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ASYMMETRIC SYNTHESIS OF TWO ENANTIOMERS OF FRONTALIN

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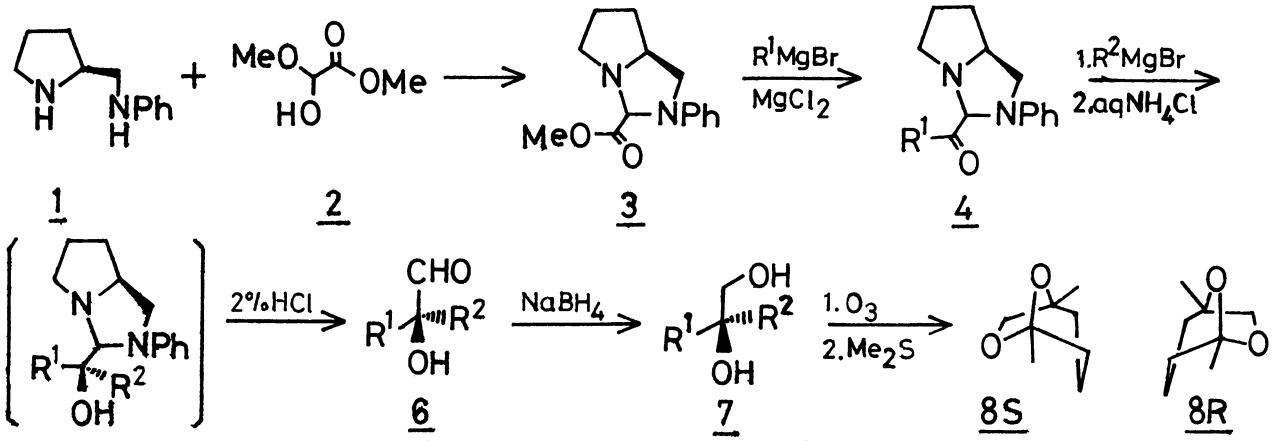
(S)-Frontalin and its antipode were separately synthesized in good yields from (S)- and (R)-2-hydroxy-2,6-dimethyl-6-heptenal, which were prepared in high optical yields by an asymmetric synthesis using (S)-2-(anilinomethyl)pyrrolidine as a chiral auxiliary.

Frontalin is a pheromone of several species of beetles belonging to the genus Dendroctonus.[1] A few reports have recently appeared concerning synthesis of optically active form of frontalin.[2-4] The synthetic methods in these reports involve a resolution of an optically active key intermediate[2] or employments of an optically active natural product as a starting material.[3,4] The absolute configuration of natural frontalin has been assigned as (s)-(-)-form and its antipode was reported to be not active.[5]

In this communication we wish to report a convenient method for the preparation of two enantiomers of frontalin by an application of a method for an asymmetric synthesis of α-hydroxy aldehydes.[6] The synthetic route of (S)-frontalin is illustrated in Fig($R^1=(CH_2)_3C(CH_3)=CH_2$, R^2=Me).



Keto aminal 4S[7] was prepared from methoxycarbonyl aminal 3 and 4-methyl-4-pentenyl

magnesium bromide in 63% yield based on diamine 1 by a similar method reported previously[6] with the exception that the Grignard reaction was carried out at -100°C. Keto aminal 4S was treated with methyl magnesium bromide at -78°C and the resulting hydroxy aminal 5S was hydrolyzed to yield α-hydroxy aldehyde 6S,[8] which was further reduced with sodium borohydride at 0°C without purification. Diol 7S[9] was obtained in 69% yield from 4S after purification by silica gel column chromatography ($[\alpha]_D^{25}$ -2.0°(c 0.98, CH_2Cl_2)). Ozonolysis of 7S at -70°C in methylene chloride followed by a reductive work up with dimethyl sulfide at a room temperature afforded (S)-frontalin 8S[10] in 91% yield after purification by alumina column chromatography, $[\alpha]_D^{20}$ -45.5° (c 1.75, ether)[11], whose optical purity was 84%-88%.[12]

(R)-frontalin was also obtained according to the present procedure only by changing the order of the introduction of substituents originated from the Grignard reagent (R^1=Me, R^2=$(CH_2)_3C(CH_3)=CH_2$). (R)-Diol 7R was obtained by a similar treatment in 71% yield from 4R,[13] $[\alpha]_D^{25}$ +2.4° (c 1.12, CH_2Cl_2), which was converted into (R)-frontalin 8R,[10] $[\alpha]_D^{25}$ +54.3°(c 3.39, ether), whose optical purity was 100% based on $[\alpha]_D$ -54.4° (c 1.33, ether)[14] reported by Ohrui and Emoto.[3] The conversions of 2 into 8S and 2 into 8R were accomplished in 40% and 47% overall yield, respectively.

In the present synthesis, high optical yield was achieved when R^2, introduced into α-hydroxy aldehyde by the second Grignard reaction, is larger than R^1, introduced into keto aminal by the first Grignard reaction. Thus, (R)-frontalin was obtained in higher optical yield than (S)-frontalin. It is noted that (S)-frontalin, natural form of the pheromone, would be obtained in optically pure form when (R)-2-(anilinomethyl)pyrrolidine is employed as a chiral auxiliary.

References and Notes

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6) T. Mukaiyama, Y. Sakito, and M. Asami, Chem. Lett., 1979, 705.
7) IR ν=1710 and 1645 cm^{-1}; NMR (CCl_4) δ=1.50-2.10(8H, m), 1.60(3H, s), 2.20-2.53 (2H, m), 2.63-3.27(3H, m), 3.50-3.87(2H, m), 4.20(1H, s), 4.50(2H, s), 6.17-7.10(5H, m).
8) IR ν=3420, 1730 and 1645 cm^{-1}; NMR ($CDCl_3$) δ=1.27(3H, s), 1.43-1.75(4H, m), 1.67(3H, s), 1.98(2H, t, J=6Hz), 3.30(1H, s), 4.57(2H, s), 9.33 (1H, s).
9) IR ν=3400 and 1645 cm^{-1}; NMR (CCl_4) δ=1.08 (3H, s), 1.40(4H, m), 1.67(3H, s), 1.97(2H, m), 3.25(2H, s), 3.53(2H, s), 4.55(2H, s).
10) The IR and NMR spectra was identical with those already reported in reference 3).
11) The sample for the measurement of specific rotation was thoroughly purified by short path distillation.
12) The optical purity was 88% based on $[\alpha]_D^{23}$ -52.0° (c 1.63, ether) reported in reference 2), or 84% based on $[\alpha]_D^{23}$ -54.4° (c 1.33, ether)reported in reference 3).
13) Preparation of keto aminal 4R was reported in reference 6).
14) Mori reported $[\alpha]_D^{23}$ +53.4° (c 2.757, ether) in reference 2).

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