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NEW LIGNAN BUTENOLIDES FROM *BUPLEURUM SALICIFOLIUM*

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ABSTRACT.—Three new lignans were obtained from the roots of *Bupleurum salicifolium* (Umbelliferae). Two proved to be butenolides, methylchasnarolide [**1**] and chasnarolide [**3**], and the other, a γ-butyrolactone, was benchequiol [**6**]. Their structures were determined by spectral and chemical means.

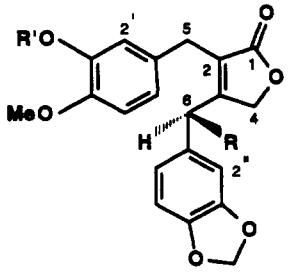
Bupleurum salicifolium Soland. (Umbelliferae) is endemic to the Canary Islands and is a good source of lignans, ten of which have recently been characterized and reported (1–5).

This paper gives an account of the isolation of two new but-2-enolide lignans of a type which is not very common in plants, methylchasnarolide [**1**] [2-(3′,4′-dimethoxyphenyl)-methyl-3-(3″,4″-dioxymethylenephenyl)-methyl-2,3-dehydro-6-hydroxy-γ-butyrolactone] and chasnarolide [**3**] [2-(3′-hydroxy-4′-methoxyphenyl)-methyl-3-(3″,4″-dioxymethylenephenyl)-methyl-2,3-dehydro-6-hydroxy-γ-butyrolactone]. These lignans are structurally related to guayadequiene [**5**] [2-(3′,4′-dimethoxyphenyl)-methyl-3-(3″,4″-dioxymethylenephenyl)-methyl-2,3-dehydro-γ-butyrolactone] isolated from the leaves of the same plant (3). Another new dibenzyl-γ-butyrolactone, benchequiol [**6**] [2-hydroxy-2-(3,4-dimethoxyphenyl)-methyl-3-(3,4-dioxymethylenephenyl)-methyl-γ-butyrolactone], was also obtained.

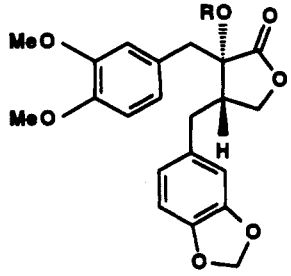
As many natural products with an unsaturated lactone ring are notable for their physiological properties with cytotoxic, antibiotic, phytotoxic, fungicidal, larvicidal, and other activities (6–8), the isolation of plant lignans with a but-2-olide ring permits the study of other possible applications of these novel substances.

RESULTS AND DISCUSSION

Three lignans hitherto undescribed in the literature were isolated from the roots of *B. salicifolium* by extraction and chromatography (see Experimental) and characterized by spectroscopy and chemical transformations as methylchasnarolide [**1**], chasnarolide [**3**], and benchequiol [**6**].



1 R=OH, R′=Me
2 R=OAc, R′=Me
3 R=OH, R′=H
4 R=OAc, R′=Ac
5 R=H, R′=Me



6 R=H
7 R=Ac

The butenolide methylchasnarolide [**1**], $[M]^+$ 384, molecular formula $C_{21}H_{20}O_7$, showed negative optical rotation and ir absorption spectra with bands for conjugated carbonyl groups (ν max 1745 cm^{-1}, λ max 324 nm) and OH groups (ν max 3537 cm^{-1}). ^{1}H-nmr spectra were observed with a 2H singlet at δ 4.56 characteristic of the methylene group in but-2-enolide type lactones and a 6H signal between δ 6.52 and δ 7.05 for four doublets, two of which had coupling constants of J=2.0 Hz and two of J=8.0 Hz, and two double doublets (J=2.0, 8.0 Hz) characteristic of 3,4-substituted benzene rings. A singlet at δ 3.87 (6H) was attributed to two OMe groups, and another significant 2H singlet at δ 5.93 was typical of a dioxymethylene group. The ms spectra of methylchasnarolide displayed a base peak at *m/z* 151 ($C_9H_{11}O_2$) which was in accordance with a 3,4-dimethoxybenzyl group on the lactone carbon C-2 and another peak at *m/z* 121 (9%) corresponding to a dioxymethylenephenyl group. A further peak at *m/z* 366 ($C_{21}H_{18}O_6$) could be attributed to loss of H_2O from the molecule. The ^{13}C-nmr shifts of the signals of carbons C-3 (160.22 ppm) and C-2 (134.65 ppm) confirmed the unsaturation of the lactone ring between these two carbons.

Acetylation of methylchasnarolide [**1**] gave the acetate **2** (ν max 1759 cm^{-1}, $[M]^+$ 426, molecular formula $C_{23}H_{22}O_6$, δ 2.17 ppm) with a fragment at *m/z* 366 as base peak in the ms $[M-HOAc]^+$ and another prominent peak at *m/z* 151 (59%). The ^{1}H nmr of **2** was distinguished by the downfield shifts (δ 6.68) of the signals for H-6 as well as those of the piperonyl group at H-2″ (δ 6.59), H-6″ (δ 6.59), and OCH_2O (δ 5.95) in relation to the corresponding signals in methylchasnarolide and can only be due to the position of the acetyl group on C-6.

The foregoing data all indicated structure **1** for the new lignan, methylchasnarolide.

The second butenolide, chasnarolide [**3**], showed ν max 3540 cm^{-1} (OH) and 1743 cm^{-1} (C=O), λ max 324 nm, $[M]^+$ 370, molecular formula $C_{20}H_{18}O_7$, and negative optical rotation. The electron fragmentation spectrum had prominent peaks at *m/z* 137 ($C_8H_9O_2$) for a 3-hydroxy-4-methylphenyl group and at *m/z* 151 ($C_8H_7O_3$) for a hydroxypiperonyl group. The ^{13}C-nmr spectrum of chasnarolide was similar to that of **1**, the most notable differences being at C-3′ and C-4′, the signals of which were shifted 3.87 ppm and 3.49 ppm upfield, respectively. The ^{1}H-nmr spectra of chasnarolide were similar to those of **1**, with the most important differences being the H-2′ which was 0.07 ppm upfield further upfield shift than the same signal in **1**, and the presence of a three-proton singlet at δ 3.89 attributable to an OMe group.

Chasnarolide [**3**] formed the diacetate **4** (ν max 1761 cm^{-1}, $[M]^+$ 454, molecular formula $C_{22}H_{24}O_9$). The most significant ^{1}H-nmr data were provided by two singlets at δ 2.17 (OAc) and 2.31 (PhOAc) and a very significant 0.36 ppm downfield shift of the H-6′ signals (δ 7.32) in comparison with the signals for the H-6′ proton in **3** (δ 6.96) which can be compared with similar shifts in guamarol, isoguamarol, and guamaroline and their corresponding acetates (5) and can only be accounted for by the OH group being on the C-3′ of an isoguayacyl group.

The structural relationship between **1** and chasnarolide was established beyond doubt by the transformation of **3** to methyl chasnarolide when treated with CH_2N_2.

Benchequiol [**6**] had the absorption spectral data of a γ-butyrolactone (ν max 1770 cm^{-1}, lactone C=O), with alcohol OH groups (ν max 3539 cm^{-1}), and $[M]^+$ 386, molecular formula $C_{21}H_{22}O_7$. Its ^{1}H-nmr spectra showed signals for six benzene protons, two singlets attributable to two non-equivalent OMe groups, and another singlet due to an OCH_2O group (see Table 1), corresponding to veratryl and piperonyl groups, respec-

TABLE 1. ^{1}H-nmr Spectra of Compounds **1–4**, **6**, and **7** (200 MHz, $CDCl_3$).[a]

Proton	Compound					
	1	**2**	**3**	**4**	**6**	**7**
H-3	—	—	—	—	2.97 m	3.01 m
H-4	4.56 s	4.53 s	4.54 s	4.53 s	4.01 m	4.01 m
H-5α	3.70 d	3.84 s	3.71 d	3.85 s	2.93 d	2.94 d
	(3.7)		(4.0)		(13.5)	(13.6)
H-5β					3.10 d	3.11 d
					(13.5)	(13.6)
H-6	5.93 m	6.68 s	5.93 m	6.68 s	2.51 m	2.52 m
H-2′	7.05 d	7.08 d	6.98 d	7.13 d	6.73 brs	6.73 d
	(2.0)	(2.0)	(2.1)	(2.3)		(1.5)
H-5′	6.83 d	6.84 d	6.84 d	6.94 d	6.82 d	6.82 d
	(8.2)	(8.3)	(8.0)	(8.4)	(7.8)	(8.0)
H-6′	6.94 dd	(6.99) dd	6.96 dd	7.32 dd	6.68 dd	6.72 dd
	(2.0, 8.2)	(2.0, 8.3)	(2.1, 8.0)	(2.3, 8.4)		
H-2″	6.52 d	6.59 brs	6.54 d	6.59 d	6.62 brs	6.62 brs
	(1.9)		(2.0)	(1.6)		
H-5″	6.76 d	6.74 d	6.72 d	6.75 d	6.78 d	6.78 d
	(8.3)	(8.3)	(8.3)	(7.7)	(7.8)	(8.0)
H-6″	6.52 dd	6.59 d	6.55 m	6.56 dd	6.57 dd	6.71 dd
	(1.9, 8.3)	(2 broad signals)		(1.6, 7.7)		
6-OH	5.62 s	—	5.66 s	—	—	—
OMe	3.87 s (6H)	3.88 s (6H)	3.89 (3H)	3.83 s (3H)	3.86 s (3H)	3.87 s (3H)
					3.88 s (3H)	3.88 s (3H)
OCH_2O	5.93 s	5.95 s	5.94 s	5.96 s	5.95 s	5.95 s
OAc	—	2.17 s	—	2.17 s	—	2.16 s
				2.31 s		

[a]Values in δ (ppm); coupling constants (Hz) in brackets.

tively. The ms spectra gave *m/z* 151 ($C_9H_{11}O_2$) as base peak for a veratryl group bonded to the carbon C-2 in a γ-butyrolactone and another prominent peak at *m/z* 135 ($C_8H_7O_2$) for a piperonyl group on C-3. The position of this latter group was verified by the presence of a peak at *m/z* 162 ($C_{10}H_{10}O_2$)[135+C_2H_3]$^+$, which was further confirmation of the presence of a proton (H-3) on C-3 and showed that the OH was on carbon C-2, making the signals of each of the protons H-5α and H-5β appear as doublets with coupling constants of J=13.5 Hz, 34 Hz apart. The ^{13}C-nmr spectra confirmed that benchequiol had a structure similar to that of guayadequiol (3), with only the stereochemistry at C-2 to differentiate the two. When acetylated, benchequiol formed the monoacetate **7** (δ 2.16, s, 3H).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Ir spectra were recorded on a Perkin-Elmer Model 681 spectrophotometer ($CHCl_3$, cm^{-1}) and uv spectra on a Perkin-Elmer 550 SE instrument (EtOH, nm). ^{1}H- and ^{13}C-nmr spectra were run on a Bruker WD spectrophotometer at 200 and 50 MHz, respectively, ($CDCl_3$) with TMS as internal standard. Eims were obtained on a Micromass ZAB-2AF spectrometer. Specific rotations were measured on a Perkin-Elmer Model 141 polarimeter with $CHCl_3$ in 5 cm cells; concentrations were

expressed in grams of product per 100 ml of solvent. Schleicher-Schüll F-100/LS 254 and preparative tlc 1510/LS 254 foils were used for tlc, while Si gel (0.2–0.63 nm thickness) and Sephadex LH-20 were used for cc.

ISOLATION OF **1**, **3**, AND **6** FROM THE ROOTS OF *B. SALICIFOLIUM*.—Root bark from *B. salicifolium* (9) (0.61 kg) collected in Barranco Río Badajoz in Güimar, Tenerife, was extracted with cold EtOH. The EtOH extract was treated repeatedly with H_2O, Me_2CO, and *n*-C_6H_{14} to afford a dark residue (27.3 g) which was chromatographed on a Sephadex column (78.5 cm×5 cm) eluted with C_6H_{14}-$CHCl_3$-MeOH (2:2:1). Five fractions, A–E, were separated and studied. All were chromatographed on Si gel using mixtures of *n*-H_6H_{14}/EtOAc of increasing polarity as eluent.

Guamarol, isoguamarol, guamaroline, kaerophyllin, isokaerophyllin, and matairesinol were obtained from the A, B, and C fractions (5). Fraction D (0.23 g) afforded methylchasnarolide [**1**] (7.8 mg), and fraction E (0.3 g) gave chasnarolide [**3**] (6.7 mg) and benchequiol [**6**] (3 mg).

Methylchasnarolide [**1**].—Amorphous substance: $[\alpha]^{20}$ D −6° (c=0.5, $CHCl_3$); uv λ max (EtOH) 282, 324; ir ν max 3537 (broad), 1745, 1665, 1596, 1515, 1504, 1490, 1465, 1442, 1263, 1248, 1187, 1154, 1140, 1027, 926, 860, 810; eims *m/z* (%) $[M]^+$ 384 (4), $[M-H_2O]^+$ 366 (3), 249 (8), 233 (9), 151 (100), 137 (34), 121 (9), 119 (5); hreims *m/z* 384.1219 (required for $C_{21}H_{20}O_7$, 384.1203), 151.0758 (required for $C_9H_{11}O_2$, 151.0746), 137.0598 (required for $C_8H_9O_2$ 137.0600); ^{1}H nmr see Table 1; ^{13}C nmr see Table 2.

Methylchasnarolide acetate [**2**].—Ac_2O (0.3 ml) was added to a solution of **1** (2.2 mg) in pyridine (1 drop), and the red solution was left at (20°) for 24 h, diluted with cold H_2O, and extracted with Et_2O to give methylchasnarolide acetate [**2**] as an oil: ir ν max 1759, 1735 (sh), 1602, 1516, 1505, 1490, 1464, 1444, 1420, 1371, 1260, 1228, 1159, 1142, 1097, 1041, 1027, 941, 924, 808; eims *m/z* (%) $[M]^+$ 426 (50), 383 (33), 366 (100), 229 (10), 193 (7), 151 (59), 137 (6), 121 (6); hreims *m/z* 366.1105 (required for $C_{21}H_{18}O_6$, 366.1098); ^{1}H nmr see Table 1.

Chasnarolide [**3**].—An orange oil: $[\alpha]^{20}$ D −2.5° (*c*=0.5, $CHCl_3$); uv λ max (EtOH) 286.324; ir ν max 3540, 1743, 1667, 1608, 1595, 1464, 1443, 1359, 1344, 1271, 1247, 1181, 1153, 1127, 1098, 1040, 940, 926; eims *m/z* (%) $[M]^+$ 370 (4), 352 (4), 247 (10), 219 (28), 151 (100), 137 (76), 123 (25), 121 (32); hreims *m/z* 151.0403 (required for $C_8H_7O_3$, 151.0393); ^{1}H nmr see Table 1; ^{13}C nmr see Table 2.

Chasnarolide acetate [**4**].—Ac_2O (0.3 ml) was added to a solution of **3** (2.5 mg) in pyridine (1 drop), and the red solution was left at room temperature (20°) for 24 h, diluted with cold H_2O, and extracted with Et_2O to form a diacetate **4**: ir ν max 1761, 1734 (sh), 1604, 1512, 1504, 1489, 1465, 1444, 1370, 1261, 1247, 1228, 1200, 1122, 1096, 1040, 940, 867, 809; eims *m/z* (%) $[M]^+$ 454 (4), 394 (26), 352 (22), 179 (6), 165 (10), 149 (36), 151 (24), 121 (13); ^{1}H nmr see Table 1.

METHOXYLATION OF CHASNAROLIDE.—When **3** (1.0 mg), dissolved in MeOH, was treated with excess CH_2N_2 in an Et_2O solution for 4 h at 0°; the substance obtained could be identified with natural methylchasnarolide [**1**] by tlc and ir, ^{1}H nmr, and ms.

Benchequiol [**6**].—Could not be crystallized: $[\alpha]^{20}$ D −8.0° (*c*=1.5, $CHCl_3$); uv λ max (EtOH) 282, 318; ir ν max 3539, 1770, 1605, 1514, 1505, 1490, 1443, 1262, 1248, 1229, 1194, 1158, 1142, 1040, 1028, 942, 928, 809; eims *m/z* (%) $[M]^+$ 386 (24), 162 (2), 151 (100), 135 (27); hreims *m/z* 386.1361 (required for $C_{21}H_{22}O_7$, 386.1365), 162.0665 (required for $C_{10}H_{10}O_2$, 162.0678); ^{1}H nmr see Table 1; ^{13}C nmr (ppm) δ 32.29 (C-6), 42.72 (C-5), 56.40 (OMe), 7043 (C-4), 77.30 (C-2), 101.49 (OCH_2O), 109.52 (C-5″), 111.72 (C-2″), 112.03 (C-5′), 114.63 (C-2′), 122.97 (C-6″), 123.48 (C-6′), 127.70 (C-1″), 132.68 (C-1′), 146.37 (C-4″), 146.48 (C-3″), 149.07 (C-4′), 149.48 (C-3′).

TABLE 2. ^{13}C-nmr Data of the Butenolides (50 MHz, $CDCl_3$).[a]

Carbon	Compound		Carbon	Compound		Carbon	Compound	
	1	3		1	3		1	3
C-1	174.10	173.94	C-1	128.54	127.96	C-1″	129.61	129.30
C-2	134.65	134.85	C-2′	112.13	112.38	C-2″	109.29	109.01
C-3	160.20	160.26	C-3′	150.01	145.94	C-3″	148.59	148.22
C-4	71.70	71.48	C-4′	149.63	145.94	C-4″	147.39	146.93
C-5	33.48	33.06	C-5′	110.43	110.80	C-5″	108.88	108.63
C-6	69.25	68.71	C-6′	118.66	117.76	C-6″	121.91	121.73
			OMe	56.35	56.04	OCH_2O	101.42	101.17

[a]Chemical shifts are given in δ (ppm).

Benchequiol acetate [**7**].—Ac_2O (0.2 ml) and a small amount of DMAP (4-dimethylaminpyridine) were added to a solution of **6** (1.3 mg) in pyridine (1 drop). The reaction mixture was left at room temperature (19°) for 18 h and diluted with H_2O/ice, forming an insoluble precipitate in the H_2O. The precipitate was washed with a solution of $NaHCO_3$ and H_2O successively, leaving a residue (1.1 mg) of benchequiol acetate [**7**]: ^1H nmr see Table 1.

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