Yucca schidigera Bark: Phenolic Constituents and Antioxidant Activity

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Two new phenolic constituents with unusual spirostructures, named yuccaols D (**1**) and E (**2**), were isolated from the MeOH extract of *Yucca schidigera* bark. Their structures were established by spectroscopic (ESIMS and NMR) analysis. The new yuccaols D and E, along with resveratrol (**3**), *trans*-3,3′,5,5′-tetrahydroxy-4′-methoxystilbene (**4**), yuccaols A−C (**5**−**7**), yuccaone A (**8**), larixinol (**9**), the MeOH extract of *Yucca schidigera* bark, and the phenolic portion of this extract, were assayed for antioxidant activity by measuring the free radical scavenging effects using two different assays, namely, the Trolox Equivalent Antioxidant Capacity (TEAC) assay and the coupled oxidation of β-carotene and linoleic acid (autoxidation assay). The significant activities exhibited by the phenolic fraction and its constituents in both tests show the potential use of *Y. schidigera* as a source of antioxidant principles.

Yucca schidigera Roezl (Agavaceae) is a tree growing in the Southern part of California and Mexico. The native Indians recognized yucca as a "tree of life" due to its health-promoting activity.[1,2] Commercially, two products of yucca are available on the market. These include dried and finely powdered logs (yucca powder) or mechanically pressed and thermally condensed juice (yucca extract). These products possess the *GRAS* label (*generally recognized as safe*) given by the FDA, which allows the use of extract and powder in soft drink (root beer), pharmaceutical, cosmetic, food, and feeding-stuffs industries.[1,2] Logs of *Y. schidigera* were shown to contain both furostanol and spirostanol saponins.[3,4] Our previous investigation of the bark of *Y. schidigera* resulted in the isolation of the stilbenic derivatives resveratrol (**3**) and *trans*-3,3′,5,5′-tetrahydroxy-4′-methoxystilbene (**4**) along with the novel yuccaols A (**5**), B (**6**), and C (**7**) and yuccaone A (**8**). Yuccaols A−C are characterized by unusual spiro structures made up of a C_{15} unit, probably derived from a flavonoid skeleton, and a stilbenic portion linked via a γ-lactone ring.[5] Yuccaone A is a novel phenolic constituent based on a spirobenzopyran-4-cyclopentan-3-one system.[6]

Resveratrol is the natural phytoalexin found in considerable amounts in the skin of grapes,[7,8] mulberries, and peanuts[9] and in some medicinal plants.[10−12] In the last 10 years this compound received a lot of attention because of its biological activities, as antimutagenic,[13] antiviral,[14] antiinflammatory,[15] and cancer preventing.[16,17] In particular it is believed that because of its antioxidant properties, resveratrol is responsible for the reduced risk of cardiovascular disease associated with a moderate consumption of red wine.[18,19] The multifunctional activities of resveratrol together with the novelty of yuccaols A−C, structurally related to resveratrol, prompted use to evaluate the antioxidant activity of the MeOH extract, its phenolic fraction, and the single phenolic constituents of *Y. schidigera* bark also with a view to the potential use of *Y. schidigera*, which already possesses the GRAS label, as an antioxidant in food stuffs. The good antioxidant activity exerted by the MeOH extract and its phenolic fraction encouraged us to further investigate the phenolic fraction by defining the HPLC-DAD profile. This study led to the isolation of two new phenolic derivatives, named yuccaols D (**1**) and E (**2**), closely related to yuccaols A−C, together with larixinol (**9**), a spirobiflavonoid previously isolated from *Larix gmelini*, which is made up of two C_{15} units of flavonoid origin.[20] Thus this paper deals with the structure elucidation of compounds **1** and **2** as well as the antioxidant evaluation of the MeOH extract of *Y. schidigera* bark, its phenolic fraction, and compounds **1**−**9** by radical scavenging activity in the Trolox Equivalent Antioxidant Capacity (TEAC) assay and in the coupled oxidation of β-carotene and linoleic acid.

The phenolic portion of the MeOH extract of powdered *Y. schidigera* bark was subjected to RP-HPLC using a linear gradient H_2O/CH_3CN to give two new phenolic spiroderivative (**1** and **2**) along with larixinol (**9**) and compounds **3**−**8**, which were identified as resveratrol (**3**), *trans*-3,3′,5,5′-tetrahydroxy-4′-methoxystilbene (**4**), yuccaol A (**5**), yuccaol B (**6**), yuccaol C (**7**),[5] and yuccaone A (**8**).[6]

The structures of compounds **1** and **2** were determined by analysis of their spectroscopic data (ESIMS, 1D and 2D NMR). The ESIMS spectra in the positive ion mode of both **1** and **2** showed an $[M + H]^+$ peak at *m/z* 543 corresponding to the molecular formula $C_{50}H_{22}O_{10}$ and significant fragment ion peaks at *m/z* 449 $[M - 94 + H]^+$ due to the loss of a phenol unit and *m/z* 417 $[M - 126 + H]^+$ due to the loss of a phloroglucinol moiety. The ^{13}C NMR spectrum of **1** showed 26 signals, four of which had double intensity (Table 1), which were attributed on the basis of ^{13}C DEPT to 16 quaternary carbons, 13 methines, and one methyl group. Analysis of ^1H and ^{13}C NMR data of this compound in comparison with those of yuccaol C (**7**) showed a close similarity between the two compounds and suggested that they should be diastereomers.[5] The ROESY experiment of compound **1** clearly showed NOE effects between H-2′ and H-α, H-β, H-2‴, whereas the ROESY spectrum of yuccaol C displayed NOE effects between H-2 and H-α, H-β. Inspection of molecular models and computer representations of the two molecular models differing in the stereochemistry at C-3 suggested that the NOE effects observed for compound **1** were expected for the isomer having the *p*-hydroxyphenyl ring of the C_{15} unit (B) and ring A of the stilbenic portion (As) at the same side (Figure 1). Thus the

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Table 1. ^{1}H and ^{13}C NMR Data of Compounds **1** and **2** in CD_3OD[a]

	1		**2**	
	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
2	94.0	6.01 s	93.6	5.87 s
3	61.4		60.8	
4	181.0		176.0	
5	156.3		156.0	
6	97.0	5.90 d (1.5)	97.1	5.95 d (1.5)
7	162.1		162.2	
8	90.8	6.29 d (1.5)	90.6	6.16 d (1.5)
9	162.9		164.9	
10	105.0		104.5	
1′	126.1		127.8	
2′	127.3	7.02 d (8.0)	128.3	6.91 d (8.0)
3′	115.4	6.54 d (8.0)	115.9	6.70 d (8.0)
4′	158.7		159.3	
5′	115.4	6.54 d (8.0)	115.9	6.70 d (8.0)
6′	127.3	7.02 d (8.0)	128.3	6.91 d (8.0)
1″	138.4		130.7	
2″	116.8		119.2	
3″	155.0		147.0	
4″	97.4	6.38 d (1.5)	133.0	
5″	159.4		151.8	
6″	106.7	6.61 d (1.5)	109.1	7.02 s
1‴	135.0		140.3	
2‴	107.0	6.47 s	106.2	6.26 d (1.5)
3‴	151.6		159.8	
4‴	136.6		103.5	6.19 d (1.5)
5‴	151.6		159.8	
6‴	107.0	6.47 s	106.2	6.26 d (1.5)
α	124.4	6.56 s	123.1	7.02 d (16.0)
β	131.0	6.56 s	132.2	6.88 d (16.0)
OMe	60.7	3.85 s	60.9	3.85 s

[a] Assignments were confirmed by DQF-COSY, HSQC, and HMBC experiments.

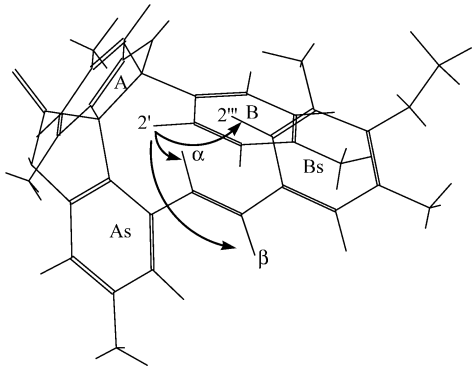


Figure 1. Computer representation of compound **1** and diagnostic NOE effects observed in the ROESY spectrum.

reported relative stereochemistry for compound **1** was assigned to be opposite of that of **7** at C-3. Compound **1** was given the trivial name yuccaol D.

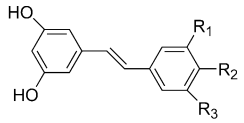
Analysis of the ^{1}H and ^{13}C NMR spectra of compound **2** in comparison with those of **1** and **7** suggested that this compound should be an isomer of yuccaols C and D.[5] Comparison of NMR data of **2** with yuccaols C (**7**) and D (**1**) indicated a close similarity in the signals of the C_{15} unit, but showed differences in the signals related to the stilbenic portion. In the ^{1}H NMR of **2** the stilbenic portion was indicated by two signals at δ 7.02 (1H, d, J = 16 Hz) and 6.88 (1H, d, J = 16 Hz) typical of a *trans* double bond, and a singlet at δ 7.02 (H-6″) and two doublets ascribable to *meta*-coupled protons at δ 6.26 (2H, d, J = 1.5 Hz, H-2‴, H-6‴) and 6.19 (1H, d, J = 1.5 Hz, H-4‴) were evident. The complete structure elucidation of compound **2** was achieved by the HMBC experiment, which showed diagnostic long-range correlations between the proton signal at δ 7.02 (H-6″) and the carbon resonances at δ 151.8 (C-5″), 133.0 (C-4″), 130.7 (C-1″), 123.1 (C-α), 119.2 (C-2″); the proton signal at δ 5.87 (H-2) and the carbon resonances at δ 128.3 (C-2′, C-6′), 127.8 (C-1′), 119.2 (C-2″), 60.8 (C-3); the proton signal at δ 6.26 (H-2‴, H-6‴) and the carbon resonances at δ 159.8 (C-3‴, C-5‴), 132.2 (C-β), 103.5 (C-4‴); and the proton signal at δ 6.19 (H-4‴) and the carbon resonances at δ 159.8 (C-3‴, C-5‴), 106.2 (C-2‴, C-6‴). These correlations suggested that in compound **2**, as in yuccaols C and D, the stilbenic portion was the *trans*-3,3′,5,5′-tetrahydroxy-4′-methoxystilbene, but in this case the linkage with the C_{15} unit involved position 2″ of the trioxygenated ring. Analysis of ^{1}H and ^{13}C NMR data, especially the chemical shifts of H-2 in the ^{1}H NMR spectrum and of C-2, C-4, C-9 in the ^{13}C NMR spectrum, suggested that the stereochemistry at C-3 of **2** is the same as that of yuccaol C. Thus, compound **2** was assigned the structure shown and was named yuccaol E.

Phenolic natural products are of particular interest because of their antioxidant activity through scavenging oxygen radicals and inhibiting peroxidation.[21] Resveratrol has been reported as a potent antioxidant of red wine.[18,19] Yuccaols A−E are characterized by unusual spirostructures made up of a C_{15} unit, probably derived from a flavonoid skeleton, and a stilbenic portion linked via a γ-lactone ring. To our knowledge, yuccaols A−E represent a unique example in nature of spirostructures including C_{15} and C_{14} units condensed to form a γ-lactone ring. Yuccaone A (**8**) is a novel phenolic constituent based on a spirobenzopyran-4-cyclopentan-3-one system, and larixinol (**9**) is a spirobiflavonoid previously isolated from *Larix gmelini* made up of two C_{15} units of flavonoid origin.[20] The antioxidant activity of the MeOH extract, the phenolic fraction, and compounds **1**−**9** was studied in the TEAC assay.[22,23] This method measures the relative ability of antioxidant substances to scavenge the radical cation 2,2′-azinobis(3-ethylbenzothiozoline-6-sulfonate) ($ABTS^{\bullet+}$) as compared to a standard amount of the synthetic antioxidant Trolox (6-hydroxy-2,5,7,8-tetramethylcroman-2-carboxylic acid), a water-soluble vitamin E analogue. The activity of the tested samples was expressed as TEAC (Trolox Equivalent Antioxidant Capacity) values; TEAC value is defined as the concentration of standard Trolox with the same antioxidant capacity as a 1mM concentration of the antioxidant investigated sample. All the tested samples exhibited good free radical scavenging activity (Table 2). The phenolic extract showed the highest activity, which was also higher than that of quercetin, the reference antioxidant compound.

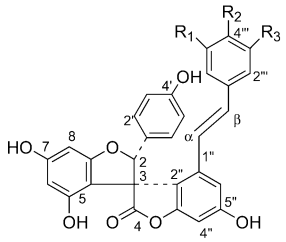
Table 2. Antioxidant Activities of MeOH Extract, Phenolic Fraction, and Compounds **1**−**9** in the TEAC and Autoxidation Assays[a]

	TEAC assay (mM) ± SD[b]	autoxidation assay	
		t = 60 min	t = 120 min
MeOH extract	1.787 ± 0.02	34.3	55.7
phenolic fraction	3.301 ± 0.01	26.4	45.7
1	1.422 ± 0.02	66.4	66.2
2	1.852 ± 0.13	74.3	79.3
3	1.896 ± 0.09	24.9	45.9
4	2.252 ± 0.12	3.1	2.9
5	0.960 ± 0.04	52.6	72.1
6	1.093 ± 0.08	76.3	72.1
7	1.598 ± 0.01	59.5	71.7
8	1.037 ± 0.04	40.6	43.4
9	1.788 ± 0.01	24.4	51.0
quercetin	2.600 ± 0.02		
BHT[c]		71.8	61.2

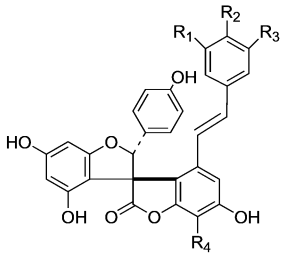
[a] For protocols used, see Experimental Section. [b] n = 3. [c] BHT = 2,6-di-*tert*-butyl-4-methoxyphenol, standard control substance.



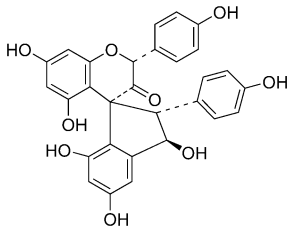
resveratrol (**3**) R_1 = H R_2 = OH R_3 = H
trans-3,3',5,5'-tetrahydroxy-4'-methoxystilbene (**4**) R_1= OH R_2 = OMe R_3 = OH



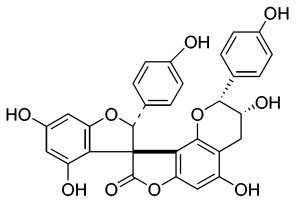
yuccaol A (**5**) R_1 = H R_2 = OH R_3 = H
yuccaol D (**1**) R_1 = OH R_2 = OMe R_3 = OH



yuccaol B (**6**) R_1 = H R_2 = OH R_3 = H R_4 = H
yuccaol C (**7**) R_1 = OH R_2 = OMe R_3 = OH R_4 =H
yuccaol E (**2**) R_1 =OH R_2 = H R_3 = OH R_4 = OMe



yuccaone A (**8**)



larixinol (**9**)

trans-3,3′,5,5′-Tetrahydroxy-4′-methoxystilbene (**4**) was more active than resveratrol (**3**); this was in good agreement with the higher activity exhibited by yuccaols C (**7**), D (**1**), and E (**2**), which possess the same stilbenic portion, *trans*-3,3′,5,5′-tetrahydroxy-4′-methoxystilbene.

Membrane lipids are rich in unsaturated fatty acids, which are susceptible to oxidative processes, linoleic acid being especially the target of lipid peroxidation.[24,25] The antioxidative effect of the MeOH extract of *Y. schidigera*, its phenolic fraction, and compounds **1**−**9** on the autoxidation of linoleic acid was also determined. The values of antioxidant activity (AA) measured at $t = 60$ and 120 min, employing bleaching of β-carotene as a model system, are reported in Table 2. The data show that all the tested samples, except compound **4**, exhibited significant activity in this test. In particular all the yuccaols showed activity higher than that of the standard phenolic antioxidant 2,6-di-*tert*-butyl-4-methoxyphenol (BHT) (at $t = 120$ min). The above results show the potential use of *Y. schidigera* as a source of antioxidant principles. It is of note that *Y. schidigera* powder possesses the GRAS label given by the FDA, which allows application of its extract and powder in soft drink (root beer), pharmaceutical, cosmetic, food, and feeding-stuff industries.[1,2]

Experimental Section

General Experimental Procedures. NMR spectra were recorded in CD_3OD using a Bruker DRX-600 spectrometer, operating at 599.19 MHz for ^{1}H and 150.86 MHz for ^{13}C. 2D experiments—^{1}H−^{1}H DQF-COSY (double quantum filtered direct chemical shift correlation spectroscopy), inverse detected ^{1}H−^{13}C HSQC (heteronuclear single quantum coherence), HMBC (heteronuclear multiple bond connectivity), and ROESY—were obtained using UX-NMR software. Selective excitation spectra, 1D-TOCSY, were acquired using waveform generator-based Gauss-shaped pulses, with mixing times ranging from 100 to 120 ms and a MLEV-17 spin-lock field of 10 kHz preceded by a 2.5 ms trim pulse. Exact masses were measured by a Q-Star Pulsar (Applied Biosystems, Foster City, CA) triple-quadropole orthogonal time-of-flight (TOF) instrument. ESIMS were performed on a Finnigan LC-Q Deca Ion Trap mass spectrometer scanned from 150 to 1200 Da. The mass spectral data were acquired and processed using Xcalibur software. Samples were dissolved in MeOH and infused in the ESI source by using a syringe pump at a flow rate of 3 μL/min. The capillary voltage was 5 V, the spray voltage 5 kV, and the tube lens offset 50 V. The capillary temperature was 220 °C. HPLC separations were carried out on an HP1100 series HPLC, equipped with a photodiode array detector, from Agilent Technologies (Palo Alto, CA), using a Waters μ-Bondapak RP18 column. TLC were performed on silica gel F254 (Merck) plates, and reagent grade chemicals (Carlo Erba) were used throughout.

Plant Material. Yucca (*Yucca schidigera* Roezl, Agavaceae) bark was collected in October 2001 in San Diego, CA. A voucher specimen is on file at Desert King International, 7024 Manya Circle, San Diego, CA 92154.

Extraction and Isolation. The MeOH extract and its phenolic fraction were obtained from yucca bark as previously reported.[5] Part of the phenolic fraction (50 mg) was chromatographed on HPLC on a Waters (μ-Bondapack RP-18) column (30 cm × 7.6 mm i.d.) applying a linear gradient of H_2O/CH_3CN (4:1) for 5 min, then a linear gradient of H_2O/CH_3CN (7:3) for 30 min, followed by isocratic elution for 10 min and a linear gradient of H_2O/CH_3CN (3:2) for 30 min (flow rate 3 mL/min). Yuccaone A (**8**) (1.0 mg, $t_R = 8.2$ min), *trans*-3,3′,5,5′-tetrahydroxy-4′-methoxystilbene (**4**) (5.1 mg, $t_R = 18.8$ min), larixinol (**9**) (2 mg, $t_R = 24.7$ min), resveratrol (**3**) (2.5 mg, $t_R = 29.9$ min), yuccaol E (**2**) (1.8 mg, $t_R = 41.8$ min), yuccaol C (**7**) (8.0 mg, $t_R = 43.9$ min), yuccaol D (**1**) (6.0 mg, $t_R = 46.4$ min), yuccaol A (**5**) (3.1 mg, $t_R = 57.8$ min), and yuccaol B (**6**) (1.8 mg, $t_R = 62.4$ min).

Yuccaol D (1): amorphous powder; $[\alpha]^{22}_D$ +6.8° (*c* 0.1, MeOH); IR (KBr) ν_{max} 2915, 1782, 1624, 1510, 1257, 1172, 1134, 1022 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; ESIMS, *m/z* 543 $[M + H]^+$, 449 $[M - 94 + H]^+$, 417 $[M - 126 + H]^+$; HRESIMS *m/z* 541.1135 (calcd for $C_{50}H_{21}O_{10}$ $[M - H]^-$, 541.1154).

Yuccaol E (2): amorphous powder; $[\alpha]^{22}_D$ +35.6° (*c* 0.1, MeOH); IR (KBr) ν_{max} 2911, 1770, 1624, 1510, 1249, 1172, 1076, 1022 cm^{-1}; ^{1}H and ^{13}C NMR, see Table 1; ESIMS, *m/z* 543 $[M + H]^+$, 449 $[M - 94 + H]^+$, 417 $[M - 126 + H]^+$; HRESIMS *m/z* 541.1127 (calcd for $C_{50}H_{21}O_{10}$ $[M - H]^-$, 541.1154).

TEAC Test. Pure compounds were tested by using the TEAC assay.[22,23] The TEAC value is based on the ability of the antioxidant to scavenge the radical cation $ABTS^{+}$ with spectrophotometric analysis. The $ABTS^{\bullet+}$ cation radical was produced by the reaction between 7 mM ABTS in H_2O and 2.45 mM potassium persulfate, stored in the dark at room temperature for 12 h. $ABTS^{\bullet+}$ is a blue-green cromogen with a characteristic absorption at 734 nm. The $ABTS^{\bullet+}$ solution was then diluted with PBS (phosphate saline buffer, pH = 7.4) to an absorbance of 0.70 at 734 nm and equilibrated at 30 °C.

Samples were diluted with methanol to produce solutions of 0.3, 0.5, 1, 1.5, and 2 mM concentration. The reaction was initiated by the addition of 1 mL of diluted ABTS to 10 μL of each sample solution. Determinations were repeated three times for each sample solution. The percentage inhibition of absorbance at 734 nm was calculated for each concentration relative to a blank absorbance (methanol) and was plotted as a function of concentration of compound or standard, 6-hydroxy-2,5,7,8-tetramethylcroman-2-carboxylic acid (Trolox, Aldrich Chemical Co., Gillingham, Dorset, UK). The percentage inhibition was plotted as a function of compound or standard concentration.

The antioxidant activities of MeOH extract, the phenolic fraction, and compounds **1**−**9** are expressed as TEAC values in comparison with TEAC activity of the reported reference compound quercetin. The TEAC value is defined as the concentration of standard Trolox solution with the same antioxidant capacity as a 1 mM concentration of the investigated compound.

Autoxidation of *β*-Carotene. Heat-induced oxidation of an aqueous emulsion system of β-carotene and linoleic acid was measured by the method described by Pratt.[24] Quantities of linoleic acid (20 mg) and Tween 20 (200 mg) were placed in a flask, and a solution of 2 mg of β-carotene in 10 mL of $CHCl_3$ was added. After removal of $CHCl_3$, 50 mL of distilled water saturated with oxygen for 30 min was added. Aliquots (200 μL) of each compound, dissolved in ethanol to a 15 μg/mL solution, were added to each flask with shaking. Samples without test compounds were used as blanks, and a sample with BHT (Aldrich Chemical Co., Gillingham, Dorset, UK) was used as a control substance. Samples were subjected to oxidation by placing in an oven at 50 °C for 3 h. The absorbance was read at 470 nm at regular intervals to monitor the rate of bleaching of β-carotene. The antioxidant activity was expressed as AA and calculated with the equation

$$\text{inhibitory ratio (AA)} = [1 - (A_0 - A_t)/(A_{00} - A_{0t})] \times 100$$

A_0 = absorbance at the beginning of the incubation, with test compound; A_t = absorbance at the time t, with test compound; A_{00} = absorbance at the beginning of the incubation, without test compound; A_{0t} = absorbance at the time t, without test compound. Each experiment was performed in triplicate.[24,25] Compounds are considered active when their AA is close to that of BHT, the positive control.

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