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Stereoselective total synthesis of (+)-pinellic acid from L-(+)-tartaric acid

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Abstract—The stereoselective total synthesis of (+)-pinellic acid, a natural product used in the treatment of influenza, was accomplished from L-(+)-tartaric acid. A key feature of the synthesis includes the elaboration of a γ-hydroxybutyramide derived from L-(+)-tartaric acid.

1. Introduction

Influenza is an infectious disease and is critical for patients possessing respiratory problems. Ōmura et al. have systematically investigated the active components of the tuber of *Pinellia ternate*, the traditional Japanese herbal (Kampo) medicine, Sho-seiryu-to, used for the treatment of cold like symptoms, and found that (−)-pinellic acid **1** is responsible for the activity (Fig. 1).[1] They have also determined the absolute configuration of pinellic acid by synthesis and also compared the activity of (−)-pinellic acid with other possible stereoisomers of pinellic acid. After the disclosure of the synthesis of **1** by Ōmura et al, the synthesis of (−)-**1** and a stereoisomer has surfaced in the literature.[2]

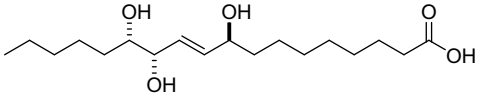
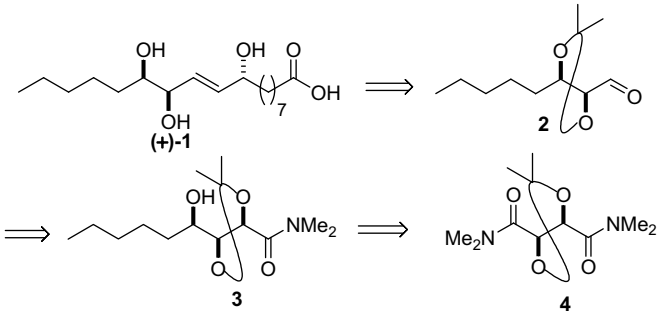


Figure 1. (−)-Pinellic acid.

2. Results and discussion

Recently, we developed a general strategy for the synthesis of γ-hydroxy butyramides from tartaric acid and have demonstrated the usefulness of these building blocks in the synthesis of a number of biologically active natural products.[3] In continuation of our efforts in the utility of these building blocks, we herein report the synthesis of (+)-pinellic acid. Our approach for the synthesis of (+)-**1** is based on the elaboration of aldehyde **2**, the synthesis of which is anticipated from γ-hydroxy butyramide **3**. The synthesis of γ-hydroxy butyramide from dimethylamide **4** derived from L-(+)-tartaric acid, involving a combination of selective Grignard reagent addition and stereoselective reduction, is envisaged (Scheme 1).



Scheme 1. Retrosynthesis for the synthesis of (+)-pinellic acid **1**.

Accordingly, the synthetic sequence commenced with the controlled addition of *n*-pentylmagnesium bromide to the bis-dimethylamide **4** derived from L-tartaric acid, resulting in the γ-oxoamide **5** in 78% yield.[4] Stereoselective reduction of the keto group in **5** with $NaBH_4/CeCl_3$ furnished a mixture of diastereomeric alcohols (dr ∼95:5 by NMR,[5] **6**

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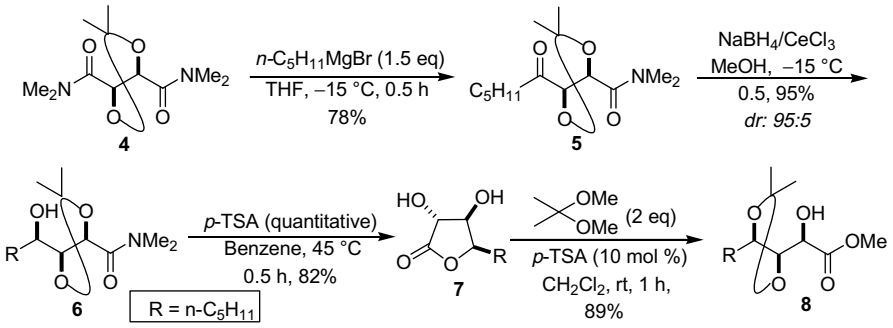


Scheme 2. Synthesis of methyl α,β,γ-trihydroxybutyrate.

being the major isomer) in 95% yield. Treatment of **6** with a quantitative amount of *p*-toluenesulfonic acid in benzene resulted in lactone **7** in 82% yield. The reaction of lactone **7** with 2,2-dimethoxypropane in the presence of catalytic amount of *p*-toluenesulfonic acid followed by column purification resulted in the pure hydroxy ester **8** in 89% yield (Scheme 2).

Reduction of ester **8** with $LiBH_4$ afforded diol **9** in 94% yield. Treatment of **9** with $Pb(OAc)_4$ in benzene furnished aldehyde **2**, which on subsequent Wittig–Horner olefination with phosphonate **10** derived from azuleic acid dimethylester[6] afforded the α,β-unsaturated ketone **11** in 40% yield for two steps. Reduction of ketone **11** with (*R*)-BINAL-H[7] followed by column purification furnished **12** in 51% yield.[8] Deprotection of the acetonide in **12** with HCl afforded the triol ester **13** in 90% yield. LiOH-mediated saponification of the ester furnished (+)-pinellic acid, the spectral and physical data of which are in complete agreement with those reported in the literature (Scheme 3).[2a]

3. Conclusion

In conclusion, a facile stereoselective synthesis of (+)-pinellic acid was accomplished from L-(+)-tartaric acid. The synthetic route is operationally simple, diastereoselective, and is applicable for the access of different analogues of pinellic acid.

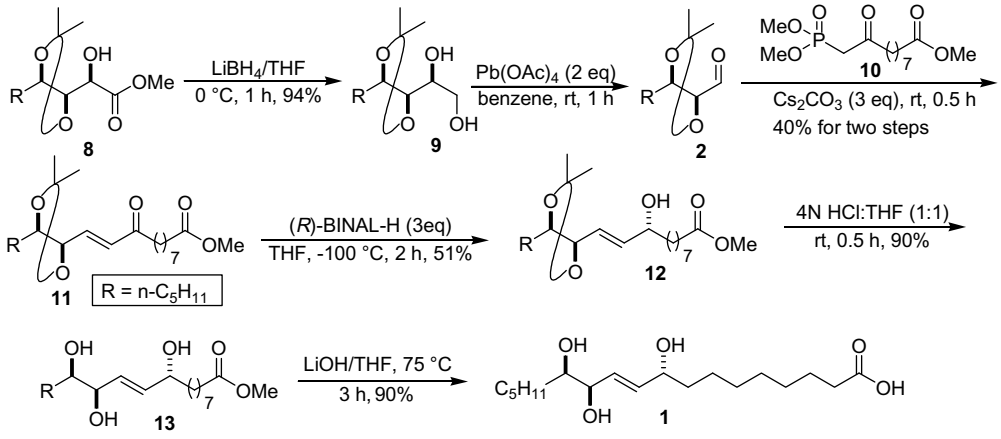
4. Experimental

4.1. General

Column chromatography was performed on silica gel, Acme grade 100–200 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray, unless noted otherwise. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points are uncorrected. Unless stated otherwise, all reactions were performed under an inert atmosphere. Optical rotations were measured on a JASCO DIP-370 digital polarimeter at 25 °C.

4.2. (4*R*,5*R*)-5-Hexanoyl-*N*,*N*,2,2-tetramethyl-1,3-dioxolane-4-carboxamide 5

In a two neck 100 mL, round-bottomed flask equipped with a magnetic stir bar, rubber septum and argon inlet was placed diamide **4** (1 g, 4.1 mmol), dissolved in 20 mL of THF and was cooled to −15 °C. A freshly prepared THF solution of *n*-$C_5H_{11}MgBr$ (12.4 mL of 0.5 M solution in THF, 6.2 mmol) was slowly added and the reaction mixture was stirred at the same temperature. Progress of the reaction was monitored by TLC and after the reaction was complete (~0.5 h), it was cautiously quenched by the addition of saturated ice cold solution of NH_4Cl (15 mL).



Scheme 3. Synthesis of (+)-pinellic acid.

It was then poured into water (10 mL) and extracted with EtOAc (3 × 10 mL). Combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. Silica gel column chromatography of the residue with petroleum ether/EtOAc (3:1) as eluent afforded **5** (0.87 g, 78%) as a colorless oil. R_f 0.5 [petroleum ether/EtOAc (1:1)]; $[\alpha]_D = +15.4$ (*c* 2.2, $CHCl_3$); IR (neat): 2935, 1718, 1657, 1378, 1056, 864 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.07 (d, 1H, $J = 6.0$ Hz), 4.74 (d, 1H, $J = 6.0$ Hz), 3.09 (s, 3H), 2.93 (s, 3H), 2.69–2.42 (m, 2H), 1.59–1.49 (m, 3H), 1.41 (s, 6H), 1.29–1.20 (m, 3H),. 0.83 (t, 3H, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.3, 168.0, 114.9, 81.9, 74.8, 39.3, 36.9, 35.8, 31.1, 26.2, 25.9, 22.6, 22.2, 13.7; HRMS: calcd for $C_{14}H_{25}NO_4 + Na$, 294.1681; found, 294.1692.

4.3. (4*R*,5*S*)-5-((*R*)-1-Hydroxyhexyl)-*N*,*N*,2,2-tetramethyl-1,3-dioxolane-4-carboxamide 6

To a solution of **5** (0.81 g, 3 mmol) in methanol (15 mL) was added $CeCl_3 \cdot 7H_2O$ (2.23 g, 6 mmol) at room temperature and stirred for 30 min. The reaction mixture was then cooled to −15 °C, and $NaBH_4$ (0.17 g, 4.5 mmol) was added portionwise over a period of 15 min and stirred at the same temperature. Progress of the reaction was monitored by TLC and after all the starting was consumed (~0.5 h), water (10 mL) was added cautiously to the reaction mixture and extracted with ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the crude residue with petroleum ether/EtOAc (7:3) as eluent gave **6** as a colorless oil (0.77 g, 95%); $R_f = 0.5$ [petroleum ether/EtOAc (2:3)]; $[\alpha]_D = -16$ (*c* 0.9, $CHCl_3$); IR (neat): 3453, 2934, 1651, 1381, 1069, 884 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.58 and 4.53 (2H, 2 × d, $J = 8$ Hz), 3.57 (br s, 1H), 3.14 (s, 3H), 2.97 (s, 3H), 2.04 (d, 1H, $J = 9.3$ Hz), 1.61–1.49 (m, 3H), 1.45 (s, 3H), 1.42–1.37 (m, 1H), 1.39 (s, 3H), 1.36–1.23 (br m, 4H), 0.89 (t, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 110.1, 80.2, 74.1, 69.9, 37.0, 35.6, 34.7, 31.6, 26.7, 26.1, 25.5, 22.5, 14.0; HRMS: calcd for $C_{14}H_{27}NO_4 + Na$, 296.1838; found, 296.1831.

4.4. (3*R*,4*R*,5*R*)-Dihydro-3,4-dihydroxy-5-pentylfuran-2(3*H*)-one 7

To a solution of hydroxy amide **6** (1.29 g, 4.7 mmol) in dry benzene (5 mL) was added *p*-toluenesulfonic acid monohydrate (1.07 g, 5.6 mmol) and stirred for 0.5 h at 45 °C. The reaction mixture was then cooled to room temperature, K_2CO_3 (0.73 g, 5.6 mmol) was added, and stirred for 10 min. The reaction mixture was filtered through a pad of Celite, and the Celite pad was washed with CH_2Cl_2 (20 mL). The filtrate was concentrated, and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (1:1) as eluent to afford **7** as a white solid (0.73 g, 82%). $R_f = 0.4$ [petroleum ether/EtOAc (2:3)]; mp 74–76 °C; $[\alpha]_D = +77.8$ (*c* 0.5, $CHCl_3$); IR (neat): 3403, 2957, 1773, 1464, 1100, 994 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 4.54 (dt, $J = 9.2$ Hz, 4.8 Hz, 1H), 4.21–4.18 (m, 1H), 4.14 (d, 1H, $J = 5.2$ Hz), 1.84–1.74 (m, 1H), 1.67–1.57 (m, 1H), 1.51–1.35 (m, 6H), 0.91 (t, 3H, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 81.5, 73.7, 73.0, 31.4, 28.8, 25.3, 22.4, 13.9; HRMS: calcd for $C_9H_{16}O_4 + Na$, 211.0946; found, 211.0934.

4.5. (*R*)-Methyl2-hydroxy-2-((4*R*,5*R*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)acetate 8

In a 100 mL oven-dried round-bottomed flask under an argon atmosphere was taken a solution of **7** (0.38 g, 2 mmol) in dry CH_2Cl_2 (5 mL). *p*-Toluenesulfonic acid monohydrate (0.04 g, 0.2 mmol) and 2,2-dimethoxypropane (0.5 mL, 4 mmol) were then introduced and stirred for 1 h at room temperature. K_2CO_3 (0.03 g) was then added to the reaction mixture and stirred for 15 min. The reaction mixture was passed through a pad of Celite, and the Celite pad was washed with CH_2Cl_2 (20 mL). The filtrate was concentrated, and purification of the residue by silica gel column chromatography with petroleum ether/EtOAc (80:20) as eluent afforded **8** (0.47 g, 89%) as a colorless oil. $R_f = 0.5$ [petroleum ether/EtOAc (3:2)]; $[\alpha]_D = +21.3$ (*c* 0.5, $CHCl_3$); IR (neat): 3507, 2934, 1747, 1380, 896, 717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.14–4.08 (m, 2H), 3.87 (dd, 1H, $J = 8.0$ Hz, 0.8 Hz), 3.84 (s, 3H), 2.98 (d, 1H, $J = 9.2$ Hz) 1.64–1.57 (m, 4H), 1.39 (s, 6H), 1.34–1.26 (m, 4H), 0.9 (t, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 109.2, 81.4, 76.4, 68.8, 52.7, 32.5, 31.8, 27.4, 26.5, 25.6, 22.5, 13.9; HRMS: calcd for $C_{13}H_{24}O_5 +$ Na, 283.1521; found, 283.1514.

4.6. (*S*)-1-((4*R*,5*R*)-2,2-Dimethyl-5-pentyl-1,3-dioxolan-4-yl)ethane-1,2-diol 9

To a solution of **8** (0.27 g, 1.03 mmol) in THF (4 mL) was added $LiBH_4$ (0.5 mL of 2 M solution in THF, 1.0 mmol). The progress of the reaction was monitored by TLC. After the reaction was complete (~0.5 h), it was cautiously quenched by water (2 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the resulting residue with petroleum ether/EtOAc (3:2) gave **9** (0.22 g, 90%) as a colorless oil. $R_f = 0.4$ [petroleum ether/EtOAc (2:3)]; $[\alpha]_D = +68.7$ (*c* 0.2, $CHCl_3$); IR (neat): 3429, 2933, 1377, 1067, 883 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.10–3.90 (m, 1H), 3.72–3.50 (m, 4H), 2.77 (br s, 2H), 1.70–1.47 (m, 3H), 1.41 (s, 6H), 1.46–1.20 (m, 5H), 0.89 (t, 3H, $J = 6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.9, 81.8, 76.5, 69.7, 65.1, 32.8, 31.8, 27.4, 26.7, 25.6, 22.4, 13.9; HRMS: calcd for $C_{12}H_{24}O_4 + Na$, 255.1572; found, 255.1568.

4.7. (4*S*,5*R*)-2,2-Dimethyl-5-pentyl-1,3-dioxolane-4-carbaldehyde 2

To a solution of **9** (0.28 g, 1.2 mmol) in dry benzene (4 mL) was added $Pb(OAc)_4$ (1.1 g, 2.4 mmol) and stirred at room temperature. After the reaction was complete (TLC) (~45 min), it was quenched by the cautious addition of water (2 mL) and passed through a pad of Celite and the Celite pad was washed with CH_2Cl_2 (15 mL). The organic layer was dried over Na_2SO_4, and the solvent was evapo-

rated off. The crude aldehyde thus obtained was used without further purification in the next reaction.

4.8. Methyl 9-(methoxyphosphono)-8-oxononanoate 10

To a pre-cooled (−78 °C) solution of dimethyl methyl phosphonate (2.76 g, 22.2 mmol) in THF (10 mL) was added *n*-BuLi (14 mL of 1.6 M solution in hexane, 22.4 mmol) dropwise under argon atmosphere. The reaction mixture was warmed up to −20 °C and allowed to stir at the same temperature for 45 min. It was again cooled to −78 °C and a THF (8 mL) solution of azuleic acid dimethylester (4 g, 18.5 mmol) was rapidly introduced into the flask. Progress of the reaction was monitored by TLC, and after 0.5 h, it was quenched with a satd NH_4Cl solution and extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (1 × 10 mL) and dried over Na_2SO_4. Evaporation of the solvent and purification by silica gel column chromatography using EtOAc/MeOH (95:5) afforded **10** (1.74 g, 31%). $R_f = 0.5$ [EtOAc/MeOH (9:1)]; IR (neat): 3467, 2934, 1715, 1256, 1029, 816 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.8 (d, 6H, $J = 11.4$ Hz), 3.69 (s, 3H), 3.1 (d, 2H, $J = 22.8$ Hz), 2.61 (t, 2H, $J = 6.5$ Hz), 2.29 (t, 2H, $J = 7.6$ Hz), 1.6–1.45 (m, 4H), 1.3 (br s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 173.8, 52.7, 52.6 (d, $J = 3.7$ Hz), 51.1, 43.7, 41.7, 33.7, 28.6, 28.5 (d, $J = 4.5$ Hz), 28.3, 24.5, 22.9; HRMS: calcd for $C_{13}H_{25}O_6P + Na$, 331.1286; found, 331.1268.

4.9. (*E*)-Methyl 11-((4*S*,5*R*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)-9-oxoundec-10-enoate 11

To a solution of **10** (0.92 g, 3 mmol) in 2- propanol (9 mL) was added Cs_2CO_3 (2.93 g, 9 mmol) under an argon atmosphere and stirred at room temperature for 15 min. A solution of the crude aldehyde **2** (0.6 g) in 2-propanol (8 mL) was added dropwise to the reaction mixture under argon atmosphere and stirred for 0.5 h. It was cautiously quenched with sat. citric acid solution (5 mL) and extracted with diethyl ether (3 × 15 mL). The combined ethereal layers were washed with brine (10 mL) and dried over Na_2SO_4. Evaporation of solvent and purification of the resulting residue by silica gel column chromatography with petroleum ether/EtOAc (9:1) as eluent afforded product **11** (40% yield for 2 steps). $R_f = 0.5$ [petroleum ether/EtOAc (4:1)]; $[\alpha]_D = +6.3$ (*c* 0.6, $CHCl_3$); IR (neat): 3453, 2859, 1743, 1463, 1050, 881 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, 1H, $J = 6$ Hz, 15.9 Hz), 6.36 (d, 1H, $J = 15.9$ Hz), 4.15 (dd, $J = 8$ Hz, 7Hz, 1H), 3.76–3.70 (m, 1H), 3.66 (s, 3H), 2.55 (t, 2H, $J = 7.4$ Hz), 2.30 (t, 2H, $J = 7.4$ Hz), 1.6–1.53 (m, 6H), 1.44 (s, 3H), 1.42 (s, 3H), 1.36–1.25 (m, 12H), 0.89 (t, 3H, $J = 6.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 174.1, 141.6, 130.3, 109.3, 84.8, 80.7, 80.4, 51.3, 40.8, 34.0, 32.0, 31.7, 28.98, 28.9, 27.2, 26.6, 25.5, 24.8, 23.8, 22.4, 13.9; HRMS: calcd for $C_{22}H_{38}O_5 + Na$, 405.2617; found, 405.2599.

4.10. (*R*,*E*)-Methyl 9-hydroxy-11-((4*S*,5*R*)-2,2-dimethyl-5-pentyl-1,3-dioxolan-4-yl)undec-10-enoate 12

A freshly prepared BINAL-H[7] (0.42 mmol) reagent was cooled to −100 °C and a solution of **11** (0.05 g, 0.13 mmol) in THF (2 mL) was added dropwise over a period of 10 min. The temperature of the reaction was maintained at −100 °C and the progress of the reaction was monitored by TLC. After 2 h, the reaction was quenched with dil HCl (2 mL) and extracted with ether (3 × 10 mL). The combined ether extracts were washed with 2 M NaOH (3 × 6 mL) and with brine (5 mL). Evaporation of the solvent and silica gel column chromatography with petroleum ether/EtOAc (85:15) afforded **12** (0.023 g, 51%). $R_f = 0.5$ [petroleum ether/EtOAc (7:3)]; $[\alpha]_D = +2.3$ (*c* 0.3, $CHCl_3$); IR (neat): 3473, 2927, 2855, 1742, 1242, 1169, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (dd, 1H, $J = 5.8$, 15.3 Hz), 5.65 (dd, 1H, $J = 7.5$, 15.3 Hz), 4.17–4.11 (m, 1H), 3.99 (dd, $J = 7.8$, 7.9 Hz), 3.69–3.6 (m, 1H), 3.67 (s, 3H), 2.3 (t, 2H, $J = 8$ Hz), 1.63–1.44 (m, 8H), 1.42 (s, 3H), 1.41 (s, 3H), 1.38–1.23 (m, 14H), 0.89 (t, 3H, $J = 8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 137.8, 127.6, 108.3, 81.8, 80.7, 72.0, 51.3, 37.0, 34.0, 31.8, 29.2, 29.1, 29.0, 27.2, 26.9, 25.6, 25.2, 24.8, 22.4, 13.9; HRMS: calcd for $C_{22}H_{40}O_5 + Na$, 407.2773; found, 407.2771.

4.11. (*E*,9*R*,12*R*,13*R*)-Methyl 9,12,13-trihydroxyoctadec-10-enoate 13

Compound **12** (0.023 g, 0.06 mmol) was dissolved in 2 mL of THF/4 M HCl (1:1). The solution was allowed to stir at room temperature and the progress of the reaction was monitored by TLC. After the starting material was completely consumed (~0.5 h), it was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over Na_2SO_4. Evaporation of solvent and purification of the resulting residue by silica gel column chromatography with petroleum ether/EtOAc (3:7) afforded triol **13** (0.018 g, 90%). $R_f = 0.4$ [EtOAc]; mp 87–90 °C; $[\alpha]_D = +10$ (*c* 0.8, $CHCl_3$); IR (neat): 3542, 3312, 2931, 2849, 1731, 1462, 1176, 1072, 974, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 and 5.65 (2 × dd, 2H, $J = 6$, 15 Hz), 4.09–4.05 (m, 1H), 3.9–3.7 (m, 1H), 3.59 (s, 3H), 3.4–3.2 (m, 1H), 2.18 (t, 5H, $J = 7.2$ Hz), 1.54–1.20 (m, 20H), 0.82 (t, 3H, $J = 6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 136.1, 129.7, 75.2, 74.6, 71.9, 51.4, 37.1, 34.0, 33.0, 31.8, 29.2, 29.0, 28.9, 25.28, 25.2, 24.8, 22.5, 13.9; HRMS: calcd for $C_{19}H_{36}O_5 + Na$, 367.2460; found, 367.2468.

4.12. (*E*,9*R*,12*R*,1*R*)-9,12,13-Trihydroxyoctadec-10-enoic acid [pinellic acid] 1

To a solution of **13** (0.02 g, 0.06 mmol) in THF (2 mL) was added an aqueous solution of LiOH (0.2 mL of 1 M solution, 0.2 mmol) and heated to 75 °C. Progress of the reaction was monitored by TLC, and after 4 h it was cooled to room temperature. The reaction mixture was concentrated under reduced pressure, and basified with LiOH. The aqueous layer was extracted with ethyl acetate (3 × 5 mL). Next it (aq layer) was acidified with 2 N HCl and extracted with chloroform (3 × 10 mL). Evaporation of the solvent under reduced pressure afforded the pure triol acid **1** (0.019 g, 90%); mp 97–99 °C, lit.[2a] mp 98–102 °C, $[\alpha]_D = +12$ (*c* 1, MeOH); IR (KBr): 3540, 3356, 2927, 2850, 1698, 1463, 1260, 1072, 726 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 5.74–5.64 (m, 2H), 4.05 (t, 1H, $J = 6$ Hz), 3.92–3.89 (m, 1H), 2.27 (t, 2H, $J = 7.4$ Hz), 1.61–1.44 (m, 6H), 1.33–

1.23 (m, 14H), 0.91 (t, 3H, $J = 6.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 136.5, 131.0, 76.5, 75.7, 73.0, 38.3, 34.9, 33.5, 33.1, 30.5, 30.3, 30.1, 26.6, 26.5, 26.0, 23.7, 14.4; HRMS: calcd for $C_{18}H_{34}O_5 + Na$, 353.2304; found, 353.2310.

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