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 *Penicillium 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*-butyldiphenylsilyl (TBDPS) 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 quatitative 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 (^{1}H-NMR) spectrum. Alkaline hydrolysis of **13** gave the hydroxy-acids (**14**). Intramolecular lactonization of **14** with 2,4,6-trichlorobenzolyl chloride and triethylamine in THF followed by treatment with 4-dimethylaminopyridine (DMAP) in refluxing xylene (modified Yamaguchi method[6]) 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 ($[\alpha]_D = +6.8°$ ($c = 0.15$, EtOH)) were identical with those of patulolide C ($[\alpha]_D = +6.6°$ ($c = 0.40$, EtOH)) reported in the literature,[2d]

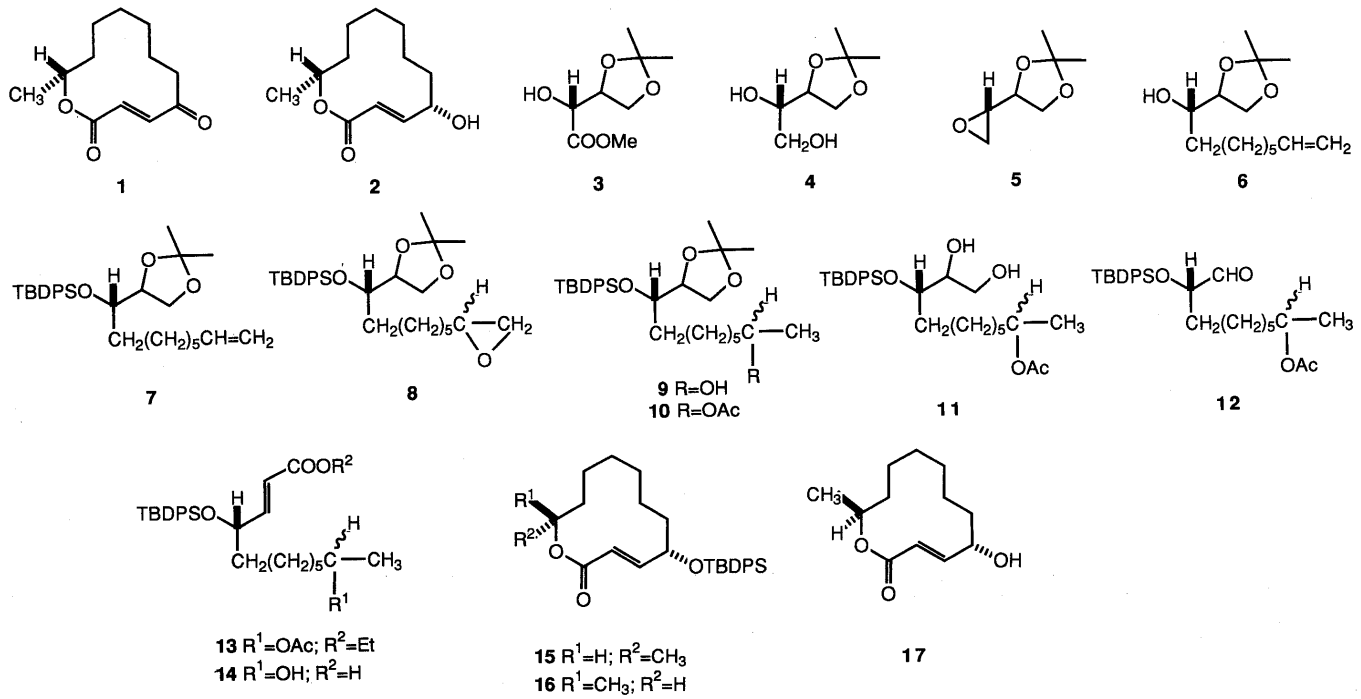

Chart 1

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

Experimental

Infrared (IR) spectra were recorded on a Shimadzu IR-408 spectrometer in chloroform. ^{1}H-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 (HR-MS) were 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.

(2*S*,3*S*)-1,2-*O*-Isopropylidenebutane-1,2,3,4-tetraol (4)[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 LAH (1.82 g, 48 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 solids were thoroughly washed with chloroform. The combined organic solution was dried ($MgSO_4$) and evaporated under reduced pressure to yield the diol (**4**) (55.92 g, 91%) as a colorless oil. IR ($CHCl_3$): 3420 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.43 (3H, s), 1.50 (3H, s), 3.62—4.45 (8H, m).

(2*S*,3*S*)-3,4-Epoxy-1,2-*O*-Isopropylidenebutane-1,2-diol (5)[4] Diethyl azodicarboxylate (DEAD, 4.70 g, 27 mmol) was added dropwise to a stirred solution of **4** (3.66 g, 22.6 mmol) and triphenylphosphine (6.85 g, 26.1 mmol) in dry benzene (50 ml). An exothermic reaction was observed. The mixture was stirred at room temperature for 2 h, then the benzene was removed under reduced pressure and the residue was distilled at 55 °C (3 mmHg) to give 3.80 g (72%) of the epoxide **5**: $[\alpha]_D$ −5.3° (c=1.15, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.32 (3H, s), 1.40 (3H, s), 2.57—2.80 (2H, m), 2.92—3.05 (1H, m), 3.72—4.13 (3H, m).

(2*S*,3*S*)-1,2-*O*-Isopropylidene-10-undecene-1,2,3-triol (6) A solution of 6-heptenyl bromide (4.31 g, 24.3 mmol) in THF (4.5 ml) was added dropwise to a stirred mixture of magnesium (614 mg, 25.6 mmol) and dry THF (3.5 ml) at room temperature. An exothermic reaction occurred. After addition was completed, the mixture was stirred at 60 °C for 1.5 h. Then the mixture was diluted with THF (3.5 ml) and cooled to −40 °C. Copper (I) iodide (231 mg, 1.22 mmol) was added to the mixture, and the whole was stirred at −40 °C for 30 min. A solution of the epoxide (**5**) (1.75 g, 12.2 mmol) in THF (7 ml) was then added dropwise and the whole was stirred at −40 °C for 2.5 h. After warming to room temperature, the mixture was partitioned between 3% aqueous NH_4Cl and ether. The aqueous layer was thoroughly extracted with ether. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and evaporated under reduced pressure to leave an oily residue, which was purified by flash chromatography. Elution with ether–hexane (1 : 3) afforded the alcohol (**6**) (2.28 g, 78%), bp 145 °C (bath temperature)/1.5 mmHg, $[\alpha]_D$ −22.5° (c=1.06, EtOH). IR ($CHCl_3$): 3600, 1640, 1000, 910 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.35 (10H, br s), 1.41 (6H, s), 1.93—2.05 (2H, m), 2.33 (1H, d, J=5.05 Hz), 3.46 (1H, m, OH), 3.64—4.07 (3H, m), 4.81—5.08 (2H, m), 5.56—6.01 (1H, m). MS m/z: 227 (M^+). HR-MS m/z: Calcd for $C_{14}H_{26}O_3$: 242.1882 (M^+). Found: 242.1887. *Anal.* Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.53; H, 10.78.

(2*S*,3*S*)-1,2-*O*-Isopropylidene-3-*tert*-butyldiphenylsiloxy-10-undecene-1,2,3-triol (7) A mixture of TBDPSCl (1.19 g, 4.33 mmol), imidazole (442 mg, 6.5 mmol), the alcohol (**6**) (524 mg, 2.16 mmol) and anhydrous pyridine (13 ml) was stirred at 100 °C for 34 h and concentrated *in vacuo*. The residue was dissolved in ethyl acetate and the ethyl acetate solution was successively washed with 2% aqueous HCl, water and brine, and dried ($MgSO_4$). Evaporation of the solvent left an oil, which was purified by flash chromatography. Elution with hexane–ethyl acetate (6 : 1) afforded **7** (1.014 g, 98%) as a colorless oil, bp 170—175 °C (bath temperature)/1.5 mmHg. ^{1}H-NMR ($CDCl_3$): 1.06 (9H, s), 1.17—1.63 (18H, m), 3.66—3.89 (4H, m), 4.85—5.08 (2H, m), 5.59—5.96 (1H, m), 7.21—7.44 (5H, m), 7.61—7.74 (5H, m). *Anal.* Calcd for $C_{30}H_{44}O_3Si$: C, 74.95; H, 9.23. Found: C, 75.18; H, 9.19.

(2*S*,3*S*)-10,11-Epoxy-1,2-*O*-isopropylidene-3-*tert*-butyldiphenylsiloxyundecane-1,2,3-triol (8) A mixture of the silyl ether (**7**) (260 mg, 0.54 mmol), MCPBA (140 mg, 0.65 mmol) and anhydrous methylene chloride (10 ml) was stirred at room temperature for 24 h. The excess peracid was decomposed with 1% aqueous $NaHSO_3$, then the mixture was extracted with ethyl acetate. The extract was washed with 2% aqeuous Na_2CO_3, water and brine, and dried ($MgSO_4$). Removal of the solvent *in vacuo* left an oily residue, which was subjected to flash chromatography. Elution with ether–hexane (1 : 4) afforded a 1 : 1 mixture of two diastereoisomeric oxides (**8**) (257 mg, 96%). ^{1}H-NMR ($CDCl_3$): 1.05 (15H, s), 1.24—1.58 (12H, m), 2.39—2.47 (1H, m), 2.68—2.78 (2H, m), 3.44—4.14 (4H, m), 7.31—7.40 (5H, m), 7.62—7.44 (5H, m). MS m/z: 481 (M^+). *Anal.* Calcd for $C_{30}H_{44}O_4Si$: C, 72.54; H, 8.93. Found: C, 72.13; H, 8.78.

(2*S*,3*S*)-1,2-*O*-Isopropylidene-3-*tert*-butyldiphenyl-siloxyundecane-1,2,3,10-tetraol (9) A solution of **8** (945 mg, 1.9 mmol) in THF (20 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (144.8 mg, 3.80 mmol) in anhydrous THF (20 ml) at room temperature. 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**) (851.5 mg, 90%), bp 185—190 °C (bath temperature)/1.5 mmHg. ^{1}H-NMR ($CDCl_3$): 1.06 (15 H, s), 1.13—1.40 (15 H, 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 $C_{30}H_{46}O_4Si$: C, 72.24; H, 9.30. Found: C, 72.41; H, 9.35.

(2*S*,3*S*)-10-Acetoxy-1,2-*O*-isopropylidene-3-*tert*-butyldiphenylsiloxyundecane-1,2,3,10-tetraol (10) A mixture 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 (18 mg, 0.15 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 ($MgSO_4$). 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 ($CHCl_3$): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 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 $C_{32}H_{48}O_5Si$: C, 71.07; H, 8.95. Found: C, 70.84; H, 9.09.

(2*S*,3*S*)-10-Acetoxy-3-*tert*-butyldiphenylsiloxyundecane-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 glycol (**11**) (211 mg, 92%). IR ($CHCl_3$): 3600, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.06 (9H, s), 1.13—1.45 (21H, m), 1.62 (1H, 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), 7.65 (5H, m). MS m/z: 483 (M^+). *Anal.* Calcd for $C_{29}H_{44}O_5Si$: C, 69.56; H, 8.86. Found: C, 69.10; H, 8.96.

(2*S*)-9-Acetoxy-2-*tert*-butyldiphenylsiloxydecanal (12) A solution of periodic acid dihydrate (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 ($MgSO_4$). Evaporation of the solvent *in vacuo* gave the aldehyde (**12**) as an oil, which was used for the next step without further purification.

Ethyl (4*S*)-11-Acetoxy-4-*tert*-butyldiphenylsiloxy-2*E*-dodecenoate (13) Triethyl phosphonoacetate (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 ($MgSO_4$). 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 ($CHCl_3$): 1710, 1660, 980 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 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 $C_{32}H_{46}O_5Si$: C, 71.34; H, 8.61. Found: C, 71.27; H, 8.57.

(4*S*)-11-Hydroxy-4-*tert*-butyldiphenylsiloxy-2*E*-dodecenoic 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 with 10% citric acid, and extracted with chloroform. The chloroform extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give a residue, which was subjected to flash

chromatography. Elution with ethyl acetate–hexane (1 : 1) afforded the hydroxy acid (**14**) (481 mg, 62%). IR ($CHCl_3$): 1695, 1650, 980 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 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, 17 Hz), 6.96 (1H, dd J=4.9, 20.5 Hz).

(4*S*,11*R*)-4-*tert*-Butyldiphenylsiloxy-2*E*-dodecen-11-olide (15) and Its 11*S* 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 $KHSO_4$ and brine, and dried ($MgSO_4$). 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 patulolide C (**15**) (100 mg, 30%) and its 11*S* isomer (**16**) (96 mg, 29%). **15**: IR ($CHCl_3$): 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 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 15.7 Hz), 6.77 (1H, dd J=5.5, 15.8 Hz), 7.25—7.43 (5H, m), 7.55—7.68 (5H, m). MS m/z: 393 (M^+). *Anal.* Calcd for $C_{28}H_{38}O_3Si$: C, 74.62; H, 8.50. Found: C, 74.74; H, 8.42. **16**: IR ($CHCl_3$): 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 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, 15.7 Hz), 6.98 (1H, dd, J=3.7, 15.8 Hz), 7.24—7.40 (5H, m), 7.56—7.71 (5H, m). MS m/z: 393 (M^+). *Anal.* Calcd for $C_{28}H_{38}OSi$: C, 74.62; H, 8.50. Found: C, 74.33; H, 8.78.

Patulolide C (2) and Its 11*S* Isomer (17) 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 ($MgSO_4$). 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 patulolide C (**2**) (5 mg, 82%). **2**: $[\alpha]_D$ +6.8° (c=0.15, EtOH). IR ($CHCl_3$): 3300, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.25—1.72 (12H, m), 1.29 (3H, d, J=6.7 Hz), 4.45 (1H, m), 5.03 (1H, m), 6.07 (1H, dd, J=0.4, 16 Hz), 6.85 (1H, m, dd, J=7, 16 Hz). A similar treatment of **16** (15.3 mg, 0.034 mmol) afforded **17** (6 mg, 83%). **17**: $[\alpha]_D$ +3.4° (c=0.05, EtOH). IR ($CHCl_3$): 3700, 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.10—2.04 (12H, m), 1.29 (3H, d, J=6.7 Hz), 4.48 (1H, m), 5.03 (1H, m), 6.03 (1H, dd, J=1.6, 17.7 Hz), 7.02 (1H, dd J=4.4, 20.3 Hz). MS m/z: 194 (M^+). HR-MS m/z: Calcd for $C_{12}H_{20}O_3$: 212.1412 (M^+). Found: 212.1416.

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