Highly Hydroxylated Triterpenes from *Salvia kronenburgii*

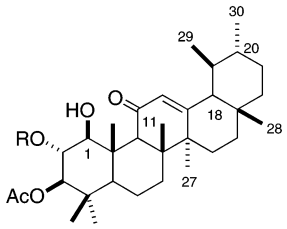
Gülaçtı Topçu,*,† Zeynep Türkmen,† Ayhan Ulubelen,† Jennifer K. Schilling,‡ and David G. I. Kingston‡

Faculty of Pharmacy, Istanbul University, 34116, Beyazit, Istanbul, Turkey, and Department of Chemistry, M/C 0212, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

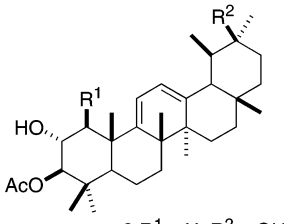
Received August 5, 2003

The three new triterpenes (**1**−**3**) and five known triterpenes and a sterol were isolated from the acetone extract of a Turkish collection of *Salvia kronenburgii*. The structures of the new triterpenes were established as 1*β*,2α-dihydroxy-3*β*-acetoxy-11-oxours-12-ene (**1**), 2α,20*β*-dihydroxy-3*β*-acetoxyurs-9(11),-12-diene (**2**), and 1*β*,2α-dihydroxy-3*β*-acetoxyurs-9(11),12-diene (**3**) on the basis of spectral analyses, including 1D and 2D NMR and mass spectroscopy. It is probable that compounds **2** and **3** are artifacts from dehydration of the corresponding allylic alcohols. 1*β*,2α,3*β*,11α-Tetrahydroxyurs-12-ene (**5**), the most abundant compound in the extract, was found to be highly cytotoxic to renal, non-small cell lung, and breast cancer cell lines.

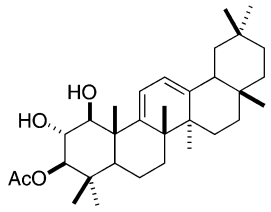
In continuation of our studies on the endemic Turkish plant *Salvia kronenburgii*[1] Rech. (Lamiaceae) we fractionated an acetone extract of its roots by a combination of CC on silica gel and preparative TLC. This work yielded eight triterpenes and a sterol, which were identified from their spectroscopic data as the three new triterpenes **1**−**3** and the five known triterpenes 1*β*,2α-dihydroxy-3*β*-acetoxy-olean-9(11),12-diene (**4**), 1*β*,2α,3*β*,11α-tetrahydroxyurs-12-ene (**5**), 3*β*-acetoxy-2α,11α-dihydroxyurs-12-ene,[2] salvinemorol,[3] salvistamineol,[4] and *β*-sitosterol.



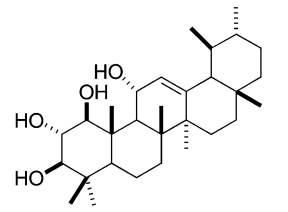
1 R = H
1a R = Ac



2 R^1 = H, R^2 = OH
3 R^1 = OH, R^2 = H



4



5

The HREIMS of compound **1** exhibited a molecular ion peak at *m/z* 514.3643, corresponding to the molecular formula $C_{32}H_{50}O_5$. This indicated the presence of eight unsaturations, of which five were accounted for by a pentacyclic ring system, one by an olefinic bond, one by a keto group, and one by an acetoxy carbonyl group. Major fragment ions in the EIMS were observed at *m/z* 499 $[M - CH_3]^+$, 482 $[M - CH_3 - H_2O]^+$, 454 $[M - HOAc]^+$, and 437 $[M - OAc - H_2O]^+$ with the base peak at *m/z* 273. The ^{1}H NMR spectrum (Table 1) indicated an ursane triterpene, with seven methyl singlets at *δ* 0.83, 0.92, 0.93, 1.03, 1.20, 1.33, and 2.14, and two methyl doublets at *δ* 0.82 and 0.91. One sharp singlet at *δ* 5.72 was assigned to the α proton of an α,*β*-unsaturated carbonyl group. The presence of an enone moiety was confirmed by the UV spectrum with a maximum at 241 nm,[5] which was in good agreement with λ_{max} for the α,*β*-unsaturated carbonyl function (239 nm),[6] and by the IR spectrum with an absorption band at 1676 cm^{-1}. A singlet at *δ* 2.66 was assigned to H-9, and the location of the keto group was verified at C-11 on the basis of HMBC correlation between H-9 and the keto carbonyl signal at *δ* 200.2. The observation of three relatively deshielded protons at *δ* 4.72 (d, J = 11 Hz), 3.75 (dd, J = 9 and 11 Hz), and 3.22 (d, J = 9 Hz) indicated the presence of three oxygenated protons. The most downfield proton (H-3) was assigned to a carbon, bearing an acetoxy group, and the acetyl methyl signal at *δ* 2.14 supported this assignment, followed by the HMBC experiment. The other two downfield signals were assigned to protons on the carbons of two secondary hydroxyl groups, specifically to the H-1 and H-2 protons at *δ* 3.22 and 3.75, respectively, on the basis of the COSY correlations between them. The latter proton also gave a COSY correlation with the signal at *δ* 4.72, indicating that the methine signal at *δ* 3.75 must be located between the secondary hydroxyl at *δ* 3.22 and

Table 1. ^{1}H NMR Data of Compounds **1**−**3** in $CDCl_3$ (J values (Hz) in parentheses)

proton	**1**	**2**	**3**
H-1α	3.22 d (9.0)	1.33 dd (10.9; 12.5)	3.56 d (9.2)
H-1*β*		2.35 dd (4.3; 12.5)	
H-2*β*	3.75 dd (9.0; 11.0)	3.78 ddd (4.3; 9.8; 10.9)	3.54 dd (9.0; 9.2)
H-3α	4.72 d (11.0)	4.42 d (9.8)	4.50 d (9.0)
H-5	0.92 m		
H-9	2.66 s		
H-11		5.56 d (5.9)	6.59 d (5.9)
H-12	5.72 s	5.38 d (5.9)	5.40 d (5.9)
H-18	1.45 d (11.2)	1.38 d (11.1)	1.42 (11.1)
Me-23	0.92 s	0.82 s	0.81 s
Me-24	0.93 s	0.83 s	0.84 s
Me-25	1.03 s	0.87 s	1.24 s
Me-26	1.33 s	0.86 s	0.86 s
Me-27	1.20 s	1.11 s	1.10 s
Me-28	0.83 s	0.78 s	0.78 s
Me-29	0.82 d (6.3)	0.73 d (6.3)	0.75 d (6.3)
Me-30	0.91 d (6.9)	1.22 s	0.84 d (6.6)
OAc	2.14 s	2.07 s	2.08 s

* To whom correspondence should be addressed. Tel: +90 212 514-0355. Fax: +90 212 5193086. E-mail: gulacti_topcu@hotmail.com.
† Istanbul University.
‡ Virginia Polytechnic Institute and State University.

10.1021/np030359b CCC: $27.50
Published on Web 01/06/2004

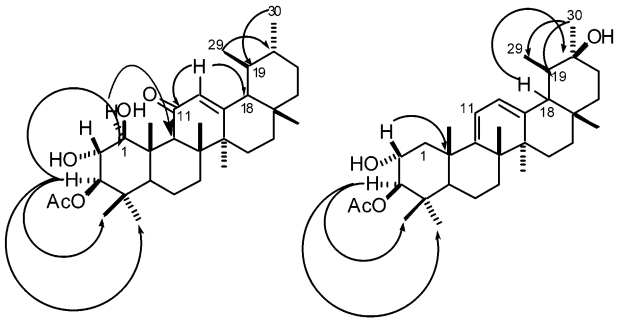


Figure 1. Selected HMBC correlations of compounds **1** and **2**.

Table 2. ^{13}C NMR Data (δ) of Compounds **1**−**4** (in $CDCl_3$)

carbon	1	2	3	4
1	77.3	44.2	79.9	80.0
2	73.6	73.2	71.7	71.8
3	81.1	79.3	81.2	81.0
4	37.9	37.9	38.6	38.6
5	55.4	46.1	45.4	45.5
6	17.9	18.7	18.2	18.2
7	34.2	31.7	31.1	31.1
8	43.8	41.6	40.9	40.8
9	62.2	151.3	152.1	152.0
10	38.0	42.6	43.1	43.1
11	200.2	120.2	120.2	119.8
12	128.5	122.1	121.0	120.0
13	169.8	148.3	149.0	150.3
14	45.2	43.7	45.2	44.8
15	28.3	27.6	27.4	27.5
16	26.4	26.5	26.1	25.8
17	32.2	32.6	31.2	33.1
18	56.3	52.1	48.2	49.0
19	39.2	40.4	39.3	46.2
20	39.3	71.2	39.4	31.2
21	32.7	36.0	31.9	33.8
22	42.4	35.4	41.8	38.0
Me-23	28.0	28.3	28.1	28.3
Me-24	16.6	17.1	17.6	16.8
Me-25	15.7	18.7	16.1	20.1
Me-26	18.4	17.9	18.4	20.5
Me-27	23.0	24.4	21.8	22.1
Me-28	28.9	28.5	28.5	28.4
Me-29	16.4	12.8	16.6	33.1
Me-30	21.9	31.0	21.6	23.2
$OCOCH_3$	21.9	21.2	21.2	21.1
$OCOCH_3$	171.9	169.8	171.5	171.6

the acetoxy-bearing carbon. This sequence is possible only on ring A in ursane triterpenes, and therefore the placement of the signal at δ 3.75 was deduced to be at C-2. The locations of the signals at δ 3.22 and 4.72 must be at C-1 and C-3 or vice versa, and these were distinguished by the HMBC correlation between H-1 and the carbon signal at δ 62.2 (C-9), indicating that the second secondary hydroxyl on ring A is located at C-1. Observation of correlations between both C-4 methyl carbons and H-3 supported this finding (Figure 1). The stereochemistries of the oxygenated groups were deduced from comparison with the J values of similar compounds.[1,2,5] Observation of NOESY correlations between both H-5 (δ 0.92) and H-9 (δ 2.66) with H-1 and H-3 and each other, not with H-2, clearly indicated β positions of C-1 and C-3 hydroxyls, while the C-2 hydroxyl should be in α position.

The ^{13}C NMR spectrum (Table 2) revealed signals for 32 carbons, consisting of nine methyls, six methylenes, nine methines, and eight quaternary carbon atoms. The acetoxy carbonyl appeared at δ 171.9 and the enone carbonyl at δ 200.2,[5] while the signals for the oxygenated carbons were at δ 77.3, 73.6, and 81.1 for carbons 1, 2, and 3, respectively.

Treatment of **1** with acetic anhydride and pyridine at room temperature yielded the monoacetate derivative **1a**. The HREIMS of this derivative gave a molecular ion peak at m/z 556.3750, corresponding to $C_{34}H_{52}O_6$ (calcd 556.3763), thus indicating that only one hydroxyl group had been acetylated. The ^{1}H NMR spectrum of **1a** indicated that acetylation had taken place at C-2, since the H-2β proton signal was shifted to δ 5.17 (dd, J = 9.2 and 10.7 Hz); the signals of the other protons resonated at almost at the same frequencies as the corresponding protons of **1**. Thus, compound **1** was determined to be 1β,2α-dihydroxy-3β-acetoxy-11-oxours-12-ene.

The HREIMS of compound **2** exhibited a molecular ion peak at m/z 498.3690 corresponding to $C_{32}H_{50}O_4$ with eight double-bond equivalents, of which five were accounted for by a pentacyclic ring system, two by two olefinic bonds, and one by an acetoxy carbonyl group. The ^{1}H NMR spectrum revealed signals for eight methyl singlets at δ 1.22, 1.11, 0.87, 0.86, 0.83, 0.82, 0.78, and 2.07 and a methyl doublet signal at δ 0.73 (J = 6.3 Hz). There were two olefinic protons at δ 5.56 and 5.38 with a coupling constant of 5.9 Hz, and this information coupled with signals for four olefinic carbons at δ 120.2, 122.1, 148.3, and 151.3 in the ^{13}C NMR spectrum indicated the presence of a conjugated diene; this was supported by a UV absorption at 279 nm typical of the homoannular diene system.[7] Two oxygenated methine protons gave signals at δ 4.42 (d, J = 9.8 Hz, H-3α) and 3.78 (ddd, J = 4.3, 9.8, 10.9 Hz, H-2β), and the methyl protons of the acetoxy group gave a signal at δ 2.07. On the basis of J values, on a COSY correlation between the signal at δ 3.78 and the signals at δ 1.33 and 2.35, and on a comparison with the spectra of triterpenes previously isolated from this plant[1] and from *Salvia argentea*,[2] the substituents at C-2 and C-3 were identified as C-3β-OAc and C-2α-OH, and the C-1 protons were assigned at δ 2.35 and 1.33. Since the spectrum showed only one methyl doublet, the remaining hydroxy group must be located either at C-19 or at C-20. The HMBC experiment (Figure 1) showed three-bond correlations between H-18 at δ 1.38 and an oxygenated quaternary carbon at δ 71.2 as well as between the C-20 methyl protons (H-30) at δ 1.22 and C-19 at δ 40.4. The location of a hydroxyl group at C-20 was supported by the paramagnetic shifts of the C-19, C-21, and C-30 signals. The 20β configuration of the hydroxyl group was confirmed by the agreement of the observed values[2] with the calculated ^{13}C NMR values for C-18 (δ 49.3), C-22 (δ 33.7), and C-29 (δ 13.0) and were significantly different from those calculated for the C-20 α epimer (45.8, 31.2, and 10.5, respectively). Thus, the structure of compound **2** was assigned as 2α,20β-dihydroxy-3β-acetoxyurs-9(11),12-diene. The 2-acetyl derivative of **2** has been previously isolated from *S. argentea*.[2]

The HREIMS of compound **3** exhibited a molecular ion peak at m/z 498.3721 corresponding to $C_{32}H_{50}O_4$ with eight double-bond equivalents, of which five were accounted for by a pentacyclic ring, two by two olefinic bonds, and one by an acetoxy carbonyl group. The ^{1}H NMR spectrum of **3** exhibited seven methyl signals as singlets at δ 1.24, 1.10, 0.86, 0.84, 0.81, 0.78, and 2.08 and two methyl doublets at δ 0.84 and 0.75. Signals for two olefinic protons appeared at δ 6.55 and 5.40 with a coupling constant of 5.9 Hz. The downfield shifts of these two protons as compared with the similar protons in **2** could be explained by the presence of a hydroxyl group at C-1; similar shifts were observed in related compounds isolated from *S. argentea*.[2] Oxygenated methine protons were observed at δ 4.50 (d, J = 9 Hz), 3.54 (dd, J = 9 and 9.2 Hz), and 3.56 (d, J = 9.2 Hz), and their

Table 3. Cytotoxicity of Triterpenes to the A2780 Ovarian Cancer Cell Line[a]

compound	IC_{50} (μg/mL)
1	26.0
2	33.3
3	37.5
4	36.9
5	27.7
6	27.9
7	32.5
8	38.5
9	34.2
salvinemorol	8.6
salvistamineol	21.0

[a] **6** = 1β,2α,3β,11α-tetrahydroxyolean-12-ene.[1] **7** = 3β-acetoxyurs-12-ene-1β,2α,11α-triol.[1] **8** = 3β-acetoxyolean-12-ene-1β,2α,11α-triol.[1] **9** = 2α-acetoxyurs-5,12-diene-3β,11α-diol.[1] Salvinemorol = 3β,11α,21α-trihydroxyolean-12-ene.[3] Salvistamineol = 3β,11α,21α-trihydroxyurs-12-ene.[4]

stereochemistries were deduced to be C-3α, C-2β, and C-1α protons, respectively, by the observation of NOESY correlations between H-5 and both C-1 and C-3 protons, as well as comparison of the similar triterpenes that have three substituents on ring A with the same stereochemistry.[1,2] The ^{13}C NMR spectrum (Table 2) gave signals for three oxygenated methine carbons at δ 79.9 (C-1), 71.7 (C-2), and 81.2 (C-3) in addition to four characteristic aliphatic methine carbon signals at δ 45.4 (C-5), 48.2 (C-18), 39.3 (C-19), and 39.4 (C-20), which were indicative of an ursane skeleton for this triterpene. The structure of compound **3** was assigned as 1β,2α-dihydroxy-3β-acetoxyurs-9(11),12-diene from these spectral data.

The oleanane isomer of **3**, 1β,2α-dihydroxy-3β-acetoxyolean-9(11),12-diene (**4**), was also isolated from the same fraction as **3**. Compound **4** has previously been isolated from *S. argentea*,[2] but it was considered to be an artifact formed by dehydration of 1β,2α,11α-trihydroxy-3β-acetoxyolean-12-ene which had been left in an NMR tube with deuteriochloroform at room temperature for 48 h.[2] Compound **2** would then be formed by dehydration of 2α,11α,-20β-trihydroxy-3β-acetoxyurs-12-ene (3β-acetoxyurs-12-ene-2α,11α,20β-triol), previously isolated from *S. argentea*,[2] while compounds **3** and **4** would be formed by dehydration of 1β,2α,11α-trihydroxy-3β-acetoxyurs-12-ene and 1β,2α,-11α-trihydroxy-3β-acetoxyolean-12-ene, respectively. Both of these latter compounds were isolated from this plant in our previous study,[1] as well as from *S. argentea*.[2]

The most abundant compound isolated from the extract was compound **5**, and this was submitted for testing to the NCI developmental therapeutics program.[8] It was found to be selectively active against only three of 60 cancer cell lines, showing growth inhibitions (log GI_{50}) of -7.66 in non-small cell lung cancer (EKVX), -6.44 in renal cancer (RXF 393), and -4.73 in breast cancer (T-47D). Of the total of 15 triterpenes isolated from this plant, 11 were tested against the A2780 human ovarian cancer cell line (Table 3), but all were found to be weakly cytotoxic to this cell line. The most active compound was salvinemorol, with an IC_{50} of 8.6 μg/mL, consistent with its selective cytotoxicity. Compound **5** was not active in this assay.

Experimental Section

General Experimental Procedures. IR and HREIMS were recorded on a ZabSpec mass (Micromass) spectrometer. ^{1}H and ^{13}C NMR were run on a Varian 400 NMR spectrometer at 400 and 100 MHz, respectively, in $CDCl_3$. UV spectra were recorded on a Varian Techtrone 535 and IR on a Perkin-Elmer 983 instrument. Silica gel 60 (70−230 mesh, E. Merck) was used for CC, and preparative TLC was performed on silica gel (UV-254 precoated) plates with 0.25 mm thickness (E. Merck, Art 5554).

Plant Material. The roots of *Salvia kronenburgii* Rech. were collected from Van in eastern Turkey in June 1997 at 2250 m altitude and were identified by Prof. Dr. M. Koyuncu and Dr. Nasip Demirkus. A voucher specimen is deposited in the Herbarium of 100. Yıl University, Van (Demirkus 5515 VANF).

Extraction and Isolation. The five main fractions A−E were obtained from powdered plant material (2.4 kg) as previously described.[1] Purification of fraction B (220 mg) by preparative TLC (CH_2Cl_2−toluene, 9:1) yielded 14 mg of sitosterol, in addition to the four known diterpenes and one new diterpene, which were reported in our previous paper.[1] Fraction C (800 mg) was subjected to a silica gel column (4 × 100 cm) and eluted with $CHCl_3$−Me_2CO (95:5) to afford compounds **1** (11 mg), **2** (14 mg), and the known compound 3β-acetoxy-2α,11α-dihydroxyurs-12-ene (11 mg), in addition to the previously reported diterpenes. Fraction D (440 mg) was also subjected to a Si gel column (3 × 80 cm) and eluted by $CHCl_3$ with increasing amounts of MeOH. Elution with 2% MeOH followed by repeated preparative TLC (CH_2Cl_2−acetone, 9:1) yielded a mixture of salvinemorol (8 mg) and salvistamineol (12 mg), identified by spectroscopic comparison with literature data.[3,4] Elution with 3% MeOH gave compound **5** and its oleanane isomer (60 mg), and final purification by preparative TLC (CH_2Cl_2−acetone, 85:15) gave pure **5** (9 mg). Preparative TLC of the polar fraction E (550 mg) using $CHCl_3$−acetone (75:25) gave compounds **3** (25 mg) and **4** (26 mg). Compounds **4** and **5** were identified by comparison of their spectroscopic data with literature data.[1] Since ^{13}C NMR data were not reported for compound **4**, they are given in Table 2.

1β,2α-Dihydroxy-3β-acetoxy-11-oxours-12-ene (1): $[\alpha]_D^{25}$ +21.2° (*c* 0.005, $CHCl_3$); UV ($CHCl_3$) λ_{max} 241 nm (log ϵ 4.0); IR ($CHCl_3$) ν_{max} 3440, 3390, 2960, 2855, 1725, 1676,1380, 1265, 1120, 1080, 890 cm^{-1}; ^{1}H and ^{13}C NMR, Tables 1 and 2; EIMS *m*/*z* (rel int) 514 [M^+] (94), 499 (17), 482 (18), 463 (23), 454 (24), 437 (100), 421 (92), 403 (18), 371 (20), 341 (40), 273 (98), 232 (67), 149 (22), 135 (85), 95 (30); HREIMS *m*/*z* 514.3643 (calcd for $C_{32}H_{50}O_5$, 514.3658).

1β-Hydroxy-2α,3β-diacetoxy-11-oxours-12-ene (1a): ^{1}H NMR δ 3.32 (d, J = 9.2 Hz, H-1α), 4.68 (d, J = 10.7 Hz, H-3α), 5.17 (dd, J = 9.2 and 10.7 Hz, H-2β), 5.62 (s, H-12), 2.62 (s, H-9), 1.96 and 1.98 (2OAc), 1.23, 1.19, 1.18, 1.17, 1.11, 0.74 (s, 6 Me), 0.89 (d, J = 7.2 Hz, 1Me), 0.83 (d, J = 7.0 Hz, 1Me); HREIMS *m*/*z* 556.3750 (calcd for $C_{34}H_{52}O_6$, 556.3763).

2α,20β-Dihydroxy-3β-acetoxyurs-9(11),12-diene (2): $[\alpha]_D^{25}$ +158.7° (*c* 0.0063 in $CHCl_3$); UV ($CHCl_3$) λ_{max} 279 nm (log ϵ 4.0); IR ($CHCl_3$) ν_{max} 3530, 3390, 2960, 1730, 1645, 1460, 1380, 1260, 1030, 980, 910, 830 cm^{-1}; ^{1}H and ^{13}C NMR, Tables 1 and 2; EIMS *m*/*z* (rel int) 498 [M^+] (100), 497 (5), 496 (55), 494 (15), 493 (45), 490 (4), 484 (38), 483 (99), 390 (5), 256 (20); HREIMS *m*/*z* 498.3690 (calcd for $C_{32}H_{50}O_4$, 498.3709).

1β,2α-Dihydroxy-3β-acetoxyurs-9(11),12-diene (3): UV ($CHCl_3$) λ_{max} 278 nm (log ϵ 3.8); IR ($CHCl_3$) ν_{max} 3440, 3390, 2960, 1725, 1640, 1460, 1380, 1255, 1030, 980, 840 cm^{-1}; ^{1}H and ^{13}C NMR, Tables 1 and 2; EIMS *m*/*z* (rel int) 498 [M^+] (100), 482 [$M^+ - H_2O$] (5), 456 (8), 439 (3), 423 (8), 405 (13), 387 (4), 345 (21), 337 (8), 306 (10), 255 (25), 171 (10), 149 (21), 123 (10), 85 (16); HREIMS *m*/*z* 498.3721 (calcd for $C_{32}H_{50}O_4$, 498.3709).

Cytotoxicity Assays. Compound **5** was evaluated in the NCI against a three-cell-line, one-dose primary anticancer assay as previously described.[8] Growth percentages were determined to be −45 against lung (H460), −25 against breast (MCF7), and 18 against central nervous system (SF-268) cell lines. Testing of **5** in the full panel of 60 cell lines over a 5-log dose range test showed growth inhibitions (log GI_{50}) of -7.66 in non-small cell lung cancer (EKVX), -6.44 in renal cancer (RXF 393), and -4.73 in breast cancer (T-47D).

Compounds **1**−**3** and the known triterpenes **4**, **5**, 3β-acetoxy-2α,11α-dihydroxyurs-12-ene,[2] salvinemorol,[3] and salvistamineol[4] and four isolated triterpenes[1] in our previous work from this plant extract—compounds **6** (1β,2α,3β,11α-tetrahydroxyolean-12-ene), **7** (3β-acetoxyurs-12-ene-1β,2α,11α-triol), **8** (3β-acetoxyolean-12-ene-1β,2α,11α-triol), and **9** (2α-acetoxyurs-5,12-diene-3β,11α-diol)—were evaluated for cytotoxicity against the A2780 human ovarian cancer cell line as previously described, using actinomycin D at 2 μg/mL and an IC_{50} value of 2−5 μg/mL as a positive control.[9] The results are shown in Table 3.

Acknowledgment. We thank the NSF-TUBITAK for support of this work with a project (TBAG-U53/INT-0002071). The authors are grateful to the National Cancer Institute, NIH, for the cytotoxicity evaluation of compound **5**. One of authors (A.U.) thanks the Turkish Academy of Sciences for partial support.

References and Notes

(1) Topcu, G.; Ulubelen, A. *J. Nat. Prod.* **1999**, *62*, 1605−1608.
(2) Bruno, M.; Savona, G.; Hueso-Rodriguez, J. A.; Pascual, C.; Rodriguez, B. *Phytochemistry* **1987**, *26*, 497−501.
(3) Topcu, G.; Eris, C.; Ulubelen, A. *Phytochemistry* **1996**, *41*, 1143−1147.
(4) Topcu, G.; Altıner, E. N.; Gozcü, S.; Halfon, B.; Aydogmus, Z.; Pezzuto, J. M.; Zhou, B.-N.; Kingston, D. G. I. *Planta Med.* **2003**, *69*, 463−467.
(5) Ikuta, A.; Kamiya, K.; Satake, T.; Saki, Y. *Phytochemistry* **1995**, *38*, 1203−1207.
(6) Woodward, R. B. *J. Am. Chem. Soc.* **1941**, *63*, 1123.
(7) Punt, P.; Rastogi, R. P. *Phytochemistry* **1978**, *19*, 575−576.
(8) Monks, A.; Scudiero, D.; Shekon, P.; Shoemaker, R.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A. *J. Nat. Cancer Inst.* **1991**, *83*, 757−766.
(9) McBrien, K. D.; Bery, R. L.; Lewes, S. E.; Neddermann, K. M.; Bursuker, I.; Huang, S.; Klehr, S. E.; Leet, J. E. *J. Antibiot.* **1995**, *48*, 1446−1452.

NP030359B