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SYNTHESIS AND PURIFICATION OF THE ALLOFARNESENES

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Abstract—The eight isomers of allofarnesene (3,7,11-trimethyl-2,4,6,10-dodecatetraene) were prepared using Wittig reactions. The four *E*-4 isomers could be separated using GC but the unstable *Z*-4 isomers required HPLC on silver nitrate impregnated silica gel for analysis. Purified samples of each isomer were prepared for spectral studies. The configuration of the pseudoionone (6,10-dimethyl-3,5,9-undecatriene-2-one) starting materials was also studied, confirming previous results.

During the course of our research on the trail pheromone of the red imported fire ant *Solenopsis invicta* (Buren), we prepared the eight isomers of allofarnesene for comparison and insect bioassay. Isomers of allofarnesene have previously been isolated from oil of *Perilla frutscens* f. viridis Makino,[1] ylang ylang oil,[2] and one isomer is believed to be identical to "sesquicitronellene",[3,1] but configuration assignment has been tentative or absent. We report our chromatographic and spectral studies as an aid in the identification and purification of these unusual natural products.

We first synthesized two isomers of allofarnesene using Wittig reagents prepared from geranyl and neryl bromide (Fig. 1). These gave high yields of single products on reaction with tiglic aldehyde. Previous work suggested that these products would have the *E*-4 configuration,[4] which would produce the *E,E,E* isomer from the geranyl bromide ylide and the *E,E,Z* **2** isomer from the neryl bromide ylide.

Allofarnesenes may also be prepared by reaction of triphenylphosphonium ethylide with pseudoionone (6,10-dimethyl-3,5,9-undecatriene-2-one, Figs. 1 and 2). Since knowledge of the correct isomeric composition of the pseudoionone starting materials was crucial in the correct identification of the allofarnesene products, a study of their spectral properties was undertaken. A sample of commerical pseudoionone, which is prepared by condensation of citral with acetone, was found by GC analysis on an SE 30 column to consist of two components in 30:70 ratio. NMR analysis of pure samples prepared by preparative GC showed that the component of longer retention time was identical to that prepared from pure geranial and acetone by Chen and Le Fevre.[5] This component would therefore have the *E,E* configuration **9**, while the component of shorter retention time would be the *E,Z* isomer **10**.

In a thorough study, Zakharova *et al.*[6a-f] found that the *Z*-3 pseudoionone isomers were available in high yield by thermolysis of 6,10-dimethyl-4,5,9-undecatriene-2-one[6a] on alumina. They found that the *Z*-3 compounds had a shorter GC retention time than the *E*-3 isomers and were unresolved on the GC columns used. Configuration of the C^5–C^6 double bond was determined using NMR by adding $Eu(fod)_3$ shift reagent to a mixture of *Z*-3 isomers to separate signals from the C^6 methyls. These peaks were selectively irradiated in turn and the effect of decoupling on the C^5 hydrogen signals was determined. Since a three bond allylic coupling constant would be expected to be greater for the *Z* than the *E* isomers, the major isomer, which showed greater peak heightening, was assigned the *Z,Z* configuration **12**. The minor isomer was therefore the *Z,E* compound **11**.

We also found that *Z*-3 allofarnesenes prepared by this method were inseparable on a variety of GC columns, including 50 m OV101 and carbowax 20 M capillary columns. Separation was possible, however, using silica gel HPLC (10 μm, 20 cm × 9 mm) with pentane:chloroform::85:15 as solvent. Since NMR shift reagents sometimes cause line broadening, we repeated the decoupling experiments on pure samples and the earlier results were confirmed. Further evidence was provided by the UV spectra which show lower extinction coefficients for the *Z*-5 isomers as expected (Table 1). Since NMR data on these compounds was previously only available for mixtures, which led to some ambiguity on peak position, our NMR spectra are listed in Table 2. Peak assignment is identical to that of Zakharova *et al.*

Allofarnesenes were prepared from pure pseudoionone isomers separated by the above methods and their structures determined. Gas chromatographic analysis (1% carbowax 20 M on Chromosorb G, 2 m × 4 mm) of compounds produced by reaction of **9** and **10** with triphenylphosphonium ethylide showed two components in each case, which would be expected to be isomeric around the C^2–C^3 bond.[4] The larger peak of longer retention time prepared from **9** was identical to **1** prepared earlier from the geranyl ylide, indicating that the lesser component had the *Z,E,E* configuration **2**. From **10**, the larger component of longer retention time was identical to **3** prepared from geranyl ylide, so **4** would have the *Z,E,Z* configuration.

Z-4 Allofarnesenes prepared from the *Z*-3 pseudoionones decomposed when subjected to GC analysis above 100°, even in all glass silanized systems. Although these compounds could be analyzed at low temperature by GC (Table 3), a milder separation method was needed for preparation of pure samples for analysis. HPLC using silica gel and reverse phase columns was unsuccessful in separating these compounds, since all eluted together. Finally, a 20% $AgNO_3$ on RSil (10 μm, 25 cm × 4 mm) column was prepared and used successfully, giving almost baseline separation of all four isomers. Using this column, it was again found that reaction of pure **11** and **12** with ethyl ylide gave two isomers, respectively. The major isomer in each case had a longer retention time, and, based on our earlier work, was believed to have the thermodynamically more stable *E*-2 configuration. This was confirmed by their UV

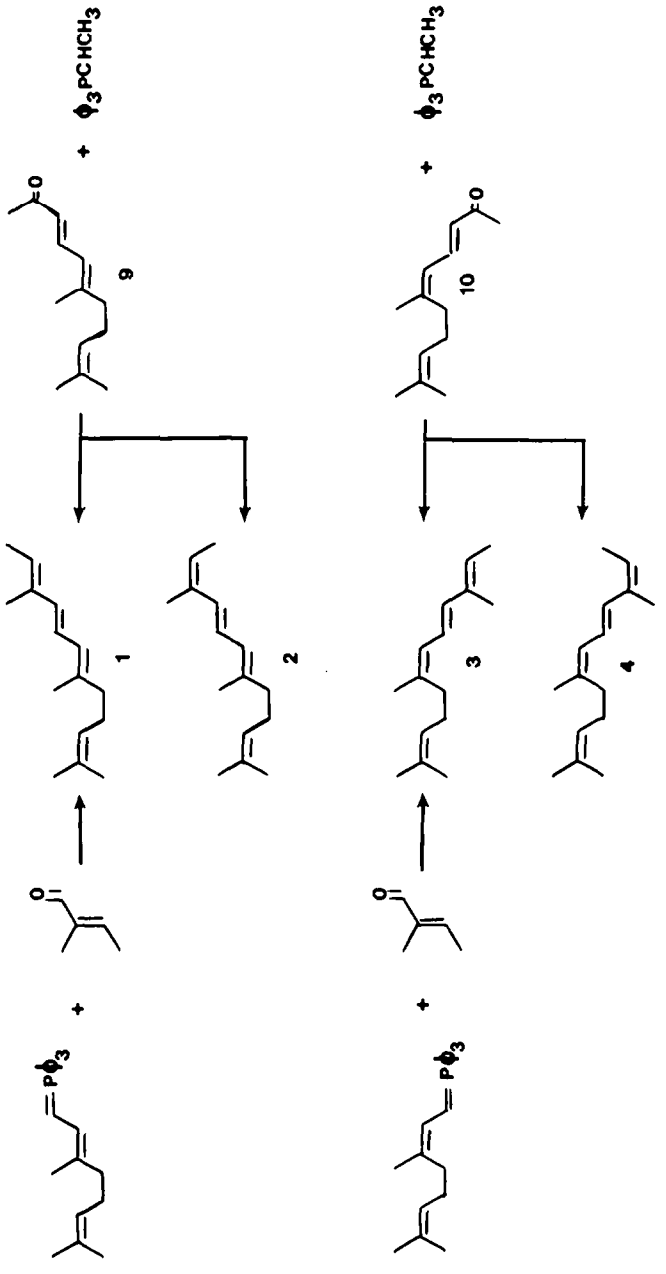

Fig. 1.

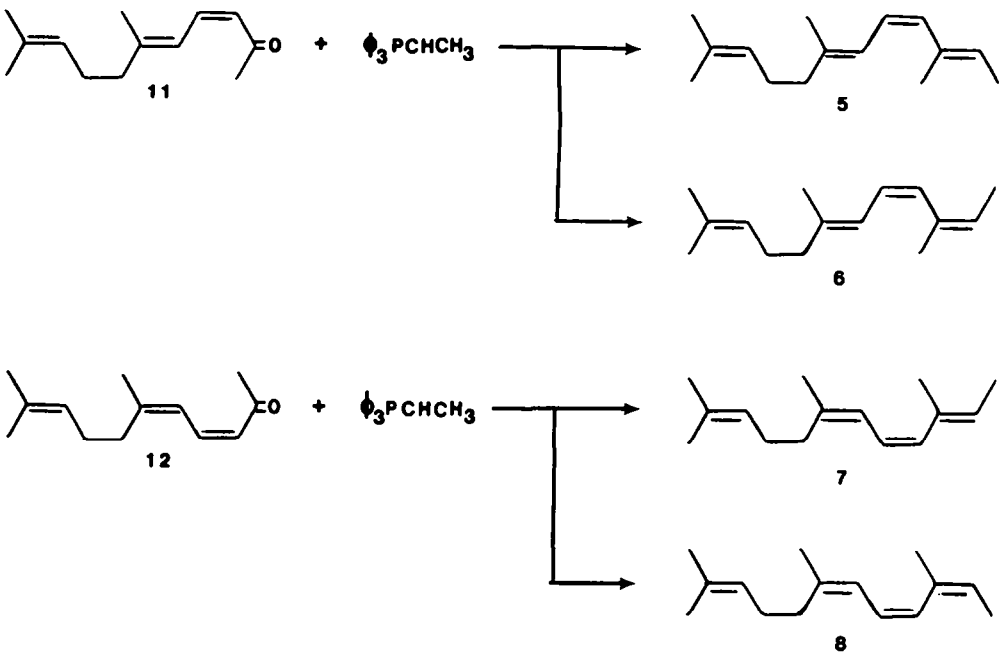

Fig. 2.

Table 1. UV spectra of pseudoionones

Compound	λ_{max}^{EtOH}	ε
9	291	26,700
10	291	21,900
11	299	17,600
12	299	16,400

spectra (Table 4), which showed λ_{max}^{EtOH} of 274 as opposed to 277 and 286 for the two *Z*-2 isomers. Therefore, since the configuration of the pseudoionone starting materials was known, the structures of allofarnesenes **5–8** were determined, as shown in Fig. 2.

NMR spectra of allofarnesenes (Table 5) show a characteristic pattern for all isomers. Several peaks for methyls occur between 1.54 and 1.86. Methylene protons produce a broad singlet between 2.05 and 2.20. H^{10} produces a broad singlet at approximately 5.18, H^2 a quartet (J=8 Hz) at 5.2, and H^4, H^5, and H^6 a multiplet between 5.8 and 7.0 which in some cases can be recognized as a triplet and a pair of doublets.

UV spectra show peaks at 264, 274 and 285 for *E*-2 isomers and peaks at 269, 278 and 289 for *Z*-2 isomers. Mass spectra of all isomers are similar (Table 4).

The material found in *S.invicta* Dufour's glands was identical in chromatographic and spectral properties with compound **8**, but all *Z*-4 isomers exhibited the trail following activity which prompted this study.

Spectral data for our compounds **1** and **2** correspond best to those reported by Sakai and Hirose[1] for compounds they called cis (C_{10}) and trans (C_{10}) allofarnesene, respectively. Since their figures are drawn correctly, we assume they were stating that the C^2 and C^3 methyls were cis or trans to each other. Cis and trans nomenclature has caused confusion in naming of other farnesene isomers.[1,7]

EXPERIMENTAL

NMR spectra were recorded on JEOL FX 90Q using benzene d-6 or carbon tetrachloride as solvent. Mass spectra were recorded on a Varian MAT CH7 GC-MS equipped with a Varian S100 data system. UV spectra were measured on a Beckman 3600 UV-visible spectrophotometer. GC analysis was performed on modified Tracor 550 or Varian 3700 instruments using silanized glass columns, with N_2 flow rate on packed columns of 60 mL/min.

Table 2. ^{1}H-NMR spectra of pseudoionones[1]

Compound	CH_3^1	$CH_2^{6,10}$	$(CH_2)_2$	H^3	H^4	H^5	H^9
9	2.16	1.60, 1.67, 1.90	2.16	5.96 d, J=15.3	7.28 d of d, J=15.3, 9.9	5.94 d, J=9.9	5.01
10	2.16	1.60, 1.66, 1.88	2.24	5.93 d, J=15.3	7.24 d of d, J=15.3, 10.8	5.93 d, J=10.8	5.05
11	2.13	1.59, 1.66, 1.92	2.17	5.79 d, J=10.8	6.55 t, J=11.7	7.19 d, J=11.7	5.03
12	2.13	1.61, 1.67, 1.83	2.17	5.80 d, J=11.7	6.56 t, J=11.7	7.17 d, J=12.6	5.05

[1]Carbon tetrachloride solvent, TMS added.

Table 3. GC retention times of allofarnesenes

Compound	R. T., min.[1]
hexadecane	3.7
6	4.7
8	5.3
heptadecane	6.3
5	7.5
7	8.2
4	9.8
3	11.2
2	14.0
1	16.0

[1] 6' x 4mm ID 1% Carbowax 20M on Chromosorb G-HP, 80-100 mesh, 60 ml/min N , 100

Table 4. UV spectra of allofarnesenes

Compound	λ_{max}^{EtOH}		
1	268	274	285
2	265	279	291
3	264	274	285
4	269	278	289
5	267	274	295
6	270	286	298
7	266	274	295
8	267	277	300

Table 5. ^{1}H-NMR spectra of allofarnesenes[1]

Compound	Methyls	Methylenes	H^2	$H^{4,5,6}$	H^{10}
1	1.53,1.62,1.70	2.09,2.13 br	5.49 q,J=6	6.08 t,J=9; 6.34-6.66 m	5.18 br
2	1.55,1.66,1.70,1.88	2.13,2.16 br	5.34 q,J=8	6.58 d,J=8; 6.58 d,J=9; 7.16s	5.22 br
3	1.53,1.61,1.73	2.22 br	5.49 q,J=7	5.87-6.60 m	5.19 br
4	1.53,1.62,1.74,1.86	2.21 br	5.34 q,J=8	6.07 br, 6.64 d, J=6; 6.65 d,J=5	5.22 br
5	1.51,1.62,1.73	2.19 br	5.61 q,J=8	5.84 d,J=14; 6.26t,J=14; 6.59 d,J=14	5.17 br
6	1.53,1.64,1.72,1.85	2.19 br	5.30 q,J=6	5.84 d,J=9; 6.24 s; 6.33 d,J=9	5.18 br
7	1.51,1.62,1.78	2.10,2.20 br	5.69 q,J=6	5.87 d,J=12; 6.21 t,J=12; 6.61 d,J=12	5.17 br
8	1.50,1.64,1.86	2.08 br	5.37 q,J=7	5.84 d,J=9; 6.24 s; 6.29 d,J=9	5.15 br

[1] Deuterated benzene solvent

Table 6. Mass spectra of allofarnesenes

Compound	Parent	1	2	3	4	5	6	7
1	204(49)	135(100)	107(98)	93(91)	91(62)	204(49)	105(39)	55(32)
2	204(30)	135(100)	107(80)	93(40)	204(30)	91(22)	105(18)	119(12)
3	204(28)	107(100)	135(90)	93(61)	91(36)	204(28)	105(26)	79(19)
4	204(21)	107(100)	135(83)	93(62)	91(40)	105(21)	79(22)	204(21)
5	204(57)	147(100)	105(95)	107(91)	69(78)	119(65)	91(60)	53(58)
6	204(61)	147(100)	105(98)	69(73)	107(68)	119(61)	53(61)	204(61)
7	204(23)	107(100)	135(81)	93(63)	91(46)	105(37)	69(28)	54(27)
8	204(22)	107(100)	135(78)	93(63)	91(44)	105(36)	53(30)	69(27)

(*E*2,*E*4,*E*6)-3,7,11-*trimethyl*-2,4,6,10-*dodecatetraene* **1**. Geranyltriphenylphosphonium bromide (4.8 g, 0.01 mol) in 20 mL of dry ether was treated over 15 min. at 25° with 0.01 mol (6.25 mL 1.6 M) n-butyl lithium and then stirred for 2 hr. Tiglic aldehyde (0.84 g, 0.01 mol) in ether (5 mL) was added over 10 min. and the mixture was stirred for an additional hour, rotary evaporated, diluted with pentane, and filtered. GC analysis showed one peak.

(*E*2,*E*4,*E*6)- *and* (*Z*2,*E*4,*E*6)-3,7,11-*trimethyl*-2,4,6,10-*dodecatetruene* **1** *and* **2**. A solution of 0.002 g (0.01 mmol) of **9** in 2 mL of dry ether was treated with 1 mL (0.01 mmol) of triphenylphosphonium ethylide and the resulting slurry was stirred for one hour, filtered and washed through a Sep Pak cartridge with 2 mL of pentane. GC analysis of the resulting solution showed 2 peaks, **1** and **2** ratio 2:1.

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