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SYNTHESIS OF THE ENANTIOMERS OF 5-HEXADECANOLIDE, THE PHEROMONE OF THE QUEEN OF THE ORIENTAL HORNET, *VESPA ORIENTALIS*, EMPLOYING ENZYMIC RESOLUTION OF (±)-2-AMINOTRIDECANOIC ACID AS THE KEY-STEP†

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Abstract—Optical resolution of (±)-2-chloroacetylaminotridecanoic acid with amino acylase gave (*S*)-2-aminotridecanoic acid, which was converted into highly optically pure (*S*)-5-hexadecanolide (the pheromone of *Vespa orientalis*). Similarly (*R*)-2-chloroacetylaminotridecanoic acid recovered after the enzymic hydrolysis yielded (*R*)-5-hexadecanolide. The existing methods for the preparation of the enantiomers of 5-hexadecanolide were critically surveyed to point out basic requisites for an effective chiral synthesis.

5-Hexadecanolide **1** was isolated from heads of the queens of the oriental hornet (*Vespa orientalis*) as a pheromone for the workers to stimulate the construction of queen cells.[1] The racemic lactone **1** could induce the worker wasps to make queen cells even in the absence of a queen.[1] Besides the synthesis of (±)-**1**,[1-3] six different syntheses of the enantiomers of **1** were recorded with the specific rotation of (*R*)-**1** ranging from +2.69° to +39.97° (THF).[4-9] Nothing is known, however, concerning the absolute configuration of the natural **1**. It is essential to prepare the optically pure enantiomers of **1** so as to obtain reliable data on their biological activities. Herein we report a synthesis of the pure enantiomers of **1** with $[\alpha]_D^{21.5} \pm 40.2°$ (THF).

The key-step in our synthesis as shown in Fig. 1 is the resolution of an unnatural long-chain α-amino acid **2a** employing amino acylase of *Aspergillus* spp. This technique was successfully employed by us previously in the syntheses of natural products including insect pheromones.[10-13] The broad substrate specificity and high enantioselectivity of the amino acylase reaction were observed in the present case, too, which led to the preparation of both the enantiomers of **2a**. (±)-2-Aminotridecanoic acid **2a**, prepared by the conventional acetamidomalonate synthesis, was acylated with chloroacetyl chloride to give (±)-**2b**. This was treated with the *Aspergillus* amino acylase at pH 7.25 in the presence of a trace amount of $CoCl_2$ for 2 days at 37° to give (*S*)-**2a** and unhydrolyzed (*R*)-**2b** in satisfactory yields. Deamination of (*S*)-**2a** with HNO_2 yielded a waxy α-hydroxy acid (*S*)-**3a**, which was esterified with MeOH–HCl to give (*S*)-**3b**. The optical purity of (*S*)-**3b** was estimated as 91.8% by the HPLC analysis of the corresponding α-methoxy-α-trifluoromethylphenylacetate (MTPA ester[14]) (*S*)-**3c**. The value (91.8% e.e.) indicated the incomplete enantioselectivity of the enzymic hydrolysis and/or the incomplete retention of configuration during the deamination and/or least probably the racemization during the esterification of (*S*)-**3a** to (*S*)-**3b**. No attempt was made to clarify the matter, since our aim was only to prepare the pure enantiomers of **1**.

Reduction of (*S*)-**3b** with LAH gave a crystalline diol (*S*)-**4**, m.p. 67–68°, $[\alpha]_D^{21} -9.63°$ (MeOH). This was converted to an epoxide (*S*)-**5** according to the general method of Golding *et al.*[15] For the elongation of the C-chain of (*S*)-**5**, we employed the method previously used in our synthesis of 6-acetoxy-5-hexadecanolide, the oviposition attractant pheromone of the mosquito *Culex pipiens fatigans*.[16] A Grignard reagent prepared from 4-methyl-3-pentenyl bromide was added to (*S*)-**5** in the presence of Cu_2Br_2[17] to give (*S*)-**6a** as a waxy solid. The corresponding acetate (*S*)-**6b** was submitted to ozonolysis. After oxidative workup with Jones CrO_3, an acetoxy acid (*S*)-**7a** was obtained as a waxy solid. Alkaline hydrolysis of (*S*)-**7a** gave (*S*)-**7b**, m.p. 67–68°, $[\alpha]_D^{20} +1.07°$ (MeOH). The optical purity of (*S*)-**7b** was determined as 100.0% by the HPLC analysis of the corresponding MTPA ester (*S*)-**7c**. The enhancement of the optical purity from 91.8% [(*S*)-**3b**] to 100.0% [(*S*)-**7b**] was obviously due to the purification of the crystalline intermediates by recrystallization. Finally, lactonization of (*S*)-**7b** with *p*-TsOH in C_6H_6 gave (*S*)-5-hexadecanolide **1**, m.p. 37° $[\alpha]_D^{21.5} -40.2°$ (THF). This was thought to be of ~100% e.e., reflecting the optical purity of (*S*)-**7b**. The overall yield of pure (*S*)-**1** from (*S*)-**2a** was 16.7% in 10 steps.

For the synthesis of (*R*)-**1**, (*R*)-2-chloroacetylaminotridecanoic acid (*R*)-**2b** was hydrolyzed with dil HCl to give (*R*)-**2a**. This gave (*R*)-**3b** in the same manner as described above. The HPLC analysis of (*R*)-**3c** revealed the optical purity of (*R*)-**3b** to be 91.3%. Reduction of (*R*)-**3b** gave crystalline (*R*)-**4**, m.p. 67–68°, $[\alpha]_D^{20} +10.1°$ (MeOH). This was converted to (*R*)-7b, m.p. 67–68°, $[\alpha]_D^{20} -1.07°$ (MeOH). Finally lactonization of (*R*)-**7b** gave (*R*)-hexadecanolide **1**, m.p. 37°, $[\alpha]_D^{21.5} +40.2°$ (THF). The optical purity of (*R*)-**7b** was 100.0% as determined by the HPLC analysis of (*R*)-**7c**. The lactone (*R*)-**1** was therefore thought to be of ~100% e.e. The overall yield of (*R*)-**1** from (*R*)-**2a** was 13.4% in 10 steps.

The wide range of the reported values (2.7–40.2°) for the specific rotation of the enantiomers of **1** as shown in Table 1 deserves comments. Scrutiny of the existing

† Pheromone Synthesis—71. Part 70, K. Mori and S. Senda, *Tetrahedron* **41**, 541 (1985). The experimental part of this work was taken from the forthcoming doctoral dissertation of T.O.

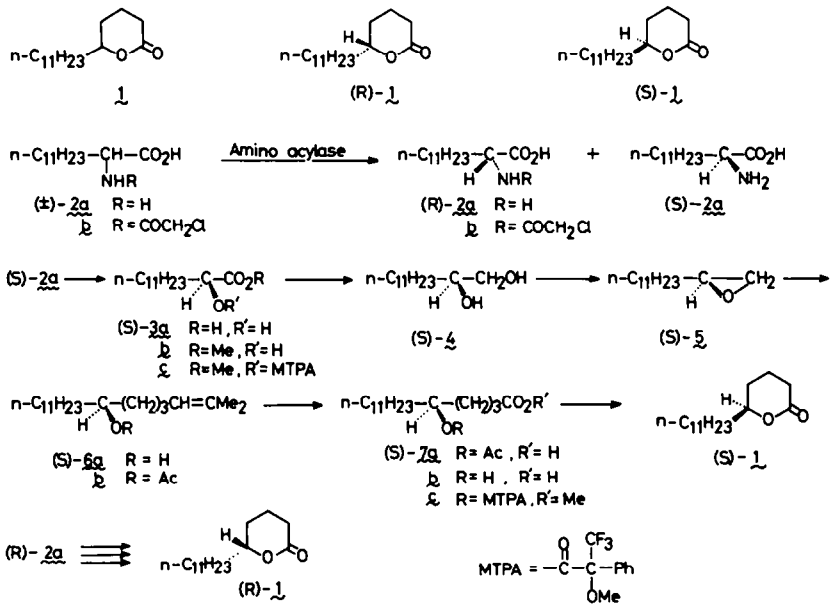

Fig. 1. Synthesis of the enantiomers of 5-hexadecanolide.

syntheses of optically active **1** tells us a lesson in designing a synthetic route for an optically pure target molecule, which is of utmost importance in studying the chirality-bioactivity relationship. The first synthesis of optically active **1** by Coke[4] depended on the classical optical resolution of **A** as shown in Table 1 and Fig. 2, and was apparently unsuccessful to give **1** of only 6.6–6.7% e.e. Pirkle's synthesis was based on more modern HPLC separation technique to achieve resolution, but yielded **1** of ~60% e.e., although he thought his **1** to be "essentially of complete enantiomeric purity".[5] Assuming that his HPLC separation of **B** was complete, a considerable racemization must have taken place in later stages. Although the LC separation of diastereomers is rapidly prevailing as one of the most reliable resolution procedures, care must be taken not to racemize the separated intermediates. Solladié's asymmetric synthesis yielded **1** of 68.7% e.e., reflecting the low e.e. (~80%) of the starting sulfoxide **C**.[6] Yeast reduction of the Na salt of a δ-keto acid **D** gave (*R*)-**1** of only 39% e.e.[7] Servi was the first to achieve a synthesis of the highly optically pure enantiomers of **1**, who used a chiral building block **E** originating from yeast reduction.[8] Servi obtained one of his intermediates, as well as **1** itself, as crystals which could be purified by recrystallization.[8] Starting from optically pure (*S*)-glutamic acid, Larcheveque prepared (*R*)-**1** of only ~91% e.e., probably because he failed to obtain any crystalline intermediate.

In our own synthesis we prepared both (*R*)- and (*S*)-**1**

Table 1. Comparison of the specific rotations of the enantiomers of 5-hexadecanolide **1** obtained by various methods

Author (year)[ref]	$[\alpha]_D$ as THF soln (optical purity) (*R*)-**1**	(*S*)-**1**	Method of preparation
Coke *et al.* (1976)[4]	+2.69° (6.7%)	−2.65° (6.6%)	Resolution of **A** by recrystallization of diastereomeric salt
Pirkle *et al.* (1979)[5]	+24.2° (60.2%)	−24.1° (60.0%)	Resolution of **B** by HPLC separation of the diastereomers
Solladié *et al.* (1982)[6]	+27.6° (68.7%)	—	Asymmetric synthesis *via* a sulfoxide **C**
Naoshima *et al.* (1983)[7]	+15.8° (39.3%)		Yeast reduction of **D**
Servi (1983)[8]	+39.97° (99.4%)	−39.2° (97.5%)	Derivation from **E** obtained by yeast reduction followed by chemical conversion
Larcheveque *et al.* (1984)[9]	+36.5° (90.8%)	—	Derivation from (*S*)-glutamic acid **F**
The present work (1984)	+40.2° (~100%)	−40.2° (~100%)	Resolution of (±)-**2a** with amino acylase followed by chemical conversion

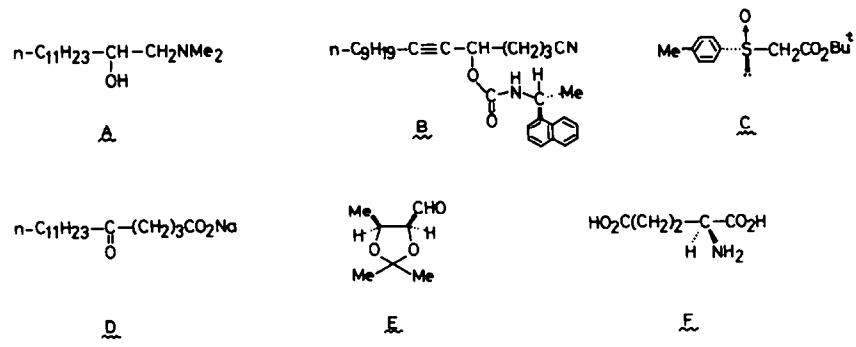

Fig. 2. Key intermediates employed in the various syntheses of the enantiomers of 5-hexadecanolide.

of ~100% optical purity. This is due to the following three reasons:

(i) The enzymic resolution yielded *the starting materials of high e.e. in sufficient quantities.*

(ii) Besides **1**, both **4** and **7b** were crystalline, which could be *purified by recrystallization.*

(iii) In designing the synthesis, use of drastic reaction conditions was avoided as far as possible to *avoid racemization.*

These three items are the basic requisites in executing an efficient chiral synthesis to obtain an optically pure target molecule. So as not to over-estimate the optical purity of the target molecule, determination of the optical purity by either chromatographic or NMR spectroscopic method should be made on the target itself or, if not possible, on an intermediate not far away from the target.

In conclusion we synthesized the optically pure enantiomers of **1** in quantities sufficient for biological works.

EXPERIMENTAL

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

(±)-2-*Aminotridecanoic acid* **2a**

A soln of diethyl N-acetylaminomalonate (60.8 g, 0.28 mol) in dry EtOH (360 ml) was added dropwise over 30 min to a stirred soln of NaOEt [from 6.44 g (0.28 g atom) of Na] in dry EtOH (150 ml) at room temp. To this was added dropwise over 30 min n-$C_{11}H_{23}Br$ (78.9 g, 0.34 mol) at room temp. The mixture was stirred and heated under reflux for 28 hr, cooled and concentrated *in vacuo*. The residue was diluted with water and extracted with ether. The ether soln was concentrated *in vacuo* and the residual oil was stirred and heated under reflux with conc HCl (100 ml) and water (340 ml). The soln was then cooled to 40° and adjusted to pH 7 with NH_3 aq. The precipitated (±)-**2a** was collected on a filter, washed successively with water, MeOH and ether, and dried over P_2O_5 to give 49.8 g (77.7%) of (±)-**2a**, m.p. 226–227° (dec). ν_{max}: 3440 (m), ~1660 (m), 1590 (s), 1520 (w) cm^{-1}. (Found: C, 67.73; H, 11.77; N, 6.07. Calc for $C_{13}H_{27}O_2N$: C, 68.07; H, 11.87; N, 6.11%.)

(±)-2-*Chloroacetylaminotridecanoic acid* **2b**

A soln of (±)-**2a** (19.0 g, 82.8 mmol) in 2 N NaOH (44 ml) and DME (44 ml) was stirred and cooled with an ice-bath. To this were added a soln of $ClCH_2COCl$ (18.7 g, 165.6 mmol) in DME (60 ml) and 2 N NaOH (104 ml) simultaneously and dropwise over 45 min with stirring and cooling at 8–14°. After the addition the soln was acidified to pH 2 with 6 N HCl. The ppt was collected on a filter and dissolved in EtOAc by washing the solid on the filter with the solvent. The EtOAc soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give (±)-**2b** as crystals. Recrystallization from acetone–n-hexane gave 14.5 g (45.0%) of pure (±)-**2b**, m.p. 91–92°, ν_{max}: 3450 (m), ~2600 (w), 1735 (s), 1640 (s), 1550 (m), 920 (m) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 0.88 (3H, deformed t, J = 7 Hz), 1.10–1.65 (18H, m), 1.65–2.10 (2H, m), 4.10 (2H, s), ~4.65 (1H, m), 7.12 (1H, d, J = 8 Hz), 9.27 (1H, s). (Found: C, 59.07; H, 9.30; N, 4.66. Calc for $C_{15}H_{28}O_3NCl$: C, 58.91; H, 9.23; N, 4.58%.)

Enzymic resolution of (±)-**2b** *to give* (R)-**2b** *and* (S)-**2a**

A soln of (±)-**2b** (44.5 g, 145.5 mmol) in NaOH aq (6 g in 1.5 l of distilled water) was warmed to 37° and adjusted to pH 7.25 with 3 N HCl. This was diluted with distilled water to the total volume of 5 l. To this were added *Aspergillus* amino acylase (Tokyo Kasei Co., 7.0 g) and $CoCl_2$ (13.7 mg) and the mixture was left to stand for 2 days at 37°. The separated (*S*)-**2a** was collected on a filter, washed with water, MeOH and Et_2O and dried over P_2O_5 to give 18.0 g (107%) of crystalline (*S*)-**2a**, m.p. 223–225° (dec), $[\alpha]_D^{19}$ + 21.7° (*c* = 0.105, AcOH); ν_{max}: ~3250 (m), 1570 (s), 1510 (m) cm^{-1}. (Found: C, 67.94; H, 11.54; N, 6.11. Calc for $C_{13}H_{27}O_2N$: C, 68.07; H, 11.87; N, 6.11%.) The aq filtrate was acidified with 3 N HCl (60 ml) and the separated (*R*)-**2b** was collected on a filter. This was dissolved in acetone (800 ml), treated with activated charcoal with stirring for 1 hr, filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOAc. The EtOAc soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized from acetone–n-hexane to give 16.4 g (73.7%) of (*R*)-**2b**, m.p. 80–81°, $[\alpha]_D^{21}$ − 30.4° (*c* = 1.39, $CHCl_3$); ν_{max}: 3330 (sh), 3300 (m), 1710 (s), 1645 (s), 1535 (s) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 0.87 (3H, deformed t, J = 7 Hz), 1.05–1.60 (~18H, m), 1.65–2.15 (2H, m), 4.10 (2H, s), ~4.60 (1H, m), 7.17 (1H, d, J = 8 Hz), 10.13 (1H, s). (Found: C, 59.10; H, 9.22; N, 4.67. Calc for $C_{15}H_{28}O_3NCl$: C, 58.91; H, 9.23; N, 4.58%.)

(R)-2-*Aminotridecanoic acid* **2a**

A mixture of (*R*)-**2b** (3.68 g, 12.0 mmol) and 4 N HCl (30 ml) was stirred and heated under reflux for 1.2 hr. After cooling, the mixture was neutralized with 15% NH_3 aq. The precipitate was collected on a filter, washed with water, MeOH and ether, and dried over P_2O_5 to give 2.65 g (96.0%) of (*R*)-**2a**, m.p. 222–223° (dec), $[\alpha]_D^{19}$ − 21.1° (*c* = 0.099, AcOH); ν_{max}: ~3250 (m), 1570 (s), 1510 (m) cm^{-1}. (Found: C, 68.24; H, 11.39; N, 6.12. Calc. for $C_{13}H_{27}O_2N$: C, 68.07; H, 11.87; N, 6.11%.)

Methyl 2-*hydroxytridecanoate* **3b**

(a) (S)-*Isomer*. (*S*)-**2a** (7.0 g, 30.5 mmol) was dissolved in 2 N H_2SO_4 (26 ml, 52 mmol) with stirring and heating at 90–93° on a water bath. To this was added a soln of $NaNO_2$ (3.77 g, 54.6 mmol) in water (50 ml) dropwise over 3 hr with vigorous

stirring and heating at 90–93°. After cooling, the separated (*S*)-**2a** (1.28 g, 18.3% recovery) was filtered off. The filtrate was extracted with ether. The ether soln was concentrated *in vacuo*. The residue was dissolved in C_6H_6 and concentrated. This was repeated several times to remove water. The residual waxy (*S*)-**3a** [4.78 g, 83.2% yield based on the consumed (*S*)-**2a**] was dissolved in MeOH (30 ml) and C_6H_6 (25 ml) containing 3 drops of conc HCl. The mixture was stirred and heated under reflux for 3 hr. It was then concentrated *in vacuo*. The residue was dissolved in ether. The ether soln was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Kieselgel 60, 50 g). Elution with EtOAc–n-hexane (5:95) gave 3.12 g [51.5% from the consumed (*S*)-**2a**] of (*S*)-**3b** as an oil. A portion of it was distilled to give an analytical sample, b.p. 102–104°/0.1 mm, n_D^{21} 1.4412; $[\alpha]_D^{21}$ +7.45° (*c* = 1.20, $CHCl_3$); ν_{max}: 3475 (m), 1735 (s), 1260 (m), 1210 (s), 1130 (s), 1095 (s) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 0.88 (3H, deformed t, J = 6 Hz), 1.10–1.55 (~18H, br s), 1.55–2.10 (2H, m), 2.85 (1H, s), 3.82 (3H, s), ~4.25 (1H, m). (Found: C, 68.85; H, 11.64. Calc for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55%.)

(b) (*R*)-*Isomer*. In the same manner as above (*R*)-**2a** (5.66 g, 24.68 mmol) yielded 3.39 g (59.0%) of (*R*)-**3b**, b.p. 105°/0.23 mm, n_D^{20} 1.4418; $[\alpha]_D^{20}$ −7.29° (*c* = 1.05, $CHCl_3$). (Found: C, 69.01; H, 11.43. Calc for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55%.) The IR and NMR spectra of (*R*)-**3b** were identical with those of (*S*)-**3b**.

The HPLC analysis of **3c** *to estimate the optical purity of* **3b**

(*R*)- and (*S*)-**3b** were converted to (*R*)- and (*S*)-**3c** in the usual manner using MTPA-Cl derived from (*R*)-MTPA or (*S*)-MTPA. HPLC analysis of (*R*)-**3c** (column, Partisil-5, 25 cm × 4.6 mm; solvent, n-hexane–THF–MeOH = 6000:100:1; press, 30 kg/cm²; flow rate, 0.95 ml/min) *R*, 12.08 min [(*R*)-**3c** with (*S*)-MTPA], 14.53 min [(*R*)-**3c** with (*R*)-MTPA]. The optical purity of (*R*)-**3b** was 91.3%. HPLC analysis of (*S*)-**3c** (column, Partisil-5, 25 cm × 4.6 mm; solvent, n-hexane–THF–MeOH = 6000:100:2; press, 30 kg/cm²; flow rate, 0.95 ml/min) *R*, 11.06 min [(*S*)-**3c** with (*R*)-MTPA], 13.11 min [(*S*)-**3c** with (*S*)-MTPA]. The optical purity of (*S*)-**3b** was 91.8%.

Tridecane-1,2-diol **4**

(a) (*S*)-*Isomer*. A soln of (*S*)-**3b** (6.18 g, 25.3 mmol) in dry THF (12 ml) was added dropwise over 15 min to a stirred and ice-cooled suspension of LAH (1.80 g, 47.5 mmol) in dry THF (30 ml) at 0°. The mixture was stirred and heated under reflux for 2.5 hr. After cooling, the excess LAH was destroyed by addition of water (100 ml). The mixture was poured into iced 3 N H_2SO_4 (120 ml) and extracted with ether. The ether soln was washed with water and $NaHCO_3$ aq, dried (Na_2SO_4) and concentrated *in vacuo* to give 5.44 g (99.5%) of crystalline (*S*)-**4**. Recrystallization from ether–pet. ether gave 5.05 g (92.3%) of (*S*)-**4** as plates, m.p. 67–68°, $[\alpha]_D^{21}$ −9.63° (*c* = 0.622, MeOH); ν_{max}: 3500 (m), 3220 (s), 1075 (m), 875 (m) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 0.86 (3H, deformed t, J = 6 Hz), 1.05–1.55 (~18H, br s), 1.65 (2H, m), 2.80 (2H, br, OH), 3.50 (3H, m). (Found: C, 72.29; H, 13.02. Calc for $C_{13}H_{28}O_2$: C, 72.16; H, 13.05%.)

(b) (*R*)-*Isomer*. In the same manner as above 3.30 g (13.5 mmol) of (*R*)-**3b** yielded 2.76 g (94.5%) of (*R*)-**4**. This was recrystallized from ether–pet. ether to give 2.19 g (75.0%) of plates, m.p. 67–68°, $[\alpha]_D^{21}$ +10.1° (*c* = 1.06, MeOH). (Found: C, 72.35; H, 13.14. Calc for $C_{13}H_{28}O_2$: C, 72.16; H, 13.05%.) The IR and NMR spectra of (*R*)-**4** were identical with those of (*S*)-**4**.

1,2-Epoxytridecane **5**

(a) (*S*)-*Isomer*. 25% HBr–AcOH (19.9 g) was added to (*S*)-**4** (4.85 g, 22.4 mmol) under ice-cooling. The mixture was stirred for 3 hr at room temp. It was then diluted with ice-water, adjusted to pH 6 by addition of Na_2CO_3 and extracted with ether. The ether soln was washed with water, $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 6.54 g of an oily acetoxy bromide. This was dissolved in MeOH (15 ml). To this was added a soln of NaOMe in MeOH (15 ml) [prepared from Na (1.24 g) and MeOH (40 ml)]. After stirring for 20 min at room temp, the soln was diluted with water (150 ml) and extracted with pentane. The pentane soln was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was distilled to give 3.81 g (85.6%) of (*S*)-**5**, b.p. 123–125°/13 mm, n_D^{20} 1.4352; $[\alpha]_D^{21}$ −11.0° (*c* = 1.20, Et_2O); ν_{max}: 3050 (m), 910 (m), 830 (s), 720 (m) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 0.86 (3H, deformed t, J = 6 Hz), 1.00–1.85 (~20H, m, a singlet at δ 1.25), 2.45 (1H, dd, J_1 = 1.5 Hz, J_2 = 3 Hz), 2.73 (1H, dd, J_1 = 6 Hz, J_2 = 3 Hz), 2.85 (1H, m). (Found: C, 78.53; H, 13.29. Calc for $C_{13}H_{26}O$: C, 78.72; H, 13.21%.)

(b) (*R*)-*Isomer*. In the same manner as above (*R*)-**4** (2.14 g, 9.9 mmol) gave 3.23 g (97.9%) of an acetoxy bromide, which yielded 1.84 g (93.9%) of (*R*)-**5**, b.p. 111–113°/7 mm, n_D^{20} 1.4358; $[\alpha]_D^{20.5}$ +11.8° (*c* = 1.09, ether). (Found: C, 78.50; H, 13.32. Calc for $C_{13}H_{26}O$: C, 78.72; H, 13.21%.) The IR and NMR spectra of (*R*)-**5** were identical with those of (*S*)-**5**.

2-Methyl-2-octadecen-7-ol **6a**

(a) (*S*)-*Isomer*. A soln of $Me_2C{=}CH(CH_2)_2MgBr$ in THF (2 M, 20 ml, 40 mmol) was added dropwise to a stirred and cooled suspension of Cu_2Br_2 (574 mg, 4 mmol) in dry THF (10 ml) at −60 to −30° under Ar. A soln of (*S*)-**5** (4.0 g, 20.2 mmol) in THF (20 ml) was added dropwise to the stirred mixture kept below −30°. After the addition, the stirring was continued for 2 hr at 0°. The mixture was poured into sat NH_4Cl aq and extracted with ether. The ether soln was washed with $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Kieselgel 60, 120 g). Elution with 12–15% (v/v) ether in n-hexane gave 5.6 g (98.3%) of (*S*)-**6a** as a waxy solid, m.p. 35°, $[\alpha]_D^{19}$ +1.14° (*c* = 1.09, MeOH); ν_{max}: 3340 (s), 3250 (s), 1125 (m), 1110 (m), 1100 (m), 1080 (m), 1060 (m), 900 (w), 840 (w), 720 (m) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 0.87 (3H, deformed t, J = 6 Hz), 1.00–1.55 (~24H, m, a singlet at δ 1.25), 1.58 (3H, s), 1.67 (3H, s), 1.75–2.20 (2H, m), 3.55 (1H, m), 5.10 (1H, m). (Found: C, 80.88; H, 13.60. Calc for $C_{19}H_{38}O$: C, 80.78; H, 13.56%.)

(b) (*R*)-*Isomer*. In the same manner as above, 1.80 g (9.1 mmol) of (*R*)-**5** gave 2.41 g (94.1%) of (*R*)-**6a**, m.p. 34.5°, $[\alpha]_D^{19.5}$ −1.21° (*c* = 1.01, MeOH). (Found: C, 80.57; H, 13.79. Calc for $C_{19}H_{38}O$: C, 80.78; H, 13.56%.) The IR and NMR spectra of (*R*)-**6a** coincided with those of (*S*)-**6a**.

7-Acetoxy-2-methyl-2-octadecene **6b**

(a) (*S*)-*Isomer*. Ac_2O (6 ml) was added to a soln of (*S*)-**6a** (4.85 g, 17.2 mmol) in dry C_5H_5N (18 ml) and the mixture was stirred overnight at room temp. Since **6a** was still detectable by TLC, a trace amount of 4-(N,N-dimethylamino)pyridine was added to the mixture and the stirring was continued for 1 hr. The mixture was diluted with ice-water and extracted with ether. The ether soln was washed with 5% HCl (× 3), $NaHCO_3$ aq (× 2) and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Kieselgel 60, 120 g). Elution with 4–6% (v/v) ether in n-hexane gave 4.77 g (85.6%) of (*S*)-**6b** after distillation, b.p. 138–139°/0.35 mm, n_D^{20} 1.4486; $[\alpha]_D^{20.5}$ −1.30° (*c* = 1.01, $CHCl_3$); ν_{max}: 1740 (s), 1240 (s), 1020 (m) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 0.88 (3H, deformed t, J = 6 Hz), 1.05–1.60 (~24H, m, a singlet at δ 1.26), 1.60 (3H, s), 1.70 (3H, s), 1.85–2.05 (2H, m), 2.05 (3H, s), 4.75–5.30 (2H, m). (Found: C, 77.87; H, 12.44. Calc for $C_{21}H_{40}O_2$: C, 77.72; H, 12.42%.)

(b) (*R*)-*Isomer*. In the same manner as above (*R*)-**6a** (2.40 g, 8 mmol) gave 2.36 g (85.6%) of (*R*)-**6b**, b.p. 141–143°/0.5 mm, $n_D^{20.5}$ 1.4480; $[\alpha]_D^{20.5}$ +1.28° (*c* = 1.50, $CHCl_3$). (Found: C, 77.77; H, 12.52. Calc for $C_{21}H_{40}O_2$: C, 77.72; H, 12.42%.) The IR and NMR spectra of (*R*)-**6b** was identical with those of (*S*)-**6b**.

5-Acetoxyhexadecanoic acid **7a**

(a) (*S*)-*Isomer*. O_3 was bubbled into a soln of (*S*)-**6b** (4.00 g, 12.3 mmol) in acetone (100 ml) for 2 hr at −65°. Excess O_3 was removed by bubbling N_2 into the soln. Jones CrO_3 (8 N, 10 ml) was added dropwise to the cooled and stirred soln and the reaction temp was gradually raised to room temp. After stirring for 2 hr at room temp, the mixture was cooled to 0° and MeOH (5 ml) was added to destroy excess CrO_3. After stirring

for 15 min, the mixture was concentrated *in vacuo*, diluted with water, made acid with 6 N HCl and extracted with ether (180 ml × 4). The ether layer was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (Kieselgel 60, 100 g). Elution with 10–30% (v/v) ether in n-hexane gave 3.18 g (82.0%) of (*S*)-**7a** as a waxy solid, m.p. 31–32°, $[\alpha]_D^{20} + 2.46°$ (*c* = 1.01, $CHCl_3$); ν_{max}: ~3200 (m), 2650 (m), 1740 (s), 1710 (s), 1240 (s), 1020 (m) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 0.87 (3H, deformed t, J = 6 Hz), 1.05–1.45 (~20H, m, a singlet at δ 1.25), 1.45–1.85 (4H, m), 2.05 (3H, s), 2.38 (2H, m), ~4.90 (1H, m). (Found: C, 68.65; H, 11.13. Calc for $C_{18}H_{34}O_4$: C, 68.75; H, 10.90%.)

(b) (*R*)-*Isomer*. In the same manner as above, 2.35 g (7.2 mmol) of (*R*)-**6b** gave 1.89 g (83.1%) of (*R*)-**7a**, m.p. 31–32°, $[\alpha]_D^{21} - 2.54°$ (*c* = 1.01, $CHCl_3$). (Found: C, 68.70; H, 10.79. Calc for $C_{18}H_{34}O_4$: C, 68.75; H, 10.90%). The IR and NMR spectra of (*R*)-**7a** were identical with those of (*S*)-**7a**.

5-Hydroxyhexadecanoic acid **7b**

(a) (S)-*Isomer*. A soln of (*S*)-**7a** (1.04 g, 3.3 mmol) in THF (5 ml) was mixed with 1 N KOH (10 ml) and the mixture was stirred for 1 hr at room temp and 10 hr at 40°. After cooling, it was acidified with 6 N HCl to pH 2 and extracted with ether (30 ml × 3). The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 998 mg of crystalline (*S*)-**7b**. This was recrystallized from ether–n-hexane to give 829.5 mg (92.8%) of pure (*S*)-**7b** as needles, m.p. 67–68°, $[\alpha]_D^{20} + 1.07°$ (*c* = 1.01, MeOH); ν_{max}: 3340 (m), 3225 (m), 1700 (s), 1205 (m), 1125 (m), 1100 (m), 1035 (w), 930 (w), 895 (m) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 0.87 (3H, deformed t, J = 6 Hz), 1.00–1.45 (~20H, m, a singlet at δ 1.25), 1.45–1.90 (4H, m), 2.35 (2H, t, J = 7 Hz), 3.55 (1H, m), 5.73 (2H, s, OH and CO_2H). (Found: C, 70.78; H, 11.77. Calc for $C_{16}H_{32}O_3$: C, 70.54; H, 11.84%.)

(b) (R)-*Isomer*. In the same manner as above, 1.70 g (5.4 mmol) of (*S*)-**7a** gave 1.51 g (quantitative) of (*R*)-**7b**. This was recrystallized from acetone–n-hexane to give 1.23 g (83.9%) of (*R*)-**7b** as needles, m.p. 67–68°, $[\alpha]_D^{20} - 1.07°$ (*c* = 1.03, MeOH). (Found: C, 70.65; H, 11.81. Calc for $C_{16}H_{32}O_3$: C, 70.54; H, 11.84%.)

The HPLC analysis of **7c** *to determine the optical purity of* **7b**

(*R*)- or (*S*)-**7b** was esterified with MeOH, toluene and conc HCl to the corresponding Me ester, which was acylated with (*R*)-MTPA-Cl in the usual manner to give **7c**. HPLC analysis of **7c** (column, Partisil 5, 25 cm × 4.6 mm; press, 55 kg/cm^2; flow rate, 1 ml/min; solvent, $ClCH_2CH_2Cl$–n-hexane, 3:7) R_t 64.59 min [(*S*)-**7c** with (*R*)-MTPA], 59.52 min [(*R*)-**7c** with (*R*)-MTPA]. These two were completely separable under this condition and both (*S*)-**7c** and (*R*)-**7c** showed a single peak. (*S*)-**7b** and (*R*)-**7b** were therefore optically pure.

5-Hexadecanolide **1**

(a) (S)-*Isomer*. A trace amount of *p*-TsOH was added to a soln of (*S*)-**7b** (680 mg) in dry C_6H_6 (150 ml) and the mixture was stirred and heated under reflux for 6 hr. After cooling, it was diluted with ether (350 ml). The soln was washed with $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 680 mg of crude (*S*)-**1**. This was recrystallized from n-hexane to give 408.3 mg (64.3%) of (*S*)-**1** as leaflets, m.p. 37°, $[\alpha]_D^{21.5} - 40.2°$ (*c* = 1.66, THF); ν_{max}: 1745 (s), 1340 (m), 1235 (s), 1170 (m), 1120 (w), 1075 (sh), 1050 (m), 970 (w), 930 (m), 850 (w), 750 (w), 720 (m) cm^{-1}; ^{1}H-NMR δ (CCl_4): 0.87 (3H, deformed t, J = 6 Hz), 1.05–1.60 (~18H, m, a singlet at δ 1.25), 1.60–2.10 (4H, m), 2.20–2.55 (2H, m), ~4.20 (1H, m). (Found: C, 75.27; H, 11.68. Calc for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89%.)

(b) (R)-*Isomer*. In the same manner as above, 1.08 g of (*R*)-**7b** yielded 1.01 g (quantitative) of crude (*R*)-**1**, which was recrystallized from n-hexane to give 588 mg (54.4%) of pure (*R*)-**1** as leaflets, m.p. 37°, $[\alpha]_D^{21.5} + 40.2°$ (*c* = 1.76, THF). (Found: C, 75.47; H, 11.81. Calc for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89%.) The IR and NMR spectra were identical with those of (*S*)-**1**.

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