Notes

New Bioactive Diterpene Polyesters from *Euphorbia decipiens*

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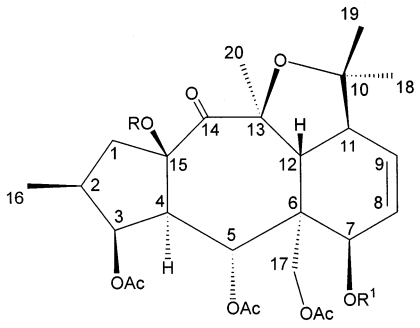
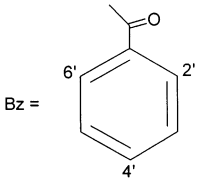
A reinvestigation with a modified extraction procedure of *Euphorbia decipiens* resulted in the isolation and structure elucidation of three new myrsinane-type diterpene esters (**1**−**3**). The structures of compounds **1**−**3** were elucidated by spectroscopic data interpretation. Compound **1** showed inhibitory activity against prolyl endopeptidase (PEP), whereas compound **2** exhibited DNA-damaging activity in a mutant yeast bioassay.

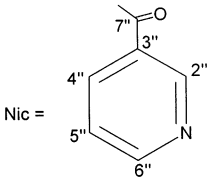
Plants belonging to the genus *Euphorbia* (Euphorbiaceae) have been the subject of many investigations for their biologically active components. Biological activities including skin irritant, tumor promotion, and proinflammatory properties are attributed to the presence of specific classes of macro- and polycyclic diterpenes.[1−3] Some species of the genus *Euphorbia* have been used as medicinal plants for the treatment of skin diseases, gonorrhea, migraine, and intestinal parasites, and as wart cures.[4] These medicinal properties prompted us to investigate *Euphorbia* species of Iran. From *Euphorbia decipiens* Boiss. & Buhse, an endemic plant from Kandovan Mountain north of Karaj, Tehran, Iran,[5] we have reported the isolation of eight new diterpene esters.[6−8] To obtain the minor compounds, the plant was again collected and extracted with acetone,[1] and another eight new diterpene esters were isolated.[9] The remaining chloroform-soluble fraction of the concentrated extract was subjected to a different chromatographic procedure, which resulted in the isolation of three diterpene esters with a myrsinane nucleus (**1**−**3**).

The $CHCl_3$ extract of the whole plant of *E. decipiens* was subjected to chromatographic purification to afford the three new polyester diterpenoids **1**−**3**. Compound **1** exhibited a molecular ion at *m*/*z* 612.2548 in the HREIMS, indicating its molecular formula as $C_{33}H_{40}O_{11}$. In the EIMS, the ions at *m*/*z* 584 ($[M - CO]^+$), 524 ($[M - CO - AcOH]^+$), 464 ($[M - CO - 2AcOH]^+$), 122 ($PhCO_2H^+$), and 105 ($PhCO^+$) indicated the presence of carbonyl, acetate, and benzoate functionalities in the molecule, which were supported by IR absorptions at 3490 (OH), 1740, 1705 (RCO_2R', RCOR′), and 1620 (C═C) cm^{-1}. The ^1H NMR spectrum of **1** (Table 1) was similar to those reported for myrsinane-type diterpenoids.[6−10]



Compound	R	R^1
1	H	Bz
2	Ac	Bz
3	Ac	Nic





The ^1H NMR spectrum of **1** (Table 1) showed five downfield signals due to the protons geminal to oxygen-bearing groups; three were from oxymethine groups [δ 5.52 (t, J = 4.5 Hz, H-3), 6.39 (d, J = 11.0 Hz, H-5), and 5.19 (d, J = 5.3 Hz, H-7)] and two from oxymethylene groups [δ 4.24 (d, J = 12.0 Hz, H-17) and 4.60 (d, J = 12.0 Hz, H-17′)], with the relatively large coupling constant (J = 12.0 Hz), suggesting the presence of free alkoxy groups on the myrsinane-type skeleton.[8] A downfield-shifted proton was observed at δ 3.15 (d, J = 12.1 Hz, H-12), which seemed to be located in an anisotropic field of carbonyl esters or the lone pair electrons of a free hydroxyl group.[8] The H-1α signal (δ 2.84 dd, J = 9.5, 15.5 Hz) was also shifted downfield due to the anisotropic effect of the carbonyl group at C-14.[8] The downfield-shifted protons of H-1α and H-12 are characteristic of a myrsinane-type

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Table 1. ^{1}H NMR and ^{13}C NMR Data of Compounds **1**−**3**

	1		**2**		**3**	
position	H[a]	^{13}C[b]	H[a]	^{13}C[b]	H[a]	^{13}C[b]
1α	2.84 dd (9.5, 15.5)	46.1	2.97 dd (9.1, 14.4)	43.0	2.87 dd (9.3, 14.1)	43.9
1*β*	1.75 dd (9.8, 15.0)		1.76 dd (9.0, 14.2)		1.75 dd (9.1, 14.2)	
2	2.23 m	35.7	2.15 m	35.7	2.19 m	34.9
3	5.52 t (4.5)	78.5	5.47 t (4.5)	77.0	5.51 t (4.3)	78.2
4	3.02 dd (4.1, 11.0)	49.7	2.89 dd (4.4, 11.0)	50.6	2.93 dd (4.2, 11.0)	50.1
5	6.39 d (11.0)	68.5	6.37 d (11.0)	68.4	6.38 d (11.0)	68.2
6		47.1		47.2		47.1
7	5.19 d (5.3)	68.8	5.23 d (5.2)	69.0	5.26 d (5.3)	68.9
8	6.03 ddd (2.8, 5.3, 9.8)	126.3	6.00 ddd (2.8, 5.2, 9.8)	126.1	6.01 ddd (2.8, 5.2, 9.7)	125.9
9	5.84 dd (2.8, 9.8)	128.7	5.84 dd (1.9, 9.8)	128.9	5.83 dd (2.7, 9.8)	128.6
10		79.3		79.3		79.4
11	2.86 br t (12.1)	47.4	2.83 br d (12.5)	46.9	2.84 br d (12.0)	47.2
12	3.15 d (12.1)	41.9	3.44 d (12.7)	41.7	3.41 d (12.7)	41.5
13		83.6		84.7		84.3
14		205.4		205.2		205.1
15		85.4		88.7		88.5
16	0.92 d (6.7)	14.6	0.90 d (6.8)	14.3	0.91 d (6.8)	14.5
17a	4.24 d (12.0)	61.2	4.13 d (12.0)	61.0	4.19 d (12.0)	61.2
17b	4.60 d (12.0)		4.57 d (12.0)		4.58 d (12.0)	
18	1.43 s	29.5	1.42 s	29.3	1.42 s	29.3
19	1.04 s	24.5	1.02 s	24.7	1.03 s	24.6
20	1.52 s	24.7	1.53 s	26.1	1.53 s	26.1
OCO*CH*$_3$						
	2.10 s	21.2	2.21 s	21.3	2.20 s	21.2
	1.90 s	20.8	2.19 s	21.1	2.18 s	21.1
	1.68 s	20.6	1.86 s	20.6	1.87 s	20.5
			1.59 s	20.5	1.60 s	20.4
OCOCH$_3$						
		170.3		170.4		170.2
		170.1		170.0		170.0
		169.7		169.9		169.8
				168.7		168.6
benzoyl						
1′		130.8		129.5		
2′, 6′	7.87 br d (7.4)	129.6	7.86 dd (1.4, 7.4)	129.3		
3′, 5′	7.38 br t (7.9)	128.3	7.37 br t (7.8)	128.9		
4′	7.51 m	133.2	7.51 m	133.2		
7′		165.1		165.0		
nicotinoyl:						
2″					9.25 br s	150.1
3″						126.0
4″					8.29 br d (7.0)	137.5
5″					7.40 dd (4.8, 7.4)	132.5
6″					8.75 br d (3.4)	152.9
7″						165.0

[a] Recorded in $CDCl_3$. [b] Assignment made by a combination of DEPT HMQC NMR data.

skeleton.[10] The ^{1}H NMR spectrum of **1** also showed signals for a disubstituted double bond at δ 6.03 (ddd, J = 2.8, 5.3, 9,8 Hz, H-8) and 5.84 (dd, J = 2.8, 9.8 Hz, H-9). Signals for a secondary methyl at δ 0.92 (d, J = 6.7 Hz, H-16) and one other tertiary methyl at δ 1.52 (s, H-20), together with three acetyl methyl singlets at δ 2.10, 1.90, and 1.68, were also observed in the ^{1}H NMR spectrum of **1**. The upfield shift of the last-mentioned acetyl signal may be related to the anisotropic effect of other ester groups and is common in poly- and macrocyclic diterpene esters.[8]

In the ^{13}C NMR spectra (BB and DEPT) of **1**, 31 signals appeared representing 33 carbons atoms, including seven methyls (three acetate), two methylenes, 12 methines, and 10 quaternary carbons (four C═O of esters). The signals at δ 78.5 (d, C-3), 68.5 (d, C-5), and 68.8 (d, C-7) represented the ester-bearing methine groups. The downfield signals at 126.3 (d, C-8) and 128.7 (d, C-9) suggested a disubstituted double bond in the molecule. The other characteristic peaks were detected at δ 83.6, 85.4 (s, C-13, C-15), 205.4 (s, C-14), and a triplet at δ 61.2, which represented an oxymethylene-bearing carbon atom. The ^{1}H−^{1}H and ^{1}H−^{13}C connectivities were determined from the ^{1}H−^{1}H-COSY and HMQC spectra. The assignment of the carbon skeleton and the ester group locations were established by HMBC (Table S1) as well as by the comparison of the ^{1}H and ^{13}C NMR chemical shifts and coupling constants observed with those of other myrsinane-type diterpenoid esters.[6−10]

The ^{1}H and ^{13}C NMR data of **1** showed (Table 1) a close resemblance in most of their features to analogous data for decipinone.[8] However, two main differences were apparent in the spectrum of compound **1**. First, one tertiary methyl signal at δ 1.43 (s, H-18) in **1** replaced the olefinic protons of decipinone appearing at δ 4.87 (m, H-18).[8] Second, there was a lack of the olefinic signal in the ^{13}C NMR spectrum of C-18 (δ 113.1) and C-10 (δ 147.1)[8] of decipinone and the appearance in **1** of a signal at δ_C 79.3 (C-10), a methyl group resonating at δ_C 29.5 (C-18). These differences pointed to a rearranged structure containing a tetrahydrofuran moiety due to an ether bridge between C-10 and C-13. Moreover, the signals at δ_C 79.3 (s) and 83.6 (s) assigned as C-10 and C-13, respectively, reflected their presence in an ether linkage between C-10 and C-13 involving sp^3 carbons. The presence of a geminal-dimethyl-substituted tetrahydrofuran moiety was also indicated in the HMBC spectrum (Table S1) by correlations of H-18 and H-19 with C-10 and C-11. The extension of the sequence

(ether bridge between C-10 and C-13) was achieved because H-11 correlated with C-10, C-12, and C-13, H-12 with C-10, C-11, and C-13, and H-20 with C-12 and C-13. The presence of a geminal-dimethyl-substituted tetrahydrofuran moiety was further confirmed by correlation between H-18/H-20 in the NOESY spectrum. The ^{1}H and ^{13}C NMR data of **1** were very similar to those recorded for cheiradone, a compound isolated from *Euphorbia cheiradenia*,[10] but there were differences with respect to those observed for the latter compound. The slightly upfield shift of H-5 at δ 6.39 (d, J = 11.0 Hz) and the downfield shift of H-7 at δ 5.19 (d, J = 5.3 Hz) showed that the position of the benzoate group changed from C-5 to C-7 in **1**.

The relative positions of the ester groups were also determined from the HMBC data (Table S1), with cross-peaks observed between the H-3, H-5, and H-17 signals and the carbonyl signal of the acetate at ca. δ 170. A relatively upfield carbonyl signal at δ 165.1 and its connectivity with H-7 (δ 5.19) in the HMBC spectrum confirmed the position of the benzoate moiety. The stereochemistry of **1** was determined by comparison of the ^{1}H NMR coupling constants of **1** with those recorded for other myrsinol esters[6−10] as well as from the NOESY NMR spectrum. The coupling constants of H-3 (t, J = 4.5 Hz) and H-4 (dd, J = 11.0, 4.1 Hz) indicated that H-2 to H-4 must lie on one face of the molecule with the same dihedral angles between H-2/H-3 and H-3/H-4. The J value (11.0 Hz) between H-4 and H-5 showed their *trans* relationship, and the coupling constant of H-12 (d, J = 12.1 Hz) indicated a *trans* relationship between H-12 and H-11. The cross-peaks between H-3/H-4, H-17/H-7, and H-11, and between H-18/H-20 in the NOESY spectrum, indicated that these protons all lie on one face of the molecule. A cross-peak between H-5/H-12 and H-19, together with the observed coupling constant (J = 11.0 Hz) between H-4 and H-5, confirmed the configuration of **1**. The absolute structure of one compound in this series has been established by an X-ray method.[10] Accordingly, compound **1** was assigned the structure 3,5,17-*O*-triacetyl-7-*O*-benzoyl-15-hydroxycheiradone.

Compound **2** was obtained as a colorless oil and assigned the molecular formula $C_{35}H_{42}O_{12}$ on the basis of its HREIMS (*m*/*z* 654.2647). Its IR spectra showed characteristic peaks for carbonyl groups at 1740 and 1705 cm^{-1} and at 1640 and 1600 cm^{-1} for unsaturation. The IR spectrum did not show any characteristic hydroxyl group absorption. The ^{1}H NMR signals of **2** at δ 5.47 (t, J = 4.5 Hz), 6.37 (d, J = 11.0 Hz), and 5.23 (d, J = 5.2 Hz) were typical for *O*-bearing methine groups at C-3, C-5, and C-7, respectively, and showed an AB pattern at δ 4.57 (d, J = 12.0 Hz) and 4.13 (d, J = 12.0 Hz) for an OCH_2 group of the myrsinane skeleton (Table 1). The ^{1}H and ^{13}C NMR spectra of **2** were very similar to those of **1**, except that it was apparent that **2** has one more acetate moiety at C-15. The ^{13}C NMR downfield shift of C-15 to δ 88.7 was compatible with the proposed structure.[9] The locations of the ester groups were also identified by the HMBC cross-peaks (Table S1) between H-3, H-5, H-17, and H-17a with acetyl carbonyl groups at ca. δ 170. The position of the benzoate moiety was also confirmed by a HMBC cross-peak between the H-7 (δ 5.23) and the benzoyl carbonyl signal (δ 165.0) (Table S1). The relative stereochemistry was confirmed by NOESY correlations and coupling constants, which were similar to compound **1**. Therefore, the structure of compound **2** was assigned as 3,5,15,17-*O*-tetraacetyl-7-*O*-benzoylcheiradone.

Compound **3** was obtained as a colorless oil. The HREIMS displayed the M$^+$ at *m*/*z* 655.2652 corresponding to the molecular formula $C_{34}H_{41}O_{12}N$. In the EIMS, the ions at *m*/*z* 106 $[C_6H_4ON]^+$ and 124 $[C_6H_5O_2N + 1]^+$ suggested the presence of a nicotinate ester unit in the molecule. The ^{1}H and ^{13}C NMR spectra of **3** (Table 1) were similar to those recorded for **2**, except that it was shown that the benzoyl moiety was substituted by a nicotinate moiety at δ 9.25 (br s, H-2″), 8.29 (br d, J = 7.0 Hz, H-4″), 7.40 (dd, J = 7.4, 4.8 Hz, H-5″), and 8.75 (br d, J = 3.4 Hz, H-6″). The ^{13}C NMR spectra (BB and DEPT) showed five signals at δ 150.1 (s, C-2″), 126.0 (d, C-3″), 137.5 (d, C-4″), 132.5 (d, C-5″), and 152.9 (d, C-6″), consistent with the presence of a nicotinate moiety. The ^{1}H−^{1}H and ^{1}H−^{13}C connectivities were supported by the ^{1}H−^{1}H-COSY and HMQC spectra of **3**. The locations of the ester groups were established from the HMBC spectrum. HMBC correlations (Table S1) between δ_C 165.0 and δ_H 5.26 (H-7) indicated that the nicotinate moiety was at C-7. HMBC correlations between the carbonyl signal at ca. δ_C 170 and δ_H 5.51 (H-3), 6.38 (H-5), and 4.19 (H-17) indicated that acetate groups were at C-3, C-5, and C-17. The relative stereochemistry of **3** was confirmed by NOESY correlations and coupling constants, which are similar to compound **2**. Compound **3** was therefore assigned the structure 3,5,15,17-*O*-tetraacetyl-7-*O*-nicotinoylcheiradone.

Prolyl endopeptidase (PEP, EC 3.4.21.26) is the only serine protease that is known to cleave a peptide substrate in the *C*-terminal side of a proline residue and plays an important role in the metabolism of peptide hormones and neuropeptides and is recognized to be involved in learning and memory.[11] Low molecular weight inhibitors of PEP have been reported in the literature, but the majority of these are of synthetic origin. In turn most of the natural PEP inhibitors are of microbial origin. Compound **1** exhibited an IC_{50} of 16.9 ± 1.3 μM, which was compared with the positive control, PEP (*Z*-Pro-prolinal, IC_{50} of 1.27 ± 0.01 nM).

During the search for natural products with DNA-damaging activity, we have utilized a mechanism-based yeast bioassay.[12,13] Compound **2** showed a positive response to DNA-damaging activity with IC_{12} values of 750 μg/mL against RS322Y (rad 52) and 1090 μg/mL against wild-type LF 15 (Rad$^+$). Camptothecin was used as the standard drug, with IC_{12} values of 12 μg/mL for mutant strain (rad 52) and 75 μg/mL for the wild type.

Experimental Section

General Experimental Procedures. UV spectra were measured in $CHCl_3$ on a Shimadzu UV 240 spectrophotometer. IR spectra were recorded in $CHCl_3$ solution on a JASCO A-302 spectrophotometer. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AM-400 spectrometer with tetramethylsilane (TMS) as external standard. 2D NMR spectra were recorded on a Bruker AMX 500 NMR spectrometer. Mass spectra (EIMS and HREIMS) were recorded on a Finnigan-MAT 12 or -MAT 312 spectrometer. Fast-atom bombardment (FABMS) mass measurements were taken as glycerol matrixes on a JEOL HX110 mass spectrometer. For column chromatography, silica gel (Merck, 230−400 mesh) was used. TLC was carried out on precoated silica gel cards (Merck).

Plant Material. The whole plant of *Euphorbia decipiens* Boiss. & Buhse (Euphorbiaceae) was collected at Mount Kandovan, north of Karaj, Iran, in 1998, and identified by Mr. Bahram Zehzad (plant taxonomist) at the Department of Biological Sciences, Shahid Beheshti University, Eveen, Tehran, Iran. A voucher specimen (No. 98112) was deposited at the herbarium of the Biology Department of Shahid Beheshti University.

Extraction and Isolation. The air-dried ground plant (4 kg) was exhaustively extracted with acetone at room temper-

ature. The extract was evaporated and the residue (62 g) defatted by extraction with hexane. The defatted extract (51 g) was extracted with chloroform. The chloroform extract (44 g) was subjected to column chromatography over a silica gel column (880 g) using hexane with a gradient of $CHCl_3$ up to 100% and followed by 100% methanol. Twenty pooled fractions were collected. Fraction 14, eluted with $CHCl_3$, was subjected to repeated column chromatography. The fraction that eluted with EtOAc−hexane (25:75) contained compounds **1**−**3** and was subjected to preparative TLC (silica gel 60 F_{254}) using hexane−EtOAc (45:55) as mobile phase (developed three times). This led to the purification of **1** [10.2 mg, 0.0003% yield, R_f 0.43 in $CHCl_3$−acetone (93:7)], **2** [9.4 mg, 0.0002% yield, R_f 0.47 in $CHCl_3$−acetone (93:7)], and **3** [6.4 mg, 0.0002% yield, R_f 0.50 in $CHCl_3$−acetone (95:5)].

3,5,17-*O*-Triacetyl-7-*O*-benzoyl-15-hydroxycheiradone (1): colorless oil; $[\alpha]^{23}_D$ −6.67° (*c* 0.21, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 229 (4.09), 202 (4.18) nm; IR ($CHCl_3$) ν_{max} 3490, 2960, 2940, 1740, 1705, 1620, 1600, 1550, 1250, 1100, 1020, 710, 600 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$) data, see Table 1; EIMS *m*/*z* 584 $[M - CO]^+$ (34), 524 $[M - CO - AcOH]^+$ (12), 464 $[M - CO - 2AcOH]^+$ (17), 122.5 ($PhCO_2H^+$), 105 ($PhCO^+$) (100), 464 (17), 293 (73), 233 (93), 191 (73), 105 (100); CIMS (CH_4) *m*/*z* 613 $[M + 1]^+$, 553 $[M + 1 - HOAc]^+$, 493 $[M + 1 - 2\times HOAc]^+$, 415, 285; HREIMS *m*/*z* 612.2548 (calcd for $C_{33}H_{40}O_{11}$, 612.2570).

3,5,15,17-*O*-Tetraacetyl-7-*O*-benzoylcheiradone (2): colorless oil; $[\alpha]^{23}_D$ −9.04° (*c* 0.188, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 230 (3.89), 203 (4.11) nm; IR ($CHCl_3$) ν_{max} 2970, 2930, 1740, 1705, 1640, 1600, 1540, 1250, 1100, 1020, 710, 600 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$) data, see Table 1; EIMS *m*/*z* 654 $[M]^+$ (3), 626 (6), 566 (5) 293 (72), 233 (93), 191 (73), 105 (100); CIMS (CH_4) *m*/*z* 655 $[M + 1]^+$, 595 $[M + 1 - HOAc]^+$, 535 $[M + 1 - 2\times HOAc]^+$, 415, 285; HREIMS *m*/*z* 654.2647 (calcd for $C_{35}H_{42}O_{12}$, 654.2676).

3,5,15,17-*O*-Tetraacetyl-7-*O*-nicotinoylcheiradone (3): colorless oil; $[\alpha]^{23}_D$ −12.5° (*c* 0.128, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 270 (2.71), 199 (3.09) nm; IR ($CHCl_3$) ν_{max} 1730, 1705, 1630, 1580, 1250, 1100, 1020, 730, 600 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$) data, see Table 1; EIMS *m*/*z* 655 $[M]^+$, 627 $[M - CO]^+$, 595 $[M - HOAc]^+$, 535 $[M - 2\times HOAc]^+$, 475 $[M - 3\times HOAc]^+$, 293 (73), 233 (93), 106 $[C_6H_4ON]^+$, 124 $[C_6H_5O_2N + 1]^+$; HREIMS *m*/*z* 655.2652 (calcd for $C_{34}H_{41}O_{12}N$, 655.2628).

Enzyme Inhibition Assay. Chemicals. Prolyl endopeptidase (PEP; *Flavobacterium meningosepticum* origin) was purchased from Seikagaku Corporation (Tokyo, Japan), and *N*-benzyloxycarbonyl-Gly-Pro-*p*NA was procured from Bachem Fine Chemicals Co. A specific inhibitor of PEP, *N*-benzyloxycarbonyl-Pro-prolinal, was kindly donated by Dr. Hideaki Shimizu, Yakult Central Institute for Microbiological Research, Tokyo, Japan.

PEP Inhibition Assay. PEP inhibition activity was assayed by a modification of the method of Yoshimoto et al.[14] Tris(hydroxymethyl)aminomethane HCl buffer (100 mM) containing 247 μL of 1 mM EDTA, pH 7.0, 15 μL of PEP (0.02 unit/300 μL), and test sample in 8 μL of MeOH were mixed in a 96-well microplate and preincubated for 10 min at 30 °C. The reaction was initiated by adding 30 μL of 2 mM *N*-benzyloxycarbonyl-Gly-Pro-*p*NA (in 40% 1,4-dioxane) as the substrate. The amount of released *p*-nitroaniline was determined spectrophotometrically at 410 nm, with a Spectramax 340 96-well microplate reader (Molecular Devices). The IC_{50} values were the average of at least three determinations performed in triplicate.

Assay for Growth Inhibition of *Saccharomyces cerevisiae*. The experimental procedures used for the mechanism-based bioassay have been described previously.[12,13] The IC_{12} values refer to the concentration in μg/mL required to produce a zone of inhibition of 12 mm around a 100 μL well of 6 mm diameter during a 48 h incubation period at 37 °C determined from dose−response experiments.

Acknowledgment. We are thankful to Mr. Bahram Zehzad for identification of the plant.

Supporting Information Available: Table showing HMBC NMR correlations for compounds **1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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