Cinnafragrins A−C, Dimeric and Trimeric Drimane Sesquiterpenoids from *Cinnamosma fragrans*, and Structure Revision of Capsicodendrin[⊥]

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Two new dimeric sesquiterpenoids and a new trimeric drimane sesquiterpenoid named cinnafragrins A−C (**1**−**3**), together with cinnamodial (**4**), D-mannitol, capsicodendrin (**5**), and a vitamin E analogue, δ-tocotrienol, were isolated from *Cinnamosma fragrans*, a Malagasy medicinal plant. The structures of the new compounds were determined on the basis of physical, chemical, and spectroscopic evidence. Capsicodendrin, previously isolated from *Capsicodendron dinisii* and tentatively suggested to be a tetramer of cinnamodial, was revised structurally as a mixture of C-12′-epimers of 12′-hydroxycinnafragrin B by extensive 2D NMR analysis and X-ray crystallography of the lactone derivative, cinnafragrolide (**6**). The chemosystematics of the family Canellaceae are discussed.

The Malagasy endemic genus *Cinnamosma* is one of the five genera (*Capsicodendron* = *Cinnamodendron*, *Canella*, *Cinnamosma*, *Pleodendron*, and *Warburgia*) of the family Canellaceae. *Cinnamosma fragrans* Baillon (Malagasy name: "mandravasarotra" or "sakarivohazo") is a tree widely distributed in the northwestern and east central parts of Madagascar. Decoctions of the bark are used traditionally for the treatment of malarial symptoms, fatigue, and muscular aches.[1] The plant is characterized by its high content of drimane-type sesquiterpenoid dialdehydes and lactones, including cinnamolide, cinnamosmolide, bemarivolide, bemadienolide, fragrolide, and the cytotoxic dialdehyde cinnamodial, which is one of the compounds responsible for its pungent taste. In a continuation of our systematic investigation of bioactive sesquiterpene dialdehydes from the family Canellaceae, three new compounds (**1**−**3**), along with four known compounds, were isolated from *C. fragrans* Baillon collected in Madagascar. This paper deals with the isolation and structure elucidation of compounds **1**−**3** and the structure revision of capsicodendrin (**5**).

Results and Discussion

A combination of Sephadex, silica gel, and ODS RP-18 column chromatography of the methanol extract of *C. fragrans* led to the isolation of two dimeric (**1**, **2**) and one trimeric (**3**) drimane sesquiterpenes, together with four known compounds, which were identified as cinnamodial (**4**), D-mannitol, capsicodendrin (**5**), and the vitamin E analogue, δ-tocotrienol, by interpretation of their physical and spectroscopical data and comparison with those reported in the literature.[2,3,5,6] The structure of cinnamodial (**4**) was confirmed by X-ray crystallography, while the structure of **5** (capsicodendrin) was revised.

HRFABMS analysis of compound **1** exhibited a sodiated molecular ion peak at *m*/*z* 639.3162 $[M + Na]^+$, corresponding to the molecular formula, $C_{34}H_{48}O_{10}$. The IR spectrum suggested the presence of two ester carbonyls (ν_{max} 1734 and 1728 cm^{-1}), an aldehyde (ν_{max} 1710, 3020 cm^{-1}), and a hydroxyl function (ν_{max} 3444 cm^{-1}). The ^1H NMR spectrum (Table 1) exhibited signals for six quaternary methyl groups at δ 1.22 and 1.14 (s, each 3H) and δ 1.13 and 1.00 (s, each 6H), two acetyl methyls at δ 2.07 (s, 6H), three signals for two acetal protons (δ 5.93, brs, C-12 and 5.75, s, C-11′) and one hemiacetal proton (δ 5.66, s, C-12′), two oxygen-bearing methines (δ 5.74, m, H-6, and δ 5.65, m, H-6′), two olefinic methines (δ 6.13, dd, J = 4.8, 1.6 Hz and δ 6.00, dd, J = 4.0, 1.6 Hz), and a signal of an aldehyde (δ 9.76, s). Inspection of the ^{13}C NMR spectroscopic data revealed the presence of two sets of signals very similar to those of cinnamodial (**4**, Table 1) with only one aldehyde signal at δ 206.0. On comparing **1** with **4**, each carbon signal was doubled, while that due to the unsaturated dialdehyde (δ 193.0) was replaced by three signals ascribable to two acetal carbons (δ 104.6 and 102.6; C-12 and -11′, respectively)

Table 1. ^1H and ^{13}C NMR Spectroscopic Data of Compounds **1**, **2**, and **4** (in $CDCl_3$)[a]

	1		**2**		**4**
position	δ_H	δ_C	δ_H	δ_C	δ_C
Unit A					
1a,b	1.28−1.42, m	44.1	1.32−1.40, m	44.0	44.0
2a	1.10, m	32.4	0.95, m	32.7	32.6
2b	1.64, brd (14.0)		1.79, td (13.1, 4.1)		
3a,b	1.46−1.66, m	17.9	1.48−1.62, m	18.0	17.6
4		33.7		33.8	34.0
5	1.92, d (4.9)	45.9	1.96, d (4.6)	46.0	45.0
6	5.74, m	66.3	5.67, m	66.8	66.0
7	6.00, dd (4.0, 1.6)	126.6	5.91 d, 3.5	125.1	148.6
8		138.2		137.9	140.1
9		92.4		90.0	90.0
10		41.7		41.7	41.6
11	9.76, s	206.0	9.86, s	203.6	193.0
12	5.93, brs	104.6	5.55, s	100.0	201.1
13	1.14, s	19.3	1.06, s	20.0	20.0
14	1.13, s	24.5	1.14, s	24.6	24.7
15	1.00, s	32.6	1.00, s	32.0	31.8
CH$_3$C=O	2.07, s	21.6	2.05, s	21.6	21.4
CH$_3$*C*=*O*		170.2		170.0	170.0
OH	3.50, s		3.95, s		
Unit B					
1′a,b	1.28−1.42, m	44.5	1.32−1.40, m	44.6	
2′a	1.28, m	32.3	1.18, m	31.7	
2′b	2.33, m		1.90, td (13.1, 4.1)		
3′a,b	1.46−1,66 m	17.8	1.48−1.62, m	17.6	
4′		33.6		33.7	
5′	2.10, d (4.6)	43.7	1.97, brd (6.0)	44.4	
6′	5.65, m	65.8	5.67, m	66.1	
7′	6.13, dd (4.8, 1.6)	124.7	6.47, dd (4.1, 0.8)	127.8	
8′		140.0		134.1	
9′		79.8		80.4	
10′		37.8		36.8	
11′	5.75, s	102.6	5.20, s	104.5	
12′	5.66, s	98.0	5.70, s	104.2	
13′	1.22, s	18.7	1.47, s	19.5	
14′	1.13, s	24.4	1.14, s	24.4	
15′	1.00, s	32.6	1.00, s	32.6	
CH$_3$C=O	2.07, s	21.6	2.06, s	21.0	
CH$_3$C=O		170.0		170.0	
OMe			3.35, s	55.1	

[a] Assignments based on the HSQC, COSY, and HMBC NMR spectra.

[⊥] Dedicated to Professor Yoshinori Asakawa, Tokushima Bunri University, on the occasion of his 65th birthday.

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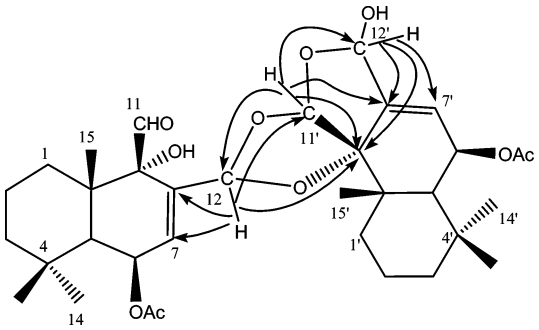
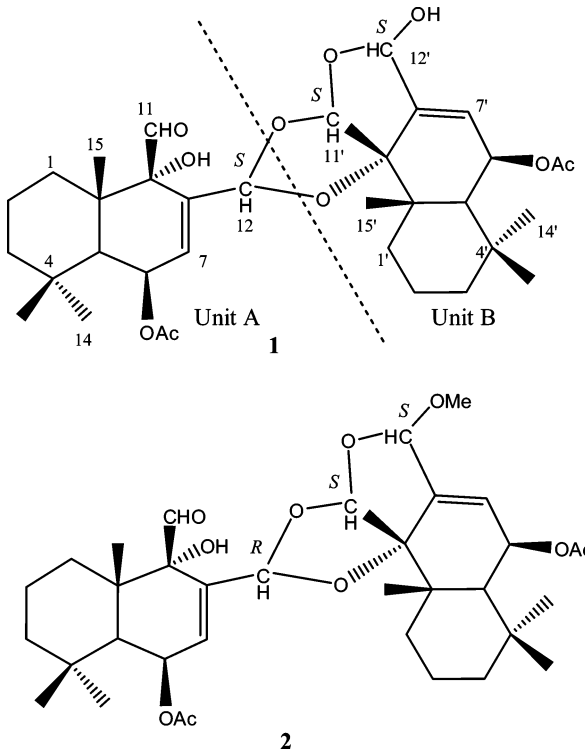


Figure 1. Important HMBC correlations observed for **1**.

and one hemiacetal (δ 98.0) carbon. To determine the structure of **1** (units A and B, Figure 1), extensive 2D NMR analysis was performed. HMBC (Figure 2) correlations between H-12 and C-7, C-8, C-9′, and C-11′; H-11′ and C-12, C-9′, and C-12′; and H-12′ and C-7′, C-8′, C-9′, and C-11′ were clearly observed, allowing the conclusion to be made that the two monomers (unit A and unit B) were connected at C-12 with C-9′ and C-11′ by acetal bonds and the latter with the C-12′ hemiacetal. The two acetoxyl groups were attached at C-6 and C-6′, respectively, due to the long-range correlations observed between H-6 (δ_H 5.74) and one acetyl carbonyl (δ_C 170.2) and H-6′ (δ_H 5.75) with the remaining acetyl carbonyl (δ_C 170.0). The relative and the absolute configuration of **1** were determined as follows. The configurations of C-12, C-11′, and C-12′ of **1** were determined to be *S*, *S*, and *S*, respectively, by the observation of NOE correlations between H-12 (δ_H 5.93) and H-1′; H-11′ and the H-15′ methyl protons; and H-12′ (δ_H 5.66) and CH_3-15′ (Figure 2). Furthermore, to establish the absolute configuration, **1** was dissolved in pyridine and allowed to stand overnight to convert into its monomer, which was identified as **4** from its spectroscopic data (including X-ray crystallography) and its optical rotation value. The presumed mechanism of conversion of **1** to **4** is shown in Scheme 1. From the above data, the structure of **1**, named cinnafragrin A, was established as depicted.

Compound **2** was assigned a molecular formula of $C_{35}H_{50}O_{10}$, as indicated by its positive HRFABMS (*m/z* 653.3297 $[M + Na]^+$, $C_{35}H_{50}O_{10}Na$). The ^1H and ^{13}C NMR spectroscopic data of **2** were very similar to those of **1** except for the presence of an additional signal due to a methoxyl group at δ_H 3.35 (δ_C 55.2), suggesting that one of the two hydroxyl groups in **1** is methylated in **2**. The location of the methoxyl group was deduced by a HMBC experiment. Long-range correlations were observed between the acetal proton at δ_H 5.70 (s) and the methoxyl carbon, indicating that the methoxyl group must be attached at C-12′. Interestingly, the carbon signal due to the aldehyde group was at δ_C 203.6 instead of δ_C 206.0 in **1**. Moreover, the NOESY spectrum did not show any NOE correlation between H-12 and H-1′, suggesting that C-12 was in the *R*-form instead of the *S*-form as found in **1**. The configurations of C-11′and C-12′ were determined as *S* and *S*, respectively, in the same manner as described above. Thus, the structure of cinnafragrin B (**2**) was deduced as shown.



The HRFABMS of cinnafragrin C (**3**) gave a sodiated molecular ion peak at *m/z* 929.4650 $[M + Na]^+$, equivalent to a molecular formula of $C_{51}H_{70}O_{14}Na$ (requires *m/z* 929.4637). The IR spectrum suggested the presence of two ester carbonyls (1741, 1735, 1238, 1228 cm^{-1}), an aldehyde (1705, 2926 cm^{-1}), an α,β-unsaturated γ-lactone (1760, 1023), and a hydroxyl group (3449 cm^{-1}). Except for the signal of a methoxyl group (δ_H 3.35), all of the resonances observed in the ^1H NMR spectrum of **2** were present in **3**, in addition to one set of signals [δ 2.05, 1.12, 1.04, and 1.00 for an acetyl methyl, CH_3-14″, CH_3-13″, and CH_3-15″ respectively; δ 5.73 (brs) and δ 4.08 (s) for two oxygen-bearing methines, and δ 4.79 and 4.59 for a hydroxymethylene (each doublet, $J = 17.0$ Hz; Table 2)] assignable to ugandensolide, previously isolated from the South American and Kenyan plants *Capsicodendron dinisii* and *Warburgia ugandensis*, respectively.[4,7] The above data coupled with the presence of a total of 17 degrees of unsaturation in the molecular

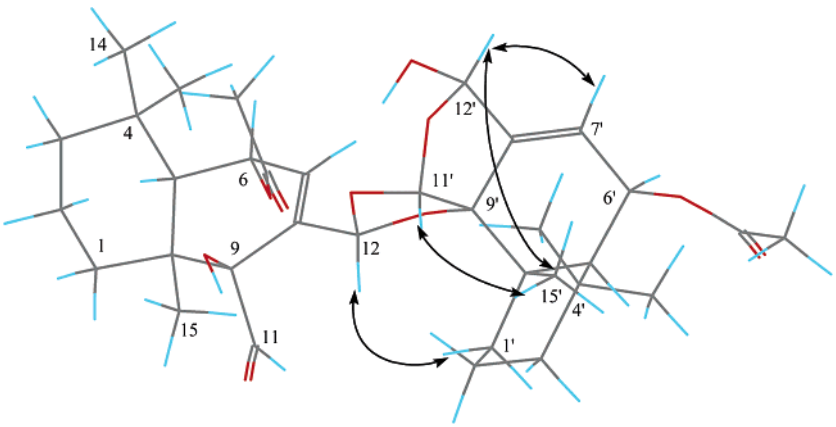
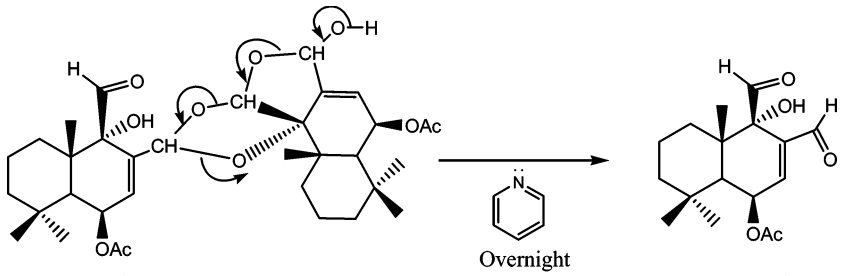


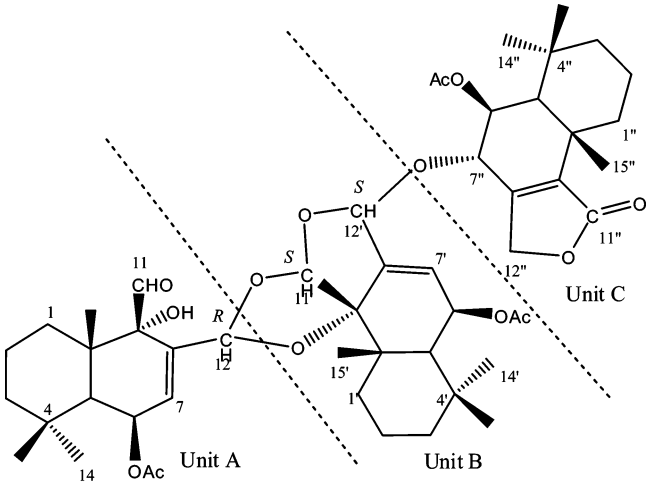
Figure 2. Important NOE correlations observed in **1**.

Scheme 1. Mechanism of Conversion of **1** to **4**



1 **4**

formula suggested that **3** is a trimeric compound having an ether linkage between **2** and ugandensolide (unit C). Resonances for 51 carbons were observed in the ^{13}C NMR spectrum of **3** (Table 2). The attachment of the ugandensolide unit at C-12′ was deduced by careful interpretation of the HMBC spectrum. A clear three-bond coupling between H-7″ (δ 4.08) and the carbon at C-12′ (δ 103.6) and the NOE cross-peak between H-7″ (δ 4.08) and H-12′ (δ 5.71) indicated that the ether linkage must be between C-12′ and C-7″. Furthermore, all of the correlations supporting the structure determination of **2** were observed in the 2D-NMR spectroscopic data of **3**, suggesting that the configurations of C-12, C-11′, and C-12′ in **3** are the same as in **2**. The equatorial orientation of H-6″ and H-7″ was substantiated by the observation of a NOE cross-peak between the acetyl group at δ 2.05 and the methyl group at C-15″ (δ 1.00) and the coupling pattern of the proton at C-7 (δ_H 4.08, singlet). Hence, the structure of **3** was deduced as shown. It is noteworthy that this is the first drimane sesquiterpene trimer found in nature.



3

The ^1H and ^{13}C NMR spectroscopic data of **5** (Table 3), as well as its physical properties, were the same as capsicodendrin reported by Mahmoud and co-workers.[7] The structure was however tentatively assigned by these authors as a cinnamodial tetramer, although the exact molecular formula was not observed and a signal reported to be at δ_H 5.26 was not discussed. The ^1H NMR spectrum of **5** showed six singlet signals at δ 5.89, 5.83, 5.74, 5.64, 5.58, and 5.25 assignable to acetals and/or hemiacetals. To determine the structure of **5**, a positive HRFABMS was obtained and a quasi-molecular ion peak at *m*/*z* 639.3122 $[M + Na]^+$, corresponding to a molecular formula of $C_{34}H_{48}O_{10}Na$ (requires 639.3123) was observed. On the basis of the above evidence, a dimeric form of **5** could be concluded. In the ^{13}C NMR spectrum, however, the presence of eight olefinic carbons (δ 140.1, 138.5, 134.7, 133.8, 128.5, 128.0, 125.0, and 124.7; four singlets and four doublets in the DEPT spectrum) together with four oxymethines (δ 66.8, 66.6, 66.1, and 66.0) and two saturated aldehydes (δ 203.5 and 203.4) were observed, suggesting the presence of two molecules similar to **2** without a methoxyl signal. Comparison of the ^{13}C NMR data of **5** with those of **2** led to the conclusion of the presence of two sets of nonmethoxylated derivatives of **2** in **5**. The results obtained by HRFABMS and the presence of two additional acetal and one additional hemiacetal carbon signal (δ 102.2, 100.2, and 97.8) suggested that capsicodendrin must be a mixture of C-12′-epimers of the C-12′-hydroxylated derivative of **2**. Interestingly, the *p*-bromobenzoyl derivatives **5a** and **5b** could be separated by reversed-phase HPLC after reaction of **5** with *p*-bromobenzoyl chloride. Compounds **5a** and **5b** have the same molecular formula (HRFABMS, *m*/*z* 821.2540 $[M + Na]^+$, $C_{41}H_{51}O_{11}Br$ requires 821.2542), suggesting that the only difference in the structure of the two compounds in the mixture was the orientation of the esterified hydroxyl group. The ^1H NMR spectrum of the two products also showed that they are epimers. Therefore, compound **5** was oxidized with pyridinium chlorochromate (PCC). A single compound (cinnafragrolide, **6**) was obtained, and the structure was established by ^1H and ^{13}C NMR (see Experimental Section) and X-ray crystallographic analysis (Figure 3) to be the C-12′ lactone derivative of **2**. Thus, the structure of capsicodendrin should be revised as a mixture of two C-12′-epimers of 12′-hydroxycinnafragrin B.

Table 2. ^1H NMR Spectroscopic Data of Compound **3** (600 MHz, in $CDCl_3$)[a]

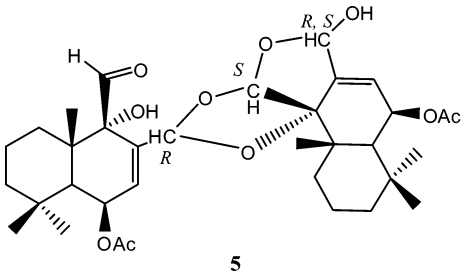
position	δ_H	δ_C	position	δ_H	δ_C
Unit A			8′		134.4
1a,	1.28−1.36, m	44.0	9′		80.3
2a	1.15, m	32.7	10′		36.8
2b	1.82, brd (14.0)		11′	5.60, s	105.0
3a,b	1.56−1.64, m	18.0	12′	5.71, brs	103.6
4		33.8	13′	1.48, s	20.7
5	1.91, d (5.2)	46.0	14′	1.13, s	23.3
6	5.65, m	66.8	15′	1.00, s	32.7
7	5.89, brd (3.5)	125.4	CH_3C═O	2.09, s	21.4
8		137.9	CH_3C═O		170.1
9		90.0			
10		41.7	Unit C		
11	9.76, s	203.1	1″a,b	1.38−1.48, m	42.8
12	5.70, s	100.1	2″a	1.04, m	33.1
13	1.34, s	20.0	2″b	1.83, brd (14.0)	
14	1.12, s	24.6	3″a,b	1.60, m	18.3
15	1.00, s	32.1	4″		33.5
CH_3C═O	2.08, s	21.6	5″	1.53, brs	49.0
CH_3C═O		170.0	6″	5.73, brs	70.5
OH	3.85, s		7″	4.08, s	72.8
			8″		151.1
Unit B			9″		139.1
1′a,b	1.28−1.42, m	44.6	10″		35.3
2′a	1.22−1.27, m	31.7	11″		171.4
2′b	1.88, m		12″a	4.79, d (17.0)	69.8
3′a,b	1.56−1.64, m	17.8	12″b	4.59, d (17.0)	
4′		33.7	13″	1.04, s	19.5
5′	1.96, d (4.4)	44.2	14″	1.12, s	24.4
6′	5.66, m	66.0	15″	1.00, s	32.6
7′	6.44, dd (5.2, 1.0)	128.2	CH_3C═O	2.05, s	21.4
			CH_3C═O		170.8

[a] Assignments based on the HSQC, COSY, and HMBC NMR spectra.

Table 3. ^{13}C NMR Spectroscopic Data for Compound **5** (150 MHz, in $CDCl_3$)

position	δ_C[a]	δ_C[b]
Unit A		
1	44.0	44.2
2	32.7, 32.7	32.8
3	18.0	18.1
4	33.6, 33.6	33.8, 33.9
5	46.3, 46.0	46.5, 46.3
6	66.8, 66.6	67.1, 66.9
7	125.0, 124.7	124.9, 124.6
8	140.1, 138.5	140.3, 139.0
9	90.4, 90.0	90.6, 90.5
10	41.8, 41.8	41.9
11	203.5, 203.4	203.5, 203.4
12	104.7, 100.2	104.8, 100.6
13	20.0. 20.0	20.0
14	24.6. 24.6	24.7. 24.4
15	32.2, 32.1	32.2
$CH_3C{=}O$	21.6, 21.6	21.6
$CH_3C{=}O$	170.0, 170.0	170.0, 170.0
Unit B		
1′	44.6, 44.6	44.8, 44.6
2′	31.8, 31.6	32.2, 31.9
3′	17.8, 17.8	17.9
4′	33.8, 33.8	33.9, 33.8
5′	44.4, 44.4	44.4, 44.4
6′	66.1,66.0	66.4,66.3
7′	128.4, 128.0	128.5, 128.0
8′	134.7, 133.8	135.1, 134.3
9′	80.3, 80.3	80.5
10′	36.8, 36.7	37.0
11′	102.2, 100.0	102.3, 100.3
12′	98.5, 97.8	98.6, 98.0
13′	19.6, 19.6	19.6
14′	24.3.24.3	24.7.24.4
15′	32.7, 32.7	32.6
$CH_3C{=}O$	21.5, 21.4	21.4
$CH_3C{=}O$	170.0, 170.0	170.0, 170.0

[a] Assigned on the basis of comparison of the ^{13}C NMR chemical shifts of cinnafragrins A and B. [b] Data obtained from Mahmoud et al.[7]



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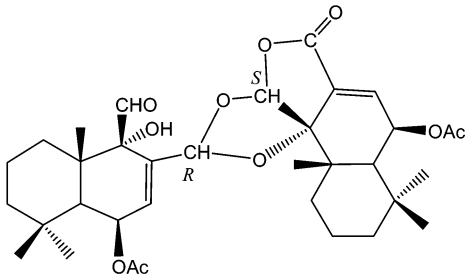

6

All of the previously investigated species belonging to the four genera (except *Pleodendron*) of the family Canellaceae contain cinnamodial (**4**), together with other drimane sesquiterpene dialdehydes and/or lactones.[2−5,7,9−11] δ-Tocotrienol has been isolated for the first time from a species in this family. The presence of these compounds in these plants supports their traditional uses, and the dimeric and trimeric compounds, cinnafragrins and capsicodendrin, may play important roles as biologically active substances. *Canella* and *Warburgia* are different chemically from the other two genera (*Capsicodendron* and *Cinnamosma*), since they contain coloratane sesquiterpenoids.[9,12] One phytochemical difference between *Canella* and *Warburgia* is that the latter contains flavonol glycosides.[10,13]

Unsaturated 1,4-dialdehydes are well-known pungent constituents of plants and mushrooms from the family Russulaceae. The sesquiterpenoid velutinal and velutinal esters are mild-tasting compounds found in the genus *Russula*, which enzymatically convert to the antimicrobial unsaturated dialdehyde isovalleral by physical injury. Velutinal and velutinal esters are chemical defense compounds of *Russula* species, and the presence of hemiacetal and acetal functions in their structures is very important for rapid enzymatic reaction in response to injury.[8] By a similar mechanism, compounds **1**−**3** in *C. fragrans* are the source of **4** since their structures present the same functionalities as vertunal and its acetal derivative.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a JASCO DIP-1000 polarimeter with MeOH as solvent. IR spectra were measured on a Perkin-Elmer Spectrum One FT-IR spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Varian Unity 600 NMR spectrometer (600 MHz for ^1H and 150 MHz for ^{13}C) unless otherwise stated, using $CDCl_3$ as a solvent. Chemical shifts are given relative to TMS (δ 0.00) as an internal standard (^1H) and δ 77.0 (ppm) from $CDCl_3$ as a standard (^{13}C). Mass spectra were recorded on a JEOL JMS AX-500 spectrometer. Column chromatography was carried out on Sephadex LH-20 (Amersham Pharmacia Biotech) and silica gel (Kieselgel 60: 0.040−0.063, Merck). Preparative HPLC was performed using a Cosmosil reversed-phase column, JASCO 880-PU pump, JASCO 875-UV UV detector, and ERC-7512 Erma CR Inc. RI detector. RP-18 F_{254S} (20 × 20 cm) was used for preparative TLC.

Plant Material. *Cinnamosma fragrans* was collected in Lakato (near Moramanga, Madagascar) in June 2005 by Fr. R. Maminiaina Romuald and L.H. and identified by comparison with the authentic sample in the Herbarium of PBZT (Parc Botanique et Zoologique de Tsimbazaza, Antananarivo, Madagascar). A voucher specimen (LivCF2005) was deposited at the Faculty of Pharmaceutical Sciences, Tokushima Bunri University.

Extraction and Isolation. Powdered *C. fragrans* (160 g) was extracted with MeOH (2 L) at room temperature for one week. The extract was filtered and concentrated in vacuo to yield a brown residue. A white precipitate (D-mannitol) was obtained by dissolving the brown extract in methanol. The remaining extract was evaporated and suspended in water before partition with ethyl acetate to give 20 g of a residue. The latter was divided into seven fractions by column chromatography on silica gel (solvent system: hexane−ethyl acetate gradient, from 3:7 to 100% EtOAc). Purification of fractions 3 and 4 by ODS RP-18 column chromatography (solvent system: MeOH−H_2O, 9:1) gave compounds **4** and **5** (3.2 and 2.9 g, respectively). Fraction 5 was subjected to ODS column chromatography (MeOH−H_2O, 9:1) to give 13 subfractions (5-1 to 5-13). Compounds **1** (9.6 mg), **2** (25.2 mg), and **3** (19.3 mg) were obtained from subfractions 5-6, 5-7, and 5-12, respectively. A combination of ODS (solvent system: MeOH−H_2O, 9:1), Sephadex column chromatography (CH_2Cl_2−MeOH, 1:1), and preparative TLC (100% MeOH) of the fraction 5-2 afforded δ-tocotrienol (103.5 mg).

Cinnafragrin A (1): white powder; $[\alpha]_D^{20}$ −28 (*c* 0.3, $CHCl_3$); IR (KBr) ν_{max} 3444, 3020, 2400, 1734, 1728, 1710, 1517, 1216, 1026 cm^{-1}; ^1H NMR and ^{13}C NMR spectra (see Tables 1 and 2); positive HRFABMS *m/z* 639.3162 $[M + Na]^+$ ($C_{34}H_{48}O_{10}Na$, requires 639.3146).

Cinnafragrin B (2): amorphous powder; $[\alpha]_D^{20}$ −22 (*c* 0.4, $CHCl_3$); IR (KBr) ν_{max} 3473, 3019, 2400, 1730, 1725, 1519, 1217, 1022 cm^{-1}; ^1H NMR and ^{13}C NMR spectra (see Tables 1 and 2); positive HRFABMS *m/z* 653.3297 $[M + Na]^+$ ($C_{35}H_{50}O_{10}Na$, requires *m/z* 653.3296).

Cinnafragrin C (3): amorphous powder; $[\alpha]_D^{20}$ −8.5 (*c* 0.6, $CHCl_3$); IR (KBr) ν_{max} 3449, 2926, 1760, 1741, 1735, 1705, 1461, 1370, 1238, 1228, 1023 cm^{-1}; ^1H NMR and ^{13}C NMR spectra (Tables 3 and 4); positive HRFABMS *m/z* 929.4650 $[M + Na]^+$ ($C_{51}H_{70}O_{14}Na$, requires *m/z* 929.4637).

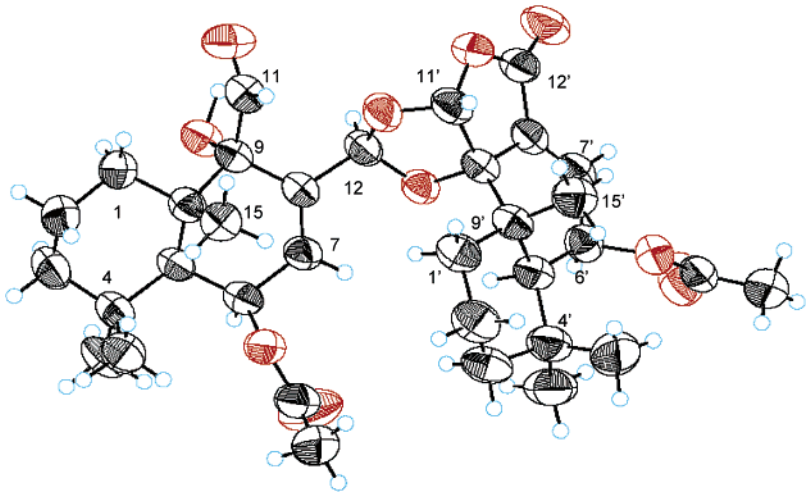

Figure 3. ORTEP drawing of compound **6**.

Capsicodendrin (5): amorphous powder; $[\alpha]_D^{20}$ −232 (*c* 0.7, $CHCl_3$); IR (KBr) ν_{max} 3453, 2943, 1467, 1032 cm^{-1}; ^{13}C NMR spectrum (see Tables 5); HRFABMS *m/z* 639.3122 $[M + Na]^+$ ($C_{34}H_{48}O_{10}Na$, requires 639.3123).

Preparation of *p*-Bromobenzoate of 5. To compound **5** (16 mg) in CH_2Cl_2 (4 mL) was added *p*-bromobenzoyl chloride (100 mg), and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and the residue partitioned between CH_2Cl_2 and H_2O. The organic layer was subjected to reversed-phase HPLC (solvent system: aqueous MeOH, 90%) to afford **5a** (10 mg) and **5b** (8 mg). **5a**: amorphous powder; positive HRFABMS *m/z* 821.2540 $[M + Na]^+$, $C_{41}H_{51}O_{11}Br$ requires 821.2542. **5b**: amorphous powder; positive HRFABMS *m/z* 821.2540 $[M + Na]^+$, $C_{41}H_{51}O_{11}Br$ requires 821.2542.

Oxidation of 5. A mixture of 30 mg of compound **5** and pyridinium chlorochromate (120 mg) in dry CH_2Cl_2 (3 mL) was stirred at room temperature for 5 h. The reaction mixture was evaporated and subjected to passage over a short column packed with silica gel (solvent system: hexane−EtOAc, 4:1) to give compound **6**.

Cinnafragrolide (6): colorless crystals; $[\alpha]_D^{22}$ −452.0 (*c* 1.9, $CHCl_3$); IR (KBr) ν_{max} 3452, 2980, 2948, 2929, 2871, 1782, 1738, 1732, 1716, 1463, 1371, 1234, 1179, 1026 cm^{-1}; ^1H NMR (300 MHz, in $CDCl_3$) δ 1.00 (3H, s, CH_3-15), 1.01 (3H, s, CH_3-14′), 1.07 (s, CH_3-13′), 1.12 (3H, s, CH_3-14), 1.14 (3H, s, CH_3-13), 1.42 (3H, s, CH_3-15′), 1.89 (1H, d, J = 4.8 Hz, H-5′), 2.03 (3H, s, CH_3C=O), 2.05 (1H, d, J = 4.6 Hz, H-5), 2.08 (3H, s, CH_3C=O), 3.90 (1H, s, OH), 5.20 (1H, s, H-11), 5.70 (1H, brt, J = 4.0 Hz, H-6′), 5.82 (1H, dd, J = 4.6 and 3.9 Hz, H-6), 5.90 (1H, s, 12-H), 6.53 (1H, brd, J = 4.8 Hz, H-7′), 6.85 (1H, dd, J = 4.0, 1.6 Hz, H-7), 9.82 (1H, s, H-11); ^{13}C NMR (75 MHz, in $CDCl_3$) δ 202.9 (C-11), 170.0 (CH_3C=*O*), 169.6 (CH_3C=*O*), 166.4 (C-12′), 138.5 (C-8), 132.8 (C-8′), 129.4 (C-7), 127.2 (C-7′), 101.2 (C-11′), 100.1 (C-12), 88.5 (C-9), 80.3 (C-9′), 66.2 (C-6), 65.9 (C-6′), 46.3 (C-5), 44.4 (C-1′ and C-5′), 44.0 (C-1), 41.9 (C-10), 37.1 (C-10′), 33.8 (C-4), 33.7 (C-4′), 32.6 (C-2, C-15′), 32.1 (C-15), 31.0 (C-2′), 24.6 (C-14), 24.3 (C-14′), 21.3 (CH_3C=O), 21.4 (CH_3C=O), 20.1 (C-13), 19.7 (C-13′), 18.0 (C-3), 17.7 (C-3′); HRFABMS *m/z* 637.7253 ($C_{34}H_{46}O_{10}Na$, requires *m/z* 637.7250).

X-ray Crystallographic Analysis of 6. Crystal data: colorless crystal; $C_{34}H_{46}O_{10}$, M_r = 614.732, orthorhombic, $P2_12_12_1$, a = 14.503-(2) Å, b = 6.4580(8) Å, c = 18.771(3) Å, α = 90.00°, β = 113.749 (5)°, γ = 90.00°, V = 1609.2(4) Å^3, Mo Kα radiation, λ = 0.71073, 3131 reflections, 398 parameters; only coordinates of H atoms refined, R(gt) = 0.0852, wR(gt) = 0.2049 (gt: intensities > 2σ), S(ref) = 1.154. Data collection: DIP image plate. Cell refinement: Scalepack (HKL). Data reduction: maXus.[14] Program used to refine structure: SHELXL-97;[15] refinement on F^2, full matrix least squares calculations. The atomic ordinates and equivalent isotropic deplacement parameters, as well as a full list of bond distances and angles and the structure factor table, are deposited as Supporting Information at the Cambridge Crystallographic Data Centre (Deposition No. CCDC 297734). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Supporting Information Available: The crystal structures of **4** and structures of ugandensolide, velutinal, velutinal esters, and isovalleral. This material is available free of charge via the Internet at http://pubs.acs.org.

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