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Absolute Stereochemistry of Benzocycloheptenone Derivatives from *Cnidoscolus phyllacanthus*

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Abstract: Three new benzocycloheptenone derivatives, favelol (**1**), isofavelol (**2**), and favelone (**3**), were isolated from the bark of *Cnidoscolus phyllacanthus*. Their structures were elucidated on the basis of the spectroscopic analysis. Application of the CD exciton chirality method to 4-methoxybenzoates of **1** and **2** led to determination of the *R* absolute configuration at C-9, which was confirmed by X-ray crystallographic analysis of the 4-bromobenzoyl derivative of **2**.

INTRODUCTION

During our study to find antitumor compounds from natural sources, five cytosidal compounds have been isolated from the Brazilian plant, Favela, *Cnidoscolus phyllacanthus* (MART.) PAX *et* HOFFM. (Euphorbiaceae).[1] The benzocycloheptenone compounds, faveline methyl ether (**4**) and related compounds,[1,2] have new skeletons and their structures have been elucidated by spectroscopic analysis. Our continuous search of this plant led to the isolation of three new benzocycloheptenone derivatives, favelol (**1**), isofavelol (**2**) and favelone (**3**). In addition to the elucidation of their relative stereochemistry we applied CD exiton chirality method to 4-methoxybenzoyl derivatives of **1** and **2**, **7** and **8** respectively, in order to determine the absolute configuration at C-9. The result was confirmed by X-ray crystallographic analysis of the 4-bromobenzoyl derivative (**9**) of **2**.

RESULTS AND DISCUSSION

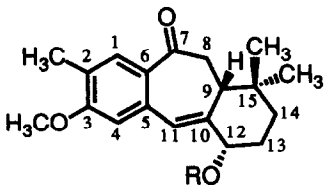
Hexane and EtOAc soluble fractions from the MeOH extract of the dried bark of *C. phyllacanthus* (450 g) were combined and subjected to silica gel chromatography with hexane and EtOAc mixtures of increasing polarity (100:0 to 0:100). The fractions eluted with hexane-EtOAc (5:1) to EtOAc were combined and rechromatographed repeatedly on silica gel with hexane and EtOAc mixture (5:1 to 2:1). Successive purification by HPLC afforded favelol (**1**, 68 mg), isofavelol (**2**, 145 mg) and favelone (**3**, 460 mg).

Structure Analysis. The molecular formula of favelol (**1**) was obtained as $C_{19}H_{24}O_3$ on the basis of HREI-MS (*m/z* 300.1734, Δ 1.0 mmu). The presence of a hydroxyl group, a conjugated ketone and an aromatic ring was indicated by the IR spectrum (ν 3630, 3470, 1675, 1620, 1515, 915 cm^{-1}). Treatment of **1** with acetic anhydride in pyridine yielded monoacetate (**5**). The ^1H and ^{13}C NMR spectra of **1** indicated the signals of three tertiary methyls (δ_H/δ_C: 0.72/20.4; 1.13/28.1; 2.19/15.6), a methoxyl (δ_H/δ_C: 3.87/55.5), three methylenes (δ_H/δ_C: 1.46/41.2; 1.55, 2.09/35.0; 3.02, 3.08/42.3), and two methines (δ_H/δ_C 2.22/49.7; 4.30/74.0), which resembled those of faveline methyl ether (**4**, Table 1) except for an oxymethine signal

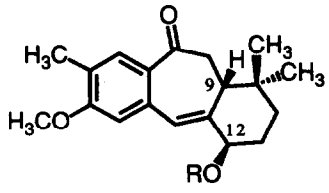
Table 1. ^{13}C and ^{1}H NMR Spectral Data for Favelol (**1**), Isofavelol (**2**), Favelone (**3**) and Faveline Methyl Ether (**4**) in $CDCl_3$.[a]

	1		**2**		**3**		**4**[c]	
No.	^{13}C[b]	^{1}H	^{13}C[b]	^{1}H	^{13}C[b]	^{1}H	^{3}C[b]	^{1}H
1	131.6 d	7.69 s	131.5 d	7.66 s	132.8 d	7.94 s	131.2 d	7.62 s
2	125.1 s		125.7 s		129.0 s		124.7 s	
3	161.1 s		160.9 s		161.3 s		160.9 s	
4	113.9 d	6.73 s	113.6 d	6.63 s	114.9 d	6.84 s	112.9 d	6.59 s
5	135.7 s		135.2 s		134.6 s		136.3 s	
6	129.3 s		130.1 s		128.5 s		129.7 s	
7	200.7 s		200.9 s		198.9 s		201.3 s	
8	42.3 t	3.02 dd (5.0, 12.8)	42.3 t	2.96 m[d]	44.6 t	2.71 dd (12.7, 14.2)	42.5 t	3.01 dd (6.0, 12.5)
		3.08 dd (5.4, 12.8)		3.08 dt (6.4, 8.2)		2.87 d (14.2)		3.04 dd (5.0, 12.5)
9	49.7 d	2.22 dd (5.0, 5.4)	45.1 d	2.97 m[d]	43.6 d	2.63 m[e]	51.3 d	2.37 dd (5.0, 6.0)
10	147.9 s		147.8 s		140.6 s		147.7 s	
11	121.5 d	6.65 s	127.3 d	6.45 s	139.2 d	7.59 d (2.7)	125.5 d	6.29 s
12	74.0 d	4.30 dd (5.4, 10.7)	76.1 d	4.42 br d (2.8)	200.4 s		41.2 t	2.31 dt (5.0, 12.5)
								2.40 m
13	35.0 t	1.55 m	31.4 t	1.88 m	34.5 t	2.51 m	25.1 t	1.67 m
		2.09 m				2.60 m[e]		1.74 m
14	41.2 t	1.46 m	36.9 t	1.24 m	35.1 t	1.78 m	43.1 t	1.45 m
				1.90 m				
15	38.3 q		38.4 q		32.4 s		38.4 s	
16[f]	20.4 q	0.72 s	20.0 q	0.72 s	20.7 q	0.95 s	20.7 q	0.76 s
17[f]	28.1 q	1.13 s	28.6 q	1.15 s	28.9 q	1.14 s	28.9 q	1.12 s
18[g]	15.6 q	2.19 s	15.6 q	2.20 s	16.1 q	2.25 s	15.6 q	2.18 s
OCH_3	55.5 q	3.87 s	55.5 q	3.88 s	55.7 q	3.90 s	55.4 q	3.87 s

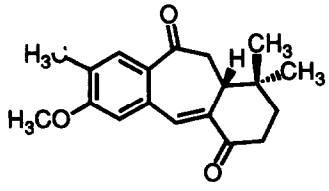
[a] Coupling constants (Hz) are given in parentheses; [b] Multiplicities were determined by DEPT experiment; [c] Reference 1; [d,e] Chemical shifts were determined by HH- and HC COSY experiments; [f] 15-CH_3; [g] 2-CH_3.



1: R=H
5: R=Ac
7: R=COC_6H_4-4-OCH_3



2: R=H
6: R=Ac
8: R=COC_6H_4-4-OCH_3
9: R=COC_6H_4-4-Br



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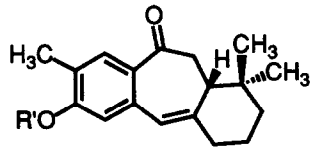


4: R'=CH_3
10: R'=H

Figure 1

(δ_H/δ_C: 4.30/74.0). The UV spectra (λ_{max} 339, 301, 259, 252sh nm) and ^{13}C NMR signals indicating eight sp^2 carbons (δ_C: 113.9, d; 121.5, d; 125.1, s; 129.3, s; 131.6, d; 135.7, s; 147.9, s; 161.1, s) of **1** were also similar to those of faveline methyl ether (**4**). The ^1H-^1H COSY spectrum indicated two partial structures, CH_2-CH and CH_2-CH_2-CH(OH), and the oxymethine (δ_C 74.0) of the latter showed long range connectivity with an olefinic hydrogen (δ_H 6.65) on the COLOC spectrum. The above data suggested that favelol (**1**) was a 12-hydroxyl form of faveline methyl ether. Analysis of the COLOC spectrum allowed unambiguous assignment of all hydrogen and carbon signals as shown in Table 1. The structure of favelol was thus elucidated as the formula **1** (Figure 1).

Isofavelol (**2**) has the same molecular formula and showed a very similar mass fragment pattern to that of **1**. It also gave a monoacetate **6** on treatment with acetic anhydride in pyridine. The ^1H NMR spectrum of **2** was similar to that of **1**, except signals for H-9 (δ 2.97), H-11 (δ 6.45), H-12 (δ 4.42), H_2-13 (δ 1.88) and H_2-14 (δ 1.24 and 1.90). The ^1H-^1H COSY and COLOC spectrum indicated that **2** had the same structure units as **1**, which suggested that **2** had an epimeric hydroxyl at C-12. The comparison of the NOESY spectra for the acetates (**5** and **6**) supported the above assumption (Figure 2). In the case of **5**, clear NOE's were detected between H-12 and H-9, H-12 and H-13, and H-11 and 12-*O*-acetyl hydrogens. On the other hand, H-12 of **6** showed NOE's with H-11 and H-13, and 12-*O*-acetyl hydrogens of **6** with H-9. The above NOE's indicated that H-12 of **5** had 1,3-diaxial relationship with H-9, while H-12 of **6** had 1,3-paralel relationship with H-11. Thus isofavelol was concluded to have the relative stereostructure **2** (Figure 1).

Favelone (**3**) has the molecular formula, $C_{19}H_{22}O_3$ [*m/z* 298.1590 (M^+), Δ 2.2 mmu]. Conjugated phenacyl system was indicated by the IR absorption at ν 1678 (sh) and 1665 cm^{-1}, and by the UV absorption at λ 333 and 272 nm. Two carbonyls showed ^{13}C NMR signals at δ_C 198.9 and 200.4. Other functional groups indicated by ^1H and ^{13}C NMR spectra of favelone were three methylenes (δ_H/δ_C: 1.78/35.1; 2.51, 2.60/34.5; 2.71, 2.87/44.6), a methine (δ_H/δ_C: 2.63/43.6), and a conjugated system (δ_C between 114.9 and 161.3, Table 1). The ^1H-^1H COSY spectrum indicated two partial structures, CH_2-CH and CH_2-CH_2. The connectivities of a methylene (δ_H 2.71 and 2.87) in the former to a carbonyl carbon (δ_C 198.9), and of a methylene (δ_H 2.51 and 2.60) in the latter to another carbonyl (δ_C 200.4) were indicated by COLOC and HMBC spectra. Those facts suggested that favelone was a 12-oxo derivative of faveline methyl ether. According to the above assumption, favelone (**3**) was treated with sodium borohydride in $CHCl_3$-MeOH to give a single product which was identical to favelol (**1**). Thus the structure of favelone was determined as 12-oxo-faveline methyl ether (**3**, Figure 1).

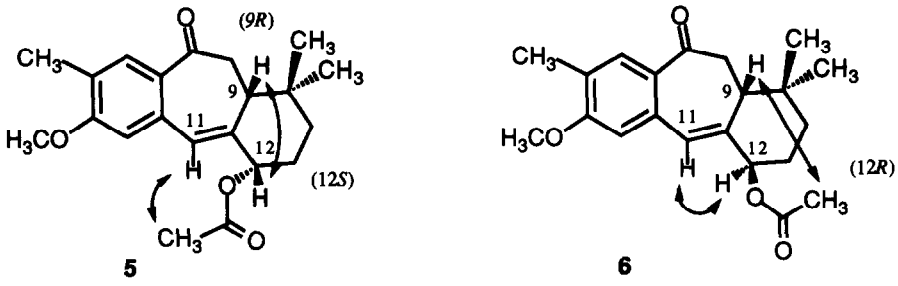


Figure 2

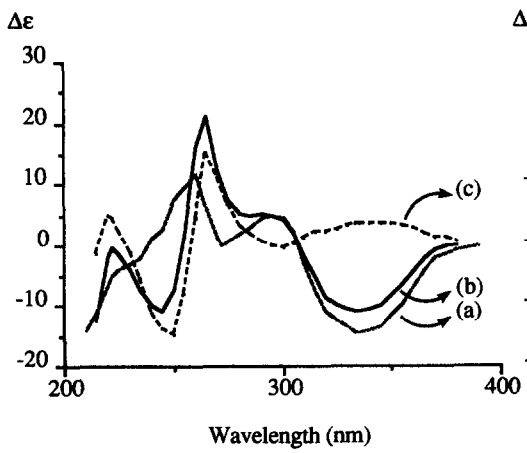


Figure 3. CD Spectra of (a) favelol (**1**), (b) methoxybenzoate (**7**), and (c) the dufference spectrum of **1** and **7**.

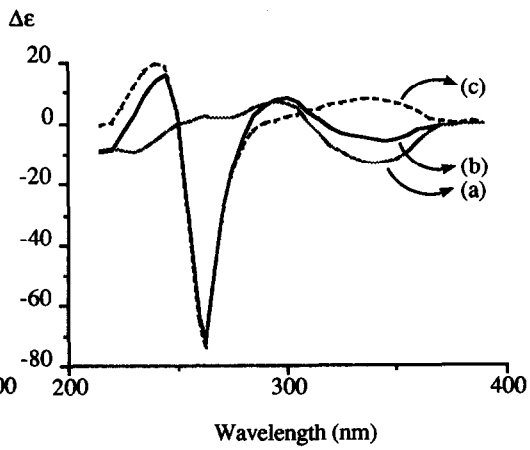


Figure 4. CD Spectra of (a) isofavelol (**2**), (b) methoxybenzoate (**8**), and (c) the dufference spectrum of **2** and **8**.

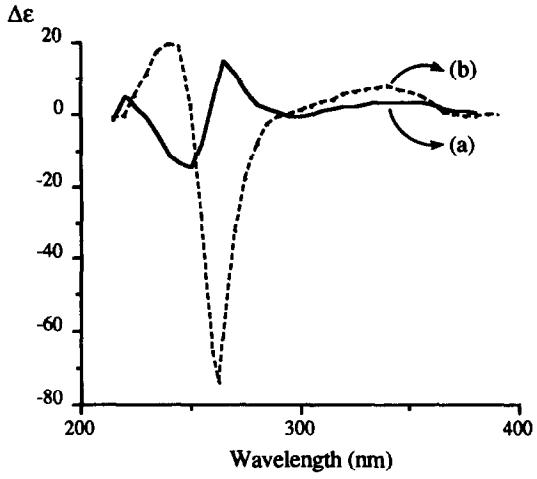
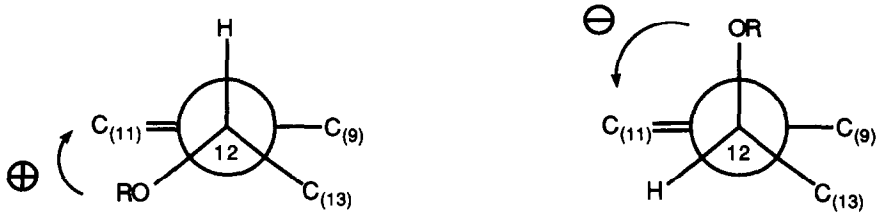


Figure 5. Comparison of CD difference Spectra of (a) methoxybenzoate (7) and (b) methoxybenzoate (8).



7 8

Figure 6

Absolute Configuration. The conjugated π-electron system of favelol and related compounds[1] generates several CD Cotton effects (CE) between 200 and 400 nm, which reflect the twisted choromophore of *o*-keto-styrene unit. A rigid conformation of the cycloheptenone ring moiety could be indicated by the clear coupling constants of ^{1}H signals for favelol (**1**), isofavelol (**2**), favelone (**3**) and other congeners (Table 1 and ref. 1).

In order to unambiguously determine their absolute configurations, we applied the CD exiton chirality method[3] to 4-methoxybenzoates (**7** and **8**) of favelol (**1**) and isofavelol (**2**). The 4-methoxybenzoate choromophore (λ_{max} 257 nm) was selected so that the $\pi \rightarrow \pi^*$ transition of *o*-keto-styrene moiety of (**1**) and (**2**) at 259-258 nm effectively couples with that of the benzoate chromophore at C_{12} position to generate intense exiton split Cotton effects.

The 4-methoxybenzoate (**7**) was prepared from favelol (**1**) by treatment with 4-methoxybenzoyl chloride, triethylamine and DMAP, while the 4-methoxybenzoate (**8**) was obtained from isofavelol (**2**) by treating with 4-methoxybenzoyl chloride in pyridine. In both cases 4-methoxybenzoylation lowered the ^{1}H NMR chemical shift at C-12 from δ 4.30 to 5.61 (for **7**) or from δ 4.42 to 5.43 (for **8**). The CD spectrum of 4-methoxybenzoate (**7**) showed new extrema at 263 nm (Δε +22.9) and at 245 nm (-10.9) (Figure 3), while the 4-methoxybenzoate (**8**) showed extrema at 262 nm (-72.1) and at 245 (+16.0) (Figure 4). In order to make

the exciton CD Cotton effects clearer, the difference CD spectral curves (**7**)-(**1**) and (**8**)-(**2**) were calculated (Figure 3 and 4). It is reasonable to consider that the bisignate Cotton effects observed in the difference CD curves are due to the exciton coupling between 4-methoxybenzoate and *o*-keto-styrene chromophores (Figure 5). The observed Cotton effects of (**7**) with positive exciton chirality lead to the 12*S* absolute configuration, while those of (**8**) with negative exciton chirality to the 12*R* configuration (Figure 6). As seen in Figure 5, methoxybenzoate (**8**) exhibits stronger exciton CD Cotton effects, in line with the exciton theory of CD spectra,[3] than the other methoxybenzoate (**7**) does. This phenomenon is explained as follows; methoxybenzoate (**8**) has a benzoate chromophore in an axial-like position and therefore the dihedral angle between benzoate and *o*-keto-styrene chromophores is ca. 90°. On the other hand, in methoxybenzoate (**7**), a benzoate chromophore is in an equatorial-like position, and the dihedral angle is ca. 30°. Since the exciton theory reveals that the exciton split Cotton effects are the largest when the dihedral angle is around 70°, the Cotton effects of axial benzoates are, in general, larger than those of equatorial benzoates.[3] From these CD and ^{1}H NMR data, the absolute configurations of favelol (-)-**1** and isofavelol (-)-**2** were determined to be (9*R*,12*S*) and (9*R*,12*R*), respectively.

The (9*R*,12*R*) absolute configuration of isofavelol (-)-**2** was confirmed by the X-ray crystallographic analysis of its 4-bromobenzoate (**9**). The structure was solved by direct methods and refined to give R and R_w indices of 0.049 and 0.060, respectively. R index of 0.066 and R_w index of 0.075 for the opposite enantiomorph were also obtained after refining. A perspective view given in Figure 7 showed the correct absolute configuration of (**9**).

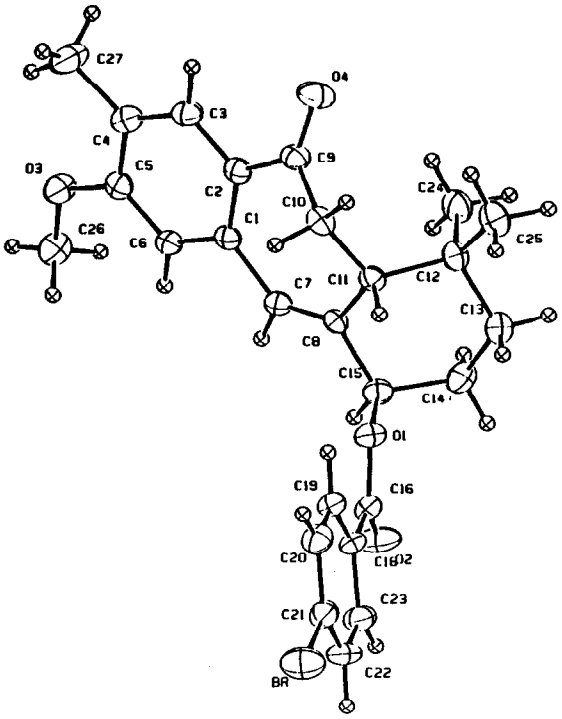


Figure 7. ORTEP Drawing of 4-Bromobenzoate (**9**).

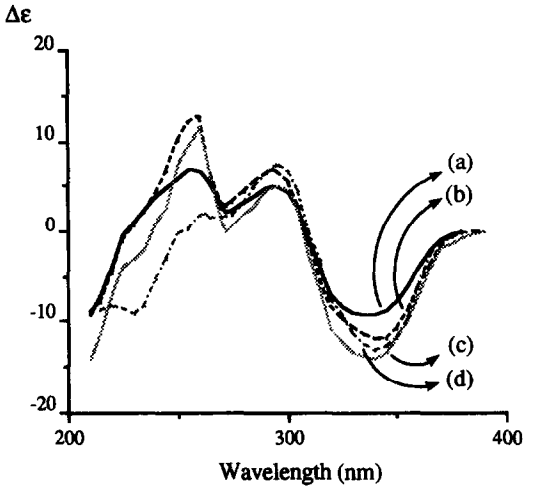


Figure 8. CD Spectra of (a) favelin (**10**), (b) favelin methyl ether (**4**), (c) favelol (**1**), and (d) isofavelol (**2**).

The congeners, faveline (**10**) and faveline methyl ether (**4**) showed similar CE's in their CD spectra indicative of the *R* configuration at C-9 for those compounds (Figure 8).

In conclusion, three new benzocycloheptenone derivatives, favelol (**1**), isofavelol (**2**) and favelone (**3**) were isolated from the bark of Brazilian plant *Cnidoscolus phyllacanthus*, their structures were elucidated by spectroscopic analysis including 2D NMR, CD and X-ray crystallography.[4] The CD study showed the congeners (**1, 2, 3, 4** and **10**) have *R* configuration at C-9.

EXPERIMENTAL

General Method. Melting points were determined in a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were recorded on a JASCO DIP-370 digital polarimeter. UV spectra were measured on a Hitachi U-3200 spectrophotometer. IR spectra were recorded on a JASCO A-100S infrared spectrophotometer. CD curve were measured on a JASCO J-400X or on a J-720 dichrograph system. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL GX-500 spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C nuclei. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS) as an internal standard and coupling constants (*J*) are expressed in Hz. Mass spectra were taken on a JEOL DX-303 or an AX-500 spectrometer. X-ray crystallographic data were measured on a Rigaku AFC5R diffractometer. Wakogel C-300 (Wako Pure Chemical Inc.) was used for silica gel chromatography. For TLC, pre-coated Silica gel 60 F_{254} plates (Merck) and spots were visualized by UV (254 and 360 nm) or 50% aq. H_2SO_4.

Isolation of favelol (1), isofavelol (2) and favelone (3). The dried and powdered bark (450 g) of *Cnidoscolus phyllacanthus* was extracted with MeOH (3 L) at room temperature for 10 days. The solvent was removed *in vacuo* to yield 34.8 g of a gummy extract, which was partitioned between water and organic solvents, hexane, EtOAc and *n*-butanol. The combined hexane and EtOAc extract, 22.8 g was chromatographed on silica gel (500 g, 50 mm id X 1000 mm) with hexane and EtOAc mixture (100:0 to 0:100). The fractions eluted with hexane-EtOAc (5:1 to 0:100) were combined to repeat silica gel (200 g)

chromatography giving two characteristic fractions by elution with hexane-EtOAc (5:1) and (2:1). The former fraction was chromatographed again and elution with $CHCl_3$-MeOH (100:1) gave favelone (**3**, 460 mg). From the latter with hexane-EtOAc (2:1), after silica gel chromatography with benzene-EtOAc (10:1), two fractions containing favelol and isofavelol, 394 mg and 554 mg, were obtained. Each fraction was purified by normal phase HPLC (SiO_2, Inertsil PREP-SIL, Gasukuro Kogyo, 20 mm id X 250 mm; eluant, $CHCl_3$, 10.0 ml/min) to give favelol (**1**, 68 mg) and isofavelol (**2**, 145 mg).

Favelol (**1**). Colorless needles, mp 197-199 °C ($CHCl_3$-hexane); $[\alpha]_D^{25}$ -373.8° (*c* 0.73, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3630, 3470 br, 1675, 1620, 1515, 915 cm^{-1}; UV (MeOH) λ_{max} 339 nm (log ε 3.92), 301 (4.02), 259 (4.63), 252 sh (4.58); CD (MeOH) λ_{ext} 333 nm (Δε -14.5), 295 (+5.0), 260 (+11.7); HREI-MS *m/z* 300.1734 (M^+, Calcd 300.1724 for $C_{19}H_{24}O_3$).

Isofavelol (**2**). Colorless needles, mp 198-200 °C ($CHCl_3$-hexane); $[\alpha]_D^{27}$ -339.6° (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3600, 3430 br, 1665, 1600, 1500, 910 cm^{-1}; UV (MeOH) λ_{max} 338 nm (log ε 3.89), 303 (4.02), 258 (4.61), 251 sh (4.58); CD (MeOH) λ_{ext} 340 nm (Δε -13.2), 296 (+7.2), 270 (+1.5), 263 (+2.1); HREI-MS *m/z* 300.1741 (M^+, Calcd 300.1724 for $C_{19}H_{24}O_3$).

Favelone (**3**). Pale yellow needles, mp 207-209 °C ($CHCl_3$-hexane); $[\alpha]_D^{26}$ -247.4° (*c* 0.93, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1678 sh, 1665, 1590, 1500, 920 cm^{-1}; UV (MeOH) λ_{max} 333 nm (log ε 4.16), 272 (4.15); CD (MeOH) λ_{ext} 347 nm (Δε -9.9), 303 (+8.2), 267 (-15.8); HREI-MS *m/z* 298.1590 (M^+, Calcd 298.1568 for $C_{19}H_{22}O_3$).

Acetylation of favelol (**1**) **and isofavelol** (**2**). Favelol (**1**, 10 mg) or isofavelol (**2**, 10 mg) was treated with acetic anhydride (1.5 ml) and pyridine (1.0 ml) at room temperature overnight. Extraction and preparative TLC (hexane-EtOAc, 5:1) gave the acetate (**5**, 9.7 mg) or (**6**, 9.8 mg). **5**: IR ($CHCl_3$) ν_{max} 1720, 1660, 1600, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (3H, s, H_3-16), 1.14 (3H, s, H_3-17), 1.52 (2H, m, H_2-14), 1.68 (1H, m, Ha-13), 2.06 (1H, m, Hb-13), 2.20 (3H, s, H_3-18), 2.25 (3H, s, $OCOCH_3$), 2.31 (1H, t, *J*=5.1, H-9), 3.01 (1H, dd, *J*=5.1, 12.3, Ha-8), 3.09 (1H, dd, *J*=5.1, 12.3, Hb-8), 3.91 (3H, s, OCH_3-3), 5.38 (1H, dd, *J*=5.0, 11,0, H-12), 6.35 (1H, s, H-11), 6.64 (1H, s, H-4), 7.70 (1H, s, H-1); EI-MS *m/z*: 342 (M^+), 299, 282. **6**: IR ($CHCl_3$) ν_{max} 1725, 1670, 1600, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.74 (3H, s, H_3-16), 1.17 (3H, s, H_3-17), 1.28 (1H, m, Ha-14), 1.77 (1H, m, Hb-14), 1.90 (2H, m, H_2-13), 2.09 (3H, s, $OCOCH_3$), 2.20 (3H, s, H_3-18), 2.77 (1H, dd *J*=5.3, 5.7, H-9), 2.99 (1H, dd, *J*=5.3, 12.6, Ha-8), 3.08 (1H, dd, *J*=5.7, 12.6, Hb-8), 3.88 (3H, s, OCH_3-3), 5.44 (1H, br s, H-12), 6.58 (1H, s, H-11), 6.68 (1H, s, H-4), 7.67 (1H, s, H-1); EI-MS *m/z*: 342 (M^+), 299, 282.

Reduction of favelone (**3**). Favelone (**3**, 5.0 mg) in $CHCl_3$-MeOH (1:1, 2.0 ml) was treated with sodium borohydride (3.8 mg) for 30 min at 0 °C. Reaction mixture was diluted with water and extracted with ether, which was washed with 5% HCl, 5% $NaHCO_3$ and sat NaCl aq, dried and evaporated. Purification of the product by preparative TLC (benzene-EtOAc, 5:1) gave the alcohol (**1**, 4.1 mg) which was identical with the natural favelol (**1**).

4-Methoxybenzoate (**7**). To a mixture of favelol (**1**, 18.4 mg) in dry CH_2Cl_2 (1.0 ml), triethylamine (0.043 ml), and DMAP (22.5 mg) 4-methoxybenzoyl chloride (31.4 mg) in dry CH_2Cl_2 (0.5 ml) was added and the mixture was stirred at room temperature for 3 h. After dilution with water, the mixture was extracted with ether, which was washed with 5% HCl, 5% $NaHCO_3$ and sat NaCl aq, dried and evaporated. Purification of the residue by preparative TLC (hexane-EtOAc, 2:1) gave the methoxybenzoate (**7**, 7.2 mg): UV (MeOH) λ_{max} 333sh nm (log ε 3.60)), 303 (3.78), 273sh (4.03), 257 (4.66), 252 (4.66); CD (MeOH) λ_{ext}

335 nm (Δε -10.9), 293 (+5.1), 285 (+4.9), 263 (+22.9), 245 (-10.9); ^{1}H NMR ($CDCl_3$) δ 0.80 (3H, s, H_3-16), 1.17 (3H, s, H_3-17), 1.58 (2H, m, H_2-14), 1.85 (1H, m, Ha-13), 2.13 (1H, m, Hb-13), 2.19 (3H, s, H_3-18), 2.40 (1H, t, *J*=5.1, H-9), 3.04 (1H, dd, *J* =5.1, 12.9, Ha-8), 3.14 (1H, dd, *J*=5.1, 12.9, Hb-8), 3.83 (3H, s, OCH_3-3), 3.91 (3H, s, OCH_3-5'), 5.61 (1H, dd, *J*=4.9, 11.2, H-12), 6.41 (1H, s, H-11), 6.55 (1H, s, H-4), 7.01 (2H, d, *J*=8.8, H-3', -7'), 7.70 (1H, s, H-1), 8.16 (2H, d, *J*=8.8, H-4', -6'); EI-MS *m/z* 434 (M^+), 299, 282, 152, 135.

4-Methoxybenzoate (8). A mixture of isofavelol (**2**, 10.7 mg), 4-methoxybenzoyl chloride (20.8 mg) and pyridine (0.5 ml) was stirred at room temperature for 15 h. After dilution with water, the mixture was extracted with ether, which was washed with 5% HCl, 5% $NaHCO_3$ and sat NaCl aq, dried and evaporated. Purification of the residue by preparative TLC (hexane-EtOAc, 2:1) gave the methoxybenzoate (**8**, 2.8 mg): UV (MeOH) λ_{max} 333sh nm (log ε 3.61)), 303 (3.79), 275sh (4.01), 259 (4.61), 251 (4.55); CD (MeOH) λ_{ext} 345 nm (Δε -5.8), 299 (+8.0), 262 (-72.1), 245 (+16.0); ^{1}H NMR ($CDCl_3$) δ 0.78 (3H, s, H_3-16), 1.21 (3H, s, H_3-17), 1.38 (1H, m, Ha-14), 1.91 (1H, m, Hb-14), 2.03 (2H, m, H_2-13), 2.20 (3H, s, H_3-18), 2.87 (1H, dd, *J*=5.4, 5.9, H-9), 3.01 (1H, dd, *J* =5.4, 12.7, Ha-8), 3.09 (1H, dd, *J*=5.9, 12.7, Hb-8), 3.87 (3H, s, OCH_3-3), 3.89 (3H, s, OCH_3-5'), 5.65 (1H, br d, *J*=2.4, H-12), 6.69 (1H, s, H-11), 6.71 (1H, s, H-4), 6.94 (2H, d, *J*=8.8, H-3', H-7'), 7.67 (1H, s, H-1), 8.02 (2H, d, *J*=8.8, H-4', -6'); EI-MS *m/z* 434 (M^+), 299, 282, 152, 135.

Table 2. Crystal Data for the Compound (**9**).

Crystal dimensions, mm	0.150 X 0.200 X 0.260
Formula	$BrC_{26}O_4H_{27}$
Formula weight	483.40
Crystal System	monoclinic
Space Group	$P2_1$ (#4)
Lattice Parameters	a= 10.348 (2) Å
	b= 7.9151 (6) Å
	c= 14.536 (2) Å
	β= 103.64 (1) °
	V= 1157.0 (5) Å^3
Z value	2
D_{calc}	1.387 g/cm^3
μ (CuKα)	26.55 cm^{-1}
Radiation (CuKα)	1.5478 Å
$2\theta_{max}$	124.1°
No. Reflections Measured	Total: 4038
	Unique: 3410
No. Reflections above 3.00 σ(I)	3060
Max. Peak in Final Diff. Map	0.32 e$^-$/Å^3
Min. Peak in Final Diff. Map	-0.46 e$^-$/Å^3
R; R_w	0.049; 0.060
R^-; R^-_w (inverted structure)	0.066; 0.075

4-Bromobenzoate (9). A mixture of isofavelol (**2**, 10.7 mg), 4-bromobenzoyl chloride (20.8 mg) and pyridine (0.5 ml) was stirred at room temperature for 15 h.. After dilution with water, the mixture was extracted with EtOAc, which was washed with 5% HCl, 5% $NaHCO_3$ and sat NaCl aq, dried and evaporated. Purification of the residue by preparative TLC (hexane-EtOAc, 5:1) gave the benzoate (**9**, 3.4 mg), mp 173-174 °C (hexane): UV (MeOH) λ_{max} 332sh (log ε 3.72)), 301 (3.87), 258 (4.67), 252 (4.67); CD (MeOH) λ_{ext} 346 nm (Δε -7.3), 299 (+12.7), 258 (+77.4), 236 (+16.6); IR ($CHCl_3$) ν_{max} 1720, 1670, 1600, 1270 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (3H, s, H_3-16), 1.21 (3H, s, H_3-17), 1.40 (1H, m, Ha-14), 1.88 (1H, m, Hb-14), 2.01 (1H, m, Ha-13), 2.07 (1H, m, Hb-13), 2.20 (3H, s, H_3-18), 2.84 (1H, dd, *J*=5.4, 5.9, H-9), 3.00 (1H, dd, *J* =5.4, 12.7, Ha-8), 3.09 (1H, dd, *J*=5.9, 12.7, Hb-8), 3.89 (3H, s, OCH_3-3), 5.68 (1H, br s, H-12), 6.70 (1H, s, H-11), 6.71 (1H, s, H-4), 7.60 (2H, d, *J*=8.3, H-3', -7'), 7.64 (1H, s, H-1), 7.91 (2H, d, *J*=8.3, H-4', -6'); EI-MS *m/z* 484 (M^++2), 482 (M^+), 299, 282, 267, 239, 202, 200, 185, 183.

X-ray Analysis. Isofavelol 4-bromobenzoate (**9**) crystallized from hexane in colorless needles, mp 173-174 °C. Crystal data for **9** are listed in Table 2. Lorenz and polarization corrections, and an empirical absorption correction were applied. The structure was solved by the direct method and refined by full-matrix least-squares method anisotropically for non-hydrogen atoms and isotropically for hydrogen atoms which were located on the D-map.

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