Ylidenebutenolide Mycotoxins. Concise Syntheses of Patulin and Neopatulin from Carbohydrate Precursors

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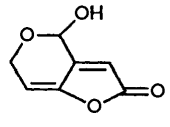
Conversion of arabinose **10** to the protected ketone **13** followed by Wittig condensation to **14**, acid-catalysed cyclisation (to lactone **16**), dehydration and deprotection provides a brief synthesis of the mycotoxic substance patulin **1**, which is produced by *Penicillium* and *Aspergillus* spp. In a similar manner, the biogenetic precursor to patulin, neopatulin **8**, is synthesized from lyxose **25** *via* the key intermediates **24**, **28** and **30**.

Patulin **1** is a mycotoxic substance which is produced by *Penicillium* and *Aspergillus* species.[1] The molecule possesses useful antibiotic and antibacterial properties, but it is also an unwelcome contaminant in food[2] and a general plant toxin.[3] Patulin belongs to the family of naturally occurring ylidenebutenolides,[1b] which are related to the fungal tetronic acid metabolites, *e.g.* penicillic acid **2**[4] and multicolanic acid **3**.[5] Patulin occupies a somewhat special position in natural product chemistry, since it has been used repeatedly as *the* model compound in which to examine the detailed enzymology of polyketide biosynthesis.[6]



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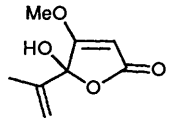

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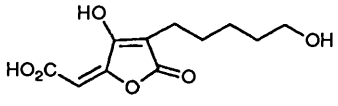

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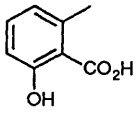

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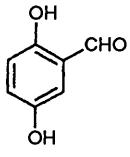

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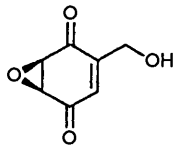

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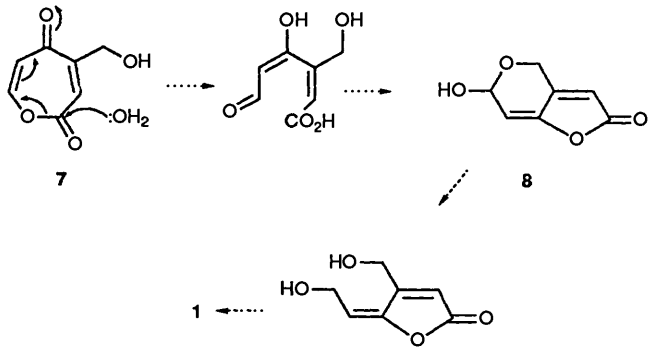
Like penicillic acid **2**[4] and multicolanic acid **3**,[5] patulin is formed in Nature *via* oxidative cleavage of a polyketide-derived aromatic intermediate, *i.e.* the tetraketide 6-methylsalicylic acid **4**. The biosynthetic pathway from precursor **4** to patulin **1** is fascinating and first involves conversion into the epoxy quinone phyllostine **6** *via* monooxygenase-mediated epoxidation of the intermediate gentisaldehyde **5**. Rearrangement of phyllostine **6** next leads to the ylidenebutenolide isomer (**8**; 'neopatulin') of patulin;[7] this rearrangement may occur *via* the novel seven-membered ring lactone compound **7**. The biosynthesis of patulin is then completed following enzymic reduction of neopatulin to (*E*)-ascladiol **9**, and oxidative ring closure of this diol by simple oxidoreductases in the presence of NADPH (Scheme 1).[8]

Examination of the somewhat simple structures of patulin **1** and neopatulin **8** belies the fact that both molecules contain a

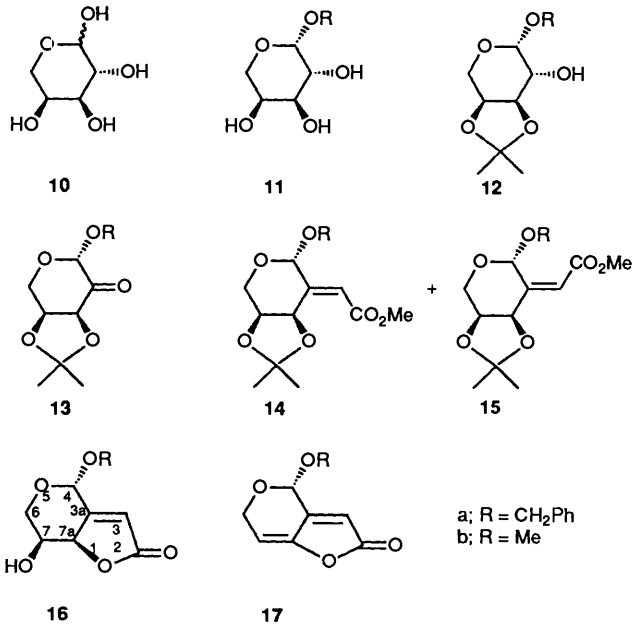


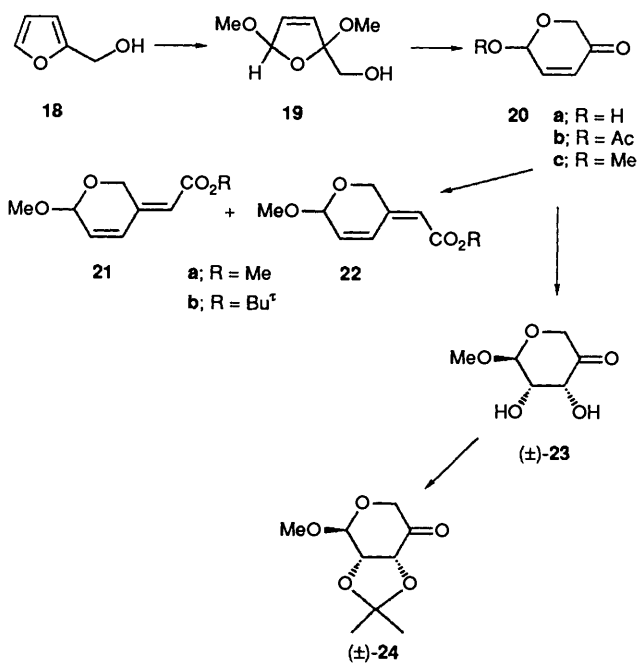
7 **8** **9**

Scheme 1

range of interesting and sensitive functionality, *i.e.* cyclic hemiacetal, enol ester, allylic acetal, conjugated dienoate, densely packed in small and reactive bicyclic ring systems. The two molecules are of course related to one another, both structurally and biogenetically, as redox isomers. Synthetic work with patulin has been limited,[9] and no studies of the synthesis of neopatulin **8** have been described. We have examined a number of complementary synthetic approaches to both patulin **1**[10] and neopatulin **8**, and in this paper we describe concise syntheses of both molecules starting from the readily available sugars arabinose **10**[11] and lyxose **25** respectively.[12]

Thus, in our synthesis of patulin **1**, L-arabinose **10** was first converted into crystalline benzyl 3,4-*O*-isopropylidene-β-L-arabinoside **12a** following reaction with benzyl alcohol–dry hydrogen chloride, and treatment of the resulting benzyl acetal **11a**[13] with acetone in the presence of sulphuric acid. Oxidation of compound **12a** using either pyridinium chlorochromate (PCC)–3 Å sieves[14a] or ruthenium dioxide–sodium periodate[14b] next led to the ketone **13a** which was obtained as a crystalline solid in ⩽90% yield. A Wittig reaction between the ketone **13a** and the phosphorane derived from methyl bromoacetate then led to a 4.6:1 mixture of *E*- and *Z*-isomers of the corresponding enoate, **14a** and **15a**, respectively, in a combined yield of 73%. A one-pot Wittig reaction procedure,[15] whereby a solution of ketone **13a** in methylene dichloride was treated with methyl bromoacetate and triphenylphosphine in the presence of propylene oxide led to a 3.7:1 mixture of esters **14a** and **15a** (88%), whereas a Peterson reaction[16] using methyl (trimethylsilyl)acetate (MTSA) in the presence of lithium diisopropylamide (LDA) produced a 2.7:1 mixture of esters **14a** and **15a** in 89% yield. Interestingly a Wadsworth–Emmons reaction between ketone **13a** and trimethylphosphonoacetate [methyl (dimethoxyphosphonyl)acetate] gave only a 1.2:1





Scheme 2

mixture of esters **14a** and **15a** (90%). Identification of the *E*- and *Z*-isomers **14a** and **15a** in these mixtures followed straightforwardly from examination of their 250 MHz ^{1}H NMR spectra. Thus, the methoxycarbonyl moiety exerts a pronounced deshielding influence on the spatially proximate H-atom (*i.e.* pyranose 3-H in **14** and pyranose 1-H in **15**) of >1.0 ppm relative to the chemical shift in the alternative isomer.

Although the geometrical isomers **14a** and **15a** could be separated by chromatography, enabling complete confirmation of the structural assignments, the mixtures were used in the final steps towards patulin without diminishing the overall yield. Thus, when a solution containing a 4:1 mixture of esters **14a** and **15a** in methanol was heated under reflux in the presence of dil. hydrochloric acid, work-up gave the benzyl acetal **16a** as a powder in 76% yield. Subsequent treatment of compound **16a** with perchloric acid in hot, aq. acetone–tetrahydrofuran (THF),[17] or under transfer-hydrogenation conditions[18] then provided the furanone **16**; R = H. Reaction between esters **14a**/**15a** and hot perchloric acid led to a mixture of acetal **16a** and hemiacetal **16**; R = H.

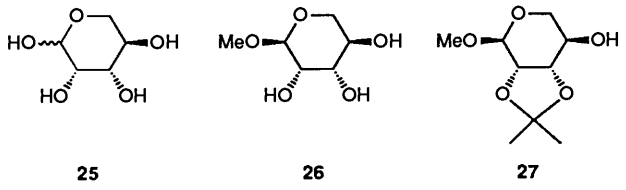
Dehydration of acetal **16a** using methanesulphonyl chloride and triethylamine afforded (*R*)-*O*-benzylpatulin **17a** in 88% yield. Unfortunately, compound **17a** proved to be labile, and various problems were encountered in attempts to effect the necessary deprotection cleanly to secure patulin **1**. However, treatment of hemiacetal **16**; R = H with trifluoroacetic anhydride (TFAA) and triethylamine in dry THF led to patulin **1** (65%), which crystallised with m.p. 109–110 °C. The synthetic material did not separate from natural patulin in chromatography and the two samples had superposable NMR and other spectroscopic data.[19] In an exactly analogous series of reactions, the methyl acetal **11b**[20] derived from arabinose was converted *via* **12b** and **13b** into a *ca.* 3:1 mixture of esters **14b**:**15b** by Wittig reaction with methyl (triphenylphosphoranylidene)acetate. Small amounts of the pure isomers were obtained by HPLC separation. The *E*-isomer **14b** was converted by treatment with aq. hydrochloric acid and methanol at reflux into the lactone **16b**. Under the same conditions the *Z*-isomer **15b** afforded a mixture of compounds containing only traces of lactone **16b**, establishing that stereomutation of the double bond in esters **14**/**15** does not occur. Nevertheless, the mixture of esters **14b** and **15b** was efficiently converted into lactone **16b** in 62% yield; the true yield based upon the amount of *E*-isomer **14b** consumed was 84.5%. Dehydration of acetal **16b** in the presence of methanesulphonyl chloride and dry pyridine, or with TFAA–triethylamine then gave (*S*)-*O*-methylpatulin **17b** as almost colourless crystals, m.p. 83–86 °C,[21] which on treatment with trifluoroacetic acid (TFA) produced patulin **1**, identical with that produced *via* the benzyl acetal series.

We next turned our attention to the synthesis of neopatulin **8**, the biogenetic precursor and redox isomer of patulin. Mindful that our route to patulin involved the systematic destruction of three chiral centres present in the starting material, we first considered a synthetic strategy that was based on achiral precursors. Methyl 2,3-dideoxy-DL-pent-2-enopyranosid-4-ulose **20c** was identified as a suitable intermediate, and it is readily available from furfuryl alcohol **18** (Scheme 2). In our hands the direct route to compound **20c** from the starting alcohol **18** involving oxidation to hemiacetal **20a**[22,23] followed by methylation[23–25] was unreliable and gave very low yields of the pyranosidulose. The indirect route to hemiacetal **20a**, however, *via* the dihydrofuran **19**[24] followed by acetylation (to give **20b**[24]) and then glycosidic acetoxy/methoxy group interchange[26] afforded the required intermediate **20c** in *ca.* 40% yield overall from furfuryl alcohol **18**.

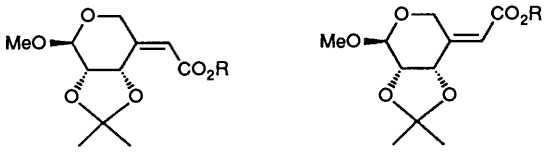
Our initial strategy to neopatulin **8** based on manipulation of intermediate **20c** was first a selective alkoxycarbonylmethylenation to give mainly the *E*-isomer **22**, and then the construction of the butenolide ring through halogenolactonisation either of an ester **22** or of the corresponding free acid. Alternatively, esters **22** might be amenable to regioselective epoxidation or *cis*-dihydroxylation as a prelude to the formation of the butenolide ring. Unfortunately, initial attempts at alkoxycarbonylmethylenation of compound **20c** gave disappointing results in that substantial amounts of the unwanted *Z*-isomer **21** were also obtained. Thus, Wittig reaction of compound **20c** with methyl(triphenylphosphoranylidene)acetate afforded a 2:1 mixture of esters **21a**:**22a**. The Horner–Emmons reaction, using the anion from methyl (dimethylphosphono)acetate with compound **20c**, gave a 1:1.3 mixture, with the *E*-isomer **22a** now the predominant product. This isomer ratio was not altered when we applied the Stille modification[27] of the Horner–Emmons procedure. We were

gratified to find that Peterson olefination of intermediate **20c** with the carbanion derived from t-butyl (trimethylsilyl) acetate (TBTSA)[28] afforded predominantly the *E*-ester **22b** (*E*:*Z* >7:1). Despite having now achieved the necessary stereochemical control (**20c** ⟶ **22b**), this route was subsequently abandoned when it was found that attempted halogenolactonisation of compound **22b** gave unpromising results.

cis-Dihydroxylation of compound **20c**, leading to racemic diol **23** and thence the protected racemate **24**, was achieved based on a literature procedure.[29] However, this route to racemic **24** proved to be much more tedious and considerably less efficient than its synthesis from D-lyxose **25** *via* intermediates **26** and **27**. Again, a Peterson olefination reaction



25 **26** **27**



28 **a**; R = Me **b**; R = Bu^t **29**

30 **31**

between the ketone **24** and the carbanion derived from TBTSA[28] produced almost exclusively the *Z*-isomer **28b** (ratio 88:12) of the expected enoate. By contrast a Wittig reaction approach, which proved so useful in the synthesis of *E*-enoate **14** from keto glycoside **13** in the patulin synthesis, produced largely the alternative *E*-isomer **29a** (>80%). When a solution containing mainly the *Z*-isomer **28b** in dil. hydrochloric acid was heated under reflux, a 65% yield of the hydroxy lactone precursor **30** to neopatulin was obtained as a crystalline solid. Subsequent treatment of compound **30** with methanesulphonyl chloride in pyridine then provided (*S*)-*O*-methylneopatulin **31**, which was smoothly converted into neopatulin **8** on warming to 50 °C in the presence of aq. TFA. The synthetic neopatulin showed identical spectroscopic data with those reported for naturally derived material.

Experimental

All solvents were distilled before use. Light petroleum refers to the fraction boiling in the range 40–60 °C unless stated to the contrary. Solutions of products in organic solvents were dried over anhydrous magnesium sulphate. Fluka Kieselgel G was used for column chromatography, and Fluka HF_{254} silica gel for TLC. A Reichert Kofler micro hot stage was used for m.p. determinations. UV Spectra were determined for ethanol solutions using a Philips PU 8720 spectrophotometer. IR spectra were recorded with a Perkin-Elmer 710B or a Pye Unicam SP3-100 instrument, and were calibrated using a standard polystyrene film. Unless stated otherwise, solutions in deuteriochloroform were used for the determination of NMR spectra. The majority of NMR spectra were recorded with a Bruker WM250 or an AM400 spectrometer and shifts are expressed in ppm downfield from Me_4Si. Signals were singlets unless specified otherwise, and *J*-values are in Hz. Mass spectra, including accurate mass measurements, were determined with a VG Micromass 7070E instrument.

Benzyl β-L-*Arabinopyranoside* **11a**.—A suspension of L-arabinose **10** (47.0 g, 0.313 mol) in freshly distilled benzyl alcohol (240 cm^3) was cooled in an ice–salt-bath and then saturated with dry hydrogen chloride gas. Efficient stirring of the mixture at room temperature for 18 h gave an off-white pulp of crystals. Work-up and purification, as described by Ballou[13a] and by Wold,[13b] gave the title compound **11a** as crystals (56.8 g, 75%), m.p. 169–171 °C (lit.,[13b] 168–171 °C); δ_H[$(CD_3)_2CO$] 3.03 (3 × OH), 3.62 (dd, *J* 12.2 and 2.4, 5-H), 3.75–3.83 (m, 2-, 3- and 4-H), 3.86 (dd, *J* 12.2 and 2.1, 5-H′), 4.52 (d, *J* 12.2, C*H*HPh), 4.74 (d, *J* 12.2, CH*H*Ph), 4.88 (d, *J* 3.3, 1-H) and 7.29–7.43 (m, Ph).

Benzyl 3,4-O-*Isopropylidene*-β-L-*arabinopyranoside* **12a**.—A suspension of benzyl β-L-arabinopyranoside **11a** (16.6 g, 0.069 mol) and anhydrous copper(II) sulphate (65 g, 0.41 mol) in AnalaR acetone (800 cm^3) was stirred under nitrogen, and conc. sulphuric acid (1 cm^3) was then added. The mixture was stirred at room temperature for 20 h, and was then neutralised (to pH 8) with dry, gaseous ammonia, whereupon it turned bright blue. Filtration through Celite and removal of the solvent under reduced pressure left a syrup, which was then dissolved in dry diethyl ether (150 cm^3); the insoluble, unchanged benzyl β-L-arabinopyranoside **11a** (1.00 g) was filtered off. Removal of the ether under reduced pressure afforded crystals. Recrystallisation from diethyl ether–light petroleum, with cooling to −10 °C, gave the acetonide **12a** (15.5 g, 80%), m.p. 57–57.5 °C (lit.,[13b] 59–59.5 °C); δ_H 1.36 (Me), 1.53 (Me), 2.37 (d, *J* 7.6, OH), 3.77–3.82 (m, 2-H), 3.93 (dd, *J* 13.2 and 1.2, 5-H), 4.01 (dd, *J* 13.2 and 2.4, 5-H′), 4.19–4.24 (m, 3- and 4-H), 4.55 (d, *J* 11.8, C*H*HPh), 4.78 (d, *J* 11.8, CH*H*Ph), 4.93 (d, *J* 3.6, 1-H) and 7.31–7.39 (m, Ph).

Benzyl 3,4-O-*Isopropylidene*-β-L-erythro-*pentopyranosid*-2-*ulose* **13a**.—(*a*) PCC (58 g, 0.27 mol) was added portionwise to a stirred solution of the alcohol **12a** (30 g, 0.107 mol) in dry methylene dichloride (500 cm^3) containing a suspension of dry 3 Å molecular sieves powder (100 g);[14a] slight cooling was occasionally necessary, and the reaction was conducted under dry nitrogen. The dark mixture was stirred at room temperature for 1.75 h and was then diluted with dry diethyl ether (550 cm^3). The mixture was filtered through a Kieselguhr pad and the filter pad was then rinsed with dry diethyl ether (2 × 200 cm^3). The dark filtrate was percolated through a 15 × 4 cm column of 60–100 mesh Florisil, which was then eluted with diethyl ether. The solvent was removed under reduced pressure and the residual syrup was then subjected to high vacuum for several hours. The syrup solidified on storage in a refrigerator (26.8 g, 90%) and recrystallisation from diethyl ether–hexane afforded *keto glycoside* **13a** as crystals, m.p. 45–47 °C (this compound has previously only been obtained as a syrup); $[\alpha]_D^{30}$ +239.6° (*c* 0.01, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1753; δ_H 1.39 (Me), 1.46 (Me), 4.10 (d, *J* 13.4, 5-H), 4.29 (dd, *J* 13.4 and 2.1, 5-H′), 4.53 (*ca.* dd, *J* 5.6 and 1.3, 4-H), 4.61 (d, *J* 11.6, C*H*HPh), 4.70 (d, *J* 5.6, 3-H), 4.80 (d, *J* 11.6, CH*H*Ph), 4.90 (1-H) and 7.31–7.40 (m, Ph); δ_C 25.9 (Me), 27.0 (Me), 58.4 (C-5), 69.8 (OCH_2Ph), 75.2 (C-4/3), 77.4 (C-3/4), 98.8 (C-1), 110.1 (CMe_2), 128.0 (aryl C-2,-2′/3,-3′), 128.2 (aryl C-4), 128.4 (aryl C-3,-3′/2,-2′), 135.8 (aryl C-1) and

198.6 (C-2 (Found: C, 64.9; H, 6.4. $C_{15}H_{18}O_5$ requires C, 64.7; H, 6.5%).

(*b*) Hydrated ruthenium dioxide (0.11 g) and water (10 cm^3) were added to a stirred solution of the alcohol **12a** (6.0 g, 21.4 mmol) in carbon tetrachloride (107 cm^3).[14b] A 0.25 mol dm^{-3} aqueous solution of sodium periodate [from $NaIO_4$ (6.1 g) in water (114 cm^3)] was then added dropwise during 1.5 h. The mixture was stirred vigorously during the addition and pH 6–7 was maintained by the co-addition of saturated aq. sodium hydrogen carbonate. On completion of the addition, the aqueous layer had assumed a yellow-green colour. The organic layer was extracted with water (3 × 50 cm^3), dried and evaporated under reduced pressure to afford a pale yellow-brown syrup (4.5 g, 75%). Distillation gave the ketone **13a** as a syrup (3.3 g, 66%), b.p. 145 °C/0.25 mmHg, showing identical spectroscopic data with those described under (*a*).

Benzyl 2-*Deoxy*-3,4-O-*isopropylidene*-2-C[(E)- *and* (Z)-*methoxycarbonylmethylene*]-β-L-erythro-*pentopyranoside* **14a** and **15a**.—(*a*) A solution of the pyranosid-2-ulose **13a** (10 g, 35.9 mmol) and methyl (triphenylphosphoranylidene)acetate (13.7 g, 40.9 mmol) in dry benzene (150 cm^3) was stirred at 55 °C under nitrogen for 6 h. The solvent was then removed under reduced pressure to leave a semi-solid residue. Light petroleum (120 cm^3) was added (to aid the precipitation of triphenylphosphine oxide) and the mixture was kept overnight, and then filtered. The solvent was removed under reduced pressure, and the residue was purified by chromatography over silica gel [eluent light petroleum–ethyl acetate (5:1)] to give the *title alkene* (4.6:1 *E*:*Z* mixture) (8.8 g, 73%), as an oil (Found: C, 64.8; H, 6.9. $C_{18}H_{22}O_6$ requires C, 64.7; H, 6.6%); $[\alpha]_D^{28}$ +168.9° (*c* 0.03, $CHCl_3$).

Careful chromatography over silica gel at 10 °C (eluent CH_2Cl_2) afforded small samples of the pure isomers: E-*isomer* **14a**: λ_{max}/nm 204 (ε_{max} 22 150); $\nu_{max}(CHCl_3)/cm^{-1}$ 2906, 1719, 1664, 1377, 1215br, 1154, 1112, 1088 and 1013; δ_H 1.40 (Me), 1.53 (Me), 3.70 (5-H), 3.71 (5-H′), 3.74 (OMe), 4.34 (dt, *J* 7.4 and 1.4, 4-H), 4.61 (d, *J* 11.9, C*H*HPh), 4.85 (d, *J* 11.9, CH*H*Ph), 5.44 (d, *J* 1.7, 1-H), 6.05 (d, *J* 7.5, 3-H), 6.42 (d, *J* 1.7, =CH) and 7.26–7.36 (m, Ph); δ_C 25.2 (C*Me*), 26.3 (C*Me*), 51.7 (OMe), 63.0 (C-5), 68.4 (C-4), 69.3 (OCH_2Ph), 75.0 (C-3), 95.7 (C-1), 110.5 (CMe_2), 123.7 (=CH), 127.8 (aryl C-4), 127.9 (aryl C-2,-2′/3,-3′), 128.5 (aryl C-3,-3′/-2,-2′), 137.5 (aryl C-1), 148.2 (C-2) and 165.8 (C=O); *m*/*z* ($M^{\cdot+}$ absent by EI); *m*/*z* (FAB) 335 (M + 1, 4%), 333 (2), 319 (3), 259 (12), 228 (13), 227 (88) and 169 (84%).

Z-*Isomer* **15a**: λ_{max}/nm 206 (ε_{max} 17 520); $\nu_{max}(CHCl_3)/cm^{-1}$ 2910, 1712, 1667, 1376, 1160, 1125, 1063 and 1008; δ_H 1.39 (Me), 1.51 (Me), 3.66 (OMe), 4.02 (d, *J* 13.2, 5-H), 4.17 (dd, *J* 13.2 and 2.6, 5-H′), 4.23 (*ca.* dd, *J* 5.4 and 2.1, 4-H), 4.64 (d, *J* 11.5, C*H*HPh), 4.77 (d, *J* 11.5, CH*H*Ph), 4.81 (*ca.* dd, *J* 5.5 and 2.1, 3-H), 6.18 (d, *J* 2.1, =CH), 6.50 (1-H) and 7.30–7.36 (m, Ph); δ_C 26.3 (C*Me*), 27.8 (C*Me*), 51.5 (OMe), 58.3 (C-5), 70.1 (OCH_2Ph), 71.6 (C-4/3), 73.9 (C-3/4), 94.0 (C-1), 109.7 (CMe_2), 118.3 (=CH), 127.9 (aryl C-(4), 128.0 (aryl C-2,-2′/3,-3′), 128.4 (aryl C-3,-3′/2,-2′), 137.3 (aryl C-1), 150.6 (C-2) and 165.5 (C=O); *m*/*z* ($M^{\cdot+}$ absent by EI); *m*/*z* (FAB) 335 (M + 1, 2%), 334 (1), 319 (3), 228 (25), 227 (100), 187 (18), 169 (56) and 139 (23%).

(*b*) A solution of the ketone **13a** (5.00 g, 17.97 mmol), triphenylphosphine (12.30 g, 46.89 mmol) and methyl bromoacetate (4.2 g, 27.45 mmol) in dry methylene dichloride (100 cm^3) was cooled to 0 °C. Propylene oxide (18.95 cm^3, 0.271 mol) was added, the flask was then stoppered, and the contents were stirred at room temperature for 2–4 days.[15] Removal of the solvent under reduced pressure left an oil, which was treated with light petroleum (3 × 50 cm^3) as in (*a*). The oily residue was purified by column chromatography, as in (*a*), to give an oil (5.21 g, 87%) which comprised a 3.7:1 mixture of esters **14a**:**15a**.

(*c*) A stirred solution of LDA (1.5 mol dm^{-3}) in cyclohexane (1.40 cm^3, 2.1 mmol) was diluted with dry THF (1.5 cm^3) under nitrogen. The solution was cooled to −78 °C and then a solution of MTSA (0.29 g, 2 mmol) in dry THF (1 cm^3) was added dropwise during 5 min. The mixture was stirred at −78 °C for 20 min and then a solution of the ketone **13a** (0.50 g, 1.8 mmol) in dry THF (2 cm^3) was added dropwise during 5 min. After a further 1.5 h at −78 °C, the mixture was allowed to warm to room temperature, when saturated aq. ammonium chloride (5 cm^3) was added. The product was extracted into methylene dichloride (4 × 10 cm^3), and the solution was dried, filtered and the solvent removed under reduced pressure. The pale yellow oily residue (0.53 g, 89%) comprised a 2.7:1 mixture of esters **14a**:**15a**.

(*d*) Sodium hydride (0.08 g, of a 60% dispersion in mineral oil; 2.0 mmol) was washed with dry benzene (2 × 2 cm^3) under nitrogen and was then covered with fresh, dry benzene (1 cm^3). A solution of trimethyl phosphonoacetate (0.33 g, 1.8 mmol) in dry benzene (2 cm^3) was added dropwise to the stirred mixture during 10 min. The mixture was then stirred for a further 1 h, and then a solution of the ketone **13a** (0.50 g, 1.8 mmol) in dry benzene (2 cm^3) was added dropwise during 10 min. The mixture was stirred at room temperature for 30 min, then at 50–55 °C for 30 min, and finally at room temperature overnight. The mixture was diluted with chloroform (10 cm^3) and then extracted with water (3 × 8 cm^3). The aq. extracts were re-extracted with chloroform (2 × 10 cm^3) and the combined organic layers were dried, filtered and the solvent was then removed under reduced pressure to leave a pale yellow oil (0.54 g, 90%) which comprised a 1.2:1 mixture of esters **14a**:**15a**.

(4S,7S,7aR)-4-*Benzyloxy*-7-*hydroxy*-7,7a-*dihydrofuro*[3,2-c]-*pyran*-2(4H,6H)-*one* **16a** *and* (4RS,7S,7aR)-4,7-*Dihydroxy*-7,7a-*dihydrofuro*[3,2-c]*pyran*-2(4H,6H)-*one* (**16**; R = H).—(*a*) A solution of a *ca.* 4:1 mixture of the alkenes **14a**/**15a** (0.54 g, 1.62 mmol) in THF (5 cm^3)–water (0.2 cm^3) was treated with 60% perchloric acid[17] (4 drops) and then heated under reflux for 1.25 h. After the solution had cooled, gaseous ammonia was passed into it until it gained pH 8. Silica gel (*ca.* 2–3 g) was added and the solvent was then removed under reduced pressure. The free running powder thus obtained was added to the top of a short column of silica gel; elution with ethyl acetate–light petroleum (2:1→100:0) afforded: (i) the *lactone* **16a** (0.15 g, 36%), m.p. 90–91 °C; $[\alpha]_D^{26}$ +241.6° (*c* 0.3233, $CHCl_3$); λ_{max}/nm 209 (ε_{max} 19 040); ν_{max}(KBr)/cm^{-1} 3415, 3035, 2935, 1789sh, 1745, 1660, 1500, 1086, 1015, 802 and 761; δ_H 3.30 (br s, OH), 3.86 (d, *J* 12.6, 6-H), 4.03 (d, *J* 12.6, 6-H′), 4.36 (br s, 7-H), 4.62 (d, *J* 11.7, C*H*HPh), 4.80 (d, *J* 11.7, CH*H*Ph), 5.16 (d, *J* 3.3, 7a-H), 5.68 (4-H), 5.96 (d, *J* 1.4, 3-H) and 7.31–7.39 (m, Ph); δ_C 61.6 (C-6), 69.5 (C-7), 69.6 (CH_2Ph), 78.4 (C-7a), 93.6 (C-4), 115.2 (C-3), 128.2 (aryl C-2,-2′/3,-3′), 128.3 (aryl C-4), 128.6 (aryl C-3,-3′/2,-2′), 136.3 (aryl C-1), 159.6 (C-3a) and 172.8 (C-2) (Found: C, 63.9; H, 5.5%; $M^{\cdot+}$, 262.0866. $C_{14}H_{14}O_5$ requires C, 64.1; H, 5.4%; M, 262.0841); *m*/*z* 262 (0.5%), 202 (5), 155 (4), 154 (4), 111 (9), 92 (61) and 91 (100); and (ii) the diol **16** (R = H) as a syrupy foam (0.075 g, 27%); λ_{max}/nm 213 (ε_{max} 5950); ν_{max}(KBr)/cm^{-1} 3400br, 2930, 1743, 1630, 1384, 1320, 1243, 1145, 1113, 1084, 1044, 1013, 958, 868, 843 and 802; $\delta_H[(CD_3)_2CO]$ (major diastereoisomer) 3.18 (2 H, OH), 3.71 (dd, *J* 12.6 and 2.3, 6-H), 4.24 (d, *J* 12.6, 6-H′), 4.35 (br m, 7-H), 5.25 (m, 7a-H), 5.96 (m, 4-H) and 5.99 (m, 3-H). Other peaks present in the ^1H spectrum due to the minor diastereoisomer were difficult to assign with certainty; $\delta_C[(CD_3)_2CO]$ (major diastereoisomer) 75.9 (C-6), 84.2 (C-7), 92.8 (C-7a), 103.4 (C-4), 128.1 (C-3), 176.8 (C-3a) and 187.6 (C-2); (minor diastereoisomer) 80.0 (C-6), 82.7 (C-7), 95.2 (C-7a), 106.1 (C-4), 127.9 (C-3), 180.0 (C-3a) and 187.3 (C-2). The ^{13}C NMR spectrum indicated an isomer ratio of *ca.* 3:1.

(*b*). A *ca.* 4:1 mixture of alkenes **14a**/**15a** (2.00 g, 5.982 mmol)

was dissolved in methanol (60 cm^3); 1.2 mol dm^{-3} hydrochloric acid (2 cm^3) was added, and the solution was then heated under reflux for 2 h. After cooling, the bulk of the methanol was removed under reduced pressure and the residue was then dissolved in methylene dichloride (60 cm^3). The solution was extracted with saturated aq. sodium hydrogen carbonate (20 cm^3). The washings were re-extracted with methylene dichloride (3 × 60 cm^3) and the combined CH_2Cl_2 solutions were then dried and filtered. The solvent was removed under reduced pressure to give the lactone **16a** (1.20 g, 76%) as a powder, m.p. 85–88 °C; recrystallisation from diisopropyl ether afforded material of m.p. 90–91 °C.

(*c*). A solution of lactone **16a** (39.5 mg, 0.15 mmol) in THF (10 cm^3)–water (0.4 cm^3)–acetone (0.5 cm^3) and 60% perchloric acid (0.2 cm^3) was heated under reflux for 48 h. After the mixture had cooled, silica gel (*ca.* 1 g) was added and the solvents were then removed under reduced pressure. The dry powder was added to the top of a *short* silica gel column. Elution with ethyl acetate gave the diol (**16**; R = H) (12.6 mg, 49%), which showed identical spectroscopic data with those described under (*a*).

(*d*). A solution of lactone **16a** (42.0 mg, 0.16 mmol) in methanol (10 cm^3)–formic acid (0.4 cm^3) was treated with 10% palladium on carbon (50 mg), and the mixture was then stirred at room temperature, under nitrogen, for 24 h. Filtration and work-up as in (*c*) gave the diol (**16**; R = H) (9.4 mg, 34%), identical with that described under (*a*).

(4R)-4-*Benzyloxyfuro*[3,2-c]*pyran*-2(4H,6H)-*one* [(*R*)-O-*Benzylpatulin*] **17a**.—A solution of methanesulphonyl chloride (0.22 g, 1.91 mmol) in methylene dichloride (2 cm^3) was added during 5 min to a solution of the lactone **16a** (0.445 g, 1.70 mmol) and triethylamine (0.519 g, 5.13 mmol) in dry methylene dichloride (8 cm^3) cooled in an ice-bath. The mixture was stirred at 0 °C for 1 h and was then poured into cold methylene dichloride (400 cm^3). This solution was washed successively with ice–water (20 cm^3), ice-cold 10% hydrochloric acid (20 cm^3), cold, saturated aq. sodium hydrogen carbonate (20 cm^3), and ice-cold brine (20 cm^3), then dried and filtered. Removal of the solvent under reduced pressure gave (*R*)-*O*-benzylpatulin **17a** (0.37 g, 88%) as a pale yellow oil. [The product was highly unstable as a thin evaporated film (*cf.* patulin [19b]), and within 2–3 min became an insoluble light brown solid; it was stable for at least several hours in chloroform (or $CDCl_3$), and was generally handled in solution.] $\lambda_{max}(CHCl_3)$/nm 279 (ε_{max} 10 550) and 233sh (ε_{max} 4200); $\nu_{max}(CHCl_3)/cm^{-1}$ 2917, 2850, 1773, 1750, 1724, 1674, 1368, 1260–1195br, 1168, 1102, 1063, 1035, 1000, 974, 880 and 853; δ_H 4.38 (dd, *J* 16.3 and 4.2, 6-H), 4.59 (d, *J* 16.3, 6-H′), 4.71 (d, *J* 11.8, C*H*HPh), 4.87 (d, *J* 11.8, CH*H*Ph), 5.77 (4-H), 5.87 (m, 7-H), 5.91 (m, 3-H) and 7.36 (m, Ph); δ_C 59.2 (C-6), 70.3 (CH_2Ph), 92.6 (C-4), 107.4 (C-7), 111.0 (C-3), 128.1 (aryl C-2,-2′/3,-3′), 128.2 (aryl C-4), 128.6 (aryl C-3,-3′/2,-2′), 136.7 (aryl C-1), 146.2 (C-7a/3a), 148.9 (C-3a/7a) and 168.5 (C-2).

(4R,S)-4-*Hydroxyfuro*[3,2-c]*pyran*-2(4H,6H)-*one* (*Patulin*) **1**.—(*a*). TFAA (0.529 g, 2.517 mmol) and triethylamine (0.428 g, 4.233 mmol) were added to a solution of the diol **16** (R = H) (0.1969 g, 1.144 mmol) in dry THF (3 cm^3). The mixture was stirred at room temperature for 0.5 h and then poured into ice–water (10 cm^3). The aq. solution was repeatedly extracted with methylene dichloride, and the combined extracts were then dried and filtered. The solution was reduced to low bulk by evaporation under reduced pressure. The residual solution was transferred into a small flask and the remaining solvent was then removed at atmospheric pressure, under nitrogen, by warming (*n.b.* patulin is unstable as a thin film [19b]) to leave a pale yellow oil (0.14 g, 80%). This material contained only one component [TLC; $CHCl_3$–EtOAc–Et_2O (5:2:1), R_f 0.33; and ^1H NMR data identical with those of authentic patulin].

Crystallization from diethyl ether gave patulin **1** as off-white crystals, m.p. 109–110 °C (lit.,[19a] 110–112 °C), mixed m.p. 108.5–110 °C; $[\alpha]_D^{26}$ 0° (*c* 0.1, EtOAc); λ_{max}/nm 275 (ε_{max} 16 900); ν_{max}(KBr)/cm^{-1} 3368, 3130, 3100, 3072, 2960, 2915, 2870, 1774, 1748, 1679, 1630, 1454, 1430, 1389, 1370, 1340, 1275, 1235, 1215, 1165, 1088, 1060, 1043, 1000, 971, 882, 849, 835, 804 and 790; $\delta_H[(CD_3)_2CO]$ 2.93 (br s, OH), 4.38 (ddd, *J* 17.3, 4.07 and 0.5, 6-H), 4.66 (ddd, *J* 17.3, 2.75 and 0.7, 6-H′) and 6.04–6.08 (m, 3-, 4- and 7-H); $\delta_C[(CD_3)_2CO]$ 59.7 (C-6), 89.4 (C-4), 108.9 (C-3/7), 110.7 (C-7/3), 147.2 (C-3a/7a), 152.9 (C-7a/3a) and 169.4 (C-2) (Found: C, 54.3; H, 4.0. Calc. for $C_7H_6O_4$: C, 54.55; H, 3.9%).

(*b*) A solution of (S)-*O*-methylpatulin **17b** (1.0 g, 5.95 mmol) in TFA (100 cm^3)–water (11 cm^3) was heated at 50 °C for 1 h. The mixture was evaporated under reduced pressure at 20 °C to low bulk and then taken up in ethyl acetate (50 cm^3). This solution was extracted with saturated aq. sodium hydrogen carbonate (25 cm^3); the aq. phase was re-extracted with ethyl acetate (4 × 50 cm^3) and the combined extracts and mother liquor were then dried, filtered through a short, 60–100 mesh Florisil column (eluent EtOAc), and evaporated under reduced pressure (but avoiding the formation of a thin film) to give patulin (0.81 g, 90%) as an off-white solid, m.p. 107–108 °C, which showed spectroscopic data identical with those described above.

Methyl β-L-*Arabinopyranoside* **11b**.—An extension of Oldham and Honeyman's method [20] was employed to give an improved yield of product. Thus, β-L-arabinose **10** (100 g) was dissolved in a 1% solution of hydrogen chloride in dry methanol [formed by the careful addition of acetyl chloride (13.5 cm^3) to dry methanol (800 cm^3)]. The solution was heated under reflux for 7 h under nitrogen, then cooled rapidly in a water-bath and stored at 0 °C overnight. The crystals were filtered with suction and washed rapidly with cold methanol (3 × 50 cm^3); after being dried *in vacuo* this first crop (34.73 g) had m.p. 162–168 °C. The combined filtrate and washings were boiled under reflux for 3.5 h, and then methanol was distilled off until *ca.* 250 cm^3 remained. The residual solution was cooled and treated as above to give a second crop (23.65 g), m.p. 158–166 °C. The combined filtrate and washings were reduced in bulk to *ca.* 125 cm^3 by distillation, and then dry diethyl ether (125 cm^3) was added to the cooled residue. Storage at −20 °C afforded a third crop (13.30 g), m.p. 156–166 °C. By extending this procedure of concentration, dilution with diethyl ether, and cooling, three further crops of crystals (11.18, 6.40 and 4.22 g), m.p. 155–167 °C were obtained. The combined crops of the product (93.48 g, 85.5%) were sufficiently pure to pass on to the next stage. Recrystallisation of a sample from ethanol afforded material of m.p. 169–170 °C (lit.,[20] 169–170 °C); $\delta_H(D_2O)$ 3.35 (Me), 3.59 (*ca.* dt, *J* 12.8, 2.0 and 1.3, 5-H), 3.78 (m, 3- and 4-H), 3.81 (d, *J* 12.8, 5-H′), 3.93 (m, 2-H) and 4.77 (d, *J* 1.7, 1-H).

Methyl 3,4-O-*Isopropylidene*-β-L-*arabinopyranoside* **12b**.—A solution of methyl β-L-arabinopyranoside **11b** (50 g, 0.305 mol) in AnalaR acetone (2.2 dm^3), containing a suspension of anhydrous copper(II) sulphate (130.4 g, 0.817 mol), was stirred under nitrogen, and then conc. sulphuric acid (2.2 cm^3) was added. The mixture was stirred for 24 h at room temperature and then dry ammonia gas was passed into the solution until it gained pH 8 (signalled by an abrupt change to a bright blue colour). The mixture was filtered through a Kieselguhr pad which was then washed with acetone. The combined organic extracts were evaporated to dryness under reduced pressure and the syrupy residue was then taken up in methylene dichloride (600 cm^3). This solution was dried, and the solvent was then removed under reduced pressure to leave the title product **12b** as a syrup (56.05 g, 90%), which was used in the next stage without further purification; δ_H 1.37 (Me), 1.54 (Me), 2.35 (d, *J* 6.7, OH),

3.45 (OMe), 3.77 (m, 2-H), 3.92 (d, *J* 12.5, 5-H), 3.94 (d, *J* 12.5, 5-H′), 4.18 (m, 3-H), 4.23 (*ca.* dt, *J* 5.9 and 1.9, 4-H) and 4.72 (d, *J* 3.6, 1-H); δ_C 26.1 (C*Me*), 28.0 (C*Me*), 55.5 (OMe), 59.1 (C-5), 70.2 (C-2/3/4), 73.2 (C-3/4/2), 76.1 (C-4/2/3), 98.4 (C-1) and 108.9 (*C*Me_2).

Methyl 3,4-O-*Isopropylidene*-β-L-erythro-*pentopyranosid*-2-*ulose* **13b**.—(*a*) Dimethyl sulphoxide (51 cm^3, 0.72 mol) was added during 15 min to a stirred solution of oxalyl dichloride (25.5 cm^3, 0.2923 mol) in dry methylene dichloride (750 cm^3) at −60 °C under nitrogen. After 30 min a solution of the alcohol **12b** (45 g, 0.22 mol) in dry methylene dichloride (150 cm^3) was added to the stirred mixture during 30 min. The mixture was stirred for 2 h and then dry triethylamine (151.5 cm^3, 1.09 mol) was added during 15 min. After a further 10 min the cooling bath was removed, the mixture was allowed to regain room temperature, and then water (250 cm^3) was added to the stirred mixture. After 5 min the mixture was poured into saturated aq. sodium hydrogen carbonate (500 cm^3), the organic layer was separated, and the aq. layer was then extracted with methylene dichloride (3 × 250 cm^3). The combined organic layers were washed with saturated brine (2 × 250 cm^3), then dried and filtered, and the solvent was evaporated off under reduced pressure. The unpleasant smelling light yellow crystalline residue was recrystallised from light petroleum (boiling range 80–100 °C) to give the ketone **13b** (34.8 g, 78%) as crystals, m.p. 95–98 °C (lit.,[30,31] for D-sugar 87–88 °C and 98–99 °C); $[\alpha]_D^{28}$ +138.3° (*c* 0.08, $CHCl_3$).

(*b*). The same procedure as that described for the preparation of the ketone **13a** [method (*a*)] was employed, involving reaction of the alcohol **12b** (22.0 g, 0.11 mol) in dry methylene dichloride (450 cm^3) with PCC (50.0 g, 0.23 mol) in the presence of dry, powdered 3 Å molecular sieves (75 g).[14a] Following similar work-up, the ketone **13b** was obtained as crystals (19.8 g, 91%), m.p. 87–90 °C. Recrystallisation from di-isopropyl ether or light petroleum (80–100 °C) gave *compound* **13b** as crystals, m.p. 99.5–100.5 °C; δ_H 1.40 (Me), 1.47 (Me), 3.49 (OMe), 4.08 (d, *J* 13.4, 5-H), 4.23 (dd, *J* 13.4 and 1.9, 5-H′), 4.54 (*ca.* d, *J* 5.0, 4-H), 4.69 (d, *J* 5.7, 3-H) and 4.70 (1-H); δ_C 26.0 (C*Me*), 27.0 (C*Me*), 55.6 (OMe), 58.2 (C-5), 75.3 (C-4/3), 77.6 (C-3/4), 100.8 (C-1), 110.3 (*C*Me_2) and 198.8 (C-2) (Found: C, 53.3; H, 7.1. $C_9H_{14}O_2$ requires C, 53.5; H, 7.0%).

Methyl 2-*Deoxy*-3,4-O-*isopropylidene*-2-C-[(E)- *and* (Z)-*methoxycarbonylmethylene*]-β-L-erythro-*pentopyranoside* **14b** and **15b**.—Reactions for the methoxycarbonylmethylenation of the ketone **13b** were investigated which were strictly analogous with those methods used, (*a*)–(*d*), for the preparation of esters **14a** and **15a**. Method (*a*) afforded a 2.75:1 mixture of products **14b**:**15b** as an oil (80%) after flash chromatography. Method (*b*), the 'one-pot' Wittig reaction of the ketone **13b** in methylene dichloride solution, gave a 1.7:1 mixture of products **14b**:**15b** as an oil (90%) after flash chromatography. Method (*d*) gave a 1:2 mixture of products **14b**:**15b** as a pale yellow oil (91%). Method (*c*), the Peterson reaction of ketone **13b** with the lithium enolate of MTSA, afforded a 2.7:1 mixture of *products* **14b**:**15b** as a pale yellow oil (92%); $[\alpha]_D^{28}$ +177° (*c* 0.05, $CHCl_3$) (Found: C, 55.8; H, 7.2. $C_{12}H_{18}O_6$ requires C, 55.8; H, 7.0%).

The isomers were not separated; λ_{max}/nm 200 (ε_{max} 14 320); ν_{max}(film)/cm^{-1} 1730, 1670 and 1250. E-*isomer* **14b**: δ_H 1.40 (Me), 1.54 (Me), 3.47 (OMe), 3.62 (dd, *J* 13.0 and 1.9, 5-H), 3.67 (dd, *J* 13.0 and 1.3, 5-H′), 3.75 (CO_2Me), 4.33 (*ca.* dt, *J* 7.5, 1.5 and 1.6, 4-H), 5.23 (d, *J* 1.8, 1-H), 6.03 (d, *J* 7.5, 3-H) and 6.35 (dd, *J* 1.8 and 0.5, =CH).

Z-*Isomer* **15b**: δ_H 1.39 (Me), 1.50 (Me), 3.47 (OMe), 3.72 (CO_2Me), 4.00 (d, *J* 13.2, 5-H), 4.10 (dd, *J* 13.2 and 2.4, 5-H′), 4.23 (*ca.* dd, *J* 5.5 and 1.6, 4-H), 4.77 (dd, *J* 5.5 and 2.1, 3-H), 6.18 (dd, *J* 2.2 and 0.4, =CH) and 6.26 (1-H).

(4S,7S,7aR)-7-*Hydroxy*-4-*methoxy*-7,7a-*dihydrofuro*[3,2-c]-*pyran*-2(4H,6H)-*one* **16b**.—A solution of a *ca.* 2.75:1 mixture of compounds **14b**:**15b** (8.0 g, 0.03 mol) in methanol (350 cm^3) was treated with 2 mol dm^{-3} hydrochloric acid (4.8 cm^3)–water (3.2 cm^3), and then heated under reflux, under nitrogen, for 2.75 h. The majority of the solvent was removed by evaporation under reduced pressure, and the residue was then taken up in methylene dichloride (150 cm^3). The solution was extracted with saturated aq. sodium hydrogen carbonate (100 cm^3) and the aq. layer was then re-extracted with methylene dichloride (3 × 150 cm^3). The combined organic solutions were dried, and the solvent was then removed under reduced pressure to give the *hydroxy lactone* **16b** (3.6 g, 62%) as a crystalline solid, m.p. 134–136 °C (from EtOAc–light petroleum); $[\alpha]_D^{24}$ +258.7° (*c* 0.29, $CHCl_3$); λ_{max}/nm 215 (ε_{max} 10 500); ν_{max}(KBr)/cm^{-1} 3480 and 1750; δ_H 3.03 (br s, OH), 3.49 (OMe), 3.85 (dd, *J* 12.7 and 2.3, 6-H), 4.00 (d, *J* 12.7, 6-H′), 4.38 (br m, 7-H), 5.15 (dd, *J* 4.0 and 1.9, 7a-H), 5.50 (4-H) and 6.01 (d, *J* 1.7, 3-H); δ_C 55.3 (OMe), 61.3 (C-6), 69.6 (C-7), 78.3 (C-7a), 95.5 (C-4), 115.3 (C-3), 159.7 (C-3a) and 172.6 (C-2) [Found: ($M^{\bullet+}$ − H_2O) 168.0388. $C_8H_8O_4^{\bullet+}$ requires *m/z* 168.0423]; *m/z* (%) 168 (55), 139 (68), 137 (50), 127 (11), 126 (100), 98 (24), 97 (25), 81 (24) and 69 (79) (Found: C, 51.7; H, 5.5. $C_8H_{10}O_5$ requires C, 51.6; H, 5.4%).

(S)-4-*Methoxyfuro*[3,2-c]*pyran*-2-(4H,6H)-*one* [(S)-O-*Methylpatulin*] **17b**.—(*a*) The hydroxy lactone **16b** (1.00 g, 5.37 mmol) was dissolved in dry pyridine (17 cm^3) and then redistilled methanesulphonyl chloride (0.7 cm^3, 9.04 mmol) was added. The mixture was stirred under dry nitrogen for 24 h, and then reduced in bulk by evaporation under reduced pressure. The residue was taken up in chloroform (100 cm^3) and the solution was extracted successively with 2 mol dm^{-3} hydrochloric acid (4 cm^3) and saturated brine (3 cm^3). The organic layer was dried, and the filtrate was then allowed to percolate through a short column of Florisil, and eluted with chloroform. Evaporation of the solvent afforded the crude product **17b** (0.84 g, 93%); recrystallisation from light petroleum (80–100 °C) or di-isopropyl ether gave (*S*)-*O*-methylpatulin **17b** (0.72 g, 80%) as an off-white solid, m.p. 83–86 °C [lit.,[21] 69–71 °C for racemic **17b**; the failure of these authors to effect purification by recrystallisation without decomposition is possibly ascribed to an inappropriate choice of solvent or, more likely in view of the lability of their material, the carry-through of an impurity in their preparation. Also, the product may not be stable as a thin evaporated film].

(*b*) The hydroxy lactone **16b** (4.0 g, 0.022 mol) was dissolved in dry THF (80 cm^3) and then TFAA (5.00 g, 0.024 mol) and dry triethylamine (5.50 g, 0.054 mol) were added. The mixture was stirred under nitrogen for 1 h at room temperature, and then the solution was reduced in bulk by evaporation under reduced pressure at room temperature. The residue was taken up in chloroform (80 cm^3) and the solution was then extracted successively with 2 mol dm^{-3} hydrochloric acid (25 cm^3), saturated aq. sodium hydrogen carbonate (25 cm^3), and water (25 cm^3). The dried solution was passed through a short column of Florisil, and the solvent was removed at reduced pressure to leave an off-white, oily solid (3.2 g, 89%). Recrystallisation as in (*a*) gave crystals of (S)-O-*methylpatulin* **17b**, m.p. 86–88 °C (2.85 g, 79%); $[\alpha]_D^{29}$ +176.9° (*c* 0.796, $CHCl_3$); λ_{max}/nm 277 (ε_{max} 14 400); ν_{max}(KBr)/cm^{-1} 3112, 3062, 3010, 1764sh, 1748, 1673, 1631, 1280, 1222 and 1186; δ_H 3.57 (OMe), 4.39 (dd, *J* 17.1 and 4.5, 6-H), 4.59 (ddd, *J* 17.1, 2.7 and 1.1, 6-H′), 5.61 (4-H), 5.92 (*ca.* quint, *J* 2.3, 7-H) and 5.98 (d, *J* 0.8, 3-H); δ_C 56.3 (OMe), 59.0 (C-6), 94.6 (C-4), 107.5 (C-7/3), 111.2 (C-3/7), 146.2 (C-7a/ 3a), 148.8 (C-3a/7a) and 168.7 (C-2) (Found: C, 56.9; H, 4.75. $C_8H_8O_4$ requires C, 57.1; H, 4.8%).

2,3-*Dideoxy*-DL-*pent*-2-*enopyranos*-4-*ulose* **20a**.—Of the three

main literature procedures available for the preparation of compound **20a** from furfuryl alcohol **18** it was found that the two direct, one-step, oxidative methods using NBS–water[22] or a peroxyacid (*i.e.*, *m*-chloroperbenzoic acid or peracetic acid)[23] were unreliable and unsuitable for all but very small-scale work. Hence the two-step procedure of Achmatowicz *et al.*[24] to compound **20a** *via* 2-(hydroxymethyl)-2,5-dimethoxy-2,5-dihydrofuran **19** was employed, with minor modification of the second step **19** ⟶ **20a** to simplify isolation of the product.

A solution of 2-(hydroxymethyl)-2,5-dimethoxy-2,5-dihydrofuran **19** (9.27 g, 0.06 mol) in 2% w/w sulphuric acid (18.6 g) was stirred magnetically, at room temperature, for 30 min [^{1}H NMR (D_2O–D_2SO_4) spectroscopy indicated that the reaction was complete in 15 min]. Solid sodium chloride was then added to the aq. solution until no more would dissolve and the mixture was then extracted with chloroform (6 × 30 cm^3). The organic layer was dried, and the solvent was then removed under reduced pressure to leave an off-white solid (6.28 g, 95%) which was sufficiently pure to be passed on to the next stage. Recrystallisation from diethyl ether–hexane afforded enone **20a** as crystals, m.p. 58–59 °C (lit.,[24] 54–58 °C).

Methyl 2,3-*Dideoxy*-DL-*pent*-2-*enopyranosid*-4-*ulose* **20c**.—In our hands, the direct methylation of hemiacetal **20a** by reaction with $(MeO)_3CH$–$SnCl_4$ in dry diethyl ether[24] or methyl iodide–Ag_2O[23,25] gave the glycoside **20c** in variable, but low, yield (10–45%). The published indirect route was found to be much more satisfactory, and involved the acetylation of compound **20a** to give compound **20b** by means of Ac_2O–pyridine[24] (~85%), followed by glycosidic acetoxy/methoxy-group interchange by means of methanol–$SnCl_4$ in ethylene dichloride (~70%).[26] The product **20c** was obtained as an oil, b.p. 75–80 °C/13 mmHg in 55–60% yield from hemiacetal **20a**.

Methyl 4-[(E)- *and* (Z)-*Alkoxycarbonylmethylene*]-2,3,4-*trideoxy*-DL-*pent*-2-*enopyranosides* **21** *and* **22**.—These olefins were prepared by the alkoxycarbonylmethylenation of keto glycoside **20c** by the use of the appropriate Wittig, Horner–Emmons, modified[27] Horner–Emmons, and Peterson reagents. Experimental conditions were identical with those used in the preparation of compounds **14a**/**15a** (see above), **28b**/**29b** (see later), or, for the modified Horner–Emmons reaction, the published[27] general procedure was used. Mixtures of products **21** and **22** were obtained (yield 85–95%), but their compositions varied as follows: $Ph_3P{=}CHCO_2Me$ (**21a**:**22a** 2:1); $(MeO)_2P(O)\bar{C}HCO_2Me$ (**21a**:**22a** 1:1.3); $(CF_3CH_2O)_2P(O)\bar{C}HCO_2Me$ (**21a**:**22a** 1:1.3); $Me_3Si\bar{C}HCO_2Bu^t$ (**21b**:**22b** >7:1). These mixtures were not separated but their compositions were determined from their ^{1}H NMR spectra. For example, the *Z*-isomer **21a** showed δ_H 3.47 (CHO*Me*), 3.72 (CO_2Me), 4.76 (dd, *J* 16.8 and 2.3, 5-H), 4.97 (d, *J* 3.0, 1-H), 5.22 (dd, *J* 16.8 and 1.6, 5-H′), 5.62 (m, =C*H*′CO_2Me), 6.10 (*ca.* dd, *J* 10.0 and 3.0, 2-H) and 6.31 (d, *J* 10.0, 3-H); and the *E*-isomer **22a** showed δ_H 3.46 (CHO*Me*), 3.72 (CO_2Me), 4.08 (d, *J* 14.2, 5-H), 4.62 (dd, *J* 14.2 and 1.8, 5-H′), 4.97 (d, *J* 3.0, 1-H), 5.62 (m, =C*H*CO_2Me), 6.10 (*ca.* dd, *J* 10.2 and 3.0, 2-H) and 7.61 (d, *J* 10.2, 3-H).

Methyl β-DL-erythro-*Pentopyranosid*-4-*ulose* (±)-**23** *and Methyl* 2,3-O-*Isopropylidene*-β-DL-erythro-*pentopyranosid*-4-*ulose* (±)-**24**.—The conversion of enone **20c** into compound (±)-**24** *via* the racemate (±)-**23** was achieved by a published procedure,[29] and the yields and physical properties were as stated.

Methyl α-D-*Lyxopyranoside* **26**.—D-Lyxose **25** (16 g, 0.107 mol) was added to a 1.5% solution of hydrogen chloride in dry methanol [prepared by the addition of freshly distilled acetyl chloride (5.72 cm^3) to dry methanol (230 cm^3) under nitrogen]. The mixture was heated under reflux under nitrogen for 1.5 h, then cooled by immersion in cold water and adjusted to pH 8 by the addition of methanolic sodium methoxide [from sodium (2.3 g, 0.100 g-atom) and dry methanol (60 cm^3)]. Removal of the solvent under reduced pressure left a yellow oil (17.8 g), which was dissolved in hot ethyl acetate (50 cm^3) and filtered to remove sodium chloride. Removal of the solvent under reduced pressure left an oily solid; crystallisation from ethyl acetate, with storage for several days, gave the ether **26** (15.1 g, 86%) as platelets, m.p. 104–106 °C (lit.,[32] 108–109 °C); δ_H[$(CD_3)_2CO$] 3.32 (OMe), 3.35–3.90 (m, 2-, 3- and 4-H, and 5-H_2), 3.82 (3 × OH) and 4.55 (d, *J* 3, 1-H).

Methyl 2,3-O-*Isopropylidene*-α-D-*lyxopyranoside* **27**.—A mixture of the methyl ether **26** (16.8 g, 0.1 mol), anhydrous copper(II) sulphate (41.7 g, 0.26 mol) and AnalaR acetone (700 cm^3) was stirred under nitrogen, and conc. sulphuric acid (0.7 cm^3) was then added. The mixture, which assumed a buff colour, was stirred at room temperature for 24 h. Neutralisation and work-up, as in the preparation of compound **12a**, gave a pale yellow syrup (20 g) which solidified upon refrigeration. This material was sufficiently pure to pass on to the next stage; recrystallisation from ethyl acetate–hexane gave off-white crystals (16.6 g, 81%) of the title product **27**, m.p. 48–51 °C (lit.,[32] 40–41 °C and, for the α-L-compound,[33] 51.5–52.5 °C); δ_H 1.35 (Me), 1.49 (Me), 3.43 (OMe), 3.65 (OH), 3.56–3.97 (m, 5-H_2), 3.97–4.30 (m, 2-, 3- and 4-H) and 4.64 (d, *J* 3, 1-H).

Methyl 2,3,-O-*Isopropylidene*-β-L-erythro-*pentopyranosid*-4-*ulose* **24**.—A mixture of the alcohol **27** (20.0 g, 0.098 mol), PCC (53.0 g, 0.246 mol) and freshly dried powdered 3 Å molecular sieves (100 g),[14a] in dry methylene dichloride (500 cm^3), was stirred vigorously for 1 h. The dark coloured mixture was diluted with dry diethyl ether (900 cm^3) and the resulting solution was then filtered through a plug of Kieselguhr. The solvent was removed under reduced pressure to leave a dark oil, which was purified by passage down a short column of silica gel with dry diethyl ether as eluent. Evaporation of the solvent under reduced pressure gave a pale yellow oil (17.2 g, 87%);[34] ν_{max}(film)/cm^{-1} 1745; δ_H 1.38 (Me), 1.51 (Me), 3.47 (OMe), 4.14 (m, 5-H_2), 4.41 (m, 2- and 3-H) and 4.78 (br s, 1-H).

Methyl 4-*Deoxy*-2,3-O-*isopropylidene*-4-[(E)- *and* (Z)-*Methoxycarbonylmethylene*]-β-L-erythro-*pentopyranoside* **29a** *and* **28a**.—Methoxycarbonylmethylenation of the ketone **24** was investigated by methods (*a*), (*b*) and (*c*) as employed for the preparation of the analogous esters **14a** and **15a**; identical relative molecular quantities, reaction conditions, and work-up were employed. In all of the reactions a pale yellow oil (85–93%) comprising a mixture of esters **29a** and **28a** was obtained. Isomer ratios were determined from high-field ^{1}H NMR integrals: methods (*a*) and (*b*): (**29a**:**28a** *ca.* 5:1); method (*c*): (**29a**:**28a** 1:1.3). These mixtures were not separated. The *E*-isomer **29a** showed δ_H 1.31 (Me), 1.44 (Me), 3.36 (OMe), 3.64 (CO_2Me), 4.09 (dd, *J* 6.7 and 2.1, 2-H), 4.52 (d, *J* 2.1, 1-H), 4.61 (d, *J* 6.7, 3-H), 4.68 (dd, *J* 17.0 and 1.8, 5-H), 4.85 (dd, *J* 17.0 and 1.2, 5-H′) and 5.98 (*ca.* d, *J* 1.3, =CH).

Z-Isomer **28a** showed δ_H 1.35 (Me), 1.46 (Me), 3.35 (OMe), 3.66 (CO_2Me), 4.00 (dd, *J* 6.8 and 3.0, 2-H), 4.08 (d, *J* 14.2, 5-H), 4.43 (dd, *J* 14.2 and 1.9, 5-H′), 4.48 (d, *J* 3.0, 1-H), 5.87 (d, *J* 6.8, 3-H) and 5.86 (=CH).

Methyl 4-[(E)- *and* (Z)-*t*-*Butoxycarbonylmethylene*]-4-*deoxy*-2,3-O-*isopropylidene*-β-L-erythro-*pentopyranoside* **29b** *and* **28b**.—A stirred solution of freshly distilled diisopropylamine (6.25 g, 0.05 mol) in dry THF (150 cm^3) under dry argon was cooled to 0 °C, and a 2.5 mol dm^{-3} solution of butyllithium in hexane (20 cm^3) was then added slowly by means of a syringe.

The mixture was stirred at 0 °C for 10 min, and then was cooled to −78 °C. A solution of TBTSA (9.4 g, 0.05 mol)[28] in dry THF (75 cm^3) was added dropwise followed, after a period of 20 min, by the dropwise addition of a solution of the ketone **24** (10 g, 0.049 mol) in dry THF (75 cm^3). The mixture was stirred at −78 °C for a further 1.5 h, and then the mixture was allowed to regain room temperature before the gradual addition of saturated aq. ammonium chloride (300 cm^3). The resulting suspension was extracted with methylene dichloride (4 × 50 cm^3), and the organic layers were dried, filtered, and evaporated under reduced pressure to leave a yellow oil. Purification by chromatography on a short column of silica gel [eluent light petroleum–ethyl acetate, (7:1)] afforded an oil (13.2 g, 88%), comprising (^{1}H NMR analysis) a 7.2:1 mixture of *Z*:*E* isomers **28b**:**29b**; $[\alpha]_D^{20}$ −4.2° (*c* 0.072, $CHCl_3$); ν_{max}(film)/cm^{-1} 1715, 1665, 1375, 1255, 1145 and 1095; which was not resolved. The *Z*-isomer **28b** showed δ_H 1.43 (Me), 1.49 (CMe_3), 1.55 (Me), 3.44 (OMe), 4.07 (dd, *J* 6.7 and 3.1, 2-H), 4.12 (d, *J* 14.5, 5-H), 4.46 (dd, *J* 14.5 and 2.0, 5-H′), 4.54 (d, *J* 2.9, 1-H), 5.86 (br s, =CH) and 5.90 (d, *J* 6.7, 3-H); δ_C 27.0 (Me), 28.4 (Me), 29.5 (CMe_3), 57.4 (OMe), 65.2 (C-5), 69.6 (C-2), 77.5 (C-3), 82.4 (CMe_3), 102.1 (C-1), 111.9 (CMe_2), 123.0 (=CH), 147.8 (C-4) and 165.7 (C=O).

E-Isomer **29b** showed δ_H 1.38 (Me), 1.47 (CMe_3), 1.51 (Me), 3.43 (OMe), 4.13 (dd, *J* 7.0 and 3.4, 2-H), 4.58 (d, *J* 2.1, 1-H), 4.65 (d, *J* 7.0, 3-H), 4.79 (dd, *J* 17.0 and 2.1, 5-H), 4.85 (dd, *J* 17.0 and 2.2, 5-H′) and 5.94 (m, =CH); δ_C 26.7 (Me), 28.1 (Me), 29.5 (CMe_3), 57.3 (OMe), 61.5 (C-5), 69.6 (C-2), 76.2 (C-3), 82.0 (CMe_3), 101.6 (C-1), 111.9 (CMe_2), 122.3 (=CH), 150.9 (C-4) and 166.2 (C=O).

(6S,7S,7aS)-7-*Hydroxy*-6-*methoxy*-7,7a-*dihydrofuro*[3,2-c]-*pyran*-2(4H,6H)-*one* **30**.—Hydrochloric acid (2 mol dm^{-3}; 3 cm^3) was added to a solution of the 7.2:1 mixture of esters **28b**:**29b** (3 g, 0.01 mol) in methanol (147 cm^3), and the mixture was then heated under reflux for 1.5 h. The solvent was removed under reduced pressure and the residue was then extracted into methylene dichloride (3 × 100 cm^3). The combined extracts were washed with saturated aq. sodium hydrogen carbonate (30 cm^3), then dried and evaporated to leave a yellow oil. Purification by chromatography over silica gel [light petroleum–ethyl acetate (1:1)] gave the *hydroxy lactone* **30** (1.12 g, 65%) as a crystalline solid, m.p. 111–112 °C; $[\alpha]_D^{20}$ +35.3° (*c* 0.034, $CHCl_3$); λ_{max}(EtOH)/nm 216, 214 and 210; ν_{max}(KBr)/cm^{-1} 3400br, 1743, 1655, 1382, 1123 and 1056; ν_{max}($CHCl_3$)/cm^{-1} 3382, 3093 and 1757; δ_H 2.99 (br s, OH), 3.49 (OMe), 4.35 (br m, 7-H), 4.46 (d, *J* 13.2, 4-H), 4.56 (d, *J* 13.2, 4-H′), 4.86 (*ca.* d, *J* 2.1, 6-H), 5.18 (m, 7a-H) and 5.97 (3-H); δ_C 56.0 (OMe), 57.7 (C-4), 69.5 (C-7), 78.8 (C-7a), 100.5 (C-6), 115.7 (C-3), 161.3 (C-3a) and 173.5 (C-2); *m*/*z* (%) 186 (1), 169 (1), 168 (1), 155 (4), 126 (89), 98 (30), 97 (100), 96 (52) and 74 (20) (Found: C, 52.1; H, 5.7. $C_8H_{10}O_5$ requires C, 51.6; H, 5.4%).

(S)-6-*Methoxyfuro*[3,2-c]*pyran*-2(4H,6H)-*one* [(S)-O-*Methylneopatulin*] **31**.—Methanesulphonyl chloride (0.43 g, 3.8 mmol) was cautiously added to a stirred and cooled solution of the hydroxy lactone **30** (0.50 g, 2.68 mmol) in dry pyridine (10 cm^3). The mixture was stirred at room temperature for 1 day after which time TLC analysis [light petroleum–ethyl acetate (1:1)] indicated that all the starting material had been consumed. The dark mixture was diluted with chloroform (200 cm^3), and the resulting solution was then washed successively with 2 mol dm^{-3} hydrochloric acid (3 × 50 cm^3), saturated brine (50 cm^3), and water (50 cm^3). The dried extract was evaporated to dryness under reduced pressure, and the residual brown oil was purified by chromatography on silica gel [eluent light petroleum–ethyl acetate (4:1)] to give *the furopyranone* **31** (0.38 g, 84%) as a solid, m.p. 91–93 °C; $[\alpha]_D^{20}$ +112.1° (*c* 0.058, $CHCl_3$); λ_{max}(MeOH)/nm 267 and 196; ν_{max}(KBr)/cm^{-1} 3120, 3075, 1790, 1687, 1620, 1365, 1120, 1060, 1000, 956 and 883; δ_H 3.51 (OMe), 4.74 (dd, *J* 16.6 and 1.1, 4-H), 4.89 (dd, *J* 16.6 and 2.1, 4-H′), 5.29 (d, *J* 3.8, 6-H), 5.81 (dd, *J* 3.8 and 1.9, 7-H) and 5.89 (m, 3-H); δ_C 56.5 (OMe), 57.1 (C-4), 95.7 (C-6), 105.3 (C-7), 110.2 (C-3), 149.5 (C-3a), 151.1 (C-7a) and 168.2 (C-2); *m*/*z* (%) 168 (4), 167 (8), 140 (5), 137 (100), 126 (54) and 85 (18) (Found: C, 57.1; H, 5.0%; $M^{\cdot+}$, 168.041 43. $C_8H_8O_4$ requires C, 57.1; H, 4.8%; M, 168.042 24).

(RS)-6-*Hydroxyfuro*[3,2-c]*pyran*-2(4H,6H)-*one* (*Neopatulin*) **8**.—A solution of *O*-methylneopatulin **31** (100 mg, 0.6 mmol) in TFA (1.5 cm^3)–water (13.5 cm^3) was heated at 50 °C for 1 h and then evaporated to one third of its volume under reduced pressure at 20 °C. Solid sodium hydrogen carbonate was added in *small* portions to the stirred mixture until pH 5–6 was attained. The aq. solution was extracted with ethyl acetate (4 × 10 cm^3) and the combined extracts were then dried, and evaporated under reduced pressure (avoiding the formation of a thin film—see patulin, above) to leave an off-white solid (84 mg, 90%). Recrystallisation from ethyl acetate gave neopatulin **8**, m.p. 86–88 °C (lit.,[7] 88–90 °C); $[\alpha]_D^{20}$ 0° (*c*. 0.1, EtOAc); λ_{max}(MeOH)/nm 269 and 199; ν_{max}($CHCl_3$)/cm^{-1} 3400, 1789, 1753, 1691, 1602, 1210, 1155, 1072 and 1028; δ_H[$(CD_3)_2CO$] 3.34 (br s, OH), 4.78 (dd, *J* 16.7 and 1.1, 4-H), 5.03 (dd, *J* 16.7 and 2.0, 4-H′), 5.75 (d, *J* 3.5, 6-H), 5.93 (dd, *J* 3.5 and 2.0, 7-H) and 6.04 (m, 3-H). In addition, the ^{1}H NMR spectrum exhibited two weak doublets, at δ 10.01 and 10.16, indicating the presence of a small equilibrium concentration of the open-chain aldehyde (*E*- and *Z*-isomer). The spectroscopic data are identical with the published data for neopatulin.[7]

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