



Absolute Configuration of Insect-Produced Epilachnene[†]

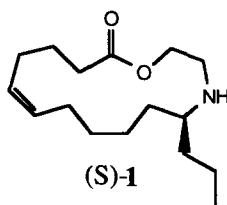
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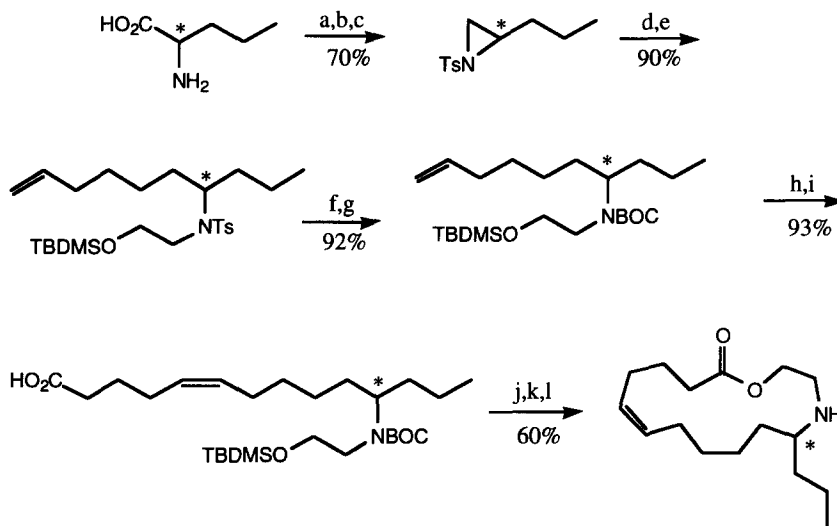
Abstract: Samples of (*R*) and (*S*)-epilachnene [(*5Z*)-11-propyl-12-azacyclotetradec-5-en-14-olide] were synthesized from (*R*) and (*S*)-norvaline. The diastereomeric α -methoxy- α -trifluoromethylphenylacetyl amides of these synthetic samples, prepared using (*S*) α -methoxy- α -trifluoromethylphenylacetyl chloride, were well resolved by gas chromatography. Analogous derivatization and gas chromatographic analysis of a sample of epilachnene from the pupal secretion of the coccinellid beetle, *Epilachna varivestis*, established that the natural product is (*S*)-epilachnene. © 1997 Elsevier Science Ltd.

Since our initial characterization of the structurally novel azamacrolide epilachnene [(*5Z*)-11-propyl-12-azacyclotetradec-5-en-14-olide] (**1**) as the major constituent of the insect-repelling secretion of pupal *Epilachna varivestis*,¹ the synthesis and biosynthesis of this compound, and in some cases of its congeners, have been the subjects of reports from several laboratories.²⁻⁸ Whether natural epilachnene consists of one pure enantiomer, or a mixture of enantiomers (racemic or otherwise) has not been defined. We have now shown, by a direct gas chromatographic comparison of its (*S*)- α -methoxy- α -trifluoromethylphenylacetyl amide (MTPA amide) with the corresponding amides of independently synthesized (*R*)- and (*S*)-epilachnene, that natural epilachnene is, in fact, a single enantiomer and that it has the *S* configuration.



The individual *R* and *S* enantiomers of epilachnene were synthesized efficiently from (*R*)- and (*S*)-norvaline *via* a reaction sequence that preserves the chirality of the starting

materials, as summarized in Scheme 1.⁹ Racemic epilachnene was obtained in similar fashion, starting from (\pm) 2-amino-1-pentanol. One particularly interesting step in this sequence is the direct treatment of an ozonide (without prior workup to produce the expected aldehyde) with a Wittig reagent to give the desired coupling product directly and in excellent yield (steps h and i in Scheme 1).¹⁰



Reaction Conditions: a) LiBH_4 , TMS-Cl, THF, r.t. 14 h. b) TsCl, pyridine, CH_2Cl_2 , -20°C 48 h. c) K_2CO_3 , acetone, r.t. 12 h. d) $\text{Mg}[(\text{CH}_2)_3\text{CH}=\text{CH}_2]_2$, CuI, Et_2O , -30°C to r.t. 14 h. e) NaH, $\text{BrCH}_2\text{CH}_2\text{OTBDMS}$, DMF, r.t. 20 h. f) Sodium naphthalide, DME, -78°C 10 min. g) $(\text{Boc})_2\text{O}$, THF, r.t. 10 h. h) O_3 , CH_2Cl_2 , -78°C i) $\text{Ph}_3\text{P}^+(\text{CH}_2)_4\text{COOHBr}^-$, $\text{KN}(\text{TMS})_2$, THF, r.t. 0.5 h. j) TBAF, THF, r.t. 6 h. k) 2-Chloro-*N*-methylpyridinium iodide, NEt_3 , DMSO, 84°C (high dilution conditions). l) CF_3COOH , r.t. 10 min.

Scheme 1

Several different gas chromatographic methods were employed in an attempt to resolve the enantiomers of epilachnene. Attempts at analysis *via* chiral column gas chromatography proved disappointing: employing a 30 m x 0.25 mm Cyclodex-BTM column, epilachnene failed to elute. Hence, the more volatile *N*-trifluoroacetyl derivatives were prepared; while these did elute, the enantiomers were not resolved. A procedure employing formation of diastereomers by reaction of epilachnene with (*S*)-MTPA chloride proved more successful.¹¹ Derivatization of racemic epilachnene gave the expected mixture of diastereomeric amides, which was well resolved into its individual components by non-chiral gas chromatography on a DB-5-coated 30 m x 0.22 mm capillary column (Figure 1). The analogously prepared amides of synthetic (*R*)-1 and (*S*)-1 proved to be the faster and slower-eluting diastereomers, respectively. Finally, the (*S*)-MTPA amide of natural epilachnene¹ was prepared and proved to be chromatographically indistinguishable from the amide of synthetic (*S*)-epilachnene, thereby establishing the stereochemistry of the natural product.

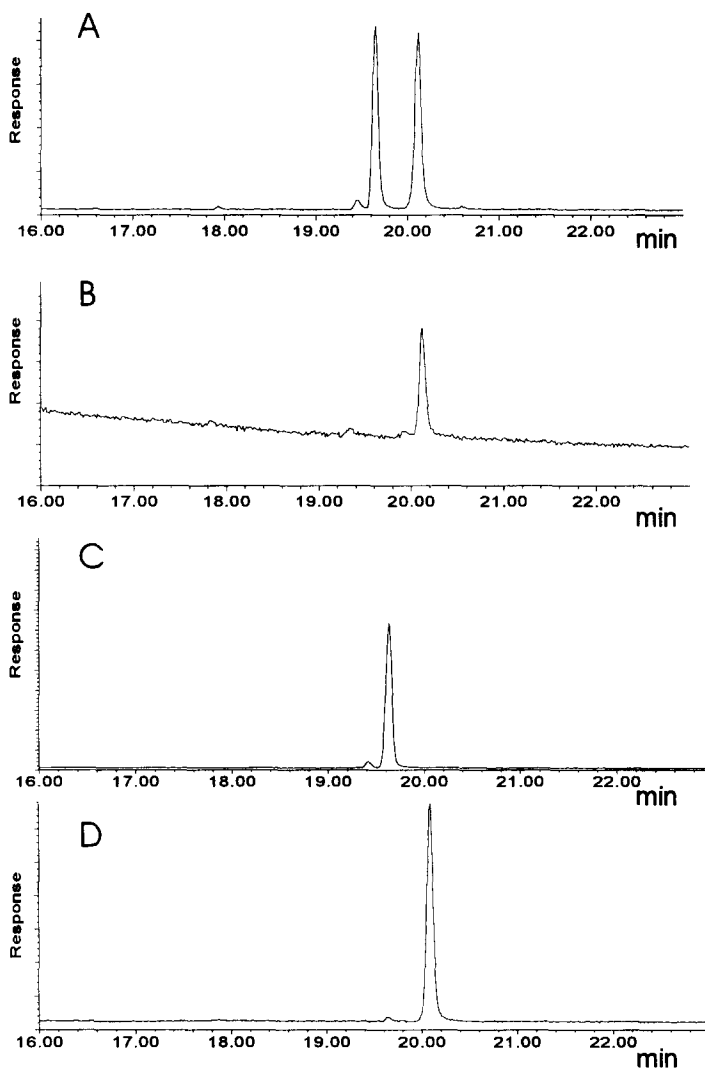


Figure 1. Reconstructed gas chromatograms obtained from analysis of (*S*)-MTPA amides of epilachnene. (A) Synthetic racemate. (B) Natural epilachnene. (C) Synthetic (*R*)-epilachnene. (D) Synthetic (*S*)-epilachnene. Analyses were performed using a DB-5-coated fused-silica column (30 m × 0.22 mm). The oven temperature was maintained at 150 °C for 1 min and raised 10 °C/min to 270 °C.

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 - For recent reviews of the remarkably diverse defensive chemistry of coccinellid beetles, see:
King, A. G.; Meinwald, J. *J. Chem. Rev.* **1996**, *96*, 1105-1122 and
Daloze, D.; Braekman, J. C.; Pasteels, J. M. *Chemoecology*, **1995**, 173-183.
 - All key intermediates were characterized on the basis of NMR and MS data. The details of this synthesis are now being prepared for publication.
 - Examples of the reaction of ozonides with stabilized phosphonium ylides ($\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$ or $\text{Ph}_3\text{P}=\text{CHCOPh}$) are well known, see:
Hon, S. H.; Lu, L.; *Tetrahedron*, **1995**, *29*, 7937-7942, and references cited therein.
To our knowledge, the reaction of an ozonide with an unstabilized Wittig reagent to give a non-conjugated product has not been previously reported.
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- † This paper is no. 144 in the series *Defensive Mechanisms of Arthropods*; paper no. 143 is: Blankespoor, C. L.; Paptas, P. W.; Eisner, T. *Parasitology*, in press.

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