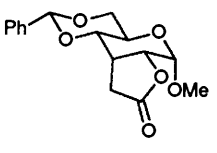
General Synthesis of Homochiral Trisubstituted γ-Butyrolactones

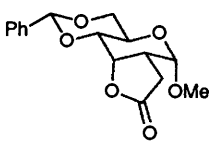
David Alker,[a] D. Neville Jones,[b] G. Mark Taylor[b] and William W. Wood*[,c]
[a] *Pfizer Central Research, Sandwich, Kent CT13 9NJ, UK*
[b] *Department of Chemistry, The University, Brook Hill, Sheffield S3 7HF, UK*
[c] *Shell Research Limited, Sittingbourne Research Centre, Sittingbourne, Kent ME9 8AG, UK*

The synthetically useful keto ester methyl 2-deoxy-2-(2-ethoxy-2-oxoethyl)-4,6-*O*-(phenylmethylene)-α-D-*ribo*-hexopyranosid-3-ulose can be prepared exclusively by reaction of the potassium enolate of methyl 2-deoxy-4,5-*O*-(phenylmethylene)-α-D-*erythro*-hexopyranosid-3-ulose and ethyl iodoacetate in toluene in 74% yield. Reduction of methyl 2-deoxy-2-(2-ethoxy-2-oxoethyl)-4,6-*O*-(phenylmethylene)-α-D-*ribo*-hexopyranosid-3-ulose and subsequent cyclisation led to methyl 2-deoxy-2-(2-oxoethyl)-4,6-*O*-(phenylmethylene)-α-D-allopyranoside 2',3 lactone, whose lithium enolate reacted with high stereoselectivity to give exclusively (>95% d.r.) methyl 5'-(*R*)-2-deoxy-5'-methyl-2-(2-oxoethyl)-4,6-*O*-(phenylmethylene)-α-D-allopyranoside 2',3 lactone, methyl 5'-(*R*)-2-deoxy-5'-(1-hexyl)-2-(2-oxoethyl)-4,6-*O*-(phenylmethylene)-α-D-allopyranoside 2',3 lactone and methyl 5'-(*R*)-2-deoxy-2-(2-oxoethyl)-4,6-*O*-(phenylmethylene)-5'-(2-propenyl)-α-D-allopyranoside 2',3 lactone derivatives. This method provides a convenient and high-yielding route to homochiral γ-butyrolactones, thereby offering an opening into a wide range of enantiomerically pure γ-lactones. The work described provides another solution to the 'off-template' problem.

In our recent papers on the development of methods for the synthesis of optically pure γ-butyrolactones by creation of chirality 'off-template' to a carbohydrate skeleton,[1–3] we have demonstrated the highly stereoselective alkylation of the two carbohydrate-fused γ-butyrolactones **1** and **2**. These complementary procedures provide a versatile new method for the synthesis of trisubstituted γ-butyrolactones of the general formula **3** and **4**. One of the advantages of using compounds such as **1** and **2** as the starting point of a synthetic strategy lies in the fact that, once stereoselective alkylation of the lactone has been achieved, manipulation of the carbohydrate skeleton may be performed with predictable control of stereochemistry in a great number of ways,[4] thus opening up the possibility of synthesising a wide range of enantiomerically pure γ-butyrolactones. The vast number of naturally occurring and biologically active γ-butyrolactones known,[5] makes general routes such as this an area of considerable interest. Having already developed a successful general strategy for the synthesis of homochiral γ-butyrolactones **3**,[1,2] we were interested in extending our studies to a short and efficient route to their enantiomers, *i.e.* lactones of the general formula **4**, for use in our studies towards the total synthesis of biologically active, naturally occurring terpenoids.[6] Following a preliminary communication of a successful solution to the problem,[3] we now present a full account of this work.



1



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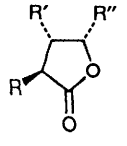

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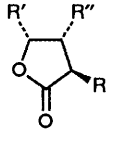

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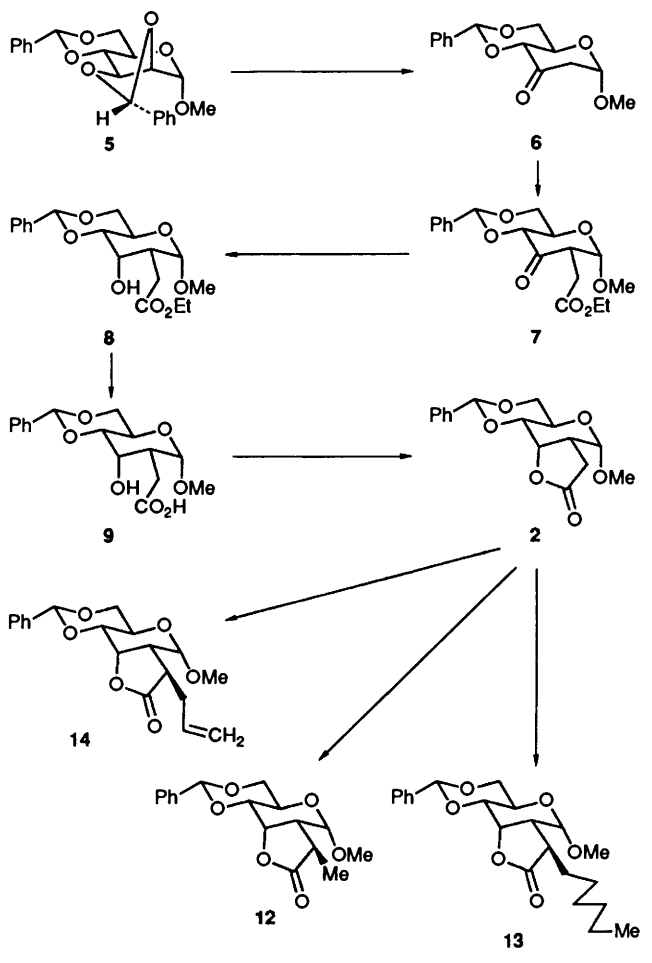
Results and Discussion

Having investigated several routes towards 2,3-fused *allo*-pyranoside γ-butyrolactones **1**, it was clear[2] that the lactone-forming process to give **2** should involve C–O bond formation, *i.e.* cyclisation by classical lactonisation. The immediate precursor to **2** was, therefore, the hydroxy ester **8** or acid **9**. It had been reported[7] that the 2-deoxy-3-ketone could be reduced with high diastereoselectivity to the axial alcohol **10** and we were, therefore, confident that **8** would be available by stereospecific reduction of the known[8] keto ester **7**, since added steric congestion at C-2 relative to **10** would further encourage α-face reduction. Since the keto ester **7** was reportedly accessible in two steps from methyl α-D-mannopyranoside, this particular strategy offered a rapid and potentially high-yielding route to the target lactone.

Starting from the known mannose derivative **5**, the keto ester **7** was prepared by *in situ* alkylation of the enolate of **6**. As we have already reported,[3] we found difficulty in repeating the published procedure and could only ever isolate the keto ester **7** on a small scale in a maximum of 30% yield. An alternative to Chapleur's 'one-pot' synthesis of the keto ester **7** was to isolate the intermediate ketone **6** and then perform the alkylation in a separate step. In this way, any interference in the alkylation step from other species resulting from the Klemer–Rodemeyer fragmentation of **5**, which we suspected were hindering the *in situ* alkylation, would be avoided. We were further encouraged by the knowledge that the ketone **6** had been shown to react with lithium and potassium dialkylamide bases to form the 2,3-enolate exclusively, which then reacted with a range of electrophiles.[9,10]

In our initial experiments using the lithium enolate of **6**,[11] DMPU and ethyl bromoacetate, extensive *O*-alkylation occurred. Addition of lithium iodide did not accelerate the reaction or decrease the amount of *O*-alkylation, however the use of ethyl iodoacetate did accelerate the rate of reaction and use of a potassium counter-ion effectively controlled competing *O*-alkylation. Finally, it was found that replacing THF with toluene prevented dialkylation, which became a problem under these more reactive conditions. These developments led to a reliable method for the large scale preparation of **7** (see Experimental section).

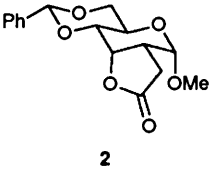


Scheme 1

As expected from literature precedent,[7] stereoselective reduction of **7** was readily accomplished using sodium borohydride in an alcohol solvent. Both TLC and the ^{1}H NMR spectrum of the crude product showed it to be homogeneous, reflecting a diastereoisomeric ratio (d.r.) of >95:5. The stereochemistry of this crucial intermediate was then assigned from its ^{1}H NMR spectrum. The proton-proton coupling patterns in the spectrum of **8** indicated an axial C-3 alcohol. $J_{2,3}$ and $J_{3,4}$ (both 3 Hz) were consistent with an axial-equatorial-axial arrangement of the three protons. Addition of trichloroacetyl isocyanate to the sample tube with subsequent formation of the 3-*O*-carbamate[12] clarified the spectrum and 3-H was clearly equatorial from its ^3J coupling pattern.

Cyclisation of **8** to the target lactone **2** occurred smoothly with sodium hydride in THF. After work-up according to the procedure adopted for its regioisomer **1**,[1,2] the lactone **2** was obtained as a white crystalline solid in 65% yield. Surprisingly, using anhydrous THF, no reaction could be detected by TLC. However, on the addition of a few drops of water to the reaction mixture, complete cyclisation to **10** occurred rapidly inside 20 min. A standard aqueous work-up, ensuring that the aqueous layer was adjusted to pH 7 before extraction, gave the desired compound. It, therefore, appeared that far from interfering with the cyclisation process, the formation of the hydroxy acid **9** was actually a pre-requisite for lactonisation. On a large (5 g) scale we found that the addition of a small amount of tetrabutylammonium bromide as a phase transfer catalyst was useful in keeping the reaction time down, since on that scale the THF and alkaline aqueous phase tended to separate.

The structure of **2** was assigned from its ^{1}H NMR spectrum, the salient features of which are given in Fig. 1. Interestingly, the value of $J_{1,2}$ (5.5)* is unusually high, being mid-way between the normal values for axial-equatorial (J 3–4) and axial-axial (J 9–10) interactions, which suggested that incorporation of the lactone ring had distorted the conformation of the pyranoside ring from a chair to something approaching a half-chair. This was also apparent in the ^{1}H NMR spectrum of the dibenzylidene compound **5**, wherein $J_{2,3}$ 5.5 and $J_{3,4}$ 7.5 also indicated that the pyranoside ring did not exist in an undistorted chair conformation. Further evidence came with the X-ray structures of the alkylated derivatives (*vide infra*).

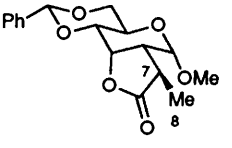


2

δ(p.p.m.)	Mult	J/Hz	Assign.
2.46	dd	16.5, 7	7-H
2.60	dd	16.5, 1	7′-H
2.85	dddd	7, 5.5, 4.5, 1	2-H
4.69	dd	4, 3.5	3-H
4.73	d	5.5	1-H

Fig. 1 Partial ^{1}H NMR spectrum of **2**

We next turned our attentions to the alkylation of **2**. As a starting point, we chose the lithium enolate since this had been successful in alkylating the regioisomer **1** and studied its reaction with four electrophiles (methyl iodide, hexyl iodide, isopropyl bromide and allyl bromide). Reaction with methyl iodide was extremely fast: as soon as the mixture had reached room temperature TLC showed one new product and no starting material. After work-up, ^{1}H NMR analysis of the crude product also showed only one product (diastereoisomeric ratio of >95:5) to have been formed. Following purification by chromatography, the α-methyl lactone **12** was obtained in 92% yield.



12

δ(p.p.m.)	Mult	J/Hz	Assign.
1.28	d	7.5	CH_3
2.48	dd	5.5, 4.5	2-H
2.80	q	7.5	7-H
3.75	t	10, 5	6-H_{ax}
3.78	dd	10, 3.5	4-H
4.18	ddd	10.5, 10, 5.5	5-H
4.35	dd	10.5, 5.5	6-H_{eq}
4.74	d	5.5	1-H
4.84	br t	4	3-H

Fig. 2 Partial ^{1}H NMR spectrum of **12**

The structure of **12** was deduced from its ^{1}H NMR spectrum which was consistent with alkylation having occurred on the *exo*-face (Fig. 2). The 7-H resonance had disappeared and 7′-H appeared as a quartet. The 2-H signal had collapsed from dddd to dd and no coupling to 7′-H was evident. The pyranoside ring was also distorted from a chair conformation, as reflected in the

* J Values recorded in Hz throughout.

Table 1 Fractional atomic coordinates for compound **12**

Atom	*x*	*y*	*z*
C(1)	0.3248(3)	0.1761(2)	0.7935(2)
O(2)	0.2654(2)	0.2106(1)	0.8728(1)
C(3)	0.3680(3)	0.2866(2)	0.9147(1)
C(4)	0.4006(3)	0.3984(2)	0.8629(1)
C(5)	0.4539(3)	0.3589(3)	0.7770(2)
O(6)	0.3472(2)	0.2780(2)	0.7421(1)
C(7)	0.3164(3)	0.3190(2)	1.0017(1)
C(8)	0.4110(3)	0.4155(2)	1.0437(2)
C(9)	0.4683(3)	0.5131(3)	0.9826(2)
O(10)	0.5149(2)	0.4643(2)	0.9039(1)
O(11)	0.1704(2)	0.3728(2)	1.0003(1)
C(12)	0.1616(3)	0.4576(2)	1.0624(2)
O(13)	0.0477(2)	0.5078(2)	1.0771(1)
C(14)	0.3052(3)	0.4657(2)	1.1079(1)
C(15)	0.2216(3)	0.0885(2)	0.7524(1)
C(16)	0.1828(3)	−0.0154(2)	0.7969(2)
C(17)	0.0887(3)	−0.1007(3)	0.7615(2)
C(18)	0.0358(3)	−0.0827(3)	0.6805(2)
C(19)	0.0744(4)	0.0197(3)	0.6364(2)
C(20)	0.1673(3)	0.1053(3)	0.6718(2)
O(21)	0.3583(2)	0.5992(2)	0.9716(1)
C(22)	0.4051(5)	0.7076(3)	0.9302(2)
C(23)	0.2964(3)	0.3897(2)	1.1886(2)

Table 2 Fractional atomic coordinates for compound **13**

Atom	*x*	*y*	*z*
O(1)	−0.1840(3)	0.4152(1)	0.0303(1)
C(2)	−0.2169(4)	0.5076(2)	0.0701(2)
O(3)	−0.0876(2)	0.5395(2)	0.1205(1)
C(4)	−0.0589(4)	0.4676(2)	0.1855(2)
C(5)	−0.0247(4)	0.3667(2)	0.1479(2)
C(6)	−0.1594(5)	0.3367(3)	0.0916(2)
C(7)	0.0672(4)	0.5024(2)	0.2437(2)
C(8)	0.1134(4)	0.4233(2)	0.3082(2)
C(9)	0.1205(4)	0.3158(3)	0.2694(2)
O(10)	0.0107(3)	0.2952(2)	0.2154(1)
O(11)	0.2143(3)	0.5251(2)	0.1995(1)
C(12)	0.3406(4)	0.5007(3)	0.2507(2)
C(13)	0.2803(4)	0.4614(3)	0.3328(2)
C(14)	−0.2468(4)	0.5867(2)	0.0052(2)
C(15)	−0.1777(4)	0.5837(3)	−0.0732(2)
C(16)	−0.1938(4)	0.6617(3)	−0.1294(2)
C(17)	−0.2858(5)	0.7441(3)	−0.1076(3)
C(18)	−0.3592(4)	0.7460(3)	−0.0310(2)
C(19)	−0.3392(5)	0.6696(3)	0.0257(2)
O(20)	0.2635(3)	0.3062(2)	0.2262(1)
C(21)	0.2960(6)	0.2066(3)	0.1984(3)
O(22)	0.4728(3)	0.5165(2)	0.2283(2)
C(23)	0.2802(4)	0.5526(3)	0.3945(2)
C(24)	0.2277(5)	0.5264(3)	0.4798(2)
C(25)	0.1006(5)	0.5632(4)	0.5160(2)

value of $J_{1,2}$ (5.5) which was outside the accepted range for an axial-equatorial interaction.

Unambiguous proof of the stereochemistry of alkylation was provided by an X-ray structure of **12** in which the newly introduced methyl group α to the lactone is clearly visible on the *exo*-face of the molecule [Fig. 3(*a*) and Table 1].* Moreover, the pyranoside ring is noticeably distorted from a chair conformation to something approaching a half-chair, confirming the conclusions made from its ^{1}H NMR spectrum (*vide supra*).

Alkylation with hexyl iodide gave the hexyl derivative **13** in 59% yield. Not surprisingly the reaction was much slower than with methyl iodide and no change was apparent by TLC when the mixture had reached room temperature. Only after the mixture had been stirred for a further 2–3 h had all the starting material disappeared (TLC), but at this temperature some decomposition of the enolate was also apparent.

Once again, the ^{1}H NMR spectrum of the product **13** was consistent with *exo*-face alkylation. The 7-H resonance had disappeared, the 2-H signal was simplified and 7′-H appeared as a triplet. The absence of any other material in this spectrum showed the same stereoselectivity (d.r. >95:5) as for the methylation.

Attempts to alkylate **2** with isopropyl bromide were unsuccessful. No reaction was observed when the reaction mixture reached room temperature and further reaction at this temperature resulted in a slow decomposition of the enolate to TLC base-line material which, after standard work-up, showed no recognisable components in the ^{1}H NMR spectrum.

Finally, under the same conditions as before the lithium enolate of **2** was allowed to react with allyl bromide. On reaching room temperature, one new product and no starting material was observed; the ^{1}H NMR spectrum of the crude product also showed only one compound (d.r. >95:5) and, after chromatography, the allyl derivative **14** was obtained as a white crystalline solid in 89% yield. *exo*-Face alkylation was again deduced from the ^{1}H NMR spectrum of **14** and unambiguous proof of structure was provided by the X-ray structure [Fig. 3(*b*) and Table 2].

* Tables of bond lengths and bond angles, thermal parameters and hydrogen atom co-ordinates have been deposited with the Cambridge Crystallographic Data Centre (see 'Instructions to Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1992, Issue 1).

Conclusions.—In conclusion, we have demonstrated an efficient and highly stereoselective route to the fused butyrolactone **2**. Reaction of the enolate of **2** with electrophiles proceeds with very high stereoselectivity in good yields, thus providing a rapid entry into optically pure γ-butyrolactones **4**. This method therefore represents another general solution to the 'off-template' problem in carbohydrate-based synthesis. As part of these studies, a practical alternative to the published preparation of ketoester **7** has been developed and conditions described by which methyl 2,3:4,6-di-*O*-(phenylmethylene)-α-D-mannopyranoside may be conveniently prepared in high yield.

Experimental

Microanalyses were determined by the University of Sheffield, Department of Chemistry microanalytical service. M.p.s were recorded with a Kofler hot-stage micro melting point apparatus and are uncorrected. Optical rotations were determined at 20 °C on a Perkin-Elmer 141 polarimeter using a 10 cm cell and $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}. Low resolution mass spectra were recorded with a Kratos MS25 mass spectrometer and DS90 data system. High resolution mass spectra were recorded with a Kratos MS80 mass spectrometer and DS90 data system. EI refers to electron impact; CI NH_3 refers to chemical ionisation with ammonia as the reagent. Unless otherwise stated, mass spectral data quoted is from electron impact measurements. IR spectra were recorded on a Perkin-Elmer 157G spectrometer and Nujol was used as the mulling agent (where stated).

^{1}H NMR spectra were recorded at room temperature in deuteriochloroform with tetramethylsilane (TMS) as internal standard and at 250 MHz unless otherwise stated. The spectra were recorded on either a Perkin-Elmer R34 (220 MHz, continuous wave), a Brucker AM250 (250 MHz, F.T.) or a General Electrics Nicolet QE300 (300 MHz, F.T.) spectrometer. The addition of trichloroacetyl isocyanate to samples followed the procedure of Butler and Müller.[12] ^{13}C NMR spectra were recorded at room temperature in deuteriochloroform on a Brucker AM250 (62.9 MHz) spectrometer. Bracketed assign-

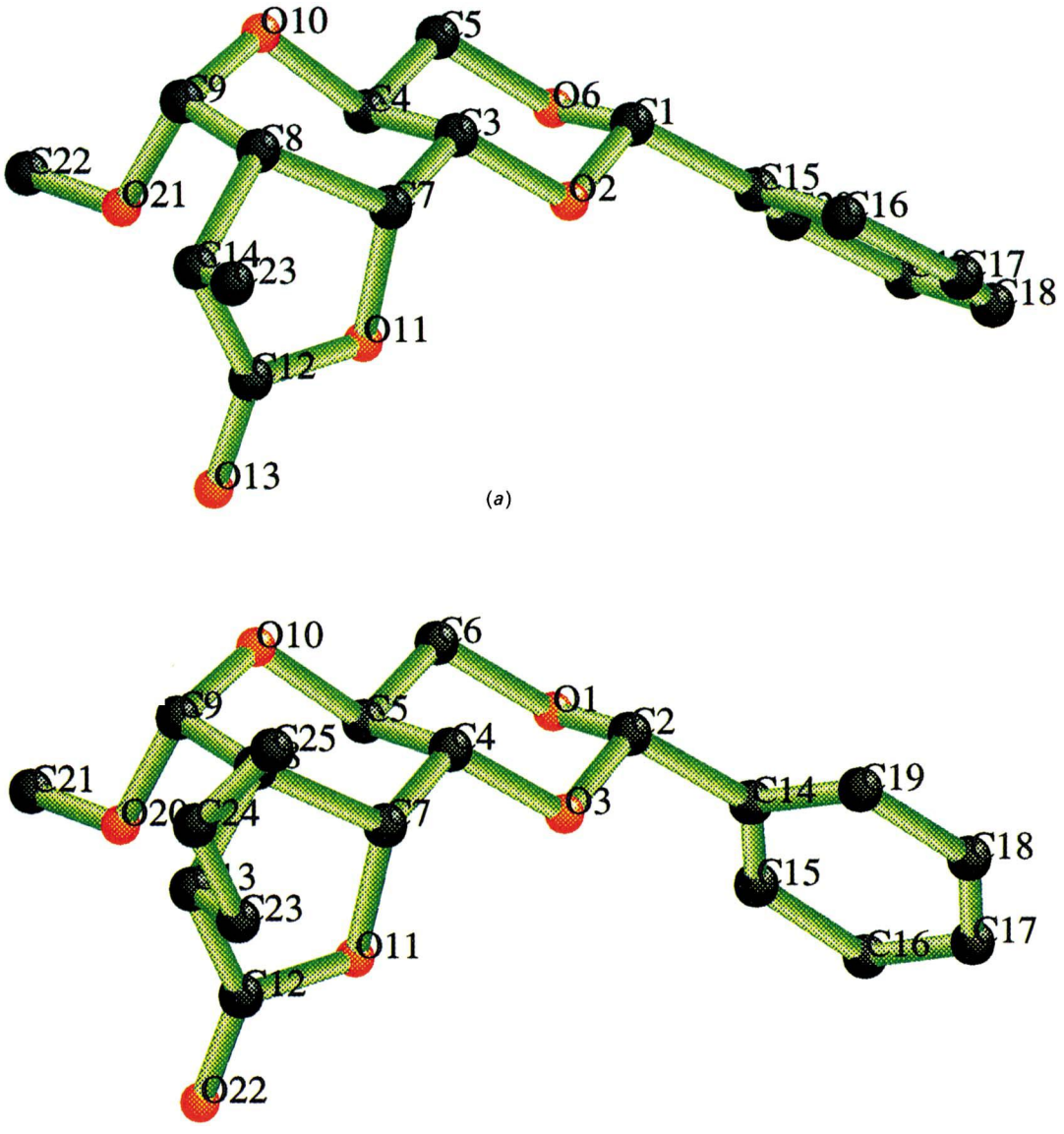


Fig. 3 Crystal structures of (*a*) **12** and (*b*) **14**

ments, *e.g.* 13.85 and 17.23 (C-6 and C-8), are not respective and may be interchanged.

Thin layer chromatography (TLC) was performed on Merck Kieselgel 60 G.F.$_{254}$ aluminium-backed plates using the stated solvent systems. Plates were visualised under UV light (where appropriate) and/or sprayed with cerium(IV) sulfate solution and flamed to develop. Merck Kieselgel 60 silica was used for flash column chromatography[13] and all solvents were distilled before use. Light petroleum refers to the fraction boiling between 40 and 60 °C. Tetrahydrofuran was dried by filtering through basic alumina followed by distillation from calcium hydride. Toluene and triethylamine were purified and dried according to standard methods;[14] toluene was stored over sodium wire and triethylamine over molecular sieves. All other solvents and reagents were used as supplied by the manufacturers.

Rigorous conditions were applied to all enolate reactions: the glassware was flame-dried and cooled under an inert atmosphere; substrates were dried by co-distillation with toluene on a rotary evaporator prior to use; and tetrahydrofuran was freshly distilled from lithium aluminium hydride immediately before use. A cooling bath temperature of −45 °C was achieved using solid CO_2 in a 3:1 mixture of carbon tetrachloride–chloroform.

Methyl 2-Deoxy-2-(2-ethoxy-2-oxoethyl)-4,6-O-(phenylmethylene)-α-D-ribohexopyranosid-3-ulose **7**.—Alkylation of the lithium enolate of methyl 2-deoxy-4,6-*O*-(phenylmethylene)-α-D-*erythro*-hexopyranosid-3-ulose **6** with ethyl bromoacetate in THF–DMPU. The ketone **6** (1.32 g, 5 mmol) was dissolved in anhydrous THF (15 cm^3) and DMPU (7.5 cm^3) and the solution cooled to −45 °C under an inert atmosphere. Lithium bis(trimethylsilyl)amide (1 mol dm^{-3} in THF; 5 ml, 5 mmol) was added in one portion and the solution stirred for 30 min. Ethyl bromoacetate (1.11 cm^3, 1.67 g, 10 mmol) in anhydrous THF (5 cm^3) was added dropwise over 20 min. The reaction was then stirred at −45 °C for 6 h after which time TLC (dichloromethane–light petroleum–ethyl acetate, 5:4:1) showed the absence of starting material. The mixture was poured quickly into rapidly stirred, saturated aqueous ammonium chloride (50 cm^3) and the organic layer separated. The aqueous phase was extracted with diethyl ether (3 × 50 cm^3) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to leave a pale yellow oil. This was purified by flash column chromatography (toluene–ethyl acetate, 15:1) to give the keto ester **7** (1.1 g, 64%), m.p. 163–164 °C (from diethyl ether), $[\alpha]_D$ +115.6 (*c* 0.5 in chloroform) (lit.,[8] m.p. 163–165 °C $[\alpha]_D$ +109, *c* 0.1 in chloroform) (Found: M$^+$, 350.1374. Calc. for

$C_{18}H_{22}O_7$: *M*, 350.1366); ν_{max}(mull)/cm^{-1} 1728s (CO) and 1735s (CO); δ_H 1.26 (3 H, t, *J* 7, CH_3CH_2O), 2.39 and 2.92 (2 × 1 H, dd, *J* 17.5 and 6.5, CH_2CO_2Et), 3.35 (1 H, td, *J* 6.5, 6.5 and 4.5, 2-H), 3.36 (3 H, s, CH_3O), 3.95 (1 H, t, *J* 10, 6-Hax.), 4.05–4.21 (3 H, m, 5-H and CH_3CH_2O), 4.37 (1 H, d, *J* 9.5, 4-H), 4.38 (1 H, dd, *J* 10 and 4, 6-Heq.), 5.13 (1 H, d, *J* 4.5, 1-H), 5.59 (1 H, s, PhC*H*) and 7.33–7.39 (5 H, m, Ph); δ_C 14.11 (CH_3CH_2O), 28.83 (C-7), 50.25 (C-2), 55.24 (CH_3O), 60.67 (CH_3CH_2O), 65.72 (C-5), 69.38 (C-6), 82.70 (C-4), 101.84 and 102.84 (C-1 and PhCH), 126.29 and 128.11 (*m*- and *o*-aromatics), 129.10 (*p*-aromatic), 136.55 (*ipso*-aromatic), 171.63 (CO, ester) and 197.26 (C-3); *m*/*z* 350 (M^+, 1.2%), 144 (100); and starting material **6** (475 mg).

Alkylation of the Lithium Enolate of Methyl 2-*Deoxy*-4,6-O-(*phenylmethylene*)-α-D-erythro-*hexopyranosid*-3-*ulose* **6** *with Ethyl Iodoacetate in THF-DMPU.*—The ketone **6** (1.32 g, 5 mmol) was dissolved in anhydrous THF (10 cm^3) and DMPU (10 cm^3) and the solution cooled to −45 °C under an inert atmosphere. Lithium bis(trimethylsilyl)amide (1 mol dm^{-3} in THF; 5 cm^3, 5 mmol) was added in one portion and the solution stirred for 30 min. Ethyl iodoacetate (0.71 cm^3; 1.28 g, 6 mmol) was added dropwise over a period of 10 min. The reaction was then stirred at −45 °C until TLC (dichloromethane–light petroleum–ethyl acetate, 5:4:1) showed the absence of starting material (typically, 2 to 3 h).

The mixture was poured into a rapidly stirred solution of ammonium chloride (10 g) in water (50 cm^3) and the organic layer separated. The aqueous phase was extracted with diethyl ether (3 × 50 cm^3) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to leave a pale yellow oil (2.5 g). This was purified by flash column chromatography (toluene–ethyl acetate, 15:1) to give the monoalkylated product **7** (1.0 g, 58%) (identical with an authentic sample prepared above by 220 MHz ^{1}H NMR and melting point) and a second product, thought to be the dialkylated material **11**, as a colourless oil, $[\alpha]_D$ +14.8 (*c* 1.0 in chloroform); δ_H 1.23 and 1.27 (2 × 3 H, t, *J* 7, CH_3CH_2O), 2.78 (1 H, d, *J* 18, 7-H**), 2.99 (1 H, dd, *J* 18, 1.5, 7-H'**), 3.13 (1 H, dd, *J* 15, 1.5, 8-H**), 3.22 (1 H, d, *J* 15, 8-H'**), 3.50 (3 H, s, CH_3O), 3.99 (1 H, q, *J* 10, 6-Hax.*), 4.05–4.19 (5 H, m, 2 × CH_3CH_2O and 5-H*), 4.37 (1 H, dd, *J* 10 and 4, 6-Heq.), 4.70 (1 H, d, *J* 10, 4-H), 5.22 (1 H, s, 1-H), 5.62 (1 H, s, PhC*H*), 7.32–7.40 and 7.48–7.54 (5 H, m, Ph); δ_C 14.00 and 14.15 (2 × CH_3CH_2O), 29.66 and 32.88 (2 × CH_2CO_2Et), 55.03 (C-2), 55.62 (CH_3O), 60.34 and 61.17 (2 × CH_3CH_2O), 66.17 (C-3), 69.45 (C-6), 80.42 (C-4), 102.06 and 104.99 (C-1 and PhCH), 126.40 and 128.16 (*m*- and *o*-aromatics), 129.16 (*p*-aromatic), 136.66 (*ipso*-aromatic), 169.65 and 171.32 (2 × CO, esters) and 198.45 (CO, ketone); *m*/*z* (EI) 427 (2.3%), 403 (7), 390 (4.4), 184 (100); *m*/*z* (CI, NH_3) 403 (100%), 319 (11), 299 (13) and 184 (68). **,* These assignments may be interchanged.

Alkylation of the Potassium Enolate of Methyl 2-*Deoxy*-4,6-O-(*phenylmethylene*)-α-D-erythro-*hexopyranosid*-3-*ulose* **6** *with Ethyl Iodoacetate in Toluene.*—The ketone **6** (6 g, 22.7 mmol) in anhydrous toluene (60 cm^3) was stirred at −45 °C under an inert atmosphere for 30 min. Potassium bis(trimethylsilyl)amide (1 mol dm^{-3} in toluene; 25 cm^3, 25 mmol) was added in one portion and the mixture stirred for a further 30 min. Ethyl iodoacetate (2.7 cm^3; 4.88 g, 22.7 mmol) was added in one portion and the mixture stirred at −45 °C for 10 min and then at 0 °C for 60 min. After this time, TLC (light petroleum–ethyl acetate, 1:1) showed the absence of starting material and one new product (R_f 0.7).

The reaction mixture was poured into a vigorously stirred solution of ammonium chloride (2 g) in water (100 cm^3). The layers were separated and the aqueous phase extracted with dichloromethane (3 × 100 cm^3). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to leave a yellow solid which was purified by flash column chromatography (toluene–ethyl acetate, 15:1). The product was obtained as a white crystalline solid (5.2 g, 74%) which was identical (220 MHz ^{1}H NMR and melting point) with an authentic sample of **7**, prepared as above.

Methyl 2-*Deoxy*-2-(2-*ethoxy*-2-*oxoethyl*)-4,6-O-(*phenylmethylene*)-α-D-*allopyranoside* **8**.—Sodium borohydride (0.55 g, 14.5 mmol) was added to a suspension of the hexopyranosidulose **7** (5 g, 14.25 mmol) in methanol (250 cm^3). The reaction was stirred at room temperature for 10 min after which time TLC (light petroleum–ethyl acetate, 2:1) showed one new product (R_f 0.5) and the absence of starting material.

The reaction was quenched with saturated aqueous ammonium chloride (50 cm^3) and the mixture extracted with dichloromethane (3 × 50 cm^3). The combined organic extracts were dried (Na_2SO_4) and concentrated to leave a white solid. This was taken up in ethyl acetate and the solution filtered through a short silica column, eluting with more ethyl acetate. Concentration of the filtrate under reduced pressure left the title compound as a white crystalline solid (5 g, quantitative), m.p. 109–110 °C (from diethyl ether), $[\alpha]_D$ +60.6 (*c* 1.0 in chloroform) (Found: C, 61.2; H, 6.75. $C_{18}H_{24}O_7$ requires C, 61.35; H, 6.9%); ν_{max}(mull)/cm^{-1} 3515s (OH) and 1720s (CO, ester); δ_H 1.27 (3 H, t, *J* 7, CH_3CH_2O), 2.44 (1 H, ddd, *J* 6, 3.5 and 3, 2-H), 2.64 (2 H, dd, *J* 7.5 and 6, 7-H and 7-H'), 2.75 (1 H, d, *J* 7.5, OH), 3.41 (3 H, s, CH_3O), 3.63 (1 H, dd, *J* 10 and 3, 4-H), 3.79 (1 H, t, *J* 10.5, 6-Hax.), 4.09 (1 H, t, *J* 3, 3-H), 4.12 (1 H, td, *J* 10, 10 and 5, 5-H), 4.16 (2 H, q, *J* 7, CH_3CH_2O), 4.36 (1 H, dd, *J* 10.5 and 5, 6-Heq.), 4.75 (1 H, d, *J* 3.5, 1-H), 5.62 (1 H, s, PhC*H*), 7.33–7.39 and 7.47–7.52 (5 H, m, Ph); δ_H(plus $Cl_3CCONCO$) 1.26 (3 H, t, *J* 7, CH_3CH_2O), 2.52 (2 H, dd, *J* 7 and 4, 7-H and 7-H'), 2.66 (1 H, m, 2-H), 3.38 (3 H, s, CH_3O), 3.77 (1 H, t, *J* 10.5, 6-Hax.), 3.79 (1 H, dd, *J* 10 and 3, 4-H), 4.16 (2 H, q, *J* 7, CH_3CH_2O), 4.18 (1 H, td, *J* 10.5, 10.5 and 5.5, 5-H), 4.73 (1 H, d, *J* 4, 1-H), 5.56 (1 H, t, *J* 3, 3-H), 5.60 (1 H, s, PhC*H*) and 7.29–7.41 (5 H, m, Ph); δ_C 14.21 (CH_3CH_2O), 32.11 (C-7), 39.77 (C-2), 55.92 (CH_3O), 57.92 (C-5), 60.56 (CH_3CH_2O), 67.90 (C-3), 69.31 (C-6), 79.93 (C-4), 100.77 (C-1), 101.97 (PhCH), 126.22 and 128.17 (*m*- and *o*-aromatics), 129.00 (*p*-aromatic), 137.30 (*ipso*-aromatic) and 172.04 (CO, ester); *m*/*z* 351 (M^+, 4%) and 105 (100).

Methyl 2-*Deoxy*-4,6-O-(*phenylmethylene*)-α-D-ribo-*hexopyranoside* **10**.—To a suspension of the hexopyranosidulose **6** (0.26 g, 1 mmol) in methanol (25 cm^3) was added sodium borohydride (0.38 g, 1 mmol). The reaction mixture was stirred at room temperature for 10 min after which time TLC (light petroleum–ethyl acetate, 1:1) showed the absence of starting material and one new product (R_f 0.5). The mixture was quenched with saturated aqueous ammonium chloride (25 cm^3) and the emulsion extracted with dichloromethane (4 × 25 cm^3). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to leave an opaque oil. This was taken up in ethyl acetate and the solution filtered through a short silica column, eluting with more ethyl acetate. The filtrate was concentrated under reduced pressure to leave a white crystalline solid (0.26 g, quantitative), m.p. 125–126 °C (from ethyl acetate), $[\alpha]_D$ +151.5 (*c* 1.0 in chloroform) (lit.,[7a] 127–128 °C, $[\alpha]_D$ +146, *c* 0.98 in chloroform and[7b] 124–125 °C, $[\alpha]_D$ +145) (Found: C, 63.1; H, 7.1. Calc. for $C_{14}H_{18}O_5$: C, 63.15; H, 6.8%); ν_{max}(mull)/cm^{-1} 3505s (OH); δ_H 2.00 (1 H, ddd, *J* 15, 4 and 3, 2-Hax.), 2.19 (1 H, ddd, *J* 15, 3 and 1, 2-Heq.), 3.02 (1 H, br s, OH), 3.40 (3 H, s, CH_3O), 3.60 (1 H, dd, *J* 9.5 and 3, 4-H), 3.77 (1 H, t, *J* 9.5, 6-Hax.), 4.14–4.25 (2 H, m, 3-H and 5-H), 4.32 (1 H, dd, *J* 9.5 and 5, 6-Heq.), 4.79 (1 H, dd, *J* 4 and 1, 1-H), 5.62 (1 H, s,

PhC*H*), 7.32–7.40 and 7.47–7.53 (5 H, m, Ph); δ_C 35.51 (C-2), 55.33 (CH_3O), 58.17 (C-5), 64.96 (C-3), 69.32 (C-6), 79.70 (C-4), 98.58 (C-1), 102.02 (PhCH), 126.22 and 128.12 (*m*- and *o*-aromatics), 128.94 (*p*-aromatic) and 137.36 (*ipso*-aromatic); *m/z* 266 (M^+, 9%), 265 ($M^+ - 1$, 16) and 105 (100).

Methyl 2-Deoxy-2-(2-oxoethyl)-4,6-O-(phenylmethylene)-α-D-allopyranoside 2',3 Lactone **2**.—*Aqueous work-up procedure.* To a solution of the allopyranoside **8** (1 g, 2.8 mmol) in THF (20 cm^3) containing a few drops of distilled water was added sodium hydride (50% dispersion in mineral oil; 150 mg, 3.12 mmol). After 20 min, TLC (light petroleum–ethyl acetate, 1:1) showed one new product (R_f 0.5) and the absence of starting material (R_f 0.9). The mixture was diluted with water (20 cm^3) and the organic phase separated. The aqueous layer was *carefully* neutralised with dilute hydrochloric acid and extracted with dichloromethane (3 × 20 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to leave a yellow oil (1.75 g). Purification by flash column chromatography (light petroleum–ethyl acetate, 1:1) gave the title compound as a white crystalline solid (860 mg, 94%), m.p. 199–200 °C (from ethyl acetate), $[\alpha]_D$ +265.0 (*c* 0.1 in chloroform) (Found: C, 62.7; H, 6.0. $C_{16}H_{18}O_6$ requires C, 62.7; H, 5.9%); ν_{max}(mull)/cm^{-1} 1760s (CO, γ-lactone); δ_H 2.46 (1 H, dd, *J* 16.5 and 7, 7-H), 2.60 (1 H, dd, *J* 16.5 and 1, 7-H'), 2.85 (1 H, dddd, *J* 7, 5.5, 4.5 and 1, 2-H), 3.36 (3 H, s, CH_3O), 3.76 (1 H, t, *J* 10.5, 6-Hax.), 3.79 (1 H, dd, *J* 10 and 3.5, 4-H), 4.18 (1 H, ddd, *J* 10.5, 10 and 5, 5-H), 4.35 (1 H, dd, *J* 10.5 and 5, 6-Heq.), 4.69 (1 H, dd, *J* 4 and 3.5, 3-H), 4.73 (1 H, d, *J* 5.5, 1-H), 5.60 (1 H, s, PhC*H*), 7.33–7.40 and 7.48–7.54 (5 H, m, Ph); δ_C 32.61 (C-7), 39.25 (C-2), 55.50 (CH_3O), 56.18 (C-5), 69.04 (C-6), 75.34 (C-3), 76.58 (C-4), 97.76 (C-1), 102.62 (PhC*H*), 126.30 and 128.17 (*m*- and *o*-aromatics), 129.12 (*p*-aromatic), 137.01 (*ipso*-aromatic) and 175.89 (CO, lactone); *m/z* 306 (M^+, 17%), 305 ($M^+ - 1$, 18) and 157 (100). ** Assignments confirmed by COHSE experiments.

Aqueous work-up procedure. To a solution of the allopyranoside **8** (800 mg, 2.27 mmol) in anhydrous THF (30 cm^3) was added sodium hydride (50% dispersion in mineral oil, prewashed with light petroleum; 0.15 g, 3.1 mmol) and the reaction mixture stirred under a silica guard tube. After 20 min, TLC (as above) showed one new product and the absence of starting material. The THF was removed under reduced pressure and the residues were taken up in anhydrous diethyl ether (50 cm^3) and filtered through a short silica column, eluting with more ether. Concentration of the filtrate left the title compound as a white crystalline solid (450 mg, 65%) which was identical [m.p. and ^1H NMR (220 MHz)] with an authentic sample.

Methyl 5'-(R)-2-Deoxy-5'-methyl-2-(2-oxoethyl)-4,6-O-(phenylmethylene)-α-D-allopyranoside 2',3 Lactone **12**.—A solution of the lactone **2** (500 mg, 1.6 mmol) in anhydrous THF (20 cm^3) was stirred at −78 °C under an inert atmosphere. Lithium bis(trimethylsilyl)amide (1 mol dm^{-3} in THF; 1.6 cm^3, 1.6 mmol) was added in one portion and the mixture stirred for 30 min. Methyl iodide (0.1 cm^3; 228 mg, 1.6 mmol) was added in one portion and after 10 min the solution was allowed to warm to room temperature at which time TLC (light petroleum–ethyl acetate, 1:1) showed one new product (R_f 0.4) and no starting material (R_f 0.2). The reaction was quenched with saturated aqueous ammonium chloride (20 cm^3) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 cm^3) and the combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure to leave a white solid (600 mg). This was taken up in ethyl acetate and the solution filtered through a short silica column, eluting with more ethyl acetate. Concentration of the filtrate left the title compound as a white crystalline solid (469 mg, 92%), 177–179 °C (from ethyl acetate), $[\alpha]_D$ +212.0 (*c* 0.99 in chloroform); ν_{max}(mull)/cm^{-1} 1780s (CO, γ-lactone); δ_H 1.28 (3 H, d, *J* 7.5, 8-H_3), 2.48 (1 H, dd, *J* 5.5 and 4.5, 2-H), 2.80 (1 H, q, *J* 7.5, 7-H'), 3.35 (3 H, s, CH_3O), 3.75 (1 H, t, *J* 10.5, 6-Hax.), 3.78 (1 H, dd, *J* 10 and 3.5, 4-H), 4.18 (1 H, ddd, *J* 10.5, 10 and 5.5, 5-H), 4.35 (1 H, dd, *J* 10.5 and 5.5, 6-Heq.), 4.74 (1 H, d, *J* 5.5, 1-H), 4.84 (1 H, br t, *J* 4, 3-H), 5.60 (1 H, s, PhC*H*), 7.33–7.39 and 7.48–7.53 (5 H, m, Ph); δ_C 13.71 (C-8), 38.19 (C-2), 46.01 (C-7), 55.54 (CH_3O), 56.26 (C-5), 69.09 (C-6), 73.35 (C-3), 76.76 (C-4), 97.74 (C-1), 102.67 (PhCH), 126.29 and 128.16 (*m*- and *o*-aromatics), 129.11 (*p*-aromatic), 136.99 (*ipso*-aromatic) and 178.99 (CO, lactone); *m/z* 320 (M^+, 64%) and 171 (100).

Methyl 5'-(R)-2-Deoxy-5'-(1-hexyl)-2-(2-oxoethyl)-4,6-O-(phenylmethylene)-α-D-allopyranoside 2',3 Lactone **13**.—A solution of the lactone **2** (200 mg, 0.65 mmol) in anhydrous THF (15 cm^3) was stirred at −78 °C under an inert atmosphere. Lithium bis(trimethylsilyl)amide (1 mol dm^{-3} in THF; 0.65 cm^3, 0.65 mmol) was added in one portion and the mixture stirred at −78 °C for 30 min. 1-Iodohexane (0.1 cm^3; 0.14 mg, 0.68 mmol) was added in one portion and after 10 min the solution was allowed to warm to room temperature; it was then stirred for a further 6 h. TLC (dichloromethane–light petroleum–ethyl acetate, 5:4:1) showed one new product (R_f 0.9), no starting material and some base-line material. The reaction was quenched with saturated aqueous ammonium chloride (15 cm^3) and the layers separated. The aqueous layer was extracted with dichloromethane (3 × 15 cm^3) and the combined organic phases were dried ($MgSO_4$) and evaporated under reduced pressure to leave a pale yellow oil (500 mg). This was purified by flash column chromatography (light petroleum–ethyl acetate, 4:1) to give the title compound as a colourless oil (116 mg, 59%) which solidified with time, m.p. 96–97 °C (from ethyl acetate), $[\alpha]_D$ +72.0 (*c* 1.0 in chloroform) (Found: M^+, 390.2028. $C_{22}H_{30}O_6$ requires *M*, 390.2042); ν_{max}/cm^{-1} 1780s (CO, γ-lactone); δ_H 0.84–0.92, 1.22–1.32, 1.40–1.50 and 1.63–1.75 (13 H, m, C_6H_{13}), 2.54 (1 H, dd, *J* 5.5 and 4.5, 2-H), 2.65 (1 H, m, 7-H'), 3.35 (3 H, s, CH_3O), 3.75 (1 H, t, *J* 10, 6-Hax.), 3.77 (1 H, dd, *J* 10 and 3.5, 4-H), 4.18 (1 H, td, *J* 10, 10 and 5, 5-H), 4.34 (1 H, dd, *J* 10.5 and 5.5, 6-Heq.), 4.72 (1 H, d, *J* 5.5, 1-H), 4.80 (1 H, br t, *J* 4, 3-H), 5.60 (1 H, s, PhC*H*), 7.33–7.39 and 7.47–7.53 (5 H, m, Ph); δ_C 13.95, 22.46, 27.54, 28.17, 28.85 and 31.46 (C_6H_{13}), 43.75 (C-2), 44.47 (C-7), 55.51 (CH_3O), 56.22 (C-5), 69.10 (C-6), 73.59 (C-3), 76.77 (C-4), 97.94 (C-1), 102.67 (PhCH), 126.29 and 128.16 (*m*- and *o*-aromatics), 129.11 (*p*-aromatic), 136.97 (*ipso*-aromatic) and 178.31 (CO, lactone); *m/z* 390 (M^+, 9%), 389 ($M^+ - 1$, 12) and 105 (100).

Reaction of Methyl 2-Deoxy-2-(2-oxoethyl)-4,6-O-(phenylmethylene)-α-D-allopyranoside 2',3 Lactone **2** *with Isopropyl Bromide.*—A solution of the lactone **2** (150 mg, 0.5 mmol) in anhydrous THF (10 cm^3) was stirred at −78 °C under an inert atmosphere. Lithium bis(trimethylsilyl)amide (1 mol dm^{-3} in THF; 0.5 cm^3, 0.5 mmol) was added in one portion and the mixture stirred at 78 °C for 30 min. 2-Bromopropane (0.05 cm^3; 66 mg, 0.5 mmol) in anhydrous THF (2 cm^3) was added dropwise over 5 min and the solution allowed to warm to room temperature. TLC (light petroleum–ethyl acetate, 1:1) at repeated intervals over 2 h showed a steady increase in base-line product and a disappearance in starting material. The reaction was quenched with saturated aqueous ammonium chloride (15 cm^3) and the organic layer separated. The aqueous layer was extracted with dichloromethane (3 × 15 cm^3) and the combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to leave a pale yellow oil; ^1H NMR (220 MHz) spectrum showed no identifiable product.

Methyl 5'-(R)-2-Deoxy-2-(2-oxoethyl)-4,6-O-(phenylmethyl-

Table 3 Single crystal X-ray analyses: crystal, data collection and refinement parameters

Crystal parameters	Compd. **12**	Compd. **13**
Formula	$C_{17}H_{20}O_6$ (320.4)	$C_{19}H_{22}O_6$ (346.4)
Crystallization medium	EtOAc–light petroleum (b.p. 40–60 °C)	EtOAc
Crystal size/mm	0.16 × 0.19 × 0.21	0.34 × 0.48 × 0.74
Cell dimensions	a = 9.129(3) Å	8.440(2) Å
	b = 11.012(4) Å	13.264(3) Å
	c = 15.923(5) Å	15.851(6) Å
	α = 90.00°	90.00°
	β = 90.00°	90.00°
	γ = 90.00°	90.00°
	V = 1601(1) Å^3	1774.5(8) Å^3
Space group	$P2_12_12_1$	$P2_12_12_1$
Molecules (unit cell)	4	4
D_o/g cm^{-3}	1.33	1.30
D_c/g cm^{-3}	1.33	7.60
Linear absorption factor/cm^{-1}	8.00	
(B) Refinement parameters		
Number of reflections	976	1085
Nonzero reflections ($I > 3.0\sigma$)	963	1065
R-Index[a]	0.029	0.033
GOF[b]	1.39	1.69
Scale factor	1.249(2)	1.256(3)
Secondary extinction factor	32(3) × 10^{-3}	5(1) × 10^{-3}

[a] R-Index = $\Sigma\|\|F_o\| - \|F_c\|\|/\Sigma|F_o|$. [b] For compound **12**: GOF = $[\Sigma w(F_o^2 - F_c^2)^2/(m-s)]^{\frac{1}{2}}$; for compound **13**: GOF = $[\Sigma w(F_o^2 - F_c^2)^2/(m-s)]^{\frac{1}{2}}$ where $w = [\sigma^2(F) + |g|F^2]^{-1}$ $g = 0.00100$.

ene)-5′-(2-*propenyl*)-α-D-*allopyranoside* 2′,3 *Lactone* **14**.—A solution of the lactone **2** (200 mg, 0.65 mmol) in anhydrous THF (15 cm^3) was stirred at −78 °C under an inert atmosphere. Lithium bis(trimethylsilyl)amide (1 mol dm^{-3} in THF; 0.65 cm^3, 0.65 mmol) was added in one portion and the mixture stirred at −78 °C for 30 min. Allyl bromide (0.1 cm^3; 0.14 g, 0.69 mmol) was added in one portion. The mixture was stirred for 10 min and then allowed to warm to room temperature; it was then stirred for a further 2 h. TLC (light petroleum–ethyl acetate, 2:1) showed one new product (R_f 0.7) and no starting material. The reaction was quenched with saturated aqueous ammonium chloride (15 cm^3) and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 15 cm^3) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to leave a white solid (300 mg). This was taken up in ethyl acetate and filtered through a short silica column eluting with more ethyl acetate. Concentration of the filtrate under reduced pressure left the title compound as a white crystalline solid (200 mg, 89%), m.p. 131–133 °C (from ethyl acetate), $[\alpha]_D$ +178.2 (*c* 0.5 in chloroform) (Found: C, 65.9; H, 6.3. $C_{19}H_{22}O_6$ requires C, 65.9; H, 6.4%); ν_{max}(mull)/cm^{-1} 1790s, 1775s; δ_H 2.24 (1 H, dddt, *J* 14.5, 10.5, 8, 1 and 1, 8-H), 2.51 (1 H, dtt, *J* 14.5, 5.5, 5.5, 1 and 1, 8-H′), 2.60 (1 H, dd, *J* 5.5 and 4.5, 2-H), 2.78 (1 H, dd, *J* 10.5 and 5.5, 7-H′), 3.35 (3 H, s, CH_3O), 3.74 (1 H, t, *J* 10, 6-Hax.), 3.77 (1 H, dd, *J* 10 and 3.5, 4-H), 4.18 (1 H, td, *J* 10, 10 and 5.5, 5-H), 4.35 (1 H, dd, *J* 10 and 5, 6-Heq.), 4.70 (1 H, d, *J* 5.5, 1-H), 4.80 (1 H, br t, *J* 4, 3-H), 5.12 (1 H, ddd, *J* 10.5, 1.5 and 1, 10-H), 5.13 (1 H, ddd, *J* 16.5, 1.5 and 1, 10-H′), 5.60 (1 H, s, PhC*H*), 5.80 (1 H, dddd, *J* 16.5, 10.5, 8 and 5.5, 9-H), 7.33–7.39 and 7.47–7.54 (5 H, m, Ph); δ_C 32.30 (C-8), 43.30 (high intensity, C-2 and C-7), 55.54 (CH_3O), 56.19 (C-5), 69.08 (C-6), 73.54 (C-3), 76.60 (C-4), 97.82 (C-1), 102.71 (Ph*C*H), 118.20 (C-10), 126.28 and 128.21 (*m*- and *o*-aromatics), 129.17 (*p*-aromatic), 134.17 (C-9), 136.88 (*ipso*-aromatic) and 177.80 (CO, lactone); *m*/*z* 346 (M$^+$, 32%) and 197 (100.

Single Crystal X-Ray Analyses.—A representative crystal of each of compounds **12** and **13** was surveyed and a 1 Å data set (maximum sin θ/λ = 0.5) was collected on a Nicolet R3m/μ diffractometer. Atomic scattering factors were taken from the International Tables for X-ray Crystallography.[15] All crystallographic calculations were facilitated by the SHELXTL[16] system. All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarised in Table 3.

A trial structure for each determination was obtained by direct methods. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least squares refinement were all less than 0.1 of their corresponding standard deviations. The final R-index was 0.029 for compound **12** and 0.033 for compound **13**. A final difference Fourier revealed no missing or misplaced electron density in either determination.

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