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A chemoenzymatic asymmetric synthesis of (9*S*,12*S*,13*S*)- and (9*S*,12*RS*,13*S*)-pinellic acids

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ABSTRACT

A brief and facile synthesis of the title compounds has been developed by using an efficient lipase-catalyzed acylation and a chiral template-directed diastereoselective alkylation for incorporating the stereogenic centres. A cross-metathesis was employed to get the required *E*-olefin geometry.

Influenza is an infectious viral disease of the respiratory tract among human beings. It is associated with fever, myalgia, pharyngitis and severe headache. The symptoms are especially acute for patients afflicted by bronchial asthma and immunosuppressive syndromes such as AIDS[1] and cardiopulmonary diseases and can assume lethal proportions. Intranasal inoculation of influenza vaccine[2] is a useful and safe prophylactic measure to treat the infection. However, it is not adequately effective to induce high levels of immunity. Therefore, novel and effective adjuvants for the vaccine are sought for potency enhancement. The Kampo medicine, Sho-seiryu-to (SST) was found to exhibit adjuvant activity by oral intake for nasally administered influenza vaccine. The activity of SST was attributed to ingredients from *Pinelliae tuber*, a component herb. Pinellic acid (9,12,13-trihydroxy-10*E*-octadecenoic acid, **1**) is the active principle of the same.[3] The initial syntheses[4a,b] of the stereomers of **1** were aimed at elucidation of absolute stereochemistry of its stereogenic centres and establishing the structure–activity relationship. These employed (i) Sharpless asymmetric dihydroxylation and a stereoselective reduction with BINAL-H as the key steps. Among the eight possible stereomers of pinellic acid, (9*S*,12*S*,13*S*)-**1** exhibited the most potent adjuvant activity.[4c] Among the 9*S*-derivatives, the adjuvant activities of the 13*S*-compounds were stronger than those of the 13*R*-compounds, while the adjuvant activity was indifferent to the stereochemistry of C-12 carbinol centre.[4a,b] In view of this, and the medicinal value of **1**, several syntheses of its different stereomers via (i) Sharpless asymmetric dihydroxylation, Sonogashira coupling and Birch reduction,[5a,b] (ii) Sharpless asymmetric epoxidation and alkyne coupling[5c] and (iii) tartaric acid as the chiral template have been reported.[5d]

Despite the impressive progress,[6a] the development of simple and efficient strategies remains a challenging area in asymmetric synthesis.[6b,c] To this end, we have extensively used inexpensive and easily accessible (*R*)-cyclohexylideneglyceraldehyde **7** as a versatile chiral template[7a–f] and/or employed biocatalytic routes[8a–d] for the asymmetric syntheses of a diverse array of natural compounds. A chemoenzymatic approach, combining both these methodologies may often provide easy access to the target compounds, as illustrated in this Letter for the syntheses of the title compounds.

For the synthesis (Scheme 1), the commercially available 1,9-nonanediol **2** was monoprotected with *para*-methoxybenzyl chloride (PMBCl) in the presence of NaH to furnish compound **3**. On oxidation with pyridinium chlorochromate (PCC), the aldehyde **4** was obtained. Its reaction with vinylmagnesium bromide afforded the allylic alcohol **5**. A Novozyme 435®-catalyzed acetylation of **5** with vinyl acetate proceeded smoothly to furnish the (*S*)-acetate **6** (41%) and (*R*)-alcohol **5** (38%) in 97% and 95% ees, respectively, after ~50% conversion. The % ees of the enantiomeric alcohols (*R*)-**5** and (*S*)-**5** were determined from the relative intensities of the methoxyl resonances of the corresponding MTPA esters, prepared using (*R*)-MTPA chloride.[9] Alkaline hydrolysis of (*S*)-**6** gave the alcohol (*S*)-**5**, while the resolved alcohol (*R*)-**5** could be converted to its antipode via a Mitsunobu inversion ($PhCO_2H/Ph_3P$/DIAD/THF, 87%).[10]

For the other synthon, following our own methodology, the known aldehyde **7** was reacted with $CH_3(CH_2)_4Li$ to furnish the *anti*-triol derivative **8** almost exclusively (dr = 97:3). The *anti*-compound **8** could be easily obtained in stereochemically pure form by column chromatography, and characterized by its typical ^1H NMR resonances.[7e,f] Its carbinol function was protected with *tert*-butyldiphenylsilyl chloride (TPSCl)/imidazole in the presence of 4-dimethylaminopyridine (DMAP) in anhydrous CH_2Cl_2 to furnish the silyl derivative **9**. The acetal function of **9** was conveniently removed with aqueous trifluoroacetic acid (TFA) to furnish the diol **10**. Treatment of **10** with $NaIO_4$ led to cleavage of the 1,2-diol function affording the aldehyde **11**, which on reaction with vinylmagnesium

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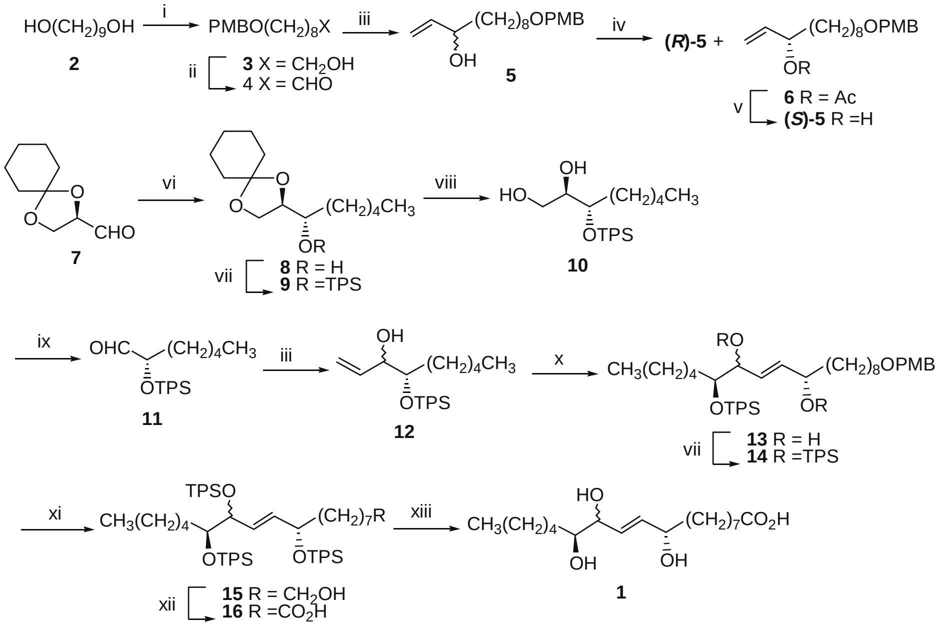
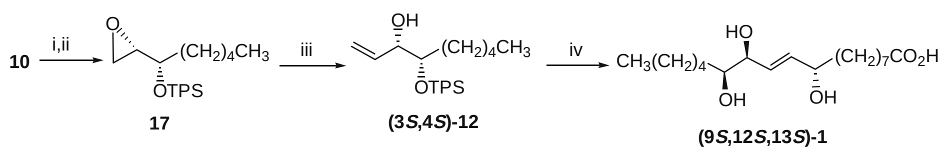


Scheme 1. Reagents and conditions: (i) NaH/PMBCl/DMF/25 °C/12 h (71%); (ii) PCC/NaOAc/CH_2Cl_2/25 °C/3 h (92%); (iii) CH_2=CHMgBr/THF/25 °C/3 h (79% for **5**, 81% for **12**); (iv) vinyl acetate/Novozyme 435/diisopropyl ether/25 °C/26 h (50% conversion); (v) K_2CO_3/MeOH/25 °C/6 h (86%); (vi) $CH_3(CH_2)_4Li$/THF/25 °C/4 h (87%); (vii) TPSCl/imidazole/DMAP/CH_2Cl_2/25 °C/18 h (84% for **9**, 80% for **14**); (viii) 80% aqueous TFA/0 °C/3 h (81%); (ix) $NaIO_4$/MeCN–H_2O (6:4)/0 °C/2 h (90%); (x) (*S*)-**5**/CH_2Cl_2/Grubbs 2nd generation catalyst/25 °C/18 h (78% based on **5**); (xi) DDQ/CH_2Cl_2–H_2O/25 °C/12 h (77%); (xii) PDC/DMF/25 °C/24 h (71%); (xiii) Bu_4NF/THF/0 °C/12 h (89%).



Scheme 2. Reagents and conditions: (i) TMSCl/EtOAc/−20 °C/20 min; MsCl/Et_3N/−20 °C/30 min; 2 N aqueous HCl/25 °C/40 min (78%); (ii) NaH/THF/0–25 °C/3 h (89%); (iii) Me_3SI/BuLi/THF/−25 °C/1 h then 25 °C/6 h (84%); (iv) As in Scheme 1.

bromide furnished the allylic alcohol **12** (*syn*:*anti* 78:22). As envisioned in our synthetic plan, the C-3 carbinol centre of **12** would eventually provide the C-12 carbinol centre of the target compound. Since, the stereochemistry at C-12 of **1** was inconsequential to its adjuvant activity, the diastereomeric mixture of **12** was used as such for the synthesis. A cross-metathesis reaction between (*S*)-**5** and **12** (1.7 equiv) in the presence of Grubbs 2nd generation catalyst proceeded smoothly to furnish the desired diol **13** in good yield. However, the Grubbs 1st and Grubbs–Hoveyda 2nd generation catalysts were ineffective for the transformation. The *E*-geometry of the olefin **13** as ascertained from its ^{1}H NMR spectrum was consistent with the proposed model for the cross-metathesis reaction.[11] Silylation of the carbinol function of **13** as above gave the trisilylated compound **14**. Oxidative removal of the PMB protection in **14** with dichlorodicyanobenzoquinone (DDQ) furnished the alcohol **15**. This was oxidized with pyridinium dichromate (PDC) in DMF to furnish the acid **16**, which on desilylation afforded the title acid (9*S*,12*RS*,13*S*)-**1**.[12]

For the synthesis of natural (9*S*,12*S*,13*S*)-**1**, the diol **10** was monosilylated at its primary carbinol site with trimethylchlorosilane (TMSCl), the adjacent hydroxyl function was mesylated with methanesulphonyl chloride (MsCl) and was subsequently desilylated in one pot. The resultant hydroxymesyl compound was treated with NaH to furnish the epoxide (2*S*,3*S*)-**17**. This on a base (*n*-BuLi)-mediated reaction $Me_3S^+I^-$ afforded (3*S*,4*S*)-**12**, which was subsequently converted to the target compound in five steps and 27% yield (Scheme 2).

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12. All the compounds were fully characterized from their spectral, optical and microanalytical data. Representative data are included. *Data for* **5**: Colourless oil; $[\alpha]_D^{23}$ −3.94 (*c* 1.41, $CHCl_3$). IR: 3427, 3074, 918 cm^{-1}; ^1H NMR: δ 1.29 (br s, 10H), 1.45–1.61 (m, 4H), 2.06 (br s, 1H), 3.44 (t, *J* = 6.6 Hz, 2H), 3.80 (s, 3H), 4.06–4.10 (m, 1H), 4..43 (s, 2H), 5.06–5.26 (m, 2H), 5.77–5.94 (m, 1H), 6.88 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR: δ 25.3, 26.1, 29.4, 29.5, 29.6, 37.0, 55.1, 70.0, 72.4, 72.9, 113.6, 114.1, 129.2, 130.6, 141.5, 159.0. Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 76.59; H, 10.04. *Data for* **8**: Colourless oil; $[\alpha]_D^{24}$ +8.6 (*c* 1.20, $CHCl_3$); IR: 3444 cm^{-1}; ^1H NMR: δ 0.88 (dist. t, *J* = 6.4 Hz, 3H), 1.29–1.47 (m, 10H), 1.58–1.68 (m, 8H), 2.10 (br s, 1H), 3.72–3.79 (m, 1H), 3.83–4.06 (m, 3H); ^{13}C NMR: δ 13.9, 22.4, 23.6, 23.8, 25.0, 25.3, 31.7, 32.7, 34.7, 36.0, 64.4, 70.7, 78.3, 109.3. Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.22; H, 10.98. *Data for* **13**: Colourless oil; $[\alpha]_D^{24}$ +10.56 (*c* 1.42, $CHCl_3$); IR: 3444 cm^{-1}; ^1H NMR: δ 0.80 (dist. t, *J* = 6.8 Hz, 3H), 1.06–1.59 (m containing a s at δ 1.09, 31H), 2.05 (br s, 2H), 3.43 (t, *J* = 6.6 Hz, 2H), 3.60–3.69 (m, 1H), 3.80 (s, 3H), 4.02–4.14 (m, 2H), 4.43 (s, 2H), 5.67 (dd, *J* = 15.4, 5.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.35–7.44 (m, 6H), 7.67–7.71 (m, 4H); ^{13}C NMR: δ 13.8, 19.4, 22.3, 24.4, 25.2, 26.0, 27.0, 29.3, 29.6, 31.6, 33.2, 36.9, 55.1, 70.1, 72.0, 72.4, 73.3, 77.5, 113.6, 127.4, 127.5, 129.1, 129.6, 130.5, 130.7, 133.4, 134.8, 135.8, 158.9. Anal. Calcd for $C_{42}H_{62}O_5Si$: C, 74.73; H, 9.26. Found: C, 74.59; H, 9.10.