945 (s), 860, 800, 765 cm^{-1}; NMR δ 6.4–7.0 (3 H, m), 5.4–5.8 (olefinic, ABX, J = 8 and 2 Hz), 3.0 (1 H, br q), 2.25 (CH_3, s), 1.2 (CH_3, s), 1.0 (CH_3, d, J = 8 Hz). Anal. Calcd for $C_{15}H_{18}O$: C, 84.11; H, 8.41. Found: C, 83.95; H, 8.29.

Method B. From the Bromide 18. The tricyclic alcohol (−)-**16** (205 mg, 0.95 mmol) in ether (24 mL) was treated with a portion of PBr_3 (100 μL) and then a second portion after 20 min (100 μL). After 1 h the mixture was poured into concentrated HBr and extracted four times with ether. The combined extracts were dried with anhydrous magnesium sulfate and then added to excess 3 M methylmagnesium bromide in ether. After 1 h the mixture was quenched with water and extracted into ether. The ether extract was washed with H_2O and brine, dried with magnesium sulfate, and concentrated. The residue was chromatographed on a silica gel plate developed with 16% ether–petroleum ether to afford 49 mg (24%) of **20**.

(−)-3a,8b-Dihydro-3,3a,6,8b-tetramethyl-1*H*-cyclopenta[*b*]benzofuran (22). A solution of **20** (80 mg, 0.37 mmol) in 1:1 toluene–isobutyl alcohol (2 mL) containing Wilkinson's catalyst [$(Ph_3P)_3RhCl$, 10 mg] and triphenylphosphine (16 mg) was heated to reflux in an open flask for 5 days. At this time the isomerization was 97% complete as determined by GC (**20**, retention time 2.4 min at 190 °C; **22**, retention time 2.25 min at 190 °C).

The mixture was poured into water overlaid with petroleum ether and extracted three times with petroleum ether. The combined extracts were washed with water and brine, dried with anhydrous magnesium sulfate, and concentrated under reduced pressure.

The crude material was chromatographed on a silica gel preparative plate developed with 2% ether in petroleum ether. The material in the major band was extracted with ether and purified by bulb to bulb distillation at 80 °C (0.05 mm) to yield 33 mg (41%) of **22**: $[\alpha]^{21}_D$ −132° (c 0.66, $CHCl_3$); IR 3040, 2960, 2920, 2840, 1615, 1585, 1490 (s), 1440, 1260, 1085, 1060, 940, 850, 795 cm^{-1}; NMR δ 6.4–7.1 (3 H, m), 5.4 (1 H, m), 2.5 (2 H, m), 2.35 (CH_3, s), 1.75 (CH_3, br), 1.4 (CH_3, s), 1.25 (CH_3, s). Anal. Calcd for $C_{15}H_{18}O$: C, 84.11; H, 8.41. Found: C, 84.31; H, 8.40.

(−)-Debromoaplysin (2). A solution of **22** (32 mg, 0.15 mmol) in ethanol (1.5 mL) with 5.6 mg of Adam's catalyst was placed in a small flask. The flask was sealed with a septum, and H_2 gas was introduced with a needle connected to a small balloon. After being flushed with H_2, the mixture was stirred rapidly for 2 h. Analysis by GC showed that **22** had all reacted and that the volatile product was 94.5% debromoaplysin (**2**, retention time 2.45 min at 180 °C) and 5.5% **21** (retention time 3.10 min at 180 °C).

The mixture was poured into water and extracted three times with petroleum ether. The combined extracts were washed with water and brine, dried with anhydrous magnesium sulfate, and concentrated to afford 33 mg of crude debromoaplysin.

The crude material was chromatographed on a silica gel preparative plate developed with 1% ether in petroleum ether. Extraction of the major band followed by bulb to bulb distillation at 70 °C (0.05 mm) yielded 22 mg (69%) of pure **2**, $[\alpha]^{21}_D$ −68°. Anal. Calcd for $C_{15}H_{20}O$: C, 83.33; H, 9.26. Found: C, 83.13; H, 9.49. This material was identical in all respects (GC, IR, NMR, TLC, analysis, optical rotation) with an authentic sample of natural debromoaplysin.[17]

(−)-Aplysin (1). Debromoaplysin (**2**; 22 mg, 0.10 mmol) was dissolved in hexane (1 mL) containing suspended anhydrous sodium carbonate (16 mg). Bromine (7 μL) was added slowly. Within 2 min after addition of the bromine, GC indicated that less than 2% of the starting material remained. The reaction mixture was filtered through a short (3 cm) column of silica gel with 10% ether in petroleum ether as an eluant to afford 30 mg of crude aplysin. Recrystallization from methanol yielded 21 mg of white needles: mp 82–83 °C; $[\alpha]^{21}_D$ −84.2° (c 0.31, $CHCl_3$). Anal. Calcd for $C_{15}H_{19}BrO$: C, 61.02; H, 6.44; Br, 27.12. Found: C, 61.10; H, 6.46; Br, 27.04. This material was identical in all respects with an authentic sample of aplysin[17] (GC, IR, NMR, TLC, analysis, optical rotation) and gave an undepressed melting point admixture.

Acknowledgment. The authors wish to thank the Research Corp., the Washington State University Research Fund, and the National Institutes of Health for their support of this work. The generous support of Tribhuvan University, Katmandu, Nepal, and the International Institute of Education for a fellowship for M.B.G. is gratefully acknowledged.

Registry No. (−)-**1**, 6790-63-2; (−)-**2**, 23444-68-0; **6**, 1196-00-5; (−)-**7**, 73286-59-6; (−)-**8**, 73286-60-9; **9**, 57234-27-2; (±)-*trans*-**10a**, 63023-42-7; (±)-*cis*-**10b**, 63023-32-5; **12**, 73286-61-0; **13**, 73346-52-8; **14**, 14847-51-9; (−)-**15**, 73286-62-1; (−)-**16**, 73307-73-0; (+)-**16**, 73307-74-1; **18**, 73286-63-2; **19**, 73286-64-3; (−)-**20**, 73307-75-2; (+)-**20**, 73307-76-3; **21**, 73307-77-4; (−)-**22**, 73307-78-5; *m*-cresol, 108-39-4; isopinocampheyl chloromethyl ether, 73286-59-6.

Synthesis of the Optical Isomers of 3-Methyl-6-isopropenyl-9-decen-1-yl Acetate, a Component of the California Red Scale Pheromone[1]

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The synthesis of the optical isomers of 3-methyl-6-isopropenyl-9-decen-1-yl acetate (**1**), a component of the California red scale pheromone, and the determination of their biological activity were completed. Initially, (±)-citronellol was converted in four steps to a mixture of all four diastereomers of **1**, the key step being the reaction of lithium di(3-butenyl)cuprate with 6,7-epoxycitronellyl acetate (**4**). This mixture strongly attracted male California red scale. To determine which of the four diastereomers of **1** were biologically active, (3*R*,6*RS*)- and (3*S*,6*RS*)-**1** were then prepared from (*R*)-(+)-citronellol and (*S*)-(−)-citronellol, respectively. Since the 3*S*,6*RS* diastereomeric mixture was found to be a powerful attractant whereas the 3*R*,6*RS* diastereomeric mixture was devoid of attractancy, the 3*S*,6*R* and 3*S*,6*S* diastereomers of **1** were then prepared. The key to the synthesis of each of these two diastereomers of **1** was the high-performance LC separation of the diastereomeric MTP esters **12a** and **12b**. Lithium aluminum hydride reduction of **12a** and **12b** gave the corresponding diols **11a** and **11b**, which were intermediates in the synthesis of (3*S*,6*R*)- and (3*S*,6*S*)-**1**, respectively. The assignment of absolute configuration at C-6 in diols **11a** and **11b** (and therefore of the diastereomers of **1**) was made on the basis of induced CD spectra of each diol and of the closely related diol of (10*S*)-JH III (**13**). The 3*S*,6*R* diastereomer of **1** was found to be more attractive to male California red scale than was the 3*S*,6*S* diastereomer. The naturally occurring pheromone component **1**, upon examination by capillary GLC under conditions which gave separation of the 3*S*,6*R* and 3*S*,6*S* diastereomers, eluted with the synthetic 3*S*,6*R* diastereomer.

The sex pheromone of the California red scale, *Aonidiella aurantii*, was recently isolated and identified as a mixture of 3-methyl-6-isopropenyl-9-decen-1-yl acetate (**1**) and the closely related (*Z*)-3-methyl-6-isopropenyl-3,9-

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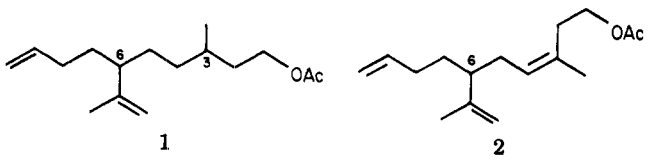
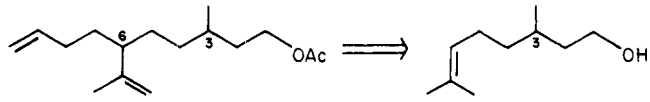


1 2

decadien-1-yl acetate (2). Because the California red scale is a significant pest of citrus, considerable field work has been recently carried out to determine the usefulness of these pheromone components in a scale-control program. As part of our continuing interest in the use of pheromones in integrated pest management and to assist in the field evaluation of the California red scale pheromone, we investigated the synthesis of both pheromone components, giving special consideration to the stereochemical features of each component. Elsewhere we have reported the synthesis and biological activity of the four geometric and optical isomers of component 2.[2,3] The naturally occurring pheromone component 2 was shown to be the *Z* isomer, and only the 6*R* isomer of 2 was attractive to male red scale. Recently, Snider and Rodini reported a synthesis of component 1.[4] Their synthesis of 1, however, provided no control of C-6 stereochemistry and gave diastereomer mixtures of low optical purity. We now present our work on the preparation of the diastereomers of component 1 in high optical purity.[5] Our synthetic approach has also been applied to the preparation of larger quantities of 1 for commercial use.

Results and Discussion

Examination of the carbon skeleton of 1 reveals that it contains the elements of the monoterpene citronellol (3)

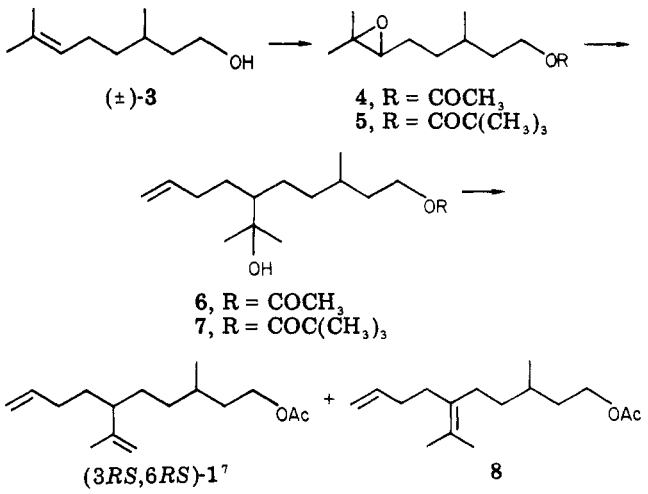


1 3

and suggests the retrosynthetic plan 1 → 3. Citronellol contains two structural features which make it an especially attractive starting material for the preparation of the various diastereoisomers of 1. First, in our retrosynthetic plan the asymmetric C-3 carbon atom in citronellol corresponds to one of the asymmetric centers in pheromone component 1. Since we had available to us from earlier work samples of both (+)- and (−)-citronellol of high optical purity,[6] we could use these enantiomers of 3 to prepare 1 of known absolute configuration at C-3. Second, the olefinic site in citronellol (3) is suitably located for the introduction of functionality necessary to accomplish alkylation at C-6. We anticipated that alkylation with a judiciously chosen 6,7-functionalized citronellyl derivative would also allow us to control the stereochemistry at C-6 of pheromone component 1.

Our synthetic approach for effecting the stereoselective introduction of a butenyl moiety into a citronellyl derivative was first carried out with (±)-citronellol. Racemic

Scheme I



(±)-3 4, R = $COCH_3$; 5, R = $COC(CH_3)_3$

6, R = $COCH_3$; 7, R = $COC(CH_3)_3$

$(3RS,6RS)$-1[7] 8

citronellol (3) was first acetylated and then epoxidized with *m*-chloroperoxybenzoic acid to give a mixture of diastereomers[7] of 6,7-epoxycitronellyl acetate (4) (see Scheme I). Initially, reaction of these epoxide diastereomers with 5 equiv of lithium di(3-butenyl)cuprate in ether followed by reacetylation gave the hydroxy acetate diastereomers 6,[7] containing the entire carbon skeleton of pheromone component 1, in a 58% yield. The reacetylation step was necessary since partial acetate cleavage occurred during the cuprate addition reaction. This addition reaction was improved during scale up preparations of 1 by modifying both the organometallic reagent and the citronellyl derivative.[8] Thus, copper(I)-catalyzed (0.1 equiv of CuI) addition of 2 equiv of 3-butenylmagnesium chloride to a diastereomeric mixture of 6,7-epoxycitronellyl 2,2-dimethylpropanoates (5) gave the hydroxy pivalate diastereomers 7[7] in 78% yield.

Dehydration of the hydroxy acetates 6 was effected by treating them with excess methanesulfonyl chloride and triethylamine (1:2, respectively) to give, in 97% yield, a mixture of diene acetates 1 and 8 in approximately a 4:1 ratio, respectively. The ratio of olefinic isomers produced was relatively insensitive to the structure of the amine used in the elimination step. The undesired minor product 8 was readily separated from 1 in the following manner. Treatment of the diene mixture 1 and 8 in dichloromethane with an amount of *m*-chloroperoxybenzoic acid equivalent to the amount of diene 8 in the mixture resulted in the selective epoxidation of the tetrasubstituted double bond of 8. Separation of 1 and the resultant epoxide of 8 by silica gel chromatography gave 1 in 75% yield as a mixture of diastereomers. The ^{13}C NMR spectrum of the mixture (6 singlets and 10 sets of closely spaced doublets; see Experimental Section) suggested about a 1:1 ratio of diastereomers, and an exact ratio of 43.1:56.9 was determined upon separation of the diastereomers by capillary GLC. The spectra of this sample were identical with those of naturally occurring 1, and the bioassay of this diastereomeric mixture showed it to be very attractive to male California red scale.[9]

To determine which of the four diastereomers of 1 were biologically active, we next chose to prepare samples of 1

(1) Contribution No. 75 from the Research Laboratory of Zoecon Corporation.

(2) Roelofs, W. L.; Gieselmann, M. J.; Cardé, A. M.; Tashiro, H.; Moreno, D. S.; Henrick, C. A.; Anderson, R. J. *Nature* **1977**, *267*, 698–9.

(3) Roelofs, W.; Gieselmann, M.; Cardé, A.; Tashiro, H.; Moreno, D. S.; Henrick, C. A.; Anderson, R. J. *J. Chem. Ecol.* **1978**, *4*, 211–24.

(4) Snider, B. B.; Rodini, D. *Tetrahedron Lett.* **1978**, 1399–1400.

(5) Presented earlier in part: Anderson, R. J.; Chinn, H. R.; Gill, K.; Henrick, C. A. "Abstracts of Papers", 175th National Meeting of the American Chemical Society, Anaheim, CA, March 1978; American Chemical Society: Washington, D.C., 1978; PEST 65.

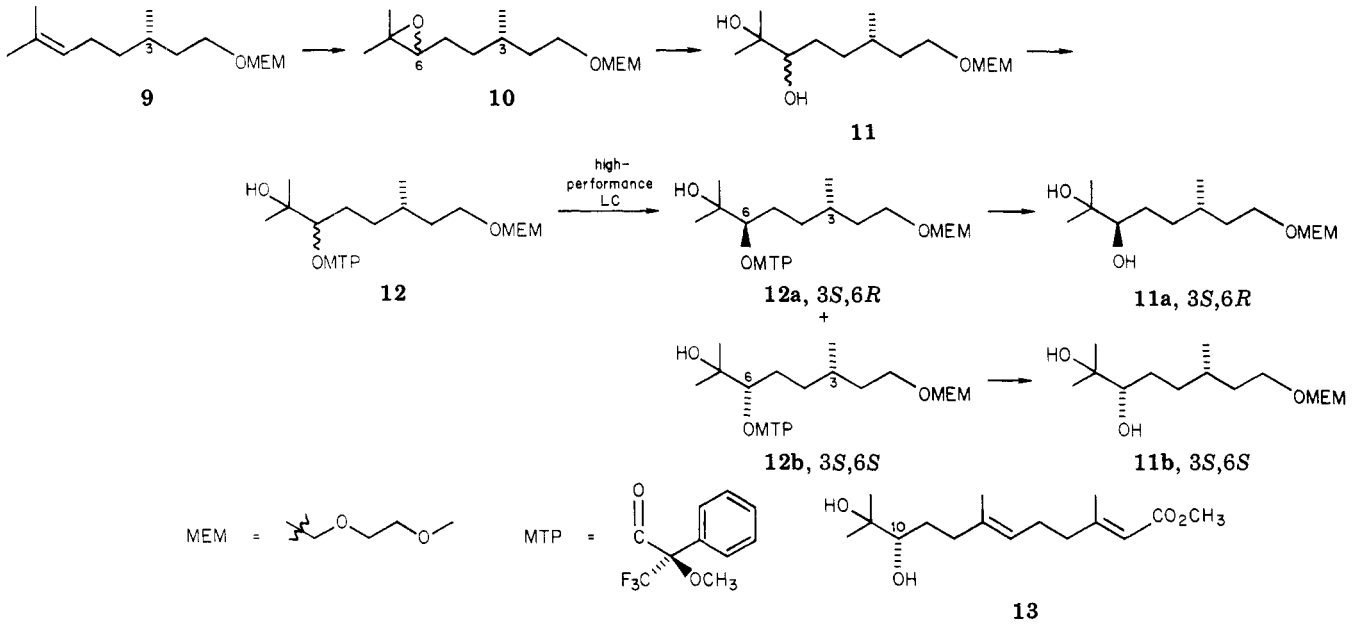
(6) Henrick, C. A.; Anderson, R. J.; Staal, G. B.; Ludvik, G. L. *J. Agric. Food Chem.* **1978**, *26*, 542–50, and references cited therein.

(7) The diastereomers were separable by capillary GLC (see Experimental Section) and were present in approximately a 1:1 ratio.

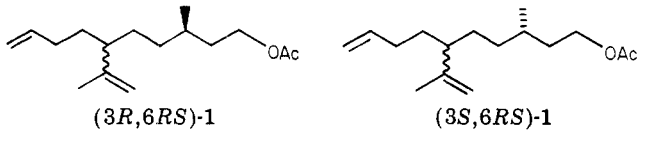
(8) Carney, R. L.; Lui, A. S., Zoecon Corporation, personal communication, 1979. These colleagues have converted hydroxy pivalate 7 to 1 in 60% yield.

(9) Gieselmann, M. J.; Henrick, C. A.; Anderson, R. J.; Moreno, D. S.; Roelofs, W. L. *J. Insect Phys.* **1980**, *26*, 179–82.

Scheme II



resolved at C-3 by starting our synthesis with optically active citronellol. (*R*)-(+)-Citronellol was prepared in high optical purity (99.5% ee)[10] from commercially available (*R*)-(+)-pulegone,[6] and (*S*)-(−)-citronellol was obtained in slightly lower optical purity (98.0% ee)[10] from a sample of (*S*)-(−)-pulegone.[6,11] The optical purity of each citronellol sample was determined by means of the following method developed earlier in our laboratories.[12] Thus, (+)- or (−)-citronellic acid, the immediate precursor of (+)- or (−)-citronellol, was converted to its acid chloride which was then treated with excess (*R*)-(+)-1-(1-naphthyl)ethylamine. The diasteromeric amides thus obtained are readily resolved by high-performance LC, and an exact optical purity for each citronellic acid (and by inference, for each citronellol) enantiomer is thus obtained. (*R*)-(+)-Citronellol was then converted to (3*R*,6*RS*)-1[7] via the route already



(3*R*,6*RS*)-1 (3*S*,6*RS*)-1

described above for (±)-citronellol and outlined in Scheme I (**3** → **4** → **6** → **1**); likewise, (*S*)-(−)-citronellol gave (3*S*,6*RS*)-1.[7] In both greenhouse bioassays and field tests, the mixture of diastereomers with the 3*R* configuration was completely unattractive to male California red scale, while the diastereomeric mixture prepared from (*S*)-(−)-citronellol was a powerful attractant.[9] The attractancy of (3*R*,6*RS*)-1 reported by Snider and Rodini[4] can be attributed to contaminating (3*S*,6*RS*)-1 present in their sample.

Since only diastereomers of **1** with the 3*S* configuration were biologically active, we next focused our attention on the preparation of (3*S*,6*R*)-1 and (3*S*,6*S*)-1. To accomplish the synthesis of these diastereomers, we first converted (*S*)-(−)-citronellol to the (methoxyethoxy)methyl (MEM) ether **9**,[13] which on treatment with *m*-chloroperoxybenzoic acid gave epoxy ether **10** (see Scheme II). Aqueous acid hydrolysis of **10** produced the mixture of diastereomeric glycols **11** which was converted to the mixture of α-methoxy-α-(trifluoromethyl)phenylacetates **12** (MTP esters)[14] with the acyl chloride of (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid and 4-(dimethylamino)pyridine in acetonitrile. Resolution of the diastereomeric MTP esters **12**, although difficult (k' values of 4.75 and 5.70; α = 1.2 from analytical high-performance LC), was nevertheless achieved by preparative high-performance LC. The faster eluting isomer **12a**, obtained in a diastereomeric purity of 96% (i.e., 96:4, **12a**:**12b**), was tentatively assigned the 3*S*,6*R* configuration by analogy with the elution order of the MTP esters of the diol **13** and its enantiomer prepared from racemic juvenile hormone III (JH III).[15] Confirmation of this assignment is described below. The slower eluting 3*S*,6*S* diastereomer **12b** was obtained in a diastereomeric purity of 96.5% (i.e., 96.5:3.5, **12b**:**12a**) after two further high-performance LC chromatographic purifications. Each of the resolved esters, **12a** and **12b**, was treated with lithium aluminum hydride to regenerate the corresponding diol, **11a** and **11b**. The absolute configuration of each diol was then determined by the recently developed procedure of Nakanishi and Dillon.[16] Circular dichroism (CD) spectra were recorded for a solution of each of the diols, **11a** and **11b**, and Ni(acac)$_2$ in CCl_4. A CD spectrum was also obtained for a solution of Ni(acac)$_2$ and (10*S*)-JH III diol (**13**) which we prepared from a sample of (10*S*)-JH III according to methods known to give 96% retention of configuration at C-10.[17] The Cotton effect at 315 nm for diol **11a** derived from the faster eluting MTP ester was positive, while the

(10) The optical purity of the citronellol enantiomers is given as the per cent enantiomeric excess and is calculated as follows: % ee of *R* enantiomer = 100(*R* − *S*)/(*R* + *S*) = %*R* − %*S*. Morrison, J. D.; Mosher, H. S. "Asymmetric Organic Reactions"; Prentice-Hall: Englewood Cliffs, NJ, 1971; p 10.

(11) The (*S*)-(−)-pulegone was graciously supplied to us by Mr. Bernard Kane of Glidden-Durkee.

(12) Bergot, B. J.; Anderson, R. J.; Schooley, D. A.; Henrick, C. A. *J. Chromatogr.* **1978**, *155*, 97–105.

(13) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809–12.

(14) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–49.

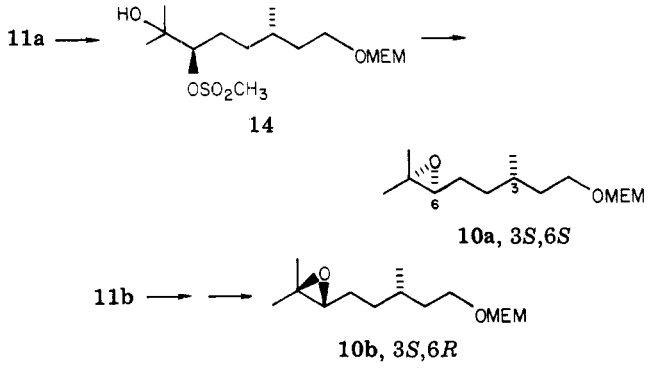
(15) Judy, K. J.; Schooley, D. A.; Dunham, L. L.; Hall, M. S.; Bergot, B. J.; Siddall, J. B. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 1509–13.

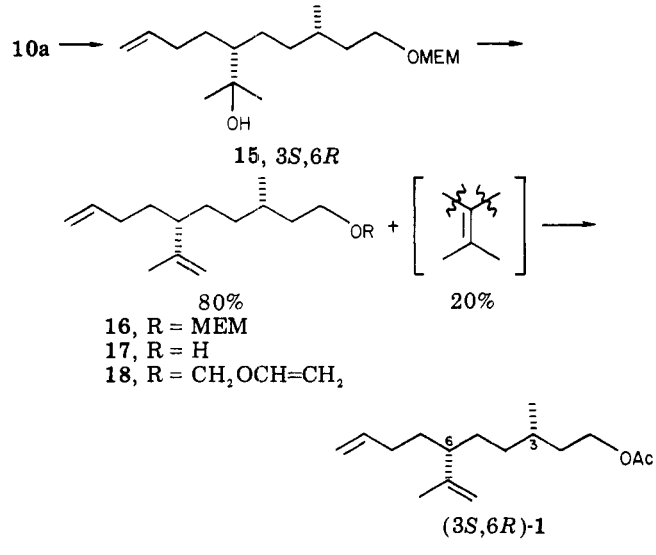
(16) Dillon, J.; Nakanishi, K. *J. Am. Chem. Soc.* **1974**, *96*, 4057–61. Dillon, J.; Nakanishi, K. *Ibid.* **1975**, *97*, 5409–22.

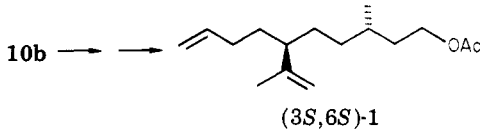
(17) Nakanishi, K.; Schooley, D. A.; Koreeda, M.; Dillon, J. *J. Chem. Soc., Chem. Commun.* **1971**, 1235–6.

Cotton effects at the same wavelength for diol **11b** and for (10*S*)-JH III diol **13** were negative. A second Cotton effect at 295 nm was also observed for each sample: negative for diol **11a** and positive for diols **11b** and **13**. The nearly superimposable CD spectra for **11b** and **13**, resulting from identical diol configurations, confirmed our more tenuous assignments of configuration above based on the high-performance LC elution order of MTP ester diastereomers.

With the configuration of diols **11a** and **11b** firmly established, we proceeded to convert each diol back to the epoxide. Thus, 3*S*,6*R* diol **11a** on reaction with methanesulfonyl chloride and triethylamine gave the mesylate **14** which was then treated with KOH in methanol to give 3*S*,6*S* epoxide **10a** with inversion at C-6. In an identical manner, 3*S*,6*S* diol **11b** was converted to 3*S*,6*R* epoxide **10b**. The butenyl chain was then introduced as before. Reaction of 3*S*,6*S* epoxide **10a** with lithium di(3-butenyl)cuprate gave hydroxy ether **15**. On the basis of earlier studies on the reaction of epoxides with organocuprates,[18] we assigned the 3*S*,6*R* configuration to **15**, the result of organocopper attack on epoxide **10a** with inversion at C-6. Dehydration of **15** was again accomplished with methanesulfonyl chloride and triethylamine to give **16** and its tetrasubstituted double bond isomer in a 4:1 ratio, respectively. Our attempts to remove the alcohol protecting group of **16** according to literature methods[13] were totally unsuccessful. We therefore developed an alternative two step sequence to cleave the (methoxyethoxy)methyl ether. Ether **16** was treated with *n*-butyllithium in hexane to give a mixture of the desired alcohol **17** and the vinyloxymethyl ether **18** in a 1:1 ratio.[19] Further treatment of this mixture with aqueous acid gave the pure alcohol **17**. Acetylation of **17** followed by peroxy acid treatment as before to selectively epoxidize the tetrasubstituted double bond and purification by chromatography gave (3*S*,6*R*)-**1**. The diastereomeric purity of this sample was determined to be 93.3% 3*S*,6*R* (and 6.7% 3*S*,6*S*) by capillary GLC. Apparently, a slight loss of optical activity occurs during the transformation of the 3*S*,6*R* MTP ester **12a** to (3*S*,6*R*)-**1**, since the diastereomeric purity of **12a** was 96%.[20] In like manner, epoxide **10b** yielded the 3*S*,6*S* diastereomer of **1**.







(3*S*,6*S*)-**1**

For this sample the diastereomeric purity, determined again by capillary GLC, was 93.4% 3*S*,6*S* (6.6% 3*S*,6*R*). With the capillary GLC retention time of each diastereomer established, we then examined the natural pheromone component. Under these same GLC conditions, the natural material eluted as a single peak with a retention time identical with that of the synthetic 3*S*,6*R* diastereomer, (and of course its enantiomer, (3*R*,6*S*)-**1**). However, the total lack of activity of synthetic (3*R*,6*S*)-**1** suggests that the natural component is the 3*S*,6*R* diastereomer and that it is enantiomerically pure.

Each of the synthetic diastereomers, (3*S*,6*R*)-**1** and (3*S*,6*S*)-**1**, was assayed as an attractant for male California red scale in both field and greenhouse situations. Under both sets of conditions, the 3*S*,6*R* diastereomer was superior to the 3*S*,6*S* diastereomer by a factor of about 3.5.[9] The attractiveness of the 3*S*,6*S* diastereomer sample may, however, be due to the presence of the 3*S*,6*R* diastereomer in approximately 7%, especially since the 3*S*,6*S* diastereomer is *not* present in the naturally occurring pheromone. It is noteworthy that the C-6 configurations of the most active diastereomer of **1** and of the active enantiomer of **2** are both *R*.

Experimental Section

General Procedures. 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. Silica plates impregnated with Rhodamine 6G dye were used to visualize those compounds lacking significant UV absorbance at 254 nm. Infrared (IR) spectra were obtained by using a Unicam SP 200 G spectrophotometer or a Perkin-Elmer Model 281 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were determined on a Varian T-60 spectrometer. ^{13}C NMR spectra were recorded on a Bruker WH-90 Fourier-transform spectrometer operating at 22.62 MHz. The temperature was maintained at 305 K during the measurement of the noise-modulated decoupled spectra, and a pulse width of 5 μs (33°) was used. Chemical shifts were measured in parts per million (δ) relative to tetramethylsilane as the internal reference. Mass spectra were measured on either a Hewlett-Packard Model 5984A or Model 5985 GLC–MS data

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(20) This slight loss of optical activity probably does *not* occur in the transformation of diol **11a** to epoxide **10a** via mesylate **14**, since this same conversion has been carried out on a closely related system with no loss of optical activity: Schooley, D. A.; Bergot, B. J.; Goodman, W.; Gilbert, L. I. *Biochem. Biophys. Res. Commun.* **1978**, *81*, 743–9.

system. Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter. Gas–liquid chromatographic (GLC) analyses were performed on Model 402 Hewlett-Packard or Model 3700 Varian (capillary GLC) instruments equipped with flame-ionization detectors. Elemental analyses were performed by Erich Meier at the Stanford University Chemistry Department microanalytical laboratories. All temperatures are in degrees Celsius.

Materials. All solvents were dried over activated 4-Å molecular sieves. (±)-Citronellol was supplied by Bush Boake Allen Ltd. (*R*)-(+)-Citronellol, $[\alpha]^{25}_D$ +5.49° (neat), was prepared as previously described[6] from (*R*)-(+)-pulegone, $[\alpha]^{25}_D$ +24.57° (neat), supplied by Givaudan Corporation. (*S*)-(−)-Citronellol was obtained from a sample of (*S*)-(−)-pulegone, $[\alpha]^{25}_D$ −22.95° (neat), supplied by Glidden-Durkee.[6,11] Treatment of each citronellol sample with acetic anhydride and pyridine followed by workup and distillation gave the corresponding citronellyl acetate.

(3*RS*,6*RS*)-6,7-Epoxycitronellyl Acetate (4). To a solution of 21 g (0.106 mol) of (±)-citronellyl acetate in 200 mL of chloroform ($CHCl_3$) at 0 °C was added portionwise 22.8 g (0.112 mol) of 85% *m*-chloroperoxybenzoic acid. After being stirred at room temperature for 24 h, the reaction mixture was filtered through Celite. The filtrate was washed with saturated $NaHSO_3$, saturated Na_2CO_3, and brine and then dried (Na_2SO_4). The solvent was removed in vacuo to give 21.6 g (0.101 mol, 95% yield) of epoxide **4**, analyzed as a mixture of diastereomers in a 47.8:52.2 ratio by capillary GLC (20 m × 0.25 mm ID wall coated open tubular glass capillary, Carbowax 20M, 115 °C, retention times 18.49 and 18.70 min, respectively): IR (neat) 1742 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 4.10 (t, 2, *J* = 6.5 Hz, CH_2OAc), 2.68 (br t, 1, *J* = 6 Hz, C-6 H), 2.03 (s, 3, CH_3CO_2), 1.30 (s, 3, C-7 CH_3), 1.25 (s, 3, C-7 CH_3), 0.92 (d, 3, C-3 CH_3); ^{13}C NMR ($CDCl_3$) δ 18.76, 19.31, 19.44, 21.07, 24.93, 26.37, 26.43, 29.81, 33.58, 35.40, 35.57, 58.26, 58.32, 62.91, 64.56, 171.32; mass spectrum (CI, CH_4), *m/e* (relative intensity) 215 (M^+ + H, 2), 155 (100).

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.27; H, 10.24.

(3*RS*,6*RS*)-6-(1-Hydroxy-1-methylethyl)-3-methyl-9-decen-1-yl Acetate (6). Lithium–1% sodium wire (2.18 g, 0.314 mol) was washed free of hydrocarbon with pentane and cut into small pieces which were suspended in 100 mL of dry ether at 0 °C under argon. To the lithium was then added a solution of 14.3 g (0.157 mol) of 4-chloro-1-butene in 50 mL of ether over a 1-h period, and the reaction was stirred for another 2 h. Titration of an aliquot[21] gave the concentration of 3-butenyllithium as 0.7 M (~71% yield).

To a suspension of 8.57 g (0.045 mol) of cuprous iodide in 50 mL of dry ether at −20 °C under argon was added 140 mL of 0.7 M 3-butenyllithium (0.098 mol). After 1 h at −20 °C, an aliquot of the mixture gave a negative Gilman color test,[22] and 3.5 g (0.016 mol) of epoxide diastereomers **4** was added. The reaction was stirred overnight at 4 °C and then quenched by the addition of aqueous $(NH_4)_2SO_4$. The mixture was filtered through Celite, and the ether layer was then separated, washed with saturated $(NH_4)_2SO_4$ and brine, and dried (Na_2SO_4). Removal of solvent gave 6.04 g of a mixture of acetate **6** and the corresponding alcohol. This mixture was treated with 3.35 g (0.033 mol) of acetic anhydride and 3.23 g (0.041 mol) of pyridine at room temperature for 20 h. Ice was added to the mixture and after 45 min the organic product was extracted with ether. The ether fraction was washed with 2 N HCl, 2 M Na_2CO_3, and brine and dried (Na_2SO_4). The residue, after solvent removal in vacuo, was purified by chromatography on seven 1 m × 20 cm preparative silica plates (Rhodamine 6G impregnated) which were developed in 20% ethyl acetate in hexane to give 1.99 g (7.4 mmol, 46% yield) of a mixture of diastereomeric acetates **6**, separable by capillary GLC and obtained in a 47.5:52.5 ratio (20 m × 0.25 mm ID wall coated open tubular glass capillary, Carbowax 20M, 100 to 200 °C, 2 °C/min, retention times 37.24 and 37.51 min, respectively): IR (neat) 3460 (OH), 3064 (H_2C=C), 1744 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 6.13–5.30 (m, 1, H_2C=C**H**), 5.17–4.70 (2, H_2C=C), 4.05 (t, 2, *J* = 6.5 Hz, CH_2OAc), 2.03 (s, 3, CH_3CO_2), 1.18 (s, 6, $(CH_3)_2COH$); ^{13}C NMR ($CDCl_3$) δ 19.44, 19.67, 21.03, 27.41, 28.32, 28.41, 30.53, 33.65, 35.27, 35.70, 36.74, 36.83, 49.25, 49.35, 63.10, 73.96, 114.56, 139.27, 171.39; mass spectrum (70 eV), *m/e* (relative intensity) 255 ($M^+ - CH_3$, 3), 81 (100).

Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.81; H, 11.22.

(3*RS*,6*RS*)-6-(1-Hydroxy-1-methylethyl)-3-methyl-9-decen-1-yl 2,2-Dimethylpropanoate (7). To a suspension of 25.5 g (1.05 mol) of magnesium turnings in 100 mL of THF under N_2 was added 10 mL of 4-chloro-1-butene followed by several drops of ethylene bromide to initiate the Grignard formation. After about 5 min, the solution turned dark, and an additional 200 mL of THF was then added, after which 63.7 mL (total of 73.7 mL, 67.9 g, 0.75 mol) of 4-chloro-1-butene was added dropwise. The temperature was maintained at 10 °C during the halide addition. After the addition was completed the solution was stirred at room temperature for 4 h. Titration of an aliquot[21] gave a concentration of 0.95 M 3-butenylmagnesium chloride.

To a mixture of 4.54 g (23.8 mmol) of cuprous iodide and 61.0 g (0.238 mol) of epoxy pivalate diastereomers **5** (prepared from citronellol and pivaloyl chloride followed by oxidation with *m*-chloroperoxybenzoic acid) in 475 mL of THF at −35 °C under N_2 was added 502 mL (0.477 mol) of 0.95 M 3-butenylmagnesium chloride over a 2-h period. After addition, the dark green solution was stirred at −30 °C for 1.5 h and −20 °C for 3 h and then maintained overnight at −20 °C in a freezer without stirring. The reaction was quenched with saturated NH_4Cl solution, and the mixture was then filtered through Celite. The filtrate was concentrated under reduced pressure, and the residue was extracted with hexane. The hexane fraction was washed with saturated NH_4Cl, water, and brine and dried ($MgSO_4$). The residue after solvent removal in vacuo was purified by fractional distillation [bp 150–155 °C (0.065 mm)] followed by column chromatography on silica gel to give 57.6 g (0.185 mol, 78% yield) of hydroxy pivalate diastereomers **7**. Capillary GLC analysis of the mixture indicated that the diastereomers were present in a 45.7:54.3 ratio (20 m × 0.25 mm ID wall coated open tubular glass capillary, Carbowax 20M, 170 °C, retention times 14.27 and 14.49 min, respectively): IR (neat) 3480 (OH), 3070 (H_2C=C), 1710 cm^{-1} (C=O); ^1H NMR (C_6D_6) δ 6.10–5.53 (m, 1, CH_2=C**H**), 5.20–4.90 (m, 2, H_2C=C), 4.10 (t, 2, *J* = 6 Hz, CH_2OCOR), 1.20 (s, 9, $(CH_3)_3CCO$), 1.05 (s, 6, $(CH_3)_2COH$); ^{13}C NMR ($CDCl_3$) δ 19.47, 19.70, 26.95, 27.24, 27.44, 28.38, 28.51, 30.59, 33.61, 35.40, 35.76, 36.74, 36.83, 38.75, 49.32, 62.91, 73.99, 114.56, 139.24, 178.80.

Anal. Calcd for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61. Found: C, 73.43; H, 11.87.

(3*RS*,6*RS*)-3-Methyl-6-isopropenyl-9-decen-1-yl Acetate (3*RS*,6*RS*-1). To a solution of 0.44 g (1.63 mmol) of hydroxy acetate diastereomers **6** and 0.51 g (5.04 mmol) of triethylamine in 6 mL of dichloromethane at 0 °C under N_2 was added dropwise 0.28 g (2.45 mmol) of methanesulfonyl chloride. After 15 min the ice bath was removed, and the reaction mixture was maintained at room temperature for 2 h. The reaction was then diluted with ether and water. The ether layer was separated and washed with 2 N HCl, saturated $NaHCO_3$, and brine and dried (Na_2SO_4). Removal of solvent in vacuo gave 0.40 g of a mixture of diene acetates **1** and **8** in a 4:1 ratio, respectively, as determined by GLC analysis (2-m 3% OV-17/0.4% Carbowax, 80 to 240 °C, 5 °C/min; retention times of 17.1 and 17.8 min, respectively).

The diene acetate mixture (0.40 g, 1.58 mmol) was dissolved in 3 mL of $CHCl_3$, and 64 mg (0.315 mmol) of 85% *m*-chloroperoxybenzoic acid was added at room temperature. After 18 h, the reaction mixture was diluted with additional $CHCl_3$, and the chloroform solution was washed with saturated $NaHSO_3$, 2 M Na_2CO_3, and brine and dried ($MgSO_4$). Removal of solvent in vacuo followed by purification of the residue on two 1 m × 20 cm preparative silica gel plates (Rhodamine 6G impregnated; developed in 5% ether in hexane) and short-path distillation [bp (bath) 60 °C (0.01 mm)] gave 0.30 g (1.19 mmol, 73% yield) of diene acetate diastereomers **1**, separable by capillary GLC and obtained in a 43.1:56.9 ratio (20 m × 0.26 mm ID wall coated open tubular glass capillary, Carbowax 20M, 125 °C, retention times 14.93 and 15.32 min, respectively): IR (CCl_4) 3065 (H_2C=C), 1742 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 5.77 (br m, 1, C=CH), 5.20–4.57 (4, H_2C=C), 4.10 (t, 2, *J* = 6.5 Hz, CH_2OAc), 2.05 (s, 3, CH_3CO_2), 1.60 (br s, 3, CH_3C=C), 0.90 (d, 3, *J* = 5 Hz, C-3 CH_3); ^{13}C NMR ($CDCl_3$) δ 17.75, 17.88, 19.41, 19.70, 21.03, 29.81, 30.07, 30.56, 30.62,

(21) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–8.
(22) Gilman, H.; Schultze, F. *J. Am. Chem. Soc.* **1925**, *47*, 2002–5.

31.70, 32.67, 32.80, 34.59, 34.72, 35.31, 35.73, 46.98, 47.14, 63.13, 111.86, 111.96, 114.30, 139.21, 147.27, 147.40, 171.39; mass spectrum (CI, CH_4), m/e (relative intensity) 253 ($M^+ + H$, 6), 252 (M^+, 2), 251 ($M^+ - H$, 12), 123 (100).

Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.43; H, 11.19.

(3*R*,6*RS*)-3-Methyl-6-isopropenyl-9-decen-1-yl Acetate (3*R*,6*RS*-1). (*R*)-(+)-Citronellol (see Materials) was converted to (3*R*,6*RS*)-1 in a manner identical with that described above. Capillary GLC analysis (18 m × 0.3 mm ID wall coated open tubular glass capillary, Superox 4, 135 °C) of the product showed it to be a mixture of diastereoisomers in the ratio of 49.5:50.5 with retention times of 14.00 and 14.33 min, respectively. IR, ^1H NMR, and mass spectra of (3*R*,6*RS*)-1 were identical with those obtained from (3*RS*,6*RS*)-1.

(3*S*,6*RS*)-3-Methyl-6-isopropenyl-9-decen-1-yl Acetate (3*S*,6*RS*-1). (*S*)-(−)-Citronellol (see Materials) was converted to (3*S*,6*RS*)-1 in a manner identical with that described above for (3*RS*,6*RS*)-1. Capillary GLC analysis (18 m × 0.3 mm ID wall coated open tubular glass capillary, Superox 4, 135 °C) of this product showed it to be a mixture of diastereomers in a 46.0:54.0 ratio with retention times of 14.01 and 14.34 min, respectively. IR, ^1H NMR, and mass spectra of (3*S*,6*RS*)-1 were identical with those obtained from (3*RS*,6*RS*)-1. The ^{13}C NMR of this mixture was also nearly identical with that of (3*RS*,6*RS*)-1, consistent with about a 1:1 ratio of diastereomers.

(3*S*)-Citronellyl (Methoxyethoxy)methyl Ether (9). To a solution of 14.7 g (94 mmol) of (*S*)-(−)-citronellol (see Materials) in 50 mL of dry THF at 0 °C under N_2 was slowly added 60 mL (96 mmol) of 1.6 M *n*-butyllithium in hexane. After 10 min, 12.0 g (96 mmol) of (methoxyethoxy)methyl chloride was added, and the solution was stirred for 4 h. Water and ether were added to the reaction, and the organic phase was separated, washed with brine, and dried (Na_2SO_4). Removal of solvent gave 22.8 g (93 mmol, 99% yield) of (methoxyethoxy)methyl ether **9**: NMR ($CDCl_3$) δ 5.12 (br t, 1, J = 7 Hz, C=CH), 4.72 (s, 2, OCH_2O), 3.42 (s, 3, OCH_3), 1.68 (br s, 3, CH_3C=C), 1.62 (br s, 3, CH_3C=C), 0.90 (d, 3, J = 5 Hz, C-3 CH_3); mass spectrum (CI, CH_4), m/e (relative intensity) 245 ($M^+ + H$, 0.9), 243 ($M^+ - H$, 4), 169 (100).

Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55. Found: C, 68.42; H, 11.54.

(3*S*,6*RS*)-6,7-Epoxycitronellyl (Methoxyethoxy)methyl Ether (10). To a solution of 22.8 g (93 mmol) of ether **9** in 250 mL of dichloromethane cooled to ice-bath temperature was added in portions 19.5 g (96 mmol) of 85% *m*-chloroperoxybenzoic acid. After 1 h, the mixture was poured into 2 M Na_2CO_3. Layers were separated, and the organic phase was washed with saturated $NaHSO_3$, 2 M Na_2CO_3, and brine and dried (Na_2SO_4). The solvent was removed in vacuo to give 23.8 g (91.5 mmol, 98% yield) of epoxide diastereomers **10**: NMR ($CDCl_3$) δ 4.70 (s, 2, OCH_2O), 3.40 (s, 3, OCH_3), 1.30 (s, 3, C-7 CH_3), 1.27 (s, 3, C-7 CH_3), 0.92 (d, 3, J = 5 Hz, C-3 CH_3); mass spectrum (CI, CH_4), m/e (relative intensity) 213 (3), 155 (100).

Anal. Calcd for $C_{14}H_{28}O_4$: C, 64.58; H, 10.84. Found: C, 64.40; H, 10.68.

(3*S*,6*RS*)-6,7-Dihydroxycitronellyl (Methoxyethoxy)-methyl Ether (11). To a solution of 23.6 g (91 mmol) of epoxide **10** in 120 mL of THF–H_2O (4:1) at room temperature was added dropwise a solution of 7% aqueous perchloric acid to obtain a pH of 2.5. After 2 h, sodium chloride was added to saturation and the mixture was extracted several times with chloroform. The combined chloroform extracts were washed with water and brine and dried ($MgSO_4$). Removal of solvent in vacuo gave 25.0 g of crude diol. Purification of 12 g of crude product by preparative TLC (1 m × 20 cm silica plates impregnated with Rhodamine 6G; developed in 5% MeOH in $CHCl_3$) gave 7.9 g of pure diol **11** as a mixture of diastereomers: IR (neat) 3500 cm^{-1} (OH); NMR ($CDCl_3$) δ 4.73 (s, 2, OCH_2O), 3.43 (s, 3, OCH_3), 1.22 (s, 3, CH_3COH), 1.17 (s, 3, CH_3COH), 0.92 (d, 3, J = 5 Hz, C-3, CH_3); mass spectrum of the bis(trimethylsilyl) ether (CI, CH_4), m/e (relative intensity) 407 ($M^+ - CH_3$, 10), 185 (73), 167 (100).

Anal. Calcd for $C_{14}H_{30}O_5$: C, 60.40; H, 10.86. Found: C, 60.5; H, 10.3.

2,6-Dimethyl-2-hydroxy-8-((methoxyethoxy)methoxy)-3-octyl 2-Methoxy-2-trifluoromethylphenylacetate (12). To a solution of 7.87 g (28.3 mmol) of diol diastereomers **11** in 100 mL of dry acetonitrile under N_2 was added 7.01 g (57.4 mmol) of 4-(dimethylamino)pyridine and 9.01 g (35.7 mmol) of the acyl chloride of (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid. The mixture was stirred overnight at room temperature, and then 4.0 mL (32 mmol) of (3-(dimethylamino)propyl)amine was added. After 30 min, the mixture was poured into ether and 2 N HCl. The organic fraction was separated, washed with 2 N HCl, water, and brine, and dried (Na_2SO_4). Removal of solvent in vacuo and purification of the residue on 1 m × 20 cm preparative silica gel plates impregnated with Rhodamine 6G (developed in 30% ethyl acetate in hexane) gave 8.4 g (60% yield) of diastereomeric MTP esters **12**. The diastereomers were resolved by analytical high-performance LC (30 cm × 0.4 cm μPorasil, 35% EtOAc in pentane, 1.8 mL/min, 360 psi) with k' values of 4.75 and 5.70 (α = 1.2): IR (neat) 3450 (OH), 1740 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.77–7.23 (m, 5, aromatic), 4.98 (m, 1, CHOCOR), 3.40 (s, 3, $OCH_2CH_2OCH_3$), 1.17 (m, 6, $(CH_3)_2COH$), 0.85 (d, 3, J = 5 Hz, C-3 CH_3); mass spectrum of the trimethylsilyl ether (CI, CH_4), m/e (relative intensity) 185 (100), 167 (92).

Anal. Calcd for $C_{24}H_{37}F_3O_7$: C, 58.29; H, 7.54; F, 11.52. Found: C, 58.10; H, 7.69; F, 11.3.

Separation of Diastereomers of 12 (12a and 12b). The diastereomers of **12** were separated by preparative high-performance LC with the Waters Prep 500 equipped with two normal-phase Prep PAK cartridges connected in tandem.

In a typical separation, 2.0 g of the mixture of diastereomers was injected onto the column which was then eluted with 35% ethyl acetate in hexane. The peak-shaving technique coupled with two recycles was used to collect each diastereomer. The faster eluting diastereomer **12a** (0.66 g) was obtained in a diastereomeric purity of 96% (i.e., **12a**:**12b**, 96:4), and the slower eluting diastereomer **12b** (0.68 g) was obtained in 84% diastereomeric purity (i.e., **12b**:**12a**, 84:16). A mixed fraction (0.42 g; **12a**:**12b**, 58:42) was also collected on the last recycle. Rechromatography of a 1.62-g sample enriched in **12b** (**12a**:**12b**, ~1:4) as before gave 1.10 g of **12b** in 91% diastereomeric purity (i.e., **12a**:**12b**, 9:91). This sample was chromatographed another time to give 0.76 g of **12b** in 96.5% diastereomeric purity (i.e., **12a**:**12b**, 3.5:96.5). The NMR spectra of **12a** and **12b** were essentially identical except for the *gem*-dimethyl groups: NMR ($CDCl_3$) of **12a** δ 1.20 and 1.15 (two s, 6, $(CH_3)_2COH$); NMR ($CDCl_3$) of **12b** δ 1.17 (s, 6, $(CH_3)_2COH$).

(3*S*,6*R*)-6,7-Dihydroxycitronellyl (Methoxyethoxy)methyl Ether (11a). To a solution of 2.23 g (4.5 mmol) of the faster eluting diastereomer **12a** in 20 mL of dry THF at 0 °C under N_2 was added dropwise 7.1 mL (18.0 mmol) of 2.54 M $LiAlH_4$ in THF. After 5 h at room temperature, excess $LiAlH_4$ was quenched by the sequential addition of 0.7 mL of water, 0.7 mL of 15% aqueous NaOH, and 2.1 mL of water. The aluminum salts were filtered off and washed several times with $CHCl_3$. The filtrate was washed with brine and dried ($MgSO_4$). Removal of solvent in vacuo and purification of the residue on a 1 m × 20 cm silica gel plate impregnated with Rhodamine 6G (developed with 5% MeOH in $CHCl_3$) gave 0.92 g (3.3 mmol, 73% yield) of (3*S*,6*R*)-**11a**, $[\alpha]^{25}_D$ +17.1° (*c* 0.0036 g/mL, MeOH). IR, NMR, and mass spectra of **11a** were identical with those of the diastereomer mixture **11**.

(3*S*,6*S*)-6,7-Dihydroxycitronellyl (Methoxyethoxy)methyl Ether (11b). In a manner identical with that above, the 3*S*,6*S* MTP ester **12b** was reduced to the 3*S*,6*S* diol **11b**, $[\alpha]^{25}_D$ −22.6° (*c* 0.010 g/mL, MeOH). IR, NMR, and mass spectra of **11b** were identical with those of the diastereomer mixture **11**.

Determination of Absolute Configuration of 11a and 11b. The procedure of Nakanishi and Dillon was used.[16] A 5.000 × 10^{-5} M solution of $Ni(acac)_2$ (1.375 mg) in CCl_4 (100 mL) was prepared. Each diastereomer, **11a** and **11b** (0.700 mg), was dissolved in 1.000 mL of the $Ni(acac)_2$ solution to give 2.514 × 10^{-3} M solutions of diols **11a** and **11b** [$Ni(acac)_2$:diol, 1:50]. Circular dichroism (CD) spectra were recorded for each sample. For **11a**, CD (CCl_4) λ ($\Delta\epsilon$) 295 (−0.13), 317 (+0.17) nm. For diastereomer **11b**, CD (CCl_4) λ ($\Delta\epsilon$) 295 (+0.19), 317 (−0.26) nm. For comparison, a CD spectrum was also recorded for (10*S*)-JH III diol **13**.[15] Thus, 0.750 mg of **13** was dissolved in 1.000 mL of a 5.000 × 10^{-5} M solution of $Ni(acac)_2$ in CCl_4. For **13**, CD (CCl_4) λ ($\Delta\epsilon$) 293 (+0.03), 315 (−0.03) nm.

(3*S*,6*S*)-6,7-Epoxycitronellyl (Methoxyethoxy)methyl Ether (10a). To a solution of 902 mg (3.24 mmol) of the 3*S*,6*R* diol **11a** in 35 mL of dry ether at 0 °C under N_2 was added 0.27

mL (3.49 mmol) of methanesulfonyl chloride, followed by 1.0 mL (7.2 mmol) of triethylamine dropwise. After 35 min at 0 °C, the mixture was poured into water and ether. The ether layer was washed with dilute aqueous HCl, saturated aqueous $NaHCO_3$, and brine and dried (Na_2SO_4). Removal of the solvent gave 925 mg of mesylate **14**: NMR ($CDCl_3$) δ 4.67 (s, 2, OCH_2O), 3.37 (s, 3, OCH_3), 3.10 (s, 3, CH_3SO_3), 1.23 (s, 6, $(CH_3)_2COH$).

To a cooled (0 °C) solution of the mesylate in 35 mL of MeOH under N_2 was added 3.6 mL (3.6 mmol) of 1 N KOH in MeOH. After 5 min, the reaction mixture was poured into water and the product was extracted into ether. The ether fraction was washed with brine and dried (Na_2SO_4). After solvent removal in vacuo, the residue was purified by preparative TLC (one 1 m × 20 cm silica gel plate impregnated with Rhodamine 6G, developed in 5% MeOH in $CHCl_3$) to give 525 mg (2.02 mmol, 62% yield from **11a**) of 3*S*,6*S* epoxide **10a**, $[\alpha]^{25}_D$ −9.6° (*c* 0.010 g/mL, MeOH). The IR, NMR, and mass spectra of **10a** were identical with those of the diastereomer mixture **10**.

(3*S*,6*R*)-6-(1-Hydroxy-1-methylethyl)-3-methyl-9-decen-1-yl (Methoxyethoxy)methyl Ether (15). To a suspension of 1.96 g (10.3 mmol) of cuprous iodide in 20 mL of ether at −20 °C under argon was added 40 mL (20.4 mmol) of a 0.51 M solution of 3-butenyllithium (see preparation of **6** above) in ether. After 40 min, an aliquot of the reaction mixture gave a negative Gilman color test,[22] so 0.516 g (1.98 mmol) of the 3*S*,6*S* epoxide **10a** in several milliliters of ether was added to the organocopper reagent. The reaction was then stirred at 4 °C for 16 h. Aqueous $(NH_4)_2SO_4$ and ether were added to the reaction mixture, and it was then filtered through Celite. The ether layer was separated and washed with aqueous $(NH_4)_2SO_4$ and brine and dried (Na_2SO_4). Removal of solvent in vacuo and purification of the residue by preparative TLC (two 1 m × 20 cm silica gel plates impregnated with Rhodamine 6G; developed in 25% EtOAc in hexane) gave 0.44 g (1.39 mmol, 70% yield) of the 3*S*,6*R* hydroxy ether **15**: IR (CCl_4) 3620 cm^{-1} (OH); NMR ($CDCl_3$) δ 6.17–5.30 (m, 1, H_2C=C**H**), 5.17–4.73 (m, 2, H_2C=C), 4.68 (s, 2, OCH_2O), 3.37 (s, 3, OCH_3), 1.17 (s, 6, $(CH_3)_2OH$), 0.88 (d, 3, J = 5 Hz, C-3 CH_3).

Anal. Calcd for $C_{18}H_{36}O_4$: C, 68.31; H, 11.47. Found: C, 67.88; H, 11.58.

(3*S*,6*R*)-3-Methyl-6-isopropenyl-9-decen-1-yl (Methoxyethoxy)methyl Ether (16). To a solution of 0.42 g (1.33 mmol) of the 3*S*,6*R* hydroxy ether **15** and 0.41 g (4.05 mmol) of triethylamine in 10 mL of dichloromethane at 0 °C under N_2 was added dropwise 0.23 g (2.0 mmol) of methanesulfonyl chloride. After 45 min at room temperature, the mixture was poured into water. The product was extracted with ether, and the ether layer was washed with 1 N HCl, 2 M Na_2CO_3, and brine and dried (Na_2SO_4). Removal of solvent in vacuo gave a residue which was purified by preparative TLC (three 1 m × 20 cm silica gel plates impregnated with Rhodamine 6G; developed twice in 15% ether in hexane) to give 0.38 g (1.27 mmol, 96% yield) of a mixture of desired diene **16** and its tetrasubstituted olefinic isomer in a 4:1 ratio (analyzed by GLC: 2 m 3% OV-17, 120 to 220 °C, 8 °C/min; retention times of 5.9 and 6.3 min, respectively): NMR ($CDCl_3$) δ 4.70 (s, 2, OCH_2O), 3.40 (s, 3, OCH_3), 1.63 and 1.58 (br s, CH_3C=C and $(CH_3)_2C$=C), 0.87 (br d, 3, J = 5 Hz, C-3 CH_3).

Anal. Calcd for $C_{18}H_{34}O_3$: C, 72.44; H, 11.48. Found: C, 72.70; H, 11.47.

(3*S*,6*R*)-3-Methyl-6-isopropenyl-9-decen-1-ol (17). To a solution of 0.38 g (1.27 mmol) of the 3*S*,6*R* diene ether **16** (containing 20% of tetrasubstituted olefinic isomer) in 5 mL of hexane under N_2 was added 2.4 mL (3.8 mmol) of 1.6 M *n*-butyllithium in hexane. After 5 h at room temperature, the excess lithium reagent was quenched with water. Ether was added, and the layers were separated. The ether fraction was washed with brine and dried ($MgSO_4$). Solvent was removed in vacuo to give a mixture of alcohol **17** and its vinyloxymethyl ether **18** (and their tetrasubstituted olefinic isomers) in a 1:1 ratio. NMR of **18** ($CDCl_3$) δ 6.35 (d of d, 1, J = 7, J = 14 Hz, OC**H**=CH_2), 4.83 (s, 2, OCH_2O), 4.40 (d of d, 1, J = 2, J = 14 Hz, trans OCH=C**H**), 4.07 (d of d, 1, J = 2, J = 7 Hz, cis OCH=C**H**). The mixture of alcohol **17** and ether **18** was dissolved in 8 mL of THF and 2 mL of H_2O. Trichloroacetic acid (30 mg) was added, and the solution was warmed to 60 °C for 2 h. The solution was diluted with ether, and the aqueous layer was separated. The ether fraction was washed with 2 M Na_2CO_3 and brine and dried ($MgSO_4$). Removal of the solvent in vacuo gave 0.27 g (1.27 mmol, 100% yield) of alcohol **17** containing 20% of its tetrasubstituted olefinic isomer: IR (CCl_4) 3630 (OH), 3075 (H_2C=C), 910 (H_2C=CH), 890 cm^{-1} (H_2C=C); NMR ($CDCl_3$) δ 3.67 (br t, 2, J = 6 Hz, CH_2OH), 1.63 and 1.60 (br s, CH_3C=C and $(CH_3)_2C$=C); mass spectrum (CI, CH_4), m/e (relative intensity) 211 (M^+ + H, 8), 209 (M^+ − H, 6), 109 (100).

Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 80.15; H, 12.33.

(3*S*,6*R*)-3-Methyl-6-isopropenyl-9-decen-1-yl Acetate (3*S*,6*R*-1). A solution of 278 mg (1.32 mmol) of alcohol **17** (containing 20% of the tetrasubstituted olefinic isomer), 0.25 mL of acetic anhydride (2.65 mmol), and 0.25 mL (3.10 mmol) of pyridine in 5 mL of ether was stirred under N_2 overnight at 25 °C. Ice was added to the solution, and the mixture was stirred another 30 min and then poured into 1 N HCl and ether. The ether layer was washed with 2 M Na_2CO_3 and brine and dried ($MgSO_4$). Removal of solvent in vacuo gave 290 mg (87% yield) of an acetate mixture.

To a solution of this acetate mixture (1.15 mmol) in 1 mL of dichloromethane at room temperature was added 54 mg (0.27 mmol) of 85% *m*-chloroperoxybenzoic acid. After 13 h, the mixture was poured into aqueous $NaHSO_3$ solution, and the product was extracted with ether. The ether layer was washed with 2 M Na_2CO_3 and brine and dried (Na_2SO_4). Removal of solvent in vacuo gave a residue which was chromatographed on one 1 m × 20 cm silica gel plate impregnated with Rhodamine 6G, developed in 10% ether in hexane. Removal of the diene acetate band followed by short-path distillation [60 °C (bath) (0.01 mm)] gave 105 mg (0.42 mmol) of (3*S*,6*R*)-**1**. Capillary GLC (20 m × 0.26 mm ID wall coated open tubular glass capillary, Carbowax 20M, 125 °C) analysis of this sample gave the diastereomer purity as 93.3% [i.e., (3*S*,6*R*)-**1**:(3*S*,6*S*)-**1**, 93.3:6.7, with retention times of 15.36 and 14.90 min, respectively). The IR, NMR, and mass spectra were identical with those of (3*RS*,6*RS*)-**1**.

(3*S*,6*S*)-3-Methyl-6-isopropenyl-9-decen-1-yl Acetate (3*S*,6*S*-1). In a manner identical with that above, the 3*S*,6*R* epoxide **10b** was converted to (3*S*,6*S*)-**1**. Capillary GLC (20 m × 0.26 mm ID wall coated open tubular glass capillary, Carbowax 20M, 125 °C) analysis of this sample showed it to be of 93.4% diastereomeric purity (i.e., (3*S*,6*S*)-**1**:(3*S*,6*R*)-**1**, 93.4:6.6, with retention times of 15.06 and 15.30 min, respectively). The IR, NMR, and mass spectra of this sample of (3*S*,6*S*)-**1** were identical with those of (3*RS*,6*RS*)-**1**.

Natural Pheromone Component 1. Capillary GLC (20 m × 0.26 mm ID wall coated open tubular glass capillary, Carbowax 20M, 125 °C) analysis of the naturally occurring pheromone component **1** showed it to be a single diastereomer with a retention time of 15.15 min. Upon co-injection with a mixture of synthetic (3*S*,6*S*)-**1** and (3*S*,6*R*)-**1** in approximately a 1:1 ratio, the natural material co-eluted with the 3*S*,6*R* diastereomer of **1** at 15.14 min, while the 3*S*,6*S* diastereomer eluted at 14.76 min. A computer-reconstructed chromatogram of the natural material indicated that the sample contained less than 0.4% of the 3*S*,6*S* diastereomer.

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Registry No. (±)-**1**, isomer 1, 73395-36-5; (±)-**1**, isomer 2, 71424-34-5; (3*R*,6*S*)-**1**, 67601-07-4; (3*R*,6*R*)-**1**, 67601-04-1; (3*S*,6*S*)-**1**, 67601-10-9; (3*S*,6*R*)-**1**, 67601-06-3; (±)-**3** acetate, 67650-82-2; (*R*)-**3**, 1117-61-9; (*S*)-**3**, 7540-51-4; (±)-**4**, isomer 1, 73367-94-9; (±)-**4**, isomer 2, 73367-95-0; (±)-**5**, isomer 1, 73367-96-1; (±)-**5**, isomer 2, 73367-97-2; (±)-**6**, isomer 1, 73367-98-3; (±)-**6**, isomer 2, 73367-99-4; (±)-**7**, isomer 1, 73368-00-0; (±)-**7**, isomer 2, 73368-01-1; (±)-**8**, 73368-02-2; (*S*)-**9**,

71256-72-9; **10a**, 73368-03-3; **10b**, 73368-04-4; **11a**, 73368-05-5; **11b**, 73368-06-6; **12a**, 73368-07-7; **12b**, 73395-37-6; **13**, 37133-77-0; **14**, 73368-08-8; **15**, 71256-74-1; **16**, 71256-75-2; **16**, tetrasubstituted olefinic isomer, 73368-09-9; **17**, 71256-76-3; **17**, tetrasubstituted olefinic isomer, 73368-10-2; **18**, 73368-11-3; **18**, tetrasubstituted olefinic isomer, 73368-12-4; 4-chloro-1-butene, 927-73-1; (methoxyethoxy)-methyl chloride, 3970-21-6; (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetoyl chloride, 20445-33-4.

Ketene Thioacetal Route to γ-Lactones. Effect of Carbonyl Hardness on Reaction-Site Selectivity and a Unique Preparation of 3-Methyl-5-phenyl-2(5*H*)-furanone

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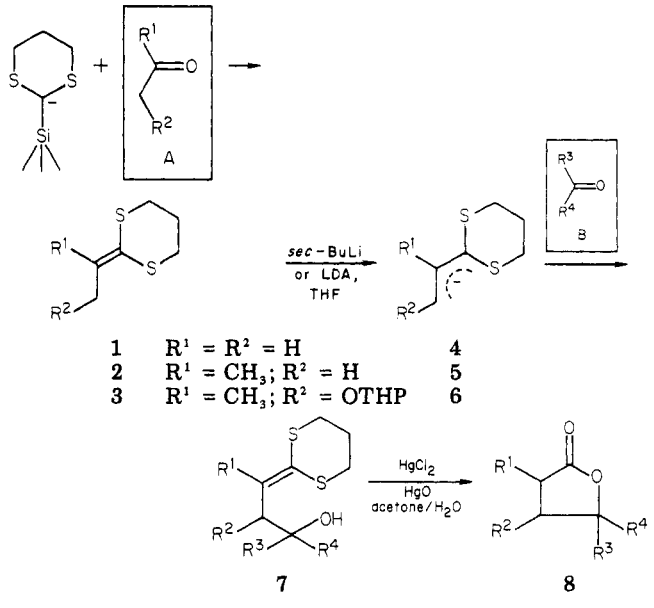
The synthesis of γ-lactones from the addition products of ketene thioacetal anions and carbonyl compounds has been achieved. A unique phenylselenenyl chloride triggered formation of dithienium ion from ketene thioacetal has been shown to directly afford a doubly protected butenolide system.

A variety of methods are now extant for the production of butanolides and their biologically important α,β-unsaturated counterparts, the butenolides. A conceptually simple method for the assembly of these products has recently been disclosed by Caine. This chemistry involves the addition of lithium β-lithiopropionate and lithium β-lithioacrylates to carbonyl compounds.[2]

We now report an alternative route to γ-lactones and a unique synthesis of 3-methyl-5-phenyl-2(5*H*)-furanone. This work is based on our observation that the carbanions prepared by direct metallation of ketene thioacetals undergo reaction predominantly at their γ-position when treated with "soft" carbonyl components (Scheme I).[3] The regiochemical course of carbonyl addition does, of course, contrast with the α-site selectivity observed in the reactions of these same anions with "hard" alkyl halides as the electrophilic addends.[4] Such a dependency of reaction-site selectivity on electrophile is well in accord with general observations previously recorded for related heteroatom-stabilized ambident nucleophiles.[5]

The results of our investigations of the reactions of ketene thioacetal anions **4**–**6** with a host of carbonyl substrates are displayed in Table I. The following points should be noted: (a) The general rule of γ-addition is violated when either cyclopentanone or cyclobutanone is employed as the electrophile (entries 5 and 6).[6] This result

Scheme I. γ-Lactone Synthesis



1 $R^1 = R^2 = H$ 4
2 $R^1 = CH_3$; $R^2 = H$ 5
3 $R^1 = CH_3$; $R^2 = OTHP$ 6

7 8

may be rationalized by the notion of hard and soft acids and bases. The four-and five-membered-ring ketones possess a carbonyl group which can be characterized as being harder (more s character in the C–O bond) and thus can be anticipated to react at the *harder α-site* of the ketene thioacetal anion. (b) Anion **6** functions in a synergistic mode, for both the oxygen and sulfur atoms direct γ to sulfur. (c) Transformation of the addition products to γ-lactones is readily brought about by hydrolysis in the presence of mercuric chloride/mercuric oxide (Table II).

Since the ketene thioacetals are most conveniently prepared by the procedure of Jones and Lappert from 2-lithio-2-(trimethylsilyl)-1,3-dithiane and a carbonyl compound,[7] ready access to diversely substituted γ-lactones is easily achieved by varying either of the two carbonyl components (A or B) employed in the reaction sequence (Scheme I).

(1) Fellow of the Alfred P. Sloan Foundation, 1978–1980.
(2) D. Caine and A. Frobese, *Tetrahedron Lett.*, 883 (1978); 5167 (1978), and references cited therein.
(3) Seebach has previously recorded the addition of two ketene thioacetals to benzophenone and the hydrolysis of one of the addition products to a γ-lactone. The generation of a mixture of α- and γ-products was suggested to take place with other aldehydes and ketones. See D. Seebach and M. Kolb, *Justus Liebigs Ann. Chem.*, 811 (1977). The generality of this approach to γ-lactones thus remained to be established.
(4) D. Seebach, M. Kolb, and B.-Th. Gröbel, *Tetrahedron Lett.*, 3171 (1974). E. J. Corey and A. P. Kozikowski, *ibid.*, 925 (1975). Allylation of ketene thioacetals can be directed toward the α-position by employing cuprous salts: F. E. Ziegler and C. C. Tam, *J. Org. Chem.*, **44**, 3428 (1979). For a study of the effect of electrophile hardness on the site of alkylation of metallated ketene thioacetals, see W. S. Murphy and S. Wattanasin, *Tetrahedron Lett.*, 1827 (1979).
(5) A. P. Kozikowski and K. Isobe, *Tetrahedron Lett.*, 833 (1979), and references cited therein.
(6) No change in the ratio of regioisomers for entry 6 was observed on allowing the reaction to proceed for longer periods of time.
(7) P. F. Jones and M. F. Lappert, *J. Chem. Soc., Chem. Commun.*, 526 (1972).

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