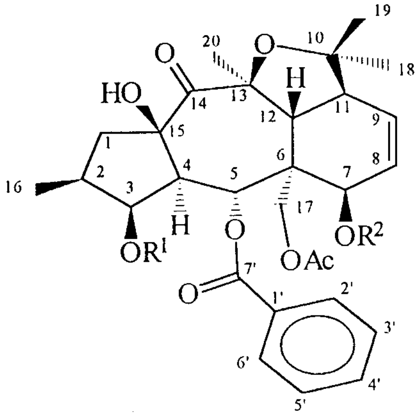
Three New Diterpenoids from *Euphorbia cheiradenia*

by **Muhammad Abbas**, **Amir Reza Jassbi**, **Muhammad Zahid**, **Zulfiqar Ali**, **Naseer Alam**, **Farzana Akhtar**, **M. Iqbal Choudhary**, and **Viqar Uddin Ahmad***

International Center for Chemical Sciences, H.E.J. Research Institute of Chemistry, University of Karachi,
Karachi 75270, Pakistan

Three new diterpene esters, cheiradone (**1**), cheiradone A (**2**), and cheiradone B (**3**), were isolated from the aerial parts of *Euphorbia cheiradenia*, collected in Iran. The structures were determined using different spectroscopic methods, including 1D and 2D NMR and X-ray diffraction analysis.

1. Introduction. – Euphorbiaceae plants are well-known to contain irritant and tumor-promoting constituents [1]. Diterpenes from Euphorbiaceae have been found to possess a number of interesting biological activities [2]. As a part of ongoing research on the diterpenoids of *Euphorbia* species from Iran [3–6], we have isolated and determined the structures of three new diterpenoids with a myrsinane-type skeleton from *Euphorbia cheiradenia* BOISS. et HOHEN. ex BOISS. collected at the Haraz and Chalus road, north of Tehran in Iran. To the best of our knowledge, the chemical constituents of this plant have not been investigated so far.



1[1]) $R^1 = R^2 = Ac$
2 $R^1 = Ac$, $R^2 = H$
3 $R^1 = H$, $R^2 = Ac$

2. Results and Discussion. – Compound **1** was purified by prep. TLC. The molecular ion was determined by CI-MS (*m/z* 613, $[M+1]^+$) and positive-ion-mode FAB-MS (*m/z* 651, $[M+K]^+$). In the EI-MS, the ions at *m/z* 584 ($[M-CO]^+$), 524 ($[M-CO-$

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[1]) Arbitrary numbering; for systematic names, see *Exper. Part.*

AcOH]$^+$), 464 ([M – CO – 2 AcOH]$^+$), 122 ($PhCO_2H^+$), and 105 ($PhCO^+$) indicated carbonyl, acetate, and benzoate functionalities in the molecule. In the IR spectrum, absorptions at 3550 (OH), 1750, 1720, 1705 (RCO_2R', RCOR′), and 1620 (C=C) cm^{-1} confirmed the presence of the above functional groups. The ^1H-NMR spectrum of **1** (*Table*) was similar to those recorded for myrsinane-type diterpenoids [3–5]. In the ^{13}C-NMR spectra (BB and DEPT) of **1**, 31 signals represented 33 C-atoms, including 7 Me (3 Ac), 2 CH_2, 12 CH, and 10 quaternary C (4 C=O of esters) (*Table*). The coupling constants in the ^1H-NMR spectrum [3–6], HMBC and NOESY experiments, and finally the single-crystal X-ray structure analysis (*Fig.*) unambiguously established the relative configuration of the molecule. Compound **1** showed inhibitory activity against α-glucosidase enzyme type V1 (*Sigma*, No. G6136) with IC_{50} = 0.32 mM.

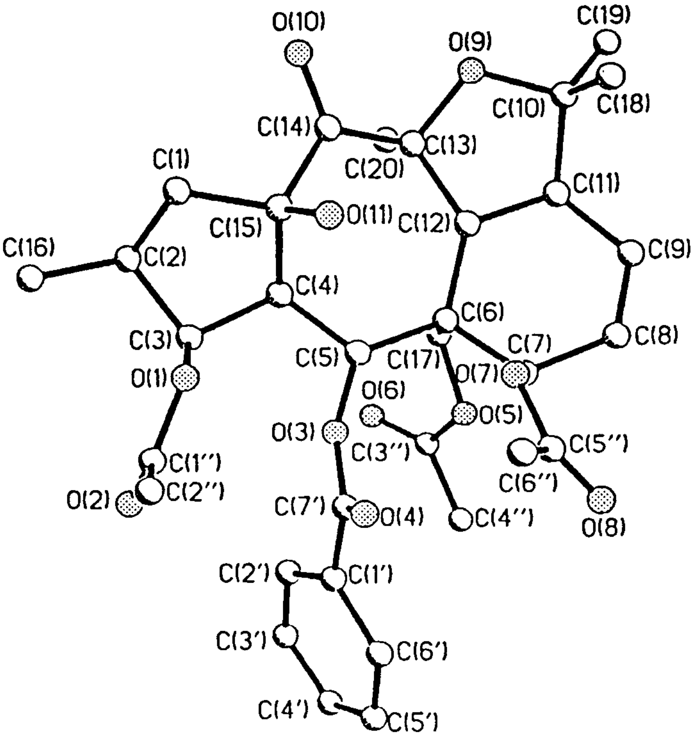

Figure. *X-Ray crystal structure of* **1**. Arbitrary numbering.

Characteristic ^1H-NMR signals of **1** were observed at δ 5.50 (H–C(3)), 6.48, (H–C(5)), and 5.06 ppm (H–C(1)), representing three oxymethine protons. Two AB ('*d*') signals at δ 4.58 and 4.22 ppm (CH_2(17)), with a relatively large coupling constant (J_{AB} = 12.1 Hz), were typical of an oxymethylene group, suggesting the presence of the free alkoxy group of the decipinone-type skeleton [3]. The downfield-shifted protons resonating at δ 3.15 (H–C(12)) and 2.88 (CH_2(1)) are characteristic of a myrsinane-type skeleton. The presence of a tetrahydrofuran moiety due to the epoxy bridge between C(10) and C(13) and, on the other hand, the absence of the ether linkage between C(17) and C(13) as in myrsinol ester diterpenoids make this compound new in structure. The lack of the olefinic signal of H–C(18) and, the presence of the signals at δ 1.03 (Me(19)) and 1.42 ppm (Me(18)) further confirmed the above-mentioned structural differences.

Table. *^{1}H-NMR* (500 MHz) *and ^{13}C-NMR* (125 MHz) *Data* (CDCl$_3$) *of Cheiradones* **1**–**3**. Arbitrary numbering; δ in ppm, J in Hz.

	δ(C) (mult.)			δ(H)		
	1	**2**	**3**	**1**	**2**	**3**
CH$_2$(1)	46.0 (*t*)	45.9 (*t*)	46.8 (*t*)	2.83 (*dd*, J = 9.7, 14.8), 1.70 (*dd*, J = 9.6, 14.8)	2.83 (*dd*, J = 9.7, 14.8), 1.71 (*dd*, J = 9.6, 14.8)	2.85 (*dd*, J = 9.8, 14.7), 1.70 (*dd*, J = 9.5, 14.7)
H−C(2)	35.8 (*d*)	35.9 (*d*)	35.6 (*d*)	2.1 (*m*)	2.1 (*m*)	2.3 (*m*)
H−C(3)	78.6 (*d*)	79.0 (*d*)	76.8 (*d*)	5.50 (*t*, J = 4.1)	5.49 (*t*, J = 4.1)	4.09 (*t*, J = 4.0)
H−C(4)	49.7 (*d*)	49.4 (*d*)	49.2 (*d*)	2.99 (*dd*, J = 4.1, 11.0)	2.99 (*dd*, J = 4.1, 11.0)	2.95 (*dd*, J = 4.0, 11.1)
H−C(5)	69.0 (*d*)	68.7 (*d*)	70.9 (*d*)	6.48 (*d*, J = 11.0)	6.12 (*d*, J = 11.0)	5.93 (*d*, J = 11.1)
C(6)	47.1 (*s*)	47.8 (*s*)	47.4 (*s*)	–	–	–
H−C(7)	67.9 (*d*)	65.8 (*d*)	67.0 (*d*)	5.06 (*d*, J = 5.3)	4.19 (*d*, J = 5.1)	5.57 (*d*, J = 5.2)
H−C(8)	126.4 (*d*)	127.1 (*d*)	126.6 (*d*)	6.00 (*ddd*, J = 2.8, 5.3, 9.7)	6.08 (*ddd*, J = 2.3, 5.1, 9.9)	6.02 (*ddd*, J = 2.5, 5.2, 9.8)
H−C(9)	128.8 (*d*)	128.7 (*d*)	128.6 (*d*)	5.82 (*dd*, J = 2.0, 9.7)	5.92 (*dd*, J = 1.8,9.9)	5.83 (*dd*, J = 1.9, 9.8)
C(10)	79.3 (*s*)	79.8 (*s*)	79.3 (*s*)	–	–	–
H−C(11)	47.4 (*d*)	46.7 (*d*)	47.3 (*d*)	2.84 (br. *d*, J = 12.7)	2.86 (br. *d*, J = 12.7)	2.83 (br. *d*, J = 12.7)
H−C(12)	41.9 (*d*)	41.0 (*d*)	40.8 (*d*)	3.15 (*d*, J = 12.7)	2.92 (*d*, J = 12.7)	3.01 (*d*, J = 12.7)
C(13)	83.6 (*s*)	84.9 (*s*)	83.5 (*s*)	–	–	–
C(14)	205.5 (*s*)	205.5 (*s*)	208.7 (*s*)	–	–	–
C(15)	85.4 (*s*)	85.3 (*s*)	86.4 (*s*)	–	–	–
Me(16)	14.7 (*q*)	14.7 (*q*)	15.7 (*q*)	0.90 (*d*, J = 6.8)	0.94 (*d*, J = 6.8)	1.10 (*d*, J = 6.7)
CH$_2$(17)	61.3 (*t*)	60.3 (*t*)	62.1 (*t*)	4.58 (*d*, J = 12.1), 4.22 (br. *d*, J = 12.1)	5.34 (*d*, J = 12.4), 4.27 (*d*, J = 12.4)	4.85 (*d*, J = 12.4), 4.25 (*d*, J = 12.4)
Me(18)	29.6 (*q*)	29.7 (*q*)	29.6 (*q*)	1.42 (*s*)	1.41 (*s*)	1.43 (*s*)
Me(19)	24.6 (*q*)	23.1 (*q*)	24.8 (*q*)	1.03 (*s*)	1.06 (*s*)	1.04 (*s*)
Me(20)	24.8 (*q*)	24.5 (*q*)	24.5 (*q*)	1.52 (*s*)	1.59 (*s*)	1.49 (*s*)
*Me*COO	21.2 (*q*), 20.8 (*q*), 20.6 (*q*)	21.4 (*q*), 20.6 (*q*)	21.0 (*q*), 20.6 (*q*)	2.14 (*s*), 1.89(*s*), 1.67(*s*)	2.35 (*s*), 1.61(*s*)	2.35 (*s*), 1.79(*s*)
Me*C*OO	170.4 (*s*), 170.1 (*s*), 169.8 (*s*)	170.5 (*s*), 172.9 (*s*)	170.5 (*s*), 170.0 (*s*)	–	–	–
C(1′)	129.6 (*s*)	129.7 (*s*)	129.8 (*s*)	–	–	–
H−C(2′,6′)	129.6 (*d*)	129.3 (*d*)	129.5 (*d*)	7.87 (br. *d*, J = 7.8)	8.03 (*dd*, J = 1.3, 7.7)	7.91 (*dd*, J = 1.4, 7.7)
H−C(3′,5′)	128.4 (*d*)	128.7 (*d*)	128.6 (*d*)	7.38 (br. *t*, J = 7.8)	7.45 (br. *t*, J = 7.7)	7.38 (br. *t*, J = 7.7)
H−C(4′)	133.2 (*d*)	133.5 (*d*)	133.3 (*d*)	7.50 (br. *t*, J = 7.4)	7.50 (*tt*, J = 1.3, 7.5)	7.51 (*tt*, J = 1.4, 7.4)
Ph*C*(7′)OO	165.1 (*s*)	166.0 (*s*)	166.3 (*s*)	–	–	–

The presence of a signal at δ(c) 79.3 (C(10)) and a Me group resonating at δ(c) 29.6 ppm (C(18)) in the ^{13}C-NMR spectra were the main differences between cheiradone (**1**) and the decipinone skeleton [3]. The chemical shifts of C(13) and C(15) of **1** at δ 83.6 and 85.4 suggested that they were non-esterified O-bearing quaternary C-atoms [5]. The presence of a cross-peak between a relatively upfield-shifted C=O signal at δ 165.1 (C(7′)) and *H*−C(5) (δ 6.48) in the HMBC plot further confirmed the position of the benzoate group. In the NOESY plot, only a cross-peak between H−C(12) and Me(19) was observed.

Compounds **2** and **3** were obtained as a mixture, which was separated by prep. TLC. The FAB-MS (positive-ion mode) of both compounds showed the $[M + \mathrm{H}]^+$ at m/z 571. The ^{1}H-NMR spectra (*Table*) established that **2** and **3** are derivatives of **1**, and their M^+ of m/z 570 indicated the loss of an acetyl group from **1**. Both the ^{1}H- and ^{13}C-NMR spectra of **2** and **3** exhibited close similarities with each other, the main differences being observed for the chemical shifts of C(3) and C(7). The ^{1}H,^{1}H and ^{13}C,^{1}H connectivities were assigned by COSY-45°, HMQC, and HMBC experiments and confirmed the proposed structures of **2** and **3**.

The signals at δ(H) 5.49 (H−C(3), **2** and 4.09 (H−C(3), **3** as well as δ(c) 79.0 (C(3), **2** and 76.8 (C(3), **3**) indicated that **2** contains an AcO group at C(3), while compound **3** has a free OH group at this position. The signals at δ(H) 4.19 (H−C(7), **2** and 5.57 (H−C(7), **3** as well as δ(c) 65.8 (C(7), **2** and 67.0 (C(7), **3**) further confirmed the C(7) position of the OH group in **2** and of the AcO group in **3**.

Experimental Part

General. Column chromatography (CC): silica gel, 70–230 mesh. Flash chromatography (FC): silica gel 220–440 mesh. TLC: Precoated silica gel *G-25-UV*$_{254}$ plates: detection at 254 and 366 nm, and by ceric sulfate reagent. Optical rotations: *Jasco-DIP-360* digital polarimeter. UV Spectra: *Hitachi-UV-3200* spectrophotometer; λ_{max} in nm. IR Spectra: *Jasco-320-A* spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR, COSY, HMQC, and HMBC: *Bruker* spectrometers operating at 500 and 400 MHz; chemical shifts δ in ppm and coupling constants J in Hz. EI-, CI- and FAB-MS (positive-ion mode): *JMS-HX-110* with a data system and *JMS-DA-500* spectrometer; m/z (rel. %).

Plant Material. The plants of *Euphorbia cheiradenia* BOISS. et HOHEN. ex BOISS. (Euphorbiaceae) was collected at the Haraz and Chalus road, northeast of Tehran, in 1998, and was identified by Mr. *Bahram Zehzad* (plant taxonomist) at the Department of Biological Sciences, Shahid Beheshti University, Evin, Tehran, Iran. The voucher specimen (No. 98/103) was deposited at the herbarium of the Biology Department of Shahid Beheshti University, Evin, Tehran, Iran.

Extraction and Isolation. The aerial parts of the air-dried ground plant (2 kg) were exhaustively extracted with acetone at r.t. The extract was evaporated and the residue (36 g) defatted by extraction with hexane. The defatted extract (23 g) was subjected to CC (silica gel (450 g), hexane/CHCl$_3$ 100 : 0 → 0 : 100, then MeOH). The CHCl$_3$-rich fractions were subjected to FC: **1** and **2/3**. Compound **1** was purified by prep. TLC (silica gel *F254*, CHCl$_3$/Me$_2$CO 8 : 2). The mixture **2/3** was separated by prep. TLC (AgNO$_3$-impregnated TLC plates, CHCl$_3$/Me$_2$CO 6.5 : 3.5).

Cheiradone (= rel-*(1R,2R,3aS,5R,5aS,6R,9S,9aS,10S,10aS)-9a-(Acetoxymethyl)-1,3,3a,5,5a,6,9,9a,10,10a-decahydro-1,3a,9,10-tetrahydroxy-2,5,11,11-tetramethyl-5,6-(epoxymethano)benz[f]azulen-4(2H)-one 1,9-Diacetate 10-Benzoate*; **1**). White needles (MeOH). M.p. 213°. $[\alpha]_D^{29} = -3.51$ ($c = 0.71$, CHCl$_3$). UV (MeOH): 230, 201. IR: 3550, 3100–2980, 1750–1720, 1705, 1610–1580. EI-MS: 584 (34, M − CO]$^+$), 524 (12, [M − CO − AcOH]$^+$), 464 (17, [M − CO − 2 AcOH]$^+$), 122 5, (PhCO$_2$H$^+$), 105 (100, PhCO)$^+$).

Crystal Data of **1**: Crystal size 0.25 × 0.30 × 0.30 mm. C$_{33}$H$_{40}$O$_{11}$; orthorhombic, space group $P2_12_12_1$; a = 11.927 (3), b = 12.139 (5), and c = 22.786 (4) Å; V = 3299 (2) Å^3; CuK_α, λ = 1.54178 Å; Z = 4, $D_{calc.}$ = 1.234 mg/m^3, F (000) = 1304; μ (CuK_α) = 0.768 mm^{-1}.

X-Ray diffraction data were collected at 293 (2) K in the range from 3.5 to 135° ($-12 \le h \le 14$; $-10 \le k \le 1$, $-23 \le l \le 1$) on a *Siemens* single-crystal X-ray diffractometer (P_4-system). Reflections collected, 3445; independent reflections, 3266 (R_{int} = 0.0455). The structure was solved by direct methods with the program SHELXTL (version 5) [7] and refined by full-matrix least-squares on F^2. Anistropic thermal parameters were refined for all the non-H-atoms. All the H-atoms were located in the difference *Fourier* map. The positional and isotropic thermal parameters of the OH H-atom were refined. Riding models were used to place the rest of the H-atoms in their idealized position. In the final least-squares refinement cycles on F^2, the model converged at R_2 = 0.0705, wR_2 = 0.1731, and g.o.f. = 1.041 for the 3445 reflections with $I > \sigma(I)$ and 407 parameters (R indices (all data): R_1 = 0.1174, wR_2 = 0.2387). In the final difference *Fourier* synthesis, the electron density fluctuated in the range of 0.306 to −0.283 eÅ^3 (absolute structure parameter 1.5(7), extinction coefficient). Full crystallography data is deposited at the *Cambridge Crystallographic Data Center*, 12 Union Road, Cambridge CB2 IEZ, U.K.

Cheiradone A (= rel-*(1R,2R,3aS,5R,5aS,6R,9S,9aS,10S,10aS)-9a-(Acetoxymethyl)-1,3,3a,5,5a,6,9,9a,10,10a-decahydro-1,3a,9,10-tetrahydroxy-2,5,11,11-tetramethyl-5,6-(epoxymethano)benz[f]azulen-4(2H)-one 1-Acetate 10-Benzoate*; **2**). M.p. 231°. $[\alpha]_D^{29} = -1.51$ ($c = 0.21$, CHCl$_3$). UV (MeOH): 228, 200. IR: 3550–3500, 3100–2980, 1750–1720, 1705, 1610–1580. EI-MS: 570 (2, M^+), 542 (29, [M − CO]$^+$, 482 (23, [M − CO − AcOH]$^+$), 122 (7, PhCO$_2$H$^+$), 105 (100, PhCO$^+$).

Cheiradone B (= rel-*(1R,2R,3aS,5R,5aS,6R,9S,9aS,10S,10aS)-9a-(Acetoxymethyl)-1,3,3a,5,5a,6,9,9a,10,10a-decahydro-1,3a,9,10-tetrahydroxy-2,5,11,11-tetramethyl-5,6-(epoxymethano)benz[f]azulen-4(2H)-one 9-Acetate 10-Benzoate*; **3**). M.p. 238°. $[\alpha]_D^{29} = -2.46$ ($c = 0.19$, CHCl$_3$). UV (MeOH): 231, 199. IR: 3550, 3100–2980, 1750–1720, 1705, 1610–1580. EI-MS: 570 (1, M^+), 552 (17, [M − H$_2$O]$^+$), 542 (21, [M − CO]$^+$), 482 (27, [M − CO − AcOH]$^+$), 122 (9, PhCO$_2$H$^+$), (100, 105 PhCO$^+$).

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