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

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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

1H and 13C NMR spectra were recorded on Bruker Avance 300 MHz and Bruker Avance 75 MHz spectrometers, respectively, using CDCl3 as solvent and SiMe4 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, 485.4 mmol), p-toluene sulfonic acid (100 mg) in CH2Cl2 (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 NaHCO3, 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, v, cm⁻¹): 2990, 1753, 1216. 1H NMR (300 MHz, CDCl3, δ, ppm): 1.31 (t, 6H, CH3-CH2-O), 1.50 (s, 6H, (CH3)2C), 4.27 (q, 4H, CH2-OCO), 4.76 (s, 2H, CH-COO).
**Figure 1.** Structure of pectinolide A–C, H and 4′-epi-pectinolide H.

Reagents and conditions: a) 2,2-DMP, PTSA (cat.), CH₂Cl₂, rt, 4 h, 90%. b) LiAlH₄, THF, 0 °C to rt, 1 h, 85%. c) TBDPSCI, NaH, THF, 0 °C to rt, 2 h, 92%. d) (i) (COCl)₂, DMSO, CH₂Cl₂, Et₃N, -78 °C. (ii) Ph₃PCHCOOEt, MeOH, -50 °C to rt, (88% in two steps). e) DIBAL-H, CH₂Cl₂, -78 °C, 30 min. f) Mg, nBuBr, THF, (66% in two steps). g) Ac₂O, DMAP, Pyridine, CH₂Cl₂, rt, 3 h, 99%. h) TBAF, THF, rt, 5 h, 92%. i) (i) (COCl)₂, DMSO, CH₂Cl₂, Et₃N, -78 °C. (ii) (F₃CCH₂O)₂POCH₂COOEt, 18-crown ether, KHMD₅, dry THF, -78 °C, 4 h, (80% in two steps). j) TsOH, MeOH, 2 h, 93%.

**Scheme 1**

1³C NMR (75 MHz, CDCl₃, δ, ppm): 13.9, 26.7, 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-diyldimethanol (8)**

A solution of compound 7 (6 g, 24.4 mmol) in THF (20 mL) was slowly added to a suspension of LiAlH₄ (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 NH₄Cl (10%, v/v, 20 mL) was added and the reaction mixture was filtered through celite. The filtrate was dried over anhydrous MgSO₄ 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, cm⁻¹): 3403. 1³H NMR (300 MHz, CDCl₃, δ, ppm): 1.43 (s, 6H, (CH₃)₂C), 2.77 (br. s, 2H, 2-OH), 3.68-3.81 (m, 4H, CH₂-OH), 3.98-3.99 (m, 2H, CH-CH₂-OH). 1³C NMR (75 MHz, CDCl₃, δ, ppm): 8 26.9, 62.0, 78.1, 109.2. ESI-MS (m/z): 162 (M⁺1), [α]D⁺ : -8.16 (c 1, CHCl₃).

2.2.3. **Synthesis of (4S,5S)-5-((tert-butylidiphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolane-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 CH₂Cl₂ (3 x 10 mL), dried over anhydrous MgSO₄ 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
2.2.4. Synthesis of (Z)-ethyl 3-(4H,5H)-5-((tert-butyl diphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolane-4-yl acrylate (10a) and (E)-ethyl 3-(4H,5H)-5-((tert-butyl diphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolane-4-yl acrylate (10b)

To a solution of oxaly chloride (0.7 mL, 8 mmol) in dry CH₂Cl₂ (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 CH₂Cl₂ (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 Et₃N (5.0 mL) and allowed to reach room temperature over 30 min. The solvent was removed on rotovap and the residue was purified by flash column chromatography (Hexane/EtOAc: 9:1) to afford compound 10a and 10b in 80:20 ratio (Scheme 1).

(Z)-Ethyl 3-(4H,5H)-5-((tert-butyl diphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolane-4-ylacrylate (10a): Colorless oil. Yield: 1.32 g, 70% FT-IR (Neat, v, cm⁻¹): 3441, 2931, 1428, 1245, 1080, 702. 1H NMR (300 MHz, CDCl₃, δ, ppm): 1.06 (s, 9H, (CH₃)₃Si), 1.38 (s, 3H, CH₂-CH₂-), 1.41 (s, 3H, CH₂-CH₂-), 3.63-3.84 (m, 4H, CH₂-CH₂-OH, CH₂-CH₂-OSi), 3.93-3.99 (m, 1H, CH-CH₂-OH), 4.04-4.10 (m, 1H, CH-CH₂-OSi), 7.37-7.43 (m, 6H, Ar-H), 7.64-7.68 (m, 4H, Ar-H). 13C NMR (75 MHz, CDCl₃, δ, ppm): 19.1, 26.7, 26.9, 27.0, 62.5, 64.1, 77.4, 79.5, 109.1, 127.7, 127.8, 129.9, 132.8, 135.5. ESI-MS (m/z): 423 (M+Na)⁺ [419 (M+Na)⁺]

(E)-Ethyl 3-(4H,5H)-5-((tert-butyl diphenylsilyloxy)methyl)-2,2-dimethyl-1,3-dioxolane-4-ylacrylate (10b): Colorless oil. Yield: 0.32 g, 18% FT-IR (Neat, v, cm⁻¹): 3401, 2931, 1428, 1245, 1080, 702. 1H NMR (300 MHz, CDCl₃, δ, ppm): 1.06 (s, 9H, (CH₃)₃Si), 1.38 (s, 3H, CH₂-CH₂-), 1.41 (s, 3H, CH₂-CH₂-), 3.63-3.84 (m, 4H, CH₂-CH₂-OH, CH₂-CH₂-OSi), 3.93-3.99 (m, 1H, CH-CH₂-OH), 4.04-4.10 (m, 1H, CH-CH₂-OSi), 7.37-7.43 (m, 6H, Ar-H), 7.64-7.68 (m, 4H, Ar-H). 13C NMR (75 MHz, CDCl₃, δ, ppm): 19.1, 26.7, 26.9, 27.0, 62.5, 64.1, 77.4, 79.5, 109.1, 127.7, 127.8, 129.9, 132.8, 135.5. ESI-MS (m/z): 423 (M+Na)⁺ [419 (M+Na)⁺]

2.2.5. Synthesis of (Z)-1-(4H,5H)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane-4-ylhept-1-en-3-yl acetate (12)

To a stirred solution of compound 10a (2.0 g, 4.27 mmol) in CH₂Cl₂ (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 NaOH (10 mL, 50%, v/v) at 0 °C. Saturated potassium carbonate solution (10 mL) was added and the contents were extracted with CH₂Cl₂. The combined organic layer was dried over anhydrous MgSO₄ concentrated under vacuum to obtain the crude aldehyde which was used in next step without further purification.

A solution of n-butylic acid (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 in THF (10 mL) was added. After 1 h the reaction was quenched with aqueous NH₄Cl filtered through a celite. The filtrate was dried anhydrous MgSO₄ 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, v, cm⁻¹): 3441, 2931, 1428, 1113. 1H NMR (300 MHz, CDCl₃, δ, ppm): 1.06 (s, 9H, (CH₃)₃Si), 1.21-1.37 (m, 4H, CH₂-CH₂-CH₂-), 1.43 (s, 6H, (CH₃)₃Si), 1.46-1.53 (m, 2H, CH₂-CH₂-CH₂-CH₂-CH₂-CH₂-CH₃), 3.69-3.86 (m, 3H, CH₂-OSi, CH₂-OSi), 4.09 (q, J, CH(OH)), 4.43 (t, 1H, CH=CH₂), 5.65 (dd, 1H, J = 8.3, 6.7 Hz, CH=CH(CH=)), 5.78 (dd, 1H, J = 9.8, 6.0 Hz, CH=CH(CH=CH(OH))), 7.35-7.43 (m, 6H, Ar-H), 7.67-7.70 (m, 4H, Ar-H). 13C NMR (75 MHz, CDCl₃, δ, ppm): 13.9, 19.2, 22.5, 26.7, 26.9, 27.0, 27.4, 36.6, 62.7, 71.9, 70.0, 81.4, 109.0, 127.4, 127.6, 129.6, 129.7, 131.3, 135.6, 137.5. ESI-MS (m/z): 505 (M+Na)⁺ [505 (M+Na)⁺]

NMR (75 MHz, CDCl3, δ, ppm): 138, 212, 223, 26.90, 26.99, 27.2, 329, 605, 73.6, 77.2, 81.0, 103.3, 129.1, 133.3, 170.2. ESI-MS (m/z): 287 (M+1); 309 (M+Na)-. HRMS calcd. for C14H20O5Na [M+Na]+: 291.1784. Found: 291.1783.

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

To a stirred solution of (COCl)2 (0.25 mL, 2.8 mmol) in dry CH2Cl2 (30 mL) was added and the resulting solution was stirred for 1 h at -78 °C. The reaction was quenched with Et3N (1.17 mL, 8.4 mmol) allowed to reach room temperature and then extracted with CH2Cl2. The combined organic layer was dried over anhydrous MgSO4 and evaporated under vacuum to obtain crude aldehyde which was employed to the next step immediately.

A solution of compound 14 (400 mg, 1.4 mmol) in CH2Cl2 was added and the resulting solution was stirred for 1 h at -78 °C. The reaction was quenched with saturated aqueous NH4Cl (5 mL) and extracted with ethyl acetate. The combined organic layers were dried over anhydrous MgSO4 and evaporated under vacuum to obtain crude aldehyde which was employed to the next step immediately.

To a stirred solution of Fadnavis (15) [6]. Deprotection of the primary alcohol with TBAF followed by Swern oxidation of the alkyl (14) gave an intermediate aldehyde which was subjected to Stille-Gennari olefination reaction [14,15] without isolation to afford the corresponding α,β-unsaturated ester (15) in 80% yield. Deprotection of the acetone 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 H and 13C 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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References


