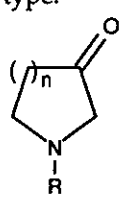
2-KETO SUGARS AS PREFORMED HETEROCYCLIC BUILDING BLOCKS. SYNTHETIC STUDIES

Andrew M. Griffin,[a,b] Nicholas J. Newcombe,[b] David Alker,[c] Michael V.J. Ramsay,[d] and Timothy Gallagher*[a,b]

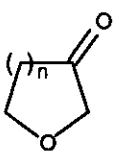
[a]School of Chemistry, University of Bristol, Bristol BS8 1TS, UK
[b]School of Chemistry, University of Bath, Bath BA2 7AY, UK
[c]Pfizer Central Research, Sandwich, Kent CT13 9NJ, UK
[d]Medicinal Chemistry Department, Glaxo Group Research, Greenford UB6 0HE, UK

Abstract- The synthesis of a series of bicyclic 2-hexulose derivatives (5), (6) and (7), which provide access to regiospecific carbohydrate-based ketone enolates, is described. The preparation of silyl enol ethers (21) and (22) from keto ether (5) and keto acetal (6), respectively, is also reported.

The methods currently available for the synthesis of complex heterocyclic molecules frequently utilise a cyclisation step to establish the primary heterocyclic framework. In principle, however, such targets may also be assembled using a preformed heterocyclic unit provided that such a unit incorporates the functionality that will be needed for further synthetic elaboration. The heterocyclic ketones (1) and (2) are representative of a simple, but nevertheless readily available class of building blocks and over recent years we have focused our attention on developing the synthetic utility of molecules of this type.[1]



(**1a**) n=1
(**1b**) n=2

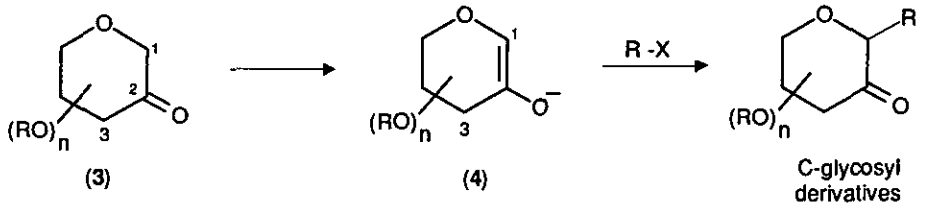


(**2a**) n=1
(**2b**) n=2

It is a great pleasure to dedicate this paper to Professor Edward C. Taylor, both on the occasion of his 70th birthday and also in recognition of the distinguished contributions that he has made to the field of heterocyclic chemistry.

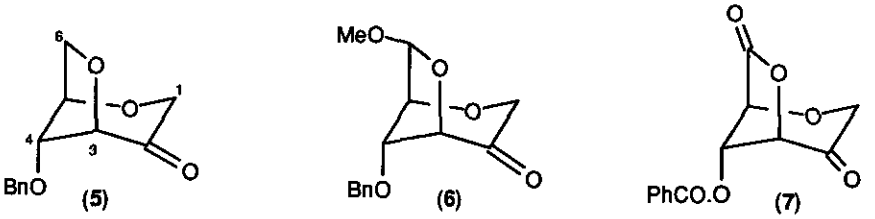
The keto function of **1a/b** and **2a/b** provides an excellent handle for manipulation of the heterocyclic core, thereby providing the synthetic flexibility necessary for future elaboration. In this context, the generation of either enolates or enamines from **1** and **2** as a vehicle for C-C bond formation is especially attractive, since the ketone carbonyl function then remains available for use at a later stage. However, there are important regiochemical issues relating to the generation of enolates adjacent to heteroatoms that must also be recognised and addressed if such chemistry is to be usefully employed. Many of these constraints can now be overcome and we recently exemplified the use of pyrrolidin-3-one (**1a**) as a preformed heterocyclic building block as a key component in the synthesis of the castanospermine class of polyhydroxy indolizidines.[2]

While the simple oxygen-based heterocycles (**2**) are also synthetically useful, the extrapolation of this general strategy to encompass heterocyclic ketones which are based on a carbohydrate nucleus would broaden its potential dramatically. Regiospecific enolization of a 2-keto sugar, such as **3**, towards C-1 (*carbohydrate numbering*)[3] would generate an "anomeric nucleophile" (**4**) that would then provide access to a range of C-glycosyl derivatives.[4] In addition, enolate reactivity of this type provides an advantage over most other existing anomeric nucleophiles in that oxygenation at C-2 may be retained.[5] In fact, the capacity for nucleophilic reactivity at C-1 is contingent upon the presence of the ketone function.



Enolate (**4**) should, following C-C bond formation at C-1, then provide access to both 2-hydroxy and 2-amino-C-glycosides (*gluco* or *manno* configuration at C-2), as well as the corresponding 2-deoxy variants, depending on the ultimate fate of the carbonyl moiety.

The enolization of both simple[6] and more complex[7] tetrahydropyranones of this type is, however, subject to specific stereoelectronic requirements.[8] Under both kinetic and thermodynamic conditions, the preferred mode of enolization is *away* from the ring-constrained oxygen atom leading to the less-useful C-3 enolate; formation of the C-1 enolate (**4**) corresponds to the disfavoured pathway. In order to redirect this regiochemical preference, stereoelectronic considerations played an important role in our design of carbohydrate-based building blocks and in this paper we describe the synthesis of three new 2-keto sugar derivatives, the bicyclic 2-hexuloses (**5**), (**6**) and (**7**).

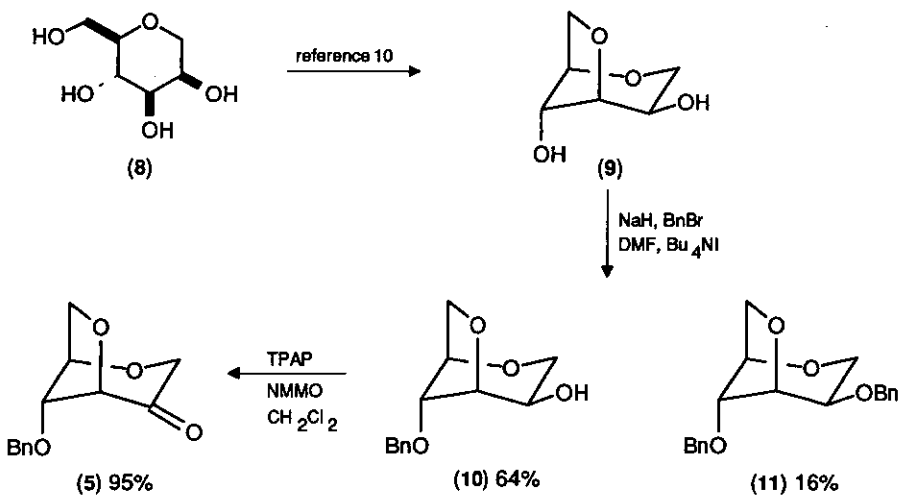


Each of these units incorporates a rigid bicyclic framework that, in accordance with Bredt's rule, restricts the mode of enolization of the 2-keto function towards C-1 thereby providing a source of nucleophilic reactivity at what is formally the anomeric site. We are also able to vary the oxidation state within the C-3/C-6 anhydro bridge, although the reactivity associated with the lactone variant (7) is somewhat limiting (*vide supra*).

Results and Discussion.

Synthesis of Ether-Bridged Ketone (5)

The synthesis of the simplest and, to date, synthetically most useful member of this class of building block is shown in **Scheme 1**. 1,5-Anhydro-D-mannitol (**8**) (prepared by acid-catalysed cyclodehydration[9] of D-mannitol) was converted to 1,5:3,6-dianhydro-D-mannitol (**9**) as described by Hockett[10] and regioselective monobenzylation[11] of **9** was achieved to give **10** in 64% yield. No trace of the other monobenzylated isomer was detected and, although similar observations have been made with other diols of this type [see **12** and **18**], the factors underpinning this selectivity are not yet clear; the major by-product of this protection step was the dibenzylated derivative (**11**).

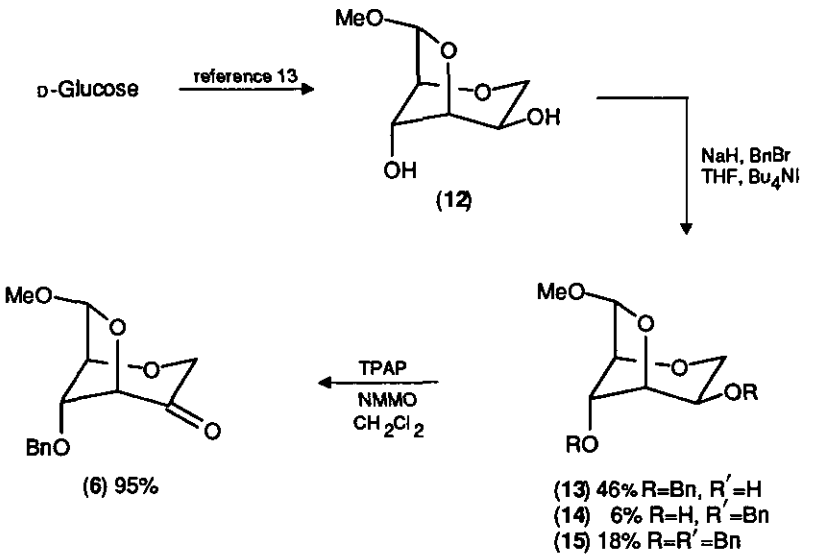


Scheme 1

Oxidation of **10** to provide the target ketone was most efficiently achieved using a catalytic amount of tetra-*n*-propylammonium perruthenate (TPAP) in the presence of *N*-methylmorpholine *N*-oxide (NMMO) as developed by Griffith and Ley[12] which gave the ether-bridged building block (**5**) as a stable, crystalline solid in 61% overall yield from **9** .

Synthesis of Acetal-Bridged Ketone (6)

In the early phase of this programme we focused on acetal (6) for use as a functionalised heterocyclic building block. This unit offered the advantage of a bridging group (an acetal) that, while stable towards bases/nucleophiles, should be readily opened with mild acid. Attaining the necessary aldehyde oxidation level at this site using methods based on 1,5-anhydro-D-mannitol has, however, proven to be elusive, but a route to **6** has nevertheless been identified. The synthetic sequence, which is shown in **Scheme 2**, is more lengthy but still provides access to useful amounts of the target ketone (6).



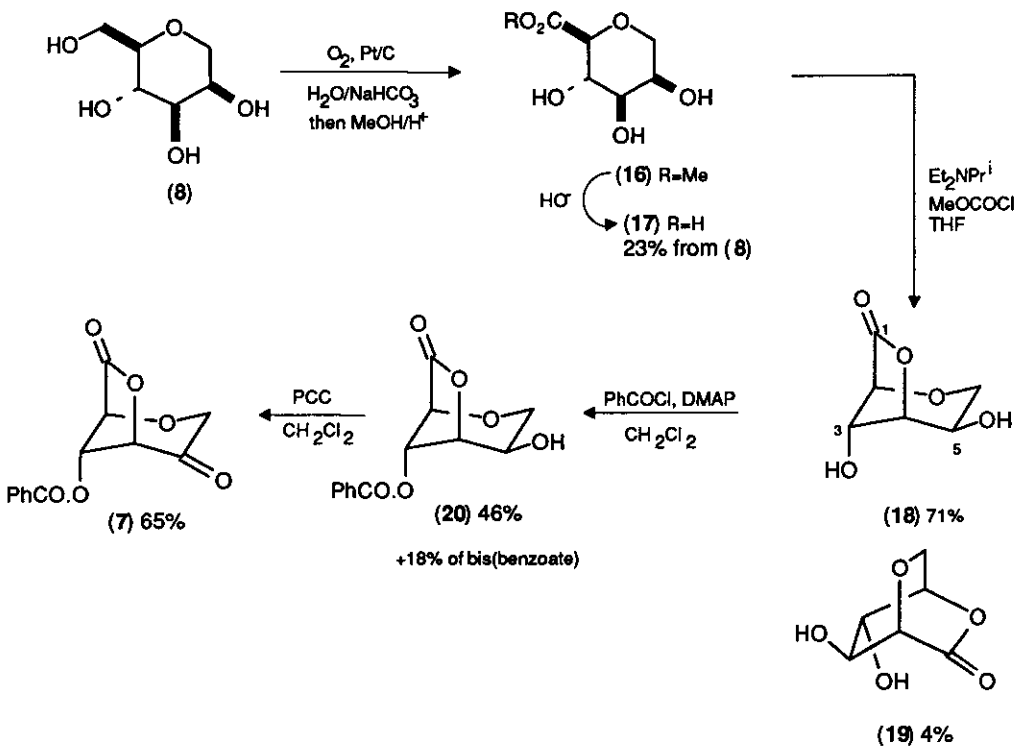
Scheme 2

Köll[13] has described the preparation of the acetal-bridged diol (12) in six steps from D-glucose. Once again, we were able to achieve regioselective monobenzylation of **12** and the mono-protected diol (13) was isolated in 46% yield although, in this case, 6% of the isomeric monobenzylated derivative (14) was produced along with 18% of the dibenzylated adduct (15) Oxidation of **13** using TPAP/NMMO proceeded smoothly and keto acetal (6) was obtained in 95% yield.

Synthesis of Lactone-Bridged Ketone (7)

The lactone-bridged ketone (7) was both the most challenging and potentially most useful of the three units that we had designed and, as with ether (5), 1,5-anhydro-D-mannitol (8) proved to be a convenient starting point. Oxidation of the primary hydroxyl function of **8** was achieved using Pt/O_2 under basic conditions.[14] Since a complex series of products was produced in this step, the crude reaction mixture was treated with acidic methanol to provide, after chromatography, the

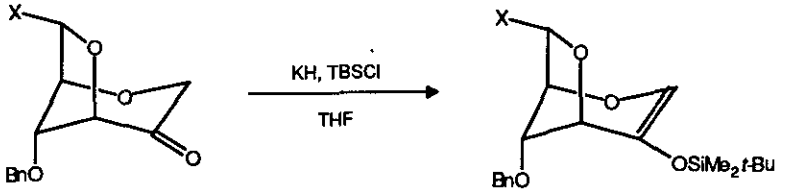
methyl ester (**16**). Saponification of **16** then gave the free acid (**17**) in 23% overall yield from **8** ; attempts to isolate **17** directly from the oxidation product mixture by a variety of methods, including ion exchange chromatography, were found to be less efficient.



Scheme 3

Lactonisation of **17** to give **18** proved to be problematic due to the lability of the newly-formed lactone moiety. A range of lactonisation procedures[15] were examined and the most efficient of these involved *in situ* generation of a mixed anhydride between **17** and methyl chloroformate. Under these conditions lactone (**18**) was produced in 71% yield together with a small amount (4%) of an isomeric lactone, which has been assigned as the [2.2.2]bicyclic derivative (**19**). Selective protection of the C-3 hydroxyl of **18** (*note altered numbering*) was achieved by benzoylation to give **20** ; the sensitivity of the lactone moiety precluded the use of the strongly basic conditions required for benzylation. Oxidation of **20** using pyridinium chlorochromate gave the target keto lactone (**7**) in 65% yield and, although this product was too labile to permit chromatography, purification was achieved by direct crystallisation. Despite the high level of functionality incorporated within ketolactone (**7**), the reactivity of the lactone ring towards cleavage under the basic/nucleophilic conditions required for enolate generation has limited further studies involving this unit.

The generation and scope of the reactivity of enolates derived from ether (**5**) and acetal (**6**) towards carbon electrophiles will be described in due course but the ether-bridged ketone (**5**) has recently been successfully used in the first synthesis of the glycosyl core of the herbicidin class of undecose nucleosides.[16] Silyl enol ethers have also found widespread use in synthesis with a mode of reactivity that is frequently complementary to that of enolates.[17] While we have been unable to isolate trimethylsilyl enol ethers derived from either **5** or **6**, the corresponding tert-butyldimethylsilyl derivatives (**21**) and (**22**) have been efficiently prepared using KH as base.[18] (**Scheme 4**).



(**5**) X=H
(**6**) X=OMe

(**21**) X=H 56%
(**22**) X=OMe 80%

Scheme 4

In summary, we have described the synthesis of a novel series of configurationally constrained carbohydrate-based ketones which offer access to nucleophilic reactivity at the anomeric site *via* a regiospecific (and enforced) mode of enolization. The application of these heterocyclic building blocks to the synthesis of a variety of biologically-important C-glycosyl derivatives is now being actively pursued.

ACKNOWLEDGEMENTS

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EXPERIMENTAL.

General

Standard methods were employed for the purification of solvents and reagents. ^{1}H Nmr spectra were obtained at 270 MHz (using the solvent shown) and ^{13}C spectra were obtained in $CDCl_3$ at 67.8 MHz.

1,5:3,6-Dianhydro-4-O-benzyl-D-mannitol (**10**)

To a solution of 1,5:3,6-dianhydro-D-mannitol (**9**) (3.90 g, 27 mmol) in dry DMF (40 ml) was slowly added NaH (1.30 g, 60% dispersion in oil, 40.5 mmol). The solution was stirred at 0°C under a nitrogen atmosphere and, after evolution of hydrogen had ceased, benzyl bromide (3.2 ml, 27 mmol) was added followed by tetra-*n*-butylammonium iodide (1.0 g, 2.7 mmol) and the solution was stirred for a further 2 hours at 0°C. The mixture was concentrated *in vacuo* and purification of the residue by flash chromatography (80:20 EtOAc/petrol) gave *alcohol* (**10**) (4.02 g, 64%) as colourless crystals, mp 102-102.5 °C (EtOAc) (Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.1; H, 6.83. Found: C, 66.4; H, 6.85.); ν_{max}/cm^{-1} (nujol) 3370; δ_H ($CDCl_3$) 2.04 (1H, d, J 10, OH), 3.43-3.52 (1H, m, 2-H), 3.94-4.13 (5H, m, 6-H, 4-H, 3-H, 1-H), 4.21 (1H, d, J 6, 6-H), 4.28 (1H, t, J 3, 5-H), 4.57 (1H, d, J 12, part of AB quartet), 4.71 (1H, d, J 12, part of AB quartet), 7.20-7.50 (5H, m, Ph); δ_C 137.3 (C), 128.5 (Ph), 128.0 (Ph), 127.8 (Ph), 77.4 (CH), 77.0 (CH), 71.9 (CH_2), 71.9 (CH), 69.1 (CH_2), 66.0 (CH_2), 64.6 (CH); m/z (EI) 236 (M^+).

1,5:3,6-Dianhydro-2,4-di-O-benzyl-D-mannitol (**11**) was also isolated in 16% from this reaction mixture as a yellow oil (Found: M^+, 326.1503. $C_{20}H_{22}O_4$ requires M, 326.1518); δ_H ($CDCl_3$) 3.71 (1H, t, J 10) 3.77-4.04 (5H, m), 4.15 (1H, t, J 2.5), 4.27 (1H, d, J 6), 4.33-4.59 (4H, m), 7.20-7.40 (10H, m, Ph); δ_C 137.9 (C), 137.2 (C), 128.3 (Ph), 128.2 (Ph), 127.8 (Ph), 127.7 (Ph), 127.6 (Ph), 127.5 (Ph), 77.7 (CH), 74.1 (CH), 72.2 (CH), 71.9 (CH_2), 71.2 (CH), 71.1 (CH_2), 63.6 (CH_2), 63.4 (CH_2); m/z (EI) 326 (M^+)

1,5:3,6-Dianhydro-4-O-benzyl-D-arabinohexulose (**5**)

To a solution of **10** (1.34 g, 5.7 mmol) in dry CH_2Cl_2 (50 ml) containing powdered 4Å molecular sieves (1 g), tetra-*n*-propylammonium perruthenate (100 mg, 0.05 equivalents) and *N*-methylmorpholine *N*-oxide (1.0 g, 8.6 mmol). After 15 min at room temperature the mixture was filtered, concentrated and the residue purified by flash chromatography (80:20 petrol/EtOAc) to give *ketone* (**5**) (1.26 g, 95%) as colourless crystals, mp 96.5-97.5°C (EtOAc/petrol) (Anal. Calcd for $C_{13}H_{14}O_4$:C, 66.7; H, 6.02. Found: C, 66.8; H, 6.09.); ν_{max}/cm^{-1} (nujol) 1760; δ_H (C_6D_6) 3.49 (1H, dd, J 3, 10.5), 3.70 (1H, dd, J 3, 6), 3.81 (1H, d, J 10.5), 3.85 (1H, t, J 3), 4.11 (1H, d, J 16.5, part of AB quartet), 4.15-4.22 (3H, m), 4.33 (1H, d, J 12, part of AB quartet), 7.07-7.19 (5H, m, Ph); δ_C 202.9 (C=O), 136.6 (C), 128.5 (Ph), 128.2 (Ph), 127.9 (Ph), 79.0 (CH), 78.5 (CH), 72.9 (CH), 72.0 (CH_2), 71.6 (CH_2), 69.2 (CH_2); m/z (CI) 235 (M^++H).

Methyl 2,6-anhydro-3-O-benzyl-α-D-mannofuranoside (**13**), methyl 2,6-anhydro-5-O-benzyl-α-D-mannofuranoside (**14**) and methyl 2,6-anhydro-3,5-di-O-benzyl-α-D-mannofuranoside (**15**)

To a solution of diol (**12**) (176 mg, 1.0 mmol) in THF (2 ml) at 0°C was added NaH (36 mg, 1.50 mmol) and the resultant suspension was stirred at 0°C for 10 min before benzyl bromide (171 mg, 1.0 mmol) was added, followed by tetra-*n*-butylammonium iodide (37 mg, 0.1

mmol). The mixture was then stirred at room temperature for 19 h, then the mixture was concentrated *in vacuo* and purification of the residue by flash chromatography (1:1 EtOAc/petrol) gave:

(i) *methyl 2,6-anhydro-3, 5-di-O-benzyl-α -D-mannofuranoside* (**15**) (65 mg, 18%) as a colourless oil (Anal. Calcd for $C_{21}H_{24}O_5$:C, 70.77; H, 6.78. Found: C, 70.80; H, 6.86.); ν_{max}/cm^{-1} 2900, 1590, 1490; δ_H ($CDCl_3$) 3.40 (3H, s, OCH_3), 3.62 (1H, brd, $J_{6a,6e}$ and $J_{6a,5}$ 10, 6a-H), 3.96 (3H, m, 2-H, 5-H and 6e-H), 4.17 (1H, dd, $J_{3,2}$ 3, $J_{3,4}$ 6, 3-H), 4.42 (1H, d, $J_{4,3}$ 6, 4-H), 4.44 (1H, d, J 12, part of AB), 4.46 (1H, d, J 12, part of AB), 4.53 (1H, d, J 12, part of AB), 4.66 (1H, d, J 12, part of AB), 5.05 (1H, s, 1-H) and 7.32 (10H, m); m/z (CI), 325 (M^+-33).

(ii) *methyl 2, 6-anhydro-5-O-benzyl-α -D-mannofuranoside* (**14**) (6 mg, 6%) as a colourless oil (Found: C, 63.10; H, 6.81. $C_{14}H_{18}O_5$ requires C, 63.14; H, 6.81%); ν_{max}/cm^{-1} 3700, 1600; δ_H (CD_3OD) 3.39 (3H, s, OCH_3), 3.56 (1H, dd, J 12, J 13.5, 6a-H), 3.73 (1H, d, $J_{2,3}$ 3, 2-H), 3.93 (2H, m, 5-H and 6e-H), 4.32 (1H, dd, $J_{3,2}$ 3, $J_{3,4}$ 6, 3-H), 4.41 (1H,br d, $J_{4,3}$ 6, 4-H), 4.58 (1H, d, J 12, part of AB), 4.60 (1H, d, J 12, part of AB), 5.04 (1H, s, 1-H) and 7.30-7.36 (5H, m); m/z (CI) 267 (M^++H).

(iii) *methyl 2,6-anhydro-3-O-benzyl-α -D-mannofuranoside* (**13**) (122 mg, 46%) as a colourless oil (Anal. Calcd for $C_{14}H_{18}O_5$:C, 63.14; H, 6.81. Found: C, 62.90; H, 6.81.); ν_{max}/cm^{-1} 3550, 1600; δ_H (CD_3OD) 3.38 (3H, s, OCH_3), 3.49 (1H, dd, $J_{6a,6e}$ 9, $J_{6a,5}$ 10, 6a-H), 3.92 (1H, dd, $J_{6e,5}$ 7, $J_{6a,6e}$ 9, 6e-H), 3.94 (1H, d, $J_{2,3}$ 3, 2-H), 4.04 (1H, m, 5-H), 4.16 (1H, dd, $J_{2,3}$ 3, $J_{3,4}$ 6, 3-H), 4.28 (1H, dd, $J_{4,3}$ 6, $J_{4,5}$ 1, 4-H), 4.54 (1H, d, J 12, part of AB), 4.66 (1H, d, J 12, part of AB), 5.04 (1H, s, 1-H) and 7.30-7.38 (5H, m); m/z (CI) 267 (M^++H).

When this procedure was carried out using **12** (1.145 g, 6.5 mmol), benzyl ether (**13**) was obtained in 43% yield but the other components, (**14**) and (**15**), were not isolated or characterised.

Methyl 2,6-anhydro-3-O-benzyl-α-D-lyxo-hexofuranoside-5-ulose (**6**)

To a solution of alcohol (**13**) (700 mg, 2.6 mmol) in CH_2Cl_2 (25 ml) containing powdered 4Å molecular sieves (1 g) was added *N*-methylmorpholine *N*-oxide (463 mg, 3.95 mmol) and the mixture was stirred at room temperature for 10 min. Tetra-*n*-propylammonium perruthenate (46 mg, 0.132 mmol) was then added and the reaction mixture stirred at room temperature for 35 min. Removal of solvent *in vacuo* followed by purification of the residue by flash chromatography (20:80 EtOAc/petrol) gave ketone (**6**) (645 mg, 95%) as a colourless oil (Found: M^++H, 265.108. $C_{14}H_{17}O_5$ requires M, 265.107); ν_{max}/cm^{-1} 3150, 1760, 1500; δ_H (CD_3OD) 3.40 (3H, s, OCH_3), 4.12 (1H, d, J 17, part of AB), 4.26 (1H, d, $J_{4,3}$ 6, 4-H), 4.27 (1H, d, $J_{2,3}$ 3, 2-H), 4.54 (1H, d, J 17, part of AB), 4.57 (1H, d, J 12, part of AB), 4.64 (1H, dd, $J_{3,4}$ 6, $J_{3,2}$ 3, 3-H), 4.67 (1H, d, J 12, part of AB), 5.22 (1H, s, 1-H) and 7.30-7.40 (5H, m); m/z (CI) 265 (M^++H).

Methyl 2,6-anhydro-D-mannonate (**16**)

Oxygen was bubbled through a fine glass frit into a rapidly stirred solution of 1,5-anhydro-D-mannitol (**8**) (9.83 g, 60 mmol) in water (750 ml) containing sodium bicarbonate (5.04 g, 60 mmol) and 5% platinum on carbon (7.86 g, 80% w/w). After 15 h the mixture was filtered. The filtrate was then freeze dried *in vacuo* and the residue used without further purification in the next step.
Acetyl chloride (7 ml) was added dropwise to dry methanol (250 ml) kept at 0°C and to this solution was added the crude acid obtained by the procedure described above. The resulting solution was stirred at room temperature for 24 h. Solid sodium bicarbonate was then added until no further effervescence was observed and the resultant suspension was filtered. The filtrate was concentrated *in vacuo* and purification of the residue by flash chromatography (10:90 methanol/CH_2Cl_2) gave methyl ester (**16**) (2.85 g, 25%) as colourless needles, mp 102-104°C (EtOAc/petrol) (Anal. Calcd for $C_7H_{12}O_6$:C, 43.75; H,.44. Found: C, 43.60;H, 6.44.);ν_{max}/cm^{-1} (Nujol) 3300, 1730; δ_H (CD_3OD) 3.55-3.62 (2H, m, 6e-H and 4-H), 3.74 (3H, s, CH_3), 3.75 (1H, d, $J_{2,3}$ 7.5, 2-H), 3.87-3.98 (3H, m, 6a-H, 5-H and 3-H); m/z (EI) 192 (M^+).

2,6-Anhydro-D-mannonic acid (**17**)

A solution of methyl ester (**16**) (1.58 g, 8.21 mmol) in water/methanol (4:1, 80 ml) was cooled to 0°C and 1M potassium hydroxide (9 ml) was added dropwise over 30 min. The resultant solution was stirred at 0°C for a further 30 min and then neutralised by addition of DOWEX-50W-X8 ion exchange resin. The resin was removed by filtration and the filtrate concentrated *in vacuo*. The residue was then triturated with isopropanol (5 ml) to afford acid (**17**) (1.31 g, 90%) as colourless plates, mp 158-159°C (EtOH/Et_2O) (Anal. Calcd for $C_6H_{10}O_6$:C, 40.45; H, 5.66. Found: C, 40.20; H, 5.85.); ν_{max}/cm^{-1} (Nujol) 3200, 1715; δ_H (CD_3OD) 3.56 (1H, dd, $J_{4,3}$ 8, $J_{4,5}$ 4, 4-H), 3.58 (1H, dd, $J_{6a,6e}$ 13.5, $J_{6e,5}$ 2, 6e-H), 3.72 (1H, d, $J_{2,3}$ 8, 2-H), 3.87 (1H, dt, $J_{5,6e}$ 2, $J_{5,6a}$ 4, $J_{5,4}$ 4, 5-H), 3.90 (1H, br t, $J_{3,4}$ and $J_{3,2}$ 8, 3-H) and 3.95 (1H, dd, $J_{6a,6e}$ 13.5, $J_{6a,5}$ 4, 6a-H); m/z (EI) 178 (M^+).

2,6-Anhydro-D-mannono-1,4-lactone (**18**)

To acid (**17**) (688 mg, 3.86 mmol) was added diisopropylethylamine (0.81 ml, 4.64 mmol) followed by dry THF (70 ml) and the resultant solution was cooled to 0°C. Methyl chloroformate (0.33 ml, 4.25 mmol) was added dropwise over 5 min and the reaction mixture was stirred at room temperature for 36 h. Solvents were removed *in vacuo* and purification of the residue by flash chromatography (70:30 EtOAc/petrol) gave:
(i)the 1,4-lactone (**18**) (440 mg, 71%) as colourless needles, mp 112-114°C (EtOAc) (Anal. Calcd for $C_6H_8O_5$:C, 45.00; H, 5.04. Found: C, 45.40; H, 5.13.); ν_{max}/cm^{-1} 3300, 1780; δ_H (CD_3OD)

3.40 (1H, dd, $J_{6a,6e}$ 11, $J_{6a,5}$ 10, 6a-H), 3.97 (1H, br d, $J_{4,3}$ 6, 4-H), 4.12 (1H, dd, $J_{6a,6e}$ 11, $J_{6e,5}$ 7.5, 6e-H), 4.27 (1H, m, 5-H), 4.36 (1H, dd, $J_{3,2}$ 3, $J_{3,4}$ 6, 3-H) and 4.66 (1H, d, $J_{2,3}$ 3, 2-H); m/z (EI) 160 (M^+).
(ii)the 1,5-lactone (**19**) (26 mg, 4%) as a colourless gum (Found: M^+, 160.0371. $C_6H_8O_5$ requires M, 160.0372); ν_{max}/cm^{-1} 3400, 1750; δ_H (CD_3OD) 3.85-3.89 (2H, m, 5-H and 3-H), 4.01 (1H, dd, $J_{6a,6e}$ 9.5, $J_{6a,5}$ 3, 6a-H), 4.06 (1H, dd, $J_{6e,6a}$ 9.5, $J_{6e,5}$ 1, 6e-H), 4.20 (1H, dd, J 1.5, J 2, 4-H), 4.79 (1H, s, 2-H); m/z (EI) 160 (M^+).

2,6-Anhydro-3-O-benzoyl-D-mannono-1,4-lactone (**20**)

A solution of lactone (**18**) (84 mg, 0.52 mmol) in CH_2Cl_2 (2 ml) containing DMAP (64 mg, 0.52 mmol) was cooled to 0°C and treated with benzoyl chloride (0.61 ml, 0.52 mmol) and the resultant solution stirred at room temperature for 24 h. Dry methanol (one drop) was then added, the reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography (1:1 EtOAc/petrol) to afford two products:
(i) the 3,5-*bis*(benzoate) [*2, 6-anhydro-3, 5-di-O-benzoyl-D-mannono-1,4-lactone*] (34 mg, 18%) as colourless needles, mp 144-146°C (EtOAc/petrol) (Anal. Calcd for $C_{20}H_{16}O_7$:C, 65.21; H, 4.38. Found: C, 64.90; H, 4.28.); ν_{max}/cm^{-1} 1800, 1720; δ_H ($CDCl_3$) 3.85 (1H, dd, $J_{6a,6e}$ 12, $J_{6a,5}$ 10, 6a-H), 4.45 (1H, dd, $J_{6a,6e}$ 12, $J_{6e,5}$ 7, 6e-H), 4.59 (1H, d, $J_{2,3}$ 3, 2-H), 5.26 (1H, d, $J_{4,3}$ 6, 4-H), 5.41 (1H, dd, $J_{3,2}$ 3, $J_{3,4}$ 6, 3-H), 5.68 (1H, ddd, $J_{5,6a}$ 10, $J_{5,6a}$ 7, $J_{5,4}$ 6, 5-H), 7.41-8.20 (10H, m); m/z (CI) 369 (M^++H).
(ii) the monobenzoate (**20**) (63 mg, 46%) as a colourless solid, m.p. 120-121°C (EtOAc/petrol) (Anal. Calcd for $C_{13}H_{12}O_6$:C, 59.09; H, 4.58. Found: C, 59.10; H, 4.49.); ν_{max}/cm^{-1} 3400, 1800, 1705; δ_H ($CDCl_3$) 3.54 (1H, dd, $J_{6a,6e}$ 11.5, $J_{6a,5}$ 9, 6a-H), 4.28 (1H, dd, $J_{6e,6a}$ 11.5, $J_{6e,5}$ 7, 6e-H), 4.40 (1H, m, 5-H), 4.50 (1H, d, $J_{4,3}$ 6, 4-H), 5.08 (1H, d, $J_{2,3}$ 3, 2-H), 5.34 (1H, dd, $J_{3,4}$ 6, $J_{3,2}$ 3, 3-H), 7.40-8.10 (5H, m); m/z (CI) 265 (M^++H).

2,6-Anhydro-3-O-benzoyl-D-lyxo-5-hexulosono-1,4-lactone (**7**)

A solution of alcohol (**20**) (8 mg, 0.03 mmol) in CH_2Cl_2 (0.5 ml) was treated with powdered 4Å molecular sieves (10 mg) followed by pyridinium chlorochromate (15 mg, 0.07 mmol) and the reaction mixture was stirred at room temperature for 2.5 h. After this time the supernatant was decanted and the residue extracted with dry Et_2O (5 x 5 ml). The combined organic extracts were filtered through Florisil and concentrated *in vacuo* to give ketone (**20**) (5 mg, 65%) as a colourless gum (Found: M^++H, 263.0560. $C_{13}H_{11}O_6$ requires M, 263.0554); ν_{max}/cm^{-1} 1820, 1760, 1740; δ_H ($CDCl_3$) 4.42 (1H, d, J 17.5, part of AB), 4.60 (1H, d, J 17.5, part of AB), 4.79 (1H, d, $J_{2,3}$ 3, 2-H), 4.98 (1H, d, $J_{4,3}$ 6, 4-H), 5.67 (1H, dd, $J_{3,2}$ 6, $J_{3,4}$ 3.5, 3-H), 7.43-8.00 (5H, m); m/z (CI) 263 (M^++H).

1,5:3,6-Dianhydro-4-O-benzyl-1,2-dideoxy-2-O-(*tert*-butyldimethylsilyl)-D-arabinohexose (**21**)

To an ice cold solution of 1,5:3,6-dianhydro-4-O-benzyl-D-arabinohexulose (**5**) (142 mg, 0.60 mmol) in THF (2 ml) under N_2 was added KH (280 mg, 35% dispersion in oil, 2.4 mmol) followed by of *tert*-butyldimethylsilyl chloride.(120 mg, 0.79 mmol). The solution was stirred for 20 h and then quenched with saturated aqueous ammonium chloride (1 ml) and the product was extracted with CH_2Cl_2 (3 x 10 ml). The organic extracts were dried (Na_2SO_4) and purification by flash chromatography (90:10 petrol/EtOAc) gave silyl enol ether (**21**) (118 mg, 56%) as a pale yellow oil; ν_{max}/cm^{-1} (neat) 1462, 1359, 1253, 1140; δ_H ($CDCl_3$) 0.14 (3H, s), 0.15 (3H, s), 0.90 (9H, s), 3.86-3.96 (2H, m), 4.05 (1H, dd, J 4, 11), 4.16 (1H, d, J 11), 4.34 (1H, t, J 4), 4.67 (1H, d, J 12, part of AB), 4.73 (1H, d, J 12, part of AB), 6.22 (1H, d, J 1), 7.25-7.37 (5H, m, Ph); m/z (EI) 348 (M^+). This product was not characterised further.

Methyl 2,6-anhydro-3-O-benzyl-5,6-dehydro-5-O-*tert*-butyldimethylsilyl -α-D-lyxo-hexofuranoside (**22**)

To a suspension of KH (170 mg, 35% dispersion in oil, 1.46 mmol) in THF (2.5 ml) at -78°C under N_2 was added a solution of ketone (**6**) (112 mg, 0.42 mmol) in THF (1.5 ml), followed by *tert*-butyldimethylsilyl chloride (83 mg, 0.55 mmol). The resulting mixture was allowed to warm to room temperature over 2 h and after this time saturated aqueous ammonium chloride solution (1 ml) was added. The mixture was extracted with CH_2Cl_2 (5 x 5 ml), the organic extracts were dried (Na_2SO_4) and evaporated to an oil. Purification of the residue by flash chromatography (80:20 EtOAc/petrol) gave silyl enol ether (**22**) (126 mg, 80%) as a colourless oil (Found: M^+, 378.183. $C_{20}H_{30}O_5Si$ requires M, 378.186); ν_{max}/cm^{-1} 2900, 1450; δ_H (CD_3OD) 0.18 (6H, s), 0.92 (9H, s), 3.32 (3H, s), 4.01 (1H, m, 4-H), 4.10 (2H, m, 2-H and 3-H), 4.62 (1H, d, J 12, part of AB), 4.70 (1H, d, J 12, part of AB), 4.97 (1H, s, 1-H), 6.08 (1H, d, J 1.5, 6-H) and 7.30-7.40 (5H, m); m/z (EI) 378 (M^+).

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*Address correspondence to this author at the University of Bristol.

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