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Total Syntheses of All Four Stereoisomers of Piscidic Acid *via* Catalytic Asymmetric Dihydroxylation of (*Z*)- and (*E*)-trisubstituted Olefins

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All four stereoisomers of (2*S*, 3*R*)-(+)-piscidic acid were synthesized with high optical purity *via* Sharpless catalytic asymmetric dihydroxylation of (*Z*)- and (*E*)-trisubstituted olefins in 6 steps from (4-hydroxyphenyl)pyruvic acid. The Wittig reaction of methyl (4-hydroxyphenyl)pyruvate with (carbomethoxymethylene)triphenylphosphorane gave (*Z*)- and (*E*)-trisubstituted olefins in a 3:1 ratio. After protecting the phenolic hydroxyl group as the *tert*-butyldimethylsilyl ether, the (*Z*)-olefin was subjected to asymmetric dihydroxylation by using the chiral ligand, dihydroquinidine 1,4-anthraquinonediyl diether, and the reaction proceeded with 89% *e.e.* Desilylation and subsequent alkaline hydrolysis gave (2*S*, 3*R*)-(+)-piscidic acid. The optical purity was increased to >99% *e.e.* by recrystallization. The use of dihydroquinine 1,4-anthraquinonediyl diether enable (2*R*, 3*S*)-(−)-piscidic acid to be obtained. In the asymmetric dihydroxylation of the (*E*)-olefin, phthalazine ligands (dihydroquinidine and dihydroquinine 1,4-phthalazinediyl diethers) gave high *e.e.* values. *Via* the same deprotection procedure, (2*S*, 3*S*)-(+)-3-*epi*-piscidic acid and (2*R*, 3*R*)-(−)-2-*epi*-piscidic acid were respectively obtained.

Key words: piscidic acid; hypnotic and narcotic drugs; phosphorous uptake; cough medicine constituent; catalytic asymmetric dihydroxylation

Piscidic acid (**1**) [Fig. 1] is known as one of the constituents of hypnotic and narcotic drugs extracted from the root bark of *Piscidia erythrina* L. (Jamaica dogwood)[1–3] and as cough medicine constituent isolated from *Dioscorea nipponica*, a medicinal plant for treating chronic bronchitis.[4,5] The absolute configuration of **1** has been determined to be the same (2*S*, 3*R*)-configuration as that of fukiic acid (**3**).[6,7] Compound **1** and 4′-*O*-methyl-piscidic acid (**2**) have recently been shown to be related to the phosphorous uptake in pigeon pea [*Cajanus cajan* (L.) Millsp.],[8,9] one of the important crops in India. Root exudates of pigeon pea contain **1** and **2** which release soluble phosphorous from insoluble iron-bound phosphorous (Fe-P) in Alfisols, the major soil types in the Indian subcontinent, by chelating Fe^{3+}. Therefore, **1** and the related compounds would be important as chemical probes to identify the mechanism for these biological activities and would be expected to apply not only to medicinal chemistry but also to agricultural cropping systems. However, few synthetic studies of such compounds have so far been reported.[10–14] Although the stoichiometric dihydroxylation of olefins possessing a 3,4-dimethoxybenzyl group has been carried out with osmium tetraoxide[10,11] and potassium permanganate[12,13] in the syntheses of *O*,*O*′-dimethylfukiic acid and its derivatives, the yield from each reaction was low, and optical resolution was required in order to obtain the optically active form.[12,13] The asymmetric synthesis of **1** and its epimer *via* the alkylation of dimethyl L-tartrate acetonide required separation and epimerization of the alkylated products.[14] We therefore planned to use Sharpless catalytic asymmetric dihydroxylation in order to simultaneously solve all these problems. We have already communicated the catalytic asymmetric total synthesis of **1**.[15] We describe here in detail the total syntheses of all four stereoisomers of **1** *via* Sharpless catalytic asymmetric dihydroxylation (AD)[16] of the (*Z*)- and (*E*)-trisubstituted olefins.

Materials and Methods

General methods. Melting point (mp) values were obtained with Yamaco MP-30 micro-melting point apparatus and are uncorrected. Specific rotation values were measured with a JASCO DIP-370 digital polarimeter. ^{1}H- and ^{13}C-NMR spectra were recorded with a JEOL JNM-EX-270 spectrometer (^{1}H at 270 MHz; ^{13}C at 67.5 MHz). In the ^{1}H-NMR spectra, chemical shifts are reported as δ (ppm) values relative to the residual proton signal of the used deuterated solvent ($CDCl_3$: δ 7.26 ppm; acetone-d_6: δ 2.05 ppm). In the ^{13}C-NMR spectra, chemical shifts are reported as δ (ppm) values relative to the carbon signal ($CDCl_3$: δ 77.0 ppm; acetone-d_6: δ 206.5 ppm). IR spectra were measured with a Perkin Elmer System 2000 FT-IR spectrometer, and mass spectra were recorded with a JEOL JMS-AX500 or JEOL JMS-SX102A spectrometer. Analytical and preparative TLC was performed on precoated silica gel 60 F_{254} plates of Merck KGaA Art.5715 (0.25 mm thickness) and

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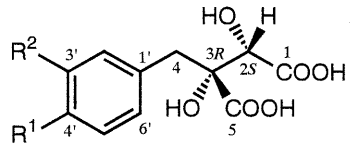
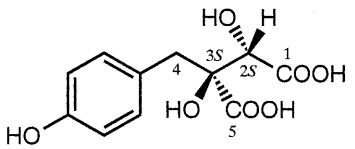
Abbreviations: AD, asymmetric dihydroxylation; TBDMS, *tert*-butyldimethylsilyl; $(DHQD)_2PHAL$, dihydroquinidine 1,4-phthalazinediyl diether; $(DHQD)_2PYR$, dihydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether; $(DHQD)_2AQN$, dihydroquinidine 1,4-anthraquinonediyl diether; (DHQD)CLB, dihydroquinidine 4-chlorobenzoate; (DHQD)IND, dihydroquinidine *N*-indolinecarbonate; DHQD, dihydroquinidine; $(DHQ)_2AQN$, dihydroquinine 1,4-anthraquinonediyl diether



Piscidic acid (**1**): R^1 = OH, R^2 = H
4'-*O*-Methyl-piscidic acid (**2**): R^1 = OMe, R^2 = H
Fukiic acid (**3**): R^1 = OH, R^2 = OH



3-*Epi*-piscidic acid (**4**)

Fig. 1. Structures of Piscidic Acid and Its Related Compounds.

Art.5544 (0.5 mm thickness), respectively. Column chromatography was carried out with silica gel 60N (spherical, neutral, 100–210 μm; Kanto Chemicals). AD-mix-α, AD-mix-β, and the chiral ligands, except for (DHQD) IND, were purchased from Aldrich Chemicals, (DHQD) IND being prepared in our laboratory.

Dimethyl (4-hydroxybenzyl)maleate (6Z) and dimethyl (4-hydroxybenzyl)fumarate (6E). To a solution of (4-hydroxyphenyl)pyruvic acid (**5**, 1.00 g, 5.6 mmol) in THF (80 ml) was added dropwise an ethereal solution of diazomethane at 0°C until **5** disappeared upon analytical TLC. The reaction mixture was concentrated under reduced pressure to give methyl (4-hydroxyphenyl)pyruvate which was used for the next Wittig reaction without purification. Data for methyl (4-hydroxyphenyl)pyruvate in its enol form: EIMS *m/z*: 194 (M^+, 55.1), 163 (M^+-CH_3O, 2.3), 121 (100), 121 (22.9), 107 (93.6), 106 (52.9), 77 (26.6); HRMS *m/z* (M^+): calcd. for $C_{10}H_{10}O_4$, 194.0579; found, 194.0597; IR ν_{max} (KBr) cm^{-1}: 3428, 1741, 1604, 1516, 1444, 1246, 828, 798, 769; ^{1}H-NMR δ ($CDCl_3$, 270 MHz): 7.67 (2H, d, *J*=8.6 Hz, Ar-*H*), 6.84 (2H, d, *J*=8.6 Hz, Ar-*H*), 6.48 (1H, s, Ar-CH=C(O*H*)COOMe), 6.28 (1H, s, Ar-C*H*=C(OH)COOMe), 5.15 (1H, br. s, Ar-O*H*), 3.90 (3H, s, COO*Me*); ^{13}C-NMR δ ($CDCl_3$, 67.5 MHz): 166.9, 155.6, 137.5, 131.7, 126.9, 115.5, 111.2, 53.2. A solution of (carbomethoxymethylene)triphenylphosphorane (5.56 g, 16.7 mmol) and methyl (4-hydroxyphenyl) pyruvate in benzene (20 ml) was refluxed for 2 h. The reaction mixture was concentrated under reduced pressure, and the resulting residue was separated by column chromatography (hexane:EtOAc=1:1) to give **6Z** (1.00 g, 72%, 2 steps) and **6E** (0.32 g, 23%, 2 steps), each as a colorless oil. The spectral data for **6Z** have already been reported.[15] Data for **6E**: EIMS *m/z*: 250 (M^+, 17.3), 219 (M^+-CH_3O, 21.9), 218 (M^+-CH_3OH, 100), 190 (31.7), 178 (29.3), 147 (46.6), 131 (29.7), 107 (28.9), 77 (7.9); HRMS *m/z* (M^+): calcd. for $C_{13}H_{14}O_5$, 250.0842; found, 250.0857; IR ν_{max} (film) cm^{-1}: 3406, 3054, 1717, 1645, 1607, 1515, 1436, 1171, 1105, 1021, 848, 800; ^{1}H-NMR δ ($CDCl_3$, 270 MHz): 7.13 (2H, d, *J*=8.6 Hz, Ar-*H*), 6.82 (1H, s, vinyl-H), 6.70 (2H, d, *J*=8.6 Hz, Ar-*H*), 5.22 (1H, br. s, Ar-O*H*), 4.11 (2H, s, Ar-CH_2), 3.80 (3H, s, COO*Me*), 3.74 (3H, s, COO*Me*); ^{13}C-NMR δ ($CDCl_3$, 67.5 MHz): 167.0, 166.1, 154.2, 146.1, 130.1, 129.7, 126.1, 115.1, 52.4, 51.7, 40.0.

Dimethyl (4-tert-butyldimethylsilyloxybenzyl)maleate (7Z). A mixture of **6Z** (3.37 g, 13.2 mmol), imidazole (1.35 g, 19.8 mmol), and *tert*-butylchlorodimethylsilane (2.39 g, 15.8 mmol) in DMF (40 ml) was stirred at room temperature for 5 h. The reaction mixture was partitioned between water (200 ml) and EtOAc (100 ml), and the aqueous layer was further extracted with EtOAc (50 ml × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (hexane:EtOAc=10:1) to give **7Z** (4.70 g, 98%) as a colorless oil. The spectral data for **7Z** have already been reported.[15]

Dimethyl (4-tert-butyldimethylsilyloxybenzyl)fumarate (7E). According to the same method as that used for **7Z**, **6E** (830 mg, 3.32 mmol) was converted into **7E** (1.13 g, 93%) as a colorless oil. EIMS *m/z*: 364 (M^+, 32.5), 332 (M^+-CH_3OH, 56.1), 275 (100), 248 (19.9), 247 (19.5), 216 (9.6), 187 (15.9), 135 (5.0), 115, (5.5), 89 (14.73), 73 (9.5); HRMS *m/z* (M^+): calcd. for $C_{19}H_{28}O_5Si$, 364.1706; found, 364.1699; IR ν_{max} (film) cm^{-1}: 3437, 3035, 2956, 2898, 2859, 1732, 1645, 1607, 1506, 1472, 1436, 1391, 1363, 1260, 1171, 1104, 1080, 1023, 916, 839, 804, 782, 687; ^{1}H-NMR δ ($CDCl_3$, 270 MHz): 7.13 (2H, d, *J*=8.6 Hz, Ar-*H*), 6.81 (1H, s, vinyl-*H*), 6.72 (2H, d, *J*=8.6 Hz, Ar-*H*), 4.12 (2H, s, Ar-CH_2), 3.79 (3H, s, COO*Me*), 3.73 (3H, s, COO*Me*), 0.96 (9H, s, SiCMe_3), (6H, s, SiMe_2); ^{13}C-NMR δ ($CDCl_3$, 67.5 MHz): 167.6, 166.1, 154.1, 146.4, 130.6, 129.8, 126.2, 119.8, 52.4, 51.8, 32.2, 25.6, 18.1, −4.5.

Dimethyl (2R, 3S)-2-(4-tert-butyldimethylsilyloxybenzyl)tartrate (8). To a stirred mixture of $(DHQD)_2AQN$ (429 mg, 0.5 mmol, 5 mol%), $K_2OsO_2(OH)_4$ (36.8 mg, 0.1 mmol, 1 mol%), $K_3Fe(CN)_6$ (9.88 g, 30 mmol), K_2CO_3 (4.15 g, 30 mmol), and $MeSO_2NH_2$ (951 mg, 10 mmol) in *tert*-BuOH (50 ml)/H_2O (50 ml) at 0°C was added a solution of **7Z** (3.64 g, 10 mmol) in *tert*-BuOH (2.5 ml)/H_2O (2.5 ml). The mixture was vigorously stirred for 72 h at 4°C. After adding Na_2SO_3 (15 g) at 4°C, the reaction mixture was allowed to warm to room temperature while stirring, and partitioned between water (200 ml) and EtOAc (200 ml). The aqueous layer was further extracted with EtOAc (50 ml × 4). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue

was purified by column chromatography (hexane:EtOAc=1:1) to give **8** (2.40 g, 60%, 89% *e.e.*) as a colorless oil; $[\alpha]_D^{24}+28.3°$ (*c* 1.65, $CHCl_3$). The spectral data for **8** have already been reported.[15] When **7***Z* (0.91 g, 2.5 mmol) was subjected to asymmetric dihydroxylation with 5 mol% each of $(DHQD)_2AQN$ and $K_2OsO_2(OH)_4$ for 20 h, **8** (0.84 g, 84%, 88% *e.e.*) was obtained after purification.

Dimethyl (2S, 3R)-2-(4-tert-butyldimethylsilyloxybenzyl)tartrate (ent-8). According to the same method as that used for **8**, **7***Z* (182 mg, 0.5 mmol) was subjected to AD by using $(DHQ)_2AQN$ (21.4 mg, 25 μmol, 5 mol%), $K_2OsO_2(OH)_4$ (1.8 mg, 5 μmol, 1 mol%), $K_3Fe(CN)_6$ (494 mg, 1.5 mmol), K_2CO_3 (207 mg, 1.5 mmol), and $MeSO_2NH_2$ (47.5 mg, 0.5 mmol) in *tert*-BuOH (2.5 ml)/H_2O (2.5 ml) for 72 h to give *ent*-**8** (90 mg, 62% based on consumed **7***Z*, 90% *e.e.*) as a colorless oil, with the recovery of **7***Z* (27%). Data for *ent*-**8**: $[\alpha]_D^{23}-22.5°$ (*c* 0.89, $CHCl_3$); HRMS *m/z* (M^+): calcd. for $C_{19}H_{30}O_7Si$, 398.1761; found, 398.1741. All other data were identical with those for **8**.[15]

Dimethyl (2S, 3S)-2-(4-tert-butyldimethylsilyloxybenzyl)tartrate (10). According to the same method as that used for **8**, **7***E* (182 mg, 0.5 mmol) was subjected to AD by using AD-mix-β (0.7 g), $(DHQD)_2PHAL$ (15.6 mg, 20 μmol, 4 mol%), $K_2OsO_2(OH)_4$ (1.1 mg, 3 μmol, 0.6 mol%), and $MeSO_2NH_2$ (47.5 mg, 0.5 mmol) in *tert*-BuOH (2.5 ml)/H_2O (2.5 ml) for 21 h to give **10** (172 mg, 86%, 88% *e.e.*) as a colorless oil; $[\alpha]_D^{20}+21.7°$ (*c* 1.36, $CHCl_3$); EIMS *m/z*: 398 (M^+, 7.5), 308 (3.1), 251 (4.9), 222 (20.1), 221 (100), 195 (6.8), 163 (7.7), 149 (6.0), 121 (5.4), 89 (6.7), 73 (14.6); HRMS *m/z* (M^+): calcd. for $C_{19}H_{30}O_7Si$, 398.1761; found, 398.1725; IR ν_{max} (film) cm^{-1}: 3500, 3034, 2957, 2897, 2859, 1746, 1609, 1512, 1463, 1441, 1391, 1362, 1255, 1116, 1052, 1007, 978, 915, 840, 779, 670; ^{1}H-NMR δ ($CDCl_3$, 270 MHz): 7.04 (2H, d, 2H, d, *J*=8.6 Hz, Ar-*H*), 6.73 (2H, d, *J*=8.6 Hz, Ar-*H*), 4.43 (1H, d, *J*=9.2 Hz, C*H*(OH)COOMe), 3.87 (3H, s, COO*Me*), 3.71 (3H, s, COO*Me*), 3.50 (1H, s, *tert*-O*H*), 3.39 (1H, d, *J*=9.2 Hz, CH(O*H*)COOMe), 3.06 (2H, s, Ar-CH_2), 0.96 (9H, s, SiC*Me*$_3$), 0.17 (6H, s, Si*Me*$_2$); ^{13}C-NMR δ ($CDCl_3$, 67.5 MHz): 173.1, 171.7, 154.8, 130.9, 127.5, 119.8, 80.6, 74.8, 52.9, 52.8, 40.1, 25.6, 18.1, −4.5.

Dimethyl (2R, 3R)-2-(4-tert-butyldimethylsilyloxybenzyl)tartrate (ent-10). According to the same method as that used for **8**, **7***E* (182 mg, 0.5 mmol) was subjected to AD by using AD-mix-α (0.7 g), $(DHQ)_2PHAL$ (15.6 mg, 20 μmol, 4 mol%), $K_2OsO_2(OH)_4$ (1.1 mg, 3 μmol, 0.6 mol%), and $MeSO_2NH_2$ (47.5 mg, 0.5 mmol) in *tert*-BuOH (2.5 ml)/H_2O (2.5 ml) for 21 h to give *ent*-**10** (162 mg, 81%, 86% *e.e.*) as a colorless oil; $[\alpha]_D^{19}-16.5°$ (*c* 1.25, $CHCl_3$); HRMS *m/z* (M^+): calcd. for $C_{19}H_{30}O_7Si$, 398.1761; found, 398.1790. All other data were identical with those for **10**.

Typical procedure for preparing the (R)- and (S)-MTPA esters of 8, ent-8, 10, and ent-10. To a solution of **8**, *ent*-**8**, **10**, or *ent*-**10** (5.0 mg, 12.5 μmol), pyridine (10 μl, 125 μmol), and dimethylaminopyridine (1.60 mg, 13.1 μmol) in CH_2Cl_2 (0.3 ml) was added (*S*)- or (*R*)-MTPACl (11 μl, 58.9 μmol) at room temperature. After being stirred overnight, the reaction mixture was directly subjected to preparative TLC (20×10 cm, hexane:EtOAc=1:1) to give the (*R*)- or (*S*)-MTPA ester quantitatively. The ^{1}H-NMR ($CDCl_3$, 270 MHz) data of the MTPA esters follow.

12 (or *ent*-**12**) δ: 7.64 (2H, m, Ar-*H* of MTPA), 7.43 (3H, m, Ar-*H* of MTPA), 6.99 (2H, d, *J*=8.6 Hz, Ar-*H*), 6.73 (2H, d, *J*=8.6 Hz, Ar-*H*), 5.72 (1H, s, C*H*(OMTPA)COOMe), 3.73 (3H, s, COO*Me*), 3.72 (3H, s, COO*Me*), 3.59 (3H, s, O*Me*), 3.41 (1H, s, O*H*), 3.11 (1H, d, *J*=13.8 Hz, ArCH), 2.94 (1H, d, *J*=13.8 Hz, ArC*H*), 0.96 (9H, s, SiC*Me*$_3$), 0.17 (6H, s, Si*Me*$_2$).

13 (or *ent*-**13**) δ: 7.72 (2H, m, Ar-*H* of MTPA), 7.42 (3H, m, Ar-H of MTPA), 6.89 (2H, d, *J*=8.6 Hz, Ar-*H*), 6.69 (2H, d, *J*=8.6 Hz, Ar-*H*), 5.70 (1H, s, C*H*(OMTPA)COOMe), 3.75 (3H, s, COO*Me*), 3.72 (3H, s, COO*Me*), 3.70 (3H, s, O*Me*), 3.33 (1H, s, O*H*), 2.81 (1H, d, *J*=13.9 Hz, ArC*H*), 2.73 (1H, d, *J*=13.9 Hz, ArC*H*), 0.96 (9H, s, SiC*Me*$_3$), 0.16 (6H, s, Si*Me*$_2$).

14 (or *ent*-**14**) δ: 7.53 (2H, m, Ar-*H* of MTPA), 7.42 (3H, m, Ar-*H* of MTPA), 7.03 (2H, d, *J*=8.6 Hz, Ar-*H*), 6.73 (2H, d, *J*=8.6 Hz, Ar-*H*), 5.44 (1H, s, C*H*(OMTPA)COOMe), 3.85 (3H, s, COO*Me*), 3.59 (3H, s, COO*Me*), 3.45 (3H, s, O*Me*), 3.43 (1H, s, O*H*), 3.25 (1H, d, *J*=13.9 Hz, ArC*H*), 3.10 (1H, d, *J*=13.9 Hz, ArC*H*), 0.96 (9H, s, SiC*Me*$_3$), 0.17 (6H, s, Si*Me*$_2$).

15 (or *ent*-**15**) δ: 7.62 (2H, m, Ar-*H* of MTPA), 7.41 (3H, m, Ar-*H* of MTPA), 6.98 (2H, d, *J*=8.6 Hz, Ar-*H*), 6.70 (2H, d, *J*=8.6 Hz, Ar-*H*), 5.35 (1H, s, C*H*(OMTPA)COOMe), 3.88 (3H, s, COO*Me*), 3.62 (3H, s, O*Me*), 3.43 (1H, s, O*H*), 3.31 (3H, s, COO*Me*), 3.18 (1H, d, *J*=13.8 Hz, ArC*H*), 3.04 (1H, d, *J*=13.8 Hz, ArC*H*), 0.95 (9H, s, SiC*Me*$_3$), 0.15 (6H, s, Si*Me*$_2$).

Dimethyl (2R, 3S)-2-(4-hydroxybenzyl)tartrate (9). A mixture of **8** (2.40 g, 6.03 mmol) and Amberlite IR-120B (H^+-form swollen in MeOH, 1.5 ml) in MeOH (30 ml) was refluxed for 38 h. After filtration, the combined filtrate and washings were concentrated under reduced pressure. The residue was purified by column chromatography ($CHCl_3$:MeOH=9:1) to give **9** (1.70 g, 99%) as a colorless oil; $[\alpha]_D^{21}+30.0°$ (*c* 1.32, $CHCl_3$). The spectral data for **9** have already been reported.[15]

Dimethyl (2S, 3R)-2-(4-hydroxybenzyl)tartrate (ent-9). According to the same method as that used for **9**, *ent*-**8** (90 mg, 223 μmol) was converted into *ent*-**9** (46 mg, 72%) as a colorless oil; $[\alpha]_D^{21}-36.2°$ (*c* 1.85, $CHCl_3$); HRMS *m/z* (M^+): calcd. for $C_{13}H_{16}O_7$, 284.0896; found, 284.0869. All other data were identical with those of **9**.[15]

Dimethyl (2S, 3S)-2-(4-hydroxybenzyl)tartrate (11). According to the same method as that used for **9**, **10** (160 mg, 400 μmol) was converted into **11** (113 mg, 99%) as a colorless oil; $[\alpha]_D^{26}+21.6°$ (*c* 0.75, $CHCl_3$); EIMS *m/z*: 284 (M^+, 284), 266 (M^+-H_2O, 5.3), 207

(16.7), 175 (6.4), 149 (6.2), 147 (3.4), 108 (10.5), 107 (100), 90 (7.8), 77 (5.3); HRMS m/z (M^+): calcd. for $C_{13}H_{16}O_7$, 284.0896; found, 284.0895; IR ν_{max} (film) cm^{-1}: 3442, 2957, 1739, 1615, 1516, 1441, 1259, 1117, 841, 755; ^{1}H-NMR δ ($CDCl_3$, 270 MHz): 7.05 (2H, d, J=8.6 Hz, Ar-*H*), 6.71 (2H, d, J=8.6 Hz, Ar-*H*), 4.86 (1H, br. s, Ar-O*H*), 4.44 (1H, d, J=9.2 Hz, C*H*(OH)COOMe), 3.88 (3H, s, COO*Me*), 3.74 (3H, s, COO*Me*), 3.50 (1H, s, *tert*-O*H*), 3.36 (1H, d, J=9.2 Hz, CH(O*H*)COOMe), 3.06 (2H, s, Ar-CH_2); ^{13}C-NMR δ ($CDCl_3$, 67.5 MHz): 173.3, 171.2, 154.8, 131.2, 126.9, 115.2, 80.7, 74.8, 53.1, 52.9, 40.0.

Dimethyl (2R, 3R)-2-(4-hydroxybenzyl)tartrate (ent-11). According to the same method as that used for **9**, *ent*-**10** (140 mg, 350 μmol) was converted into *ent*-**11** (99 mg, 99%) as a colorless oil; $[\alpha]_D^{24}$ −17.6° (*c* 1.23, $CHCl_3$); HRMS m/z (M^+): calcd. for $C_{13}H_{16}O_7$, 284.0896; found, 284.0884. All other data were identical with those of **11**.

(2S, 3R)-(+)-Piscidic Acid (1). A mixture of **9** (1.68 g, 5.9 mmol), 2 M KOH (29.5 ml, 59 mmol), and MeOH (25 ml) was refluxed for 1 h. After cooling to room temperature, the reaction mixture was passed through a column packed with Amberlite IR-120B (H^+-form swollen in H_2O, 150 ml). The eluate containing **1** was concentrated under reduced pressure to give **1** (1.43 g, 95%, 90% *e.e.*) as colorless crystals; mp 182–184°C; $[\alpha]_D^{22}$ +32.3° (*c* 1.35, H_2O). The spectral data for **1** have already been reported.[15] Examples of the recrystallization conditions, which were not optimized, are shown next. The first recrystallization of **1** (930 mg, 90% *e.e.*) from acetone (10 ml) and $CHCl_3$ (20 ml) gave **1** (710 mg, 76% recovery, 98% *e.e.*); mp 185–187°C; $[\alpha]_D^{24}$ +40.5° (*c* 2.00, H_2O). The second recrystallization of **1** (200 mg, 98% *e.e.*) from acetone (2.0 ml) and $CHCl_3$ (2.0 ml) gave **1** (106 mg, 53% recovery, >99% *e.e.*); mp 186–188°C; $[\alpha]_D^{23}$ +42.5° (*c* 2.00, H_2O).

(2R, 3S)-(−)-Piscidic Acid (ent-1). According to the same method as that used for **1**, *ent*-**9** (113 mg, 398 μmol) was converted into *ent*-**1** (83.0 mg, 81%, 90% *e.e.*) as colorless crystals; mp 181–182°C; $[\alpha]_D^{22}$ −29.9° (*c* 1.01, H_2O); HRMS m/z (M^+): calcd. for $C_{11}H_{12}O_7$, 256.0583; found, 256.0576. All other data were identical with those of **1**.[15]

(2S, 3S)-(+)-3-Epi-piscidic Acid (4). According to the same method as that used for **1**, **11** (110 mg, 390 μmol) was converted into **4** (83.0 mg, 84%, 90% *e.e.*) as colorless crystals; mp 207–209°C; $[\alpha]_D^{21}$ +2.71° (*c* 0.96, H_2O); HRMS m/z (M^+): calcd. for $C_{11}H_{12}O_7$, 256.0583; found, 256.0596; IR ν_{max} (KBr) cm^{-1}: 3600–2300, 2953, 1730, 1614, 1515, 1448, 1341, 1217, 1118, 836, 782; ^{1}H-NMR δ (acetone-d_6, 270 MHz): 8.14 (1H, br. s, Ar-O*H*), 7.11 (2H, d, J=8.6 Hz, Ar-*H*), 6.69 (2H, d, J=8.6 Hz, Ar-*H*), 4.43 (1H, d, J=9.2 Hz, C*H*(OH)COOH), 5.70–3.30 (4H, COO*H*×2 and O*H*×2), 3.20 (1H, d, J=13.9 Hz, Ar-C*H*), 3.05 (1H, d, J=13.9 Hz, Ar-C*H*); ^{13}C-NMR δ (acetone-d_6, 67.5 MHz): 174.5, 173.0, 157.3, 132.5, 127.8, 115.8, 81.4, 75.9, 40.8.

(2R, 3R)-(−)-2-Epi-piscidic Acid (ent-4). According to the same method as that used for **1**, *ent*-**11** (151 mg, 532 μmol) was converted into *ent*-**4** (124 mg, 91%, 87% *e.e.*) as colorless crystals; mp 202–204°C; $[\alpha]_D^{24}$ −3.49° (*c* 0.86, H_2O); HRMS m/z (M^+): calcd. for $C_{11}H_{12}O_7$, 256.0583; found, 256.0602. All other data were identical with those of **4**.

Typical procedure for preparing the bis-(R)- and bis-(S)-MTPA esters of 1, ent-1, 4, and ent-4. A solution of **1**, *ent*-**1**, **4**, or *ent*-**4** (5.00 mg, 19.5 μmol) in THF (0.30 ml) was treated with an ethereal solution of diazomethane (excess) at 0°C. After evaporation under reduced pressure, the resulting residue was dissolved in CH_2Cl_2 (0.30 ml). To this solution were added pyridine (20.0 μl, 247 μmol), dimethylaminopyridine (2.40 mg, 19.6 μmol), and (*S*)- or (*R*)-MTPACl (20.0 μl, 107 μmol) at room temperature. After being stirred overnight, the reaction mixture was directly subjected to preparative TLC (20×10 cm, hexane:EtOAc=1:1) to give the bis-(*R*)- or bis-(*S*)-MTPA ester quantitatively. The ^{1}H-NMR ($CDCl_3$, 270 MHz) data of the bis-MTPA esters follow.

16 (or *ent*-**16**) δ: 7.62 (4H, m, Ar-H of MTPA), 7.45 (6H, m, Ar-*H* of MTPA), 7.19 (2H, d, J=8.6 Hz, Ar-*H*), 7.05 (2H, 2H, d, J=8.6 Hz, Ar-*H*), 5.70 (1H, s, CH(OMTPA)COOMe), 3.75 (3H, s, COO*Me*), 3.73 (3H, s, COO*Me*), 3.67 (3H, s, O*Me*), 3.58 (3H, s, O*Me*), 3.46 (1H, s, *tert*-O*H*), 3.17 (1H, d, J=13.5 Hz, Ar-C*H*), 3.01 (1H, d, J=13.5 Hz, Ar-C*H*).

17 (or *ent*-**17**) δ: 7.75 (4H, m, Ar-*H* of MTPA), 7.40 (6H, m, Ar-*H* of MTPA), 7.09 (2H, d, J=8.6 Hz, Ar-*H*), 7.00 (2H, d, J=8.6 Hz, Ar-*H*), 5.69 (1H, s, C*H*(OMTPA)COOMe), 3.76 (3H, s, COO*Me*), 3.74 (3H, s, COO*Me*), 3.71 (3H, s, O*Me*), 3.66 (3H, s, O*Me*), 3.38 (1H, s, *tert*-O*H*), 2.85 (H, d, J=13.5 Hz, Ar-C*H*), 2.77 (H, d, J=13.5 Hz, Ar-C*H*).

18 (or *ent*-**18**) δ: 7.63 (2H, m, Ar-*H* of MTPA), 7.52 (2H, m, Ar-*H* of MTPA), 7.44 (6H, m, Ar-*H* of MTPA), 7.22 (2H, d, J=8.6 Hz, Ar-*H*), 7.03 (2H, d, J=8.6 Hz, Ar-*H*), 5.43 (1H, s, C*H*(OMTPA)COOMe), 3.86 (3H, s, COO*Me*), 3.67 (3H, s, O*Me*), 3.60 (3H, s, COO*Me*), 3.47 (1H, s, *tert*-O*H*), 3.45 (3H, s, O*Me*), 3.34 (H, d, J=13.9 Hz, Ar-C*H*), 3.17 (H, d, J=13.9 Hz, Ar-C*H*).

19 (or *ent*-**19**) δ: 7.62 (4H, m, Ar-*H* of MTPA), 7.43 (6H, m, Ar-*H* of MTPA), 7.18 (2H, d, J=8.6 Hz, Ar-*H*), 7.01 (2H, d, J=8.6 Hz, Ar-*H*), 5.34 (1H, s, C*H*(OMTPA)COOMe), 3.89 (3H, s, COO*Me*), 3.74 (3H, s, O*Me*), 3.71 (3H, s, O*Me*), 3.66 (3H, s, COO*Me*), 3.47 (1H, s, *tert*-O*H*), 3.38 (1H, s, *tert*-O*H*), 3.28 (H, d, J=13.5 Hz, Ar-C*H*), 3.11 (H, d, J=13.5 Hz, Ar-C*H*).

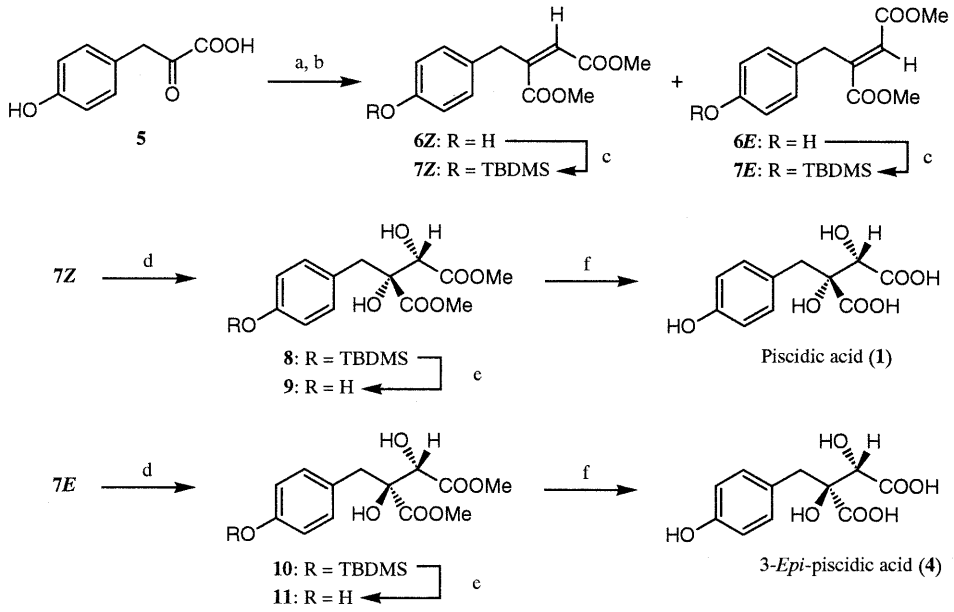
Dimethyl (2S, 3S)-2-(4-benzyloxybenzyl)-2,3-O-isopropylidene-tartrate (20). A solution of **11** (10.0 mg, 35.2 μmol), 2,2-dimethoxypropane (43.2 μl, 350 μmol), and *p*-toluenesulfonic acid (3.30 mg, 17.6 μmol) in benzene (0.15 ml) was refluxed for 2 h. The reaction mixture

was then concentrated under reduced pressure. The resulting residue was purified by preparative TLC to give dimethyl (2*S*, 3*S*)-2-(4-hydroxybenzyl)-2,3-*O*-isopropylidene-tartrate (6.80 mg, 60%) which was then treated with potassium carbonate (4.35 mg, 31.5 μmol) and benzyl bromide (5.00 μl, 42.0 μmol) in DMF (0.10 ml). After being stirred for 21 h at room temperature, the mixture was partitioned between EtOAc (5 ml) and water (5 ml). The organic layer was washed with brine (5 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative TLC to give **20** (4.40 mg, 51%) as a colorless oil: $[\alpha]_D^{24}$ +32.7° (*c* 0.44, $CHCl_3$); HRMS *m/z* (M^+): calcd. for $C_{23}H_{26}O_7$, 414.1679; found, 414.1708; IR ν_{max} (film) cm^{-1}: 2953, 1760, 1612, 1512, 1437, 1384, 1214, 1114, 837, 742; ^{1}H-NMR δ ($CDCl_3$, 270 MHz): 7.34 (5H, m, $C_6H_5CH_2O$), 7.10 (2H, d, *J*=8.9 Hz, Ar-*H*), 6.87 (2H, d, *J*=8.9 Hz, Ar-*H*), 5.02 (2H, s, $C_6H_5CH_2O$), 4.94 (1H, s, C*H*(OR)COOMe), 3.85 (3H, s, COO*Me*), 3.66 (3H, s, COO*Me*), 3.07 (1H, d, *J*=13.5 Hz, Ar-C*H*), 2.85 (1H, d, *J*=13.5 Hz, Ar-C*H*), 1.71 (3H, s, CCH_3), 1.42 (3H, s, CCH_3).

Results and Discussion

The syntheses were started from commercially available (4-hydroxyphenyl)pyruvic acid (**5**) [Scheme 1]. Methyl esterification of **5** with diazomethane and the subsequent Wittig reaction with (carbomethoxymethylene)triphenylphosphorane gave a mixture of trisubstituted olefins **6*Z*** [16] and **6*E***, which could be readily separated by column chromatography on silica gel, in a 95% yield (2 steps) and in a 3:1 ratio.[12,13] In this case, methylation of the phenolic hydroxyl group did not occur, giving only **6*Z*** and **6*E***. The geometries of **6*Z*** and **6*E*** were determined in comparison with those of the synthetic intermediates of fukiic acid derivatives from the ^{1}H-NMR spectra.[10-13] Although the AD treatment of **6*Z*** was first carried out with AD-mix-β [a pre-mixed reagent containing dihydroquinidine 1,4-phthalazinediyl diether, $(DHQD)_2PHAL$] and methanesulfonamide (1.0 eq.) under the usual AD conditions,[16] no desired product could be obtained from the organic layers by continuously extracting from the reaction mixture, in spite of the disappearance of **6*Z***. We next examined AD of **7*Z*** which was obtained by protecting the phenolic hydroxyl group as *tert*-butyldimethylsilyl (TBDMS) ether in a 98% yield. The bulkiness of the TBDMS group would have prevented chelation of the ethereal oxygen to osmium. When AD-mix-β was used, diol **8** could not be detected by analytical TLC, and only **7*Z*** was detected (Table 1, entry 1). Under the usual AD conditions, as well as that of entry 1, the stoichiometry of $(DHQD)_2PHAL$ and osmium in AD-mix-β was 1.0 and 0.4 mol%, respectively. Increasing the stoichiometry is usually known to accelerate the reaction. By increasing the stoichiometry of $(DHQD)_2PHAL$ (5 mol%) and osmium (1 mol%),[16] the reaction gave **8** in a 43% yield after 14 h at 4°C with 31% of unreacted **7*Z*** (entry 2). The optical purity was determined to be 27% *e.e.* from the integral value of the corresponding MTPA ester in the ^{1}H-NMR spectrum. The secondary hydroxyl group of **8** only underwent esterification to give the (*R*)- and (*S*)-MTPA esters (**12** and **13** in Scheme 2), whose signals from the benzylic methylene protons were completely separated from each other. In the subsequent entries, the optical purity was determined by using the same method. Attempts to separate the enantiomers of **8** by HPLC with several chiral columns were unsuccessful. When dihydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether, $(DHQD)_2PYR$ (5 mol%) and osmium (10 mol%) were used,[16] the best yield (92%) was recorded with 89% *e.e.* without any recovery of **7*Z*** (entry 3). By decreasing the stoichiometry of osmium (1 mol%) with no change of the ligand, the reaction took a long time and gave a moderate yield (72%) with 86% *e.e.* (entry 4). When dihydroquinidine 1,4-anthraquinonediyl diether, $(DHQD)_2AQN$ (5 mol%) and osmium (1 mol%) were used,[17] the yield was moderate (69%) with 90% *e.e.* (entry 5). In the case of using 5 mol% of osmium with no change of the ligand, the optical purity (93% *e.e.*) was best (entry 6). When dihydroquinidine 4-chlorobenzoate, (DHQD)CLB (entry 7)[16] and dihydroquinidine *N*-indolinecarbonate, (DHQD)IND (entry 8)[16] were used as ligands, the optical purity was lower than those of entries 3–6. In entries 4–8, several by-products were detected by analytical TLC. One of them was isolated and determined by spectral methods to be methyl 3-(4-*tert*-butyldimethylsilyloxyphenyl)-2-hydroxypropionate which would have been formed *via* a retro-Aldol condensation. In all entries (2–8), the absolute configuration of obtained major enantiomer **8** was identical and was determined to be the same (2*S*, 3*R*)-configuration as that of **1** from the sign of the specific rotation after its conversion to **1** (*vide infra*). The enantiofacial selectivity for **7*Z*** with dihydroquinidine (DHQD) ligands is in agreement with the usual prediction in Sharpless AD.[16] Thus, $(DHQD)_2PYR$ and $(DHQD)_2AQN$ (entries 3–6), which gave **8** in approximately 90% *e.e.*, were found to be useful chiral ligands of AD for **7*Z***. Although the PHAL ligand is usually recommended for the trisubstituted class of olefins, $(DHQD)_2PHAL$ was ineffective for **7*Z***.

By following the conditions for entry 5, up-scaling (from 0.5 to 10 mmol) of the AD treatment of **7*Z*** was achieved, being directed toward the catalytic asymmetric synthesis of **1**, to give **8** in a 60% yield with 89% *e.e.* Deprotection of the TBDMS ether of **8** was carried out in the presence of the ion-exchange resin, Amberlite IR-120B (H^+-form), in refluxing MeOH to give **9** corresponding to the dimethyl ester of **1**[15] quantitatively. Synthetic **9** was identical to that derived from natural **1** that had been isolated from *Narcissus poeticus* bulbs[3] by a direct comparison of their ^{1}H-NMR spectra (270 MHz). Final alkaline hydrolysis with 2 M KOH in refluxing MeOH gave **1** as colorless powder in a 95% yield. HRMS: calcd. for $C_{11}H_{12}O_7$ (M^+), *m/z* 256.0583; found, 256.0557; mp 182–184°C; $[\alpha]_D^{22}$ +32.3° (*c* 1.35, H_2O) [lit.[2] mp 186–187°C; $[\alpha]_D^{22}$ +41.03° (*c* 2.65, H_2O)]. The spectral data (^{1}H-NMR, ^{13}C-NMR and IR) for synthetic **1**[15] were identical with those of natural **1** isolated from *Narcissus poeticus* bulbs.[3] The sign for specific ro-



Scheme 1. (a) CH_2N_2/Et_2O-THF, 0°C; (b) $Ph_3P{=}CHCOOMe$/benzene, reflux, **6*Z*:6*E***=3:1, 95% (2 steps); (c) TBDMSCl, imidazole/DMF, r.t., 98% for **7*Z***; 93% for **7*E***; (d) Sharpless asymmetric dihydroxylation (see Table 1 and experimental); (e) Amberlite IR-120B (H^+-form)/MeOH, reflux, 99% for **9**, 72% for *ent*-**9**, 99% for **11**, 99% for *ent*-**11**; (f) 2M KOH/MeOH, reflux, 95% for **1**, 81% for *ent*-**1**, 84% for **4**, 91% for *ent*-**4**.

Table 1. Asymmetric Dihydroxylation of **7*Z*** and **7*E*** to **8** and **10** with Various Chiral Ligands[a]

Entry	SM	Ligand	$K_2OsO_2(OH)_4$	Time	Product	Yield	Optical purity[b]
1[c]	**7*Z***	$(DHQD)_2PHAL$ 1 mol%	0.4 mol%	20 h	**8**	No reaction[d]	—
2[e]		$(DHQD)_2PHAL$ 5 mol%	1 mol%	14 h		43%[f]	27% *e.e.*
3		$(DHQD)_2PYR$ 5 mol%	10 mol%	24 h		92%	89% *e.e.*
4		$(DHQD)_2PYR$ 5 mol%	1 mol%	72 h		72%[g]	86% *e.e.*
5		$(DHQD)_2AQN$ 5 mol%	1 mol%	72 h		69%[h]	90% *e.e.*
6		$(DHQD)_2AQN$ 5 mol%	5 mol%	24 h		68%[i]	93% *e.e.*
7		(DHQD)CLB 10 mol%	1 mol%	72 h		61%[j]	20% *e.e.*
8		(DHQD)IND 10 mol%	1 mol%	72 h		36%[k]	74% *e.e.*
9	**7*E***	$(DHQD)_2PHAL$ 1 mol%	0.4 mol%	72 h	**10**	60%[l]	82% *e.e.*
10		$(DHQD)_2AQN$ 1 mol%	0.4 mol%	72 h		72%[l]	83% *e.e.*
11		$(DHQD)_2PYR$ 1 mol%	0.4 mol%	72 h		73%[l]	49% *e.e.*
12		(DHQD)CLB 2 mol%	0.4 mol%	72 h		56%[l]	39% *e.e.*
13		(DHQD)IND 2 mol%	0.4 mol%	72 h		53%[l]	54% *e.e.*

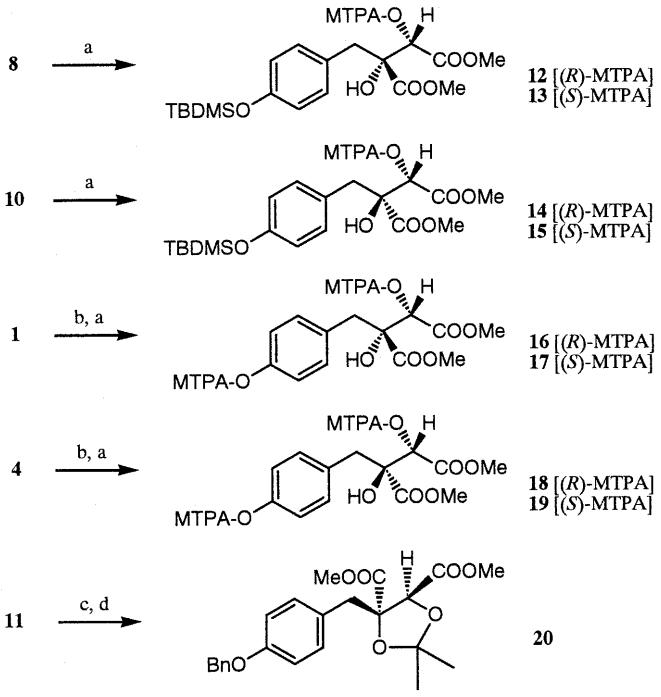
[a]All reactions (0.5-mmol scale) were carried out in the presence of $K_3Fe(CN)_6$ (3 eq.), K_2CO_3 (3 eq.), and $MeSO_2NH_2$ (1 eq.) in *t*-BuOH/H_2O (1:1) at 4°C. [b]Optical purity (enantiomeric excess) was determined from the integral value of the corresponding MTPA ester in the ^{1}H-NMR spectrum. [c]AD-mix-*β* (0.7 g) was used. [d]Diol **8** could not be detected by analytical TLC. [e]$(DHQD)_2PHAL$ (4 mol%) and $K_2OsO_2(OH)_4$ (0.6 mol%) were added to AD-mix-*β* (0.7 g). [f]Unreacted **7*Z*** (31%) was recovered. [g]**7*Z*** (2%). [h]**7*Z*** (8%). [i]**7*Z*** (4%). [j]**7*Z*** (9%). [k]**7*Z*** (29%) [l]SM (**7*E***) disappeared or remained (*ca.* 3–5%).

tation was also identical with that of **1**. The optical purity was determined to be 90% *e.e.* after treating synthetic **1** with diazomethane to give dimethyl piscidate (**9**) which was converted into the bis-(*R*)- and bis-(*S*)-MTPA esters (**16** and **17** in Scheme 2), because the enantiomers of **9** could not be separated by HPLC with some chiral columns. In this case, the secondary and phenolic hydroxyl groups underwent esterification with MTPACl. In the ^{1}H-NMR spectrum, the signals of the benzylic methylene protons were again separated from each other without overlapping. Therefore, it was confirmed that no epimerization occurred at the C_2-position under the alkaline hydrolysis conditions. In order to increase the optical purity, **1** (90% *e.e.*) was recrystallized twice from acetone-$CHCl_3$. The optical purity of the resulting crystals [mp 186–188°C, $[\alpha]_D^{23}+42.5°$ (*c* 2.00, H_2O)], was judged to be >99% *e.e.* after its conversion into **16** and **17**.

Unnatural (2*R*, 3*S*)-piscidic acid (*ent*-**1**) was synthesized by using dihydroquinine 1,4-anthraquinonediyl diether [$(DHQ)_2AQN$] instead of $(DHQD)_2AQN$ in the AD treatment of **7*Z***. *Ent*-**8** was obtained in a 62% yield (based on consumed **7*Z***) in a 0.5 mmol-scale reaction. The optical purity of *ent*-**8** was determined to be 90% *e.e.* after its conversion to the corresponding MTPA esters (*ent*-**12** and *ent*-**13**). Desilylation of *ent*-**8** and the subsequent alkaline hydrolysis gave *ent*-**1**.

Next, the syntheses of unatural (2*S*, 3*S*)-3-*epi*-piscid-

ic acid (**4**) and its enantiomer, (2*R*, 3*R*)-2-*epi*-piscidic acid (*ent*-**4**) were carried out from **6***E*. The phenolic hydroxyl group of **6***E* was protected as the TBDMS ether to give **7***E* in a 93% yield. The enantiofacial selectivity of five DHQD ligands for **7***E*, as well as that for **7***Z*, was then examined (Table 1). It is considered that DHQD ligands would give **10** predominantly based on the device for predicting the enantiofacial selectivity in AD. When AD-mix-β [containing $(DHQD)_2PHAL$ (1 mol%) and osmium (0.4 mol%) for **7***E*] was used at 4°C for 72 h, **10** was obtained in a 60% yield (entry 9). The optical purity was determined to be 82% *e.e.* from the integral value of the corresponding MTPA ester in the ^{1}H-NMR spectrum. The secondary hydroxyl group of **10** only underwent esterification to give the (*R*)- and (*S*)-MTPA esters (**14** and **15** in Scheme 2), whose signals for the acyloxymethine protons were completely separated from each other. In the subsequent entries, the optical purity was determined by using the same method, because attempts to separate the enantiomers by HPLC with several chiral columns were also unsuccessful. The absolute configuration of **10** was determined to be (2*S*, 3*S*). Desilylation of **10** was carried out by the same method as that used for **9** to give **11** quantitatively. Treatment of **11** with *p*-toluenesulfonic acid and 2,2-dimethoxypropane and the subsequent benzylation with potassium carbonate and benzyl bromide gave a benzyl ether (**20**), $[\alpha]_D^{22}+32.3°$ (*c* 1.35, $CHCl_3$). The ^{1}H-NMR spectrum of **20** was identical with that of the (2*R*, 3*R*)-isomer (*ent*-**20**), $[\alpha]_D^{13}-37.6°$ (*c* 4.78, $CHCl_3$), which had been prepared by Nie *et al.*[14] Therefore, the absolute configuration of **11** was determined from the fact that the signs of both specific rotation values were opposite. Although $(DHQD)_2PHAL$ was ineffective for **7***Z* with respect to giving a high *e.e.* value, it was effective for **7***E*. Furthermore, the reaction procceded to a moderate yield without adding $(DHQD)_2PHAL$ or osmium to AD-mix-β, in contrast to AD of **7***Z* which required acceleration by the addition of ligands and osmium. When $(DHQD)_2AQN$ was used (entry 10), the optical purity (83% *e.e.*) of **10** was almost the same as that obtained in entry 9. When $(DHQD)_2PYR$ (entry 11), (DHQD)CLB (entry 12) and (DHQD)IND (entry 13) were used as ligands, the optical purity was lower than that of entries 9 and 10. In all entries (9–13), **10** was obtained as the major enantiomer. Although $(DHQD)_2PYR$ was effective for **7***Z* with respect to giving a high *e.e.* value, it was ineffective for **7***E*. Furthermore, although $(DHQD)_2AQN$ was effective for both **7***Z* and **7***E*, $(DHQD)_2PYR$ was only effective for **7***Z*. In practice, acceleration of the AD reaction for **7***E* by adding $(DHQD)_2PHAL$ (total of 5 mol%) and osmium (total of 1 mol%) to AD-mix-β resulted in giving **10** in a better yield (86%) and optical purity (88% *e.e.*) after 21 h. By using the modified AD-mix-α [$(DHQ)_2PHAL$ (total of 5 mol%) and osmium (total of 1 mol%)], *ent*-**10** was also obtained in an 81% yield with 86% *e.e.* By the same method as that used for **1** and *ent*-**1**, **10** and *ent*-**10** were converted into **4** and *ent*-**4**, respectively, whose spectral data (^{1}H-NMR, IR and MS) were identical with those reported by Nie *et al.*[14] The final optical purity of **4** and



Scheme 2. (a) (*S*)- or (*R*)-MTPACl, pyridine, DMAP/CH_2Cl_2, r.t.; (b) CH_2N_2/Et_2O-THF, 0°C; (c) *p*-TsOH, 2,2-dimethoxypropane/acetone, reflux; (d) K_2CO_3, BnBr/DMF, r.t.

ent-**4** was determined as the corresponding bis-(*R*)- and bis-(*S*)-MTPA esters (**18** and **19** in Scheme 2).

Thus, catalytic asymmetric syntheses of all four stereoisomers of (+)-(2*S*, 3*R*)-piscidic acid (**1**) were efficiently accomplished *via* Sharpless AD in 6 steps. Whereas the AQN or PYR ligand was effective for the AD treatment of **7***Z*, the PHAL or AQN ligand was effective for the AD treatment of **7***E*. It was proved that the appropriate selection of a chiral ligand, depending on the olefin as the substrate of the AD reaction, was required to increase the optical purity in our case. Our syntheses will supply a sufficient amount of all four stereoisomers of **1** for studies on various biological activities; in practice, **1** could be synthesized to give more than one gram. Further up-scaling and increasing the optical purity of other unnatural isomers would be possible.

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References

1) Freer, P. C. and Clover, A. M., On the constituents of Jamaica dogwood. *Amer. Chem. J.*, **25**, 390–413 (1901).
2) Bridge, W., Coleman, F., and Robertson, A., Constituents of "*Cortex Piscidia erythrina*" Part I. The structure of piscidic acid. *J. Chem. Soc.*, 257–260 (1948).
3) Smeby, R. R., Zbinovsky, V., Burris, R. H., and Strong, F. M., The organic acids of *Narcissus poeticus*. *J. Am. Chem. Soc.*, **76**, 6127–6130 (1954).

4) Ho, P.-C., Liu, C.-Y., Chin, K.-S., and Li, Y.-M., Isolation and identification of *p*-hydroxybenzyltartaric acid (piscidic acid): a water soluble active constituent of *Dioscorea nipponica*. *Yao Hsueh T'ung Pao* (in Chinese), **15**, 39 (1980).
5) He, B.-J., Liu, Z.-Y., Jin, G.-S., and Li, Y.-M., Studies on an aqueous soluble active constituent of *Dioscorea nipponica* Makino. I. Isolation and identification of *p*-hydroxybenzyltartaric acid (piscidic acid). *Yao Hsueh Hsueh Pao* (in Chinese), **15**, 764–765 (1980).
6) Yoshihara, T., Ichihara, A., Sakamura, S., Sugita, M., Imamoto, S., and Senoh, S., The stereochemistry of fukiic acid and piscidic acid. *Tetrahedron Lett.*, 3809–3812 (1971).
7) Yoshihara, T., Ichihara, A., Nuibe, H., Sakamura, S., Sugita, M., Imamoto, S., and Senoh, S., The stereochemistry of fukiic acid and its correlation with piscidic acid. *Agric. Biol. Chem.*, **38**, 121–126 (1974).
8) Ae, N., Arihara, J., Okada, K., Yoshihara, T., and Johansen, C., Phosphorus uptake by pigeon pea and its role in cropping systems of the Indian subcontinent. *Science*, **248**, 477–480 (1990).
9) Otani, T., Ae, N., and Tanaka, H., Phosphorus (P) uptake mechanisms of crops grown in soils with low P status. II. Significance of organic acids in root exudates of pigeon pea. *Soil Sci. Plant Nutr.*, **42**, 533–560 (1996).
10) Yoshihara, T., Ichihara, A., and Sakamura, S., The synthesis of dimethyl esters of *dl*-*O*,*O*′-dimethylfukiic acid acid and *dl*-*O*,*O*′-dimethylepifukiic acid. *Agric. Biol. Chem.*, **35**, 1822–1824 (1971).
11) Yoshihara, T., Ichihara, A., and Sakamura, S., The synthesis of dimethyl esters of *dl*-*O*,*O*′-dimethylfukiic acid and *dl*-*O*,*O*′-dimethylepifukiic acid. *Agric. Biol. Chem.*, **39**, 2217–2221 (1975).
12) Matsumoto, T., Hidaka, K., Nakayama, T., and Fukui, K., The synthesis and configuration of fukiic acid derivatives. *Chem. Lett.*, 1–4 (1972).
13) Matsumoto, T., Hidaka, K., Nakayama, T., and Fukui, K., The synthesis and configuration of fukiic acid derivatives. *Bull. Chem. Soc. Jpn.*, **45**, 1501–1504 (1972).
14) Nie, X., Wang, Q., Li, Y., and Pan, X., Synthesis of piscidic acid and its epimer. *Gaodeng Xuexiao Huaxue Xuebao* (in Chinese), **8**, 620–622 (1987).
15) Toshima, H., Saito, M., and Yoshihara, T., Total synthesis of (+)-(2*S*, 3*R*)-piscidic acid *via* catalytic asymmetric dihydroxylation of a trisubstituted olefin. *Biosci. Biotechnol. Biochem.*, **63**, 964–967 (1999).
16) Kolb, H. C., VanNieuwenhze, M. S., and Sharpless, K. B., Catalytic asymmetric dihydroxylation. *Chem. Rev.*, **94**, 2483–2547 (1994).
17) Becker, H. and Sharpless, K. B., A new ligand class for the asymmetric dihydroxylation of olefins. *Angew. Chem. Int. Ed. Engl.*, **35**, 448–451 (1996).