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6-OXODENDROLASIN, 6-HYDROXYDENDROLASIN, 9-OXOFARNESOL AND 9-HYDROXYFARNESOL, STRESS METABOLITES OF THE SWEET POTATO

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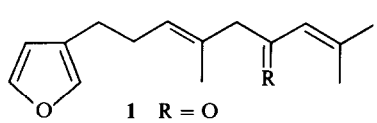
Key Word Index—*Ipomoea batatas*; Convolvulaceae; sweet potato; sesquiterpenes; stress metabolites; biosynthesis; synthesis.

Abstract—Four sesquiterpene stress metabolites, 6-oxodendrolasin, 6-hydroxydendrolasin, 9-oxofarnesol, and 9-hydroxyfarnesol have been isolated from mercuric chloride-treated sweet potatoes. The metabolites have been synthesized and feeding studies have been carried out to determine the extent of incorporation of ^{14}C-labelled 6-oxodendrolasin and 9-hydroxyfarnesol into ipomeamarone.

INTRODUCTION

For some time we have been interested in the furanosesquiterpenoid stress metabolites of the sweet potato, including their biosynthesis. We have recently isolated four new compounds from this plant which offer insight into the oxygenation sequence leading from farnesol (or farnesyl pyrophosphate) to ipomeamarone and other furanosesquiterpenes. The compounds isolated were two furans, 6-oxodendrolasin (**1**) and 6-hydroxydendrolasin (**2**), and two oxygenated farnesols, 9-oxofarnesol (**3**) and 9-hydroxyfarnesol (**4**).



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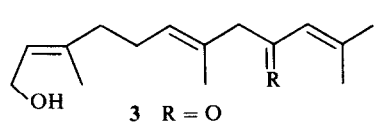
2 R = OH, H



3 R = O
4 R = OH, H

RESULTS AND DISCUSSION

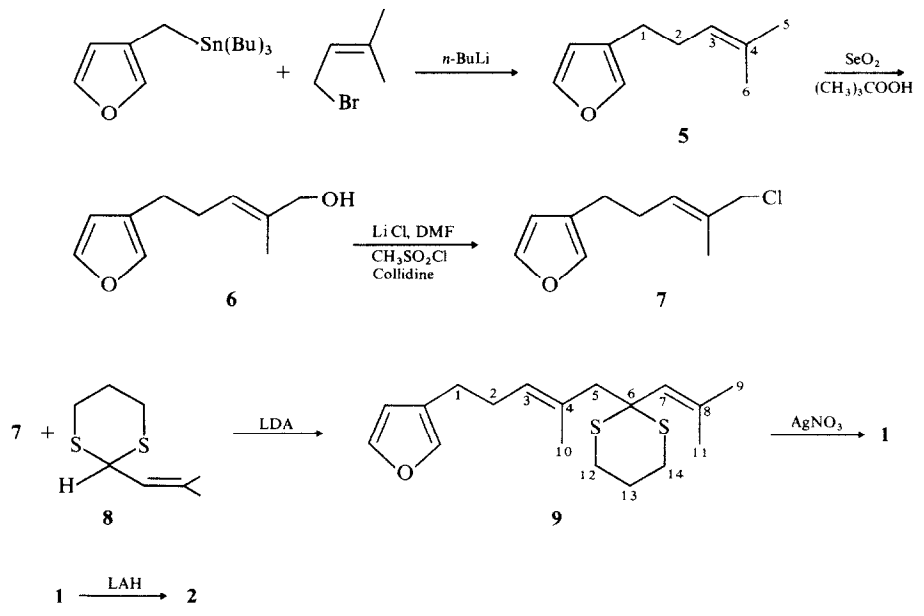
The terpenes were obtained from a methanol–methylene chloride extract of mercuric chloride-treated sweet potato slices. They were purified by short-column chromatography on Si gel followed by HPLC on μ-Porasil or C-18 μ-Bondapak columns, and their structures determined by comparing their NMR and mass spectra to those of previously isolated compounds. The final proof of their structures was provided by the syntheses described later. Approximately 8.5 mg of **1**, 1.2 mg of **2**, 0.7 mg of **3**, and 12.6 mg of **4** were isolated per kg of treated sweet potato slices. Compound **1** has been isolated from extracts of a plant of the species *Athanasia* [1] and from fusel oil from fermentation of sweet potatoes [2, 3]. Akazawa reported being unable to detect **1** in *C. fimbriata*-infected sweet potatoes [4]. Oxofarnesol (**3**) has been isolated as a nonvolatile constituent of *Cinnamonium camphora* by Hiroi and Takaoka [5]. As far as we can determine, **2** and **4** have not been isolated from any other plant source.

The synthesis of dendrolasins **1** and **2** is outlined in Scheme 1. (3-Furyl)methyl lithium, prepared via tin–lithium exchange, was reacted with 1-bromo-3-methyl-2-butene to give perillene (**5**). Oxidation of **5** with *t*-butylhydroperoxide and catalytic SeO_2 [6] gave only one alcohol, which was assumed to have structure **6** on the basis of previous studies [6, 7]. Perillene alcohol (**6**) was converted to the known allylic chloride [8] **7** via the mesylate [9]. The anion of the dithiane **8** [10] was reacted with **7** to give protected oxodendrolasin (**9**) which was treated with $AgNO_3$ to give **1**. Reduction of **1** gave **2**. The spectra of synthetic **1** and **2** were identical to those of the natural products.

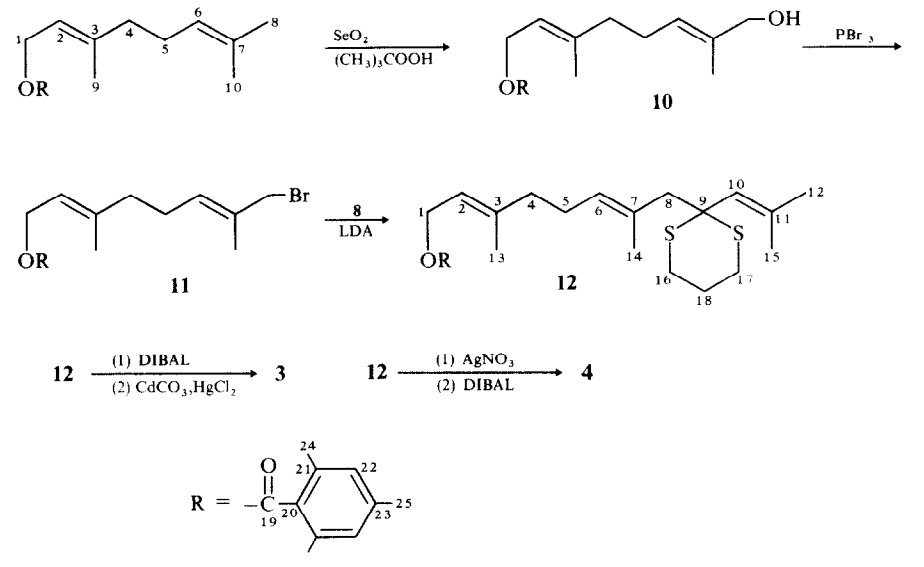
Farnesols **3** and **4** were prepared as shown in Scheme 2. Geranyl mesitoate was oxidized by the catalytic SeO_2 method to give **10**. Allylic alcohol **10** was converted to the bromide **11** which was reacted with the anion of **8** to give dithiane mesitoate **12**. Reduction of **12** followed by dithiane removal using $CdCO_3$–$HgCl_2$ gave **3**. 9-Hydroxyfarnesol was prepared by first removing the dithiane with $AgNO_3$ followed by DIBAL reduction.

The utilization of **1**–**4** as precursors of ipomeamarone (**13**) by the sweet potato was investigated by feeding studies with ^{14}C-labelled-**1** and -**4**. Radiolabelled sesquiterpenes were prepared from **8**-[methyl-^{14}C]. The labelled dithiane was prepared via addition of the ylid from methyltriphenyl phosphonium iodide-[methyl-^{14}C] to 4,4-dimethoxybutan-2-one. Acidic work-up gave 3,3-dimethyl acrolein which was subjected to BF_3 etherate-catalyzed ketalization with 1,3-propanedithiol. Compounds **1** and **4** were prepared labelled in the terminal methyl positions by using **8**-[methyl-^{14}C] in the previously described sequences.

Incorporation studies with the radiolabelled precursors were carried out using what have been standard



Scheme 1. Synthesis of 6-oxodendrolasin (**1**) and 6-hydroxydendrolasin (**2**).



Scheme 2. Synthesis of 9-oxofarnesol (**3**) and 9-hydroxyfarnesol (**4**).

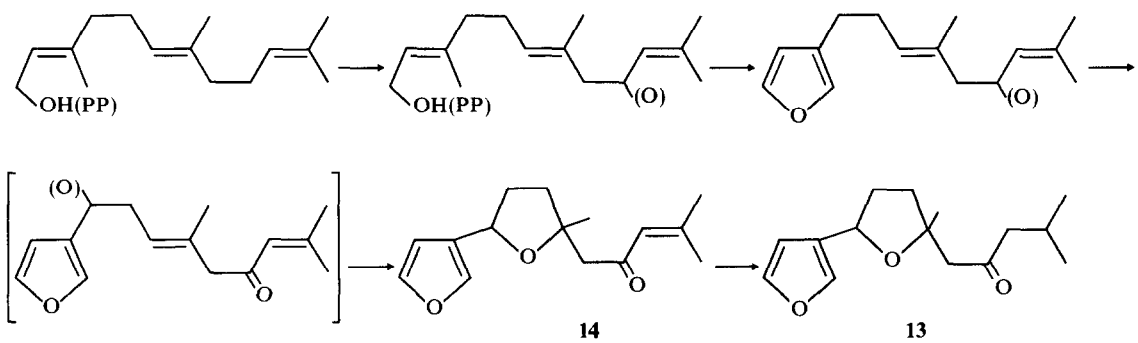
conditions in our work. The conditions are not maximized for each compound, but allow comparisons to be drawn from one feeding study to another. They also allow the isolation of enough **13** to derivatize and recrystallize to constant specific activity without adding unlabelled **13**. The labelled sesquiterpenes were added along with the $HgCl_2$ solution to sweet potato slices at a rate of 5–6 mg per 100 g of slices. Qualitatively the labelled material had no inhibitory effect on stress metabolite production. The amount of **13** formed was comparable to amounts formed in the absence of added labelled precursors. Both precursors were incorporated into **13** to an extent that is quite high for complex precursors in higher plants. In three experiments with 9-hydroxyfarnesol (**4**) the incorporation was about 2% (Table 1). Oxodendrolasin **1** was incorporated somewhat less efficiently at about 1%. In both cases the dilution values were around 500. In one experiment addition of the labelled material was delayed for 24 hr after $HgCl_2$ treatment. This delay had no significant effect on incorporation.

The isolation and incorporation studies delineate one pathway leading from farnesol to ipomeamarone which is shown in Scheme 3. In the scheme a single-bonded oxygen represents either a ketone or an alcohol. Thus, farnesol, probably as the pyrophosphate, is oxygenated at C_4 (sesquiterpene numbering) followed by furan ring formation. Furan ring formation in similar secondary

Table 1. Incorporation of ^{14}C-precursors into ipomeamarone (**13**)

Substrate	Specific activity (10^5 dpm/mmol)		Subtrate added (mg/100 g)	**13**-Isolated (mg/100 g)	Incorporation (%)	Dilution value
	Substrate	**13**				
9-Hydroxyfarnesol	1080	2.3	5.5	67	2.4	480
9-Hydroxyfarnesol	1080	4.4	5.2	31	2.3	250
9-Hydroxyfarnesol*	1080	2.3	5.2	52	2.0	470
6-Oxodendrolasin	540	0.95	5.9	34	0.94	570
6-Oxodendrolasin	540	1.0	5.9	25	0.74	540

* Substrate added 24 hr after mercuric chloride treatment.

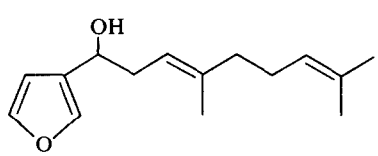


Scheme 3. Biosynthesis of ipomeamarone (**13**) from farnesol (or farnesyl pyrophosphate).

metabolites has been postulated by Sutherland and Park [12] to involve oxygenation of the methyl group, oxidation of one of the hydroxyls to an aldehyde and 1,4-dehydration of the corresponding hemiacetal. Oxygenation of the carbon next to the furan ring is postulated as the next step. Dehydroipomeamarone (**14**) would arise by conjugation of the $\Delta^{3,4}$-double bond followed by ring closure in a Michael fashion. Oguni and Uritani [11] have shown that **14** is efficiently incorporated into **13**. This scheme may not represent the only pathway leading from farnesol to **13** used by the plant, however, all but one of the precursors shown have been isolated and one compound from each of the first three stages of oxygenation has been efficiently incorporated into **13**.

We have been unable to isolate a diene with the oxygenation pattern shown in brackets in Scheme 3, however, myoporone and related 1,6-dioxygenated compounds are stress metabolites of the sweet potato [13]. Both the dienedione and the 1-hydroxy-6-oxo-compound have been synthesized (Burka, L. T. and Thorsen, A., unpublished work) but we have been unable to detect them in $HgCl_2$-stressed sweet potatoes. It may be that rearrangement of the double bond and oxygenation occurs, if not concurrently, then in such a manner that the 1,6-dioxygenated species is not released from the enzyme surface before cyclization takes place. In a synthesis of **13** via a similar Michael-like ring closure it was found that the cyclization was rapid and gave a 1:1 mixture of epimers [14]. Since only one epimer is formed by the plant, it would seem that the cyclization does take place on an enzyme surface.

Alternate pathways to that outlined in Scheme 3 could be considered. For instance, oxygenation of farnesol at C_9 (sesquiterpene numbering) and furan formation would lead to hydroxydendrolasin (**15**). A synthetic sample of **15** [15] was used to determine chromatographic parameters for this compound. No **15** was detected in stressed sweet potatoes. Another alternate pathway that involves oxygenation of farnesol at both C_9 and C_4 before furan formation would lead to intermediates like **16**. These compounds have not been isolated from sweet potatoes (or reported in any other plant). Thus far we have been unsuccessful in synthesizing them and the possibility of **16** as an intermediate remains untested.



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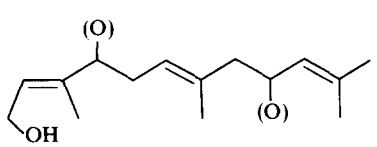

16

Hydroxyfarnesol (**4**) is somewhat more efficiently incorporated into **13** than is oxodendrolasin (**1**) under the conditions used in this work. If **1** is intermediate between **4** and ipomeamarone in the biosynthetic sequence, one might expect a higher incorporation rate of **1** than **4**. This inconsistency may arise from a preference in uptake of **4** over **1** by the plant or it may indicate a preference for a pathway with **16** as an intermediate. The resolution of this

problem as well as the exact sequence of steps involved in furan ring formation remain as problems to be solved in future studies.

EXPERIMENTAL

Infrared spectra were recorded in a Perkin-Elmer Model 727 spectrophotometer. The NMR spectra were obtained from JEOL MH100 and FX90Q instruments. Mass spectra were measured at 70 eV in an LKB Type 9000 spectrometer. HPLC was carried out on a Waters Associates ALC202 or a system comprised of Laboratory Data Control components. Waters Associates C-18μ Bondapak and μ-Porasil columns were used. Open column chromatography was carried out by the short column technique using Merck Type 60 TLC Si gel. A Beckman Model LS100 instrument was used for scintillation counting. Samples were counted for 10 min or 10^4 counts. Counting efficiency for each sample was determined by adding an aliquot of toluene-[^{14}C] and recounting. Micro-analyses were performed by Galbraith Laboratories (Knoxville, TN, U.S.A.).

Isolation of stress metabolites. Sweet potatoes were cut into 5 mm thick slices and immersed in 1% $HgCl_2$ soln for several minutes. The slices were placed in trays, covered, and left at room temp. for 3–5 days. After this time the slices were homogenized in an equal volume of MeOH. The homogenate was filtered and the solid material was rehomogenized in CH_2Cl_2 and then filtered. The CH_2Cl_2 soln was used to extract the MeOH; then dried and concd. The residue was subjected to an initial short column chromatography using EtOAc–hexane (1:1) as the solvent.

6-Oxodendrolasin (**1**) was isolated after an additional partitioning on Si gel using EtOAc–hexane (1:49) followed by HPLC on a 60 cm μ-Porasil column eluted with EtOAc–isooctane (1:49). Approximately 8.5 mg of **1** were isolated from each kg of treated sweet potato slices. IR ν_{max}^{film} cm^{-1}: 2950, 2850, 1680, 1620, 1500, 1450, 1380 and 870; ^{1}H NMR ($CDCl_3$): δ 1.62 (*s*, 3H, 10-Me), 1.88 (*s*, 3H, 9-Me), 2.17 (*s*, 3H, 11-Me), 2.2–2.6 (*m*, 4H, 1- and 2-CH_2), 3.05 (*s*, 2H, 5-CH_2), 5.33 (*br. t*, 1H, 3-CH), 6.13 (*br. s*, 1H, 7-CH), 6.33 (*s*, 1H, 4-furyl), 7.27 (*s*, 1H, 2-furyl) and 7.38 (*s*, 1H, 5-furyl); MS *m/e* (rel. int.): 232 (2), 217 (2), 151 (40), 134 (31), 84 (11), 83 (100), 55 (18).

6-Hydroxydendrolasin (**2**) was isolated after an additional chromatography on Si gel with EtOAc–hexane (1:10) followed by HPLC on a 60 cm C-18μ Bondapak column eluted with MeOH–H_2O (2:1) (1.6 ml/min). The yield of **2** was 1.2 mg per kg of treated sweet potato slices. $[\alpha]_D^{25}$ −24°, c = 1.6 MeOH. IR ν_{max}^{film} cm^{-1}: 3400, 2930, 1500, 1440, 1380, 1160, 1020, 870 and 775; ^{1}H NMR ($CDCl_3$): δ 1.65 (*s*, 3H, 10-Me), 1.68 (*s*, 3H, Me), 1.72 (*s*, 3H, Me), 2.14 (*d* on *m*, J = 6 Hz, 2H, 6-CH_2), 2.1–2.6 (*m*, 4H, 1- and 2-CH_2), 4.42 (4 line *m*, 1H, 6-CH), 5.0–5.5 (*m*, 2H, vinyl-CH), 6.28 (*s*, 1H, 4-furyl), 7.23 (*s*, 1H, 5-furyl) and 7.35 (*s*, 1H, 2-furyl). Irradiation of the multiplet at 4.42 resulted in collapse of the doublet at 2.14; the multiplet at 5.0–5.5 became a broad singlet centered at 5.2 superimposed on a triplet at 5.34. MS *m/e* (rel. int.) 234 (0.3), 216 (6), 151 (13), 150 (100), 136 (34), 135 (24), 107 (13), 84 (13) and 83 (17). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.10; H, 9.58%.

9-Oxofarnesol (**3**) was isolated after an additional partitioning on Si gel using EtOAc–hexane (3:17) followed by consecutive separations on HPLC using a 30 cm C-18μ column (H_2O–MeOH (5:2), 1.2 ml/min) and a 60 cm μ-Porasil column (EtOAc–hexane (2:3), 2 ml/min). The yield of **3** was 0.7 mg per kg of treated sweet potato slices. ^{1}H NMR ($CDCl_3$): δ 1.64 (*s*, 3H, Me), 1.70 (*s*, 3H, Me), 1.88 (*s*, 3H, Me), 2.14 (*s* on *m*, 15-Me, 4- and 5-CH_3), 3.06 (*s*, 2H, 8-CH_2), 4.13 (*d*, J = 6 Hz, 2H, 1-CH_2), 5.21 (*m*, 1H, 6-CH), 5.42 (three line *m*, 1H, 2-CH) and 6.12 (*br.s*, 1H, 10-CH); MS *m/e* (rel. int.): 236 (3), 218 (1), 149 (1), 138 (1), 121 (1), 107 (2), 93 (3), 84 (6) and 83 (100).

9-Hydroxyfarnesol (**4**) was isolated after an additional chromatography on Si gel (EtOAc–hexane, 1:2) and HPLC on a 30 cm C-18μ column using MeOH–H_2O (3:2). The yield of **4** was 12.6 mg per kg of treated sweet potato slices. IR ν_{max}^{film} cm^{-1}: 3550, 2925, 1440, 1375 and 1010; ^{1}H NMR ($CDCl_3$): δ 1.58 (*br. s*, 12H, 4 × Me), 1.88 (*br. s*, 2H, OH), 2.14 (*m*, 6H, 3 × CH_2), 4.10 (*d*, J = 7 Hz, 2H, 1-CH_2), 4.32 (*q*, J = 7 Hz, 1H, 9-CH) and 5.0–5.5 (*m*, 3H, vinyl-CH); MS *m/e* (rel. int.): 220 (2, P-H_2O), 205 (4), 136 (13), 121 (10), 107 (10), 93 (20), 85 (100) and 83 (22).

Synthesis of 6-*oxodendrolasin* (**1**) *and* 6-*hydroxydendrolasin* (**2**). 3-Furylmethyl chloride was prepared from 3-furylmethanol using an adaptation of the method of Collington and Meyers [9]. The chloride (3.3 g, 28 mmol) in 3 ml of THF was added slowly at −78° under argon to 28 mmol of tri-*n*-butylstannyllithium (prepared from tri-*n*-butyltin hydride and lithium diisopropylamide [15]. After 15 min at −78° the reaction mixture was poured into ice-water and extracted with pentane. After drying ($MgSO_4$) the solvent was removed and the residue distilled (116–9°, 0.55 torr) to give 6.4 g (61%) of (3-furyl)methyl-tri-*n*-butylstannane. IR ν_{max}^{film} cm^{-1}: 2950, 2925, 2850, 1580, 1550, 1495, 1460, 1415, 1375, 1250, 1160, 1060, 1020, 960, 870 and 760; ^{1}H NMR ($CDCl_3$): δ 0.9 (*t*, 9H, Me), 1.4 (*m*, 18H, CH_2), 2.0 (*s*, 2H, CH_2), 6.2 (*s*, 1H, furyl), 7.2 (*s*, 1H, furyl) and 7.4 (*s*, 1H, furyl). Calcd for $C_{17}H_{32}OSn$: C, 55.02; H, 8.70. Found: C, 55.12; H, 9.04%. (3-Furyl)methyl-tri-*n*-butylstannane (11.1 g, 30 mmol) was dissolved in 75 ml of THF and 75 ml of DME. The soln was cooled to −78° under N_2 and 12 ml of 2.5 M *n*-butyllithium was added. After stirring for 5 min at −78°, 3,3-dimethylallyl bromide (4.5 g, 30 mmol) was added in 15 ml of THF. The mixture was stirred at −78° for an additional 10 min then poured into 200 ml of H_2O and extracted with 2 × 200 ml of pentane. The pentane layer was washed with H_2O, then brine, dried and concd. The residue was distilled (bp 86–90°, 17 torr) to give 3.7 g (80%) of **5**. ^{1}H NMR ($CDCl_3$): δ 1.57 (*s*, 3H, Me), 1.67 (*s*, 3H, Me), 1.9–2.6 (*m*, 4H, CH_2CH_2), 5.15 (*br. t*, 1H, vinyl-CH), 6.24 (*s*, 1H, 4-furyl), 7.20 (*s*, 1H, 5-furyl) and 7.31 (*s*, 1H, 2-furyl). ^{13}C NMR ($CDCl_3$): δ 17.7 (C-6), 22.7 (C-5), 25.7 (C-1 or C-2), 28.8 (C-2 or C-1), 111.2 (4-furyl), 124.2 (C-3), 125.1 (3-furyl), 132.0 (C-4), 139.0 (2-furyl) and 142.6 (5-furyl).

The catalytic SeO_2 oxidation method of Umbreit and Sharpless [6] was adapted for the oxidation of **5**. Thus, 3.7 g (24 mmol) of **5** was added to a mixture of 12 ml of *t*-butylhydroperoxide (90%), 60 mg of SeO_2 and 420 mg of salicylic acid in 10 ml of CH_2Cl_2. The mixture was stirred at 25° for 25 hr and then diluted with 50 ml of Et_2O and extracted with 4 × 25 ml of 10% KOH. The Et_2O layer was washed with H_2O, then brine, dried and concd. Most of the remaining hydroperoxide was removed under vac. (2 torr) at room temp. Partitioning of the residue (3.7 g) on Si gel using EtOAc–hexane (1:4) as the eluent gave 1.34 g of **5**, 0.89 g of **6** (34% yield, 22% conversion), and 0.2 g of the aldehyde corresponding to **6**. IR ν_{max}^{film} cm^{-1}: 3375, 3175, 2990, 2940, 2875, 1500, 1450, 1390, 1240, 1190, 1160, 1060, 1020, 1000, 875, 870 and 730; ^{1}H NMR ($CDCl_3$): δ 1.64 (*s*, 3H, Me), 1.86 (*br.s*, 1H, OH), 2.1–2.6 (*m*, 4H, CH_2CH_2), 4.01 (*s*, 2H, 5-CH_2), 5.46 (*t*, J = 6 Hz, 1H, vinyl-CH), 6.32 (*s*, 1H, 4-furyl), 7.25 (*s*, 1H, 5-furyl) and 7.37 (*s*, 1H, 2-furyl); ^{13}C NMR ($CDCl_3$): δ 13.5 (C-6), 24.6 (C-1 or C-2), 28.0 (C-2 or C-1), 6.84 (C-5), 110.9 (4-furyl), 124.6 (3-furyl), 124.9 (C-3), 135.4 (C-4), 138.8 (2-furyl) and 142.5 (5-furyl); MS *m/e* (rel. int.): 116 (10), 105 (11), 84 (14), 83 (20), 82 (42), 81 (100) and 53 (22). Calcd for $C_{10}H_{14}O_2$: C, 72.25; H, 8.43. Found: C, 72.26; H, 8.37%.

Chloroperillene (**7**) was obtained using Collington and Meyers' method for allylic chlorides [9]. Reaction of 0.5 g of **6** gave 0.4 g (73% yield) of **7** which was used without purification.

^{1}H NMR ($CDCl_3$): δ 1.72 (*s*, 3H, Me), 2.2–2.6 (*m*, 4H, CH_2CH_2), 4.00 (*s*, 2H, 5-CH_2), 5.57 (*t*, J = 6 Hz, 1H, vinyl-CH), 6.28 (*s*, 1H, 4-furyl), 7.21 (*s*, 1H, 5-furyl) and 7.34 (*s*, 1H, 2-furyl). The IR showed no hydroxyl absorption.

2-(2′-Methylpropen-1′-yl)-1,3-dithiane (**8**) was prepared as described by Poulter and Hughes [10]. Dithiane (**8**) (310 mg, 1.8 mmol) was dissolved in 20 ml of THF; the soln was cooled, under N_2, to −50° and 1 equivalent of *n*-butyllithium was added. The yellow soln was stirred at −50° for 2 hr, then 330 mg (1.8 mmol) of **7** in 2 ml of THF was added and the soln was stirred at −50° for 2 hr. After this time the solution was poured into H_2O and extracted with pentane. The pentane solution was dried and concd. Dithiane (**9**) could not be cleanly separated from starting material **8** on Si gel (EtOAc–hexane, 1:49). Samples for analysis and spectra were prepared by HPLC using a 30 cm C-18μ column with H_2O–MeOH (1:4) as solvent. IR ν_{max}^{film} cm^{-1}: 2940, 2880, 1680, 1500, 1480, 1390, 1280, 1250, 1200, 1170, 1070, 1030, 910, 875, 780 and 730; ^{1}H NMR ($CDCl_3$): δ 1.75 (*s*, 3H, Me), 1.79 (*s*, 3H, Me), 1.98 (*s* on *m*, 5H, Me, 13-CH_2), 2.2–2.7 (*m*, 4H, 1- and 2-CH_2), 2.7–3.1 (*m*, 6H, 5-, 12- and 13-CH_2), 5.40 (*t*, J = 7 Hz, 1H, 3-vinyl CH), 5.58 (*br. s*, 1H, 7-vinyl CH), 6.34 (*s*, 1H, 4-furyl), 7.31 (*s*, 1H, 5-furyl) and 7.41 (*s*, 1H, 2-furyl); MS *m/e* (rel. int.): 322 (7), 247 (7), 175 (10), 174 (11), 173 (100), 165 (23), 99 (10) and 81 (10). Calcd for $C_{18}H_{26}OS_2$: C, 67.03; H, 8.13. Found: C, 67.35; H, 8.00%.

The crude product from reaction of 330 mg of **8** as described above was treated with 700 mg of $AgNO_3$ in 5 ml of H_2O and 50 ml of EtOH at 40° for 2 hr. After this time the mixture was poured into 200 ml of H_2O and extracted with pentane. The pentane was washed with H_2O, then brine, dried and concd. 6-Oxodendrolasin was isolated by prep. TLC on Si gel using EtOAc–hexane (1:9) as eluent (80 mg, 19%). The ^{1}H NMR and IR spectra of synthetic **1** were identical to those of the natural product. ^{13}C NMR ($CDCl_3$): δ 16.5 (C-10), 20.7 (C-11), 24.8 (C-1 or C-2), 27.6 (C-9), 28.7 (C-2 or C-1), 55.4 (C-5), 111.1 (4-furyl), 123.1 (C-7), 123.6 (C-3), 124.8 (3-furyl), 130.6 (C-4), 139.0 (2-furyl), 142.6 (5-furyl), 155.4 (C-8) and 199.0 (C-6).

Synthetic **1** (50 mg) was treated with an excess of LAH in Et_2O. After work-up of the reaction with satd Na_2SO_4, the Et_2O soln was dried and concd to give a quantitative yield of **2** with ^{1}H NMR and IR spectra identical to the natural product. ^{13}C NMR ($CDCl_3$): δ 16.3 (C-10), 18.1 (C-11), 24.8 (C-1 or C-2), 25.7 (C-9), 28.7 (C-2 or C-1), 48.2 (C-5), 66.1 (C-6), 110.9 (4-furyl), 124.7 (3-furyl), 127.7 (C-3 and C-7), 132.5 (C-4), 134.7 (C-8), 133.9 (2-furyl) and 142.7 (5-furyl).

Synthesis of 9-oxofarnesol (**3**) *and 9-hydroxyfarnesol* (**4**). Geranyl mesitoate was oxidized to allylic alcohol **10** with SeO_2 according to the method of Umbreit and Sharpless [6]. The ester (9.2 g, 30.7 mmol) was added at room temp. to 10 ml of CH_2Cl_2 containing SeO_2 (0.08 g, 0.72 mmol), salicyclic acid (490 mg, 3.6 mmol) and 90% *t*-butylhydroperoxide (13.8 ml). The soln was left at room temp. for 27 hr. C_6H_6 (25 ml) was added and the CH_2Cl_2 removed *in vacuo*. Et_2O was added, followed by extraction with several volumes of H_2O. The organic layer was dried and concd. Excess *t*-butylhydroperoxide was removed under vacuum. The residue was chromatographed on Si gel with EtOAc–hexane (3:17) to give 2.9 g (30%) of alcohol **10**. ^{1}H NMR ($CDCl_3$): δ 1.66 (*s*, 3H, Me), 1.76 (*s*, 3H, Me), 2.13 (*m*, 2H, 4- or 5-CH_2), 2.28 (*s* on *m*, 11H, 3 × aryl-Me, 4- or 5-CH_2), 3.16 (*br. s*, 1H, OH), 3.96 (*s*, 2H, 8-CH_2), 2.86 (*d*, 2H, 1-CH_2), 5.3–5.6 (*m*, 2H, 2- and 6-CH) and 6.84 (*s*, 2H, aryl-CH).

Allylic alcohol **10** (2.65 g, 8.4 mmol) was dissolved in 15 ml of dry Et_2O and treated with PBr_3 (0.33 ml, 3.5 mmol) at 0° for 4 hr. The reaction was quenched with ice-water and extracted with pentane. The pentane soln was dried and concd. The crude bromo compound **11** was used immediately without further purification. ^{1}H NMR ($CDCl_3$): δ 1.72 (*s*, 6H, Me), 2.08 (*m*, 2H, 4- or 5-CH_2), 2.29 (*s* on *m*, 11H, 3 × aryl-CH_3, 4- or 5-CH_2), 3.94 (*s*, 2H, 8-CH_2), 4.83 (*d*, 2H, 1-CH_2), 5.4–5.7 (*m*, 2H, 2- and 6-CH) and 6.86 (*s*, 2H, aryl-CH).

n-Butyllithium (9.5 mmol) was added to thioacetal **8** (1.65 g, 9.5 mmol) in 10 ml of dry THF at −40°. The mixture was maintained at −25° for 2 hr. After cooling to −78°, bromo compound **11** was slowly added. After 2 hr at −78°, the mixture was stored at −15° overnight. The soln was poured into H_2O and extracted with Et_2O. The Et_2O soln was dried and concd. The crude product (3.4 g, 86%) was used without further purification. An analytical sample was obtained by HPLC on a 60 cm μ-Porasil column with EtOAc–hexane (1:49) (1.5 ml/min). IR ν_{max}^{film} cm^{-1}: 2950, 1720, 1610, 1440, 1380, 1260, 1170, 1080, 1040, 900 and 850; ^{1}H NMR ($CDCl_3$): δ 1.67 (*s*, 3H, Me), 1.73 (*s*, 6H, 2 × Me), 1.90 (*s* on *m*, 5H, 4- or 5-CH_2, CH_3), 2.12 (*m*, 4H, 4- or 5-CH_2, 16-CH_2), 2.28 (*s*, 9H, 3 × aryl-CH_3), 2.6–3.0 (*m*, 6H, 8-, 15- and 17-CH_2), 4.82 (*d*, 2H, 1-CH_2), 5.2–5.6 (*m*, 3H, 2-, 6- and 10-CH) and 6.8 (*s*, 2H, aryl-CH); MS *m/e* (rel. int.): 473 (14), 472 (46), 175 (9), 174 (11), 173 (100), 165 (20), 164 (6), 136 (12), 147 (48), 146 (12), 135 (7), 119 (27), 117 (11), 115 (7), 111 (6), 107 (13), 106 (6), 105 (13), 104 (6), 103 (8), 99 (27), 93 (15), 12 (6) and 91 (34). Calcd for $C_{28}H_{40}O_2S_2$: C, 71.14; H, 8.53. Found: C, 71.38; H, 8.78%.

Dithiane mesitoate (**12**) (578 mg, 1.22 mmol) in 15 ml of Et_2O was treated with 5 mmol of diisobutylaluminum hydride (DIBAL) at room temp. for 4 hr. Excess DIBAL was destroyed with MeOH, followed by satd Na_2SO_4. The mixture was filtered and the Et_2O soln concd. The crude dithiane alcohol was dissolved in 20 ml of Me_2CO and added to a suspension of $CdCO_3$ (0.4 g, 2.4 mmol) and $HgCl_2$ (560 mg, 2.4 mmol) in 1 ml of H_2O. After 4.5 hr at room temp. the mixture was filtered. The filtrate was diluted with H_2O and extracted with Et_2O. The Et_2O soln was dried and concd. Compound **3** was isolated from the residue by HPLC on a 60 cm μ-Porasil column with EtOAc–hexane (1:1) (1.3 ml/min) as solvent. The 9-oxofarnesol obtained (58 mg, 20%) gave ^{1}H NMR and MS identical to the natural product. ^{13}C NMR ($CDCl_3$): δ 16.1 (C-13 or C-14), 16.5 (C-14 or C-13), 20.6 (C-15), 26.4 (C-5), 27.6 (C-12), 29.1 (C-4), 55.1 (C-8), 59.3 (C-1), 123.1 (C-10), 124.1 (C-2), 128.7 (C-6), 130.0 (C-7), 139.0 (C-3), 155.5 (C-11) and 199.2 (C-9).

$AgNO_3$ (750 mg, 4.4 mmol) in 4 ml of H_2O was added slowly to dithiane **12** (1.0 g, 2.1 mmol) in EtOH at 40°. After 2 hr at 40°, the mixture was filtered, poured into brine and extracted with pentane. The residue obtained from drying and concn of the pentane soln was dissolved in 15 ml of Et_2O and treated with 12 mmol of DIBAL at room temp. After 4 hr the reaction was worked up as above. Prep. TLC on Si gel (EtOAc–hexane, 2:1) gave 120 mg (24%) of **4**. The ^{1}H NMR and IR spectra of synthetic **4** were identical to those of the natural product. ^{13}C NMR ($CDCl_3$): δ 15.9 (C-13 or C-14), 16.2 (C-14 or C-13), 18.1 (C-15), 25.7 (C-12), 25.9 (C-5), 39.2 (C-4), 48.2 (C-8), 59.2 (C-1), 65.5 (C-9), 124.6 (C-2), 127.5 (C-6 or C-10), 128.1 (C-6 or C-10), 132.2 (C-11 or C-7), 134.8 (C-7 or C-11) and 138.9 (C-3). Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.66; H, 11.15%.

Synthesis of 2-(2′-*methylpropen*-1′-*yl*)-1,3-*dithiane*-[^{14}C-*methyl*] (**8**-[^{14}C]). ^{14}C-Methyltriphenylphosphonium iodide [prepared from 5.2 g (20 mmol) of triphenylphosphine and 2.8 g (20 mmol) of MeI containing 3 mCi of ^{14}C-methyl iodide] was suspended in 50 ml of THF and cooled to −30° under N_2. *n*-Butyllithium (20 mmol) was added at a rate to maintain a temperature of 0° or less. As the mixture was stirred at 0 to −28°, the solid gradually dissolved to give a yellow soln to which was added 2.64 g (20 mmol) of 4,4-dimethoxybutan-2-one. After 30 min at −30° the mixture was allowed to warm to room temp. and poured into 50 ml of pentane, filtered, and concd to 10 ml.

The crude 4,4-dimethoxy-2-methylbut-1-ene was treated with 1 ml of conc HCl to give dimethylacrolein. The dithiane was prepared [9] to give 660 mg (19%) of **1**-[^{14}C] 3.3×10^8 dpm/mmol).

The synthesis of **1** described above was repeated using 450 mg of **8**-[^{14}C](0.49×10^8 dpm/mmol) to give 87 mg of **1**-[^{14}C] after prep. TLC on Si gel (EtOAc-hexane, 1:9).

The synthesis of **4** described above was repeated using 620 mg of **8**-[^{14}C](1.1×10^8 dpm/mmol) to give 84 mg of **4**-[^{14}C] after chromatography on Si gel (EtOAc–hexane, 3:7).

Feeding studies using ^{14}C-*sesquiterpenes.* Sweet potato slices (200–300 g) were treated with 1% $HgCl_2$ soln as described above and placed on filter paper discs saturated with 1% $HgCl_2$ soln in Petri dishes. The compound being fed was suspended in 8–10 ml of H_2O containing a drop of Tween 80 and applied to the surface of the slices, usually immediately after the $HgCl_2$ treatment. The dishes were covered and allowed to stand at room temp. for 2–3 days. After this time the slices were extracted with MeOH–CH_2Cl_2 and the extract subjected to short column chromatography on Si gel (EtOAc–hexane, 1:3). The ipomeamarone isolated from the column was derivatized as the semicarbazone and recrystallized from CCl_4–hexane (usually 4–5 times) to constant specific activity.

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