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A NEW SYNTHESIS OF THE CALIFORNIA RED SCALE PHEROMONE FROM S-(+)-CARVONE [1]

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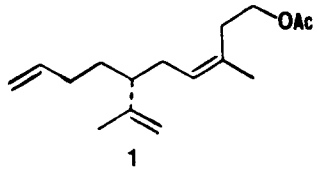
Abstract : A Retroaldol-Wittig olefination of the S-(+)-carvone derivative 3 is used as a key step in the synthesis of pheromone 1.

(3Z,6R)-3-Methyl-6-isopropenyl-3,9-decadien-1-yl acetate (1) is the sex pheromone of the California red scale, a major citrus pest in some parts of the world.[2] Syntheses of the racemic form of 1 have been accomplished by [2,3]-sigmatropic rearrangement of an allylic alkoxymethyllithium species[3] and by methodology involving conjugate addition-alkylation of an unsaturated acylphosphorane.[4] A 52:48 mixture of 1 and the corresponding R,E-isomer was also produced in a ten-step sequence from the epoxyenone 2 derived from S-(+)-carvone.[2b]



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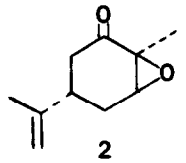

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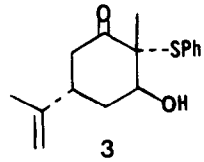

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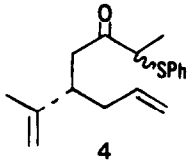

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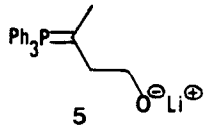

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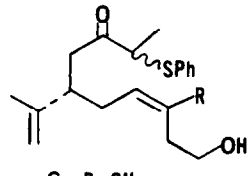
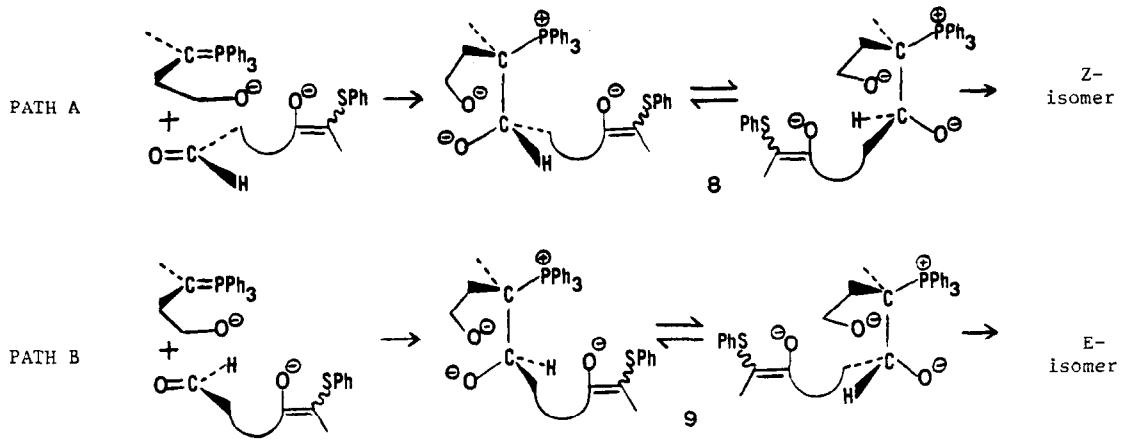


6a R=CH_3
6b R=H

Recently, we reported that reaction of the β-hydroxy-α-phenylsulfenyl ketone 3, obtained by treatment of epoxy ketone 2 with thiophenol and triethylamine in acetonitrile, with methylene triphenylphosphorane gave enone 4 by a retroaldol reaction and Wittig olefination of the open-chain aldehydo enolate intermediate.[5] We now wish to report the application of this type of methodology as a key step in the synthesis of the natural product 1.

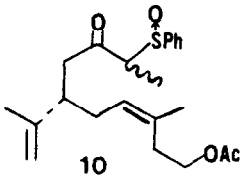
The Wittig reagent 5[2b,6] was generated in situ by a sequence involving (1) treatment of 3-hydroxypropyltriphenylphosphonium bromide in tetrahydrofuran (THF) at 0°C for 1 h with 2.0 equiv. of n-butyllithium, (2) methylation of the resulting ylid by addition of 1.1 equiv. of methyl iodide at 0°C followed by stirring for 3 h at room temperature, (3) removal of the supernatant liquid which remained after the salt was allowed to stand for 0.5 h at room temperature, (4) addition of fresh THF and 4 equiv. (with respect to Li^+ cations) of hexamethylphosphoramide (HMPA), and (5) deprotonation using 1.0 equiv. of n-butyllithium at 0°C. After stirring for 1 h at 0°C, the ylid solution was treated with 0.5 equiv. of the hydroxyketone 3 to give in 83% yield after chromatography, the diastereomeric Z-trisubstituted olefins 6a[7] and Z-disubstituted olefins 6b[7] in an 85:15 ratio.[8]

SCHEME I



One can rationalize the observed stereoselectivity in the olefination of 3 by considering electrostatic, steric, and medium effects.[9] In the presence of 4-fold excess HMPA it is expected that the negatively charged enolate and alkoxide moieties are not strongly coordinated by lithium cations and that decomposition of the kinetically preferred erythro-betaine 8 (Path A) is faster than dissociation back to the ylid and aldehydo enolate. If steric effects alone were

involved, then one would not anticipate that formation of the threo-betaine 9 would be kinetically precluded. Therefore, it is suggested that Path B which leads to the E-isomer is kinetically unfavorable because of the electrostatic repulsion of the negatively charged side-chains which would be involved in the formation of threo-betaine 9. It should be noted that Z-disubstituted alkenes are produced with a high degree of stereoselectivity in other Wittig reactions in which the aldehyde and ylid components bear a negative charge.[10] The question of mechanism notwithstanding, the results of our procedure contrast strikingly with the 1:1 mixture of E- and Z-trisubstituted olefins obtained by reaction of the ylid 5 with (R)-3-isopropenyl-6-heptenal.[2b]



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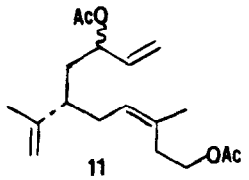

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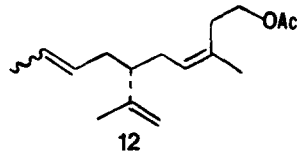

12

Without purification[11], the 85:15 mixture of 6a and 6b was converted into the pheromone 1 by a six step sequence. Acetylation (acetic anhydride, pyridine, 12 h, 25°C), and oxidation of the sulfide to the sulfoxide[12] (1.0 equiv m-chloroperoxybenzoic acid, methylene chloride, -5°C, 15 min.) followed by chromatography gave in 85% yield ketosulfoxide 10[7] contaminated with the 6b-derived product. Thermal elimination[12] (Kugelrohr distillation, 135°C, 0.15 mm Hg) gave the crude trienone acetate which was reduced[13] ($NaBH_4$, $CeCl_3.7H_2O$, methanol, 25°C), and acetylated (Ac_2O, py) to give in 52% after chromatography the diacetate 11[7]. (The two chromatographic steps of this sequence allowed removal of most of the 6b-derived contaminants.) Chemoselective hydrogenolysis[14] of the allylic acetate (0.01 equiv. $PdCl_2(PPh_3)_2$, 2.0 equiv. NH_4O_2CH, dioxane, reflux, 15 min.) gave after flash chromatography an 89:11 mixture of pheromone 1, and the double bond isomer 12[7]. Also, a trace of 6b-derived triene could be detected by GLC.

The synthetic product showed the expected GLC retention time and exhibited ^1H NMR spectral properties identical to those reported[2b] for the pheromone 1 with a Z-configuration of the trisubstituted double bond.[15] This approach has the advantages of being somewhat shorter than the previous synthesis of 1 from epoxyenone 2, and especially, of yielding exclusively material with the natural configuration about the trisubstituted double bond.

REFERENCES AND NOTES

1. This research was supported by a grant from the Petroleum Research Fund (ACS-PRF 14439-AC1) for which we are grateful.

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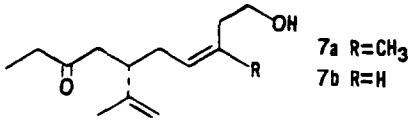
6. We thank Dr. R. J. Anderson of Zoecon Corporation for guidance in the preparation of ylid 5.

7. All new compounds gave the expected ir, nmr, and mass spectral data.

8. The stereoselective formation of Z-olefins 6a and 6b was confirmed by reductive removal of the α-phenylsulfenyl group with lithium/liquid ammonia followed by preparative GLC to give pure samples of 7a[7] and 7b[7] in an 85:15 ratio. Irradiation of the nmr signal of the vinyl methyl group of the trisubstituted double bond of 7a resulted in a 23% enhancement (Nuclear Overhauser Effect) of the cis vinyl proton signal.



7a R=CH$_3$
7b R=H

9. For a detailed discussion of factors influencing the stereochemistry of the Wittig reaction, see: House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; p 707.

10. For example, see: (a) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. J. Am. Chem. Soc. 1969, 91, 5675. (b) Ohuchida, S.; Hahl, R. Ibid. 1984, 106, 3875.

11. Compounds 6a and 6b can be readily separated on a Waters 500 HPLC using a silica gel column (1:4 ethyl acetate/hexane).

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15. We are grateful to Dr. R. J. Anderson of Zoecon Corporation for kindly providing a sample of a ca. 1:1 mixture of the pheromone and its E-isomer.

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