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STEREOCONTROLLED SYNTHESIS OF ALL OF THE FOUR POSSIBLE STEREOISOMERS OF ERYTHRO-3,7-DIMETHYL-PENTADEC-2-YL ACETATE AND PROPIONATE, THE SEX PHEROMONE OF THE PINE SAWFLIES[1]

Kenji Mori,* Shigeharu Tamada and Masanao Matsui

Department of Agricultural Chemistry, The University of Tokyo,

Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

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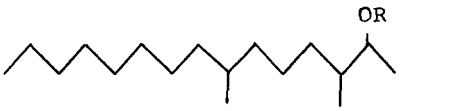
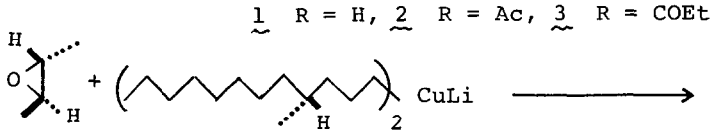
In 1976, Jewett et al. identified 3,7-dimethylpentadecan-2-ol (1) as the free alcohol in three species from two genera of pine sawflies (Hymenoptera : Diprionidae).[2] In Neodiprion lecontei and N. sertifer, the acetate (2) of this alcohol was the major component of their sex attractant, while in Diprion similis, it is the propionate (3).[1] Two syntheses of a stereoisomeric mixture of 1 were reported.[2,3] The alcohol 1 possesses three asymmetric carbon atoms and therefore can exist in eight stereoisomeric forms. However, the C-2 : C-3 erythro structure, as illustrated in 1a, was suggested[2] and confirmed by the synthesis of (±)-erythro-1.[4] This reduced the numbers of the possible stereoisomers to four.

A suggestion was made that the subtle specificity existing at the level of the genus might be due to optical isomerism in the alcohol moiety.[2] This prompted us to synthesize all of the four possible stereoisomers of the each of the pheromones 2 and 3 in optically pure forms. This Letter describes our synthesis based on a stereoselective oxirane cleavage reaction (A + B → 1a). The S_N2 attack of a chiral organocopper reagent (B) to a chiral epoxide (A) provides the chiral alcohol (1a).

The epoxides were prepared from tartaric acids. D-(-)-Tartaric acid (4) was converted to (2R, 3R)-(-)-2,3-butanediol (5), $[\alpha]_D^{22}$ -11.9° (neat), by the known methods.[5,6] This was treated with HBr-AcOH (0°, 30 min, then 40~50°,

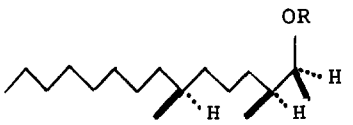


1 R = H, 2 R = Ac, 3 R = COEt

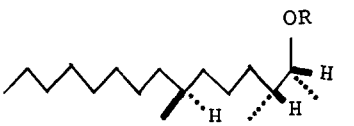


A B

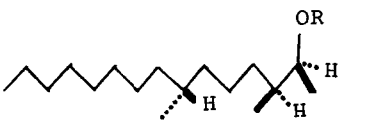
1a R=H (2R, 3R, 7R)
2a R=Ac 3a R=COEt



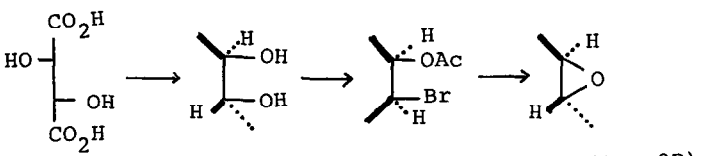
1a' R=H (2S, 3S, 7S)
2a' R=Ac 3a' R=COEt



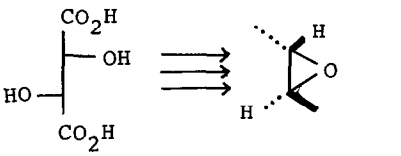
1b R=H (2R, 3R, 7S)
2b R=Ac 3b R=COEt



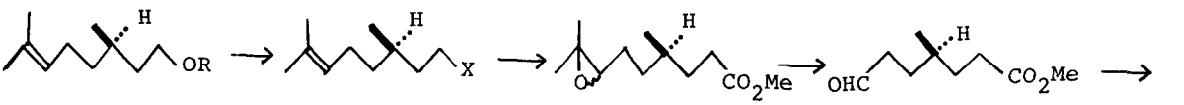
1b' R=H (2S, 3S, 7R)
2b' R=Ac, 3b' R=COEt



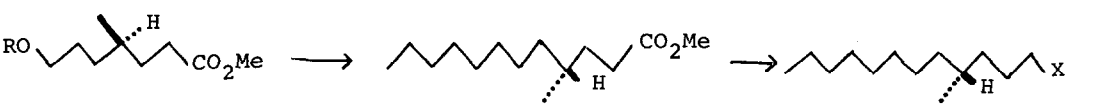
4 5 6 7 (2R, 3R)



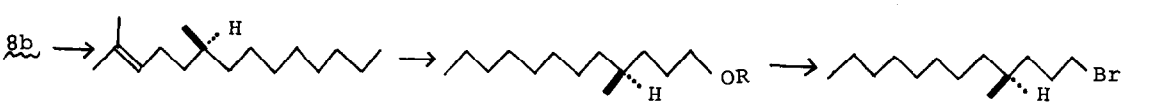
4' 7' (2S, 3S)



8a R=H, b R=Ts 9 X=CN
10a X=CO_2H, b X=CO_2Me
11 12



13 a R=H, b R=Ts 14
15a X=OH b X=OTs
16 X=Br (R)



17 15a' R=H, b' R=Ts 16' (S)

1 hr) to give an acetoxybromide (6), which was heated with KOH aq soln[cf. 7,8] to give (2R, 3R)-(+)-2,3-epoxybutane (7), bp 52~55°, n_D^{21} 1.3755, $[\alpha]_D^{21}$ + 55.4° (c= 1.9, ether), δ 1.20 (6H, d, J=5Hz), 2.51 (2H, dq, J_1= 1.5, J_2 = 5Hz). In the same manner, L-(+)-tartaric acid (4') yielded (2S, 3S)-(-)-epoxide (7'), bp 52~53.5°, n_D^{21} 1.3745, $[\alpha]_D^{21}$ -57.5° (c=1.2, ether). The method of preparation of these epoxides[7] ensures their high purities which were supported by very clean NMR spectra indicating no contamination with the erythro isomers.

Another part of the molecule, the chiral bromides 16 and 16', was prepared from (R)-(+)-citronellol (8a) derived from (R)-(+)-citronellic acid previously shown by us to be highly optically pure.[9] The tosylate (8b) was treated with NaCN in aq EtOH to give a nitrile (9), $[\alpha]_D^{21}$ + 4.41° (neat).[10] Hydrolysis (NaOH) of 9 gave an acid 10a which was treated with CH_2N_2 to give an ester 10b, $[\alpha]_D^{21}$ -0.98°(neat). Epoxidation of 10b with m-chloroperbenzoic acid yielded an epoxide (11) which was cleaved (HIO_4-THF-ether) to an aldehyde (12), $[\alpha]_D^{21}$ -0.71° (neat). This was reduced with $NaBH_4$-MeOH to give an alcohol (13a), $[\alpha]_D^{21}$ -0.98° (neat), whose tosylate (13b) was reacted with $(n\text{-}C_5H_{11})_2CuLi$ to give an ester (14), $[\alpha]_D^{21}$ +0.49° (neat). Reduction of 14 with $LiAlH_4$ gave 15a, $[\alpha]_D^{22}$+1.88° (±0.03°, neat). The corresponding tosylate (15b) was treated with LiBr-acetone to give (R)-(-)-1-bromo-4-methyldodecane (16), bp 91~96°/2mm, n_D^{22} 1.4575, $[\alpha]_D^{22}$ -2.16° (±0.02°, neat). The enantiomer (16') was obtained in simpler manner. The tosylate (8b) was treated with $(n\text{-}C_6H_{13})_2CuLi$ to give 17, $[\alpha]_D^{21.5}$ -1.26° (neat). This was oxidized with O_3 and the ozonide was reduced with $NaBH_4$ and $LiAlH_4$ to give the (S)-alcohol (15'), $[\alpha]_D^{22}$ -1.54° (±0.02°, neat). The (S)-bromide (16'), bp 96~102°/2.5mm, n_D^{21} 1.4580, $[\alpha]_D^{21}$+2.29° (±0.01°, neat), was obtained via 15b' in the same manner as described for the preparation of 16.

The coupling reaction (A+B) was best accomplished with R_2CuLi type reagents. Thus (R)-bromide (16) in ether was converted to R_2CuLi reagent[9,11] and reacted with 7 in ether (-50°, 3 hr; -20~-15°, overnight) to give (2R, 3R, 7R)-1a, bp 115~117°/0.4mm, n_D^{22}1.4518; $[\alpha]_D^{21}$+9.66° (±0.06°, neat) in 80% yield after chromatographic purification. In the same manner, 7' and 16' gave (2S, 3S, 7S)-1a', n_D^{21} 1.4504, $[\alpha]_D^{21}$-9.82° (±0.06°, neat); 7 and 16' yielded (2R, 3R, 7S)-1b, n_D^{21} 1.4507, $[\alpha]_D^{21}$+10.80° (±0.04°, neat); 7' and 16 afforded (2S, 3S, 7R)-1b', n_D^{21}

1.4503, $[\alpha]_D^{21}$ -11.10° (±0.08°, neat). These alcohols were converted to the acetates (2a, 2a', 2b, 2b') and propionates (3a, 3a', 3b, 3b') in the usual manner. The stereochemical and optical purities of these products were fully examined by GLC[12], ^{1}H-NMR[13] and ^{13}C-NMR.[14] The obtained data were compared with those of a stereoisomeric mixture of 1 or 2 prepared by a new synthetic route.[15] The products were shown to be pure erythro isomers with high optical purities, whose biological evaluation will certainly deepen our present knowledge on stereochemistry-activity relationship among insect pheromones.

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10. Satisfactory spectral and analytical data were obtained for all the compounds described in this paper.
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12. Each of our alcohols 1a, 1a' 1b and 1b' shows a single peak on GLC analysis (PEG 20M, 50m x 0.28 mm i.d. at 180°) under the condition where erythro- and threo-isomers were separable.
13. The ^{1}H-NMR spectrum of 1a (20 mg) in CCl_4 (0.5 ml) in the presence of Eu(fod)$_3$ (12 mg) showed signals at δ 1.38 (3H, d, J=7Hz, Me at C-3) and 2.02(3H, d, J=7Hz, C-1 Me) at 100 MHz. The ^{1}H-NMR spectra of 2a, 2a', 2b and 2b' in C_6H_6-d_6 showed a 3H-doublet at δ 1.07 (J=7Hz), while the stereoisomeric mixture exhibited a pair of doublets at δ0.98 (1.4H, d, J=7Hz) and 1.07 (1.6H, d, J=7Hz) at 100 MHz.cf. 2,15 The ^{1}H-NMR spectra of 1a and 1a' were measured in the presence of Eu(hfmc)$_3$ to reveal no splitting of the C-1 Me confirming the high optical purities.
14. The ^{13}C-NMR spectra of 2a, 2a', 2b and 2b' in C_6H_6-d_6 showed a sharp signal at δ 72.8 ppm (CHOAc), while the stereoisomeric mixture exhibited signals at δ 72.8 and 73.1 ppm.4
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