POTENTIAL ANTICANCER AGENTS. XVI. ISOLATION OF BICYCLOFARNESANE SESQUITERPENOIDS FROM *CAPSICODENDRON DINISII*[1, 2]

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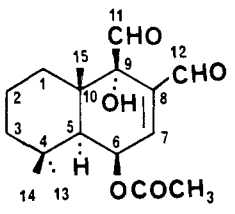
ABSTRACT.—The cytotoxic drimane derivatives cinnamodial (**1**), capsicodendrin (**2**), a partially characterized tetramer of **1**, and cinnamosmolide (**3**) were obtained from *Capsicodendron dinisii* (Canellaceae). A new compound, 6β-acetoxyisodrimenin (**4**) and ugandensolide (**5**) and futronolide (**6**) were also isolated, but were not cytotoxic.

In a continuing search for anticancer and cytotoxic agents from plants, chloroform extracts of stem bark and leaf-twig samples of the South American arboreal species *Capsicodendron dinisii* (Canellaceae) were found to exhibit cytotoxic activity against the Eagle's 9KB carcinoma of the nasopharynx in cell culture (1).[3] Separation of active fractions from the root bark by column chromatography over silica gel[4] resulted in the isolation of two cytotoxic compounds, cinnamodial (**1**) and capsicodendrin (**2**). Three inactive compounds, 6β-acetoxyisodrimenin (**4**), ugandensolide (**5**) and futronolide (**6**) were also obtained. The cytotoxic compound cinnamosmolide (**3**) was isolated from the leaf-twig extract of *C. dinisii*.



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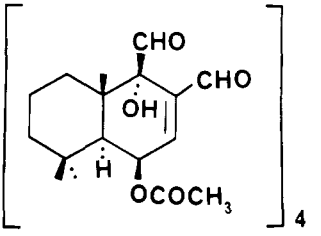

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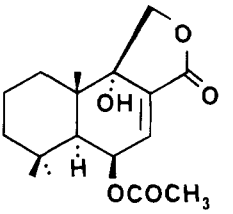

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In this communication we present evidence for the partial structural characterization of capsicodendrin (**2**), which is the first sesquiterpene tetramer to be discovered. The structure of 6β-acetoxyisodrimenin (**4**) was assigned by analysis of mass and pmr spectral data, and the known compounds **1**, **3**, **5** and **6** were identified by comparison with authentic samples or published spectral data.

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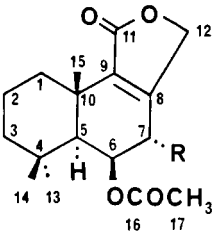
[1]For the previous paper in this series see Gunasekera, S. P., G. A. Cordell and N. R. Farnsworth, *Phytochemistry*, in press.

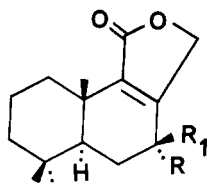
[2]A summary of the present work was presented at the 20th Annual Meeting of the American Society of Pharmacognosy, held at Purdue University, West Lafayette, Indiana, July 29–August 3, 1979.

[3]The extracts, fractions and compound were tested under the auspices of the Developmental Therapeutics Program of the National Cancer Institute. An isolate is considered active if it shows an $ED_{50} \leq 4$ μg/ml in the 9KB and P388 *in vitro* cell culture assays, and $T/C \geq 130\%$ in the P-388 *in vivo* assay.

[4]E. Merck, Darmstadt, W. Germany.



	R
4	H
5	OH
7	$OCOCH_3$



	R	R_1
6	OH	H
8	H	OH
9	$OCOCH_3$	H

EXPERIMENTAL[5]

PLANT MATERIAL.—The stem bark and leaves and twigs of *Capsicodendron dinisii* (Schwacke) Occhioni were collected in Brazil in October, 1975, and the plant was authenticated[6] under the direction of Dr. R. E. Perdue, Jr.

EXTRACTION AND FRACTIONATION.—The dried, milled stem bark of *C. dinisii* (58 kg) was extracted with 600 liters of methanol. Following removal of the solvent, the residue (3.5 kg) was partitioned between water (4 liters) and chloroform (10×2 liters). The dried chloroform extract (2.8 kg) was shown to be active (ED_{50} 2.8 μg/ml) in the 9KB cell culture test system, while the aqueous extract and interfacial materials were inactive. A portion of the chloroform extract (205 g) was repeatedly chromatographed by gradient elution over columns loaded with silica gel[4], successively with mixtures of benzene, chloroform and methanol as solvents. Purification of cytotoxic fractions yielded, in order, crystals of cinnamodial (**1**), 6β-acetoxyisodrimenin (**4**), ugandensolide (**5**), futronolide (**6**) and capsicodendrin (**2**).

When a similar procedure was repeated for a mixture of the leaves and twigs of *C. dinisii* (1.2 kg), crystalline cinnamosmolide (**3**) was isolated.

CHARACTERIZATION OF CINNAMODIAL (**1**).—Cinnamodial (**1**, 0.31 g, 0.0073%) mp 135–137°, $[\alpha]^{27}D$ −416 (c 0.5, $CHCl_3$), exhibited the following spectral properties, uv, λ max (MeOH) 215 nm (log ε 4.14), ir, ν max (KBr) 3440, 2870, 2710, 1740, 1725, 1700, 1390, 1370, 1240 and 1045 cm^{-1}; pmr, ($CDCl_3$) δ 1.02 (3H, s), 1.16 (3H, s), 1.34 (3H, s, 10-CH_3), 2.05 (1H, d, J=4.6 Hz, 5-H), 2.14 (3H, s, $-OCOCH_3$), 4.01 (1H, br s, exchanged with D_2O, 9-OH), 5.87 (1H, t, J=4.6 Hz, 6-H), 7.04 (1H, d, J=4.6 Hz, 7-H), 9.47 (1H, s, 12-CHO) and 9.75 (1H, d, J=1.5 Hz; s after D_2O exchange, 11-CHO); cmr, ($CDCl_3$), see table 1; ms, *m/e*, M^+ 308 (28%), 279 (24), 278 (97), 248 (82), 237 (100), 220 (83), 205 (28), 124 (22) and 95 (11). These physical data are in agreement with those published for cinnamodial (**1**) (known also as ugandensidial) (2–4), and the identity was confirmed (mmp, pmr, ms, tlc) by comparison with an authentic sample.[7]

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[5]Melting points were determined using a Koffler hot-stage instrument, and are uncorrected. Specific rotations were obtained on a Carl Zeiss 0.05 circle polarimeter. Uv spectra were measured on a Beckman DB-G grating spectrophotometer, and ir spectra on a Beckman model 18-A spectrophotometer, with polystyrene calibration at 1601 cm^{-1}. Pmr and certain cmr spectra were recorded on a Varian model T-60A instrument, operated at 60 MHz and 15.06 MHz, respectively, equipped with a Nicolet model TT-7 Fourier Transform attachment. Tetramethylsilane was used as internal standard, and chemical shifts are reported on the δ (ppm) scale. Low-resolution mass spectra were obtained on a Hitachi Perkin-Elmer, model RMU-6D single-focusing instrument, operating at 70 eV. The high resolution mass spectrum was obtained on a Varian MAT 112S spectrometer, equipped with an EI ion source, maintained at 220°, and operated at 70 eV. Elemental analysis was determined on a Perkin-Elmer 240 CHN analyzer, and osmometric determination of molecular weight was performed on a Wescan Vapor Pressure Osmometer, operated at a temperature of 47°.

[6]The plant material was supplied through the auspices of the Developmental Therapeutics Program of the National Cancer Institute by the Economic Botany Laboratory, BARC-East, U.S.D.A., Beltsville, Maryland. An herbarium specimen documenting the collection is deposited in the National Arboretum, Agricultural Research Service, U.S. Department of Agriculture, Washington, D.C.

[7]Generously supplied by Dr. A. Corbella, University of Milan, Italy.

TABLE 1. Comparison of cmr spectra of cinnamodial (**1**) and capsicodendrin (**2**).

Carbon number[a]	Cinnamodial (**1**)	Capsicodendrin (**2**)[b]
11	201.0	203.5
		203.4
12	192.9	
16	170.0	170.0[c]
7	148.5	140.3
		139.0
		135.1
		134.3
8	141.3	128.5
		128.0
		124.9
		124.6
		104.8
		102.3
		100.6
		100.3
		98.6
		98.0
9	77.5	90.6
		90.5
		80.5
		——[d]
6	66.2	67.1
		66.9
		66.4
		66.3
5	45.2[e]	46.5
		46.3
3	44.2[e]	44.8
		44.6
		44.2
10	41.7	41.9
		37.0
4	34.0	33.9
		33.8
13	32.6	32.8
		32.6
1	31.9	32.2
		31.9
17	24.7	24.7
		24.4
14	21.3	21.6
		21.4
2	19.9	20.0
		19.6
15	17.7	18.1
		17.9

[a]Numbering of carbons applies to **1** only.
[b]Complete resolution of **2** into the projected number of carbon atoms was not observed.
[c]Peak intensity indicated four carbon atoms.
[d]Signal obscured by $CDCl_3$ signal.
[e]Assignment may be reversed.

CHARACTERIZATION OF CAPSICODENDRIN (**2**).—Capsicodendrin (**2**, 3.8 g, 0.089%), mp 210–211°, $[\alpha]^{27}D$ −278 (c 0.5, $CHCl_3$), exhibited the following spectral properties, uv λ max (MeOH) 214 nm (log ε 3.88), ir, ν max (KBr) 3500, 2870, 1735, 1725, 1470, 1390, 1368, 1240 and 1020 cm^{-1}; pmr, ($CDCl_3$) δ 1.06 (3H, s), 1.16 (3H, s), 1.43 (3H, s), 2.03 (3H, s, $-OCOCH_3$), 3.96 (1H, br s, exchanged with D_2O, –OH), 5.26 (1H, s), 5.79 (1H, m), 6.48 (1H, m) and 9.84 (1H, d, J=1.5 Hz); cmr, ($CDCl_3$), see table 1; ms, *m/e*, M^- not observed, fragment ions at 279 (42%), 248

(36), 205 (24), 124 (16), 92 (20) and 43 (100). Elemental analysis[8], calculated for $C_{17}H_{24}O_5$ (or multiple thereof) C, 66.20%, H, 7.80; found, C, 66.09, H, 7.84.

ATTEMPTED KETALIZATION OF **2**.—Capsicodendrin (**2**, 200 mg) in 80 ml of dry toluene was treated with 30 mg of *p*-toluene sulfonic acid in 2 ml of ethylene glycol, and maintained at 60° for 12 hr. A single reaction product (mp, 270°, decomp.) was crystallized from methylene chloride and exhibited a chemical shift for a proton at 9.84 ppm in the pmr spectrum.

ATTEMPTED ACETYLATION OF **2**.—Capsicodendrin (**2**, 50 mg) was reacted with acetic anhydride-pyridine (1:1, 2 ml) at 25° for 24 hr. Two products, with R_f values 0.64 and 0.69, were separated by preparative tlc on silica gel[9] in chloroform-methanol (97:3). Both products exhibited a chemical shift in their pmr spectra for a deuterium-exchangeable proton at about 3.90 ppm.

CONVERSION OF **2** TO **1**.—Capsicodendrin (**2**, 10 mg) was treated with 0.5 ml pyridine for 24 hr at ambient temperature. Removal of pyridine under nitrogen, and preparative tlc on silica gel[9] in chloroform-acetone (97:3) of a band with R_f 0.29, afforded a product identical to (mmp, pmr, ms and tlc) cinnamodial (**1**, 6 mg).

CHARACTERIZATION OF CINNAMOSMOLIDE (**3**).—Cinnamosmolide (**3**, 0.14 g, 0.012%), mp, 197–198°, $[\alpha]^{27}D$ −336 (c 0.5, $CHCl_3$), exhibited the following spectral properties, uv, λ max (MeOH) 212 nm (log ε 3.96), ir ν max (KBr) 3410, 1750, 1730, 1467, 1390, 1368, 1230 and 1070 cm^{-1}; pmr, ($CDCl_3$) δ 1.03 (3H, s), 1.13 (3H, s) 1.15 (3H, s), 2.08 (3H, s $-OCOCH_3$), 3.18 (1H, br s, exchanged with D_2O, 9-OH), 4.36 (2H, q, J=9.9 Hz, 11-H_2), 5.78 (1H, t, J=4.1 Hz, 6-H) and 6.72 (1H, d, J=4.1 Hz, 7-H); cmr, ($CDCl_3$), see table 2; ms, *m/e*, M^- 308 (35%), 291 (67), 248 (83), 231 (50), 192 (42), 142 (77), 109 (92), 91 (38) and 43 (100). These physical data are in agreement with those reported for cinnamosmolide (**3**) (2, 3), and the identity was confirmed (mmp, pmr, ms, tlc) by comparison with an authentic sample.[7]

TABLE 2. Cmr spectra of bicyclofarnesane sesquiterpenoids.

Carbon number	Cinnamosmolide (**3**)	Ugandensolide (**5**)	Futronolide (**6**)
1	31.8	33.1	35.0
2	19.6	20.8	22.0
3	44.5	43.1	42.5
4	33.7	35.4[b]	33.7
5	45.0	49.3	47.0
6	75.2	69.8	61.9
7	134.9	73.8	70.3
8	132.2	154.5	160.6
9	76.9	137.9	136.4
10	39.0	36.5[b]	35.8
11	66.5	172.1[c]	172.4
12	169.4[a]	66.1	67.4
13	32.9	33.4	39.2
14	21.4	21.4	29.3
15	18.4	18.4	19.1
16	170.0[a]	170.9[c]	
17	24.3	23.1	

Assignments bearing the same alphabetical superscript are tentative and may be reversed.

CHARACTERIZATION OF 6β-ACETOXYISODRIMENIN (**4**).—6β-Acetoxyisodrimenin (**4**, 0.008 g, 0.0002%), mp, 220–224°, $[\alpha]^{27}D$ −272 (c 0.2, $CHCl_3$), exhibited the following spectral properties, uv, λ max (MeOH) 212 nm (log ε 3.77), ir, ν max (KBr) 1745, 1730, 1470, 1380, 1360 and 1240 cm^{-1}; pmr, ($CDCl_3$) δ 0.93 (3H, s), 0.99 (3H, s), 1.14 (3H, s), 1.36 (1H, d, J=4.3 Hz, 5-H), 2.06 (3H, s, $-OCOCH_3$), 2.33 (1H, d of m, J=5.1 Hz, 1-βH), 5.47 (2H, s, 12-H_2) and 5.75 (1H, m, 6-H); ms, *m/e* M^+ 292 (7%), 232 (47), 217 (27), 109 (50), 95 (30), 69 (63) and 43 (100). Mass measurement: Found, 232.1463, Calcd. for $C_{15}H_{20}O_2$, 232.1480.

CHARACTERIZATION OF UGANDENSOLIDE (**5**).—Ugandensolide (**5**, 0.58 g, 0.014%), mp, 213–216°, $[\alpha]^{27}D$ 28 (c 0.5, $CHCl_3$), exhibited the following spectral properties, uv, λ max (MeOH)

[8]Performed by Micro-Tech Laboratories, Inc., Skokie, IL.

[9]Prepared plates (0.25 mm thick) (E. Merck, Darmstadt, W. Germany) visualized with 70% w/w sulfuric acid.

214 nm (log ϵ 4.11), ir, ν max (KBr) 3450, 1740, 1735, 1385, 1368, 1250, 1140 and 1020 cm^{-1}; pmr, ($CDCl_3$) δ 1.03 (6H, s, 4,4^1-CH_3), 1.47 (3H, s, 10-CH_3), 2.08 (3H, s, -$OCOCH_3$), 2.51 (1H, d of m, J=12 Hz, 1-βH), 3.15 (1H, br s, exchanged with D_2O, 7-OH), 4.21 (1H, br s, 7-H), 4.57 (1H, d, J=17 Hz, 12-H), 4.95 (1H, d, J=17 Hz, 12-H) and 5.35 (1H, m, 6-H); cmr, ($CDCl_3$), see table 2; ms, m/e M^- 308 (22%), 266 (68), 248 (94), 234 (17), 205 (10), 165 (24), 95 (12) and 43 (100). These physical data are in agreement with those reported for ugandensolide (**5**) (4), and the identity was confirmed (mmp, pmr, ms, tlc) by comparison with an authentic sample.[10]

Ugandensolide (**5**, 10 mg) was treated overnight with acetic anhydride-pyridine (1:1, 0.5 ml). Following removal of excess reagents and crystallization from acetone, the acetylation product (**7**, 6 mg), mp, 103–104°, exhibited the following spectral properties, uv, λ max (MeOH) 212 nm (log ϵ 3.9), ir, ν max (KBr) 1770, 1760, 1390, 1370 and 1240 cm^{-1}; pmr ($CDCl_3$) δ 1.04 (6H, s, 4,4^1-CH_3), 1.50 (3H, s, 10-CH_3), 2.07 (3H, s, -$OCOCH_3$), 2.14 (3H, s, -$OCOCH_3$), 2.56 (1H, d of m, J=12 Hz, 1-βH), 4.64 (2H, br s, 12-H_2), 5.14 (1H, m, 7-H) and 5.54 (1H, m, 6-H); ms, m/e M^- 350 (4%), 308 (7), 290 (26), 248 (37), 230 (3), 109 (11) and 55 (100).

CHARACTERIZATION OF FUTRONOLIDE (**6**).—Futronolide (**6**, 0.42 g, 0.001%), mp, 212–214°, $[\alpha]^{27}D$ 119 (c 0.5, $CHCl_3$), exhibited the following spectral properties, uv, (MeOH) λ max 218 nm (log ϵ 4.84), ir, ν max (KBr) 3410, 1735, 1670, 1387, 1368 and 1070 cm^{-1}; pmr, ($CDCl_3$) δ 0.91 (3H, s), 0.95 (3H, s), 1.12 (3H, s), 2.57 (1H, d of m, J=12 Hz, 1-βH), 4.48 (1H, m, 7-H), 4.77 (2H, AB system, 12-H_2); cmr, see table 2; ms, m/e, M^- 250 (95%), 235 (54), 232 (13), 217 (84), 128 (100), 124 (81) and 95 (24). The identity of **6** as futronolide was confirmed by comparison of the ir and pmr data with the spectra of epifutronolide (**8**) and futronolide (**6**), obtained synthetically (5)[11].

Futronolide (**6**, 10 mg) was treated overnight at room temperature with acetic anhydride-pyridine (1:1, 0.5 ml). Following removal of excess reagents and crystallization from methanol, the acetylation product (**9**, 7 mg), mp, 119–121°, exhibited the following spectral properties, uv, (MeOH) λ max 216 nm (log ϵ 4.2), ir, ν max (KBr) 1760, 1740, 1390, 1368 and 1240 cm^{-1}; pmr, ($CDCl_3$) δ 0.92 (6H, br, s), 1.13 (3H, s), 2.09 (3H, s, -$OCOCH_3$), 2.60 (1H, d of m, J=12 Hz, 1-βH), 4.63 (2H, s, 12-H_2) and 5.47 (1H, m, 7-H); ms, m/e, M^- 292 (93%), 232 (100), 217 (65), 119 (50) and 116 (39).

BIOLOGICAL ACTIVITY OF THE ISOLATES.—Cinnamodial (**1**, NSC-277293) and capsicodendrin (**2**, NSC-277291) showed ED_{50}'s of 2.2 and 2.9 μg/ml, respectively, in the P-388 test system *in vitro*. Cinnamosmolide (**3**, NSC-277292) exhibited an ED_{50} of 1.2 μg/ml in the 9KB5 cell culture system. None of the isodrimenin derivatives (**4–6**) demonstrated cytotoxic activity in either the 9KB or P388 *in vitro* assays. All isolates (**1–6**) were devoid of *in vivo* activity in the P-388 lymphocytic leukemia test system.

DISCUSSION

Although no phytochemical or pharmacological studies on plants in the genus *Capsicodendron* have appeared in the literature, bicyclofarnesane (2–4, 6–9) and eremophilane type (10) sesquiterpenes have been isolated from other genera in the Canellaceae. Among the known compounds (**1**, **3**, **5**, **6**) identified in this study, only futronolide (**6**) has not previously been found in this family.

Capsicodendrin (**2**), the major sesquiterpene constituent of *C. dinisii* stem bark obtained in this study, was found to be a molecule of considerable complexity. While differing substantially from cinnamodial (**1**) in melting point and specific rotation, the uv, ir and ms data of the two compounds were very similar and demonstrated the presence of hydroxy, aldehyde and acetate groups. In addition, the signals assigned to *gem*-dimethyl (ir, 1390, 1368 cm^{-1}; pmr, 1.06, 1.16 ppm), angular methyl (pmr, 1.43 ppm) and olefinic functionalities (pmr 6.48 ppm) indicated that **2** was a drimane derivative (2, 3). Since the resonance at 9.84 ppm in the pmr spectrum of **2** became a singlet from a doublet on the addition of D_2O, the aldehyde group was shown to be attached to carbon bearing a hydroxy group (2–4).

Efforts were made to prepare derivatives of capsiodendrin (**2**) that would further clarify the nature of the functional groups present in the molecule. The

[10]Generously supplied by Prof. C. J. W. Brooks, University of Glasgow, Scotland.
[11]Kindly provided by Dr. T. Kato, Tohuku University, Sendai, Japan.

persistence of a deuterium oxide-exchangeable proton, absorbing at about 3.90 ppm in the pmr spectra of two products obtained on attempted acetylation of **2**, indicated that the hydroxy group was tertiary. Likewise, pmr experiments on the reaction product of an attempted ketalization of **2** showed the presence of a saturated aldehyde group, leading to the conclusion that, unlike cinnamodial (**1**), no adjacent aldehyde groups were present in **2**. The close relationship of **2** with **1** was established by the inherent instability of capsicodendrin (**2**) in pyridine, resulting in the generation of cinnamodial (**1**) as the sole sesquiterpene product.

The proton-noise decoupled cmr spectrum of capsicodendrin (**2**) indicated the presence of at least 44 carbon atoms in the molecule. Eight olefinic and four acetate carbonyl resonances were in evidence, as well as six resonances assignable to carbons attached to two oxygen atoms each, and eight carbons attached to one oxygen atom. Of significance was the absence of any resonance attributable to an unsaturated aldehyde, analogous to that appearing at 192.9 ppm in cinnamodial (**1**). Accordingly, cmr confirmed the previous observation of the lack of an $\alpha\beta$-unsaturated aldehyde group in **2**, although two signals (203.5 and 203.4 ppm) at approximately equivalent chemical shifts to the C–11 aldehyde group in cinnamodial (**1**), were observed in the cmr spectrum of capsicodendrin (**2**) (11).

Experiments have not yet led to a definitive molecular weight for capsicodendrin (**2**), although a molecular weight of over 1200 seems likely, as determined by osmometry.[12] It should be pointed out that the similarity of capsicodendrin (**2**) with cinnamodial (**1**) was further established by elemental analysis of **2**, since the same molecular formula for both compounds is evident.

Therefore, it may be tentatively suggested that capsicodendrin (**2**) is a tetrameric conjugate of cinnamodial (**1**), apparently free of bound water. The linkage of the four constituent monomers of **2** appears to be between the four $\alpha\beta$-unsaturated aldehyde groups and only two of the saturated aldehyde functionalities. Field-desorption mass spectrometry has indicated that capsicodendrin (**2**) is free of dimeric and trimeric forms of cinnamodial (**1**).[13] Since there are over 80 structural possibilities for capsicodendrin (**2**) that satisfy the criteria discussed thus far, attempts are currently being made to produce crystals of the compound suitable for X-ray crystallography.

Capsicodendrin (**2**) is apparently the first sesquiterpene tetramer to be found in nature, although a drimenoid trimer from *Drimys winteri* Forst. was recently described (11). In an attempt to satisfy the question of whether capsicodendrin (**2**) or cinnamodial (**1**) were artifacts, both isolates were resubjected to the extraction and chromatographic procedures used in their work-up. Since no breakdown of either compound and no interconversions were apparent, both **1** and **2** appear to be naturally occurring compounds.

6β-Acetoxyisodrimenin (**4**), a trace constituent of *C. dinisii* root bark, was assigned an isodrimenin, rather than a drimane, skeleton from the absence of an olefinic proton in the pmr spectrum and the appearance of a doublet of multiplets at 2.33 ppm. The latter signal is due to the deshielding of the C-1β-equatorial proton by the lactone carbonyl group, which is located in the same plane (4).

One functional group, an acetate, was evident from characteristic signals in the ir, pmr and mass spectra of **4**. The observation of typical methyl signals in the pmr spectrum of **4** for an isodrimenin compound with no ring A substitution,

[12]Performed by Galbraith Laboratories, Inc., Knoxville, TN.

[13]We are grateful to Dr. B. W. Wilson, Mass Spectrometry Facility, Massachusetts Institute of Technology, Cambridge, Mass. for these data.

limits the possibilities for the placement of the acetate group to either C–6 or C–7. Since the chemical shift of the methine proton (5.75 ppm) was closely comparable to that of cinnamosmolide (3), but further downfield than the C–7 acetylated compounds **7** and **9**, the acetate in **4** was placed at C–6, by analogy.

In spite of the fact that the C–6 proton in **4** occurred as a complex multiplet, the small coupling constant (4.3 Hz) of the C–5 proton at 1.36 ppm, indicated the C–6 methine proton to be α- and equatorial. Hence the structure of **4** is tentatively assigned as 6β-acetoxyisodrimenin. The fact that all naturally occurring 6-acetylated bicyclofarnesane sesquiterpenoids isolated to date also possess this same stereochemistry supports this proposal on biogenetic grounds.

This study is the first to demonstrate the cytotoxic activity of bicyclofarnesane sesquiterpenes, although compounds of this class have been found with pungency (12–15), insect antifeedant (8, 9, 16) and antibiotic activities (16). Since only the drimane compounds **1–3** were cytotoxic, activity may be attributed to the presence of a double bond allylic to either a lactone carbonyl function or an aldehyde group. Although no $\alpha\beta$-unsaturated aldehyde was thought to be evident in **2**, the activity of this compound may be due to decomposition to **1** in the biological test diluent. Compounds **4–6** were not cytotoxic, possibly because, in the isodrimenin skeleton, the C–8, C–9 double bond is endocyclic to the lactone ring.

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