Insect Juvenile Hormone Activity of Optically Active Alkyl (2*E*,4*E*)-3,7,11-Trimethyl-2,4-dodecadienoates and of Arylterpenoid Analogues

Clive A. Henrick,* Richard J. Anderson, Gerardus B. Staal, and George F. Ludvik

Optically active samples of a number of alkyl (2*E*,4*E*)-3,7,11-trimethyl-2,4-dodecadienoates were prepared and bioassayed (along with the racemic mixtures) for juvenile hormone activity on the yellow-fever mosquito (*Aedes aegypti*), the greater wax moth (*Galleria mellonella*), the yellow mealworm (*Tenebrio molitor*), the house fly (*Musca domestica*), and the tobacco budworm (*Heliothis virescens*). The (*S*)-(+) enantiomers, in general, showed considerably higher activity on these species than did the (*R*)-(−) enantiomers. The juvenile hormone activity of the enantiomers of the phenyl ether, 6,7-epoxy-1-(4-ethylphenoxy)-3,7-dimethyloctane and of the arylterpenoid analogue, 8-ethoxy-1-(4-isopropyl-phenyl)-4,8-dimethylnonane were also studied as examples of different types of juvenile hormone analogues. The differences in activity observed for all of these analogues implies that a chiral receptor system (and possibly more than one such system) is involved in the insect juvenile hormone response to these compounds.

The alkyl (2*E*,4*E*)-3,7,11-trimethyl-2,4-dodecadienoates (Henrick, 1972, 1977; Henrick and Siddall, 1972, 1975; Henrick et al., 1973) are potent insect growth regulators (IGRs) with juvenile hormone activity (Menn and Beroza, 1972; Slama et al., 1974; Staal, 1975; Menn and Pallos, 1975). In previous papers we have discussed general synthetic routes to these compounds (Henrick et al., 1975a,b,c) and detailed structure–biological activity relationships for this class of juvenile hormone analogues (Henrick et al., 1973, 1975b, 1976a,b). There is an asymmetric carbon atom at C-7 in these compounds, and we describe here the considerable differences in biological activity observed for the *R* and *S* enantiomers of some of these dienoates. The 2*E*,4*E* stereoisomers of these dienoates show much higher biological activity than do the other three possible stereoisomers (Henrick et al., 1973, 1975b) and therefore all of the samples of dienoates discussed in this paper have the *E*,*E* configuration.

RESULTS AND DISCUSSION

The enantiomers of the juvenile hormone analogues were prepared as described in the Experimental Section. The enantiomeric composition of each sample was determined by high-resolution liquid chromatographic analysis of the diastereomeric amide pairs prepared from the intermediate citronellic, dihydrocitronellic, or 7-methoxycitronellic acid (Bergot et al., 1978; see below).

Samples of (+)-citronellol and of (+)-citronellal obtained from natural sources are usually at most about 80% optically pure (cf. Valentine et al., 1976). However, (*R*)-(+)-citronellol of high enantiomeric purity can be easily prepared from the readily available commercial (*R*)-(+)-pulegone by the procedure of Plesek (1957) (see also Overberger and Kaye, 1967; Overberger and Weise, 1968). The optical purity of (−)-citronellol and of (−)-citronellal isolated from natural sources is low, and even though (*S*)-(−)-pulegone does occur in the volatile oils of some plant species, the pure compound is not commercially available. A sample of (−)-citronellol prepared from (+)-α-pinene via *cis*-(+)-pinane (Rienäcker and Ohloff, 1961; this sample was obtained from Firmenich and Cie) was found to be only 69.6% enantiomerically pure (in this case the enantiomeric composition was determined on the corresponding *dihydro*citronellic acid; see Experimental

Section). Although it is possible to convert (*R*)-(+)-pulegone to the (*S*)-(−) enantiomer by the procedure of Ensley and Carr (1977), we were able to obtain a sample of pure (*S*)-(−)-pulegone from Bernard J. Kane of Glidden-Durkee and to convert it, by the method of Plesek (1957), to (*S*)-(−)-citronellol of 98.08% enantiomeric purity (i.e., enantiomeric composition of 99.04% *S* and 0.96% *R*).

The bioassay data for the optically active samples and of the racemic mixtures of the dienoates 1–5 are given in

1, R = OCH₃; R' = CH(CH₃)₂
2, R = H; R' = CH₂CH₃
3, R = H; R' = CH₂C≡CH
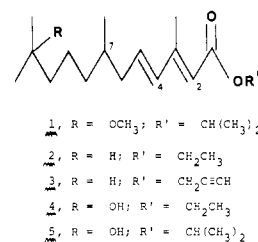4, R = OH; R' = CH₂CH₃
5, R = OH; R' = CH(CH₃)₂

Table I. The (*S*)-(+) enantiomers of the dienoates show, in general, considerably higher juvenile hormone activity on the insect species in Table I than do the corresponding (*R*)-(−) enantiomers. For example, methoprene [trademark Altosid IGR; ZR-515; isopropyl (2*E*,4*E*)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate (1C)] as a racemic mixture is highly effective in controlling many dipterous species (by the disruption of metamorphosis). However, the results in Table I indicate that essentially all of this activity is due to the (*S*)-(+) enantiomer. The sample 1A was prepared from (*S*)-(−)-7-methoxycitronellal of 98.1% enantiomeric purity (enantiomeric excess) [i.e., enantiomeric composition of 99.04% of the *S* and 0.96% of the *R* enantiomer] whereas the sample 1E was prepared from (*R*)-(+)-7-methoxycitronellal of 99.5% enantiomeric purity [i.e., 99.75% *R* and 0.25% *S* enantiomer]. For Diptera (*Aedes aegypti* and *Musca domestica*) the *S* enantiomer 1A was found to be ca. 2.3 times more active than was the racemic sample 1C. The *R* enantiomer 1E on the other hand was relatively inactive. Against *A. aegypti* 1E was ca. 330 times less active than 1A, and against *M. domestica* 1E was ca. 100 times less active than 1A. Since the sample 1E still contained ca. 0.25% of the *S* enantiomer all of the activity shown for 1E could have been due to this contaminant. Similar results were obtained on *Galleria mellonella*, *Tenebrio molitor*, and *Heliothis virescens*. In each case the *S* enantiomer showed approximately twice the activity of the racemic mixture and the *R* enantiomer showed very low activity. No marked synergism or in-

Alkyl (2E,4E)-3,7,11-Trimethyl-2,4-dodecadienoate

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Table I. ID$_{50}$ Values for Optically Active Juvenile Hormone Analogues on Sensitive Synchronized Instars[a]

No.	Structure	Configuration	Percent enantiomeric purity (excess)[b]	$[\alpha]^{25}$D CH$_3$OH	Aedes aegypti, ppm	Galleria mellonella, μg/pupa	Tenebrio molitor, μg/pupa	Musca domestica, μg/prepupa	Heliothis virescens, ppm in medium
1A		(S)-(+)	98.1	+5.1°	0.000075[c]	2.5	0.0022	0.0015[c]	0.35
1B[d]		(S)-(+)	69.6	+3.8°	0.00010[c]	3.6	0.0024	0.0020[c]	0.47
1C[e]		(±)	0.0	0.0°	0.00017[c]	5.70	0.0040	0.0035[c]	0.77
1D		(R)-(-)	66.2	-3.6°	0.00044[c]	140	0.013	0.011[c]	10
1E		(R)-(-)	99.5	-5.4°	0.025[c]	>100	0.70	0.15[c]	23
2A[d]		(S)-(+)	69.6	+2.9°	0.0045[c]	0.041	0.18	4.7	0.20
2B[f]		(±)	0.0	0.0°	0.0078[c]	0.040	0.25	18	0.30
2C[d]		(R)-(-)	97.8	-3.8°	0.19[c]	0.49	1.7	32	2.14
3A[d]		(S)-(+)	73.4	+2.5°	>0.1	0.24	1.0		7.1
3B[g]		(±)	0.0	0.0°	0.23	0.64	1.3	>100	9.2
3C[d]		(R)-(-)	97.8	-4.3°		8.7	15		>100
4A[d]		(S)-(+)	69.6	+4.3°	0.00037[c]	0.0035	11	2.7	0.020
4B		(±)	0.0	0.0°	0.00047[c]	0.0041	~100	2.4	0.035
4C[d]		(R)-(-)	73.4	-4.7°	0.0051[c]	0.013	>100	2.0	0.10
5A[d]		(S)-(+)	69.6	+4.1°	0.00013[c]	0.023	0.011	0.0041[c]	0.062
5B		(±)	0.0	0.0°	0.00026[c]	0.054	0.014	0.0077[c]	0.25
5C[d]		(R)-(-)	73.4	-4.4°	0.0014[c]	0.40	0.10	0.030	0.90
6A[d,h]		(3S)-(-)	81.2	-5.3°	0.074[c]	4.8	0.10	2.6	>100
6B		(±)	0.0	0.0°	0.054[c]	2.2	0.019	3.9	>100
6C[i]		(3R)-(+)		+5.5°	0.011[c]	1.9	0.020	8.5	>100
6D		(3R)-(+)	99.5	+6.1°	0.013[c]	2.0	0.011	8.7	>100
7A[d]		(R)-(+)	81.2	+2.3°	0.030		100[j]	0.66[c]	
7B		(±)	0.0	0.0°	0.019		70[j]	0.16[c]	
7C[k]		(S)-(-)		-2.7°	0.0036	>100	30[j]	0.093[c]	>100
7D		(S)-(-)	99.5	-3.2°	0.0031		200[j]	0.10[c]	

[a] Bioassays were performed as previously described (Henrick et al., 1973, 1975b). [b] Enantiomeric purities were determined by the method of Bergot et al. (1978). [c] Data obtained by probit analysis (cf. Finney, 1971). [d] Enantiomeric composition was determined on the dihydrocitronellic acid (see Experimental Section). [e] Methoprene (trademark Altosid IGR; ZR 515, Henrick and Siddall, 1975c). [f] Hydroprene (trademark Altozar IGR; ZR 512; Henrick, 1977). [g] Kinoprene (trademark Enstar IGR; ZR 777; Henrick 1977). [h] This analogue has asymmetric carbon atoms at C-3 and at C-6. All samples were R,S mixtures at C-6. [i] ZR 442. [j] ID$_{50}$ values are unreliable as the dose response curves were almost horizontal at the 50% level. [k] This sample was supplied by M. Schwarz (AI3-36093).

hibition of the activity of one enantiomer by the other is apparent from these results. As expected the samples **1B** (enantiomeric composition 84.8% *S* and 15.2% *R* enantiomer) and **1D** (16.9% *S* and 83.1% *R* enantiomer) showed activities in between those observed for **1A** and **1E** in agreement with their enantiomeric compositions. The samples **1B** and **1C** were also bioassayed on *Culex pipiens quinquefasciatus* (fourth instar larvae) and the ID_{50} values were found to be 0.0032 and 0.0061 ppm, respectively (data obtained by probit analysis). Thus the *S* enantiomer is also more active on this mosquito species than is the racemic mixture (cf. *Aedes aegypti*, Table I).

The racemic ethyl ester **2B** (hydroprene; trademark Altozar IGR; ZR 512) is highly active on many insect species of the orders Lepidoptera, Coleoptera, and Homoptera. The sample **2A** of 69.6% enantiomeric purity (84.8% *S* and 15.2% *R* enantiomer) was found to be more active than was the racemic mixture **2B** on *A. aegypti, T. molitor, M. domestica*, and *H. virescens*. However, the *R* enantiomer **2C** was considerably less active than were both the sample **2A**, enriched in the *S* enantiomer, and the racemic mixture **2B** (Table I).

The racemic 2-propynyl ester **3B** (kinoprene; trademark Enstar IGR; ZR 777) shows considerable activity on many homopterous insect species (Henrick et al., 1976b) but shows only low activity against *A. aegypti* and *M. domestica*. However, on the other species in Table I, the *R* enantiomer **3C** was found to be less active than the racemic mixture **3B** or the sample **3A** which was enriched in the *S* enantiomer. We have also bioassayed **3A–C** on third instar nymphs of *Aphis fabae* and found, in agreement with the results cited above, that the morphogenetic activity of the sample **3A** was ca. 1.3 times that of the racemic mixture **3B**, and that the (*R*)-(–)-enantiomer **3C** was 21 times less active than **3B**. In contrast, the acute toxicities of the three samples **3A–C** (at much higher concentrations) against *A. fabae* were found to be essentially identical (this acute toxicity is not considered to be associated with the juvenile hormone activity of these compounds, and stages of *A. fabae* are affected that are not normally susceptible to juvenile hormone action; the acute toxicity does contribute to the overall efficacy of kinoprene in insect control).

Similar results were obtained for the 11-hydroxy analogues **4** and **5**. The samples **4A** and **5A** were shown to have an enantiomeric composition of 84.8% *S* and 15.2% *R*, whereas the samples **4C** and **5C** contained 86.7% *R* and 13.3% *S* enantiomers. With the exception of the results of **4** against *M. domestica*, the samples enriched in the *R* enantiomer were in each case less active than the samples enriched in the *S* enantiomer or the racemic mixtures. The bioassay data for the analogue **5** on *A. aegypti* and *M. domestica* were obtained by probit analysis (cf. Finney, 1971) and the sample **5A** (enriched in the *S* enantiomer) was found to be approximately twice as active as the racemic mixture **5B**, whereas the sample **5C** (enriched in the *R* enantiomer) was, as expected, considerably less active.

Some aromatic terpenoid ethers show high morphogenetic activity on a number of insect species (Bowers, 1969; Pallos et al., 1971; Menn and Pallos, 1975; Henrick et al., 1976b). The 6,7-epoxycitronellyl ethers such as **6** (Jakob, 1972; Strong and Diekmann, 1973; Menn and Beroza, 1972, p 291) have an asymmetric carbon atom at C-3 (and also one at C-6) and for comparison with the 2,4-dienoates we prepared samples of **6** enriched in the 3*S* and the 3*R* enantiomers (all samples were 1:1 *R,S* mixtures at C-6). In contrast with the results obtained with **1–5**,

the (3*R*)-(+) sample **6D** [prepared from (*R*)-(+)-citronellol] showed higher activity on some of the insect species in Table I than did the sample **6A** enriched in the (3*S*)-(–) enantiomer.
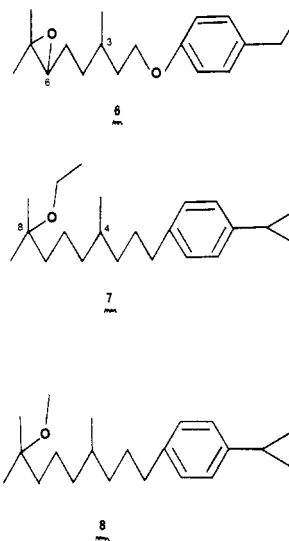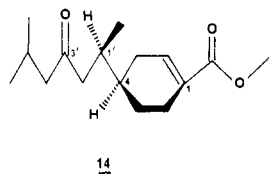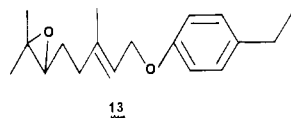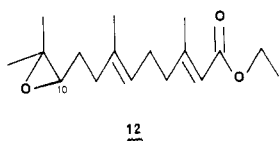

The arylterpenoid compound **7** has good activity on Diptera and shows promise in controlling a number of species of flies (Schwarz et al., 1974; Wright et al., 1976) and of mosquitoes (Lowe et al., 1975; Schaefer et al., 1976). This analogue **7** is selective for Diptera and has low activity on other orders of insects (Schwarz et al., 1974). Thus useful bioassay data on *Galleria mellonella, Heliothis virescens*, and *Tenebrio molitor* could not be obtained (Table I). However, when tested on *Aedes aegypti* and *Musca domestica*, the (*S*)-(–) enantiomer **7D** [prepared from (*R*)-(+)-citronellol] showed higher activity than did the sample **7A** enriched in the (*R*)-(+) enantiomer. The sample **7C** was supplied by M. Schwarz and was prepared from (+)-citronellal. Schwarz (1977) has prepared (–) and (+) samples of the closely related analogue **8** (this compound, with unspecified enantiomeric composition, has been described previously; Schwarz et al., 1974; Schaefer et al., 1976) with α_D (neat) values of –1.7° and +1.3°, respectively. The (–) enantiomer [prepared from (*R*)-(+)-7-methoxycitronellal] was found to be ca. five to ten times more active on *Culex pipiens quinquefasciatus* (fourth-instar larvae) and also on *Anopheles quadrimaculatus* (fourth-instar larvae) than was the (+) enantiomer. Similar results were obtained when these samples were bioassayed on *Aedes aegypti* (larvae) and on *Musca domestica* (pupae) (Schwarz, 1977).

The known natural juvenile hormones JH I (**9**) and JH II (**10**) contain asymmetric carbon atoms at C-10 and C-11, and JH III (**11**) has a chiral center at C-10. The absolute configuration of the natural (+)-JH I (**9**) has been established as 10*R*,11*S* by asymmetric synthesis (Loew and Johnson, 1971; Faulkner and Peterson, 1971), by determination of the chirality of the derived 10,11-diol (Nakanishi et al., 1971), and by asymmetric esterification of this diol (Meyer et al., 1971; cf. Meyer and Hanzmann, 1970). The natural (+)-(10*R*,11*S*) enantiomer of **9** shows considerably more juvenile hormone activity than does the (–)-(10*S*,11*R*) enantiomer. Thus the (+) enantiomer was found to be ca. nine times more active than the (–) enantiomer when bioassayed on *Galleria mellonella* (Loew and Johnson, 1971) and six to eight times more active on *Tenebrio molitor*. This particular sample of the (–) enantiomer was shown to contain up to ca. 10% of the (+) enantiomer. The presence of the latter could account for

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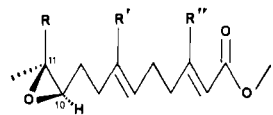
9, R = R' = CH₂CH₃, R" = CH₃ (JH I)

10, R = CH₂CH₃, R' = R" = CH₃ (JH II)

11, R = R' = R" = CH₃ (JH III)

12

13

most or even all of the activity observed for the levoro-tatory sample. Recently, Imai et al. (1976) prepared samples, of high enantiomeric purity, of the 10R and 10S enantiomers of the analogue 12 and bioassayed these isomers on *Bombyx mori* larvae. The (R)-(+) isomer showed about 50 times higher juvenile hormone activity than did the "pure" (S)-(-) enantiomer, although the latter sample still showed weak activity.

14

(+)-Juvabione (14) was isolated by W. Bowers et al. (1966) from the wood of balsam fir (*Abies balsamea*) of North American origin and was shown to have insect juvenile hormone activity (14 is one of the components of "the paper factor"; Manville, 1975, 1976). Compounds of this type show, in general, very low activity on the insect species in Table I (although some activity has been claimed on *Tenebrio molitor*; Bowers et al., 1966; Rogers et al., 1974; see, however, Manville, 1976) but show high activity on some hemipterous species such as *Pyrrhocoris apterus* and *Dysdercus cingulatus*. The structure 14 contains two asymmetric carbon atoms (C-4 and C-1') and the two sets of enantiomers of this compound have been synthesized (Pawson et al., 1970) and bioassayed (Sorm, 1971). The correct absolute configurations for the four isomers are (+)-juvabione (4R,1'R isomer), (+)-epijuvabione (4R,1'S isomer), (-)-juvabione (4S,1'S isomer), and (-)-epijuvabione (4S,1'R isomer) [Manville, 1975; (+)-epijuvabione has been isolated from a Slovak fir. In the papers of Sorm (1971) and Pawson et al. (1970), the names are incorrect and the structure of (+)-juvabione is assigned to (+)-epijuvabione and vice versa]. It is interesting that all four of the isomers show juvenile hormone activity on *P. apterus* and *D. cingulatus*. (+)-Juvabione (R,R isomer) appears to be the most active isomer and is somewhat more active than its enantiomer (-)-juvabione (S,S isomer) whereas the diastereoisomers (+)- and (-)-epijuvabione have essentially identical activity (Sorm, 1971). (±)-Juvabione was reported to show about half the activity of (+)-juvabione on *P. apterus* (Mori and Matsui, 1968).
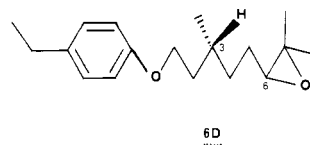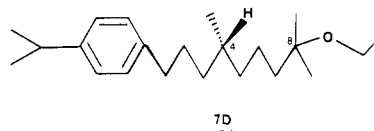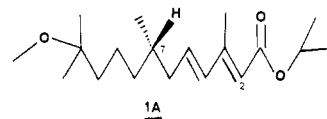

7D

6D

Figure 1.

The differences in biological activity observed in Table I and noted above for the enantiomers of 8, 9, and 12 strongly suggest that a chiral receptor system is involved in the juvenile hormone response. Selective metabolism in the insect species could also play a part in the observed differences in activity. It is particularly interesting that for the aromatic juvenile hormone analogues 6, 7, and 8 *the samples prepared from (R)-(+)-citronellol were, in general, more active* than those prepared from (S)-(-)-citronellol whereas for the 2,4-dienoates 1–5, *the enantiomers prepared from (S)-(-)-citronellol were the more active.* Thus it is possible that in some insect species the analogues 1–5 bind to a different chiral receptor protein than do the analogues 6–8. Alternatively, a single chiral binding site may be present in the insect which recognizes only one absolute configuration at the chiral carbon atom in the middle of these juvenile hormone analogues. If this hypothesis is correct then it would require that the dienoate analogues 1–5 bind in a reverse fashion compared with the analogues 6–8, such that the ester moiety occupies approximately the same space as does the epoxide function of 6 or the ether function of 7 and 8 (see Figure 1).

However, such comparisons of the biological activities of the enantiomers of compounds 1–5 with those of 6–8 must also take into account the observation that these 2,4-dienoates show, in general, much higher juvenile hormone activity in the bioassays under discussion than do the analogues 6–8. Thus the compounds 6–8 may bind poorly at the active site in many insect species. In the case of the 6,7-epoxycitronellyl ether 6, even the generally more active (R)-(+) enantiomer 6D is considerably less active on most insect species than is the corresponding 6,7-epoxygeranyl phenyl ether 13 (Henrick et al., 1976b) which does *not* contain a chiral carbon atom in the middle of the molecule. It should be noted that the known natural juvenile hormones 9–11 also do *not* contain an asymmetric carbon atom in the middle of the molecule as do the analogues 1–8. Racemic samples of 9–11 also show, on many insect species, much lower juvenile hormone activity in these bioassays than do some of the 2,4-dienoate analogues 1–5 (Henrick et al., 1976b).

In view of the findings cited above, any studies carried out on the binding of radiolabeled samples of 1 with macromolecules (cf. Schmialek et al., 1975) should preferably be carried out with the pure enantiomers of 1. One would expect that only specific binding demonstrable for the biologically active (7S)-(+) enantiomer of 1 would be relevant to the mechanism of action of this juvenile hormone analogue.

BIOASSAY PROCEDURES

Bioassays were performed on synchronized sensitive stages of the five insect species and the activities are expressed as ID_{50} or IC_{50} values (dose or concentration required to produce 50% inhibition of metamorphosis). The procedures for bioassay against *Aedes aegypti* (last larval instars), *Galleria mellonella* (fresh pupae), and *Tenebrio molitor* (fresh pupae) have been described previously by Henrick et al., (1973). The bioassay procedures for *Musca domestica* (full grown larvae) and *Heliothis virescens* (larvae) have also been previously described (Henrick et al., 1975b). The responses were calculated as percentages of the maximum attainable on a graded-response scale and plotted against the dose on semilogarithmic paper; the ID_{50} dose was taken from the intersection of the plotted line with the 50% effect level. For each series of enantiomers comparative bioassays were performed on the same day, and this procedure was replicated several times. The standard error of the bioassays for juvenile hormone activity leaves a margin of uncertainty that precludes very exact conclusions unless a great many replicate assays are performed. In several cases (indicated in Table I) many repeated sets of fractional dilutions of each of the enantiomers were bioassayed on the same day in order to obtain more precise dose–response curves. In these examples the LC_{50} values were obtained by probit analysis (cf. Finney, 1971) using a HP 9830 computer program.

EXPERIMENTAL SECTION

Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter. Preparative thin-layer chromatography (TLC) was carried out on 1 m × 20 cm plates coated with 1.3 mm of Merck (Darmstadt) silica gel PF-254. NMR spectra were determined on a Varian T-60 spectrometer. Mass spectra were measured on a Hewlett-Packard Model 5984A GLC–MS data system. Gas-liquid chromatographic (GLC) analyses were performed on Model 402 Hewlett-Packard instruments equipped with hydrogen flame ionization detectors. GLC resolution of the 2*E*,4*E*- and the 2*Z*,4*E*-dienoates **1**–**3** was accomplished on a 2 mm × 2 m glass column of 3% OV-101 on Chromosorb W, 100–120 mesh, at 150 to 250 °C and a helium flow rate of 60 mL/min, while resolution of the same isomers of dienoates **4** and **5** was carried out on a 2 mm × 2 m glass column of 3% OV-225 on Chromosorb W, 100–120 mesh, at 180 to 260 °C and a helium flow rate of 60 mL/min. All the new compounds mentioned in Table I were characterized by their NMR, IR, and mass spectra.

Isopropyl (2*E*,4*E*)-11-Methoxy-3,7,11-trimethyl-2,4-dodecadienoate (1). **(*S*)-(+) Enantiomer (1A).** (*S*)-(–)-Pulegone [supplied by Glidden-Durkee; d_4^{21} 0.9341, $[\alpha]^{25}_D$ −22.95° (neat), chemical purity 98% as indicated by GLC] was converted to (*S*)-(−)-citronellic acid by application of the procedure of Plesek (1957) as modified by Overberger and Weise (1968). Thus, a sample of (*S*)-(−)-pulegone was saturated with dry hydrogen chloride gas at 5 °C, and the mixture was allowed to stand overnight at room temperature. Addition of the intermediate hydrochloride (without isolation) to aqueous NaOH at 5 °C, with stirring, gave (*S*)-(−)-citronellic acid, bp 85 °C (0.1 mm), $[\alpha]^{25}_D$ −8.8° (c, 0.010 g/mL, CH_3OH). The enantiomeric purity of this sample was found (see below) to be 98.08% (i.e., 99.04% *S* and 0.96% *R* enantiomer). Reduction of this acid with $LiAlH_4$ in tetrahydrofuran then gave pure (*S*)-(−)-citronellol.

Acetylation of this alcohol with acetic anhydride in pyridine at room temperature overnight gave (*S*)-(−)-citronellyl acetate. To a solution of 6.8 g (34 mmol) of this acetate in 90 mL of dry methanol at room temperature was added 11.5 g (36 mmol) of mercuric acetate (Brown and Rei, 1969; Wakabayashi, 1969). After the solution had been stirred for 3 h it was cooled at 0 °C and a solution of 13.8 g (0.25 mol) of KOH in 30 mL of water was added followed immediately by 1.37 g (36 mmol) of $NaBH_4$. To allow for complete hydrolysis of the acetate group, the mixture was stirred overnight and the mercury was then removed by filtering the mixture through a pad of Celite. The filtrate was then concentrated and ether and brine were added to the residue. Working up the ether extracts in the usual manner gave 6.27 g (97% yield) of (*S*)-(−)-7-methoxycitronellol. Oxidation with the chromium trioxide–dipyridine complex in dichloromethane (Collins et al., 1968; Ratcliffe and Rodehorst, 1970) at 0 °C gave a 95% yield of (*S*)-(−)-7-methoxycitronellal. This aldehyde was condensed with the anion generated with NaH from diisopropyl 3-isopropoxycarbonyl-2-methyl-2-propenylphosphonate (Henrick et al., 1973) in dimethylformamide and the product was hydrolyzed with excess NaOH in aqueous ethanol at 60 °C to give the crude 2,4-dienoic acid (as a mixture of the 2*E*,4*E* and 2*Z*,4*E* isomers).

The pure (2*E*,4*E*)-dienoic acid was isolated via the ammonium salt as follows (Henrick et al., 1975a): Dry ammonia gas was bubbled into a solution of 7 g of the crude acid in 35 mL of hexane for 3 h. The suspension of salt was heated at 50 °C for 1 h with stirring under a NH_3 atmosphere and then the mixture was filtered. The collected solid was resuspended in fresh hexane and the mixture was filtered again to yield 2.5 g of the pure 2*E*,4*E* ammonium salt. Esterification was carried out using the procedure developed by Carney (1975). Thus, to a suspension of 2.43 g (8 mmol) of the ammonium salt in 20 mL of hexane under N_2 was added 3.46 g (12.2 mmol) of titanium tetraisopropoxide. After the hexane had been distilled off the residual mixture was heated at 145 °C for 4 h in vacuo (ca. 100 mm). To the cooled reaction mixture was then added a mixture of hexane and 8 N aqueous H_2SO_4. The combined hexane extracts were washed with saturated aqueous $NaHCO_3$, brine, dried ($CaSO_4$), and the solvent was removed in vacuo. The residue (2.6 g) was purified by preparative TLC on silica gel (developed with 12% ethyl acetate in hexane) to give 2.1 g (6.8 mmol; 84% yield) of (*S*)-(+)-isopropyl (2*E*,4*E*)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate (**1A**); bp (bath, short path) 120 °C (0.05 mm), $[\alpha]^{25}_D$ + 5.1° (c, 0.010 g/mL, CH_3OH). GLC analysis showed it to contain 99% of the required 2*E*,4*E* isomer and 1% of the 2*Z*,4*E* isomer.

(*S*)-(+) Enantiomer (1B). This sample was prepared from (*S*)-(−)-citronellol of 69.6% enantiomeric purity [supplied by Firmenich; d_4^{21} 0.8536, $[\alpha]^{25}_D$ −4.05° (neat); NMR analysis of the alcohol showed it to contain ca. 12% of 3,7-dimethyl-7-octen-1-ol; enantiomeric composition was determined on the corresponding *dihydro*citronellic acid (see below)]. The same synthetic route was used as described above for **1A**. The ester **1B** showed $[\alpha]^{25}_D$ +3.8° (c, 0.030 g/mL, CH_3OH) and by GLC analysis it contained a 99:1 ratio of the 2*E*,4*E*:2*Z*,4*E* isomers.

The racemic esters **1C**, **2B**, **3B**, **4B**, and **5B** were prepared as previously described (Henrick et al., 1973, 1975a, 1976b).

(*R*)-(−) Enantiomer (1E). (*R*)-(+)-Pulegone [purchased from Givaudan Corp and purified by spinning-band distillation; d_4^{21} 0.9370 $[\alpha]^{25}_D$ +24.57° (neat), chemical purity 96% as determined by GLC analysis] was converted to (*R*)-(+)-citronellic acid by the procedure of Overberger and Weise (1968). The acid was found (Bergot et al., 1978) to be 99.5% enantiomerically pure (i.e., 99.75% *R* and

0.25% S enantiomers; cf. Valentine et al., 1976; Chan et al., 1976) and showed d_4^{21} 0.9229, $[\alpha]^{25}_D$ +8.44° (neat), $[\alpha]^{24}_D$ +8.7° (c, 0.032 g/mL, CH_3OH) [lit. Plesek (1957) $[\alpha]^{20}_D$ +8.18°; Lukes et al. (1957), +8.40° (neat); Overberger and Kaye (1967), $[\alpha]^{25}_D$ +8.48°, +8.72° (neat); Overberger and Weise (1968) $[\alpha]^{25}_D$ +9.05° (CH_3OH); Chan et al. (1976), $[\alpha]^{25}_D$ +8.56° (neat)]. Reduction with $LiAlH_4$ in tetrahydrofuran gave (R)-(+)-citronellol, d_4^{21} 0.8667 $[\alpha]^{23}_D$ +5.49° (neat), chemical purity 99% by GLC analysis [lit. Plesek (1957) $[\alpha]^{20}_D$ +5.37° (neat); Overberger and Kaye (1967) $[\alpha]^{25}_D$ +5.51° (neat); Chan et al. (1976), $[\alpha]^{25}_D$ +5.45° (neat); Valentine et al. (1976), $[\alpha]_D$ +5.37° (neat)]. This alcohol was converted to the dienoic ester **1E** by the route described above under **1A**. The ester **1E** showed $[\alpha]^{25}_D$ −5.4° (c, 0.010 g/mL, CH_3OH) and by GLC analysis it contained a 99:1 ratio of the 2E,4E:2Z,4E isomers.

The ester **1D** was prepared by the phosphonate route starting from a sample of 7-methoxy-3,7-dimethyl-1-octanal obtained from Bush Boake Allen Ltd [prepared from (−)-α-pinene]. This methoxycitronellal sample showed d_4^{21} 0.9056, $[\alpha]^{25}_D$ +7.72° (neat), $[\alpha]^{25}_D$ +7.73° (c, 0.020 g/mL, dioxane); chemical purity 95%; and was found to be 66.2% enantiomerically pure by the method described below (i.e., 83.1% R and 16.9% S enantiomers). The ester **1D** showed $[\alpha]^{25}_D$ −3.6° (c, 0.020 g/mL, CH_3OH) and by GLC analysis it contained a 96:4 ratio of the 2E,4E:2Z,4E isomers.

Ethyl (2E,4E)-3,7,11-Trimethyl-2,4-dodecadienoate (2). (S)-(+)-Enantiomer (2A).

A 3.2-g sample of (S)-(−)-citronellol (obtained from Firmenich; 69.6% enantiomeric purity, see under **1B** above) in 25 mL of ethanol was stirred with hydrogen at room temperature in the presence of 10% palladium-on-charcoal (80 mg) for 18 h. The catalyst was filtered off and the solvent removed in vacuo to give (S)-(−)-dihydrocitronellol. Oxidation with a 7:1 mol ratio of the CrO_3–dipyridine complex in dichloromethane (Collins et al., 1968) at 0 °C for 2 h in the usual manner gave (S)-(−)-dihydrocitronellal. To 2.0 g (0.013 mol) of the latter in 25 mL of dry dimethylformamide at 0 °C under N_2 was added 3.92 g (0.013 mol) of diisopropyl 3-isopropoxycarbonyl-2-methyl-2-propenylphosphonate, followed by 513 mg (0.013 mol) of NaOH (180 mesh pellets) (Henrick et al., 1973). The reaction mixture was stirred at 0 °C for 30 min, followed by stirring at room temperature for 2 h, and then was poured into a mixture of hexane and water. The organic layer was washed with brine and dried, and the solvent was removed in vacuo. The residue was hydrolyzed with NaOH in aqueous ethanol and the recovered crude dienoic acid was dissolved in 15 mL of dichloromethane and dry ammonia gas was bubbled into the solution for 2.5 h. The precipitated salt was filtered off and washed with 10 mL of fresh dichloromethane. The salt was then added to a mixture of ether and 10% aqueous H_2SO_4 and the ether extract was then washed with brine and was dried ($CaSO_4$). Removal of the solvent gave 0.35 g of the (2E,4E)-3,7,11-trimethyl-2,4-dodecadienoic acid. The acid was dissolved in 700 mg of N,N-dimethylformamide diethyl acetal and the solution was heated at 80 °C for 45 min. The product was purified by preparative TLC on silica gel (developed with 4% ethyl acetate in hexane) to give 0.335 g of the (S)-(+) ester **2A**, bp (bath, short path) 80 °C (0.05 mm), $[\alpha]^{25}_D$ +2.9° (c, 0.020 g/mL, CH_3OH). GLC analysis showed it to contain 99% of the required 2E,4E isomer (and 1% of the 2Z,4E isomer).

(R)-(−)-Enantiomer (2C). This isomer was prepared from (R)-(+)-citronellol [obtained from (R)-(+)-pulegone; see under **1E** above; 99.5% enantiomeric purity] in a manner essentially identical with that described above

under **2A**. The ester **2C** showed $[\alpha]^{25}_D$ −3.8° (c, 0.020 g/mL, CH_3OH) and by GLC analysis contained a 99:1 ratio of the 2E,4E:2Z,4E isomers. Direct determination of the enantiomeric composition of the (R)-(+)-dihydocitronellic acid gave a result of 97.8% enantiomeric purity [the (R)-(+)-citronellic acid prior to hydrogenation was shown to be 99.5% enantiomerically pure; see below].

2-Propynyl (2E,4E)-3,7,11-Trimethyl-2,4-dodecadienoate. (S)-(+)-Enantiomer (3A).

In a manner similar to that described under **2A** above, a sample of (S)-(2E,-4E)-3,7,11-trimethyl-2,4-dodecadienoic acid was prepared from (S)-(−)-citronellol [supplied by Bush Boake Allen Ltd; d_4^{21} 0.8486, $[\alpha]^{25}_D$ −4.10° (neat); enantiomeric purity was found to be 73.4%; enantiomeric composition was determined on the corresponding dihydrocitronellic acid]. To 0.30 g of the dienoic acid in 5 mL of ether at 0 °C was added 0.15 mL of $SOCl_2$ and 0.03 mL of dimethylformamide. After 4 h at 0 °C the solvent was removed in vacuo and the residue was dissolved in 5 mL of fresh ether. The solution was then cooled to 0 °C and 150 mg of propargyl alcohol plus 0.40 mL of pyridine were added. After 4 h the mixture was diluted with water and ether, and the organic phase was washed with 5% aqueous HCl, 2 N aqueous Na_2CO_3, and brine and was dried ($CaSO_4$). Removal of the solvent and purification of the residue by preparative TLC on silica gel (developed with 3% ethyl acetate in hexane) gave 0.23 g of **3A**, bp (bath, short path) 110 °C (0.1 mm), $[\alpha]^{25}_D$ +2.5° (c, 0.010 g/mL, CH_3OH). GLC analysis showed it to contain a 97:3 ratio of the 2E,4E:2Z,4E isomers.

(R)-(−)-Enantiomer (3C). In a similar manner this isomer was prepared from the (R)-dienoic acid which was synthesized from (R)-(+)-dihydrocitronellic acid (enantiomeric purity 97.8%, see under **2C** above). The ester **3C** showed $[\alpha]^{25}_D$ −4.3° (c, 0.010 g/mL, CH_3OH); 97:3 ratio of 2E,4E:2Z,4E isomers.

Alkyl (2E,4E)-11-Hydroxy-3,7,11-trimethyl-2,4-dodecadienoates. Ethyl (S)-(+)-Enantiomer (4A).

To a suspension of 20.7 g (65 mmol) of mercuric acetate in 65 mL of water and 65 mL of tetrahydrofuran (cf. Brown and Geoghegan, 1967) at room temperature was added 11.64 g (58.5 mmol) of (S)-(−)-citronellyl acetate [prepared from Firmenich (−)-citronellol of 69.6% enantiomeric purity; see under **1B** above] dissolved in 20 mL of tetrahydrofuran. After the mixture had been stirred for 1.5 h, 65 mL of 3 M aqueous NaOH, was added followed by 65 mL of a solution of 0.5 M $NaBH_4$ in 3 M aqueous NaOH. The two-phase system was stirred vigorously for 2 days and then the mercury was removed by filtration through Celite. The aqueous phase was saturated with salt and the mixture was extracted thoroughly with ether. The combined organic extracts were washed with brine and dried ($CaSO_4$), and the solvent was removed to give 9.80 g (56.5 mmol, 97% yield) of (S)-(−)-7-hydroxy-3,7-dimethyl-1-octanol. Oxidation of this diol with a 7:1 mol ratio of the CrO_3–dipyridine complex in dichloromethane at 0 °C for 1.5 h in the usual manner gave (S)-(−)-7-hydroxycitronellal in 80% yield. Reaction of this aldehyde (6 g) with 1 equiv of diisopropyl 3-isopropoxycarbonyl-2-methyl-2-propenylphosphonate (NaH in dimethylformamide at room temperature; cf. Henrick et al., 1973, 1976b) gave the 11-hydroxydienoic ester which was then hydrolyzed with NaOH in aqueous ethanol at 70 °C to give the dienoic acid.

The crude acid (8 g) was dissolved in a mixture of 40 mL of dichloromethane plus 15 mL of hexane and dry ammonia gas was bubbled through the solution for 5 h. The salt (2 g) was filtered off and washed with hexane.

A 0.75-g sample of this ammonium salt was added to a mixture of ether and 10% aqueous H_2SO_4 with stirring. The organic layer was washed with brine and dried $(CaSO_4)$, and the solvent was removed to give the 2E,4E acid (0.53 g). To a solution of this hydroxy acid in ether (20 mL) was added 0.72 g of 1-ethyl-3-*p*-tolyltriazene (White and Scherrer, 1961; White et al., 1968) and the solution was heated under reflux for 24 h. To the cooled solution was added aqueous HCl and then the organic layer was worked up in the normal manner. Purification of the product by preparative TLC on silica gel (developed with 25% ethyl acetate in hexane) gave 0.40 g of the ethyl (S)-(+)-ester **4A**, bp (bath, short path) 110 °C (0.05 mm), $[\alpha]^{25}_D$ +4.3° (*c*, 0.020 g/mL, CH_3OH); 94:6 ratio of 2E,-4E:2Z,4E isomers by GLC analysis.

Ethyl (R)-(-) Enantiomer (**4C**). This ester was prepared from commercial (R)-(+)-7-hydroxycitronellal [Laurene pure, purchased from Givaudan Corp; d_4^{21} 0.9189, $[\alpha]^{25}_D$ +10.6° (neat), +10.9° (*c*, 0.071 g/mL, $CHCl_3$); chemical purity ≥99% as indicated by GLC analysis] which was found (see below) to have an enantiomeric purity of 73.4% (i.e., 86.7% R and 13.3% S enantiomers). The ester was synthesized by the phosphonate route as outlined under **4A** above. The resulting (R)-dienoate **4C** (98:2 ratio of 2E,4E:2Z,4E isomers) showed $[\alpha]^{25}_D$ -4.7° (*c*, 0.010 g/mL, CH_3OH).

Isopropyl (S)-(+)-Enantiomer (**5A**). To 1.13 g (3.95 mmol) of the ammonium salt of (S)-(2E,4E)-11-hydroxy-3,7,11-trimethyl-2,4-dodecadienoic acid (prepared under **4A** above) in 10 mL of hexane was added 1.75 mL (5.95 mmol) of titanium tetraisopropoxide (Carney, 1975) and then the hexane was distilled off at 100 mm. The residue was then heated at 145 °C for 3 h under a vacuum of 100 mm. To the cooled mixture was added 8 N aqueous H_2SO_4 and ether with shaking. Hexane was then added and the hexane–ether (9:1) layer was washed with 6% aqueous hydroxyacetic acid, 5% aqueous NaOH, and brine and then was dried $(CaSO_4)$. Removal of the solvent and purification of the residue by preparative TLC on silica gel (developed with 25% ethyl acetate in hexane) gave 0.3 g of **5A**, bp (bath, short path) 110 °C (0.05 mm), $[\alpha]^{25}_D$ +4.1° (*c*, 0.020 g/mL, CH_3OH); 95:5 ratio of 2E,4E:2Z,4E isomers by GLC analysis.

Isopropyl (R)-(-)-Enantiomer (**5C**). This sample was prepared in a similar manner starting from (R)-(+)-7-hydroxycitronellal ["Laurene pure", see under **4C** above]. The ester **5C** showed $[\alpha]^{25}_D$ -4.4° (*c*, 0.020 g/mL, CH_3OH) and contained a 99:1 ratio of 2E,4E:2Z,4E isomers.

6,7-Epoxy-1-(4-ethylphenoxy)-3,7-dimethyloctane. (3S;6R,S)-(-) *Enantiomers* (**6A**). This sample was prepared from (S)-(-)-citronellol [purchased from Givaudan Corp. d_4^{21} 0.8521, $[\alpha]^{25}_D$ -4.01° (neat); NMR analysis showed the presence of ca. 17% of 3,7-dimethyl-7-octen-1-ol; enantiomeric purity was found to be 81.2%; i.e., 90.6% S and 9.4% R enantiomers; enantiomeric composition was determined on the corresponding *dihydro*-citronellic acid]. To 0.70 g (4.5 mmol) of this alcohol in 12 mL of dichloromethane at 0 °C was added 0.83 mL (6 mmol) of triethylamine and 0.58 g (5 mmol) of methanesulfonyl chloride. After 2 h water was added followed by additional CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$, brine, and dried (Na_2SO_4), and the solvent was removed to give 1.0 g of (S)-(-)-citronellyl mesylate.

4-Ethylphenol (0.55 g, 4.5 mmol) was added with stirring to 1.86 g (13.5 mmol) of K_2CO_3 in 20 mL of dimethylformamide under N_2. After 30 min the above mesylate (1.0 g, 4.3 mmol) dissolved in 1 mL of dimethylformamide was

added and the mixture was stirred at 20 °C for 10 h followed by stirring at 70 °C for 3 days. After cooling, the mixture was added to hexane plus water. The organic layer was washed with brine and dried $(CaSO_4)$, and the solvent was removed. Column chromatography on Florisil (20 g) and elution with hexane gave 0.78 g of the phenyl ether. To 0.70 g (2.7 mmol) of this phenyl ether in 25 mL of CH_2Cl_2 at 0 °C was added 0.40 g (2.0 mmol) of 85% *m*-chloroperbenzoic acid (only 0.7 equiv of peracid was used to avoid epoxidation of the 7-octene impurity). After 2 h the product was isolated in the usual manner and purified by preparative TLC on silica gel (developed with 10% ethyl acetate in hexane) to give 0.48 g of the epoxide **6A**, $[\alpha]^{25}_D$ -5.3° (*c*, 0.020 g/mL, CH_3OH).

(3R;6R,S)-(+)-*Enantiomers* (**6D**). This sample was prepared in a similar manner starting from pure (R)-(+)-citronellol [prepared from (R)-(+)-pulegone; see under **1E** above]. In this case 1 equiv of peracid was used in the epoxidation step since the starting citronellol did not contain any of the 7-octene as a contaminant. The epoxide **6D** showed $[\alpha]^{25}_D$ +6.1° (*c*, 0.010 g/mL, CH_3OH).

The racemic epoxide **6B** was prepared in a similar way from racemic citronellol.

8-Ethoxy-1-(4-isopropylphenyl)-4,8-dimethylnonane. (R)-(+)-*Enantiomer* (**7A**). A sample of (S)-(-)-citronellol (81.2% enantiomeric purity; purchased from Givaudan Corp; see under **6A** above) was acetylated and the acetate was treated with 1 equiv of mercuric acetate in dry ethanol (Brown and Rei, 1969; Wakabayashi, 1969) followed by alkaline $NaBH_4$ (cf. the reaction conditions described under **1A** above) to give (S)-(-)-7-ethoxycitronellol. Oxidation with the chromium trioxide–dipyridine complex in dichloromethane at 0 °C then gave (S)-(-)-7-ethoxy-citronellal in 80% yield. Reaction of this aldehyde with triphenylphosphonium 4-isopropylbenzylide in dimethylformamide at 20 °C for 15 h gave 8-ethoxy-1-(4-isopropylphenyl)-4,8-dimethyl-1-nonene in 70% yield (56:44 ratio of olefinic isomers) after purification by preparative TLC. The olefin was hydrogenated in ethyl acetate over platinum oxide at room temperature to give **7A**, bp (bath, short path) 120 °C (0.1 mm), $[\alpha]^{25}_D$ +2.3° (*c*, 0.020 g/mL, CH_3OH).

(S)-(-)-*Enantiomer* (**7D**). This isomer was prepared in an identical manner starting from pure (R)-(+)-citronellol [prepared from (R)-(+)-pulegone; see under **1E** above] and had $[\alpha]^{25}_D$ -3.2° (*c*, 0.020 g/mL, CH_3OH).

The sample **7C** was supplied by M. Schwarz and the racemic sample **7B** was prepared from racemic 7-ethoxycitronellal obtained from Glidden-Durkee.

DETERMINATIONS OF ENANTIOMERIC PURITY

The optical purity of a compound is defined as the ratio of its observed rotation to the specific rotation of the pure enantiomer. Enantiomeric purity (enantiomeric excess) measures the excess of one enantiomer over the other and is equal to the magnitude of the optical purity. Enantiomeric purity of

$$E_+ = \frac{E_+ - E_-}{E_+ + E_-} = 2E_+ - 1$$

where E_+ and E_- are the mole fractions of the enantiomers. Percent enantiomeric purity (excess) of

$$E_+ = 100\frac{(E_+ - E_-)}{(E_+ + E_-)} = \%E_+ - \%E_-$$

The calculation of the optical purity of a sample requires that the specific rotation of the pure enantiomer be determined, in addition to the measurement of the specific

rotation of that particular optically active sample. Alternately, enantiomeric purity and hence optical purity can be determined by a direct measurement of the proportions of the enantiomers present in a mixture.

The enantiomeric compositions of the various samples discussed above were determined by a direct method involving the high-resolution liquid chromatographic (HRLC) analysis of the corresponding diastereomeric 1-(1-naphthyl)ethylamide pairs prepared from the corresponding acids (Bergot et al., 1978). This method gives directly the R/S enantiomer ratios from samples of the acids (cf. Valentine et al., 1976).

The various samples of citronellol, dihydrocitronellol, or 7-methoxycitronellal were oxidized to the corresponding acids by treatment with an excess of Jones reagent in acetone at 0 °C for 30 min (Bowden et al., 1946; Curtis et al., 1953; Djerassi at. al., 1956). The acids after isolation with ether in the normal manner were then treated at 0 °C with excess $SOCl_2$ in ether containing a catalytic amount of dimethylformamide to form the corresponding acid chlorides. Reaction of the recovered acid chlorides in ether with enantiomerically pure (>99.9%) (R)-(+)-1-naphthyl)ethylamine in the presence of pyridine (overnight at room temperature) gave the crude diastereomeric amides which were purified by preparative TLC on silica gel (developed with ethyl acetate–hexane mixtures) before HRLC analysis. In this preliminary TLC cleanup the diastereomers did not separate and care was taken to remove the entire amide band from the TLC plate to avoid selective removal of one diastereomer from the other during this step. The HRLC analyses were carried out as described elsewhere (Bergot et al., 1978) and the diastereomeric ratios were determined by peak area computation. Complete and rapid resolution of the R,R and S,R 1-(1-naphthyl)ethylamides was readily obtained in the citronellic and dihydrocitronellic acid series. With the more polar diastereomeric amide mixtures prepared from samples of 7-methoxycitronellic acid, obtaining baseline separation was found to be more difficult, but excellent HRLC resolution could be obtained under modified conditions (Bergot et al., 1978).

In several cases (indicated in Table I) the determination of the enantiomeric composition was carried out on the *dihydrocitronellic acid. It was noted that a small amount of racemization of the chiral center appeared to occur during the hydrogenation step.* For example, (R)-(+)-citronellic acid prepared from (R)-(+)-pulegone was found to have an enantiomeric composition of 99.75% R and 0.25% S. Reduction of this acid to (R)-(+)-citronellol followed by hydrogenation in ethanol over 10% palladium-on-charcoal and then reoxidation gave (R)-(+)-dihydrocitronellic acid which was found to contain 98.9% R and 1.1% S enantiomers (cf. Valentine et al., 1976). This partial racemization most likely occurs via double bond migration during the hydrogenation reaction (cf. Chan et al., 1976).

The measurement of the specific rotation of a sample of citronellol is often not an accurate method of determining the optical purity since optically active samples of citronellol usually contain 10–20% of the 7-octene as an impurity.

As may be noted from Table I, the measurement of the specific rotation of a sample of one of the dienoates 1–5 does allow the approximate determination of the optical purity. However, this method can only be used for the pure stereoisomers since the 2Z,4E stereoisomers have considerably higher specific rotations than do the 2E,4E isomers. For example, a sample of 2C (enantiomeric purity

of 97.8%) containing a 2E,4E:2Z,4E ratio of 1:3 showed $[\alpha]^{25}_D$ −7.9° (c, 0.020 g/mL, CH_3OH). A sample of 5C (enantiomeric purity of 73.4%) containing a 2E,4E:2Z,4E ratio of 78:22 showed $[\alpha]^{25}_D$ −5.5° (c, 0.020 g/mL, CH_3OH). For comparison the sample of 2C in Table I showed $[\alpha]^{25}_D$ −3.8° (99:1 ratio of 2E,4E:2Z,4E isomers) and 5C showed $[\alpha]^{25}_D$ −4.4° (99:1 ratio of 2E,4E:2Z,4E isomers).

(R)-(+)-7-Hydroxycitronellal. This aldehyde ["Laurene pure" purchased from Givaudan Corp; $[\alpha]^{25}_D$ +10.9° (c, 0.071 g/mL, $CHCl_3$)] was found to be ca. 73.4% enantiomerically pure (i.e., 86.7:13.3 ratio of R and S enantiomers) via conversion to *dihydro*citronellic acid. Thus, the hydroxycitronellal was reduced with $NaBH_4$ in methanol at 0 °C and the resulting primary alcohol was acetylated with Ac_2O in pyridine. The recovered 7-hydroxy-3,7-dimethyloctan-1-yl acetate, dissolved in a mixture of pyridine and toluene, was then treated with thionyl chloride at 0 °C for 1.5 h. Isolation with ether in the normal manner gave a mixture of the two possible olefinic acetates plus 7-chlorocitronellyl acetate.

The crude dehydration mixture in ethanol was catalytically hydrogenated over 10% palladium-on-charcoal and the product was purified by preparative TLC on silica gel impregnated with Rhodamine 6G (developed with 5% ethyl acetate in hexane) to give the dihydrocitronellyl acetate (30% yield from Laurene). This acetate was hydrolyzed (K_2CO_3 in CH_3OH) to give dihydrocitronellol which was then oxidized, and the resulting acid was derivatized and analyzed as described above. The enantiomeric composition was found to be 86.7% R and 13.3% S enantiomers.

Optically pure (R)-(+)-7-hydroxycitronellal [prepared from (R)-(+)-pulegone] was reported by Skorianetz et al. (1971) to have $[\alpha]^{20}_D$ ($CHCl_3$) +10°. However, in view of the above result the specific rotation of the pure enantiomer should be ca. +14.9°.

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Selective Toxicity of N,N'-Thiodicarbamates

Mohamed A. H. Fahmy, N. Moorthy Mallipudi, and T. Roy Fukuto*

A series of N-(alkyl alkylcarbamylosulfenyl) derivatives of methylcarbamate insecticides were prepared and examined for toxicity to house flies, mosquito larvae, and white mice. Compared to the parent methylcarbamate, the derivatives were generally of equal toxicity to the house fly, substantially more toxic to mosquito larvae, and much less toxic to mice. Toxicities to mosquito larvae and white mice were related to octanol–water partition coefficients.

In a previous paper from this laboratory, we described the favorable toxicological properties of a series of N-substituted biscarbamoyl sulfides (Fahmy et al., 1974). These biscarbamoyl sulfide derivatives of methylcarbamate insecticides still retained the good insecticidal activity of the parent methylcarbamate but were substantially less toxic to the white mouse. Based on an earlier study (Black et al., 1973a) of the comparative metabolism in the white mouse and house fly of a related sulfenylated derivative, N-(2-toluenesulfenyl)carbofuran, the selective toxicity of the biscarbamoyl sulfides was attributed to differences in rates and routes of metabolism in insects and mammals.

High toxicity to insects was ascribed to an activation process which occurred primarily in insects, resulting in the liberation of the toxic methylcarbamate in vivo; low toxicity to the mouse was attributed to preferential degradation of the carbamate ester linkage, possibly by carboxylesterase action, to the nontoxic phenols.

Because of the desired order of selectivity demonstrated by the biscarbamoyl sulfides, it was of interest to examine other derivatives of this type for selective toxicity. This report is concerned with the synthesis and toxicological properties of a series of unsymmetrical N,N'-thiodicarbamate derivatives of the general structure I where Ar
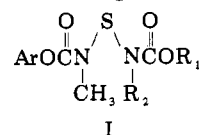
Division of Toxicology and Physiology, Department of Entomology, University of California, Riverside, California 92521.

$$\text{ArO} \overset{\overset{O}{\|}}{C} \underset{\underset{CH_3}{|}}{N} \diagdown \overset{S}{} \diagup \underset{\underset{R_2}{|}}{N} \overset{\overset{O}{\|}}{C} OR_1$$

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