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ACETONIDES OF α-HYDROXY-δ-ALTRONOLACTONES

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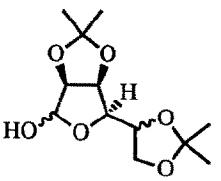
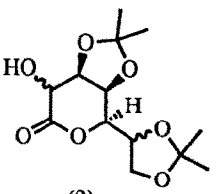
The preparation and characterisation of some derivatives of α-hydroxy-δ-lactones, in which the δ-carbon substituent on the lactone ring is *trans* to an adjacent isopropylidene protected diol, are described; the X-ray crystal structures of 3,4-*O*-isopropylidene-**D**-altrono-1,5-lactone and of 3,4:6,7-di-*O*-isopropylidene-**D**-*glycero*-**D**-*altro*-heptono-1,5-lactone are reported.

γ-Hydroxy-δ-lactones are prone to isomerise to the more stable γ-lactones, so that the chemistry of highly functionalised δ-lactones derived from sugars has been relatively little studied. The Kiliani ascension[1,2] of aldoses with a protecting group on the C-3 hydroxyl group should provide easy access to such a class of compounds. Recently, the potential of α-hydroxy-δ-lactones for the synthesis of such diverse targets as complex nitrogen heterocycles - including piperidines,[3] pyrrolizidines[4,5] castanospermines,[6] and alexines[7,8] - 2,5-substituted tetrahydrofurans - such as C-nucleoside analogues[9] - and very highly functionalised carbocycles[10] has been demonstrated. The preceding paper[11] describes the synthesis from diacetonides of gulose and mannose (1) of protected derivatives of α-hydroxy-δ-lactones (2) in which the carbon substituent on the lactone is *cis* to the adjacent isopropylidene protected diol; the preparation of protected derivatives of α-hydroxy-δ-lactones (3), in which the carbon substituent on the lactone is *trans* to the adjacent isopropylidene protected diol, from acetonides of allose and ribose (4) is described in this paper.


(1)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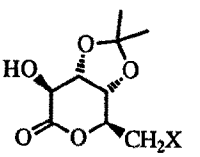
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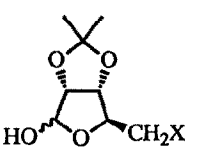
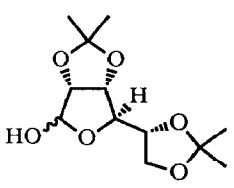

(4)

When diacetone allose (5)[12] was subjected to the Kiliani reaction with sodium cyanide, a mixture of heptonolactone diacetonides was isolated in 26% yield from which the predominant isomer [about 90% of the mixture] could be crystallised and was shown by X-ray crystallographic analysis (Figure 1) to be the **D**-*glycero*-**D**-*altro*-diacetonide (6). The readily available isopropylidene ribose (7) was also treated under the



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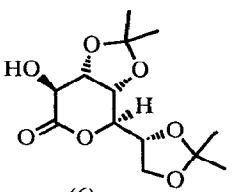
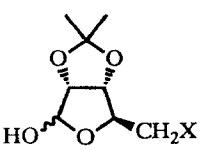
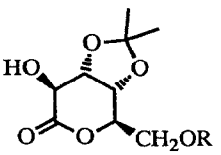


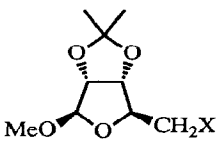
(6)



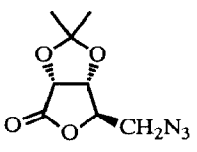
(7) X=OH
(8) X=N_3



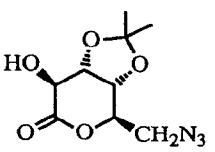
(9) R=H (10) R=$SiMe_2Bu^t$
(11) R= SO_2CF_3



(12) X=OTs (13) X=N_3



(14)



(15)

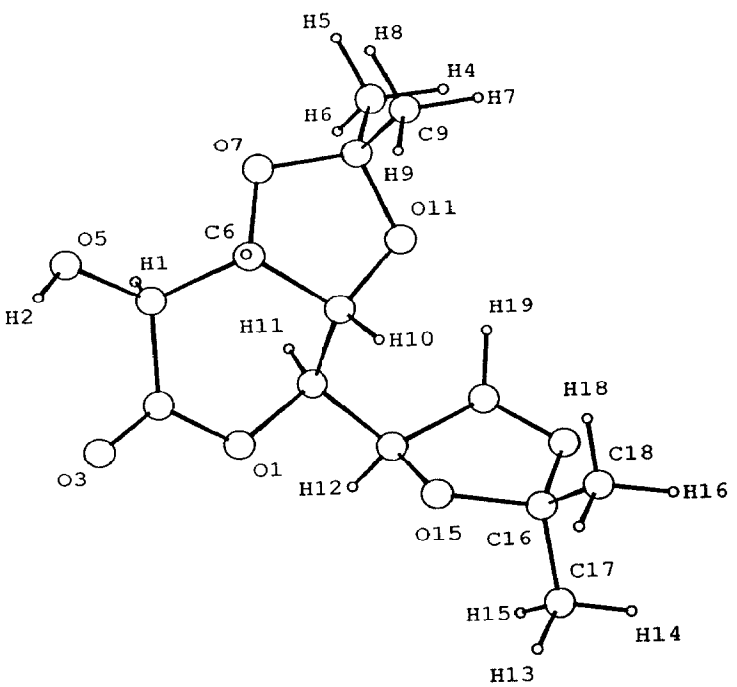


Figure 1. X-Ray molecular structure of 3,4:6,7-di-*O*-isopropylidene-**D**-*glycero*-**D**-*altro*-heptono-1,5-lactone (6) showing crystallographic numbering scheme.

same conditions and the altronolactone (9) (Figure 2) was the only product isolated [approximately 10% yield based on crude isopropylidene ribose ((7)]. The primary hydroxyl group in (9) was efficiently protected as the corresponding 6-*O*-*tert*-butyldimethylsilyl ether (10) [83% yield], in which only the α-hydroxyl group of the δ-lactone remained unprotected. However, attempts to make 6-*O*-silyl ethers, such as (10), by cyanide chain extension of the corresponding 5-*O*-silyl ethers of isopropylidene ribose (7) were completely unsuccessful.

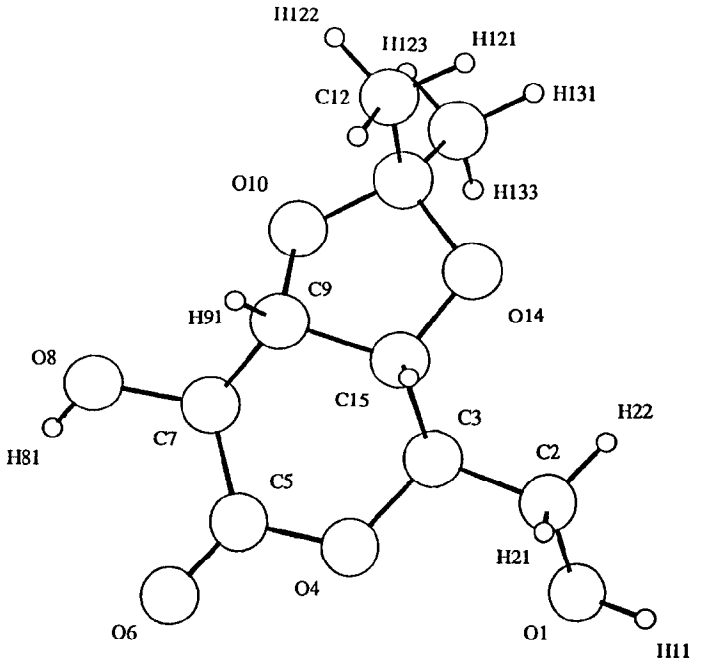


Figure 2. X-Ray molecular structure of 3,4-*O*-isopropylidene-**D**-altrono-1,5-lactone (9) showing crystallographic numbering scheme.

The 5-azidoribofuranose (8) was prepared by diisobutylaluminium hydride reduction of the known azidolactone (14).[13] More conveniently for larger scales, azide displacement of the tosylate in (12)[14] with azide ion gave the corresponding azide (13) [80% yield] from which the anomeric methyl group could be removed by acid hydrolysis to afford the required azidofuranose (8) in 72% yield. Treatment of (8) with sodium cyanide led to the isolation of the 6-azido-δ-lactone (15) in 27% yield; the stereochemistry of the free α-hydroxyl group in (15) was established by treating the altrono-lactone (9) with trifluoromethanesulphonic anhydride to give the corresponding triflate (11) which with sodium azide gave (15), identical to the material from the Kiliani ascension.

Thorough investigations by Isbell[15] have elucidated many features of the cyanide chain extension. The yields for the Kiliani ascension for these reactions are disappointingly low when compared with those for the diacetonides of gulose and mannose (1)[11,16] which afford the α-hydroxy-δ-lactones (2) in yields of 35-40%. However, the poor yields of chain extended products found with Bucherer-Kiliani reactions of acetonides of aldoses[17] have been attributed to the sensitivity of the isopropylidene groups in these situations to base catalysed fragmentation. We investigated the effects of solvent, temperature and pH on the reactions of the above furanoses with cyanide; NMR studies on the reaction mixtures of cyanide with isopropylidene ribose (7) indicated that the majority of the material loses the isopropylidene protecting group over a wide range of pH. In summary, the synthesis of acetonides of altrono-1,5-lactones by the Kiliani reaction of ribose and allose 2,3-isopropylidene ketals proceeds only in low yield. Although sufficient quantities can be made to establish the value of such α-hydroxy-δ-lactones as intermediates, large amounts would be difficult to make by this route; alternative procedures for their synthesis are currently being studied.

X-Ray Crystal Structure Analyses

The structures of 3,4-*O*-isopropylidene-**D**-altrono-1,5-lactone (9) (crystallised from hexane/ethyl acetate) and 3,4:6,7-di-*O*-isopropylidene-**D**-*glycero*-**D**-*altro*-heptono-1,5-lactone (6) (from hexane/ethyl acetate) were established by single crystal X-ray analysis. For both compounds, cell dimensions and intensity data were measured with an Enraf-Nonius CAD4-F diffractometer up to $\theta = 75^{o}$ (Cu-Kα radiation). The data were corrected for absorption, Lorentz and polarisation effects. All calculations were carried out on a Microvax 3800 computer using SHELXS-86[18] for direct methods and CRYSTALS[19] for all other calculations. Atomic scattering factors were taken from International Tables.[20] Atomic coordinates for both compounds have been deposited at the Cambridge Crystallographic Data Centre.[21] The coordinates of all non-hydrogen atoms were given by SHELXS-86. The hydrogen atoms were placed geometrically except for the hydroxyl hydrogens which were found by Fourier difference maps. The structures were refined by full-matrix least-squares with isotropic temperature factors for the hydrogen atoms and anisotropic temperature factors for all other atoms using data with merged Friedel pairs. Corrections for secondary extinction were applied,[22] and the models refined almost to convergence. The data were refined using Chebyshev weighting schemes[23] to give a final value of R = 0.0336 for 3,4-*O*-isopropylidene-**D**-altrono-1,5-lactone (9) and a final value of R = 0.0609 for 3,4:6,7-di-*O*-isopropylidene-**D**-*glycero*-**D**-*altro*-heptono-1,5-lactone (6)

Crystal Data for 3,4-di-*O*-isopropylidene-**D**-altrono-1,5-lactone (9).

Molecular formula $C_9H_{14}O_6$ Formula weight 218.206

Crystal data:

Crystal system orthorhombic

a/Å 7.004(4) $\alpha/^{o}$ 90

b/Å 8.954(6) $\beta/^{o}$ 90

c/Å 16.738(3) $\gamma/^{o}$ 90

space group $P2_12_12_1$ $D_C/g\ cm^{-3}$ 1.385

linear absorption coeff. /cm^{-1} 9.65

Crystal size /mm 0.1 x 0.2 x 0.6

Data collection:

X-radiation λ = 1.5418 Å Cu-Kα

θ min., max. /^{o} 0, 75

ω-scan parameters: A, B (^{o}) (A + B tanθ) A = 0 B = 0

Horizontal aperture parameters: A, B (mm) (A + B tanθ) A = 0.6 B = 0.15

Scan speed/^{o} min^{-1} 1.1 (min.) to 1.7 (max.)

Total data 1823 Total unique data 1211

Observed data 838, for [I>nσ(I)] where n = 3

Absorption correction, Psi scan: min 1.00, max 1.12 Sheldrick Merging R 3.36%

Refinement: Solved by SHELXS-86

Weighting Scheme type Chebyshev 4 coefficients, 2.00, -1.35, 1.25, -0.859

Extinction parameter 47(4)

Maximum residual electron density/ $eÅ^{-3}$ 1.4

Final R 3.62% R_w 4.13%

Fractional atomic coordinates and equivalent isotropic temperature factors U(equ) with standard deviations in parentheses for 3,4-di-*O*-isopropylidene-**D**-altrono-1,5-lactone (9).

Atom	x/a	y/b	z/c	U(iso)
O(1)	0.0062(4)	-0.2930(3)	-0.2993(1)	0.0422
C(2)	-0.0056(6)	-0.1379(4)	-0.3163(2)	0.0412
C(3)	0.1331(5)	-0.1002(3)	-0.3818(2)	0.0347
O(4)	0.0656(4)	-0.1753(3)	-0.4535(1)	0.0402
C(5)	0.1542(5)	-0.1433(4)	-0.5233(2)	0.0381
O(6)	0.1029(4)	-0.2077(3)	-0.5829(1)	0.0497
C(7)	0.3166(5)	-0.0327(4)	-0.5194(2)	0.0364
O(8)	0.3712(4)	0.0144(3)	-0.5963(1)	0.046
C(9)	0.2670(5)	0.1043(3)	-0.4699(2)	0.0340
O(10)	0.4371(4)	0.1576(3)	-0.4328(1)	0.0448
C(11)	0.3880(5)	0.2246(4)	-0.3590(2)	0.0431
C(12)	0.3339(7)	0.3870(4)	-0.3692(3)	0.0597
C(13)	0.5476(8)	0.2012(8)	-0.3004(3)	0.0834
O(14)	0.2215(4)	0.1418(3)	-0.3326(1)	0.0452
C(15)	0.1367(5)	0.0672(4)	-0.3989(2)	0.0366

Final anisotropic temperature factors with standard deviations in parentheses for 3,4-di-*O*-isopropylidene-**D**-altrono-1,5-lactone (9).

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
O(1)	0.065(2)	0.038(1)	0.033(1)	0.002(1)	0.010(1)	-0.010(1)
C(2)	0.060(2)	0.038(2)	0.034(2)	-0.003(1)	0.014(2)	-0.006(2)
C(3)	0.045(2)	0.035(2)	0.028(1)	-0.005(1)	0.006(1)	-0.002(2)
O(4)	0.058(1)	0.041(1)	0.031(1)	-0.0052(9)	0.007(1)	-0.015(1)
C(5)	0.049(2)	0.034(2)	0.033(2)	-0.001(1)	0.004(1)	0.001(2)
O(6)	0.069(2)	0.053(1)	0.036(1)	-0.008(1)	0.002(1)	0.010(1)
C(7)	0.047(2)	0.036(2)	0.030(2)	-0.001(1)	0.009(1)	-0.001(2)
O(8)	0.078(2)	0.042(1)	0.038(1)	-0.001(1)	0.024(1)	-0.003(1)
C(9)	0.043(2)	0.032(1)	0.030(1)	0.001(1)	0.004(1)	-0.000(2)
O(10)	0.044(1)	0.053(1)	0.044(1)	-0.013(1)	0.010(1)	-0.007(1)
C(11)	0.051(2)	0.044(2)	0.037(2)	-0.006(1)	0.005(2)	-0.003(2)
C(12)	0.077(3)	0.039(2)	0.084(3)	-0.009(2)	0.028(3)	-0.011(2)
C(13)	0.083(3)	0.128(5)	0.063(3)	-0.009(4)	-0.026(3)	0.009(4)
O(14)	0.074(2)	0.049(1)	0.038(1)	-0.015(1)	0.021(1)	-0.024(2)
C(15)	0.042(2)	0.034(2)	0.036(2)	-0.002(1)	0.009(2)	0.002(2)

Bond lengths (in Å) for the non-hydrogen atoms with standard deviations in parentheses for 3,4-di-*O*-isopropylidene-**D**-altrono-1,5-lactone (9).

O(1) - C(2)	1.418(4)	C(2) - C(3)	1.503(4)
C(3) - O(4)	1.452(3)	C(3) - C(15)	1.524(5)
O(4) - C(5)	1.353(4)	C(5) - O(6)	1.206(4)
C(5) - C(7)	1.508(5)	C(7) - O(8)	1.407(4)
C(7) - C(9)	1.518(4)	C(9) - O(10)	1.424(4)
C(9) - C(15)	1.533(4)	O(10) - C(11)	1.415(4)
C(11) - C(12)	1.510(5)	C(11) - C(13)	1.501(6)
C(11) - O(14)	1.449(4)	O(14) - C(15)	1.423(4)

Bond angles (in degrees) for the non-hydrogen atoms with standard deviations in parentheses for 3,4-di-*O*-isopropylidene-**D**-altrono-1,5-lactone (9).

C(3) - C(2) - O(1)	109.1(3)	O(4) - C(3) - C(2)	106.7(3)
C(15) - C(3) - C(2)	111.6(3)	C(15) - C(3) - O(4)	107.8(3)
C(5) - O(4) - C(3)	117.7(2)	O(6) - C(5) - O(4)	118.4(3)
C(7) - C(5) - O(4)	116.5(3)	C(7) - C(5) - O(6)	125.0(3)
O(8) - C(7) - C(5)	111.2(3)	C(9) - C(7) - C(5)	112.4(3)
C(9) - C(7) - O(8)	108.6(3)	O(10) - C(9) - C(7)	108.4(3)
C(15) - C(9) - C(7)	112.6(3)	C(15) - C(9) - O(10)	103.5(2)
C(11) - O(10) - C(9)	108.6(3)	C(12) - C(11) - O(10)	111.7(3)
C(13) - C(11) - O(10)	109.3(3)	C(13) - C(11) - C(12)	113.3(4)
O(14) - C(11) - O(10)	104.1(3)	O(14) - C(11) - C(12)	108.9(3)
O(14) - C(11) - C(13)	109.2(3)	C(15) - O(14) - C(11)	109.7(2)
C(9) - C(15) - C(3)	111.5(3)	O(14) - C(15) - C(3)	108.7(3)
O(14) - C(15) - C(9)	104.7(3)		

Crystal Data for 3,4:6,7-di-*O*-isopropylidene-**D**-*glycero*-**D**-*altro*-heptono-1,5-lactone (6).

Molecular formula	$C_{13}H_{20}O_7$	Formula weight	288.30
Crystal data:			
Crystal system	orthorhombic primitive		
a/Å	8.781(0.003)	α/°	90
b/Å	6.928(0.002)	β/°	90
c/Å	24.059(0.003)	γ/°	90
space group	$P2_12_12_1$	D_c/g cm^{-3}	1.308
linear absorption coeff. /cm^{-1}	8.63		
Crystal size /mm	0.2 x 0.7 x 1.1		
Data collection:			
X-radiation	λ = 1.5418 Å Cu-Kα		
θ min., max. /°	0, 75		
ω-scan parameters:	A, B (°) (A + B tanθ) A = 1.2 B = 0.15		
Horizontal aperture parameters:	A, B (mm) (A + B tanθ) A = 3.0 B = 0		
Scan speed/° min^{-1}	1.8 (min.) to 6.7 (max.)		
Total data	1731		
Observed data	1588 for [I>nσ(I)] where n = 3		
Absorption correction:	min 1.16 , max 1.65	Merging R	3.32 %
Refinement:	Solved by SHELXS-86		
Weighting Scheme type Chebyshev 3 coefficients	16.56 7.26 11.71		
Extinction parameter	76.66		
Maximum residual electron density/ eÅ^{-3}	0.8		
Final R	6.11 %	R_w	8.78 %

Fractional atomic coordinates and equivalent isotropic temperature factors U(equ) with standard devia parentheses for 3,4:6,7-di-O-isopropylidene-**D**-*glycero*-**D**-*altro*-heptono-1,5-lactone (6)

Atom	x/a	y/b	z/c	U(iso)
O(1)	-0.3906(3)	-0.1197(4)	-0.97654(9)	0.0476
O(3)	-0.4888(4)	-0.2327(4)	-1.0544(1)	0.0616
O(5)	-0.7009(4)	0.0552(4)	-1.0626(1)	0.0560
O(7)	-0.7351(4)	0.2465(4)	-0.9510(1)	0.0575
O(11)	-0.5982(3)	0.1718(5)	-0.8747(1)	0.0565
O(15)	-0.3136(3)	-0.2220(4)	-0.8691(1)	0.0530
O(119)	-0.307(1)	-0.027(1)	-0.7955(3)	0.0668
O(219)	-0.212(1)	-0.040(1)	-0.7985(3)	0.0714
C(2)	-0.4907(4)	-0.1140(5)	-1.0185(1)	0.0496
C(4)	-0.6020(4)	0.0551(5)	-1.0169(1)	0.0457
C(6)	-0.6809(4)	0.0559(5)	-0.9612(1)	0.0452
C(8)	-0.7212(5)	0.2839(7)	-0.8936(2)	0.0604
C(9)	-0.8682(7)	0.218(1)	-0.8649(2)	0.0918
C(10)	-0.692(1)	0.485(1)	-0.8808(4)	0.1102
C(12)	-0.5716(4)	0.0182(5)	-0.9127(1)	0.0436
C(13)	-0.4050(4)	0.0212(5)	-0.9324(1)	0.0439
C(14)	-0.2853(4)	-0.0336(5)	-0.8899(2)	0.0483
C(16)	-0.2681(6)	-0.2262(6)	-0.8120(2)	0.0590
C(17)	-0.1167(8)	-0.325(2)	-0.8066(2)	0.0937
C(18)	-0.3848(8)	-0.334(1)	-0.7802(2)	0.0924
C(20)	-0.2775(5)	0.0919(6)	-0.8377(2)	0.0580

Final anisotropic temperature factors with standard deviations in parentheses for 3,4:6,7-di-O-isopropylidene-**D**-*glycero*-**D**-*altro*-heptono-1,5-lactone (6)

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
O(1)	0.043(1)	0.051(1)	0.053(1)	-0.008(1)	-0.003(1)	0.008(1)
O(3)	0.063(2)	0.068(2)	0.065(2)	-0.025(1)	-0.008(1)	0.011(1)
O(5)	0.071(2)	0.050(1)	0.055(1)	-0.004(1)	-0.016(1)	0.011(1)
O(7)	0.069(2)	0.057(2)	0.057(1)	-0.006(1)	-0.010(1)	0.022(1)
O(11)	0.051(1)	0.074(2)	0.056(1)	-0.014(1)	-0.009(1)	0.019(1)
O(15)	0.065(2)	0.048(1)	0.051(1)	-0.004(1)	-0.012(1)	0.005(1)
O(119)	0.070(4)	0.079(4)	0.064(3)	-0.025(3)	0.012(3)	-0.010(4)
O(219)	0.086(5)	0.074(4)	0.078(4)	-0.024(4)	-0.034(4)	0.005(5)
C(2)	0.048(2)	0.048(2)	0.052(2)	-0.002(1)	0.003(1)	0.001(2)
C(4)	0.047(2)	0.041(2)	0.049(2)	-0.000(1)	-0.003(1)	0.002(1)
C(6)	0.038(2)	0.048(2)	0.052(2)	0.002(1)	-0.002(1)	-0.001(1)
C(8)	0.058(2)	0.075(3)	0.069(2)	-0.021(2)	-0.022(2)	0.024(2)
C(9)	0.067(3)	0.182(8)	0.075(3)	0.010(4)	0.016(2)	0.037(4)
C(10)	0.174(8)	0.095(5)	0.181(8)	-0.076(5)	-0.097(7)	0.056(5)
C(12)	0.045(2)	0.037(1)	0.051(2)	0.004(1)	0.001(1)	0.003(1)
C(13)	0.043(2)	0.039(1)	0.051(2)	0.001(1)	0.002(1)	-0.005(1)
C(14)	0.043(2)	0.044(2)	0.061(2)	-0.009(1)	-0.004(2)	0.001(1)
C(16)	0.075(3)	0.063(2)	0.045(2)	-0.009(2)	-0.007(2)	0.002(2)
C(17)	0.079(4)	0.201(8)	0.060(2)	-0.003(4)	-0.015(2)	0.038(5)
C(18)	0.091(4)	0.142(6)	0.063(2)	0.007(3)	-0.006(3)	-0.020(4)
C(20)	0.056(2)	0.059(2)	0.070(2)	-0.019(2)	-0.016(2)	0.002(2)

Bond lengths (in Å) for the non-hydrogen atoms with standard deviations in parentheses for 3,4:6,7-di-O-isopropylidene-**D**-*glycero*-**D**-*altro*-heptono-1,5-lactone (6)

O(1) - C(2)	1.339(4)	O(1) - C(13)	1.449(4)
O(3) - C(2)	1.193(4)	O(5) - C(4)	1.400(4)
O(7) - C(6)	1.425(4)	O(7) - C(8)	1.411(5)
O(11) - C(8)	1.407(5)	O(11) - C(12)	1.421(4)
O(15) - C(14)	1.420(5)	O(15) - C(16)	1.431(4)
O(119)- O(219)	0.842(9)	O(119)- C(16)	1.473(9)
O(119)- C(20)	1.335(9)	O(219)- C(16)	1.421(9)
O(219)- C(20)	1.433(9)	C(2) - C(4)	1.527(5)
C(4) - C(6)	1.509(4)	C(6) - C(12)	1.534(4)
C(8) - C(9)	1.534(8)	C(8) - C(10)	1.451(8)
C(12) - C(13)	1.538(5)	C(13) - C(14)	1.513(5)
C(14) - C(20)	1.529(5)	C(16) - C(17)	1.501(8)
C(16) - C(18)	1.479(8)		

Bond angles (in degrees) for the non-hydrogen atoms with standard deviations in parentheses for 3,4:6,7-di-O-isopropylidene-**D**-*glycero*-**D**-*altro*-heptono-1,5-lactone (6)

C(13) - O(1) - C(2)	118.4(3)	C(8) - O(7) - C(6)	108.0(3)
C(12) - O(11) - C(8)	109.4(3)	C(16) - O(15) - C(14)	108.0(3)
C(16) - O(119)- O(219)	69.7(9)	C(20) - O(119)- O(219)	78.8(9)
C(20) - O(119)- C(16)	109.2(5)	C(16) - O(219)- O(119)	76.6(10)
C(20) - O(219)- O(119)	66.0(9)	C(20) - O(219)- C(16)	106.8(5)
O(3) - C(2) - O(1)	121.1(3)	C(4) - C(2) - O(1)	115.1(3)
C(4) - C(2) - O(3)	123.7(3)	C(2) - C(4) - O(5)	112.2(3)
C(6) - C(4) - O(5)	114.4(3)	C(6) - C(4) - C(2)	108.5(3)
C(4) - C(6) - O(7)	108.0(3)	C(12) - C(6) - O(7)	103.6(3)
C(12) - C(6) - C(4)	112.9(3)	O(11) - C(8) - O(7)	106.4(3)
C(9) - C(8) - O(7)	108.3(4)	C(9) - C(8) - O(11)	109.6(5)
C(10) - C(8) - O(7)	113.5(5)	C(10) - C(8) - O(11)	109.1(5)
C(10) - C(8) - C(9)	109.8(7)	C(6) - C(12) - O(11)	105.0(3)
C(13) - C(12) - O(11)	110.1(3)	C(13) - C(12) - C(6)	111.0(3)

C(12) - C(13) - O(1)	107.4(3)	C(14) - C(13) - O(1)	105.4(3)
C(14) - C(13) - C(12)	116.7(3)	C(13) - C(14) - O(15)	110.4(3)
C(20) - C(14) - O(15)	103.9(3)	C(20) - C(14) - C(13)	116.2(3)
O(119)- C(16) - O(15)	100.0(4)	O(219)- C(16) - O(15)	107.3(4)
O(219)- C(16) - O(119)	33.8(4)	C(17) - C(16) - O(15)	109.9(4)
C(17) - C(16) - O(119)	127.4(7)	C(17) - C(16) - O(219)	95.0(7)
C(18) - C(16) - O(15)	108.2(4)	C(18) - C(16) - O(119)	99.8(5)
C(18) - C(16) - O(219)	125.4(6)	C(18) - C(16) - C(17)	109.9(5)
O(219)- C(20) - O(119)	35.2(4)	C(14) - C(20) - O(119)	105.3(4)
C(14) - C(20) - O(219)	101.4(4)		

Experimental

General Methods. Melting points were recorded on a Kofler hot block. Proton nuclear magnetic resonance (δ_H) spectra were recorded on Varian Gemini 200 (at 200 MHz) or Bruker WH 300 (300 MHz) spectrometers. ^{13}C Nuclear magnetic resonance (δ_C) spectra were recorded on a Varian Gemini 200 (50 MHz) spectrometer and multiplicities were assigned using DEPT sequence. ^{13}C spectra run in D_2O were referenced to methanol (δ_C 49.6 ppm) as an internal standard. All chemical shifts are quoted on the δ-scale. Infra-red spectra were recorded on a Perkin-Elmer 781, or on a Perkin-Elmer 1750 FT spectrophotometer. Mass spectra were recorded on VG Micromass 30F, ZAB 1F, Masslab 20-250 or Trio-1 GCMS (DB-5 column) spectrometers using desorption chemical ionisation (NH_3, DCI) or chemical ionisation (NH_3, CI), as stated. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 ml. Microanalyses were performed by the microanalysis service of the Dyson-Perrins laboratory. Thin layer chromatography (t.l.c.) was carried out on aluminium sheets coated with $60F_{254}$ silica or glass plates coated with silica Blend 41. Plates were developed using a spray of 0.2% w/v cerium (IV) sulphate and 5% ammonium molybdate in 2M sulphuric acid. Flash chromatography was carried out using Sorbsil C60 40/60 silica. Solvents and commercially available reagents were dried and purified before use according to standard procedures; dichloromethane was refluxed over and distilled from calcium hydride, methanol was distilled from magnesium methoxide, pyridine was distilled from, and stored over, potassium hydroxide; tetrahydrofuran was distilled, under nitrogen, from a solution dried with sodium in the presence of benzophenone. Hexane was distilled at 68°C before use to remove involatile fractions. 2,3:5,6-Di-*O*-isopropylidene-**D**-allofuranose (5),[12] 5-azido-5-deoxy-2,3-*O*-isopropylidene-**D**-*ribono*-1,4-lactone (14)[13] and methyl 2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulphonyl-β-**D**-ribofuranoside (12)[14] were prepared according to literature procedures.

3,4:6,7-Di-*O*-isopropylidene-**D**-*glycero*-**D**-*altro*-heptono-1,5-lactone (6). Sodium cyanide (450 mg, 1.1 equiv) was added to a suspension of 2,3:5,6-di-*O*-isopropylidene-**D**-allofuranose (5) (2.16 g, 8.3 mmol) in water (30 ml), and the reaction mixture was refluxed for 3 h during which time ammonia was evolved. The reaction mixture was acidified with aqueous hydrochloric acid and extracted with dichloromethane in order to recover unreacted diacetone allose (214 mg, 10%). The aqueous layer was then extracted with ethyl acetate (4 x 30 ml) and the organic layer was dried (magnesium sulphate). Unlike the cases of the many other heptonolactones, no lactonisation to the δ-lactone took place, so that the solvent was removed and the residue dissolved in dry toluene and treated with dicyclohexyl carbodiimide. After 10 h at room temperature, all the acid had cyclised as judged by t.l.c. The reaction mixture was filtered through a silica plug, the solvent removed *in vacuo*, and the residue purified by flash chromatography (hexane : ethyl acetate, 1 : 1) to give the *altro* heptonolactone (6), R_f 0.35 in hexane : ethyl acetate, 1 : 1, (544 mg, 26%), contaminated with *ca.* 10% of the *allo* isomer. Recrystallisation from ethyl acetate/hexane gave pure *3,4:6,7-di-O-isopropylidene-D-*

glycero-D-altro-heptono-1,5-lactone , m.p. 140°C; $[\alpha]_D^{20}$ +81.2 (*c*, 1.15 in $CHCl_3$); υ_{max} ($CHCl_3$): 3520 (br, OH), 1763 (C=O) cm^{-1}; δ_H ($CDCl_3$): 1.39 (3H, s, Me), 1.41 (3H, s, Me), 1.48 (3H, s, Me), 1.55 (3H, s, Me), 3.40 (1H, d, OH, J 3.4 Hz), 4.10 (2H, AB of ABX, H-7, H-7'), 4.32 (3H, m, H-3, H-4, H-5), 4.45 (2H, m, H-2, H-6); δ_C ($CDCl_3$): 24.26, 25.13, 25.95, 26.62 (4 x q, 4 x MeC), 64.30 (t, C-7) 70.63, 71.56, 74.95, 76.40, 77.70 (5 x d, C-2, C-3, C-4, C-5, C-6), 110.32, 112.61 (2 x s, 2 x $\underline{C}Me_2$), 172.23 (s, C-1); *m/z* (NH_3, DCI): 306 ($M+NH_4^+$, 70%) , 289 ($M+H^+$, 100%). (Found: C, 54.46; H, 7.28. $C_{13}H_{20}O_7$ requires: C, 54.16; H, 6.99%).

3,4-*O*-Isopropylidene-altrono-1,5-lactone (9). D-Ribose (3.07 g, 20 mmol), Dowex 50W-X8 [H^+] ion exchange resin (1.5 g) and dried 3A molecular sieves (1.5 g, bead form) were stirred vigorously at room temperature in acetone (50 ml, dried over $MgSO_4$). After 3 h t.l.c. (ethyl acetate) indicated complete consumption of starting material (R_f 0.1), and the formation of 2,3-isopropylidene ribose (7) as a major product (R_f 0.6), together with other minor products (R_f 0.8 and R_f 0.3). The suspension was then filtered, the solvent removed and the residue co-evaporated with acetonitrile (2 x 10 ml) to remove traces of acetone yielding a crude syrup (2.1 g, 55%) which was used directly without further purification or characterisation. The crude syrup was stirred at room temperature together with sodium cyanide (0.7 g, 14 mmol) in water (40 ml) overnight. The mixture was then refluxed for 6 h. T.l.c. (ethyl acetate) indicated a major product at the baseline, together with some unreacted material (R_f 0.3). The solution was cooled and extracted with ethyl acetate (3 x 50 ml) to remove unreacted starting material. The aqueous extract was then adjusted to pH 4 by careful addition of concentrated sulphuric acid and the solvent then removed. The residue was co-evaporated with toluene (2 x 10 ml), dissolved in acetic acid (50 ml), and stirred at room temperature overnight. T.l.c. (ethyl acetate) indicated the formation of a product (R_f 0.5) together with a large amount of baseline material. The solvent was removed, the residue co-evaporated with toluene (2 x 10 ml), and then dissolved in ethyl acetate by heating at reflux for several hours. The solution was cooled, filtered through a silica plug topped with Celite and the solvent removed to yield a residue that was purified by repeated flash chromatography (hexane : ethyl acetate 1 : 1) to yield *3,4-O-isopropylidene-D-altrono-1,5-lactone* (9), (223 mg, 10% based on crude isopropylidene ribose), as a white crystalline solid, m.p. 120-122°C; $[\alpha]_D^{20}$ +101.3 (*c*, 0.9 in EtOH); υ_{max} (KBr): 3400 (br, OH), 1768 (C=O) cm^{-1}; δ_H (CD_3OD): 1.37 (3H, s, Me), 1.50 (3H, s, Me), 3.72 (1H, dd, H-6, $J_{5,6}$ 5.0 Hz, $J_{6,6'}$ 12.8 Hz), 3.89 (1H, dd, H-6', $J_{5,6'}$ 2.1 Hz), 4.24 (1H, ddd, H-5, $J_{4,5}$ 9.5 Hz), 4.29 (1H, m, H-3, $J_{2,3}$ 7.4 Hz, $J_{3,4}$ 8.0 Hz), 4.38 (1H, dd, H-4), 4.51 (1H, d, H-2); δ_C (CD_3OD): 24.2, 26.5 (2 x q, 2 x MeC), 61.2 (t, C-6), 71.2, 71.4, 78.5, 79.0 (4 x d, C-2, C-3, C-4, C-5), 112.6 (s, $\underline{C}Me_2$), 173.7 (s, C-1); *m/z* (NH_3, DCI): 236 ($M+NH_4^+$, 100%), 219 ($M+H^+$). (Found: C, 49.20; H, 6.41. $C_9H_{14}O_6$ requires: C, 49.54; H, 6.47%).

6-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-isopropylidene-altrono-1,5-lactone (10). 3,4-*O*-Isopropylidene-D-altrono-1,5-lactone (9) (300 mg, 1.4 mmol) and imidazole (247 mg, 3.6 mmol) were stirred under nitrogen in dry *N,N*-dimethylformamide (15 ml) at 0°C. *tert*-Butyldimethylsilylchloride (300 mg, 2.0 mmol) was added and the mixture allowed to warm to room temperature. After 30 min t.l.c. (hexane : ethyl acetate 1 : 1) showed complete consumption of starting material (R_f 0.3) and the formation of a single product (R_f 0.7). The solvent was removed in vacuo and ether (20 ml) was added. The mixture was shaken with water (20 ml), which was then further extracted with ether (2 x 20 ml). The combined organic extracts were then dried (magnesium sulphate), filtered and the residue purified by flash chromatography (hexane : ethyl acetate, 3 : 1) to yield *6-O-*

tert-butyldimethylsilyl-3,4-O-isopropylidene-altrono-1,5-lactone (10), (378 mg, 83%), as a white crystalline solid, m.p. 140-143°C; $[\alpha]_D^{20}$ +78.2 (*c*, 1.04 in $CHCl_3$); υ_{max} ($CHCl_3$): 3500 (br, OH), 1760 (C=O) cm^{-1}; δ_H ($CDCl_3$): 0.11 (6H, s, Me_2Si), 0.92 (9H, s, Bu^t), 1.39 (3H, s, Me), 1.54 (3H, s, Me), 3.35 (1H, br, OH), 3.88 (1H, dd, H-6, $J_{5,6}$ 4.5 Hz, $J_{6,6'}$ 12.0 Hz), 4.03 (1H, dd, H-6', $J_{5,6'}$ 2.0 Hz), 4.16 (1H, ddd, H-5), 4.28-4.30 (2H, m, H-3, H-4), 4.42 (1H, d, H-2, $J_{2,3}$ 7.7 Hz); δ_C ($CDCl_3$): -5.6 (q, $\underline{Me}_2Si$), 18.2 (s, $Si\underline{C}Me_3$), 24.3, 26.6 (2 x q, 2 x $\underline{Me}C$), 25.7 (q, Bu^t), 61.8 (t, C-6), 70.0, 70.8, 77.4, 78.5 (4 x d, C-2, C-3, C-4, C-5), 112.2 (s, $\underline{C}Me_2$), 172.9 (s, C-1); *m/z* (NH_3, DCI): 350 ($M+NH_4^+$, 100%), 333 ($M+H^+$). (Found: C, 54.37; H, 8.72. $C_{15}H_{28}O_6Si$ requires: C, 54.19; H, 8.49%).

Methyl 5-azido-5-deoxy-2,3-*O*-isopropylidene-β-**D**-ribofuranoside (13). Methyl 2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulphonyl-β-**D**-ribofuranoside (12) (1.98 g, 5.5 mmol) [m.p. 81-83°C (Lit. 83-85°C)] and sodium azide (0.75 g, 11 mmol) were dissolved in dry *N,N*-dimethylformamide (30 ml) and stirred under nitrogen at 50°C. After 10 h, t.l.c. (ether : hexane, 2 : 1) revealed the formation of a single product (R_f 0.6). Butanol (3 ml) was added and the solvents removed under reduced pressure. The residue was dissolved in water (50 ml) and extracted with ether (3 x 50 ml). The combined organic extracts were washed with brine (100 ml) dried (magnesium sulphate) and filtered. The solvent was then removed to yield a crude yellow oil which after purification by flash column chromatography (ether : hexane, 1 : 2) yielded *methyl 5-azido-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside* (13) as a colourless oil (1.07 g, 80%), $[\alpha]_D^{20}$ -61.8 (*c*, 0.98 in $CHCl_3$); ν_{max} (film): 2103 (N_3) cm^{-1}; δ_H ($CDCl_3$): 1.33 (3H, s, Me), 1.49 (3H, s, Me), 3.27 (1H, dd, H-5, $J_{4,5}$ 6.8 Hz, $J_{5,5'}$ 12.5 Hz), 3.38 (3H, s, MeO), 3.46 (1H, dd, H-5', $J_{4,5'}$ 7.7 Hz), 4.30 (1H, m, H-4), 4.61 (2H, s, H-2, H-3), 5.00 (1H, s, H-1); δ_C ($CDCl_3$): 24.72, 26.21 (2 x q, 2 x $\underline{Me}C$), 53.66 (t, C-5), 55.11 (q, $\underline{Me}O$), 82.03, 85.11, 85.38 (3 x d, C-2, C-3, C-4), 109.88 (d, C-1), 112.73 (s, $\underline{C}Me_2$); *m/z* (NH_3, CI): 215 ($M+NH_4^+$-MeOH, 60%), 202 ($M+H^+-N_2$, 90%), 172 ($M+NH_4^+$-MeOH-NH_3, 100%). (Found: C, 47.22; H, 6.87; N, 18.74. $C_9H_{15}N_3O_4$ requires: C, 47.16; H, 6.60; N, 18.33%).

5-Azido-5-deoxy-2,3-*O*-isopropylidene-**D**-ribofuranose(8) (i) Methyl 5-azido-5-deoxy-2,3-*O*-isopropylidene-β-**D**-ribofuranoside (13) (561 mg, 2.45 mmol) was stirred at room temperature in 50% aqueous trifluoroacetic acid (8ml). T.l.c. (ethyl acetate) showed immediate consumption of the starting material (R_f 0.8) and formation of a major product (R_f 0.4), identified as methyl 5-azido-5-deoxy-**D**-ribofuranose and also a minor product (R_f 0.1), 5-azido-5-deoxy-**D**-ribofuranose. After 3 hours t.l.c. showed only one product (R_f 0.1). The solvent was removed *in vacuo* and the residue co-evaporated with toluene (3 x 10 ml). The crude product was dissolved in acetone (10 ml). Camphor sulphonic acid (60 mg, 0.25 mmol) and 2,2-dimethoxypropane (2 ml, 16.4 mmol) were added and the reaction mixture stirred at 50°C for 30 min when t.l.c. (ethyl acetate) revealed an absence of starting material (R_f 0.3) and one major product (R_f 0.8). The mixture was neutralised with saturated sodium bicarbonate solution and the solvent removed under reduced pressure. The residue was dissolved in ethyl acetate (20 ml), washed with water (20 ml) and with brine (40 ml). The organic layer was dried (magnesium sulphate) and the solvent removed under reduced pressure. Purification by flash chromatography (ethyl acetate : hexane, 2 : 3) gave *5-azido-5-deoxy-2,3-O-isopropylidene-D-ribofuranose* (8), (357 mg, 72%), as a colourless oil, $[\alpha]_D^{20}$ +8.2 (*c*, 1.05 in $CHCl_3$); υ_{max} (film): 2105 (N_3) cm^{-1}; δ_H ($CDCl_3$): 1.34 (3H, s, Me), 1.50 (3H, s, Me), 3.23 (1H, d, OH, J 5.0 Hz), 3.41 (1H, dd, H-5, $J_{4,5}$ 5.6 Hz, $J_{5,5'}$ 12.5 Hz), 3.59 (1H, dd, H-5', $J_{4,5'}$ 7.0 Hz), 4.35 (1H, m, H-4), 4.65 (2H, m, H-2, H-3), 5.47 (1H, d, H-1); δ_C ($CDCl_3$): 24.68, 26.22 (2 x q, 2 x $\underline{Me}C$), 53.86 (t, C-5), 82.12, 85.44, 85.95 (3 x d, C-2, C-3, C-

4), 103.35 (d, C-1), 112.83 (s, CMe2); *m/z* (NH_3, CI): 188 ($M+H^+-N_2$, 40%), 172 ($M+NH_4^+-H_2O-HN_3$, 100%). (Found: C, 44.50; H, 6.33; N, 19.56. $C_8H_{13}N_3O_4$ requires: C, 44.65; H, 6.09; N, 19.53%).
(ii) Di-isobutylaluminium hydride (1M in heptane, 1.9 ml, 1.9 mmol) was added under nitrogen to a stirred solution of 5-azido-5-deoxy-2,3-*O*-isopropylidene-**D**-ribono-1,4-lactone (14), (339 mg, 1.6 mmol), in dry tetrahydrofuran (5 ml) at -50°C. After 6 h at -50°C t.l.c. (ether : hexane, 7 : 3) indicated one major product (R_f 0.4) and a trace of starting material (R_f 0.2). Saturated aqueous ammonium sulphate (1 ml) was added and the mixture stirred for 15 minutes until a white gelatinous precipitate formed. The precipitate was triturated with ethyl acetate (7 x 20 ml) and the washings were filtered through a plug of silica topped with celite and dried (magnesium sulphate). The filtrate was removed under reduced pressure and the residue purified by flash column chromatography (ether : hexane, 1 : 3) to yield the azidofuranose (8), (188 mg, 55%), identical in all respects to the material prepared by method (i).

6-Azido-6-deoxy-3,4-*O*-isopropylidene-**D**-altrono-1,5-lactone (15). (i) Sodium cyanide (136 mg, 2.78 mmol) was added to a vigorously stirred solution of 5-azido-5-deoxy-2,3-*O*-isopropylidene-**D**-ribofuranose (8) (368 mg, 1.71 mmol) in water (10 ml) at room temperature. After 24 h the solution was heated at reflux for 4 h. The aqueous solution was allowed to cool to room temperature and then extracted with dichloromethane (3 x 10 ml) to remove unreacted starting material (20 mg, 5%). The aqueous solution was adjusted to pH 5 by the cautious addition of concentrated sulphuric acid and extracted with ethyl acetate (8 x 15 ml). The combined organic extracts were dried (magnesium sulphate) and the solvent removed under reduced pressure. The residue was dissolved in acetic acid (10 ml) and heated at 70°C for 1 h when t.l.c. (ethyl acetate : hexane, 1 : 1) showed that most of the residual acid (R_f 0.0) had been converted to a major lactone product (R_f 0.4). The solvent was removed under reduced pressure and purification by flash column chromatography (ethyl acetate : hexane, 1 : 3) yielded *6-azido-6-deoxy-3,4-O-isopropylidene-**D**-altrono-1,5-lactone* (15), (111 mg, 27%), as a colourless solid, m.p. 66-68°C; $[\alpha]_D^{20}$ +127.5 (*c*, 1.01 in $CHCl_3$); υ_{max} ($CHCl_3$): 2110 (N_3), 1768 (C=O) cm^{-1} ; δ_H ($CDCl_3$): 1.39 (3H, s, Me), 1.54 (3H, s, Me), 3.37 (1H, br s, OH), 3.58 (1H, dd, H-6, $J_{5,6}$ 5.2 Hz, $J_{6,6'}$ 13.7 Hz), 3.77 (1H, dd, H-6', $J_{5,6'}$ 2.3 Hz), 4.23-4.47 (4H, m, H-2, H-3, H-4, H-5); δ_C ($CDCl_3$): 24.27, 26.53 (2 x q, 2 x MeC), 50.84 (t, C-6), 70.73, 71.06, 76.55, 77.43 (4 x d, C-2, C-3, C-4, C-5), 112.76 (s, CMe2), 172.10 (s, C-1); *m/z* (NH_3, CI): 231 ($M+NH_4^+-N_2-H_2O$, 45%), 198 ($M+H^+-N_2-H_2O$, 100%). (Found: C, 44.48; H, 5.26; N, 16.90. $C_9H_{13}N_3O_5$ requires: C, 44.45; H, 5.39; N, 17.28%).
(ii) 3,4-*O*-Isopropylidene-**D**-altrono-1,5-lactone (9) (72 mg, 0.33 mmol) and pyridine (0.064 ml, 0.79 mmol) were stirred in dry dichloromethane (5 ml) at -50°C under nitrogen. Trifluoromethanesulphonic anhydride (0.067 ml, 0.40 mmol) was added and after 10 min t.l.c. (ethyl acetate : hexane, 1 : 1) revealed complete comsumption of the starting material (R_f 0.1). The reaction mixture was diluted with dichloromethane (10 ml) and washed with 10 ml portions of 2M hydrochloric acid, water and saturated aqueous sodium bicarbonate. The organic layer was dried (magnesium sulphate) and the solvent removed under reduced pressure. The residue was dissolved in dry *N,N*-dimethylformamide (10 ml) together with sodium azide (67 mg, 0.99 mmol) and the mixture stirred under nitrogen. After 3 h t.l.c. (ethyl acetate : hexane, 1 : 1) revealed two major products (Rf 0.3 and 0.4 (azide)). The solvent was removed, the residue dissolved in water (10 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organic extracts were washed with brine (30 ml), dried (magnesium sulphate) and the solvent removed to give a crude yellow oil. Purification by flash column chromatography (ethyl acetate : hexane, 1 : 3) yielded 6-azido-6-deoxy-3,4-*O*-isopropylidene-**D**-altrono-1,5-

lactone (15) (16 mg, 20%) as a white crystalline solid identical in all respects to the compound described above.

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