ENANTIO- AND DIASTEREOSELECTIVE SYNTHESIS OF (+)-ASPERLIN BY THE SHARPLESS ASYMMETRIC KINETIC RESOLUTION OF AN UNSYMMETRICAL DIVINYLCARBINOL

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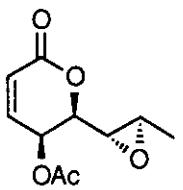
Abstract — An enantio- and diastereoselective synthesis of (+)-asperlin was achieved by employing the Sharpless asymmetric kinetic resolution of an unsymmetrical divinylcarbinol.

(+)-Asperlin (**1**), isolated from *Aspergillus nidulans* and *A. caespitosus*,[1] is a naturally occurring α,β-unsaturated δ-lactonic antibiotic exhibiting antitumor and antibacterial activities and its structure including the absolute configuration was determined by chemical and spectroscopical studies and also by syntheses.[2,3]



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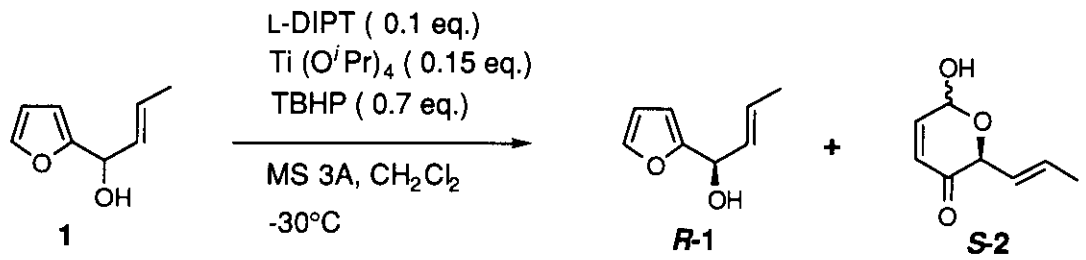
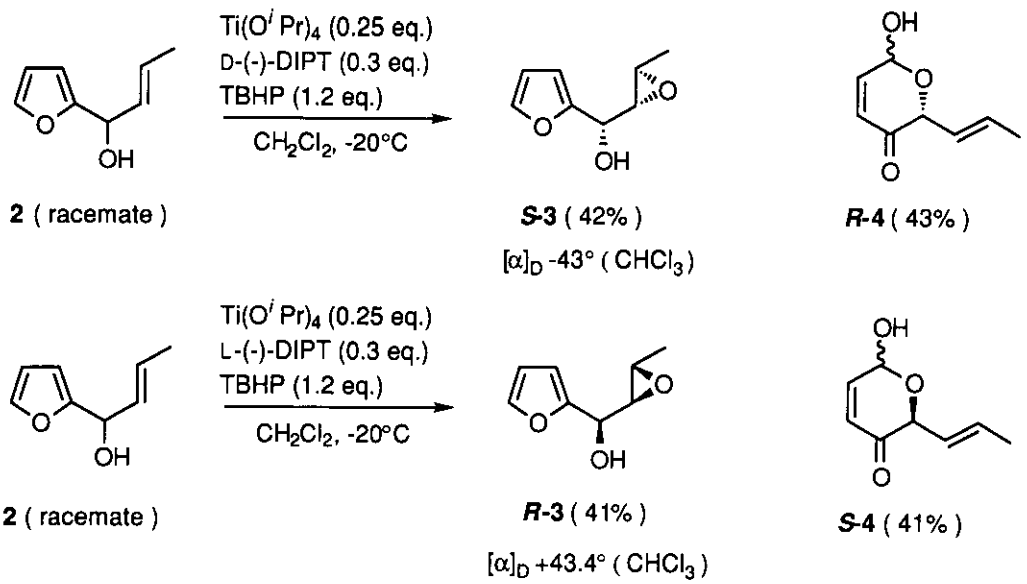
We have already developed the kinetic resolution of 2-furylcarbinols under the Sharpless asymmetric epoxidation reaction conditions to give the optically active 2-furylcarbinols in high enantiomeric excess.[4] (Scheme 1)

This strategy could further be applied to unsymmetrical divinylcarbinols, where we found that the reactivity of the double bonds presented in the substrates varied with the chirality of diisopropyl tartrate

(DIPT) employed in the reaction.[5,6] When racemic (*E*)-(2-furyl)-but-2-en-1-ol (**2**) was subjected to the Sharpless kinetic resolution with 1.2 equivalents of *tert*-butyl hydroperoxide (TBHP) in the presence of

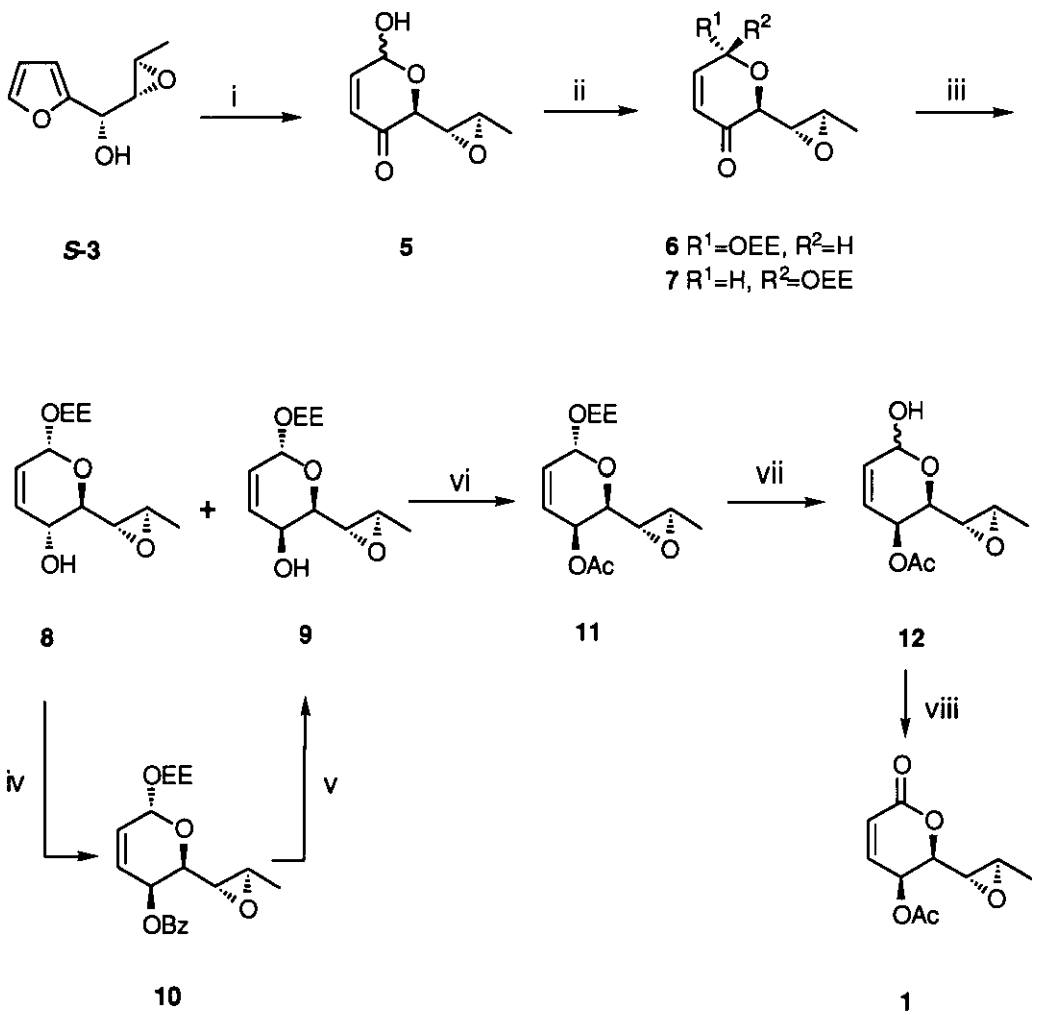


D-(-)-DIPT, the optically active (*S*)-epoxide (***S*-3**) and (*R*)-pyranone (***R*-4**)[4] were isolated in 42 and 43% yields, respectively, with >97% enantiomeric excess. Conversely, oxidation of **2** with L-(+)-DIPT gave the optically pure (*R*)-epoxide (***R*-3**) and (*S*)-pyranone (***S*-4**) in 41 and 41% yields, respectively.



Scheme 2

In both cases, the epoxidation proceeded entirely in diastereofacial-selective manner and none of the epoxide diastereomers were observed in these reactions. (Scheme 2) By application of this methodology to natural product synthesis and also in order to determine the absolute configurations at the C-2 and C-3 positions of the (*S*)-epoxide, a concise enantioselective synthesis of (+)-asperlin (**1**) was investigated as follows. (Scheme 3)



Scheme 3. *Reagents and conditions*: i, NBS, aq. THF (66%); ii, ethyl vinyl ether, PPTS, CH_2Cl_2 (**6**; 60%, **7**; 27%); iii, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH (**8**; 90%, **9**; 9%); iv, $PhCO_2H$, DEAD, Ph_3P, THF (87%); v, K_2CO_3, MeOH (100%); vi, Ac_2O, Py, DMAP, CH_2Cl_2 (100%); vii, aq. AcOH, THF (96%); viii, PCC, Celite, AcONa,CH_2Cl_2 (91%).

Oxidation of the optically pure (*S*)-epoxide (***S*-3**) obtained above with aqueous *N*-bromosuccinimide[7] afforded the pyranone derivative (**5**), which on treatment with ethyl vinyl ether and PPTS gave the ethoxyethyl ethers (**6** and **7**) in 60 and 27% yields, respectively. The major isomer (**6**) was reduced with sodium borohydride in the presence of cerium(III) chloride to give the allylic alcohols (**8** and **9**) in 90 and 9% yields, respectively. Mitsunobu reaction[8] of the major alcohol (**8**) with benzoic acid gave the benzoate (**10**), which on hydrolysis with potassium carbonate in methanol furnished the desired alcohol (**9**), in 87% two-steps yield, with the correct configuration for the natural product. Acetylation of the alcohol (**9**) with acetic anhydride provided the acetate (**11**) in quantitative yield. Finally the acetate (**11**) was converted into (+)-asperlin (**1**), mp 71.5-72.0°C (benzene-Et_2O) (lit.,[3] 71-73°C), by two steps involving acidic deprotection of the ethoxyethyl group and subsequent oxidation of the resulting lactol (**12**) with PCC in 87% yield. The spectroscopic data including the specific optical rotation {$[\alpha]_D$ +342.4° (c 1.0, EtOH), lit.,[3] $[\alpha]_D$ +345° (c 0.9, EtOH)}, of the synthetic compound were identical with those reported.[3]

Thus, we could establish the facile enantio- and diastereoselective synthesis of (+)-asperlin (**1**) by employing the Sharpless kinetic resolution of the unsymmetrical divinylcarbinol and this strategy would be applicable to the synthesis of various types of natural products in optically active forms.

EXPERIMENTAL SECTION

IR spectra were recorded for thin films on a JASCO FT/IR-200 Fourier transform IR spectrophotometer. ^{1}H-NMR spectra were obtained for solution in $CDCl_3$ on a JEOL PMX-270 instrument, and chemical shifts are reported on the δ-scale from internal TMS. MS spectra were measured with a JEOL JMS D-300 spectrometer. Optical rotations were taken with a JASCO DIP-360 polarimeter.

Kinetic Resolution of Racemic (*E*)-(2-Furyl)but-2-en-1-ol (**2**) ----- To a stirred suspension of MS 3Å (75 mg) and CaH_2 (15 mg, 0.36 mmol) in CH_2Cl_2 (1 mL) was added $Ti(O^iPr)_4$ (0.14 mL, 0.45 mmol) at rt and the resulting mixture was cooled to -20°C. To this mixture was added a solution of L-(+)-DIPT (127 mg, 0.54 mmol) in CH_2Cl_2 (1.2 mL) and the whole was stirred for further 30 min at the same temperature. A solution of racemic (*E*)-(2-furyl)but-2-en-1-ol (**2**) (250 mg, 1.81 mmol) in CH_2Cl_2 (2.5

mL) was added to the mixture and stirred for 30 min. After addition of TBHP (5.27M solution in isooctane; 0.41 mL, 2.2 mmol), the resulting mixture was stirred at -20°C for 12 h. Dimethyl sulfide (0.17 mL, 2.35 mmol) was slowly added and the mixture was stirred for further 30 min at the same temperature. To this mixture were added 10% aqueous tartaric acid (0.55 mL, 0.36 mmol) and Et_2O (4 mL), and the resulting mixture was vigorously stirred for 2 h at ambient temperature. The precipitate was filtered off through a pad of Celite and the filtrate was concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (2:1, v/v) gave the (*S*)-**3** (114.4 mg, 41%) as an amorphous powder and (*R*)-**4** (114.3 mg, 41%) as an oil. Optical purity of (*S*)-**3** was determined to be 100% based on the comparison of its optical rotation with that of authentic sample derived from the optically pure (*S*)-(*E*)-(2-furyl)but-2-en-1-ol.[4]

(*S*)-**3**: $[\alpha]_D$ +43.4° (c 1.0, $CHCl_3$). IR 3400 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (3H, d, J=4.9 Hz, Me), 2.94 (1H, br s, OH), 3.03 (1H, dd, J=2.5 and 3.4 Hz, 2-H), 3.22 (1H, dd, J=2.5 and 5.5 Hz, 3-H), 4.08 (1H, d, J=3.4 Hz, 1-H), 6.33-6.37 (2H, m, furyl protons), 7.40-7.41 (1H, m, furyl proton); MS *m/z* 154 (M^+).

The epoxide (*R*)-**3** (42%) and the pyranone (*S*)-**4** (43%) were also obtained by the Sharpless kinetic resolution of racemic **2** employing D-(-)-DIPT.

(2*S*)-6-Hydroxy-2-[(1*R*,2*R*)-1',2'-epoxypropyl]-2,6-dihydropyran-3-one (**5**) ----- To a stirred solution of the furylalcohol (*S*-**3**) (367 mg, 2.38 mmol) and anhydrous sodium acetate (215 mg, 2.62 mmol) in aqueous THF (4.5 mL, THF:H_2O=4:1) was added portionwise *N*-bromosuccinimide (467 mg, 2.62 mmol) at 0°C, and the mixture was stirred for further 30 min at the same temperature. After addition of 10% aqueous KI solution and saturated sodium thiosulfate solution, the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (1:1, v/v) gave the lactol (**5**) (266 mg, 66%) as a colorless oil; IR 3400 and 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (2.25H, d, J=4.9 Hz, Me), 1.35 (0.75H, d, J=4.9 Hz, Me), 3.14 (0.25H, dq, J=2.5 and 4.9 Hz, 2'-H), 3.16 (0.75H, dq, J=2.5 and 4.9 Hz, 2'-H), 3.25 (0.25H, t, J=2.5 Hz, 1'-H), 3.31 (0.75H, t, J=2.5 Hz, 1'-H), 4.06 (0.75H, d, J=4.9 Hz, OH), 4.17 (0.25H, d, J=9.8 Hz, OH), 4.49 (0.25H, d, J=2.5 Hz, 2-H), 4.78 (0.75H, d, J=2.5 Hz, 2-H), 5.60 (0.25H, dd, J=3.1 and 9.8 Hz, 6-H), 5.70

(0.75H, dd, J=3.7 and 4.9 Hz, 6-H), 6.13 (1H, d, J=10.4 Hz, 4-H), 6.94 (0.75H, dd, J=3.7 and 10.4 Hz, 5-H), 6.97 (0.25H, dd, J=3.1 and 10.4 Hz, 5-H); Anal. Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 55.98; H, 5.93.

(2*S*,6*R*)-6-Ethoxyethoxy-2-[(1*R*,2*R*)-1',2'-epoxypropyl]-2,6-dihydropyran-3-one (**6**) and (2*S*,6*S*)-6-Ethoxyethoxy-2-[(1*R*,2*R*)-1',2'-epoxypropyl]-2,6-dihydropyran-3-one (**7**) ----- To a stirred solution of the lactol (**5**) (503 mg, 2.96 mmol) in CH_2Cl_2 (5 mL) were added ethyl vinyl ether (2.8 mL, 29.6 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate at 0°C, and the resulting mixture was stirred for further 5 h at rt. After addition of saturated $NaHCO_3$ solution, the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (5:1, v/v) gave the α-ethoxyethyl ether (**6**) (430 mg, 60%) as a colorless oil; IR 1695 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (3H, t, J=7.3 Hz, OCH_2CH_3), 1.33 (3H, d, J=4.9 Hz, Me), 1.38 and 1.41 (each 1.5H, each d, J=5.5 Hz, $OCHCH_3$), 3.10-3.25 (2H, m, 1' and 2'-H), 3.47-3.84 (2H, m, OCH_2CH_3), 4.55 and 4.62 (each 0.5H, each d, J=3.1 Hz, 2-H), 4.95 and 5.00 (each 0.5H, each q, J=5.5 Hz, $OCHCH_3$), 5.55 and 5.57 (each 0.5H, each d, J=3.7 Hz, 6-H), 6.12 and 6.14 (each 0.5H, each d, J=10.4 Hz, 4-H), 6.83 and 6.88 (each 0.5H, each dd, J=3.7 and 10.4 Hz, 5-H); Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.34; H, 7.63. Further elution with the same solvent system afforded the β-ethoxyethyl ether (**7**) (193 mg, 27%) as colorless needles; mp 78-80°C (hexane-Et_2O); IR 1695 cm^{-1}; NMR ($CDCl_3$) δ 1.22 and 1.24 (each 1.5H, each t, J=7.3 Hz, OCH_2CH_3), 1.33 (3H, d, J=5.5 Hz, Me), 1.40 and 1.44 (each 1.5H, each d, J=5.5 Hz, $OCHCH_3$), 3.07 and 3.08 (each 0.5H, each dq, J=1.8 and 5.5 Hz, 2'-H), 3.19 and 3.25 (each 0.5H, each dd, J=1.8 and 3.1 Hz, 1'-H), 3.49-3.85 (2H, m, OCH_2CH_3), 4.17 and 4.20 (each 0.5H, each d, J=3.1 Hz, 2-H), 5.01 and 5.13 (each 0.5H, each q, J=5.5 Hz, $OCHCH_3$), 5.62 (1H, br s, 6-H), 6.17 and 6.18 (each 0.5H, each dd, J=1.2 and 10.4 Hz, 4-H), 6.85 and 6.92 (each 0.5H, each dd, J=2.4 and 10.4 Hz, 5-H); Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.61; H, 7.64.

(2*S*,3*R*,6*R*)-6-Ethoxyethoxy-2-[(1*R*,2*R*)-1',2'-epoxypropyl]-2,6-dihydropyran-3-ol (**8**) and (2*S*,3*S*,6*R*)-6-Ethoxyethoxy-2-[(1*R*,2*R*)-1',2'-epoxypropyl]-2,6-dihydropyran-3-ol (**9**) ----- To a

stirred solution of the enone (**6**) (440 mg, 1.82 mmol) and $CeCl_3 \cdot 7H_2O$ (1.02 g, 2.72 mmol) in methanol (6.5 mL) was added $NaBH_4$ (6.9 mg, 1.82 mmol) at 0°C, and the resulting mixture was stirred for 10 min at the same temperature. After addition of saturated ammonium chloride solution, insoluble material was filtered off and the filtrate was extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (2:1, v/v) gave the α-alcohol (**8**) (398 mg, 90%) as a colorless oil; IR 3530 cm^{-1}; NMR ($CDCl_3$) δ 1.21 and 1.22 (each 1.5H, each t, J=7.3 Hz, OCH_2CH_3), 1.34-1.37 (6H, m, Me and $OCHCH_3$), 2.40 and 2.45 (each 0.5H, each d, J=6.1 Hz, OH), 2.94 and 2.95 (each 0.5H, each dd, J=1.8 and 4.3 Hz, 1'-H), 3.08-3.14 (1H, m, 2'-H), 3.43-3.84 (3H, m, 3-H and OCH_2CH_3), 4.17-4.23 (1H, m, 2-H), 4.88 and 4.94 (each 0.5H, each q, J=5.5 Hz, $OCHCH_3$), 5.18 and 5.25 (each 0.5H, each br s, 6-H), 5.64 and 5.76 (each 0.5H, each dt, J=2.4 and 10.4 Hz, 5-H), 5.94 (1H, br d, J=10.4 Hz, 4-H); Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.02; H, 8.44. $[\alpha]_D$ -66.3° (c 0.7, $CHCl_3$). Further elution with the same solvent system afforded the β-alcohol (**9**) (38 mg, 9%) as a colorless oil; IR 3490 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (3H, t, J=7.3 Hz, OCH_2CH_3), 1.35 and 1.38 (each 1.5H, each d, J=5.5 Hz, $OCHCH_3$), 1.37 (3H, d, J=5.5 Hz, Me), 2.01 and 2.04 (each 0.5H, each br s, OH), 3.02-3.13 (2H, m, 1' and 2'-H), 3.43-3.81 (2H, m, OCH_2CH_3), 3.85 and 3.91 (each 0.5H, each dd, J=2.4 and 4.9 Hz, 2-H), 3.91-3.95 (1H, m, 3-H), 4.89 and 4.96 (each 0.5H, each q, J=5.5 Hz, $OCHCH_3$), 5.27 and 5.32 (each 0.5H, each d, J=3.1 Hz, 6-H), 5.85 and 5.92 (each 0.5H, each dd, J=3.1 and 10.4 Hz, 5-H), 6.15-6.22 (1H, m, 4-H); Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.48; H, 8.56. $[\alpha]_D$ +74.9° (c 0.8, $CHCl_3$).

(2*S*,3*R*,6*R*)-3-Benzoyloxy-6-ethoxyethoxy-2-[(1*R*,2*R*)-1',2'-epoxypropyl]-2,6-dihydropyran (**10**) --- To a stirred solution of diethyl azodicarboxylate (0.21 mL, 1.36 mmol) and benzoic acid (170 mg, 1.39 mmol) in dry THF (3 mL) was added dropwise a solution of the alcohol (**8**) (170 mg, 0.70 mmol) and triphenylphosphine (365 mg, 1.39 mmol) in THF (2 mL) at 0°C, and the resulting mixture was stirred for further 5 h at rt under argon. After treatment with saturated ammonium chloride solution, most of the organic solvent was removed to leave an oil, which was extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was subjected to

column chromatography on silica gel. Elution with hexane-ethyl acetate (5:1, v/v) gave the benzoate (**10**) (210 mg, 87%) as colorless needles; mp 66-68°C (hexane-Et_2O); IR 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.20-1.26 (6H, m, 2×Me), 1.38 and 1.40 (each 1.5H, each d, J=5.5 Hz, Me), 2.94-2.96 (1H, m, 1'-H), 3.09-3.14 (1H, m, 2'-H), 3.46-3.84 (2H, m, OCH_2CH_3), 4.14 and 4.19 (each 0.5H, each dd, J=2.5 and 4.9 Hz, 2-H), 4.92 and 4.98 (each 0.5H, each q, J=5.5 Hz, $OCHCH_3$), 5.35 and 5.40 (each 0.5H, each d, J=3.1 Hz, 6-H), 5.36 (1H, dd, J=2.5 and 5.5 Hz, 3-H), 6.00 and 6.08 (each 0.5H, each dd, J=3.1 and 10.4 Hz, 5-H), 6.28 (1H, dd, J=5.5 and 10.4 Hz, 4-H), 7.42-7.61 (3H, m, aromatic protons), 8.07 (2H, d, J=7.3 Hz, aromatic protons); Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.37; H, 6.99. $[\alpha]_D$ +230.0° (c 0.6, $CHCl_3$).

Hydrolysis of the Benzoate (**10**) ----- To a stirred solution of the benzoate (**10**) (250 mg, 0.72 mmol) in methanol (5 mL) was added portionwise potassium carbonate (99 mg, 0.72 mmol) at 0°C, and the resulting mixture was stirred for further 2 h at rt. After treatment with saturated ammonium chloride solution, the mixture was extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (3:2, v/v) gave the alcohol (**9**) (175 mg, 100%) as a colorless oil, which was identical with the authentic sample obtained above.

(2*S*,3*R*,6*R*)-3-Acetoxy-6-ethoxyethoxy-2-[(1*R*,2*R*)-1',2'-epoxypropyl]-2,6-dihydropyran (**11**) ---- A solution of the alcohol (**9**) (140 mg, 0.57 mmol), 4-dimethylaminopyridine (14 mg, 0.12 mmol), pyridine (0.14 mL, 1.72 mmol), and acetic anhydride (0.14 mL, 1.43 mmol) in CH_2Cl_2 (2 mL) was stirred for 1 h at 0°C under argon. The solution was treated with brine and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (5:1, v/v) gave the acetate (**11**) (164 mg, 100%) as a colorless oil; IR 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (3H, t, J=7.3 Hz, OCH_2CH_3) 1.24-1.38 (6H, m, $OCHCH_3$ and Me), 2.11 (3H, s, Ac), 2.87 (1H, dd, J=2.4 and 5.5 Hz, 1'-H), 3.07 (1H, dq, J=2.4 and 5.5 Hz, 2'-H), 3.48 and 3.52 (each 0.5H, each dq, J=7.3 and 9.2 Hz, $OCHHCH_3$), 3.67 and 3.77 (each 0.5H, each dq, J=7.3 and 9.2 Hz, $OCHHCH_3$), 3.97 and 4.02 (each 0.5H, each dd, J=2.4 and 5.5 Hz, 2-H), 4.88 and 4.94 (each 0.5H, each q, J=5.5 Hz,

OC*H*CH_3), 5.10 (1H, dd, J=2.4 and 5.5 Hz, 3-H), 5.31 and 5.35 (each 0.5H, each d, J=3.1 Hz, 6-H), 5.96 and 6.03 (each 0.5H, each dd, J=3.1 and 9.8 Hz, 5-H), 6.17 (1H, dd, J=5.5 and 9.8 Hz, 4-H); Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 58.90; H, 8.00. $[\alpha]_D$ +163.2° (c 0.8, $CHCl_3$).

(2*S*,3*R*)-3-Acetoxy-2-[(1*R*,2*R*)-1',2'-epoxypropyl]-2,6-dihydropyran-6-ol (**12**) ---- To a stirred solution of the ethoxyethyl ether (**11**) (190 mg, 0.66 mmol) in THF (0.9 mL) was added aqueous acetic acid (3.6 mL, H_2O: AcOH = 1:3) at 0°C, and the resulting solution was stirred for 24 h at ambient temperature. Saturated $NaHCO_3$ solution was added to the above solution and the whole was stirred for 20 min at rt, and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4, and concentrated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (5:2, v/v) gave the lactol (**12**) (137 mg, 96%) as colorless needles; mp 74-74.5°C (hexane-Et_2O); IR 3380 and 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (3H, d, J=5.5 Hz, Me), 2.11 (3H, s, Ac), 2.90 (1H, dd, J=2.4 and 4.9 Hz, 1'-H), 3.00-3.26 (2H, m, 2'-H and OH), 3.68 (0.1H, dd, J=2.4 and 4.9 Hz, 6-H), 4.14 (0.9H, dd, J=2.4 and 4.9 Hz, 6-H), 5.11 (0.9H, dd, J=2.4 and 5.5 Hz, 5-H), 5.17-5.20 (0.1H, m, 5-H), 5.35-5.37 (0.1H, m, 2-H), 5.45-5.55 (0.9H, m, 2-H), 6.07 (1H, dd, J=3.1 and 10.4 Hz, 3-H), 6.17 (1H, dd, J=5.5 and 10.4 Hz, 4-H); Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.08; H, 6.71. $[\alpha]_D$ +240.0° (c 0.8, $CHCl_3$).

(+)-Asperlin (**1**) ----- To a stirred suspension of PCC (363 mg, 1.68 mmol), anhydrous sodium acetate (138 mg, 1.68 mmol), and Celite (300 mg) in dry CH_2Cl_2 (1 mL) was added dropwise a solution of the lactol (**12**) (120 mg, 0.56 mmol) in CH_2Cl_2 (2 mL) at rt under argon, and the resulting solution was stirred for further 1 h. An excess of Et_2O was added to the solution and the insoluble material was filtered off. The filtrate was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (2:1, v/v) gave (+)-asperlin (**1**) (108 mg, 91%) as colorless plates; mp 71.5-72°C (hexane-Et_2O); IR 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.39 (3H, d, J=5.5 Hz, Me), 2.14 (3H, s, Ac), 3.04-3.12 (2H, m, 1' and 2'-H), 4.11 (1H, dd, J=3.1 and 6.7 Hz, 6-H), 5.32 (1H, dd, J=3.1 and 5.5 Hz, 5-H), 6.22 (1H, d, J=9.8 Hz, 3-H), 7.09 (1H, dd, J=5.5

and 9.8 Hz, 4-H). These spectroscopic data including specific optical rotation were identical with those reported.[3]

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REFERENCES

1. a) A. D. Argoudelis, J. H. Coats, and R. R. Herr, *Antimicrob. Agents Chemother.*, 1965, 801; b) S. P. Owen and B. K. Bhuynan, *ibid.*, 1965, 804; c) A. D. Argoudelis and J. F. Zieseri, *Tetrahedron Lett.*, 1966, 1969; d) S. Mizuba, K. Lee, and J. Liu, *Can. J. Microbiol.*, 1975, **21**, 1781; e) K. Fukuyama, Y. Katsube, A. Noda, T. Hamasaki, and Y. Hatsuda, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 3175.
2. T. K. M. Shing and M. Aloui, *J. Chem. Soc., Chem. Commun.*, 1988, 1525.
3. a) S. Lesage and A. S. Perlin, *Can. J. Chem.*, 1978, **56**, 2889; b) T. Maruyama, T. Sugiyama, and K. Yamashita, *Agric. Biol. Chem.*, 1986, **50**, 1923; c) T. Maruyama, T. Sugiyama, and K. Yamashita, *ibid.*, 1987, **51**, 2055; d) H. Hiraoka, K. Furuta, N. Ikeda, and H. Yamamoto, *Agric. Biol. Chem.*, 1987, **65**, 339; e) S. Ramesh and R. W. Franck, *Tetrahedron:Asymmetry*, 1990, **1**, 137; f) Y. Masaki, T. Imaeda, H. Oda, A. Itoh, and M. Shiro, *Chemistry Lett.*, 1992, 1209; g) A. M. Gómez, B. L. de Uralde, S. Valverde, and J. C. López, *Chem. Commun.*, 1997, 1647.
4. a) T. Kametani, M. Tsubuki, Y. Tatsuzaki, and T. Honda, *Heterocycles*, 1988, **27**, 2107; b) T. Kametani, M. Tsubuki, and T. Honda, *Chem. Pharm. Bull.*, 1988, **36**, 3706; c) T. Kametani, M. Tsubuki, Y. Tatsuzaki, and T. Honda, *J. Chem. Soc., Perkin Trans. 1*, 1990, 639.
5. a) T. Honda, N. Sano, and K. Kanai, *Heterocycles*, 1995, **41**, 425; b) T. Honda, H. Mizutani, and K. Kanai, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1729; c) T. Honda, M. Ohta, and H. Mizutani, *Heterocycles*, 1997, **46**, 137.

6. After publication of this work as a preliminary communication (ref. 5a), a similar work was reported by Zhou and his co-workers: Z. -C. Yang and W. -S. Zhou, *Tetrahedron Lett.*, 1995, **36**, 5617; Z. -C. Yang, X. -B. Jiang, and W. -S. Zhou, *J. Chem. Soc., Perkin Trans. 1*, 1997, 317; Z. -C. Yang and W. -S. Zhou, *Heterocycles*, 1997, **45**, 367.

7. M. P. Georgiadis and E. A. Couladouros, *J. Org. Chem.*, 1986, **51**, 2725.

8. O. Mitsunobu, *Synthesis*, 1981, 1.

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