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Enantioselective synthesis of (−)-pinellic acid

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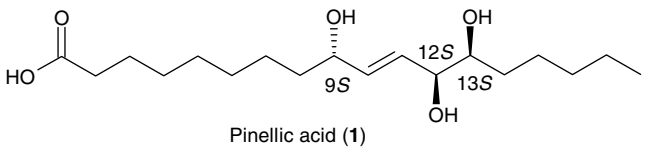
Abstract—An enantioselective convergent approach toward the total synthesis of pinellic acid **1** from 1,9-nonanediol is described. The synthetic strategy features iterative Sharpless asymmetric dihydroxylation, Sonogashira coupling and Birch reduction.

Influenza, is an infectious disease that infects birds and mammals (primarily the upper airways and lungs in mammals) and is caused by an RNA virus of the *Orthomyxoviridae* family (the influenza viruses). The most common and characteristic symptoms of influenza in humans are fever, pharyngitis, myalgia, severe headache, coughing, and malaise. Flu rapidly spreads around the world in seasonal epidemics,[1] killing millions of people in pandemic years and hundreds of thousands in nonpandemic years.

Kampo medicine, 'Sho-seiryu-to' was found to possess potent adjuvant activity by oral administration on nasal influenza infection and nasal influenza vaccination.[2] Pinellic acid (9*S*,12*S*,13*S*-trihydroxy-10*E*-octadecenoic acid, Fig. 1) was isolated from the tubers of *Pinellia ternata*, one of the eight component herbs of the Kampo formula, Sho-seiryu-to (SST).[3] Pinellic acid is a novel and potentially useful oral adjuvant when used in conjunction with intranasal inoculation of influenza HA vaccines.[3a] Pinellic acid showed no hemolytic activity.[3a] Among the series of pinellic acid isomers, the (9*S*,12*S*,13*S*)-compound, which is a natural product, exhibited the most potent adjuvant activity.[4]



Pinellic acid (**1**)

Figure 1.

Ōmura and co-workers reported the first synthesis of (−)-pinellic acid **1** and determined its absolute configuration by synthesizing all its isomers via regioselective Sharpless asymmetric dihydroxylation and stereoselective reduction.[5] As a part of our research program aimed at developing enantioselective syntheses of naturally occurring lactones[6] and amino alcohols,[7] we have accomplished the enantioselective synthesis of (−)-pinellic acid **1** employing the Sharpless asymmetric dihydroxylation as the source of chirality starting from commercially available 1,9-nonanediol.

Our retrosynthetic strategy for the synthesis of (−)-pinellic acid **1** is outlined in Scheme 1. We envisioned that the 12*S*,13*S* *syn*-diol could be prepared from 1,3-enyne **12**, which in turn could be prepared from acetylene **10** by Sonogashira coupling with vinyl iodide **11**. Acetylene **10** could be obtained from 1,9-nonane diol **2**. In this strategy, the 9*S* hydroxy could be installed through Sharpless asymmetric dihydroxylation of an olefin, which in turn would be prepared from 1,9-nonane diol **2**.

The synthesis of (−)-pinellic acid **1** started from commercially available 1,9-nonane diol **2** as illustrated in Schemes 2 and 3. Thus, selective mono hydroxyl protection of **2** with *p*-methoxybenzyl bromide in the presence of NaH gave the monoprotected diol **3** in 95% yield, which was oxidized to the corresponding aldehyde under Swern conditions[8] and subsequently treated with (ethoxycarbonylmethylene)triphenylphosphorane in benzene under reflux to furnish *trans*-olefin **4** in 91% yield.

Olefin **4** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of

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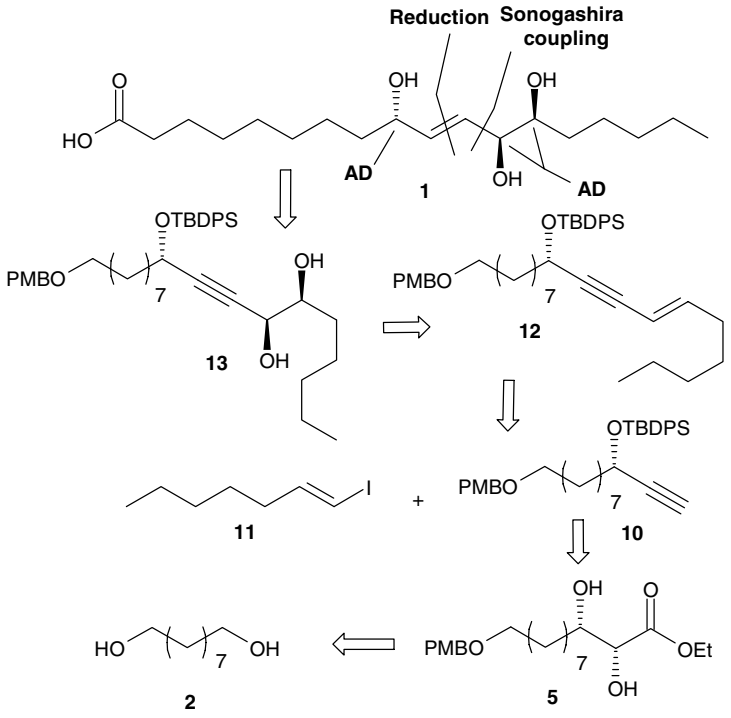
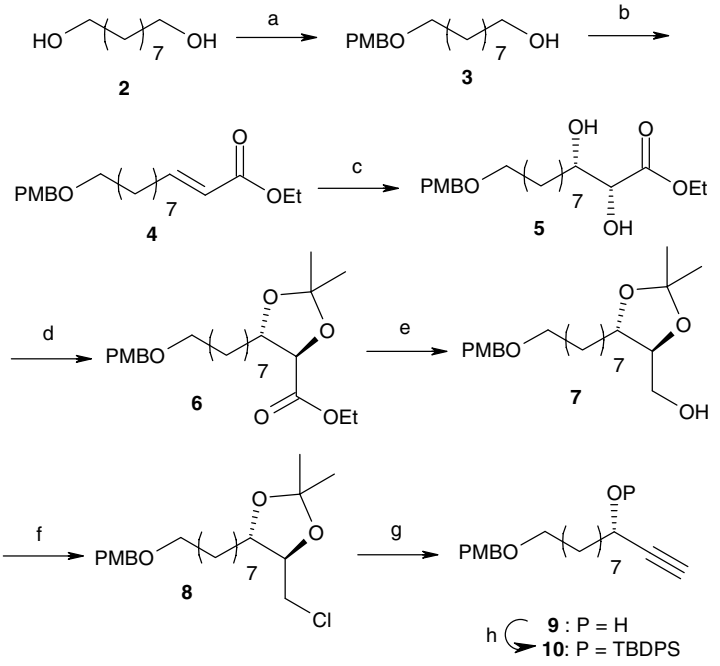
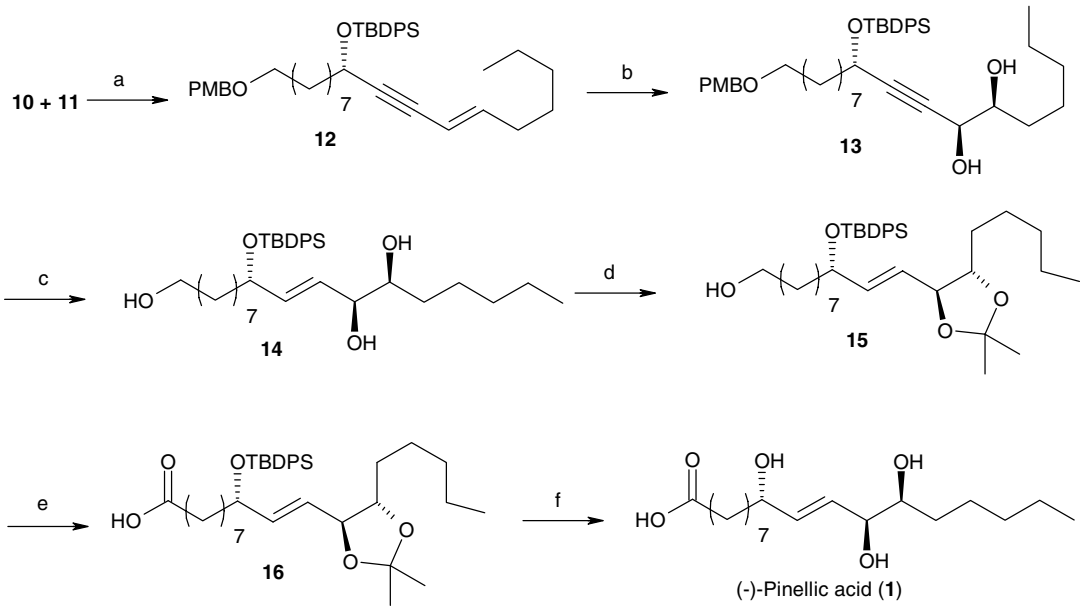


Scheme 1. Retrosynthetic analysis of pinellic acid (**1**).



Scheme 2. Reagents and conditions: (a) (i) *p*-$CH_3OC_6H_4CH_2Br$, NaH, dry DMF, cat. TBAI, 0 °C–rt, 1 h, 95%; (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to −60 °C; (ii) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 4 h, 91%; (c) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, OsO_4 (0.1 M solution in toluene), *t*-BuOH/H_2O (1:1), 0 °C, 24 h, 96%; (d) *p*-TSA, 2,2-DMP, CH_2Cl_2, overnight, 96%; (e) DIBAL-H, CH_2Cl_2, 0 °C–rt, 2 h, 96%; (f) *N*-chlorosuccinimide, PPh_3, CH_2Cl_2, 0 °C to rt, 3 h, 89%; (g) (i) *n*-BuLi, HMPA, THF, −42 °C–rt, 30 min, 82%; (ii) TBDPSCl, imidazole, CH_2Cl_2, 0 °C–rt, overnight, 98%.

$(DHQ)_2PHAL$ ligand under asymmetric dihydroxylation (AD) conditions[9] to give diol **5** in 96% yield with 99% ee.[10] Treatment of diol **5** with 2,2-dimethoxypropane in the presence of *p*-TSA gave compound **6**, which on reduction with DIBAL-H furnished alcohol **7** in excellent yield. Alcohol **7** was converted to chloride **8** in 89% yield via Mitsunobu reaction.[11] Propargylic alcohol **9** was obtained by treatment of **8** with *n*-BuLi in the



Scheme 3. Reagents and conditions: (a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 6 h, 86%; (b) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, OsO_4 (0.1 M in toluene), *t*-BuOH/H_2O 1:1, 0 °C, 24 h, 96%; (c) Na/liq NH_3, THF, −40 °C, 89%; (d) *p*-TSA, 2,2-DMP, CH_2Cl_2, overnight, 92%; (e) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to −60 °C; (ii) $NaClO_2$, DMSO, NaH_2PO_4, rt, overnight; (f) HCl (cat), MeOH, rt, overnight, 78% overall yield from **15**.

presence of HMPA[12] in 82% yield. The free hydroxy group of **9** was protected with TBDPSCl to furnish compound **10**.[13]

In order to generate the *trans*-olefin to execute the second Sharpless asymmetric dihydroxylation, Sonogashira coupling[14] was employed in the next step. Thus, coupling of **10** with *trans*-vinyl iodide **11**[15] using $Pd(PPh_3)_2Cl_2$ and CuI in triethylamine furnished 1,3-enyne product **12** in excellent yield. Enantioselective AD of 1,3-enyne **12** under standard conditions gave acetylenic diol **13**[16] in good yield with high diastereomeric excess (de = >96%) as judged by ^1H and ^{13}C NMR spectral analysis. Reduction of alkyne **13** to the *E*-alkene and concomitant removal of the PMB group proceeded smoothly under Birch conditions using Na/liq NH_3[17] to afford **14** in 89% yield. Diol **14** was protected as its isopropylidene derivative **15** in the presence of 2,2-dimethoxypropane and a catalytic amount of *p*-TSA in good yield.

Oxidation of the primary alcohol in **15** to the corresponding aldehyde using Swern conditions and further oxidation using $NaClO_2$ in DMSO under buffered conditions[18] furnished acid **16**. Finally, the acetonide and TBDPS groups were deprotected under acidic conditions (catalytic HCl in MeOH) to afford the target molecule **1** in 78% overall yield from **15**. The physical and spectroscopic data of **1** were identical with those reported.[4,5]

In conclusion, a convergent and efficient total synthesis of (−)-pinellic acid **1**, with high enantioselectivities has been developed in which all the stereocenters were established by Sharpless asymmetric dihydroxylation. Notable features of this approach include Sonogashira coupling and Birch reduction to establish the C10–C11 *trans*-olefin geometry. Further application of this methodology to the syntheses of related compounds for structure activity relationship studies is currently underway in our laboratory.

Acknowledgments

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10. The enantiomeric purity of diol **5** was estimated to be >99% by chiral HPLC analysis (Chiralcel OD, petroleum ether/*i*-PrOH (96:4), 1 mL/min, 240 nm). *Spectral data of compound* **5**: $[\alpha]_D^{25}$ −6.7 (*c* 1.7, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3440, 2938, 2864, 1736, 1612, 1513, 1248, 1130, 1032 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.25–1.36 (m, 13H), 1.50–1.74 (m, 4H), 2.51 (br s, 2H), 3.46 (t, $J = 6.6$ Hz, 2H), 3.82 (s, 3H), 3.90 (d, $J = 6.6$ Hz, 1H), 4.06–4.16 (m, 1H), 4.32 (q, $J = 7.0$ Hz, 2H), 4.46 (s, 2H), 6.93 (d, $J = 8.5$ Hz, 2H), 7.31 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.0, 25.5, 26.0, 29.2, 29.3, 29.5, 33.5, 55.0, 61.6, 70.0, 72.3, 73.0, 73.1, 113.6, 128.9, 130.7, 158.9, 173.4. Anal. Calcd for $C_{21}H_{34}O_6$ (382.50): C, 65.94; H, 8.96. Found: C, 66.09; H, 8.81.
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13. *Spectral data of compound* **10**: colorless oil, $[\alpha]_D^{25}$ −1.75 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3440, 2938, 2864, 1736, 1612, 1513, 1248, 1130, 1032 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.10 (s, 9H), 1.24 (br s, 10H), 1.53–1.72 (m, 4H), 2.33 (d, $J = 2.0$ Hz, 1H), 3.44 (t, $J = 6.6$ Hz, 2H), 3.82 (s, 3H), 3.35 (dd, $J = 6.1$, 1.9 Hz, 1H), 4.45 (s, 2H), 6.92 (d, $J = 8.7$ Hz, 2H), 7.31 (d, $J = 8.6$ Hz, 2H), 7.37–7.45 (m, 6H), 7.64–7.79 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.2, 24.3, 24.5, 26.1, 26.5, 26.8, 28.9, 29.25, 29.28, 29.7, 37.2, 38.1, 55.0, 63.6, 69.2, 70.0, 72.4, 85.0, 113.6, 117.0, 127.3, 127.5, 129.1, 129.4, 129.56, 129.65, 129.7, 130.7, 133.9, 134.7, 135.7, 135.9, 159.0. Anal. Calcd for $C_{35}H_{46}O_3Si$ (542.82): C, 77.44; H, 8.54. Found: C, 77.51; H, 8.45.
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16. *Spectral data of compound* **13**: colorless oil, $[\alpha]_D^{25}$ +8.8 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3440, 2938, 2864, 1736, 1612, 1513, 1248, 1130, 1032 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.90 (t, $J = 6.8$ Hz, 3H), 1.07 (s, 9H), 1.27 (br s, 18H), 1.57–1.73 (m, 4H), 2.34 (br s, 2H), 3.29–3.34 (m, 2H), 3.81 (s, 3H), 3.90 (t, $J = 7.3$ Hz, 2H), 4.23–4.34 (m, 1H), 4.45 (s, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 7.30 (d, $J = 8.7$ Hz, 2H), 7.35–7.49 (m, 6H), 7.69–7.78 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.9, 19.1, 22.5, 24.8, 25.1, 26.1, 26.8, 29.0, 29.3, 29.4, 29.7, 31.7, 32.1, 38.2, 55.2, 63.7, 65.9, 70.1, 72.4, 74.5, 83.2, 87.7, 113.7, 127.3, 127.6, 129.2, 129.6, 129.8, 130.7, 133.4, 134.1, 135.8, 135.9, 159.1. Anal. Calcd for $C_{42}H_{60}O_5Si$ (673.01): C, 74.95; H, 8.99; Si, 4.17. Found: C, 75.10; H, 8.80; Si, 4.09.
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