

SYNTHESIS OF NATURAL AND UNNATURAL FRONTALIN

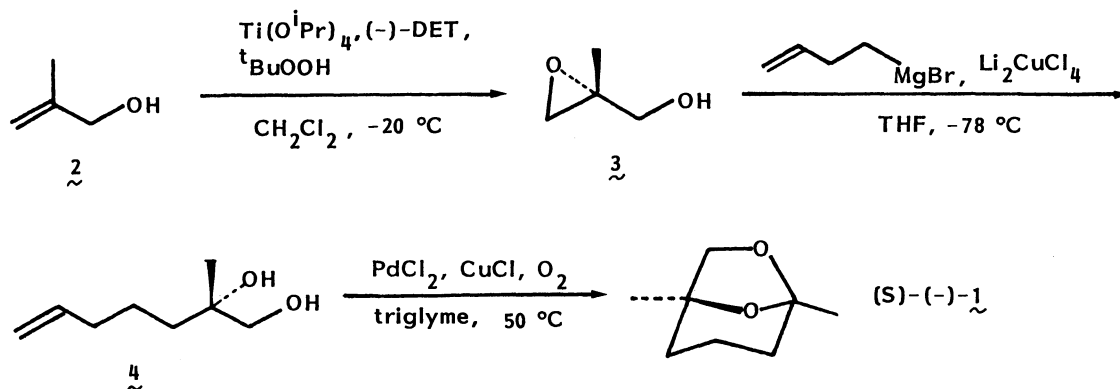
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(S)-(-)- and (R)-(+)-Frontalin were synthesized, respectively, in high enantiomer excess from β -methallyl alcohol (**2**) by three-step procedure; (i) asymmetric epoxidation of **2**, (ii) the epoxide opening with homoallylmagnesium bromide, and (iii) Pd(II)-catalyzed intramolecular acetalization.

(S)-(-)-Frontalin (**1**) is known to be the aggregation pheromone of the southern pine beetle *Dendroctonus frontalis*.¹⁾ Although the synthesis of this compound in optically active form has been accomplished by the derivation of either optically active natural products,^{2,3)} or optically resolved compounds,⁴⁾ the reports on its asymmetric synthesis are rare. One is the work of Mukaiyama⁵⁾ in which the diastereoselective alkylation of keto aminal is utilized as the key step. The other is the procedures of Lee⁶⁾ and Scharf⁷⁾ where the chiral center is constructed by the enantioselective epoxidation of allylic alcohols.⁸⁾ Described herein is the shortest route to (+)- and (-)-frontalin with readily available reagents.

The straightforward, three-step synthesis of (S)-(-)-frontalin (**1**) is illustrated in Scheme 1. β -Methallyl alcohol (**2**) was enantioselectively epoxidized by the procedure of Katsuki-Sharpless⁹⁾ (2 equiv. of *t*-BuOOH, CH_2Cl_2 ,



Scheme 1.

-20 °C) using (D)-(-)-diethyl tartrate {Aldrich, $[\alpha]_D^{25}$ -8.5 (neat)} in 44% yield. The epoxy alcohol **3** $\{[\alpha]_D^{25} +10.7$ (CHCl₃)} thus obtained was converted into olefinic diol **4** in 85% yield upon treatment with homoallylmagnesium bromide in the presence of 0.1 equiv. of Li₂CuCl₄ (THF, -78 °C).¹⁰⁾ The intramolecular acetalization¹¹⁾ of **4** catalyzed by PdCl₂ (0.1 equiv.) in the presence of CuCl (1 equiv.) and O₂ (1 atm) in triglyme at 50 °C gave a 92% ee²⁾ of (-)-frontalin $\{[\alpha]_D^{23}$ -50.9 (ether)} in 76% isolated yield. In this acetalization, the use of triglyme as the solvent allowed us to make the isolation of volatile frontalin easier.¹²⁾

According to the same sequence described in Scheme 1, unnatural (R)-(+)-frontalin was obtained in 83% ee from (-)-epoxy alcohol prepared by the asymmetric epoxidation of **2** with (L)-(+)-diethyl tartrate {Tokyo Kasei, $[\alpha]_D^{20}$ +7.6 (neat)}. Optically active pheromones such as brevicomin¹³⁾ and multistriatin¹⁴⁾ are constituted of the same structural unit of bicyclic acetal as that of frontalin. Our approach outlined here provides a high potentiality for the asymmetric synthesis of these insect pheromones.

References

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