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NOVEL SECOIRIDOID LACTONES FROM *JASMINUM MULTIFLORUM*

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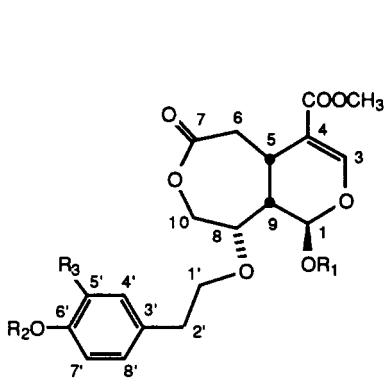
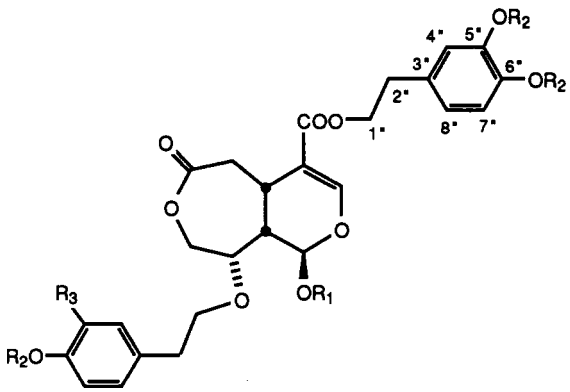
ABSTRACT.—Four new secoiridoid lactones, jasmolactones A [**1**], B [**2**], C [**3**], and D [**4**], were isolated from the aerial part of *Jasminum multiflorum*. The structures of these compounds, which contain a novel bicyclic 2-oxo-oxepano[4,5-*c*]pyran ring system, were established by spectral analyses and chemical correlations. Pharmacological testing revealed that jasmolactones B and D possess coronary vasodilating and cardiotropic activities.

Members of the genus *Jasminum* were known for their medicinal applications in Chinese folklore (1). Among various secondary metabolites examined, some secoiridoids exhibited a wide spectrum of biological activities (2). Of particular interest are oleuropein and its aglycone from the olive tree, which showed hypotensive and related cardiovascular activities (3). As part of our biological evaluation of oleaceous plants native to Taiwan, we have examined *Jasminum multiflorum* (Burm. f.) Andr. (Oleaceae), which was found to be quite rich in secoiridoids. A pharmacological screening revealed that this fraction possesses coronary vasodilating and cardiotropic activities. This prompted an investigation of the origin of these active components. *J. multiflorum* is a cultivated, evergreen shrub that is employed locally as an ornamental plant (4). To date there have been no previous phytochemical or biological studies on this plant. In this present communication, we will report the isolation, structural characterization, and pharmacological activities of four novel lactone secoiridoids, jasmolactones A [**1**], B [**2**], C [**3**], and D [**4**], from this species.

RESULTS AND DISCUSSION

The EtOH extract of the fresh leaves and flowers of *J. multiflorum* was fractionated by solvent partitions as described in the Experimental. A combination of cc and preparative tlc allowed the isolation of compound **1** from the $CHCl_3$-soluble fraction, and compounds **2**, **3**, and **4** from the *n*-BuOH-soluble fraction.



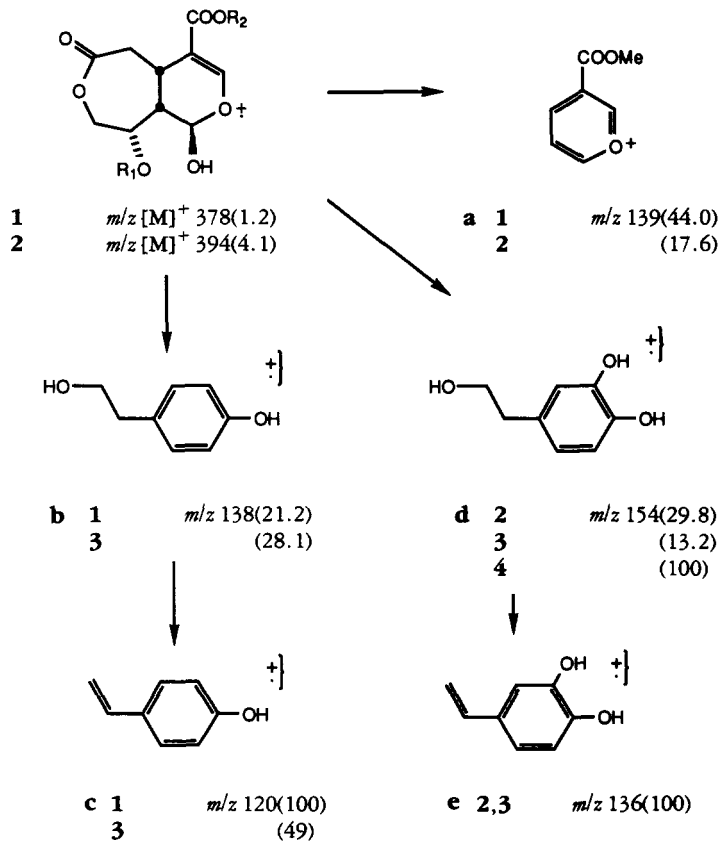


	R_1	R_2	R_3
1	H	H	H
2	H	H	OH
5	H	Me	OMe
6	Ac	Ac	OAc
7	Ac	Ac	H

	R_1	R_2	R_3
3	H	H	H
4	H	H	OH
8	Ac	Ac	OAc
9	H	Me	OMe
10	Ac	Ac	H

Jasmolactone B [**2**], $[\alpha]_D$ +100.1° (MeOH), was isolated as a pale yellow gum. The molecular formula $C_{19}H_{22}O_9$ was deduced from a molecular ion at *m/z* 394 in its eims, which was also confirmed by fabms (*m/z* 418 $[M+Na+H]^+$) and DEPT ^{13}C nmr. The ir and uv spectra of **2** showed typical absorptions of an enol ether system conjugated with a carbonyl group (1700, 1625 cm^{-1}, 226.4 nm), contained in a secoiridoid skeleton (5), and, in addition, a catecholic chromophore (1515, 1440 cm^{-1}, 280.4 nm). The ^1H-nmr spectrum of **2** (Table 1) displayed signals of a hemiacetalic proton at δ 5.18 (d, J = 7.0 Hz) and a low field olefinic proton at δ 7.57 (d, J = 1.7 Hz), belonging, respectively, to H-1 and H-3 of the secoiridoid ring (6,7). The presence of a methoxyl singlet at δ 3.65, together with the fragment ion **a** at *m/z* 139 in the eims of **2** (Scheme 1), suggested that it is a 4-methoxycarbonyl secoiridoid (8,9). In addition, a set of proton signals comprised of an aromatic AMX and an aliphatic AA'BB' spin system were ascribable to a 3,4-dihydroxyphenethoxyl moiety, which is also reflected in the fragment ion **d** at *m/z* 154. In support of these structural features, the ^{13}C-nmr spectrum of **2** (Table 2) was comparable to other secoiridoids (10) concerning the portion of 4-carbomethoxydihydropyran ring, and also comparable to other phenylpropanoids (11) regarding the 3,4-dihydroxyphenethoxyl moiety.

Upon methylation with CH_2N_2, **2** yielded a dimethylate **5**, the ^1H nmr of which showed two aromatic methoxyl singlets (δ 3.83 and 3.84). Conventional acetylation of



SCHEME 1. Eims fragmentations of jasmolactones A [**1**], B [**2**], C [**3**], and D [**4**]. For **1**, R_1 = 4-hydroxyphenethoxyl, R_2 = Me; **2**, R_1 = 3,4-dihydroxyphenethoxyl, R_2 = Me; **3**, R_1 = 4-hydroxyphenethoxyl, R_2 = 3,4-dihydroxyphenethoxyl; **4**, $R_1 = R_2$ = 3,4-dihydroxyphenethoxyl.

TABLE 1. ^{1}H-nmr (300 MHz) Spectral Data of Jasmolactones A [**1**], B [**2**], C [**3**], and D [**4**]. (δ in ppm, *J* in Hz)

Proton	Compound					
	1 $CDCl_3$	**2** C_2D_6CO	**2** CD_3OD	**3** C_2D_6CO	**4** C_2D_6CO	**4** CD_3OD
H-1	5.20 d (6.9)	5.23 d (6.2)	5.18 d (7.0)	5.22 d (6.8)	5.22	5.20 d (7.1)
H-3	7.53 d (1.0)	7.54 d (1.9)	7.57 d (1.7)	7.49 d (2.0)	7.51 d (1.4)	7.52 brs
H-5	3.26 m	3.30 m	3.3 m	3.28 m	3.29 m	3.27 m
H-6α	2.28 dd (17.5)	2.36 dd (17.1,9.8)	2.34 dd (17.2,9.8)	2.32 dd (17.0,10.1)	2.32 dd (16.8,10)	2.29 dd (17.3,11.1)
H-6β	3.32 dd (17.5,4.3)	3.22 dd (17.1,4.4)	3.21 dd (17.2,4.8)	3.19 dd (17.0,4.2)	3.22 dd (16.8,4.2)	3.18 dd (17.3,4.3)
H-8	4.36 dd (3.4,2.0)	4.59 dd (3.6,2.2)	4.49 dd (3.6,2.2)	4.57 dd (3.6,2.1)	4.57 dd (3.6,2.0)	4.43 brs
H-9	2.53 ddd (6.9,3.4)	2.65 ddd (6.2,3.6)	2.55 ddd (6.5,3.6,7.0)	2.55	2.64 ddd (6.6,3.6,7.0)	2.53 m
H-10α	3.95 d (9.9)	3.86 d (9.9)	3.90 d (10.0)	3.85 d (10.0)	3.86 d (10.0)	3.91 d (9.8)
H-10β	4.06 dd (9.9,2.0)	4.09 dd (9.9,2.2)	4.08 dd (10.0,2.2)	4.08 dd (10.0,2.1)	4.08 dd (10.0,2.0)	4.14 d (9.8)
H-1′	4.27 t (6.8)	4.18 dt (7.4,1.7)	4.21 dt (7.1,1.8)	4.16 m (6.8)	4.18 m (6.7)	4.26 t (6.7)
H-2′	2.82 t (6.8)	2.77 dt (7.4,1.7)	2.78 dt (7.1,1.8)	2.76 t	2.78 t (6.7)	2.78 t (6.7)
H-4′	7.02 d (8.4)	6.75 d (1.8)	6.68 d (2.0)	7.08 d (8.4)	6.75 s	6.70
H-5′	6.73 d (8.4)			6.73 d (8.4)		
H-7′	6.73 d (8.4)	6.73 d (7.9)	6.71 d (8.1)	6.73 d (8.4)	6.73 d (8.0)	6.70
H-8′	7.02 d (8.4)	6.59 dd (7.9,1.8)	6.54 dd (8.1,2.0)	7.08 d (8.4)	6.59 d (8.0)	6.55 d (7.7)
H-1″					4.18 m	4.26 t (6.7)
H-2″				2.79 t (6.8)	2.78 t (6.7)	2.78 t (6.7)
H-4″				6.75	6.75 s	6.70
H-7″				6.75	6.73 d (8.0)	6.70
H-8″				6.57 dd (7.5,1.7)	6.59 d (8.0)	6.57 dd (7.7,1.6)
OMe	3.66 s	3.63 s	3.65 s			
OH		3.05 brs 7.78 brs			3.14 brs 7.76 brs	

2 gave a triacetate **6**, $C_{25}H_{28}O_{12}$ (*m/z* $[M]^+$ 520), which exhibited two aromatic acetyl singlets (δ 2.22 and 2.23) in addition to one aliphatic acetyl singlet (δ 1.93). In comparison with **2**, a downfield acetylation shift for the signal of H-1 was observed, which implies a free hydroxyl group at C-1 position of **2**.

The relationship of each methylene and methine proton on **2** was ascertained by spin-spin decoupling and ^{1}H-homonuclear COSY 45 studies (Figure 1). The olefinic proton H-3 (δ 7.57) was correlated via a long range coupling with a multiplet of H-5 at δ 3.30, which, in turn, showed correlations with a methine proton H-9 (δ 2.55) and a pair of methylene protons H-6α and H-6β (δ 2.34 and δ 3.21, respectively). The signal of H-9 showed correlations with both methine protons, H-1 (δ 5.18) and H-8 (δ 4.49), and the latter proton was coupled with a pair of methylene protons, H-10α and H-10β (δ 3.90 and δ 4.08, respectively). In the ^{13}C-nmr spectrum of **2**, the chemical shifts of the methine carbon C-8 (δ 80.17) and the methylene carbon C-10 (δ 72.06) indicated that they are oxygenated. By way of exclusion, the remaining methylene carbon would be allocated to C-6 (δ 35.25), which is associated with a carbonyl carbon C-7 (δ 173.83). Now, eight of the nine unsaturations having been accounted for, one more

ring would be required in addition to the dihydropyran ring. Consequently, this called for a lactone linkage between C-7 and one of the oxygenated carbons, C-8 or C-10, giving, in each case, a δ-lactone **A** or a ϵ-lactone **B** as illustrated in Figure 2. The ir spectrum of **2**, which exhibited strong multiple absorptions around 1700 cm^{-1}, is only consistent with structure **B**, a seven-membered lactone ring. Although an iridoid of such a structural type is without precedent in the literature, δ-lactone iridoids of structural type **A** do exist, as exemplified by kingiside (12), which showed absorption of the lactone function at 1745 cm^{-1}. The long-range ^{1}H-^{13}C correlation studies of **6** (Table 3) revealed significant correlations between C-10 and H-6β as well as C-1′ and H-8, which effectively eliminated δ-lactone structure **A** from consideration. All other correlations are also consistent with the proposed structure of type **B**. Also, the coupling pattern of H-10α (d), H-10β (dd), H-8 (dd), and H-9 (ddd) protons ($J_{10\alpha,\beta} = 10$, $J_{10\alpha,8} = 0$, $J_{10\beta,8} = 2.2$, $J_{8,9} = 3.6$ Hz) suggests a fixed conformation for the C-10 methylene protons, which can only be accommodated in a seven-membered lactone structure **B**. As a result, in both **2** and **6**, the pair of C-6 methylene protons showed a wide spread in chemical shifts ($\Delta\delta = 0.9$, 1.4 ppm), which is quite large compared with the same pair of protons in kingiside aglycone acetate (13) ($\Delta\delta = 0.5$ ppm). Fur-

TABLE 2. ^{13}C-nmr (75.47 MHz) Spectral Data[a] for Jasmolactones A [**1**], B [**2**], C [**3**], and D [**4**].

Carbon	Compound			
	1 $CDCl_3$	**2** CD_3OD	**3** CD_3OD	**4** CD_3OD
C-1	98.90 d	99.87 d	99.96 d	99.54 d
C-3	155.48 d	156.69 d	156.58 d	156.40 d
C-4	105.25 s	106.42 s	106.83 s	106.22 s
C-5	24.83 d	26.11 d	26.22 d	25.74 d
C-6	34.14 t[c]	35.25 t[c]	35.22 t[c]	35.11 t[b]
C-7	172.79 s	173.83 s	173.86 s	173.67 s
C-8	78.44 d	80.17 d	80.26 d	79.69 d
C-9	45.95 d	47.29 d	47.32 d	46.75 d[b]
C-10	71.33 t	72.06 t	72.13 t	71.84 t[b]
C-11	167.35 s	168.85 s	168.54 s	168.16 s
C-1′	65.27 t	66.47 t	66.54 t	66.22 t
C-2′	33.92 t[c]	35.17 t[c]	35.33 t[c]	34.93 t[c]
C-3′	129.57 s	130.83 s	130.17 s	130.57 s[d]
C-4′	129.94 d	116.19 d	130.93 d	116.08 d[e]
C-5′	115.36 d	146.02 s	116.25 d	145.58 s[f]
C-6′	155.95 s	144.68 s	157.00 s	144.22 s[g]
C-7′	115.36 d	117.01 d	116.25 d	116.65 d[h]
C-8′	129.94 d	121.21 d	130.93 d	121.08 d[i]
C-1″			66.16 t	65.84 t
C-2″			35.22 t[c]	34.86 t[c]
C-3″			131.00 s	130.60 s[d]
C-4″			116.41 d	116.08 d[e]
C-5″			146.16 s	145.65 s[f]
C-6″			144.82 s	144.28 s[g]
C-7″			117.11 d	116.78 d[h]
C-8″			121.27 d	121.06 d[i]
OMe	51.27 q	51.65 q		

[a]Multiplicities were obtained from DEPT spectra.
[b]These assignments were confirmed by SFORD spectra.
[c–i]Assignments of the same superscript in the same column may be interchanged.

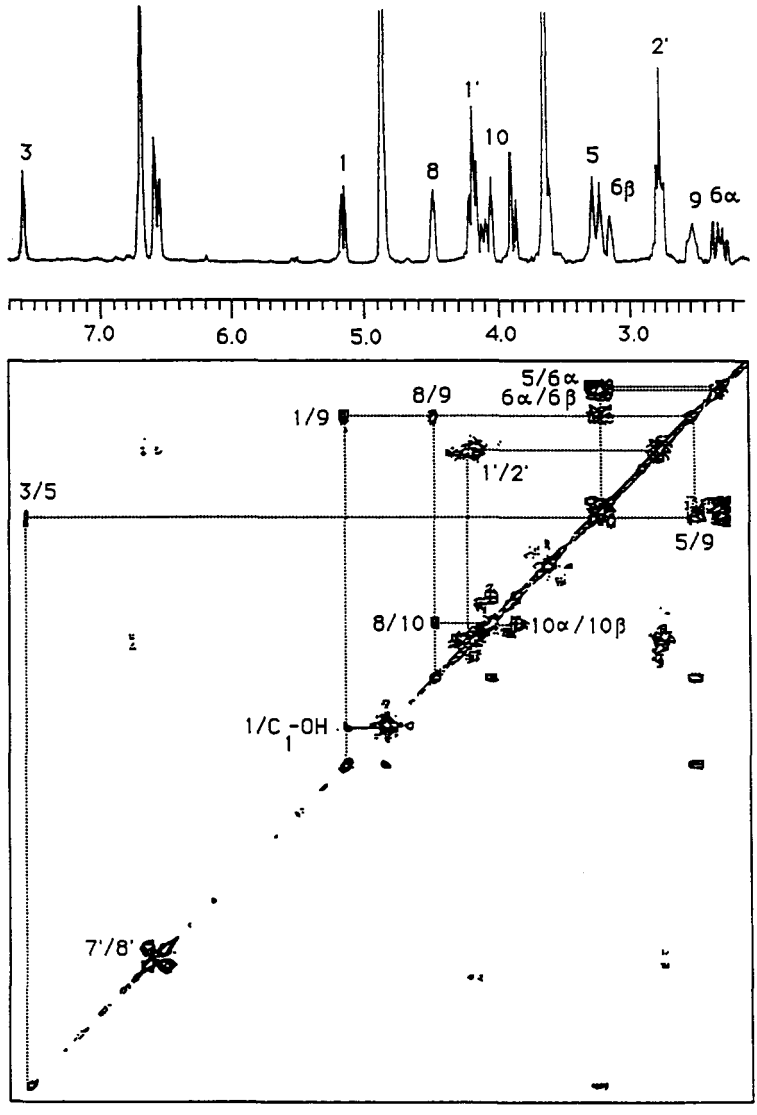


FIGURE 1. COSY 45 spectrum of jasmolactone B [**2**].

thermore, the results from nOe difference studies (Figure 3) are in full agreement with this endocyclic arrangement of the C-10 methylene group.

Assuming that **2** has the same absolute configurations at C-5 and C-9 as other naturally occurring iridoids (5), extensive nOe difference studies were performed on **2** and its triacetate **6** (Figure 3) to ascertain the relative stereochemistry around other chiral centers. The presence of mutual enhancements between H-5, H-9, and H-8 agreed with an all-cis relationship among these protons. The absence of nOe between H-1 and H-9 in **2** and the small enhancement between them in **6** suggested a trans-disposition and hence an α-orientation for H-1. In support of this conclusion, irradiation of the H-1 signal caused significant enhancement of signals at δ 2.34 in **2** and δ 2.01 in **6**, both assignable to the H-6α proton. The coupling constants, $J_{5,9}$ (6.5 Hz) and $J_{9,8}$ (3.6 Hz), were compatible with a cis ring junction and cis relationship between H-9 and H-8. This is in contrast with an iridoid with a trans ring junction such as xyllomolin (14), where a large coupling of $J_{5,9}$ (>10 Hz) was observed. The magnitude of coupling be-

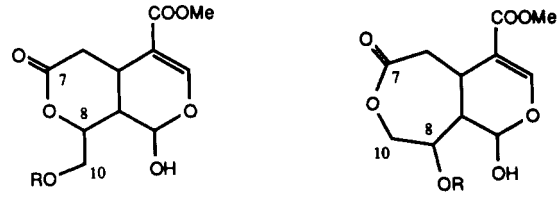


FIGURE 2. Two alternative structures of jasmolactone B [**2**] (R = 3,4-dihydroxyphenethyl).

tween H-1 and H-9 (6–7 Hz) also agreed with a trans disposition among them and implied a β-oriented hydroxyl group at C-1 position. The shielding effect of the C-8 alkoxy group on the chemical shift of C-9 carbon (δ 47.29) indicated that it is within the range (δ< 50.0) of a C-8α alkoxy group, as shown among iridoids of similar configuration at the C-8 position (15,16).

The positive nOe between H-1 and H-6α suggested their proximity in space. With this constraint imposed, a Dreiding model revealed a conformation of **2** in which both H-1 and C-5–C-6 bonds are held in pseudodiaxial disposition relative to the dihydropyran ring (Figure 3). As a consequence, this ring is frozen in a conformation in which the torsional angle ω C-1–O–C-3–C-4 assumes positive value. The Cotton effect of this inherently chiral enol ether system is determined in theory by this torsional angle (17,18). The observed cd spectrum of **2** showed a strong positive Cotton effect at 238 nm, in good accord with the above prediction.

Jasmolactone A [**1**], $[\alpha]_D$ +122.4° ($CHCl_3$), was obtained as a pale yellow solid.

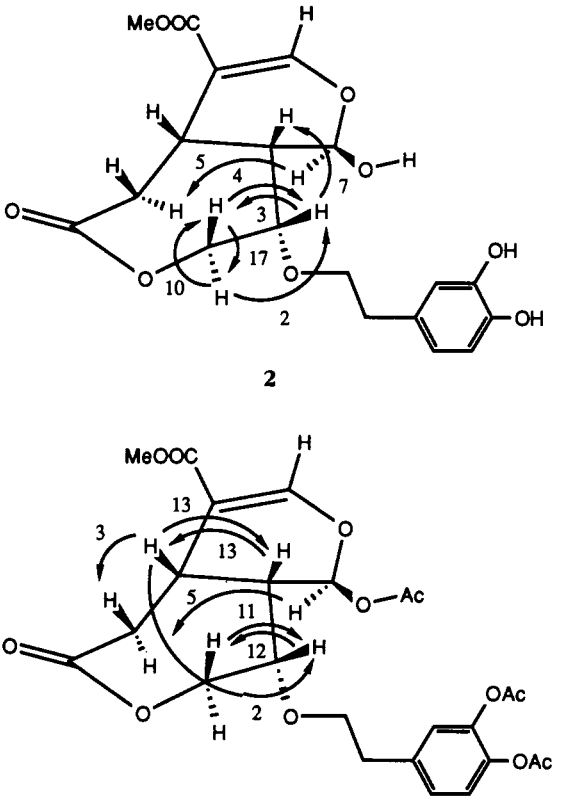
TABLE 3. Long Range ^1H-^{13}C Correlation Data for Jasmolactone B [**2**] and Its Triacetate **6**.

Carbon	^1H-^{13}C Connectivities[a]	
	Compound	
	2	**6**
C-5	6α, 6β, (3)	6α, 6β, 3, (1)
C-7	6α, (6β)	6α, (6β)
C-8	3[b], 10α, 10β	3[b], (10α, 10β)
C-9	10α, (6α)	10α, 10β, (6α)
C-10	1[c]	1[c], (6β)[c]
C-11	3, OCH_3	3, OCH_3
C-1′	2′	2′, (8)
C-2′	1′, (4′, 8′)	
C-3′	(1′), 2′, 7′	2′, 7′
C-4′	8′, 2′	8′, 2′
C-5′	7′	7′
C-6′	4′	8′, 4′
C-8′	2′, 4′	2′, 4′
OCOMe		OCH_3

[a] ^1H-^{13}C cross-peaks corresponding to 2-bond or 3-bond C-H connectivities. The number refers to the proton giving a cross-peak with a particular carbon. Weak cross-peaks are listed in parentheses.

[b] These represent 5-bond correlations.

[c] These represent 4-bond correlations.



2

6

FIGURE 3. Relative stereochemistry of **2** and **6** by nOe difference studies.

The molecular formula, $C_{19}H_{22}O_8$, was derived from the molecular ion (*m/z* 378) in its eims and also from DEPT ^{13}C-nmr spectra. The uv absorptions (226 and 277.2 nm) and the ir bands (1705, 1625, 1515, and 1440 cm^{-1}) resembled those of jasmolactone B [**2**], suggesting a similar analogue. The presence of the fragment ion **a** (*m/z* 139) in its eims (Scheme 1) and the methoxyl singlet (δ 3.66) in its ^{1}H-nmr spectrum clearly suggested characteristics of a 4-methoxycarbonyl secoiridoid. Indeed, except for the difference in signals of side chain, the ^{1}H- and ^{13}C-nmr spectra of **1** were superimposable with those of **2** concerning those signals arising from the main ring skeleton. The nature of the side chain was revealed by a group of proton signals comprising an AA′BB′ spin system (Table 1) and corresponding symmetric carbon signals (Table 2) in the aromatic region, which were assignable to a 4-hydroxyphenethoxyl moiety. This formulation was also supported by the eims of **1** which displayed a base peak ion **c** at *m/z* 120, originating from fragmentation of the side chain ion **b** at *m/z* 138. Upon acetylation, **1** yielded a diacetate **7** that revealed in its ^{1}H nmr an aliphatic acetyl (δ 1.91) and an aromatic acetyl (δ 2.23) singlet. A downfield shift of H-1 signal of **7**, in comparison with **1**, was indicative of a free C-1 hydroxyl group in **1**. As all the chemical shifts and coupling patterns of ring protons in **1** are similar to those in **2**, both compounds must assume identical ring structure. All these spectral evidences pointed to structure **1** for jasmolactone A.

Jasmolactone D [**4**], [α]D +28.5° (MeOH), was the major component and appeared as an amorphous powder; it gave a pentaacetate **8** upon acetylation and a tetramethylate **9** upon methylation. Both the uv and ir spectra of **4** were similar to, and

suggested, a close analogue of jasmolactone B [**2**]. Both ^{1}H-nmr and ^{13}C-nmr spectra of **4** showed peaks superimposable with those of **2** concerning the dihydropyran and lactone skeleton, except for signals arising from side chains. The ^{1}H-nmr spectrum of **9** revealed four aromatic methoxyl singlets, and that of **8** displayed an aliphatic acetyl signal, in addition to four aromatic acetyl singlets. The downfield shift of the H-1 signal of **8**, in comparison with **4**, was indicative of a C-1 hydroxyl group in the latter compound. The nature of the side chains was revealed by the observation of two sets of methylene protons, which appeared as ABX_2 and $AA'XX'$ spin systems, along with signals of two aromatic rings in the ^{1}H-nmr of **8**. Taken together, these signals reflected the presence of two nonequivalent 3,4-diacetoxyphenethoxyl groups attached with the main skeleton, obviously, at C-11 and C-8 positions. The eims spectrum of **4** revealed a base peak at *m/z* 154 that is compatible with a 3,4-dihydroxyphenethanol ion **d**. As the chemical shifts and coupling patterns of ^{1}H- and ^{13}C-nmr spectra of **4** are similar to those of **2**, an identical skeleton is assumed; therefore, structure **4** is established for jasmolactone D. The assignments of carbon signals were based in part on SFORD (single frequency off-resonance decoupling) and cross comparison with jasmolactone B [**2**], where a methoxycarbonyl group is attached at C-4.

Jasmolactone C [**3**], $[\alpha]_D$ +48.6° (MeOH), was a minor component and appeared as brown gum. Upon acetylation, it gave a tetraacetate **10**. The uv absorptions and ir bands of **3** were similar to those of jasmolactone D [**4**], suggesting a close analogue. Its eims spectrum (Scheme 1) showed fragment ions **c** (*m/z* 154) and **b** (*m/z* 138), indicating clearly that compound **3** contains both 3,4-dihydroxyphenethoxyl and 4-hydroxyphenethoxyl moieties as side chains. Comparison of the ^{1}H- and ^{13}C-nmr spectra of **3** with those of jasmolactone D [**4**] revealed a strong resemblance in the signals of the main ring skeletal part as well as the 3,4-dihydroxyphenethoxyl ester moiety at the C-11 position. However, for the C-8 ethereal substituent an additional set of signals corresponding to spin systems of a 4-hydroxyphenethoxyl moiety was observed, which is comparable in chemical shifts and coupling patterns to the C-8 substituent of jasmolactone A [**1**]. Thus, based on these cross comparisons, the placement of each substituent was accomplished, and structure **3** was established for jasmolactone C.

The established structures of **1**, **2**, **3**, and **4** belong to a 2-oxo-oxepano[4,5-*c*]pyran ring system, which is a new skeleton among secoiridoids known to date. (The nomenclature and numbering system are adopted according to the criteria described in Chemical Abstracts.) Therefore, the names jasmolactones A, B, C, and D, respectively, were designated for these new compounds.

General pharmacological screening revealed that both jasmolactones B [**2**] and D [**4**] possess coronary dilatory and cardiotropic activities as tested on isolated guinea pig heart preparations as shown in Table 4. Although less potent than isoproterenol, they

TABLE 4. Pharmacological Activities of Jasmolactones B [**2**] and D [**4**].

Activity	Compound		
	2	**4**	isoproterenol
Coronary dilation[a]	1.3×10^{-5}	4.8×10^{-6}	4.7×10^{-7}
Cardiotropic[a]	2.5×10^{-5} (ID+/CD−)[b]	9.7×10^{-6} (ID+/CD−)	4.7×10^{-8} (IS+/CS+)[c]
Anti-arrhythmic (ip 100 mg/kg)	marginal	marginal	

[a]Minimum effective concentrations (MEC) are presented in mole (M).
[b]ID represents negative inotropy, and CD represents negative chronotropy.
[c]IS represents positive inotropy, and CS represents positive chronotropy.

are quite significant in sharing the common structural fragment of 3,4-dihydroxyphenethoxyl catecholic moiety.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Ir and uv spectra were measured on Perkin-Elmer 577 and Hitachi 150-20 spectrometers, respectively. Optical rotations were measured on a JASCO DIP-181 digital polarimeter. Eims and fabms spectra were recorded on a JEOL JMS-D300 and Finnigan 4023 mass spectrometers, respectively. The ^{1}H-nmr (300 MHz), ^{13}C-nmr (75.47 MHz), DEPT, and ^{1}H-^{13}C correlation spectra were recorded on a Bruker AM 300 instrument using TMS as internal standard in appropriate solvents. The chemical shifts are given in δ (ppm) and coupling constants in Hz. Spectra of COSY 45, SFORD and nOe differences were measured with a Bruker WM 250 instrument, using standard pulse sequences. Cd spectra were measured in MeOH on a JASCO J-500A spectropolarimeter and recorded in molar ellipticity [θ] units. For analytical and preparative tlc, Si gel plates (Merck) were used, and detection was made by visualization under uv light or spraying with anisaldehyde-H_2SO_4 reagent after heating for a few minutes.

PLANT MATERIAL.—*J. multiflorum* was collected in a suburb of Taipei in December, 1985. A voucher specimen is preserved in the Herbarium of School of Pharmacy, National Taiwan University.

EXTRACTION AND ISOLATION.—The plant material (1.6 kg), consisting of fresh leaves with flowers attached, was homogenized and extracted with 95% EtOH (4 liters × 3). The EtOH extract was concentrated in vacuo to give an aqueous suspension. After dilution with an equal volume of H_2O, it was extracted successively with $CHCl_3$ and *n*-BuOH. The $CHCl_3$-soluble fraction was partitioned between hexane and MeOH-H_2O (4:3:1). The MeOH-H_2O solution was then concentrated and extracted exhaustively with EtOAc. The EtOAc extract (2.9 g) was chromatographed on a Si gel (160 g) column and eluted with $CHCl_3$ and increasing concentrations (1–15%) of MeOH, to give fractions A–G. Fraction E (248 mg) was repeatedly subjected to preparative tlc [2 mm plates, EtOAc-C_6H_6 (2:1), followed by 1 mm plates, $CHCl_3$-MeOH (10:1)] to give jasmolactone A [**1**] (165 mg).

The *n*-BuOH-soluble fraction was concentrated under vacuum to give a brown residue (80 g). Part of this crude secoiridoid residue (75 g) was chromatographed on a Si gel (750 g) column and eluted with $CHCl_3$ and increasing amounts (5–30%) of MeOH to yield fractions I–XIV. A portion of fraction I (105 mg) was purified with preparative tlc [1 mm plates, $CHCl_3$-MeOH (10:1) followed by 1 mm plates, C_6H_6-EtOAc (1:2)] to give jasmolactone B [**2**] (30 mg). Part of fraction IV (100 mg) was separated with preparative tlc (2 mm plates followed by 1 mm plates, Et_2O) and mplc [RP-C18, MeOH-H_2O (1:1)] to give jasmolactone C [**3**] (20 mg). Jasmolactone D [**4**] (3 g) was obtained directly from fraction VII.

JASMOLACTONE A [**1**].—Amorphous, $[\alpha]^{28}D$ +122.4° (*c* = 1.0, $CHCl_3$); uv λ max (MeOH) (log ε) 200 (4.20), 226 (4.14), 277.2 (3.37) nm; ir ν max (neat) 3400, 1705, 1625, 1515, 1440, 765 cm^{-1}; eims *m/z* (rel. int.) $[M]^+$ 378 (1.2), 361 (3.3), $[M-H_2O]^+$ 360 (16), $[M-2H_2O]^+$ 342 (3.1), $[M-H_2O-OAc]^+$ 301 (0.8), 259 (15), 256 (3.0), 249 (6.2), 248 (40), 241 (15), $[M-138]^+$ 240 (8), 209 (4.8), 203 (17), 194 (12), 181 (5.8), 180 (3.7), 167 (5.7), 162 (6.4), 153 (11), 149 (17), $[C_7H_7O_3]^+$ 139 (44), $[C_8H_{10}O_2]^+$ 138 (21.5), 136 (20), 122 (40), $[C_8H_9O]^+$ 121 (100), $[C_8H_8O]^+$ 120 (100).

JASMOLACTONE A DIACETATE [**7**].—Jasmolactone A (90 mg) was treated with a mixture of Ac_2O (1 ml) in pyridine (1 ml), and kept at room temperature for 6 h. The reaction mixture was treated with MeOH (20 ml) and, after standing for 30 min, was evaporated under vacuum to give a brown residue (120 mg). Purification with preparative tlc [1 mm plates, C_6H_6-EtOAc (1:1)] yielded jasmolactone A diacetate [**7**] (65 mg), $[\alpha]^{28}D$ +110.8° (*c* = 0.9, $CHCl_3$); ^{1}H nmr δ ($CDCl_3$); 5.97 (1H, d, *J* = 6.5, H-1), 7.53 (1H, d, *J* = 1.1, H-3), 3.28 (1H, m, H-5), 1.98 (1H, dd, *J* = 17.4, 10.8, H-6α), 3.42 (1H, dd, *J* = 17.4, 4.40, H-6β), 4.44 (1H, d, *J* = 3.9, H-8), 2.78 (1H, ddd, *J* = 3.9, 6.5, H-9), 4.01 (2H, brs, H-10), 4.38, 4.16 (2H, J_{AB} = 10.8, J_{AX} = J_{BX} = 6.8, H-1′) (*J* values were calculated from second-order analyses), 2.90 (2H, t, *J* = 6.8, H-2′), 7.19 (2H, d, *J* = 8.3, H-4′, -8′), 6.98 (2H, d, *J* = 8.3, H-5′, -7′), 3.63 (3H, s, OMe), 1.91 (3H, s, OAc), 2.23 (3H, s, OAc); ^{13}C nmr δ ($CDCl_3$) 97.36 (d, C-1), 155.50 (d, C-3), 104.34 (s, C-4), 24.86 (d, C-5), 34.25 (t, C-6), 171.51 (s, C-7), 77.65 (d, C-8), 72.73 (t, C-10), 166.79 (s, C-11), 64.8 (t, C-1′), 33.96 (t, C-2′), 135.25 (s, C-3′), 129.7 (d, C-4′), 121.52 (d, C-5′), 149.29 (s, C-6′), 121.52 (d, C-7′), 129.7 (s, C-8′), 51.11 (q, OMe), 20.82, 20.95 (q, $OCOCH_3$), 169.35, 169.90 (s, OCOMe); eims *m/z* (rel. int.) $[M-HOAc]^+$ 402 (5.9), 370 (8.9), 342 (3.0), 194 (11.9), 181 (4.4), 163 (31.1), 162 (20.7), 149 (6.7), 136 (5.9), 122 (7.4), 121 (71.8), $[C_8H_8O]^+$ 120 (100).

JASMOLACTONE B [**2**].—Amorphous, $[\alpha]^{28}D$ +100.1° (*c* = 0.1, MeOH); uv λ max (MeOH) (log ε) 201.2 (4.75), 226.4 (4.34), 280.4 (3.83); cd (*c* = 1.0 × 10^{-5}, MeOH) $[\theta]_{238}$ +3.98 × 10^4, $[\theta]_{279}$ +2.19 × 10^2; ir ν max (neat) 3400, 1700, 1625, 1515, 1440, 810, 760 cm^{-1}; eims *m/z* (rel. int.)

$[M]^+$ 394 (4.1), $[M-H_2O]^+$ 376 (9.0), 344 (10.7), 318 (15.7), 241 (6.6), $[M-154]^+$ 240 (4.1), 223 (4.1), 209 (6.6), 167 (6.2), 165 (4.2), $[C_8H_{10}O_3]^+$ 154 (29.8), $[C_7H_7O_3]^+$ 139 (17.6), 138 (28.1), 137 (76.8), $[C_8H_8O_2]^+$ 136 (100), 123 (47.9), 120 (34.3), 107 (39.7).

JASMOLACTONE B TRIACETATE [**6**].—Jasmolactone B [**2**] (130 mg) was treated with Ac_2O (1.5 ml) in pyridine (1 ml). Following usual workup and purification by preparative tlc [1 mm plates, C_6H_6-EtOAc (1:1)] gave 80 mg of jasmolactone B triacetate [**6**], $[\alpha]^{28}D$ +208.4° (*c* = 1.0, $CHCl_3$); ^1H nmr δ ($CHCl_3$) 5.96 (1H, d, *J* = 6.7, H-1), 7.53 (1H, d, *J* = 2.0, H-3), 3.27 (1H, m, H-5), 2.01 (1H, dd, *J* = 17.4, 10.4, H-6α), 3.40 (1H, dd, *J* = 17.4, 4.62, H-6β), 4.46 (1H, d, *J* = 3.9, H-8), 2.75 (1H, ddd, *J* = 3.9, 6.7, 6.7, H-9), 4.01 (2H, brs, H-10), 4.39, 4.18 (2H, J_{AB} = 10.98, J_{AX} = 6.84, J_{BX} = 6.65, H-1′) (*J* values were calculated from second order analyses), 2.90 (2H, dd, *J* = 6.63, 6.66, H-2′), 7.07 (H-4′, -7′), 7.03 (H-8′), 3.63 (3H, s, OMe), 1.93, 2.22, 2.23 (9H, s, OAc); ^{13}C nmr δ ($CHCl_3$) 97.30 (d, C-1), 155.5 (d, C-3), 104.24 (s, C-4), 24.77 (d, C-5), 34.1 (t, C-6), 171.45 (s, C-7), 77.61 (d, C-8), 44.43 (d, C-9), 72.7 (t, C-10), 166.78 (s, C-11), 64.32 (t, C-1′), 34.01 (t, C-2′), 136.53 (s, C-3′), 123.22 (d, C-4′), 141.81 (s, C-5′), 140.56 (s, C-6′), 123.67 (d, C-7′), 126.75 (d, C-8′), 51.08 (q, OMe), 20.83, 20.44 (q, $OCOCH_3$), 168.07, 168.16, 169.95 (s, OCOMe); eims *m/z* (rel. int.) $[M]^+$ 520 (0.24), 502 (0.78), $[M-OMe]^+$ 489 (1.4), $[M-HOAc]^+$ 460 (6.9), 428 (13.6), 400 (7.3), 386 (8.7), 376 (4.4), 344 (10.7), 283 (2.0), $[M-238]^+$ 282 (1.2), 241 (3.9), 240 (2.4), $[C_{12}H_{14}O_5]^+$ 238 (1.2), 221 (7.1), 220 (7.2), 196 (5.8), 194 (13.6), 179 (31.1), 178 (35.9), 162 (8.7), 154 (12.6), 137 (29.1), $[C_8H_8O_2]^+$ 136 (100), 120 (20.4).

JASMOLACTONE B DIMETHYLATE [**5**].—Jasmolactone B (130 mg) was treated overnight at room temperature with freshly prepared CH_2N_2 in Et_2O. Usual workup and purification by preparative tlc plate (1 mm, Et_2O) yielded jasmolactone B dimethylate [**5**] (43 mg): ^1H nmr δ ($CDCl_3$) 5.23 (1H, d, *J* = 6.7, H-1), 7.54 (1H, brs, H-3), 3.30 (1H, m, H-5), 2.30 (1H, dd, *J* = 18.5, 11.5, H-6α), 3.33 (1H, dd, *J* = 18.5, H-6β), 4.41 (1H, dd, *J* = 3.6, 2.2, H-8), 2.62 (1H, ddd, *J* = 6.7, 3.6, H-9), 3.97 (2H, d, *J* = 10.0, H-10), 4.29 (1H, dd, *J* = 6.4, 6.5, H-1′), 4.27 (1H, dd, *J* = 7.0, 6.9, H-1′), 2.86 (2H, t, *J* = 6.7, H-2′), 6.71–6.79 (3H, H-4′, -7′, -8′), 3.66, 3.83, 3.84 (9H, s, OMe); ^{13}C nmr δ ($CDCl_3$) 98.9 (d, C-1), 155.33 (d, C-3), 105.21 (s, C-4), 25.84 (d, C-5), 34.55 (t, C-6), 172.43 (s, C-7), 78.49 (d, C-8), 46.35 (d, C-9), 71.34 (t, C-10), 167.07 (s, C-11), 64.98 (t, C-1′), 34.47 (t, C-2′), 130.38 (s, C-3″), 111.19 (d, C-4′), 148.81 (s, C-5′), 147.57 (s, C-6′), 112.17 (d, C-7′), 120.76 (d, C-8′), 51.5, 55.81 (q, OMe).

JASMOLACTONE C [**3**].—$[\alpha]^{28}D$ +48.6° (*c* = 1.0, MeOH); uv λ max (MeOH) (log ε) 203.6 (4.54), 223.2 (4.22), 279.2 (3.72); ir ν max (neat) 3400, 1700, 1625, 1615, 1515, 1450, 818 cm^{-1}; eims *m/z* (rel. int.) 180 (0.03), $[C_8H_{10}O_3]^+$ 154 (13), $[C_8H_{10}O_2]^+$ 138 (28), 137 (22), $[154-H_2O]^+$ 136 (100), 123 (37), 121 (17), $[138-H_2O]^+$ 120 (49), 107 (85).

JASMOLACTONE C TETRAACETATE [**10**].—Jasmolactone C [**3**] (30 mg) was treated with Ac_2O (1.5 ml) in pyridine (1 ml). Usual workup and purification by preparative tlc yielded jasmolactone C tetraacetate [**10**] (15 mg): ^1H nmr δ ($CDCl_3$) 5.98 (1H, d, *J* = 6.6, H-1), 7.49 (1H, brs, H-3), 3.29 (1H, m, H-5), 2.00 (1H, H-6), 3.40 (1H, dd, *J* = 17.3, 4.5, H-6), 4.47 (1H, d, *J* = 4.1, H-8), 2.78 (1H, ddd, H-9), 4.04 (2H, brs, H-10), 4.27 (1H, t, *J* = 6.7, H-1′), 2.91 (2H, t, *J* = 6.7, H-2′), 7.19 (2H, d, *J* = 8.4, H-4′, -8′), 7.00 (2H, d, *J* = 8.4, H-5′, -7′), 7.09 (1H, H-4″), 7.08 (1H, H-7″), 7.03 (1H, H-8″), 1.95, 2.25, 2.26 (12H, OAc).

JASMOLACTONE D [**4**].—$[\alpha]^{28}D$ +28.5° (*c* = 1.0, MeOH); uv λ max (MeOH) (log ε) 202.8 (4.95), 224.4 (4.47), 281.6 (4.04) nm; ir ν max (KBr) 3400, 1700, 1620, 1525, 1448, 815 cm^{-1}; eims *m/z* (rel. int.) $[M-154]^+$ 362 (0.51), $[M-154-CO]^+$ 334 (0.76), $[M-154-CO_2]^+$ 318 (1.43), $[334-H_2O]^+$ 316 (1.0), $[M-2\times154]^+$ 208 (0.63), $[208-CO]^+$ 180 (3.8), $[C_8H_{10}O_3]^+$ 154 (100), $[154-H_2O]^+$ 136 (63.3), 123 (46.8).

JASMOLACTONE D PENTAACETATE [**8**].—Jasmolactone D [**4**] (50 mg) was treated with a mixture of Ac_2O (1 ml) in pyridine (0.5 ml) and followed by usual workup to give jasmolactone D pentaacetate [**8**] (56 mg): $[\alpha]^{28}D$ +65.8° (*c* = 1.0, $CHCl_3$); ^1H nmr δ ($CDCl_3$) 5.98 (1H, d, *J* = 6.7, H-1), 7.49 (1H, d, *J* = 1.7, H-3), 3.28 (1H, m, H-5), 2.00 (1H, dd, *J* = 17.3, 10.6, H-6α), 3.40 (1H, dd, *J* = 17.3, 4.3, H-6β), 4.46 (1H, d, *J* = 3.6, H-8), 2.76 (1H, ddd, *J* = 3.6, 6.7, H-9), 4.03 (2H, brs, H-10), 4.40, 4.18 (2H, J_{AB} = 11.01, J_{AX} = 6.91, J_{BX} = 6.47, H-1′) (*J* values were calculated from second order analyses), 2.92 (2H, t, *J* = 6.4, H-2′), 4.26 (2H, H-1″), 2.90 (2H, t, *J* = 6.45, H-2″), 7.09 (4H, H-4′, -4″, -7′, -7″), 7.03 (2H, d, *J* = 7.1, H-8′, -8″), 1.94, 2.24, 2.25 (15H, s, OAc); ^{13}C nmr δ ($CDCl_3$) 97.56 (d, C-1), 155.64 (d, C-3), 104.24 (s, C-4), 24.78 (d, C-5), 34.35 (t, C-6), 171.43 (s, C-7), 77.61 (d, C-8), 44.38 (d, C-9), 72.74 (t, C-10), 166.15 (s, C-11), 64.35 (t, C-1′), 34.15 (t, C-2″), 136.56 (s, C-3′), 123.26 (d, C-4′), 141.81 (s, C-5′), 140.54 (s, C-6′), 123.70 (d, C-7′), 126.80 (d, C-8′), 63.95 (t,

C-1″), 33.91 (t, C-2″), 136.66 (s, C-3″), 123.26 (d, C-4″), 141.85 (s, C-5″), 140.59 (s, C-6″), 123.72 (d, C-7″), 126.82 (d, C-8″), 20.86, 20.5 (q, $OCOCH_3$), 168.09, 168.15, 168.23, 168.97 (s, OCOMe); eims *m/z* (rel. int.) $[M-HOAc]^+$ 666 (2.1), $[666-Ac]^+$ 624 (1.5), $[624-HOAc]^+$ 564 (0.56), 506 (2.0), $[M-238]^+$ 488 (5.6), 471 (4.2), 470 (4.0), 429 (9), 428 (14), 402 (7.3), 400 (7.2), 399 (6.1), 386 (7.2), 360 (6.8), 344 (8.0), 318 (4.8), $[C_{12}H_{14}O_5]^+$ 238 (16.8), 237 (3.1), 221 (12.2), 220 (17.2), 209 (3.3), 208 (3.2), 197 (5.2), 196 (45), $[C_9H_8O_4]^+$ 180 (4.4), 179 (31.4), 178 (45), $[C_8H_{10}O_3]^+$ 154 (100), 136 (100).

JASMOLACTONE D TETRAMETHYLATE [**9**].—Jasmolactone D [**4**] (100 mg) was treated with an excess amount of CH_2N_2 in Et_2O. Usual workup and purification by preparative tlc (1 mm plate, Et_2O) provided jasmolactone D tetramethylate [**9**] (32 mg): ^1H nmr ($CDCl_3$) 5.22 (1H, d, $J=6.7$, H-1), 7.51 (1H, brs, H-3), 3.24 (1H, m, H-5), 3.31 (1H, dd, H-6), 4.39 (1H, dd, H-8), 2.63 (1H, ddd, H-9), 3.97 (2H, d, $J=9.9$, H-10), 4.27 (4H, m, H-1′, -1″), 2.87 (4H, m, H-2′, -2″), 6.71–6.79 (6H, H-4′, -7′, -8′, -4″, -7″, -8″), 3.82, 3.83, 3.84, 3.85, (12H, s, OMe).

PHARMACOLOGICAL ACTIVITIES.—The isolated guinea pig heart was perfused in a system of a modified Langendorff apparatus (19). Coronary dilating activity was determined by the measurement of perfusion pressure (cm) before and after administration of the tested compound. An increase of 20% in flow was considered positive in comparison with a control that was treated with Ringer-Locke solution. Cardiotropic activity was simultaneously measured by observation of inotropic (amplitude) or chronotropic (rate) effects, and an increase or decrease of more than 10% was regarded as effective. In all these studies, isoproterenol was used as a standard.

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