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An efficient synthesis of (−)-pestalotin and its enantiomer using Sharpless asymmetric dihydroxylation

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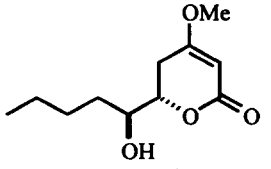
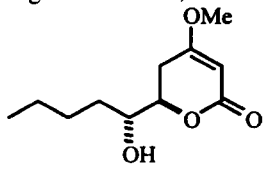
Abstract: With Sharpless asymmetric dihydroxylation as a key step, syntheses of (−)-pestalotin and its enantiomer have been accomplished in a four-step sequence in high stereoselectivity. © 1997 Published by Elsevier Science Ltd

(−)-Pestalotin **1** is a gibberellin synergist isolated from the culture filtrate of a phytopathogenic fungus *Pestaltia cryptomeriaecola* by Kimuro *et al.*[1] and has also been obtained from an unidentified *Penicillium* species by Ellestad *et al.*[2] It has a 5,6-dihydro-4-methoxy-2H-pyran-2-one skeleton with one hydroxyl group on the side chain. The absolute configuration is 6S, 1′S.[1–3]



1



2

The presence of the two contiguous stereogenic centers in (−)-pestalotin **1** has made it an attractive synthetic target since its discovery. To date, more than ten synthetic routes have been reported including the synthesis of (±)-pestalotin[1b,4,5] and optically active forms.[6–15] In these syntheses the two chiral centers were built stepwise and in some of them the stereoselectivity was low. In connection with our interest in the stereocontrolled construction of stereogenic centers by metal-catalyzed asymmetric reactions, we report here the facile synthesis of (−)-pestalotin **1** and its enantiomer **2**. Our strategy involves the simultaneous and highly stereoselective establishment of the two stereogenic centers by a Sharpless asymmetric dihydroxylation[16] (AD) reaction.

Our starting material, 2-hepten-1-ol **3**, is commercially available and also can be prepared from propargyl alcohol by routine procedures.[17] Conversion of the allylic alcohol **3** to chloride **4** can be achieved in a system of Ph_3P–CCl_4 at r.t.[18] in 93% yield (Scheme 1). Reaction of **4** with methyl propiolate in the presence of CuI and DBU[19] in a mixed solvent of THF and HMPA gave a coupling product **5** in 65% yield. The enyne **5** was then treated with AD-mix-α[16] in the presence of methanesulfonamide in *tert*-butanol and water at 0°C to furnish **6** [m.p. 54–56°C, $[\alpha]_D^{25}$ +14.0 (c, 0.5, CH_3OH)] in 94% yield. Treatment of **6** with MeONa–MeOH[6] followed by acidification afforded the lactonized Michael adduct (−)-pestalotin **1** [m.p. 89–92°C, $[\alpha]_D^{20}$ −88.7 (c, 1.7, CH_3OH); lit.[1a] m.p. 83.0–84.5°C, $[\alpha]_D$ −90.2 (c, 1.17, CH_3OH). Its enantiomeric excess was shown to be 90% by analysis of the ^{1}H-NMR (300 MHz) data of the corresponding (*R*)-MTPA ester. The overall yield from **3** is 53.4%.

Similarly, dihydroxylation of **5** with AD-mix-β instead of AD-mix-α followed by Michael addition and lactonization finally yields (+)-pestalotin **2** (Scheme 2) [m.p. 85–90°C, $[\alpha]_D^{20}$ +91.1 (c, 1.34, CH_3OH); lit.[11] m.p. 83.0–84.5°C, $[\alpha]_D^{20}$ +88.7 (c, 1.0, CH_3OH)]. Its enantiomeric excess was shown to be 95% by the same method as mentioned above.

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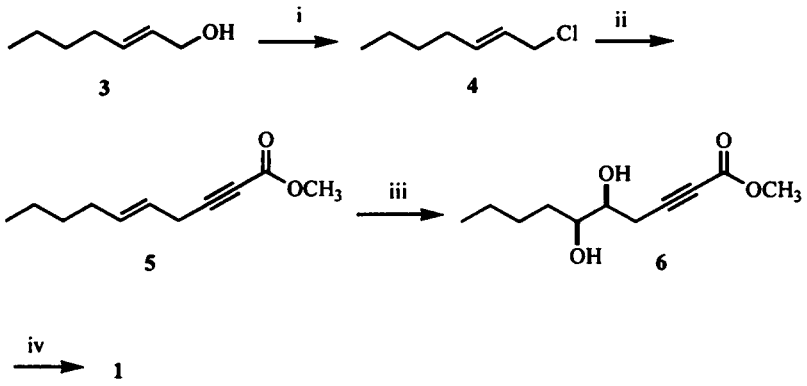
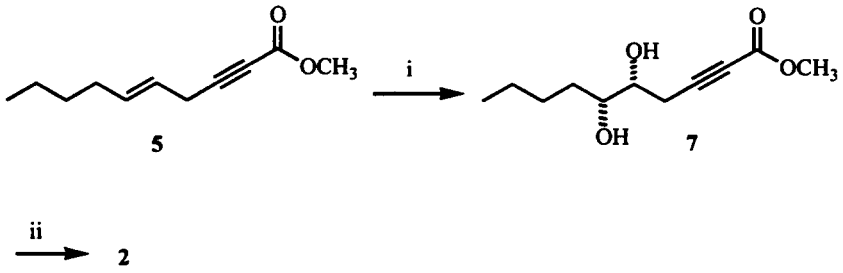


Scheme 1. *Reagents.* i: CCl_4, PPh_3, r.t. (91%); ii: Methyl propiolate, DBU, CuI, phenothiazine, $NH_2OH \cdot H_2O$, HMPA/THF, 60°C (65%); iii: AD-mix-α, 0°C (94%); iv: MeONa, MeOH, 0°C (94%).



Scheme 2. *Reagents.* i: AD-mix-β, 0°C (79%); ii: MeONa, MeOH, 0°C (90%).

In conclusion, this work demonstrates that the Sharpless AD as the key step offers a convenient and highly stereoselective method to synthesize natural products with two contiguous stereogenic centers such as pestalotin.

Experimental section

General procedure

Melting points are uncorrected. IR spectra were taken for solid samples in KBr pellets and for liquid samples on film, on a Shimadzu-440 spectrophotometer. ^1H NMR spectra were recorded on a Bruker AM300 instrument with TMS as an internal standard. Mass spectra were obtained from an HP 5890A spectrometer. Optical rotations were measured on a Perkin–Elmer 241MC polarimeter.

2-Heptenyl chloride 4

2-Hepten-1-ol **3** (4.75 g, 42 mmol) was dissolved in 20 mL of carbon tetrachloride containing triphenylphosphine (11 g, 42 mmol) and stirred at ambient temperature for 48 hours. After filtration the residue was washed four times with ether. The filtrate was concentrated and petroleum ether was added. Flash chromatography furnished 2-heptenyl chloride **4** (5.04 g, 91% yield) as a colorless oil. IR (neat): 1465, 1441, 1252, 119, 971, 677; ^1H NMR (300 MHz, $CDCl_3$): δ 5.79 (1H, m), 5.62 (1H, m), 4.05 (2H, d, J=7.1 Hz), 2.07 (2H, m), 1.37 (4H, m), 0.90 (3H, t, J=7.1 Hz); EIMS (m/z): 132 (M^+, 24.79), 104 (9.72), 97 (41.41), 90 (11.31), 83 (15.34), 81 (35.30), 70 (20.45), 67 (30.40), 55 (100.00), 43 (31.77).

Methyl 5-decen-2-ynoate 5

DBU (2.28 g, 30 mmol) and CuI (2.85 g, 30 mmol) were dissolved in 15 mL of THF containing hydroxylamine hydrochloride (10 mg) and phenothiazine (10 mg). Then methyl propiolate (1.385 g,

16 mmol) dissolved in 5 mL of THF was added to the mixture. After the resulting mixture was stirred at 40°C for 30 minutes, HMPA (1.5 mL) and 2-heptenyl chloride **4** (1.325 g, 10 mmol) was added. The mixture was warmed to 60°C. After stirring for 2 hours, saturated aqueous NH_4Cl (10 mL) was added and the reaction mixture was extracted with ether (3×10 mL). The organic phases were washed with brine, dried (Na_2SO_4) and evaporated. Purification of the crude product by flash chromatography yielded the required compound **5** (1.172 g, 65% yield) as a colorless oil. IR (neat): 2950, 2265, 1953, 1439; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.68 (1H, m), 5.37 (1H, m), 3.76 (3H, s), 3.04 (2H, m), 2.07 (2H, m), 1.34 (6H, m), 0.92 (3H, t, *J*=7.0 Hz); EIMS (m/z): 181(M^++1, 47.35); HRMS for $C_{11}H_{16}O_2$: 180.1150; Found: 180.1161.

Methyl (5S,6S)-5,6-dihydroxy-2-decynoate 6

To a stirred solution of AD-mix-α [K_2CO_3 (828 mg, 6 mmol), $K_3Fe(CN)_6$ (2 g, 6 mmol), $NaHCO_3$ (504 mg, 6 mmol), $CH_3SO_2NH_2$ (190 mg, 2 mmol), $K_2OsO_2(OH)_4$ (7.5 mg) and $(DHQ)_2PHAL$ (16 mg, 0.02 mmol)], in 50% aqueous *t*-BuOH (20 mL) was added trans-olefin **5**. The resulting mixture was stirred for 4 hours at 0°C. Sodium sulfide (3 g) was added. The mixture was stirred for 3 hours and extracted with ethyl acetate. The extract was washed with 5% aqueous HCl and brine, dried over Na_2SO_4. After evaporation, the crude product was purified by flash chromatography to afford **6** (400 mg, 94% yield) as a white solid. m.p. 54–56°C; $[\alpha]_D^{25}$ +14.0 (c, 0.5, CH_3OH); IR (neat): 3320, 2050, 1729, 1604, 1439; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (3H, s), 3.70 (1H, m), 3.60 (1H, m), 2.62 (2H, d, *J*=6.0 Hz), 2.50–2.10 (2H, br), 1.70–1.20 (6H, m), 0.91 (3H, t, *J*=7.1 Hz); EIMS (m/z): 215 (M+1, 16.77); Elemental analysis for $C_{11}H_{18}O_4$ C: 61.66, H: 8.40; Found: C: 61.56, H: 8.42.

(6S,1′S)-(−)-5,6-Dihydro-6-(1′-hydroxypentyl)-4-methoxy-pyran-2-one 1

Sodium (0.1 g) was dissolved in MeOH (50 mL). A portion of this solution (2 mL) was added to a stirred solution of **6** (107 mg, 0.5 mmol) in MeOH (1 mL). The mixture was stirred for 24 hours at room temperature. It was then poured into the mixture of ice and diluted AcOH (0.3 mL of AcOH in 25 mL of ice–water). After checking its pH (~4), the mixture was extracted with ether. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **1** (101 mg, 94%) as a white solid. m.p. 89–92°C; $[\alpha]_D^{20}$ −88.7 (c, 1.7, CH_3OH); IR (neat): 3420, 1634, 1439; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.36 (1H, d, *J*=1.0 Hz), 4.38 (1H, m), 4.20 (1H, m), 3.66 (3H, s), 3.50 (1H, d, *J*=18.6 Hz), 3.05 (1H, ddd, *J*=18.6, 5.0, 2.1 Hz), 1.73 (1H, m), 1.70–1.30 (6H, m), 0.91 (3H, t, *J*=7.1 Hz); EIMS (m/z): 214 (M^+, 43.07), 197 (23.94), 183 (54.99), 165 (27.35), 137 (21.89), 121 (13.89), 116 (56.49), 69 (100.00); Elemental analysis for $C_{11}H_{18}O_4$: C: 61.66, H: 8.40; Found: C: 61.55, H: 8.47.

Methyl (5R,6R)-5,6-dihydroxy-2-decynoate 7

To a stirred solution of AD-mix-β [K_2CO_3 (414 mg, 3 mmol), $K_3Fe(CN)_6$ (987 mg, 3 mmol), $NaHCO_3$ (252 mg, 3 mmol), $CH_3SO_2NH_2$ (95 mg, 1mmol), $K_2OsO_2(OH)_4$ (4 mg) and $(DHQD)_2PHAL$ (40 mg)] in 50% aqueous *t*-BuOH (10 mL) was added trans-olefin **5**. The resulting mixture was stirred for 4 hours at r.t. Sodium sulfide (1.5 g) was added. The mixture was stirred for 3 hours and extracted with ethyl acetate. The extract was washed with 5% aqueous HCl and brine, and then dried over Na_2SO_4. After evaporation, the crude product was purified by flash chromatography to afford **7** (169 mg, 79% yield) as a white solid. m.p. 55–57°C; $[\alpha]_D^{25}$ −14.8 (c, 0.5, CH_3OH); IR (neat): 3350, 2265, 1727, 1438; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (3H, s), 3.72 (1H, m), 3.60 (1H, m), 2.63 (2H, d, *J*=6.2 Hz), 2.16 (2H, br), 1.57–1.23 (6H, m), 0.9 (3H, t, *J*=7.0 Hz); EIMS (m/z): 215 (M^++1, 1.51), 137 (3.69), 125 (22.16), 117 (18.17), 98 (89.74), 69 (100.00), 43 (29.85).

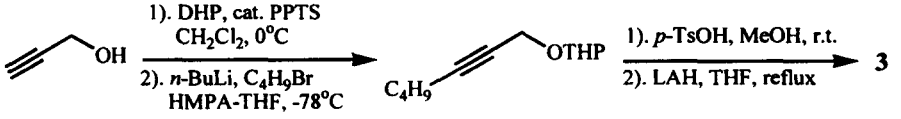
(6R,1′R)-(−)-5,6-Dihydro-6-(1′-hydroxypentyl)-4-methoxy-pyran-2-one 2

Sodium (0.1 g) was dissolved in MeOH (50 mL). A portion of this solution (2 mL) was added to a stirred solution of **7** (100 mg, 0.5 mmol) in MeOH (1 mL). The mixture was stirred for 24 hours at room temperature. It was then poured into the mixture of ice and diluted AcOH (0.3 mL of AcOH in

25 mL of ice–water). After checking its pH (~4), the mixture was extracted with ether. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **2** (90 mg, 90%) as a white solid. m.p. 85–90°C; $[\alpha]_D^{20}$ +91.1 (c, 1.34, CH_3OH); IR (neat): 2915, 1697, 1629, 1440, 1380, 1339, 1133, 1042, 813; ^1H NMR (300 MHz, $CDCl_3$): δ 5.32 (1H, d, *J*=1.0 Hz), 4.36 (1H, m), 4.15 (1H, m), 3.63 (3H, s), 3.48 (1H, d, *J*=18.7 Hz), 2.97 (1H, ddd, *J*=18.7, 5.3, 2.3 Hz), 1.71 (1H, m), 136 (6H, m), 0.87 (3H, t, *J*=7.1Hz); EIMS (m/z): 214 (M^+, 5.31), 183 (4.97), 165 (2.35), 153 (3.03), 139 (2.01), 126 (2.75), 113 (3.31), 101 (17.79), 84 (12.47), 69 (49.28), 43 (100.00).

References

1. a). Kimura, Y.; Katagiri, K.; Tamura, T. *Tetrahedron Lett.* **1971**, 3137. b). Kimura, Y.; Katagiri, K.; Tamura, T. *Agric. Biol. Chem.* **1972**, 1925.
2. Ellestad, W. J.; McGahren, G. A.; Kunstmann, M. P. *J. Org. Chem.* **1972**, *37*, 2045.
3. McGahren, G. A.; Ellestad, W. J.; Morten, G. O.; Kunstmann, M. P.; Mullen, P. *J. Org. Chem.* **1973**, *38*, 3542.
4. Carlson, R. M.; Ogler, A. R. *Tetrahedron Lett.* **1974**, 2615.
5. Izawa, T.; Mukaiyama, T. *Chem. Lett.* **1978**, 409.
6. Mori, K.; Oda, M.; Matsui, M. *Tetrahedron Lett.* **1976**, 3173.
7. Masaki, Y.; Nagata, K.; Serizawa, Y.; Kaji, K. *Tetrahedron Lett.* **1984**, *25*, 95.
8. Kirihata, M.; Ohta, K.; Yamamoto, S.; Ichimoto, I.; Ueda, H. *Abstract of Papers, Annual Meeting of the Agricultural Chemical Society of Japan*, **1980**, Fukuoka, p. 211.
9. Meyer, H.; Seebach, D. *Liebigs Ann. Chem.* **1975**, 2261.
10. Seebach, D.; Meyer, H. *Angew Chem Int. Ed. Engl.* **1974**, *13*, 77.
11. Mori, K.; Otsuka, T.; Oda, M. *Tetrahedron* **1984**, *40*, 2929.
12. Midland, M. M.; Graham, R. S. *J. Am. Chem. Soc.* **1984**, *106*, 4294.
13. Zhang, J. C.; Curran, D. P. *J. Chem. Soc. Perkin I*, **1991**, 2627.
14. Hagiwara, H.; Kimura, K.; Uda, H. *J. Chem. Soc. Trans. Perkin I*, **1992**, 693.
15. Hagiwara, H.; Kimura, K.; Uda, H. *J. Chem. Soc. Chem. Commun.* **1986**, 860.
16. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L., *J. Org. Chem.* **1992**, *57*, 2768.
17. Compound **3** was prepared starting from propargyl alcohol as shown below:



18. Snyder, E. I. *J. Org. Chem.* **1972**, *37*, 1466.
19. Eiter, K.; Lieb, F.; Disselnkötter H.; Oediger, H. *Liebigs Ann. Chem.* **1978**, 658.

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