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ALLYLIC SUBSTITUTIONS IN TRI-*O*-ACETYL-GLYCALS AND RELATED COMPOUNDS*†

R. D. (Gus) Guthrie and Robert W. Irvine
School of Science, Griffith University, Nathan, Queensland 4111 (Australia)
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ABSTRACT

The reaction of tri-*O*-acetyl-D-allal or -D-glucal, ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside, or 1,4,6-tri-*O*-acetyl-α,β-D-*erythro*-hex-2-enopyranose with sodium azide in acetonitrile under catalysis by boron trifluoride diethyl etherate yields a mixture of 4,6-di-*O*-acetyl-3-azido-3-deoxy-D-allal and -D-glucal, together with both anomers of 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl azide. The mechanism of these reactions is discussed. 3-Amino-3-deoxy-D-allal and -D-glucal and their derivatives are described.

INTRODUCTION

The chemotherapeutic success of the aminocyclitol antibiotics (particularly of the 4,6-*O*-linked type) has stimulated interest in the synthesis of analogues. One approach has been *via* the Lemieux–Nagabhushan reaction[1], involving the addition of nitrosyl chloride to the double bond of a glycal (a 1,5-anhydro-2-deoxy-hex-1-enitol). Semi-synthetic antibiotics may be constructed by this method from a pseudo-disaccharide and a glycal in either of two ways, with the glycal being the synthon for either the "prime ring" or the "double-prime ring"[2].

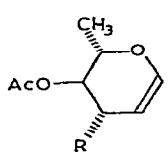
A well-established mechanism[3] by which resistant bacteria carrying an R-factor may inactivate aminocyclitols is typified by the kanamycins, where the most important mechanism for inactivation is by phosphorylation of the 3′-hydroxyl group. Thus, naturally occurring antibiotics (such as sisomicin and tobramycin), or synthetic analogues that lack this 3′-hydroxyl group, are active against kanamycin-resistant bacteria[3]. Also, all of the significant, natural aminocyclitol antibiotics have an amino group at C-3″. Thus analogues prepared from glycals modified at C-3 would be of interest as synthons for either the "prime ring" or the "double-prime ring".

This paper and following ones describe work originating from attempts to synthesize 3-amino-3-deoxy-glycals. Although an allylic alcohol group may be

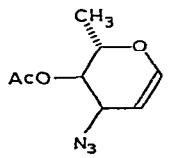
*Dedicated to Professor Stephen J. Angyal on the occasion of his retirement.
†Part I of the series "Allylic Nucleophilic Substitution Reactions in Sugars". For Part II, see following paper.

replaced directly by an acetamido group[4], the more-usual amination procedure employed in carbohydrate chemistry has involved displacement of a suitable leaving-group with azide ion, followed by reduction of the azido group. 3-Azido-3-deoxy-glycals would be useful for synthesis of modified antibiotics of the foregoing type, as such glycals could be directly incorporated into an antibiotic framework, and the azide group reduced at a later stage.

3-Azido-3-deoxy-glycals were unknown until recently when Heyns' group published papers that overlapped with our work. 3,4-Di-*O*-acetyl-L-rhamnal (**1**) was shown[5] to react with sodium azide in acetonitrile under catalysis by boron



1 R = OAc
2 R = N_3



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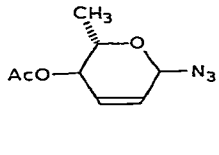

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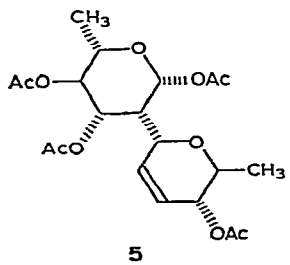

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trifluoride to give the isomeric azides **2**, **3**, and **4**, together with the dimer **5**: Heyns and Hohlweg[6] published details of analogous reactions of other glycals with sodium azide and other nucleophiles, and Heyns and Lim[7] reported the extension of the reaction of sodium azide to unsaturated disaccharides. Heyns and Hohlweg[8] also reported the preparation of 2,3-diamino-2,3-dideoxy-α-glycosides by using 3-azido-3-deoxy-glycals, in an extension of the Lemieux–Nagabhushan method[1].

In this and the following paper[9], we report on the reactions of some unsaturated sugars with sodium azide in acetonitrile under boron trifluoride catalysis, and compare and contrast our results with those reported by Heyns and Hohlweg[6]. The successful synthesis of 3-amino-3-deoxy-glycals and other 3-*N*-substituted derivatives is also described.

RESULTS AND DISCUSSION

Glycals react with a variety of nucleophiles in the presence of acid[10,11], and in examples for which the mechanism has been studied, the reaction was claimed to proceed *via* an oxocarbonium ion of the type **6**. With one exception[12], nucleophilic

TABLE I

^{13}C-N.M.R. DATA (CHLOROFORM-*d*)

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*Other*
7	145.5	99.3	67.5	67.3	74.0	61.3	C=O 169.1, 169.9; CH_3 20.8
8	145.8	98.1	57.7	67.6	74.5	61.5	C=O 169.5, 170.4; CH_3 20.6
9	144.6	101.6	48.2	68.3	74.8	61.6	C=O 170.5; CH_3 23.1, 20.8
10	145.2	98.7	54.4	68.0	74.5	61.6	C=O 170.9; CH_3 20.9
11	147.7	97.4	62.5	66.1	70.4	61.6	C=O 169.2, 170.2; CH_3 20.4
12	147.0	96.6	53.5	68.1	70.8	61.8	C=O 170.4; CH_3 20.0
13	145.9	98.9	41.6	66.8	71.0	62.2	C=O 170.6, 169.8; CH_3 23.3, 20.8
16	81.4	126.5[a]	129.7[a]	69.0	64.7	62.9	C=O 170.4; CH_3 20.0
19	84.4	128.1[a]	128.6[a]	74.0	64.0	62.6	C=O 169.4, 170.6; CH_3 20.6
22	143.7	104.9	52.4	72.6	80.4	62.3	
24	144.0	103.2	45.0	66.6	76.1	61.4	
25	147.1	100.3	52.1	66.1	76.2	62.1	CH_3 28.9, 26.9
17, **20**[b]	88.1 87.4	125.9[a] 126.3[a]	130.6[a] 128.4[a]	69.1 73.2	64.7 63.2	62.6 63.2	C=O 170.7, 170.0, 169.6 CH_3 21.0, 20.7

[a]Values in a row may be interchanged. [b]Mixture.

attack was at C-1. An exceptional nucleophile is the carbanion derived from methyl dicyanoacetate, which in acetonitrile under boron trifluoride catalysis attacks exclusively at C-3. The reason for this anomalous behaviour remains unclear, but it may be significant that this example constitutes the only successful carbon nucleophile utilized in such reactions. In terms of Pearson's concept[13] of hard and soft acids and bases, the majority of the other nucleophiles have been "hard" bases and would be expected to attack the more electropositive (namely, "harder acid") centre C-1, whereas the carbon nucleophile is a "soft" base and would attack the "softer" acid centre (namely, C-3 in the ion **6**). At the outset of this work, it was thought that, for the powerfully nucleophilic azide ion (which in Pearson's terms is a "borderline" base), attack at C-3 might successfully compete with attack at C-1.

3,4,6-Tri-*O*-acetyl-D-glucal (**7**) reacted with an excess of sodium azide in acetonitrile in the presence of a large excess of boron trifluoride–diethyl etherate to give a mixture of four products, shown by ^{13}C-n.m.r. and 270-MHz ^{1}H-n.m.r. spectroscopy to consist of 4,6-di-*O*-acetyl-3-azido-3-deoxy-allal (**12**, major component), the glucal isomer (**8**), 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl azide (**16**), and the β anomer (**19**). The fourth component was present only to a very small extent. The mixture could not be completely resolved by chromatography (compare ref. 6), but deacetylation followed by column chromatography allowed partial resolution of the resulting mixture into four fractions (*A*–*D*), of which that eluted first (*A*) was crystalline; its ^{1}H-n.m.r. spectrum indicated it to be 3-azido-3-deoxy-D-glucal (**21**), and conclusive proof was provided by its conversion into a

TABLE II

CHEMICAL SHIFTS AND COUPLING CONSTANTS FROM 270-MHz ^{1}H-N.M.R. SPECTRA IN CHLOROFORM-*d*

Compound	*Chemical shifts (δ)*								
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*		
8	6.50dd	4.81dd	4.08ddd	5.16dd	[a]	[a]	4.35dd		
12	6.53d	4.91t	[a]	5.11dd	[a]	[a]	4.35dd		
16	5.58ddd	5.78ddd	5.96ddd	5.26dddd	[a]	[a]	[a]		
19	5.34ddd	5.86ddd	6.04ddd	5.26dddd	4.01ddd	[a]	[a]		
	Coupling constants (Hz)								
	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	$J_{1,3}$	$J_{1,4}$	$J_{2,4}$
8	6.1	2.6	7.5	9.1	[a]	7.3	12.6	1.8	[a]	[a]
12	6.0	6.0	4.6	10.8	[a]	7.6	12.6	[a]	[a]	[a]
16	2.9	9.6	2.0	9.5	[a]	[a]	[a]	1.8	1.6	1.8
19	2.0	10.2	3.1	6.9	4.2	5.9	[a]	2.0	2.0	2.0

[a]Not assigned.

compound indistinguishable from authentic[14] 3-acetamido-4,6-di-*O*-acetyl-3-deoxy-D-glucal (**9**, see later).

Acetylation of **21** afforded a syrupy mixture of *two* compounds, of which the major component was 4,6-di-*O*-acetyl-3-azido-3-deoxy-D-glucal (**8**). Carbon resonances of the minor component were also present in the ^{13}C-n.m.r. spectrum of the original mixture, and corresponded to those attributed to structure **19**.

The 270-MHz, ^{1}H-n.m.r. spectrum of the mixture of **8** and **19** could not be completely assigned. The H-5 and H-6 resonances of **8** appeared as a second-order multiplet and obscured the H-6 and H-6′ resonances of **19**. However, complete assignment of the remainder of the spectrum of **8** was possible, and the results are presented in Table II.

Complete assignment of the remainder of the spectrum of **19** gave the results presented in Table II. Comparison of the derived coupling-constants with those calculated for the two conformations of the six isomeric conduritols (3,4,5,6-tetrahydroxycyclohex-1-enes)[15] provides additional evidence for the β configuration. In addition to being outside the range of couplings observed[16–19] in *N*-glycosyl analogues of **19**, the homoallylic $^5J_{1,4}$ coupling of 2.0 Hz lies outside the range of 0.7–1.6 Hz calculated for the conduritols corresponding to the α anomer **16**, but inside the calculated range (0–3 Hz) corresponding to the β anomer **19**. Introduction of the oxygen atom into the ring and the difference in the substituents may cause deviations from these optimized couplings, but these are unlikely to be sufficient to increase the $^5J_{1,4}$ coupling greatly.

Isomerizations of allylic azides have been well documented[20–24] and are generally believed to proceed *via* an intramolecular (SNi′) mechanism involving a transition state of negligible polarity. Consequently, the appearance of **19** as a product of the acetylation of **21** is explained by a stereospecific rearrangement between **8** and **19**.

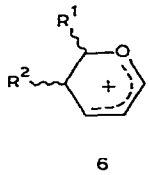
The stereospecificity of the rearrangement (and hence its intramolecular character) was demonstrated by the failure to detect any epimerization at C-3 or at C-1 when mixtures of **8** and **19** were boiled under reflux for 100 h in nitromethane, or stored neat at ambient temperature for 12 months. The observation that mixtures of **8** and **19**, enriched in either isomer by chromatography, re-equilibrated at 25° to a constant ratio of **8**:**19** = 17:3 demonstrates that the isomerization is reversible.

The third chromatographic fraction (*C*) contained two compounds, and was free of the azido-glucal **21**. The ^{1}H-n.m.r. spectrum indicated that at least 90% of this mixture was 3-azido-3-deoxy-D-allal (**23**). Acetylation afforded a mixture of two compounds, and the 270-MHz ^{1}H-n.m.r. spectrum indicated the major component to have structure **12**. Although the H-5 and H-6 resonances of **12** were unresolved and obscured the H-5, 6, and 6′ resonances of the other component, the remainder of the spectrum was completely assigned (Table II).

Four of the protons of the minor component of the mixture were completely resolved (Table II), and comparison of the coupling constants with those of the conduritols[15] and *N*-glycosyl analogues provides additional evidence for the α anomer. The homoallylic coupling ($^5J_{1,4}$ 1.6 Hz) is within the range expected for a mixture of both possible conformations of **16**, and the other coupling-constants are consistent with this structure. Curiously, the $^3J_{4,5}$ coupling (9.5 Hz) is outside the range of all of the corresponding couplings in the conduritols, but the introduction of the bulky acetoxymethyl group at C-5 is likely to cause the C-4–C-5–H-5 bond-angle in **16** to be more "perpendicular" than in the conduritols, thus decreasing the value of the $^3J_{4,5}$ coupling. The ^{13}C-n.m.r. spectrum of the mixture confirmed the assignment of structures **12** and **16** (Table I). Chloroform solutions enriched in either **12** or **16** by chromatography also underwent an equilibration ($t_{1/2}$ ~20 h) to a constant composition of **12**:**16** = 69:31 at 23°, and no trace of epimerization was observed when such a mixture was boiled under reflux for 100 h in nitromethane.

The second (*B*) and fourth (*D*) fractions obtained from the column were mixtures of **21** and **23**, and two other compounds whose ^{1}H-n.m.r. spectra were consistent with the structures **26** and **27**. These compounds were not isolated, but the two fractions were combined, and further chromatography afforded additional **21** and **23**.

The optical rotations of **12** and **16** were derived from a plot of the rotation of a series of samples, variously enriched by chromatography in either isomer, against the mole fraction of one isomer as determined by ^{1}H-n.m.r. (Fig. 1), and they were found to be +442 and +206° (in chloroform), respectively. These values are in reasonable agreement with those reported by Heyns and Hohlweg[6] (+429 and +206°, respectively) for samples stated to have been obtained pure after a single chromato-



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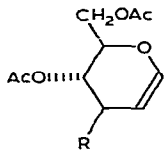
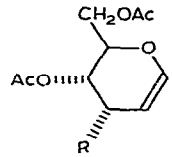
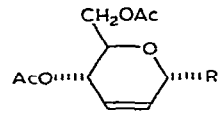


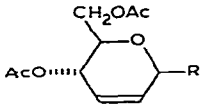
7 R = OAc
8 R = N_3
9 R = NHAc
10 R = NCS



11 R = OAc
12 R = N_3
13 R = NHAc
14 R = N=CMe_2
15 R = NCS



16 R = N_3
17 R = OAc
18 R = OEt



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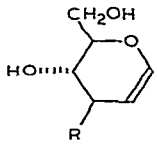
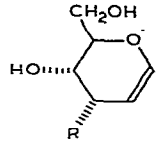
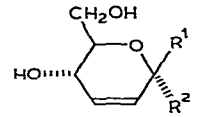
20 R = OAc



21 R = N_3
22 R = NH_2



23 R = N_3
24 R = NH_2
25 R = N=CMe_2



26 R^1 = H, R^2 = N_3
27 R^1 = N_3, R^2 = H

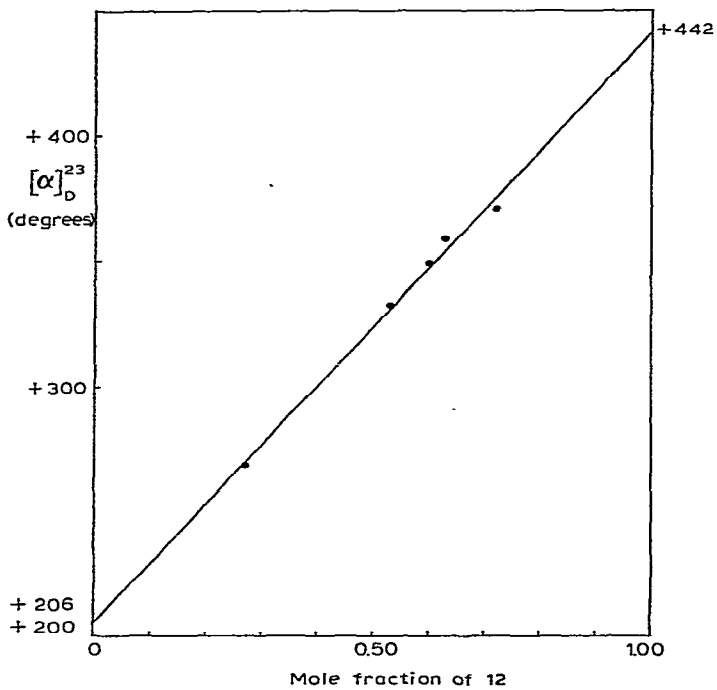


Fig. 1. Calculation of the optical rotations of **12** and **16**.

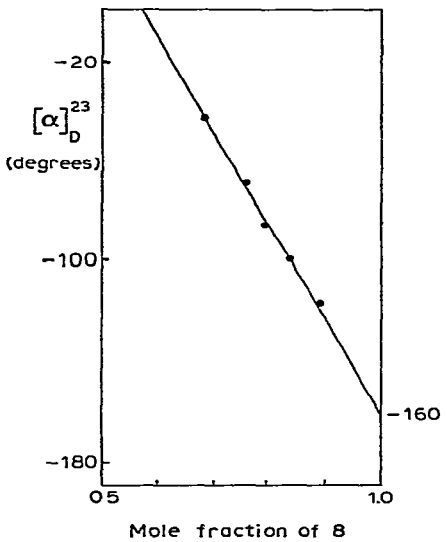
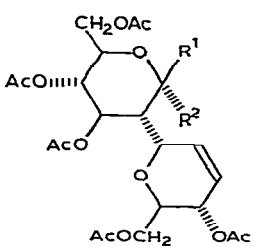


Fig. 2. Calculation of the optical rotations of **8** and **19**.

graphic development. The optical rotations of the azidoglucal **8** and the β-azide **19** were determined similarly and found to be −160 and +211°, respectively (Fig. 2). However, there is a substantial difference between these rotations and those reported[6], namely −35.6 and +74°, respectively. As the correlation coefficient of the plot is −0.999, it is unlikely that an error in our results could account for these significant discrepancies. In view of the difficulty encountered in attempted chromatographic separation of compounds **8** and **19**, and also their facile sigmatropic interconversion, the diminished $[\alpha]_D$ values obtained by Heyns and Hohlweg[6] (relative to our derived values) strongly suggest that the samples used by those authors were mixtures of isomers.

The overall yield of the mixture of compounds **8**, **12**, **16**, and **19** was optimized at 95%, but the yield was extremely sensitive to the reaction conditions. Variation in proportions of reagents or in reaction times resulted in either failure to react, or in competitive formation of the dimers[25] **28** and **29**.



28 R^1 = H, R^2 = OAc
29 R^1 = OAc, R^2 = H

TABLE III

PRODUCT RATIOS (±2%) FOR COMPOUNDS **8**, **12**, **16**, AND **19** (BY ^{1}H-N.M.R. SPECTROSCOPY)

Substrate	*Equiv. of* NaN_3	*Equiv. of* $BF_3 \cdot Et_2O$	*Percent yields*		
			12	**8**	**(16 + 19)**
7	5.5	40	50	24	26
11	5.5	40	48	24	28
18	5.5	40	49	24	27
(17 + 20)	5.5	10	49	24	27
(12 + 16)	5.5	40	63	15	22
(8 + 12)	5.5	40	40	40	20

Treatment of 3,4,6-tri-*O*-acetyl-D-allal (**11**) or ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**18**) with sodium azide and boron trifluoride–diethyl etherate in acetonitrile also afforded a mixture of compounds **8**, **12**, **16**, and **19**, in 85 and 75% yields, respectively. Optimal yields were obtained in all three instances when boron trifluoride–diethyl etherate was added in four equal aliquots at 0.5-h intervals. The finely powdered sodium azide dissolved in part after the addition of each aliquot, and was dissolved completely only after the fourth addition. T.l.c. indicated that starting material was still present prior to the fourth addition.

Mixtures of 1,4,6-tri-*O*-acetyl-2,3-dideoxy-α- and -β-D-*erythro*-hex-2-enopyranoses (**17** and **20**, respectively), enriched in either isomer by chromatography, also reacted, but required only one aliquot of boron trifluoride–diethyl etherate. In this instance, competitive dimerization could not be eliminated, and considerable sodium azide remained undissolved after t.l.c. had indicated that no starting material remained. The ratios of the azides **8**, **12**, **16**, and **19** in the mixtures (by ^{1}H-n.m.r. spectroscopy) obtained from the foregoing substrates (namely, **7**, **11**, and **17/20**) were essentially identical, and are presented in Table III. (It should be noted that the values deviate considerably from those reported by Heyns and Hohlweg[6].)

This similarity of ratios recorded in Table III indicates thermodynamic control and a common intermediate. However, an immediate assignment of the mechanism as of the SNl′ type was precluded by the observation that mixtures of both **12** and **16** and **8** and **19** epimerized under the reaction conditions. In both cases, the product-mixture contained more of the starting material than was present in the thermodynamically equilibrated mixture (Table III). Furthermore, the attainment of equilibrium from the azidolysis of **17** and **20** required less boron trifluoride (1 × 10 equiv.) than did the glycals **7** or **11**, and the pyranoside **18** (4 × 10 equiv.). When a mixture of the azides **12** and **16** was treated under the reaction conditions for **17** and **20**, the products were <5% epimerized. These results strongly implicate a common intermediate in the azidolysis reactions.

When the azidolysis of **7** was forced to completion rapidly (at the expense of yield) by adding the boron trifluoride–diethyl etherate in two aliquots in 0.04 of the

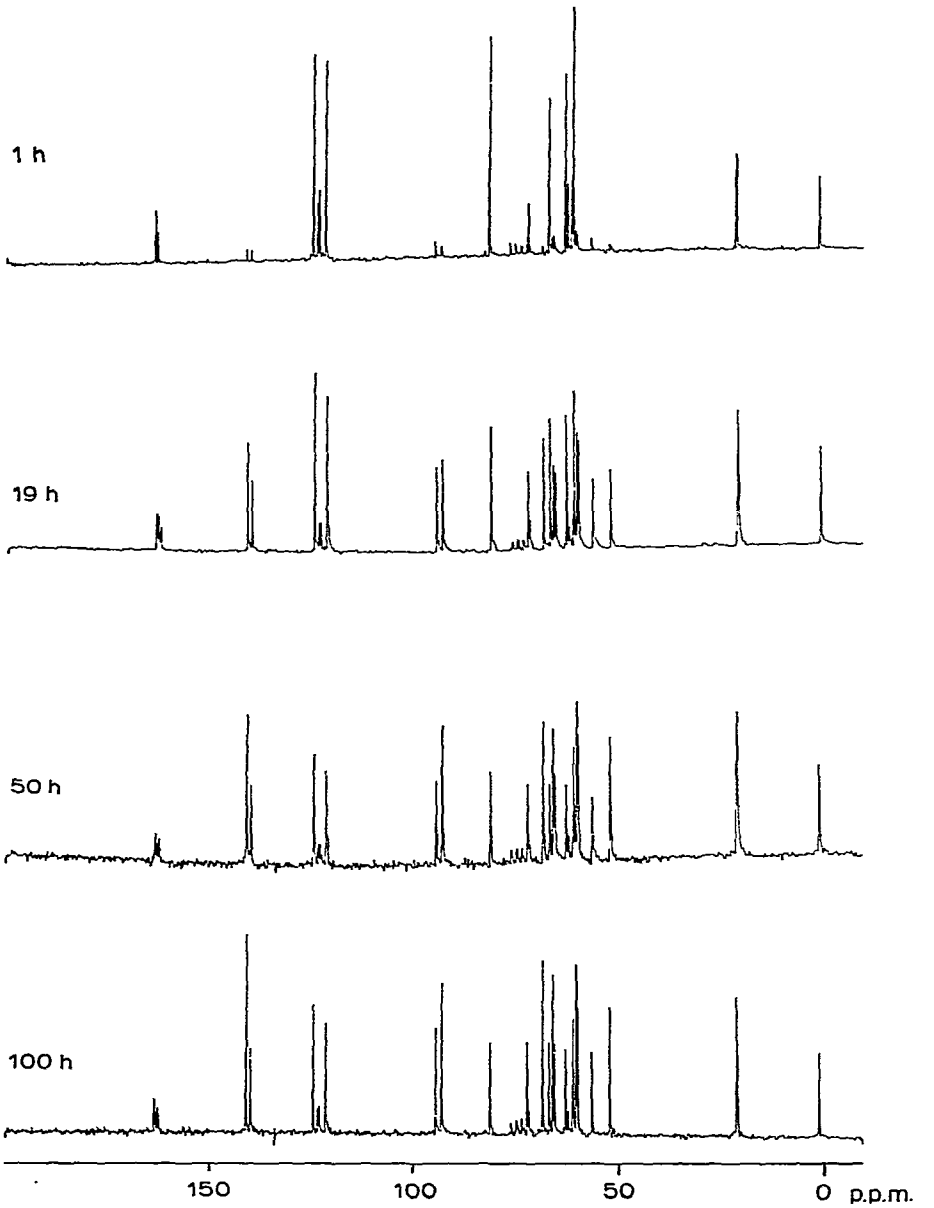


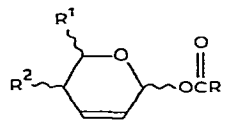
Fig. 3. Changes in the ^{13}C-n.m.r. spectrum (chloroform-*d*) in the products from the reaction of **7** with sodium azide in acetonitrile with rapid addition of $BF_3 \cdot Et_2O$.

normal reaction-time, and processing at 4°, the ^1H- and ^{13}C-n.m.r. spectra of the products (Fig. 3) indicated that the glycals **8** and **12** were completely absent. Signals corresponding to these compounds appeared during several h, and equilibrium was reached within one week.

^1H-N.m.r. spectra showed similar changes with time. Similar results were

obtained from the glycoside **18** and from a mixture of **17** and **20**, although in the former instance, the reaction was quenched at a stage when considerable starting material remained. The site of initial attack by azide is therefore at C-1, and any mechanism postulating nucleophilic attack at C-3 is highly unlikely. These results are similar to those reported by Ferrier and Ponpipom[18] for the acid-catalyzed reactions of **7**, **17**, and **20** with 2,6-dichloropurine: the 1-substituted, 2,3-unsaturated compounds initially formed equilibrated with the thermodynamically more-stable, 3-substituted glycals.

The nature of the common intermediate in the azidolysis reaction is of interest, and the possibilities include intimate or solvent-separated ion pairs, a free carbonium ion, or a complex that includes substrate, nucleophile, catalyst, and possibly solvent. In several acid-catalyzed reactions of glycals with nucleophiles in which the mechanism has been studied, it has been proposed[18,25-27] that initial isomerization of the glycal to the corresponding 1-*O*-acyl, 2,3-unsaturated compound (**30**), followed by ionization of the anomeric substituent, gives the resonance-stabilized carbonium ion **6**. In none of these examples was **30** isolated, and evidence to support this mechanism was provided in that it also reacted to give the same products as did the glycals.



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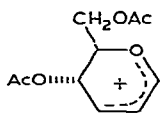
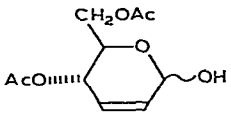


31

In other examples where an ion of the type **6** has been proposed as an intermediate[28-38], nucleophilic attack has occurred at C-1. This course may be due to a greater stabilization of the positive charge at C-1 by direct conjugation with the ring oxygen atom and the double bond, whereas at C-3, the conjugative effect of the ring oxygen atom must be transmitted through the double bond. Many of these examples refer to reactions performed in solvents of low polarity, where free carbonium-ion intermediates would have been unlikely. However, the existence of a free carbonium ion (**31**) has been implicated by the work of Paulsen and Thiem[35], who obtained identical product-ratios of anomeric hex-2-enopyranosyl dialkylphosphonates from the boron trifluoride-catalyzed reaction of dialkyl phosphites with both **7**, **11**, and the other glycals; none of the products epimerized or isomerized under the reaction conditions. It is probable that **31** is the common intermediate in the boron trifluoride-catalyzed reaction of the unsaturated sugars with sodium azide in acetonitrile.

The mechanism of the formation of **31** from **17** and **20** is clear cut. Leaving-groups attached to C-1 of such compounds have been observed to be much more labile than either those of their saturated counterparts, or the C-3 substituent of the corresponding glycals. For example, whereas **17** and **20** were readily converted by exposure to atmospheric moisture into 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranose (**32**), 1,2,3,4,6-penta-*O*-acetyl-α- and -β-glucopyranoses, and the glycals



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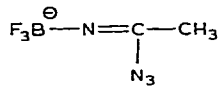

33

7 and **11**, were stable under these conditions. Under the conditions of azidolysis, therefore, **17** and **20** would be expected to ionize readily by way of complex formation with boron trifluoride. The glycoside **18** could also undergo a similar direct ionization, with the larger amount of catalyst required probably reflecting the decreased basicity of the ethoxide oxygen atom relative to its counterpart in the triacetate **17**.

For the glycals **7** and **11**, there are two possible routes to **31**: either an initial SNi′ isomerization to **17** and **20** followed by ionization, or a direct ionization of the C-3 acetoxyl group.

Acid-catalyzed rearrangements of glycals to the corresponding hex-2-enoses have been well documented[25,36,39], and in inert solvents are thought to proceed by an SNi′ mechanism, with the possibility of some ionic separation in the transition state. However, Lemieux and co-workers[40] proposed that isomerization of 2-acetoxy-3,4,6-tri-*O*-acetyl-D-glucal in acetic acid involved a direct ionization of the 3-acetoxyl group.

The rearrangement products **17** and **20**, being more reactive than **7** and **11**, would not be detectable in the azidolysis reactions. Treatment of **7** with boron trifluoride–diethyl etherate in acetonitrile resulted in the rapid formation of the dimers **28** and **29**. In the absence of conclusive evidence, no definite choice between the two routes to the ion **31** from **7** and **11** could be made.

Although the fourfold increase in the amount of catalyst required for the complete reaction of the glycoside **18** relative to the triacetates **17** and **20** probably reflects variations in the lability of the leaving-groups, an extension of this argument to the glycals **7** and **11** does not immediately follow. Because the reaction was heterogenous, the degree of reaction per aliquot of catalyst — the only available estimation of the relative rates of these reactions — was profoundly influenced by the quality of the sodium azide and the dynamics of stirring of the mixture. Sodium azide is virtually insoluble in acetonitrile, and only very finely powdered sodium azide suspended by vigorous stirring underwent dissolution upon addition of each aliquot of catalyst. Even after protracted stirring for 24 h, during which time much of the remaining, coarser crystals were pulverized and dispersed, no additional sodium azide

dissolved after the initial dissolution observed upon addition of an aliquot of catalyst. These observations imply that, during the partitioning of the boron trifluoride between the sugar and the sodium azide, a considerable portion also co-ordinates with the solvent.

As in the course of the partitioning of the first aliquot of catalyst (10 equiv.), ~25% of the sodium azide (namely 1.25 equiv.) dissolved, sufficient azide ion and catalyst must have been theoretically present in solution to effect complete azidolysis of the sugar. The readily ionized hex-2-enoses **17** and **20** *were* completely converted into the glycosyl azides **16** and **19** under these conditions. It follows, therefore, that only that portion of the sugar which had ionized very soon after the partitioning of the catalyst could react at that time, and that azide ion in solution was for some reason unavailable for further reaction with any carbonium ion subsequently formed (until further catalyst had been added).

A possible explanation for the scavenging of the solvated azide ion is that azide may attack the solvent–catalyst complex to form an ion of the type **33**, and that decomposition of this ion may be very slow.

Glycals bearing a free amino-group at C-3 were previously unknown. Attempted reduction of mixtures of the unsaturated azido sugars **8**, **12**, **16**, and **19** with sodium borohydride in methanol resulted only in partial deacetylation. However, 3-azido-3-deoxy-D-glucal (**21**) was conveniently reduced by lithium aluminium hydride in ether to give 3-amino-3-deoxy-D-glucal (**22**) as a colourless syrup that slowly crystallized. Acetylation of **22** afforded a 96% yield of the known[14] 3-acetamido-4,6-di-*O*-acetyl-3-deoxy-D-glucal (**9**), prepared by a different route.

Similar reduction of a mixture of 3-azido-3-deoxy-D-allal (**23**) and 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl azide (**26**) afforded 44% of syrupy 3-amino-3-deoxy-D-allal (**24**), and no trace of the α-unsaturated glycosylamine was detected. This result is not surprising, as the only other reported compound of this type was very unstable[40]. Acetylation of **24** afforded a crystalline compound (96%) of which the i.r., ^{1}H-n.m.r., and ^{13}C-n.m.r. spectra were consistent with the structure of 3-acetamido-4,6-di-*O*-acetyl-3-deoxy-D-allal (**13**). When acetone was used in the isolation procedure, a crystalline compound for which the spectral data were consistent with 3-deoxy-3-isopropylideneamino-D-allal (**25**) was obtained. The ^{1}H-n.m.r. spectrum was unique among the spectra of derivatives of D-allal studied in that the H-2 signal appeared as a well-defined doublet of doublets at δ 5.15, showing a $^3J_{2,3}$ coupling of 4.0 Hz. In all other allal derivatives, this coupling was 5.90 ±0.10 Hz. Further characterization was provided by acetylation, which afforded the syrupy diacetate. The i.r. spectrum retained the $\nu_{C=N}$ absorbance at 1640 cm^{-1}, and displayed an absorbance corresponding to an ester carbonyl group but no amide carbonyl absorbance. The structure of the diacetate was therefore assigned as **14**. Both **14** and **25** were very acid-labile.

Treatment of a mixture of **12** and **16** with triphenylphosphine in carbon disulphide afforded 32% of crystalline 4,6-di-*O*-acetyl-3-deoxy-3-isothiocyanato-D-allal (**15**), whose physical constants were in good agreement with those reported for

15 prepared by the boron trifluoride-catalyzed reaction of **7** with potassium thiocyanate in acetonitrile[6]. Similar treatment of a mixture of the azido-glucal **8** and β-azide **19** gave 4,6-di-*O*-acetyl-3-deoxy-3-isothiocyanato-D-glucal (**10**) as a very unstable syrup in 18% yield. No trace of any 2,3-unsaturated glycosyl isothiocyanate was observed in either reaction.

EXPERIMENTAL

General methods. — Melting points were determined on a Büchi "Tottoli" apparatus and are uncorrected. Specific rotations were determined with a Perkin–Elmer 241 polarimeter and are for solutions in chloroform unless otherwise stated. Mass spectra were recorded at the University of Queensland with an AEI MS902-S spectrometer (by courtesy of Dr. R. F. Evans). Microanalyses were performed at the University of Queensland (by Mr. J. Kemp). I.r. spectra were determined with a Perkin–Elmer Model 377 spectrophotometer. ^{1}H-N.m.r. spectra were determined on a Varian EM-360 or Bruker HX-270 instrument (Australian National NMR Centre), and are for solutions in chloroform-*d* unless otherwise stated. Proton-decoupled ^{13}C-n.m.r. spectra (see Table I) were obtained with a Bruker HX-90 spectrometer.

T.l.c. was performed on Silica Gel (Merck GF_{254}). Acetonitrile was pre-dried over calcium hydride and then purified by the method of Coetzee[41]. Boron trifluoride–diethyl etherate was distilled from calcium hydride under diminished pressure. Evaporation of organic solvents was performed *in vacuo* with a bath temperature $<50°$.

General procedure for the reaction of unsaturated sugars with sodium azide in acetonitrile under boron trifluoride–diethyl etherate catalysis. — The sugar (1 mmol) and sodium azide (5 mmol) were stirred in acetonitrile (50 mL) for 0.5 h at room temperature, and boron trifluoride–diethyl etherate (x mL) was added in y aliquots at 0.5-h intervals. After a further 0.5 h, solid anhydrous sodium carbonate was added and the mixture stirred for 2 h. The mixture was filtered and the solvent evaporated (40°). The residue was partitioned between dichloromethane (40 mL) and saturated sodium carbonate solution (20 mL), and the organic phase washed with water and dried. Evaporation of the solvent afforded mixtures of the various product-azides, together (in some instances) with unreacted starting-material. The respective experimental data for individual substrates are given next:

(*a*) *3,4,6-Tri*-O-*acetyl*-D-*glucal* (**7**): $x = 1.00$, $y = 4$, yield 96%. Separation on a 4-mmol scale was effected as follows. The residue obtained after evaporation of the solvent was dissolved in methanol (100 mL), sodium (5 mg) was added, and the vessel was stoppered and kept for 16 h at room temperature. After neutralization with solid carbon dioxide, the methanol was evaporated and the residue extracted with boiling ethyl acetate (3 × 50 mL). Filtration of the solid and evaporation of the solvent yielded a syrup (720 mg) which, after column chromatography (acetone–

hexane, 1:5), gave four fractions: *A* (115 mg), *B* (185 mg), *C* (340 mg), and *D* (42 mg), in order of elution.

Fraction *A* was chromatographically homogenous and crystallized on standing. Recrystallization from acetone–hexane gave 3-azido-3-deoxy-D-glucal (**21**) as colourless needles, m.p. 111.5–112°, $[\alpha]_D^{19}$ −93.7° (*c* 1.24, ethanol); ν_{max}^{Nujol} 2100 (N_3) and 1652 cm^{-1} (C=C–O); ^{1}H-n.m.r. (acetone-d_6): δ 6.46 (dd, 1 H, $J_{1,2}$ 6.0, $J_{1,3}$ 1.8 Hz, H-1), 4.94 (bs, 1 H, OH, diminishes on addition of D_2O), 4.63 (dd, 1 H, $J_{2,3}$ 2.0 Hz, H-2), 4.00 (bs, 1 H, OH, diminishes on addition of D_2O), and 3.6–4.30 (m, 5 H, H-3,4,5,6,6′).

Anal. Calc. for $C_6H_9N_3O_3$: C, 42.1; H, 5.3. Found: C, 41.8; H, 5.3.

Conventional acetylation with acetic anhydride and pyridine gave a syrupy mixture of 4,6-di-*O*-acetyl-3-azido-3-deoxy-D-glucal (**8**) and 4,6-di-*O*-acetyl-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranosyl azide (**19**) in 86% yield. The optical rotations, determined as described in the Discussion section (see Fig. 2), were: **8**, $[\alpha]_D^{23}$ −160° (chloroform) {lit.[6] $[\alpha]_D^{20}$ −35.6° (*c* 0.7, chloroform)}; and **19**, $[\alpha]_D^{23}$ +211° (chloroform) {lit.[6] $[\alpha]_D^{20}$ +74° (*c* 0.6, chloroform)}.

Anal. Calc. for $C_{10}H_{13}N_3O_5$: C, 47.1; H, 5.1; N, 16.5. Found (for the mixture of **8** and **19**): C, 47.2; H, 5.1; N, 16.8.

Fraction *C*, containing (by ^{1}H-n.m.r.) only 3-azido-3-deoxy-D-allal (**23**) and 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl azide (**26**), was treated with acetic anhydride in pyridine. Processing gave a syrupy mixture of 4,6-di-*O*-acetyl-3-azido-3-deoxy-D-allal (**12**) and 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl azide (**16**). The optical rotations, determined as described in the Discussion section (see Fig. 1) were: **12**, $[\alpha]_D^{20}$ +442° (chloroform) {lit.[6] $[\alpha]_D^{20}$ +429° (*c* 0.6, chloroform)}; and **16**, $[\alpha]_D^{20}$ +206° (chloroform) {lit.[6] $[\alpha]_D$ +206° (*c* 0.5, chloroform)}.

Fractions *B* and *D*, both mixtures of compounds **21**, **23**, **26**, and **27**, were combined and rechromatographed.

(*b*) *3,4,6-Tri*-O-*acetyl*-D-*allal*[42] (**11**): $x = 1.00$, $y = 4$, yield 85% (see Table III). The products were separated as in (*a*).

(*c*) *1,4,6-Tri*-O-*acetyl*-α,β-D-erythro-*hex-2-enopyranose*[25] (**17** and **20**): $x = 0.25$, $y = 1$, yield 81% (see Table III). Traces of dimeric material were also obtained. Products were separated as in (*a*).

(*d*) *Ethyl 4,6-di*-O-*acetyl-2,3-dideoxy*-α-D-erythro-*hex-2-enopyranoside*[29] (**18**): $x = 1.00$, $y = 4$, yield 75% (see Table III). Products were separated as in (*a*).

(*e*) *4,6-Di*-O-*acetyl-3-azido-3-deoxy*-D-*allal* (**12**) *and 4,6-di*-O-*acetyl-2,3-dideoxy*-α-D-erythro-*hex-2-enopyranosyl azide* (**16**): $x = 1.00$, $y = 4$, yield 93% (see Table III).

(*f*) *4,6-Di*-O-*acetyl-3-azido-3-deoxy*-D-*glucal* (**8**) *and 4,6-di*-O-*acetyl-2,3-dideoxy*-β-D-erythro-*hex-2-enopyranosyl azide* (**19**): $x = 1.00$, $y = 4$, yield 86% (see Table III).

Reduction of 3-azido-3-deoxy-D-*glucal* (**21**). — A solution of 3-azido-3-deoxy-D-glucal (**21**, 200 mg) in anhydrous ether (25 mL) was introduced dropwise into a stirred suspension of lithium aluminium hydride (400 mg) in ether (50 mL) boiling

under reflux under a nitrogen atmosphere. The mixture was boiled for a further 2 h, cooled, and the excess of hydride made neutral with ice. The solids were removed by filtration, washed with warm methanol, and the solvent evaporated, leaving a semi-crystalline residue that was extracted with warm ethanol (10 mL). Column chromatography of the concentrated solution (3% ammonium hydroxide in ethanol) gave 3-amino-3-deoxy-D-glucal (**22**) as a pale-yellow syrup that slowly crystallized (150 mg, 88%). Recrystallization from pyridine–ligroin afforded pale-yellow cubes, m.p. 129–130.5°, $[\alpha]_D^{20}$ −35.0° (*c* 0.56, ethanol). A minute amount of an intensely yellow impurity could not be removed by further crystallization, nor by treatment with charcoal; ^{1}H-n.m.r. (pyridine-d_5): δ 6.55 (dd, 1 H, $J_{1,2}$ 6.0, $J_{1,3}$ 1.8 Hz, H-1), 5.19 (bs, 4 H, HOD), 4.90 (dd, 1 H, $J_{2,3}$ 1.3 Hz, H-2), 4.30–4.53 (m, 2 H, H-4,6′), 4.02–4.28 (m, 2 H, H-5,6), and 3.86 (m, 1 H, H-3); *m/e* 144.066 ($M^+ - 1$), $C_6H_{10}NO_3$ requires 144.066.

Crystalline samples were stable under nitrogen at −15°, but decomposed at room temperature.

*3-Acetamido-4,6-*O*-acetyl-3-deoxy-*D*-glucal* (**9**). — The crude, semi-crystalline residue obtained prior to chromatography in the preparation of **21** was acetylated with pyridine–acetic anhydride at room temperature for 16 h to afford crystals that were recrystallized from acetone–hexane to give **9** (270 mg, 96%) as colourless prisms, m.p. 150–151°, $[\alpha]_D^{19}$ +66.2° (*c* 0.81) (lit.[14] m.p. 156–158°, $[\alpha]_D$ +63°). In admixture with an authentic sample* the melting point of **9** was undepressed, and **9** was chromatographically homogenous (t.l.c.) in three solvent-systems. The ^{1}H-n.m.r. and i.r. spectra of the samples were indistinguishable.

*3-Amino-3-deoxy-*D*-allal* (**24**). — An equilibrium mixture of 3-azido-3-deoxy-D-allal (**23**) and 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl azide (**26**, 500 mg) in anhydrous ether (25 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (800 mg) in ether (50 mL) boiling under reflux under a nitrogen atmosphere. Boiling was continued for a further 2.5 h, and then the solution was cooled, and the excess of hydride made neutral with ice. After removal of solids by filtration, and evaporation of the solvent from the filtrate, the residue was chromatographed (3% ammonium hydroxide in ethanol) to give **24** as a pale-yellow syrup (185 mg, 44%), $[\alpha]_D^{22}$ +211° (*c* 1.30, methanol); ^{1}H-n.m.r. (pyridine-d_5): δ 6.55 (d, 1 H, $J_{1,2}$ 6.0 Hz, H-1), 5.02 (t, 1 H, $J_{2,3}$ 6.0 Hz, H-2), 4.81 (bs, 4 H, HOD), 4.10–4.50 (m, 4 H, H-4,5,6,6′), and 3.60 (m, 1 H, H-3). The product was very unstable and no satisfactory microanalytical data could be obtained.

*3-Acetamido-4,6-di-*O*-acetyl-3-deoxy-*D*-allal* (**13**). — The residue obtained prior to chromatography in the preparation of **23** was extracted with pyridine (10 mL) and treated with acetic anhydride (1.0 mL) for 16 h at room temperature. The crystalline product was recrystallized from ether to give **13** as colourless prisms (400 mg, 50%), m.p. 124.5–125°, $[\alpha]_D^{20}$ +201° (*c* 1.14); ^{1}H-n.m.r.: δ 6.80 (d, 1 H, $J_{1,2}$ 6.0 Hz, H-1), 5.65 (bs, 1 H, *J* ~8.0 Hz, NH), 5.10 (dd, 1 H, $J_{3,4}$ 4.0,

*We are indebted to Prof. A. Jordaan for an authentic sample.

$J_{4,5}$ 10.5 Hz, H-4), 4.68–4.97 (m, 2 H, H-2,3), 3.93–4.40 (m, 3 H, H-5,6,6'), 2.10 (s, 3 H, *O*-acetyl), 2.03 (s, 3 H, *O*-acetyl), 2.03 (s, 3 H, *O*-acetyl), and 2.00 (s, 3 H, *N*-acetyl).

Anal. Calc. for $C_{12}H_{17}NO_6$: C, 53.1; H, 6.3; N, 5.2. Found: C, 53.4; H, 6.5; N, 5.1.

*3-Deoxy-3-isopropylidenamino-*D*-allal* (**25**). — A mixture of **23** and **26** was reduced as described. After neutralization of the excess of lithium aluminium hydride with ice, acetone (20 mL) was added and the mixture stirred overnight at room temperature. The solids were removed by filtration, washed with acetone, and the solvent evaporated. Column chromatography of the residue (acetone–hexane, 1:1), followed by recrystallization from ether, afforded **25** as colourless rods (185 mg, 54%), m.p. 91–92°, $[\alpha]_D^{25}$ +161° (*c* 0.90); ^{1}H-n.m.r.: δ 6.52 (d, 1 H, $J_{1,2}$ 6.0 Hz, H-1), 5.15 (dd, 1 H, $J_{2,3}$ 4.0 Hz, H-2), 3.60–4.17 (m, 4 H, H-3,5,6,6'), 3.20 (m, 1 H, $J_{3,4}$ 6.0 Hz, H-4), 2.35 (bs, 2 H, OH, diminishes on addition of D_2O), 1.45 (s, 3 H, CH_3), and 1.32 (s, 3 H, CH_3); *m/e* 170.081 ($M^+ - CH_3$), $C_8H_{12}NO_3$ requires 170.081.

A solution of **25** in pyridine was treated with acetic anhydride for 16 h at 5° to afford 4,6-di-*O*-acetyl-3-deoxy-3-isopropylideneamino-D-allal (**14**) as a colourless syrup (510 mg, 96%), $[\alpha]_D^{20}$ +240° (*c* 0.45, ethanol); ^{1}H-n.m.r.: δ 6.31 (d, 1 H, $J_{1,2}$ 6.0 Hz, H-1), 4.73 (dd, 1 H, $J_{2,3}$ 4.0 Hz, H-2), 4.18–4.60 (m, 5 H, H-3,4,5,6,6'), 2.12 (s, 6 H, *O*-acetyl), 1.64 (s, 3 H, C–CH_3), and 1.61 (s, 3 H, C–CH_3); *m/e* 269.124 (M^+), $C_{13}H_{19}NO_5$ requires 269.126.

*4,6-Di-*O*-acetyl-3-deoxy-3-isothiocyanato-*D*-allal* (**15**). — An equilibrium mixture of 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl azide (**16**) and 4,6-di-*O*-acetyl-3-azido-3-deoxy-D-allal (**12**, 850 mg) in carbon disulphide (20 mL) was introduced dropwise into a stirred solution of triphenylphosphine (960 mg, 1.1 equiv.) in carbon disulphide (35 mL) boiling under reflux. The mixture was boiled for 6 h, cooled, and the solvent evaporated. The residue was extracted with anhydrous ether (20 mL), the mixture filtered, and the ether evaporated. Four additional extractions of the residue (left after evaporation of the ether from the previous extraction) with decreasing volumes of anhydrous ether yielded a non-crystalline residue that was subjected to column chromatography (hexane–dichloromethane–acetone, 30:6:1) to give **15** as a crystalline mass (240 mg, 32%). Recrystallization from ether–hexane afforded colourless cubes, m.p. 66.5–67.5°, $[\alpha]_D^{20}$ +686° (*c* 0.41) (lit.[6] m.p. 67–68°, $[\alpha]_D$ +687°); ν_{max}^{Nujol} 2060 (–N=C=S); ^{1}H-n.m.r.: δ 6.47 (d, 1 H, $J_{1,2}$ 6.0 Hz, H-1), 5.01 (dd, 1 H, $J_{3,4}$ 5.0, $J_{4,5}$ 10.0 Hz, H-4), 4.94 (t, 1 H, $J_{2,3}$ 6.0 Hz, H-2), 4.63 (dd, 1 H, H-3), 4.25 (m, 1 H, H-5), 4.30–4.50 (m, 2 H, H-6,6'), 2.16 (s, 3 H, acetyl), and 2.07 (s, 3 H, acetyl).

Anal. Calc. for $C_{11}H_{13}NO_5S$: C, 48.7; H, 4.8. Found: C, 48.3; H, 4.7.

*4,6-Di-*O*-acetyl-3-deoxy-3-isothiocyanato-*D*-glucal* (**10**). — A solution of an equilibrium mixture of 4,6-di-*O*-acetyl-3-azido-3-deoxy-D-glucal (**8**) and 4,6-di-*O*-acetyl-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranosyl azide (**19**, 1.25 g) in carbon disulphide (20 mL) was added dropwise to a stirred solution of triphenylphosphine (1.50 g, 1.1 equiv.) in carbon disulphide (50 mL). The mixture was boiled for 2 h

under reflux, the solvent was evaporated off at room temperature, and the residue extracted with anhydrous ether. The residue obtained upon evaporation of the ether was repeatedly re-extracted with anhydrous ether in the manner already described until evaporation of the ether left a non-crystalline residue. The pale-yellow syrup thus obtained (1.35 g) was subjected to column chromatography (acetone–hexane, 1:12), to give **10** as a colourless syrup (240 mg, 18%); $[\alpha]_D^{20}$ −60° (*c* 1.42); ^{1}H-n.m.r.: δ 6.40 (dd, 1 H, $J_{1,2}$ 5.9, $J_{1,3}$ 2.0 Hz, H-1), 5.17 (dd, 1 H, $J_{3,4}$ 7.9, $J_{4,5}$ 8.5 Hz, H-4), 4.79 (dd, 1 H, $J_{2,3}$ 2.5 Hz, H-2), 4.44 (dt, 1 H, H-3), 4.13–4.36 (m, 2 H, H-6,6'), 4.09 (m, 1 H, H-5), 2.20 (s, 3 H, acetyl), and 2.12 (s, 3 H, acetyl); *m/e* 270.043, (M^+ − 1) requires 270.043.

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