# The 'Off-template' Problem: Towards a General Solution

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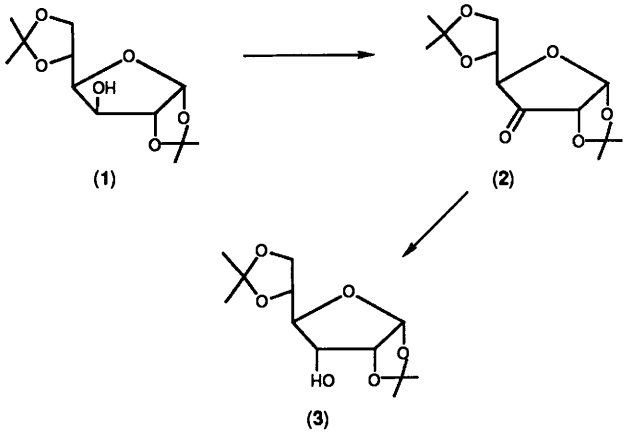
Wittig reaction of the t-butyldimethylsilylated C-3 ketone methyl 4,6-*O*-benzylidene-2-*O*-(t-butyldimethylsilyl)-α-D-*ribo*-hexopyranosid-3-uloside leads exclusively to C-2 alkenes, providing an efficient synthesis of these potentially useful intermediates. Alternatively, the corresponding t-butyldiphenylsilyl ether, prepared with complete regiospecificity from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside, gives a C-3 alkene on oxidation and Wittig reaction. Deprotection, hydrogenation and cyclization of this product leads to the *cis*-fused butyrolactone, methyl 4,6-*O*-benzylidene-3-deoxy-3-(ethoxycarbonyl)-2,3-butyrolacto-α-D-allopyranoside, which is alkylated stereospecifically to give methyl 4,6-*O*-benzylidene-3-deoxy-3-(prop-2-yloxycarbonyl)-2,3-butyrolacto-α-D-allopyranoside. This procedure provides a general solution to the 'off-template' problem of carbohydrate-based natural product synthesis.

Carbohydrates continue to provide a valuable source of cheap, optically pure starting materials for organic synthesis. A large number of different target molecules have succumbed to enantiospecific total synthesis using carbohydrate precursors, ensuring the technique a significant place in the repertoire of asymmetric synthesis.[1] For the majority of these undertakings, the carbohydrate itself provides all the necessary chiral centres of the target molecule, requiring the chemist only to devise means of introducing or removing excess functionality with as higher degree of stereocontrol as possible. However this approach is obviously not suitable for all target molecules since, in some cases, the original carbohydrate skeleton cannot provide all the requisite chiral centres. In these instances new asymmetric carbon atoms must be created. This poses a new problem for the chemist as the inherent chirality of the carbohydrate must now be used as a source of bias in a diastereoselective reaction. We have been exploring general routes for overcoming this 'off-template' problem and report herein, for the first time in full, one successful method for its solution.[2]




(1) (2) (3)

**Scheme 1.** Inversion of stereochemistry at C-3 of a glucose derivative.

## Results and Discussion

In seeking a general solution to the 'off-template' problem, we recognized that conformational bias plays an important role in controlling stereochemistry in many reactions in conventional carbohydrate chemistry. Thus, in the well-known sequence of reactions used to convert *gluco-* to *allo*-stereochemistry,[3] the stereospecificity of the reduction of (**2**) to (**3**) stems entirely from the shape of the substrate, inherent in its *cis*-fused [3.3.0.] bicyclic structure (Scheme 1). If similar structures could be devised in which one of the rings were made up of atoms not derived from the original carbohydrate, the chirality of the original ring would then provide the necessary bias for a diastereocontrolled reaction. To test this hypothesis we designed the *cis*-fused butyrolactone (**4**), as a representative of a series of compounds which would provide methods of preparing C-2, -3 or -4 branched chain precursors with chiral centres at the carbon atom adjacent to the carbohydrate template. Thus we expected butyrolactones such as (**4**) to undergo alkylation, or other reactions, at the activated methylene of the butyrolactone ring with complete stereospecificity. This would therefore provide a general solution to the 'off-template' problem.

Clearly, since we anticipated making use of (**4**) and its diastereo- and regioisomers in a number of synthetic projects, it was important to establish efficient routes to the compounds. Consequently a variety of avenues were explored in the hope of finding rapid entry-points to the system. These are summarized in Scheme 2.

Glucopyranoside derivatives acylated at C-2 were attractive starting materials for this synthesis due to their ready availability *via* the tin-mediated regioselective acylation method of Munavu and Szmant.[4] The simple C-2 acyl derivatives thus obtained would then be ideally placed to undergo an aldol-type condensation with a C-3 ketone. Starting from the diol (**5**), the esters (**6**) were prepared regiospecifically according to the published procedure.[4] Both (**6a**) and (**6b**) were resistant to oxidation under a number of standard conditions. Oxidation of (**6c**) was successfully achieved using pyridinium chlorochromate to give the ketone (**7c**) in 81% yield. The keto ester (**7c**) was then subjected to a variety of basic conditions. However, under all the conditions examined no aldol condensation was observed. In a related alternative approach, the 3-hydroxy group in (**6c**) was converted to the trifluoromethanesulphonate ester (**8c**).

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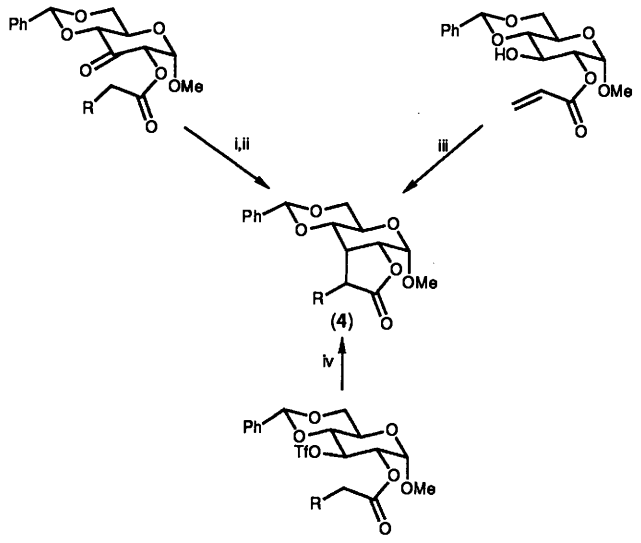
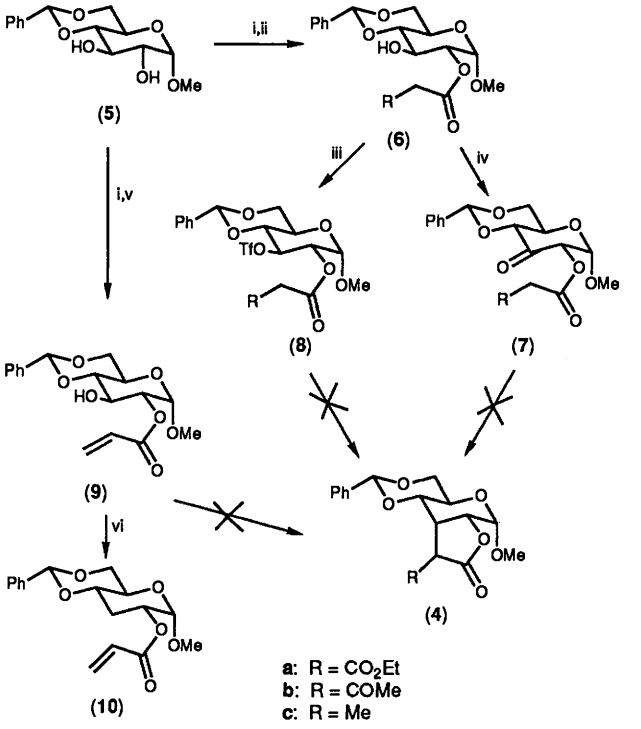


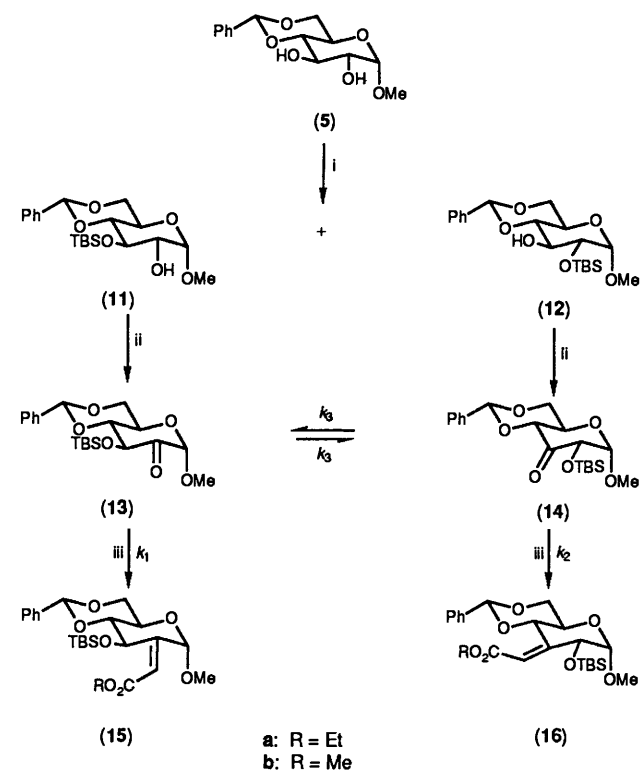
**Scheme 2.** Possible routes to a fused butyrolactone from C-2 esters. *Conditions:* i, condensation; ii, reduction; iii, radical cyclization; iv, base.



**Scheme 3.** Attempted routes to fused butyrolactones. *Reagents and conditions:* i, $Bu_2SnO$, dioxane; ii, $RCH_2COCl$, $Et_3N$; iii, $Tf_2O$; iv, PCC, $CH_2Cl_2$; v, acryloyl chloride; vi, $Bu_3SnH$, AIBN.

Treatment of (**8c**) with lithium hexamethyldisilazide (−78 °C to room temperature) followed by aqueous work-up caused cleavage of the propionate ester and displacement of the trifluoromethanesulphonate group in an intramolecular reaction leading to the epoxide, methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside in 91% yield. The failure of these nucleophilic reactions was presumably due to the inability of the pendant nucleophile to attain the correct angle of approach for an $S_N2$ reaction. An alternative approach to the problem, using radical chemistry was therefore considered.

The acryloyl ester (**9**) was prepared, *via* the stannylene



**Scheme 4.** Fraser-Reid's route to (**15**) and (**16**). *Reagents:* i, TBDMSCl, py; ii, PCC, $CH_2Cl_2$; iii, $Ph_3P{=}CHCO_2R$, MeCN.

method,[4] with a view to exploring a radical cyclization process. This compound was converted to the C-3 xanthate ester by the Barton and McCombie method[5] and was then treated with tributyltin hydride and a catalytic amount of AIBN in refluxing toluene. However the only product isolated from this reaction was the C-3 deoxy derivative (**10**). It was apparent that in this case, the C-3 radical was formed, but quenching by tin-hydride predominated over ring closure, probably due to the inability of the comparatively rigid acryloyl system to achieve the correct trajectory of approach. Various attempts were made to reduce the rate of quenching reaction by lowering the reaction temperature or by using the more bulky triphenyl tin hydride, but in none of these experiments was any of the cyclized product isolated.

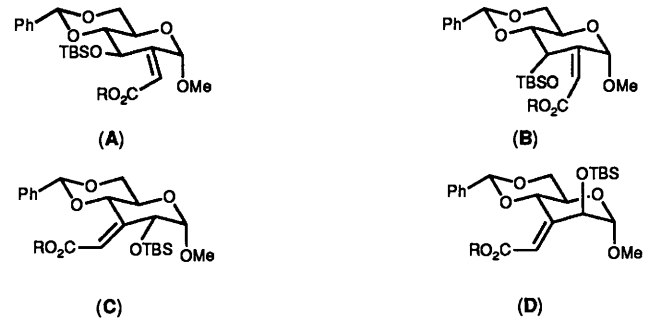
The failure of the radical cyclization approach was disappointing, particularly as this type of reaction is not without precedent.[6] In our particular example, however, the comparatively rigid acrylate system could act to prevent approach of the double bond to the radical centre, thus leading to the observed results. At this stage in the project, it became apparent that forming the butyrolactone ring *via* a carbon–carbon bond-forming reaction was fraught with difficulties. We therefore considered the alternative strategy of lactonization *via* carbon–oxygen bond formation, and prepared a 2-hydroxy-3-C-acetate derivative, which we expected to lactonise readily, repeating Fraser-Reid's synthesis of the required alkenic precursor (**16**).[7]

Thus the diol (**5**) was treated with t-butyldimethylsilyl chloride to give a mixture of (**11**) and (**12**) (3:1, respectively) (Scheme 4). These compounds were separated by column chromatography and oxidized separately to give (**13**) and (**14**) using pyridinium chlorochromate in dichloromethane. However, in direct contrast to the literature report, separate treatment of both (**13**) and (**14**) with an activated Wittig reagent in refluxing acetonitrile gave a single product.

Analysis of the spectral data for this product showed it to be a

**Table.** NMR spectral data for compound (**15**).

| δ/ppm | Multiplicity | Integration | *J*/Hz | Assignment |
|---|---|---|---|---|
| 7.50 | m | 2 | — | aromatic |
| 7.35 | m | 3 | — | aromatic |
| 6.38 | s | 1 | — | H-7 |
| 6.20 | d | 1 | 2.0 | H-8 |
| 5.51 | s | 1 | — | H-1 |
| 4.69 | dd | 1 | 2.0, 10.0 | H-3 |
| 4.28 | dd | 1 | 5.0, 10.0 | H-6′ |
| 4.01 | td | 1 | 5.0, 10.0 | H-5 |
| 3.73 | s | 3 | — | COOMe |
| 3.72 | t | 1 | 10.0 | H-6 |
| 3.48 | s | 3 | — | OMe |
| 3.45 | t | 1 | 10.0 | H-4 |
| 0.88 | s | 9 | — | t-Bu |
| 0.07 | s | 6 | — | 2 × MeSi |




**Scheme 5.**

silylated alkene with a 4,6-benzylidene group and an α-anomeric methoxy group. Only four structures [Scheme 5, (**A**)–(**D**)] were consistent with these features, but it was not clear, at first, which of the four had been formed. However analysis of the $^1$H NMR spectrum of the product led to an unambiguous answer to the problem (Table). The crucial feature of this spectrum was the presence of three coupling constants which were >9.5 Hz. All the structures shown in Scheme 5 would be expected to exhibit two coupling constants of this size: an axial–axial coupling between H-4 and H-5 and a geminal coupling between the diastereotopic pair of protons on C-6, but only structure (**A**) can exhibit a third large coupling due to the *trans*-diaxial relationship between H-3 and H-4 in this structure. Thus the Wittig product was identified as structure (**A**). The geometry of the double bond in this and the other alkenic products was assumed to be in accordance with the literature precedent,[7] but was not proven. Other spectral data were consistent with this structural assignment.

This unexpected result was in direct contrast to the course of the reaction reported originally, although re-evaluation by the original authors has confirmed our observations.[8] Treatment of either (**13**) or (**14**) with triethylamine in refluxing acetonitrile resulted in an equilibrium mixture of the two ketones [(**14**):(**13**), (4:1)]. Thus the sole formation of (**15**) cannot be explained on the basis of simple thermodynamics. It would appear, therefore, that under the Wittig reaction conditions (**13**) and (**14**) are in equilibrium (Scheme 4), but the rates at which the two ketones react with the Wittig reagent differ. Thus if $k_1 > k_2$, as would be expected on steric and electronic grounds, (**13**) would be removed from the (**13**) ⇌ (**14**) equilibrium more rapidly than (**14**) and more (**14**) would be converted into (**13**). Thus the formation of (**15**) as the sole product in virtually quantitative yield can be explained.

This serendipitous discovery made preparation of (**15**) a simple and high-yielding process, since it was no longer necessary to separate the two silylated regioisomers (**11**) and (**12**) prior to subjecting them to the oxidation/Wittig sequence. We were thus able to obtain the potentially useful intermediate (**15**) in 40% overall yield. Unfortunately the alkene required for the preparation of (**4**) was the C-3 alkene (**16**) and we were therefore required to devise an alternative strategy.

While this work was in hand, Hara *et al.* reported a similar problem on a related substrate and resolved the difficulty by using the Petersen reaction on the benzoate ester (**18**; R = PhCO).[9] Although we were able to repeat this work, in our hands this particular Petersen reaction proved unreliable and we therefore developed a different solution to the problem.

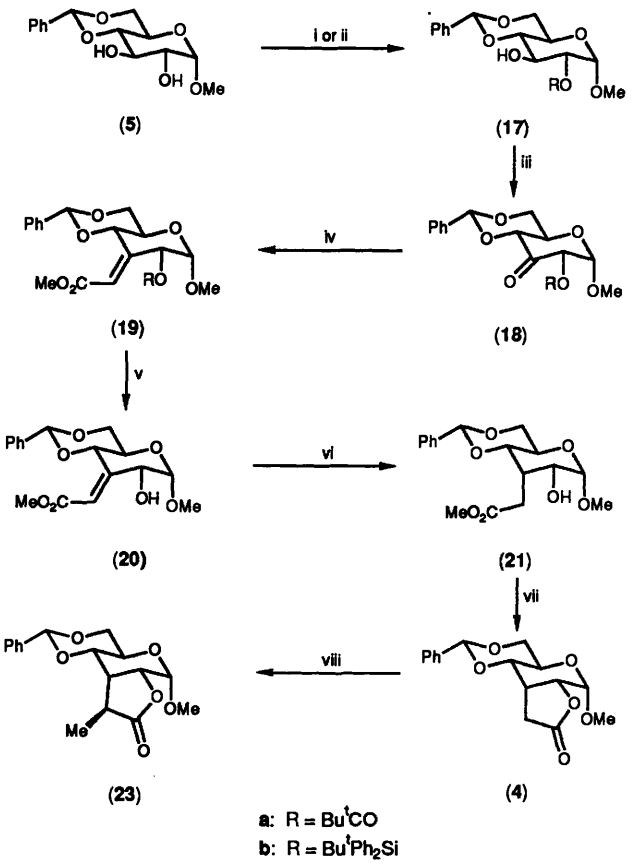
The key to the problem lay in the equilibrium established between (**13**) and (**14**) under the basic conditions of the Wittig reaction. If it were possible to slow the rate at which the equilibrium between (**13**) and (**14**) was established ($k_3/k_{-3}$) to a point where the rate of the desired Wittig reaction ($k_2$) was able to compete effectively with it, then the Wittig reaction would occur before silyl transfer could take place. One way of achieving this end was to increase the bulk of the C-2 protecting group and thereby decrease the rate at which it would migrate into the relatively more hindered environment at C-3. The protecting groups initially selected as suitable for this role were t-butyldiphenylsilyl ether and pivaloyl ester.

The C-2 pivaloyl ester (**17a**) was prepared *via* a stannylene with complete regiospecificity and in good yield, and was oxidized to the ketone (**18a**) using pyridinium chlorochromate. Treatment of (**18a**) under the Wittig conditions used previously led to a 3:1 mixture of products, with the desired C-3 alkene (**19a**) in excess. Alternatively the t-butyldiphenylsilyl ether (**17b**) was prepared, again with complete regiospecificity [in contrast to the reaction of (**5**) with t-butyldimethylsilyl chloride] by treating (**5**) with the corresponding silyl chloride in pyridine. Oxidation of (**17b**) following by Wittig reaction gave a 3:1 mixture of products with the C-3 alkene (**19b**) in excess.

With the required C-3 alkenes (**19a**) and (**19b**) in hand, the synthesis of the fused butyrolactone (**4**) was completed. The alkenes (**19a**) and (**19b**) were resistant to hydrogenation prior to deprotection of the C-2 oxygen, presumably due to steric hindrance. However, removal of the pivaloyl ester proved problematic and could only be achieved in 40% yield. This route was therefore abandoned. The silyl ether (**19b**) was deprotected in good yield under standard conditions and could be selectively hydrogenated at atmospheric pressure over Pd/C to give (**21**) as the sole product in excellent yield. Treatment of this compound with sodium hydride gave the desired butyrolactone (**4**) in 89% yield.

In order to confirm our prediction that alkylation of (**4**) would occur stereospecifically on the *exo*-face, the compound was treated with lithium hexamethyldisilazide at −78 °C and the resulting anion quenched with iodomethane. A single new product was obtained in 90% yield and was identified as (**23**) on the basis of an analysis of its $^1$H NMR spectrum. The $^1$H NMR spectrum of the unsubstituted butyrolactone (Scheme 7) contained a large axial-axial coupling between H-3 and H-8$_{endo}$ (13 Hz) and a smaller axial-equatorial coupling (9 Hz) between H-3 and H-8$_{exo}$. In the $^1$H NMR spectrum of (**23**) the H-3 proton and that on H-8 coupled with a coupling constant of 13 Hz indicating that the methyl group had replaced the equatorial proton and was therefore on the *exo*-face.

In conclusion, we have demonstrated a short and efficient synthesis of the fused butyrolactone (**4**) and have shown that compounds of this type can provide a useful solution to the 'off-template' problem. We have also uncovered an unusual kinetic/thermodynamic feature of a Wittig reaction as well as identifying an efficient, regiospecific, one-step protection for C-2 of 4,6-benzylidene glucose derivatives using the t-butyldiphenylsilyl protecting group.




**Scheme 6.** *Reagents:* i, $Bu_2SnO$, dioxane; $Bu^tCOCl$, $Et_3N$; ii, $Bu^tPh_2SiCl$, pyridine, imidazole; iii, PCC, $CH_2Cl_2$; iv, $Ph_3P{=}CH{-}CO_2Me$, MeCN; v, $Bu_4NF$, THF; vi, $H_2$, Pd–C; vii, NaH, THF; viii, $LiNTMS_2$, MeI, THF.


**Scheme 7.**

## Experimental

Microanalyses were determined by the departmental microanalytical service. M.p.s were recorded wtih a Kofler hot-stage micro melting point apparatus, and are uncorrected. Optical rotations were determined on a Perkin-Elmer 141 polarimeter, using a 10 cm cell. Low resolution mass spectra were recorded with a Kratos MS25 mass spectrometer and DS55 data system. High resolution mass spectra were recorded with a Kratos MS80 spectrometer and DS55 data system. IR spectra were recorded with a Perkin-Elmer 157G spectrometer. Mulls were prepared with Nujol. $^1H$ NMR spectra were recorded with either a Perkin-Elmer R34 (220 MHz) or a Bruker AM250 (250 MHz) spectrometer in $CDCl_3$ with TMS as internal standard, at room temperature. $^{13}C$ NMR spectra were recorded with a Bruker AM250 (62.9 MHz) spectrometer in $CDCl_3$. Thin layer chromatography (TLC) was performed on Merck Kieselgel 60 $GF_{254}$ aluminium-backed plates with the stated solvents. Plates were visualized under UV light (where appropriate) and/or sprayed with cerium(III) sulphate solution and flamed to develop. Merck Kieselgel 60 was used for flash column chromatography and all solvents were distilled before use. THF was dried over sodium and benzophenone, distilled and stored over calcium hydride. Ether (diethyl ether) and benzene were dried over sodium wire. Pyridine was heated under reflux over calcium hydride, distilled and stored. Light petroleum refers to the fraction b.p. 40–60 °C over potassium hydroxide pellets. Unless stated otherwise solvents and reagents were used as supplied by the manufacturers.

*Stannylene Derivative of Methyl* 4,6-O-*Benzylidene*-α-D-*glucopyranoside*.—Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (2.0 g, 7 mmol) was dissolved in dry benzene (150 ml) and dry methanol (15 ml) containing dibutyltin oxide (1.8 g, 7.0 mmol). The mixture was heated under reflux in a stream of dry nitrogen until it became clear. The solution was cooled and the solvents removed under reduced pressure to leave a white solid. This was not purified further.

*Methyl* 2-O-*Ethoxycarbonylacetoxy*-4,6-O-*benzylidene*-α-D-*glucopyranoside* (**6a**).—The stannylene derivative described above (5.14 g, 10 mmol) was dissolved in dry dioxane (100 ml) containing triethylamine (1.4 ml, 10 mmol) to which was added ethyl malonyl chloride (1.5 g, 10 mmol), dissolved in dioxane (10 ml). The reaction mixture was stirred for 12 h at room temperature, quenched with water, and then concentrated under reduced pressure. The residue was taken up in chloroform, washed with water and saturated sodium hydrogen carbonate, dried over magnesium sulphate, filtered and concentrated to give an oil which was purified by column chromatography (light petroleum–ethyl acetate, 1:1) to give compound (**6a**) as a white solid (1.2 g, 75%); m.p. 104–105 °C; $[\alpha]_D^{20}$ +82.4° ($c$ = 1 in $CHCl_3$) (Found: C, 57.8; H, 6.1. $C_{19}H_{24}O_9$ requires C, 57.6; H, 6.1%); $\nu_{max}$(mull) 3 451 (O–H), 1 738 ($CO_2Et$), and 1 716 $cm^{-1}$ (C=O); $\delta_H$ 7.51 (2 H, m, *o*-aromatics), 7.37 (3 H, m, *m*- and *p*-aromatics), 5.57 (1 H, s, PhC*H*), 4.90 (2 H, m, 1-H and 2-H), 4.31 (1 H, dd, *J* 4.0 and 9.5 Hz, 6-$H_{eq}$), 4.21 (1 H, td, *J* 2.5 and 9.5 Hz, 3-H), 4.21 (2 H, q, *J* 7.0 Hz, $CH_3CH_2$), 3.88 (1 H, td, *J* 4.5 and 9.5 Hz, 5-H), 3.78 (1 H, t, *J* 9.5 Hz, 6-$H_{ax}$), 3.50 (2 H, d, *J* 6.0 Hz, $COCH_2CO$), and 3.42 (3 H, s, $OCH_3$); *m*/*z* (CI reagent methane) 397 ($M^+$ + H).

*Methyl* 2-O-*Acetoacetyl*-4,6-O-*benzylidene*-α-D-*glucopyranoside* (**6b**).—To the stannylene derivative (5.14 g, 10 mmol) in dry dioxane (100 ml) was added triethylamine (5 drops) followed by diketene (0.8 ml; 10 mmol). The reaction mixture was allowed to stir at room temperature for 12 h. The solvent was then removed and the residue taken up in chloroform (200 ml), washed with water and saturated sodium hydrogen carbonate and dried over magnesium sulphate. The solution was filtered, concentrated and the resulting solid purified by column chromatography (chloroform–ethyl acetate) to give compound (**6b**) (2.9 g, 80%); m.p. 120–121 °C; $[\alpha]_D^{20}$ + 90.0° ($c$ = 1 in $CHCl_3$) (Found: C, 59.1; H, 6.1. $C_{18}H_{22}O_8$ requires C, 59.0; H, 6.1%); $\nu_{max}$(mull) 3 444 (O–H), 1 765 and 1 720 $cm^{-1}$ (C=O); $\delta_H$(400 MHz) 7.51 (2 H, m, *o*-aromatics), 7.37 (3 H, m, *m*- and *p*-aromatics), 5.56 (1 H, s, PhC*H*), 4.93 (2 H, m, 1-H and 2-H), 4.31 (1 H, dd, *J* 4.5 and 10.0 Hz, 6-$H_{eq}$), 4.19 (1 H, m, 3-H), 3.87 (1 H, td, *J* 4.5 and 10.0 Hz, 5-H), 3.78 (1 H, t, *J* 10.0 Hz, 6-$H_{ax}$), 3.61 (1 H, t, *J* 10.0 Hz, 4-H), 3.60 (2 H, d, *J* 4.0 Hz, $CH_3COCH_2$–), 3.42 (3 H, s, $OCH_3$), and 2.27 (3 H, s, $CH_3COCH_2$–); *m*/*z* (CI reagent methane) 367 ($M^+$ + H).

*Methyl* 4,6-O-*Benzylidene*-2-O-*propionyl*-α-D-*glucopyranoside* (**6c**).—To the stannylene compound described above (5.14 g, 10 mmol) in dry dioxane (100 ml) was added dry triethylamine (1.4 ml, 10 mmol) followed by propionyl chloride (0.92 g, 10 mmol). After being stirred overnight, the reaction mixture was concentrated under reduced pressure and the residue was taken up in chloroform (200 ml), washed with water (2 × 100 ml) and dried over anhydrous magnesium sulphate.

Filtration and concentration under reduced pressure gave an oil which was purified by column chromatography (light petroleum ethyl acetate, 3:2) to give compound (**6c**) as a clear oil (3.2 g, 94%); $[\alpha]_D^{20}$ + 134° (*c* = 1 in $CHCl_3$). (Found: C, 59.7; H, 6.5. $C_{17}H_{22}O_7$ requires C, 60.4; H, 6.5%); $\delta_H$ 7.5 (2 H, m, *o*-aromatics), 7.39 (3 H, m, *m*- and *p*-aromatics), 5.55 (1 H, s, PhC*H*), 4.95 (1 H, d, *J* 3.5 Hz, 1-H), 4.81 (1 H, dd, *J* 3.5 and 9.5 Hz, 2-H), 4.30 (1 H, dd, *J* 3.8 and 9.0, 6-$H_{eq}$), 4.18 (1 H, t, *J* 9.5 Hz, 3-H), 3.83 (1 H, m, 5-H), 3.74 (1 H, d, *J* 9.0 Hz, 6-$H_{ax}$), 3.55 (1 H, t, *J* 9.5 Hz, 4-H), 3.40 (3 H, s, $OCH_3$), 2.44 (2 H, q, *J* 7.5 Hz, $CH_2CH_3$), and 1.17 (3 H, t, *J* 7.5 Hz, $CH_2CH_3$); *m/z* (EI) 337 ($M^+$ − H).

*Methyl* 2-O-*Acryloyl*-4,6-O-*benzylidene*-α-D-*glucopyranoside* (**9**).—The stannylene derivative from above (1.0 g, 1.95 mmol) was dissolved in dry dioxane (50 ml) containing acryloyl chloride (0.16 ml, 1.97 mmol) and dry triethylamine (0.3 ml, 2.0 mmol), and the mixture was stirred at room temperature. After 30 min, no starting material remained by TLC (light petroleum–diethyl ether, 1:1) and one major spot was observed along with a faint, higher-running component, assumed to be the di-acylated material. The solvent was removed under reduced pressure and the residues were taken up in chloroform (40 ml) and washed with water (2 × 20 ml). The organic layer was dried over sodium sulphate and concentrated to leave an off-white solid (1.4 g). Purification by flash column chromatography (silica; ether–light petroleum, 1:1) left a colourless, viscous oil (500 mg, 75%); $\delta_H$ 7.35–7.55 (5 H, m, aromatics), 6.52 and 6.23 (1 H, ABX, *J* 1.5, 10.0, and 17 Hz, =$CH_2$), 5.92 (1 H, dd, *J* 1.5 and 10.0 Hz, C*H*=$CH_2$), 5.57 (1 H, s, PhC*H*), 5.05 (1 H, d, *J* 3.5, 1-H), 4.89 (1 H, dd, *J* 3.5 and 9.5 Hz, 2-H), 4.24 (1 H, t, *J* 9.5 Hz, 3-H), 4.11 (1 H, dd, *J* 7.5 and 9.0 Hz, 6-$H_{eq}$), 3.79 (1 H, t, *J* 9.0 Hz, 6-$H_{ax}$), 3.87 (1 H, td, *J* 9.0, 9.0, and 4.0 Hz, 5-H), 3.60 (1 H, t, *J* 9.5 Hz, 4-H), 3.41 (3 H, s, $OCH_3$), and 2.53 (1 H, br s, O-H); $\delta_C$ 165.7 (C=O), 136.8 (*ipso*-aromatic), 132.2 ($CH_2$=), 129.2 and 126.2 (*o*- and *m*-aromatics), 127.5 (=CH), 101.9 (PhCH), 97.4 (C-1), 81.2 (C-4), 73.6 (C-2), 68.7 (C-6), 68.5 (C-3), 61.9 (C-5), and 55.3 ($OCH_3$); *m/z* 335 ($M^+$ + H), 305 ($M^+$ − OMe); CI ($NH_3$) 337 ($M^+$ + H), 305 ($M^+$ − OMe) (Found: $M^+$, 336.1247. $C_{17}H_{22}O_7$ requires 336.1251).

*Methyl* 4,6-O-*Benzylidene*-3-O-*propionyl*-α-D-ribo-*hexopyranosid*-3-*ulose* (**7c**).—Methyl 4,6-*O*-benzylidene-3-*O*-propionyl-α-D-glucopyranoside (1.0 g, 3 mmol) was dissolved in dry dichloromethane (100 ml) and pyridinium chlorochromate (2.6 g, 12 mmol) and anhydrous sodium acetate (0.5 g) were added to the solution. The mixture was heated under reflux with vigorous stirring for 12 h and then diluted with ethyl acetate (100 ml). The whole mixture was passed through a short silica column eluting with ethyl acetate. Evaporation of the solvent gave compound (**7c**) as a white crystalline solid (0.8 g, 81%); $[\alpha]_D^{20}$ + 59° (*c* = 1 in $CHCl_3$) (Found: C, 60.8; H, 6.2. $C_{17}H_{20}O_7$ requires C, 60.7; H, 6.0%); *m/z* 337 ($M^+$ + H).

*Methyl* 4,6-O-*Benzylidene*-3-O-(*t-butyldimethylsilyl*)-α-D-*glucopyranoside* (**11**) *and Methyl* 4,6-O-*Benzylidene*-2-O-(*t-butyldimethylsilyl*)-α-D-*glucopyranoside* (**12**).—Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (8.4 g, 30 mmol) and t-butyldimethylsilyl chloride (4.5 g, 30 mmol) were dissolved in dry pyridine (100 ml) and stirred at room temperature for 12 h. The mixture was then concentrated at reduced pressure and the residue was taken up in ethyl acetate. The resulting solution was washed with water, dried over magnesium sulphate, filtered and concentrated. The residue was taken up in ethyl acetate–light petroleum (1:1), filtered (to remove starting material), and then concentrated to give an oil which was chromatographed to give compound (**11**) (1.5 g, 23%) and compound (**12**) (5.0 g, 66%) both as oils which crystallized on standing.

*Compound* (**11**): M.p. 78–80 °C; $[\alpha]_D^{20}$ + 66.5° (*c* = 1 in $CHCl_3$) (Found: C, 60.9; H, 8.3. $C_{20}H_{32}O_6Si$ requires C, 60.1; H, 8.1%); $\nu_{max}$ 3 493 $cm^{-1}$ (O–H); $\delta_H$ 7.48 (2 H, m, *o*-aromatics), 7.35 (3 H, m, *m*- and *p*-aromatics), 5.53 (1 H, s, PhC*H*), 4.65 (1 H, d, *J* 4.0 Hz, 1-H), 4.29 (1 H, dd, *J* 4.5 and 9.5 Hz, 6-$H_{eq}$), 4.00 (1 H, dt, *J* 9.5 and 2.5 Hz, 3-H), 3.84 (1 H, td, *J* 4.5 and 9.5 Hz, 5-H), 3.73 (1 H, t, *J* 9.5 Hz, 6-$H_{ax}$), 3.67 (1 H, dd, *J* 4.0 and 9.5 Hz, 2-H), 3.50 (1 H, t, *J* 9.5 Hz, 4-H), 3.43 (3 H, s, $OCH_3$), 2.36 (1 H, d, *J* 2.5 Hz, OH). 0.91 [9 H, s, $(CH_3)_3CSi$], and 0.13 [6 H, s, $(CH_3)_2Si$]. *m/z* (CI reagent ammonia) 397 ($M^+$ + H).

*Compound* (**12**): M.p. 80–81 °C; $[\alpha]_D^{20}$ + 85.7° (*c* = 1 in $CHCl_3$) (Found: C, 60.9; H, 8.1. $C_{20}H_{32}O_6Si$ requires C, 60.1; H, 8.1%). $\nu_{max}$ 3 518 $cm^{-1}$ (O–H); $\delta_H$ 7.48 (2 H, m, *o*-aromatics), 7.35 (3 H, m, *m*- and *p*-aromatics), 5.50 (1 H, s, PhC*H*), 4.80 (1 H, d, *J* 4.0 Hz, 1-H), 4.27 (1 H, dd, *J* 5.0 and 9.0 Hz, 6-$H_{eq}$), 3.90 (1 H, t, *J* 9.0, 3-H), 3.81 (1 H, td, *J* 5.0 and 9.0 Hz, 5-H), 3.72 (1 H, t, *J* 9.0 Hz, 6-$H_{ax}$), 3.58 (1 H, dd, *J* 4.0 and 9.0 Hz, 2-H), 3.44 (3 H, s, $OCH_3$), 3.43 (1 H, t, *J* 9.0 Hz, 4-H), 0.86 [9 H, s, $(OCH_3)_3CSi$], and 0.095 and 0.015 [each 3 H, s, $(CH_3)_2Si$]; *m/z* (CI reagent ammonia) 397 ($M^+$ + H).

*Methyl* 4,6-O-*Benzylidene*-2-O-(*t-butyldimethylsilyl*)-α-D-ribo-*hexopyranosid*-3-*uloside* (**14**).—Methyl 4,6-O-benzylidene-2-O-(t-butyldimethylsilyl)-α-D-glucopyranoside (3.9 g, 10 mmol) was dissolved in dry dichloromethane (250 ml) and pyridinium chlorochromate (8.5 g, 40 mmol) and anhydrous sodium acetate (2.0 g) were added. The mixture was heated under reflux for 12 h with vigorous mechanical stiring. The reaction mixture was then diluted with ethyl acetate (200 ml) and the whole mixture was passed through a short silica column, eluting with ethyl acetate. Evaporation of the solvent gave compound (**14**) (3.0 g, 79%); $[\alpha]_D^{20}$ + 56° (*c* = 1 in $CHCl_3$) (Found: C, 60.8; H, 6.2. $C_{20}H_{30}O_6Si$ requires C, 60.7; H, 6.0%); $\nu_{max}$(mull) 1 750 $cm^{-1}$ (C=O); $\delta_H$ 7.49 (2 H, m, *o*-aromatics), 7.35 (3 H, m, *m*- and *p*-aromatics), 5.54 (1 H, s, PhC*H*), 5.03 (1 H, d, *J* 4.5 Hz, 1-H), 4.45 (1 H, dd, *J* 4.5 and 1.5 Hz, 2-H), 4.40 (1 H, dd, *J* 4.5 and 10.0 Hz, 6-$H_{eq}$), 4.23 (1 H, dd, *J* 1.5 and 10.0 Hz, 4-H), 4.07 (1 H, td, *J* 4.5 and 10.0 Hz, 5-H), 3.92 (1 H, t, *J* 10.0 Hz, 6-$H_{ax}$), 3.45 (3 H, s, $OCH_3$), 0.91 [9 H, s, $(CH_3)_3CSi$], 0.17 [3 H, s, $(CH_3)Si$], and 0.07 [3 H, s, $(CH_3)Si$]; $\delta_C$ 196.7 (C-2, 136.4, *ipso*-aromatics), 129.2 (*p*-aromatic), 128.1 and 126.4 (*o*- and *m*-aromatics), 104.0 and 101.9 (C-1 and PhCH), 81.9, 76.6, 65.2 (C-2, C-4, and C-5), 69.5 (C-6), 55.9 ($OCH_3$), 25.7 [$(CH_3)_3CSi$], 18.5 [$(CH_3)_3CSi$], and −4.4 and −5.2 [$(CH_3)_2Si$]. *m/z* (CI reagent ammonia) 395 ($M^+$ + H).

*Methyl* 4,6-O-*Benzylidene*-3-O-(*t-butyldimethylsilyl*)-α-D-lyxo-*hexopyranosid*-2-*uloside* (**13**).—Compound (**13**) was prepared by the method described above in 90% yield; m.p. 105–107 °C; $[\alpha]_D^{20}$ + 18° (*c* = 1 in $CHCl_3$). (Found: C, 61.1; H, 7.3. $C_{20}H_{30}O_6Si$ requires C, 60.9; H, 7.6%). $\nu_{max}$(mull) 1 750 $cm^{-1}$ C=O); $\delta_H$ 7.49 (2 H, m, *o*-aromatics), 7.36 (3 H, m, *m*- and *p*-aromatics), 5.55 (1 H, s, PhC*H*), 4.74 (1 H, s, 1-H), 4.69 (1 H, d, *J* 10.0 Hz, 3-H), 4.39 (1 H, dd, *J* 5.0 and 10.0 Hz, 6-$H_{eq}$), 4.18 (1 H, td, *J* 5.0 and 10.0 Hz, 5-H), 3.80 (1 H, t, *J* 10.0 Hz, 4-H), 3.72 (1 H, t, *J* 10.0 Hz, 6-$H_{ax}$), 3.47 (3 H, s, $OCH_3$), 0.90 [9 H, s, $(CH_3)_3CSi$], 0.14 [3 H, s, $(CH_3)Si$], and 0.04 [3 H, s, $(CH_3)Si$]; $\delta_C$ 197.8 (C-3), 137.0 (*ipso*-aromatic), 128.9 (*p*-aromatic), 128.1 and 126.0 (*m*- and *o*-aromatics), 102.0 and 101.2 (C-1 and PhCH), 83.5, 76.2, 63.3 (C-3, C-4, and C-5), 68.8 (C-6), 55.7 ($OCH_3$), 25.7 [$(CH_3)_3CSi$], 18.6 [$(CH_3)_3CSi$], −4.9 [$(CH_3)Si$)], and −5.3 [$(CH_3)Si$]; *m/z* (CI reagent ammonia) 395 ($M^+$ + H).

*Methyl* 4,6-O-*Benzylidene*-3-O-(*t-butyldimethylsilyl*)-2-*deoxy*-2-C-(*methoxycarbonylmethylene*)-α-D-ribo-*hexopyranoside* (**15b**).—Methyl 4,6-*O*-benzylidene-3-*O*-(t-butyldimethyl silyl)-α-D-*ribo*-hexopyranosid-2-uloside (1.6 g, 4 mmol) and

methoxycarbonylmethylene triphenylphosphorane (3.5 g, 10 mmol) were dissolved in dry acetonitrile (50 ml) and heated under reflux for 6 h under a nitrogen atmosphere. After being cooled, the reaction mixture was concentrated under reduced pressure and the residue was taken up in diethyl ether. The resulting mixture was filtered and the filtrate concentrated. The product (**15b**) was obtained as a white crystalline solid (1.7 g, 93%) by column chromatography (light petroleum–ethyl acetate, 4.1); m.p. 100–102 °C $[\alpha]_D^{20}$ − 46° (*c* = 1 in $CHCl_3$) (Found: C, 61.6; H, 7.4. $C_{23}H_{34}O_7Si$ requires C, 61.3; H, 7.6%); $\nu_{max}$(mull) 1 725 $cm^{-1}$ (C=O); $\delta_H$ 7.48 (2 H, m, *o*-aromatics), 7.36 (3 H, m, *m*- and *p*-aromatics), 6.38 (1 H, d, *J* 0.5 Hz, 1-H), 6.20 (1 H, dd, *J* 0.5 and 2.0 Hz, C=C*H*), 5.51 (1 H, s, PhC*H*), 4.69 (1 H, ddd, *J* 0.5, 2.0, and 9.5 Hz, 3-H), 4.28 (1 H, dd, *J* 5.0 and 10.0, 6-$H_{eq}$), 4.01 (1 H, td, *J* 5.0 and 10.0 Hz, 5-H), 3.73 (3 H, s, $CO_2CH_3$), 3.72 (1 H, t, *J* 10.0 Hz, 6-$H_{ax}$), 3.48 (3 H, s, $OCH_3$), 3.45 (1 H, t, *J* 10.0 Hz, 4-H), 0.88 [9 H, s, $(CH_3)_3Si$], and 0.07 and 0.01 [each 3 H, s, $(CH_3)_2Si$]; $\delta_C$ 166.0 (C=O), 153.2 (C-2), 137.5 (*ipso*-aromatic), 129.0 (*p*-aromatic), 128.1 and 126.3 (*o*- and *m*-aromatics), 115.6 (=CH), 101.9 (PhCH), 96.2 (C-1), 84.2, 70.7, and 634.1 (C-3, C-4, and C-5), 69.0 (C-6), 55.3 ($OCH_3$), 51.5 ($CO_2CH_3$), 25.8 [$(CH_3)_3CSi$], 18.4 [$(CH_3)_3CSi$], and −4.5 and 5.0 [$(CH_3)_2Si$]; *m*/*z* (CI reagent ammonia) 451 ($M^+$ + H).

*Methyl* 4,6-O-*Benzylidene*-3-O-(*t-butyldimethylsilyl*)-2-*deoxy*-2-C-(*ethoxycarbonylmethylene*)-α-D-ribo-*hexopyranoside* (**15a**).—Methyl 4,6-*O*-benzylidene-2-*O*-(t-butyldimethylsilyl)-α-D-hexopyranosid-3-uloside (0.2 g, 0.5 mmol) and ethoxycarbonylmethylene triphenylphosphorane (0.35 g, 1 mmol) were dissolved in dry acetonitrile (40 ml) under a nitrogen atmosphere and heated under reflux for 12 h. The mixture was cooled and concentrated, and the residue was taken up in ether. After filtration, the solution was concentrated and purified by column chromatography (light petroleum–ethyl acetate, 8:2), to give compound (**15a**) as an oil (0.21 g, 91%); $[\alpha]_D^{20}$ − 42° (*c* = 1 in $CHCl_3$) (Found: C, 61.7; H, 7.7. $C_{24}H_{36}O_7$ requires C, 62.0; H, 7.8%); $\nu_{max}$(film) 1 725 $cm^{-1}$ (C=O); $\delta_H$ 7.48 (2 H, m, *o*-aromatics), 7.36 (3 H, m, *p*- and *m*-aromatics), 6.37 (1 H, d, *J* 0.5 Hz, 1-H), 6.19 (1 H, dd, *J* 0.5 and 2.0 Hz, C=CH), 5.51 (1 H, s, PhC*H*), 4.69 (1 H, ddd, *J* 0.5, 2.0, and 9.5 Hz, 3-H), 4.28 (1 H, dd, *J* 5.0 and 10.0 Hz, 6-$H_{eq}$), 4.19 (2 H, m, $OCH_2CH_3$), 4.00 (1 H, td, *J* 5.0 and 10.0 Hz, 5-H), 3.72 (1 H, t, *J* 10.0 Hz, 6-$H_{ax}$), 3.48 (3 H, s, $OCH_3$), 3.45 (1 H, t, *J* 9.5 Hz, 4-H), 1.30 (3 H, t, *J* 7.0 Hz, $OCH_2CH_3$), 0.88 [9 H, s, $(CH_3)_3CSi$], 0.72 (3 H, s, $CH_3Si$), and 0.012 (3 H, s, $CH_3Si$).

*Wittig Reaction of Methyl* 4,6-O-*benzylidene*-2-O-(*t-butyldimethylsilyl*)-α-D-lyxo-*hexopyranosid*-3-*uloside* (**14**).—The title compound (**14**) (0.39 g, 1 mmol) and methoxycarbonylmethylene triphenylphosphorane (0.7 g, 2 mmol) were dissolved in dry acetonitrile (40 ml) and heated under reflux in a nitrogen atmosphere for 12 h. The mixture was then concentrated under reduced pressure and the residue taken up in ether, filtered and concentrated to give a crude product which was purified by column chromatography (light petroleum–ethyl acetate, 9:1). Yield 0.4 g (91%). The product was identical in all respects to compound (**15b**); m.p. 98–100 °C; $[\alpha]_D^{20}$ − 46° (*c* = 1 in $CHCl_3$).

*Methyl* 4,6-O-*Benzylidene*-3-O-(*t-butyldimethylsilyl*)-2-*deoxy*-2-C-(*methoxycarbonylmethylene*)-α-D-ribo-*hexopyranoside* (*Without Isolation of Intermediates*).—Methyl α-D-glucopyranoside (5.64 g, 20 mmol), imidazole (4.0 g, 60 mmol) and t-butyldimethylsilyl chloride (3.62 g, 24 mmol) were dissolved in dry *N*,*N*-dimethylformamide (50 ml) and the mixture was stirred at room temperature (silica gel guard tube) until TLC (light petroleum–ethyl acetate, 2:1) showed no starting material and two new spots $R_F$ 0.85 and 0.63. The mixture was then diluted with ether (200 ml) and washed with water (3 × 100 ml). The organic layer was filtered through a silica bed and the filtrate dried over anhydrous sodium sulphate. Evaporation of the solvent left a colourless oil (7.1 g, 90%).

A mixture of the above two alcohols (1.5 g, 3.8 mmol) was dissolved in dry dichloromethane (100 ml). Solid pyridinium chlorochromate (3.28 g, 15.2 mmol), anhydrous sodium acetate (0.75 g) and Hyflo (3.3 g) were added and the mixture was heated at 40 °C under a stream of dry nitrogen with vigorous stirring. After 14 h, TLC (light petroleum–ethyl acetate, 4:1) showed no starting material with two new spots almost overlapping at $R_F$ 0.59. The mixture was diluted with ethyl acetate (100 ml) and stirred for 10 min. After being cooled the mixture was filtered through a short silica column, eluting with more ethyl acetate. Concentration of the filtrate under reduced pressure left a colourless oil, (1.1 g, 73%).

The mixture from above (0.39 g, 1.0 mmol) was dissolved in dry acetonitrile (25 ml) containing the ylide ($Ph_3P$=$CHCO_2Me$) (0.7 g, 2 mmol). The mixture was heated under reflux in a stream of dry nitrogen until TLC (light petroleum–ethyl acetate, 4:1) showed no starting material and one new product $R_F$ 0.74. The mixture was cooled and the solvent removed under reduced pressure. The residues were triturated with ether and the solids filtered off. Evaporation of the filtrate left an off-white solid (1.4 g) which was purified by flash column chromatography (light petroelum–ethyl acetate, 9:1) to give a colourless oil (275 mg, 61%) which solidified on standing. The product was identical in all aspects to that obtained previously.

*Methyl* 4,6-O-*Benzylidene*-2-O-*pivaloyl*-α-D-*glucopyranoside* (**17a**).—To a solution of the above stannylene compound (5.14 g, 10 mmol) in dry dioxane (50 ml) was added dry triethylamine (1.4 ml, 10 mmol) and pivaloyl chloride (1.2 g, 10 mmol). The reaction mixture was stirred at room temperature for 4 h and then concentrated. The residue was taken up in dichloromethane (100 ml), washed with water and dried over magnesium sulphate. After removal of the solvent, the product was obtained as a crystalline solid by column chromatography (light petroleum–ethyl acetate). Yield (3.0 g, 83%); m.p. 152–154 °C; $[\alpha]_D^{20}$ + 46° (*c* = 1 in $CHCl_3$) (Found: C, 62.2; H, 7.3. $C_{19}H_{26}O_7$ requires C, 62.3; H, 7.1%); $\nu_{max}$(mull) 3 510 (O–H), 1 725 $cm^{-1}$ ($CO_2Bu^t$); $\delta_H$ 7.49 and 7.37 (5 H, m, aromatics), 5.55 (1 H, s, PhC*H*), 4.93 (1 H, d, *J* 4.0 Hz, 1-H), 4.74 (1 H, dd, *J* 4.0 and 10.0 Hz, 2-H), 4.29 (1 H, dd, *J* 4.0 and 9.0 Hz, 6-$H_{eq}$), 4.19 (1 H, dt, *J* 2.0 and 10.0 Hz, 3-H), 3.75 (1 H, td, *J* 4.0 and 10.0 Hz, 5-H), 3.76 (1 H, t, *J* 10.0 Hz, 4-H), 3.56 (1 H, t, *J* 9.5 Hz, 6-$H_{ax}$), 3.38 (3 H, s, $OCH_3$), 1.58 (1 H, br s, O-H), and 1.24 [9 H, s, $C(CH_3)_3$]; $\delta_C$ 178.1 ($CO_2Bu^t$), 137.1 (*ipso*-aromatic), 129.1 (*p*-aromatic), 128.2 and 126.3 (*o*- and *m*-aromatics), 101.9 and 97.6 (PhCH and C-1), 81.4, 73.4, 68.8, and 62.0 (C-2, C-3, C-4, and C-5), 68.9 (C-6), 55.5 ($OCH_3$), 38.8 [$C(CH_3)_3$], and 27.0 [$C(CH_3)_3$]; *m*/*z* (CI reagent ammonia) 367 ($M^+$ + H).

*Methyl* 4,6-O-*Benzylidene*-2-O-(*t-butyldiphenylsilyl*)-α-D-*glucopyranoside* (**17b**).—Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (2.8 g, 10 mmol) and t-butyldiphenylsilylchloride (2.7 g, 10 mmol) were dissolved in dry pyridine (50 ml) and imidazole (1.4 g, 20 mmol) was added. After 6 h, TLC (ethyl acetate–light petroleum, 1:4) showed the presence of a new product. The reaction mixture was concentrated under reduced pressure and the residue was taken up in ethyl acetate, washed with water, dried over magnesium sulphate and concentrated under reduced pressure to give a crude product. Column chromatography (ethyl acetate–light petroleum, 1:9) gave pure compound (**17b**) (4.0 g, 94%). $[\alpha]_D^{20}$ + 176° (*c* = 1.0 in $CHCl_3$) (Found: C, 70.1; H, 7.3. $C_{30}H_{36}O_6Si$ requires C, 69.2; H, 6.9%); $\nu_{max}$(film) 3 480br $cm^{-1}$ (O–H); $\delta_H$ 7.73 (6 H, m, aromatics),

7.40 (9 H, m, aromatics), 5.46 (1 H, s, PhC*H*), 4.26 (1 H, d, *J* 4.0 Hz, 1-H), 4.20 (1 H, dd, *J* 5.0 and 10.0 Hz, 6-$H_{eq}$), 4.16 (1 H, t, *J* 9.0 Hz, 3-Hz), 3.80 (1 H, td, *J* 5.0 and 10.0 Hz, 5-H), 3.70 (1 H, dd, *J* 4.0 and 9.0 Hz, 2-H), 3.62 (1 H, t, *J* 10.0 Hz, 6-$H_{ax}$), 3.38 (1 H, t, *J* 9.0 Hz, 4-H), 3.28 (3 H, s, $OCH_3$), and 1.09 [9 H, s, $(CH_3)_3CSi$]; $\delta_C$ 137–126 (aromatics), 101.7 and 100.1 (C-1 and PhCH), 81.0 (C-4), 74.5 and 71.1 (C-2 and C-3), 68.9 (C-6), 62.0 (C-5), 55.0 ($OCH_3$), 26.9 [$C(CH_3)_3$], and 19.4 [$C(CH_3)_3$]; *m/z* (CI reagent ammonia) 520 ($M^+$).

*Methyl* 4,6-O-*Benzylidene*-2-O-*pivaloyl*-α-D-ribo-*hexopyranosid*-3-*uloside* (**18a**).—Methyl 4,6-*O*-benzylidene-2-*O*-pivaloyl-α-D-glucopyranoside (2.2 g, 6 mmol), pyridinium chlorochromate (5.3 g, 25 mmol) and anhydrous sodium acetate (0.5 g) were heated in dichloromethane (150 ml) for 12 h. The reaction mixture was diluted with diethyl ether (150 ml) and stirred vigorously for 5 min. The solution was passed through a short silica column eluting with ethyl acetate. Evaporation of the solvent gave compound (**18a**) as an oil (2.2 g, quant.); $[\alpha]_D^{20}$ + 35° (*c* = 2 in $CHCl_3$) (Found: C, 62.2; H, 6.8. $C_{19}H_{24}O_7$ requires C, 62.6; H, 6.6%); $\nu_{max}$($CHCl_3$) 1 765 (C=O), 1 730 $cm^{-1}$ (OCOBu$^t$); $\delta_H$ 7.50 and 7.36 (5 H, m, aromatics), 5.58 (1 H, s, PhC*H*), 5.36 (1 H, dd, *J* 1.5 and 4.0 Hz, 2-H), 5.21 (1 H, d, *J* 4.0 Hz, 1-H), 4.42 (1 H, dd, *J* 5.0 and 10.0 Hz, 6-$H_{eq}$), 4.36 (1 H, dd, *J* 1.5 and 10.0 Hz, 4-H), 4.13 (1 H, td, *J* 5.0 and 10.0 Hz, 5-H), 3.96 (1 H, t, *J* 10.0, 6-$H_{ax}$), 3.46 (3 H, s, $OCH_3$), and 1.28 [9 H, s, $C(CH_3)_3$]; $\delta_C$ 192.0 (C-3), 177.3 (O*C*OBu$^t$), 136.4 (*ipso*-aromatic), 129.2 (*p*-aromatic), 128.2 and 126.3 (*o*- and *m*-aromatics), 101.9 and 101.5 (Ph*C*H and C-1), 82.1, 74.3, and 65.4 (C-2, C-4, and C-5), 69.4 (C-6), 55.8 ($OCH_3$), 39.0 [$C(CH_3)_3$], and 27.1 [$C(CH_3)_3$]; *m/z* (CI reagent ammonia) 365 ($M^+$ + H).

*Methyl* 4,6-O-*Benzylidene*-2-O-(*t-butyldiphenylsilyl*)-α-D-ribo-*hexopyranosid*-3-*uloside* (**18b**).—Methyl 4,6-*O*-benzylidene-2-*O*-(t-butyldiphenylsilyl)-α-D-glucopyranoside (2.0 g, 3.8 mmol) was dissolved in dry dichloromethane (150 ml), and pyridinium chlorochromate (3.2 g, 15 mmol) and anhydrous sodium acetate (1 g) was added. The reaction mixture was heated under reflux under a nitrogen atmosphere for 16 h. The reaction mixture was then diluted with ethyl acetate (100 ml) and the whole mixture was passed through a short silica column, eluting with ethyl acetate. Compound (**18b**) (1.6 g, 80%) was obtained as an oil on evaporation of the solvent; $[\alpha]_D^{20}$ − 12° (*c* = 1 in $CHCl_3$) (Found: C, 69.4; H, 6.7. $C_{30}H_{34}O_6Si$ requires C, 69.5; H, 6.6%); $\nu_{max}$(film) 1 755 (C=O) $cm^{-1}$; $\delta_H$ 7.70 (6 H, m, aromatics), 7.40 (9 H, m, aromatics), 5.45 (1 H, s, PhC*H*), 4.73 (1 H, d, *J* 4.0 Hz, 1-H), 4.31 (1 H, dd, *J* 4.5 and 10.0 Hz, 6-$H_{eq}$) 4.28 (1 H, dd, *J* 4.0 and 1.0 Hz, 2-H), 4.06 (1 H, dt, *J* 4.5 and 10.0 Hz, 5-H), 4.01 (1 H, dd, *J* 10.0 and 1.0 Hz, 4-H), 3.78 (1 H, dt, *J* 10.0 Hz, 6-$H_{ax}$), 3.42 (3 H, s, $OCH_3$), and 1.15 [9 H, s, $(CH_3)_3C$]; $\delta_C$ 195.9 (C-3), 136–126 (aromatics) 103.7 and 101.9 (C-1 and PhCH), 81.8 (C-4), 76.2 (C-2), 69.4 (C-6), 65.1 (C-5), 55.7 ($OCH_3$), 26.7 [$C(CH_3)_3$], and 19.4 [$C(CH_3)_3$]; *m/z* (EI) 517 ($M^+$ − H).

*Methyl* 4,6-O-*Benzylidene*-3-C-(*methoxycarbonylmethylene*)-3-*deoxy*-2-O-*pivaloyl*-α-D-ribo-*hexopyranoside* (**19a**).—Methyl 4,6-*O*-benzylidene-2-*O*-pivaloyl-α-D-hexopyranosid-3-ulose (1.8 g, 5 mmol) and ethoxycarbonylmethylene triphenylphosphorane (2.5 g, 7.0 mmol) were dissolved in dry acetonitrile (50 ml) and heated under reflux in a nitrogen atmosphere for 4 h. The mixture was then cooled, concentrated under reduced pressure and the residue was chromatographed on silica gel (light petroleum–ethyl acetate, 9:1) to give compound (**19a**) (mixture of geometric isomers) as an oil (1.4 g, 67%) together with the regioisomer, also as an oil (0.5 g, 19%) (Found: C, 62.7; H, 6.8. $C_{23}H_{30}O_8$ requires C, 63.6; H, 6.9%); $\nu_{max}$(mull) 1 733 and 1 742 $cm^{-1}$ (C=O); $\delta_H$ (maj and min refer to the major and minor geometric isomers, respectively) 7.47 (2 H, m, *o*-aromatics), 7.36 (3 H, m, *m*- and *p*-aromatics), 6.03 (1 $H_{maj}$, d, *J* 2.0 Hz, =CH), 5.99 (1 $H_{min}$, t, *J* 2.0 Hz, =CH), 5.62 (1 $H_{maj}$, s, PhC*H*), 5.57 (1 $H_{min}$, s, PhC*H*), 5.32 (1 $H_{min}$, m, 1-H), 5.23 (1 $H_{maj}$, br d, *J* 1.5 Hz, 1-H), 4.94 (1 $H_{min}$, d, *J* 4.0 Hz, 2-H), 4.65 (1 $H_{maj}$, *J* 1.5 Hz, 2-H), 4.48 (1 $H_{maj}$, dd, *J* 2.0 and 9.5 Hz, 4-H), 4.02–3.70 (6 H, m, $CH_2CH_3$, 6-H, 4-H, and 5-H), 3.41 (3 $H_{maj}$, s, $OCH_3$), 3.40 (3 $H_{min}$, s, $OCH_3$), 1.28 (9 $H_{min}$, s, Bu$^t$), 1.25 (9 $H_{maj}$, s, Bu$^t$), 0.99 (3 $H_{maj}$, t, *J* 7.0 Hz, $CH_3$), and 0.97 (3 $H_{min}$, t, *J* 7.0 Hz, $CH_3$); *m/z* (CI reagent ammonia) 433 ($M^+$ + H).

*Methyl* 4,6-O-*Benzylidene*-3-*deoxy*-3-C-[(E)-*methoxycarbonylmethylene*]-2-O-(*t-butyldiphenylsilyl*)-α-D-ribo-*hexopyranoside* (**19b**).—Methyl 4,6-*O*-benzylidene-2-*O*-(t-butyldiphenylsilyl)-α-D-*ribo*-hexopyran-3-uloside (1.0 g, 1.9 mmol) and ethoxycarbonylmethylidene triphenylphosphorane (1.4 g, 4.0 mmol) were dissolved in dry acetonitrile (50 ml) and heated under reflux for 4 days under a nitrogen atmosphere. The mixture was then concentrated and the residue taken up in diethyl ether, filtered and concentrated to give a glass. The product was purified by flash column chromatography (light petroleum–ethyl acetate, 9:1) to give compound (**19b**) as a gum (0.67 g, 60%) and its regioisomer, also as a gum (0.22 g, 20%). Compound (**19b**): $[\alpha]_D^{20}$ − 48° (*c* = 1 in $CHCl_3$) (Found: C, 68.7; H, 6.7. $C_{33}H_{38}O_7Si$ requires C, 69.0; H, 6.6%); $\nu_{max}$(mull) 1 740 $cm^{-1}$ (C=O); $\delta_H$ 7.69 (6 H, m, *o*-aromatics), 7.41 (9 H, m, *m*- and *p*-aromatics), 6.40 (1 H, t, *J* 2.0 Hz, C=CH), 5.49 (1 H, s, PhC*H*), 4.28 (1 H, dd, *J* 5.0 and 2.0 Hz, 2-H), 4.18 (1 H, dd, *J* 10.0 and 5.0 Hz, 6-$H_{eq}$), 4.12 (1 H, d, *J* 5.0 Hz, 1-H), 4.08 (1 H, dd, *J* 10.0 and 2.0 Hz, 4-H), 3.82 (1 H, td, *J* 10.0 and 5.0 Hz, 5-H), 3.63 (1 H, t, *J* 10.0 Hz, 6-$H_{ax}$), 3.37 (3 H, s, $CO_2CH_3$), 3.24 (3 H, s, $OCH_3$), and 1.11 [9 H, s, $(CH_3)_3CSi$]; $\delta_C$ 169.2 (*C*$O_2$Me), 139.1 (C-3), 139–126 (aromatics), 113.8 (=*C*HCO$_2$Me), 101.7 and 100.6 (Ph*C*H and C-1), 78.8 (C-4), 71.3 (C-2), 69.3 (C-6), 64.8 (C-5), 55.1 ($OCH_3$), 51.4 ($CO_2CH_3$), 26.9 [$C(CH_3)_3$], and 19.4 [$C(CH_3)_3$].

*Methyl* 4,6-O-*Benzylidene*-3-*deoxy*-3-C-(*methoxycarbonylmethylene*)-α-D-ribo-*hexopyranoside* (**20**).—Methyl 4,6-O-benzylidene-3-*C*-(methoxycarbonylmethylene)-3-deoxy-2-*O*-(t-butyldiphenylsilyl)-α-D-*ribo*-hexopyranoside (0.3 g, 0.5 mmol) was dissolved in dry tetrahydrofuran (THF) (10 ml) and tetrabutylammonium fluoride (1M in THF, 0.6 ml; 0.6 mmol) was added. After 2 h the mixture was concentrated and chromatographed directly on a silica column (light petroleum–ethyl acetate, 1:1) to give compound (**20**) as an oil (0.13 g, 76%). $[\alpha]_D^{20}$ + 150° (*c* = 1 in $CHCl_3$) (Found: C, 60.3; H, 6.1. $C_{17}H_{20}O_7$ requires C, 60.7; H, 6.0%); $\delta_H$ 7.5 (2 H, m, *o*-aromatics), 7.4 (3 H, m, *m*- and *p*-aromatics), 6.11 (1 H, t, *J* 2.0 Hz, C=CH), 5.55 (1 H, s, PhC*H*), 4.85 (1 H, d, *J* 4.0 Hz, 1-H), 4.31 (1 H, dd, *J* 4.0 and 10.0, 6-$H_{eq}$), 4.23 (1 H, ddd, *J* 1 0, 2.0, and 4.0 Hz, 2-H), 4.15 (1 H, dd, *J* 2.0 and 9.0 Hz, 4-H), 3.86 (1 H, td, *J* 4.0, 10.0, and 9.0 Hz, 5-H), 3.76 (1 H, t, *J* 10.0 Hz, 6-$H_{ax}$), 3.72 (1 H, d, *J* 1.0 Hz, OH), 3.47 (3 H, s, $CO_2CH_3$), and 3.31 (3 H, s, $OCH_3$); $\delta_C$ 168.8 (C=O), 140.1 (C-3), 137.0 (*ipso*-aromatic), 129.1 (*p*-aromatic), 128.1 and 126.4 (*o*- and *m*-aromatic), 113.5 (C=CH), 101.8 and 100.0 (C-1 and PhCH), 78.2 (C-4), 69.5 (C-2), 69.3 (C-6), 64.6 (C-5), 55.5 ($OCH_3$), and 51.4 ($CO_2CH_3$); *m/z* (CI reagent ammonia) 337 ($M^+$ + H).

*Methyl* 4,6-O-*Benzylidene*-3-*deoxy*-3-C-(*methoxycarbonylmethyl*)-α-D-*allopyranoside* (**21**).—Methyl 4,6-O-benzylidene-3-deoxy-3-*C*-(methoxycarbonylmethylene)-α-D-*ribo*-hexopyranoside (0.1 g, 0.3 mmol) was dissolved in ethanol (95%, 10 ml) and Pd–C (10%, 20 mg) was added. The mixture was hydrogenated at atmospheric pressure for 18 h. The solvent was removed under reduced pressure and the residue taken up in

ethyl acetate. The resulting solution was passed through a column of silica gel eluting with ethyl acetate. Evaporation of the solvent gave compound (**21**) as an oil (0.1 g, quant.); $[\alpha]_D^{20}$ + 40° ($c$ = 1 in $CHCl_3$) (Found: C, 60.4; H, 6.7. $C_{17}H_{22}O_7$ requires C, 60.4; H, 6.5%); $\delta_H$ 7.44 (2 H, m, *o*-aromatics), 7.36 (3 H, m, *m*- and *p*-aromatics), 5.52 (1 H, s, PhC*H*), 4.70 (1 H, d, *J* 4.0 Hz, 1-H), 4.30 (1 H, dd, *J* 4.0 and 10.0 Hz, 6-$H_{eq}$), 3.96 (1 H, m, 2-H), 3.73 (1 H, td, *J* 4.0 and 10.0 Hz, 5-H), 3.62 (1 H, dd, *J* 4.0 and 10.0 Hz, 4-H), 3.59 (3 H, s, $CO_2CH_3$), 3.44 (3 H, s, $OCH_3$), 3.42 (1 H, t, *J* 10.0 Hz, 6-$H_{ax}$), 3.11 (1 H, m, 3-H), and 2.90 and 2.78 (2 H, ABX, *J* 16.0, 7.0, and 6.0 Hz, $CH_2CO_2CH_3$).

*Methyl* 4,6-O-*Benzylidene*-3-*deoxy*-3-(*ethoxycarbonyl*)-2,3-*butyrolacto*-α-D-*allopyranoside* (**4**).—Methyl 4,6-*O*-benzylidene-3-deoxy-3-(methoxycarbonylmethyl)-α-D-allopyranoside (0.1 g, 0.33 mmol), dissolved in dry THF (10 ml) was added to sodium hydride (50% dispersion in oil, prewashed with dry THF; 0.024 g, 0.5 mmol) under nitrogen and the reaction mixture was stirred for 30 min. The reaction mixture was then evaporated to dryness and the residue was taken up in ethyl acetate and passed through a short column of silica, eluting with ethyl acetate. Concentration of the resulting solution gave compound (**4**) (0.089 g, 89%) as an oil; $[\alpha]_D^{20}$ + 28° ($c$ = 1 in $CHCl_3$). (Found: C, 62.8; H, 5.8. $C_{16}H_{18}O_6$ requires C, 62.7; H, 5.9%); $\nu_{max}$(mull) 1 785 (C=O) $cm^{-1}$; $\delta_H$ 7.46 (2 H, m, *o*-aromatics), 7.39 (3 H, m, *m*- and *p*-aromatics), 5.58 (1 H, s, PhC*H*–), 4.86 (1 H, d, *J* 5.0 Hz, 1-H), 4.64 (1 H, dd, *J* 7.0 and 5.0 Hz, 2-H), 4.36 (1 H, dd, *J* 10.0 and 5.0 Hz, 6-$H_{eq}$), 3.99 (1 H, td, *J* 5.0 and 10.0 Hz, 5-H), 3.88 (1 H, dd, *J* 6.0 and 10.0 Hz, 4-H), 3.79 (1 H, t, *J* 10.0, 6-$H_{ax}$), 3.44 (3 H, s, $OCH_3$), 3.23 (1 H, m, 3-H), 3.43 (3 H, s, $OCH_3$), and 2.84 and 2.43 (2 H, ABX, *J* 17.0, 13.0, and 9.0 Hz, 8-H and 8-H′); $m/z$ (CI, reagent ammonia) 307 ($M^+$ + H).

*Methyl* 4,6-O-*Benzylidene*-3-*deoxy*-3-(*prop*-2-*yloxycarbonyl*)-2,3-*butyrolactone*-α-D-*allopyranoside* (**23**).—Compound (**4**) (0.15 g, 0.5 mmol), dissolved in dry THF (5 ml) was added dropwise to a solution of lithium hexamethyldisilazide (1M; 1 ml, 1 mmol) in dry THF (10 ml) and the mixture was stirred at −78 °C under a nitrogen atmosphere for 30 min. Iodomethane (0.07 g, 0.5 mmol), dissolved in THF (5 ml), was added, dropwise, and the mixture was allowed to warm slowly to room temperature, with stirring, for a total of 2 h. The reaction mixture was then quenched with water, and concentrated to dryness under reduced pressure. The residue was taken up in ethyl acetate, washed twice with water, and purified by flash chromatography (light petroleum–ethyl acetate) to give compound (**23**) as an oil (0.14 g, 90%) (Found: C, 63.4; H, 6.6. $C_{17}H_{20}O_6$ requires C, 63.7; H, 6.3%); $\delta_H$ 7.45 (2 H, m, aromatics), 7.38 (3 H, m, aromatics), 5.57 (1 H, s, PhC*H*), 4.84 (1 H, d, *J* 5.0 Hz, 1-H), 4.56 (1 H, dd, *J* 5.0 and 8.0 Hz, 2-H), 4.35 (1 H, dd, *J* 5.0 and 10.0 Hz, 6-$H_{eq}$), 3.94 (1 H, td, *J* 5.0 and 10.0 Hz, 5-H), 3.96 (1 H, dd, *J* 10.0 and 5.0 Hz, 4-H), 3.78 (1 H, t, *J* 10.0 Hz, 6-$H_{ax}$, 3.40 (3 H, s, $OCH_3$), 3.03 (1 H, dd, *J* 7.0 and 13.0 Hz, 8-H), 2.83 (1 H, ddd, *J* 5.0, 8.0, and 13.0 Hz, 3-H), and 1.31 (1 H, d, *J* 7.0 Hz, $CH_3$); $m/z$ (CI reagent ammonia) 321 ($M^+$ + H).

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## References

1 'Total Synthesis of Natural Products: The "Chiron" Approach,' S. Hanessian, Pergamon Press, Oxford, 1983.
2 W. W. Wood and A. Rashid, *Tetrahedron Lett.*, 1987, **28**, 1933.
3 W. Sowa and G. Thomas, *Can. J. Chem.*, 1966, **44**, 836.
4 R. M. Munavu and H. H. Szmant, *J. Org. Chem.*, 1976, **41**, 1832.
5 D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1574.
6 R. J. Ferrier, Royal Society of Chemistry, Carbohydrate Group Meeting, Oxford, 1988.
7 D. B. Tulshian, R. Tsang, and B. Fraser-Reid, *J. Org. Chem.*, 1984, **49**, 2347.
8 B. Fraser-Reid, personal communication.
9 K. Hara, H. Fujimoto, K-I. Sato, H. Hashimoto, and J. Yoshimura, *Carbohydr. Res.*, 1987, **159**, 65.

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