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Stereoselective total synthesis of pectinolide H and 4'-epi-pectinolide H

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ABSTRACT

The total synthesis of pectinolide H and 4'-*epi*-pectinolide H was accomplished with 27% yield in nine steps from inexpensive and commercially available compound, (+)-diethyl tartrate ((+)DET)) by employing swern oxidation, Wittig olefination, Grignard and lactonization reactions.

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1. Introduction

Pectinolide H (**1**) (Figure 1) isolated from aerial parts of a Mexican terrestrial plant *Hyptis pectinata* displays significant antimicrobial activity against a panel of multidrug-resistant strains of *Staphylococcus aureus* [1]. The molecule possesses an α,β-unsaturated γ-lactone motif common to many natural products exhibiting antibacterial and anti-inflammatory activities. Many compounds with similar structures have also been reported to be potentially useful as anticancer agents and enzyme inhibitors [2-10]. Considering the importance of new antimicrobial agents for multidrug resistant microorganisms, synthesis of molecules such as Pectinolide H in a simple and straightforward manner is necessary.

To the best of our knowledge, two reports exist for the synthesis of pectinolide H (**1**) [11,12]. Herein, we report an easy approach to compound **1** carried out in nine simple steps. Our synthetic strategy also provides the epimer 4'-epi-pectinolide H (**2**).

2. Experimental

All commercially available chemicals were purchased from Sigma Aldrich and used without purification. All experiments were carried out under an inert nitrogen atmosphere.

2.1. Instrumentation

^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 MHz and Bruker Avance 75 MHz spectrometers, respectively, using $CDCl_3$ as solvent and $SiMe_4$ as the internal standard. FT-IR analyses were performed using Perkin Elmer RX1 FT-IR spectrophotometer. Mass spectra analyses were performed on VG Auto spec instrument. Optical rotations were determined using Jasco Dip 360 digital polarimeter.

2.2. Synthesis

2.2.1. Synthesis of diethyl (4R,5R)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (7)

A solution of compound **6** (10 g, 48.54 mmol), *p*-toluene sulfonic acid (100 mg) in CH_2Cl_2 (100 mL) and 2,2-dimethoxypropane (12 mL, 97 mmol) was stirred at room temperature for 4 h. The reaction mixture was quenched with solid $NaHCO_3$, filtered, solvent was evaporated under vacuum. The crude product was purified by flash column chromatography (Hexane:EtOAc, 98:2, *v*:*v*) to give compound **7**. Color: Colorless liquid. Yield: 10.75 g, 90%. FT-IR (Neat, ν, cm^{-1}): 2990, 1753, 1216. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.31 (t, 6H, CH_3-CH_2-O), 1.50 (s, 6H, $(CH_3)_2C$), 4.27 (q, 4H, CH_2-OCO), 4.76 (s, 2H, CH-COO).

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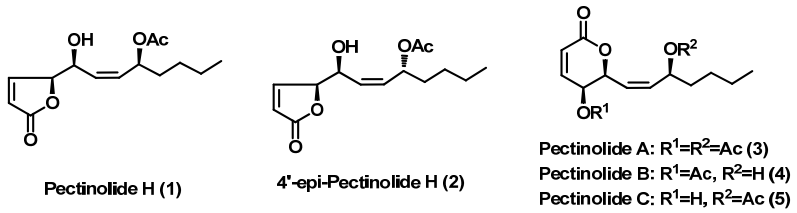
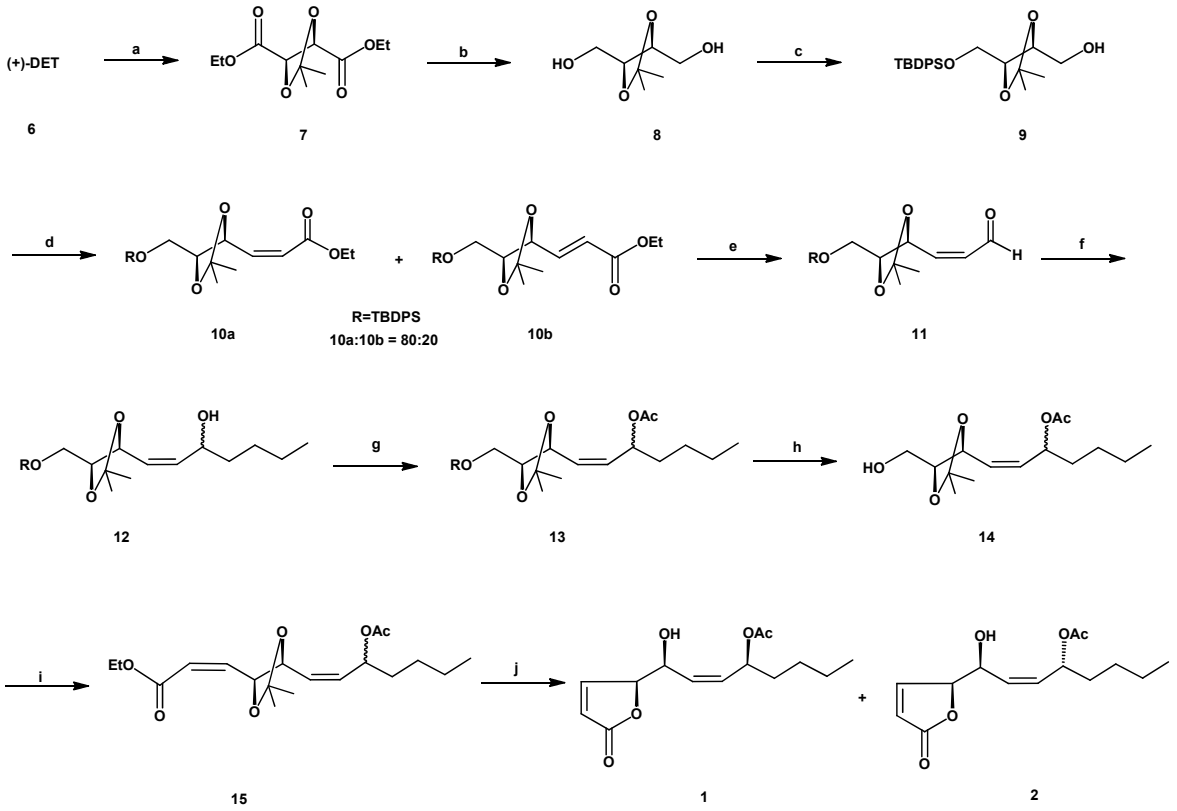


Figure 1. Structure of pectinolide A-C, H and 4′-epi-pectinolide H.



Reagents and conditions: a) 2,2-DMP, PTSA(cat.) CH_2Cl_2, rt, 4 h, 90 %. b) $LiAlH_4$, THF, 0 °C to rt, 1 h, 85%. c) TBDPSCl, NaH, THF, 0 °C to rt, 2h, 90%. d) (i) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78 °C. (ii) $Ph_3PCHCOOEt$, MeOH, -50 °C to rt, (88% in two steps). e) DIBAL-H, CH_2Cl_2, -78 °C, 30 min. f) Mg, nBuBr, THF, (66% in two steps). g) Ac_2O, DMAP, Pyridine, CH_2Cl_2, rt, 3 h, 99%. h) TBAF, THF, rt, 5 h, 92%. i) (i) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78 °C. (ii) $(F_3CCH_2O)_2POCH_2COOEt$, 18-crown ether, KHMDS, dry THF, -78 °C, 4 h, (80% in two steps). j) TsOH, MeOH, 2 h, 93%.

Scheme 1

^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 13.9, 26.2, 61.7, 76.9, 113.5, 169.5. ESI-MS (*m/z*): 247 $(M+1)^+$, 269 $(M+Na)^+$.

2.2.2. Synthesis of ((4S,5S)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanol (8)

A solution of compound **7** (6 g, 24.4 mmol) in THF (20 mL) was slowly added to a suspension of $LiAlH_4$ (3.7 g, 97.5 mmol) in THF (100 mL) at 0 °C over a period of 20 min under nitrogen atmosphere. After 2 h, aqueous NH_4Cl (10%, *w*:*v*, 20 mL) was added and the reaction mixture was filtered through celite. The filtrate was dried over anhydrous $MgSO_4$ and evaporated under vacuum. The crude product was purified by flash column chromatography using EtOAc as eluent to afford pure compound **8** (Scheme 1). Color: Colorless liquid. Yield: 3.35 g, 85%. FT-IR (Neat, ν, cm^{-1}): 3403. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.43 (s, 6H, $(CH_3)_2C$), 2.77 (br. s, 2H, 2 -OH), 3.68-3.81 (m, 4H, CH_2-OH), 3.98-3.99 (m, 2H, CH-CH_2-OH). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): δ 26.9, 62.0, 78.1, 109.2. ESI-MS (*m/z*): 162 (M^+). $[\alpha]_D^{25}$: -8.16 (*c* 1, $CHCl_3$).

2.2.3. Synthesis of ((4S,5S)-5-((tert-butyldiphenylsilyloxy) methyl)-2,2-dimethyl-1,3-dioxolan-4-yl) methanol (9)

To a stirred solution of diol (**8**) (1.62 g, 10 mmol) in anhydrous THF (50 mL), NaH (264 mg, 11 mmol) was added at 0 °C under nitrogen atmosphere and the contents were stirred for 30 min. A solution of *tert*-butylchlorodiphenylsilane (TBDPS-Cl) (2.74 g, 10 mmol) dissolved in anhydrous THF (20 mL) was added and stirring was continued for 2 h at room temperature. The reaction mixture was quenched with water (40 mL) and THF was evaporated. The residue was extracted with CH_2Cl_2 (3×10 mL), dried over anhydrous $MgSO_4$, and concentrated under vacuum. The crude product was subjected to flash column chromatography (Hexane:EtOAc, 4:1, *v*:*v*) to afford compound **9** (Scheme 1). Color: Colorless oil. Yield: 3.6

g, 90%. FT-IR (Neat, ν, cm^{-1}): 3466, 2931, 1428, 1245, 1080, 702. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.06 (s, 9H, $(CH_3)_3C$-Si), 1.38 (s, 3H, CH_3-C-O), 1.41 (s, 3H, CH_3-C-O), 3.63-3.84 (m, 4H, CH_2-OH, CH_2-OSi), 3.93-3.99 (m, 1H, C*H*-CH_2-OH), 4.04-4.10 (m, 1H, CH-CH_2-OSi), 7.36-7.43 (m, 6H, Ar-H), 7.64-7.68 (m, 4H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 19.1, 26.7, 26.9, 27.0, 62.5, 64.1, 77.4, 79.5, 109.1, 127.7, 127.8, 129.8, 129.9, 132.8, 135.5. ESI-MS (*m/z*): 423 $(M+Na)^+$. $[\alpha]_D^{25}$: -1.5 (*c* 14.5, $CHCl_3$).

2.2.4. Synthesis of (Z)-ethyl 3-((4S,5S)-5-((tert-butyl diphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan -4-yl) acrylate (10a) and (E)-ethyl 3-((4S,5S)-5-((tert-butyl diphenylsilyloxy) methyl)-2,2-dimethyl-1,3-dioxolan-4-yl) acrylate (10b)

To a solution of oxalyl chloride (0.7 mL, 8 mmol) in dry CH_2Cl_2 (20 mL), DMSO was added drop-wise (1.14 mL, 16 mmol) at -78 °C over 20 min under nitrogen atmosphere and stirred for 30 min at the same temperature. To this reaction mixture, compound **9** (1.6 g, 4 mmol) in CH_2Cl_2 (5.0 mL) was added drop-wise over 15 min at -78 °C, and resulting mixture was stirred for 3 h at same temperature. The reaction was quenched with Et_3N (5.0 mL) and allowed to reach room temperature over 30 min. The solvent was removed on rotavapor and the residue was purified by a flash column chromatography (Hexane:EtOAc, 10:1, *v*:*v*) to obtain crude aldehyde which was employed in the next step immediately.

The solution of crude aldehyde (1.52 g, 3.82 mmol) in MeOH (15 mL) was added to a solution of Ph_3P=CHCOOEt (4 g, 11.5 mmol) in MeOH (100 mL) at -50 °C drop-wise over 30 min. The resulting solution was stirred for 1 h at same temperature, diluted with water and extracted with CH_2Cl_2 (3×25 mL). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by flash column chromatography (Hexane:EtOAc, 50:1, *v*:*v*) to obtain pure compounds **10a** and **10b** in 80:20 ratio (Scheme 1).

(Z)-Ethyl 3-((4S,5S)-5-((tert-butyldiphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolan -4-yl)acrylate (**10a**): Color: Colorless oil. Yield: 1.32 g, 70%. FT-IR (Neat, ν, cm^{-1}): 2932, 1720, 1111. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.04 (s, 9H, $(CH_3)_3C$-Si), 1.21 (t, 3H, CH_3-CH_2-O), 1.432 (s, 3H, CH_3-C-O), 1.439 (s, 3H, CH_3-C-O), 3.80-3.88 (m, 3H, CH_2-OSi, CH-CH_2-OSi), 4.07 (q, 2H, CH_2-OCO), 5.44-5.52 (m, 1H, CH-CH=CH), 5.86 (dd, 1H, *J* = 10.5, 1.5 Hz, HC-COO), 6.12 (dd, 1H, *J* = 9.0, 3.0 Hz, HC=CH-COO), 7.32-7.43 (m, 6H, Ar-H), 7.67-7.69 (m, 4H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 14.1, 19.1, 26.7, 27.0, 27.1, 60.3, 64.1, 73.4, 82.1, 117.0, 122.9, 127.5, 127.7, 129.5, 130, 135.6, 135.7, 145.3, (C=O not seen). ESI-MS (*m/z*): 469 $(M+1)^+$, 491 $(M+Na)^+$.

(E)-Ethyl 3-((4S,5S)-5-((tert-butyldiphenylsilyloxy) methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (**10b**): Color: Colorless oil. Yield: 0.33 g, 18%. FT-IR (Neat, ν, cm^{-1}): 2933, 1719, 1112. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.07 (s, 9H, $(CH_3)_3C$-Si), 1.29 (t, 3H, CH_3-CH_2-O), 1.4 (s, 3H, CH_3-C-O), 1.44 (s, 3H, CH_3-C-O), 3.81-3.88 (m, 3H, CH_2-OSi, CH-CH_2-OSi), 4.20 (q, 2H, CH_2-OCO), 4.57-4.62 (m, 1H, CH-CH=CH), 6.10 (dd, 1H, *J* = 15.8, 1.5 Hz, HC-COO), 6.93 (dd, 1H, *J* = 10.5, 5.2 Hz, HC=CH-COO), 7.35-7.43 (m, 6H, Ar-H), 7.65-7.70 (m, 4H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 14.2, 19.1, 26.7, 26.9, 27.0, 60.4, 63.1, 77.4, 80.7, 109.8, 122.1, 127.5, 127.7, 129.5, 129.7, 132.8, 135.5, 135.7, 144.4, 165.9. ESI-MS (*m/z*): 469 $(M+1)^+$, 491 $(M+Na)^+$.

2.2.5. Synthesis of (Z)-1-((4S,5S)-5-((tert-butyldiphenylsilyl oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hept-1-en-3-ol (12)

To a stirred solution of compound **10a** (2.0 g, 4.27 mmol) in CH_2Cl_2 (50 mL), diisobutylaluminium hydride (DIBAL-H) (2.48 mL, 4.27 mmol) was added drop-wise at -78 °C, and the reaction mixture was stirred for 30 min at same temperature. The reaction was quenched with aqueous MeOH (10 mL, 50%, *v*:*v*) at 0 °C. Saturated sodium potassium tartrate solution (10 mL) was added and the contents were extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$, concentrated under vacuum to obtain the crude aldehyde **11** which was used in next step without further purification.

A solution of *n*-butyl bromide (0.92 mL, 8.54 mmol) in THF (5 mL) was added to a suspension of Mg (0.2 g, 8.33 mmol) in THF (30 mL) and refluxed for 20 min. The reaction mixture was cooled to 0 °C and solution of crude aldehyde **11** in THF (10 mL) was added. After 1 h the reaction was quenched with aqueous NH_4Cl, filtered through a celite. The filtrate was dried anhydrous $MgSO_4$, concentrated under vacuum, and purified by flash column chromatography (Hexane:EtOAc, 80:20, *v*:*v*) to afford diastereoisomeric mixture of compound **12** (Scheme 1). Color: Pale yellow oil. Yield: 1.36 g. 66%. FT-IR (Neat, ν, cm^{-1}): 3441, 2931, 1428, 1113. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 0.89 (t, 3H, CH_3-CH_2-), 1.06 (s, 9H, $(CH_3)_3C$-Si), 1.23-1.37 (m, 4H, CH_2-CH_2-CH_3), 1.43 (s, 6H, $(CH_3)_2C$), 1.46-1.53 (m, 2H, CH_2-$(CH_2)_2$-CH_3), 3.69-3.86 (m, 3H, CH_2-OSi, CH-CH_2-OSi), 4.09 (q, 1H, CH(OH)), 4.43 (t, 1H, HC-CH=), 5.65 (dd, 1H, *J* = 8.3, 6.7 Hz, =C*H*-CH(OH)), 5.78 (dd, 1H, *J* = 9.8, 6.0 Hz, CH=CH-CH(OH)), 7.35-7.43 (m, 6H, Ar-H), 7.65-7.70 (m, 4H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 13.9, 19.2, 22.5, 26.7, 26.9, 27.0, 27.4, 36.6, 62.7, 71.9, 78.0, 81.4, 109.0, 127.4, 127.6, 129.6, 129.7, 133.1, 135.6, 137.5. ESI-MS (*m/z*): 505 $(M+Na)^+$. HRMS calcd. for $C_{29}H_{42}O_4NaSi$ $[M+Na]^+$: 505.27446, Found: 505.27282.

2.2.6. Synthesis of (Z)-1-((4S,5S)-5-((tert-butyldiphenylsilyl oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hept-1-en-3-yl acetate (13)

To a stirred solution of alcohol **12** (482 mg, 1.03 mmol) in CH_2C1_2 (10 mL) were added catalytic amount (5 mg) of 4-dimethylaminopyridine (DMAP) and pyridine (0.126 mL, 1.55 mmol) at 0 °C. Under stirring at same temperature, acetic anhydride (0.147 mL, 1.55 mmol) was added and the resulting mixture was stirred for 3 h at room temperature. The reaction mixture was quenched with aqueous $NaHCO_3$ solution (10%, *w*:*v*, 5 mL), and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, concentrated under vacuum, and purified by flash column chromatography (Hexane:EtOAc, 9:1, *v*:*v*) to afford compound **13** (Scheme 1). Color: Colorless oil. Yield: 0.54 g, 99%. FT-IR (Neat, ν, cm^{-1}): 2932, 1740, 1238, 1113. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 0.87 (t, 3H, CH_3-CH_2-), 1.06 (s, 9H, $(CH_3)_3C$-Si), 1.20-1.34 (m, 4H, CH_2-CH_2-CH_3), 1.43 (s, 6H, $(CH_3)_2C$), 1.51-1.65 (m, 2H, CH_2-$(CH_2)_2$-CH_3), 2.05 (s, 3H, CH_3-CO), 3.68-3.84 (m, 3H, CH_2-OSi, CH-CH_2-OSi), 4.44-4.50 (m, 1H, HC-CH=), 5.21-5.27 (m, 1H, CH(OAc)), 5.68-5.72 (m, 2H, CH=CH), 7.35-7.43 (m, 6H, Ar-H), 7.65-7.70 (m, 4H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 13.8, 19.1, 21.1, 22.3, 26.7, 26.8, 26.9, 27.1, 33.9, 62.5, 73.5, 77.8, 81.2, 109, 127.6, 129.4, 129.6, 131.9, 133.0, 135.5, 170. ESI-MS (*m/z*): 547 $(M+Na)^+$. HRMS calcd. for $C_{31}H_{44}O_5SiNa$ $[M+Na]^+$: 547.2964, Found: 547.2954.

2.2.7. Synthesis of (Z)-1-((4S,5S)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hept-1-en-3-yl acetate (14)

To a stirred solution of compound **13** (945 mg, 1.8 mmol) in dry THF (20 mL), TBAF (5.45 mL, 1 M in THF, 5.41 mmol) was added at room temperature and the resulting solution was stirred for 5 h. The solvent was evaporated under vacuum and purified by flash column chromatography (Hexane:EtOAc, 6:1, *v*:*v*) to afford compound **14** (Scheme 1). Color: Colorless oil. Yield: 0.493 g, 92%. FT-IR (Neat, ν, cm^{-1}): 3451, 2934, 2873, 1738, 1240, 1048. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 0.89 (t, 3H, CH_3-CH_2), 1.25-1.36 (m, 4H, CH_2-CH_2-CH_3), 1.43 (s, 6H, $(CH_3)_2C$), 1.59-1.63 (m, 2H, CH_2-$(CH_2)_2$-CH_3), 2.04 (s, 3H, CH_3-CO), 3.55-3.85 (m, 3H, CH_2-OH, C*H*-CH_2-OH), 4.32 (m, 1H, HC-CH=), 5.25 (m, 1H, CH(OAc)), 5.63-5.83 (m, 2H, CH=CH). ^{13}C

NMR (75 MHz, $CDCl_3$, δ, ppm): 13.8, 21.2, 22.3, 26.90, 26.99, 27.2, 33.9, 60.5, 73.6, 77.2, 81.0, 109.3, 129.1, 133.3, 170.3. ESI-MS (*m/z*): 287 $(M+1)^+$, 309 $(M+Na)^+$. HRMS calcd. for $C_{15}H_{27}O_5$ $[M+H]^+$: 287.1781, Found: 287.1652.

2.2.8. Synthesis of (Z)-ethyl 3-((4S,5S)-5-((Z)-3-acetoxyhept-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (15)

To a stirred solution of $(COCl)_2$ (0.25 mL, 2.8 mmol) in dry CH_2Cl_2 (30 mL) was added anhydrous DMSO (0.4 mL, 5.6 mmol) at -78 °C over a period of 20 min under nitrogen atmosphere, and the reaction mixture was stirred for 30 min. A solution of compound **14** (400 mg, 1.4 mmol.) in CH_2Cl_2 was added and the resulting solution was stirred for 1 h at -78 °C. The reaction was quenched with Et_3N (1.17 mL, 8.4 mmol), allowed to reach room temperature and then extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated under vacuum to obtain crude aldehyde which was employed to the next step immediately.

To a stirred solution of $(F_3CCH_2O)_2POCH_2COOEt$ (0.354 mL, 1.67 mmol), 18-crown-6 (1.478 g, 5.6 mmol) in dry THF (2 mL) at -78 °C was added KHMDS (0.362 g, 1081 mmol) and stirred for 30 min. The solution of crude aldehyde in THF (5 mL) was added, reaction mixture was stirred for 4 h at same temperature. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, concentrated under vacuum, and the residue was purified by flash column chromatography (Hexane:EtOAc, 8:2, *v*:*v*) to afford compound **15** (Scheme 1). Color: Colorless oil. Yield: 0.396 g, 80%. FT-IR (Neat, ν, cm^{-1}): 2937, 1725, 1371, 1234, 1048. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 0.88 (t, 3H, CH_3-$(CH_2)_2$), 1.25-1.31 (m, 7H, $((CH_2)_2$-CH_3, CH_3-CH_2-O), 1.45 (s, 6H, $(CH_3)_2C$), 1.53-1.66 (m, 2H, CH_2-$(CH_2)_2$-CH_3), 2.0 (s, 3H, CH_3-CO), 4.03-4.22 (m, 3H, O-CH_2-CH_3, CH-CH=CH), 5.22-5.30 (m, 1H, CH-CH=CH-COO), 5.38-5.46 (m, 1H, CH(OAc)), 5.71-5.76 (m, 2H, CH=CH-CH(OAc)), 5.93 (d, 1H, *J* = 11.3 Hz, CH-COOEt), 6.12 (dd, 1H, *J* = 8.3, 3.0 Hz, HC=CH-COOEt). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 13.8, 14.0, 21.1, 22.3, 26.9, 27.01, 27.06, 33.8, 60.2, 73.2, 75.8, 81.4, 109.8, 123.3, 127.9, 133.2, 143.8, 164.9, 170.0. ESI-MS (*m/z*): 377 $(M+Na)^+$. HRMS calcd. for $C_{19}H_{30}O_6Na$ $[M+Na]^+$: 377.2042, Found: 377.1987.

2.2.9. Synthesis of pectinolide H (1) and 4′-epi-pectinolide H (2)

A solution of compound **15** (25 mg, 0.706 mmol) in MeOH (10 mL) was stirred with a catalytic amount of PTSA (2 mg) at room temperature. After 4 h MeOH was evaporated and the crude product was purified by preparative thin layer chromatography (Hexane: EtOAc, 1:1, *v*:*v*) to obtain pure compounds **1** and **2** in 1.2 : 1 ratio (Scheme 1).

(1S,4S,Z)-1-hydroxy-1-((S)-5-oxo-2,5-dihydrofuran-2-yl)oct-2-en-4-yl acetate (Pectinolide H) (**1**): Color: Colorless oil. Yield: 9.6 mg, 50.8 %. FT-IR (Neat, ν, cm^{-1}): 3439, 2931, 2862, 1750, 1241, 1042. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 0.89 (t, 3H, CH_3-$(CH_2)_2$), 1.22-1.36 (m, 4H, $(CH_2)_2$-CH_3), 1.50-1.70 (m, 2H, CH_2-$(CH_2)_2$-CH_3), 2.06 (s, 3H, CH_3-CO), 3.07 (br. 1H, OH), 4.28-4.33 (m, 1H, CH-OH), 5.00-5.04 (m, 1H, CH(OAc)), 5.15-5.22 (m, 1H, CH-CH=CH-COO), 5.62-5.84 (m, 2H, CH=CH-CH(OAc)), 6.19 (dd, 1H, *J* = 4.5, 1.5 Hz, =CH-COO), 7.47 (dd, 1H, *J* = 6.7, 1.5 Hz, CH=CH-COO). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 13.8, 21.1, 22.2, 27.0, 33.7, 72.2, 73.7, 85.5, 122.9, 128.4, 133.2, 153.2, 170.5, 172.6. ESI-MS (*m/z*): 291 $(M+Na)^+$. $[\alpha]_D^{25}$: -39.0 (*c* 0.32, $CHCl_3$). HRMS calcd. for $C_{14}H_{20}O_5Na$ $[M+Na]^+$: 291.1202; Found: 291.1200.

(1S,4R,Z)-1-hydroxy-1-((S)-5-oxo-2,5-dihydrofuran-2-yl)oct-2-en-4-yl acetate (4′-epi-pectinolide H) (**2**): Color: Colorless oil. Yield: 8 mg, 42.3%. FT-IR (Neat, ν, cm^{-1}): 3444, 2928, 2856, 1750, 1241, 1043. ^1H NMR (300 MHz, $CDCl_3$, δ, ppm): 0.89 (t, 3H, CH_3-$(CH_2)_2$), 1.24-1.31 (m, 4H, $(CH_2)_2$-CH_3), 1.54-1.68 (m, 2H, CH_2-$(CH_2)_2$-CH_3), 2.06 (s, 3H, CH_3-CO), 2.76 (br. 1H, OH), 4.27-4.30 (m, 1H, CH-OH), 4.99-5.01 (m, 1H, CH(OAc)), 5.18-5.24 (m, 1H, CH-CH=CH-COO), 5.64-5.84 (m, 2H, CH=CH-CH(OAc)), 6.18 (d, 1H, *J* = 4.7 Hz, =CH-COO), 7.43 (dd, 1H, *J* = 5.7, 4.7 Hz, CH=CH-COO). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 13.8, 21.2, 22.3, 27.1, 33.8, 72.5, 73.7, 85.5, 123.0, 128.3, 133.5, 153.1, 170.5, 172.5. ESI-MS (*m/z*): 291 $(M+Na)^+$. $[\alpha]_D^{25}$: +21.9 (*c* 0.1, $CHCl_3$). HRMS calcd. for $C_{14}H_{20}O_5Na$ $[M+Na]^+$: 291.1202, Found: 291.1188.

3. Results and discussion

A cursory look at the structure of compound **1** shows that (+)-diethyl L-tartrate (**6**) possesses the required (2*S*,3*S*)-stereochemistry. Protection of the vicinal hydroxy groups as an acetonide and reduction of compound **7** with $LiAlH_4$ gave the corresponding diol (**8**) in 85% yield. Selective mono-protection of compound **8** was achieved with 1 equiv. of (*tert*-butyl diphenylsilyl chloride (TBDPSCl) in presence of NaH in THF. The mono protected alcohol (**9**) was oxidized to the corresponding aldehyde by Swern oxidation. The crude aldehyde was subjected to Wittig olefination in methanol to obtain a mixture of *E* and *Z*-alkene (**10**) with *E* to *Z* ratio of 20:80. The isomers were easily separated by column chromatography [13]. Reduction of the ester group of *Z*-(**10a**) with DIBAL-H in CH_2Cl_2 and Grignard reaction of the aldehyde (**11**) with *n*-butyl magnesium bromide gave a diastereo-isomeric mixture of secondary alcohols (**12**). Acetylation with Ac_2O in pyridine provided a mixture of diastereomers (**13**). Deprotection of the primary alcohol with TBAF followed by Swern oxidation of the alcohol (**14**) gave an intermediate aldehyde which was subjected to Still-Gennari olefination reaction [14,15] without isolation to afford the corresponding α,β-unsaturated ester (**15**) in 80% yield. Deprotection of the acetonide and subsequent *in situ* lactonization of ester (**15**) with *p*-toluenesulfonic acid in MeOH afforded a diastereomeric mixture of pectinolide H (**1**) and 4'-epi-pectinolide H (**2**) in 98% yield (Scheme 1). Both the diastereomers were separated by preparative TLC. The ^1H and ^{13}C NMR spectral data and optical rotation of pectinolide H were in excellent agreement with the data previously reported in literature [11,12].

4. Conclusion

In conclusion, a simple stereoselective total synthesis of pectinolide H and 4'-*epi*-pectinolide H have been achieved from (+)-DET in nine steps with 27% overall yield. Our synthetic strategy provides pectinolide H and the epimer 4'-*epi*-pectinolide H.

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