Journal of Natural Products
Vol. 53, No. 2, pp. 396-406, Mar-Apr 1990

FURANOID LIGNANS FROM *LARREA TRIDENTATA*[1]

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ABSTRACT.—From the leaves and stems of *Larrea tridentata* six new furanoid lignans, compounds **1–6**, have been isolated and their structures determined through interpretation of physical and spectroscopic properties. The use of 1D and 2D nOe experiments was of particular importance in assigning the stereochemistry.

As part of our continuing studies on the constituents of the creosote bush, *Larrea tridentata* (DC.) Coville (Zygophyllaceae) (1,2), a plant used in Mexico as a contraceptive agent (3), we report here on the isolation of six new furanoid lignans **1–6** from the phenolic fractions of the leaves and twigs. In the recent literature relating to the botanical aspects of this plant, there is a tendency towards the recognition of *L. tridentata* Cov., native to the southwestern U.S. and northern Mexico, as a separate species from *Larrea divaricata* Cav., native to northwestern Argentina (1,2). Because the material used in this study was collected in Arizona, we have used the name *L. tridentata*. *L. tridentata* extracts have been reported to display uterine relaxation activity in vitro (4), and previous work has indicated the presence of flavonoids, lignans, volatile oils, and saponins (5–13). We have recently reported on the structure elucidation of two new triterpenes from the stems (14), on new 1-aryl tetralin lignans (15), on a novel naphthoquinone, larreantin (16), and on the bioassay-directed isolation of the active anti-implantation agent, 3′-demethoxy-6-*O*-demethylisoguaiacin [**16**], from the leaf and twig parts (17) of this plant.

Further fractionation of the phenolic fraction of the leaves and twigs of *L. tridentata* led to the isolation of 4-*epi*-larreatricin [**1**], mp 230–232°, displaying an hrms molecular ion at *m/z* 284.1398 (calcd 284.1412), indicating a molecular formula of $C_{18}H_{20}O_3$. The ir spectrum revealed the presence of hydroxyl group absorption (ν max 3370 cm^{-1}), which was substantiated to be phenolic from a bathochromic shift in the uv spectrum. In the ^1H nmr in Me_2CO-d_6, a three-proton doublet at 1.00 ppm ($J = 5.7$ Hz) due to a methyl group, a multiplet at 1.74 ppm due to its attached methine proton, a doublet at 4.59 ppm ($J = 9.1$ Hz) due to an oxymethine proton, and an A_2B_2 type pattern at 6.82 and 7.24 ppm ($J = 8.6$ Hz) due to a 1,4-disubstituted aromatic nucleus were observed. The homonuclear COSY spectrum confirmed the coupling between the methyl group and the methine multiplet at 1.74 ppm, and between

[1]This work was presented in part at the 28th Annual Meeting of the American Society of Pharmacognosy, University of Rhode Island, Kingston, RI, July, 1987.

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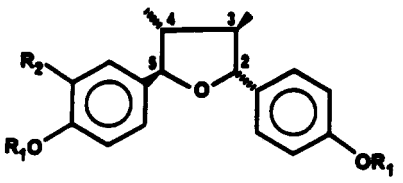
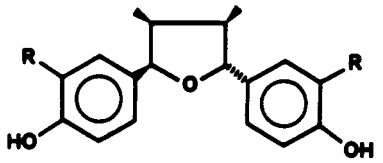
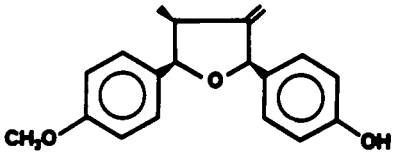


1 $R_1=R_2=H$
2 $R_1=H$, $R_2=OH$
8 $R_1=Me$, $R_2=H$
11 $R_1=Me$, $R_2=OMe$
17 $R_1=Ac$, $R_2=H$



3 R=H
4 R=OMe



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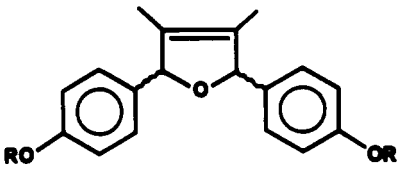
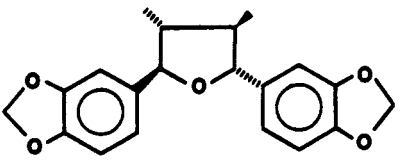


6 R=H
18 R=Ac



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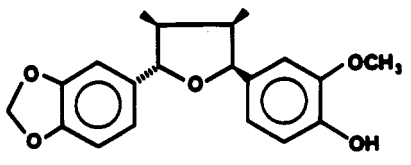

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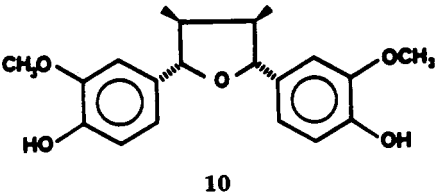

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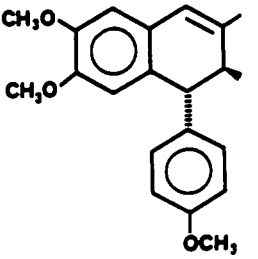

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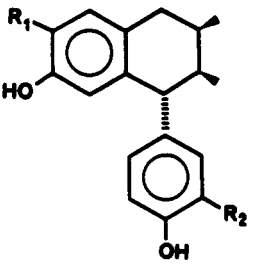
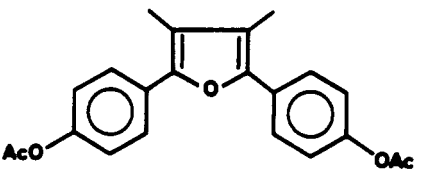


13 $R_1=R_2=OH$
14 $R_1=OH$, $R_2=OMe$
15 $R_1=R_2=OMe$
16 $R_1=OH$, $R_2=H$



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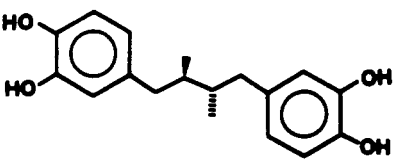

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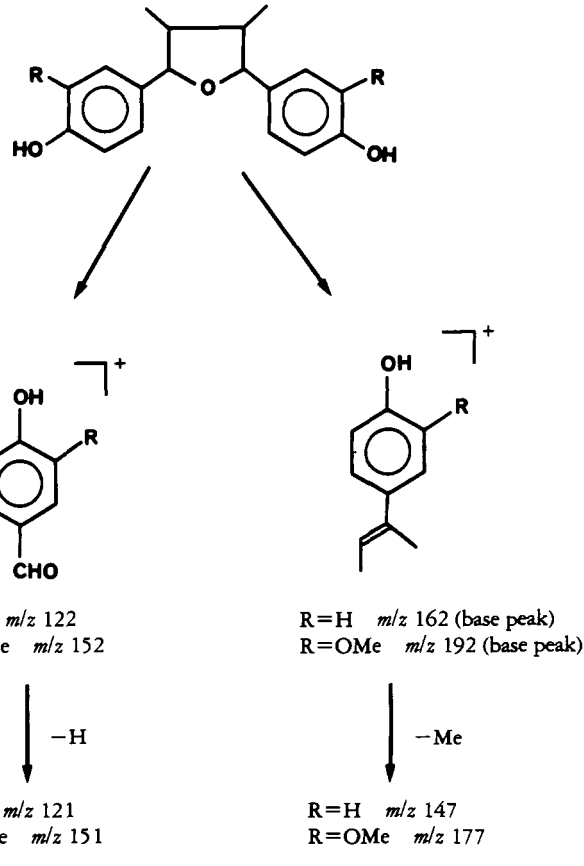
this signal and the methine doublet at 4.59 ppm. The ^{13}C-nmr spectrum showed signals at 134.0, 128.3, 115.8, and 157.6 ppm, comparable to those of the 4-hydroxyphenyl moiety in ephedradine D (18). From the foregoing data and the molecular formula, it was considered that 4-*epi*-larreatricin had a symmetrical structure represented by formula **1**, excluding stereochemistry. Mass spectral fragmentation ions at *m/z* 162, 147, 122, and 121 supported this conclusion (Scheme 1).

In the ^{1}H-nmr spectrum, the chemical shifts of the methyl and methine signals were essentially identical with those of the corresponding groups in galbacin [**7**] (19), as were the coupling constants between H-2 and H-3 ($J = 9$ Hz). This suggested that the relative stereochemistry between H-2, H-3, H-4, and H-5 in 4-*epi*-larreatricin was all trans. The 2D nOe spectrum, obtained in pyridine-d_6, gave evidence of the spatial proximity of 3-Me and H-3, of 3-Me and H-2, and of H-2 and H-4, indicating that 4-*epi*-larreatricin may be represented by the stereostructure **1**.

Methylation of 4-*epi*-larreatricin with Me_2SO_4 and K_2CO_3 in Me_2CO afforded a dimethyl derivative **8** ([M]$^+$ 312, $C_{20}H_{24}O_3$), which now displayed two aromatic methoxyl groups at 3.80 ppm in the ^{1}H-nmr spectrum. When **1** was acetylated with Ac_2O, diacetate **17** was obtained. The chemical shifts of both the methyl and methine (H-3 and H-4) signals in **8** and **17** were similar to those of the corresponding signals in (+)-galbacin [**7**] (19) and quite different from those in chicanine [**9**] (20) and malabaricanol [**10**] (21), thereby further substantiating the relative stereostructure of 4-*epi*-larreatricin.

3″-Hydroxy-4-*epi*-larreatricin [**2**], mp 188–190°, displayed a molecular ion at *m/z*



SCHEME 1. General mass fragmentation scheme of compounds **1–4**.

300.1312, analyzing for $C_{18}H_{20}O_4$ (calcd 300.1361), one oxygen atom more than 4-*epi*-larreatricin. The ^{1}H-nmr spectrum in Me_2CO-d_6 revealed the presence of two methyl doublets (0.99 and 1.01 ppm, $J = 5.4$ Hz), a two-proton multiplet at 1.72 ppm, and two methine doublets at 4.54 and 4.56 ppm ($J = 8.4$ Hz). The aromatic region displayed a set of A_2B_2 signals at 6.82 and 7.24 ppm ($J = 8.6$ Hz), and a set of ABC signals at 6.74 ($J = 2.1$ and 7.7 Hz), 6.79 ($J = 7.7$ Hz), and 6.92 ppm ($J = 2.1$ Hz) on a second aromatic system. Except for the latter set of signals, both the chemical shifts and the coupling constants of these signals were quite close to those of **1**. It was therefore proposed that the additional oxygen atom was present in a 3,4-dihydroxyphenyl moiety in **2**. This deduction was confirmed by the ^{13}C-nmr spectrum which showed two separate sets of aromatic carbon atoms: one due to a 4-hydroxyphenyl moiety [δ 134.8, 115.8 (2C), 128.4 (2C), and 157.6], and one due to a 3,4-dihydroxyphenyl unit (δ 135.8, 114.2, 145.1, 145.8, 115.7, and 118.7).

Interproton couplings were established though a homonuclear COSY spectrum in pyridine-d_5. The methyl signal at 0.97 ppm was coupled with the methine signal at 1.84 ppm, which itself was coupled with an oxymethine signal at 4.76 ppm. On the other hand, the methyl signal at 1.01 ppm was coupled with the methine signal at 1.84 ppm, which was itself coupled with the oxymethine signal at 4.81 ppm. The aromatic proton resonance at 7.29 ppm was coupled with the signal at 7.07 ppm, which also coupled with the signal at 7.52 ppm. As expected, the signals at 7.49 and 7.23 ppm were found to be coupled. These data suggested that compound **2** was 3″-hydroxy-4-*epi*-larreatricin, excepting stereochemical assignments.

In the ^{1}H-nmr spectrum obtained in Me_2CO-d_6, the aliphatic portion of the spectrum was essentially identical to that of 4-*epi*-larreatricin [**1**], indicating that H-2, H-3, H-4, and H-5 all have a trans relationship. In pyridine-d_5, the 2D nOe spectrum revealed the proximity of the 3-Me with both H-2 and H-3, of the 4-Me and H-4 and H-5, and of H-2 and H-4, and H-3 and H-5 in the aliphatic region. The chemical shift of the methine protons H-3 and H-4 (1.72 ppm) was very similar to that observed (1.74 ppm) for 4-*epi*-larreatricin [**1**], suggesting that the relative stereochemistry of **2** was the same as that of **1**. This was confirmed through comparison of the ^{13}C-nmr signals of the tetrahydrofuran moiety in **2** (Table 1).

To confirm the absolute stereostructure, trimethyl 3″-hydroxy-4-*epi*-larreatricin [**11**], $[M]^+$ at *m/z* 342, was prepared and treated with acid to afford **12** (21). In the ^{1}H-nmr spectrum, a methyl doublet (1.08 ppm), a vinyl methyl signal (1.78 ppm), two methine signals (2.36 and 3.62 ppm), three methoxy signals (3.75, 3.78, and 3.89 ppm), a broad olefinic singlet (6.13 ppm), two singlet aromatic protons (6.55 and 6.62 ppm), and a pair of A_2B_2 signals (6.75 and 6.96 ppm) were observed. These signals were very similar to those of *trans*-4-(3,4-dimethoxyphenyl)-3,4-dihydro-6,7-dimethoxy-2,3-dimethylnaphthalene, except for the signals due to the phenyl group (21).

The cd curve of **12** displayed Cotton effects at 237 nm ([θ] −1,800) and 285 nm ([θ] +1,000), suggesting that the absolute stereochemistry of **12** at C-1 is the same as that in 6,3′-di-*O*-demethyl-isoguaiacin [**13**] (15). Because the acid-mediated rearrangement does not affect the stereochemistry at this center, the absolute configuration of 3″-hydroxy-4-*epi*-larreatricin [**2**] is represented by (3*R*,4*R*)-dimethyl-(2*R*)-(4-hydroxyphenyl)-(5*R*)-(3,4-dihydroxyphenyl)-tetrahydrofuran.

Separate examination of the stems of *L. tridentata* led to the isolation of three known lignans, 6-*O*-demethylisoguaiacin [**14**] (10), isoguaiacin [**15**] (22), and 3′-demethoxy-6-*O*-demethylisoguaiacin [**16**] (17), and four new furanoid lignans, compounds **3–6**. The first of these, larreatricin [**3**], mp 161–163°, displayed a molecular ion at *m/z* 284.1378, indicating a molecular formula of $C_{18}H_{20}O_3$ (calcd 284.1412). In its ir

TABLE 1. ^{13}C-nmr Spectral Data of Lignans **1–6**.[a]

Carbon	Compound					
	1	**2**	**3**	**4**	**5**	**6**
C-2	88.7	88.8	86.1	85.9	82.6	91.8
C-3	51.9	51.9	48.4	47.9	159.7	131.7
C-4	51.9	52.0	44.0	43.6	43.7	131.7
C-5	88.7	88.8	85.2	84.7	84.0	91.8
C-1′	134.0	134.8	135.5	135.5	133.1	134.4
C-2′	128.3	128.4	128.3	109.1	129.8	129.1
C-3′	115.8	115.8	115.8	147.1	115.9	115.8
C-4′	157.6	157.6	157.6	145.9	158.0	157.8
C-5′	115.8	115.8	115.8	114.7	115.9	115.8
C-6′	128.3	128.4	128.3	119.6	129.8	129.1
C-1″	134.0	135.8	132.8	133.0	132.5	134.4
C-2″	128.3	114.2	127.9	108.9	128.3	129.1
C-3″	115.8	145.8	115.5	146.9	114.1	115.8
C-4″	157.6	145.1	157.6	145.2	159.9	157.8
C-5″	115.8	115.7	115.5	114.5	114.1	115.8
C-6″	128.3	118.7	127.9	119.1	128.3	129.1
3-Me	13.9	14.1	12.1	11.9	—	10.4
4-Me	13.9	14.0	9.7	9.5	17.5	10.4
3-CH_2=	—	—	—	—	106.8	—

[a]Recorded in Me_2CO-d_6 except **4** (in C_6H_6-d_6). Chemical shift values are reported as δ values (ppm) from internal TMS. APT experiments were performed to aid in assignment.

spectrum the presence of hydroxy groups (ν max 3260 cm^{-1}) was indicated, and in the ^{1}H-nmr spectrum, two methyl doublets (0.58 and 0.96 ppm), a two-proton methine multiplet (2.42 ppm), two methine doublets (4.60 and 5.42 ppm), and two A_2B_2 sets of aromatic signals (6.82, 6.83, 7.18, and 7.25 ppm) were observed. The ^{13}C-nmr spectrum revealed two sets of aromatic nuclei, and comparison with the signals of the 4-hydroxyphenyl group in ephedradine D (18) suggested that the isolate had two 4-hydroxyphenyl moieties. Two methyl carbons (9.7 and 12.1 ppm), two methine carbons (44.0 and 48.4 ppm), and two oxymethine carbons (85.2 and 86.1 ppm) were also observed.

The homonuclear COSY spectrum indicated coupling between each methyl signal and the methine signal at 2.42 ppm, which itself was further coupled to the methine signals at 4.60 and 5.42 ppm. The coupling patterns and the chemical shifts of these signals led to the conclusion that the isolate had the same overall structure as 4-*epi*-larreatricin [**1**], and this was further supported by the fragment ion peaks at *m/z* 162, 147, 122, and 121 (Scheme 1). The chemical shifts and coupling constants of 3-Me and H-2 were similar to those of 4-Me and H-5 in chicanine [**9**] (20), as were the chemical shifts of 4-Me and H-5 with 3-Me and H-2 in chicanine. These data indicated that H-2 and H-3 are trans, and that H-4 and H-5 are cis in the isolate. The relative stereochemistries were established through a series of nOe experiments. Thus the 3-Me displayed nOe effects with H-2 (4.1%), H-3 (3.3%), and the 4-Me (1.6%). Likewise the 4-Me showed nOe effects with H-2 (8.5%), the 3-Me (1.1%), H-4 (3.3%), and H-2″ (H-6″) (0.9%). These results indicate the relative stereochemistry of larreatricin as depicted in **3**. The ^{13}C-nmr spectrum was assigned by comparison with that of **1**; the set of aromatic resonances at higher field was assigned to the aryl ring at C-5 because of its cis orientation to the 4-Me group (23).

The second new lignan, **4**, from the stems of *L. tridentata* displayed a molecular ion

at *m/z* 344.1556, indicating a molecular formula of $C_{20}H_{24}O_5$ (calcd 344.1624). The ir spectrum indicated the presence of hydroxyl functionality (ν max 3350 cm^{-1}). The ^{1}H-nmr spectrum of the isolate was very similar to that of **3** with the exception that aromatic methoxy signals were observed at 3.83 and 3.86 ppm and only six aromatic protons were apparent. The latter were shown clearly in C_6H_6-d_6 in the form of two ABC systems (6.78, 7.06, and 7.12 ppm and 6.82, 6.92, and 7.07 ppm), leading to the conclusion that the isolate has two hydroxymethoxyphenyl moieties; this was supported by the mass spectrum, which showed a base peak at *m/z* 192 and significant fragments at *m/z* 177, 152, and 151 (Scheme 1).

The 2D nOe spectrum in C_6H_6-d_6 displayed nOe's between a methoxy signal at 3.20 ppm and a meta-coupled aromatic proton at 6.92 ppm, and also between a methoxy signal at 3.22 ppm and a second meta-coupled aromatic proton at 7.06 ppm. From the ^{13}C-nmr spectrum, which showed the presence of four aromatic carbons bearing oxygen (145.2, 145.9, 146.9, and 147.1 ppm), and the chemical shifts of the remaining aromatic carbons, it was apparent that two 3-methoxy-4-hydroxyphenyl moieties were present (16,24). The COSY spectrum in C_6H_6-d_6 indicated coupling between the methyl signal at 0.61 ppm and the methine signal at 2.10 ppm, which was also coupled to the oxygenated methine at 5.37 ppm. On the other hand, the methine signal at 2.25 ppm was coupled to the methyl signal at 0.86 ppm and the methine signal at 4.65 ppm. The 2D nOe spectrum established a close spatial relationship between 3-Me (0.86 ppm) and H-2 and H-3, and for the 4-Me (0.61 ppm) with H-2, H-4, and H-2″ at 6.92 ppm. Comparison of the chemical shift of the aliphatic carbons indicated that they were extremely close to those of **3**, leading to the conclusion that the isolate is 3′,3″-dimethoxylarreatricin [**4**].

Repeated chromatography of the MeOH extract of the dried stems of *L. tridentata* also gave larreatridenticin [**5**] and a mixture of 4-*epi*-larreatricin [**1**] and 3,4-dehydrolarreatricin [**6**]. Larreatridenticin [**5**], mp 152–153°, had a molecular formula $C_{19}H_{20}O_3$ (*m/z* 296.1349, calcd 296.1412). Its ir spectrum suggested the presence of hydroxyl groups (ν max 3340 cm^{-1}), and the ^{1}H-nmr spectrum in Me_2CO-d_6 showed two sets of A_2B_2 type of signals at δ 6.87 and 7.31 (J = 8.6 Hz) and at δ 6.93 and 7.32 (J = 8.9 Hz), suggesting that larreatridenticin has two 4-substituted phenyl groups. An nOe effect was observed between a methoxyl group (δ 3.80) and an aromatic signal at δ 6.93, leading to the conclusion that a 4-methoxyphenyl group was present.

In the ^{13}C-nmr spectrum, two sets of signals [δ 132.5 and 133.1, 128.3 (2C) and 129.8 (2C), 114.1 (2C) and 115.9 (2C), 158.0 and 159.9] for the phenyl groups were observed, whose chemical shifts were very similar to those in **1**. Mass spectral fragment ions at *m/z* 121 and 135 substantiated these assignments.

The ^{1}H-nmr spectrum also showed a methyl (δ 0.73), a methine (δ 3.10), a terminal methylene (δ 4.64 and 5.02), and two methine protons adjacent to oxygen (δ 5.09 and 5.25). The COSY spectrum revealed couplings between a methyl signal at δ 0.73 and a methine signal at δ 3.10, between the methine signal at δ 3.10 and the terminal methylene signals at δ 4.64 and 5.02, between the methine signal at δ 3.10 and a methine signal at δ 5.09, and between the methine signal at δ 5.25 and the methylene at δ 4.64 and 5.02, indicating that the isolate has the furanoid skeleton shown in **5**. This conclusion was also supported by the ^{13}C-nmr resonances (δ 17.5, 43.7, 82.6, 84.0, 106.8, and 159.7) of the furanoid moiety.

The respective locations of the 4-methoxyphenyl and 4-hydroxyphenyl groups were determined from the COSY spectrum. Thus couplings were observed between H-5 (δ 5.09) and H-2″/H-6″ (δ 7.32), and between H-2″/H-6″ and H-3″/H-5″ (δ 6.93); the latter signal also showed nOe with the methoxyl signal (δ 3.80). On the other aromatic ring, couplings were observed between H-2 (δ 5.25) and H-2′/H-6′ (δ 7.31) and be-

tween H-2′/H-6′ and H-3′/H-5′ (δ 6.87). In the 2D nOe spectrum of **5**, H-5 was shown to have an nOe with both H-2 and H-4, but not with the 4-Me group. Nor was there any observed nOe between the 4-Me and H-2. These results suggested a cis relationship between the substituents on C-2, C-4, and C-5 in larreatridenticin [**5**].

The mixture of lignans **1** and **6** was acetylated with Ac_2O/pyridine and separated to afford diacetyl-4-*epi*-larreatricin [**17**] and diacetyl 3,4-dehydrolarreatricin [**18**]. These diacetates were separated and hydrolyzed to yield the parent lignans. The spectral properties of **17** clearly indicated that it was the diacetyl derivative of **1**. Indeed, its hydrolytic product was identified as 4-*epi*-larreatricin [**1**] by comparison with a sample isolated from the leaves and twigs of *L. tridentata*.

Spectroscopic analysis of **18** suggested a symmetrical lignan structure bearing a substituted 2,5-dihydrofuran ring. The natural deacetylated compound, 3,4-dehydrolarreatricin [**6**], mp 211–213°, had a molecular formula $C_{18}H_{18}O_3$ ($[M]^+$ *m/z* 282). The ir spectrum displayed a hydroxyl band (ν max 3370 cm^{-1}), and in the ^{1}H-nmr spectrum, a vinyl methyl singlet (δ 1.49), a methine singlet (δ 5.64), due to a methine adjacent to oxygen, and two A_2B_2 type systems (δ 6.82 and 7.15, $J = 8.5$ Hz) were observed. A 4-hydroxyphenyl moiety was confirmed from the ^{13}C-nmr spectrum showing signals at δ 134.4, 129.1, 115.8, and 157.8, which were essentially identical with those of the 4-hydroxyphenyl unit in **1**. The mass spectrum showed a base peak at *m/z* 162 and a fragment ion at *m/z* 121 (96%) due to the 4-hydroxyphenyl moiety. These data, and the molecular formula, suggested that the 3,4-dehydrolarreatricin is symmetrical and has the structure **6**. The stereochemistry of **6** has not been determined.

Diacetyl 3,4-dehydrolarreatricin [**18**] and possibly 3,4-dehydrolarreatricin [**6**] were unstable at room temperature. A degradation product was purified and shown to be the furan derivative **19**. Examination of its ^{1}H-nmr spectrum revealed a symmetrical structure with two olefinic methyl groups (δ 2.26) and two 4-hydroxyphenyl rings (δ 7.23 and 7.77), in addition to two acetyl groups (δ 2.28). A molecular ion at *m/z* 364 ($C_{22}H_{20}O_5$), together with a base peak at *m/z* 121, supported the structural assignment of this compound.

ANTI-IMPLANTATION ACTIVITY.—Details of the bioassays and post-coital activity of the plant extracts, fractions, and isolates have been previously described (17). In summary, 3′-demethoxy-6-*O*-demethylisoguaiacin [**16**], 6-*O*-demethylisoguaiacin [**14**], 4-*epi*-larreatricin [**1**], and nor-dihydroguaiaretic acid [**20**] were evaluated in timed pregnant Sprague-Dawley rats on days 4–6 of gestation. A dose-dependent response was observed for 3′-demethoxy-6-*O*-demethylisoguaiacin with no effects at the oral dose of 5 mg/kg; presence of implantation sites but no viable fetuses at 15 mg/kg; a significant decrease in implantation sites and fertility at 30 mg/kg; and no implantation sites at 60 mg/kg. The compound demonstrated estrogenic activity at 30 mg/kg (17).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Kofler-type hot-stage apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. Cd spectra were recorded on a JASCO J-40A automatic recording spectropolarimeter using a quartz cell of 20 mm length and 3.5 ml volume. Uv spectra were recorded with a Beckman model DU-7 spectrophotometer and ir spectra were obtained with a Nicolet MX-1 interferometer. Mass spectra were determined with a Varian MAT 112S double focusing mass spectrometer at 80 eV. The ^{1}H-nmr spectra were obtained with either a Nicolet NMC 360 instrument operating at 360 MHz or a Varian XL-300 instrument operating at 300 MHz. TMS was used as the internal standard and chemical shifts are reported in δ ppm downfield from TMS. ^{13}C-nmr spectra were obtained with a Nicolet NMC 360 instrument operating at 90.8 MHz.

Homonuclear COSY spectra were recorded at 1K with a Varian XL 300 spectrometer. Standard Varian pulse sequences were used. NOe difference spectra were measured on a Nicolet NMC 360 spectrometer. The samples were degassed by using a repeated freeze-pump-thaw cycle and then closed under N_2.

Data sets of 16K covering a spectral width of 2 MHz were acquired. A 2.0 Hz line broadening was applied to the data prior to Fourier transformation.

PLANT MATERIAL.—The plant samples of *L. tridentata* used in this study were collected by Mr. V.M. Gass and Ms. Wendy Hodgson, Desert Botanical Garden, Phoenix, Arizona, in the vicinity of Phoenix, Arizona in June 1983 and identified by one of us (D.D.S.). Herbarium specimens representing the collection are deposited in the herbarium of the Desert Botanical Garden and in the John G. Searle Herbarium, Field Museum of Natural History, Chicago, Illinois.

ISOLATION OF LIGNANS **1** AND **2** FROM LEAVES AND TWIGS.—Details of the extraction and chromatography of the phenolic fraction have been described previously (15,17). Fraction F-037 was rechromatographed on Si gel eluting with C_6H_6-EtOAc (8:2), followed by overpressure layer chromatography (oplc) (25) of the resulting subfraction, F-074, on Si gel and crystallization from Me_2CO to afford 4-*epi*-larreatricin [**1**] (77 mg, 0.0003%) as colorless needles: mp 230–232°; cd $[\theta]_{228}$ −7500 ($c = 0.019$, MeOH); ir ν max (KBr) 3370 cm^{-1}; uv λ max (MeOH) (log ϵ) 229 (4.48), 276 (4.64) nm, (MeOH + NaOH) 228 (4.71), 245 (4.80), 274 (4.08) nm; ^{1}H nmr (Me_2CO-d_6) δ 1.00 (6H, d, $J = 5.7$ Hz, 3- and 4-Me), 1.74 (2H, m, H-3, -4), 4.59 (2H, d, $J = 9.1$ Hz, H-2, -5), 6.82 (4H, d, $J = 8.6$ Hz, H-3′, -5′, -3″, -5″), 7.24 (4H, d, $J = 8.6$ Hz, H-2′, -6′, -2″, -6″); ^{1}H nmr (pyridine-d_5) δ 1.00 (6H, d, $J = 5.8$ Hz, 3- and 4-Me), 1.85 (2H, m, H-3, -4), 4.82 (2H, d, $J = 9.0$ Hz, H-2, -5), 7.27 (4H, d, $J = 8.5$ Hz, H-3′, -5′, -3″, -5″), 7.56 (4H, d, $J = 8.5$ Hz, H-2′, -6′, -2″, -6″); ^{13}C nmr (Me_2CO-d_6) see Table 1; ms *m/z* (rel. int.) $[M]^+$ 284 (4), 163 (73), 162 (100), 148 (61), 147 (99), 134 (18), 133 (20), 122 (10), 121 (19), 108 (13), 107 (25), 94 (14), 77 (16).

Repeated cc of a portion of fraction F-064 on Si gel and alumina by continuous elution with C_6H_6-EtOAc (7:3) followed by recrystallization from a mixture of hexane/$CHCl_3$/Me_2CO yielded 3″-hydroxy-4-*epi*-larreatricin [**2**] (190 mg, 0.0008%) as colorless plates: mp 188–190°; cd $[\theta]_{207}$ −32,100, $[\theta]_{230}$ −52,400, $[\theta]_{278}$ −3,200 ($c = 0.005$, MeOH); ir ν max (KBr) 3300 cm^{-1}; uv λ max (MeOH) (log ϵ) 225 (4.36), 281 (3.72) nm; (MeOH + NaOH) 225 (4.62), 246 (4.39), 285 (4.04) nm; ^{1}H nmr (Me_2CO-d_6) δ 0.99 (3H, d, $J = 5.4$ Hz, 3-Me), 1.01 (3H, d, $J = 5.4$ Hz, 4-Me), 1.72 (2H, m, H-3, -4), 4.54 (1H, d, $J = 8.4$ Hz, H-2), 4.56 (1H, d, $J = 8.4$ Hz, H-5), 6.74 (1H, dd, $J = 7.7$, 2.1 Hz, H-6″), 6.79 (1H, d, $J = 7.7$ Hz, H-5″), 6.82 (2H, d, $J = 8.6$ Hz, H-3′, -5′), 6.92 (1H, d, $J = 2.1$ Hz, H-2″), 7.24 (2H, d, $J = 8.6$ Hz, H-2′, -6′); ^{1}H nmr (pyridine-d_5) δ 0.97 (3H, d, $J = 5.5$ Hz, 3-Me), 1.01 (3H, d, $J = 5.5$ Hz, 4-Me), 1.84 (2H, m, H-3, -4), 4.76 (1H, d, $J = 8.5$ Hz, H-2), 4.81 (1H, d, $J = 8.5$ Hz, H-5), 7.07 (1H, dd, $J = 7.7$, 2.1 Hz, H-6″), 7.23 (2H, d, $J = 8.7$ Hz, H-3′, -5′), 7.29 (1H, d, $J = 7.5$ Hz, H-5″), 7.49 (2H, d, $J = 8.7$ Hz, H-2′, -6′), 7.52 (1H, d, $J = 2.1$ Hz, H-2″); ^{13}C nmr (Me_2CO-d_6) see Table 1; ms *m/z* (rel. int.) $[M]^+$ 300 (23), 215 (3), 178 (86), 163 (49), 162 (100), 150 (31), 147 (97), 138 (3), 137 (12), 134 (16), 123 (16), 122 (17), 121 (19), 107 (26), 94 (14).

METHYLATION OF LIGNANS **1** AND **2**.—4-*epi*-Larreatricin [**1**] (10 mg) was refluxed with K_2CO_3 (700 mg) and Me_2SO_4 (0.3 ml) in dry Me_2CO (10 ml) for 3 h. The solution was filtered and evaporated in vacuo. To the residue, H_2O and dilute NH_4OH were added to give a solid which, upon crystallization from MeOH, afforded dimethyl 4-*epi*-larreatricin [**8**] (8 mg) as colorless prisms: mp 51–53°; ^{1}H nmr ($CDCl_3$) δ 1.02 (6H, d, $J = 5.4$ Hz, 3- and 4-Me), 1.80 (2H, m, H-3, -4), 3.80 (6H, s, OMe), 4.65 (2H, d, $J = 8.4$ Hz, H-2, -5), 6.89 (4H, d, $J = 8.4$ Hz, H-2′, -6′, -2″, -6″), 7.33 (4H, d, $J = 8.4$ Hz, H-3′, -5′, -3″, -5″); ms *m/z* (rel. int.) $[M]^+$ 312 (5), 176 (98), 161 (100), 148 (11), 136 (95), 135 (18), 121 (15).

3″-Hydroxy-4-*epi*-larreatricin [**2**] (110 mg) was methylated in a similar manner. The reaction product **11** was purified by passing through a Si gel column eluting with hexane-$CHCl_3$ (2:3) to afford a colorless gum (98 mg): ^{1}H nmr ($CDCl_3$) δ 1.04 (6H, d, $J = 6$ Hz, 3- and 4-Me), 1.81 (2H, m, H-3, -4), 3.81 (3H, s, OMe), 3.88 (3H, s, OMe), 3.92 (3H, s, OMe), 4.65 (1H, d, $J = 9$ Hz, H-2), 4.67 (1H, d, $J = 9$ Hz, H-5), 6.84 (1H, d, $J = 8.2$ Hz, H-5″), 6.90 (2H, d, $J = 7.8$ Hz, H-3′, -5′), 6.92 (1H, dd, $J = 8.2$, 2.5 Hz, H-6″), 6.97 (1H, d, $J = 2.5$ Hz, H-2″), 7.33 (2H, d, $J = 7.8$ Hz, H-2′, -6′); ms *m/z* (rel. int.) $[M]^+$ 342 (13), 219 (3), 206 (40), 205 (3), 191 (37), 176 (77), 165 (19), 161 (100).

ACID REARRANGEMENT OF **11**.—To an Me_2CO solution of the methylation product **11** (50 mg), 10% perchloric acid in HOAc (1 ml) was added and the mixture stirred for 45 min. The reaction mixture was poured into dilute NaOH and extracted with C_6H_6. The C_6H_6 extract, after concentration in vacuo, was chromatographed over Si gel to yield lignan **12** (1.5 mg) as a colorless gum: ^{1}H nmr ($CDCl_3$) δ 1.08 (3H, d, $J = 7.5$ Hz, 2-Me), 1.78 (3H, bs, 3-Me), 2.36 (1H, m, H-2), 3.62 (1H, d, $J = 6.1$ Hz, H-1), 3.75 (3H, s, OMe), 3.78 (3H, s, OMe), 3.89 (3H, s, OMe), 6.13 (1H, s, H-4), 6.55 (1H, s, H-5), 6.62 (1H, s, H-8), 6.75 (2H, d, $J = 8.4$ Hz, H-3′, -5′), 6.96 (2H, d, $J = 8.4$ Hz, H-2′, -6′); ms *m/z* (rel. int.) $[M]^+$ 324 (100), 309 (87), 294 (29), 278 (19), 203 (19), 165 (11), 149 (15), 135 (20), 121 (36).

ISOLATION OF LIGNANS FROM THE STEMS OF *L. TRIDENTATA*.—Dried ground stems of *L. tridentata* (34.2 kg) were exhaustively extracted with MeOH at room temperature to give an MeOH extract

(3.49 kg), a sample of which (3.33 kg) was chromatographed over Si gel (5 kg) with increasingly polar mixtures of $CHCl_3$/MeOH to yield $CHCl_3$ (158 g), $CHCl_3$-MeOH (95:5) (88 g), $CHCl_3$-MeOH (90:10) (147 g), $CHCl_3$-MeOH (80:20) (105 g), and MeOH (2.43 kg) fractions (17). The $CHCl_3$ fraction was repeatedly chromatographed over Si gel, and elution with $CHCl_3$/MeOH led to the isolation of β-sitosterol. A lignan-containing fraction was further chromatographed over Si gel followed by oplc [Si gel, $CHCl_3$-Me_2CO-hexane (6:5:5)] to give *isoguaiacin* [**15**] (7 mg, 0.00021%) identical with authentic material.

The $CHCl_3$-MeOH (95:5) fraction (88.4 g) was repeatedly chromatographed over Si gel eluting with C_6H_6/EtOAc. Elution of a subfraction by low pressure cc on Si gel with C_6H_6-EtOAc (9:1) gave 3′,3″-*dimethoxylarreatricin* [**4**] (66 mg, 0.0002%) as a gum: cd $[\theta]_{203}$ +10,600, $[\theta]_{210}$ −10,600, $[\theta]_{230}$ −12,200 (c = 0.0084, MeOH); ir ν max (KBr) 3350 cm^{-1}; uv λ max (MeOH) (log ε) 205 (4.73), 230 (4.27), 281 (3.84) nm, (MeOH + NaOH) 207 (4.88), 228 (4.49), 249 (4.18), 281 (4.02) nm; ^1H nmr (Me_2CO-d_6) δ 0.59 (3H, d, J = 7.6 Hz, 4-Me), 0.98 (3H, d, J = 6.2 Hz, 3-Me), 2.45 (2H, m, H-3, -4), 3.83 (3H, s, 3″-OMe), 3.86 (3H, s, 3′-OMe), 4.62 (1H, d, J = 9.3 Hz, H-2), 5.45 (1H, d, J = 4.4 Hz, H-5), 6.80 (3H, m, H-2″, -5′, -5″), 6.84 (1H, dd, J = 8.1 and 1.8 Hz, H-6′), 6.98 (1H, br s, H-2′), 7.06 (1H, dd, J = 8.1 and 1.2 Hz, H-6″); ^1H nmr (C_6D_6) δ 0.61 (3H, d, J = 6.5 Hz, 4-Me), 0.86 (3H, d, J = 6.9 Hz, 3-Me), 2.10 (1H, m, H-4), 2.25 (1H, m, H-3), 3.20 (3H, s, 3″-OMe), 3.22 (3H, s, 3′-OMe), 4.65 (1H, d, J = 9.8 Hz, H-2), 5.37 (1H, d, J = 4.3 Hz, H-5), 6.78 (1H, dd, J = 8.5 and 2.7 Hz, H-6′), 6.82 (1H, d, J = 8.5 and 2.2 Hz, H-6″), 6.92 (1H, d, J = 2.2 Hz, H-2″), 7.06 (1H, br s, H-2′), 7.07 (1H, d, J = 8.5 Hz, H-5″), 7.12 (1H, d, J = 8.5 Hz, H-5′); ^{13}C nmr (C_6H_6-d_6) see Table 1; ms *m/z* (rel. int.) $[M]^+$ 344 (26), 192 (100), 177 (25), 175 (12), 164 (27), 163 (12), 161 (15), 152 (5), 151 (24), 137 (21), 124 (13), 91 (14), 77 (12), 65 (13), 55 (15).

Further development of the low pressure column yielding **4**, followed by recrystallization from Me_2CO, afforded larreatridenticin [**5**] (28 mg, 0.0001%) as colorless prisms: mp 152–153°; cd $[\theta]_{220}$ −16,733 (c = 0.015, MeOH); ir ν max (KBr) 3340 cm^{-1}; uv λ max (MeOH) (log ε) 227 (4.42), 275 (3.61) nm, (MeOH + NaOH) 227 (4.47), 245 (4.20), 275 (3.76) nm; ^1H nmr (Me_2CO-d_6) δ 0.73 (3H, d, J = 7.3 Hz, 4-Me), 3.10 (1H, m, H-4), 3.80 (3H, s, 4″-OMe), 4.64 (1H, t, J = 1.8 Hz, H-3a), 5.02 (1H, t, J = 1.8 Hz, H-3b), 5.09 (1H, d, J = 6.6 Hz, H-5), 5.25 (1H, br s, H-2), 6.87 (2H, d, J = 8.6 Hz, H-3′, -5′), 6.93 (2H, d, J = 8.9 Hz, H-3″, -5″), 7.31 (2H, d, J = 8.6 Hz, H-2′, -6′), 7.32 (2H, d, J = 8.9 Hz, H-2″, -6″); ^{13}C nmr (Me_2CO-d_6) see Table 1; ms *m/z* (rel. int.) $[M]^+$ 296 (1), 160 (98), 145 (100), 135 (10), 121 (10), 77 (11).

The $CHCl_3$-MeOH (90:10) fraction (162 g) from the first chromatography was divided into two portions and rechromatographed over Si gel eluting with an increasingly polar mixture of C_6H_6/EtOAc. A C_6H_6-EtOAc (7:3) fraction (F-116, 3.3 g) was further chromatographed over Si gel [$CHCl_3$-MeOH (97:3)], followed by crystallization from a mixture of $CHCl_3$ and Me_2CO to yield 6-*O*-demethylisoguaiacin [**14**] (980 mg, 0.003%), mp 153–155° [lit. (10) 148–149°], identical to authentic material.

Successive chromatography of a C_6H_6-EtOAc (7:3) fraction (F-118, 11.4 g) and recrystallization from a mixture of C_6H_6 and Et_2O gave larreatricin [**3**] (331 mg, 0.001%) as colorless needles: mp 161–163°, cd $[\theta]_{208}$ −22,000, $[\theta]_{229}$ −60,500 (c = 0.013, MeOH); ir ν max (KBr) 3260 cm^{-1}; uv λ max (MeOH) (log ε) 228 (4.68), 277 (3.78) nm; ^1H nmr (Me_2CO-d_6) δ 0.58 (3H, d, J = 6.7 Hz, 4-Me), 0.96 (3H, d, J = 6.7 Hz, 3-Me), 2.42 (2H, m, H-3, -4), 4.60 (1H, d, J = 8.5 Hz, H-2), 5.42 (1H, d, J = 4.5 Hz, H-5), 6.82 (2H, d, J = 8.6 Hz, H-3″, -5″), 6.83 (2H, d, J = 8.6 Hz, H-3′), 7.18 (2H, d, J = 8.6 Hz, H-2″, -6″), 7.25 (2H, d, J = 8.6 Hz, H-2′, -6′); ^{13}C nmr (Me_2CO-d_6) see Table 1; ms *m/z* (rel. int.) $[M]^+$ 284 (4), 163 (12), 162 (100), 147 (82), 134 (12), 122 (2), 121 (13), 107 (18), 94 (10).

Further elution of fraction F-118 with the same solvent followed by recrystallization from a mixture of C_6H_6 and Et_2O yielded 3′-demethoxy-6-*O*-demethylisoguaiacin [**16**] as colorless needles, mp 161–163°, identical with an authentic sample. Elution with $CHCl_3$-MeOH (93:7) from the same chromatographic column and rechromatography over Si gel, eluting with C_6H_6-EtOAc (8:2), afforded a mixture (2:3) of 4-*epi*-larreatricin [**1**] and 3,4-dehydrolarreatricin [**6**], ^1H nmr (Me_2CO-d_6) δ 1.00 (6H, d, J = 5.3 Hz), 1.49 (6H, s), 1.74 (2H, m), 4.59 (2H, J = 8.8 Hz), 5.64 (2H, s), 6.82 (8H, d, J = 8.4 Hz), 7.15 (4H, d, J = 8.4 Hz), 7.24 (4H, d, J = 8.4 Hz).

A mixture of lignans **1** and **6** (200 mg) in pyridine-Ac_2O (1:1) (3 ml) was allowed to stand at room temperature for 16 h, and the reaction mixture was worked up in the usual way and chromatographed over Si gel (26 g). Elution with C_6H_6-EtOAc (8:2) gave **17** (12 mg) as colorless needles: mp 104–105°; ir ν max (KBr) 1715 cm^{-1}; uv λ max (MeOH) (log ε) 221 (4.40), 260 (4.17), 270 (3.15) nm, (MeOH + NaOH) 220 (4.60), 248 (4.18) nm; ^1H nmr (Me_2CO-d_6) δ 1.03 (6H, d, J = 6.0 Hz, 3- and 4-Me), 1.77 (2H, m, H-3, -4), 2.24 (6H, s, OAc), 4.74 (2H, d, J = 9.3 Hz, H-2, -5), 7.11 (4H, d, J = 9.0 Hz, H-3′, -5′, -3″, -5″), 7.45 (4H, d, J = 9.0 Hz, H-2′, -6′, -2″, -6″); ms *m/z* (rel. int.) $[M]^+$ 368 (1), 325 (1), 309 (1), 205 (5), 204 (32), 163 (15), 162 (100), 161 (6), 147 (60), 134 (11), 121 (16), 77 (9).

Successive elution with the same solvent yielded diacetate **18** (44 mg) as colorless needles: mp 87–89°, ^1H nmr (Me_2CO-d_6) δ 1.52 (6H, s, 3- and 4-Me), 2.25 (6H, s, 2 × Ac), 5.81 (2H, s, H-2, -5), 7.22 (4H, d, J = 7.8 Hz, H-3′, -5′, -3″, -5″), 7.39 (4H, d, J = 7.8 Hz, H-2′, -6′, -2″, -6″); ms *m/z* (rel. int.)

$[M]^+$ 366 (3), 323 (4), 280 (9), 188 (18), 121 (100). Diacetate **18** was set aside in HOAc/EtOAc at room temperature for 3 days and then evaporated to dryness. The residue was extracted with Et_2O, and the extract was evaporated under reduced pressure to give a powder. Recrystallization from Et_2O gave **6** (3 mg) as colorless needles: mp 211–213°, cd $[\theta]_{230}$ −6,800 (c = 0.014, MeOH); ir ν max (KBr) 3370 cm^{-1}; uv λ max (MeOH) (log ϵ) 232 (4.76), 277 (3.83) nm, (MeOH + NaOH) 250 (4.06), 276 (3.54) nm; ^1H nmr (Me_2CO-d_6) δ 1.49 (6H, s, 3- and 4-Me), 5.64 (2H, s, H-2, -5), 6.82 (4H, d, J = 8.5 Hz, H-3′, -5′, -3″, -5″), 7.15 (4H, d, J = 8.5 Hz, H-2′, -6′, -2″, -6″); ^{13}C nmr (Me_2CO-d_6) see Table 1; ms *m/z* (rel. int.) $[M]^+$ 282 (10), 188 (14), 163 (13), 162 (100), 161 (48), 148 (10), 147 (87), 134 (9), 133 (16), 121 (96), 107 (27), 94 (10), 65 (21).

AUTOXIDATION OF THE DIACETATE **18**.—The diacetate **18** (24 mg) was set aside at room temperature for 3 days. Chromatography of the residue on Si gel (4 gm) eluting with C_6H_6-EtOAc-hexane (2:0.5:1.5) and recrystallization from Et_2O gave **19** (10 mg) as colorless prisms: mp 142–143°, ir ν max (KBr) 1757 cm^{-1}; ^1H nmr (Me_2CO-d_6) δ 2.26 (6H, s, 3- and 4-Me), 2.28 (6H, s, OAc), 7.23 (4H, d, J = 8.7 Hz, H-3′, -5′, -3″, -5″), 7.77 (4H, d, J = 8.7 Hz, H-2′, -6′, -2″, -6″), ms *m/z* (rel. int.) $[M]^+$ 364 (14), 322 (16), 280 (69), 188 (10), 163 (32), 161 (26), 159 (25), 121 (100), 107 (11), 93 (13).

ACKNOWLEDGMENTS

This work was supported, in part, by a grant (HRP Project 77918c) from the Task Force on Indigenous Plants for Fertility Regulation, Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, Geneva, Switzerland. The authors thank Mr. Victor M. Gass and Ms. Wendy Hodgson, Desert Botanical Garden, 1201 North Galvin Parkway, Phoenix, Arizona 85008, for the provision of the plant material used in this study. The authors also thank the Research Resources Center of the University of Illinois at Chicago for the provision of nmr and mass spectral facilities and Dr. J. Liesch of Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey, for the provision of high resolution mass spectral data.

LITERATURE CITED

1. O. Solbrig, in: "Creosote Bush: Biology and Chemistry of *Larrea* in New World Deserts." Ed. by T.J. Mabry, J.H. Hunziker, and D.R. DiFeo Jr., Dowden, Hutchinson and Ross, Stroudsburg, PA, 1977, p. 1.
2. J.H. Hunziker, R.A. Palacias, L. Poggio, C.A. Naranjo, and T.W. Wang, in: "Creosote Bush: Biology and Chemistry of *Larrea* in New World Deserts." Ed. by T.J. Mabry, J.H. Hunziker, and D.R. DiFeo Jr., Dowden, Hutchinson and Ross, Stroudsburg, PA, 1977, p. 10.
3. M.B. Moser, *The Kiva*, **35**, 201 (1970).
4. M.S.F. Moreno, *C.R. Seances Soc. Biol. Ses Fil.*, **87**, 563 (1922).
5. C.W. Waller and O. Gisvold, *J. Am. Pharm. Assoc., Sci. Ed.*, **34**, 78 (1945).
6. J.O. Page, *Anal. Chem.*, **27**, 1266 (1955).
7. C.R. Smart, H.H. Hogle, R.K. Robins, A.D. Broom, and D.B. Bartholomew, *Cancer Chemother. Rep., Part 1*, **53**, 147 (1969).
8. J.J. Chirikdjian, *Z. Naturforsch.*, **28C**, 32 (1973).
9. J.J. Chirikdjian, *Sci. Pharm.*, **41**, 206 (1973).
10. O. Gisvold and E. Thaker, *J. Pharm. Sci.*, **63**, 1905 (1974).
11. D.S. Seigler, J. Jakupcak, and T.J. Mabry, *Phytochemistry*, **13**, 983 (1974).
12. M. Sakakibara, D.R. DiFeo Jr., N. Nakatani, B. Timmerman, and T.J. Mabry, *Phytochemistry*, **15**, 727 (1976).
13. T.J. Mabry, D.R. DiFeo Jr., M. Sakakibara, C.F. Bohnstedt, and D.S. Seigler, in: "Creosote Bush: Biology and Chemistry of *Larrea* in New World Deserts." Ed. by T.J. Mabry, J.H. Hunziker, and D.R. DiFeo Jr., Dowden, Hutchinson and Ross, Stroudsburg, PA, 1977, p. 115.
14. H.-Z. Xue, Z.-Z. Lu, C. Konno, D.D. Soejarto, G.A. Cordell, H.H.S. Fong, and W. Hodgson, *Phytochemistry*, **27**, 233 (1988).
15. C. Konno, H.-Z. Xue, Z.-Z. Lu, B.-X. Ma, C.A.J. Erdelmeier, C.-T. Che, G.A. Cordell, D.D. Soejarto, D.P. Waller, and H.H.S. Fong, *J. Nat. Prod.*, **52**, 1113 (1989).
16. Z.-Z. Lu, D. Meksuriyen, H.H.S. Fong, and G.A. Cordell, *J. Org. Chem.*, **53**, 2183 (1988).
17. C. Konno, A. Martin, B.-X. Ma, Z.-Z. Lu, H.-Z. Xue, C.A.J. Erdelmeier, N.A. Nuzzo, D.D. Soejarto, G.A. Cordell, D.P. Waller, and H.H.S. Fong, "Proceedings of Princess Congress I," Bangkok, Thailand, 1989, Vol. 2, pp. 328-337.
18. H. Hikino, M. Ogata, and C. Konno, *Heterocycles*, **17**, 155 (1982).
19. D. Takaoka, D. Watanabe, and M. Hiroi, *Bull. Chem. Soc. Jpn*, **49**, 3564 (1976).
20. J.-S. Liu, M.-F. Huang, Y.-L. Gao, and J.A. Findley, *Can. J. Chem.*, **59**, 1680 (1981).
21. K.K. Purushothaman, A. Sarada, and J.D. Connolly, *Indian J. Chem.*, **23B**, 46 (1984).

22. F.E. King and J.G. Wilson, *J. Chem. Soc.*, 4011 (1964).
23. S.F. Fonseca, L.E.S. Barata, E.A. Ruveda, and P.M. Baker, *Can. J. Chem.*, **57**, 441 (1979).
24. M. Arisawa, S.S. Handa, D.M. McPherson, D.C. Lankin, G.A. Cordell, H.H.S. Fong, and N.R. Farnsworth, *J. Nat. Prod.*, **47**, 300 (1984).
25. Sz. Nyiredy, C.A.J. Erdelmeier, K. Dallenbach-Toelke, K. Nyiredy-Mikita, and O. Sticher, *J. Nat. Prod.*, **49**, 885 (1986).

Received 11 September 1989