Structure–Activity Relationships of Phytotoxic Sesquiterpenoids from *Canella winterana*

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The structure–activity relationships of 14 drimane sesquiterpenoids isolated from *Canella winterana* plus 5 derivatives were examined in a plant growth inhibitory bioassay. It was found that the 11,12-dialdehyde was the essential moiety and the 9-hydroxy group was not important for activity. The compound with β-configuration of the 11-aldehyde or 3-acetoxy group showed greater activity than its α-isomer.

Keywords: *Structure–activity relationship; drimane sesquiterpenoid; Canella winterana; plant growth inhibition*

INTRODUCTION

Drimane sesquiterpenoids containing an unsaturated dialdehyde functionality have been isolated from various natural resources, such as higher plants (Barnes and Loder, 1962; El-Feraly et al., 1978; Kubo et al., 1976), liverworts (Asakawa et al., 1976), and marine organisms (Okuda and Scheuer, 1983; Butler and Capon, 1993). Most of the unsaturated dialdehydes are very hot tasting (Kubo and Ganjian, 1981), and some have antifeedant activity (Kubo et al., 1977), molluscicidal activity (Nakanishi and Kubo, 1977), and antimicrobial activity (Taniguchi et al., 1984). Polygodial and polygonal were found to completely inhibit the germination of rice at ca. 100 and 500 ppm, respectively (Asakawa and Takemoto, 1979). No other plant growth regulatory activity of drimane-type sesquiterpenoids has been reported.

Canella winterana (L.) Gaertn., a small tree, is a rich source of drimane-type dialdehydes. Eight drimane sesquiterpenes, muzigadial (1) (El-Feraly, 1978), warburganal, mukaadial, 9α-hydroxycinnamolide (Kioy et al., 1989), 3β,9α-dihydroxycinnamolide (Kioy et al., 1990), 9-deoxymuzigadial, 9-deoxyisomuzigadial, and 3β-acetoxypolygodial (Al-Said et al., 1990), have been isolated from the bark of this plant. 4,13α-Epoxymuzigadial was isolated from its leaves (Al-Said et al., 1989).

The crude extract of the leaves of *C. winterana* exhibited phytotoxic activity in a *Lemna minor* bioassay. Bioassay-guided fractionation led us to the isolation of nine new drimane sesquiterpenoids, 3α-acetoxypolygodial (**2**), 3α-acetoxypolygodial 12-dimethyl acetal (**3**), 9-deoxymuzigadial 12α-acetal (**4**), 9-deoxymuzigadial 12β-acetal (**5**), 3β-acetoxypolygodial 12α-acetal (**6**), 3β-acetoxypolygodial 12β-acetal (**7**), 9-epideoxymuzigadial (**8**), 3β-acetoxypolygonal (**9**), and muzigaal (**10**) (Figure 1), together with five other known compounds (**1**, **11**–**14**) (Ying et al., 1995). The plant growth inhibitory activity data of these 14 compounds revealed their structure–activity relationship (Table 3). To further study this relationship, five acetal derivatives (**15**–**19**) of muzigadial were synthesized.

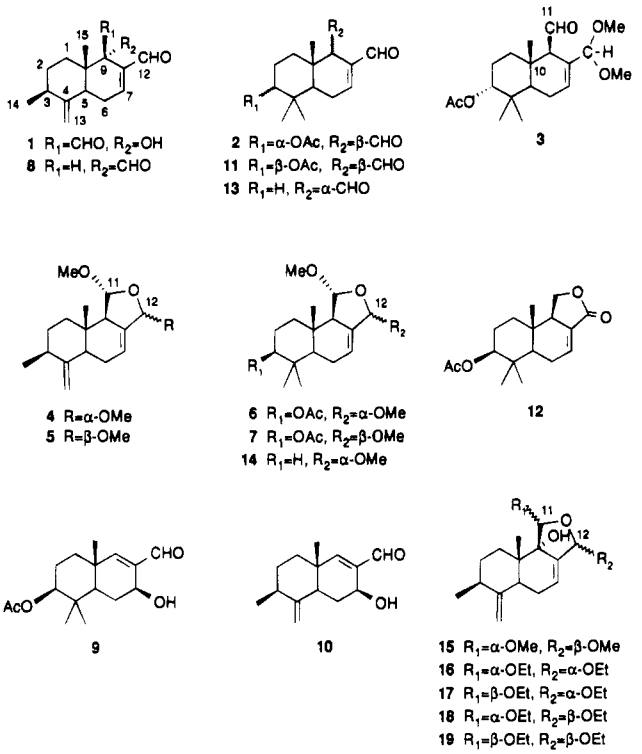

Figure 1. Chemical structures of natural sesquiterpenoids (**1**–**14**) and derivatives (**15**–**19**).

MATERIALS AND METHODS

Plant Material. The leaves of *C. winterana* were collected and identified in Puerto Rico by J. A. Cedeño and D. A. Kolterman. A voucher specimen was deposited in the Herbarium, University of Puerto Rico, Mayagüez.

Extraction and Purification of Muzigadial (1). The dried leaves (529 g) of *C. winterana* were extracted with methanol at ambient temperature. The methanol extract was concentrated under reduced pressure and partitioned with pentane and methylene chloride sequentially. The pentane phase was evaporated to yield 50.26 g of oil which showed growth inhibitory activity in a *L. minor* bioassay at 20 ppm. The pentane fraction was dissolved in methylene chloride and separated by a Sephadex LH-20 column to provide five fractions. The active fraction (no. 2) was further fractionated by centrifugal partition chromatography (Sanki NMF instrument, hexane–ethyl acetate–methanol–water 8:2:8:2, ascending mode) to give 11 fractions. The second fraction was

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Table 1. ^1H and ^{13}C NMR Spectral Data of Compounds 15–19, 4, and 5

	15		16		17		18		19		4		5	
	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
1	1.20	32.52	1.24	32.70	1.22	32.59	1.20	32.56	1.25	32.55	1.53	40.0	1.49	40.0
	1.68		1.70		1.67		1.69		1.68		1.74		1.82	
2	1.30	31.74	1.24	31.48	1.44	31.37	1.25	31.74	1.44	31.67	1.23	32.5	1.23	32.5
	2.02		2.18		2.29		2.02		2.24		1.65		1.66	
3	2.02	38.48	2.04	38.42	2.05	38.42	2.04	38.49	2.05	38.52	2.02	38.7	2.02	38.8
4		153.28		153.89		153.77		153.38		153.34		152.9		152.8
5	2.60	40.24	2.79	40.30	2.71	41.79	2.60	40.38	2.58	41.58	2.11	46.3	2.07	46.1
6	2.16	26.28	2.17	26.07	2.19	26.68	2.15	26.21	2.1–2.3	26.71	2.11	25.5	2.11	25.9
7	6.01	126.18	5.93	124.29	6.05	126.18	6.00	125.63	6.04	126.43	5.93	120.7	5.84	121.4
8		137.58		138.37		139.02		137.79		139.61		136.9		136.4
9		78.24		76.96		79.34		78.13		81.14	2.64	55.5	2.40	56.9
10		41.51		40.23		40.82		40.26		41.13		35.7		36.0
11	5.08	104.07	5.03	103.09	5.19	110.66	5.19	102.52	5.01	109.13	4.94	107.2	4.92	105.7
12	5.61	102.86	5.25	102.92	5.50	102.63	5.71	101.87	5.64	102.67	5.13	104.2	5.44	102.4
13	α4.85	105.07	4.84	104.71	4.85	104.94	4.84	104.98	4.86	105.20	4.83	104.8	4.83	104.8
	β4.71		4.70		4.68		4.71		4.70		4.68		4.68	
14	1.07	18.71	1.07	18.74	1.07	18.75	1.07	18.71	1.08	18.74	1.08	18.6	1.08	18.7
15	0.73	15.25	0.67	14.95	0.83	15.54	0.73	15.30	0.88	15.95	0.62	12.9	0.67	13.2
OMe-11	3.49	55.86									3.49	56.0	3.47	55.5
OMe-12	3.62	57.24									3.42	54.3	3.52	56.7
OCH_2-11			3.70	65.01	3.46	64.02	3.72	65.61	3.65	63.54				
OCH_2-11			3.96		3.78		3.98		3.82					
CH_2Me-11			1.29	15.32	1.18	15.39	1.28	15.40	1.26	15.44				
OCH_2-12			3.54	63.05	3.60	64.02	3.63	64.39	3.44	63.15				
OCH_2-12			3.82		3.87		3.85		3.78					
CH_2Me-12			1.24	15.32	1.26	15.13	1.26	15.40	1.18	14.98				
OH	3.19						3.27							

crystallized from hexane–methylene chloride to give crude muzigadial, which was recrystallized from the same solvent to give 947 mg of pure compound (colorless needles, mp 128–129 °C). From this fraction and other fractions, 13 other sesquiterpenoids were isolated by low-pressure silica gel column chromatography and recycling preparative HPLC (JAI LC-09, Asahipak GS310P/MeOH, Chemcosorb 5-ODS-H/75% MeOH, or Nucleosil/hexane–ethyl acetate) (Ying et al., 1995).

Nuclear Magnetic Resonance Spectroscopy. All spectra were recorded on a Varian Gemini 300 MHz spectrometer. The NMR spectra were measured as solutions in chloroform-*d* in 5 mm o.d. tubes for ^1H and ^{13}C. Tetramethylsilane was used as internal standard in both measurements. Standard Varian Gemini pulse sequences were used for homonuclear and heteronuclear correlation experiments.

Mass Spectroscopy. EI-MS and positive CI-MS spectra were recorded on a Finnigan MAT SSQ 710 quadrupole spectrometer.

Preparation of Cyclic Dimethyl Acetal (15) of Muzigadial. *p*-TsOH (1.3 mg) was added to a methanol solution (10 mL) of muzigadial (21.3 mg) and stirred at room temperature for 24 h. The reaction product was purified on recycling HPLC (JAI LC-09, column, Asahipak GS310P, 20 × 500 mm; solvent, methanol; flow rate, 4 mL/min; detectors, UV at 215 nm and RI) to yield a pure acetal **15**, mp 79–80.5 °C.

Preparation of Cyclic Diethyl Acetals (16–19) of Muzigadial. *p*-TsOH (1.0 mg) was added to the anhydrous ethanol solution (10 mL) of muzigadial (129 mg) and stirred at room temperature for 24 h. The reaction product was purified on a silica gel column [J. T. Baker silica gel 40 μm, 20 × 330 mm, eluted with hexane–ethyl acetate (9:1)] to give three products: **A** (24 mg, $R_f = 0.46$), **B** (**18**, 81 mg, $R_f = 0.41$), and **C** (**19**, 35 mg, $R_f = 0.27$). NMR analysis showed that product **A** was a mixture. Further purification was achieved on a recycling HPLC (JAI LC-09, column, Chemcosorb 5-ODS-H, 20 × 250 mm; solvent, methanol–water 4:1; flow rate, 4 mL/min; detectors, UV at 215 nm and RI) to yield pure acetals **16** (13.7 mg) and **17** (9.6 mg).

***L. minor* Bioassay.** The *L. minor* bioassay was conducted as described previously (Einhellig et al., 1985). In brief the assay was conducted aseptically in 24-well tissue culture plates. Test compounds were dissolved in DMSO and added to the wells, and their effect upon the growth of *L. minor* under continuous fluorescent light (90 μEinstein·m^{-2}·s^{-1}) at 29 °C was determined after 7 days.

Stability of 9-Deoxymuzigadial 12α-Acetal (4) in the Growth Medium of *L. minor*. The stability of 9-deoxymuzigadial 12α-acetal (**4**) in the *L. minor* growth medium was determined by measuring its UV absorption spectrum at various times for approximately 3 days. The growth medium, pH 4.6–4.8, was prepared according to the method of Einhellig et al. (1985).

RESULTS AND DISCUSSION

Cyclic Dimethyl Acetal (15) of Muzigadial. The ^1H and ^{13}C NMR spectra of **15** were very similar to that of **4** and **5** (Table 1). Their assignments were confirmed by ^1H–^1H COSY and ^{13}C–^1H COSY experiments. In the NOESY spectrum of **15**, there was a cross peak between H-11 (δ 5.08) and CH_3-15 (δ 0.73), indicating the β-configuration of H-11. The chemical shift of H-12 (δ 5.61) in **15** was close to that in **5** (δ 5.44), but not to that in **4** (δ 5.13), suggesting that the H-12 had an α-configuration. The same was true for the signals of C-11, C-12, and two methoxy groups (both ^1H and ^{13}C). Therefore, **15** was determined to be the cyclic 11α,12β-dimethyl acetal of muzigadial: IR: ν_{max}(film) 3475 (OH), 2954, 2910, 2850, 1639 (C=C), 1457, 1378, 1289, 1200, 1149, 1094, 1052, 993, 936, 886, 862, 848 cm^{-1}; EI-MS: *m*/*z* (rel intensity) 263 (M^+ − 31, 1%), 234 (M − 60, 62), 220 (16), 219 (100), 201 (16), 187 (14), 177 (12), 159 (26), 135 (36), 91 (32); positive CI-MS *m*/*z* (rel intensity) 293 (M^+ − 1, 0.5%), 276 (M − 18, 2), 263 (8), 235 (14), 234 (M − 60, 100), 159 (17), 135 (15), 107 (10), 91 (11).

Cyclic Diethyl Acetals 16–19. There are four possible isomers (11α,12α; 11α,12β; 11β,12α; and 11β,12β) of the cyclic diethyl acetal of muzigadial. The ^1H and ^{13}C signals at positions 11, 12, and 13 of **18** were very similar to those of **15**, suggesting that **18** had the same stereochemistry (11α,12β-diethoxy) as that of **15**. This conclusion was supported by the fact that the H-11 had an NOE on the H-1 in the NOESY spectrum.

Compound **16** had very similar ^1H and ^{13}C NMR spectra to that of **18**, except for H-12. The signal of H-12 appeared at a higher field (δ 5.25) than that in **18** (δ

Table 2. Chemical Shifts of C-9

compd		chemical shift
4	12α-methoxy	55.48
5	12β-methoxy	56.94
6	12α-methoxy	57.64
7	12β-methoxy	58.78
16	12α-ethoxy	76.96
18	12β-ethoxy	78.13
17	12α-ethoxy	79.34
19	12β-ethoxy	81.14

5.71), suggesting **16** was the 11α,12α-diethyl acetal of muzigadial. The same relationship was observed among **4** and **5**, and **6** and **7** (Ying et al., 1995).

The other two compounds (**17** and **19**) should have 11β-ethoxy configuration. The ^1H and ^{13}C NMR spectral data of **17** and **19** were very similar. The only significant difference was the chemical shifts of the C-9 signals. Careful comparison of the chemical shifts of C-9 in three pairs of isomers (**4** and **5**, **6** and **7**, **17** and **19**) revealed that the C-9 signals in the 12β-isomers always appeared at 1.1−1.8 ppm lower field (Table 2). Therefore, the ethoxy group in **17** had 12α-configuration, and one in **19** had 12β-configuration. The stereochemistry of these four ethyl acetals matches their TLC behaviors. Compound **16** had two α-ethoxy groups which covered the 9α-hydroxy group; therefore, it had the highest R_f value. On the other hand, **19** had two β-ethoxy groups, and its 9α-hydroxy group was exposed most. Therefore, **19** moved most slowly on TLC.

16: IR ν_{max}(film) 3538 (OH), 2947, 2923, 2862, 1637 (C=C), 1457, 1300, 1143, 1126, 1101, 1056, 1010, 946, 889 cm^{-1}; EI-MS *m/z* (rel intensity) 277 (4%, M^+ − OEt), 248 (20, M − 74), 220 (16), 219 (100), 177 (11), 160 (10), 135 (31), 91 (18); positive CI-MS *m/z* (rel intensity) 321 (3%, M^+ − 1), 305 (12, M − OH), 277 (100, M − OEt), 273 (61), 247 (25), 203 (59), 185 (16). **17:** IR ν_{max}(film) 3470 (OH), 2964, 2916, 2862, 1637 (C=C), 1452, 1407, 1372, 1325, 1278, 1165, 1136, 1118, 1096, 1023, 940, 891, 811, 794 cm^{-1}; EI-MS *m/z* (rel intensity) 277 (7%, M^+ − OEt), 248 (18, M − 74), 219 (100), 177 (12), 159 (13), 135 (34), 97 (35), 71 (36); positive CI-MS *m/z* (rel intensity) 321 (2.5%, M^+ − 1), 305 (17, M − OH), 277 (100, M − OEt), 263 (16), 247 (31), 231 (21), 220 (14), 219 (73), 213 (20), 203 (16), 187 (19), 185 (59), 159 (37), 135 (19), 109 (12), 107 (12), 91 (11). **18:** IR ν_{max}(film) 3500 (OH), 2963, 2909, 2872, 1637 (C=C), 1457, 1377, 1279, 1144, 1100, 1057, 1008, 974, 945, 936, 889, 874, 862, 848 cm^{-1}; EI-MS *m/z* (rel intensity) 277 (4%, M^+ − OEt), 248 (18, M − 74), 220 (16), 219 (100), 177 (10), 159 (9), 135 (30), 119 (9), 109 (14), 107 (15), 105 (15), 91 (17); positive CI-MS *m/z* (rel intensity) 321 (4%, M^+ − 1), 305 (8, M − OH), 278 (19), 277 (100, M − OEt), 248 (31), 231 (3), 220 (15), 219 (96), 173 (12), 135 (16). **19:** IR ν_{max}(film) 3460 (OH), 2974, 2916, 2861, 1637 (C=C), 1457, 1373, 1331, 1301, 1168, 1111, 1097, 1013, 935, 888 cm^{-1}; EI-MS *m/z* (rel intensity) 305 (1%), 277 (7%, M^+ − OEt), 248 (20, M − 74), 220 (21), 219 (100), 177 (15), 173 (11), 159 (13), 135 (43), 119 (11), 109 (17), 107 (26), 105 (22), 91 (30); positive CI-MS *m/z* (rel intensity) 321 (1%, M^+ − 1), 305 (16, M − OH), 277 (53), 248 (56), 219 (100), 177 (29), 173 (23), 135 (78), 107 (56), 91 (61).

The phytotoxic activities of **1**−**19** in the *L. minor* bioassay are summarized in Table 3.

From the chemical and biological data, the following structure−activity relationship can be concluded.

1. An 11,12-dialdehyde is an essential moiety. The compounds with only one aldehyde group showed no phytotoxic activity; e.g., **3** has only the 11-aldehyde group, and its 12-aldehyde is protected as dimethyl acetal. Compounds **9** and **10** that have a 12-unsaturated aldehyde group but no 11-CHO group have very weak phytotoxic activity. When the 11,12-dialdehyde group of 3β-acetoxypolygodial (**11**) was cyclized to form a lactone ring (to become 3β-acetoxycinnamolide, **12**), the activity disappeared.

Table 3. Phytotoxic Activities of 1−19

compd	IG_{50} (μM)
muzigadial (**1**)	8−16
3α-acetoxypolygodial (**2**)	340
3α-acetoxypolygodial 12-dimethyl acetal (**3**)	>150
9-deoxymuzigadial 12α-acetal (**4**)	18
9-deoxymuzigadial 12β-acetal (**5**)	8
3β-acetoxypolygodial 12α-acetal (**6**)	60
3β-acetoxypolygodial 12β-acetal (**7**)	30
9-epideoxymuzigadial (**8**)	100
3β-acetoxypolygonal (**9**)	250
muzigaal (**10**)	350
3β-acetoxypolygodial (**11**)	50
3β-acetoxycinnamolide (**12**)	>700
isopolygodial (**13**)	45
polygodial 12α-acetal (**14**)	18
11α,12β-dimethyl acetal of muzigadial (**15**)	40
11α,12α-diethyl acetal of muzigadial (**16**)	40
11β,12α-diethyl acetal of muzigadial (**17**)	17
11α,12β-diethyl acetal of muzigadial (**18**)	60
11β,12β-diethyl acetal of muzigadial (**19**)	40

2. The compounds that have a cyclic acetal structure (**4**−**7** and **14**−**19**) are as active as those with an 11,12-dialdehyde moiety. Therefore, the acetal moiety can be considered as a masked form of dialdehyde. (See Stability of Acetals in *L. minor* Bioassay.)

3. The β-configuration of 11-CHO is important for the activity. Comparison of the activity of **8** and **13** with that of muzigadial (**1**) indicated that the activity of the α-isomer was 5−10 times less than that of its β-isomer. This is similar to the activity relationship for human taste of those compounds. Polygodial, the β-isomer, is very hot to human taste, while isopolygodial (**13**) is tasteless (Kubo and Ganjian, 1981).

4. The phytotoxic activities of **8** and **13** are at the same level, as are those of **4** and **14**, suggesting that the double bond at C_4−C_{13} and a methyl group at C-3 in muzigadial are not essential for the activity.

5. Introduction of a 3β-acetoxy group can decrease the activity. For example, the growth inhibitory activity IG_{50} of **6** was approximately 3 times less than that of **14** (60 vs 18 μM). However, among compounds containing the 3-acetoxy group, the β-isomer (**11**) was more active than the α-isomer (**2**) (35−70 vs 340 μM). It indicates that other parts of the molecule are important, besides the dialdehyde moiety.

6. The cyclic acetals with the 12β-methoxy group showed stronger activity than the acetals with the 12α-methoxy group (compare the activities of **5** vs **4** and **7** vs **6**). Similarly, the acetals with the 11β-ethoxy group had greater activity than those with the 11α-ethoxy group (compare the activities of **17** vs **16** and **19** vs **18**). Interestingly, however, this relationship was not true for the configuration of the 12-ethoxy group. With these acetals, the compounds with the 12α-ethoxy group had somewhat greater activity than those with the 12β-ethoxy group (compare the activities of **16** vs **18** and **17** vs **19**). Further experiments would be necessary to better understand these results. There are several factors that determine the overall activity. In addition to activity at the active site(s), uptake, translocation,

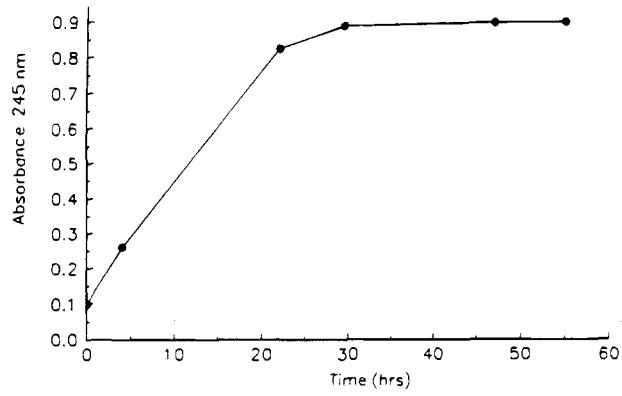

Figure 2. Change in absorbance at 245 nm for 9-deoxymuzigadial 12α-acetal (**4**) held in *L. minor* growth medium (pH 4.6–4.8) over 56 h.

and metabolism of the compound can also influence the measured activity.

7. The 9-hydroxy group does not appear to be essential for activity. In the one example where a direct comparison can be made, 9-deoxymuzigadial 12β-acetal (**5**) actually had greater activity than the 11α,12β-dimethyl acetal of muzigadial (**15**).

Stability of Acetals in *L. minor* Bioassay. Since the activity of some of the acetal compounds, i.e., **4** and **5**, was very similar to that of muzigadial, we suspected that the acetal may break down in the *L. minor* growth medium to give the dialdehyde. Since the growth medium was at pH 4.6–4.8, the acetals would not be expected to be stable in acidic conditions. To examine this possibility, we followed the UV absorption spectrum of **5** (9-deoxymuzigadial 12β-acetal) in *L. minor* growth medium over 56 h. We did observe a large increase in the absorption spectrum with a peak maximum at 245 nm (Figure 2). This information supports the view that the acetal compounds were unstable in the *L. minor* growth medium and the activity we measured was probably due to the dialdehyde rather than the acetal itself. Since the acetal broke down in the bioassay growth medium, this raises the question whether this would occur if the acetal was applied directly to the tissue. Therefore, it is uncertain if the acetal per se was active or if only the dialdehyde was active. Further experiments are necessary to clarify this question.

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