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SYNTHESIS OF ALL OF THE FOUR ENERGETICALLY POSSIBLE STEREOISOMERS OF 7-ETHYL-2-METHYL-1,6-DIOXASPIRO[4.5]DECANE

A PHEROMONE PRODUCED BY BEES *PARAVESPURA VULGARIS* L. AND *ANDRENA HAEMORRHOA* F.†

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Abstract—All of the four energetically possible stereoisomers[(2*R*,5*R*,7*R*)-, (2*R*,5*S*,7*S*)-, (2*S*,5*R*,7*R*)- and (2*S*,5*S*,7*S*)- isomers] of 7-ethyl-2-methyl-1,6-dioxaspiro[4.5]decane were synthesized starting from ethyl (*S*)-lactate and dimethyl (*S*)-malate or methyl (*R*)-β-hydroxy-valerate employing dianion alkylation as the key-step.

Spiroacetals have been isolated by Francke *et al.* as pheromones of several insect species.[1,2] As a part of our continuing efforts to synthesize optically active pheromones,[3] we accomplished the syntheses of optically active forms of 2-ethyl-1,6-dioxaspiro[4.4]nonane (chalcogran **A**)[4], 2,8-dimethyl-1,7-dioxaspiro-[5.5]undecane **B**[5] and 2-methyl-1,7-dioxaspiro[5.6]dodecane **C**[6]. All of our previous syntheses employed dianion alkylation as the key-step. Herein we report a chiral synthesis of all of the four energetically possible stereoisomers of 7-ethyl-2-methyl-1,6-dioxaspiro[4.5]decane **1**, again employing dianion alkylation as the key-step.

The two diastereomers of the spiroacetal **1** were first found in the pentane extracts of workers of *Paravespula vulgaris* L. and serve as constituents of their antiaggregative pheromones.[7] The two diastereomers of **1** were also found in the complex volatile secretion from the mandibular glands of *Andrena haemorrhoa* F.[8] Up to now nothing is known about the absolute configuration of the natural diastereomers of **1**. We therefore planned a chiral synthesis of **1** so as to obtain the optically active stereoisomers in quantities sufficient for field tests.

A number of syntheses of 1,6-dioxaspiro[4.5]decane were reported either as racemates[9-13] or as optically active forms.[14,15] There appeared no report, however, concerning the synthesis of optically active 1,6-dioxaspiro[4,5]decane with *two* alkyl substituents such as **1**, although Seebach *et al.*[14] and Schurig *et al.*[15] prepared the spiroacetals with only *one* alkyl substituent. Retrosynthetic analysis of **1** as shown in Fig. 1 demands the prparation of the two chiral building blocks **4** and **5**. Alkylation of the dianion derived from **4** gives **3**, which leads to **1** via **2**.

The synthesis of both the enantiomers of α-acetyl-γ-valerolactone **4** is shown in Fig. 2. The starting material was ethyl (*S*)-(−)-lactate **6a**, whose optical purity was determined as 94.3% by analyzing the diastereomeric ratio of the corresponding (*S*)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester) **6b**[16] by capillary GLC. Protection of the OH group in **6a** as the ethoxyethyl (EE) ether gave **6c**, which was converted to (*S*)-(−)-propylene oxide **7**, $[\alpha]_D^{23}$ − 13.1° (neat) [lit.[17] $[\alpha]_D$ − 12.5° (neat)], in 58.8% overall yield by the method of Seuring and Seebach.[17] (*R*)-(+)-Propylene oxide **7**, $[\alpha]_D^{23}$ + 12.9° (neat) [lit.[18] $[\alpha]_D^{22}$ + 13.0° (neat)], was also prepared from **6a** in 43.7% overall yield according to Hills and Ronald.[18] Basing on their analysis of **7** by complexation GLC, Schurig *et al.* calculated the $[\alpha]_D$ value of optically pure **7** to be $[\alpha]_D^{20}$ ± 14.6° (neat).[19] The optical purity of our enantiomers of **7** was therefore estimated to be 89 ~ 90% suggesting the occurrence of the slight partial racemization during the preparation. Addition of **7** to methyl acetoacetate was effected in the presence of NaOMe in MeOH to give, after two weeks, **4** in 44 ~ 46% yield, $[\alpha]_D^{22}$ ± 14.2° (EtOH). The overall yield of (*R*)-**4** from (*S*)-**6a** was 19.2% (4 steps), while that of (*S*)-**4** was 27.0% (6 steps).

Another building block **5** was synthesized by two different methods. At first we prepared both the enantiomers of **5** from (*S*)-(−)-malic acid **8a** as shown in Fig. 3. The optical purity of **8b** was confirmed as 100% by comparing the 400 MHz ^{1}H-NMR spectrum of its (*S*)-MTPA ester **8c** with that of the (*S*)-MTPA ester of dimethyl (*R*)-malate. The EE ether **8d** derived from **8b** was reduced with LAH to give **9a**. Treatment of **9a** with $BF_3{\cdot}Et_2O$[20] yielded **10a**. Acylation of **10a** gave **10b**, which was heated with AcOH aq to give **9b**. Conversion of **9b** to the epoxide (*S*)-**12a** was effected by Golding's general method of epoxide formation,[21] which was known to result in the retention of configuration at C-2. Treatment of **9b** with HBr–AcOH gave a mixture of two acetoxy bromides, whose major component was **11**. It then yielded (*S*)-**12a**, $[\alpha]_D^{24}$ − 30.6° (CH_2Cl_2), when treated with K_2CO_3. The antipodal epoxide (*R*)-**12a**, $[\alpha]_D^{24}$ + 29.5° (CH_2Cl_2) [lit.[22] $[\alpha]_D^{23}$ + 23.42° (CH_2Cl_2)], was synthesized from **9e** according to Boger and Panek[22] with a slight modification of employing an EE protective group instead of 1-methyl-1-methoxyethyl group. This modification

† Pheromone Synthesis—65. Part 64, K. Mori and M. Katsurada, *Liebigs Ann. Chem.* 157 (1984). The experimental part of this work was taken from the M. Sc. thesis of M. Ikunaka (March, 1984).

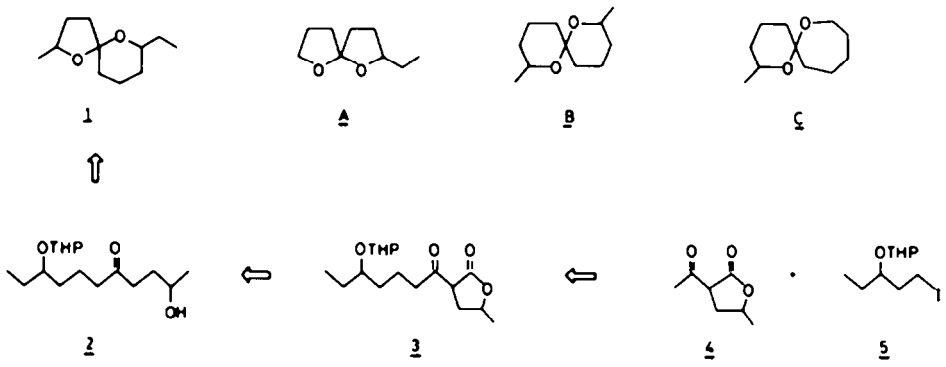

Fig. 1. Synthetic plan.

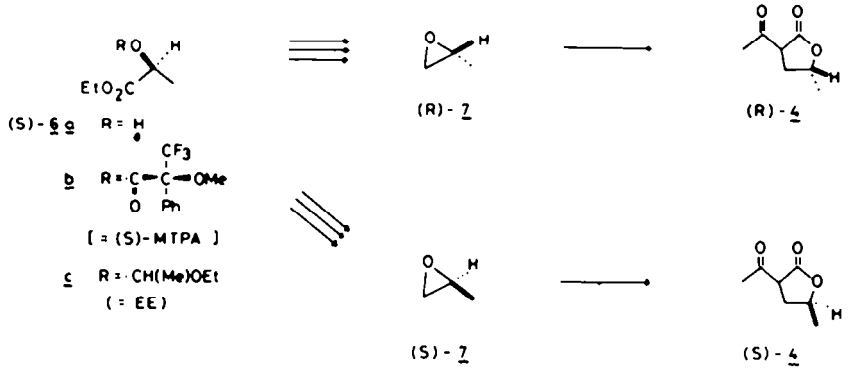

Fig. 2. Synthesis of the enantiomers of α-acetyl-γ-valerolactone.

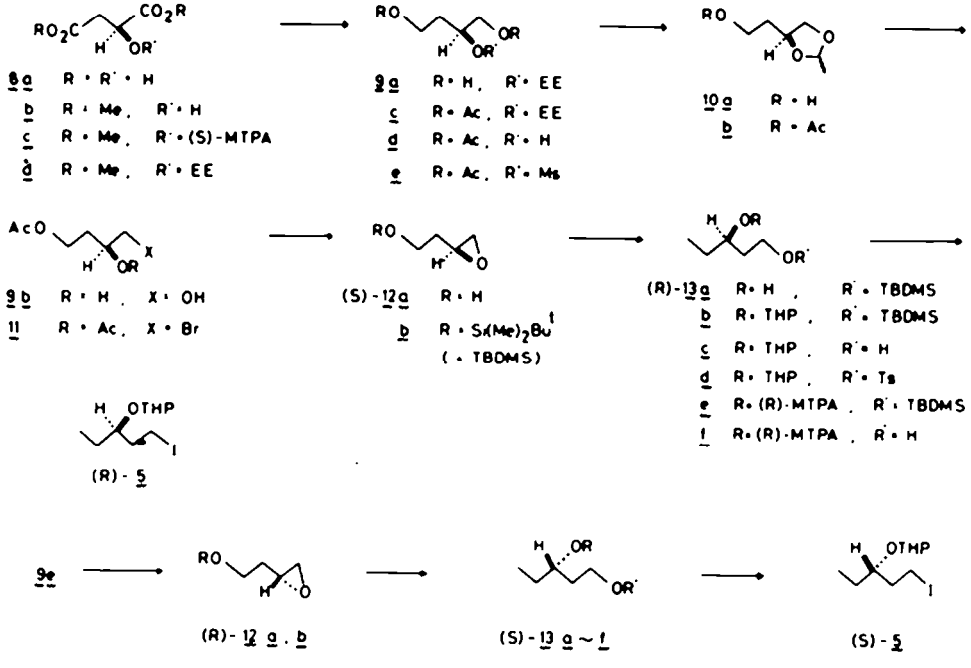

Fig. 3. Synthesis of the enantiomers of 3-tetrahydropyranyloxypentyl iodide.

enabled us to obtain (*R*)-**12a** in 89.9% overall yield from **8b** via **9c**, **9d** and **9e**, while in the case of Boger and Panek[22] the overall yield was 40 ~ 45%.

Protection of the OH group in (*S*)-**12a** as a t-butyldimethylsilyl (TBDMS) ether[23] gave (*S*)-**12b**, which was treated with MeMgBr in the presence of CuBr[24] to effect the regioselective cleavage of the epoxy ring giving (*R*)-**13a** with retention of the configuration at C-3. Protection of the OH group in (*R*)-**13a** as a THP ether by treatment with dihydropyran in the presence of Amberlyst-15 in n-hexane[25] gave (*R*)-**13b**. This was mixed with $(n\text{-}Bu)_4NF$ to remove the TBDMS group. Tosylation of the resulting (*R*)-**13c** yielded (*R*)-**13d**, which was treated with NaI to give (*R*)-**5**. The overall yield of (*R*)-**5** from (*S*)-(—)-malic acid **8a** was 13.2% in 14 steps. In the same manner (*R*)-**12a** was converted to (*S*)-**5** in 37.7% overall yield (14 steps) via (*R*)-**12b** and (*S*)-**3a–b**.

To check the optical purity of **5**, we first tried to determine the optical purity of **12a**. Boger and Panek reported that their (*R*)-**12a** with $[\alpha]_D^{23} + 23.42°$ (CH_2Cl_2) was of 98 ± 2% e.e. by measuring the ^{1}H-NMR spectrum of the corresponding epoxy iodide in the presence of tris [3-(trifluoromethylhydroxymethylene)-*d*-camphorato] europium (III) [Eu(tfc)$_3$].[22] We reexamined their procedure by converting our (*R*)-**12a**, $[\alpha]_D^{24} + 29.5°$ (CH_2Cl_2), and (*S*)-**12a**, $[\alpha]_D^{24} - 30.6°$ (CH_2Cl_2), to the corresponding iodides. Upon addition of Eu(tfc)$_3$, those signals due to CH_2O- and CHO- protons suffered the down-field shifts. However, these appeared as multiplets and became broader when the amount of Eu(tfc)$_3$ was increased to observe satisfactory down-field shift. This NMR method was therefore thought to be inadequate. We next attempted to determine the optical purity of **13a**. In the conventional manner,[16] **13a** was converted to the corresponding (*R*)-MTPA ester **13e**. However, the HPLC analysis of **13e** resulted in no clean separation of the diastereomers. Then the TBDMS protective group in **13e** was removed by treatment with AcOH aq and the resulting **13f** was analyzed by HPLC. Fortunately in this case, the diastereomers were separable and the optical purity of (*R*)-**13a** and that of (*S*)-**13a** were estimated to be >99% and 93%, respectively. The optical purity of (*R*)-**5** and that of (*S*)-**5** were therefore thought to be >99% and 93%, respectively.

The second and simpler synthesis of **5** was carried out as shown in Fig. 4. After the completion of the synthesis of (*R*)- and (*S*)-**5** from (*S*)-(−)-malic acid, we had the opportunity to obtain methyl (*R*)-(−)-β-hydroxyvalerate **14a**, which was prepared by microbial β-hydroxylation of valeric acid by *Candida rugosa* IFO 0750.[26] Although the optical purity of (*R*)-**14a** kindly given to us by Dr. Hasegawa was *ca* 84%, it could be enhanced to 100% by recrystallizing the corresponding 3,5-dinitrobenzoate **14b**.[27] Hydrolysis of the purified **14b** with KOH gave (*R*)-**14a**, whose optical purity was confirmed to be 100% by the HPLC analysis of the MTPA ester **14d**. Conversion of (*R*)-**14a** to (*R*)-**5** was straightforward. Protection of the OH group in **14a** as the THP ether gave **14c**, which was reduced with LAH to give (*R*)-**13c**. The corresponding tosylate **13d** gave (*R*)-**5** when treated with NaI.

For the preparation of (*S*)-**5**, the configuration at C-3 in **13c** must be inverted. Benzylation of (*R*)-**13c** to **13g** was followed by acid hydrolysis to give (*R*)-**13h**, $[\alpha]_D^{22} + 8.88°$ ($CHCl_3$). This was submitted to the Walden inversion under the Mitsunobu condition.[28] Thus (*R*)-**13h** was treated with Ph_3P, 3,5-dinitrobenzoic acid and $EtO_2CN{=}NCO_2Et$ in THF to give (*S*)-**13i**, m.p. 58.8 ~ 59°. The use of 3,5-dinitrobenzoic acid instead of benzoic acid in the original procedure[28] is very effective, because 3,5-dinitrobenzoates of alcohols are usually crystalline and can be purified by recrystallization. Hydrolysis of (*S*)-**13i** with KOH gave (*S*)-**13h**, $[\alpha]_D^{20} - 9.08°$ ($CHCl_3$). The corresponding THP ether (*S*)-**13g** was hydrogenolyzed over Pd–C to give (*S*)-**13c**, which was converted to (*S*)-**5** via (*S*)-**13d**. The overall yield of (*R*)-**5** from (*R*)-**14a** (84% e.e.)

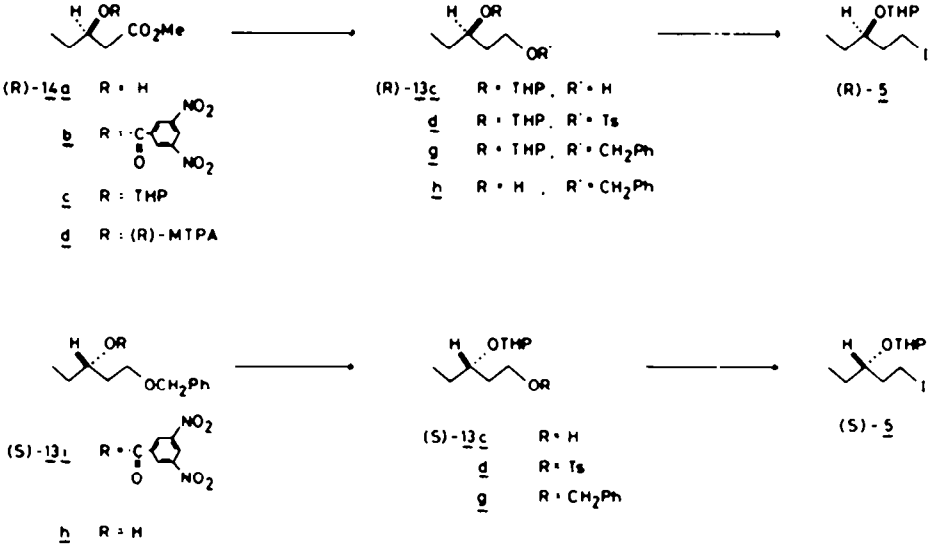

Fig. 4. An alternative synthesis of the enantiomers of **5**.

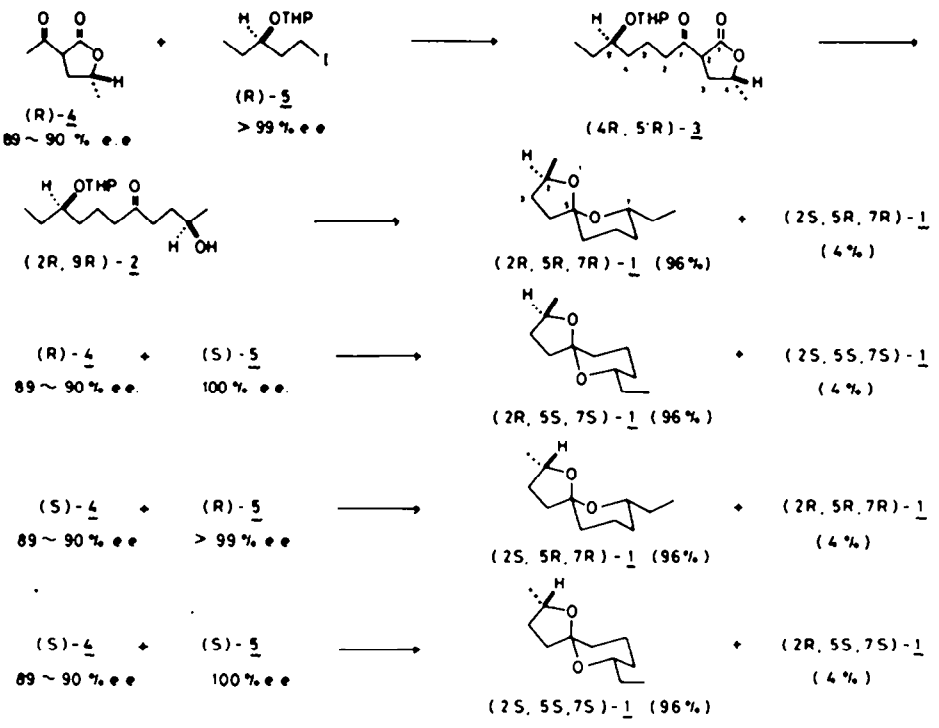

Fig. 5. Synthesis of the stereoisomers of 7-ethyl-2-methyl-1,6-dioxaspiro[4.5]decane.

was 39% in 6 steps, while that of (*S*)-**5** was 19% in 12 steps. The optical purity of (*R*)-**5** and that of (*S*)-**5** prepared from (*R*)-**14a** were thought to be 100%, reflecting the optical purity of the purified (*R*)-**14a**. It is evident that methyl (*R*)-(−)-β-hydroxyvalerate **14a** is a better starting material for the synthesis of (*R*)-**5**. Utilization of **14a** in the synthesis of sericornin (cigarette beetle pheromone) will be reported separately.[27]

Having secured the starting materials **4** and **5**, we proceeded to the connection of these two building blocks by dianion alkylation[29] as shown in Fig. 5. The dianion of (*R*)-**4** was prepared by treating (*R*)-**4** with NaH followed by n-Buli in THF-HMPA. Its alkylation with (*R*)-**5** gave (4*R*,5'*R*)-**3**, which was hydrolyzed with KOH to give (2*R*,9*R*)-**2**. This was treated with dil HCl to give (2*R*,5*R*,7*R*)-**1**, $[\alpha]_D^{24}$ + 78.4° (n-pentane), in 42.6% overall yield from (*R*)-**4**. Because the optical purity of the lactone (*R*)-**4** was only 89 ~ 90%, our sample of (2*R*,5*R*,7*R*)-**1** was contaminated with a small amount (4 ~ 5%) of (2*S*,5*R*,7*R*)-**1**. It should be noted that only (2*R*,5*R*,7*R*)-**1** was generated upon acetalization without the formation of any detectable amount of (2*R*,5*S*,7*R*)-**1**. We and others already reported the analogous observation in the cases of other spiroacetals.[5,6,9] This is due to two reasons: (i) the Et group prefers the eq orientation; and (ii) the diaxial-like position of O at the spiro center is the more stable one owing to the anomeric effect.[5,6,9,30,31] In the same manner, (*R*)-**4** and (*S*)-**5** yielded (2*R*,5*S*,7*S*)-**1**, $[\alpha]_D^{20}$ − 97.5° (n-pentane), (*S*)-**4** and (*R*)-**5** gave (2*S*,5*R*,7*R*)-**1**, $[\alpha]_D^{22}$ + 102° (n-pentane), and (*S*)-**4** and (*S*)-**5** afforded (2*S*,5*S*,7*S*)-**1**, $[\alpha]_D^{23}$ − 76.1° (n-pentane).

In conclusion, we synthesized all of the four energetically possible stereoisomers of **1** with three chiral centers. Dianion alkylation was again proved to be a very effective method to synthesize spiroacetals. Bioassay of these stereoisomers of **1** is now in progress in cooperation with Dr. W. Francke, the result of which will hopefully clarify the absolute configuration of the natural pheromones.

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 automatic polarimeter. HPLC analyses were performed on a Shimadzu LC-2 chromatograph. GLC analyses were performed on a Hitachi 163 or on a Jeolco JGC-20K or on a Hewlett-Packard 5840A gas chromatograph.

Determination of the optical purity of (S)-**6a**. Commercially available (*S*)-**6a** (Kanto Kagaku Co., 99.94% chemical purity as checked by GLC.), $[\alpha]_D^{24.5}$ − 10.9° (neat, $d_4^{24.5}$ 1.02), was converted to (*S*)-MTPA ester **6b**,[16] which was analyzed by GLC (Column, PEG 20M, 50m × 0.28 mm at 70 ~ 220° (+3°/min); Carrier gas, He, 1.0 kg/cm²); R_t 53.00 min (97.17%), 53 min 44 sec (2.83%). The optical purity of (*S*)-**6a** was therefore 94.3%.

(S)-(−)-*propylene oxide* **7**. This was prepared by the method of Seuring and Seebach[17], b.p. 34 ~ 38°; $[\alpha]_D^{23}$ − 13.1° (neat, d_4^{23} 0.827) [lit.[17] $[\alpha]_D$ − 12.5° (neat)]; δ ($CDCl_3$) 1.30 (3H, d, J = 5.0 Hz), 2.30 ~ 2.50 (1H, m), 2.60 ~ 2.86 (1H, m); 2.88 ~ 3.15 (1H, m).

(R)-(+)-*Propylene oxide* **7**. This was prepared by the method of Hills and Ronald,[18] b.p. 34°; $[\alpha]_D^{23}$ + 12.9° (neat, d_4^{23} 0.823 [lit.[18] $[\alpha]_D^{22}$ + 13.0° (neat)].

(4S)-(−)-2-*Acetyl-4-pentanolide* **4**. $AcCH_2CO_2Me$ (83.7 g) was added to a stirred soln of NaOMe (from 16.9 g of Na) in MeOH (290 ml) at 46 ~ 49°. To this was added dropwise (*S*)-**7** (41.9 g) with stirring at 0° under Ar. The mixture was stirred for two weeks at room temp. During this period the mixture became white yellow paste and then turned to a deep red clear soln. It was then neutralized with AcOH

(48 ml) and H_2O (100 ml). The mixture was concentrated *in vacuo*. The residue was extracted with ether. The ether soln was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was distilled to give 47.0 g (46%) of (4*S*)-**4**, b.p. 81 ~ 85°/3 mm; n_D^{22} 1.4459; $[\alpha]_D^{22}$ − 14.2° (*c* = 3.15, EtOH); ν_{max} 1765 (s), 1722 (s), 1655 (m), 1180 (s), 1160 (s), 955 (s) cm^{-1}; δ (CCl_4) 1.43 (3H, d, J = 6 Hz), 2.34 and 2.37 (each s, total 3H), 1.65 ~ 3.00 (2H, m), 3.48 ~ 3.90 (1H, m), 4.35 ~ 4.90 (1H, m); GLC (Column, 5% FFAP, 2 m × 4 mm at 150°; Carrier gas, N_2, 0.8 kg/cm^2): *R*, 9.9 min (97.3%); MS: *m/z* 142 (M^+). (Found: C, 58.63; H, 7.14. Calc for $C_7H_{10}O_3$: C, 59.14; H, 7.09%.)

(4*R*)-(+)-2-*Acetyl*-4-*pentanolide* **4**. In the same manner as described above, (*R*)-**7** (35.2 g) gave (4*R*)-**4** (37.8 g, 44%), b.p. 83 ~ 85°/3 mm; n_D^{22} 1.4459; $[\alpha]_D^{22}$ + 14.2° (*c* = 3.24, EtOH); GLC (Column, 5% FFAP, 2 m × 4 mm at 150°; Carrier gas, N_2, 0.8 kg/cm^2): *R*, 9.5 min (97.3%); MS: *m/z* 142 (M^+). (Found: C, 58.10; H, 7.07. Calc for $C_7H_{10}O_3$: C, 59.14; H, 7.09%.) The IR and NMR spectra of (4*R*)-**4** were identical with those of (4*S*)-**4**.

Dimethyl (S)-(−)-*malate* **8b**. Commercially available (*S*)-(−)-malic acid **8a**, m.p. 105°, $[\alpha]_D^{23}$ − 28.2° (*c* = 5.57, C_5H_5N), was used as the starting material. AcCl (100 ml) was slowly added to ice-salt-cooled MeOH (1330 ml). To this was added (*S*)-**8a** (200 g) and the mixture was stirred for 2 days. It was then concentrated *in vacuo*. The residue was distilled to give 202.1 g (74%) of **8b**, b.p. 88 ~ 91°/3 mm; n_D^{25} 1.4330; $[\alpha]_D^{25}$ − 7.10° (neat, d_4^{25} 1.21) [lit.[22] $[\alpha]_D^{25}$ − 7.57° (neat)].

Determination of the optical purity of (S)-**8b**. (*S*)-MTPA esters of (±)-**8b** and (*S*)-(−)-**8b** were prepared as usual.[16] NMR of (*S*)-MTPA ester of (±)-**8b**: δ (400 MHz, $CDCl_3$) 3.55 and 3.63 (OCH_3 of MTPA), 3.57 and 3.70 ($CH(OH)CO_2CH_3$), 3.76 and 3.80 ($CH_2CO_2CH_3$). NMR of **8c**: δ (400 MHz, $CDCl_3$) 3.57 (3H, s), 3.63 (3H, s), 3.80 (3H, s). This proved the optical purity of (*S*)-**8b** to be 100%. HPLC analysis of (*S*)-MTPA ester of (±)-**8b** (Column, Partisil 5, 25 cm × 4.6 mm; Eluent, n-hexane–THF = 40 : 1; 25 kg/cm^2): *R*, 164.0 min, 171.1 min. HPLC analysis of **8c** (under the same condition): *R*, 164.0 min. This also proved the optical purity of (*S*)-**8b** to be 100%.

Dimethyl (S)-*malate EE ether* **8d**. CF_3CO_2H (0.2 ml) was added dropwise to a stirred and cooled soln of **8b** (10.25 g) in ethyl vinyl ether (100 ml) at −10°. The mixture was stirred for 2 days at room temp. The stirring was continued for further 2 hr after the addition of Na_2CO_3 (0.2 g). The mixture was filtered and the filtrate was concentrated *in vacuo* to give **8d** (14.3 g, quantitative), ν_{max} 1750 (s), 1170 (s) cm^{-1}. This was employed in the next step without further purification.

(S)-1,2,4-*Butanetriol* 2-*EE ether* **9a**. This was prepared from **8d** (16.8 g) according to Ref. 14 yielding 10.9 g (97.3% from **8b**) of **9a**, ν_{max} 3400 (s), 1125 (s), 1092 (s), 1050 (s) cm^{-1}.

(S)-1,2,4-*Butanetriol* 1,2-*ethylidene acetal* 4-*acetate* **10b**. A soln of BF_3·Et_2O in ether (47%; 0.3 ml) was added to a soln of **9a** (71.0 g) in dry ether (130 ml). The mixture was stirred overnight at room temp. It was then diluted with dry C_5H_5N (75 ml) and dry CH_2Cl_2 (220 ml). To the cooled and stirred mixture were added Ac_2O (78 ml) and 4-*N*,*N*-dimethylaminopyridine (DMAP, 31.5 mg) at −5 ~ 0°. The stirring was continued overnight at room temp. This was poured into crushed ice (110 g) and conc HCl (17.9 ml). The organic layer was separated and the aq layer was extracted with CH_2Cl_2. The combined organic soln was washed with sat $CuSO_4$aq, H_2O, sat $NaHCO_3$aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 78.4 g of a crude oil. A portion of it was distilled to give pure **10b**, b.p. 108 ~ 109°/27 mm; n_D^{25} 1.4329; $[\alpha]_D^{25}$ + 19.4° (*c* = 1.32, $CHCl_3$); ν_{max} 1745 (s), 1377 (s), 1245 (s), 1160 (s), 1135 (s) cm^{-1}; δ (CCl_4) 1.25 (3H, d, J = 5 Hz), 1.12 ~ 1.89 (2H, m), 2.06 (3H, s), 3.32 ~ 4.31 (5H, m), 4.62 (1H, q, J = 5 Hz). (Found: C, 55.23; H, 8.18. Calc for $C_8H_{14}O_4$: C, 55.16; H, 8.10%.)

(S)-1,2,4-*Butanetriol* 4-*acetate* **9b**. A mixture of the crude **10b** (102.2 g), AcOH (280 ml) and water (230 ml) was stirred and heated under reflux for 16 hr. It was then concentrated *in vacuo*. The residue was diluted with C_6H_6 and concentrated *in vacuo*. This was repeated several times to give 77.6 g (98.4% from **8b**) of crude **9b**, ν_{max} 3410 (s), 1730 (s), 1370 (s), 1245 (s), 1050 (s) cm^{-1}; δ ($CDCl_3$) 1.78 (2H, q, J = 6.0 Hz), 2.08 (3H, s), 3.20 ~ 3.99 (3H, m), 4.25 (2H, t, J = 7 Hz), 4.69 (2H, s). This was employed in the next step without further purification.

(S)-1-*Bromo*-2,4-*butanediol* 2,4-*diacetate* **11**. A soln of HBr in AcOH (30%; 200 ml) was added dropwise over 8 min to **9b** (35.9 g) with stirring and cooling (ice-salt bath). After the addition, the mixture was stirred for 50 min at room temp. It was then poured into ice-water, neutralized with Na_2CO_3 and extracted with ether. The ether soln was dried ($MgSO_4$) and concentrated *in vacuo* to give 53.0 g of crude **11**, ν_{max} 1745 (s), 1230 (s), 1045 (s) cm^{-1}; δ (CCl_4) 1.90 ~ 2.46 (2H, m), 1.96 (3H, s), 2.02 (3H, s), 3.39 (2H, d, J = 5 Hz), 3.99 (2H, t, J = 7 Hz), 4.65 ~ 5.25 (1H, m). This was employed in the next step without further purification.

(S)-1,2-*Epoxy*-4-*butanol* (S)-**12a**. Crude **11** (112 g) was added to a suspension of K_2CO_3 (62 g) in MeOH (650 ml) and THF (650 ml) and the mixture was stirred overnight vigorously. It was then concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 and filtered. The solid was thoroughly washed with CH_2Cl_2. The combined filtrate and washings were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 400 g). Elution with ether gave (*S*)-**12a** (9.8 g, 29.8% from **9b**) as a pale yellow oil, n_D^{24} 1.4259; $[\alpha]_D^{24}$ − 30.6° (*c* = 5.10, CH_2Cl_2); ν_{max} 3420 (s), 1055 (s) cm^{-1}; δ ($CDCl_3$) 1.25 ~ 2.28 (2H, m), 2.28 ~ 2.62 (1H, dd, J = 2 and 4 Hz), 2.62 ~ 2.88 (1H, t, J = 4 Hz), 2.88 ~ 3.24 (1H, m), 3.32 ~ 3.95 (3H, m). (Found: C, 53.99; H, 9.09. Calc for $C_4H_8O_2$: C, 54.53; H, 9.15%.)

(S)-1,2-*Epoxy*-4-*butanol TBDMS ether* (S)-**12b**. A soln of (*S*)-**12a** (11.5 g) in dry CH_2Cl_2 (50 ml) was added dropwise over 13 min to a soln of TBDMS-Cl (30 g) and DMAP (640 mg) in CH_2Cl_2 (150 ml) and Et_3N (40 ml) with stirring and cooling (ice-salt bath). The stirring was continued overnight at 4°. The mixture was diluted with ether (250 ml), washed with H_2O, sat NH_4Claq and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give 33.9 g of crude **12b**. A portion of it was distilled to give pure (*S*)-**12b**, b.p. 64 ~ 67°/5 mm; n_D^{26} 1.4241; $[\alpha]_D^{26}$ − 12.8° (*c* = 2.11, $CHCl_3$); ν_{max} 1255 (s), 1105 (s), 835 (s), 775 (s) cm^{-1}; δ (CCl_4) 0.04 (6H, s), 0.86 (9H, s), 1.40 ~ 1.85 (2H, m), 2.30 (1H, dd, J = 2 and 5 Hz), 2.56 (1H, t, J = 4 Hz), 2.77 ~ 2.99 (1H, m), 3.65 (2H, t, J = 6 Hz). (Found: C, 58.90; H, 10.67. Calc for $C_{10}H_{22}O_2Si$: C, 59.34; H, 10.98%.)

(R)-1,3-*Pentanediol* 1-*TBDMS ether* (R)-**13a**. A soln of MeMgBr in THF was prepared from Mg (8.2 g), MeBr (38.6 g) and THF (450 ml). To this was added CuBr (5.0 g) with stirring at −60 ~ −55° under Ar. A soln of (*S*)-**12b** (50.5 g) in THF (110 ml) was added dropwise to the stirred and cooled soln of MeMgBr–CuBr at −40 ~ −30°. The stirring was continued for 2 hr at 4°. The mixture was poured into sat NH_4Claq and extracted with ether. The ether soln was wahsed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 54.0 g of crude (*R*)-**13a**. A portion of it was purified by SiO_2 chromatography and distilled to give pure (*R*)-**13a**, b.p. 78 ~ 86°/6 mm; n_D^{21} 1.4317; $[\alpha]_D^{21}$ + 10.5° (*c* = 1.32, $CHCl_3$); ν_{max} 3530 (m), 1275 (s), 1115 (s), 855(s), 800 (s) cm^{-1}; δ (CCl_4) 0.05 (6H, s), 0.88 (9H, s), 0.70 ~ 1.10 (3H, t, J = 6 Hz), 1.14 ~ 1.77 (4H, m), 2.47 (1H, d, J = 2 Hz), 3.77 (2H, t, J = 6 Hz); GLC (Column, PEG 20M, 2 m × 4 mm at 100 ~ 190° (+4°/min); Carrier gas, N_2, 1.0 kg/cm^2): *R*, 13.5 min (98.5 ~ 99.0%). (Found: C, 60.38; H, 11.98. Calc for $C_{11}H_{26}O_2Si$: C, 60.48; H, 12.00%.)

(R)-1,3-*Pentanediol* 1-*TBDMS*,3-*THP ether* (R)-**13b**. A soln of (*R*)-**13a** (68.6 g) and dihydropyran (43 ml) in n-hexane (63 ml) was added dropwise to a stirred and cooled (ice-salt bath) suspension of Amberlyst-15 (7.86 g) in n-

hexane (63 ml). The mixture was stirred at 4° for 5 hr. It was then filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to give 110.0 g of crude (*R*)-**13b** as a pale yellow oil, ν_{max} 1255 (s), 1120 (s), 1075 (s), 1030 (s), 1020 (s), 830 (s), 770 (s) cm^{-1}; δ (CCl_4) 0.02 (6H, s), 0.81 (9H, s), 0.62 ~ 1.00 (3H, m), 1.00 ~ 1.99 (10H, m), 3.00 ~ 3.81 (5H, m), 4.39 (1H, s). This was employed in the next step without further purification.

(R)-1,3-*Pentanediol* 3-*THP ether* (R)-**13c**. A soln of (*R*)-**13b** (50.9 g) in dry THF (150 ml) was added dropwise to a stirred soln of (n-Bu)$_4$NF (1.32.3 g) in dry THF (400 ml) at room temp. The stirring was continued overnight at room temp. The mixture was then concentrated *in vacuo*. The residue was diluted with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 soln was dried over $MgSO_4$–Na_2CO_3. The residual red-brown oil (61.6 g) was chromatographed over SiO_2 (Merck Kieselgel 60, 450 g). Elution with n-hexane–Et_2O (4:1) gave (*R*)-**13c** (22.1 g, 80% from (*S*)-**12a**). A portion of it was distilled *in vacuo* over K_2CO_3 to give pure (*R*)-**13c**, b.p. 120 ~ 122°/3 mm; $[\alpha]_D^{15}$ − 31.9° (*c* = 1.03, $CHCl_3$); ν_{max} 3520 (m), 1075 (s), 1023 (s) cm^{-1}; δ ($CDCl_3$) 0.89 and 0.93 (total 3H, each t, J = 7 Hz), 1.14 ~ 2.35 (11H, m), 2.95 ~ 4.33 (5H, m), 4.60 (1H, br. s); MS: *m/z* 188 (M^+), 187 ($M^+ - 1$).

(R)-1,3-*Pentanediol* 3-*THP ether* 1-*tosylate* (R)-**13d**. A soln of (*R*)-**13c** (14.9 g) in CH_2Cl_2 (23 ml) was added dropwise to a stirred and cooled soln of TsCl (19.6 g) and C_5H_5N (25 ml) in CH_2Cl_2 (78 ml) at −15 ~ −10°. The mixture was stirred overnight at 4°. The excess TsCl was destroyed by the addition of H_2O (10 ml). The mixture was poured into ice-dil HCl and extracted with CH_2Cl_2. The CH_2Cl_2 soln was washed with sat $CuSO_4$aq, H_2O, sat $NaHCO_3$aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 31.5 g (quantitative) of crude (*R*)-**13d**, ν_{max} 1600 (m), 1360 (s), 1188 (s), 1175(s), 1035 (s) cm^{-1}; δ (CCl_4) 0.80 and 0.82 (total 3H, each t, J = 7 Hz), 1.05 ~ 2.10 (10H, m), 2.42 (3H, s), 3.05 ~ 3.82 (3H, m), 4.03 (2H, q, J = 7 Hz), 4.27 ~ 4.63 (1H), 7.26 (2H, d, J = 8 Hz), 7.71 (2H, d, J = 8 Hz).

(R)-1-*Iodo*-3-*pentanol THP ether* (R)-**5**. K_2CO_3 (3.28 g) and NaI (47.4 g) were added to a soln of (*R*)-**13d** (31.5 g) in acetone (385 ml) with stirring and ice-cooling. The mixture was stirred for 2 days at room temp. It was then concentrated *in vacuo*. The residue was diluted with H_2O and extracted with ether. The ether extract was washed with $Na_2S_2O_3$aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 400 g). Elution with n-hexane-ether (8:1) gave (*R*)-**5** (17.9 g, 80% from (*R*)-**13c**), ν_{max} 1130 (s), 1075(s), 1033 (s), 1020 (s), 995 (s) cm^{-1}; δ (CCl_4) 0.88 and 0.93 (total 3H, each t, J = 7 Hz), 1.08 ~ 2.38 (10H, m), 3.00 ~ 4.15 (5H, m), 4.40 ~ 4.78 (1H). This was unstable and used immediately after the preparation.

(S)-1,2,4-*Butanetriol* 1,4-*diacetate* 2-*EE ether* **9c**. Ac_2O (37 ml) and DMAP (17.5 mg) were added to a stirred and ice-cooled soln of **9a** (21.6 g) and C_5H_5N (37 ml) in CH_2Cl_2 (194 ml). The mixture was stirred overnight at room temp. It was then poured into ice-dil HCl and extracted with CH_2Cl_2. The CH_2Cl_2 soln was washed with sat $CuSO_4$aq, H_2O, sat $NaHCO_3$aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 30.7 g (quantitative) of crude **9c**, ν_{max} 1730 (s), 1230 (s) cm^{-1}; δ ($CDCl_3$) 0.80 ~ 1.32 (6H, m), 1.95 (3H, s), 1.97 (3H, s), 1.42 ~ 2.40 (2H, m), 3.15 ~ 4.35 (6H, m), 4.45 ~ 4.90 (1H, m). This was employed in the next step without further purification.

(S)-1,2,4-*Butanetriol* 1,4-*diacetate* **9d**. Conc HCl (0.5 ml) was added to a stirred soln of **9c** (51.8 g) in THF (100 ml) and H_2O (200 ml). The stirring was continued overnight at room temp. The mixture was concentrated *in vacuo*. The residue was neutralized with $NaHCO_3$ (1.6 g), saturated with NaCl and extracted with CH_2Cl_2. The CH_2Cl_2 soln was dried ($MgSO_4$) and concentrated *in vacuo* to give 37.6 g (quantitative) of crude **9d**, ν_{max} 3460 (m), 1740 (s), 1240 (s), 1050 (s) cm^{-1}; δ ($CDCl_3$) 1.53 ~ 1.98 (2H, m), 2.05 (3H, s), 2.09 (3H, s), 2.75 (1H, br. s), 3.50 ~ 4.56 (5H, m). This was employed in the next step without further purification.

(S)-1,2,4-*Butanetriol* 1,4-*diacetate* 2-*mesylate* **9e**. MsCl (28 ml) was added dropwise to a stirred and cooled soln of **9b** (42.6 g) and Et_3N (57 ml) in CH_2Cl_2 (426 ml) at −15 ~ 0°. The mixture was stirred for 1 hr at −15°. It was then poured into ice-dil HCl, and extracted with CH_2Cl_2. The CH_2Cl_2 soln was washed with dil HCl, sat $NaHCO_3$aq and H_2O, dried ($MgSO_4$) and concentrated *in vacuo* to give 59.3 g of crude **9e**. This was chromatographed over SiO_2 (Merck Kieselgel 60, 1.2 kg). Elution with ether gave 52.5 g (quantitative from **9a**) of **9e**, ν_{max} 1235 (s), 1075 (s), 1055 (s), 923 (s) cm^{-1}; δ (CCl_4) 1.70 ~ 2.08 (2H, m), 2.01 (3H, s), 2.05 (3H, s), 2.98 (3H, s), 3.90 ~ 4.30 (4H, m), 4.65 ~ 5.05 (1H, m). This was immediately used in the next step.

(R)-1,2-*Epoxy*-4-*butanol* (R)-**12a**. K_2CO_3 (59.6 g) was added to a soln of **9e** (52.5 g) in MeOH (666 ml) and THF (666 ml). The suspension was stirred overnight vigorously. It was then concentrated *in vacuo*. The residue was diluted with CH_2Cl_2 and filtered. The solid was washed thoroughly with CH_2Cl_2. The combined filtrate and washings were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 670 g). Elution with ether gave (*R*)-**12a** (15.9 g, 92.4%), n_D^{23} 1.4286; $[\alpha]_D^{23}$ + 29.5° (*c* = 5.01, CH_2Cl_2). The IR and NMR spectra were identical with those of (*S*)-**12a**.

(R)-1,2-*Epoxy*-4-*butanol TBDMS ether* (R)-**12b**. In the same manner as described for the prepn of (*S*)-**12b**, (*R*)-**12a** was converted to (*R*)-**12b**, b.p. 63 ~ 65°/4 mm; n_D^{26} 1.4241; $[\alpha]_D^{26}$ + 12.5° (*c* = 2.11, $CHCl_3$). (Found: C, 59.07; H, 10.92. Calc for $C_{10}H_{22}O_2Si$: C, 59.34; H, 10.98%.) The IR and NMR spectra were identical with those of (*S*)-**12b**.

(S)-1,3-*Pentanediol* 1-*TBDMS ether* (S)-**13a**. In the same manner as described for the prepn of (*R*)-**13a**, (*R*)-**12b** was converted to (*S*)-**13a**, b.p. 86 ~ 92°/7 mm; n_D^{21} 1.4316; $[\alpha]_D^{21}$ − 9.3° (*c* = 1.32, $CHCl_3$). (Found: C, 59.91; H, 11.89. Calc for $C_{11}H_{26}O_2Si$: C, 60.48; H, 12.00%.) The IR and NMR spectra were identical with those of (*R*)-**13a**.

(S)-1,3-*Pentanediol* 1-*TBDMS ether* 3-*THP ether* (S)-**13b**. In the same manner as described for the prepn of (*R*)-**13b**, (*S*)-**13a** was converted to (*S*)-**13b**, whose spectral data were identical with those of (*R*)-**13b**.

(S)-1,3-*Pentanediol* 3-*THP ether* (S)-**13c**. In the same manner as described for the prepn of (*R*)-**13c**, (*S*)-**13b** was converted to (*S*)-**13c** in 71% overall yield from (*R*)-**12a**. A portion of it was distilled to give pure (*S*)-**13c**, b.p. 105 ~ 110°/6 mm; $[\alpha]_D^{21.5}$ + 16.2° (*c* = 1.10, $CHCl_3$); MS: *m/z* 188 (M^+), 187 ($M^+ - 1$), 85 (base peak). The spectral data were identical with those of (*R*)-**13c**.

(S)-1,3-*Pentanediol* 3-*THP ether* 1-*tosylate* (S)-**13d**. In the same manner as described for the prepn of (*R*)-**13d**, (*S*)-**13c** was converted to (*S*)-**13d**, whose spectral data were identical with those of (*R*)-**13d**.

(S)-1-*Iodo*-3-*pentanol THP ether* (S)-**5**. In the same manner as described for the prepn of (*R*)-**5**, (*S*)-**13d** was converted to (*S*)-**5** in 80% yield form (*S*)-**13c**.

Determination of the optical purity of **13a**

(a) *Prepn of* 1,3-*pentanediol* 3-(R)-*MTPA ester* 1-*TBDMS ether* **13e**. (*R*)-**13a** (43.7 mg) and (+)-MTPA Cl (52 μl) yielded 81.4 mg of (*R*)-**13e** in the usual manner.[16] Similarly, 84.8 mg of (*S*)-**13e** was obtained.

(b) *Prepn of* 1,3-*pentanediol* 3-(R)-*MTPA ester* **13f**. (*R*)-**13e** (81.4 mg) was dissolved in a mixture of AcOH (0.72 ml), THF (0.24 ml) and H_2O (0.24 ml) and the soln was stirred overnight at room temp. It was then neutralized with sat $NaHCO_3$aq and extracted with CH_2Cl_2. The CH_2Cl_2 soln was washed with H_2O, sat $NaHCO_3$aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by prep TLC [Merck Kieselgel G; developed with ether-n-hexane (3:1)] to give 53.1 mg [83.6% from (*R*)-**13a**] of (*R*)-**13f** as an oil, δ ($CDCl_3$) 0.93 (3H, t, J = 7 Hz), 1.27 (1H, s), 1.45 ~ 2.08 (4H, m), 3.58 (3H, s), 3.20 ~ 3.72 (2H,

m), 5.71 (1H, quint, J = 6 Hz), 7.15 ~ 7.80 (5H, m). Similarly, 39.5 mg [62.2% from (*S*)-**13a**] of (*S*)-**13f** was obtained.

(c) *HPLC analysis of* **13f**, (Column, Partisil 5, 25 cm × 4.6 mm; Eluent, n-hexane–THF (10:1); Press, 30 kg/cm²): *R*, 135.2 min [(*S*)-**13f**] and 143.6 min [(*R*)-**13f**]. The diastereomeric ratio of (*R*)-**13f** was 0:100, while that of (*S*)-**13f** was 96.5: 3.5. The optical purity of (*R*)-**13a** was therefore >99% and that of (*S*)-**13a** was 93%.

Methyl (R)-3-(3′,5′-*dinitrobenzoyloxy*)*pentanoate* **14b**. Optically impure **14a** [17.0 g; $[\alpha]_D^{21}$ − 31.6° (*c* = 1.11, $CHCl_3$); $n_D^{20.5}$ 1.4216] was treated with DCC (32.3 g), DMAP (1.3 g) and 3,5-dinitrobenzoic acid (41.2 g) in CH_2Cl_2 (258 ml). Subsequent work-up as reported in Ref. 27 gave crude **14b** (40.7 g, 97%). This was fractionally recrystallized from n-hexane–ether (7:3) to give 20.6 g (51% recovery) of pure **14b** as pale yellow needles, m.p. 65.5 ~ 66.0°; $[\alpha]_D^{23}$ − 9.50 ± 0.05° (*c* = 2.18, $CHCl_3$). The spectral data were identical with those reported in Ref. 27 (Found: C, 47.98; H, 4.33; N, 8.54. Calc for $C_{13}H_{14}O_8N_2$: C, 47.85; H, 4.33; N, 8.59%.)

Methyl (R)-3-*hydroxypentanoate* **14a**. N KOH (69 ml) was added dropwise over 11 min to a stirred and cooled (ice-salt bath) soln of pure **14b** (20.6 g) in THF-MeOH (1:1, 252 ml). The soln turned deep-red. The stirring was continued for 50 min at − 10 ~ − 15°. The mixture was diluted with sat $NaHCO_3$aq (194 ml). The white solid was filtered off and the filtrate was extracted with CH_2Cl_2. The CH_2Cl_2 soln was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was distilled to give 7.5 g (90%) of pure **14a**, b.p. 75 ~ 80.8 /21 mm; n_D^{23} 1.4224; $[\alpha]_D^{23}$ − 37.8° (*c* = 1.30, $CHCl_3$); GLC (Column, PEG 20M, 2 m × 4 mm at 83°; Carrier gas, N_2, 1 kg/cm²): *R*, 14.4 min (99.1%). The spectral data were identical with those reported before.[27] The optical purity of **14a** was proved to be 100% by analyzing **14d** by HPLC as reported in Ref. 27.

Methyl (R)-3-*tetrahydropyranyloxypentanoate* **14c**. PPTS (1.4 g) was added to a stirred soln of optically pure **14a** (7.50 g) and dihydropyran (7.7 ml) in dry CH_2Cl_2 (75 ml). The stirring was continued for 3 hr at room temp. The mixture was diluted with ether, washed with sat $NaHCO_3$ aq and brine, dried ($MgSO_4$–Na_2CO_3) and concentrated *in vacuo*. The residue was distilled in the presence of a trace amount of K_2CO_3 to give 11.8 g (96%) of **14c**, b.p. 101 ~ 102°/7 mm; n_D^{23} 1.4426; $[\alpha]_D^{20.5}$ − 11.8° (*c* = 1.17, $CHCl_3$); ν_{max} 1747 (s), 1025 (s) cm^{-1}; δ (CCl_4) 0.88 and 0.92 (total 3H, each t, J = 7 Hz), 1.15 ~ 1.95 (8H, m), 2.10 ~ 2.60 (2H, m), 3.55 (3H, s), 3.10 ~ 4.10 (3H, m), 4.53 (1H, br. s); GLC (Column, PEG 20M, 2 m × 4 mm at 140°; Carrier gas, N_2, 0.8 kg/cm²): *R*, 10.3 min (89.7%), 6.0 min (7.4%), 7.1 min (2.2%). (Found: C, 61.26; H, 9.22. Calc for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32%.)

(R)-1,3-*Pentanediol* 3-*THP ether* (R)-**13c**. A soln of **14c** (11.5 g) in dry ether (40 ml) was added dropwise to a stirred and cooled (ice-salt bath) suspension of LAH (4.0 g) in ether (122 ml) at − 8 ~ − 6°. The mixture was stirred overnight at room temp. Excess LAH was destroyed by successive addition of H_2O (4 ml), 10% NaOH aq (4 ml) and H_2O (12 ml) to the stirred and ice-cooled mixture. Then THF (90 ml) was added to the mixture and the stirring was continued for further 1 hr. The mixture was filtered by suction. The filter-cake was washed thoroughly with THF. The combined filtrate and washings were dried ($MgSO_4$–K_2CO_3) and concentrated *in vacuo*. The residue was distilled in the presence of a trace amount of K_2CO_3 to give 10.1 g (quantitative) of (*R*)-**13c**, b.p. 85 ~ 103 /4 mm. A portion of it was redistilled to give an analytical sample, b.p. 102°/4 mm; n_D^{22} 1.4544; $[\alpha]_D^{22}$ 14.8° (*c* = 1.14, $CHCl_3$). (Found: C, 63.40; H, 10.75. Calc for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71%.) The spectral data were identical with those described earlier in this paper. This was converted to (*R*)-1-iodo-3-pentanol THP ether (*R*)-**5** as described earlier in this paper.

(R)-1,3-*Pentanediol* 1-*benzyl*,3-*THP ether* **13g**. A soln of (*R*)-**13c** (10.1 g) in dry THF (47 ml) was added dropwise to a stirred suspension of NaH (50%, 4.2 g) in dry THF (76 ml) at room temp. The mixture was stirred and heated under reflux for 1 hr. A soln of $PhCH_2Cl$ (8.6 ml) in dry THF (25 ml) was added dropwise to the stirred mixture under reflux. The stirring was continued for 3.5 hr at reflux temp. The mixture was then poured into ice-water and concentrated *in vacuo* to remove THF. The residue was saturated with NaCl and extracted with ether. The ether soln was wahsed with H_2O, sat $NaHCO_3$aq and brine, dried ($MgSO_4$–K_2CO_3) and concentrated *in vacuo*. The residual yellow oil (19.9 g) was chromatographed over SiO_2 (Merck Kieselgel 60, 150 g). Elution with n-hexane—EtOAc (30:1→10:1→5:1) gave 16.4 g of an oil. This was distilled in the presence of a trace amount of K_2CO_3 to give 14.0 g (94%) of **13g**, b.p. 115 ~ 127°/0.25 mm. A portion of it was redistilled to give an analytical sample, b.p. 121 ~ 123°/0.25 mm; n_D^{24} 1.4939; $[\alpha]_D^{23}$ − 19.2° (*c* = 1.59, $CHCl_3$); ν_{max} 1120 (s), 1080 (s), 1030 (s), 1000 (s) cm^{-1}; δ (CCl_4) 0.84 and 0.90 (total 3H, each t, J = 7 Hz), 1.13 ~ 1.97 (10H, m), 3.05 ~3.99 (5H, m), 4.37 (2H, s), 4.35 ~ 4.68 (1H, br), 7.18 (5H, s); GLC (Column, PEG 20M, 2 m × 4 mm at 180°; Carrier gas, N_2, 1.2 kg/cm²): *R*, 17.5 min (98.8%). (Found: C, 73.26; H, 9.29. Calc for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41%).

(R)-1,3-*Pentanediol* 1-*benzyl ether* (R)-**13h**. *p*-TsOH·H_2O (300 mg) was added to a stirred soln of **13g** (14.0 g) in MeOH (200 ml). The stirring was continued overnight at room temp. The soln was neutralized with $NaHCO_3$ (2.0 g) and concentrated *in vacuo*. The residue was diluted with ether and filtered. The filtrate was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by SiO_2 chromatography (Merck Kieselgel 60, 300 g). Elution with n-hexane–EtOAc (30:1→10:1→5:1) gave 9.0 g of an oil. This wad distilled to give 8.8 g (90%) of **13h**, b.p. 101 ~ 107°/3 mm. A portion of it was redistilled to give an analytical sample, b.p. 106 ~ 107°/3 mm; n_D^{23} 1.5001; $[\alpha]_D^{22}$ + 8.88 (*c* = 1.07, $CHCl_3$); ν_{max} 3485 (m), 1100 (s), 740 (s), 700 (s) cm^{-1}; δ (CCl_4) 0.87 (3H, t, J = 6 Hz), 1.10 ~ 1.84 (4H, m), 2.38 (1H, s), 3.51 (2H, t, J = 6 Hz), 3.30 ~ 3.80 (1H, m), 4.38 (2H, s), 7.16 (5H, s); GLC (Column, PEG 20M, 2 m × 4 mm at 166°; Carrier gas, N_2, 1.2 kg/cm²): *R*, 10.1 min (99.7%); MS: *m/z* 194 (M^+), 176 (M^+ − 18), 91 ($PhCH_2^+$).

(S)-1,3-*Pentanediol* 1-*benzyl ether* 3-(3′5′-*dinitro*)*benzoate* **13i**. (*R*)-**13h** (8.8 g), Ph_3P (23.7 g) and 3,5-dinitrobenzoic acid (19.1 g) were dissolved in dry THF (197 ml). To this soln was added a soln of $EtO_2CN{=}NCO_2Et$ (13.9 ml) in dry THF (70 ml) with stirring and cooling (ice-salt bath). After the addition, the mixture was stirred overnight at room temp. It was then concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Merck Kieselgel 60, 700 g). Elution with C_6H_6–EtOAc (30:1) gave crude **13i**, which was rechromatographed over SiO_2(Merck Kieselgel 60, 700 g). Elution with n-hexane–EtOAc (30:1→25:1→20:1) gave 17.6 g of **13i** as crystals. A portion of it was recrystallized from ether–n-hexane (1:5) to give pure **13i** as yellow rods, m.p. 58.8 ~ 59.0°; $[\alpha]_D^{22}$ + 22.7° (*c* = 0.91, $CHCl_3$); ν_{max} 1730 (s), 1640 (m), 1605 (w), 1545 (s), 1350 (s), 1290 (s), 1175 (s), 730 (s), 720 (s) cm^{-1}; δ (CCl_4) 0.99 (3H, t, J = 7 Hz), 1.40 ~ 2.23 (4H, m), 3.53 (2H, t, J = 6 Hz), 4.27 (2H, s), 5.27 (1H, tt, J = 6 Hz), 7.01 (5H, s), 8.84 (2H, d, J = 2 Hz), 8.95 (1H, d, J = 2 Hz). (Found: C, 59.19; H, 5.33; N, 7.22. Calc for $C_{19}H_{20}O_7N_2$: C, 58.76; H, 5.19; N, 7.21%.)

(S)-1,3-*Pentanediol* 1-*benzyl ether* (S)-**13h**. N-KOH aq (80 ml) was added dropwise over 20 min to a stirred and cooled (ice-salt bath) soln of **13i** (17.6 g) in THF-99% EtOH (1:1, 184 ml). The color of the soln turned red immediately and then changed to dark red and finally to dark violet. The stirring was continued for 1 hr under ice-salt cooling. Then sat $NaHCO_3$aq (140 ml) was added to the soln and the white precipitate were removed by filtration. The filtrate was concentrated *in vacuo* to remove THF. The residue was extracted with CH_2Cl_2. The CH_2Cl_2 soln was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 8.2 g [94% from (*R*)-**13h**] of (*S*)-**13h**, b.p. 108 ~ 116°/4 mm.

A portion of it was redistilled to give an analytical sample, b.p. 114 ~ 115°/4 mm; n_D^{23} 1.4999; $[\alpha]_D^{20}$ − 9.08° (*c* = 0.76, $CHCl_3$); GLC (Column, PEG 20M, 2 m × 4 mm at 169°; Carrier gas, N_2, 1.0 kg/cm²): *R*, 13.6 min (98.8%). The IR, NMR and MS data of (*S*)-**13h** were identical with those of (*R*)-**13h**.

(S)-1,3-*Pentanediol* 1-*benzyl*, 3-*THP ether* (S)-**13g**. PPTS (1.1 g) was added to a stirred soln of (*S*)-**13h** (8.2 g) and dihydropyran (5.8 ml) in dry CH_2Cl_2 (56 ml). After stirring for 4 hr at room temp., the mixture was diluted with ether, washed with sat $NaHCO_3$ aq and brine, dried ($MgSO_4$–K_2CO_3) and concentrated *in vacuo*. The residue was distilled in the presence of a small amount of K_2CO_3 to give 12.0 g (quantitative) of (*S*)-**13g**, b.p. 90 ~ 131°/0.35 mm. A portion of it was redistilled to give an analytical sample, b.p. 130°/0.35 mm; n_D^{22} 1.4934; $[\alpha]_D^{9}$ + 19.7° (*c* = 1.96, $CHCl_3$); MS: *m/z* 278 (M⁺), 91 ($PhCH_2^+$); GLC (Column, PEG 20M, 2 m × 4 mm at 185°; Carrier gas, N_2, 1.0 kg/cm²): *R*, 23.6 min (97.5%). Its IR and NMR spectra were identical with those of (*R*)-**13g**.

(S)-1,3-*Pentanediol* 3-*THP ether* (S)-**13c**. 10% Pd–C (5.2 g) and $NaHCO_3$ (960 mg) were added to a soln of (*S*)-**13g** (12.0 g) in 99% EtOH (194 ml) and the mixture was shaken under H_2 (atm press) with occasional heating at 40 ~ 50°. After 24 hr, (*S*)-**13g** disappeared as checked by TLC. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give 8.4 g of an oil. This was chromatographed over SiO_2 (Merck Kieselgel 60, 250 g). Elution with n-hexane–EtOAc (15:1→5:1) gave 7.4 g of an oil. This was distilled in the presence of a trace amount of K_2CO_3 to give 7.1 g (90%) of (*S*)-**13c**, b.p. 87 ~ 102°/3 mm. A portion of it was redistilled to give an analytical sample, b.p. 101°/3 mm, n_D^{27} 1.4514; $[\alpha]_D^{24}$ + 27.0° (*c* = 1.10, $CHCl_3$); GLC (Column, PEG 20M, 2 m × 4 mm at 162°; Carrier gas, N_2, 0.9 kg/cm²): *R*, 7.8 min (56.3%), 10.3 min (42.0%). (Found: C, 63.27; H, 10.80. Calc for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71%.) Its IR and NMR spectra were identical with those of a sample prepared from (*S*)-malic acid. (*S*)-**13c** was converted into (*S*)-**5** via (*S*)-**13d** in 61.4% overall yield.

(4R,5'S)-2-(5'-*Hydroxy*-1'-*oxoheptyl*)-4-*pentanolide THP ether* **3**. A soln of (*R*)-**4** (2.79 g) in dry THF (6 ml) was added dropwise to a suspension of NaH (50%, 1.13 g) in dry THF (9 ml) and dry HMPA (15 ml) with stirring and cooling (ice-salt bath) at − 12 ~ 0° under Ar. The reaction temp was raised gradually to 25 ~ 28° and kept at 25 ~ 28° for 10 min. A soln of n-BuLi in n-hexane (1.5 N, 15 ml) was added dropwise to the stirred and cooled mixture at − 15 ~ 0°. The reaction temp was again raised gradually to 23° and kept at 23° for 10 min to complete the formation of the dianion. To this red-orange soln was added dropwise a soln of (*S*)-**5** (3.9 g) in dry THF (5 ml) with stirring and cooling at − 15 ~ − 4°. At the end of the addition, the color of the soln turned from red to orange. The stirring was continued for 30 min at − 15 ~ −4°. Then the reaction temp was raised gradually to room temp and the stirring was continued for 3 hr. The mixture was neutralized by addition of 30% AcOH aq under cooling. It was then diluted with H_2O and extracted with C_6H_6. The C_6H_6 soln was washed with H_2O and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give 6 g of an oil. This was chromatographed over SiO_2 (Merck Kieselgel 60, 120 g). Elution with ether gave 3.7 g (90%) of (4*R*,5'*S*)-**3**, ν_{max} 1765 (s), 1720 (s), 1650 (w), 1175 (s), 1120 (s), 1075 (s), 1030 (s), 1025 (s), 995 (s) cm⁻¹; δ ($CDCl_3$) 0.65 ~ 1.10 (3H, m), 1.10 ~ 2.05 (15H, m), 2.05 ~ 3.00 (4H, m), 3.15 ~ 4.20 (4H, m), 4.39 ~ 4.88 (2H, br. s). This was employed in the next step without further purification. In the same manner, (4*R*,5'*R*)-**3** (4*S*,5'*S*)-**3** and (4*S*,5'*R*)-**3** were prepared. Their IR and NMR spectra were almost identical with those of (4*R*,5'*S*)-**3**.

(2R,9S)-2,9-*Dihydroxyundecan*-5-*one* 9-*THP ether* **2**. A soln of KOH (1.7 g) in H_2O (17 ml) was added to a soln of (4*R*,5'*S*)-**3** (3.7 g) in MeOH (50 ml) under Ar. The soln was stirred and heated under reflux overnight. It was then concentrated *in vacuo*. The residue was saturated with NaCl and extracted with ether. The ether soln was dried (Na_2SO_4) and concentrated *in vacuo* to give 2.8 g (82%) of (2*R*,9*S*)-**2**, ν_{max} 3430 (s), 1710 (s), 1130 (s), 1075 (s), 1020 (s), 995 (s) cm⁻¹; δ ($CDCl_3$) 0.84 and 0.92 (total 3H, each t, J = 7 Hz), 1.16 (3H, d, J = 6 Hz), 1.30 ~ 2.20 (14H, m), 2.20 ~ 2.85 (5H, m), 3.18 ~ 4.20 (4H, m), 4.64 (1H, br. s). This was employed in the next step without further purification. In the same manner, (2*R*,9*R*)-**2**, (2*S*,9*S*)-**2** and (2*S*,9*R*)-**2** were prepared. Their IR and NMR spectra were similar to those of (2*R*,9*S*)-**2**.

(2R,5S,7S)-7-*Ethyl*-2-*methyl*-1,6-*dioxaspiro*[4.5]*decane* **1**. 2N-HCl (3 ml) was added to (2*R*,9*S*)-**2** (2.8 g) under ice-cooling with stirring at 0 ~ 5°. The reaction temp was raised gradually to room temp and the stirring was continued overnight. Then the soln was made alkaline by the addition of 2.5N NaOH (3.2 ml). It was then extracted with n-pentane. The pentane soln was washed with brine, dried ($MgSO_4$) and concentrated under atm press. The residue was chromatographed over SiO_2 (Kieselgel 60, 70 g). Elution with n-pentane ether (12:1) gave an oil, which was distilled in the presence of a small amount of K_2CO_3 to give 826 mg (46%) of (2*R*,5*S*,7*S*)-**1**, b.p. 107 ~ 109°/47 mm. This was redistilled to give 500 mg of pure (2*R*,5*S*,7*S*)-**1**, b.p. 104 ~ 108°/49 mm; n_D^{21} 1.4421; $[\alpha]_D^{20}$ − 97.5° (*c* = 1.18, n-pentane); ν_{max} 2960 (s), 2945 (s), 2880 (s), 1460 (s), 1440 (s), 1375 (s), 1365 (m), 1355 (sh), 1330 (w), 1315 (m), 1295 (w), 1275 (m), 1265 (m), 1225 (s), 1162 (s), 1115 (s), 1095 (s), 1070 (s), 1060 (s), 1040 (sh), 1025 (s), 1010 (s), 975 (s), 940 (s), 910 (m), 895 (m), 875 (s), 865 (s), 840 (w), 815 (m), 790 (w) 745 (w) cm⁻¹; δ (C_6D_6) 0.92 (3H, t, J = 7 Hz), 1.25 (3H, d, J = 6 Hz), 1.33 ~ 2.37 (12H, m), 3.50 ~ 4.47 (2H, m); ^{13}C-NMR δ (25 MHz in C_6D_6) 10.4, 20.9, 23.5, 29.8, 31.3, 32.4, 34.2, 39.8, 71.2, 76.6, 105.9 (lit.[9] for the racemate: δ 10.4, 21.0, 23.5, 29.9, 31.4, 32.4, 34.4, 39.3, 71.4, 76.7, 106.1); GLC (Column 5% PEG 20M, 2 m × 4 mm at 100°; Carrier gas, N_2, 0.6 kg/cm²): *R*, 3.9 min [4%, (2*S*,5*S*,7*S*)-**1**] 4.6 min (92%); MS (JEOL DX-300, EI, 70eV): *m/z* 184.1475 (M⁺) Calc for $C_{11}H_{20}O_2$: 184.1464.

(2R,5R,7R) - 7 - *Ethyl*-2-*methyl*-1,6-*dioxaspiro*[4.5]*decane* **1**. In the same manner as described above, (2*R*,9*R*)-**2** (7.0 g) yielded 3.01 g [67% from (4*R*,5'*R*)-**3**] of (2*R*,5*R*,7*R*)-**1**, b.p. 105 ~ 107°/40 mm; n_D^{23} 1.4424; $[\alpha]_D^{24}$ + 78.4° (*c* = 1.26, n-pentane); ν_{max} 2960 (s), 2945 (s), 2880 (s), 1460 (s), 1440 (s), 1380 (s), 1365 (m), 1350 (m), 1305 (m), 1275 (m), 1260 (w), 1225 (s), 1163 (s), 1115 (s), 1090 (sh), 1075 (s), 1040 (sh), 1025 (s), 1010 (s), 975 (s), 940 (s), 910 (w), 890 (m), 875 (s), 865 (s), 840 (w), 800 (w), 745 (w) cm⁻¹; δ (C_6D_6) 0.91 (3H, t, J = 7 Hz), 1.15 (3H, d, J = 6 Hz), 1.25 ~ 2.35 (12H, m), 3.40 ~ 3.96 (1H, m), 3.96 ~ 4.45 (1H, m); ^{13}C-NMR δ (25 MHz, C_6D_6) 10.2, 20.9, 21.4, 29.6, 31.0, 31.9, 34.2, 38.4, 71.5, 73.6, 106.1 (lit.[9] for the racemate: δ 10.2, 20.9, 21.5, 29.7, 31.0, 32.0, 34.3, 38.5, 71.6, 73.8, 106.1); GLC (Column, LAC, 2 m × 4 mm at 100°; Carrier gas, N_2, 0.8 kg/cm²): *R*, 5.95 min (95.7%), 7.3 min [3.2%, (2*R*,5*R*,7*R*)-**1**]; MS: *m/z* 184.1465 (M⁺); Calc for $C_{11}H_{20}O_2$: 184.1464.

(2S,5S,7S)-7-*Ethyl*-2-*methyl*-1,6-*dioxaspiro*[4.5]*decane* **1**. In the same manner as described abdve (2*S*,9*S*)-**2** (3.5 g) yielded 962 mg [42.8% from (4*S*,5'*S*)-**3**] of (2*S*,5*S*,7*S*)-**1**, b.p. 118 ~ 122°/73 mm; n_D^{24} 1.4424; $[\alpha]_D^{23}$ − 76.1° (*c* = 1.27, n-pentane); GLC (Column, 5% PEG 20M, 2 m × 4 mm at 96°; Carrier gas, N_2, 0.8 kg/cm²): *R*, 9.4 min (96%), 11.4 min [3%, (2*R*,5*S*,7*S*)-**1**]; MS: *m/z* 184.1454 (M⁺); Calc for $C_{11}H_{20}O_2$: 184.1464. Its IR, ^{1}H-NMR and ^{13}C-NMR spectral data were identical with those of (2*R*,5*R*,7*R*)-**1**.

(2S,5R,7R)-*Ethyl*-2-*methyl*-1,6-*dioxaspiro*[4.5]*decane* **1**. In the same manner as described above (2*S*,9*R*)-**2** (12.3 g) yielded 6.15 g (78%) of (2*S*,5*R*,7*R*)-**1**, b.p. 107 ~ 110°/38 mm; n_D^{22} 1.4424; $[\alpha]_D^{22}$ + 102° (*c* = 1.17, n-pentane); GLC (Column, LAC, 2 m × 4 mm at 110°; Carrier gas, N_2, 0.8 kg/cm²): *R*, 3.6 min [4.3%, (2*R*,5*R*,7*R*)-**1**], 4.5 min (94.9%); MS: *m/z* 184.1484 (M⁺); Calc for $C_{11}H_{20}O_2$: 184.1464. Its IR, ^{1}H-NMR and ^{13}C-NMR spectra were identical with those of (2*R*,5*S*,7*S*)-**1**.

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REFERENCES

[1]W. Francke, *Mitt. Dtsch. Ges. Allg. Angew. Entomol.* **2**, 248 (1981).
[2]W. Francke, *Les Colloques de l'INRA* 7 (Les Médiateurs chimiques agissant sur le comportement des insectes), pp. 81 84. Institut National de la Recherche Agronomique, Paris (1982).
[3]K. Mori, The synthesis of insect pheromones, *The Total Synthesis of Natural Products* (Edited by J. ApSimon), Vol. 4, pp. 109–168. Wiley, New York (1981).
[4]K. Mori, M. Sasaki, S. Tamada, T. Suguro and S. Masuda, *Tetrahedron* **35**, 1601 (1979).
[5]K. Mori and K. Tanida, *Ibid.* **37**, 3221 (1981).
[6]K. Mori and M. Katsurada, *Liebigs Ann. Chem.* 157 (1984).
[7]W. Francke, G. Hindorf and W. Reith, *Naturwissenschaften* **66**, 618 (1979).
[8]G. Bergström, J. Tengö, W. Reith and W. Francke, *Z. Naturforsch.* **37c**, 1124 (1982).
[9]W. Francke, W. Reith and V. Sinnwell, *Chem. Ber.* **113**, 2686 (1980).
[10]C. Phillips, R. Jacobson, B. Abrahams, H. J. Williams and L. R. Smith, *J. Org. Chem.* **45**, 1920 (1980).
[11]R. E. Ireland and D. Häbich, *Tetrahedron Letters* **21**, 1389 (1980).
[12]T. Kożluk, L. Cottier and G. Descotes, *Tetrahedron* **37**, 1875 (1981).
[13]S. V. Ley and B. Lygo, *Tetrahedron Letters* **23**, 4625 (1982).
[14]E. Hungerbühler, R. Naef, D. Wasmuth and D. Seebach, *Helv. Chim. Acta* **63**, 1960 (1980).
[15]K. Hinzer, R. Weber and V. Schurig, *Tetrahedron Letters* **22**, 55 (1981).
[16]J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.* **95**, 512 (1973).
[17]B. Seuring and D. Seebach, *Helv. Chim. Acta* **60**, 1175 (1977).
[18]L. R. Hills and R. C. Ronald, *J. Org. Chem.* **46**, 3348 (1981).
[19]V. Schurig, B. Koppenhofer and W. Bürke, *Angew. Chem. Int. Ed. Engl.* **17**, 937 (1978).
[20]E. J. Corey, H. Niwa and J. Knolle, *J. Am. Chem. Soc.* **100**, 1942 (1978).
[21]B. T. Golding, D. R. Hall and S. Sakrikar, *J. Chem. Soc. Perkin I* 1214 (1973).
[22]D. L. Boger and J. S. Panek, *J. Org. Chem.* **46**, 1208 (1981).
[23]E. J. Corey and A. Venkataswarlu, *J. Am. Chem. Soc.* **94**, 6190 (1972).
[24]C. Huynh, F. Derguini-Boumechal and G. Linstrumelle, *Tetrahedron Letters* 1503 (1979).
[25]A. Bongini, G. Cardillo, M. Orena and S. Sandri, *Synthesis* 618 (1979).
[26]J. Hasegawa, S. Hamaguchi, M. Ogura and K. Watanabe, *J. Ferment. Technol.* **59**, 257 (1981).
[27]K. Mori and H. Watanabe, *Tetrahedron*, in press.
[28]O. Mitsunobu, *Synthesis* 1 (1981).
[29]S. N. Huckin and L. Weiler, *J. Am. Chem. Soc.* **96**, 1082 (1974).
[30]P. Deslongchamps, D. D. Rowan, N. Pothiers, T. Sauvé and J. K. Saunders, *Can. J. Chem.* **59**, 1105 (1981).
[31]P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry* pp. 4 53. Pergamon Press, Oxford (1983).