Stereospecific Synthesis of Suspensolide, a Male-Produced Pheromone of the Caribbean Fruit Fly, *Anastrepha suspensa* (Loew), and the Mexican Fruit Fly, *Anastrepha ludens* (Loew)

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An efficient synthesis of (*E,E*)-4,8-dimethyl-3,8-decadien-10-olide, suspensolide, a major component of the pheromone blend of the Caribbean and Mexican fruit flies, is described. The synthesis involves dicarboalumination of 1,6-heptadiyne with *in situ* conversion to a dialanate and reaction with paraformaldehyde. Monoprotection of the symmetrical diol formed in this process as the mono-THP derivative allowed conversion of the free hydroxyl to the chloride (NCS/DMS). Addition of one carbon to the chain was achieved by displacement of the chloride by cyanide (phase-transfer conditions) or the lithium salt of a thioorthoester. Hydrolysis of the masked carbonyls and deprotection of the ω-hydroxyl gave (*E,E*)-4,8-dimethyl-10-hydroxy-3,8-decadienoic acid. This diunsaturated hydroxy acid was cyclized to suspensolide in 30% yield using Mitsunobu conditions. The overall yield of suspensolide in this eight-step synthesis was 10%.

Introduction

The Caribbean fruit fly, *Anastrepha suspensa* (Loew), and the Mexican fruit fly, *Anastrepha ludens* (Loew), are major fruit pests in Central and neotropical North America.[1] The observation that males of the genus *Anastrepha* attracted females in a process that eventually resulted to mating led to the identification of sex pheromones for these species.[2,3]

It is known that males of both species release similar mixtures of pheromones,[3] including, among others, the (*E,E*)-4,8-dimethyl-3,8-decadien-10-olide, **1**, suspensolide,[4] and the two epimeric bicyclic lactones anastrephin, **2**, and epianastrephin, **3**[3] (Figure 1).

Lactones **2** and **3** have been synthesized in racemic[5] and chiral[6] form. Suspensolide, **1**, was first prepared by the Battiste group in Florida in 1988.[7] The procedure involved two chromatographic separations of geometrical isomers of intermediates which rendered the preparation impractical for useful quantities of the pheromone. Mori and Nakazono recently also prepared **1** from geraniol in a rather lengthy process.[8]

Several strategies for the synthesis of **1** emerge from a consideration of its nearly symmetrical structure. The presence of two *E* trisubstituted olefins suggest carboalumination as a useful process in the elaboration of the carbon skeleton.[9] Our initial strategy involved the monocarboalumination of **4** while a latter and more successful strategy took advantage of dicarboalumination of this symmetrical diyne (Scheme 1). In all strategies it was envisioned that **1** would be produced by cyclization of hydroxy acid **5**.

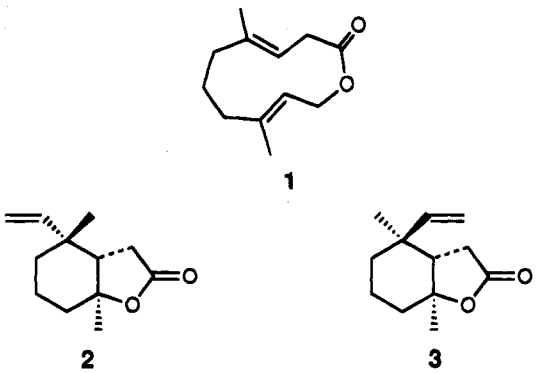

Figure 1.

Results and Discussion

Our initial approach to **1** envisioned that commercially available 1,6-heptadiyne **4** could be monocarboaluminated and elaborated to **5**. Monocarboalumination of **4** was explored using ratios of $AlMe_3$:$ZrCp_2Cl_2$:**4** in the range of 2.5–1:0.2–1:1 and a 0.1 M concentration of **4**. A 57% yield of monocarboaluminated product could be obtained using a ratio of reagents of 2:1:1.[10] When this process was extended to include conversion to the alanate and reaction with ethylene oxide the yield dropped to 30%.[10] A much better process was developed involving double carboalumination of **4** (Scheme 2). The double carboalumination of **4** was optimal using a $AlMe_3$:$ZrCp_2Cl_2$:**4** ratio of 3.5–4:1.5:1 (Table 1). *In situ* activation of the alanate with *n*-butyllithium and coupling with paraformaldehyde gave diol **6** in 85% yield. Negishi obtained an 87% yield for the carboalumination, activation, and coupling with paraformaldehyde of 6-methyl-5-hepten-1-yne using a ratio of reagents of 2:1:1.[9]

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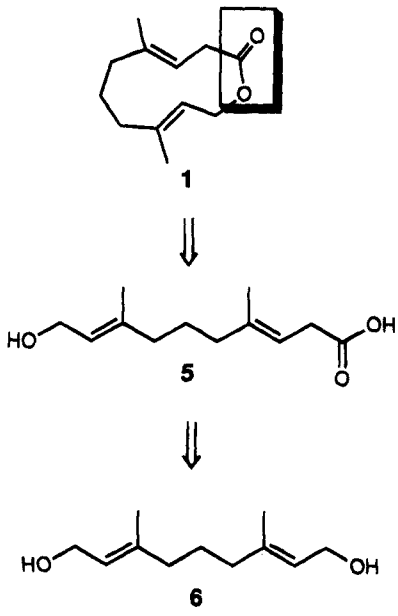
Scheme 1



Chain extension of **6** at one end required monoprotection. Several methods of monoprotection of 1,*n*-diols gave unsatisfactory results.[11] Thus, reaction of **6** with 1 equiv of NaH according to the procedure of McDougal caused precipitation. Silylation gave only 10–20% yields of the monoprotected diol. Use of butyllithium in this strategy was less successful.[12]

Monoprotection of **6** with 1 equiv of DHP using TosOH as a catalyst under high dilution conditions led to a statistical distribution of products (Scheme 2).[13] Purification of the reaction mixture by column chromatography gave the monotetrahydropyranyl derivative **7** in 70% from **6** after one recycle.

Halogenation of **7** with triphenylphosphine in carbon tetrachloride was problematic.[14] Chlorination of **7** by reaction with *N*-chlorosuccinimide and dimethyl sulfide in methylene chloride at −25 °C[15] gave **8** in 90% yield (Scheme 2).

Extension of the chain of **8** was conducted by two different methods. The first (Scheme 3) involved nucleophilic attack by cyanide anion on the allylic halide under phase-transfer conditions to give the nitrile, **9**, in 95% yield.[16]

Hydrolysis of homoallylic nitriles to the acid, without isomerization, reported by Hoye and Kurth,[17] failed in our hands. We isolated 2:1 *E*:*Z* mixtures of isomers of the corresponding carboxylic acid **10** which were identified by the ^{13}C NMR. An alternative method involved hydrolysis of the nitrile to the corresponding amide **11** in 92% using basic hydrogen peroxide under phase-transfer conditions (Scheme 3).[18]

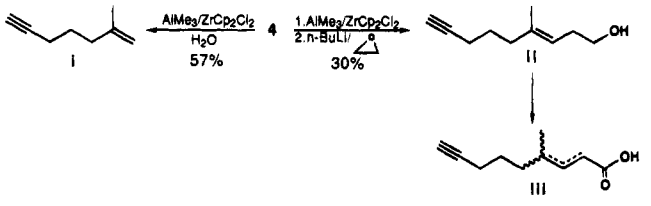
The hydrolysis of **11** as performed under very mild conditions using an aqueous solution of sodium peroxide[19] to obtain the (*E*,*E*)-carboxylic acid **10** in 90% yield.

The THP group was successfully removed with dilute aqueous acetic acid and THF.[20] After 6 h of reaction at room temperature, the (*E*,*E*)-hydroxy acid **5** was isolated in 80% yield. This corresponds to an overall yield over seven steps of 34%.

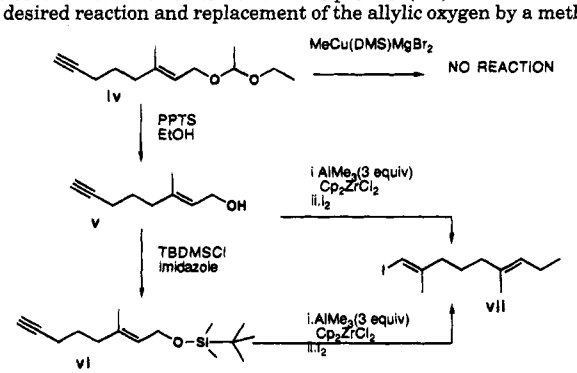
Numerous macrolactonizations were attempted on **5** in a published work,[4] with less than satisfactory results. We found that **5** lactonized in the presence of triphenylphosphine and diethyl azodicarboxylate to give **1** in 30% yield. Accompanying **1** in the reaction mixture were the two anastrephins **2** and **3** in a combined yield of 40%. The anastrephins were presumably formed by cyclization of **1** catalyzed by small amounts of acetic acid present in the hydroxy acid **5**.[21]

The ^1H and ^{13}C NMR spectra of **1** are in agreement with previously published data.[22] The ^1H NMR spectrum contains a broad band at 4.6 ppm corresponding to the C10-hydrogens consistent with conformational interconversion that is slow on the NMR time scale.[21]

(10) Quenching this reaction after 45 min led to a yield of 57% of monoaluminated product (**i**). Monoalumination followed by activation of the vinylaluminum intermediate and coupling with ethylene oxide to give **ii** was more problematic. During the solvent and catalyst removal carboalumination continued such that **ii** was obtained in 30% yield. Several attempts to oxidize **ii** to **iii** resulted in mixtures of isomers.



A second approach utilizing carbometalation of **iv**–**vi** failed. In the case of carboalumination of **v** and **vi** the product (**vii**) was derived from the desired reaction and replacement of the allylic oxygen by a methyl.



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(12) While use of 0.5 equiv of HMDS and trimethylchlorosilane gave a 1:2:2 ratio of diol to monosilylated to disilylated product the subsequent conversion of the monosilylated diol by NBS in dimethyl sulfide gave mixtures of products resulting from partial loss of the silyl group.

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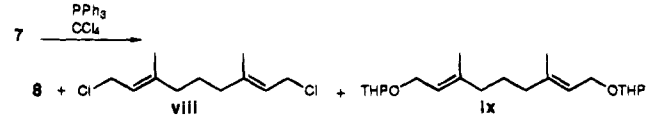
(14) Reaction of **7** with triphenylphosphine in CCl_4 unexpectedly gave a mixture of **8**, **viii**, and **ix** in a ratio of 3:1:1. Formation of **viii** probably involves reaction of triphenylphosphine dichloride with the THP analogous to that known to occur with epoxides (Oehlschlager, A. C.; Pope, P.; Thakore, A. N. *Tetrahedron* **1971**, *27*, 2617).



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Scheme 2

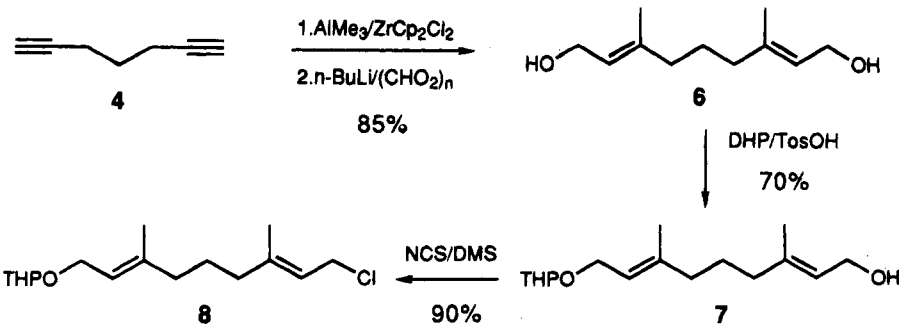
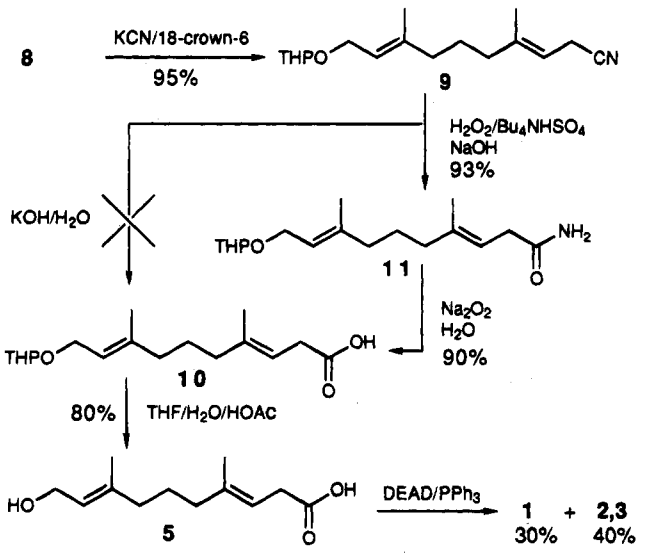


Table 1. Carboalumination, Activation, and Reaction of 1,6-Heptadiyne with Paraformaldehyde

entry	$AlMe_3$ (M)	$ZrCp_2Cl_2$[a] (M)	yield (Isolated) (%)
1	0.4	0.2	20
2	0.4	catalytic	15
3	0.5	0.3	54
4	0.7	0.3	85
5	0.8	0.3	85

[a] Concentration of 1,6-heptadiyne was 0.2 M.

Scheme 3

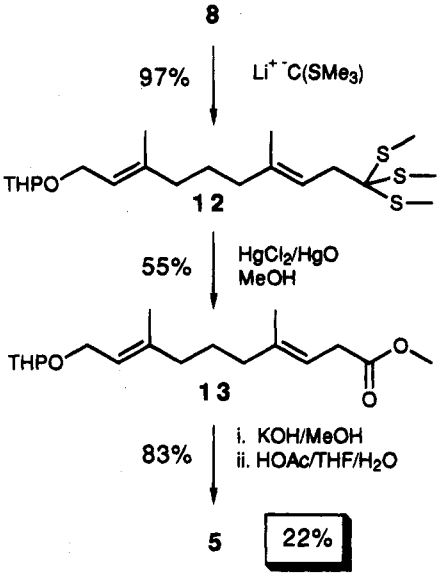


The total synthesis of suspensolide was realized in eight steps with 10% overall yield. The low yield reaction was the cyclization step. To improve this step cleavage the THP group should be conducted with PPTS in water rather than acetic acid. The former is easier to remove from **5**. Acid-free **5** would probably not yield the anastrephins when lactonized.

The second method of chain extension of **8** (Scheme 4) utilized a lithio orthothioformate as a carboxy anion equivalent.[23,24] Nucleophilic displacement of the allylic chloride was effected by the treatment with [tris(methylthio)methyl]lithium at low temperature (−70 to −60 °C) to give the alkylated orthothio ester **12** in excellent yield.

Orthothiocarboxylates are usually unmasked with NBS[25] or $HgCl_2/HgO$.[26] Because of the unsaturation in **12**, mercury(II) in methanol was employed. Addition of

Scheme 4



1 equiv of base neutralized liberated HCl and avoided isomerization. The process produced **13** in 55% yield.

Saponification of **13** with KOH in MeOH at room temperature proceeded without loss of olefin geometry. Cleavage of the THP was achieved with a solution of HOAc in THF/H_2O to give **5** in 83% yield in seven steps and an overall yield of 22%.

This is the shortest and most efficient synthesis of **1** to date.

Experimental Section

Ambiguous assignments 1D spectra were resolved on the basis of 2D H-H and C-H correlations. Elemental analyses were performed by Mr. M. Yang of the Department of Biological Sciences. Diethyl ether and THF were freshly distilled from sodium benzophenone ketyl. Dichloromethane and 1,2-dichloroethane were distilled from P_2O_5. The following reagents were dried under vacuum: NCS, 10 h at 70 °C; paraformaldehyde, 40 °C for 24 h; KCN, ground, 100 °C for 24 h. Chemicals obtained from commercial sources were used without further purification. All moisture- and air-sensitive reactions were conducted under argon. Column chromatography refers to flash chromatography using silica gel 60 (230–400-mesh E. Merck, Darmstadt).[27] Gas chromatographic analyses were conducted on a Hewlett-Packard 5881 instrument using a 30-m × 0.25-mm i.d. fused silica column coated with DB-1 with FID detection.

Preparation of (*E,E*)-3,7-Dimethyl-2,7-nonadiene-1,9-diol (6). To a solution of $ZrCp_2Cl_2$ (4.38 g, 15 mmol) in 40 mL of 1,2-dichloroethane was added trimethylaluminum (2.52 g, 3.35 mL, 35 mmol) at 0 °C. To the yellow solution thus

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obtained was added **4** (0.92 g, 1.13 mL, 10 mmol) dropwise in 10 mL of 1,2-dichloroethane at room temperature. After the mixture stirred for 3 h, volatile compounds were evaporated at reduced pressure. The residue was extracted with *n*-hexane which allowed the removal of the soluble product by filtration under inert atmosphere. To the extract at −78 °C was added *n*-butyllithium in hexane (8 mL, 2.5 M, 20 mmol). THF was added to dissolve the precipitate which formed, and paraformaldehyde (1.8 g, 60 mmol) was then added. The reaction mixture was stirred overnight, quenched with ice-cold water, and extracted with ether (3 × 50 mL). The extract was dried over anhyd $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography using ether as the eluant to give 1.56 g (85%) of **4**: IR (film) 3354, 2932, 1660, 1458, 1175, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.41 (ttq, J = 7.0, 1.5, 1.5 Hz; 2H), 4.15 (d, J = 7.0 Hz; 4H), 2.10 (H4, H6; t, J = 7.5 Hz; 4H), 1.67 (s; 6H), 1.56 (tt, J = 7.5, 7.5 Hz, 2H), 1.46 (s; 1H) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 139.57, 123.57, 59.38, 39.07, 16.5, 16.1 ppm. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.58; H, 11.02.

Preparation of (*E,E*)-3,7-Dimethyl-9(tetrahydropyran-2′-yloxy)-2,7-nonadien-1-ol (7). To a solution of **6** (2.5 g, 14 mmol) in ether (320 mL) was added 1.27 mL (1.17 g, 14 mmol) of DHP and 4.7 mg of TosOH. The solution was stirred at room temperature. Aliquots were periodically withdrawn from the reaction mixture, quenched, extracted, and analyzed by gas chromatography. When 50% of **7** was produced water (3 mL) was added and the organic phase was washed with 2% $NaHCO_3$ (25 mL) and brine (15 mL), dried over anhyd. $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by column chromatography using ether: hexane, 4:1 as the eluant. The diol isolated was recycled to give a combined yield of 2.62 g of **7** (70%): IR (film) 3415, 2940, 1667, 1440, 1382, 1353, 1321, 1261, 1199, 1183, 1117, 1076, 1024, 906, 867, 813, 733 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 5.39 (ttq, J = 6.5, 1.1, 1.1 Hz; 1H), 5.34 (ttq, J = 7.0, 1.1, 1.1 Hz; 1H), 4.60 (bt, J = 3.2 Hz; 1H), 4.22 and 4.01 (dd, J = 6.4, 11.92 Hz; 2H), 4.13 (bd, J = 6.5 Hz; 2H), 3.87 and 3.49 (m; 2H), 2.00 (bt, J = 6.7 Hz; 2H), 1.98 (t, J = 6.7 Hz; 2H), 1.65 (s; 3H), 1.61 (s; 3H), 1.54 (m; 6H), 1.47 (tt, J = 6.7, 6.7 Hz; 3H), 1.40 (s; 1H) ppm; ^{13}C NMR (C_6D_6, 100.6 MHz) δ 139.80, 139.06, 123.63, 120.77, 97.68, 63.52, 62.11, 59.10, 39.04, 38.99, 30.58, 25.51, 25.38, 19.45, 16.16, 16.02 (C11) ppm. Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.59; H, 10.52. Found: C, 71.18; H, 10.58.

Preparation of (*E,E*)-9-Chloro-3,7-dimethyl-1-(tetrahydropyran-2′-yloxy)-2,7-nonadiene (8). To a magnetically stirred solution of 1.41 g (10.56 mmol) of *N*-chlorosuccinimide in 10 mL of anhydrous CH_2Cl_2, under argon, was added dropwise at 0 °C 0.90 mL (11.52 mmol) of dimethyl sulfide. The reaction was cooled to −20 °C, and 2.41 g (9 mmol) of **7** in 5 mL of CH_2Cl_2 was added over 5 min. The resulting solution was warmed to 0 °C, stirred for 1 h, and poured in 40 mL of ice-cold brine. The aqueous phase was extracted with two 20-mL portions of ether. The combined organic phase was washed with two 20-mL portions of cold brine and dried over anhyd $MgSO_4$. Filtration and concentration *in vacuo* gave 2.32 g of **8** (90%): IR (film) 2939, 2869, 1663, 1440, 1384, 1353, 1254, 1199, 1182, 1132, 1117, 1077, 1024, 976, 906, 869, 814, 667 cm^{-1}. ^1H NMR (C_6D_6, 400 MHz) δ 5.58 (ttq, J = 6.5, 1.0, 1.0 Hz; 1H), 5.54 (ttq, J = 8.0, 1.1, 1.1 Hz; 1H), 4.77 (bt, J = 3.3 Hz; 1H), 4.46 and 4.15 (ddd, J = 6.5, 12.3; 0.6, Hz; 2H), 3.92 (H6′, axial: ddd, J = 11.0; 9.6, 3.0 Hz; 1H), 3.81 (H9: d, J = 8.0 Hz; 2H), 3.48 (dddd, J = 11.03; 4.5, 4.5, 1.2 Hz; 1H), 1.79 (bt, J = 7.2 Hz; 2H), 1.88 (bt, J = 7.6 Hz; 2H), 1.80−1.5 (m; 6H), 1.58 (s; 3H), 1.47 (m; 2H), 1.37 (s; 3H) ppm; ^{13}C NMR (C_6D_6, 100.6 MHz) δ 142.25, 138.84, 122.27, 120.98, 97.58, 63.65, 61.57, 40.82, 39.17, 39.00, 31.07, 25.98, 25.67, 19.61, 16.23, 15.6 ppm. Anal. Calcd for $C_{16}H_{27}O_2Cl$: C, 67.09; H, 9.51. Found: C, 67.20; H, 9.61.

Preparation of (*E,E*)-3,7-Dimethyl-9-(tetrahydropyran-2′-yloxy)-2,7-nonadiene 1-Cyanide (9). Into a 5-mL round bottom flask equipped with a magnetic stirring bar and under argon atmosphere were placed 0.84 g (12 mmol) of dry KCN and 2.5 mL of an acetonitrile solution containing 1.71 g of **8** (6 mmol) and 12 mg (0.045 mmol) of 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6). The two-phase system was stirred for 12 h at room temperature. Solvent removal left a residue which was tritured with 3:1 hexane/EtOAc and filtered to separate the 18-crown-6. Solvent removal left **9** as a colorless oil (3.19 g, 96%) of sufficient purity for the subsequent step. The nitrile could be purified by column chromatography using ether:hexane, 1:1, as the eluant: IR (film) 2934, 2214, 1738, 1668, 1454, 1383, 1353, 1241, 1116, 1023, 905, 869 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 5.92 (J = 6.5, 1.0, 1.0 Hz; 1H), 4.79 (ttq; J = 8.0, 1.1, 1.1 Hz; 1H), 4.76 (bt; J = 3.3 Hz; 1H), 4.46 and 4.15 (ddd; J = 6.5, 12.3, 0.6 Hz; 2H), 3.93 (ddd; J = 11.0, 9.6, 3.0 Hz; 1H), 3.47 (dddd, J = 11.03, 4.5, 4.5, 1.2 Hz; 1H), 2.23 (J = 8.0 Hz; 2H), 1.85 (J = 7.2 Hz; 2H), 1.75 (J = 7.6 Hz; 2H), 1.58 (s; 3H), 1.35 (m; 2H), 1.2 (s; 3H), 1.80−1.30 (m; 6H) ppm; ^{13}C NMR (C_6D_6, 100.6 MHz) δ 141.51, 138.74, 122.38, 118.02, 112.58, 97.74, 63.73, 61.67, 39.18, 38.76, 31.11, 25.98, 25.65, 19.45, 16.26, 15.75, 15.71 (C11) ppm. Anal. Calcd for $C_{17}H_{27}O_2N$: C, 73.61; H, 9.81; N, 5.05. Found: C, 71.34; H, 9.31; N, 5.19.

Preparation of (*E,E*)-4,8-Dimethyl-10-(tetrahydropyran-2′-yloxy)-3,8-decadienamide (11). To a magnetically stirred CH_2Cl_2 solution (2 mL) of **9** (1.29 g, 4.6 mmol) cooled in an ice bath was added 30% hydrogen peroxide (2.2 mL), tetrabutylammonium hydrogen sulfate (0.35 g, 1.0 mmol), and a 20% aqueous solution of sodium hydroxide (2 mL). The reaction mixture was allowed to warm to room temperature with stirring. After 8 h CH_2Cl_2 was added, and the organic layer was separated, washed with saturated sodium chloride solution, and dried over anhyd sodium sulfate. The solvent was removed *in vacuo* to give an oil, purified by chromatography using ether:hexane, 4:1, as the initial eluant. When the impurities were eluted the eluant was changed to ether to give 1.24 g (93%) of **11**: IR (film) 3340, 3196, 2936, 1681, 1441, 1384, 1322, 1263, 1200, 1182, 1158, 1117, 1023, 905, 869, 813 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 6.82 (bs, 2H), 5.60 (bt, J = 7.0 Hz; 1H), 5.28 (bt, J = 7.3; 1H), 4.75 (bt, J = 3.4 Hz; 1H), 4.45 and 4.15 (dd, J = 11.9; 7.1 Hz; 2H), 3.91 and 3.50 (m, 2H), δ 2.80 (d, J = 7.3 Hz; 2H), 1.95 (t, J = 7.6 Hz; 2H), 1.88 (t, J = 7.4 Hz; 2H), δ 1.62 (bs; 3H), 1.67−1.10 (m; 6H), 1.46 (m; 2H), 1.42 (bs; 3H) ppm; ^{13}C NMR (C_6D_6, 100.6 MHz) δ 173.85, 139.48, 139.15, 122.12, 117.79, 97.70, 63.74, 61.68, 39.34, 38.27, 35.64, 31.07, 26.02, 25.94, 19.54, 16.27, 15.99 (C11) ppm. Anal. Calcd for $C_{17}H_{29}O_3N$: C, 69.12; H, 9.89; N, 4.74. Found: C, 68.93; H, 10.04; N, 4.58.

Preparation of (*E,E*)-4,8-Dimethyl-10-(tetrahydropyran-2′-yloxy)-3,8-decadienecarboxylic Acid (10). (*E,E*)-4,8-Dimethyl-10-(tetrahydropyran-2′-yloxy)-3,8-decadienamide, **11** (0.5 g, 1.60 mmol), was suspended in 5 mL of water. Sodium peroxide (0.129 g, 1.29 mmol) was then added with care [the reaction can be exothermic when conducted on a large scale]. After being heated at 80 °C for 8 h, the resulting solution was cooled to 0 °C and carefully acidified to pH 5 by dropwise addition of cold 2 M HCl. The solution was extracted with CH_2Cl_2 (3 × 3 mL), and the extracts were dried over anhyd $MgSO_4$. Removal of the solvent *in vacuo* gave 0.42 g (90%) of **10**: IR (film) 3530, 2938, 1741, 1668, 1436, 1384, 1318, 1261, 1200, 1023, 906, 869, 814 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 9.0−8.0 (bs, 1H), δ 5.60 (ttq, J = 7.0, 1.1, 1.1 Hz; 1H), 5.40 (ttq, J = 7.3, 1.1, 1.1; 1H), 4.78 (bt, J = 3.3 Hz; 1H), 4.45 and 4.17 (dd, J = 12.0, 6.3 Hz; 2H), 3.92 (ddd, J = 11.0, 9.6, 3.0 Hz; 1H), 3.47 (dddd, J = 11.03, 4.5, 4.5, 1.2 Hz; 1H), 2.93 (d, J = 7.0 Hz; 2H), 1.93 (t, J = 7.5 Hz; 2H), 1.89 (t, J = 7.5 Hz; 2H), 1.60 (bs; 3H), 1.68−1.10 (m; 6H), 1.47 (m; 2H), 1.41 (bs; 3H) ppm; ^{13}C NMR (C_6D_6, 100.6 MHz) δ 170.95, 139.20, 138.88, 122.05, 115.96, 97.57, 63.72, 61.57, 39.28, 39.22, 33.58, 31.04, 25.94, 25.94, 19.56, 16.25, 16.07 ppm. Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 66.88; H, 9.44.

Preparation of (*E,E*)-10-Hydroxy-4,8-dimethyl-3,8-decadienoic Acid (5). (*E,E*)-4,8-Dimethyl-10-(tetrahydropyran-2′-yloxy)-3,8-decadienecarboxylic acid, **10** (0.30 g, 1.01 mmol), was dissolved in 10 mL of 4:2:1 acetic acid-tetrahydrofuran−water. The resulting solution was heated at 45 °C for 4 h. The mixture was extracted with three 5-mL portions of ether, and the organic phase was washed with water and brine and dried over anhyd $MgSO_4$. Concentration *in vacuo* gave 0.17 g (80%) of pure hydroxy acid **5**: IR (film) 3500, 2933, 1714, 1385, 1285, 998 cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 9.0−

8.0 (bs, 1H), 5.54 (ttq; J = 7.1, 1.2, 1.1 Hz; 1H), 5.48 (ttq J = 7.0, 1.1, 1.1; 1H), 4.01 (bd; J = 6.6 Hz; 2H), 3.00 (J = 7.0 Hz; 2H), 1.94 (t; J = 7.5 Hz; 2H), 1.91 (t; J = 7.5 Hz; 2H), 1.49 (bs; 6H), 1.47 (m; 3H) ppm; ^{13}C NMR (C_6D_6, 100.6 MHz) δ 171.69, 138.46, 137.94, 125.09, 116.95, 59.31, 39.20, 39.13, 33.95, 25.87, 16.10, 15.98 ppm.

Preparation of (*E,E*)-4,8-Dimethyl-3,8-decadien-10-olide (1). A solution of **5** (260 mg, 1.2 mmol), DEAD (0.30 mL, 1.8 mmol), and triphenylphosphine (0.47 g, 1.8 mmol) in 102 mL of anhydrous benzene was stirred at 23 °C for 12 h. Concentration of the mixture *in vacuo* followed by chromatography using ether:hexane (3:7) as the eluant gave, in order of elution, a mixture of anastrephin, **2**, epianastrephin, **3** (93 mg, 40%), and suspensolide, **5** (70 mg, 30%). Suspensolide: IR (film) 2932, 1772, 1633, 1454, 1370, 1268, 1104, 1043, 1006, 914, 770 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 5.11 (t; J = 8.0 Hz; 1H), 4.85 (t; J = 8.1 Hz; 1H), 4.62 (bs; 2H), 3.00 (bs; 2H), 2.21 (m; 4H), 1.87 (m; 2H), 1.67 (bs; 3H), 1.60 (bs; 3H) ppm; ^{13}C NMR (C_6D_6, 100.6 MHz) δ 170.4, 144.7, 142.7, 120.0, 115.9, 61.1, 41.5, 35.7, 25.6, 15.1, 14.0 ppm. Anastrephin: ^{1}H NMR (C_6D_6, 400 MHz) δ 5.27 (dd; J = 10.7, 17.4 Hz; 1H), 4.80 (H3: dd; J = 10.7, 0.9 Hz; 1H), 4.71 (dd; J = 17.4, 0.9 Hz; ^{H}), 3.00 (m; 2H), 1.95 (s; 3H), 1.47 (s; 3H), 2.10–1.55 (m; 6H) ppm. Epianastrephin: ^{1}H NMR (C_6D_6, 400 MHz) δ 5.68 (dd; J = 10.6, 17.4 Hz; 1H), 5.01 (dd; J = 10.6, 2.0 Hz; 1H), 4.87 (dd; J = 17.4, 2.0 Hz; 1H), 3.00 (m; 2H), 1.95 (s; 3H), 1.47 (s; 3H), 2.10–1.55 (m; 6H) ppm.

Preparation of (*E,E*)-Trimethyl orthothio 4,8-Dimethyl-10-(tetrahydropyran-2′-yloxy)orthothio-3,8-decadienoate (12). *n*-Butyllithium (1.7 mmol, 0.68 mL of a solution 2.5 M) was added to a solution of tris(methylthio)-methane (0.5 mL, 3.84 mmol) in 7 mL of THF. The mixture was stirred at −70 °C for 30 min, and then a solution of **8** (0.43 g, 1.5 mmol) in 6 mL of THF was added. The mixture was stirred for 4 h while the temparature increased from −70 to −20 °C. The reaction was quenched with 15 mL of saturated ammonium chloride solution at −60 °C. After the mixture was warmed to room temperature, the layers were separated and the aqueous layer was extracted with ether (2 × 15 mL). The combined organic layers were washed with brine (15 mL) and dried over anhyd $MgSO_4$. Removal of the solvent *in vacuo* gave a yellow oil which was purified by chromatography using ether:hexane (1:9) as the eluant to give 0.58 g (97%) of pure **12**: IR (film) 2918, 1666, 1434, 1383, 1261, 1199, 1183, 1132, 1116, 1023, 906,3, 869, 814 cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 5.80 (bt, J = 6.4 Hz; 1H), 5.66 (bt, J = 6.3; 1H), 4.77 (t, J = 3.3 Hz; 1H), 4.45 and 4.17 (dd, J = 12.0, 6.3 Hz; 2H), 3.91 (ddd, J = 11.0; 11.3, 3.0 Hz; 1H), 3.48 (dddd, J = 11.3, 4.4, 3.0, 1.0 Hz; 1H), 2.73 (bd, J = 6.4 Hz; 2H), 2.05 (m; 4H), 1.99 (s, 9H), 1.60 (m; 2H), 1.86–1.30 (m; 6H), 1.63 (bs; 3H), 1.57 (bs; 3H) ppm; ^{13}C NMR (C_6D_6, 100.6 MHz) δ 139.32, 137.42, 122.16, 119.65, 97.54, 83.5, 67.71, 61.55, 39.59, 39.29, 37.47, 31.11, 26.19, 26.02, 19.62, 16.45, 16.31, 13.05 ppm. Anal. Calcd for $C_{20}H_{36}O_3S_3$: C, 59.36; H, 8.97. Found: C, 59.20; H, 9.09.

Preparation of (*E,E*)-Methyl 4,8-Dimethyl-10-(tetrahydropyran-2′-yloxy)-3,8-decadienoate (13). A mixture of 200 mg (0.5 mmol) of **12**, 0.54 g (2 mmol) of mercuric chloride, and 0.108 g (0.5 mmol) of mercuric oxide in 13 mL of 12:1 methanol:water was stirred at room temperature for 4 h. The mixture was filtered, and the solid residue was washed with CH_2Cl_2 (2 × 6 mL) and saturated ammonium chloride solution (2 × 6 mL) and dried over anhyd $MgSO_4$. Removal of the solvent *in vacuo* gave 80 mg of **13** (55%): IR (film) 2918, 1666, 1434, 1383, 1261, 1199, 1183, 1132, 116, 1023, 906,3, 869, 814 (cm^{-1}; ^{1}H NMR (C_6D_6, 400 MHz) δ 5.80 (bt, J = 6.4 Hz; 1H), 5.66 (bt, J = 6.3; 1H), 4.77 (t, J = 3.3 Hz; 1H), 4.45 and 4.17 (dd, J = 12.0, 6.3 Hz; 2H), 3.91 (ddd, J = 11.0; 11.3, 3.0 Hz; 1H), δ 3.48 (dddd, J = 11.3, 4.4, 3.0, 1.0 Hz; 1H), 4.77 (d, J = 6.4 Hz; 2H), 2.05 (m; 4H), 1.99 (s; 3H), 1.60 (m; 2H), 1.86–1.42 (m; 6H), 1.63 (bs; 3H), 1.57 (m; 3H) ppm. ^{13}C NMR (C_6D_6, 100.6 MHz) δ 172.91, 139.35, 138.90, 122.05, 115.50, 97.56, 63.73, 61.60, 51.70, 39.01, 38.95, 33.45, 31.10, 25.93, 25.95, 19.50, 16.23, 16.31 ppm.

Preparation of (*E,E*)-4,8-Dimethyl-10-hydroxy-3,8-decadienoic Acid (5). (*E,E*)-Methyl 4,8-dimethyl-10-(tetrahydropyran-2′-yloxy)-3,8-decadienoate, **13** (80 mg, 0.26 mmol), was dissolved in 2.7 mL of a solution of 10% of KOH/MeOH. The mixture was stirred for 2 h at room temperature. Acidification of the reaction mixture and extraction with ether (2 × 5 mL) followed by concentration *in vacuo* gave an oil that was dissolved in 3 mL of 4:2:1 acetic acid–tetrahydrofuran–water. The resulting solution was heated at 45 °C for 4 h, and the mixture was extracted with three 5-mL portions of ether. The organic phase was washed with water and brine and dried over anhyd $MgSO_4$. Removal of the solvent *in vacuo* gave 47 mg (83%) of pure hydroxy acid **5**.

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