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# 7-Epizingiberene, A Novel Bisabolane Sesquiterpene from Wild Tomato Leaves

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***Abstract.*** A $C_{15}$ hydrocarbon isolated from the leaves of 2 wild tomato species, *Lycopersicon hirsutum* f. *glabratum* PI 199381 and *Lycopersicon hirsutum* PI 365906, has been identified as 7-epizingiberene (**2**), a diastereomer of zingiberene (**1**) that occurs in essential oil of ginger. The structure assignment for **2** is based upon its $^1H$ NMR, $^{13}C$ NMR, IR, UV, and mass spectral characteristics. All spectral data for zingiberene and epizingiberene are identical except for 9 of 15 $^{13}C$ NMR resonances, which establish the diastereomeric relationship of these sesquiterpenes. The 4*S*, 7*R* stereochemistry of epizingiberene was proven by dehydrogenation to (7*R*)-$\alpha$-curcumene (**4**).

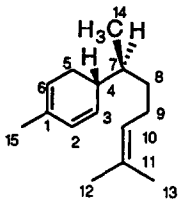
The opposite 7*R* and 7*S* stereochemistry of the zingiberenes implicates the probable occurrence of opposite sidechain rotations of a common (*S*)-bisabolyl carbocation intermediate (**10A**) to allow stereoelectronically favorable hydride shifts in their respective biosyntheses from (*E*, *E*)-farnesyl diphosphate.

The bisabolane-type sesquiterpene zingiberene (**1**) is the major constituent of ginger essential oil from the rhizomes of *Zingiber officinale* (Roscoe).[1,2,3] The structure was established by Eschenmoser and Schinz in 1950,[4a] and the 7*S* configuration at the sidechain stereocenter was proved by Arigoni and Jeger.[4b] The 4*S* stereochemistry was predicted by Mills in 1952, based on molecular rotations.[5] The credibility of this assignment is diminished by the likely presence of other optically active sesquiterpenes in purified zingiberene.[6] The 4*S*, 7*S* stereochemistry was confirmed by X-ray crystallographic structure determination of isozingiberene dihydrochloride, a bicyclic derivative of zingiberene.[7] Total syntheses of ( ) zingiberene[8] and (4*S*,7*S*) zingiberene[9,10,11] have been reported, albeit as mixtures of double bond isomers and/or diastereomers.

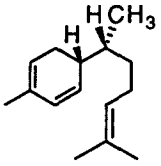
Recently, a sesquiterpene hydrocarbon present in the leaves of various wild tomato species has been identified as zingiberene on the basis of GC/MS, GC retention time, and IR spectral analysis.[12a,b,13,14] This sesquiterpene is proposed as a useful chemotaxonomic marker for certain *Lycopersicon* accessions,[12b] and it may be responsible for plant resistance to the Colorado potato beetle.[13,14]

As part of a study on the isolation and identification of kairomones from Solanaceae species for the *Helicoverpa zea* moth,[15,16] we have isolated a sesquiterpene which is evidently identical to the putative

zingiberene reported to occur in related tomato species.[12,13] However, we prove that this compound is actually the (4*S*, 7*R*) diastereomer of the zingiberene that occurs in ginger.



1



2

## ISOLATION AND STRUCTURE DETERMINATION

7-Epizingiberene was isolated from two wild tomato accessions PI 199381 and PI 365906 and purified by chromatography. The gross structure is evident from its NMR spectra (see Table 1). The $^{1}H$ NMR spectrum shows 4 vinylic protons and 4 methyl groups (2 vinyl C*H*$_3$ singlets, 1 vinyl doublet, and 1 CHC*H*$_3$ doublet). $^{13}C$ NMR APT reveals 6 vinylic carbons (2 quaternary and 4 methine), 4 methyl groups, and 3

**Table 1. $^{1}H$ and $^{13}C$ NMR Spectral Data for Zingiberene (1) and 7-Epizingiberene (2)[a]**

| Carbon No. | $^{1}H$ (400 MHz, $CDCl_3$)[b] (1) | $^{1}H$ (400 MHz, $CDCl_3$)[b] (2) | $^{13}C$ (100 MHz, $CDCl_3$)[c] (1) | $^{13}C$ (100 MHz, $CDCl_3$)[c] (2)[d] | Δδ |
|---|---|---|---|---|---|
| 1 | ---- | ---- | 131.22 | 131.22 | 0.00 |
| 2 | 5.65 (dd, *J* = 9.8, 2.9 Hz,1H) | 5.64 (dd, *J* = 9.8, 2.9 Hz, 1H) | 128.17 | 127.82 | 0.35 |
| 3 | 5.78 (dt, *J* = 9.8, 2.0 Hz,1H) | 5.78 (dt, *J* = 9.8, 2.0 Hz,1H) | 129.71 | 131.08 | -1.37 |
| 4 | 2.25 (m, 1H) | 2.28 (m, 1H) | 38.36 | 37.99 | 0.47 |
| 5 | 2.04 (m, 2H) | 2.04 (m, 2H) | 34.10 | 34.22 | -0.12 |
| 6 | 5.44 (s, 1H) | 5.45 (s, 1H) | 124.81 | 124.78 | 0.03 |
| 7 | 1.17 (m, 1H) | 1.18 (m, 1H) | 35.96 | 35.96 | 0.00 |
| 8 | 1.48 (m, 2H) | 1.43 (m, 2H) | 26.31 | 25.90 | 0.41 |
| 9 | 2.04 (m, 2H) | 2.03 (m, 2H) | 25.87 | 24.33 | 0.54 |
| 10 | 5.09 (br t, *J* = 7.1 Hz, 1H) | 5.11 (br t, *J* = 7.6 Hz, 1H) | 120.57 | 120.38 | 0.19 |
| 11 | ---- | ---- | 131.08 | 131.08 | 0.00 |
| 12 | 1.58 (s, 3H) | 1.61 (s, 3H) | 16.69 | 16.53 | 0.16 |
| 13 | 1.67 (s, 3H) | 1.68 (d, 1.0 Hz, 3H) | 17.66 | 17.66 | 0.00 |
| 14 | 0.87 (d, *J* = 6.6 Hz, 3H) | 0.87 (d, *J* = 6.8 Hz, 3H) | 21.11 | 21.11 | 0.00 |
| 15 | 1.70 (d, *J* = 1.7 Hz, 3H) | 1.72 (d, *J* = 1.7 Hz, 3H) | 25.72 | 25.72 | 0.00 |

a $^{1}H$ nmr spectra taken on individual compounds; $^{13}C$ nmr spectrum taken on an equimolar mixture of **1** and **2**.

b "----" indicates quaternary center with no protons.

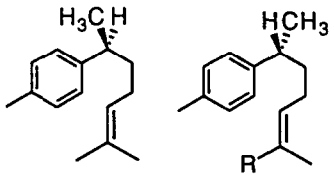
c Digital resolution was 0.0076 ppm per point. Standard deviations of chemical shifts from three different spectra were ±0.004-0.010.

d $^{13}C$ APT shows carbons 2, 3, 4, 6, 7, 10, 12, 13, 14 and 15 as (+), and carbons 1, 5, 8, 9 and 11 as (-).

methylenes, none of which are vinylic. The combination of the $^{1}H$ and $^{13}C$ NMR data indicate a monocyclic nucleus, and the UV absorption spectrum ($\lambda_{max}$ 262 nm) is consistent with a homoannular diene. The IR spectrum of the tomato sesquiterpene is essentially identical to a published spectrum of a GC-purified sample of zingiberene from ginger essential oil,[17] and the optical rotation ($[\alpha]_D$-76.1°)is similar to that reported for zingiberene ($[\alpha]_D$-67.2°).[4a]

An authentic specimen of zingiberene was isolated from ginger essential oil for direct comparisons. Although the purity was only 72% after repeated chromatography, it was nevertheless sufficient to obtain good quality $^{1}H$ and $^{13}C$ NMR spectra and for GC comparisons. The $^{1}H$ NMR spectra of the tomato and ginger sesquiterpenes (Table 1) are virtually identical, the two compounds exhibit coincident retention times on capillary GC, and they have superimposible GC/MS. Although the $^{13}C$ NMR spectra are very similar, significant differences in chemical shifts are discernible in 7-8 resonances. The diastereomeric relationship of the sesquiterpenes from tomato and ginger was proven unequivocally by the $^{13}C$ NMR spectrum of a 1:1 mixture of the two compounds, which displayed 24 distinct signals. $^{13}C$ NMR chemical shift differences ($\Delta\delta_C$ = -1.37 to + 0.03) are observed for 5 of the 6 ring carbons as well as four side chain carbons ($\Delta\delta_C$ = 0.16 to 0.54).

(-)-(*R*)-(*ar*)-Curcumene (**4**) and (-)-(*R*)-(*ar*)-curcumen-12-oic acid(**5**) were also isolated from *Lycopersicon* accession PI 199381 which suggested that all 3 sesquiterpenes have the same 7*R* side chain stereochemistry. It has been noted several times in the literature that zingiberene[18,19,20] and what we now assign as epizingiberene[12,13] undergo air oxidation to *ar*-curcumenes during steam distillation or storage. This stereochemical inference was verified by palladium/charcoal induced dehydrogenation of epizingiberene to (*R*)-(*ar*)-curcumene in refluxing benzene. Authentic samples of (*S*)-(*ar*)-curcumene (**3**) were obtained by isolation of the hydrocarbon from ginger oil and by dehydrogenation of zingiberene. The assignment of the (7*R*) stereochemistry to epizingiberene and its dehydrogenation product is based upon GC analyses on a cyclodextrin B column, which separated the enantiomeric curcumenes. We conclude that epizingiberene from tomato leaves is (4*S*, 7*R*)-bisabola-1(6), 2,10-triene (**2**).



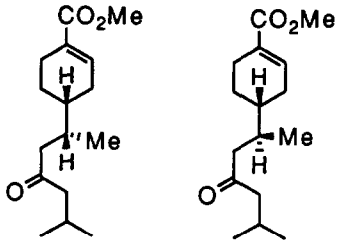

**3** **4** (R =$CH_3$)
**5** (R = COOH)

## BIOGENESIS OF ZINGIBERENE AND EPIZINGIBERENE

Zingiberene and epizingiberene are sesquiterpene analogs of the well-known monoterpene, α-phellandrene. They appear to be the only known C4/C7 diastereomeric pair of bisabolane sesquiterpenes which occur naturally at the correct oxidation level to be unmodified enzymatic cyclization products of

farnesyl diphosphate and which presumably arise by ring-to-sidechain hydride shifts.[21] Although numerous bisabolane sesquiterpenes bearing the telltale C4 and C7 hydrogens have been reported in the literature, either the stereochemistry at one or both stereocenters is unknown or uncertain, or the natural product isolated has been modified significantly by redox metabolism which could have affected the C4 or C7 positions.[22]

Juvabione (4*R*, 7*R* or *threo*: **6**) and epijuvabione (4*R*, 7*S* or *erythro*: **7**) are prominent examples of diastereomeric bisabolane sesquiterpenes.[23,24,25,26] Although the C4 and C7 stereochemistry is well established,[27,28] there is a distinct possibility that the configuration at these positions has been altered during post-cyclization transformations such as well-precedented α, β–enone reductions in the sidechain and/or double bond migration or reduction in the ring.[22]

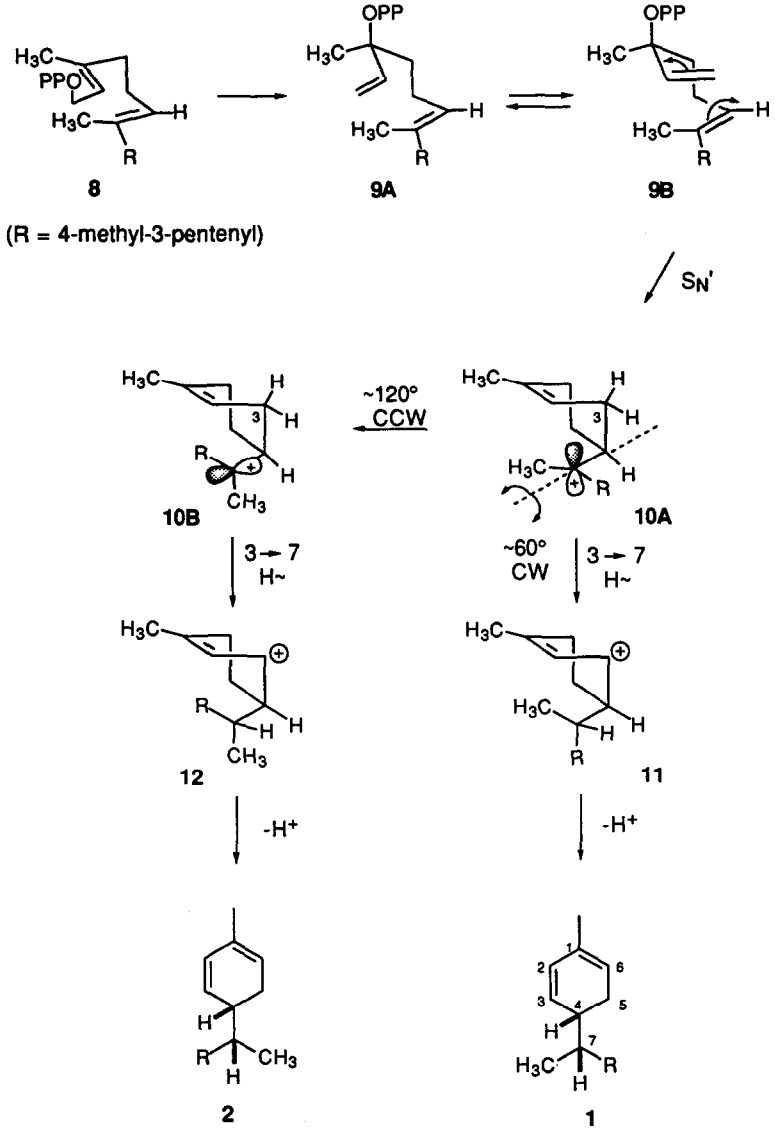



**6** **7**

The existence of zingiberene and 7-epizingiberene as naturally occurring sesquiterpenes raises interesting questions concerning the stereochemistry and mechanism of their biosynthesis. It is reasonable to assume that these similar sesquiterpenes are produced by enzymatic cyclization of (*E, E*)-farnesyl diphosphate (**8**) via its initial isomerization to the tertiary allylic isomer, nerolidyl diphosphate (**9**) (Scheme 1), a now common and experimentally supported process for numerous monoterpene cyclases[22] and for related sesquiterpene cyclases.[29,30,31,32] $S_N'$ cyclization of (*S*)-**9** in its *anti, endo,* conformation (**9B**)[33] would generate the (*S*)-bisabolyl carbocation **10A**, analogous to the cyclization of linalyl diphosphate (**9**, R = $CH_3$) in monoterpene biosynthesis. If the remaining steps in zingiberene biosynthesis parallel those determined recently for the related monoterpene, (*S*)-(-)-β–phellandrene,[34] 3,7 hydride shifts and C6 proton eliminations would complete the formation of the sidechain stereocenters and the endocyclic dienes in zingiberene and epizingiberene. Further precedent for this tandem cyclization/1, 3-hydride shift forming allylic carbocation intermediates may be found in the biosynthesis of cadalene, sativene, and longifolene sesquiterpenes.[35,29]

It is noteworthy that the 3, 7 hydride shifts must occur to the opposite *re* and *si* faces of the bisabolyl intermediate to generate the 7*S* and 7*R* sidechain stereochemistry of zingiberene and epizingiberene, respectively. While a minimal 30-60° bond CW rotation about the C4-C7 bond would presumably provide favorable orbital alignment for a 1,3-hydride shift leading to zingiberene, a maximum 120-150° CCW rotation would be required to enable the hydride shift to the opposite face on the pathway to epizingiberene. Thus, the probable occurrence of a "maximum rotation" process in epizingiberene biosynthesis is indicated.[36,37,38,39]

Several reasonable alternative mechanistic possibilities should be explicitly acknowledged. Although it is currently believed that (*E*, *E*)farnesyl diphosphate(**8**) is the usual substrate for sesquiterpene cyclases,[29,30,31,32] enzymatic cyclization of (*E*, *Z*)-**8** (R and $CH_3$ interchanged) would allow formation of epizingiberene via Scheme 1 with a minimal rotation of the sidechain. A different mechanism involving two sequential 1,2-hydride shifts has precedent in the cyclization of oxidosqualene to lanolsterol and related




Scheme1. Proposed Biogenesis of Zingiberene (**1**) and 7-Epizingiberene (**2**)

tetracyclic triterpenes,[38,39,40] and, in part, by the 4, 7 hydride shift shown to occur in sabinene hydrate biosynthesis.[41,42] Another plausible option would be a 5,7-hydride shift instead of the 3,7 shift. Finally, the possibility of proton elimination to bisabolenes[43] or sesquicarenes[44] as stable intermediates should be mentioned. Experimental evidence on the stereochemistry of the substrate and the nature of the hydrogen rearrangements in the biosynthesis of these bisabolene sesquiterpenes must await the isolation of the corresponding synthase enzymes and investigations with stereospecifically labeled substrates.

## EXPERIMENTAL

*Isolation Procedures.* Leaves of wild and cultivated *Lycopersicon* species were extracted with two, 400mL portions of hexane. The extracts were filtered, combined, and concentrated to a final concentration equivalent to extracts from 0.5 g leaf tissue per mL of hexane, and stored in a -20° C freezer for later GC analysis and oviposition bioassay. The hexane extracts were washed with 10% $Na_2CO_3$ and 10% HCl aqueous solutions, and dried over $MgSO_4$. Flash chromatography[45] of the neutral fraction on silica gel separated the alkane wax fraction from the remaining phytochemicals, and further fractionation was performed by another chromatography on 15% w/w silver nitrate silica gel. The acid fraction was esterified with diazomethane in ether, and the methyl esters were purified by chromatography on silica gel and then on 15% w/w sliver nitrate silica gel.

*General Experimental Procedures.* GC analyses were performed with a 12.5-m crosslinked methyl silicone capillary column (0.2 mm I.D., with a 0.33 mm thick 100% dimethylpolysiloxane liquid phase). GC analysis of the *ar*-curcumene enantiomers was performed on a 30-m J & W cyclodextrin B column. $^1H$ and $^{13}C$ NMR spectra were obtained on $CDCl_3$ solutions (400 MHz for $^1H$, 100 MHz for $^{13}C$) and chemical shifts were referenced to $CDCl_3$. Silver nitrate impregnated silica gel was prepared by dissolving 15 g of $AgNO_3$ in $CH_3CN$, mixing with 85 g of silica gel, and removing the solvent at reduced pressure overnight. Thin-layer plates for argentic chromatography (20 x 20 cm, 0.025 cm thick, either 10% or 15% w/w silver nitrate-silica gel) were obtained from Alltech Associates, Inc. Plates were visualized by spraying with 5% phosphomolybdic acid in 95% ethanol and heating.

*(-)-(4S,7S)-Bisabola-1(6), 2, 10-triene (Zingiberene, 1).* This compound was isolated from the essential oil of ginger, purchased locally. The oil contained approximately 42% zingiberene by GC analysis. Chromatography of 0.60 g of ginger essential oil on 15% w/w silver nitrate-silica gel provided 0.392 g of zingiberene (65% purity). Repeated chromatography on 10% and 20% w/w silver nitrate silica gel enhanced the purity of zingiberene to 72%, with three other minor components comprising 11%, 8% and 5% of the total GC peak area. GC showed co-elution with epizingiberene from PI 199381. $^1H$ and $^{13}C$ NMR spectral values are presented in Table 1.

*(-)-(4S, 7R)-Bisabola-1(6), 2,10-triene (7-Epizingiberene, 2).* This sesquiterpene was isolated by chromatography of 1.391 g of the neutral fraction of the hexane wash of *Lycopersicon hirsutum* f. *glabratum* accession number PI 199381 on silica gel, which provided 45 mg of **2** (95% purity): $[\alpha]^{26}_D$-76.1° ($CHCl_3$, 2.57 mg/mL); [lit.[3] for zingiberene, $[\alpha]_D$-67.2°, solvent unspecified]; UV $_{max}$ (pentane): 262 nm, (log e 3.29); HRMS obs. 204.1872, calcd. for $C_{15}H_{24}$, 204.1878; GC/MS (EI/70 eV) *m/e* (relative intensity): 204 ($M^+$, 13), 189(3), 161(3), 133(3), 119 (100), 109(5),105 (16), 93(92), 92(17), 91(37), 79(8), 77(30), 69(37),

56(15), 55(15); IR (neat): 2965, 2918, 2872, 1450, 1377, 3024, 727, 792, 827, 1172, 1115, 1035, 986, 1404. The IR spectrum matches that published for zingiberene,[17] and the UV spectrum matches that for zingiberene.[8] $^1H$ and $^{13}C$ NMR spectral values are given in Table 1.

*(7S)-2-Methyl-6-(4-methylphenyl)-2-heptene ((S)-(ar)-Curcumene, 3).*

*A. By isolation from ginger essential oil.* Compound **3** was isolated from ginger essential oil (70.6% purity, with one 14% impurity and 2 impurities less than 5%). Its capillary GC retention time and GC/MS match those for **4** below. The stereochemistry of this product was confirmed by chiral GC analysis of it with isolated **4**, which gave the two retention times listed below.

*B. By dehydrogenation of zingiberene.* (*S*)-(*ar*)-Curcumene was synthesized by dehydrogenation of **1** (5 mg, 75.6% purity, one impurity of 13%, another 8.6%) to 4 mg of **3** (75% purity) by the method given below for **4**. Chromatography provided 3 mg of **3** (91.3% purity by GC), whose $^1H$ NMR spectrum, capillary GC retention time, and GC/MS are identical with those for **4** below. The stereochemistry of this product was confirmed by chiral GC analysis of an equimolar mixture of it with synthetic **4**, which gave the two retention times listed below. Chiral GC analysis of an equimolar mixture of the synthetic and isolated (*R*) and (*S*) curcumenes also gave only the two peaks with the retention times given below.

*(7R)-2-Methyl-6-(4-methylphenyl)-2-heptene ((R)(-)-(ar)-Curcumene, 4). A. By isolation from leaf extracts.* This aromatic sesquiterpene hydrocarbon was isolated from *Lycopersicon hirsutum* f. *glabratum* PI 199381 (21 mg, 93% purity) HRMS obs. 202.1709, calc. for $C_{15}H_{22}$ 202.1721. $[\alpha]^{26}_D$-33.5° ($CHCl_3$, 4.33 mg/mL), [lit.[9] $[\alpha]_D$-28.7° (*c*, 2.7); lit.[46] for (S)-(+)-*ar*-curcumene $[\alpha]_D$+45.1($CHCL_3$, 0.75mg/mL)]. Identification was accomplished through comparisons of its $^1H$ and $^{13}C$ NMR spectral data and its optical rotation with those in the literature. The $^1H$ NMR and $^{13}C$ NMR data agree with the published values.[47,48] GC/MS matches that for (*ar*)-curcumene isolated from a *Lycopersicon* species accession.[14] The stereochemistry was confirmed by chiral GC analysis of an equimolar mixture of it and isolated **3**, which gave two peaks of equal area, with a retention time of 21.54 min for **4** and 21.30 min for **3**.

*B. By dehydrogenation of epizingiberene.* (*R*)-(*ar*)-Curcumene was synthesized by dehydrogenation of 18 mg of **2** in 1 mL of benzene with 70 mg of 10% Pd on charcoal (Aldrich), by the method of La Fever and Croteau (1993).[34] The reaction mixture was refluxed for 8 h. Conversion into *ar*-curcumene was 64% by GC (retention time on $Rt_X$-200, 7.46 min). The two principal byproducts (one at 7.53 min, 24.4%; the other at 7.08 min, 9%) had molecular weights of 206, indicating that they are likely formed by hydrogenation of **2**. Chromatography of 12 mg of the product mixture provided 3 mg of **4** (purity 94% by GC), whose GC/MS, capillary GC elution time, and $^1H$ NMR spectrum are identical with those of authentic **4** isolated from the plant. The stereochemistry of this product was confirmed by chiral GC of an equimolar mixture of it and *(7S)-(ar)*-curcumene (**3**) obtained from dehydrogenation of zingiberene (**1**), which gave the retention times listed above.

*(7 R)-2-Methyl-6-(4-methylphenyl)-2-heptenoic Acid. ((-)-(ar)-Curcumen-12-oic Acid, 5).* This acid was isolated by base extraction of the hexane wash of *Lycopersicon hirsutum* f. *glabratum* accession PI 199381. Esterification with diazomethane, and subsequent chromatographic fractionation first on silica gel and then on 15% w/w silver nitrate-silica gel provided 51 mg of the methyl ester of **5** (95% purity by GC). Saponification of 26 mg of the methyl ester (95% purity) in 0.7 mL of absolute EtOH with 0.10 mL of 2 M

aqueous KOH with stirring for 24 h provided 18 mg of **5** (82% purity). For the acid (82% purity), $[\alpha]^{26}_D$ -61.5°, ($CHCl_3$, 2.5 mg/mL), [Lit.[49] for synthetic (+) *ar*-curcumenoic acid, $[\alpha]_D$ + 39.0°, no solvent or concentration reported] ; HRMS obs. 232.1461, calc. for $C_{15}H_{20}O_2$, 232.1463; GC/MS (EI/70 eV) *m/e* (relative intensity): 232($M^+$, 5), 214(5), 199(4), 186(20), 172(8), 171(9), 159(20), 158(14), 146(9), 133(11), 132(12), 131(7), 120(27), 119(100), 117(9), 113(9), 105(23), 91(14). For methyl *ar*-curcumenoate (93% purity): $[\alpha]_D$ = -43.1° ($CHCl_3$, 5.0 mg/mL); GC/MS (EI/70 eV) *m/e* (relative intensity): 246($M^+$, 7), 215(4), 214(4), 186(13), 171(3), 159(22), 158(17), 156(7), 146(10), 143(7), 133(6), 132(14), 131(9), 120(18), 119(100). 117(15), 115(8), 114(8), 105(28), 101(13), 91(19), 77(6), 65(4). $^1H$ NMR δ: 1.23 (d, $J$ = 7.0 Hz, 3H),1.72 (d, 0.7 Hz, 3H), 1.69 (dt, $J$ = 6.1, 4.1 Hz, 2H), 2.04 (q, $J$ =3.1 Hz, 2H), 2.31 (s, 3H), 2.66 (sextet, $J$ = 7.0 Hz, 1H), 3.71 (s, 3H), 6.73 (dt, $J$ = 7.3, 1.4 Hz, 1H), 7.08 (dd, $J$ = 10.2, 8.1 Hz, 4H). $^{13}C$ NMR δ: 12.3, 21.0, 22.5, 26.8, 36.9, 39.1, 51.6, 126.8 (2 overlapping peaks), 127.4,129.0 (2 overlapping peaks), 135.4, 142.5, 143.6, 168.6. $^1H$ NMR data for the methyl ester show good agreement with those of (±) methyl *ar*-curcumenoate.[49]

## ACKNOWLEDGEMENT

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