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Preliminary Communication

Total Synthesis of (+)-(2*S*,3*R*)-Piscidic Acid *via* Catalytic Asymmetric Dihydroxylation of a Trisubstituted Olefin

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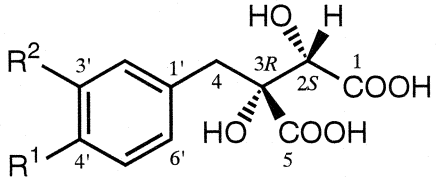
(+)-(2*S*,3*R*)-Piscidic acid was efficiently synthesized with high optical purity (90% *e.e.*) *via* Sharpless catalytic asymmetric dihydroxylation of a trisubstituted olefin in only 6 steps from commercially available 4-hydroxyphenylpyruvic acid as the starting material. The reaction proceeded with high optical purity by using the chiral ligands, dihydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether or dihydroquinidine 1,4-anthraquinonediyl diether.

Key words: piscidic acid; asymmetric dihydroxylation; catalytic asymmetric synthesis

Piscidic acid (**1**) [Fig. 1] is known as one of the constituents of hypnotic and narcotic drugs extracted from the root of bark of *Piscidia erythrina* L. (Jamaica dogwood)[1–3] and as an active constituent of *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 its related compounds would be important chemical probes to identfy the mechanism for these biological activities. However, few synthetic studies on such compounds have so far been reported.[10–14] We describe here the total synthesis of (+)-(2*S*,3*R*)-piscidic acid *via* Sharpless catalytic asymmetric dihydroxylation (AD)[15] of a trisubstituted olefin.

The synthesis was started from commercially available 4-hydroxyphenylpyruvic acid (**4**) [Scheme 1]. Methyl esterification of **4** with diazomethane and the subsequent Wittig reaction with methoxycarbonylmethylenetriphenylphosphorane gave a mixture of trisubstituted olefins **5Z**[16] and **5E**, which could be readily separated by column chromatography on silica gel, in a 90% yield (2 steps) and in a 3:1 ratio.[12,13] The geometry of **5Z** and **5E** was determined in comparison with that of the synthetic intermediates of fukiic acid derivatives from ^{1}H-NMR spectra.[10–13] Although the stoichiometric dihydroxylation of (*Z*)-olefins possessing a 3,4-dimethoxybenzyl group has been carried out with osmium tetroxide[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* alkylation of dimethyl L-tartrate acetonide required the separation and epimerization of alkylated products.[14] So we planned to use Sharpless catalytic asymmetric dihydroxylation in order to solve all these problems at the same time. Although AD of **5Z** was first carried out with AD-mix-β [a pre-mixed reagent containing the dihydroquinidine 1,4-phthalazinediyl diether, $(DHQD)_2PHAL$] and methanesulfonamide under the usual AD conditions,[15] no desired product could be obtained from the organic layers continuously extracted from the reaction mixture, in spite of the disappearance of **5Z**. Next, we examined AD of **6Z** which was obtained quantitatively by protecting the phenolic hydroxyl group as *tert*-butyldimethylsilyl (TBDMS) ether in a 96% yield.[16] The bulkiness of the TBDMS group would prevent chelation of the ethereal oxygen to osmium.



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

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

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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*-indolinecarboate; DHQD, dihydroquinidine; DHQ, dihydroquinine

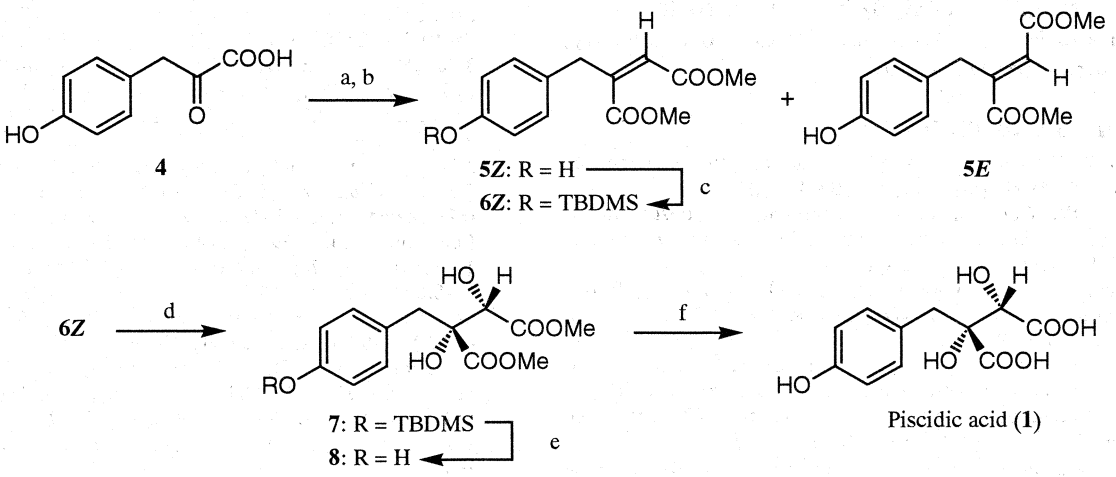
Table 1. Asymmetric Dihydroxylation of **6Z** to **7** with Various Chiral Ligands[a]

Entry	Ligand		$K_2OsO_2(OH)_4$	Time	Yield	Optical purity[b]
1[c]	$(DHQD)_2PHAL$	1 mol %	0.4 mol %	20 h	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.*

[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 **7** could not be detected by analytical TLC. [e] $(DHQD)_2$ PHAL (4 mol %) and $K_2OsO_2(OH)_4$(0.6 mol %) were added to AD-mix-β (0.7 g). [f] Unreacted **6Z** (31%) was recovered. [g] **6Z** (2%). [h] **6Z** (8%). [i] **6Z** (4%). [j] **6Z** (9%). [k] **6Z** (29%).

When AD-mix-β was used, diol **7** could not be detected by analytical TLC, and only **6Z** was detected (Table 1, entry 1). By increasing the quantities of $(DHQD)_2PHAL$ (5 mol %) and osmium (1 mol %), the reaction proceeded to give **7**[16] in a 43% yield after stirring for 14 h at 4°C with 31% of unreacted **6Z** (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 **7** only underwent esterification to give the (*S*)- and (*R*)-MTPA esters, whose signals for the benzylic methylene protons were completely separated from each other. In the subsequent entries, the optical purity was determined by using the same method. When dihydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether, $(DHQD)_2PYR$ (5 mol %) and osmium (10 mol %) were used,[15] the best yield (92%) was recorded with 89% *e.e.* without any recovery of **6Z** (entry 3). By decreasing the quantity of osmium (1 mol %) with no change in 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 in the ligand, the optical purity (93% *e.e.*) was best (entry 6). When other ligands of dihydroquinidine 4-chlorobenzoate, (DHQD)CLB (entry 7)[15] and dihydroquinidine *N*-indolinecarboate, (DHQD)IND (entry 8)[15] were used, the optical purity was lower than those of entries 3–6. In entries 4–8, several by-products were detected by analytical TLC. In all entries, the absolute configuration of the major enantiomer that was obtained was identical and was determined to have 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 **6Z** with dihydroquinidine (DHQD) ligands is in agreement with the usual prediction for Sharpless AD.[15] Thus, $(DHQD)_2PYR$ and $(DHQD)_2AQN$ (entries 3–6), which gave **7** in approximately 90% *e.e.*, were found to be useful chiral ligands of AD for **6Z**. Although the PHAL ligand is usually recommended for the trisubstituted class of olefins, $(DHQD)_2PHAL$ was ineffective for our substrate.

By following the conditions of entry 5, up-scaling (from 0.5 to 10 mmol) for AD of **6Z** was achieved, being directed toward the catalytic asymmetric synthesis of **1**, to give **7** in a 60% yield with 89% *e.e.* Deprotection of



Scheme 1. (a) CH_2N_2/Et_2O-THF, 0°C, 10 min; (b) Ph_3P=CHCOOMe/benzene, reflux, 2 h, **5Z**:**5E**=3:1, 90% (2 steps); (c) TBDMSCl, imidazole/DMF, r.t., 5 h, 99%; (d) Sharpless asymmetric dihydroxylation (see Table 1); (e) Amberlite IR-120B (H^+-form)/MeOH, reflux, 38 h, 99%; (f) 2M KOH/MeOH, reflux, 1 h, 95%.

the TBDMS ether of **7** was carried out in the presence of the ion-exchange resin, Amberlite IR-120B (H^+-form), in refluxing MeOH to quantitatively give **8** corresponding to the dimethyl ester of **1**.[16] Synthetic **8** 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**[18] were identical with those of natural **1** isolated from *Narcissus poeticus* bulbs.[3] The sign of specific rotation was also identical with that of **1**. The optical purity was determined to be 90% *e.e.* after treating **1** with diazomethane to give dimethyl piscidate which was converted into (*R*)- and (*S*)-bis-MTPA esters. 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. In order to increase the optical purity, optimization of the recrystallization conditions is now in progress.

In conclusion, the catalytic asymmetric synthesis of (+)-(2*S*,3*R*)-piscidic acid (**1**) was efficiently accomplished *via* Sharpless AD by using $(DHQD)_2AQN$ as the chiral ligand. It is obvious that the enantiomer of **1** would be synthesized by using dihydroquinine (DHQ) ligands.[15] In preliminary experiments, it was proved that Sharpless AD with AD-mix-β for the TBDMS ether of **5E** also proceeded to give the corresponding diol with 88% *e.e.* Therefore, all stereoisomers of **1** could be obtained in the near future, and the result will be reported elsewhere. Furthermore, methylation of **8** with methyl iodide and potassium carbonate gave the dimethyl ester of **2**,[7] which was converted into **2** *via* alkaline hydrolysis.

Acknowledgments

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16) Spectral data for the new compounds are as follows:
Dimethyl (4-Hydroxybenzyl)maleate (**5Z**). HRMS m/z (M^+): calcd. for $C_{13}H_{14}O_5$, 250.0842; found, 250.0865; IR ν_{max} (film) cm^{-1}: 3393, 3026, 2955, 2847, 1716, 1652, 1603, 1516, 1441, 1373, 1218, 1173, 1104, 1021, 971, 926, 837, 804, 757; ^{1}H-NMR δ ($CDCl_3$, 270 MHz): 7.01 (2H, d, *J*=8.6 Hz, Ar-*H*), 6.77 (2H, d, *J*=8.6 Hz, Ar-*H*), 5.84 (1H, br. s, OH), 5.66 (1H, t, *J*=1.9 Hz, C=C-*H*), 3.77 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.58 (2H, d, *J*=1.9 Hz, Ar-CH_2); ^{13}C-NMR δ ($CDCl_3$, 67.5 MHz): 169.2, 165.7, 155.1, 149.7, 130.5, 126.9, 120.7, 115.7, 52.5, 51.9, 39.3.
Dimethyl (4-tert-butyldimethylsilyloxybenzyl)maleate (**6Z**). HRMS m/z (M^+): calcd. for $C_{19}H_{28}O_5Si$, 364.1706; found, 364.1733; IR ν_{max} (film) cm^{-1}: 3032, 2954, 2897, 2859 ,1733, 1652, 1610, 1512, 1473, 1436, 1372, 1258, 1168, 1101, 1022, 975, 915, 840, 783; ^{1}H-NMR δ ($CDCl_3$, 270 MHz): 7.03 (2H, d, *J*=8.6 Hz, Ar-*H*), 6.79 (2H, d, *J*=8.6 Hz, Ar-*H*), 5.62 (1H, t, *J*=1.9 Hz, C=C-*H*), 3.76 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.58 (2H, d, *J*=1.9 Hz, Ar-CH_2), 0.97 (9H, s, Si-C(CH_3)$_3$), 0.19 (6H, s, Si- (CH_3)$_2$); ^{13}C-NMR δ ($CDCl_3$, 67.5 MHz): 168.8, 165.4, 154.7, 149.7, 130.3, 127.8, 120.5, 120.3, 52.2, 51.7, 39.3, 25.6, 18.1, −4.5.
Dimethyl (2S,3R)-3-(4-tert-butyldimethylsilyloxybenzyl)tartrate (**7**). $[\alpha]_D^{24}$ +28.3° (*c* 1.65, $CHCl_3$) as 89% *e.e.* purity; HRMS m/z (M^+): calcd. for $C_{19}H_{30}O_7Si$, 398.1761; found, 398.1764; IR ν_{max} (film) cm^{-1}: 3481, 2957, 2859, 1746, 1609, 1512, 1442, 1254, 1117, 916, 839, 778; ^{1}H-NMR δ ($CDCl_3$, 270 MHz): 7.02 (2H, d, *J*=8.6 Hz, Ar-*H*), 6.73 (2H, d, *J*=8.6 Hz, Ar-*H*), 4.55 (1H, d, *J*=8.6 Hz, C(OH)*H*COOMe), 3.75 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.30 (1H, d, *J*=8.6 Hz, C(O*H*)HCOOMe), 3.25 (1H, d, *J*=13.9 Hz, Ar-C*H*H), 3.25 (1H, s, O*H*), 3.03 (1H, d, *J*=13.9 Hz, Ar-CH*H*), 0.96 (9H, s, SiC(CH_3)$_3$), 0.17 (6H, s, 6H, Si(CH_3)$_2$); ^{13}C-NMR δ ($CDCl_3$, 67.5 MHz): 173.7, 172.1, 155.3, 131.5, 128.1, 120.4, 80.6, 75.6, 53.3, 53.2, 41.2, 26.1, 18.6, −4.0.
Dimethyl (2S,3R)-3-(4-hydroxybenzyl)tartrate (**8**). $[\alpha]_D^{21}$ +30.0° (*c* 1.32, $CHCl_3$); HRMS m/z (M^+): calcd. for $C_{13}H_{16}O_7$, 284.0896; found, 284.0859; IR ν_{max} (film) cm^{-1}: 3431, 3021,

2956, 1739, 1615, 1597, 1516, 1442, 1223, 1114, 977, 842, 753, 702; ^{1}H-NMR δ ($CDCl_3$, 270 MHz): 6.99 (2H, d, J=8.6 Hz, Ar-*H*), 6.68 (2H, d, J=8.6 Hz, Ar-*H*), 5.92 (1H, br. s, Ar-O*H*), 4.56 (1H, s, C(OH)*H*COOMe), 3.73 (6H, s, OCH_3), 3.42 (2H, br. s, O*H*×2), 3.26 (1H, d, J=13.9 Hz, Ar-C*H*H), 3.03 (1H, d, J=13.9 Hz, Ar-CH*H*); ^{13}C-NMR δ ($CDCl_3$, 67.5 MHz): 173.4, 171.7, 154.9, 131.1, 126.6, 115.2, 80.3, 75.1, 52.9, 40.6.

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18) *(2S,3R)-Piscidic acid* (**1**). IR ν_{max} (KBr) cm^{-1}: 3400–2500, 3387, 1718, 1617, 1517, 1445, 1358, 1232, 1113, 1091, 838, 780; ^{1}H-NMR δ (acetone-d_6, 270 MHz): 8.14 (1H, br. s, Ar-O*H*), 7.07 (2H, d, J=8.6 Hz, Ar-*H*), 6.69 (2H, d, J=8.6 Hz, Ar-*H*), 4.54 (1H, s, C(OH)*H*COOH), 3.21 (1H, d, J=13.9 Hz, Ar-C*H*H), 3.00 (1H, d, J=13.9 Hz, Ar-CH*H*), 5.40–3.20 (4H, br. signal, COO*H*×2 and O*H*×2); ^{13}C-NMR δ (acetone-d_6, 67.5 MHz): 174.5, 173.1, 157.3, 132.5, 127.8, 115.8, 80.9, 76.0, 41.6.