

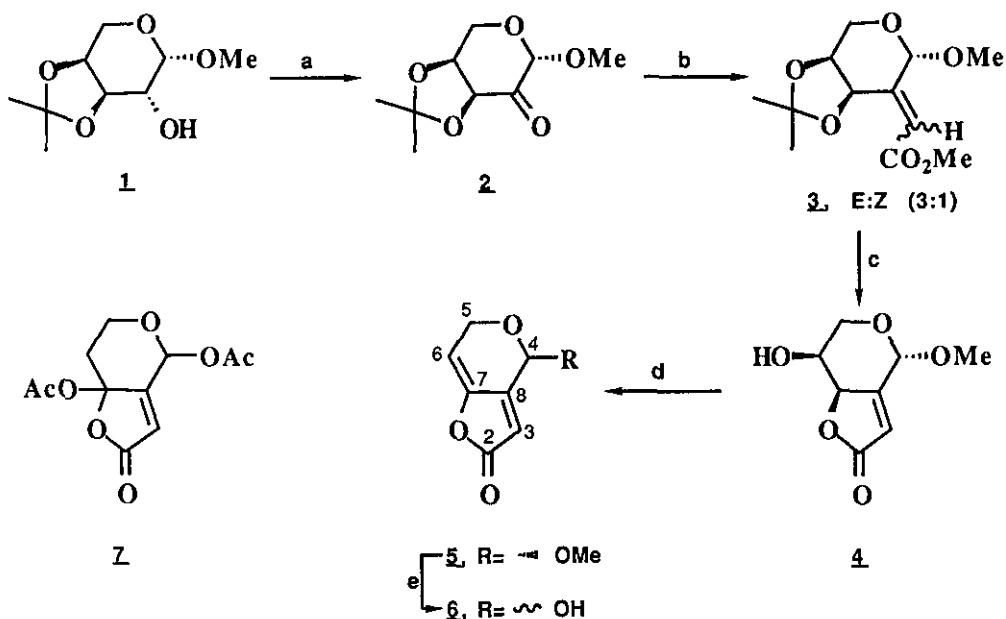
## NEW TOTAL SYNTHESIS OF PATULIN

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**Abstract**—The total synthesis of the mycotoxin patulin from L-arabinose is described.

Patulin (**6**), a potent antibiotic and mycotoxin produced by *Penicillium* and *Aspergillus* species, is synthesized biologically from acetylcoenzyme A<sup>1</sup>. Its  $\alpha,\beta$ -unsaturated five-membered lactone structure was determined by total synthesis by Woodward and Singh<sup>2</sup>, though they only obtained a very low yield. Since then no improvement in the yield nor new synthesis has been reported despite the large number of reports of its detection and isolation from different sources<sup>1</sup>. Here we report a new synthesis of patulin that affords a 23% overall yield from L-arabinose, an inexpensive, readily available aldopentose. Since arabinose has a *cis*-configuration at C-3 and C-4, the hemiacetal ring of **6** with its double bond, can be formed from its pyranoside form.



a) PCC, molecular sieves,  $\text{Cl}_2\text{CH}_2$ ; b)  $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$ , benzene,  $50^\circ\text{C}$ ;  
 c)  $\text{MeOH-HCl}$ , reflux; d)  $\text{MsCl}$ , Py; e)  $\text{TFA:H}_2\text{O}$  (9:1),  $50^\circ\text{C}$

Methyl-3,4-O-isopropylidene- $\alpha$ -L-arabinopyranoside (**1**) was prepared from L-arabinose as previously described<sup>3</sup> except for a modification of the isopropylideneation step that raised the yield to 70% from L-arabinose. Oxidation of **1** with pyridinium chlorochromate (PCC) gave an 87% yield of the ketone **2**. Compound **2** was previously prepared by oxidation of methyl-3,4-O-isopropylidene- $\alpha$ -L-arabinopyranoside by different reagents<sup>4,5</sup>. Wittig olefination of **2** with (carbomethoxymethylene)triphenylphosphorane afforded **3** as a 3:1 mixture of E-Z stereoisomers that could not be separated by chromatography, and hydrolysis of the isopropylidene group of **3** yielded the lactone **4** (68%). When **4** was treated with methanesulphonyl chloride in pyridine at 0°C and left 1 day at room temperature, spontaneous anti-elimination occurred affording (S)-O-methylpatulin (**5**) in 85% yield, whereas in Woodward and Singh's route to patulin, conversion of the diacetate **7** to acetylpatulin occurs in only 1-2% yield. Hydrolysis of the methoxy group of **5** was carried out in 90% aqueous trifluoroacetic acid (TFA) at 50°C during 1 h to afford patulin (**6**) in 79% yield. Lower TFA/H<sub>2</sub>O ratios meant longer reaction times and the formation of polymers.

## EXPERIMENTAL

Melting points were determined using a Büchi apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer 710B spectrophotometer, uv spectra with a Kontron Uvicon 820 spectrophotometer, nmr spectra (in the solvent specified and with Me<sub>4</sub>Si as internal standard) on a Bruker WP-250 operating at 250 MHz (for <sup>1</sup>H) or 62.85 MHz (for <sup>13</sup>C) and mass spectra on a Kratos MS-50 apparatus. Optical rotations were measured on a Perkin-Elmer 141 polarimeter (concentrations are given in g/100 ml). The adsorbent used for flash column chromatography was silica gel (Merck Kieselgel 60, 230-400 mesh) and the plates used for tlc were coated with silica gel (Merck Kieselgel 60 HF<sub>254</sub>). Solutions in organic solvents were dried with anhydrous sodium sulphate; solvents were removed under reduced pressure. Dichloromethane and pyridine were distilled from P<sub>2</sub>O<sub>5</sub> and KOH, respectively. Methyl  $\alpha$ -L-arabinopyranoside was prepared from L-arabinose in 81% yield<sup>3</sup>.

Methyl 3,4-O-isopropylidene- $\alpha$ -L-arabinopyranoside (**1**).- A mixture of anhydrous copper(II) sulphate (30 g) and methyl  $\alpha$ -L-arabinopyranoside (11.5 g, 70.12 mmol) in acetone (AR grade, 500 ml) was stirred with (98%) sulphuric acid (0.5 ml) at room temperature for 1 day. The mixture was neutralized with concentrated aqueous ammonium hydroxide, filtered through a celite plug which was then washed with acetone, and the solvent was removed. The residue was dissolved in dichloromethane (300 ml) and dried, and the solvent was evaporated to give methyl 3,4-O-isopropylidene- $\alpha$ -L-arabinopyranoside (**1**) (12.3 g, 86%), as a syrup which could be used for the next stage without any further purification. [ $\alpha$ ]<sub>D</sub> +200° (c 1.5, chloroform).

Methyl 3,4-O-isopropylidene- $\alpha$ -L-erythro-pentopyranosid-2-ulose (2).- A mixture of methyl 3,4-O-isopropylidene- $\alpha$ -L-arabinopyranoside (1) (12.3 g, 60.3 mmol), pyridinium chlorochromate (27.0 g, 125.3 mmol) and powdered 3Å molecular sieves (21.4 g) in dry dichloromethane (250 ml) was stirred at room temperature for 3 h. The mixture was diluted with ether and filtered through a silica gel plug (eluted with 1:1 ethyl acetate-hexane) to give methyl 3,4-O-isopropylidene- $\alpha$ -L-erythro-pentopyranosid-2-ulose (2) (10.6 g, 87%). mp 88-91°C (lit<sup>5</sup> 87-88°C);  $[\alpha]_D^{25} +148^\circ$  (c 1.33, chloroform); ir  $\nu_{\max}$  (KBr) 1760  $\text{cm}^{-1}$ .

Wittig reaction of methyl-3,4-O-isopropylidene- $\alpha$ -L-erythro-pentopyranosid-2-ulose.- Methyl-3,4-O-isopropylidene- $\alpha$ -L-erythro-pentopyranosid-2-ulose (2) (10.60 g, 52.5 mmol) was dissolved in benzene (150 ml) and stirred at 50°C with (carbomethoxymethylene)triphenylphosphorane (19.9 g, 59.6 mmol) for 6 h. The solvent was removed and the residue was purified by flash chromatography (eluted with 3:7 ethyl acetate-hexane) to afford the 3:1 mixture of E:Z alkene isomers 3 (11.35 g, 84%), as a colourless oil.  $[\alpha]_D^{25} +129.7^\circ$  (c 3.21,  $\text{CHCl}_3$ ); ir  $\nu_{\max}$  (KBr, film) 1740, 1695  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  6.4-3.8 (5H, m), 3.75 (2.2H, s,  $\text{CO}_2\text{CH}_3$ ), 3.72 (0.8H, s,  $\text{CO}_2\text{CH}_3$ ), 3.65 (1H, m), 3.48 (3H, s,  $\text{OCH}_3$ ), 1.54 (2.2H, s,  $\text{CH}_3$ ), 1.51 (0.8H, s,  $\text{CH}_3$ ), 1.40 (3H, s,  $\text{CH}_3$ ); ms m/z (relative intensity) 243 ( $\text{M}^+ - \text{CH}_3$ , 0.3), 227 ( $\text{M}^+ - \text{OMe}$ , 0.7), 126 (100), 69 (58). Found C, 55.62; H, 7.25.  $\text{C}_{12}\text{H}_{18}\text{O}_6$  requires C, 55.81; H, 7.02%.

Synthesis of the lactone 4.- The mixture of alkenes 3 (926 mg, 3.59 mmol) described above was dissolved in methanol-1.2 N hydrochloric acid (49 ml : 1 ml) and refluxed for 1.5 h. The solvent was removed and the residue was partitioned between saturated aqueous sodium bicarbonate solution (10 ml) and dichloromethane (4 x 60 ml). The organic layer was dried and evaporated to give the lactone 4 (453 mg, 68%) as a white solid. mp 129-131°C ( $\text{CH}_2\text{Cl}_2 - \text{Et}_2\text{O}$ );  $[\alpha]_D^{25} +241^\circ$  (c 1.55,  $\text{CHCl}_3$ ); ir  $\nu_{\max}$  (KBr) 3450, 1740  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  6.01 (1H, d,  $J_{3,7} = 1.5$  Hz, H-3), 5.50 (1H, s, H-4), 5.15 (1H, dd,  $J_{7,6} = 3.9$  Hz,  $J_{7,3} = 1.8$  Hz, H-7), 4.38 (1H, m, H-6), 4.02 (1H, d,  $J_{\text{gem}} = 12.7$  Hz, H-5), 3.86 (1H, dd,  $J_{\text{gem}} = 12.7$  Hz,  $J_{5,6} = 2.3$  Hz, H-5'), 3.50 (3H, s,  $\text{OCH}_3$ );  $^{13}\text{C}$  nmr ( $\text{CDCl}_3$ )  $\delta$  172.5 (C-2), 159.6 (C-8), 115.2 (C-3), 95.4 (C-4), 78.2 (C-7), 69.4 (C-6), 61.2 (C-5), 55.2 ( $\text{OCH}_3$ ); ms m/z (relative intensity) 187 ( $\text{M}^+ + 1$ , 0.4), 168 (2), 155 (14), 126 (100), 111 (20), 99 (31), 69 (70). Found C, 51.48; H, 5.36.  $\text{C}_8\text{H}_{10}\text{O}_5$  requires C, 51.61; H, 5.41%.

Synthesis of (S)-O-methylpatulin (5).- Compound 4 (600 mg, 3.23 mmol) was treated with methanesulphonyl chloride (0.37 ml, 4.57 mmol) in dry pyridine (10 ml) at 0°C and left 1 day at room temperature. The solution was concentrated, diluted with chloroform (100 ml) and washed successively with

aqueous hydrochloric acid (3 M, 3 ml) and brine (2 ml). The chloroform layer was then dried and evaporated to give crude (S)-O-methylpatulin (**5**), which was purified by flash chromatography (2:8 ethyl acetate-hexane) to give pure **5** (458 mg, 85%) as a white solid. mp 70-73°C (lit.<sup>6</sup> 69-71°C, racemic **5**).  $[\alpha]_D^{25} +174.7^\circ$  (c 1.04, CHCl<sub>3</sub>); uv  $\lambda_{max}$  (EtOH) 276 nm; ir  $\nu_{max}$  (KBr) 1770, 1750 cm<sup>-1</sup>; <sup>1</sup>H nmr (CDCl<sub>3</sub>)  $\delta$  5.90 (1H, br s, H-3), 5.86 (1H, m, H-6), 5.55 (1H, s, H-4), 4.55 (1H, br d,  $J_{gem} = 17.2$  Hz, H-5), 4.30 (1H, dd,  $J_{gem} = 17.2$  Hz,  $J_{5',6} = 4.4$  Hz, H-5'), 3.49 (3H, s, OCH<sub>3</sub>); <sup>13</sup>C nmr (CDCl<sub>3</sub>)  $\delta$  168.5 (C-2), 148.7 (C-7), 146.0 (C-8), 110.1 (C-3), 107.4 (C-6), 94.3 (C-4), 58.7 (C-5), 55.9 (OCH<sub>3</sub>); ms m/z (rel. int.) 168 (M<sup>+</sup>, 2), 137 (2), 126 (2), 112 (2), 97 (2), 55 (9), 44(100).

**Patulin (6).**- O-Methylpatulin (**5**) (201 mg, 1.19 mmol) was dissolved in 90% aqueous trifluoroacetic acid (30 ml) and heated at 50 °C for 1 h. The solvent was removed (without heating) and the residue was partitioned between saturated aqueous sodium bicarbonate solution (5 ml) and ethyl acetate (5 x 20 ml). The organic layer was dried, evaporated and purified by PTLC (1:1 ethyl acetate-hexane) to give patulin (**6**) (145 mg, 79%), as a white solid. mp 106-7°C (lit.<sup>6</sup> 110-11°C),  $[\alpha]_D^{25} 0^\circ$  (c 0.5, EtOAc); uv  $\lambda_{max}$  (EtOH) 276 nm; ir  $\nu_{max}$  (KBr) 1765, 1750 cm<sup>-1</sup>; <sup>1</sup>H nmr (CDCl<sub>3</sub> + CD<sub>3</sub>OD)  $\delta$  6.02 (2H, br s, H-4, H-3), 5.97 (1H, m, H-6), 4.70 (1H, dd,  $J_{gem} = 17.4$  Hz,  $J_{5,6} = 3.0$  Hz, H-5), 4.41 (1H, dd,  $J_{gem} = 17.4$  Hz,  $J_{5',6} = 4.0$  Hz, H-5'); <sup>13</sup>C nmr ((CD<sub>3</sub>)<sub>2</sub>CO)  $\delta$  169.5 (C-2), 153.0 (C-7), 147.3 (C-8), 110.7 (C-3), 109.0 (C-6), 89.4 (C-4), 59.7 (C-5); MS m/z (rel. int.) 154 (M<sup>+</sup>, 14), 136 (36), 126 (36), 110 (100), 97 (21), 82 (44), 55 (69).

#### ACKNOWLEDGMENTS

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