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# SYNTHESIS OF ALL OF THE FOUR POSSIBLE STEREOISOMERS OF PESTALOTIN, A GIBBERELLIN SYNERGIST ISOLATED FROM *PESTALOTIA CRYPTOMERIAECOLA* SAWADA†

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**Abstract**—(−)-Pestalotin [(6*S*, 1′*S*)-6-(1′-hydroxypentyl)-4-methoxy-5,6-dihydro-2-pyrone **1a**] and its three other stereoisomers were synthesized either by utilizing the Sharpless asymmetric epoxidation as the keystep or by derivation from D-(+)-glyceraldehyde acetonide.

(−)-Pestalotin **1a** is a gibberellin synergist isolated from culture filtrate of a phytopathogenic fungus *Pestalotia cryptomeriaecola* Sawada by Kimura *et al.*[1,2] Quite independently, Ellestad *et al.* isolated **1a** from unidentified penicillium species and gave a code number LLP-880α.[3] The (6*S*, 1′*S*)-stereochemistry of pestalotin as depicted in **1a** was deduced from its CD[1-4] and induced CD[5] data. As to its synthesis, three groups were successful in preparing (±)-pestalotin.[2,6,7] Optically active forms of pestalotin were also attractive synthetic targets, because of the presence of the two contiguous chiral centers in **1a**. Meyer and Seebach were the first to prepare (−)-pestalotin **1a** and (−)-epipestalotin **2a** by an asymmetric synthesis followed by repeated recrystallization of the products.[8] We then reported, in a preliminary form, a synthesis of (+)-pestalotin **1a′** and (+)-epipestalotin **2a′** starting from D-(+)-glyceraldehyde acetonide.[9] Very recently, Ichimoto *et al.* synthesized (−)-**1a** from D-glucose,[10] while Masaki *et al.* converted L-(+)-tartaric acid into (−)-**1a**.[11] Herein we report in full detail our synthesis of all of the four possible stereoisomers (Fig. 1) of pestalotin.

Our strategy for the pestalotin synthesis was very simple as shown in Fig. 1. As the target molecule **A** posseses two chiral centers, an epoxide **B** with two chiral centers of correct stereochemistry will give stereospecifically the α-pyrone **A**. For the synthesis of **B**, two different methods were employed: one was the derivation from D-(+)-glyceraldehyde acetonide (Fig. 2) and the other was the application of the Sharpless asymmetric epoxidation (Fig. 3).

D-(+)-Glyceraldehyde acetonide **3** is a readily available chiral building block with an asymmetric C atom of (*R*)-configuration.[12,13] Addition of *n*-BuMgBr to **3** gave a diastereomeric mixture of **4a** in 77% yield. This was converted to the corresponding benzyl ether **4b**. Acid hydrolysis of **4b** gave a diastereomeric mixture of a glycol **5a**, which was treated with 1 eq of *p*-TsCl to give **5b**. KOH aq converted **5b** into the key epoxide **6**, $[\alpha]_D^{23}$ − 7.39°($C_6H_6$), as a diastereomeric mixture in 65.6% yield from **4a**. Construction of the α-pyrone ring system was carried out according to Carlson's general method of pyrone synthesis.[14] The epoxide **6** was added to a dianion derived from propiolic acid and $LiNPr_2^i$ yielding an acid **7a**, which was methyl-

†Synthetic Microbial Chemistry-V. Part IV, K. Mori and T. Fujioka, *Tetrahedron* **40**, 2711 (1984). The experimental part of this work was taken from the M.Sc. theses of M. Oda (March, 1977) and T. Otsuka (March, 1983).

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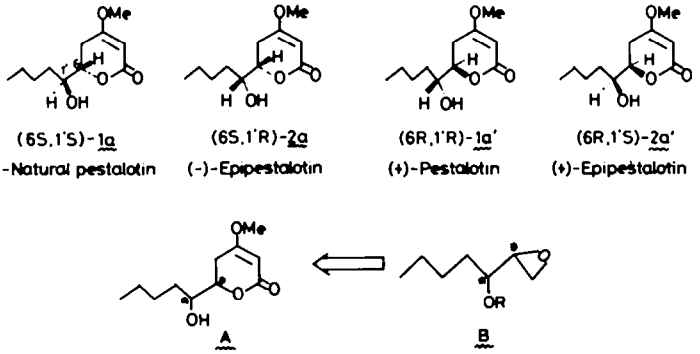


Fig. 1. Structures of the four stereoisomers of pestalotin and the synthetic plan.

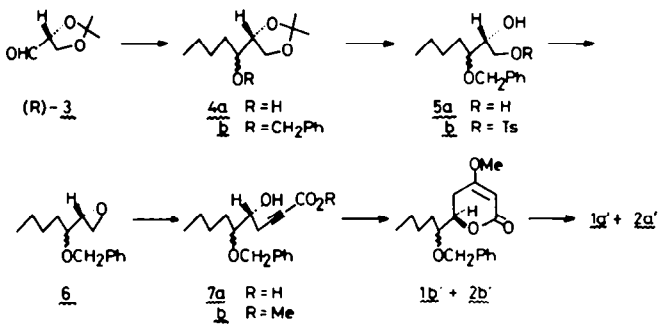

Fig. 2. Synthesis of (+)-pestalotin and (+)-epipestalotin.

ated to **7b** in 41% yield from **6**. Treatment of **7b** with NaOMe–MeOH was followed by acidification to give the lactonized Michael adduct as a diastereomeric mixture of **1b'** and **2b'**. This was hydrogenolyzed with $H_2$/Pd–C to give a mixture of (6*R*, 1'*R*)-**1a'** and (6*R*, 1'*S*)-**2a'**. These were separable by $SiO_2$ chromatography. The more readily eluted fractions gave (6*R*, 1'*R*)-(+)-pestalotin **1a'**, m.p. 83.0 ~ 84.5°, $[\alpha]_D^{21}$ + 75.9° (MeOH), while the later fractions gave (6*R*, 1'*R*)-(+)-pestalotin **1a'**, m.p. 83.0 ~ 84.5°, $[\alpha]_D^{21}$ + 88.7° (MeOH). The IR and NMR spectra of (+)-**1a'** was entirely identical to those of natural (−)-pestalotin **1a** kindly provided by Dr. Y. Kimura. The ratio of **1a'** to **2a'** was 1:2.5, which reflected the predominant Cram mode of the addition of the Grignard reagent to D-glyceraldehyde acetonide **3**. Since the asymmetry existing in (*R*)-**3** was retained throughout the synthesis, the present chiral synthesis confirmed the (6*S*)-configuration of the natural and levorotatory pestalotin **1a**.[9] The overall yields from (*R*)-**3** of (+)-**1a'** and (+)-**2a'** were 1.0 and 2.6%, respectively.

For the synthesis of the natural pestalotin **1a**, L-(−)-glyceraldehyde acetonide (*S*)-**3** was required as the starting material. However, we abandoned this approach from (*S*)-**3** for two reasons: (i) (*S*)-**3** is not so readily available as (*R*)-**3**, even after the publication of Jung's new method for the conversion of vitamin C into (*S*)-**3**[15], and (ii) the approach employing **3** with a single chiral center as the starting material does not allow the unambiguous assignment of the absolute configuration at C-1' of pestalotin. At this time we became aware that the asymmetric epoxidation method as developed by Sharpless for the kinetic resolution of the racemates of sec-allylic alcohols might be the best choice for our purpose, because the two chiral centers of known absolute configuration in the epoxide **B** can be established in one operation by this method.[16] As shown in Fig. 3, (±)-1-hepten-3-ol **8**[17] was epoxidized with t-BuOOH in the presence of $Ti(OPr^i)_4$ and diisopropyl D-(−)-tartrate [D-(−)-DIPT] in $CH_2Cl_2$ at −20° for 40 hr[16] to give (2*S*, 3*R*)-**9a**, $[\alpha]_D^{22}$ −24.5° ($CHCl_3$), in 74% yield (or 37% yield from (±)-**8**). Its optical purity was determined to be ~94% e.e. by carrying out the HPLC analysis of its (*R*)- or (*S*)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester) **9d**. This epoxy alcohol **9a** led to (6*S*, 1'*R*)-(−)-epipestalotin **2a** in 5 steps. After protecting the OH group of **9a** as an ethoxyethyl ether (EE), the epoxide **9b** was reacted with the dianion of propiolic acid to give **11a**, whose methylation yielded **11b** in 21.5% yield from **9b**. The Michael addition of MeOH to **11b** was followed by lactonization to give **2b**. This was treated with 70% AcOH to remove the EE protective group, affording (6*S*, 1'*R*)-(−)-epipe-

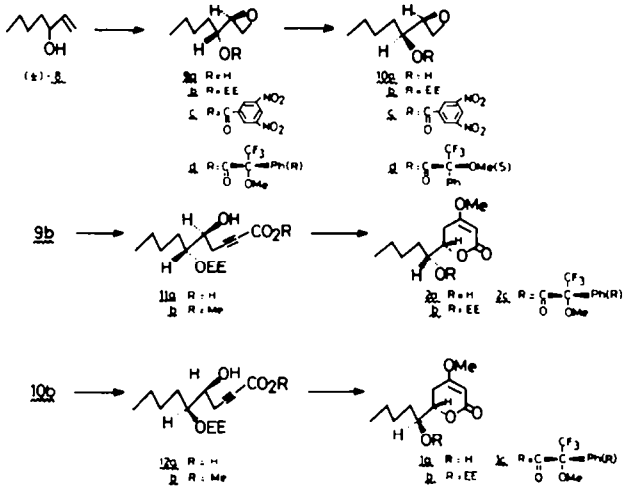

Fig. 3. Synthesis of the natural (−)-pestalotin and (−)-epipestalotin.

stalotin **2a**, m.p. 90.7 ~ 91.2°, $[\alpha]_D^{17}$ − 75.6° (MeOH), in 55% yield from **11b** or 8.8% overall yield from (*R*)-**8**.

For the synthesis of (6*S*, 1′*S*)-(−)-pestalotin **1a**, the natural product itself, a Walden inversion must be executed at C-3 of the epoxide **9a**. According to the Mitsunobu procedure,[18] **9a** was treated with 3,5-dinitrobenzoic acid, $Ph_3P$ and ethyl diazodicarboxylate in THF to give **10c**, m.p. 41 ~ 42°, in 98.4% yield. The use of 3,5-dinitrobenzoic acid instead of benzoic acid in the original procedure is recommended, because it gives in many cases the crystalline 3,5-dinitrobenzoates of the inverted alcohols. Recrystallization of **10c** ensured the high stereochemical purity of our material as checked by the HPLC analysis of **10c** (99.8% *threo*).† Hydrolysis of **10c** with KOH gave (2*S*, 3*S*)-**10a**, $[\alpha]_D^{23}$ + 5.01° ($CHCl_3$), in 72.6% yield. Its optical purity was shown to be 94 ~ 95% e.e. by the HPLC analysis of the corresponding (*R*)- or (*S*)-MTPA esters **10d**. Hereafter the synthesis followed the established route. Thus the protected epoxide **10b** was converted into (6*S*, 1′*S*)-(−)-pestalotin **1a** in 27.7% yield *via* **12a**, **12b** and **1b**. The overall yield of **1a** was 3.7% from (*R*)-**8**. Our synthetic pestalotin **1a**, m.p. 85.8 ~ 86.0°, $[\alpha]_D^{20.5}$ − 90.2° (MeOH) [lit.[1,3] m.p. 88 ~ 89°, $[\alpha]_D$ − 86.2° (MeOH)], showed the IR and NMR spectra identical to those of the natural product. The optical purities of our final products were determined by measuring the 400 MHz, $^1$H-NMR spectra of their (*R*)-MTPA esters **1c**, **1c′**, **2c** and **2c′** as follows: the natural (−)-**1a**, 100%; (+)-**1a′**, 97%; (−)-**2a**, 96%; (+)-**2a′**, 99%.

In conclusion, all of the four possible stereoisomers of pestalotin were synthesized in amounts sufficient for biological studies to clarify the synergistic effect on the action of the gibberellins. A preliminary account of the biological works on (+)-pestalotin **1a′** and (+)-epipestalotin **2a′** has already been published by Kimura *et al.*[19].

## EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films for oils or as Nujol mulls for solids on a Jasco IRA-1 or IRA-102 spectrometer unless otherwise stated. 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-4 or DIP-140 polarimeter. HPLC analyses were performed on a Shimadzu LC-2 chromatograph.

(2*R*, 3*RS*)-(+)-1,2,3-*Heptanetriol*-1,2-*acetonide* **4a**. A soln of (*R*)-**3** (29g) in ether (100 ml) was added dropwise to a stirred and ice-cooled soln of n-BuMgBr prepared from n-BuBr (110 g) and Mg (20 g) in ether (300 ml) at 0 ~ 15°. The mixture was left to stand overnight at room temp. It was then poured into ice and sat $NH_4Cl$ aq. The ether layer was separated and the aq layer was extracted with EtOAc. The combined organic soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 32.4 g (77.2% from **3**) of **4a**, b.p. 91 ~ 98°/6 mm, $n_D^{23}$ 1.4377; $[\alpha]_D^{23}$ + 16.8° (*c* = 2.65, $C_6H_6$); $\nu_{max}$ 3440 (m), 1070 (s) cm$^{-1}$; $\delta$ ($CCl_4$) 0.92 (3H, t, J = 6 Hz), 1.15 ~ 1.70 (6H, m), 1.28 (3H, s), 1.34 (3H, s), 2.27 (1H, OH), 3.4 ~ 3.9 (2H, m), 3.81 (2H, d, J = 2.5 Hz). (Found: C, 63.93; H, 10.64; Calc for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71%).

(2*R*, 3*RS*)-(+)-1,2,3-*Heptanetriol*-1,2-*acetonide*-3-*benzyl ether* **4b**.

Powdered NaOH (18 g) was dissolved in DMSO (180 ml). To this was added with stirring a soln of **4a** (12 g) in DMSO (50 ml) over 1 hr at room temp under $N_2$. Subsequently $PhCH_2Cl$ (45 g) was added dropwise to the stirred mixture at 30 ~ 40°. The stirring was continued for 2 hr at 30 ~ 40°. The mixture was poured into water and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 16.4 g (92.4%) of **4b**, b.p. 129 ~ 134°/0.6 mm, $n_D^{25}$ 1.4869; $[\alpha]_D^{25}$ + 22.9° (*c* = 3.07, $C_6H_6$); $\nu_{max}$ 1610 (w), 1070 (s) cm$^{-1}$; $\delta$ ($CCl_4$) 0.92 (3H, t, J = 6 Hz), 1.15 ~ 1.70 (6H, m), 1.28 (3H, s), 1.34 (3 H, s), 3.3 ~ 4.1 (2 H, m), 4.0 (2 H, d, J = 3 Hz), 4.56 (2H, s), 7.26 (5H, s). (Found: C, 73.70; H, 9.19. Calc for $C_{17}F_{26}O_3$: C, 73.34; H, 9.41%).

(2*R*, 3*RS*)-(+)-1,2,3-*Heptanetriol*-3-*benzyl ether* **5a**. Conc HCl (25 ml) and water (60 ml) were added to a stirred soln of **4b** (46 g) in MeOH (160 ml) The mixture was stirred and heated at 60° for 1 hr to give a homogeneous soln. It was then concentrated *in vacuo* to remove MeOH. The residue was diluted with ice–water and extracted with ether. The ether soln was washed with water and brine, dried ($K_2CO_3$) and concentrated *in vacuo*. The residue was distilled to give 34.3 g (87%) of **5a**, b.p. 131 ~ 136°/0.35 mm, $n_D^{25}$ 1.5086; $[\alpha]_D^{25}$ + 3.17° (*c* = 3.03, $C_6H_6$); $\nu_{max}$ 3400 (s), 1605 (w), 1095 (s), 1070 (s), 1030 (m), 740 (s), 700 (s) cm$^{-1}$; $\delta$ ($CCl_4$) 0.89 (3H, t, J = 6 Hz), 1.00 ~ 1.70 (6H, m), 3.2 ~ 4.1 (2H, m), 3.6 (2H, d, J = 3.0 Hz), 4.05 (2H, OH), 4.52 (2H, s), 7.28 (5H, s). (Found: C, 70.24; H, 9.11. Calc for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31%).

(2*R*, 3*RS*)-(−)-1,2-*Epoxy*-3-*benzyloxyheptane* **6**. *p*-TsCl (28 g) was added to a stirred and cooled soln of **5a** (30 g) in $C_5H_5N$ (100 ml) at −10°. The stirring was continued at −10 ~ 0° for 2 hr. KOH (30 g) in water (30 ml) was slowly added to the stirred and cooled mixture. The stirring was continued for 30 min at room temp. The mixture was poured into ice-water and extracted with ether. The ether soln was washed with water, $CuSO_4$ aq, water and brine, dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was distilled to give 22.9 g (82%) of **6**, b.p. 125 ~ 133°/3 mm, $n_D^{23}$ 1.4948; $[\alpha]_D^{23}$ − 7.39° (*c* = 2.678, $C_6H_6$); $\nu_{max}$ 1605 (w), 1595 (w), 1110 (s), 1070 (s), 1030 (m), 745 (s), 705 (s) cm$^{-1}$; $\delta$ 0.92 (3H, t, J = 6 Hz), 1.15 ~ 1.70 (6H, m), 2.58 (2H, d, J = 3.5 Hz), 2.75 (1H, m), 2.32 and 3.18 [total 1 H, (ca 1:2), q, J = 5 Hz], 4.52 (2H, d, J = 4 Hz), 7.27 (5H, s), (Found: C, 76.63; H, 9.10. Calc for $C_{14}H_{20}O_2$: C, 76.32; H, 9.13%).

*Methyl* (5*R*, 6*RS*)-6-*benzyloxy*-5-*hydroxy*-2-*decynoate* **7b**. A soln of $LiNPr^i_2$ in THF was prepared by the dropwise addition of n-BuLi (1.3 M in hexane, 21.5 ml) to a stirred and cooled soln of $(i\text{-}Pr)_2NH$ (4.5 ml) in THF (8 ml) at −45° under $N_2$. After stirring for 10 min, $HC{\equiv}CCO_2H$ (0.87 ml) and HMPA (8 ml) were added to the soln at −45°. The stirring was continued for 2 hr with gradual raise of the temp to −10°. To the mixture was added **6** (3.1 g) and the stirring was continued for 36 hr at room temp. The mixture was poured into ice–water and extracted with $CH_2Cl_2$. The aq layer was ice–cooled, acidified with dil HCl to pH 1 and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and filtered. To this soln was added $CH_2N_2$ in ether. After 5 min, the excess $CH_2N_2$ was destroyed by the addition of AcOH. The ether soln was washed with water, sat $NaHCO_3$, water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over $SiO_2$ (Mallinckrodt CC-7). Elution with hexane–ether (7:3) gave 1.8 g (41.2%) of crude **7b**, $\nu_{max}$ 3400 (m), 2230 (m), 1720 (s), 1260 (s), 1080 (s) cm$^{-1}$. This was employed in the next step without further purification.

(6*R*, 1′*RS*)-6-(1′-*Benzyloxypentyl*)-4-*methoxy*-5,6-*dihydro*-2-*pyrone* **1b′** + **2b′**. Na (0.2 g) was dissolved in MeOH (100 ml). A portion of this soln (10 ml) was added dropwise to a soln of **7b** (1.05 g) in MeOH (2 ml) under $N_2$. The stirring was continued for 24 hr at room temp. The mixture was poured into aq AcOH (0.5 ml AcOH in 100 ml of ice–water) and extracted with ether. The ether soln was

†HPLC analysis of **9c** revealed it to be ~100% *erythro*.

washed with sat $NaHCO_3$ aq, water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 0.86 g (85%) of a crude mixture of **1b'** and **2b'**. This was employed in the next step without further purification.

(6R, 1'R)-(+)-*Pestalotin* [6-(1'-hydroxypentyl)-4-methoxy-5,6-dihydro-2-pyrone] **1a'** *and* (6R, 1'S)-(+)-*epipestalotin* **2a'**. 10% Pd-C (0.54 g) was added to a soln of **1b'** + **2b'** (2.1 g) in EtOH (70 ml) and the mixture was shaken under $H_2$. Hydrogenation was interrupted at the time when 155.8 ml of $H_2$ was absorbed. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was chromatographed over $SiO_2$ (Mallinckrodt CC-7). Elution with n-hexane–ether gave (+)-**2a'** first, followed by a mixture of (+)-**2a'** and (+)-**1a'**, and finally (+)-**1a'**. From 18.5 g of **6**, 361 mg (2.0% overall yield from **6**) of (+)-**1a'** and 904 mg (5.1% overall yield from **6**) of (+)-**2a'** were obtained together with a mixture (713 mg, 4.0% from **6**) of **1a'** and **2a'**. (6*R*, 1'*R*)-(+)-**1a'** was obtained as plates from $C_6H_6$-n-hexane, m.p. 83.0 ~ 84.5°, $[\alpha]_D^{21}$ + 88.7° (*c* = 0.65, MeOH); $\nu_{max}$ 3450 (m), 1710 (s), 1625 (s), 1255 (m), 1240 (s), 840 (s) $cm^{-1}$; $\delta$ ($CDCl_3$) 0.91 (3H, t, J = 6 Hz), 1.30 ~ 1.60 (6H, m), 2.25 (1H, dd, J = 4, 17 Hz), 2.79 (1H, ddd, J = 2, 12, 17 Hz), 3.62 (1H, m), 3.77 (3H, s), 4.29 (1H, dt, J = 4, 12 Hz), 5.13 (1H, d, J = 2 Hz). These IR and NMR spectra were identical with the authentic spectra of (−)-**1a**. (Found: C, 61.41; H, 8.24. Calc for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47%). (6*R*, 1'*S*)-(+)-**2a'** was obtained as needles from $C_6H_6$-n-hexane, m.p. 93.0 ~ 94.0°, $[\alpha]_D^{21}$ + 75.9° (*c* = 0.39, MeOH); $\nu_{max}$ 3360 (m), 1695 (s), 1685 (s), 1635 (s), 1230 (s), 1080 (m), 1060 (m), 1000 (m), 830 (m) $cm^{-1}$; $\delta$ (100 MHz $CDCl_3$) 0.91 (3H, t, J = 6 Hz), 1.28 ~ 1.53 (6H, m), 2.25 (1H, dd, J = 2,4 Hz), 2.82 (1H, ddd, J = 2,12, 17 Hz), 3.74 (3H, s), 3.87 (1H, m), 4.31 (1H, dt, J = 4,12 Hz), 5.12 (1H, d, J = 2 Hz). (Found: C, 61.52; H, 8.33. Calc for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47%).

(±)-1-*Hepten-3-ol* **8**. A soln of $CH_2$=CHMgBr in THF was prepared in the usual manner under Ar from $CH_2$=CHBr (16.0 g) and Mg (3.7 g) in THF (45 ml). A soln of n-$C_4H_9CHO$ (12.9 g) in THF (30 ml) was added dropwise over 30 min to the Grignard reagent with stirring and ice-cooling. The stirring was continued for 1 hr. The mixture was then poured into ice and sat $NH_4Cl$ aq and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 9.96 g (67.7%) of **8**, b.p. 83°/15 mm or 62 ~ 70°/24 mm, $n_D^{21}$ 1.4276 (lit.[17] b.p. 153.5 ~ 154°, $n_D^{24}$ 1.4275); $\nu_{max}$ 3360 (s), 3080 (w) $cm^{-1}$; $\delta$ ($CCl_4$) 0.90 (3H, deformed t, J = 6 Hz), 1.05 ~ 1.60 (6H, br.), 3.16 (1H, br. s), 3.95 (1H, br), 4.95 (1H, dd, J = 4, 10 Hz), 5.08 (1H, dd, J = 4, 15 Hz), 5.78 (1H, ddd, J = 4, 10, 15 Hz); MS: *m/z* 114 ($M^+$). This was employed directly in the next step.

(2S, 3R)-(−)-1,2-*Epoxy*-3-*heptanol* **9a**. To a stirred and well-cooled $CH_2Cl_2$ (450 ml) at −20° under Ar, the reagents were added in the following order: (i) $Ti(OPr^i)_4$ (21.4 ml, 72 mmole), (ii) D-(−)-DIPT (17.9 ml, 84.6 mmole) (5 min's stirring after the addition) (iii) (±)-**8** (10 ml, 72 mmole) and (iv) 7.32M-t-BuOOH (18.0 ml, 100 mmole). The mixture was left to stand at −20° for 40.5 hr. The mixture was then cooled in a cooling bath at −20°. 10% L-(+)-Tartaric acid aq (175 ml) was added to the stirred mixture. The stirring was continued for 30 min at −20° and 1.5 hr at room temp. The organic layer was separated, washed with water, dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was diluted with ether (400 ml). The ether soln was stirred and cooled to 0°. N-NaOH (250 ml) was added to the soln and the mixture was stirred for 30 min. The ether layer was separated, washed with brine, dried ($Na_2SO_4$) and concentrated *in vacuo*. The products from three batches of the above epoxidation were combined and chromatographed over $SiO_2$ (Merck Kieselgel 60, Art 7734, 1kg). Elution with n-hexane–EtOAc (20:1) gave 10.4 g (74% from (*R*)-**8** of **9a**, b.p. 72 ~ 78°/1.2 mm; $n_D^{22}$ 1.5228; $[\alpha]_D^{20}$ − 24.5° (*c* = 1.22, $CHCl_3$)); $\nu_{max}$ 3450 (sα), 1070 (m) $cm^{-1}$; $\delta$ ($CCl_4$) 0.92 (3H, deformed t, J = 5 Hz), 1.11 ~ 1.60 (6H, m), 2.20 (1H, br, s, −OH), 2.48 ~ 2.73 (2H, m), 2.82 (1H, dd, J = 3,9 Hz), 3.61 (1H, m). (Found: C, 63.81; H, 11.36. Calc for $C_7H_{14}O_2$: C, 64.58; H, 10.84%). For the determination of the optical purity of **9a**, it was converted into (*R*)- and (*S*)-MTPA esters **9d** in the conventional manner.[20] HPLC analysis of **9d** (Column, Partisil 5, 25 cm × 4.6 mm; eluant, n-hexane–$ClCH_2CH_2Cl$ = 3:1; pressure, 30 kg/$cm^2$): $R_t$ 36.4 min [(*S*)-MTPA ester of **9a**], 44.4 min [(*R*)-MTPA ester of **9a**]. The optical purity of our **9a** was estimated to be 92.4 ~ 94.6%.

(2S, 3R)-(+)-1,2-*Epoxy*-3-*heptanol* EE *ether* **9b**. p-TsOH·$H_2O$ (10 mg) and ethyl vinyl ether (30 ml) were added to a soln of **9a** (4.24 g) in dry ether (10 ml) with stirring and ice-cooling. The stirring was continued at 0° for 10 min and at room temp for 2 hr. The soln was washed with sat $NaHCO_3$ aq, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 5.46 g (82.9%) of **9b**, b.p. 62 ~ 64°/0.75 mm; $n_D^{20}$ 1.4323; $\nu_{max}$ 1130 (s), 1085 (s), 1055 (m), 950 (m) $cm^{-1}$; $\delta$ ($CCl_4$) 0.95 (3H, deformed t, J = 6 Hz), 1.05 (3H, t, J = 6 Hz), 1.0 ~ 1.7 (6H, m), 2.5 ~ 2.9 (4H, m), 3.0 ~ 3.7 (3H, m), 4.7 (1H, m). (Found: C, 64.88; H, 10.89. Calc for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96%).

*Methyl* ((5S, 6R)-6-*ethoxyethoxy*-5-*hydroxy*-2-*decynoate* **11b**. A soln of $LiNPr_2^i$ in THF was prepared by the dropwise addition of n-BuLi in n-hexane (36 ml, 55 mmole) to a stirred and cooled soln of $(i\text{-}Pr)_2NH$ (0.355 ml), 5 mmole) in dry THF (14.3 ml) at −45° under Ar. After stirring for 10 min at −45°, HMPA (14.3 ml) and HC≡$CCO_2H$ (0.31 ml, 5 mmole) was added slowly. The mixture was stirred for 2 hr with gradual raise of reaction temp to −10°. To the stirred and cooled mixture was added **9b** (1.01 g) at −10°. The mixture was stirred for 50 hr at room temp. Then it was poured into ice-water and extracted with $CH_2Cl_2$. The aq layer was ice-cooled, acidified with dil HCl to pH 4 ~ 5 and extracted with ether. The ether soln was dried ($Na_2SO_4$) and concentrated *in vacuo*. When a half amount of the ether was removed, the concentration was interrupted and the ether soln was treated with $CH_2N_2$ in ether. The excess $CH_2N_2$ was destroyed with AcOH and the ether soln was washed with water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residual brown oil was chromatographed over $SiO_2$ (Mallinckrodt CC-7). After the recovery of **9b** (518.6 mg), 307.6 mg (21.2%) of **11b** was obtained, $\nu_{max}$ 3430 (m), 2230 (m), 1715 (s), 1250 (s), 1070 (s), 1050 (s) $cm^{-1}$; $\delta$ ($CCl_4$) 0.92 (3H, deformed t, J = 6 Hz), 1.16 (3H, t, J = 7 Hz), 1.0 ~ 1.7 (9H, m), 2.48 (2H, d, J = 6 Hz), 3.25 ~ 4.0. (3H, m), 3.67 (3H, s), 4.73 (1H, m). This was employed in the next step without further purification.

(6S, 1'R)-6-(1'-*Ethoxyethoxypentyl*)-4-*methoxy*-5,6-*dihydro*-2-*pyrone* **2b**. Na (0.2 g) was dissolved in MeOH (100 ml). A portion of it (5 ml) was added to **11b** (470 mg) and the mixture was stirred for 24 hr at room temp. It was then poured into water and extracted with ether. The ether soln was dried ($MgSO_4$) and concentrated *in vacuo* to give 365.0 mg (77.0%) of **2b**, $\delta$ ($CCl_4$) 3.67 (3H, s, -$OCH_3$), 4.95 (1H, d, J = 2 Hz, C=C**H**). This was employed directly in the next step.

(6S, 1'R)-(−)-*Epipestalotin* **2a**. A soln of **2b** (365.0 mg) in 70% AcOH (4 ml) was stirred and heated at 35 ~ 45° for 20 min. The mixture was diluted with water and extracted with ether. The ether soln was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over $SiO_2$ (Mallinckrodt CC-7). Elution with n-hexane-ether (1:1) gave 139.7 mg (51.2%) of **2a**, which was recrystallized from $C_6H_6$-n-hexane to give needles, (102.9 mg, 37.7%), m.p. 90.7 ~ 91.2°; $[\alpha]_D^{17}$ − 75.6° (*c* = 0.58, MeOH); $\nu_{max}$ 3425 (m), 1710 (s), 1685 (s), 1625 (s), 1225 (s), 1080 (m), 1050 (m), 995 (m), 820 (m) $cm^{-1}$; $\delta$ ($CDCl_3$) 0.91 (3H, deformed t, J = 6 Hz), 1.30 ~ 1.60 (6H, m), 1.8 ~ 2.2 (1H, m), 2.2 ~ 2.6 (1H, m), 3.68 (3H, s), 3.75 (1H, m), 4.05 ~ 4.40 (1H, m), 5.05 (1H, d, J=2 Hz). (Found: C, 61.71; H, 8.39. Calc for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47%). The IR spectrum was identical with that of (+)-**2a'**.

(2S, 3S)-(+)-1,2-*Epoxy*-3-*heptanol* 3,5-*dinitrobenzoate*

**10c**. A soln of **9a** (1.02 g), 3,5-dinitrobenzoic acid (1.80 g) and $Ph_3P$ (2.23 g) in THF (20 ml) was stirred and ice-cooled. A soln of ethyl diazodicarboxylate (1.48 g) in THF (7 ml) was added dropwise over 15 min to the stirred and ice-cooled mixture. The stirring was continued overnight at room temp. The color of the reaction mixture changed from yellow to green, blue, violet, red and finally became brown. The mixture was concentrated *in vacuo* to remove THF and the residue was chromatographed over $SiO_2$ (Merck Kieselgel 60, Art 7734, 200 g). Elution with THF-$CHCl_3$ (1:10) gave 2.50 g (98.4%) of **10c**, which was recrystallized from ether-n-pentane to give needles, m.p. 41 ~ 42°, $[\alpha]_D^{28.5}$ + 6.60° ($c$ = 1.30, $CHCl_3$); $\nu_{max}$ (KBr) 1735 (s), 1630 (w), 1550 (s), 1350 (s), 1285 (s), 1170 (m) $cm^{-1}$; $\delta$ ($CDCl_3$) 0.93 (3H, deformed t, J = 6 Hz), 1.15 ~ 1.62 (4H, m), 1.70 ~ 2.10 (2H, m), 2.72 (1H, dd, J=2,4 Hz), 2.93 (1H, dd, J = 4, 4Hz), 3.23 (1H, ddd, J = 2, 4, 7 Hz), 4.96 (1H, dt, J=7, 7 Hz), 9.20 (3H, br. s). (Found: C, 51.59; H, 4.98; N, 8.61. Calc for $C_{14}H_{16}O_7N_2$: C, 51.85; H, 4.97; N, 8.64%). By acylating **9a**, **9c** was prepared and the HPLC analysis of both **9c** and **10c** was carried out to estimate their diastereomeric purities. HPLC analysis of **9c** (Column, Partisil 5, 25 cm × 4.6 mm; eluant, n-hexane–$ClCH_2CH_2Cl$=1:1; pressure, 30 kg/$cm^2$): $R_t$ 80.4 min (single peak, 100% *erythro*); HPLC analysis of **10c** under the same condition: Rt 80.4 min (0.2%). 120.8 min (99.8% *threo*).

(2S, 3S)-(+)-1,2-Epoxy-3-*heptanol* **10a**. A soln of KOH [1N-KOH (43 ml) was diluted with MeOH-water (1:1, 108 ml)] was added dropwise over 10 min to a stirred and ice-cooled soln of **10c** (13.0 g) in THF-MeOH (1:1, 100 ml) at 0 ~ 5°. The mixture was stirred for 15 min at 0 ~ 5°, and diluted with $CH_2Cl_2$. The $CH_2Cl_2$ soln was washed with sat $KHCO_3$ aq, dried ($Na_2SO_4$) and concentrated *in vacuo*. The residue was chromatographed over $SiO_2$ (Merck Kieselgel 60, Art 7734, 100 g). Elution with n-hexane–EtOAc (10:1) yielded crude **10a**, which was distilled to give 3.61 g (72.6%) of pure **10a**, b.p. 63°/0.55 mm; $n_D^{23}$ 1.4349; $[\alpha]_D^{23}$ + 5.01° ($c$ = 1.39, $CHCl_3$); $\nu_{max}$ 3420 (vs), 1250 (m), 1090 (m), 1050 (m), 1030 (m), 925 (m), 900 (m), 880 (m) $cm^{-1}$; $\delta$ ($CCl_4$) 0.90 (3H, deformed t, J=5 Hz), 1.15 ~ 1.65 (6H, m), 2.22 (1H, d, J=5.5 Hz), 2.60 (1H, m), 2.75 (2H, m), 3.25 (1H, br). (Found: C, 64.81; H, 11.04. Calc for $C_7H_{14}O_2$: C, 64.58; H, 10.84%). Acylation of **10a** with (*R*)- or (*S*)-MTPA chloride in the usual manner[20] gave (*R*)- or (*S*)-**10d**. These were analyzed by HPLC: HPLC analysis of (*R*)-**10d** (Column, Partisil-5, 25 cm × 4.6 mm; eluant, *n*-hexane-$ClCH_2CH_2Cl$ = 5:2; pressure, 30 kg/$cm^2$): $R_t$ 16.0 min (97.2%), 18.8 min (2.8%); HPLC analysis of (*S*)-**10d** under the same condition: $R_t$ 16.0 min (2.3%), 18.8 min (97.7%). This allowed us to estimate the optical purity of **10a** to be 94.4 ~ 95.4%.

(2S, 3S)-(−)-1,2-*Epoxy*-3-*heptanol* EE *ether* **10b**. p-TsOH·$H_2O$ (40 mg) was added to a stirred and ice-cooled soln of **10a** (4.15 g) in ethyl vinyl ether (30 ml) and ether (10 ml). The mixture was stirred for 2 hr at 0 ~ 5°, and then diluted with ether. The ether soln was washed with sat $NaHCO_3$aq, water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was passed through a short column of $SiO_2$ (Merck Kieselgel 60, Art 7734, 80 g). Elution with n-hexane-EtOAc (40:1) gave crude **10b**, which was distilled to give 6.06 g (94.0%) of pure **10b**, b.p. 64 ~ 68°/3 mm; $n_D^{22}$ 1.4234; $[\alpha]_D^{22}$ − 30.4° ($c$=1.48, $CHCl_3$); $\nu_{max}$ 1130 (s), 1080 (s), 1050 (s) $cm^{-1}$; $\delta$ ($CCl_4$) 0.7 ~ 1.7 (15H, m), 2.35 (1H, m), 2.5 ~ 3.2 (3H, m), 3.2 ~ 3.75 (2H, m), 4.5 ~ 4.9 (1H, m), (Found: C, 65.20; H, 11.10. Calc for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96%).

*Methyl* (5S, 6S)-6-*ethoxyethoxy*-5-*hydroxy*-2-*decynoate* **12b**. A soln of $LiNPr^i_2$ in THF was prepared by the addition of n-BuLi (1.74 M in n-hexane, 12 ml, 21 mmole) to a stirred and cooled soln of $(i\text{-}Pr)_2NH$ (1.4 ml, 20 mmole) in THF (3 ml) at −45° under Ar. The soln was stirred for 10 min at −45°. To this were added HMPA (3 ml) and a soln of $HC{\equiv}CCO_2H$ (0.31 ml, 10 mmole) in THF-HMPA (1:1, 1 ml) at −45°. The stirring was continued for 2 hr with gradual raise of temp to −10°. Then **10b** (1.10 ml, 5 mmole) was added dropwise to the mixture. After the addition, the temp was gradually raised to room temp and the stirring was continued for 48 hr. The mixture was poured into ice-water and extracted with ether to recover remaining **10b**. The aq layer was acidified with dil HCl to pH 3 and extracted with ether repeatedly (× 6). The ether soln was washed with brine, dried ($MgSO_4$) and concentrated to reduce the total volume to 200 ml. $CH_2N_2$ in ether was added to this soln containing **12a**. After 30 min, the excess $CH_2N_2$ was destroyed with AcOH. The ether soln was washed with water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over $SiO_2$ (Mallinckrodt CC-7, 50 g). Elution with n-hexane-ether (2:1) gave 381.2 mg (26.8%) of **12b**, $\nu_{max}$ 3440 (m), 2230 (m), 1720 (s), 1255 (s), 1125 (m), 1075 (s), 1050 (m) $cm^{-1}$; $\delta$ ($CCl_4$) 0.7 ~ 1.1 (6H, m), 1.1 ~ 1.7 (9H, m), 3.3 ~ 3.8 (5H, m), 3.65 (3H, s), 4.5 ~ 4.9 (1H, m). This was employed in the next step without further purification.

(6S, 1'S)-6-(1'-*Ethoxyethoxypentyl*)-4-*methoxy*-5,6-*dihydro*-2-*pyrone* **1b**.Na (0.2 g) was dissolved in MeOH (100 ml). A portion of this soln (4 ml) was added to a stirred soln of **12b** (380 mg) in MeOH (1 ml). The mixture was stirred for 24 hr at room temp. It was then poured into ice and dil AcOH (0.75 ml of AcOH in 50 ml of ice-water). After checking its pH (~4), the mixture was extracted with ether. The ether soln was washed with sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 317.7 mg (83.6%) of crude **1b** as a brown oil, $\nu_{max}$ 1725 (s), 1635 (s), 1600 (w), 1230 (s), 1060 (s) $cm^{-1}$ $\delta$ 0.91 (3H, m), 1.03 (3H, m), 1.1 ~ 1.7 (~9H, m), 2.1 ~ 2.6 (2H, m), 3.1 ~ 3.7 (3H, m), 3.70 (3H, s), 4.10 ~ 4.55 (1H, m), 4.75 (1H, q, J=6 Hz), 5.01 (1H, s), This was employed in the next step without further purification.

(6S, 1'S)-(−)-*Pestalotin* **1a**. A soln of **1b** (310 mg) in 70% AcOH aq (5 ml) was stirred and heated at 45° for 5 min. This was diluted with ether (50 ml) and the soln was washed with water, sat $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over $SiO_2$ (Mallinckrodt CC-7, 15 g). Elution with n-hexane-ether (1:1) gave 76.7 mg (33.1%) of **1a** as crystals. Recrystallization from $C_6H_6$-n-hexane gave 59.2 mg of **1a**, m.p. 83.0 ~ 84.5°, $[\alpha]_D^{28}$ − 97.3° ($c$ = 0.68, MeOH). This was further recrystallized from $C_6H_6$-n-hexane to give 44.0 mg of pure **1a**, m.p. 85.8 ~ 86.0°, $[\alpha]_D^{28.5}$ − 90.2° ($c$ = 1.17, MeOH); $\nu_{max}$ (KBr) 3450 (s), 2950 (m), 2870 (m), 1705 (vs), 1685 (sh), 1615 (s), 1450 (m), 1385 (s), 1350 (m), 1285 (w), (1245 (m), 1230 (s), 1190 (m), 1140 (w), 1110 (w), 1080 (m), 1060 (w), 1015 (w), 995 (m), ~980 (m), 910 (w), 840 (m), 730 (w), 655 (m) $cm^{-1}$; $\delta$ (400 MHz, $CDCl_3$) 0.917 (3H, t, J = 7.2 Hz), 1.290 ~ 1.443 (3H, m), 1.438 ~ 1,642 (3H, m), 2.164 (1H, d, J = 7.0 Hz), 2.796 (1H, ddd, J = 1.7, 13.1, 17.5 Hz), 3.623 (1H, m), 3.750 (3H, s), 4.297 (1H, dt, J = 13.1, 4.0 Hz), 5.145 (1H, d, J = 1.7 Hz). (Found: C, 61.80; H, 8.54. Calc for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47%).

*Determination of the optical purities of* **1a** *and* **1a'**. To determine the optical purities of **1a** and **1a'**, they were converted into the corresponding (*R*)-MTPA ester **1c** and **1c'**, and their $^1$HNMR spectra were measured at 400 MHz. $^1$H-NMR of **1c** (400 MHz, $CDCl_3$) 0.891 (3H, t, J = 7.0 Hz), 1.244 ~ 1.410 (4H, m), 1.708 ~ 1.900 (2H, m), 2.085 (1H, dd, J = 3.9, 16.5 Hz), 2.430 (1H, ddd, J = 1.8, 12.8, 16.5 Hz), 3.562 (3H, d, J = 1.1 Hz), 3.716 (3H, s, $-OCH_3$ of MTPA), 4.489 (1H, ddd, J = 3.9, 4.5, 12.8 Hz), 5.100 (1H, d, J = 1.8 Hz), 5.235 (1H, dt, J = 4.5, 8.0 Hz), 7.38 ~ 7.45 (3H, m), 7.56 ~ 7.60 (2H, m). $^1$H-NMR of **1c'** (400 MHz, $CDCl_3$) 0.832 (3H, t, J = 7.1 Hz), 1.120 ~ 1.350 (4H, m), 1.613 ~ 1.767 (2H, m), 2.270 (1H, dd, J = 4.0, 17.0 Hz), 2.545 (1H, ddd, J = 1.8, 12.4, 17.0 Hz), 3.562 (0.045H, d, J = 1.1 Hz), 3.587 (2.955H, d, J = 1.1 Hz, $-OCH_3$ on the pyrone ring), 3.716 (0.045 H, s), 3.749 (2.955H, s, $-OCH_3$ of MTPA), 4.489 (1H, ddd, J = 4.0, 5.5, 12.4 Hz), 5.150 (1H, d, J = 1.8 Hz), 5.230 (1H, dt, J = 5.5, 7.2 Hz), 7.38 ~ 7.44 (3H, m), 7.57 ~ 7.65 (2H, m). The above data especially concerning the signals due to $OCH_3$ showed that **1a** was 100% optically pure, while the optical purity of **1a'** was 97%.

*Determination of the optical purities of* **2a** *and* **2a'**. In the same manner as described above, 400 MHz $^1$H-NMR spectra of **2c** and **2c'** were measured. $^1$H-NMR of **2c** (400 MHz, $CDCl_3$) 0.87 (3H, t, J = 7 Hz), 1.19 ~ 1.37 (4H, m), 1.55 ~ 1.75 (2H, m), 2.26 (1H, dd, J = 4, 17 Hz), 2.63 (1H, ddd, J = 2, 12.5, 17 Hz), 3.522 (2.94H, d, J = 1.1 Hz, $-OCH_3$ on the pyrone ring), 3.562 (0.06H, d, J = 1.1 Hz), 3.713 (0.06H, s), 3.749 (2.94H, s, $-OCH_3$ of MTPA), 4.52 (1H, ddd, J = 4, 4, 12.5 Hz), 5.13 (1H, d, J = 2 Hz), 5.42 (1H, m). $^1$H-NMR of **2c'** (400 MHz, $CDCl_3$) 0.89 (3H, t, J = 7 Hz), 1.25 ~ 1.41 (4H, m), 1.67 ~ 1.78 (2H, m), 2.18 (1H, dd, J = 4, 17 Hz), 2.46 (1H, ddd, J = 2, 12, 17 Hz), 3.522 (2.99H, d, J = 1.1 Hz, $-OCH_3$ on the pyrone ring), 3.586 (0.01H, d, J = 1.1 Hz), 3.713 (0.01H, s), 3.749 (2.99H, s, $-OCH_3$ of MTPA), 4.42 (1H, ddd, J = 4, 4, 12 Hz), 5.09 (1H, d, J = 2 Hz), 5.42 (1H, m). The above data especially concerning the signals due to $OCH_3$ showed that **2a** was 96% optically pure, while the optical purity of **2a'** was 99%. Meyer and Seebach's claim[8] that the optically pure **2a'** should show $[\alpha]_D$ value of +88.5° (MeOH) was therefore proved to be untrue. Our **2a'** showed $[\alpha]_D^{11}$ + 75.9° (MeOH).

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