Pergamon

Tetrahedron Vol. 51, No. 9, pp. 2477-2488, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00018-6

Two New Bioactive Triterpenoids from *Melia volkensii* (Meliaceae)

Lu Zeng, Zhe-ming Gu, Xin-ping Fang, Phillip E. Fanwick,† Ching-jer Chang, David L. Smith, and Jerry L. McLaughlin*

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, †Department of Chemistry, School of Sciences, Purdue University, West Lafayette, IN 47907, U. S. A.

Key Words: Melia volkensii; meliavolin; meliavolkin; brine shrimp lethality; human solid tumor cytotoxicities.

Abstract: Meliavolin (**1**), a new triterpene with an apotirucallane skeleton, and meliavolkin (**2**), a new tetranortriterpene, together with melianin A, a known compound, have been isolated from the root bark of *Melia volkensii* (Meliaceae) by using activity-directed fractionation with brine shrimp. The structures have been elucidated by spectral data. The relative and absolute stereochemistry of meliavolin (**1**) was determined by analysis of Mosher ester derivatives, **1e** and **1f**, and by X-ray crystallographic analysis of meliavolin diacetate, **1c**. **1** and melianin A showed marginal cytotoxicities to certain human tumor cell lines, but **2** was significantly more cytotoxic, showing equivalent potency to adriamycin against the human breast tumor cell line (MCF-7).

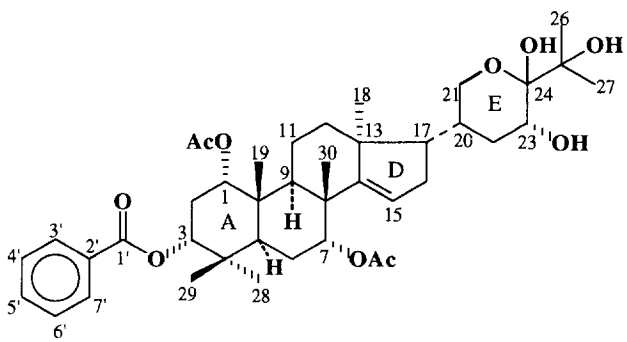
INTRODUCTIONS

Melia volkensii Gurke (Meliaceae) is a subtropical tree which is distributed in the eastern region of Africa. In the local folk medicine, a tea prepared from the bark is used to alleviate pain and is reported to be poisonous in overdoses.[1] The extracts of the seed kernels have been reported to have potential antifeedant activities against locusts.[2] Several limonoids, namely, volkensin, salanin, 1-cinnamoyltrichilinin, 1-tigloyl-trichilinin, and 1-acetyltrichilinin with high antifeedant activity, were isolated from the fruits.[3, 4] In our continuing interest in anticancer agents, the root bark of *M. volkensii*, collected in Kenya, showed bioactivity in our screens and was investigated by fractionations directed by a test for brine shrimp lethality (BST).[5, 6] From the ethanol extracts of the root bark, meliavolin (**1**), a new triterpene with an apotirucallane skeleton, meliavolkin (**2**), a new tetranortriterpene, and melianin A, a known apotirucallane triterpene,[7] have been isolated. The structures have been elucidated by MS, ^{1}H and ^{13}C NMR, COSY, NOESY, HETCOR, and COLOC spectra. The relative and absolute stereochemistry of meliavolin (**1**) was determined by ^{1}H NMR analysis of the Mosher esters, **1e** and **1f**, and by X-ray crystallographic analysis of meliavolin diacetate (**1c**). **1**, **2**, and melianin A

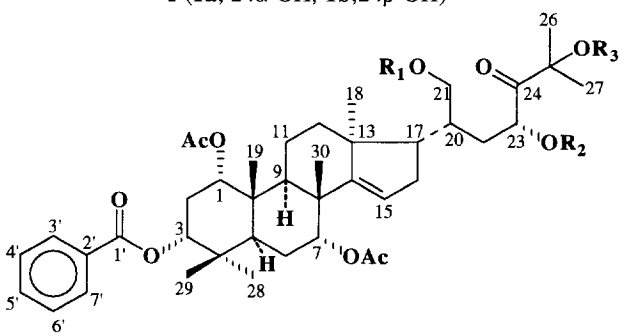
showed cytotoxicities to certain human solid tumor cell lines in culture, with **2** being, by about one order of magnitude, the most active.

RESULTS AND DISCUSSION

Meliavolin (**1**) was isolated as a white powder. The molecular weight of **1** was indicated by a peak at m/z 733 ($M+Na^+$) in the m-nitrobenzyl alcohol (m-NBA) fabms. High resolution fabms gave m/z 733.3919 (calcd. 733.3928) for the $M+Na^+$, corresponding to the formula, $C_{41}H_{58}O_{10}$. The ^1H NMR and ^{13}C NMR spectra of **1** appeared as the equilibrium mixture of anomers, **1a** and **1b**, in the proportion of 6:1 in $CDCl_3$ solution (5 mg/0.6 ml). The hemiacetal carbon signals were observed at δ 95.7 and δ 97.4 in the ^{13}C NMR spectrum of **1**. All other signals appeared as pairs arising from the two anomers (Table 1). The ^1H and ^{13}C NMR spectra of the major anomer **1a** showed signals due to seven tertiary methyls, seven methylenes, one of which is oxygenated, eight methines, four of which are oxygenated, and one trisubstituted double bond, together with two acetates and one benzoate (Table 1). The ^{13}C NMR spectrum of **1a** also showed four quaternary carbon signals, one hydroxytertiary carbon signal, and one hemiacetal signal. These data suggested that **1** is a triterpene with an apotirucallane skeleton. Three oxygenated methines in **1a** appeared at δ 4.70, δ 4.90 and δ 5.19 and were placed at the C-1, 3, and 7 positions based on the observations of cross peaks between C-1 to H-19, C-3



1 (**1a**, 24α-OH, **1b**,24β-OH)



1c	R_1=Ac,	R_2=Ac,	R_3=H
1d	R_1=Ac,	R_2=Ac,	R_3=Ac
1e	R_1=*S*-MTPA,	R_2=*S*-MTPA,	R_3=H
1f	R_1=*R*-MTPA,	R_2=*R*-MTPA,	R_3=H

to H-28 and 29, and C-7 to H-30 in the COLOC spectra *via* J = 7 or 10 Hz. These three protons were concluded to take the equatorial orientation because the coupling constants are of 3 Hz, respectively, and arise from vicinal methylene protons. The NOESY spectrum showed a cross peak between a triplet signal at δ 4.90 (H-3) and a doublet of doublets at δ 8.09 (3', 7'-H) indicating that the benzoate was substituted at the C-3 position. It then followed that the two acetates were substituted at the C-1 and C-7 positions. The cross peaks between C-14 to H-

Table 1. ^{1}H- and ^{13}C-NMR Data of **1a** and **1b**.

	1a					**1b**				
No.	δ_C*		δ_H	Coupling (Hz)	$^{13}C/^1H$ Correlation	δ_C*		δ_H	Coupling (Hz)	$^{13}C/^1H$ Correlation
1	72.7	CH	4.70	t, 3.0	H-19	72.6	CH	4.72	t, 3.0	H-19
2	25.4	CH_2	2.22	td 3.0, 16.0		25.5	CH_2	2.17	td 3.0, 16.0	
			2.30	td 3.0, 16.0				2.30	td 3.0, 16.0	
3	77.1	CH	4.90	t, 3.0	H-28, 29-H	77.1	CH	4.90	t, 3.0	H-28, H-29
4	36.5	C			H-2, H-28, 29-H	36.5	C			H-2, H-28, H-29
5	37.4	CH	2.54	d, 7.5	H-28, 29-H	37.4	CH	2.54	d, 7.5	H-28, H-29
6	22.8	CH_2	1.85	dd, 3.0, 7.5		22.8	CH_2	1.85	dd, 3.0, 7.5	
			1.85	dd, 3.0, 7.5				1.85	dd, 3.0, 7.5	
7	75.5	CH	5.19	t, 3.0	H-30	75.7	CH	5.19	t, 3.0	H-30
8	42.0	C			H-30	42.1	C			H-30
9	35.3	CH	2.66	dd, 6.0, 10.0	H-30	35.2	CH	2.66	dd, 6.0, 10.0	H-30
10	40.2	C			H-19	40.2	C			H-19
11	16.0	CH_2	1.28	m		16.1	CH_2	1.28	m	
			1.48	m				1.48	m	
12	34.7	CH_2	1.46	m	H-18	34.9	CH_2	1.46	m	H-18
			1.62	m				1.62	m	
13	46.4	C			H-15, H-18	46.3	C			H-15, H-18
14	158.9	C			H-18, H-30	159.2	C			H-18, H-30
15	119.3	CH	5.33	br d, 2.5	H-16	119.9	CH	5.37	br d, 2.5	
16	33.8	CH_2	1.96	m		33.8	CH_2	1.96	m	
			2.20	m				2.20	m	
17	56.9	CH	1.41	m	H-15	51.7	CH	2.00	m	H-18
18	20.0	CH_3	1.11	s		20.4	CH_3	1.01	s	
19	16.1	CH_3	1.01	s		16.2	CH_3	1.01	s	
20	29.2	CH	2.18	m		34.1	CH	1.70	m	
21	65.4	CH_2	3.60	t, 11.0		62.0	CH_2	3.60	t, 11.0	
			3.79	dd, 3.0, 11.0				3.90	dd, 2.0, 11.0	
22	32.7	CH_2	1.68	m		32.2	CH_2	1.72	m	
			1.80	m				1.85	m	
23	67.5	CH	3.90	br s $W_{1/2}$ 3.5		64.1	CH	3.96	br s $W_{1/2}$ 3.0	
24	95.7	C			H-21, H-26, H 27	97.4	C			H-21, H-26, H-27
25	76.3	C			H-26, H-27	76.7	C			H-26, H-27
26	23.2	CH_3	1.27	s	H-27	24.1	CH_3	1.31	s	H-27
27	24.1	CH_3	1.41	s	H-26	24.5	CH_3	1.32	s	H-26
28	28.0	CH_3	0.91	s	H-29	28.0	CH_3	0.91	s	H-29
29	21.4	CH_3	1.00	s	H-28	21.4	CH_3	1.00	s	H-28
30	26.9	CH_3	1.13	s		26.7	CH_3	1.18	s	
AcO	169.7	C				169.7	C			
	20.9	CH_3	1.63	s	AcO	21.0	CH_3	1.63	s	AcO
AcO	170.1	C				170.0	C			
	21.0	CH_3	2.06	s	AcO	21.0	CH_3	2.06	s	AcO
1'	165.2	C			H-3', 7'-H	165.2	C			H-3', H-7'
2'	130.6	C			H-4', H-6'	130.6	C			H-4', H-6'
3'	129.4	CH	8.09	dd, 1.5, 8.0		129.4	CH	8.09	dd, 1.5, 8.0	
4'	128.2	CH	7.44	t, 8.0		128.2	CH	7.43	t, 8.0	
5'	133.0	CH	7.58	tt, 1.5, 8.0	H-4'	133.0	CH	7.57	tt, 1.5, 8.0	H-4'
6'	128.2	CH	7.44	t, 8.0		128.2	CH	7.43	t, 8.0	
7'	129.4	CH	8.09	dd, 1.5, 8.0		129.4	CH	8.09	dd, 1.5, 8.0	

*The assignments are made by DEPT, COSY, HETCOR, COLOC *via* J = 7 and 10 Hz.

18 and H-30 and between C-15 to H-16 in the COLOC spectrum indicated that the double bond was located between C-14 and C-15. The chemical shift value of the olefinic proton appeared at δ 5.33 and also indicated that the hydroxyl at C-7 was replaced by an acetate.[8] All of these data suggested that **1** is a 1α, 7α-diacetoxy, 3α-benzoxy-apotirucall-14 (15)-ene with a 17α side chain.

The structure of the side chain was determined by analysis of the COLOC spectra of **1**. One oxymethylene proton at δ 3.79 (H-21) showed a cross peak to a hemiacetal carbon at δ 95.7 (C-24) for the major anomer (**1a**), which indicated that there is an ether bridge across the oxymethylene and hemiacetal. Two methyls in the 2-hydroxyisopropyl group, which appeared at δ 1.27 (H-26) and δ 1.41 (H-27), also showed cross peaks to the hemiacetal carbon at δ 95.7 (C-24), and this suggested that the 2-hydroxyisopropyl group is connected to the hemiacetal. Treatment of **1** with acetic anhydride in pyridine gave one keto diacetate derivative (**1c**) and one keto triacetate derivative (**1d**) (Figure 1). The carbonyl group (C-24) in **1c** was indicated by a carbonyl carbon signal at δ 211.3 in the ^{13}C NMR spectra. In the COSY spectrum of **1c**, the acetoxymethylene protons at δ 3.89

Table 2. ^{1}H NMR Data of **1c-1f**.

	1c		**1d**		**1e*** (*S*-MTPA)		**1f**** (*R*-MTPA)		Δδ
No.	δ_H	Coupling in Hz	δ_H	Coupling in Hz	δ_H	Coupling in Hz	δ_H	Coupling in Hz	(δ_{1e}-δ_{1f})***
1	4.69	t, 3.0	4.68	t, 3.0	4.69	t, 2.5	4.65	t, 2.5	+0.04
2	2.18	td, 3.0, 16.0	2.18	td, 3.0, 16.0	2.18	td, 2.5, 16.0	2.18	td, 2.5, 16.0	
	2.30	td, 3.0, 16.0	2.29	td, 3.0, 16.0	2.29	td, 2.5, 16.0	2.29	td, 2.5, 16.0	
3	4.90	t, 3.0	4.90	t, 3.0	4.90	t, 2.5	4.90	t, 2.5	
5	2.54	dd, 6.5, 8.5	2.54	dd, 6.5, 9.5	2.53	dd, 6.5, 9.0	2.50	dd, 6.0, 9.5	+0.03
6	1.85	dd, 3.0, 6.5	1.85	dd, 3.0, 6.5	1.85	dd, 3.0, 6.5	1.80	dd, 3.0, 6.0	+0.05
	1.85	dd, 3.0, 8.5	1.85	dd, 3.0, 9.5	1.85	dd, 3.0, 9.0	1.80	dd, 3.0, 9.5	+0.05
7	5.19	t, 3.0	5.19	t, 3.0	5.17	t, 3.0	5.15	t, 3.0	+0.02
9	2.65	dd, 6.0, 11.0	2.65	dd, 7.0, 11.5	2.62	dd, 5.5, 11.5	2.55	dd, 6.5, 12.0	+0.07
11	1.26	m	1.27	m	1.26	m	1.10	m	+0.16
	1.48	m	1.50	m	1.42	m	1.25	m	+0.17
12	1.65	m	1.60	m	1.44	m	1.30	m	+0.14
	1.75	m	1.70	m	1.50	m	1.38	m	+0.12
15	5.36	br d, 3.0	5.35	br d, 3.0	5.29	br d, 2.0	5.25	br d, 3.0	+0.04
16	2.00	m	2.04	m	1.92	m	1.90	m	+0.02
	2.35	ddd, 3.0, 8.0, 15.0	2.31	ddd, 3.0, 8.0, 15.0	2.28	m	2.25	m	+0.03
17	1.80	m	1.75	m	1.75	m	1.58	m	+0.17
18	1.15	s	1.14	s	1.10	s	0.91	s	+0.19
19	1.00	s	1.00	s	1.00	s	0.98	s	+0.02
20	2.03	m	1.94	m	2.15	m	1.95	m	+0.20
21	3.89	dd, 6.0, 11.5	3.86	dd, 5.5, 11.5	4.09	dd, 6.0, 11.5	3.93	dd, 4.5, 11.0	+0.16
	4.28	dd, 2.5, 11.5	4.25	dd, 3.5, 11.5	4.57	dd, 3.0, 11.5	4.12	dd, 3.0, 11.0	+0.45
22	1.75	m	1.73	m	1.68	m	1.68	m	
	1.90	td, 3.5, 16.0	2.05	m	2.12	m	2.00	m	+0.12
23	5.62	dd, 3.5, 9.5	5.57	dd, 4.5, 8.5	5.82	dd, 3.0, 9.5	5.74	dd, 3.0, 10.0	+0.08
26	1.40	s	1.53	s	1.27	s	1.39	s	-0.12
27	1.44	s	1.61	s	1.42	s	1.48	s	-0.06
28	0.91	s	0.90	s	0.91	s	0.91	s	
29	0.99	s	0.99	s	1.00	s	0.99	s	+0.01
30	1.08	s	1.07	s	1.03	s	1.01	s	+0.02
AcO	1.65	s	1.64	s	1.67	s	1.66	s	+0.01
	2.07	s	2.07	s	2.06	s	2.05	s	+0.01
	2.07	s	2.07	s					
	2.08	s	2.08	s					
			2.08	s					
3'	8.09	dd, 1.5, 8.0	8.09	dd, 1.5, 8.0	8.09	dd, 1.5, 8.0	8.09	dd, 1.5, 8.0	
4'	7.43	t, 8.0	7.43	t, 8.0	7.44	m	7.44	m	
5'	7.57	tt, 1.5, 8.5	7.57	tt, 1.5, 8.5	7.58	tt, 1.5, 8.5	7.58	tt, 1.5, 8.5	
6'	7.43	t, 8.0	7.43	t, 8.0	7.44	m	7.44	m	
7'	8.09	dd, 1.5, 8.0	8.09	dd, 1.5, 8.0	8.09	dd, 1.5, 8.0	8.09	dd, 1.5, 8.0	

*For MTPA signals: 3.46, 3.49 (each 3H, s, MeO), 7.40-7.50 (10 H, m, phenyl protons). **For MTPA signals: 3.46, 3.60 (each 3H, s, MeO), 7.38-7.52 (10 H, m, phenyl protons). ***Only chemical shift changes are listed in this column.

(H-21) and δ 4.28 (H-21) showed cross peaks to the methine proton at δ 2.03 (H-20). This methine proton also showed cross peaks to methylene protons at δ 1.75 (H-22) and δ 1.90 (H-22) which were further connected to an acetoxymethine at δ 5.26 (H-23) through a cross peak. This comparatively low field acetoxymethine was obviously influenced by an adjacent carbonyl. Therefore, the structure of the side chain of **1** was determined as a 2-hydroxy-2-(2-hydroxyisopropyl)-3-hydroxy-5-substituted tetrahydropyran (shown as E in structure **1**), in which C-5 of the tetrahydropyran ring is connected to the core of the molecule.

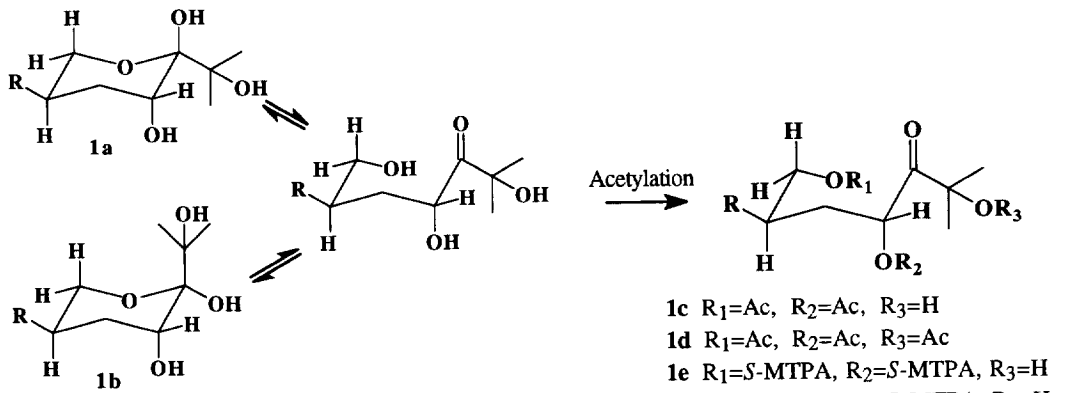


Figure 1. Anomer formation and acetylation of E ring of **1**.

Two kinds of chair ring conformers are possible for the E ring of **1**, and they are illustrated in Figure 2 as form-I and form-II based on the ^{1}H NMR data of H-20 and H-21. The oxygenated methylene protons for H-21 at δ 3.60 and δ 3.79 showed a large coupling constant J = 11.0 Hz; irradiation of one of the protons at δ 3.79, leaving the other one at δ 3.60 remain as a doublet with a large coupling constant J = 11.0 Hz, indicated that the H-20 proton and one of the H-21 protons assume an axial orientation. The hydroxyl at C-23 was placed axially since the proton attached to the same carbon appeared as a broad singlet. All these data suggested that **1** either has the form-I with C-20*S* and C-23*R* configurations or the form-II with C-20*R* and C-23*S* configurations (Figure 2). X-ray crystallographic data subsequently confirmed that **1c** has the configurations either as C-23*R* and C-20*S* or C-23*S* and C-20*R* (Figure 3).

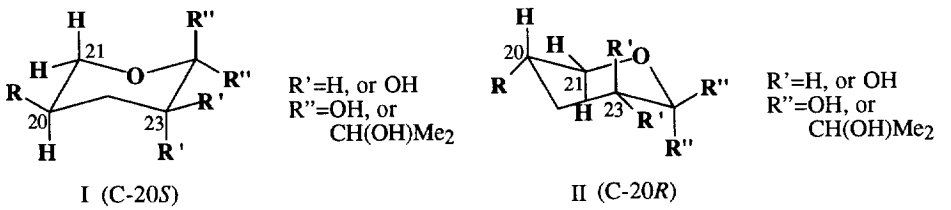


Figure 2. Two possible conformations for E ring of **1**.

Recently, a modified Mosher methodology, developed by Ohtani and co-workers, has been successfully applied to the determination of the absolute configuration of stereogenic centers bearing a hydroxyl group.[9-11] The method, using *S*- and *R*- Mosher esters [(methoxy-(trifluoromethyl)-phenyl acetate or MTPA] introduces

more shielded effects or less shielded effects on different substituents of the chiral carbon, and the chemical shifts of the ^{1}H NMR spectra of these substituents change accordingly. Following Ohtani's procedure, **1** was treated with *R*- and *S*-methoxy-(trifluoromethyl)-phenylacetyl chloride to give the *S*- and *R*-Mosher esters, **1e** and **1f**. The chemical shifts of the *S*-MTPA ester (**1e**) and the *R*-MTPA ester (**1f**) were assigned by careful analysis of the COSY spectra and showed $\Delta\delta_H(\delta_S\text{-}\delta_R)$ changes of the core side to the 2-hydroxyisopropyl side, from positive to negative (Table 2), which indicated that the C-23 was of the *R*-configuration. Thus, the E-ring of **1** has the form-I conformation. Consequently, the structure of **1a** is 1α, 7α-diacetoxy-3α-benzoxy-17α-20*S*-21, 24-epoxy-apotirucall-14(15)-ene-23*R*, 24α,25-triol; **1b** is 1α, 7α-diacetoxy-3α-benzoxy-17α-20*S*-21, 24-epoxy-apotirucall-14(15)-ene-23*R*, 24β,25-triol; and **1c** is 1α, 7α, 21, 23*R*-tetra-acetoxy-3α-benzoxy-17α-20*S*-apotirucall-14(15)-ene-25-ol. It is of interest that melianin A, which was isolated from the same plant, has a different E-ring conformation from that of **1**. Melianin A has a form-II conformation, in whose structure a proton is substituted at C-24 instead of a hydroxyl.

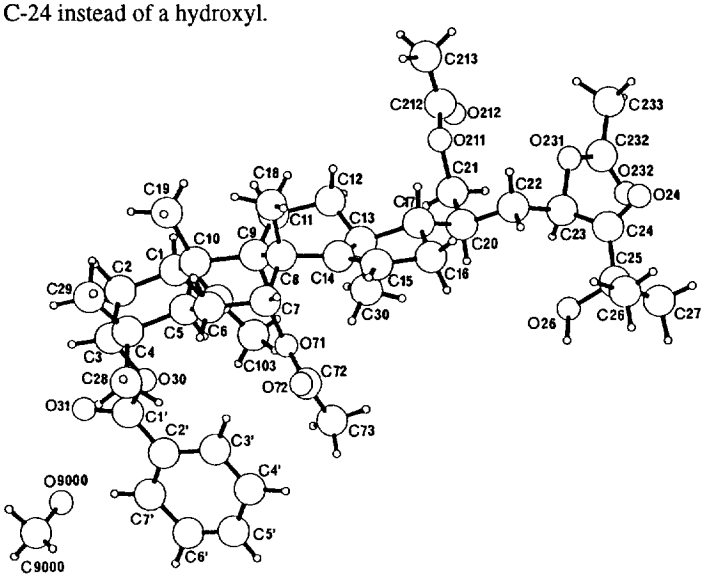
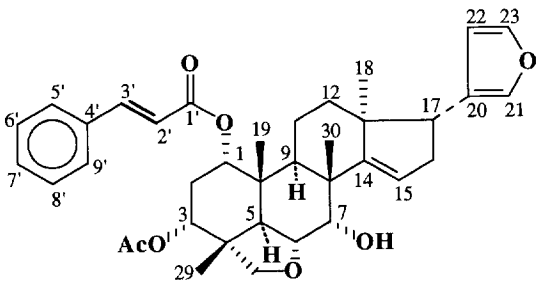


Figure 3. ORTEP plot of meliavolin diacetate (**1c**).

Meliavokin (**2**) was also isolated as a white powder. The molecular weight of **2** was indicated by a peak at m/z 601 ($M+H^+$) in the m-NBA fabms. High resolution fabms gave m/z 601.3173 (calcd. 601.3165) for the $M+H^+$, corresponding to the formula, $C_{37}H_{42}O_7$. The ^{1}H NMR spectrum showed the signals of four methyls, one oxygenated methylene, four methylenes, four oxygenated methines, three methines, one olefinic proton, and one 3-substituted furan ring, as well as the signals of one acetoxyl methyl, two trans olefinic protons, and a phenyl ring of a cinnamoyl group. These ^{1}H NMR data suggested that **2** is a tetranortriterpene substituted with an acetoxyl and a cinnamoyl group. In the COSY spectrum of **2**, a correlation between a doublet at δ 2.87 (H-5) and a doublet of doublets at δ 4.21 (H-6) was observed, and the latter was further correlated to a doublet at δ 4.25 (H-7); a correlation between a triplet at δ 4.82 (H-1) and two methylene protons at δ 2.20, δ 2.26 (H-2) was also observed, and these methylenes further correlated to another triplet at δ 4.96 (H-3). In the COLOC spectra *via J* = 7 or 10 Hz, one hydroxymethine at δ 72.8 (C-7) showed correlation to a methyl singlet at δ 1.14 (H-30); one



2

oxygenated methine at δ 72.1 (C-1) showed correlation to a methyl singlet at δ 1.05 (H-19); and one oxygenated methine at δ 71.7 (C-3) showed correlation to a methyl singlet at δ 1.24 (H-29). These observations demonstrated that the oxygenated carbons were located at the C-1, 3, 6, and 7 positions. The chemical shift of the olefinic proton at δ 5.63 showed that the C-7 has a free hydroxyl since acetylation of a 7α hydroxyl will cause a distinct upfield shift.[12, 13] A NOESY experiment showed a cross peak between one of the double bond protons of the cinnamoyl group to the oxygenated methine proton at the C-1 position; thus, the cinnamoyl group was placed at the C-1 position. The resulting structure of meliavolkin is as illustrated for **2**.

Table 3. ^{1}H- and ^{13}C- NMR Data of **2**.

No.	δ_C*		δ_H	Coupling, Hz	$^{13}C/^{1}H$ Correlation	No.	δ_C*		δ_H	Coupling, Hz	$^{13}C/^{1}H$ Correlation
1	72.1	CH	4.82	t, 3.0	H-19	19	15.3	CH_3	1.05	s	H-5
2	27.5	CH_2	2.20	td, 3.0, 16.0		20	124.3	C			H-21
			2.26	td, 3.0, 16.0		21	139.6	CH	7.20	br s	
3	71.7	CH	4.96	t, 3.0	H-29	22	110.9	CH	6.20	dd, 1.0, 1.5	H-23
4	42.4	C			H-5, H-29	23	142.4	CH	7.34	t, 1.5	H-22
5	39.6	CH	2.87	d, 7.5	H-19, H-29	28	77.8	CH_2	3.62	d, 7.5	H-29
6	73.9	CH	4.21	dd, 3.0, 7.5	H-5				3.69	d, 7.5	
7	72.8	CH	4.25	d, 3.0	H-30	29	19.5	CH_3	1.24	s	H-5
8	45.9	C			H-30	30	26.3	CH_3	1.14	s	
9	33.5	CH	2.69	dd, 6.5, 12.5	H-19, H-30	AcO	170.2	C			AcO
10	39.5	C			H-19		21.9	CH_3	1.88	s	
11	15.1	CH_2	1.40	m		1'	165.4	C			H-2'
			1.62	m		2'	117.8	CH	6.37	d, 16.5	
12	32.70	CH_2	1.54	m	H-18	3'	145.6	CH	7.74	d, 16.5	H-2'
			1.78	dd, 6.5, 12.5		4'	124.3	C			H-3'
13	47.3	C			H-15, H-18	5'	128.9	CH	7.36	dd, 1.0, 8.0	
14	160.1	C			H-18, H-30	6'	127.9	CH	7.44	dd, 1.5, 8.0	H-7'
15	120.5	CH	5.63	dd, 3.5, 1.5	H-16	7'	130.4	CH	7.38	m	
16	34.2	CH_2	2.40	ddd, 3.5, 6.5, 15.5		8'	127.9	CH	7.44	dd, 1.5, 8.0	H-7'
17	51.5	CH	2.55	ddd, 3.5, 6.5, 15.5	H-15, H-18	9'	128.9	CH	7.36	dd, 1.0, 8.0	
18	20.7	CH_3	0.74	s							

*The assignments are made by DEPT, COSY, HETCOR, COLOC *via J* = 7 and 10 Hz.

Meliavolin (**1**), meliavolkin (**2**), and melianin A were significantly active in the brine shrimp test (**1**, BST LC_{50} 0.34 μg/ml; **2**, BST LC_{50} 1.83 μg/ml; melianin A BST LC_{50} 1.83 μg/ml), and they were marginally cytotoxic against human tumor cell lines [**1**, ED_{50} 11.25, 5.34, and 0.95 μg/ml, **2**, ED_{50} 0.57, 0.26, and 0.12 μg/ml, and melianin A, ED_{50} 6.65, 3.61, and 2.31 μg/ml in A-549 (human lung carcinoma),[14] MCF-7 (human breast carcinoma),[15] and HT-29 (human colon adenocarcinoma)[16] cells, respectively. Adriamycin, as a positive

control, gave ED_{50} values of 1.54 x 10^{-2}, 2.49 x 10^{-1}, and 3.99 x 10^{-2} μg/ml, respectively, when compounds **1**, **2** and melianin A were tested in the same run]. Thus, **2** was the most active and even showed cytotoxic activity equivalent to that of adriamycin against the human breast tumor cell line (MCF-7). Compounds showing cytotoxic ED_{50} values less than 4 μg/ml are considered significantly active in the search for new antitumor drugs; however, borderline cytotoxicity may be an indication of other useful bioactivities.

EXPERIMENTAL

General Experimental Procedures. Mps were determined on a Mettler FP5 hot-stage apparatus and are uncorrected. The optical rotations were determined on a Perkin-Elmer 241 polarimeter. UV spectra were taken in MeOH on a Beckman DU-7 spectrophotometer. Low resolution MS were recorded on a Finnigan 4000 mass spectrometer. The exact masses were determined on a Kratos 50 mass spectrometer through peak matching. All of the 1D and 2D NMR spectra were recorded on a Varian VXR-500S spectrometer, using Varian software systems. HPLC was performed on a Dynamax software system (Rainin Instrument Company, Inc.), a Rainin HPXL solvent delivery system (2 Rainin HPXL pumps), a Dynamax UV-1 variable wavelength detector which was set at 284 nm, Dynamax-60 A 8 μm silica gel columns (a 21.4 mm I. D. x 250 mm column and a 10 mm, I. D. x 250 mm column for separations and a 4.6 mm I. D. x 250 mm column for purity determinations). Either hexane-ethyl acetate (15:1) or hexane-MeOH-THF (10:0.9:0.1) were used as mobile phases. *R*- and *S*-Methoxy-(trifluoromethyl)-phenylacetyl chloride are Aldrich products.

Plant Material. The root bark of M. *volkensii* (B-644035, BRS-2-193) was collected in Kenya for the Natural Cancer Institute, under the auspices of Dr. Robert E. Perdue, Medicinal Plant Laboratory, U. S. D. A., Beltsville, Maryland, where voucher specimens are maintained.

Bioassays. The extracts, fractions, and compounds isolated from the title plant were routinely evaluated for lethality to brine shrimp larvae (BST).[5, 6] The cytotoxicity tests against A-549 (human lung carcinoma),[14] MCF-7 (human breast carcinoma),[15] and HT-29 (human colon adenocarcinoma)[16] cells were performed at the Purdue Cell Culture Laboratory, Purdue Cancer Center, using standard protocols (7-day runs, MTT determinations) with adriamycin as a positive standard control.

Extraction and Isolation. The crude residue (502 g) of the 95% EtOH extract of 10 kg of the root bark of the title plant was partitioned between H_2O and CH_2Cl_2 to give a H_2O layer and a CH_2Cl_2 layer; the residue of the CH_2Cl_2 layer was further partitioned between hexane and 10% H_2O in MeOH to give a MeOH layer (*ca.* 160 g dry residue) and a hexane layer. The MeOH residue was repeatedly chromatographed over silica gel columns, directed by BST activity, using gradients of hexane-CH_2Cl_2, CH_2Cl_2, CH_2Cl_2-ethyl acetate and then purified by HPLC to give colorless prisms of melianin A (40 mg), a white powder of **1** (25 mg), and a white powder of **2** (60 mg).

***Meliavolin* (1).** White powder, $[\alpha]^{22}_D$ - 39.1 (c 0.58 in $CHCl_3$); uv λ_{max} (MeOH): 208 nm (log ε 3.45), 228 nm (log ε 3.95); ir ν_{max} (film) cm^{-1}: 3464, 2953, 1717, 1278, 1046; fabms (m-NBA) m/z (%): 733 ($M+Na^+$), 693 ($M+Na^+-H_2O$, 28), 675 ($M+Na^+-2xH_2O$, 100), 630 (70), 553 ($M+Na^+-2xH_2O$-PhCOOH, 5), 551 (10), 469 (50); hrfabms (m-NBA) m/z: 733.3919 for $C_{41}H_{58}O_{10}$ Na ($M+Na^+$) calcd. 733.3928; ^1H and ^{13}C NMR (see Table l); COSY (500 MHz, nt 16, ni 256, d1 3.0, 2K x 2K); NOESY (500 MHz, nt 16, ni 340, mix 0.04 sec, dm 'nnn', 2K x 2K); HETCOR (125 MHz, nt 32, ni 256, d1 2.0, j1xh 150, 4 K x 4 K); COLOC (same as HETCOR, jnxh 7.0 or 10.0).

***Meliavolin Diacetate* (1c) and *Meliavolin Triacetate* (1d).** Compound **1** (15 mg) was acetylated by Ac_2O-pyridine, 24 h, room temp., and the mixture was partitioned between water and $CHCl_3$. The $CHCl_3$ extract was concentrated and purified by HPLC using hexane-ethyl acetate (12:1) as a mobile phase to afford **1c** (10 mg) and **1d** (2 mg).

1c. Colorless prisms, mp 164-165°C, ir ν_{max} (film) cm^{-1}: 3502, 2952, 1732, 1718, 1246, 1047; fabms (m-NBA) m/z (%): 817 ($M+Na^+$, 90), 795 (MH^+, 10), 749 (60), 735 (44), 675 (100), 613 (75), 553 (MNa^+-2xAcOH-PhCOOH, 95); ^1H NMR (see Table 1); ^{13}C NMR (125 MHz) δ 16.10 (C-11), 16.16 (C-18), 19.51 (AcO), 20.55 (C-19), 20.89 (AcO), 21.05 (AcO), 21.46 (C-29), 21.46 (AcO), 22.83 (C-6), 25.46 (C-2), 26.85 (C-30), 27.37 (C-27), 27.68 (C-26), 28.04 (C-28), 31.21 (C-22), 34.24 (C-16), 34.82 (C-12), 35.33 (C-9), 36.52 (C-4), 36.59 (C-20), 37.44 (C-5), 40.30 (C-10), 42.15 (C-8), 46.54 (C-13), 55.35 (C-17), 65.45 (C-21), 72.59 (C-1), 73.41 (C-23), 75.47 (C-7), 77.02 (C-3), 77.45 (C-25), 119.25 (C-15), 128.28 (C-4'), 128.28 (C-6'), 129.51 (C-3'), 129.51 (C-7'), 130.76 (C-2'), 133.00 (C-5), 159.36 (C-14), 165.22 (C-1'), 169.68 (AcO), 169.98 (AcO), 170.74 (AcO), 171.06 (AcO), 211.33 (C-24); COSY (500 MHz, nt 16, ni 256, d1 3.0, 2K x 2K).

1d. White powder, ^1H NMR (see Table 1).

Table 4. Atomic Fractional Co-ordinates of **1c** with esds in Parentheses and Equivalent Isotopic Atomic Displacement Factors.

Atom	x	y	z	B(Å²)	Atom	x	y	z	B(Å²)
C(1)	0.793(1)	0.5985(9)	0.3224(6)	4.0(4) *	C(72)	0.623(2)	0.929(1)	0.2851(7)	5.8(5) *
C(2)	0.836(2)	0.5854(9)	0.3786(6)	3.9(4) *	C(73)	0.735(2)	0.966(1)	0.2621(7)	6.1(5) *
C(3)	0.834(2)	0.6603(9)	0.4137(6)	4.0(4) *	C(102)	0.976(2)	0.607(1)	0.2688(7)	5.4(5) *
C(4)	0.712(1)	0.7030(9)	0.4133(6)	3.8(4) *	C(103)	1.051(2)	0.660(1)	0.2416(7)	5.0(5) *
C(5)	0.667(1)	0.7153(9)	0.3542(6)	3.6(4) *	C(212)	0.601(3)	0.549(2)	0.011(1)	11.6(8) *
C(6)	0.552(1)	0.7678(9)	0.3485(6)	3.8(4) *	C(213)	0.494(2)	0.498(1)	0.015(1)	10.0(7) *
C(7)	0.535(1)	0.7968(9)	0.2947(6)	3.7(4) *	C(232)	0.634(2)	0.719(1)	-0.1188(9)	8.8(7) *
C(8)	0.538(1)	0.7296(8)	0.2542(6)	2.5(3) *	C(233)	0.599(2)	0.646(1)	-0.1493(9)	9.7(7) *
C(9)	0.646(1)	0.6739(9)	0.2617(6)	3.1(4) *	C(1')	1.034(1)	0.7219(9)	0.4056(6)	3.5(4) *
C(10)	0.669(1)	0.6422(9)	0.3187(6)	2.9(4) *	C(2')	1.104(1)	0.7863(9)	0.3827(6)	3.6(4) *
C(11)	0.660(2)	0.611(1)	0.2193(7)	4.5(4) *	C(3')	1.054(2)	0.829(1)	0.3397(6)	4.7(4) *
C(12)	0.622(1)	0.6375(9)	0.1629(6)	3.7(4) *	C(4')	1.116(2)	0.893(1)	0.3184(8)	6.8(6) *
C(13)	0.617(1)	0.7268(9)	0.1568(6)	3.3(4) *	C(5')	1.233(2)	0.911(1)	0.3375(8)	6.7(6) *
C(14)	0.537(1)	0.7665(9)	0.1990(6)	3.4(4) *	C(6')	1.279(2)	0.870(1)	0.3745(7)	6.6(5) *
C(15)	0.472(2)	0.826(1)	0.1775(7)	4.7(4) *	C(7')	1.218(2)	0.806(1)	0.3999(7)	5.3(5) *
C(16)	0.492(2)	0.838(1)	0.1200(7)	5.5(5) *	O(30)	0.920(1)	0.7186(6)	0.3905(4)	4.7(3) *
C(17)	0.545(1)	0.7545(9)	0.1042(6)	3.7(4) *	O(31)	1.077(1)	0.6753(7)	0.4378(5)	6.9(4) *
C(18)	0.744(2)	0.764(1)	0.1574(7)	4.3(4) *	O(101)	0.8810(9)	0.6451(6)	0.2930(4)	3.6(2) *
C(19)	0.572(2)	0.578(1)	0.3343(6)	4.5(4) *	O(102)	0.988(1)	0.5351(7)	0.2751(4)	5.7(3) *
C(20)	0.613(2)	0.7581(9)	0.0533(7)	4.7(5)	O(24)	0.466(1)	0.8679(8)	-0.1062(5)	6.8(3) *
C(21)	0.671(2)	0.677(1)	0.0355(7)	5.5(5) *	O(26)	0.665(1)	0.9420(7)	-0.0099(5)	8.3(4)
C(22)	0.529(2)	0.789(1)	0.0090(6)	4.7(5)	O(71)	0.6397(9)	0.8460(6)	0.2817(4)	3.2(2) *
C(23)	0.590(2)	0.801(1)	-0.0449(7)	5.3(5)	O(72)	0.538(1)	0.9566(9)	0.3042(6)	9.6(4) *
C(24)	0.542(2)	0.874(1)	-0.0723(7)	5.1(5)	O(211)	0.574(1)	0.6193(7)	0.0352(5)	5.8(3) *
C(25)	0.585(2)	0.954(1)	-0.0554(7)	7.1(6)	O(212)	0.690(2)	0.541(1)	-0.0112(6)	11.4(5) *
C(26)	0.667(2)	0.982(1)	-0.1004(9)	10.1(8)	O(231)	0.567(1)	0.7281(7)	-0.0759(5)	5.6(3) *
C(27)	0.492(2)	1.010(1)	-0.045(1)	9.7(8)	O(232)	0.703(1)	0.7697(8)	-0.1333(5)	8.5(4) *
C(28)	0.625(2)	0.655(1)	0.4451(7)	6.4(5) *	O(9000)	0.775(2)	0.927(1)	0.5591(7)	12.5(6) *
C(29)	0.728(2)	0.782(1)	0.4400(7)	6.1(5) *	C(9000)	0.747(4)	0.973(2)	0.605(1)	19(1) *
C(30)	0.411(2)	0.684(1)	0.2564(6)	4.2(4) *					

Starred atoms were refined isotropically. Anisotropically refined atoms are given in the form of the isotropic equivalent temperature factor defined as: $(4/3) * [a^2*\beta(1,1) + b^2*\beta(2,2) + c^2*\beta(3,3) + ab(\cos\gamma)*\beta(1,2) + ac(\cos\beta)*\beta(1,3) + bc(\cos\alpha)*\beta(2,3)]$

***X-Ray Crystallographic Analysis of Meliavolin Diacetate* (1c).** Crystals were obtained as transparent prisms by recrystallization from MeOH.

Crystal Data. $C_{45}H_{62}O_{12} \cdot MeOH$, M = 827.03. Orthorhombic, a = 10.9683 (8) Å, b = 16.702 (1) Å, c = 25.333 (3) Å, V = 4640 (1) Å^3, (by least-squares refinement, using the setting angles of 20 reflections in the range $18 < \theta < 25°$, measured by the computer-controlled diagonal slit method of centering), λ (Mo-Kα) = 1.54184 Å, space group $P2_12_12_1$ (No. 19), Z = 4, Dx = 1.184 g cm^{-3}. Crystal dimensions 0.25 x 0.20 x 0.08 mm, λ (Mo-Kα) = 6.66 cm^{-1}.

Data Collection and Processing. Enraf-Nonius CAD4 diffractometer, $\omega/2\theta$ mode with ω scan width = 0.67 + 0.31 tan θ, 2θ range 5.32-121.70 deg, take-off angle 6.00 deg, scan rate 1-16 deg min^{-1}, graphite monochromated radiation; 3984 reflections measured (*h, k, l* limits: -12 to 0, -18 to 0, -28 to 0), 3984 unique, giving 1376 with $I > 3.0\sigma(I)$. Corrections were applied for Lorentz and polarization factors, but not for absorption.

Table 5. Bond Angles in Degrees for **1c** with esds in Parentheses*.

Atoms	Angle	Atoms	Angle	Atoms	Angle
C(1)-O(101)-C(102)	119(1)	C(12)-C(13)-C(17)	113(1)	C(3')-C(4')-C(5')	119(2)
C(1)-C(10)-C(9)	111(1)	C(12)-C(13)-C(14)	112(1)	C(4')-C(5')-C(6')	120(2)
C(1)-C(10)-C(5)	111(1)	C(12)-C(13)-C(18)	112(2)	C(5')-C(6')-C(7')	124(2)
C(1)-C(10)-C(18)	105(1)	C(13)-C(17)-C(20)	118(2)	O(101)-C(1)-C(2)	111(1)
C(2)-C(1)-C(10)	113(2)	C(13)-C(14)-C(8)	117(1)	O(101)-C(1)-C(10)	108(1)
C(3)-O(30)-C(1')	122(2)	C(14)-C(13)-C(18)	110(1)	O(101)-C(102)-O(102)	119(2)
C(3)-C(4)-C(5)	110(2)	C(14)-C(8)-C(30)	103(1)	O(101)-C(102)-C(102)	112(2)
C(3)-C(4)-C(28)	108(2)	C(15)-C(14)-C(13)	110(2)	O(102)-C(102)-C(102)	129(2)
C(3)-C(4)-C(29)	108(2)	C(15)-C(14)-C(8)	132(2)	O(211)-C(21)-C(20)	107(2)
C(3)-C(2)-C(1)	115(2)	C(16)-C(17)-C(13)	103(1)	O(211)-C(212)-O(212)	121(4)
C(4)-C(3)-C(2)	113(2)	C(16)-C(17)-C(20)	112(2)	O(211)-C(212)-C(213)	107(3)
C(4)-C(5)-C(6)	115(2)	C(16)-C(15)-C(14)	115(2)	O(212)-C(212)-C(213)	132(4)
C(4)-C(5)-C(10)	117(1)	C(17)-C(13)-C(14)	100(1)	O(231)-C(23)-C(22)	107(2)
C(5)-C(4)-C(28)	112(2)	C(17)-C(13)-C(18)	110(1)	O(231)-C(23)-C(24)	111(2)
C(5)-C(4)-C(29)	110(2)	C(17)-C(20)-C(22)	110(2)	O(231)-C(232)-O(232)	122(3)
C(5)-C(10)-C(19)	113(1)	C(17)-C(20)-C(21)	115(2)	O(231)-C(232)-C(233)	112(3)
C(6)-C(7)-C(8)	113(1)	C(17)-C(16)-C(15)	100(2)	O(232)-C(232)-C(233)	125(3)
C(6)-C(5)-C(10)	114(1)	C(21)-O(211)-C(212)	115(2)	O(24)-C(24)-C(23)	121(2)
C(7)-O(71)-C(72)	116(2)	C(20)-C(22)-C(23)	116(2)	O(24)-C(24)-C(25)	120(2)
C(7)-C(6)-C(5)	113(2)	C(22)-C(20)-C(21)	109(2)	O(26)-C(25)-C(24)	107(2)
C(7)-C(8)-C(9)	113(1)	C(22)-C(23)-C(24)	112(2)	O(26)-C(25)-C(26)	106(3)
C(7)-C(8)-C(14)	109(1)	C(23)-O(231)-C(232)	116(2)	O(26)-C(25)-C(27)	112(2)
C(7)-C(8)-C(30)	108(1)	C(23)-C(24)-C(25)	119(2)	O(30)-C(3)-C(4)	104(1)
C(9)-C(10)-C(5)	106(1)	C(24)-C(25)-C(26)	104(2)	O(30)-C(3)-C(2)	107(1)
C(9)-C(10)-C(19)	111(1)	C(24)-C(25)-C(27)	115(3)	O(30)-C(1')-O(31)	122(2)
C(9)-C(8)-C(14)	111(1)	C(26)-C(25)-C(27)	111(2)	O(30)-C(1')-C(2')	115(2)
C(9)-C(8)-C(30)	113(1)	C(28)-C(4)-C(29)	108(2)	O(31)-C(1')-C(2')	123(2)
C(10)-C(9)-(8)	117(1)	C(1')-C(2')-C(3')	119(2)	O(71)-C(7)-C(6)	107(1)
C(11)-C(12)-C(13)	113(2)	C(1')-C(2')-C(7')	122(2)	O(71)-C(7)-C(8)	104(1)
C(11)-C(9)-C(10)	114(1)	C(2')-C(3')-C(4')	120(2)	O(71)-C(72)-O(72)	122(2)
C(11)-C(9)-C(8)	115(2)	C(2')-C(7')-C(6')	118(2)	O(71)-C(72)-C(73)	106(2)
C(12)-C(11)-C(9)	116(2)	C(3')-C(2')-C(7')	119(2)	O(72)-C(72)-(73)	131(2)

*Numbers in parentheses are estimated standard deviations in the least significant digits

Structure Analysis and Refinement. The structure was solved by direct methods using SHELX-86. The remaining atoms were located in succeeding difference Fourier syntheses. Hydrogen atoms were located and added to the structure factor calculations, but their positions were not refined. The structure was refined in full-matrix least-squares where the function minimized was $\sum w(|Fo|-|Fc|)^2$ and the weight w is defined as per the Killean and Lawrence method with terms of 0.02 and 1.0.[17] Scattering factors were taken from Cromer and Waber.[18] Anomalous dispersion effects were included in Fc;[19] the values for $\delta f'$ and $\delta f''$ were those of Cromer and Waber.[18] Only the 1376 reflections having intensities greater than 3.0 times their standard deviation were used in the refinements. The final cycle of refinement included 277 variable parameters and converged with unweighted and weighted agreement factors R = 0.085, and R_W = 0.096. The standard deviation of an observation of unit weight was 1.98. There were no correlation coefficients >0.50. Plots of $\sum w(|Fo|-|Fc|)^2$ *versus* [Fo], reflection order in data collection, sin θ/λ, and various classes of indices showed no unusual trends. All calculations were performed on a VAX computer using SDP/VAX.

1d. White powder, ^{1}H NMR (see Table 1); COSY (500 MHz, nt 16, ni 256, d1 3.0, 2K x 2K).

Table 6. Bond Distances in Angstroms for **1c** with esds in Parentheses*.

Atoms	Distance	Atoms	Distance	Atoms	Distance
C(1)-C(10)	1.55(2)	C(15)-C(14)	1.34(2)	C(5')-C(6')	1.27(3)
C(2)-C(1)	1.52(2)	C(16)-C(15)	1.49(2)	C(6')-C(7')	1.41(3)
C(3)-C(2)	1.53(2)	C(17)-C(16)	1.57(2)	O(101)-C(1)	1.44(2)
C(4)-C(3)	1.51(2)	C(17)-C(13)	1.62(2)	O(101)-C(102)	1.37(2)
C(4)-C(5)	1.59(2)	C(17)-C(20)	1.49(2)	O(102)-C(102)	1.22(2)
C(4)-C(28)	1.49(2)	C(20)-C(22)	1.54(3)	O(211)-C(21)	1.43(2)
C(4)-C(29)	1.50(2)	C(20)-C(21)	1.56(2)	O(211)-C(212)	1.37(3)
C(6)-C(5)	1.54(2)	C(22)-C(23)	1.53(3)	O(212)-C(212)	1.13(4)
C(7)-C(6)	1.46(2)	C(23)-C(24)	1.49(3)	O(231)-C(23)	1.47(2)
C(7)-C(8)	1.52(2)	C(24)-C(25)	1.49(3)	O(231)-C(232)	1.32(3)
C(8)-C(30)	1.59(2)	C(25)-C(26)	1.52(3)	O(232)-C(232)	1.19(3)
C(9)-C(8)	1.52(2)	C(25)-C(27)	1.41(3)	O(24)-C(24)	1.21(2)
C(10)-C(9)	1.56(2)	C(72)-C(73)	1.50(3)	O(26)-C(25)	1.46(3)
C(10)-C(5)	1.52(2)	C(102)-C(103)	1.39(2)	O(30)-C(3)	1.48(2)
C(10)-C(19)	1.57(2)	C(212)-C(213)	1.45(4)	O(30)-C(1')	1.31(2)
C(11)-C12)	1.55(2)	C(232)-C(233)	1.49(3)	O(31)-C(1')	1.22(2)
C(11)-C(9)	1.51(2)	C(1')-C(2')	1.44(2)	O(71)-C(7)	1.45(2)
C(12)-C(13)	1.50(2)	C(2')-C(3')	1.41(2)	O(71)-C(72)	1.39(2)
C(13)-C(14)	1.53(2)	C(2')-C(7')	1.37(2)	O(72)-C(72)	1.15(2)
C(13)-C(18)	1.53(2)	C(3')-C(4')	1.38(3)	O(9000)- C(9000)	1.42(4)
C(14)-C(9)	1.53(2)	C(4')-C(5')	1.40(3)		

*Numbers in parentheses are estimated standard deviations in the least significant digits.

***Meliavolkin* (2).** White powder, $[\alpha]^{25}_D$ + 4.9° (c 1.85 in $CHCl_3$); uv λ_{max} (MeOH): 284 nm (log ε 4.10); ir ν_{max} (film) cm^{-1}: 3450, 2931, 1732, 1714, 1637, 1374, 1052, 757; fabms (m-NBA) m/z (%): 601 (MH^+, 2); hrfabms (m-NBA) m/z: 601.3173 for $C_{37}H_{43}O_7$ (MH^+) calcd. 601.3165; ^{1}H and ^{13}C NMR (see

Table 1); COSY (500 MHz, nt 16, ni 256, d1 3.0, 2K x 2K); NOESY (500 MHz, nt 16, ni 332, mix 0.04 sec, dm 'nnn', 2K x 2K); HETCOR (125 MHz, nt 32, ni 256, d1 2.0, j1xh 150, 4 K x 4 K); COLOC (same as HETCOR, jnxh 7.0 or 10.0).

Melianin A. Colorless prisms, mp 253-254°C; $[\alpha]^{25}_{D}$ -18.4° (c 0.50 in $CHCl_3$).[7]

ACKNOWLEDGMENTS

This investigation was supported by a contract from FMC and Xenova Corporations and R01 grant no. CA30909 from the National Cancer Institute, National Institutes of Health. Thanks are due to the Cell Culture Laboratory, Purdue Cancer Center, for cytotoxicity testing.

REFERENCES

1. Kokwaro, J. O. *"Medicinal Plants of East Africa"*, East African Literature Bureau, Nairobi, Kenya, **1976**, p. 157.
2. Mwangi, W. R. *Entomol. Exp. Appl.* **1982**, *32*, 277.
3. Rajab, M. S.; Bentley, M. D.; Alford, A. R.; Mendel, M. J. *J. Nat. Prod.* **1988**, *51*, 168.
4. Rajab, M. S.; Bentley, M. D. *J. Nat. Prod.* **1988**, *51*, 840.
5. Meyer, B. M.; Ferrigni, N. R.; Putnam, J. E.; Jacobsen, L. B.; Nichols, D. E.; McLaughlin, J. L. *Planta Medica* **1982**, *45*, 31.
6. McLaughlin, J. L. *"Methods in Plant Biochemistry"*, Vol. 6, Ed. by Hostettmann, K., Academic Press, London, **1991**, p. 1.
7. Okogun, J. I.; Fakunle, C. O.; Ekong, E. U. *J. Chem. Soc. Perkin I* **1975**, 1352.
8. Connolly, J. D.; Labbe, C.; Rycroft, D. S.; Taylor, A. H. *J. Chem. Soc.* **1979**, 2959.
9. Ohtani, I; Kusumi, T.; Kashman, Y.; Kakizawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
10. Rieser, M. J.; Hui, Y.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10203.
11. Gu, Z. M.; Fang, X. P.; Zeng, L.; McLaughlin, J. L. *Heterocycles* **1993**, *36*, 2221.
12. Buchanan, J.G. St. C.; Halsall, T. G. *J. Chem. Soc.* **1970**, 2280.
13. Kraus, W.; Cramer, R. *Liebigs Ann. Chem.* **1981**, 181.
14. Giard, S. J.; Aronson, S. A.; Todaro, G. J.; Arnstein, P.; Kersey, J. H.; Dosik, H.; Parks, W. P. *J. Natl. Cancer Inst.* **1973**, *51*, 1417.
15. Soule, H. D.; Vazquez, J.; Long, A.; Albert, S.; Brennan, M., *J. Natl. Cancer Inst.* **1973**, *51*, 1409.
16. Fogh, J.; Trempe, G. "*Human Tumor Cell sin Vitro*", Ed. by Fogh, J., Plenum Press, New York, **1975**, p. 115.
17. Killian, R. C. G. and Lawrence, J. L., *Acta Crystallogr. Sect. B* **1969**, *25*, 1750.
18. Cromer, D. T.; Waber, J. T. *"International Tables for X-Ray Crystallography"*, Vol. 4, The Kynoch Press, Birmingham, England, **1974**, Table 2.2B.
19. Ibers, J. A.; Hamilton, W. C. *Acta Crystallogr.* **1964**, *17*, 781.

(*Received in USA* 9 *November* 1994; *revised* 30 *December* 1994; *accepted* 5 *January* 1995)