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SYNTHESIS OF MEVALONOLACTONE (HIOCHIC ACID LACTONE) EMPLOYING ASYMMETRIC EPOXIDATION AS THE KEY-STEP†

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Abstract—(*R*)-(−)-Mevalonolactone (hiochic acid lactone) of 91–93% e.e. was synthesized from an achiral starting material employing the Sharpless asymmetric epoxidation as the key-step.

Mevalonolactone **1** was isolated from distiller's solubles as an acetate-replacing factor for *Lactobacilli* and identified by degradation and synthesis as 3-hydroxy-3-methyl-5-pentanolide **1** by Folkers *et al.*[1,2] Quite independently at the same time, Tamura isolated from the broth of *Aspergillus oryzae* a growth factor for true hiochi bacteria, *Lactobacillus homohiochi* and *L. heterohiochi*.[3] He named it hiochic acid lactone and proposed **2** as its most probable structure.[3] Later Tamura revised the structure from **2** to **1** by synthesizing **1**.[4] The identity of hiochic acid lactone with mevalonolactone was confirmed on the basis of identical IR spectra and biological activities.[5] Subsequently Arigoni determined the absolute configuration of mevalonolactone **1** as *R* by correlation with quinic acid.[6]

Because of the key-role of mevalonolactone in isoprenoid biosynthesis,[2] a number of chiral syntheses of (*R*)-**1** has been reported.[6–12] Herein we report a new synthesis of (*R*)-(−)-mevalonolactone **1** employing the Sharpless asymmetric epoxidation[13] as the key-step (**5** → **6a**) to introduce the chirality at C-3.

Our synthesis started from a chloroalcohol **3**,[14] whose coupling with a Grignard reagent **4** yielded an allylic alcohol **5** in 88.3% yield. This was oxidized with t-BuOOH in the presence of $Ti(Oi\text{-}Pr)_4$ and diethyl L-(+)-tartrate in CH_2Cl_2[13] to give an epoxy alcohol (2*S*,3*S*)-**6a**, $[\alpha]_D^{21.5} - 0.99°$ ($CHCl_3$), in 67.8% yield. The corresponding (*S*)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester)[15] **6b** was analyzed by HPLC to determine the diastereomeric ratio as 97.6 : 2.4. The optical purity of **6a** was therefore deduced to be 95.2%. Reduction of **6a** with LAH yielded a diol **7a**, whose acetylation gave **7b**. Ozonolysis of **7b** was followed by oxidative workup with the Jones CrO_3 to give an acid **8**. This was hydrolyzed and lactonized to yield (*R*)-(−)-mevalonolactone **1**, $[\alpha]_D^{18.5} - 18.8°$ (EtOH) [lit.[3] $[\alpha]_D^{20} - 19.9°$ (EtOH)]. Its IR spectrum was identical with the published spectrum[3] of (*R*)-**1**. The overall yield of (*R*)-**1** from **3** was 38.7% in six steps.

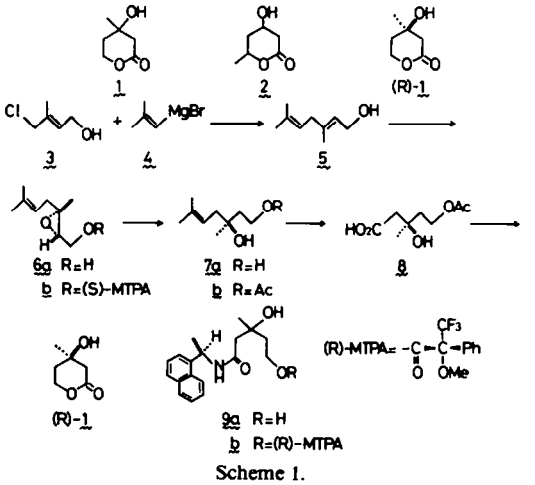
The optical purity of our (*R*)-**1** was estimated by the method of Bergot *et al.*[16] as follows. Treatment of (*R*)-**1** with (*R*)-(+)-1-(1'-naphthyl)ethylamine gave **9a**, which was acylated with MTPA chloride to give **9b**. This was analyzed by HPLC showing the diastereomeric ratio of 90.9 : 9.1. The optical purity of (*R*)-**1** was therefore 81.8%. The NMR measurement of **9b** at 400 MHz indicated its diastereomeric purity to be 92.5% [(*R*)-**1** was therefore estimated to be of 85.0% e.e.] in gross agreement with the value obtained by the HPLC analysis. The observed optical purity (81.8–85.0%) of (*R*)-**1** means that partial racemization took place during the synthetic sequence by the retro Michael–Michael process at C-3.

So as to provide a sample of (*R*)-**1** with higher optical purity, we purified it *via* its quinine salt as described by Tamura.[3,17] The recrystallized quinine salt, m.p. 137.0–137.5° (lit.[3,17] m.p. 137–138°), $[\alpha]_D^{20.5} - 111.3°$ ($CHCl_3$), was treated with acid to give (*R*)-**1**, $[\alpha]_D^{20} - 20.9°$ (EtOH). The HPLC and 400 MHz ^{1}H-NMR analyses of the corresponding **9b** revealed the purified (*R*)-**1** to be of 91–93% e.e.

In conclusion we achieved an asymmetric synthesis of the natural enantiomer of mevalonolactone (hiochic acid lactone) in only six steps from readily available starting materials.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra refer to films for oils and nujol mulls for solids and were measured on a Jasco A-102 spectrometer. NMR spectra were recorded at 60 MHz



Scheme 1.

† This paper is cordially dedicated to Professor Gakuzo Tamura, the discoverer of hiochic acid, on the occasion of his 60th birthday on August 20, 1984. Synthetic Microbial Chemistry—VI. Part V, K. Mori, T. Otsuka and M. Oda, *Tetrahedron* **40**, 2929 (1984).

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with TMS as an internal standard on a Hitachi R-24A spectrometer. Optical rotations were measured on a Jasco DIP-140 polarimeter. GLC analyses were performed on a Jeol-20K or Hitachi 163 gas chromatograph.

(E)-3,6-*Dimethyl*-2,5-*heptadien*-1-*ol* **5**

The Grignard reagent **4** was prepared from 1-bromo-2-methylpropene (13.5 g) and Mg (4.83 g) in THF (30 ml) under Ar. The soln was cooled below −50° and diluted with ether (35 ml). CuI (1.6 g) was added to the soln to give a brown viscous mixture. To this was added dropwise a soln of **3** (3.92 g) in ether (25 ml) with stirring and cooling at −50°. The stirring was continued for 2 hr at < −50°. The mixture was left to stand overnight with gradual rise of the reaction temp to room temp. The black reaction mixture was cooled with an ice-bath, quenched with NH_4Cl aq, and extracted with ether. The ether soln was washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by SiO_2 chromatography and distillation to give 4.22 g (88.3%) of **5**, b.p. 88–89°/6 mm, n_D^{24} 1.4698; ν_{max}: 3400 (s), 1680 (m), 1000 (s) cm^{-1}; ^{1}H-NMR δ (CCl_4): 1.62 (6H, s), 1.70 (3H, s), 2.65 (2H, d, J = 7 Hz), ~2.80 (1H, br), 4.00 (2H, d, J = 8 Hz), 4.95–5.55 (2H, m); GLC (Column, 5% PEG 20M, 2 m × 2 mm at 145°; Carrier gas, N_2) R_t 4.2 min [3.9%, (*Z*)-isomer], 4.9 min [96.1%, (*E*)-isomer]; MS: *m/z* 140 (M^+), 122 ($M^+ - 18$).

(2S,3S)-(−)-2,3-*Epoxy*-3,6-*dimethyl*-5-*hepten*-1-*ol* **6a**

Ti(Oi-Pr)$_4$ (38.2 ml) and diethyl L-(+)-tartrate (22 ml) were added to the stirred and cooled dry CH_2Cl_2 (500 ml) at −40° to −30° under Ar. The stirring was continued for 5 min. To the mixture were added **5** (9 g) and t-BuOOH (7.32 N, 17.5 ml) and the stirring was continued overnight at < −20°. It was then diluted with ether (400 ml). Sat Na_2SO_4 aq (18 ml) was added to the mixture and the vigorous stirring was continued for 2 hr gradually raising the inner temp to room temp, when the mixture turned to be a viscous mass. This was filtered through Celite. The filter cake was washed several times with ether. The combined ether soln was concentrated *in vacuo* below 30°. The residue was dissolved in ether (500 ml). To the ice-cooled and stirred ether soln was added 10% NaOH aq (180 ml) at 0–5°. The stirring was continued for 30 min. The ether layer was separated, washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over SiO_2. Elution with pentane–EtOAc gave **6a**. This was distilled to give 6.8 g (67.8%) of pure **6a**, b.p. 83–85°/0.5 mm, n_D^{22} 1.4596; $[\alpha]_D^{21.5}$ −0.99° (*c* = 10.1, $CHCl_3$); ν_{max}: 3460 (s), 1660 (w), 1080 (m), 1030 (s), 865 (m) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$ + D_2O): 1.27 (3H, s), 1.62 (3H, s), 1.72 (3H, s), 2.26 (2H, d, J = 7 Hz), 2.98 (1H, t, J = 5 Hz), 3.60–3.90 (2H, m), 5.17 (1H, t, J = 7 Hz); ^{13}C-NMR δ (25 MHz, $CDCl_3$): 17.0, 18.0, 25.8, 36.9, 61.3, 61.5, 62.7, 118.5, 134.8. (Found: C, 69.74; H, 10.09. Calc for $C_9H_{16}O_2$: C, 69.19; H, 10.32%.) HPLC analysis of **6b** (Column, Partisil-5, 25 cm × 4.6 mm; Press, 30 kg/cm^2; Eluent, *n*-hexane–$ClCH_2CH_2Cl$, 3:1): R_t 67.2 min (2.4%), 71.7 min (97.6%). Therefore **6a** was of 95.2% e.e.

(S)-(−)-3,6-*Dimethyl*-5-*heptene*-1,3-*diol* **7a**

A soln of **6a** (4.6 g) in dry ether (50 ml) was added dropwise to a stirred and ice-cooled suspension of LAH (1.7 g) in dry ether (400 ml). The stirring was continued overnight at room temp. The excess LAH was destroyed by the successive addition of water (1.7 ml), 15% NaOH aq (3.4 ml) and water (1.7 ml) to the stirred and ice-cooled mixture. After stirring for several hr at room temp, the mixture was filtered and the filter-cake was washed thoroughly with THF. The combined filtrate and washings were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was distilled to give 3.9 g (83.7%) of **7a**, b.p. 83–86°/0.25 mm, $n_D^{20.5}$ 1.4678; $[\alpha]_D^{20.5}$ −2.52° (*c* = 1.11, $CHCl_3$); ν_{max}: 3400 (s), 1680 (w), 1130 (s), 1100 (s), 1060 (s) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 1.21 (3H, s), 1.63 (3H, s), 1.73 (3H, s), 1.70–1.85 (2H, m), 2.22 (2H, d, J = 7 Hz), 2.83 (1H, s, OH), 3.29 (1H, t, J = 6 Hz, OH), 3.85 (2H, dt, J_1 = 6 Hz, J_2 = 6 Hz), 5.20 (1H, t, J = 7 Hz); ^{13}C-NMR δ (25 MHz, $CDCl_3$): 18.0, 26.0, 26.6, 41.1, 41.5, 59.3, 74.0, 119.7, 134.2; MS: *m/z* 158 (M^+), 143 ($M^+ - 15$), 140 ($M^+ - 18$). (Found: C, 68.05; H, 11.32. Calc for $C_9H_{18}O_2$: C, 68.31; H, 11.47%.)

(S)-(−)-3,6-*Dimethyl*-5-*heptene*-1,3-*diol*-1-*acetate* **7b**

Ac_2O (5 ml) was added to a stirred soln of **7a** (3.4 g) in dry C_5H_5N (30 ml). The stirring was continued overnight at room temp. The mixture was poured into ice-cooled dil HCl and extracted with ether. The ether soln was washed with 10% $NaHCO_3$ aq, water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 4.2 g (97%) of **7b**, b.p. 113–114°/6 mm, n_D^{21} 1.4539; $[\alpha]_D^{21.5}$ −3.57° (*c* = 1.15, $CHCl_3$); ν_{max}: 3460 (m), 1750 (s), 1660 (w), 1250 (s), 1035 (m) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 1.20 (3H, s), 1.62 (3H, s), 1.75 (3H, s), 1.70–1.81 (2H, m), 2.05 (3H, s), ~2.00 (1H, OH), 2.20 (2H, d, J = 8 Hz), 4.25 (2H, t, J = 8 Hz), 5.22 (1H, t, J = 8 Hz); ^{13}C-NMR δ (25 MHz, $CDCl_3$): 18.0, 21.0, 26.0, 26.9, 39.7, 41.1, 61.4, 72.0, 119.3, 134.9, 171.8. (Found: C, 65.78; H, 9.95. Calc for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07%.)

(R)-(+)-5-*Acetoxy*-3-*hydroxy*-3-*methylpentanoic acid* **8**

O_3 was bubbled into a stirred and cooled soln of **7b** (3.5 g) in acetone (50 ml) for 3 hr at −60°. Excess O_3 was removed by bubbling N_2 into the soln. Jones CrO_3 (8 N, 6 ml) was added dropwise to the stirred and cooled soln at −60°. The stirring was continued for 1 hr at −60° and then for another 1 hr at 0–5°. The excess CrO_3 was destroyed by the addition of i-PrOH. The acetone soln was separated by decantation. The residue was dissolved by the addition of water and extracted with $CHCl_3$. The combined acetone and $CHCl_3$ soln was dried (Na_2SO_4) and concentrated *in vacuo* to give 3.3 g (quantitative) of **8**, $n_D^{19.5}$ 1.4429; $[\alpha]_D^{19.5}$ +0.20° (*c* = 10.4, $CHCl_3$); ν_{max}: ~3500 (m), ~2600 (w), 1740 (s), 1250 (s), 965 (m), 935 (m) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 1.32 (3H, s), 1.92 (2H, t, J = 7 Hz), 2.55 (2H, s), 4.21 (2H, t, J = 7 Hz), 6.70–7.30 (2H, br, CO_2H and OH). This was employed in the next step without further purification.

(R)-(−)-*Mevalonolactone* **1**

A soln of **8** (3.3 g) in 2 N NaOH aq (80 ml) was stirred overnight at room temp. (This step might have caused partial racemization.) It was then cooled (0–5°), neutralized with 4 N H_2SO_4 aq to pH 6, and extracted with $CHCl_3$ to remove neutral impurities. The aq layer was further acidified to pH 4, stirred for 3 hr at room temp, and extracted with $CHCl_3$ (20 ml × 40) after saturation with NaCl. The $CHCl_3$ soln was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was chromatographed over SiO_2. Elution with *n*-hexane–EtOAc (2:3) gave **1**. This was distilled to give 1.80 g (79.7%) of **1**, b.p. 126–127°/0.18 mm; $[\alpha]_D^{18.5}$ −18.8° (*c* = 1.07, EtOH); ν_{max}: 3500 (s), 3030 (m), 2980 (m), 1740 (vs), 1485 (m), 1410 (s), 1390 (sh), 1350 (w), 1310 (m), 1270 (s), 1240 (s), 1160 (m), 1135 (s), 1075 (s), 1030 (m), 990 (w), 970 (w), 940 (m), 910 (w), 885 (w), 805 (m), 760 (w) cm^{-1}; ^{1}H-NMR δ ($CDCl_3$): 1.37 (3H, s), 1.70–2.05 (2H, m), 2.55 (2H, d, J = 2 Hz), 3.42 (1H, s, OH), 4.10–4.85 (2H, m). This was further purified *via* the quinine salt.

Determination of the optical purity of **1** *by analyzing* **9b**

The above (*R*)-(−)-**1** (50 mg) was stirred and heated with (*R*)-(+)-1-(1'-naphthyl)ethylamine prepared from the corresponding tartrate salt (250 mg) at 70–80° for 3 hr. After cooling, the mixture was dissolved in $CHCl_3$. The $CHCl_3$ soln was washed with dil HCl and water, dried ($MgSO_4$) and concentrated *in vacuo* to give 64 mg (55%) of **9a**, ν_{max} 3320 (s), 1635 (s), 1600 (m), 1540 (s), 800 (s), 775 (s), 730 (s) cm^{-1}. To a soln of the crude **9a** (15 mg) in dry C_5H_5N (1 ml) was added MTPA-Cl (19 mg) prepared from (*R*)-MTPA. After stirring overnight at room temp, the mixture was poured into sat $CuSO_4$ aq and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with sat $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by prep TLC to give **9b** (10 mg); ν_{max}: 3400 (m), 3330 (m), 1745 (s), 1640 (s), 1535 (s), ~1260 (s), 1160 (s), 1120 (s), 1020 (s), 1000 (s), 800 (m), 775 (s), 755 (m), 730 (m), 715 (s), 695 (m) cm^{-1}; 400 MHz

^{1}H-NMR of **9b** derived from (*R*)-**1**, δ($CDCl_3$): 1.15 (3H, s), 1.60 (3H, d, J = 6 Hz), 1.82 (2H, t, J = 6 Hz), 1.89 (1H, d, J = 15 Hz), 2.08 (1H, d, J = 15 Hz), 3.40 (3H, s), 4.35 (1H, dt, J_1 = 10 Hz, J_2 = 6 Hz), 4.45 (1H, dt, J_1 = 10 Hz, J_2 = 6 Hz), 5.77 (1H, d, J = 8 Hz), 5.88 (1H, seemingly quint, J = 8 Hz), 7.20–7.26 (4H, m), 7.42–7.55 (5H, m), 7.80–8.05 (3H, m); 400 MHz ^{1}H-NMR of **9b** derived from (±)-**1** δ ($CDCl_3$): 1.126 and 1.190 (each s, total 3H); ^{1}H-NMR of **9b** derived from the above described (*R*)-**1** showed signals at δ 1.105 and 1.169 in a ratio of 5.5:70.5, which implied that our (*R*)-**1** of 85% e.e.; HPLC analysis of **9b** (Column, Partisil-5, 25 cm × 4.6 mm; Press, 30 kg/cm^2; Eluent: n-hexane–$ClCH_2CH_2Cl$, 3:1) R_t 52 min (9.1%), 60 min (90.9%). The optical purity of (*R*)-**1** was therefore 81.8%.

Further purification of (R)-**1** *via the quinine salt of* (R)-*mevalonic acid*

(a) *Purification of the quinine salt.* A soln of KOH (50 mg) in EtOH (1 ml) was gradually added to a soln of (*R*)-**1** (100 mg) in EtOH (0.5 ml). The addition was stopped immediately after the soln became slightly alkaline. To this was added quinine hydrochloride (0.31 g). The mixture was heated at 40° for 10 min and filtered to remove KCl. The filtrate was concentrated *in vacuo* to remove EtOH and left to stand overnight in a vacuum desiccator. The crystalline mass was dissolved in $CHCl_3$ and separated from insoluble impurities by decantation. The $CHCl_3$ soln was concentrated *in vacuo*. The residue was dissolved in a small amount of $CHCl_3$. To this was added C_6H_6 and the soln was left to stand at room temp to give 0.30 g of the salt, m.p. 136–137°; $[\alpha]_D^{21}$ − 111.0° (*c* = 0.983, $CHCl_3$). Recrystallization of this from $CHCl_3$–C_6H_6 gave 0.27 g of the salt, m.p. 139–140°; $[\alpha]_D^{19}$ − 112.3° (*c* = 0.944, $CHCl_3$). Final recrystallization from $CHCl_3$–C_6H_6 gave 0.24 g of the salt, m.p. 137–137.5°; $[\alpha]_D^{20.5}$ − 111.3° (*c* = 1.091, $CHCl_3$). (Found: C, 65.89; H, 7.30; N, 5.85. Calc for $C_{26}H_{36}O_6N_2$: C, 66.08; H, 7.68; N, 5.93%.)

(b) *Purified* (R)-**1**. The above quinine salt (0.24 g) was dissolved in water (2 ml), and made alkaline with KOH aq to liberate quinine, which was removed by extraction with $CHCl_3$. The aq layer was acidified with 0.33 N HCl to pH 2.2 and extracted with $CHCl_3$–EtOH (9:1; 10 ml × 15). Subsequent workup gave 46 mg (46%) of the purified (*R*)-**1**, $[\alpha]_D^{20}$ − 20.9° (*c* = 1.05, EtOH). Its optical purity was estimated to be 91% by the HPLC analysis of the corresponding **9b**. ^{1}H-NMR analysis (400 MHz) of the corresponding **9b** revealed the optical purity of (*R*)-**1** to be 93%. (Found: C, 55.23; H, 7.85. Calc for $C_6H_{10}O_3$: C, 55.37; H, 7.75%.)

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