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Synthesis of tetrahydropyrans from sugar lactones

Juan C. Estevez[a], Antony J. Fairbanks[b*] and George W.J. Fleet[b*]

a) Departamento de Química Orgánica, Universidade de Santiago de Compostela, e Unidade Asociada do C.S.I.C, 15706 Santiago de Compostela, Spain

b) Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford, OX1 3QY, UK

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Abstract

Dehydration of both γ– and δ– hexonolactones, either by intramolecular nucleophilic displacement of triflate leaving groups at C-2, or by Mitsunobu type displacement of the OH-6, provides access to bicyclic lactones which contain tetrahydropyran rings. Reduction or nucleophilic ring opening of these bicyclic lactones furnishes polyfunctionalised tetrahydropyrans in good yield.

Keywords: carbohydrates; lactones; pyrans; Mitsunobu reactions

1. Introduction

Formal dehydration involving ring closure between two hydroxyl groups of a suitably protected hexonolactone may result in the formation of either an oxetane,[1] or a tetrahydrofuran,[2,3] via a ring contraction reaction, or in the formation of a tetrahydropyran[4] by direct cyclisation and subsequent lactone opening (as exemplified by ester formation, Figure 1).

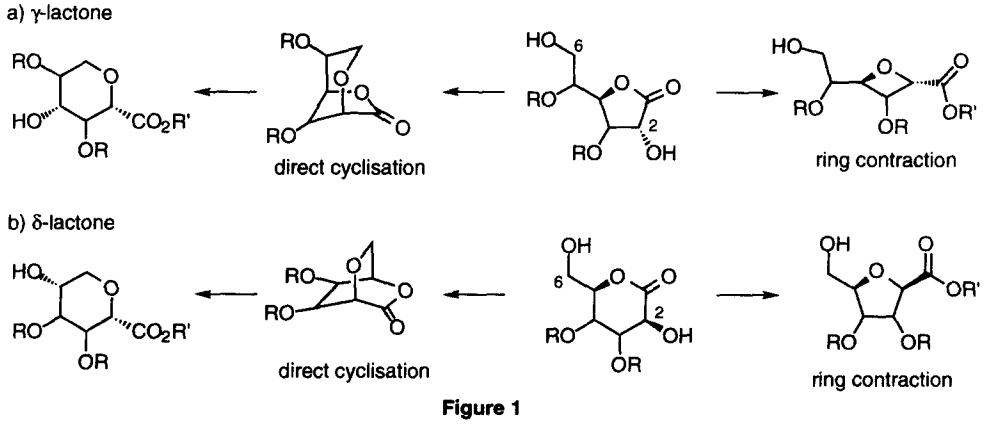

Figure 1

Each of these three heterocycles are widely occurring structural subunits in nature and are thus important targets for synthesis.[5,6] Cyclic ethers themselves derived directly from sugars are formally classified as anhydrosugars, and the formation and properties of such materials have been extensively investigated and reviewed.[7,8,9]

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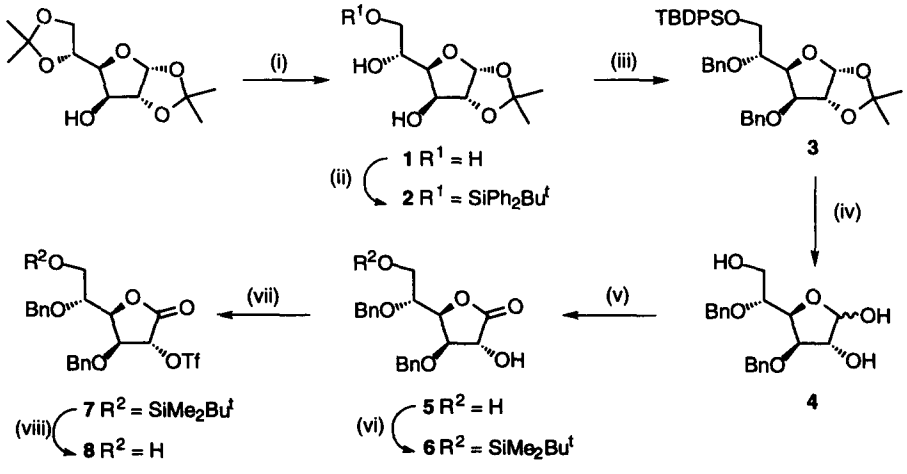
A non-reductive specific synthesis of tetrahydropyrans from hexonolactones must necessarily involve ring closure between the C-6 and C-2 hydroxyls. However this could be achieved in either sense, namely either by displacement of a leaving group at C-6 by the 2-OH or by displacement of a leaving group at C-2 by the 6-OH. The latter case would be expected to be accompanied with inversion of configuration at C-2. In both cases the reaction products would be bicyclic lactones and subsequent reduction of these materials would furnish members of the rare class of naturally occurring 1,5-anhydroalditols.[9] Alternatively ring opening by alcohols or amines would lead to polyhydroxylated tetrahydropyranyl esters or amides. In this paper we describe various strategies employed in an attempt to achieve tetrahydropyran formation in the *gluco*, *allo* and *altro* hexonolactone series and also report the observation of other competitive processes under particular sets of reaction conditions.

2. Results and discussion

Cyclisation studies were undertaken in the γ-*gluco*, γ-*allo* and δ-*altro* lactone series, with suitable hydroxyl group protection. Investigations centred on attempts to achieve nucleophilic displacement of a series of C-2 triflates with a free OH-6 hydroxyl group. Because of the possibility of competitive ring contraction reactions a variety of cyclisation conditions were investigated in order to maximize tetrahydropyran formation. The syntheses of the cyclisation precursors in all three sugar series are now detailed, before the outcomes of the various cyclisation reactions are detailed and then discussed.

2.1. Synthesis of gluco γ-lactone triflates

Monoacetone glucose **1**,[10] was selectively protected by treatment with *tert*-butyldiphenylsilyl chloride in DMF in the presence of imidazole, to give the silyl diol **2**[11] in 96% yield (Scheme 1). Benzylation of **2** with sodium hydride and benzyl bromide in DMF gave the completely protected furanose **3** in 72% yield.

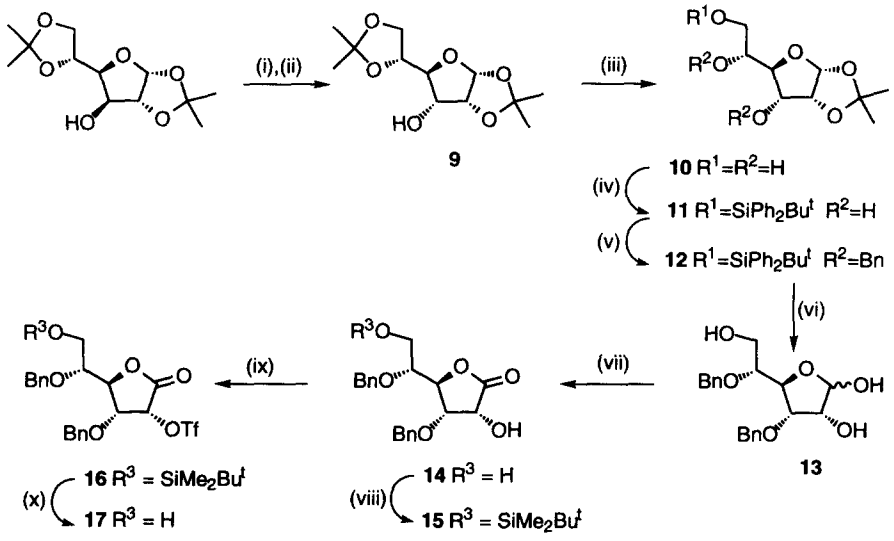


Scheme 1 (i) $AcOH/H_2O$ (2:1), 80% yield (ii) $^tBuPh_2SiCl$, imidazole, DMF, 96% yield (iii) NaH, BnBr, DMF, Bu_4NI, 72% yield (iv) CF_3CO_2H / dioxan / H_2O, (1:1:1), 76% yield (v) Br_2, $BaCO_3$, dioxan / H_2O (2:1), 88% yield (vi) $^tBuMe_2$ SiCl, imidazole, DMF, 89% yield (vii) Tf_2O, pyridine, CH_2Cl_2, 98% yield (viii) CF_3CO_2H / dioxan / H_2O, (1:1:1), 86% yield.

Concomitant removal of the acetonide and silyl protecting groups by treatment with a mixture of trifluoroacetic acid / dioxan / water (1:1:1) gave 3,5-di-*O*-benzyl-glucofuranose **4** in 76% yield. Oxidation with bromine and barium carbonate in dioxan / water (2:1) afforded the lactone **5** in 88% yield. Subsequent selective protection of the primary alcohol of **5**, with *tert*-butyldimethylsilyl chloride and imidazole in DMF, gave the silyl lactone **6** in 89% yield. Reaction with triflic anhydride and pyridine in dichloromethane then gave the unstable *gluco* triflate **7** (89% yield). Finally, removal of the silyl group by treatment with a mixture of trifluoroacetic acid / dioxan / water (1:1:1) gave the unstable alcohol **8** in 86% yield (25% overall yield from diacetone glucose over 8 steps).

2.2. *Synthesis of allo γ-lactone triflates*

Diacetone allose **9** was prepared (Scheme 2) from diacetone glucose in 84% yield by PCC oxidation and subsequent reduction.[12] Selective hydrolysis of the primary acetonide of **9** with a mixture of acetic acid / water (2:1) gave the monoacetonide **10**[13] in 98% yield. Selective protection of the primary hydroxyl of **10** by reaction with *tert*-butyldiphenylsilyl chloride and imidazole in DMF gave the silyl diol **11** in 98% yield. Benzylation by treatment with sodium hydride and benzyl bromide in DMF then gave the completely protected *allo* furanose **12** (76% yield). Removal of the silyl and acetonide protecting groups with a mixture of trifluoroacetic acid / dioxan / water (1:1:1) gave 3,5-di-*O*-benzyl-allofuranose **13** (82% yield), which was subsequently oxidized to the lactone **14** (bromine and barium carbonate in a mixture of dioxan / water, 2 : 1, 90% yield).



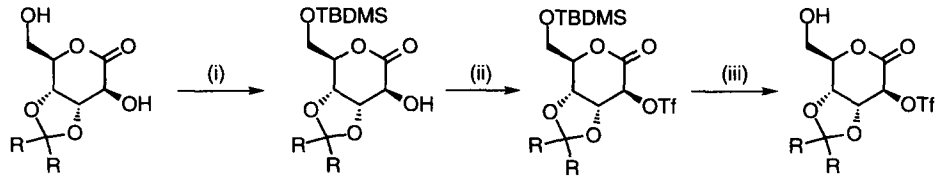
Scheme 2 (i) PCC, sieves, CH_2Cl_2 (ii) $NaBH_4$, EtOH / H_2O, (9:1), 84% yield over 2 steps (iii) AcOH / H_2O (2:1), 98% yield (iv) $^tBuPh_2SiCl$, imidazole, DMF, 98% yield (v) NaH, BnBr, DMF, Bu_4NI, 76% yield (vi) CF_3CO_2H / dioxan / H_2O, (1:1:1), 82% yield (vii) Br_2, $BaCO_3$ in dioxan / H_2O (2:1), 90% yield (viii) $^tBuMe_2SiCl$, imidazole, DMF, 41% yield (ix) Tf_2O, pyridine, CH_2Cl_2, quant. yield (x) CF_3CO_2H / dioxan / H_2O, (1:1:1), 86% yield.

Selective protection of the primary hydroxyl of the *allo* lactone **14** was attempted by treatment with *tert*-butyldimethylsilyl chloride in DMF in the presence of imidazole to give the *allo* alcohol **15**, with only the C-2 hydroxyl free (41% yield). Reaction of **15** with triflic

anhydride and pyridine in dichloromethane then gave the unstable silyl triflate **16** in quantitative yield. Finally, removal of the silyl protecting group with a mixture of trifluoroacetic acid/ dioxan / water (1:1:1) gave the *allo* alcohol **17** in 86% yield (16% overall yield from diacetone glucose over 10 steps).

2.3. Synthesis of altro δ-lactone triflates

In the *altro* series, studies were performed with both isopropylidene (**a**) and cyclohexylidene (**b**) protection. Thus the previously described[14] isopropylidene *altro* lactone **18a** was selectively silylated at the 6-OH with *tert*-butyldimethylsilyl chloride and imidazole in DMF to yield the alcohol **19a** (83% yield). Treatment with triflic anhydride and pyridine in dichloromethane then yielded the silyl triflate **20a** (quantitative yield). A directly analogous series of reactions, which has been previously described,[15] was performed in the more readily available cyclohexylidene protected series, and extended to the synthesis of the hydroxy triflate **21b**. Thus, the cyclohexylidene alcohol **21b** was produced by desilylation of the known silyl triflate **20b**[12] by treatment with 80% aqueous acetic acid (70% yield); it should be noted that attempts at desilylation with tetra-*n*-butyl ammonium fluoride in THF led to complete decomposition, presumably due to base sensitivity.



a) Series R=Me b) Series R=cyclohexylidene

Scheme 3 (i) Bu^tMe_2SiCl, imidazole, DMF, **a)** 83% **b)** 92% yield (ii) Tf_2O, pyridine, CH_2Cl_2, **a)** quant. **b)** quant. yield (iii) 80% aqueous AcOH, **b)** 70% yield.

2.4. Studies on gluco triflates

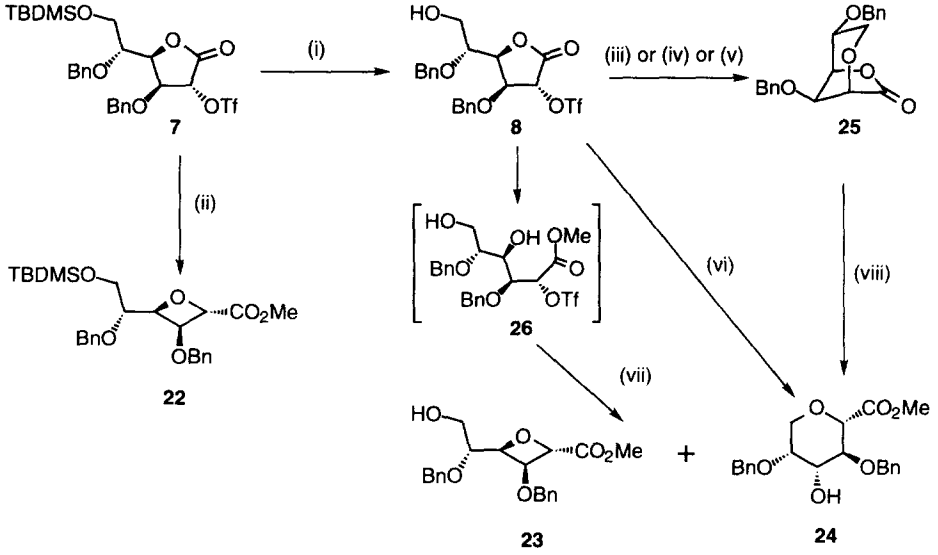
2.4.1. Reactions in basic and neutral media (Scheme 4)

Treatment of the fully protected *gluco* triflate **7** with potassium carbonate in methanol resulted in the formation of the oxetane **22** as the sole isolated product in 75% yield, with an inversion of configuration at C-2.[16] However when the same reaction conditions were applied to the *gluco* triflate **8**, possessing a free OH group at C-6, a mixture of the oxetane **23** (60% yield), and the tetrahydropyran **24** (20% yield) was obtained. Thus, in the latter case nucleophilic displacement of the triflate at C-2 by the free 6-OH hydroxyl competes to some extent with the ring contraction reaction.

Reaction conditions that may promote only this intramolecular nucleophilic substitution reaction were therefore investigated. Thus, when the triflate **8** was treated with pyridine in acetone the bicyclic tetrahydropyran **25** was obtained in 88% yield. Similarly, treatment of **8** with sodium acetate in DMF led to the formation of **25**, albeit with a slightly reduced yield (64%). When compound **8** was treated with pyridine in methanol the tetrahydropyran methyl ester **24** was obtained in 65% yield as the sole isolated product.

These differing results may be rationalized by the relative rates of a number of competing reactions. When potassium carbonate in methanol is used, opening of the lactone ring by

catalytic methoxide may occur first, to yield the open chain material **26** (itself unobserved). This material can then undergo either one of two possible cyclizations: the 4-OH onto C-2 to give the oxetane **23**, or the 6-OH onto C-2 to give the tetrahydropyran **24**. However with pyridine in methanol ring closure of the 6-OH onto C-2 to give the bicyclic material **25** probably occurs first and is then followed by opening of the bicyclic lactone by methanol to give the methyl ester **24**; such a sequence of events would explain the absence of tetrahydrofuran product in this case. The formation of the bicyclic material **25** by treatment with sodium acetate in DMF clearly results from nucleophilic substitution of the C-2 triflate by OH-6, with no competitive lactone opening processes. The bicyclic material **25** itself could also be readily ring opened under acidic conditions; treatment with 1% HCl in methanol gave the methyl ester **24** in 90% yield.

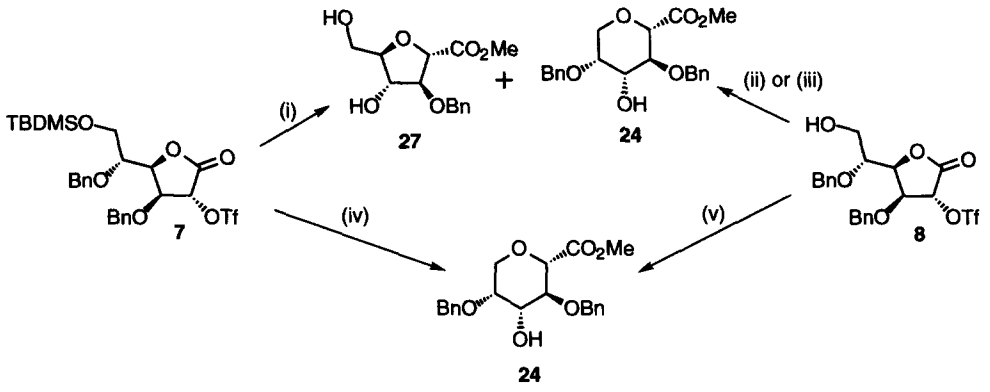


Scheme 4 (i) CF_3COOH / dioxan / H_2O (1:1:1), 86% yield (ii) K_2CO_3, MeOH, 75%yield (iii) acetone / pyridine, 88% yield (iv) NaOAc, DMF, 64% yield (v) DMF, 85% yield (vi) pyridine, MeOH, 65% yield (vii) K_2CO_3, MeOH, 60% yield of **23**, 20% yield of **24** (viii) HCl, MeOH, 90% yield.

2.4.2. Reactions in acid media (Scheme 5)

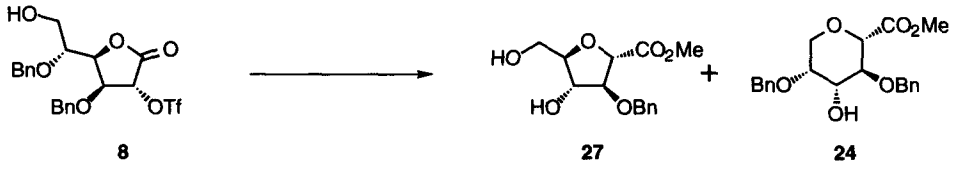
Reaction of the completely protected *gluco* lactone **7** under acidic ring contraction conditions[3] (1% HCl in methanol) gave a mixture of tetrahydrofuran **27** (70% yield), and the tetrahydropyran **24** (15% yield), rather than any of the expected oxetane. In fact similar results were obtained with lactone **8**, which lacks the OH-6 silyl group, and gave a mixture of the tetrahydrofuran **27** (52% yield) and the tetrahydropyran **24** (30% yield). The increased proportion of 6-ring product results from the lack of OH-6 protection and an increased rate of cyclisation of the 6-OH onto C-2, but again no oxetane product was observed.

Almost all of these the observations may be explained by the initial formation of bicyclic intermediates, containing either tetrahydrofuran (the 5-OBn onto C-2) or tetrahydropyran (the 6-O[Si] onto C-2) rings, before subsequent opening of the lactone by methanol to yield **27** or **24** respectively. However the intermediacy of an open chain intermediate such as **26** cannot be completely ruled out, since here the relative rates of the possible nucleophilic ring closures may be vastly different compared to those under basic conditions.



Scheme 5 (i) HCl, MeOH, 70% yield of **27**, 15% yield of **24** (ii) HCl, MeOH, 52% yield of **27**, 30% yield of **24** (iii) camphorsulphonic acid, MeOH, 45% yield of **27**, 40% yield of **24** (iv) camphor sulphonic acid, THF, MeOH, 90% yield (v) camphorsulphonic acid, THF, MeOH, 82% yield.

An increased yield (40%) of the tetrahydropyran **24** was obtained by changing the acid to camphorsulfonic. Continuing this trend it was found that different results were obtained when the two *gluco* lactones **7** and **8** were treated with camphorsulfonic acid in a mixture of THF and methanol (3 : 5). In both cases under these modified conditions only the tetrahydropyran **24** was isolated (90% yield from **7** and 82% yield from **8**). Following on from these results further investigations of the reactivity of compounds **7** and **8** were undertaken, involving both changes in the nature of the acid and the solvent, and are detailed in **Table 1**.



SOLVENT		ACID		PRODUCTS	
% Methanol	%THF	HCl	CSA	% Furan **27**	% Pyran **24**
100	-	excess	-	52	30
37	63	excess	-	21	60
37	63	2.5 equiv.	-	10	65
-	100	excess	-	No Reaction	
100	-	-	2.5 equiv.	45	40
37	63	-	2.5 equiv.	0	82
-	100	-	2.5 equiv.	No Reaction	

Table 1.

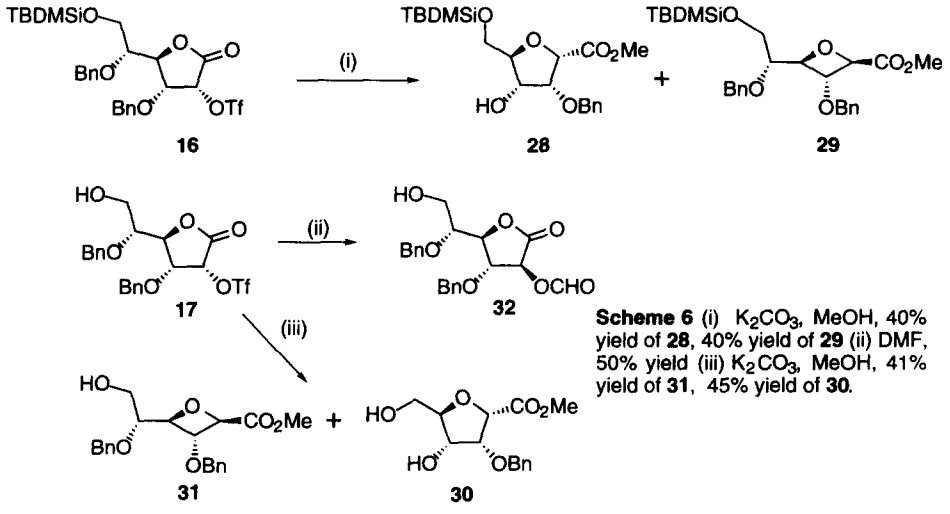
It is clear that the use of acidic conditions (HCl) and a nucleophilic solvent (MeOH) give us a higher proportion of the furan product **27**.

2.5. Studies on allo triflates

When the same set of reaction conditions were applied to the *allo* lactone triflates **16** and **17** very different results were obtained. These are outlined as follows:

2.5.1. Reactions in basic and neutral media (Scheme 6)

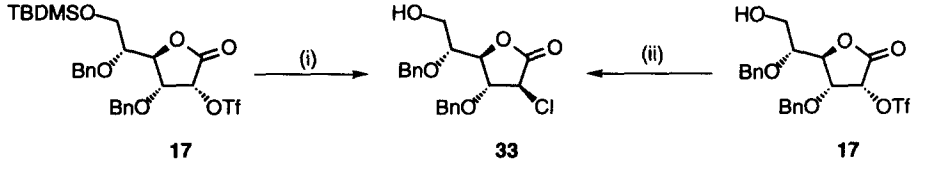
Treatment of the silyl *allo* triflate **16** with potassium carbonate in methanol surprisingly gave a 1:1 mixture of the tetrahydrofuran **28** (40% yield) and the oxetane **29** (40% yield). In an attempt to facilitate closure of OH-6 onto C-2 the desilylated triflate **17** was subjected to the same reaction conditions. However again a mixture of a furan **30** (45% yield) and an oxetane **31** (41% yield) was obtained; no tetrahydropyran product was isolated. Attempted cyclisation of triflate **17** under neutral conditions by simply stirring in DMF at room temperature produced the formate **32** in 50% yield; no traces of any bicyclic material were observed.



Scheme 6 (i) K_2CO_3, MeOH, 40% yield of **28**, 40% yield of **29** (ii) DMF, 50% yield (iii) K_2CO_3, MeOH, 41% yield of **31**, 45% yield of **30**.

2.5.2. Reactions in acidic media (Scheme 7)

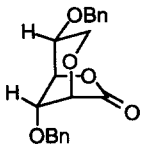
After the failure of the base catalyzed reactions to furnish any pyran products in the *allo* series attention was turned to an acid catalysed process. However again the reactivity of the *allo* compounds was found to be in marked contrast to that of the *gluco* counterparts. Thus treatment of either of the triflates **16** and 17 with HCl in methanol simply produced the chloride **33** (45% and 50% yields respectively). We observed no tetrahydropyran formation in the *allo* series.



Scheme 7 (i) HCl, MeOH, 45% yield (ii) HCl, MeOH, 50% yield

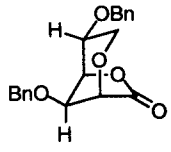
The difference in product distribution between the *gluco* and *allo* series may be due to a kinetic, and presumably electronic, effect. It might be expected that the unobserved *allo*

derived bicycle **34** would be thermodynamically more stable than the *gluco* derived counterpart **25** as the former has the C-3 substituent in a equatorial rather than an axial orientation. However it should also be born in mind that since the chair is a tetrahydropyran then this C-3 axial substituent only encounters one axial hydrogen atom.



34

Allo series



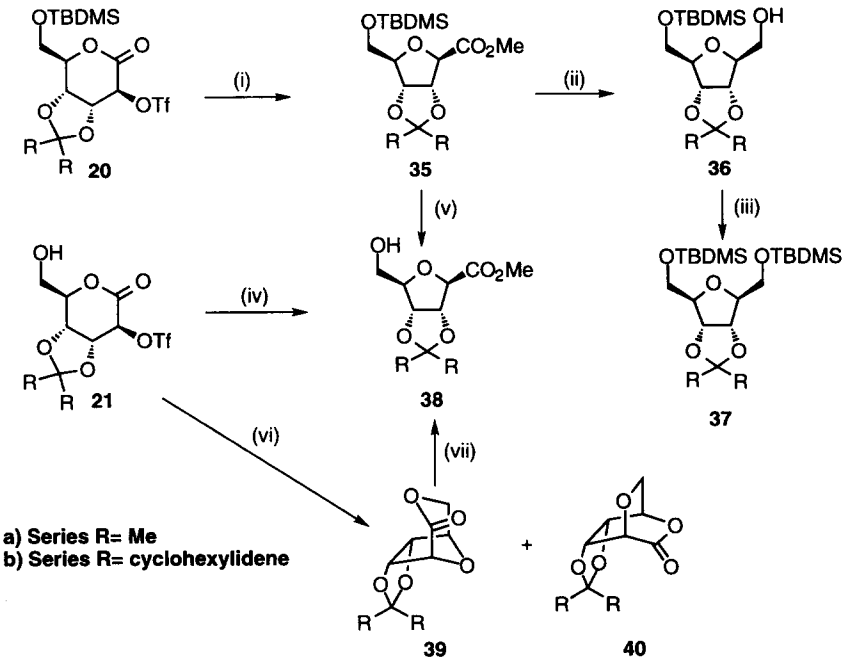
25

Gluco series

2.6. Studies on altro lactones

2.6.1. Reactions in basic media (Scheme 8)

Treatment of the cyclohexylidene *altro* silyl triflate **20b** with potassium carbonate in methanol yielded the cyclohexylidene *allo* silyl tetrahydrofuran **35b** as the major product (68% yield), with inversion of configuration at C-2[†] (Scheme 8). The identity of this material was confirmed by a two step conversion into the symmetrical disilyated tetrahydrofuran **37b** involving $LiAlH_4$ reduction to the alcohol **36b** followed by silylation with *tert*-butyldimethylsilyl chloride and imidazole in DMF. Similarly, potassium carbonate-induced ring contraction of the isopropylidene silyl lactone **20a** proceeded to yield the *allo* tetrahydrofuran acetonide **35a** in 58% yield.



Scheme 8 (i) K_2CO_3, MeOH, **a)** 58% yield, **b)** 68% yield (ii) $LiAlH_4$, THF, 94% yield (iii) Bu^tMe_2SiCl, imidazole, DMF, 88% yield (iv) K_2CO_3, MeOH, 94% yield (v) AcOH / H_2O, (4:1), 60% yield (vi) NaOAc, DMF, 46% of **39b** and 26% of **40b** (vii) K_2CO_3, MeOH, 63% yield.

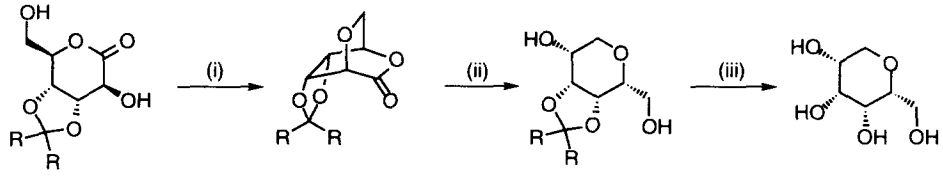
[†] A small amount of the epimeric *altro* material was also obtained.

Removal of the silyl protecting group would allow possible competition of tetrahydropyran formation with this ring contraction process. Thus, the cyclohexylidene triflate **21b** was treated with potassium carbonate in methanol. However the sole isolated product was found to be the ring contracted methyl ester **38b**. This material was also synthesized by desilylation of methyl ester **35b**. Therefore the ring contraction reaction competes effectively over possible tetrahydropyran formation in this system under these conditions. When the triflate **21b** was treated with sodium acetate in DMF a mixture of bicyclic products **39b** and **40b** was obtained. The identity of bicycle **39b** was confirmed by methanolic ring opening to yield the tetrahydrofuran methyl ester **38b**. However the formation of the bicycle **40b** indicates that under these conditions tetrahydropyran formation begins to compete with the ring contraction reaction.

2.6.2. Mitsunobu reactions (Scheme 9)

Due to the effective competition of THF over THP formation observed above, an alternative strategy for the synthesis of tetrahydropyrans in the *altro* series was investigated. It should be noted that cyclisation of the 6-OH onto C-2 in the *altro* case requires epimerisation of the triflate at C-2 before nucleophilic displacement can take place.

Unfortunately the previous set of results seemed to indicate that tetrahydrofuran formation would be the major product under basic conditions where we may be able to achieve this epimerisation. Therefore the alternative strategy for tetrahydropyran formation, consisting of cyclisation of the 2-OH onto C-6 was investigated. The first approach involved the use of the Mitsunobu reaction to achieve this and proved very successful. Thus simple treatment of either the isopropylidene **18a** or cyclohexylidene **18b** lactone diols with triphenylphosphine and diethyl azodicarboxylate in THF resulted in formation of the bicyclic pyrans **40a** and **40b** as the sole reaction products in both cases (60% and 69% yields respectively).



18 **40** **41** **42**

Scheme 9 (i) Ph_3P, $EtO_2CN{=}NCO_2Et$, THF, **a)** 60% yield **b)** 69% yield (ii) $LiBH_4$, THF, 93% yield (iii) CF_3CO_2H / H_2O, (2:3), 89% yield.

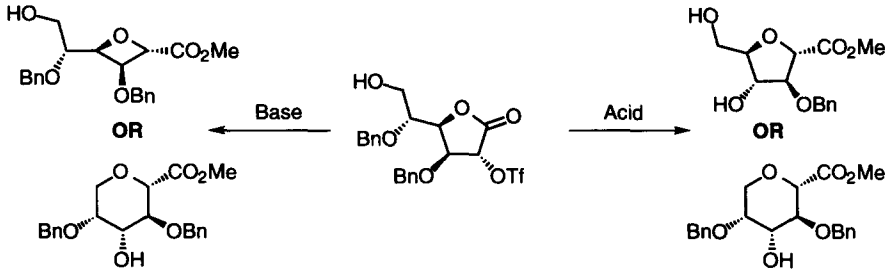
a) Series R= Me
b) Series R= cyclcohexylidene

The identity of the bicyclic cyclohexylidene pyran **40b** was confirmed by conversion to the known 2,6-anhydro-D-altritol **42**[17] by reduction with lithium borohydride to produce the alcohol **41b** and subsequent removal of the cyclohexylidene protecting group.

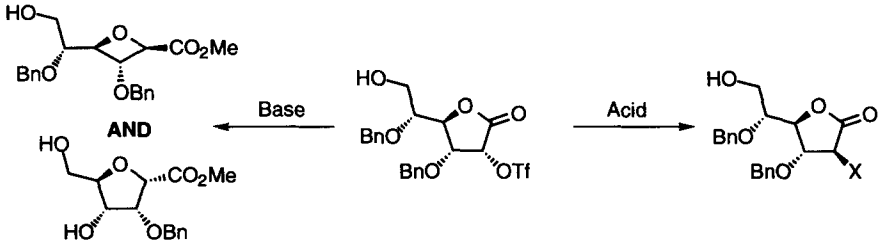
3. Summary and conclusion

In summary we have synthesized a series of γ-*gluco*, γ-*allo* and δ-*altro* hexonolactones and their C-2 triflates. The possible mode of cyclisation of these materials, and in particular the propensity for tetrahydropyran formation, was investigated for each series under various sets of reaction conditions.

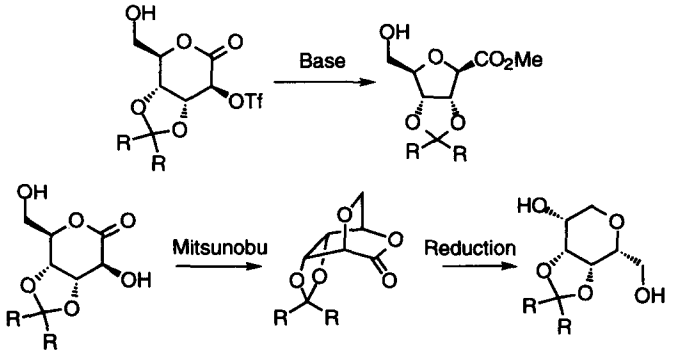
In the *gluco* series base catalysed reaction allows access either to oxetane or tetrahydropyran products; tetrahydropyran formation can be maximized by judicious choice of the reaction conditions. Under acidic conditions tetrahydrofuran and tetrahydropyran formation are the competing processes; again high yields of tetrahydropyran products can be achieved by choice of the reaction conditions.



In the *allo* series the reactivity of the C-2 triflates completely contrasted with those of the *gluco* compounds. Under basic conditions oxetane and tetrahydrofuran formation were completely competitive; no tetrahydropyran formation was achieved. Under neutral or acidic conditions intermolecular nucleophilic displacement was found to be the predominant process; again no tetrahydropyran formation was achieved.



In the *altro* series, where cyclisation of the OH-6 onto C-2 must be preceded by epimerisation of the leaving group at C-2, under basic conditions tetrahydrofuran formation was always the dominant, but not exclusive, process. However tetrahydropyran formation was simply and efficiently achieved by ring closure of the OH-2 onto C-6 by a Mitsunobu reaction.



4. Experimental

Melting points were recorded on a Kofler hot block. Proton nuclear magnetic resonance (δ_H) spectra were recorded on a Varian Gemini 200 (200 MHz) or Bruker AM 500 (500 MHz) spectrometers. Carbon nuclear magnetic resonance (δ_C) spectra were recorded on a Varian Gemini 200 (50.3 MHz). Multiplicities were assigned using DEPT sequence. Spectra run in D_2O were referenced to dioxan (δ_C 67.3) or methanol (δ_C 49.7) as internal standards. All chemical shifts are quoted on the δ-scale. Infrared spectra were recorded on a Perkin-Elmer 150 Fourier Transform spectrophotometer. Mass spectra were recorded on VG Micromass 30F, ZAB 1F, Masslab20-250 or trio-1 GCMS (DB-5 column) spectrometers, using desorption chemical ionization (NH_3 DCI), electron impact (EI), chemical ionization (NH_3 CI) and fast atom bombardment (FAB) techniques as stated. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given g/100 ml. Hydrogenations were run under an atmosphere of hydrogen gas maintained by inflated balloon. Microanalyses were performed by the microanalyses service of the Dyson Perrins laboratory. Thin layer chromatography (t.l.c.) was carried out on aluminium sheets coated with $60F_{254}$ silica. Plates were developed using 0.2% w/v cerium (IV) sulfate and 5% ammonium molybdate in 2M sulfuric acid. Flash chromatography was carried out using Sorbsil C60 40/60 silica. Solvents and available reagents were dried and purified before use according to standard procedures; methanol was distilled from magnesium methoxide, pyridine was distilled from calcium hydride and stored over potassium hydroxide, and tetrahydrofuran was distilled from a solution of sodium benzophenone ketyl immediately before use. *p*-Toluenesulfonyl chloride and imidazole were recrystallised from hexane and ethanol respectively. Hexane was distilled at 68 °C before use to remove involatile fractions.

4.1. 6-O-tert-Butyldiphenylsilyl-1,2-O-isopropylidene-α-D-glucofuranose **2**.

The monoacetonide **1** (8.03 g, 0.036 mol) was dissolved in dry DMF (70 ml) and cooled to -20 °C under nitrogen. Imidazole (4.97 g, 0.073 mol), followed by *tert*-butylchlorodiphenylsilane (9.70 ml, 0.036 mol) were added, and the mixture was stirred for 2 h at - 20 °C. At this point t.l.c. (ethyl acetate: hexane, 1:1) then showed no starting material (R_f 0.1) and a single product (R_f 0.5). Removal of the solvent gave a yellow oil which was dissolved in ethyl acetate (100 ml) and washed with water (3 x 20 ml). The organic layer was separated, dried (anhydrous sodium sulfate), filtered, and concentrated. Purification by flash chromatography (diethyl ether:hexane, 1:1) gave the silyl diol **2** (16.07 g, 96%) as a clear gum; $[\alpha]_D^{20}$ -17.6 (*c*, 0.9 in $CHCl_3$) [Lit. -18.7 (*c*, 0.8 in $CHCl_3$)][11]; δ_H (200 MHz, $CDCl_3$) 1.08 (9H, s, 3 x CH_3), 1.33 and 1.48 (6H, 2 x s, 2 x CH_3), 2.86 (1H, br s, exchange with D_2O, OH), 3.31 (1H, br s, exchange with D_2O, OH), 3.82 (1H, dd, $J_{5,6}$ 5.1 Hz, $J_{6,6'}$ 10.7 Hz, H-6), 3.92 (1H, dd, $J_{5,6'}$ 3.7 Hz, H-6'), 4.07-4.20 (2H, m, H-5 and H-4), 4.39 (1H, d, H-3), 4.55 (1H, d, $J_{1,2}$ 3.7 Hz, H-2), 5.97 (1H, d, H-1), 7.36-7.70 (10H, m, 10 x Ar-H).

4.2. 3,5-Di-O-benzyl-6-O-tert-butyldiphenylsilyl-1,2-O-isopropylidene-α-D-glucofuranose **3**.

Sodium hydride (60 % dispersion in oil, 1.08 g, 27.0 mmol) was washed with hexane (3 x 10 ml) under nitrogen. The silyl diol **2** (4.94 g, 10.8 mmol) was dissolved in dry DMF (50

ml), added slowly to the sodium hydride, and then the resulting mixture stirred for 1 h. Benzyl bromide (3.93 ml, 32.4 mmol) and tetra-*n*-butylammonium iodide (1.0 g) were then added and the reaction was stirred for 24 h at room temperature. After this time, t.l.c. (diethylether:hexane, 1:5) showed no starting material (R_f 0.05), and the title compound (R_f 0.3) as the major product. Methanol was added slowly until effervescence ceased, and the reaction then stirred for a further 10 min at room temperature. The solvent was removed, diethyl ether (200 ml) was added, and the resulting solution then filtered through Celite. The filtrate was then concentrated and purification by flash chromatography (diethyl ether:hexane, 1:5) gave the furanose **3** (4.50 g, 7.05 mmol, 65 %) as a clear gum; $[\alpha]_D^{20}$ -35.0 (*c*, 1.0 in $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 1.07 (9H, s, 3 x CH_3), 1.32 and 1.47 (6H, 2 x s, 2 x CH_3), 3.91 (1H, dd, $J_{6,6'}$ 11.2 Hz, $J_{5,6}$ 4.9 Hz, H-6), 3.97 (1H, ddd, $J_{5,6'}$ 1.8 Hz, $J_{4,5}$ 9.3 Hz, H-5), 4.07 (1H, dd, H-6'), 4.16 (1H, d, $J_{3,4}$ 3.0 Hz, H-3), 4.44 (1H, dd, H-4), 4.61 (1H, d, $J_{1,2}$ 3.8 Hz, H-2), 4.52 and 4.65 (2H, ABq, $J_{A,B}$ 11.7 Hz, CH_2Ph), 4.49 and 4.84 (2H, ABq, $J_{A,B}$ 11.3 Hz, CH_2Ph,), 5.92 (1H, d, H-1), 7.25-7.76 (20H, m, 20 x ArH); δ_C ($CDCl_3$) 19.2 (s, $\underline{C}(CH_3)_3$, 26.5 (q, $C(\underline{C}H_3)_2$), 26.7 (q, $C(\underline{C}H_3)_3$), 63.9, (t, C-6), 72.0, 72.4 (2 x t, 2 x $\underline{C}H_2Ph$), 76.94, 78.6, 81.9, 82.0 (4 x d, C-2, C-3, C-4, C-5), 105.3 (d, C-1), 111.8 (s, $\underline{C}(CH_3)_2$), 127.7, 128.5, 129.7 (3 x d, Ar CH), 133.6 (s, Ar C), 135.0, 135.9, (2 x d , Ar CH), 137.9, 139.0 (2 x s, Ar C); *m/z* (CI, NH_3) 656 (MNH_4^+, 21%), 639 (MH^+, 30%), 91 ($C_7H_7^+$, 100%). HRMS Calcd. for $C_{39}H_{50}NO_6Si$ (MNH_4^+) 656.3407. Found 656.3409.

4.3. 3,5-Di-O-benzyl-glucofuranose 4.

The furanose **3** (1.74 g, 2.73 mmol) was dissolved in dioxan (30 ml). and a mixture of trifluoroacetic acid / water (1:1, 60 ml) was added slowly to the resulting solution. The reaction mixture was then stirred for 45 h at room temperature after which time t.l.c. (ethyl acetate:hexane, 5:1) showed partial conversion of the starting material (R_f 0.9) to a major product (R_f 0.2). Evaporation of the solvents and purification of the residue by flash chromatography (ethyl acetate:hexane, 5:1) gave the lactol **4** (0.75 g, 2.08 mmol, 76%) as a clear gum; $[\alpha]_D^{20}$ -48.5 (*c*, 0.8 in $CHCl_3$); ν_{max} (film) 3400 (br, OH) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.05 (3H, br s, exchange with D_2O, 3 x OH), 3.86 (3H, m), 4.09 (1.6 H, dd), 4.23 (0.4H, s), 4.46 (3H, m), 4.62 (2H, m), 5.16 (0.4H, s, H-α-1), 5.40 (0.6H, d, H-β-1), 7.10-7.28 (10H, m, 10 x Ar-H);); δ_C ($CDCl_3$) 60.8, 71.7, 72.4 (3 x t), 73.9, 76.2, 77.0, 77.2 (4 x d), 83.4, 97.3 (2 x d, C-1-α, C-1-β), 127.8, 127.9, 128.2, 128.5 (4 x d, Ar CH), 137.9, 138.2 (2 x s, Ar C); *m/z* (CI, NH_3) 378 (MNH_4^+, 28%), 361 (MH^+, 13%), 360 ($M\text{-}H_2O\text{+}NH_4^+$, 36%), 91 ($C_7H_7^+$, 100%). (Found: C, 66.84; H, 6.47; $C_{20}H_{24}O_6$ requires: C, 66.65; H, 6.71%).

4.4. 3,5-Di-O-benzyl-D-glucono-1,4-lactone 5.

The lactol **4** (170 mg, 0.47 mmol) was dissolved in a mixture of dioxan and water (2:1, 9 ml). Barium carbonate (102 mg, 0.52 mmol), and then bromine (0.06 ml, 1.18 mmol) were added, and the reaction stirred for 2 h at room temperature in the dark. T.l.c. (ethyl acetate: hexane, 5:1) then showed no starting material (R_f 0.35) and the formation of a single product (R_f 0.7). The reaction was quenched with saturated aqueous sodium thiosulfate solution and the resulting mixture then extracted with ethyl acetate (3 x 25 ml). The ethyl acetate extracts were then combined, dried (anhydrous sodium sulfate), filtered and the solvent evaporated to

give a crude residue that was purified by flash chromatography (ethyl acetate:hexane, 1:1) to give the lactone **5** (139 mg, 0.39 mmol, 88%) as a clear gum; $[\alpha]_D^{20}$ +10.0 (*c*, 1.0 in $CHCl_3$); ν_{max} (film) 3420 (br, OH), 1785 (C=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.80 (1H, dd, $J_{6,6'}$ 12.0 Hz, $J_{5,6}$ 4.0 Hz, H-6), 3.91 (1H, dd, $J_{5,6'}$ 4.3 Hz, H-6'), 3.96 (1H, ddd, $J_{4,5}$ 5.1 Hz, H-5), 4.37 (1H, dd, $J_{2,3}$ 6.1 Hz, $J_{3,4}$ 6.7 Hz, H-3), 4.61 (2H, ABq, J_{AB} 11.4 Hz, CH_2Ph), 4.65 (1H, d, H-2), 4.75 (1H, dd, H-4), 4.79 (2H, ABq, J_{AB} 11.7 Hz, CH_2Ph), 7.27-7.36 (10H, m, 10 x Ar-H); δ_C ($CDCl_3$) 60.7 (t, C-6), 72.5, 72.7 (2 x t, CH_2Ph), 71.8, 77.6, 78.8, 80.0 (4 x d, C-2, C-3, C-4, C-5), 128.0, 128.3, 128.7 (3 x d, Ar CH), 137.0, 137.8 (2 x s, Ar C), 175.5 (s, C-1); *m/z* (CI, NH_3) 376 (MNH_4^+, 15%), 359 (MH^+, 15%), 91 ($C_7H_7^+$, 100%). (Found: C, 67.17; H, 6.11; $C_{20}H_{22}O_6$ requires: C, 67.03; H, 6.19%).

4.5. 3,5-Di-O-benzyl-6-O-tert-butyldimethylsilyl-D-glucono-1,4-lactone 6.

The lactone **5** (650 mg, 1.81 mmol) and imidazole (2.45 mg, 36 mmol) were dissolved in dry DMF (7.5 ml) and the solution was cooled to -65 °C under nitrogen. *tert*-Butylchlorodimethylsilane (280 mg, 1.80 mmol) was added and the reaction was stirred for 2 h. T.l.c. (ethyl acetate:hexane, 1:2) then showed the complete conversion of the starting material (R_f 0.2) to a single product (R_f 0.55). The reaction was quenched with methanol (1.5 ml) and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (30 ml) and washed with water (2 x 15 ml). The organic layer was then dried (magnesium sulfate) and concentrated. Purification by flash chromatography (ethyl acetate:hexane, 1:3) gave the silyl lactone **6** (767 mg, 1.62 mmol, 89%) as clear gum; $[\alpha]_D^{20}$ + 22.5 (*c*, 1.0 in $CHCl_3$); ν_{max} (film) 3440 (br, OH), 1790 (C=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.04 (6H, s, 2 x CH_3), 0.90 (9H, s, 3 x CH_3), 2.70 (1H, bs, exchange with D_2O, OH), 3.92 (3H, m, H-5, H-6, H-6'), 4.38 (1H, t, H-3), 4.60 (2H, dq, CH_2Ph), 4.76 (4H, m, CH_2Ph, H-4, H-2), 7.28-7.34 (10H, m, 10 x Ar-H); δ_C ($CDCl_3$) -5.7 (q, $\underline{C}H_3)_2$), 18.1 (s, $\underline{C}(CH_3)_3$), 25.7 (q, $C(\underline{C}H_3)_3$), 62.5 (t, C-6), 72.6, 73.8 (2 x t, CH_2Ph), 72.1, 77.7, 79.9, 81.0 (4 x d, C-2, C-3, C-4, C-5), 127.8, 127.9, 128.1, 128.6 (4 x d, Ar CH), 137.5, 138.2 (2 x s, Ar C), 175.6 (s, C-1); *m/z* (DCI, NH_3) 490 (MNH_4^+, 5%), 473 (MH^+, 4%), 91 ($C_7H_7^+$, 100%). (Found: C, 65.81; H, 7.49; $C_{26}H_{36}O_6$ Si requires: C, 66.07; H, 7.68%).

4.6. 3,5-Di-O-benzyl-6-O-tert-butyldimethylsilyl-2-O-trifluoromethanesulfonyl-D-glucono-1,4-lactone 7.

The silyl lactone **6** (100 mg, 0.21 mmol) was dissolved in dry dichloromethane (2.5 ml) and cooled to -50 °C under nitrogen. Pyridine (0.064 ml, 0.79 mmol) and trifluoromethanesulfonic anhydride (0.064 ml, 0.38 mmol) were added and the mixture stirred for 1 h at -50 °C. T.l.c. (ethyl acetate:hexane, 1:3) then showed no starting material (R_f 0.3) and a major product (R_f 0.6). The reaction was diluted with dichloromethane (20 ml), washed with dilute hydrochloric acid (10 ml) and brine (10 ml). The organic layer was dried (anhydrous sodium sulfate), filtered, and concentrated. Purification by flash chromatography (ethyl acetate:hexane, 1:4) gave the silyl triflate **7** (123 mg, 0.2 mmol, 96 %) as an unstable gum; $[\alpha]_D^{20}$ + 23.5 (*c*, 1.1 in $CHCl_3$); ν_{max} (film) 1810 (C=O) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.04 (6H, s, 2 x CH_3), 0.90 (9H, s, 3 x CH_3), 3.89 (3H, m, H-5, H-6, H-6'), 4.68

(6H, m, 2 x CH_2Ph, H-3, H-4), 5.83 (1H, d, $J_{2,3}$ 7.6 Hz, H-2), 7.25-7.40 (10H, m, 10 x Ar-H); δ_C ($CDCl_3$) -5.8 (q, $\underline{C}H_3)_2$), 18.0 (s, $\underline{C}(CH_3)_3$), 25.7 (q, $C(\underline{C}H_3)_3$), 61.6 (t, C-6), 73.4, 74.2 (2 x t, $\underline{C}H_2Ph$), 77.1, 78.4, 79.9, 81.8 (4 x d, C-2, C-3, C-4, C-5), 118.5 (q, $SO_2\underline{C}F_3$), 128.1, 128.3, 128.7, 128.9 (4 x d, Ar CH), 136.0, 137.2 (2 x s, Ar C), 166.8 (s, C-1); *m/z* (DCI, NH_3) 622 (MNH_4^+, 100%), 605 (MH^+, 2%).

4.7. *3,5-Di-O-benzyl-2-O-trifluoromethanesulfonyl-D-glucono-1,4-lactone* **8**.

The silyl triflate **7** (750 mg, 1.24 mmol) was dissolved in dioxane (20 ml) and a mixture of trifluoroacetic acid and water (1:1, 40 ml) was added. The reaction mixture was stirred at room temperature for 15 min after which time t.l.c. (ethyl acetate:hexane, 1:1) showed no starting material (R_f 0.7) and the formation of a major product (R_f 0.4). The reaction was quenched by addition of water (25 ml). Evaporation to dryness followed by flash chromatography (ethyl acetate:hexane, 1:1) gave the triflate **8** (520 mg, 1.06 mmol, 86%) as an unstable gum; δ_H (200 MHz, $CDCl_3$) 3.86-3.98 (3H, m), 4.53-4.80 (6H, m), 5.69 (1H, d, $J_{2,3}$ 6.3 Hz, H-2), 7.22-7.44 (10H, m, 10 x Ar-H).

4.8. *1,2,:5,6-Di-O-isopropylidene-α-D-allofuranose* **9**.

Pyridinium chlorochromate (25.8 g, 0.12 mol) and powdered molecular sieves (4Å, 30 g) were added to solution of diacetone glucose (15.67 g, 0.06 mol) in dry dichloromethane (100 ml), and the mixture was stirred at room temperature for 3 h. The suspension was then diluted with ether (100 ml), and filtered through a silica plug (eluting with ether). The resulting colourless solution was concentrated, affording the crude ketone, which was dissolved in a mixture of ethanol (90 ml) and water (10 ml) and cooled to 0° C. Sodium borohydride (6 g, 0.16 mol) was then added and the reaction mixture stirred for 1 h. After this time an excess of solid ammonium chloride was added to quench unreacted borohydride and then the resulting solution was concentrated. The crude residue was dissolved in chloroform (200 ml) and washed with water (2 x 100 ml), dried (anhydrous sodium sulfate), filtered and concentrated to afford diacetone allose **9** (12.37 g, 84%) as a colourless solid that was recrystallized from toluene, m.p. 70-72 °C [Lit. m.p. 75-76 °C][12]; $[\alpha]_D^{20}$ + 34.6 (*c*, 1.0 in $CHCl_3$) [Lit. +37.2 (*c*, 0.8 in $CHCl_3$)][12]; δ_H (200 MHz, $CHCl_3$) 1.39, 1.40, 1.50 and 1.60 (12H, 4 x s, 4 x CH_3), 2.65 (1H, bs, exchange with D_2O, OH), 3.85 (1H, dd, $J_{2,3}$ 8.5 Hz, $J_{3,4}$ 4.6 Hz, H-3), 4.05 (3H, m, H-4, H-6 and H-6'), 4.35 (1H, ddd, H-5), 4.67 (1H, dd, H-2), 5.85 (1H, d, $J_{1,2}$ 3.8 Hz, H-1).

4.9. *1,2-O-Isopropylidene-α-D-allofuranose* **10**.

The diacetonide **9** (19 g, 73 mmol) was suspended in a mixture of acetic acid and water (7:3, 300 ml) and stirred at room temperature for 16 h. After this time t.l.c. (ethyl acetate: hexane, 1:1) indicated no starting material (R_f 0.6) and the formation of a single product (R_f 0.05). The solvent was then removed *in vacuo* and the residue was co-evaporated with toluene (2 x 30 ml) to give the monoacetonide **10** (15.7 g, 98 %) as a colourless solid that was recrystallized from methanol / ether (3:1), m.p. 130-132 °C [Lit. m.p. 133 °C][13]; $[\alpha]_D^{20}$ +46.0

(*c*, 1 in H_2O) [Lit. +43 (*c*, 1.5 in H_2O)][13]; δ_H (200 MHz, D_2O) 1.16 and 1.33 (6H, 2 x s, 2 x CH_3), 3.35-3.55 (m, 2H, H-6 and H-6'), 3.71-3.81 (m, 2H, H-5 and H-4), 3.94-4.02 (m, 1H, H-3), 4.48-4.51 (m, 1H, H-2), 5.64 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1); *m/z* (CI, NH_3, %) 238 (MNH_4^+, 25), 220 (MH^+, 10), 180 (100).

4.10. 6-O-tert-Butyldiphenylsilyl-1,2-O-isopropylidene-α-D-allofuranose **11**.

The monoacetonide **10** (14 g, 63.7 mol) was dissolved in dry DMF (126 ml) and cooled to -20 °C under nitrogen. Imidazole (8.75 g, 127.4 mol) followed by *tert*-butylchlorodiphenylsilane (17.5 ml, 63.7 mol) was added, and the mixture then stirred for 2 h at - 20 °C. After this time t.l.c. (ethyl acetate: hexane, 1:1) showed no starting material (R_f 0.05) and the formation of a single product (R_f 0.2). Removal of the solvent gave a yellow oil which was dissolved in ethyl acetate (250 ml) and washed with water (3 x 50 ml). The organic layer was separated, dried (anhydrous sodium sulfate), filtered, and concentrated. Purification by flash chromatography (diethyl ether: hexane, 1:1) gave the diol **11** (28.5 g, 98%) as a white solid that was recrystallized from (ether:hexane, 1:1), m.p. 72-74 °C; $[\alpha]_D^{20}$ +5.6 (*c*, 1 in $CHCl_3$); ν_{max} (film) 3500 (br, OH) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.09 (9H, s, 3 x CH_3), 1.36 and 1.58 (6H, 2 x s, 2 x CH_3), 2.84 and 3.10 (2H, 2 x bs, exchange with D_2O, 2 x OH), 3.81-4.01 (m, 4H), 4.58-4.62 (m, 1H), 5.77 (1H, d, $J_{1,2}$ 3.7 Hz, H-1), 7.37- 7.43 (5H, m, 5 x Ar-H), 7.69-7.74 (5H, m, 5 x Ar-H); δ_C ($CDCl_3$) 19.2 (s, $\underline{C}(CH_3)_3$, 26.5, 26.6 (2 x q, $C(\underline{C}H_3)_2$), 27.0 (q, $C(\underline{C}H_3)_3$), 64.6, (t, C-6), 72.1, 72.3, 79.3 (3 x d, C-2, C-3, C-4, C-5), 103.9 (d, C-1), 112.8 (s, $\underline{C}(CH_3)_2$), 127.8, 129.9 (2 x d, Ar CH), 132.8 (s, Ar C), 135.5, 135.6, (2 x d , Ar CH); *m/z* (CI, NH_3, %) 476 (MNH_4^+, 11), 459 (MH^+, 8), 418 (100), 221 (84), 196 (90), 180 (54), 91 (20). HRMS Calcd. for $C_{25}H_{38}NO_6Si$ (MNH_4^+) 476.2468. Found 476.2475.

4.11. 3,5-Di-O-benzyl-6-O-tert-butyldiphenylsilyl-1,2-O-isopropylidene-α-D-allofuranose **12**.

Sodium hydride (60 % dispersion in oil, 3.23 g, 81 mmol) was washed with hexane (3 x 20 ml) under nitrogen. The diol **11** (15 g, 32.8 mmol) was dissolved in dry DMF (150 ml), added slowly to the sodium hydride and stirred for 1 h. Benzyl bromide (11.8 ml, 99.4 mmol) and tetra-*n*-butylammonium iodide (3 g) were then added and the reaction was stirred for 26 h at room temperature. T.l.c. (diethyl ether:hexane, 1:4) then showed no starting material (R_f 0.05), and the title compound (R_f 0.25) as the major product. Methanol was added until effervescence ceased, and the reaction was stirred for further 5 minutes at room temperature. The solvent was removed, diethyl ether (250 ml) added to the residue and the solution then filtered through Celite. The filtrate was concentrated and purification by flash chromatography (diethyl ether:hexane, 1:4) gave the furanose **12** (16 g, 76 %) as a clear gum; $[\alpha]_D^{20}$ +35.6 (*c*, 1 in $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 1.09 (s, 9H, 3 x CH_3), 1.38 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 3.83-4.36 (m, 5H), 4.48 and 4.66 (ABq, 2H, J_{AB}11.7 Hz, CH_2Ph), 4.54 (t, 1H), 4.70 and 4.79 (ABq, 2H, J_{AB} 11.7 Hz, CH_2Ph), 5.73 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 6.26-6.44 (m, 14H, 14 x Ar-H), 7.63-7.79 (m, 6H, 6 x Ar-H); δ_C ($CDCl_3$) 19.2 (s, $\underline{C}(CH_3)_3$, 26.7, 26.9 (2 x q, $C(\underline{C}H_3)_2$), 26.8 (q, $C(\underline{C}H_3)_3$), 63.8, (t, C-6), 72.0, 73.9 (2 x t, 2 x $\underline{C}H_2Ph$),

76.7, 77.8, 79.1, 79.4 (4 x d, C-2, C-3, C-4, C-5), 104.1 (d, C-1), 112.9 (s, $\underline{C}(CH_3)_2$), 127.3, 127.5, 127.7, 128.0, 128.2, 128.3, 129.6 (7 x d, Ar CH), 133.4 (s, Ar C), 135.6, 135.7, (2 x d , Ar CH), 137.6, 139.0 (2 x s, Ar C); *m/z* (CI, NH_3, %) 653 (MNH_4^+, 14), 598 (4), 365 (31), 91 (100). HRMS Calcd. for $C_{39}H_{50}NO_6Si$ (MNH_4^+) 656.3407. Found 656.3409.

4.12. 3,5-Di-O-benzyl-allofuranose **13**

The furanose **12** (1.74 g, 2.73 mmol) was dissolved in dioxane (30 ml). A mixture of trifluoroacetic acid and water (1:1, 60 ml) was then added slowly and the reaction mixture was stirred for 45 h at room temperature. At this point t.l.c. (ethyl acetate:hexane, 5:1) showed partial conversion of the starting material (R_f 0.8) to a major product (R_f 0.2). Evaporation of the solvents and purification of the residue by flash chromatography (ethyl acetate:hexane, 5:1) gave the lactol **13** (0.80 g, 82%) as a white solid which was recrystallized from ether:hexane (1:1), m.p. 59-61 °C; $[\alpha]_D^{20}$ +22.2 (*c*, 1 in $CHCl_3$); ν_{max} (film) 3400 (br, OH) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.50-3.80 (m, 3H), 4.00-4.34 (m, 3H), 4.53-4.72 (m, 4H), 5.21-5.27 (m, 1H), 7.23-7.34 (m, 10H, 10 x Ar-H); δ_C ($CDCl_3$) 61.2, 70.9, 72.6, 72., 73.0, 74.0, 78.8, 78.9, 79.4, 81.5, 81.6, 96.7, 102.3 (2 x d, C-1-α, C-1-β), 127.9, 128.1, 128.2, 128.3, 128.5, 128.6 (6 x d, Ar CH), 136.9, 137.7 (2 x s, Ar C); *m/z* (CI, NH_3, %) 378 (MNH_4^+, 10), 360 (M^+, 12), 108 (27), 91 (100). HRMS Calcd. for $C_{20}H_{28}NO_6$ (MNH_4^+) 378.1917. Found 378.1916. Calcd. for $C_{20}H_{26}NO_5$ (MNH_4^+-H_2O) 360.1811. Found 360.1812.

4.13. 3,5-Di-O-benzyl-D-allono-1,4-lactone **14**.

Lactol **13** (460 mg, 1.27 mmol) was dissolved in a mixture of dioxane and water (2:1, 25 ml). Barium carbonate (275 mg, 1.4 mmol), and then bromine (0.16 ml, 3.19 mmol) were added and the reaction was stirred for 2 h at room temperature in the dark. At this point t.l.c. (ethyl acetate: hexane, 1:1) showed no remaining starting material (R_f 0.1) and a single product (R_f 0.6). The reaction was quenched with saturated aqueous sodium thiosulfate solution and then extracted into ethyl acetate (3 x 25 ml). The ethyl acetate extracts were then dried (anhydrous sodium sulfate), filtered, and the solvent evaporated to give a crude residue that was purified by flash chromatography (ethyl acetate:hexane, 1:1) to give the lactone **14** (412 mg, 90%) as a white solid that was then recrystallized from diethyl ether / hexane (1:1), m.p. 87-89 °C; $[\alpha]_D^{20}$ -6.0 (*c*, 1 in $CHCl_3$); ν_{max} (film) 340 (br, OH), 1764 (C=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 2.94 (2H, bs, exchange with D_2O, 2 x OH), 3.67- 3.70 (3H, m), 4.35 (1H, d), 4.47 and 4.59 (2H, dd, ABq, J_{AB} 11.9 Hz, CH_2Ph), 4.54 (1H, d), 4.61-5.28 (3H, m), 7.21-7.23 (2H, m, 2 x Ar-H), 7.29-7.36 (8H, m, 8 x Ar-H); δ_C ($CDCl_3$) 60.4 (t, C-6), 68.6, 72.2, 73.3, 74.2, 78.2, 82.9 (4 x d, 2 x t, CH_2Ph, C-2, C-3, C-4, C-5), 127.7, 128.0, 128.1, 128.3, 128.7 (5 x d, Ar CH), 136.7, 137.0 (2 x s, Ar C), 175.9 (s, C-1); *m/z* (CI, NH_3, %) 376 (MNH_4^+, 23), 267 (14), 181 (19), 108 (21), 91 (100). HRMS Calcd. for $C_{20}H_{26}NO_6$ (MNH_4^+) 376.1760. Found 376.1764.

4.14. 3,5-Di-O-benzyl-6-O-tert-butyldimethylsilyl-D-allono-1,4-lactone **15**.

The lactone **14** (580 mg, 1.62 mmol) and imidazole (220 mg, 3.2 mol) were dissolved in dry DMF (8 ml) and the solution was cooled to -65 °C under nitrogen. *tert*-Butylchlorodimethylsilane (252 mg, 1.67 mmol) was added and the reaction stirred for 2 h. After this time t.l.c. (ethyl acetate:hexane, 1:2) showed the presence of a mixture of compounds including starting material (R_f 0.2) and a major product (R_f 0.6). The reaction was quenched with methanol (1 ml) and the solvent removed under reduced pressure. The residue was then dissolved in ethyl acetate (60 ml) and washed with water (2 x 15 ml). The organic layer was dried (magnesium sulfate), filtered, and concentrated. Purification by flash chromatography (ethyl acetate:hexane, 1:3) gave the silyl alcohol **15** (317 mg, 41%) as clear gum; $[\alpha]_D^{20}$ -11.0 (*c*, 1 in $CHCl_3$); ν_{max} (film) 3470 (br, OH), 1789 (C=O) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.07 (6H, s, 2 x CH_3), 0.91 (9H, s, 3 x CH_3), 2.84 (d, 1H, J 9.6 Hz, OH), 3.60-3.75 (3H, m), 4.30 (1H, m), 4.46-4.76 (5H, m), 7.21-7.35 (10H, m, 10 x Ar-H); δ_C ($CDCl_3$) -5.4 (q, $\underline{C}H_3)_2$), 18.2 (s, $\underline{C}(CH_3)_3$), 25.7, 25.8 (2 x q, $C(\underline{C}H_3)_3$), 61.4 (t, C-6), 68.7, 72.0, 73.7, 73.8, 78.7, 82.6 (4 x d, 2 x t, CH_2Ph, C-2, C-3, C-4, C-5), 127.8, 128.1, 128.2, 128.3, 128.4, 128.4, 128.6, 128.7 (8 x d, Ar CH), 136.6, 137.0 (2 x s, Ar C), 175.7 (s, C-1); *m/z* (CI, NH_3, %) 490 (MNH_4^+, 12), 376 (11), 373 (MH^+, 6), 181 (21), 108 (27), 91 (100). HRMS Calcd. for $C_{26}H_{37}O_6Si$ (MH^+) 473.2359. Found 473.2362.

4.15. 3,5-Di-O-benzyl-6-O-tert-butyldimethylsilyl-2-O-trifluoromethanesulfonyl-D-allono-1,4-lactone **16**.

The silyl alcohol **15** (200 mg, 0.33 mmol) was dissolved in dry dichloromethane (5 ml) and cooled to -50 °C under nitrogen. Pyridine (0.13 ml, 1.58 mmol) and trifluoromethanesulfonic anhydride (0.13 ml, 0.76 mmol) were added and the mixture stirred for 1 h at -50 °C. After this time t.l.c. (ethyl acetate:hexane, 1:3) showed no starting material (R_f 0.3) and the formation of a major product (R_f 0.5). The reaction was diluted with dichloromethane (40 ml), and washed with dilute hydrochloric acid (20 ml) and brine (20 ml). The organic layer was dried (anhydrous sodium sulfate), filtered, and concentrated. Purification by flash chromatography (ethyl acetate:hexane, 1:4) gave the silyl triflate **16** (255 mg, quantitative) as an unstable gum; δ_H (200 MHz, $CDCl_3$) 0.10 (6H, s, 2 x CH_3), 0.90 (9H, s, 3 x CH_3), 3.60-3.79 (3H, m), 4.45-4.83 (6H, m), 5.58 (1H, d, $J_{1,2}$ 3.6 Hz, H-1), 7.21-7.40 (10H, m, 10 x Ar-H).

4.16. 3,5-Di-O-benzyl-2-O-trifluoromethanesulfonyl-D-allono-1,4-lactone **17**.

The silyl triflate **16** (100 mg, 0.17 mmol) was dissolved in dioxane (3 ml) and a mixture of trifluoroacetic acid and water (1:1, 6 ml) was added. The reaction mixture was then stirred at room temperature for 15 minutes after which time t.l.c. (ethyl acetate:hexane, 1:1) showed no starting material (R_f 0.7) and the formation of a major product (R_f 0.4). The reaction was quenched by addition of water (25 ml). Evaporation to dryness followed by flash chromatography (ethyl acetate:hexane, 1:1) gave the triflate **17** (69 mg, 86%) as an unstable gum; δ_H (200 MHz, $CDCl_3$) 3.67-3.70 (2H, m), 3.75-3.78 (1H, m), 4.45-4.76 (6H, m), 5.56 (1H, d, $J_{1,2}$ 5.6 Hz, H-1), 7.20-7.35 (10H, m, 10 x Ar-H).

4.17. *6-O-tert-Butyldimethylsilyl-3,4-O-isopropylidene-D-altrono-1,5-lactone* **19a**.

The lactone **18a**[14] (300 mg, 1.4 mmol) and imidazole (247 mg, 3.6 mmol) were stirred under nitrogen in dry DMF (15 ml) at 0 °C. *tert*-Butyldimethylsilylchloride (300 mg, 2.0 mmol) was added and the mixture allowed to warm to room temperature. After 30 min, t.l.c. (hexane:ethyl acetate, 1:1) showed complete consumption of starting material (R_f 0.3) and the formation of a single product (R_f 0.7). The solvent was removed *in vacuo* and ether (20 ml) was added. The mixture was shaken with water (20 ml), which was then further extracted with ether (2 x 20 ml). The combined organic extracts were then dried (magnesium sulfate), filtered, and the residue purified by flash chromatography (hexane:ethyl acetate, 3:1) to yield the silyl alcohol **19a** (378 mg, 83%), as a white crystalline solid, m.p. 140-143 °C (ether / hexane); $[\alpha]_D^{20}$ +78.2 (*c*, 1.04 in $CHCl_3$); ν_{max} ($CHCl_3$) 3500 (br, OH), 1760 (C=O) cm^{-1}; δ_H ($CDCl_3$) 0.11 (6H, s, Me_2Si), 0.92 (9H, s, Bu^t), 1.39 (3H, s, Me), 1.54 (3H, s, Me), 3.35 (1H, br, OH), 3.88 (1H, dd, H-6, $J_{5,6}$ 4.5 Hz, $J_{6,6'}$ 12.0 Hz), 4.03 (1H, dd, H-6', $J_{5,6'}$ 2.0 Hz), 4.16 (1H, m, H-5), 4.28-4.30 (2H, m, H-3, H-4), 4.42 (1H, d, H-2, $J_{2,3}$ 7.7 Hz); δ_C ($CDCl_3$) -5.6 (q, Me_2Si), 18.2 (s, $SiCMe_3$), 24.3, 26.6 (2 x q, $\underline{Me}_2C$), 25.7 (q, Bu^t), 61.8 (t, C-6), 70.0, 70.8, 77.4, 78.5 (4 x d, C-2, C-3, C-4, C-5), 112.2 (s, $\underline{C}Me_2$), 172.9 (s, C-1); *m/z* (NH_3, DCI) 350 (MNH_4^+, 100%), 333 (MH^+). (Found: C, 54.37; H, 8.72. $C_{15}H_{28}O_6Si$ requires: C, 54.19; H, 8.49%).

4.18. *6-O-tert-Butyldimethylsilyl-3,4-O-isopropylidene-2-O-trifluoromethanesulfonyl-D-altrono-1,5-lactone* **20a**.

The silyl alcohol **19a** (303 mg, 0.9 mmol) and dry pyridine (0.180 ml, 2.5 equiv.) were stirred under nitrogen in dry dichloromethane (2 ml) at -20 °C. Trifluoromethanesulfonic anhydride (0.23 ml, 1.5 equiv.) was added. After 10 min t.l.c. (hexane:ethyl acetate, 3:1) indicated complete product formation (R_f 0.7) and a further 5 ml of dichloromethane was then added. The reaction mixture was then shaken with water (5 ml, containing a few drops of 1M HCl). The aqueous layer was then further extracted with dichloromethane (2 x 5 ml). The combined organic extracts were then dried (magnesium sulfate) and filtered. The solvent was then removed and the residue purified by flash chromatography (hexane:ethyl acetate, 4:1) to yield the silyl triflate **20a** (420 mg, quantitative) as a colourless oil; ν_{max} (film) 1784 (C=O) cm^{-1} ; δ_H ($CDCl_3$) 0.11 (6H, s, Me_2Si), 0.92 (9H, s, Bu^t), 1.41, 1.55 (6H, 2 x s, Me_2C), 3.89 (1H, dd, H-6, $J_{5,6}$ 4 Hz, $J_{6,6'}$ 12 Hz), 4.03 (1H, dd, H-6', $J_{5,6'}$ 2.2 Hz), 4.25 (1H, m, H-5), 4.51-4.56 (2H, m, H-3, H-4), 5.23 (1H, d, H-2, $J_{2,3}$ 7 Hz); δ_C ($CDCl_3$) -5.7 (q, Me_2Si), 18.2 (s, Me_3CSi), 24.5, 26.5 (2 x q, $\underline{Me}_2C$), 25.6 (q, Bu^t), 61.7 (t, C-6), 70.4, 74.2, 78.8, 81.7 (4 x d, C-2, C-3, C-4, C-5), 113.2 (s, $\underline{C}Me_2$), 164.2 (s, C-1); *m/z* (NH_3, DCI) 482 (MNH_4^+, 100%).

4.19. *3,4-O-Cyclohexylidene-2-O-trifluoromethanesulfonyl-D-altrono-1,5-lactone* **21b**.

The cyclohexylidene silyl triflate **20b**[15] (492 mg, 0.98 mmol) was stirred in a mixture of acetic acid (8 ml) and water (2 ml) at room temperature. After 13 h, t.l.c. (hexane:ethyl acetate, 3:1) indicated the formation of a single product (R_f 0.2). The solvent was removed, the residue co-evaporated with toluene (2 x 5 ml) and purified by flash chromatography (hexane:ethyl acetate, 2:1) to yield the cyclohexylidene alcohol **21b** (267 mg, 70%) as a white

crystalline solid, m.p. 109-111 °C (ether / hexane); $[\alpha]_D^{20}$ +29.0 (*c*, 0.9 in $CHCl_3$); ν_{max} (KBr) 3614 (OH), 1786 (C=O) cm^{-1}; δ_H ($CDCl_3$) 1.39-1.76 (10H, m, cyclohexylidene), 2.93 (1H, br, OH), 3.85 (1H, br d, H-6, $J_{6,6'}$ 12.3 Hz), 4.09 (1H, br d, H-6'), 4.27-4.32 (1H, m, H-5), 4.54-4.63 (2H, m, H-3, H-4), 5.26 (1H, d, H-2, $J_{2,3}$ 2.4 Hz); δ_C ($CDCl_3$) 23.3, 23.6, 24.6, 34.0, 36.5 (5 x t, cyclohexylidene), 61.0 (t, C-6), 69.9, 73.8, 79.1, 81.9 (4 x d, C-2, C-3, C-4, C-5), 114.5 (s, cyclohexylidene), 165.0 (s, C-1); *m/z* (NH_3, DCI) 408 (MNH_4^+, 100%), 390 (MNH_4^+-H_2O). (Found: C, 40.09; H, 4.43; $C_{13}H_{17}O_8F_3S$ requires: C, 40.00; H, 4.39%).

4.20. *Methyl-2,4-anhydro-3,5-di-O-benzyl-6-O-tert-butyldimethylsilyl-D-mannonate* **22**.

The silyl triflate **7** (150 mg, 0.25 mmol) was dissolved in freshly distilled methanol (3 ml) and potassium carbonate (36 mg, 0.26 mmol) was then added. The reaction mixture was stirred at room temperature under nitrogen for 10 min, after which time t.l.c. (ethyl acetate: hexane, 1:3) showed complete consumption of starting material (R_f 0.5) and the formation of a major product (R_f 0.4). The reaction mixture was then partitioned between ethyl acetate (15 ml) and water (10 ml). The organic layer was then washed with brine (10 ml), dried (anhydrous sodium sulfate) and filtered. Removal of the solvents followed by flash chromatography (ethyl acetate: hexane, 1:4) gave the silyl oxetane **22** (91 mg, 75%) as a clear gum; $[\alpha]_D^{20}$ -29.0 (*c*, 0.8 in $CHCl_3$); ν_{max} (film) 1759 (C=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 0.069 and 0.074 (6H, 2 x s, 2 x CH_3), 0.92 (9H, s, 3 x CH_3), 3.76 (1H, dd, $J_{5,6}$ 6.6 Hz, $J_{6,6'}$ 11.1 Hz, H-6), 3.81 (3H, s, CH_3), 4.00 (1H, dd, $J_{5,6'}$ 2.5 Hz, H-6'), 4.23 (1H, ddd, $J_{4,5}$ 8.9 Hz, H-5), 4.56-4.65 (3H, m, CH_2Ph and H-3), 4.62-4.89 (1H, ABq, J_{AB} 11.1 Hz, CH_2Ph), 4.78 (1H, dd, $J_{3,4}$ 6.5 Hz, H-4), 5.05 (1H, d, $J_{2,3}$ 4.8 Hz, H-2), 7.25-7.34 (10H, m, 10 x Ar-H); δ_C ($CDCl_3$) –5.6 (q, $SiMe_2$), 18.2 (s, $\underline{C}Me_3$), 25.8 (q, $\underline{Me}_3C$), 52.4 (q, Me), 63.2(t, C-6), 71.7, 73.1 (2 x t, 2 x CH_2Ph), 75.5, 77.8, 82.8, 83.9 (4 x d, C-2, C-3, C-4, C-5), 127.6, 127.9, 128.1, 128.4, 128.6 (5 x d, Ar-C), 137.4, 139.1 (2 x s, Ar-C), 171.2 (s, C-1); *m/z* (DCI, NH_3, %) 504 (MNH_4^+, 5), 487 (MH^+, 10), 91 (100). (Found: C, 66.37; H, 8.11; $C_{27}H_{38}O_6Si$ requires: C, 66.63; H, 7.87%).

4.21. *Methyl-2,4-anhydro-3,5-di-O-benzyl-D-mannonate* **23**.

The triflate **8** (230 mg, 0,47 mmol) was dissolved in freshly distilled methanol (16 ml) and potassium carbonate (104 mg, 0.75 mmol) was added. The reaction mixture was stirred at room temperature under nitrogen for 15 min after which time t.l.c. (ethyl acetate:hexane, 1:1) showed complete consumption of starting material (R_f 0.45), and the formation of a major product (R_f 0.3) and a minor product (R_f 0.5). The reaction mixture was then partitioned between ethyl acetate (50 ml) and water (30 ml). The organic layer was washed with brine (30 ml), dried (anhydrous sodium sulfate) and filtered. Removal of the solvents followed by flash chromatography (ethyl acetate:hexane, 1:1) gave the tetrahydropyran **24** (34 mg, 20%) as a clear gum, (identical to the material described below) and the oxetane **23** (100 mg, 60%) as clear gum; $[\alpha]_D^{20}$ -45 (*c*, 0.4 in $CHCl_3$); ν_{max} (film) 3490 (br, OH), 1754 (C=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.79 (1H, dd, $J_{5,6}$ 4.1 Hz, $J_{6,6'}$ 12.0 Hz, H-6), 3.82 (3H, s, OCH_3), 3.90 (1H, dd, $J_{5,6'}$ 4.1 Hz, H-6'), 4.23 (1H, dt, $J_{4,5}$ 8.3 Hz, H-5), 4.56-4.69 (5H, m, 2 x CH_2Ph and H-3), 4.92 (1H, ddd, $J_{3,4}$ 6.6 Hz and $J_{2,4}$ 0.7 Hz, H-4), 5.05 (1H, dd, $J_{2,3}$ 4.7 Hz, H-

2), 7.26-7.35 (10H, m, 10 x Ar-H); δ_C ($CDCl_3$) 52.3 (q, Me), 60.9(t, C-6), 71.8, 72.3 (2 x t, 2 x CH_2Ph), 75.5, 76.6, 83.8, 84.1 (4 x d, C-2, C-3, C-4, C-5), 127.7, 127.8, 128.1, 128.4, 128.5 (5 x d, Ar-C), 136.9, 138.4 (2 x s, Ar-C), 170.6 (s, C-1); *m/z* (DCI, NH_3, %) 390 (MNH_4^+, 10), 373 (MH^+, 10), 91 (100). (Found: C, 67.09; H, 6.85; $C_{21}H_{24}O_6$ requires: C, 67.36; H, 7.00%).

4.22. (5S, 8R)-5,8-Di-O-benzyl-3,7-dioxa-bicycle [3.2.1] octane-2-one **25**.

4.22.1.

The triflate **8** (0.054 g, 0.11 mmol) was dissolved in dry acetone (2.5 ml) and dry pyridine (0.1 ml) was then added. The resulting solution was stirred at room temperature under nitrogen for 8 h. After this time t.l.c. (ethyl acetate:hexane, 1:1) showed no starting material (R_f 0.4) and the formation of a single product (R_f 0.65). The solvent was then removed *in vacuo* and the residue purified by flash chromatography (ethyl acetate:hexane, 1:4) to give the bicycle **25** (0.033 g, 88%) as a clear gum; $[\alpha]_D^{20}$ -31.2 (*c*, 1 in $CHCl_3$); ν_{max} (film) 1791 (C=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$) 3.60-3.65 (1H, m), 4.05 (1H, dd), 4.12-4.17 (3H, m), 4.49-4.58 (3H, m), 4.70 (1H, d, ABq, J_{AB} 11.8 Hz, CH_2Ph), 4.76 (1H, d), 7.21-7.41 (10H, m, 10 x Ar-H); δ_C (50.3 MHz, $CDCl_3$) 64.94, 71.82 and 72.16 (3 x t, C-6, 2 x CH_2Ph), 69.86, 71.06, 75.53 and 77.39 (4 x d, C-2, C-3, C-4, C-5), 127.97, 128.31, 128.51, 128.78, 128.97 (5 x d, Ar-C), 136.67, 137.66 (2 x s, Ar-C), 170.78 (s, C-1); *m/z* (CI, NH_3, %) 359 (MNH_4+1$^+$, 16), 358 (MNH_4^+, 95), 108 (56), 91 (100). (Found: C, 70.38; H, 5.89; $C_{21}H_{20}O_5$ requires: C, 70.57; H, 5.92%).

4.22.2.

The triflate **8** (58 mg, 0.12 mmol) was dissolved in dry DMF (3 ml) and sodium acetate (30 mg, 0.3 mmol) was added. The resulting suspension was stirred at room temperature under nitrogen for 12 h. After this time t.l.c. (ethyl acetate:hexane, 1:1) showed no starting material (R_f 0.3) and the formation of a single product (R_f 0.65). The solvent was removed *in vacuo* and the residue suspended in water (30 ml) and extracted with chloroform (2 x 15 ml). The combined organic layers were then dried (anhydrous sodium sulfate), filtered, and evaporated to give a residue that was purified by flash chromatography (ethyl acetate:hexane, 1:4) to give the bicycle **25** (26 mg, 64%) as a clear gum.

4.22.3.

The triflate **8** (0.5 g, 1.02 mmol) was dissolved in dry DMF (23 ml) and the resulting solution stirred at room temperature under nitrogen for 24 h. After this time t.l.c. (ethyl acetate:hexane, 1:1) shown no residual starting material (R_f 0.4) and the formation of a single product (R_f 0.65). The solvent was removed *in vacuo* and the residue purified by flash chromatography (ethyl acetate:hexane, 1:4) to give the bicycle **25** (0.3 g, 85%) as a clear gum.

4.23. Methyl-2,6-anhydro-3,5-di-O-benzyl-D-mannonate **24**.

4.23.1.

The triflate **8** (89 mg, 0.19 mmol) was dissolved in dry methanol (3.5 ml) and dry pyridine (0.5 ml) was added. The reaction mixture was then stirred at room temperature

under nitrogen for 24 h. After this time t.l.c. (ethyl acetate:hexane, 1:1) showed no starting material (R_f 0.4) and the formation of a main product (R_f 0.5). The reaction mixture was poured into aqueous hydrochloric acid (25 ml) and extracted with ethyl acetate (2 x 30 ml). The combined organic layers were then washed with brine (25 ml), dried (anhydrous sodium sulfate), filtered, and the solvent removed *in vacuo* to produce a residue that was purified by flash chromatography (ethyl acetate:hexane, 1:1) to give the tetrahydropyran **24** (43 mg, 65%) as a clear gum; $[\alpha]_D^{20}$ -17.5 (*c*, 1 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 2.44 (1H, d, exchange with D_2O, J 4.9 Hz, OH), 3.58 (1H, dd, $J_{5,5'}$ 12.3 Hz, $J_{4,5}$ 3.3 Hz, H-5), 3.75 (3H, s, CH_3), 3.84-3.86 (1H, m, H-4), 3.93-3.94 (1H, m, H-3), 4.03-4.07 (2H, m, H-2 and H-1), 4.18 (1H, dd $J_{4,5'}$ 6.1 Hz, H-5'), 4.52 (1H, d, ABq, J_{AB} 11.7 Hz, CH_2Ph), 4.66-4.75 (3H, m, CH_2Ph), 7.26-7.39 (10H, m, 10 x Ar-H). δ_C (50.3 MHz, $CDCl_3$) 52.21 (q, OCH_3), 63.68, 71.42, 73.78 (3 x t, C-6, 2 x CH_2Ph), 70 76, 73.78, 75.46, 77.68 (4 x d, C-2, C-3, C-4, C-5), 128.10, 128.31, 128.67, 128.82 (4 x d, Ar-C), 137.80, 138.10 (2 x s, Ar-C), 170.19 (s, C-1); *m/z* (CI, NH_3, %) 391 (MNH_4+1$^+$, 8), 390 (MNH_4^+, 20), 108 (29), 91 (100). (Found: C, 67.95; H, 6.37. $C_{21}H_{24}O_6$ requires: C, 67.71; H, 6.50).

4.23.2.

The bicycle **25** (40 mg, 0.12 mmol) was dissolved in a solution of MeOH/HCl (1%) (3 ml) and stirred under nitrogen at room temperature for 12 h. After this time, t.l.c. (ethyl acetate:hexane, 1:1) showed no starting material (R_f 0.6) and the formation of a single product (R_f 0.5). The reaction mixture was then added to ethyl acetate (20 ml) and the mixture extracted with water (2 x 10 ml). The organic layer was then dried (anhydrous sodium sulfate), filtered, and the solvent removed *in vacuo* to give the crude tetrahydropyran **24** (39 mg, 90%) as a clear gum.

4.23.3.

The triflate **8** (80 mg, 0.16 mmol) was dissolved in a mixture of dry THF and MeOH (5:3, 8 ml). Camphorsulfonic acid (82 mg, 0.35 mmol) was added and the reaction mixture then stirred at room temperature under nitrogen for 12 h. After this time the solvent was removed *in vacuo* to and ethyl acetate (50 ml) was then added. The resulting solution was extracted with 10% aqueous sodium hydroxide solution (15 ml) and water (15 ml). The organic layer was then dried (anhydrous sodium sulfate), filtered, and concentrated to give a residue that was purified by flash chromatography (ethyl acetate:hexane, 1:2) to give the tetrahydropyran **24** (44 mg, 90%) as a clear gum.

4.23.4.

The triflate **8** (100 mg, 0.2 mmol) was dissolved in a mixture of dry THF and MeOH (5:3, 8 ml) and camphorsulfonic acid (120 mg, 0.5 mmol) was then added. The reaction mixture was then stirred at room temperature under a nitrogen atmosphere for 48 h. After this time t.l.c. (ethyl acetate:hexane, 1:1) showed no starting material (R_f 0.4) and the formation of a major product (R_f 0.7). The solvent was then removed *in vacuo* to give a residue that was dissolved into ethyl acetate (50 ml) and then washed with 10% aqueous sodium hydroxide solution (15 ml) and water (15 ml). The organic layer was then dried (anhydrous sodium sulfate), filtered, and concentrated to give a residue that was purified by flash chromatography (ethyl acetate:hexane, 1:2) to give the tetrahydropyran **24** (63 mg, 82%) as a clear gum.

4.23.5.

The triflate **8** (34 mg, 0.07 mmol) was dissolved in dry THF (2.5 ml) and stirred at room temperature under nitrogen. A solution of HCl in MeOH (1%, 1.5 ml) was then added and the resulting mixture stirred for 24 h at room temperature. After this time the reaction mixture was concentrated *in vacuo* and 10% aqueous sodium hydroxide solution (20 ml) was then added. The resulting mixture was extracted with chloroform (2 x 15 ml) and the organic layers were then combined, washed with water (20 ml), dried (anhydrous sodium sulfate), filtered, and concentrated to give a residue that was purified by flash chromatography (ethyl acetate:hexane, 1:1) to give the tetrahydropyran **24** (16 mg, 60%) as a clear gum and the tetrahydrofuran **26** (4 mg, 21%) also as a clear gum.

4.24. Methyl-2,5-anhydro-3-O-benzyl-D-mannonate **27** *and methyl-2,6-anhydro-3,5-di-O-benzyl-D-mannonate* **24**.

4.24.1.

The silyl triflate **7** (300 mg, 0.5 mmol) was dissolved in a 1% solution of HCl in MeOH (9 ml) and stirred under nitrogen at room temperature for 6 h. After this time t.l.c. (ethyl acetate:hexane, 1:1) showed no starting material (R_f 0.8) and the formation of a major product (R_f 0.1) and a minor product (R_f 0.6). The reaction mixture was then suspended in ethyl acetate (50 ml) and the mixture extracted with water (50 ml). The organic layer was dried (anhydrous sodium sulfate), filtered, and the solvent removed *in vacuo* to give a residue which was purified by flash chromatography (ethyl acetate:hexane, 1:1) to yield the tetrahydropyran **24** (28 mg, 15%) as a clear gum, identical to the material described previously. Further elution (ethyl acetate:hexane, 3:1) gave the tetrahydrofuran **27** (98 mg, 70 %) as a clear gum; $[\alpha]_D^{20}$ +45.0 (*c*, 0.4 in $CHCl_3$); ν_{max} (film) 3420 (br, OH), 1740 (C=O) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.10 (2H, bs, exchange with D_2O, 2 x OH), 3.77 (5H, m, 2 x CH, OCH_3), 4.14-4.24 (3H, m), 4.61-4.66 (3H, m), 7.27-7.35 (10H, m, 10 x Ar-H); δ_C (50.3 MHz, $CDCl_3$,) 52.53 (q, OCH_3), 62.01, 72.11 (2 x t, C-6, CH_2Ph), 76.30, 81.05, 86.48, 87.93 (4 x d, C-2, C-3, C-4, C-5), 128.08, 128.28, 128.75 (3 x d, Ar-C), 137.23 (s, Ar-C), 172.46 (s, C-1); *m/z* (CI, NH_3, %) 300 (MNH_4^+, 79), 283 (MH^+, 15), 108 (30), 91 (100). HRMS Calcd. for $C_{14}H_{19}O_6$ (MH^+) 283.1181. Found 283.1187. Calcd. for $C_{14}H_{22}NO_6$ (MNH_4^+) 300.1447. Found 300.1447.

4.24.2.

The triflate **8** (37 mg, 0.075 mmol) was dissolved in a 1% solution of HCl in MeOH (3 ml) and stirred under nitrogen at room temperature for 12 h. After this time t.l.c. (ethyl acetate:hexane, 1:1) showed no starting material (R_f 0.4) and the formation of a major product (R_f 0.2), together with a minor product (R_f 0.6). The reaction mixture was dissolved in ethyl acetate (50 ml) and then extracted with water (3 x 15 ml). The organic layer was then dried (anhydrous sodium sulfate), filtered, and the solvent evaporated *in vacuo* to produce a residue that was purified by flash chromatography (ethyl acetate: hexane, 1:1) to give the tetrahydropyran **24** (8.4 mg, 30%) as a clear gum, and the tetrahydrofuran **27** (11 mg, 52%) as a clear gum.

4.24.3.

The triflate **8** (53 mg, 0.11 mmol) was dissolved in dry methanol (5 ml) and camphorsulfonic acid (63 mg, 0.27 mmol) was added. The reaction mixture was then stirred

at room temperature under nitrogen for 12 h. After this time, t.l.c. (ethyl acetate:hexane, 1:1) showed no starting material (R_f 0.4), and the formation of a major product (R_f 0.7) and a minor product (R_f 0.2). The solvent was then evaporated *in vacuo* to give a residue that was dissolved in aqueous sodium hydroxide (20 ml) and extracted into chloroform (2 x 15 ml). The organic layers were combined and then washed with water (20 ml), dried (anhydrous sodium sulfate), filtered, and concentrated to give a residue that was purified by flash chromatography (ethyl acetate:hexane, 1:1) to give the tetrahydropyran **24** (18 mg, 45%) as a clear gum, and the tetrahydrofuran **27** (12 mg, 40%) as a clear gum.

4.25. Methyl-2,5-anhydro-3-O-benzyl-6-tert-butyldimethylsilyl-D-altronate 28 and methyl-2,4-anhydro-3,5-di-O-benzyl-6-tert-butyldimethylsilyl-D-allonate 29.

The silyl triflate **16** (42 mg, 0.07 mmol) was dissolved in freshly distilled methanol (2.5 ml) and potassium carbonate (10 mg, 0.07 mmol) was then added. The reaction mixture was stirred at room temperature under nitrogen for 15 min, after which time t.l.c. (ethyl acetate:hexane, 1:3) showed no starting material (R_f 0.75), and the formation of a major product (R_f 0.4) and a minor product (R_f 0.7). The reaction mixture was then partitioned between ethyl acetate (30 ml) and water (15 ml). The organic layer was then washed with brine (15 ml), dried (anhydrous sodium sulfate) and filtered. Removal of the solvents followed by flash chromatography (ethyl acetate:hexane, 1:3) gave the silyl oxetane **29** (14 mg, 40%) as a clear gum; $[\alpha]_D^{20}$ +13.8 (*c*, 0.6 in $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 0.04 (6H, s, 2 x CH_3), 0.89 (9H, s, $Si(CH_3)_3$), 3.59-3.69 (5H, m, 2 x H, OCH_3), 4.53-4.84 (4H, m), 4.99 (1H, d), 7.20-7.33 (10H, m, 10 x Ar-H); δ_C (50.3 MHz, $CDCl_3$) -5.69 (q, 2 x $SiCH_3$), 25.75 (q, 3 x $C\underline{C}H_3$), 52.00 (q, OCH_3), 61.47, 71.25, 73.38 (3 x t, C-6, 2 x CH_2Ph), 76.12, 78.98, 82.23, 86.19 (4 x d, C-2, C-3, C-4, C-5), 127.71, 127.91, 128.05, 128.46, 128.60 (5 x d, 5 x Ar-C), 128.13, 137.50, 138.83 (3 x s, 3 x Ar-C), 170.89 (s, C-1); *m/z* (CI, NH_3, %) 487 (MH^+, 7), 108 (20), 91 (100). (Found: C, 66.50; H, 8.03. $C_{27}H_{38}O_6Si$ requires: C, 66.63; H, 7.88%).

and the silyl tetrahydrofuran **28** (10 mg, 40%) as clear gum; $[\alpha]_D^{20}$ -0.7 (*c*, 1 in $CHCl_3$); δ_H ($CDCl_3$, 500 MHz) 0.04 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.09 (9H, s, $Si(CH_3)_3$), 3.74 (1H, dd, $J_{6,6'}$ 11.1 Hz, $J_{6,5}$ 3.9 Hz, H-6), 3.75 (1H, s, OCH_3), 3.79 (1H, dd, $J_{6',5}$ 3.4 Hz, H-6'), 4.02 (1H, dd, $J_{5,4}$ 8.0 Hz, H-5), 4.06 (m, 1H, H-4), 4.20 (t, 1H, $J_{3,4}$ 5.1 Hz, $J_{3,2}$ 5,1 Hz, H-3), 4.50 (d, 1H, H-2), 4.65, 4.75 (2H, ABq, $J_{A,B}$ 11.7 Hz, CH_2Ph), 7.32-7.39 (5H, m, 5 x Ar-H). δ_C ($CDCl_3$, 50.3 MHz) -5.08, -5.70 (2 x q, 2 x $SiCH_3$), 25.76 (q, $C(\underline{C}H_3)_3$), 52.20 (q, $O\underline{C}H_3$), 63.66, 72.70 (2 x t, C-6, $\underline{C}H_2Ph$), 71.57, 80.00, 81.11, 85.58 (4 x d, C-2, C-3, C-4, C-5), 128.27, 128.46, 128.82 (3 x d, 5 x Ar-CH), 128.17, 131.15 (2 x s, 2 x ArC), 171.48 (s, C-1); *m/z* (CI, NH_3, %) 414 (MNH_4^+, 19), 397 (MH^+, 100), 339 (30), 108 (21), 91 (95). (Found: C, 60.69; H, 7.89. $C_{20}H_{32}O_6Si$ requires: C, 60.58; H, 8.14%).

4.26. Methyl-2,4-anhydro-3,5-di-O-benzyl-D-allonate 31 and methyl-2,5-anhydro-3-O-benzyl-D-altronate 30.

The triflate **17** (54 mg, 0.11 mmol) was dissolved in freshly distilled methanol (3 ml) and potassium carbonate (17 mg, 0.12 mmol) was then added. The reaction mixture was stirred at room temperature under nitrogen for 15 min after which time t.l.c. (ethyl acetate:hexane, 1:1) indicated a compound with the same R_f as the starting material (R_f 0.5), and the

formation of another product (R_f 0.2). The reaction mixture was then partitioned between ethyl acetate (50 ml) and water (20 ml), and the organic layer was then washed with brine (20 ml), dried (anhydrous sodium sulfate) and filtered. Removal of the solvents followed by flash chromatography (ethyl acetate:hexane, 1:1) gave the oxetane **31** (17 mg, 41%) as a clear gum; $[\alpha]_D^{20}$ +32.2 (*c*, 0.4 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 3.62 (1H, dd, $J_{5,6}$ 4.5 Hz, $J_{6,6'}$ 11.1 Hz, H-6), 3.63-3.83 (5H, m), 4.52-4.63 (2H, m), 4.65 and 4.82 (2H, ABq, J_{AB} 11.7 Hz, CH_2Ph), 4.78 (1H, t), 5.02 (1H, d, $J_{2,3}$ 5.2 Hz, H-2), 7.30-7.37 (10H, m, 10 x Ar-H); δ_C (50.3 MHz, $CDCl_3$) 52.24 (q, OCH_3), 60.71, 71.58, 73.17 (3 x t, C-6, 2 x CH_2Ph), 76.37, 78.62, 82.40, 86.49 (4 x d, C-2, C-3, C-4, C-5), 128.07, 128.27, 128.70 (3 x d, Ar-C), 137.19, 138.09 (2 x s, Ar-C), 170.80 (s, C-1); *m/z* (CI, NH_3, %) 390 (MNH_4^+, 6), 373 (MH^+, 11), 108 (14), 91 (100). (Found: C, 67.42; H, 6.49. $C_{21}H_{24}O_6$. requires: C, 67.73; H, 6.50%);

and the tetrahydrofuran **30** (14 mg, 45%) as a clear gum; $[\alpha]_D^{20}$ -17.3 (*c*, 0.8 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 3.66 (1H, dd, $J_{6,6'}$ 12.4 Hz, $J_{5,6}$ 2.3 Hz, H-6), 3.78 (3H, s, OCH_3), 3.93 (1H, dd, $J_{5,6'}$ 2.6 Hz, H-6'), 4.06-4.08 (1H, m), 4.16-4.18 (1H, m), 4.26 (1H, dd), 4.58 (1H, d, $J_{2,3}$ 3.2 Hz, H-2), 4.65, 4.77 (2H, dd, ABq, J_{AB} 11.7 Hz, CH_2Ph), 7.33-7.41 (5H, m, 5 x Ar-H); δ_C (50.3 MHz, $CDCl_3$) 52.74 (q, OCH_3), 61.35 , 72.64 (2 x t, C-6, CH_2Ph), 70.29, 79.57, 82.05, 85.26 (4 x d, C-2, C-3, C-4, C-5), 128.27, 128.59, 128.89 (3 x d, Ar-C), 136.82 (s, Ar-C), 172.93 (s, C-1); *m/z* (CI, NH_3, %) 300 (MNH_4^+, 95) 283 (MH^+, 54), 108 (70), 91 (100). (Found: C, 59.57; H, 6.48. $C_{14}H_{18}O_6$ requires: C, 59.57; H, 6.43%).

4.27. 3,5-Di-O-benzyl-2-formyl-D-altrono-1,4-lactone 32.

The triflate **17** (100 mg, 0.2 mmol) was dissolved in dry DMF (5 ml) and the resulting solution stirred at room temperature under nitrogen for 12 h. After this time, t.l.c. (ethyl acetate:hexane, 1:1) showed no starting material (R_f 0.4) and the formation of a major product (R_f 0.6). The solvent was removed *in vacuo* and the residue purified by flash chromatography (ethyl acetate:hexane, 1:1) to yield the formate **32** (40 mg, 50% yield) as a clear gum; $[\alpha]_D^{20}$ + 51.4 (*c*, 1.0 in $CHCl_3$); ν_{max} (film) 3468 (OH), 1796 (C=O), 1733 (CHO) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.69-3.73 (2H, m), 3.86-3.93 (1H, m), 4.53-4.74 (7H, m), 5.68 (1H, d, $J_{2,3}$ 5.6 Hz, H-2), 7.28-7.40 (10H, m, 10 x Ar-H), 8.02 (1H, s, CHO); δ_C (50.3 MHz, $CDCl_3$) 60.68, 72.78 (2 x t, C-6, 2 x CH_2Ph), 73.70, 77.46, 77.68, 80.74 (4 x d, C-2, C-3, C-4, C-5), 128.30, 128.39, 128.63, 128.82 (4 x d, Ar-C), 136.64, 137.58 (2 x s, Ar-C), 159.10 (d, CHO), 169.40 (s, C-1); *m/z* (CI, NH_3, %) 405 (MNH_4^++1, 8), 404 (MNH_4^+, 18), 377 (5), 376 (11), 108 (60), 91 (100). HRMS Calcd. for $C_{21}H_{26}NO_7$ (MNH_4^+) 404.1709. Found 404.1716.

4.28. 3,5-Di-O-benzyl-2-chloro-D-altrono-1,4-lactone 33.

4.28.1.

The silyl triflate **16** (330 mg, 0.55 mmol) was dissolved in a 1% solution of HCl in MeOH (15 ml) and stirred under nitrogen at room temperature for 12 h. After this time, t.l.c. (ethyl acetate:hexane, 1:3) showed no starting material (R_f 0.75) and the formation of a major product (R_f 0.35). The reaction mixture was then dissolved in ethyl acetate (50 ml) and extracted with water (3 x 15 ml). The organic layer was dried (anhydrous sodium sulfate),

filtered, and the solvent evaporated *in vacuo* to give a residue that was purified by flash chromatography (ethyl acetate:hexane, 1:3) to give the chloride **33** (93 mg, 45%) as a clear gum; $[\alpha]_D^{20}$ +30 (*c*, 1.0 in $CHCl_3$); ν_{max} (film) 3467 (OH), 1795 (C=O) cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.56-3.61 (2H, m), 3.72-3.76 (1H, m), 4.42-4.46 (3H, m), 4.52-4.58 (3H, m), 4.71 (1H, d, ABq, J_{AB} 11.4 Hz, CH_2Ph), 7.16-7.30 (10H, m, 10 x Ar-H); δ_C (50.3 MHz, $CDCl_3$) 60.48, 72.58, 73.51 (3 x t, C-6, 2 x CH_2Ph), 55.74, 77.30, 81.22, 81.80 (4 x d, C-2, C-3, C-4, C-5), 128.24, 128.36, 128.57, 128.76 (4 x d, Ar-C), 136.40, 137.35 (2 x s, Ar-C), 170.12 (s, C-1); *m/z* (CI, NH_3, %) 394 (MNH_4^+, 19), 288 (17), 286 (31), 108 (89), 91 (100). (Found: C, 63.67; H, 5.26. $C_{20}H_{21}O_5Cl$ requires: C, 63.75; H, 5.62%).

4.28.2.

The triflate **17** (100 mg, 0.21 mmol) was dissolved in a 1% solution of HCl in MeOH (8 ml) and stirred under nitrogen at room temperature for 36 h. After this time, t.l.c. (ethyl acetate:hexane, 1:1) showed no starting material (R_f 0.4) and the formation of a major product (R_f 0.7). The reaction mixture was added to ethyl acetate (50 ml) and extracted with water (3 x 15 ml). The organic layer was then dried (anhydrous sodium sulfate), filtered, and the solvent evaporated *in vacuo* to give a residue that was purified by flash chromatography (ethyl acetate:hexane, 1:1) to give the chloride **33** (38 mg, 50%) as a clear gum.

*4.29. Methyl 2,5-anhydro-6-O-tert-butyldimethylsilyl-3,4-O-cyclohexylidene-D-allonate **35b**.*

The cyclohexylidene silyl triflate **20b** (2.06 g, 4.1 mmol) was dissolved in methanol (80 ml). Potassium carbonate (566 mg, 4.1 mmol) was added and the resultant mixture stirred at room temperature. After 10 min, t.l.c. (hexane:ethyl acetate, 3:1) indicated complete consumption of starting material (R_f 0.7) and the formation of a major product (R_f 0.6), together with a small amount of more polar material (R_f 0.5). The solvent was removed and the residue shaken with dichloromethane (75 ml). The resultant suspension was filtered, the solvent removed and the residue purified by flash chromatography (hexane:ethyl acetate, 7:1) to yield the cyclohexylidene silyl tetrahydrofuran **35b** (1.07 g, 68%, R_f 0.6) as a colourless oil; $[\alpha]_D^{20}$ -36.7 (*c*, 1.2 in $CHCl_3$); ν_{max} (film) 1761, 1741 (C=O) cm^{-1}; δ_H ($CDCl_3$) 0.05, 0.07 (6H, 2 x s, Me_2Si), 0.89 (9H, s, Bu^t), 1.39-1.79 (10H, m, cyclohexylidene), 3.73 (2H, d, H-6, H-6', J 3.9 Hz), 3.77 (3H, s, Me), 4.30 (1H, m, H-5), 4.50 (1H, d, H-2, $J_{2,3}$ 3.3 Hz), 4.69 (1H, dd, H-4, $J_{3,4}$ 6.1 Hz, $J_{4,5}$ 1.2 Hz), 4.96 (1H, dd, H-3); δ_C ($CDCl_3$) -5.8, -5.7 (2 x q, Me_2Si), 18.2 (s, $Me_3\underline{C}Si$), 23.5, 23.8, 24.8 (3 x t, cyclohexylidene), 25.7 (q, Bu^t), 34.6, 36.8 (2 x t, cyclohexylidene), 52.1 (q, MeO), 61.4 (t, C-6), 82.2, 83.3, 84.8, 86.2 (4 x d, C-2, C-3, C-4, C-5), 114.1 (s, cyclohexylidene), 171.2 (s, C-1); *m/z* (NH_3, DCI) 404 (MNH_4^+), 387 (MH^+, 100%). (Found: C, 59.24; H, 8.98. $C_{19}H_{34}O_6Si$ requires: C, 59.04; H, 8.87%).

*4.30. Methyl 2,5-anhydro-6-O-tert-butyldimethylsilyl-3,4-O-isopropylideneylidene-D-allonate **35a**.*

The isopropylidene silyl triflate **20a** (119 mg, 0.26 mmol) and potassium carbonate (36 mg, 0.26 mol) were stirred in dry methanol (10 ml) at room temperature under nitrogen. After 10 min the solvent was removed and the residue purified by flash chromatography (hexane:ether, 3:1) to yield the isopropylidene silyl tetrahydrofuran **35a** (51 mg, 58%, R_f

0.6) as a white crystalline solid, m.p. 33-34 °C (ether / hexane); $[\alpha]_D$ -32.8 (*c*, 1.0 in $CHCl_3$); ν_{max} (film) 1762, 1740 (C=O) cm^{-1}; δ_H ($CDCl_3$) 0.06, 0.07 (6H, 2 x s, Me_2Si), 0.89 (9H, s, Bu^t), 1.38, 1.56 (6H, 2 x s, Me_2C), 3.70-3.76 (2H, m, H-6, H-6'), 3.77 (3H, s, Me), 4.29 (1H, dt, H-5, $J_{4,5}$ 1.7 Hz, $J_{5,6}$ 4.0 Hz, $J_{5,6'}$ 4.0 Hz), 4.51 (1H, d, H-2, $J_{2,3}$ 3.4 Hz), 4.71 (1H, dd, H-4, $J_{3,4}$ 6.1 Hz), 4.96 (1H, dd, H-3); δ_C ($CDCl_3$) -5.9, -5.7 (2 x q, Me_2Si), 18.2 (s, $Me_3\underline{C}Si$), 25.1, 27.0 (2 x q, $\underline{Me}_2C$), 25.7 (q, Bu^t), 52.2 (q, MeO), 64.1 (t, C-6), 82.6, 82.7, 84.6, 86.2 (4 x d, C-2, C-3, C-4, C-5), 113.4 (s, $\underline{C}Me_2$), 171.1 (s, C-1); *m/z* (NH_3, DCI) 364 (MNH_4^+), 347 (MH^+, 100%). (Found: C, 55.24; H, 8.84. $C_{16}H_{30}O_6Si$ requires: C, 55.46; H, 8.73%).

*4.31. 2,5-Anhydro-1-O-tert-butyldimethylsilyl-3,4-O-cyclohexylidene-L-allitol **36b**.*

The methyl ester **35b** (112 mg, 0.29 mmol) was stirred in THF (3 ml) at room temperature under nitrogen. Lithium aluminium hydride (12 mg, 0.29 mmol) was added and after 5 min t.l.c. (hexane:ethyl acetate, 3:1) indicated complete consumption of starting material (R_f 0.6) and formation of a single product (R_f 0.4). The reaction was quenched by addition of ethyl acetate (1 ml), the resulting solution filtered through a silica plug (eluant hexane:ethyl acetate, 3:1) and the solvent removed to yield the alcohol **36b** (98 mg, 94%) as a colourless oil; $[\alpha]_D^{20}$ +13.6 (*c*, 1.04 in $CHCl_3$); ν_{max} (film) 3435 (br, OH) cm^{-1}; δ_H ($CDCl_3$) 0.11 (6H, 2 x s, Me_2Si), 0.93 (9H, s, Bu^t), 1.40-1.77 (10H, m, cyclohexylidene), 3.00 (1H, br, OH), 3.62 (1H, br m, H-6), 3.79-3.84 (2H, m, H-6', H-1'), 3.90 (1H, dd, H-1, $J_{1,2}$ 2.7 Hz, $J_{1,1'}$ 11.2 Hz), 4.08 (1H, m, H-2), 4.23 (1H, dd, H-5, $J_{4,5}$ 2.6 Hz), 4.70 (1H, dd, H-4, $J_{3,4}$ 6.1 Hz), 4.74 (1H, dd, H-3, $J_{2,3}$ 4.2 Hz); δ_C ($CDCl_3$) -5.8 (q, Me_2Si), 18.3 (s, $Me_3\underline{C}Si$), 23.5, 23.9, 24.8 (3 x t, cyclohexylidene), 25.7 (q, Bu^t), 34.8, 37.3 (2 x t, cyclohexylidene), 63.9 (t, C-1, C-6), 80.6, 82.3, 85.0, 85.8 (4 x d, C-2, C-3, C-4, C-5), 113.8 (s, cyclohexylidene); *m/z* (NH_3, DCI) 376 (MNH_4^+), 359 (MH^+, 100%). (Found: C, 60.28; H, 9.74. $C_{18}H_{34}O_5Si$ requires: C, 60.30; H, 9.56%).

*4.32. 2,5-Anhydro-3,4-O-cyclohexylidene-1,6-di-O-tert-butyldimethylsilyl-allitol **37b**.*

The alcohol **36b** (56 mg, 0.16 mmol) and imidazole (43 mg, 0.63 mmol) were stirred under nitrogen in dry DMF (3 ml) at 0 °C. *tert*-Butyldimethylsilylchloride (47 mg, 0.31 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 1 h, t.l.c. (hexane:ethyl acetate, 3:1) indicated complete consumption of starting material (R_f 0.4) and formation of a single product (R_f 0.8). The solvent was removed and ether (10 ml) was added. The mixture was shaken with water (10 ml) and the aqueous layer further extracted with ether (10 ml). The combined organic extracts were dried (magnesium sulfate), filtered, the solvent removed and the residue purified by flash chromatography (hexane:ether, 4:1) to yield the disilyl tetrahydrofuran **37b** (65 mg, 88%) as a colourless oil; $[\alpha]_D^{20}$ +0.0 (*c*, 1.98 in $CHCl_3$); δ_H ($CDCl_3$) 0.07 (12H, s, 2 x Me_2Si), 0.91 (18H, s, 2 x Bu^t), 1.38-1.77 (10H, m, cyclohexylidene), 3.68 (2H, d, H-1, H-6, $J_{1,1'}$ 10.8 Hz, $J_{1,2}$ 4.7 Hz), 3.71 (2H, dd, H-1', H-6', $J_{1',2}$ 4.7 Hz), 4.05 (2H, ddt, H-2, H-5, $J_{2,3}$ 2.2 Hz, $J_{2,4}$ 0.9 Hz), 4.54 (2H, dd, H-3, H-4); δ_C ($CDCl_3$) -5.6 (q, Me_2Si), 18.2 (s, $Me_3\underline{C}Si$), 23.5, 23.9, 24.9 (3 x t, cyclohexylidene), 25.8 (q, Bu^t), 35.0, 37.2 (2 x t, cyclohexylidene), 64.1 (t, C-1, C-6), 81.7, 85.3 (2 x d, C-2, C-3, C-4,

C-5), 114.0 (s, cyclohexylidene); *m/z* (NH_3, DCI) 490 (MNH_4^+), 473 (MH^+, 100%). (Found: C, 60.86; H, 10.15. $C_{24}H_{48}O_5Si_2$ requires: C, 60.97; H, 10.23%).

4.33. Methyl 2,5-anhydro-3,4-O-cyclohexylidene-D-allonate ***38b***.

4.33.1.

The silyl tetrahydrofuran **35b** (90 mg, 0.23 mmol) was stirred in a mixture of acetic acid (4 ml) and water (1 ml) at room temperature. After 24 h, t.l.c. (hexane:ethyl acetate, 1:1) indicated the formation of a single product (R_f 0.4). The solvent was removed, the residue co-evaporated with toluene (2 x 5 ml) and purified by flash chromatography (hexane:ethyl acetate, 1:1) to yield the tetrahydrofuran alcohol **38b** (36 mg, 60%) as a colourless oil; $[\alpha]_D^{20}$ -58.3 (*c*, 0.47 in $CHCl_3$); ν_{max} (film) 3400-3200 (br, OH) 1741 (C=O) cm^{-1}; δ_H ($CDCl_3$) 1.39-1.79 (10H, m, cyclohexylidene), 3.55 (1H, dd, H-6, $J_{5,6}$ 3.7 Hz, $J_{6,6'}$ 12.6 Hz), 3.82 (3H, s, Me), 3.85 (1H, dd, H-6', $J_{5,6'}$ 2.7 Hz), 4.40-4.43 (1H, m, H-5), 4.61 (1H, d, H-2, $J_{2,3}$ 3.1 Hz), 4.75 (1H, dd, H-4, $J_{3,4}$ 6.0 Hz, $J_{4,5}$ 1.6 Hz), 4.86 (1H, dd, H-3); δ_C ($CDCl_3$) 23.5, 23.8, 24.8, 34.5, 36.7 (5 x t, cyclohexylidene), 52.7 (q, MeO), 63.1 (t, C-6), 82.0, 84.3, 84.4, 87.6 (4 x d, C-2, C-3, C-4, C-5), 114.4 (s, cyclohexylidene), 173.9 (s, C-1); *m/z* (NH_3, DCI) 290 (MNH_4^+), 273 (MH^+). (Found: C, 57.30; H, 7.47. $C_{13}H_{20}O_6$ requires: C, 57.34; H, 7.40%).

4.33.2.

The triflate **21b** (82 mg, 0.21 mmol) and potassium carbonate (29 mg, 0.21) were stirred in dry methanol (4 ml) at room temperature under nitrogen. After 10 min, t.l.c. (hexane:ethyl acetate, 1:1) indicated complete consumption of starting material (R_f 0.5) and the formation of a single product (R_f 0.4). Acetic acid (0.5 ml) was added, the solvent removed and the residue purified by flash chromatography (hexane:ethyl acetate, 2:1) to yield the alcohol **38b** (52 mg, 94%) as a colourless oil, identical to the material described above.

4.33.3.

The tetrahydrofuran bicycle **39b** (19 mg, 0.08 mmol) and potassium carbonate (11.5 mg, 0.08 mmol) were stirred together in dry methanol (2 ml). After 30 min, acetic acid (0.1 ml) was added, the solvent removed and the residue purified by flash chromatography (hexane:ethyl acetate, 2:1) to yield the tetrahydrofuran alcohol **38b** (13 mg, 63%) as a colourless oil, identical to the material described above.

4.34. 2,5-Anhydro-3,4-O-cyclohexylidene-D-allono-1,6-lactone ***39b***.

The triflate **21b** (50 mg, 0.13 mmol) and sodium acetate (53 mg, 0.64 mmol) were stirred in dry DMF (3 ml) at room temperature under nitrogen. After 3 h, t.l.c. (hexane:ethyl acetate, 2:1) indicated the formation of two products (R_f 0.5 and R_f 0.4). The solvent was removed and the residue purified by flash chromatography (hexane:ethyl acetate, 3:1) to yield the tetrahydrofuran bicycle **39b** (14 mg, 46%, R_f 0.5) as a white crystalline solid, m.p. 76-80 °C (ethyl acetate / hexane); $[\alpha]_D^{20}$ +40.9 (*c*, 0.64 in $CHCl_3$); ν_{max} (KBr) 1751 (C=O) cm^{-1} ; δ_H ($CDCl_3$) 1.40-1.78 (10H, m, cyclohexylidene), 4.22 (1H, d, H-6, $J_{6,6'}$ 11.5 Hz), 4.44 (1H, d, J 4.1 Hz), 4.56 (1H, dd, H-6', $J_{5,6}$ 4.2 Hz), 4.65 (1H, s), 4.80-4.87 (2H, m); δ_C ($CDCl_3$) 23.5, 23.8, 24.6, 34.3, 35.5 (5 x t, cyclohexylidene), 69.7 (t, C-6), 77.6, 81.0, 81.9, 82.9 (4 x d, C-

2, C-3, C-4, C-5), 115.0 (s, cyclohexylidene), 165.8 (s, C-1); *m/z* (NH_3, DCI) 258 (MNH_4^+, 100%), 240 (MH^+-H_2O); together with the tetrahydropyran bicycle **40b** (8 mg, 26%) identical to the material described below.

4.35. *2,6-Anhydro-3,4-O-cyclohexylidene-D-altrono-1,5-lactone **40b**.*

The cyclohexylidene diol **18b** (1.26 g, 4.8 mmol) and triphenylphosphine (1.92 g, 7.3 mmol) were stirred in dry THF (40 ml) at room temperature under nitrogen. Diethyl azodicarboxylate (3.5 ml, 38% soln in toluene) was added and after 1 h t.l.c. (hexane:ethyl acetate, 1:1) indicated the consumption of starting material and the formation of a major product (R_f 0.6). The solvent was removed and the residue purified by flash chromatography (hexane:ethyl acetate, 2:1) to yield the cyclohexylidene tetrahydropyran bicycle **40b** (813 mg, 69%) as a white crystalline solid, m.p. 204-205 °C (ethyl acetate / hexane); $[\alpha]_D^{20}$ -43.8 (*c*, 1.1 in $CHCl_3$); ν_{max} (KBr) 1765 (C=O) cm^{-1} ; δ_H ($CDCl_3$) 1.39-1.74 (10H, m, cyclohexylidene), 3.78 (1H, d, H-6, $J_{6,6'}$ 10.5 Hz), 4.03 (1H, dd, H-6', $J_{5,6'}$ 2.5 Hz), 4.36 (1H, dd, H-4, $J_{3,4}$ 7.4 Hz, $J_{4,5}$ 2.3 Hz), 4.44 (1H, d, H-2, $J_{2,3}$ 4.4 Hz), 4.59 (1H, dd, H-3), 4.85 (1H, m, H-5); δ_C ($CDCl_3$) 23.5, 23.7, 24.8, 33.9, 35.2 (5 x t, cyclohexylidene), 62.8 (t, C-6), 70.6, 72.4, 73.5, 73.6 (4 x d, C-2, C-3, C-4, C-5), 112.1 (s, cyclohexylidene), 168.0 (s, C-1); *m/z* (NH_3, DCI) 258 (MNH_4^+, 100%), 241 (MH^+). (Found: C, 59.88; H, 6.67. $C_{12}H_{16}O_5$ requires: C, 59.99; H, 6.71%).

4.36. *2,6-Anhydro-3,4-O-isopropylidene-D-altrono-1,5-lactone **40a**.*

The isopropylidene diol **18a** (80 mg, 0.37 mmol) and triphenylphosphine (144 mg, 0.55 mmol) were stirred in dry THF (4 ml) at room temperature under nitrogen. Diethyl azodicarboxylate (0.26 ml, 38% solution in toluene) was added and after 1 h, t.l.c. (hexane:ethyl acetate, 1:1) indicated the disappearance of starting material and the formation of a major product (R_f 0.5). The solvent was removed and the residue purified by flash chromatography (hexane:ethyl acetate, 2:1) to yield the isopropylidene tetrahydropyran bicycle **40a** (44 mg, 60%) as a white crystalline solid, m.p. 190-192 °C (ethyl acetate / hexane); $[\alpha]_D^{20}$ -46.0 (*c*, 0.88 in $CHCl_3$); ν_{max} (KBr) 1772 (C=O) cm^{-1}; δ_H ($CDCl_3$) 1.37, 1.48 (6H, 2 x s, Me_2C), 3.81 (1H, d, H-6, $J_{6,6'}$ 10.5 Hz), 4.03 (1H, dd, H-6', $J_{5,6'}$ 2.8 Hz), 4.37 (1H, dd, H-4, $J_{3,4}$ 7.4 Hz, $J_{4,5}$ 2.2 Hz), 4.44 (1H, d, H-2, $J_{2,3}$ 4.4 Hz), 4.61 (1H, dd, H-3), 4.85 (1H, t, H-5); δ_C (CD_3CN) 23.4, 23.6 (2 x q, $\underline{Me}_2C$), 62.5 (t, C-6), 70.3, 72.5, 73.7, 73.8 (4 x d, C-2, C-3, C-4, C-5), 110.5 (s, $\underline{C}Me_2$), 168.6 (s, C-1); *m/z* (NH_3, DCI) 218 (MNH_4^+, 100%). (Found: C, 54.06; H, 6.01. $C_9H_{12}O_5$ requires: C, 54.00; H, 6.04%).

4.37. *2,6-Anhydro-3,4-O-cyclohexylidene-D-altritol **41b**.*

The cyclohexylidene tetrahydropyran bicycle **40b** (111 mg, 0.46 mmol) was dissolved in dry THF (10 ml) and stirred at 0 °C under nitrogen. Lithium borohydride (0.46 ml, 2.0 M solution in THF) was added and the mixture allowed to warm to room temperature. After 4 h, t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.8) and the formation of a single product (R_f 0.2). Ammonium chloride (50 mg) was added carefully,

followed by methanol (10 ml) and the mixture stirred for 10 min. The solvent was removed, the residue co-evaporated with methanol (2 x 10 ml), pre-absorbed onto silica and purified by flash chromatography (ethyl acetate) to yield the diol **41b** (105 mg, 93%) as a colourless oil; $[\alpha]_D^{20}$ +21.9 (*c*, 1.13 in $CHCl_3$); ν_{max} (film) 3600-3200 (br, OH) cm^{-1}; δ_H ($CDCl_3$) 1.38-1.89 (10H, m, cyclohexylidene), 3.50 (1H, d, H-6, $J_{5,6}$ 2.0 Hz, $J_{6,6'}$ 10.5 Hz), 3.74 (1H, m, H-2), 3.79 (2H, m, H-1, H-5), 3.98 (1H, dd, H-1', $J_{1,1'}$ 11.8 Hz, $J_{1',2}$ 7.4 Hz), 4.07 (1H, dd, H-6', $J_{5,6'}$ 3.9 Hz), 4.20 (1H, dd, H-3, $J_{2,3}$ 2.6 Hz, $J_{3,4}$ 6.3 Hz), 4.28 (1H, dd, H-4, $J_{4,5}$ 5.1 Hz); δ_C ($CDCl_3$) 23.6, 23.9, 24.9, 34.3, 35.3 (5 x t, cyclohexylidene), 62.8 (t, C-6), 68.0 (t, C-1), 64.1, 71.7, 72.4, 75.9 (4 x d, C-2, C-3, C-4, C-5), 110.7 (s, cyclohexylidene); *m/z* (NH_3, DCI) 262 (MNH_4^+, 100%), 245 (MH^+). (Found: C, 59.28; H, 8.53. $C_{12}H_{20}O_5$ requires: C, 59.0; H, 8.25%).

4.38. 2,6-Anhydro-D-altritol **42**.

The diol **41b** (105 mg, 0.43 mmol) was stirred in a mixture of trifluoroacetic acid (4 ml) and water (6 ml) at room temperature. After 12 h, t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.2) and the formation of a single product (R_f 0.0). The solvent was removed, the residue co-evaporated with toluene (2 x 5 ml) and then purified by flash chromatography (ethyl acetate:methanol, 9:1) to yield the tetrol **42** (63 mg, 89%) as a viscous gum; $[\alpha]_D^{20}$ -7.5 (*c*, 0.72 in H_2O)(Lit. -11.5 (*c*, 4.85 in H_2O))[17]; ν_{max} (film) 3600-3200 (br, OH) cm^{-1}; δ_H (D_2O) 3.46 (1H, ddd, H-2, $J_{1,2}$ 4.0 Hz, $J_{1',2}$ 8.0 Hz, $J_{2,3}$ 1.0 Hz), 3.56 (1H, dd, H-6, $J_{5,6}$ 1.0 Hz, $J_{6,6'}$ 12.7 Hz), 3.62 (1H, dd, H-1, $J_{1,1'}$ 11.8 Hz), 3.69 (1H, d, J 3.4 Hz), 3.71 (1H, dd, H-1'), 3.80 (1H, m), 3.85 (1H, m), 3.94 (1H, dd, H-6', $J_{5,6'}$ 2.2 Hz); δ_C (CD_3OD) 61.6 (t, C-6), 68.8, 69.8, 70.1, 79.9 (4 x d, C-2, C-3, C-4, C-5), 70.9 (t, C-1); *m/z* (NH_3, CI) 182 (MNH_4^+), 165 (MH^+, 100%).

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6. References

1. Witty, D.R.; Fleet, G.W.J.; Choi, S.; Vogt, K.; Wilson, F.X.; Wang, Y.; Storer, R.; Myers, P.L.; Wallis, C.J. *Tetrahedron Lett.* **1990**, *31*, 6927-6930 and references contained therein.
2. Choi, S.S.; Myerscough, P.M.; Fairbanks, A.J.; Skead, B.M.; Bichard, C.J.F.; Mantell, S.J.; Son, J.C.; Fleet, G.W.J.; Saunders, J.; Brown, D. *J. Chem. Soc., Chem. Commun.* **1992**, 1605-1607.
3. Weatley, J.R.; Bichard, C.J.F.; Mantell, S.; Son, J.C.; Hughes, D.J.; Fleet, G.W.J.; Brown, D. *J. Chem. Soc., Chem. Commun.* **1993**, 1065-1067.
4. For a preliminary communication of some of these results see: Estevez, J.C.; Fairbanks, A.J.; Hsia, K.Y.; Ward, P.; Fleet, G.W.J. *Tetrahedron Lett.* **1994**, *35*, 3361-3364.
5. For some reviews see: (a) Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J.L.; Martín, J.D. *Chem. Rev.* **1995**, *95*, 1953-1980; (b) Harmange, J.-C.; Figadère, B. *Tetrahedron:*

Asymmetry **1993**, *4*, 1711-1754; (c) Boivin, T.L.B. *Tetrahedron* **1987**, *43*, 3309-3362.

6. For some recent tetrahydropyran syntheses see: (a) Banwell, M.G.; Bissett, B.D.; Bui, C.T.; Pham, H.T.T.; Simpson, G.W. *Aus. J. Chem.* **1998**, *51*, 9-18; (b) Takagi, R.; Sasaoka, A.; Kojima, S.; Ohkata, K. *Heterocycles* **1997**, *45*, 2313-2316; (c) Craig, D.C.; Edwards, G.L.; Muldoon, C.A. *Synlett* **1997**, 1318-1320; (d) Schneider, C. *Synlett* **1997**, 815-817; (e) Mori, Y. *Chem. Eur. J.* **1997**, *3*, 849-852; (f) Betancort, J.M.; Martín, V.S.; Padrón, J.M.; Palazón, J.M.; Ramírez, M.A.; Soler, M.A. *J. Org. Chem.* **1997**,.*62*, 4570-4583; (g) Hu, Y.Q.; Skalitzky, D.J.; Rychnovsky, S.D. *Tetrahedron Lett.* **1996**, *37*, 8679-8682.
7. For a review on sugar epoxides see: Williams, N.R. *Adv. Carbohydr. Chem. Biochem.*, **1970**, *25*, 109-179.
8. For a review on 2,5-anhydrosugars see Defaye, J. *Adv. Carbohydr. Chem. Biochem.*, **1970**, *25*, 181-228.
9. For a general review on anhydroalditols see Soltzberg, S. *Adv. Carbohydr. Chem. Biochem.*, **1970**, *25*, 229-283.
10. Schmidt, O.T. *Methods in Carbohydr. Chem.* **1963**, *2*, 318-325.
11. Åkerfeldt, K.; Bartlett, P.A. *Carbohydr. Res.* **1986**, *158*, 137-145.
12. (a) Wood, W.W.; Watson, G.M. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 2681-2688. (b) Sowa, W.; Thomas, G.H. S. *Can. J. Chem.*, **1966**, *44*, 836-838.
13. (a) Fischer, J.-C.; Horton, D. *Carbohydr. Res.*, **1977**, *59*, 477-503. (b) Theander, O. *Acta Chem. Scand.*, **1963**, *17*, 1751-1760.
14. Bichard, C.J.F.; Fairbanks, A.J.; Fleet, G.W.J.; Ramsden, N.G.; Vogt, K.; Doherty, O.; Pearce, L.; Watkin, D.J. *Tetrahedron: Asymmetry*, **1991**, *2*, 901-912.
15. Fairbanks, A.J.; Fleet, G.W.J. *Tetrahedron* **1995**, *51*, 3881-3894.
16. For a discussion of the stereochemical consequences of oxetane formation by ring contraction reactions see: (a) Witty, D.R.; Fleet, G.W.J.; Vogt, K.; Wilson, F.X.; Wang, Y.; Storer, R.; Myers, P.L.; Wallis, C.J. *Tetrahedron Lett.* **1990**, *31*, 4787-4790. (b) Austin, G.N.; Fleet, G.W.J.; Peach, J.M.; Prout, K.; Son, J.C. *Tetrahedron Lett.* **1987**, *28*, 4741-4744.
17. Rosenfeld, D.A.; Richtmyer, N.K.; and Hudson, C.S. *J. Am. Chem. Soc.*, 1948, **70**, 2201.