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SYNTHESIS OF BOTH THE ENANTIOMERS OF *ERYTHRO*-6-ACETOXY-5-HEXADECANOLIDE

THE MAJOR COMPONENT OF A MOSQUITO OVIPOSITION ATTRACTANT PHEROMONE†

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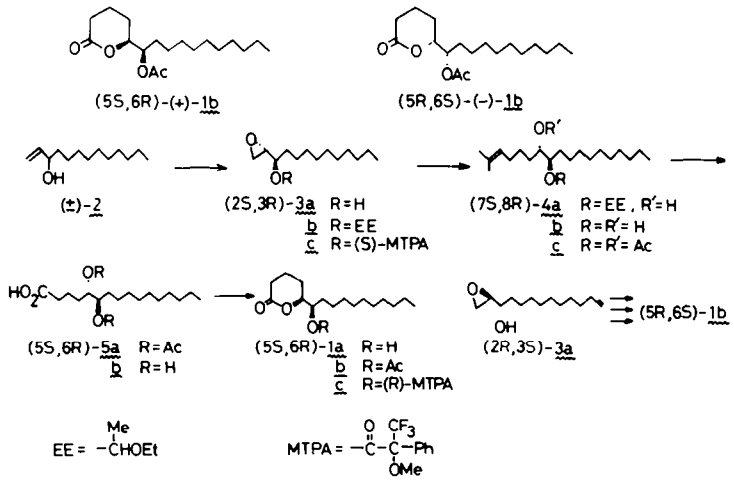
Abstract—Both (5*S*, 6*R*)-(+)- and (5*R*, 6*S*)-(−)-6-acetoxy-5-hexadecanolide, the oviposition attractant pheromone of the mosquito *Culex pipiens fatigans*, were synthesized employing the Sharpless asymmetric epoxidation as the starting step.

The major component of the oviposition attractant pheromone from the apical droplet of eggs of the mosquito *Culex pipiens fatigans* was shown to be *erythro*-6-acetoxy-5-hexadecanolide **1b** by Laurence and Pickett.[1] Their synthetic racemate **1b** was active as the attractant. The absolute configuration of the natural pheromone, however, remained unknown. In collaboration with Dr. John A. Pickett, we initiated attempts to solve this stereochemical problem. The first stage of our effort was a synthesis of both (5*S*, 6*R*)-(+)- and (5*R*, 6*S*)-(−)-**1b** so as to clarify the stereochemistry-pheromone activity relationship. Herein we report the successful account of our synthesis as shown in the Scheme.

The first step of the synthesis was the kinetic resolution of (±)-1-tridecen-3-ol **2** by enantioselective epoxidation using diisopropyl tartrate according to the procedure of Sharpless, *et al.*[2] Employing diisopropyl D-tartrate as the chiral source and interrupting the reaction after 17 hr at −20° in the presence of t-BuOOH and $Ti(i\text{-}PrO)_4$, an optically active epoxy alcohol (2*S*, 3*R*)-**3a**, m.p. 25 ~ 26°, $[\alpha]_D^{20}$ − 16.6° ($CHCl_3$), was obtained in 55.7% yield. The optical purity of (2*S*, 3*R*)-**3a** could be estimated by the HPLC analysis of the corresponding (*S*)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester[3]) **3c**. Several batches of (2*S*, 3*R*)-**3a** with 91 ~ 94.5% e.e. were combined and treated with ethyl vinyl ether and *p*-TsOH to give **3b** in 85% yield. A Grignard reagent prepared from 4-methyl-3-pentenyl bromide was added to the epoxide **3b** in the presence of Cu_2Br_2[4] to effect the C-chain elongation yielding (7*S*, 8*R*)-**4a** in 94.5% yield. The removal of the ethoxyethyl (EE) protective group with acid gave a crystalline diol (7*S*, 8*R*)-**4b**, m.p. 87 ~ 88°, in 94.4% yield. The corresponding diacetate **4c** was oxidized to an acid (5*S*, 6*R*)-**5a** in 96.6% yield by the Sharpless' modification of the catalytic RuO_4 oxidation.[5] The crude diacetoxy acid **5a** was treated with K_2CO_3–MeOH to give a crystalline dihydroxy acid (5*S*, 6*R*)-**5b**, m.p. 135 ~ 138°. Upon heating at 160° for 20 min, the acid **5b** lactonized to give a δ-lactone (5*S*, 6*R*)-**1a**, m.p. 66.5 ~ 68°, $[\alpha]_D^{20}$ + 12.7° ($CHCl_3$). The optical purity of the recrystallized lactone **1a** was determined by the 400 MHz ^{1}H-NMR analysis of the (*R*)-MTPA ester **1c** of the hydroxy lactone **1a** to be 100%. At 400 MHz, the difference between the chemical shift of the OMe signal

†Pheromone Synthesis-59. Part 58, T. Uematsu, T. Umemura and K. Mori, *Agric. Biol. Chem.* **47**, 597 (1983). The experimental part of this work was taken from the M.Sc. Thesis of T.O. (March 1983).



Scheme 1.

of **1c** (δ 3.508) and that of its diastereomer (δ 3.570) was large enough to allow us to determine the optical purity of **1a** without recourse to the NMR shift reagent. It should also be mentioned that the recrystallized lactone (5*S*, 6*R*)-**1a** was entirely free of its *threo*-isomer as judged by its 400 MHz ^{1}H-NMR spectrum. Acetylation of the recrystallized lactone **1a** gave the final product (5*S*, 6*R*)-**1b**, $[\alpha]_D^{21.5}$ + 38.8° ($CHCl_3$). Alternatively, the treatment of (5*S*, 6*R*)-**5b** with Ac_2O–C_5H_5N gave directly (5*S*, 6*R*)-6-acetoxy-5-hexadecanolide **1b**, $[\alpha]_D^{21}$ + 38.4° ($CHCl_3$). However, the sample prepared by the latter procedure contained about 7% of its *threo*-isomer as revealed by the 400 MHz ^{1}H-NMR analysis. The acid (5*S*, 6*R*)-**5b** was therefore of 93% purity with regard to the *erythro-threo* isomerism. This means that the Sharpless epoxidation was at most 93% *erythro*-selective in the present case. The attempts to determine directly the *erythro-threo* ratio of **3a** were unsuccessful.

In the same manner as above, starting from the (2*R*, 3*S*)-epoxide **3a**, the hydroxy lactone (5*R*, 6*S*)-**1a**, m.p. 67 ~ 68°, $[\alpha]_D^{20}$ − 12.5° ($CHCl_3$), was obtained. Its optical purity, as determined by the NMR analysis of the corresponding (*R*)-MTPA ester, was 98%. Acetylation of the recrystallized lactone yielded the acetoxy lactone (5*R*, 6*S*)-**1b**, $[\alpha]_D^{21.5}$ − 38.5° ($CHCl_3$), free of its *threo*-isomer. Alternatively, a larger scale preparation of (5*R*, 6*S*)-**1b** by direct acetylation of (5*R*, 6*S*)-**5b** with Ac_2O–C_5H_5N gave (5*R*, 6*S*)-**1b**, $[\alpha]_D^{21}$ − 36.2° ($CHCl_3$), contaminated with 14 ~ 15% of its *threo*-isomer as revealed by the 400 MHz ^{1}H-NMR analysis. Comparison of the MS of our synthetic enantiomers of **1b** with those of the natural and racemic **1b** confirmed the mutual identity.

In conclusion, we synthesized both the enantiomers of *erythro*-6-acetoxy-5-hexadecanolide **1b** by a short and stereoselective route. The bioassay of our materials is now under way in England by Dr. Pickett *et al.* After the completion of the present synthesis, we became aware of a preliminary communication of Fuganti *et al.*[6] reporting a lengthy and non-stereoselective synthesis of both (5*S*, 6*R*)- and (5*R*, 6*S*)-**1b**.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were determined as films for oils and as nujol mulls for crystals 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. HPLC analyses were performed on a Shimadzu LC-2 chromatograph.

1,2-*Epoxy*-3-*tridecanol* **3a**

(a) (2*S*, 3*R*)-*Isomer.* Ti(i-PrO)$_4$ (14.9 ml) and diisopropyl D-(−)-tartrate (12.5 ml) were added to stirred and cooled dry CH_2Cl_2 (500 ml) at − 23° (dry-ice and CCl_4) under Ar. This was stirred for 5 min. Subsequently (±)-**2** (9.92 g) and t-BuOOH in CH_2Cl_2 (7.32 M, 13.7 ml) were added to the stirred and cooled mixture. After the addition, the mixture was left to stand for 17 hr at − 20° in a deep-freezer. The flask was then cooled again at − 23° with stirring. To the stirred and cooled mixture was added 10% L-(+)-tartaric acid in H_2O (125 ml). The stirring was continued for 30 min at − 23° and for 1.5 hr at room temp. The organic soln was separated, washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was diluted with ether (375 ml) and cooled at 0 ~ 5° with stirring. This was mixed with N-NaOH (150 ml) and the mixture was stirred for 30 min at 0 ~ 5°. The ether soln was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2) and distillation to give 2.99 g (55.7%) of (2*S*, 3*R*)-**3a**, b.p. 112 ~ 113°/0.35 mm; m.p. 25 ~ 26°; $[\alpha]_D^{20}$ − 16.6° (c = 1.12, $CHCl_3$); ω_{max} 3400 (s), 1065 (m), 850 (m), 835 (m) cm^{-1}; δ ($CDCl_3$) 0.89 (3H, deformed t, *J* = 7 Hz), 1.0 ~ 1.7 (18H, br), 2.02 (1H, br), 2.60 ~ 3.08 (3H, m), 3.80 (1H, m). (Found: C, 72.78; H, 12.22. Calc for $C_{13}H_{26}O_2$: C, 72.84; H, 12.23%.)

(b) (2*R*, 3*S*)-*Isomer.* In the same manner as above but employing diisopropyl L-(+)-tartrate, (±)-**2** (9.92 g) yielded 2.70 g (50.2%) of (2*R*, 3*S*)-**3a**, b.p. 109 ~ 110°/0.25 mm; m.p. 25 ~ 26°; $[\alpha]_D^{20}$ + 16.2° (c = 1.01, $CHCl_3$). (Found: C, 72.79; H, 12.20. Calc for $C_{13}H_{26}O_2$: C, 72.84; H, 12.23%.)

Determination of the optical purity of **3a**

(a) (2*S*, 3*R*)-*Isomer.* A sample of (2*S*, 3*R*)-**3a**, $[\alpha]_D^{20}$ − 16.1° (*c* = 2.48, $CHCl_3$), was converted to **3c** in the usual manner.[3] HPLC analysis of **3c** (Column, Partisil 5, 25 cm × 4.6 mm; Solvent, n-hexane: $ClCH_2CH_2Cl$ = 2 : 1; 30 kg/cm^2; Detection at 217 nm) revealed that the optical purity of this sample was 92.1%. Rt of (2*S*, 3*R*)-**3a**-(*S*)-MTPA ester: 29.2 min; R_t of (2*R*, 3*S*)-**3a**-(*S*)-MTPA ester: 25.2 min.

(b) (2*R*, 3*S*) - *Isomer.* Under the same condition as above, a sample of (2*R*, 3*S*)-**3a**, $[\alpha]_D^{20}$ + 15.7° (*c* = 2.09, $CHCl_3$), was converted to the (S)-MTPA ester, which was analyzed by HPLC and shown to be of 86.6% e.e. Only those batches of **3a** with 91 ~ 94.5% e.e. were employed for the next step.

1,2-*Epoxy*-3-*tridecanol EE ether* **3b**

(a) (2*S*, 3*R*)-*Isomer.* Ethyl vinyl ether (13 ml) and *p*-TsOH (30 mg) were added to a stirred and ice-cooled soln of (2*S*, 3*R*)-**3a** (2.99 g) in dry ether (4 ml). The stirring was continued for 4 hr at 0 ~ 5° and for 1 hr at room temp. The mixture was washed with $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2) and distillation to give 3.68 g (85.1%) of (2*S*, 3*R*)-**3b**, b.p. 107 ~ 112°/0.35 mm; $n_D^{21.5}$ 1.4359; ν_{max} 1130 (m), 1090 (m), 1060 (m) cm^{-1}; δ (CCl_4) 2.5 ~ 2.8 (3H, m), 3.0 ~ 3.7 (3H, m), 4.62 (1H, m). (Found: C, 71.58; H, 12.06. Calc for $C_{17}H_{34}O_3$: C, 71.28; H, 11.96%.)

(b) (2*R*, 3*S*)-*Isomer.* In the same manner as above 2.70 g, of (2*R*, 3*S*)-**3a** gave 3.33 g (85.3%) of (2*R*, 3*S*)-**3b**, b.p. 107 ~ 112°/0.35 mm; $n_D^{21.5}$ 1.4359. (Found: C, 71.29; H, 12.14. Calc for $C_{17}H_{34}O_3$: C, 71.28; H, 11.96%.)

2-*Methyl*-2-*octadecene*-7,8-*diol* 8-*EE ether* **4a**

(a) (7*S*, 8*R*)-*Isomer.* A soln of $Me_2C{=}CH(CH_2)_2MgBr$ in dry THF (1.23 M, 33 ml) was added dropwise to a stirred and cooled (dry-ice and diethyl ketone) suspension of Cu_2Br_2 (550 mg) in dry THF (8 ml) at − 30° under Ar. The stirring was continued for 10 min. A soln of (2*S*, 3*R*)-**3b** (3.68 g) in dry THF (5 ml) was added dropwise to the stirred and cooled mixture at − 30°. The stirring was continued overnight with gradual raise of the temp to 0°. The mixture was poured into sat NH_4Cl soln (150 ml) and extracted with n-hexane (600 ml). The extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2) to give 4.47 g (94.5%) of (7*S*, 8*R*)-**4a**. This was directly employed for the next step without further characterization.

(c) (7*R*, 8*S*)-*Isomer.* In the same manner as above, (2*R*, 3*S*)-**3b** (3.33 g) yielded 4.16 g (96.4%) of (7*R*, 8*S*)-**4a**.

2-*Methyl*-2-*octadecene*-7,8-*diol* **4b**

(a) (7*S*, 8*R*) *Isomer.* A soln of (7*S*, 8*R*)-**4a** (44.7 g) in THF (20 ml) and 0.5 N HCl (4 ml) was stirred for 1 hr at 0° and for 1 hr at room temp. The soln was then neutralized with sat $NaHCO_3$ aq and extracted with ether. The ether soln was dired ($MgSO_4$) and concentrated *in vacuo* to give 3.40 g (94.4%) of (7*S*, 8*R*)-**4b** as crystals. An analytical sample was recrystallized from *n*-hexane, m.p. 87 ~ 88°, $[\alpha]_D^{21.5}$ − 1.07° (*c* = 0.80, $CHCl_3$); ν_{max} 3320 (s), 3230 (s), 1070 (s) cm^{-1}; δ (100 MHz, $CDCl_3$) 0.84 (3H, deformed t, *J* = 7 Hz), 1.0 ~ 1.5 (~ 22 H), 1.56 (3 H, s), 1.60 (3H, s), 1.7 ~ 2.3 (2H), 1.96 (2H, s), 3.40 (2H, m), 4.85 (1H, m); MS: *m/z* 298.2890 (Calc for $C_{19}H_{38}O_2$: 298.2872).

(b) (7*R*, 8*S*)-*Isomer.* In the same manner as above, (7*R*, 8*S*)-**4a** (4.16 g) gave 3.28 g (97.9%) of (7*R*, 8*S*)-**4b**, m.p. 87 ~ 88°; $[\alpha]_D^{21.5}$

+1.08° (c = 1.02, $CHCl_3$); MS: m/z 298.2838 (Calc for $C_{19}H_{38}O_2$: 298.2872).

2-*Methyl*-2-*octadecene*-7,8-*diol diacetate* **4c**

(a) (7*S*, 8*R*)-Isomer. Ac_2O (8 ml) was added to a stirred soln of (7*S*, 8*R*)-**4b** (3.21 g) in C_5H_5N (25 ml). After stirring for 4 hr at room temp, 4-N,N-dimethylaminopyridine (DMAP, a trace amount) was added to the mixture and the stirring was continued for 30 min. The mixture was then diluted with ether (200 ml), washed with N HCl soln, $CuSO_4$ soln, sat $NaHCO_3$ soln, water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (SiO_2) and distillation to give 2.28 g (55.5%) of (7*S*, 8*R*)-**4c**, b.p. 142 ~ 145°/0.08 mm; $n_D^{21.5}$ 1.4479; $[\alpha]_D^{21.5}$ − 1.26° (c = 1.19, $CHCl_3$); ν_{max} 1743 (s), 1368 (m), 1242 (s), 1225 (s), 1020 (m) cm^{-1}; δ (CCl_4) 0.88 (3H, deformed t, J = 7 Hz), 1.1 ~ 1.5 (~ 22H), 1.58 (3H, s), 1.66 (3H, s), 1.98 (6H, s), 1.85 ~ 2.20 (2H), 4.7 ~ 5.3 (3H, m). (Found: C, 72.38; H, 11.16. Calc for $C_{23}H_{42}O_4$: C, 72.20; H, 11.07%.)

(b) (7*R*, 8*S*)-*Isomer*. In the same manner as above (7*R*, 8*S*)-**4b** (3.21 g) gave 2.93 g (71%) of (7*R*, 8*S*)-**4c**, b.p. 144 ~ 146°/0.12 mm; $n_D^{21.1}$ 1.4477; $[\alpha]_D^{20.8}$ − 1.28° (c = 1.09, $CHCl_3$). (Found: C, 72.34; H, 11.10. Calc for $C_{23}H_{42}O_4$: C, 72.20; H, 11.07%.)

5,6-*Diacetoxyhexadecanoic acid* **5a**

(a) (5*S*, 6*R*)-*Isomer*. To a mixture of (7*S*, 8*R*)-**4c** (1.16 g) and $NaIO_4$ (2.63 g) in CCl_4 (6 ml)-MeCN (6 ml)-H_2O (9 ml) was added $RuCl_3 \cdot (H_2O)_n$ (16 mg) with vigorous stirring. The stirring was continued for 4.5 hr. The mixture was then diluted with CH_2Cl_2 (40 ml) and H_2O (15 ml). The organic layer was separated and the aq layer was extracted with CH_2Cl_2. The combined organic soln was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was diluted with ether (60 ml) and filtered through Celite. The ether soln was dried ($MgSO_4$) and concentrated *in vacuo* to give a dark and oily (5*S*, 6*R*)-**5a** (1.09 g, 96.6%). This was employed for the next step without further purification.

(b) (5*R*, 6*S*)-*Isomer*. In the same manner as above, (7*R*, 8*S*)-**4c** (1.15 g) gave 1.09 g (97.3%) of (5*R*, 6*S*)-**5a**.

5,6-*Dihydroxyhexadecanoic acid* **5b**.

(a) (5*S*, 6*R*)-*Isomer*. K_2CO_3 (1.0 g) was added to a soln of (5*S*, 6*R*)-**5a** (1.09 g) in MeOH (15 ml). The mixture was stirred for 2 hr at room temp, diluted with H_2O (100 ml), acidified with N HCl to pH 2 and extracted with ether. The ether soln was dried ($MgSO_4$) and concentrated *in vacuo* to give 950 mg (quantitative) of (5*S*, 6*R*)-**5b** as a solid. A portion (500 mg) of it was recrystallized twice from EtOH-pet. ether to give 169.4 mg of pure (5*S*, 6*R*)-**5b**, m.p. 135 ~ 138°; $[\alpha]_D^{20}$ + 2.36° (c = 0.51, MeOH); ν_{max} 3260 (s), 3160 (s), 1710 (s), 1695 (s), 1070 (s), 1035 (m), 935 (m) cm^{-1}; δ (C_5D_5N) 0.86 (3H, deformed *t*, J = 7 Hz), 3.90 (2H, br), 8.20 (3H, br). (Found: C, 66.83; H, 11.03. Calc for $C_{16}H_{32}O_4$: C, 66.63; H, 11.18%.)

(b) (5*R*, 6*S*)-*Isomer*. In the same manner as described above, 1.09 g of (5*R*, 6*S*)-**5a** gave 860 mg (quantitative) of crude (5*R*, 6*S*)-**5b**. A portion (500 mg) of it was recrystallized twice to give 140.3 mg of (5*R*, 6*S*)-**5b** as plates, m.p. 136.5 ~ 138°; $[\alpha]_D^{20}$ − 2.39° (c = 0.55, MeOH). (Found: C, 66.65; H, 11.33. Calc for $C_{16}H_{32}O_4$: C, 66.63; H, 11.18%.)

erythro-6-*Hydroxy*-5-*hexadecanolide* **1a**

(a) (5*S*, 6*R*)-*Isomer*. (5*S*, 6*R*)-**5b** (34.6 mg) was heated at 160° for 20 min under reduced pressure. The residue was purified by prep TLC to give 28.3 mg (87.3%) of (5*S*, 6*R*)-**1a**. This crude lactone (39.1 mg) was recrystallized from n-hexane to give 28.3 mg of pure (5*S*, 6*R*)-**1a**, m.p. 66.5 ~ 68°; $[\alpha]_D^{20}$ + 12.7° (c = 0.96, $CHCl_3$); ν_{max} (KBr) 3440 (m), 2920 (s), 2850 (m), 1715 (s), 1265 (m), 1055 (m) cm^{-1}; δ (400 MHz, $CDCl_3$) 0.88 (3H, t, J = 7 Hz), 1.26 (16H, br s), 1.42 ~ 1.56 (2H, m), 1.73 ~ 1.90 (3H, m), 1.94 ~ 2.01 (1H, m), 2.03 (1H, d, J = 6 Hz), 2.40 ~ 2.50 (1H, m), 2.57 ~ 2.66 (1H, m), 3.82 (1H, m), 4.25 (1H, dt, J_1 = 12, J_2 = 8 Hz). (Found: C, 71.33; H, 11.08. Calc for $C_{16}H_{30}O_3$; C, 71.07; H, 11.18%.)

(b) (5*R*, 6*S*)-*Isomer*. In the same manner as above, (5*R*, 6*S*)-**5b** (26.5 mg) gave 24.9 mg (~ 100%) of (5*R*, 6*S*)-**1a**, m.p. 67 ~ 68°; $[\alpha]_D^{20}$ − 12.5° (c = 0.54, $CHCl_3$). (Found: C, 70.86; H, 11.02. Calc. for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18%.)

Determination of the optical purity of **1a**

(a) (5S, 6R)-*Isomer*. (5*S*, 6*R*)-**1a** was converted to the corresponding (*R*)-MTPA ester **1c** in the usual manner.[3] Its NMR spectrum was measured at 400 MHz. This proved the absence of the (*R*)-MTPA ester of (5*R*, 6*S*)-**1a**: δ (400 MHz, $CDCl_3$) 0.89 (3H, t, J = 7 Hz), ~ 1.25 (16H, br.), 1.51 ~ 1.96 (6H, m), 2.31 (1H, dq, J_1 = 14, J_2 = 8 Hz), 2.54 ~ 2.63 (1H, m), 3.508 (3H, s, OMe), 4.45 (1H, dt, J_1 = 14, J_2 = 5 Hz), 5.32 (1H, m), 7.40 (3H, m), 7.54 (2H, m).

(b)(5R, 6S)-*Isomer*. (5*R*, 6*S*)-**1a** was converted to the corresponding (*R*)-MTPA ester **1c**: δ (400 MHz, $CDCl_3$) 0.885 (3H, t, J = 7 Hz), ~ 1.25 (16H, br), 1.45 ~ 1.90 (6H, m), 2.20 (1H, dq, J_1 = 14, J_2 = 8 Hz) 2.47 ~ 2.56 (1H, m), 3.508 (0.03H, s, -OMe), 3.570 (2.97H, s, -OMe), 4.35 (1H, dt, J_1 = 14, J_2 = 5 Hz), 5.35 (1H, dt, J_1 = J_2 = 5 Hz), 7.39 (3H, m), 7.54 (2H, m). The optical purity of (5*R*, 6*S*)-**1a** was thus estimated to be ~ 98%.

erythro-6-*Acetoxy*-5-*hexadecanolide* **1b**

(a) (5S, 6R)-*Isomer*. The recrystallized lactone (5*S*, 6*R*)-**1a** (34 mg) was mixed with Ac_2O (0.1 ml) and C_5H_5N (1 ml). The soln was left to stand overnight at room temp. The conventional work-up gave 35.5 mg (90%) of (5*S*, 6*R*)-**1b**, $[\alpha]_D^{21.5}$ + 38.8° (c = 1.21, $CHCl_3$). Alternatively, Ac_2O (0.65 ml) was added to a soln of (5*S*, 6*R*)-**5b** (55.0 mg) in C_5H_5N (3.1 ml) with stirring at 0 ~ 5°. The stirring was continued for 3 hr. The mixture was then diluted with ether (20 ml). The ether soln was washed with 2N HCl, H_2O, $CuSO_4$ soln, H_2O, sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by prep TLC to give 43.4 mg (80.1%) of (5*S*, 6*R*)-**1b**, $[\alpha]_D^{21}$ + 38.4° (c = 1.41, $CHCl_3$); ν_{max} 2930 (s), 2850 (m), 1745 (vs), 1460 (w), 1370 (m), 1225 (s), 1190 (w), 1160 (w), 1050 (m), 1015 (w), 950 (w), 925 (w) cm^{-1}; δ (400 MHz, $CDCl_3$) 0.88 (3H, t, J = 7 Hz), 1.26 (16H, br. s), 1.58 ~ 1.70 (3H, m), 1.75 ~ 1.88 (1H, m), 1.88 ~ 2.01 (2H, m), 2.08 (3H, s), 2.40 ~ 2.50 (1H, m), 2.56 ~ 2.65 (1H, m), 3.69 (0.07H, m), 4.35 (0.93H, m), 4.86 (0.07H, m), 4.95 ~ 5.01 (0.93H, m). This sample was thus shown to contain 7% of the *threo*-isomer of **1b**. (Found: C, 69.02; H, 10.30. Calc for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32%.)

(b) (5R, 6S)-*Isomer*. In the same manner as described above 19.2 mg of the recrystallized (5*R*, 6*S*)-**1a** was treated with Ac_2O (0.1 ml) and C_5H_5N (1 ml). The work-up gave 16.4 mg (72%) of (5*R*, 6*S*)-**1b**, $[\alpha]_D^{21.5}$ − 38.5° (c = 0.51, $CHCl_3$). Alternatively 50 mg of (5*R*, 6*S*)-**5b** gave 49.7 mg (83.4%) of (5*R*, 6*S*)-**1b**, $[\alpha]_D^{21}$ − 36.2° (c = 1.39, $CHCl_3$). This sample contained 14 ~ 15% of the *threo*-isomer as revealed by its 400 MHz NMR spectrum: δ (400 MHz, $CDCl_3$) 3.69 (0.15H, m), 4.32 ~ 4.39 (0.85H, m), 4.86 (0.14H, m), 4.95 ~ 5.01 (0.86H, m). (Found: C, 69.34; H, 10.17. Calc for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32%.) The samples of **1b** prepared from **1a** were free of the *threo*-isomers and employed for the final bioassay.

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