Open-chain acetonides of D-galactono-1,4-lactone as starting materials for pyrrolidines, azepanes and 5-azidomethyltetrahydrofuran-2-carboxylates: monomers for polyhydroxylated nylon and for tetrahydrofuran carbopeptoids

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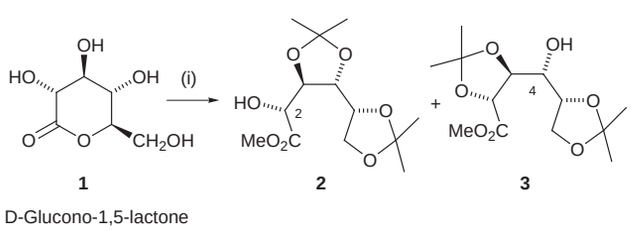
Received (in Cambridge) 11th December 1998, Accepted 26th February 1999

Treatment of D-galactono-1,4-lactone with dimethoxypropane in acetone in the presence of tosic acid forms methyl 2,3:5,6-di-*O*-isopropylidene-D-galactonate **6** (with only the secondary hydroxy group at C-4 unprotected) and methyl 2,3:4,5-di-*O*-isopropylidene-D-galactonate **5** (with only the primary hydroxy group at C-6 unprotected) in yields of 20% and 78%, respectively. The value of such easily accessible intermediates is illustrated by the synthesis of 1,4-dideoxy-1,4-imino-D-glucitol **16** (a pyrrolidine), and for the efficient preparation of 6-azido-6-deoxy-D-galactono-1,4-lactone **22**. The conversion of **22** to a seven-membered galactonolactam **21** (a tetrahydroxycaprolactam) may provide access to hydroxylated nylon polymers. The galactonolactam **21** has no significant inhibitory effect on a number of glycosidases. Reaction of **22** with triflic anhydride gives two epimeric 5-(azidomethyl)tetrahydrofuran-2-carboxylates which provide starting materials for two series of carbopeptoids, one of which probably has a helical structure and the other a structure reminiscent of a β-turn.

1 Introduction

Carbohydrate lactones with five, six, seven or eight carbons, are an accessible and diverse class of valuable homochiral starting materials for the synthesis of carbohydrate derivatives and other highly functionalised targets.[1] Hexonolactones with methanol, acid and acetone may form open-chain diacetonide esters with only a single hydroxy group remaining unprotected; for such intermediates to be useful, such protection should produce readily separated diacetonides (or ideally a single product). Chittenden[2] pioneered this strategy with the report of the reaction of D-glucono-1,5-lactone **1** with 2,2-dimethoxypropane (DMP) in acetone in the presence of acid to give gluconate **2** (in which only the C-2 hydroxy group is unprotected) in good yield (Scheme 1); **2** has been used in the synthesis of several complex targets.[3] Variation of the amount of tosic acid (TsOH) and other reactions conditions developed by Chapleur allowed the isolation of the isomeric diacetonide **3** in reasonable yield.[4] As part of a project involved in the synthesis of mimics of both D- and L-galactose, this paper reports the protection of D-galactonolactone **4** as two separable open-chain diacetonide methyl esters **5** and **6** with the hydroxy groups at C-6 and C-4 as the only unprotected functional groups. The potential of such intermediates is illustrated by the conversion of **5** to a tetrahydroxycaprolactam **21** and two stereoisomeric 5-(azidomethyl)tetrahydrofuran-2-carboxylates, all three of which may prove to be useful monomers for the preparation of novel oligomeric and polymeric materials. The lack of any significant effect of **21** on a number of glycosidases is reported. The value of compound **6**, with only the C-4 hydroxy group unprotected, is shown by the efficient synthesis of the pyrrolidine **16**.



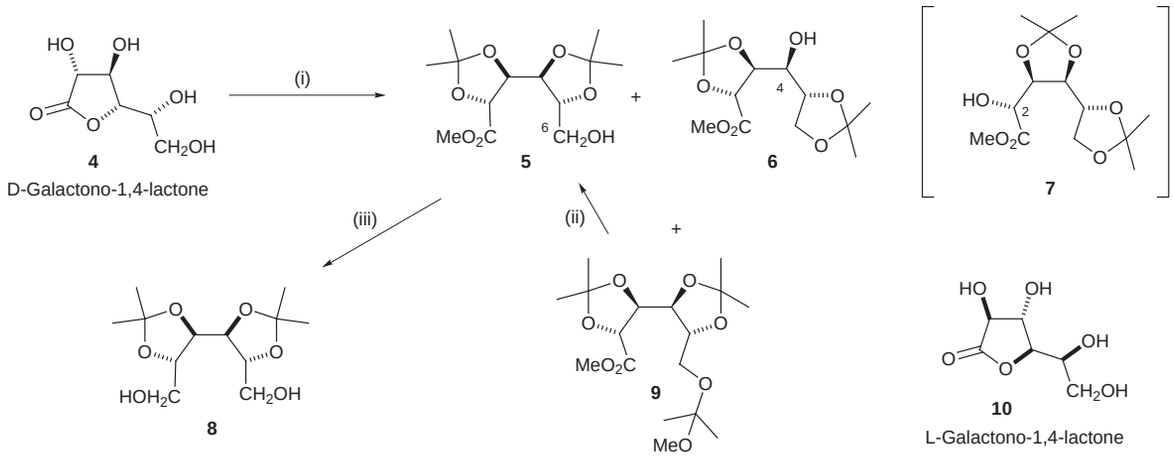
1 D-Glucono-1,5-lactone **2** **3**

Scheme 1 *Reagents*: (i) acetone, 2,2-DMP, MeOH, TsOH.

2 Results and discussion

(a) Preparation of open-chain acetonides of D-galactonolactone 4

D-Galactono-1,4-lactone **4** was treated with acetone and 2,2-dimethoxypropane with 0.5 equivalents of toluene-*p*-sulfonic acid at 40 °C for 18 h under conditions previously reported (Scheme 2);[4] the three products obtained in our hands were the *galacto* diacetonide ester **6** bearing a free hydroxy group at C-4, the *galacto* diacetonide ester **5** bearing a free hydroxy group at C-6, and a ketal intermediate **9**. The ketal **9** was not fully characterised but the ^{1}H NMR ($CDCl_3$, 200 MHz) showed the presence of 18 alkyl protons at δ 1.4–1.5 (corresponding to acetonide and ketal methyl groups) and a 3-proton singlet at δ 3.2 (corresponding to the methyl ether of the ketal); no peaks corresponding to a hydroxylic proton were observed. Upon treatment with aqueous acetic acid, the ketal intermediate **9** was



Scheme 2 *Reagents and conditions*: (i) acetone, 2,2-DMP, MeOH, 0.5 equiv. TsOH; (ii) aq. AcOH, 2 min; (iii) $LiBH_4$, THF.

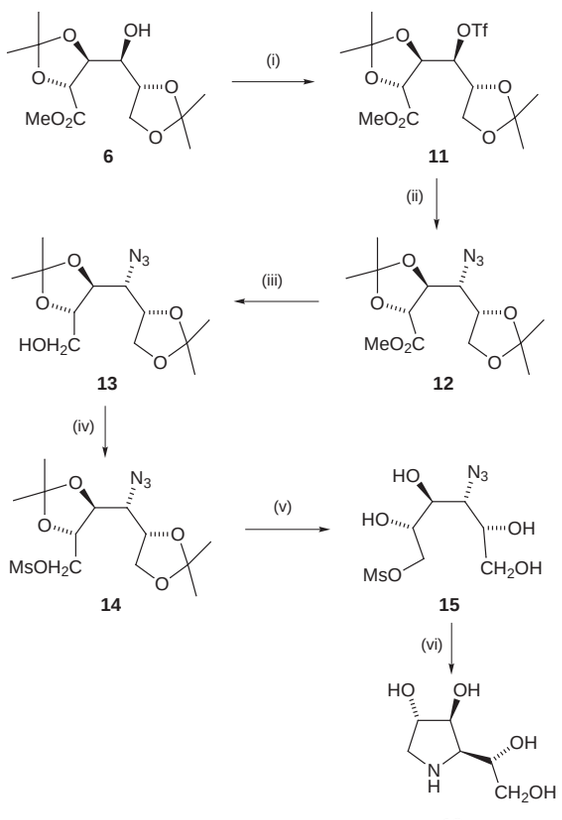
immediately converted to the *galacto* diacetonide ester **5** bearing a free hydroxy group at C-6. Overall, the 6-hydroxy ester **5** was obtained in 78% yield and the 4-hydroxy ester **6** in 20% yield. Some of this work has been previously reported[4] but it is noteworthy that there is *no formation of* 2-hydroxygalactonate **7**, the compound epimeric at C-4 with gluconate **2** which is the major product in the reaction of D-glucono-1,5-lactone.[5]

The ^1H NMR ($CDCl_3$, 500 MHz) of compound **5** showed the hydroxy proton at δ 2.21 to be a dd signal and was shown by homonuclear chemical-shift correlation (COSY) analysis to couple strongly to two adjacent protons (H-6 and H′-6) at δ 3.70 and δ 3.83. These protons (H-6 and H′-6) gave a ddd and m signal, respectively, and a D_2O shake experiment resulted in loss of the hydroxy proton and a simplification of both methylene C-6 protons to dd signals. An unequivocal proof of the structure of the 6-hydroxy ester **5** was obtained by lithium borohydride reduction in THF to the known dulcitol derivative **8**[6] in 91% yield. The symmetrical *meso*-hexitol diacetonide **8** possesses C_s symmetry and this is reflected by the zero optical rotation and the ^{13}C NMR which reveals only 2 carbon doublets and one carbon triplet corresponding to the carbon chain of the sugar. These experiments firmly establish the structure of the major product as **5**.

It is difficult to predict either on kinetic or thermodynamic grounds the outcome of conversions of lactones to open chain ester acetonides; several hexonolactones, such as altronolactone and allonolactone, did not in our hands produce any easily isolated single diacetonide methyl ester.[7] It is noteworthy that L-galactono-1,4-lactone **10** is also readily available, so that the enantiomers of diacetonides **5** and **6** would be easily accessible. Access to C-4 of galactose—which is in an axial site in the pyranose form—usually requires extensive protecting group manipulation. The minor product **6** from the acetonation reaction—which is nonetheless available in multigram quantities—provides access to the C-4 hydroxy group relatively efficiently, allowing C-4 substituted glucose derivatives to be readily available.

(b) Use of the open-chain diacetonide of D-galactonolactone 6 with unprotected C-4 OH

The value of the minor diacetonide **6** as a synthetic intermediate is illustrated by its conversion to the α-glucosidase inhibitor 1,4-dideoxy-1,4-imino-D-glucitol **16** (Scheme 3). Esterification of the free hydroxy group in **6** with triflic anhydride in dichloromethane (DCM) in the presence of pyridine gave the stable crystalline triflate **11** in 96% yield. Treatment of the triflate **11** with sodium azide in DMF yielded the 4-azido *gluco* ester **12** in 88% yield. Chemoselective reduction of the azido ester **12** with lithium borohydride in THF afforded the primary alcohol **13** in 97% yield which, on treatment with methanesulfonyl chloride in

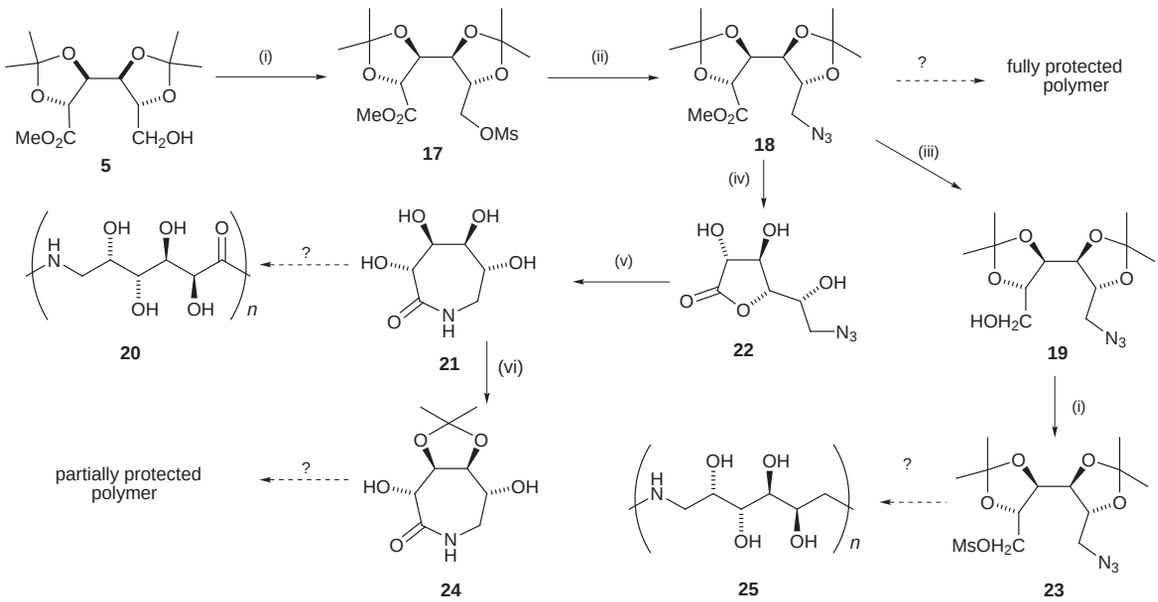


Scheme 3 *Reagents and conditions*: (i) Tf_2O, pyridine, CH_2Cl_2; (ii) NaN_3, DMF; (iii) $LiBH_4$, THF; (iv) MsCl, pyridine, DMAP; (v) aq. TFA; (vi) H_2, Pd-black, EtOH; then water, NaOAc, 80 °C.

pyridine in the presence of 4-dimethylaminopyridine (DMAP), formed the corresponding mesylate **14** (98% yield). Removal of the acetonide protecting groups in **14** with aqueous trifluoroacetic acid (TFA) gave the relatively unstable triol **15** (79% yield). Hydrogenation of the azido mesylate **15** in the presence of palladium black in ethanol gave an amine, which in the presence of sodium acetate in water cyclised to give after purification by ion-exchange chromatography the pyrrolidine **16** in 73% yield. This six step synthesis of the potent α-glucosidase inhibitor **16** proceeds in 46% overall yield from the acetonide ester **6** and compares favourably with most of the previous synthetic routes.[8]

(c) Use of the open-chain diacetonide of D-galactonolactone 5 with unprotected C-6 OH

The major product diacetonide **5** may be used to access seven-



Scheme 4 *Reagents*: (i) MsCl, pyridine, DMAP; (ii) NaN_3, DMF; (iii) $LiBH_4$, THF; (iv) aq. TFA; (v) H_2, Pd-black; (vi) acetone, 2,2-DMP, TsOH.

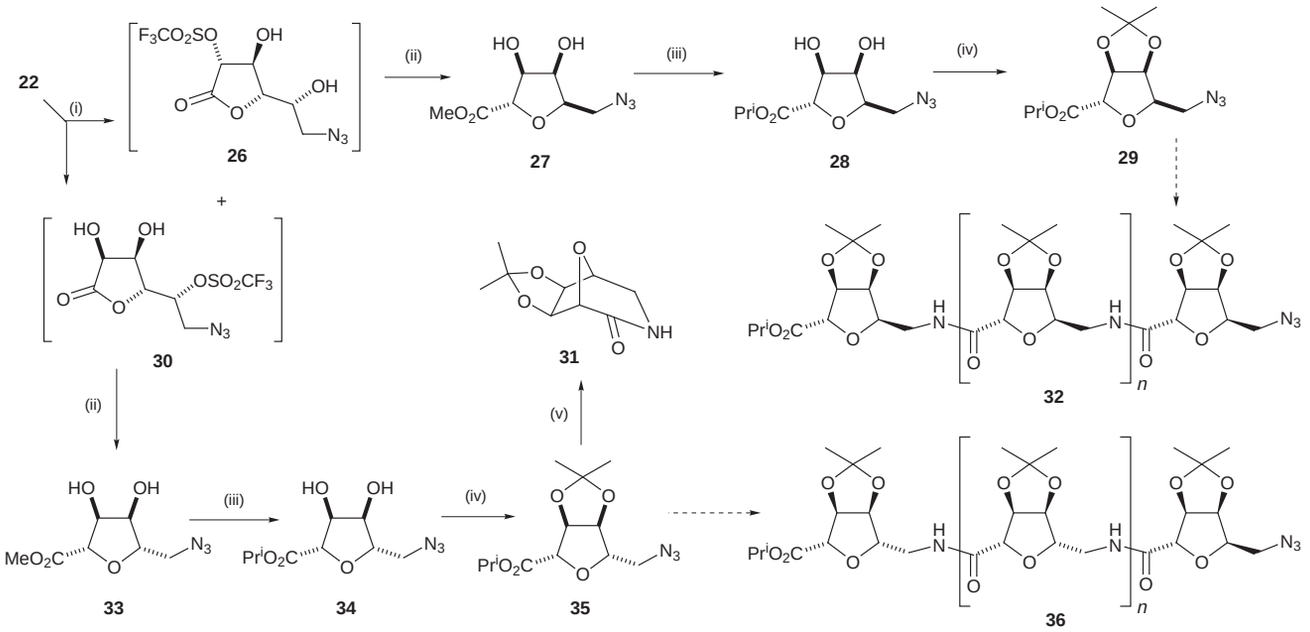
membered nitrogen heterocycles with a D-*galacto* configuration *via* introduction of an azide group at C-6. Functionalisation at C-6 of a D-galactonolactone derivative usually requires lengthy protecting group manipulations or relatively inefficient functionalisation of the unprotected lactone.[9] This potential is illustrated by the formation of the seven-membered ring ε-galactonolactam **21**, previously synthesised by Hanessian from a galactopyranoside.[10] Reaction of **5** with mesyl chloride in pyridine in the presence of DMAP gave the primary mesylate **17** (95% yield) which, on subsequent treatment with sodium azide in DMF afforded the fully protected azido ester **18** (90% yield) (Scheme 4). Removal of the isopropylidene protecting groups in azide **18** by acidic hydrolysis allowed the subsequent cyclisation to give the azidogalactonolactone **22** in 91% yield (61% overall yield from D-galactono-1,4-lactone **4**). Hydrogenation of **22** gave the seven membered ring ε-galactonolactam **21** in 90% yield. Reaction of the unprotected lactam **21** with acetone and DMP in the presence of tosic acid led to the formation of the monoacetonide **24** (66% yield). The tetrahydroxycaprolactam **21** might also be viewed as a suitable monomer for polymerisation to afford hydroxylated oligomers and polymers of nylon, such as species **20**.[11,12] The partially protected lactam **24** as well as the diacetonide **18** may also allow the formation of partially and fully protected hydroxylated nylon polymers, respectively. Some tetrahydroxyazepanes have been shown to be very powerful inhibitors of D-galactosidases,[13] and D-galactono-1,5-lactam[14] is also a galactosidase inhibitor. However, the seven-membered ring galactonolactam **21** (1.4 mM) was not inhibitory to any of the following glycosidases:[15] α-glucosidase (yeast), β-glucosidase (almonds), α-mannosidase (Jack bean), α-galactosidase (*Aspergillus niger*, green coffee bean), β-galactosidase (bovine liver, *Aspergillus niger*), α-L-fucosidase (bovine kidney, human placenta), naringinase (*Penicillium decumbens*), and β-*N*-acetylglucosaminidase (bovine kidney).

Reduction of the azido ester **18** with lithium borohydride in THF afforded the primary alcohol **19** (80% yield) which on treatment with mesyl chloride in pyridine in the presence of DMAP gave the azido mesylate **23** (100% yield). Compound **23** may also be a suitable monomer for the preparation of novel polymeric hydroxylamines, perhaps of a protected form of species **25**.

In a project aimed at generating secondary structure from short oligomers of tetrahydrofuran amino acids,[16] the azidogalactonolactone **22** may be used as the starting material for the synthesis of two epimeric 5-(azidomethyl)tetrahydrofuran-2-carboxylates, **29** and **35** (Scheme 5). Selective esterification, with trifluoromethanesulfonic anhydride, of the unprotected 6-azido galactonolactone **22** was attempted using a range of solvents and conditions; in all cases, TLC analysis indicated the formation of a major product which was found to be unstable to a variety of work-up conditions. It was assumed that a triflate or mixture of regioisomeric triflates constituted the major product and the crude reaction mixture was thus subjected to a range of ring rearrangement conditions. Treatment with acidic methanol was investigated but it became apparent that methanolysis of the lactone could be effected in the presence of pyridine. Optimal conversion was found to occur according to reaction of **22** with trifluoromethanesulfonic anhydride (1.5 equiv.) in the presence of pyridine (5.0 equiv.) in anhydrous ethyl acetate at −10 °C for a period of 15 minutes. Excess methanol was immediately added to the crude reaction mixture and an inseparable mixture of sugar carboxylates was obtained in 46% yield in a ratio of 2.5 : 1. The product ratio was found to be dependent upon the reaction conditions. Analysis of the product mixture and subsequent conversions indicated that the C-5 epimeric methyl esters **27** and **33** had been formed.

The formation of the D-*talo*-isomer **27** arises from the expected preferential triflation of **22** at the C-2 hydroxy group to give the triflate **26**; methanolysis of intermediate **26** to give an open-chain methyl ester would allow THF ring formation by displacement of the C-2 triflate with inversion of configuration by the OH group at C-5. The formation of the L-*allo*-isomer **33** required inversion of configuration at both C-2 and C-5 in **22**; a plausible pathway might involve initial epimerisation at C-2 of **22** prior, or subsequent to, triflate ester formation at C-5, giving the triflate **30**—ring opening with methanol would form an open-chain hydroxy triflate from which the THF ring would be constructed by attack of the C-2 OH group onto C-5, giving the second inversion.

Since it was known that a more hindered ester than methyl was necessary for use in elaboration of the monomeric azido acid derivatives to oligomers, the inseparable mixture of methyl esters **27** and **33** was subjected to transesterification by a solution of HCl in propan-2-ol; the resulting isopropyl esters **28** and **34** were also inseparable. However, addition of acetone to the transesterification reaction mixture gave the isopropylidene derivatives **29** and **35**, separable by careful silica-gel column chromatography, in yields of 65% and 23%, respectively. The formation of the *cis*-fused five-membered ring acetonide of both epimeric products **29** and **35** was shown by the characteristic singlets in the ^{13}C NMR spectra at δ 113 and 114, respect-



Scheme 5 *Reagents*: (i) Tf_2O, pyridine, EtOAc; (ii) MeOH; (iii) ^{i}PrOH, HCl; (iv) acetone; (v) H_2, Pd-black.

ively. NOE studies of each pure sample revealed a very similar spatial orientation of the sugar protons except for the H-4, H-5 interaction. For the major product ester **29** an NOE of 8% was observed between H-4 and H-5, compared with a value of only 2.7% for ester **35**. In addition, the *trans* nature of H-4 and H-5 of the ester **35** was reflected in the observed NOE (2.7%) between H-4 and the methylene H-6 protons. All ^{1}H NMR data were consistent with the structural assignments; a complete proof of the identity of the 2,5-*cis*-substituted azido ester **35** was provided by its conversion to the bicyclic lactam **31**, the enantiomer of which has been prepared by an unambiguous route.[17] Catalytic hydrogenation of the azide moiety of **35** in either THF or propan-2-ol initially form the corresponding amine, which spontaneously cyclised on drying under vacuum to give the bicyclic lactam **31** in quantitative yield.

Although the ring conversion from triol **22** to the azidofurancarboxylates proceeded relatively inefficiently, the ready availability of the D-galactono-1,4-lactone as a starting material allowed the preparation of substantial quantities of the two isopropylidene-protected isopropyl esters **29** and **35** which have been elaborated to oligomers **32** and **36**, respectively.[18] Oligomers derived from the major isomer **29** appear to adopt helical structures whereas those from the minor product **35** prefer β-turn-like conformations.[19]

In summary, this paper reports the preparation of two readily available open chain D-galactonolactone derivatives with only the hydroxy groups at C-6 (**5**) or C-4 (**6**) unprotected. These intermediates, together with the protected open chain forms derived from D-glucono-1,5-lactone **1**, are likely to be valuable intermediates in the synthesis of galactose and glucose derivatives. In particular, the azido lactone **22**, available in multigram amounts from the primary alcohol **5**, is a key intermediate in the synthesis of some tetrahydrofuran amino acid oligomers in a project related to the generation of secondary structure in short carbopeptoids. The oligomerisation of compounds **18**, **21** and **24** to unprotected and protected derivatives of hydroxylated nylon is also under investigation.

4 Experimental

Hexanes refers to petroleum ether boiling in the range 60–80 °C, distilled before use. All other solvents were used as supplied (AR or HPLC grade). Super-Hydride® refers to lithium triethylborohydride. Other reagents were used as supplied. Aqueous orthophosphate solution buffering to pH 7 (pH 7 buffer) was prepared through the dissolution of 85 g of KH_2PO_4 and 14.5 g of NaOH in 950 ml distilled water. TLC was performed on aluminium or plastic sheets coated with silica gel 60 F_{254}, visualisation being effected using 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid. Column chromatography was performed on Sorbsil C 60 40/60 silica, and ion-exchange chromatography was performed on Amberlite IR-120 (H^+ form) and Dowex 1X8-400 (basic form). Melting points were recorded on a Kofler hot block and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} and concentrations are quoted in g per 100 ml. ^{1}H NMR spectra were recorded, unless otherwise stated, on either a Bruker AM 500 or AMX 500 spectrometer (500 MHz) or, where stated, on a Varian Gemini 200 or Bruker AC 200 spectrometer (200 MHz). ^{13}C NMR spectra were recorded, unless otherwise stated, on a Bruker AM 500 or AMX 500 spectrometer (125.3 MHz) or, where stated, on a Varian Gemini 200 or Bruker AC 200 spectrometer (50.3 MHz). Chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz; a- indicates an apparent splitting pattern. Residual signals from solvents were used as internal reference, and ^{13}C NMR spectra in D_2O were referenced to 1,4-dioxane (δ_C 67.4). IR spectra were recorded on a Perkin-Elmer Paragon 1000 spectrophotometer using either thin films on NaCl plates (film) or KBr discs (KBr). Low resolution mass spectra were recorded on either a VG MASS LAB 20-250 using chemical ionisation (CI, NH_3) or fast atom bombardment (FAB), or on a VG Platform using atmospheric pressure chemical ionisation (APCI). High resolution mass spectra (HRMS) were recorded on a VG Autospec spectrometer. Elemental analyses were carried out by the microanalysis service of the Dyson Perrins Laboratory or the Oxford University Inorganic Chemistry Laboratory.

Methyl 2,3:5,6-di-*O*-isopropylidene-D-galactonate 6 and methyl 2,3:4,5-di-*O*-isopropylidene-D-galactonate 5

The conditions in this procedure are similar to those reported by Chapleur. Toluene-*p*-sulfonic acid monohydrate (10.8 g, 56.2 mmol) was added to a stirred suspension of D-galactono-1,4-lactone **4** (20.0 g, 0.112 mol) in 2,2-dimethoxypropane (400 ml) and acetone (30 ml). The reaction mixture was stirred at 40 °C for 18 h, under an atmosphere of nitrogen. TLC (ethyl acetate–

hexanes 3:2) indicated complete conversion of the starting material (R_f 0.0) to three products (R_f 0.9, 0.6 and 0.5). Sodium carbonate was added to neutralise the mixture which was then filtered through Celite. The solvent was removed *in vacuo* and the residue dissolved in dichloromethane (400 ml) and washed with water (2 × 150 ml). The aqueous phase was extracted with dichloromethane (100 ml) and the combined organic extracts dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by repeated flash chromatography (ethyl acetate–hexanes 3:7) to give *methyl 2,3:5,6-di-O-isopropylidene*-D-*galactonate* **6** (6.43 g, 20%) (R_f 0.6, ethyl acetate–hexanes 3:2); $[\alpha]_D^{23}$ −19.5 (*c*, 1.00 in $CHCl_3$) [lit.,[4] $[\alpha]_D^{20}$ −10.8 (*c*, 1.16 in $CHCl_3$)]; δ_H ($CDCl_3$): 1.38, 1.42, 1.45, 1.47 (12H, 4 × s, 2 × C(CH_3)$_2$), 2.47 (1H, d, $J_{OH,4}$ 6.8 Hz, OH), 3.59 (1H, ddd, $J_{4,5}$ 4.0 Hz, H-4), 3.81 (3H, s, CO_2CH_3), 3.92 (1H, dd, $J_{6,5}$ 6.8 Hz, $J_{6,6'}$ 8.3 Hz, H-6), 4.09 (1H, dd, $J_{6',5}$ 6.7 Hz, H′-6), 4.26 (1H, ddd, H-5), 4.30 (1H, dd, $J_{3,2}$ 5.9 Hz, $J_{3,4}$ 7.3 Hz, H-3), 4.62 (1H, d, H-2); *methyl 2,3:4,5-di-O-isopropylidene*-D-*galactonate* **5** (11.8 g) (R_f 0.5, ethyl acetate–hexanes 3:2), and a *hemiacetal intermediate* **9** (approx. 22 g) (R_f 0.9, ethyl acetate–hexanes 3:2); δ_H ($CDCl_3$, 200 MHz): 1.36, 1.44, 1.48 (18H, 3 × s, 2 × C(CH_3)$_2$, OC(CH_3)$_2$OCH_3), 3.23 (3H, s, OC(CH_3)$_2$OCH_3), 3.53 (1H, dd, $J_{6,5}$ 5.7 Hz, $J_{6,6'}$ 10.3 Hz, H-6), 3.64 (1H, dd, $J_{6',5}$ 4.0 Hz, H′-6), 3.80 (3H, s, CO_2CH_3), 4.01 (1H, dd, $J_{4,3}$ 6.0 Hz, $J_{4,5}$ 7.3 Hz, H-4), 4.17 (1H, ddd, H-5), 4.40 (1H, a-t, H-3), 4.60 (1H, d, $J_{2,3}$ 5.7 Hz, H-2), which was not fully characterised but stirred in acetic acid–water (7:3, 50 ml) at room temperature for 2 min. The solvent was removed *in vacuo* (co-evaporation with toluene) to give a further amount of *methyl 2,3:4,5-di-O-isopropylidene*-D-*galactonate* **5** (13.5 g) (total amount 25.3 g, 78%); $[\alpha]_D^{23}$ −20.7 (*c*, 1.00 in $CHCl_3$) [lit.,[4] $[\alpha]_D^{20}$ −15.0 (*c*, 1.13 in $CHCl_3$)]; δ_H ($CDCl_3$, COSY): 1.39, 1.41, 1.41, 1.45 (12H, 4 × s, 2 × C(CH_3)$_2$), 2.21 (1H, dd, $J_{OH,6}$ 7.9 Hz, $J_{OH,6'}$ 4.9 Hz, OH), 3.70 (1H, ddd, $J_{6,5}$ 4.4 Hz, $J_{6,6'}$ 12.1 Hz, H-6), 3.78 (3H, s, CO_2CH_3), 3.83 (1H, m, H-6′), 3.93 (1H, a-t, H-4), 4.09 (1H, m, H-5), 4.36 (1H, dd, $J_{3,2}$ 5.4 Hz, $J_{3,4}$ 7.4 Hz, H-3), 4.55 (1H, d, H-2).

2,3:4,5-Di-*O*-isopropylidene-*meso*-galactitol 8

Lithium borohydride (247 mg, 11.33 mmol) was added to a solution of methyl 2,3:4,5-di-*O*-isopropylidene-D-galactonate **5** (1.64 g, 5.67 mmol) in THF (25 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 5 h 30 min, under an atmosphere of nitrogen. TLC (ethyl acetate–hexanes 1:1) indicated complete conversion of the starting material (R_f 0.4) to a major product (R_f 0.2). Saturated ammonium chloride solution (5 ml) was added and the mixture diluted with ethyl acetate (100 ml) and washed with saturated ammonium chloride solution (2 × 20 ml) and brine (15 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate–hexanes 1:1) to yield the known *diacetonide* **8** (1.36 g, 91%) as a white crystalline solid; mp 111 °C (diethyl ether–hexane) [lit.,[6] mp 111 °C]; $[\alpha]_D^{23}$ 0.0 (*c*, 0.75 in $CHCl_3$); δ_H ($CDCl_3$): 1.40, 1.42 (12H, 2 × s, 2 × C(CH_3)$_2$), 2.28–2.30 (2H, dd, *J* 4.1 Hz, *J* 8.7 Hz, 2 × OH), 3.74–3.87 (6H, m), 4.04–4.10 (2H, m); δ_C ($CDCl_3$, 50.3 MHz): 26.8, 26.9 (2 × q, 2 × C(CH_3)$_2$), 62.3 (t, C-1, C-6), 78.4, 81.3 (2 × d, C-2, C-3, C-4, C-5) and 109.8 (s, 2 × *C*(CH_3)$_2$).

Methyl 2,3:5,6-di-*O*-isopropylidene-4-*O*-trifluoromethylsulfonyl-D-galactonate 11

Triflic anhydride (1.72 ml, 10.20 mmol) was added to a stirred solution of the secondary alcohol **6** (2.47 g, 8.50 mmol) in dichloromethane (50 ml) and dry pyridine (2.06 ml, 22.51 mmol) at −20 °C, under an atmosphere of nitrogen. The reaction mixture was allowed to warm to −5 °C over 45 min. TLC (hexanes–ethyl acetate 5:3) indicated complete conversion of the starting material (R_f 0.3) to a major product (R_f 0.5). The reaction mixture was diluted with dichloromethane (150 ml) and washed with 2 M hydrochloric acid (60 ml) and pH 7 buffer (60 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes–ethyl acetate 5:3) to yield *the triflate* **11** (3.44 g, 96%) as a white solid (Found: C, 40.22; H, 4.85. $C_{14}H_{21}O_9SF_3$ requires: C, 39.81; H, 5.01%); mp 62–63 °C (diethyl ether–hexane); $[\alpha]_D^{24}$ −21.2 (*c*, 1.0 in $CHCl_3$); ν_{max} (KBr disc): 1745 (C=O, ester) cm^{-1}; δ_H ($CHCl_3$): 1.33, 1.39, 1.44, 1.53 (12H, 4 × s, 2 × C(CH_3)$_2$), 3.82 (3H, s, CO_2CH_3), 3.94 (1H, dd, $J_{6,5}$ 5.3 Hz, $J_{6,6'}$ 9.2 Hz, H-6), 4.18 (1H, dd, $J_{6',5}$ 6.8 Hz, H′-6), 4.31 (1H, a-q, H-5), 4.55 (1H, dd, $J_{3,2}$ 6.9 Hz, $J_{3,4}$ 2.4 Hz, H-3), 4.60 (1H, d, H-2), 5.09 (1H, dd, $J_{4,5}$ 5.7 Hz, H-4); δ_C ($CDCl_3$): 25.1, 25.2, 25.7, 25.8 (4 × q, 2 × C(CH_3)$_2$), 52.7 (q, CO_2CH_3), 65.5 (t, C-6), 73.6, 74.1, 77.1, 85.2 (4 × d, C-2, C-3, C-4, C-5), 110.7, 111.6 (2 × s, 2 × *C*(CH_3)$_2$), 118.4 (q, *J* 19.3 Hz, SO_2CF_3), 170.9 (s, C=O).

Methyl 4-azido-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-gluconate 12

Sodium azide (584 mg, 8.98 mmol) was added to a stirred solution of the triflate **11** (3.44 g, 8.16 mmol) in DMF (30 ml). The reaction mixture was stirred at room temperature for 1 h, under an atmosphere of nitrogen. TLC (ethyl acetate–hexanes 3:5) indicated complete conversion of the starting material (R_f 0.5) to a major product (R_f 0.6). The solvent was removed *in vacuo* (co-evaporation with toluene) and the residue dissolved in ethyl acetate (100 ml) and washed with water (2 × 30 ml). The aqueous phase was extracted with ethyl acetate (30 ml) and the combined organic extracts were washed with brine (10 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* (co-evaporated with toluene). The residue was purified by flash chromatography (ethyl acetate–hexanes 1:6) to afford *the azide* **12** (2.26 g, 88%) as a colourless oil (Found: C, 49.59; H, 6.79. $C_{13}H_{21}O_6N_3$ requires: C, 49.52; H, 6.71%) (HRMS − N_2 + H^+: 288.144018. $C_{13}H_{21}O_6N_3$ − N_2 + H^+ requires: 288.144713); $[\alpha]_D^{23}$ −60.9 (*c*, 1.1 in $CHCl_3$); ν_{max} (thin film) 2111 (N_3), 1764 (C=O, ester) cm^{-1}; δ_H ($CHCl_3$): 1.37, 1.43, 1.46, 1.51 (12H, 4 × s, 2 × C(CH_3)$_2$), 3.49 (1H, dd, $J_{4,3}$ 2.9, Hz, $J_{4,5}$ 7.3, H-4), 3.80 (3H, s, CO_2CH_3), 4.05 (1H, dd, $J_{6,5}$ 5.4 Hz, $J_{6,6'}$ 8.9 Hz, H-6), 4.14 (1H, dd, $J_{6',5}$ 6.0 Hz, H′-6), 4.33 (1H, a-q, H-5), 4.42 (1H, dd, $J_{3,2}$ 7.6 Hz, H-3), 4.60 (1H, d, H-2); δ_C ($CDCl_3$, 50.3 MHz): 25.2, 25.7, 26.3, 26.5 (4 × q, 2 × C(CH_3)$_2$), 52.5 (q, CO_2CH_3), 62.0 (d, C-4), 66.7 (t, C-6), 75.1, 75.6, 78.1 (3 × d, C-2, C-3, C-5), 109.8, 112.0 (2 × s, 2 × *C*(CH_3)$_2$), 170.6 (s, C=O); *m/z* (APCI + ve): 288.3 (M − N_2 + H^+, 100%).

4-Azido-4-deoxy-2,3:5,6-di-*O*-isopropylidene-D-glucitol 13

Lithium borohydride (179 mg, 8.20 mmol) was added to a solution of the azido ester **12** (1.29 g, 4.10 mmol) in THF (25 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 6 h, under an atmosphere of nitrogen. TLC (ethyl acetate–hexanes 3:5) indicated complete conversion of the starting material (R_f 0.6) to a major product (R_f 0.3). Saturated ammonium chloride solution (5 ml) was added and the mixture diluted with ethyl acetate (80 ml) and washed with saturated ammonium chloride solution (2 × 15 ml) and brine (15 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate–hexanes 3:5) to give the protected *azido alcohol* **13** (1.14 g, 97%) as a colourless oil (Found: C, 50.19; H, 7.74. $C_{12}H_{21}O_5N_3$ requires: C, 50.16; H, 7.37%) (HRMS − N_2 + H^+: 260.149496. $C_{12}H_{21}O_5N_3$ − N_2 + H^+ requires: 260.149798); $[\alpha]_D^{23}$ −46.0 (*c*, 1.325 in $CHCl_3$); ν_{max} (thin film): 3469 (OH) and 2110 (N_3) cm^{-1}; δ_H ($CHCl_3$): 1.37, 1.43, 1.46 (12H, 3 × s, 2 × C(CH_3)$_2$), 1.95 (1H, br s, OH, exchanges in D_2O), 3.41 (1H, dd, $J_{4,3}$ 3.5 Hz, $J_{4,5}$ 6.7 Hz, H-4), 3.70 (1H, m, H-1), 3.84 (1H, m, H′-1), 4.03 (1H, dd, $J_{6,5}$ 6.1 Hz, $J_{6,6'}$ 8.8 Hz, H-6), 4.11–4.15 (2H, m, H-3, H′-6), 4.21 (1H, m, H-2/5), 4.26

(1H, a-q, H-5/2); δ_C ($CDCl_3$, 50.3 MHz): 25.2, 26.4, 26.7, 27.1 (4 × q, 2 × C(CH_3)$_2$), 61.7 (t, C-1), 62.0 (d, C-4), 66.7 (t, C-6), 75.7, 77.1, 77.7 (3 × d, C-2, C-3, C-5), 109.7, 109.9 (2 × s, 2 × C(CH_3)$_2$); *m/z* (APCI +): 260.2 (M − N_2 + H^+, 100%).

4-Azido-4-deoxy-1-*O*-methylsulfonyl-2,3:5,6-di-*O*-isopropylidene-D-glucitol 14

Methanesulfonyl chloride (60 μl, 0.78 mmol) was added to a stirred solution of the azido alcohol **13** (160 mg, 0.56 mmol) and 4-dimethylaminopyridine (10 mg, catalytic) in pyridine (3 ml) at 0 °C, under an atmosphere of nitrogen. After 1.5 h, TLC (ethyl acetate–hexanes 1:1) indicated complete conversion of the starting material (R_f 0.5) to a single product (R_f 0.6). The solvent was removed *in vacuo* (co-evaporated with toluene) and the residue dissolved in dichloromethane (15 ml) and washed with water (5 ml) and brine (5 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate–hexanes 1:3) to give *the mesylate* **14** (199 mg, 98%) as a colourless oil (Found: C, 42.96; H, 6.31. $C_{13}H_{23}O_7N_3S$ requires: C, 42.73; H, 6.34%) (HRMS − N_2 + H^+: 338.126450. $C_{13}H_{23}O_7N_3S$ − N_2 + H^+ requires: 338.127349); $[\alpha]_D^{23}$ −37.8 (*c*, 1.20 in $CHCl_3$); ν_{max} (thin film): 2113 (N_3) cm^{-1}; δ_H ($CDCl_3$, COSY): 1.37, 1.43, 1.45, 1.47 (12H, 4 × s, 2 × C(CH_3)$_2$), 3.08 (3H, s, SO_2CH_3), 3.36 (1H, dd, $J_{4,3}$ 4.0 Hz, $J_{4,5}$ 7.4 Hz, H-4), 4.01 (1H, dd, $J_{6,5}$ 5.8 Hz, $J_{6,6'}$ 8.8 Hz, H-6), 4.12 (1H, dd, $J_{3,2}$ 7.6 Hz, H-3), 4.14 (1H, dd, $J_{6',5}$ 6.3 Hz, H′-6), 4.21 (1H, a-q, H-5), 4.33–4.38 (2H, m, H-1, H-2), 4.39–4.43 (1H, m, H′-1); δ_C ($CDCl_3$, 50.3 MHz): 25.1, 26.4, 26.6, 26.9 (4 × q, 2 × C(CH_3)$_2$), 37.6 (q, SO_2CH_3), 62.7 (d, C-4), 66.9, 68.4 (2 × t, C-1, C-6), 75.2, 75.4, 77.7 (3 × d, C-2, C-3, C-5), 109.9, 110.6 (2 × s, 2 × C(CH_3)$_2$); *m/z* (APCI + ve): 338.0 (M + H^+, 100%).

4-Azido-4-deoxy-1-*O*-methylsulfonyl-D-glucitol 15

The azido mesylate **14** (108 mg, 2.96 mmol) was stirred in trifluoroacetic acid–water (3:2, 6 ml) at room temperature for 1.5 h. TLC (ethyl acetate) indicated complete conversion of the starting material (R_f 1.0) to a major product (R_f 0.2). The solvent was removed *in vacuo* (co-evaporation with toluene) and the residue preadsorbed onto silica and purified by flash chromatography (ethyl acetate) to form *the azidotetraol* **15** (67 mg, 79%) as an unstable, colourless oil; ν_{max} (thin film): 3392 (OH), 2116 (N_3) cm^{-1}; δ_H (MeOD, 200 MHz): 3.12 (3H, SO_2CH_3), 3.57 (1H, dd, H-4), 3.64 (1H, dd, H-6), 3.73 (1H, dd, H′-6), 3.84–3.96 (2H, m, H-3, H-2/H-5), 4.03 (1H, m, H-5/H-2), 4.22-4.42 (2H, m, H-1, H′-1); δ_C (CD_3CN, 50.3 MHz): 37.5 (q, SO_2CH_3), 63.6 (t, C-6), 64.8 (d, C-4), 70.8, 70.9, 71.8 (3 × d, C-2, C-3, C-5), 72.1 (t, C-1).

1,4-Dideoxy-1,4-imino-D-glucitol 16

A solution of the unprotected azide **15** (67 mg, 0.24 mmol) in ethanol (5 ml) was stirred under an atmosphere of hydrogen in the presence of palladium black (10 mg). After 1.5 h, TLC (ethyl acetate) indicated complete conversion of the starting material (R_f 0.2) to a major product (R_f 0.0). The reaction mixture was filtered through Celite (eluted with EtOH) and the solvent removed *in vacuo.* The residue was dissolved in water (4 ml), sodium acetate (77 mg, 0.94 mmol) added to the solution and the reaction mixture heated at 80 °C for 36 h. The mixture was then concentrated *in vacuo* and purified by acidic ion exchange and basic ion exchange to yield 1,4-dideoxy-1,4-imino-D-glucitol **16** (28 mg, 73%) as a crystalline solid; mp 194–195 °C [lit.,[8] mp 194–196 °C]; $[\alpha]_D^{26}$ −10.7 (*c*, 0.775 in H_2O) [lit.,[8] $[\alpha]_D^{20}$ −11.0 (H_2O)]; δ_H (D_2O): 2.65 (1H, dd, $J_{1,1'}$ 12.9 Hz, H-1), 3.03 (1H, dd, *J* 3.5 Hz, *J* 9.3 Hz, H-4), 3.19 (1H, dd, $J_{1',2}$ 4.9 Hz, H′-1), 3.49 (1H, m, H-5), 3.67–3.73 (2H, m, H-6, H-6′), 4.06–4.08 (2H, m, H-2, H-3); δ_C (D_2O): 51.3 (t, C-6), 60.8 (d, C-4), 64.2 (t, C-1), 69.9, 76.4, 76.6 (3 × d, C-2, C-3, C-5).

Methyl 2,3:4,5-di-*O*-isopropylidene-6-*O*-methylsulfonyl-D-galactonate 17

Methanesulfonyl chloride (1.38 ml, 17.9 mmol) was added to a stirred solution of the primary alcohol **5** (4.32 g, 14.9 mmol) and DMAP (100 mg, catalytic) in pyridine (40 ml) at 0 °C under an atmosphere of nitrogen. After 1.5 h, TLC (ethyl acetate–hexanes 1:2) indicated complete conversion of the starting material (R_f 0.2) to a single product (R_f 0.3). The solvent was removed *in vacuo* (co-evaporated with toluene) and the residue dissolved in dichloromethane (200 ml) and washed with water (80 ml) and brine (50 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate–hexanes 1:2) to yield *the mesylate* **17** (5.23 g, 95%) as a crystalline solid (Found: C, 45.75; H, 6.76. $C_{14}H_{24}O_9S$ requires: C, 45.64; H, 6.57%); mp 98–99 °C (diethyl ether–hexane); $[\alpha]_D^{23}$ −6.1 (*c*, 1.00 in $CHCl_3$); ν_{max} (thin film): 1755 (C=O, ester) cm^{-1}; δ_H ($CDCl_3$): 1.42, 1.44, 1.47 (12H, 3 × s, 2 × C(CH_3)$_2$), 3.08 (3H, s, SO_2CH_3), 3.81 (3H, s, CO_2CH_3), 3.93 (1H, a-t, H-4), 4.26 (1H, ddd, $J_{5,4}$ 7.6 Hz, $J_{5,6}$ 5.3 Hz, $J_{5,6'}$ 2.8 Hz H-5), 4.32 (1H, dd, $J_{6,6'}$ 11.1, 6-H), 4.37 (1H, dd, $J_{3,4}$ 7.6 Hz, $J_{3,2}$ 5.3 Hz, H-3), 4.49 (1H, dd, H′-6), 4.55 (1H, d, H-2); δ_C ($CDCl_3$): 25.9, 26.8, 26.9, 27.1 (4 × q, 2 × C(CH_3)$_2$), 37.5 (q, SO_2CH_3), 52.5 (q, CO_2CH_3), 68.8 (t, C-6), 77.0, 77.3, 77.4, 79.5 (4 × d, C-2, C-3, C-4, C-5), 110.7, 112.3 (2 × s, 2 × C(CH_3)$_2$), 171.0 (s, C=O); *m/z* (FAB + ve): 369.16 (M + H^+, 84%).

Methyl 6-azido-6-deoxy-2,3:4,5-di-*O*-isopropylidene-D-galactonate 18

Sodium azide (1.02 g, 15.6 mmol) was added to a stirred solution of the mesylate **17** (5.23 g, 14.2 mmol) in DMF (50 ml). The reaction mixture was stirred at 85 °C for 36 h, under an atmosphere of nitrogen. TLC (ethyl acetate–hexanes 1:2) indicated complete conversion of the starting material (R_f 0.2) to a major product (R_f 0.6). The solvent was removed *in vacuo* (co-evaporation with toluene) and the residue dissolved in ethyl acetate (200 ml) and washed with water (2 × 40 ml). The aqueous phase was extracted with ethyl acetate (50 ml) and the combined organic extracts washed with brine (40 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo* (co-evaporated with toluene). The residue was purified by flash chromatography (ethyl acetate–hexanes 1:6) to give *the azido ester* **18** (4.02 g, 90%) as a colourless oil (Found: C, 49.32; H, 6.84. $C_{13}H_{21}O_6N_3$ requires: C, 49.52; H, 6.71%) (HRMS − N_2 + H^+: 288.144394. $C_{13}H_{21}O_6N_3$ − N_2 + H^+ requires: 288.144713); $[\alpha]_D^{23}$ +30.9 (*c*, 2.125 in $CHCl_3$); ν_{max} (thin film): 2104 (N_3), 1756 (C=O, ester) cm^{-1}; δ_H ($CDCl_3$): 1.41, 1.42, 1.46, 1.47 (12H, 4 × s, 2 × C(CH_3)$_2$), 3.33 (1H, dd, $J_{6,5}$ 5.1 Hz, $J_{6,6'}$ 13.2 Hz, H-6), 3.65 (1H, dd, $J_{6',5}$ 3.2 Hz, H′-6), 3.80 (3H, s, CO_2CH_3), 3.95 (1H, a-t, H-4), 4.17 (1H, m, H-5), 4.34 (1H, dd, $J_{3,2}$ 5.3 Hz, $J_{3,4}$ 7.6 Hz, H-3), 4.56 (1H, d, H-2); δ_C ($CDCl_3$, 50.3 MHz): 26.0, 26.8, 27.2 (3 × q, 2 × C(CH_3)$_2$), 51.9 (t, C-6), 52.4 (q, CO_2CH_3), 77.4, 77.8, 78.8, 79.8 (4 × d, C-2, C-3, C-4, C-5), 110.4, 112.2 (2 × s, 2 × C(CH_3)$_2$), 171.1 (s, C=O); *m/z* (APCI + ve): 288.1 (M − N_2 + H^+, 100%).

6-Azido-6-deoxy-D-galactono-1,4-lactone 22

The protected azido ester **18** (11.35 g, 36.0 mmol) was stirred in trifluoroacetic acid–water (3:2, 160 ml) at room temperature for 3 h. TLC (ethyl acetate–hexanes 4:1) indicated conversion of the starting material (R_f 0.9) to a single product (R_f 0.4). The solvent was removed *in vacuo* (co-evaporation with toluene) and the residue preadsorbed onto silica and purified by flash chromatography (ethyl acetate–hexanes 4:1) to yield *6-azido-6-deoxy-D-galactono-1,4-lactone* **22** (6.64 g, 91%) as a hygroscopic oil; $[\alpha]_D^{23}$ −70.6 (*c*, 1.65 in D_2O); $[\alpha]_D^{23}$ −70.3 (*c*, 1.05 in EtOAc); ν_{max} (thin film): 2112 (N_3), 1778 (C=O, lactone) cm^{-1}; δ_H (d_6-DMSO): 3.32 (1H, dd, $J_{6,5}$ 4.6 Hz, $J_{6,6'}$ 12.6 Hz, H-6),

3.39 (1H, dd, $J_{6',5}$ 7.9 Hz, H′-6), 3.78 (1H, m, H-5), 3.97 (1H, dd, $J_{4,3}$ 8.2 Hz, $J_{4,5}$ 3.0 Hz, H-4), 4.07 (1H, a-dt, $J_{3,OH}$ 5.9 Hz, H-3), 4.26 (1H, dd, $J_{2,3}$ 8.9 Hz, $J_{2,OH}$ 6.7 Hz, H-2), 5.66 (1H, d, OH-2/OH-5), 5.86 (1H, d, OH-3), 6.09 (1H, d, OH-5/OH-2); δ_C (d_6-DMSO): 53.0 (t, C-6), 67.8, 72.9, 73.9, 80.3 (4 × d, C-2, C-3, C-4, C-5), 174.6 (s, C=O); *m*/*z* (APCI − ve): 202.0 (M − H^+, 100%).

6-Amino-6-deoxy-D-galactono-1,6-lactam 21

A solution of the azido lactone **22** (1.03 g, 5.07 mmol) in methanol (50 ml) was stirred under an atmosphere of hydrogen in the presence of palladium black (70 mg). After 48 h, TLC (ethyl acetate) indicated complete conversion of the starting material (R_f 0.5) to a major product (R_f 0.0). The reaction mixture was filtered through Celite (eluted with MeOH and H_2O) and the solvent removed *in vacuo.* The residue was dissolved in hot methanol, filtered and the solvent removed *in vacuo* to give the *ε-lactam* **21** (794 mg, 90%) as an off white solid (Found: C, 40.51; H, 6.14; N, 7.63. $C_6H_{11}O_5N$ requires: C, 40.68; H, 6.26; N, 7.91%); mp 175–176 °C (foam) [lit.,[10] mp 175–177 °C (foam)]; $[\alpha]_D^{25}$ −16.3 (*c*, 1.00 in H_2O) [lit.,[10] $[\alpha]_D^{20}$ −22.0 (*c*, 1.30 in H_2O)]; ν_{max} (thin film): 1660 (C=O, lactam) cm^{-1}; δ_H (d_6-DMSO, COSY): 2.99 (1H, br s, H-6), 3.34 (1H, br s, H′-6), 3.52 (2H, m, H-3, H-5), 3.69 (1H, br s, H-4), 4.20 (1H, m, H-2), 4.53 (2H, br s, OH-2, OH-5), 4.92 (2H, br s, OH-3, OH-4), 7.71 (1H, br s, NH); δ_C (D_2O, 50.3 MHz): 41.0 (t, C-6), 69.5, 73.7 (2 × d, C-2, C-3, C-4, C-5), 176.8 (s, C=O); *m*/*z* (APCI-ve): 178.0 (M + H^+, 100%).

6-Amino-6-deoxy-3,4-*O*-isopropylidene-D-galactono-1,6-lactam 24

Toluene-*p*-sulfonic acid monohydrate (10 mg, catalytic) was added to a stirred suspension of the unprotected lactam **21** (118 mg, 0.67 mmol) in 2,2-dimethoxypropane (1 ml) and acetone (4 ml). The reaction mixture was stirred at 80 °C for 3 h, under an atmosphere of nitrogen. TLC (ethyl acetate–methanol 4 : 1) indicated complete conversion of starting material (R_f 0.25) to a major product (R_f 0.45). Sodium carbonate (200 mg) was added to neutralise the mixture which was then filtered through Celite. The solvent was removed *in vacuo* and the residue purified by flash chromatography (ethyl acetate–methanol 19 : 1 to 9 : 1) to yield *the lactam monoacetonide* **24** (96 mg, 66%) as a white crystalline solid (Found: C, 49.66; H, 7.08; N, 6.33. $C_9H_{15}O_5N$ requires: C, 49.76; H, 6.96; N, 6.45%); mp 168 °C (ethyl acetate–methanol); $[\alpha]_D^{23}$ +10.8 (*c*, 0.48 in MeOH); ν_{max} (thin film): 3436 (OH, NH), 1640 (C=O, lactam) cm^{-1}; δ_H (D_2O): 1.38, 1.40 (6H, 2 × s, $C(CH_3)_2$), 3.16 (1H, dd, $J_{6,5}$ 5.3 Hz, $J_{6,6'}$ 15.9 Hz, H-6), 3.62 (1H, a-d, H-6'), 3.83 (1H, a-t, H-5), 4.12 (1H, dd, $J_{3,2}$ 9.8 Hz, $J_{3,4}$ 2.3 Hz, H-3), 4.15 (1H, a-t, H-4), 4.87 (1H, d, H-2); δ_C (D_2O): 25.2, 25.7 (2 × q, $C(CH_3)_2$), 39.7 (t, C-6), 68.2, 68.3, 71.6, 75.1 (4 × d, C-2, C-3, C-4, C-5), 111.4 (s, $C(CH_3)_2$), 173.8 (s, C=O); *m*/*z* (APCI + ve): 218.1 (M − H^+, 100%).

6-Azido-6-deoxy-2,3 : 4,5-di-*O*-isopropylidene-D-galactitol 19

Lithium borohydride (0.86 ml, 2 M in THF) was added to a solution of the azido ester **18** (544 mg, 1.73 mmol) in THF (10 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 10 h, under an atmosphere of nitrogen. TLC (ethyl acetate–hexanes 1 : 1) indicated complete conversion of the starting material (R_f 0.7) to a major product (R_f 0.45). Saturated ammonium chloride solution (2 ml) was added and the mixture diluted with ethyl acetate (30 ml) and washed with saturated ammonium chloride solution (2 × 10 ml) and brine (20 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate–hexanes 1 : 2) to yield *the azido alcohol* **19** (397 mg, 80%) as a colourless oil which solidified upon standing to an amorphous solid (Found: C, 50.23; H, 7.51; N, 14.37. $C_{12}H_{21}O_5N_3$ requires: C, 50.17; H, 7.37; N, 14.63%); $[\alpha]_D^{23}$ +59.9 (*c*, 0.82 in $CHCl_3$); ν_{max} (thin film): 3448 (OH), 2102 (N_3) cm^{-1}; δ_H ($CDCl_3$): 1.37, 1.39, 1.40, 1.46 (12H, 4 × s, 2 × $C(CH_3)_2$), 2.32 (1H, br s, OH), 3.33 (1H, dd, $J_{6,5}$ 5.2 Hz, $J_{6,6'}$ 13.2 Hz, H-6), 3.68 (1H, dd, $J_{6',5}$ 2.7 Hz, H′-6), 3.73–3.85 (4H, m, H-1, H-1′, H-3, H-4), 4.05 (1H, m, $J_{4,5}$ 7.7 Hz, H-2), 4.14 (1H, ddd, H-5); δ_C ($CDCl_3$): 26.8, 26.9 (2 × q, 2 × $C(CH_3)_2$), 51.7, 62.3 (2 × t, C-1, C-6), 78.0, 78.7, 80.1, 81.2 (4 × d, C-2, C-3, C-4, C-5), 109.9, 110.5 (2 × s, 2 × $C(CH_3)_2$); *m*/*z* (APCI + ve): 260.2 (M − N_2 + H^+, 100%).

6-Azido-6-deoxy-2,3 : 4,5-di-*O*-isopropylidene-1-*O*-methylsulfonyl-D-galactitol 23

Methanesulfonyl chloride (66 µl, 0.85 mmol) was added to a stirred solution of the azido alcohol **19** (204 mg, 0.71 mmol) and 4-dimethylaminopyridine (4 mg, catalytic) in pyridine (4 ml) at 0 °C, under an atmosphere of nitrogen. After 2.5 h, TLC (ethyl acetate–hexanes 1 : 2) indicated complete conversion of the starting material (R_f 0.2) to a single product (R_f 0.25). The solvent was removed *in vacuo* (co-evaporated with toluene) and the residue dissolved in dichloromethane (50 ml) and washed with water (20 ml) and brine (10 ml). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate–hexanes 1 : 2) to give the azido mesylate **23** (259 mg, 100%) as an amorphous solid (Found: C, 42.64; H, 6.30; N, 11.29. $C_{13}H_{23}O_7N_3S$ requires: C, 42.73; H, 6.34; N, 11.50%); $[\alpha]_D^{23}$ +32.8 (*c*, 1.33 in $CHCl_3$); ν_{max} (thin film): 2103 (N_3) cm^{-1}; δ_H ($CDCl_3$): 1.43, 1.44, 1.47, 1.51 (12H, 4 × s, 2 × $C(CH_3)_2$), 3.13 (3H, s, SO_2CH_3), 3.38 (1H, dd, $J_{6,5}$ 5.0 Hz, $J_{6,6'}$ 13.2 Hz, H-6), 3.74 (1H, dd, $J_{6',5}$ 2.7 Hz, H′-6), 3.85 (2H, m, H-3, H-4), 4.19 (1H, ddd, $J_{5,4}$ Hz, H-5), 4.26 (1H, ddd, H-2), 4.38 (1H, dd, $J_{1,1'}$ 11.3 Hz, $J_{1,2}$ 5.4 Hz, H-1), 4.58 (1H, dd, $J_{1',2}$ 2.3 Hz, H′-1); δ_C ($CDCl_3$): 25.8, 26.9 (2 × q, 2 × $C(CH_3)_2$), 37.7 (q, SO_2CH_3), 51.6, 68.8 (2 × t, C-1, C-6), 77.4, 78.0, 78.7, 80.0 (4 × d, C-2, C-3, C-4, C-5), 110.7, 110.9 (2 × s, 2 × $C(CH_3)_2$); *m*/*z* (APCI + ve): 338.1 (M − N_2 + H^+, 100%).

Methyl 2,5-anhydro-6-azido-6-deoxy-D-talonate 27 and methyl 2,5-anhydro-6-azido-6-deoxy-L-allonate 33

Trifluoromethanesulfonic anhydride (2.83 ml, 16.8 mmol) was added to a stirred solution of the azido lactone **22** (2.27 g, 11.2 mmol) in anhydrous ethyl acetate (80 ml) and dry pyridine (4.53 ml, 56.0 mmol) at −10 °C, under an atmosphere of nitrogen. The reaction mixture was stirred at −10 °C for 15 min. TLC (ethyl acetate–hexanes 3 : 1) indicated complete conversion of the starting material (R_f 0.3) to a major product (R_f 0.8). Methanol (160 ml) was added and the reaction mixture allowed to warm to room temperature and stirred for 40 h. TLC (ethyl acetate–hexanes 3 : 1) indicated conversion of the triflate (R_f 0.8) to a major product (R_f 0.3). The solvent was removed *in vacuo* (co-evaporation with toluene) and the residue preadsorbed onto silica and purified by flash chromatography (ethyl acetate–hexanes 1 : 1 to 2 : 1) to yield an inseparable mixture of *methyl* D-*talonate* **27** and *methyl* L-*allonate* **33** (1.12 g, 46%) as a colourless oil (HRMS − N_2 + H^+: 190.071801. $C_7H_{11}O_5N_3$ − N_2 + H^+ requires: 190.071548); ν_{max} (thin film): 3436 (OH), 2107 (N_3), 1740 (C=O, ester) cm^{-1}; δ_H (CD_3OD), *methyl* D-*talonate* **27**: 3.48 (2H, a-d, H-6, H′-6), 3.76 (3H, s, CO_2CH_3), 4.14 (1H, a-t, H-4), 4.22 (1H, m, H-5), 4.28–4.32 (2H, m, H-2, H-3); δ_H (CD_3OD) *methyl* L-*allonate* **33**: 3.41 (1H, dd, $J_{6,5}$ 6.0 Hz, $J_{6,6'}$ 13.2 Hz, H-6), 3.48 (1H, dd, $JJ_{6',5}$ 3.2 Hz, H′-6), 3.75 (3H, s, CO_2CH_3), 3.94 (1H, dd, $J_{4,3}$ 5.0 Hz, $J_{4,5}$ 6.6 Hz, H-4), 4.01 (1H, m, H-5), 4.19 (1H, dd, $J_{3,2}$ 3.4 Hz, H-3), 4.36 (1H, d, H-2); δ_C (CD_3OD, 50.3 MHz) *methyl* D-*talonate* **27**: 50.2 (t, C-6), 51.4 (q, CO_2CH_3), 71.5, 75.8, 80.3, 80.6 (4 × d, C-2, C-3, C-4, C-5), 173.2 (s, C=O), δ_C (CD_3OD, 50.3 MHz) *methyl* L-*allonate* **33**: 51.4 (q, CO_2CH_3), 52.2 (t, C-6), 72.3, 74.2, 82.3, 82.5 (4 × d, C-2, C-3, C-4, C-5), 171.9 (s, C=O); *m*/*z*

(APCI + ve): 190 (M − N_2 + H^+, 36%), *m/z* (APCI − ve): 216 ([M − H]$^-$, 100%).

Isopropyl 2,5-anhydro-6-azido-6-deoxy-3,4-*O*-isopropylidene-D-talonate 29 and isopropyl 2,5-anhydro-6-azido-6-deoxy-3,4-*O*-isopropylidene-L-allonate 35

A mixture of the methyl esters **27** and **33** (1.12 g, 5.16 mmol) was stirred in a 5% v/v solution of hydrogen chloride in propan-2-ol (20 ml), at 70 °C, under an atmosphere of nitrogen. After 4 h, TLC (ethyl acetate–hexanes 2:1) indicated complete conversion of the starting material (R_f 0.4) to a major product (R_f 0.5). The reaction mixture was cooled and acetone (40 ml) added. After 2 h, TLC (ethyl acetate–hexanes 1:1) indicated the formation of a major product (R_f 0.8). Sodium hydrogen carbonate (7 g, excess) was added and the reaction mixture stirred for 1 h and then filtered through Celite. The solvent was removed *in vacuo* and the residue purified by flash chromatography (diethyl ether–hexanes 1:10) to yield *isopropyl* D-*talonate* **29** (861 mg, 65%) as a colourless oil (Found: C, 50.52; H, 7.01; N, 14.55. $C_{12}H_{19}O_5N_3$ requires: C, 50.52; H, 6.71; N, 14.73%); $[\alpha]_D^{26}$ −7.0 (*c*, 0.93 in $CHCl_3$); ν_{max} (thin film): 2101 (N_3), 1745 (C=O, ester) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.28 (6H, a-d, *J* 6.2 Hz, CH(CH_3)$_2$), 1.35, 1.51 (6H, 2 × s, C(CH_3)$_2$), 3.56 (1H, dd, $J_{6,5}$ 6.2 Hz, $J_{6,6'}$ 12.7 Hz, H-6), 3.61 (1H, dd, $J_{6',5}$ 6.8 Hz, H′-6), 4.26 (1H, m, H-5), 4.54 (1H, br s, H-2), 4.74 (1H, dd, $J_{4,3}$ 5.9 Hz, $J_{4,5}$ 3.8 Hz, H-4), 4.93 (1H, dd, $J_{3,2}$ 0.6 Hz, H-3), 5.07 (1H, septet, CH(CH_3)$_2$); δ_C ($CDCl_3$, 50.3 MHz): 21.6 (q, CH(CH_3)$_2$), 24.8, 25.9 (2 × q, C(CH_3)$_2$), 49.5 (t, C-6), 69.1, 80.3, 80.5, 82.7, 84.2 (5 × d, C-2, C-3, C-4, C-5, *C*H(CH_3)$_2$), 113.3 (s, *C*(CH_3)$_2$), 169.4 (s, *C*=O); *m/z* (APCI + ve): 258 (M − N_2 + H^+, 100%); and *isopropyl* L-*allonate* **35** (345 mg, 23%) (Found: C, 50.59; H, 7.01; N, 14.57. $C_{12}H_{19}O_5N_3$ requires: C, 50.52; H, 6.71; N, 14.73%); $[\alpha]_D^{26}$ −23.9 (*c*, 1.04 in $CHCl_3$); ν_{max} (thin film): 2104 (N_3), 1745 (C=O, ester) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.28 (6H, a-d, *J* 6.2 Hz, CH(CH_3)$_2$), 1.36, 1.55 (6H, 2 × s, C(CH_3)$_2$), 3.40 (1H, dd, $J_{6,5}$ 4.9 Hz, 12.9 Hz, H-6), 3.56 (1H, dd, $J_{6',5}$ 6.1 Hz, H′-6), 4.31 (1H, m, H-5), 4.55 (1H, d, $J_{2,3}$ 2.8 Hz, H-2), 4.59 (1H, dd, $J_{4,3}$ 6.3 Hz, $J_{4,5}$ 2.5 Hz, H-4), 4.91 (1H, dd, H-3), 5.10 (1H, septet, C*H*(CH_3)$_2$); δ_C ($CDCl_3$, 100.6 MHz): 21.6, 21.7 (2 × q, CH(*C*H_3)$_2$), 25.3, 26.9 (2 × q, C(*C*H_3)$_2$), 52.5 (t, C-6), 69.4, 82.6, 83.8, 84.2, 84.9 (5 × d, C-2, C-3, C-4, C-5, *C*H(CH_3)$_2$), 114.0 (s, *C*(CH_3)$_2$), 169.9 (s, *C*=O); *m/z* (APCI + ve): 258 (M − N_2 + H^+, 100%).

6-Amino-2,5-anhydro-6-deoxy-3,4-*O*-isopropylidene-L-allono-1,6-lactam 31

A solution of isopropyl L-allonate **35** (37 mg, 0.13 mmol) in propan-2-ol (2 ml) was stirred under an atmosphere of hydrogen in the presence of palladium black (5 mg). After 1.5 h, TLC (ethyl acetate–hexanes 2:1) indicated conversion of the starting material (R_f 0.5) to a major product (R_f 0.0). The reaction mixture was filtered through Celite (eluted with propan-2-ol) and the solvent removed *in vacuo* to give a mixture of the corresponding amine and the lactam **31**. Upon prolonged drying of the crude product, the lactam **31** (R_f 0.3 in ethyl acetate) was the sole product and was purified by flash chromatography (ethyl acetate) to afford *the tricycle* D-*allonolactam* **31** (26 mg, 100%) as a white crystalline solid (Found: C, 54.36; H, 6.89 N, 7.09. $C_9H_{13}O_4N$ requires: C, 54.26; H, 6.58; N, 7.03%); mp 192 °C (ethyl acetate); $[\alpha]_D^{23}$ −39.2 (*c*, 0.75 in $CHCl_3$), $[\alpha]_D^{22}$ −25.7 (*c*, 0.75 in EtOH); ν_{max} (thin film): 3210 (NH), 1699, 1675 (C=O, amide) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.33, 1.51 (6H, 2 × s, C(CH_3)$_2$), 3.11 (1H, dd, $J_{6,5}$ 2.6 Hz, $J_{6,6'}$ 12.0 Hz, H-6), 3.65 (1H, dd, $J_{6',5}$ 4.8 Hz, H′-6), 4.42–4.45 (2H, m, H-2, H-5), 4.71, 4.82 (2H, 2 × d, $J_{3,4}$ 5.8 Hz, H-3, H-4), 6.61 (1H, br s, NH); δ_C (CD_3OD, 100.6 MHz): 24.8, 26.0 (2 × q, C(*C*H_3)$_2$), 43.4 (t, C-6), 77.6, 81.8, 83.6, 84.2 (4 × d, C-2, C-3, C-4, C-5), 113.3 (s, *C*(CH_3)$_2$), 168.8 (s, *C*=O); *m/z* (APCI + ve): 200 (M + H^+, 100%).

3 Acknowledgements

This paper is in fond and respectful memory of Ralph Raphael, a rare combination of a very fine chemist and a very fine gentleman. This work was supported by GlaxoWellcome, EPSRC and BBSRC.

4 References

1 S. Y. Han, M. M. Jouillie, V. V. Fokin and N. A. Petasis, *Tetrahedron: Asymmetry.*, 1994, **5**, 2535.
2 H. Regeling, E. de Rouville and G. J. F. Chittenden, *Recl. Trav. Chim. Pays-Bas*, 1987, **106**, 461.
3 R. Csuk, M. Hugener and A. Vasella, *Helv. Chim. Acta*, 1988, **71**, 609; I. R. Vlahov, P. I. Vlahova and R. R. Schmidt, *Tetrahedron: Asymmetry*, 1993, **4**, 293; D. D. Long, S. M. Frederiksen, D. G. Marquess, A. L. Lane, D. J. Watkin, D. A. Winkler and G. W. J. Fleet, *Tetrahedron Lett.*, 1998, **39**, 6091.
4 C. Taillefumier, S. Colle and Y. Chapleur, *Carbohydr. Lett.*, 1996, **2**, 39.
5 In ref. 4, structure **7** is proposed on the basis of NMR evidence but the product formed is **5.**
6 R. M. Hann, W. D. Maclay and C. S. Hudson, *J. Am. Chem. Soc.*, 1939, **61**, 2432; G. J. F. Chittenden, *Recl. Trav. Chim. Pays-Bas*, 1989, **108**, 14.
7 Unpublished results.
8 J. Kuszmann and L. Kiss, *Carbohydr. Res.*, 1986, **153**, 45; G. W. J. Fleet and J. C. Son, *Tetrahedron*, 1988, **44**, 2637; J. G. Buchanan, K. W. Lumbard, R. J. Sturgeon, D. K. Thompson and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1.*, 1990, 699; R. C. Bernotas, *Tetrahedron Lett.*, 1990, **31**, 469.
9 I. Lundt and R. Madsen, *Synthesis*, 1992, 1129.
10 S. Hanessian, *J. Org. Chem.*, 1969, **34**, 675.
11 L. Chen and D. E. Kiely, *J. Org. Chem.*, 1996, **61**, 5847; D. E. Kiely, L. Chen and T. H. Lin, *J. Am. Chem. Soc.*, 1994, **116**, 571.
12 R. J. E. Stetz and G. W. J. Fleet, manuscript in preparation.
13 F. Moris-Varas, X.-H. Qian and C.-H. Wong, *J. Am. Chem. Soc.*, 1996, **118**, 7647.
14 G. Legler, *Adv. Carbohydr. Chem. Biochem.*, 1990, **48**, 319.
15 Assays were carried out in microtitre plates. The incubation mixture consisted of 20 µl of enzyme solution (approx. 0. 1 unit per ml), 20 µl of inhibitor solution and 100 µl of 5 mM of the appropriate *p*-nitrophenylglycoside as substrate made up in 50 mM phosphate citrate buffer at the optimum pH for the enzyme. Enzymes were tested at 30 °C apart from those extracted from animal tissues which were tested at 37 °C. For further details of the assay methods of the glycosidases, see A. A. Watson, R. J. Nash, M. R. Wormald, D. J. Harvey, S. Dealler, E. Lees, N. Asano, H. Kizu, A. Kato, R. C. Griffiths, A. J. Cairns and G. W. J. Fleet, *Phytochemistry*, 1997, **46**, 255.
16 M. D. Smith, D. D. Long, D. G. Marquess, T. D. W. Claridge and G. W. J. Fleet, *Chem. Commun.*, 1998, 2039; M. D. Smith, T. D. W. Claridge, G. E. Tranter, M. S. P. Sansom and G. W. J. Fleet, *Chem. Commun.*, 1998, 2041; D. D. Long, M. D. Smith, D. G. Marquess, T. D. W. Claridge and G. W. J. Fleet, *Tetrahedron Lett.*, 1998, **39**, 9293.
17 S. S. Choi, P. M. Myerscough, A. J. Fairbanks, B. M. Skead, C. J. F. Bichard and G. W. J. Fleet, *J. Chem. Soc., Chem. Commun.*, 1992, 1605; N. L. Hungerford and G. W. J. Fleet, unpublished results.
18 D. D. Long, N. L. Hungerford, M. D. Smith, D. E. A. Brittain, T. D. W. Claridge and G. W. J. Fleet, *Tetrahedron Lett.*, 1999, **40**, 2195.
19 T. D. W. Claridge, D. D. Long, N. L. Hungerford, M. D. Smith, R. T. Aplin, D. G. Marquess and G. W. J. Fleet, *Tetrahedron Lett.*, 1999, **40**, 2199.

Paper 8/09807G