Preparation of Optically Pure (3*S*,5*S*)- and (3*R*,5*R*)-2,6-Dimethyl-3,5-heptanediol

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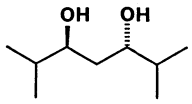
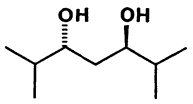
Optically pure 2,6-dimethyl-3,5-heptanediol (**1**), a new chiral auxiliary, has been prepared by the enantio-differentiating hydrogenation of 2,6-dimethyl-3,5-heptanedione over tartaric acid-NaBr-modified Raney nickel catalyst (TA-NaBr-MRNi), and the preferential recrystallization of the hydrogenation product. Absolute configuration of **1** was determined to be 3*S*, 5*S* by the chemical correlation with (−)-ethyl (*S*)-3-hydroxy-4-methylpentanoate.

This report deals with a facile preparation of optically pure (3*S*,5*S*)- and (3*R*,5*R*)-2,6-dimethyl-3,5-heptanediol(**1**), promising chiral auxiliaries for enantio- and diastereo-differentiating reactions. The characteristics of **1** are the presence of bulky isopropyl groups on its chiral centers and its nonhygroscopic nature. Thus, **1** is expected to be a more efficient and handy chiral auxiliary than (2*R*,4*R*)- and (2*S*,4*S*)-2,4-pentanediol (PD) which have been developed by our group and commercialized.[1] The excellence of **1** as a chiral auxiliary has been proved by our preliminary study on diastereo-differentiating Simmons-Smith reaction.[2]



(3S,5S)-1



(3R,5R)-1

Results and Discussion

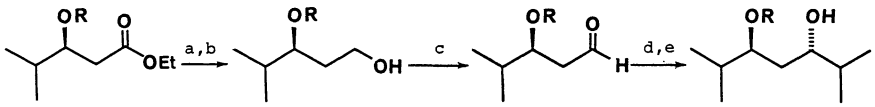
The preparation procedure of an optically pure **1** consists of the enantio-differentiating hydrogenation of 2,6-dimethyl-3,5-heptanedione(**2**) over tartaric acid-NaBr-modified Raney nickel (TA-NaBr-MRNi)[1] and the subsequent enantiomeric and diastereomeric purification of the hydrogenation product by conventional recrystallizations from ether.

The starting material **2** was prepared from methyl isobutyrate and methyl isopropyl ketone by Claisen condensation.[3] Carefully purified **2** was hydrogenated over TA-NaBr-MRNi under the same conditions employed for the preparation of PD from 2,4-pentanedione. The hydrogenation of **2** proceeded in two steps, via 5-hydroxy-2,6-dimethyl-3-heptanone (**3**) as an intermediate. The second step of hydrogenation was found to be much slower than the first step and the reaction time to complete the reduction was 5 to 10 times longer than that in the case of PD.

The hydrogenation of **2** over (*R*,*R*)-TA-NaBr-MRNi gave a levorotatory hydrogenation product as a mixture of (3*R**,5*R**)-**1** and (3*R**,5*S**)-**1** (meso isomer) in a ratio of 80 to 20. Two to three successive recrystallizations of the reaction product from diethyl ether gave optically and diastereomerically pure (−)-(3*R**,5*R**)-**1** as colorless needles. The overall yield of (−)-(3*R**,5*R**)-**1** was 25 to 30% based on **2**. The optical purity of this compound was proved both by HPLC analysis with an asymmetrically modified column and by NMR with a chiral shift reagent, (+)-Eu(hfmc)$_3$.

Optically pure (+)-(3*R**,5*R**)-**1** was also obtained by the same procedures as described above except for the use of (*S*,*S*)-TA-NaBr-MRNi instead of (*R*,*R*)-TA-NaBr-MRNi as the catalyst.

The absolute configuration of (−)-(3*R**,5*R**)-**1** was assigned to be 3*S*,5*S* by the chemical correlation as shown in Scheme 1. That is, (−)-ethyl 3-hydroxy-4-methylpentanoate(**4**), prepared by hydrogenation of ethyl 3-oxo-4-methylpentanoate with (*R*,*R*)-TA-



4 R=H
5 R=MEM

6 R=MEM

7 R=MEM

8 R=MEM
1 R=H

a:MEMCl,i-Pr$_2$EtN,CH$_2$Cl$_2$; b:LAH,ether; c:PCC,CH$_2$Cl$_2$; d:i-PrMgBr,ether;
e:HClO$_4$-H$_2$O-THF

Scheme 1.

NaBr-MRNi, was converted to the 2-methoxyethoxymethyl(MEM) ether(**5**) which was reduced by lithium aluminum hydride to give alcohol (**6**) in 55.2% yield. Oxidation of **6** with PCC followed by the addition of the Grignard reagent prepared from isopropyl bromide and magnesium afforded **8**. The deprotection of the MEM group in **8** with perchloric acid in aqueous THF gave (−)-**1** and *meso*-**1** in a ratio of 96.2 to 3.8. Since the absolute configuration of (+)-**4** has been assigned to be *R* by chemical correlation with (−)-(*R*)-dihydrotubaic acid,[4] absolute configuration of (−)-**1** was assigned to be 3*S*,5*S* and that of (+)-**1** was 3*R*,5*R*.

Experimental

All the temperatures are uncorrected. NMR and IR spectra were taken with a JEOL GX-400 spectrometer and a JASCO IR-810 spectrometer. Optical rotation was measured with a JASCO DIP-360 polarimeter. Analytical GLC was conducted with a Shimadzu GC-6A gas chromatograph using 3m-3mm i.d. glass column packed with 5% NPGS on Shimalite W. Preparative MPLC was carried out with a Lobar column (Lichroprep-Si 60, MERCK) using a Waters R403 refractometer as a detector. Analytical HPLC was conducted with a Waters HPLC system using Chiro Pack OT$^+$ column (Daicel Chemical Industries, Ltd.). All chemicals except 2,6-dimethyl-3,5-heptanedione(**2**) and ethyl 3-oxo-4-methylpentanoate were obtained from commercial sources.

2,6-Dimethyl-3,5-heptanedione(2). This was obtained from methyl isobutyrate and methyl isopropyl ketone by the reported method,[3] and distilled twice (bp 78—80 °C/16 mmHg; 1 mmHg≈133.322 Pa)

TA-NaBr-MRNi. This was prepared from 38 g of Raney alloy (Ni/Al=42/58, Kawaken Fine Chemicals Co.) by the method reported before except for modification temperature (90—95 °C).[1]

Hydrogenation of 2. In an autoclave (1000 ml capacity) were introduced 102 g of **2**, 220 ml of THF, 2 ml of acetic acid, and (*R*,*R*)-TA-NaBr-MRNi prepared above. The autoclave was charged with hydrogen to a pressure of 100 kg cm^{-2} and the mixture in the autoclave was kept at 100 °C for a week with shaking. After cooling the autoclave and evacuation of hydrogen, contents of the autoclave was taken out and filtered. Evaporation of solvent from the filtrate gave 101 g of colorless solid.

Analysis of Hydrogenation Products. A small portion of the product was subjected to MPLC separation over silica gel to afford (3*R**,5*R**)-**1** and (3*R**,5*S**)-**1**, whose yields were 66% and 16%, respectively. Reaction intermediate(**3**) was also isolated in 17% yield ($[\alpha]_D^{20}$=−29.8 ° (*c* 1.0, methanol), 59% e.e. of *S*). The e.e. value of (3*R**,5*R**)-**1** ($[\alpha]_D^{20}$=−53.9° (*c* 1.0, methanol)) isolated by the MPLC was determined to be 85% by both the HPLC analysis and the ^{1}H NMR measurement of its derivatives.

(3*S*,5*S*)-2,6-Dimethyl-3,5-heptanediol (1). A major portion (99 g) of the hydrogenation product was recrystallized three times from 200 ml each of ether to give (3*S*,5*S*)-**1** as colorless needles (28.7 g, 29% yield based on **2**), mp 89—91 °C, Found: C, 67.01; H, 12.59%. Calcd for $C_9H_{20}O_2$: C, 67.45; H, 12.58%, $[\alpha]_D^{20}$=−64.5° (*c* 1.0, methanol). IR(KBr) 3360, 2980, 2920, 1410, 1390, 1040 cm^{-1}; ^{1}H NMR($CDCl_3$) δ=3.65 (m, 2H, C<u>H</u>-OH), 2.13 (brs, 2H, O<u>H</u>), 1.70 (m, 2H, C<u>H</u>-CH$_3$), 1.60 (m, 2H, C<u>H</u>$_2$), 0.93 (d, *J*=7.1 Hz, 12H, C<u>H</u>$_3$). The optical purity of this sample was determined to be over 99.5% by two following methods.

HPLC Analysis of the Optical Purity of 1. Dibenzoate derived from **1** was purified by MPLC and subjected to HPLC analysis on Chiro Pack OT$^+$ column(supplied by courtesy of Daicel Chemical Industries, Ltd.) with a mixture of MeOH-EtOH (1:2) as an eluent (5 °C, 0.5 ml min^{-1}). Dibenzoate of (3*S*,5*S*)-**1** had a longer retention time (49.7 min) than that of (3*R*,5*R*)-**1** (32.6 min).

MPLC Analysis of the Optical Purity of 1. The sample was acetylated with acetic anhydride (1 equiv) in pyridine and the monoacetate was isolated by MPLC on silica gel (hexane : ethyl acetate=9 : 1). ^{1}H NMR spectra of a solution of the monoacetate in $CDCl_3$ was measured in the presence of (+)-Eu(hfmc)$_3$. The signal due to the acetyl group of (3*S*,5*S*)-enantiomer was appeared in a lower field than that of (3*R*,5*R*)-enantiomer on the addition of the shift reagent.

(3*R*,5*R*)-2,6-Dimethyl-3,5-heptanediol (1). The hydrogenation product of **2** over (*S*,*S*)-TA-NaBr-MRNi was recrystallized by the same procedure as above to give optically pure (+)-(3*R*,5*R*)-**1**, $[\alpha]_D^{20}$=+64.5° (*c* 1.0, methanol).

Partial Oxidation of (3*S*,5*S*)-1. A mixture of 478 mg of (3*S*,5*S*)-**1** (67% e.e.), 720 mg of PCC and 20 ml of dichloromethane was stirred and the reaction was monitored by thin-layer chromatogram. When a new compound, **3**, became a major component, saturated aqueous solution of sodium hydrogencarbonate was poured into the reaction mixture. The crude mixture was subjected to MPLC separation over silica gel to afford 186.7 mg of (−)-**3** (39.6% yield); $[\alpha]_D^{20}$= −33.8° (*c* 1.0, methanol). ^{1}H NMR and IR spectra were consistent with those of the compound in a literature.[5]

(−)-Ethyl (*S*)-3-Hydroxy-4-methylpentanoate (4). This was obtained from ethyl 3-oxo-4-methylpentanoate by the reported method.[6] $[\alpha]_D^{20}$=−14.3° (*c* 0.3, methanol), bp 79—80 °C/5 mmHg. The enantiomeric purity was determined to be 80% e.e. by NMR analysis of its methyl ester using (+)-Eu(hfmc)$_3$.

(−)-(*S*)-3-(2-Methoxyethoxymethoxy)-4-methyl-1-pentanol (6). Into a solution of 1.60 g of (−)-ethyl (*S*)-3-hydroxy-4-methylpentanoate(**4**) and 3.5 ml of *N*,*N*-diisopropylethylamine in 100 ml of dichloromethane was added dropwise 1.75 ml of 2-methoxyethoxymethyl chloride at room temperature and the solution was kept stirring overnight. The reaction mixture was treated with water and ether with shaking. The separated ether layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give 2.71 g of an oily residue. The solution of 2.61 g of the residue in 15 ml of ether was added dropwise to a suspension of 293 mg of lithium aluminum hydride in 29 ml of ether at room temperature and stirred vigorously for 30 minutes. The reaction mixture was treated with ethyl acetate and saturated solution of Na_2SO_4 was added dropwise till the slurry became clear. The solution was taken out by decantation, washed with brine, dried over Na_2SO_4 and concentrated to give 2.93 g of crude product. This was subjected to column chromatogram separation to obtain 1.14 g of **6** (55.2% yield from **4**), $[\alpha]_D^{20}$=−24.6° (*c* 1.14, methanol). IR(neat) 3450, 2950, 2870, 1465, 1385, 1365, 1200, 1100, 1040, 925 and 845 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=4.79 (d, *J*=6.9 Hz, 1H, O-C<u>H</u>$_2$-O), 4.74 (d, *J*=6.9 Hz, 1H,

O-C$\underline{H}_2$-O), 3.9—3.83 (m, 1H, C$\underline{H}$-OCH$_2$), 3.9—3.75 (m, 1H, C$\underline{H}_a$H$_b$OH), 3.73—3.66 (m, 1H, CH$_a\underline{H}_b$OH), 3.67—3.62 (m, 2H, OCH$_2$CH$_2$O), 3.6—3.55 (m, 2H, OCH$_2$CH$_2$O), 3.40 (s, 3H, OC$\underline{H}_3$), 2.82 (t, J=6.2 Hz , 1H, O$\underline{H}$), 1.95—1.85 (m 1H, C$\underline{H}$-CH$_3$), 1.8—1.7 (m, 1H, C$\underline{H}_a$H$_b$CH$_2$OH), 1.65—1.55 (m, 1H, CH$_a\underline{H}_b$CH$_2$OH), 0.90 (d, J=7.0 Hz, 3H, Ca$\underline{H}_3$CH), 0.90 (d, J=6.8 Hz, 3H, C$_b\underline{H}$CH).

(−)-(*S*)-3-(2-Methoxyethoxymethoxy)-4-methylpentanal (7). To a solution of 1.14 g of **6** in 75 ml of dichloromethane was added 11.13 g of powdered molecular sieves 3A and then 2.16 g of PCC. The mixture was kept stirring for 2 hours. The reaction mixture was filtered and the filtrate was washed with saturated solution of $NaHCO_3$ and with brine, dried over Na_2SO_4 and concentrated to give 812.4 mg of crude **7**. This was subjected to MPLC separation to afford 597.4 mg of **7** in 53.1% yield, $[\alpha]_D^{20}=-26.3°$ (c 1.01, $CHCl_3$). IR(neat) 2960, 2880, 1730, 1470, 1390, 1370, 1280, 1240, 1200, 1170, 1105, 1040, 930, 850 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=9.81 (dd, J=2.9, 1.5 Hz, 1H, C$\underline{H}$=O), 4.78 (d, J=7.3 Hz, 1H, OC$\underline{H}_a$H$_b$O), 4.75 (d, J=7.3 Hz, 1H, OCH$_a\underline{H}_b$O), 4.0—3.95 (m, 1H, C$\underline{H}$-O), 3.75—3.6 (m, 2H, OCH$_2$CH$_2$O), 3.56—3.52 (m, 2H, OCH$_2$CH$_2$O), 3.38 (s, 3H, OC$\underline{H}_3$), 2.60 (ddd, J=16.1, 8.1, 2.9 Hz, 1H, C$\underline{H}_a$H$_b$CH=O), 2.49 (ddd, J=16.1, 4.0, 1.5 Hz, 1H, CH$_a\underline{H}_b$CH=O), 2.0—1.9 (m, 1H, C$\underline{H}$-CH$_3$), 0.92 (d, J=7.0 Hz, 3H, C$_a\underline{H}_3$-CH), 0.92 (d, J=6.6 Hz, 3H, C$_b\underline{H}_3$-CH).

(−)-(*S*)-5-(2-Methoxyethoxymethoxy)-2,6-dimethyl-3-heptanol (8). To a solution of 597.4 mg of **7** in 8 ml of ether was added 6 ml of 1 M ethereal solution of Grignard reagent prepared from isopropyl bromide and magnesium turnings. After stirring for ten minutes, the reaction mixture was treated with saturated solution of NH_4Cl. The ethereal extract was washed with brine, dried over Na_2SO_4 and concentrated to give 519.6 mg of crude **8**, 71.5% yield.

(3*S*,5*S*)-2,6-Dimethyl-3,5-heptanediol (1) from 8. A solution of 508.6 mg of the crude **8**, 112 ml of THF, 24 ml of 70% aqueous solution of $HClO_4$ and 24 ml of water was kept stirring for 1.5 hours. The reaction mixture was poured into saturated solution of $NaHCO_3$ and extracted with ether. The ethereal layer was washed with brine, dried over Na_2SO_4 and concentrated to give 262.3 mg of a residue. A part of the residue was subjected to the capillary GLC analysis (PEG 20M, 25 m) to determine that a ratio of (3*R**,5*R**)-**1** and *meso*-**1** was 96.2 to 3.8. This was subjected to the MPLC separation to obtain 68.6 mg of levorotatory **1** (20.9% yield, $[\alpha]_D^{20}=-41.3°$ (c 1.03, methanol).

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