African Elephant Sesquiterpenes. II. Identification and Synthesis of New Derivatives of 2,3-Dihydrofarnesol

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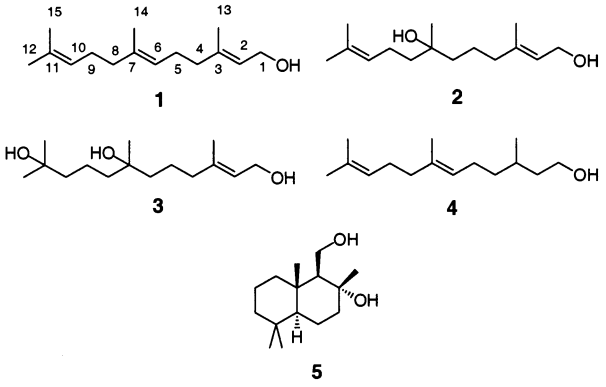
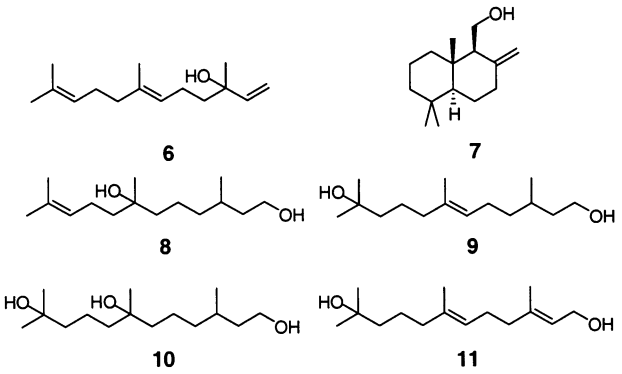
A search for potential semiochemicals revealed nerolidol (**6**), albicanol (**7**), and the new 2,3-dihydrofarnesol derivatives **8**−**10** in the temporal gland secretions of African elephants. A novel synthesis from (*E*,*E*)-farnesol (**1**) provided compounds **8**−**10** for GC−MS comparison to the natural products. This study confirms the farnesol family as frequently occurring secondary metabolites in African elephant temporal gland secretions.

Wheeler and co-workers reported the discovery of (*E*,*E*)-farnesol (**1**) and related sesquiterpenes **2** and **3** in the temporal gland secretions (TGS) of male and female African elephants (*Loxodonta africana* L.).[1] Subsequently, these compounds were observed in TGS from several male African elephants.[2] We have identified 2,3-dihydrofarnesol (**4**) and drimane-8α,11-diol (**5**) in TGS samples from a male African elephant.[3−6]



In our earlier work, triol **3** was observed as a minor component of TGS samples from one male African elephant, while farnesol (**1**) and diol **2** were not found.[3] Subsequently, we analyzed additional TGS samples from the same male and one other, as well as five female African elephants. These analyses revealed farnesol (**1**) in TGS from two males and four females and diol **2** in TGS of two males and three females. While we have not yet observed triol **3** in TGS samples from any additional elephant, compounds **4** and **5** have been found in TGS from one female and two males. These studies and the present one combine with prior work[1,2] to confirm the farnesol family as frequently occurring secondary metabolites in African elephant TGS.

We now report the identification of (*E*)-nerolidol (**6**) in TGS from two female and two male African elephants.[7] In addition, one TGS sample from a male elephant was found to contain albicanol (**7**), the first time that this compound has been observed in a mammal.[8] We also disclose the discovery in African elephant TGS of three new compounds (**8**−**10**) related to (*E*)-2,3-dihydrofarnesol (**4**). The isolation of these organic compounds from TGS was carried out by solid-phase microextraction (SPME)[9,10] or solvent extraction.[3] In the discussion below, structural assignments gleaned from gas chromatography−mass spectrometry (GC−MS) analyses will be explained. Finally, a novel synthesis of the new compounds from (*E*,*E*)-farnesol (**1**) will be described.



Our GC−MS analyses of TGS revealed several major components (apparently terpenes), for which structures could not be assigned using a variety of commercial mass spectral libraries (NIST; NBS; Wiley). Upon the basis of analysis of the fragmentation pattern of one unknown compound as briefly illustrated in Figure 1, the structure was proposed to be the 2,3-dihydrofarnesol analogue **8**. Additional unknowns were suspected to be the similar alcohols **9** and **10**, by analogy with farnesol derivatives **11** and **3**, respectively. To the best of our knowledge, compounds **8**−**10** have neither been synthesized previously nor been reported as natural products. These structural assignments were confirmed by comparison to samples synthesized as described below.

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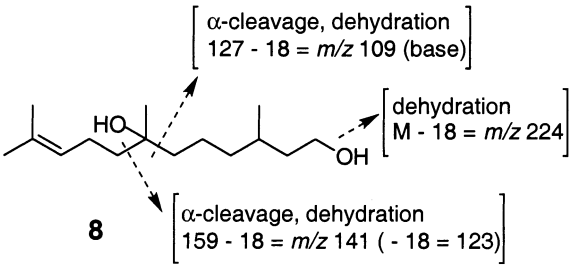

Figure 1. Proposed mass spectral fragmentation of diol **8**.

Table 1. ^{13}C NMR Spectral Data for Farnesol Derivatives **2**−**4** and **8**−**11** (δ, $CDCl_3$)[19]

carbon	2	3	4	8	9	10	11
1	59.4	59.3	61.2	61.0	61.0	60.9	59.3
2	123.9	123.9	39.9	39.9	39.9	39.7	124.0
3	139.7	139.6	29.2	29.2	29.1	29.1	139.2
4	39.9	39.8	37.1	37.6	37.1	37.5	39.4
5	22.6	18.5	25.3	22.6	25.2	18.5	26.1
6	41.7	42.3	124.5	42.1	124.9	42.1	124.3
7	72.7	72.7	135.4	72.8	134.8	72.8	135.3
8	41.6	41.4	39.7	43.1	39.9	42.3	39.9
9	22.0	21.9	26.7	21.1	22.5	21.1	22.5
10	124.7	44.3	124.7	124.6	43.3	44.3	43.3
11	131.7	71.0	131.3	131.7	71.0	70.9	71.0
12	25.5	29.2	25.5	25.6	29.2	29.3	29.1
13	16.0	16.1	19.5	19.5	19.4	19.6	16.0
14	26.8	26.9	15.8	26.7	15.7	26.9	15.7
15	17.5	29.2	17.5	17.5	29.2	29.3	29.1

A convenient synthesis was developed to provide simultaneously the three alcohols **8**−**10** via reduction of epoxide precursors. Racemic (*E*)-2,3-dihydrofarnesol (**4**)[3,11] was reacted with 30% H_2O_2 in the presence of a catalytic amount of methyltrioxorhenium (MTO),[12] followed by lithium aluminum hydride reduction.[13] This resulted in a mixture of products that included the three new TGS-derived compounds **8**−**10**, as confirmed by GC retention times and comparison of mass spectra.[14,15] This synthesis protocol would be expected to yield a mixture of all possible stereoisomers including not only racemic mixtures, but also a pair of diastereomers for each of the compounds **8** and **10**. However, the synthetic product mixture was consistently dominated by three components that exactly matched TGS-derived compounds **8**−**10** by GC−MS.

Flash chromatography[18] of the synthetic mixture provides a fraction that is seen by GC−MS to contain two major components of interest (I, III), plus a minor one (II). A more polar fraction has one GC peak (IV). On the basis of analysis of mass spectra (see the following paragraph) and ^{13}C NMR spectra (see Table 1),[19] GC peak I was attributed to diol **9**, which can exist only as a pair of enantiomers. GC peak II was attributed to the racemic minor diastereomer of diol **8** (designated **8a**), while peak III appeared to be the racemic major diastereomer of diol **8** (designated **8A**; the mass spectrum of this diastereomer matched that of the naturally derived **8**). Component IV was apparently a mixture of the two racemic diastereomers of triol **10**.

In the mass spectra of compounds **8a**, **8A**, and **10**, the base peak at *m*/*z* 109 is likely generated as shown in Figure 1 above (assuming initial dehydration of **10** to **8**). For triol **10**, abundant fragments are seen at *m*/*z* 159 and 59 as well, owing to α-cleavage of the 7,8 and 10,11 C−C bonds, respectively. The base peak of diol **9** at *m*/*z* 81 is likely due to fragment **12** (Figure 2) and is reminiscent of a well-documented fragmentation of methyl 10,11-epoxyfarnesoate, which involves two carbon−carbon bond cleavages as well as a hydrogen atom transfer.[20] Further support for this analysis is seen in the mass spectrum for the analogous farnesol derivative **11**, for which the base peak is also *m*/*z* 81.

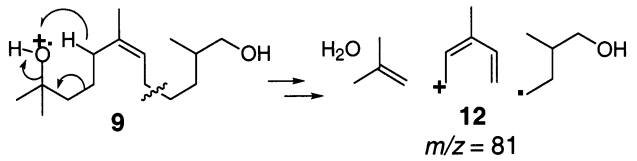

Figure 2. Proposed mass spectral fragmentation of diol **9**.

In summary, sesquiterpenes nerolidol (**6**), albicanol (**7**), and the new 2,3-dihydrofarnesol derivatives **8**−**10** have been identified for the first time in the temporal gland secretions of African elephants using solid-phase microextraction or solvent extraction, followed by gas chromatography−mass spectrometry.[21] Comparison of novel compounds was made to samples synthesized by a new route from (*E*,*E*)-farnesol (**1**). While it is possible that concentrations of specific compounds in TGS depend predictably upon such factors as elephant gender, age, and/or physiological state (e.g., estrus or musth[2]), a larger data set will be required before any definitive trends can be discerned.

The studies reported in the present work are part of a larger project to identify semiochemicals[22] that may play a role in chemical communication among the two extant species of elephants, African (*L. africana*) and Asian (*Elephas maximus* L.).[23] In addition to analysis of elephant TGS and urine,[10] secretions from elephant interdigital glands[24] and putative ear glands[25] are also under investigation. Field bioassays of the novel sesquiterpenes discussed herein are underway; results will be reported in due course.[26]

Experimental Section

General Experimental Procedures. Reagents and solvents were used as received from Fisher Scientific, Pharmco, or Sigma Aldrich Chemical Co. Commercial (*E*,*E*)-farnesol (**1**), starting material for the (*E*)-2,3-dihydrofarnesol (**4**) synthesis, and (*E*)-nerolidol (**6**) were labeled as 96% and 95% pure, respectively (Aldrich). Solutions of unpurified reaction products were dried over anhydrous Na_2SO_4. Flash chromatography[18] was carried out on Merck silica gel, grade 60, 230−400 mesh. For TLC, Bakerflex IB-F silica gel sheets were utilized. TLC visualization was carried out with an iodine chamber. FT-IR spectra were recorded on a Nicolet Magna-IR 550 spectrometer. NMR spectra were measured in $CDCl_3$ or CD_2Cl_2 containing TMS at either 300 or 400 MHz for ^1H and either 75 or 100 MHz for ^{13}C (Varian Gemini 300 or Mercury 400 spectrometer, respectively). All ^{13}C NMR data are listed in Table 1. High-resolution mass spectra were obtained on a Kratos triple sector MS-50 TA spectrometer. Sample ionization was performed by fast atom bombardment (FAB) ionization using 3-nitrobenzyl alcohol with added lithium chloride as the matrix. Accurate mass measurements were performed by peak matching with the instrument operating at a resolving power of 10 000. Reference peaks from a mixture of cesium iodide/glycerol were used for peak matching.

Animal Material, Solvent Extraction, SPME, GC−MS. All TGS samples were obtained humanely and noninvasively from live, unsedated elephants at irregular intervals from 1995 to 2001. Methods for TGS collection and storage have been described, as has the procedure for extraction with CH_2Cl_2.[3] For SPME, TGS samples (15 μL) were placed into truncated melting point capillary tubes with a microliter GC syringe. Dissolved organic compounds in TGS were adsorbed onto a 1 cm SPME fiber (100 μm poly(dimethylsiloxane) (PDMS); Supelco) at ambient temperature for 20 min, then desorbed into a GC inlet oven at 250 °C for 20 min. The GC−MS instrumentation has been described.[3] The GC capillary HP-1

column was 60 m × 0.32 mm (i.d.), with 1 μm film thickness. The column oven was programmed to hold at 45 °C for 1 min, ramp at 6 °C/min to 200 °C and hold for 10 min, then ramp at 2 °C/min to 210 °C and hold for 80 min.

(±)-6,7-Epoxy-3,7,11-trimethyl-10-dodecen-1-ol, (±)-(*E*)-10,11-Epoxy-3,7,11-trimethyl-6-dodecen-1-ol, and (±)-6,7,-10,11-Diepoxy-3,7,11-trimethyl-1-dodecanol. This procedure is based upon one by Villa et al.[27] Methyltrioxorhenium (1.4 mg, 0.0057 mmol) was dissolved in cold 30% aqueous H_2O_2 (195 μL; 1.72 mmol H_2O_2) and stirred for 5 min in an ice bath, yielding a yellow solution. This solution was added to a cold, stirred solution of (±)-(*E*)-2,3-dihydrofarnesol (**4**) (258 mg, 1.15 mmol) and pyridine (39 μL, 0.48 mmol) in CH_2Cl_2 (1.2 mL). The resulting mixture was stirred for 1.5 h in an ice/salt bath, diluted with water (2 mL), and extracted with CH_2Cl_2 (4 × 1 mL). The combined organic extracts were washed with water (3 × 2 mL), dried, and concentrated to yield the product mixture as a pale yellow oil (177 mg), which was used directly in the next reaction.

(±)-3,7,11-Trimethyl-10-dodecen-1,7-diol (8), (±)-(*E*)-3,7,11-Trimethyl-6-dodecen-1,11-diol (9), and (±)-3,7,11-Trimethyl-1,7,11-dodecanetriol (10). $LiAlH_4$ (179 mg, 4.72 mmol) was slowly added to a stirred solution of the preceding mixture of epoxides (177 mg) in anhydrous Et_2O (50 mL) in an ice bath. The solution was stirred at reflux for 2.5 h, cooled in an ice bath, then treated by slow, dropwise, sequential addition of water (177 μL), 15% aqueous NaOH (177 μL), and water (531 μL). The resulting white suspension was filtered over Celite, dried, and concentrated to yield a yellow oil (177 mg). Separation of the product by flash chromatography[18] (silica gel; 9:1 EtOAc−acetone) provided a mixture of diols **8** and **9** (0.078 mg), as well as triol **10** (0.097 g), as colorless oils. Due largely to weak and overlapping signals, unambiguous NMR spectral assignments could not be made for minor diastereomers of **8** and **10**; therefore specific peak assignments are given only for the major diastereomers. Due to some incomplete resolutions in the ^{1}H NMR spectrum of the isomer mix, some reported integrals should be viewed as approximate.

Spectroscopic data from a mixture of compounds 8 and 9: IR (neat) ν_{max} 3364, 1667, 1650 cm^{-1}; ^{1}H NMR δ 5.12 (2H, br t, $J \approx 7.1$ Hz, H-10, **8A** + H-6, **9**), 3.74−3.62 (4H, m, H-1, **8A** + **9**), 2.08−1.73 (6H, br m, H-9, **8A**, + H-5,8, **9**), 1.69, 1.63 (each 3H, s, H-12,15, **8A**), 1.59 (3H, s, H-14, **9**), 1.72−1.12 (24H, br m, H-2,3,4,5,6,8, 2 OH, **8A**, + H-2,3,4,9,10, 2 OH, **9**), 1.21 (6H, s, H-12,15, **9**), 1.17 (3H, s, H-14, **8A**), 0.91 (3H, d, J = 6.6 Hz, H-13, **9**), 0.88 (3H, d, J = 6.6 Hz, H-13, **8A**); EIMS **8A**, *m*/*z* 224 [M$^+$ − 18] (9), 123 (21), 109 (100), 95 (16), 82 (20), 81 (25), 69 (56), 55 (20), 43 (31), 41 (26); EIMS **8a**, *m*/*z* 224 [M$^+$ − 18] (4), 123 (45), 109 (100), 95 (49), 81 (75), 69 (73), 68 (39), 55 (48), 43 (52), 41 (43); EIMS **9**, *m*/*z* 224 [M$^+$ − 18] (7), 135 (22), 121 (43), 109 (40), 95 (65), 81 (100), 69 (67), 68 (46), 67 (39), 59 (29), 55 (39), 41 (43); HRFABMS *m*/*z* 249.2398 (calcd for $C_{15}H_{30}LiO_2$, 249.2406).

Spectroscopic data for compound 10: IR (neat) ν_{max} 3380 cm^{-1}; ^{1}H NMR δ 3.68 (2H, m, H-1), 1.72−1.52 (4H, br m, 3 OH, H-3), 1.50−1.24 (14H, br m, H-2, 4, 5, 6, 8, 9, 10), 1.23 (6H, s, H-12,15), 1.18 (3H, s, H-14), 0.91 (3H, d, J = 6.3 Hz, H-13); EIMS *m*/*z* 224 [M$^+$ − 18−18] (3), 159 (20), 127 (45), 123 (37), 109 (100), 95 (24), 81 (37), 71 (26), 69 (49), 59 (23), 55 (29), 43 (47); HRFABMS *m*/*z* 267.2502 (calcd for $C_{15}H_{32}LiO_3$, 267.2511).

(±)-6,7,10,11-Diepoxy-3,7,11-trimethyl-1-dodecanol. This bis-epoxidation was carried out as described above, using methyltrioxorhenium (5.4 mg, 0.022 mmol), excess 30% aqueous H_2O_2 (1.234 mL; 10.88 mmol H_2O_2), (±)-(*E*)-2,3-dihydrofarnesol (**4**) (488 mg, 2.17 mmol), and pyridine (148 μL, 1.83 mmol) in CH_2Cl_2 (2.2 mL). The product, a pale yellow oil (520 mg), was used directly in the next reaction.

(±)-3,7,11-Trimethyl-1,7,11-dodecanetriol (10). Reduction of the unpurified diepoxide (520 mg) from the previous step was carried out as described above using $LiAlH_4$ (573 mg, 15.1 mmol) in anhydrous Et_2O (50 mL). Workup provided a yellow oil (536 mg). Purification by flash chromatography[18] (silica gel; 9:1 EtOAc−acetone) provided triol **10** as a colorless liquid (424 mg, 75% over two steps). Spectral data are given above for this compound.[15]

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Supporting Information Available: Mass spectral comparisons of synthetic samples with elephant-derived compounds **6**−**10**; gas chromatogram of unpurified mixture (peaks I−IV) from epoxidation/reduction of 2,3-dihydrofarnesol (**4**); tabular report of results from SPME and solvent extraction of TGS; "typical" gas chromatogram from an SPME TGS sample. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) We have also prepared alcohols **2**, **3**, and **11** by MTO-catalyzed epoxidation of farnesol (**1**) with H_2O_2 and subsequent $LiAlH_4$ reduction. The ratio of **2**:**3**:**11** as determined by GC−MS is typically around 1.0:4.0:3.3, although some variability was observed. These compounds have been prepared previously from farnesol by MnO_2 oxidation to farnesal, followed by *m*-chloroperoxybenzoic acid epoxidation and $LiAlH_4$ reduction.[1]
(14) Triol **10** can be prepared in 75% yield (over two steps) after chromatography of the crude product from $LiAlH_4$ reduction of the unpurified epoxide mixture from reaction of (*E*)-2,3-dihydrofarnesol (**4**), catalytic MTO, and excess H_2O_2.

(15) Compounds **3** and **10** may be thought of as "dihydrates" of farnesol (**1**) and 2,3-dihydrofarnesol (**4**), respectively. As such, they are reminiscent of the natural product caparrapitriol, the analogous "6,7,-10,11-dihydrate" of nerolidol (**6**).[16] Such compounds may be classified among the "polyisoprenepolyols", some of which have elicited interest due to their properties as emulsifiers and detergents.[17]
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(19) (a) The inclusion of a comprehensive set of ^{13}C NMR spectral assignments (Table 1) is prompted by the unavailability of these data elsewhere in the literature. Assignments are based upon DEPT spectra, as well as data reported for farnesol (**1**): Bradesi, P.; Tomi, F.; Casanova, J. *Can. J. Appl. Spectrosc.* **1995**, *40*, 76−81. (b) ^{13}C NMR assignments for the major diastereomer of compound **8** (i.e., **8A**) are given in Table 1. In the 100 MHz ^{13}C NMR spectrum, additional peaks for the minor diastereomer **8a** are seen only for C-3, C-5, and C-14 (29.7, 22.9, and 26.8 ppm, respectively). Other resonances for the minor diastereomer could not be determined due to weak and/or overlapping absorbances. (c) Table 1 lists ^{13}C NMR peaks for the major diasteromer of triol **10**. As part of the 100 MHz ^{13}C NMR spectrum of triol **10**, absorbances are seen at 29.12, 29.23, 29.36, 29.46, and 29.54 ppm. The DEPT spectra reveal that these peaks represent not only C-12 and C-15 but also C-3. The large number of peaks is due not only to the presence of two diastereomers but also to the fact that C-12 and C-15 in triol **10** are diastereotopic. These carbons are diastereotopic also in compounds **3** and **9**, yet spectral differences were not discernible. Observable resonances of the minor diastereomer of triol **10** (not listed in Table 1) are δ 37.8 (C-4), 18.4 (C-5), 42.0 and 41.9 (C-6 and C-8), 21.0 (C-9), and 27.0 (C-14). Other peaks for the minor diastereomer could not be determined due to weak and/or overlapping absorbances.
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