Synthesis of the Simple Macrolides, Patulolide A and Patulolide C

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Two simple macrolides, patulolides A and C, were synthesized from vitamin C as a chiral starting material.

Keywords: Macrolide; patulolide A; patulolide C; vitamin C; chiral starting material; Mitsunobu reaction; lactonization; Yamaguchi method

As a continuation of our synthetic work on natural products from vitamin C as a chiral starting material,1) we report here the synthesis of two simple macrolides,2) patulolides A (1) and C (2), having antifungal activities.3) These compounds had been isolated from Penicil- lium urticae S11R59 and characterized by Yamada and his co-workers.3) Reduction of the ester (3), readily prepared from vitamin C,4) with lithium aluminum hydride (LAH) gave the glycol (4). Treatment of 4 with diisopropyl azodicarboxylate and triphenylphosphine in benzene (Mitsunobu reaction)5) furnished the epoxide (5) as the sole product in 58% yield. Epoxide ring-opening reaction of 5 with 6-heptenylmagnesium bromide in the presence of copper(I) iodide in tetrahydrofuran (THF) gave the alcohol (6) in 78% yield. After protection of the hydroxyl group as the tert-butylidiphenylsilyl (TBDS) ether, oxidation of the silyl ether (7) with m-chloroperbenzoic acid (MCPBA) in methylene chloride gave a 1:1 mixture of two diastereoisomeric epoxides (8). Attempts to isolate each epoxide in pure form by flash and preparative thin layer chromatographies, however, were unsuccessful. Reduction of the mixture with LAH gave the alcohols (9) in 90% yield, and these were smoothly converted to the acetates (10) in quantitative yield. Hydrolysis of the acetonide moiety of 10 with 70% aqueous acetic acid followed by oxidation of the resulting glycols (11) with periodic acid in aqueous THF gave the aldehydes (12). The latter was, without further purification, subjected to a Wadsworth–Emmons reaction with triethyl phosphonoacetate and sodium hydride in THF, giving rise to the olefinic esters (13) in 88% yield. The stereochemistry of the newly formed double bond was confirmed to be trans by observation of the coupling constant (15.7 Hz) of the olefinic protons in the proton magnetic resonance (1H-NMR) spectrum. Alkaline hydrolysis of 13 gave the hydroxy-acids (14). Intramolecular lactonization of 14 with 2,4,6-trichlorobenzoyl chloride and triethylamine in THF followed by treatment with 4-dimethylaminopyridine (DMAP) in refluxing xylene (modified Yamaguchi method6) gave the patulolide C O-silyl ether (15) and its 11-epimer (16). At this stage, the two stereoisomeric lactones were separable by using preparative thin layer chromatography (TLC) in 30% and 29% yields, respectively. Removal of the silyl group in the lactones 15 and 16 with tetrabutylammonium fluoride in THF gave patulolide C (2) and its 11-epimer (17) in 82 and 83% yields, respectively. The spectroscopic properties of the former including its optical rotation (\([\alpha]_D^2 = +6.8^\circ \quad (c=0.15, \text{EtOH})\) were identical with those of patulolide C (\([\alpha]_D^2 = +6.6^\circ \quad (c=0.40, \text{EtOH})\)) reported in the literature.2d

![Chemical structures](chart1.png)

Chart 1

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indicating the accomplishment of the synthesis of patulolid B. Since patulolid C has been converted to patulolid A (1), our synthesis of patulolid C is also a synthesis of I in the formal sense.

Experimental

Infrared (IR) spectra were recorded on a Shimadzu IR-408 spectrometer in chloroform. 1H-NMR spectra were recorded on a JEOL FX 90Q spectrometer with tetramethylsilane as an internal standard and chemical shifts are given in δ (ppm). Optical rotations were measured with a JASCO DIP-181 digital polarimeter at 20 °C and high-resolution mass spectra were measured using an automatic JEOL M-3X mass spectrometer. TLC was taken with a JEOL JMS-DX303 instrument. Merck Kieselgel Art. 9385 was used for flash column chromatography, and Merck Kieselgel precoated silica gel 60 F-254 plates were used for preparative TLC.

(2S,3S)-1,2-O-Isopropylidenedibutane-1,2,3,4-tetraol (4) A solution of the ester (3) (7.60 g, 40 mmol) in dry THF (50 ml) was added dropwise to a stirred suspension of L sprawling hydroxide (1.32 g, 46 mmol) in THF (50 ml) at room temperature. After being stirred for 5 h, the reaction mixture was cooled to 0 °C and the excess hydride was decomposed by addition of wet ether followed by a minimum amount of water. Inorganic precipitates were filtered off and the filtrate was evaporated under reduced pressure to give a residue, which was subjected to flash chromatography. Elution with ethyl ether (1:1) afforded a 1:1 mixture of two diastereoisomeric oxides (8) (257 mg, 96%). 1H-NMR (CDCl3): 1.05 (15H, s), 1.24—1.58 (12H, m), 2.69—2.78 (2H, m), 4.46—4.54 (4H, m), 7.31—7.40 (5H, m), 7.62—7.74 (5H, m). MS m/z: 481 (M+). Anal. Calcd for C36H48O7Si: C, 72.54; H, 8.93. Found: C, 72.13; H, 8.78.

(2S,3S)-1,2-0-Isopropylidenedi-3-tert-butyldimethylsiloxystyrene-1,2,3,10-tetraol (9) A solution of 8 (945 mg, 1.9 mol) in THF (20 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (144.8 mg, 3.8 mmol) in anhydrous THF (20 ml) at 0 °C. The resulting mixture was stirred at 50 °C for 1 h, and cooled to 0 °C, and the excess hydride was decomposed by addition of wet ether followed by a minimum amount of water. The inorganic precipitates were filtered off and the filtrate was evaporated under reduced pressure to give a residue, which was subjected to flash chromatography. Elution with hexane-ether (1:1) afforded the alcohol (9) (85.1 mg, 90%), bp 185—190 °C (bath temperature)/1.5 mmHg. 1H-NMR (CDCl3): 1.06 (15H, s), 1.13—1.40 (15H, m), 3.66—4.02 (5H, m), 7.30—7.42 (5H, m), 7.61—7.73 (5H, m). MS m/z: 483 (M+). Anal. Calcd for C40H54O7Si: C, 72.24; H, 9.30. Found: C, 72.41; H, 9.35.

(2S,3S)-10-Acetoxy-1,2-O-Isopropylidenedi-3-tert-butyldimethylsiloxystyrene-1,2,3,10-tetraol (10) A solution of 9 (835.3 mg, 1.67 mmol), pyridine (1.63 ml, 24.0 mmol), acetic anhydride (0.47 ml, 5.01 mmol), 4-dimethylaminopyridine (0.18 mg, 1.05 mmol), and anhydrous methylene chloride (20 ml) was stirred at room temperature for 14 h, poured into cold water, and extracted with ethyl acetate. The ethyl acetate extracts were washed with water and brine, and dried (MgSO4). Evaporation of the solvents in vacuo gave an oily residue, which was subjected to flash chromatography. Elution with ether-hexane (1:3) afforded the acetate (10) (861 mg, 96%). IR (CHCl3): 1720 cm⁻1. 1H-NMR (CDCl3): 1.08 (15H, s), 1.18—1.42 (15H, m), 2.03 (3H, s), 3.68—4.11 (4H, m), 4.84 (1H, m), 7.29—7.43 (5H, m), 7.65—7.77 (5H, m). MS m/z: 525 (M+). Anal. Calcd for C42H56O8Si: C, 71.07; H, 8.95. Found: C, 70.84; H, 9.09.

(2S,3S)-10-Acetoxy-3-tert-butyldimethylsiloxystyrene-1,2,3,10-tetraol (11) A solution of the acetate (10) (250 mg, 0.46 mmol) in 70% aqueous acetic acid (8 ml) was stirred at 60 °C for 3 h and diluted with ethyl acetate (20 ml). Removal of the solvents in vacuo gave a residue, which was subjected to flash chromatography. Elution with hexane-ether (1:1) afforded the alcohol (11) (211 mg, 92%). IR (CHCl3): 3600, 1720 cm⁻1. 1H-NMR (CDCl3): 1.06 (9H, s), 1.13—1.45 (21H, m), 1.62 (2H, s), 2.00 (3H, s), 2.40 (1H, s, OH), 3.50 (4H, m), 4.82 (1H, m), 7.40 (5H, m), 7.65 (5H, m). MS m/z: 483 (M+). Anal. Calcd for C42H54O7Si: C, 69.66; H, 8.86. Found: C, 69.20; H, 8.90.

(2S,3S)-10-Acetoxy-2-tert-butyldimethylsiloxystyrene-1,2,3,10-tetraol (12) A solution of periodic acid dihydride (1.30 g, 5.68 mmol) and the glycol (11) (947 mg, 1.89 mmol) in anhydrous THF (30 ml) was stirred at room temperature for 40 min and diluted with ethyl acetate. The solution was washed twice with brine, and dried (MgSO4). Evaporation of the solvent in vacuo gave the aldehyde (12) as an oil, which was used for the next step without further purification.

Ethyl (4S)-11-Acetoxy-4-tert-butyldimethylsiloxystyrene-2-E-2-deconate (13) Triethyl phosphonooctate (0.53 ml, 2.69 mmol) was added to a suspension of sodium hydride (92 mg, 2.29 mmol) in anhydrous THF (3 ml) at 0 °C and the resulting mixture was stirred at the same temperature for 30 min. A solution of the aldehyde (12) (823 mg, 1.76 mmol) in anhydrous THF (15 ml) was added to the mixture at –30 °C. After being stirred at –30 to –5 °C for 2 h, the reaction mixture was diluted with ethyl acetate and the solution was washed with brine, and dried (MgSO4). Evaporation of the solvent under reduced pressure left an oil, which was subjected to flash chromatography. Elution with hexane-ether (3:1) afforded the olefinic ester (13) (192 mg, 88% from the glycol (11)). IR (CHCl3): 1710, 1660, 980 cm⁻1. 1H-NMR (CDCl3): 1.08—1.62 (27H, m), 2.02 (3H, m), 4.29—4.37 (3H, m), 4.75—4.88 (1H, m), 5.87 (1H, dd, J = 1.5, 15.7 Hz), 6.85 (1H, dd, J = 5.2, 15.7 Hz), 7.25—7.44 (5H, m), 7.55—7.72 (5H, m). Anal. Calcd for C44H56O7Si: C, 71.34; H, 8.61. Found: C, 71.27; H, 8.53.

(4S)-1-Hydroxy-4-tert-butyldimethylsiloxystyrene-2-E-2-deconic Acid (14) A mixture of the acetate (13) (896 mg, 1.67 mmol), 0.35 n aqueous NaOH (22 ml, 7.7 mmol), and ethanol (34 ml) was stirred at 50 °C for 5.5 h, cooled to 0 °C, acidified to 10% citric acid, and extracted with chloroform. The chloriform extract was washed with brine, dried (MgSO4), and concentrated in vacuo to give a residue, which was subjected to flash chromatography.
chromatography. Elution with ethyl acetate-hexane (1:1) afforded the hydroxy acid (14) (481 mg, 62%). IR (CHCl₃): 1695, 1650, 980 cm⁻¹. ¹H-NMR (CDCl₃): 1.06—1.08 (12H, m), 1.20—1.45 (12H, m), 3.37—3.53 (2H, m), 4.34 (1H, m), 5.91 (2H, dd, J=1.0, 17Hz), 6.96 (1H, dd, J=4.9, 20.5Hz).

(4S,11R)-4-tert-Butylhexylsiloxy-2E-dodecen-11-olide (15) and Its 11S Isomer A mixture of the hydroxy acids (14) (342 mg, 0.73 mmol), triethylamine (0.14 ml, 1.02 mmol), and anhydrous THF (15 ml) was stirred at room temperature for 10 min. Then 2,4,6-trichlorobenzoyl chloride (0.15 ml, 0.93 mmol) was added and the resulting mixture was stirred at room temperature for 3 h. THF was evaporated off in vacuo and the residue was dissolved in toluene (474 ml) containing 4-dimethylaminopyridine (2.84 g, 23.3 mmol), and the solution was refluxed for 12 h, washed with 2% aqueous KHSO₄ and brine, and dried (MgSO₄). Evaporation of the solvent in vacuo left an oily residue, which was subjected to preparative TLC on silica gel. Development with hexane–ether (8:1) furnished the pure O-silyl ether of patulolidic acid C (15) (100 mg, 30%) and its 11S isomer (16) (96 mg, 29%). ¹H-NMR (CDCl₃): 1.08 (9H, s), 1.26—1.78 (12H, m), 4.42 (1H, m), 5.02 (1H, m), 6.04 (1H, dd, J=1.1 and 15.7Hz), 6.77 (1H, dd, J=5.5 and 15.8Hz), 7.25—7.43 (5H, m), 7.55—7.68 (5H, m). MS m/z: 393 (M⁺). Anal. Calcd for C₁₂H₁₉O₅Si: C, 74.62; H, 8.50. Found: C, 74.74; H, 8.42. ¹H-NMR (CDCl₃): 1700 cm⁻¹. ¹H-NMR (CDCl₃): 1.07 (9H, s), 1.23—1.60 (12H, m), 4.45 (1H, m), 5.00 (1H, m), 6.11 (1H, dd, J=1.7 and 15.7Hz), 6.98 (1H, dd, J=3.7, 15.8Hz), 7.24—7.40 (5H, m), 7.56—7.71 (5H, m). MS m/z: 393 (M⁺). Anal. Calcd for C₁₂H₁₉O₅Si: C, 74.62; H, 8.50. Found: C, 74.33; H, 8.78.

Patulolidic acid C (2) and Its 11S Isomer A solution of tetrabutylammonium fluoride (58 μl, 0.058 mmol) and the O-silyl ether (15) (13 mg, 0.029 mmol) in anhydrous THF (1 ml) was stirred at 0°C for 3 h and at room temperature for 8 h and diluted with ethyl acetate. The solution was washed with saturated brine, and dried (MgSO₄). Evaporation of the solvent gave a residue, which was subjected to preparative TLC on silica gel. Development with hexane–ethyl acetate (4:1) afforded pure patulolidic acid C (2) (5 mg, 82%). ¹H-NMR (CDCl₃): 1.25—1.72 (12H, m), 1.29 (3H, d, J=6.7Hz), 4.45 (1H, m), 5.03 (1H, m), 6.07 (1H, dd, J=0.4, 16Hz), 6.85 (1H, m, dd, J=7, 16Hz). A similar treatment of 16 (15.3 mg, 0.034 mmol) afforded 17 (6 mg, 83%). ¹H-NMR (CDCl₃): 1.10—2.04 (12H, m), 1.29 (3H, d, J=6.7Hz), 4.48 (1H, m), 5.03 (1H, m), 6.03 (1H, dd, J=1.6, 17.7Hz), 7.02 (1H, dd, J=4.4, 20.3Hz). MS m/z: 194 (M⁺). HR-MS m/z: Caled for C₁₂H₁₉O₂: 212.1412 (M⁺). Found: 212.1416.

References