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Total synthesis of (9*S*,12*R*,13*S*)-pinellic acid☆

Gowravaram Sabitha,* E. Venkata Reddy, M. Bhikshapathi and J. S. Yadav

Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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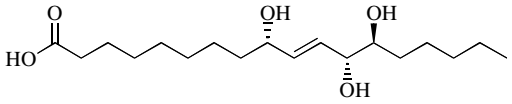
Abstract—The total synthesis of (9*S*,12*R*,13*S*)-pinellic acid, a novel and potentially useful oral adjuvant, isolated from *Pinelliae tuber* has been accomplished.

Influenza is caused by viruses, which usually affect the general population in a cyclical fashion every year as the seasons change. While once influenza was a very serious illness, today it is primarily dangerous to the elderly and the very young. Influenza virus infection is sometimes critical for patients with respiratory diseases such as bronchial, asthma and immunosuppressive syndromes such as AIDS. Therefore, the development of effective adjuvants for influenza vaccines is necessary to enhance the potency of the vaccine.



Pinellic acid 1

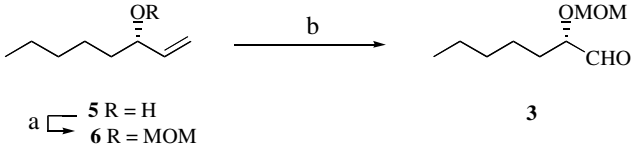
All the possible isomers of pinellic acid were isolated from an oriental medicine, *Pinellae tuber*. Pinellic acid is a novel and potentially useful oral adjuvant when used in conjunction with intranasal inoculation of influenza HA vaccines.[1] The absolute configurations of the pinellic acids were determined by Omura and co-workers,[2] who were the first to attempt the total synthesis of all isomers of pinellic acid. Among the C9-isomers of pinellic acid, 9*S*-compounds showed much stronger activity compared with the 9*R*-compounds. Thus, the stereochemistry at the C-9 hydroxyl group is very important for adjuvant activity. Among the 9*S*-derivatives, the adjuvant activities of the 13*S*-compounds were stronger than those of the 13*R*-compounds. However, the stereochemistry of the C-12 hydroxyl group was not important for adjuvant activity.[3] This stimulated us to investigate the synthesis of pinellic acid **1**.

Our strategy for the synthesis of pinellic acid **1** involved disconnecting the carbon backbone at C11–C12, thus dividing the target into two key fragments C1–C11 **2** and C12–C18 **3**. Fragments **2** and **3** can be obtained from alkyl halide **4** and allylic alcohol **5**, respectively.

The known allylic alcohol **5**[4] was converted into methoxy methyl ether **6** in 90% yield by treatment with 2 equiv of Hunig's base and 3 equiv of MOMCl for 2 h at room temperature. Olefin **6** was subjected to ozonolysis to give the required aldehyde **3** in 80% yield.[5] The IR spectrum of **3** showed a strong absorption band at 1734 cm^{-1} for the aldehyde group (Scheme 1).

Propargyl alcohol **7** was treated with bromide **4** in liquid ammonia and Li at −33 °C to give compound **8** in 70% yield. Acetylenic alcohol **8** was reduced with 1.5 equiv of $LiAlH_4$ in refluxing dry THF to afford the *trans*-allylic alcohol **9** in 80% yield.

The *E*-allyl alcohol **9** was subjected to Sharpless asymmetric epoxidation[6] by treatment with 0.2 equiv of



Scheme 1. Reagents and conditions: (a) MOMCl, DIPEA, 2 h, 90%; (b) O_3, DMS, DCM, −78 °C–rt, 3 h, 80%.

Keywords: Total synthesis; Natural product; Influenza; Propargyl alcohol.

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* Corresponding author. Tel./fax: +91 40 27160512; e-mail: sabitha@iictnet.org

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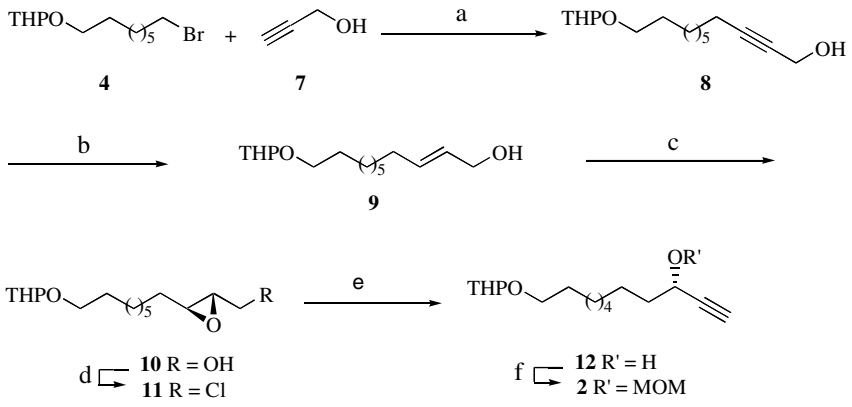
L-(+) DET, 0.2 equiv of $Ti(O^iPr)_4$ and 1.5 equiv of TBHP (3.3 M in toluene) in dry DCM at −24 °C to afford epoxy alcohol **10** in 80% yield. Epoxy alcohol **10** was converted into the corresponding epoxy chloride **11** in 90% yield by using TPP and $NaHCO_3$ in dry CCl_4 at reflux for 4 h. Accordingly, compound **11** was subjected to reaction with lithium amide in liquid ammonia at −33 °C for 4 h to afford the chiral propargyl alcohol **12** in 76% yield. The secondary hydroxyl functionality of compound **12** was then protected as its methoxymethyl ether to afford compound **2** in 90% yield (Scheme 2).

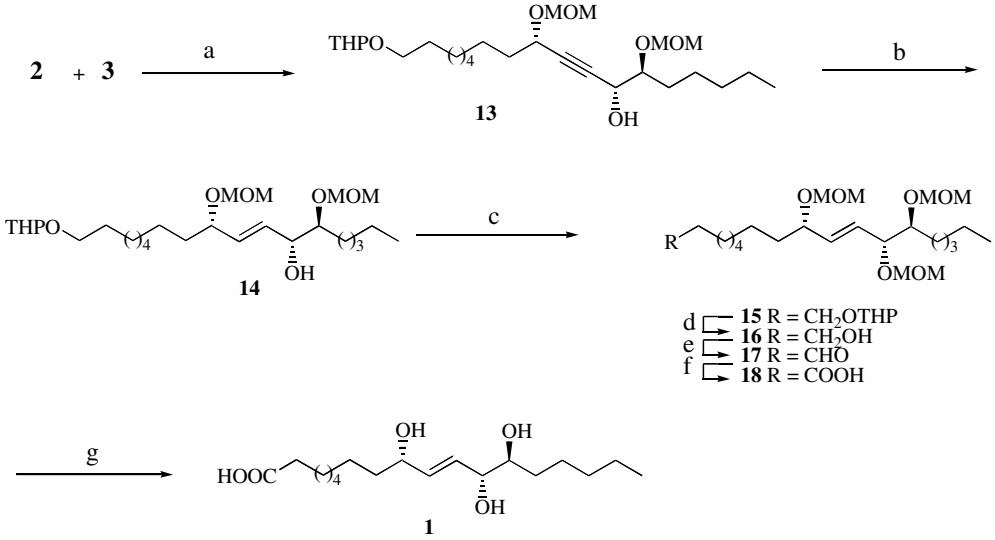
After successful completion of the syntheses of the two fragments C1–C11 **2** and C12–C18 **3**, our next aim was to couple the fragments (Scheme 3). MOM protected alkyne **2** was lithiated using *n*-BuLi at −78 °C followed by addition of aldehyde **3** to afford an 18:2 mixture of diastereoisomers in favour of **13** in 70% yield.[7] Alkyne **13** was reduced to *trans*-allyl alcohol **14** using $LiAlH_4$ in dry THF at reflux. Compound **14** was protected as its methoxymethyl ether using Hunig's base and MOMCl in dry DCM at room temperature to afford alkene **15** in 90% yield.[8]

Deprotection of the THP group of compound **15** with catalytic PPTS in methanol at room temperature yielded **16** in 80% yield.[9] Alcohol **16** was oxidized with DMP reagent in dry DCM to afford aldehyde **17** in 85% yield.[10] Oxidation of **17** with $NaClO_2$ and NaH_2PO_4 in DMSO and water afforded the corresponding acid **18** in 79% yield. Finally, acid **18** was subjected to MOM deprotection using a catalytic amount of PTSA in THF to afford the target compound **1** in 70% yield (Scheme 3).

In conclusion, we have accomplished the total synthesis of (9*S*,12*R*,13*S*)-pinellic acid.[11] Further, synthesis of other stereoisomers is under progress.



Scheme 2. Reagents and conditions: (a) Li, liq. NH_3, $Fe(NO_3)_3$, −33 °C, 6 h, 70%; (b) $LiAlH_4$, dry THF 0 °C–reflux, 2 h, 80%; (c) (+) DET, $Ti(O^iPr)_4$, dry DCM, TBHP, −24 °C, 4 h, 80%; (d) TPP, dry CCl_4, reflux, 4 h, 90%; (e) Li, liq. NH_3, $Fe(NO_3)_3$, −33 °C, 1 h, 76%; (f) MOMCl, DIPEA, dry DCM, 0 °C–rt, 2 h, 90%.



Scheme 3. Reagents and conditions: (a) *n*-BuLi, HMPA, dry THF, −78 °C, 2 h, 70% (mixture 18:2); (b) $LiAlH_4$, dry THF 0 °C–reflux, 2 h, 80%; (c) MOMCl, DIPEA, dry DCM, 0 °C–rt, 2 h, 90%; (d) MeOH, PPTS, 6 h, 80%; (e) DMP, dry DCM, 1 h, 85%; (f) DMSO, NaH_2PO_4, $NaClO_2$, H_2O, 4 h, 79%; (g) PTSA, THF, 10 h, 70%.

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11. *Spectral data for selected compounds:*
(2S)-2-(Methoxymethoxy)heptanal (**3**): $[\alpha]_D^{25}$ −60.5 (*c* 1, $CHCl_3$); IR (neat): 2930, 2860, 1734, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 9.51 (d, 1H, $J = 2.3$ Hz), 4.63 (dd, 2H, $J = 6.8$, 12.8 Hz), 3.75 (dt, 1H, $J = 2.2$, 6.7 Hz), 3.33 (s, 3H), 1.58 (q, 2H, $J = 7.5$, 14.3 Hz), 1.38–1.20 (m, 6H), 0.84 (t, 3H, $J = 6.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.4, 96.2, 75.2, 56.0, 33.9, 32.5, 31.3, 24.7, 13.9. ESIMS: 175 (M^++1).
2-[(9S)-9-(Methoxymethoxy)-10-undecynyl]oxytetrahydro-2H-pyran (**2**): $[\alpha]_D^{25}$ −72.4 (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 4.92 (d, 1H, $J = 6.7$ Hz), 4.56–4.52 (m, 2H), 4.25 (t, 1H, $J = 3.7$ Hz), 3.82–3.50 (m, 3H), 3.36–3.30 (m, 4H), 2.38 (d, 1H, $J = 2.2$ Hz), 2.04–1.33 (m, 20H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 98.6, 93.8, 82.4, 67.4, 65.2, 62.1, 55.4, 35.4, 30.6, 29.3, 29.2, 29.0, 26.0, 25.6, 25.33, 24.7, 19.5, 14.0; ESIMS: 335 (M^++Na).
(6S,7R,10S)-6,10-Di(methoxymethoxy)-18-(tetrahydro-2H-2-pyranyloxy)-8-octadecyn-7-ol (**13**): $[\alpha]_D^{25}$ −44.5 (*c* 1, $CHCl_3$); IR (neat): 3432, 2927, 2360, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 4.90 (d, 1H, $J = 6.7$ Hz), 4.75–4.60 (Abq, 2H, $J = 7.8$ Hz), 4.53 (t, 1H, $J = 3.7$ Hz), 4.50 (d, 1H, $J = 6.7$ Hz), 4.38–3.60 (m, 5H), 3.43 (s, 3H), 3.36 (s, 3H), 1.90–1.30 (m, 31H), 0.93 (t, 3H, $J = 6.7$Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 98.8, 97.6, 97.4, 94.1, 84.8, 84.6, 83.5, 83.0, 67.6, 65.7, 65.3, 62.2, 55.8, 55.5, 35.7, 31.6, 31.4, 30.8, 29.4, 29.2, 26.2, 25.5, 25.3, 24.8, 22.4, 19.6, 13.9; ESIMS: 509 (M^++23).
(6S,7R,8E,10S)-6,10-Di(methoxymethoxy)-18-(tetrahydro-2H-2-pyranyloxy)-8-octadecen-7-ol (**14**): $[\alpha]_D^{25}$ −38.6 (*c* 1, $CHCl_3$); IR (neat): 3432, 2927, 2360, 1620, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 5.60–5.55 (m, 2H, olefinic), 4.90–4.60 (m, 5H), 4.10–3.50 (m, 7H), 3.37 (s, 3H), 3.34 (s, 3H), 1.90–1.30 (m, 29H), 0.93 (t, 3H, $J = 6.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 132.7, 131.2, 98.8, 97.5, 93.7, 76.4, 73.9, 73.6, 67.6, 62.3, 55.8, 35.7, 31.9, 31.7, 31.3, 31.0, 30.7, 29.7, 29.6, 29.5, 29.4, 26.2, 25.5, 25.4, 22.5, 19.7, 13.9; ESIMS: 511 (M^++23).
(9S,10E,12R,13S)-9,12,13-Trihydroxy-10-octadecenoic acid (**1**): $[\alpha]_D^{25}$ +7.9 (*c* 0.5, MeOH, lit. $[\alpha]_D^{25}$ +7.9 (*c* 0.18, MeOH); IR (KBr): 3432, 2928, 2369, 1620, 1032 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO, 300 MHz): δ 5.60–5.55 (m, 2H, olefinic), 4.12–3.90 (m, 2H), 3.42–3.39 (m, 1H) 2.32 (t, 2H, $J = 6.7$ Hz), 1.73–1.26 (m, 22H), 0.91, (t, 3H, $J = 6.7$ Hz); ^{13}C NMR (DMSO, 75 MHz): δ 178.4, 136.5, 131.4, 76.4, 75.3, 73.4, 38.5, 36.2, 33.2, 30.7, 30.3, 30.1, 29.8, 26.3, 26.2, 26.0, 23.5, 14.2; ESIMS: 353 (M^++23).