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Enantiospecific Synthesis of (+)-Altholactone and its Three Stereoisomers

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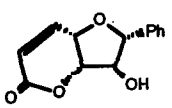
Abstract:—(+)-Altholactone **1** and (+)-7-*epi*-altholactone **3** were constructed from D-gulonolactone whereas their respective enantiomers (-)-altholactone **2** and (-)-7-*epi*-altholactone **4** were synthesised from D-mannose, involving stereocontrolled reduction of the lactols **21** and **12** as a key step.

Introduction

(+)-Altholactone was first isolated from an unidentified Polyalthea species and its gross structure was determined on the basis of chemical degradation and spectral analyses as a novel tetrahydro-5*H*-furo[3,2-*b*]pyran-5-one.[1] Later the same compound was found from the ethanol extracts of the stem bark of *Goniothalamus giganteus* (Annonaceae) and was shown to be active against P388 leukemia *in vivo* and cytotoxic to brine shrimp *in vitro*.[2] The relative stereochemistry of altholactone was determined by X-ray crystallographic analysis.[2] The intriguing structure and the potent bioactivity of altholactone has attracted considerable attention from the synthetic chemists. The first total synthesis of altholactone which confirmed its absolute configuration as **1** was achieved by Gesson and his co-workers.[3] This was followed by reports from Tadano *et al.*,[4] from us[5] and from Kang and Kim.[6] Interestingly, all the four syntheses started from different sugar precursors and involved different tactics and strategies to accomplish the same goal. Very recently, a synthesis of (+)-altholactone **1** from a chiral furylglycerol was reported.[7] Herein, we describe in detail our synthetic endeavor towards the construction of (+)-altholactone **1**, its enantiomer (-)-altholactone **2**, (+)-7-*epi*-altholactone **3**, and (-)-7-*epi*-altholactone **4**.



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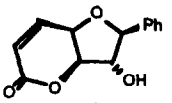

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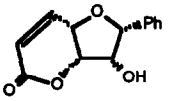

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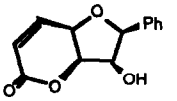

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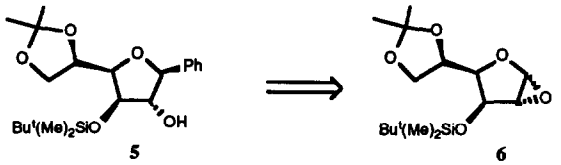
Results and Discussion

A. Initial attempt

At the beginning of our research, we arbitrarily chose **2** as our synthetic target since only the relative stereochemistry of altholactone was known[2] at the time. Altholactone could

be regarded as a *C*-glycoside[8] and carbohydrates would be the most logical homochiral precursors. The problems encountered were the stereoselective introduction of the phenyl moiety at C-1 and the control of the stereochemistry at C-2. Our initial attempted solution to these problems involves the furanosyl epoxide **6** as a key intermediate, which would be ring-opened with PhMgBr regioselectively to give the phenyl *C*-glycoside **5** with the correct stereochemistry.



5 **6**

D-Mannose was used as the starting material for **6** and was easily converted into the protected lactol, 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose **7** under standard conditions[9] (Me_2CO/H_2SO_4). Furanosyl chloride **8**[10] was prepared from **7** using the Castro's reagent[11] {$[Me_2N]_3P/CCl_4$} in dry tetrahydrofuran (THF) at -78 °C. The ^{1}H-NMR of **8** showed that the chlorine atom was in the α-position. The coupling constants between vicinal *trans*-disposed protons in such furanoid ring systems are normally small (less than 1 Hz). As the anomeric proton appeared as a singlet, the chlorine atom could therefore be assigned in the α-position.

At this stage, we were diverted from our original pathway in an attempt to introduce the phenyl group at C-1 by displacing the chlorine atom in **8** with PhMgBr. Thus, the reaction gave *C*-phenyl α-D-furanoside **9** in 11% yield. The ^{1}H-NMR spectrum of **9** showed the anomeric proton appearing as a singlet (δ 4.5). This, as in the case of **8**, showed that the anomeric proton was *trans* to the proton on C-2 and therefore the phenyl group was in the undesired α-position. A possible rationalisation could be that the furanosyl chloride existed in equilibrium between two forms, with the chlorine atom in the α- or β-position. The Grignard reagent attacked the thermodynamically less stable β-form as its approach was less hindered. The resulting product, therefore, had the phenyl group in the α-position. As attempts at introducing the phenyl ring with correct stereochemistry failed at this stage, we therefore reverted back to the original plan.

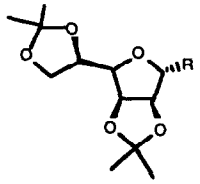
The conversion of the furanosyl chloride **8** into the glycal **10** has been studied with a variety of radical anions by Ireland *et al.*[12] and lithium 4,4-di-t-butylbiphenyl was found to give the best results. The glycal **10** was found to be very acid sensitive as two large batches of glycal were decomposed when dissolved in chloroform for only a short time. ^{1}H-NMR of the major component of the decomposition products indicated that it was a furan derivative which was formed by loss of water in **10**.

The hydroxyl group in **10** was then protected as a silyl ether **11** by stirring with t-butyldimethylsilyl chloride and imidazole[13] in DMF. Epoxidation of the alkene in **11** was expected to occur at the face opposite to the silyl ether because of steric reasons to give the furanosyl oxirane **6**. However, all attempts including the use of Sharpless epoxidising agent[14] [$Vo(acac)_2/^tBuO_2H$] and buffered as well as unbuffered m-chloroperbenzoic acid (MCPBA) to

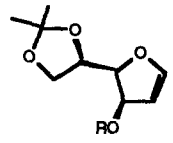
prepare **6** were unsuccessful. In all cases, the starting glycal **11** was consumed and a complex mixture was obtained. Addition of PhMgBr to the epoxidising reaction to ring-open any epoxide formed also afforded a complex mixture. The problem encountered appeared to be that the epoxidising reagent itself, or any other nucleophile present in the reaction mixture spontaneously opened up the labile epoxide.

In one case, the MCPBA epoxidation of **11** buffered by Na_2CO_3 was repeated, except this time a few drops of methanol were added. The major product was analysed spectroscopically to be a methyl furanoside **12**. The methoxyl and hydroxyl groups appeared to be *trans*-disposed as the anomeric proton was shown to be a singlet on the ^{1}H-NMR spectrum. This reaction showed that any nucleophile present in the reaction mixture would open the labile oxirane spontaneously.

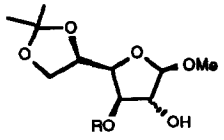
At this stage it was decided that attempts at the epoxide formation should be abandoned and another pathway investigated.



7 R = OH
8 R = Cl
9 R = Ph



10 R = H
11 R = $Si(Me)_2Bu^t$

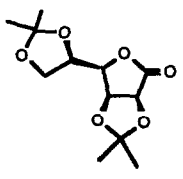


12 R = $Si(Me)_2Bu^t$

B. Synthesis of (-)-altholactone 2 and (-)-7-*epi*-altholactone 4

The second approach to (-)-altholactone **2** is now described. It was envisaged that the phenyl group could be introduced by the attack of PhLi onto the lactone **13**. The hydroxyl group on C-2 remains throughout the reaction, protected as an acetonide and its chirality originating from D-mannose. The 2-pyrone moiety would be constructed *via* a Wittig type reaction. This, however, means that at some stage of the route, the hydroxyl group at C-2 must be inverted.

The lactol **7** was oxidised into the lactone **13** by pyridinium chlorochromate (PCC)[15] in CH_2Cl_2. This reaction was performed many times before yields of over 90% could be consistently obtained.[16] Addition of 1 eqv of PhLi to **13** at -78 °C produced only one product **14** in 94% yield. If more than 1 eqv of PhLi were used, the corresponding diol containing two phenyl groups could also be isolated. The stereochemistry of **14** could not be assigned from its NMR spectrum but the phenyl group would be expected in the α-position as shown since β-attack was reasoned to be hindered by the acetonide protecting groups.



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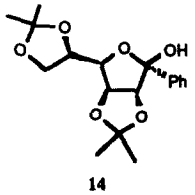

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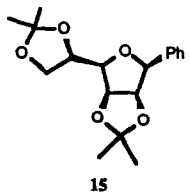

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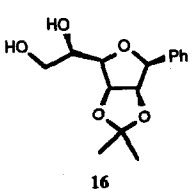

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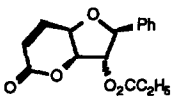

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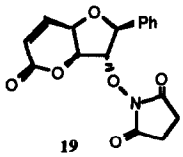

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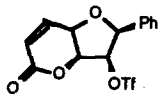

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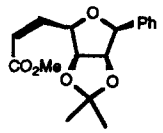


17

The anomeric hydroxyl group was removed upon reduction with Et_3SiH and $BF_3{\cdot}Et_2O$[17] to the *C*-phenyl β-D-furanoside **15**. This occurs in an S_N1 type reaction pathway, whereby the alcohol coordinates with BF_3, and is then relatively easily lost. The resultant carbocation is stabilized by both the phenyl group and the ring oxygen. The carbocation is then attacked by the hydride provided by Et_3SiH from the less hindered side of the molecule. The hydrogen is therefore delivered to the α-position, leaving the phenyl group in the β-position. The NMR spectrum of **15** showed that the anomeric proton appearing as a doublet, $J_{1,2}$ = 3.5 Hz. The "anomeric" proton in **15** should be *cis*-disposed to H-2 and the phenyl group would therefore be in the desired β-position. This was confirmed later by n.O.e. experiments (*vide infra*).

The $BF_3{\cdot}Et_2O$ also cleaved the 5,6-isopropylidene group in **15** partially to produce *C*-phenyl 2,3-*O*-isopropylidene-β-D-mannofuranoside **16**. The ratio of the two products **15** and **16**, depended on the rate of addition of $BF_3{\cdot}Et_2O$ and on the reaction time. The faster $BF_3{\cdot}Et_2O$ was added and the longer the reaction time, the more **16** was formed. Complete conversion of the diacetonide **14** into the diol **16** would be desirable as **16** was the succeeding intermediate in our synthetic sequence. Selective hydrolysis of the 5,6-*O*-isopropylidene protecting group in **15** to give **16** was uneventful.

Glycol cleavage oxidation[18] of the diol in **16** with $NaIO_4$ gave the corresponding aldehyde to which was added *ca.* 2 eqv of $Ph_3P{=}CHCO_2Me$. An excess of the reagent was required as traces of $NaIO_4$ and $NaIO_3$ still present oxidised it to the phosphonium oxide. This Wittig reaction afforded stereoselectively[19] the *Z*-alkene **17** as the major product. The ratio of *Z*:*E*-isomers produced varied from 5:1 up to 8:1. The *Z* and *E*-isomers were differentiated by the characteristic coupling constants of 10 Hz and 16 Hz between the olefinic protons, respectively.

Hydrolysis of the 2,3-*O*-isopropylidene group in **17** and subsequent transesterification to give (-)-7-*epi*-altholactone **4** proceeded under acidic conditions. The use of 2N HCl in THF (74% yield) was successful but use of aqueous trifluoroacetic acid (TFA) gave better results (88% yield). The stereochemistry of the phenyl group in **4** was confirmed at this stage by n.O.e. experiments. Irradiation of H-2 gave a significant 12% increase in the intensity of the H-1 peak. This was considerably greater than the n.O.e. effect expected if H-1 and H-2 were *trans*-disposed. Therefore H-1 and H-2 must be *cis*-disposed and the phenyl group must be in the β-position.

To complete the synthesis of (-)-altholactone **2**, the configuration at C-7 in **4** must be inverted. Our first approach was to try the Mitsunobu inversion,[20] but met with no success. Our next attempt was to form a good leaving group such as a triflate which could then be replaced by a suitable nucleophile *via* an S_N2 type reaction. The hydroxyl group in **4** was readily converted into **18** in 85% yield. However, S_N2 type displacement of **18** by $^nBu_4NOAc$ in

DMF or NaOAc in aqueous acetone failed to afford the desired product. Displacement of **18** using *N*-hydroxy-succinimide, a reagent usually used for the preparation of activated esters in peptide synthesis, was then investigated. The triflate was stirred with 3 eqv of *N*-hydroxysuccinimide and 5 eqv of diisopropylethylamine (Hünig's base), leading to compound **19** as a pale-yellow solid in 52% yield. Curiously a similar reaction using t-butyl hydroperoxide as the nucleophile was unsuccessful.

The reductive cleavage of the N-O bond in **19**, a conversion which would complete the synthesis of (-)-altholactone **2**, proved troublesome in practice. All attempts at N-O bond cleavage to give **2** had so far failed. The use of chromium dichloride,[21] iron in acetic acid[22] or stannous chloride dihydrate and sodium borohydride in ethanol[23] left the substrate **19** unchanged; titanium trichloride[24] or ammonium formate with 10% palladium on charcoal in methanol[25] gave complex reaction mixture; sodium dithionite[26] or Raney nickel in 95% ethanol[27] did not cleave the N-O bond but a simple reduction of the olefinic bond had occurred; zinc powder in aqueous acetic acid cleaved the furanoid ring instead. It was decided that all further attempts at N-O bond cleavage should be abandoned in favour of an alternative route.

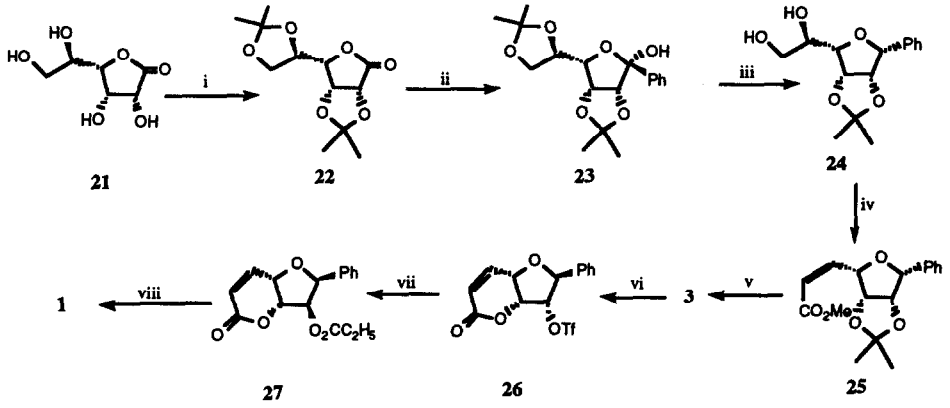
The triflate **18** reacted with cesium propionate in DMF with inversion of configuration[28] to give the ester **20** in low yield. Hydrolysis of the propionate ester **20** should furnish the desired (-)-altholactone **2**. It was found that Michael type addition of methanol onto the conjugated alkene occurred during methanolysis and that the lactone was hydrolysed more easily than the propionate ester. We therefore decided to try hydrolysis conditions under which both the lactone and propionate ester moieties were hydrolysed. This was achieved by using 1N NaOH in aqueous ethanol. Recyclisation of the acid with TFA gave (-)-altholactone **2**.

The spectroscopic data (infrared, mass and ^{1}H-NMR) of the synthetic material **2** was identical to those reported for the natural altholactone.[2] However the $[\alpha]_D$ values of the synthetic material **2** and naturally occurring altholactone are - 180.5 (*c* 0.2, EtOH) and + 184.7 (EtOH)[2] respectively. Therefore the synthetic material **2** must be the enantiomer of the natural material.

C. Synthesis of (+)-altholactone 1 and (+)-7-*epi*-altholactone 3

The same methodology used for the synthesis of (-)-altholactone from D-mannose were employed to give the naturally occurring antitumour pyrone (+)-altholactone from D-gulonolactone **21**. D-Gulonolactone **21** differs from L-mannonolactone only in the chirality at C-5, but this chiral centre is removed at the glycol cleavage oxidation (*vide infra*).

As illustrated in Scheme 1, commercially available D-gulonolactone **21** was protected as the acetonide **22** which with 1 equivalent of PhLi produced only one adduct **23** in 92% yield. Stereocontrolled reduction of **23** with triethylsilane and boron trifluoride etherate occurred with concomitant partial deacetonation, giving *C*-phenyl 2,3-*O*-isopropylidene-α-D-gulofuranoside **24**.



Scheme 1. *Reagents*: i, Me_2CO, conc. H_2SO_4; ii, PhLi, THF, -78 °C; iii, Et_3SiH, $BF_3{\cdot}Et_2O$, MeCN, -20 °C; iv, $NaIO_4$, aq. MeOH, then $Ph_3P{=}CHCO_2Me$; v, aq. TFA, vi, $(CF_3SO_2)_2O$, CH_2Cl_2, pyridine, -10 °C; vii, $EtCO_2Cs$, DMF; viii, aq. NaOH, then TFA.

Glycol cleavage oxidation of the diol in **24** to the corresponding aldehyde was followed by immediate Wittig alkenation in aqueous MeOH to give the *Z*-alkene **25** (*Z*:*E* = 6:1), which is enantiomeric to **17**. Acidic removal of the remaining acetonide proceeded with concomitant lactonisation to yield the (+)-7-*epi*-altholactone **3**. This compound has also been synthesised by Tadano *et al.*[4] The alcohol **3** was then converted into the triflate **26** and into the propionic ester **27**. To complete the synthesis, the propionate ester **27** was hydrolysed by 1N sodium hydroxide in aqueous ethanol and the resulting acid was recyclised to give (+)-altholactone **1** by adding an excess of TFA. The spectroscopic data (infrared, mass and ^{1}H-NMR) of the synthetic material **1** was identical to those reported for the naturally occurring altholactone.[2] The absolute configuration of the natural altholactone must be **1** as the $[\alpha]_D$ values of the synthetic and natural altholactones are + 185.2 (*c* 0.2 in EtOH) and + 184.7 (EtOH)[2] respectively.

Experimental

M.p.s were recorded on a Kofler block. ^{1}H-NMR spectra were recorded on a Varian SC300 spectrometer at 300 MHz using deuteriochloroform as solvent unless otherwise stated. Infrared (IR) spectra were recorded on a Perkin-Elmer 1710 Fourier Transform Spectrophotometer. Mass spectra were recorded on a Kratos MS25 instrument. Ultraviolet (u.v.) spectra were recorded on a Shimadzu UV-260 UV/VIS Spectrophotometer as solutions in ethanol. Optical rotations were measured on an AA-100 polarimeter using $CHCl_3$ as solvent unless otherwise stated. T.l.c. was performed on glass plates precoated with Merck silica $60F_{254}$, and compounds were visualised with a spray of 5% w/v dodeca-molybdophosphoric acid in ethanol and subsequent heating. Dry and flash chromatography were performed on silica gel. THF was distilled from sodium and benzophenone under dry nitrogen. CH_2Cl_2 was distilled from P_2O_5 under dry nitrogen. Pyridine was distilled from barium oxide. Petrol [petroleum ether (b.p. 40—60 °C)] was used as solvent unless otherwise stated.

2,3:5,6-*Di*-O-*isopropylidene*-α-D-*mannofuranosyl chloride* 8

To a stirred solution of diacetone-D-mannose 7[9] (520 mg, 2.0 mmol) and CCl_4 (0.23 ml, 2.4 mmol) in THF (5 ml) under N_2 at - 78 °C, was added dropwise, distilled $(Me_2N)_3P$ (0.39 ml, 2.4 mmol). After 30 min, the solution was warmed to rt and then stirred for 50 min. The solvent was evaporated and the phosphonium oxide removed by passing through a layer of silica gel using EtOAc:petrol (1:5, v/v) as the eluting solvent. The concentrated eluant was flash chromatographed (EtOAc:petrol, 1:5 v/v) to give the *chloride* 8 as a clear oil (435 mg, 78%), $[\alpha]_D^{20}$ + 108.2 (*c* 1.0); δ 1.34, 1.40 (6H, 2s, CMe_2), 1.44 (6H, s, CMe_2), 4.10 (2H, m, H-6), 4.24 (lH, q, H-4, *J* = 8 Hz); 4.48 (lH, m, H-5), 4.92 (lH, dd, H-3, *J* = 11, 8 Hz), 5.0 (lH, d, H-2, *J* = 11 Hz), 6.1 (lH, s, H-l); *m/z* (CI) (296, 279, 263, 221, 185).

C-*Phenyl* 2,3:5,6-*di*-O-*isopropylidene*-α-D-*mannofuranoside* 9

To a stirred solution of 8 (200 mg, 0.72 mmol) in THF (5 ml) under N_2 at - 78 °C was added dropwise 3M PhMgBr in THF (0.24 ml). The solution was slowly raised to rt and left to stir overnight. The reaction was quenched with saturated NH_4Cl (34 ml) and extracted with CH_2Cl_2 (3 × 5 ml). The combined extracts were washed with brine (10 ml) and dried (Na_2SO_4). The filtered solution was concentrated and the residue flash chromatographed (ether:petrol; 1:4 v/v) to afford the C-*glycoside* 9 as a yellow oil (25 mg, 11%), $[\alpha]_D^{20}$ + 133.5 (*c* 1.0); δ 1,38 (6H, s, CMe_2), 1.46, 1.58 (6H, 2s, CMe_2), 3.92 (lH, q, H-4, *J* = 4.8 Hz), 4.24 (2H, d, H-6, *J* = 8.4 Hz), 4.50 (lH, m, H-5), 4.78 (lH, dd, H-3, *J* = 8.4, 4.8 Hz), 5.0 (lH, d, H-2, *J* = 7.2 Hz), 5.23 (lH, s, H-l), 7.3-7.4 (5H, m, PhH); *m/z* (CI) (338, 321); (Found: C, 67.2 ; H, 7.8. $C_{18}H_{24}O_5$ requires C, 67.5; H, 7.6%).

1,4-*Anhydro*-2-*deoxy*-5,6-O-*isopropylidene*-D-arabino-*hex*-l-*enitol* 10

To a stirred solution of di-t-butylbiphenyl (1.24 g, 4.65 mmol) in THF (23 ml) was added, under N_2, an excess of lithium shot cut into 15 pieces. Before addition, each piece was dipped briefly in methanol, rinsed in ether, and then added to the THF solution while still wet with ether. Having turned deep blue-green (30 min), the solution was cooled to 0 °C and stirred for a further 6 h. To this solution at - 78 °C was added over 5 min a solution of 8 (177 mg, 0.64 mmol) in THF (5 ml). Reaction was complete in 15 min and water (5 ml) was then added. The solution was warmed to rt and then poured into ether (30 ml), washed with brine (10 ml) and then dried over Na_2SO_4. The filtered solution was concentrated and the residue flash chromatographed (EtOAc:petrol, 1:3 v/v) to give the *glycal* 10 as a pale yellow oil (95 mg, 80%), $[\alpha]_D^{20}$ - 98.5 (*c* 1.1) {lit.,[12] $[\alpha]_D^{23}$ - 100 (*c* 1.0)}; δ 1.32, 1.40 (6H, 2s, CMe_2), 2.07 (lH, bs, OH), 4.04 (2H, m, H-6), 4.14 (lH, q, H-4, *J* = 6.5 Hz) 4.40 (1H, q, H-5, *J* = 9.5 Hz), 4.77-5.07 (1H, m, H-2), 5.24 (lH, dd, H-3, *J* = 6.5, 3 Hz), 6.57 (lH, d, H-1, *J* = 3 Hz).

1,4-*Anhydro*-3-O-*t-butyldimethylsilyl*-2-*deoxy*-5,6-O-*isopropylidene*-D-arabino-*hex*-l-*enitol* 11

To a stirred solution of 10 (91 mg, 0.05 mmol) in dry DMF (0.5 ml) was added, imidazole (102 mg, 1.5 mmol) and t-butyldimethylsilyl chloride (151 mg, 1.0 mmol) and the solution stirred under N_2 for 48 h. The reaction was quenched with water (5 ml), then extracted with CH_2Cl_2 (3

× 5 ml) and the combined extracts dried over Na_2SO_4. The filtered solution was concentrated and the residue flash chromatographed (EtOAc:petrol, 1:7 v/v) to yield the *silyl ether* **11** as a clear oil (136 mg, 92%), $[\alpha]_D$ - 88.5 (*c* 1.1) ; δ 0.03 (6H, s, SiMe), 0.86 (9H, s, $SiBu^t$), 1.32, 1.42 (6H, 2s, CMe_2), 1.65 (lH, s, OH), 4.0 (2H, m, H-6), 4.32 (lH, dd, H-4, *J* = 8, 5 Hz), 4.47 (lH, m, H-5), 4.90 (lH, m, H-3), 5.06 (lH, t, H-2, *J* = 3 Hz), 5.56 (lH, d, H-l, *J* = 3 Hz), *m/z* (CI, NH_3) 301, 299, 243, 225, 185; (Found: C, 59.9; H, 9.6. $C_{15}H_{28}O_4Si$ requires C, 60.0; H, 9.4%).

***Methyl* 3-O-*t*-*butyldimethylsilyl*-5,6-O-*isopropylidene*-β-D-*glucofuranoside* 12**

To a solution of **11** (8.4 mg, 0.028 mmol) in dry CH_2Cl_2 (3 ml) was added MeOH (4 drops) and a spatula tip of Na_2CO_3. The solution was put under N_2, cooled to 0 °C and a solution of MCPBA (6 mg, 0.034 mmol) in CH_2Cl_2 (l ml) was added. After 1 h, water (5 ml) was added to the solution which was extracted with CH_2Cl_2 (3 × 5 ml), washed with brine (5 ml) and finally dried over Na_2SO_4. The filtered solution was concentrated and the residue flash chromatographed (EtOAc:petrol; 1:3 v/v) to give the *title compound* **12** (4 mg, 41%) as an oil, $[\alpha]_D$ + 65.8 (*c* 1.3); δ 0.04 (6H, s, SiMe), 0.84 (9H, s, $SiBu^t$), 1.30, 1.36 (6H, 2s, CMe_2), 3.31 (3H, s, OMe), 3.98 (2H, m, H-6), 4.04 (lH, m, H-5), 4.14 (lH, dd, H-2, *J* = 5, 2 Hz), 4.24 (lH, q, H-4, *J* = 5 Hz), 4.28 (lH, d, H-3, *J* = 6.5 Hz), 4.86 (lH, s, H-l); *m/z* (CI, NH_3) 349, 333, 317, 291, 259, 233, 201; (Found: C, 54.9; H, 9.4. $C_{16}H_{32}O_4Si$ requires C, 55.14; H, 9.25%).

2,3:5,6-*Di*-O-*isopropylidene*-D-*mannono*-1,4-*lactone* 13

Method I To a stirred solution of 7[9] (0.46 g, 2.1 mmol) in dry CH_2Cl_2 (10 ml) was added a spatula tip of powdered 3Å molecular sieves and PCC (1.91 g, 8 mmol). The reaction mixture was stirred under N_2 at rt for 24 h, diluted with ether (30 ml) and then passed through a pad of silica gel to remove the inorganics. The solvent was removed from the filtrate under reduced pressure to afford the *lactone* **13** as a white solid (0.4g, 86%); m.p. 121—22 °C; $[\alpha]_D^{20}$ + 83.3 (*c* 1.0), {lit.,[16] m.p. 126 °C, $[\alpha]_D^{20}$ + 50 (*c* 1.5)}; $\nu_{max.}$ 1771, 1741 cm^{-1} (C=O) δ 1.40, 1.45, 1.49 (3, 3 and 6H, 3s, CMe_2), 4.12 (2H, m, H-6), 4.45 (2H, m, H-4, H-5), 4.90 (2H, apparent s, H-2, H-3); *m/z* (CI, NH_3) 276, 259, 243.

Method II To a solution of 7[9] (1.3 g, 5 mmol) in dry Me_2SO (10 ml) was added dropwise Ac_2O (3 ml, 32 mmol) and stirred at rt. After 24 h, the solution was concentrated and flash chromatographed (EtOAc:petrol, 1:3 v/v) to afford the *lactone* **13** as a white solid (0.52 g, 40%).

2,3:5,6-*Di*-O-*isopropylidene*-1-C-*phenyl*-D-*mannofuranose* 14

To a solution of **13** (99 mg, 0.39 mmol) in THF (3 ml), at - 78 °C under N_2, was added 1.7M PhLi (0.27 ml, 0.39 mmol, 1 eqv). After 15 min, saturated NH_4Cl (5 ml) was added and the reaction mixture extracted with CH_2Cl_2 (3 × 5 ml), washed with brine (5 ml), dried over Na_2SO_4 and then filtered. Solvent removal followed by flash chromatography (ether:petrol; 1:2 v/v) afforded the *title compound* **14** as a white solid (119 mg, 94%); m.p. 111—112 °C $[\alpha]_D^{20}$ + 49.0 (*c* 1.3); $\nu_{max.}$ 3369 cm^{-1} (OH); δ 1.20, 1.30, 1.37, 1.43 (12H, 4s, CMe_2), 2.56 (lH, s, OH), 4.10 (2H, d, H-6, *J* = 6 Hz), 4.34 (lH, q, H-4, *J* = 4 Hz), 4.54 (lH, m, H-5), 4.68 (lH, d, H-2, *J* = 6 Hz), 4.94 (lH, dd, H-3, *J* = 6, 4 Hz),

7.3-7.6 (5H, m, PhH); *m/z* (CI, NH_3) 319, 279; (Found: C, 64.0; H, 7.6. $C_{18}H_{24}O_6$ requires C, 64.3; H, 7.1%).

C-*Phenyl* 2,3:5,6-*di*-O-*isopropylidene*-β-D-*mannofuranoside* 15

To a stirred solution of **14** (345 mg, 1.03 mmol) and $BF_3{\cdot}Et_2O$ (0.13 ml, 1.03 mmol) in dry MeCN (10 ml), under N_2 at - 20 °C, was added Et_3SiH (0.20 ml, 1.23 mmol). After 1 h, the solution was neutralized with K_2CO_3 and then filtered through Celite. Solvent removal followed by flash chromatography (EtOAc:petrol; 1:2 v/v) gave the *title compound* **15** as a colourless oil (66 mg, 20%). The more polar *C*-phenyl 2,3-*O*-isopropylidene-β-D-mannofuranoside **16** was also isolated as a white solid (238 mg, 72%). The diacetonide **15** had $[\alpha]_D^{20}$ + 175.1 (*c* 1.0 in CH_2Cl_2); δ 1.26, 1.40, 1.44, 1.46 (12H, 4s, CMe_2), 3.70 (1H, q, H-4, *J* = 3.5 Hz), 4.16 (2H, d, H-6, *J* = 6 Hz), 4.56 (1H, m, H-5), 4.63 (1H, d, H-1, *J* = 4 Hz), 4.84 (1H, dd, H-2, *J* = 5.5, 4 Hz), 4.88 (1H, dd, H-3, *J* = 5.5, 4 Hz), 7.3-7.4 (6H, m, PhH); *m/z* (CI, NH_3) 338, 321; (Found: MH^+ 321.17013. $C_{18}H_{25}O_5$ requires 321.17019).

C-*Phenyl* 2,3-O-*isopropylidene*-β-D-*mannofuranoside* 16

The diacetonide **15** (20 mg, 0.062 mmol) was stirred with 80% aqueous AcOH (10 ml) at rt for 6 h. The reaction was concentrated and the residue purified by dry column chromatography (EtOAc:petrol; 2:1 v/v) to give the *diol* **16** as a white solid (13 mg, 74%), m.p. 104—106 °C; $[\alpha]_D^{20}$ + 62.0 (*c* 1.6); $\nu_{max.}$ 3412 cm^{-1} (OH); δ 1.28, 1.46 (6H, 2s, CMe_2), 2.11 (1H, bs, OH), 2.76 (1H, bs, OH), 3.72 (1H, q, H-4, *J* = 4 Hz), 3.88 (2H, m, H-6), 4.19 (1H, m, H-5), 4.64 (1H, d, H-1, *J* = 4 Hz), 4.84 (1H, dd, H-2, *J* = 6, 3.5 Hz), 4.96 (1H, dd, H-3, *J* = 6, 3.5 Hz), 7.3-7.4 (5H, m, PhH); *m/z* (CI, NH_3) 298, 281; (Found: C, 64.2; H, 7.4. $C_{15}H_{20}O_5$ requires C, 64.3; H, 7.2%).

***Z*-*Methyl* (C-*phenyl*-5,6-*dideoxy*-2,3-O-*isopropylidene*-α-D-lyxo-*heptofuranosi*)-*uro*-5-*enoate* 17**

To a stirred solution of **16** (51 mg, 0.18 mmol) in methanol (10 ml) was added a solution of $NaIO_4$ (43 mg, 0.19 mmol) in water (2 ml). After 30 min, the reaction was filtered through Celite to remove $NaIO_3$. To the filtrate was added $Ph_3P{=}CHCO_2Me$ (180 mg, 0.39 mmol); an excess amount being required as any $NaIO_4$ or $NaIO_3$ present oxidized the phosphorane. After 1 h, the reaction was filtered through silica and washed with ether. The filtrate was concentrated and the residue flash chromatographed (EtOAc:petrol, 1:2 v/v) to give the *Z-alkene* **17** as a colourless oil (37 mg, 68%). The *trans* isomer was also isolated as a colourless oil (10 mg, 18%). The *Z-alkene* **17** had $[\alpha]_D^{20}$ - 57.5 (*c* 1.0 in CH_2Cl_2); $\nu_{max.}$ 1719 (C=O), 1657 cm^{-1} (C=C); $\lambda_{max.}$ 210 nm (ε 12,000); δ 1.24, 1.42 (6H, 2s, CMe_2); 3.74 (3H, s, OMe), 4.66 (1H, d, H-l, *J* = 4 Hz), 4.86 (1H, q, H-2, *J* = 5 Hz), 5.16-5.20 (2H, m, H-3, H-4), 6.15 (1H, d, H-6, *J* = 10 Hz), 6.90 (1H, dd, H-5, *J* = 10, 4 Hz), 7.3-7.4 (5H, m, PhH); *m/z* (CI, NH_3) 322, 305; (Found: MH^+ 305.1388. $C_{17}H_{21}O_5$ requires 305.1389).

(-)-7-epi-*Altholactone* 4

Method I A solution of **17** (109 mg, 0.36 mmol) in THF (l ml) was added to 50% aq. TFA (10 ml) and stirred at rt for 40 h. Solvent removal followed by flash chromatography (EtOAc:petrol, 1:l v/v) furnished (-)-7-epi-*altholactone* **4** as white crystals (76 mg, 93%); m.p. 121—122 °C, $[\alpha]_D^{20}$

- 24.1 (*c* 1.0 in EtOH); $\nu_{max.}$ 3425 (OH), 1732 (C=O) cm^{-1}; δ 1.88 (1H, s, OH), 4.58 (1H, q, H-2, *J* = 5 Hz), 4.84 (1H, q, H-4, *J* = 4 Hz), 5.10 (1H, d, H-1, *J* = 4 Hz); 5.24 (1H, q, *J* = 4 Hz), 6.16 (1H, d, H-6, *J* = 10 Hz), 6.90 (1H, dd, H-5, *J* = 10, 4 Hz), 7.3-7.4 (5H, m, PhH), δ_C 58, 74, 80, 81 (C-4, C-1, C-3, C-2), 112, 128, 129, 129, 136, 1.42 (C=C and aromatic protons), 162 (C=O); *m/z* (CI, NH_3) 250, 233 (Found: M^+ 232.0737. $C_{13}H_{12}O_4$ requires 232.0736)

Method II A solution of **17** (36 mg, 0.12 mmol) in THF (2 ml) was added to 2N HCl (6 ml) and heated under reflux for 1 h. Solvent removal followed by flash chromatography (EtOAc:petrol, 1:1 v/v) gave the *title compound* as a white solid (20 mg, 74%).

***Z*-(C-*Phenyl* 5,6-*dideoxy*-2-O-*trifluoromethanesulphonyl*-α-D-lyxo-*heptofuranosi*)*uro*-5-*enono*-3,7-*lactone* 18**

To a solution of **4** (96.5 mg, 0.42 mmol) in dry CH_2Cl_2 (10 ml) at - 22 °C under N_2, was added pyridine (500 µl, 6.2 mmol) and then $(CF_3SO_2)_2O$ (500 µl, 4.7 mmol). After 2 h, water (5 ml) was added to the reaction which was extracted with CH_2Cl_2 (3 × 5 ml), washed with brine (5 ml) and then dried over Na_2SO_4. Solvent removal followed by flash chromatography (EtOAc:petrol, 1:1 v/v) gave the *triflate* **18** as an off-white solid (133 mg, 90%), m.p. 138—40 °C; $[\alpha]^{20}$ - 16.2 (*c* 1.0); $\nu_{max.}$ 1745 cm^{-1}; λ_{max} 212 (ε = 7,000); δ 4.97 (1H, m, H-4), 5.20 (1H, d, *J* = 3 Hz), 5.40 (1H, m, H-3), 5.37 (1H, q, H-2, *J* = 5 Hz), 6.18 (1H, d, H-6, *J* = 10 Hz), 6.90 (1H, dd, H-5, *J* = 10, 3 Hz), 7.3-7.4 (5H, m, PhH); *m/z* (CI, NH_3) 382, 365, 215; (Found: C, 46.4; H, 3.2; S, 8.7. $C_{13}H_{18}O_6$ requires C, 46.1; H, 3.1; S, 8.8 %).

***Z*-(C-*Phenyl* 5,6-*dideoxy*-2-O-*succinimyl*-α-D-lyxo-*heptofuranosi*)*uro*-5-*enono*-3,7-*lactone* 19**

To a solution of **18** (50 mg, 0.14 mmol) and *N*-hydroxysuccinimide (78 mg, 0.68 mmol) in dry MeCN (5 ml) under N_2 was added Hünig's base (150 µl, 0.86 mmol) and stirred for 48 h. Water (5 ml) was added to the reaction mixture which was extracted with CH_2Cl_2 (2 × 5 ml), washed with brine (5 ml) and then dried over Na_2SO_4. Solvent removal followed by flash chromatography (EtOAc:petrol, 3:2 v/v) provided the *title compound* **19** as a pale yellow oil (24 mg, 52%), $[\alpha]^{20}$ + 8.3 (*c* 0.9); $\nu_{max.}$ 1729 (C=O) cm^{-1}; λ_{max} 212.5 nm (ε = 14,000); δ 2.70 (4H, s, CH_2CH_2), 4.74 (1H, t, H-4, *J* = 5 Hz), 4.82 (1H, d, H-2, *J* = 4 Hz), 5.11 (1H, d, H-1, *J* = 5 Hz), 5.28 (1H, d, H-3, *J* = 5 Hz), 7.3-7.4 (5H, m, PhH); *m/z* (CI, NH_3) 347; (Found: MNH_4^+ 347.1246. $C_{17}H_{19}N_2O_6$ requires 347.1243).

***Z*-(C-*Phenyl* 5,6-*dideoxy*-2-O-*propanoyl*-β-D-xylo-*heptofuranosi*)*uro*-5-*enono*-3,7-*lactone* 20**

To a stirred solution of cesium propionate (60 mg, 0.29 mmol) in dry DMF (10 ml) at rt under N_2, was added a solution of triflate **18** (50 mg, 0.14 mmol) in DMF (2 ml). After 20 min, water (10 ml) was added to the reaction which was extracted with CH_2Cl_2 (4 × 5 ml), washing with brine (5 ml) and then dried over Na_2SO_4. Solvent removal gave a yellow residue which was passed firstly through a thin layer of silica (eluting with EtOAc) and then purified by flash chromatography (EtOAc:petrol, 3:2 v/v) to give the *propionate ester* **20** as an off-white solid (22 mg, 53%), m.p. 174—176 °C, $[\alpha]_D^{23}$ - 127 (*c* 0.8); ν_{max} 1741 cm^{-1} (C=O); δ 1.18 (3H, t, $-CH_3$, *J* = 8

Hz), 2.43 (2H, q, -CH_2-, J = 8 Hz), 4.64 (1H, dd, H-4, J = 4.5, 5.5 Hz), 4.95 (1H, dd, H-3, J = 1, 4.5 Hz), 4.98 (1H, d, H-1, J = 3.5 Hz), 6.28 (1H, d, H-6, J = 10 Hz), 7.04 (1H, dd, H-5, J = 10, 5 Hz), 7.37 (5H, m, PhH); *m/z* (EI) 289 (15%, MH^+); (Found: MH^+, 289.1075. $C_{16}H_{17}O_5$ requires 289.1076).

(-)-Altholactone **2**

To a stirred solution of ester **20** (22 mg, 0.076 mmol) in 50% aq. ethanol (3 ml) and THF (1 ml) at rt was added NaOH (30 mg, 0.75 mmol). After stirring overnight, the pH of reaction mixture was adjusted to 1(*ca.* 40 drops of TFA) and the solution left to stir for 48 h. The reaction was extracted with CH_2Cl_2 (6 × 5 ml), washed with brine and then dried over Na_2SO_4. Solvent removal followed by flash chromatography (EtOAc:petrol, 3:2 v/v) gave (-)-altholactone **2** as a white crystalline solid (11 mg, 62%), m.p. 111 °C; $[\alpha]_D^{22}$ - 180.5 (*c*, 0.2 in EtOH), ν_{max} 3406, 2924, 2853, 1732, 1642 cm^{-1}; δ 4.44 (1H, d, H-2, J = 2.5, 5.8 Hz), 4.65 (1H, t, H-4 J = 5.1 Hz), 4.73 (1H, d, H-1, J = 5.8 Hz), 4.93 (1H, dd, H-3, J = 2.5, 5.1 Hz), 6.22 (1H, d, H-6, J = 10 Hz), 6.99 (1H, dd, H-5, J = 5, 10 Hz), 7.38 (5H, m, PhH); *m/z* (EI) 232 (40%, M^+); (Found: M^+ 232.0737. $C_{13}H_{12}O_4$ requires 232.0736).

2,3:5,6-Di-O-isopropylidene-D-gulonolactone **22**

D-Gulonolactone **21** (23 g, 129 mmol) was vigorously stirred with anhydrous acetone (700 ml) and conc. H_2SO_4 (3 ml) for 24 h. The solution was neutralized with Na_2CO_3, filtered and the filtrate concentrated to give a solid residue. The solid was dissolved in $CHCl_3$ and the solution passed through a thin pad of silica to remove any monoacetonide (eluting with EtOAc:petrol, 1:2 v/v). The eluant was concentrated and the solid residue recrystallized from ether-petrol to give the *diacetonide* **22** (22g, 66%), m.p. 149—150 °C; $[\alpha]_D^{23}$ - 65 (*c*, 2.1); ν_{max} 1776 cm^{-1} (C=O); δ 1.38 (1H, m, H-5), 4.22 (1H, m, H-4), 4.42 (2H, m, H-6, H-6'), 4.74 (1H, dd, H-3, J = 3.5, 6 Hz), 4.83 (1H, d, H-2, J = 6 Hz); *m/z* (CI, NH_3) 259 (90%, MH^+) (Found: C, 55.5; H, 7.1. $C_{12}H_{18}O_6$ requires C, 55.8; H, 7.0%).

2,3:5,6-Di-O-isopropylidene-1-C-phenyl-D-gulofuranose **23**

To a solution of **22** (0.83 g, 3.21 mmol) in THF (10 ml), at - 78 °C under N_2, was added 1.7M PhLi in cyclohexane-ether (2.0 ml, 3.5 mmol, 1.1 eqv.). After 15 min, saturated NH_4Cl (5 ml) was added to the reaction which was extracted with CH_2Cl_2 (3 × 15 ml), washed with brine, dried over Na_2SO_4 and filtered. Solvent removal followed by flash chromatography (ether:petrol, 1:1 v/v) provided the *lactol* **23** as a white solid (0.93 g, 86%); m.p. 103—105 °C, $[\alpha]_D^{23}$ - 54.5 (*c* 1.4); ν_{max} 3369 (OH), 1729 cm^{-1} (C=O); δ 1.20, 1.34, 1.42, 1.48 (12H, 4s, CMe_2), 2.16 (1H, s, OH), 3.80 (1H, dd, H-5, J = 7, 10 Hz), 4.26-4.31 (2H, m, H-6, H-4), 4.50 (1H, dd, H-6, J = 7, 10 Hz) 4.67 (1H, d, H-2, J = 6 Hz), 4.83 (1H, dd, H-3, J = 4, 6 Hz), 7.3-7.6 (5H, m, ArH); *m/z* (EI) 321 {40%, (M^+-CH_3) (Found: C. 64.1; H, 7.3. $C_{18}H_{24}O_6$ requires C, 64.3; H, 7.1%).

C-Phenyl 2,3-O-isopropylidene-α-D-gulofuranoside **24**

To a stirred solution of **23** (0.19g, 2.7 mmol), $BF_3{\cdot}Et_2O$ (0.34 ml, 2.76 mmol) in MeCN (10 ml), under N_2 at - 20 °C, was added Et_3SiH (0.52 ml, 3.26 mmol). After 2 h, the solution was neutralized with K_2CO_3 and filtered through Celite. Solvent removal followed by flash chromatography

(EtOAc:petrol, 2:1 v/v) gave the *diol* **24** (74 mg, 74%) as an oil, $[\alpha]_D^{22}$ — 45.0 (*c* 0.3); ν_{max} 3412 cm^{-1} (OH); δ 1.37, 1.47 (2 × 3H, s, CMe_2), 1.60-1.70 (2H, bs, 2 × OH), 3.73 (1H, dd, H-4, *J* = 3.5, 6.5 Hz), 3.85 (2H, m, H-6), 4.23 (1H, m, H-5), 4.61 (1H, d, H-1, *J* = 3.5 Hz), 4.83-4.88 (2H, m, H-2, H-3), 7.30-7.45 (5H, m, PhH); *m/z* (CI, NH_3), 281 (100%, MH^+); (Found: M^+-CH_3, 265.1070. $C_{14}H_{17}O_5$ requires 265.1076).

***Z-Methyl* (C-*phenyl* 5,6-*dideoxy*-2,3-O-*isopropylidene*-α-L-lyxo-*heptofurano*-*si*)*uro*-5-*enoate* 25**

To a stirred solution of **24** (450 mg, 1.60 mmol) in MeOH (40 ml) was added $NaIO_4$ (400 mg, 1.87 mmol). After 30 min, the reaction was filtered through Celite. To the filtrate was added $Ph_3P{=}CHCO_2Me$ (1.2 g, 3.60 mmol, 2.2 eqv.). After 1 h, the mixture was filtered through Celite. Solvent removal followed by flash chromatography (EtOAc:petrol, 1:2 v/v) yielded the *Z-alkene* **25** (380 mg, 70%) as a colourless oil. The *trans*-isomer was also isolated as a colourless oil (45 mg, 10%). The *Z*-alkene **25** had $[\alpha]_D^{22}$ + 55 (*c* 0.4); ν_{max} 1719 (C=O), 1657 cm^{-1} (C=C); δ 1.23, 1.42 (6H, 2s, CMe_2), 3.76 (3H, s, OMe), 4.64 (1H, d, H-1, *J* = 3.5 Hz), 4.85 (1H, dd, H-2, *J* = 3.5, 5 Hz), 5.13-5.19 (2H, m, H-3, H-4), 6.02 (1H, dd, H-6, *J* = 1.5, 12.5 Hz), 6.51 (1H, dd, H-5, *J* = 6.5, 12.5 Hz), 7.28-7.40 (5H, m, PhH); *m/z* (CI, NH_3) 305 (100%, MH^+); (Found: MH^+, 305.1391. $C_{17}H_{21}O_5$ requires 305.1389).

(+)-7-epi-*altholactone* 3

A solution of **25** (360 mg, 1.18 mmol) in THF (2 ml) was added to 50% aq. TFA (20 ml) and stirred at rt for 48 h. Concentration and flash chromatography (EtOAc:petrol, 1:1 v/v) gave (+)-7-epi-*altholactone* **3** as white crystals (255 mg, 92%), m.p. 121—123 °C; $[\alpha]_D^{22}$ + 23.5 (*c* 0.4 in EtOH); ν_{max} 3425 (OH), 1732 cm^{-1} (C=O); δ 1.90 (1H, s, OH), 4.58 (1H, dd, H-2, *J* = 4 Hz), 4.84 (1H, q, H-4, *J* = 4 Hz), 5.10 (1H, d, H-1, *J* = 4 Hz), 5.24 (1H, dd, H-3, *J* = 4, 5 Hz), 6.16 (1H, d, H-6, *J* = 10 Hz), 6.90 (1H, dd, H-5, *J* = 4, 10 Hz), 7.3-7.45 (5H, m, PhH); *m/z* (EI) 232 (30%, M^+); (Found: M^+, 232.0737. $C_{13}H_{12}O_4$ requires 232.0736).

***Z*-(C-*Phenyl* 5,6-*dideoxy*-2-O-*trifluoromethanesulphonyl*-α-L-lyxo-*heptofu*-*ranosi*)*uro*-5-*enono*-3,7-*lactone* 26**

To a solution of **3** (217 mg, 0.93 mmol) in dry CH_2Cl_2 (20 ml) at - 22 °C, under N_2, was added firstly pyridine (1.0 ml, 12.41 mmol) and then triflic anhydride (1.0 ml, 9.40 mmol). After 2.5 h, water (10 ml) was added to the reaction mixture. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 ml). The combined extracts were washed with brine, dried over Na_2SO_4 and the solvent then removed under reduced pressure. The residue was flash chromatographed (EtOAc:petrol, 1:1 v/v) to afford the *triflate* **26** as an off-white solid (307 mg, 90%), m.p. 139—41 °C; $[\alpha]_D^{22}$ + 15 (*c* 0.8); ν_{max} 1745 cm^{-1} (C=O); δ 4.96 (1H, m, H-4), 5.20 (1H, d, H-1, *J* = 3 Hz), 5.40 (1H, m, H-2), 5.57 (1H, q, H-3, *J* = 5 Hz), 6.18 (1H, d, H-6, *J* = 10 Hz), 6.90 (1H, dd, H-5, *J* = 3, 10 Hz), 7.30-7.45 (5H, m, PhH); *m/z* (CI, NH_3) 382 (100%, MNH_3^+) (Found: C, 46.4; H, 3.2; F, 15.6 : S, 8.7. $C_{14}H_{11}O_6$ requires C, 46.1; H, 3.11; F, 15.7; S, 8.8%).

***Z*-(C-*Phenyl* 5,6-*dideoxy*-2-O-*propanoyl*-β-L-lyxo-*heptofuranosi*)*uro*-5-*enono*-3,7-*lactone* 27**

To a stirred solution of cesium propionate (70 mg, 0.34 mmol) in dry DMF (10 ml) at rt, under N_2, was added a solution of **26** (112 mg, 0.31 mmol) in DMF (3 ml). After 30 min, DMF was evaporated, water (5 ml) was added to the residue and the organics extracted with CH_2Cl_2 (3 × 15 ml), washed with brine (5 ml) and then dried over Na_2SO_4. Solvent removal followed by flash chromatography (ether:petrol, 4:1 v/v) to afford the *ester* **27** as a white solid (51 mg, 59%) m.p. 174—75 °C, $[\alpha]_D^{22}$ + 139.0 (*c* 0.7); ν_{max} 2923, 1741, 1455, 1357, 1246, 1172, 1103, 1026, 820; δ 1.18 (3H, t, $-CH_3$, *J* = 8 Hz), 2.43 (2H, q, $-CH_2-$, *J* = 8 Hz), 4.64 (1H, dd, H-4, *J* = 4.5, 5.5 Hz), 4.95 (1H, dd, H-3, *J* = 1, 4.5 Hz), 4.99 (1H, d, H-1, *J* = 3.5 Hz), 6.26 (1H, d, H-6, *J* = 10 Hz), 7.04 (1H, dd, H-5, *J* = 10, 5.5 Hz), 7.35-7.40 (5H, m, PhH); *m/z* (EI) 289 (15%, M^+); (Found: MH^+, 289.1073. $C_{16}H_{17}O_5$ requires 289.1076).

(+)-*Altholactone* 1

To a stirred solution of **27** (40 mg, 0.14 mmol) in 50% aq. EtOH (3 ml) and THF (2 ml) at rt was added NaOH (55 mg, 1.37 mmol). After stirring overnight, the pH of reaction mixture was adjusted to 1(*ca.* 40 drops of TFA) and the solution left to stir for 48 h. The reaction was extracted with CH_2Cl_2 (6 × 5 ml), washed with brine and then dried over Na_2SO_4. Solvent removal followed by flash chromatography (EtOAc:petrol, 3:2 v/v) yielded (+)-*altholactone* **1** as a white crystalline solid (21 mg, 65%), m.p. 117—118 °C; $[\alpha]_D^{23}$ + 185.2 (*c* 0.2 in EtOH); ν_{max} 3406, 2924, 1732, 1642, 1494, 1453, 1373, 1249, 1153, 1098, 913; δ 4.44 (1H, dd, H-2, *J* = 2.5, 5.8 Hz),), 4.64 (1H, dd, H-3, *J* = 2.5, 5 Hz), 6.22 (1H, d, H-6, *J* = 10 Hz), 6.99 (1H, dd, H-5, *J* = 10, 5 Hz), 7.35-7.40 (5H, m, PhH), *m/z* (EI) 232 (45%, M^+); (Found: M^+, 232.0736. $C_{13}H_{12}O_4$ requires 232.0736).

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