1118, 1043; HR-FAB MS (positive ion mode) *m*/*z*: $[M+H]^+$ 462.2611, calculated for $[C_{26}H_{36}O_7+H]^+$ 462.2593; NMR spectral data: see Tables 2–4.

## References


Adolf, W., Hecker, E., 1971. Further new diterpene esters from the irritant and cocarcinogenic seed oil and latex of the caper spurge (*Euphorbia lathyris* L. Experientia 27, 1393–1394.

Ahmad, V.U., Jassbi, A.R., 1998. Three tricyclic diterpenoids from *Euphorbia decipiens*. Planta Medica 64, 732–735.

Appendino, G., Tron, G.C., Cravotto, G., Palmisano, Jakupovic, J., 1999. An expeditious procedure for the isolation of ingenol from seeds of *Euphorbia lathyris*. J. Natural Products 62, 76–79.

Ferreira, M.J.U., Ascenso, J.R., 1999. Steroids and a tetracyclic diterpene from *Euphorbia boetica*. Phytochemistry 51, 439–444.

Günther, G., Hohmann, J., Vasas, A., Máthé, I., Dombi, G., Jerkovich, G., 1998. Jatrophane diterpenoids from *Euphorbia esula*. Phytochemistry 47, 1309–1313.

Hohmann, J., Evanics, F., Berta, L., Bartók, T., 2000. Diterpenoids from *Euphorbia peplus*. Planta Medica 66, 291–294.

Hohmann, J., Vasas, A., Günther, G., Dombi, G., Blazsó, G., Falkay, G., Máthé, I., Jerkovich, G., 1999. Jatrophane diterpenoids from *Euphorbia peplus*. Phytochemistry 51, 673–677.

Itokawa, H., Ichihara, Y., Yahagi, M., Watanabe, K., Takeya, K., 1990. Lathyrane diterpenes from *Euphorbia lathyris*. Phytochemistry 29, 2025–2026.

Jakupovic, J., Jeske, F., Morgenstern, T., Tsichritzis, F., Marco, J.A., Berendsohn, W., 1998. Diterpenes from *Euphorbia segetalis*. Phytochemistry 47, 1583–1600.

Marco, J.A., Sanz, Cervera, J.F., Yuste, A., Jakupovic, J., Jeske, F., 1998. Jathrophane derivatives and a rearranged jatrophane from *Euphorbia terracina*. Phytochemistry 47, 1621–1630.

Marco, J.A., Sanz, Cervera, J.F., Checa, J., Palomares, E., Fraga, B.M., 1999. Jatrophane and tigliane diterpenes from the latex of *Euphorbia obtusifolia*. Phytochemistry 52, 479–485.

Moore, D.M., Valentine, D.H., Tutin, T.G., Heywood, V.H., Burges, N.A., Walters, S.M., Webb, D.A., 1968. Flora Europaea 2. Cambridge University Press, Cambridge.

Öksüz, S., Ulubelen, A., Barla, A., Kohlbau, H.-J., Voelter, W., 1999. Triterpenoids and a diterpene from *Euphorbia iberica*. Planta Medica 65, 475–477.

Onwukaeme, N.D., Rowan, M.G., 1992. Jatrophane and lathyrane diterpenoid esters from North American leafy spurge seed. Phytochemistry 31, 3479–3482.

Singla, A.K., Pathak, K., 1990. Phytoconstituents of *Euphorbia* species. Fitoterapia 61, 483–516.

Vogg, G., Mattes, E., Rothenburger, J., Hertkorn, N., Achatz, S., Sandermann, Jr. H., 1999. Tumor promoting diterpenes from *Euphorbia leuconeura* L. Phytochemistry 51, 289–295.