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# A CONCISE SYNTHESIS OF PATULIN FROM ARABINOSE

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Summary: Conversion of arabinose (5) to the protected ketone (7), followed by Wittig condensation to (9), acid catalysed cyclisation (to 10), and dehydration, provides a brief synthesis of the fungal metabolite patulin (1), produced by Penicillium and Aspergillus sp.

The ylidenebutenolide patulin (1), which is produced by Penicillium and Aspergillus species, occupies a somewhat special place in natural product chemistry. First isolated in the late 1930's, the molecule (which also became known as clavicin, claviformin, clavatin and expansin) aroused immediate interest due to its particularly potent antibiotic and antibacterial properties[1]. Indeed, there is even an early report of field trials with patulin in the treatment of the common cold![2] Although this early interest in the biological activity of patulin abated with the finding that the molecule was also toxic to mammals, in recent years patulin has been recognized as a possible contaminant in food[3] and also as a general plant toxin[4]. Another feature that has put patulin in a special place in natural product chemistry, is the fact that it has been used repeatedly as the model compound to examine the detailed enzymology of polyketide biosynthesis[5]. These studies have shown, that like the related fungal tetronic acid metabolites, penicillic acid (2) and multicolic acid (4), patulin is formed in Nature via oxidative cleavage of a polyketide derived aromatic intermediate, i.e. 6-methylsalicylic acid;[6] cf. (2) and (4) from (3)[7,8].

A cursory inspection of the somewhat simple structure of patulin (1) belies the fact that the molecule contains a range of interesting and sensitive functionality, which is densely packed in a small and reactive bicycle. Indeed these features have combined to make the task of structural determination of patulin a particularly difficult one[9]. Synthetic work with patulin and relatives has also been difficult and limited. No details of an earlier claimed, low yielding, synthesis of patulin acetate[10] have been forthcoming, and only Serratosa[11] has described a synthesis of patulin oxime. We have examined a number of complementary synthetic approaches to patulin, and in this Letter we

outline a particularly concise synthesis of this intriguing molecule, starting from the readily available sugar, arabinose (**5**)(Scheme).

Thus, arabinose (**5**)[12] was first converted into the crystalline benzyl 3,4-O-isopropylidene arabinoside (**6**), m.p. 57-57.5°C ($Et_2O$-petrol)[13] following reaction with benzyl alcohol-dry hydrogen chloride, and treatment of the resulting benzyl ether (m.p. 168-71°C; from ethanol) with acetone in the presence of sulphuric acid. Oxidation of (**6**) using ruthenium dioxide - sodium periodate[14] next led to the ketone (**7**, 66%) which was obtained as a colourless syrup, b.p.145°C at 0.25mm Hg. A one-pot Wittig reaction procedure[15] whereby a solution of the ketone (**7**) in methylene dichloride was reacted with methyl bromoacetate and triphenylphosphine in the presence of propylene oxide then led to a 4:1 mixture of E- and Z-isomers of the enoate (**9**) in a combined yield of 88%[16]. Although the geometrical isomers of (**9**) could be separated by chromatography, the 4:1 mixture was used in the final steps to patulin without diminishing the overall yields. Thus, when a solution of (**9**; 4:1 E/Z) in tetrahydrofuran-water (25:1) was heated under reflux in the presence of perchloric acid (60%; 1.25 hr)[17] chromatography separated the furanone (**10**; 33%) together with the corresponding benzyl ether (**8**; 44%). Subsequent treatment of (**8**), under transfer-hydrogenation conditions (Pd-C, cyclohexene or Pd-C, MeOH, $HCO_2H$) provided further quantities of the furanone (**10**). Finally, treatment of (**10**) with trifluoroacetic acid anhydride and triethylamine in dry tetrahydrofuran (25°C, 10 min) then led to patulin (**1**, 65%) which crystallised from diethyl ether as colourless crystals, m.p.109-110°C. The synthetic material did not separate from natural patulin (m.p. 110-1°C, mixed m.p.109-110°C) in chromatography, and the two samples had superimposable nmr and ir spectra.

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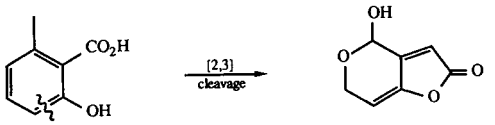
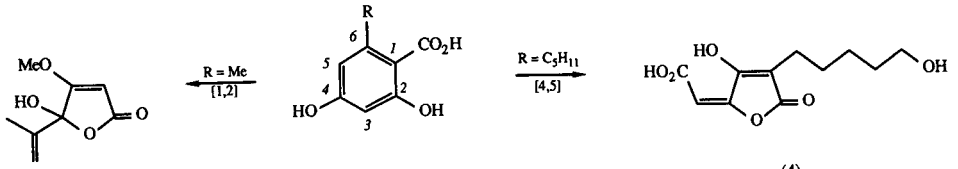
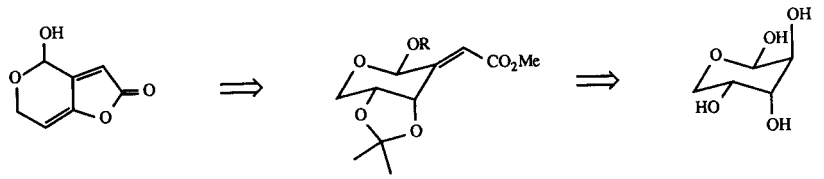


(1)

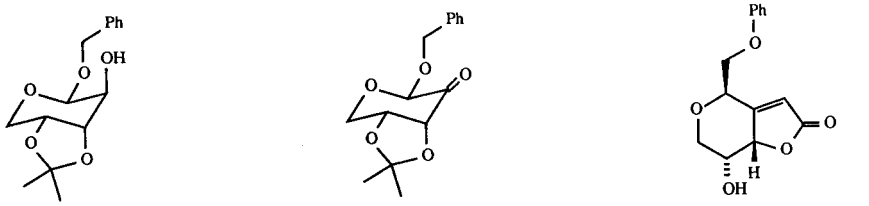


(2) (3) (4)

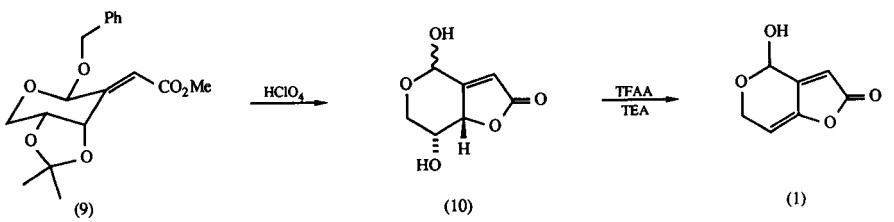


(5)

Scheme



(6) (7) (8)



(9) (10) (1)

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12. The synthetic approach is applicable to both D- and L-arabinose. L-Arabinose was used in the present work because of its lower cost, whereas the formulae are of the D-series, which affords a more simple view of the six-membered ring and its appendages.

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16. Satisfactory spectroscopic data, together with microanalytical and/or mass spectrometry data were obtained for all new compounds. The benzyl 3, 4-isopropylidene arabinoside (**6**) showed: $\delta_H$ 1.36 (Me), 1.53 (Me), 2.37 (d, J 7.6 Hz, CHOH), 3.79 (m, CHOH), 3.91-4.02 (AB of ABX, $J_{AB}$ 13.2 Hz , H-5, 5'), 4.21 (m, HC($OCMe_2$0)CH), 4.55 (d, J 11.8Hz, Ph CHH), 4.79 (d, J 11.8 Hz, PhCHH), 4.93 (d, J 3.6Hz, H-1), 7.35 (m, ArH), and the ketone (**7**) showed: $\nu_{max}$ (KBr) 1757 $cm.^{-1}$, $\delta_H$ 1.38 (Me), 1.45 (Me), 3.98-4.24 (AB of ABX, $J_{AB}$ 13.4 Hz, H-5,5'), 4.54 (ca. dd, H-4), 4.60 (d, J 11.6Hz, PhCHH), 4.67(H-3), 4.78(d, J 11.6 Hz, PhCHH), 4.89 (s,H-1), 7.34 (m, ArH). The E-isomer (**9**), a colourless syrup, showed relevant data: $\delta_H$ 3.60-3.75 (m, H-5,5'), 5.43 (d, J 1.7Hz, H-1), 6.04 (d, J 7.5Hz, H-3), 6.41 (d, J 1.2Hz, :CH); $\delta_C$ 25.4 (q), 26.5(q), 51.6 (q), 63.2 (t),68.7 (d), 69.4 (t), 75.2 (d), 95.8 (d), 110.5, 123.5 (d), 148.1, 165.6; whereas the corresponding Z-isomer of (**9**) displayed data: $\delta_H$ 4.00-4.19 (AB of ABX, $J_{AB}$ 13.26 Hz, H-5,5'), 4.81 (ca.dd, H-3), 6.18 (d, J 2Hz, :CH), 6.50 (s, H-1); $\delta_C$ 26.3(q), 27.9(q), 51.5(q), 58.3(t), 70.1(t), 71.6(d), 73.9(d), 93.9(d), 109.7, 118.3(d), 150.6, 165.5 p.p.m. The major diastereoisomer of (**10**) exhibited $\delta_C$ 75.9(t), 84.2(d), 92.8(d), 103.4(d), 128.1(d), 176.8 and 187.6 p.p.m.

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