

Total Synthesis of (+)- and (–)-Frontalin

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Both enantiomers of frontalin were synthesized in high optical purity using Katsuki–Sharpless asymmetric epoxidation as a key step.

Frontalin (**1**) is an active component of the synergistic pheromone of several species of pine beetles. Since its detection,¹ it has been subjected to extensive entomological² and synthetic^{3a,b} studies. In order to evaluate the behavioural and physiological aspects of the pheromone, it is desirable to have both enantiomers in optically pure form. We report here an efficient synthesis of both enantiomers of frontalin in high optical purity using the Katsuki–Sharpless asymmetric epoxidation⁴ as the key reaction.

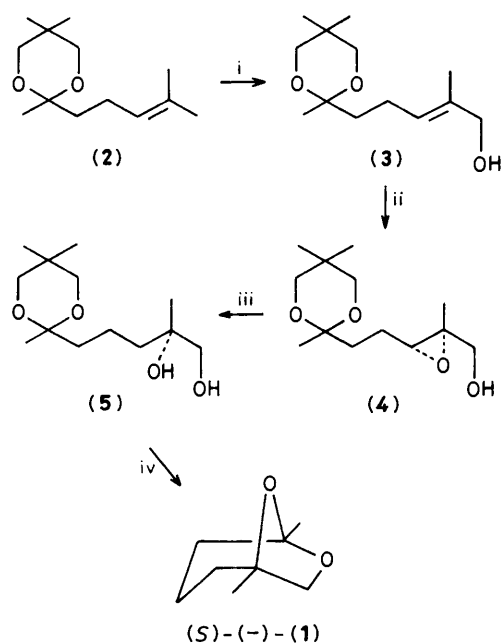
Although frontalin contains two asymmetric centres, only one needs to be considered owing to its bicyclic structure, so our initial target was the diol (**5**) in which only the chirality of the tertiary alcohol has to be controlled. The acetal (**2**)‡ was

prepared from commercially available 6-methylhept-5-en-2-one by the standard azeotropic procedure (2,2-dimethylpropane-1,3-diol; *p*-MeC₆H₄SO₃H, C₆H₆). Selenium dioxide allylic oxidation using the catalytic procedure⁵ due to Sharpless afforded the allylic alcohol (**3**)‡ in good yield.

Asymmetric epoxidation⁴ with (–)-diethyl tartrate gave the epoxy-alcohol (**4**)‡ ([α]_D²⁵ +9°, EtOH, *c* 2) in 92% chemical yield and $\geq 95\%$ enantiomeric excess.⁶ The use of a bulky acetal derived from 2,2-dimethylpropane-1,3-diol as the protecting group was crucial in this synthesis. With the simple ethylene acetal, the chemical and the optical yields in the epoxidation step were low. This complication is probably due to the opening of the newly generated epoxide function during the titanium-mediated epoxidation leading to furan or pyran formation. In fact, this type of cyclization process has been used to prepare highly functionalized chiral tetrahydropyrans.⁷ To complete the synthesis, the epoxy-alcohol (**4**) was opened smoothly to give the diol (**5**)‡ ([α]_D²⁰ –0.9°, EtOH, *c* 2.7) with an excess of LiAlH₄. Upon treatment with dilute

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‡ The structural assignments for all new compounds are supported by satisfactory spectroscopic data (250 MHz n.m.r., i.r., and mass).



Scheme 1. Reagents: i, SeO_2 , $\text{Bu}^t\text{O}_2\text{H}$, CH_2Cl_2 ; ii, asymmetric epoxidation (ref. 4); iii, LiAlH_4 , Et_2O ; iv, H_3O^+ , $\text{H}_2\text{O}-\text{C}_5\text{H}_{12}$.

mineral acid, (5) was cyclized spontaneously to yield (S)-(-)-frontalin ($[\alpha]_{\text{D}}^{23} -51.8^\circ$, ether, c 2.35; lit.^{3a} $[\alpha]_{\text{D}}^{23} -52^\circ$, ether, c 1.63%) in good overall yield.

By using (+)-diethyl tartrate in the asymmetric epoxida-

tion, the unnatural enantiomer (R)-(+)-frontalin ($[\alpha]_{\text{D}}^{21} +52.4^\circ$, ether, c 4.0) was prepared in 67% overall yield.⁸

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