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PHYTOTOXIC SESQUITERPENOIDS FROM *CANELLA WINTERANA*

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Key Word Index—*Canella winterana*; Canellaceae; drimane sesquiterpenoid; muzigadial; 3α-acetoxypolygodial; 3α-acetoxypolygodial 12-dimethyl acetal; 9-deoxymuzigadial 12α-acetal; 9-deoxymuzigadial 12β-acetal; 3β-acetoxypolygodial 12α-acetal; 3β-acetoxypolygodial 12β-acetal; 9-epideoxymuzigadial; 3β-acetoxypolygonal; muzigaal; 3β-acetoxypolygodial; 3β-acetoxycinnamolide; isopolygodial; polygodial 12α-acetal; drimenol; phytotoxicity.

Abstract—Nine new drimane-type sesquiterpenoids: 3α-acetoxypolygodial, 3α-acetoxypolygodial 12-dimethyl acetal, 9-deoxymuzigadial 12α-acetal, 9-deoxymuzigadial 12β-acetal, 3β-acetoxypolygodial 12α-acetal, 3β-acetoxypolygodial 12β-acetal, 9-epideoxymuzigadial, 3β-acetoxypolygonal and muzigaal, were isolated from the leaves of *Canella winterana*, together with six previously known sesquiterpenoids: muzigadial, 3β-acetoxypolygodial, 3β-acetoxycinnamolide, isopolygodial, polygodial 12α-acetal and drimenol. Unambiguous assignments of all ^1H and ^{13}C signals of 15 sesquiterpenoids were established by 2D NMR experiments.

INTRODUCTION

Canella winterana (L.) Gaertn. is a tree which grows in the Caribbean and subtropical area of Florida. Eight drimane sesquiterpenes, muzigadial (**1**) [1], warburganal, mukaadial, 9α-hydroxycinnamolide [2], 3β,9α-dihydroxycinnamolide [3], 9-deoxymuzigadial, 9-deoxyisomuzigadial and 3β-acetoxypolygodial [4], have been found from the bark of this plant. 4,13α-Epoxymuzigadial was isolated from its leaves [5]. Muzigadial and warburganal showed potent insect antifeedant [6], antifungal [7] and molluscicidal [8] activities.

In our search for bioactive compounds we found that the crude extract of the leaves of *C. winterana* exhibited phytotoxic activity. Bioassay-guided fractionation using the *Lemna minor* bioassay led to the isolation of nine new drimane sesquiterpenoids. In this paper, we report their isolation and structure determination.

RESULTS AND DISCUSSION

A combination of column chromatography on Sephadex LH-20, centrifugal partition chromatography (CPC) and recycling preparative HPLC of the pentane fraction of *C. winterana* resulted in the isolation of a major active compound, muzigadial (**1**) and 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**), along with known 3β-acetoxypolygodial (**11**) [4], 3β-acetoxycinnamolide (**12**) [9], isopolygodial (**13**) [10–12], polygodial 12α-acetal (**14**) [13] and drimenol (**15**) [11, 14, 15]. This is the first report of the isolation of **12**–**15** from this plant.

The ^1H and ^{13}C NMR (Table 1) spectra of **2** indicated the presence of two aldehyde groups (δ_H 9.43, 9.85, δ_C 192.5, 201.4), one methine group (δ_H 4.45, δ_C 79.8) bearing one acetoxy group (δ_H 2.06, δ_C 21.2, 170.6), three tertiary methyl groups (δ_H 0.92, 0.98, 0.98, δ_C 16.4, 21.6, 27.6), a trisubstituted conjugated olefinic bond (δ_H 7.10, δ_C 137.3, 152.5), three methylenes, one methine and two quaternary carbons. All these spectral features were very similar to those of **11**. The signals of C-1 and C-5 in **2** were significantly shifted upfield 3 ~ 5 ppm due to γ-interaction with the 3α-acetoxy group, suggesting that **2** was 3α-acetoxypolygodial. The complete assignment of ^1H and ^{13}C signals was achieved by ^1H–^1H COSY, ^{13}C–^1H COSY, long-range ^1H–^1H COSY and long-range ^{13}C–^1H COSY experiments.

There were 19 signals in the ^{13}C NMR spectrum (Table 1) of **3**: one saturated aldehyde group (δ_C 202.5), one acetoxy group (δ_C 21.2, 170.7), two methoxy groups (δ_C 53.5, 54.3), three tertiary methyl groups (δ_C 16.4, 21.5, 27.6), three methylenes, three methines, and two olefinic and three quaternary carbons. The chemical shifts of the AB ring carbons were similar to those of **2**, indicating that **3** was a derivative of **2**. The presence of two methoxy groups and an acetal carbon (δ_H 4.40, δ_C 105.5) suggested

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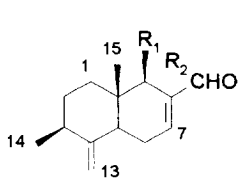

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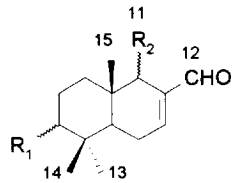
8 R_1=H, R_2=CHO
16 R_1=CHO, R_2=H



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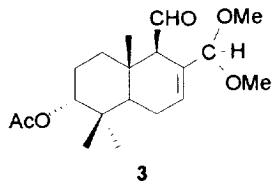

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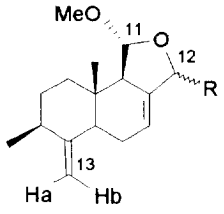

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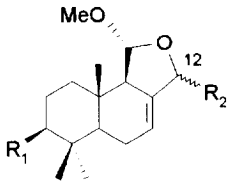
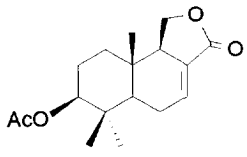
5 R=β-OMe



6 R_1=OAc, R_2=α-OMe
7 R_1=OAc, R_2=β-OMe
14 R_1=H, R_2=α-OMe



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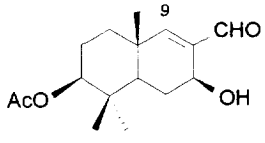

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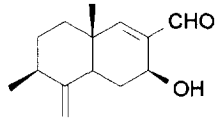

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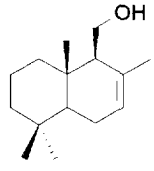

15

that **3** had an acetal structure at C-12 instead of an aldehyde as in **2**. Therefore, **3** was 3α-acetoxypolygodial 12-dimethyl acetal. The assignment of all NMR signals was confirmed by ^{13}C–^{1}H COSY spectrum.

The ^{1}H and ^{13}C NMR spectra (Table 1) of **4** and **5** were almost identical. There was one tertiary methyl, one secondary methyl and one exomethylene group in both **4** and **5**, indicating that they had similar structures to that of muzigadial. The lack of a carbon signal around δ77 and the presence of a tertiary carbon (δ_C55.5 and δ_H2.64 in **4**; δ_C56.9 and δ_H2.40 in **5**) indicated that there was no hydroxyl group at the 9 position. Both compounds had two methoxy groups (δ_C54.3, 56.0, δ_H3.49 and 3.42 in **4**; δ_C55.5, 56.7, δ_H3.47 and 3.52 in **5**), and two methine carbons bearing two oxygens [δ_C107.2 (C-11), 104.2 (C-12) and δ_H5.13 (H-12) in **4**; δ_C105.7 (C-11), 102.4 (C-12) and δ_H5.44 (H-12) in **5**] which were very similar to those of **14**. Therefore, **4** and **5** were acetals of 9-deoxymuzigadial. The assignment of all ^{1}H and ^{13}C signals was supported by the ^{13}C–^{1}H COSY spectrum and confirmed by the long-range ^{13}C–^{1}H COSY spectrum. For example, in the long-range ^{13}H–^{1}H COSY spectrum of **4**, the cross-peaks between C-15 and H-9, C-9 and H-15, and C-9 and H-7 confirmed the structure around C-9. The correlation between MeO-12 and H-12, C-12 and MeO-12, MeO-11 and H-11, and C-11 and MeO-11 confirmed the assignment of those signals. The stereochemistry of C-11 and C-12 was determined by an NOESY experiment. In the NOESY spectrum of **4**, the cross-peaks between H-11 and Me-15, and MeO-11 and H-5 indicated the α-configuration of the methoxy group at the 11-position. On the other hand, the correlation between MeO-12 and H-9, and MeO-12 and H-5 revealed the α-configuration of MeO-12. Thus, the structure of **4** was established to be 9-deoxymuzigadial 12α-acetal. The assignment of H-13a and H-13b was decided based on the cross-peaks between Me-14 (δ1.08) and H-13a (δ4.83), and H-5 (δ2.11) and H-13b (δ4.68) in its NOESY spectrum.

In the NOESY spectrum of **5**, there were cross-peaks between MeO-11 and H-12, and MeO-12 and Me-15. The structure of **5** was determined as 9-deoxymuzigadial 12β-acetal.

There were 19 signals in the ^{13}C NMR spectra (Table 1) of **6** and **7**, including one methine carbon bearing an acetoxy group, two methoxy groups, two acetal carbons and no aldehyde signal, indicating that **6** and **7** were acetals, similar to **4** and **5**. In addition, there

Table 1. ^{13}C NMR spectral data of **1–15** (75 MHz, $CDCl_3$)

C	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	31.7	34.2	34.6	40.0	40.0	37.1	37.3	37.1	35.7	31.8	37.0	36.9	37.1	39.8	39.9
2	30.9	23.6	23.7	32.5	32.5	23.7	23.4	31.9	23.6	29.1	23.3	23.5	18.4	18.5	18.8
3	38.2	79.8	80.2	38.7	38.8	80.6	80.6	38.5	79.8	38.2	79.8	80.1	42.0	42.3	42.2
4	151.6	37.5	37.7	152.9	152.8	37.7	37.3	151.7	37.5	152.4	37.8	34.0	32.9	32.9	31.8
5	40.2	43.6	43.7	46.3	46.1	49.1	49.2	41.3	47.4	43.1	48.6	49.3	44.2	49.6	49.9
6	27.6	25.0	23.3	25.5	25.9	23.2	23.7	27.3	26.5	37.4	24.8	24.6	25.5	23.6	23.6
7	155.8	152.5	129.0	120.7	121.4	120.9	121.4	152.6	67.3	61.6	153.3	135.8	153.5	121.4	124.2
8	139.9	137.3	129.9	136.9	136.4	137.2	136.7	137.2	139.1	139.2	138.3	127.2	137.4	137.2	132.9
9	77.6	58.0	60.8	55.5	56.9	57.6	58.8	55.8	162.7	162.9	59.9	50.6	58.5	57.8	57.3
10	42.4	37.2	36.6	35.7	36.0	32.9	33.3	39.1	37.8	39.2	36.4	37.6	37.7	33.3	36.1
11	201.3	201.4	202.5	107.2	105.7	106.8	104.9	202.3			201.2	67.0	202.3	107.0	61.0
12	192.7	192.5	105.5	104.2	102.4	104.4	102.5	193.0	196.1	195.5	192.9	169.8	192.8	104.6	22.0
13	106.1	27.6	27.6	104.8	104.8	27.6	27.9	105.6	27.8	104.5	28.0	27.3	32.7	21.5	33.4
14	18.4	21.6	21.5	18.6	18.7	16.1	16.2	18.4	20.2	18.1	16.6	16.0	21.5	33.0	22.1
15	15.1	16.4	16.4	12.9	13.2	14.1	14.5	19.2	16.5	17.3	15.3	13.5	21.9	14.1	15.0
MeCO		170.6	170.7			170.8	170.8		170.9		170.7	170.8			
MeCO		21.2	21.2			21.3	21.3		21.3		21.2	21.2			
MeO-11				56.0	55.0	56.0	55.6							56.0	
MeO-12			53.5	54.3	56.7	54.4	56.6							54.3	
MeO-12			54.3												

was one double bond, three tertiary methyl groups, two other methine carbons and two quaternary carbons, suggesting that their carbon skeleton was the same as that of polygodial. The chemical shifts of C-1 and C-5 signals of **6** and **7** were very similar to those of **11** and **12**, but not to those of **2** and **3**, revealing that there was a 3β-acetoxy group in **6** and **7**. The β-configuration of the acetoxy group was supported by the coupling constants of H-3 (*dd*, 4.3, 11.0 Hz in **6**; *dd*, 5.5, 10.1 Hz in **7**) which indicated that H-3 had an axial configuration. The stereochemistry of C-11 and C-12 of **6** was established based on the similarity of the chemical shifts of C-11, MeO-11, H-11, C-12, MeO-12 and H-12 between **6** and **4** (δ_C104.4, 56.0, δ_H4.92, δ_C106.8, 54.4 and δ_H5.13 in **6**; δ_C104.2, 56.0, δ_H4.94, δ_C107.2, 54.3 and δ_H5.13 in **4**). Therefore **6** was determined to be 3β-acetoxypolygodial 12α-acetal. Since a similar relationship could be observed between **7** and **5**, **7** was deduced to be 3α-acetoxypolygodial 12β-acetal.

The ^{1}H and ^{13}C NMR spectra (Table 1) of **8** were very similar to those of 9-deoxymuzigadial (**16**) [4]. The only differences were that the signals of C-1, C-5 and C-9 shifted upfield 2, 4 and 2.5 ppm, respectively. This indicated that the aldehyde group at C-9 in **8** had an α-configuration (pseudoaxial) and **8** was thus 9-epideoxymuzigadial. The assignment of all ^{1}H and ^{13}C NMR signals was confirmed by ^{1}H–^{1}H COSY and ^{13}C–^{1}H COSY experiments.

The ^{13}C NMR spectrum (Table 1) of **9** indicated that there was an acetoxy group (δ_C21.3, 170.9) and 14 other signals, including one aldehyde (δ_C 196.1), three tertiary methyl, two olefinic, three methylene, three methine and two quaternary carbons. The ^{1}H–^{1}H COSY, long-range ^{1}H–^{1}H COSY and ^{13}C–^{1}H COSY spectra clearly showed the relationship between all carbon and proton signals, indicating that **9** was a norsesquiterpenoid, either acetoxypolygonal or acetoxyisopolygonal. The coupling constants (9.6 and 7.4 Hz) of the H-7 signal (δ_H4.64, *dd*) clearly indicated that H-7 had an α-configuration; therefore, **9** was an acetoxyisopolygonal. The similarity of chemical shifts of C-1 through C-5 between **9** and **7** indicated that the acetoxy group was located at the C-3 position. The β-configuration of the acetoxy group was evident from the *J* value (11.2 and 5.0 Hz). Thus, the structure of **9** was 3β-acetoxyisopolygonal.

The ^{13}C–^{1}H COSY spectrum of **10** clearly revealed the relationship between its 14 carbon signals and proton signals: one aldehyde (δ_C195.5, δ_H9.49), one tertiary methyl group (δ_C17.3, δ_H0.82), one secondary methyl group (δ_C18.1, δ_H1.09), one exomethylene group (δ_C104.5, δ_H4.82 and 4.61, δ_C152.4), one tri-substituted olefinic bond (δ_C139.2 and 162.9, δ_H6.71), three methylene groups (δ_C29.1, δ_H1.66 and 1.81; δ_C31.8, δ_H1.36 and 1.79; δ_C37.4, δ_H1.74 and 1.91), three methine groups (δ_C38.2, δ_H2.10; δ_C43.1, δ_H2.38; δ_C61.6, δ_H4.67) and one tertiary carbon (δ_C39.2). The spectral data suggested that **10** was a derivative of muzigadial with one aldehyde group. The chemical shifts of the olefinic carbon and proton (δ_C162.9, δ_H6.71) indicated that this double bond was conjugated with the aldehyde group. Since the olefinic proton signal was a very sharp singlet, it had no adjacent proton. This proton could only be located at the 9-position. In the ^{1}H–^{1}H COSY spectrum there were cross-peaks among the signal at δ2.38 and the signals at δ1.74 and 1.91, which correlated with the signal at δ4.67, suggesting that there was a partial structure of $-\overset{|}{C}H-CH_2-\overset{|}{C}H-OH$. Therefore, the only position possible for the hydroxyl group was C-7. The broad doublet (J = 4.3 Hz) of the δ4.67 signal indicated that the proton had a β-configuration. Thus, the structure of **10** was elucidated as 3,4,4a,5,6,7,8,8a-octohydro-3α-hydroxy-6β,8a-dimethyl-5-methylene-2-naphthalenecarboxaldehyde. The trivial name muzigaal was given to this compound.

In addition to the nine new compounds (**2**–**10**), six known sesquiterpenoids (**1**, **11**–**15**) were identified by spectral analyses. The most abundant component from the leaves was **1** which had been previously isolated from the stem bark of this plant [1] and from the stem bark of the African plants *Warburgia stuhlmanni* and *W. ugandensis*. The ^{1}H and ^{13}C NMR spectral data of muzigadial in the literature were either incomplete or assigned incorrectly. By 2D NMR study, all ^{1}H and ^{13}C signals were assigned unambiguously.

Both ^{1}H and ^{13}C NMR spectral data of **11** exactly matched the literature data of 3β-acetoxypolygodial which was isolated from the stem bark of *C. winterana* [4].

Compound **12** showed the same ^{1}H and ^{13}C NMR spectral data (Table 1) as that of 3β-acetoxycinnamolide, a component from the stem bark of *W. ugandensis* [9]. However, the assignment of the ^{13}C NMR signals needed to be corrected. On the ^{13}C–^{1}H COSY spectrum, there were cross-peaks between the signals at δ_C27.3 and δ_H0.93, and at δ_C13.5 and δ_H0.84, indicating that the signal at δ_C27.3 was C-13 and the signal at δ_C13.5 was C-15. The signal at δ_C24.6 correlated with the signals of δ_H2.22 and 2.44, indicating that this signal should be assigned to C-6. Based on the correlation between the signals at δ_C50.6 and δ_H2.81, and δ_C49.3 and δ_H1.48, these two carbon signals could be assigned to C-9 and C-5, respectively. There has been no previous report of the isolation of 3β-acetoxycinnamolide from *C. winterana*.

The identification of **13** was based on the comparison of its ^{13}C NMR spectral data with that of isopolygodial [12], which has been isolated from the seeds [10] and leaves [11] of *Polygonum hydropiper* and the leaves of *Pseudowinterana colorata* [12]. This is the first time that **13** was isolated from *C. winterana*.

Compound **14** had characteristic ^{1}H and ^{13}C NMR signals of cyclic dimethyl acetal (δ_H3.40 and 3.47, δ_C54.3 and 56.0, and δ_H4.91 and 5.12, δ_C 104.6 and 107.0) found from **4**–**7**. The presence of three tertiary methyl groups suggested that **14** was a derivative of polygodial. Comparison of the ^{13}C NMR spectral data of **14** with the published data of polygodial acetal (isolated from *P. hydropiper*) [13] revealed that **14** was an epimeric isomer of polygodial acetal. Fukuyama *et al.* [13] separated two isomers of polygodial acetals, but did not determine their stereochemistry. Recently, Tozyo *et al.* [14] prepared these two isomers, acetal-1 and acetal-2, from polygodial and determined their configurations. Therefore, the struc-

ture of **14** was elucidated as polygodial 12α-acetal. The ^1H and ^{13}C signal assignments were established based on the ^1H–^1H COSY and ^{13}C–^1H COSY spectra. For example, the signal of H-12 (δ_H5.12, *s*) correlated with the signal at δ_H3.40, and the signal of H-11 (δ_H4.91, *d*, J = 3.3 Hz) correlated with the signal of H-9 (δ_H2.45). Therefore, the methoxy signal at δ_H3.40 was assigned at the C-12 position. The cross-peaks between the signals at δ_C104.6 and δ_H5.12, δ_C107.0 and δ_H4.91, δ_C56.0 and δ_H3.47, and δ_C54.3 and δ_H3.40 confirmed their assignments. In the long range ^{13}C–^1H COSY spectrum the signal at δ_C33.3 correlated with the Me-15 signal (δ0.77). Thus, this signal was assigned to C-10, and another quaternary carbon signal (δ 32.9) was assigned to C-4. All equivocal assignments on ^1H and ^{13}C NMR data were clarified.

In **15** there was one methyl group (δ_C22.0 and δ_H1.79) attached to an olefinic bond in addition to three tertiary methyl groups (δ_C15.0 and δ_H0.82, δ_C22.1 and δ_H0.89, and δ_C33.4 and δ_H0.87). Another characteristic of this compound was that there was a hydroxymethylene group (δ_C61.0, and δ_H3.76 and 3.86). Compound **15** was identified as drimenol which has been isolated from *Porella vernicosa* (a liverwort) [14], *Polygonum hydropiper* [11] and *Drimys winteri* [15].

There are several papers [16–19] that discuss the possible transformation of dialdehydes during extraction and separation processes. In our case, the dried plant material was extracted with methanol at room temperature and separated by two very mild methods (Sephadex LH-20 and centrifugal partition chromatography). Furthermore, the separation was monitored by LC-MS, ^{13}C and ^1H NMR, in addition to routine TLC. When the plant was extracted with methylene chloride, the ^{13}C and ^1H NMR spectra of the crude methylene chloride extract showed acetal signals clearly. The possibility of artifact formation cannot be completely excluded. At the very least the yield of each compound isolated may not be the same as the content of the original plant.

The phytotoxic activities of **1** through **14** in the *Lemna minor* bioassay are summarized in Table 2.

Table 2. Phytotoxic activities of **1**–**14**

Compound	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**)	45–200
3β-Acetoxypolygonal (**9**)	180–360
Muzigaal (**10**)	230–460
3β-Acetoxypolygodial (**11**)	35–70
3β-Acetoxycinnamolide (**12**)	> 700
Isopolygodial (**13**)	45
Polygodial 12α-acetal (14)	18

EXPERIMENTAL

General. Mp: uncorr.; UV (MeOH); IR: film; NMR (300 MHz for ^1H and 75 MHz for ^{13}C) $CDCl_3$, TMS as int. standard; CI-MS: CH_4 as reactant gas.

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.

Bioassay. The *Lemna minor* bioassay was conducted as described previously [20].

Extraction and isolation. The dried leaves (529 g) of *C. winterana* were extracted with MeOH at room temp. The MeOH extract was concd under red. pres. and partitioned with pentane and CH_2Cl_2 sequentially. The pentane phase was evapd to yield 50.26 g of oil which showed phytotoxic activity in the *Lemna minor* assay at 20 ppm. The pentane fr. was dissolved in CH_2Cl_2 and sepd on a Sephadex LH-20 column to provide 5 frs. The active fr. (no. 2) was further fractionated by centrifugal partition chromatography (Sanki NMF, hexane–EtOAc–MeOH–H_2O, 8:2:8:2, ascending mode) to give 11 frs. The final purification was carried out mainly by recycling prep. HPLC (GS-310P column/MeOH, ODS/75% MeOH, or Nucleosil/hexane–EtOAc) to obtain muzigadial (947 mg), 3α-acetoxypolygodial (4 mg), 3α-acetoxypolygodial 12-dimethyl acetal (26 mg), 9-deoxymuzigadial 12α-acetal (744 mg), 9-deoxymuzigadial 12β-acetal (101 mg), 3β-acetoxypolygodial 12α-acetal (24 mg), 3β-acetoxypolygodial 12β-acetal (26 mg), 9-epideoxymuzigadial (96 mg), 3β-acetoxypolygonal (11 mg), muzigaal (33 mg), 3β-acetoxypolygodial (27 mg), 3β-acetoxycinnamolide (14 mg), isopolygodial (39 mg), polygodial 12α-acetal (263 mg) and drimenol (13 mg).

Muzigadial (**1**). Needles (from hexane–CH_2Cl_2), mp 128–129°. UV λ_{max} nm: 225 (log ε 3.73). IR ν_{max} cm^{-1}: 3460, 2958, 2914, 2872, 1716, 1674, 1657, 1408, 1339, 1207, 1137, 1022, 992, 900, 844, 810, 791. ^1H NMR: δ0.88 (3H, *s*, Me-15), 1.07 (1H, *m*, H-2), 1.08 (3H, *s*, Me-14), 1.10 (1H, *m*, H-1) 1.68 (1H, *m*, H-1), 2.00 (2H, *m*, H-2 and H-3), 2.51 (2H, *m*, CH_2-6), 2.62 (1H, *m*, H-5), 4.77 (1H, *s*, H-13b), 4.94 (1H, *s*, H-13a), 7.25 (1H, *br t*, J = 3.3 Hz, H-7), 4.45 (1H, *m*, H-3), 9.45 (1H, *s*, H-12), 9.66 (1H, *s*, H-11). EI-MS *m/z* (rel. int.): 249 $[M + 1]^+$ (1), 219 (100), 187 (12), 177 (16), 159 (17), 135 (42), 107 (36), 107 (36), 91 (38); positive CI-MS *m/z* (rel. int.): 248 $[M]^+$ (28), 220 (20), 219 [M − CHO] (100).

3α-Acetoxypolygodial (**2**). Oil. UV λ_{max} nm: 220. IR ν_{max} cm^{-1}: 2996, 2912, 1725, 1437. 1407, 1312, 1250, 955, 701, 671. ^1H NMR: δ0.92 (3H, *s*, Me-13), 0.98 (6H, *s*, Me-14 and 15), 1.62 (1H, *m*, H-5), 1.7 (2H, *m*, CH_2-2), 1.8 (2H, *m*, CH_2-1), 2.06 (3H, *s*, MeCO), 2.31 (1H, *dd*, J = 11.4, 20.4 Hz, H-6β), 2.60 (1H, *ddd*, J = 4.8, 5.1, 20.4 Hz, H-6α), 3.32 (1H, *br s*, H-9), 4.45 (1H, *m*, H-3), 7.10 (1H, *dd*, J = 2.8, 4.8 Hz, H-7), 9.43 (1H, *s*, H-12), 9.85 (1H, *d*, J = 2.5 Hz). EI-MS *m/z* (rel. int.): 264 $[M - 28]^+$ (5), 218 (14), 204 $[M - 28 - 60]^+$ (100), 189 $[M - 28 - 60 - 15]^+$ (87), 174 (32), 133 (36), 122 (72), 107 (83), 69 (66), 55 (71). Negative CI-MS *m/z* (rel. int.): 308 $[M + CH_4]^-$ (80), 306 (82), 294 (97), 278 (100), 218 (97), 166 (86), 112 (46), 98 (58).

3α-*Acetoxypolygodial 12-dimethyl acetal* (**3**). Oil. IR ν_{max} cm^{-1}: 2967, 2878, 1728, 1688, 1459, 1442, 1396, 1375, 1247, 1032, 983, 736. ^{1}H NMR: δ0.91 (3H, *s*, Me-13), 0.95 (3H, *s*, Me-15), 0.97 (3H, *s*, Me-14), 1.6 (2H, *m*, CH_2-1), 1.7 (3H, *m*, H-5 and CH_2-2), 2.1 (1H, *m*, H-6), 2.05 (3H, *s*, MeCO), 2.35 (1H, *ddd*, *J* = 4.7, 5.1, 18.5 Hz, H-6), 2.76 (1H, *br d*, *J* = 4.1 Hz, H-9), 3.24 (3H, *s*, MeO-11), 3.29 (3H, *s*, MeO-12), 4.40 (1H, *s*, H-12), 4.47 (1H, *br t*, *J* = 7.7 Hz, H-3), 6.12 (1H, *dd*, *J* = 2.6, 4.4 Hz, H-7), 9.65 (1H, *d*, *J* = 4.2 Hz, H-11). EI-MS *m/z* (rel. int.): 309 [M − CHO]$^+$ (20), 277 [M − 60 − 1]$^+$ (32), 218 (45), 204 (76), 189 (64), 173 (47), 122 (79), 107 (88), 69 (93), 57 (100). Negative CI-MS *m/z* (rel. int.): 278 [M − 60]$^-$ (100).

9-*Deoxymuzigadial 12α-acetal* (**4**). Mp 69–71°. IR ν_{max} cm^{-1}: 2958, 2855, 2820, 1718, 1674, 1640, 1456, 1384, 1326, 1253, 1191, 1084, 980, 949, 833. ^{1}H NMR: δ0.62 (3H, *s*, Me-15), 1.08 (3H, *d*, *J* = 6.5 Hz, Me-14), 1.23 (1H, *ddd*, *J* = 3, 12, 25 Hz, H-2), 1.53 (1H, *ddd*, *J* = 3, 13, 13 Hz, H-1), 1.65 (1H, *m*, H-2), 1.74 (1H, *ddd*, *J* = 3, 3, 13 Hz, H-1), 2.02 (1H, *m*, H-3), 2.11 (3H, *m*, H-5 and CH_2-6), 2.64 (1H, *br t*, *J* = 3 Hz, H-9), 3.42 (3H, *s*, MeO-12), 3.49 (3H, *s*, MeO-11), 4.68 (1H, *br s*, H-13b), 4.83 (1H, *br s*, H-13a), 4.94 (1H, *d*, *J* = 4.7 Hz, H-11), 5.13 (1H, *s*, H-12), 5.93 (1H, *br t*, *J* = 2 Hz, H-7). EI-MS *m/z* (rel. int.): 263 [M − 15]$^+$ (4), 247 [M − OMe]$^+$ (26), 218 (100), 203 (49), 189 (64), 173 (48), 171 (47), 131 (51), 109 (77), 91 (87), 65 (76). Positive CI-MS *m/z* (rel. int.): 279 [M + 1]$^+$ (38), 263 [M − 15]$^+$ (60), 261 (64), 247 [M − OMe]$^+$ (100).

9-*Deoxymuzigadial 12β-acetal* (**5**). Oil. ^{1}H NMR: δ0.67 (3H, *s*, Me-15), 1.08 (3H, *d*, *J* = 6.5 Hz, Me-14), 1.23 (1H, *ddd*, *J* = 3.3, 12.7, 25.6 Hz, H-2), 1.49 (1H, *ddd*, *J* = 3, 3, 13.3 Hz, H-1), 1.66 (1H, *ddd*, *J* = 3.8, 6.9, 12.7 Hz, H-2), 1.82 (1H, *ddd*, *J* = 3.6, 13.3, 13.3 Hz, H-1), 2.02 (1H, *m*, H-3), 2.07 (1H, *m*, H-5), 2.11 (2H, *dd*, *J* = 11.4, 20.4 Hz, H-6), 2.40 (1H, *dd*, *J* = 3.3, 6.7 Hz, H-9), 3.47 (3H, *s*, MeO-11), 3.52 (3H, *s*, MeO-12), 4.68 (1H, *br s*, H-13b), 4.83 (1H, *br s*, H-13a), 4.92 (1H, *d*, *J* = 6.7 Hz, H-11), 5.44 (1H, *br s*, H-12), 5.84 (1H, *br d*, *J* = 3 Hz, H-7).

3β-*Acetoxypolygodial 12α-acetal* (**6**). Oil. IR ν_{max} cm^{-1}: 2920, 1732, 1465, 1444, 1389, 1368, 1246, 1191, 1091, 1023, 964, 923, 826. ^{1}H NMR: δ0.79 (3H, *s*, Me-15), 0.88 (3H, *s*, Me-13), 0.96 (3H, *s*, Me-14), 1.41 (1H, *dd*, *J* = 5.5, 11.3 Hz, H-5), 1.44 (1H, *m*, H-1), 1.67 (2H, *m*, CH_2-2), 2.1 (1H, *m*, H-6), 2.06 (3H, *s*, MeCO), 2.20 (1H, *m*, H-6), 2.44 (1H, *br t*, *J* = 3.5 Hz, H-9), 3.41 (3H, *s*, MeO-12), 3.46 (3H, *s*, MeO-11), 4.53 (1H, *dd*, *J* = 4.2, 10.9 Hz, H-3), 4.92 (1H, *d*, *J* = 3.9 Hz, H-11), 5.13 (1H, *s*, H-12), 5.81 (1H, *br d*, *J* = 3.0 Hz, H-7). EI-MS *m/z* (rel. int.): 337 [M − 1]$^+$ (2), 307 [M − OMe]$^+$ (52), 278 [M − 60]$^+$ (56), 218 [M − 60 − 60]$^+$ (99), 203 (100), 187 (10), 175 (10), 173 (16), 171 (27). Positive CI-MS *m/z* (rel. int.): 337 [M − 1]$^+$ (1.5), 307 [M − OMe]$^+$ (52), 278 [M − 60]$^+$ (57), 218 [M − 60 − 60]$^+$ (100), 203 (99), 171 (26), 105 (22), 91 (28).

3β-*Acetoxypolygodial 12β-acetal* (**7**). Mp. 110–113°. IR ν_{max} cm^{-1}: 2930, 1732, 1444, 1395, 1374, 1246, 1193, 1102, 1022, 986, 931. ^{1}H NMR: δ0.87 (3H, *s*, Me-15), 0.89 (3H, *s*, Me-13), 0.96 (3H, *s*, Me-14), 1.33 (1H, *dd*, *J* = 5.3, 11.4 Hz, H-5), 1.45 (1H, *m*, H-1), 1.6 ~ 1.85 (5H, *m*), 2.06 (3H, *s*, MeCO), 2.21 (1H, *m*, H-9), 3.46 (3H, *s*, MeO-11), 3.48 (3H, *s*, MeO-12), 4.53 (1H, *dd*, *J* = 5.5, 10.1 Hz, H-3), 4.92 (1H, *d*, *J* = 5.9 Hz, H-11), 5.39 (1H, *s*, H-12), 5.80 (1H, *br s*, H-7).

9-*Epideoxymuzigadial* (**8**). Oil. ^{1}H NMR: δ0.77 (3H, *s*, Me-15), 1.08 (3H, *d*, *J* = 6.5 Hz, Me-14), 1.29 (1H, *ddd*, *J* = 4, 12, 24 Hz, H-2α), 1.61 (1H, *m*, H-1α), 1.70 (1H, *m*, H-2β), 1.82 (1H, *m*, H-1β), 1.95 (1H, *m*, H-3), 2.38 (1H, *br s*, H-5), 2.48 (2H, *m*, CH_2-6), 3.45 (1H, *br d*, *J* = 2.7 Hz, H-9), 4.73 (1H, *s*, H-13b), 4.89 (1H, *s*, H-13a), 7.14 (1H, *dd*, *J* = 2.7, 4.2 Hz, H-7), 9.44 (1H, *s*, H-12), 9.91 (1H, *d*, *J* = 2.7 Hz, H-11); EI-MS *m/z* (rel. int.): 232 [M]$^+$ (100), 217 (39), 214 (90), 203 (59), 199 (57), 189 (48), 173 (70), 159 58); negative CI-MS *m/z* (rel. int.): 249 [M + CH_4 + 1]$^-$ (34), 235 (100), 219 (79).

3β-*Acetoxypolygonal* (**9**). Oil. UV λ_{max} nm: 226 (log ε 4.05). IR ν_{max} cm^{-1}: 3484, 2968, 2872, 1732, 1676, 1458, 1374, 1247, 1029, 736: ^{1}H NMR: δ0.93 (3H, *s*, Me-15), 0.94 (3H, *s*, Me-13), 1.12 (1H, *m*, H-5), 1.18 (3H, *s*, Me-14), 1.47 (1H, *m*, H-1α), 1.54 (1H, *m*, H-6), 1.70 (1H, *m*, H-1β), 1.81 (2H, *m*, CH_2-2), 2.07 (3H, *s*, MeCO), 2.18 (1H, *dd*, *J* = 7.0, 12.8 Hz, H-6), 3.65 (1H, *br s*, OH), 4.50 (1H, *dd*, *J* = 5.0, 11.3 Hz, H-3), 4.64 (1H, *dd*, *J* = 7.4, 9.6 Hz, H-7), 6.46 (1H, *s*, H-9), 9.40 (1H, *s*, H-12).

Muzigaal (**10**). Mp 100–101°. UV λ_{max} nm: 225 (log ε 4.15). IR ν_{max} cm^{-1}: 3528, 3460, 3385, 2957, 2917, 1667, 1636, 1450, 1405, 1385, 1369, 1242, 1224, 1181, 1128, 1050, 1023, 999, 960, 908, 882, 723, 634. ^{1}H NMR: δ0.82 (3H, *s*, Me-15), 1.09 (3H, *d*, *J* = 6.4 Hz, Me-14), 1.36 (1H, *ddd*, *J* = 8.4, 12.6, 22.3 Hz, H-1), 1.66 (1H, *m*, H-2), 1.74 (1H, *m*, H-6), 1.79 (1H, *m*, H-1), 1.81 (1H, *m*, H-2), 1.91 (1H, *br d*, *J* = 13.8 Hz, H-6), 2.10 (1H, *dq*, *J* = 5.8, 6.4 Hz, H-3), 2.38 (1H, *br d*, *J* = 12.8 Hz, H-5), 4.61 (1H, *s*, H-13b), 4.67 (1H, *br d*, *J* = 4.3 Hz, H-7), 4.82 (1H, *s*, H-13a), 6.71 (1H, *s*, H-9), 9.49 (1H, *s*, H-12).

3β-*Acetoxypolygodial* (**11**). Oil. IR ν_{max} cm^{-1}: 3434, 2967, 1732, 1682, 1644, 1372, 1247, 1033, 736. ^{1}H NMR: δ0.93 (3H, *s*, Me-13), 0.97 (3H, *s*, Me-15), 1.01 (3H, *s*, Me-14), 1.36 (1H, *dd*, *J* = 5.1, 11.4 Hz, H-5), 1.64 (1H, *m*, H-1), 1.70 (2H, *m*, CH_2-2), 1.90 (1H, *m*, H-1), 2.50 (2H, *m*, CH_2-6), 2.82 (1H, *br s*, H-9), 4.57 (1H, *dd*, *J* = 4.3, 10.8 Hz, H-3), 7.14 (1H, *ddd*, *J* = 2.2, 4.2, 6.1 Hz, H-7), 9.48 (1H, *s*, H-12), 9.54 (1H, *d*, *J* = 4.2 Hz, H-11). EI-MS *m/z* (rel. int.): 264 [M-28]$^+$ (6), 204 [M − 28 − 60]$^+$ (100), 189 [M − 28 − 60 − 15]$^+$ (92), 133 (34), 122 (54), 107 (64), 69 (77), 57 (95). Negative CI-MS *m/z* (rel. int.): 308 [M + CH_4]$^-$ (100), 306 (90), 291 [M − 1]$^-$ (76), 278 (68), 251 (82), 235 (65).

3β-*Acetoxycinnamolide* (**12**). Oil. IR ν_{max} cm^{-1}: 2970, 2955, 1754, 1728, 1682, 1482, 1461, 1444, 1422, 1396, 1376, 1244, 1201, 1140, 1095, 1041, 1040, 1010, 967, 742. ^{1}H NMR: δ0.84 (3H, *s*, Me-15), 0.93 (3H, *s*, Me-13), 1.00 (3H, *s*, Me-14), 1.42 (1H, *m*, H-1), 1.48 (1H, *dd*, *J* = 5.5, 11.4 Hz, H-5), 1.64 (1H, *m*, H-1), 1.73 (2H, *m*, CH_2-2), 2.08 (3H, *s*, MeCO), 2.22 (1H, *ddd*, *J* = 4.7, 11.4, 16 Hz, H-6), 2.44 (1H, *ddd*, *J* = 5.5, 9, 16 Hz, H-6), 4.05 (1H, *t*, *J* = 9 Hz, H-11), 4.40 (1H, *t*, *J* = 9 Hz, H-11), 4.55 (1H, *dd*, *J* = 5, 11 Hz, H-3), 6.89 (1H, *dd*, *J* = 3.3, 6.8 Hz, H-7). EI-MS *m/z* (rel. int.): 293 [M + 1]$^+$ (1), 232 [M − 60]$^+$ (5), 122 (100), 107 (44), 96 (17), 57 (95); negative CI-MS *m/z* (rel.

int.): 291 $[M-1]^-$ (100), 251 (38), 249 (27), 235 (42), 233 (27), 67 (65). Positive CI-MS *m/z* (rel. int.): 293 $[M+1]^+$ (95), 249 (3), 233 (14), 122 (100), 107 (19).

Isopolygodial (**13**). Oil. IR ν_{max} cm^{-1}: 2928, 1722, 1682, 1657, 1461, 1418, 1391, 1368, 1211, 1034, 970, 953, 735, ^1H NMR: δ0.91 (3H, *s*, Me-13), 0.94 (3H, *s*, Me-15), 0.97 (3H, *s*, Me-14), 1.16 (1H, *ddd*, J = 3.8, 13.4, 13.4 Hz, H-3α), 1.47 (1H, *m*, H-3β), 1.5 (2H, *m*, H-1 and H-2), 1.6 (1H, *m*, H-5), 1.64 (1H, *m*, H-2β), 1.79 (1H, *br d*, J = 11 Hz, H-1β), 2.22 (1H, *dd*, J = 11.6, 20.5 Hz, H-6β), 2.57 (1H, *ddd*, J = 4.7, 5.1, 20.5 Hz, H-6α), 3.26 (1H, *br s*, H-9), 7.11 (1H, *dd*, J = 2.5, 4.7 Hz, H-7), 9.41 (1H, *s*, H-12), 9.86 (1H, *br s*, H-11). EI-MS *m/z* (rel. int.): 206 $[M-28]^+$ (84), 191 (31), 121 (69), 109 (100), 91 (52). Negative CI-MS *m/z* (rel. int.): 251 $[M+CH_4+1]^-$ (16), 237 (100), 221 (77), 128 (53); positive CI-MS *m/z* (rel. int.): 235 $[M+1]^+$ (16), 221 (74), 205 $[M-CHO]^+$ (100), 139 (43), 109 (70).

Polygodial 12α-acetal (**14**). Oil. IR ν_{max} cm^{-1}: 2940, 2923, 2846 1460, 1443, 1390, 1365, 1326, 1278, 1257, 1205, 1192, 1113, 1094, 1077, 1017, 963, 923, 824. ^1H NMR: δ0.77 (3H, *s*, Me-15), 0.87 (3H, *s*, Me-14), 0.91 (3H, *s*, Me-13), 1.22 (1H, *dddd*, J = 3.5, 3.5, 10, 13 Hz, H-1), 1.32 (1H, *dd*, J = 5.5, 11.5 Hz, H-5), 1.40 (2H, *m*, CH_2-3), 1.5 (2H, *m*, CH_2-2), 1.66 (1H, *m*, H-1), 1.93 (1H, *dddd*, J = 3.3, 3.5, 11.5, 18.4 Hz, H-6β), 2.16 (1H, *ddd*, J = 3.5, 8.4, 18.4 Hz, H-6α), 2.45 (1H, *br t*, J = 3.2 Hz, H-9), 3.40 (3H, *s*, MeO-12), 3.47 (3H, *s*, MeO-11), 4.91 (1H, *d*, J = 3.9 Hz, H-11), 5.12 (1H, *s*, H-12), 5.80 (1H, *br d*, J = 3.0 Hz, H-7). EI-MS *m/z* (rel. int.): 279 $[M-1]^+$ (0.4), 249 $[M-OMe]^+$ (17), 220 $[M-60]^+$ (75), 205 $[M-60-15]^+$ (100), 173 (11), 135 (55), 111 (53), 91 (24). Positive CI-MS *m/z* (rel. int.): 279 $[M-1]^+$ (1), 249 $[M-OMe]^+$ (30), 220 $[M-60]^+$ (100), 205 $[M-60-15]^+$ (89), 135 (42), 111 (38), 91 (29).

Drimenol (**15**). Oil. IR ν_{max} cm^{-1}: 3405, 2922, 2848, 1443, 1383, 1250, 1213, 1175, 1155, 1032, 784, 742, 641. ^1H NMR: δ0.82 (3H, *s*, Me-15), 0.87 (3H, *s*, Me-13), 0.89 (3H, *s*, Me-14), 1.07 (1H, *m*, H-1), 1.20 (2H, *m*, H-3 and H-5), 1.41 (1H, *m*, H-3), 1.48 (2H, *m*, CH_2-2), 1.79 (3H, *s*, Me-12), 1.86 (1H, *m*, H-9), 1.92 (1H, *m*, H-6), 1.95 (1H, *m*, H-1), 1.97 (1H, *m*, H-6), 3.76 (1H, *m*, H-11), 3.86 (1H, *m*, H-11), 5.55 (1H, *br t*, J = 2.1 Hz, H-7). EI-MS *m/z* (rel. int.): 222 $[M]^+$ (17), 191 $[M-CH_2OH]^+$ (10), 124 $[M-60]^+$ (65), 109 (100).

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