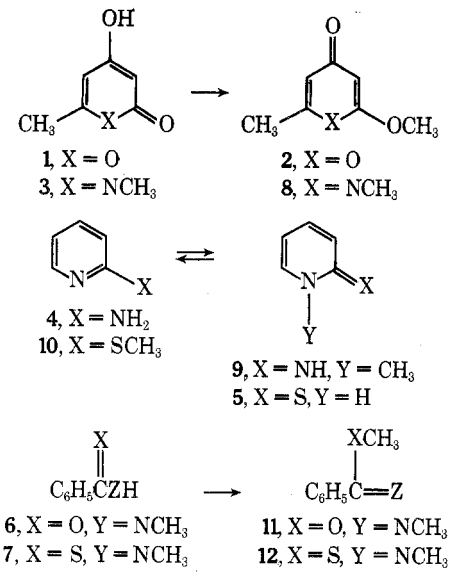
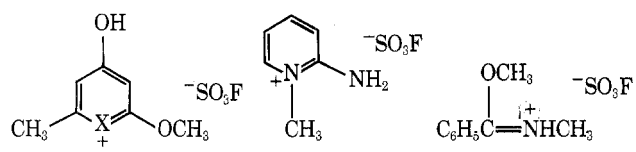


A scheme which accounts for these results has fast equilibration of the protomers with the ratio of products being determined by kinetically controlled methylation[6] in accord with the Curtin–Hammett principle.[8] Since the transition state energy differences are in the same direction as the ground-state energy differences[3,9,10] and the initial kinetic products are stable and can be deprotonated in the second step, a regiospecific synthesis results in which the proton appears to have acted as a directing group. Support for this interpretation is provided by the fact that the intermediate salts **13–16** can be isolated and identified by



13, X = O
14, X = NCH_3

15 **16**

nmr and ir spectroscopy after reaction of **1, 3, 4,** and **6** with methylfluorosulfonate.

Although cases can be anticipated in which the alkylating agent might not exhibit the requisite selectivity,[11] the synthetic potential of the regioselective synthesis suggested by these results appears to be significant. The fact that the less stable,[1,3,5b,12] and therefore often more reactive, alkyl substituted isomer may be produced easily and in high yield may prove of particular value.

Acknowledgment. We are grateful to the National Science Foundation and the National Institutes of Health for support of this work.

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(10) One possibility is that the respective transition states resemble the reactants. Practically the transition state energy difference should be greater than ~3 kcal/mol for regioselective synthesis.
(11) See, for example, M. G. Ahmed and R. W. Alder, *Chem. Commun.*, 1389 (1969).
(12) The less stable isomer will be produced under this hypothesis if the relative stabilities of structually similar methylthropic and prototropic isomers are in the same order.

Roger Adams Laboratory
Department of Chemistry
University of Illinois
Urbana, Illinois 61801

Peter Beak*
Jae-Keun Lee

Received September 17, 1974

Applications of Sulfenylations of Ester Enolates. Synthesis of Pheromones of the Honey Bee

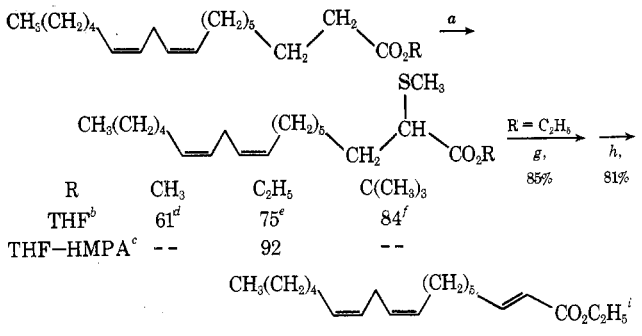
Summary: By the sulfenylation–dehydrosulfenylation method, the queen substance and the pollen attractant of honey bees have been synthesized and a new approach to α-keto esters by direct bissulfenylation has been demonstrated.

Sir: In conjunction with our continuing interest in the application of new synthetic methods to the chemistry of insect pheromones, we have developed short syntheses of the esters of the queen substance[1,2] and the pollen attractant of honey bees.[3,4] In the course of this study we have developed a new synthesis of α-keto esters and have determined the dependence of the sulfenylation reaction on the choice of carboxylic ester.

Sulfenylation[5] of the esters of linoleic acid in THF at 0° (generation of the enolate at −78°) led to the α-methylthiolinoleates in yields that paralleled enolate stability (see Scheme I). Since enolates of methyl and ethyl esters are frequently unstable at this temperature,[6a] decomposition competes with sulfenylation. On the other hand, the enolate of the *tert*-butyl ester[6b] is thermally stable and sulfenylation proceeds smoothly. Enhancing the rate of sulfeny-

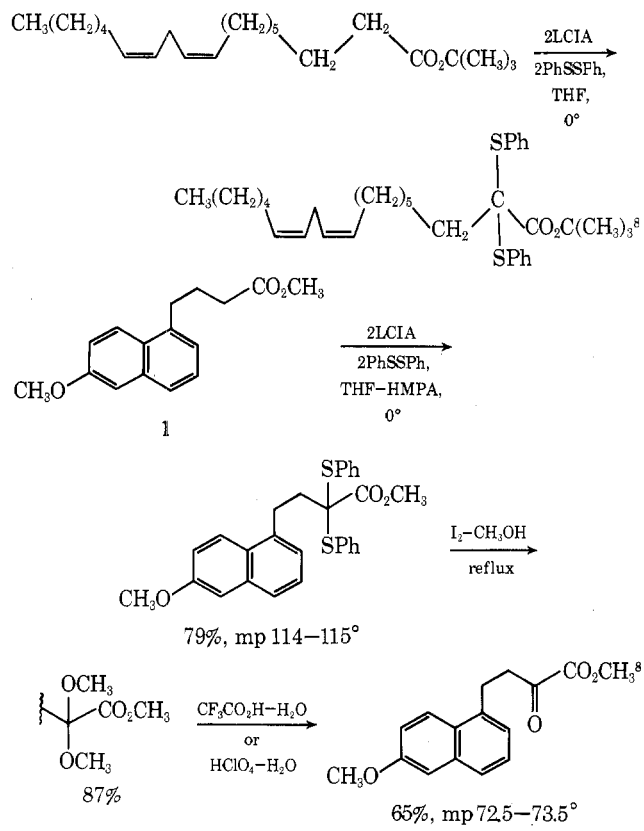
lation by utilizing a THF–HMPA mixture overcomes the enolate instability and raises the yield of sulfenylation of ethyl linoleate to 92%. Long reaction times (>1 hr) after quenching of the enolate with the disulfide are also detrimental and effect desulfenylation back to starting ester.

Scheme I
Synthesis of Ethyl Octadeca-(*E*)-2-(*Z*,*Z*)-9,12-trienoate



[a] LCIA (see ref 7), THF, −78°. [b] CH_3SSCH_3, THF. [c] CH_3SSCH_3, THF–HMPA. [d] Inverse quench with disulfide at 0°. [e] Inverse quench with disulfide at 25°. [f] Direct addition of disulfide at 0°. [g] 1 equiv of *m*-chloroperbenzoic acid, CH_2Cl_2, −40°. [h] $PhCH_3$, $CaCO_3$, 110°. [i] See ref 8.

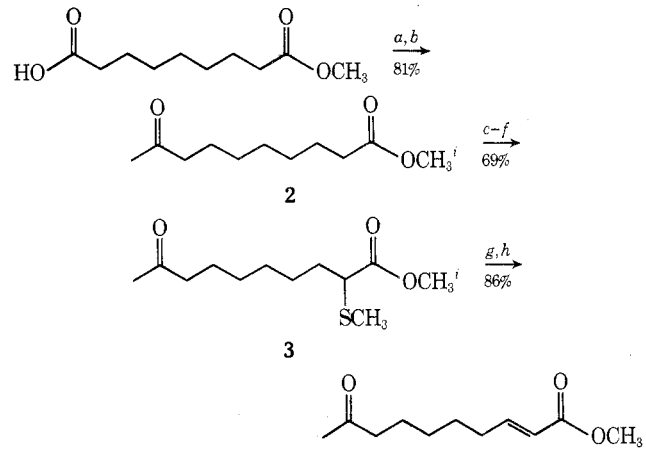
Using 2 equiv of amide base and 2 equiv of diphenyl disulfide led to the α,α-bissulfenylated ester in 90% yield.[9,10] Since this represented the direct introduction of a carbonyl group α to an ester, application to a second system, *i.e.*, **1**,



was investigated. Indeed, bissulfenylation occurs smoothly. Hydrolysis to the α-keto ester was effected first by transketalization using a methanolic solution of iodine followed by acid treatment.

Oxidation of ethyl 2-methylthiolinoleate was sluggish with sodium metaperiodate, but could be accomplished with *tert*-butyl hydroperoxide in the presence of vanadyl acetylacetonate or best with *m*-chloroperbenzoic acid. Elimination of the sulfoxide required 16 hr in hot toluene.

Sulfenylation–dehydrosulfenylation offers an especially attractive approach to queen's substance (9-oxo-2-decenoic acid), an important pheromone of queen bees[1] and one which has been implicated as a pheromone of termites.[11] Methyl 9-oxodecanoate (**2**) is available in 81% overall yield



[a] $SOCl_2$, neat, 25°. [b] $Li(CH_3)_2Cu$, ether, −78°. [c] $HOCH_2CH_2OH$, TsOH, PhH, reflux. [d] LCIA, THF, −78°. [e] CH_3SSCH_3, HMPA, 25°. [f] Oxalic acid, H_2O, 25°. [g] $NaIO_4$, C_2H_5OH, H_2O, 25°. [h] $PhCH_3$, $CaCO_3$, 110°. [i] See ref 8.

from commercially available azelaic acid monomethyl ester.[12] Chemospecific sulfenylation of **2** with dimethyl disulfide led to a maximum of 30% of the desired product **3** contaminated with decomposed starting material. The instability of the dienolate is apparently responsible for the low yield. On the other hand, protection of the ketone as the ethylene ketal and sulfenylation by siphoning the enolate solution in THF (generated at −78°) into a room temperature solution of dimethyl disulfide in HMPA, followed by hydrolysis, gave the desired **3** in 69% overall yield. Oxidation with sodium metaperiodate and elimination in hot toluene in the presence of calcium carbonate (16 hr) gave the methyl ester of the queen substance in 86% yield and in 47% overall yield from azelaic acid monomethyl ester.

The spectral data for our synthetic materials agreed with the published spectral data. Note that in both cases the desired *trans* isomer is the exclusive product of elimination.

Acknowledgments. We wish to thank the National Science Foundation and the National Institutes of Health for their generous support of our programs.

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Department of Chemistry
University of Wisconsin
Madison, Wisconsin 53706

Barry M. Trost*[13]
Thomas N. Salzmann

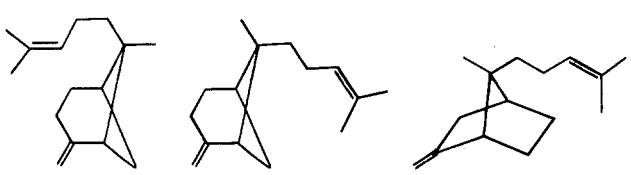
Received October 10, 1974

Synthesis of the *Valeriana Waalichi* Hydrocarbon Sesquifenchene. A Route to Specifically Functionalized 7,7-Disubstituted Bicyclo[2.2.1]heptane Derivatives

Summary: A highly stereoselective route to C-8 methyl, C-9 functionalized bicyclo[2.2.1]heptane derivatives from norbornadiene is reported which has been employed in a total synthesis of sesquifenchene.

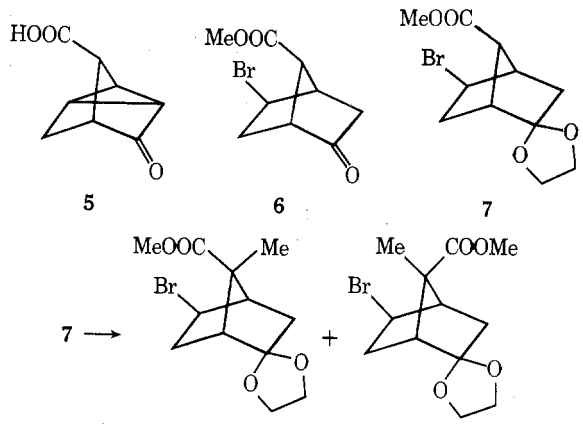
Sir: Bhattacharyya[1] reported some time ago the isolation of a new bicyclic sesquiterpene hydrocarbon from Indian Valerian root oil and proposed the β-*cis*-bergamotene structure **1** on the basis of chemical and spectroscopic studies.[1] Erman[2] demonstrated structure **1** to be untenable by synthesis and revised the structure to the trans isomer **2**. A recent report[3] on an unambiguous synthesis of **2** clearly ruled out structure **2** for Bhattacharyya's sesquiterpene which appeared not even to be a member of the bergamotene class.

Based on the close resemblance of the ir and nmr spectra of Bhattacharyya's compound and those of β- and epi-β-santalene, it has been suggested[3,4] that this compound [sesquifenchene (**3**)][4] is a substitution product of α-fenchene with a γ,γ-dimethyllallyl grouping present. Two recent syntheses have confirmed the structure **3**.[5] We wish to report the details of our synthesis of sesquifenchene which contains a highly stereoselective route to C-8 methyl, C-9 functionalized bicyclo[2.2.1]heptane derivatives.



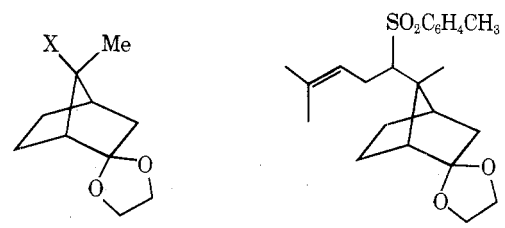
1 **2** **3**

The starting point of our synthesis was the cyclopropyl keto acid **5**, mp 143–144°, obtained in 55–60% overall yield from norbornadiene (**4**).[6] Reaction of acid **5** with refluxing 48% HBr–acetic acid (1:1) for 1.5 hr produced cleanly a bromo acid,[6b] mp 92° (90%).[7] Ketalization (2-methyl-2-ethyl-1,3-dioxalane–benzene–TsOH, 18 hr) of **6** resulted in a 90% yield of pure crystalline bromo ketal **7**, mp 74–75°. Alkylation of the ester enolate derived from **7** (lithium diisopropylamide–THF, −78°) with methyl iodide (−78° → 0°, 1.5 hr) resulted in a 75% isolated yield after chromatography on silica gel of the bicyclo[2.2.1]heptane derivative **8**.



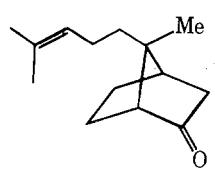
5 **6** **7**

8 **9**



10, X = COOMe
11, X = CH_2I
12, X = $CH_2SO_2C_6H_4CH_3$
14, X = $CH_2CH_2C{=}C(CH_3)_2$

13



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The nmr spectrum of **8** (mp 77–78°) included methyl resonances at δ 1.28 (s, 3 H) and 3.62 (s, 3 H). The corresponding isomer **9** (nmr indicated methyl resonances at δ 1.58 and 3.58) could be isolated in ~5% yield. Initial evidence for structure **8** was obtained in the following manner. Deketalization of **8** afforded a bromo ketone (**16**) whose methyl resonance moved upfield to δ 1.30 owing to shielding by the carbonyl. The bromo ketone derived from **9** exhibited no difference in the chemical shift of the methyl group. The conversion of **8** to sesquifenchene corroborates the stereochemical assignment.

The conversion of **8** to sesquifenchene requires (a) reductive cleavage of the carbon–bromine bond, (b) side-chain elaboration of the γ,γ-dimethylallyl grouping, and (c) methylenation of the protected keto function. Treatment of **8** with tributyltin hydride (1.5 equiv) in benzene containing azobisisobutyronitrile at 50–55° for 1.5 hr resulted in a 94% isolated pure yield of ester **10**. Reduction ($LiAlH_4$–ether, 4.5 hr) of ester **10** followed by tosylation [*p*-toluenesulfonyl chloride (1 equiv)/pyridine, 0°] and exchange with iodide [sodium iodide (3 equiv)–acetone, reflux] produced a 78% overall yield of iodide **11** from **10**. Sulfone formation was carried out in 77% yield (pure) with 2 equiv of sodium *p*-toluenesulfinate in anhydrous DMF at 135–140° (15 hr). The nmr spectrum of **12**, mp 117–118°, exhibited peaks at δ 1.46 (s, 3 H, CCH_3), 2.45 (s, 3 H, $ArCH_3$), 3.02 (s, 2 H, CH_2S), 3.82 (m, 4 H, OCH_2CH_2O), and an AB quartet (aromatic protons, J = 8 Hz) centered at 7.45. Metalation of sulfone **12** at −20° with *n*-butyllithium (1.3 equiv) in THF followed by cooling to −78°, addition of 1-bromo-3-methyl-2-butene (1.6 equiv), and gradual warming to 0° over 1.5 hr resulted in formation of sulfone **13** in near-