Complex tetrahydrofurans from carbohydrate lactones: THF amino acids as building blocks for unnatural biopolymers

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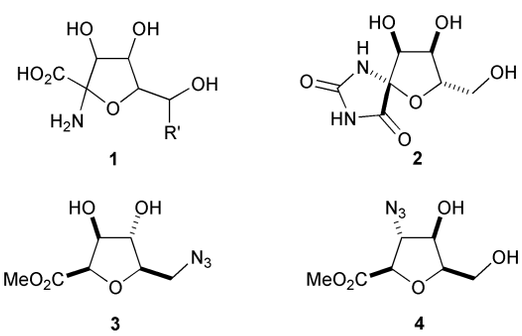
The multi-gram syntheses of two epimeric six-carbon tetrahydrofurancarboxylates based upon a D-arabinofuranose template are described. An approach to 3-*O*-benzyl protected derivatives is also detailed. Introduction of nitrogen at C-6 of these scaffolds leads to the generation of building blocks suitable for the generation of oligomers which possess well defined secondary structures. Radical bromination facilitates introduction of nitrogen at C-2, to afford anomeric α-amino acid derivatives which are elaborated to two unnatural diastereomers of the potent herbicidal natural product hydantocidin. X-Ray crystal structures of *N*-methyl-2-azido-2-deoxy-α-D-*arabino*-hex-2-ulofuranosonamide and *N*-dodecyl-2-azido-2-deoxy-β-D-*arabino*-hex-2-ulofuranosonamide are also disclosed.

Introduction

Carbohydrates bearing both an amino and a carboxylic acid functionality have been extensively investigated, and proposed both as combinatorial building blocks[1] and as peptidomimetics.[2–5] Syntheses of α-amino acids that incorporate the anomeric centre of a carbohydrate have been described[6–9] and α,α-disubstituted amino acids that incorporate the anomeric centres of glucofuranose and glucopyranose have been shown to be inhibitors of glycogen phosphorylase.[10–12] The anomeric amino acid motif **1** is also found as a component of the natural herbicide hydantocidin **2**.[13,14] In addition, anomeric amino acids as exemplified by **1** (and their pyranose analogues) have been incorporated into short peptide sequences with a view to influencing secondary structural propensities.[15–17] Unnatural oligomers which possess well defined secondary structure (foldamers)[18] have the potential for novel catalytic or selective recognition properties and this has initiated efforts directed toward their design and synthesis. The potential of THF amino acids in this regard has been demonstrated through the homo-oligomerisation of 5-(azidomethyl)-tetrahydrofuran-2-carboxylates such as **3**; both turns[19] and helices[20] have been reported for these carbopeptoids. It has been shown that an isomeric unit of **3** is an effective isostere for gly–gly in enkephalins through the synthesis of analogues with much the same biological activity as that of the natural products.[21] A similar approach has been adopted for the generation of somatostatin analogues[22] and β-hairpin peptides.[23] Recent reports[24–28] detailing the strong propensity of relatively short β-peptides to adopt secondary structures have also prompted the synthesis of 3-azidotetrahydrofuran-2-carboxylates **4**[29] and oligomeric oxetane β-amino acids which populate a 10-helical conformation.[30,31]

This paper describes the generation of α- and β-D-arabinofuranose *C*-glycosyl derivatives, including two previously unreported stereoisomers of hydantocidin **2**. The syntheses of monomeric building blocks that have been utilised in the synthesis of homo-oligomeric THF amino acids that adopt well-defined secondary structures are also reported.[19] Certain aspects of this work have been published in a preliminary form.[32]



Results and discussion

Synthesis of the THF Nucleus

2-*O*-Trifluoromethanesulfonates of carbohydrate γ- and δ- lactones in basic[33] or acidic[34] methanol give good to excellent yields of highly substituted tetrahydrofurancarboxylates. Such a procedure has been utilised for the synthesis of *C*-glycosyl derivatives of glucofuranose,[35] which have provided scaffolds for the generation of glucofuranose libraries.[36,37] Although the corresponding tosyl[38,39] and mesyl[40] esters also form tetrahydrofurans, triflates consistently produce the optimum yields of tetrahydrofurancarboxylates.

1. From D-mannonolactone 5. Application of this methodology to the synthesis of **3** indicated that the key intermediate **7** was required [Scheme 1]; in order to introduce the triflate at C-2, it is necessary to protect the primary hydroxy group at C-6 in D-mannono-1,4-lactone **5**. Kinetic acetonation of the side-chain diol in **5** by 2-methoxypropene in dimethylformamide (DMF) in the presence of toluene-*p*-sulfonic acid acid (*p*-TsOH) gave the monoacetonide **6** [89% yield]; this represents a modification of the published procedure.[41] Treatment of **6** with trifluoromethanesulfonic anhydride in dichloromethane in

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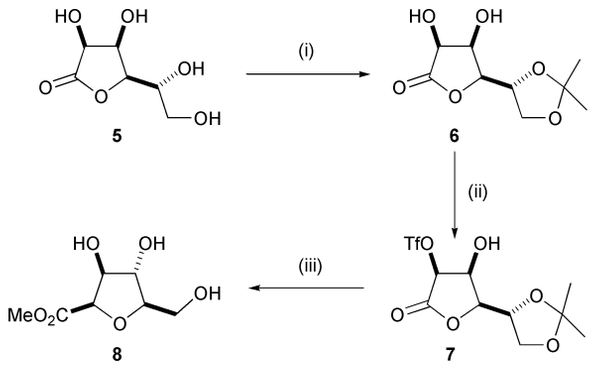
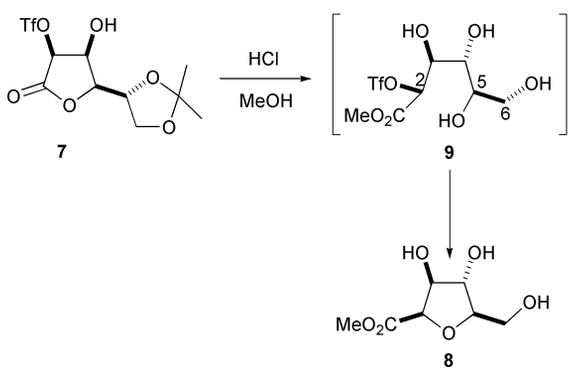


Scheme 1 (i) 2-Methoxypropene, DMF, *p*-TsOH; (ii) Tf_2O, CH_2Cl_2, Pyridine, −40 °C; (iii) 1% HCl in MeOH.

the presence of pyridine effected a highly regioselective esterification of the more nucleophilic hydroxy group α- to the lactone, to give the stable triflate **7** which could be isolated in 85% yield; however, treatment of the crude triflate **7** with hydrogen chloride in methanol gave the required ester **8** in an overall yield of 84% from **6**.

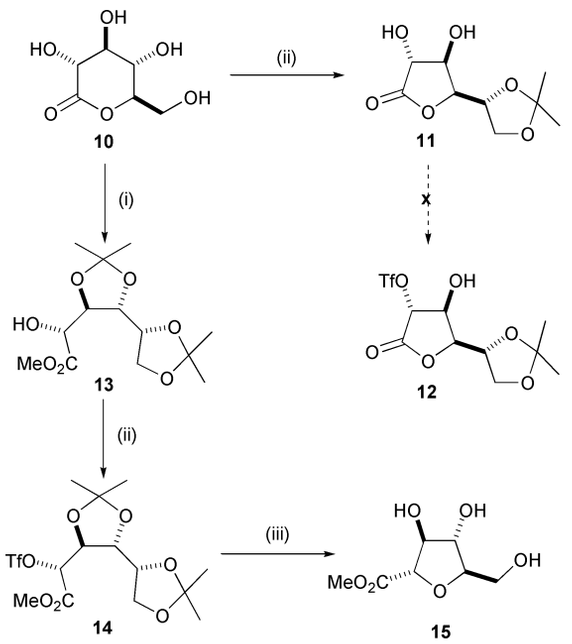
Formation of the triflate **7** has been previously reported but in significantly poorer yield.[42] Thus, multi-gram amounts of **8** may readily be prepared from **5** in an overall yield of 76%. Structural proof of the stereochemistry of the carboxylate in **8** is given later in the paper. The formation of **8** from **7** proceeds with hydrolysis of the side-chain acetonide, methanolysis of the lactone and subsequent intramolecular S_N2 closure of the resulting open-chain hydroxy triflate **9** with inversion of configuration at C-2 [Scheme 2]. No *C*-glycopyranosides (arising



Scheme 2 Mechanistic rationale for generation of the THF-carboxylate **8**.

from attack of the C-6 rather than the C-5 hydroxy group) were isolated; ring closures to *C*-glycopyranoses by nucleophilic displacement at C-2 of a sugar are rare.[43]

2. From D-gluconolactone 10. A similar sequence to that described above could be applied to the D-glucono-1,4-lactone acetonide **11** – and might allow similarly easy access to the corresponding carboxylate **15**. However, all attempts to prepare **12** – either as an isolable compound or as an intermediate for direct conversion to **15** – were unsuccessful [Scheme 3]. It is frequently the case that triflates of *cis*-diol structures on rings without protection of the neighbouring hydroxy function are useful intermediates (such as 7), but triflates derived from *trans*-1,2-diols are not easily handled, presumably because of the ready formation of epoxides. It is thus necessary to protect the C-3 hydroxy group of a suitable gluconolactone derivative and this can readily be achieved by using an open-chain triflate. Thus, reaction of the readily available D-glucono-1,5-lactone **10** with a mixture of acetone, 2,2-dimethoxypropane and methanol in the presence of toluene-*p*-sulfonic acid gave the diisopropylidene derivative **13**[44,45] in which only C-2 is unprotected [79% yield]; esterification of **13** gave the stable



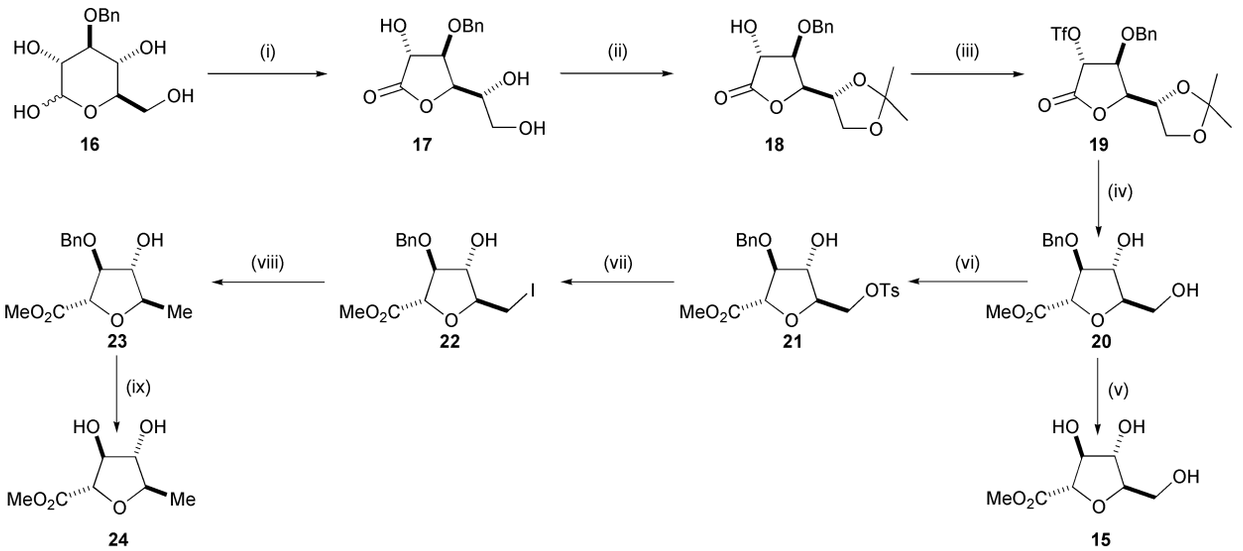
Scheme 3 (i) Acetone, $(CH_3)_2C(OMe)_2$, *p*-TsOH, MeOH; (ii) Tf_2O, CH_2Cl_2, pyridine, −40 °C; (iii) 1% HCl in MeOH.

triflate **14** [89% yield], as previously described.[46] Treatment of **14** with hydrogen chloride in methanol effected clean, quantitative conversion to the α-arabinofuranoside **15** *via* hydrolysis of the 3,4- and 5,6-*O*-isopropylidene groups and S_N2 displacement of the C-2 triflate by the C-5 hydroxy group. Thus, large quantities of **15** is easily prepared from **10** in only three steps and an overall yield of 70%.

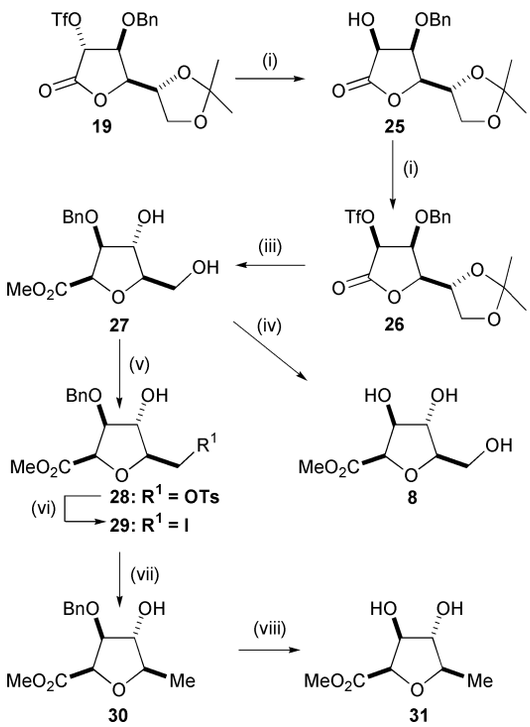
c. From 3-*O*-benzyl-D-glucose 16. An alternative approach to a 3-hydroxy-protected gluconolactone derivative is shown in Scheme 4, starting from 3-*O*-benzylglucose **16**.[47–49] Oxidation of the lactol **16** with bromine water buffered by barium carbonate gave the lactone **17** in 79% yield; the structure ascribed to **17** as the γ- rather than the δ-lactone is on the basis of the carbonyl stretch at 1780 cm^{-1}. Reaction of the lactone **17** with acetone in the presence of camphorsulfonic acid (CSA) afforded the acetonide **18** [80% yield], which upon esterification with triflic anhydride in dichloromethane in the presence of pyridine at −40 °C gave the unstable triflate **19** [86% yield]. Treatment of the triflate **19** with hydrogen chloride in methanol gave the tetrahydrofuran **20** in 98% yield. Thus, the overall yield of the protected α-D-arabinofuranosecarboxylate **20** from 3-*O*-benzylglucose **16** is 52%. It is noteworthy that none of the epimeric methyl ester **8** is formed under these conditions, since it might have been anticipated that the *trans*-triflate **19** would undergo rapid equilibration to the more stable *cis*-epimer.[50] Hydrogenation of **20** in methanol gave the unprotected α-arabinofuranose derivative **15** in 89% yield, identical in all respects to that described earlier.

Structural proof of the configuration at C-2 of the methyl carboxylate in **20** was provided by its conversion to **24**. Thus, reaction of **20** with toluene-*p*-sulfonyl chloride in dichloromethane in the presence of pyridine gave the corresponding tosyl derivative **21** [60% yield, together with 26% of recovered **20**], which with sodium iodide in butanone gave the iodide **22** [77% yield]. Hydrogenation of the iodide **22** in methanol in the presence of sodium acetate and 10% palladium on charcoal gave **23** [98% yield], from which the benzyl protecting group was removed by further hydrogenation in methanol containing a few drops of acetic acid with palladium black as the catalyst to give **24** [89% yield].

The C-2 epimer **31** of **24** was prepared by generation of the 3-*O*-benzyl mannonolactone derivative **25**. Comparison with **31**, prepared below, showed that the ring contraction of the



Scheme 4 (i) Br_2, H_2O, $BaCO_3$; (ii) acetone, CSA; (iii) Tf_2O, pyridine, CH_2Cl_2; (iv) HCl, MeOH; (v) H_2, Pd–C, MeOH; (vi) TsCl, pyridine, CH_2Cl_2; (vii) NaI, EtCOMe; (viii) H_2, Pd–C, NaOAc, MeOH; (ix) H_2, Pd-black, AcOH, MeOH.



Scheme 5 (i) CF_3CO_2Na, DMF; H_2O; (ii) Tf_2O, pyridine, CH_2Cl_2; (iii) HCl, MeOH; (iv) H_2, Pd–C, MeOH; (v) TsCl, pyridine, CH_2Cl_2; (vi) NaI, EtCOMe; (vii) H_2, Pd–C, NaOAc, MeOH; (viii) H_2, Pd-black, AcOH, MeOH.

triflate **19** to give **15** had occurred with clean inversion of configuration at C-2, [Scheme 5].

Initial reaction of **19** with sodium trifluoroacetate in dimethylformamide, followed by aqueous work-up with concomitant hydrolysis of the resulting trifluoroacetate ester, gave the inverted *manno*-alcohol **25** [93% yield]. Esterification of the free hydroxy group in **25** with trifluoromethanesulfonic anhydride gave the triflate **26** [87% yield]. Treatment of the triflate **26** with methanolic hydrogen chloride afforded the target tetrahydrofuran **27** [100% yield]. Hydrogenation of **27** in methanol in the presence of palladium on charcoal caused removal of the benzyl ether to give **8**, demonstrating that both the benzylated **26** and unbenzylated **7** triflates give the tetrahydrofurans **27** and **8** respectively, with inversion of configuration at C-2. Structural proof for **27** was obtained by conversion to **31**. Tosylation of **27** gave **28** [70% yield], which with sodium iodide gave **29** [90% yield]; sequential hydrogenation of **29** in the presence of palladium catalysts gave first the benzyl ether **30** [83% yield] and then the required methyl ester **31** [97% yield]. The properties of **31**, other than its specific rotation, were identical to those of a sample of its enantiomer, the structure of which has been determined by X-ray crystallographic analysis.[51]

The structural relationship of the tetrahydrofurans reported in this paper to the enantiomer of **31** provides unequivocal evidence for the structures proposed.

Synthesis of α-azido acid building blocks

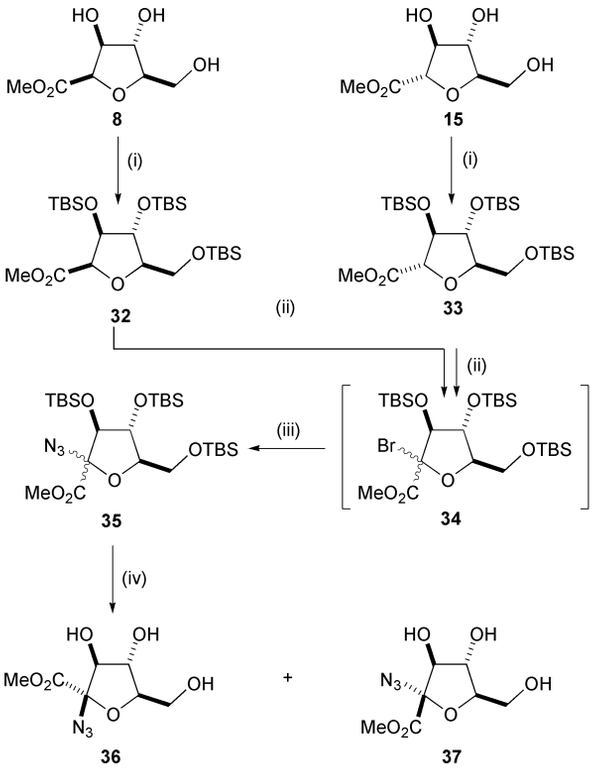
The generation of THF α-amino acid derivatives requires functionalisation at C-2; suitably protected carbohydrate carboxylates are susceptible to selective captodative radical formation[52] and readily undergo radical bromination at this position.[53]

Persilylation of carboxylates **8** and **15** with *tert*-butyldimethylsilyl chloride (TBSCl) in DMF in the presence of imidazole at 85 °C afforded the trisilyl derivatives **32** (97%) and **33** (84%), respectively [Scheme 6]. Reaction of either **32** or **33** with *N*-bromosuccinimide in tetrachloromethane at 80 °C in the presence of catalytic benzoyl peroxide afforded an unstable bromide mixture **34**, which upon treatment with sodium azide in DMF yielded an identical, inseparable mixture of epimeric anomeric amino acid derivatives **35** in an overall yield of 89% (from **32**) and 59% (from **33**), respectively.

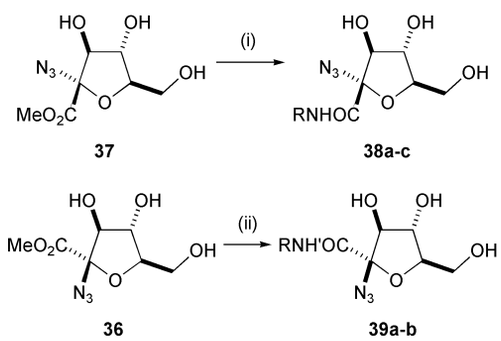
Azide displacement of bromide at the 'anomeric' position of a *C*-glycosyl carboxylate has been shown to proceed with inversion of configuration *via* an S_N2 mechanism.[54] Thus, loss of the stereointegrity at the anomeric position of the carboxylates **32** and **33** occurs during the bromination step rather than the azide displacement. Stereoselective bromination is most often observed with substrates possessing a 3,4-*O*-isopropylidene-protected *cis*-diol function.[6] Removal of the silyl protection of the epimeric azido ester mixture **35** with methanolic HCl allowed for ready separation of the products **36** (46%) and **37** (47%) by silica gel chromatography. The 1 : 1 ratio of these materials implies that the bromination of the carboxylates **32** and **33** proceeds in a non-stereoselective fashion.

The THF α-amino acid derivatives **36** and **37** were each treated with a series of primary amines in methanol in an attempt to prepare crystalline derivatives. This afforded the amido derivatives **38a**–**c** (78–89% yield) and **39a**,**b** (94, 95% yield), respectively [Scheme 7].

The absolute stereochemistry of the azide derivatives in this synthetic sequence was established *via* the X-ray crystal-structure determination of both the methylamide **38a** and the



Scheme 6 (i) TBSCl, DMF, imidazole; (ii) NBS, CCl_4, $(PhCOO)_2$; (iii) NaN_3, DMF; (iv) HCl in MeOH.



Scheme 7 (i) RNH_2, MeOH where R = (**a**) Me, (**b**) ^{n}Bu, (**c**) $CH_3(CH_2)_{11}$ (ii) RNH_2, MeOH where R = (**a**) ^{n}Bu, (**b**) $CH_3(CH_2)_{11}$.

dodecylamide **39b** [Fig. 1]. The azide substituent of the methylamide **38a** is clearly on the opposite side of the molecule to its adjacent hydroxy group at C-3. In contrast, the azide group of the dodecylamide **39b** (found to contain two asymmetric units in the unit cell), derived from the ester **36**, is on the same face of the molecule as the adjacent C-3 hydroxy group.

Formation of hydantocidin analogues

The successful formation of the THF α-amino acid derivatives **35** facilitated conversion to the remaining two diastereomers of hyantocidin **2** which have yet to be described in their deprotected forms.[55,56] Using established methodology for the construction of a spiro-hydantoin ring, the epimeric mixture **35** was first subjected to palladium-catalysed hydrogenation in methanol to afford the epimeric amino esters **40** and **41** in a total yield of 99% (with a variable diastereoisomeric ratio) [Scheme 8]. Separation of the epimers on a silica gel column was possible but it was found that both the pure products **40** and **41** slowly epimerised in solution, presumably *via* an open-chain imine. Thus, a mixture of the amines **40** and **41** was treated with potassium cyanate in acetic acid to afford the configurationally stable, separable ureas **42** (46%) and **43** (18%) together with an N-acylated side product as an anomeric mixture (31%). Hydantoin-ring formation from ureido esters has

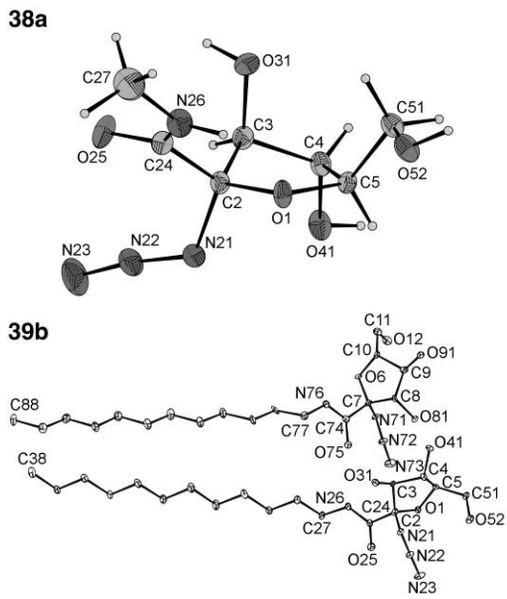
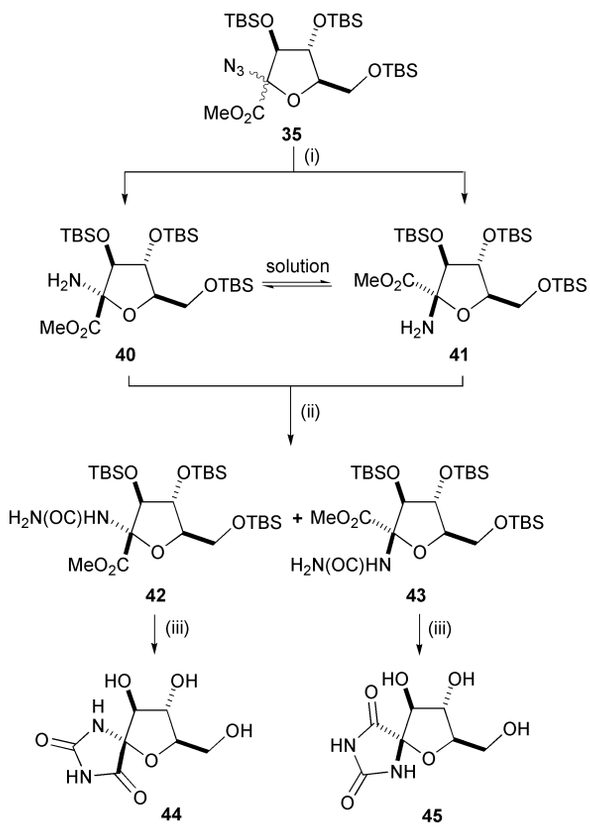


Fig. 1 X-Ray crystal structures of *N*-methyl-2-azido-2-deoxy-α-D-*arabino*-hex-2-ulofuranosonamide **38a** and *N*-dodecyl-2-azido-2-deoxy-β-D-*arabino*-hex-2-ulofuranosonamide **39b**, showing crystallographic numbering scheme.



Scheme 8 (i) H_2, Pd-black, MeOH (ii) KOCN, AcOH (iii) TBAF, THF.

previously been accomplished under both acidic and basic conditions[57,58] and both approaches appeared compatible with concomitant silyl removal. Treatment of either pure urea **42** or **43** with aqueous TFA resulted in hydantoin-ring formation in high yield and complete silyl ether cleavage. However, in all cases the reaction was accompanied by significant epimerisation at C-2 to give an inseparable mixture of final compounds **44** and **45**. Epimerisation of ureido esters and the hydantoin ring itself has been observed in strongly acidic or basic conditions. Employing tetrabutylammonium fluoride (TBAF) in THF resulted in formation of the deprotected hydantoins **44**

and **45** in quantitative yield from their respective ureido esters **42** and **43**. Inspection of the 500 MHz ^{1}H NMR spectrum of each sample of **44** and **45** prepared by the TBAF method revealed that both were very slightly contaminated with their C-2 epimer (less than 5% epimerisation in each case). A pure sample of the hydantoin **45** was obtained by crystallisation. The stereochemical assignment at C-2 of the ureas **42** and **43** was determined from NOE studies, and by analogy the absolute configuration of the hydantoins **44** and **45** was established. The NH of the urea moiety of ureido ester **42** showed a very strong NOE to H-3 and a weak NOE to the *tert*-butyl of the silyl group on OH-3 [Fig. 2]. This is consistent with the urea being

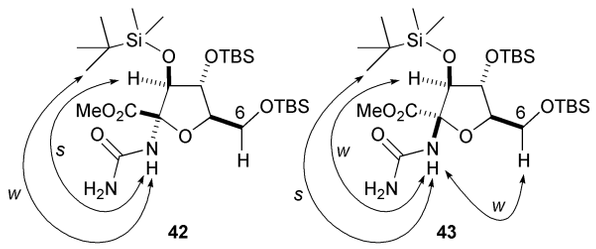


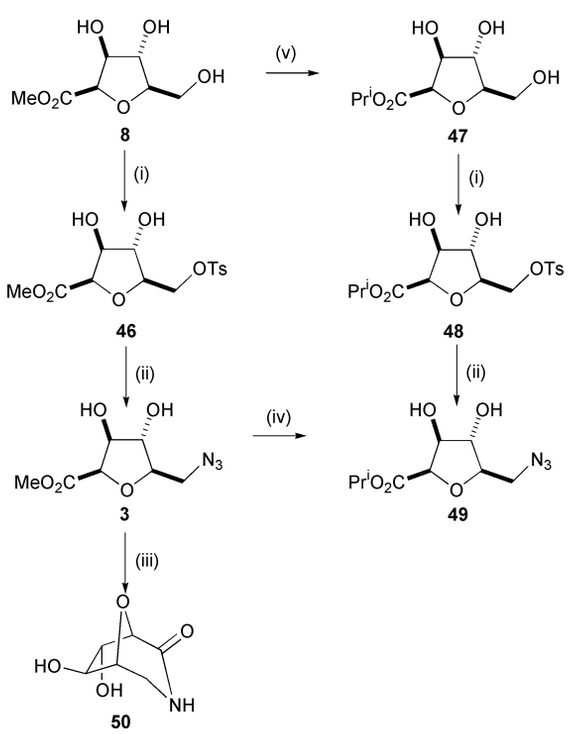
Fig. 2 Significant NOE enhancements observed for the epimeric ureas **42** and **43** (*s* = strong, *w* = weak).

found on the same side of the ring as the H-3 proton. Ureido ester **43** showed a weak NOE between the urea NH and H-3, H-4 and H_2-6. This is indicative of the urea being orientated on the same side of the ring as the methylene C-6. The strong NOE between the NH and the *tert*-butyl of the silyl group on OH-3 further supported this assertion.

δ-Amino acid building blocks: dipeptide isosteres

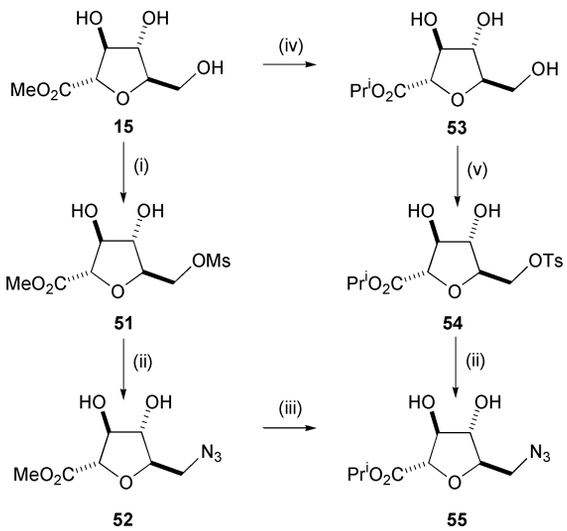
Elaboration of the methyl carboxylates **8** and **15** to THF amino derivatives necessitated selective introduction of nitrogen at C-6. Accordingly, the ester **8** was treated with toluene-*p*-sulfonyl chloride in pyridine in the presence of 3Å molecular sieves at 0 °C to afford the C-6 tosyl ester **46** in 79% yield [Scheme 9].

Reaction of the sulfonate ester **46** with sodium azide in DMF at 90 °C gave the 6-azido compound **3** in 85% yield. Reaction of



Scheme 9 (i) TsCl, pyridine, 3 Å sieves; (ii) NaN_3, DMF; (iii) H_2, Pd, MeOH; (iv) K_2CO_3, IPA; (v) NaOH(aq.); then IPA, H_2SO_4.

the crude tosylester **46** with sodium azide afforded the THF amino acid derivative **3** in an improved yield of 71% over the two steps (**8** ⟶ **46** ⟶ **3**). Through a modification of this procedure, ester **15** reacted with methanesulfonyl chloride in pyridine in the presence of 4-(dimethylamino)pyridine (DMAP) to yield the mesyl derivative **51** in 72%, which was subsequently displaced with azide to afford the azido compound **52** in 98% yield [Scheme 10].



Scheme 10 (i) MsCl, pyridine, DMAP; (ii) NaN_3, DMF; (iii) K_2CO_3, IPA; (iv) NaOH(aq.); then IPA, H_2SO_4; (v) TsCl, pyridine, 3 Å sieves.

The 6-azido methyl carboxylates **3** and **52** each represent a THF amino acid derivative in which both the amino and carboxylic acid function are present in a protected form. Differential deprotection of such frameworks allows isolation of amino and acid components.[59] Reduction of the azide functionality of the methyl ester **3** through catalytic hydrogenation conditions afforded the bicyclic lactam **50**, presumably *via* spontaneous intramolecular closure of a non-isolable C-6 amine onto the ester across the tetrahydrofuran. Hydrogenation of **52**, in which the azide functionality is *trans* to the methyl ester, resulted in complex mixtures, probably arising from uncontrolled intermolecular condensations. It was envisaged that a more hindered, less reactive ester could (in both cases) facilitate isolation of a 6-amino component. Transesterification of **3** and **52** was best achieved with propan-2-ol (IPA) in the presence of potassium carbonate at 70 °C to afford the isopropyl esters **49** and **55** in 78% and 85% yield, respectively. An alternative route could be envisaged through formation of the isopropyl ester prior to the introduction of azide at C-6. It was found that transesterification of the methyl esters **8** and **15** was best achieved *via* a two-step protocol; initial hydrolysis with aqueous sodium hydroxide and subsequent treatment with IPA and conc. sulfuric acid at 80 °C afforded the isopropyl esters **47** and **53** in 97% and 90% yield, respectively. Esterification of the C-6 hydroxy groups of **47** and **53** with toluene-*p*-sulfonyl chloride in pyridine in the presence of 3Å molecular sieves gave the tosyl esters **48** (83%) and **54** (62%), which both underwent efficient displacement by sodium azide in DMF at 90 °C to yield the azides **49** (78%) and **55** (99%), respectively.

Conclusions

The generation of THF carboxylates from carbohydrate lactones has been demonstrated to be a short and efficent process. Elaboration of these intermediates through functionalisation at either C-2 or C-6 provides access to THF amino acid derivatives; this prompted the total syntheses of two unknown diastereoisomers of the natural herbicide hydantocidin and also provided monomeric components suitable for oligomerisation to the carbopeptoid class of foldamers.

Experimental

Hexane refers to petroleum ether boiling in the range 60–80 °C, distilled before use; CH_2Cl_2 was distilled from calcium hydride. All other solvents were used as supplied (AR or HPLC grade). 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 of 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(VI) in 2 M sulfuric acid. Column chromatography was performed on Sorbsil C 60 40/60 silica. 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; concentrations are quoted in g (100 mL) and $[\alpha]_D$-values are in units of 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR spectra were recorded, unless otherwise stated, on either a Bruker AM 500 or an AMX 500 spectrometer (500 MHz) or, where stated, on a Varian Gemini 200 or a Bruker AC 200 spectrometer (200 MHz). ^{13}C NMR spectra were recorded, unless otherwise stated, on a Bruker AM 500 or an AMX 500 spectrometer (125.3 MHz) or, where stated, on a Varian Gemini 200 or a Bruker AC 200 spectrometer (50.3 MHz), and multiplicities were assigned using DEPT sequence. Chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. 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). The following abbreviations were used to explain multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; a, apparent. IR spectra were recorded on a Perkin–Elmer Paragon 1000 spectrophotometer using either thin films on NaCl plates (thin film) or KBr discs (KBr). Low-resolution mass spectra were recorded on either a VG MASS LAB 20–250 using desorption chemical ionisation (DCI; NH_3), 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. A solution of HCl in MeOH was generated by the addition of acetyl chloride to dry methanol. Elemental analyses were carried out by the microanalysis service of the Dyson Perrins Laboratory or the Oxford University Inorganic Chemistry Laboratory.

5,6-*O*-isopropylidene-D-mannono-1,4-lactone 6

Toluene-*p*-sulfonic acid monohydrate (100 mg, catalytic) was added to a stirred solution of D-mannono-1,4-lactone **5** (10.89 g, 61.2 mmol) in DMF (40 mL) at 0 °C, under an atmosphere of nitrogen. 2-Methoxypropene (7.25 mL, 73.4 mmol) was added dropwise at 0 °C and the stirred solution was allowed to warm to room temperature. After 20 h, TLC (ethyl acetate) indicated conversion of the starting material (R_f 0.0) to a major product (R_f 0.5). Sodium carbonate (5 g, excess) was added and the reaction mixture stirred for 2 h and then filtered through Celite. The solvent was removed *in vacuo* (co-evaporation with toluene). The residue was pre-adsorbed onto silica and purified by flash chromatography (ethyl acetate–hexane 4 : 1) to yield 5,6-*O*-isopropylidene-D-mannono-1,4-lactone **6** (11.82 g, 89%) as a white solid; m.p. 136–137 °C (ethyl acetate) [Lit.,[60] m.p. 138–139 °C]; $[\alpha]_D^{21}$ +58.5 (*c*, 1.00 in H_2O) {Lit.,[60] $[\alpha]_D^{20}$ +59.0 (*c*, 1.20 in H_2O)}; δ_H (CD_3CN; D_2O shake): 1.33, 1.39 (6H, 2 × s, C(CH_3)$_2$), 3.92 (1H, dd, $J_{6,5}$ 4.9, $J_{6,6}$ 8.9, H-6), 4.09 (1H, dd, $J_{6',5}$ 6.1, H-6′), 4.33–4.39 (3H, m, H-3, H-4, H-5), 4.47 (1H, d, $J_{2,3}$ 4.3, H-2).

5,6-*O*-Isopropylidene-2-*O*-trifluoromethylsulfonyl-D-mannono-1,4-lactone 7

Trifluoromethanesulfonic anhydride (426 μL, 2.53 mmol) was added to a stirred solution of 5,6-*O*-isopropylidene-D-mannono-1,4-lactone **6** (425 mg, 1.95 mmol) in dichloromethane (20 mL) containing dry pyridine (0.63 mL, 7.80 mmol) at −30 °C, under an atmosphere of nitrogen. The reaction mixture was stirred at −30 °C for 30 min. TLC (ethyl acetate–hexane 1 : 1) indicated complete conversion of the starting material (R_f 0.1) to a major product (R_f 0.6). Three drops of water were added and the reaction mixture was passed through a silica plug (ethyl acetate–hexane 1 : 1) topped with $MgSO_4$. The solvent was removed *in vacuo* (co-evaporation with toluene) and the residue was purified by flash chromatography (ethyl acetate–hexane 1 : 2) to yield 5,6-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-mannono-1,4-lactone **7** (580 mg, 85%) as a white solid (Found: C, 34.59; H, 3.67. $C_{10}H_{13}O_8F_3S$ requires C, 34.29; H, 3.74%); m.p. 109–110 °C (decomp.); $[\alpha]_D^{21}$ +13.6 (*c*, 1.00 in $CHCl_3$); ν_{max} (KBr): 3375 (OH), 1775 (C=O, lactone) cm^{-1}; δ_H ($CDCl_3$; 200 MHz): 1.38, 1.46 (6H, 2 × s, C(CH_3)$_2$), 2.94 (1H, b–s, OH), 4.08 (1H, dd, $J_{6,5}$ 3.6, $J_{6,6'}$ 9.3, H-6), 4.21 (1H, dd, $J_{6',5}$ 5.8, H-6′), 4.31 (1H, dd, $J_{4,3}$ 2.8, $J_{4,5}$ 8.4, H-4), 4.47 (1H, ddd, H-5), 4.80 (1H, a–dd, H-3), 5.38 (1H, d, $J_{2,3}$ 4.7, H-2); δ_C ($CDCl_3$; 50.3 MHz): 24.2, 25.9 (2 × q, C(*C*H$_3$)$_2$), 65.5 (t, C-6), 68.1, 72.1, 79.8, 80.8 (4 × d, C-2, C-3, C-4, C-5), 109.3 (s, *C*(CH$_3$)$_2$), 115.4 (q, SO_2CF_3), 168.6 (s, *C*=O); *m*/*z* (CI; NH_3): 368 (M + NH_4^+, 100), 351 (M + H^+, 30%).

Methyl 2,5-anhydro-D-gluconate 8

Method (i). Trifluoromethanesulfonic anhydride (11.3 mL, 67.1 mmol) was added to a stirred solution of 5,6-*O*-isopropylidene-D-mannono-1,4-lactone **6** (11.25 g, 51.6 mmol) in a mixture of dichloromethane (180 mL) and dry pyridine (16.7 mL, 206.4 mmol) at −30 °C, under an atmosphere of nitrogen. The reaction mixture was stirred at −30 °C for 1 h. TLC (ethyl acetate–hexane 1 : 1) indicated complete conversion of the starting material (R_f 0.1) to a major product (R_f 0.6). Water (0.6 mL) was added and the reaction mixture was passed through a silica plug (ethyl acetate–hexane 1 : 1) topped with $MgSO_4$. The solvent was removed *in vacuo* (co-evaporation with toluene) to give 5,6-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-mannono-1,4-lactone **7** as an off-white solid, which was used without further purification. The crude 5,6-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-mannono-1,4-lactone **7** was stirred in a 1% v/v solution of hydrogen chloride in methanol (65 mL), at room temperature, under an atmosphere of nitrogen. After 20 h, TLC (chloroform–methanol 7.5%) indicated complete conversion of the starting material (R_f 0.8) to a major product (R_f 0.2). Sodium hydrogen carbonate (6.5 g, excess) was added and the reaction mixture was stirred for 2 h and then filtered through Celite. The solvent was removed *in vacuo* and the residue was pre-adsorbed onto silica and purified by flash chromatography (chloroform–methanol 7.5%) to yield methyl 2,5-anhydro-D-gluconate **8** (8.28 g, 84% over two steps) as a yellow oil which solidified upon prolonged drying (Found: C, 43.70; H, 6.39. $C_7H_{12}O_6$ requires C, 43.75; H, 6.29%); m.p. 97–98 °C; $[\alpha]_D^{21}$ +27.8 (*c*, 1.00 in MeOH); ν_{max} (thin film): 3371 (OH), 1742 (C=O, ester) cm^{-1}; δ_H (CD_3CN; D_2O shake): 3.64 (1H, dd, $J_{6,5}$ 3.7, $J_{6,6'}$ 11.9, H-6), 3.70 (1H, dd, $J_{6',5}$ 3.4, H-6′), 3.71 (3H, s, CO_2CH_3), 3.87 (1H, a–dd, H-5), 4.02 (1H, a–t, H-4), 4.12 (1H, dd, $J_{3,2}$ 4.2, $J_{3,4}$ 1.7, H-3), 4.60 (1H, d, H-2); δ_C (CD_3CN): 54.0 (q, CO_2CH_3), 61.9 (t, C-6), 78.0, 78.8, 82.6, 88.3 (4 × d, C-2, C-3, C-4, C-5), 174.4 (s, *C*=O); *m*/*z* (CI; NH_3): 210 (M + NH_4^+, 100), 193 (M + H^+, 60%).

Method (ii). A solution of methyl 2,5-anhydro-3-*O*-benzyl-D-gluconate **27** (see below) (180 mg, 0.64 mmol) in methanol (10 mL) was stirred under an atmosphere of hydrogen in the presence of 10% palladium on activated carbon (10 mg). After 10 h, TLC (ethyl acetate) indicated complete conversion of the starting material (R_f 0.3) to a single product (R_f 0.0; R_f 0.2, chloroform–methanol, 37 : 3). The reaction mixture was filtered through Celite (eluted with MeOH) and the solvent was

removed *in vacuo*. The residue was purified by flash chromatography (chloroform–methanol, 37 : 3) to yield methyl 2,5-anhydro-D-gluconate **8** (84 mg, 69%). Data identical to those of product formed by method (i).

Methyl 3,4:5,6-di-*O*-isopropylidene-D-gluconate 13

Toluene-*p*-sulfonic acid monohydrate (150 mg, catalytic) was added to a stirred suspension of D-glucono-1,5-lactone **10** (10.0 g, 56.0 mmol) in a mixture of 2,2-dimethoxypropane (20 mL), acetone (6 mL) and methanol (2 mL). The reaction mixture was stirred at room temperature for 50 h, under an atmosphere of nitrogen. TLC (ethyl acetate–methanol 10%) indicated complete conversion of the starting material (R_f 0.2) to a major product (R_f 0.9). Sodium hydrogen carbonate (1 g, excess) was added and the reaction mixture was stirred for 1 h and then filtered through Celite. The solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (50 mL) and washed with water (10 mL). The aqueous phase was extracted with dichloromethane (40 mL) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate–hexane 1 : 3) to yield methyl 3,4:5,6-di-*O*-isopropylidene-D-gluconate **13** (12.9 g, 79%) as a colourless oil; $[\alpha]_D^{21}$ −2.3 (*c*, 1.00 in $CHCl_3$) [Lit.,[44,45] $[\alpha]_D^{20}$ +10.3 (*c*, 1.00 in $CHCl_3$) after distillation, −1.7 (*c*, 1.18 in $CHCl_3$) after silica gel column]; δ_H ($CDCl_3$): 1.34, 1.35, 1.38, 1.42 (12H, 4 × s, 2 × C(CH_3)$_2$), 3.05 (1H, a–dd, OH), 3.83 (3H, s, CO_2CH_3), 3.98 (1H, dd, $J_{6,5}$ 3.9, $J_{6,6'}$ 8.4, H-6), 4.05 (1H, m, H-4), 4.09 (1H, m, H-5), 4.14 (1H, dd, $J_{6',5}$ 5.8, H-6′), 4.22 (1H, a–dd, H-3), 4.34 (1H, dd, $J_{2,OH}$ 9.1, $J_{2,3}$ 1.3, H-2); δ_C ($CDCl_3$): 25.2, 26.4, 26.6, 27.1 (4 × q, 2 × C(CH_3)$_2$), 52.6 (q, CO_2CH_3), 67.8 (t, C-6), 69.4, 76.4, 77.2, 80.8 (4 × d, C-2, C-3, C-4, C-5), 109.8, 110.0 (2 × s, 2 × $C(CH_3)_2$), 172.9 (s, *C*=O).

Methyl 3,4:5,6-di-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-gluconate 14

Trifluoromethanesulfonic anhydride (8.60 mL, 51.1 mmol) was added to a stirred solution of methyl 3,4:5,6-di-*O*-isopropylidene-D-gluconate **13** (11.4 g, 39.3 mmol) in dichloromethane (100 mL) containing dry pyridine (9.54 mL, 0.12 mol) at −10 °C, under an atmosphere of nitrogen. The reaction mixture was stirred at −10 °C for 15 min. TLC (ethyl acetate–hexane 1 : 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 (100 mL) and washed successively with 2M hydrochloric acid (50 mL) and pH 7 buffer (50 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate–hexane 1 : 4) to yield methyl 3,4:5,6-di-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-gluconate **14** (14.7 g, 89%) as a white solid; m.p. 67–68 °C (ethyl acetate–hexane) [Lit.,[46] m.p. 66–67 °C]; $[\alpha]_D^{22}$ +49.8 (*c*, 1.00 in $CHCl_3$) {Lit..[44,45] $[\alpha]_D^{20}$ +44.2 (*c*, 1.10 in $CHCl_3$)}; δ_H ($CDCl_3$): 1.36, 1.40, 1.41 (12H, 3 × s, 2 × C(CH_3)$_2$), 3.87 (1H, dd, $J_{4,3}$ 7.5, $J_{4,5}$ 8.4, H-4), 3.91 (1H, dd, $J_{6,5}$ 5.8, $J_{6,6'}$ 8.8, H-6), 3.91 (3H, s, CO_2CH_3), 4.07 (1H, m, H-5), 4.22 (1H, dd, $J_{6',5}$ 6.3, H-6′), 4.55 (1H, dd, $J_{3,2}$ 1.9, H-3), 5.33 (1H, d, H-2); δ_C ($CDCl_3$): 25.0, 26.0, 27.2 (3 × q, 2 × C(CH_3)$_2$), 53.5 (q, CO_2CH_3), 68.1 (t, C-6), 76.9, 79.2, 80.4 (3 × d, C-2, C-3, C-4, C-5), 110.1, 111.4 (2 × s, 2 × $C(CH_3)_2$), 118.3 (q, *J* 19.7, SO_2CF_3), 165.4 (s, *C*=O).

Methyl 2,5-anhydro-D-mannonate 15

Method (i). Methyl 3,4:5,6-di-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-gluconate **14** (11.0 g, 26.1 mmol) was stirred in a 1% v/v solution of hydrogen chloride in methanol (40 mL), at room temperature, under an atmosphere of nitrogen. After 15 h, TLC (ethyl acetate) indicated complete conversion of the starting material (R_f 0.9) to a major product (R_f 0.1). Sodium hydrogen carbonate (5 g, excess) was added and the reaction mixture was stirred for 1 h and then filtered through Celite. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (ethyl acetate) to yield methyl 2,5-anhydro-D-mannonate **15** (5.0 g, 100%) as a colourless oil; (HRMS + H^+: 193.070494. $C_7H_{13}O_6$ requires *m*/*z*, 193.071213); $[\alpha]_D^{23}$ +47.2 (*c*, 1.00 in MeOH); ν_{max} (thin film): 3402 (OH), 1742 (C=O, ester) cm^{-1}; δ_H (D_2O): 3.69 (1H, dd, $J_{6,5}$ 5.0, $J_{6,6'}$ 12.3, H-6), 3.76 (1H, m, H-6′), 3.77 (3H, s, CO_2CH_3), 4.04–4.07 (2H, m, H-4, H-5), 4.35 (1H, at, H-3), 4.51 (1H, d, $J_{2,3}$ 4.0, H-2); δ_C (D_2O; 50.3 MHz): 53.6 (q, CO_2CH_3), 61.7 (t, C-6), 76.9, 80.2, 82.2, 85.8 (4 × d, C-2, C-3, C-4, C-5), 173.9 (s, *C*=O); *m*/*z* (APCI+ve): 193 (M + H^+, 100%).

Method (ii). A solution of methyl 2,5-anhydro-3-*O*-benzyl-D-mannonate **20** (see below) (133 mg, 0.47 mmol) in methanol (10 mL) was stirred under an atmosphere of hydrogen in the presence of 10% palladium on activated carbon (10 mg). After 17 h, TLC (ethyl acetate) indicated complete conversion of the starting material (R_f 0.3) to a single product (R_f 0.1; R_f 0.3, ethyl acetate–methanol, 9 : 1). The reaction mixture was filtered through Celite (eluted with MeOH) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (ethyl acetate–methanol, 9 : 1) to yield methyl 2,5-anhydro-D-mannonate **15** (81 mg, 89%). Data identical to those of product formed by method (i).

3-*O*-Benzyl-D-glucono-1,4-lactone 17

Bromine (1.14 mL, 22.37 mmol) was slowly added to a stirred solution of 3-*O*-benzyl-D-glucopyranose **16** (5.00 g, 18.60 mmol) and barium carbonate (5.52 g, 27.97 mmol) in water (50 mL) at 0 °C in the dark. The reaction mixture was allowed to warm to room temperature and was stirred for 4 h. TLC (ethyl acetate–methanol, 9 : 1) indicated complete conversion of the starting material (R_f 0.3) to a single product (R_f 0.5). The reaction mixture was filtered through Celite (eluted with water and ethyl acetate), and air was bubbled through the filtrate until the excess of bromine was removed. The solvent was removed *in vacuo* to give a white slurry. Ethyl acetate (100 mL) was added to the slurry and the mixture was refluxed for 30 min. The solution was decanted and this extraction procedure was repeated a further three times. The combined organic extracts were filtered, the solvent was removed *in vacuo*, and the residue was purified by flash chromatography (ethyl acetate–hexane, 7 : 3) to yield 3-*O*-benzyl-D-glucono-1,4-lactone **17** (3.93 g, 79%) (Found: C, 57.97; H, 6.33. $C_{13}H_{16}O_6$ requires C, 58.20; H, 6.01%); $[\alpha]_D^{20}$ +34.4 (*c*, 1.15 in CH_3OH); ν_{max} (thin film): 3401 (br, OH), 1780 (C=O) cm^{-1}; δ_H (CD_3OD): 3.69 (1H, dd, $J_{6,5}$ 5.9, $J_{6,6'}$ 11.5, H-6), 3.77 (1H, dd, $J_{6',5}$ 3.9, H-6′), 4.00 (1H, m, H-5), 4.27 (1H, dd, $J_{3,2}$ 4.8, $J_{3,4}$ 5.7, H-3), 4.49 (1H, d, H-2), 4.64 (1H, a–t, H-4), 4.69–4.76 (2H, AB-q, *J* 11.6, CH_2Ar), 7.27–7.51 (5H, m, Ar); δ_C (CD_3OD; 50.3 MHz): 62.9 (t, C-6), 70.4, 71.6, 79.1, 80.8 (4 × d, C-2, C-3, C-4, C-5), 72.3 (t, CH_2Ar), 127.7, 128.1, 128.3 (3 × d, Ar), 137.8 (s, Ar), 175.8 (s, *C*=O); *m*/*z* (DCI; NH_3): 286 (M + NH_4^+, 100), 269 (M + H^+, 20%).

3-*O*-Benzyl-5,6-*O*-isopropylidene-D-glucono-1,4-lactone 18

DL-Camphor-*iso*-sulfonic acid (CSA) was added to a stirred solution of 3-*O*-benzyl-D-glucono-1,4-lactone **17** (3.93 g, 14.60 mmol) in acetone (100 mL) until the solution reached pH 2. The reacion mixture was stirred at room temperature for 17 h, under an atmosphere of nitrogen. TLC (ethyl acetate–methanol, 9 : 1) indicated complete conversion of the starting material (R_f 0.5) to a major product (R_f 0.8). Sodium hydrogen carbonate (500 mg, excess) was added and the reaction mixture was stirred for 1 h and then filtered through Celite. The solvent

was removed *in vacuo* and the residue was dissolved in ethyl acetate (70 mL) and washed successively with water (15 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–hexane, 1 : 2) to yield 3-*O*-benzyl-5,6-*O*-isopropylidene-D-glucono-1,4-lactone **18** (3.62 g, 80%) as an oil (Found: C, 62.44; H, 6.36. $C_{16}H_{20}O_6$ requires C, 62.33; H, 6.54%); $[\alpha]_D^{20}$ +54.7 (*c*, 1.00 in $CHCl_3$); ν_{max} (thin film): 3401 (br, OH), 1789 (C=O) cm^{-1}; δ_H ($CDCl_3$; 500 MHz): 1.39, 1.45 (6H, 2 × s, 2 × C(CH_3)$_2$), 3.97 (1H, dd, $J_{6,5}$ 6.2, $J_{6,6'}$ 8.7, H-6), 4.12 (1H, dd, $J_{6',5}$ 6.4, H-6′), 4.28 (1H, dd, $J_{3,2}$ 4.2, $J_{3,4}$ 5.7, H-3), 4.42 (1H, b–d, H-2), 4.46 (1H, m, H-5), 4.71 (1H, dd, $J_{4,5}$ 6.3, H-4), 4.69–4.71 (2H, AB-q, *J* 11.6, CH_2Ar), 7.31–7.38 (5H, m, Ar); δ_C ($CDCl_3$; 50.3 M): 25.3, 26.5 (2 × q, C(CH_3)$_2$), 66.1 (t, C-6), 71.9, 73.0, 79.6, 80.6 (4 × d, C-2, C-3, C-4, C-5), 72.6 (t, CH_2Ar), 109.9 (s, C(CH_3)$_2$), 128.0, 128.3, 128.7 (3 × d, Ar), 137.2 (s, Ar), 175.4 (s, Ar); *m*/*z* (CI; NH_3): 326 (M + NH_4^+, 45), 309 (M + H^+, 55%).

3-*O*-Benzyl-5,6-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-glucono-1,4-lactone 19

Trifluoromethanesulfonic anhydride (1.94 mL, 11.48 mmol) was added to a stirred solution of 3-*O*-benzyl-5,6-*O*-isopropylidene-D-glucono-1,4-lactone **18** (2.36 g, 7.65 mmol) in dichloromethane (15 mL) containing and dry pyridine (1.81 mL, 23.00 mmol) at −40 °C, under an atmosphere of nitrogen. The reaction mixture was stirred at −40 °C for 2 h. TLC (ethyl acetate–hexane, 1 : 1) indicated complete conversion of the starting material (R_f 0.5) to a major product (R_f 0.6). The reaction mixture was diluted with diethyl ether (40 mL) and washed successively with water (5 mL) and 2M hydrochloric acid (11.5 mL). The aqueous phase was extracted with diethyl ether (40 mL) and the combined organic extracts washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate–hexane, 1 : 4) to yield 3-*O*-benzyl-5,6-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-glucono-1,4-lactone **19** (2.88 g, 86%), as an unstable oil (Found: C, 46.17; H, 4.62. $C_{17}H_{19}SO_8F_3$ requires C, 46.37; H, 4.35%); $[\alpha]_D^{20}$ +9.2 (*c*, 1.15 in $CHCl_3$); ν_{max} (thin film): 1810 (C=O), 1375, 1142 (S=O) cm^{-1}; δ_H ($CDCl_3$): 1.39, 1.46 (6H, 2 × s, C(CH_3)$_2$), 4.03 (1H, dd, $J_{6,5}$ 5.6, $J_{6,6'}$ 8.8, H-6), 4.14 (1H, dd, $J_{6',5}$ 6.6, H-6′), 4.44–4.48 (2H, m, H-3, H-5), 4.61 (1H, dd, $J_{4,3}$ 5.2, $J_{4,5}$ 6.8, H-4), 4.70–4.75 (2H, AB-q, *J* 11.6, CH_2Ar), 5.31 (1H, d, $J_{2,3}$ 3.7, H-2), 7.34–7.41 (5H, m, Ar); δ_C ($CDCl_3$; 50.3 MHz): 25.1, 26.5 (2 × q, C(CH_3)$_2$), 66.2 (t, C-6), 72.6, 76.9, 80.2, 80.5 (4 × d, C-2, C-3, C-4, C-5), 73.3 (t, CH_2Ar), 110.5 (s, C(CH_3)$_2$), 128.4, 128.7, 128.9 (3 × d, Ar), 135.9 (s, Ar), 166.5 (s, *C*=O); *m*/*z* (CI; NH_3): 458 (M + NH_4^+, 10), 441 (M + H^+, 5%).

Methyl 2,5-anhydro-3-*O*-benzyl-D-mannonate 20

3-*O*-Benzyl-5,6-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-glucono-1,4-lactone **19** (2.52 g, 0.57 mmol) was stirred in a 1% v/v solution of hydrogen chloride in methanol (8 mL), at room temperature, under an atmosphere of nitrogen. After 2 h, TLC (ethyl acetate–hexane, 1 : 1) indicated complete conversion of the starting material (R_f 0.6) to a major product (R_f 0.05), (R_f 0.3 in ethyl acetate). The reaction mixture was diluted with ethyl acetate (40 mL) and washed successively with water (10 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–hexane, 4 : 1) to yield methyl 2,5-anhydro-3-*O*-benzyl-D-mannonate **20** (1.16 g, 98%), as a white solid (Found C, 59.39; H, 6.12. $C_{14}H_{18}O_6$ requires C, 59.57; H, 6.43%); m.p. 79–85 °C (diethyl ether–hexane); $[\alpha]_D^{20}$ +56.0 (*c*, 1.0 in $CHCl_3$); ν_{max} (thin film): 1741 (C=O) cm^{-1}; δ_H ($CDCl_3$): 3.77 (1H, dd, $J_{6,5}$ 5.0, $J_{6,6'}$ 11.8, H-6), 3.79 (3H, s, CO_2CH_3), 3.84 (1H, dd, $J_{6,5}$ 3.6, $J_{6,6'}$ 11.9, H-6), 4.19 (1H, a–t, H-3), 4.23 (1H, a–q, H-5), 4.28 (1H, dd, $J_{4,3}$ 2.3, $J_{4,5}$ 3.8, H-4), 4.63–4.79 (2H, AB-q, *J* 11.7, CH_2Ar), 4.64 (1H, d, $J_{2,3}$ 2.2, H-2), 7.27–7.51 (5H, m, Ar); δ_C ($CDCl_3$; 50.3 M): 52.5 (q, CO_2CH_3), 62.0 (t, C-6), 72.1 (t, CH_2Ar), 76.1, 80.9, 86.4, 87.9 (4 × d, C-2, C-3, C-4, C-5), 128.1, 128.2, 128.7 (3 × d, Ar), 137.3 (s, Ar), 172.5 (s, *C*=O); *m*/*z* (DCI; NH_3): 300 (M + NH_4^+, 40), 283 (M + H^+, 10%).

Methyl 2,5-anhydro-3-*O*-benzyl-6-*O*-*p*-tolylsulfonyl-D-mannonate 21

Toluene-*p*-sulfonyl chloride (85 mg, 0.45 mmol) was added to a stirred solution of methyl 2,5-anhydro-3-*O*-benzyl-D-mannonate **20** (105 mg, 0.37 mmol) in dichloromethane (2 mL) containing and dry pyridine (0.09 mL, 1.11 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 22 h, under an atmosphere of nitrogen. TLC (ethyl acetate) indicated partial conversion of the starting material (R_f 0.3) to a single product (R_f 0.65). The reaction mixture was acidified with 2M hydrochloric acid, diluted with ethyl acetate (40 mL), and washed successively with water (10 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–hexane, 1 : 1), to yield recovered methyl 2,5-anhydro-3-*O*-benzyl-D-mannonate **20** (27 mg, 26%), and methyl 2,5-anhydro-3-*O*-benzyl-6-*O*-*p*-tolylsulfonyl-D-mannonate **21** (98 mg, 60%) as a white crystalline solid (Found: C, 57.88; H, 5.59. $C_{21}H_{24}O_8S$ requires C, 57.79; H, 5.54%); m.p. 103–106 °C (diethyl ether–hexane); $[\alpha]_D^{20}$ +49.2 (*c*, 1.00 in $CHCl_3$); ν_{max} (thin film): 1741 (C=O) 1361, 1177 (S=O) cm^{-1}; δ_H ($CDCl_3$): 2.44 (3H, s, ArCH_3), 3.77 (3H, s, CO_2CH_3), 4.14 (1H, a–t, H-3), 4.17 (2H, a–d, H_2-6), 4.24 (1H, m, H-4), 4.30 (1H, dt, $J_{4,5}$ 3.4, $J_{5,6}$ = $J_{5,6'}$ = 5.9, H-5), 4.54 (1H, d, $J_{2,3}$ 2.2, H-2), 4.57–4.63 (2H, AB-q, *J* 11.8, CH_2Ar), 7.30–7.39 (7H, m, Ar), 7.78–7.79 (2H, m, Ar); δ_C ($CDCl_3$; 50.3 MHz): 21.5 (q, ArCH_3), 52.6 (q, CO_2CH_3), 68.4 (t, C-6), 72.1 (t, CH_2Ar), 76.1, 81.4, 83.7, 87.5 (4 × d, C-2, C-3, C-4, C-5), 127.9, 128.2, 128.7, 130.1 (4 × d, Ar), 137.2, 132.7, 145.3 (3 × s, Ar), 172.1 (s, *C*=O); *m*/*z* (CI; NH_3): 454 (M + NH_4^+, 35%).

Methyl 2,5-anhydro-3-*O*-benzyl-6-deoxy-6-iodo-D-mannonate 22

Sodium iodide (119 mg, 0.80 mmol) was added to a stirred solution of methyl 2,5-anhydro-3-*O*-benzyl-6-*O*-*p*-tolylsulfonyl-D-mannonate **21** (69 mg, 0.16 mmol) in butanone (3 mL). The reaction mixture was stirred for 7 h at reflux, under an atmosphere of nitrogen. TLC (diethyl ether) indicated conversion of the starting material (R_f 0.4) to a single product (R_f 0.6). The solvent was removed *in vacuo* and the residue was dissolved in diethyl ether (40 mL) and washed successively 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 (diethyl ether–hexane, 3 : 2) to yield recovered methyl 2,5-anhydro-3-*O*-benzyl-6-*O*-*p*-tolylsulfonyl-D-mannonate **21** (5 mg, 7%), and methyl 2,5-anhydro-3-*O*-benzyl-6-deoxy-6-iodo-D-mannonate **22** (48 mg, 77%) as an oil (Found: C, 42.89; H, 4.23. $C_{14}H_{17}O_5I$ requires C, 42.88; H, 4.37%); $[\alpha]_D^{20}$ +14.8 (*c*, 0.9 in $CHCl_3$); ν_{max} (thin film): 3463 (br, OH), 1741 (C=O) cm^{-1}; δ_H ($CDCl_3$): 3.33 (1H, dd, $J_{6,5}$ 5.7, $J_{6,6'}$ 10.1, H-6), 3.38 (1H, dd, $J_{6',5}$ 8.2, H-6′), 3.79 (3H, s, CO_2CH_3), 4.19 (1H, a–t, H-3), 4.29–4.33 (2H, m, H-4, H-5), 4.62–4.69 (2H, AB-q, *J* 11.8, CH_2Ar), 4.71 (1H, d, $J_{2,3}$ 2.1, H-2), 7.32–7.40 (5H, m, Ar); δ_C ($CDCl_3$; 50.3 MHz): 5.1 (t, C-6), 52.7 (q, CO_2CH_3), 72.3 (t, CH_2Ar), 78.9, 81.9, 86.7, 87.8, (4 × d, C-2, C-3, C-4, C-5), 128.1, 128.4, 128.8 (3 × d, Ar), 137.2 (s, Ar), 172.3 (s, *C*=O); *m*/*z* (CI; NH_3): 410 (M + NH_4^+, 40), 393 (M + H^+, 10%).

Methyl 2,5-anhydro-3-*O*-benzyl-6-deoxy-D-mannonate 23

Sodium acetate (64 mg, 0.79 mmol) was added to a solution of methyl 2,5-anhydro-3-*O*-benzyl-6-deoxy-6-iodo-D-mannonate

22 (77 mg, 0.20 mmol) in methanol (4 mL) and the mixture was stirred under an atmosphere of hydrogen in the presence of 10% palladium on activated carbon (5 mg). After 6 h, TLC (diethyl ether) indicated complete conversion of the starting material (R_f 0.6) to a single product (R_f 0.5). The reaction mixture was filtered through Celite (eluted with MeOH) and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (40 mL), acidified with 2M hydrochloric acid and washed successively with water (20 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified through a silica plug (chloroform) to yield methyl 2,5-anhydro-3-*O*-benzyl-6-deoxy-D-mannonate **23** (51 mg, 98%) as an oil (Found: C, 62.95; H, 6.74. $C_{14}H_{18}O_5$ requires C, 63.15; H, 6.81%); $[\alpha]_D^{20}$ +37.1 (*c*, 1.5 in $CHCl_3$); ν_{max} (thin film): 3435 (OH), 1739 (C=O) cm^{-1}; δ_H ($CDCl_3$; 200 MHz): 1.36 (3H, d, $J_{6,5}$ 6.5, CH_3), 3.78 (3H, s, CO_2CH_3), 3.94 (1H, dd, $J_{4,3}$ 3.0, $J_{4,5}$ 4.6, H-4), 4.14 (1H, a–t, H-3), 4.18 (1H, m, H-5), 4.61–4.72 (2H, AB-q, *J* 11.8, CH_2Ar), 4.60 (1H, d, $J_{2,3}$ 2.7, H-2), 7.34–7.38 (5H, m, Ar); δ_C ($CHCl_3$; 50.3 MHz): 18.5 (q, C-6), 52.9 (q, CO_2CH_3), 72.4 (t, CH_2Ar), 80.9, 81.3, 82.1, 88.8 (4 × d, C-2, C-3, C-4, C-5), 128.1, 128.2, 128.8 (3 × d, Ar), 137.6 (s, Ar), 172.9 (s, C=O); *m/z* (CI; NH_3): 284 (M + NH_4^+, 60), 267 (M + H^+, 20%).

Methyl 2,5-anhydro-6-deoxy-D-mannonate 24

A solution of methyl 2,5-anhydro-3-*O*-benzyl-6-deoxy-D-mannonate **23** (46 mg, 0.17 mmol) and acetic acid (4 drops) in methanol (4 mL) was stirred under an atmosphere of hydrogen in the presence of palladium-black (10 mg). After 6 h, TLC (diethyl ether) indicated complete conversion of the starting material (R_f 0.5) to a single product (R_f 0.1). The reaction mixture was filtered through Celite (eluted with MeOH) and the solvent was removed *in vacuo* to yield methyl 2,5-anhydro-6-deoxy-D-mannonate **24** (27 mg, 89%) as an oil; $[\alpha]_D^{20}$ +41.2 (*c*, 0.95 in CH_3OH); ν_{max} (thin film): 3401 (br, OH), 1738 (C=O) cm^{-1}; δ_H (CD_3OD; 500 MHz): 0.86 (3H, d, $J_{6,5}$ 6.4, CH_3) 3.20 (1H, dd, $J_{4,3}$ 4.1, $J_{4,5}$ 5.9, H-4), 3.30 (3H, s, CO_2CH_3), 3.54 (1H, m, H-5), 3.77 (1H, a–t, H-3), 3.87 (1H, d, $J_{2,3}$ 3.9, H-2); δ_C (CD_3OD; 50.3 MHz): 17.4 (q, C-6), 51.1 (q, CO_2CH_3), 80.7, 81.0, 82.0, 82.1 (4 × d, C-2, C-3, C-4, C-5), 172.8 (s, C=O); *m/z* (DCI; NH_3): 194 (M + NH_4^+, 100), 177 (M + H^+, 35%).

3-*O*-Benzyl-5,6-*O*-isopropylidene-D-mannono-1,4-lactone 25

Sodium trifluoroacetate (2.39 g, 17.50 mmol) was added to a stirred solution of 3-*O*-benzyl-5,6-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-glucono-1,4-lactone **19** (772 mg, 1.75 mmol) in dimethylformamide (5 mL). The reaction mixture was stirred for 17 h at room temperature, under an atmosphere of nitrogen. TLC (ethyl acetate–hexane, 1 : 1) indicated complete conversion of the starting material (R_f 0.7) to a single product (R_f 0.4). The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (70 mL), filtered, and washed successively with water (30 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–hexane, 1 : 2) to yield 3-*O*-benzyl-5,6-*O*-isopropylidene-D-mannono-1,4-lactone **25** (503 mg, 93%) as a white solid (Found: C, 62.49; H, 6.62. $C_{16}H_{20}O_6$ requires C, 62.33; H, 6.54%); m.p. 68–70 °C (diethyl ether–hexane); $[\alpha]_D^{25}$ +7.3 (*c*, 1.0 in $CHCl_3$); ν_{max} (thin film): 3436 (br, OH), 1790 (C=O) cm^{-1}; δ_H ($CDCl_3$; 500 MHz): 1.40, 1.46 (6H, 2 × s, $C(CH_3)_2$), 4.05 (1H, dd, $J_{6,5}$ 4.6, $J_{6,6'}$ 9.1, H-6), 4.18 (1H, dd, $J_{6',5}$ 6.0, H-6′), 4.27 (1H, dd, $J_{4,3}$ 2.9, $J_{4,5}$ 8.3, H-4), 4.36 (1H, dd, $J_{3,2}$ 4.9, H-3), 4.42 (1H, ddd, H-5), 4.46 (1H, d, H-2), 4.78–4.89 (2H, AB-q, *J* 11.3, CH_2Ar), 7.33–7.51 (5H, m, Ar); δ_C ($CDCl_3$; 50.3 MHz): 25.1, 26.8 (2 × q, $C(CH_3)_2$), 66.8 (t, C-6), 70.8, 72.0, 76.1, 79.6 (4 × d, C-2, C-3, C-4, C-5), 74.5 (t, CH_2Ar), 109.9 (s, $C(CH_3)_2$), 128.4, 128.8, 129.9, 131.8 (3 × d, Ar), 137.3 (s, Ar), 175.3 (s, C=O); *m/z* (CI; NH_3): 326 (M + NH_4^+, 100), 309 (M + H^+, 55%).

3-*O*-Benzyl-5,6-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-mannono-1,4-lactone 26

Trifluoromethanesulfonic anhydride (0.16 mL, 0.96 mmol) was added to a stirred solution 3-*O*-benzyl-5,6-*O*-isopropylidene-D-mannono-1,4-lactone **25** (228 mg, 0.74 mmol) in dichloromethane (3 mL) containing dry pyridine (0.18 mL, 2.22 mmol) at −40 °C, under an atmosphere of nitrogen. The reaction mixture was stirred at −40 °C for 2 h. TLC (ethyl acetate–hexane, 1 : 1) indicated complete conversion of the starting material (R_f 0.4) to a major product (R_f 0.7). The reaction mixture was diluted with diethyl ether (40 mL) and washed successively with water (5 mL) and 2M hydrochloric acid (1 mL). The aqueous phase was extracted with diethyl ether (40 mL) and the combined organic extracts washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate–hexane, 1 : 5) to yield 3-*O*-benzyl-5,6-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-mannono-1,4-lactone **26** (282 mg, 87%) as an unstable oil (Found: C, 46.43; H, 4.44. $C_{17}H_{19}SO_8F_3$ requires C, 46.37; H, 4.35%); ν_{max} (thin film): 1811 (C=O), 1375, 1142 (S=O) cm^{-1}; δ_H ($CDCl_3$; 200 MHz): 1.40, 1.46 (6H, 2 × s, $C(CH_3)_2$), 4.05 (1H, dd, $J_{6,5}$ 4.0, $J_{6,6'}$ 9.2, H-6), 4.14 (1H, dd, $J_{6',5}$ 5.9, H-6′), 4.21 (1H, dd, $J_{4,3}$ 2.9, $J_{4,5}$ 8.6, H-4), 4.42 (1H, m, H-5), 4.55 (1H, dd, $J_{3,2}$ 4.7, H-3), 4.67–4.92 (2H, m, CH_2Ar), 5.36 (1H, d, H-2), 7.27–7.56 (5H, m, Ar); δ_C ($CDCl_3$; 50.3 MHz): 24.9, 26.8 (2 × q, $C(CH_3)_2$), 66.5 (t, C-6), 71.5, 74.9, 78.8, 79.8 (4 × d, C-2, C-3, C-4, C-5), 74.8 (t, CH_2Ar), 110.2 (s, $C(CH_3)_2$), 128.6, 128.7, 129.0 (3 × d, Ar), 136.3 (s, Ar), 167.1 (s, C=O); *m/z* (CI; NH_3): 458 (M + NH_4^+, 55), 441 (M + H^+, 5%).

Methyl 2,5-anhydro-3-*O*-benzyl-D-gluconate 27

3-*O*-Benzyl-5,6-*O*-isopropylidene-2-*O*-trifluoromethylsulfonyl-D-mannono-1,4-lactone **26** (282 mg, 0.64 mmol) was stirred in a 1% v/v solution of hydrogen chloride in methanol (8 mL), at room temperature, under an atmosphere of nitrogen. After 6 h, TLC (ethyl acetate–hexane, 1 : 1) indicated complete conversion of the starting material (R_f 0.6) to a single product (R_f 0.05; R_f 0.6 in ethyl acetate). The reaction mixture was diluted with ethyl acetate (40 mL) and washed successively with water (10 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–hexane, 4 : 1) to yield methyl 2,5-anhydro-3-*O*-benzyl-D-gluconate **27** (180 mg, quant) as an oil (Found: C, 59.50; H, 6.25. $C_{14}H_{18}O_6$ requires C, 59.57; H, 6.43%); $[\alpha]_D^{25}$ −48.3 (*c*, 1.15 in $CHCl_3$); ν_{max} (thin film): 1743 (C=O) cm^{-1}; δ_H ($CDCl_3$): 3.75 (3H, s, CO_2CH_3), 3.78 (1H, m, H-6), 3.88 (1H, dd, $J_{6',5}$ 3.1, $J_{6',6}$ 12.2, H-6′), 3.99 (1H, ddd, $J_{5,4}$ 5.9, $J_{5,6}$ 5.9, H-5), 4.28 (1H, dd, $J_{3,2}$ 6.8, $J_{3,4}$ 5.1, H-3), 4.45 (1H, a–t, H-4), 4.64–4.79 (2H, AB-q, *J* 11.7, CH_2Ar), 4.78 (1H, d, H-2), 7.29–7.49 (5H, m, Ar); δ_C ($CDCl_3$; 50.3 MHz): 52.3 (q, CO_2CH_3), 61.5 (t, C-6), 72.4 (t, CH_2Ar), 74.0, 78.9, 85.2, 86.0 (4 × d, C-2, C-3, C-4, C-5), 127.8, 128.1, 128.6 (3 × d, Ar), 137.5 (s, Ar), 171.9 (s, C=O); *m/z* (CI; NH_3): 300 (M + NH_4^+, 100), 283 (M + H^+, 25%).

Methyl 2,5-anhydro-3-*O*-benzyl-6-*O*-*p*-tolylsulfonyl-D-gluconate 28

Toluene-*p*-sulfonyl chloride (139 mg, 0.73 mmol) was added to a stirred solution of methyl 2,5-anhydro-3-*O*-benzyl-D-gluconate **27** (175 mg, 0.61 mmol) in dichloromethane (2 mL) containing dry pyridine (0.15 mL, 1.28 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 22 h, under an atmosphere of nitrogen. TLC (ethyl acetate) indicated partial conversion of the starting material (R_f 0.3) to a single product (R_f 0.65). The reaction mixture was acidified with 2M hydrochloric acid, diluted with ethyl acetate (40 mL), and washed successively with water (10 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–hexane, 1 : 1), to yield recovered methyl 2,5-anhydro-3-*O*-benzyl-D-gluconate **27** (12 mg, 7%), and methyl 2,5-anhydro-3-*O*-benzyl-6-*O*-*p*-tolylsulfonyl-D-gluconate **28** (185 mg, 70%) as an oil (Found: C, 58.03; H, 5.33. $C_{21}H_{24}O_8S$ requires C, 57.79; H, 5.54%); $[\alpha]_D^{20}$ +34.3 (*c*, 1.2 in $CHCl_3$); ν_{max} (thin film): 1746 (C=O) 1361, 1177 (S=O) cm^{-1}; δ_H ($CDCl_3$): 2.30 (1H, b–s, OH), 2.43 (3H, s, ArCH_3), 3.70 (3H, s, CO_2CH_3), 4.14 (1H, m, H-5), 4.19 (1H, dd, $J_{3,2}$ 5.4, $J_{3,4}$ 2.7, H-3), 4.20 (1H, dd, $J_{6,5}$ 5.5, $J_{6,6'}$ 10.2, H-6), 4.25 (1H, dd, $J_{6',5}$ 8.0, H-6′), 4.38 (1H, b–s, H-4), 4.53–4.60 (2H, AB-q, *J* 11.8, CH_2Ar), 4.77 (1H, d, H-2), 7.24–7.37 (7H, m, Ar), 7.76–7.79 (2H, m, Ar); δ_C ($CDCl_3$; 50.3 MHz): 21.5 (q, ArCH_3), 52.0 (q, CO_2CH_3), 69.2 (t, C-6), 72.4 (t, CH_2Ar), 75.0, 80.3, 83.5, 84.8 (4 × d, C-2, C-3, C-4, C-5), 127.8, 128.0, 128.1, 128.2, 128.6, 130.2 (6 × d, Ar), 132.5, 137.4, 145.3 (3 × s, Ar), 169.9 (s, *C*=O); *m*/*z* (DCI; NH_3): 454 (M + NH_4^+, 100), 437 (M + H^+, 5%).

Methyl 2,5-anhydro-3-*O*-benzyl-6-deoxy-6-iodo-D-gluconate 29

Sodium iodide (225 mg, 1.50 mmol) was added to a stirred solution of methyl 2,5-anhydro-3-*O*-benzyl-6-*O*-*p*-tolylsulfonyl-D-gluconate **28** (131 mg, 0.30 mmol) in butanone (3 mL). The reaction mixture was stirred for 7 h at reflux, under an atmosphere of nitrogen. TLC (diethyl ether) indicated conversion of the starting material (R_f 0.4) to a single product (R_f 0.6). The solvent was removed *in vacuo* and the residue was pre-adsorbed onto silica and purified by flash chromatography (diethyl ether–hexane, 1 : 1) to yield methyl 2,5-anhydro-3-*O*-benzyl-6-deoxy-6-iodo-D-gluconate **29** (106 mg, 90%) as an oil (Found: C, 42.99; H, 4.39. $C_{14}H_{17}O_5I$ requires C, 42.88; H, 4.37%); $[\alpha]_D^{20}$ −48.3 (*c*, 1.20 in $CHCl_3$); ν_{max} (thin film): 3468 (OH), 1746 (C=O) cm^{-1}; δ_H ($CDCl_3$): 1.98 (1H, d, *J* 4.0, OH, D_2O exchanges), 3.41 (1H, dd, $J_{6,5}$ 5.7, $J_{6,6'}$ 9.8, H-6), 3.47 (1H, a–t, H-6′), 3.75 (3H, s, CO_2CH_3), 4.16 (1H, ddd, $J_{5,4}$ 3.1, $J_{5,6'}$ 9.2, H-5), 4.23 (1H, dd, $J_{3,2}$ 5.7, $J_{3,4}$ 2.9, H-3), 4.40 (1H, b-q, H-4, collapses to a–t upon D_2O exchange), 4.61–4.64 (2H, AB-q, *J* 11.8, CH_2Ar), 4.82 (1H, d, H-2), 7.28–7.38 (5H, m, Ar); δ_C ($CDCl_3$; 50.3 MHz): 5.2 (t, C-6), 52.2 (q, CO_2CH_3), 72.8 (t, CH_2Ar), 77.5, 80.8, 85.1, 86.5 (4 × d, C-2, C-3, C-4, C-5), 127.9, 128.3, 128.7 (3 × d, Ar), 137.3 (s, Ar), 170.4 (s, *C*=O); *m*/*z* (DCI; NH_3): 410 (M + NH_4^+, 70), 393 (M + H^+, 15%).

Methyl 2,5-anhydro-3-*O*-benzyl-6-deoxy-D-gluconate 30

Sodium acetate (89 mg, 1.08 mmol) was added to a solution of methyl 2,5-anhydro-3-*O*-benzyl-6-deoxy-6-iodo-D-gluconate **29** (106 mg, 0.27 mmol) in methanol (4 mL) and the mixture was stirred under an atmosphere of hydrogen in the presence of 10% palladium on activated carbon (5 mg). After 17 h, TLC (diethyl ether) indicated complete conversion of the starting material (R_f 0.6) to a single product (R_f 0.5). The reaction mixture was filtered through Celite (eluted with MeOH) and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (40 mL), acidified with 2M hydrochloric acid, and washed successively 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 (diethyl ether–hexane, 2 : 3) to yield recovered methyl 2,5-anhydro-3-*O*-benzyl-6-deoxy-6-iodo-D-gluconate **29** (17 mg, 16%), and methyl 2,5-anhydro-3-*O*-benzyl-6-deoxy-D-gluconate **30** (60 mg, 83%) as an oil (Found: C, 62.91; H, 6.66. $C_{14}H_{18}O_5$ requires C, 63.15; H, 6.81%); $[\alpha]_D^{25}$ −27.7 (*c*, 0.9 in $CHCl_3$); ν_{max} (thin film): 3472 (OH), 1747 (C=O) cm^{-1}; δ_H ($CDCl_3$): 1.44 (3H, d, $J_{6,5}$ 6.4, CH_3), 1.53 (1H, d, *J* 4.3, OH, D_2O exchanges), 3.76 (3H, s, CO_2CH_3), 3.91 (1H, m, H-5), 4.00 (1H, m, H-4), 4.17 (1H, dd, $J_{3,2}$ 6.0, $J_{3,4}$ 3.6, H-3), 4.61–4.66 (2H, AB-q, *J* 11.9, CH_2Ar), 4.72 (1H, d, H-2), 7.29–7.38 (5H, m, Ar); δ_C ($CDCl_3$; 50.3 MHz): 18.7 (q, C-6), 52.0 (q, CO_2CH_3), 72.4 (t, CH_2Ar), 79.4, 79.9, 81.5, 85.9 (4 × d, C-2, C-3, C-4, C-5), 127.8, 128.1, 128.6 (3 × d, Ar), 137.8 (s, Ar), 170.5 (s, *C*=O); *m*/*z* (CI; NH_3): 284 (M + NH_4^+, 100), 267 (M + H^+, 25%).

Methyl 2,5-anhydro-6-deoxy-D-gluconate 31

A solution of methyl 2,5-anhydro-3-*O*-benzyl-6-deoxy-D-gluconate **30** (81 mg, 0.30 mmol) and acetic acid (5 drops) in methanol (2 mL) was stirred under an atmosphere of hydrogen in the presence of palladium-black (10 mg). After 9 h, TLC (diethyl ether) indicated complete conversion of the starting material (R_f 0.5) to a single product (R_f 0.1). The reaction mixture was filtered through Celite (eluted with MeOH) and the solvent was removed *in vacuo* (co-evaporation with toluene). The residue was pre-adsorbed onto silica and purified by flash chromatography (ethyl acetate–hexane, 3 : 2) to yield methyl 2,5-anhydro-6-deoxy-D-gluconate **31** (52 mg, 97%) as a white crystalline solid (Found: C, 47.53; H, 6.86. $C_7H_{12}O_5$ requires C, 47.73; H, 6.87%); m.p. 81–82 °C; $[\alpha]_D^{25}$ +10.5 (*c*, 1.00 in CH_3CN) {Lit.,[33] for enantiomer m.p. 83–84 °C; $[\alpha]_D^{20}$ −12.4 (*c*, 1.00 in CH_3CN)}; ν_{max} (KBr): 3436 (OH), 1747 (C=O) cm^{-1}; δ_H ($CDCl_3$; 500 MHz): 1.45 (3H, d, $J_{6,5}$ 6.3, CH_3), 2.08 (1H, d, *J* 3.8, OH-4, D_2O exchanges), 2.54 (1H, d, *J* 5.4, OH-3, D_2O exchanges), 3.38 (3H, s, CO_2CH_3), 3.92 (1H, m, H-5), 3.94 (1H, dt, $J_{4,3}$ 2.6, H-4), 4.36 (1H, m, H-3), 4.61 (1H, d, $J_{2,3}$ 4.9, H-2); δ_C (CD_3CN; 50.3 MHz): 18.2 (q, C-6), 51.2 (q, CO_2CH_3), 78.9, 80.4, 81.3, 82.2 (4 × d, C-2, C-3, C-4, C-5), 170.4 (s, *C*=O); *m*/*z* (CI; NH_3): 194 (M + NH_4^+, 100), 177 (M + H^+, 50%). These properties are identical to those of a sample of the enantiomer.[51]

Methyl 2,5-anhydro-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-D-gluconate 32

tert-Butyldimethylsilyl chloride (8.48 g, 56.3 mmol) was added to a stirred solution of methyl 2,5-anhydro-D-gluconate **8** (3.00 g, 15.6 mmol) and imidazole (7.98 g, 117.2 mmol) in DMF (25 mL). The reaction mixture was stirred at 85 °C for 20 h, under an atmosphere of nitrogen. TLC (ethyl acetate–hexane 1 : 2) indicated complete conversion of the starting material (R_f 0.0) to a single product (R_f 0.9). The solvent was removed *in vacuo* (co-evaporation with toluene). The residue was dissolved in ethyl acetate (100 mL) and washed successively with water (40 mL) and pH 7 buffer (40 mL). The aqueous phase was extracted with ethyl acetate (25 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (diethyl ether–hexane, 1 : 10) to yield methyl 2,5-anhydro-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-D-gluconate **32** (8.10 g, 97%) as a colourless oil (Found: C, 55.96; H, 10.53. $C_{25}H_{54}O_6Si_3$ requires C, 56.13; H, 10.17%); $[\alpha]_D^{21}$ +13.6 (*c*, 1.00 in $CHCl_3$); ν_{max} (thin film): 1746 (C=O, ester) cm^{-1}; δ_H ($CDCl_3$): 0.06, 0.06, 0.11, 0.11, 0.12 (18H, 5 × s, 3 × Si(CH_3)$_2$), 0.86, 0.90, 0.90 (27H, 3 × s, 3 × SiC(CH_3)$_3$), 3.71 (1H, a–t, H-5), 3.75 (3H, s, CO_2CH_3), 3.84 (1H, dd, $J_{6,5}$ 9.7, $J_{6,6'}$ 5.5, H-6), 3.94 (1H, dd, $J_{6',5}$ 10.0, H-6′), 4.18 (1H, s, H-4), 4.21 (1H, a–d, H-3), 4.71 (1H, d, $J_{2,3}$ 3.4, H-2); δ_C ($CDCl_3$; 50.3 MHz): −5.6, −5.5, −5.4, −4.8, −4.6 (5 × q, 3 × Si(CH_3)$_2$), 17.8, 18.2 (2 × s, 3 × SiC(CH_3)$_3$), 25.5, 25.6, 25.8 (3 × q, 3 × SiC(CH_3)$_3$), 51.7 (q, CO_2CH_3), 63.1 (t, C-6), 78.3, 80.0, 81.8, 88.3 (4 × d, C-2, C-3, C-4, C-5), 169.7 (s, *C*=O); *m*/*z* (CI; NH_3): 552 (M + NH_4^+, 11), 535 (M + H^+, 100%).

Methyl 2,5-anhydro-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-D-mannonate 33

tert-Butyldimethylsilyl chloride (3.73 g, 24.7 mmol) was added to a stirred solution of methyl 2,5-anhydro-D-mannonate **15** (1.32 g, 6.9 mmol) and imidazole (3.71 g, 51.5 mmol) in DMF (11 mL). The reaction mixture was stirred at 85 °C for 14 h, under an atmosphere of nitrogen. TLC (ethyl acetate–hexane,

1 : 2) indicated complete conversion of the starting material (R_f 0.0) to a single product (R_f 0.9). The solvent was removed *in vacuo* (co-evaporation with toluene). The residue was dissolved in ethyl acetate (40 mL) and washed with water (15 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate–hexane, 5 : 95) to yield methyl 2,5-anhydro-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-D-mannonate **33** (3.07 g, 84%) as a colourless oil (Found: C, 56.26; H, 10.40. $C_{25}H_{54}O_6Si_3$ requires C, 56.13; H, 10.17%); $[\alpha]_D^{21}$ +16.0 (*c*, 1.00 in $CHCl_3$); ν_{max} (thin film): 1735 (C=O, ester) cm^{-1}; δ_H ($CDCl_3$): 0.05, 0.06, 0.07, 0.14 (18H, 4 × s, 3 × $Si(CH_3)_2$), 0.85, 0.90, 0.91 (27H, 3 × s, 3 × $SiC(CH_3)_3$), 3.68 (1H, a–t, H-5), 3.73 (3H, s, CO_2CH_3), 3.74 (1H, dd, $J_{6,5}$ 9.7, $J_{6,6'}$ 5.5, H-6), 4.09 (1H, s, H-4), 4.12 (1H, dd, $J_{6',5}$ 9.5, H-6′), 4.39, 4.42 (2H, 2 × s, H-2, H-3); δ_C ($CDCl_3$): −5.7, −5.6, −5.2, −5.1, −5.0 (5 × q, 3 × $Si(CH_3)_2$), 17.5, 17.7, 18.1 (3 × s, 3 × $SiC(CH_3)_3$), 25.4, 25.5, 25.8 (3 × q, 3 × $SiC(CH_3)_3$), 51.9 (q, CO_2CH_3), 63.2 (t, C-6), 78.4, 82.6, 84.7, 88.8 (4 × d, C-2, C-3, C-4, C-5), 171.4 (s, C=O); *m*/*z* (APCI+ve): 552 (M + NH_4^+, 26), 535 (M + H^+, 100%).

Methyl 2-azido-2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-α/β-D-*arabino*-hex-2-ulofuranosonate 35

Method 1. *N*-Bromosuccinimide (2.95 g, 16.6 mmol) was added to a stirred solution of methyl 2,5-anhydro-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-D-gluconate **32** (8.09 g, 15.1 mmol) and benzoyl peroxide (80 mg, catalytic) in tetrachloromethane (100 mL). The reaction mixture was degassed and stirred at reflux (80 °C) for 30 min, under an atmosphere of nitrogen. TLC (diethyl ether–hexane 1 : 8) indicated complete conversion of the starting material (R_f 0.3) to a major product (R_f 0.55). The reaction mixture was cooled, filtered, and the solvent was removed *in vacuo*. The crude residue was used without further purification.

Sodium azide (1.28 g, 19.7 mmol) was added to a stirred solution of the crude residue in DMF (50 mL). The reaction mixture was stirred at room temperature for 18 h, under an atmosphere of nitrogen. TLC (diethyl ether–hexane, 1 : 8) indicated conversion of the starting material (R_f 0.55) to a single product (R_f 0.6). The reaction mixture was concentrated to 15 mL and then diluted with ethyl acetate (150 mL) and washed with water (2 × 30 mL). The aqueous phase was extracted with ethyl acetate (100 mL) and the combined organic phrases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* (co-evaporation with toluene). The residue was purified by flash chromatography (diethyl ether–hexane, 1 : 19) to give an inseparable mixture of methyl 2-azido-2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-α/β-D-*arabino*-hex-2-ulofuranosonate **35** (7.74 g, 89% over two steps) as a colourless oil (HRMS − N2 + H^+: 548.326991. $C_{25}H_{54}O_6NSi_3$ requires *m*/*z*, 548.325899); ν_{max} (thin film): 2128 (N_3), 1773 (C=O, ester), 1753 (C=O, ester) cm^{-1}; δ_H ($CDCl_3$): 0.07, 0.08, 0.08, 0.13, 0.13, 0.14, 0.17, 0.18 (36H, 8 × s, 6 × $Si(CH_3)_2$), 0.86, 0.86, 0.90, 0.92, 0.95 (54H, 5 × s, 6 × $SiC(CH_3)_3$), 3.70 (1H, a–t), 3.74–3.81 (2H, m), 3.77, 3.79 (6H, 2 × s, 2 × CO_2CH_3), 3.88 (1H, dd, *J* 10.0, *J* 5.5), 4.08 (1H, ddd, *J* 1.2, *J* 5.4, *J* 6.7), 4.20 (2H, m, H-3), 4.24 (1H, b–s), 4.30 (1H, b–dd, *J* 5.5, *J* 9.5), 4.41 (1H, b–d, *J* 1.7); δ_C ($CDCl_3$; 50.3 MHz): −5.5, −5.2, −5.1, −5.0, −4.9, −4.7, −4.6 (7 × q, 6 × $Si(CH_3)_2$), 17.6, 17.7, 18.0, 18.2 (4 × s, 6 × $SiC(CH_3)_3$), 25.4, 25.6, 25.8 (3 × q, 6 × $SiC(CH_3)_3$), 51.7, 52.8 (2 × q, 2 × CO_2CH_3), 62.3, 62.8 (2 × t, 2 × C-6), 77.0, 78.1, 82.2, 83.6, 87.4, 91.2 (6 × d, 2 × (C-3, C-4, C-5)), 96.9, 99.0 (2 × s, 2 × C-2), 166.4, 167.8 (2 × s, 2 × C=O); *m*/*z* (DCI; NH_3): 593 (M − NH_4^+, 19), 548 (M − N_2 + H^+, 74%).

Method 2. *N*-Bromosuccinimide (748 mg, 4.20 mmol) was added to a stirred solution of methyl 2,5-anhydro-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-D-mannonate **33** (2.04 g, 3.82 mmol) and benzoyl peroxide (25 mg, catalytic) in tetrachloromethane (36 mL). The reaction mixture was degassed and stirred at reflux (80 °C) for 2 h 30 min, under an atmosphere of nitrogen. TLC (diethyl ether–hexane, 1 : 8) indicated complete conversion of the starting material (R_f 0.3) to a major product (R_f 0.55). The reaction mixture was cooled, filtered, and the solvent removed *in vacuo*. The crude residue was used without further purification.

Sodium azide (323 mg, 4.97 mmol) was added to a stirred solution of the crude residue in DMF (24 mL). The reaction mixture was stirred at room temperature for 20 h, under an atmosphere of nitrogen. TLC (diethyl ether–hexane, 1 : 8) indicated conversion of the starting material (R_f 0.55) to a single product (R_f 0.6). The reaction mixture was concentrated *in vacuo* (co-evaporation with toluene) and the residue was purified by flash chromatography (diethyl ether–hexane, 1 : 18) to give an inseparable mixture of methyl 2-azido-2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-α/β-D-*arabino*-hex-2-ulofuranosonate **35** (1.30 g, 59% over two steps) as a colourless oil identical to the compound mixture previously described.

Methyl 2-azido-2-deoxy-α-D-*arabino*-hex-2-ulofuranosonate 37 and methyl 2-azido-2-deoxy-β-D-*arabino*-hex-2-ulofuronosonate 36

A mixture of methyl 2-azido-2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-α/β-D-*arabino*-hex-2-ulofuranosonate **35** (3.5 g, 6.09 mmol) was stirred in a 3% v/v solution of hydrogen chloride in methanol (50 mL) at room temperature, under an atmosphere of nitrogen. After 21 h, TLC (diethyl ether–hexane, 1 : 8) indicated complete conversion of the starting material (R_f 0.6) to two major products (R_f 0.3 and R_f 0.25 in chloroform–methanol, 9 : 1). Sodium hydrogen carbonate (3 g, excess) was added and the reaction mixture was stirred for 2 h and then filtered through Celite. The solvent was removed *in vacuo* and the residue was pre-adsorbed onto silica and purified by flash chromatography (chloroform–methanol, 4% to 8% to 10%) to yield methyl 2-azido-2-deoxy-α-D-*arabino*-hex-2-ulofuranosonate **37** as a colourless oil (667 mg, 47%) (Found: C, 35.47; H, 4.94; N, 18.09. $C_7H_{11}O_6N_3$ requires C, 36.06; H, 4.75; N, 18.02%) (HRMS − N_2 + H^+: 206.066961. $C_7H_{12}O_6N$ requires *m*/*z*, 206.066462); $[\alpha]_D^{23}$ +108.9 (*c*, 1.03 in MeOH); ν_{max} (thin film): 3368 (OH), 2120 (N_3), 1748 (C=O, ester) cm^{-1}; δ_H (CD_3CN): 3.45 (1H, a–t, OH-6, exchanges with D_2O), 3.65–3.69 (2H, m, H-6, OH-4, exchanges with D_2O), 3.67 (1H, ddd, $J_{6',5}$ 3.2, $J_{6',6}$ 12.0, $J_{6',OH}$ 4.5, H-6′), 3.78 (3H, s, CO_2CH_3), 4.03 (1H, dd, $J_{3,4}$ 2.8, $J_{3,OH}$ 8.1, H-3), 4.09 (1H, m, H-4), 4.20 (1H, a–dd, H-5), 4.42 (1H, d, OH-3, exchanges with D_2O); δ_C (CD_3OD): 52.1 (q, CO_2CH_3), 61.5 (t, C-6), 76.3, 82.4, 86.9 (3 × d, C-3, C-4, C-5), 99.1 (s, C-2), 167.7 (s, C=O); *m*/*z* (APCI+ve): 206.36 (M − N_2 + H^+, 40), 104 (100%); and methyl 2-azido-2-deoxy-β-D-*arabino*-hex-2-ulofuranosonate **36** (652 mg, 46%) as a colourless oil (Found: C, 35.88; H, 4.98, N, 18.19. $C_7H_{11}O_6N_3$ requires C, 36.06; H, 4.75; N, 18.02%); $[\alpha]_D^{21}$ −36.0 (*c*, 1.08 in MeOH); ν_{max} (thin film): 3368 (OH), 2129 (N_3), 1742 (C=O, ester) cm^{-1}; δ_H (CD_3CN; D_2O shake): 3.60 (1H, dd, $J_{6,5}$ 4.8, $J_{6,6'}$ 12.3, H-6), 3.73 (1H, dd, $J_{6',5}$ 3.0, H-6′), 3.80 (3H, s, CO_2CH_3), 3.89 (1H, ddd, $J_{5,4}$ 6.8, H-5), 4.02 (1H, a–t, H-4), 4.32 (1H, d, $J_{3,4}$ 6.7, H-3); δ_C (CD_3OD): 52.2 (q, CO_2CH_3), 61.9 (t, C-6), 74.0, 79.7, 83.8 (3 × d, C-3, C-4, C-5), 94.6 (s, C-2), 168.4 (s, C=O); *m*/*z* (APCI+ve): 206.34 (M − N_2 + H^+, 57), 104 (100%).

N-Methyl-2-azido-2-deoxy-α-D-*arabino*-hex-2-ulofuranosonamide 38a

A solution of methylamine (33% w/w in industrial methylated spirits) (0.27 mL, 20.6 mmol) was added to a stirred solution of methyl 2-azido-2-deoxy-α-D-*arabino*-hex-2-ulofuranosonate **37** (48 mg, 0.206 mmol) in methanol (1 mL). The reaction mixture was stirred at room temperature for 30 min, under an

atmosphere of nitrogen. TLC (ethyl acetate–methanol, 9 : 1) indicated complete conversion of the starting material (R_f 0.6) to a major product (R_f 0.3). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (ethyl acetate–methanol, 9 : 1) to yield *N*-methyl-2-azido-2-deoxy-α-D-*arabino*-hex-2-ulofuranosonamide **38a** (43 mg, 84%) as a colourless oil which later crystallised (Found: C, 35.98; H, 5.14; N, 23.81. $C_7H_{12}O_5N_4$ requires C, 36.21; H, 5.21; N, 24.13%); m.p. 130–131 °C (ethyl acetate–hexane); $[a]_D^{21}$ +170.8 (*c*, 0.25 in MeOH); ν_{max} (KBr disc): 3369 (OH, NH), 2118 (N_3), 1669 (C=O, amide I), 1541 (amide II) cm^{-1}; δ_H (CD_3OD): 2.79 (3H, s, NCH_3), 3.73 (1H, dd, $J_{6,5}$ 5.3, $J_{6,6'}$ 12.5, H-6), 3.81 (1H, dd, $J_{6',5}$ 3.3, H-6′), 4.01 (1H, dd, $J_{4,3}$ 2.7, $J_{4,5}$ 4.6, H-4), 4.09 (1H, d, $J_{3,4}$ 2.7, H-3), 4.15 (1H, ddd, H-5); δ_C (CD_3OD): 26.2 (q, NCH_3), 62.4 (t, C-6), 78.3, 83.2, 89.1 (3 × d, C-3, C-4, C-5), 101.1 (s, C-2), 169.2 (s, *C*=O); *m*/*z* (APCI−ve): 231.10 ([M − H]$^-$ 100%).

N-Butyl-2-azido-2-deoxy-α-D-*arabino*-hex-2-ulofuranosonamide 38b

″Butylamine (0.21 mL, 2.15 mmol) was added to a stirred solution of methyl 2-azido-2-deoxy-α-D-*arabino*-hex-2-ulofuranosonate **37** (50 mg, 0.215 mmol) in methanol (1 mL). The reaction mixture was stirred at room temperature for 20 min, under an atmosphere of nitrogen. TLC (ethyl acetate–methanol, 10%) indicated complete conversion of the starting material (R_f 0.6) to a major product (R_f 0.5). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (ethyl acetate–methanol, 5%) to yield *N*-butyl-2-azido-2-deoxy-α-D-*arabino*-hex-2-ulofuranosonamide **38b** (58 mg, 89%) as a colourless oil (HRMS − N_2 + H^+: 247.129242. $C_{10}H_{19}O_5N_2$ requires *m*/*z*, 247.129397); $[a]_D^{21}$ +94.1 (*c*, 0.80 in MeOH); ν_{max} (thin film): 3338 (OH, NH), 2115 (N_3), 1663 (C=O, amide I), 1544 (C=O, amide II) cm^{-1}; δ_H (CD_3OD): 0.93 (3H, t, *J* 7.4, CH_2CH_3), 1.33–1.41 (2H, m, CH_2), 1.49–1.55 (2H, m, CH_2CH_3), 3.21–3.29 (2H, m, NHCH_2), 3.74 (1H, dd, $J_{6,5}$ 5.1, $J_{6,6'}$ 12.1, H-6), 3.82 (1H, dd, $J_{6',5}$ 3.1, H-6′), 4.02 (1H, dd, $J_{4,3}$ 2.9, $J_{4,5}$ 4.8, H-4), 4.09 (1H, d, H-3), 4.15 (1H, ddd, H-5); δ_C (CD_3OD): 12.6 (q, CH_2CH_3), 19.5, 30.9, 38.7 (3 × t, 3 × CH_2), 60.8 (t, C-6), 76.6, 81.8, 87.4 (3 × d, C-3, C-4, C-5), 99.8 (s, C-2), 167.5 (s, *C*=O); *m*/*z* (APCI−ve): 273.51 ([M − H]$^-$, 100%).

N-Dodecyl-2-azido-2-deoxy-α-D-*arabino*-hex-2-ulofuranosonamide 38c

A solution of dodecylamine (244 mg, 1.29 mmol) in methanol (0.5 mL) was added to a stirred solution of methyl 2-azido-2-deoxy-α-D-*arabino*-hex-2-ulofuranosonate **37** (30 mg, 0.129 mmol) in methanol (0.5 mL). The reaction mixture was stirred at reflux (65 °C) for 1 h, under an atmosphere of nitrogen. The crude infrared spectrum indicated loss of the ester peak (1748 cm^{-1}) and formation of an amide peak (1667 cm^{-1}). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (ethyl acetate–hexane, 5 : 1) to yield *N*-dodecyl-2-azido-2-deoxy-α-D-*arabino*-hex-2-ulofuranosonamide **38c** (39 mg, 78%) as a yellow oil (Found: C, 55.96; H, 9.27; N, 14.94. $C_{18}H_{34}O_5N_4$ requires C, 55.94; H, 8.87; N, 14.50%) (HRMS) − N_2 + H^+: 359.254870. $C_{18}H_{35}O_5N_2$ requires *m*/*z*, 359.254598); $[a]_D^{21}$ +80.2 (*c*, 0.58 in MeOH); ν_{max} (KBr disc): 3401 (OH, NH), 2116 (N_3), 1667 (C=O, amide I), 1549 (C=O, amide II) cm^{-1}; δ_H (CD_3OD): 0.89 (3H, t, *J* 7.0, CH_2CH_3), 1.28–1.32 (18H, m, $(CH_2)_9$), 1.51–1.55 (2H, m, CH_2CH_3), 3.19–3.29 (2H, m, NHCH_2), 3.73 (1H, dd, $J_{6,5}$ 5.2, $J_{6,6'}$ 12.1, H-6), 3.82 (1H, dd, $J_{6',5}$ 3.2, H-6′), 4.02 (1H, dd, $J_{4,3}$ 2.9, $J_{4,5}$ 4.7, H-4), 4.09 (1H, d, H-3), 4.16 (1H, ddd, H-5); δ_C (CD_3OD): 12.9 (q, CH_2CH_3), 22.2, 26.4, 28.8, 29.0, 29.3, 31.6, 39.0 (7 × t, 11 × CH_2), 60.8 (t, C-6), 76.7, 81.8, 87.5 (3 × d, C-3, C-4, C-5), 99.9 (s, C-2), 167.5 (s, *C*=O); *m*/*z* (APCI−ve): 385.60 ([M − H]$^-$, 100%).

N-Butyl-2-azido-2-deoxy-β-D-*arabino*-hex-2-ulofuranosonamide 39a

″Butylamine (0.20 mL, 2.06 mmol) was added to a stirred solution of methyl 2-azido-2-deoxy-β-D-*arabino*-hex-2-ulofuranosonate **36** (48 mg, 0.206 mmol) in methanol (1 mL). The reaction mixture was stirred at room temperature for 35 min, under an atmosphere of nitrogen. TLC (ethyl acetate–methanol, 10%) indicated complete conversion of the starting material (R_f 0.6) to a major product (R_f 0.5). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (ethyl acetate–methanol, 5%) to yield *N*-butyl-2-azido-2-deoxy-β-D-*arabino*-hex-2-ulofuranosonamide **39a** (53 mg, 94%) as a colourless oil (HRMS − N_2 + H^+: 247.130027. $C_{10}H_{19}O_5N_2$ requires *m*/*z*, 247.129397); $[a]_D^{23}$ −40.0 (*c*, 0.78 in MeOH); ν_{max} (thin film): 3340 (OH, NH), 2124 (N_3), 1669 (C=O, amide I), 1540 (C=O, amide II) cm^{-1}; δ_H (CD_3OD): 0.95 (3H, t, *J* 7.4, CH_2CH_3), 1.33–1.40 (2H, m, CH_2), 1.49–1.55 (2H, m, CH_2CH_3), 3.21–3.24 (2H, m, NHCH_2), 3.67 (1H, dd, $J_{6,5}$ 6.0, $J_{6,6'}$ 12.0, H-6), 3.79 (1H, dd, $J_{6',5}$ 3.4, H-6′), 3.95 (1H, ddd, H-5), 3.99 (1H, a–t, H-4), 4.20 (1H, d, $J_{3,4}$ 6.3, H-3); δ_C (CD_3OD): 12.6 (q, CH_2CH_3), 19.5, 31.0, 38.7 (3 × t, 3 × CH_2), 62.0 (t, C-6), 74.9, 81.0, 83.9 (3 × d, C-3, C-4, C-5), 95.3 (s, C-2), 169.0 (s, *C*=O); *m*/*z* (APCI−ve): 273.30 ([M − H]$^-$, 100%).

N-Dodecyl-2-azido-2-deoxy-β-D-*arabino*-hex-2-ulofuranosonamide 39b

A solution of dodecylamine (211 mg, 1.12 mmol) in methanol (0.5 mL) was added to a stirred solution of methyl 2-azido-2-deoxy-β-D-*arabino*-hex-2-ulofuranosonate **36** (26 mg, 0.112 mmol) in methanol (0.5 mL). The reaction mixture was stirred at room temperature for 30 min, under an atmosphere of nitrogen. The crude infared spectrum indicated loss of the ester peak (1748 cm^{-1}) and formation of an amide peak (1667 cm^{-1}). The solvent was removed *in vacuo* and the residue was purified by flash chromatography (ethyl acetate) to yield *N*-dodecyl-2-azido-2-deoxy-β-D-*arabino*-hex-2-ulofuranosonamide **39b** (41 mg, 95%) as a yellow oil which later crystallised (Found: C, 55.97; H, 9.11; N, 14.10. $C_{18}H_{34}O_5N_4$ requires C, 55.94; H, 8.87; N, 14.50%) (HRMS − N_2 + H^+ 359.254632. $C_{18}H_{35}O_5N_2$ requires *m*/*z*, 359.254598); m.p. 64–65 °C (ethyl acetate–hexane); $[a]_D^{21}$ −27.9 (*c*, 0.58 in MeOH); ν_{max} (KBr disc): 3401 (OH, NH), 2126 (N_3), 1653 (C=O, amide I), 1541 (C=O, amide II) cm^{-1}; δ_H (CD_3OD): 0.89 (3H, t, *J* 7.0, CH_2CH_3), 1.29–1.32 (18H, m, $(CH_2)_9$), 1.51–1.54 (2H, m, CH_2CH_3), 3.19–3.23 (2H, m, NHCH_2), 3.66 (1H, dd, $J_{6,5}$ 6.1, $J_{6,6'}$ 12.0, H-6), 3.78 (1H, dd, $J_{6',5}$ 3.4, H-6′), 3.94 (1H, ddd, H-5), 3.99 (1H, a–t, H-4), 4.19 (1H, d, $J_{3,4}$ 6.3, H-3); δ_C (CD_3OD): 12.9 (q, CH_2CH_3), 22.2, 26.4, 28.6, 29.0, 29.2, 31.6, 39.0 (7 × t, 11 × CH_2), 62.0 (t, C-6), 74.9, 81.0, 83.9 (3 × d, C-3, C-4, C-5), 95.3 (s, C-2), 169.0 (s, *C*=O); *m*/*z* (APCI−ve): 385.59 ([M − H]$^-$, 100%).

Methyl 2-amino-2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-α-D-*arabino*-hex-2-ulofuranosonate 40 and methyl 2-amino-2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-β-D-*arabino*-hex-2-ulofuranosonate 41

A solution of methyl 2-azido-2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-α/β-D-*arabino*-hex-2-ulofuranosonate **35** (1.414 g, 2.46 mmol) in methanol (25 mL) was stirred under an atmosphere of hydrogen in the presence of palladium black (100 mg, catalytic). After 18 h, TLC (diethyl ether–hexane, 1 : 1) indicated complete conversion of the starting material (R_f 0.9) to two products (R_f 0.4, R_f 0.3). The reaction mixture was filtered through Celite (eluted with methanol) and the solvent was removed *in vacuo.* The residue was purified by flash chromatography (diethyl ether–hexane, 1 : 1) to yield a mixture of methyl 2-amino-2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-α-D-*arabino*-hex-2-ulofuranosonate **40** and methyl 2-amino-2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-β-

D-*arabino*-hex-2-ulofuranosonate **41** (1.391 g, 99%) as a colourless oil. Further flash chromatography (diethyl ether–hexane, 3 : 4) of the mixture **40** and **41** (which epimerises in solution) gave pure methyl 2-amino-2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-α-D-*arabino*-hex-2-ulofuranosonate **40** as a white solid (Found: C, 54.79; H, 10.21; N, 2.23. $C_{25}H_{55}O_6NSi_3$ requires C, 54.60; H, 10.08; N, 2.55%); m.p. 70–71 °C (ethyl acetate–hexane); ν_{max} (KBr disc): 3405, 3324 (OH, NH), 1749 (C=O, ester) cm^{-1}; δ_H (C_6D_6): 0.06, 0.08, 0.13, 0.15, 0.16, 0.19, (18H, 6 × s, 3 × Si(CH_3)$_2$), 0.95, 0.96, 0.97 (27H, 3 × s, 3 × SiC(CH_3)$_3$), 2.21 (2H, b–s, NH_2), 3.43 (3H, s, CO_2CH_3), 3.82 (1H, dd, $J_{6,5}$ 7.4, $J_{6,6'}$ 10.2, H-6), 3.86 (1H, dd, $J_{6',5}$ 5.0, H-6′), 4.14 (1H, ddd, $J_{5,4}$ 2.8, H-5), 4.31 (1H, a–t, H-4), 4.73 (1H, d, $J_{3,4}$ 2.5, H-3); δ_C (C_6D_6, 50.3 MHz): −5.1, −4.6, −4.5, −4.3 (4 × q, 3 × Si(CH_3)$_2$), 18.1, 18.4, 18.6 (3 × s, 3 × SiC(CH$_3$)$_3$), 26.0, 26.1, 26.2 (3 × q, 3 × SiC(CH_3)$_3$), 51.9 (q, CO_2CH_3), 64.0 (t, C-6), 78.9, 80.9, 85.3 (3 × d, C-3, C-4, C-5), 94.3 (s, C-2), 171.3 (s, C=O); *m*/*z* (APCI+ve): 550.74 (M + H^+, 100%); and methyl 2-amino-2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-β-D-*arabino*-hex-2-ulofuranosonate **41** (contaminated with **40**); δ_H (C_6D_6): 0.07, 0.12, 0.14, 0.14, 0.14 (18H, 5 × s, 3 × Si(CH_3)$_2$), 0.92, 0.95, 0.96 (27H, 3 × s, 3 × SiC(CH_3)$_3$), 2.20 (2H, b–s, NH_2), 3.44 (3H, s, CO_2CH_3), 3.92 (1H, dd, $J_{6,5}$ 8.0, $J_{6,6'}$ 10.2, H-6), 3.97 (1H, dd, $J_{6',5}$ 5.6, H-6′), 4.22 (1H, d, $J_{3,4}$ 2.2, H-3), 4.29 (1H, ddd, $J_{5,4}$ 2.4, H-5), 4.33 (1H, a–t, H-4); δ_C (C_6D_6, 50.3 MHz): −5.1, −4.6, −4.5, −4.3 (4 × q, 3 × Si(CH_3)$_2$), 18.1, 18.4, 18.6 (3 × s, 3 × SiC(CH$_3$)$_3$), 26.0, 26.1, 26.2 (3 × q, 3 × SiC(CH_3)$_3$), 51.6 (q, CO_2CH_3), 64.5 (t, C-6), 79.3, 84.8, 87.0 (3 × d, C-3, C-4, C-5), 97.3 (s, C-2), 169.8 (s, C=O).

Methyl 2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-2-ureido-α-D-*arabino*-hex-2-ulofuranosonate 42, methyl 2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-2-ureido-β-D-*arabino*-hex-2-ulofuranosonate 43 and methyl 2-acetamido-2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-α/β-D-*arabino*-hex-2-ulofuranosonate

Potassium cyanate (554 mg, 6.83 mmol) was added to a stirred solution of methyl 2-amino-2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-α-D-*arabino*-hex-2-ulofuranosonate **40** and methyl 2-amino-2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-β-D-*arabino*-hex-2-ulofuranosonate **41** (1.25 g, 2.28 mmol) in acetic acid (30 mL). The solution was stirred at room temperature, under an atmosphere of nitrogen for 1h 45 min. TLC (diethyl ether–hexane, 1 : 1) indicated complete conversion of the starting material mixture (R_f 0.4, R_f 0.3) to three major products (R_f 0.1, R_f 0.0 and R_f 0.0). The solvent was removed *in vacuo* (co-evaporation with toluene) and the residue was dissolved in ethyl acetate (100 mL) and washed with water (2 × 30 mL). The aqueous phase was extracted with ethyl acetate (50 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (diethyl ether–hexane 1 : 2; then diethyl ether; then ethyl acetate–hexane, 5 : 4) to yield methyl 2-acetamido-2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-α/β-D-*arabino*-hex-2-ulofuranosonate (420 mg, 31%) as a colourless oil (HRMS + H^+: 592.351016. $C_{27}H_{58}O_7NSi_3$ requires *m*/*z*, 592.352114); ν_{max} (KBr disc): 3428 (NH), 1746 (C=O, ester), 1707 (C=O, amide) cm^{-1}; δ_H ($CDCl_3$): 0.05, 0.08, 0.09, 0.12, 0.17, 0.20, 0.23 (36H, 7 × s, 6 × Si(CH_3)$_2$), 0.87, 0.87, 0.89, 0.94, 0.99 (54H, 5 × s, 6 × SiC(CH_3)$_3$), 1.94, 1.98 (6H, 2 × s, 2 × CH_3CONH), 3.57, 3.67 (2H, 2 × a–t, 2 × H-6), 3.78, 3.79 (2H, 2 × dd, 2 × H-6′), 3.78, 3.79 (6H, 2 × s, 2 × CO_2CH_3), 4.10–4.16 (3H, m), 4.18–4.20 (3H, m), 6.60, 7.22 (2H, 2 × s, 2 × NH); δ_C ($CDCl_3$; 50.3 MHz): −5.7, −5.4, −5.2, −4.8, −4.7 (5 × q, 6 × Si(CH_3)$_2$), 17.5, 17.6, 17.9, 18.2 (4 × s, 6 × SiC(CH$_3$)$_3$), 23.0 (q, 2 × CH_3CONH), 25.4, 25.5, 25.8 (3 × q, 6 × SiC(CH_3)$_3$), 52.5, 52.8 (2 × q, 2 × CO_2CH_3), 63.2 (t, 2 × C-6), 77.6, 78.7, 82.8, 83.4, 87.6, 88.6 (6 × d, 2 × (C-3, C-4, C-5), 90.4, 93.5 (2 × s, 2 × C-2), 167.4, 169.5, 169.6, 170.2 (4 × s, 2 × CO_2CH_3, 2 × CH_3CONH); *m*/*z* (APCI+ve): 592.3 (M + H^+, 100%); methyl 2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-2-ureido-α-D-*arabino*-hex-2-ulofuranosonate **42** (568 mg, 46%) as a white solid (Found: C, 52.53; H, 9.81; N, 4.37. $C_{26}H_{56}O_7N_2Si_3$ requires C, 52.66; H, 9.52; N, 4.72%); m.p. 73–74 °C (ethyl acetate–hexane); $[\alpha]_D^{21}$ +60.6 (*c*, 1.00 in $CHCl_3$); ν_{max} (KBr disc): 3381 (NH), 1750 (C=O, ester), 1684 (C=O, urea I), 1523 (C=O, urea II) cm^{-1}; δ_H (C_6D_6): 0.06, 0.06, 0.08, 0.08, 0.15, 0.16, (18H, 6 × s, 3 × Si(CH_3)$_2$), 0.87, 0.90, 0.93 (27H, 3 × s, 3 × SiC(CH_3)$_3$), 3.67 (1H, a–t, H-6), 3.79 (3H, s, CO_2CH_3), 3.90 (1H, dd, $J_{6',5}$ 5.4, $J_{6',6}$ 9.9, H-6′), 4.15–4.18 (3H, m, H-3, H-4, H-5), 4.46 (2H, b–s, NH_2), 6.13 (1H, b–s, NH); δ_C ($CDCl_3$; 50.3 MHz): −5.6, −5.1, −4.7 (3 × q, 3 × Si(CH_3)$_2$), 17.5, 18.2 (2 × s, 3 × SiC(CH$_3$)$_3$), 25.4, 25.6, 25.8 (3 × q, 3 × SiC(CH_3)$_3$), 52.6 (q, CO_2CH_3), 63.3 (t, C-6), 78.8, 83.1, 88.3 (3 × d, C-3, C-4, C-5), 94.6 (s, C-2), 157.3 (s, NH_2CONH), 168.0 (s, CO_2CH_3); *m*/*z* (ES): 637 (M + $HCOO^-$, 100%); and methyl 2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-2-ureido-β-D-*arabino*-hex-2-ulofuranosonate **43** (244 mg, 18%) as a white solid (Found: C, 52.60; H, 9.71; N, 4.46. $C_{26}H_{56}O_7N_2Si_3$ requires C, 52.66; H, 9.52; N, 4.72%); m.p. 65–67 °C (ethyl acetate–hexane); $[\alpha]_D^{21}$ −22.0 (*c*, 0.25 in $CHCl_3$); ν_{max} (KBr disc): 3435 (NH), 1747 (C=O, ester), 1687 (C=O, urea I), 1505 (C=O, urea II) cm^{-1}; δ_H (C_6D_6): 0.05, 0.08, 0.09, 0.17, 0.17, (18H, 5 × s, 3 × Si(CH_3)$_2$), 0.87, 0.89, 0.96 (27H, 3 × s, 3 × SiC(CH_3)$_3$), 3.64 (1H, dd, $J_{6,5}$ 8.3, $J_{6,6'}$ 10.2, H-6), 3.76 (1H, dd, $J_{6',5}$ 5.4, H-6′), 3.79 (3H, s, CO_2CH_3), 4.10 (1H, ddd, $J_{5,4}$ 2.3, H-5), 4.15 (1H, a–t, H-4), 4.27 (1H, d, $J_{3,4}$ 2.2, H-3), 4.82 (2H, b–s, NH_2), 5.60 (1H, b–s, NH); δ_C ($CDCl_3$; 50.3 MHz): −5.4, −5.1, −4.8, −4.7 (4 × q, 3 × Si(CH_3)$_2$), 17.7, 18.0, 18.3 (3 × s, 3 × SiC(CH$_3$)$_3$), 25.6, 25.7, 25.8 (3 × q, 3 × SiC(CH_3)$_3$), 53.0 (q, CO_2CH_3), 63.0 (t, C-6), 77.4, 83.0, 86.9 (3 × d, C-3, C-4, C-5), 90.7 (s, C-2), 157.2 (s, NH_2CONH), 170.2 (s, CO_2CH_3); *m*/*z* (ES): 637 (M + $HCOO^-$, 100%).

(2*R*,3*S*,4*S*,5*R*)-3,4-Dihydroxy-2-hydroxymethyl-7,9-dioxo-1-oxa-6,8-diazaspiro[4.4]nonane 44

A solution of tetrabutylammonium fluoride (1.0M in THF) (0.59 mL, 0.59 mmol) was added to a stirred solution of methyl 2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-2-ureido-α-D-*arabino*-hex-2-ulofuranosonate **42** (116 mg, 0.20 mmol) in THF (4 mL). The reaction mixture was stirred for 24 h at room temperature, under an atmosphere of nitrogen. TLC CMAW (chloroform–methanol–acetic acid–water 60 : 30 : 3 : 5) indicated complete conversion of the starting material (R_f 1.0) to a single product (R_f 0.6). The solvent was removed *in vacuo* and the residue was purified by flash chromatography CMAW (chloroform–methanol–acetic acid–water 60 : 30 : 3 : 5) and reversed-phase chromatography (H_2O) to yield (2*R*,3*S*,4*S*,5*R*)-3,4-dihydroxy-2-hydroxymethyl-7,9-dioxo-1-oxa-6,8-diazaspiro[4.4]nonane **44** (43 mg, 100%, contaminated with <5% of its epimer) as a white solid. A pure sample was obtained by crystallisation (EtOH–H_2O) (Found: C, 38.44; H, 4.66; N, 12.73. $C_7H_{10}O_6N_2$ requires C, 38.54; H, 4.62; N, 12.84%); m.p. 198–200 °C (EtOH–H_2O); $[\alpha]_D^{22}$ −5.95 (*c*, 0.19 in MeOH); ν_{max} (KBr disc): 3382 (NH), 1777, 1723 (C=O, hydantoin) cm^{-1}; δ_H (CD_3OD): 3.71 (1H, dd, $J_{2a,2}$ 6.9 $J_{2a,2b}$ 12.0 H-2a(CHHOH)), 3.77 (1H, dd, $J_{2b,2}$ 2.7 H-2b(CHHOH)), 3.92 (1H, ddd, $J_{2,3}$ 8.3 H-2), 4.13 (1H, d, $J_{4,3}$ 8.7 H-4), 4.26 (1H, at, H-3); δ_C (D_2O: 50.3 MHz): 62.3 (t, CH_2OH), 72.9, 79.3, 82.2 (3 × d, C-2, C-3, C-4), 93.7 (s, C-5), 158.7 (s, C-7), 174.5 (s, C-9); *m*/*z* (APCI−ve): 217.1 ([M − H]$^-$, 100%).

(2*R*,3*S*,4*S*,5*S*)-3,4-Dihydroxy-2-hydroxymethyl-7,9-dioxo-1-oxa-6,8-diazaspiro[4.4]nonane 45

A solution of tetrabutylammonium fluoride (1.0M in THF) (0.40 mL, 0.40 mmol) was added to a stirred solution of methyl 2-deoxy-3,4,6-tris-*O*-*tert*-butyldimethylsilyl-2-ureido-β-D-*arabino*-hex-2-ulofuranosonate **43** (79 mg, 0.13 mmol) in THF

(3 mL). The reaction mixture was stirred for 24 h at room temperature, under an atmosphere of nitrogen. TLC CMAW (chloroform–methanol–acetic acid–water 60 : 30 : 3 : 5) indicated complete conversion of the starting material (R_f 1.0) to a single product (R_f 0.6). The solvent was removed *in vacuo* and the residue was purified by flash chromatography CMAW (chloroform–methanol–acetic acid–water 60 : 30 : 3 : 5) and reversed-phase chromatography (H_2O) to yield (2*R*,3*S*,4*S*,5*S*)-3,4-dihydroxy-2-hydroxymethyl-7,9-dioxo-1-oxa-6,8-diaza-spiro[4.4]nonane **45** (29 mg, 100%, contaminated with <5% of its epimer) as a white solid; δ_H (CD_3OD): 3.60 (1H, dd, $J_{2a,2}$ 5.1 $J_{2a,2b}$ 12.2 H-2a(C*H*HOH)), 3.75 (1H, dd, $J_{2b,2}$ 2.6 H-2b-(CH*H*OH)), 3.83 (1H, ddd, $J_{2,3}$ 8.0, H-2), 3.94 (1H, at, H-3), 4.28 (1H, d, $J_{4,3}$ 8.2, H-4); δ_C (D_2O; 50.3 MHz): 60.3 (t, CH_2OH), 72.8, 76.4, 81.3 (3 × d, C-2, C-3, C-4), 91.2 (s, C-5), 159.3 (s, C-7), 176.6 (s, C-9); *m*/*z* (APCI−ve): 217.1 ([M − H]$^-$, 100%).

Methyl 2,5-anhydro-6-*O*-*p*-tolylsulfonyl-D-gluconate 46

Toluene-*p*-sulfonyl chloride (1.21 g, 6.4 mmol) was added to a stirred solution of methyl 2,5-anhydro-D-gluconate **8** (1.25 g, 6.5 mmol) and 3Å molecular sieves (1.2 g) in pyridine (15 mL) at −10 °C under an atmosphere of nitrogen. After 3 h, TLC (ethyl acetate) indicated the presence of a major compound (R_f 0.5) and no starting material (R_f 0.1). The reaction mixture was warmed to room temperature, filtered through Celite (eluent: dichloromethane), and washed with buffer (pH 7; 20 mL) and the aqueous layer was extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a white solid, which was pre-adsorbed onto silica and purified by flash chromatography (ethyl acetate–hexane, 2 : 1) to afford methyl 2,5-anhydro-6-*O*-*p*-tolylsulfonyl-D-gluconate **46** as a white crystalline solid (1.78 g, 79%) (Found: C, 48.60; H, 5.19. $C_{14}H_{18}O_8S$ requires C, 48.55; H 5.24 %); m.p. 136–138 °C; $[\alpha]_D^{24}$ +62.5 (*c*, 0.20 in methanol); ν_{max} (KBr disc): 3508 (br, OH), 1744 (s, $COOCH_3$) cm^{-1}; δ_H (CD_3CN): 2.45 (3H, s, C*H*$_3$Ar), 3.67 (3H, s, $COOCH_3$), 3.91 (1H, a–t, *J* 2.7, H-4), 3.95 (1H, ddd, $J_{5,4}$ 2.9, $J_{5,6}$ 5.6, $J_{5,6'}$ 6.5, H-5), 4.13 (1H, dd, $J_{5,6'}$ 6.6, $J_{6,6'}$ 10.3, H-6′), 4.15 (1H, dd, $J_{6,5}$ 5.5, $J_{6,6'}$ 10.3, H-6), 4.22 (1H, dd, $J_{3,4}$ 2.2, $J_{2,3}$ 4.8, H-3), 4.59 (1H, d, $J_{3,2}$ 4.8, H-2), 7.44 (2H, d, *J* 8.2, 2 × ArH), 7.80–7.82 (2H, m, 2 × ArH); δ_C (CD_3CN; 50.3 MHz): 12.7 (1 × q, CH_3Ar), 52.3 (1 × q, $COOCH_3$), 71.1 (1 × t, C-6), 78.4, 78.6, 81.9, 84.1 (4 × d, C-2, C-3, C-4, C-5), 128.8, 131.1 (2 × d, 4 × Ar–*C*H), 133.6, 146.5 (OSO_2C, CH_3–Ar*C*), 170.5 (1 × s, C=O). *m*/*z* (APCI+ve): 369 (M + Na$^+$, 13), 347 (M + H$^+$, 85%).

Methyl 2,5-anhydro-6-azido-6-deoxy-D-gluconate 3

Method 1. Sodium azide (374 mg, 5.7 mmol) was added to a stirred solution of methyl 2,5-anhydro-6-*O*-*p*-tolylsulfonyl-D-gluconate **46** (1.33 g, 3.8 mmol) in DMF (10 mL), under an atmosphere of nitrogen. The mixture was heated at 90 °C for 18 h, when TLC (ethyl acetate) indicated the presence of a major product (R_f 0.6) and no starting material (UV-visible, R_f 0.5). The reaction mixture was cooled to room temperature, diluted with ethyl acetate (25 mL), and washed with water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 25 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (ethyl acetate–hexane, 2 : 1) to afford methyl 2,5-anhydro-6-azido-6-deoxy-D-gluconate **3** as a white crystalline solid (706 mg, 85%).

Method 2. Toluene-*p*-sulfonyl chloride (3.058 g, 16.0 mmol) was added to a stirred solution of methyl 2,5-anhydro-D-gluconate **8** (1.3 g, 16.0 mmol) and 3Å molecular sieves (2 g) in pyridine (20 mL) at −10 °C, under an atmosphere of nitrogen. After 3 h, TLC (ethyl acetate) indicated the presence of a major compound (R_f 0.5) and no starting material (R_f 0.1). The reaction mixture was warmed to room temperature, filtered through Celite (eluent: dichloromethane), and washed with buffer (pH 7; 10 mL) and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give methyl 2,5-anhydro-6-*O*-*p*-tolylsulfonyl-D-gluconate **46** as white solid which was used without further purification. Sodium azide (1.56 g, 24.1 mmol) was added to a stirred solution of crude methyl 2,5-anhydro-6-*O*-*p*-tolylsulfonyl-D-gluconate **46** in DMF (30 mL), under an atmosphere of nitrogen. The mixture was heated at 90 °C for 18 h, when TLC (ethyl acetate–hexane, 2 : 1) indicated the presence of a major product (R_f 0.3) and no starting material (UV-visible, R_f 0.2). The reaction mixture was cooled to room temperature, concentrated to approximately 5 mL, diluted with ethyl acetate (100 mL), and washed with buffer (pH 7; 40 mL). The aqueous layer was extracted with ethyl acetate (2 × 100 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (ethyl acetate–hexane, 2 : 1) to afford methyl 2,5-anhydro-6-azido-6-deoxy-D-gluconate **3** as a white crystalline solid (2.495 g, 71% over two steps) (Found: C, 39.00; H, 5.16; N, 18.77. $C_7H_{11}O_5N_3$ requires C, 38.71; H, 5.11; N, 19.35%); m.p. 77–78 °C; $[\alpha]_D^{24}$ +48.8 (*c*, 1.0 in methanol); ν_{max} (KBr disc) 3420 (br, OH), 2126, 2099 (N_3), 1740 (C=O) cm^{-1}; δ_H (D_2O; 500 MHz): 3.57 (2H, d, $J_{6,5}$ 5.7, H_2-6), 3.77 (3H, s, $COOCH_3$), 4.02 (1H, dt, $J_{5,4}$ 3.6, $J_{5,6}$ 5.7, H-5), 4.07 (1H, dd, $J_{4,3}$ 2.3, $J_{4,5}$ 3.6, H-4), 4.42 (1H, dd, $J_{3,4}$ 2.3, $J_{3,2}$ 4.9, H-3), 4.79 (1H, d, $J_{2,3}$ 4.9, H-2); δ_C (D_2O; 50 MHz): 52.6 (1 × t, C-6), 53.4 (1 × q, $COOCH_3$), 78.2, 78.5, 81.4, 85.0 (4 × d, C-2, C-3, C-4, C-5), 172.1 (1 × s, C=O); *m*/*z* ($CINH_3$): 235 (M + NH_4^+, 100), 218 (M + H$^+$, 18), 192 (59), 190 (M + H$^+$ − N_2, 60%).

6-Amino-2,5-anhydro-6-deoxy-D-glucono-1,6-lactam 50

A solution of methyl 2,5-anhydro-6-azido-6-deoxy-D-gluconate **3** (100 mg, 0.46 mmol) in methanol (5 mL) was stirred under an atmosphere of hydrogen, in the presence of 10% palladium on carbon (25 mg). After 1 h, TLC (ethyl acetate–methanol, 9 : 1) indicated conversion of the starting material (R_f 0.8) to a major product (R_f 0.1). The reaction mixture was filtered through Celite (eluted with methanol) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography CMAW (chloroform–methanol–acetic acid–water 60 : 30 : 3 : 5) to yield 6-amino-2,5-anhydro-6-deoxy-D-glucono-1,6-lactam **50** (34 mg, 46%) as an orange, amorphous solid; m.p. 221–225 °C; $[\alpha]_D^{21}$ −22.2 (*c*, 0.95 in MeOH); ν_{max} (thin film): 3500, 3152 (OH, NH), 1689 (C=O, amide) cm^{-1}; δ_H (D_2O): 3.26 (1H, m, H-6), 3.59 (1H, dd, $J_{6',5}$ 12.8 $J_{6',6}$ 12.8, H-6′), 4.12 (1H, a–dd, H-4), 4.30 (1H, m, H-5), 4.35 (1H, m, H-3), 4.41 (1H, d, $J_{2,3}$ 7.0); δ_C (D_2O; 50.3 MHz): 44.8 (t, C-6), 79.6, 80.6, 81.9, 82. (4 × d, C-2, C-3, C-4, C-5), 190.9 (s, *C*=O); *m*/*z* (APCI−ve): 158 ([M − H]$^-$, 96%).

Isopropyl 2,5-anhydro-D-gluconate 47

Sodium hydroxide solution (0.5M aq; 25 mL, 12.5 mmol) was added to a stirred solution of methyl 2,5-anhydro-D-gluconate **8** (2.4 g, 12.5 mmol) in 1,4-dioxane (10 mL) at room temperature. After 10 min, TLC (ethyl acetate) indicated the presence of a single product (R_f 0.0) and no starting material (R_f 0.1). The mixture was concentrated *in vacuo* (co-evaporation with toluene), suspended in propan-2-ol (25 mL) and cooled to 0 °C. Concentrated sulfuric acid (0.2 mL) was added dropwise and the mixture was heated at 80 °C for 18 h, when TLC (ethyl acetate–methanol, 19 : 1) indicated the presence of a single product (R_f 0.5) and no starting material (R_f 0.0). Sodium hydieyescarbonate (4 g) was added and the mixture was stirred for 2 h when pH 7 was reached. The reaction mixture was filtered through Celite (eluent: propan-2-ol) and concentrated *in vacuo.* The residue was purified by flash chromatography (ethyl

acetate–methanol, 19 : 1) to afford isopropyl 2,5-anhydro-D-gluconate **47** as a white crystalline solid (2.643 g, 97%); (Found: C, 48.82; H, 7.27. $C_9H_{16}O_6$ requires : C, 49.09; H, 7.32%); m.p. 98 °C (ethyl acetate); $[a]_D^{25}$ +38.4 (*c*, 1.0 in methanol); ν_{max} (thin film): 3369 (br, OH), 1732 (s, C=O) cm^{-1}; δ_H (CD_3OD; 500 MHz): 1.27 (6H, a–t, *J* 6.3, $(CH_3)_2CH$), 3.72 (2H, d, $J_{6,5}$ 2.8, H_2-6), 3.90 (1H, dt, $J_{5,6}$ 2.8, *J* 4.4, H-5), 4.02 (1H, a–t, *J* 2.5, H-4), 4.19 (1H, dd, *J* 2.1, $J_{3,2}$ 4.5, H-3), 4.58 (1H, d, $J_{2,3}$ 4.5, H-2), 5.08 (1H, septet, *J* 6.3, $(CH_3)_2CH$); δ_C (CD_3OD; 50 MHz): 21.0 (1 × q, 2 × $(CH_3)_2CH$), 61.9 (1 × t, C-6), 69.0, 77.6, 78.1, 80.8, 86.9 (5 × d, C-2, C-3, C-4, C-5, $(CH_3)_2CH$), 170.3 (1 × s, C=O); *m*/*z* (APCI+ve): 243 (M + Na^+, 9%), 221 (M + H^+, 55%), 179.0 (100%).

Isopropyl 2,5-anhydro-6-O-*p*-tolylsulfonyl-D-gluconate 48

Toluene-*p*-sulfonyl chloride (86 mg, 0.45 mmol) was added to a stirred solution of isopropyl 2,5-anhydro-D-gluconate **47** (100 mg, 0.45 mmol) and 3Å molecular sieves (100 mg) in pyridine (3 mL) at −10 °C, under an atmosphere of nitrogen. After 18 h, TLC (ethyl acetate) indicated the presence of a major compound (R_f 0.7) and no starting material (R_f 0.2). The reaction mixture was warmed to room temperature, filtered through Celite (eluent: dichloromethane), and washed with buffer (pH 7; 30 mL) and the aqueous layer was extracted with ethyl acetate (3 × 35 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a white solid, which was pre-adsorbed onto silica and purified by flash chromatography (ethyl acetate–hexane, 2 : 1) to afford isopropyl 2,5-anhydro-6-*O*-*p*-tolylsulfonyl-D-gluconate **48** as a white crystalline solid (140 mg, 83%) (Found: C, 51.33; H, 5.93. $C_{16}H_{22}O_8S$ requires C, 51.33; 5.84%); m.p. 148–151 °C (ethyl acetate); $[a]_D^{23}$ +41.0 (*c*, 0.81 in methanol); ν_{max} (thin film): 3455, 3399 (OH), 1730 (C=O) cm^{-1}; δ_H (acetone-d_6, 500 MHz): 1.19 (3H, d, *J* 6.3, $(CH_3)_2CH$), 1.20 (3H, d, *J* 6.3, $(CH_3)_2CH$), 2.46 (3H, s, CH_3Ar), 4.00–4.03 (1H, m, H-5), 4.07–4.09 (1H, m, H-4), 4.20 (1H, dd, $J_{6,5}$ 6.8, $J_{6,6'}$ 10.1, H-6), 4.25 (1H, d, $J_{6',5}$ 5.8, $J_{6,6}$ 10.1, H-6′), 4.35 (1H, a–dt, *J* 2.7, $J_{3,2}$ 5.1, H-3), 4.56 (1H, d, $J_{2,3}$ 5.1, H-2), 4.69 (1H, $J_{OH,4}$ 4.3, exchanges with D_2O, OH-4), 4.71 (1H, d, $J_{OH,3}$ 5.0, exchanges with D_2O, OH-3), 5.07 (1H, septet, *J* 6.3, $(CH_3)_2CH$), 7.48 (2H, d, *J* 8.2, 2 × ArH), 7.82–7.85 (2H, m, 2 × ArH); δ_C (CD_3CN, 50 MHz): 20.3, 20.6, 20.7 (3 × q, CH_3Ar, $(CH_3)_2CH$), 69.7 (1 × t, C-6), 68.7, 77.5, 81.0, 83.3 (4 × d, $(CH_3)_2CH$), C-2, C-3, C-4, C-5), 127.7, 129.7 (2 × d, 4 × Ar–CH), 132.8, 145.1 (2 × s, OSO_2C, CH_3–Ar*C*), 169.5 (1 × s, C=O); *m*/*z* (APCI+ve), 397 (M + Na^+, 8), 375 (M + H^+, 35), 333 (100%).

Isopropyl 2,5-anhydro-6-azido-6-deoxy-D-gluconate 49

Method 1. Sodium azide (29 mg, 0.44 mmol) was added to a stirred solution of isopropyl 2,5-anhydro-6-*O*-*p*-tolylsulfonyl-D-gluconate **48** (see also method 3, below), (110 mg, 0.29 mmol) in DMF (3 mL), under an atmosphere of nitrogen. The mixture was heated at 90 °C for 18 h, when TLC (ethyl acetate–hexane, 2 : 1) indicated the presence of a major product (R_f 0.3) and no starting material (UV-visible, R_f 0.4). The reaction mixture was cooled to room temperature, diluted with ethyl acetate (20 mL), and washed with water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 25 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (ethyl acetate–hexane, 2 : 1) to afford isopropyl 2,5-anhydro-6-azido-6-deoxy-D-gluconate **49** as a white crystalline solid (62 mg, 86%).

Method 2. Potassium carbonate (51 mg, 0.37 mmol) was added to a stirred solution of methyl 2,5-anhydro-6-azido-6-deoxy-D-gluconate **3** (80 mg, 0.37 mmol) in propan-2-ol (5 mL). The reaction mixture was stirred at room temperature for 18 h, when TLC (ethyl acetate–hexane, 2 : 1) indicated the presence of a single product (R_f 0.4) and no starting material (R_f 0.3). The reaction mixture was filtered through Celite and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (ethyl acetate–hexane, 2 : 1) to afford isopropyl 2,5-anhydro-6-azido-6-deoxy-D-gluconate **49** as a white crystalline solid (70 mg, 78%).

Method 3. Toluene-*p*-sulfonyl chloride (1.126 g, 5.9 mmol) was added to a stirred solution of isopropyl 2,5-anhydro-D-gluconate **47** (1.3 g, 5.9 mmol) and 3Å molecular sieves (1 g) in pyridine (10 mL) at −10 °C, under an atmosphere of nitrogen. After 18 h, TLC (ethyl acetate) indicated the presence of a major compound (R_f 0.7) and no starting material (R_f 0.2). The reaction mixture was warmed to room temperature, filtered through Celite (eluent: dichloromethane), and washed with buffer (pH 7, 50 mL) and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give isopropyl 2,5-anhydro-6-*O*-*p*-tolylsulfonyl-D-gluconate **48** as white solid which was used without further purification. Sodium azide (576 mg, 8.9 mmol) was added to a stirred solution of crude isopropyl 2,5-anhydro-6-*O*-*p*-toluylsulfonyl-D-gluconate **48** in DMF (15 mL), under an atmosphere of nitrogen. The mixture was heated at 90 °C for 18 h, when TLC (ethyl acetate–hexane, 2 : 1) indicated the presence of a major product (R_f 0.3) and no starting material (UV visible, R_f 0.4). The reaction mixture was cooled to room temperature, concentrated to approximately 5 mL, diluted with ethyl acetate (50 mL), and washed with buffer (pH 7; 30 mL). The aqueous layer was extracted with ethyl acetate (3 × 60 mL) and the combined organic phares were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (ethyl acetate–hexane, 2 : 1) to afford isopropyl 2,5-anhydro-6-azido-6-deoxy-D-gluconate **49** as a white crystalline solid (1.09 g, 74% over two steps) (Found: C, 44.35; H, 6.16; N, 17.00. $C_9H_{15}O_5N_3$ requires C, 44.08; H, 6.16; N, 17.13%); m.p. 88–91 °C (ethyl acetate); $[a]_D^{25}$ +61.9 (*c*, 1.0 in methanol); ν_{max} (KBr disc): 3444 (br, OH), 2113 (N_3), 1733 (C=O) cm^{-1}; δ_H (CD_3OD, 500 MHz): 1.27 (6H, a–t, *J* 6.2, $(CH_3)_2CH$), 3.38 (1H, dd, $J_{6',5}$ 4.7, $J_{6',6}$ 12.7, H-6′), 3.62 (1H, dd, $J_{6,5}$ 7.5, $J_{6,6'}$ 12.7, H-6), 3.91–3.94 (1H, m, H-5), 3.95 (1H, dd, $J_{4,3}$ 3.0, $J_{4,5}$ 5.7, H-4), 4.26 (1H, dd, $J_{3,4}$ 2.7, $J_{3,2}$ 5.1, H-3), 4.61 (1H, d, $J_{2,3}$ 5.1, H-2), 5.07 (1H, septet, *J* 6.2, $(CH_3)_2CH$): δ_C (CD_3OD; 50 MHz): 20.6, 20.7 (2 × q, $(CH_3)_2CH$), 52.2 (1 × t, C-6), 68.5, 77.8, 78.1, 80.9, 84.9 (5 × d, C-2, C-3, C-4, C-5, $(CH_3)_2CH$), 169.6 (1 × s, C=O); *m*/*z* (APCI+ve): 268 (M + Na^+, 6), 246 (M + H^+, 5), 218 (M + H^+ − N_2, 100), 182 (35), 140 (37%).

Methyl 2,5-anhydro-6-*O*-methylsulfonyl-D-mannonate 51

Methanesulfonyl chloride (300 μL, 3.94 mmol) was added dropwise to a stirred solution of methyl 2,5-anhydro-D-mannonate **15** (445 mg, 2.32 mmol) and 4-(dimethylamino)-pyridine (28 mg, 0.23 mmol) in pyridine (6 mL) at −20 °C, under an atmosphere of nitrogen. After 2.5 h, TLC (ethyl acetate) indicated the presence of a major compound (R_f 0.4) and no starting material (R_f 0.2). Buffer solution (pH 7; 1 mL) was added and the mixture was concentrated *in vacuo* to give a residue, which was purified by flash chromatography (ethyl acetate–hexane, 9 : 1) to afford methyl 2,5-anhydro-6-*O*-methylsulfonyl-D-mannonate **51** (450 mg, 72%) as a white crystalline solid (Found: C, 35.73; H, 5.03. $C_8H_{14}O_8S$ requires C, 35.55; H, 5.22%); m.p. 74–75 °C; $[a]_D^{21}$ +41.7 (*c*, 1.02 in methanol); ν_{max} (thin film): 3466 (OH) 1738 (C=O), 1349, 1173 (OSO_2Me) cm^{-1}; δ_H (CD_3CN; 500 MHz): 3.07 (3H, s, $COOCH_3$), 3.63 (1H, d, *J* 4.6, OH), 3.71 (3H, s, OSO_2CH_3), 3.82 (1H, d, *J* 4.7, OH), 3.94 (1H, a–q, *J* 4.5, H-4), 4.15 (1H, ddd, $J_{5,6'}$ 4.0, $J_{5,4}$ 4.6, $J_{5,6}$ 6.6, H-5), 4.24 (1H, a–q, *J* 3.6, H-3), 4.28 (1H, dd, $J_{6,5}$ 6.5, $J_{6,6'}$ 11.0, H-6), 4.34 (1H, dd, $J_{6',5}$ 3.8, $J_{6',6}$ 11.0, H-6′), 4.38 (1H, d, $J_{2,3}$ 3.4, H-2); δ_C (CD_3CN; 125 MHz): 37.8 (1 × q, OSO_2CH_3), 52.7

(1 × q, COO*C*H$_3$), 70.7 (1 × t, C-6), 78.1, 81.3, 83.7, 83.8 (4 × d, C-2, C-3, C-4, C-5), 172.2 (1 × s, C=O); *m*/*z* (APCI+ve): 293 (M + Na$^+$, 40), 271 (M + H$^+$, 100%).

Methyl 2,5-anhydro-6-deoxy-6-azido-D-mannonate 52

Sodium azide (142 mg, 2.19 mmol) was added to a stirred solution of methyl 2,5-anhydro-6-*O*-methylsulfonyl-D-mannonate **51** (422 mg, 1.56 mmol) in DMF (12 mL) and the mixture was heated to 65 °C. After 23 h, TLC (ethyl acetate) indicated the presence of a major product (R_f 0.5) and no starting material (R_f 0.3). The mixture was concentrated *in vacuo*, suspended in ethyl acetate (30 mL), washed with buffer solution (pH 7; 5 mL), and extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (ethyl acetate–hexane, 3 : 2) to afford methyl 2,5-anhydro-6-deoxy-6-azido-D-mannonate **52** as a colourless oil (329 mg, 98%) (Found: C, 38.67; H, 5.43; N, 19.21. $C_7H_{11}O_5N_3$ requires C, 38.71; H, 5.10; N, 19.35%); $[\alpha]_D^{21}$ +70.2 (*c*, 0.88 in methanol); ν_{max} (thin film) 3401 (OH), 2104 (N_3), 1737 (C=O) cm^{-1}; δ_H (D_2O; 500 MHz): 3.52 (1H, dd, $J_{6,5}$ 6.4, $J_{6,6'}$ 13.4, H-6), 3.64 (1H, dd, $J_{6',5}$ 3.8, $J_{6',6}$ 13.5, H-6′), 3.80 (3H, s, COOCH_3), 4.09 (1H, dd, $J_{4,3}$ 4.2, $J_{4,5}$ 4,7, H-4), 4.16 (1H, ddd, $J_{5,6'}$ 3.9, $J_{5,4}$ 4.8, $J_{5,6}$ 6.4, H-5), 4.40 (1H, a–t, *J* 4.0, H-3), 4.58 (1H, d, $J_{2,3}$ 4.0, H-2); δ_C (125 MHz; D_2O) 51.3 (1 × t, C-6), 52.7 (1 × q, COOCH_3), 76.8, 79.3, 81.4, 83.4 (4 × d, C-2, C-3, C-4, C-5), 173.1 (1 × s, C=O); *m*/*z* (CI; NH_3): 235 (M + NH_4^+, 100%), 218 (M + H$^+$, 19%).

Isopropyl 2,5-anhydro-6-azido-6-deoxy-D-mannonate 55

Method 1. Sodium azide (26 mg, 0.4 mmol) was added to a stirred solution of isopropyl 2,5-anhydro-6-*O*-*p*-tolylsulfonyl-D-mannonate **54** (see below) (100 mg, 26 mmol) in DMF (3 mL) and the mixture was heated to 80 °C. After 18 h, TLC (ethyl acetate–hexane, 3 : 1) indicated the presence of a major product (R_f 0.6) and no starting material (R_f 0.5, UV-visible). The mixture was cooled, concentrated *in vacuo*, suspended in ethyl acetate (50 mL), washed with buffer solution (pH 7; 10 mL), and extracted with ethyl acetate (2 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (ethyl acetate–hexane, 3 : 1) to afford isopropyl 2,5-anhydro-6-deoxy-6-azido-D-mannonate **55** as a white crystalline solid (58 mg, 99%).

Method 2. Potassium carbonate (658 mg, 4.77 mmol) was added to a stirred solution of methyl 2,5-anhydro-6-azido-6-deoxy-D-mannonate **52** (950 mg, 4.34 mmol) in propan-2-ol (5 mL). The reaction mixture was stirred at room temperature for 26 h, when TLC (ethyl acetate–hexane, 3 : 1) indicated the presence of a single product (R_f 0.6) and no starting material (R_f 0.5). The reaction mixture was filtered through Celite and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (ethyl acetate–hexane, 2 : 1) to afford isopropyl 2,5-anhydro-6-azido-6-deoxy-D-mannonate **55** as a white crystalline solid (900 mg, 85%) (Found: C, 44.16; H, 6.01; N, 17.13 . $C_9H_{15}O_5N_3$ requires C, 44.08; H, 6.16; N, 17.13%); m.p. 47–53 °C (ethyl acetate); $[\alpha]_D^{23}$ +58.6 (*c*, 1.0 in methanol); ν_{max} (thin film): 3362 (br, OH), 2100 (N_3), 1728 (C=O) cm^{-1}; δ_H (CD_3OD; 500 MHz): 1.26 (6H, d, *J* 6.3, (CH_3)$_2$CH), 3.42 (1H, dd, $J_{6,5}$ 6.3, $J_{6,6'}$13.1, H-6′), 3.47 (1H, dd, $J_{6',5}$ 4.3, $J_{6',6'}$ 13.1, H-6′), 3.92 (1H, dd, $J_{4,3}$ 3.5, $J_{4,5}$ 4.7, H-4), 4.09 (1H, a–dt, *J* 4.5, $J_{5,6'}$ 6.3, H-5), 4.25 (1H, a–t, *J* 3.4, H-3), 4.33 (1H, d, $J_{2,3}$ 3.4, H-2), 5.05 (1H, septet, *J* 6.3, (CH_3)$_2$CH); δ_C (CD_3OD, 50 MHz): 22.0 (2 × q, (*C*H$_3$)$_2$CH), 53.3 (1 × t, C-6), 70.3, 79.3, 82.1, 84.2, 85.7 (5 × d, C-2, C-3, C-4, C-5, (CH$_3$)$_2$*C*H), 172.5 (1 × s, C=O); *m*/*z* (APCI−ve): 244 ([M − H]$^+$, 10%), 216 ([M − H − N_2]$^+$, 5%), 129 (100%). (APCI+ve): 218.1 (M + H$^+$ − N_2, 60), 200.1 (100), 176 (50), 157.9 (70%).

Isopropyl 2,5-anhydro-D-mannonate 53

A solution of methyl 2,5-anhydro-D-mannonate **15** (9.8 g, 51.0 mmol) in 0.5M aqueous sodium hydroxide (103 mL, 51.5 mmol) was stirred at room temperature for 1 h, when TLC (ethyl acetate–methanol, 19 : 1) indicated the presence of a single compound (R_f 0.0) and no starting material (R_f 0.4). The mixture was concentrated *in vacuo* by co-evaporation with toluene to afford an amorphous white solid. The mixture was suspended in propan-2-ol (140 mL), conc. sulfuric acid (3 mL) was added, and the suspension was heated to 80 °C. After 14 h, TLC (ethyl acetate–methanol, 9 : 1) indicated the presence of a single compound (R_f 0.5). Sodium dydrogen carbonate (10 g) was added and the mixture was stirred for 1 h before being filtered, and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (ethyl acetate–methanol, 19 : 1) to afford isopropyl 2,5-anhydro-D-mannonate **53** as a white solid (10.1 g, 90%), m.p. 61–65 °C (ethyl acetate) (Found: C, 48.81; H, 7.32. $C_9H_{16}O_6$ requires C, 49.09; H, 7.32%); $[\alpha]_D^{25}$ +44.1 (*c*, 1.0 in methanol); ν_{max} (thin film) 3399 (br, OH), 1729 (C=O) cm^{-1}; δ_H (CD_3OD; 500 MHz): 1.26 (6H, d,*J* 6.3, (CH_3)$_2$CH), 3.64 (1H, dd, $J_{6,5}$ 4.7, $J_{6,6'}$ 11.8, H-6), 3.72 (1H, dd, $J_{6',5}$ 3.9, $J_{6',6}$ 11.8, H-6′), 3.98 (1H, a–t, H-4), 4.04 (1H, a–q,*J* 4.2, H-5), 4.24 (1H, a–t,*J* 3.0, H-3), 4.33 (1H, d, $J_{2,3}$ 3.0, H-2), 5.04 (1H, septet, *J* 6.3, (CH$_3$)$_2$C*H*); δ_C (CD_3OD, 125 MHz): 21.9 (2 × q, (*C*H$_3$)$_2$CH), 63.0 (1 × t, C-6), 70.2, 78.7, 82.0, 84.4, 87.7 (5 × d, C-2, C-3, C-4, C-5, (CH$_3$)$_2$*C*H), 172.6 (1 × s, C=O); *m*/*z* (APCI−ve): 219.1 (20%, [M − H]$^+$).

Isopropyl 2,5-anhydro-6-*O*-*p*-tolylsulfonyl-D-mannonate 54

Toluene-*p*-sulfonyl chloride (1.08 g, 5.66 mmol) was added to a stirred solution of isopropyl 2,5-anhydro-D-mannonate **53** (1.09 g, 4.95 mmol) and 3Å molecular sieves (1 g) in pyridine (15 mL) at −10 °C, under an atmosphere of nitrogen. After 24 h, TLC (ethyl acetate) indicated the presence of a major product (R_f 0.5) and no starting material (R_f 0.1). The mixture was filtered through Celite (eluent–acetonitrile) and concentrated *in vacuo*. The residue was diluted with ethyl acetate (40 mL), washed with buffer (pH 7; 20 mL), and the aqueous layer was extracted with ethyl acetate (2 × 40 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (ethyl acetate–hexane, 5 : 1) to afford isopropyl 2,5-anhydro-6-*O*-*p*-tolylsulfonyl-D-mannonate **54** as a white crystalline solid (1.31 g, 62%); (Found C, 51.33; H, 5.84. $C_{16}H_{22}O_8S$ requires C, 51.33; H, 5.84 %); m.p. 120–123 °C; $[\alpha]_D^{24}$ +46.6 (*c*, 0.85 in methanol); ν_{max} (thin film): 3422 (OH), 1716 (COOCH_3) cm^{-1}; δ_H (acetone-d_6, 400 MHz): 1.23 (3H, d, *J* 6.2, (CH_3)$_2$CH), 1.24 (3H, d, *J* 6.2, (CH_3)$_2$CH), 4.01 (1H, m, H-4), 4.13–4.20 (2H, m, H-6, H-5), 4.23 (1H, m, H-6′), 4.27 (1H, d, $J_{2,3}$ 2.9, H-2), 4.32–4.35 (1H, m, H-3), 4.58 (1H, d, $J_{OH,4}$ 4.3, OH-4), 4.79 (1H, d, $J_{OH,3}$ 4.6, OH-3), 5.00 (1H, septet, *J* 6.2, (CH$_3$)$_2$C*H*), 7.51 (2H, d, *J* 8.0, 2 × ArH), 7.84–7.86 (2H, m, 2 × ArH); δ_C (CD_3OD; 50 MHz): 21.8 (1 × q, *C*H$_3$–Ar), 22.1 (2 × q, (*C*H$_3$)$_2$CH), 70.8 (1 × t, C-6), 70.5, 78.4, 81.7, 83.4, 84.5 (5 × d, C-2, C-3, C-4, C-5, (CH$_3$)$_2$*C*H), 129.2, 131.2 (2 × d, 4 × Ar–CH), 134.1, 146.7 (2 × s, OSO_2C, CH$_3$–Ar*C*), 172.2 (1 × s, C=O); *m*/*z* (APCI+ve): 397 (M + Na$^+$, 10), 333.1 (50), (287.1, 50%).

X-Ray determination †

Crystal structure determination of 39b. Crystals of **39b** were recrystallised from ethyl acetate–hexane.

Crystal data. $C_{18}H_{34}O_5N_4$, M_r 772.52 g mol^{-1} (2 asymmetric units in the unit cell), Monoclinic, *a* (Å) 18.382, *b* (Å) 8.655, *c* (Å) 27.054, *V* (Å^3) 4201.35, *T* (K) 293, Space group: *C*121,

† CCDC reference number(s) 182246–182247. See http://www.rsc.org/suppdata/p1/b1/b111258a/ for crystallographic files in .cif or other electronic format.

$Z = 8$, $Z' = 2$, $\mu = 0.70$ mm^{-1}, No. of independent reflections: 4202, R_{int}: 0.013, No. of reflections used: 3762, R 0.0745, wR 0.0971.

Crystal- structure determination of 38a. Crystals of **38a** were recrystallised from ethyl acetate–hexane.

Crystal data. $C_7H_{12}O_5N_4$, M_r 232.20 g mol^{-1}, Monoclinic, a (Å) 7.147, b (Å) 6.349, c (Å) 11.384, V (Å^3) 496.46, T (K) 293, Space group: $P12_11$, $Z = 2$, $\mu = 1.10$ mm^{-1}, No. of independent reflections: 3127, R_{int}: 0.019 No. of reflections used: 1978 R 0.0275, wR 0.0230.

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