Tetrahedron Vol. 41, No. 3, pp. 541 to 546, 1985
Printed in Great Britain.

0040-4020/85 $3.00 + .00

SYNTHESIS OF THE ENANTIOMERS OF *CIS*-2-METHYL-5-HEXANOLIDE, THE MAJOR COMPONENT OF THE SEX PHEROMONE OF THE CARPENTER BEE†

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(*Received in Japan* 29 *June* 1984)

Abstract—(2*R*,5*S*)-2-Methyl-5-hexanolide and its antipode were synthesized in highly optically pure state (≥98–99% e.e.) starting from ethyl (*S*)-lactate and the enantiomers of methyl β-hydroxyisobutyrate. The specific rotations of our samples were $[\alpha]_D \pm 91.0$–$93.5°$ ($CHCl_3$), while the reported values of the samples prepared by resolution or asymmetric synthesis were ± 64.5–$65.6°$.

cis-2-Methyl-5-hexanolide **1** is the major component of the pheromonal blend of the mandibular gland secretions of the male carpenter bee *Xylocopa hirutissima* which function as sex pheromones.[1] Although the synthesis of its racemate[1,2] as well as that of its optically active forms[3,4] were reported, the absolute configuration of the natural pheromone itself has remained unknown.

This paper describes a new synthesis of the optically pure enantiomers of **1** which serve as the reference samples in determining the absolute configuration of the natural pheromone.

The existing synthesis of optically active **1** employed either the resolution of an intermediate[3] or the asymmetric synthesis.[4] However, no attempt was made to synthesize **1** by connecting chiral building blocks. In our experience, this type of approach often enabled us to prepare highly optically pure pheromones by carefully planning the synthetic route to avoid racemization.[5]

Disconnection of the C—C bond between C-3 and C-4 of **1** made us recognize two possible building blocks: a phenylsulfone **6** and propylene oxide **7**. The enantiomers of these two compounds were the key-intermediates in our synthesis. As our starting materials we used the enantiomers of methyl β-hydroxyisobutyrate **2a** and ethyl (*S*)-lactate **3a**. Both the enantiomers of β-hydroxyisobutyric acid recently became available by microbial oxidation of isobutyric acid employing *Candida rugosa* IFO 0750 and IFO 1542, respectively.[6] The enantiomers of the corresponding Me ester **2a** were kindly given to us by Dr. J. Hasegawa of Kanegafuchi Chemical Industry Co., Ltd. Ethyl (*S*)-lactate is commercially available.

Our synthesis of **1** was straightforward as shown in Scheme 1. The optical purities of (*R*)- and (*S*)-**2a** were determined by the HPLC analysis[7] of their (*S*) - α - methoxy - α - trifluoromethylphenylacetate (MTPA ester)[8] as 97% e.e. and 98% e.e., respectively. Treatment of (*S*)-**2a** with dihydropyran and *p*-TsOH gave (*S*)-**2b**. This was reduced with LAH to (*R*)-**4a**. The corresponding tosylate (*S*)-**4b** was treated with PhSNa to give a phenyl sulfide (*S*)-**5**, whose oxidation with MCPBA gave the desired phenylsulfone (*S*)-**6** in 86% overall yield from (*S*)-**2a**. Similarly (*R*)-**6** was prepared in 67% overall yield from (*R*)-**2a**. In this case, however, the (*R*)-enantiomer of the phenyl sulfide **5** was prepared *via* a mesylate (*R*)-**4c** and a bromide (*R*)-**4d**.

(*S*)-Propylene oxide **7**, another key-intermediate, was prepared from (*S*)-**3a** *via* **8** according to the method of Seuring and Seebach.[9] Since the optical purity of the starting (*S*)-**3a** was not satisfactory (90–94% e.e.),[10] the crystalline intermediate **8** was repeatedly recrystallized to improve the optical purity. The purified **8**, m.p. 31–32°, gave (*S*)-propylene oxide **7**, $[\alpha]_D^{20.5} - 13.8°$ (neat) [lit.[9] $[\alpha]_D - 12.5°$ (neat)]. Basing on their analysis of **7** by complexation GLC, Schurig *et al.* calculated the $[\alpha]_D$ value of optically pure propylene oxide **7** to be $[\alpha]_D^{20} \pm 14.6°$ (neat).[11] The optical purity of our (*S*)-**7** was therefore estimated to be 94.5% e.e. (*R*)-Propylene oxide **7** was prepared from (*S*)-**3a** *via* crystalline (*S*)-**3b**, m.p. 31.5–32.5°, as reported by Johnston and Slessor.[12] The specific rotation of our (*R*)-**7**, $[\alpha]_D^{21.5} + 14.2°$ (neat), indicated its optical purity to be 97.3% e.e.

The next stage was the coupling of the two building blocks. Treatment of a carbanion derived from (*S*)-**6** with (*S*)-**7** gave a new phenyl sulfone (2*S*,5*S*)-**9**. It was then reduced with Na–Hg to give (2*R*,5*S*)-**10a**. Acetylation of (2*R*,5*S*)-**10a** gave **10b**, whose THP protective group was removed by treatment with *p*-TsOH–MeOH to give (2*R*,5*S*)-**10c**. This was oxidized with Jones CrO_3 in acetone to give an acetoxy acid (2*R*,5*S*)-**11a**. Finally alkaline hydrolysis (K_2CO_3–MeOH) of **11a** was followed by acidification (dil HCl) to give (2*R*,5*S*)-**1** in 63% overall yield from (*S*)-**6**. The product was repeatedly recrystallized from n-hexane to give pure (2*R*,5*S*)-**1**, m.p. 49–50°. This was shown to be 99.4% chemically pure containing 0.6% of the *trans*-lactone as analyzed by GLC. Similarly (*R*)-**6** and (*R*)-**7** afforded (2*S*,5*R*)-**1**, m.p. 49–50°, in 36% overall yield. The chemical purity of (2*S*,5*R*)-**1** was 99.5% with 0.5% of the *trans*-isomer.

As shown in Table 1, the specific rotations of our enantiomers of *cis*-2-methyl-5-hexanolide **1** were different from those reported by others.[3,4] We therefore carefully checked the optical purities of our samples. According to Pirkle's procedure,[13] the NMR nonequivalence induced by a chiral solvating reagent (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol **12** upon its addition to the enantiomers of **1** was carefully

† Pheromone Synthesis—70. Part 69, N. Nakagawa and K. Mori, *Agric. Biol. Chem.* **48**, 2799 (1984).

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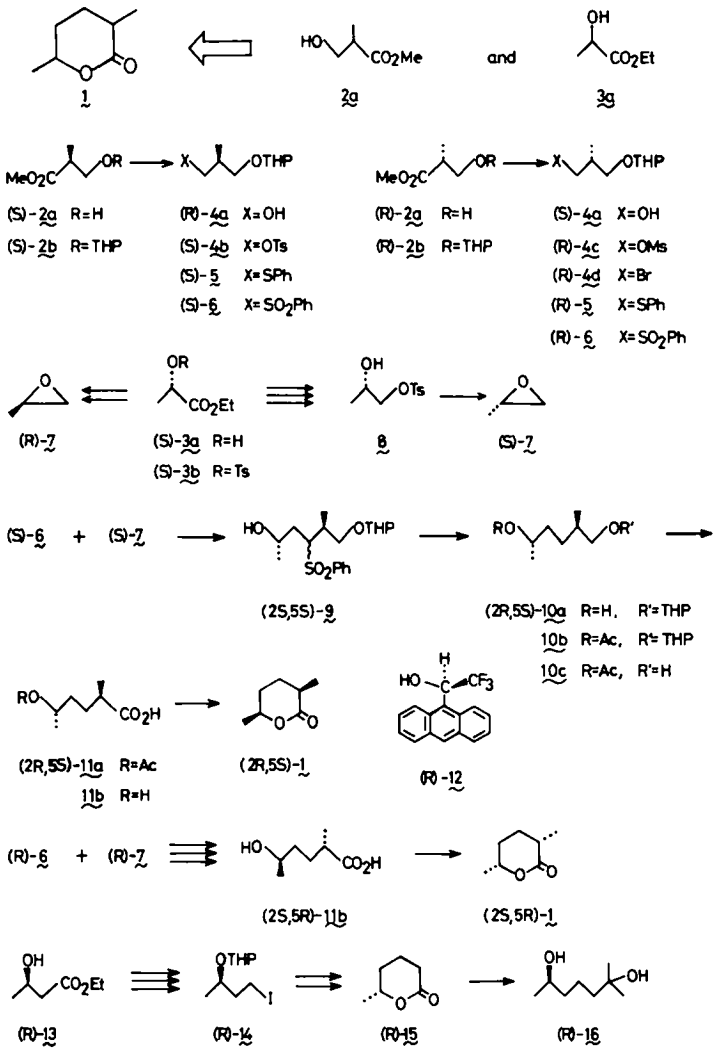

Scheme 1.

examined. The spectra measured at 60 MHz showed that the doublet due to protons of a Me group at the δ-position of (±)-**1** split into a pair of two doublets ($\Delta\delta$ = 0.02 p.p.m.) upon addition of **12**. Due to the low resolution of the signals at 60 MHz, however, it was difficult to draw a definite conclusion except that our enantiomers were virtually optically pure. Further examinations of the NMR nonequivalence at 400 MHz ($\Delta\delta$ = 0.04 p.p.m.) enabled us to accurately determine the optical purities of our enantiomers: 98.6% e.e. for (2*S*,5*R*)-**1** and 99.8% e.e. for (2*R*,5*S*)-**1**.

Since the starting (*S*)- and (*R*)-**2a** were of 98 and 97% e.e., respectively, the e.e.'s of the present enantiomers of **1** (98.6 and 99.8%) indicated the "optical enrichment" in the course of the synthesis. Repeated recrystallization of the crude (2*R*,5*S*)-**1** from n-hexane (eight times) raised its $[\alpha]_D$ value from −86.5° to −91.0° ($CHCl_3$). GLC analysis showed that the crude (2*R*,5*S*)-**1** prior to recrystallization contained 4.1% of *trans*-**1** [(2*R*,5*R*)- and (2*S*,5*S*)-**1**], while the recrystallized sample contained only 0.6% of *trans*-**1**. This removal of the unwanted diastereomer by recrystallization enabled us to obtain the "optically enriched" target molecule. A similar phenomenon was observed in our previous

Table 1. Optical rotations and m.ps of the enantiomers of *cis*-2-methyl-5-hexanolide **1**

Compound		$[\alpha]_D$ (in $CHCl_3$)	m.p.
Pirkle's (ref. 3)	(2*R*,5*S*)-**1**	−64.4° (*c* = 0.51, at 22.6°)	46.5–48°
	(2*S*,5*R*)-**1**	+64.8° (*c* = 0.73, at 23.7°)	46.5–48°
Katsuki's (ref. 4)	(2*R*,5*S*)-**1**	−65.6° (*c* = 0.68, at 23°)	
Our	(2*R*,5*S*)-**1**	−91.0° (*c* = 0.730, at 20°)	49–50°
	(2*S*,5*R*)-**1**	+93.5° (*c* = 0.795, at 21°)	49–50°

Table 2. Optical rotations of the enantiomers of 5-hexanolide **15**

Compound	$[\alpha]_D$ of (*R*)-**15**	$[\alpha]_D$ of (*S*)-**15**
Pirkle's **15**[3]	+30.9° (*c* = 2.0, EtOH, at 22.5°)	−30.4° (*c* = 1.6, EtOH, at 23°)
Kuhn's **15**[18]		−39.1° (*c* = 4.1, EtOH, at 24°)
Kuhn's **15**[19]		−51.4° (EtOH, at 19°)
MacMillan's **15**[20]	+18.4° (*c* = 1.7, MeOH, at 20°)	
Our **15**	+37.2° (*c* = 1.825, EtOH, at 20°)	−34.3° (*c* = 2.075, EtOH, at 21.5°)

synthesis of (2*R*,6*S*,8*R*)-2,8-dimethyl-1,7-dioxaspiro [5.5]undecane and its enantiomer.[14,15]

So as to further confirm the correctness of our $[\alpha]_D$ values of the enantiomers of **1**, we carried out a synthesis of both the enantiomers of 5-hexanolide **15**. This lactone served as the key-intermediate in Pirkle's synthesis of **1**. Starting from the enantiomers of ethyl β-hydroxybutyrate (*R*)-**13** (100% e.e.) and (*S*)-**13** (*ca* 85–88% e.e.), the enantiomers of **14** were prepared according to our procedure.[16] Alkylation of diethyl malonate with (*R*)-**14** was followed by saponification, decarboxylation and lactonization to give (*R*)-**15**, $[\alpha]_D^{20}$ +37.2° (EtOH). In the same manner (*S*)-**14** yielded (*S*)-**15**, $[\alpha]_D^{20}$ −34.3° (EtOH). Since the optical purities of (*R*)- and (*S*)-**15** could not be estimated by the NMR method using **12**, they were determined as follows by the method of Jakovac and Jones.[17] Treatment of **15** with MeLi gave **16**. The 400 MHz NMR spectra of (*R*)- and (*S*)-**16** were measured in the presence of a chiral shift reagent tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato] europium (III) [Eu(tfc)$_3$]. The intensities of the signals due to $(CH_3)_2C(OH)$— were carefully estimated to reveal the optical purities of (*R*)- and (*S*)-**16**, which reflected the optical purities of (*R*)- and (*S*)-**15**. The results indicated that (*R*)-**15** was of 93.7% e.e., while (*S*)-**15** was of 87.7% e.e. From these data we calculated the $[\alpha]_D$ values of the optically pure enantiomers of **15** to be ±39.1 ~ 39.7°. In Table 2 we listed the specific rotations of the enantiomers of **15** as reported by Pirkle,[3] Kuhn[18,19] and MacMillan,[20] which were compared with ours. (*S*)-**15** prepared by Kuhn and Kum from (+)-sorbinol isolated from *Sorbus aucuparia* seems to be optically pure.[18] Pirkle's **15** was of only ~78% e.e. This strongly suggests that there was something wrong about the preparation of the enantiomers of **15** by Pirkle and Adams.[3] The large $[\alpha]_D$ values of our enantiomers of **1** must be taken as correct. The enantiomers of **1** prepared by Pirkle[3] and Katsuki[4] seem to be of ~71% e.e. judging from their $[\alpha]_D$ values.

In summary we synthesized both the enantiomers of *cis*-2-methyl-5-hexanolide **1**. We emphasize that the connection of highly optically pure building blocks is one of the safest ways to secure a highly optically pure product. This is true especially when the unwanted diastereomeric by-product can be removed from the major product by some means, resulting in the optical enrichment.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as film or as Nujol mull on a Jasco A-102 spectrometer. NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer unless otherwise stated. Optical rotations were measured on a Jasco DIP-140 polarimeter.

Methyl 2-methyl-3-tetrahydropyranyloxypropanoate **2b**

(a) (S)-*Isomer*. The starting material (*S*)-(+)-**2a**, $[\alpha]_D^{20}$ +26.7° (*c* = 4.01, MeOH), was a gift from Kanegafuchi Chemical Industry Co., Ltd., Takasago, Hyogo 676. Its optical purity was determined by the HPLC analysis of the corresponding (*S*)-MTPA ester:[8] apparatus, Shimadzu LC-2; column, Partisil 5, 25 cm × 4.6 mm; eluent, n-hexane–THF–MeOH, 6000:100:2, 1 ml/min; detection at 217 nm: *R*, 12.7 min (1%), 13.5 min (99%), optical purity = 98%. *p*-TsOH (0.1 g) was added to a soln of **2a** (10 g, 84.7 mmol) and dihydropyran (10 g, 118.9 mmol) in dry THF (200 ml). The mixture was stirred overnight at room temp. It was then poured into ice-water and extracted with ether. The ether soln was washed with sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 19.0 g (quantitative) of crude (*S*)-**2b**; ν_{max}: 1740 (s), 1200 (s), 1120 (s), 1060 (s), 1030 (s) cm^{-1}; ^{1}H-NMR δ(CCl_4): 1.16 (3H, d, J = 7 Hz), 1.25–1.90 (6H, br), 2.30–2.90 (1H, m), 3.00–3.90 (4H, m), 3.65 (3H, s), 4.56 (1H, br). This was employed directly in the next step without further purification. The IR and NMR spectra were identical with those reported for the antipode (*R*)-**2b**.[7]

(a) (R)-*Isomer*. In the same manner as described above (*R*)-(−)-**2a** (11 g), $[\alpha]_D^{25}$ −26.3° (*c* = 2, MeOH); 97% e.e., gave 17.2 g (quantitative) of (*R*)-**2b**.

2-Methyl-3-tetrahydropyranyloxy-1-propanol **4a**

(a) (R)-*Isomer*. A soln of (*S*)-**2b** (19 g, 84.7 mmol) in dry ether (30 ml) was added dropwise during 40 min to a stirred and ice-cooled suspension of LAH (3.21 g, 84.7 mmol) in dry ether (300 ml). The stirring was continued overnight at room temp. The excess LAH was decomposed by the successive addition of water (8 ml), 15% NaOH soln (8 ml) and water (24 ml) to the stirred and ice-cooled mixture. After stirring for 10 min at room temp, the mixture was filtered. The filtrate was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 13.8 g [93.8% from (*S*)-**2a**] of (*R*)-**4a**, b.p. 96–99°/4 mm, n_D^{19} 1.4534; $[\alpha]_D^{20.5}$ +0.84° (*c* = 1.506, ether); $[\alpha]_D^{20}$ +12.3° (*c* = 1.058, $CHCl_3$); ν_{max}: 3440 (m), 1030 (s) cm^{-1}; ^{1}H-NMR δ (CCl_4): 0.89 (3H, d, J = 7 Hz), 1.30–2.20 (7H, m), 2.80–4.20 (7H, m), 4.54 (1H, br s). (Found: C, 61.81; H, 10.35. Calc for $C_9H_{18}O_3$: C, 62.04; H, 10.41%.)

(b) (S)-*Isomer*. In the same manner as described above (*R*)-**2b** (15 g) was reduced with LAH (4.82 g) to give 12.8 g [90.4% from (*R*)-**2a**] of (*S*)-4a, b.p. 85–89°/3.5 mm, n_D^{20} 1.4518; $[\alpha]_D^{20}$ −1.2° (*c* = 1.485, ether); $[\alpha]_D^{20}$ −12.2° (*c* = 1.082, $CHCl_3$) [lit.[7] $[\alpha]_D^{21}$ −1.2° (*c* = 1.471, ether)]. The IR and NMR spectra were identical with those reported previously.[7]

(S)-2-*Methyl-3-tetrahydropyranyloxypropyl tosylate* **4b**

p-TsCl (13.1 g, 68.9 mmol) was added portionwise during 5 min to a soln of (*R*)-**4a** (10 g, 57.4 mmol) in dry C_5H_5N (100 ml) with stirring and ice-cooling. The mixture was stirred for a day at 3°. Then an additional amount of *p*-TsCl (3.3 g, 17.3 mmol) was added to the mixture. After stirring for a day at 3°, the mixture was poured into ice-water and extracted with ether. The ether soln was washed with cooled 0.5 N HCl soln, sat $CuSO_4$ aq, water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated to give 19.5 g (quantitative) of (*S*)-**4b**; ν_{max}: 1595 (m), 1185 (s), 1170 (s), 1030 (s), 970 (s), 810 (s) cm^{-1}; ^{1}H-NMR δ($CDCl_3$): 0.89 (3H, d, J = 7 Hz), 1.00–2.20 (7H, m), 2.38 (3H, s), 2.90–4.30 (6H, m), 4.40 (1H, br s), 7.34 (2H, d, J = 8 Hz),

7.80 (2H, d, J = 8 Hz). This was employed in the next step without further purification.

(R)-2-*Methyl*-3-*tetrahydropyranyloxypropyl mesylate* **4c**

MsCl (9.07 g, 79.2 mmol) was added dropwise during 20 min to a soln of (*S*)-**4a** (9.20 g, 52.8 mmol) in Et_3N (8.71 g, 86.1 mmol) and dry CH_2Cl_2 (300 ml) with stirring and cooling at $-10°$. The mixture was stirred at $-10°$ for 1 hr. It was then poured into water. The organic soln was washed with water, 1 N HCl, sat $NaHCO_3$ aq and brine, dried (Na_2SO_4) and concentrated to give 14.5 g (quantitative) of crude **4c**; ν_{max}: 1360 (s), 1180 (s), 1035 (s), 965 (s) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 1.04 (3H, d, J = 7 Hz), 1.20–2.80 (7H, m), 3.01 (3H, s), 3.00–4.00 (4H, m), 4.24 (2H, d, J = 6 Hz), 4.57 (1H, br s). This was employed in the next step without further purification.

(R)-2-*Methyl*-3-*tetrahydropyranyloxypropyl bromide* **4d**

A soln of (*R*)-**4c** (crude, 14.5 g, 79.2 mmol) in dry acetone (10 ml) was added to a soln of LiBr (6.88 g, 79.2 mmol) in dry acetone (100 ml) containing $NaHCO_3$ (6.65 g, 79.2 mmol). To this was added dry DMF (50 ml) and the mixture was stirred and heated overnight at 65–70°. It was then filtered and the filtrate was concentrated *in vacuo* to remove acetone. The residue was diluted with water and extracted with ether. The ether soln was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 300 g). Elution with n-hexane–ether gave an oil. This was distilled to give 10.2 g [81.5% from (*S*)-**4a**] of (*R*)-**4d**, b.p. 82–85°/4 mm, n_D^{21} 1.4718; $[\alpha]_D^{21} - 13.5°$ (c = 1.037, $CHCl_3$); ν_{max}: 1140 (s), 1130 (s), 1080 (s), 1070 (s), 1035 (s) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 1.04 (3H, d, J = 7 Hz), 1.30–2.70 (7H, m), 3.00–4.10 (6H, m), 4.58 (1H, br s). (Found: C, 45.56; H, 7.48. Calc for $C_9H_{17}O_2Br$: C, 45.58; H, 7.23%.)

2-*Methyl*-3-*phenylthio*-1-*propanol THP ether* **5**

(a) (S)-*Isomer*. A soln of (*S*)-**4b** (19.5 g, 57.4 mmol) in EtOH (20 ml) was added dropwise during 5 min to a soln of PhSNa prepared from PhSH (8.22 g, 74.6 mmol) and Na (2.06 g, 89.5 mg atom) in EtOH (100 ml) with stirring at room temp. The mixture was stirred and heated under reflux for 2.5 hr. The stirring was continued overnight at room temp. The mixture was poured into iced 2 N NaOH and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 15.5 g (quantitative) of (*S*)-**5**; ν_{max}: 1585 (m), 1130 (s), 1115 (s), 1070 (s), 1060 (s), 1030 (s) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 1.05 (3H, d, J = 7 Hz), 1.20–2.40 (7H, m), 2.50–4.10 (6H, m), 4.54 (1H, br s), 7.31 (5H, br s). This was employed in the next step without further purification.

(b) (R)-*Isomer*. In the same manner as described above (*R*)-**4d** (3.60 g, 15 mmol) and PhSH (2.42 g, 22 mmol) gave 4.25 g (quantitative) of (*R*)-**5**. The IR and NMR spectra of (*R*)-**5** were identical with those of (*S*)-**5**.

2-*Methyl*-3-*phenylsulfonyl*-1-*propanol THP ether* **6**

(a) (S)-*Isomer*. $NaHCO_3$ (13.3 g, 157.9 mmol) was added to a stirred soln of (*S*)-**5** (15.5 g, 57.4 mmol) in dry CH_2Cl_2 (200 ml) and the mixture was cooled to $-25°$. To this was added with stirring and cooling a soln of MCPBA (31.0 g, 143.5 mmol) in dry CH_2Cl_2 (300 ml) during 40 min at -25 to $-15°$. The mixture was stirred overnight at room temp. It was then washed with sat $NaHCO_3$ soln and brine, dried (K_2CO_3) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 400 g). Elution with n-hexane–ether gave 15.7 g [91.8% from (*R*)-**4a**] of (*S*)-**6**, n_D^{20} 1.5172; $[\alpha]_D^{20}$ + 7.0° (c = 1.145, $CHCl_3$); ν_{max}: 1580 (w), 1300 (s), 1145 (s), 1070 (s), 1030 (s) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 1.09 (3H, d, J = 7 Hz), 1.20–2.00 (6H, m; br s at δ 1.51), 2.00–2.60 (1H, m), 2.65–4.00 (6H, m), 4.45 (1H, br), 7.20–8.10 (5H, m). (Found: C, 60.07; H, 7.30. Calc for $C_{15}H_{22}O_4S$: C, 60.37; H, 7.43%.)

(b) (R)-*Isomer*. In the same manner as described above (*R*)-**5** (4.25 g, 15 mmol) and MCPBA (7.80 g) yielded 4.05 g [90.4% from (*R*)-**5**] of (*R*)-**6**, n_D^{20} 1.5177; $[\alpha]_D^{20} - 6.7°$ (c = 1.130, $CHCl_3$). The IR and NMR spectra of (*R*)-**6** were identical with those of (*S*)-**6**. (Found: C, 60.17; H, 7.30. Calc for $C_{15}H_{22}O_4S$: C, 60.37; H, 7.43%.)

p-*Toluenesulfonic ester* **3b** *of ethyl* (S)-*lactate*

p-TsCl (100 g, 520 mmol) was added portionwise during 15 min to a soln of (*S*)-**3a** [50 g; 0.423 mol; Kanto Chemicals Co., $[\alpha]_D^{22} - 10.2°$ (neat) d_4^{22} 1.0252] in C_5H_5N (500 ml) with stirring and cooling at -5 to $-10°$. The mixture was stirred at a temp between -10 and $-5°$ for 1 hr and then at 7° overnight. It was poured into ice-water and extracted with ether. The ether soln was washed with 1 N HCl, sat $CuSO_4$ aq, water and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give 129 g of crude **3b**. This was recrystallized from $CHCl_3$–pet. ether to give 109.8 g (95.5%) of crystalline **3b**. This was further recrystallized from $CHCl_3$–pet. ether to give 43.4 g of **3b**, m.p. 31.5–32.5°; $[\alpha]_D^{21} - 36.3°$ (c = 5.155, $CHCl_3$) [lit.[12] m.p. 31°; $[\alpha]_D^{23} - 33.2°$ (c = 5.05, $CHCl_3$)]; ν_{max}: 1760 (s), 1605 (m), 1370 (s), 1195 (s), 1180 (s), 1080 (s), 940 (s) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 1.21 (3H, t, J = 7 Hz), 1.55 (3H, d, J = 7 Hz), 2.50 (3H, s), 4.24 (2H, q, J = 7 Hz), 5.08 (1H, q, J = 7 Hz), 7.56 (2H, d, J = 8 Hz), 8.18 (2H, d, J = 8 Hz).

(R)-1,2-*Epoxypropane* **7**

(*S*)-**3b** (41 g, 0.151 mol) was mixed with 1.3 N BH_3 · THF (400 ml) and the mixture was left to stand for 5 days at room temp then for 1 day at 40–50°. Subsequent workup[12] gave (*S*)-1,2-propanediol 2-tosylate (36.9 g, quantitative); ν_{max}: ~3500 (m), 1605 (m), 1355 (s), 1190 (s), 1175 (s), 915 (s) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 1.24 (3H, d, J = 7 Hz), 2.46 (3H, s), 2.55 (1H, br s), 3.62 (2H, d, J = 6 Hz), 4.66 (1H, m), 7.40 (2H, d, J = 8 Hz), 7.90 (2H, d, J = 8 Hz). This (36.9 g, 0.151 mol) was added to a stirred and heated soln of KOH (25 g) in water (25 ml) at 70°. The soln was diluted with water (30 ml) and heated at 80°. The distillate was collected in a flask cooled with dry ice–acetone. It was distilled over KOH pellets to give 5.69 g (65%) of (*R*)-**7**, b.p. 34.5–36.0°; $[\alpha]_D^{21.5} + 14.2°$ (neat, $d_4^{21.5}$ 0.8298) [lit.[11] $[\alpha]_D + 14.6 \pm 0.3°$ (neat)]; ν_{max}: 2910 (s), 1410 (s), 1020 (s), 945 (s), 825 (vs) cm^{-1}; ^{1}H-NMR δ (CCl_4): 1.32 (3H, d, J = 6 Hz), 2.20–3.30 (3H, m). The optical purity of this sample was thought to be 97% [(14.2/14.6) × 100].

(S)-1,2-*Propanediol* 1-*tosylate* **8**

This was prepared according to Seuring and Seebach.[9] The crude **8** (170 g) was recrystallized twice from EtOAc–n-pentane to give 45.2 g of pure (*S*)-**8**, m.p. 31–32°, $[\alpha]_D^{20} + 12.2°$ (c = 1.059, $CHCl_3$) [lit.[9] m.p. 36°, $[\alpha]_D + 11.3°$ (c = 1.1, $CHCl_3$)]; ν_{max}: 3550 (m), 3420 (m), 1600 (m), 1350 (s), 1190 (s), 1175 (s), 1095 (s), 985 (s), 920 (s), 815 (s) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 1.15 (3H, d, J = 7 Hz), 2.44 (3H, s), 2.20–2.50 (1H, m), 3.60–4.30 (3H, m), 7.36 (2H, d, J = 8 Hz), 7.84 (2H, d, J = 8 Hz).

(S)-1,2-*Epoxypropane* **7**

Melted **8** (42.5 g, 0.185 mol) was added dropwise to a stirred soln of KOH (25 g) in water (25 ml). Water (10 ml) was added to the mixture. The epoxide generated by heating the mixture was collected in a flask cooled with dry ice–acetone. The crude (*S*)-**7** was distilled over KOH pellets to give 6.89 g (64.3%) of (*S*)-**7**, b.p. 33–33.5°, $[\alpha]_D^{20.5} - 13.8°$ (neat, $d_4^{20.5}$ 0.8268) [lit.[9] $[\alpha]_D$ − 12.5° (neat, without describing d)]. The IR and NMR spectra of (*S*)-**7** were identical with those of (*R*)-**7**. The optical purity of our (*S*)-**7** was (13.8/14.6) × 100 = 94%.

2-*Methyl*-3-*phenylsulfonyl*-1,5-*hexanediol* 1-*THP ether* **9**

(a) (2S,5S)-*Isomer*. A soln of n-BuLi in hexane (1.54 N, 24.0 ml, 36.9 mmol) was added dropwise during 10 min to a stirred and cooled soln of (*S*)-**6** (10 g, 33.5 mmol) in dry THF (100 ml) at $-78°$ under Ar. The mixture was stirred for 25 min at $-78°$. Then HMPA (7.0 ml, 40.2 mmol) was added dropwise during 3 min at $-78°$. The stirring was continued for 10 min. A soln of (*S*)-**7** (2.33 g, 40.2 mmol) in dry THF (20 ml) was added to the stirred and cooled mixture during 15 min at $-78°$. The mixture was stirred for 4 hr at $-78°$ and overnight at room

temp. It was then poured into ice-water and extracted with ether. The ether soln was washed with sat NH_4Cl aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 300 g). Elution with hexane–ether gave 10.9 g (91.3%) of (2*S*,5*S*)-**9** as a viscous oil, n_D^{20} 1.5150; $[\alpha]_D^{20}$ + 8.4° (*c* = 1.536, $CHCl_3$); ν_{max}: 3500 (m), 3060 (w), 2940 (s), 1580 (w), 1440 (m), 1290 (s), 1140 (s), 1120 (s), 1070 (s), 1025 (s) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 0.60–1.30 (6H, m), 1.30–3.00 (10H, m), 3.00–4.65 (7H, m), 7.20–8.00 (5H, m). (Found: C, 60.19; H, 7.95. Calc for $C_{18}H_{28}O_5S$: C, 60.64; H, 7.92%.)

(b) (2R,5R)-*Isomer*. In the same manner as described above (*R*)-**6** (2.0 g, 6.70 mmol) in dry THF (20 ml) was treated with n-BuLi in hexane (1.36 N, 5.5 ml, 7.48 mmol). To the mixture was added HMPA (1.3 ml, 7.48 mmol) and a soln of (*R*)-**7** (354 mg, 6.09 mmol) in dry THF (4 ml). Subsequent workup gave 1.94 g (89.2%) of (2*R*,5*R*)-**9**, n_D^{21} 1.5164; $[\alpha]_D^{21}$ − 8.7° (*c* = 0.799, $CHCl_3$). (Found: C, 60.20; H, 7.81. Calc for $C_{18}H_{28}O_5S$: C, 60.64; H, 7.92%.)

2-Methyl-1,5-hexanediol 1-THP ether **10a**

(a) (2R,5S)-*Isomer*. A soln of (2*S*,5*S*)-**9** (10 g, 28.05 mmol) in dry EtOH (250 ml) was added dropwise during 15 min to Na–Hg prepared from Na (12.9 g, 561 mg atom) and Hg (202 g) with stirring at room temp. The stirring was continued overnight. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was diluted with ether. The ether soln was washed with sat NH_4Cl aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residual oil was chromatographed over SiO_2 (Merck Kieselgel 60, 60 g). Elution with hexane–ether gave 6.03 g (99.4%) of (2*R*,5*S*)-**10a**; ν_{max}: 3450 (m), 1125 (s), 1080 (s), 1065 (s), 1035 (s) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 0.93 (3H, d, J = 6 Hz), 1.18 (3H, d, J = 6 Hz), 1.20–2.20 (11H, m), 2.32 (1H, s), 3.00–4.30 (5H, m), 4.57 (1H, br s). This was employed in the next step without further purification.

(b) (2S,5R)-*Isomer*. In the same manner as described above, (2*R*,5*R*)-**9** (1.60 g, 4.49 mmol) was reduced with Na–Hg (from 2.25 g of Na and 36 g of Hg) and dry EtOH (40 ml) to give 0.88 g (90.6%) of (2*S*,5*R*)-**10a**. The IR and NMR spectra of (2*S*,5*R*)-**10a** was identical with those of (2*R*,5*S*)-**10a**.

2-Methyl-1,5-hexanediol 2-acetate 1-THP ether **10b**

(a) (2R,5S)-*Isomer*. Ac_2O (4.29 g = 4.0 ml, 42 mmol) and 4-(N,N-dimethylamino)pyridine (DMAP, 30 mg) were added to a soln of (2*R*,5*S*)-**10a** (6.03 g, 28.5 mmol) in dry C_5H_5N (4.5 ml, 56 mmol) and dry CH_2Cl_2 (400 ml). The mixture was stirred overnight at room temp and then heated under reflux for 6 hr. To complete the reaction Ac_2O (7.9 ml, 84.0 mmol), dry C_5H_5N (9.0 ml, 112 mmol) and DMAP (600 mg) were added to the mixture and the stirring was continued overnight at room temp. The mixture was partitioned between ether and water. The organic soln was separated, washed with sat $CuSO_4$ soln, water, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Kieselgel 60, 200 g). Elution with hexane–ether gave 6.71 g (91.1%) of (2*R*,5*S*)-**10b**. A portion of it was distilled to give an analytical sample, b.p. 100–110° (bath temp)/0.05 mm, $n_D^{20.5}$ 1.4430; $[\alpha]_D^{20.5}$ + 0.7° (*c* = 1.097, $CHCl_3$); ν_{max}: 1740 (s), 1240 (s), 1030 (s) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 0.92 (3H, d, J = 6 Hz), 1.21 (3H, d, J = 6 Hz), 1.20–2.00 (11H, m), 2.01 (3H, s), 2.90–4.20 (4H, m), 4.55 (1H, br s), 4.50–5.30 (1H, m). (Found: C, 64.96; H, 10.18. Calc for $C_{14}H_{26}O_4$: C, 65.08; H, 10.14%.)

(b) (2S,5R)-*Isomer*. In the same manner as described above (2*S*,5*R*)-**10a** (800 mg, 3.70 mmol) was acetylated to give 693 mg (72.6%) of (2*S*,5*R*)-**10b** together with 160 mg (20.1%) of the recovered **10a**. The non-distilled (2*S*,5*R*)-**10b** showed the following properties: n_D^{21} 1.4416; $[\alpha]_D^{21}$ − 3.1° (*c* = 1.109, $CHCl_3$). (Found: C, 64.94; H, 10.21. Calc for $C_{14}H_{26}O_4$: C, 65.08; H, 10.14%.)

2-Methyl-1,5-hexanediol 2-acetate **10c**

(a) (2R,5S)-*Isomer*. *p*-TsOH (20 mg) was added to a soln of (2*R*,5*S*)-**10b** (500 mg, 1.94 mmol) in MeOH (40 ml). After stirring for 1 hr at room temp, the mixture was concentrated *in vacuo*. The residue was dissolved in ether. The ether soln was washed with sat $NaHCO_3$ aq and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 10 g). Elution with hexane–ether gave 286 mg (91.4% basing on the consumed **10b**) of (2*R*,5*S*)-**10c** together with 36.5 mg (7.3%) of the recovered (2*R*,5*S*)-**10b**. A portion of (2*R*,5*S*)-**10c** was distilled to give an analytical sample, b.p. 77°/0.25 mm, n_D^{19} 1.4348; $[\alpha]_D^{19}$ + 10.3° (*c* = 1.032, $CHCl_3$); ν_{max}: 3430 (m), 1740 (s), 1370 (s), 1240 (s), 1020 (s) cm^{-1}; ^{1}H-NMR: δ 0.90 (3H, d, J = 6 Hz), 1.21 (3H, d, J = 6 Hz), 1.20–1.90 (5H, m), 2.02 (3H, s), 2.38 (1H, br s), 3.42 (2H, d, J = 6 Hz), 4.50–5.20 (1H, m). (Found: C, 61.91; H, 10.59. Calc for $C_9H_{18}O_3$: C, 62.04; H, 10.41%.)

(b) (2S,5R)-*Isomer*. In the same manner as described above (2*S*,5*R*)-**10b** (956 mg, 3.70 mmol) gave 530 mg (82.2%) of (2*S*,5*R*)-**10c**, b.p. 100–130° (bath temp)/0.15 mm, n_D^{21} 1.4349; $[\alpha]_D^{21}$ − 9.9° (*c* = 1.055, $CHCl_3$). The IR and NMR spectra of (2*S*,5*R*)-**10c** were identical with those of (2*R*,5*S*)-**10c**. (Found: C, 61.54; H, 10.49. Calc for $C_9H_{18}O_3$: C, 62.04; H, 10.41%.)

5-Acetoxy-2-methylhexanoic acid **11a**

(a) (2R,5S)-*Isomer*. Jones CrO_3 (8 N, 5 ml) was added dropwise during 5 min to a stirred and ice-cooled soln of (2*R*,5*S*)-**10c** (1.50 g, 8.61 mmol) in acetone (75 ml). The mixture was stirred for 1.5 hr at 0–5° and for 1 hr at room temp. The excess CrO_3 was destroyed by the addition of i-PrOH (5 ml). The mixture was concentrated *in vacuo* and the residue was diluted with water (40 ml). It was then extracted with $CHCl_3$–THF (9:1). The organic soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 1.93 g (quantitative) of (2*R*,5*S*)-**11a**; ν_{max}: ~3200 (m), ~2700 (m), 1735 (s), 1705 (s), 1240 (s), 950 (m) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 1.20 (3H, d, J = 7 Hz), 1.22 (3H, d, J = 6 Hz), 1.30–1.95 (4H, br m), 2.02 (3H, s), 2.05–2.70 (1H, m), 4.50–5.20 (1H, br m), 10.48 (1H, br s). This was employed in the next step without further purification.

(b) (2S,5R)-*Isomer*. In the same manner as described above (2*S*,5*R*)-**10c** (410 mg, 2.35 mmol) was oxidized to give 510 mg (quantitative) of crude (2*S*,5*R*)-**11a**, whose spectral data were identical with those of (2*R*,5*S*)-**11a**.

2-Methyl-5-hexanolide **1**

(a) (2R,5S)-*Isomer*. K_2CO_3 (1.43 g, 10.3 mmol) was added to a soln of crude (2*R*,5*S*)-**11a** (1.93 g, 8.61 mmol) in MeOH (60 ml). The mixture was stirred overnight at room temp. Then an additional amount (0.35 g, 2.5 mmol) of K_2CO_3 was added and the mixture was stirred for 7 hr at room temp. It was then concentrated *in vacuo* and the residue was dissolved in water (50 ml). This was extracted with ether to remove neutral impurities. The aq soln was acidified with 1 N HCl to pH 2. To this was added about an equal vol of $CHCl_3$, and the mixture was stirred overnight. The $CHCl_3$ soln was separated. The aq layer was saturated with NaCl and extracted with $CHCl_3$–THF (9:1). The combined organic soln was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Kieselgel 60, 20 g). Elution with hexane–ether gave 920 mg [83.4% from (2*R*,5*S*)-**10c**] of (2*R*,5*S*)-**1** as crystals. This was recrystallized eight times from hexane to give pure (2*R*,5*S*)-**1** as needles, m.p. 49–50°; $[\alpha]_D^{20}$ − 91.0° (*c* = 0.730, $CHCl_3$) [lit.[3] m.p. 46.5–48°; $[\alpha]_D^{22.6}$ − 64.4° (*c* = 0.51, $CHCl_3$)]; ν_{max} (nujol): 1745 (s), 1720 (sh), 1320 (w), 1295 (w), 1260 (m), 1220 (m), 1200 (m), 1130 (s), 1085 (s), 1070 (s), 1030 (m), 1010 (m), 965 (m), 940 (w), 900 (w), 745 (w), 690 (w) cm^{-1}; ^{1}H-NMR δ (400 MHz, $CDCl_3$): 1.23 (3H, d, J = 6.8 Hz), 1.36 (3H, d, J = 6.3 Hz), 1.48–1.68 (2H, m), 1.89–1.97 (1H, m), 2.04–2.14 (1H, m), 2.54–2.64 (1H, m), 4.42–4.51 (1H, m); ^{13}C-NMR δ (25 MHz, $CDCl_3$): 16.3, 21.1, 25.7, 28.5, 33.0, 74.4, 176.2; GLC (Column, 5% PEG 20M, 2 m × 2.5 mm at 150° + 10°/min; Carrier gas, N_2, 1.3 kg/cm^2) R_t 4.59 min (0.6%), 4.92 min (99.4%). (Found: C, 65.52; H, 9.25. Calc for $C_7H_{12}O_2$: C, 65.59; H, 9.44%.)

(b) (2S,5R)-*Isomer*. In the same manner as described above (2*S*,5*R*)-**11a** (510 mg, 2.85 mmol) yielded 180 mg [60.0% from

(2*S*,5*R*)-**10c**] of crystalline (2*S*,5*R*)-**1**. This was repeatedly recrystallized from hexane to give pure (2*S*,5*R*)-**1**, m.p. 49–50°; $[\alpha]_D^{21}$ + 93.5° (*c* = 0.795, $CHCl_3$) [lit.[3] m.p. 46.5–48°, $[\alpha]_D^{23.7}$ + 64.8° (*c* = 0.73, $CHCl_3$)]; GLC (column, 5% PEG 20M, 2 m × 2.5 mm at 150° + 10°/min; carrier gas, N_2, 1.3 kg/cm²) R_t 4.17 min (0.5%), 4.49 min (99.5%). (Found: C, 65.44; H, 9.53. Calc for $C_7H_{12}O_2$: C, 65.59; H, 9.44%.)

Determination of the optical purity of **1**

According to the method of Pirkle *et al.*[13] the 400 MHz NMR spectra of (2*RS*,5*SR*)-**1**, (2*R*,5*S*)-**1** and (2*S*,5*R*)-**1** were measured in the presence of (*R*)-**12**. ^{1}H-NMR of (2*RS*,5*SR*)-**1** [8.5 mg (0.066 mmol) of **1** + 51.2 mg (0.185 mmol) of **12** in CCl_4 (0.3 ml) and $CDCl_3$ (0.1 ml)] δ 0.92 [d, J = 6 Hz, due to (2*S*,5*R*)-**1**] and 0.96 [d, J = 6 Hz, due to (2*R*,5*S*)-**1**]. ^{1}H-NMR of (2*R*,5*S*)-**1** [7.5 mg of **1** and 48.7 mg of **12** in CCl_4 (0.3 ml) and $CDCl_3$ (0.1 ml)] showed it to be of 98.6% e.e. while that of (2*S*,5*R*)-**1** [7.5 mg of **1** and 48.6 mg of **12** in CCl_4 (0.3 ml) and $CDCl_3$ (0.1 ml)]showed it to be of 99.8% e.e.

5-Hexanolide **15**

(a) (*R*)-*Isomer*. Diethyl malonate (2.04 g = 1.93 ml, 12.7 mmol) was added to a soln of NaOEt prepared from Na (270 mg, 11.7 mg atom) and dry EtOH (5 ml). To the stirred mixture was added (*R*)-**14** (3.00 g, 10.6 mmol) during 3 min at 50°. The stirring was continued for 3 hr. The mixture was poured into ice-water and extracted with ether. The ether soln was washed with brine and concentrated *in vacuo* to give 3.41 g of the alkylation product as a crude oil. This was mixed with 2 N NaOH (50 ml) and the mixture was stirred and heated under reflux for 4 hr. It was then acidified with H_2SO_4 to pH 2, stirred overnight at room temp and then heated under reflux for 3 hr. The mixture was extracted with $CHCl_3$. The $CHCl_3$ soln was concentrated *in vacuo* and the residue was dissolved in 2 N NaOH (20 ml). The alkaline soln was washed with ether to remove neutral impurities. The aq layer was acidified with H_2SO_4 to pH 2, heated overnight under reflux and extracted with $CHCl_3$. The $CHCl_3$ soln was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 450 mg (37.1%) of (*R*)-**15**, b.p. 65–70°/4 mm, $[\alpha]_D^{20}$ + 35.5° (*c* = 2.005, EtOH). A portion of it was further purified by chromatography (Kieselgel 60, n-hexane–ether) and distillation to give pure (*R*)-**15**, b.p. 85–90° (bath temp)/3 mm, $n_D^{21.5}$ 1.4430; m.p. 22–24°; $[\alpha]_D^{20}$ + 37.2° (*c* = 1.825, EtOH); ν_{max}: 1730 (s), 1240 (s), 1065 (s) cm^{-1}; ^{1}H-NMR δ (CCl_4): 1.32 (3H, d, J = 6 Hz), 1.55–2.10 (4H, m), 2.15–2.55 (2H, m), 4.00–4.50 (1H, m); GLC (column, 10% PEG 20M, 2 m × 2 mm at 160°; carrier gas, N_2, 1.1 kg/cm²) R_t 9.56 min (99.8%); MS *m/z* 114.0673 (M^+, $C_6H_{10}O_2$ = 114.0681).

(b) (S)-*Isomer*. The crude alkylation product (3.54 g) was prepared from (*S*)-**14** (3.00 g, 10.6 mmol), diethyl malonate (1.93 ml, 12.7 mmol), Na (270 mg, 11.7 mg atom) and EtOH (5 ml). To this was added 2 N NaOH (20 ml) and the mixture was stirred and heated under reflux for 3 hr. It was then acidified with AcOH to pH 3 and stirred and heated under reflux for 2 hr. Then it was made alkaline with NaOH to pH 12. The soln was washed with ether to remove neutral impurities. The aq layer was acidified with HCl to pH 2. To it was added $CHCl_3$ (50 ml) and the mixture was stirred overnight at room temp. The $CHCl_3$ layer was separated and the aq layer was extracted with $CHCl_3$ after saturation with NaCl. The combined $CHCl_3$ soln was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (Kieselgel 60, n-hexane–ether) and distillation to give 0.50 g (41.4%) of (*S*)-**15**, b.p. 60–65°/3 mm, $[\alpha]_D^{22}$ − 32.0° (*c* = 1.965, EtOH). A portion of it was further purified by chromatography and distillation to give pure (*S*)-**15**, b.p. 80–90° (bath temp)/3 mm, $n_D^{21.5}$ 1.4431; m.p. 15–20°; $[\alpha]_D^{21.5}$ − 34.3° (*c* = 2.075, EtOH); GLC (column, 10% PEG 20M, 2 m × 2 mm at 162°; carrier gas, N_2, 1.0 kg/cm²) R_t 12.09 min (100%); MS *m/z* 114.0667 (M^+, $C_6H_{10}O_2$ = 114.0681).

2-Methyl-2,6-heptanediol **16**

(a) (R)-*Isomer*. A soln of 1.54 N MeLi in ether (0.86 ml, 1.32 mmol) was added to a stirred and cooled soln of (*R*)-**15** (50 mg, 0.44 mmol) in dry THF (1 ml) at −78° under Ar. The mixture was stirred for 3 hr at room temp. It was then poured into water and extracted with ether. The ether soln was dried (Na_2SO_4) and concentrated *in vacuo* to give 51 mg (79%) of (*R*)-**16**, ν_{max}: 3375 (br s), 1370 (s), 1150 (s), 1120 (s) cm^{-1}; ^{1}H-NMR δ (CCl_4): 1.12 (3H, d, J = 6 Hz), 1.14 (6H, s), 1.20–1.70 (6H, m), 2.80 (2H, br s), 3.40–4.00 (1H, m). This was used for the 400 MHz NMR measurement without further purification.

(b) (S)-*Isomer*. In the same manner as described above (*S*)-**15** (50 mg, 0.44 mmol) was treated with MeLi to give 52 mg (81%) of (*S*)-**16**. Its IR and NMR spectra were identical with those of (*R*)-**16**.

Determination of the optical purity of **16**

According to the method of Jakovac and Jones,[17] the 400 MHz NMR spectra of (*RS*)-**16**, (*R*)-**16** and (*S*)-**16** were measured in the presence of $Eu(tfc)_3$. ^{1}H-NMR of (*RS*)-**16** [6 mg (0.045 mmol) of (*RS*)-**16** + 51.0 mg of $Eu(tfc)_3$ in CCl_4 (0.3 ml) and $CDCl_3$ (0.1 ml)] δ 4.26 [s, due to (*S*)-**16**], 4.35 [s, due to (*R*)-**16**], 4.45 [s, due to (*R*)-**16**], 4.61 [s, due to (*S*)-**16**]. ^{1}H-NMR of (*R*)-**16** [10.5 mg of (*R*)-**16** and 51.0 mg of $Eu(tfc)_3$ in CCl_4 (0.3 ml) and $CDCl_3$ (0.1 ml)] showed it to be of 93.7% e.e., while that of (*S*)-**16** [10.3 mg of (*S*)-**16** and 51.0 mg of $Eu(tfc)_3$ in CCl_4 (0.3 ml) and $CDCl_3$ (0.1 ml)] showed it to be of 87.7% e.e.

Acknowledgements—Our thanks are due to Dr. J. Hasegawa (Kanegafuchi Chemical Industry Co., Ltd.) for his kind gift of the enantiomers of methyl β-hydroxyisobutyrate. Financial support by Nitto Denko Co., Ltd. is acknowledged with thanks.

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