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Synthesis of Optically Active Common Precursor of Sex Pheromone of Pine Sawflies: An Application of Enantioface-Differentiating Hydrogenation with Modified Nickel

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Synthesis of optically active 3,7-dimethylpentadecan-2-ol (1), a common precursor of sex pheromone of pine sawflies, was carried out. (+)-(*2S,3S*)-, (-)-(*2R,3R*)-, and (±)-(*2R*,3S**)-1 were prepared from (+)-(*2R,3S*)-, (-)-(*2S,3R*)-, and (±)-(*2R*,3S**)-3-hydroxy-2-methylbutyric acid, respectively under the conservation of their stereochemistry. Enantioface-differentiating (asymmetric) hydrogenation of methyl 2-methyl-3-oxobutyrate over tartaric acid-modified nickel catalyst gave methyl 3-hydroxy-2-methylbutyrate in high diastereomer and enantiomer excess, enabling us to obtain the optically active starting materials in high yields.

The sex pheromones of several species of pine sawflies have a common alcohol moiety, 3,7-dimethylpentadecan-2-ol (1). *Neodiprion lecontei* and *sertifer* use the acetate of 1 as the major component of their pheromone, *Diprion similis* uses the propionate of 1. The investigation on the natural pheromone has revealed that, while the choice of acid is the primary factor for the discrimination, subtle chemical specificity based on the stereochemical difference in alcohol moiety exsists at the level of the genus.[1] The synthesis of optically active 1 is quite important for the ultimate identification of the pheromone.[2]

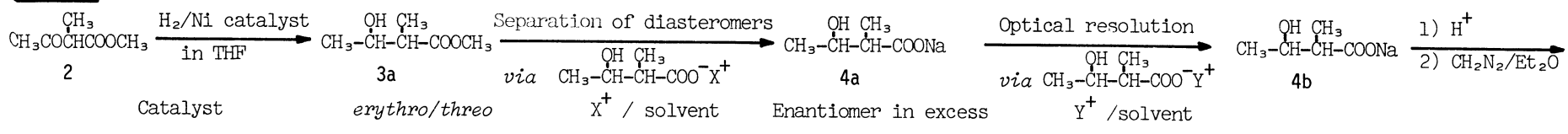
As a preliminary step of the complete stereospecific synthesis, (+)-(*2R,3R*)-, (-)-(*2S,3S*)-, and (±)-(*2R*,3S**)-1 were prepared. The synthetic process and the relation of the configuration in each step are shown in Scheme 1.

The key step of the C_5 unit synthesis is an enantioface-differentiating hydrogenation[3] of 2 over nickel catalyst modified with optically active substances (MNi). Insofaras we examined, tartaric acid-MNi was the best catalyst for the preparation of optically active *erythro*-3.[4] The MNi catalyst was easily obtained by soaking the reduced nickel powder prepared by the hydrogenolysis of nickel carbonate, for 1 h at 85°C in 1% tartaric acid solution of which pH was adjusted to 4.1 with sodium hydroxide. Hydrogenation of 2 over MNi under 100 kg/cm^2 of hydrogen pressure at 100°C gave **3a** in 90% yield. The ratio of *erythro*- and *threo*-**3a**[5] in the product is shown in Scheme 1.

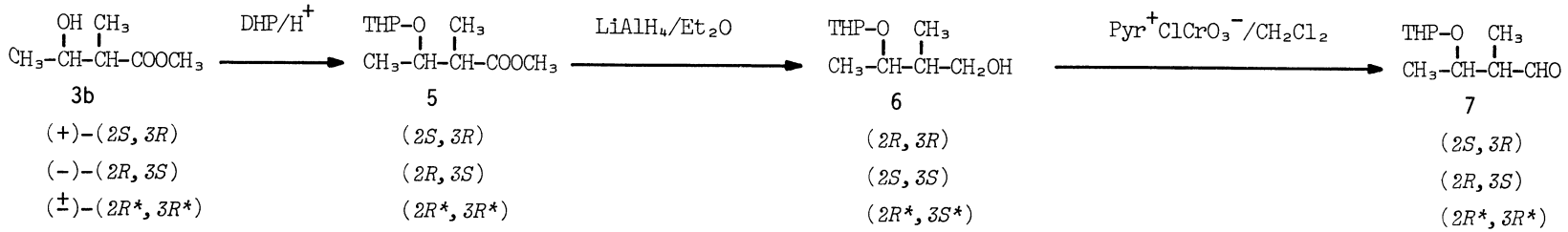
After saponification of **3a** with aqueous sodium hydroxide, the resulting acid was converted to cyclohexylammonium salt. Three successive recrystallizations from ethanol gave *erythro*-3-hydroxy-2-methylbutyric acid as a cyclohexylammonium salt in 55-62% yield based on **3a**. After the removal of cyclohexylamine by ion exchange resin, the acid liberated was converted to sodium salt (**4a**) in 95% yield. (-)-*Erythro*-**4a** ($[\alpha]_D^{20}$-4.4 (c 10, H_2O), optical purity 56%) and (+)-*erythro*-**4a** ($[\alpha]_D^{20}$+4.7 (c 10, H_2O), optical purity 60%) were obtained from the hydrogenation product with (*2R,3R*)-tartaric acid-MNi and (*2S,3S*)-tartaric acid-MNi, respectively. The optical purity of 60% resulted in great advantage for the further optical resolution of **4a**. The bases and solvent used for the optical resolution are shown in Scheme 1. Three recrystallizations in

Scheme 1 Synthetic Route of 3,7-Dimethypentadecan-2-ol

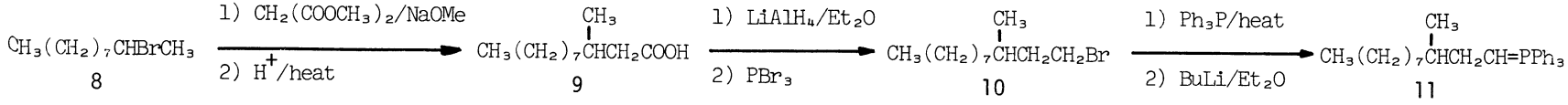
C_5 unit



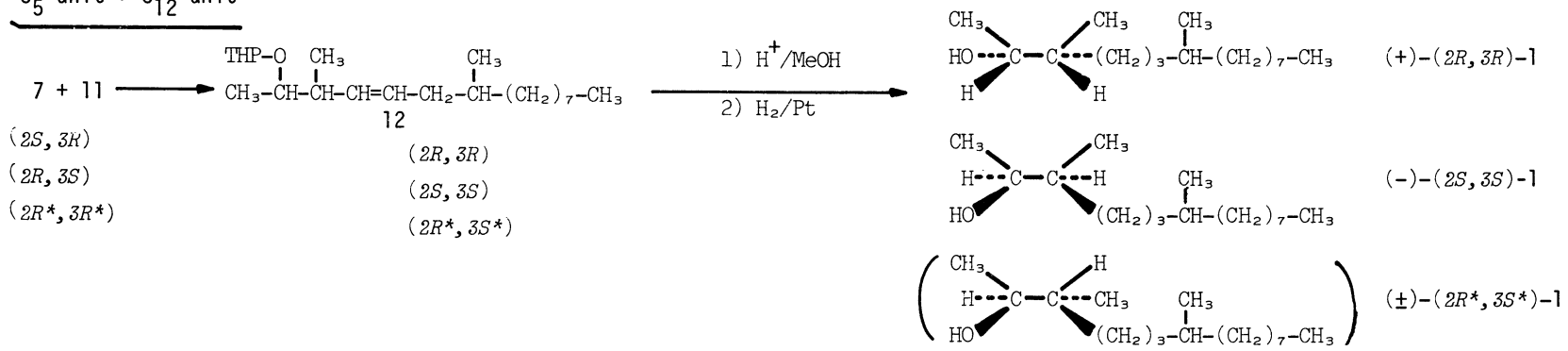
Catalyst	*erythro/threo*	X^+ / solvent	Enantiomer in excess	Y^+ /solvent	
(*R*,*R*)-Tartaric acid-MNi	78/22	Cyclohexylammonium/EtOH	(−)-*erythro*	Quinine/EtOH	(−)-*erythro*
(*S*,*S*)-Tartaric acid-MNi	75/25	Cyclohexylammonium/EtOH	(+)-*erythro*	Quinidine/Acetone	(+)-*erythro*
Unmodified Ni with AcOH	45/55	Sodium/MeOH-Acetone	*threo*	————	(±)-*threo*



C_{12} unit



C_5 unit + C_{12} unit

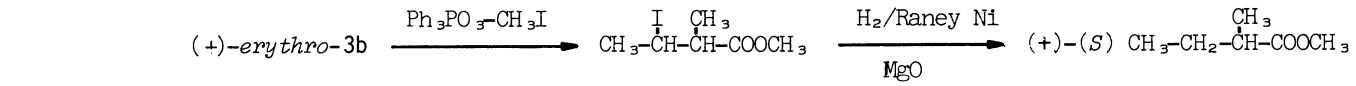


both cases gave optically pure products.[6] The removal of the base on treatment sodium hydroxide gave *erythro*-**4b**. (-)-*Erythro*-**4b**, 58% yield based on **4a**, mp 174°C, $[\alpha]_D^{20}$-7.80° (c 10, H_2O) and (+)-*erythro*-**4b**, 62% yield based on **4a**, mp 174°C, $[\alpha]_D^{20}$+7.82°(c 10, H_2O) were obtained from the quinine and quinidine salt, respectively.

The hydrogenation of **2** over unmodified nickel catalyst in the presence of a small amount of acetic acid gave *threo*-**3a** in excess, which was then converted to sodium salt. Four successive recrystallizations from methanol-acetone gave pure (±)-*threo*-**4b**, mp 218°, in 37% yield based on **3a**.

The esterification of **4b** with diazomethane gave **3b** in an average yield of 95%. (-)-*Erythro*-**4b** was converted to (+)-*erythro*-**3b** and (+)-*erythro*-**4b** to (-)-*erythro*-**3b**. (+)-*erythro*-**3b**: bp 75°C/15mmHg, $[\alpha]_D^{20}$+11.35° (neat), GLC(NPGS-5%/Chromosorb-W, 100°C), single peak at 14 min, NMR($CDCl_3$, TMS), δ=1.18 (3H, d, J=6.4 Hz), 1.19 (3H, d, J=7.0 HZ), 2.46 (1H, broad signal), 2.51 (1H, m), 3.70 (3H, s), and 4.06 (1H, m), IR(neat), 3550, 2990, 2960, 1730, 1200, 1085, and 1030 cm^{-1}. (-)-*erythro*-**3b**: $[\alpha]_D^{20}$-11.39° (neat). Bp, retention time of GLC, and NMR and IR spectra were identical with those of (+)-isomer. (±)-*threo*-**3b**: bp, 75°C/15mmHg, GLC, single peak at 13 min, NMR($CDCl_3$, TMS), δ=1.18 (3H, d, J=7.2 Hz), 1.22 (3H, d, J=6.3 Hz), 1.93 (1H, broad signal), 2.47 (1H, m), 3.71 (3H, s), and 3.82 (1H, m), IR(neat), 3550, 2990, 2960, 1730, 1200, 1110, and 1040 cm^{-1}.

The configuration at C-2 of (+)-*erythro*-**3b** was correlated to (+)-(*S*)-methyl 2-methylbutyrate as follows.[7]



The configuration at C-3 of (+)-*erythro*-**3b** was assigned to *R* by Horeau's method[8]. The configuration of each isomer of **3b** is listed in Scheme 1[9].

The reaction of **3b** with dihydropyran gave **5**, which was then reduced to **6** with $LiAlH_4$. An average yield from **3b** to **6** was 80%. (*2R,3R*)-**6**: bp 105°C/3.5mmHg, Found: C, 63.58; H, 10.94, Calcd: C, 63.79; H, 10.71. (*2S,3S*)-**6**: Found: C, 63.60; H, 10.82. (*2R*,3S**)-**6**: Found: C, 64.00; H, 10.91.

The oxidation of **6** to **7** was carried out with pyridinium chlorochromate in dry methylene chloride at 5°C[10]. The crude **7** isolated from the reaction mixture by Florisil column at 0°C was used in the next step immediately after the work up.

Nonanal was used as a starting material of C_{12} unit synthesis. The treatment with PBr_3 of 2-hydroxydecane obtained by the reaction of nonanal and CH_3MgBr gave **8**, bp 110-115°C/20mmHg.

Elongation of the carbon chain of **8** with dimethyl malonate and following decarboxylation gave **9**, bp 131/1.3mmHg. The reduction of **9** with $LiAlH_4$ and subsequent bromination with PBr_3 gave **10**, bp 95-6°C/1mmHg, Found: C, 57.62; H, 10.46; Calcd: C, 57.90; H, 10.00, NMR(CCl_4, TMS), δ=0.90 and 0.91 (6H, overlapped d and t, CH_3 at C-10 and C-3), 1.25 (14H, envelope, $-(CH_2)_7-$), 1.75, (3H, envelope, $-CH_2-CH_2Br$ and $-CH-$), and 3.75 (2H, t, $-CH_2Br$).

Phosphonium salt of **10** was obtained by heating an equimolar mixture of **10** and Ph_3P at 180°C for 30 h and subsequent crystallization in dry ether. The addition of BuLi into a suspension of the phosphonium salt in ether gave red solution of **11**.

The coupling of **7** and **11** carried out at 10°C gave **12** in 40 to 45% yield based on **7**. The epimerization at C-2 of **7** was minimized by gradual addition of **7** to the slightly excess amount of **11** with vigorous stirring. The concomitant epimer in the product was the order of a few per cent.[11]

The removal of THP from **12**, and the hydrogenation of the resulting alcohol over Adams Pt catalyst at room temperature under atmospheric pressure of hydrogen gave **1** in an average yield of 86% based on **12**. (+)-(*2R,3R*)-**1**: bp 108°C/0.05mmHg, Found: C, 79.11; H, 14.47, Calcd for $C_{17}H_{36}O$: C, 79.61; H, 14.15, NMR(CCl_4, TMS) δ=0.89 (9H, envelope which could be resolved into two d and one t by the addition of EuDPM, CH_3- at C-3, C-7, and terminal), 1.08 (3H, d, J=7 Hz, CH_3-CH(OH)-), 1.22 (22H, envelope, -$(CH)_n$- and -CH- at C-3 and C-7), 3.55 (1H, m, -CH(OH)-), IR (neat), 3370, 1465, 1380, and 1100 cm^{-1} $[\alpha]_D^{20}$ + 7.94° (neat). GLC(NPGS-5%/Chromosorb W, 180°C) indicated 99% purity, retention time 8.3 min, with 1% unidentified impurity, retention time 7.0 min. NMR taken in the presence of shift reagent (EuDPM and EuHFMC) showed the presence of ca. 3% of epimer, (*2R,3S*)-**1**, in the optically pure (*2R,3R*)-**1**. (-)-(*2S,3S*)-**1**: All physical and analytical data were identical with those of (+)-**1** except for optical rotation, $[\alpha]_D^{20}$- 8.02° (neat). (±)-(*2R*,3S**)-**1**: GLC indicated 99% chemical purity. NMR taken in the presence of EuDPM showed the presence of ca. 3% of epimer. NMR (CCl_4, TMS) showed signals, δ=0.89(9H, envelope which could be resolved into two d and one t by the addition of EuDPM, CH_3- at C-3, C-7 and terminal), 1.06 (3H, d, J=6 Hz, CH_3-CH(OH)-), 1.22 (22H, envelope), 3.56 (1H, m, -CH(OH)-). Retention time in GLC and IR spectra were identical with those of *erythro*-isomer.

Bioasseys of acetate and propionate of **1** are now progressing.

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References and Notes

1) D. M. Jewett, F. Matsumura, and H. C. Coppel, Science, 192, 51, (1976)

2) Diastereomeric mixture of **1** has been synthesized by D. M. Jewett and *et al.* (reference 1), and by P. J. Kocienski and J. M. Ansell, J. Org. Chem., 42, 1102 (1977). (±)-*Erythro*-**1** has been synthesized by G. Magnusson, Tetrahedron Lett., 1977, 2731.

3) T. Harada, S. Onaka, A. Tai, and Y. Izumi, Chem. Lett., 1977, 1131.

4) Details of the hydrogenation of **2** will be published elsewhere.

5) K. Maskens and N. Polgar, J. Chem. Soc. Perkin Trans. 1, 1973 109. By convention the *erythro* form is defined as follows; viewing the molecule along the C-2 and C-3 bond axis, when the two methyl group are in the eclipsed position, then the two H-groups are also in the eclipsed position. In the case of **3**, *erythro*-isomer corresponds to (*2R*,3S**)-isomer.

6) At this stage of recrystallization, the optical rotation of **4** derived from quinine or quinidine salt reached steady value and unchanged by three further recrystallizations. The mixed melting point determination of quinine or quinidine salt at each recrystallization showed that the samples of this stage were homogeneous. The purities of **3b** derived from **4** were also checked by NMR with EuTFMC.

7) From partially resolved (+)-*erythro*-**3**, α_D^{20}+ 7.1°, (+)-methyl 2-methylbutyrate, $[\alpha]_D^{20}$ +14.4° (c 4, methanol), was obtained.

8) A. Horeau, Tetrahedron Lett., 1961 506.

9) The details on the stereochemistry of **3** will be published in near future.

10) E. J. Corey and J. W. Suggs, Tetrahedron Lett., 1975 2647.

11) Estimated from the peak areas of methyl proton at C-1 in NMR spectra of **1** taken in the presence of EuDPM.

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